



**Development of 2-Aminoquinoline
Derivatives as Ligands for Tec SH3 Domain**

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SUMMARY

Src Homology 3 (SH3) domains are small, non-catalytic protein-protein interaction domains comprising of approximately 50-70 amino acids. Protein complexes containing SH3 domains are found in a variety of cell signalling pathways controlling processes such as cell proliferation, apoptosis and gene expression. SH3 domains mediate these pathways by binding to proline-rich sequences on partner proteins thereby controlling the assembly of large multiprotein complexes. Many of these pathways, when deregulated, lead to diseases such as osteoporosis and cancer, therefore making SH3 domains appealing targets for the development of potential therapeutics.

Numerous SH3 domain structures have been determined by NMR or X-ray crystallography, including the solution structure of the murine Tec kinase SH3 domain, which was determined by NMR spectroscopy. The binding site for the native proline-rich peptide to the Tec SH3 domain was determined to be a shallow indentation on the surface of the protein. The development of high affinity small molecule ligands for the SH3 domain is of particular interest within our research group and has involved the murine Tec SH3 domain as a model system for structure based drug design. Initial studies determined that 2-aminoquinoline binds to the same shallow indentation on the SH3 domain surface as the native peptide with a K_d of 125 μM . 2-Aminoquinoline therefore serves as the lead compound for our investigations.

Previous studies in the development of small molecule ligands with improved affinity for the Tec SH3 domain have involved substitution at all positions of the 2-aminoquinoline core structure, including substitution at the amino nitrogen. Substituents in the 6-position appear to make favourable contacts with the protein surface and these have provided some of the highest affinity ligands to date, with the highest affinity ligand displaying a K_d of 9 μM .

This thesis describes the further development of small molecule ligands with substituents at the 6-position of 2-aminoquinoline and relevant structure activity relationship studies. Over 40 6-substituted ligands of three general classes have been prepared with the overall aim of improving the affinity of these ligands for the SH3 domain and gaining further insight into the binding mode of these ligands with the SH3 domain.

Previous studies of 6-substituted 2-aminoquinolines have involved ligands substituted with an acetal group at the 6-position of 2-aminoquinoline. This functionality is however, unstable under physiological conditions. The first class of ligands were synthesised in order to extend on this previous acetal-substituted work with the aim of increasing the stability of the ligands in addition to improving the affinity for the SH3 domain. This class of ligand contains a saturated *N*-heterocyclic substituent at the 6-position. These ligands were prepared using palladium catalysed Buchwald-Hartwig chemistry and required significant investigation into the optimal reaction conditions to effect the desired transformations. The binding affinity studies of the newly prepared ligands is also discussed.

The second class of ligands contain an aryloxymethyl or arylthiomethyl substituent at the 6-position. These ligands were prepared to complete previous studies involving simple 6-phenoxyethyl substituents. The final class of ligands combines both concepts of the first two classes of ligands and links a phenoxyethyl substituent with a saturated *N*-heterocycle in an extended 6-substituted ligand. The preparation of these ligands involved further investigations into Buchwald-Hartwig aminations.

The research presented in this thesis demonstrates that a 6-heterocyclic substituent can improve the binding affinity of 2-aminoquinoline for the Tec SH3 domain with some of the ligands prepared displaying equal or similar affinity to the highest affinity ligands previously reported. Similarly, 6-aryloxymethyl and 6-arylthiomethyl substitution has provided ligands with improved binding affinity relative to 2-aminoquinoline. Furthermore, a few of these ligands displayed the highest affinity for the Tec SH3 domain of all the ligands prepared to date. Some of these ligands, and also a number of the extended 6-substituted ligands, however, displayed unusual behaviour in the NMR assay and appear to bind through a different mode to other 2-aminoquinolines with more simple substitution. It is proposed that these ligands bind to the Tec SH3 domain through a 'see-saw' type mechanism; however, further studies of the binding interaction of these types of compounds are required to confirm this. These additional studies would also provide valuable information for the design of additional 2-aminoquinoline ligands with improved affinity for the Tec SH3 domain.

STATEMENT

This thesis contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution. To the best of my knowledge and belief, it contains no material previously published or written by another person, except where due reference has been made in the text. In addition, no work performed by another person has been presented, without due reference in the text.

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Jessica Smith, February 2009.

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Finally, I must thank my family and friends. To my husband Matt, thank you for being you! Your endless love, patience and understanding have been invaluable during my PhD and I am so grateful. Thank you also for caring and listening to each and every one of my chemistry

problems, even though they made no sense to you whatsoever! To the rest of my extended family, particularly my mum, thank you for everything. Without all of your love and support, I would have never made it to where I am today. Finally, I need to thank Dr Kristina Konstas (aka Dr Party). You have been such an enormous help on so many levels. Thank you for your assistance with all things chemistry both in and out of the lab. Thank you for immense support and for being available at any time for questions, problems and everything else. Most importantly, thank you for your friendship.

LIST OF ABBREVIATIONS

COSY	Correlation Spectroscopy
DABCO	1,4-Diazabicyclo[2,2,2]octane
DMAP	<i>N,N</i> -Dimethylaminopyridine
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
FP	Fluorescence Polarisation
Grb2	Growth factor receptor-bound protein 2
HMBC	Heteronuclear Multiple Bond Coherence
HSQC	Heteronuclear Single Quantum Coherence
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide
<i>m</i> -CPBA	<i>meta</i> -Chloroperbenzoic acid
NBS	<i>N</i> -Bromosuccinimide
PH	Plekstrin Homology
PMB	<i>para</i> -Methoxybenzyl (as protecting group)
ROESY	Rotating Frame Overhauser Enhanced Spectroscopy
SAR	Structure Activity Relationship
SH2	Src Homology 2
SH3	Src Homology 3
SOS	Son of Sevenless protein
TBAI	Tetra-(<i>n</i> -butyl)ammonium iodide
TBDMS	<i>tert</i> -Butyldimethylsilyl
TFA	Trifluoroacetic acid
TH	Tec Homology
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

Chapter 1:

INTRODUCTION

1.1 The SH3 Domain

1.1.1 Signal Transduction

In multicellular organisms a multitude of different signal transduction processes are required for coordinating the behaviour of individual cells to support the function of the organism as a whole. Signal transduction involves the assembly of transient protein-protein complexes, which subsequently initiate intracellular biochemical pathways resulting in a cellular response. This response may involve progression through the cell cycle, changes in gene expression, migration and metabolism. Modular intracellular protein-protein interaction domains such as the Src homology 2 and 3 domains (SH2 and SH3) mediate the formation of many of these protein complexes. Many disease processes such as heart disease and cancer arise from defects in signal transduction pathways and consequently the SH2 and SH3 domains have become appealing targets for the development of potential therapeutics.^{1,2}

1.1.2 SH3 Domains

SH3 domains were first recognised as non-catalytic regions of sequence similarity between divergent signalling proteins such as the Src family of enzymes, the Crk adaptor protein and phospholipase C- γ . These domains have now been identified in an extensive number of proteins including kinases, lipases, GTPases, adaptor proteins and structural proteins. The function of the SH3 domain is to mediate the assembly of large multi-protein complexes by binding to specific proline-rich sequences on target proteins. Protein complexes containing SH3 domains are found in a variety of signalling pathways controlling processes such as cell proliferation, apoptosis and gene expression.^{1,3,4}

A well characterised role of an SH3 domain in the formation of multi-protein complexes involved in cell signalling is found in the Grb2 protein. Grb2 is an adaptor protein found in the Ras signal transduction pathway and contains an SH2 domain and two flanking SH3 domains. In this pathway, Grb2 is localised near the cell membrane by interaction of the SH2 domain with phosphorylated tyrosine residues of a membrane receptor protein following extracellular stimuli. Grb2 then recruits SOS through the SH3 domains interaction with the proline-rich regions of SOS. SOS subsequently activates additional enzymes including Ras,

resulting in a signal cascade leading to cellular growth and differentiation (Figure 1).^{1,4}

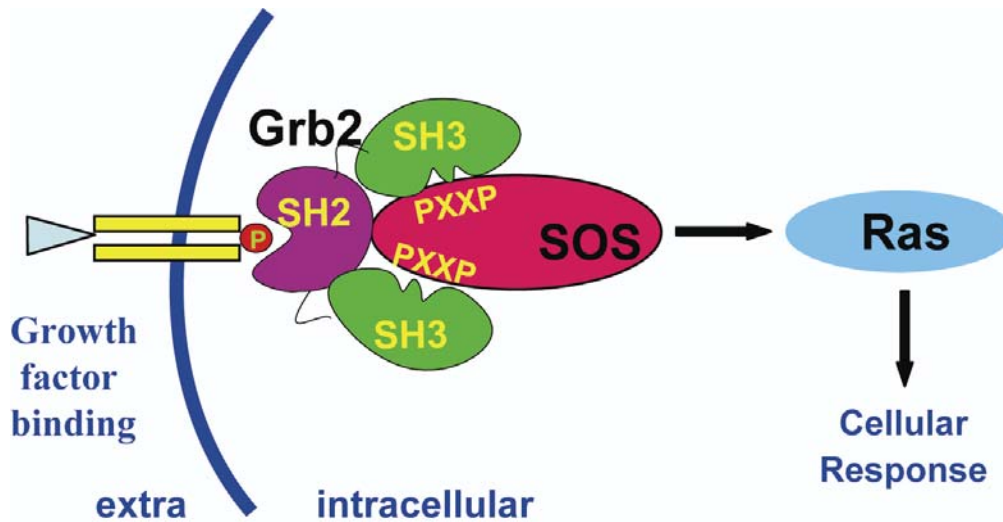


Figure 1: Schematic diagram of the Grb2 signal transduction pathway. Adapted from Figure 1 in Vidal.⁴

1.1.3 The Tec Family of Tyrosine Kinases

The Tec family is the second largest family of the cytoplasmic protein-tyrosine kinases (PTKs) and consists of five members, namely Tec, Btk, Itk/Emt/Tsk, Bmx and Txk/Rlk.^{5,6} Numerous members of the Tec family are expressed in haematopoietic tissues, where they are presumed to function in growth and differentiation of blood cells.⁷ Although, the precise molecular mechanisms of Tec regulation on cell growth and differentiation are unclear, there is evidence indicating their roles in calcium mobilisation, activation of MAP kinases, inducing transcription factor activity and regulating the actin cytoskeleton.^{8,9}

The Tec family of proteins consist of five domains; a Pleckstrin homology (PH) domain, Tec homology (TH) domain, SH3 domain, SH2 domain and an SH1/kinase domain (Figure 2).⁷ PH domains are found only in the Tec family of kinases and bind to both other proteins and phospholipids to localise the protein to the membrane.^{6,7,10} The TH domain, consisting of a Btk homology (BH) region and one or two proline-rich regions, together with the PH domain constitute a binding site for heterotrimeric G-proteins. In addition, the TH domain is presumed to bind intramolecularly to its own SH3 domains, therefore maintaining the kinase in an inactive state.^{7,10,11} The SH3 domain, as mentioned previously, binds to proline-rich sequences and also negatively regulates kinase activity. The SH2 domain binds to phosphorylated tyrosine residues whilst the kinase domain phosphorylates additional tyrosine residues.^{7,10}

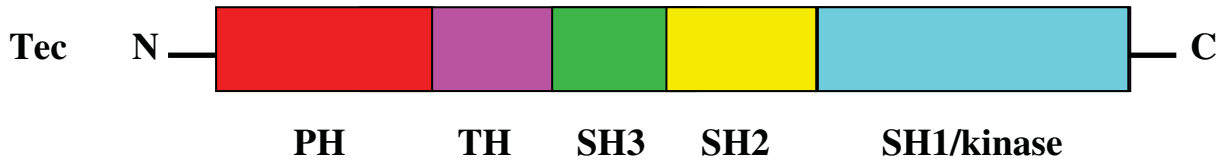


Figure 2: Schematic representation of the Tec family of protein tyrosine kinases.

1.1.4 SH3 Domain Structure

SH3 domains are small protein regions typically 50-70 amino acids long. Numerous SH3 domain structures have been determined by NMR spectroscopy or X-ray crystallography, some in complex with ligands. SH3 domains contain a canonical β barrel, which consist of five β strands arranged as two perpendicular antiparallel β sheets. A variable 'RT' (arginine-threonine) loop links two of the β strands (β A and β B) and an additional variable 'n-Src' loop links β B to β C. In addition there is a 3_{10} helix connecting the β D and β E strands.^{4,12-15} Three pockets exist on the SH3 binding surface, two hydrophobic leucine-proline ('Leu-Pro') pockets and the 'specificity pocket'. The 'Leu-Pro' pockets constitute a shallow groove approximately 25 Å long and 10 Å wide that accommodate two hydrophobic dipeptide segments of the ligand. The specificity pocket is occupied by a conserved basic residue of the ligand that forms a salt bridge with the protein.¹⁶ The general structure of the SH3 domain can be seen below in a diagram of the *murine* Tec SH3 domain, which was determined by NMR spectroscopy (Figure 3).¹⁵

NOTE:
This figure is included on page 3
of the print copy of the thesis held in
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Figure 3: Structure of the *murine* Tec SH3 domain, with β -sheets, RT loop, n-Src loop and 3_{10} helix illustrated.¹⁵

1.2 SH3 Domain Ligands

1.2.1 SH3 Domain Native Ligands

SH3 domains bind to native peptides with moderate to low affinity displaying equilibrium dissociation binding constants (K_d) of 1-200 μM .¹⁷ SH3 domains recognise peptide sequences containing the core binding motif PpXP, where P is proline, p is any amino acid but tends to be proline and X is any amino acid but has a tendency to be an aliphatic amino acid. Residues that flank the PpXP motif provide the selectivity involved in the recognition of SH3 domains for specific interactions.¹⁸

There are two classes of SH3 domain peptide ligands, namely Class I and Class II. Class I peptides (R/KXXPXXP) contain an N-terminal arginine or lysine residue whereas Class II peptides (XPXXPXR/K) contain a C-terminal arginine or lysine residue (Figure 4). Both classes of peptides bind in a left-handed poly-proline type 2 helix (PPII), with the direction of binding being determined by a salt bridge between the basic residue (R or K) of the ligand and a conserved acidic residue of the SH3 domain.¹²

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Figure 4: Schematic diagram of Class I and II ligands binding to the surface of the SH3 domain. Figure from Mayer.¹

1.2.2 Peptide and 'Peptoid' SH3 Domain Ligands

Despite SH3 domains being attractive targets for drug design, SH3 domains have proved to be difficult targets for drug development.¹⁹ For most SH3 domains, ligand interactions are of relatively low affinity as mentioned above and SH3 ligands show high cross-reactivity with a number of SH3 domains. The low affinity and low specificity of SH3 domain ligands is a result of the relatively small and featureless binding site.

However, in recent years a number of developments have been made in the search for novel ligands for SH3 domains. One such study utilised protein structure-based combinatorial chemistry to identify SH3 ligands based on the Class I ligand structure.^{20,21} Ligands (such as those shown in Figure 5) contained a **PLPPLP** motif linked to a novel monomeric non-peptide

binding element. The use of numerous 2D NMR spectroscopic methods demonstrated the interaction of these ligands with the native ligand binding site (including the specificity pocket) of the SH3 domain. Some of the ligands identified displayed high affinity for the SH3 domain with K_d s in the range of 3-20 μ M as determined by fluorescence polarisation studies. In addition, these ligands were found to be selective for the Src SH3 domain over the SH3 domain of P13K.^{20,21}

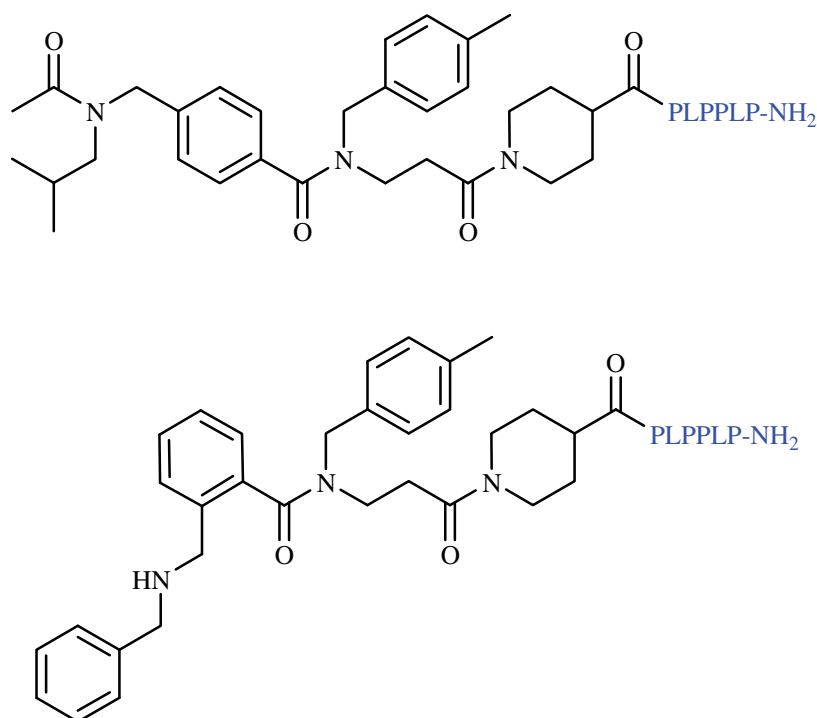


Figure 5: Examples of novel ligands developed from protein structure-based combinatorial chemistry using the core elements of Class I ligands.^{20,21}

Using a similar combinatorial approach, Nguyen *et al* described a series of ‘peptoid’ ligands that act as SH3 inhibitors.^{17,22} This research was based on the premise that the SH3 domains recognise proline-rich sequences because proline is the only endogenous *N*-substituted amino acid. Using a chemical minimisation scheme, key proline residues were identified and a series of peptoids containing non-natural *N*-substituted amino acids were tested for binding to the SH3 domains of Sem5, Crk, Grb2 and Src. A number of these peptoids demonstrated the ability to bind the SH3 domains with similar or greater affinities than the natural proline-rich peptides. Of particular interest was a peptoid that bound the SH3 domain of Grb2 with an affinity ($K_d = 40$ nM) of more than 100 times greater than the natural peptide, demonstrating the strength of this technique for providing high affinity ligands. In addition, variation of the peptoid flanking sequences allowed for the targeting of ligands to specific SH3 domains. For

example, the ligand shown in Figure 6 was found to bind to the SH3 domain of Crk with a $K_d = 2 \mu\text{M}$, but did not bind to either the Grb2 or Src SH3 domain.^{17,22}

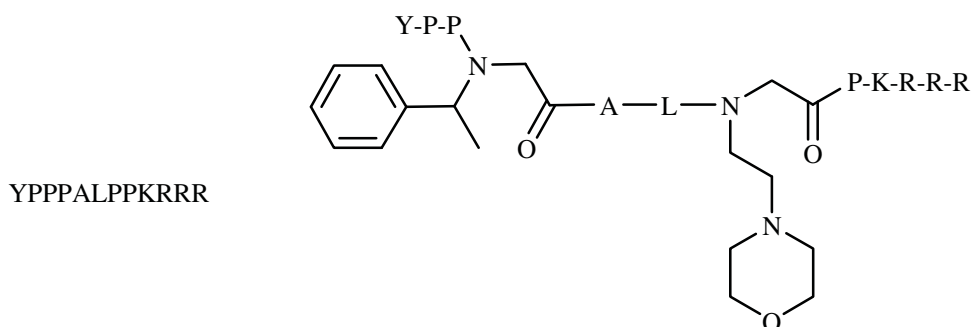


Figure 6: The native Crk-specific peptide ligand (left) and the Crk-specific peptoid ligand (right).^{17,22}

A recent study into the development of SH3 domain ligands has involved the preparation of peptides containing C^β -substituted proline residues (Figure 7).²³ In this study, the authors proposed that a C^β -substituted proline in the position adjacent to the site of Nguyen's *N*-substituted ligands, would project the β -substituent in the same direction as the *N*-substituent resulting in high affinity ligands. A number of ligands of this type were prepared and assessed for binding affinity. One of the C^β -substituted ligands ($R = \text{Me}$), displayed a 3-fold improvement in affinity for the Grb2 SH3 domain over a decapeptide taken from the native ligand. Other C^β -substituted ligands however, showed no binding to the SH3 domain.²³ The results of this research appear to indicate that *N*-substitution makes a more favourable contact with the protein surface than an adjacent C^β -substituted proline residue. A C^β -substituted proline residue can however, provide an improvement in binding affinity for the SH3 domain and further exploration of these types of ligands may be provide an alternate class of high affinity ligands.

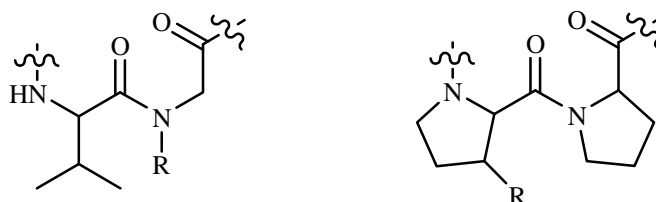


Figure 7: Comparison of the ligands designed by Nguyen *et al*²² and the C^β -substituted ligands.²³

Although high affinity peptide ligands have been developed for SH3 domains, there are a number of disadvantages associated with using such ligands as therapeutic agents. The major problem with peptides and peptidomimetics is their lack of cellular penetration and often

peptide inhibitors need to be conjugated with a cell-permeable moiety. In addition, peptides are easily broken down within the stomach and need to be injected rather than administered orally in order to have a chance of being effective.^{4,24} The development of small molecule inhibitors of SH3 domains with increased cell permeability is therefore appropriate.

1.3 Small Molecule Ligands for the Tec SH3 Domain

1.3.1 Earlier Studies

Despite significant interest in designing ligands for the SH3 domain, the design of small molecule SH3 inhibitors has received little attention. Some small molecule compounds have been reported to inhibit SH3/proline-rich peptide interaction, including **UCS15A** and its analogues (shown in Figure 8). This inhibition however, is thought to be mediated by the binding of the small molecule to the peptide rather than the protein.^{25,26}

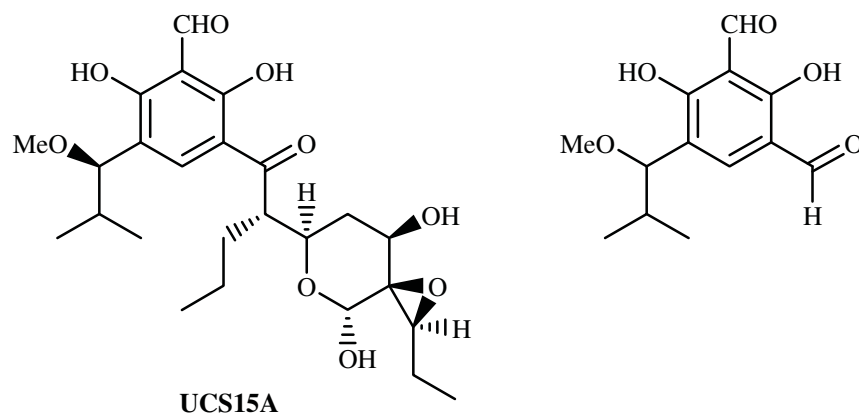
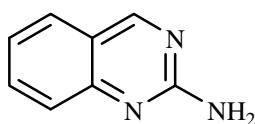


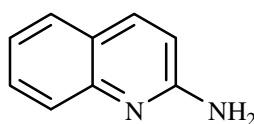
Figure 8: Structure of **UCS15A** and an analogue found to inhibit SH3/peptide interactions.^{25,26}

1.3.2 Identification of a Lead Compound in the Present Study

Using the solution structure of the Tec SH3 domain, *in silico* screens of small molecules were performed using LUDI software to discover a lead compound.²⁷ LUDI uses a combination of statistical data from small-molecule crystal structures to identify potential binding sites on a target protein or protein domain. Small molecule fragments are placed onto the potential binding sites in orientations that optimise interactions such as hydrogen bonding and hydrophobic contacts. LUDI then links the fragments with simple linkers such as CH₂, to give a compound predicted to bind to the protein surface.²⁷ From the molecular modelling studies, 2-aminoquinazoline **1** was predicted to bind to the specificity pocket of the Tec SH3 domain. The structurally related 2-aminoquinoline **2** was also selected for initial binding studies.²⁸



1



2

1.4 Determination of Binding Affinity

1.4.1 Fluorescence Polarisation Assay

To determine the binding affinities of ligands for the Tec SH3 domain, a fluorescence polarisation (FP) assay has been employed. Fluorescence polarisation is based on the observation that when a fluorescent molecule in solution is excited with polarised light, it will emit polarised light.²⁹ The emission can be depolarised by a number of factors, the most important being rotational diffusion. This means that when a fast tumbling, low molecular weight fluorophore is excited by plane-polarised light, the light emitted is random with respect to the plane of polarisation. Such fluorophores therefore result in low polarisation values. High molecular weight compounds, when excited by plane-polarised light conversely result in high polarisation values. This intrinsic property of a fluorophore can be utilised in a competitive binding assay. Fluorescent probes of low molecular weight will have low polarisation values when free in solution. The binding of such a probe to a target molecule of much larger molecular weight will cause an increase in the polarisation value of the probe. Thus, the change of polarisation reflects the extent of interaction between the fluorophore and the molecular target.³⁰

In this FP assay, the fluorescent tracer molecule employed is the fluorescein labelled peptide shown in Figure 9 and is referred to as PRP-1. PRP-1 is comprised of a small proline rich peptide ligand, known to bind to Tec SH3 domain linked to a fluorescent label (fluorescein-5-thiourea) at the N-terminus. To determine the binding affinity of ligands for the Tec SH3 domain a constant concentration of PRP-1 and Tec SH3 domain is titrated with increasing concentrations of a small molecule ligand. The change in polarisation upon the addition of the ligand reflects the ability of the ligand to displace the fluorescent tracer and allows for binding affinities (EC_{50}) to be determined. The EC_{50} of the ligand is defined as the concentration of the ligand required to displace 50% of the fluorescent tracer.

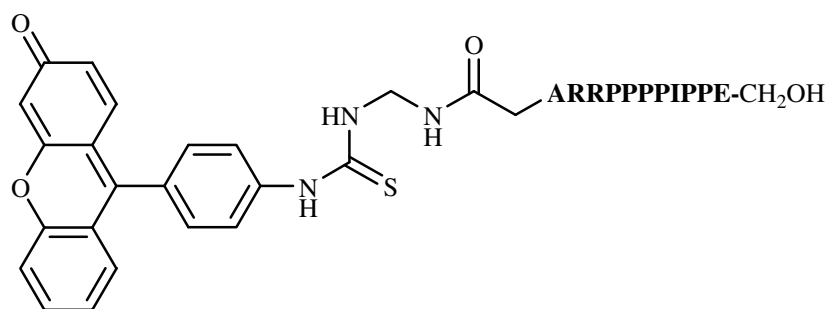


Figure 9: Structure of the fluorescently labelled tracer molecule, PRP-1.

1.4.2 [^1H , ^{15}N] HSQC NMR Chemical Shift Perturbation Assay

NMR chemical shift perturbation analysis utilising [^1H , ^{15}N] Heteronuclear Single Quantum Coherence (HSQC) NMR experiments can be used to determine binding affinities of small molecule ligands for a target protein. In addition to providing information on binding affinity, this method can also provide detailed structural information about binding interactions and has been employed for the determination of binding affinities of small molecule ligands for the Tec SH3 domain. In this assay, a constant concentration of uniformly ^{15}N -labelled protein is titrated with a small molecule ligand and [^1H , ^{15}N] HSQC NMR spectra are recorded after the addition of each aliquot of ligand. Increasing concentrations of the ligand causes incremental changes in the chemical shifts of the amino acid residues involved in the binding of the ligand. Residues whose chemical shift are altered by a significant amount ($\geq 0.08 - 0.1$ ppm) at saturation binding are used to generate a binding isotherm from which equilibrium dissociation binding constants (K_d) can be determined. The K_d of the ligand is defined as the concentration at which 50% of the ligand is bound to the protein and 50% of the ligand is unbound. An example of an overlaid HSQC experiment and the binding isotherm is shown in Figure 10.

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Figure 10: (A) A region of overlaid NMR [^1H , ^{15}N] HSQC spectra from the assay of **2**. (B) Chemical shift mapping of amino acid residues effected upon binding of **2**. (C) Binding isotherm derived from the HSQC NMR assay of **2**.³⁴

Fast, Intermediate and Slow Exchange

For all amino acid residues that are affected upon ligand binding, only one signal should be observed if the data is to be used to determine K_{ds} . The signal observed is the population weighted average resonance between bound and unbound states and indicates that the protein and the protein-ligand complex are in fast exchange (see Figure 11).

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Figure 11: Schematic representation of slow exchange (A), intermediate exchange (B) and fast exchange (C).³¹

When the rate of exchange between bound and unbound is slow two signals can be seen; one for the free protein and the other for the protein-ligand complex. The rate of exchange can be in between that of fast and slow exchange and is referred to as intermediate exchange. In intermediate exchange, peaks may become substantially broadened and may also have a much lower intensity than what is normally observed and peaks are often difficult to discriminate from the noise of the spectrum. Analysing a protein-ligand complex that is in intermediate exchange is often difficult for these reasons. In addition, the inability to discriminate signals from the noise of the spectrum results in fewer amino acid residues that can be used to determine binding affinities and can result in greater experimental error in the assay.

1.4.3 Binding Affinity of the Lead Compound

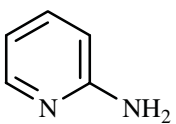
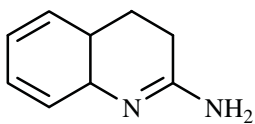
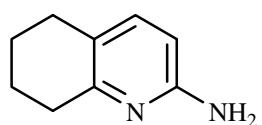
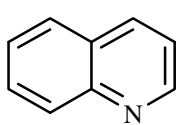
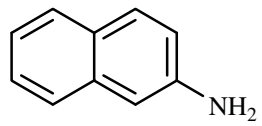
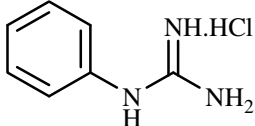
The binding of both **1** and **2** to the Tec SH3 domain were determined using the HSQC NMR assay. Mapping the chemical shift changes induced by **1** and **2** onto the SH3 domain indicated that both ligands bound to the same location of the protein specified by the LUDI design. The predicted lead compound **1** was determined to bind the Tec SH3 with

$K_d = 800 \mu\text{M}$. Compound **2** however, demonstrated a much higher affinity for the protein, $K_d = 125 \mu\text{M}$.²⁸ In a fluorescence polarisation (FP) peptide displacement assay, compound **2** was able to displace the labelled peptide PRP-1 with an EC_{50} of $160 \pm 35 \mu\text{M}$, confirming the overlap between the binding sites of **2** and the labelled peptide.²⁸

1.4.4 Model for Mechanism of Binding

A series of structurally related compounds including **3-8** were prepared and analysed for binding, using either the HSQC NMR assay or FP assay in order to gain insight into the binding interaction of 2-aminoquinoline **2** with the SH3 domain (Table 1). 2-Aminopyridine **3** displayed a significantly reduced affinity for the Tec SH3 domain as compared to **2**, indicating the importance of the bicyclic ring system. Ligands **4** and **5** have less aromatic character as compared to **2**, however bind to the SH3 domain with similar affinity to **2**. This indicates that the bicyclic system does not need to be completely aromatic. Removal of the 2-amino functionality as in **6** or the ring nitrogen as in **7** results in complete loss of binding indicating the significance of both the amino functionalities. Replacement of the ring containing the amino functionality with a flexible side chain containing similar amino functionality as in ligand **8** results in a reduction in binding affinity suggesting flexibility is not tolerated. The results of this SAR study therefore indicate that the minimum structure required for binding to the SH3 domain is a rigid, bicyclic ring system that may be fully or partially aromatic but must contain an amino functionality ortho to the quinoline nitrogen.

Table 1: Binding affinities of 2-aminoquinoline analogues.

Compound	Binding Affinity (μM)	Compound	Binding Affinity (μM)
3 	$> 4000^{28}$	4 	$\sim 125 \mu\text{M}^{32 a}$
5 	215^{28}	6 	No binding ²⁸
7 	No binding ²⁸	8 	$> 125 \mu\text{M}^{32 a}$

^a An exact binding affinity has not been determined.

The SAR information provided from assaying these compounds in combination with the chemical shift mapping of the [¹H,¹⁵N] HSQC NMR experiments allowed for binding of the compounds to the SH3 domain to be characterised and a model for the mechanism of binding to be proposed.²⁸ The largest change in ¹H NMR (H-N) chemical shift observed for the protein on binding of the ligand was the indole side chain of tryptophan 215 (W215ε1), a highly conserved residue in the binding site of SH3 domains. Aspartic acid 196 (D196), also highly conserved, displays a change in chemical shift upon ligand binding. This information suggests that the quinoline ring of the ligand is involved in π-π stacking with the indole side-chain of the tryptophan residue, and a salt bridge is formed between the positively charged ligand and the negatively charged aspartate residue under physiological conditions (Figure 12).²⁸

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Figure 12: Proposed binding model of 2-aminoquinoline **2** with the Tec SH3 domain involving key residues W215 and D196.³⁴

Further evidence for the role of D196 in ligand binding was provided by site-directed mutagenesis of the native SH3 protein. A series of mutants (D196A, D196E, D196N and D196T) were prepared as GST-fusion proteins and investigated for binding to the labelled peptide PRP-1 using the FP assay. The mutant proteins bound the peptide with a reduced affinity relative to the native protein, however **2** was unable to displace the labelled peptide from any of the mutants. This indicated that a negatively charged polar group is necessary at the D196 position in order for **2** to bind to the Tec SH3 domain and supported the proposed ligand-binding model. An experimentally determined 3D structure of the **2**/SH3 domain complex would allow for the confirmation of this model, however the binding of **2** is in fast exchange on the NMR timescale and therefore a 3D structure can not be obtained by NMR methods.²⁸

1.5 2-Aminoquinolines with Improved Affinity

1.5.1 Potential Protein Contacts

Additional substitution on the quinoline ring has been investigated in an endeavour to improve the binding affinity of **2** for the Tec SH3 domain. Inspection of the SH3 domain shows the presence of hydrophilic residues (N211, D212 and H214) and the hydrophobic L213 residue near the binding site (Figure 13).³³ To investigate the type of contacts that could be made between the ligand and the protein in this region, a variety of substituents have been placed at all positions around the 2-aminoquinoline core structure.

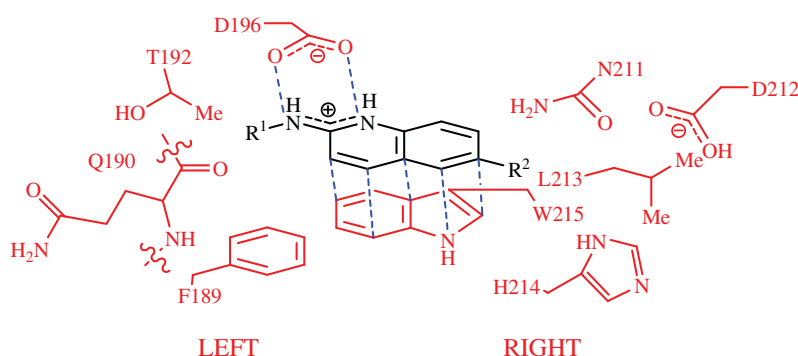
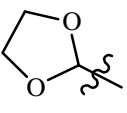
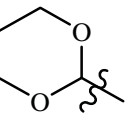


Figure 13: Model for mechanism of binding of **2** to the Tec SH3 domain, and regions predicted to make contacts with substituents attached to the 2-aminoquinoline backbone on the ‘left’ and ‘right’ sides of the binding site.³⁶

1.5.2 5- and 7-Substituted 2-Aminoquinolines

Ligands with substituents at either the 5- or 7-position have been prepared in order to determine if additional contacts on the protein surface could be made by substitution in these positions (see Table 2). The data provided from these assays indicated that ligands with substituents at the 5-position of the 2-aminoquinoline (**9-12**) displayed lower affinities for the SH3 domain than **2** and do not appear to make any additional contacts with the protein surface, regardless of their chemical properties. This is consistent with the computational prediction that a substituent in this position would be directed away from the protein surface. Similarly, substitution at the 7-position in ligands **13-16** did not lead to an improvement in binding affinity, with 7-substituted ligands demonstrating an equal or lower affinity for the Tec SH3 domain relative to **2**.³⁴

Table 2: 5- and 7-Substituted-2-aminoquinolines and their binding affinities.³⁴

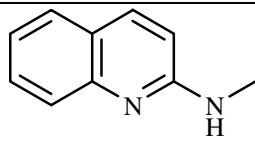
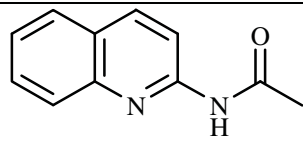
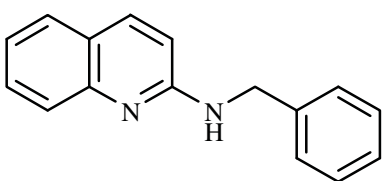
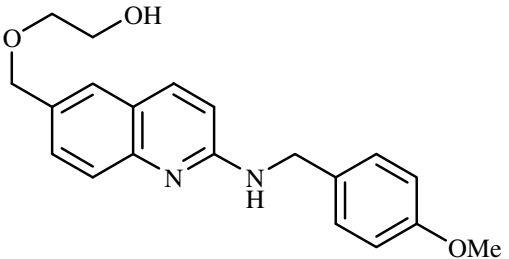
Substituent	5-Position		7-Position	
	Compound	EC ₅₀ (μM)	Compound	K _d (μM)
	9	249 ± 39	13	207 ± 48
	10	269 ± 83	14	439 ± 101
HO(CH ₂) ₂ OCH ₂	11	238 ± 42	15	176 ± 44
HOCH ₂	12	76 ± 11	16	195 ± 34

Note: K_d was determined by NMR assay, EC₅₀ was determined by fluorescence polarisation assay.

1.5.3 N-Substituted-2-Aminoquinolines

A number of N-substituted-2-aminoquinolines have been prepared and assayed for binding affinity to determine the importance of the salt bridge and whether additional contacts on the protein surface could be made by substituents in this position (see Table 3).³³

Table 3: N-Substituted-2-aminoquinolines and their binding affinities.³³

Compound	K _d (μM)	Compound	K _d (μM)
 17	380 ²⁸	 18	Does not bind ²⁸
 19	190 ³³	 20	80 ³⁵

Substitution on the 2-amino nitrogen with a methyl group as in ligand **17** resulted in an approximately 3-fold reduction in binding affinity. The reduction in affinity of **17** for the SH3 domain can be explained by taking into consideration the rotamers that exist around the C-NRH bond. As shown in Figure 14, rotamer 1 has the N-H facing toward D196 and is able

to form a salt bridge. Rotamer 2 however, has the methyl group directed at the protein surface and can not form a salt bridge. The ability of only one rotamer to interact favourably with D196 leads to a reduction in binding affinity as compared to **2**, where both rotamers can be involved in the formation of a salt bridge. The loss of binding in ligand **18** is likely due to the electron withdrawing carbonyl group, which would reduce electron density through resonance and thereby reduce the ability of the ligand to form a salt bridge with D196. The results of these binding studies therefore show the high importance of the salt bridge in the binding of ligands to the SH3 domain.

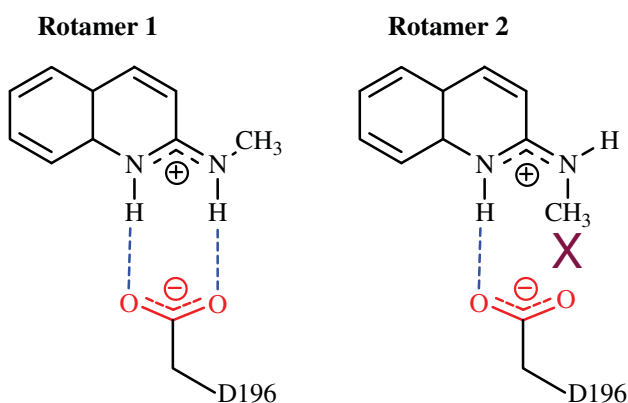


Figure 14: Rotamers of **17** and their interaction with D196.

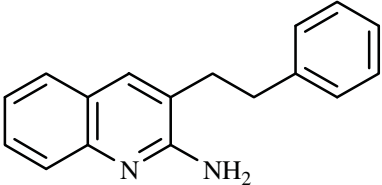
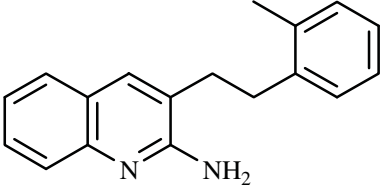
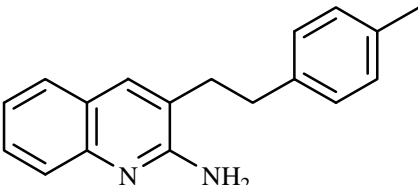
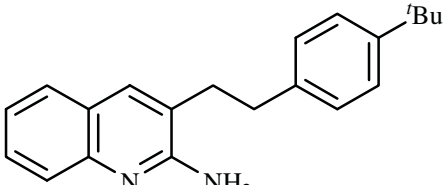
The loss of binding that results from *N*-substitution can be partially counteracted by including a bulky substituent as in **19**. This suggests that the bulky substituent is able to make an additional hydrophobic contact with the protein surface which offsets some of the reduction in binding associated with *N*-methylation of 2-aminoquinoline. The binding affinity is still however reduced as compared to **2**. When the 2-aminoquinoline is substituted at the 6-position as well as *N*-substituted (as in **20**) a further improvement in binding affinity is obtained compared to **2**. This improvement in binding affinity is due to the substituents making two additional contacts with the protein surface causing the ligand to bind more tightly.

1.5.4 3-Substituted 2-Aminoquinolines

Ligands have also been prepared with substituents at the 3-position of 2-aminoquinoline (Table 4).³¹ These ligands were prepared in an endeavour to make similar contacts with the protein surface as the *N*-substituted ligands. Results of the SAR study showed that a phenylethyl substituent in the 3-position, as in **21**, can be tolerated and binds to the SH3

domain with similar affinity to **2**. A substituent in the *para* position of the phenyl ring such as a methyl group, leads to an improvement in binding affinity. A further improvement in binding is achieved with a bulky *tert*-butyl group in this position.

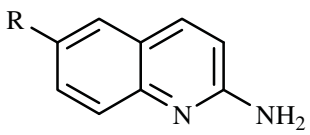
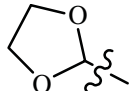
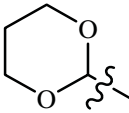
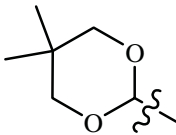
Table 4: Binding data of 3-substituted-2-aminoquinolines.³¹

Compound	K_d (μM)	Compound	K_d (μM)
 <p>21</p>	128	 <p>22</p>	130
 <p>23</p>	74	 <p>24</p>	40

1.5.5 6-Substituted 2-Aminoquinolines

From the established binding model, 2-aminoquinolines with substituents in the 6-position were predicted to make contacts with the charged amino acid side chains adjacent to the W215 residue (see Figure 13). 2-Aminoquinolines were prepared with a range of 6-substituents including simple (methyl and halogen), bulky lipophilic (cyclic acetals) and hydrophilic substituents and were assayed for binding affinity for the Tec SH3 domain. A number of these, along with their binding affinities, are shown in Table 5.²⁸

Table 5: Binding affinities of a number of 6-substituted-2-aminoquinolines.^{34,37}

 R	FP Assay EC₅₀ (μM)	NMR Assay K_d (μM)
25 Me	75 ± 15	61 ± 6
26 	34 ± 5	40 ± 8
27 	26 ± 6	52 ± 16
28 	-	22 ± 5
29 HO(CH ₂) ₂ OCH ₂	40 ± 8	38 ± 9

The SAR information from these experiments suggests that a new lipophilic contact is made between the substituent of the quinoline ring and the SH3 protein surface. When a simple lipophilic group occupies the 6-position (as in **25**), a contact is made which results in an improvement in binding affinity. A larger and more complex substituent at the 6-position (such as the cyclic acetals **26-28** and the open chain alcohol **29**) leads to further improvement in binding affinity by making a greater contact with the protein surface.^{28,34}

Although the acetal substituted ligands have provided some of the highest affinity ligands to date, the acetal substituents are not stable in aqueous conditions and are therefore not suitable as potential therapeutics. Recently, simple phoxymethyl substituents at the 6-position of the 2-aminoquinoline have been investigated as an alternate functionality to occupy a similar area of the protein surface as the acetal-substituted ligands with increased aqueous stability (Table 6). These studies have found that these types of ligands display similar or improved affinity for the Tec SH3 domain as compared to the acetal-substituted ligands.

NOTE:

This table is included on page 18 of the print copy of the thesis held in the University of Adelaide Library.

1.6 Aims for the PhD Project

1.6.1 General Aims

The overall aim of this research project was to prepare a variety of ligands based on the core structure of 2-aminoquinoline with improved affinity for the SH3 domain. In addition, it was hoped that a ligand could be prepared that bound with high enough affinity to the SH3 domain that a 3D structure could be determined of the ligand-protein complex using NMR methods (this would however, require the ligand to be in slow exchange on the NMR timescale) or X-ray crystallography. A 3D structure of the protein-ligand complex would allow for the confirmation of the proposed binding model and would facilitate the design of new 2-aminoquinolines.

Of the 2-aminoquinolines prepared to date, the highest affinity ligands are 6-substituted compounds with bulky lipophilic functionality. Due to the ability of a substituent at the 6-position to make an additional favourable contact with the protein surface further investigation of this position with alternate types of substituents is warranted and was the focus of this research.

1.6.2 Synthetic Targets

6-N-Heterocyclic-2-Aminoquinolines

Previous studies of 6-substituted compounds have involved ligands substituted with an acetal group at the 6-position of 2-aminoquinoline. This functionality is however, unstable under physiological conditions. Replacement of the biologically unstable acetal with an alternate *N*-heterocyclic substituent as in **30**, may provide similar or increased affinity to the 6-substituted acetal ligands with an increase in stability of the compound (see Figure 15). Additionally, such ligands would provide information as to whether the heteroatom and its position are important for increased binding affinity.

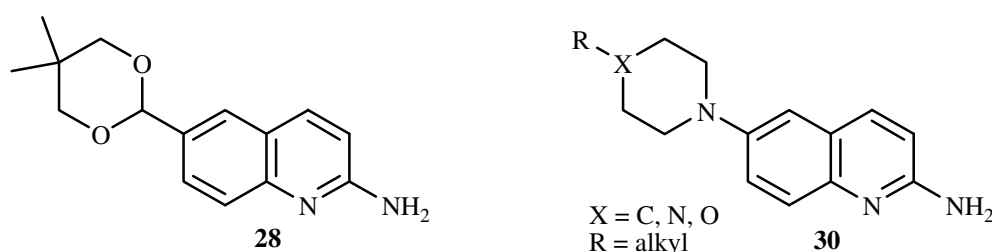


Figure 15: Previously prepared 6-acetal substituted ligand **28** and 6-heterocyclic-2-aminoquinoline target ligands **30**.

6-Phenoxymethyl-2-Aminoquinolines

A number of 6-phenoxymethyl-2-aminoquinolines have been prepared with simple alkyl and halogen substitution on the phenoxy ring. Further studies involving different types of substituents including large, lipophilic substituents and multiple substitution on the phenoxy ring is required to complete the SAR study of this type of ligand (see Figure 16).

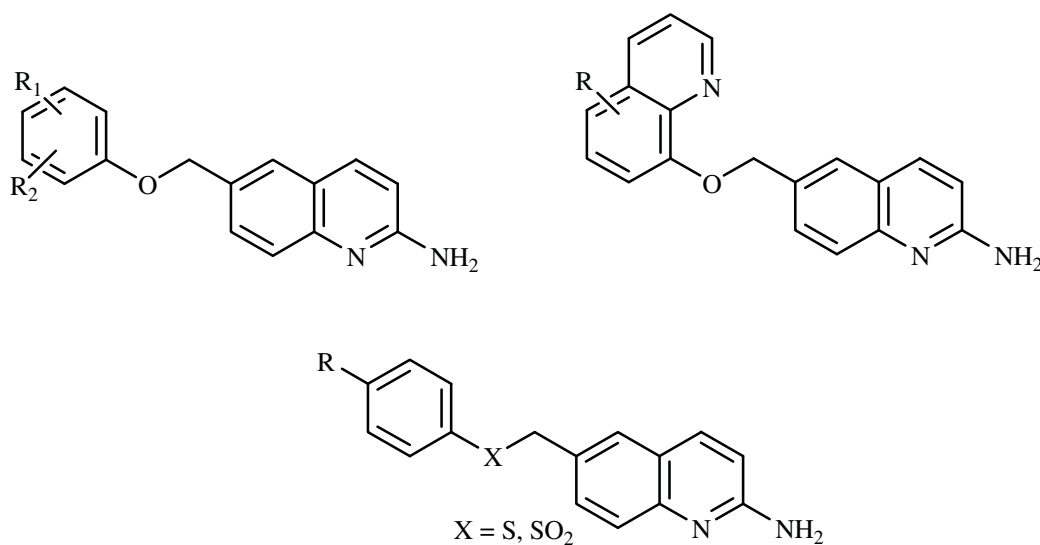


Figure 16: 6-Aryloxymethyl- and 6-arylthiomethyl-2-aminoquinoline target ligands.

The preparation of these ligands would provide information on which functional groups are tolerated and whether larger substituents can make additional protein contacts and provide higher affinity ligands. In addition, replacement of the oxygen atom in the linker with a sulphur functionality would also provide information as to the importance of the heteroatom in binding.

6-(N-Heterocyclic-Phenoxymethyl)-2-Aminoquinolines

Further extension on the 6-phenoxymethyl substituent with heterocyclic functionality would combine both concepts of the first two classes of ligands in an extended ligand (see Figure 17). These ligands have a much larger substituent and may provide further contacts with the protein surface and provide for high affinity ligands. The potential for these compounds to make a greater contact with the protein surface may also provide a slow exchange ligand and allow for a 3D structure to be determined by NMR methods. The preparation of these ligands was therefore desired.

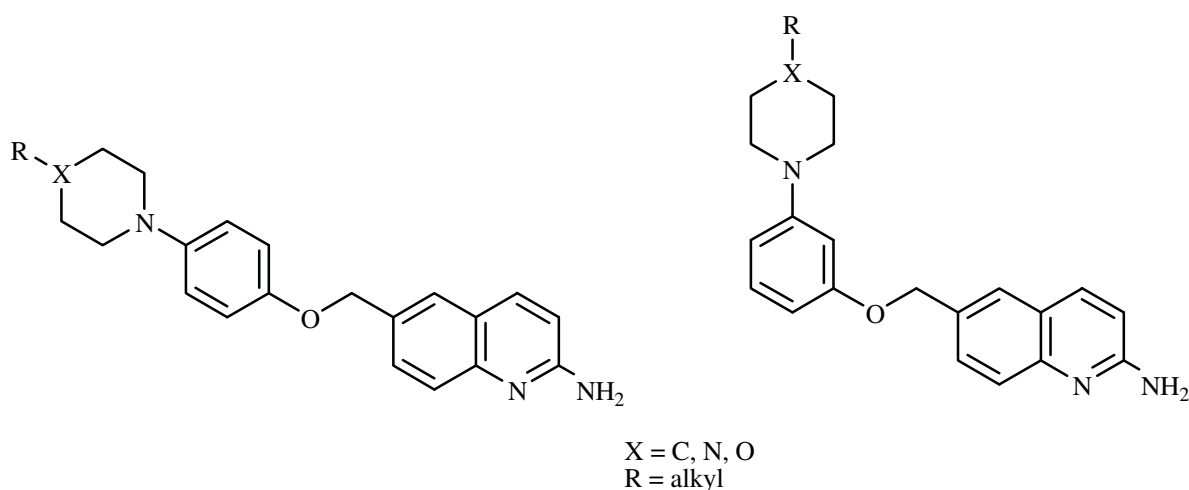


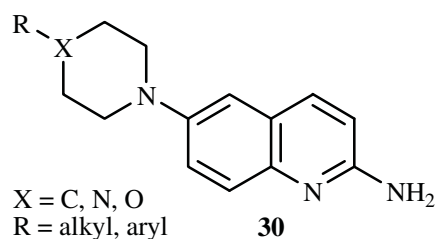
Figure 17: Extended 6-substituted-2-aminoquinoline target ligands.

Chapter 2:

SYNTHESIS AND BINDING STUDIES OF 6-HETEROCYCLIC-2-AMINOQUINOLINES

2.1 Introduction

2-Aminoquinolines have previously been prepared that contain acetal functionality at the 6-position of the quinoline ring system (**26-28**, refer to Section 1.5.5). These ligands display moderate affinity for the Tec SH3 domain and have equilibrium dissociation binding constants (K_d) in the range of 20-50 μM .³⁴ The acetal functionality of these ligands however, is not suitable for use in therapeutic agents as the acetals hydrolyse to carbonyl compounds under physiological aqueous conditions.²⁸ It was envisaged that replacement of the biologically labile acetal with an alternate saturated heterocyclic substituent, as shown in **30**, would provide ligands with increased stability and may also provide ligands with similar or increased affinity for the SH3 domain relative to ligands **26-28**. Additionally, such ligands would provide information as to whether the nature of the heteroatom and its location in the heterocycle at the 6-position are important for increased binding affinity.

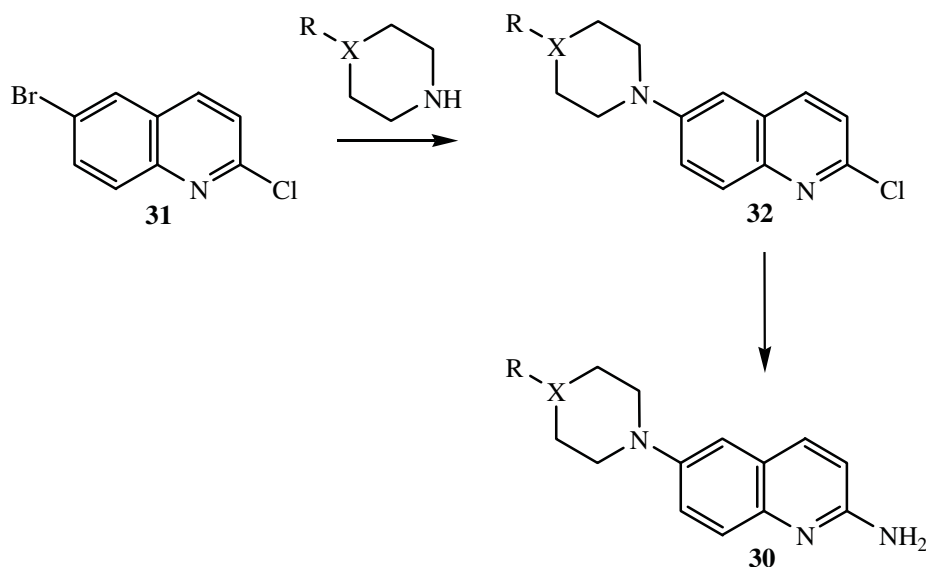


A range of 6-substituted ligands of this type have been prepared and their binding affinities determined using the HSQC NMR assay. Buchwald-Hartwig chemistry was required to prepare these compounds, which involved a significant investigation into the optimisation of the reaction conditions. The details of this are also presented and discussed in this chapter.

2.2 Buchwald-Hartwig Aminations

Initially 6-bromo-2-chloroquinoline **31** was envisaged as the key intermediate for the synthesis of 6-heterocyclic-2-aminoquinolines because it contains two halide functionalities. The halide functionality at the 6-position would allow for the initial introduction of a heterocyclic substituent and the halide at the 2-position would allow for the subsequent introduction of the 2-amino group (see Scheme 1). This synthetic route would, however,

require selectivity for the 6-position over the 2-position (and hence selectivity for the bromine in the presence of the activated chlorine) in the initial introduction of the heterocycle.



Scheme 1: Proposed synthesis of 6-heterocyclic-2-aminoquinolines from **31**.

Traditional methods for the formation of a C-N bond in the synthesis of arylamines, such as nucleophilic aromatic substitution and Ullmann-type couplings, are typically conducted using relatively harsh reaction conditions and have limited generality.^{36,37} However, palladium-catalysed methods (Buchwald-Hartwig aminations) have recently emerged as a powerful and useful method for the preparation of arylamines.

Palladium has found wide use in organic synthesis because it can be employed to effect a number of different reactions including C-C, C-O and C-N bond formation. Most palladium-catalysed reactions can be conducted under relatively mild conditions and are stereo- and regioselective and do not require activating groups.³⁸⁻⁴⁰ The first accounts of the direct C-N bond formation catalysed by palladium were reported independently by Buchwald⁴¹ and Hartwig.⁴² Since the initial investigations a vast number of reports have followed and Buchwald-Hartwig chemistry has become a rapidly developing field of interest due to the importance of amino-substituted aryl derivatives.

Buchwald-Hartwig aminations involve the reaction of an aryl halide with an amine in the presence of a palladium catalyst. The general mechanism for the reaction is shown in Figure 18.⁴⁰ Initially, oxidative addition of the aryl halide to a palladium(0) catalyst occurs to give the palladium(II) intermediate A. The coordination of the nitrogen atom to this intermediate

and substitution of the halide gives the intermediate B. Reductive elimination affords the aryl amine and regenerates the palladium catalyst.

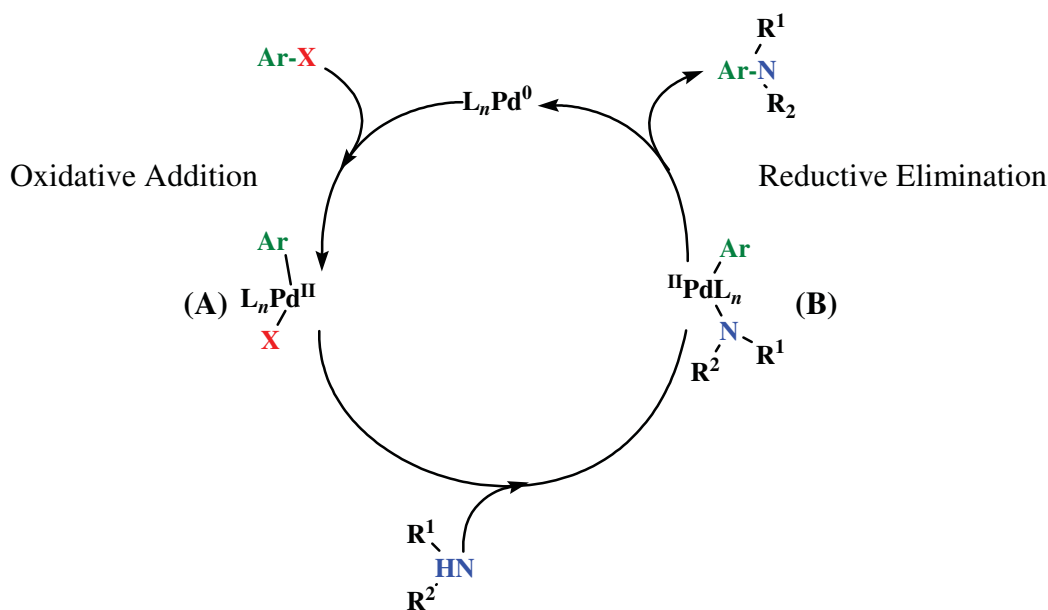


Figure 18: Mechanism for the Buchwald-Hartwig amination.

The palladium catalyst is comprised of a palladium precursor, typically $Pd(OAc)_2$ or $Pd_2(dba)_3$, and a ligand which is required to stabilise the palladium catalyst in solution. In addition, the ligand acts to increase the electron density at the metal centre to facilitate oxidative addition and also provides bulkiness to promote C-N formation by accelerating the reductive elimination process. A base is also needed to deprotonate the amine before or after coordination to the palladium centre and an appropriate solvent is required to solubilise the components of the reaction and provide a sufficient temperature window for the reaction. The components of the catalytic system are critical and can greatly effect the outcome of any given Buchwald-Hartwig reaction.⁴³

In the beginning, Buchwald-Hartwig aminations were typically couplings between an aryl bromide substrate and an amine. The amination of aryl bromides has significantly advanced with extensive studies into the reaction conditions for these reactions and has allowed for the coupling of aryl bromides with almost any amine nucleophile including amides,⁴⁴ ureas⁴⁵ and sulfoximines.⁴⁶

Initially, simple phosphine based ligands (such as $P(o-Tol)_3$ ^{47,48} and $P(t-Bu)_3$ ^{49,50}) and bisphosphine ligands (BINAP)⁵¹ were employed to carry out Buchwald-Hartwig aminations

of aryl bromides. However, in recent years, the development of higher reactivity ligands for use in the catalytic system has received a great deal of attention. The development of large, bulky phosphine ligands has greatly enhanced the scope of aminations and allowed for coupling of a large range of substrates under mild conditions.⁴³

Ligands which have facilitated these developments include the bulky, biphenyl based ligands reported by Buchwald.⁵²⁻⁵⁴ These ligands have allowed for the room temperature catalytic amination of many aryl chloride and aryl bromide substrates. In addition, aryl triflates and aryl tosylates can be employed as the substrate in the presence of these ligands (see Figure 19).^{52,54} The effectiveness of these ligands is believed to be due to a combination of steric and electronic properties. Specifically, the electron rich nature of the phosphine is thought to promote oxidative addition whilst the steric bulk is thought to facilitate reductive elimination.

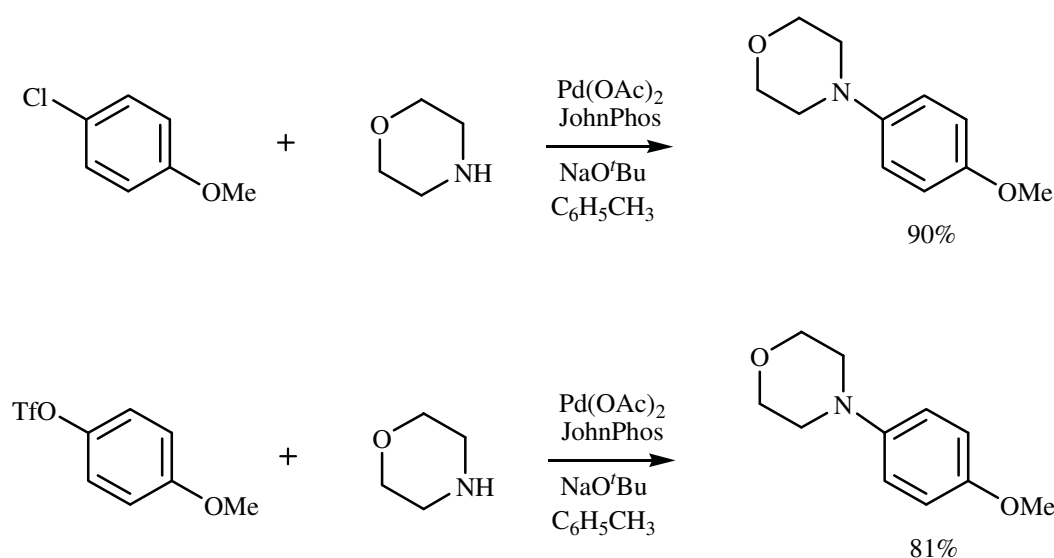


Figure 19: Room temperature amination of aryl chlorides and aryl triflates.⁵⁴ See Section 2.3.4.3 for structure of JohnPhos ligand.

Adamantyl substituted alkyl-phosphines have been reported by Beller.^{55,56} These ligands have also been useful for the amination reactions of aryl chlorides. In addition, they have been particularly useful in the coupling of very sterically hindered substrates (see Figure 20).⁵⁶ *N*-Heterocyclic carbenes have also been investigated for use in these types of reactions and proved successful in a number of cases.^{57,58} Their use in palladium catalysed amination reactions however, is not as widespread as the phosphine based ligands.

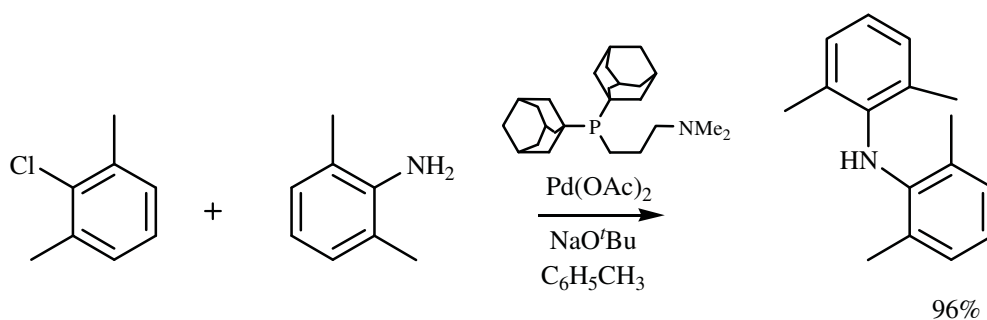


Figure 20: Preparation of sterically hindered aryl amines using adamantyl substituted alkyl-phosphine ligands.⁵⁶

The development of Buchwald-Hartwig aminations has also involved the exploration into the effects of base and solvent, however to a lesser extent. The relative base strength determines the functional group tolerance with the most commonly used bases (NaO^tBu and KO^tBu) displaying low functional group tolerance. The use of alternate bases including Cs₂CO₃,⁵⁹ K₃PO₄,⁵³ or KOH and NaOH^{52,60} have allowed for the transformations of a wider range of substrates. Lithium bis(trimethylsilyl)amide (LHMDS) has greatly increased the substrate scope of Buchwald-Hartwig aminations and has been especially useful in aminations involving aryl halides possessing polar substituents including hydroxyl, amide and enolizable keto groups.^{61,62} The effectiveness of LHMDS as a base for reactions involving these substrates is thought to be due to the ability of LHMDS to protect the sensitive functional groups. Typically, when LHMDS is employed 2-3 equivalents are used. It is suggested that the first equivalent of LHMDS deprotonates the base sensitive functionality of the substrate with the resultant formation *in situ* of a bound lithium which acts to protect the functional group and prevent coordination to the palladium catalyst. Alternatively, migration of a trimethylsilyl group from the base could also act to protect the deprotonated functionality.⁶² The remaining equivalents of LHMDS are therefore able to act as a base and deprotonate the amine in the desired Buchwald-Hartwig reaction.

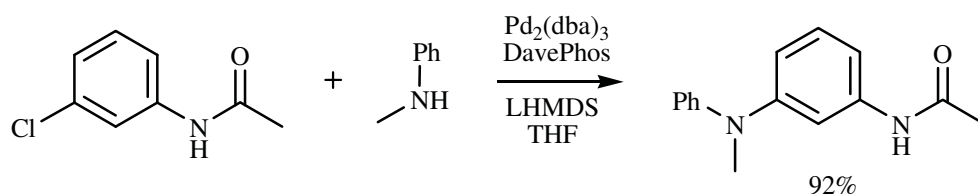


Figure 21: Example of the use of LHMDS as a base for the amination of substrates containing base sensitive functionalities.⁶¹ See Section 2.3.4.3 for structure of DavePhos ligand.

The solvent employed in these types of reactions has a number of roles. The solvent must be able to dissolve the reactants and the components of the catalytic system and also needs to provide an appropriate temperature window for the reaction. In addition, the solvent plays a crucial role in stabilising the intermediates of the catalytic cycle.⁴³ Most Buchwald-Hartwig aminations are carried out in toluene, however alternate solvents including DME, THF, dioxane and DMF have been effective in some instances, particularly where solubility in toluene is an issue. The addition of *tert*-butyl alcohol^{63,64} can lead to improvements in conversions and the addition of water can also be beneficial in reactions with aqueous bases.⁵² These additives however, have limited generality.

2.3 Synthesis of 6-Heterocyclic-2-Aminoquinolines

2.3.1 Synthetic Scheme for the Preparation of 6-Heterocyclic-2-Aminoquinolines

To prepare the desired 6-substituted-2-aminoquinolines, the retrosynthetic scheme depicted below was initially envisaged (Figure 22). In this pathway, the desired 6-heterocyclic-2-aminoquinoline ligands **30** could be prepared from the corresponding 6-heterocyclic-2-chloroquinoline **32** utilising the method of Kóródi.⁶⁵ These 6-heterocyclic-2-chloroquinolines could be synthesised from the key intermediate 6-bromo-2-chloroquinoline **31** and an appropriate amine using Buchwald-Hartwig chemistry. The intermediate **31** could in turn be easily prepared from commercially available 4-bromoaniline and cinnamoyl chloride.

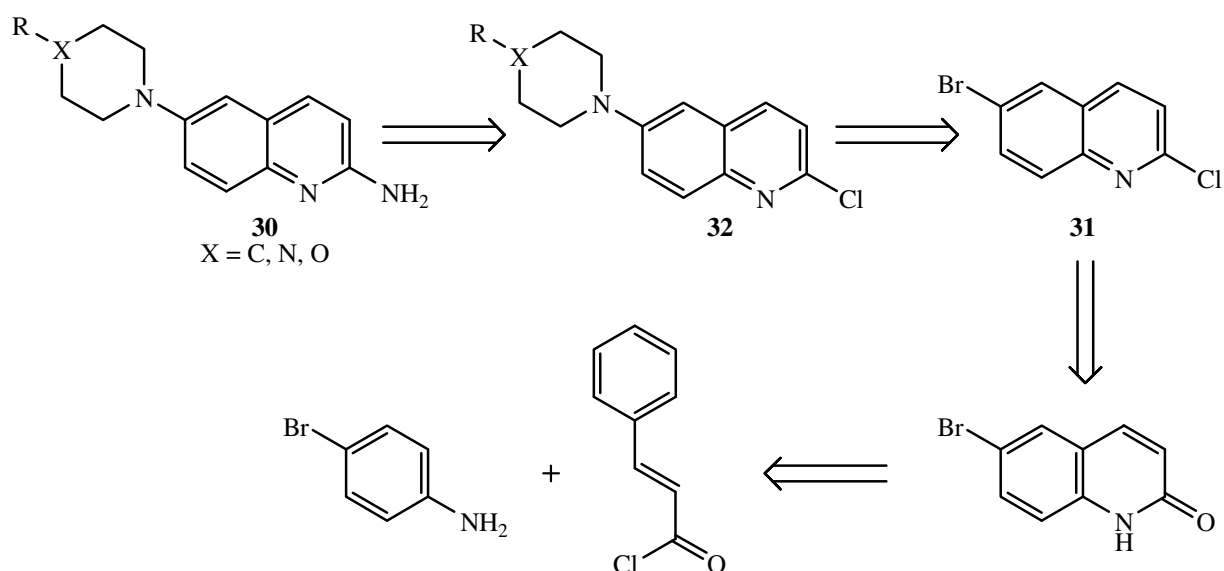
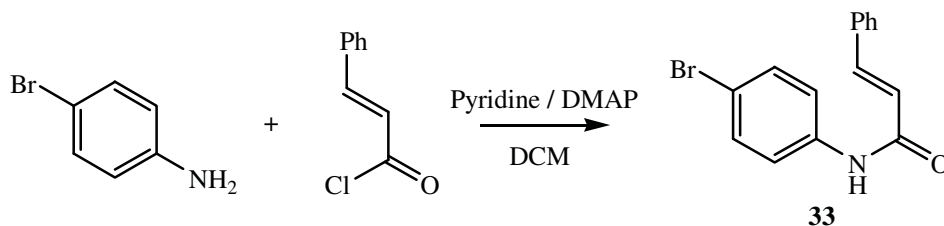


Figure 22: The retro-synthetic pathway for the synthesis of 6-heterocyclic-2-aminoquinolines.

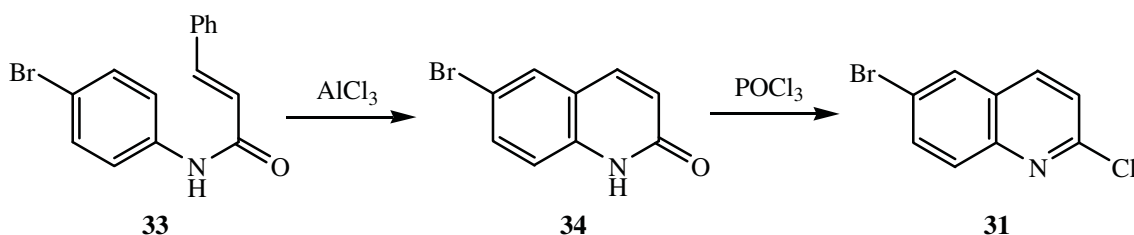
2.3.2 Preparation of 6-Bromo-2-Chloroquinoline

The first step in the synthesis of **31** was the formation of cinnamanilide **33**, through a nucleophilic acyl substitution reaction using a literature procedure (Scheme 2).²⁸ Cinnamanilide **33** was prepared in good yield (78%) and displayed characteristic peaks in the ¹H NMR spectrum including two doublets with a *trans* coupling constant ($J = 15.6$ Hz) for the hydrogens of the alkene.



Scheme 2: Synthesis of **33**.

The cinnamanilide **33** was subsequently converted to 6-bromoquinolin-2(1*H*)-one **34** by treatment with aluminium chloride as a melt in a Friedel-Crafts acylation (Scheme 3).⁶⁶ A peak at 1700 cm^{-1} in the IR spectrum was observed confirming the presence of the carbonyl. The ¹H NMR spectrum displayed a characteristic change in the coupling constant, from $J = 15.6$ Hz for the *trans* **33** to $J = 9.3$ Hz for **34**, indicating ring closure and formation of the desired product. The quinolone **34** obtained from the reaction was used without further purification and was treated with phosphorus oxychloride to afford **31**. Compound **31** was obtained in moderate yield over two steps (58%) and displayed a melting point ($157\text{-}158\text{ }^{\circ}\text{C}$) consistent with the literature value ($157\text{ }^{\circ}\text{C}$).⁶⁷ The ¹H NMR spectrum showed a large downfield shift in the signal for H3 (c.f. **34** $\delta_{\text{H}} = 6.73$ ppm; **31** $\delta_{\text{H}} = 7.44$ ppm), which is consistent with the conversion of the quinolone to the quinoline. The disappearance of the carbonyl stretch in the IR spectrum of **31** is also diagnostic and indicates the formation of the desired product.



Scheme 3: Synthesis of **31**.

Having prepared **31**, the next step in the synthesis of 6-heterocyclic-2-aminoquinolines involved the introduction of the substituent at the 6-position by the formation of a C-N bond to afford 6-heterocyclic-2-chloroquinolines (Scheme 1).

2.3.3 Buchwald-Hartwig Amination for the Preparation of 6-Heterocyclic-2-Chloroquinolines

Initial studies on the Buchwald-Hartwig reaction of **31** utilised the diadamantyl phosphine ligand, CataCXium[®] A **35** (Figure 23).⁵⁵ This class of sterically demanding phosphine ligand has been recently reported to be suitable for a range of palladium-catalysed reactions including Sonogashira⁶⁸ and Suzuki couplings.^{69,70} Buchwald-Hartwig aminations have also been reported using this class of ligands.^{71,72} Recently, Tewari *et al*⁷¹ employed CataCXium[®] A ligand **35** and CataCXium[®] A ligand **36** (Figure 23) for the amination of activated and unactivated aryl chlorides with a range of amines. The aryl amines were prepared in high yield (73-99%) in the presence of low amounts of catalyst (see Figure 24 for example). The authors also reported the high stability of the ligands towards air and moisture.

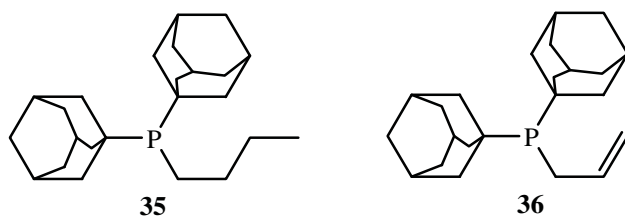


Figure 23: CataCXium[®] A ligand **35** and CataCXium[®] A ligand **36**.

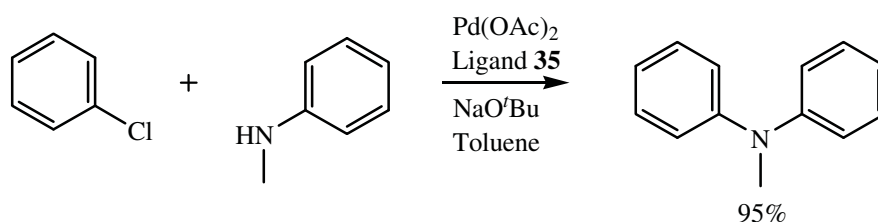
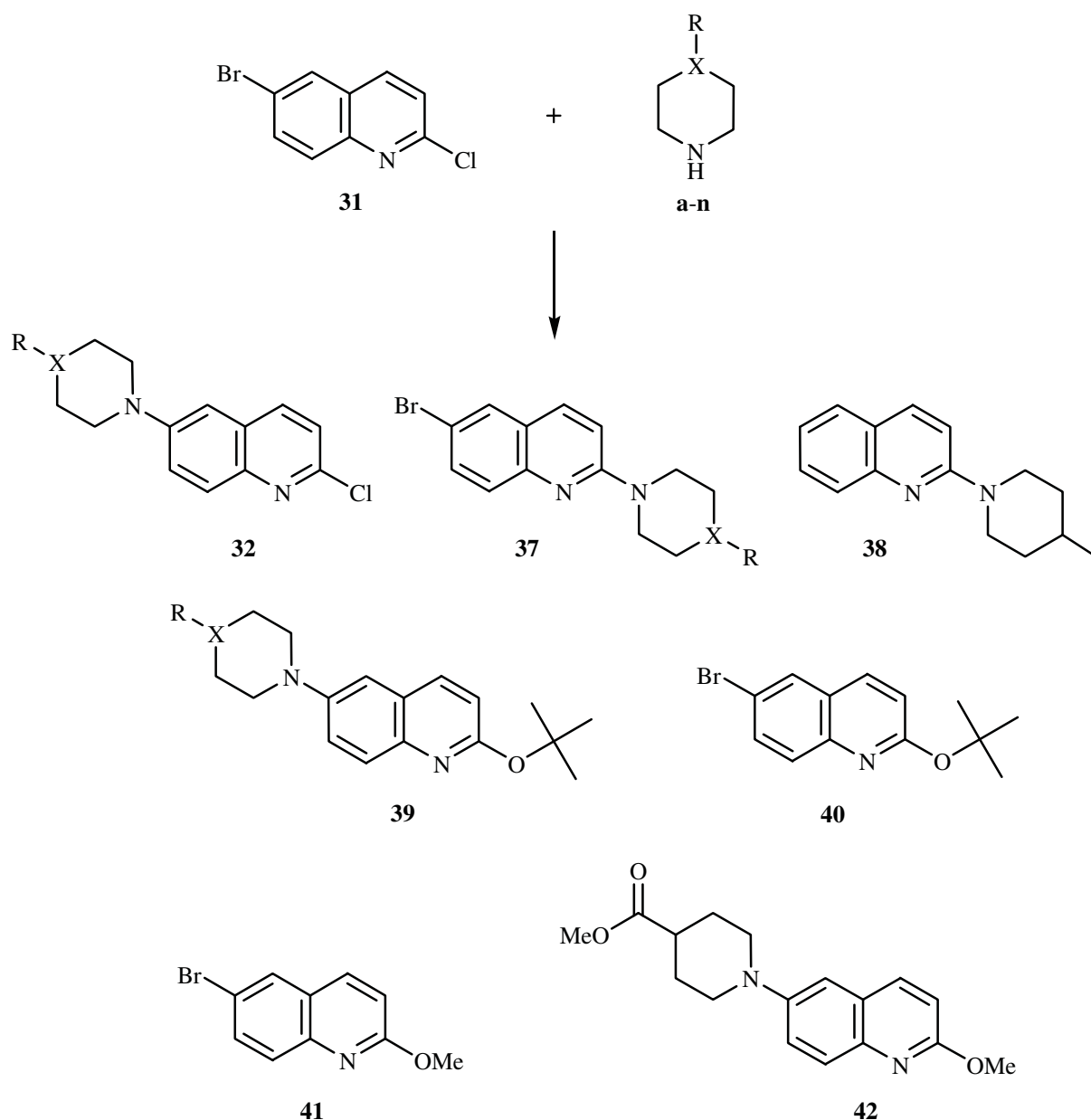


Figure 24: Amination of aryl chlorides using ligand **35**.⁷¹

The reaction of **31** and a variety of cyclic amines **a-n** was carried out using the conditions reported by Tewari *et al*⁷¹ involving Pd(OAc)₂ and KO^tBu in toluene at 120 °C under pressure overnight. Using this method a range of 6-heterocyclic-2-chloroquinolines **32a-n** were prepared in significantly varied yields (1-94%) (see Scheme 4 and Table 7). In addition to the

desired products however, substitution at the 2-position was also observed to produce compounds **37**. Although the potential for palladium-catalysed coupling at two sites on **31** (i.e. 6-Br and 2-Cl) was noted in the development of this synthetic route, it was anticipated that selectivity for the 6-position could be achieved in the presence of the chlorine at the 2-position due to the increased reactivity of the bromine relative to the chlorine. In this particular reaction, coupling at the 6-position was evidently not as selective as initially anticipated.



Scheme 4: Synthesis of 6-heterocyclic substituted-2-chloroquinolines. Reaction conditions: Pd(OAc)₂/**35**, KO^tBu, in toluene at 120 °C under pressure.

Table 7: Buchwald-Hartwig amination of **31** and a range of cyclic amines showing distribution of products.^a

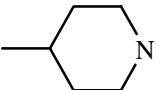

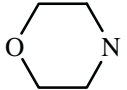
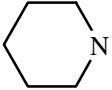
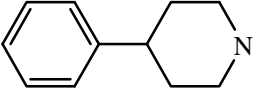
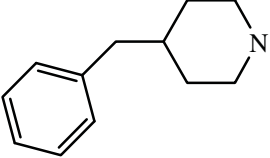
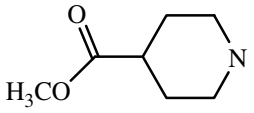
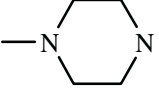
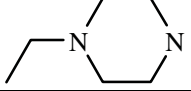
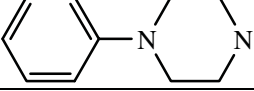
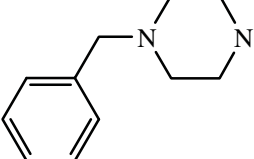
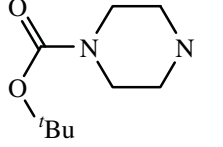
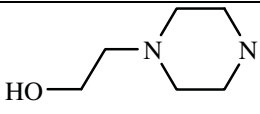
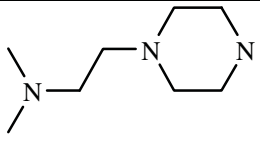
	Amine	32^b (%)	32^c (%)	37 (%)	39 (%)	Other (%)
a		57	44 ^d	25	9 ^d	38 ; 15
b		63	52	<i>e</i>	<i>f</i>	<i>g</i>
c		98	94			
d		65	54			
e		62	44	<i>e</i>	<i>c</i>	<i>g</i>
f		50	40 ^d	<i>e</i>	7 ^d	<i>g</i>
g		4	1 ^d			41 ; 40 42^d ; 2
h		34	32 ^d	<i>e</i>	<i>f</i>	31^d ; 5 <i>g</i>
i		63	58 ^d	30 ^d	10	<i>g</i>
j		57	44	15	<i>f</i>	
k		39	26 ^d	11 ^d	6	<i>g</i>
l		85	80		7	<i>g</i>

Table 7 continued.^a

m		2		37		
n		50	30		<i>f</i>	<i>g</i>

^a Reaction conditions: **31** (1 eq), amine (1.2 eq), KO^tBu (1.2 eq), Pd(OAc)₂ (0.5 mol %) and **35** (1 mol %) in toluene at 120 °C under pressure. ^b Yields determined by ¹H NMR analysis of the crude material. ^c Isolated yield after chromatography. ^d Indicates isolated as a mixture which could not be separated, yields refer to individual components. ^e Observed by ¹H NMR analysis but not isolated. ^f **39** was also observed by ¹H NMR analysis but was not isolated. ^g **40** was also observed by ¹H NMR analysis but was not isolated.

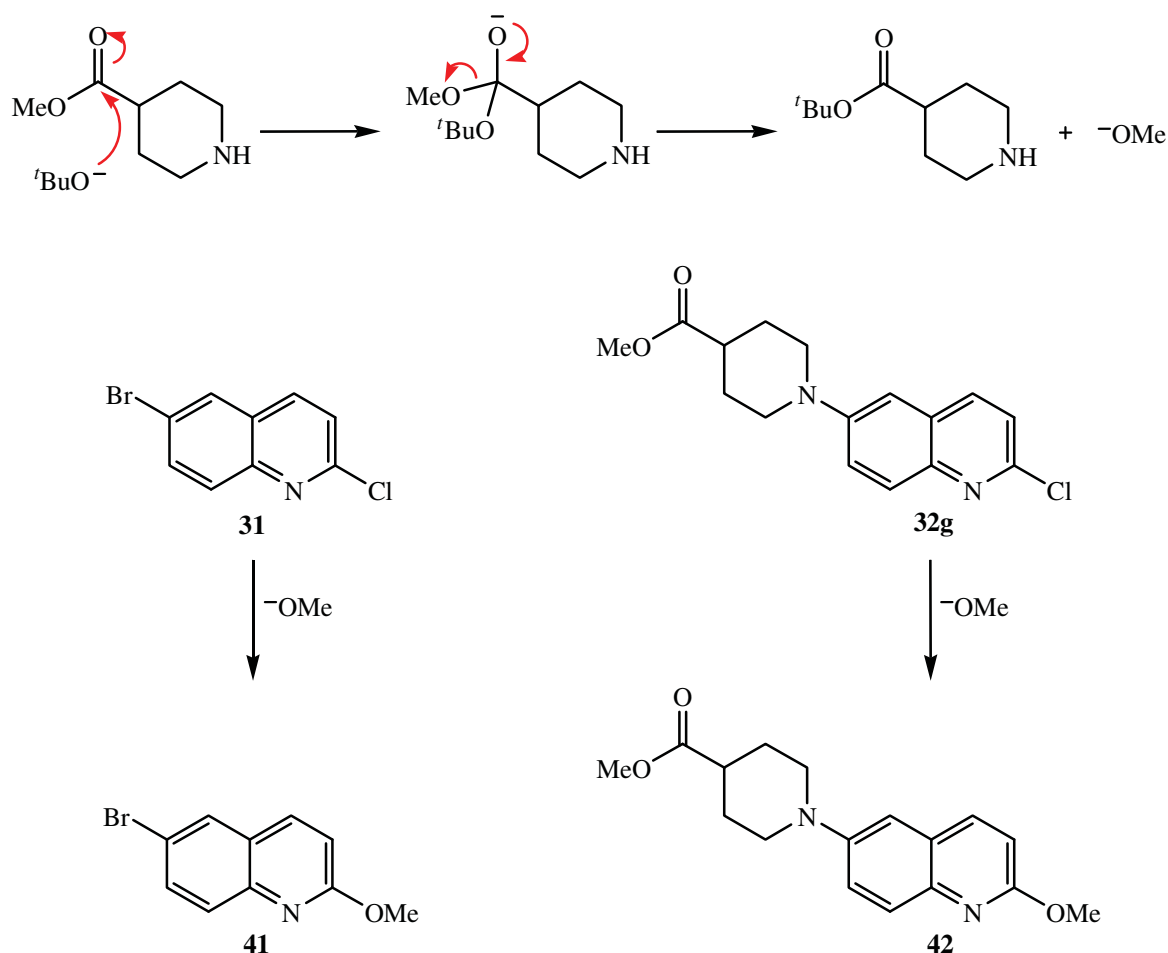
In the reactions with heterocycles **c** and **l**, the expected reactivity was observed with **32** predominating in good yields and none of **37** was observed (see Table 7). However, in the reactions with heterocycles **b**, **d-f**, **h-k** and **m**, low to moderate yields of **32** were obtained. In these reactions notable amounts of **37** were observed and in many cases **37** was isolated in significant yield. In the case of heterocycle **g** only trace amounts of the desired product **32g** was observed and for heterocycle **m**, product **37m** was the only isolated product.

In the development of the synthetic scheme for the preparation of 6-heterocyclic-2-aminoquinolines the possible amination reaction at the 2-position was recognised. It was however, thought that the amination reaction at the 6-position would predominate given the increased reactivity of bromine relative to the chlorine. The competing amination at chlorine in the presence of the more reactive bromine in these reactions is due to the activation of the chlorine substituent from the adjacent quinoline nitrogen. This activation makes the 2-position more susceptible to nucleophilic attack and hence the resultant formation of compounds **37**. The activation of the 2-position also results in the formation of compounds **39** and **40**, which are seen in varying amounts and result from the displacement of the chloride by the base (see Scheme 4).

In the reaction with **a** product **38** was also observed (Scheme 4). This product is the result of substitution at the 2-position and reduction of the 6-bromine functionality. The low resolution mass spectrum for this product showed a peak at *m/z* 226 which is consistent with the calculated mass and the ¹H NMR spectrum showed an upfield shift in the signal for H3 (c.f. **31** $\delta_{\text{H}} = 7.44$ ppm to $\delta_{\text{H}} = 7.00$ ppm) from the introduction of the electron donating

heterocycle. The reduction of the bromine functionality and incorporation of a heterocycle at the 2-position is only observed when amine **a** is employed and not with any of the other amines.

In the reaction with amine **g** side products **41** and **42** were also observed. These products both contain a 2-methoxy substituent and result from methoxy displacement of the chlorine substituent of **31** and **32g**. A possible pathway for the formation of these compounds would involve nucleophilic attack of the *tert*-butoxy anion on the ester functionality of the amine with displacement of the methoxy group in a transesterification reaction. The methoxy anion could then attack the 2-position of either **31** or **32g** and displace the chlorine functionality resulting in the products **41** and **42** (Scheme 5).



Scheme 5: Proposed mechanism for the formation of compounds **41** and **42**.

A high resolution mass spectrum was obtained for **42** and was consistent with the calculated mass for this product. The ^1H NMR spectra of these compounds contained a characteristic singlet peak at 4.03 ppm corresponding to the methoxy group at the 2-position along with the required peaks for the quinoline in both **41** and **42** and the heterocycle for **42**. For **42** an upfield shift in the signals for the H5 and H7 hydrogens was also observed. 2D NMR spectroscopy including ROESY, COSY, HMQC and HMBC was utilised to confirm the identity of these products. Verification of the methoxy functionality at the 2-position was provided by the presence of an HMBC correlation between the hydrogens of the methoxy group and the carbon at the 2-position of the quinoline in both of these compounds (see Figure 25).

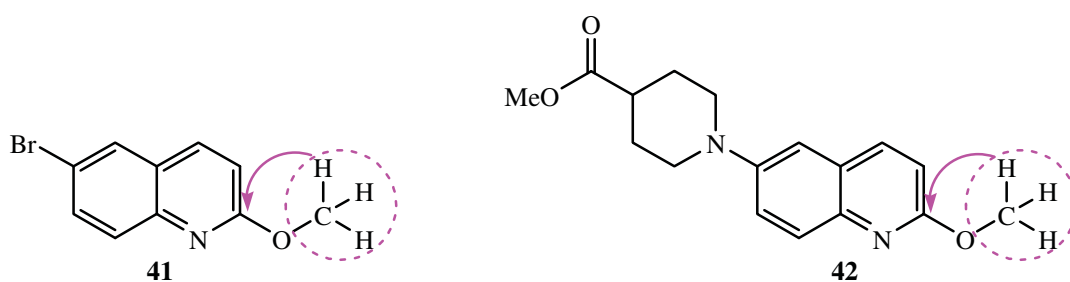


Figure 25: HMBC correlations between the hydrogens of the methoxy group and the C2 carbon in both compounds **41** and **42**.

The formation of side products in these reactions caused a reduction in the yield of the desired product and additionally complicated the purification process. In a number of cases, the desired products were unable to be separated from the unwanted side products even after numerous attempts of recrystallisation, flash chromatography and/or preparative TLC.

The characterisation of compounds **32b-f, j** and **l** that were isolated pure was relatively simple. Similarly, the characterisation of **32h**, which was isolated with **31**, and **32n**, which was isolated with only minor impurities, was also relatively simple. A high resolution mass spectrum and/or elemental analysis that was consistent with the desired product in each case were obtained. Each of the low resolution mass spectra showed the isotopic distributions for chlorine confirming the presence of the 2-chloro substituent. In the case of **32l**, the IR spectrum displayed a characteristic carbonyl peak at 1694 cm^{-1} . The ^1H NMR spectra of these compounds also showed absorptions characteristic of the newly formed 6-heterocyclic-2-chloroquinoline. Specifically signals corresponding to the heterocyclic substituent were observed together with a characteristic upfield change in chemical shift for the signal for H5 (c.f. **31** $\delta_{\text{H}} = 7.99\text{ ppm}$ to $\delta_{\text{H}} = 6.60\text{-}7.06\text{ ppm}$) and H7 (c.f. **31** $\delta_{\text{H}} = 7.81\text{ ppm}$ to $\delta_{\text{H}} = 7.17\text{-}$

7.55 ppm), indicating the presence of the electron-donating heterocycle (see Table 8 for chemical shift comparisons with by products). 2D NMR spectroscopy, including ROESY, COSY, HMQC and HMBC were also used to confirm the identity of compounds **32**. ROESY data was particularly useful in confirming the substitution of the heterocycle at the 6-position of the quinoline as correlations were observed between the H5 and H7 hydrogens of the quinoline and the H2' and H6' hydrogens of the heterocycle (see Figure 26).

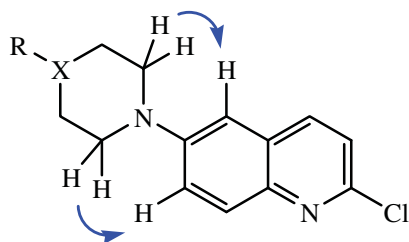


Figure 26: ROESY correlations between H5 and H7 hydrogens and the H2' and H6' hydrogens of the heterocyclic substituent in compounds **32**.

Characterisation of compounds isolated as a mixture was slightly more complicated. Quinoline **32a** was isolated as a mixture with the corresponding 6-heterocyclic-2-*t*-butoxyquinoline **39a**. A high resolution mass spectrum was obtained and was consistent with the desired product **32a**. The low resolution mass spectra once again showed the isotopic distributions for chlorine in compound **32a** and a peak corresponding to 242 mass units, which results from the loss of C₄H₈ from **39a** (see Figure 27).

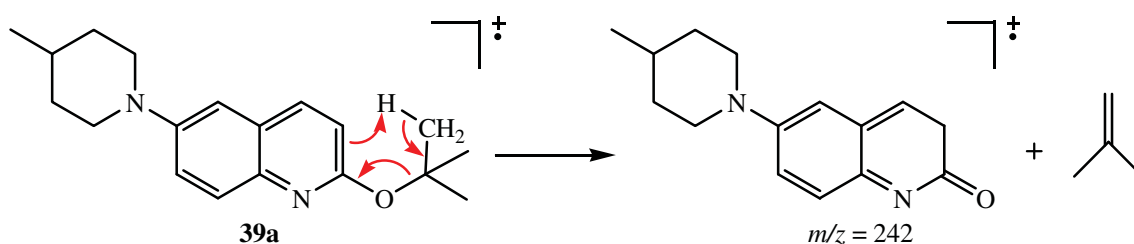


Figure 27: Cleavage from the mas spectrum of **39a**.

The ¹H NMR spectrum showed the characteristic upfield change in chemical shift of the signals for H5 and H7 for both compounds **32a** and **39a**, indicating the presence of the electron-donating heterocycle. For **39a**, a *tert*-butyl group singlet was observed at $\delta_{\text{H}} = 1.66$ ppm and the signal for H3 underwent an upfield change in chemical shift (c.f. **31** $\delta_{\text{H}} = 7.44$ ppm to $\delta_{\text{H}} = 6.73$ ppm) indicating the presence of the electron donating *tert*-butoxy group (see Table 8). 2D NMR spectroscopy was employed to confirm the identity of both compounds of

the mixture. ROESY 2D NMR spectroscopy once again confirmed the heterocycle at the 6-position in both compounds **32a** and **39a** with the ROESY spectrum showing correlations between hydrogens H5 and H7 with the H2' and H6' hydrogens of the heterocycle. For **39a**, a ROESY correlation was also observed between the *tert*-butoxy group at the 2-position and the H3 hydrogen of the quinoline (see Figure 28).

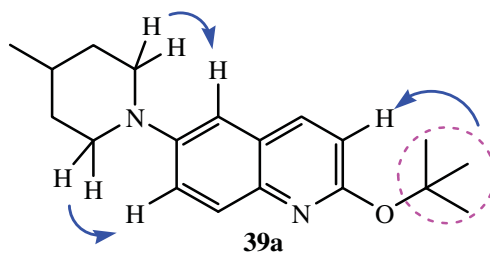


Figure 28: ROESY correlations between H5 and H7 hydrogens and the H2' and H6' hydrogens of the heterocyclic substituent and 2-*tert*-butoxy hydrogens and H3 hydrogen in **39a**.

Compounds **32i** and **32k** were isolated as a mixture with the corresponding 6-bromo-2-heterocyclicquinoline **37i** and **37k** respectively. A high resolution mass spectrum was obtained for both compounds **32** and **37** in each mixture and was consistent with the desired products. The low resolution mass spectra showed the isotopic distributions for chlorine in compounds **32** and bromine for compounds **37**. The ^1H NMR spectrum for each mixture showed the characteristic upfield change in chemical shift for the signals for H5 and H7 for compounds **32** and the upfield shift of the signal for H3 in compounds **37** was also observed, indicating the introduction of the heterocyclic substituent in the *ortho* position (see Table 8). The use of 2D NMR spectroscopy was used to confirm the identity of the compounds of the mixture. Again, ROESY spectroscopy was employed in the determination of the position of the heterocyclic substituent. Compounds **32** showed the characteristic ROESY correlations described above and compounds **37** displayed ROESY correlations between the H3 hydrogen of the quinoline and the H2' hydrogens of the heterocycle confirming substitution at the 2-position (see Figure 29).

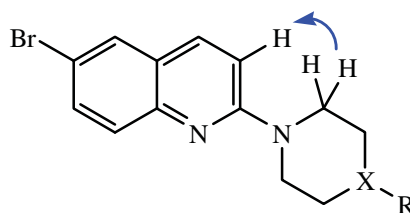


Figure 29: ROESY correlations between the H3 hydrogen of the quinoline and H2' hydrogens of the heterocyclic substituent in compounds **37**.

The characterisation of byproducts isolated pure from these reactions was accomplished largely by NMR spectroscopy. As shown in Table 8, products **32**, **37** and **39** all display characteristic changes in the ^1H NMR spectrum and were indicative of the formation of each type of compound. The desired products displayed upfield changes in the chemical shifts of the signals for H5 and H7 of the quinoline as mentioned previously. 2-Heterocyclic substituted compounds **37** show an upfield change in the chemical shifts of the signal for H3 and compounds **39** show upfield changes in the signals for H5, H7 and H3. In many instances additional data from either IR spectroscopy and mass spectrometry were used to confirm the identity of the byproduct. The use of 2D NMR spectroscopy, particularly ROESY as described above, was also helpful in the characterisation of these byproducts.

Table 8: Comparison of chemical shifts (δ , ppm) for H3, H5 and H7 hydrogens of 6-heterocyclic-2-chloroquinolines and for byproducts.

	$\delta_{\text{H H5}}$	$\delta_{\text{H H7}}$	$\delta_{\text{H H3}}$		$\delta_{\text{H H5}}$	$\delta_{\text{H H7}}$	$\delta_{\text{H H3}}$
31	7.99	7.81	7.24	37a	7.70	7.54	7.00
32a	6.97	7.47	7.22	37i	7.71	7.57	6.97
32b	6.60	7.17	7.27	37j	7.76	7.62	7.06
32c	6.98	7.45	7.24	37k	7.69	7.55	6.93
32d	6.99	7.48	7.26	37m	7.86	7.68	6.94
32e	7.06	7.55	7.26	38	7.70	7.39	7.00
32f	6.98	7.48	7.27	39a	7.26	7.39	6.73
32g	7.01	7.49	7.29	39f	6.99	7.36	6.72
32h	7.01	7.49	7.27	39i	7.01	7.37	6.75
32i	7.00	7.49	7.31	39k	7.01	7.35	6.75
32j	7.06	7.54	7.25	39l	7.14	7.43	6.76
32k	6.96	7.42	7.30	41	7.85	7.67	6.91
32l	7.03	7.48	7.30	42	7.04	7.40	6.83
32n	6.99	7.48	7.27				

2.3.4 Investigations into the Buchwald-Hartwig Amination

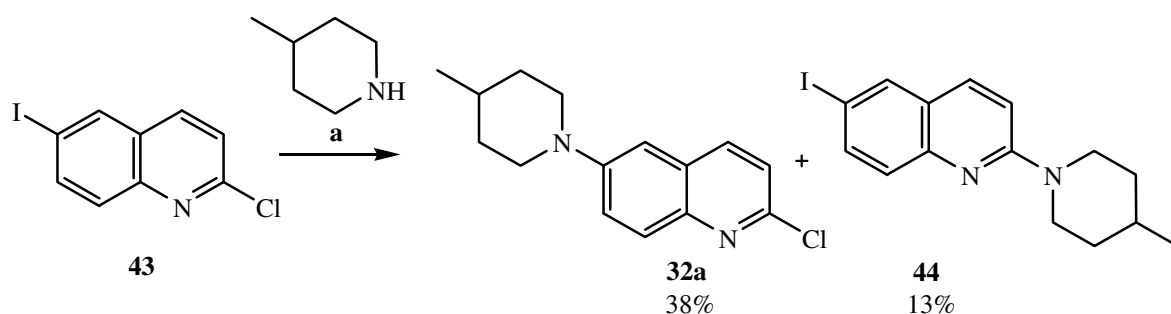
The method of Tewari *et al*⁷¹ allowed for the preparation of a range of 6-heterocyclic-2-chloroquinoline compounds in significantly varied yields. Due to the variation and often low yields of product and also the complexity associated with the purification process, further examination of the Buchwald-Hartwig reaction was required. Of particular importance was

improving the selectivity of this reaction and the exclusive introduction of the heterocycle at the 6-position. This examination involved the investigation of the aryl halide substrate, the addition of a copper co-catalyst, the type of catalytic system, the use of microwave heating and also the effects of both solvent and base.

2.3.4.1 Investigations into Alternative Aryl Halide Substrates

Replacing the Bromine with Iodine: 6-Iodo-2-Chloroquinoline

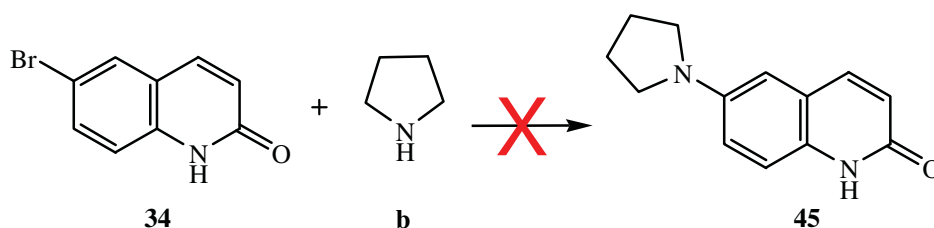
An initial attempt aimed at improving the selectivity involved replacement of the bromine atom at C-6 with an iodine atom, compound **43**. It was anticipated that the iodine equivalent would be more susceptible toward oxidative addition of palladium than the bromide counterpart and would therefore provide an improvement in selectivity for the 6-position (see Scheme 6). The Buchwald-Hartwig reaction was carried out using the method of Tewari with amine **a**, Pd(OAc)₂/**35** and NaO^tBu as the base in toluene. Using **43** as the aryl halide the desired product **32a** was isolated in only 38% yield. In addition, the corresponding 2-substituted compound **44** was isolated in 13% yield. This indicated that the aryl iodide was less reactive under the reaction conditions employed despite the anticipated increased reactivity of the iodine relative to bromine. The analogous reaction employing **c** as the amine similarly afforded the desired product **32c** in a reduced yield of 61% (c.f. with **31** 94%) confirming the reduction in selectivity for the 6-position. The apparent reduced reactivity of iodine compared to bromine in this particular Buchwald-Hartwig amination is consistent with several reports that show that aryl iodides are often less effective than their bromide equivalents and display significantly different reactivities in amination reactions.^{73,74}



Scheme 6: Buchwald-Hartwig amination of **43**. Reaction conditions; Pd(OAc)₂/**35**, NaO^tBu in toluene at 120 °C under pressure.

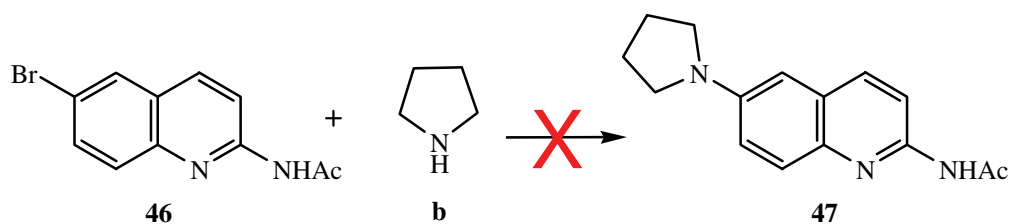
Employing a Substrate with Only One Site for Buchwald-Hartwig Amination

It was hoped that by utilising a different substrate, in which only one site was available for Buchwald-Hartwig coupling, 6-substituted quinolones could be prepared in higher yield. Quinolone **34** could be utilised as the aryl halide in the Buchwald-Hartwig amination. Using **34** would mean that the heterocycle could only be coupled to the 6-position of the quinolone. After the heterocycle had been introduced at the 6-position of **34**, the 2-chloro functionality could be introduced using phosphorous oxychloride as described above and subsequent amination at C-2 would afford the desired 6-heterocyclic-2-aminoquinolones. The reaction of **34** and amine **b**, was carried out using the above method with Pd(OAc)₂/**35** and KO^tBu as the base in toluene (see Scheme 7). This reaction was however, unsuccessful in affording any of the desired 6-substituted compound **45** and only starting material was recovered. The failure of this reaction is likely to be due to the insolubility of **34** in the reaction solvent.



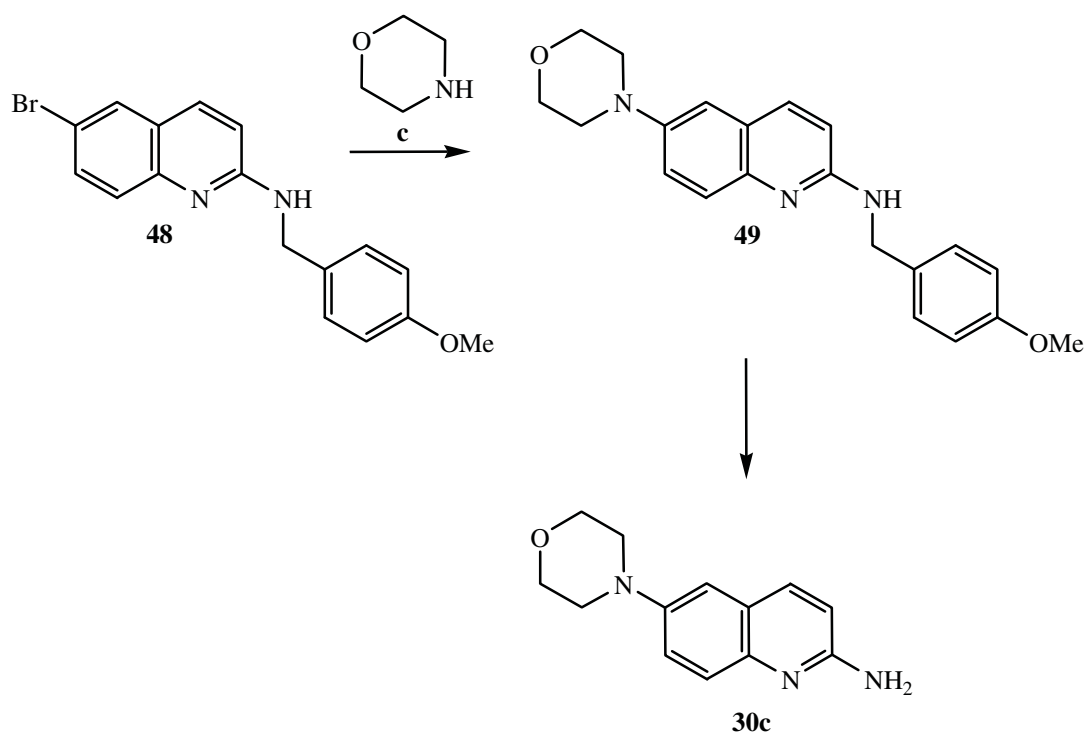
Scheme 7: Proposed method for the preparation of 6-substituted quinolones. Reaction conditions; Pd(OAc)₂/**35**, KO^tBu in toluene at 120 °C under pressure.

Compound **46** similarly contains only one site for Buchwald-Hartwig amination and also has the advantage that the 2-amino functionality is already present in the protected form of the acetamide. Acetamide **46** can be simply prepared from **31** in moderate yield (49%) by treatment with acetamide and K₂CO₃ using the method of Watanabe *et al.*⁷⁵ Buchwald-Hartwig coupling to **46** followed by deprotection of the acetamide functionality could provide 6-substituted-2-aminoquinolones. Acetamide **46** was employed in the Buchwald-Hartwig reaction with amine **b** (Scheme 8). This reaction led to the recovery of starting material and some other unidentified by products. ¹H NMR analysis of the crude material did not however, indicate the formation of the desired product.



Scheme 8: Proposed method for the preparation of 6-substituted-2-acetamidoquinolines. Reaction conditions; Pd(OAc)₂/35, KO^tBu in toluene at 120 °C under pressure.

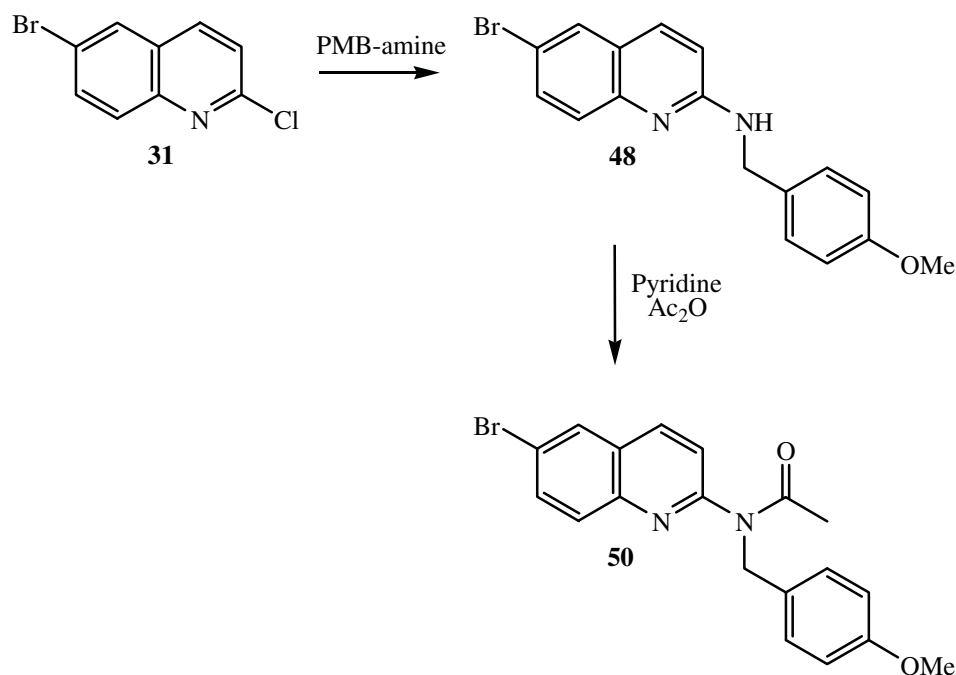
The use of *p*-methoxybenzyl (PMB) as an alternative to the acetamide protecting group was also investigated in the analogous reaction with heterocycle **c** (see Scheme 9). It was envisaged that a Buchwald-Hartwig coupling could be carried out on the PMB-protected **48**, producing the 6-substituted equivalent **49**. Deprotection of the amino group would provide the desired 6-substituted-2-aminoquinoline **30c**.



Scheme 9: Proposed synthesis of **30c** from the PMB-protected **48**.

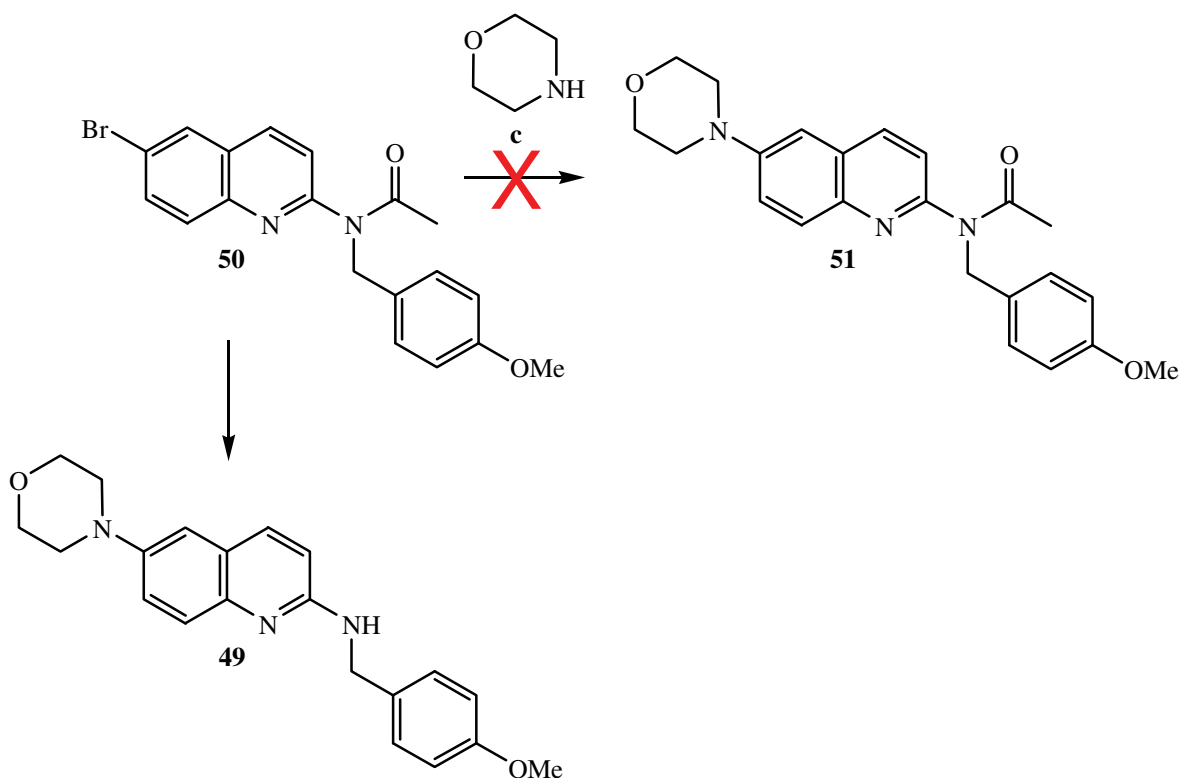
The protected quinoline **48** was prepared by treatment of **31** with *p*-methoxybenzyl amine (PMB-amine) at 140 °C overnight (see Scheme 10). Attempts to purify this compound by chromatography were unsuccessful and consecutive attempts led to the slight decomposition of the product and additional inseparable impurities. Given that **48** could not be purified this crude material was converted to the di-protected compound **50** by treatment with acetic

anhydride and pyridine at 100 °C. The di-protected **50** was prepared free of impurities and in high yield (94%). The IR spectrum showed a peak at 1670 cm⁻¹ corresponding to the carbonyl group of the acyl protecting group and the ¹H NMR spectrum showed characteristic peaks for both the acyl and PMB protecting groups (singlet at $\delta_{\text{H}} = 2.19$ ppm for CH₃ and two multiplets at $\delta_{\text{H}} = 6.78$ ppm and 7.17 ppm for the PMB).



Scheme 10: Synthesis of **48** and **50**.

The Buchwald-Hartwig amination of **50** with **c** did not afford the expected product **51** (see Scheme 11). The isolated product displayed the characteristic upfield changes in the signals corresponding to H5 and H7 in the ¹H NMR spectrum indicative of the introduction of a heterocyclic substituent at the 6-position. In addition, the peaks corresponding to the PMB-protecting group were observed however, no methyl peak corresponding to the acyl protecting group was present. The IR spectrum also lacked a carbonyl stretch confirming the removal of the acyl functionality and indicating the isolated product was **49**. The apparent acyl deprotection that occurs in the coupling reaction is of no consequence in this particular instance, as both protecting groups would need to be removed to afford **30c**.

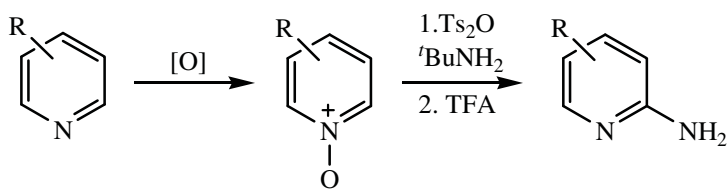


Scheme 11: Attempted synthesis of **51** and formation of **49**. Reaction conditions; Pd(OAc)₂/35, KO^tBu in toluene at 120 °C under pressure.

Purification of **49** proved to be difficult as the product displayed a large bandwidth whilst eluting during column chromatography. The addition of triethylamine (~0.2%) to the eluting solvent reduced the bandwidth slightly, however chromatography needed to be repeated several times to afford the pure product. The purification difficulties experienced with this compound are attributed to the PMB protecting group and are a common issue associated with the use of this protecting group in this work. Quinoline **49** was afforded in moderate yield (55%) however, due to the considerable difficulties in the preparation and purification the final step of the synthetic pathway was not pursued.

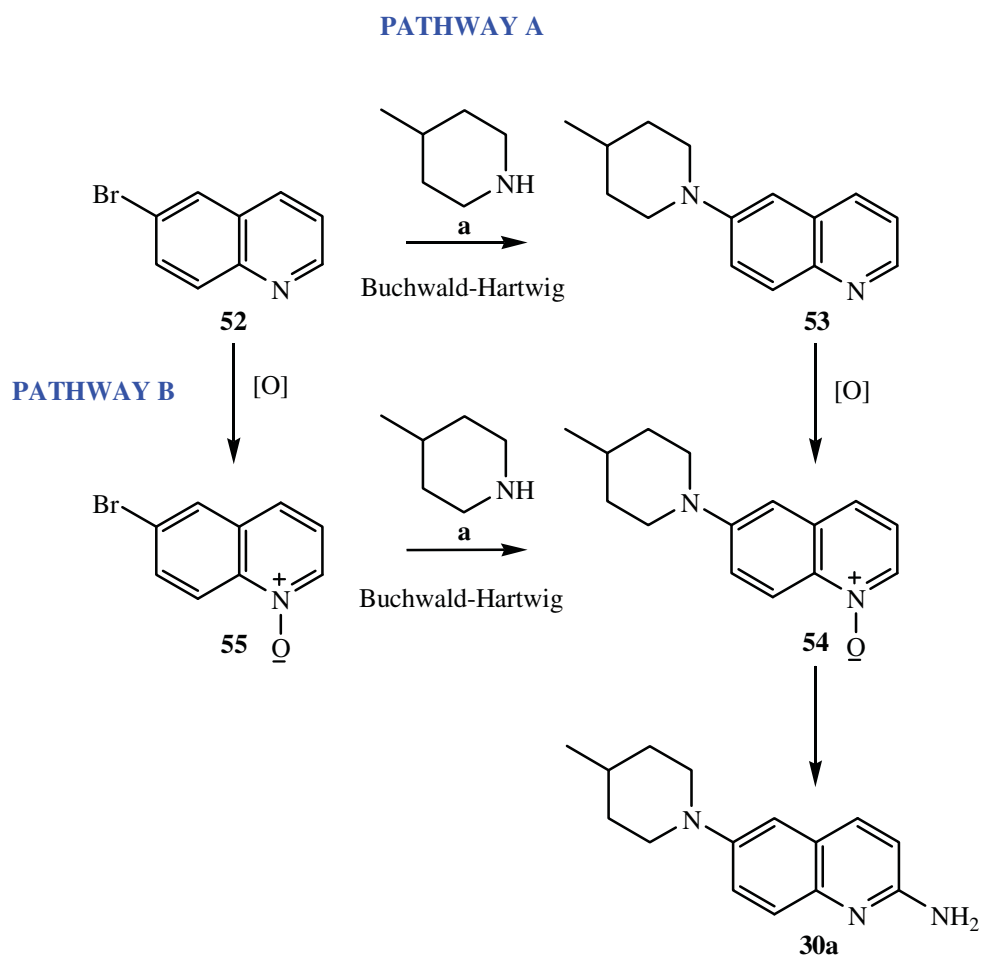
***N*-Oxides**

Recently, Yin *et al*⁷⁶ reported a method for the one step synthesis of 2-aminopyridines and 2-aminoquinolines from *N*-oxides (Scheme 12). In this method the pyridine or 2-aminoquinoline *N*-oxide was treated with *tert*-butylamine and tosic anhydride to afford the corresponding 2-*tert*-butylamino compound. *In situ* deprotection with TFA afforded the desired 2-aminopyridines and 2-aminoquinolines in high yield in a single step. It was thought that this procedure could be applied to the present context in the preparation of 6-heterocyclic-2-aminoquinolines.



