

# **Investigating 2-Aminoquinoline Derivatives as Small Molecule Ligands for the Tec SH3 Domain**

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**PhD Thesis**

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# SUMMARY

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SH3 domains are small non-catalytic protein domains of around 50-70 amino acids in length. They are found in a variety of proteins and have a number of different functions including roles within cellular signalling pathways, that when deregulated, may lead to diseases such as cancer and osteoporosis. Therefore SH3 domains provide an attractive target for drug design studies.

Many SH3 domains, in their native state, have been found to bind to proline rich peptides. The murine Tec protein contains an SH3 domain that binds to a native proline rich peptide sequence. The structure of the Tec SH3 domain has been solved by NMR methods and is therefore a good starting point for research into small molecule ligand design for the SH3 domain. Within our research group, studies have been undertaken in order to find a small molecule ligand for the SH3 domain. The lead compound for these investigations, 2-aminoquinoline, was found to bind to the Tec SH3 domain in the same region as the native proline rich peptide with a  $K_d$  of 125  $\mu$ M.

Previous structure activity relationship (SAR) studies within our research group have focused on including substituents at the 4-, 5-, 6-, 7- and 8-positions around the quinoline ring as well as substitution at the amino nitrogen. Introducing a substituent at the 6-position has improved the binding affinity of the 2-aminoquinoline ligand and has yielded the best ligand to date with a  $K_d$  of 25  $\mu$ M. Preliminary results have shown that substituents at the 5- and 7-positions did not improve the affinity of the ligand for the SH3 domain.

This thesis describes a number of ways in which SAR studies of 2-aminoquinoline ligands have been further investigated. Substituents have been introduced into a number of positions around the quinoline ring with the aim of improving upon the best ligand to date and also investigating the possibility of finding another region of potential protein-ligand interaction on the protein surface.

A large number of ligands of three general classes have been synthesised in order to achieve the aims of this project. The first class of ligands contain a substituent in either the 5- or 7-position of 2-aminoquinoline. These were synthesised in order to extend and complete the research into the effect of introducing a substituent in these positions. The second class of

ligands included a variety of 2-aminoquinoline derivatives that all contained a substituent at the 6-position. The goal of synthesising these 2-aminoquinoline derivatives is to extend the research that has already been done in this area