Scheme 12: Method for the preparation of 2-aminopyridines and 2-aminoquinolines.⁷⁶

There are two possible synthetic pathways that could be envisaged to prepare 6-heterocyclic-2-aminoquinolines using the aforementioned method (see Scheme 13). Both pathways begin from the common starting material 6-bromoquinoline **52**, which can be easily prepared according to a literature procedure.⁷⁷ The first pathway (A) would involve the initial Buchwald-Hartwig amination of **52** to afford the 6-substituted quinoline. Oxidation of the 6-substituted quinoline with *m*-CPBA followed by amination by sequential treatment with *tert*-butylamine/tosic anhydride and TFA would afford the desired 2-aminoquinoline.



Scheme 13: Proposed method for the preparation of 6-heterocyclic-2-aminoquinolines. Reaction conditions: Buchwald-Hartwig amination; Pd(OAc)₂/**35**, NaO^tBu in toluene at 120 °C under pressure; oxidation; *m*-CPBA, DCM.

The potential of this pathway was examined with heterocycle **a**. The Buchwald-Hartwig amination of **52** with **a** using the conditions described above, afforded the desired compound **53** in a moderate yield of 65%. The ^1H NMR spectrum of **53** showed a large upfield shift in the signals for H5 (c.f. **52** $\delta_{\text{H}} = 8.05$ ppm; **53** $\delta_{\text{H}} = 7.02$ ppm) and H7 (c.f. **52** $\delta_{\text{H}} = 7.80$ ppm; **53** $\delta_{\text{H}} = 7.51$ ppm), which is consistent with the introduction of an electron donating heterocycle at the 6-position. The oxidation of **53** in an attempt to provide **54** was conducted with *m*-CPBA in DCM using the procedure outlined by Senechal-David *et al.*⁷⁸ Oxidation however, led to a complex mixture of products that was not purified. It is presumed that the presence of the additional nitrogen of the heterocycle complicates the oxidation reaction resulting in a mixture of products.

The alternate pathway (B) to prepare 6-substituted-2-aminoquinolines would involve initial oxidation of **52** followed by Buchwald-Hartwig amination of the *N*-oxide to introduce the 6-substituent (see Scheme 13). Treatment with *tert*-butylamine/tosic anhydride and TFA would then afford the desired 2-aminoquinoline. Oxidation of **52** with *m*-CPBA in DCM proceeded effectively and **55** was prepared in high yield (90%). The Buchwald-Hartwig amination of **55** with **a** however, produced a complex mixture of products.

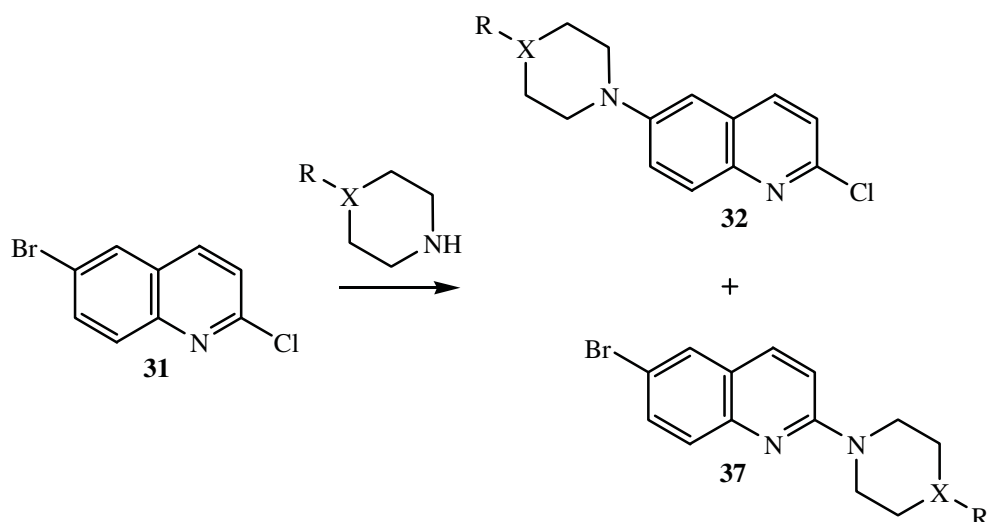
The addition of a copper(I) salt in the palladium-catalysed coupling reactions for the preparation of biaryls from *N*-oxide substrates has been recently reported.⁷⁹ In these coupling reactions the addition of either CuBr or CuCN was found to overcome catalyst poisoning resulting from the *N*-oxide reagent. In light of this, the use of a Cu(I) salt was investigated through the addition of CuBr in the coupling reaction of **55** with **a**. The addition of CuBr in this instance reduced the amount of products observed in the ^1H NMR spectrum of the crude reaction material. In addition, a small amount of the desired product **54** was isolated as a slightly impure mixture (14%). Further attempts to purify this compound however, led to its decomposition. A high resolution mass spectrum consistent with the molecular mass of the desired product was obtained and the low resolution mass spectrum showed a peak corresponding to 226 mass units, which is equivalent to loss of the oxygen. The ^1H NMR was also consistent with the desired product showing the typical upfield shifts of the signals corresponding to H5 and H7. Due to the low yield and instability of **54** the final step in the pathway of introducing the 2-amino substituent was not carried out.

The investigation into alternate aryl halide substrates for the present Buchwald-Hartwig amination indicated that **31** was in fact the most appropriate substrate as none of the other substrates proved advantageous. Further investigations into the Buchwald-Hartwig reaction were therefore conducted with the aim of improving selectivity for the introduction of the heterocycle at the 6-position.

2.3.4.2 Investigations into the Addition of Cu(I)

In addition to the use of copper in palladium-catalysed reactions involving *N*-oxide substrates, a number of authors have reported that other coupling reactions can be improved by the addition of a copper (I) salt as a cocatalyst.⁸⁰⁻⁸² The specific role of the copper in these reactions is not known but it has been suggested that the copper may facilitate the transmetallation step.⁸¹

The effect of copper was investigated with the Buchwald-Hartwig coupling of **31** and a number of cyclic amines through the addition of CuBr. The reactions were performed with Pd(OAc)₂/**35**, KO^tBu and CuBr (10 mol%) in toluene at 120 °C under pressure (see Scheme 14). The addition of Cu(I) improved the amount of **32** substantially when **a** and **h** were used as the amine and slightly in the cases of **f** and **k** (Table 9). In the case of **j**, a substantial decrease in production of **32** was observed. In these reactions, the addition of Cu(I) decreased the amount of by product **37** substantially when **a** and **h** were used as the amine, however in the cases of **f**, **j** and **k** a substantial increase in the amount of product **37** was observed.



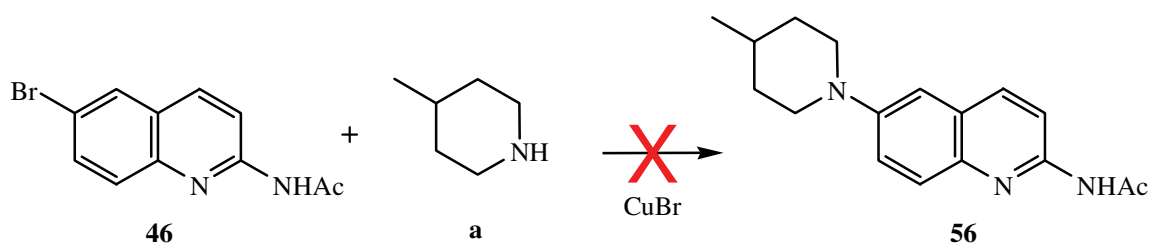
Scheme 14: Synthesis of 6-heterocyclic substituted-2-chloroquinolines. Reaction conditions: Pd(OAc)₂/**35**, KO^tBu, CuBr in toluene at 120 °C under pressure.

The use of Cu(I) in this particular palladium catalysed reaction therefore appeared to be inconsistent across the amines used, showing no constant improvement in selectivity. The addition of Cu(I) however, consistently prevented the formation of compounds **39** and **40** as little to none of these compounds were observed in all of the reactions involving CuBr. The absence of these side products is likely to be the main contribution to the improvement in the formation of **32** and **37** where they were observed.

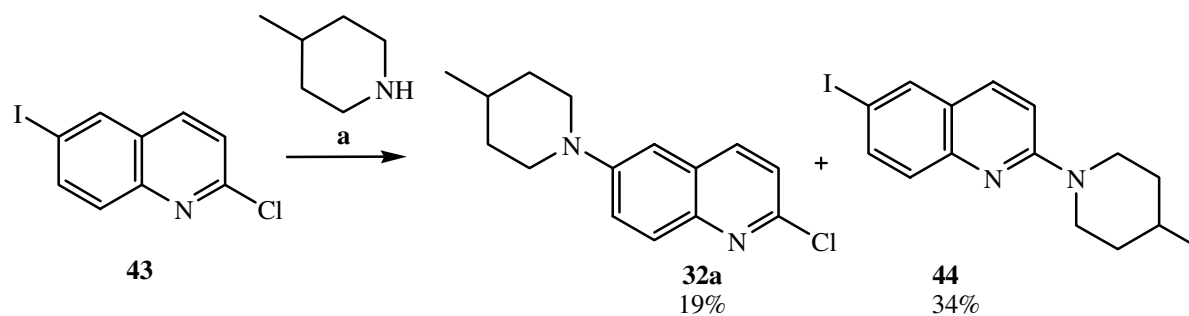
Table 9: Comparison of Buchwald-Hartwig amination of **31** with and without CuBr cocatalysis.

Amine	32 (%) No CuBr	37 (%) No CuBr	32 (%) With CuBr	37 (%) With CuBr
a	57	30	72	6
f	50	10	58	47
h	34	22	78	0
j	57	26	9	50
k	39	11	45	45

The effect of CuBr on Buchwald-Hartwig aminations of different aryl halide substrates was also examined with **46** and **43** as examples (see Scheme 15 and Scheme 16 respectively). The addition of CuBr to the reaction of **46** with **a** had little effect on the reaction and similarly to the corresponding reaction without CuBr, none of the desired product **56** was formed and only starting material was recovered. In the reaction of **43** and **a**, Cu(I) appeared to facilitate amination at the 2-position and afforded **44** in 34% and **32a** in only 19% yield. The use of copper in this particular instance resulted in less selectivity for the desired reaction at the 6-position then in the absence of CuBr (c.f. 38% of **32a** and 13% of **44**).



Scheme 15: Attempted synthesis of 6-substituted-2-acetamidoquinoline with CuBr cocatalysis. Reaction conditions; Pd(OAc)₂/**35**, KO^tBu and CuBr in toluene at 120 °C under pressure.



Scheme 16: Synthesis of **32a** with CuBr cocatalysis employing aryl halide **43**. Reaction conditions; Pd(OAc)₂/35, KO^tBu and CuBr in toluene at 120 °C under pressure.

2.3.4.3 Investigations into the Catalytic System

Having established that the addition of a copper co-catalyst did not provide an improvement in the selectivity of the reaction for the 6-position, the catalytic system was then investigated. The choice of the catalytic system, comprised of a palladium source and ligand, can greatly effect the outcome of a given Buchwald-Hartwig amination. Biphenyl based ‘Buchwald Ligands’,^{52,53} **57-62** were examined due to their high prevalence in palladium-catalysed reactions (see Table 10).^{54,83,84} These ligands are notable for being both bulky, which accelerates reductive elimination, and electron rich, which facilitates oxidative addition.⁸⁵ They also offer increased air stability relative to traditional phosphine ligands and the development of such biphenyl ligands has expanded the substrate scope of Buchwald-Hartwig aminations.^{53,54}

Table 10: Buchwald-Hartwig amination of **31** with a range of catalytic systems.^a

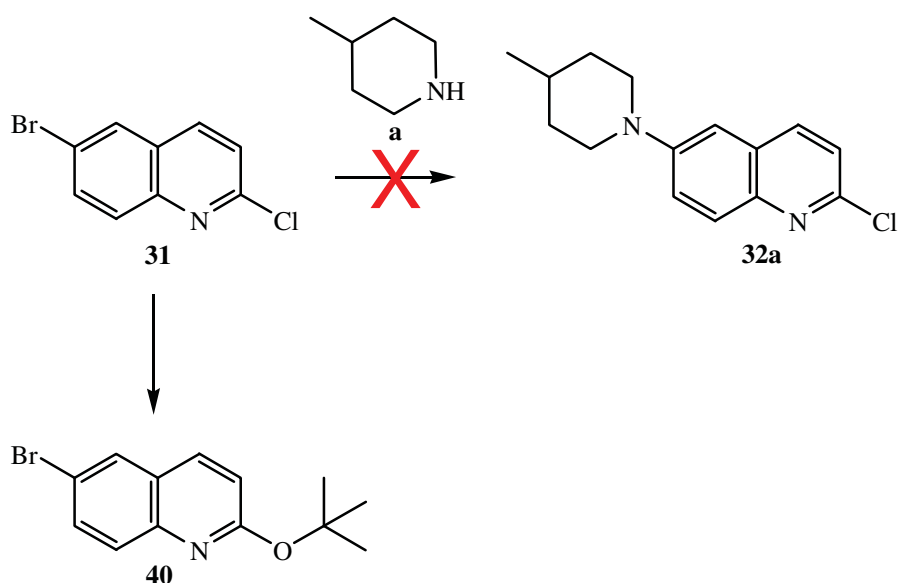
	Catalyst system ^b	32a (%) No CuBr	37a (%) No CuBr	32a (%) With CuBr	37a (%) With CuBr
57 DavePhos		15	15	25	58
58 XPhos		40	20	21	43
59 SPhos		31	15	0	68
60 ^t BuXPhos		0	21	0	80
61 CyJohnPhos		54	16	21	61
62 JohnPhos		0	0	0	0
63 PEPPSI™		0	<i>b</i>		
35 CataCXium A		57	14		

^a Reaction conditions: **31** (1 eq), 4-methylpiperidine **a** (1.2 eq), KO^tBu (1.2 eq), Pd(OAc)₂ (0.5 mol %), ligand (1 mol %) and CuBr (10%) where appropriate, in toluene at 110 °C. Yields determined by ¹H NMR analysis of the crude material. The reaction employing **35** was carried out under pressure at 120 °C. Pd(OAc)₂ was used as the source of palladium in all cases except for **63**. ^b Only **40** isolated.

The biphenyl ligands **57-62** were examined in combination with Pd(OAc)₂ and KO^tBu in toluene at 110 °C overnight employing **a**, as the model amine (Table 10). Of these ligands, CyJohnPhos **61**, was the most effective ligand and afforded a moderate conversion of the starting material to the desired product **32a** (54%), an outcome similar to that using ligand **35** (**32a** 57%). In addition to the desired product however, substitution at the 2-position was also observed to produce compound **37a** under these conditions (see Table 10; formation of **37a** was observed with all the biphenyl ligands, excluding **62**). Ligands XPhos **58** and SPhos **59** demonstrated a reduced ability to afford the desired product **32a** under the reaction conditions employed. ^tBuXPhos **60**, and JohnPhos **62** were unsuccessful in affording any **32a**.

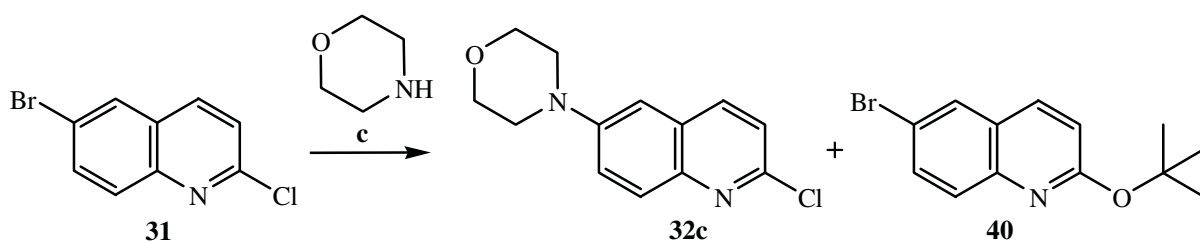
The corresponding reactions were also carried out in the presence of CuBr and the results are shown in Table 10. The use of CuBr with the Buchwald Ligands resulted in a decrease in **32a** with all ligands except DavePhos **57**, which showed a slight increase in the amount of **32a** formed. Interestingly, a substantial increase in the amount of **37a** was observed with all ligands excluding JohnPhos **62** which did not afford either **32a** or **37a**. This indicated that the addition of copper in these reactions favoured the formation of the 2-substituted product.

Use of the *N*-heterocyclic carbene (NHC) palladium complex PEPPSI™ (Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation) **63** was also explored as it reportedly offers a number of advantages over traditional palladium complexes. It is stable to air and moisture and has been reported to have improved or comparable activity to known palladium catalysts in a range of coupling reactions including Buchwald-Hartwig aminations.^{86,87} The use of **63** as a superior catalyst for C-N bond formation in the present context, specifically with improved selectivity for bromine, was also explored with heterocycle **a**. The reaction of **31** and **a** in the presence of **63** according to the method of Organ *et al*^{86,87} afforded 2-^tbutoxy-6-bromoquinoline **40** in almost quantitative yield in 1.5 hours (see Scheme 17). However, repetition of this reaction with no catalyst produced a similar result. This indicates that **63** did not facilitate the desired C-N bond formation required in this particular amination reaction and the formation of **40** is the result of nucleophilic attack of the base at the 2-position.



Scheme 17: Attempted synthesis of **32a** with **63**. Reaction conditions; **63**, KO^tBu in DME at 50 °C.

The use of catalyst **63** was also examined with heterocycle **c** (Scheme 18). The reaction of **31** and **c** in the presence of **63** and KO^tBu in DME at 50 °C for one hour afforded a 3:1 mixture of **32c:40**. The formation of the desired product in reasonable conversion in only one hour was encouraging and it was hoped that by varying the reaction temperature a higher conversion of **32c** could be obtained. At room temperature a 1:2 mixture of **32c:40** was produced after 2.5 hours, whilst heating at 85 °C for 45 minutes afforded a 1:3 mixture of **32c:40**. The results of these experiments indicated that the optimal temperature to achieve the highest conversion to **32c** was 50 °C and also demonstrated a substantial increase in the rate of the reaction with **63** (c.f. 20 hours with Pd(OAc)₂/**35**). The use of **63**, however, resulted in reduction in the formation of the desired product as compared to Pd(OAc)₂/**35** (c.f. 66% with **63** and 94% with Pd(OAc)₂/**35**).

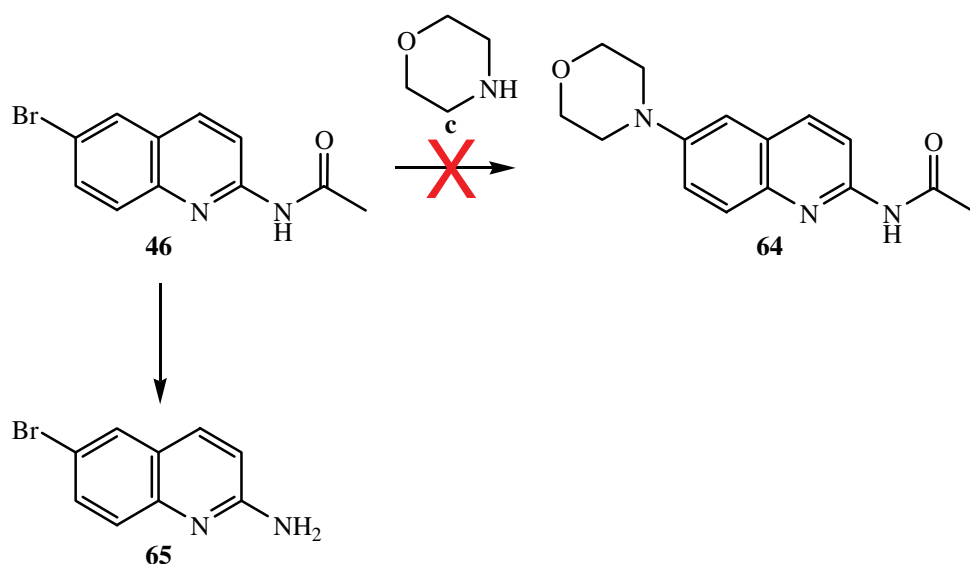


Scheme 18: Synthesis of **32c** with **63**. Reaction conditions; **63**, KO^tBu in DME.

Due to the observed reactivity of **63** in the above reaction, this catalyst was also investigated for the amination of a number of different aryl halide substrates with only the halide

functionality at the 6-position. This could potentially lead to 6-substituted compounds in high yield. It would also allow further comparison of **63** with the catalytic system of Pd(OAc)₂/**35**.

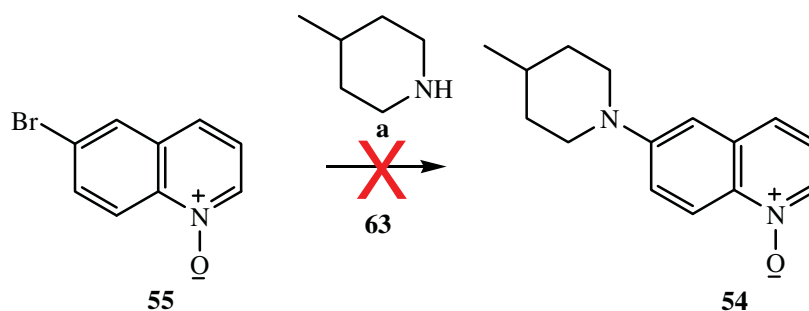
The use of **46**, **55** or **52** as the aryl halide would eliminate the competing reaction at the 2-position and was therefore hoped to provide 6-substituted compounds in high yield. The reaction of **46** and **c** with **63**, did not afford the desired 6-substituted compound **64** however, 6-bromo-2-aminoquinoline **65** was isolated in almost quantitative yield and is the result of acetamide deprotection (Scheme 19). Evidence for the formation of this product included an upfield shift in the signal for H3 (c.f. **46** δ_{H} = 8.44 ppm; **65** δ_{H} = 6.77 ppm) resulting from the increased electron donating ability of the amino group relative to the acetamide functionality and a melting point (144-147 °C) that was consistent with the literature value (141-148 °C²⁸).



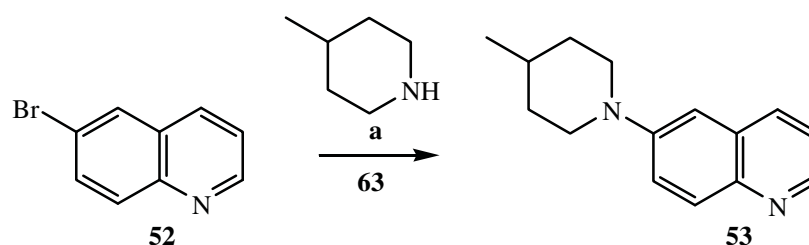
Scheme 19: Attempted coupling of **46** and **c** with **63**. Reaction conditions; **63**, KO^tBu in DME.

The reaction of the *N*-oxide **55** and **a**, similarly was unsuccessful and did not afford the desired product **54** but led to the recovery of starting material (Scheme 20). The reaction of **52** and **a** however, afforded the 6-substituted product **53** in average yield (55%) (Scheme 21). Although catalyst **63** afforded the desired product in this instance, the yield obtained was lower than that achieved with Pd(OAc)₂/**35** (c.f. 65%). In the reaction with **31** and amine **a**, the use of Pd(OAc)₂/**35** afforded the desired product **32a** in the highest yield as compared to the biphenyl ligands **57-62**. The use of **63** was also less effective for use in this particular coupling reaction with none of **32a** observed. In addition catalyst **63**, displayed inconsistent reactivities with the different amines employed. The investigation into the catalytic system therefore indicated that the original system of Pd(OAc)₂/**35** was in fact the most appropriate

as none of the other systems investigated provided an improvement in selectivity for amination at the 6-position.



Scheme 20: Attempted coupling of 55 and a with 63. Reaction conditions; 63, KO^tBu in DME.



Scheme 21: Coupling of 52 and a with 63. Reaction conditions; 63, KO^tBu in DME.

2.3.4.4 Investigations into Microwave Assisted Buchwald-Hartwig Aminations

Microwave assisted organic synthesis has become increasingly popular over the past twenty years due to the potential improvements that can be achieved in chemical reaction times, yields, reaction purities and selectivities. The use of microwave heating in palladium catalysed reactions, including Buchwald-Hartwig aminations, has been reported and has provided improvements in reaction times and in some instances improvements in yield have also been obtained.^{88,89}

The group of Maes have employed microwave heating for the coupling of electron rich and neutral aryl chlorides with aliphatic amines (see Figure 30).⁸⁹ These reactions were carried out using low catalyst loadings and completed in only ten minutes. The yields of the arylamines were high and in most cases were similar to the corresponding reactions carried out under thermal conditions.

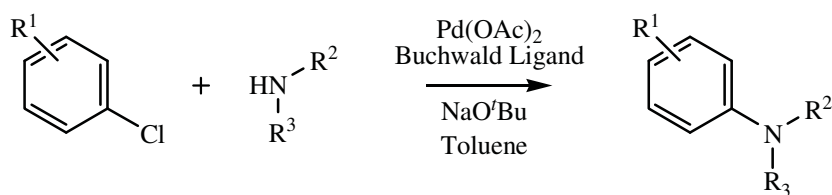


Figure 30: Microwave assisted coupling of aryl chlorides and a range of amines reported by the Maes group.⁸⁹

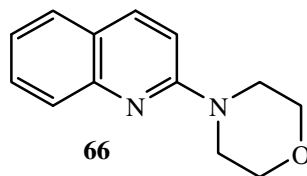
The present Buchwald-Hartwig reaction was therefore investigated with the use of microwave irradiation using the catalytic system of Pd(OAc)₂/**35** and **c** as the model amine in this instance. The reaction of **31** and **c** was initially carried out in toluene in the presence of NaO^tBu as these conditions were favourable for the corresponding reaction under thermal conditions. Under these conditions the desired product **32c** was isolated in good yield (80%) in 15 minutes of irradiation (Table 11). Incomplete conversion of the starting material was observed and is likely a consequence of the inability of the reaction mixture to reach the required temperature of 150 °C in a short period of time. The reaction mixture only reached a maximum of 130 °C after 15 minutes at maximum power (1200W) in a MARS (CEM) microwave system. The poor heating ability of toluene has been reported previously along with differences in heating profiles of common solvents and their use in various microwave systems.⁹⁰

Table 11: Results of the Buchwald-Hartwig amination of **31** and **c** under microwave irradiation in various solvents.

Base	Yield of 32c (%)					
	C ₆ H ₅ CH ₃	C ₆ H ₅ CF ₃	DME	DMF	DMF/Water	Water
NaO ^t Bu	80	95	0	0	0	
Cs ₂ CO ₃						0

Due to the poor heating ability of toluene for use in microwave reactions a number of alternate solvents were investigated including DME, DMF, DMF/water, water and trifluoromethylbenzene (C₆H₅CF₃) (Table 11). The reactions were carried out in the presence of NaO^tBu except for the reaction in water, which was conducted in the presence of Cs₂CO₃. The use of DME and water as solvents were unsuccessful and led to the recovery of starting material. The reactions employing DMF and DMF/H₂O as the solvent led to the formation of complex mixtures of products with trace amounts of the desired product being observed in the crude material but were not isolated. In the case of DMF/H₂O, 2-morpholinoquinoline **66** was

isolated in 9% yield. The formation of this product results from reduction of the bromine at the 6-position and amination by morpholine at the 2-position. The spectral data obtained for **66** was consistent with that reported in the literature.⁹¹



In addition to **66**, a mixture of two unknown compounds was also isolated from this reaction. The low resolution mass spectrum of one of the components displayed peaks at m/z 256 and 128. The peak at m/z 256 was thought to correspond to a molecular formula of $C_{18}H_{12}N_2$ and the reduced homocoupled product **67** shown below in Figure 31. The peak at m/z 128 would also be consistent with this structure and would correspond to one quinoline portion of this compound.

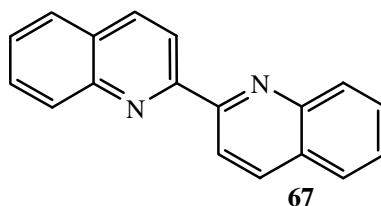


Figure 31: Proposed structure of one of the unknown components of the mixture **67** obtained from the reaction carried out in DMF/H₂O.

The ¹H NMR spectrum for **67** displayed only six signals in the aromatic region and no other signals were observed. One of these signals was significantly downfield at $\delta_H = 8.85$ ppm and corresponded to the hydrogens at the 3-position of the quinolines. These observations were consistent with the proposed homocoupled product as both sets of quinoline hydrogens are expected to be the same given the symmetry of this compound. Due to the orthogonal orientation of the quinoline systems, which would result in anisotropic deshielding of H3, this signal would also be expected to be significantly downfield. The COSY spectrum also showed the expected correlations between the adjacent hydrogens of the quinoline systems. Importantly, the hydrogen at H6 was confirmed by correlations between this hydrogen and the H5 and H7 hydrogens. Evidence for the substituent at the 2-position included the presence of two doublets in the ¹H NMR spectrum corresponding to H3 and H4 and the observation of only one COSY correlation between H3 and H4 and no other correlation for H3. The carbon

at the 2-position was also shifted significantly downfield ($\delta_{\text{C}} = 156.2$ ppm) confirming the quinoline substituent and a HMBC correlation was observed between this carbon and H3. The remaining 2D NMR spectroscopic data was also consistent with the formation of this product. One of the components of the mixture was therefore identified as the homocoupled 2-(quinolin-2-yl)quinoline **67**. The second component of the mixture could not, however, be completely identified. This unknown component displayed the same splitting patterns in the ^1H NMR spectrum as the homocoupled product **67**, although the chemical shifts were quite different. Similarly to **67** this compound no longer contained a bromine at the 6-position of the quinoline as evidenced by the presence of six aromatic hydrogen signals in the ^1H NMR spectrum with COSY correlations confirming the H6 hydrogen. This compound also contained a substituent at the 2-position however, the nature of this substituent could not be determined (see Figure 32). The low resolution mass spectrum displayed peaks at m/z 316, 302 and 135 however, this was not useful for the identification of the substituent at the 2-position and hence the overall identity of the unknown compound.

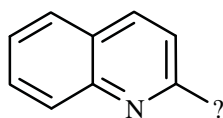


Figure 32: Partial structure of the second component of the mixture.

The group of Maes has also reported the use of trifluoromethylbenzene ($\text{C}_6\text{H}_5\text{CF}_3$) as a solvent for large scale microwave assisted Buchwald-Hartwig reactions. This solvent allowed for the rapid heating of the reaction mixture and provided moderate to good yields of the desired coupled products.⁹⁰ The reaction of **31** with **c** was therefore examined with trifluoromethylbenzene as the solvent at 150 °C under microwave irradiation (see Table 11). The use of trifluoromethylbenzene allowed for rapid heating of the reaction mixture (typically 1 minute) and for the consumption of all starting material. The reaction afforded the desired product **32c** in higher yield than the corresponding reaction in toluene (95% c.f. 80% in toluene). The yield obtained was also equivalent to the reaction of **31** with **c** conducted under thermal conditions in toluene, however the reaction time was significantly reduced to just 15 minutes.

To confirm the usefulness of trifluoromethylbenzene as a solvent for this microwave assisted Buchwald-Hartwig amination, the reaction of **31** was carried out with other cyclic amines (see Table 12). This method was successful for all amines employed and provided the compounds

32e, f, and h in good to high yield. All of the yields obtained are improvements on the thermal reactions in toluene and were achieved in 20 minutes or less of microwave irradiation. It should be noted that these yields have not been optimised.

Table 12: Comparison of Buchwald-Hartwig amination of **31** using $C_6H_5CF_3$ with microwave irradiation and $C_6H_5CH_3$ under thermal conditions.^a

Amine	Yield 32 (%)	
	$C_6H_5CF_3$ (Microwave)	$C_6H_5CH_3$ (Thermal)
c	95	94
e	50	44
f	78	40
h	50	32

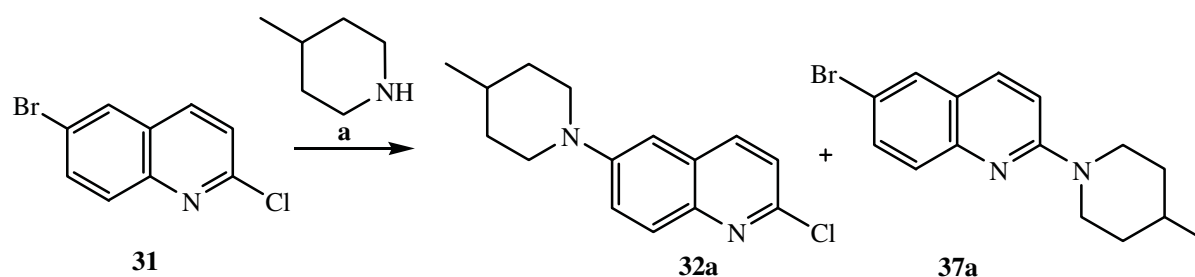
^a Reaction conditions: **31** (1 eq), amine (1.2 eq), NaO^tBu (1.2 eq), Pd(OAc)₂ (0.5 mol %) and **35** (1 mol %). Reaction in toluene was conducted at 120 °C under pressure. Reaction in trifluoromethylbenzene was conducted at 150 °C with microwave irradiation for 15-20 minutes. Yields are not optimised and refer to isolated yields.

2.3.4.5 Investigations into the Base and Solvent

A brief investigation into the nature of the base and solvent employed in these reactions involved a comparison of the reaction with KO^tBu in toluene with the reactions employing NaO^tBu and Cs₂CO₃ in the solvents trifluoromethylbenzene and 1,4-dioxane. The bases NaO^tBu and Cs₂CO₃ and the solvent 1,4-dioxane were examined due to their high prevalence in a range of Buchwald-Hartwig reactions. Trifluoromethylbenzene was also examined due to its success in the reactions carried out under microwave conditions. The use of trifluoromethylbenzene for Buchwald-Hartwig aminations under thermal conditions had not been reported previously.

The catalytic system of Pd(OAc)₂/**35** was once again employed in the reaction of **31** and **a** (Scheme 22). In toluene, it was found that NaO^tBu was effective for the amination reaction of **31** displaying similar amounts of both **32a** and **37a** as when KO^tBu was used as the base (see Table 13). The weak base Cs₂CO₃ on the other hand, was less effective in this reaction and resulted in a substantially lower yield of **32a** being obtained. It is however, worth noting that in this case no **37a** was observed. In trifluoromethylbenzene, NaO^tBu resulted in a substantial improvement in the conversion to **32a** as compared to toluene (93% in trifluoromethylbenzene vs. 60% in toluene) and only a small amount of **37a** was observed. Cs₂CO₃, was not effective however, and only trace amounts of **32a** was observed. In

1,4-dioxane, NaO^tBu was once again effective for this reaction displaying a similar amount of **32a** as when trifluoromethylbenzene was used as the solvent. Cs₂CO₃ however, showed significantly different activity in this instance and afforded a moderate yield of **37a** (46%) and only minor amounts of the desired product **32a**. The formation of a substantial amount of the 2-substituted product in 1,4-dioxane could be due to an increase in nucleophilic attack by the amine at the 2-position of the quinoline which is promoted by the increased polarity of the solvent as compared to toluene or trifluoromethylbenzene.



Scheme 22: Buchwald-Hartwig amination of **31** and amine **a**.

Table 13: Effect of base and solvent on thermal Buchwald-Hartwig amination of **31**.^a

Base	Solvent					
	C ₆ H ₅ CH ₃		C ₆ H ₅ CF ₃		1,4-Dioxane	
	Yield 32a (%)	Yield 37a (%)	Yield 32a (%)	Yield 37a (%)	Yield 32a (%)	Yield 37a (%)
KO^tBu	57	14				
NaO^tBu	60	11	93	6	90	4
Cs₂CO₃	30	0	2		8	46

^a Reaction conditions: **31** (1 eq), **a** (1.2 eq), base (1.2 eq), Pd(OAc)₂ (0.5 mol %) and **35** (1 mol %) in solvent indicated. The reaction carried out in toluene was conducted at 120 °C under pressure. Yields determined by ¹H NMR analysis of the crude material.

The results of the solvent and base investigation indicated that the combination of either 1,4-dioxane or trifluoromethylbenzene with NaO^tBu could allow for the preparation of 6-substituted-2-chloroquinolines in high yield with high selectivity for the 6-position. Trifluoromethylbenzene was chosen as the solvent for further investigation due its additional success as a solvent in the microwave reactions reported previously.

The general applicability of trifluoromethylbenzene was assessed with additional Buchwald-

Hartwig aminations with a range of amines (Table 14). Gratifyingly, employing trifluoromethylbenzene as a solvent in the thermal amination of **31** with NaO^tBu in the presence of Pd(OAc)₂/**35** produced substantial increases in the yields of compounds **32** with a range of cyclic amines (see Table 14). In all instances, the conversion of starting material to **32** was 80% or greater (80-95%) and only minor amounts of **37** were observed. In addition, in most cases none of the by-products **39** or **40** were observed.

Table 14: Effect of solvent on the Buchwald-Hartwig amination of **31** with a range of amines under thermal conditions.^a

Amine	Yield 32 (%)	
	C ₆ H ₅ CH ₃	C ₆ H ₅ CF ₃
a	57	93
c	98	95
e	62	80
f	50	88
h	34	80
j	57	91
k	39	90

^a Reaction conditions: **31** (1 eq), amine (1.2 eq), NaO^tBu (1.2 eq), Pd(OAc)₂ (0.5 mol %) and **35** (1 mol %) in toluene at 120 °C or trifluoromethylbenzene at 100 °C under pressure. Yields determined by ¹H NMR analysis of the crude material.

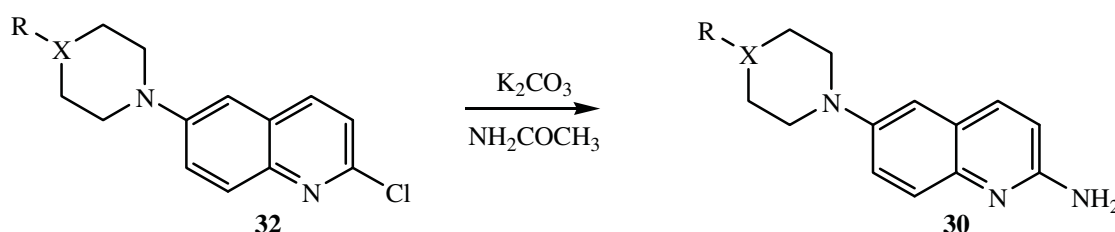
Reaction Conditions for the Selective Amination of 6-Bromo-2-Chloroquinoline

After significant investigation, reaction conditions have been developed that allow for the selective amination of 6-bromo-2-chloroquinoline **31** at the 6-bromine in the presence of the activated 2-chlorine with a variety of cyclic amines using Buchwald-Hartwig chemistry. These conditions include the catalytic system of Pd(OAc)₂/**35** and NaO^tBu in trifluoromethylbenzene and have allowed for the preparation of a range of 6-heterocyclic-2-chloroquinolines in high yield. The yields obtained and selectivity for the 6-position were both significantly improved compared to the corresponding reactions employing the initial reaction conditions. In addition, the preparation of these compounds can be achieved with microwave heating and results in vast improvements in reaction time.

2.3.5 Preparation of 6-Heterocyclic-2-Aminoquinolines

The final step in the synthesis of 6-heterocyclic-2-aminoquinolines **30** was the introduction of

the amino functionality at the 2-position of the 2-chloroquinolines. Previous studies have utilised the method of Kóródi⁶⁵ to convert 2-chloroquinolines to 2-aminoquinolines.^{28,34} This method involves treating the 2-chloroquinoline with an excess of acetamide and K_2CO_3 and heating at 200 °C for 1-3 hours. Using this method, the 2-chloroquinolines prepared (**32a-f**, **h-l** and **n**) were converted to 2-aminoquinolines (**30a-f**, **h-l** and **n**) (see Scheme 23).



Scheme 23: Kóródi amination of 6-substituted-2-chloroquinolines. Reaction conditions: **32** (1 eq), NH_2COCH_3 (20-40 eq), K_2CO_3 (20 eq) at 200 °C for 1-3 h.

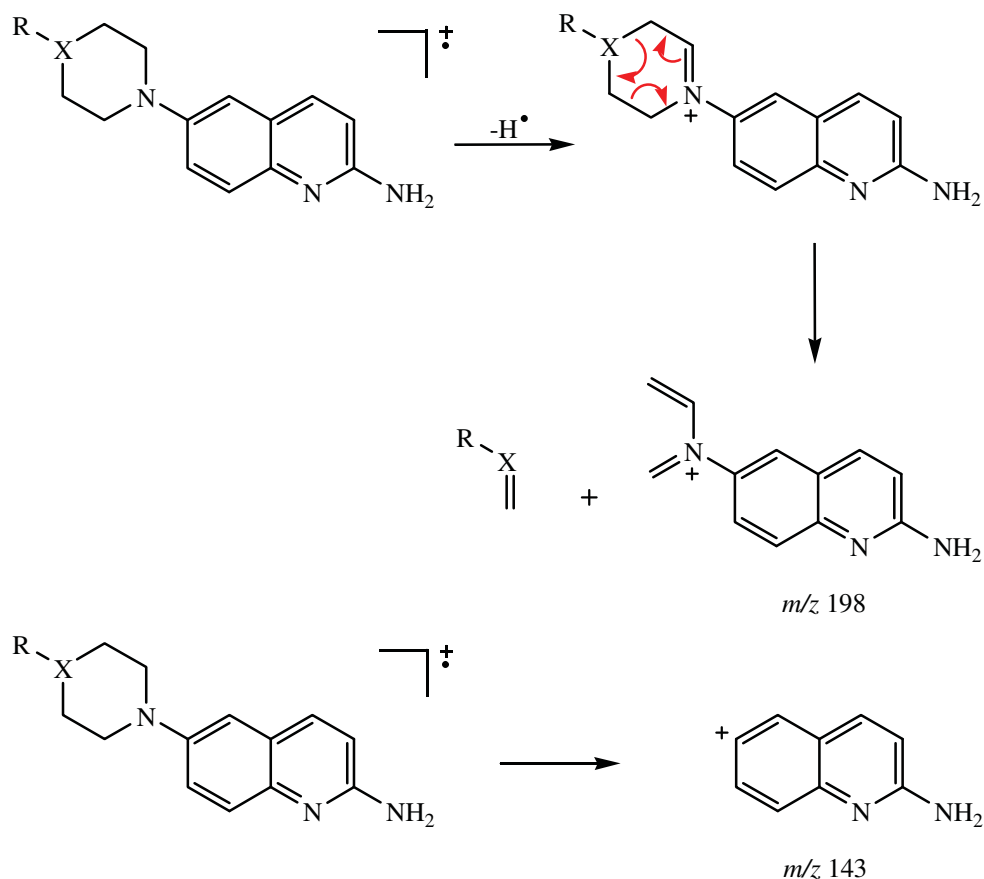
The yields obtained however, varied substantially (4-64%) and in many cases were poor (see Table 15). A complex mixture of products was generally formed during these reactions and contributed to the low yields displayed in most cases. The complex mixture of products that was obtained from the Kóródi reactions also caused considerable difficulties in the purification process.

Table 15: Yields for 6-heterocyclic-2-aminoquinolines **30** prepared using the method of Kóródi.⁶⁵

Amine	Yield 30 (%)	Amine	Yield 30 (%)
a	40	h	11
b	56	i	26
c	32	j	46
d	64	k	4 ^a
e	40	l	47
f	25	n	23 ^b

^a Purified on C18 preparative TLC plates. ^b Decomposed readily and could not be completely purified.

For all of the 2-aminoquinolines prepared above a high resolution mass spectrum was obtained which was consistent with the molecular formula of the desired product. The low resolution mass spectra of each compound showed peaks at m/z 198 and 143. The peaks at m/z 198 and 143 result from the partial and full cleavage of the heterocyclic substituent respectively, as shown in Scheme 24.



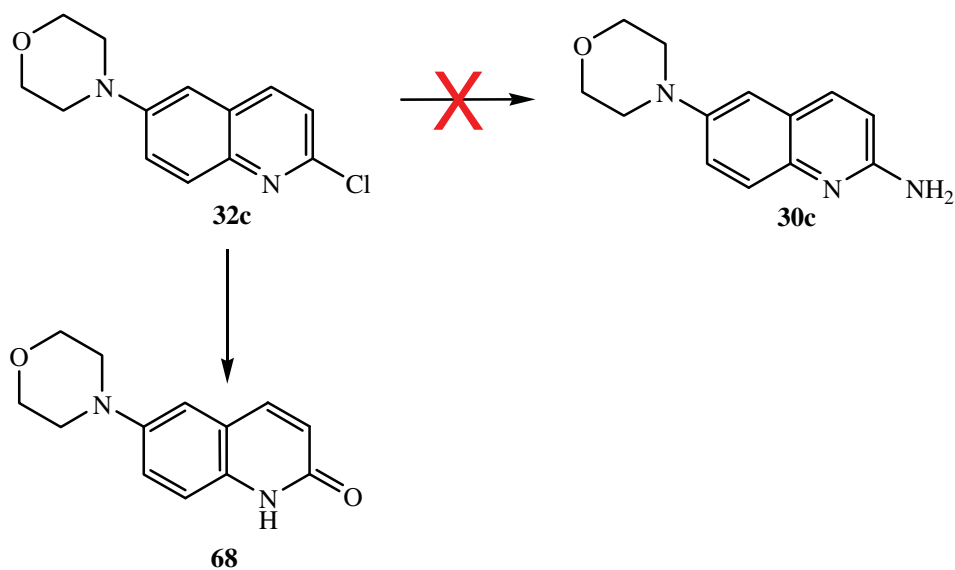
Scheme 24: Characteristic partial and full loss of the heterocyclic substituent in the mass spectrum of 2-aminoquinolines **30**.

The ^1H NMR spectra for these compounds showed a characteristic upfield shift in the signal for H3 (~ 0.5 ppm) (Table 16). This is consistent with the replacement of the electron withdrawing chlorine atom with the electron donating amino functionality. In addition, a broad singlet in the region of 4.50-5.90 ppm was observed for the amino functionality. The IR spectra also showed the appearance of peaks in the region of 3100-3400 cm^{-1} corresponding to the amino group. For compound **30j**, an elemental analysis was obtained that was consistent with the theoretical elemental composition. Compounds **30a**, **c**, **e** and **f** were converted to the corresponding maleate salts in order to obtain elemental analyses. In these cases, the obtained elemental analyses were consistent with the theoretical composition of the products with the inclusion of varying amounts of waters of crystallisation.

Table 16: Comparison of H3 chemical shifts of 6-substituted-2-chloroquinolines **32** and 6-substituted-2-aminoquinolines **30**.

32	$\delta_{\text{H H3}}$	30	$\delta_{\text{H H3}}$
a	7.22	a	6.67
b	7.27	b	6.88
c	7.24	c	6.71
d	7.26	d	6.83
e	7.26	e	6.69
f	7.27	f	6.66
h	7.27	h	6.70
i	7.31	i	6.68
j	7.25	j	6.70
k	7.30	k	6.66
l	7.30	l	6.74
n	7.27	n	6.73

Due to the purification difficulties and low yields obtained with the Kóródi reaction, an alternate procedure for amination was desirable. Initially, it was thought that conducting the Kóródi reaction under microwave irradiation might alleviate the formation of by-products and provide an improvement in the yields of 2-aminoquinolines. The Kóródi reaction of **32c** was examined under microwave irradiation as an example. After 1 hour at 230 °C at 300 W in a CEM MARS system all starting material had been consumed. Analysis of the obtained product indicated the formation of the corresponding quinolone **68** and not the desired product (Scheme 25).



Scheme 25: Attempted synthesis of **30c** using the method of Kóródi under microwave irradiation.

A high resolution mass spectrum of this compound was obtained and was consistent with the molecular mass of **68**. The ^1H NMR spectrum was also consistent with this product and displayed a significant upfield shift in the signal for the H3 hydrogen (from $\delta_{\text{H}} = 7.27$ ppm in **32c** to $\delta_{\text{H}} = 6.91$ ppm in **68**) confirming the conversion of quinoline **32c** to quinolone **68**. The corresponding amination reaction under microwave conditions was also conducted with **32j**. In this particular instance however, microwave irradiation led to the formation of a complex mixture of products.

A recent report by Sagi *et al*⁹² demonstrated the conversion of a 2-chloroquinoline to a 2-aminoquinoline using ammonium acetate and phenol (see Figure 33). It was hoped that this method could be used as an alternative to the Kóródi reaction. The conversion of **32c** to **30c** was examined under these conditions however led to the recovery of starting material only.

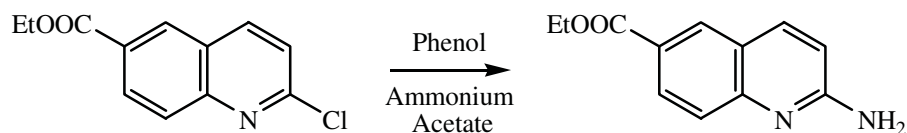


Figure 33: Conversion of a 2-chloroquinoline to a 2-aminoquinoline using phenol and ammonium acetate.⁹²

Chen *et al*⁹³ have also reported an alternate method involving the use of ammonium hydroxide under pressure for the preparation of 2-aminoquinolines. The use of the conditions reported by Chen *et al* was similarly unsuccessful in the conversion of **32c** to **30c**.

Recently, a few reports have described the use of palladium chemistry to convert aryl halides to simple anilines. These reactions have utilised LHMDS as an ammonia equivalent in the palladium-catalysed coupling to aryl halides.^{61,94} A wide range of anilines have been prepared by Hartwig *et al*⁹⁴ using LHMDS and the catalytic system of $\text{Pd}(\text{dba})_2$ and $\text{P}(\text{tBu})_3$ (see Figure 34 for examples). These anilines were prepared at room temperature or 50 °C and were isolated in high yield, typically 85-98%.

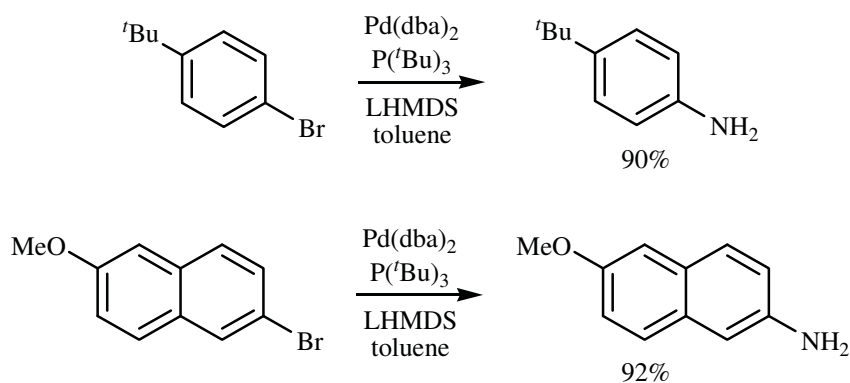


Figure 34: Examples of anilines prepared using $\text{Pd}(\text{dba})_2$ and $\text{P}(\text{tBu})_3$ with LHMDS as an ammonia equivalent.⁹⁴

Buchwald *et al*⁶¹ have also reported the use of LHMDS as an ammonia equivalent in the synthesis of 4-aminoacetanilide (Figure 35). In this reaction, $\text{Pd}_2(\text{dba})_3$ and DavePhos **57** were employed as the catalytic system.

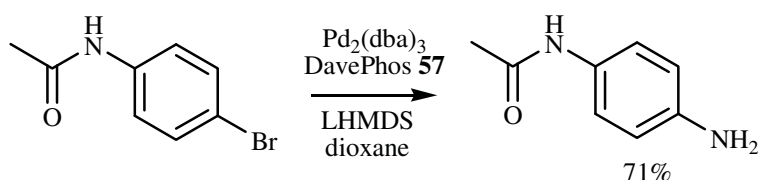
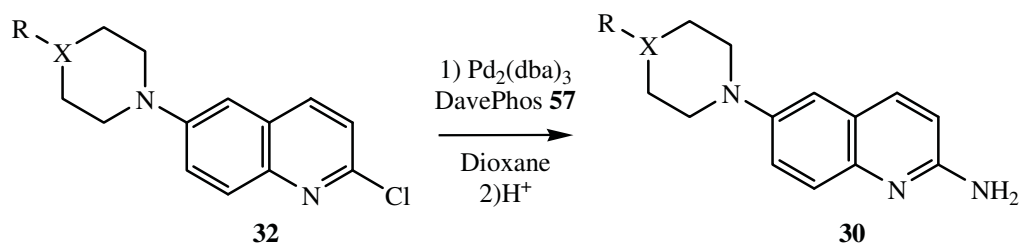


Figure 35: Preparation of 4-bromoacetanilide using $\text{Pd}_2(\text{dba})_3$ and DavePhos **57** with LHMDS as an ammonia equivalent.⁶¹

It was envisaged that this methodology could be applied to compounds **32** in the preparation of 2-aminoquinolines **30** (see Scheme 26). The reaction of a number of 2-chloroquinolines using the method described by Buchwald *et al*⁶¹ involving $\text{Pd}_2(\text{dba})_3$ and DavePhos **57** in dioxane at 100 °C under pressure verified the usefulness of LHMDS for this type of amination process (see Table 17). In all instances **30** was obtained from work up of the reaction with only trace amounts of impurities observed (less than 2% impurities by ^1H NMR analysis in the cases of **30a**, **c**, **j** and **k** and less than 5% impurities by ^1H NMR analysis in the case of **30h**). Compounds **30** were afforded in high yield (88-98%) with an average improvement in yield of 70% compared to the corresponding Kóródi reactions. This method is therefore a significant improvement on the Kóródi methodology, which gave a complex mixture of products and low yields of **30**. In addition, this method provides an alternate pathway for the preparation of 2-aminoquinolines using palladium chemistry.



Scheme 26: Amination of **32** using LHMDS as an ammonia equivalent. Reaction conditions: **32** (1 eq), LHMDS (2.2 eq), Pd₂(dba)₃ (1 mol %) and **57** (1.2 mol %) in dioxane at 100 °C under pressure.

Table 17: Comparison of methods for the preparation of 2-aminoquinolines **30**.

Amine	Yield 30 (%)	
	Kóródi amination	Pd-catalysed amination
a	40	97 ^b
b	56	
c	32	98 ^b
d	64	
e	40	
f	25	
h	11	90 ^b
i	26	
j	46	96 ^b
k	4 ^a	88 ^b
l	47	
n	23 ^c	

^a Purified on C18 preparative TLC plates. ^b Yields determined by ¹H NMR analysis of the crude material.

^c Decomposes readily and could not be completely purified.

The investigation into the Buchwald-Hartwig amination in this particular research has provided reaction conditions for the preparation of 6-heterocyclic-2-aminoquinoline ligands. These reaction conditions allow for the initial introduction of a heterocyclic substituent at the 6-position of 6-bromo-2-chloroquinoline and subsequent amination at the 2-position to provide the desired ligands. These conditions therefore allow for the selective and sequential functionalisation of the aryl halide substrate and provide the desired ligands in high yield.

2.4 Binding Studies of 6-Heterocyclic-2-Aminoquinolines

The 6-substituted-2-aminoquinolines **30a**, **c-f**, **h-k**[‡] prepared were assayed for binding to the Tec SH3 domain using the [¹H,¹⁵N] HSQC NMR chemical shift perturbation assay. The K_d s (equilibrium binding dissociation constants) of the ligands are shown in Table 18. All of the ligands, except for **30h**, bound to the Tec SH3 domain surface with improved affinity relative to the lead compound **2** ($K_d = 125 \mu\text{M}$).

Table 18: K_d s of **30** as determined by the NMR assay.

Ligand 30	K_d (μM)
a	23 ± 7
c	27 ± 3
d	91 ± 9
e	49 ± 13
f	16 ± 3
h	113 ± 30
i	28 ± 6
j	31 ± 5
k	28 ± 8

2.4.1 Problems with Determination of K_d

For some of the ligands assayed the calculated curves generated by GraphPad Prism⁹⁵ fit the data obtained from the assay and the derived K_d s are an accurate representation of the binding affinity (see Figure 36: A as an example). For ligands **30a**, **e-h** the calculated curves did not however, fit the data obtained. In these instances, the ligands approach saturation as evidenced by no changes in the chemical shift after the addition of the last two ligand aliquots in the NMR assay. However, the calculated curves are still rising, indicating that saturation has not been approached and therefore the binding isotherms are not a true representation of the obtained data (see Figure 36: B and C as examples).

[‡] **30b** was not assayed due to its instability. **30l** was not assayed due to its insolubility in the assay solution. **30n** was not assayed due to insufficient purity.

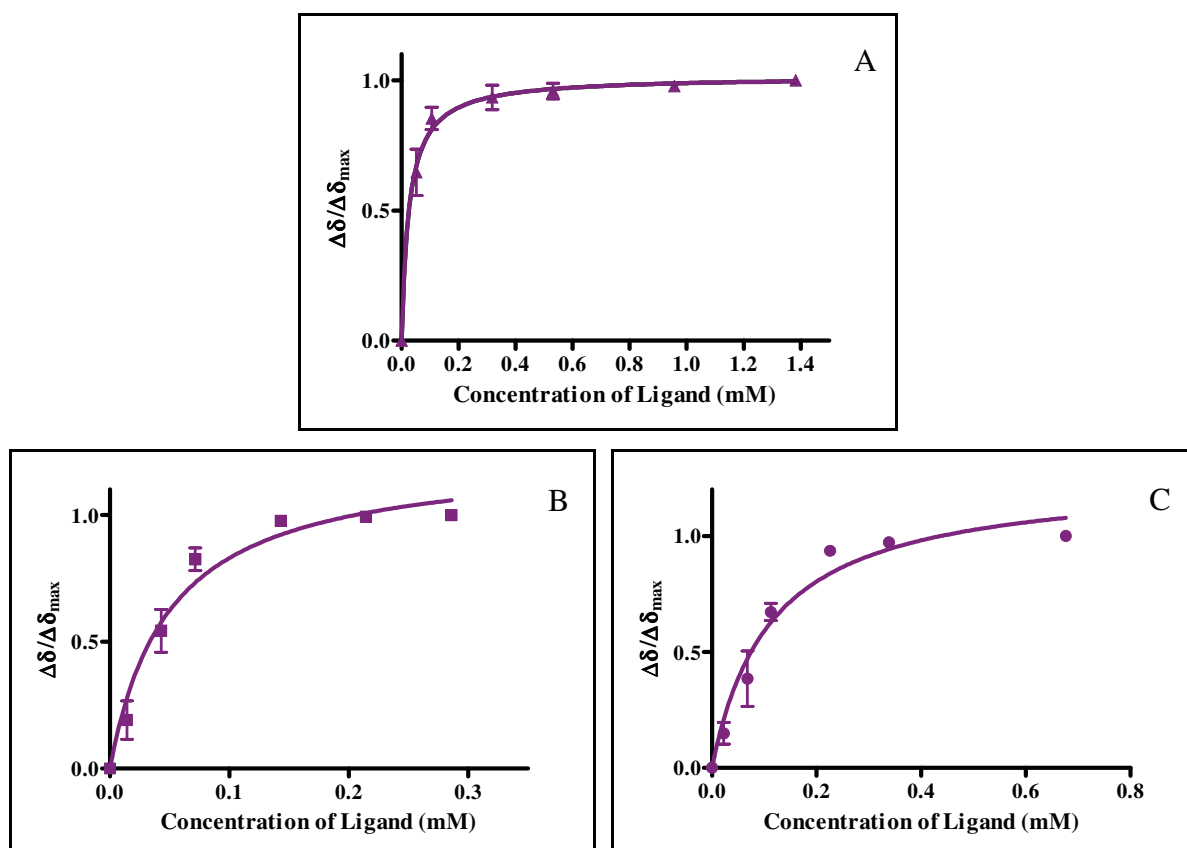


Figure 36: The equilibrium binding dissociation isotherms for: A. 30c; B. 30e; C. 30h.

This occurrence has been observed in binding studies of other 6-substituted-2-aminoquinolines.³¹ An investigation into the cause of this has been conducted previously and included the examination of equilibration time, the curve fitting model (and the possibility of two-site binding) and also intermediate exchange of the protein-ligand complex on the NMR timescale. The probable cause was determined to be the intermediate exchange of the protein-ligand complexes, as discussed in Section 1.4.2. In intermediate exchange, cross peaks in the HSQC spectra may become substantially broadened which causes difficulty in assigning peaks of the residues affected by the addition of the ligand. In addition, cross peaks may also have a much lower intensity than what is normally observed in fast exchange spectra, which can make it hard to recognise the peaks amongst the noise of the spectra. Given the difficulties associated with analysing spectral data obtained from an NMR assay of a ligand in intermediate exchange, significant experimental error may be introduced and result in binding isotherms, and hence K_d s, that are not a true representation of the data obtained.

To overcome intermediate exchange issues the protein-ligand complex needs to be forced back into fast exchange. This could potentially be achieved by conducting the experiments on a lower frequency spectrometer or at a higher temperature. Due to the lack of availability of a

lower frequency spectrometer with appropriate hardware, the effect of increasing the temperature has been investigated previously.³¹ The results of this investigation indicated that increasing the temperature to 35 °C for the HSQC assay provided a small improvement on the intermediate exchange of the protein-ligand complex. Increasing the temperature resulted in slightly less signal broadening and loss of signal intensity than the corresponding assay conducted at room temperature. However, increasing the temperature to 35 °C was not sufficient to induce fast exchange of the protein-ligand complex and further increases in the assay temperature could not be investigated due to the likely instability of the protein at higher temperatures.

Since the protein-ligand complex cannot be forced into fast exchange, the data obtained from the HSQC assay of a protein-ligand complex in intermediate exchange is used to determine the K_d . In instances such as this, where significant line broadening and loss of signal intensity is observed, it is often difficult to assign the centre of the cross peaks accurately and consequently the $\Delta\delta$ values may not be precise. This means that data points affected in this manner may not be an accurate representation of the correct values and explains why the curves generated by GraphPad Prism do not appear to fit the data points obtained.

The effects of intermediate exchange for this particular class of ligands can be seen in the HSQC overlay of **30h** shown below in Figure 37. In the expansion of the overlay of the 1D ¹H NMR traces for the Q190 residue it can be seen that the signals at 0.2 and 0.4 equivalents of **30h** (orange and yellow traces) are much broader and of lower intensity than where no ligand is present (red trace). The signals at 0.6 and 1 equivalents of **30h** (green and turquoise traces) are also broad and of significantly lower intensity and are almost lost amongst the noise of the spectrum. As can be seen, accurately assigning the centre of the peaks in cases such as these is difficult. These data points therefore contain significant error. If a significant number of the residues used to determine the K_d contain this error, then the curve generated and hence the K_d obtained also contains significant error. Excluding these data points reduces the error and the calculated curves and derived K_d s are a better representation of the data obtained. This is seen by the curves fitting the data better and showing that the protein-ligand complexes do in fact approach saturation. For some ligands the extent of intermediate exchange experienced is relatively small and therefore only one data point contains significant error and needs to be removed for the determination of K_d . For other ligands the extent of intermediate exchange is much greater and more than one data point contains significant error

and must be removed.

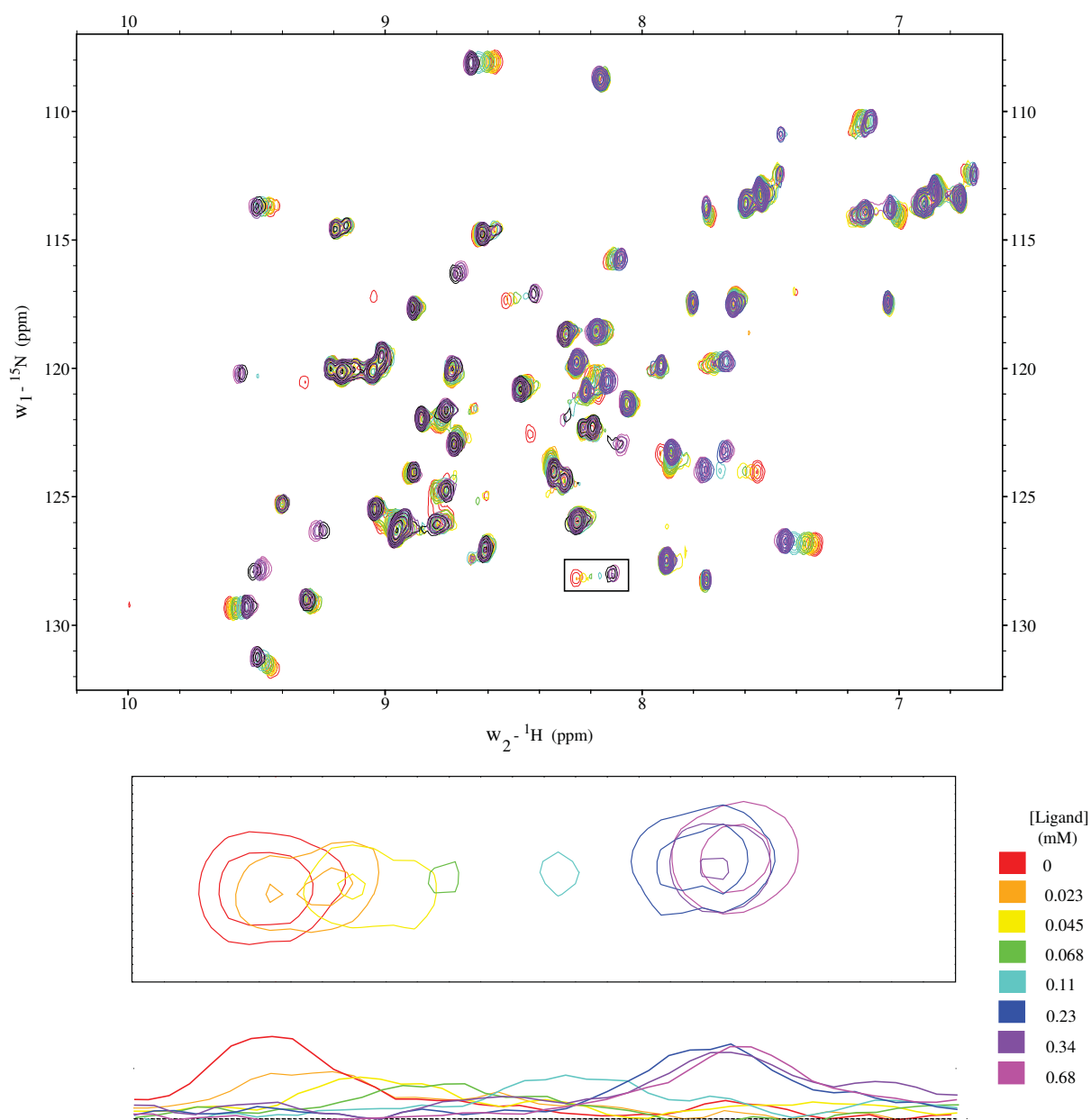


Figure 37: Overlay of NMR spectra from the HSQC NMR experiment of **30h** with an enlargement of the peak due to Q190 and the 1D traces for the same peak at all ligand concentrations.

The removal of the data points containing significant error for the ligands in intermediate exchange allowed for revised binding constants to be calculated and a more accurate representation of the data obtained. Removal of the first two data points after the addition of the ligand in the binding isotherm for **30h** is shown in Figure 38. As can be seen in Figure 38, the removal of the effected data points resulted in a curve that passes through the obtained data points and approaches saturation. The binding constant was calculated from the revised

curve and indicates that **30h** binds to the SH3 domain with higher affinity than determined from the initial binding isotherm and also contains less error in the K_d (c.f. initial K_d 113 ± 30 and revised K_d 67 ± 18). The R^2 and the absolute sum of squares are also much improved (see Table 19).

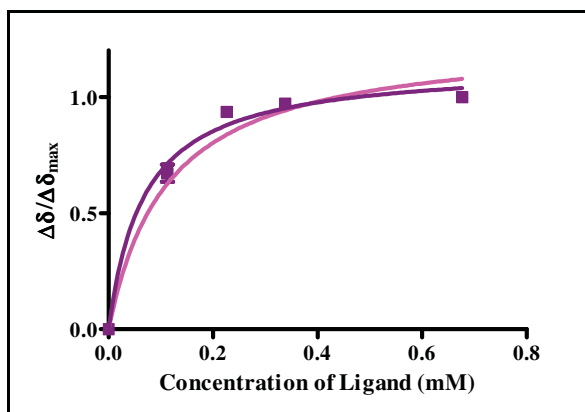


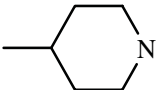
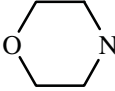
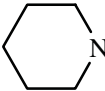
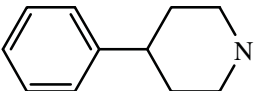
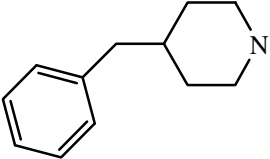
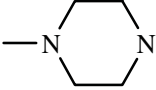
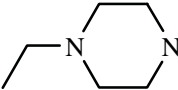
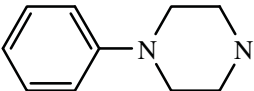
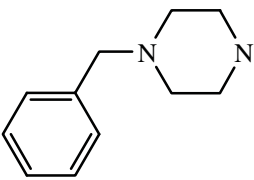
Figure 38: Binding isotherm of **30h** showing the curve obtained with the first two data points removed in purple. The original curve is also shown in pink for comparison.

Table 19: The initial and revised K_d for **30h** and the corresponding statistical data.

	Initial K_d (μM)	Revised K_d (μM)	Initial R^2	Revised R^2	Initial Sum of Squares 	Revised Sum of Squares
30h	113 ± 30	67 ± 18	0.9712	0.9904	0.07684	0.04770

Similarly, the removal of data points affected by the intermediate exchange phenomena for the remaining ligands **30a**, **e** and **f** allowed for revised binding constants to be determined. These revised binding constants are also a better representation of the data obtained and can be seen in Table 20.

Table 20: Initial and revised K_d s of **30** as determined by the NMR assay.

	Ligand 30	Initial K_d (μM)	Revised K_d (μM)
a		23 ± 7	12 ± 2^a
c		27 ± 3	
d		91 ± 9	
e		49 ± 13	22 ± 4^b
f		16 ± 3	9 ± 1^a
h		126 ± 30	67 ± 18^a
i		28 ± 6	
j		31 ± 5	
k		28 ± 8	

^a First and second data points removed. ^b First data point removed.

2.4.2 Revised Binding Affinities

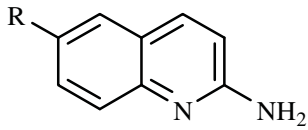
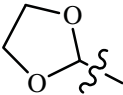
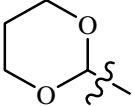
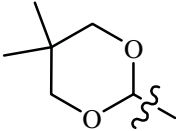
With the revised data available, evaluation of the binding affinity of this class of ligands could occur. The introduction of a simple piperidine substituent, as in **30d**, provides a small improvement in binding affinity ($K_d = 90 \mu\text{M}$) as compared to the lead compound. Further extension on the piperidine substituent as in ligands **30a**, **30e** and **30f**, provides a further improvement (6-10 fold; K_d s = 9-22 μM) in binding affinity. The incorporation of an oxygen in ligand **30c** displayed a similar improvement in binding affinity ($K_d = 27 \mu\text{M}$). The incorporation of an additional nitrogen in the piperazine heterocycle in **30h** ($K_d = 67 \mu\text{M}$) gave an approximately 2-fold improvement in binding. Extension on the piperazine

substituent similarly improves the binding affinity further ($K_{dS} = 28\text{-}31 \mu\text{M}$). Ligands **30a** and **30f** were found to be equal to the highest affinity ligands prepared to date.³¹

The SAR information provided from the assay results suggests that the appended heterocycle makes an additional hydrophobic contact with the protein surface, which provides an improvement in binding affinity of compounds **30** relative to **2**. Extension on the heterocyclic substituent may provide a further contact with the protein surface leading to a greater improvement in binding. The assay results also indicate that the second nitrogen in the piperazine ring appears to reduce the binding affinity of these compounds. Extension on the piperazine however, regains some of the lost binding affinity presumably by making an additional contact with the protein surface.

The binding affinities of compounds **30** were compared to those of the acetal substituted ligands **26-28** (see Table 21; $K_{dS} = 40, 52$ and $22 \mu\text{M}$ respectively). Of the ligands assayed **30d** and **30h** displayed a reduced affinity for the Tec SH3 domain relative to ligands **26-28**. **30c**, **30e** and **30i-k** showed similar affinity to the acetal substituted ligands whilst **30a** and **30f** had improved affinities.

Table 21: K_{dS} of 6-acetal-substituted ligands.

		K_d (μM)
	R	
26		40 ± 8
27		52 ± 16
28		22 ± 5

The overall similarity of the binding affinities of ligands **30** with **26-28** is consistent with our prediction that the acetal functionality could be replaced with an alternate heterocycle. The replacement of the acetal with the above mentioned heterocycles affords compounds with

increased chemical stability and provides improvements in binding affinity relative to **2**. Additionally, the binding data from these ligands indicates that the oxygen atoms and their position in the heterocycle are not responsible for the increased binding affinity of the acetal substituted ligands.

2.4.3 Chemical Shift Mapping

The residues that underwent significant changes in chemical shift ($\delta_H > 0.08$ ppm) during the NMR assay were mapped onto the backbone of the protein to gain an understanding of the type of interactions that occur upon binding of these ligands to the Tec SH3 domain. This is shown in Figure 39.

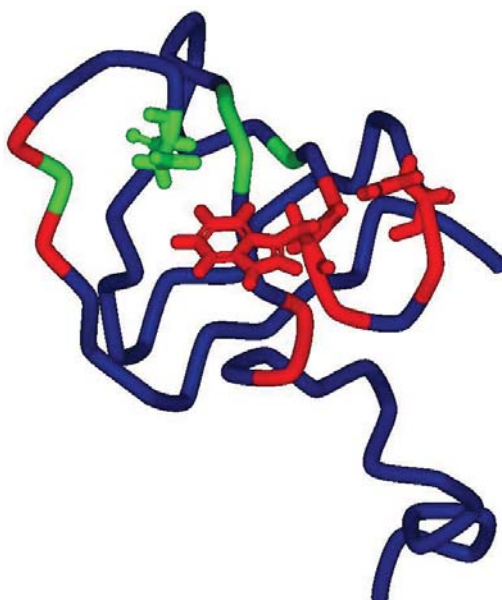


Figure 39: Chemical shift mapping of the backbone of the Tec SH3 domain with the 6-heterocyclic substituted ligands **30** where $\delta_H > 0.08$ ppm for the majority of ligands. Downfield shifts are marked in green and upfield shifts are marked in red. W215 and D196 are shown as stick diagrams in the middle of the protein backbone to indicate the region where the 2-aminoquinoline ligand binds. N211 is also shown as a stick diagram on the right hand side.

A number of signals for amino acid residues towards the N-terminus relative to W215 (shown on the right side of W215) were affected by the addition of the ligands. Inspection of the chemical shift map suggested that the substituent at the 6-position would effect these residues upon binding and be the likely cause of changes in chemical shift. Analysis of the residues involved in the binding of 2-aminoquinoline indicates that the movement is a result of the substituent at the 6-position as these signals are not affected upon 2-aminoquinoline

binding.²⁸ Docking of one of the 6-substituted ligands **30c** onto the SH3 domain backbone with Dock 4.0^{96,97} also demonstrates how the 6-substituent can make an additional contact with the protein surface effecting residues towards the N-terminus, particularly the side chain of N211 (see Figure 40).[§] These residues are also affected upon the binding of 6-phenoxyethyl-2-aminoquinolines prepared previously.³¹ This suggests that the heterocyclic substituent occupies a similar area on the protein surface as the 6-phenoxyethyl substituents. The residues that are affected towards the C-terminus relative to W215 (shown on the left side) are also affected when 2-aminoquinoline is the ligand, indicating that these chemical shifts are due to the quinoline ring system.

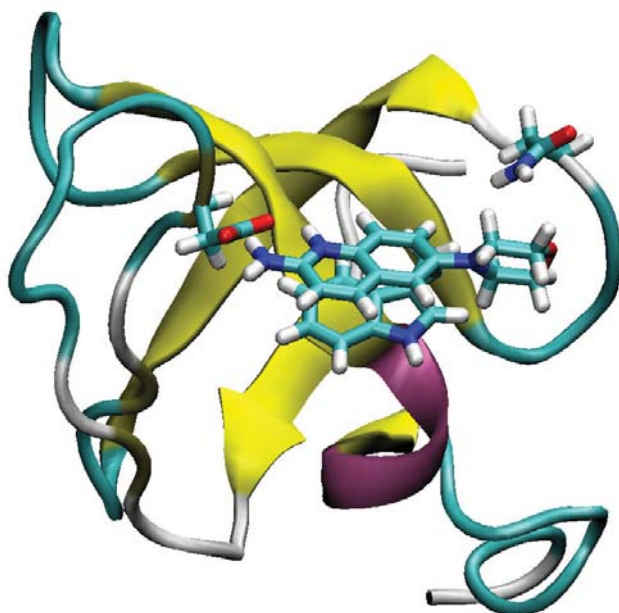


Figure 40: Tec SH3 domain with docked **30c** showing the interactions of the 6-substituent with the side chain of N211.

[§] Docking of **30c** was performed by Cvetan Stojkoski, School of Molecular and Biomedical Science, University of Adelaide.

Chapter 3:

SYNTHESIS OF 6-ARYLOXYMETHYL- AND 6-ARYLTHIOMETHYL-2-AMINOQUINOLINES

3.1 Introduction

An alternative to a heterocyclic substituent at the 6-position to replace the biologically unstable acetal functionality is an aryloxymethyl substituent (see Figure 41). It was anticipated that this type of substituent could occupy a similar space on the protein surface as the 6-acetal substituent in ligands **26-28** and may provide further improvements in binding affinity and compound stability similarly to the heterocyclic-substituted compounds.

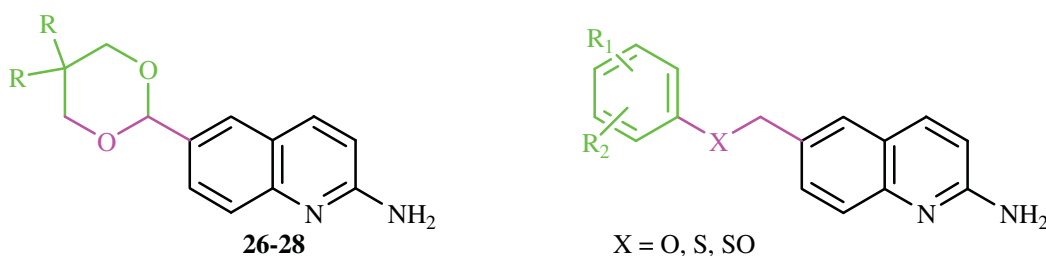


Figure 41: Comparison of previously prepared 6-acetal substituted ligands **28-30** and 6-aryloxymethyl and 6-arylthiomethyl-2-aminoquinoline target ligands.

A number of 6-phenoxyethyl-2-aminoquinolines have been prepared with simple alkyl and halogen substitution on the phenoxy ring and are some of the highest affinity ligands prepared to date.³¹ In this work, the preparation of further ligands of this type including those substituted with large, lipophilic groups and multiple substitutions on the phenoxy ring have been prepared and assayed for binding affinity. In addition, replacement of the oxygen atom in the linker with a sulphur functionality has also been explored to assess the importance of the heteroatom. The results of this study are presented in this chapter.

3.2 Synthesis of 6-Aryloxymethyl- and 6-Arylthiomethyl-2-Aminoquinolines

3.2.1 Synthetic Scheme

In order to prepare the 6-substituted ligands the synthetic procedure described below was employed (Figure 42). In this pathway, the desired ligands are prepared from **69** in a substitution reaction with a range of substituted phenols and thiophenols followed by simple deprotection of the 2-acyl protecting group. Compound **69** can in turn be prepared from 2-chloro-6-methylquinoline **70** in two simple steps. Quinoline **70** is prepared from quinolone

71, which in turn is prepared from *p*-toluidine and cinnamoyl chloride in two steps in an analogous manner to **31**.

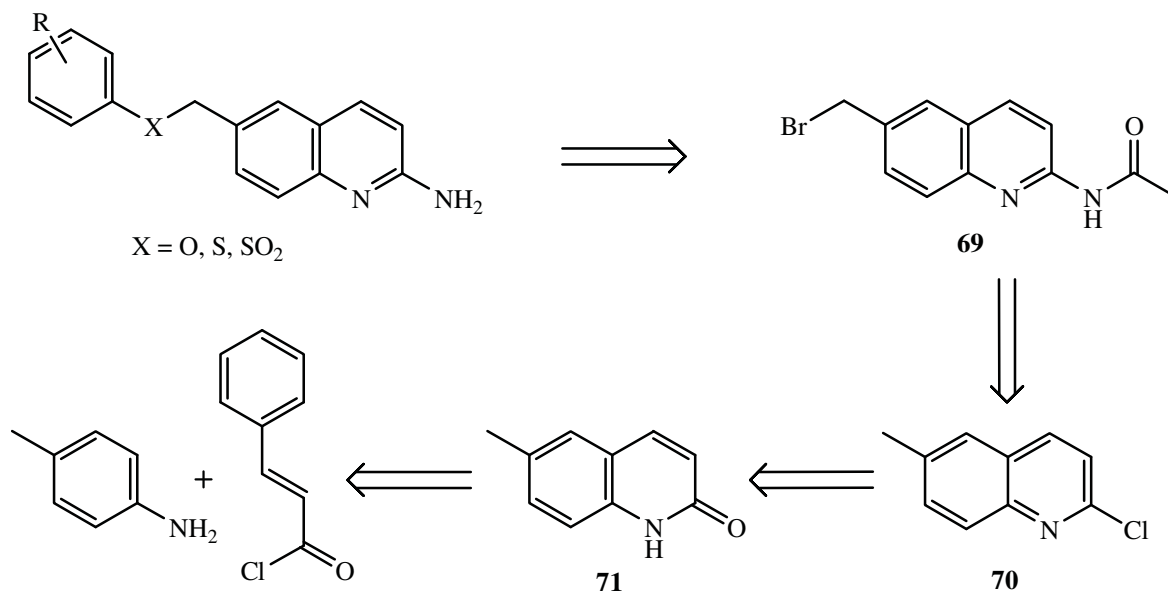
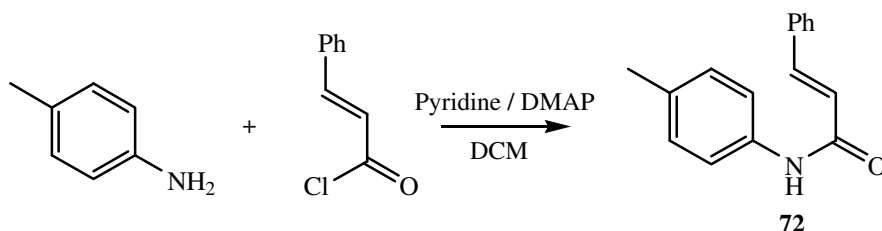


Figure 42: The retro synthetic pathway for the synthesis of 6-aryloxymethyl and 6-aryltiomethyl-2-aminoquinolines.

3.2.2 Synthesis of 6-Aryloxymethyl- and 6-Aryltiomethyl-2-Aminoquinolines

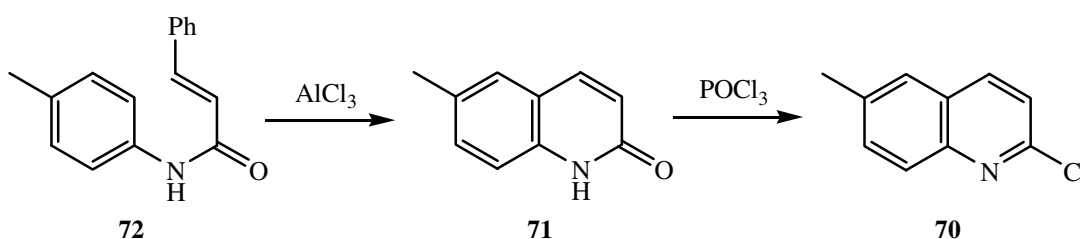
The first step in the synthesis of these compounds involved the preparation of cinnamanilide **72** (see Scheme 27). Cinnamanilide **72** was prepared using a literature procedure and was obtained in almost quantitative yield (96%).⁹⁸ The melting point (159-162 °C) was consistent with the literature value (162 °C)⁹⁸ and the IR and ¹H NMR spectra were also diagnostic. The IR spectrum showed a characteristic peak at 1661 cm⁻¹ that corresponds to the amide carbonyl stretch. The ¹H NMR spectrum of **72** also showed a characteristic *trans* coupling constant (*J* = 15.6 Hz) due to the hydrogens of the double bond.



Scheme 27: Synthesis of cinnamanilide **72**.

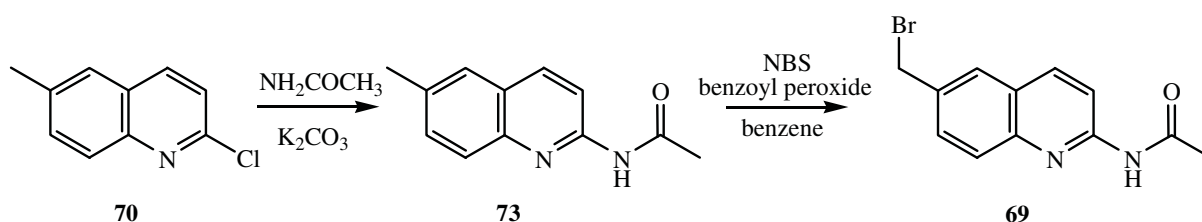
Compound **72** was then converted to 6-methylquinolin-2(1*H*)-one **71** by treatment with aluminium chloride as a melt in a Friedel-Crafts acylation (Scheme 28).⁶⁶ The crude

quinolone **71** obtained from the reaction was used without further purification and treated with phosphorus oxychloride to afford **70**. Quinoline **70** was obtained in quantitative yield over the two steps (96%) and displayed a melting point (112-114 °C) consistent with the literature value (111-114 °C).⁹⁹ The disappearance of the carbonyl stretch in the IR spectrum was diagnostic and indicated the formation of the desired product. The ¹H NMR spectrum also showed a large downfield shift in the signal for H3 (c.f. **71** δ_{H} = 6.70 ppm; **70** δ_{H} = 7.35 ppm), which is consistent with the conversion of the quinolone to the quinoline.



Scheme 28: Synthesis of 6-methyl-2-chloroquinoline **70**.

The next step in the synthesis involved the introduction of the nitrogen in the 2-position in the protected form as the acetamide (Scheme 29). This was conducted using the method of Watanabe *et al.*⁷⁵ The protect quinoline **73** displayed a melting point (181-185 °C) consistent with the literature value (181-184 °C)³⁴ and was prepared in moderate yield (44%). The IR spectrum showed a peak at 1693 cm⁻¹ that corresponds to the carbonyl of the acetamide functionality.



Scheme 29: Synthesis of **73** and **69**.

The ¹H NMR spectrum showed the appearance of a methyl peak at δ_{H} = 2.20 ppm and a broadened peak corresponding to the NH at δ_{H} = 9.18 ppm. The signal for H3 was also shifted downfield due to an anisotropic deshielding from the acetamido group at the 2-position (c.f. **70** δ_{H} = 7.35 ppm; **73** δ_{H} = 8.39 ppm). In addition, the signal for H3 was broadened due to intermediate exchange. This broadening of the signal for H3 has been observed in several other quinolin-2-yl acetamides. The broadening occurs because a number

of resonance contributors give rise to a partial double bond within the acetamido group (Figure 43). There are four possible conformations of the acetamide functionality and each of these conformations results in a different chemical environment, and therefore a different chemical shift for the signal of H3. The partial double bond character in the acetamide group means that the rotation of the bond that gives rise to the different conformations occurs slowly and therefore **73** enters into intermediate exchange.

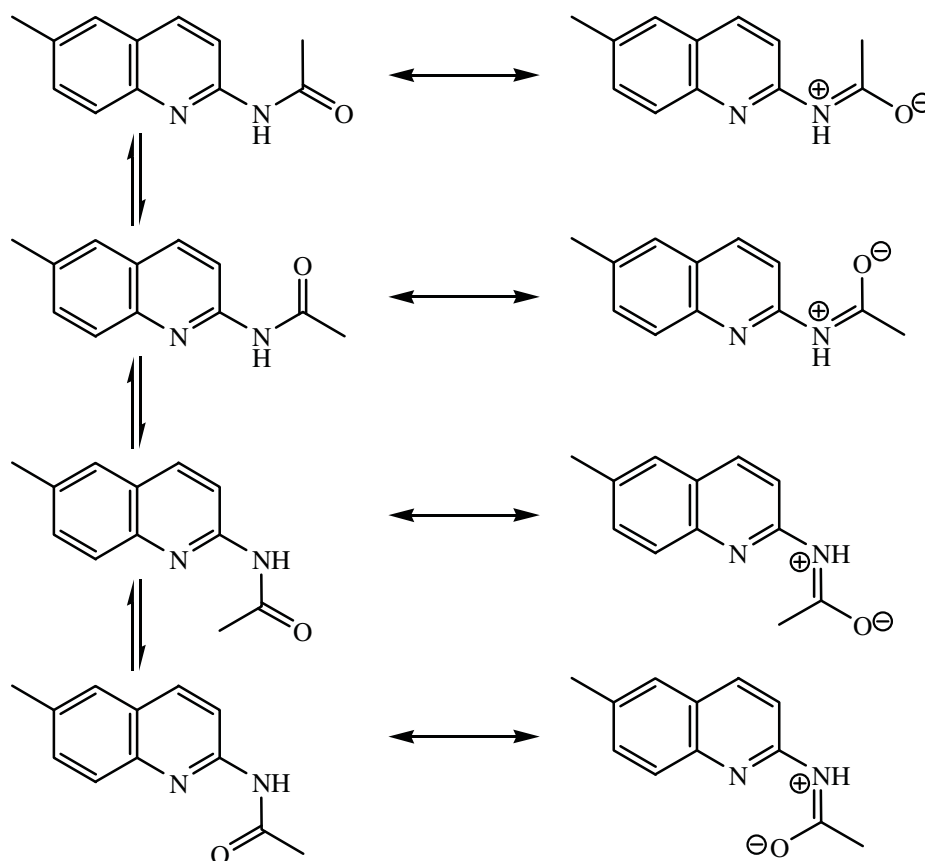
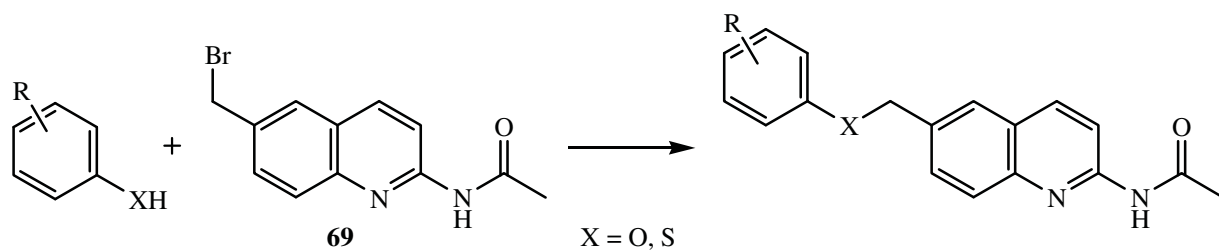


Figure 43: The resonance contributors which afford the broadened signal for H3 in the ^1H NMR spectrum of **73**.

Compound **73** was then converted to the 6-bromomethyl-substituted quinoline derivative **69** through a radical bromination reaction employing *N*-bromosuccinamide (Scheme 29). This reaction afforded **69** in good yield (63%) and the melting point (183-186 °C) was consistent with the literature value (185-187 °C).³⁴ The benzylic hydrogens showed a downfield shift (c.f. **73** $\delta_{\text{H}} = 2.51$ ppm; **69** $\delta_{\text{H}} = 4.65$ ppm) in the ^1H NMR spectrum consistent with the introduction of an electron withdrawing bromine functionality.

Having prepared **69**, it was possible to prepare a range of 6-substituted derivatives using a simple substitution reaction involving either a phenol or a thiophenol (Scheme 30).



Scheme 30: Synthesis of 6-substituted-2-acetamidoquinolines. Reaction conditions: K_2CO_3 and acetonitrile at reflux.

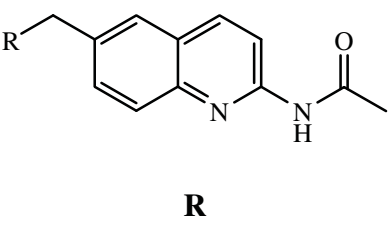
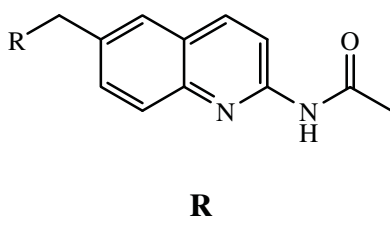
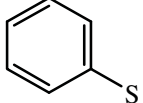
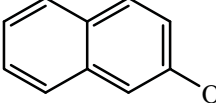
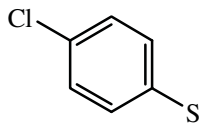
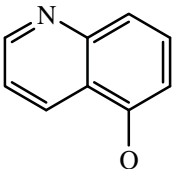
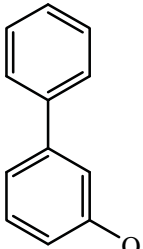
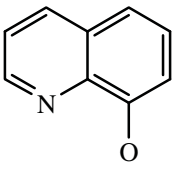
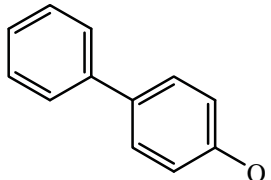
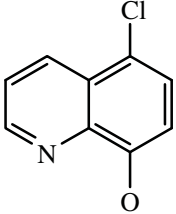
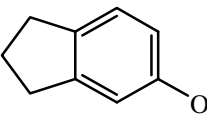
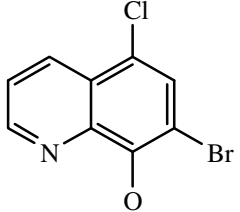
A series of 6-phenoxyethyl-2-acetamidoquinolines **74-85** containing mono and di-substitution on the phenoxy functionality were prepared using this method and were isolated in moderate to high yield (50-94%, see Table 22).

Table 22: Isolated yields of 6-phenoxyethyl-2-acetamidoquinolines **74-85**.

		Yield (%)		Yield (%)	
74		82	80		72
75		81	81		85
76		90	82		50
77		58	83		60
78		88	84		94
79		68	85		82

In addition to these, a number of 2-acetamidoquinolines with alternate substitution at the 6-position, including thiophenols, phenylphenols, quinolinol and indanol derivatives, were also prepared (see Table 23). The 2-acetamidoquinolines **86-95** were isolated in varying yields (25-97%).

Table 23: Isolated yields of 6-aryloxymethyl- and 6-arylthiomethyl-2-acetamidoquinolines **86-95**.

	Yield (%)		Yield (%)
R		R	
86 	83	91 	41
87 	97	92 	40
88 	71	93 	25
89 	82	94 	53
90 	38	95 	81

In the preparation of **88**, the reaction was carried out with commercial 3-phenylphenol which was purchased as a mixture with 4-phenylphenol (85% 3-phenylphenol). It was hoped that the reaction could be carried out with the mixture of phenols and that the desired (3-phenylphenoxy)methyl substituted compound could be separated from the

(4-phenyphenoxy)methyl compound. The reaction was successful and both products were identified in the crude material. Attempts to separate these compounds were however unsuccessful and the desired (3-phenylphenoxy)methyl product **88** was isolated as a 9:1 mixture with the (4-phenylphenoxy)methyl product **89**. An elemental analysis was obtained of this mixture, which was consistent with the elemental composition confirming the purity. Since separation could not be achieved at this stage the mixture was carried through to the next step in the hope that these products would be able to be separated.

A high resolution mass spectrum consistent with the calculated mass and/or an elemental analysis consistent with the theoretical composition of the desired product was obtained for each 6-substituted-2-acetamidoquinoline. The low resolution mass spectra for each compound showed characteristic fragmentations. All compounds showed a peak at 199 mass units corresponding to the loss of the aryloxy or arylthio functionality. In addition, a peak at 157 mass units was also observed for all compounds and is the result of a McLafferty style rearrangement of the above daughter ion (Figure 44).

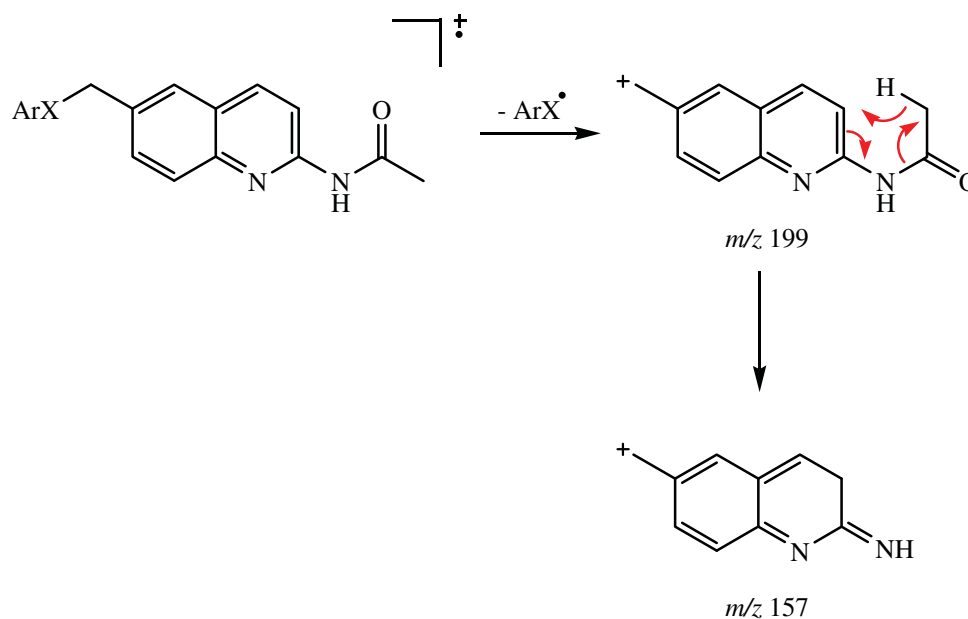


Figure 44: Characteristic cleavages from the mass spectra of 6-aryloxymethyl- and 6-arylthiomethyl 2-acetamidoquinolines.

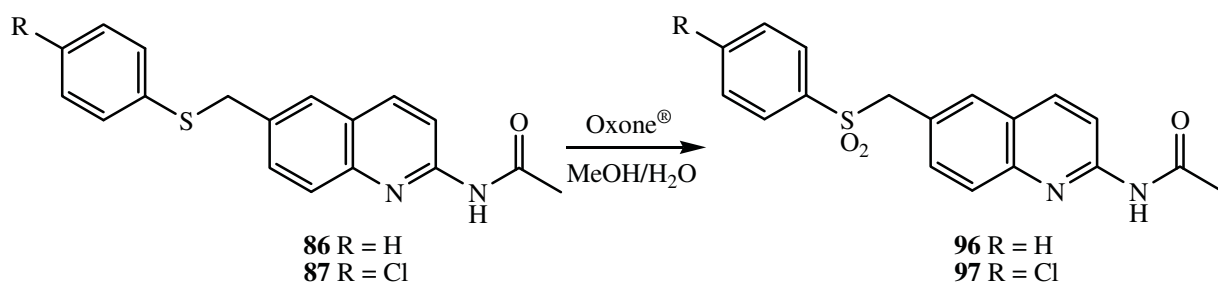
The ^1H NMR spectra of these derivatives displayed peaks corresponding to the new aromatic substituent at the 6-position and also showed a shift of the signal for the methylene hydrogens (see Table 24). For the majority of compounds a downfield shift in the signal for the methylene hydrogens was observed to the range of $\delta_{\text{H}} = \sim 5.20\text{-}5.30$ ppm (c.f. **69** $\delta_{\text{H}} = 4.65$

ppm). This downfield shift is consistent with the increased electronegativity of the oxygen in the substituent relative to the bromine functionality. A further downfield shift of the signal for the methylene hydrogens ($\delta_{\text{H}} = \sim 5.34\text{-}5.58$ ppm) was observed for compounds containing highly electronegative groups on the aromatic ring of the substituent (including **74** and **80**) and for the bulkier naphthyl and quinolyl substituents (including **91** and **95**). On the other hand, for compounds **86** and **87** an upfield change in chemical shift was observed. This is due to the sulfur in the linker of the substituent and is a result of the reduction in electronegativity of the sulphur relative to the bromine.

Table 24: Comparison of methylene hydrogens chemical shifts in compounds **74-95**.

	$\delta_{\text{H}} \text{CH}_2$		$\delta_{\text{H}} \text{CH}_2$
74	5.34	85	5.21
75	5.27	86	4.24
76	5.17	87	4.22
77	5.20	88	5.35
78	5.21	89	5.26
79	5.20	90	5.18
80	5.63	91	5.38
81	5.29	92	5.42
82	5.22	93	5.59
83	5.22	94	5.58
84	5.28	95	5.63

The 6-arylthiomethyl compounds **86** and **87** were oxidised to the corresponding sulfonyl compounds **96** and **97** respectively (see Scheme 31), by treatment with Oxone[®] in a solution of methanol:water. Using this method the desired products were prepared in moderate yield (**96** 78% and **97** 53%). The ¹H NMR spectra of both compounds showed a small downfield shift in the signal for the methylene hydrogens and also the signals for the aromatic hydrogens (*ortho* and *para* in the case of **96** and *ortho* in the case of **97**) confirming the oxidation of the thioether (see Table 25). A high resolution mass spectrum was obtained for both compounds and was consistent with the mass of the desired sulfonyl compound. Furthermore, the low resolution mass spectra showed the characteristic fragmentations described previously with peaks observed at 199 and 157 mass units.

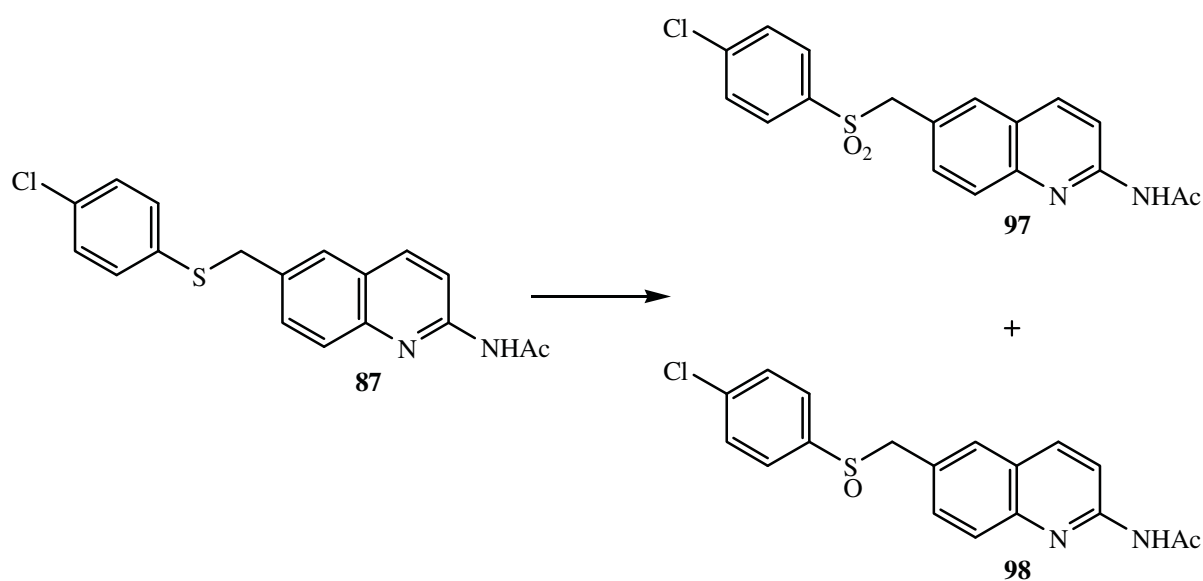


Scheme 31: Oxidation of 6-arylthiomethyl-2-acetamidoquinolines.

Table 25: Comparison of methylene and aromatic hydrogen chemical shifts.

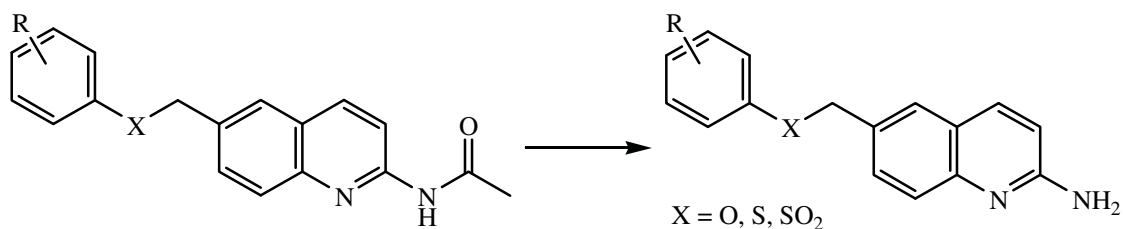
	$\delta_{\text{H}} \text{CH}_2$	$\delta_{\text{H}} \text{H}(2'/6')$	$\delta_{\text{H}} \text{H}4'$
86	4.24	7.49	7.22
96	4.47	7.65	7.59
87	4.22	7.20	-
97	4.47	7.56	-

In the oxidation reaction of **87** the corresponding sulfinyl compound **98** was also isolated (see Scheme 32). An elemental analysis was obtained for this compound, which was consistent with the theoretical molecular composition. The low resolution mass spectrum once again showed the characteristic fragmentations with peaks being observed at 199 and 157 mass units.



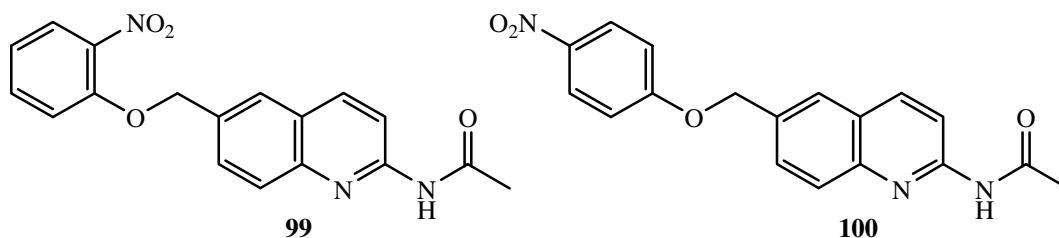
Scheme 32: Oxidation of **87**. Reaction conditions: Oxone[®], methanol:H₂O.

Having prepared a variety of 6-substituted-2-acetamidoquinolines, the final step in the synthesis of these types of ligands, was the removal of the protecting acyl group to provide the free 2-amino functionality (Scheme 33).



Scheme 33: Preparation of 6-substituted-2-aminoquinolines by deprotection of 6-substituted-2-acetamidoquinolines. Reaction conditions; K₂CO₃, methanol.

Treatment of the 6-substituted-2-acetamidoquinolines **74-97** prepared above and two additional compounds **99** and **100**** with an excess of K₂CO₃ in methanol at 60 °C afforded the desired 2-aminoquinoline ligands **101-126** in moderate to quantitative yield (45-97%, see Table 26 and Table 27), except in the case of **80** in the attempted synthesis of **109**.



** Compounds **99** and **100** were provided by Martina Marinkovic.

Table 26: Isolated yields of 6-phenoxyethyl-2-aminoquinolines **101-114**.

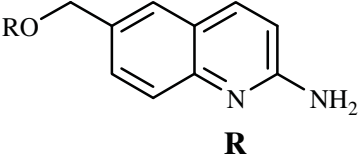
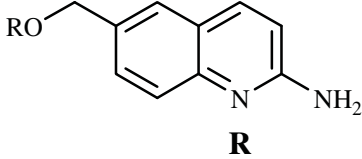
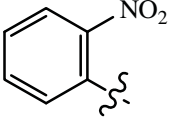
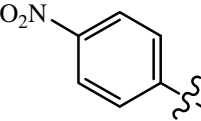
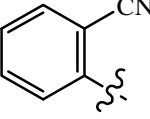
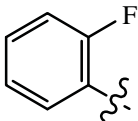
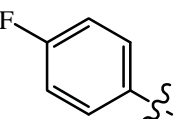
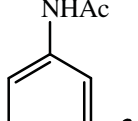
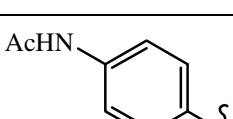
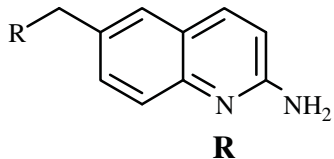
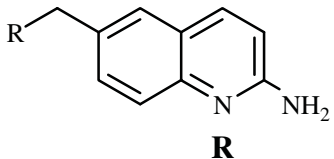
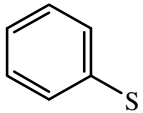
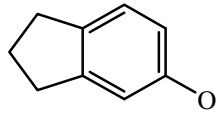
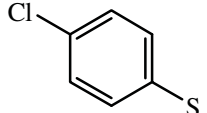
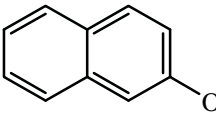
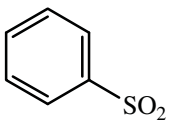
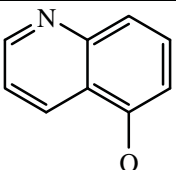
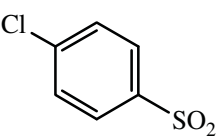
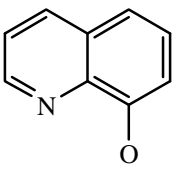
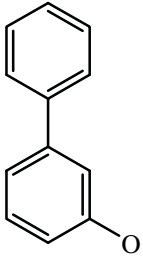
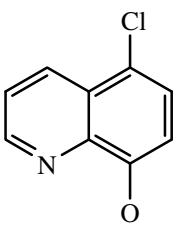
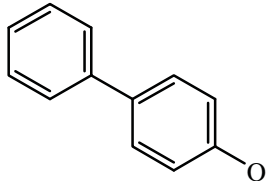
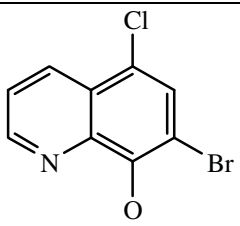
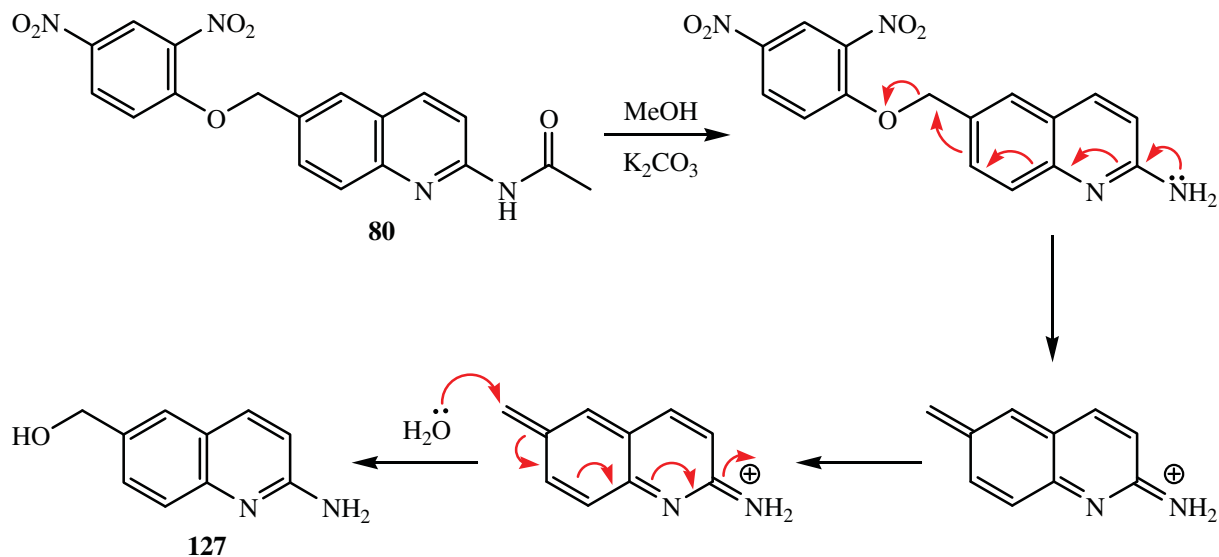
		Yield (%)		Yield (%)
101		76	108	79
102		52	109	0
103		77	110	98
104		92	111	78
105		79	112	73
106		68	113	90
107		59	114	91

Table 27: Isolated yields of 6-aryloxymethyl- and 6-arylthiomethyl-2-aminoquinolines **115-126**.

 R	Yield (%)	 R	Yield (%)
115 	97	121 	72
116 	70	122 	49
117 	93	123 	80
118 	93	124 	70
119 	84	125 	70
120 	45	126 	60

Treatment of **80** with K_2CO_3 in methanol however, did not afford the desired 2-aminoquinoline compound but rather 6-(hydroxymethyl)quinoline-2-amine **127** was isolated in 66% yield. The formation of this product is likely due to the resonance electron donating effect of the amino group at the 2-position after deprotection of the acetamide. This resonance effect can cause the displacement of the 2,4-dinitrophenolate anion resulting in an activated alkene intermediate which is susceptible to attack by water and would result in the formation of **127** (see Scheme 32). This occurs when 2,4-dinitrophenol is the substituent

because the two electron withdrawing nitro groups stabilise the phenoxide anion that is formed, therefore making this reaction more favourable.



Scheme 34: Proposed mechanism for the formation of **127**.

Quinoline **127** displayed a melting point (215-219 °C) consistent with the literature (210-220 °C)³⁴ and characteristic signals in the ¹H NMR spectrum were also observed. Specifically, a broad doublet at $\delta_{\text{H}} = 4.54$ ppm and a broad triplet at $\delta_{\text{H}} = 5.17$ ppm were observed corresponding to the methylene hydrogens and the hydroxyl group respectively. The acetyl methyl signal from the acetamide protecting group was no longer present and a broad singlet was observed for the amino functionality at the 2-position. The characterisation of this compound was also confirmed by 2D NMR analysis including ROESY, COSY, HMBC and HMQC.

In most cases for the deprotection step, an elemental analysis of the product was obtained which was consistent with the elemental composition of the desired product. In those instances where an elemental analysis could not be obtained a high resolution mass spectrum was obtained and was consistent with the mass of the desired product. The low resolution mass spectrum for all products showed a characteristic fragmentation at 157 mass units, which results from the loss of the aryloxy or arylthio substituent as shown in Figure 45.

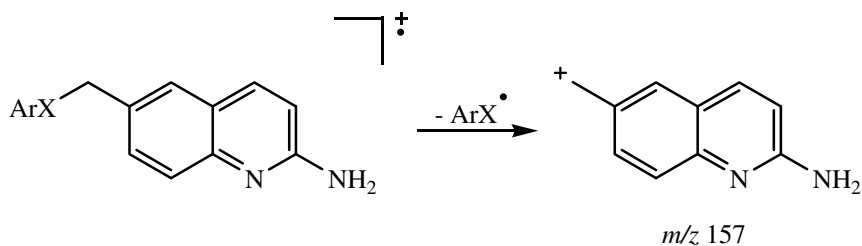


Figure 45: Characteristic fragmentation of 6-substituted-2-aminoquinolines resulting in the ion m/z 157 in the low resolution mass spectrum.

The ^1H NMR spectrum for each of the compounds showed very little change in the signals corresponding to the hydrogens of the aryloxy or arylthio substituent. The signal for H4 of the quinoline was observed to shift upfield slightly (from $\delta_{\text{H}} = \sim 8.03\text{--}8.37$ ppm to $\delta_{\text{H}} = \sim 7.79\text{--}7.94$ ppm) and the signal for H3 shifted significantly upfield (from $\delta_{\text{H}} = \sim 8.28\text{--}8.51$ ppm to $\delta_{\text{H}} \sim 6.71\text{--}6.81$ ppm). The upfield shift of the signals corresponding to H3 occurs as a result of the resonance donation of the lone pair of electrons on the amino group. In the protected compounds, the lone pair of electrons is involved in the partial double bond (shown in Figure 43) which upon deprotection are able to donate into the quinoline ring system and therefore shield the hydrogen at H3 (Figure 46). The ^1H NMR spectra also no longer displayed signals corresponding to the methyl of the protecting group and the ^{13}C NMR spectra similarly did not show signals for the methyl and the carbonyl peak at $\sim \delta_{\text{C}} = 170$ ppm was also no longer present confirming the deprotection of the acetamide functionality.

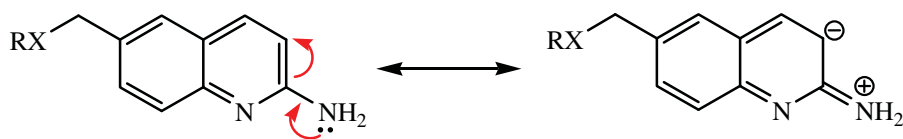


Figure 46: The resonance donation of the lone pair of electrons of the amino functionality which shields the H3 hydrogens in the ^1H NMR spectra of compounds **101-126**.

As mentioned above, **88** could not be completely purified and was obtained as a mixture with the (4-phenylphenoxy)methyl equivalent **89**. Treatment of this mixture with K_2CO_3 produced a mixture of the two deprotected compounds **119** and **120** as expected. Attempts to separate this mixture or at least provide a small amount of the desired pure product **119** included numerous attempts at flash chromatography and recrystallisation. None of these were

however successful and **119** was obtained as a 7:1 mixture with the (4-phenylphenoxy)methyl equivalent **120** which was used in the NMR assay for the determination of binding affinity. Results of the binding studies of the ligands **101-126** prepared in this chapter will be discussed in Chapter 5.

Chapter 4: SYNTHESIS OF EXTENDED 6-PHOXYMETHYL-2-AMINOQUINOLINES

4.1 Introduction

Having prepared both the 6-heterocyclic-2-aminoquinolines and the 6-phenoxyethyl-2-aminoquinolines it was hoped that both concepts of these ligands could be combined in an extended ligand (Figure 47). These ligands would have a much larger substituent in the 6-position, which could potentially provide further contacts with the protein surface and provide for high affinity ligands. A number of these ligands were prepared and assayed for binding affinity with the Tec SH3 domain. The development of the synthetic pathway required to prepare these ligands is presented in this chapter.

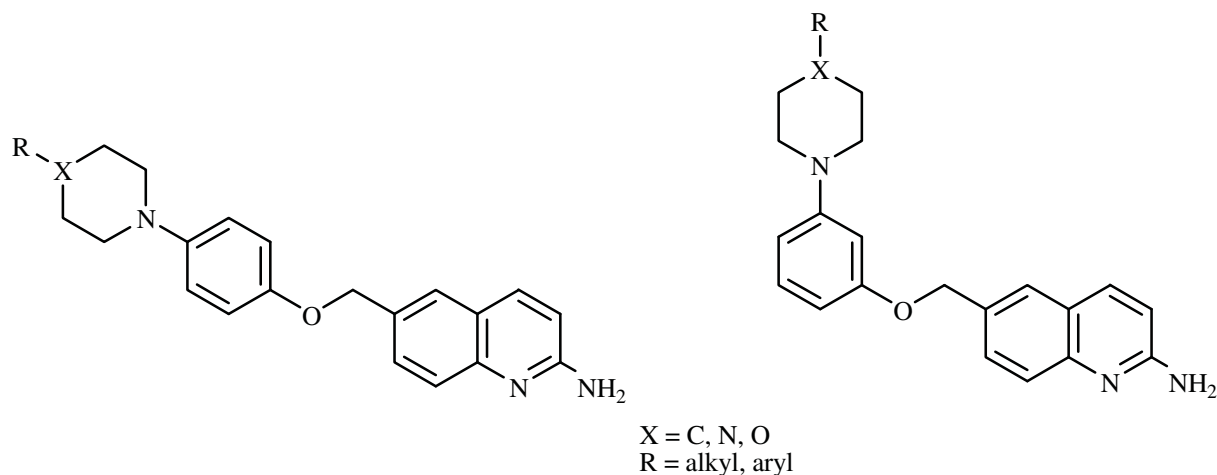


Figure 47: Extended 6-substituted-2-aminoquinoline target ligands.

4.2 Synthesis of Extended 6-Phenoxyethyl-2-Aminoquinolines

4.2.1 Synthetic Scheme for the Preparation of Extended 6-Phenoxyethyl-2-Aminoquinolines

To prepare the extended 6-substituted ligands, a similar approach to the preparation of 6-phenoxyethyl-2-aminoquinolines was used and the synthetic pathway employed is shown below in Figure 48. In this pathway, the desired ligands are prepared from precursor **69** in a substitution reaction with a range of substituted phenols. These phenols can be prepared from 3- or 4-bromophenol and an appropriate amine using Buchwald-Hartwig chemistry. Simple removal of the 2-acyl protecting group would again provide the desired 6-substituted-2-aminoquinolines.

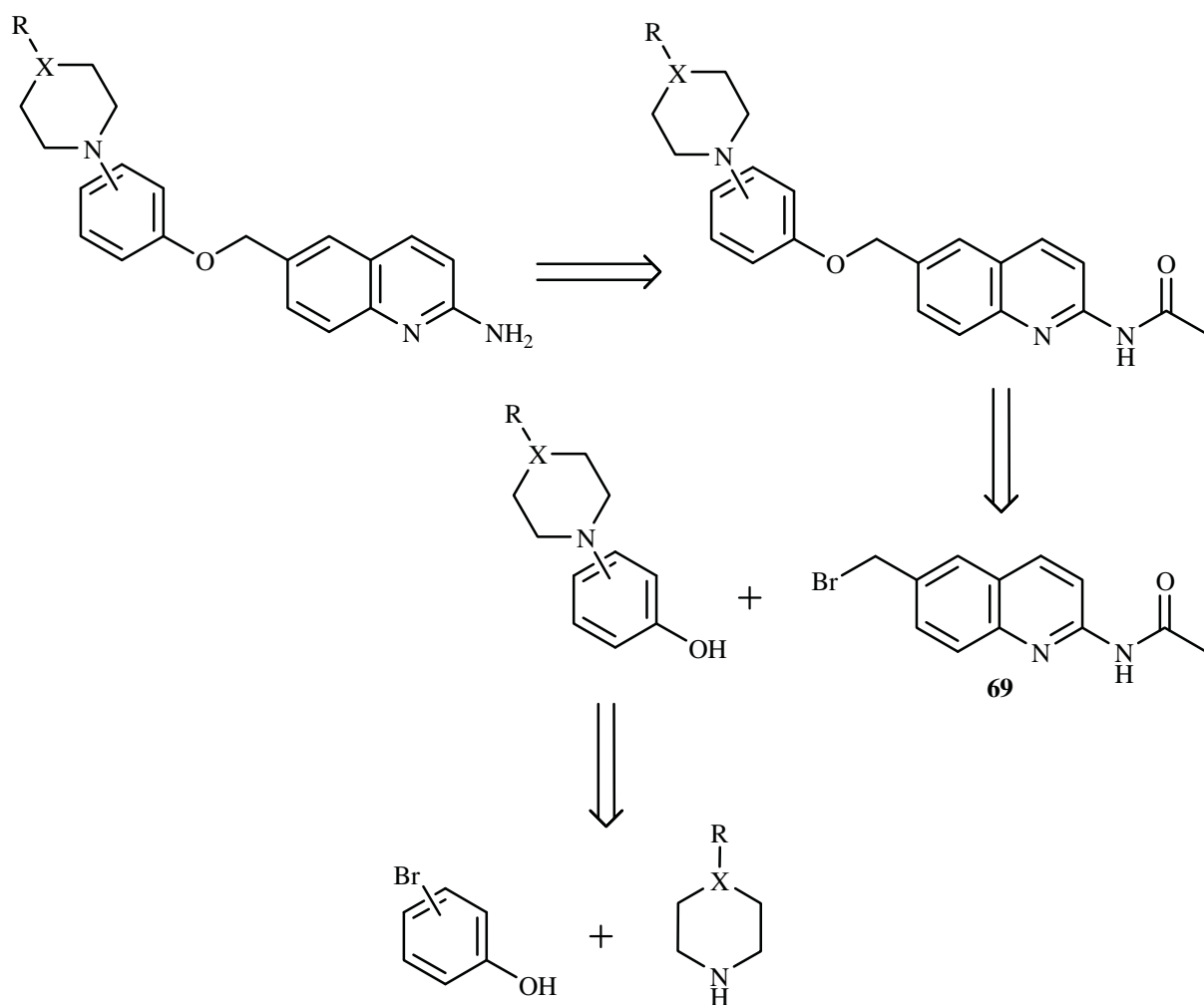
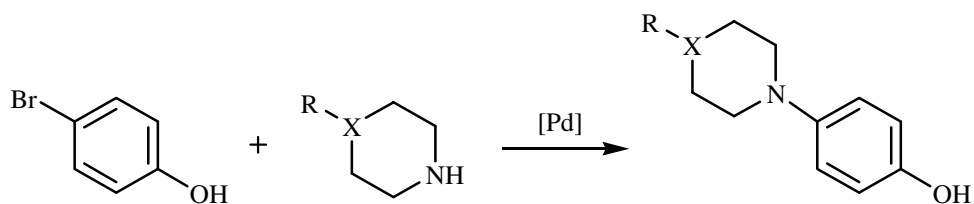


Figure 48: The retro-synthetic pathway for the preparation of extended 6-substituted-2-aminoquinolines.

4.2.2 Synthesis of Phenols

4.2.2.1 Synthesis of 4-Heterocyclic-Phenols

To prepare the desired 4-substituted phenols, Buchwald-Hartwig chemistry was once again employed. It was envisaged that the desired substituted phenols could be prepared from 4-bromophenol and a range of amines without the need for a protecting group (see Scheme 35). It was thought that the conditions developed for previous Buchwald-Hartwig aminations would not be suitable for this particular Buchwald-Hartwig amination, due to the use of the base NaO^tBu. Strong bases such as NaO^tBu are typically not suitable in Buchwald-Hartwig aminations with substrates containing base sensitive functional groups, including ester, amide, hydroxyl and nitro functionality.⁴³ The suggested reason for this functional group incompatibility is that under the reaction conditions the base sensitive functionality becomes deprotonated and binds to the palladium catalyst preventing the desired reaction from occurring.⁶¹



Scheme 35: Proposed method for the preparation of 4-substituted phenols.

There have recently been a few reports demonstrating the use of LHMDS as an alternate base for Buchwald-Hartwig aminations.^{61,100} A report by Buchwald *et al*⁶¹ demonstrated the use of this base in the amination reactions of aryl halides containing hydroxyl, amide and enolizable keto groups without the need for protecting groups (see Figure 49). In these reactions bulky biphenyl ‘Buchwald’ ligands (described in Chapter 2) were employed to carry out these aminations and the desired products were obtained in high yield. An additional report by Urgaonkar and Verkade⁶² also demonstrated the use of LHMDS as a base in reactions with similar aryl halides with the proazaphosphatrane ligand P(^{*t*}BuNCH₂CH₂)₃N.

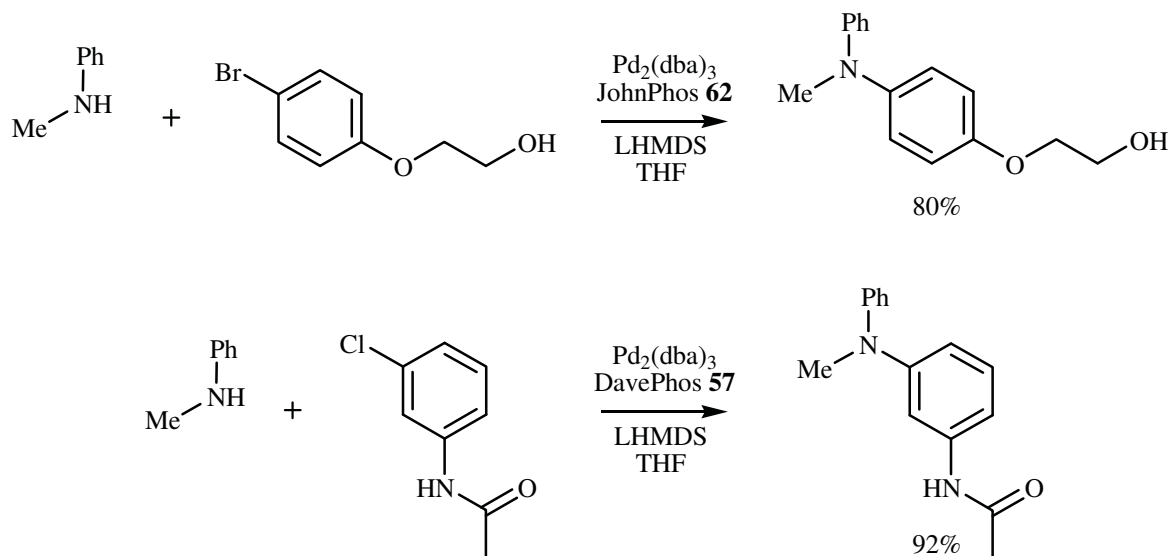


Figure 49: Example reactions carried out by Buchwald *et al*⁶¹ using LHMDS as a base in Buchwald-Hartwig aminations.

In addition, these reports provided a couple of examples of the preparation of 4-heterocyclic substituted phenols from a phenolic substrate without the need for a protecting group (see Figure 50 for examples).^{61,62} Both of these reports employed different catalytic systems however, the substituted phenols were obtained in high yield.

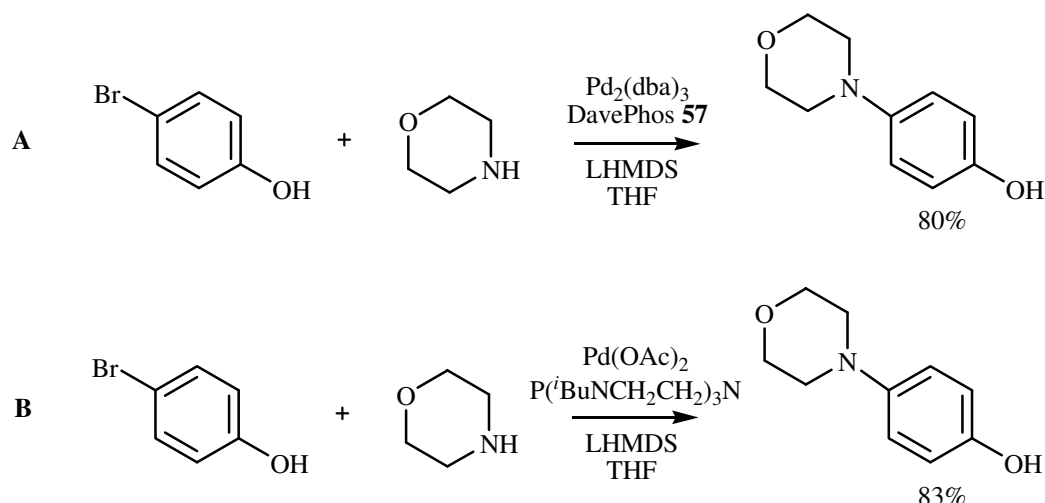


Figure 50: Examples of reaction conditions reported (A) by Buchwald *et al*⁶¹ and (B) Urgaonkar and Verkade⁶² for the preparation of 4-heterocyclic phenols using Buchwald-Hartwig chemistry.

A further search of the literature provided only one other reference by Hartwig *et al*¹⁰¹ for the palladium catalysed synthesis of 4-substituted phenols from a phenolic substrate. The two examples of 4-substituted phenols in this report were prepared from 4-chlorophenol and primary amines and were obtained in good yield. LHMDS was once again employed as the base, however, the catalytic system in this case consisted of Pd(OAc)₂ and the ferrocene ligand, Josiphos (Figure 51).

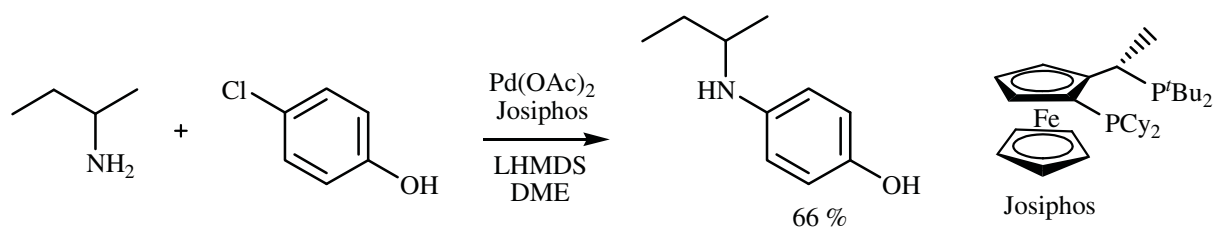
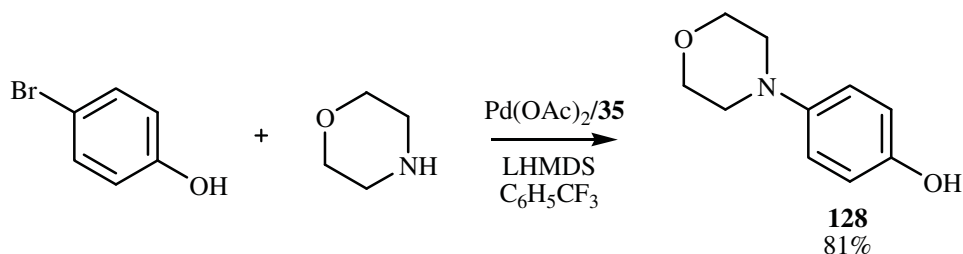


Figure 51: Reaction conditions reported for the preparation of 4-substituted phenols using the Josiphos ligand.¹⁰¹

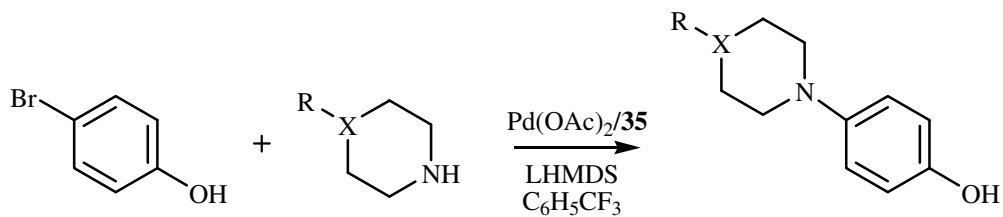
The ability of LHMDS to act as a superior base in these cases is likely to be due to the ability of the LHMDS to block the sensitive functionality as discussed in Section 2.2. In the literature methods mentioned above, 2.2-2.4 equivalents of LHMDS were employed and it is thought that the first equivalent of LHMDS acts to block the phenol whilst the remaining equivalents of LHMDS act as a base and deprotonate the amine in the desired Buchwald-Hartwig reaction.

The use of LHMDS as a base for the preparation of the desired phenols in this particular case was therefore examined with $\text{Pd}(\text{OAc})_2$ and CataCXium[®] A ligand **35** in trifluoromethylbenzene due to the success of these conditions in previous Buchwald-Hartwig aminations. In this work, the reaction of 4-bromophenol with morpholine was initially investigated to allow for a comparison of the proposed method with the two literature methods (see Scheme 36). The reaction of 4-bromophenol with morpholine in the presence of 2.4 equivalents of LHMDS and $\text{Pd}(\text{OAc})_2$ /**35** was successful and afforded the desired product **128** in 81% yield. This yield is equivalent to the yields obtained by Buchwald *et al*⁶¹ and Urgaonkar and Verkade⁶² (80% and 83% respectively) and indicated that these conditions would be suitable for the preparation of 4-heterocyclic substituted phenols.



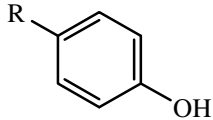
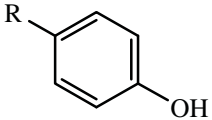
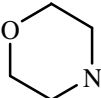
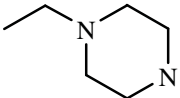
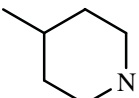
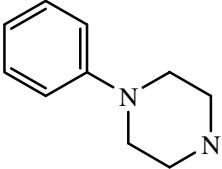
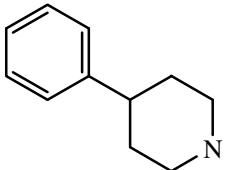
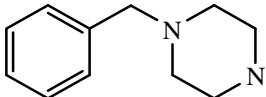
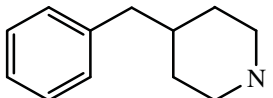
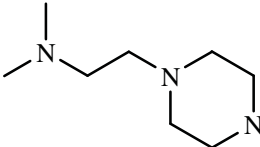
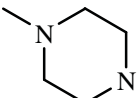
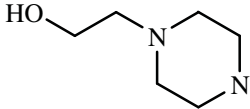
Scheme 36: Synthesis of **128**.

The conditions described above were employed for the preparation of a number of 4-substituted phenols. The reaction of 4-bromophenol with a range of amines was successful in affording the desired 4-heterocyclic substituted phenols **129-136** in all cases except when 4-(2-hydroxyethyl)piperazine was employed as the amine in the attempted synthesis of **137** (see Scheme 37 and Table 28). The yield obtained of the desired phenols was typically between ~ 50-80% except in a couple of instances where low yields of ~ 20-30% were obtained. In these cases, the conversion of 4-bromophenol to the substituted product occurred in reasonable yield, however, substantial difficulties in the purification of the phenols resulted in lower isolated yields.



Scheme 37: Synthesis of 4-heterocyclic substituted phenols using Buchwald-Hartwig chemistry.

Table 28: Isolated yields of 4-heterocyclic phenols.

 R	Yield (%)	 R	Yield (%)
 128	81	 133	59
 129	81	 134	23
 130	43	 135	27
 131	69	 136	46
 132	57	 137	0

The ^1H NMR spectra of these compounds showed characteristic features for the newly formed 4-heterocyclic phenol. Specifically the signals corresponding to the heterocycle were observed along with an upfield shift in the signals for the H3 and H5 hydrogens of the aromatic ring (from $\delta_{\text{H}} = 7.31$ ppm in 4-bromophenol to $\delta_{\text{H}} = 6.81$ -6.96 ppm). This upfield shift results from the introduction of the electron donating heterocyclic nitrogen atom at C4.

Elemental analyses for all compounds excluding **128**, **132** and **135** were obtained and were consistent with the elemental composition of the desired product in each instance. For **135**, a high resolution mass spectrum consistent with the molecular mass of the desired product was

obtained instead of an elemental analysis. Phenols **128**^{62,102} and **132**⁶² have been previously reported and both displayed ¹H NMR spectroscopic data consistent with that in the literature. Phenol **128** also displayed a melting point (165-168 °C) similar to the literature value (174-176 °C),¹⁰² however, no literature melting point for **132** was reported. The low resolution mass spectrum of these compounds showed a characteristic peak at 148 mass units. This peak results from the partial cleavage of the heterocyclic substituent as shown in Figure 52. The IR spectrum of these compounds also showed an absorption in the region of 3300-3500 cm⁻¹ corresponding to the phenoxy functionality.

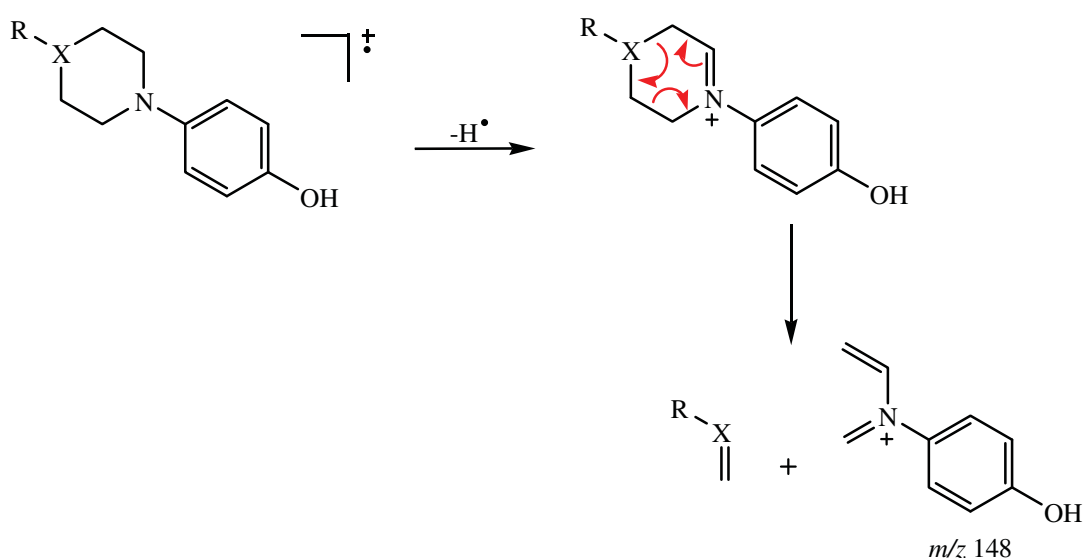
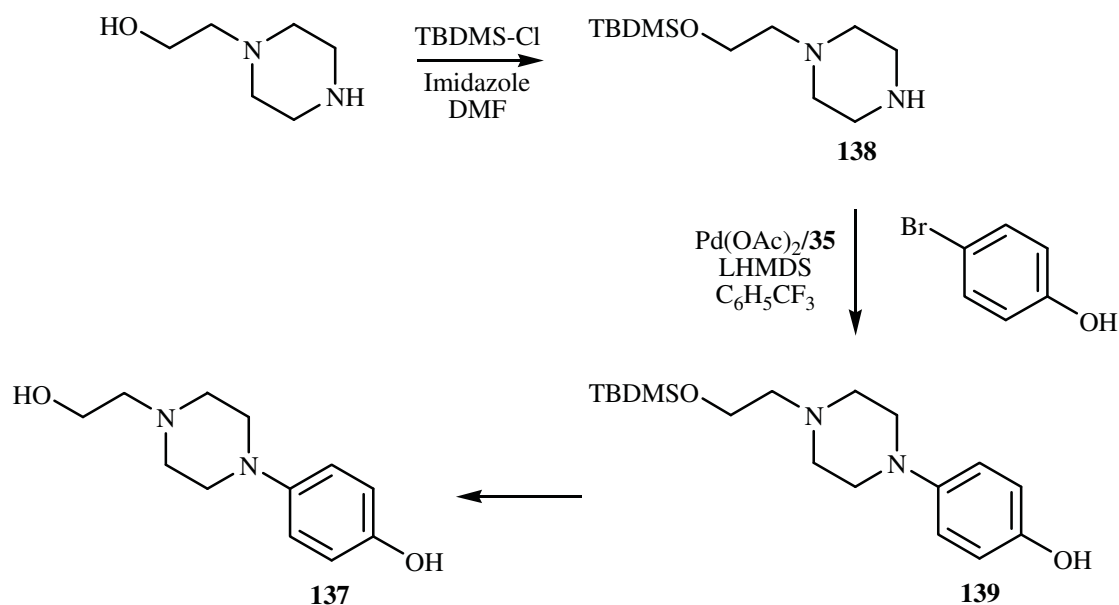


Figure 52: Characteristic cleavage of the 4-substituted phenols.

As mentioned above, when 4-(hydroxyethyl)piperazine was employed as the amine none of the desired product **137** was observed and only starting material was recovered. This result is likely to be due to the free hydroxyl functionality coordinating to the palladium catalyst and thereby preventing the formation of the desired product. It was thought that protection of the hydroxyl functionality as a silyl ether in **138** would allow for this heterocycle to be coupled to 4-bromophenol and afford the protected substituted phenol **139**. Removal of the protecting group would then provide the desired phenol **137** (Scheme 38).



Scheme 38: Proposed scheme for the preparation of **137**.

To protect the hydroxyl functionality of the heterocycle as the *tert*-butyldimethylsilyl ether, 4-(hydroxyethyl)piperazine was treated with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole in DMF.¹⁰³ ^1H NMR analysis of the product obtained from this reaction indicated that the hydroxyl functionality had been successfully protected as the silyl ether as evidenced by the signals at $\delta_{\text{H}} = 0.07$ ppm and 0.90 ppm, corresponding to the two methyl groups and the *tert*-butyl group respectively (see Figure 53). In addition, six triplet signals were observed in the region of $\delta_{\text{H}} = 2.44$ -3.71 ppm and a broad singlet at $\delta_{\text{H}} = 7.95$ ppm was also observed. The presence of six triplet signals was surprising as the desired product would be expected to display only four triplet signals in the ^1H NMR spectrum due to the symmetry of the piperazine ring. The broad singlet at $\delta_{\text{H}} = 7.95$ ppm was also surprising as the signal for the amino functionality was not expected to experience such a downfield shift. The ^1H NMR spectrum therefore did not appear to be consistent with the formation of the desired product **139**.

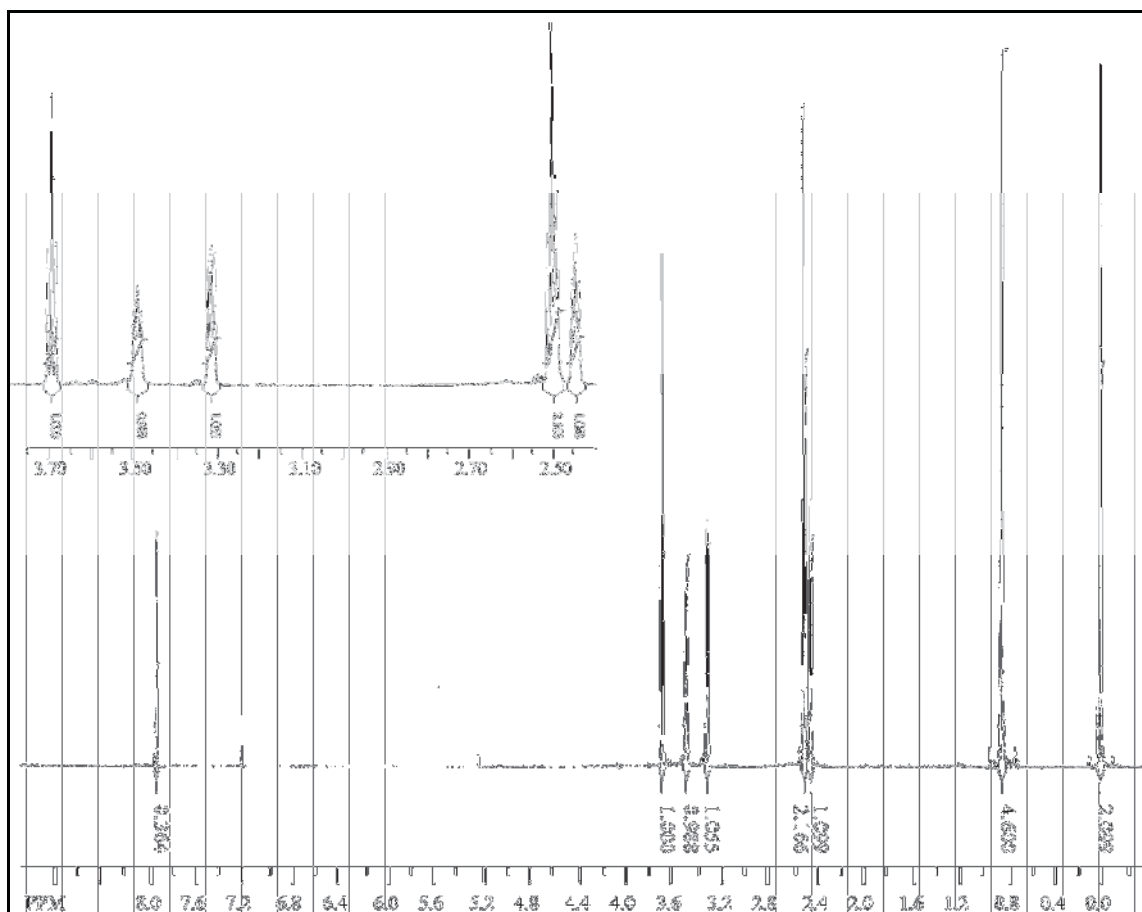
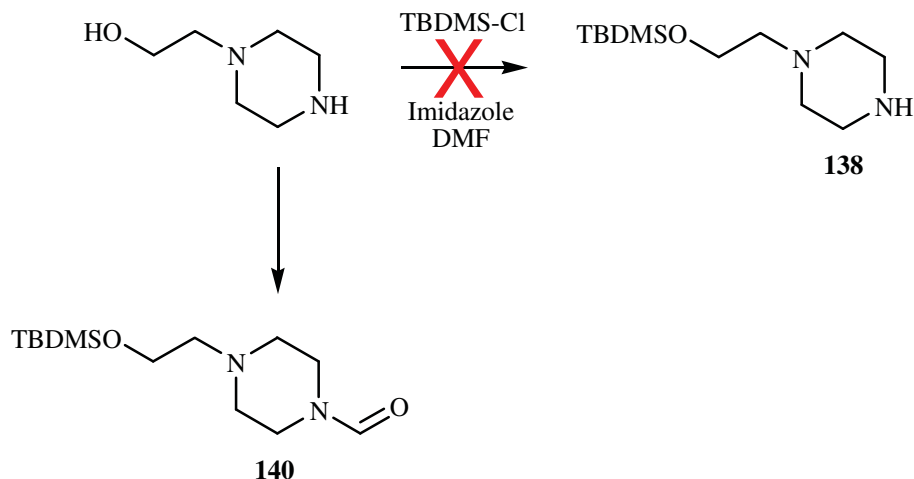


Figure 53: ^1H NMR spectrum of the product from the reaction of 4-(hydroxyethyl)piperazine and TBDMS-Cl.

The ^{13}C NMR spectrum was also not consistent with the formation of the desired product. Six signals were observed in the region of $\delta_{\text{C}} = \sim 40\text{-}60$ ppm and suggested that the piperazine ring was no longer symmetrical. An additional signal was also observed at $\delta_{\text{C}} = 160$ ppm indicating the presence of a carbonyl functionality. This was likely to be a formamide group given the broad singlet observed at $\delta_{\text{H}} = 7.95$ ppm in the ^1H NMR spectrum. Given that the piperazine appeared to contain a formamide functionality and a silyl protected hydroxyl group the unknown product was proposed to be the protected formamide **140** (see Scheme 39). The protected formamide **140** would be expected to be unsymmetrical due to the delocalisation of the nitrogen lone pair of electrons onto the carbonyl, resulting in partial double bond character and preventing free rotation about the carbon-nitrogen bond. This would mean that the methylene hydrogens of the heterocycle on the same side as the carbonyl would experience anisotropic deshielding and would no longer be equivalent to the methylene hydrogens on the opposite side of the heterocycle.



Scheme 39: Attempted synthesis of the protected phenol **138** and the formation of **140**.

The formation of this product is rationalised as the product from the reaction of the amine with the solvent, DMF. A proposed mechanism for this reaction is shown below and would involve the attack of the protected amine on the carbonyl of DMF, with subsequent elimination of dimethylamine (see Figure 54).

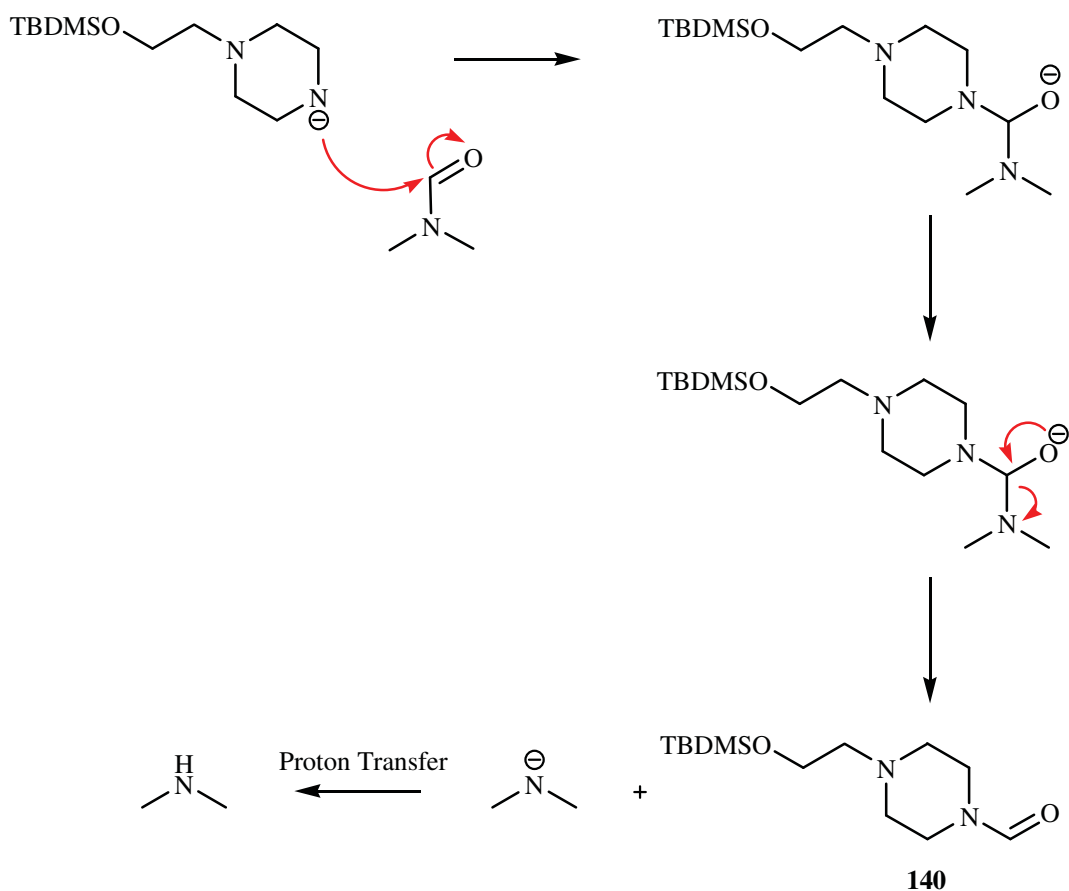


Figure 54: Proposed mechanism for the formation of **140**.

The IR spectrum of this product displayed a characteristic signal at 1673 cm^{-1} corresponding to the formamide functionality. In addition, the low resolution mass spectrum showed a signal at 215 mass units which would result from the loss of the *tert*-butyl group from the silyl protecting group (Figure 55).

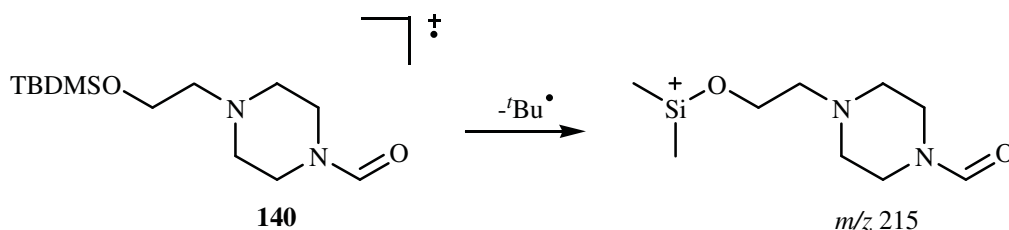


Figure 55: Fragmentation of **140** that results in the peak at *m/z* 215.

The use of 2D NMR spectroscopy, including ROESY, COSY, HSQC and HMBC, was also employed to characterise the product. Evidence confirming the formation of **140** included the six triplet signals observed in the ^1H NMR spectrum. Four of these signals were broadened and corresponded to the methylene hydrogens of the piperazine. Each of the piperazine signals displayed a unique chemical shift in the ^{13}C NMR spectrum confirming the loss of symmetry and the formation of the formamide **140**. The ROESY spectrum displayed a correlation between the formamide hydrogen and one of the methylene signals of the piperazine ring. The HMBC spectrum also showed correlations between the formamide hydrogen and the carbons of the nearby methylene groups of the piperazine (see Figure 56).

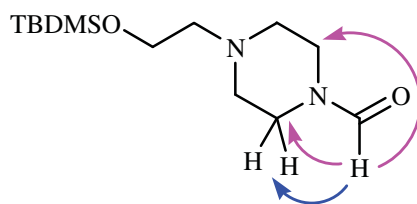
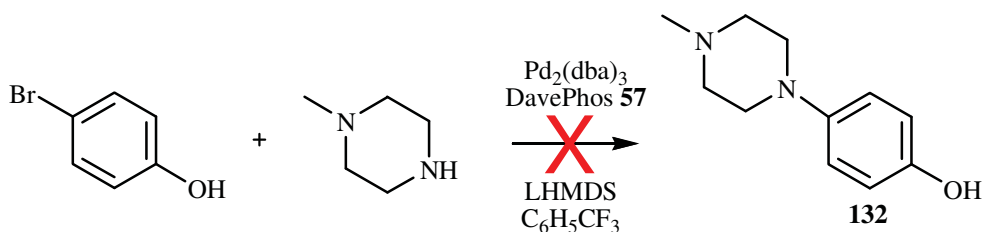


Figure 56: ROESY correlation between the formamide hydrogen and the methylene hydrogens of the piperazine in **140** (shown in blue). HMBC correlations between the formamide hydrogen and the methylene carbons in **140** (shown in pink).

To allow for comparison of the catalytic system $\text{Pd}(\text{OAc})_2/\mathbf{35}$ with the catalyst reported by Buchwald *et al.*,⁶¹ the reaction of 4-bromophenol with 1-methylpiperazine was also carried out with $\text{Pd}_2(\text{dba})_3$ and DavePhos **57** in trifluoromethylbenzene (Scheme 40). In this particular reaction, no palladium catalysed coupling was observed to occur and only starting material

was recovered. The coupling reactions reported by Buchwald *et al*⁶¹ all employed THF as the solvent and the unreactivity in this case could be due to the use of the different solvent trifluoromethylbenzene. Further investigations into the use of the catalytic system of Pd₂(dba)₃ and DavePhos **57** were not conducted given the effectiveness of the catalytic system Pd(OAc)₂/**35**.



Scheme 40: Attempted synthesis of **132** with alternate catalytic system.

4.2.2.2 Synthesis of 3-Heterocyclic-Phenols

In addition to the range of 4-heterocyclic phenols prepared, 3-substituted phenols were also desired. Similarly to the 4-substituted phenols, a survey of the literature provided only a few examples of Buchwald-Hartwig aminations for the preparation of 3-substituted phenols from a phenolic substrate. The catalytic systems described by Buchwald *et al*,⁶¹ Urgaonkar and Verkade⁶² and Hartwig *et al*¹⁰¹ described in Section 4.2.2.1 have also been effective in the preparation of some 3-substituted phenols.

An additional report also demonstrated the use of the catalytic system of Pd(OAc)₂ and the benzamide derived phosphine ligand ^tBu-Bphos for the preparation of two 3-substituted phenols (see Figure 57).¹⁰⁴ In these instances, 3-chlorophenol was employed as the substrate and the reaction was carried out in toluene. Interestingly, these reactions did not employ LHMDS as the base and instead utilised K₃PO₄. The phenols prepared under these conditions were isolated in good yield.

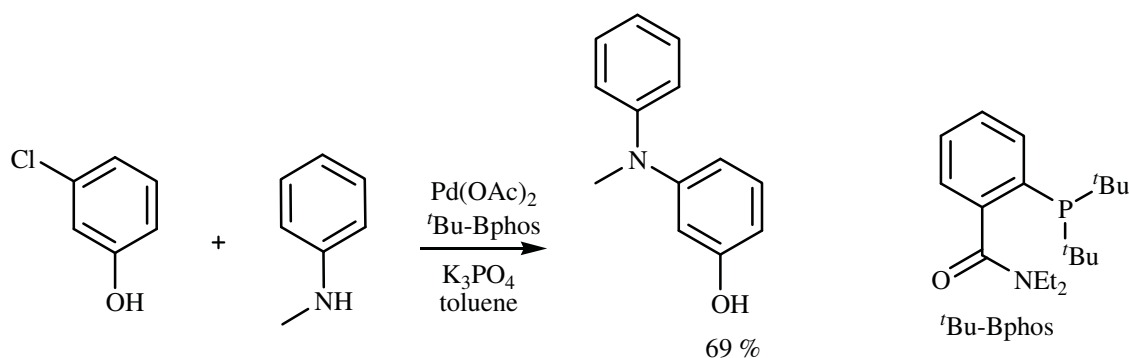
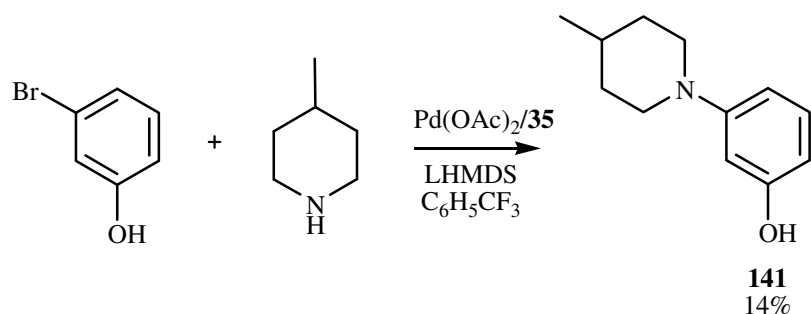


Figure 57: Reaction conditions reported for the preparation of 3-substituted phenols using the t-Bu-Bphos ligand and K₃PO₄.¹⁰⁴

Given that there was once again little literature precedent for the preparation of 3-substituted phenols, it was thought that the reaction conditions used to prepare the 4-substituted phenols could be applied for the preparation of the desired 3-substituted phenols. The use of these reaction conditions was assessed in the reaction of 3-bromophenol and 4-methylpiperidine (Scheme 41) under an atmosphere of nitrogen. These conditions afforded the desired product **141**, although the yield obtained was low (14%).



Scheme 41: Synthesis of **141**.

A high resolution mass spectrum of the product was obtained and was found to be consistent with the desired product, **141**. The low resolution mass spectrum showed the characteristic fragmentation seen with the 4-substituted phenols with a peak at 148 mass units being observed (see Figure 52). The ¹H NMR spectrum of **141** showed characteristic signals corresponding to the 4-methylpiperidine substituent (see Figure 58). An upfield shift in the signals for the H₂, H₄ and H₆ hydrogens of the aromatic ring from δ_H = 6.99, 7.05 and 6.75 ppm respectively in 3-bromophenol to δ_H = 6.41, 6.53 and 6.30 ppm respectively in **141** was also observed. This upfield shift results from the introduction of the electron donating heterocycle. The IR spectrum of **141** also showed an absorption at 3598 cm⁻¹ corresponding to the phenoxy functionality.

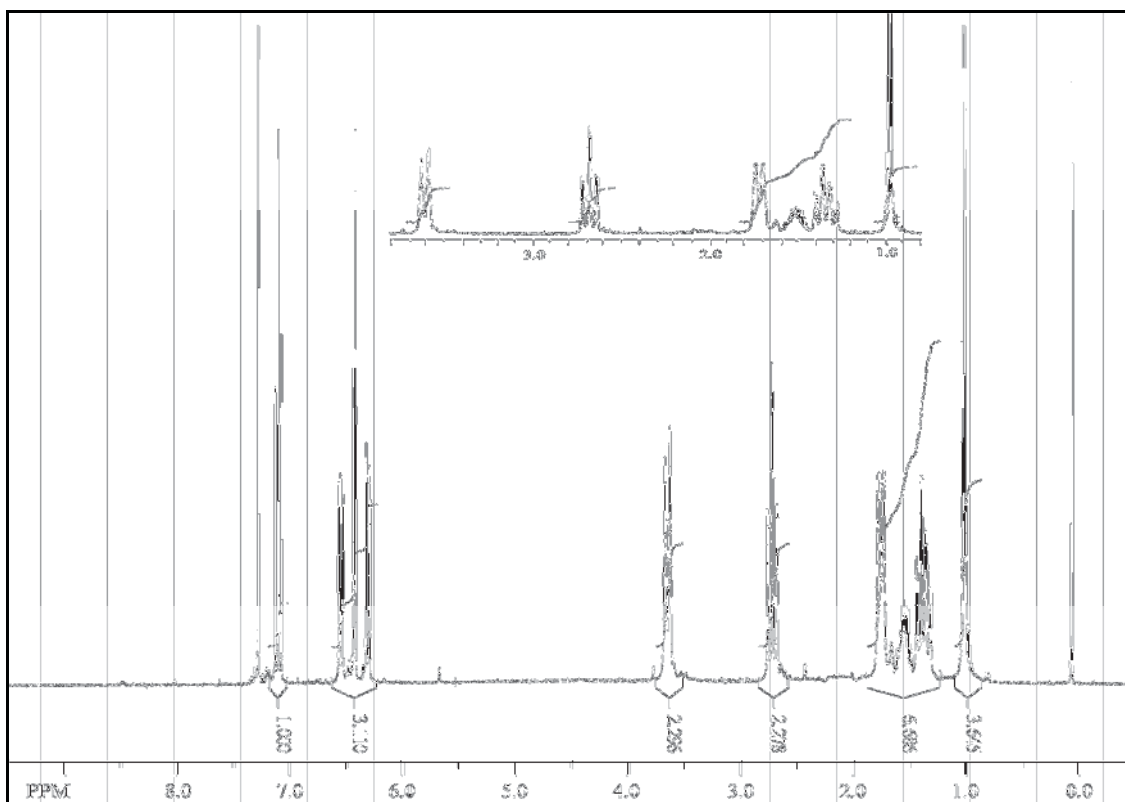


Figure 58: ^1H NMR spectrum of **141**.

In addition to isolation of the desired product, a mixture (ratio ~ 4:5) of two unknown products was also isolated. The ^1H NMR spectrum of this mixture was significantly different to that of **141** and appeared to contain only four aromatic signals (Figure 59). Inspection of the integration of these four signals however, suggested that two of these four signals represented two hydrogens each and that there was therefore actually six aromatic hydrogens in the mixture. The integration also revealed that each component of the mixture possessed three aromatic hydrogens suggesting that both components of the mixture were tri-substituted aromatic systems (see Figure 59 and Figure 61). In addition to the aromatic hydrogens, an extensive number of signals in the region of $\delta_{\text{H}} = 0.87\text{--}4.40$ ppm were observed. The number of signals in this region was much greater than would be expected for a simple mixture of two products similar to **141**. The ^1H NMR spectrum also contained a broad peak at $\delta_{\text{H}} = 8.50$ ppm.

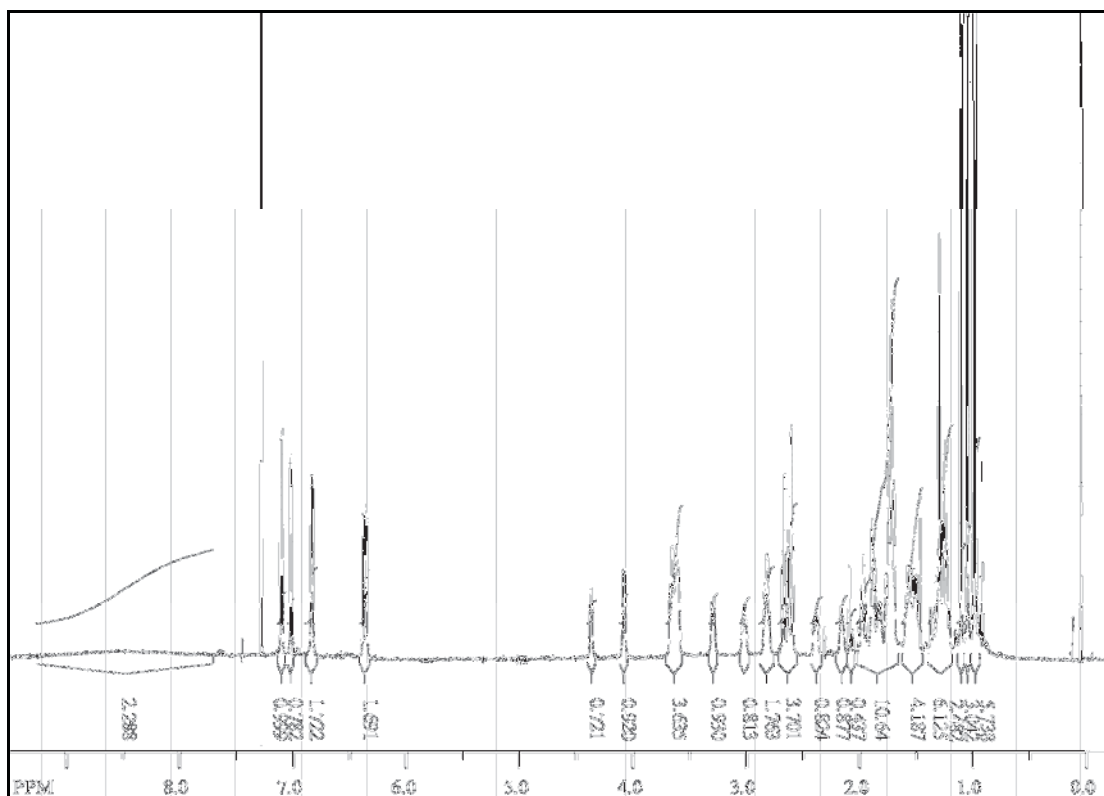


Figure 59: ^1H NMR spectrum of the mixture of the two unknown compounds isolated from the reaction of 3-bromophenol and 4-methylpiperidine under nitrogen.

The low resolution mass spectrum showed two predominant peaks at 288 and 245 mass units. The peak at 288 mass units was thought to correspond to a molecular formula of $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}$. A high resolution mass spectrum of this peak confirmed that this was the most likely molecular formula. This suggested that one or both of the components of the mixture was a 4-methylpiperidine di-substituted phenol of the structure shown in Figure 60. This type of structure is also supported by the ^1H NMR spectrum which shows three aromatic signals for each component.

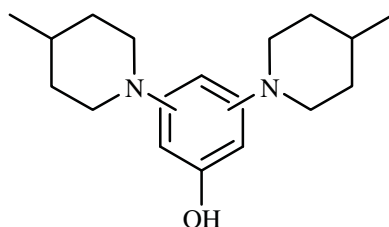


Figure 60: Possible di-substituted phenol.

Analysis of the splitting patterns of the peaks in the aromatic region of the ^1H NMR spectrum indicated that both components of the mixture were 1,3,4-trisubstituted. The splitting patterns of the aromatic peaks can be seen in Figure 61. Figure 61 also shows the designation of the peaks to specific positions on the aromatic ring for both component **A** and **B** of the mixture. The similarity in chemical shift of the aromatic peaks for each component suggested that these compounds were very similar in structure. 2D NMR experiments were therefore employed to characterise the components of the mixture.

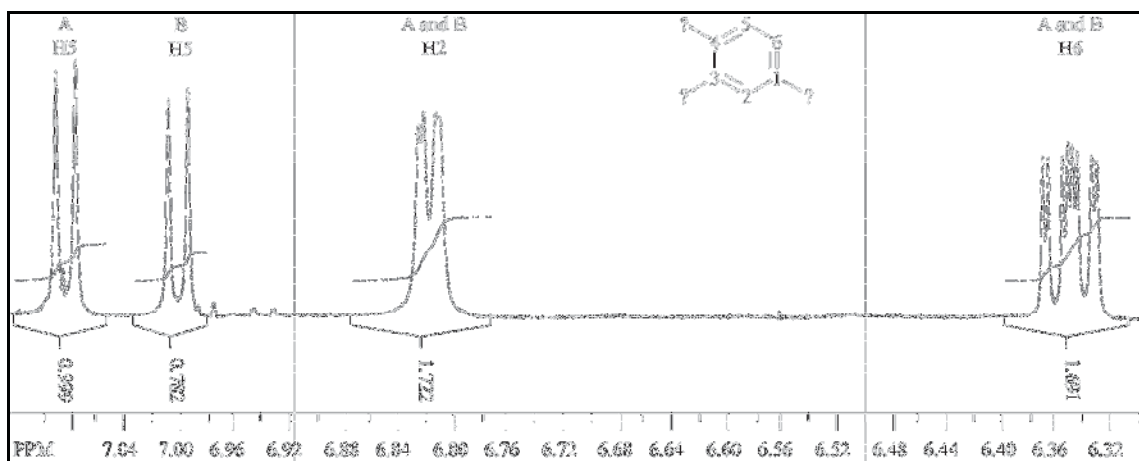


Figure 61: Expansion of the aromatic region of the ^1H NMR spectrum of the mixture of products. Hydrogens are assigned to either component **A** or **B** of the mixture.

Analysis of the 2D NMR data for component **A** of the mixture indicated that the Buchwald-Hartwig amination had occurred at the 3-position of the phenol and a 4-methylpiperidine substituent had been introduced as desired. The signals for the 4-methylpiperidine hydrogens were slightly overlapped with other signals, however, these signals displayed the typical chemical shifts and splitting patterns for a 4-methylpiperidine substituent. In addition, these signals were very similar to the 4-methylpiperidine signals in **141** (c.f. Figure 62 and Figure 58). In particular they exhibited the expected COSY and ROESY correlations with nearby hydrogens of the 4-methylpiperidine. Confirmation of the 4-methylpiperidine substituent at the 3-position of the phenol was obtained by ROESY correlations between the H2 hydrogen of the phenol and H2' hydrogens of the 4-methylpiperidine substituent (Figure 63). Further evidence for an additional substituent at the 4-position was provided by the absence of a ROESY correlation between H4 of the phenol and the H6' hydrogens of the 4-methylpiperidine.

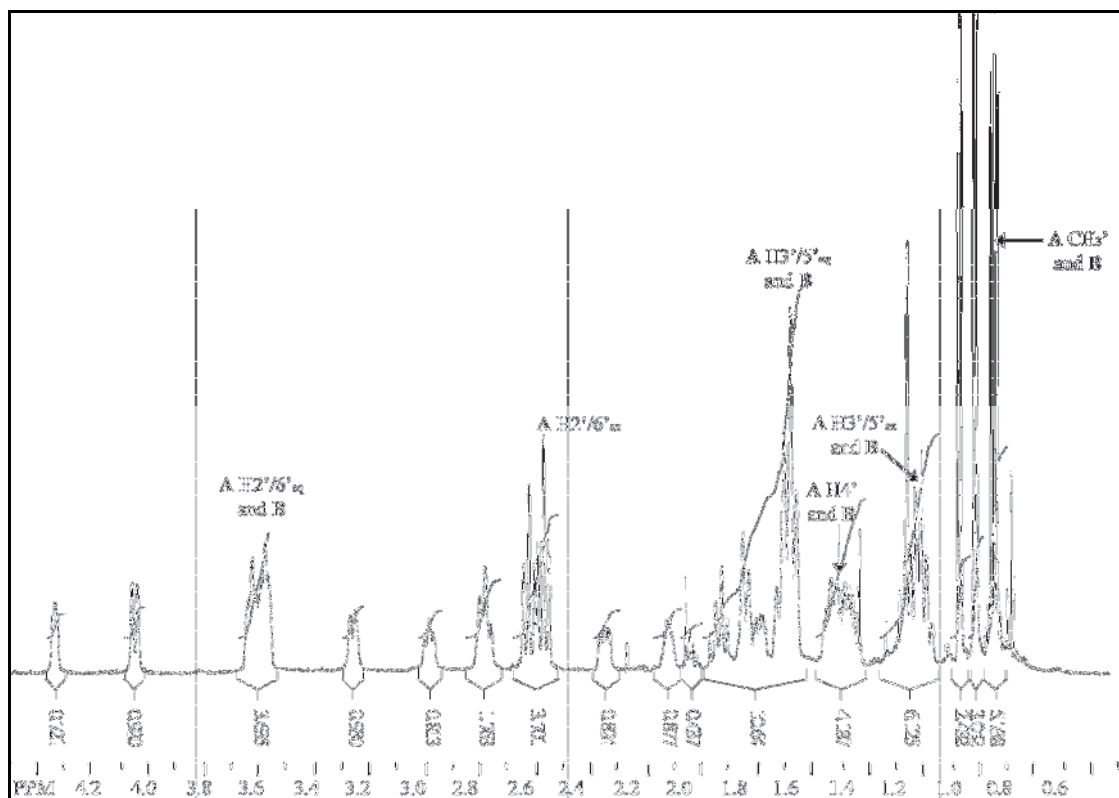


Figure 62: Alkyl region of the ^1H NMR spectrum of component A.

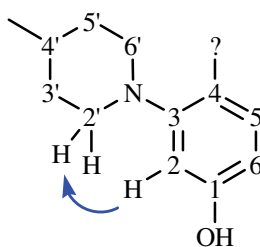


Figure 63: ROESY correlation between H2 hydrogen of the phenol and the H2' hydrogens of the 4-methylpiperidine substituent in component A of the mixture.

Having established that a 4-methylpiperidine substituent had been introduced at the 3-position, it was thought that the structure of component A was as shown in Figure 64, given the molecular formula and the aromatic region of the ^1H NMR spectrum. The alkyl region of the ^1H NMR spectrum however, was not consistent with this proposed structure.

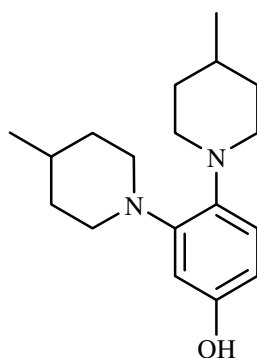


Figure 64: Proposed structure of component **A**.

Analysis of the spectral data indicated that the substituent at the 4-position was a 4-methylpiperidine however, it was no longer symmetric. In particular there were three ROESY correlations between the H5 hydrogen of the phenol and three individual one hydrogen signals of the substituent. Two of the three hydrogens were attached to the same carbon (as determined from HSQC data) and these hydrogens both displayed HMBC correlations to the carbon of the remaining hydrogen signal. COSY and ROESY correlations were also observed between these three signals. The carbon with only one hydrogen attached displayed a HMBC correlation to the H5 hydrogen of the phenol indicating that this carbon was attached at the 3-position of the phenol. This hydrogen was also significantly downfield ($\delta_{\text{H}} = 4.05$ ppm) suggesting it was adjacent to the nitrogen of the ring. This evidence suggested that the structure of component **A** was that of **142** as shown in Figure 65 and that the second 4-methylpiperidine substituent had formed a carbon-carbon bond with the phenol and not a carbon-nitrogen bond as initially thought. Figure 65 also shows the ROESY and HMBC correlations mentioned above.

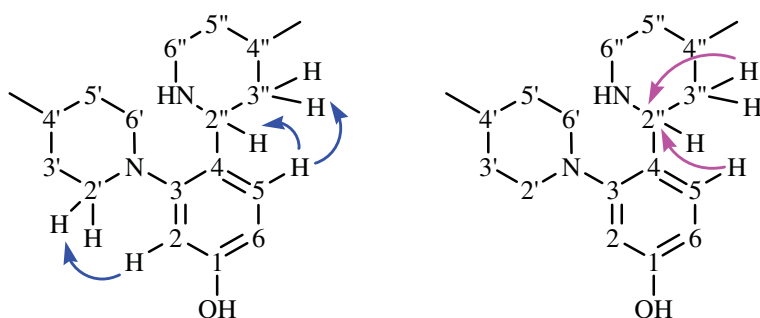


Figure 65: Structure of component **A** (**142**) and the ROESY correlations shown in blue and HMBC correlations shown in pink. The ROESY correlation between H2 of the phenol and the H2' hydrogens of the 3-substituent is also shown.

Analysis of the remaining NMR spectral data was consistent with the proposed structure **142** and the assignment of the alkyl region for component **A** is shown in Figure 66. Further confirmation for the formation of this product was obtained from the low resolution mass spectrum. As mentioned previously a peak at 288 mass units was observed which is consistent with this structure. A peak at 273 mass units was also observed and would result from the loss of a methyl group. The characteristic partial and full loss of the 4-methylpiperidine substituent is once again seen and results in peaks at 218 and 190 mass units respectively (see Figure 67).

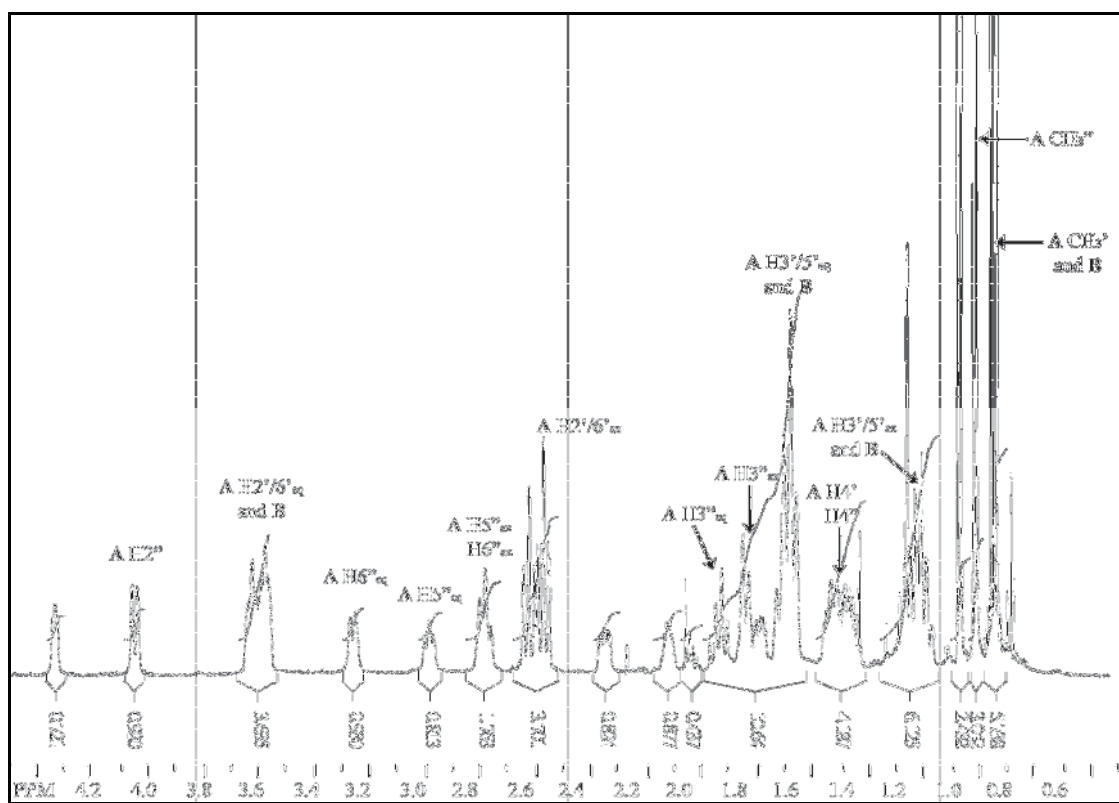


Figure 66: Assignment of the alkyl region of the ¹H NMR spectrum for component **A** of the mixture, **142**.

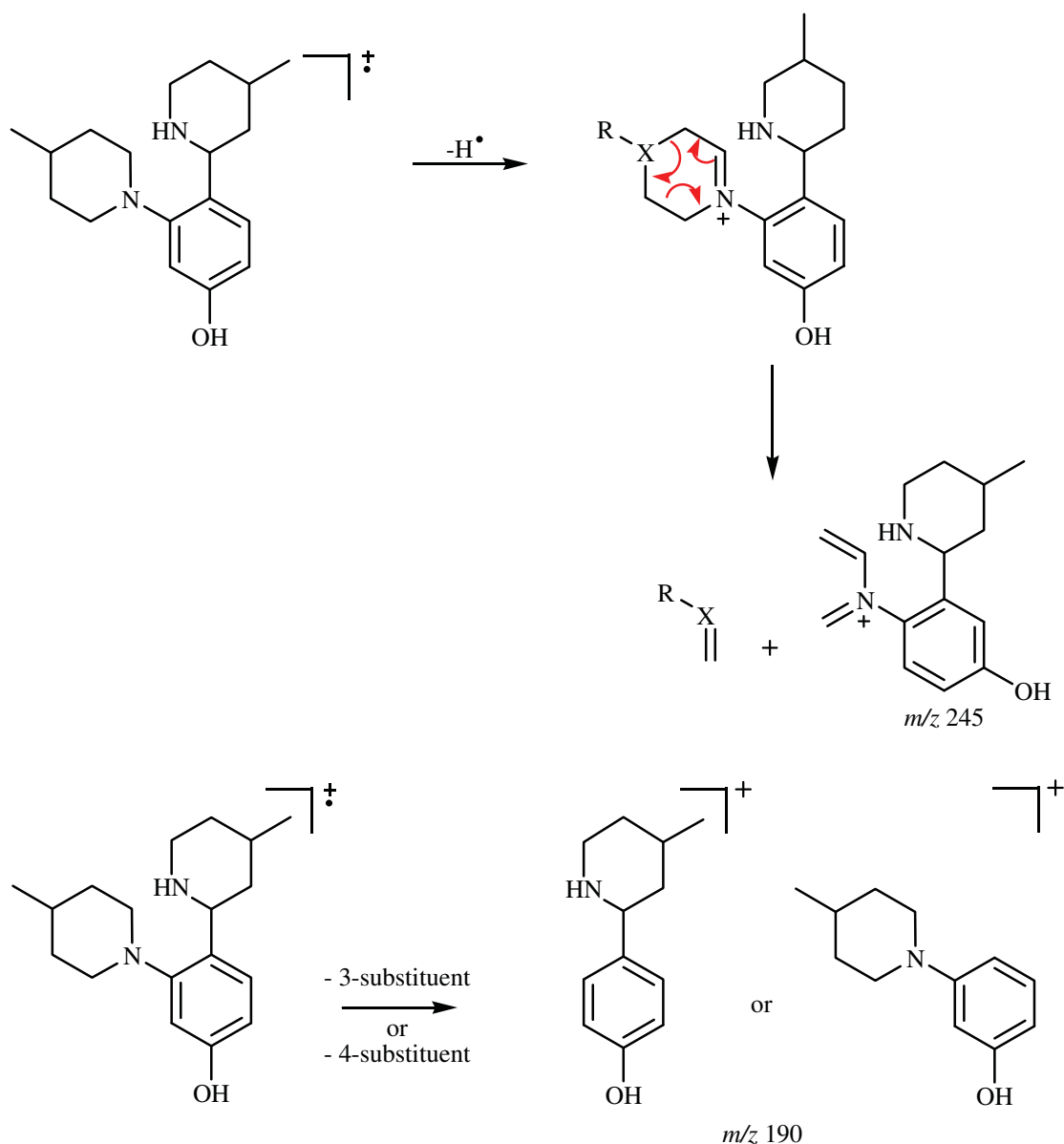


Figure 67: Characteristic fragmentation of component A (**142**) resulting in peaks at 245 and 190 mass units in the low resolution mass spectrum.

Component **A** of the mixture was therefore identified as 3-(4-methylpiperidin-1-yl)-4-(4-methylpiperidin-2-yl)phenol **142** and was obtained in 20% yield. Component **B** could not however, be completely identified. Component **B** displayed very similar aromatic chemical shifts as component **A** and is, as mentioned previously, thought to be another 1,3,4-trisubstituted phenol. The 2D NMR data suggested that component **B** also contained a 4-methylpiperidine at the 3-position of the phenol. Like component **A**, component **B** displayed characteristic COSY and ROESY correlations between the hydrogens of the 4-methylpiperidine substituent. These signals were slightly overlapped with the 4-methylpiperidine signals of component **A**. ROESY correlations between the H2 hydrogen

of the phenol and H2' hydrogens of the 4-methylpiperidine substituent were also seen as in component **A** (Figure 68).

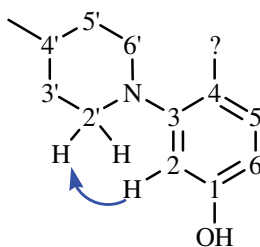


Figure 68: ROESY correlation between H2 hydrogen of the phenol and the H2' hydrogens of the 4-methylpiperidine substituent in component **B** of the mixture.

The substituent at the 4-position could not however, be unambiguously determined. A ROESY correlation between a one hydrogen signal at $\delta_{\text{H}} = 4.34$ ppm and the H5 hydrogen of the phenol was observed along with a HMBC correlation between the H5 hydrogen of the phenol and the carbon of the hydrogen signal at $\delta_{\text{H}} = 4.34$ ppm. This suggests that this carbon is attached to the 4-position of the phenol. The determination of the exact nature of the 4-substituent could not be achieved due to the overlap of the signals in the alkyl region.

The reason for the formation of these di-substituted by-products is unclear. Especially given that no di-substituted products were observed in the preparation of 4-substituted phenols. It was thought that conducting the reaction under argon rather than nitrogen may provide an improvement in this reaction and allow for the preparation of the desired product in higher yield. Therefore, the corresponding reaction was carried out under argon.

The corresponding reaction under argon however, afforded only trace amounts of the desired product as determined by ^1H NMR analysis of the crude material and chromatographic separation afforded an additional unknown compound. The identification of this compound was much simpler having already identified component **A** from the mixture obtained in the previous reaction as **142** and due to the fact that this compound was isolated with only minor impurities. A high resolution mass spectrum of the product obtained indicated that this compound had the same molecular formula as component **A**, $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}$. The fragmentations observed in the low resolution spectrum were also identical to component **A**. The ^1H NMR spectra however, were quite different (c.f. Figure 69 and Figure 59). This suggested that the unknown could be an isomer of component **A**.

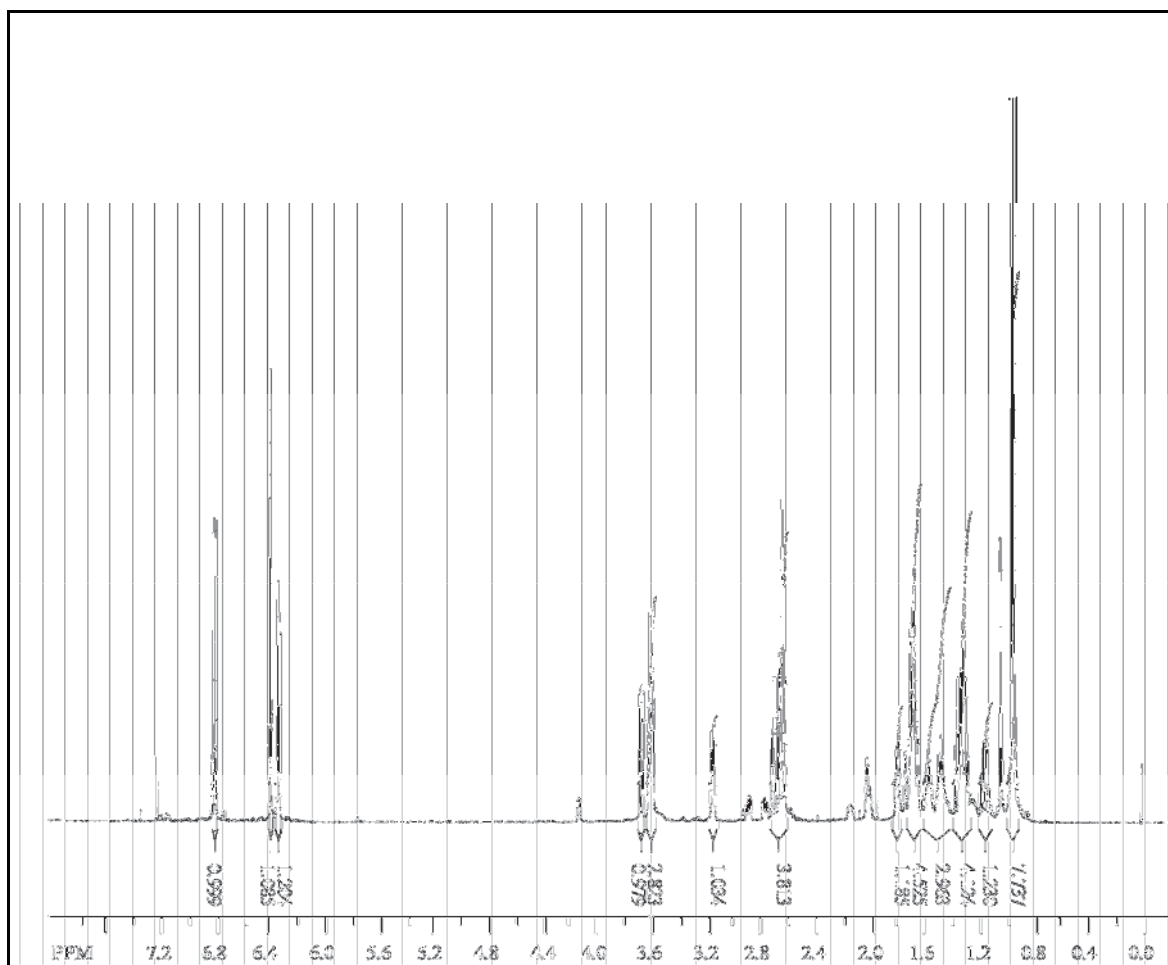


Figure 69: ^1H NMR spectrum of the unknown isolated from the reaction of 3-bromophenol and 4-methylpiperidine under argon.

2D NMR analysis was once again employed to characterise the product and the unknown was identified as **143** as shown in Figure 70. The desired amination at the 3-position was confirmed by ROESY correlations between the H2 and H4 hydrogens of the phenol and the H2' and H6' hydrogens of the 4-methylpiperidine substituent. HMBC correlations were also observed from the H2' and H6' hydrogens of the 4-methylpiperidine substituent with the C3 carbon.

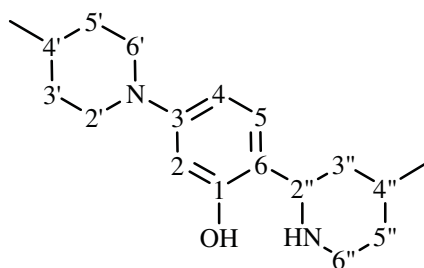


Figure 70: Structure of unknown **143**.

Analysis of the spectral data confirmed that the second 4-methylpiperidine substituent was

attached by a carbon-carbon bond, this time at the 6-position of the aromatic ring. ROESY correlations were observed between the H5 hydrogen of the phenol and the H2'' and H3'' hydrogens of the 4-methylpiperidine substituent (see Figure 71). HMBC correlations were observed between the H2'' hydrogen and the C1, C5 and C6 carbons of the aromatic ring.

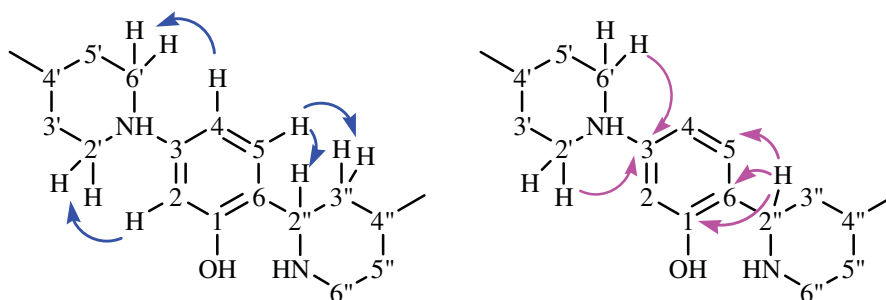
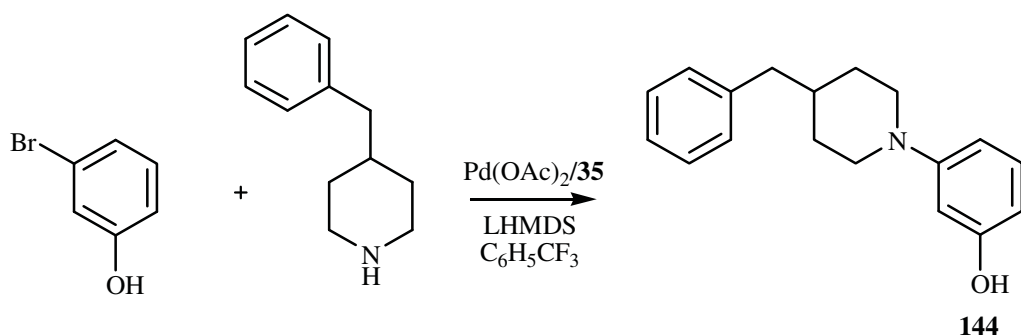


Figure 71: ROESY correlations of **143** shown in blue and HMBC correlations shown in pink.

Analysis of the remaining NMR spectral data was consistent with the proposed structure of **143**. The low resolution mass spectrum, as mentioned above, contained the same characteristic fragmentations as component **A 142** with the loss of a methyl group, and partial and full loss of one of the 4-methylpiperidine substituents (see Figure 67). The spectral data of **143** was also compared to the spectral data for the unknown component **B** of the mixture obtained from the corresponding reaction carried out under nitrogen. This comparison indicated that component **B** was not the same as **143**.

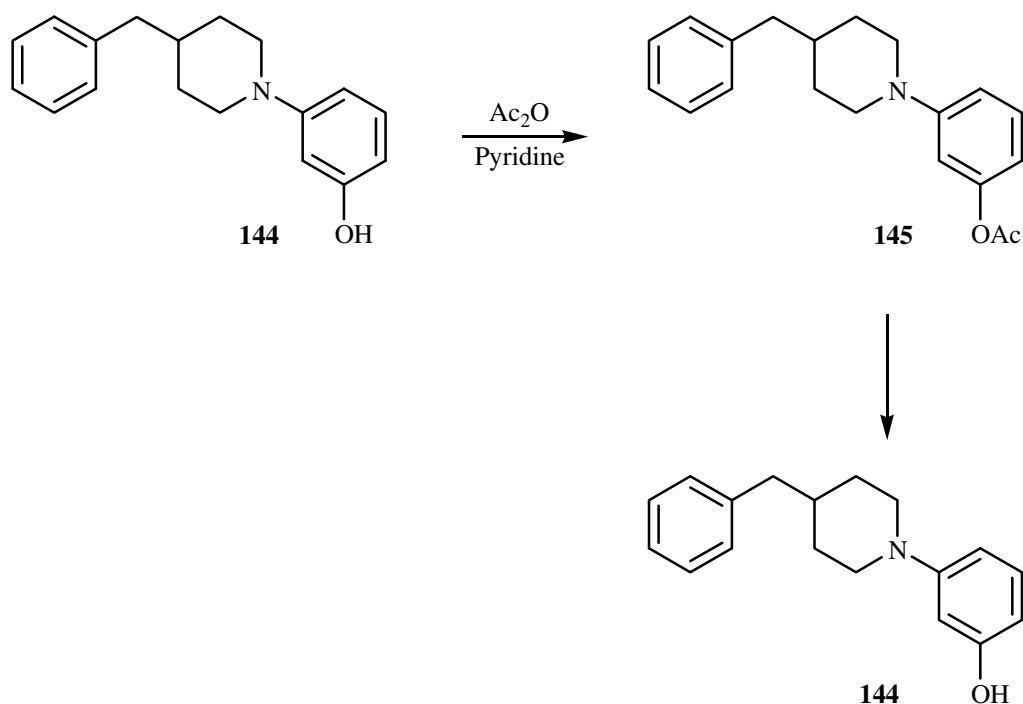
As for components **A** and **B**, the reason for the formation of **143** is similarly not clear. It is also not clear as to why under nitrogen the formation of the isomer **142** is favoured, however, when the reaction is conducted under argon the formation of the isomer **143** is favoured. Both **142** and **143** were obtained in significant yield (47% and 20% respectively).

The corresponding reaction employing LHMDS as the base in the presence of Pd(OAc)₂/**35** was also examined with the amine 4-benzylpiperidine (Scheme 42). In this reaction, a mixture of products was formed and the desired product **144** was observed in the ¹H NMR spectrum of the crude material.



Scheme 42: Buchwald-Hartwig amination of 3-bromophenol with 4-benzylpiperidine.

Complete purification of the desired product could not however, be achieved. It was thought that the crude phenol could be converted to the acyl protected equivalent **145** which may allow for easier separation of the mixture of products. Deprotection of the acyl protected phenol would then provide the desired 3-substituted phenol (Scheme 43).



Scheme 43: Proposed scheme for the purification of **144**.

The impure 3-substituted phenol **144** was treated with acetic anhydride and pyridine and heated for three hours. Chromatographic separation of the resultant mixture provided the desired acyl protected phenol **145**. An elemental analysis was obtained of **145** which was consistent with the elemental composition of the desired product. The ^1H NMR spectrum of **145** showed an upfield shift in the signals for the H2 and H4 hydrogens of the aromatic ring from $\delta_{\text{H}} = 6.99$ and 7.05 ppm respectively in 3-bromophenol to $\delta_{\text{H}} = 6.60$ and 6.52 ppm

respectively in **145**. This upfield shift results from the introduction of the electron donating heterocycle. A signal at $\delta_{\text{H}} = 2.29$ ppm was also observed for the methyl of the acyl protecting group. In addition, the introduction of the protecting group was confirmed by the ^{13}C NMR spectrum which displayed a characteristic signal at $\delta_{\text{C}} = 169.7$ ppm for the carbonyl functionality and the IR spectrum which showed a characteristic peak at 1764 cm^{-1} . The protected phenol **145** however, was isolated in only 12% yield over the two steps. Due to the low yield of this product the deprotection step to afford the desired phenol was not conducted.

The reaction conditions described above employing LHMDS and $\text{Pd}(\text{OAc})_2/\mathbf{35}$ for the Buchwald-Hartwig amination of 3-bromophenol were therefore not appropriate for the preparation of 3-heterocyclic phenols and an alternative approach was required.

The combination of LDA/ NaO^tBu has been reported for use in Buchwald-Hartwig aminations. Urgaonkar and Verkade⁶² have used this combination of bases for the preparation of aryl amines containing base sensitive functionality, including 3-substituted phenols (see Figure 72). In these cases, it is thought that the LDA deprotonates the base sensitive functionality and acts to protect it whilst the NaO^tBu functions as the standard base for the Buchwald-Hartwig amination. The aryl amines prepared using this method were isolated in moderate yield.

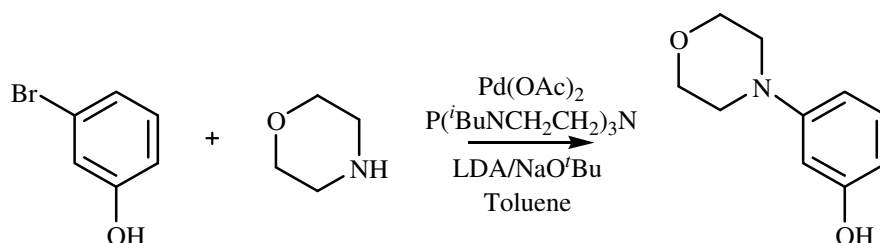


Figure 72: Preparation of aryl amines using LDA/ NaO^tBu as reported by Urgaonkar and Verkade.⁶²

The use of this base combination was investigated in the reaction of 3-bromophenol and 4-methylpiperidine using the catalytic system of $\text{Pd}(\text{OAc})_2/\mathbf{35}$ (Figure 73). In this reaction, LDA was initially added to 3-bromophenol and stirred for 30 minutes before the addition of the other reagents. This was to ensure that the phenol functionality was blocked to allow for the desired coupling reaction to occur. ^1H NMR analysis of the crude material after 20 hours after the addition of the catalytic system however, did not show the presence of the desired product.

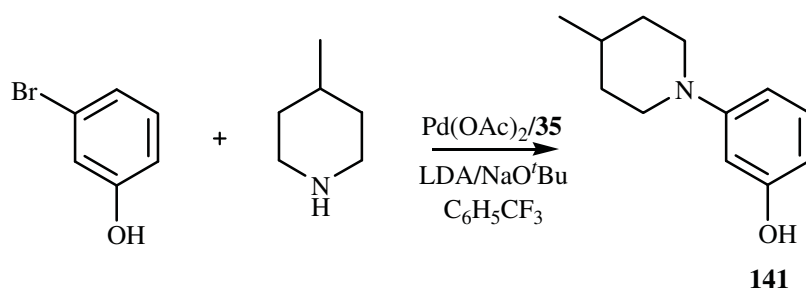
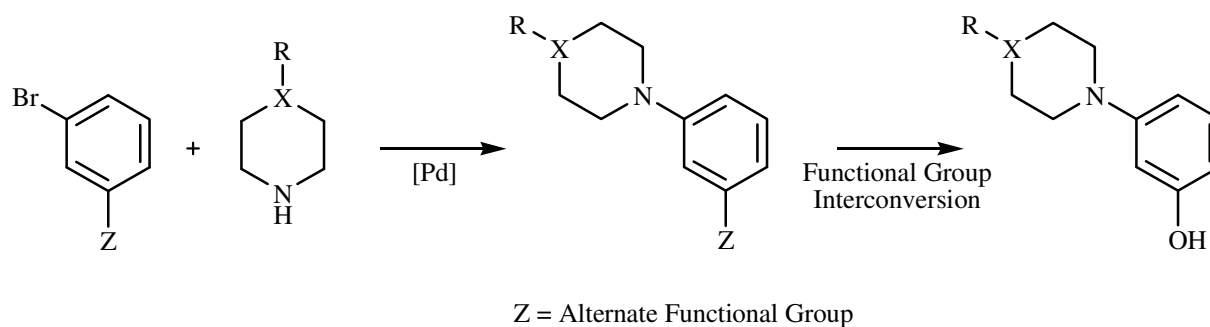


Figure 73: Attempted synthesis of **141** using LDA/NaO^tBu as the base.

The use of different catalytic systems was also examined for use in this particular amination in the hope that one would be successful for the preparation of 3-substituted phenols. Both Pd(OAc)₂ and Pd₂(dba)₃ were examined in combination with each of the Buchwald ligands **57-62** (refer to Table 10 in Chapter 2). Disappointingly, all led to the recovery of predominantly starting material.

4.2.2.3 Investigating Alternate Pathways for the Synthesis of 3-Heterocyclic-Phenols

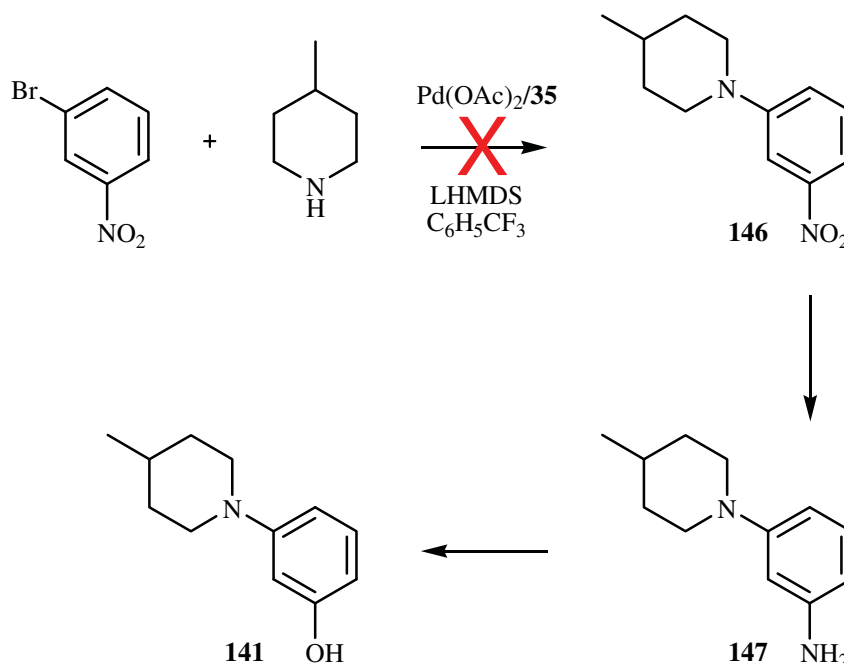
Due to the fact that 3-substituted phenols could not be prepared in reasonable yield from 3-bromophenol, alternate pathways were investigated. It was envisaged that the use of an alternate functionality at the phenoxy position would allow for the desired Buchwald-Hartwig amination to be achieved (Scheme 44). The alternate functionality could then be converted to a phenoxy functionality affording the desired substituted phenols.



Scheme 44: Proposed scheme for the preparation of 3-substituted phenols using functional group interconversion.

This type of pathway was investigated with a nitro functional group in place of the phenoxy functionality in 1-bromo-3-nitrobenzene (Scheme 45). It was thought that Buchwald-Hartwig amination between this substrate and 4-methylpiperidine could occur affording **146**. The substituted **146** could then be converted to the corresponding phenol affording the desired

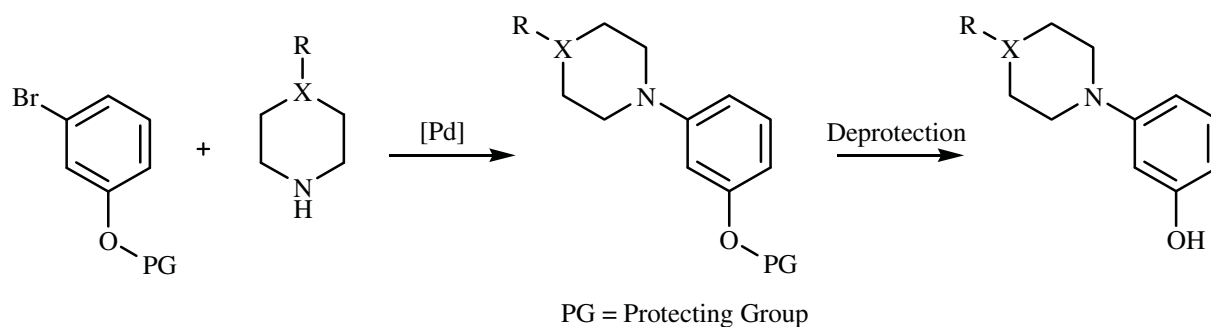
product **141**. A potential pathway for interconversion of the nitro group to the phenol could employ reduction of the nitro to the corresponding amine **147** followed by a Sandmeyer-type replacement reaction.¹⁰⁵



Scheme 45: Proposed scheme for the synthesis of **141** from 1-bromo-3-nitrobenzene.

The reaction of 1-bromo-3-nitrobenzene and 4-methylpiperidine using the conditions of $\text{Pd}(\text{OAc})_2/35$ and LHMDS in trifluoromethylbenzene led to the formation of a complex mixture of products. Due to the formation of a significant number of products during this reaction, attempts to purify this material were not made and an alternate pathway for the preparation of the desired phenols was investigated.

The use of a phenolic protecting group was then investigated for the preparation of 3-substituted phenols. An appropriate protecting group could allow the desired Buchwald-Hartwig amination to be achieved and removal of the protecting group would subsequently afford the desired phenol (Scheme 46). A number of protecting groups have been investigated for use in this particular pathway.

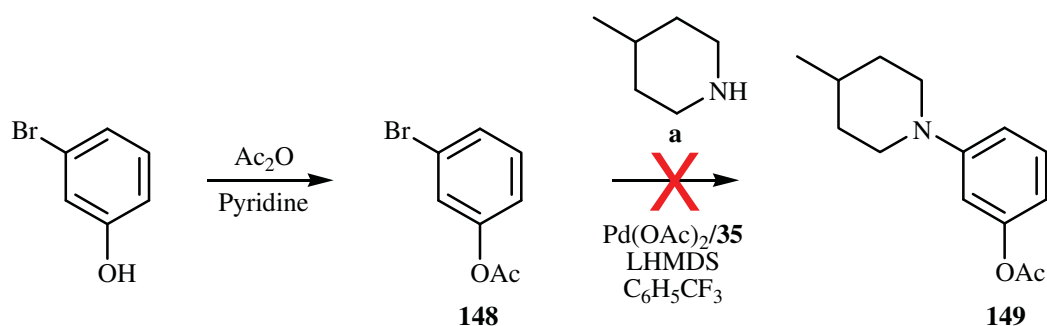


Scheme 46: Proposed scheme for the preparation of 3-substituted phenols using a phenolic protecting group.

Acyl protection.

The use of an acyl group had been investigated previously for the purpose of purifying a 3-substituted phenol (see Section 4.2.2.2). The use of an acyl group was also explored for the protection of 3-bromophenol to allow for Buchwald-Hartwig coupling and introduction of a heterocyclic substituent. The applicability of this protecting group was once again assessed with 4-methylpiperidine.

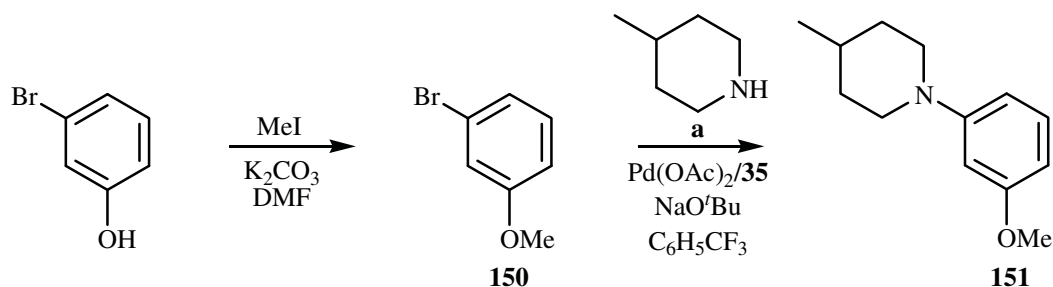
Introduction of the acyl group was achieved simply by treatment of 3-bromophenol with acetic anhydride and pyridine affording **148** (isolated in 94% yield). Confirmation of the introduction of the protecting group was provided by the ^1H NMR spectrum which showed a peak at $\delta_{\text{H}} = 2.30$ ppm corresponding to the acyl methyl group. The protected phenol **149** was then employed in a Buchwald-Hartwig amination with 4-methylpiperidine in the presence of $\text{Pd}(\text{OAc})_2/\mathbf{35}$ and LHMDS. This reaction however, afforded a mixture of products as determined by ^1H NMR analysis of the crude material. Due to the complexity of products no attempts to purify the mixture were made.



Scheme 47: Preparation of **148** and attempted Buchwald-Hartwig amination for the preparation of **149**.

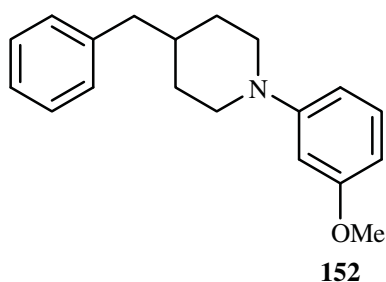
Methyl protection.

Given that the acyl protecting group proved to be inappropriate, the use of a methyl protecting group was investigated. 3-Bromophenol was protected as the methyl ether in compound **150** by treatment with methyl iodide and K_2CO_3 in DMF using a literature procedure (Scheme 48).¹⁰⁶ Compound **150** displayed spectroscopic data consistent with that reported for the commercially available material.¹⁰⁷



Scheme 48: Synthesis of **150** and **151**.

The amination reaction of **150** with 4-methylpiperidine was carried out using the catalytic system of $Pd(OAc)_2/35$. Because the phenoxy functionality was protected and was no longer base sensitive, $NaOtBu$ was employed as the base. This reaction afforded the desired product **151** in 80% yield. The corresponding reaction with 4-benzylpiperidine was also successful and afforded the desired product **152** in a slightly lower yield (62%). These results indicated that methyl protection of 3-bromophenol allowed for the introduction of a heterocycle at the 3-position.



A high resolution mass spectrum was obtained of **151** and an elemental analysis was obtained for **152**. Both results were consistent with the formation of the desired product in each case. The 1H NMR spectra for both of these compounds showed the characteristic signals for the introduction of the heterocyclic substituent. In addition, an upfield shift (~ 0.5 ppm) in the signals for the H2 and H4 hydrogens of the aromatic ring was observed. The low resolution mass spectra also showed characteristic fragment peaks for both compounds. The loss of the methyl and benzyl substituents of the piperidine ring was observed for **151** and **152**

respectively resulting in a peak at 190 mass units for both compounds (see Figure 74). The partial cleavage of the heterocycle substituent observed in other heterocyclic substituted compounds was also seen in compounds **151** and **152** resulting in fragment peaks at 162 mass units.

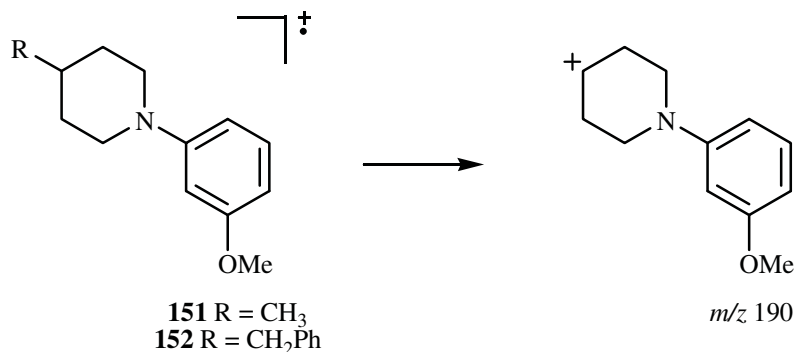
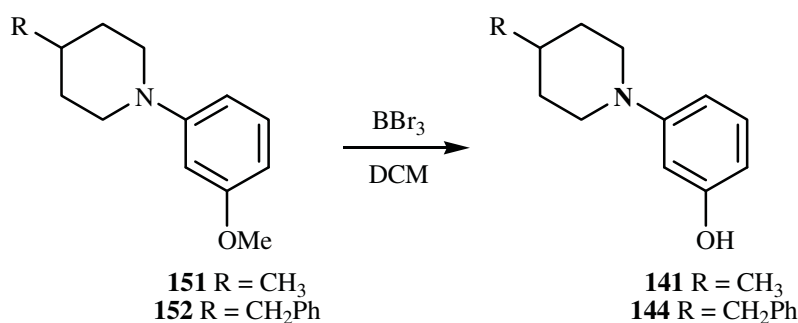


Figure 74: Loss of the methyl and benzyl substituents in the low resolution mass spectra of **151** and **152** respectively.

Having introduced the heterocycle, the next step was to remove the protecting group. One of the most common methods for the deprotection of a methyl ether involves cleavage with boron tribromide.^{108,109} This method was envisaged for the deprotection of **151** and **152** (Scheme 49).



Scheme 49: Proposed method for deprotection of methyl ethers using BBr₃.

Both **151** and **152** were treated with boron tribromide in DCM at -78 °C for 30 minutes then stirred at room temperature for 1-2 hours. A high resolution mass spectrum was obtained for the products **141** and **144** isolated from the deprotection reactions of **151** and **152** respectively. In both cases, the high resolution mass spectrum was consistent with molecular mass of the desired product. The ¹H NMR spectra for both of these products also no longer contained a signal for the methyl protecting group indicating that deprotection had been successful. The ¹H NMR spectrum of **141** however, was not consistent with the spectrum of the previously characterised **141** prepared from the Buchwald-Hartwig amination of the unprotected phenol as described in Section 4.2.2.2 (see Figure 75).

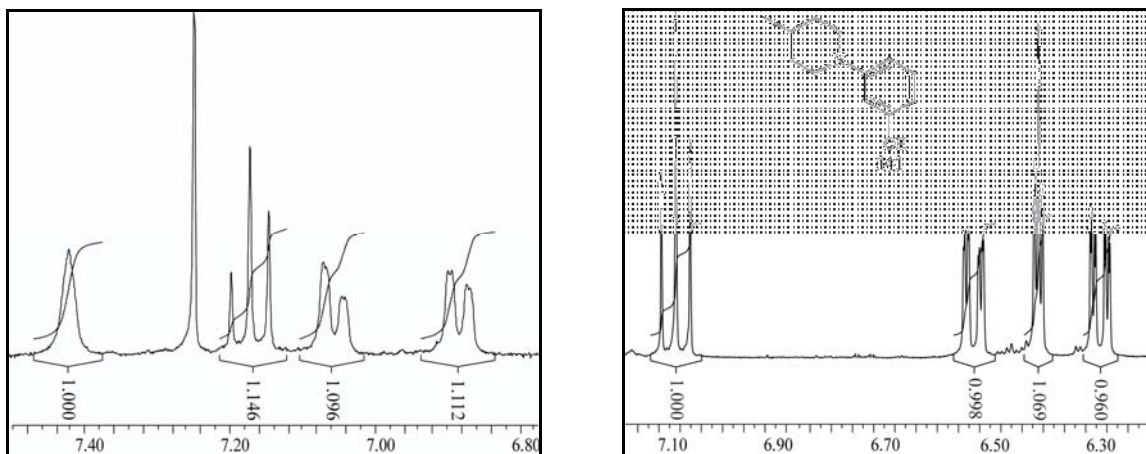


Figure 75: Aromatic regions of ^1H NMR spectra for **141** obtained from the deprotection of **141** (left) and the previously prepared and characterised **141** (right).

Specifically, four aromatic hydrogens were observed however, all four of these signals were broadened and much further downfield than the four aromatic signals observed in the previously obtained **141**. The aromatic signals for this compound were also shifted significantly downfield (Δ 0.05-0.1 ppm) compared to the protected equivalent **151**. The signals for the 4-methylpiperidine displayed the characteristic splitting patterns for this substituent however these were further downfield than what was observed in the spectrum of the previously obtained **141**. The ^1H NMR spectrum for **144** was also not consistent with what was expected for the desired product. The ^1H NMR spectrum for **144** similarly showed broadened signals for the phenolic hydrogens which were further downfield than expected and were also shifted significantly downfield compared to the protected equivalent **152**.

2D NMR experiments of **144** were employed to determine the identity of this product. Analysis of the data obtained from the 2D experiments indicated that **144** was in fact the desired phenol, with the expected COSY, ROESY, HMBC and HMQC correlations for this product being observed. However, as mentioned above the signals for the phenolic hydrogens were broadened and further downfield than expected and were not consistent with the desired product. Given this, it was thought that boron may still be coordinated to the phenolic oxygen causing the changes in the chemical shift for the phenolic hydrogens and differences in the observed NMR to what was expected. To confirm this, a ^1H NMR spectrum and a ^{13}C NMR spectrum were obtained of a ~ 1:1 mixture of **144** obtained from the deprotection of **152** and a known sample of **144** prepared by an alternate method as discussed below (see Figure 76 and Figure 77).

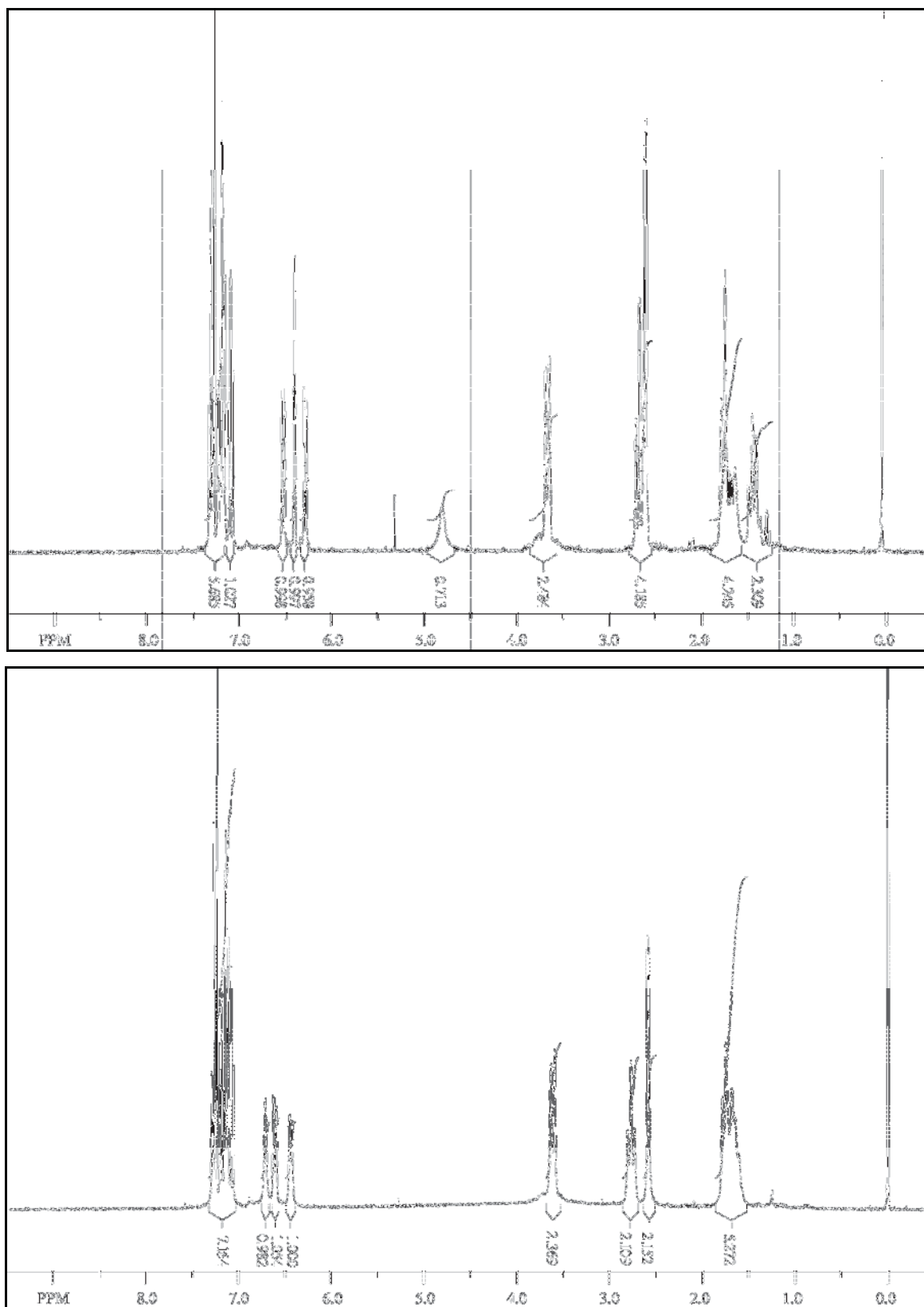


Figure 76: ¹H NMR spectra of a characterised sample of **144** (top) and ~ 1:1 mixed sample of characterised **144** and **144** obtained from the deprotection of **152** (bottom).

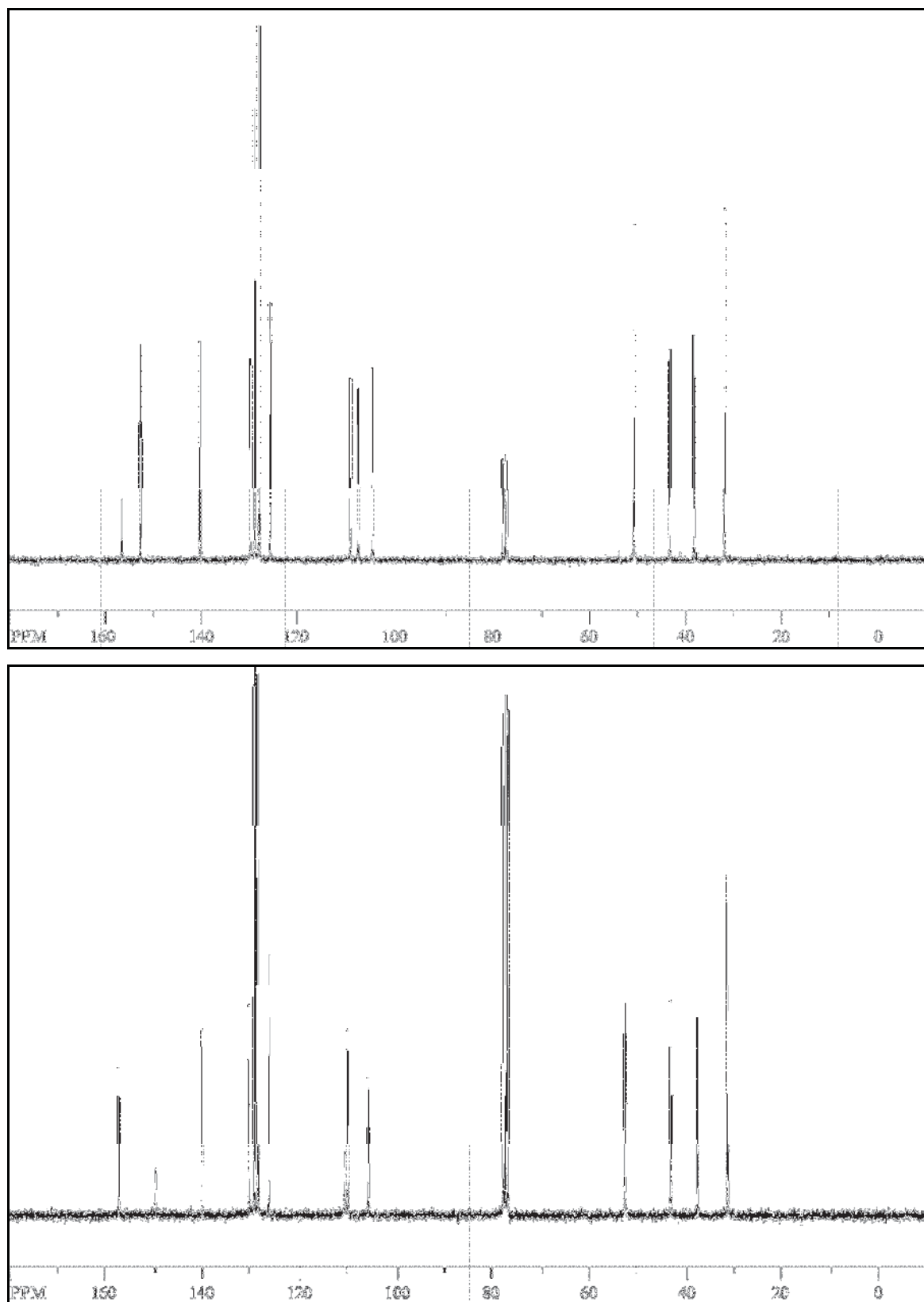
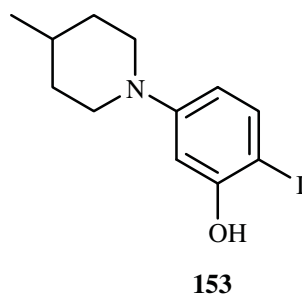


Figure 77: ^{13}C NMR spectra of a characterised sample of **144** (top) and ~ 1:1 mixed sample of characterised **144** and **144** obtained from the deprotection of **152** (bottom).

The mixed ^1H NMR spectrum showed the presence of only one compound and was similar to that of the known sample of **144** except that most of the signals were now significantly broadened. There was also a slight downfield shift in the signals for the phenolic hydrogens and some of the signals for the piperidinyll hydrogens. The mixed ^{13}C NMR spectrum similarly showed only one compound, however some changes in the chemical shifts of the signals for the phenolic hydrogens was observed. The mixed NMR spectra therefore confirmed that **144** was the desired phenol, however, the phenol appeared to still be coordinated to the boron atom. If the phenol was coordinated to the boron atom in a borate species then there would be an exchange process of the coordinated phenol with the free phenol in solution. This exchange process would be consistent with the observed broadening of the signals in the ^1H NMR spectrum. To confirm the borate species an electrospray mass spectrum (positive ion) was obtained up to 1000 mass units. However, no compound of higher molecular mass was observed. It is likely that the borate species is not of high enough stability to be observed in the mass spectrum. The molecular ion of the phenol and the M+H and M-H equivalents were however observed.

To determine the identity of **141** obtained from the deprotection of **151**, mixed NMR spectra of this compound and the known sample of **141** prepared previously were also obtained. Similarly to **144**, these NMR spectra showed the presence of only one compound and were similar to that of the known sample of **141**. This confirmed that **141** was the desired phenol however, **141** also appeared to be still coordinated to the boron atom.

Given the difficulties associated with the BBr_3 method for deprotection of the methyl ethers to afford the desired phenols, alternative methods were examined. The combination of boron trichloride and tetra-(*n*-butyl)ammonium iodide has been used as a milder alternative to boron tribromide for the deprotection of methyl ethers.¹¹⁰ This method was assessed in the deprotection reaction of **151**. Treatment of **151** with boron trichloride and tetra-(*n*-butyl)ammonium iodide did not however, afford the desired product **141**. The major product isolated from this reaction was in fact **153**.



A high resolution mass spectrum was obtained and was consistent with the introduction of the iodine in **153**. The low resolution mass spectrum showed the partial loss of the heterocyclic substituent with a peak at 247 mass units and also the loss of the iodine with a peak at 190 mass units. The ^{13}C NMR spectrum displayed a characteristic peak at $\delta_{\text{C}} = 72.0$ ppm corresponding to the carbon attached to the iodine. Confirmation of the position of the iodine was provided from 2D NMR experiments. Specifically, a ROESY correlation was observed between the H2 and H4 hydrogens of the phenol and the H2/6 hydrogens the 4-methylpiperidine substituent (see Figure 78). This therefore confirmed that the iodine was not in either of the positions *ortho* to the 4-methylpiperidine substituent. The H4 hydrogen of the phenol had coupling constants of $J = 3.0$ and 8.7 Hz indicating that it was coupled to both an *ortho* (H5) and a *meta* (H2) hydrogen suggesting the iodine was attached at the 6-position. A correlation was observed between the H2 hydrogen of the phenol and the carbon with the iodine attached in the HMBC spectrum. This confirmed that the iodine had inserted at the 6-position of the phenol.

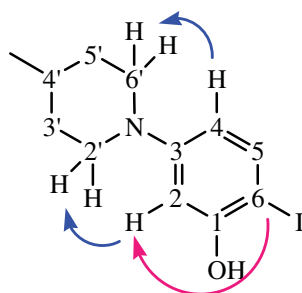
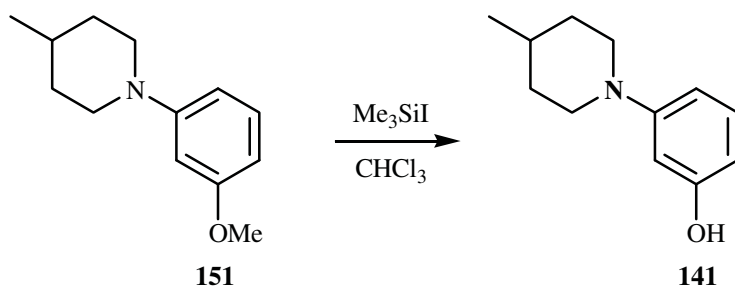


Figure 78: ROESY correlations of **153** shown in blue and HMBC correlation shown in pink.

Trimethylsilyl iodide was also investigated as an another alternative reagent for the deprotection of **151** as it has been reported for the deprotection of both aromatic methyl ethers and simple alkyl methyl ethers.^{111,112} Treatment of **151** with trimethylsilyl iodide lead to the deprotection of the methyl ether and afforded the desired product **141** (Scheme 50). The spectroscopic data obtained for this product was consistent with the previously obtained data for this compound. Disappointingly **141** was however, isolated in only 22% yield.

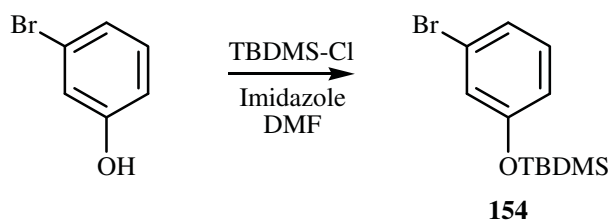


Scheme 50: Deprotection of **151** with Me_3SiI .

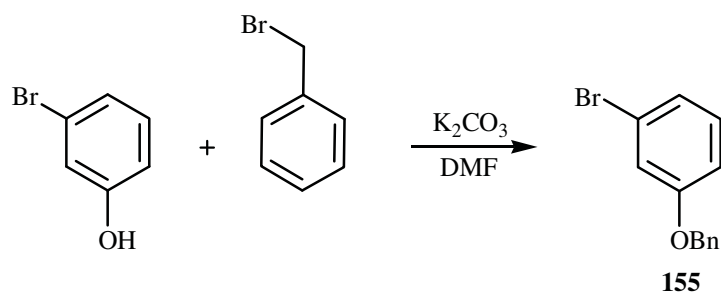
Although the introduction of the methyl protecting group and the Buchwald-Hartwig coupling occur in good yield, the use of the methyl ether as a protecting group is not sufficient for the preparation of 3-heterocyclic phenols. This is due to the issues associated with the deprotection step which affords the desired phenol in low yield. The low yield in this step results in an overall yield of only 15% over the phenolic protection, Buchwald-Hartwig amination and deprotection steps.

^tButyldimethylsilyl, Benzyl and p-Methoxybenzyl Protection.

Three additional protecting groups, ^tbutyldimethylsilyl (TBDMS), benzyl (bn) and *p*-methoxybenzyl (PMB), were also investigated as protecting groups given the difficulties associated with the deprotection of the methyl protecting group. The TBDMS ether **154** was prepared from 3-bromophenol and ^tbutyldimethylsilyl chloride in 76% yield using the method of Keana *et al*¹⁰³ (Scheme 51). The benzyl ether **155** was prepared in 83% yield using the method of Kim *et al*¹¹³ which involved the reaction of 3-bromophenol and benzyl bromide (Scheme 52). Both of these protected phenols displayed ¹H NMR spectra consistent with those reported in the literature. The protected **155** also displayed a melting point (61 °C) the same as that reported previously (61-62 °C).¹¹³

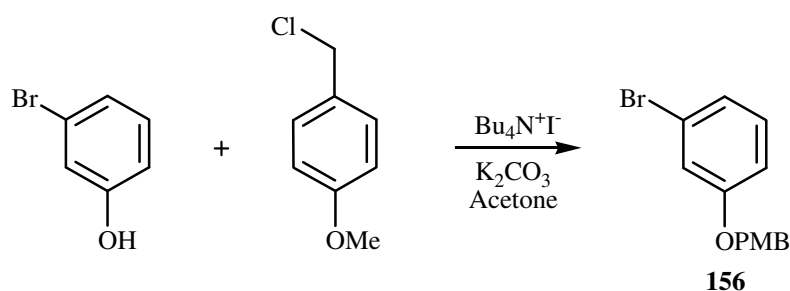


Scheme 51: Synthesis of **154**.



Scheme 52: Synthesis of **155**.

The PMB protected phenol **156** was obtained in good yield (73%) from the reaction of 3-bromophenol and *p*-methoxybenzyl chloride in the presence of K_2CO_3 and tetra-*n*-butylammonium iodide (Scheme 53).¹¹⁴ A high resolution mass spectrum of **156** was obtained and was consistent with the molecular mass of the desired product. The 1H NMR spectrum showed the presence of a peak at $\delta_H = 3.82$ ppm for the methyl and at $\delta_H = 4.96$ ppm for the CH_2 functionality of the protecting group. Characteristic peaks for the aromatic hydrogens of the *p*-methoxybenzyl group were also observed at $\delta_H = 6.92$ and 7.34 ppm.



Scheme 53: Synthesis of **156**.

Having prepared the three protected phenols, these were then employed in the amination reaction with 4-methylpiperidine (Figure 79). In each case the reaction was carried out using the catalytic system of $Pd(OAc)_2/35$, with NaO^tBu as the base.

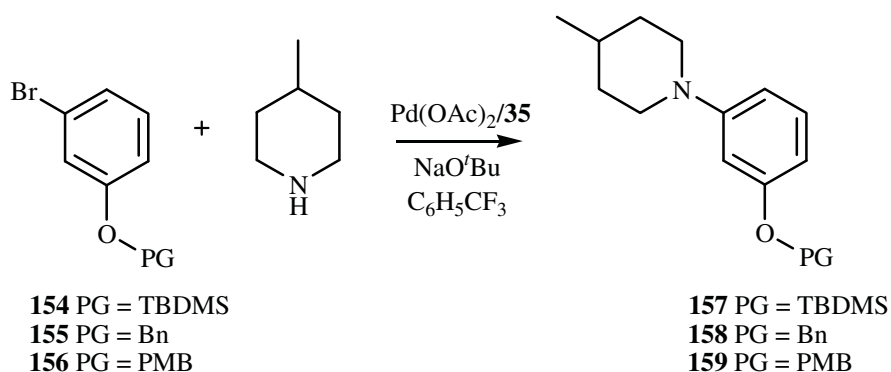
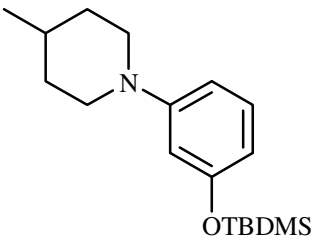
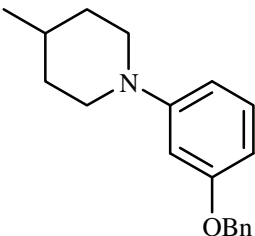
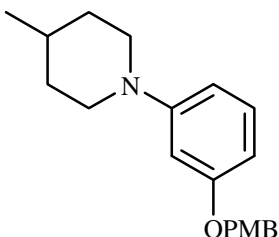


Figure 79: Reaction conditions for the Buchwald-Hartwig amination of the protected phenols.

The use of all of these protecting groups allowed for the desired Buchwald-Hartwig amination at the 3-position to occur. Both the benzyl and PMB protecting groups afforded the desired products **158** and **159** respectively, in moderate yield (see Table 29). The use of the TBDMS protecting group was however, less effective in this reaction and afforded a much lower yield of the coupled product **157** (32%). This lower yield was partially a result of purification difficulties.

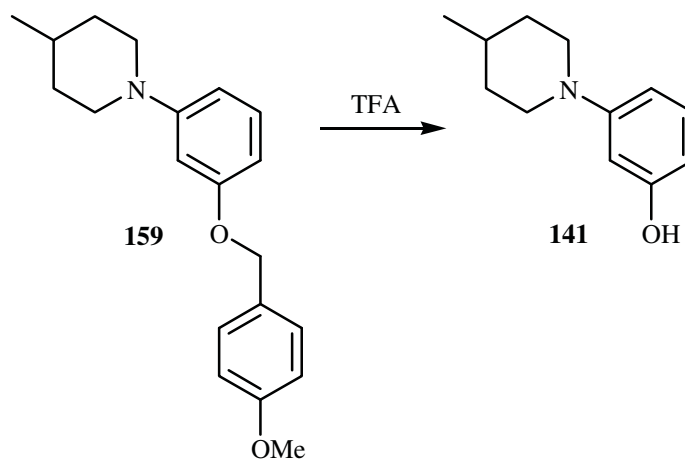
Table 29: Yields of 3-(4-methylpiperidine) substituted protected phenols.

Protected Product	Yield (%)
<p>157</p> 	32
<p>158</p> 	65
<p>159</p> 	64

A high resolution mass spectrum for each of these compounds was obtained and was consistent with the molecular mass in each case. The ^1H NMR spectra showed the characteristic upfield shift in the signals for the H2 and H4 hydrogens of the phenol from the introduction of the heterocycle. These spectra also showed evidence of the protecting groups confirming that the protecting groups had withstood the amination process. The low resolution mass spectra in each case showed characteristic cleavage patterns of the desired products.

Due to the low yield obtained with the TBDMS protecting group deprotection of **157** was not conducted and the use of this protecting group was not pursued any further. Based on the yields of the coupled products either of the benzyl or *p*-methoxybenzyl protecting groups would be suitable for the preparation of 3-substituted phenols. It was thought that the removal of the *p*-methoxybenzyl protecting group could however, be achieved more readily and therefore the use of this protecting group was examined further.

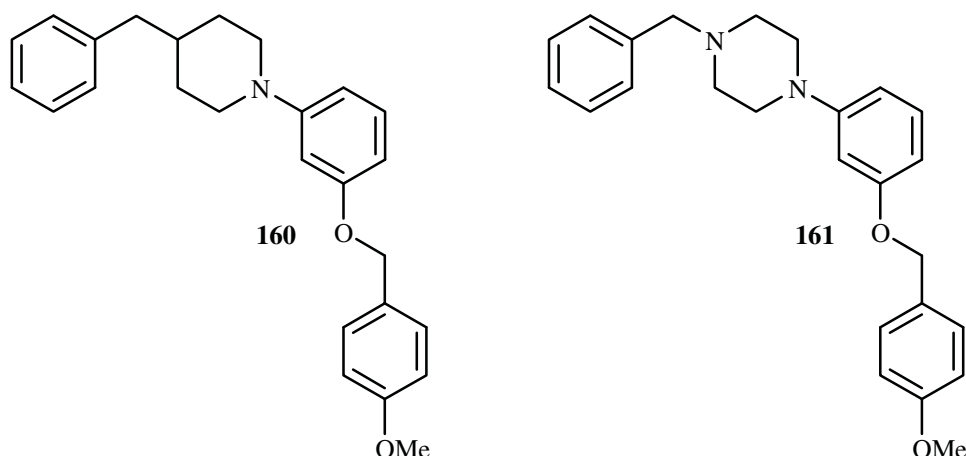
To confirm that the *p*-methoxybenzyl group could be removed easily the deprotection of **159** was carried out. TFA has previously been used for the deprotection of PMB amines in the preparation of 2-aminoquinolines.³¹ The use of TFA has also been reported for the deprotection of PMB protected phenols and was therefore examined for this purpose.¹¹⁴ The protected **159** was treated with TFA at 60 °C (Scheme 54). Chromatographic separation of the crude material from this reaction afforded the desired phenol **141** in good yield (82%). The ¹H NMR spectrum showed the absence of the signals for the PMB group and showed a small shift in the signals for the H2 and H6 hydrogens of the phenol (c.f. $\delta_{\text{H}} = 6.57$ ppm and 6.46 ppm for H2 and H6 respectively in **159** and $\delta_{\text{H}} = 6.41$ ppm and 6.30 ppm for H2 and H6 respectively in **141**). The remaining spectral data was consistent with that obtained for **141** prepared previously.



Scheme 54: Deprotection of **159** with TFA.

Having prepared **141** in reasonable yield (53% over the two steps) using PMB as a protecting group, it was hoped that other 3-substituted phenols could be prepared using this method. The amination reaction employing the catalytic system of Pd(OAc)₂/**35**, with NaO^tBu was carried out with both 4-benzylpiperidine and 1-benzylpiperazine. In both cases, the desired

PMB protected products **160** and **161** were obtained in good yield (68% and 82% respectively).



The formation of these compounds was confirmed by a high resolution mass spectrum in the case of **160** and an elemental analysis in the case of **161**. The ^1H NMR spectrum for each compound showed the characteristic features described above for **159**. The low resolution mass spectra also showed the characteristic cleavage of the *p*-methoxybenzyl group to give a peak at 121 mass units (Figure 80).

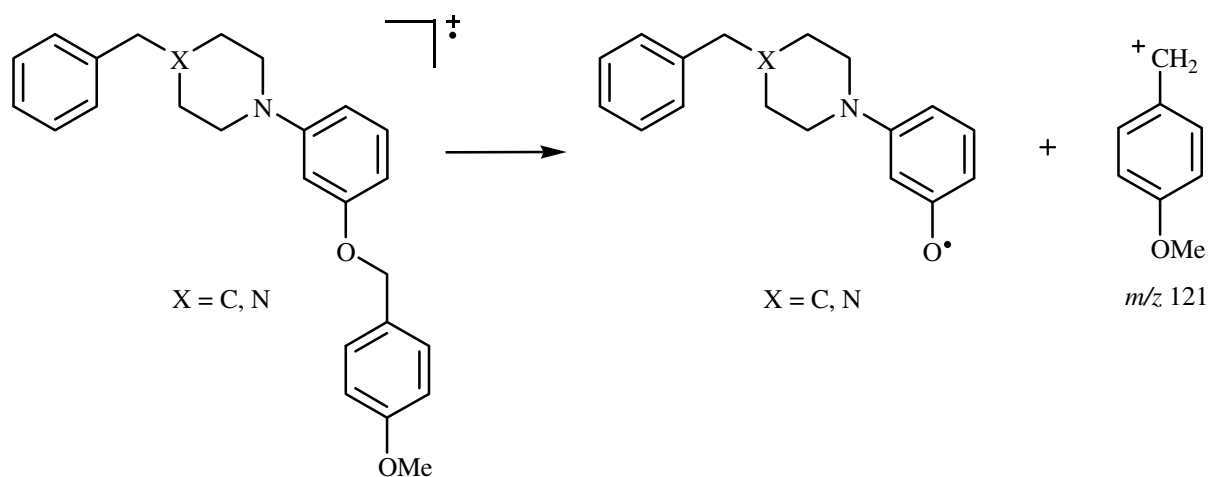


Figure 80: Cleavage in the mass spectrum of **160** and **161** resulting in a peak at 121 mass units.

Compounds **160** and **161** were then deprotected using TFA to give the corresponding phenols **144** and **162**. Both **144** and **162** were isolated in high yield (86% and 81% respectively) after chromatographic separation of the crude material. The ^1H NMR spectra showed the absence of the signals for the PMB group and similarly to **141** showed a small shift in the signals for the H2 and H6 hydrogens of the phenol. The IR spectra displayed a peak at 3597 cm^{-1} for **144**

and 3405 cm^{-1} for **162** corresponding to the phenol functionality and confirming the deprotection. The low resolution mass spectra also showed a peak at 148 mass units resulting from the characteristic partial loss of the heterocyclic substituent observed consistently in heterocyclic substituted compounds. Both also showed the loss of the benzyl group which results in a peak at 91 mass units. The loss of the benzyl group also results in the peaks at 176 and 177 mass units for the phenolic fragments of **144** and **162** respectively (Figure 81).

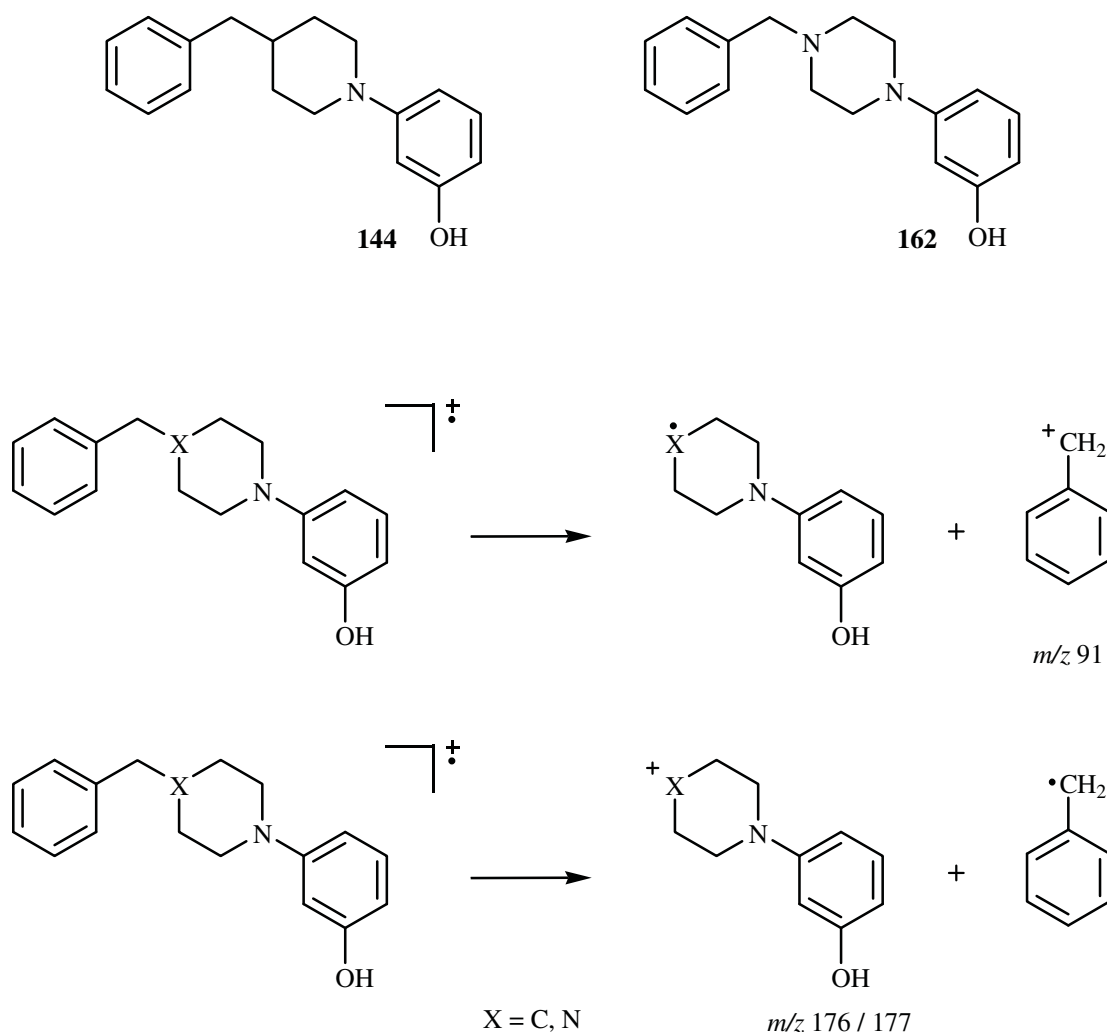
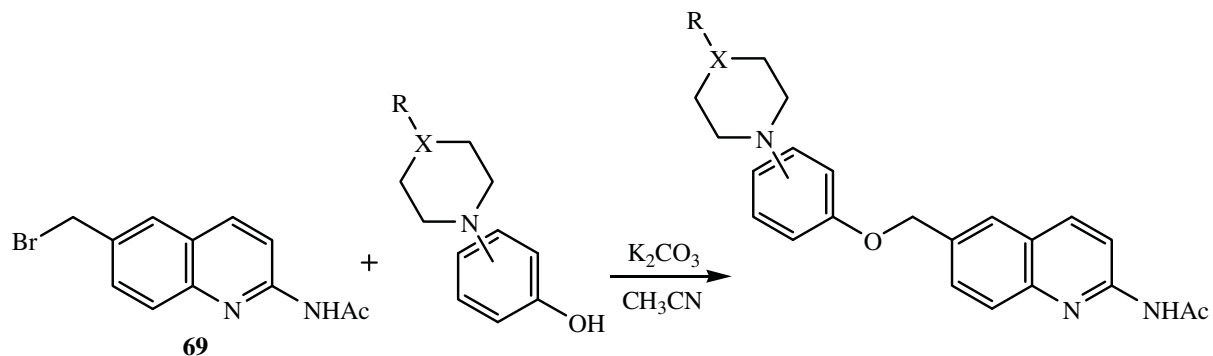


Figure 81: Cleavage in the mass spectra of **144** and **162** resulting in the peaks at 91, 176 and 177 mass units.

4.2.3 Synthesis of Extended 6-Phenoxymethyl-2-Acetamidoquinolines

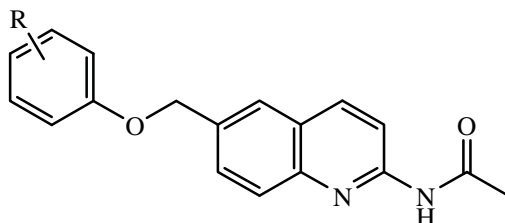
Having prepared a number of 4- and 3-heterocyclic substituted phenols, the next step in the synthetic pathway was to prepare the extended 6-phenoxymethyl-2-acetamidoquinolines. The substitution reaction employed to prepare simple 6-phenoxymethyl-2-acetamidoquinolines

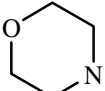
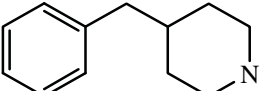
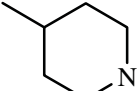
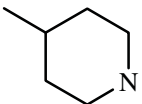
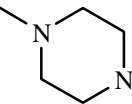
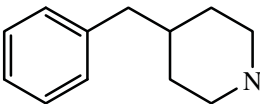
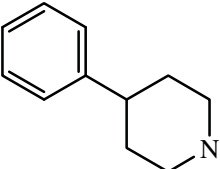
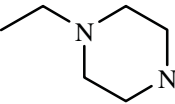
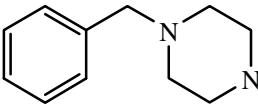
involving K_2CO_3 in acetonitrile was used in the preparation of the desired compounds (Scheme 55). A number of 6-phenoxyethyl-2-acetamidoquinolines were prepared using this method. The yields of these compounds varied significantly (0-78%) and can be seen in Table 30.



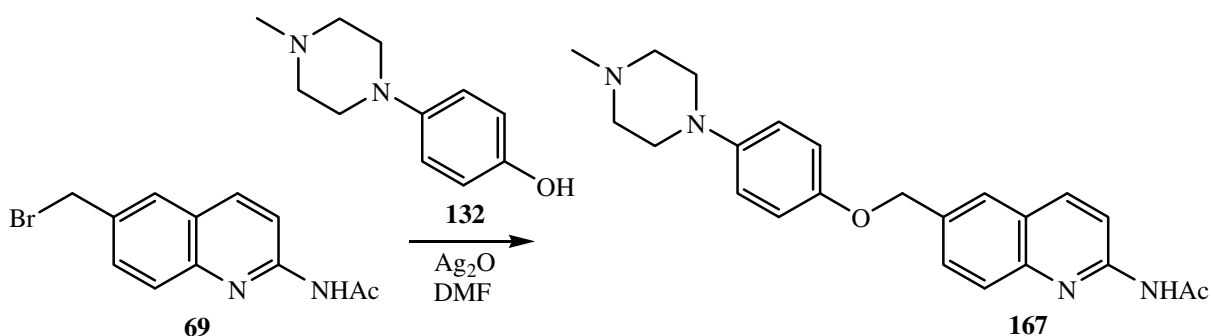
Scheme 55: Preparation of extended 6-phenoxyethyl-2-acetamidoquinolines.

Table 30: Yields of extended 6-phenoxyethyl-2-acetamidoquinolines prepared using the standard substitution procedure.



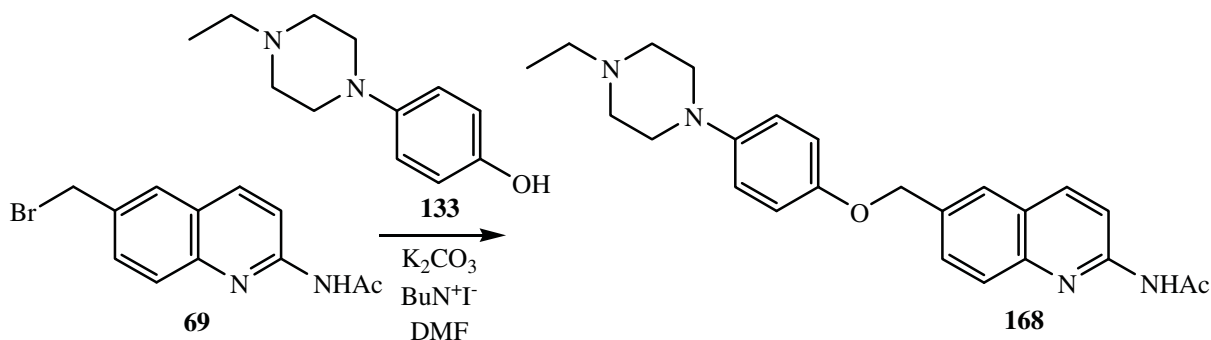
4-Substituent (R)	Yield (%)	4-Substituent (R)	Yield (%)	3-Substituent (R)	Yield (%)
 163	15	 166	47	 169	16
 164	51	 167	0	 170	78
 165	44	 168	10	 171	0

Due to the variation in yield and the inability of this method to provide **167** and **171** an alternate procedure for the preparation of these compounds was required. Silver(I) oxide has been previously used in the alkylation of alcohols and carboxylic acids¹¹⁵⁻¹¹⁷ and has also been employed successfully for the alkylation of phenols.¹¹⁸ The use of silver(I) oxide was therefore examined in this particular case in the reaction of **132** and acetamide **69** (see Scheme 56). In this reaction, predominantly starting material was isolated and only trace amounts of the desired product was observed in the ¹H NMR spectrum of the crude material.



Scheme 56: Attempted synthesis of **167** using silver (I) oxide.

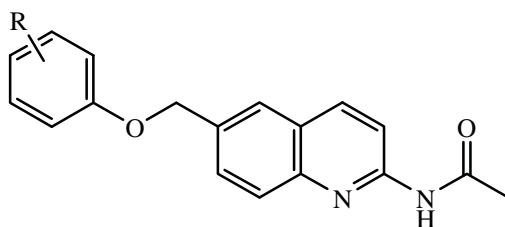
An additional method has been reported for the alkylation of phenols which involves K_2CO_3 and tetra-(*n*-butyl)ammonium iodide in DMF.^{119,120} The use of these conditions for the preparation of **167** afforded a mixture of products and once again only trace amounts of the desired product was observed in the ¹H NMR spectrum of the crude material. No further attempts to prepare **167** were undertaken. These reaction conditions were also employed in the corresponding reaction of **133** and acetamide **69** (see Scheme 57). In this case however, the desired product **168** was isolated in 68% yield. This was a substantial improvement in yield compared to the corresponding reaction carried out in acetonitrile with K_2CO_3 (c.f. 10%).

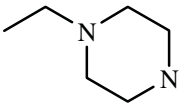
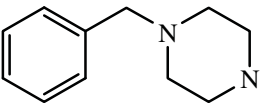
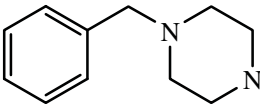
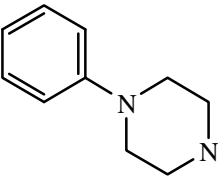
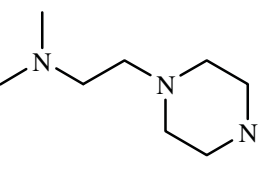


Scheme 57: Synthesis of **168** using K_2CO_3 and $\text{Bu}_4\text{N}^+\text{I}^-$ in DMF.

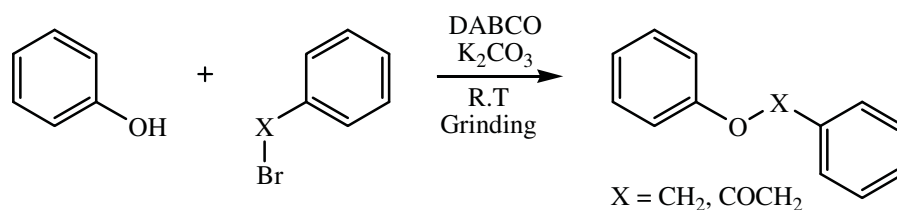
These reaction conditions were then employed to prepare a number of other extended 6-phenoxyethyl-2-acetamidoquinolines. The yields of these compounds can be seen in Table 31. The reactions employing **134** and **135** as the phenols were successful and afforded the desired substituted products **172** and **173** in 94% and 53% yield respectively. In the reaction with **136** as the phenol in the preparation of **174** a complex mixture of products was formed as indicated by the ^1H NMR spectrum of the crude material. No attempts were made to purify this mixture and no further attempts to prepare **174** were undertaken. In the reaction with **162** as the phenol in the preparation of **171** however, only starting material was observed in the crude material as determined by ^1H NMR.

Table 31: Yields of extended 6-phenoxyethyl-2-acetamidoquinolines prepared using K_2CO_3 and BuN^+T in DMF.



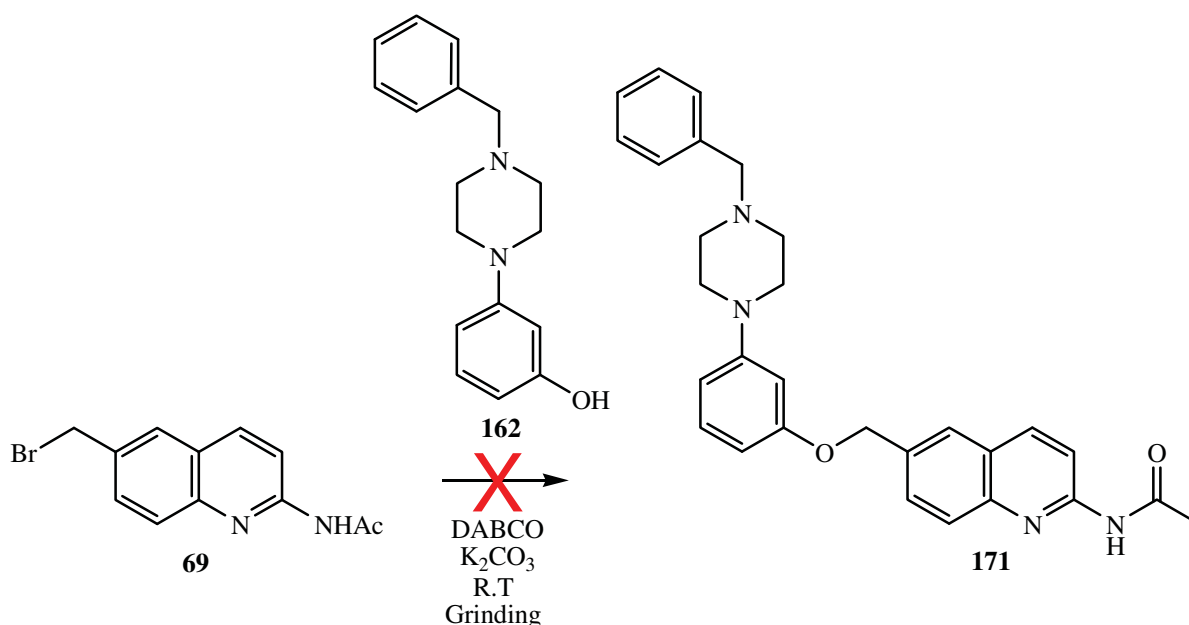
4-Substituent (R)	Yield (%)	4-Substituent (R)	Yield (%)	3-Substituent (R)	Yield (%)
 168	68	 173	53	 171	0
 172	94	 174	0		

A further attempt to prepare **171** was carried out using a method recently reported by Bu *et al.*¹²¹ This report detailed the preparation of phenacyl ethers and phenyl ethers from the corresponding phenols and phenacyl bromide or benzyl bromide respectively under solvent free conditions. These reactions involved the periodic grinding of the reagents of the reaction in the presence of the organic base 1,4-diazabicyclo[2,2,2] octane (DABCO) (Scheme 58). The yields obtained were typically 80% or greater and were achieved in 5-60 minutes of grinding.



Scheme 58: Alkylation of phenols under solvent free conditions as reported by Bu *et al.*¹²¹

The reaction of **162** and acetamide **69** was attempted using the reported conditions (Scheme 59). After periodic grinding for two hours none of the desired product **171** was observed in the ¹H NMR spectrum of the crude material and only starting material was observed. These reaction conditions were therefore not suitable for the preparation of **171**. No additional attempts to prepare **171** were made.



Scheme 59: Attempted synthesis of **171** under solvent free conditions.

For the prepared 6-phenoxyethyl-2-acetamidoquinolines a high resolution mass spectrum consistent with the calculated mass and/or an elemental analysis consistent with the theoretical composition of the desired product was obtained. The low resolution mass spectra for each compound showed the characteristic fragmentations observed with the simple 6-phenoxyethyl-2-acetamidoquinolines. Specifically, a peak at 199 mass units corresponding to the loss of the phenolic functionality was observed and a peak at 157 mass units was also observed resulting from a McLafferty style rearrangement of the above daughter ion (Figure 82).

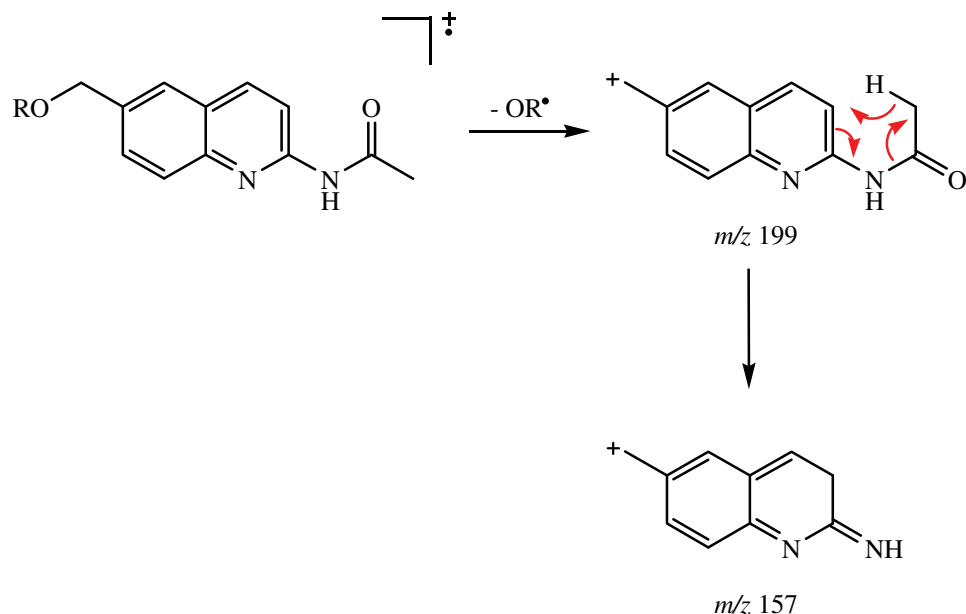


Figure 82: Characteristic cleavages from the mass spectra of 6-substituted-2-acetamidoquinolines.

The ^1H NMR spectra displayed peaks corresponding to the new substituent at the 6-position and also showed a shift in the methylene hydrogens. For all of the compounds a downfield shift in the signal for the methylene hydrogens was observed to the range of $\delta_{\text{H}} = 5.16\text{-}5.21$ ppm (c.f. **69** $\delta_{\text{H}} = 4.65$ ppm). This downfield shift was similarly observed with the introduction of the simple phenoxy substituents as described in Chapter 3.

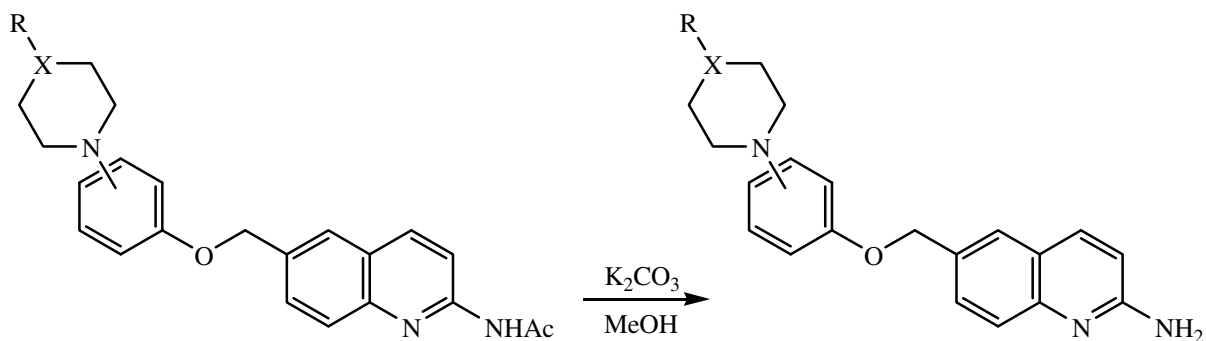
For the 4-heterocyclic phenoxyethyl compounds the two sets of equivalent phenolic hydrogens H(2/6) and H(3/5) displayed a small downfield shift from $\delta_{\text{H}} = 6.73\text{-}6.80$ ppm for H(2/6) and $\delta_{\text{H}} = 6.84\text{-}6.93$ ppm for H(3/5) in the phenols to $\delta_{\text{H}} = 6.90\text{-}6.96$ ppm for both H(2/6) and H(3/5). This downfield shift indicated the change in the electron donating ability of the free phenol to the phenyl ether functionality. These phenolic H(2/6) and H(3/5) signals were observed to overlap in the region of $\delta_{\text{H}} = 6.90\text{-}6.96$ ppm (Table 32) for the 4-heterocyclic phenoxyethyl compounds. Compound **163** was the only exception to this and displayed two distinct signals for the H(2'/6') and H(3'/5') hydrogens at $\delta_{\text{H}} = 6.90$ and 6.96 ppm respectively. The 3-heterocyclic substituted compounds also displayed a small downfield shift in the signals for the phenolic H2 and H6 hydrogen signals (from $\delta_{\text{H}} = \sim 6.29$ ppm for H2 and $\delta_{\text{H}} = 6.40$ ppm for H6 in the phenols to $\delta_{\text{H}} = \sim 6.46$ for H2 and $\delta_{\text{H}} = \sim 6.59$ ppm H6). The ^{13}C NMR spectra for all of these compounds also showed a large downfield shift in the signal corresponding to the methylene group from $\delta_{\text{C}} = 33.6$ ppm in **69** to $\delta_{\text{C}} = \sim 70$ ppm confirming the introduction of the phenoxy functional group.

Table 32: Comparison of the phenolic H(2/6) and H(3/5) hydrogens chemical shifts in the 6-(4-heterocyclic phenoxy)methyl-2-acetamidoquinolines.

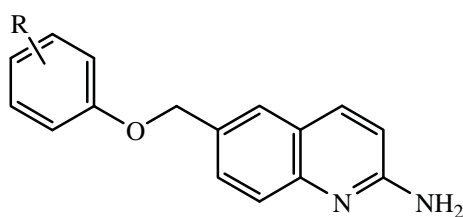
	δ_{H}
	H(2/6) H(3/5)
163	6.90, 6.96
164	6.93
165	6.96
166	6.90
168	6.90
172	6.95
173	6.90

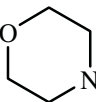
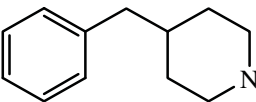
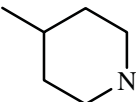
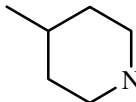
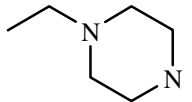
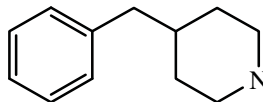
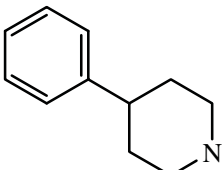
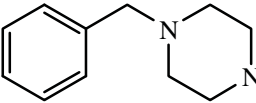
4.2.4 Synthesis of Extended 6-Phenoxyethyl-2-Aminoquinolines

The final step in the synthetic pathway for the preparation of the extended 6-phenoxyethyl-2-aminoquinolines was the removal of the acyl protecting group. This was carried out with the same method used for the preparation of the simple 6-phenoxyethyl-2-aminoquinolines involving treatment with K_2CO_3 in methanol (Scheme 60). In all cases, except for the reaction involving **172**, this procedure was successful for the removal of the acyl group and afforded the desired 2-aminoquinoline ligands in good to high yield (Table 33).

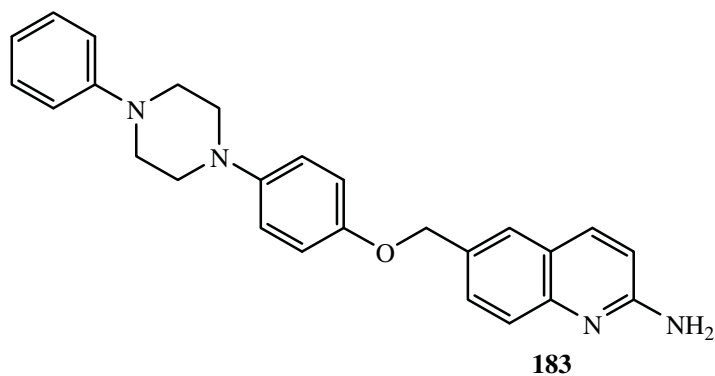


Scheme 60: Deprotection of 6-phenoxyethyl-2-acetamidoquinolines.

Table 33: Yields of extended 6-phenoxyethyl-2-aminoquinolines.

4-Substituent (R)	Yield (%)	4-Substituent (R)	Yield (%)	3-Substituent (R)	Yield (%)
 175	90	 178	83	 181	83
 176	85	 179	77	 182	77
 177	75	 180	64		

In the case of **172**, treatment with K_2CO_3 in methanol did not lead to the desired product **183** and only starting material was recovered from this reaction. The failure of this reaction was thought to be due to the incomplete solubility of **172** in the reaction solvent. A suitable organic solvent to completely dissolve **172** could not be found and further attempts to deprotect this compound using K_2CO_3 were made in solvents in which **172** was only partially soluble. These solvents included DMF, THF, acetonitrile and DMSO/water and in every instance only starting material was recovered from the reaction. An additional attempt to deprotect **172** involved treatment with hydrochloric acid (3 M) and heating at reflux. This method however, led to the decomposition of **172** and not the formation of the desired product. Treatment of **172** with sodium hydroxide (3 M) with heating at 50 °C similarly did not afford the desired product and only starting material was recovered.



Elemental analyses of the products **176**, **177**, **179-182** were obtained which were consistent with the elemental compositions of the desired products. High resolution mass spectra were obtained for products **175** and **178** and were also consistent with the desired products. The low resolution mass spectra for all of the products, except **179** and **180** (which had LSIMS analyses performed) showed a characteristic fragmentation at m/z 157, which results from the loss of the phenolic substituent. The loss of the phenolic substituent was also observed in the low resolution mass spectra of the 6-phenoxyethyl ligands discussed in Chapter 3.

The ^1H NMR spectra for the extended 6-phenoxyethyl substituted compounds also displayed similar characteristic changes to the ligands described in Chapter 3. The signal for H4 was observed to shift upfield slightly and the signal for H3 shifted significantly upfield (from $\delta_{\text{H}} = \sim 8.38\text{-}8.44$ ppm to $\delta_{\text{H}} = \sim 6.57\text{-}6.75$ ppm). The upfield shift of the signals corresponding to H3 occurs as a result of the resonance donation of the lone pair of electrons on the amino group which shields the hydrogen at H3 (as discussed in Chapter 3; see Figure 43 and Figure 46). The ^1H NMR spectra no longer displayed a signal corresponding to the methyl of the protecting group and the ^{13}C NMR spectra similarly did not show a signal for the methyl and the carbonyl peak at $\delta_{\text{C}} = \sim 170$ ppm was no longer present. The IR spectra also showed two peaks in the region of $3400\text{-}3700\text{ cm}^{-1}$ corresponding to the free amino functionality.

All of the extended 6-substituted-2-aminoquinolines prepared **175-182** were assayed for binding affinity for the Tec SH3 domain using the [^1H , ^{15}N] HSQC NMR assay. The binding affinities of these ligands and the SAR study is discussed in Chapter 5.

Chapter 5:

BINDING STUDIES OF 6-ARYLOXYMETHYL-, 6-ARYLTHIOMETHYL- AND EXTENDED 6-PHENOXYMETHYL-2-AMINOQUINOLINES

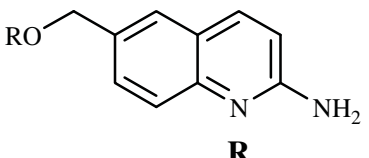
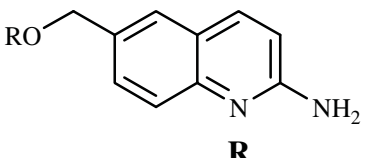
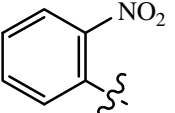
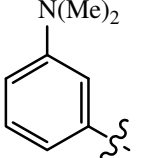
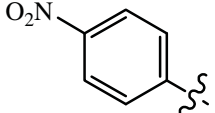
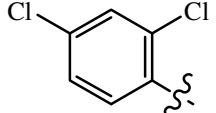
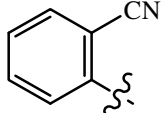
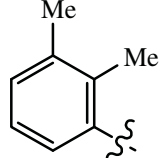
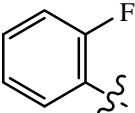
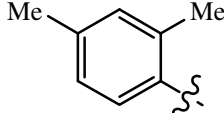
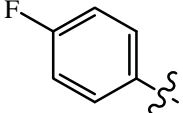
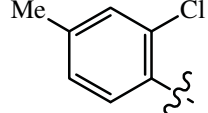
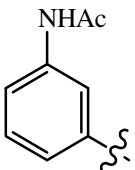
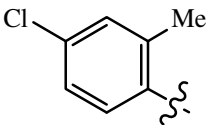
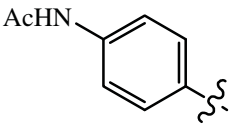
5.1 Binding Affinities of 6-Aryloxymethyl-, 6-Arylthiomethyl- and Extended 6-Phenoxymethyl-2-Aminoquinolines for the Tec SH3 Domain

The 6-aryloxymethyl- and 6-arylthiomethyl-2-aminoquinolines **101-108** and **110-126**[†] prepared in Chapter 3 were assayed for binding affinity for the Tec SH3 domain using the [¹H, ¹⁵N] HSQC NMR assay. The K_d s of the ligands **101-108** and **110-114** (Group 1) are given in Table 34 and ligands **115-124** and **126** (Group 2) in Table 35 respectively. Similarly to the 6-heterocyclic substituted ligands, the phenomenon of intermediate exchange was encountered with ligand **110** (see Section 2.3.1). In this particular instance, the first data point was removed to reduce the experimental error and allow for the calculated binding isotherm and K_d to better represent the data obtained from the NMR assay. The revised K_d is shown in Table 34. As shown in Table 34 and Table 35, all of the ligands displayed improved affinity for the Tec SH3 domain compared to the lead compound **2** ($K_d = 125 \mu\text{M}$).

The extended 6-phenoxymethyl-2-aminoquinolines **175-182** (Group 3) prepared in Chapter 4 were also assayed for binding affinity for the Tec SH3 domain using the NMR assay. The K_d s of the Group 3 ligands are given in Table 36. As can be seen in Table 36 the binding affinities for some of the Group 3 ligands could not be determined. For those ligands whose binding affinities could be obtained, all ligands showed improved binding affinity relative to the lead compound **2** and were in the range of 18 - 50 μM .

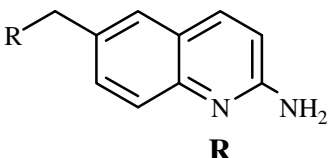
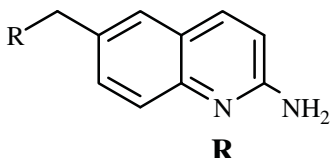
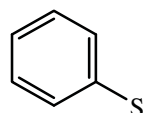
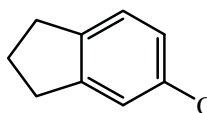
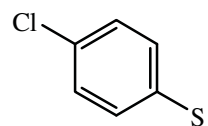
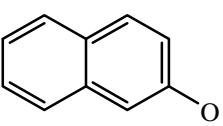
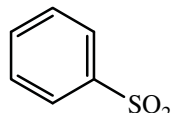
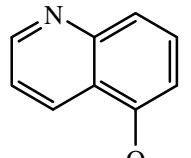
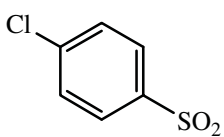
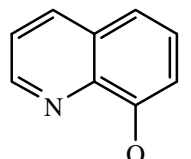
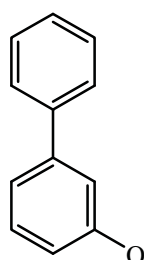
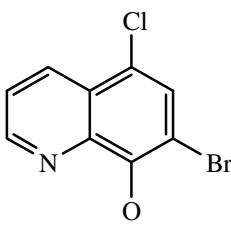
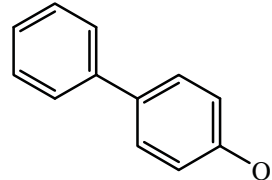
[†] **125** was not assayed due to its insolubility in assay medium.

Table 34: K_d s of Group 1 Ligands **101-108** and **110-114**.

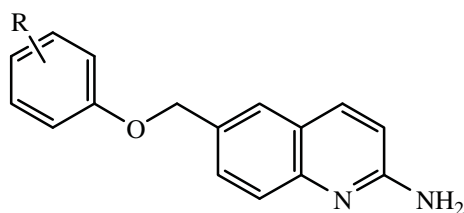
		K_d (μM)		K_d (μM)	
101		24 ± 2	108		34 ± 3
102		38 ± 2	110		28 ± 5^a
103		44 ± 13	111		18 ± 6
104		25 ± 1	112		43 ± 4
105		29 ± 2	113		39 ± 16
106		35 ± 8	114		70 ± 10
107		24 ± 3			

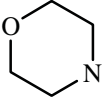
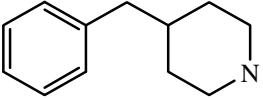
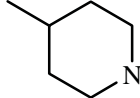
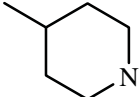
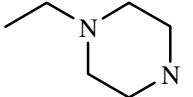
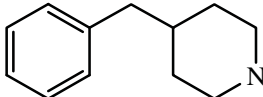
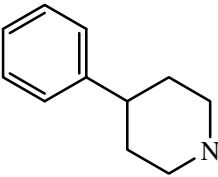
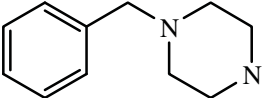
^a First data point removed.

Table 35: K_d s of Group 2 Ligands **115-124** and **126**.

 R		K_d (μM)	 R		K_d (μM)
115		29 ± 9	121		33 ± 11
116		19 ± 4	122		8 ± 2
117		42 ± 10	123		29 ± 3
118		38 ± 10	124		21 ± 6
119		$8 \pm 3^\dagger$	126		22 ± 4
120		7 ± 2			

[†] **119** was assayed as a 7:1 mixture with **120**.

Table 36: K_d s of Group 3 Ligands **175-182**.

4-Substituent (R)	K_d (μM)	4-Substituent (R)	K_d (μM)	3-Substituent (R)	K_d (μM)
 175	23 ± 3	 178	†	 181	49 ± 4
 176	†	 179	26 ± 6	 182	18 ± 4
 177	†	 180	†		

† K_d could not be determined from NMR assay.

5.2 Typical Characteristics of the [^1H , ^{15}N] HSQC NMR Assay

In the HSQC NMR assay, the addition of a ligand typically results in a number of amino acid residues being affected upon binding of the small molecule ligand to the SH3 domain. This results in changes in the ^1H chemical shifts of the signals for these residues in the [^1H , ^{15}N] HSQC NMR spectra (fast exchange). Residues whose ^1H chemical shift is altered by > 0.08 ppm at saturation binding can be used to determine the K_d of the ligand. In addition to changes in the ^1H chemical shift of the signal for the residues affected by the binding of the ligand, some amino acid signals also disappear and can no longer be seen in the [^1H , ^{15}N] HSQC NMR spectra (intermediate exchange). For the 6-heterocyclic and 6-phenoxy-methyl-2-aminoquinoline ligands shown in Table 20 and Table 38 respectively (approximately 40 ligands), the addition of a ligand to the SH3 domain results in typically twelve to fifteen residues being effected as determined by significant changes in the ^1H chemical shift or the signal for the residue disappearing.

Of the amino acid residues that are effected the two key residues proposed to comprise part of the binding site, the side chain of W215 (W215 ϵ 1) and D196, are indicative of the ligand binding at this site. Typically, the signal for the side chain of W215 disappears (due to intermediate exchange) after the addition of the first or second aliquot of the ligand. In many cases, the signal for the side chain of W215 can be observed again as further aliquots of the ligand are added (Figure 83). Generally, the signal for the side chain of the W215 residue is shifted upfield significantly in the ^1H dimension ($\Delta\delta$ 0.4 ppm) and also in the ^{15}N dimension (see Table 37).

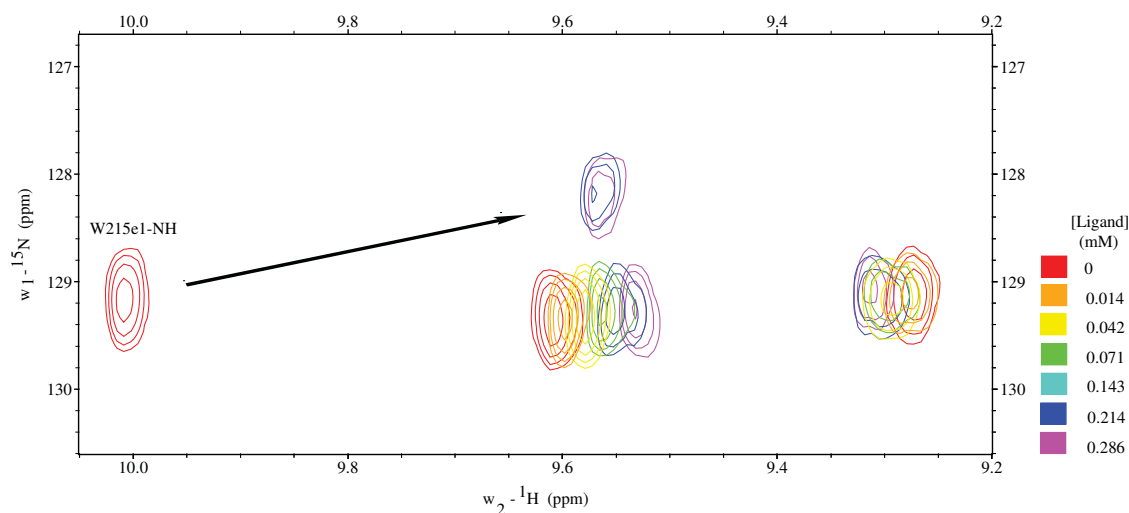


Figure 83: Example of the characteristic disappearance and reappearance of the signal for the sidechain of W215 in the [^1H , ^{15}N] HSQC NMR spectra.

Table 37: Table showing the typical changes in the chemical shifts of the signals for the D196 residue and the side chain of the W215 residue.

	$\Delta\delta$ ^1H	$\Delta\delta$ ^{15}N
W215 ϵ1	-0.4	-1.2
D196	+0.1	+0.3

An upfield change in chemical shift is denoted with a (-) and a downfield change is denoted with a (+).

The signal for the D196 residue is typically significantly shifted downfield in the ^1H dimension upon addition of the ligand to the SH3 domain ($\Delta\delta$ 0.1 ppm). A small downfield shift in the ^{15}N dimension is also commonly observed for this residue (see Table 37 and Figure 84).

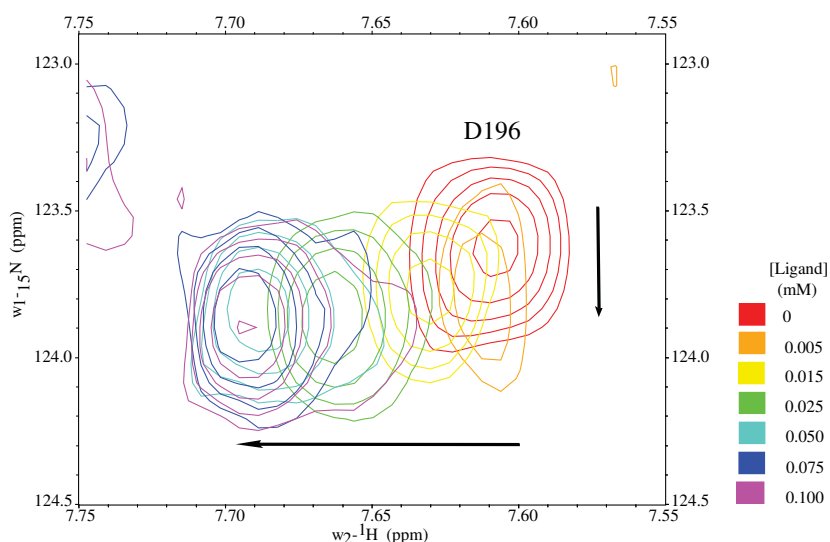


Figure 84: Example of the characteristic downfield shift in the signal for D196 in the [^1H , ^{15}N] HSQC NMR spectra.

5.3 Binding Studies of 6-Aryloxymethyl-, 6-Arylthiomethyl- and Extended 6-Phenoxymethyl-2-Aminoquinolines for the Tec SH3 Domain

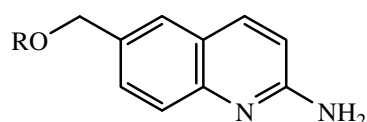
5.3.1.1 Binding Studies of Group 1 Ligands

For the ligands **101-108** and **110-114** (Group 1) typical behaviour was observed in the HSQC NMR assay and an average of fourteen amino acid residues were affected upon the addition of these ligands to the Tec SH3 domain. In addition, the signals for the D196 residue and the sidechain of the W215 residue displayed characteristic changes in the HSQC spectra. For the ligands **115-124** and **126** (Group 2) shown in Table 35, the typical behaviour was not observed and an average of only six residues were consistently affected upon the addition of the ligand to the SH3 domain. Interestingly, the signal for one of the key residues, D196, displayed particularly unusual behaviour. Due to the unusual behaviour displayed by the Group 2 ligands in the NMR assay, the binding affinities of these ligands will be discussed separately to that of the Group 1 ligands, which displayed normal behaviour in the NMR assay.

The binding affinity of the Group 1 ligands **101-108** and **110-114** were found to be in the range of $\sim 20\text{-}40\ \mu\text{M}$, except for **114**. This is a 3-6 fold improvement in binding affinity as compared to the lead compound **2** ($K_d = 125\ \mu\text{M}$). This suggests that the phenoxymethyl substituent makes an additional contact with the protein surface providing a substantial improvement in binding affinity. Initial analysis of the binding affinities of the Group 1 ligands however, did not show any obvious trends in the binding affinities of the ligands and the nature of the substituent on the phenoxymethyl functionality. To obtain a better

understanding of the binding interactions of the 6-phenoxyethyl-2-aminoquinolines with the Tec SH3 domain, the Group 1 ligands prepared in this work were analysed with the other 6-phenoxyethyl-2-aminoquinoline ligands prepared previously (see Table 38).^{31,35} Intermediate exchange issues were also encountered in the NMR assays of some of the previously prepared ligands. These issues have been addressed previously and the revised binding data is shown in Table 38.³¹

Table 38: K_d s of 6-phenoxyethyl-2-aminoquinolines.



		2-Subs	3-Subs	4-Subs	2,3-Di-Subs	2,4-Di-Subs
R	K_d (μ M)	K_d (μ M)	K_d (μ M)	K_d (μ M)	K_d (μ M)	K_d (μ M)
C_6H_5	184 32 ± 4					
Me- $C_6H_{3/4}$		185 37 ± 5	186 39 ± 4	187 23 ± 4	111 18 ± 6	112 43 ± 4
^t Pr- C_6H_4		188 34 ± 9		189 13 ± 1		
^t Bu- C_6H_4			190 58 ± 8	191 14 ± 2		
OMe- C_6H_4			192 40 ± 4	193 15 ± 1		
N(Me) ₂ - C_6H_4			108 34 ± 3			
F- C_6H_4		104 25 ± 1		105 29 ± 2		
Cl- $C_6H_{3/4}$		194 13 ± 2		195 9 ± 2		110^a 28 ± 5
Br- C_6H_4		196 12 ± 3		197 10 ± 3		
CN- C_6H_4		103 44 ± 13				
NO ₂ - C_6H_4		101 24 ± 2		102 38 ± 2		
NHAc- C_6H_4		198 54 ± 6	106 35 ± 8	107 24 ± 3		
2-Me-4-Cl- C_6H_3						114 70 ± 10
2-Cl-4-Me- C_6H_3						113 39 ± 17

^a First data point removed.

With all of the 6-phenoxyethyl-2-aminoquinoline ligand binding data to hand, an evaluation could take place and several trends were apparent in the binding affinities. The parent phenyl ether **184** displayed an approximately 4-fold improvement in binding affinity for the Tec SH3 domain ($K_d = 32 \mu\text{M}$ c.f. **2** $K_d = 125 \mu\text{M}$). This improvement is likely due to the formation of a hydrophobic contact between the phenoxyethyl substituent and the protein surface. Substitution on the phenolic functionality provides differences in binding affinities of the ligands.

In regard to the alkyl substituents (**185-191**), a substituent in the *para* position provides a small improvement in binding affinity relative to the parent phenol. However, an alkyl substituent in either the *meta* or *ortho* position causes a slight reduction in binding affinity. This suggests that a substituent in the *para* position is more favourable than in other positions around the aromatic ring. It would also appear that a larger substituent, such as the *iso*-propyl and *tert*-butyl groups, is more favoured over the smaller methyl substituent. The improvement in binding is also likely to be due to an additional hydrophobic contact, which is most favourable when the substituent is in the *para* position. Interestingly, the 2,3-dimethylsubstituted ligand **111**, has similar affinity to the *para* substituted equivalent **187** (c.f. **111** $K_d = 18 \mu\text{M}$; **187** $K_d = 23 \mu\text{M}$). However, the 2,4-dimethylsubstituted ligand **112**, has a reduced affinity and is similar to the *ortho* and *meta* substituted equivalents **185** and **186** (c.f. **112** $K_d = 43 \mu\text{M}$; **185** $K_d = 37 \mu\text{M}$ and **186** $K_d = 39 \mu\text{M}$). The improvement in affinity for the Tec SH3 domain of **111** compared to either **185** or **186** could be due to the second substituent leading to an enhanced hydrophobic contact. However, for **112** the second substituent presumably causes an unfavourable interaction, which leads to a reduction in binding affinity.

Ligands with electron donating substituents as in **108**, **192** and **193** displayed similar binding affinities (K_d 's = 34, 15 and 40 μM respectively) to the alkyl substituted equivalents, with the methoxy substituent being preferred similarly in the *para* position. Ligands containing inductively withdrawing halogen atoms on the phenoxy group (**104**, **105**, **194-197**) displayed a 4-14 fold improvement in binding affinity relative to **2** and are amongst the highest affinity ligands prepared thus far (K_d 's = 25, 29, 13, 9, 12 and 10 μM respectively). The halogen substituted ligands have a greater affinity for the Tec SH3 domain than the parent phenyl ether **184** and the alkyl substituted ligands with the larger halogens, chlorine and bromine, displaying a slightly higher affinity than the fluorine equivalents. The position of the halogen

on the ring does not appear to effect the binding affinity significantly and the improvement in binding affinity could be attributed to hydrophobic interactions with the SH3 domain surface. Similarly to **112**, 2,4-dichloro substitution in ligand **110**, leads to a reduction in binding affinity ($K_d = 28 \mu\text{M}$ c.f. $K_d = 13$ and $9 = \mu\text{M}$ for **194** and **195** respectively). Mixed methyl and chloro di-substituted ligands **113** and **114** also displayed reduced binding affinity for the Tec SH3 domain as compared to the *ortho* or *para* substituted equivalents (**113** $K_d = 39 \mu\text{M}$ and **114** $K_d = 70 \mu\text{M}$). Once again, it is thought that the second substituent on the ring causes an unfavourable interaction with the protein surface leading to a reduction in binding affinity.

Ligand **103** containing a nitrile substituent and ligands **106**, **107** and **198**, containing acetamido substituents displayed similar affinities to their methyl substituted counterparts (K_d 's = 44, 35, 24 and 54 μM respectively). Again, the acetamido substituent is preferred in the *para* position in ligand **107**. Ligands containing a nitro substituent **101** and **102** however, displayed the reverse pattern in binding affinities, with the nitro substituent being preferred in the *ortho* position (K_d 's = 24, and 38 μM respectively).

The information obtained from analysis of the binding affinities therefore suggests that a large hydrophobic substituent (as in the alkyl substituted ligands and **187**, **189** and **191** and the halogen substituted ligands **195** and **197**) is preferred in the *para* position of the phenolic functionality. Di-substitution with either an alkyl or halogen substituent (or combination of both) however, results in a reduction in binding affinity relative to the mono substituted equivalents. A hydrophilic substituent on the phenolic functionality is generally not as well tolerated as a hydrophobic substituent and may be preferred in the *ortho* position as in ligand **101**.

To determine if there was a true correlation between the binding affinity of the ligand and the hydrophobicity and size of the substituent on the phenolic functionality, the activity of the ligands was compared to the hydrophobicity constants and the molar refractivity of the substituents (see Figure 85 and Figure 86).^{122,123} The phenyl substituted derivatives **119** and **120** were also included in this analysis.

Figure 85: The correlation between the hydrophobicity of the substituent on the phenoxymethyl group and the activity of the ligand. The number indicates the position of the substituent on the phenolic functionality.¹²²

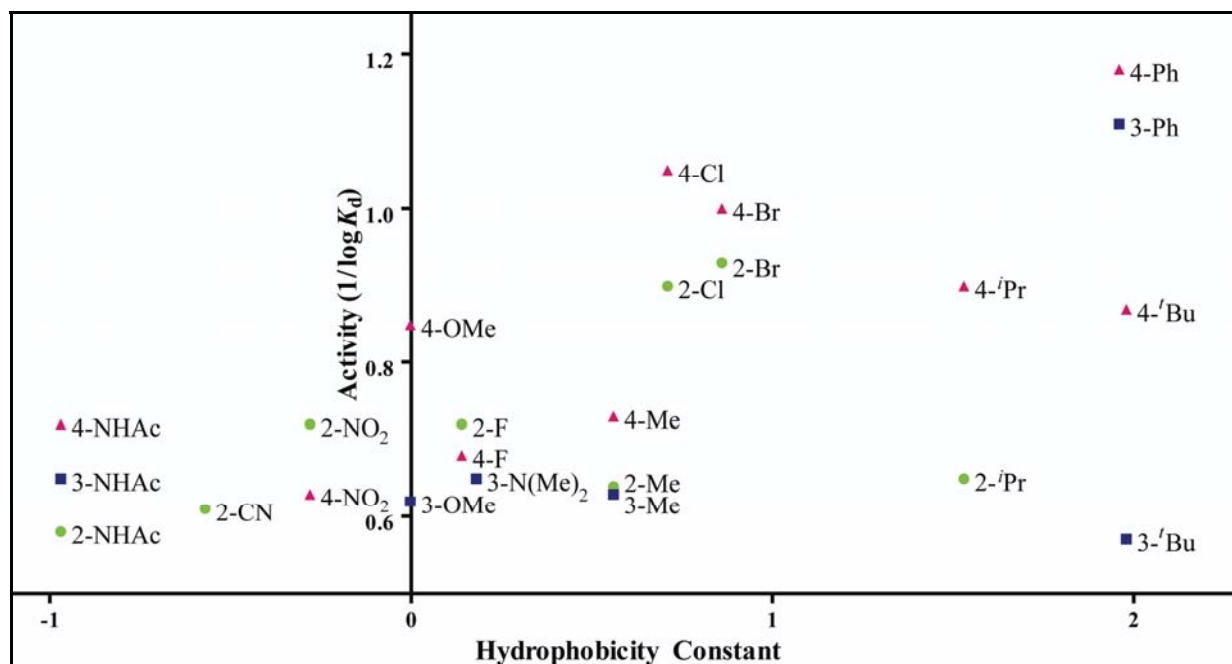
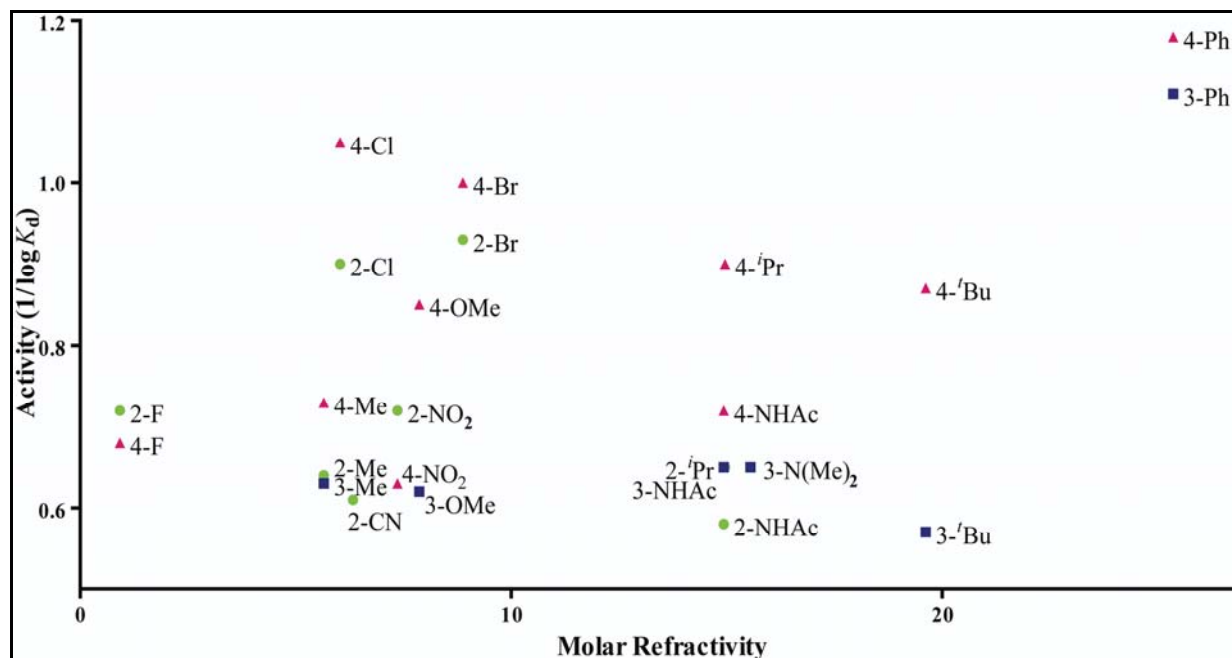


Figure 86: The correlation between the molar refractivity of the substituent on the phenoxymethyl group and the activity of the ligand. The number indicates the position of the substituent on the phenolic functionality.¹²³



Inspection of Figure 85 indicates that as the hydrophobicity increases the binding affinity of the ligand typically improves. The major exceptions to this are the 2-*iso*-propyl ligand **188** and the 3-*tert*-butyl ligand **190**, which display significantly reduced binding affinities compared to their *para*-substituted equivalents. This therefore indicates that these substituents are favoured in the *para* position. The preference for a substituent in the *para* position is also observed for the majority of the substituents. This is consistent with the initial analysis that a hydrophobic substituent in the *para* position can make an additional contact with the protein surface and provide for improved binding affinities. Interestingly, the phenyl substituted ligands **119** and **120** displayed the highest affinities for the Tec SH3 domain and display higher affinities than the *tert*-butyl equivalents **190** and **191** even though both substituents have the same hydrophobicity constant. This indicates that the shape of the substituent is also important for improved binding affinity. Ligands **119** and **120** are large and hydrophobic and appear to be the appropriate shape to make a good contact with the surface of the Tec SH3 domain. Analysis of Figure 86 however, indicates that there is no significant correlation between the size of the substituent and the binding affinity of the ligand and therefore, the size of the substituent does not play a significant part in improved binding affinity. It is likely however, that the size of the substituent plays a minor role in the binding affinity of the ligands for the Tec SH3 domain. From all of the above information, the development of other ligands with bulky hydrophobic aryl substituents was warranted and can be found in the Group 2 ligands **115-124** and **126** discussed in Section 5.3.2.

5.3.1.2 Chemical Shift Mapping of the Group 1 Ligands

The residues that were affected by the addition of the Group 1 ligands (as determined by a chemical shift change of $> \sim 0.08$ ppm) were mapped onto the protein backbone and compared to the 6-heterocyclic-2-aminoquinoline ligands (see Figure 87). Most of the residues affected upon binding of the 6-phenoxyethyl-2-aminoquinoline ligands were also affected by the binding of 6-heterocyclic-2-aminoquinoline ligands. This indicates that these two different classes of 6-substituents occupy a similar area on the protein surface.

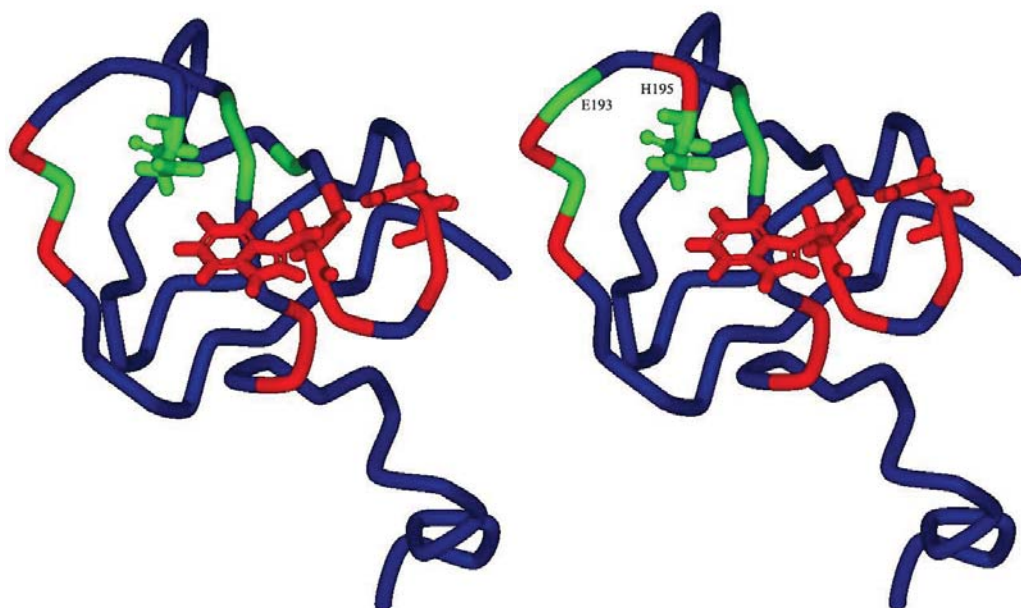


Figure 87: Comparison of chemical shift mapping of the backbone of the Tec SH3 domain with the 6-heterocyclic substituted ligands (left) and the Group 1 ligands (right) where $\delta_H > \sim 0.08$ ppm for the majority of ligands. Downfield shifts are marked in green and upfield shifts are marked in red. W215 and D196 are shown as stick diagrams on the protein backbone to indicate the region where the 2-aminoquinoline ligand binds.

Upon comparison of the two chemical shift maps, it can also be seen that there are two residues (E193 and H195 on the left side of the protein) effected in the 6-phenoxyethyl-2-aminoquinoline ligands that do not appear on the chemical shift map of the 6-heterocyclic-2-aminoquinoline ligands. Although these residues do not appear on the chemical shift map for the 6-heterocyclic-2-aminoquinoline ligands, they are affected by the binding of some of these ligands. However, the effect on these residues, when observed, is significantly less than with the phenoxyethyl ligands with a typical difference in chemical shift of only ~ 0.05 ppm (c.f. $\Delta > 0.1$ ppm). These residues are therefore not used to determine binding affinities as they are not significantly affected by the binding of the 6-heterocyclic ligands.

The greater effect on the residues E193 and H195 with the 6-phenoxyethyl ligands is particularly interesting given that these residues are not in the region where the 6-substituent is directed on the surface of the protein. It is proposed therefore, that the effect is not the result of a specific interaction between the 6-substituent and these residues, but rather a secondary induced effect caused by the interaction of the substituent with other amino acid residues, which subsequently causes changes in the chemical shifts of the E193 and H195 residues. Analysis of the residues involved in the binding of the lead compound **2**, showed

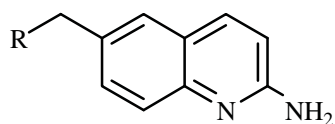
that H195 is significantly affected in the binding event, whereas E193 is not affected. This suggests that the effects on H195 and possibly E193 are also related to the 2-aminoquinoline ring system in addition to the 6-substituent.

5.3.2.1 Atypical Behaviour of the Group 2 Ligands in the [¹H,¹⁵N] HSQC NMR Assay

As mentioned in Section 5.3.1.1, the Group 2 ligands **115-124** and **126** (shown again in Table 39) did not display the typical behaviour in the NMR assay. For these ligands an average of only six residues were observed to be consistently affected upon the addition of the ligand to the SH3 domain. This is substantially fewer residues than are typically affected (see Figure 88 for comparison with Group 1 ligands). Some of the residues not consistently affected by the binding of these ligands include Q190, A191, D196 (on the ‘left’ side of the protein), the side chain of W216 and G226 (around the binding site of the protein).^{††} The apparent absence of any effect on these residues is interesting as all of these residues are affected by the binding of the majority of 2-aminoquinolines prepared to date, regardless of the position and nature of the substituent. Residues N211, D212 (on the ‘right’ side of the protein) and N231 (in the middle lower part of the protein) are also not consistently affected by the addition of the Group 2 ligands. These residues are however, affected by the addition of the 6-heterocyclic-2-aminoquinolines, the Group 1 ligands and the other 6-phenoxy-methyl-2-aminoquinolines prepared previously.³¹

^{††} Some of these residues are significantly affected by the addition of a specific ligand, however, they are not affected by the addition of the majority of ligands.

Table 39: Group 2 Ligands **115-124** and **126**.



115		119		123	
116		120		124	
117		121		126	
118		122			

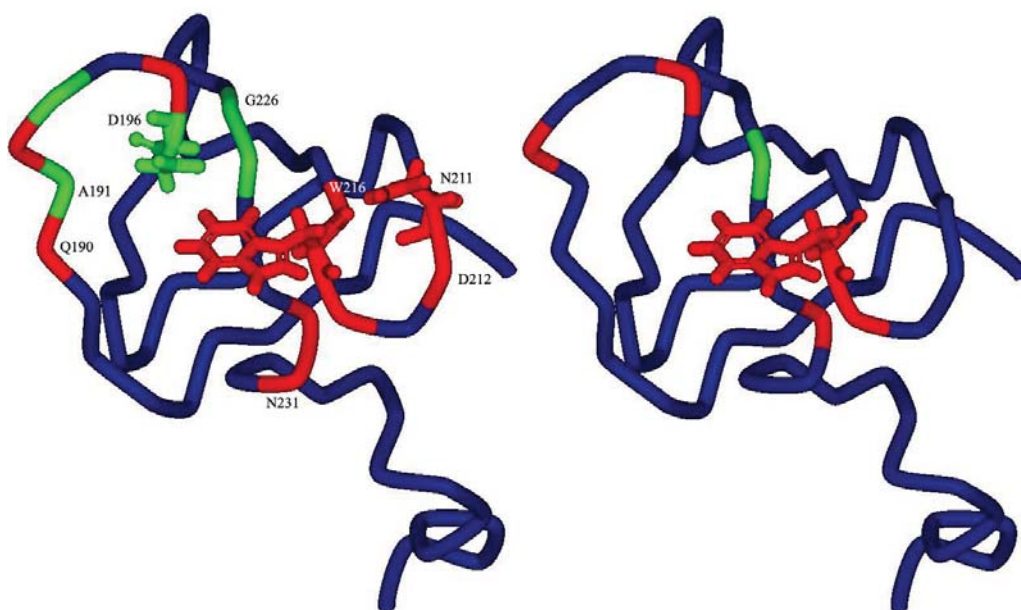


Figure 88: Comparison of chemical shift mapping of the backbone of the Tec SH3 domain with the Group 1 ligands (left) and the Group 2 ligands (right) where $\delta_H > 0.08$ ppm for the majority of ligands. Downfield shifts are marked in green and upfield shifts are marked in red.

The effect of the Group 2 ligands on the D196 residue is particularly interesting. The addition of a ligand to the SH3 domain typically causes the signal for the D196 residue to be shifted significantly downfield in the ^1H dimension and only slightly downfield in the ^{15}N dimension in the [$^1\text{H},^{15}\text{N}$] HSQC NMR spectra. The addition of only one of the ligands, **123**, resulted in the typical behaviour of this residue, with a significant downfield shift in the ^1H dimension being observed along with a small downfield shift in the ^{15}N dimension (see Table 40). Ligand **121** displayed a similar result; however, the downfield shift in the ^1H dimension was much less. Ligands **115** and **117** similarly resulted in only a small downfield shift in the ^1H dimension, however, the downfield shift in the ^{15}N dimension was greater than what is typically observed. Ligands **116** and **124** also resulted in a large downfield shift in the ^{15}N dimension, however a small upfield shift in the ^1H dimension was observed. All of the remaining ligands resulted in an upfield shift in the ^1H dimension of the signal for D196 and a downfield shift in the ^{15}N dimension. For ligands **119**, **122**, and **126** both the upfield shift in the ^1H dimension and the downfield shift in the ^{15}N dimension were small. For **118**, the shift in the ^1H dimension was small however, the downfield shift in the ^{15}N dimension was significant ($\Delta \sim 1.1$ ppm) (see Figure 89 c.f. Figure 84). For **120**, the reverse was observed and the shift in the ^{15}N dimension was small and the upfield shift in the ^1H dimension was significant ($\Delta \sim 0.8$ ppm) (see Figure 89 c.f. Figure 84).

Table 40: Table showing the changes in the chemical shifts of the signal for the D196 residue in the NMR assays of the Group 2 ligands. The typical change in the chemical shifts is included for comparison.

Ligand	$\Delta\delta$ ^1H	$\Delta\delta$ ^{15}N
Typical	+0.1	+0.3
123	+0.08	+0.2
121	+0.03	+0.3
115	+0.04	+0.5
117	+0.01	+0.7
116	-0.03	+0.8
124	-0.02	+0.7
119	-0.03	+0.4
122	-0.02	+0.4
126	-0.01	+0.4
118	-0.04	+1.1
120	-0.08	+0.5

An upfield change in chemical shift is denoted with a (-) and a downfield change is denoted with a (+).

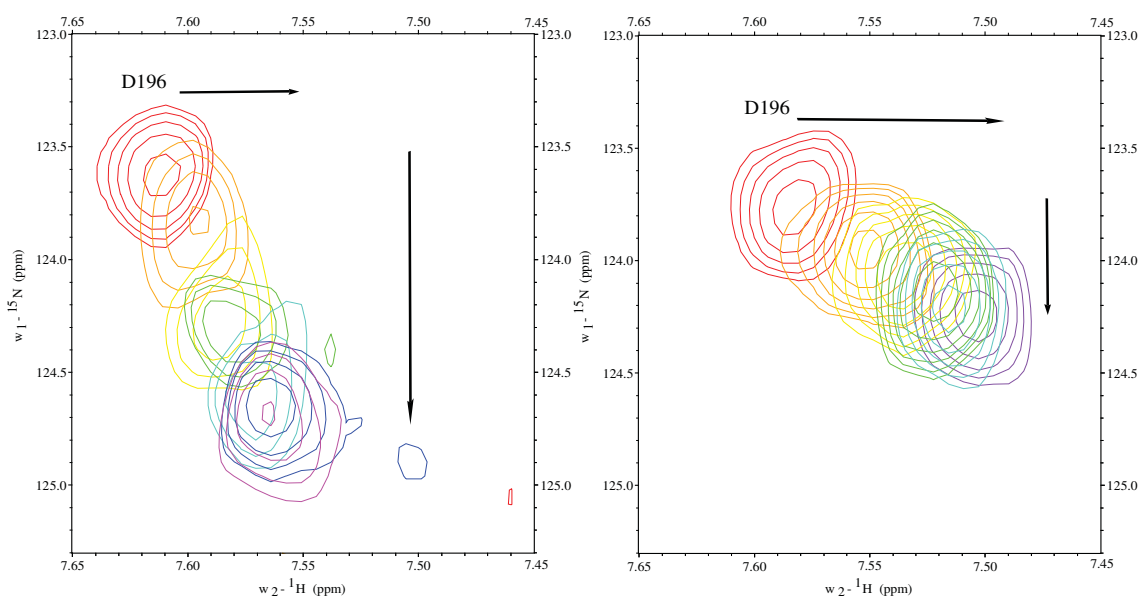


Figure 89: $[^1\text{H}, ^{15}\text{N}]$ HSQC NMR spectra of the signal for D196 in **118** (left) and **120** (right).

As mentioned previously, D196 is thought to play a key role in the binding of 2-aminoquinolines derivatives to the Tec SH3 domain by the formation of a salt bridge between the negatively charged D196 and the positively charged ligand under physiological conditions (see Figure 90). The reason for the different behaviour of D196 upon the addition of the Group 2 ligands is puzzling given that these ligands still have the ability to form a salt bridge. This different behaviour could therefore suggest that these ligands bind in a slightly different orientation in the binding site of the Tec SH3 domain. These ligands may not be able to occupy the precise position occupied by the Group 1 ligands or other ligands prepared previously, due to the size and/or shape of the extended C6-substituent and may be forced to bind in a slightly different orientation and/or position. This could then result in a less than optimal salt bridge with D196 resulting in the different behaviour of this residue in the $[^1\text{H}, ^{15}\text{N}]$ HSQC NMR spectra. The fact that the other residues typically affected upon the addition of a ligand are not affected by the addition of these ligands, as discussed above, would also support the idea of these ligands occupying a slightly different orientation and/or position in the binding site.

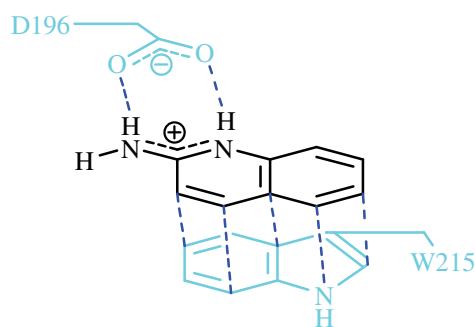


Figure 90: Interaction of 2-aminoquinoline with D196 and W215.

For all of the Group 2 ligands, excluding **120**, the side chain of W215 displayed normal behaviour in the NMR assay. Specifically for ligands **115-119**, **123**, **126** and **127** the signal for the side chain of W215 was observed to disappear upon the addition of the ligand to the SH3 domain. For ligand **122** a significant change in the ^1H chemical shift was observed for this signal. The normal behaviour of the side chain of W215 in these instances indicates that the Group 2 ligands bind in the same region as other ligands with more simple substitution that display typical behaviour in the NMR assay. This would also be consistent with the ligand occupying a slightly different orientation and/or position on the binding site.

The addition of **120** did not result in typical behaviour for the side chain of W215 and no effect on the chemical shift of this residue was observed. Ligand **120** also displayed aberrant behaviour at D196 with a significant upfield shift in the ^1H dimension being observed as discussed above. This could suggest that **120** does not occupy the normal binding site on the Tec SH3 domain. However, the residues that are affected upon the binding of **120** are residues that are also typically affected by the binding of 2-aminoquinoline ligands. This would therefore suggest that the binding of **120** is in the normal binding site of the Tec SH3 domain however, the mode of binding is somewhat different.

Ligand **120** contains a bulky phenyl substituent at the 4-position of the phenol. It is possible that this substituent is too large or not the right shape due to the approximately orthogonal orientation of the biphenyl functionality to allow the ligand to make complete contact with the protein surface. This could mean that the ligand is changing between different points of contact with the protein surface in a sort of ‘see-saw’ action (see Figure 91). This would result in different residues being affected depending on which part of the ligand was in contact with the protein surface. This see-saw action could explain why typical binding residues are effected when there is no apparent effect on the side chain of W215 and abnormal

effects on D196. This see-saw action could also provide an explanation for the different behaviour observed with the other Group 2 ligands above which, for the most part, contain bulky substitution on the phenol functionality. Interestingly, the thiomethyl derivatives **115-118** are included in this group of ligands that display aberrant behaviour in the binding assay. The different behaviour observed in thiomethyl derivatives could be due to the different C-S-C bond angle relative to the C-O-C bond angle in the phenoxyethyl derivatives, which may force the ligand to bind in a slightly different orientation and/or position or by the proposed see-saw mechanism.

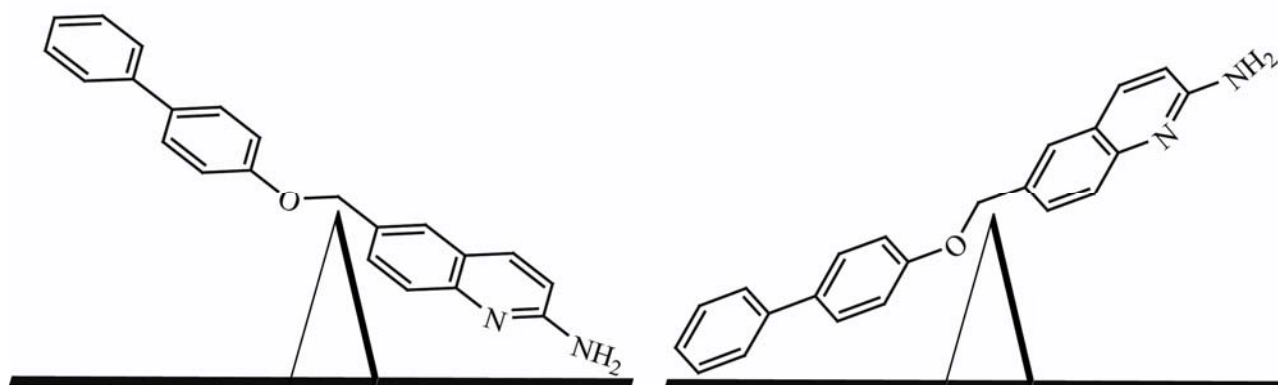


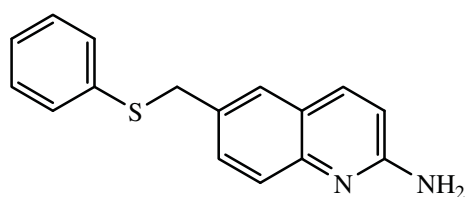
Figure 91: Schematic representation of the proposed see-saw effect experienced by **120**.

Although it appears that the Group 2 ligands bind to the Tec SH3 domain through a different mode there is no conclusive evidence to confirm this. A 3D solution structure of a protein/ligand complex would allow for the complete characterisation of the binding event. However, these ligands are in intermediate exchange on the NMR timescale and slow exchange is required for structure determination. Given that the binding mode of these ligands cannot be confirmed, the analysis of the binding data must be taken with some caution.

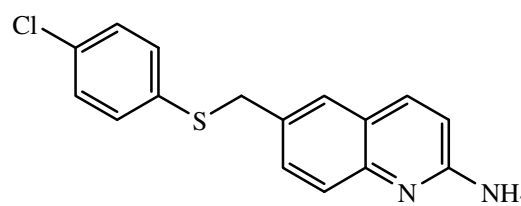
5.3.2.2 Analysis of Binding Affinities of Group 2 Ligands

From analysis of the binding affinities it appears that replacing the oxygen functionality with a sulfur as in the thioether ligands **115** and **116** had little effect in the binding affinity of these ligands as compared to the phenolic equivalents (c.f. **115** $K_d = 29 \mu\text{M}$; **184** $K_d = 32 \mu\text{M}$ and c.f. **116** $K_d = 19 \mu\text{M}$; **195** $K_d = 9 \mu\text{M}$). This suggests once again that the improvements in binding affinity are due to the formation of an additional hydrophobic contact between the phenol and the protein surface. Oxidation of the thioethers to the corresponding sulfonyl compounds in ligands **117** and **118** caused a reduction in binding affinity compared to either the phenoxy or thiophenoxy equivalents (**117** $K_d = 42 \mu\text{M}$ and **118** $K_d = 38 \mu\text{M}$). This decrease in binding

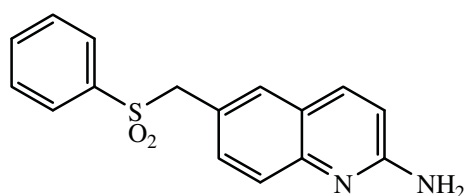
affinity could be due to the increase in hydrophilic character of the sulfonyl functionality as compared to the oxygen or sulfur functionality, which is not as well tolerated by the hydrophobic surface of the protein. This would be consistent with previous findings (Chapter 3) that a hydrophobic substituent is preferred over a hydrophilic substituent. Alternatively, the reduction in binding affinity could be due to a change in steric requirements for the sulfonyl derivatives as compared to the phenoxy or thiophenoxy derivatives.



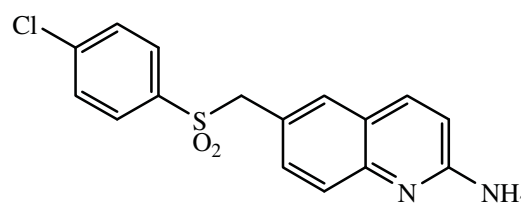
115



116

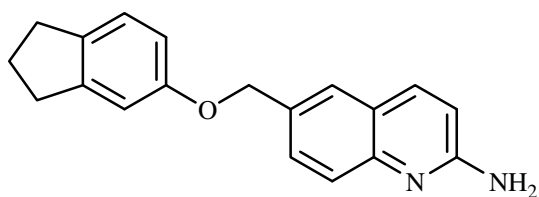


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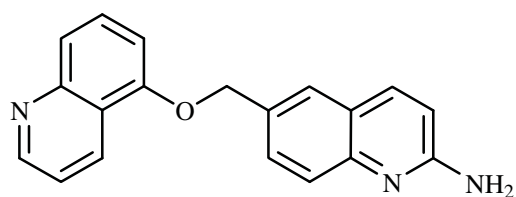


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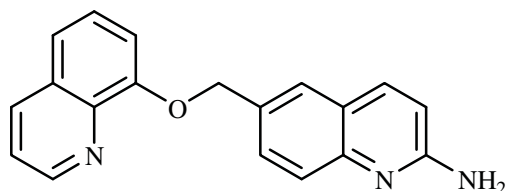
Ligands **123**, **124** and **126** contained an additional fused pyridine ring on the phenol functionality and displayed an approximately 4-6 fold improvement in binding affinity compared to the lead compound ($K_{dS} = 29$, 21 and 22 μM respectively). These binding affinities were slightly better than that of the parent phenol **184** ($K_d = 32$ μM). This would suggest that an additional ring on the phenoxy methyl substituent can form a greater hydrophobic contact with the protein surface than the simple phenol and provide a small improvement in binding affinity. Ligand **121** contained a fused cyclopentane ring on the phenoxy methyl substituent instead of a pyridine and displayed similar affinity to the lead compound. This suggests that an additional aromatic ring on the phenolic functionality can provide a slightly better contact with the protein surface than the cyclopentane ring.



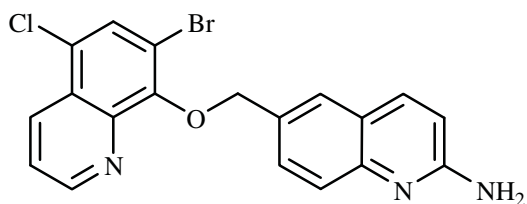
121



123

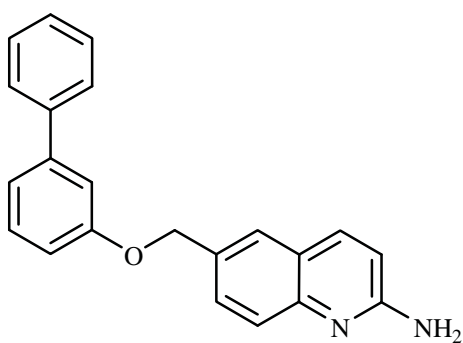


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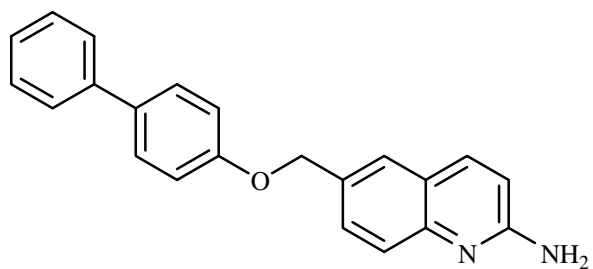


126

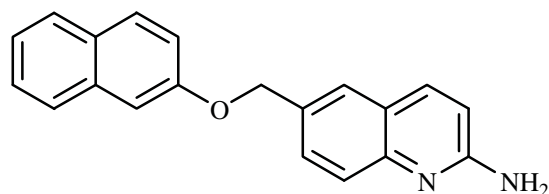
Ligands **119**, **120** and **122** display substantial improvements in binding affinity compared to the lead compound **2** ($K_{dS} = 8, 7$ and $8 \mu\text{M}$ respectively) and are the highest affinity ligands reported to date. Ligand **119** was assayed as a 7:1 mixture with **120** and therefore the K_d reflects the binding affinity of both of these ligands. Given that the mixture of these two ligands resulted in a binding affinity almost identical to that obtained for the pure **120** it is possible that the actual binding affinity of **119** is similar to this value. It is also possible that the binding affinity is actually better than that of the mixture and the K_d is lowered by the presence of **120**. Binding affinity of a pure sample of **119** would be particularly useful in determining if there is a preference for the phenyl substituent in either the 3- or 4- position.



119



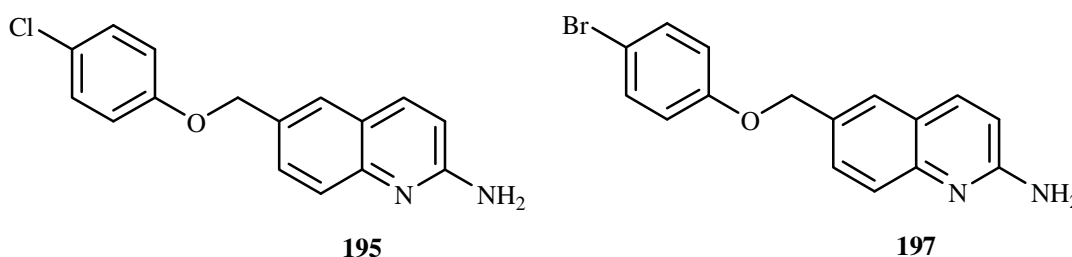
120



122

It would appear that the extension on the phenol in these ligands makes a greater hydrophobic contact with the protein surface, which leads to further improvements in binding affinity relative to the other Group 2 ligands. The ability of these ligands to form a greater contact with the protein surface could be due to the different size and shape of the substituents, which allows for a better fit onto the protein surface. However, this would not be consistent with the proposed see-saw binding mechanism which presumes that the ligands are too large or not the right shape to make complete contact with the protein surface. If these ligands are binding by this mechanism then it is possible that the bulky substituent makes an extensive contact with the protein surface in this region that could potentially provide a substantial improvement in binding affinity. However, the overall improvement in binding affinity is not as great as it should be due to the inability of the quinoline part of the ligand to make contact with the protein surface at the same time as the 6-substituent.

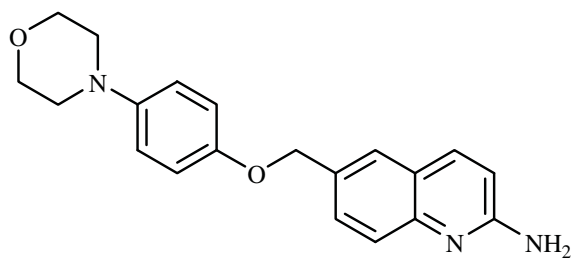
The binding affinity of ligands **119**, **120** and **122** is very similar to the 6-phenoxyethyl ligands with halogens at the 4-position (**195** $K_d = 9 \mu\text{M}$ and **197** $K_d = 10 \mu\text{M}$). Ligand **195** and **197** however, displayed normal behaviour in the NMR assay indicating that the aberrant behaviour of the Group 2 ligands is the result of the size and shape of the substituent in these ligands, which forces the ligands to bind through the proposed see-saw mechanism. This may also support the argument that the 6-substituent makes a substantial contact with the protein surface however, the see-saw binding mechanism reduces the overall binding affinity of the ligand.



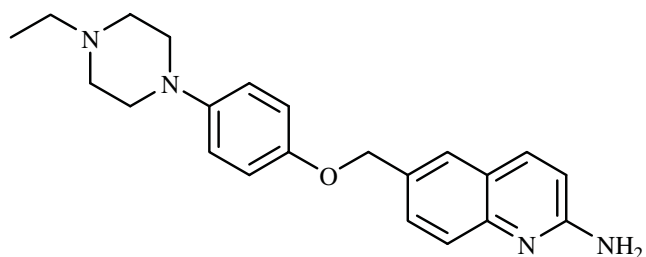
5.3.3.1 Atypical Behaviour of Extended 6-Phenoxyethyl-2-Aminoquinolines (Group 3) Ligands in the [¹H,¹⁵N] HSQC NMR Assay.

Of the eight extended 6-phenoxyethyl ligands assayed, the binding affinity for only four of the ligands could be determined. These ligands were **175**, **179**, **181** and **182** and displayed $K_{d\text{s}} = 23, 26, 49$ and $18 \mu\text{M}$ respectively. For ligands **175**, **179** and **181** relatively normal behaviour was observed in the HSQC assay with a substantial number of residues affected

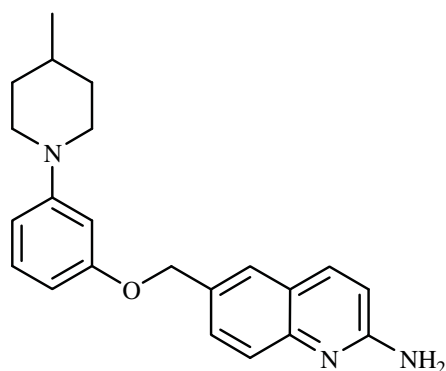
upon the addition of the ligand to the protein. On average twelve residues were affected with nine residues affected consistently across these ligands (see Figure 92). In these cases, the side chain of W215 displayed typical behaviour and disappeared upon the addition of the ligands. Residue D196 also displayed relatively typical behaviour for **179** and **181** with a small downfield shift observed in both the ^{15}N and ^1H dimensions. Conversely, for **175** a large downfield shift in the ^{15}N dimension was observed with no change in the ^1H dimension.



175



179



181

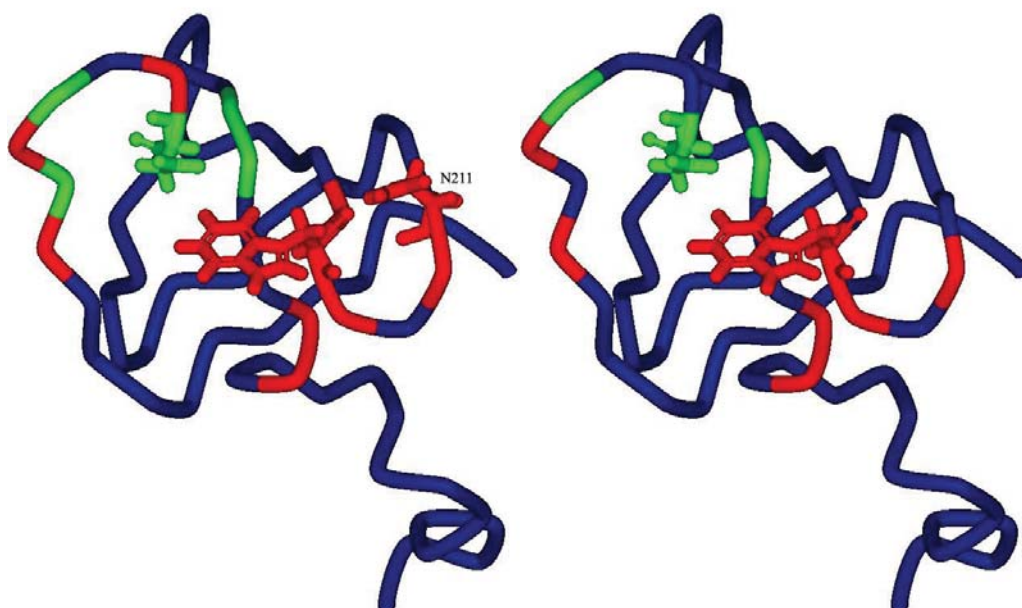


Figure 92: Comparison of chemical shift mapping of the backbone of the Tec SH3 domain with the Group 1 ligands (left) and the extended 6-phenoxyethyl-2-aminoquinolines (right) where $\delta_H > 0.08$ ppm for the majority of ligands. Downfield shifts are marked in green and upfield shifts are marked in red.

As can be seen in Figure 92, ligands **175**, **179** and **181** resulted in slightly fewer residues being effected than with the Group 1 ligands. The residues that were affected however were also affected by the addition of the Group 1 ligands and the 6-heterocyclic ligands (c.f. Figure 92 and Figure 39). Interestingly, residue N211 (backbone and side chain) was not affected by the addition of ligands **175**, **179** and **181** but is affected by the addition of both the Group 1 ligands and the 6-heterocyclic ligands and is thought to be in the region where the 6-substituent would make contact with the protein surface. However, given the general overlap of residues involved in the binding of these ligands and the other 6-substituted ligands, it appears that these ligands occupy a very similar position in the binding site of the Tec SH3 domain. It is possible that these ligands also experience the proposed see-saw mechanism of binding and therefore may make contact with all of the typical residues including N211. It is also possible that the effect on N211 with other 2-aminoquinoline ligands is the result of a secondary induced shift rather than a direct effect caused by interaction of this residue with the substituent at the 6-position.

During the analysis of the [^1H , ^{15}N] HSQC spectra for ligand **175** a few unusual peaks which appeared to be approaching slow exchange were observed. These peaks corresponded to the backbone NH of H195 and the side chain NH of W216. Figure 93 shows the HSQC overlay

and the individual HSQC spectra for the signal corresponding to the H195 residue.

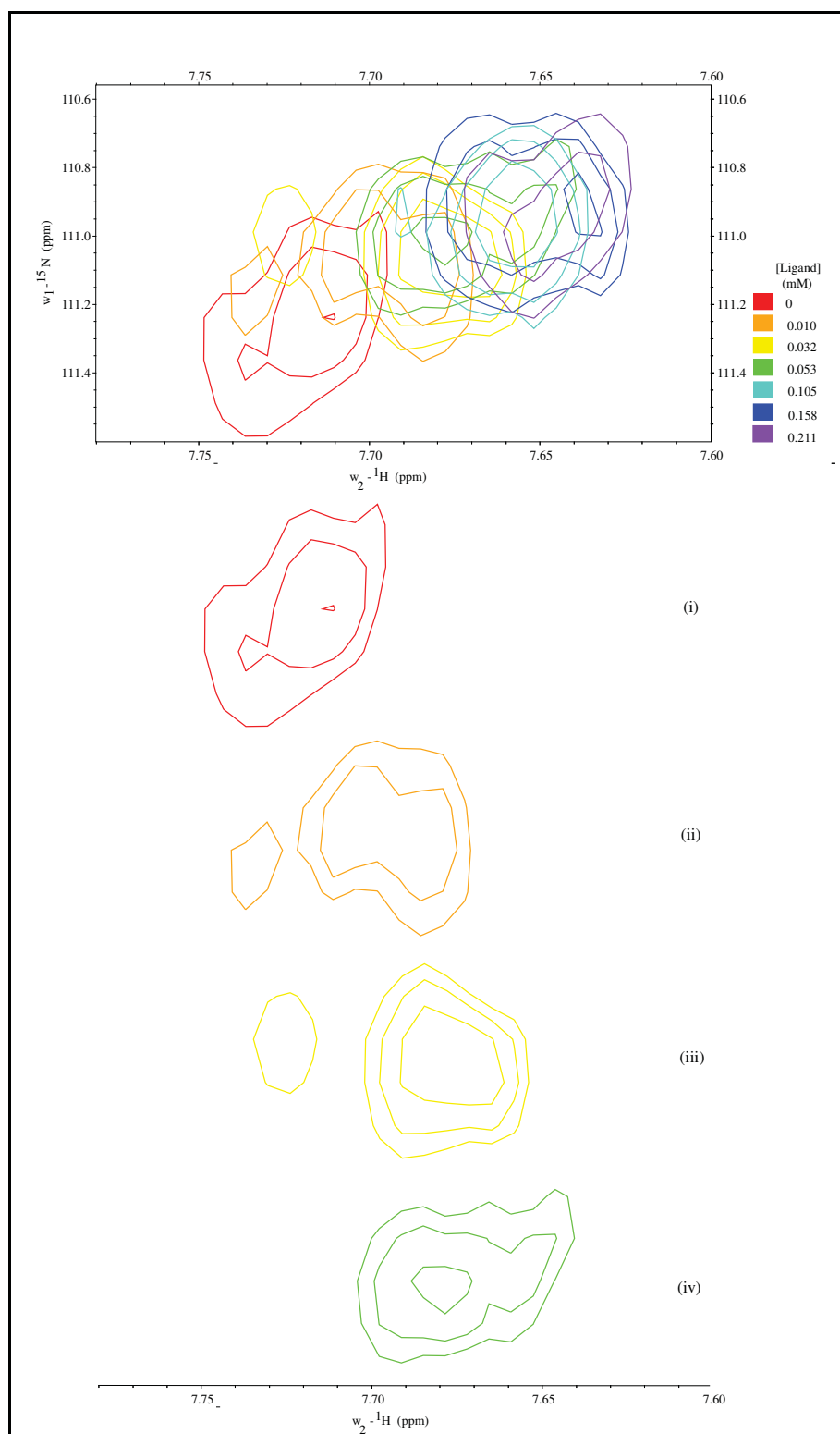
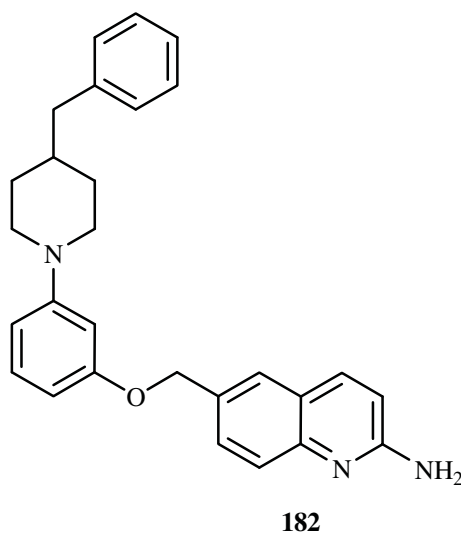


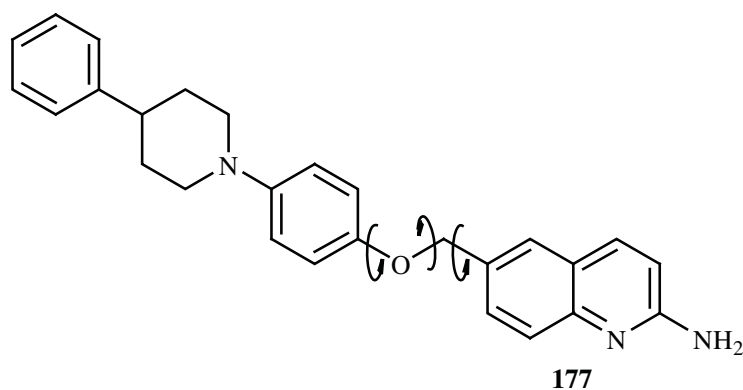
Figure 93: $[\text{}^1\text{H}, \text{}^{15}\text{N}]$ HSQC NMR spectra overlay of the signal for H195 and the individual $[\text{}^1\text{H}, \text{}^{15}\text{N}]$ HSQC NMR spectra for the first three aliquots of the ligand **175**. Concentration (mM) of **175** (i) 0 (ii) 0.010, (iii) 0.032, (iv) 0.053.

As can be seen in this figure, the addition of the first two aliquots of **175** results in the formation of one large broadened peak shifted upfield in the ^1H dimension from the original signal in the absence of any ligand and a smaller peak in the same position as the original signal. The addition of further aliquots of this ligand to the SH3 domain however, resulted in only one broadened signal upfield (in the ^1H dimension) of the original signal. The signal for the side chain for W216 displayed similar characteristics to the signal for the H195 residue. If a ligand was in slow exchange on the NMR timescale, then two signals would be expected; one signal for the unbound ligand and one signal for the bound ligand/protein complex. Given that only two residues show two signals upon the addition of initial aliquots of the ligand to the SH3 domain it would appear that the protein/ligand complex is still in intermediate exchange. However, it is likely that the ligand is closer to slow exchange than other ligands prepared previously.

The addition of **182** to the SH3 domain resulted in only five residues of the Tec SH3 domain being effected in the NMR assay with only four of these being used to calculate the binding affinity. These five residues are however, consistently affected upon the addition of any 2-aminoquinoline ligand to the SH3 domain. As for the above ligands, the side chain of W215 displayed normal behaviour and disappeared upon the addition of the ligand. However, the signal for D196 once again showed abnormal behaviour with only a very small upfield shift in the ^1H dimension being observed. This behaviour once again suggests that this ligand occupies the same binding site as other 2-aminoquinoline ligands, however the binding mode is likely to be through the proposed see-saw mechanism.



For the remaining ligands **176-178** and **180** the behaviour observed in the NMR assay was significantly different. The addition of ligand **177** to the SH3 domain did not result in significant movement of any of the normally effected residues with only four residues showing minimal effects upon the addition of **177** (see Figure 94). These were Y227 and the side chain NH of W215, which showed a reduction in the intensity of the peaks and H195 and T192, which showed a very small change in the ^1H chemical shift ($\Delta = 0.01$ and 0.025 ppm respectively). There was however, no change in the ^1H chemical shift or the intensity of the signal for the D196 residue. Due to the lack of residues displaying significant changes in the ^1H chemical shift a K_d could not be determined for this ligand. The lack of change in the HSQC spectra for this assay would suggest that **177** does not bind to the SH3 domain. This is supported by the fact that there is no effect on residue D196 indicating that no salt bridge is formed. However, a reduction in the intensity of the peak for the side chain for W215 is observed. This could suggest that the ligand is in fact binding to the SH3 domain though the interaction is relatively weak. Ligand **177** contains a 4-phenylpiperidine in the 4-position of the phoxymethyl substituent. This makes quite a long, linear substituent at the 6-position of the quinoline and it is possible that this substituent is the wrong shape or too large to fit onto the binding site resulting in only a weak interaction with the SH3 domain. The extended 6-substituent of **177** also contains only three single bonds in the substituent linker that allow for any significant rotation and therefore this ligand has limited flexibility. It is likely that this limited flexibility also reduces the ability of this ligand to bind to the SH3 domain.



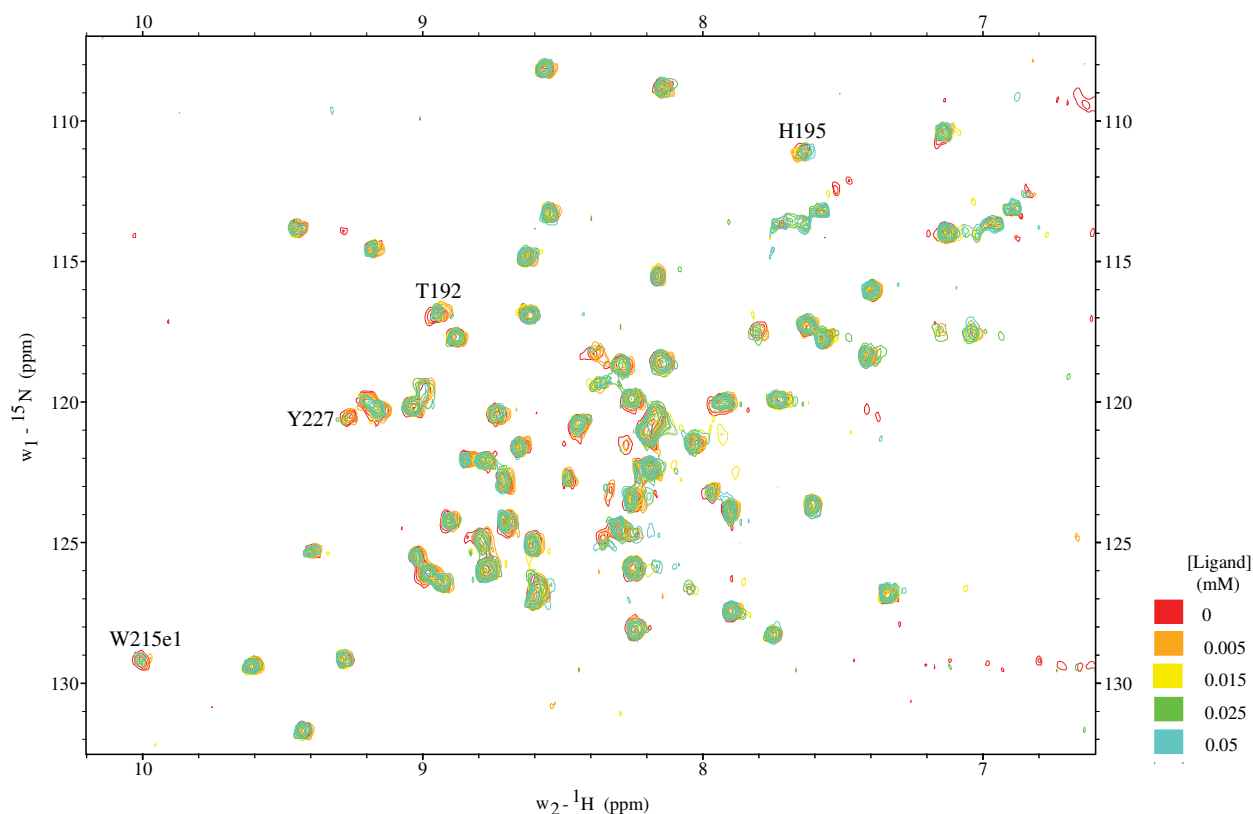
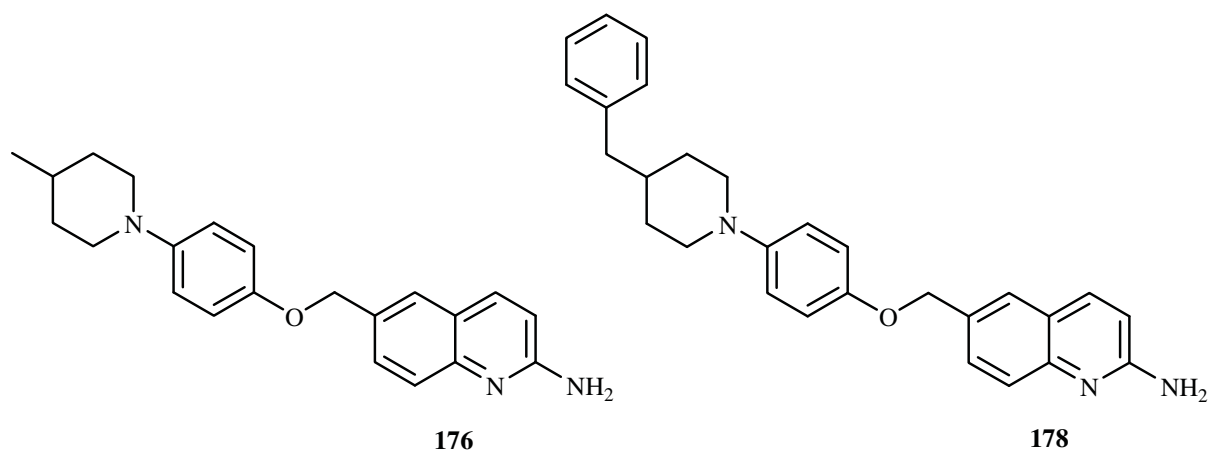
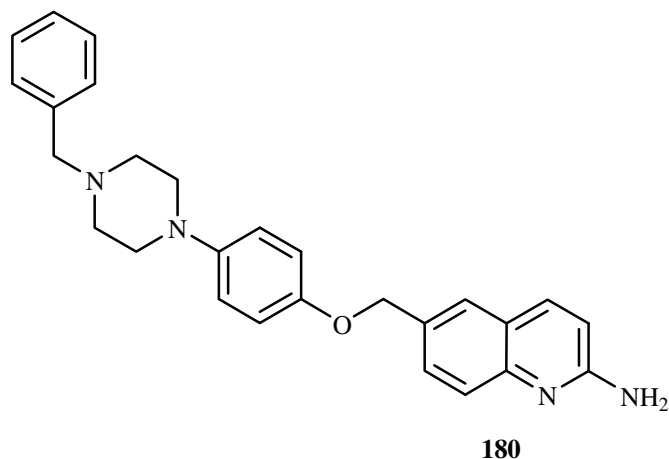


Figure 94: Overlay of NMR spectra from the [^1H , ^{15}N] HSQC NMR experiment of **177**.

176 and **178** displayed similar behaviour to **177** in the NMR assay in that minimal changes were observed in the HSQC spectra. For both of these ligands, the signal for the H195 residue was observed to undergo a significant upfield shift in the ^1H dimension. For **176**, the side chain of W215 and T192 were also significantly effected as determined by the disappearance of the signals for these residues in the NMR spectra. Interestingly, for **178** the side chain of W215 was not affected by the addition of this ligand. The signal for the D196 residue displayed only a very small upfield shift in both the ^1H and ^{15}N dimensions and only four other residues displayed very small changes in chemical shift upon the addition of either of these ligands. These residues are however, observed to be affected upon the binding of most ligands to the Tec SH3 domain. Once again, the lack of significant change in the HSQC spectra for ligands **176** and **178** could suggest that these ligands do not bind to the SH3 domain. However, given that some residues that are normally affected upon the addition of other ligands are slightly affected in these cases, it is more likely that these ligands also bind very weakly to the SH3 domain. This weak interaction could once again be the result of the extended 6-substituent being the wrong shape or too large to fit onto the binding site of the Tec SH3 domain.



The HSQC spectra obtained from the addition of **180** to the SH3 domain was different to that observed for any of the other ligands. In this HSQC assay, all of the signals for the residues affected upon the addition of the ligand were in intermediate exchange and disappeared after either the first or second aliquot of the ligand. As mentioned above, the addition of a ligand to the SH3 domain typically results in significant changes in the ^1H chemical shift of the signals for a number of residues involved in the binding event. For a few of the residues involved in the binding event, particularly for the side chain of W215, the signal for the residue disappears upon the addition of the ligand. In the NMR assay of **180** ^1H chemical shift changes in the signals for only four residues was observed and these chemical shift changes were only very small ($\Delta\delta = 0.02\text{-}0.04$ ppm). For the most part, the signals for the residues that were affected by the ligand disappeared after addition of either the first or second aliquot of the ligand. These residues are the same as those effected for the binding of ligands **176-178**, suggesting that **180** binds to the SH3 domain in the same manner as the other extended 6-phenoxyethyl ligands via the proposed see-saw mechanism described above.



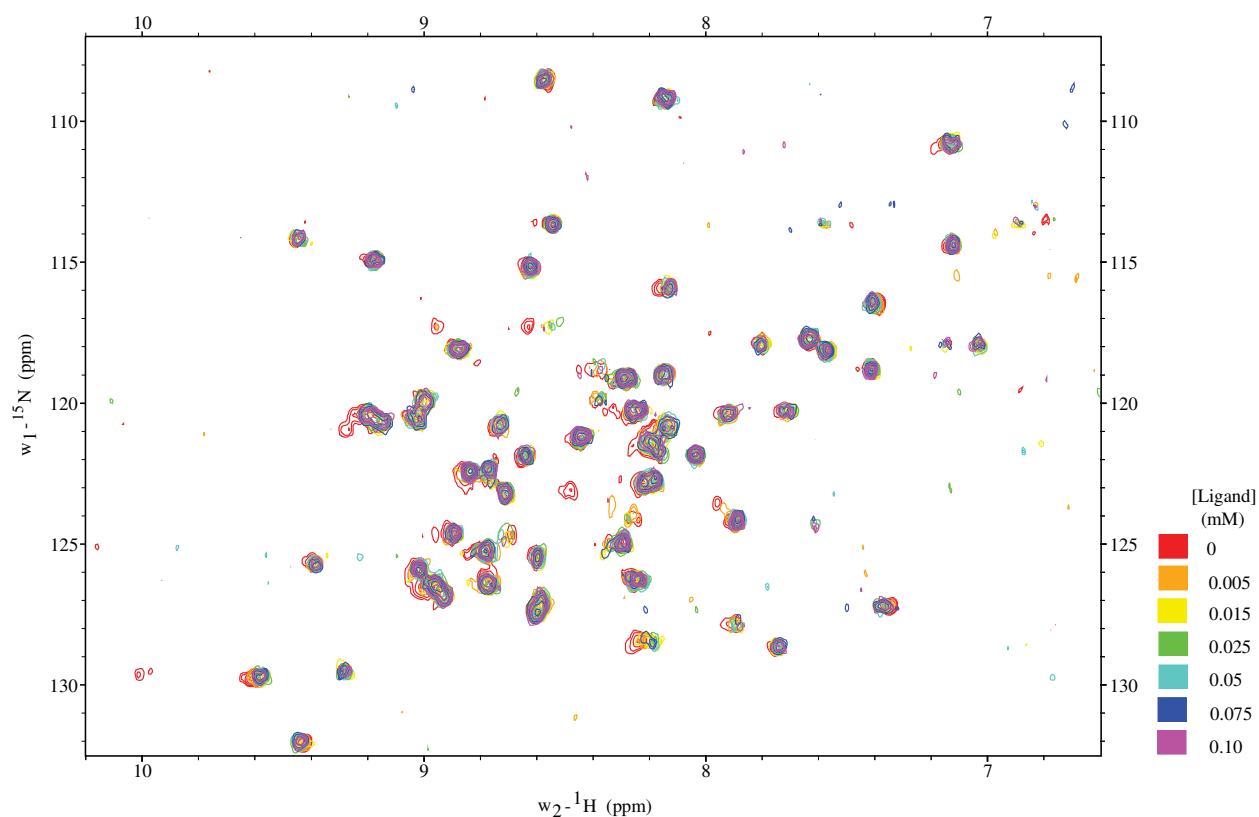
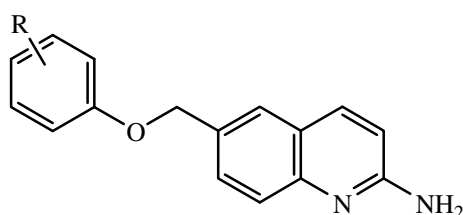
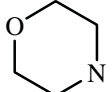
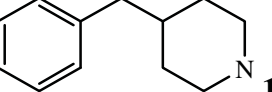
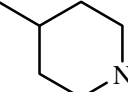
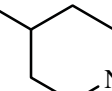
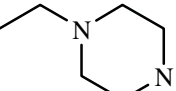
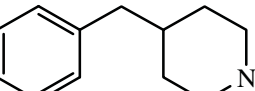
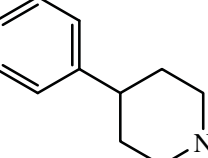
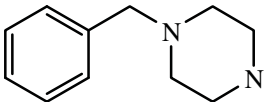


Figure 95: Overlay of NMR spectra from the [^1H , ^{15}N] HSQC NMR experiment of **180**.

5.3.3.2 Analysis of Binding Affinities of Group 3 Ligands

Having analysed the HSQC spectral data for all of the extended 6-phenoxyethyl ligands an interpretation of the binding data could occur (see Table 41). For the piperidinyl substituted 4-phenoxyethyl ligands **176-178** the interaction with the SH3 domain appears to be relatively weak as evidenced by the lack of significant changes in the HSQC spectra of the NMR assay. This would suggest that a piperidinyl substituent in the 4-position of the phenoxyethyl functionality is not tolerated at the binding site of the protein. This could be due to the relatively linear nature of the extended 6-substituent which may be the wrong shape or too large to allow the ligands to bind to the Tec SH3 domain. The limited flexibility of the extended 6-substituent may also reduce the ability of these ligands to bind to the SH3 domain.

Table 41: K_d s of Group 3 Ligands **175-182**.

4-Substituent (R)	K_d (μM)	4-Substituent (R)	K_d (μM)	3-Substituent (R)	K_d (μM)
 175	23 ± 3	 78	†	 181	49 ± 4
 176	†	 179	26 ± 6	 182	18 ± 4
 177	†	 180	†		

† K_d could not be determined from NMR assay.

Interestingly, **175** (with 4-morpholino functionality) and **179** (with 4-ethylpiperazinyl functionality) are tolerated and display relatively good affinity for the Tec SH3 domain (K_d s = 23 and 26 μM respectively). Ligand **180** (with 4-benzylpiperazinyl functionality) may also be tolerated at the binding site however, a K_d could not be determined for this ligand due to most of the signals for the residues effected being in intermediate exchange on the NMR timescale. The difference between these ligands and the piperidinyl substituted 4-phenoxyethyl ligands **176-178** is likely to be due to the second heteroatom in the ring. This second heteroatom may form an additional interaction with the protein surface, which provides for improved binding affinities. If these ligands are binding through the proposed see-saw mechanism than this interaction may allow for more of the ligand to stay in contact with the protein surface at the same time and hence allow for a more typical mode of binding. Alternatively, the shape of the heterocycle in these ligands may also better compliment the binding surface on the protein.

Ligand **181**, with a 4-methylpiperidinyl substituent at the 3-position of the phenolic functionality, displayed relatively good affinity for the Tec SH3 domain ($K_d = 49 \mu\text{M}$). Extension on the piperidinyl substituent with a benzyl functionality instead of a methyl as in

ligand **182** resulted in an improvement in binding affinity ($K_d = 18 \mu\text{M}$). This improvement in binding affinity is once again likely to be due to the ability of the benzyl functionality to form a larger hydrophobic contact with the protein surface. Although only two extended 3-substituted phenoxyethyl ligands could be prepared, it would appear that a substituent in the 3-position of the phenol functionality is favoured over a substituent in the 4-position of the phenol. The different orientation of the substituent provided by substitution at the 3-position compared to substitution at the 4-position appears to provide an extended 6-substituent with a better shape to bind to the Tec SH3 domain. Interestingly, **181** displayed relatively normal behaviour in the NMR assay whereas **182** did not. This could be due to the larger size or the additional flexibility introduced with the 4-benzylpiperidinyl substituent, which may cause the ligand to bind through the proposed see-saw mechanism, resulting in the aberrant behaviour in the NMR assay. An accurate binding affinity of the 3-phenyl substituted 6-phenoxyethyl ligand **119** would also be useful in determining if a bulky substituent is preferred in the 3-position of the phenoxy functionality by comparison with the 4-phenyl equivalent **120**.

For most of the ligands (excluding **177**), the side chain of W215 was affected by the addition of the ligand suggesting that these ligands bind at the same site on the SH3 domain as other 2-aminoquinoline ligands. The inconsistencies in the effect on the D196 residue and other residues typically involved in the binding of 2-aminoquinoline ligands however, all support the argument that these ligands occupy either a slightly different orientation or position in the binding site of the Tec SH3 domain. It is likely that this different orientation or position of the ligand involves the proposed see-saw binding mechanism, similarly to the Group 2 ligands. Whilst some of the extended ligands displayed good affinity for the Tec SH3 domain, similar and better binding affinities can be achieved with both the simple 6-phenoxyethyl ligands and also the 6-heterocyclic ligands which displayed normal behaviour in the NMR assay. Further studies are required however, to determine the differences in binding modes and confirm or refute the proposed see-saw mechanism.

Chapter 6:

CONCLUSIONS AND FUTURE DIRECTIONS

6.1 6-Heterocyclic-2-Aminoquinolines

A range of 6-heterocyclic-2-aminoquinoline ligands have been prepared and their binding affinity for the Tec SH3 domain has been evaluated. The heterocyclic substituted ligands were proposed as a potentially more stable alternative to the acetal substituted ligands **27** and **28** prepared previously. Gratifyingly, the ligands prepared in this work demonstrated enhanced stability and also displayed improved binding affinities for the Tec SH3 domain compared to the lead compound **2** and similar affinities to the acetal substituted ligands. A number of these ligands were amongst the highest affinity ligands prepared to date (**30a** $K_d = 12 \mu\text{M}$ and **30f** $K_d = 9 \mu\text{M}$ see Figure 96).

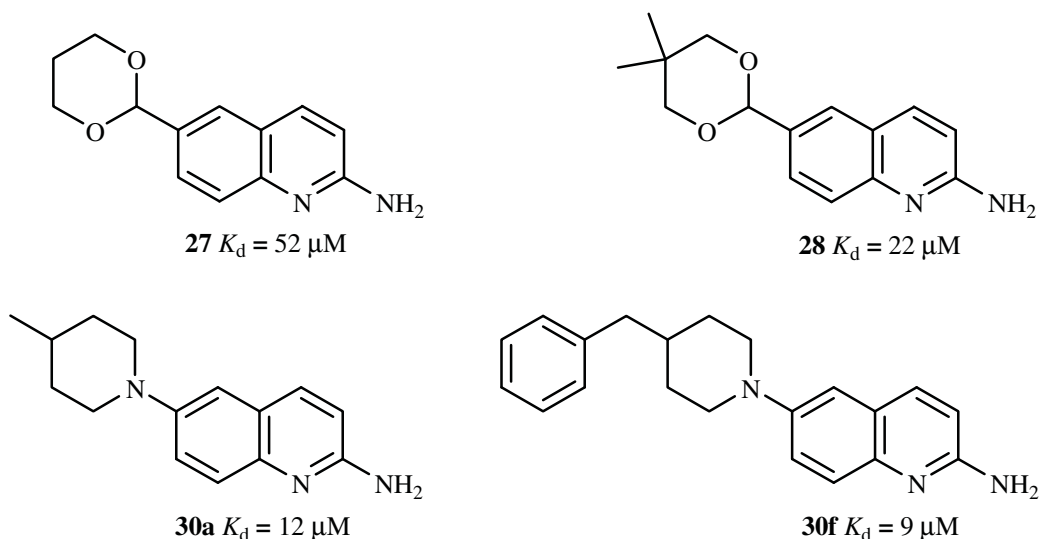


Figure 96: The highest affinity 6-heterocyclic-2-aminoquinolines **30a** and **30f**.

In order to prepare the heterocyclic substituted ligands a detailed investigation into Buchwald-Hartwig chemistry was undertaken. This investigation involved the examination of reaction conditions required to selectively introduce the heterocyclic substituent in the 6-position of the quinoline core by reaction with the 6-bromo functionality in the presence of the activated 2-chloro group. An alternate method for the incorporation of the 2-amino functionality has also been established using additional Buchwald-Hartwig chemistry employing LHMDS as an ammonia source. The established reaction conditions therefore allow for the selective and sequential functionalisation of the aryl halide substrate, providing the desired ligands in high yield (see Figure 97).

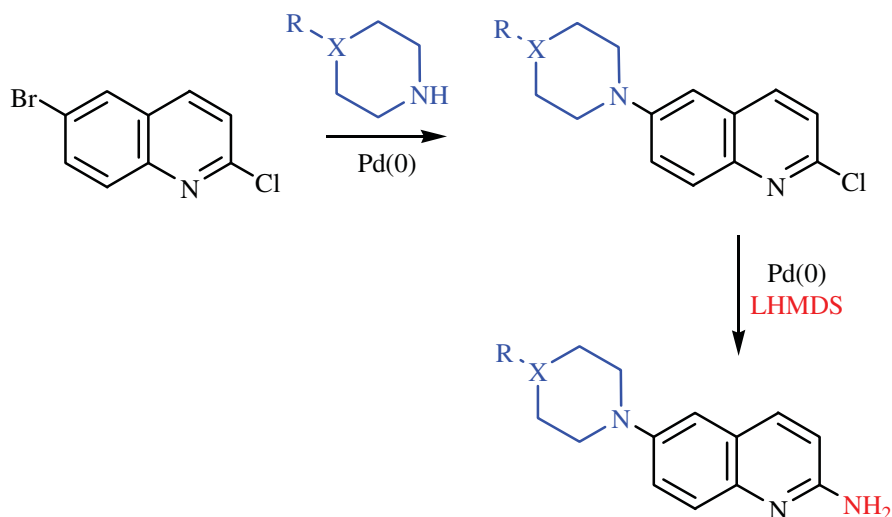


Figure 97: Selective and sequential amination of 6-bromo-2-chloroquinoline.

6.2 6-Aryloxymethyl- and 6-Arylthiomethyl-2-Aminoquinolines

A large number of 6-aryloxymethyl- and 6-arylthiomethyl-2-aminoquinolines have been prepared in order to extend on previous work involving simple 6-phenoxyethyl-2-aminoquinoline ligands. The previously prepared 6-phenoxyethyl-2-aminoquinoline ligands contained alkyl or halogen substituents on the phenoxy ring and many of these displayed high affinity for the Tec SH3 domain. The preparation of compounds with either multiple substitutions on the phenoxy ring, large lipophilic groups or sulphur derivatives provided a range of ligands that all displayed an improved affinity relative to **2**. Comparison of the binding affinities of the mono substituted ligands with the size and hydrophobicity of the substituents indicated that a hydrophobic substituent in the *para* position of the phenol provides for the greatest improvement in binding affinity. The shape of the substituent was also found to be important for the improved binding affinities.

Of the 6-aryloxymethyl- and 6-arylthiomethyl-2-aminoquinoline ligands prepared, **119**, **120** and **122** displayed the highest binding affinities with K_{d} s = 8, 7 and 8 μ M respectively (see Figure 98). Although these ligands displayed high affinity for the Tec SH3 domain, atypical behaviour was observed in the NMR assay. A number of other 6-aryloxymethyl- and 6-arylthiomethyl-2-aminoquinoline ligands also displayed different behaviour in the NMR assay. It appears that the 2-aminoquinoline ligands containing 6-arylthiomethyl and bulkier 6-aryloxymethyl substituents bind in a subtly different manner to the more simple 6-phenoxyethyl-2-aminoquinoline ligands which contain mono- or di-substitution on the phenolic functionality. It is proposed that the size and/or shape of the 6-substituents in these

ligands causes the ligands to bind through a see-saw type mechanism. This type of binding mechanism would not allow for the whole of the ligand to interact with the protein surface simultaneously, resulting in the type of behaviour observed in the NMR assay.

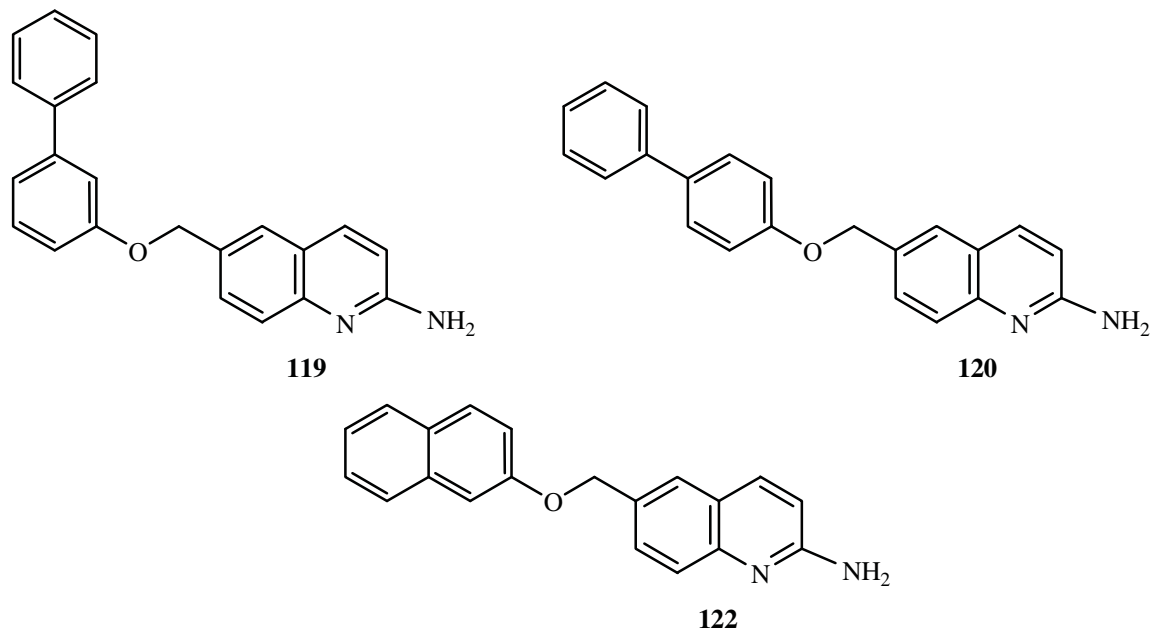


Figure 98: The highest affinity 6-aryloxymethyl-2-aminoquinoline ligands.

6.3 Extended 6-Phenoxymethyl-2-Aminoquinolines

The information provided from the binding assays of the 6-aryloxymethyl- and 6-arylthiomethyl-2-aminoquinolines indicated that a hydrophobic substituent of the correct shape was desirable on the phenoxy functionality. Building on this, extended 6-phenoxymethyl ligands were prepared which contained heterocyclic functionality at both the *para* and *meta* positions of the phenol. To prepare these ligands additional Buchwald-Hartwig chemistry was developed including reaction conditions that allowed for the amination of a phenolic substrate with cyclic amines.

Of the extended ligands prepared, **175**, **179** and **182** displayed binding affinities of approximately 5-7 fold improvement compared to **2** ($K_{d}s = 23, 26$ and $18 \mu\text{M}$ respectively, see Figure 99). A number of the extended 6-phenoxymethyl ligands also displayed different behaviour in the NMR assay similarly to some of the 6-aryloxymethyl and 6-thiomethyl-2-aminoquinoline ligands prepared in Chapter 3. For these ligands, binding to the Tec SH3 domain is once again proposed to be via the see-saw type mechanism.

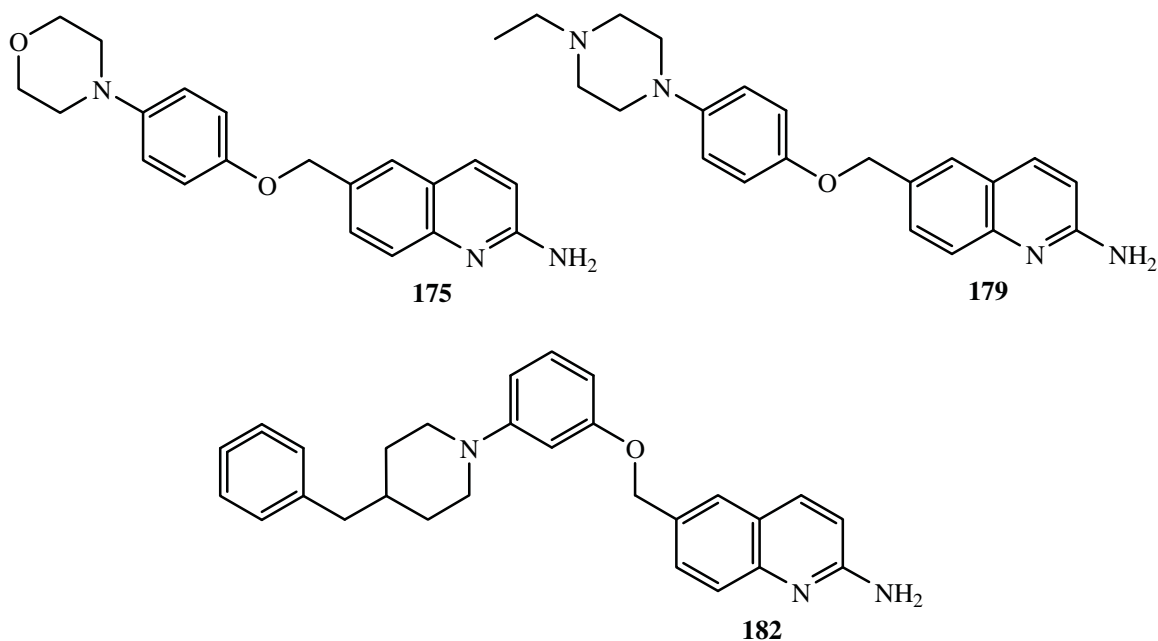


Figure 99: The highest affinity extended 6-aryloxymethyl-2-aminoquinoline ligands.

From the binding studies, it appears that a heterocyclic substituent is favoured in the *meta* position of the phenol functionality, with extension on the heterocycle providing greater improvements in binding affinity. Ligands containing a heterocyclic substituent in the *para* position of the phenol functionality however, are not able to bind to the protein unless the heterocyclic substituent contains a second heteroatom. Given that a hydrophobic substituent of a particular shape is preferred in the *para* position of the simple, mono substituted phenoxyethyl derivatives it is thought that the inability of the *para*-substituted piperidinyl extended ligands to bind to the Tec SH3 domain is due to the shape of the 6-substituent. The *para*-piperidinyl extended substituents are relatively linear and also lack any significant flexibility and may therefore not be the correct shape to allow binding to the Tec SH3 domain surface. The ability of the *para*-substituted morpholino and piperazinyl extended ligands to bind however is likely to result from the formation of an additional interaction between the second heteroatom and the protein. This additional interaction may allow for more of the ligand to stay in contact with the protein surface simultaneously, thereby allowing for a more typical mode of binding.

6.4 Proposed Future Work

6.4.1 Further investigations into Buchwald-Hartwig aminations

There are a number of potential aspects of the developed Buchwald-Hartwig chemistry that could be investigated further. Firstly, improving the reaction times of the amination reactions for introducing the heterocycle at the 6-position of the 2-aminoquinoline would be beneficial, as currently reactions conducted under thermal conditions require typically greater than 16 hours. Whilst some improvement in the reaction time has been achieved with microwave irradiation, these reaction conditions have not been optimised and the yields of the products vary. Further development of the microwave assisted Buchwald-Hartwig aminations would likely lead to high yields of the desired products with substantial improvements in reaction time.

An investigation into reversing the selectivity of the Buchwald-Hartwig reaction for amination at the 2-chlorine substituent in the presence of the more reactive 6-bromine would also be of interest (see Figure 100). Given the apparent reversal of selectivity that is observed when the reaction is carried out in dioxane with Cs_2CO_3 as the base, achievement of the reversed selectivity is thought to be possible.

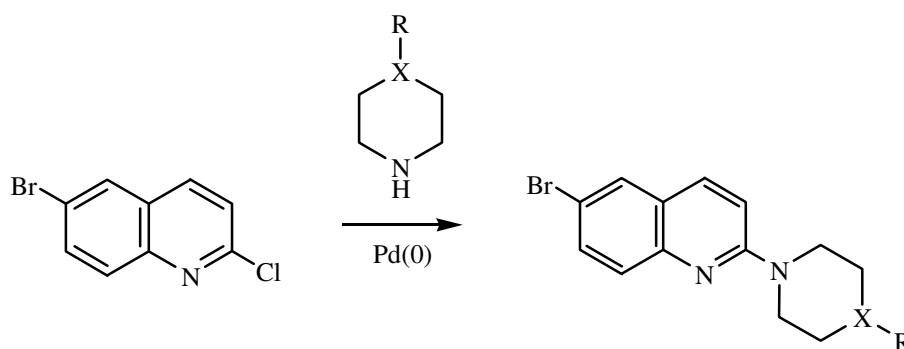


Figure 100: Selectivity for Buchwald-Hartwig amination at the 2-position of 6-bromo-2-chloroquinoline.

6.4.2 Determination of mode of binding

Given that a number of the 6-aryloxymethyl and 6-arylthiomethyl-2-aminoquinolines and also the extended 6-phenoxyethyl-2-aminoquinoline ligands displayed different behaviour in the NMR assay, an investigation into the binding modes of these ligands is of particular importance. Determination of the mode of binding would confirm whether or not the proposed see-saw mechanism is involved and also the reasons why this or an alternative mode of binding is required. Information of the binding mode would also provide further

understanding of the interaction of 2-aminoquinoline ligands with the Tec SH3 domain and would likely assist in the development of other 2-aminoquinoline ligands with improved affinity for the protein.

6.4.3 Combining Substituents

Introducing a substituent at the 6-position of 2-aminoquinoline has provided ligands with up to approximately 18-fold improvement in binding affinity for the Tec SH3 domain in comparison to the lead compound **2**. As mentioned in Chapter 1, substituents at the 3-position can also provide improvements in binding affinity and ligands have been prepared that display binding affinities of up to 3-fold improvement compared to **2**.³¹ Therefore, combining both substituents in a 3-, 6-disubstituted-2-aminoquinoline ligand should provide for a substantial improvement in binding affinity, providing that no additional geometric constraints are introduced for protein-ligand binding.

Given that both the 6-aryloxymethyl and the 6-arylthiomethyl-2-aminoquinoline ligands and also the 6-heterocyclic-2-aminoquinoline ligands display high affinities for the Tec SH3 domain, two different classes of di-substituted ligands could be envisaged (see Figure 101).

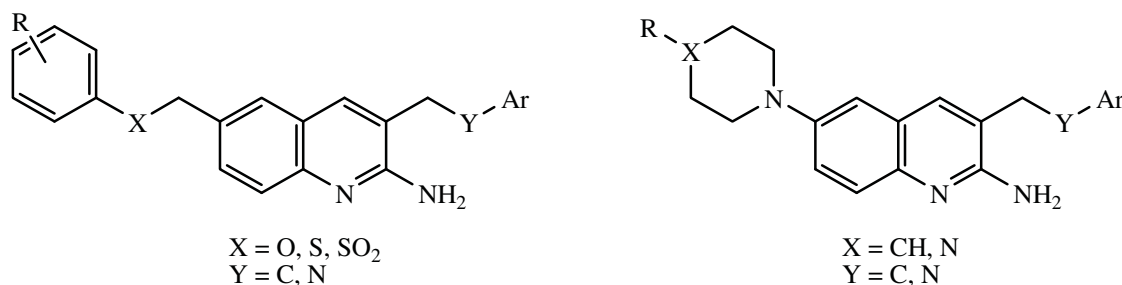


Figure 101: Proposed 3-, 6-disubstituted 2-aminoquinoline ligands.

To prepare either of these classes of ligands the combination of methods utilised for the preparation of the mono substituted ligands could be employed. For the 3-phenethyl-6-aryloxymethyl- and 3-phenethyl-6-arylthiomethyl-2-aminoquinolines the retro synthetic pathway is shown below in Figure 102. This pathway would involve two key steps; the substitution reaction to introduce the 6-substituent and a Wittig reaction (or variant) to introduce the substituent at the 3-position. Preparation of the related 3-((phenylamino)methyl)-6-substituted-2-aminoquinolines could be achieved using a similar pathway involving a reductive amination of the same carbaldehyde intermediate.

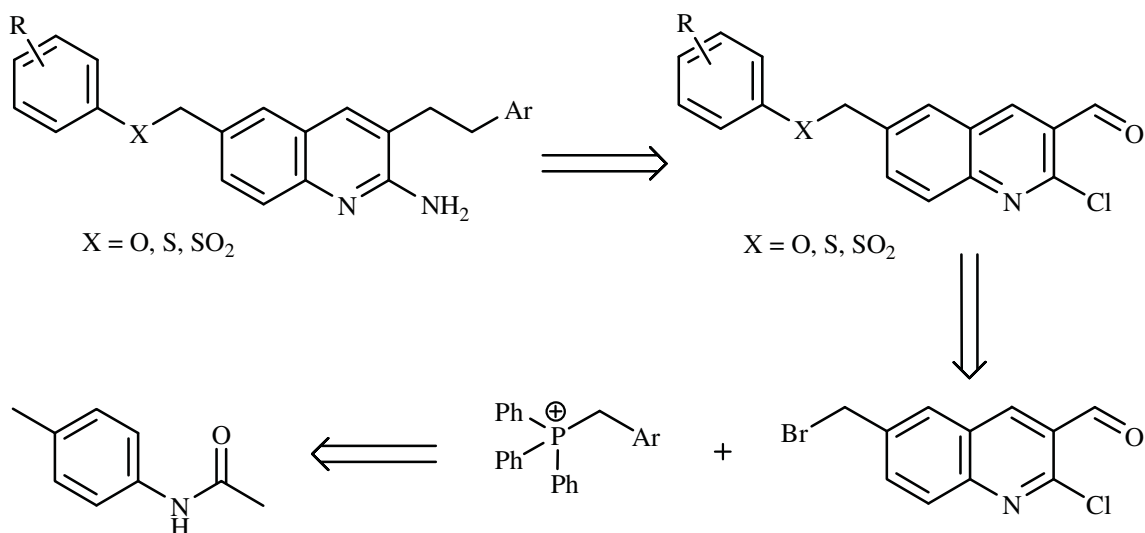


Figure 102: Retrosynthetic pathway for the synthesis of 3-substituted-6-aryloxymethyl and 3-substituted-6-aryltiomethyl-2-aminoquinoline ligands.

For the 3-phenethyl-6-heterocyclic-2-aminoquinolines the retrosynthetic pathway is shown below in Figure 103 and would similarly involve two key steps. The Wittig reaction (or variant) would be utilised once again to introduce the 3-substituent and the Buchwald-Hartwig amination would be required to introduce the substituent at the 6-position. Preparation of the 3-(phenylamino)methyl equivalents could be achieved by employing a reductive amination reaction of the carbaldehyde intermediate.

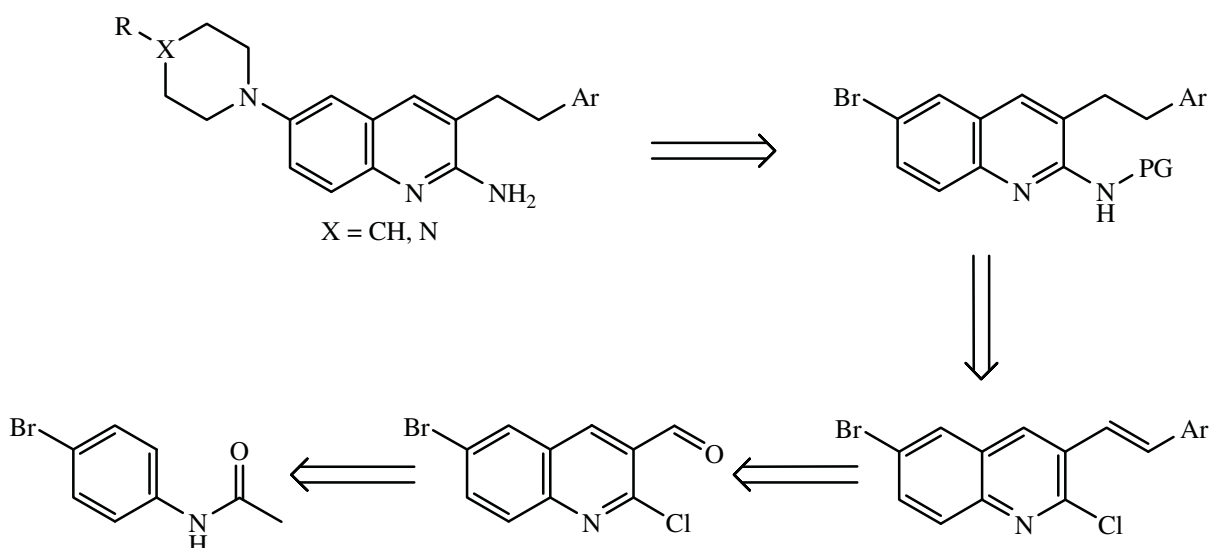


Figure 103: Retrosynthetic pathway for the synthesis of 3-substituted-6-heterocyclic-2-aminoquinoline ligands.

The preparation of the di-substituted ligands may provide ligands that bind to the Tec SH3 domain with sufficient affinity that the protein-ligand complex would be in slow exchange on the NMR timescale. This would allow for the mode of binding to be characterised by NMR spectroscopic methods. Alternatively, a sufficiently high affinity ligand may also allow the binding mode to be characterised by X-ray crystallography.

6.4.4 Slow Exchange

If a high affinity ligand for characterisation of the binding mode cannot be achieved by di-substitution (or mono substitution) of the 2-aminoquinoline then it may be possible to force a protein-ligand complex into slow exchange on the NMR timescale. Forcing a protein-ligand complex into slow exchange could potentially be achieved by using a higher field strength NMR spectrometer. Alternatively, a decrease in the temperature of the solution during the NMR assay could produce the desired result. The samples for the NMR assay however, contain 10% d_6 -DMSO and it is unlikely that a substantial reduction in temperature could be achieved. Also, a reduction in temperature may lead to problems with solubilities of the ligands in the assay solution. Given the possible issues associated with decreasing the temperature, the most appropriate way to force a protein-ligand complex into slow exchange on the NMR timescale would be to use a higher field strength NMR spectrometer. Given that a number of the ligands prepared thus far are in intermediate exchange any of these could potentially be used in an attempt to obtain a slow exchange complex.

Chapter 7:

EXPERIMENTAL

General Procedures

All commercially available reagents and reagent grade solvents were used without further purification unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium wire and sodium benzophenone under a nitrogen atmosphere immediately prior to use. Dimethoxyethane (DME) and 1,4-dioxane were vigorously pre-dried and distilled from sodium wire and sodium benzophenone and stored over 4Å molecular sieves. Toluene and trifluoromethylbenzene were distilled and stored over 4Å molecular sieves. Commercially available lithium bis(trimethylsilyl)amide (LHMDS) was used as a 1.0 M solution in THF or toluene.

Where possible reactions were monitored by analytical thin layer chromatography (TLC) on MERCK aluminium-backed silica gel 60 F₂₅₄ plates and visualised under UV light at 254 nm. Flash column chromatography was performed using Scharlau silica gel 60 (particle size 0.040 – 0.063 mm) using the guidelines outlined by Still, Kahn and Mitra.¹²⁴ Reverse phase chromatography was performed using Waters preparative C18 silica (particle size 0.055 – 0.105 mm). Preparative thin layer chromatograms were run on Whatman C18 silica F₂₅₄ plates (20 x 20 cm, 0.20 mm thickness).

¹H and ¹³C NMR spectra were obtained using either Varian Gemini 2000 Spectrometers (¹H: 199.954, ¹³C: 50.283 MHz and ¹H: 300.145, ¹³C: 75.479 MHz) or a Varian INOVA Spectrometer (¹H: 599.842, ¹³C: 150.842 MHz) at 25 °C. All spectra were recorded as solutions in d₆-acetone, CD₃CN, d₆-DMSO or CDCl₃. Chemical shifts (δ) were calibrated against the solvent peak in all cases except for CDCl₃ which used tetramethylsilane as an internal reference. The following abbreviations for hydrogen multiplicities are used: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; br, broad; m, multiplet. ‡ Indicates a(n) unresolved J value(s). ¹H and ¹³C NMR signals for a significant proportion of new compounds were assigned using a combination of COSY, ROESY, heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC) spectral data. Comparison of these spectra allowed for the assignment of the remaining compounds of the same general structure.

All infrared spectra were obtained using a Perkin Elmer BX FT-IR spectrometer as nujol mulls between sodium chloride plates or as solutions in DCM or chloroform. Melting points were determined using a Kofler hot-stage apparatus fitted with a Reichart microscope. Electron impact (EI) mass spectra were recorded on a Shimadzu mass spectrometer at the University of Adelaide or Kratos Concept high resolution mass spectrometer at the University of Tasmania (Tasmania, Australia). All LSIMS and HRMS were performed at the University of Tasmania. Elemental analyses were performed at the University of Otago (Dunedin, New Zealand). Samples for mass spectral analysis and elemental analysis were dried under reduced pressure at 25 °C for a minimum of 5 and 10 days respectively.

Microwave reactions were carried out in either a CEM MARS multimode platform system or CEM Discover single mode system.

¹⁵N labelled protein was prepared by Cvetan Stojkoski, Iain Murchland, Hui Huang, and Melissa Perrotta, School of Molecular and Biomedical Science, University of Adelaide.

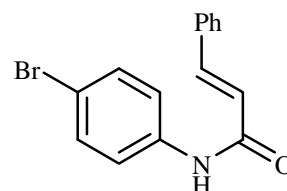
N-{6-[(2-Nitrophenoxy)methyl]quinolin-2-yl}acetamide **99** and *N*-{6-[(4-nitrophenoxy)-methyl]-quinolin-2-yl}acetamide **100** were provided by Martina Marinkovic. Samples of **128-133** were also prepared by Michael Ly.

7.1 Synthesis of 6-Heterocyclic-2-Aminoquinolines

7.1.1 Synthesis of Starting Materials

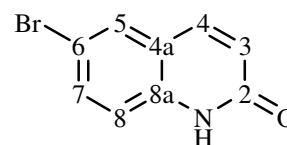
(2*E*)-*N*-(4-Bromophenyl)-3-phenylacrylamide (**33**)²⁸

A solution of cinnamoyl chloride (20.01 g, 120.1 mmol) in DCM (50 mL) was added dropwise to a mixture of DMAP (1.48 g, 12.0 mmol) and pyridine (9.70 mL, 120.0 mmol) in DCM at 0 °C under a nitrogen atmosphere. The mixture was stirred for 15 min and a solution of 4-bromoaniline (20.65 g, 120.0 mmol) in DCM (50 mL) was added over a 15 min period. The solution was stirred for 15 min at 0 °C before warming to room temperature and stirring for a further 30 min. The precipitate that formed was filtered, washed with DCM and dried to afford the title compound as an off-white powder, mp 193-195 °C (28.10 g, 78%). IR (nujol mull): ν/cm^{-1} : 3291, 3088, 2289, 1901, 1661, 1621, 1585 and 1514. ¹H NMR (300 MHz, CDCl₃); δ : 6.85 (1H, d, $J = 15.6$ Hz, =CH), 7.39-7.46 (10H, m, Ar H's & NH), 7.71 (1H, d, $J = 15.6$ Hz, =CH).



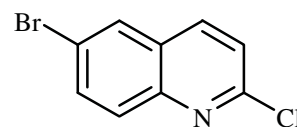
6-Bromoquinolin-2(1*H*)-one (**34**)¹²⁵

33 (24.98 g, 82.7 mmol) and AlCl₃ (33.10 g, 248.2 mmol) were ground together in a mortar and pestle to form an intimate mixture. The reaction mixture was transferred to a round bottom flask and heated rapidly with a heat gun to melting and then maintained at 110 °C for 1.5 h. The mixture was cooled to room temperature and quenched with ice water. The resultant precipitate was filtered, washed with water and dried to afford the title compound as a pink powder, mp 272-274 °C (lit.,¹²⁵ 272-274 °C), (19.03 g, 100%) and was used without further purification. IR (nujol mull): ν/cm^{-1} : 2724, 1700, 1636 and 1597. ¹H NMR (300 MHz, CDCl₃); δ : 6.76 (1H, d, $J = 9.3$ Hz, H3), 7.34 (1H, d, $J = 8.7$ Hz, H8), 7.61 (1H, dd, $J = 2.1, 8.7$ Hz, H7), 7.73 (1H, d, $J = 2.1$ Hz, H5), 7.77 (1H, d, $J = 9.3$ Hz, H4), 12.10 (1H, br s, NH).



6-Bromo-2-chloroquinoline (**31**)⁶⁷

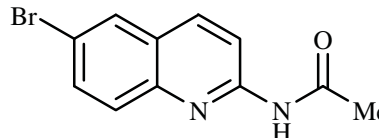
A mixture of **34** (8.52 g, 38.0 mmol) and phosphorus oxychloride (40 mL, 380.0 mmol) was heated at reflux for 1 h. The solution was cooled to room temperature and excess reagent was removed under reduced pressure. The remaining mixture was quenched with ice water and the



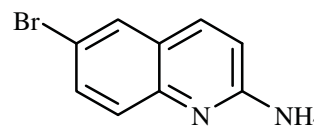
resultant solid was filtered and washed with water. The solid was recrystallised from hexane to afford the title compound as a pale pink powder, mp 157-158 °C (lit.,⁶⁷ 157 °C), (5.34 g, 58%). IR (nujol mull): ν/cm^{-1} : 3300, 1582, 1567 and 1552. ¹H NMR (300 MHz, CDCl₃); δ : 7.44 (1H, d, $J = 8.4$ Hz, H3), 7.81 (1H, dd, $J = 2.1, 9.0$ Hz, H7), 7.90 (1H, d, $J = 9.0$ Hz, H8), 7.99 (1H, d, $J = 2.1$ Hz, H5), 8.03 (1H, d, $J = 8.4$ Hz, H4).

***N*-(6-Bromoquinolin-2-yl)acetamide (46)**

(i) A mixture of **31** (4.51 g, 18.56 mmol), acetamide (87.4 g, 1.48 mol) and potassium carbonate (12.83 g, 92.83 mmol) was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and added to water (100 mL). The organic material was extracted with DCM, washed with water, dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was chromatographed over silica gel eluting with DCM:ethyl acetate (9:1) to afford the title compound as fine cream crystals, mp 208-210 °C (2.39 g, 49%). IR (nujol mull): ν/cm^{-1} : 3230, 1675, 1595 and 1526. ¹H NMR (300 MHz, CDCl₃); δ : 7.68 (1H, d, $J = 9.0$ Hz, H8), 7.74 (1H, dd, $J = 2.1, 9.0$ Hz, H7), 7.95 (1H, d, $J = 2.1$ Hz, H5), 8.09 (1H, d, $J = 9.0$ Hz, H4), 8.38 (1H, br s, NH), 8.44 (1H, br d, $J = 9.0$ Hz, H3).



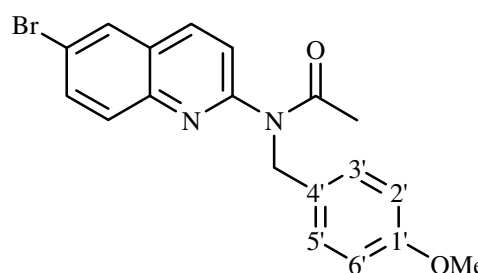
(ii) **Attempted synthesis using microwave irradiation.** A high pressure microwave vessel was loaded with **31** (200 mg, 0.82 mmol) and acetamide (2.44 g, 41.2 mmol). The mixture was heated at 230 °C (300W) for 20 min (including ramp time). After cooling, the mixture was extracted with DCM, washed with water and dried over MgSO₄. The solvent was removed under reduced pressure and the crude product chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford 6-bromo-2-aminoquinoline **65**, mp 144-147 °C (lit.²⁸ 141-146 °C) (117 mg, 65%). IR (nujol mull): ν/cm^{-1} : 3470, 3350, 1650 and 1610. ¹H NMR (300 MHz, CDCl₃); δ : 5.20 (2H, br s, NH₂), 6.77 (1H, d, $J = 9.0$ Hz, H3), 7.56 (1H, d, $J = 9.0$ Hz, H8), 7.65 (1H, dd, $J = 2.7, 9.0$ Hz, H7), 7.79 (1H, d, $J = 2.7$ Hz, H5), 7.83 (1H, d, $J = 9.0$ Hz, H4).



This data is consistent with that reported previously.²⁸

***N*-(4-Methoxybenzyl)-*N*-(6-bromoquinolin-2-yl)acetamide (50)**¹²⁶

31 (202 mg, 0.83 mmol) and *p*-methoxybenzyl amine (2.4 mL, 18.5 mmol) were combined and heated at 140 °C for 26 h under and an atmosphere of nitrogen. The mixture was cooled to room temperature and excess *p*-methoxybenzyl amine was removed under reduced pressure. Attempts to purify

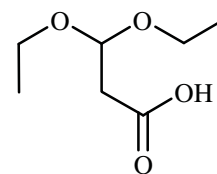


this compound by column chromatography over silica gel were unsuccessful and was therefore used without further purification. The mixture was treated with acetic anhydride (1 mL) and pyridine (1 mL) and heated at 100 °C for 2 h under an atmosphere of nitrogen. The mixture was cooled to room temperature and ice water was added. The organic material was extracted with DCM, washed with 5% HCl and water, dried over Na₂SO₄ and the solvent removed under reduced pressure to afford the title compound as a brown oil (300 mg, 94% over 2 steps). IR (nujol mull): ν/cm^{-1} : 3310, 1670, 1613, 1591, 1557, 1513 and 1487. ¹H NMR (300 MHz, CDCl₃); δ : 2.19 (3H, s, CH₃CO), 3.74 (3H, s, OCH₃), 5.19 (2H, s, CH₂), 6.78 (2H, m, H(2'/6')), 7.17 (2H, m, H(3'/5')), 7.34 (1H, d, *J* = 9.0 Hz, H3), 7.76 (1H, dd, *J* = 1.8, 9.0 Hz, H7), 7.84 (1H, d, *J* = 9.0 Hz, H8), 7.93 (1H, d, *J* = 1.8 Hz, H5), 8.00 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (75 MHz, CDCl₃); δ : 23.7 (CH₃CO), 50.5 (CH₂), 55.1 (OCH₃), 113.9 (C2'/6'), 120.3 (C6), 120.5 (C3), 127.6 (C4a), 129.0 (C5), 129.4 (C3'/5'), 129.6 (C4'), 130.4 (C8), 133.4 (C7), 136.8 (C4), 145.6 (C8a), 154.6 (C1'), 158.8 (C2), 171.0 (C=O).

6-Iodo-2-chloroquinoline (43)

***3,3*-Diethoxypropanoic acid**¹²⁷

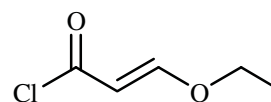
Ethyl 3,3-diethoxyproprionate (5 mL, 25.7 mmol) was added dropwise to a solution of NaOH (1.40 g, 35.0 mmol) in water (10 mL) and heated at 110 °C for 30 min. The reaction was cooled to room temperature and acidified slowly with concentrated HCl (32 mL). The mixture was



extracted with DCM, washed with water and dried over Na₂SO₄. The solvent was removed under reduced pressure to afford the title compound as a pale yellow liquid (2.86 g, 69%). IR (liquid film): ν/cm^{-1} : 3176, 3094, 1742, 1716 and 1621. ¹H NMR (300 MHz, CDCl₃); δ : 1.25 (6H, t, *J* = 7.2 Hz, 2 x CH₃), 2.73 (2H, d, *J* = 5.4 Hz, CH₂), 3.53-3.77 (4H, m, 2 x OCH₂), 4.94 (1H, t, *J* = 5.4 Hz, CH).

(E)-3-Ethoxyacryloyl chloride¹²⁷

Thionyl chloride (7 mL) was added dropwise to 3,3-diethoxypropanoic acid (2.80 g, 17.2 mmol) whereby a vigorous evolution of gas was observed. The reaction was heated at 80 °C for

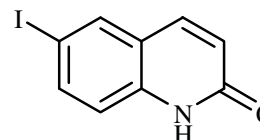


1 h and then cooled to room temperature. Residual thionyl chloride was removed carefully ($T < 50$ °C at 37 mm Hg) under reduced pressure to afford the title compound as a yellow liquid (1.9 g, 82%) which was used without further purification. IR (nujol mull): ν/cm^{-1} : 1744, 1614. ^1H NMR (300 MHz, CDCl_3); δ : 1.41 (3H, t, $J = 7.2$ Hz, CH_3), 4.04 (2H, q, $J = 7.2$ Hz, OCH_2), 5.53 (1H, d, $J = 12.0$ Hz, CH) 7.79 (1H, d, $J = 12.0$ Hz, CH).

The ^1H NMR spectrum is consistent with that reported previously.¹²⁷

*6-Iodoquinolin-2(1H)-one*⁶⁷

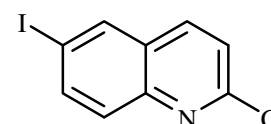
A solution of (*E*)-3-ethoxyacryloyl chloride (800 mg, 5.95 mmol) in DCM (10 mL) was added dropwise to a mixture of DMAP (73 mg, 0.60 mmol) and pyridine (480 μL , 5.95 mmol) in DCM at 0 °C under



a nitrogen atmosphere. The mixture was stirred for 10 min and a solution of 4-iodoaniline (1.30 g, 5.95 mmol) in DCM (10 mL) was added dropwise over a period of 10 min. The solution was stirred for 30 min at 0 °C, before warming to room temperature and stirring for a further 7 h. The solution was washed with water, then the organic phase was dried over Na_2SO_4 . The solvent was removed under reduced pressure to afford the crude title compound as a black viscous solid. The crude material (1.38 g) was treated with concentrated sulfuric acid (2 mL) at 0 °C and stirred at room temperature for 1.5 h. The reaction mixture was poured over ice and the resultant precipitate was filtered and washed with water affording the title compound as an orange solid, mp 257-260 °C (lit.,⁶⁷ 260-263 °C), (1.04 g, 66% over 2 steps). IR (nujol mull): ν/cm^{-1} : 3364, 1696, 1664, 1606, 1593 and 1553. ^1H NMR (300 MHz, CDCl_3); δ : 6.72 (1H, d, $J = 9.6$ Hz, H3), 7.15 (1H, d, $J = 8.7$ Hz, H8), 7.72 (1H, d, $J = 9.6$ Hz, H4), 7.78 (1H, dd, $J = 2.1, 8.7$ Hz, H7), 7.92 (1H, d, $J = 2.1$ Hz, H5), 11.70 (1H, br s, NH).

*6-Iodo-2-chloroquinoline (43)*⁶⁷

A mixture of 6-iodoquinolin-2(1H)-one (507 mg, 1.87 mmol) and phosphorus oxychloride (5 mL, 47.5 mmol) was heated at reflux for 2 h. The solution was cooled to room temperature and quenched with

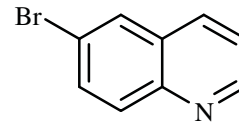


ice water. The resultant solid was filtered and washed with water to afford the title compound as a yellow powder, mp 146-150 °C (445 mg, 82%). IR (nujol mull): ν/cm^{-1} : 1600, 1578 and 1547. ^1H NMR (300 MHz, CDCl_3); δ : 7.42 (1H, d, $J = 8.7$ Hz, H3), 7.77 (1H, d, $J = 9.0$ Hz,

H8), 7.98 (1H, dd, $J = 2.1, 9.0$ Hz, H7), 8.00 (1H, d, $J = 8.7$ Hz, H4), 8.22 (1H, d, $J = 2.1$ Hz, H5). ^{13}C NMR (75 MHz, CDCl_3); δ : 92.7 (C6), 123.4 (C3), 128.6 (C4a), 130.2 (C8), 136.5 (C5), 137.9 (C4), 139.6 (C7), 146.8 (C8a), 151.4 (C2).

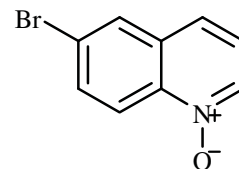
6-Bromoquinoline (**52**)⁷⁷

4-Bromoaniline (10.0 g, 58 mmol), glycerol (15.1 g, 164.0 mmol) and sodium 3-nitrobenzenesulfonate (23.3 g, 103.0 mmol) were combined. Sulfuric acid (65%, 50 mL) was added dropwise and the reaction mixture was heated at reflux for 4 h. The mixture was cooled to 0 °C, basified with NaOH and steam distilled to afford the title compound as an orange liquid (4.50 g, 60%). IR (DCM): ν/cm^{-1} : 3039, 2925, 1614, 1589, 1567 and 1488. ^1H NMR (300 MHz, CDCl_3); δ : 7.43 (1H, dd, $J = 4.2, 8.4$ Hz, H3), 7.80 (1H, dd, $J = 2.1, 9.0$ Hz, H7), 7.98 (1H, d, $J = 9.0$ Hz, H8), 8.00 (1H, br s, H5), 8.08 (1H, d, $J = 8.4$ Hz, H4), 8.93 (1H, dd, $J = 1.5, 4.2$ Hz, H2). ^{13}C NMR (75 MHz, CDCl_3); δ : 120.5 (C6), 121.9 (C3), 129.3 (C4a), 129.9 (C5), 131.2 (C8), 132.9 (C7), 135.1 (C4), 146.8 (C8a), 150.7 (C2).



6-Bromoquinoline-*N*-oxide (**55**)⁷⁸

m-Chloroperbenzoic acid (500 mg, 2.90 mmol) in DCM (5 mL) was added to a solution of **52** (201 mg, 0.96 mmol) in DCM (5 mL) at 0 °C under a nitrogen atmosphere and the reaction mixture was stirred for 2 h. The mixture was neutralised with 5% NaOH and extracted with DCM. The organic layer was washed with NaOH (x 4) and water, dried over MgSO_4 and the solvent removed to afford the title compound as a yellow sticky solid (396 mg, 90%). IR (nujol mull): ν/cm^{-1} : 1651, 1557, 1500 and 1490. ^1H NMR (300 MHz, CDCl_3); δ : 7.33 (1H, dd, $J = 6.0, 8.4$ Hz, H3), 7.65 (1H, d, $J = 8.4$ Hz, H4), 7.83 (1H, dd, $J = 2.1, 9.3$ Hz, H7), 8.05 (1H, d, $J = 2.1$ Hz, H5), 8.53 (1H, d, $J = 6.0$ Hz, H2), 8.64 (1H, d, $J = 9.3$ Hz, H8).



7.1.2 Buchwald-Hartwig Amination for the Preparation of 6-Heterocyclic-2-chloroquinolines

General Procedure 1: Buchwald-Hartwig amination in toluene⁷¹

A pressure tube was loaded with $\text{Pd}(\text{OAc})_2$ (0.5 mol %), ligand precursor (1 mol %) and base (1.2 eq) under a nitrogen atmosphere. Anhydrous toluene was added, followed by the aryl

halide (1 eq) and the amine (1.2 eq). The tube was evacuated, backfilled with nitrogen, sealed and the mixture was heated for 18-26 h at 120 °C. After cooling, the mixture was diluted with an organic solvent and washed with water and/or brine. The organic phase was dried over MgSO₄ or Na₂SO₄, and the solvent was removed under reduced pressure. Alternatively, the crude material was filtered through celite and the solvent was removed under reduced pressure. The product was isolated by flash chromatography on silica gel with the appropriate solvent mixtures.

General Procedure 2: Buchwald-Hartwig amination in trifluoromethylbenzene^{71,90}

General Procedure 1 was employed with trifluoromethylbenzene or 1,4-dioxane as the solvent except that the reaction was heated at 100 °C for the specified time. The product was isolated by flash chromatography on silica gel eluting with appropriate solvent mixtures or alternatively quantitative determinations were obtained by ¹H NMR analysis of the crude material.

General Procedure 3: Buchwald-Hartwig amination in the presence of CuBr⁸²

General Procedure 1 was employed with KO^tBu as the base and with the addition of CuBr (10 mol %). Quantitative determinations of product yields were obtained by ¹H NMR analysis of the crude material.

General Procedure 4: Buchwald-Hartwig amination with microwave irradiation⁹⁰

A high pressure microwave vessel was loaded with the alkyl halide (1 eq) and amine (1.2 eq) in the solvent described. Pd(OAc)₂ (0.5 mol %), CataCXium[®] A ligand **35** (1 mol %) and NaO^tBu (1.2 eq) were added, then the vessel was evacuated, backfilled with nitrogen and sealed. The mixture was heated at the temperature and power indicated for the specified time. After cooling, the mixture was filtered through celite and the solvent was removed under reduced pressure. The product was isolated by flash chromatography on silica gel with appropriate solvent mixtures.

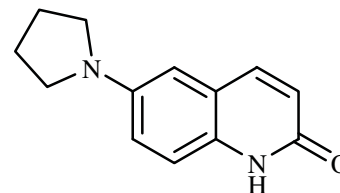
General Procedure 5: Buchwald-Hartwig amination with PEPPSI[™]^{86,87}

The aryl halide (1 eq) was dissolved in dry DME and added to a reaction vessel loaded with KO^tBu (1.5 eq) and PEPPSI[™] **63** (2 mol %) in DME under argon. The amine (1.1 eq) was added dropwise and the solution stirred at 50 °C for the prescribed time. After cooling to room temperature the mixture was extracted with an appropriate organic solvent, washed with water

and brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the product was isolated by flash chromatography on silica gel eluting with appropriate solvent mixtures.

Attempted synthesis of 6-(pyrrolidin-1-yl)quinolin-2(1H)-one (45)

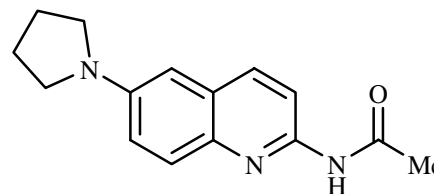
Using General Procedure 1, **34** (141 mg, 0.62 mmol) and pyrrolidine **b** (62 μ L, 0.74 mmol) were added to a mixture of Pd(OAc)₂ (0.70 mg, 3.1 μ mol), CataCXium[®] A ligand **35** (2.2 mg, 6.2 μ mol) and KO^tBu (84 mg, 0.74 mmol) in toluene (1 mL)



and the reaction was heated for 26 h. The crude material was extracted with diethyl ether and the solvent removed under reduced pressure. Analysis of the crude material by ¹H NMR did not indicate the presence of any desired product and predominantly starting material was observed.

Attempted synthesis of N-(6-(pyrrolidin-1-yl)quinolin-2-yl)acetamide (47)

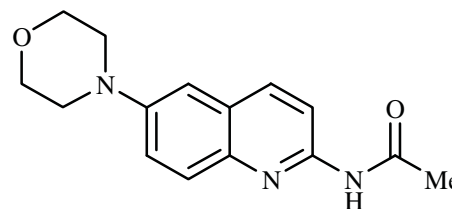
Using General Procedure 1, **46** (142 mg, 0.54 mmol) and pyrrolidine **b** (55 μ L, 0.66 mmol) were added to a mixture of Pd(OAc)₂ (0.60 mg, 2.7 μ mol), CataCXium[®] A ligand **35** (1.9 mg, 5.3 μ mol) and KO^tBu (72 mg, 0.64



mmol) in toluene (3 mL) and the reaction was heated for 25 h. Extraction with diethyl ether and chromatographic separation eluting with DCM:ethyl acetate (3:2) afforded starting material and some other unidentified by-products.

Attempted synthesis of N-(6-(morpholino)quinolin-2-yl)acetamide (64)

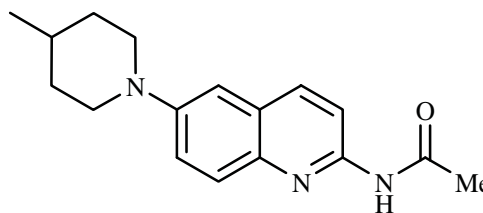
Using General Procedure 5, **46** (437 mg, 1.65 mmol), KO^tBu (278 mg, 2.48 mmol) and PEPPSI[™] **63** (22 mg, 33 μ mol) were combined in DME (10 mL). Morpholine **c** (158 μ L, 1.82 mmol) was added dropwise and the solution stirred for 24 h. Work-up



with ethyl acetate afforded 6-bromo-2-aminoquinoline **65**, mp 144-147 °C (350 mg, 96%). Data as above.

Attempted synthesis of *N*-(6-(4-methylpiperidin-1-yl)quinolin-2-yl)acetamide (**56**)

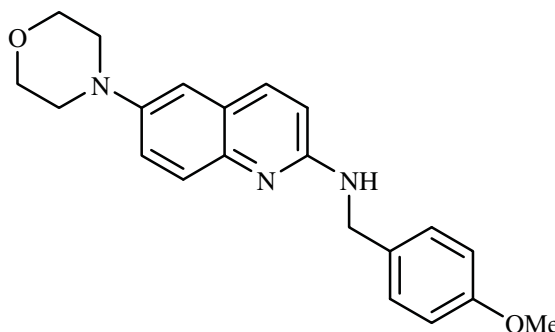
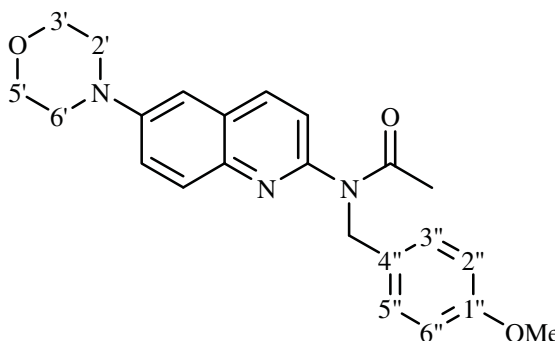
(i) Using General Procedure 2, **46** (55 mg, 0.21 mmol) and 4-methylpiperidine **a** (30 μ L, 0.25 mmol) were added to a mixture of Pd(OAc)₂ (0.22 mg, 1.0 μ mol), CataCXium[®] A ligand **35** (0.7 mg, 1.9 μ mol) and NaO^tBu (24 mg, 0.25 mmol) in trifluoromethylbenzene (3 mL) and the reaction was heated for 20 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM:ethyl acetate (3:2) afforded 6-bromo-2-aminoquinoline (**65**) (22 mg, 47%). Data as above.



(ii) Using General Procedure 3, **46** (55 mg, 0.21 mmol) and 4-methylpiperidine **a** (30 μ L, 0.25 mmol) were added to a mixture of Pd(OAc)₂ (0.22 mg, 1.0 μ mol), CataCXium[®] A ligand **35** (0.7 mg, 1.9 μ mol), CuBr (3.1 mg, 21 μ mol) and KO^tBu (28 mg, 0.25 mmol) in toluene (3 mL) and the reaction was heated for 21 h. Extraction with chloroform:isopropanol (3:1 mix) led to the recovery of starting materials only.

Attempted synthesis of *N*-(4-methoxybenzyl)-*N*-(6-morpholinoquinolin-2-yl)acetamide (**51**)

Using General Procedure 1, **50** (102 mg, 0.26 mmol) and morpholine **c** (27 μ L, 0.31 mmol) were added to a mixture of Pd(OAc)₂ (0.3 mg, 1.3 μ mol), CataCXium[®] A ligand **35** (0.9 mg, 2.6 μ mol) and KO^tBu (35 mg, 0.31 mmol) in toluene (1 mL) and the reaction was heated for 21 h. The crude material was extracted with ethyl acetate and the solvent was removed under reduced pressure. Chromatographic separation eluting with DCM afforded *N*-(4-methoxybenzyl)-6-morpholinoquinolin-2-amine **49** as a brown oil (50 mg, 55%). IR (nujol mull): ν/cm^{-1} : 3400, 1670, 1640 and 1513. ¹H NMR (600 MHz, CDCl₃); δ : 3.18

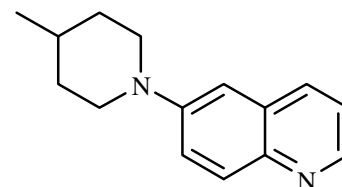


(4H, t, $J = 4.8$ Hz, 2 x CH₂, H(2'/6')), 3.81 (3H, s, OCH₃), 3.88 (4H, t, $J = 4.8$ Hz, 2 x CH₂, H(3'/5')), 4.63 (2H, d, $J = 4.8$ Hz, CH₂), 5.84 (1H, br s, NH), 6.65 (1H, d, $J = 9.0$ Hz, H3), 6.87 (2H, m, H(2''/6'')), 6.95 (1H, d, $J = 2.4$ Hz, H5), 7.32-7.34 (3H, m, H7, H(3''/5'')), 7.68

(1H, d, $J = 9.0$ Hz, H8), 7.75 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, CDCl_3); δ : 45.5 (CH_2), 49.7 ($\text{C}2'/6'$), 55.2 (CH_3), 66.9 ($\text{C}3'/5'$), 110.9 ($\text{C}5$), 111.1 ($\text{C}3$), 122.4 ($\text{C}7$), 123.6 ($\text{C}4\text{a}$), 125.5 ($\text{C}8$), 128.9 ($\text{C}2''/6''$), 130.8 ($\text{C}4''$), 137.5 ($\text{C}4$), 141.0 ($\text{C}8\text{a}$), 146.9 ($\text{C}6$), 155.1 ($\text{C}1$), 158.9 ($\text{C}1''$).

6-(4-Methylpiperidin-1-yl)quinoline (53)

(i) Using General Procedure 1, **52** (201 mg, 0.96 mmol) and 4-methylpiperidine **a** (136 μL , 1.15 mmol) were added to a mixture of $\text{Pd}(\text{OAc})_2$ (1 mg, 4.8 μmol), CataCXium[®] A ligand **35** (3.4 mg, 9.6 μmol) and KO^tBu (132 mg, 1.15 mmol) in

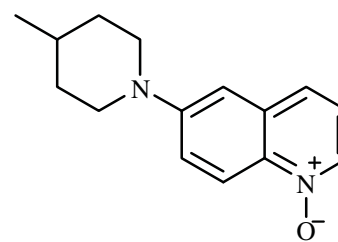


toluene (2 mL) and the reaction was heated for 20 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM:ethyl acetate (9:1) afforded the title compound as a yellow oil (140 mg, 65%). IR (nujol mull): ν/cm^{-1} : 1654, 1616, 1602, 1578 and 1479. ^1H NMR (300 MHz, CDCl_3); δ : 1.10 (3H, d, $J = 6.6$ Hz, CH_3), 1.39 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, 4'} = 12.6$ Hz, 2 x CH, $\text{H}(3'/5')_{\text{ax}}$), 1.60 (1H, br m, CH, $\text{H}4'$), 1.80 (2H, br d^\ddagger , $J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, $\text{H}(3'/5')_{\text{eq}}$), 2.81 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.6$ Hz, 2 x CH, $\text{H}(2'/6')_{\text{ax}}$), 3.81 (2H, br d^\ddagger , $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, $\text{H}(2'/6')_{\text{eq}}$), 7.02 (1H, d, $J = 3.0$ Hz, H5), 7.29 (1H, dd, $J = 4.2, 8.7$ Hz, H3), 7.51 (1H, dd, $J = 3.0, 9.3$ Hz, H7), 7.94-7.99 (2H, m, H4, H8), 8.69 (1H, dd, $J = 1.5, 4.2$ Hz, H2). ^{13}C NMR (75 MHz, CDCl_3); δ : 22.1 (CH_3), 30.9 ($\text{C}4'$), 34.2 ($\text{C}3'/5'$), 50.1 ($\text{C}2'/6'$), 109.3 ($\text{C}5$), 121.5 ($\text{C}3$), 129.4 ($\text{C}7$), 129.8 ($\text{C}4\text{a}$), 130.7 ($\text{C}8$), 134.7 ($\text{C}4$), 143.9 ($\text{C}8\text{a}$), 147.5 ($\text{C}2$), 150.1 ($\text{C}6$).

(ii) Using General Procedure 5, **52** (203 mg, 0.96 mmol), KO^tBu (162 mg, 1.44 mmol) and PEPPSI[™] **63** (13 mg, 19 μmol) were combined in DME (2 mL). 4-Methylpiperidine **a** (125 μL , 1.05 mmol) was added dropwise and the solution heated for 2 h. Work-up with chloroform:isopropanol (3:1 mix) afforded the title compound as a yellow oil (120 mg, 55%). Data as above.

Attempted synthesis of 6-(4-methylpiperidin-1-yl)quinoline-*N*-oxide (**54**)

(i) Using General Procedure 3, **55** (96 mg, 0.43 mmol) and 4-methylpiperidine **a** (62 μ L, 0.52 mmol) were added to a mixture of Pd(OAc)₂ (0.5 mg, 2.2 μ mol), CataCXium[®] A ligand **35** (1.5 mg, 4.3 μ mol), CuBr (6.2 mg, 43 μ mol) and KO^tBu (58 mg, 0.52 mmol) in toluene (1 mL) and the reaction was heated



for 18 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation over silica gel eluting with DCM:ethanol (49:1) afforded the title compound as an impure mixture (15 mg, 14%). Further attempts to purify the title compound by chromatography over silica gel and preparative TLC lead to the decomposition of the product. HRMS found: 242.1414; C₁₅H₁₈N₂O requires 242.1419. IR (DCM): ν/cm^{-1} : 3100, 2950, 1672, 1608, 1551 and 1502. ¹H NMR (200 MHz, CDCl₃); δ : 1.00 (3H, d, $J = 6.6$ Hz, CH₃), 1.39 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, 4'} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.60 (1H, br m, CH, H4'), 1.79 (2H, br d[‡], $J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.86 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.85 (2H, br d[‡], $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 7.00 (1H, d, $J = 2.4$ Hz, H5), 7.17 (1H, dd, $J = 6.0, 8.7$ Hz, H3), 7.50 (1H, dd, $J = 2.4, 9.6$ Hz, H7), 7.55 (1H, d, $J = 8.7$ Hz, H4), 8.30 (1H, d, $J = 6.0$ Hz, H2), 8.57 (1H, d, $J = 9.6$ Hz, H7). m/z (EI): 242 (M⁺, 10%), 226 (90), 225 (100), 209 (15), 183 (30), 171 (25), 155 (30), 128 (30).

(ii) Using General Procedure 1, **55** (96 mg, 0.43 mmol) and 4-methylpiperidine **a** (62 μ L, 0.52 mmol) were added to a mixture of Pd(OAc)₂ (0.5 mg, 2.2 μ mol), CataCXium[®] A ligand **35** (1.5 mg, 4.3 μ mol) and KO^tBu (58 mg, 0.52 mmol) in toluene (2 mL) and the reaction was heated for 20 h. Work-up with chloroform:isopropanol (3:1 mix) afforded a complex mixture of products which was not purified.

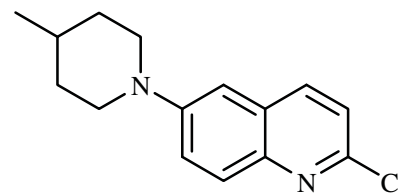
(iii) Using General Procedure 5, **55** (98 mg, 0.44 mmol) KO^tBu (74 mg, 0.66 mmol) and PEPPSI[™] **63** (6 mg, 8.8 μ mol) were combined in DME (2 mL). 4-Methylpiperidine **a** (57 μ L, 0.48 mmol) was added dropwise and the solution heated for 22 h. Work-up with chloroform:isopropanol (3:1 mix) led to the recovery of starting material only.

(iv)⁷⁸ *m*-Chloroperbenzoic acid (228 mg, 1.32 mmol) in DCM (2 mL) was added to a solution of **53** (99 mg, 0.44 mmol) in DCM (1 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 4 h. The mixture was neutralised with 5% NaOH and extracted with DCM. The organic material was washed with NaOH (x 4) and water, dried over MgSO₄ and the solvent removed under reduced pressure. NMR

analysis of the crude material indicated a complex mixture of products that was not purified.

2-Chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**)

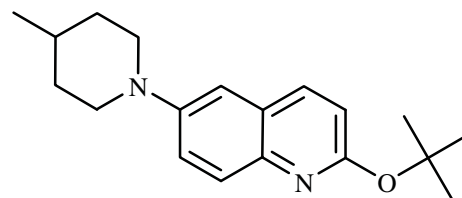
(i) Using General Procedure 1, **31** (520 mg, 2.13 mmol) and 4-methylpiperidine (300 μ L, 2.56 mmol) were added to a mixture of Pd(OAc)₂ (2.4 mg, 10.6 μ mol), CataCXium[®] A ligand **35** (7.6 mg, 21.3 μ mol) and KO^tBu (287 mg, 2.56 mmol) in toluene (3 mL) and the reaction was heated for 21 h. Extraction with ethyl acetate and chromatographic separation eluting with DCM:ethyl acetate (50:1) afforded the title compound **32a** as a 5:1 mixture with 2-^tbutoxy-6-(4-methylpiperidin-1-yl)quinoline **39a** (combined yield 297 mg; **32a** 44%, **39a** 9%). 6-Bromo-2-(4-methylpiperidin-1-yl)quinoline **37a** (yellow crystals, mp 76-80 °C, 140 mg, 25%) and 2-(4-methylpiperidin-1-yl)quinoline **38** (yellow oil, 71 mg, 15%), were also isolated.



2-Chloro-6-(4-methylpiperidin-1-yl)quinoline (32a): HRMS found: 259.1000; C₁₅H₁₇³⁵ClN₂-H requires 259.1002. IR (nujol mull): ν /cm⁻¹: 1654, 1616, 1600 and 1578. ¹H NMR (600 MHz, CDCl₃); δ : 0.99 (3H, d, J = 6.6 Hz, CH₃), 1.37 (2H, dq, $J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{ax}}} = 2.4$ Hz, $J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}} = J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = J_{(3'/5')_{\text{ax}}, 4'} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.56 (1H, br m, CH, H4'), 1.77 (2H, br d[‡], $J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.79 (2H, dt, $J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{eq}}} = 2.4$ Hz, $J_{(2'/6')_{\text{ax}}, (2'/6')_{\text{eq}}} = J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.77 (2H, br d[‡], $J_{(2'/6')_{\text{ax}}, (2'/6')_{\text{eq}}} = J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 6.97 (1H, d, J = 2.4 Hz, H5), 7.24 (1H, d, J = 9.0 Hz, H3), 7.47 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.84 (1H, d, J = 9.0 Hz, H8), 7.87 (1H, d, J = 9.0 Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 27.7 (CH₃), 30.6 (C4'), 33.8 (C3'/5'), 49.6 (C2'/6'), 108.6 (C5), 122.2 (C3), 123.5 (C7), 128.1 (C4a), 128.9 (C8), 137.3 (C4), 142.8 (C8a), 147.0 (C2), 150.0 (C6). m/z (EI): 262 (M+H⁺ [³⁷Cl], 30%), 261 (M⁺ [³⁷Cl], 40), 260 (M+H⁺ [³⁵Cl], 100), 259 (M⁺ [³⁵Cl], 100), 164 (6), 162 (18).

2-^tButoxy-6-(4-methylpiperidin-1-yl)quinoline (39a):

¹H NMR (600 MHz, CDCl₃); δ : 0.99 (3H, d, J = 6.6 Hz, CH₃), 1.37 (2H, dq, $J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{ax}}} = 2.4$ Hz, $J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}} = J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = J_{(3'/5')_{\text{ax}}, 4'} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.56 (1H, br m, CH, H4'), 1.66 (9H, s, ^tBu), 1.77 (2H, br d[‡], $J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.73 (2H, m, 2 x CH, H(2'/6')_{ax}), 3.67 (2H, br d[‡], $J_{(2'/6')_{\text{ax}}, (2'/6')_{\text{eq}}} = J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 6.73 (1H, d, J = 9.0 Hz, H3), 7.26 (1H, d, J = 1.2 Hz, H5), 7.39 (1H, br d[‡], J = 9.0 Hz, H7), 7.68 (1H, d, J = 9.0 Hz, H8),



7.78 (1H, d, $J = 9.0$ Hz, H4). m/z (EI): 242 (M^+ - C_4H_8 , 100%).

6-Bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**):

HRMS (EI+) found: 304.0575; $C_{15}H_{17}^{79}BrN_2$ requires 304.0575. IR (nujol mull): ν/cm^{-1} : 1642, 1615, 1598, 1546

and 1493. 1H NMR (600 MHz, $CDCl_3$); δ : 0.98 (3H, d, $J =$

6.6 Hz, CH_3), 1.26 (2H, m, 2 x CH, $H(3'/5')_{ax}$), 1.65 (1H, br m, CH, $H4'$), 1.77 (2H, br d^\ddagger ,

$J_{(3'/5')_{ax}, (3'/5')_{eq}} = J_{(2'/6')_{eq}, (3'/5')_{eq}} = 12.6$ Hz, 2 x CH, $H(3'/5')_{eq}$), 2.95 (2H, br s^\ddagger , 2 x CH,

$H(2'/6')_{ax}$), 4.53 (2H, br s^\ddagger , 2 x CH, $H(2'/6')_{eq}$), 7.00 (1H, d, $J = 9.0$ Hz, H3), 7.54 (2H, br s,

H7, H8), 7.70 (1H, d, $J = 1.2$ Hz, H5), 7.76 (1H, d, $J = 9.0$ Hz, H4). m/z (EI): 306 (M^+ [^{81}Br],

50%), 304 (M^+ [^{79}Br], 50), 277 (30), 263 (35), 261 (35), 249 (100), 237 (50), 235 (50), 224

(40), 222 (40), 208 (50), 127(50).

2-(4-methylpiperidin-1-yl)quinoline (**38**): IR (nujol mull):

ν/cm^{-1} : 1675, 1619, 1603, 1556 and 1505. 1H NMR (600 MHz,

$CDCl_3$); δ : 1.00 (3H, d, $J = 6.6$ Hz, CH_3), 1.27 (2H, dq, $J_{(2'/6')_{eq},$

$(3'/5')_{ax} = 2.4$ Hz, $J_{(2'/6')_{ax}, (3'/5')_{ax}} = J_{(3'/5')_{ax}, (3'/5')_{eq}} = J_{(3'/5')_{ax}, 4' =$

12.6 Hz, 2 x CH, $H(3'/5')_{ax}$), 1.68 (1H, br m, CH, $H4'$), 1.77 (2H, br d^\ddagger , $J_{(3'/5')_{ax}, (3'/5')_{eq}} =$

$J_{(2'/6')_{eq}, (3'/5')_{eq}} = 12.6$ Hz, 2 x CH, $H(3'/5')_{eq}$), 2.95 (2H, dt, $J_{(2'/6')_{ax}, (3'/5')_{eq}} = 2.4$ Hz, $J_{(2'/6')_{ax},$

$(2'/6')_{eq} = J_{(2'/6')_{ax}, (3'/5')_{ax}} = 12.6$ Hz, 2 x CH, $H(2'/6')_{ax}$), 4.53 (2H, br d^\ddagger , $J_{(2'/6')_{ax}, (2'/6')_{eq}} = J_{(2'/6')_{eq},$

$(3'/5')_{eq} = 12.6$ Hz, 2 x CH, $H(2'/6')_{eq}$), 7.00 (1H, d, $J = 9.0$ Hz, H3), 7.20 (1H, dt, $J = 0.9, 7.8$

Hz, H6), 7.39 (1H, dt, $J = 1.5, 7.8$ Hz, H7), 7.58 (1H, br d^\ddagger , $J = 7.8$ Hz, H8), 7.70 (1H, br d^\ddagger , J

$= 7.8$ Hz, H5), 7.86 (1H, d, $J = 9.0$ Hz, H4). m/z (EI): 226 (M^+ , 100%).

(ii) Employing 43 as the aryl halide. Using General Procedure 1, **43** (100 mg, 0.35 mmol)

and 4-methylpiperidine **a** (35 μ L, 0.41 mmol) were added to a mixture of $Pd(OAc)_2$ (0.4 mg,

1.8 μ mol), CataCXium[®] A ligand **35** (1.2 mg, 3.5 μ mol) and NaO^tBu (40 mg, 0.41 mmol) in

toluene (3 mL) and the reaction mixture was heated for 21 h. Extraction with ethyl acetate

and chromatographic separation eluting with DCM:ethyl acetate (50:1) afforded the title

compound **32a** as a yellow solid (35 mg 38%). Data as above. 6-Iodo-2-(4-methylpiperidin-

1-yl)quinoline **44** was also isolated (yellow glass, 16 mg, 13%).

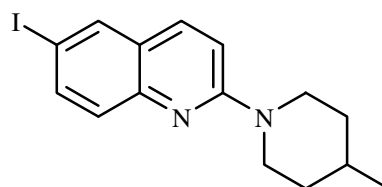
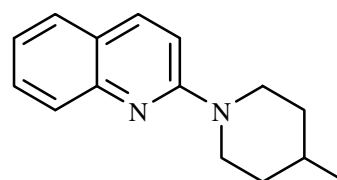
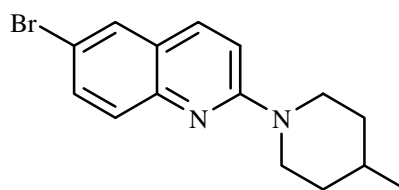
6-Iodo-2-(4-methylpiperidin-1-yl)quinoline (**44**): HRMS

(EI+) found: 352.0435; $C_{15}H_{17}IN_2$ requires 352.0436. IR

(nujol mull): ν/cm^{-1} : 1646, 1615, 1598, 1560 and 1500. 1H

NMR (300 MHz, $CDCl_3$); δ : 1.00 (3H, d, $J = 6.3$ Hz, CH_3),

1.28 (2H, dq, $J_{(2'/6')_{eq}, (3'/5')_{ax}} = 3.0$ Hz, $J_{(2'/6')_{ax}, (3'/5')_{ax}} =$



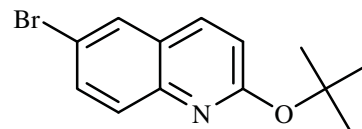
$J_{(3'/5')_{ax}, (3'/5')_{eq}} = J_{(3'/5')_{ax}, 4'} = 12.3$ Hz, 2 x CH, H(3'/5')_{ax}), 1.69 (1H, br m, CH, H4'), 1.80 (2H, br d[‡], $J_{(3'/5')_{ax}, (3'/5')_{eq}} = J_{(2'/6')_{eq}, (3'/5')_{eq}} = 12.3$ Hz, 2 x CH, H(3'/5')_{eq}), 3.00 (2H, br t[‡], $J = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 4.54 (2H, br d[‡], $J_{(2'/6')_{ax}, (2'/6')_{eq}} = J_{(2'/6')_{eq}, (3'/5')_{eq}} = 12.3$ Hz, 2 x CH, H(2'/6')_{eq}), 6.98 (1H, br d, $J = 6.3$ Hz, H3), 7.59 (1H, br d, $J = 7.2$ Hz, H8), 7.71-7.76 (2H, m, H4, H7), 7.92 (1H, d, $J = 1.5$ Hz, H5). m/z (EI): 352 (M⁺, 100%), 254 (30).

(iii) Using General Procedure 2, **31** (50 mg, 0.21 mmol) and 4-methylpiperidine **a** (30 μ L, 0.25 mmol) were added to a mixture of Pd(OAc)₂ (0.2 mg, 1.0 μ mol), CataCXium[®] A ligand **35** (0.8 mg, 2.2 μ mol) and NaO^tBu (24 mg, 0.25 mmol) in trifluoromethylbenzene (1 mL) and the reaction was heated for 20 h. Work up as above afforded the title compound (51 mg, 93%). Yield determined by ¹H NMR analysis. Data as above.

(iv) Using General Procedure 3, **31** (104 mg, 0.43 mmol) and 4-methylpiperidine **a** (62 μ L, 0.52 mmol) were added to a mixture of Pd(OAc)₂ (0.5 mg, 2.2 μ mol), CataCXium[®] A ligand **35** (1.5 mg, 4.3 μ mol), CuBr (6.2 mg, 43 μ mol) and KO^tBu (58 mg, 0.52 mmol) in toluene (1 mL) and the reaction mixture was heated for 18 h. The mixture was filtered through celite and the solvent removed under reduced pressure to afford the title compound (80 mg, 72%). Yield determined by ¹H NMR analysis. Data as above.

(v) **Employing 43 as the aryl halide in the presence of CuBr.** Using General Procedure 3, **43** (61 mg, 0.21 mmol) and 4-methylpiperidine **a** (30 μ L, 0.25 mmol) were added to a mixture of Pd(OAc)₂ (0.2 mg, 1.0 μ mol), CataCXium[®] A ligand **35** (0.7 mg, 1.9 μ mol), CuBr (3.1 mg, 21 μ mol) and KO^tBu (28 mg, 0.25 mmol) in toluene (3 mL) and the reaction mixture was heated for 21 h. The mixture was filtered through celite and the solvent removed under reduced pressure. Chromatographic separation eluting with DCM:ethyl acetate (19:1) afforded the title compound as a yellow solid (10 mg, 19%). 6-Iodo-2-(4-methylpiperidin-1-yl)quinoline **44** was also isolated (25 mg, 34%). Data as above.

(vi) Using General Procedure 5, **31** (50 mg, 0.21 mmol), KO^tBu (35 mg, 0.32 mmol) and PEPPSI[™] **63** (3 mg, 4.4 μ mol) were combined in DME (5 mL). 4-Methylpiperidine **a** (27 μ L,



0.23 mmol) was added dropwise and the solution heated for 1.5 h. Work-up with chloroform:isopropanol (3:1 mix) afforded 2-^tbutoxy-6-bromoquinoline **40** as a pink glass (50 mg, 87%). Data as above.

(vii) **Catalyst screen with 31.** Using General Procedure 1, **31** (50 mg, 0.21 mmol) and 4-methylpiperidine **a** (30 μ L, 0.25 mmol) were added to a mixture of Pd(OAc)₂ (0.22 mg, 1.0 μ mol), Buchwald ligand (2.1 μ mol) and KO^tBu (28 mg, 0.25 mmol) in toluene (1 mL) and the reaction was heated at 110 °C for approximately 22 h. The mixture was filtered through celite

and the solvent removed under reduced pressure. Yields were determined by ^1H NMR analysis of the crude material. The corresponding reaction was also conducted in the presence of CuBr (3.1 mg, 21 μmol) using General Procedure 3.

a) With DavePhos (57). Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (15%), 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (15%) and 2- t butoxy-6-bromoquinoline (**40**) (50%). **With DavePhos (57) and CuBr.** Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (25%) and 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (58%).

b) With X-Phos (58). Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (40%), 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (20%) and 2- t butoxy-6-(4-methylpiperidin-1-yl) (**39a**) (15%). **With X-Phos (58) and CuBr.** Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (21%) and 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (43%).

c) With SPhos (59). Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (31%), 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (15%) and 2- t butoxy-6-bromoquinoline (**40**) (25%). **With SPhos (59) and CuBr.** Afforded 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (68%).

d) With t Bu X-Phos (60). Afforded 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (21%) and 2- t butoxy-6-bromoquinoline (**40**) (65%). **With t Bu X-Phos (60) and CuBr.** Afforded 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (80%).

e) With CyJohnPhos (61). Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (54%), 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (16%), 2- t butoxy-6-(4-methylpiperidin-1-yl) (**39a**) (10%) and 2- t butoxy-6-bromoquinoline (**40**) (10%). **With CyJohnPhos (61) and CuBr.** Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (21%) and 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (61%).

f) With JohnPhos (63). Afforded 2- t butoxy-6-bromoquinoline (**40**) (65%). **With JohnPhos (63) and CuBr.** Afforded starting material only.

(viii) Base and solvent screen with 31. Using General Procedure 1 or 2, **31** (50 mg, 0.21 mmol) and 4-methylpiperidine **a** (30 μL , 0.25 mmol) were added to a mixture of Pd(OAc)₂ (0.22 mg, 1.0 μmol), CataCXium[®] A ligand **35** (0.8 mg, 2.1 μmol) and base (0.25 mmol) in the described solvent (1 mL) and the reaction was heated for approximately 20 h. The mixture was filtered through celite and the solvent removed under reduced pressure. Yields were determined by ^1H NMR analysis of the crude material.

a) With toluene and KO^tBu. Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (57%) and 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (14%).

b) With toluene and NaO^tBu. Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (60%) and 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (11%).

c) With toluene and Cs₂CO₃. Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (30%).

d) With trifluoromethylbenzene and NaO^tBu. Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (93%) and 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (6%).

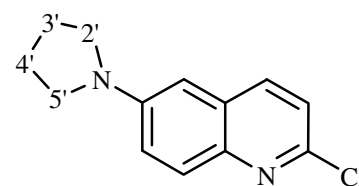
e) With trifluoromethylbenzene and Cs₂CO₃. Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (2%).

f) With 1,4-dioxane and NaO^tBu. Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (90%) and 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (4%).

g) With 1,4-dioxane and Cs₂CO₃. Afforded 2-chloro-6-(4-methylpiperidin-1-yl)quinoline (**32a**) (8%) and 6-bromo-2-(4-methylpiperidin-1-yl)quinoline (**37a**) (46%).

2-Chloro-6-(pyrrolidin-1-yl)quinoline (**32b**)

Using General Procedure 1, **31** (140 mg, 0.58 mmol) and pyrrolidine **b** (58 μ L, 0.69 mmol) were added to a mixture of Pd(OAc)₂ (0.65 mg, 2.9 μ mol), CataCXium[®] A ligand **35** (2.1 mg, 5.8 μ mol) and KO^tBu (79 mg, 0.70 mmol) in toluene (2

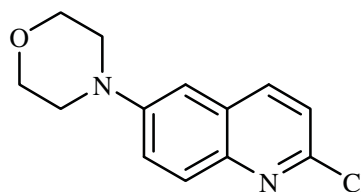


mL) and the reaction was heated for 20 h. Extraction with diethyl ether and chromatographic separation eluting with DCM:hexane (4:1) afforded the title compound as a brown solid which decomposed above 250 °C (70 mg, 52%). HRMS found: 232.0761; C₁₃H₁₃³⁵ClN₂ requires 232.0767. Analysis found: C, 67.05; H, 5.63; N, 12.10. C₁₃H₁₃ClN₂ requires C, 67.10; H, 5.63; N, 12.04%. IR (nujol mull): ν /cm⁻¹: 1658, 1616, 1563 and 1517. ¹H NMR (200 MHz, CDCl₃); δ : 2.07 (4H, q, *J* = 3.3 Hz, 2 x CH₂, H(3'/4')), 3.39 (4H, t, *J* = 6.6 Hz, 2 x CH₂, H(2'/5')), 6.60 (1H, d, *J* = 2.7 Hz, H5), 7.17 (1H, dd, *J* = 2.7, 9.0 Hz, H7), 7.22 (1H, d, *J* = 8.7 Hz, H3), 7.83 (1H, d, *J* = 9.0 Hz, H8), 7.86 (1H, d, *J* = 8.7 Hz, H4). ¹³C NMR (150 MHz,

CDCl₃); δ : 25.8 (C3'/4'), 48.3 (C2'/5'), 104.0 (C5), 119.8 (C3), 122.5 (C7), 128.7 (C4a), 129.3 (C8), 136.9 (C4), 143.2 (C8a), 149.2 (C2), 152.5 (C6). *m/z* (EI): 234 (M⁺ [³⁷Cl], 25%), 233 (M-H⁺ [³⁷Cl], 25), 232 (M⁺ [³⁵Cl], 80), 231 (M-H⁺ [³⁵Cl], 100), 176 (35).

2-Chloro-6-morpholinoquinoline (32c)

(i) Using General Procedure 1, **31** (102 mg, 0.42 mmol) and morpholine **c** (44 μ L, 0.51 mmol) were added to a mixture of Pd(OAc)₂ (0.5 mg, 2.2 μ mol), CataCXium[®] A ligand **35** (1.5 mg, 4.2 μ mol) and KO^tBu (57 mg, 0.51 mmol) in toluene (1



mL) and the reaction was heated for 20 h. Extraction with ethyl acetate and chromatographic separation eluting with DCM afforded the title compound as a yellow solid, mp 88-91 °C (98 mg, 94%). HRMS found: 248.0707; C₁₃H₁₃³⁵ClN₂O requires 248.0716. Analysis found: C, 62.80; H, 5.23; N, 11.26. C₁₃H₁₃ClN₂O requires C, 62.78; H, 5.27; N, 11.26%. IR (nujol mull): ν /cm⁻¹: 1652, 1621, 1563 and 1503. ¹H NMR (600 MHz, CDCl₃); δ : 3.26 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(2'/6')), 3.90 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(3'/5')), 6.98 (1H, d, *J* = 2.7 Hz, H5), 7.27 (1H, d, *J* = 8.7 Hz, H3), 7.45 (1H, dd, *J* = 2.7, 9.6 Hz, H7), 7.88 (1H, d, *J* = 9.6 Hz, H8), 7.91 (1H, d, *J* = 8.7 Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 49.1 (C2'/6'), 66.7 (C3'/5'), 110.4 (C5), 122.4 (C7), 122.5 (C3), 127.9 (C4a), 128.2 (C8), 137.1 (C4), 143.2 (C8a), 147.6 (C2), 149.5 (C6). *m/z* (EI): 250 (M⁺ [³⁷Cl], 15%), 248 (M⁺ [³⁵Cl], 50), 192 (30), 190 (100), 162 (20), 127 (20), 40 (30).

(ii) **Employing 43 as the aryl halide.** Using General Procedure 1, **43** (100 mg, 0.35 mmol) and morpholine **c** (36 μ L, 0.41 mmol) were added to a mixture of Pd(OAc)₂ (0.4 mg, 1.7 μ mol), CataCXium[®] A ligand **35** (1.2 mg, 3.5 μ mol) and NaO^tBu (40 mg, 0.41 mmol) in toluene (2 mL) and the reaction was heated for 21 h. The crude material was filtered through celite and the solvent removed under reduced pressure. Chromatographic separation over silica gel eluting with DCM afforded the title compound **32c** as a yellow solid (53 mg, 61%). Data as above.

(iii) Using General Procedure 2, **31** (51 mg, 0.21 mmol) and morpholine **c** (22 μ L, 0.26 mmol) were added to a mixture of Pd(OAc)₂ (0.3 mg, 1.2 μ mol), CataCXium[®] A ligand **35** (0.7 mg, 2.1 μ mol) and NaO^tBu (25 mg, 0.26 mmol) in trifluoromethylbenzene (1 mL) and the reaction was heated for 20 h. Extraction with chloroform:isopropanol (3:1 mix) afforded the title compound **32c** as a yellow solid (49 mg, 95%). Yield determined by ¹H NMR analysis. Data as above.

(iv) Using General Procedure 4, **31** (200 mg, 0.82 mmol) and morpholine **c** (86 μ L, 0.98 mmol) were combined in toluene (10 mL). Pd(OAc)₂ (1.0 mg, 4.1 μ mol), CataCXium[®] A ligand **35** (3.0 mg, 8.2 μ mol) and NaO^tBu (94 mg, 0.98 mmol) were added then the vessel was evacuated, backfilled with nitrogen and sealed. The mixture was heated at 130 °C at 1200 W in a MARS microwave system for 15 min (including 5 min ramp time). Chromatographic separation eluting with DCM afforded the title compound **32c** as a yellow solid (195 mg, 80%). Data as above.

(v) Using General Procedure 4, **31** (45 mg, 0.19 mmol) and morpholine **c** (20 μ L, 0.23 mmol) were combined in trifluoromethylbenzene (2 mL). Pd(OAc)₂ (0.2 mg, 1.0 μ mol), CataCXium[®] A ligand **35** (0.8 mg, 2.1 μ mol) and NaO^tBu (22 mg, 0.23 mmol) were added then the vessel was evacuated, backfilled with nitrogen and sealed. The mixture was heated at 150 °C at 300 W in a Discover microwave system for 15 min (including 1 min ramp time). Work-up afforded the title compound **32c** as a yellow solid (45 mg, 95%). Data as above.

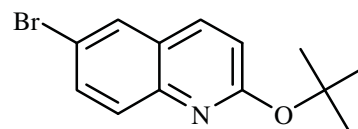
(vi) Using General Procedure 5, **31** (102 mg, 0.42 mmol), KO^tBu (71 mg, 0.63 mmol) and PEPPSI[™] **63** (6 mg, 8.8 μ mol) were combined in DME (5 mL). Morpholine **c** (40 μ L, 0.46 mmol) was added dropwise then the solution was stirred for 2 h. Work-up with chloroform:isopropanol (3:1 mix) afforded the title compound **32c** as a 3:1 mixture with 2-^tbutoxy-6-bromoquinoline **40** (combined yield 95 mg; **32c** 66%, 2-^tbutoxy-6-bromoquinoline **40** 22%). The corresponding reaction at room temperature and at reflux similarly resulted in mixtures of the title compound with **40**. Product ratios of 1:2.5 and 1:3 respectively were obtained. Data as above.

2-^tButoxy-6-bromoquinoline (**40**): HRMS found: 280.0332;

C₁₃H₁₄⁷⁹BrNO+H requires 280.0332. IR (DCM): ν /cm⁻¹:

1667, 1613, 1602 and 1561. ¹H NMR (300 MHz, CDCl₃); δ :

1.69 (9H, s, ^tBu), 6.76 (1H, d, *J* = 9.0 Hz, H3), 7.65 (2H, s, H7, H8), 7.81 (1H, d, *J* = 2.7 Hz, H5), 7.83 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 28.7 (C(CH₃)₃), 80.7 (C(CH₃)₃), 116.2 (C3), 116.9 (C6), 125.9 (C4a), 129.4 (C5), 129.5 (C8), 132.4 (C7), 137.1 (C4), 145.3 (C8a), 162.3 (C2). *m/z* (EI): 282 ([⁸¹Br], 25%), 280 ([⁷⁹Br], 25), 225 ([⁸¹Br], 100), 223 ([⁷⁹Br], 100), 197 ([⁸¹Br], 40), 195 ([⁷⁹Br], 40), 116 (75), 97 (20), 89 (45), 57 (30), 44 (35).



(vii) **Base and solvent screen with microwave irradiation:** Using General Procedure 4, **31** (102 mg, 0.42 mmol) and morpholine **c** (43 μ L, 0.49 mmol) were combined in the described solvent (10 mL). Pd(OAc)₂ (0.5 mg, 2.1 μ mol), CataCXium[®] A ligand **35** (1.5 mg, 4.1 μ mol)

and base (0.49 mmol) were added then the vessel was evacuated, backfilled with nitrogen and sealed. The mixture was heated at 130 °C at 400 W in a MARS microwave system for the prescribed time. The crude material was filtered through celite and the solvent removed under reduced pressure. In the cases where water was used as a solvent the organic material was extracted with DCM, washed with water, dried over Na₂SO₄ and the solvent removed under reduced pressure. Yields were determined by NMR analysis of the crude material.

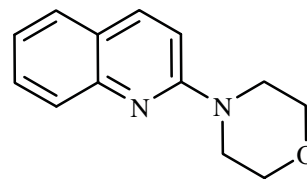
a) With water and Cs₂CO₃. Led to the recovery of starting material only.

b) With DME and NaO^tBu. Led to the recovery of starting material only.

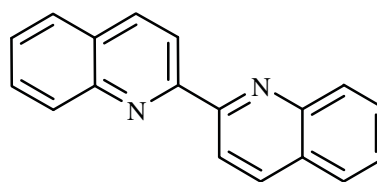
c) With DMF and NaO^tBu. Led to the formation of a complex mixture of products that was not purified.

d) With DMF:H₂O and NaO^tBu. Chromatographic separation eluting with DCM:ethyl acetate (17:3) afforded 2-morpholinoquinoline **66** as a yellow glass (5 mg, 9%) and a ~ 1:1 mixture of the homocoupled product 2-(quinolin-2-yl)quinoline **67** and an unknown product (combined yield 60 mg).

2-Morpholinoquinoline (66): IR (nujol mull): ν/cm^{-1} : 1621, 1600 and 1563. ¹H NMR (600 MHz, CDCl₃); δ : 3.72 (4H, br t, $J = 4.8$ Hz, 2 x CH₂, H(2'/6')), 3.86 (4H, br t, $J = 4.8$ Hz, 2 x CH₂, H(3'/5')), 6.96 (1H, d, $J = 9.0$ Hz, H3), 7.27 (1H, t, $J = 7.4$ Hz, H6), 7.49 (1H, t, $J = 7.2$ Hz, H7), 7.62 (1H, dd, $J = 1.8, 7.4$ Hz, H5), 7.72 (1H, d, $J = 7.2$ Hz, H8), 7.92 (1H, d, $J = 9.0$ Hz, H4). The data was consistent with that reported in the literature.⁹¹



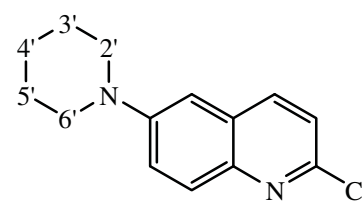
2-(Quinolin-2-yl)quinoline (67): IR (nujol mull): ν/cm^{-1} : 1650, 1610, 1600 and 1578. ¹H NMR (600 MHz, CDCl₃); δ : 7.58 (1H, dt, $J = 1.2, 8.4$ Hz, H6), 7.74 (1H, dt, $J = 1.2, 8.4$ Hz, H7), 7.88 (1H, dd, $J = 1.2, 8.4$ Hz, H5), 8.02 (1H, d, $J = 8.4$ Hz, H8), 8.32 (1H, d, $J = 8.4$ Hz, H4), 8.85 (1H, d, $J = 8.4$ Hz, H3). ¹³C NMR (150 MHz, CDCl₃); δ : 119.4 (C3), 126.9 (C6), 127.6 (C5), 128.5 (C4a), 128.6 (C8), 129.5 (C7), 136.7 (C4), 147.9 (C8a), 156.2 (C2). m/z (EI): 256 (M⁺, 100%), 255 (M⁺-H, 80), 128 (40), 101 (20).



The data was consistent with that reported in the literature.^{128,129}

2-Chloro-6-(piperidin-1-yl)quinoline (32d)

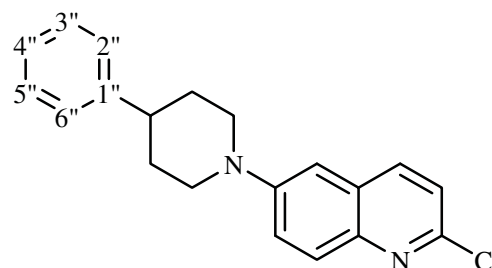
Using General Procedure 1, **31** (600 mg, 2.47 mmol) and piperidine **d** (300 μ L, 3.03 mmol) were added to a mixture of Pd(OAc)₂ (2.8 mg, 12.5 μ mol), CataCXium[®] A ligand **35** (9.1 mg, 25.4 μ mol) and KO^tBu (341 mg, 3.04 mmol) in toluene (2



mL) and the reaction was heated for 24 h. Extraction with ethyl acetate and chromatographic separation eluting with DCM:hexane (3:2) afforded the title compound as an orange solid, mp 127-130 °C (330 mg, 54%). HRMS found: 246.0915; C₁₄H₁₅³⁵ClN₂ requires 246.0924. Analysis found: C, 68.13; H, 6.07; N, 11.52. C₁₄H₁₅ClN₂ requires C, 68.15; H, 6.13; N, 11.35%. IR (nujol mull): ν /cm⁻¹: 1685, 1620, 1583 and 1500. ¹H NMR (300 MHz, CDCl₃); δ : 1.60 (2H, m, CH₂, H4'), 1.74 (4H, br qn, J = 5.4 Hz, 2 x CH₂, H(3'/5')), 3.27 (4H, t, J = 5.4 Hz, 2 x CH₂, H(2'/6')), 6.99 (1H, br s, H5), 7.24 (1H, d, J = 8.4 Hz, H3), 7.48 (1H, dd, J = 2.7, 9.3 Hz, H7), 7.84 (1H, d, J = 9.3 Hz, H8), 7.88 (1H, d, J = 8.4 Hz, H4). ¹³C NMR (75 MHz, CDCl₃); δ : 24.4 (C4'), 25.8 (C3'/5'), 50.5 (C2'/6'), 109.0 (C5), 122.4 (C3), 123.7 (C7), 128.3 (C4a), 129.1 (C8), 137.5 (C4), 143.1 (C8a), 147.3 (C2), 150.4 (C6). m/z (EI): 248 (M⁺ [³⁷Cl], 25%), 247 (M-H⁺ [³⁷Cl], 100), 246 (M⁺ [³⁵Cl], 80), 245 (M-H⁺ [³⁵Cl], 100), 190 (25).

2-Chloro-6-(4-phenylpiperidin-1-yl)quinoline (32e)

(i) Using General Procedure 1, **31** (600 mg, 2.47 mmol) and 4-phenylpiperidine **e** (480 mg, 2.98 mmol) were added to a mixture of Pd(OAc)₂ (2.8 mg, 12.4 μ mol), CataCXium[®] A ligand **35** (8.9 mg, 24.7 μ mol) and KO^tBu (332 mg, 2.96 mmol) in toluene (5 mL) and the reaction was heated for 20 h.



Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM:hexane (4:1) afforded the title compound as a cream powder, mp 165-167 °C (346 mg, 44%). Analysis found: C, 74.57; H, 5.94; N, 8.62. C₂₀H₁₉ClN₂ requires C, 74.41; H, 5.93; N, 8.68%. IR (nujol mull): ν /cm⁻¹: 1618, 1574 and 1500. ¹H NMR (600 MHz, CDCl₃); δ : 1.94 (2H, dq, $J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{ax}}} = 3.6$ Hz, $J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}} = J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = 12.0$ Hz, 2 x CH, H(3'/5')_{ax}), 2.03 (2H, br d[‡], $J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = 12.0$ Hz, 2 x CH, H(3'/5')_{eq}), 2.73 (1H, m, CH, H4'), 2.95 (2H, dt, $J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{eq}}} = 2.4$ Hz, $J_{(2'/6')_{\text{ax}}, (2'/6')_{\text{eq}}} = J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}} = 12.0$ Hz, 2 x CH, H(2'/6')_{ax}), 3.96 (2H, br d[‡], $J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = J_{(2'/6')_{\text{eq}}, (2'/6')_{\text{ax}}} = 12.0$ Hz, 2 x CH, H(2'/6')_{eq}), 7.06 (1H, d, J = 2.4 Hz, H5), 7.23 (1H, tt, J = 1.8, 7.2 Hz, H4''), 7.26-7.29

(3H, m, H3, H(3''/5'')), 7.34 (2H, tt, $J = 1.8, 7.2$ Hz, H(2''/6'')), 7.55 (1H, d, $J = 3.0, 9.6$ Hz, H7), 7.89 (1H, d, $J = 9.6$ Hz, H8), 7.93 (1H, d, $J = 8.4$ Hz, H4). ^{13}C NMR (150 MHz, CDCl_3); δ : 33.1 (C3'/5'), 42.4 (C4'), 50.2 (C2'/6'), 109.0 (C5), 122.4 (C3), 123.7 (C7), 126.4 (C4''), 126.8 (C3''/5''), 128.2 (C4a), 128.6 (C2''/6''), 129.1 (C8), 137.4 (C4), 143.0 (C8a), 145.7 (C1''), 147.4 (C2), 150.0 (C6). m/z (EI): 324 (M^+ [^{37}Cl], 35%), 322 (M^+ [^{35}Cl], 100), 266 (20), 217 (50), 189 (40).

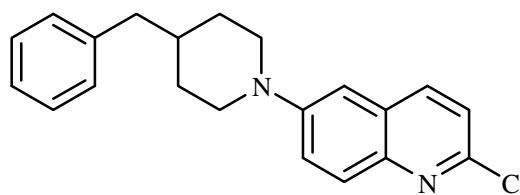
6-Bromo-2-(4-phenylpiperidin-1-yl)quinoline **37e** was also observed in the crude material but was not isolated.

(ii) Using General Procedure 2, **31** (50 mg, 0.21 mmol) and 4-phenylpiperidine **e** (40 mg, 0.25 mmol) were added to a mixture of $\text{Pd}(\text{OAc})_2$ (0.2 mg, 1.0 μmol), CataCXium[®] A ligand **35** (0.8 mg, 2.2 μmol) and NaO^tBu (24 mg, 0.25 mmol) in trifluoromethylbenzene (3 mL) and the reaction was heated for 20 h. Work up as above afforded the title compound (55 mg, 80%). Yield determined by ^1H NMR analysis. Data as above.

(iii) Using General Procedure 4, **31** (45 mg, 0.19 mmol) and 4-phenylpiperidine **e** (37 mg, 0.23 mmol) were combined in trifluoromethylbenzene (2 mL). $\text{Pd}(\text{OAc})_2$ (0.2 mg, 1.0 μmol), CataCXium[®] A ligand **35** (0.8 mg, 2.1 μmol) and NaO^tBu (22 mg, 0.23 mmol) were added then the vessel was evacuated, backfilled with nitrogen and sealed. The mixture was heated at 150 °C at 300 W in a Discover system for 17 min (including 1 min ramp time). Chromatographic separation eluting with DCM:ethanol (49:1) afforded the title compound as a cream solid (30 mg, 50%). Data as above.

2-Chloro-6-(4-benzylpiperidin-1-yl)quinoline (**32f**)

(i) Using General Procedure 1, **31** (600 mg, 2.47 mmol) and 4-benzylpiperidine **f** (530 μL , 2.98 mmol) were added to a mixture of $\text{Pd}(\text{OAc})_2$ (2.8 mg, 12.4 μmol), CataCXium[®] A ligand **35** (8.9 mg,



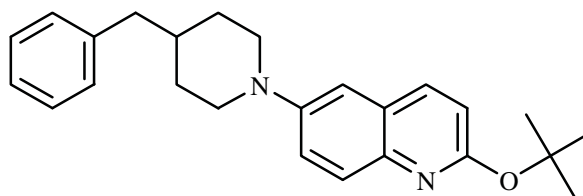
24.7 μmol) and KO^tBu (335 mg, 2.99 mmol) in toluene (5 mL) and the reaction was heated for 16 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM:hexane (4:1) afforded the title compound **32f** as a 6:1 mixture with 2-*t*-butoxy-6-(4-benzylpiperidin-1-yl)quinoline **39f** (yellow solid, combined yield; 390 mg, **32f** 40%, 2-*t*-butoxy-6-(4-benzylpiperidin-1-yl)quinoline **39f** 7%). An analytical sample of **32f** was obtained by recrystallisation from hexane, mp 114-117 °C.

2-Chloro-6-(4-benzylpiperidin-1-yl)quinoline (**32f**): HRMS found: 336.1388; $\text{C}_{21}\text{H}_{21}^{35}\text{ClN}_2$ requires 336.1393. Analysis found: C, 75.05; H, 6.59; N, 8.08; $\text{C}_{21}\text{H}_{21}\text{ClN}_2$ requires C, 74.88;

H, 6.28; N, 8.32%. IR (nujol mull): ν/cm^{-1} : 1653, 1558 and 1505. ^1H NMR (600 MHz, CDCl_3); δ : 1.44 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 4.2$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.74 (1H, m, CH, H4'), 1.80 (2H, br d ‡ , $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.60 (2H, d, $J = 7.2$ Hz, CH_2), 2.77 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 4.2$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.80 (2H, br d ‡ , $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (2'/6')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 6.98 (1H, d, $J = 3.0$ Hz, H5), 7.18 (2H, d, $J = 7.8$ Hz, H(2''/6'')), 7.22 (1H, t, $J = 7.8$ Hz, H4''), 7.26 (1H, d, $J = 8.4$ Hz, H3), 7.31 (2H, t, $J = 7.8$ Hz, H(3''/5'')), 7.48 (1H, dd, $J = 3.0, 9.6$ Hz, H7), 7.85 (1H, d, $J = 9.6$ Hz, H8), 7.90 (1H, d, $J = 8.4$ Hz, H4). ^{13}C NMR (150 MHz, CDCl_3); δ : 28.7 (C4'), 31.8 (C3'/5'), 43.1 (CH_2) 49.7 (C2'/6'), 108.8 (C5), 122.3 (C3), 123.6 (C7), 126.0 (C4''), 128.2 (C4a), 128.3 (C3''/5''), 129.0 (C8), 129.1 (C2''/6''), 137.4 (C4), 140.3 (C1''), 142.9 (C8a), 147.2 (C2), 150.4 (C6). m/z (EI): 338 (M^+ [^{37}Cl], 30%), 336 (M^+ [^{35}Cl], 100), 302 (20), 162 (16).

2-*t*-Butoxy-6-(4-benzylpiperidin-1-yl)quinoline (**39f**):

^1H NMR (600 MHz, CDCl_3); δ : 1.47 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 4.2$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.66 (9H, s, ^tBu), 1.72 (1H, m, CH, H4'), 1.80 (2H, br d ‡ , $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.60 (2H, d, $J = 7.2$ Hz, CH_2), 2.68 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 4.2$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.69 (2H, br d ‡ , $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (2'/6')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 6.72 (1H, d, $J = 8.4$ Hz, H3), 6.99 (1H, d, $J = 3.0$ Hz, H5), 7.18 (2H, d, $J = 7.8$ Hz, H(2''/6'')), 7.22 (1H, t, $J = 7.8$ Hz, H4''), 7.31 (2H, t, $J = 7.8$ Hz, H(3''/5'')), 7.36 (1H, dd, $J = 3.0, 9.6$ Hz, H7), 7.67 (1H, d, $J = 9.6$ Hz, H8), 7.77 (1H, d, $J = 8.4$ Hz, H4). ^{13}C NMR (150 MHz, CDCl_3); δ : 28.7 (C4'), 32.1 (C3'/5'), 43.1 (CH_2), 50.9 (C2'/6'), 110.9 (C5), 115.0 (C3), 123.6 (C7), 125.0 (C4a), 125.9 (C4''), 128.0 (C8), 128.1 (C3''/5''), 129.1 (C2''/6''), 137.1 (C4), 140.5 (C1''), 141.5 (C8a), 147.5 (C6), 161.2 (C2). m/z (EI): 374 (M^+ , 7%), 318 (100), 144 (30).



(ii) Using General Procedure 2, **31** (50 mg, 0.21 mmol) and 4-benzylpiperidine **f** (45 μL , 0.25 mmol) were added to a mixture of $\text{Pd}(\text{OAc})_2$ (0.2 mg, 1.0 μmol), CataCXium[®] A ligand **35** (0.8 mg, 2.2 μmol) and NaO^tBu (24 mg, 0.25 mmol) in trifluoromethylbenzene (1 mL) and the reaction was heated for 20 h. Work up as above afforded the title compound (70 mg, 88%). Yield determined by ^1H NMR analysis. Data as above.

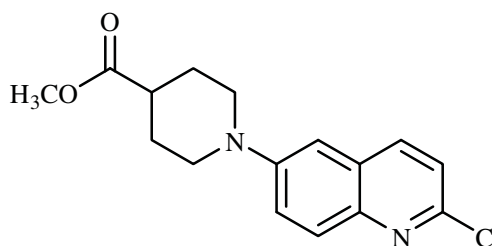
(iii) Using General Procedure 3, **31** (50 mg, 0.21 mmol) and 4-benzylpiperidine **f** (45 μL , 0.25

mmol) were added to a mixture of Pd(OAc)₂ (0.2 mg, 1.0 μmol), CataCXium[®] A ligand **35** (0.8 mg, 2.2 μmol), CuBr (3.1 mg, 22 μmol) and KO^tBu (28 mg, 0.25 mmol) in toluene (1 mL) and the reaction mixture was heated for 19 h. The mixture was filtered through celite and the solvent removed under reduced pressure to afford the title compound (41 mg, 58%). Yield determined by ¹H NMR analysis. Data as above.

(iv) Using General Procedure 4, **31** (45 mg, 0.19 mmol) and 4-benzylpiperidine **f** (41 μL, 0.23 mmol) were combined in trifluoromethylbenzene (2 mL). Pd(OAc)₂ (0.2 mg, 1.0 μmol), CataCXium[®] A ligand (0.8 mg, 2.1 μmol) and NaO^tBu (22 mg, 0.23 mmol) were added then the vessel was evacuated, backfilled with nitrogen and sealed. The mixture was heated at 150 °C at 300 W in a Discover system for 20 min (including 1 min ramp time). Chromatographic separation eluting with DCM afforded the title compound as a yellow solid (50 mg, 78%). Data as above.

Methyl 1-(2-chloroquinolin-6-yl)piperidine-4-carboxylate (**32g**)

Using General Procedure 1, **31** (509 mg, 2.10 mmol) and methyl isonipecotate (340 μL, 2.52 mmol) were added to a mixture of Pd(OAc)₂ (2.3 mg, 10.5 μmol), CataCXium[®] A ligand **35** (7.5 mg, 21.0 μmol) and KO^tBu (283 mg, 2.52 mmol) in toluene (2 mL) and



the reaction was heated for 22 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation on C18 silica eluting with water:methanol (1:1) afforded 6-bromo-2-methoxyquinoline **41**, mp 96-98 °C (lit.,³⁷ 98 °C), (200 mg, 40%). The title compound **32g** was isolated as an impure mixture with methyl 1-(2-methoxyquinolin-6-yl)piperidine-4-carboxylate **42** (combined yield 20 mg; **32g** 1%, **42** 2%).

Methyl 1-(2-chloroquinolin-6-yl)piperidine-4-carboxylate (32g): HRMS found: 304.0974; C₁₆H₁₇³⁵ClN₂O₂ requires 304.0978. IR (nujol mull): ν/cm⁻¹: 1694, 1602 and 1503. ¹H NMR (600 MHz, CDCl₃); δ: 1.94 (2H, m, 2 x CH, H(3'/5')_{ax}), 2.07 (2H, m, 2 x CH, H(3'/5')_{eq}), 2.53 (1H, m, CH, H4'), 2.93 (2H, dt, J_{(2'/6')ax, (3'/5')eq} = 3.0 Hz, J_{(2'/6')ax, (2'/6')eq} = J_{(2'/6')ax, (3'/5')ax} = 12.6 Hz, 2 x CH, H(2'/6')_{ax}), 3.77 (2H, m, 2 x CH, H(2'/6')_{eq}), 4.03 (3H, s, OCH₃), 7.01 (1H, d, J = 3.0 Hz, H5), 7.27 (1H, d, J = 8.7 Hz, H3), 7.49 (1H, dd, J = 3.0, 9.3 Hz, H7), 7.87 (1H, d, J = 9.3 Hz, H8), 7.91 (1H, d, J = 8.7 Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ: 27.9 (C3'/5'), 40.8 (C4'), 48.9 (C2'/6'), 51.8 (CH₃), 109.2 (C5), 122.4 (C3), 123.7 (C7), 128.1 (C4a), 129.2 (C8), 137.4 (C4), 143.1 (C8a), 147.5 (C2), 149.7 (C6), 175.0 (C=O). m/z (EI):

306 (M^+ [^{37}Cl], 33%), 304 (M^+ [^{35}Cl], 100), 269 (25).

Methyl 1-(2-methoxyquinolin-6-yl)piperidine-4-carboxylate (42):

HRMS found: 300.1471; $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_3$ requires

300.1474. ^1H NMR (600 MHz, CDCl_3); δ : 1.94 (2H,

m, 2 x CH, $\text{H}(3'/5')_{\text{ax}}$), 2.07 (2H, m, 2 x CH,

$\text{H}(3'/5')_{\text{eq}}$), 2.48 (1H, m, CH, $\text{H}4'$), 2.84 (2H, dt,

$J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{eq}}} = 3.0 \text{ Hz}$ $J_{(2'/6')_{\text{ax}}, (2'/6')_{\text{eq}}} = J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}}$

= 12.6 Hz, 2 x CH, $\text{H}(2'/6')_{\text{ax}}$), 3.70 (2H, m, 2 x CH, $\text{H}(2'/6')_{\text{eq}}$), 3.72 (3H, s, OCH_3), 4.03

(3H, s, OCH_3), 6.83 (1H, d, $J = 8.4 \text{ Hz}$, H3), 7.04 (1H, d, $J = 2.4 \text{ Hz}$, H5), 7.40 (1H, dd, $J =$

2.4, 9.6 Hz, H7), 7.73 (1H, d, $J = 9.6 \text{ Hz}$, H8), 7.84 (1H, d, $J = 8.4 \text{ Hz}$, H4). ^{13}C NMR (150

MHz, CDCl_3); δ : 28.2 ($\text{C}3'/5'$), 40.9 ($\text{C}4'$), 49.9 ($\text{C}2'/6'$), 50.0 (OCH_3), 53.2 (OCH_3), 111.2

(C5), 113.0 (C3), 123.7 (C7), 125.7 (C4a), 128.1 (C8), 137.8 (C4), 143.1 (C8a), 148.1 (C6),

161.2 (C2), 175.0 (C=O). m/z (EI): 300 (M^+ , 100%), 285 (20), 269 (9).

6-Bromo-2-methoxyquinoline (41): IR (nujol mull): ν/cm^{-1} : 1614,

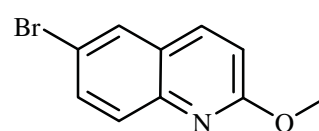
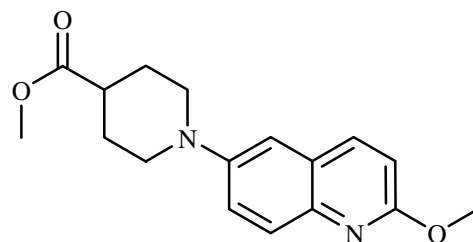
1597 and 1567. ^1H NMR (600 MHz, CDCl_3); δ : 4.06 (3H, s,

OCH_3), 6.91 (1H, d, $J = 8.7 \text{ Hz}$, H3), 7.67 (1H, dd, $J = 2.1, 8.7 \text{ Hz}$,

H7), 7.72 (1H, d, $J = 8.7 \text{ Hz}$, H8), 7.85 (1H, d, $J = 2.1 \text{ Hz}$, H5), 7.87 (1H, d, $J = 8.7 \text{ Hz}$, H4).

^{13}C NMR (75 MHz, CDCl_3); δ : 53.5 (OCH_3), 114.1 (C3), 117.1 (C6), 126.3 (C4a), 129.0 (C8),

129.5 (C5), 132.7 (C7), 137.6 (C4), 145.3 (C8a), 162.6 (C2).



2-Chloro-6-(4-methylpiperazin-1-yl)quinoline (32h)

(i) Using General Procedure 1, **31** (601 mg, 2.47 mmol) and

1-methylpiperazine **h** (330 μL , 2.96 mmol) were added to a

mixture of $\text{Pd}(\text{OAc})_2$ (2.8 mg, 12.5 μmol), CataCXium[®] A

ligand **35** (8.8 mg, 24.7 μmol) and KO^tBu (334 mg, 2.96

mmol) in toluene (2 mL) and the reaction was heated for 20 h. Extraction with

chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM

afforded the title compound **32h** as a 6:1 mixture with 6-bromo-2-chloroquinoline **31**

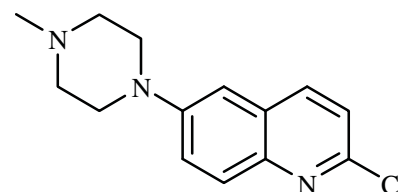
(combined yield 241 mg; **32h** 32%, **31**, 5%).

2-Chloro-6-(4-methylpiperazin-1-yl)quinoline (32h): HRMS found: 261.1042; $\text{C}_{14}\text{H}_{16}^{35}\text{ClN}_3$

requires 261.1033. IR (nujol mull): ν/cm^{-1} : 3150, 1654, 1616, 1600 and 1578. ^1H NMR (600

MHz, CDCl_3); δ : 2.40 (3H, s, CH_3), 2.65 (4H, br t, $J = 4.8 \text{ Hz}$, 2 x CH_2 , $\text{H}(3'/5')$), 3.36 (4H,

br t, $J = 4.8 \text{ Hz}$, 2 x CH_2 , $\text{H}(2'/6')$), 7.01 (1H, d, $J = 3.0 \text{ Hz}$, H5), 7.29 (1H, d, $J = 9.0 \text{ Hz}$, H3),



7.49 (1H, dd, $J = 3.0, 9.0$ Hz, H7), 7.88 (1H, d, $J = 9.0$ Hz, H8), 7.92 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, CDCl_3); δ : 46.0 (CH_3), 48.8 ($\text{C}2'/6'$), 54.8 ($\text{C}3'/5'$), 108.9 ($\text{C}5$), 123.1 ($\text{C}3$), 123.3 ($\text{C}7$), 128.0 ($\text{C}4\text{a}$), 129.2 ($\text{C}8$), 137.8 ($\text{C}4$), 143.2 ($\text{C}8\text{a}$), 147.6 ($\text{C}2$), 149.5 ($\text{C}6$). m/z (EI): 263 (M^+ [^{37}Cl], 7%), 261 (M^+ [^{35}Cl], 20), 245 (30), 243 (100), 241 (70), 208 (50).

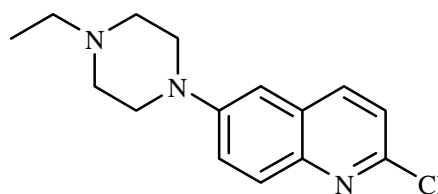
(ii) Using General Procedure 2, **31** (100 mg, 0.42 mmol) and 4-methylpiperazine **h** (56 μL , 0.50 mmol) were added to a mixture of $\text{Pd}(\text{OAc})_2$ (0.4 mg, 2.0 μmol), CataCXium[®] A ligand **35** (1.6 mg, 4.4 μmol) and NaO^tBu (48 mg, 0.50 mmol) in trifluoromethylbenzene (1 mL) and the reaction was heated for 22 h. Work up as above afforded the title compound (87 mg, 80%). Yield determined by ^1H NMR analysis.

(iii) Using General Procedure 3, **31** (50 mg, 0.21 mmol) and 4-methylpiperazine **h** (22 μL , 0.25 mmol) were added to a mixture of $\text{Pd}(\text{OAc})_2$ (0.2 mg, 1.0 μmol), CataCXium[®] A ligand **35** (0.8 mg, 2.2 μmol), CuBr (2.9 mg, 20 μmol) and KO^tBu (28 mg, 0.25 mmol) in toluene (1 mL) and the reaction mixture was heated for 19 h. The mixture was filtered through celite and the solvent removed under reduced pressure to afford the title compound (41 mg, 78%). Yield determined by ^1H NMR analysis. Data as above.

(iv) Using General Procedure 4, **31** (45 mg, 0.19 mmol) and 4-benzylpiperidine **h** (26 μL , 0.23 mmol) were combined in trifluoromethylbenzene (2 mL). $\text{Pd}(\text{OAc})_2$ (0.2 mg, 1.0 μmol), CataCXium[®] A ligand **35** (0.8 mg, 2.1 μmol) and NaO^tBu (22 mg, 0.23 mmol) were added then the vessel was evacuated, backfilled with nitrogen and sealed. The mixture was heated at 150 $^\circ\text{C}$ at 300 W in a Discover system for 20 min (including 1 min ramp time). Chromatographic separation eluting with $\text{DCM}:\text{ethanol}$ (49:1) afforded the title compound as a yellow solid (26 mg, 50%). Data as above.

2-Chloro-6-(4-ethylpiperazin-1-yl)quinoline (**32i**)

Using General Procedure 1, **31** (502 mg, 2.06 mmol) and 1-ethylpiperazine **i** (314 μL , 2.47 mmol) were added to a mixture of $\text{Pd}(\text{OAc})_2$ (2.3 mg, 10.3 μmol), CataCXium[®] A ligand **35** (7.4 mg, 20.6 μmol) and KO^tBu (279 mg,

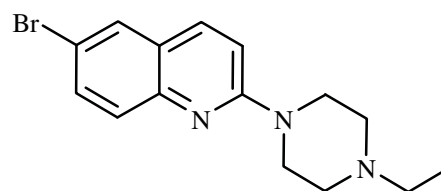


2.47 mmol) in toluene (2 mL) and the reaction was heated for 20 h. Extraction with ethyl acetate and chromatographic separation eluting with $\text{DCM}:\text{hexane}$ (4:1) afforded the title compound **32i** as 2.5:1 mixture with 6-bromo-2-(4-ethylpiperazin-1-yl)quinoline **37i** (combined yield 480 mg; **32i** 58%, **37i** 30%). Pure 6-bromo-2-(4-ethylpiperazin-1-yl)quinoline **37i** was also isolated, mp 140-144 $^\circ\text{C}$ (40 mg, 7%) along with 2-*t*-butoxy-6-(4-ethylpiperazin-1-yl)quinoline **39i** mp 107-109 $^\circ\text{C}$ (63 mg, 10%).

2-Chloro-6-(4-ethylpiperazin-1-yl)quinoline (32i): HRMS found: 275.1186; $C_{15}H_{18}^{35}ClN_3$ requires 275.1189. IR (nujol mull): ν/cm^{-1} : 1650, 1618, 1600, 1582 and 1500. 1H NMR (600 MHz, $CDCl_3$); δ : 1.16 (3H, t, $J = 7.2$ Hz, CH_3), 2.52 (2H, m, CH_2), 2.67 (4H, br t, $J = 4.8$ Hz, 2 x CH_2 , H(3'/5')), 3.36 (4H, br t, $J = 4.8$ Hz, 2 x CH_2 , H(2'/6')), 7.00 (1H, d, $J = 2.7$ Hz, H5), 7.27 (1H, d, $J = 9.0$ Hz, H3), 7.49 (1H, dd, $J = 2.7, 9.0$ Hz, H7), 7.87 (1H, d, $J = 9.0$ Hz, H8), 7.92 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 11.9 (CH_3), 48.8 ($C2'/6'$), 52.4 (CH_2), 52.6 ($C3'/5'$), 108.7 (C5), 122.4 (C3), 123.0 (C7), 128.2 (C4a), 129.2 (C8), 137.1 (C4), 143.1 (C8a), 147.5 (C2), 149.6 (C6). m/z (EI): 277 (M^+ [^{37}Cl], 30%), 275 (M^+ [^{35}Cl], 90), 262 (20), 260 (60), 192 (15), 190 (35), 97 (40), 84 (100).

6-Bromo-2-(4-ethylpiperazin-1-yl)quinoline (37i):

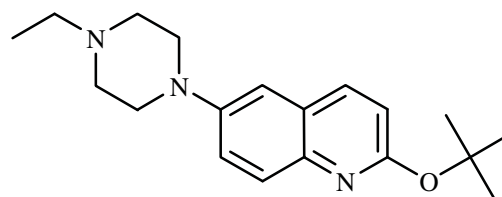
HRMS found: 319.0689; $C_{15}H_{18}^{79}BrN_3$ requires 319.0684. IR (nujol mull): ν/cm^{-1} : 1617, 1597 and 1542.



1H NMR (600 MHz, $CDCl_3$); δ : 1.16 (3H, t, $J = 7.2$ Hz, CH_3), 2.52 (2H, m, CH_2), 2.59 (4H, br t, $J = 4.8$ Hz, 2 x CH_2 , H(3'/5')), 3.80 (4H, br t, $J = 4.8$ Hz, 2 x CH_2 , H(2'/6')), 6.97 (1H, d, $J = 9.3$ Hz, H3), 7.57 (1H, d, $J = 9.0$ Hz, H8), 7.57 (1H, dd, $J = 1.8, 9.0$ Hz, H7), 7.71 (1H, d, $J = 1.8$ Hz, H5), 7.80 (1H, d, $J = 9.3$ Hz, H4). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 11.9 (CH_3), 45.0 ($C2'/6'$), 52.3 (CH_2), 54.5 ($C3'/5'$), 110.7 (C3), 115.2 (C6), 124.2 (C4a), 128.3 (C5), 129.1 (C8), 132.6 (C7), 137.1 (C4), 146.6 (C8a), 157.3 (C2). m/z (EI): 321 (M^+ [^{81}Br], 100%), 319 (M^+ [^{79}Br], 100), 306 (13), 304 (13).

2-*t*-Butoxy-6-(4-ethylpiperazin-1-yl)quinoline (39i):

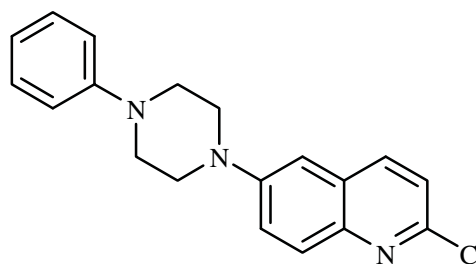
1H NMR (300 MHz, $CDCl_3$); δ : 1.16 (3H, t, $J = 7.2$ Hz, CH_3), 1.68 (9H, s, *t*Bu), 2.49 (2H, q, $J = 7.2$ Hz, CH_2), 2.67 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(3'/5')), 3.28 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(2'/6')), 6.75



(1H, d, $J = 8.8$ Hz, H3), 7.01 (1H, d, $J = 2.8$ Hz, H5), 7.37 (1H, dd, $J = 2.8, 9.0$ Hz, H7), 7.70 (1H, d, $J = 9.0$ Hz, H8), 7.80 (1H, d, $J = 8.8$ Hz, H4). m/z (EI): 313 (M^+ , 40%), 257 (100), 242 (60), 173 (20), 84 (65), 57 (45).

2-Chloro-6-(4-phenylpiperazin-1-yl)quinoline (32j)

(i) Using General Procedure 1, **31** (501 mg, 2.06 mmol) and 1-phenylpiperazine **j** (375 μ L, 2.47 mmol) were added to a mixture of Pd(OAc)₂ (2.3 mg, 10.3 μ mol), CataCXium[®] A ligand **35** (7.4 mg, 20.6 μ mol) and KO^tBu (279 mg, 2.47 mmol) in toluene (2 mL)

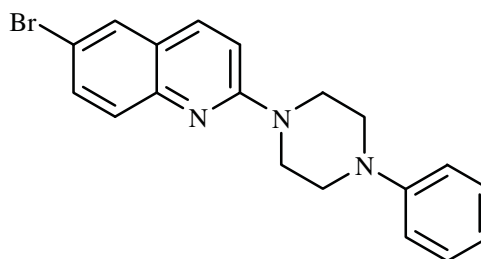


and the reaction was heated for 20 h. Extraction with ethyl acetate and chromatographic separation eluting with DCM:hexane (4:1) afforded the title compound **32j** as a yellow solid, mp 182-185 °C (290 mg, 44%). 6-Bromo-2-(4-phenylpiperazin-1-yl)quinoline **37j** was also isolated as a yellow solid, mp 155-159 C (110 mg, 15%).

2-Chloro-6-(4-phenylpiperazin-1-yl)quinoline (32j): HRMS found: 323.1185; C₁₉H₁₈³⁵ClN₃ requires 323.1189. Analysis found: C, 70.37; H, 5.77; N, 12.62. C₁₉H₁₈ClN₃ requires C, 70.47; H, 5.60; N, 12.98%. IR (nujol mull): ν/cm^{-1} : 1669, 1615, 1600 and 1574. ¹H NMR (300 MHz, CDCl₃); δ : 3.39 (4H, br t, $J = 4.8$ Hz, 2 x CH₂, H(3'/5')), 3.47 (4H, br t, $J = 4.8$ Hz, 2 x CH₂, H(2'/6')), 6.92 (1H, t, $J = 7.2$ Hz, H4''), 7.01 (2H, d, $J = 7.8$ Hz, H(2''/6'')), 7.06 (1H, d, $J = 2.7$ Hz, H5), 7.28-7.34 (3H, m, H3, H(3''/5'')), 7.54 (1H, dd, $J = 2.7, 9.0$ Hz, H7), 7.91 (1H, d, $J = 9.0$ Hz, H8), 7.85 (1H, d, $J = 8.4$ Hz, H4). ¹³C NMR (75 MHz, CDCl₃); δ : 49.2 (C2'/6'), 49.3 (C3'/5'), 109.1 (C5), 116.4 (C2''/6''), 120.3 (C4''), 122.5 (C3), 123.2 (C7), 128.0 (C4a), 129.2 (C8), 129.3 (C3''/5''), 137.5 (C4), 143.2 (C8a), 147.7 (C2), 149.5 (C1''), 151.0 (C6). m/z (EI): 325 (M⁺ [³⁷Cl], 15%), 323 (M⁺ [³⁵Cl], 50), 190 (30), 157 (50), 132 (100), 105 (50), 77 (25).

6-Bromo-2-(4-phenylpiperazin-1-yl)quinoline (37j):

HRMS found: 367.0677; C₁₉H₁₈⁷⁹BrN₃ requires 367.0684. IR (nujol mull): ν/cm^{-1} : 1608, 1594 and 1545. ¹H NMR (600 MHz, CDCl₃); δ : 3.39 (4H, br t, $J = 4.8$ Hz, 2 x CH₂, H(3'/5')), 3.47 (4H, br t, $J = 4.8$ Hz, 2 x CH₂, H(2'/6')), 6.90 (1H, t, $J = 8.1$ Hz, H4''),



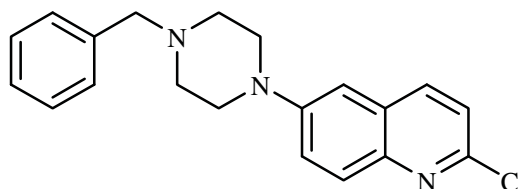
7.01 (2H, d, $J = 8.1$ Hz, H(2''/6'')), 7.06 (1H, d, $J = 9.3$ Hz, H3), 7.32 (2H, t, $J = 8.1$ Hz, H(3''/5'')), 7.62 (2H, br s, H7, H8), 7.76 (1H, br s, H5), 7.82 (1H, d, $J = 9.3$ Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 45.2 (C2'/6'), 49.4 (C3'/5'), 110.5 (C3), 115.4 (C6), 116.5 (C2''/6''), 120.3 (C4''), 124.4 (C4a), 128.5 (C5), 129.2 (C8), 129.4 (C3''/5''), 132.9 (C7), 136.7 (C4), 146.7 (C8a), 151.3 (C1''), 157.4 (C2). m/z (EI): 369 (M⁺ [⁸¹Br], 10%), 367 (M⁺ [⁷⁹Br], 10), 235 (100), 145 (20), 132 (30), 104 (25), 77 (20).

(ii) Using General Procedure 2, **31** (50 mg, 0.21 mmol) and 4-phenylpiperazine **j** (38 μ L, 0.25 mmol) were added to a mixture of Pd(OAc)₂ (0.2 mg, 1.0 μ mol), CataCXium[®] A ligand **35** (0.8 mg, 2.2 μ mol) and NaO^tBu (24 mg, 0.25 mmol) in trifluoromethylbenzene (1 mL) and the reaction was heated for 20 h. Work up as above afforded the title compound (62 mg, 91%). Yield determined by ¹H NMR analysis. Data as above.

(iii) Using General Procedure 3, **31** (50 mg, 0.21 mmol) and 4-phenylpiperazine **j** (38 μ L, 0.25 mmol) were added to a mixture of Pd(OAc)₂ (0.2 mg, 1.0 μ mol), CataCXium[®] A ligand **35** (0.8 mg, 2.2 μ mol), CuBr (3.1 mg, 22 μ mol) and KO^tBu (28 mg, 0.25 mmol) in toluene (1 mL) and the reaction mixture was heated for 19 h. The mixture was filtered through celite and the solvent removed under reduced pressure to afford the title compound (6 mg, 9%). Yield determined by ¹H NMR analysis. Data as above.

6-(4-Benzylpiperazin-1-yl)-2-chloroquinoline (**32k**)

(i) Using General Procedure 1, **31** (500 mg, 2.06 mmol) and 1-benzylpiperazine **k** (428 μ L, 2.47 mmol) were added to a mixture of Pd(OAc)₂ (2.3 mg, 10.3 μ mol), CataCXium[®] A ligand **35** (7.4



mg, 20.6 μ mol) and KO^tBu (277 mg, 2.47 mmol) in toluene (3 mL) and the reaction was heated for 20 h. Extraction with ethyl acetate and chromatographic separation eluting with DCM afforded the title compound **32k** as 2.5:1 mixture with 2-(4-benzylpiperazin-1-yl)-6-bromoquinoline **37k** (combined yield 260 mg; **32k** 26%, **37k** 11%). 2-^tButoxy-6-(4-benzylpiperazin-1-yl)quinoline **39k** was also isolated as a dark yellow solid, mp 127-131 °C (50 mg, 6%).

6-(4-Benzylpiperazin-1-yl)-2-chloroquinoline (**32k**): HRMS found: 337.1345; C₂₀H₂₀³⁵ClN₃ requires 337.1346. IR (nujol mull): ν /cm⁻¹: 1650, 1615, 1576 and 1503. ¹H NMR (600 MHz, CDCl₃); δ : 2.66 (4H, br t, J = 4.8 Hz, 2 x CH₂, H(3'/5')), 3.32 (4H, br t, J = 4.8 Hz, 2 x CH₂, H(2'/6')), 3.60 (2H, s, CH₂), 6.96 (1H, d, J = 2.4 Hz, H5), 7.25 (1H, d, J = 9.0 Hz, H3), 7.34-7.40 (5H, m, Ph), 7.42 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.85 (1H, d, J = 9.0 Hz, H8), 7.92 (1H, d, J = 9.0 Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 48.8 (C2'/6'), 52.8 (C3'/5'), 62.9 (CH₂), 108.7 (C5), 122.3 (C3), 123.0 (C7), 127.2 (C4''), 128.0 (C4a), 128.3 (C3''/5''), 129.1 (C2''/6''), 129.2 (C8), 137.4 (C4), 137.6 (C1''), 143.0 (C8a), 147.4 (C2), 149.6 (C6). m/z (EI): 339 (M⁺ [³⁷Cl], 30%), 337 (M⁺ [³⁵Cl], 90), 193 (25), 191 (70), 119 (20), 91 (100).

2-(4-Benzylpiperazin-1-yl)-6-bromoquinoline (37k):

HRMS found: 381.0842; C₂₀H₂₀⁷⁹BrN₃ requires

381.0842. ¹H NMR (600 MHz, CDCl₃); δ: 2.58

(4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(3'/5')), 3.58 (2H,

s, CH₂), 3.75 (4H, br t, *J* = 4.8 Hz, 2 x CH₂,

H(2'/6')), 6.93 (1H, d, *J* = 9.0 Hz, H3), 7.26-7.30 (5H, m, Ph), 7.53 (1H, d, *J* = 9.0 Hz, H8),

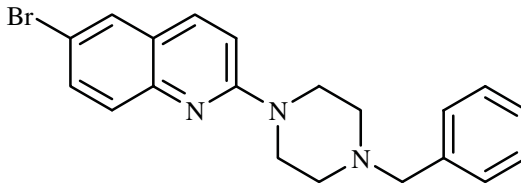
7.55 (1H, dd, *J* = 2.4, 9.0 Hz, H7), 7.69 (1H, d, *J* = 2.4 Hz, H5), 7.73 (1H, d, *J* = 9.0 Hz, H4).

¹³C NMR (150 MHz, CDCl₃); δ: 44.8 (C2'/6'), 52.8 (C3'/5'), 62.9 (CH₂), 110.2 (C3), 115.0

(C6), 124.1 (C4a), 127.2 (C4''), 128.3 (C3''/5''), 129.1 (C5), 129.2 (C2''/6''), 129.2 (C8),

132.5 (C7), 136.3 (C4), 137.6 (C1''), 146.6 (C8a), 157.3 (C2). *m/z* (EI): 383 (M⁺ [⁸¹Br],

10%), 381 (M⁺ [⁷⁹Br], 10), 237 (30), 235 (30), 159 (50), 146 (90), 119 (20), 91 (100).



2-^tButoxy-6-(4-benzylpiperazin-1-yl)quinoline (39k):

IR (nujol mull): ν/cm^{-1} : 1654, 1597, 1560

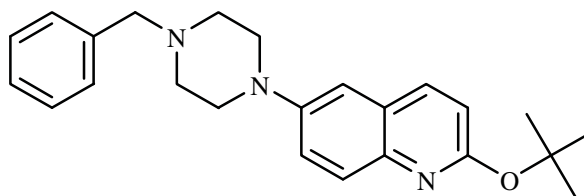
and 1505. ¹H NMR (300 MHz, CDCl₃); δ:

1.67 (9H, s, ^tBu), 2.77 (4H, br s, 2 x CH₂,

H(3'/5')), 3.33 (4H, br s, 2 x CH₂, H(2'/6')),

3.70 (2H, s, CH₂), 6.75 (1H, d, *J* = 9.0 Hz, H3), 7.01 (1H, d, *J* = 2.4 Hz, H5), 7.31-7.42 (6H,

m, H7, Ph), 7.70 (1H, d, *J* = 9.0 Hz, H8), 7.80 (1H, d, *J* = 9.0 Hz, H4).



(ii) Using General Procedure 2, **31** (100 mg, 0.42 mmol) and 4-benzylpiperazine **k** (87 μL ,

0.50 mmol) were added to a mixture of Pd(OAc)₂ (0.4 mg, 2.0 μmol), CataCXium[®] A ligand

35 (1.6 mg, 4.4 μmol) and NaO^tBu (48 mg, 0.50 mmol) in trifluoromethylbenzene (3 mL) and

the reaction was heated for 22 h. Work up as above afforded the title compound (127 mg,

90%). Yield determined by ¹H NMR analysis. Data as above.

(iii) Using General Procedure 3, **31** (50 mg, 0.21 mmol) and 4-benzylpiperazine **k** (43 μL ,

0.25 mmol) were added to a mixture of Pd(OAc)₂ (0.2 mg, 1.0 μmol), CataCXium[®] A ligand

35 (0.8 mg, 2.2 μmol), CuBr (3.1 mg, 22 μmol) and KO^tBu (28 mg, 0.25 mmol) in toluene (1

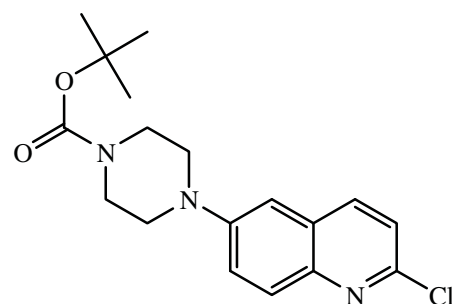
mL) and the reaction mixture was heated for 19 h. The mixture was filtered through celite

and the solvent removed under reduced pressure to afford the title compound (32 mg, 45%).

Yield determined by ¹H NMR analysis. Data as above.

***t*-Butyl 4-(2-chloroquinolin-6-yl)piperazine-1-carboxylate (32I)**

Using General Procedure 1, **31** (510 mg, 2.10 mmol) and *t*-butyl piperazine-1-carboxylate **1** (472 mg, 2.52 mmol) were added to a mixture of Pd(OAc)₂ (2.3 mg, 10.5 μmol), CataCXium® A ligand **35** (7.5 mg, 21.0 μmol) and KO^{*t*}Bu (284 mg, 2.53 mmol) in toluene (3 mL) and the reaction was heated for 20 h. Extraction



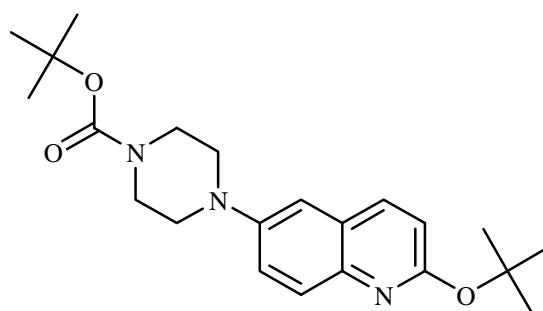
with ethyl acetate and chromatographic separation eluting with DCM afforded the title compound as a yellow glass (580 mg, 80%). The compound, *t*-butyl 4-(2-*t*-butoxyquinolin-6-yl)piperazine-1-carboxylate **39I**, was also isolated as a brown solid, mp 119-122 °C (52 mg, 7%).

t-Butyl 4-(2-chloroquinolin-6-yl)piperazine-1-carboxylate (**32I**): HRMS found: 347.1397; C₁₈H₂₂³⁵ClN₃O₂ requires 347.1401. IR (nujol mull): ν/cm⁻¹: 1694, 1602 and 1503. ¹H NMR (600 MHz, CDCl₃); δ: 1.50 (9H, s, *t*Bu), 3.27 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(2'/6')), 3.64 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(3'/5')), 7.03 (1H, br s[‡], H5), 7.30 (1H, d, *J* = 9.0 Hz, H3), 7.48 (1H, br d[‡], *J* = 9.0 Hz, H7), 7.90 (1H, d, *J* = 9.0 Hz, H8), 7.93 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ: 28.4 (C(CH₃)₃), 43.2 (C3'/5'), 49.2 (C2'/6'), 80.1 (C(CH₃)₃), 109.6 (C5), 122.5 (C3), 123.4 (C7), 127.9 (C4a), 129.3 (C8), 137.5 (C4), 143.3 (C8a), 147.9 (C2), 149.4 (C6), 154.6 (C=O). *m/z* (EI): 349 (M⁺ [³⁷Cl], 45%), 347 (M⁺ [³⁵Cl], 15), 293 (15), 291 (50), 247 (20), 219 (10), 217 (30), 207 (30), 205 (100), 190 (20), 57 (20).

t-Butyl 4-(2-*t*-butoxyquinolin-6-yl)piperazine-1-carboxylate (**39I**):

IR (nujol mull): ν/cm⁻¹: 1706, 1694 and 1602.

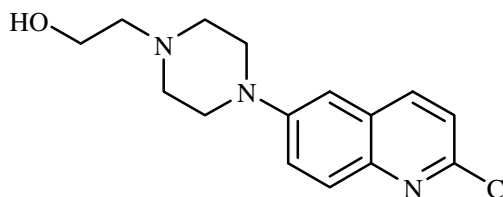
¹H NMR (600 MHz, DMSO); δ: 1.42 (9H, s, *t*Bu), 1.62 (9H, s, *t*Bu), 3.12 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(2'/6')), 3.48 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(3'/5')), 6.76 (1H, d, *J* = 9.0 Hz, H3), 7.14 (1H, d, *J* = 2.4 Hz, H5), 7.43 (1H, dd, *J* = 2.4, 9.0 Hz, H7), 7.57 (1H, d, *J* = 9.0 Hz, H8),



7.96 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (150 MHz, DMSO); δ: 28.0 (C(CH₃)₃), 28.3 (C(CH₃)₃), 43.2 (C3'/5'), 49.0 (C2'/6'), 78.9 (C(CH₃)₃), 79.1 (C(CH₃)₃), 110.5 (C5), 114.6 (C3), 122.2 (C7), 124.8 (C4a), 127.4 (C8), 137.7 (C4), 140.6 (C8a), 147.3 (C6), 153.8 (C=O), 159.9 (C2).

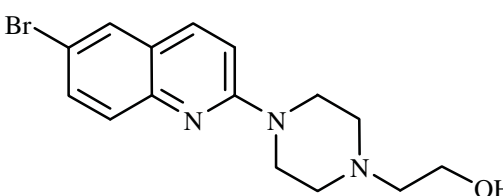
Attempted synthesis of 2-chloro-6-(4-(2-hydroxy)ethylpiperazin-1-yl)quinoline (32m)

Using General Procedure 1, **31** (507 mg, 2.10 mmol) and 1-(2-hydroxyethyl) piperazine **m** (310 μ L, 2.52 mmol) were added to a mixture of Pd(OAc)₂ (2.3 mg, 10.5 μ mol), CataCXium[®] A ligand **35** (7.5 mg, 21.0 μ mol) and KO^tBu (287 mg, 2.56 mmol) in toluene (2 mL) and the reaction was heated for 22 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation on C18 silica eluting with methanol:water (3:2) did not afford the title compound, however, 6-bromo-2-(4-(2-hydroxy)ethylpiperazin-1-yl)quinoline **37m** was obtained, mp 75-80 °C (241 mg, 37%).



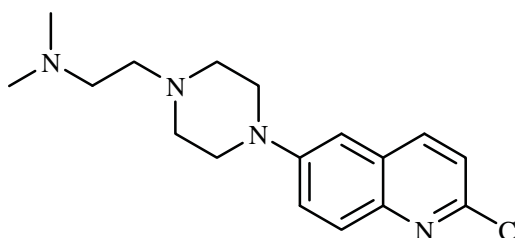
6-Bromo-2-(4-(2-hydroxy)ethylpiperazin-1-yl)quinoline (37m):

HRMS found: 336.0714; C₁₅H₁₈⁷⁹BrN₃O+H requires 336.0711. IR (nujol mull): ν /cm⁻¹: 3455, 3379, 3236, 1659, 1613, 1597 and 1567. ¹H NMR (200 MHz, CDCl₃); δ : 2.58 (4H, br t, *J* = 4.4 Hz, 2 x CH₂, H(3'/5')), 2.84 (2H, t, *J* = 6.0 Hz, CH₂N), 2.93 (4H, br t, *J* = 4.4 Hz, 2 x CH₂, H(2'/6')), 4.62 (2H, t, *J* = 6.0 Hz, CH₂OH), 6.94 (1H, d, *J* = 8.7 Hz, H3), 7.68 (2H, br s, H7, H8), 7.86 (1H, br s, H5), 7.88 (1H, d, *J* = 8.7 Hz, H4). ¹³C NMR (75 MHz, CDCl₃); δ : 44.8 (C2'/6'), 52.4 (C3'/5'), 53.1 (2 x CH₂), 57.2 (CH₂N), 63.3 (CH₂OH), 114.4 (C3), 117.4 (C6), 126.4 (C4a), 129.1 (C5), 129.6 (C8), 132.9 (C7), 137.9 (C4), 145.2 (C8a), 162.1 (C2). *m/z* (EI): 337 (M⁺ [⁸¹Br], < 1%), 335 (M⁺ [⁷⁹Br], < 1), 225 ([⁸¹Br], 20), 223 ([⁷⁹Br], 20), 210 (20), 208 (20), 140 (20), 127 (40), 112, (100), 99 (80), 84 (30), 70 (100), 56 (60), 42 (20).



2-Chloro-6-(4-(2-(dimethylamino)ethyl)piperazin-1-yl)quinoline (32n)

Using General Procedure 1, **31** (520 mg, 2.13 mmol) and 1-(2-(dimethylamino)ethyl)piperazine **n** (406 mg, 2.56 mmol) were added to a mixture of Pd(OAc)₂ (2.4 mg, 10.6 μ mol), CataCXium[®] A ligand **35** (7.6 mg, 21.3 μ mol) and KO^tBu (286 mg, 2.56 mmol) in toluene (3 mL) and the reaction was heated for 21 h. Extraction with ethyl acetate and chromatographic separation eluting with DCM:hexane (4:1) afforded the title compound as a mixture with unidentified impurities (impure yield 480 mg, ~ 30%). HRMS found: 318.1560; C₁₇H₂₃³⁵ClN₄ requires 318.1611. IR (nujol mull): ν /cm⁻¹: 1648, 1605, 1578



and 1511. ¹H NMR (600 MHz, CDCl₃); δ: 2.40 (6H, s, 2 x N-CH₃), 2.63 (4H, s, 2 x N-CH₂), 2.68 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(3'/5')), 3.33 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(2'/6')), 6.99 (1H, d, *J* = 2.4 Hz, H5), 7.27 (1H, d, *J* = 8.7 Hz, H3), 7.48 (1H, dd, *J* = 2.4, 9.3 Hz, H7), 7.86 (1H, d, *J* = 9.3 Hz, H8), 7.92 (1H, d, *J* = 8.7 Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ: 45.3 (2 x CH₃), 48.7 (C2'/6'), 53.1 (2 x CH₂), 53.5 (C3'/5'), 108.7 (C5), 122.3 (C3), 123.0 (C7), 128.0 (C4a), 129.1 (C8), 137.5 (C4), 143.0 (C8a), 146.5 (C2), 149.2 (C6). *m/z* (EI): 262 (M⁺ [³⁷Cl], 35%), 260 (M⁺ [³⁵Cl], 100), 217 (30), 70 (50), 58 (90), 41 (20).

7.1.3 Preparation of 6-Heterocyclic-2-Aminoquinolines

General Procedure 6: Kóródi amination of 2-chloroquinolines⁶⁵

The 2-chloroquinoline (1 eq) was treated with acetamide (20-40 eq) and potassium carbonate (20 eq) and heated at 200 °C for 1-3 h. After cooling, water was added and the mixture extracted with either ethyl acetate or chloroform:isopropanol (3:1 mix). The organic layers were washed with brine, dried over Na₂SO₄ and the solvent removed under reduced pressure. The product was isolated by flash chromatography with appropriate solvent mixtures.

General Procedure 7: Buchwald-Hartwig amination of 2-chloroquinolines using LHMDS⁶¹

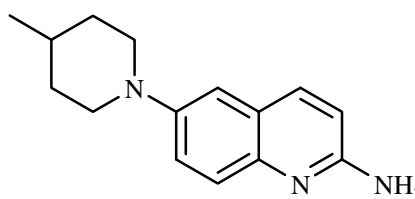
A pressure tube was loaded with Pd₂(dba)₃ (1 mol %), DavePhos **57** (1.2 mol %) and the 2-chloroquinoline derivative (1.0 eq). Dry 1,4-dioxane was added followed by LHMDS solution (1.0 M in THF, 2.2 eq). The pressure tube was evacuated, backfilled with nitrogen, sealed and the mixture stirred for 18-24 h at 100 °C. After cooling to room temperature the mixture was quenched with 1 M HCl and stirred for 10 min. The solution was then basified by the addition of NaOH. The aqueous phase was extracted with chloroform:isopropanol (3:1 mix), washed with water and dried over Na₂SO₄, then the solvent was removed under reduced pressure. Quantitative determinations of product yields were obtained by ¹H NMR analysis.

General Procedure 8: Preparation of maleate salts

The 2-aminoquinoline (1.0 eq) was dissolved in acetone and a solution of maleic acid (1.0 eq) in acetone was added dropwise at room temperature. The reaction mixture was then stirred at 0 °C for 1 h. The resulting precipitate was filtered and recrystallised from ethanol:water to afford the corresponding maleate salt.

6-(4-Methylpiperidin-1-yl)quinolin-2-amine (30a)

(i) Using General Procedure 6, an inseparable mixture of **32a** and 2-*t*-butoxy-6-(4-methylpiperidin-1-yl)quinoline **39a** (290 mg, 0.93 mmol) was treated with acetamide



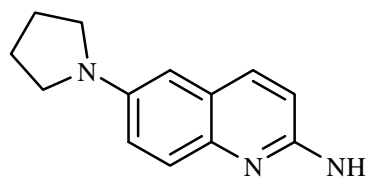
(1.31 g, 22.2 mmol) and K_2CO_3 (760 mg, 5.55 mmol) for 2 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM:ethanol (19:1) afforded the title compound as a pale orange solid, mp 166-174 °C (90 mg, 40%). HRMS found: 241.1572; $C_{15}H_{19}N_3$ requires 241.1579. IR (nujol mull): ν/cm^{-1} : 3441, 3295, 3105, 2354, 1645, 1600, 1557 and 1505. 1H NMR (600 MHz, $CDCl_3$); δ : 0.99 (3H, d, $J = 6.6$ Hz, CH_3), 1.41 (2H, dq, $J_{(2'/6')_{eq}, (3'/5')_{ax}} = 2.4$ Hz, $J_{(2'/6')_{ax}, (3'/5')_{ax}} = J_{(3'/5')_{ax}, (3'/5')_{eq}} = J_{(3'/5')_{ax}, 4'} = 12.6$ Hz, 2 x CH, H($3'/5'$)_{ax}), 1.52 (1H, m, CH, H4'), 1.78 (2H, m, Hz, 2 x CH, H($3'/5'$)_{eq}), 2.71 (2H, dt, $J_{(2'/6')_{ax}, (3'/5')_{eq}} = 2.4$ Hz, $J_{(2'/6')_{ax}, (2'/6')_{eq}} = J_{(2'/6')_{ax}, (3'/5')_{ax}} = 12.6$ Hz, 2 x CH, H($2'/6'$)_{ax}), 3.66, (2H, br d^{\ddagger} , $J_{(2'/6')_{ax}, (2'/6')_{eq}} = J_{(2'/6')_{eq}, (3'/5')_{eq}} = 12.6$ Hz, 2 x CH, H($2'/6'$)_{eq}), 4.66 (2H, br s, NH_2), 6.67 (1H, d, $J = 9.0$ Hz, H3), 6.97 (1H, d, $J = 2.4$ Hz, H5), 7.38 (1H, dd, $J = 2.4, 9.0$ Hz, H7), 7.58 (1H, d, $J = 9.0$ Hz, H8), 7.76 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 21.9 (CH_3), 30.7 ($C4'$), 34.2 ($C3'/5'$), 50.8 ($C2'/6'$), 111.1 ($C5$), 111.6 ($C3$), 123.6 ($C7$), 124.2 ($C4a$), 126.4 ($C8$), 137.3 ($C4$), 142.2 ($C8a$), 147.8 ($C6$), 155.2 ($C2$). m/z (EI): 241 (M^+ , 100%), 198 (20), 171 (40), 143 (20).

30a was converted to the corresponding maleate salt, mp 190-200 °C, using General Procedure 8 for the purpose of obtaining a microanalysis. Analysis found: C, 62.32; H, 6.58, N, 11.39. $C_{19}H_{23}N_3O_4 \cdot 0.5H_2O$ requires C, 62.28; H, 6.60, N, 11.47%.

(ii) Using General Procedure 7, $Pd_2(dba)_3$ (1.9 mg, 2.1 μ mol), DavePhos **57** (1.0 mg, 2.5 μ mol) and **32a** (55 mg, 0.21 mmol) were combined in 1,4-dioxane (1 mL). LHMDS solution (1.0 M in THF, 460 μ L) was added then the reaction was heated for 22h. Work-up afforded the title compound (49 mg, 97%). Data as above.

6-(Pyrrolidin-1-yl)quinolin-2-amine (30b)

Using General Procedure 6, **32b** (160 mg, 0.66 mmol) was treated with acetamide (3.34 g, 56.60 mmol)* and K_2CO_3 (477 mg, 3.45 mmol) for 1.5 h. Extraction with ethyl acetate and chromatographic separation eluting with DCM:ethanol (9:1)



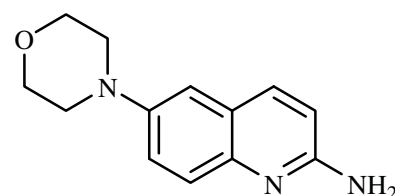
afforded the title compound as a yellow solid (79 mg, 56%). This compound decomposed at room temperature and was therefore unable to be assayed for binding affinity for the Tec SH3 domain using the HSQC NMR assay. HRMS found: 213.1260; $C_{13}H_{15}N_3$ requires 213.1266.

IR (nujol mull): ν/cm^{-1} : 3392, 1673, 1618, and 1523. ^1H NMR (300 MHz, CDCl_3); δ : 2.04 (4H, t, $J = 6.6$ Hz, 2 x CH_2 , H(3'/4')), 3.32 (4H, t, $J = 6.6$ Hz, 2 x CH_2 , H(2'/5')), 6.42 (2H, br s, NH_2), 6.56 (1H, d, $J = 2.4$ Hz, H5), 6.88 (1H, d, $J = 9.0$ Hz, H3), 7.02 (1H, dd, $J = 2.4, 9.0$ Hz, H7), 7.58 (1H, d, $J = 9.0$ Hz, H8), 7.82 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (75 MHz, CDCl_3); δ : 25.78 (C3'/4'), 48.1 (C2'/5'), 105.8 (C5), 112.5 (C3), 119.3 (C7), 122.5 (C4a), 124.1 (C8), 133.3 (C4), 139.7 (8a), 145.2 (C6), 153.3 (C2). m/z (EI): 213 (M^+ , 100%), 198 (2), 171 (20), 170 (20), 157 (20), 143 (20), 87 (20), 71 (20), 57 (30), 47 (30).

* Note: deviation in the amount of acetamide used in this reaction.

6-Morpholinoquinolin-2-amine (30c)

(i) Using General Procedure 6, **32c** (370 mg, 1.49 mmol) was treated with acetamide (1.76 g, 29.8 mmol) and K_2CO_3 (1.03 g, 7.4 mmol) for 2.5 h. Extraction with ethyl acetate and chromatographic separation eluting with DCM:ethanol



(9:1) afforded the title compound as a pale orange solid, mp 224-228 °C (111 mg, 32%). HRMS found: 229.1208; $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}$ requires 229.1215. IR (nujol mull): ν/cm^{-1} : 3379, 3300, 3154, 1661, 1603 and 1567. ^1H NMR (300 MHz, CDCl_3); δ : 3.20 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(2'/6')), 3.90 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(3'/5')), 5.46 (2H, br s, NH_2), 6.71 (1H, d, $J = 9.0$ Hz, H3), 6.97 (1H, d, $J = 2.4$ Hz, H5), 7.33 (1H, dd, $J = 2.4, 9.0$ Hz, H7), 7.61 (1H, d, $J = 9.0$ Hz, H8), 7.80 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (75 MHz, CDCl_3); δ : 50.2 (C2'/6'), 66.9 (C3'/5'), 110.8 (C5), 112.1 (C3), 122.5 (C7), 124.0 (C4a), 126.1 (C8), 137.7 (C4), 141.7 (C8a), 147.1 (C6), 155.4 (C2). m/z (EI): 229 (M^+ , 60%), 198 (1), 171 (100), 143 (20).

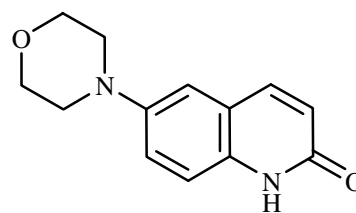
30c was converted to the corresponding maleate salt, mp 194-200 °C, using General Procedure 8 for the purpose of obtaining a microanalysis. Analysis found: C, 57.47; H, 5.39; N, 11.66. $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_5 \cdot 0.5\text{H}_2\text{O}$ requires C, 57.62; H, 5.69; N, 11.86%.

(ii) Using General Procedure 7, $\text{Pd}_2(\text{dba})_3$ (1.9 mg, 2.1 μmol), DavePhos **57** (1.0 mg, 2.5 μmol) and **32c** (52 mg, 0.21 mmol) were combined in 1,4-dioxane (3 mL). LHMDS solution (1.0 M in THF, 460 μL) was added and the reaction was heated for 22 h. Work-up afforded the title compound (47 mg, 98%). Data as above.

(iii) **32c** (59 mg, 0.24 mmol) was combined with acetamide (5.0 g, 84.6 mmol) and K_2CO_3 (164 mg, 1.2 mmol) in a microwave vessel. The mixture was heated at 230°C at 300 W in a CEM MARS system for 1 h. Extraction with DCM and chromatographic separation eluting with DCM:ethanol (9:1) afforded 6-morpholinoquinolin-2(1H)-one **68** as a sticky orange solid

(40 mg, 73%). HRMS found: 230.1056; C₁₃H₁₄N₂O₂ requires 230.1056. IR (nujol mull): ν/cm^{-1} : 3290, 1650, 1619 and 1600.

¹H NMR (300 MHz, CDCl₃); δ : 3.17 (4H, t, $J = 4.8$ Hz, 2 x CH₂, H(2'/6')), 3.90 (4H, t, $J = 4.8$ Hz, 2 x CH₂, H(3'/5')), 6.71 (1H, d, $J = 8.7$ Hz, H3), 6.99 (1H, d, $J = 2.7$ Hz, H5), 7.33 (1H, dd, $J = 2.7, 8.7$ Hz, H7), 7.36 (1H, d, $J = 8.7$ Hz, H8), 7.74 (1H, d, $J = 8.7$ Hz, H4), 12.0 (1H, br s, NH). ¹³C NMR (75 MHz, CDCl₃); δ : 50.6 (C2'/6'), 66.7 (C3'/5'), 113.2 (C8a), 116.9 (C5), 120.3 (C7), 121.5 (C3), 122.3 (C8), 133.6 (C4a), 140.2 (C4), 163.1 (C6), 171.1 (C2). m/z (EI): 230 (M⁺, 70%), 172 (100), 144 (10), 116 (10), 89 (5).

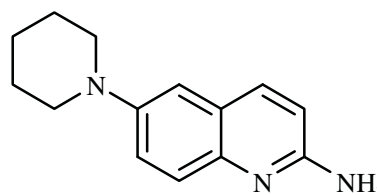


(iv)⁹² **32c** (110 mg, 0.44 mmol) and phenol (300 mg, 3.2 mmol) were combined and heated at 70 °C for 15 min. Ammonium acetate (302 mg, 3.9 mmol) was added to the mixture and heated for an additional 22 h. The mixture was cooled to room temperature, extracted with ethyl acetate, washed with 5% NaOH and water and dried over MgSO₄. The solvent was removed under reduced pressure leading to the recovery of starting material only.

(v)⁹³ **32c** (38 mg, 0.15 mmol) and ammonium hydroxide (1 mL) were combined in a pressure tube and heated at 140 °C for 48 hr. The mixture was cooled to room temperature, extracted with chloroform:isopropanol (3:1 mix), washed with water and dried over MgSO₄. The solvent was removed under reduced pressure leading to the recovery of starting material only.

6-(Piperidin-1-yl)quinolin-2-amine (**30d**)

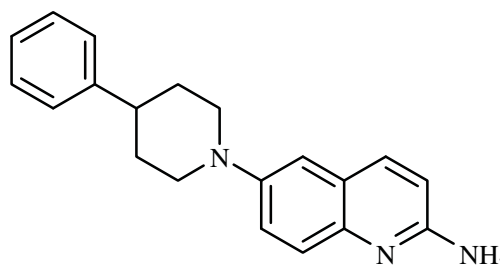
Using General Procedure 6, **32d** (300 mg, 1.2 mmol) was treated with acetamide (1.42 g, 24.0 mmol) and K₂CO₃ (830 mg, 6.0 mmol) for 1.5 h. Extraction with ethyl acetate and chromatographic separation eluting with DCM:ethyl acetate



(3:2) afforded the title compound as a pale brown solid, mp 120-122 °C (175 mg, 64%). HRMS found: 227.1428; C₁₄H₁₇N₃ requires 227.1422. IR (nujol mull): ν/cm^{-1} : 3400, 3210, 1685 and 1618. ¹H NMR (300 MHz, CDCl₃); δ : 1.59 (2H, br d, $J = 4.8$ Hz, CH₂, H4'), 1.72 (4H, br d, $J = 4.8$ Hz, 2 x CH₂, H(3'/5')), 3.16 (4H, br t, $J = 4.8$ Hz, 2 x CH₂, H(2'/6')), 5.82 (2H, br s, NH₂), 6.83 (1H, d, $J = 9.0$ Hz, H3), 6.97 (1H, d, $J = 2.7$ Hz, H5), 7.38 (1H, dd, $J = 2.7, 9.0$ Hz, H7), 7.60 (1H, d, $J = 9.0$ Hz, H8), 7.82 (1H, d, $J = 9.0$ Hz, H4). ¹³C NMR (75 MHz, CDCl₃); δ : 25.7 (C4'), 29.6 (C3'/5'), 51.0 (C2'/6'), 111.4 (C5), 113.1 (C3), 120.8 (C8), 122.6 (C4a), 124.1 (C7), 134.3 (C8a), 139.7 (C4), 148.9 (C6), 154.2 (C2). m/z (EI): 227 (M⁺, 100%), 198 (5), 171 (50), 143 (30), 116 (20).

6-(4-Phenylpiperidin-1-yl)quinolin-2-amine (30e)

Using General Procedure 6, **32e** (132 mg, 0.41 mmol) was treated with acetamide (486 mg, 8.23 mmol) and K_2CO_3 (283 mg, 2.05 mmol) for 2 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM:ethanol (19:1) afforded the title compound as

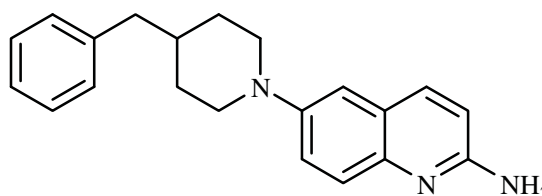


a pale yellow powder, mp 187-194 °C (50 mg, 40%). HRMS found: 303.173; $C_{20}H_{21}N_3$ requires 303.174. IR (nujol mull): ν/cm^{-1} : 3431, 3250, 1637, 1599 and 1565. 1H NMR (600 MHz, $CDCl_3$); δ : 1.95 (2H, dq, $J_{(2'/6')_{eq}, (3'/5')_{ax}} = 3.0$ Hz, $J_{(2'/6')_{ax}, (3'/5')_{ax}} = J_{(3'/5')_{ax}, (3'/5')_{eq}} = 12.0$ Hz, 2 x CH, H(3'/5')_{ax}), 2.01 (2H, br d[‡], $J_{(2'/6')_{eq}, (3'/5')_{eq}} = J_{(3'/5')_{ax}, (3'/5')_{eq}} = 12.0$ Hz, 2 x CH, H(3'/5')_{eq}), 2.65 (1H, m, CH, H4'), 2.85 (2H, dt, $J_{(2'/6')_{ax}, (3'/5')_{eq}} = 3.0$ Hz, $J_{(2'/6')_{ax}, (2'/6')_{eq}} = J_{(2'/6')_{ax}, (3'/5')_{ax}} = 12.0$ Hz, 2 x CH, H(2'/6')_{ax}), 3.84, (2H, br d[‡], $J_{(2'/6')_{eq}, (3'/5')_{eq}} = J_{(2'/6')_{eq}, (2'/6')_{ax}} = 12.0$ Hz, 2 x CH, H(2'/6')_{eq}), 4.66 (2H, br s, NH₂), 6.69 (1H, d, $J = 9.0$ Hz, H3), 7.03 (1H, d, $J = 3.0$ Hz, H5), 7.22 (1H, t, $J = 7.2$ Hz, H4''), 7.27 (2H, m, H(3''/5'')), 7.32 (2H, t, $J = 7.2$ Hz, H(2''/6'')), 7.42 (1H, dd, $J = 3.0, 9.0$ Hz, H7), 7.60 (1H, d, $J = 9.0$ Hz, H8), 7.79 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 33.4 (C3'/5'), 42.5 (C4'), 51.4 (C2'/6'), 111.4 (C5), 111.7 (C3), 123.6 (C7), 124.2 (C4a), 126.3 (C4''), 126.5 (C8), 126.9 (C3''/5''), 128.5 (C2''/6''), 137.4 (C4), 142.4 (C8a), 146.0 (C1''), 147.6 (C6), 155.3 (C2). m/z (EI): 303 (M^+ , 100%), 198 (30), 171 (40), 143 (20).

30e was converted to the corresponding maleate salt, mp 197-207 °C, using General Procedure 8 for the purpose of obtaining a microanalysis. Analysis found: C, 65.45; H, 6.01; N, 9.35. $C_{24}H_{25}N_3O_4 \cdot 1H_2O$ requires C, 65.89; H, 6.22; N, 9.60%.

6-(4-Benzylpiperidin-1-yl)quinolin-2-amine (30f)

Using General Procedure 6, an inseparable mixture of **32f** and **39f** (390 mg, 1.0 mmol) was treated with acetamide (1.20 g, 20.3 mmol) and K_2CO_3 (698 mg, 5.0 mmol) for 2.5 h.



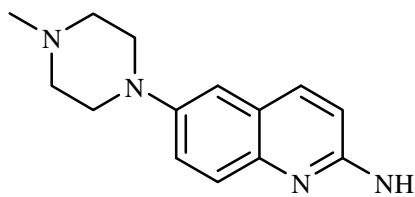
Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM afforded the title compound as a yellow/brown solid, mp 169-174 °C (78 mg, 25%). HRMS found: 317.1884; $C_{21}H_{23}N_3$ requires 317.1892. IR (nujol mull): ν/cm^{-1} : 3456, 3309, 3120, 1650, 1601, 1566 and 1502. 1H NMR (600 MHz, $CDCl_3$); δ : 1.47 (2H, dq,

$J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{ax}}} = 4.2 \text{ Hz}$, $J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}} = J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = 12.6 \text{ Hz}$, 2 x CH, H(3'/5')_{ax}), 1.70 (1H, m, CH, H4'), 1.79 (2H, br d[‡], $J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = 12.6 \text{ Hz}$, 2 x CH, H(3'/5')_{eq}), 2.60 (2H, d, $J = 7.2 \text{ Hz}$, CH₂), 2.69 (2H, dt, $J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{eq}}} = 4.2 \text{ Hz}$, $J_{(2'/6')_{\text{ax}}, (2'/6')_{\text{eq}}} = J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}} = 12.6 \text{ Hz}$, 2 x CH, H(2'/6')_{ax}), 3.68, (2H, br d[‡], $J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = J_{(2'/6')_{\text{eq}}, (2'/6')_{\text{ax}}} = 12.6 \text{ Hz}$, 2 x CH, H(2'/6')_{eq}), 4.59 (2H, br s, NH₂), 6.66 (1H, d, $J = 9.0 \text{ Hz}$, H3), 6.95 (1H, d, $J = 2.4 \text{ Hz}$, H5), 7.18 (1H, t, $J = 7.2 \text{ Hz}$, H4''), 7.21 (2H, m, H(2''/6'')), 7.30 (2H, t, $J = 7.2 \text{ Hz}$, H(3''/5'')), 7.35 (1H, dd, $J = 2.4, 9.0 \text{ Hz}$, H7), 7.56 (1H, d, $J = 9.0 \text{ Hz}$, H8), 7.76 (1H, d, $J = 9.0 \text{ Hz}$, H4). ¹³C NMR (150 MHz, CDCl₃); δ: 32.1 (C3'/5'), 37.8 (C4'), 43.2 (CH₂), 50.8 (C2'/6'), 111.2 (C5), 111.7 (C3), 123.6 (C7), 124.3 (C4a), 125.9 (C4''), 126.5 (C8), 128.2 (C3''/5''), 129.2 (C2''/6''), 137.3 (C4), 140.5 (C1''), 142.5 (C8a), 147.7 (C6), 155.3 (C2). *m/z* (EI): 317 (M⁺, 100%), 224 (40), 198 (20), 172 (30), 171 (30), 170 (30), 143 (20).

30f was converted to the corresponding maleate salt, mp 188-195 °C, using General Procedure 8 for the purpose of obtaining a microanalysis. Analysis found: C, 67.69; H, 6.38; N, 9.33. C₂₅H₂₇N₃O₄·0.5H₂O requires C, 67.86; H, 6.38; N, 9.50%.

6-(4-Methylpiperazin-1-yl)quinolin-2-amine (30h)

(i) Using General Procedure 6, an inseparable mixture of **32h** and **31** (200 mg, 0.77 mmol) was treated with acetamide (912 mg, 15.3 mmol) and K₂CO₃ (527 mg, 3.84 mmol) for 2.5 h. Extraction with chloroform:isopropanol



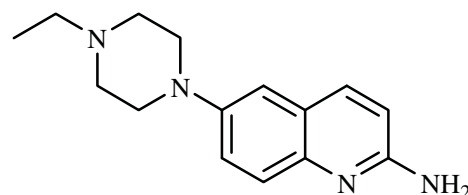
(3:1 mix) and chromatographic separation on C18 silica eluting with methanol:water (3:2) afforded the title compound as a pale yellow powder, mp 171-181 °C (20 mg, 11%). HRMS found: 242.1531; C₁₄H₁₈N₄ requires 242.1531. IR (nujol mull): ν/cm⁻¹: 3299, 3181, 1603 and 1505. ¹H NMR (600 MHz, CDCl₃); δ: 2.39 (3H, s, CH₃), 2.64 (4H, t, $J = 4.8 \text{ Hz}$, 2 x CH₂, H(3'/5')), 3.26 (4H, t, $J = 4.8 \text{ Hz}$, 2 x CH₂, H(2'/6')), 4.94 (2H, br s, NH₂), 6.70 (1H, d, $J = 8.6 \text{ Hz}$, H3), 6.98 (1H, d, $J = 2.6 \text{ Hz}$, H5), 7.36 (1H, dd, $J = 2.6, 9.0 \text{ Hz}$, H7), 7.60 (1H, d, $J = 9.0 \text{ Hz}$, H8), 7.79 (1H, d, $J = 8.6 \text{ Hz}$, H4). ¹³C NMR (150 MHz, CDCl₃); δ: 46.1 (CH₃), 49.8 (C2'/6'), 55.1 (C3'/5'), 111.0 (C5), 111.9 (C3), 122.9 (C7), 124.0 (C4a), 126.0 (C8), 137.8 (C4), 141.5 (C8a), 147.1 (C6), 155.2 (C2). *m/z* (EI): 242 (M⁺, 20%), 198 (5), 171 (10), 144 (100), 117 (50).

(ii) Using General Procedure 7, Pd₂(dba)₃ (1.7 mg, 1.9 μmol), DavePhos 57 (0.9 mg, 2.2 μmol) and **32h** (65 mg, 0.19 mmol) were combined in 1,4-dioxane (1 mL). LHMDS solution (1.0 M in THF, 420 μL) was added then the reaction was heated for 24 h. Work-up afforded

the title compound (41 mg, 90%). Data as above.

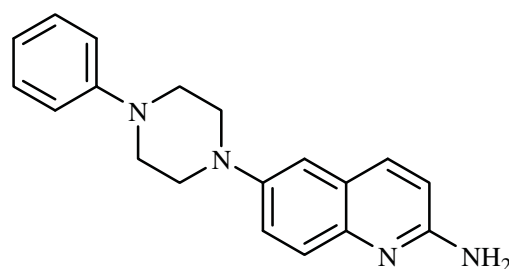
6-(4-Ethylpiperazin-1-yl)quinolin-2-amine (30i)

Using General Procedure 6, an inseparable mixture of **32i** and **37i** (220 mg, 0.80 mmol) was treated with acetamide (946 mg, 16.0 mmol) and K_2CO_3 (553 mg, 4.0 mmol) for 2.5 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation on C18 silica eluting with methanol:water (3:2) afforded the title compound as a pale yellow powder, mp 166-169 °C (17 mg, 8%). Additional product was also isolated as a mixture with an unidentified product that could not be purified further (combined yield 45 mg; **30i** ~ 18%). HRMS found: 256.1688; $C_{15}H_{20}N_4$ requires 256.1688. IR (nujol mull): ν/cm^{-1} : 3466, 3730, 3210, 1639 and 1601. 1H NMR (600 MHz, $CDCl_3$); δ : 1.15 (3H, t, $J = 7.2$ Hz, CH_3), 2.51 (2H, q, $J = 7.2$ Hz, CH_2), 2.67 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(3'/5')), 3.27 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(2'/6')), 4.68 (2H, br s, NH_2), 6.68 (1H, d, $J = 9.0$ Hz, H3), 6.97 (1H, d, $J = 2.4$ Hz, H5), 7.36 (1H, dd, $J = 2.4, 9.0$ Hz, H7), 7.59 (1H, d, $J = 9.0$ Hz, H8), 7.78 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 11.9 (CH_3), 49.9 ($C2'/6'$), 52.3 (CH_2), 52.9 ($C3'/5'$), 110.9 (C5), 111.8 (C3), 122.8 (C7), 124.2 (C4a), 126.5 (C8), 137.4 (C4), 142.4 (C8a), 147.1 (C6), 155.3 (C2). m/z (EI): 256 (M^+ , 100%), 241 (50), 198 (15), 172 (40), 171 (40), 143 (10), 84 (40), 57 (30).



6-(4-Phenylpiperazin-1-yl)quinolin-2-amine (30j)

(i) Using General Procedure 6, **32j** (150 mg, 0.46 mmol) was treated with acetamide (550 mg, 9.3 mmol) and K_2CO_3 (320 mg, 2.3 mmol) for 1.5 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM:ethanol (19:1) afforded the title compound as a yellow powder, mp 233-240 °C (65 mg, 46%). HRMS found: 304.1682; $C_{19}H_{20}N_4$ requires 304.1688. Analysis found: C, 72.56; H, 6.63; N, 17.42. $C_{19}H_{20}N_4 \cdot 0.5H_2O$ requires C, 72.82; H, 6.75; N, 17.88%. IR (nujol mull): ν/cm^{-1} : 3435, 3301, 3112, 1646 and 1602. 1H NMR (600 MHz, $CDCl_3$); δ : 3.39 (8H, br s, 4 x CH_2 , H(2'/6'), H(3'/5')), 5.38 (2H, br s, NH_2), 6.70 (1H, d, $J = 9.0$ Hz, H3), 6.92 (1H, t, $J = 8.1$ Hz, H4''), 7.00 (2H, d, $J = 8.1$ Hz, H(2''/6'')), 7.05 (1H, d, $J = 2.7$ Hz, H5), 7.29 (2H, m, H(3''/5'')), 7.43 (1H, dd, $J = 2.7, 9.0$ Hz, H7), 7.65 (1H, d, $J = 9.0$ Hz, H8), 7.87 (1H, d, $J =$



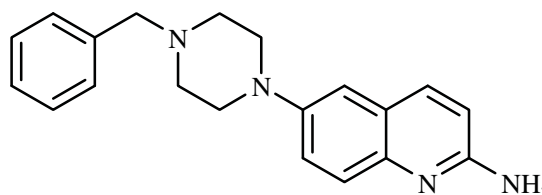
9.0 Hz, H4). ^{13}C NMR (150 MHz, CDCl_3); δ : 49.7 (C2'/6'), 50.4 (C3'/5'), 111.5 (C3), 112.1 (C4''), 116.6 (C2''/6''), 120.3 (C5), 123.3 (C7), 124.3 (C4a), 126.7 (C8), 129.4 (C3''/5''), 142.5 (C4), 142.5 (C8a), 147.3 (C6), 151.5 (C1''), 155.6 (C2). m/z (EI): 304 (M^+ , 100%), 198 (20), 171 (60), 143 (20), 132 (60), 105 (30).

(ii) Using General Procedure 7, $\text{Pd}_2(\text{dba})_3$ (1.4 mg, 1.5 μmol), DavePhos **57** (0.7 mg, 1.8 μmol) and **32j** (50 mg, 0.15 mmol) were combined in 1,4-dioxane (1 mL). LHMDS solution (1.0 M in THF, 330 μL) was added then the reaction was heated for 18 h. Work-up afforded the title compound (44 mg, 96%). Data as above.

(iii) **32j** (50 mg, 0.15 mmol) was combined with acetamide (5.0 g, 84.6 mmol) and K_2CO_3 (110 mg, 1.2 mmol) in a microwave vessel. The mixture was heated at 230 $^\circ\text{C}$ at 300 W in a CEM MARS system for 1 h. The crude material was extracted with DCM, washed with water, dried over MgSO_4 and the solvent removed under reduced pressure. ^1H NMR analysis of the crude material indicated a complex mixture of products that was not purified.

6-(4-Benzylpiperazin-1-yl)quinolin-2-amine (30k)

(i) Using General Procedure 6, an inseparable mixture of **32k** and **37k** (575 mg, 1.71 mmol) was treated with acetamide (2.0 g, 34.1 mmol) and K_2CO_3 (1.18 g, 8.5 mmol) for 2 h.



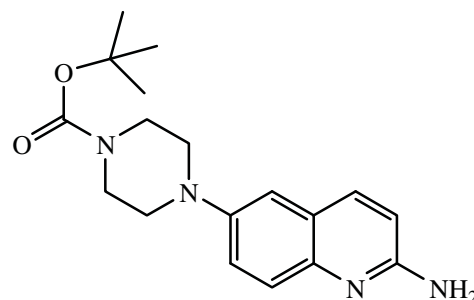
Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation on C18 silica eluting with methanol:water (4:1) afforded the title compound as an impure mixture (90 mg). Additional attempts to purify the product on C18 preparative plates afforded a small amount of the pure title compound as a cream powder, mp 194-196 $^\circ\text{C}$ (20 mg, 4%). HRMS found: 318.1847; $\text{C}_{20}\text{H}_{22}\text{N}_4$ requires 318.1844. IR (nujol mull): ν/cm^{-1} : 3439, 3301, 2354, 1647, 1599 and 1560. ^1H NMR (600 MHz, CDCl_3); δ : 2.64 (4H, m, 2 x CH_2 , H(3'/5')), 3.23 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(2'/6')), 3.58 (2H, s, CH_2), 4.66 (2H, br s, NH_2), 6.66 (1H, d, $J = 9.0$ Hz, H3), 6.94 (1H, d, $J = 3.0$ Hz, H5), 7.25-7.37 (6H, m, H7, Ph), 7.57 (1H, d, $J = 9.0$ Hz, H8), 7.75 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, CDCl_3); δ : 49.9 (C2'/6'), 53.1 (C3'/5'), 63.0 (CH_2), 110.8 (C5), 112.8 (C3), 121.9 (C7), 124.2 (C4a), 126.7 (C8), 127.1 (C4''), 128.3 (C2''/6''), 129.1 (C3''/5''), 137.9 (C4), 138.15 (C1''), 142.8 (C8a), 147.0 (C6), 155.5 (C2). m/z (EI): 318 (M^+ , 100%), 198 (10), 172 (70), 171 (45), 146 (30), 143 (15), 91 (50).

(ii) Using General Procedure 7, $\text{Pd}_2(\text{dba})_3$ (2.6 mg, 2.8 μmol), DavePhos **57** (1.3 mg, 3.3

μmol) and pure **32k** (96 mg, 0.15 mmol) were combined in 1,4-dioxane (1 mL). LHMDS solution (1.0 M in THF, 620 μL) was added then the reaction was heated for 24 h. Work-up afforded the title compound (80 mg, 88%). Data as above.

***t*-Butyl 4-(2-aminoquinolin-6-yl)piperazine-1-carboxylate (30l)**

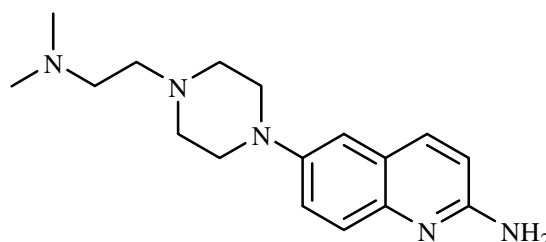
Using General Procedure 6, **32l** (200 mg, 0.58 mmol) was treated with acetamide (685 mg, 11.6 mmol) and K_2CO_3 (400 mg, 2.9 mmol) for 1.5 h. Extraction with chloroform:isopropanol (3:1 mix) and chromatographic separation eluting with DCM:ethanol (9:1) afforded the title compound as a green-brown



solid, mp 220-228 $^{\circ}\text{C}$ (90 mg, 47%). IR (nujol mull): ν/cm^{-1} : 3336, 3157, 1658, 1621 and 1604. HRMS found: 328.1895; $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}_2$ requires 328.1899. ^1H NMR (600 MHz, CDCl_3); δ : 1.26 (9H, s, *t*Bu), 3.22 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(2'/6')), 3.66 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(3'/5')), 5.17 (2H, br s, NH_2), 6.74 (1H, d, $J = 8.4$ Hz, H3), 6.97 (1H, d, $J = 2.4$ Hz, H5), 7.35 (1H, dd, $J = 2.4, 9.0$ Hz, H7), 7.62 (1H, d, $J = 9.0$ Hz, H8), 7.81 (1H, d, $J = 8.4$ Hz, H4). ^{13}C NMR (150 MHz, CDCl_3); δ : 29.7 ($\text{C}(\text{CH}_3)_3$), 41.4 ($\text{C}3'/5'$), 49.9 ($\text{C}2'/6'$), 80.10 ($\text{C}(\text{CH}_3)_3$), 111.9 ($\text{C}5$), 112.2 ($\text{C}3$), 123.4 ($\text{C}7$), 123.8 ($\text{C}4\text{a}$), 125.9 ($\text{C}8$), 135.1 ($\text{C}4$), 138.0 ($\text{C}8\text{a}$), 146.8 ($\text{C}6$), 155.4 ($\text{C}2$), 169.0 ($\text{C}=\text{O}$). m/z (EI): 328 (M^+ , 1%), 270 ($\text{M}^+ - \text{tBu}$, 90), 198 (100), 185 (30), 172 (40), 171 (50), 170 (50) 143 (30), 83 (30), 56 (30).

6-(4-(2-(Dimethylamino)ethyl)piperazin-1-yl)quinolin-2-amine (30n)

Using General Procedure 6, an impure mixture of **32n** (440 mg, 1.38 mmol) was treated with acetamide (1.63 g, 27.6 mmol) and K_2CO_3 (945 mg, 6.90 mmol) for 2 h. Extraction with chloroform:isopropanol (3:1 mix) and



chromatographic separation on C18 silica eluting with methanol:water (4:1) afforded the title compound as an impure mixture (120 mg, 23%). Additional attempts to purify the product indicated the decomposition of the compound on C18 preparative plates and therefore further purification was unsuccessful. Crude data: IR (nujol mull): ν/cm^{-1} : 3325, 3251, 1731 and 1651. ^1H NMR (300 MHz, CDCl_3); δ : 2.33 (6H, s, 2 x CH_3), 2.57 (4H, m, 2 x CH_2), 2.74 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(3'/5')), 3.30 (4H, t, $J = 4.8$ Hz, 2 x CH_2 , H(2'/6')), 4.65 (2H, br s,

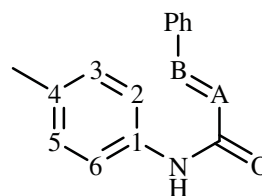
NH₂), 6.73 (1H, d, $J = 9.0$ Hz, H₃), 7.01 (1H, d, $J = 2.7$ Hz, H₅), 7.41 (1H, dd, $J = 2.7, 9.0$ Hz, H₇), 7.63 (1H, d, $J = 9.0$ Hz, H₈), 7.83 (1H, d, $J = 9.0$ Hz, H₄). m/z (EI): 198 (10%), 171 (10), 143 (10), 85 (30), 70 (30), 58 (40), 44 (100).

7.2 6-Aryloxymethyl- and 6-Arylthiomethyl-2-Aminoquinolines

7.2.1 Synthesis of Starting Materials

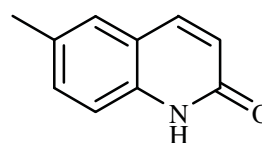
(2E)-N-(4-Methylphenyl)-3-phenylacrylamide (72)^{28,98}

A solution of cinnamoyl chloride (15.55 g, 93.3 mmol) in DCM (50 mL) was added dropwise to a mixture of DMAP (1.14 g, 9.33 mmol) and pyridine (7.5 mL, 93.3 mmol) in DCM (10 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 15 min and a solution of *p*-toluidine (10.05 g, 93.8 mmol) in DCM (50 mL) was added over a 15 min period. The mixture was stirred at room temperature until the solution became homogeneous. The solution was diluted with DCM (100 mL) and washed with 5% HCl (2 x 350 mL), 10% NaOH (2 x 350 mL) and water (1 x 350 mL). The organic phase was dried over Na₂SO₄ and the solvent removed under reduced pressure to afford the title compound as a white solid, mp 159-162 °C (lit.,^{28,98} 162 °C), (21.30g, 96%). IR (nujol mull): ν/cm^{-1} : 3254, 1661, 1622, 1598 and 1541. ¹H NMR (200 MHz, CDCl₃); δ : 2.29 (3H, s, CH₃), 6.61 (1H, d, $J = 15.6$ Hz, H_A), 7.10 (2H, br d, $J = 8.0$ Hz, H(3/5)), 7.26-7.45 (5H, m, Ph), 7.53 (2H, br m, $J = 8.0$ Hz, H(2/6)), 7.72 (1H, d, $J = 15.6$ Hz, H_B), 8.02 (1H, br s, NH).



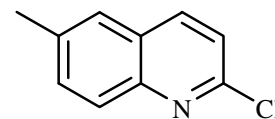
6-Methylquinolin-2(1H)-one (71)²⁸

72 (19.55 g, 82.0 mmol) and AlCl₃ (32.97 g, 247.0 mmol) were ground together in a mortar and pestle to form an intimate mixture. The mixture was transferred to a round bottom flask then heated rapidly with a heat gun to melting and then maintained at 110 °C for 1.5 h. The mixture was cooled to room temperature and quenched with ice water. The resultant precipitate was filtered, washed with water and dried over Na₂SO₄ to afford the title compound as an orange solid (16.96 g) and was used without further purification. IR (nujol mull): ν/cm^{-1} : 3452, 3278, 1662, 1624 and 1563. ¹H NMR (200 MHz, CDCl₃); δ : 2.42 (3H, s, CH₃), 6.70 (1H, d, $J = 9.6$ Hz, H₃), 7.34-7.35 (3H, m, H₅, H₇, H₈), 7.76 (1H, d, $J = 9.6$ Hz, H₄), 12.22 (1H, br s, NH).



2-Chloro-6-methylquinoline (**70**)^{28,99}

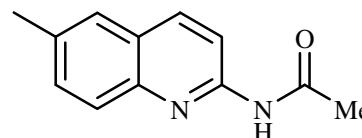
A mixture of crude **71** (16.9 g) and phosphorus oxychloride (97 mL, 1.06 mol) were heated at reflux for 1 h. The solution was cooled to



room temperature and excess reagent was removed under reduced pressure. The remaining mixture was quenched with ice water and the resultant solid filtered and washed with water. The solid was recrystallised from hexane to afford the title compound as a pale orange powder, mp 112-114 °C (lit.,⁹⁹ 111-114 °C), (14.02 g, 96% over two steps). IR (nujol mull): ν/cm^{-1} : 1585, 1566 and 1504. ¹H NMR (200 MHz, CDCl₃); δ : 2.53 (3H, s, CH₃), 7.35 (1H, d, $J = 8.6$ Hz, H3), 7.54-7.58 (2H, m, H7, H5), 7.92 (1H, d, $J = 9.4$ Hz, H8), 8.01 (1H, d, $J = 8.6$ Hz, H4).

N-(6-Methylquinolin-2-yl)acetamide (**73**)⁷⁵

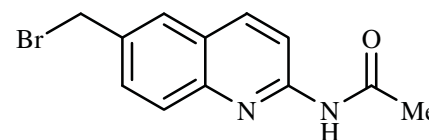
A mixture of **70** (12.0 g, 67.6 mmol), acetamide (200.0 g, 3.38 mol) and K₂CO₃ (46.7 g, 0.34 mol) were heated at reflux for 16 h. The acetamide was removed by distillation. Water (300



mL) was added to the residue and the resulting solution extracted with DCM. The combined organic extracts were washed with water and dried over Na₂SO₄. The solvent was removed under reduced pressure and the resulting solid was filtered through silica gel eluting with DCM:ethyl acetate (17:3) to give the title compound as a white solid, mp 181-185 °C (lit.,^{34,75} 181-184 °C), (6.0 g, 44%). IR (nujol mull): ν/cm^{-1} : 3647, 3213, 1732, 1693, 1660, 1597, 1537 and 1491. ¹H NMR (200 MHz, CDCl₃); δ : 2.20 (3H, s, COCH₃), 2.51 (3H, s, CH₃), 7.49 (1H, dd, $J = 2.0, 8.6$ Hz, H7), 7.55 (1H, d, $J = 2.0$ Hz, H5), 7.72 (1H, d, $J = 8.6$ Hz, H8), 8.10 (1H, d, $J = 8.4$ Hz, H4), 8.38 (1H, br d, $J = 8.4$ Hz, H3), 9.18 (1H, br s, NH).

N-[6-(Bromomethyl)quinolin-2-yl]acetamide (**69**)³⁴

A mixture of **73** (7.5 g, 37.5 mmol), *N*-bromosuccinamide (7.35 g, 41.3 mmol), benzoyl peroxide (0.91 g, 3.75 mmol) and benzene (50 mL) were heated at reflux for 5 h. The



solution was cooled to room temperature and benzene was removed under reduced pressure. DCM was added and the resulting solution washed with 10% NaHCO₃ solution (3 x 150 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the resulting solid purified by flash chromatography eluting with DCM:ethyl acetate (17:3) to afford the title compound as a pale yellow powder, mp 183-186 °C (lit.,³⁴ 185-187 °C), (6.64 g, 63%).

IR (nujol mull): ν/cm^{-1} : 3237, 1663, 1598, 1581, 1537 and 1491. ^1H NMR (200 MHz, CDCl_3); δ : 2.27 (3H, s, COCH_3), 4.65 (2H, s, CH_2Br), 7.70 (1H, dd, $J = 1.8, 8.8$ Hz, H7), 7.78-7.83 (2H, m, H5, H8), 8.16 (1H, d, $J = 9.0$ Hz, H4), 8.44 (1H, br d, $J = 9.0$ Hz, H3), 8.62 (1H, br s, NH).

7.2.2 Synthesis of *N*-[6-(Aryloxymethyl)quinolin-2-yl]acetamides and *N*-[6-(Arylthiomethyl)-quinolin-2-yl]acetamides

General Procedure 9: Synthesis of *N*-[6-(Aryloxymethyl)quinolin-2-yl]acetamides and *N*-[6-(Arylthiomethyl)quinolin-2-yl]acetamides in Acetonitrile

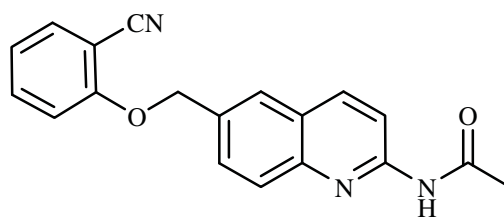
69 (1 mol eq), a substituted phenol or thiophenol (1.1 mol eq) and K_2CO_3 (3 mol eq) were added to acetonitrile and the mixture was heated at reflux under a nitrogen atmosphere until the reaction was complete by TLC. The mixture was then cooled and the solvent removed under reduced pressure. The remaining residue was suspended in ethyl acetate, DCM or chloroform:isopropanol (3:1 mix) washed with 10% NaHCO_3 solution and water (2 x). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was isolated by flash chromatography on silica gel with appropriate solvent mixtures.

General Procedure 10: Synthesis of *N*-[6-(Phenoxymethyl)quinolin-2-yl]acetamides in DMF¹²⁰

A substituted phenol (1.0 mol eq) was dissolved in dry DMF at room temperature under an atmosphere of argon. K_2CO_3 (1.5 mol eq), tetrabutylammonium iodide (TBAI) (0.33 eq) and **69** (1.4 mol eq) were added then the mixture was stirred until the reaction was complete by TLC. The mixture was extracted with chloroform:isopropanol (3:1 mix), washed with 10% NaHCO_3 solution and water (2 x). The organic phase was dried over Na_2SO_4 , then the solvent was removed. The product was isolated by flash chromatography on silica gel or recrystallisation with appropriate solvent mixtures.

***N*-{6-[(2-Cyanophenoxy)methyl]quinolin-2-yl}acetamide (74)**

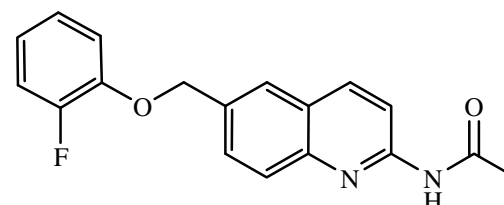
Using General Procedure 9, **69** (202 mg, 0.72 mmol), 2-cyanophenol (94 mg, 0.79 mmol), K₂CO₃ (298 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 4 h. After work up with ethyl acetate the crude product was chromatographed



over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a cream solid, mp 205-208 °C (188 mg, 82%). Analysis found: C, 71.99; H, 5.03; N, 12.89. C₁₉H₁₅N₃O₂ requires C, 71.91, H, 4.76, N, 13.24%. IR (nujol mull): ν/cm^{-1} : 3340, 2231, 1691, 1602 and 1581. ¹H NMR (300 MHz, CDCl₃); δ : 2.23 (3H, s, CH₃), 5.34 (2H, s, CH₂), 6.99 (1H, d, $J = 8.4$ Hz, H6'), 7.00 (1H, d, $J = 8.4$ Hz, H4'), 7.48 (1H, ddd, $J = 1.8, 8.4$ Hz, H5'), 7.58 (1H, dd, $J = 1.8, 8.4$ Hz, H3'), 7.71 (1H, dd, $J = 1.8, 8.7$ Hz, H7), 7.81 (1H, d, $J = 8.7$ Hz, H8), 7.84 (1H, br s, H5), 8.16 (1H, d, $J = 9.0$ Hz, H4), 8.29 (1H, br s, NH), 8.40 (1H, br d, $J = 9.0$ Hz, H3). ¹³C NMR (75 MHz, CDCl₃); δ : 25.2 (COCH₃), 70.6 (CH₂), 102.8 (C2'), 113.1 (C3), 114.8 (C6'), 116.6 (CN), 121.5 (C4'), 126.0 (C5), 126.3 (C4a), 128.2 (C8), 129.0 (C7), 132.8 (C6), 134.2 (C3'), 134.5 (C5'), 138.9 (C4), 146.6 (C8a), 151.4 (C2), 160.3 (C1'), 169.3 (C=O). m/z (EI): 317 (M⁺, 2%), 199 (60), 157 (100).

***N*-{6-[(2-Fluorophenoxy)methyl]quinolin-2-yl}acetamide (75)**

Using General Procedure 9, **69** (202 mg, 0.72 mmol), 2-fluorophenol (71 μ L, 0.79 mmol), K₂CO₃ (298 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 4 h. After work up with

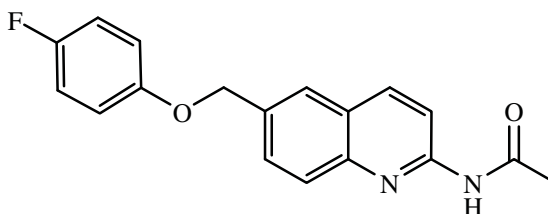


chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a cream solid, mp 145-148 °C (180 mg, 81%). Analysis found: C, 69.91; H, 4.82; N, 9.18. C₁₈H₁₅FN₂O₂ requires C, 69.67; H, 4.87; N, 9.03%. IR (nujol mull): ν/cm^{-1} : 3251, 3193, 1673, 1597, 1538 and 1504. ¹H NMR (600 MHz, CDCl₃); δ : 2.21 (3H, s, CH₃), 5.27 (2H, s, CH₂), 6.92 (1H, dddd, ⁴ $J_{4',6'}$ = 2.4 Hz, ⁴ $J_{4',F}$ = 4.2 Hz, ³ $J_{3',4'}$ = 7.8 Hz, ³ $J_{4',5'}$ = 8.1 Hz, H4'), 7.02 (2H, m, H5', H6'), 7.10 (1H, ddd, ⁴ $J_{3',5'}$ = 1.2 Hz, ³ $J_{3',4'}$ = 7.8 Hz, ³ $J_{3',F}$ = 11.4 Hz, H3'), 7.73 (1H, dd, $J = 1.8, 8.4$ Hz, H7), 7.82 (1H, d, $J = 8.4$ Hz, H8), 7.83 (1H, br s, H5), 8.15 (1H, d, $J = 9.0$ Hz, H4), 8.42 (1H, br s, H3), 8.96 (1H, br s, NH). ¹³C NMR (150 MHz, CDCl₃); δ : 24.8 (COCH₃), 71.1 (CH₂), 114.5 (C3), 115.9 (d, ³ $J_{C,F}$ = 1.4 Hz, C6'), 116.5 (d, ² $J_{C,F}$ = 18.6 Hz, C3'), 121.7 (d, ³ $J_{C,F}$ = 6.6 Hz,

C4'), 124.2 (d, $^4J_{C,F} = 3.8$ Hz, C5'), 125.9 (C4a), 126.1 (C5), 127.7 (C8), 129.4 (C7), 133.5 (C6), 138.7 (C4), 146.3 (C8a), 146.5 (d, $^2J_{C,F} = 10.4$ Hz, C1'), 151.3 (C2), 160.3 (d, $^1J_{C,F} = 244.8$ Hz, C2'), 169.2 (C=O). m/z (ED): 310 (M^+ , 0.5%), 199 (65), 157 (100).

***N*-{6-[(4-Fluorophenoxy)methyl]quinolin-2-yl}acetamide (76)**

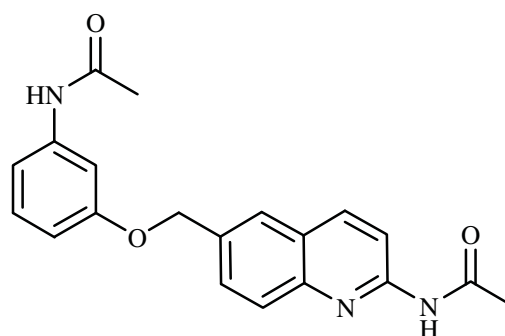
Using General Procedure 9, **69** (200 mg, 0.72 mmol), 4-fluorophenol (89 mg, 0.79 mmol), K_2CO_3 (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 4 h. After work up with chloroform:isopropanol (3:1 mix) the



crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a cream solid, mp 186-189 °C (200 mg, 90%). Analysis found: C, 69.65; H, 4.85; N, 9.04. $C_{18}H_{15}FN_2O_2$ requires C, 69.67; H, 4.87, N; 9.03%. IR (nujol mull): ν/cm^{-1} : 3261, 3189, 1672, 1598, 1579 and 1535. 1H NMR (600 MHz, $CDCl_3$); δ : 2.24 (3H, s, CH_3), 5.17 (2H, s, CH_2), 6.93-7.03 (4H, m, H(2'/6'), H(3'/5')), 7.71 (1H, dd, $J = 1.8, 9.0$ Hz, H7), 7.82 (1H, br d, $J = 1.8$ Hz, H5), 7.83 (1H, d, $J = 9.0$ Hz, H8), 8.17 (1H, d, $J = 9.0$ Hz, H4), 8.42 (1H, br d, $J = 9.0$ Hz, H3), 8.52 (1H, br s, NH). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 24.9 ($COCH_3$), 70.4 (CH_2), 114.6 (C3), 115.9 (d, $^2J_{C,F} = 22.2$ Hz, C(3'/5')), 115.9 (d, $^3J_{C,F} = 6.6$ Hz, C(2'/6')), 126.0 (C5), 126.1 (C4a), 127.7 (C8), 129.4 (C7), 133.9 (C6), 138.7 (C4), 146.2 (C8a), 151.2 (C2), 154.7 (d, $^4J_{C,F} = 2.3$ Hz, C1'), 157.5 (d, $^1J_{C,F} = 244.8$ Hz, C4'), 169.1 (C=O). m/z (ED): 363 (M^+ , < 1%), 199 (20), 157 (100).

***N*-{6-[(3-Acetamidophenoxy)methyl]quinolin-2-yl}acetamide (77)**

Using General Procedure 9, **69** (145 mg, 0.52 mmol), 3-acetamidophenol (87 mg, 0.57 mmol), K_2CO_3 (215 mg, 1.56 mmol) and acetonitrile (10 mL) were heated for 7 h. After work up with chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel eluting with

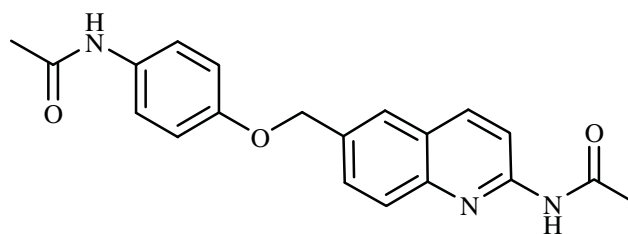


DCM:ethanol (19:1) to afford the title compound as a cream powder, mp 201-205 °C (105 mg, 58%). HRMS found: 349.1424; $C_{20}H_{19}N_3O_3$ requires 349.1426. Analysis found: C, 68.24; H, 5.56; N, 11.86. $C_{20}H_{19}N_3O_3 \cdot 0.2H_2O$ requires C, 68.05; H, 5.54; N, 11.90%. IR (nujol mull): ν/cm^{-1} : 3235, 3199, 3145, 1666 and 1600. 1H

NMR (300 MHz, CDCl₃); δ : 2.18 (3H, s, CH₃), 2.26 (3H, s, CH₃), 5.20 (2H, s, CH₂), 6.76 (1H, br dd, $J = 2.1, 8.1$ Hz, H6'), 6.97 (1H, br d, $J = 8.1$ Hz, H4'), 7.22 (1H, dd, $J = 8.1$ Hz, H5'), 7.37 (1H, br s, NH), 7.47 (1H, br s, H2'), 7.71 (1H, br dd, $J = 1.5, 8.4$ Hz, H7), 7.80 (1H, d, $J = 8.4$ Hz, H8), 7.83 (1H, br s, H5), 8.16 (1H, d, $J = 9.0$ Hz, H4), 8.34 (1H, d, $J = 9.0$ Hz, H3), 8.45 (1H, br s, NH). ¹³C NMR (75 MHz, CDCl₃); δ : 24.1 (COCH₃), 24.2 (COCH₃), 68.9 (CH₂), 105.8 (C2'), 109.1 (C6'), 111.6 (C4'), 114.5 (C3), 125.3 (C4a), 126.2 (C5), 127.1 (C8), 129.5 (C5'), 129.7 (C7), 133.6 (C6), 138.3 (C3'), 140.5 (C4), 145.9 (C8a), 151.9 (C2), 158.5 (C1'), 168.4 (C=O), 169.9 (C=O). m/z (EI): 349 (M⁺, 5%), 199 (60), 157 (100).

***N*-{6-[(4-Acetamidophenoxy)methyl]quinolin-2-yl}acetamide (78)**

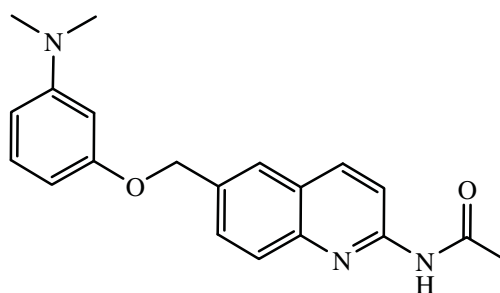
Using General Procedure 9, **69** (150 mg, 0.54 mmol), 4-acetamidophenol (89 mg, 0.59 mmol), K₂CO₃ (224 mg, 1.62 mmol) and acetonitrile (10 mL) were heated for 8 h. After work up with



chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel eluting with DCM:ethanol (19:1) to afford the title compound as a pale yellow powder, mp 224-225 °C (165 mg, 88%). HRMS found: 349.1424; C₂₀H₁₉N₃O₃ requires 349.1426. Analysis found: C, 67.04; H, 5.77; N, 11.57. C₂₀H₁₉N₃O₃.0.5H₂O requires C, 67.03; H, 5.62; N, 11.72%. IR (nujol mull): ν/cm^{-1} : 3262, 3235, 3201, 1675, 1660 and 1602. ¹H NMR (300 MHz, CDCl₃); δ : 2.17 (3H, s, CH₃), 2.32 (3H, s, CH₃), 5.21 (2H, s, CH₂), 6.97 (2H, d, $J = 9.0$ Hz, H(2'/6')), 7.08 (1H, br s, NH), 7.42 (2H, d, $J = 9.0$ Hz, H(3'/5')), 7.55 (1H, dd, $J = 1.5, 8.4$ Hz, H7), 7.85 (1H, d, $J = 8.4$ Hz, H8), 7.86 (1H, d, $J = 1.5$ Hz, H5), 8.23 (1H, d, $J = 9.0$ Hz, H4), 8.47 (1H, d, $J = 9.0$ Hz, H3), 9.0 (1H, br s, NH). ¹³C NMR (75 MHz, CDCl₃); δ : 23.9 (COCH₃), 24.1 (COCH₃), 69.2 (CH₂), 114.5 (C3), 115.0 (C2'/6'), 120.6 (C3'/5'), 125.3 (C4a), 126.3 (C5), 127.2 (C8), 129.8 (C7), 132.9 (C6), 133.9 (C4'), 138.3 (C4), 146.0 (C8a), 151.9 (C2), 154.0 (C1'), 167.9 (C=O), 170.0 (C=O). m/z (EI): 349 (M⁺, 3%), 199 (60), 157 (100).

***N*-{6-[(3-(Dimethylamino)phenoxy)methyl]quinolin-2-yl}acetamide (79)**

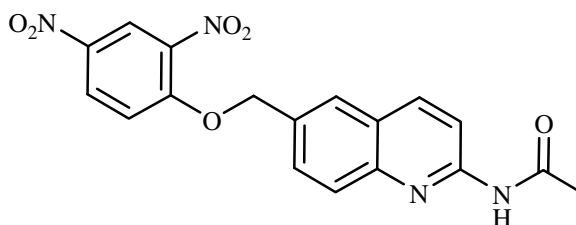
Using General Procedure 9, **69** (200 mg, 0.72 mmol), 3-(dimethylamino)phenol (109 mg, 0.79 mmol), K₂CO₃ (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 5 h. After work up with chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel



eluting with DCM:ethyl acetate (17:3) and recrystallised from ethanol:water to afford the title compound as pale orange crystals, mp 175-180 °C (165 mg, 68%). HRMS found: 335.1634; C₂₀H₂₁N₃O₂ requires 335.1634. IR (DCM): ν/cm^{-1} : 3405, 3053, 1701, 1578 and 1540. ¹H NMR (300 MHz, CDCl₃); δ : 2.27 (3H, s, COCH₃), 2.95 (6H, s, N(CH₃)₂), 5.20 (2H, s, CH₂), 6.39-6.42 (3H, m, H2', H4', H6'), 7.17 (1H, dd, *J* = 9.0 Hz, H5'), 7.74 (1H, dd, *J* = 1.8, 8.7 Hz, H7), 7.83 (1H, d, *J* = 8.7 Hz, H8), 7.86 (1H, br s, H5), 8.18 (2H, d, *J* = 9.0 Hz, H4, NH), 8.41 (1H, br d, *J* = 9.0 Hz, H3). ¹³C NMR (75 MHz, CDCl₃); δ : 25.1 (COCH₃), 40.7 (N(CH₃)₂), 69.7 (CH₂), 100.2 (C2'), 102.3 (C6'), 106.3 (C4'), 114.7 (C3), 126.3 (C4a), 126.4 (C5), 127.8 (C8), 129.8 (C7), 130.0 (C5'), 134.6 (C6), 138.9 (C4), 146.3 (C8a), 151.3 (C2), 152.2 (C3'), 160.0 (C1'), 169.4 (C=O). *m/z* (EI): 335 (M⁺, 30%), 199 (50), 157 (100).

***N*-{6-[(2,4-Dinitrophenoxy)methyl]quinolin-2-yl}acetamide (80)**

Using General Procedure 9, **69** (203 mg, 0.73 mmol), 2,4-dinitrophenol (147 mg, 0.80 mmol), K₂CO₃ (303 mg, 2.18 mmol) and acetonitrile (10 mL) were heated for 6 h. After work up with ethyl acetate the crude

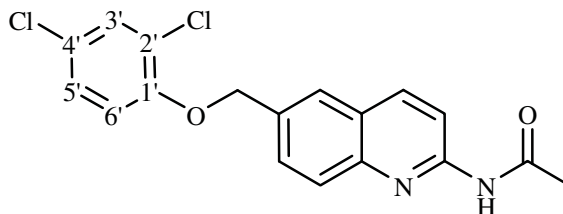


product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a pale yellow solid, mp 234-235 °C (200 mg, 72%). HRMS found: 382.0914; C₁₈H₁₄N₄O₆ requires 382.0913. IR (DCM): ν/cm^{-1} : 3404, 3053, 1703, 1604 and 1530. ¹H NMR (600 MHz, d₆-DMSO); δ : 2.15 (3H, s, CH₃), 5.63 (2H, s, CH₂), 7.73 (1H, d, *J* = 9.0 Hz, H6'), 7.77 (1H, dd, *J* = 1.8, 9.0 Hz, H7), 7.85 (1H, d, *J* = 9.0 Hz, H8), 7.98 (1H, d, *J* = 1.8 Hz, H5), 8.29 (1H, d, *J* = 9.0 Hz, H3), 8.35 (1H, d, *J* = 9.0 Hz, H4), 8.52 (1H, dd, *J* = 2.4, 9.0 Hz, H5'), 8.78 (1H, d, *J* = 2.4 Hz, H3'), 10.86 (1H, br s, NH). ¹³C NMR (150 MHz, d₆-DMSO); δ : 24.0 (COCH₃), 71.5 (CH₂), 114.6 (C3), 116.2 (C6'), 121.2 (C3'), 125.1 (C4a), 126.7 (C5), 127.3 (C8), 129.3 (C5'), 129.5 (C7), 131.5 (C6), 138.4 (C4), 138.8 (C2'), 139.8

(C4'), 146.0 (C8a), 152.1 (C2), 155.5 (C1'), 169.9 (C=O). m/z (EI): 382 (M^+ , 2%), 199 (50), 157 (100).

***N*-{6-[(2,4-Dichlorophenoxy)methyl]quinolin-2-yl}acetamide (81)**

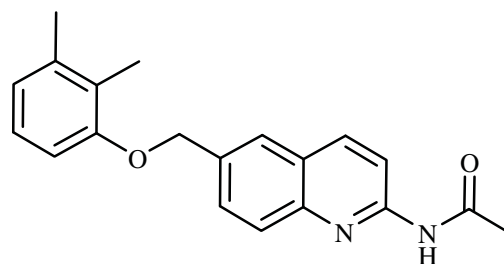
Using General Procedure 9, **69** (230 mg, 0.83 mmol), 2,4-dichlorophenol (154 mg, 0.95 mmol), K_2CO_3 (378 mg, 2.59 mmol) and acetonitrile (10 mL) were heated for 4 h.



After work up with ethyl acetate the crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a cream solid, mp 169-170 °C (254 mg, 85%). HRMS found: 360.0424; $C_{18}H_{14}^{35}Cl_2N_2O_2$ requires 360.0432. Analysis found: C, 60.31; H, 4.02; N, 7.74. $C_{18}H_{14}Cl_2N_2O_2$ requires C, 59.85; H, 3.91; N, 7.76%. IR (nujol mull): ν/cm^{-1} : 3203, 1660, 1606, 1583 and 1537. 1H NMR (300 MHz, $CDCl_3$); δ : 2.27 (3H, s, CH_3), 5.29 (2H, s, CH_2), 6.93 (1H, d, $J = 8.7$ Hz, H6'), 7.17 (1H, dd, $J = 2.4, 8.7$ Hz, H5'), 7.41 (1H, d, $J = 2.4$ Hz, H3'), 7.40 (1H, dd, $J = 1.8, 8.7$ Hz, H7), 7.84 (2H, m, H5, H8), 8.18 (1H, d, $J = 9.0$ Hz, H4), 8.43 (1H, br d, $J = 9.0$ Hz, H3), 8.62 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$); δ : 25.1 ($COCH_3$), 71.1 (CH_2), 114.8 (C3), 115.1 (C6'), 124.4 (C4a), 126.0 (C5), 126.3 (C2'), 126.6 (C4'), 127.8 (C8), 128.1 (C5'), 129.2 (C7), 130.4 (C3'), 133.2 (C6), 138.9 (C4), 146.5 (C8a), 151.4 (C2), 153.0 (C1'), 169.3 (C=O). m/z (EI): 364 (M^+ [^{37}Cl , ^{37}Cl], 4%), 363 (8), 362 (M^+ [^{35}Cl , ^{37}Cl], 14), 361 (15), 360 (M^+ [^{35}Cl , ^{35}Cl], 20), 321 ([^{37}Cl , ^{37}Cl], 7), 320 (15), 319 ([^{35}Cl , ^{37}Cl], 25), 318 (15), 317 ([^{35}Cl , ^{35}Cl], 40), 284 ([^{37}Cl], 25), 283 (60), 282 ([^{35}Cl], 35), 281 (60), 280 (25), 279 (100), 199 (40), 157 (80).

***N*-{6-[(2,3-Dimethylphenoxy)methyl]quinolin-2-yl}acetamide (82)**

Using General Procedure 9, **69** (200 mg, 0.72 mmol), 2,3-dimethylphenol (97 mg, 0.79 mmol), K_2CO_3 (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 7 h. After work up with

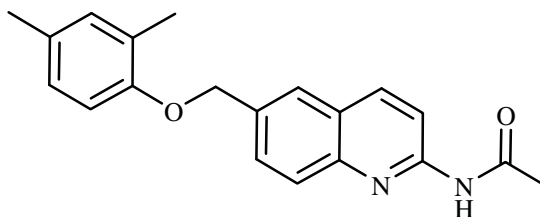


chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a cream powder, mp 170-175 °C (115 mg, 50%). Analysis found: C, 75.01; H, 6.40; N, 8.70. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74%. IR (DCM): ν/cm^{-1} : 3405, 3050, 1702, 1601, 1581 and 1523. 1H NMR (300 MHz, $CDCl_3$); δ : 2.25 (3H, s, $COCH_3$),

2.28 (3H, s, PhCH₃), 2.31 (3H, s, PhCH₃), 5.22 (2H, s, CH₂), 6.81-6.83 (2H, m, H4', H6'), 7.06 (1H, t, *J* = 7.8 Hz, H5'), 7.75 (1H, dd, *J* = 1.8, 9.0 Hz, H7), 7.84 (1H, d, *J* = 9.0 Hz, H8), 7.85 (1H, br s, H5), 8.18 (2H, br d, *J* = 8.4 Hz, H4, NH), 8.42 (1H, br d, *J* = 8.4 Hz, H3). ¹³C NMR (75 MHz, CDCl₃); δ: 12.0 (C2'CH₃), 20.3 (C3'CH₃), 24.9 (COCH₃), 70.0 (CH₂), 109.6 (C6'), 114.9 (C3), 122.9 (C4'), 125.7 (C4a), 125.8 (C2'), 126.0 (C5), 126.2 (C5'), 127.6 (C8), 129.5 (C7), 134.8 (C6), 138.3 (C3'), 138.9 (C4), 146.1 (C8a), 151.5 (C2), 156.7 (C1'), 169.6 (C=O). *m/z* (EI): 320 (M⁺, 1%), 199 (70), 157 (100).

N-{6-[(2,4-Dimethylphenoxy)methyl]quinolin-2-yl}acetamide (83)

Using General Procedure 9, **69** (200 mg, 0.72 mmol), 2,4-dimethylphenol (97 mg, 0.79 mmol), K₂CO₃ (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 7 h. After work up with chloroform:isopropanol (3:1 mix) the crude

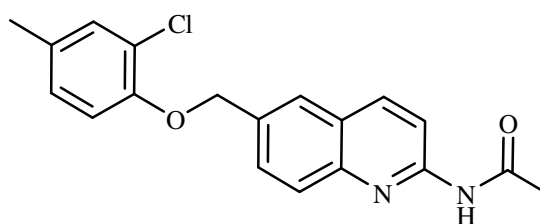


product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a cream powder, mp 101-105 °C (137 mg, 60%). Analysis found: C, 75.01; H, 6.40; N, 8.61. C₂₀H₂₀N₂O₂ requires C, 74.98; H, 6.29; N, 8.74%. IR (DCM): ν/cm⁻¹: 3404, 3052, 1702, 1601 and 1578. ¹H NMR (300 MHz, CDCl₃); δ: 2.26 (3H, s, COCH₃), 2.28 (3H, s, PhCH₃), 2.31 (3H, s, PhCH₃), 5.22 (2H, s, CH₂), 6.83 (1H, d, *J* = 8.4 Hz, H6'), 6.97 (1H, br d, *J* = 8.4 Hz, H5'), 7.01 (1H, br s, H3'), 7.75 (1H, br dd, *J* = 1.5, 8.4 Hz, H7), 7.84 (1H, d, *J* = 8.4 Hz, H8), 7.85 (1H, br s, H5), 8.19 (1H, d, *J* = 8.4 Hz, H4), 8.43 (2H, br d, *J* = 8.4 Hz, H3, NH). ¹³C NMR (75 MHz, CDCl₃); δ: 16.6 (C2'CH₃), 20.7 (C3'CH₃), 25.0 (COCH₃), 70.0 (CH₂), 111.9 (C6'), 115.0 (C3), 125.8 (C4a), 125.9 (C2'), 126.3 (C5)[†], 127.1 (C5')[†], 127.3 (C8), 129.7 (C7), 130.4 (C4'), 132.0 (C3'), 135.1 (C6), 139.2 (C4), 146.0 (C8a), 151.6 (C2), 154.9 (C1'), 169.9 (C=O). *m/z* (EI): 320 (M⁺, 1%), 199 (70), 157 (100).

[†]Assignments may be reversed.

N-{6-[(2-Chloro-4-methylphenoxy)methyl]quinolin-2-yl}acetamide (84)

Using General Procedure 9, **69** (200 mg, 0.72 mmol), 2-chloro-4-methylphenol (93 μL, 0.79 mmol), K₂CO₃ (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 7 h. After work up with chloroform:isopropanol (3:1 mix)

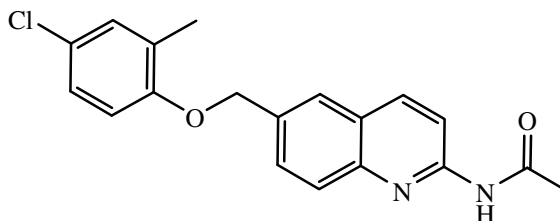


the crude product was recrystallised from ethanol:water to afford the title compound as white

crystals, mp 144-147 °C (230 mg, 94%). Analysis found: C, 66.84; H, 5.22; N, 8.21. $C_{19}H_{17}N_2O_2Cl$ requires C, 66.96; H, 5.03; N, 8.22%. IR (DCM): ν/cm^{-1} : 3400, 3054, 1703 and 1602. 1H NMR (300 MHz, $CDCl_3$); δ : 2.28 (1H, s, CH_3), 2.29 (1H, s, CH_3), 5.28 (1H, s, CH_2), 6.90 (1H, d, $J = 8.7$ Hz, $H6'$), 7.00 (1H, dd, $J = 0.9, 8.7$ Hz, $H5'$), 7.23 (1H, d, $J = 0.9$ Hz, $H3'$), 7.76 (1H, dd, $J = 2.1, 8.7$ Hz, $H7$), 7.83 (1H, d, $J = 8.7$ Hz, $H8$), 7.86 (1H, br d, $J = 2.1$ Hz, $H5$), 8.11 (1H, br s, NH), 8.18 (1H, d, $J = 9.0$ Hz, $H4$), 8.40 (1H, br d, $J = 9.0$ Hz, $H3$). ^{13}C NMR (75 MHz, $CDCl_3$); δ : 20.5 (CH_3), 25.0 ($COCH_3$), 70.9 (CH_2), 114.5 ($C6'$), 114.9 ($C3$), 123.1 ($C4'$), 125.9 ($C8$), 126.2 ($C4a$), 127.7 ($C5$), 128.3 ($C5'$), 129.4 ($C7$), 131.0 ($C3'$), 132.0 ($C2'$), 133.9 ($C6$), 139.0 ($C4$), 146.2 ($C8a$), 151.5 ($C2$), 152.0 ($C1'$), 169.6 ($C=O$). m/z (EI): 340 (M^+ [^{35}Cl], < 1%), 199 (75), 157 (100).

***N*-{6-[(4-Chloro-2-methylphenoxy)methyl]quinolin-2-yl}acetamide (85)**

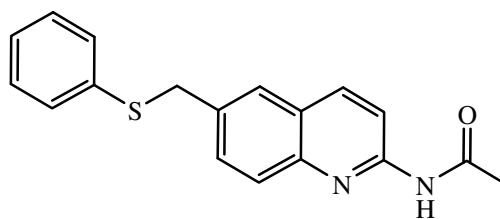
Using General Procedure 9, **69** (200 mg, 0.72 mmol), 4-chloro-2-methylphenol (112 mg, 0.79 mmol), K_2CO_3 (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 7 h. After work up with chloroform:isopropanol



(3:1 mix) the crude product was recrystallised from ethanol:water to afford the title compound as a pale yellow powder, mp 158-161 °C (202 mg, 82%). Analysis found: C, 65.21, H, 5.29, N, 7.97. $C_{19}H_{17}N_2O_2Cl \cdot 0.5H_2O$ requires C, 65.24; H, 5.19; N, 8.01%. IR (DCM): ν/cm^{-1} : 3403, 3081, 1702 and 1600. 1H NMR (300 MHz, $CDCl_3$); δ : 2.27 (1H, s, CH_3), 2.29 (1H, s, CH_3), 5.21 (1H, s, CH_2), 6.83 (1H, d, $J = 8.7$ Hz, $H6'$), 7.10 (1H, dd, $J = 3.0, 8.7$ Hz, $H5'$), 7.16 (1H, d, $J = 3.0$ Hz, $H3'$), 7.72 (1H, dd, $J = 2.1, 8.7$ Hz, $H7$), 7.82 (1H, br s, $H5$), 7.84 (1H, d, $J = 8.7$ Hz, $H8$), 8.18 (1H, d, $J = 9.0$ Hz, $H4$), 8.20 (1H, br s, NH), 8.43 (1H, br d, $J = 9.0$ Hz, $H3$). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 15.8 (CH_3), 24.9 (CH_3), 69.9 (CH_2), 112.6 ($C6'$), 114.5 ($C3$), 125.5 ($C2'$), 125.6 ($C5$), 125.6 ($C4a$), 126.4 ($C5'$), 127.7 ($C8$), 129.0 ($C4'$), 129.2 ($C7$), 130.9 ($C3'$), 134.0 ($C6$), 138.6 ($C4$), 146.2 ($C8a$), 151.1 ($C2$), 155.3 ($C1'$), 169.1 ($C=O$). m/z (EI): 340 (M^+ [^{35}Cl], < 1%), 199 (70), 157 (100).

***N*-{6-[(Phenylthio)methyl]quinolin-2-yl}acetamide (86)¹³⁰**

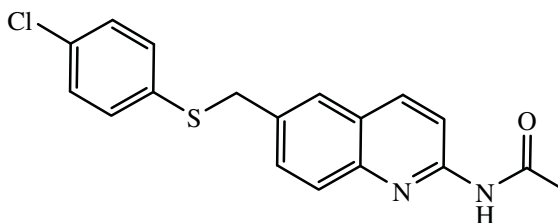
Using General Procedure 9, **69** (200 mg, 0.72 mmol), thiophenol (81 μ L, 0.79 mmol), K_2CO_3 (300 mg, 2.16 mmol) and acetonitrile (8 mL) were heated for 6 h. After work up with chloroform:isopropanol (3:1 mix) the crude product



was recrystallised from ethanol:water to afford the title compound as a low melting yellow solid, (183 mg, 83%). Analysis found: C, 68.24; H, 5.25; N, 8.58. $C_{18}H_{16}N_2OS \cdot 0.5H_2O$ requires C, 68.11; H, 5.40; N, 8.83%. IR (nujol mull): ν/cm^{-1} : 3417, 3293, 3186, 1673, 1597, 1580 and 1537. 1H NMR (600 MHz, $CDCl_3$): δ : 2.22 (3H, s, CH_3), 4.24 (2H, s, CH_2), 7.22 (1H, t, $J = 7.8$ Hz, $H_{4'}$), 7.29 (2H, t, $J = 7.8$ Hz, $H(3'/5')$), 7.49 (2H, d, $J = 7.8$ Hz, $H(2'/6')$), 7.57 (1H, d, $J = 1.8$ Hz, H_5), 7.63 (1H, dd, $J = 1.8, 9.0$ Hz, H_7), 7.74 (1H, d, $J = 9.0$ Hz, H_8), 8.04 (1H, d, $J = 9.0$ Hz, H_4), 8.37 (1H, d, $J = 9.0$ Hz, H_3), 8.53 (1H, br s, NH). $\nu^{13}C$ NMR (150 MHz, $CDCl_3$): δ : 24.8 ($COCH_3$), 39.2 (CH_2), 114.4 (C3), 126.0 (C4a), 126.7 (C5), 127.0 (C4'), 127.1 (C8), 128.9 (C2'/6'), 129.0 (C3'/5'), 131.1 (C7), 134.5 (C6), 137.0 (C1'), 138.3 (C4), 145.7 (C8a), 150.9 (C2), 169.0 (C=O). m/z (EI): 308 (M^+ , 5%), 199 (50), 157 (100).

***N*-{6-[(4-Chlorophenylthio)methyl]quinolin-2-yl}acetamide (87)¹³⁰**

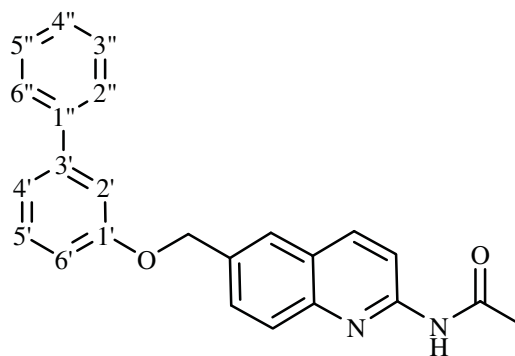
Using General Procedure 9, **69** (200 mg, 0.72 mmol), 4-chlorothiophenol (114 mg, 0.79 mmol), K_2CO_3 (300 mg, 2.16 mmol) and acetonitrile (8 mL) were heated for 7 h. After work up with chloroform:isopropanol (3:1 mix)



the crude product was recrystallised from ethanol:water to afford the title compound as orange crystals, mp 184-188 $^{\circ}C$ (240 mg, 97%). HRMS found: 342.0892. $C_{18}H_{15}^{35}ClN_2OS$ requires 342.0594. IR (nujol mull): ν/cm^{-1} : 3436, 3234, 1666, 1595 and 1531. 1H NMR (300 MHz, $CDCl_3$): δ : 2.26 (3H, s, $COCH_3$), 4.22 (2H, s, CH_2), 7.20 (4H, br s, $H(2'/6')$, $H(3'/5')$), 7.57 (1H, br d, $J = 2.1$ Hz, H_5), 7.62 (1H, dd, $J = 2.1, 8.7$ Hz, H_7), 7.75 (1H, d, $J = 8.7$ Hz, H_8), 8.08 (1H, d, $J = 9.0$ Hz, H_4), 8.20 (1H, br s, NH), 8.38 (1H, br d, $J = 9.0$ Hz, H_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ : 25.1 ($COCH_3$), 39.6 (CH_2), 114.8 (C3), 126.2 (C4a), 127.3 (C4'), 127.8 (C8), 129.2 (C2'/C6'), 129.5 (C5), 131.2 (C7), 132.0 (C3'/C5'), 133.1 (C6), 134.2 (C1'), 138.6 (C4), 145.9 (C8a), 151.3 (C2), 169.4 (C=O). m/z (EI): 344 (M^+ [^{37}Cl], 2%), 342 (M^+ [^{35}Cl], 6), 199 (80), 157 (100).

***N*-{6-[(3-Phenylphenoxy)methyl]quinolin-2-yl}acetamide (88)**

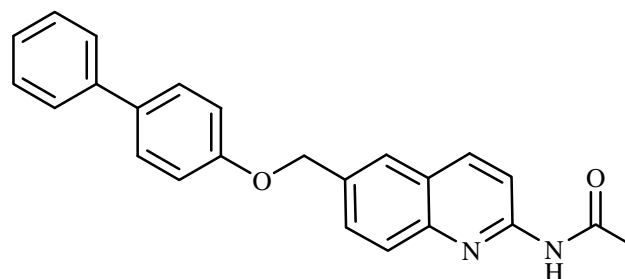
Using General Procedure 9, **69** (165 mg, 0.59 mmol), 3-phenylphenol (as a mixture with 4-phenylphenol, 85% purity) (121 mg, 0.71 mmol), K₂CO₃ (245 mg, 1.77 mmol) and acetonitrile (10 mL) were heated for 8 h. After work up with chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel



eluting with DCM:ethanol (49:1) to afford the title compound as a white solid as a 9:1 mixture with *N*-{6-[(4-phenylphenoxy)methyl]quinolin-2-yl}acetamide **89** (172 mg combined yield, 71% **88**). A small sample was recrystallised from ethanol for the purpose of obtaining a microanalysis. HRMS found: 368.1525; C₂₄H₂₀N₂O₂ requires 368.1525. Analysis found: C, 74.66; H, 5.46; N, 7.23. C₂₄H₂₀N₂O₂·H₂O requires C, 74.59; H, 5.74; N, 7.25%. IR (nujol mull): ν/cm⁻¹: 3230, 1673, 1602 and 1581. ¹H NMR (600 MHz, d₆-DMSO); δ: 2.14 (3H, s, CH₃), 5.35 (2H, s, CH₂), 7.05 (1H, ddd, *J* = 0.6, 1.8, 8.4 Hz, H6'), 7.24 (1H, ddd, *J* = 0.6, 1.8, 7.8 Hz, H4'), 7.32 (1H, dd, *J* = 1.8, Hz, H2'), 7.38 (2H, m, H5', H4''), 7.50 (2H, dd, *J* = 7.8 Hz, H(3''/5'')), 7.66 (2H, dd, *J* = 7.8 Hz, H(2''/6'')), 7.79 (1H, dd, *J* = 1.8, 8.4 Hz, H7), 7.81 (1H, d, *J* = 8.4 Hz, H8), 7.99 (1H, d, *J* = 1.8 Hz, H5), 8.28 (1H, d, *J* = 9.0 Hz, H3), 8.34 (1H, d, *J* = 9.0 Hz, H4), 10.80 (1H, br s, NH). ¹³C NMR (150 MHz, d₆-DMSO); δ: 24.0 (COCH₃), 69.1 (CH₂), 113.2 (C2'), 114.0 (C6'), 114.5 (C3), 119.3 (C4'), 125.3 (C4a), 126.2 (C5), 126.8 (C2''/6''), 127.1 (C8), 127.6 (C4''), 128.9 (C3''/5''), 129.7 (C7), 130.0 (C5'), 133.6 (C6), 138.2 (C4), 140.0 (C3'), 141.7 (C1''), 146.0 (C8a), 151.8 (C2), 158.8 (C1'), 169.8 (C=O). *m/z* (EI): 368 (M⁺, 2%), 199 (70), 157 (100).

***N*-{6-[(4-Phenylphenoxy)methyl]quinolin-2-yl}acetamide (89)**

Using General Procedure 9, **69** (170 mg, 0.61 mmol), 4-phenylphenol (114 mg, 0.67 mmol), K₂CO₃ (253 mg, 1.83 mmol) and acetonitrile (20 mL) were heated for 8 h. After work up with chloroform:isopropanol (3:1 mix) the

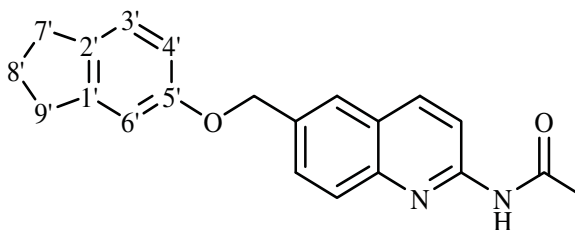


crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a white solid, mp 224-227 °C (185 mg, 82%). HRMS found: 368.1525; C₂₄H₂₀N₂O₂ requires 368.1525. Analysis found: C, 78.23; H, 5.56; N, 7.59.

$C_{24}H_{20}N_2O_2$ requires C, 78.24; H, 5.47; N, 7.60%. IR (DCM): ν/cm^{-1} : 3404, 3061, 1702, 1602, 1582 and 1518. 1H NMR (600 MHz, $CDCl_3$); δ : 2.26 (3H, s, CH_3), 5.26 (2H, s, CH_2), 7.05 (2H, m, H(2'/6')), 7.31 (1H, dd, $J = 1.2, 7.2$ Hz, H4''), 7.41 (2H, dd, $J = 7.2$, Hz, H(3''/5'')), 7.55 (4H, m, H(3'/5'), H(2''/6'')), 7.75 (1H, dd, $J = 1.8, 9.0$ Hz, H7), 7.84 (1H, d, $J = 9.0$ Hz, H8), 7.99 (1H, br d, $J = 1.8$ Hz, H5), 8.18 (1H, d, $J = 9.0$ Hz, H4), 8.20 (1H, br s, NH), 8.41 (1H, d, $J = 9.0$ Hz, H3). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 24.9 ($COCH_3$), 69.8 (CH_2), 114.4 (C3), 115.2 (C2'/6'), 126.0 (C5), 126.2 (C4a), 126.7 (C2''/6''), 126.8 (C4''), 127.8 (C8), 128.2 (C3'/5'), 128.7 (C3''/5''), 129.4 (C7), 134.0 (C6), 134.3 (C4'), 138.6 (C4), 140.7 (C1''), 146.7 (C8a), 151.0 (C2), 158.2 (C1'), 168.9 (C=O). m/z (EI): 368 (M^+ , 10%), 199 (100), 157 (50).

***N*-{6-[(2,3-Dihydro-1*H*-inden-5-yl)oxy]phenoxy}methylquinolin-2-yl}acetamide (90)**

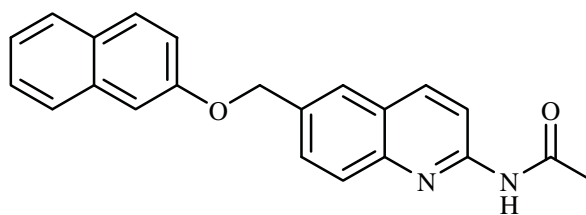
Using General Procedure 9, **69** (200 mg, 0.72 mmol), 5-indanol (106 mg, 0.79 mmol), K_2CO_3 (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 16 h. After work up with chloroform:isopropanol (3:1 mix)



the crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a yellow solid, mp 144-148 °C (88 mg, 38%). Analysis found: C, 74.34; H, 6.41; N, 8.26. $C_{21}H_{20}N_2O_2 \cdot 0.33H_2O$ requires C, 74.55; H, 6.15; N, 8.28%. IR (DCM): ν/cm^{-1} : 3404, 1702, 1582 and 1524. 1H NMR (600 MHz, $CDCl_3$); δ : 2.07 (2H, qn, $J = 7.8$ Hz, H8'), 2.22 (3H, s, $COCH_3$), 2.83-2.89 (4H, 2 x t, $J = 7.8$ Hz, H7', H9'), 5.18 (2H, s, CH_2), 6.79 (1H, dd, $J = 2.1, 8.1$ Hz, H4'), 6.89 (1H, d, $J = 2.1$ Hz, H6'), 7.11 (1H, d, $J = 8.1$ Hz, H3'), 7.71 (1H, dd, $J = 1.8, 9.0$ Hz, H7), 7.82 (1H, d, $J = 9.0$ Hz, H8), 7.83 (1H, br s, H5), 8.15 (1H, d, $J = 9.0$ Hz, H4), 8.41 (1H, br d, $J = 9.0$ Hz, H3), 8.79 (1H, br s, NH). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 24.8 ($COCH_3$), 25.8 (C8'), 32.0 (C9'), 33.1 (C7'), 69.9 (CH_2), 111.0 (C6'), 112.9 (C4'), 114.5 (C3), 124.8 (C3'), 125.9 (C5), 126.1 (C4a), 127.5 (C8), 129.5 (C7), 134.4 (C6), 136.7 (C2'), 138.7 (C4), 145.8 (C1'), 146.1 (C8a), 151.2 (C2), 157.6 (C5'), 169.2 (C=O). m/z (EI): 332 (M^+ , 10%), 199 (75), 157 (100).

***N*-{6-[(Naphthalen-2-yloxy)methyl]quinolin-2-yl}acetamide (91)**

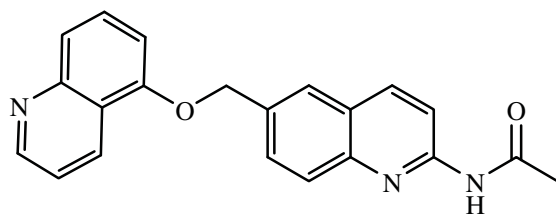
Using General Procedure 9, **69** (160 mg, 0.57 mmol), 2-naphthol (91 mg, 0.63 mmol), K₂CO₃ (240 mg, 1.70 mmol) and acetonitrile (10 mL) were heated for 7 h. After work up with chloroform:isopropanol (3:1 mix) the



crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a white solid, mp 180-185 °C (80 mg, 41%). HRMS found: 342.1367; C₂₂H₁₈N₂O₂ requires 342.1368. IR (DCM): ν/cm^{-1} : 3405, 3054, 1702, 1630, 1600 and 1581. ¹H NMR (600MHz, d₆-DMSO); δ : 2.14 (3H, s, CH₃), 5.38 (2H, s, CH₂), 7.27 (1H, dd, *J* = 2.4, 9.0 Hz, H3'), 7.34 (1H, ddd, *J* = 1.2, 6.6, 8.4 Hz, H6'), 7.45 (1H, ddd, *J* = 1.2, 6.6, 8.4 Hz, H7'), 7.47 (1H, d, *J* = 2.4 Hz, H1'), 7.79-7.86 (5H, m, H7, H8, H4', H5', H8'), 8.02 (1H, br s, H5), 8.29 (1H, d, *J* = 9.0 Hz, H3), 8.34 (1H, d, *J* = 9.0 Hz, H4), 10.81 (1H, br s, NH). ¹³C NMR (150 MHz, d₆-DMSO); δ : 24.0 (COCH₃), 69.1 (CH₂), 107.4 (C1'), 114.4 (C3), 118.8 (C3'), 123.7 (C6'), 125.3 (C4a), 126.4 (C5), 126.4 (C7'), 126.7 (C8'), 127.1 (C4'), 127.5 (C8), 128.6 (C4a'), 129.4 (C7), 129.8 (C5'), 1333.5 (C8a'), 134.2 (C6), 138.2 (C4), 146.0 (C8a), 151.9 (C2), 156.2 (C2'), 169.9 (C=O). *m/z* (EI): 342 (M⁺, 5%), 199 (90), 157 (100).

***N*-{6-[(Quinolin-5-yloxy)methyl]quinolin-2-yl}acetamide (92)**

Using General Procedure 9, **69** (200 mg, 0.72 mmol), 5-hydroxyquinoline (115 mg, 0.79 mmol), K₂CO₃ (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 7 h. After work up with chloroform:isopropanol (3:1 mix)

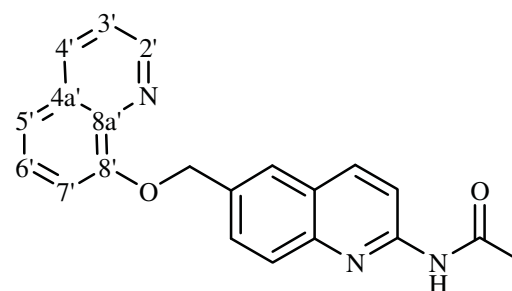


the crude product was chromatographed over silica gel eluting with DCM:ethanol (19:1) to afford the title compound as a pale yellow solid, mp 210-216 °C (100 mg, 40%). HRMS found: 343.1320; C₂₁H₁₇N₅O₂ requires 343.1321. IR (nujol mull): ν/cm^{-1} : 3251, 3193, 1695, 1602 and 1538. ¹H NMR (300 MHz, CDCl₃); δ : 2.29 (3H, s, CH₃), 5.42 (2H, s, CH₂), 7.00 (1H, d, *J* = 7.5 Hz, H6'), 7.42 (1H, dd, *J* = 4.2, 8.7 Hz, H3'), 7.62 (1H, dd, *J* = 7.5, 8.4 Hz, H7'), 7.75 (1H, d, *J* = 8.4 Hz, H8'), 7.81 (1H, dd, *J* = 1.8, 8.7 Hz, H7), 7.87 (1H, d, *J* = 8.7 Hz, H8), 7.90 (1H, br s, H5), 8.13 (1H, br s, NH), 8.21 (1H, d, *J* = 9.0 Hz, H4), 8.45 (1H, br d, *J* = 9.0 Hz, H3), 8.68 (1H, br d, *J* = 8.7 Hz, H4'), 8.94 (1H, dd, *J* = 1.8, 4.2 Hz, H2'). ¹³C NMR

(75 MHz, d_6 -DMSO); δ : 24.1 (COCH₃), 69.6 (CH₂), 106.3 (C6'), 114.5 (C3), 120.2 (C4a'), 120.8 (C3'), 121.3 (C4a), 125.3 (C8'), 126.3 (C5), 127.3 (C8), 129.6 (C7), 129.6 (C7'), 130.3 (C4'), 133.3 (C6), 138.3 (C4), 146.1 (C8a), 148.6 (C8a'), 150.8 (C2'), 152.0 (C2), 153.6 (C5'), 169.9 (C=O). m/z (EI): 343 (M⁺, 5%), 199 (80), 157 (100).

***N*-{6-[(Quinolin-8-yloxy)methyl]quinolin-2-yl}acetamide (93)**

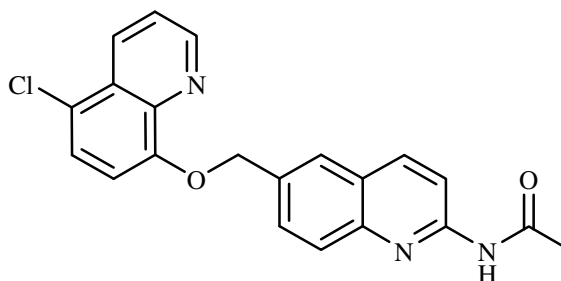
Using General Procedure 9, **69** (200 mg, 0.72 mmol), 8-hydroxyquinoline (118 mg, 0.81 mmol), K₂CO₃ (300 mg, 2.16 mmol) and acetonitrile (5 mL) were heated for 4 h. After work up with chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel



eluting with DCM:ethanol (49:1) to afford the title compound as a cream solid, mp 180-184 °C (61 mg, 25%). HRMS found: 343.1320; C₂₁H₁₇N₃O₂ requires 343.1321. IR (DCM): ν/cm^{-1} : 3405, 3051, 1702, 1601 and 1580. ¹H NMR (600 MHz, CDCl₃); δ : 2.24 (3H, s, CH₃), 5.59 (2H, s, CH₂), 7.08 (1H, dd, $J = 1.8, 8.4$ Hz, H7'), 7.37 (1H, dd, $J = 8.4$ Hz, H6'), 7.40 (1H, dd, $J = 1.8, 8.4$ Hz, H5'), 7.45 (1H, dd, $J = 1.8, 4.2$ Hz, H3'), 7.83 (2H, br s, H7, H8), 7.93 (1H, br s, H5), 8.14 (2H, m, H4, H4'), 8.38 (2H, br s, H3, NH), 8.99 (1H, dd $J = 1.8, 4.2$ Hz, H2'). ¹³C NMR (150 MHz, CDCl₃); δ : 24.9 (COCH₃), 70.5 (CH₂), 110.0 (C7'), 114.4 (C3), 120.2 (C5'), 121.7 (C3'), 125.8 (C5), 126.2 (C4a), 126.6 (C6'), 127.8 (C7), 129.2 (C8), 129.6 (C4a'), 133.9 (C6), 135.9 (C4'), 138.6 (C4), 140.5 (C8a'), 146.2 (C8a), 149.5 (C2'), 151.0 (C2), 154.2 (C8'), 169.9 (C=O). m/z (EI): 343 (M⁺, 20%), 199 (50), 157 (100).

***N*-{6-[(5-Chloroquinolin-8-yloxy)methyl]quinolin-2-yl}acetamide (94)**

Using General Procedure 9, **69** (200 mg, 0.72 mmol), 5-chloro-8-hydroxyquinoline (142 mg, 0.79 mmol), K₂CO₃ (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 9 h. After work up with chloroform:isopropanol (3:1 mix) the crude product was

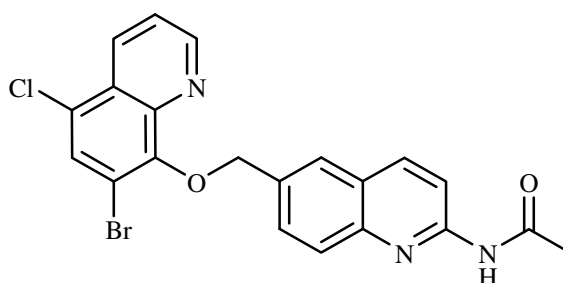


chromatographed over silica gel eluting with DCM:ethanol (49:1) to afford the title compound as a cream powder, mp 183-185 °C (143 mg, 53%). HRMS found: 377.0929; C₂₁H₁₆³⁵ClN₃O₂ requires 377.0931. IR (nujol mull): ν/cm^{-1} : 3475, 3340, 3193, 1673, 1600

and 1585. ^1H NMR (300 MHz, CDCl_3); δ : 2.27 (3H, s, CH_3), 5.58 (2H, s, CH_2), 6.99 (1H, d, $J = 8.4$ Hz, $\text{H}7'$), 7.45 (1H, d, $J = 8.4$ Hz, $\text{H}6'$), 7.59 (1H, dd, $J = 4.2, 8.7$ Hz, $\text{H}3'$), 7.83 (2H, br s, $\text{H}7, \text{H}8$), 7.93 (1H, br s, $\text{H}5$), 8.18 (1H, d, $J = 9.0$ Hz, $\text{H}4$), 8.43 (1H, br d, $J = 9.0$ Hz, $\text{H}3$), 8.56 (1H, dd, $J = 1.8, 8.7$ Hz, $\text{H}4'$), 8.76 (1H, br s, NH), 9.05 (1H, dd $J = 1.8, 4.2$ Hz, $\text{H}2'$). ^{13}C NMR (150 MHz, CDCl_3); δ : 24.9 (COCH_3), 70.7 (CH_2), 110.0 ($\text{C}7'$), 114.5 ($\text{C}3$), 122.4 ($\text{C}3'$), 122.8 ($\text{C}5'$), 125.9 ($\text{C}5$), 126.2 ($\text{C}4\text{a}$), 126.3 ($\text{C}6'$), 127.2 ($\text{C}4\text{a}'$), 127.9 ($\text{C}8$), 129.0 ($\text{C}7$), 133.0 ($\text{C}4'$), 133.4 ($\text{C}6$), 138.6 ($\text{C}4$), 141.0 ($\text{C}8\text{a}'$), 146.3 ($\text{C}8\text{a}$), 149.9 ($\text{C}2'$), 151.1 ($\text{C}2$), 153.2 ($\text{C}8'$), 169.0 ($\text{C}=\text{O}$). m/z (EI): 379 (M^+ , [^{37}Cl], 3%), 377 (M^+ , [^{35}Cl], 10), 199 (70), 157 (100).

***N*-{6-[(7-Bromo-5-chloroquinolin-8-yloxy)methyl]quinolin-2-yl}acetamide (95)**

Using General Procedure 9, **69** (200 mg, 0.72 mmol), 7-bromo-5-chloro-8-hydroxyquinoline (204 mg, 0.79 mmol), K_2CO_3 (300 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 8 h. After work up with chloroform:isopropanol (3:1 mix) the crude



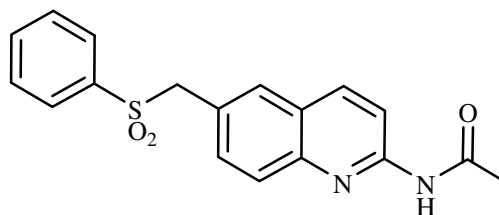
product was chromatographed over silica gel eluting with DCM:ethyl acetate (2:3) to afford the title compound as a cream solid, mp 200-203 °C (265 mg, 81%). HRMS found: 455.0036; $\text{C}_{21}\text{H}_{15}^{79}\text{Br}^{35}\text{ClN}_3\text{O}_2$ requires 455.0036. IR (nujol mull): ν/cm^{-1} : 3237, 3199, 3064, 1660, 1606 and 1579. ^1H NMR (300 MHz, CDCl_3); δ : 2.35 (3H, s, CH_3), 5.63 (2H, s, CH_2), 7.59 (1H, dd, $J = 4.2, 8.7$ Hz, $\text{H}3'$), 7.82 (1H, s, $\text{H}6'$), 7.83 (2H, br d, $J = 8.7$ Hz, $\text{H}7$), 8.09 (1H, d, $J = 8.7$ Hz, $\text{H}8$), 8.10 (1H, br s, $\text{H}5$), 8.32 (1H, d, $J = 9.0$ Hz, $\text{H}4$), 8.51 (1H, br d, $J = 9.0$ Hz, $\text{H}3$), 8.56 (1H, dd, $J = 1.8, 8.7$ Hz, $\text{H}4'$), 9.04 (1H, dd $J = 1.8, 4.2$ Hz, $\text{H}2'$), 9.70 (1H, br s, NH). ^{13}C NMR (75 MHz, CDCl_3); δ : 25.1 (COCH_3), 76.3 (CH_2), 114.6 ($\text{C}3$), 116.5 ($\text{C}7'$), 122.5 ($\text{C}3'$), 126.2 ($\text{C}5'$), 126.9 ($\text{C}4\text{a}$) † , 127.0 ($\text{C}4\text{a}'$) † , 127.4 ($\text{C}5$), 127.5 ($\text{C}8$), 130.4 ($\text{C}6'$), 131.0 ($\text{C}7$), 133.7 ($\text{C}4'$), 134.3 ($\text{C}6$), 139.1 ($\text{C}4$), 143.8 ($\text{C}8\text{a}'$), 146.5 ($\text{C}8\text{a}$), 151.0 ($\text{C}2'$), 151.4 ($\text{C}2$), 151.7 ($\text{C}8'$), 169.4 ($\text{C}=\text{O}$). m/z (EI): 459 (M^+ , [^{37}Cl , ^{81}Br], < 0.5%), 457 (M^+ , [^{35}Cl , ^{81}Br and ^{37}Cl , ^{79}Br], 2), 455 (M^+ , [^{35}Cl , ^{79}Br], 2), 259 (25), 199 (70), 157 (100).

† Assignments may be reversed.

7.2.3 Oxidation of *N*-[6-(Phenylthiomethyl)quinolin-2-yl]acetamides

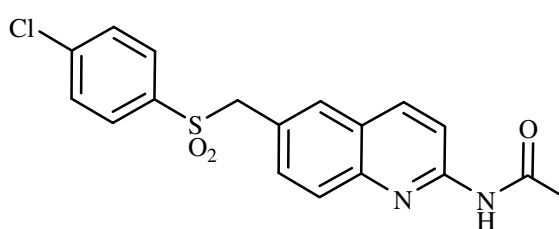
N-{6-[(Phenylsulfonyl)methyl]quinolin-2-yl}acetamide (**96**)

A solution of **86** (110 mg, 0.36 mmol) in methanol (10 mL) was treated with a solution of Oxone[®] (241 mg, 0.39 mmol) in water (10 mL) and stirred at room temperature for 4 h. The reaction mixture was extracted with chloroform:isopropanol (3:1 mix) and washed with water. The organic phase was dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a white solid, mp 232-235 °C (96 mg, 78%). HRMS found: 340.0884; C₁₈H₁₆N₂O₃S requires 340.0882. IR (DCM): ν/cm⁻¹: 3354, 1689, 1675, 1599, 1580 and 1531. ¹H NMR (600 MHz, CDCl₃); δ: 2.25 (3H, s, COCH₃), 4.47 (2H, s, CH₂), 7.37 (1H, dd, *J* = 1.8, 8.4 Hz, H7), 7.40 (2H, t, *J* = 7.8 Hz, H(3'/5')), 7.49 (1H, d, *J* = 1.8 Hz, H5), 7.59 (1H, t, *J* = 7.8 Hz, H4'), 7.65 (2H, d, *J* = 7.8 Hz, H(2'/6')), 7.69 (1H, d, *J* = 8.4 Hz, H8), 8.03 (1H, d, *J* = 8.0 Hz, H4), 8.40 (1H, br d, *J* = 8.0 Hz, H3), 8.46 (1H, br s, NH). ¹³C NMR (150 MHz, CDCl₃); δ: 24.8 (COCH₃), 62.6 (CH₂), 114.8 (C3), 124.9 (C6), 125.9 (C4a), 127.6 (C8), 128.6 (C2'/6'), 129.0 (C3'/5'), 130.1 (C5), 132.0 (C7), 133.9 (C4'), 137.7 (C1'), 138.5 (C4), 146.3 (C8a), 151.6 (C2), 169.1 (C=O). *m/z* (EI): 340 (M⁺, 1%), 199 (60), 157 (100).



N-{6-[(4-Chlorophenylsulfonyl)methyl]quinolin-2-yl}acetamide (**97**)

A suspension of **87** (240 mg, 0.70 mmol), in methanol (20 mL) was treated with a solution of Oxone[®] (430 mg, 0.70 mmol) in water (20 mL) and stirred at room temperature for 5 h. The reaction mixture was extracted with chloroform:isopropanol (3:1 mix) and washed with water (x 3). The organic phase was dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (4:1) to afford the title compound as a white powder, mp 215-220 °C (140 mg, 53%). *N*-{6-[(4-Chlorophenylsulfonyl)methyl]quinolin-2-yl}acetamide **98** was also isolated as a white powder, mp 221-225 °C (44 mg, 18%).



N-[6-[(4-Chlorophenylsulfonyl)methyl]quinolin-2-yl]acetamide (**97**): HRMS found: 374.0492; C₁₈H₁₄N₂O₃³⁵ClS requires 374.0492. IR (DCM): ν/cm^{-1} : 3409, 3064, 1702 and 1601. ¹H NMR (300 MHz, CDCl₃); δ : 2.28 (3H, s, COCH₃), 4.47 (2H, s, CH₂), 7.38 (1H, dd, $J = 1.8, 8.7$ Hz, H7), 7.41 (2H, m, H(3'/5')), 7.54 (1H, d, $J = 1.8$ Hz, H5), 7.56 (2H, m, H(2'/6')), 7.72 (1H, d, $J = 8.7$ Hz, H8), 8.08 (1H, d, $J = 9.0$ Hz, H4), 8.10 (1H, br s, NH), 8.43 (1H, br d, $J = 9.0$ Hz, H3). ¹³C NMR (75 MHz, CDCl₃); δ : 24.6 (COCH₃), 62.5 (CH₂), 115.1 (C3), 124.2 (C6), 125.7 (C4a), 127.7 (C8), 129.3 (C2'/6'), 130.0 (C3'/5'), 130.1 (C5), 131.6 (C7), 136.2 (C1'), 138.2 (C4), 140.6 (C4'), 146.5 (C8a), 152.2 (C2), 170.0 (C=O). m/z (EI): 374 (M⁺ [³⁵Cl], 0.5%), 199 (70), 157 (100).

N-[6-[(4-Chlorophenylsulfinyl)methyl]quinolin-2-yl]acetamide (**98**):

Analysis found: C, 60.23; H, 4.42; N, 7.47.

C₁₈H₁₅N₂O₂ClS requires C, 60.25; H, 4.21; N,

7.81%. IR (DCM): ν/cm^{-1} : 3685, 3594, 1700,

1601, 1578 and 1522. ¹H NMR (300 MHz,

CDCl₃); δ : 2.28 (3H, s, COCH₃), 4.18 (2H, s,

CH₂), 7.22 (1H, dd, $J = 1.8, 8.7$ Hz, H7), 7.28 (2H, m, H(3'/5')), 7.39 (1H, m, H(2'/6')), 7.43

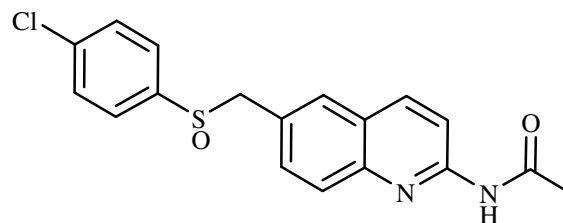
(1H, d, $J = 1.8$ Hz, H5), 7.68 (1H, d, $J = 8.7$ Hz, H8), 8.08 (1H, d, $J = 8.7$ Hz, H4), 8.10 (1H,

br s, NH), 8.41 (1H, br d, $J = 8.7$ Hz, H3). ¹³C NMR (75 MHz, CDCl₃); δ : 23.2 (COCH₃),

61.1 (CH₂), 113.8 (C3), 124.2 (C6), 124.4 (C4a), 124.8 (C2'/6'), 125.9 (C8), 127.8 (C3'/5'),

128.3 (C5), 130.5 (C7), 135.5 (C1'), 136.6 (C4), 140.6 (C4'), 145.1 (C8a), 151.0 (C2), 169.0

(C=O). m/z (EI): 199 (60%), 157 (100).



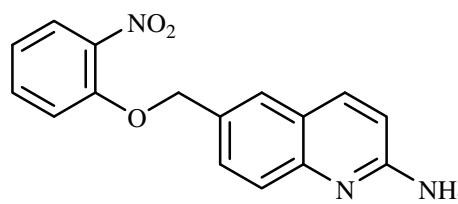
7.2.4 Synthesis of 6-Aryloxymethyl- and 6-Arylthiomethyl-2-Aminoquinolines

General Procedure 11: Synthesis of 6-(Phenoxymethyl)quinolin-2-amines³⁴

The acetamide protected quinoline (1 mol. eq) was stirred with K₂CO₃ (1.0 – 3.0 mol. eq) in methanol at 60 °C for the prescribed length of time. The reaction mixture was allowed to cool, water was added and the resulting precipitate was filtered and washed with water to afford the desired 2-aminoquinoline derivative.

6-[(2-Nitrophenoxy)methyl]quinoline-2-amine (101)

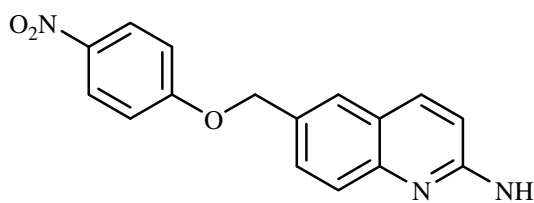
Using General Procedure 11, **99** (270 mg, 0.80 mmol), K_2CO_3 (110 mg, 0.80 mmol) and methanol (15 mL) were heated for 2 h. The work up was carried out with



5 mL of water to give the title compound as a pale orange powder, mp 200-203 °C (180 mg, 76%). HRMS found: 295.0956; $C_{16}H_{13}N_3O_3$ requires 295.0957. Analysis found: C, 64.98; H, 4.58; N, 14.21. $C_{16}H_{13}N_3O_3$ requires C, 65.08; H, 4.44; N, 14.23%. IR (nujol mull): ν/cm^{-1} : 3477, 3310, 1649, 1602, 1581 and 1528. 1H NMR (600MHz, d_6 -DMSO); δ : 5.33 (2H, s, CH_2), 6.47 (2H, br s, NH_2), 6.76 (1H, d, $J = 9.0$ Hz, H3), 7.10 (1H, ddd, $J = 1.2, 7.8$ Hz, H4'), 7.47 (1H, br dd, $J = 7.8$ Hz, H6'), 7.48 (1H, d, $J = 8.4$ Hz, H8), 7.52 (1H, dd, $J = 1.8, 8.4$ Hz, H7), 7.63 (1H, ddd, $J = 1.8, 7.8$ Hz, H5'), 7.68 (1H, d, $J = 1.8$ Hz, H5), 7.85 (1H, dd, $J = 1.8, 7.8$ Hz, H3'), 7.86 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, d_6 -DMSO); δ : 70.7 (CH_2), 112.8 (C3), 115.7 (C6'), 120.7 (C4'), 122.3 (C4a), 124.9 (C3') 125.4 (C8), 126.8 (C5), 128.3 (C6), 128.9 (C7), 134.3 (C5'), 136.9 (C4), 139.9 (C2'), 147.8 (C8a), 150.9 (C1'), 158.5 (C2). m/z (EI): 295 (M^+ , 2%), 157 (100).

6-[(4-Nitrophenoxy)methyl]quinoline-2-amine (102)

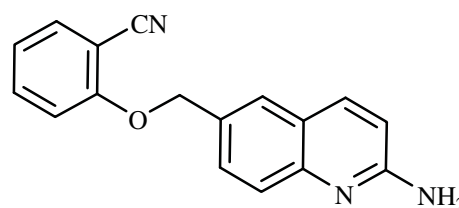
Using General Procedure 11, **100** (110 mg, 0.33 mmol), K_2CO_3 (45 mg, 0.33 mmol) and methanol (6 mL) were heated for 2 h. The work up was carried out with 5 mL of water to give



the crude product. Trituration with chloroform afforded the title compound as a pale orange powder, mp 232-236 °C (50 mg, 52%). HRMS found: 295.0956; $C_{16}H_{13}N_3O_3$ requires 295.0957. IR (nujol mull): ν/cm^{-1} : 3433, 3332, 3156, 1658, 1610, 1593 and 1565. 1H NMR (300MHz, d_6 -DMSO); δ : 5.31 (2H, s, CH_2), 6.49 (2H, br s, NH_2), 6.76 (1H, d, $J = 9.0$ Hz, H3), 7.25 (2H, m, H(2'/6')), 7.46 (1H, d, $J = 8.7$ Hz, H8), 7.55 (1H, dd, $J = 1.8, 8.7$ Hz, H7), 7.72 (1H, d, $J = 1.8$ Hz, H5), 7.89 (1H, d, $J = 9.0$ Hz, H4), 8.21 (2H, m, H(3'/5')). ^{13}C NMR (75 MHz, d_6 -DMSO); δ : 70.4 (CH_2), 112.8 (C3), 115.4 (C2'/6'), 122.3 (C4a), 125.4 (C8), 125.9 (C3'/5'), 127.2 (C5), 128.3 (C6), 129.2 (C7), 136.9 (C4), 140.9 (C4'), 147.9 (C8a), 158.6 (C1'), 163.8 (C2). m/z (EI): 295 (M^+ , 2%), 199 (10), 157 (100).

6-[(2-Cyanophenoxy)methyl]quinoline-2-amine (103)

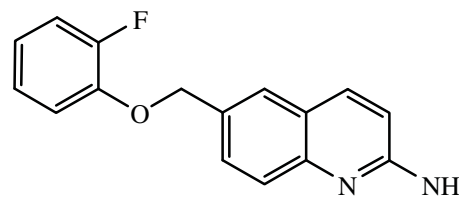
Using General Procedure 11, **74** (138 mg, 0.43 mmol), K_2CO_3 (61 mg, 0.43 mmol) and methanol (10 mL) were heated for 3 h. The work up was carried out with 5 mL of water to give the crude product.



Chromatographic separation over silica gel eluting with DCM:ethyl acetate (17:3) afforded the title compound as cream crystals, mp 215-220 °C (91 mg, 77%). Analysis found: C, 74.10; H, 4.79; N, 15.28. $C_{17}H_{13}N_3O$ requires C, 74.17; H, 4.76; N, 15.28%. IR (nujol mull): ν/cm^{-1} : 3459, 3311, 2220, 1648, 1594 and 1577. 1H NMR (300 MHz, $CDCl_3$); δ : 4.92 (2H, br s, NH_2), 5.31 (2H, s, CH_2), 6.76 (1H, d, $J = 9.0$ Hz, H3), 7.00-7.06 (2H, m, $H_{4'}$, $H_{6'}$), 7.50 (1H, ddd, $J = 1.8, 7.5$ Hz, $H_{5'}$), 7.59-7.53 (2H, m, $H_{3'}$, H7), 7.70 (1H, d, $J = 8.4$ Hz, H8), 7.73 (1H, br s, H5), 7.92 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (75 MHz, d_6 -DMSO); δ 70.3 (CH_2), 100.9 ($C_{2'}$), 112.9 (C3), 113.6 ($C_{6'}$), 116.5 (CN), 121.2 ($C_{4'}$), 122.3 (C4a), 125.5 (C8), 127.1 (C5), 128.4 (C6), 129.0 (C7), 133.8 ($C_{3'}$), 135.0 ($C_{5'}$), 136.9 (C4), 147.9 (C8a), 158.6 (C2), 160.0 ($C_{1'}$). m/z (EI): 275 (M^+ , 5%), 157 (100).

6-[(2-Fluorophenoxy)methyl]quinoline-2-amine (104)

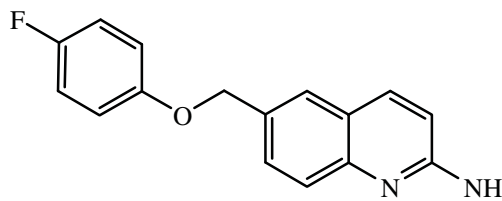
Using General Procedure 11, **75** (115 mg, 0.37 mmol), K_2CO_3 (153 mg, 1.11 mmol) and methanol (10 mL) were heated for 5 h. The work up was carried out with 10 mL of water to give the title compound as a cream



powder, mp 168-171 °C (91 mg, 92%). Analysis found: C, 71.72; H, 4.77; N, 10.55. $C_{16}H_{13}FN_2O$ requires C, 71.63; H, 4.88; N, 10.44%. IR (nujol mull): ν/cm^{-1} : 3401, 3303, 3141, 1625 and 1569. 1H NMR (600 MHz, d_6 -DMSO); δ : 5.20 (2H, s, CH_2), 6.46 (2H, br s, NH_2), 6.76 (1H, br s, H3), 6.93 (1H, dddd, $^4J_{4',6'} = 1.2$ Hz, $^4J_{4',F} = 4.8$ Hz, $^3J_{3',4'} = 7.8$ Hz, $^3J_{4',5'} = 7.8$ Hz, $H_{4'}$), 7.09 (1H, dd, $^3J_{4',5'} = 7.8$ Hz, $^3J_{5',6'} = 9.0$ Hz, $H_{5'}$), 7.19 (1H, ddd, $^4J_{3',5'} = 1.8$ Hz, $^3J_{3',4'} = 7.8$ Hz, $^3J_{3',F} = 12.0$ Hz, $H_{3'}$), 7.27 (1H, ddd, $^4J_{4',6'} = 1.2$ Hz, $^4J_{6',F} = 8.4$ Hz, $^3J_{5',6'} = 9.0$ Hz, $H_{6'}$), 7.46 (1H, d, $J = 8.4$ Hz, H8), 7.53 (1H, dd, $J = 1.2, 8.7$ Hz, H7), 7.83 (1H, d, $J = 1.2$ Hz, H5), 7.88 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 70.4 (CH_2), 112.7 (C3), 115.6 (d, $^3J_{C,F} = 2.3$ Hz, $C_{6'}$), 116.0 (d, $^2J_{C,F} = 17.6$ Hz, $C_{3'}$), 121.2 (d, $^3J_{C,F} = 6.6$ Hz, $C_{4'}$), 122.3 (C4a), 124.7 (d, $^3J_{C,F} = 3.3$ Hz, $C_{5'}$), 125.3 (C8), 127.0 (C5), 128.9 (C6), 129.2 (C7), 136.9 (C4), 146.2 (d, $^2J_{C,F} = 11.0$ Hz, $C_{1'}$), 147.8 (C8a), 151.9 (d, $^1J_{C,F} = 241.8$ Hz, $C_{2'}$), 158.5 (C2). m/z (EI): 268 (M^+ , 2%), 157 (100).

6-[(4-Fluorophenoxy)methyl]quinoline-2-amine (105)

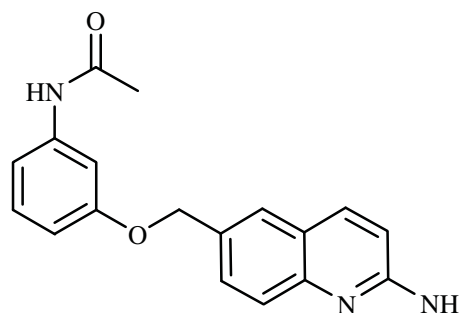
Using General Procedure 11, **76** (120 mg, 0.39 mmol), K₂CO₃ (160 mg, 1.16 mmol) and methanol (10 mL) were heated for 5 h. The work up was carried out with 10 mL of water to give the title



compound as a cream powder, mp 180-183°C (82 mg, 79%). Analysis found: C, 71.36; H, 5.05; N, 10.39. C₁₆H₁₃FN₂O requires C, 71.63; H, 4.88; N, 10.44%. IR (nujol mull): ν/cm^{-1} : 3434, 3257, 3135, 1660 and 1567. ¹H NMR (600 MHz, d₆-DMSO); δ : 5.10 (2H, s, CH₂), 6.44 (2H, br s, NH₂), 6.75 (1H, d, $J = 8.4$ Hz, H3), 7.01-7.04 (2H, m, H(2'/6')), 7.09-7.12 (2H, m, H(3'/5')), 7.44 (1H, d, $J = 8.4$ Hz, H8), 7.51 (1H, dd, $J = 2.4, 8.4$ Hz, H7), 7.66 (1H, br d, $J = 1.2$ Hz, H5), 7.87 (1H, d, $J = 8.4$ Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 69.2 (CH₂), 112.7 (C3), 115.8 (d, ²J_{C,F} = 21.9 Hz, C(3'/5')), 116.1 (d, ³J_{C,F} = 8.7 Hz, C(2'/6')), 122.3 (C4a), 125.3 (C8), 126.8 (C5), 129.1 (C7), 129.4 (C6), 136.8 (C4), 147.7 (C8a), 154.7 (d, ⁴J_{C,F} = 2.3 Hz, C1'), 156.0 (d, ¹J_{C,F} = 234.2 Hz, C4'), 158.5 (C2). m/z (EI): 268 (M⁺, 2%), 157 (100).

6-[(3-Acetamidophenoxy)methyl]quinoline-2-amine (106)

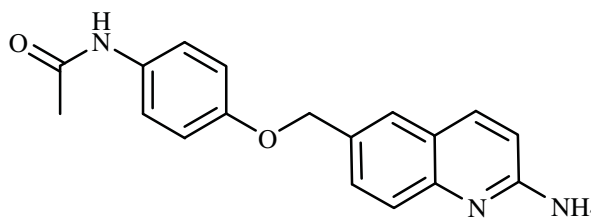
Using General Procedure 11, **77** (84 mg, 0.24 mmol), K₂CO₃ (100 mg, 0.72 mmol) and methanol (6 mL) were heated for 5 h. The work up was carried out with 5 mL of water to give the crude product. Recrystallisation from ethanol afforded the title compound as a cream powder, mp 185-188 °C (34 mg,



68%). HRMS found: 307.1319; C₁₈H₁₇N₃O₂ requires 307.1321. Analysis found: C, 70.47; H, 5.80; N, 13.79. C₂₈H₁₇N₃O₂ requires C, 70.34; H, 5.58; N, 13.67%. IR (nujol mull): ν/cm^{-1} : 3293, 3126, 1654, 1529 and 1511. ¹H NMR (300MHz, CDCl₃); δ : 2.18 (CH₃), 4.77 (2H, br s, NH₂), 5.17 (2H, s, CH₂), 6.75 (1H, d, $J = 9.0$ Hz, H3), 6.79 (1H, d, $J = 1.8$ Hz, H2'), 6.98 (1H, br d, $J = 8.1$ Hz, H6'), 7.14 (1H, br s, NH), 7.23 (1H, dd, $J = 8.1$ Hz, H5'), 7.41 (1H, br s, H4'), 7.61 (1H, dd, $J = 1.8, 8.7$ Hz, H7), 7.68 (1H, d, $J = 8.7$ Hz, H8), 7.70 (1H, br s, H5), 7.90 (1H, d, $J = 9.0$ Hz, H4). ¹³C NMR (75 MHz, d₆-DMSO); δ : 24.1 (COCH₃), 69.3 (CH₂), 105.9 (C2'), 109.2 (C6'), 111.5 (C3), 112.7 (C4'), 122.4 (C4a), 125.3 (C8), 126.7 (C5), 129.1 (C7), 129.5 (C6), 129.5 (C5'), 136.9 (C4), 140.5 (C3'), 147.7 (C8a), 158.5 (C1'), 158.7 (C2), 168.4 (C=O). m/z (EI): 307 (M⁺, 2%), 157 (100).

6-[(4-Acetamidophenoxy)methyl]quinoline-2-amine (107)

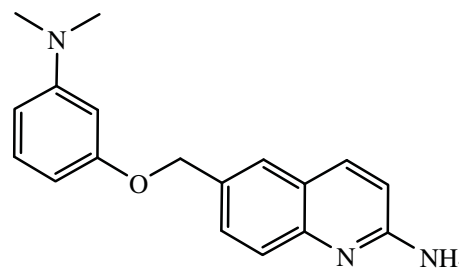
Using General Procedure 11, **78** (125 mg, 0.36 mmol), K₂CO₃ (148 mg, 1.07 mmol) and methanol (6 mL) were heated for 5 h. The work up was carried out with 5 mL of water to give the crude product.



Recrystallisation from ethanol afforded the title compound as a white powder, mp 234-236 °C (66 mg, 59%). HRMS found: 307.1321; C₁₈H₁₇N₃O₂ requires 307.1321. Analysis found: C, 70.49; H, 5.82; N, 13.76. C₂₈H₁₇N₃O₂ requires C, 70.34; H, 5.58; N, 13.67%. IR (nujol mull): ν/cm^{-1} : 3297, 3135, 1656, 1596 and 1531. ¹H NMR (300MHz, CDCl₃); δ : 2.18 (CH₃), 4.78 (2H, br s, NH₂), 5.15 (2H, s, CH₂), 6.75 (1H, d, *J* = 9.0 Hz, H3), 6.97 (2H, m, H(2'/6')), 7.05 (1H, br s, NH), 7.40 (2H, m, H(3'/5')), 7.60 (1H, dd, *J* = 1.8, 8.7 Hz, H7), 7.67 (1H, br s, H5), 7.82 (1H, d, *J* = 8.7 Hz, H8), 7.89 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (75 MHz, d₆-DMSO); δ : 23.9 (COCH₃), 69.5 (CH₂), 112.7 (C3), 114.9 (C2'/6'), 120.5 (C3'/5'), 122.4 (C4a), 125.3 (C8), 126.8 (C5), 129.2 (C7), 129.7 (C6), 132.7 (C4'), 136.9 (C4), 147.7 (C8a), 154.2 (C1'), 158.5 (C2), 167.8 (C=O). *m/z* (EI): 199 (65%), 157 (100%).

6-[(3-(Dimethylamino)phenoxy)methyl]quinoline-2-amine (108)

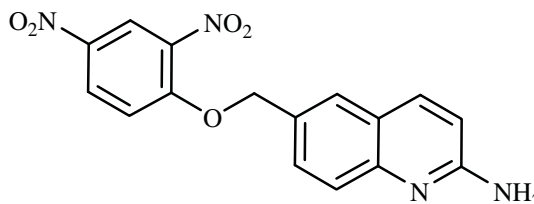
Using General Procedure 11, **79** (45 mg, 0.13 mmol), K₂CO₃ (56 mg, 0.40 mmol) and methanol (5 mL) were heated for 2 h. The work up was carried out with 5 mL of water to give the title compound as a cream solid,



mp 172-174 °C (30 mg, 79%). Analysis found: C, 73.44; H, 6.66; N, 14.32. C₁₈H₁₉N₃O requires C, 73.69; H, 6.53; N, 14.32%. IR (DCM): ν/cm^{-1} : 3402, 3066, 3045, 1617, 1573 and 1503. ¹H NMR (300 MHz, CDCl₃); δ : 2.94 (6H, s, 2 x CH₃), 4.89 (2H, br s, NH₂), 5.16 (2H, s, CH₂), 6.39-6.41 (3H, m, H2', H4', H6'), 6.74 (1H, d, *J* = 8.7 Hz, H3), 7.17 (1H, dd, *J* = 8.7 Hz, H5'), 7.65 (1H, dd, *J* = 2.1, 8.4 Hz, H7), 7.70 (1H, d, *J* = 8.4 Hz, H8), 7.71 (1H, br s, H5), 7.90 (1H, d, *J* = 8.7 Hz, H4). ¹³C NMR (75 MHz, d₆-DMSO); δ : 40.4 (N(CH₃)₂), 69.1 (CH₂), 99.5 (C2'), 102.3 (C6'), 105.5 (C4'), 112.7 (C3), 122.4 (C4a), 125.2 (C5), 126.7 (C8), 129.1 (C7), 129.6 (C5'), 129.9 (C6), 136.9 (C4), 147.7 (C8a), 151.8 (C3'), 158.4 (C2), 159.4 (C1'). *m/z* (EI): 157 (100%).

Attempted synthesis of 6-[(2,4-Dinitrophenoxy)methyl]quinoline-2-amine (109)

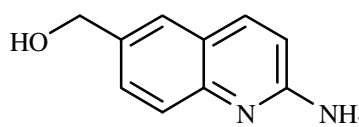
Using General Procedure 11, **80** (84 mg, 0.22 mmol), K_2CO_3 (31 mg, 0.22 mmol) and methanol (10 mL) were heated for 1.5 h. The work up was carried out with 5 mL of water and the precipitate was collected by vacuum filtration affording 2,4-dinitrophenol.



Chromatographic separation of the filtrate residue did not afford the desired product, however, 6-(hydroxymethyl)quinoline-2-amine (**127**) was isolated as a cream solid, mp 215-219 °C (lit.,³⁴ 210-220 °C), (25 mg, 66%).

6-(Hydroxymethyl)quinoline-2-amine (**127**):

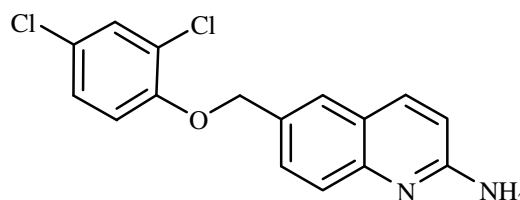
IR (nujol mull): ν/cm^{-1} : 3459, 3311, 1680, 1633, 1626, 1610 and 1570. 1H NMR (200MHz, d_6 -DMSO); δ : 4.54 (2H, br d, J = 5.6 Hz, CH_2), 5.17 (1H, t, J = 5.6 Hz, OH), 6.40 (2H, br s,



NH_2), 6.73 (1H, d, J = 9.0 Hz, H3), 7.41 (2H, br s, H7, H8), 7.53 (1H, br s, H5), 7.87 (1H, d, J = 9.0 Hz, H4). ^{13}C NMR (75 MHz, d_6 -DMSO); 62.8 (CH_2), 122.1 (C4a), 124.0 (C5), 124.9 (C8), 128.7 (C7), 135.8 (C6), 137.5 (C4), 145.6 (C8a), 158.2 (C2).

6-[(2,4-Dichlorophenoxy)methyl]quinoline-2-amine (110)

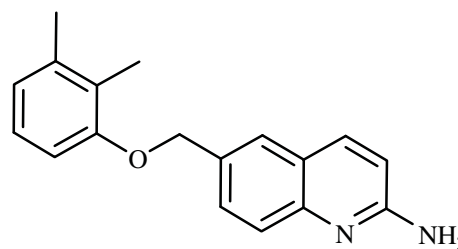
Using General Procedure 11, **81** (190 mg, 0.53 mmol), K_2CO_3 (73 mg, 0.53 mmol) and methanol (10 mL) were heated for 2 h. The work up was carried out with 5 mL of water to give the title compound as a white powder, mp 184-186 °C (165 mg, 98%). Analysis found: C, 60.07; H,



3.82; N, 8.71. $C_{16}H_{12}Cl_2N_2O$ requires C, 60.21; H, 3.79; N, 8.78%. IR (nujol mull): ν/cm^{-1} : 3457, 3301, 3122, 1641, 1610 and 1593. 1H NMR (300MHz, $CDCl_3$); δ : 4.78 (2H, br s, NH_2), 5.24 (2H, s, CH_2), 6.75 (1H, d, J = 9.0 Hz, H3), 6.92 (1H, d, J = 8.7 Hz, H6'), 7.15 (1H, dd, J = 2.4, 8.7 Hz, H5'), 7.40 (1H, d, J = 2.4 Hz, H5'), 7.62 (1H, dd, J = 1.8, 8.7 Hz, H7), 7.69 (2H, m, H5, H8), 7.85 (1H, dd, J = 1.8, 7.8 Hz, H3'), 7.90 (1H, d, J = 9.0 Hz, H4). ^{13}C NMR (75 MHz, d_6 -DMSO); δ : 71.4 (CH_2), 112.2 (C3), 115.2 (C6'), 123.6 (C4a), 124.4 (C2') 125.2 (C4'), 126.3 (C5), 126.8 (C8), 127.8 (C5'), 129.1 (C7), 130.3 (C3'), 130.4 (C6), 138.3 (C4), 147.8 (C8a), 153.2 (C1'), 157.4 (C2). m/z (EI): 322 (M^+ , [^{37}Cl , ^{37}Cl], < 0.5%), 320 (M^+ , [^{35}Cl , ^{37}Cl], 1), 318 (M^+ , [^{35}Cl , ^{35}Cl], 3), 157 (100).

6-[(2,3-Dimethylphenoxy)methyl]quinoline-2-amine (111)

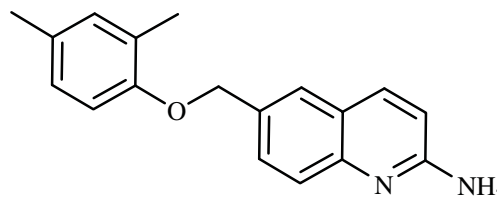
Using General Procedure 11, **82** (73 mg, 0.23 mmol), K₂CO₃ (94 mg, 0.68 mmol) and methanol (10 mL) were heated for 6 h. The work up was carried out with 10 mL of water to give the title compound as a cream powder, mp 191-193 °C (50 mg, 78%). Analysis found:



C, 77.47; H, 6.52; N, 10.10. C₁₈H₁₈N₂O requires C, 77.67; H, 6.52; N, 10.06%. IR (nujol mull): ν/cm^{-1} : 3448, 3305, 3120, 1660, 1610, 1585 and 1567. ¹H NMR (600 MHz, d₆-DMSO); δ : 2.11 (3H, s, PhCH₃), 2.20 (3H, s, PhCH₃), 5.10 (2H, s, CH₂), 6.41 (2H, br s, NH₂), 6.74 (1H, d, $J = 8.4$ Hz, H4'), 6.75 (1H, d, $J = 8.4$ Hz, H3), 6.89 (1H, d, $J = 8.4$ Hz, H6'), 7.01 (1H, t, $J = 8.4$ Hz, H5'), 7.45 (1H, d, $J = 8.4$ Hz, H8), 7.53 (1H, dd, $J = 1.8, 8.4$ Hz, H7), 7.67 (1H, br s, H5), 7.87 (1H, d, $J = 8.4$ Hz, H4). ¹³C NMR (150 MHz, d₆-DMSO); δ : 11.6 (C2'CH₃), 19.7 (C3'CH₃), 69.6 (CH₂), 109.9 (C6'), 112.7 (C3), 122.2 (C4'), 122.3 (C4a), 124.5 (C2'), 125.3 (C8), 125.9 (C5'), 126.3 (C5), 128.8 (C7), 130.6 (C6), 136.9 (C4), 137.3 (C3'), 147.6 (C8a), 156.3 (C1') 158.4 (C2). m/z (EI): 278 (M⁺, 1%), 157 (100).

6-[(2,4-Dimethylphenoxy)methyl]quinoline-2-amine (112)

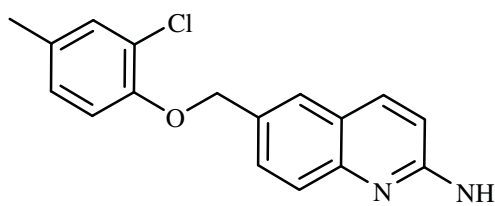
Using General Procedure 11, **83** (97 mg, 0.30 mmol), K₂CO₃ (126 mg, 0.91 mmol) and methanol (5 mL) were heated for 6 h. The work up was carried out with 5 mL of water to give the title



compound as a cream powder, mp 165-172 °C (60 mg, 73%). Analysis found: C, 77.37; H, 6.54; N, 10.14. C₁₈H₁₈N₂O requires C, 77.67; H, 6.52; N, 10.06%. IR (DCM): ν/cm^{-1} : 3507, 3402, 1623, 1570 and 1505. ¹H NMR (600 MHz, d₆-DMSO); δ : 2.14 (3H, s, PhCH₃), 2.18 (3H, s, PhCH₃), 5.10 (2H, s, CH₂), 6.40 (2H, br s, NH₂), 6.74 (1H, d, $J = 8.4$ Hz, H3), 6.91 (3H, m, H3', H5', H6'), 7.44 (1H, d, $J = 8.4$ Hz, H8), 7.44 (1H, dd, $J = 1.8, 8.4$ Hz, H7), 7.65 (1H, d, $J = 1.8$ Hz, H5), 7.87 (1H, d, $J = 8.4$ Hz, H4). ¹³C NMR (150 MHz, d₆-DMSO); δ : 16.1 (C2'CH₃), 20.1 (C4'CH₃), 69.4 (CH₂), 112.0 (C6'), 112.6 (C3), 122.3 (C4a), 125.3 (C8), 125.8 (C2'), 126.3 (C5), 127.0 (C5'), 128.8 (C7), 128.9 (C4'), 130.1 (C6), 131.2 (C3'), 136.9 (C4), 147.1 (C8a), 154.3 (C1'), 158.4 (C2). m/z (EI): 278 (M⁺, 1%), 157 (100).

6-[(2-Chloro-4-methylphenoxy)quinoline-2-amine (113)

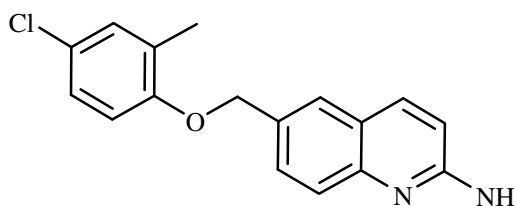
Using General Procedure 11, **84** (113 mg, 0.33 mmol), K₂CO₃ (46 mg, 0.33 mmol) and methanol (10 mL) were heated for 5 h. The work up was carried out with 10 mL of water to give the title



compound as a white precipitate, mp 181-185 °C (89 mg, 90%). Analysis found: C, 68.52; H, 5.14; N, 9.47. C₁₇H₁₅N₂OCl requires C, 68.34; H, 5.06; N, 9.38%. IR (DCM): ν/cm^{-1} : 3507, 3401, 3052, 1619 and 1569. ¹H NMR (600 MHz, d₆-DMSO); δ : 2.21 (1H, s, CH₃), 5.18 (1H, s, CH₂), 6.44 (2H, br s, NH₂), 6.75 (1H, d, *J* = 9.0 Hz, H3), 7.06 (1H, br d, *J* = 8.4 Hz, H5'), 7.12 (1H, d, *J* = 8.4 Hz, H6'), 7.23 (1H, br s, H3'), 7.45 (1H, d, *J* = 9.0 Hz, H8), 7.53 (1H, dd, *J* = 1.8, 9.0 Hz, H7), 7.67 (1H, br s, H5), 7.87 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (150 MHz, d₆-DMSO); δ : 19.7 (CH₃), 70.3 (CH₂), 112.7 (C3), 114.5 (C6'), 121.3 (C4'), 122.3 (C4a), 125.3 (C8), 126.6 (C5), 128.5 (C5'), 129.2 (C7), 129.2 (C6), 130.2 (C3'), 131.0 (C2'), 136.9 (C4), 147.7 (C8a), 151.5 (C1'), 158.5 (C2). *m/z* (EI): 298 (M⁺, < 1%), 157 (100).

6-[(4-Chloro-2-methylphenoxy)quinoline-2-amine (114)

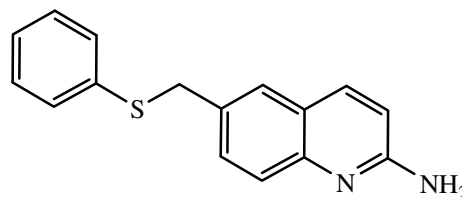
Using General Procedure 11, **85** (113 mg, 0.33 mmol), K₂CO₃ (46 mg, 0.33 mmol) and methanol (10 mL) were heated for 5 h. The work up was carried out with 10 mL of water to give the title



compound as a cream solid, mp 165-170 °C (90 mg, 91%). Analysis found: C, 68.25; H, 5.01; N, 9.36. C₁₇H₁₅N₂OCl requires C, 68.34; H, 5.06; N, 9.38%. IR (DCM): ν/cm^{-1} : 3507, 3401, 3052, 1619 and 1569. ¹H NMR (300 MHz, CDCl₃); δ : 2.27 (1H, s, CH₃), 5.21 (1H, s, CH₂), 4.78 (2H, br s, NH₂), 6.75 (1H, br d, *J* = 9.0 Hz, H3), 6.83 (1H, d, *J* = 8.7 Hz, H6'), 7.10 (1H, dd, *J* = 2.7, 8.7 Hz, H5'), 7.15 (1H, d, *J* = 2.7 Hz, H3'), 7.61 (1H, dd, *J* = 2.1, 8.7 Hz, H7), 7.66 (1H, br s, H5), 7.69 (1H, d, *J* = 8.7 Hz, H8), 7.88 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (75 MHz, CDCl₃); δ : 16.5 (CH₃), 70.4 (CH₂), 112.2 (C6'), 112.9 (C3), 123.6 (C4a), 125.5 (C2'), 126.2 (C5), 126.5 (C8), 126.6 (C3'), 129.2 (C4'), 129.3 (C7), 130.7 (C5'), 131.4 (C6), 138.2 (C4), 147.7 (C8a), 155.7 (C2), 157.3 (C1'). *m/z* (EI): 298 (M⁺, < 1%), 157 (100).

6-[(Phenylthio)methyl]quinoline-2-amine (115)

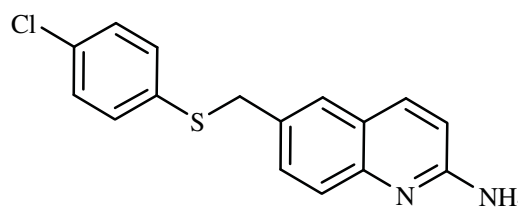
Using General Procedure 11, **86** (100 mg, 0.32 mmol), K_2CO_3 (134 mg, 0.97 mmol) and methanol (10 mL) were heated for 2 h. The work up was carried out with



10 mL of water to give the title compound as a yellow solid, mp 170-180 °C (70 mg, 97%). HRMS found: 266.0879; $C_{16}H_{14}N_2S$ requires 266.0877. IR (DCM): ν/cm^{-1} : 3507, 3403, 1683, 1620, 1579 and 1504. 1H NMR (600 MHz, d_6 -DMSO): δ : 4.29 (2H, s, CH_2), 6.37 (2H, br s, NH_2), 6.71 (1H, d, $J = 8.7$ Hz, H3), 7.15 (1H, t, $J = 7.8$ Hz, H4'), 7.27 (2H, t, $J = 7.8$ Hz, H(3'/5')), 7.32 (2H, d, $J = 7.8$ Hz, H(2'/6')), 7.38 (1H, d, $J = 9.0$ Hz, H8), 7.45 (1H, dd, $J = 1.8, 9.0$ Hz, H7), 7.53 (1H, d, $J = 1.8$ Hz, H5), 7.79 (1H, d, $J = 8.7$ Hz, H4). ^{13}C NMR (150 MHz, d_6 -DMSO): δ : 36.7 (CH_2), 112.6 (C3), 122.3 (C4a), 125.2 (C8), 125.8 (C4'), 127.1 (C5), 128.3 (C2'/6'), 128.9 (C3'/5'), 129.5 (C6), 130.1 (C7), 136.3 (C1'), 136.6 (C4), 147.1 (C8a), 158.2 (C2). m/z (EI): 266 (M^+ , 5%), 157 (100).

6-[(4-Chlorophenylthio)methyl]quinolin-2-amine (116)

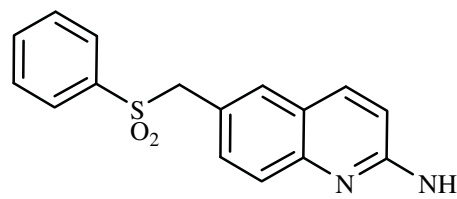
Using General Procedure 11, **87** (80 mg, 0.23 mmol), K_2CO_3 (32 mg, 0.23 mmol) and methanol (5 mL) were heated for 4.5 h. The work up was



carried out with 10 mL of water to give the title compound as a cream powder, mp 162-166 °C (48 mg, 70%). Analysis found: C, 63.72; H, 4.51; N, 9.15. $C_{16}H_{13}ClN_2S$ requires C, 63.89; H, 4.36; N, 9.31%. IR (nujol mull): ν/cm^{-1} : 3507, 3403, 3051, 1680, 1569, 1541 and 1503. 1H NMR (600 MHz, d_6 -DMSO): 4.30 (2H, s, CH_2), 6.39 (2H, br s, NH_2), 6.72 (1H, br d, $J = 9.0$ Hz, H3), 7.31-7.35 (4H, m, H(2'/6'), H(3'/5')), 7.38 (1H, dd, $J = 9.0$ Hz, H8), 7.45 (1H, dd, $J = 1.8, 9.0$ Hz, H7), 7.53 (1H, d, $J = 1.8$ Hz, H5), 7.79 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, d_6 -DMSO); δ : 36.7 (CH_2), 112.6 (C3), 122.3 (C4a), 125.3 (C8), 127.2 (C5), 128.8 (C2'/6'), 129.4 (C4'), 130.0 (C7), 130.0 (C3'/5'), 130.4 (C6), 135.3 (C1'), 136.6 (C4), 147.1 (C8a), 158.2 (C2). m/z (EI): 302 (M^+ [^{37}Cl], 1%), 300 (M^+ [^{35}Cl], 3), 157 (100).

6-[(Phenylsulfonyl)methyl]quinoline-2-amine (117)

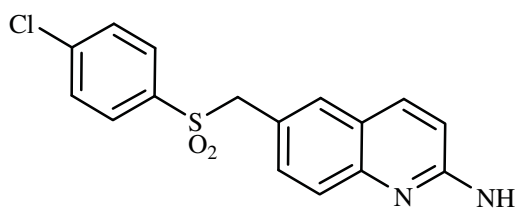
Using General Procedure 11, **96** (60 mg, 0.18 mmol), K_2CO_3 (24 mg, 0.18 mmol) and methanol (10 mL) were heated for 3.5 h. The work up was carried out with 10 mL of water to give the title compound as a



white solid, mp > 300 °C (50 mg, 93%). HRMS found: 298.0774; $C_{16}H_{14}N_2O_2S$ requires 298.0776. IR (DCM): ν/cm^{-1} : 3403, 3053, 2927, 1623, 1570 and 1505. 1H NMR (600 MHz, $CDCl_3$); δ : 4.42 (2H, s, CH_2), 4.80 (2H, br s, NH_2), 6.73 (1H, d, $J = 8.7$ Hz, H3), 7.16 (1H, dd, $J = 2.1, 8.7$ Hz, H7), 7.40-7.44 (3H, m, H5, H(3'/5')), 7.50 (1H, d, $J = 8.7$ Hz, H8), 7.57-7.64 (3H, m, H4', H(2'/6')), 7.80 (1H, d, $J = 8.7$ Hz, H4). ^{13}C NMR (75 MHz, $CDCl_3$); δ : 60.7 (CH_2), 112.9 (C3), 120.9 (C6), 122.3 (C4a), 124.9 (C8), 128.1 (C2'/6'), 129.2 (C3'/5'), 130.2 (C5), 131.5 (C7), 133.8 (C4'), 136.7 (C4), 138.5 (C1'), 147.8 (C8a), 158.7 (C2). m/z (EI): 298 (M^+ , 4%), 157 (100).

6-[(4-Chlorophenylsulfonyl)methyl]quinolin-2-amine (118)

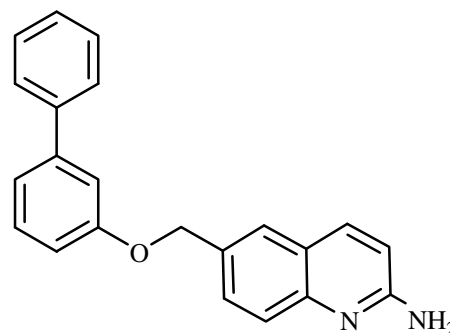
Using General Procedure 11, **97** (77 mg, 0.21 mmol), K_2CO_3 (28 mg, 0.21 mmol) and methanol (10 mL) were heated for 4 h. The work up was carried out with 10 mL of water to give the title



compound as a white precipitate, mp 231-234 °C (65 mg, 93%). Analysis found: C, 56.41; H, 4.12; N, 8.08. $C_{16}H_{13}ClN_2O_2S \cdot 0.5H_2O$ requires C, 56.22; H, 4.13; N, 8.20%. IR (DCM): ν/cm^{-1} : 3512, 3400, 1622, 1570 and 1507. 1H NMR (300 MHz, $CDCl_3$); δ : 4.45 (2H, s, CH_2), 4.86 (2H, br s, NH_2), 6.77 (1H, br d, $J = 9.0$ Hz, H3), 7.20 (1H, dd, $J = 2.1, 8.4$ Hz, H7), 7.43 (2H, m, H(3'/5')), 7.46 (1H, d, $J = 2.1$ Hz, H5), 7.56 (3H, m, H8, H(2'/6')), 7.84 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (75 MHz, $CDCl_3$); δ : 60.6 (CH_2), 112.9 (C3), 120.7 (C6), 122.3 (C4a), 125.0 (C8), 129.3 (C2'/6'), 130.2 (C3'/5'), 130.2 (C5), 131.5 (C7), 136.8 (C1'), 137.3 (C4), 138.9 (C4'), 147.8 (C8a), 158.7 (C2). m/z (EI): 332 (M^+ , 2%), 157 (100).

6-[(3-Phenylphenoxy)methyl]quinoline-2-amine (119)

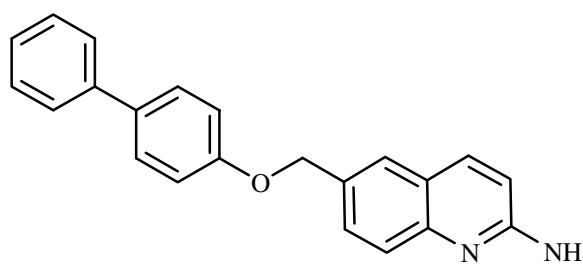
Using General Procedure 11, an inseparable mixture of **88** and **89** (122 mg, 0.33 mmol), K₂CO₃ (45 mg, 0.33 mmol) and methanol (5 mL) were heated for 6 h. The work up was carried out with 5 mL of water to give the title compound as a 7:1 mixture with **120** (100 mg combined yield, 84% **119**). Attempts to isolate pure **119** through flash chromatography and recrystallisation



were unsuccessful. HRMS found: 326.1412; C₂₂H₁₈N₂O requires 326.1419. Analysis found: C, 79.07; H, 5.60; N, 8.35. C₂₂H₁₈N₂O.0.5 H₂O requires C, 78.78; H, 5.71; N, 8.35%. IR (nujol mull): ν/cm^{-1} : 3434, 3278, 1658, 1585 and 1563. ¹H NMR (600 MHz, CDCl₃); δ : 4.77 (2H, br s, NH₂), 5.20 (2H, s, CH₂), 6.73 (1H, d, *J* = 9.0 Hz, H3), 7.00 (1H, ddd, *J* = 0.6, 1.8, 8.4 Hz, H6'), 7.21 (1H, ddd, *J* = 0.6, 1.8, 7.8 Hz, H4'), 7.25 (1H, dd, *J* = 1.8, Hz, H2'), 7.37 (2H, m, H5', H4''), 7.43 (2H, dd, *J* = 7.8 Hz, H(3''/5'')), 7.57 (2H, dd, *J* = 7.8 Hz, H(2''/6'')), 7.65 (1H, dd, *J* = 1.8, 8.4 Hz, H7), 7.70 (1H, d, *J* = 8.4 Hz, H8), 7.71 (1H, d, *J* = 1.8 Hz, H5), 7.89 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 70.1 (CH₂), 111.9 (C3), 113.6 (C6'), 114.0 (C2'), 119.3 (C4'), 123.5 (C4a), 126.4 (C5), 126.5 (C8), 127.1 (C2''/6''), 127.4 (C4''), 128.7 (C3''/5''), 129.4 (C7), 129.8 (C5'), 131.2 (C6), 138.1 (C4), 141.0 (C3'), 142.8 (C1''), 147.5 (C8a), 157.1 (C2), 159.2 (C1'). *m/z* (EI): 326 (M⁺, 4%), 157 (100).

6-[(4-Phenylphenoxy)methyl]quinoline-2-amine 120

Using General Procedure 11, **89** (150 mg, 0.41 mmol), K₂CO₃ (56 mg, 0.41 mmol) and methanol (5 mL) were heated for 6 h. The work up was carried out with 5 mL of water to give the crude product. Recrystallisation

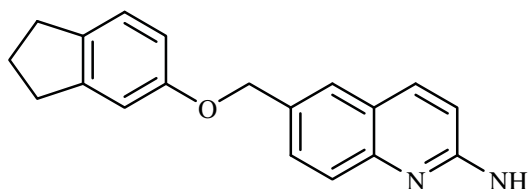


in THF afforded the title compound as white crystals, mp 210-220 °C (60 mg, 45%). HRMS found: 326.1419; C₂₂H₁₈N₂O requires 326.1419. Analysis found: C, 80.26; H, 5.65; N, 8.84. C₂₂H₁₈N₂O.0.2H₂O requires C, 80.07; H, 5.62; N, 8.59%. IR (nujol mull): ν/cm^{-1} : 3390, 3197, 1671, 1602 and 1577. ¹H NMR (600 MHz, d₆-DMSO); δ : 5.18 (2H, s, CH₂), 6.42 (2H, br s, NH₂), 6.76 (1H, d, *J* = 9.0 Hz, H3), 7.10 (2H, m, H(2''/6'')), 7.29 (1H, dd, *J* = 1.2, 7.28 Hz, H4''), 7.42 (2H, dd, *J* = 7.8, Hz, H(3''/5'')), 7.46 (1H, d, *J* = 8.4 Hz, H8), 7.54 (1H, dd, *J* = 1.8, 8.4 Hz, H7), 7.58 (4H, m, H(3'/5'), H(2''/6'')), 7.69 (1H, br d, *J* = 1.8 Hz, H5), 7.88 (1H, d, *J*

= 9.0 Hz, H4). ^{13}C NMR (150 MHz, d_6 -DMSO); δ : 69.5 (CH_2), 112.7 (C3), 115.4 (C2'/6'), 122.4 (C4a), 125.3 (C8), 126.2 (C2''/6''), 126.8 (C5), 126.8 (C4''), 127.8 (C3'/5'), 128.9 (C3''/5''), 129.1 (C6), 129.6 (C7), 132.7 (C4'), 137.0 (C4), 139.8 (C1''), 147.7 (C8a), 158.1 (C2), 158.4 (C1'). m/z (EI): 326 (M^+ , 4%), 157 (100).

6-[(2,3-Dihydro-1H-inden-5-yloxy)methyl]quinoline-2-amine (121)

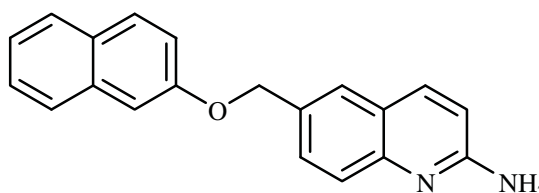
Using General Procedure 11, **90** (54 mg, 0.16 mmol) K_2CO_3 (67 mg, 0.49 mmol) and methanol (5 mL) were heated for 3 h. The work up was carried out with 5 mL of water to give the title



compound as a cream powder, mp 188-191 °C (33 mg, 72%). HRMS found: 290.1417; $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$ requires 290.1419. Analysis found: C, 77.65; H, 6.34; N, 9.44. $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O} \cdot 0.2\text{H}_2\text{O}$ requires C, 77.39; H, 6.32; N, 9.50%. IR (DCM): ν/cm^{-1} : 3679, 3401, 1673 and 1621. ^1H NMR (600 MHz, d_6 -DMSO); δ : 1.97 (2H, qn, $J = 7.2$ Hz, H8'), 2.74 (2H, t, $J = 7.2$ Hz, H9'), 2.79 (2H, t, $J = 7.2$ Hz, H7'), 5.08 (2H, s, CH_2), 6.41 (2H, br s, NH_2), 6.75 (2H, m, H3, H4'), 6.88 (1H, br s, H6'), 7.07 (1H, d, $J = 8.4$ Hz, H3'), 7.43 (1H, d, $J = 8.1$ Hz, H8), 7.50 (1H, dd, $J = 1.8, 8.1$ Hz, H7), 7.65 (1H, br s, H5), 7.86 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (150 MHz, d_6 -DMSO); δ : 25.4 (C8'), 31.5 (C9'), 32.6 (C7'), 69.4 (CH_2), 110.8 (C6'), 112.7 (C3), 112.9 (C4'), 122.3 (C4a), 124.6 (C3'), 125.3 (C8), 126.5 (C5), 129.0 (C7), 129.9 (C6), 135.6 (C2'), 136.9 (C4), 145.1 (C1'), 147.6 (C8a), 157.3 (C5'), 158.4 (C2). m/z (EI): 290 (M^+ , 1%), 157 (100).

6-[(Naphthalen-2-yloxy)methyl]quinoline-2-amine (122)

Using General Procedure 11, **91** (65 mg, 0.22 mmol), K_2CO_3 (30 mg, 0.22 mmol) and methanol (10 mL) were heated for 5 h. The work up was carried out with 5 mL of water to

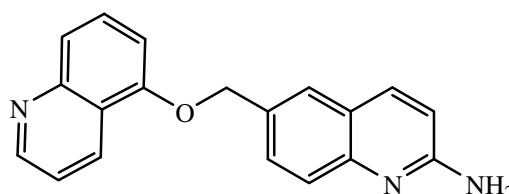


give the crude product. Recrystallisation in ethanol afforded the title compound as a cream powder, mp 231-235 °C (32 mg, 49%). HRMS found: 300.1262; $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}$ requires 300.1262. IR (DCM): ν/cm^{-1} : 3403, 3052, 1684, 1621, 1601, 1570 and 1508. ^1H NMR (300 MHz, CDCl_3); δ : 5.12 (2H, br s, NH_2), 5.29 (2H, s, CH_2), 6.77 (1H, d, $J = 8.7$ Hz, H3), 7.27 (2H, m, H1', H3'), 7.36 (1H, ddd, $J = 1.5, 6.9, 8.1$ Hz, H6'), 7.43 (1H, ddd, $J = 1.5, 6.9, 8.1$ Hz, H7'), 7.69-7.86 (6H, m, H5, H7, H8, H4', H5', H8'), 7.94 (1H, d, $J = 8.7$ Hz, H4). ^{13}C

NMR (75 MHz, CDCl₃); δ : 69.5 (CH₂), 107.3 (C1'), 112.8 (C3), 118.9 (C3'), 122.4 (C4a), 123.7 (C6'), 125.4 (C5), 126.5 (C7'), 126.8 (C8'), 127.0 (C4'), 127.6 (C8), 128.6 (C4a'), 129.4 (C7), 129.4 (C5'), 129.5 (C6), 134.3 (8a'), 137.0 (C4), 147.8 (C8a), 156.4 (C2'), 158.6 (C2). *m/z* (EI): 157 (100%), 144 (50).

6-[(Quinolin-5-yloxy)methyl]quinoline-2-amine (123)

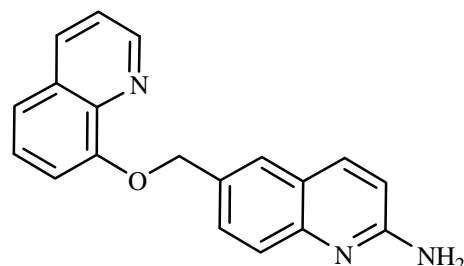
Using General Procedure 11, **92** (100 mg, 0.29 mmol) K₂CO₃ (121 mg, 0.87 mmol) and methanol (10 mL) were heated for 3 h. The work up was carried out with 10 mL of water to give the title



compound as a cream powder, mp 239-245 °C (70 mg, 80%). HRMS found: 301.1215; C₁₉H₁₅N₃O requires 301.1215. IR (nujol mull): ν /cm⁻¹: 3313, 3137, 1654, 1621, 1611 and 1575. ¹H NMR (600 MHz, d₆-DMSO); δ : 5.36 (2H, s, CH₂), 6.45 (2H, br s, NH₂), 6.76 (1H, d, *J* = 9.0 Hz, H3), 7.20 (1H, d, *J* = 7.8 Hz, H6'), 7.49 (2H, m, H3', H8'), 7.59 (1H, d, *J* = 8.7 Hz, H8), 7.62 (1H, dd, *J* = 1.8, 8.7 Hz, H7), 7.67 (1H, dd, *J* = 7.8, 8.4 Hz, H7'), 7.90 (1H, d, *J* = 1.8 Hz, H5), 7.91 (1H, d, *J* = 9.0 Hz, H4), 8.56 (1H, dd, *J* = 1.8 Hz, 8.4 Hz, H4'), 8.88 (1H, dd *J* = 1.8, 4.2 Hz, H2'). ¹³C NMR (150 MHz, d₆-DMSO); δ : 70.1 (CH₂), 106.3 (C6'), 112.7 (C3), 120.2 (C4a'), 120.7 (C3'), 121.1 (C8'), 122.4 (C4a), 125.4 (C8), 126.7 (C5), 129.0 (C7), 129.2 (C6), 129.6 (C7'), 130.2 (C4'), 136.9 (C4), 147.8 (C8a), 148.6 (C8a'), 150.7 (C2'), 153.7 (C5'), 158.5 (C2). *m/z* (EI): 301 (M⁺, 2%), 199 (80), 157 (100).

6-[(Quinolin-8-yloxy)methyl]quinoline-2-amine (124)

Using General Procedure 11, **93** (75 mg, 0.22 mmol), K₂CO₃ (30 mg, 0.22 mmol) and methanol (4 mL) were heated for 4 h. The work up was carried out with 5 mL of water to give the title compound as a cream powder,

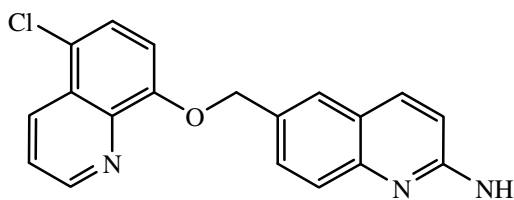


mp 213-221 °C (46 mg, 70%). HRMS found: 301.1215; C₁₉H₁₅N₃O requires 301.1215. IR (nujol mull): ν /cm⁻¹: 3313, 3137, 1654 and 1611. ¹H NMR (300MHz, CDCl₃); δ : 4.75 (2H, br s, NH₂), 5.55 (2H, s, CH₂), 6.72 (1H, d, *J* = 9.0 Hz, H3), 7.09 (1H, dd, *J* = 3.3, 5.7 Hz, H7'), 7.40 (2H, m, H5', H6'), 7.45 (1H, dd, *J* = 3.9, 8.4 Hz, H3'), 7.67 (1H, d, *J* = 8.4 Hz, H8), 7.72 (1H, dd, *J* = 2.1, 8.4 Hz, H7), 7.78 (1H, br s, H5), 7.86 (1H, d, *J* = 9.0 Hz, H4), 8.14 (1H, dd, *J* = 1.8, 8.4 Hz, H4'), 8.99 (1H, dd *J* = 1.8, 3.9 Hz, H2'). ¹³C NMR (150 MHz, CDCl₃); δ : 70.2 (CH₂), 110.1 (C7'), 112.8 (C3), 119.8

(C5'), 121.9 (C3'), 122.4 (C4a), 125.3 (C5), 126.8 (C6'), 127.1 (C7), 129.1 (C8), 129.5 (C4a'), 129.5 (C6), 135.9 (C4'), 137.0 (C4), 139.9 (C8a'), 147.8 (C8a), 149.1 (C2'), 154.3 (C8'), 158.5 (C2). m/z (EI): 301 (M^+ , 40%), 300 ($M^+ - H$, 10), 284 (10), 158 (100), 157 (100).

6-[(5-Chloroquinolin-8-yloxy)methyl]quinoline-2-amine (125)

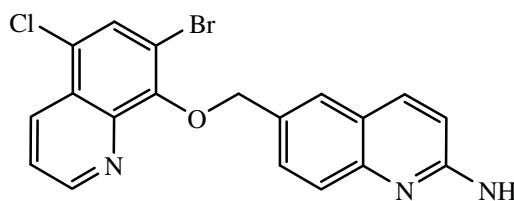
Using General Procedure 11, **94** (100 mg, 0.26 mmol), K_2CO_3 (110 mg, 0.79 mmol) and methanol (10 mL) were heated for 6 h. The work up was carried out with 10 mL of water to give



the crude product. Recrystallisation from methanol afforded the title compound as a yellow powder, mp 252-259 °C (60 mg, 70%). Analysis found: C, 67.81; H, 4.37; N, 12.30. $C_{19}H_{14}N_3OCl$ requires C, 67.96; H, 4.20; N, 12.51%. IR (nujol mull): ν/cm^{-1} : 3328, 3133, 1664 and 1614. 1H NMR (300MHz, d_6 -DMSO); δ : 5.39 (2H, s, CH_2), 6.50 (2H, br s, NH_2), 6.78 (1H, d, $J = 9.0$ Hz, H3), 7.38 (1H, d, $J = 8.4$ Hz, H7'), 7.51 (1H, d, $J = 8.7$ Hz, H8), 7.65 (1H, br d, $J = 8.7$ Hz, H7), 7.72-7.78 (3H, m, H5, H3', H6'), 7.86 (1H, d, $J = 9.0$ Hz, H4), 8.53 (1H, br d, $J = 8.4$ Hz, H4'), 8.99 (1H, br d $J = 3.0$ Hz, H2'). ^{13}C NMR (150 MHz, d_6 -DMSO); δ : 70.4 (CH_2), 110.2 (C7'), 112.7 (C3), 120.8 (C5'), 122.3 (C4a), 123.0 (C3'), 125.3 (C8), 126.2 (C4a'), 126.8 (C6'), 127.1 (C5), 129.0 (C6), 129.4 (C7), 132.2 (C4'), 136.8 (C4), 140.4 (C8a'), 147.8 (C8a), 149.8 (C2'), 153.7 (C8'), 157.5 (C2). m/z (EI): 335 (M^+ , < 1%), 157 (100).

6-[(7-Bromo-5-chloroquinolin-8-yloxy)methyl]quinoline-2-amine (126)

Using General Procedure 11, **95** (145 mg, 0.32 mmol), K_2CO_3 (132 mg, 0.952 mmol) and methanol (10 mL) were heated for 6 h. The work up was carried out with 10 mL of water to give



the crude product. Chromatographic separation over silica gel eluting with DCM:ethanol (9:1) afforded the title compound as a pale yellow powder, mp 154-157 °C (80 mg, 60%). HRMS found: 414.9892; $C_{19}H_{13}^{81}Br^{35}ClN_3O$ requires 414.9931. IR (nujol mull): ν/cm^{-1} : 3303, 3149, 1629, 1600 and 1573. 1H NMR (600MHz, d_6 -DMSO); δ : 5.49 (2H, s, CH_2), 6.46 (2H, br s, NH_2), 6.75 (1H, d, $J = 8.4$ Hz, H3), 7.45 (1H, d, $J = 8.7$ Hz, H8), 7.72 (1H, dd, $J = 1.8$ Hz, 8.7 Hz, H7), 7.73 (1H, d, $J = 1.8$ Hz, H5), 7.75 (1H, dd, $J = 3.9$ Hz, 8.7 Hz, H3'), 7.87 (1H, d, $J = 8.4$ Hz, H4), 8.02 (1H, s, H6'), 8.55 (1H, dd, $J = 1.2$ Hz, 8.7 Hz, H4'), 9.11 (1H, dd, $J = 1.2$ Hz, 3.9 Hz, H2'). ^{13}C NMR (150 MHz, d_6 -DMSO); δ : 76.1 (CH_2), 112.7 (C3), 115.7 (C7'),

122.1 (C4a), 123.2 (C3'), 125.0 (C8), 125.5 (C5'), 126.2 (C4a'), 127.5 (C5), 129.5 (C6), 129.8 (C6'), 129.7 (C7), 133.2 (C4'), 137.0 (C4), 142.9 (C8a'), 147.8 (C8a), 151.3 (C8'), 151.4 (C2'), 158.5 (C2). *m/z* (EI): 418 (M⁺, [³⁷Cl, ⁸¹Br], < 1%), 416 (M⁺, [³⁵Cl, ⁸¹Br and ³⁷Cl, ⁷⁹Br], < 1), 414 (M⁺, [³⁵Cl, ⁷⁹Br], < 1), 259 (15), 157 (100).

7.3 Extended 6-Phenoxymethyl-2-Aminoquinolines

7.3.1 Synthesis of Phenols

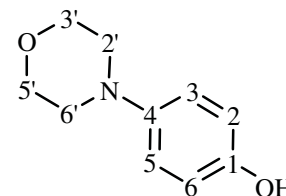
General Procedure 12: Synthesis of Heterocyclic-Substituted Phenols^{61,62}

A pressure tube was loaded with Pd(OAc)₂ and CataCXium[®] A ligand **35** or Pd₂(dba)₃ (2 mol %) and Buchwald ligand (4 mol %) and the aryl halide (1.0 eq) under an inert atmosphere. Dry trifluoromethylbenzene was added followed by the amine (1.2 eq) and the pressure tube was evacuated and backfilled with an inert gas. LHMDs (1.0 M solution, 2.4 eq) was added and the pressure tube was sealed and the mixture heated for 18-24 h at 110 °C. After cooling to room temperature the mixture was quenched with 3 M HCl and stirred for 10 min. The aqueous phase was extracted with chloroform:isopropanol (3:1 mix), neutralised with saturated NaHCO₃ and extracted further. The combined organic material was washed with water, dried over Na₂SO₄ and the solvent removed under reduced pressure. The product was isolated by flash chromatography on silica gel or C18 silica with appropriate solvent mixtures.

7.3.1.1 Synthesis of 4-Substituted Phenols

4-(Morpholin-yl)phenol (**128**)⁶²

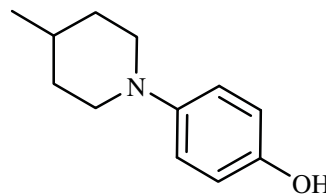
Using General Procedure 12, Pd(OAc)₂ (3 mg, 12 μmol), CataCXium[®] A ligand **35** (8 mg, 23 μmol), 4-bromophenol (100 mg, 0.58 mmol), morpholine (61 μL, 0.69 mmol) and LHMDs (1.0 M in toluene, 4.3 mL) were combined in trifluoromethylbenzene (1 mL) under nitrogen and heated for 20 h. Following work up as above



the crude material was purified by chromatography eluting with DCM:ethanol (49:1) affording the title compound as a cream powder, mp 165-168 °C (lit.,¹⁰² 174-176 °C) (80 mg, 81%). IR (nujol mull): ν/cm^{-1} : 3339, 1513, 1500 and 1459. ¹H NMR (300 MHz, CDCl₃); δ : 3.05 (4H, br t, *J* = 4.5 Hz, 2 x CH₂, H(3'/5')), 3.87 (4H, br t, *J* = 4.5 Hz, 2 x CH₂, H(2'/6')), 4.90 (1H, br s, OH), 6.78 (2H, m, H(2/6)), 6.85 (2H, m, H(3/5)).

4-(4-Methylpiperidin-1-yl)phenol (129)

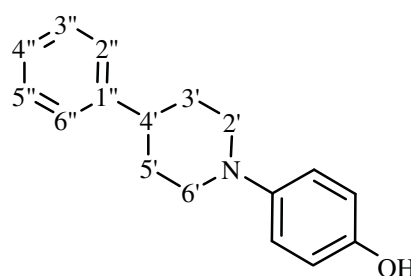
Using General Procedure 12, Pd(OAc)₂ (8 mg, 36 μmol), CataCXium[®] A ligand **35** (26 mg, 71 μmol), 4-bromophenol (308 mg, 1.78 mmol), 4-methylpiperidine (250 μL, 2.14 mmol) and LHMDS (1.0 M in toluene, 4.3 mL) were combined in



trifluoromethylbenzene (1 mL) under nitrogen and was heated for 19 h. Following work up as above the crude material was purified by chromatography eluting with DCM:ethanol (49:1) affording the title compound as a cream solid, mp 116-119 °C (275 mg, 81%). Analysis found: C, 75.20; H, 8.90; N, 7.12. C₁₁H₁₂NO requires C, 75.35; H, 8.96; N, 7.32%. IR (nujol mull): ν/cm^{-1} : 3301, 1613, 1591 and 1515. ¹H NMR (300 MHz, CDCl₃); δ : 0.98 (3H, d, $J = 6.0$ Hz, CH₃), 1.43 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, 4'} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.45 (1H, m, CH, H4'), 1.74 (2H, br d[‡], $J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.61 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.46 (2H, br d[‡], $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 4.75 (1H, br s, OH), 6.75 (2H, m, H(2/6)), 6.88 (2H, m, H(3/5)). ¹³C NMR (75 MHz, CDCl₃); δ : 22.0 (CH₃), 30.6 (C4'), 34.3 (C3'/5'), 52.4 (C2'/6'), 116.1 (C2/6), 119.7 (C3/5), 145.9 (C4) 150.5 (C1). m/z (EI): 190 (M-H⁺, 100%), 148 (20), 122 (10), 121 (20), 120 (20).

4-(4-Phenylpiperidin-1-yl)phenol (130)

Using General Procedure 12, Pd(OAc)₂ (8 mg, 36 μmol), CataCXium[®] A ligand **35** (25 mg, 70 μmol), 4-bromophenol (305 mg, 1.76 mmol), 4-phenylpiperidine (340 mg, 2.11 mmol) and LHMDS (1.0 M in toluene, 4.2 mL) were combined in trifluoromethylbenzene (1 mL) under nitrogen and was heated for 22 h. Following work

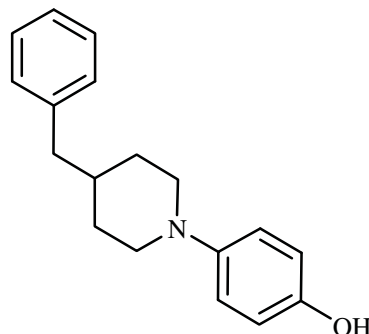


up as above the crude material was purified by chromatography eluting with DCM:ethyl acetate (17:3) affording the title compound as a pale pink solid, mp 163-164 °C (189 mg, 43%). Analysis found: C, 80.73; H, 7.46; N, 5.53. C₁₇H₁₉NO requires C, 80.60; H, 7.56; N, 5.53%. IR (nujol mull): ν/cm^{-1} : 3460, 1601 and 1514. ¹H NMR (200 MHz, CDCl₃); δ : 1.95-1.99 (4H, m, H(3'/5')_{ax}, H(3'/5')_{eq}), 2.58-2.82 (3H, m, 3 x CH, H4', H(2'/6')_{ax}), 3.66 (2H, br d[‡], $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (2'/6')\text{ax}} = 12.0$ Hz, 2 x CH, H(2'/6')_{eq}), 4.53 (1H, br s, OH), 6.78 (2H, m, H(2/6)), 6.93 (2H, br d, $J = 8.7$, H(3/5)), 7.22-7.33 (5H, m, Ph). ¹³C NMR (75 MHz, CDCl₃); δ : 33.5 (C3'/5'), 42.4 (C4'), 52.8 (C2'/6'), 116.22 (C4''), 119.8 (C2/6), 126.5 (C3/5),

127.1 (C2''/6''), 128.7 (C3''/5''), 145.9 (C1''), 146.2 (C4) 150.5 (C1). *m/z* (EI): 253 (M⁺, 100%), 148 (45), 122 (10), 121 (30), 120 (30), 57 (20).

4-(4-Benzylpiperidin-1-yl)phenol (131)

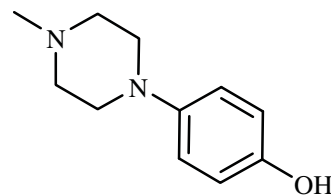
Using General Procedure 12, Pd(OAc)₂ (8 mg, 36 μmol), CataCXium[®] A ligand **35** (25 mg, 70 μmol), 4-bromophenol (301 mg, 1.74 mmol), 4-benzylpiperidine (370 μL, 2.10 mmol) and LHMDS (1.0 M in toluene, 4.2 mL) were combined in trifluoromethylbenzene (2 mL) under nitrogen and was heated for 24 h. Following work up as above the crude material was purified by chromatography eluting with DCM:ethanol (24:1)



affording the title compound as a pink powder, mp 200-204 °C (317 mg, 69%). Analysis found: C, 79.03; H, 7.74; N, 5.12. C₁₈H₂₀NO.0.33H₂O requires C, 79.08; H, 7.99; N, 5.12%. IR (nujol mull): ν/cm^{-1} : 3310, 1614, 1592 and 1511. ¹H NMR (200 MHz, CDCl₃); δ : 1.44 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 4.2$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.74 (1H, m, CH, H4'), 1.80 (2H, br d[‡], $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.50-2.61 (4H, m, CH₂, 2 x CH, H(2'/6')_{ax}), 3.46 (2H, br d[‡], $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (2'/6')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 4.50 (1H, br s, OH), 6.73 (2H, m, H(2/6)), 6.86 (2H, m, H(3/5)), 7.15-7.30 (5H, m, Ph). ¹³C NMR (75 MHz, CDCl₃); δ : 32.2 (C3'/5'), 37.5 (C4'), 43.0 (CH₂), 51.8 (C2'/6'), 115.6 (C2/6), 118.9 (C3/5), 125.6 (C4''), 128.0 (C2''/6''), 129.0 (C3''/5''), 140.4 (C1''), 145.0 (C4), 151.0 (C1). *m/z* (EI): 267 (M⁺, 100%), 161 (30), 148 (25), 122 (30), 121 (15), 120 (20), 55 (20).

4-(4-Methylpiperazin-1-yl)phenol (132)⁶²

(i) Using General Procedure 12, Pd(OAc)₂ (8 mg, 36 μmol), CataCXium[®] A ligand **35** (25 mg, 70 μmol), 4-bromophenol (300 mg, 1.73 mmol), 1-methylpiperazine (230 μL, 2.10 mmol) and LHMDS (1.0 M in toluene, 4.2 mL) were combined in



trifluoromethylbenzene (1 mL) under nitrogen and was heated for 24 h. Following work up as above the crude material was purified by chromatography on C18 silica eluting with methanol:water (3:2) affording the title compound as a cream solid, mp 195-197 °C (190 mg, 57%). IR (DCM): ν/cm^{-1} : 3300, 3000, 1654, 1604, 1551 and 1513. ¹H NMR (200 MHz, CDCl₃); δ : 2.39 (3H, s, CH₃), 2.66 (4H, t, $J = 4.8$ Hz, H(3'/5')), 3.12 (4H, br t, $J = 4.8$ Hz,

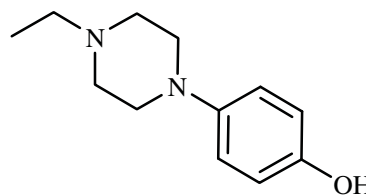
H(2'/6')), 6.75 (2H, m, H(2/6)), 6.85 (2H, m, H(3/5)).

The ^1H NMR data is consistent with that reported in the literature.⁶² No melting point was reported.

(ii)⁶¹ Using General Procedure 12, $\text{Pd}_2(\text{dba})_3$ (10 mg, 12 μmol), Dave Phos **57** (9 mg, 23 μmol), 4-bromophenol (100 mg, 0.58 mmol), 1-methylpiperazine (77 μL , 0.70 mmol) and LHMDS (1.0 M in toluene, 1.4 mL) were combined in trifluoromethylbenzene (1 mL) under nitrogen and heated for 22 h. Work up as above afforded starting material only.

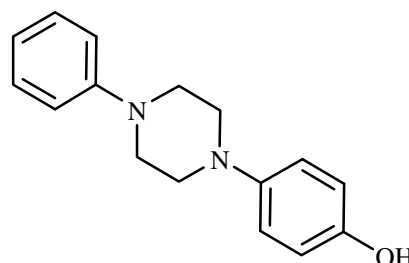
4-(4-Ethylpiperazin-1-yl)phenol (**133**)

Using General Procedure 12, $\text{Pd}(\text{OAc})_2$ (8 mg, 36 μmol), CataCXium[®] A ligand **35** (25 mg, 70 μmol), 4-bromophenol (300 mg, 1.73 mmol), 1-ethylpiperazine (265 μL , 2.10 mmol) and LHMDS (1.0 M in toluene, 4.2 mL) were combined in trifluoromethylbenzene (1 mL) under nitrogen and was heated for 24 h. Following work up as above the crude material was purified by chromatography on C18 silica eluting with methanol:water (3:2) affording the title compound as an orange solid, mp 238-240 °C (210 mg, 59%). Analysis found: C, 69.87; H, 8.73; N, 13.62. $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$ requires C, 69.87; H, 8.80; N, 13.58%. IR (nujol mull): ν/cm^{-1} : 3301, 1654, 1613, 1588 and 1513. ^1H NMR (300 MHz, CDCl_3); δ : 1.14 (3H, t, $J = 7.2$ Hz, CH_3), 2.50 (2H, q, $J = 7.2$ Hz, CH_2), 2.63 (4H, br t, $J = 4.8$ Hz, H(3'/5')), 3.12 (4H, br t, $J = 4.8$ Hz, H(2'/6')), 6.77 (2H, m, H(2/6)), 6.87 (2H, m, H(3/5)). ^{13}C NMR (75 MHz, CDCl_3); δ : 11.7 (CH_3), 50.6 ($\text{C}2'/6'$), 52.2 (CH_2), 52.8 ($\text{C}3'/5'$), 115.8 ($\text{C}2/6$), 118.5 ($\text{C}3/5$), 144.4 ($\text{C}4$), 151.4 ($\text{C}1$). m/z (EI): 206 (M^+ , 100%), 191 (20), 127 (15), 122 (25), 121 (40), 120 (20), 70 (20), 57 (65).



4-(4-Phenylpiperazin-1-yl)phenol (**134**)

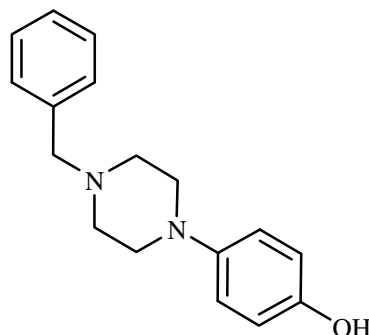
Using General Procedure 12, $\text{Pd}(\text{OAc})_2$ (13 mg, 58 μmol), CataCXium[®] A ligand **35** (42 mg, 120 μmol), 4-bromophenol (500 mg, 2.90 mmol), 1-phenylpiperazine (530 μL , 3.48 mmol) and LHMDS (1.0 M in toluene, 7.0 mL) were combined in trifluoromethylbenzene (1 mL) under nitrogen and was heated for 24 h. Following work up as above the crude material was purified by chromatography eluting with DCM:ethyl acetate (17:3) affording the title compound as a cream solid, mp 186-188 °C (172 mg, 23%). HRMS found: 254.1415;



$C_{16}H_{18}N_2O$ requires 254.1419. Analysis found: C, 74.81; H, 7.15; N, 10.82. $C_{16}H_{19}N_2O \cdot 0.2H_2O$ requires C, 74.51; H, 7.19; N, 10.86%. IR (nujol mull): ν/cm^{-1} : 3350, 1600, 1513 and 1500. 1H NMR (300 MHz, $CDCl_3$); δ : 3.24 (4H, br t, $J = 4.8$ Hz, H(3'/5')), 3.35 (4H, br t, $J = 4.8$ Hz, H(2'/6')), 4.62 (1H, br s, OH), 6.80 (2H, m, H(2/6)), 6.88-6.96 (3H, m, H(3/5), H4''), 7.00 (2H, dd, $J = 1.2, 9.0$ Hz, H(2''/6'')), 7.30 (2H, dd, $J = 9.0$ Hz, H(3''/5'')). ^{13}C NMR (75 MHz, $CDCl_3$); δ : 49.7 (C2'/6'), 51.3 (C3'/5'), 116.4 (C2/6), 116.6 (C2''/6''), 119.1 (C3/5), 120.4 (C4''), 129.4 (C3''/5''), 145.4 (C4), 150.4 (C1), 151.3 (C1''). m/z (EI): 254 (M^+ , 100%), 148 (20), 132 (20), 122 (5), 121 (45), 120 (25), 105 (40).

4-(4-Benzylpiperazin-1-yl)phenol (135)

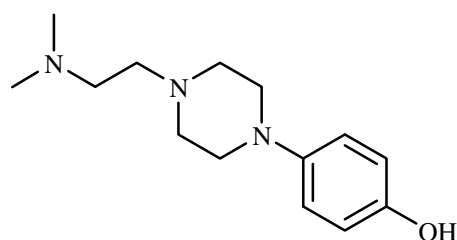
Using General Procedure 12, $Pd(OAc)_2$ (13 mg, 58 μ mol), CataCXium[®] A ligand **35** (41 mg, 120 μ mol), 4-bromophenol (500 mg, 2.90 mmol), 1-benzylpiperazine (600 μ L, 3.48 mmol) and LHMDS (1.0 M in toluene, 7.0 mL) were combined in trifluoromethylbenzene (2 mL) under nitrogen and was heated for 24 h. Following work up as above the crude material was purified by chromatography eluting with DCM:ethanol (19:1)



affording the title compound as an orange solid, mp 170-173 $^{\circ}C$ (210 mg, 27%). HRMS found: 268.1576; $C_{17}H_{20}N_2O$ requires 268.1576. IR (chloroform): ν/cm^{-1} : 3668, 3599, 3087, 3066, 2853, 2819, 2772, 1665, 1609, 1513 and 1496. 1H NMR (300 MHz, $CDCl_3$); δ : 2.07 (1H, br s, OH), 2.64 (4H, br t, $J = 4.8$ Hz, 2 x CH_2 , H(3'/5')), 3.09 (4H, br t, $J = 4.8$ Hz, 2 x CH_2 , H(2'/6')), 3.60 (2H, s, CH_2), 6.75 (2H, m, H(2/6)), 6.84 (2H, m, H(3/5)), 7.27-7.39 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$); δ : 50.8 (C2'/6'), 53.2 (C3'/5'), 63.15 (CH_2), 116.5 (C2/6), 118.8 (C3/5), 127.5 (C4''), 128.6 (C3''/5''), 129.7 (C2''/6''), 137.4 (C1''), 145.3 (C4), 150.6 (C1). m/z (EI): 268 (M^+ , 100%), 177 (20), 148 (10), 146 (25), 122 (55), 121 (40), 120 (30), 91 (55).

4-{4-[2-(Dimethylamino)ethyl]piperazin-1-yl}phenol (136)

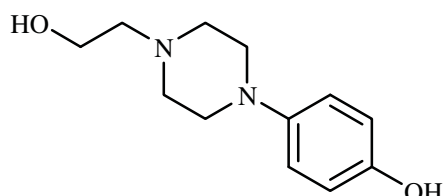
Using General Procedure 12, Pd(OAc)₂ (13 mg, 58 μmol), CataCXium[®] A ligand **35** (39 mg, 116 μmol), 4-bromophenol (500 mg, 2.9 mmol), 4-(*N,N*-dimethylaminoethyl)piperazine (547 mg, 3.5 mmol) and LHMDS (1.0 M in toluene, 7.0 mL) were combined in



trifluoromethylbenzene (2 mL) under nitrogen and was heated for 21 h. Following work up as above the crude material was purified by chromatography on C18 silica eluting with methanol:water (3:2) affording the title compound as an orange solid, mp 128-130 °C (332 mg, 46%). HRMS found: 249.1839; C₁₄H₂₃N₃O requires 249.1841. IR (nujol mull): ν/cm⁻¹: 3400, 1667, 1620, 1608 and 1513. ¹H NMR (200 MHz, CDCl₃); δ: 2.30 (6H, s, 2 x CH₃), 2.54 (4H, m, 2 x CH₂), 2.64 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(3'/5')), 3.04 (4H, br t, *J* = 4.8 Hz, 2 x CH₂, H(2'/6')), 6.73 (2H, m, H(2/6)), 6.81 (2H, m, H(3/5)). ¹³C NMR (75 MHz, CDCl₃); δ: 45.5 (2 x CH₃), 50.2 (C2'/6'), 52.9 (CH₂), 53.3 (CH₂), 57.3 (C3'/5'), 115.5 (C2/6), 117.7 (C3/5), 144.0 (C4), 151.3 (C1). *m/z* (EI): 191 (100%), 148 (30), 120 (10), 70 (30), 58 (20).

Attempted synthesis of 4-{4-[2-(hydroxyethyl)piperazin-1-yl}phenol (137)

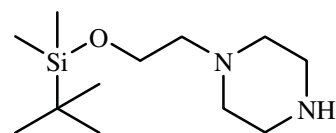
Using General Procedure 12, Pd(OAc)₂ (2.6 mg, 12 μmol), CataCXium[®] A ligand **35** (8 mg, 23 μmol), 4-bromophenol (100 mg, 0.58 mmol), 4-(2-hydroxyethyl)piperazine (91 mg, 0.70 mmol) and



LHMDS (1.0 M in toluene, 1.4 mL) were combined in trifluoromethylbenzene (2 mL) under nitrogen and was heated for 22 h. Work up as above led to the recovery of starting material only.

Attempted protection of 4-(2-hydroxyethyl)piperazine as the TBDMS ether (138)¹⁰³

4-(2-Hydroxyethyl)piperazine (600 mg, 4.60 mmol), ^tbutyldimethylsilyl chloride (832 mg, 5.52 mmol) and imidazole (783 mg, 11.5 mmol) were combined in DMF (2 mL) and the

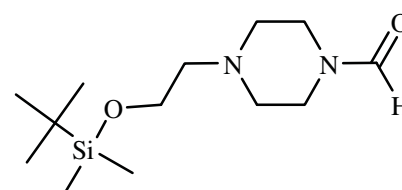


reaction was heated at 50 °C for 20 h. The mixture was cooled to room temperature and extracted with chloroform:isopropanol (3:1 mix) and washed with saturated NaHCO₃ and water. The organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude material was chromatographed over silica gel eluting with DCM affording the protected aldehyde (4-(2-hydroxyethyl)piperazine-

1-carbaldehyde)-*t*-butyldimethylsilane **140** as a clear liquid (900 mg, 80%).

IR (nujol mull): ν/cm^{-1} : 3667, 3440, 1673 and 1442. ^1H

NMR (600 MHz, CDCl_3); δ : 0.07 (6H, s, 2 x CH_3), 0.90 (9H, s, *t*-Bu), 2.49 (2H, t, $J = 5.1$ Hz, CH_2 , H3), 2.55-2.59 (4H, m, 2 x CH_2 , H5, CH_2 -N), 3.38 (2H, t, $J = 5.1$ Hz, CH_2 ,



H6), 3.56 (2H, t, $J = 5.1$ Hz, CH_2 , H2), 3.76 (2H, t, $J = 6.0$ Hz, CH_2 -O), 7.95 (1H, s CHO).

^{13}C NMR (150 MHz, CDCl_3); δ : -5.4 (2 x CH_3), 18.2 ($\text{C}(\text{CH}_3)_3$), 25.8 ($\text{C}(\text{CH}_3)_3$), 39.9 (C2), 45.6 (C6), 52.9 (C3), 54.1 (C5), 60.3 (CH_2 -N), 61.2 (CH_2 -O), 160.6 (CHO). m/z (EI): 215 (M^+ -*t*-Bu, 100%), 171 (40), 141 (20), 127 (40), 111 (35), 97 (45), 73 (55), 57 (65), 43 (50).

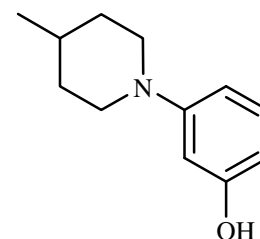
7.3.1.2 Synthesis of 3-Substituted Phenols

Buchwald-Hartwig Amination of 3-Bromophenol

3-(4-Methylpiperidin-1-yl)phenol (**141**)

(i) Under nitrogen

Using General Procedure 12, $\text{Pd}(\text{OAc})_2$ (13 mg, 58 μmol), CataCXium[®] A ligand **35** (39 mg, 120 μmol), 3-bromophenol (500 mg, 2.9 mmol), 4-methylpiperidine (412 μL , 3.48 mmol) and LHMDS (1.0 M in toluene, 7.0 mL) were combined in trifluoromethylbenzene (5 mL)



under nitrogen and was heated for 24 h. Following work up as above the crude material was chromatographed over silica gel eluting with DCM:ethanol (19:1) to afford the title compound **141** as a brown low melting solid (75 mg, 14%). In addition, 3-(4-methylpiperidin-1-yl)-4-(4-methylpiperidin-2-yl)phenol **142** was also isolated as a 1:1 mixture with an unidentified product (combined yield 200 mg, **142** ~20%).

3-(4-Methylpiperidin-1-yl)phenol (141): HRMS found: 191.1306; $\text{C}_{12}\text{H}_{17}\text{NO}$ requires 191.1310. IR (DCM): ν/cm^{-1} : 3598, 2927, 1615, 1586 and 1496. ^1H NMR (300 MHz, CDCl_3); δ : 0.98 (3H, d, $J = 6.3$ Hz, CH_3), 1.34 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, 4'} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.50 (1H, m, CH, H4'), 1.72 (2H, br d[‡], $J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.68 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.61 (2H, br d[‡], $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 6.30 (1H, ddd, $J = 2.4, 8.4$ Hz, H6), 6.41 (1H, t, $J = 2.4$ Hz, H2), 6.53 (1H, ddd, $J = 2.4, 8.4$, H4), 7.09 (1H, t, $J = 8.4$ Hz,

H5). ^{13}C NMR (150 MHz, CDCl_3); δ : 22.0 (CH_3), 30.9 ($\text{C4}'$), 34.0 ($\text{C3}'/5'$), 50.2 ($\text{C2}'/6'$), 104.0 (C2), 106.8 (C6), 109.2 (C4), 130.1 (C5), 153.3 (C3), 156.9 (C1). m/z (EI): 191 (M^+ , 70%), 190 ($\text{M}-\text{H}^+$, 100), 148 (25), 122 (10), 121 (20), 120 (10).

3-(4-Methylpiperidin-1-yl)-4-(4-methylpiperidin-2-yl)phenol (142):

HRMS found: 288.2197; $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}$ requires 288.2201. IR (DCM):

ν/cm^{-1} : 3133, 2956, 2928, 1619, 1582, 1524 and 1456. ^1H NMR

(600 MHz, CDCl_3); δ : 0.94 (3H, d, $J = 7.8$ Hz, CH_3'), 1.00 (3H, d, J

$= 7.2$ Hz, CH_3''), 1.21 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 2.4$ Hz, $J_{(2'/6')\text{ax},$

$(3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, 4'} = 12.0$ Hz, 2 x CH, $\text{H}(3'/5')\text{ax}$),

1.43-1.47 (2H, m, CH, $\text{H4}'$, $\text{H4}''$), 1.68 (2H, br t ‡ , $J_{(3'/5')\text{ax}, (3'/5')\text{eq}} =$

$J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.0$ Hz, 2 x CH, $\text{H}(3'/5')\text{eq}$), 1.82 (1H, d ‡ , $J_{2''\text{ax}, 3''\text{ax}} = J_{3''\text{ax}, 4''} = 12.0$ Hz,

$\text{H3}''\text{ax}$), 1.93 (1H, br t ‡ , $J_{2''\text{ax}, 3''\text{eq}} = 2.4$ Hz, $J_{2''\text{eq}, 3''\text{eq}} = J_{3''\text{ax}, 3''\text{eq}} = J_{3''\text{eq}, 4''} = 12.0$ Hz, $\text{H3}''\text{eq}$),

2.57 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.0$ Hz, 2 x CH,

$\text{H}(2'/6')\text{ax}$), 2.76-2.80 (2H, m, $\text{H5}''\text{ax}$, $\text{H6}''\text{ax}$), 2.98 (1H, m, $\text{H5}''\text{eq}$), 3.26 (1H, d ‡ , $J_{6''\text{ax}, 6''\text{eq}} =$

$J_{5''\text{eq}, 6''\text{eq}} = 12.0$ Hz, $\text{H6}''\text{eq}$), 3.61 (2H, br d ‡ , $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.0$ Hz, 2 x CH,

$\text{H}(2'/6')\text{eq}$), 4.05 (1H, dd, $J_{3''\text{eq}, 2''} = 2.4$ Hz, $J_{3''\text{ax}, 2''} = 12.0$ Hz, $\text{H2}''$), 6.35 (1H, dd, $J = 1.8, 8.7$

Hz, H6), 6.82 (1H, d, $J = 1.8$ Hz, H2), 7.08 (1H, d, $J = 8.7$ Hz, H5), 8.50 (1H, br s, OH). ^{13}C

NMR (150 MHz, CDCl_3); δ : 21.8 (CH_3'), 22.2 (CH_3''), 30.7 ($\text{C4}'$), 31.1 ($\text{C4}''$), 33.9 ($\text{C3}''$),

34.0 ($\text{C3}'/5'$), 40.4 ($\text{C5}''$), 46.9 ($\text{C2}''$), 49.6 ($\text{C2}'/6'$), 60.0 ($\text{C6}''$), 104.5 (C6), 107.1 (C4),

118.6 (C2), 127.3 (C3), 152.4 (C5), 157.9 (C1). m/z (EI): 288 (M^+ , 70%), 273 (15), 259 (15),

245 (100), 232 (20), 218 (30), 204 (20), 190 (30), 122 (15), 121 (10), 120 (10).

(ii) Under argon

Using General Procedure 12, $\text{Pd}(\text{OAc})_2$ (13 mg, 58 μmol),

CataCXium[®] A ligand **35** (39 mg, 120 μmol) and

3-bromophenol (500 mg, 2.9 mmol), 4-methylpiperidine

(412 μL , 3.48 mmol) and LHMDS (1.0 M in toluene, 7.0

mL) were combined in trifluoromethylbenzene (2 mL)

under argon and heated for 24 h. Following work up as

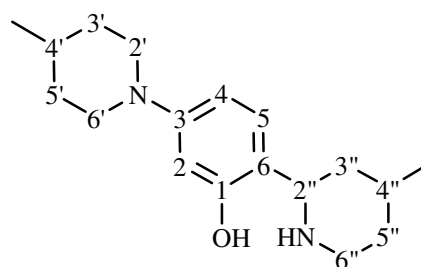
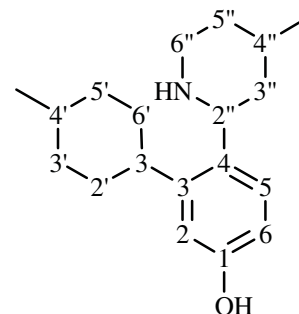
above the crude material was chromatographed over silica gel eluting with DCM:ethanol

(19:1) to afford 3-(4-methylpiperidin-1-yl)-6-(4-methylpiperidin-2-yl)phenol **143**, as a brown

sticky solid (233 mg, 47%).

3-(4-Methylpiperidin-1-yl)-6-(4-methylpiperidin-2-yl)phenol (143): HRMS found: 288.2201;

$\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}$ requires 288.2201. IR (DCM): ν/cm^{-1} : 2954, 2927, 1625, 1570, 1515 and 1456.



^1H NMR (600 MHz, CDCl_3); δ : 0.94 (3H, d, $J = 5.4$ Hz, CH_3''), 0.95 (3H, d, $J = 5.4$ Hz, CH_3'), 1.16 (1H, dq, $J_{5''\text{ax}, 6''\text{eq}} = 2.4$ Hz, $J_{5''\text{ax}, 6''\text{ax}} = J_{5''\text{ax}, 5''\text{eq}} = J_{4'', 5''\text{ax}} = 12.6$ Hz, $\text{H}5''_{\text{ax}}$), 1.32 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, 4'} = 12.6$ Hz, 2 x CH, $\text{H}(3'/5')_{\text{ax}}$), 1.33 (1H, m, $\text{H}3''_{\text{ax}}$), 1.48 (1H, m, CH, $\text{H}4'$), 1.57 (1H, m, CH, $\text{H}4''$), 1.66 (1H, br d^\ddagger , $J_{5''\text{eq}, 5''\text{ax}} = J_{6''\text{eq}, 5''\text{eq}} = 12.6$ Hz, $\text{H}5''_{\text{eq}}$), 1.69 (2H, br d^\ddagger , $J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, $\text{H}(3'/5')_{\text{eq}}$), 1.80 (1H, br d^\ddagger , $J_{3''\text{ax}, 3''\text{eq}} = 12.6$ Hz, $\text{H}3''_{\text{eq}}$), 2.67 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.6$ Hz, 2 x CH, $\text{H}(2'/6')_{\text{ax}}$), 2.70 (1H, dt, $J_{5''\text{eq}, 6''\text{ax}} = 2.4$ Hz, $J_{6''\text{eq}, 6''\text{ax}} = J_{5''\text{ax}, 6''\text{ax}} = 12.6$ Hz, $\text{H}6''_{\text{ax}}$), 3.17 (1H, dt, $J_{5''\text{ax}, 6''\text{eq}} = 2.4$, $J_{6''\text{ax}, 6''\text{eq}} = J_{5''\text{eq}, 6''\text{eq}} = 12.6$ Hz, $\text{H}6''_{\text{eq}}$), 3.61 (2H, br d^\ddagger , $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, $\text{H}(2'/6')_{\text{eq}}$), 3.69 (1H, dd, $J_{2'', 3''\text{eq}} = 2.4$ Hz, $J_{2'', 3''\text{ax}} = 12.6$ Hz, $\text{H}2''$), 6.36 (1H, dd, $J = 2.4$, 9.0 Hz, $\text{H}4$), 6.42 (1H, t, $J = 2.4$ Hz, $\text{H}6$), 6.83 (1H, d, $J = 9.0$ Hz, $\text{H}3$). ^{13}C NMR (150 MHz, CDCl_3); δ : 21.8 (CH_3'), 22.2 (CH_3''), 30.7 ($\text{C}4'$), 31.1 ($\text{C}4''$), 33.9 ($\text{C}3''$), 34.0 ($\text{C}3'/5'$), 40.4 ($\text{C}5''$), 46.9 ($\text{C}2''$), 49.6 ($\text{C}2'/6'$), 60.0 ($\text{C}6''$), 104.5 ($\text{C}6$), 107.1 ($\text{C}4$), 118.6 ($\text{C}2$), 127.3 ($\text{C}3$), 152.4 ($\text{C}5$), 157.9 ($\text{C}1$). m/z (EI): 288 (M^+ , 80%), 273 (20), 259 (20), 245 (100), 232 (100), 218 (40), 204 (20), 190 (15), 148 (15), 121 (10).

(iii) With LDA/ NaO^tBu ⁶²

A pressure tube was loaded with 3-bromophenol (50 mg, 0.29 mmol) in trifluoromethylbenzene (2 mL) and LDA (0.29 mmol in THF) was added under an argon atmosphere. The reaction mixture was allowed to stir for 30 min at room temperature and $\text{Pd}(\text{OAc})_2$ (1.3 mg, 6 μmol), CataCXium[®] A ligand **35** (4.2 mg, 12 μmol), NaO^tBu (39 mg, 0.41 mmol) and 4-methylpiperidine (41 μL , 0.35 mmol) were added. The pressure tube was evacuated, backfilled with argon, sealed and the mixture stirred for 20 h at 100 °C. After cooling to room temperature the mixture was quenched with 3 M HCl and stirred for 10 min. The aqueous phase was extracted with chloroform:isopropanol (3:1 mix), neutralised with saturated NaHCO_3 and extracted further. The combined organic material was washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure. NMR analysis of the crude material showed no evidence of the desired product.

(iv) Catalyst screen. General Procedure 13.⁶¹ A pressure tube was loaded with $\text{Pd}(\text{OAc})_2$ (1.3 mg, 6 μmol), or $\text{Pd}_2(\text{dba})_3$ (5.3 mg, 6 μmol), Buchwald ligand (4 mol %) and 3-bromophenol (50 mg, 0.29 mmol) under an argon atmosphere. Dry trifluoromethylbenzene (2 mL) was added followed by 4-methylpiperidine (41 μL , 0.35 mmol) and LHMDs (1.0 M in toluene, 0.7 mL). The pressure tube was evacuated, backfilled with argon, sealed and the mixture stirred at 90 °C for 19 h. After cooling to room temperature the mixture was quenched with 3 M HCl and stirred for 10 min. The aqueous phase was extracted with

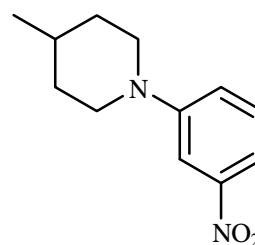
chloroform:isopropanol (3:1 mix), neutralised with saturated NaHCO₃ and extracted further. The combined organic material was washed with water, dried over Na₂SO₄ and the solvent removed under reduced pressure.

a) **With Pd(OAc)₂.** The use of Pd(OAc)₂ and one of the Buchwald Ligands DavePhos **57**, X-Phos **58**, S-Phos **59**, ^tBu X-Phos **60**, CyJohnPhos **61** and ^tBu Phos **62** using General Procedure 13 all lead to the recovery of predominantly starting material.

b) **With Pd₂(dba)₃.** The use of Pd₂(dba)₃ and one of the Buchwald Ligands DavePhos **57**, X-Phos **58**, S-Phos **59**, ^tBu X-Phos **60**, CyJohnPhos **61** and ^tBu Phos **62** using General Procedure 13 all led to the recovery of predominantly starting material.

Attempted synthesis of 3-(4-methylpiperidin-1-yl)nitrobenzene (**146**)

(i) Using General Procedure 12, Pd(OAc)₂ (2.2 mg, 10 μmol), CataCXium[®] A ligand **35** (7 mg, 20 μmol), 1-bromo-3-nitrobenzene (100 mg, 0.50 mmol), 4-methylpiperidine (71 μL, 0.60 mmol) and LHMDS (1.0M solution, 1.1 mL) were combined in trifluoromethylbenzene (1 mL) under an argon atmosphere and was



heated for 19 h. Following work up as above, NMR analysis of the crude material indicated a complex mixture of products that was not purified.

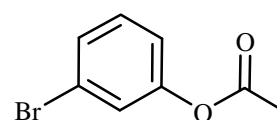
(ii)⁵⁴ Using General Procedure 12, Pd₂(dba)₃ (9.0 mg, 10 μmol), Dave Phos **57** (8 mg, 20 μmol), 1-bromo-3-nitrobenzene (100 mg, 0.50 mmol), 4-methylpiperidine (71 μL, 0.60 mmol) and LHMDS (1.0M solution, 1.1 mL) were combined in trifluoromethylbenzene (1 mL) under an argon atmosphere and heated for 19 h. Following work up as above NMR analysis of the crude material indicated a complex mixture of products that was not purified.

Phenol Protection

1. Acyl Protection

3-Bromophenyl acetate (**148**)¹²⁶

3-Bromophenol (3.0 g, 17.0 mmol) was dissolved in pyridine (8 mL, 100.0 mmol) and acetic anhydride (8.0 mL, 85.0 mmol) and the reaction was heated at 100 °C under an atmosphere of nitrogen for

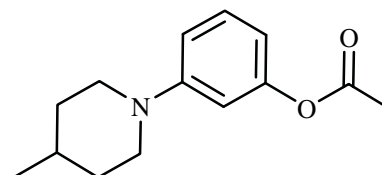


3 h. The mixture was cooled to room temperature and ice water was added. The organic material was extracted with DCM, washed with 5% HCl (x 2), water and dried over MgSO₄. The solvent was removed under reduced pressure to afford the title compound as a yellow

liquid (3.52 g, 96%). IR (neat): ν/cm^{-1} : 3519, 3023, 2937, 1762, 1583 and 1471. ^1H NMR (300 MHz, CDCl_3); δ : 2.30 (3H, s, CH_3), 7.04 (1H, ddd, $J = 1.8, 2.1, 8.1$ Hz, H6), 7.25 (1H, t, $J = 8.1$ Hz, H5), 7.29 (1H, t, $J = 1.8$ Hz, H2), 7.37 (1H, ddd, $J = 1.8, 2.1, 8.1$ Hz, H4).

Attempted synthesis of 3-(4-methylpiperidin-1-yl)phenyl acetate (**149**)

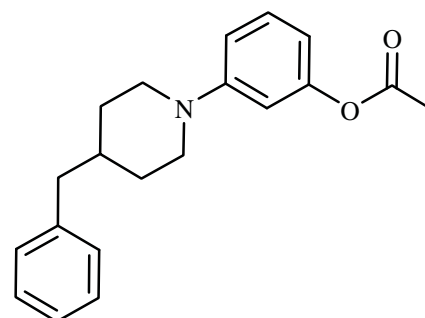
Using General Procedure 12, $\text{Pd}(\text{OAc})_2$ (13 mg, 58 μmol), CataCXium[®] A ligand **35** (39 mg, 120 μmol), **148** (623 mg, 2.9 mmol), 4-methylpiperidine (412 μL , 3.48 mmol) and LHMDS (1.0 M in toluene, 7.0 mL) were combined in



trifluoromethylbenzene (2 mL) under an argon atmosphere and was heated for 24 h. Following work up as above NMR analysis of the crude material indicated a complex mixture of products that was not purified.

3-(4-Benzylpiperidin-1-yl)phenyl acetate (**145**)¹²⁶

Using General Procedure 12, $\text{Pd}(\text{OAc})_2$ (13 mg, 58 μmol), CataCXium[®] A ligand **35** (39 mg, 120 μmol), 3-bromophenol (500 mg, 2.9 mmol), 4-benzylpiperidine (620 μL , 3.48 mmol) and LHMDS (1.0 M in toluene, 7.0 mL) were combined in trifluoromethylbenzene (2 mL) under an argon atmosphere and was heated for 20 h.



Following work up as above the crude material was chromatographed over alumina eluting with DCM:hexane (17:3) affording 3-(4-benzylpiperidin-1-yl)phenol **144** as an impure mixture. This impure mixture (420 mg, 70% purity), was dissolved in pyridine (1.0 mL) and acetic anhydride (1.0 mL) and the reaction was heated at 100 °C under an atmosphere of nitrogen for 3 h. The mixture was cooled to room temperature and ice water was added. The organic material was extracted with DCM, washed with 5% HCl (x 2) and water and dried over MgSO_4 . The solvent was removed under reduced pressure and the crude material was chromatographed over silica gel eluting with DCM:ethyl acetate (9:1) affording the title compound **145** as an orange oil (120 mg, 12% over 2 steps). Analysis found: C, 77.45; H, 7.79; N, 4.44. $\text{C}_{20}\text{H}_{23}\text{NO}_2$ requires C, 77.64; H, 7.49; N, 4.53%. IR (neat): ν/cm^{-1} : 3066, 3029, 2927, 2850, 1764, 1606 and 1579. ^1H NMR (300 MHz, CDCl_3); δ : 1.41 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 4.2$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.64 (1H, m, CH, H4'), 1.74 (2H, br d[‡], $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH,

H(3'/5')_{eq}), 2.29 (3H, s, CH₃), 2.58 (2H, d, $J = 7.2$ Hz, CH₂), 2.68 (2H, dt, $J_{(2'/6')_{ax}, (3'/5')_{eq}} = 4.2$ Hz, $J_{(2'/6')_{ax}, (2'/6')_{eq}} = J_{(2'/6')_{ax}, (3'/5')_{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.65 (2H, br d[‡], $J_{(2'/6')_{eq}, (3'/5')_{eq}} = J_{(2'/6')_{eq}, (2'/6')_{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 6.52 (1H, ddd, $J = 2.1, 2.4, 7.8$ Hz, H6), 6.60 (1H, t, $J = 2.1$ Hz, H2), 6.78 (1H, ddd, $J = 2.1, 2.4, 7.8$ Hz, H4), 7.16-7.33 (6H, m, H5, Ph). ¹³C NMR (75 MHz, CDCl₃); 21.3 (CH₃), 31.9 (C3'/5'), 38.0 (C4'), 43.2 (CH₂), 49.6 (C2'/6'), 109.3 (C2), 111.8 (C6), 113.7 (C4), 126.1 (C4''), 128.4 (C2''/6''), 129.3 (C3''/5''), 129.7 (C5), 140.5 (C1''), 151.8 (C3), 153.0 (C1) 169.7 (C=O). *m/z* (EI): 309 (M⁺, 100), 267 (50), 203 (35), 148 (20), 122 (20), 91 (25), 55 (25).

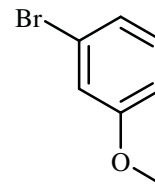
General Procedure 14: Buchwald Hartwig Amination of Protected 3-Bromophenols^{54,71,90}

A pressure tube was loaded with Pd(OAc)₂ (2 mol %), CataCXium[®] A ligand **35** (4 mol %) and NaO^tBu (1.2 eq) under an argon atmosphere. Anhydrous trifluoromethylbenzene was added, followed by the protected 3-bromophenol (1 eq) and the amine (1.2 eq). The tube was evacuated, backfilled with argon, sealed and then the mixture was stirred for the described time at 100 °C. After cooling, the mixture was either filtered through celite and the solvent removed under reduced pressure or diluted with an organic solvent and washed with water and/or brine, dried over MgSO₄ and the solvent was removed under reduced pressure. The product was isolated by flash chromatography over silica gel with appropriate solvent mixtures.

2. Methyl Protection

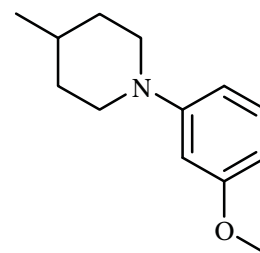
3-Bromoanisole (150)¹⁰⁶

3-Bromophenol (2.0 g, 11.6 mmol) was dissolved in DMF (20 mL) and K₂CO₃ (3.21 g, 23.2 mmol) added under nitrogen. MeI (3.29 g, 23.2 mmol) was added and the reaction stirred at room temperature for 19 h. The reaction mixture was extracted with chloroform:isopropanol (3:1 mix), acidified with 5% HCl and extracted further. The combined organic material was washed with saturated brine (x 3) and water (x 2), dried over Na₂SO₄ and the solvent removed under reduced pressure to afford the title compound as a clear liquid (1.8 g, 83%). IR (neat): ν/cm^{-1} : 3067, 3004, 2959, 2937, 2835, 1590, 1573 and 1478. ¹H NMR (300 MHz, CDCl₃); δ : 3.80 (3H, s, OCH₃), 6.84 (1H, ddd, $J = 1.8, 8.1$ Hz, H6), 7.06 (1H, t, $J = 1.8$ Hz, H2), 7.08 (1H, dt, $J = 1.8, 8.1$ Hz, H4), 7.14 (1H, t, $J = 8.1$ Hz, H5). This data is consistent with that reported for the commercially available 3-bromoanisole (Sigma Aldrich).



3-(4-Methylpiperidin-1-yl)anisole (151)

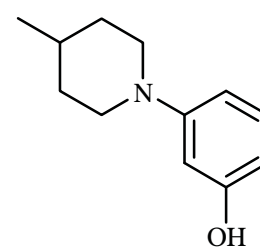
Using General Procedure 14, **150** (500 mg, 2.7 mmol) and 4-methylpiperidine (385 μ L, 3.25 mmol) were added to a mixture of Pd(OAc)₂ (12 mg, 54 μ mol), CataCXium[®] A ligand **35** (35 mg, 108 μ mol) and NaO^tBu (365 mg, 3.8 mmol) in trifluoromethylbenzene (10 mL) and the reaction was heated for 20 h. After cooling, the reaction



mixture was filtered through celite and the crude material chromatographed over silica eluting with DCM to afford the title compound as a yellow liquid (440 mg, 80%). HRMS found: 205.1464; C₁₃H₁₉NO requires 205.1467. IR (chloroform): ν /cm⁻¹: 2954, 2927, 1600, 1580 and 1455. ¹H NMR (300 MHz, CDCl₃); δ : 0.97 (3H, d, J = 6.6 Hz, CH₃), 1.36 (2H, dq, $J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{ax}}} = 2.4$ Hz, $J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}} = J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = J_{(3'/5')_{\text{ax}}, 4'} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.52 (1H, m, CH, H4'), 1.73 (2H, br d[‡], $J_{(3'/5')_{\text{ax}}, (3'/5')_{\text{eq}}} = J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.70 (2H, dt, $J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{eq}}} = 2.4$ Hz, $J_{(2'/6')_{\text{ax}}, (2'/6')_{\text{eq}}} = J_{(2'/6')_{\text{ax}}, (3'/5')_{\text{ax}}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.65 (2H, br d[‡], $J_{(2'/6')_{\text{ax}}, (2'/6')_{\text{eq}}} = J_{(2'/6')_{\text{eq}}, (3'/5')_{\text{eq}}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 3.80 (3H, s, OMe), 6.39 (1H, dd, J = 2.1, 8.1 Hz, H6), 6.51 (1H, br s[‡], H2), 6.57 (1H, dd, J = 2.1, 8.1 Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 22.1 (CH₃), 30.9 (C4'), 34.2 (C3'/5'), 50.0 (C2'/6'), 55.3 (OMe), 102.9 (C2), 104.0 (C6), 109.4 (C4), 129.8 (C5), 153.4 (C3), 160.7 (C1). m/z (ED): 205 (M+H⁺, 70%), 204 (M⁺, 100), 190 (10), 162 (30), 135 (30).

3-(4-Methylpiperidin-1-yl)phenol (141)

i) **With trimethylsilyl iodide.**¹¹¹ **151** (50 mg, 0.24 mmol) was dissolved in dry chloroform (2 mL) under nitrogen. Trimethylsilyl iodide (44 μ L, 0.31 mmol) was added and the reaction mixture was heated at 50 °C for 24 h. Water was added and the mixture extracted with chloroform:isopropanol (3:1 mix), washed with sodium



metabisulfite, saturated NaHCO₃, saturated brine and water. The organic material was dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was chromatographed over silica eluting with DCM to afford the title compound as a cream low melting solid (10 mg, 22%). Data was consistent with that obtained previously.

ii) **With TBAI and BCl₃.**¹¹⁰ **151** (50 mg, 0.24 mmol) was dissolved in dry DCM (3 mL) under nitrogen. TBAI (115 mg, 0.31 mmol) was added followed by BCl₃ (1.0 M in DCM, 0.6 mL, 0.6 mmol) at -78 °C over 5 min. The reaction mixture was stirred for 5 min and allowed

to warm to 0 °C and stirred for 4 h. Water was added and the reaction mixture extracted with DCM, washed with water, dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was chromatographed over silica eluting with DCM to afford 6-iodo-3-(4-methylpiperidin-1-yl)phenol **153** as a yellow sticky solid as a mixture with an unidentified compound (18 mg, ~24%).

6-Iodo-3-(4-methylpiperidin-1-yl)phenol **153**: HRMS found:

317.0276; C₁₂H₁₆INO requires 317.0277. IR (chloroform): ν/cm^{-1} :

3699, 2966, 2936, 2877, 1590, 1500 and 1460. ¹H NMR (600 MHz,

CDCl₃); δ : 0.95 (3H, d, $J = 5.4$ Hz, CH₃), 1.32 (2H, dq, $J_{(2'/6')\text{eq}}$,

$(3'/5')\text{ax} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, 4'} = 12.0$

Hz, 2 x CH, H(3'/5')_{ax}), 1.48 (1H, m, CH, H4'), 1.69 (2H, br d[‡], $J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}}$,

$(3'/5')\text{eq} = 12.0$ Hz, 2 x CH, H(3'/5')_{eq}), 2.65 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 2.4$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} =$

$J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.0$ Hz, 2 x CH, H(2'/6')_{ax}), 3.62 (2H, br d[‡], $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}}$

$= 12.0$ Hz, 2 x CH, H(2'/6')_{eq}), 6.23 (1H, dd, $J = 3.0, 8.7$ Hz, H4), 6.88 (1H, d, $J = 3.0$ Hz,

H2), 7.39 (1H, d, $J = 8.7$ Hz, H5). ¹³C NMR (150 MHz, CDCl₃); δ : 21.8 (CH₃'), 30.7 (C4'),

33.9 (C3'/5'), 49.8 (C2'/6'), 72.0 (C6), 103.8 (C2), 110.0 (C4), 137.9 (C5), 153.4 (C3), 157.0

(C1). m/z (EI): 317 (M⁺, 100), 316 (M-H⁺, 85), 274 (20), 247 (20), 190 (35), 148 (10), 121

(10).

iii) With BBr₃.¹⁰⁹ **151** (100 mg, 0.49 mmol) was dissolved in dry DCM (5 mL) under

nitrogen. BBr₃ (51 μL , 0.54 mmol) was added at -78 °C and the reaction stirred for 30 min at

-78 °C and at room temperature for 1 h. The mixture was poured onto ice water and stirred

for 15 min, then saturated with salt, extracted with chloroform:isopropanol (3:1 mix), washed

with water, dried over Na₂SO₄ and the solvent removed under reduced pressure to afford the

title compound as a yellow glass (75 mg, 80 %). HRMS found: 191.1300; C₁₂H₁₇NO requires

191.1310. IR (chloroform): ν/cm^{-1} : 3619, 3192, 2692, 2876, 1621, 1599 and 1508. ¹H NMR

(300 MHz, CDCl₃); δ : 1.06 (3H, d, $J = 6.1$ Hz, CH₃), 1.70-1.92 (3H, m, 2 x CH, H(3'/5')_{ax},

H4'), 2.12 (2H, m, 2 x CH, H(3'/5')_{eq}), 3.25 (2H, br t[‡], $J = 12.0$ Hz, 2 x CH, H(2'/6')_{ax}), 3.62

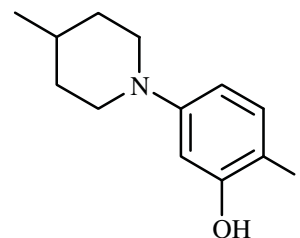
(2H, br d[‡], $J = 12.0$ Hz, 2 x CH, H(2'/6')_{eq}), 6.88 (1H, br dd, $J = 1.2, 7.8$ Hz, H6), 7.06 (1H, br

dd, $J = 1.2, 7.8$ Hz, H4), 7.19 (1H, t, $J = 7.8$ Hz, H5), 7.45 (1H, br s, H2), 8.18 (1H, br s, OH).

¹³C NMR (75 MHz, CDCl₃); 21.4 (CH₃'), 29.9 (C4'), 32.1 (C3'/5'), 54.9 (C2'/6'), 107.6 (C2),

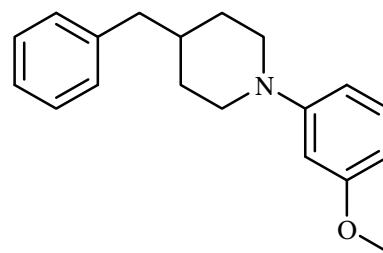
110.6 (C4), 114.3 (C6), 130.9 (C5), 146.3 (C5), 146.3 (C3), 158.2 (C1). m/z (EI): 191 (M⁺,

70%), 190 (100), 148 (25), 121 (25).



3-(4-Benzylpiperidin-1-yl)anisole (152)

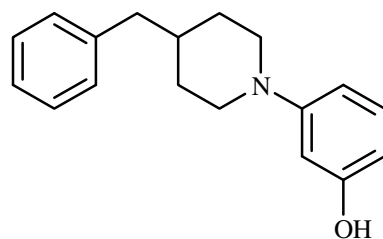
Using General Procedure 14, **150** (500 mg, 2.7 mmol) and 4-benzylpiperidine (578 μL , 3.25 mmol) were added to a mixture of $\text{Pd}(\text{OAc})_2$ (12 mg, 54 μmol), CataCXium[®] A ligand **35** (35 mg, 108 μmol) and NaO^tBu (365 mg, 3.8 mmol) in trifluoromethylbenzene (5 mL) and the reaction



was heated for 20 h. After cooling to room temperature the mixture was extracted with chloroform:isopropanol (3:1 mix), washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was chromatographed over silica eluting with DCM:hexane (4:1) to afford the title compound as a yellow solid, mp 76-77 $^\circ\text{C}$ (467 mg, 62%). Analysis found: C, 80.85; H, 8.49; N, 4.99. $\text{C}_{19}\text{H}_{23}\text{NO}$ requires C, 81.10; H, 8.49; N, 4.99%. IR (nujol mull): ν/cm^{-1} : 3375, 1592, 1575 and 1457. ^1H NMR (300 MHz, CDCl_3); δ : 1.38 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 4.2$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.55 (1H, m, CH, H4'), 1.72 (2H, br d[‡], $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.55 (2H, d, $J = 6.6$ Hz, CH_2), 2.63 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 4.2$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.64 (2H, br d[‡], $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (2'/6')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 6.37 (1H, dd, $J = 2.1, 8.1$ Hz, H6), 6.51 (1H, t, $J = 2.1$ Hz, H2), 6.52 (1H, dd, $J = 2.1, 8.1$ Hz, H4), 7.10-7.30 (5H, m, Ph). ^{13}C NMR (75 MHz, CDCl_3); δ : 32.2 (C3'/5'), 38.1 (C4'), 43.4 (CH_2), 50.1 (C2'/6'), 55.3 (OCH_3), 103.0 (C2), 104.2 (C6), 109.6 (C4), 126.9 (C4''), 128.4 (C2''/6''), 129.3 (C3''/5''), 129.9 (C5), 140.7 (C4''), 153.4 (C3), 160.8 (C1). m/z (EI): 281 (M^+ , 100%), 280 ($\text{M}-\text{H}^+$, 60), 190 (25), 175 (50), 162 (50), 135 (35), 127 (35), 55 (35).

Synthesis of 3-(4-benzylpiperidin-1-yl)phenol with BBr_3 (**144**)¹⁰⁹

152 (350 mg, 1.24 mmol) was dissolved in dry DCM (2 mL) under nitrogen. BBr_3 (129 μL , 1.37 mmol) was added at -78 $^\circ\text{C}$ and the reaction stirred for 30 min at -78 $^\circ\text{C}$ and at room temperature for 2 h. Additional BBr_3 (59 μL , 0.62 mmol) was added at -78 $^\circ\text{C}$ and the reaction stirred at room



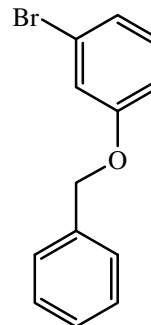
temperature for a further 1.5 h. The mixture was poured onto ice water and stirred for 15 min, then saturated with salt, extracted with chloroform:isopropanol (3:1 mix), washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was chromatographed over C18 silica eluting with methanol:water (4:1) to afford the title compound as cream crystals, mp 74-76 $^\circ\text{C}$ (320 mg, 97%). HRMS found: 267.1620;

$C_{18}H_{21}NO$ requires: 267.1623. IR (nujol mull): ν/cm^{-1} : 3200, 1598, 1580 and 1461. 1H NMR (600 MHz, $CDCl_3$); δ : 1.83 (2H, br d^{\ddagger} , $J_{(2'/6')_{ax}, (3'/5')_{ax}} = J_{(3'/5')_{ax}, (3'/5')_{eq}} = 12.0$ Hz, 2 x CH, H(3'/5')_{ax}) 1.89 (1H, m, CH, H4'), 2.12 (2H, br q^{\ddagger} , $J_{(2'/6')_{eq}, (3'/5')_{eq}} = J_{(3'/5')_{ax}, (3'/5')_{eq}} = 12.0$ Hz, 2 x CH, H(3'/5')_{eq}), 2.58 (2H, d, $J = 6.6$ Hz, CH_2), 3.24 (2H, br t^{\ddagger} , $J_{(2'/6')_{ax}, (2'/6')_{eq}} = J_{(2'/6')_{ax}, (3'/5')_{ax}} = 12.0$ Hz, 2 x CH, H(2'/6')_{ax}), 3.51 (2H, br d^{\ddagger} , $J_{(2'/6')_{eq}, (3'/5')_{eq}} = J_{(2'/6')_{eq}, (2'/6')_{ax}} = 12.0$ Hz, 2 x CH, H(2'/6')_{eq}), 6.91 (1H, d, $J = 7.8$ Hz, H6), 7.11 (3H, m, H5, H(2''/6'')), 7.17 (2H, m, H4, H4''), 7.25 (2H, m, H(3''/5'')), 7.36 (1H, br s, H2), 9.03 (1H, br s, OH). ^{13}C NMR (150 MHz, $CDCl_3$); δ : 29.6 (C3'/5'), 35.4 (C4'), 41.9 (CH_2), 56.1 (C2'/6'), 107.9 (C2), 111.6 (C4), 111.6 (C6), 126.3 (C4''), 128.4 (C3''/5''), 128.9 (C2''/6''), 130.8 (C5), 139.1 (C1''), 143.5 (C3), 158.4 (C1). m/z (EI): 267 (M^+ , 100%), 266 ($M-H^+$, 90), 176 (45), 161 (50), 148 (50), 122 (50).

3. Benzyl Protection

1-(Benzyloxy)-3-bromobenzene (155)¹¹³

3-Bromophenol (500 mg, 2.9 mmol) was dissolved in DMF (20 mL) and K_2CO_3 (799 mg, 5.78 mmol) added under nitrogen. Benzyl bromide (741 mg, 4.33 mmol) was added and the reaction stirred at room temperature for 20 h. The reaction mixture was filtered and the solvent removed under reduced pressure. The crude material was dissolved in ethyl acetate, washed with 5% HCl (x 2) and saturated brine, dried over Na_2SO_4 and the solvent removed under reduced pressure. Recrystallisation from hexane afforded the title

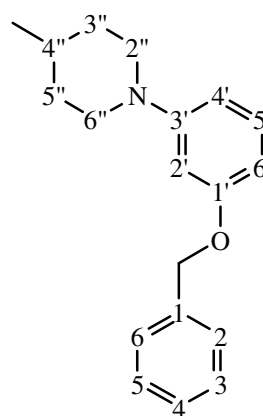


compound as white crystals, mp 61 °C (lit.,¹¹³ 61-62 °C) (1.8 g, 83%). IR (nujol mull): ν/cm^{-1} : 1590, 1573 and 1456. 1H NMR (300 MHz, $CDCl_3$); δ : 5.06 (2H, s, CH_2), 6.92 (1H, ddd, $J = 1.5, 2.4, 7.8$ Hz, H6), 7.10 (1H, dt, $J = 1.5, 7.8$ Hz, H4), 7.12-7.19 (2H, m, H2, H5), 7.32-7.46 (5H, m, Ph).

The 1H NMR data was consistent with that reported in the literature.¹¹³

1-(Benzyloxy)phenyl-3-(4-methylpiperidine) (158)

Using General Procedure 14, **155** (92 mg, 0.35 mmol) and 4-methylpiperidine (50 μ L, 0.42 mmol) were added to a mixture of Pd(OAc)₂ (1.6 mg, 7 μ mol), CataCXium[®] A ligand **35** (4.7 mg, 14 μ mol) and NaO^tBu (47 mg, 0.49 mmol) in trifluoromethylbenzene (2 mL) and the reaction was heated for 22 h. After cooling to room temperature the mixture was filtered through celite and the solvent removed under reduced pressure. The crude material was chromatographed over silica gel eluting with DCM to afford the title

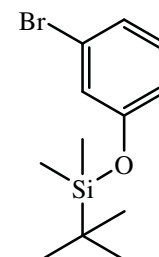


compound as an orange oil (64 mg, 65%). HRMS found: 281.1774; C₁₉H₂₃NO requires: 281.1780. IR (chloroform): ν/cm^{-1} : 3034, 2953, 2927, 2814, 1598, 1495 and 1455. ¹H NMR (300 MHz, CDCl₃); δ : 0.98 (3H, d, $J = 6.6$ Hz, CH₃), 1.33 (2H, dq, $J_{(2''/6'')\text{eq}, (3''/5'')\text{ax}} = 2.7$ Hz, $J_{(2''/6'')\text{ax}, (3''/5'')\text{ax}} = J_{(3''/5'')\text{ax}, (3''/5'')\text{eq}} = J_{(3''/5'')\text{ax}, 4''} = 12.6$ Hz, 2 x CH, H(3''/5'')_{ax}), 1.52 (1H, m, CH, H4''), 1.73 (2H, br d[‡], $J_{(3''/5'')\text{ax}, (3''/5'')\text{eq}} = J_{(2''/6'')\text{eq}, (3''/5'')\text{eq}} = 12.6$ Hz, 2 x CH, H(3''/5'')_{eq}), 2.70 (2H, dt, $J_{(2''/6'')\text{ax}, (3''/5'')\text{eq}} = 2.7$ Hz, $J_{(2''/6'')\text{ax}, (2''/6'')\text{eq}} = J_{(2''/6'')\text{ax}, (3''/5'')\text{ax}} = 12.6$ Hz, 2 x CH, H(2''/6'')_{ax}), 3.66 (2H, br d[‡], $J_{(2''/6'')\text{ax}, (2''/6'')\text{eq}} = J_{(2''/6'')\text{eq}, (3''/5'')\text{eq}} = 12.6$ Hz, 2 x CH, H(2''/6'')_{eq}), 5.05 (2H, s, CH₂), 6.46 (1H, ddd, $J = 0.9, 2.4, 8.4$ Hz, H6'), 6.58-6.60 (2H, m, H2', H4'), 7.16 (1H, t, $J = 8.4$ Hz, H5'), 7.30-7.47 (5H, m, Ph). ¹³C NMR (75 MHz, CDCl₃); δ : 22.1 (CH₃), 31.0 (4''), 34.2 (C3''/5''), 50.0 (C2''/6''), 70.1 (CH₂), 103.8 (C2'), 104.8 (C6'), 109.7 (C4'), 127.8 (C2/6), 128.1 (C4), 128.8 (C3/5), 129.9 (C5'), 137.5 (C1), 153.4 (C3'), 160.0 (C1'). m/z (EI): 282 (M⁺+H, 30%), 281 (M⁺, 100), 280 (M⁺-H, 40), 238 (5), 190, (25), 162 (30), 91 (55).

4. TBDMS Protection

(3-Bromophenoxy)(^tbutyl)dimethylsilane (154)¹⁰³

3-Bromophenol (250 mg, 1.45 mmol) was dissolved in DMF (2 mL) and imidazole (247 mg, 3.63 mmol) added under nitrogen. ^tButyldimethylsilyl chloride (261 mg, 1.73 mmol) was added and the reaction was heated at 50 °C for 3.5 h. The reaction mixture was cooled to room temperature and extracted with chloroform:isopropanol (3:1 mix), washed with 5% HCl and water, dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was chromatographed over silica gel eluting with hexane:DCM (3:1 mix) to afford the title compound as a clear liquid (355 mg, 76%). IR (chloroform): ν/cm^{-1} : 3067, 2931, 2886, 2859,

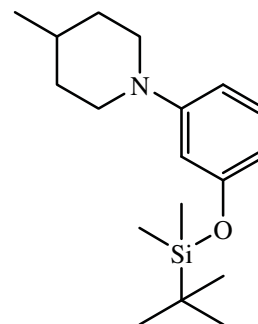


1587 and 1474. ^1H NMR (300 MHz, CDCl_3); δ : 0.21 (6H, s, 2 x CH_3), 0.99 (9H, s, ^tBu), 6.74-6.81 (1H, m, H6), 7.02 (1H, ddd, $J = 0.6, 1.4, 3.0$ Hz, H2), 7.09-7.11 (2H, m, H4, H5).

The ^1H NMR data was consistent with that reported in the literature.¹⁰³

3-(4-Methylpiperidin-1-yl)phenoxy(t butyl)dimethylsilane (157)

Using General Procedure 14, **154** (100 mg, 0.35 mmol) and 4-methylpiperidine (50 μL , 0.42 mmol) were added to a mixture of $\text{Pd}(\text{OAc})_2$ (1.6 mg, 7 μmol), CataCXium[®] A ligand **35** (4.7 mg, 14 μmol) and NaO^tBu (47 mg, 0.49 mmol) in trifluoromethylbenzene (2 mL) and the reaction was heated for 22 h. After cooling to room temperature the mixture was filtered through celite and the solvent removed under reduced pressure. The crude material was

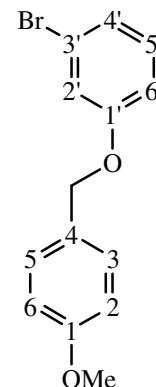


chromatographed over silica gel eluting with $\text{DCM}:\text{hexane}$ (1:1) to afford the title compound as an orange oil (34 mg, 32%). HRMS found: 305.2171; $\text{C}_{18}\text{H}_{31}\text{NOSi}$ requires: 305.2175. IR (chloroform): ν/cm^{-1} : 2929, 2859, 2815, 1717, 1596 and 1490. ^1H NMR (300 MHz, CDCl_3); δ : 0.20 (6H, s, 2 x CH_3), 0.98-1.00 (12H, m, ^tBu , CH_3), 1.38 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 2.7$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, 4'} = 12.3$ Hz, 2 x CH, H($3'/5'$)_{ax}), 1.41 (1H, m, CH, H4'), 1.73 (2H, br d^\ddagger , $J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.3$ Hz, 2 x CH, H($3'/5'$)_{eq}), 2.68 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 2.7$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.3$ Hz, 2 x CH, H($2'/6'$)_{ax}), 3.63 (2H, br d^\ddagger , $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = 12.3$ Hz, 2 x CH, H($2'/6'$)_{eq}), 6.32 (1H, dd, $J = 2.1, 8.1$ Hz, H6), 6.43 (1H, t, $J = 2.1$ Hz, H2), 6.56 (1H, dd, $J = 2.1, 8.1$, H4), 7.09 (1H, t, $J = 8.1$, H5). ^{13}C NMR (75 MHz, CDCl_3); δ : -4.1 (2 x CH_3), 18.4 ($\text{C}(\text{CH}_3)_3$), 22.1 (CH_3), 25.9 ($\text{C}(\text{CH}_3)_3$), 30.9 ($\text{C}4'$), 34.2 ($\text{C}3'/5'$), 50.2 ($\text{C}2'/6'$), 108.8 ($\text{C}2$), 110.0 ($\text{C}4$), 111.2 ($\text{C}6$), 129.7 ($\text{C}5$), 153.4 ($\text{C}3$), 156.7 ($\text{C}1$). m/z (EI): 305 (M^+ , 100%), 248 (75).

6. PMB Protection

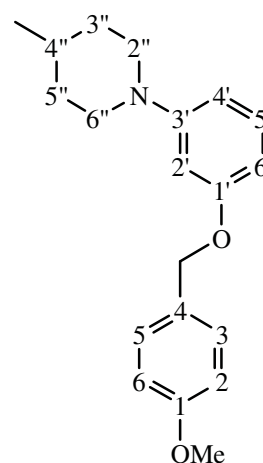
1-(4-Methoxybenzyloxy)-3-bromobenzene (**156**)¹¹⁴

3-Bromophenol (1.0 g, 5.8 mmol) was dissolved in acetone (10 mL) and K_2CO_3 (1.60 g, 11.6 mmol) added under nitrogen. *p*-Methoxybenzyl chloride (1.09 mg, 7.0 mmol) and TBAI (216 mg, 0.60 mmol) were added and the reaction was heated at 50 °C for 7 h. The reaction mixture was cooled to room temperature and extracted with chloroform:isopropanol (3:1 mix), washed with 5% HCl (x 2) and water, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was chromatographed over silica gel eluting with hexane:DCM (3:1 mix) to afford the title compound as a white solid, mp 84-85 °C (1.23 g, 73%). HRMS found: 292.0089; $C_{14}H_{13}^{79}BrO_2$ requires: 292.0099. IR (chloroform): ν/cm^{-1} : 3007, 2937, 2839, 1613, 1588, 1574, 1515 and 1475. 1H NMR (300 MHz, $CDCl_3$); δ : 3.82 (3H, s, OCH_3), 4.96 (2H, s, CH_2), 6.87 (1H, ddd, $J = 1.5, 2.4, 8.1$ Hz, $H_{6'}$), 6.92 (2H, m, $H_{(2/6)}$), 7.07 (1H, dt, $J = 1.5, 8.1$ Hz, $H_{4'}$), 7.11-7.16 (2H, m, $H_{2'}$, $H_{5'}$), 7.34 (2H, m, $H_{(3/5)}$). ^{13}C NMR (75 MHz, $CDCl_3$); δ : 55.4 (OCH_3), 70.1 (CH_2), 114.0 ($C_{6'}$), 114.2 ($C_{(2/6)}$), 118.3 ($C_{2'}$), 122.9 ($C_{3'}$), 122.9 ($C_{4'}$), 128.5 (C_4), 129.5 ($C_{(3/5)}$), 130.7 ($C_{5'}$), 159.7 ($C_1, C_{1'}$). m/z (EI): 294 (M^+ , [^{81}Br], 10%), 292 (M^+ , [^{79}Br], 10), 213, (10), 121 (100), 78 (20).



1-(4-Methoxybenzyloxy)phenyl-3-(4-methylpiperidine) (**159**)

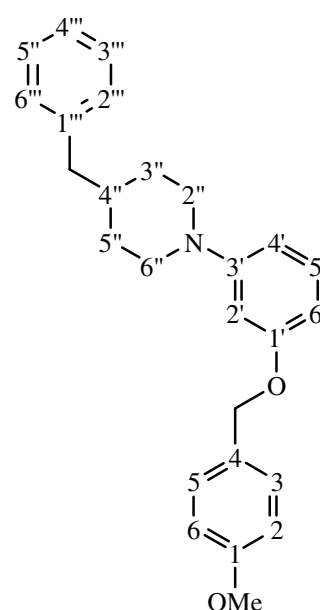
Using General Procedure 14, **156** (103 mg, 0.35 mmol) and 4-methylpiperidine (50 μ L, 0.42 mmol) were added to a mixture of $Pd(OAc)_2$ (1.6 mg, 7 μ mol), CataCXium[®] A ligand **35** (4.7 mg, 14 μ mol) and NaO^tBu (47 mg, 0.49 mmol) in trifluoromethylbenzene (2 mL) and the reaction was heated for 20 h. After cooling to room temperature the mixture was filtered through celite and the solvent removed under reduced pressure. The crude material was chromatographed over silica gel eluting with DCM to afford the title compound as a yellow glass (70 mg, 64%). HRMS found: 311.1884; $C_{20}H_{25}NO_2$ requires: 311.1885. IR (chloroform): ν/cm^{-1} : 2940, 2928, 1611, 1515 and 1464. 1H NMR (300 MHz, $CDCl_3$); δ : 0.98 (3H, d, $J = 6.6$ Hz, CH_3), 1.35 (2H, dq, $J_{(2''/6'')_{ax}, (3''/5'')_{ax}} = 2.7$ Hz, $J_{(2''/6'')_{ax}, (3''/5'')_{eq}} = J_{(3''/5'')_{ax}, (3''/5'')_{eq}} = J_{(3''/5'')_{ax}, 4''} = 12.6$ Hz, 2 x CH, $H_{(3''/5'')_{ax}}$), 1.52 (1H, m, CH, $H_{4''}$), 1.73 (2H, br d^{\ddagger} , $J_{(3''/5'')_{ax}, (3''/5'')_{eq}} = J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = 12.6$ Hz, 2 x CH, $H_{(3''/5'')_{eq}}$),



2.67 (2H, dt, $J_{(2''/6'')_{ax}, (3''/5'')_{eq}} = 2.7$ Hz, $J_{(2''/6'')_{ax}, (2''/6'')_{eq}} = J_{(2''/6'')_{ax}, (3''/5'')_{ax}} = 12.6$ Hz, 2 x CH, $H_{(2''/6'')_{ax}}$), 3.66 (2H, br d^{\ddagger} , $J_{(2''/6'')_{ax}, (2''/6'')_{eq}} = J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = 12.3$ Hz, 2 x CH, $H_{(2''/6'')_{eq}}$), 3.83 (3H, s, OCH₃), 4.98 (2H, s, CH₂), 6.46 (1H, ddd, $J = 0.9, 2.4, 8.1$ Hz, H6'), 6.57 (1H, t, $J = 2.4$ Hz, H2'), 6.60 (1H, ddd, $J = 0.9, 2.4, 8.1$ Hz, H4'), 6.93 (2H, m, H(2/6)), 7.17 (1H, t, $J = 8.1$ Hz, H5'), 7.38 (2H, m, H(3/5)). ¹³C NMR (75 MHz, CDCl₃); δ : 22.1 (CH₃), 31.0 (4''), 34.2 (C3''/5''), 50.0 (C2''/6''), 55.5 (OCH₃), 69.9 (CH₂), 103.8 (C2'), 104.8 (C6'), 109.9 (C4'), 114.2 (C2/6), 129.5 (C3/5), 129.8 (C4, C5'), 153.4 (C3'), 159.6 (C1), 160.0 (C1'). *m/z* (EI): 311 (M⁺, 80%), 268 (5), 267, (25), 120 (100).

1-(4-Methoxybenzyloxy)phenyl-3-(4-methylpiperidine) (160)

Using General Procedure 14, **156** (500 mg, 1.70 mmol) and 4-benzylpiperidine (356 μ L, 2.0 mmol) were added to a mixture of Pd(OAc)₂ (7.6 mg, 34 μ mol), CataCXium[®] A ligand **35** (23 mg, 68 μ mol) and NaO^tBu (229 mg, 2.4 mmol) in trifluoromethylbenzene (5 mL) and the reaction was heated for 22 h. After cooling to room temperature the mixture was filtered through celite and the solvent removed under reduced pressure. The crude material was chromatographed over silica gel eluting with DCM:hexane (1:1) to afford the title compound as a yellow solid, mp 89-91°C (450 mg, 68%). HRMS found: 387.2198; C₂₆H₂₉NO₂ requires: 387.2198. IR (chloroform): ν/cm^{-1} : 3029, 2928, 2840, 1610, 1515, 1494 and 1464. ¹H NMR (300 MHz,

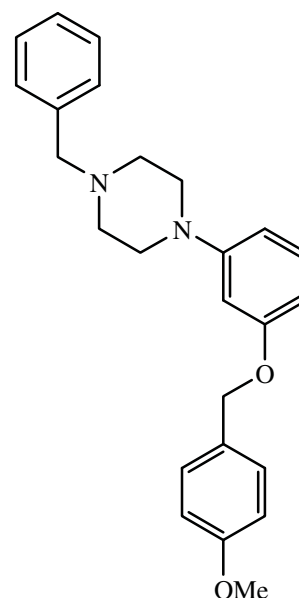


CDCl₃); δ : 1.40 (2H, dq, $J_{(2''/6'')_{eq}, 3''/5''_{ax}} = 4.2$ Hz, $J_{(2''/6'')_{ax}, (3''/5'')_{ax}} = J_{(3''/5'')_{ax}, (3''/5'')_{eq}} = 12.6$ Hz, 2 x CH, $H_{(3''/5'')_{ax}}$), 1.65 (1H, m, CH, H4''), 1.72 (2H, br d^{\ddagger} , $J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = J_{(3''/5'')_{ax}, (3''/5'')_{eq}} = 12.6$ Hz, 2 x CH, $H_{(3''/5'')_{eq}}$), 2.55 (2H, d, $J = 6.4$ Hz, CH₂), 2.65 (2H, dt, $J_{(2''/6'')_{ax}, (3''/5'')_{eq}} = 4.2$ Hz, $J_{(2''/6'')_{ax}, (2''/6'')_{eq}} = J_{(2''/6'')_{ax}, (3''/5'')_{ax}} = 12.6$ Hz, 2 x CH, $H_{(2''/6'')_{ax}}$), 3.64 (2H, br d^{\ddagger} , $J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = J_{(2''/6'')_{eq}, (2''/6'')_{ax}} = 12.6$ Hz, 2 x CH, $H_{(2''/6'')_{eq}}$), 3.80 (3H, s, OCH₃), 4.95 (2H, s, CH₂), 6.44 (1H, ddd, $J = 0.9, 2.4, 8.1$ Hz, H6'), 6.52-6.57 (2H, m H2', H4'), 6.90 (2H, m, H(2/6)), 7.09-7.37 (8H, m, H(3/5), H5', Ph). ¹³C NMR (75 MHz, CDCl₃); δ : 32.1 (C3''/5''), 38.1 (C4''), 43.4 (CH₂), 50.0 (C2''/6''), 55.5 (OCH₃), 69.9 (CH₂), 103.9 (C2'), 104.9 (C6'), 109.7 (C4'), 114.2 (C2/6), 126.1 (C4'''), 128.4 (C3'''/5'''), 129.3 (C3/5, C2'''/6'''), 129.8 (C4, C5'), 140.7 (C1'''), 153.3 (C3'), 159.6 (C1), 160.0 (C1'). *m/z* (EI): 387 (M⁺, 20%), 328, (30), 268 (5), 121 (100).

1-(4-Methoxybenzyloxy)phenyl-3-(4-benzylpiperazine) (161)

Using General Procedure 14, **156** (500 mg, 1.70 mmol) and 4-benzylpiperazine (347 μ L, 2.0 mmol) were added to a mixture of Pd(OAc)₂ (7.6 mg, 34 μ mol), CataCXium[®] A ligand **35** (23 mg, 68 μ mol) and NaO^tBu (229 mg, 2.4 mmol) in trifluoromethylbenzene (5 mL) and the reaction was heated for 22 h. After cooling to room temperature the mixture was filtered through celite and the solvent removed under reduced pressure. The crude material was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as an orange solid, mp 98-99 °C (540 mg, 82%). Analysis found: C, 76.89; H, 7.17; N, 7.30. C₂₅H₂₈N₂O₂ requires C, 77.29; H, 7.26; N, 7.21%. IR (chloroform): ν/cm^{-1} : 3032, 2913, 2820, 1611, 1515 and 1494. ¹H

NMR (300 MHz, CDCl₃); δ : 2.60 (4H, br t, $J = 4.8$ Hz, 2 x CH₂, H(3''/5'')), 3.20 (4H, br t, $J = 4.8$ Hz, 2 x CH₂, H(2''/6'')), 3.57 (2H, s, CH₂), 3.83 (3H, s, OCH₃), 4.97 (2H, s, CH₂), 6.47 (1H, ddd, $J = 0.9, 3.0, 8.1$ Hz, H6'), 6.53-6.57 (2H, m, H2', H4'), 6.92 (2H, m, H(2/6)), 7.17 (1H, t, $J = 8.1$ Hz, H5'), 7.09-7.37 (7H, m, H(3/5), Ph). ¹³C NMR (75 MHz, CDCl₃); δ : 49.2 (C2''/6''), 53.3 (C3''/5''), 55.5 (OCH₃), 63.3 (CH₂N), 69.9 (CH₂O), 103.5 (C2'), 105.3 (C6'), 109.2 (C4'), 114.2 (C2/6), 127.3 (C4'''), 128.5 (C3/5), 129.4 (C2'''/6''', C3'''/5'''), 129.5 (C5'), 129.9 (C4), 138.2 (C1'''), 152.9 (C3'), 159.6 (C1), 160.0 (C1'). m/z (EI): 357 (M⁺, 20%), 268 (5), 121, (100), 91 (20).

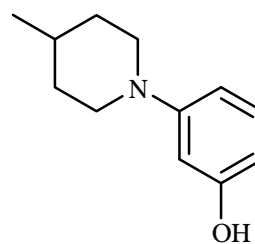


General Procedure 15: TFA deprotection of PMB ethers¹¹⁴

The PMB ether was dissolved in TFA and the reaction mixture was heated at 60 °C for 1.5 h. The mixture was then cooled to room temperature and added slowly to saturated NaHCO₃. The aqueous phase was extracted with chloroform:isopropanol (3:1 mix), acidified with 5% HCl and extracted further. The combined organic material was washed with water, dried over Na₂SO₄ and the solvent removed under reduced pressure. The product was isolated by flash chromatography over silica gel with appropriate solvent mixtures.

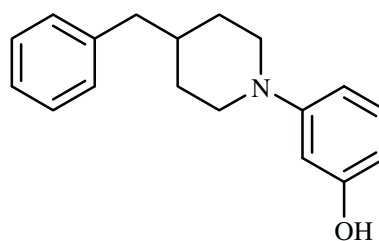
3-(4-Methylpiperidin-1-yl)phenol (141)

Using General Procedure 15, **159** (300 mg, 0.96 mmol) was dissolved in TFA (5 mL) and heated as described above. Work up followed by chromatography eluting with DCM:ethanol (39:1) afforded the title compound as a cream solid, mp 97-99 °C (150 mg, 82%). Data as above.



3-(4-Benzylpiperidin-1-yl)phenol (144)

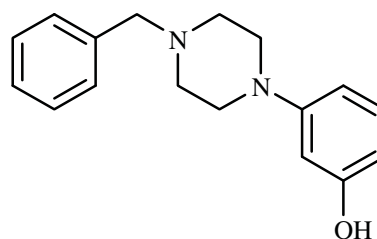
Using General Procedure 15, **160** (390 mg, 1.0 mmol) was dissolved in TFA (7 mL) and heated as described above. Work up followed by chromatography eluting with DCM:ethanol (39:1) afforded the title compound as a yellow glass (230 mg, 86%). HRMS found: 267.1623; C₁₈H₂₁NO



requires: 267.1623. IR (chloroform): ν/cm^{-1} : 3597, 3064, 3028, 2927, 2849, 1605, 1590 and 1495. ¹H NMR (300 MHz, CDCl₃); δ : 1.41 (2H, dq, $J_{(2'/6')\text{eq}, (3'/5')\text{ax}} = 3.6$ Hz, $J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{ax}), 1.65 (1H, m, CH, H4'), 1.75 (2H, br d[‡], $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(3'/5')\text{ax}, (3'/5')\text{eq}} = 12.6$ Hz, 2 x CH, H(3'/5')_{eq}), 2.58 (2H, d, $J = 6.6$ Hz, CH₂), 2.67 (2H, dt, $J_{(2'/6')\text{ax}, (3'/5')\text{eq}} = 3.6$ Hz, $J_{(2'/6')\text{ax}, (2'/6')\text{eq}} = J_{(2'/6')\text{ax}, (3'/5')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{ax}), 3.65 (2H, br d[‡], $J_{(2'/6')\text{eq}, (3'/5')\text{eq}} = J_{(2'/6')\text{eq}, (2'/6')\text{ax}} = 12.6$ Hz, 2 x CH, H(2'/6')_{eq}), 5.31 (1H, br s, OH), 6.28 (1H, ddd, $J = 0.9, 2.4, 7.8$ Hz, H6), 6.40 (1H, t, $J = 2.4$ Hz, H2), 6.52 (1H, ddd, $J = 0.9, 2.4, 7.8$ Hz, H4), 7.09 (1H, dt, $J = 0.9, 7.8$ Hz, H5), 7.16-7.33 (5H, m, Ph). ¹³C NMR (75 MHz, CDCl₃); δ : 31.6 (C3'/5'), 37.9 (C4'), 43.1 (CH₂), 50.5 (C2'/6'), 104.8 (C2), 107.7 (C6), 109.4 (C4), 126.0 (C4''), 128.4 (C3''/5''), 129.3 (C2''/6''), 130.1 (C5), 140.5 (C1''), 152.9 (C3), 157.9 (C1). m/z (EI): 267 (M⁺, 100%), 266 (M-H⁺, 80), 176 (30), 160 (55), 148 (40), 122 (30), 121 (15), 120 (15), 91 (20), 55 (25).

3-(4-Benzylpiperazin-1-yl)phenol (162)

Using General Procedure 15, **161** (438 mg, 1.13 mmol) was dissolved in TFA (8 mL) and heated as described above. Work up followed by chromatography eluting with DCM:ethanol (39:1) and recrystallisation from acetonitrile:water afforded the title compound as cream crystals, mp 197-201 °C (245 mg, 81%). IR (chloroform): ν/cm^{-1} : 3182, 2842, 1698, 1667,



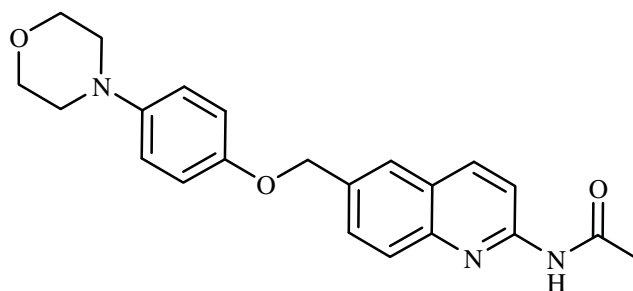
1593 and 1507. ¹H NMR (300 MHz, CDCl₃); δ: 2.61 (4H, t, *J* = 5.1 Hz, 2 x CH₂, H(3'/5')), 3.18 (4H, t, *J* = 5.1 Hz, 2 x CH₂, H(2'/6')), 3.58 (2H, s, CH₂), 5.19 (1H, br s, OH), 6.29 (1H, ddd, *J* = 0.9, 2.4, 7.8 Hz, H6), 6.37 (1H, t, *J* = 2.4 Hz, H2), 6.50 (1H, ddd, *J* = 0.9, 2.4, 7.8 Hz, H4), 7.10 (1H, t, *J* = 7.8 Hz, H5), 7.26-7.38 (5H, m, Ph). ¹³C NMR (75 MHz, CDCl₃); δ: 48.9 (C3'/5'), 53.2 (C2'/6'), 63.2 (CH₂), 103.3 (C2), 106.9 (C6), 108.9 (C4), 127.6 (C4''), 128.6 (C3''/5''), 129.7 (C2''/6''), 130.2 (C5), 138.0 (C1''), 153.0 (C3), 156.9 (C1). *m/z* (EI): 268 (M⁺, 80%), 253 (M-H⁺, 15), 177 (15), 148 (15), 146 (50), 122 (35), 121 (25), 120 (15), 119 (50), 91 (100), 56 (50).

The corresponding TFA salt was used for the micro analysis. Analysis found: C, 59.71; H, 5.66; N, 7.30. C₁₇H₂₀N₂O.CF₃COOH requires: C, 59.68; H, 5.54; N, 7.33%.

7.3.2 Synthesis of Extended *N*-[6-(Phenoxymethyl)quinolin-2-yl]acetamides

N-{6-[(4-Morpholinophenoxy)methyl]quinolin-2-yl}acetamide (163)

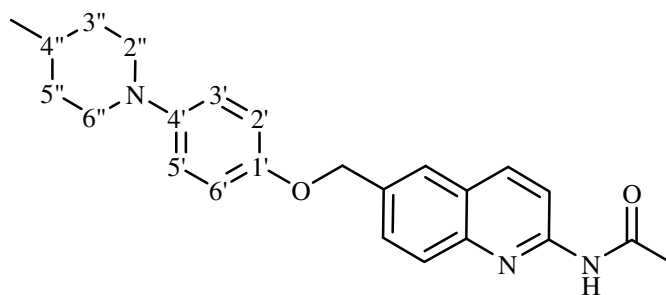
Using General Procedure 9, **69** (201 mg, 0.72 mmol), **119** (142 mg, 0.79 mmol), K₂CO₃ (299 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 6 h. After work up with chloroform:isopropanol (3:1 mix) the



crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (4:1). The title compound was found to decompose on silica gel and was isolated as an impure mixture which was further purified by recrystallisation from ethanol:water to afford the title compound as a yellow powder, mp 228-230 °C (40 mg, 15%). HRMS found: 377.1739; C₂₂H₂₃N₃O₃ requires 377.1739. IR (DCM): ν/cm⁻¹: 3405, 3053, 1699, 1601, 1580, 1510 and 1488. ¹H NMR (300 MHz, CDCl₃); δ: 3.08 (4H, t, *J* = 4.5 Hz, 2 x CH₂, H(3''/5'')), 3.87 (4H, t, *J* = 4.5 Hz, 2 x CH₂, H(2''/6'')), 5.18 (1H, s, CH₂), 6.90 (2H, m, H(2'/6')), 6.96 (4H, 2H, m, H(3'/5')), 7.72 (1H, dd, *J* = 2.1, 8.7 Hz, H7), 7.83 (1H, d, *J* = 8.7 Hz, H8), 7.84 (1H, br s, H5), 8.17 (1H, d, *J* = 9.0 Hz, H4), 8.22 (1H, br s, NH), 8.42 (1H, br d, *J* = 9.0 Hz, H3). ¹³C NMR (75 MHz, CDCl₃); δ: 23.8 (COCH₃), 49.9 (C2''/6''), 66.3 (C3''/5''), 69.4 (CH₂), 114.5 (C3), 115.5 (C2'/6'), 117.0 (C3'/5'), 125.4 (C4a), 126.1 (C5), 127.2 (C8), 129.5 (C7), 134.1 (C6), 138.1 (C4), 145.9 (C8a), 146.2 (C4'), 152.1 (C2), 152.3 (C1'), 169.8 (C=O). *m/z* (EI): 377 (M⁺, 15%), 199 (20), 178 (100), 157 (40).

N-{6-[(4-(4-Methylpiperidin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (**164**)

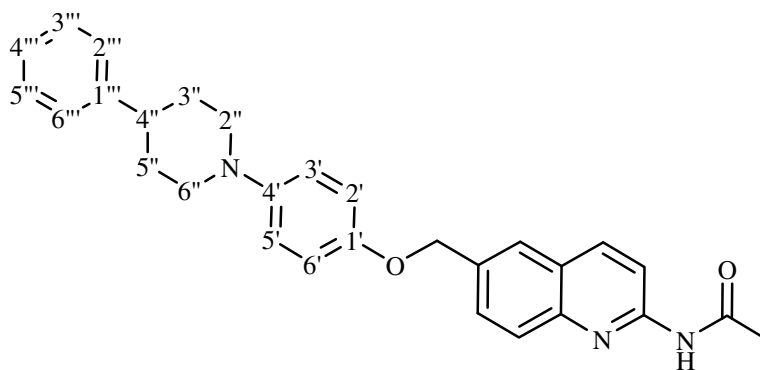
Using General Procedure 9, **69** (173 mg, 0.62 mmol), **129** (130 mg, 0.68 mmol), K₂CO₃ (282 mg, 2.0 mmol) and acetonitrile (10 mL) were heated for 5 h. After work up with chloroform:isopropanol (3:1 mix) the



crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (4:1) to afford the title compound as a cream powder, mp 218-221 °C (135 mg, 51%). HRMS found: 389.2102. C₂₄H₂₇N₃O₂ requires 389.2103. Analysis found: C, 73.81; H, 7.08; N, 10.63. C₂₄H₂₇N₃O₂ requires C, 74.01; H, 6.99; N, 10.79%. IR (DCM): ν/cm^{-1} : 3405, 1702, 1600, 1580, 1551 and 1509. ¹H NMR (300 MHz, CDCl₃): δ : 0.98 (3H, d, $J = 6.6$ Hz, CH₃), 1.43 (2H, dq, $J_{(2''/6'')\text{eq}, (3''/5'')\text{ax}} = 2.4$ Hz, $J_{(2''/6'')\text{ax}, (3''/5'')\text{ax}} = J_{(3''/5'')\text{ax}, (3''/5'')\text{eq}} = J_{(3''/5'')\text{ax}, 4''} = 12.6$ Hz, 2 x CH, H(3''/5'')_{ax}), 1.45 (1H, m, CH, H4''), 1.75 (2H, br d[‡], $J_{(3''/5'')\text{ax}, (3''/5'')\text{eq}} = J_{(2''/6'')\text{eq}, (3''/5'')\text{eq}} = 12.6$ Hz, 2 x CH, H(3''/5'')_{eq}), 2.27 (3H, s, COCH₃), 2.62 (2H, dt, $J_{(2''/6'')\text{ax}, (3''/5'')\text{eq}} = 2.4$ Hz, $J_{(2''/6'')\text{ax}, (2''/6'')\text{eq}} = J_{(2''/6'')\text{ax}, (3''/5'')\text{ax}} = 12.6$ Hz, 2 x CH, H(2''/6'')_{ax}), 3.49 (2H, br d[‡], $J_{(2''/6'')\text{ax}, (2''/6'')\text{eq}} = J_{(2''/6'')\text{eq}, (3''/5'')\text{eq}} = 12.6$ Hz, 2 x CH, H(2''/6'')_{eq}), 5.17 (2H, s, CH₂), 6.93 (4H, br s, H(2'/6'), H(3'/5')), 7.72 (1H, dd, $J = 1.8, 8.7$ Hz, H7), 7.82 (1H, d, $J = 8.7$ Hz, H8), 7.83 (1H, s, H5), 8.18 (1H, d, $J = 9.0$ Hz, H4), 8.19 (1H, br s, NH), 8.41 (1H, br d, $J = 9.0$ Hz, H3). ¹³C NMR (75 MHz, CDCl₃): δ : 21.7 (CH₃), 24.5 (COCH₃), 30.4 (C4''), 34.2 (C3''/5''), 51.2 (C2''/6''), 70.0 (CH₂), 114.6 (C3), 115.3 (C2'/6'), 118.3 (C3'/5'), 125.8 (C4a), 125.9 (C5), 127.4 (C8), 129.2 (C7), 133.9 (C6), 138.0 (C4), 146.2 (C8a), 146.7 (C4'), 151.5 (C2), 152.2 (C1'), 169.9 (C=O). m/z (EI): 389 (M⁺, 10%), 199 (100), 157 (20).

N-{6-[(4-(4-Phenylpiperidin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (**165**)

Using General Procedure 9, **69** (160 mg, 0.57 mmol), **130** (160 mg, 0.63 mmol), K₂CO₃ (237 mg, 1.70 mmol) and acetonitrile (10 mL) were heated for 6 h. After work up with chloroform:isopropanol

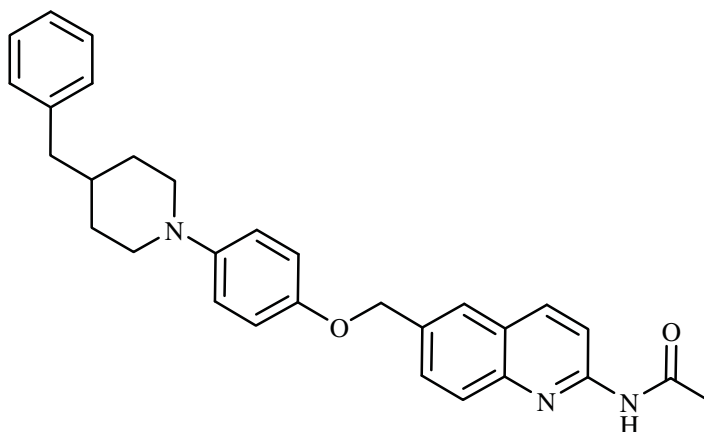


(3:1 mix) the crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a cream powder, mp 170-180 °C (124 mg, 44%).

HRMS found: 451.2262; C₂₉H₂₉N₃O₂ requires 451.2260. IR (nujol mull): ν/cm^{-1} : 3432, 3197, 1720, 1681, 1600 and 1513. ¹H NMR (600 MHz, CDCl₃); δ : 1.90-1.95 (4H, m, H(3''/5'')_{ax}, H(3''/5'')_{eq}), 2.27 (1H, s, CH₃), 2.61 (1H, m, CH, H4''), 2.76 (2H, dt, $J_{(2''/6'')ax, (3''/5'')eq} = 3.0$ Hz, $J_{(2''/6'')ax, (2''/6'')eq} = J_{(2''/6'')ax, (3''/5'')ax} = 12.0$ Hz, 2 x CH, H(2''/6'')_{ax}), 3.65 (2H, br d[‡], $J_{(2''/6'')eq, (3''/5'')eq} = J_{(2''/6'')eq, (2''/6'')ax} = 12.0$ Hz, 2 x CH, H(2''/6'')_{eq}), 5.18 (2H, s, CH₂), 6.96 (4H, br s, H(2'/6'), H(3'/5')), 7.22 (1H, t, $J = 7.2$ Hz, H4'''), 7.26 (2H, d, $J = 7.2$ Hz, H(2'''/6''')), 7.32 (2H, t, $J = 7.2$ Hz, H(3'''/5''')), 7.77 (1H, dd, $J = 1.8, 8.4$ Hz, H7), 7.82 (1H, d, $J = 8.4$ Hz, H8), 7.84 (1H, br s, H5), 8.17 (1H, d, $J = 9.0$ Hz, H4), 8.42 (1H, br d, $J = 9.0$ Hz, H3), 8.59 (1H, br s, NH). ¹³C NMR (150 MHz, CDCl₃); δ : 24.9 (COCH₃), 29.7 (C3''/5''), 42.4 (C4''), 51.9 (C2''/6''), 70.2 (CH₂), 114.5 (C3), 115.6 (C2'/6'), 118.7 (C3'/5'), 125.9 (C5), 126.1 (C4a), 126.2 (C4'''), 126.6 (C2'''/6'''), 127.4 (C8), 128.5 (C3'''/5'''), 129.6 (C7), 134.5 (C6), 138.8 (C4), 146.0 (C8a), 146.1 (C1'''), 146.8 (C4'), 151.1 (C2), 152.7 (C1'), 169.1 (C=O). *m/z* (EI): 451 (M⁺, 15%), 252 (100), 199 (5), 157 (20).

***N*-{6-[(4-(4-Benzylpiperidin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (166)**

Using General Procedure 9, **69** (167 mg, 0.60 mmol), **131** (160 mg, 0.60 mmol), K₂CO₃ (248 mg, 1.80 mmol) and acetonitrile (12 mL) were heated for 5 h. After work up with chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel eluting with DCM:ethyl acetate

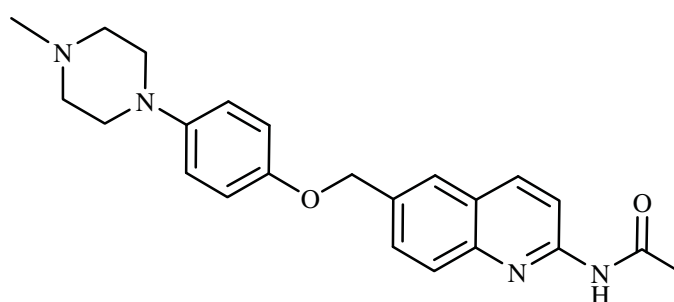


(17:3) to afford the title compound as a white powder, mp 145-147 °C (120 mg, 47%). HRMS found: 465.2419; C₃₀H₃₁N₃O₂ requires 465.2416. Analysis found: C, 76.82; H, 6.70; N, 8.81. C₃₀H₃₁N₃O₂.0.33H₂O requires C, 76.41; H, 6.77; N, 8.91%. IR (DCM): ν/cm^{-1} : 3404, 3059, 2927, 2854, 1700, 1620, 1600, 1580 and 1511. ¹H NMR (600 MHz, CDCl₃); δ : 1.45 (2H, dq, $J_{(2''/6'')eq, (3''/5'')ax} = 4.2$ Hz, $J_{(2''/6'')ax, (3''/5'')ax} = J_{(3''/5'')ax, (3''/5'')eq} = 12.0$ Hz, 2 x CH, H(3''/5'')_{ax}), 1.64 (1H, m, CH, H4''), 1.75 (2H, br d[‡], $J_{(2''/6'')eq, (3''/5'')eq} = J_{(3''/5'')ax, (3''/5'')eq} = 12.0$ Hz, 2 x CH, H(3''/5'')_{eq}), 2.28 (3H, s, CH₃), 2.56 (2H, dt, $J_{(2''/6'')ax, (3''/5'')eq} = 4.2$ Hz, $J_{(2''/6'')ax, (2''/6'')eq} = J_{(2''/6'')ax, (3''/5'')ax} = 12.0$ Hz, 2 x CH, H(2''/6'')_{ax}), 2.58 (2H, d, $J = 7.2$ Hz, CH₂), 3.50 (2H, br d[‡], $J_{(2''/6'')eq, (3''/5'')eq} = J_{(2''/6'')eq, (2''/6'')ax} = 12.0$ Hz, 2 x CH, H(2''/6'')_{eq}), 5.16 (2H, s, CH₂),

6.90 (4H, m, H(2'/6'), H(3'/5')), 7.17 (2H, d, $J = 8.4$ Hz, H(2'''/6''')), 7.20 (1H, d, $J = 8.4$ Hz, H4'''), 7.28 (2H, d, $J = 8.4$ Hz, H(3'''/5''')), 7.71 (1H, dd, $J = 1.8, 8.4$ Hz, H7), 7.80 (1H, d, $J = 8.4$ Hz, H8), 7.82 (1H, br s, H5), 8.14 (1H, d, $J = 9.0$ Hz, H4), 8.40 (2H, br d, $J = 9.0$ Hz, H3, NH). ^{13}C NMR (150 MHz, CDCl_3); δ : 24.9 (COCH₃), 32.3 (C3''/5''), 37.5 (C4''), 43.2 (CH₂), 51.4 (C2''/6''), 70.2 (CH₂), 114.4 (C3), 115.5 (C2'/6'), 118.6 (C3'/5'), 125.9 (C5), 125.9 (C4'''), 126.1 (C4a), 127.6 (C8), 128.2 (C3'''/5'''), 129.1 (C2'''/6'''), 129.5 (C7), 134.5 (C6), 138.6 (C4), 140.5 (C1'''), 146.2 (C8a), 146.8 (C4'), 151.0 (C2), 152.3 (C1'), 169.0 (C=O). m/z (EI): 465 (M^+ , 20%), 372 (20), 266 (100), 199 (10), 157 (20).

Attempted synthesis of *N*-{6-[(4-(4-methylpiperazin-1-yl)phenoxy)methyl]quinolin-2-yl}-acetamide (167)

(i) Using General Procedure 9, **69** (50 mg, 0.18 mmol), **132** (38 mg, 0.20 mmol), K_2CO_3 (75 mg, 0.54 mmol) and acetonitrile (10 mL) were heated for 7 h. NMR analysis of the crude material showed a mixture of products



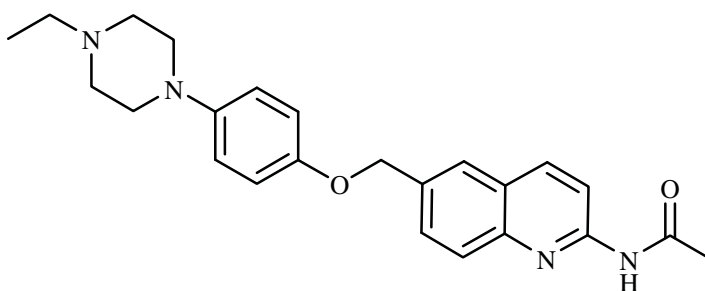
with little of the desired product observed and was therefore not purified.

(ii) Using General Procedure 10, **132** (90 mg, 0.47 mmol) was dissolved in DMF (5 mL). K_2CO_3 (97 mg, 0.71 mmol), TBAI (57 mg, 0.16 mmol) and **69** (184 mg, 0.66 mmol) were added and the reaction mixture stirred as described above for 20 h. NMR analysis of the crude material indicated predominantly starting material and only trace amounts of the desired product. The crude material was therefore not purified.

(iii) With Ag_2O .¹¹⁵ **69** (190 mg, 0.68 mmol) and **132** (156 mg, 0.81 mmol) were combined in DMF (5 mL) and treated with Ag_2O (220 mg, 0.95 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 30 h. The crude material was filtered through celite and the solvent removed under reduced pressure. NMR analysis of the crude material showed a mixture of products which was not purified.

***N*-{6-[(4-(4-Ethylpiperazin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (168)**

(i) Using General Procedure 9, **69** (200 mg, 0.72 mmol), **133** (162 mg, 0.78 mmol), K₂CO₃ (299 mg, 2.16 mmol) and acetonitrile (10 mL) were heated for 6 h. After work up with chloroform:isopropanol (3:1



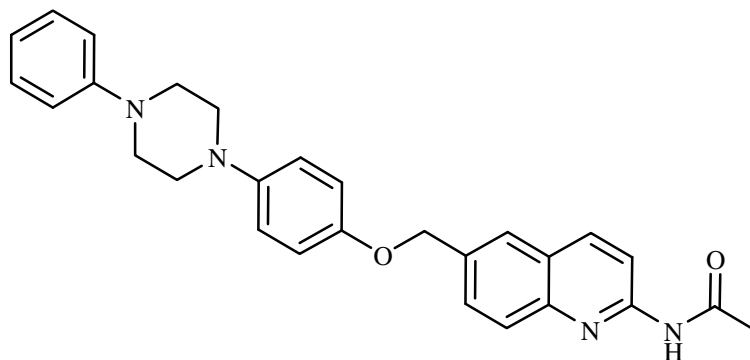
mix) the crude product was chromatographed over C18 silica eluting with water:methanol (3:2) and recrystallised from ethanol:water to afford the title compound as an off-white powder, mp 185-190 °C (30 mg, 10%). HRMS found: 405.2289; C₂₄H₂₈N₄O₂+H requires 405.2291. IR (DCM): ν/cm^{-1} : 3415, 2926, 1700, 1600, 1509 and 1488. ¹H NMR (300 MHz, CDCl₃); δ : 1.17 (3H, t, *J* = 6.0, CH₂CH₃), 2.52 (2H, q, *J* = 6.0, CH₂CH₃), 2.66 (4H, t, *J* = 4.5 Hz, 2 x CH₂, H(3''/5'')), 3.17 (4H, t, *J* = 4.5 Hz, 2 x CH₂, H(2''/6'')), 5.21 (1H, s, CH₂), 6.90 (4H, m, H(2'/6'), H(3'/5')), 7.76 (1H, dd, *J* = 1.8, 8.7 Hz, H7), 7.86 (1H, d, *J* = 8.7 Hz, H8), 7.87 (1H, br s, H5), 8.21 (1H, d, *J* = 9.0 Hz, H4), 8.26 (1H, br s, NH), 8.44 (1H, br d, *J* = 9.0 Hz, H3). ¹³C NMR (75 MHz, CDCl₃); δ : 12.2 (CH₃), 25.1 (COCH₃), 50.6 (C2''/6''), 52.5 (CH₂), 53.2 (C3''/5''), 70.3 (CH₂), 114.7 (C3), 115.8 (C2'/6'), 118.2 (C3'/5'), 126.2 (C5), 126.3 (C4a), 127.8 (C8), 129.8 (C7), 134.6 (C6), 138.8 (C4), 146.3 (C8a)[†], 146.4 (C4')[†], 151.3 (C2), 152.9 (C1'), 169.4 (C=O). *m/z* (LSIMS): 405 (M⁺, 40%), 242 (100), 205 (35).

[†] Assignments may be reversed.

(ii) Using General Procedure 10, **133** (97 mg, 0.47 mmol), K₂CO₃ (97 mg, 0.71 mmol), TBAI (57 mg, 0.15 mmol) and **69** (184 mg, 0.66 mmol) were dissolved in DMF (10 mL) and the reaction mixture stirred for 20 h. After work up the crude material was chromatographed over C18 silica eluting with methanol:water (3:2) to afford the title compound as a cream powder (130 mg, 68%). Data as above.

***N*-{6-[(4-(4-Phenylpiperazin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (172)**

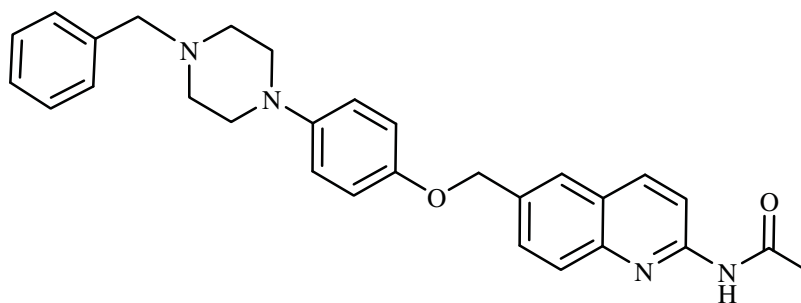
Using General Procedure 10, **134** (120 mg, 0.47 mmol), K₂CO₃ (97 mg, 0.71 mmol), TBAI (57 mg, 0.15 mmol) and **69** (184 mg, 0.66 mmol) were dissolved in DMF (10 mL) and



the reaction mixture stirred for 22 h. After work up the crude material was recrystallised from ethanol to afford the title compound as a cream powder, mp 250-252 °C (200 mg, 94%). Analysis found: C, 74.40; H, 6.44; N, 12.50. C₂₈H₂₈N₄O₂ requires C, 74.31; H, 6.24; N, 12.38%. IR (DCM): ν/cm^{-1} : 3081, 3054, 2825, 1702, 1675, 1600, 1581 and 1488. ¹H NMR (600 MHz, CDCl₃); δ : 2.26 (1H, s, CH₃), 3.25 (4H, t, *J* = 4.8 Hz, H(3''/5'')), 3.33 (4H, t, *J* = 4.8 Hz, H(2''/6'')), 5.18 (2H, s, CH₂), 6.87 (1H, t, *J* = 7.2 Hz, H4'''), 6.95 (4H, s, H(2'/6'), H(3'/5')), 6.97 (2H, d, *J* = 7.2 Hz, H(2'''/6''')), 7.27 (2H, dd, *J* = 7.2 Hz, H(3'''/5''')), 7.70 (1H, dd, *J* = 1.8, 9.0 Hz, H7), 7.81 (1H, d, *J* = 9.0 Hz, H8), 7.83 (1H, br s, H5), 8.14 (1H, d, *J* = 9.0 Hz, H4), 8.38 (1H, br d, *J* = 9.0 Hz, H3), 8.10 (1H, br s, NH). ¹³C NMR (75 MHz, CDCl₃); δ : 24.0 (COCH₃), 48.8 (C2''/6''), 50.0 (C3''/5''), 69.6 (CH₂), 114.3 (C3), 115.1 (C2'/6'), 115.6 (C2'''/6'''), 117.7 (C3'/5'), 119.3 (C4'''), 125.2 (C4a), 125.4 (C5), 127.0 (C8), 128.5 (C3'''/5'''), 128.6 (C7), 133.3 (C6), 137.4 (C4), 145.4 (C4'), 145.9 (C8a), 151.2 (C1'''), 151.9 (C2), 152.3 (C1'), 169.5 (C=O). *m/z* (EI): 452 (M⁺, 2%), 199 (80), 157 (100).

***N*-{6-[4-(4-Benzylpiperazin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (173)**

Using General Procedure 10, **135** (132 mg, 0.49 mmol), K₂CO₃ (102 mg, 0.74 mmol), TBAI (60 mg, 0.16 mmol) and **69** (193 mg, 0.69 mmol) were dissolved

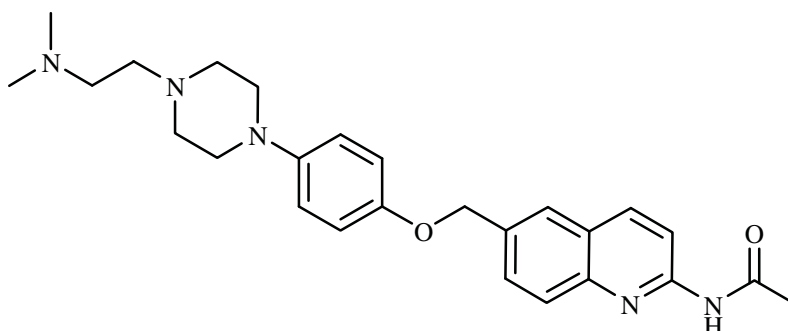


in DMF (10 mL) and the reaction mixture stirred for 24 h. After work up the crude material was chromatographed over silica gel eluting with DCM:ethyl acetate (4:1) to afford the title compound as a cream powder, mp 179-180 °C (120 mg, 53%). HRMS found: 466.2369. C₂₉H₃₀N₄O₂ requires 466.2369. IR (nujol mull): ν/cm^{-1} : 3523, 3355, 1670, 1602, 1579, 1511 and 1462. ¹H NMR (300 MHz, CDCl₃); δ : 2.27 (1H, s, CH₃), 2.65 (4H, t, *J* = 4.5 Hz, H(3''/5'')), 3.12 (4H, t, *J* = 4.5 Hz, H(2''/6'')), 3.59 (2H, s, CH₂), 5.17 (2H, s, CH₂), 6.90 (4H, m, H(2'/6'), H(3'/5')), 7.27-7.37 (5H, m, Ph), 7.74 (1H, dd, *J* = 1.8, 8.4 Hz, H7), 7.82 (1H, d, *J* = 8.4 Hz, H8), 7.84 (1H, s, H5), 8.10 (1H, br s, NH), 8.17 (1H, d, *J* = 9.0 Hz, H4), 8.40 (1H, br d, *J* = 9.0 Hz, H3). ¹³C NMR (75 MHz, CDCl₃); δ : 24.5 (COCH₃), 50.5 (C2''/6''), 53.3 (C3''/5''), 63.1 (CH₂-N), 70.3 (CH₂-O), 114.7 (C3), 115.7 (C2'/6'), 118.2 (C3'/5'), 126.1 (C5), 126.2 (C4a), 127.4 (C8), 127.4 (C4'''), 128.4 (C3'''/5'''), 129.5 (C2'''/6'''), 129.7 (C7), 134.5 (C6), 137.7 (C1'''), 138.8 (C4), 146.2 (C8a), 146.3 (C4'), 151.3 (C2), 152.9 (C1'), 169.4

(C=O). m/z (EI): 466 (M^+ , 15%), 318 (30), 267 (100), 199 (10), 157 (25), 135 (70), 91 (50), 57 (20).

Attempted synthesis of *N*-{6-[(4-(4-(2-(dimethylamino)ethyl)piperazin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (174)

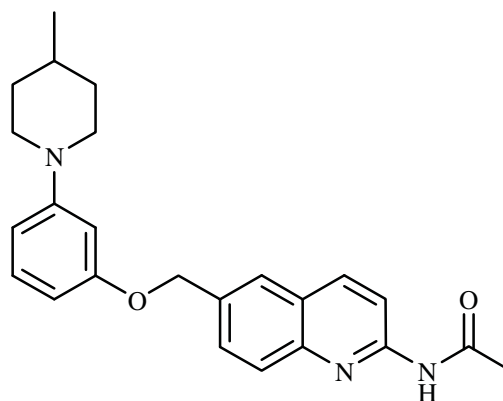
Using General Procedure 10, **136** (104 mg, 0.42 mmol) was dissolved in DMF (5 mL). K_2CO_3 (87 mg, 0.63 mmol), TBAI (51 mg, 0.14 mmol) and **69** (163 mg, 0.58 mmol) were added and the



reaction mixture stirred as described above for 24 h. NMR analysis of the crude material indicated a complex mixture of products which was not purified.

***N*-{6-[(3-(4-Methylpiperidin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (169)**

Using General Procedure 9, **69** (173 mg, 0.62 mmol), **141** (130 mg, 0.68 mmol), K_2CO_3 (257 mg, 1.86 mmol) and acetonitrile (10 mL) were heated for 5 h. After work up with chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a cream glass (38 mg, 16%).

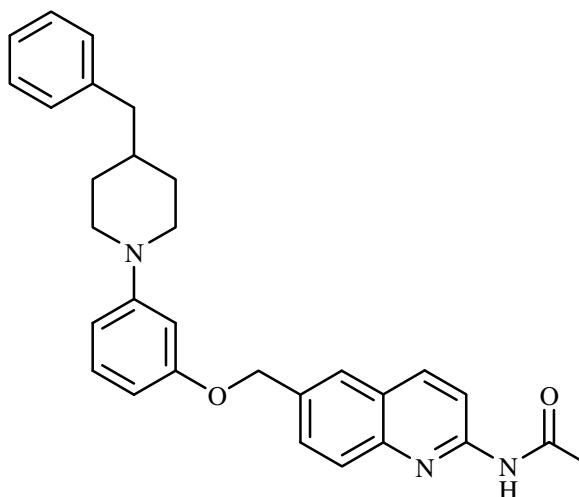


HRMS found: 389.2103. $C_{24}H_{27}N_3O_2$ requires: 389.2103. IR (DCM): ν/cm^{-1} : 3420, 3015, 2926, 2800, 1710, 1601, 1560, 1522 and 1462. 1H NMR (600 MHz, $CDCl_3$); δ : 0.96 (3H, d, $J = 6.6$ Hz, CH_3), 1.32 (2H, dq, $J_{(2''/6'')_{eq}, (3''/5'')_{ax}} = 2.4$ Hz, $J_{(2''/6'')_{ax}, (3''/5'')_{ax}} = J_{(3''/5'')_{ax}, (3''/5'')_{eq}} = J_{(3''/5'')_{ax}, 4''} = 12.0$ Hz, 2 x CH, $H(3''/5'')_{ax}$), 1.51 (1H, m, CH, $H4''$), 1.71 (2H, br d^\ddagger , $J_{(3''/5'')_{ax}, (3''/5'')_{eq}} = J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = 12.0$ Hz, 2 x CH, $H(3''/5'')_{eq}$), 2.20 (3H, s, CH_3), 2.70 (2H, dt, $J_{(2''/6'')_{ax}, (3''/5'')_{eq}} = 2.4$ Hz, $J_{(2''/6'')_{ax}, (2''/6'')_{eq}} = J_{(2''/6'')_{ax}, (3''/5'')_{ax}} = 12.0$ Hz, 2 x CH, $H(2''/6'')_{ax}$), 3.56 (2H, br d^\ddagger , $J_{(2''/6'')_{ax}, (2''/6'')_{eq}} = J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = 12.0$ Hz, 2 x CH, $H(2''/6'')_{eq}$), 5.19 (2H, s, CH_2), 6.47 (1H, dd, $J = 1.8, 7.8$ Hz, $H6'$), 6.58-6.60 (2H, m, $H2', H4'$), 7.15 (1H, t, $J = 7.8$ Hz, $H5'$), 7.71 (1H, dd, $J = 3.0, 9.0$ Hz, $H7$), 7.82 (1H, d, $J = 9.0$ Hz, $H8$), 7.84 (1H, br s, $H5$), 8.16 (1H, d, $J = 9.0$ Hz, $H4$), 8.42 (1H, br d, $J = 9.0$ Hz, $H3$), 8.70 (1H, br s, NH). ^{13}C NMR (150 MHz,

CDCl₃): δ : 21.9 (CH₃), 24.8 (COCH₃), 30.7 (C4''), 34.0 (C3''/5''), 49.7 (C2''/6''), 69.6 (CH₂), 103.6 (C2'), 104.5 (C6'), 109.7 (C4'), 114.5 (C3), 126.0 (C5), 126.1 (C4a), 127.4 (C8), 129.6 (C7), 129.7 (C5'), 134.4 (C6), 138.8 (C4), 146.0 (C8a), 151.1 (C2), 153.3 (C3'), 159.6 (C1'), 169.2 (C=O). *m/z* (EI): 389 (M⁺, 25%), 199 (55), 157 (100), 43 (30).

***N*-{6-[(3-(4-Benzylpiperidin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (170)**

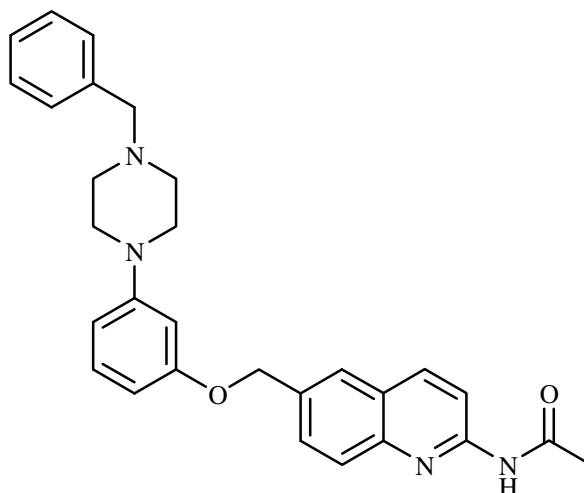
Using General Procedure 9, **69** (123 mg, 0.44 mmol), **144** (130 mg, 0.49 mmol), K₂CO₃ (182 mg, 1.32 mmol) and acetonitrile (10 mL) were heated for 5 h. After work up with chloroform:isopropanol (3:1 mix) the crude product was chromatographed over silica gel eluting with DCM:ethyl acetate (17:3) to afford the title compound as a cream powder, mp 80-83 °C (154 mg, 78%). Analysis found: C, 77.58; H, 6.73; N, 9.02.



C₃₀H₃₁N₃O₂ requires C, 77.39; H, 6.71; N, 9.02%. IR (DCM): ν /cm⁻¹: 3415, 3029, 2926, 2814, 1699, 1601, 1580 and 1522. ¹H NMR (600 MHz, CDCl₃): δ : 1.41 (2H, dq, $J_{(2''/6'')_{ax}, (3''/5'')_{ax}} = 4.2$ Hz, $J_{(2''/6'')_{ax}, (3''/5'')_{eq}} = 12.6$ Hz, 2 x CH, H(3''/5'')_{ax}), 1.53 (1H, m, CH, H4''), 1.71 (2H, br d[‡], $J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = J_{(3''/5'')_{ax}, (3''/5'')_{eq}} = 12.6$ Hz, 2 x CH, H(3''/5'')_{eq}), 2.19 (3H, s, CH₃), 2.56 (2H, d, $J = 7.2$ Hz, CH₂), 2.64 (2H, dt, $J_{(2''/6'')_{ax}, (3''/5'')_{eq}} = 4.2$ Hz, $J_{(2''/6'')_{ax}, (2''/6'')_{eq}} = J_{(2''/6'')_{ax}, (3''/5'')_{ax}} = 12.6$ Hz, 2 x CH, H(2''/6'')_{ax}), 3.66 (2H, br d[‡], $J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = J_{(2''/6'')_{eq}, (2''/6'')_{ax}} = 12.6$ Hz, 2 x CH, H(2''/6'')_{eq}), 5.17 (2H, s, CH₂), 6.44-6.59 (3H, m, H6', H2', H4'), 7.11-7.33 (6H, m, H5', Ph), 7.70 (1H, dd, $J = 1.8, 8.7$ Hz, H7), 7.81 (1H, s, H5), 7.83 (1H, d, $J = 8.7$ Hz, H8), 8.15 (1H, d, $J = 9.0$ Hz, H4), 8.42 (1H, br d, $J = 9.0$ Hz, H3), 8.10 (1H, br s, NH). ¹³C NMR (150 MHz, CDCl₃): δ : 24.9 (COCH₃), 32.1 (C3''/5''), 38.1 (C4''), 43.3 (CH₂), 49.9 (C2''/6''), 69.8 (CH₂), 103.9 (C2'), 104.9 (C6'), 109.9 (C4'), 114.9 (C3), 126.1 (C4a), 126.1 (C4'''), 126.3 (C5), 127.7 (C8), 128.4 (C3'''/5'''), 129.3 (C2'''/6'''), 129.7 (C7), 129.9 (C5'), 134.5 (C6), 138.8 (C4), 140.6 (C1'''), 146.4 (C8a), 151.5 (C2), 153.4 (C3'), 159.9 (C1'), 169.4 (C=O). *m/z* (EI): 466 (M⁺+H, 30%), 465 (M⁺, 80), 267 (80), 199 (60), 157 (20), 57 (60).

Attempted synthesis of *N*-{6-[3-(4-benzylpiperazin-1-yl)phenoxy)methyl]quinolin-2-yl}acetamide (171)

(i) Using General Procedure 9, **69** (38 mg, 0.14 mmol), **162** (40 mg, 0.15 mmol), K_2CO_3 (58 mg, 0.42 mmol) and acetonitrile (10 mL) were heated for 6 h. Work up with chloroform:isopropanol (3:1 mix) and chromatography over silica gel eluting with DCM:ethanol (39:1) led to the recovery of starting materials only.



(ii) Using General Procedure 10, **162** (20 mg, 0.07 mmol), K_2CO_3 (15 mg, 0.11 mmol),

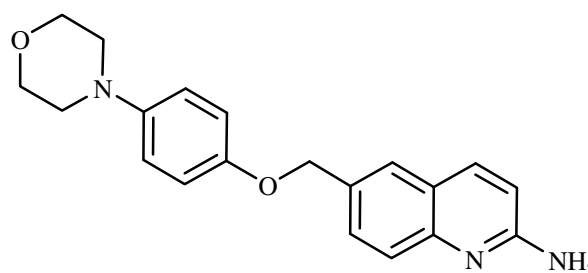
TBAI (9 mg, 0.02 mmol) and **69** (29 mg, 0.10 mmol) were dissolved in DMF (5 mL) and the reaction mixture stirred for 24 h. NMR analysis of the crude material indicated the presence of starting material only.

(iii)¹²¹ **162** (88 mg, 0.33 mmol), K_2CO_3 (59 mg, 0.43 mmol), **69** (92 mg, 0.33 mmol) and DABCO (5 mg, 45 μ mol) were combined in a mortar and ground intermittently for 2 h using a pestle. NMR analysis of the crude material indicated the presence of starting material only.

7.3.3 Synthesis of Extended 6-(Phenoxymethyl)-2-Aminoquinolines

6-[4-(4-Morpholinylphenoxy)methyl]quinolin-2-amine (175)

Using General Procedure 11, **163** (19 mg, 0.05 mmol), K_2CO_3 (7 mg, 0.05 mmol) and methanol (5 mL) were heated for 8 h. The work up was carried out with 5 mL of water to give the title compound as a white solid, mp 240-242 °C (15 mg, 90%). HRMS found:

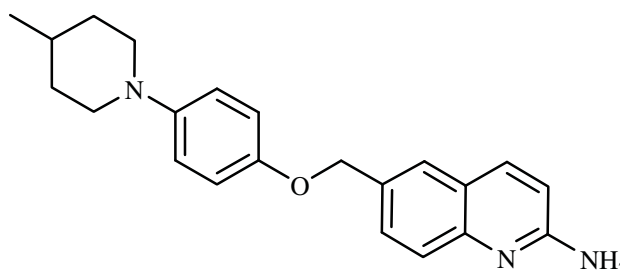


335.1634; $C_{20}H_{21}N_3O_2$ requires 335.1634. IR (chloroform): ν/cm^{-1} : 3518, 3411, 2926, 2856, 1621, 1570, 1509 and 1487. 1H NMR (600 MHz, d_6 -DMSO); δ : 2.96 (4H, t, $J = 4.2$ Hz, 2 x CH_2 , H(3''/5'')), 3.70 (4H, t, $J = 4.2$ Hz, 2 x CH_2 , H(2''/6'')), 5.05 (1H, s, CH_2), 6.40 (2H, br s, NH_2), 6.74 (1H, d, $J = 8.7$ Hz, H3), 6.86 (2H, m, H(3'/5')), 6.92 (2H, m, H(2'/6')), 7.43 (1H, d, $J = 8.7$ Hz, H8), 7.50 (1H, dd, $J = 2.1, 8.7$ Hz, H7), 7.64 (1H, br s, H5), 7.87 (1H, d, $J = 8.7$

Hz, H4). ¹³C NMR (150 MHz, d₆-DMSO); δ: 49.7 (C3''/5''), 66.2 (C2''/6''), 69.7 (CH₂), 112.6 (C3), 115.5 (C2'/6'), 117.0 (C3'/5'), 122.3 (C4a), 125.2 (C8), 126.5 (C5), 129.0 (C7), 130.0 (C6), 136.8 (C4), 145.5 (C4'), 147.6 (C8a), 152.1 (C1'), 158.4 (C2). *m/z* (EI): 336 (M+H⁺, 15%), 335 (M⁺, 40), 178 (40), 157 (100).

6-[[4-(4-Methylpiperidin-1-yl)phenoxy]methyl]quinolin-2-amine (176)

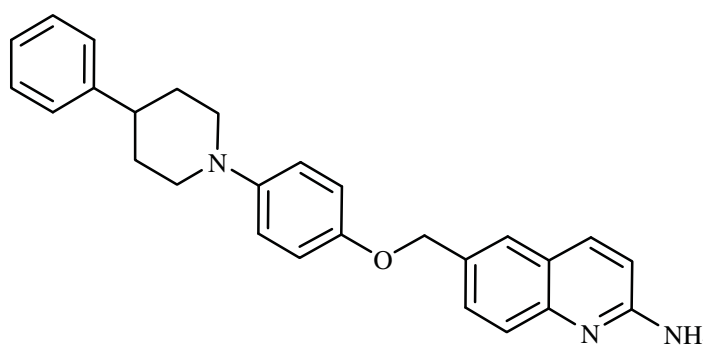
Using General Procedure 11, **163** (80 mg, 0.21 mmol), K₂CO₃ (28 mg, 0.21 mmol) and methanol (10 mL) were heated for 8 h. The work up was carried out with 10 mL of water to give the title compound as a



white solid, mp 227-231 °C (60 mg, 85%). HRMS found: 347.1996; C₂₂H₂₅N₃O requires 347.1998. Analysis found: C, 74.83; H, 7.23; N, 11.71. C₂₂H₂₅N₃O.0.33H₂O requires C, 74.77; H, 7.32; N, 11.89%. IR (DCM): ν/cm⁻¹: 3684, 3402, 3056, 2926, 1620 and 1509. ¹H NMR (300 MHz, CDCl₃); δ: 0.98 (3H, d, *J* = 6.0 Hz, CH₃), 1.40 (2H, dq, *J*(2''/6'')_{eq}, (3''/5'')_{ax} = 2.4 Hz, *J*(2''/6'')_{ax}, (3''/5'')_{ax} = *J*(3''/5'')_{ax}, (3''/5'')_{eq} = *J*(3''/5'')_{ax}, 4'' = 12.0 Hz, 2 x CH, H(3''/5'')_{ax}), 1.44 (1H, m, CH, H4''), 1.74 (2H, br d[‡], *J*(3''/5'')_{ax}, (3''/5'')_{eq} = *J*(2''/6'')_{eq}, (3''/5'')_{eq} = 12.0 Hz, 2 x CH, H(3''/5'')_{eq}), 2.61 (2H, dt, *J*(2''/6'')_{ax}, (3''/5'')_{eq} = 2.4 Hz, *J*(2''/6'')_{ax}, (2''/6'')_{eq} = *J*(2''/6'')_{ax}, (3''/5'')_{ax} = 12.0 Hz, 2 x CH, H(2''/6'')_{ax}), 3.49 (2H, br d[‡], *J*(2''/6'')_{ax}, (2''/6'')_{eq} = *J*(2''/6'')_{eq}, (3''/5'')_{eq} = 12.0 Hz, 2 x CH, H(2''/6'')_{eq}), 4.75 (2H, br s, NH₂), 5.11 (2H, s, CH₂), 6.74 (1H, br d, *J* = 9.0 Hz, H3), 6.93 (4H, br s, H(2'/6'), H(3'/5')), 7.61 (1H, dd, *J* = 1.8, 8.7 Hz, H7), 7.68 (1H, d, *J* = 8.7 Hz, H8), 7.68 (1H, br s, H5), 7.89 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (75 MHz, CDCl₃); δ: 22.5 (CH₃), 30.8 (C4''), 34.5 (C3''/5''), 51.0 (C2''/6''), 70.4 (CH₂), 113.4 (C3), 116.1 (C2'/6'), 118.5 (C3'/5'), 123.0 (C4a), 125.9 (C8), 127.2 (C5), 129.7 (C7), 130.7 (C6), 137.6 (C4), 146.9 (C4'), 148.4 (C8a), 152.5 (C1'), 159.1 (C2). *m/z* (EI): 347 (M⁺, 20%), 190 (100), 157 (95).

6-[[4-(4-Phenylpiperidin-1-yl)phenoxy]methyl]quinolin-2-amine (177)

Using General Procedure 11, **165** (80 mg, 0.18 mmol), K₂CO₃ (25 mg, 0.18 mmol) and methanol (10 mL) were heated for 5 h. The work up was carried out with 10 mL of water to give the title compound as

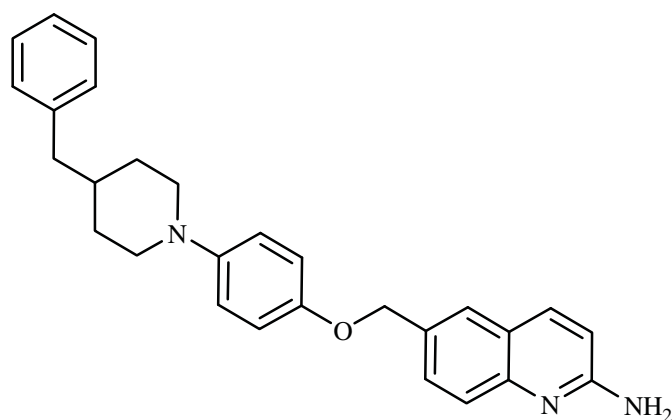


a cream solid, mp 235-238 °C (55 mg, 75%). Analysis found: C, 77.08; H, 6.70; N, 9.89. $C_{27}H_{27}N_3O \cdot 0.5H_2O$ requires C, 77.38; H, 6.74; N, 10.04%. IR (DCM): ν/cm^{-1} : 3451, 3307, 3137, 2923, 2854, 1656, 1606, 1567, 1510, 1492 and 1463. 1H NMR (300 MHz, $CDCl_3$); δ : 1.95-1.98 (4H, m, $H(3''/5'')$ _{ax}, $H(3''/5'')$ _{eq}), 2.62 (1H, m, CH, $H4''$), 2.77 (2H, dt, $J_{(2''/6'')ax, (3''/5'')eq} = 3.0$ Hz, $J_{(2''/6'')ax, (2''/6'')eq} = J_{(2''/6'')ax, (3''/5'')ax} = 12.0$ Hz, 2 x CH, $H(2''/6'')$ _{ax}), 3.67, (2H, br d^\ddagger , $J_{(2''/6'')eq, (3''/5'')eq} = J_{(2''/6'')eq, (2''/6'')ax} = 12.0$ Hz, 2 x CH, $H(2''/6'')$ _{eq}), 4.75 (2H, br s, NH_2), 5.13 (2H, s, CH_2), 6.74 (1H, br d, $J = 9.0$ Hz, H3), 6.97 (4H, s, $H(2'/6')$, $H(3'/5')$), 7.23-7.36 (5H, m, Ph), 7.62 (1H, dd, $J = 1.8, 8.7$ Hz, H7), 7.69 (1H, d, $J = 8.7$ Hz, H8), 7.70 (1H, br s, H5), 7.89 (1H, d, $J = 9.0$ Hz, H4). ^{13}C NMR (75 MHz, $CDCl_3$); δ : 33.1 ($C3''/5''$), 41.6 ($C4''$), 50.9 ($C2''/6''$), 69.6 (CH_2), 112.7 (C3), 115.4 ($C2'/6'$), 118.0 ($C3'/5'$), 122.4 (C4a), 125.3 (C8), 126.2 ($C4'''$), 126.6 (C5), 126.8 ($C2'''/6'''$), 128.5 ($C3'''/5'''$), 129.1 (C7), 130.1 (C6), 137.0 (C4), 146.1 ($C1'''$), ‡ 146.2 ($C4'$), ‡ 147.7 (C8a), 152.0 ($C1'$), 158.5 (C2). m/z (EI): 409 (M^+ , 20%), 252 (90), 157 (100).

‡ Assignments may be reversed.

6-[[4-(4-Benzylpiperidin-1-yl)phenoxy]methyl]quinolin-2-amine (178)

Using General Procedure 11, **166** (97 mg, 0.21 mmol), K_2CO_3 (29 mg, 0.21 mmol) and methanol (10 mL) were heated for 5 h. The work up was carried out with 10 mL of water to give the title compound as a white solid, mp 225-229 °C (74 mg, 83%). HRMS found: 423.2304; $C_{28}H_{29}N_3O$ requires

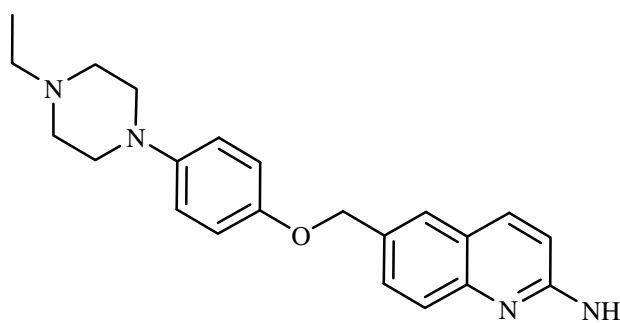


423.2311. IR (chloroform): ν/cm^{-1} : 3451, 3403, 3062, 2928, 2851, 2812, 1621, 1563 and 1508. 1H NMR (300 MHz, $CDCl_3$); δ : 1.45 (2H, dq, $J_{(2''/6'')eq, (3''/5'')ax} = 4.2$ Hz, $J_{(2''/6'')ax, (3''/5'')ax} = J_{(3''/5'')ax, (3''/5'')eq} = 12.0$ Hz, 2 x CH, $H(3''/5'')$ _{ax}), 1.60 (1H, m, CH, $H4''$), 1.75 (2H, br d^\ddagger , $J_{(2''/6'')eq, (3''/5'')eq} = J_{(3''/5'')ax, (3''/5'')eq} = 12.0$ Hz, 2 x CH, $H(3''/5'')$ _{eq}), 2.58 (2H, dt, $J_{(2''/6'')ax, (3''/5'')eq} = 4.2$ Hz, $J_{(2''/6'')ax, (2''/6'')eq} = J_{(2''/6'')ax, (3''/5'')ax} = 12.0$ Hz, 2 x CH, $H(2''/6'')$ _{ax}), 2.59 (2H, d, $J = 7.2$ Hz, CH_2), 3.50 (2H, br d^\ddagger , $J_{(2''/6'')eq, (3''/5'')eq} = J_{(2''/6'')eq, (2''/6'')ax} = 12.0$ Hz, 2 x CH, $H(2''/6'')$ _{eq}), 4.75 (2H, br s, NH_2), 5.10 (2H, s, CH_2), 6.73 (1H, d, $J = 8.7$ Hz, H3), 6.92 (4H, s, $H(2'/6')$, $H(3'/5')$), 7.17-7.33 (5H, m, Ph), 7.62 (1H, dd, $J = 1.8, 8.4$ Hz, H7), 7.66 (1H, d, $J = 8.4$ Hz, H8), 7.67 (1H, br s, H5), 7.88 (1H, d, $J = 8.7$ Hz, H4). ^{13}C NMR (75 MHz, $CDCl_3$); δ : 31.7

(C3''/5''), 38.7 (C4''), 42.4 (CH₂), 50.3 (C2''/6''), 69.6 (CH₂), 112.7 (C3), 115.4 (C2'/6'), 117.9 (C3'/5'), 122.4 (C4a), 125.3 (C8), 125.8 (C4'''), 126.6 (C5), 128.2 (C2'''/6'''), 129.1 (C3'''/5'''), 129.3 (C7), 130.0 (C6), 136.9 (C4), 140.4 (C1'''), 146.1 (C4'), 147.6 (C8a), 151.8 (C1'), 158.4 (C2). *m/z* (EI): 423 (M⁺, 20%), 330 (10), 266 (100), 157 (65).

6-{{[4-(4-Ethylpiperazin-1-yl)phenoxy]methyl}quinolin-2-amine (179)

Using General Procedure 11, **426** (25 mg, 0.06 mmol), K₂CO₃ (9 mg, 0.06 mmol) and methanol (5 mL) were heated for 3 h. The work up was carried out with 5 mL of water to give the title compound as a cream solid, mp 215-220 °C (17 mg, 77%).

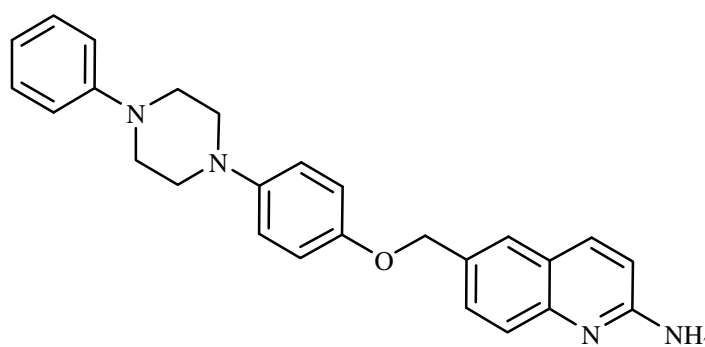


HRMS found: 363.2182; C₂₂H₂₆N₄O+H

requires 363.2185. Analysis found: C, 72.84; H, 7.24; N, 15.56. C₂₂H₂₆N₄O requires C, 72.90; H, 7.23; N, 15.46%. IR (chloroform): ν/cm^{-1} : 3690, 3412, 3052, 2985, 2928, 1621, 1602, 1509 and 1488. ¹H NMR (300 MHz, CDCl₃); δ : 0.90 (3H, t, *J* = 7.2, CH₂CH₃), 2.25 (2H, q, *J* = 7.2, CH₂CH₃), 2.38 (4H, t, *J* = 4.5 Hz, 2 x CH₂, H(3''/5'')), 2.89 (4H, t, *J* = 4.5 Hz, 2 x CH₂, H(2''/6'')), 4.86 (1H, s, CH₂), 5.15 (1H, br s, NH₂), 6.57 (1H, br d, *J* = 9.0 Hz, H3), 6.69 (4H, m, H(2'/6'), H(3'/5')), 7.36 (2H, m, H7, H8), 7.42 (1H, s, H5), 7.62 (1H, d, *J* = 9.0 Hz, H4). ¹³C NMR (75 MHz, CDCl₃); δ : 11.9 (CH₃), 49.4 (C2''/6''), 51.6 (CH₂), 52.4 (C3''/5''), 69.7 (CH₂), 112.6 (C3), 115.4 (C2'/6'), 117.1 (C3'/5'), 125.2 (C4a, C8), 126.5 (C5), 129.0 (C7), 130.0 (C6), 136.8 (C4), 145.6 (C4'), 147.6 (C8a), 151.9 (C1'), 158.3 (C2). *m/z* (LSIMS): 363 (M+H⁺, 100%), 362 (M⁺, 70), 291 (20), 205 (60).

Attempted synthesis of 6-{{[4-(4-phenylpiperazin-1-yl)phenoxy]methyl}quinolin-2-amine (183)

(i) Using General Procedure 11, **172** (127 mg, 0.28 mmol), K₂CO₃ (39 mg, 0.28 mmol) and methanol (10 mL) were heated for 5 h. The work up was carried out with 10 mL of water and led to the recovery of starting material only. Further



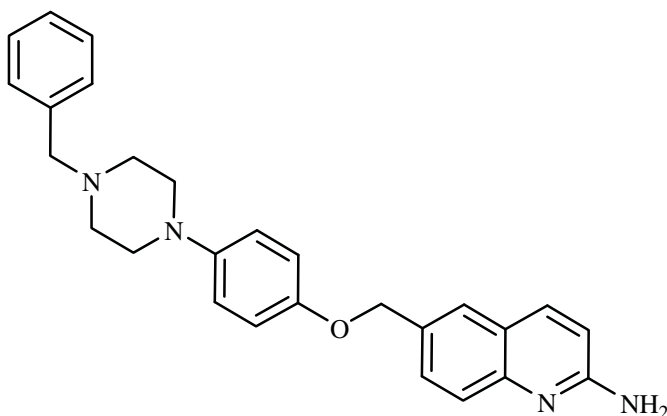
attempts to deprotect **172** in alternate solvents including DMF, THF acetonitrile, and

DMSO:water were similarly unsuccessful.

(ii) A mixture of **172** (50 mg, 0.11 mmol) and 3M HCl was heated at 100 °C for 5 h. The reaction mixture was cooled to room temperature and neutralized with saturated NaHCO₃. Organic material was extracted with chloroform:isopropanol (3:1 mix), washed with water, dried over Na₂SO₄ and the solvent was removed. ¹H NMR analysis of the crude material showed the decomposition of the starting material with none of the desired product being observed.

6-[[4-(4-Benzylpiperazin-1-yl)phenoxy]methyl]quinolin-2-amine (**180**)

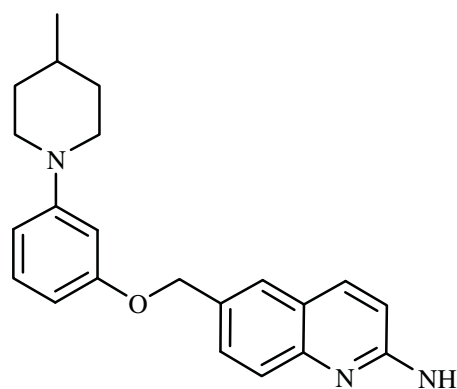
Using General Procedure 11, **173** (60 mg, 0.13 mmol), K₂CO₃ (18 mg, 0.13 mmol) and methanol (10 mL) were heated for 3.5 h. The work up was carried out with 10 mL of water to give the title compound as a cream solid, mp 225-229 °C (35 mg, 64%). HRMS found: 425.2321; C₂₇H₂₈N₄O+H



requires 425.2341. Analysis found: C, 75.91; H, 6.97; N, 12.80. C₂₇H₂₈N₄O requires C, 76.39; H, 6.65; N, 13.20%. IR (chloroform): ν/cm^{-1} : 3453, 3412, 2928, 2773, 1621, 1540 and 1487. ¹H NMR (600 MHz, d₆-DMSO); δ : 2.42 (4H, t, $J = 4.8$ Hz, H(3''/5'')), 2.95 (4H, $J = 4.8$ Hz, H(2''/6'')), 3.46 (2H, s, CH₂-N), 5.00 (2H, s, CH₂-O), 6.36 (2H, br s, NH₂), 6.70 (1H, d, $J = 9.0$ Hz, H3), 6.80 (2H, m, H(3'/5')), 6.85 (2H, m, H(2'/6')), 7.21 (1H, m, H4'''), 7.26-7.29 (4H, m, Ph), 7.39 (1H, d, $J = 9.0$ Hz, H8), 7.45 (1H, dd, $J = 1.8, 9.0$ Hz, H7), 7.60 (1H, br s, H5), 7.82 (1H, d, $J = 9.0$ Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 49.5 (C2''/6''), 52.6 (C3''/5''), 62.0 (CH₂-N), 69.6 (CH₂-O), 112.6 (C3), 115.4 (C2'/6'), 117.2 (C3'/5'), 122.3 (C4a), 125.2 (C8), 126.5 (C5), 126.9 (C4'''), 128.2 (C3'''/5'''), 128.9 (C2'''/6'''), 129.0 (C7), 130.0 (C6), 136.8 (C4), 138.1 (C1'''), 145.5 (C4'), 147.6 (C8a), 151.9 (C1'), 158.3 (C2). m/z (LSIMS): 425 (M+H⁺, 100%), 424 (M⁺, 80), 423 (M-H⁺, 30), 267 (80).

6-{{3-(4-Methylpiperidin-1-yl)phenoxy}methyl}quinolin-2-amine (181)

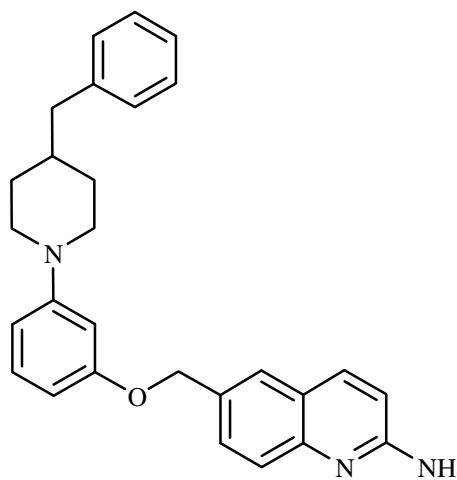
Using General Procedure 11, **169** (25 mg, 67 μmol), K_2CO_3 (10 mg, 67 μmol) and methanol (5 mL) were heated for 4 h. The work up was carried out with 5 mL of water to give the title compound as a cream solid, mp 173-175 $^\circ\text{C}$ (19 mg, 83%). Analysis found: C, 75.89; H, 7.25; N, 11.91. $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}$ requires C, 76.05; H, 7.25; N, 12.09%. IR (DCM): ν/cm^{-1} : 3516, 3411, 2953, 2927, 2814, 1625, 1600 and 1506. ^1H NMR



(300 MHz, CDCl_3); δ : 0.96 (3H, d, $J = 6.6$ Hz, CH_3), 1.31 (2H, dq, $J_{(2''/6'')\text{eq}, (3''/5'')\text{ax}} = 3.0$ Hz, $J_{(2''/6'')\text{ax}, (3''/5'')\text{ax}} = J_{(3''/5'')\text{ax}, (3''/5'')\text{eq}} = J_{(3''/5'')\text{ax}, 4''} = 12.6$ Hz, 2 x CH, $\text{H}(3''/5'')\text{ax}$), 1.50 (1H, m, CH, $\text{H}4''$), 1.71 (2H, br d^\ddagger , $J_{(3''/5'')\text{ax}, (3''/5'')\text{eq}} = J_{(2''/6'')\text{eq}, (3''/5'')\text{eq}} = 12.6$ Hz, 2 x CH, $\text{H}(3''/5'')\text{eq}$), 2.69 (2H, dt, $J_{(2''/6'')\text{ax}, (3''/5'')\text{eq}} = 3.0$ Hz, $J_{(2''/6'')\text{ax}, (2''/6'')\text{eq}} = J_{(2''/6'')\text{ax}, (3''/5'')\text{ax}} = 12.6$ Hz, 2 x CH, $\text{H}(2''/6'')\text{ax}$), 3.65 (2H, br d^\ddagger , $J_{(2''/6'')\text{ax}, (2''/6'')\text{eq}} = J_{(2''/6'')\text{eq}, (3''/5'')\text{eq}} = 12.6$ Hz, 2 x CH, $\text{H}(2''/6'')\text{eq}$), 4.74 (2H, br s, NH_2), 5.13 (2H, s, CH_2), 6.47 (1H, dd, $J = 1.8, 7.8$ Hz, $\text{H}6'$), 6.56-6.60 (2H, m, $\text{H}2', \text{H}4'$), 6.73 (1H, br d, $J = 8.7$ Hz, $\text{H}3$), 7.17 (1H, t, $J = 7.8$ Hz $\text{H}5'$), 7.61 (1H, dd, $J = 1.8, 8.7$ Hz, $\text{H}7$), 7.67 (1H, d, $J = 8.7$ Hz, $\text{H}8$), 7.69 (1H, d, $J = 1.8$ Hz, $\text{H}5$), 7.88 (1H, d, $J = 8.7$ Hz, $\text{H}4$). ^{13}C NMR (75 MHz, CDCl_3); δ : 21.9 (CH_3), 30.3 ($\text{C}4''$), 33.4 ($\text{C}3''/5''$), 48.7 ($\text{C}2''/6''$), 69.1 (CH_2), 102.6 ($\text{C}2'$), 104.5 ($\text{C}6'$), 108.6 ($\text{C}4'$), 112.7 ($\text{C}3$), 122.2 ($\text{C}4\text{a}$), 125.3 ($\text{C}8$), 126.7 ($\text{C}5$), 129.2 ($\text{C}7$), 129.6 ($\text{C}5'$), 129.9 ($\text{C}6$), 136.8 ($\text{C}4$), 147.7 ($\text{C}8\text{a}$), 152.6 ($\text{C}3'$), 158.4 ($\text{C}2$), 159.4 ($\text{C}1'$). m/z (EI): 347 (M^+ , 30%), 191 (15), 157 (20).

6-{{3-(4-Benzylpiperidin-1-yl)phenoxy}methyl}quinolin-2-amine (182)

Using General Procedure 11, **170** (90 mg, 0.20 mmol), K_2CO_3 (28 mg, 0.20 mmol) and methanol (10 mL) were heated for 4 h. The work up was carried out with 10 mL of water to give the title compound as a cream solid, mp 167-168 $^\circ\text{C}$ (65 mg, 77%). Analysis found: C, 79.05; H, 6.88; N, 9.92. $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}$ requires C, 79.40; H, 6.90; N, 9.92%. IR (chloroform): ν/cm^{-1} : 3516, 3411, 3029, 2927, 2850, 1601, 1575 and 1465. ^1H NMR (600 MHz, $\text{d}_6\text{-DMSO}$); δ : 1.23 (2H, dq, $J_{(2''/6'')\text{eq}, (3''/5'')\text{ax}} = 3.6$ Hz, $J_{(2''/6'')\text{ax}, (3''/5'')\text{ax}} = J_{(3''/5'')\text{ax}}$,



($3''/5''$)_{eq} = 12.6 Hz, 2 x CH, H($3''/5''$)_{ax}), 1.59 (2H, br d[‡], $J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = J_{(3''/5'')_{ax}, (3''/5'')_{eq}} = 12.6$ Hz, 2 x CH, H($3''/5''$)_{eq}), 1.65 (1H, m, CH, H4''), 2.49 (2H, d, $J = 7.2$ Hz, CH₂), 2.56 (2H, dt, $J_{(2''/6'')_{ax}, (3''/5'')_{eq}} = 3.6$ Hz, $J_{(2''/6'')_{ax}, (2''/6'')_{eq}} = J_{(2''/6'')_{ax}, (3''/5'')_{ax}} = 12.6$ Hz, 2 x CH, H($2''/6''$)_{ax}), 3.64 (2H, br d[‡], $J_{(2''/6'')_{eq}, (3''/5'')_{eq}} = J_{(2''/6'')_{eq}, (2''/6'')_{ax}} = 12.6$ Hz, 2 x CH, H($2''/6''$)_{eq}), 5.07 (2H, s, CH₂), 6.39-6.40 (3H, m, H6', NH₂), 6.47-6.50 (2H, m, H2', H4'), 6.75 (1H, d, $J = 8.4$ Hz, H3), 7.05 (1H, t, $J = 8.4$ Hz, H5'), 7.16-7.18 (3H, m, H($2'''/6'''$), H4'''), 7.27 (2H, t, $J = 7.5$ Hz, H($3'''/5'''$)), 7.43 (1H, d, $J = 9.0$ Hz, H8), 7.50 (1H, dd, $J = 1.8, 9.0$ Hz, H7), 7.65 (1H, d, $J = 1.8$ Hz, H5), 7.66 (1H, d, $J = 9.0$ Hz, H4). ¹³C NMR (150 MHz, CDCl₃); δ : 31.2 (C3''/5''), 37.4 (C4''), 42.3 (CH₂), 48.7 (C2''/6''), 69.1 (CH₂), 102.7 (C2'), 104.4 (C6'), 108.6 (C4'), 112.7 (C3), 122.4 (C4a), 125.2 (C8), 125.8 (C4'''), 126.6 (C5), 128.1 (C3'''/5'''), 129.0 (C2'''/6'''), 129.1 (C7), 129.5 (C5'), 129.9 (C6), 136.8 (C4), 140.2 (C1'''), 147.6 (C8a), 152.5 (C3'), 158.4 (C2), 159.4 (C1'). *m/z* (EI): 423 (M⁺, 10%), 267 (45), 199 (35), 157 (100).

7.4 The [¹H, ¹⁵N] HSQC NMR Chemical Shift Perturbation Assay²⁸

NMR spectra were recorded using a Varian INOVA 600 Spectrometer (3 RF channels) using a 5mm ¹H{¹³C/¹⁵N} inverse triple resonance PFG probe fitted with z-axis gradients. Sensitivity enhanced [¹H, ¹⁵N] Heteronuclear Single Quantum Coherence (HSQC) spectra were recorded at 25 °C with spectral widths of 8000 and 2000 Hz in F1 and F2 respectively, with 32 t₁ increments and 12 transients. Alternatively, HSQC NMR spectra were recorded using a Varian 7700 5mm ¹³C enhanced cryoprobe. The same parameters were employed as above however, the number of transients was reduced to 8.

A solution of the uniformly ¹⁵N labeled Tec SH3 domain (50 μ M – 150 μ M) in 10 mM Na₂HPO₄, 10% v/v D₂O, 10% v/v d₆-DMSO, 0.01% w/v NaN₃ to a total volume of 550 μ L and pH 6.6 - 6.7 was prepared. Stock solutions of ligands to be assayed were prepared by completely dissolving the ligand in d₆-DMSO.

A HSQC spectrum of the protein in the absence of any ligand was first recorded. The ligand was then titrated into the protein solution in aliquots of 2 μ L at varying concentrations of 0.1 to 3 molar equivalents of protein. HSQC spectra were recorded after the addition of each aliquot and the process repeated until there was little or no change in the spectrum, or the ligand was no longer soluble in the assay solution. An example of an overlay of the HSQC spectra from the assay of 6-(3-acetamidophenoxy)methyl-2-aminoquinoline **106** is shown in Figure 104.

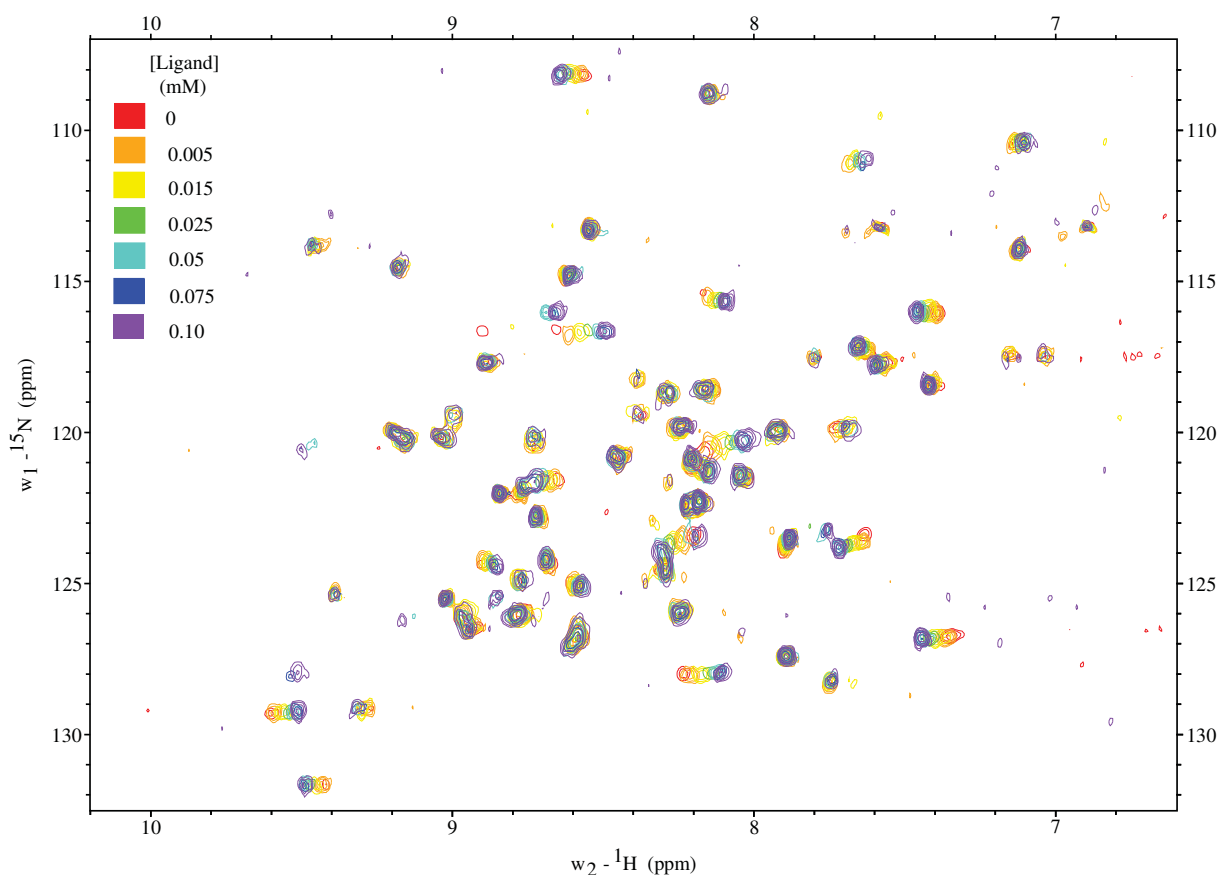


Figure 104: The overlay of the [^1H , ^{15}N] HSQC NMR spectra from the chemical shift perturbation assay of **106**.

Processed HSQC NMR spectra were then analysed using SPARKY.¹³¹ Those residues whose δ_{H} chemical shift were significantly affected (maximum change in chemical shift ≥ 0.08 ppm) upon ligand addition were used to determine binding affinity. $\Delta\delta = \delta_{\text{L}} - \delta_0$ values were calculated (where δ_{L} is δ_{H} for the protein in the presence of the ligand [L] and δ_0 is δ_{H} for the protein in the absence of the ligand). The $|\Delta\delta/\Delta\delta_{\text{max}}|$ values were then calculated to give a normalised value to allow for comparison of amino acid residues. These values were then averaged over all the residues involved in binding and GraphPad Prism⁹⁵ utilised to plot these against the ligand concentration using a one-site hyperbola binding model. GraphPad Prism generates a binding isotherm and calculates the binding affinity, $K_{\text{d}} \pm$ standard error. An example of data acquired from the NMR assay, the calculated $\Delta\delta$ and $|\Delta\delta/\Delta\delta_{\text{max}}|$ values and the results of the GraphPad Prism analysis are shown below as an example with **106** (see Figure 105 and Figure 106).

[106] mM	$\Delta\delta$ ¹ H (H-N) (ppm)														
	A191	D196	E193	H214	N231	R217 (sc)	W215	Y227	A218	D212	G226	N211	Q190	T192	W216 (sc)
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.005	0.014	0.004	0.046	0.044	0.017	0.011	0.058	0.036	0.015	0.020	0.017	0.017	0.020	0.025	0.013
0.015	0.053	0.035	0.073	0.085	0.038	0.033	0.147	0.148	0.037	0.056	0.039	0.036	0.059	0.099	0.039
0.025	0.069	0.057	0.087	0.116	0.051	0.047	0.206	0.178	0.055	0.083	0.058	0.053	0.093	0.164	0.056
0.050	0.091	0.079	0.105	0.146	0.068	0.061	0.272	0.220	0.068	0.112	0.072	0.065	0.112	0.220	0.077
0.076	0.097	0.084	0.111	0.159	0.074	0.065	0.296	0.240	0.071	0.126	0.077	0.079	0.123	0.239	0.091
0.101	0.097	0.085	0.114	0.165	0.075	0.072	0.307	0.253	0.071	0.137	0.080	0.080	0.124	0.246	0.094

[106] mM	$\Delta\delta/\Delta\delta_{\max}$ ¹ H (H-N) (ppm)															Avg	Std Dev	
	A191	D196	E193	H214	N231	R217 (sc)	W215	Y227	A218	D212	G226	N211	Q190	T192	W216 (sc)			
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.005	0.144	0.047	0.404	0.267	0.227	0.153	0.189	0.142	0.211	0.146	0.213	0.213	0.161	0.102	0.138	0.184	0.082	
0.015	0.546	0.412	0.640	0.515	0.507	0.458	0.479	0.585	0.521	0.409	0.488	0.450	0.476	0.402	0.415	0.487	0.068	
0.025	0.711	0.671	0.763	0.703	0.680	0.653	0.671	0.704	0.775	0.606	0.725	0.663	0.750	0.667	0.596	0.689	0.052	
0.050	0.938	0.929	0.921	0.885	0.907	0.847	0.886	0.870	0.958	0.818	0.900	0.813	0.903	0.894	0.819	0.886	0.045	
0.076	1.000	0.988	0.974	0.964	0.987	0.903	0.964	0.949	1.000	0.920	0.962	0.988	0.992	0.972	0.968	0.969	0.028	
0.101	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.000	

Figure 105: The change in chemical shifts for all residues whose corresponding signals shifted significantly ($> \sim 0.1$ ppm) during the assay of **106** (above) and the normalised values and averages for the same assay (below).

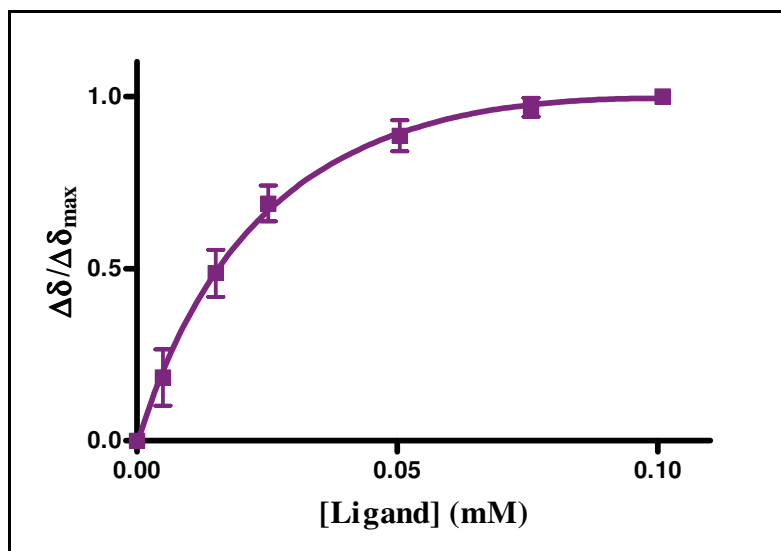


Figure 106: The binding isotherm generated by GraphPad Prism from the data presented above that was used to calculate the equilibrium binding dissociation constant of 6-(3-acetamidophenoxy)methyl-2-aminoquinoline **106**.

Chemical shift mapping of residues involved in binding was performed using Accelrys DS Visualizer 2.0.1.¹³²

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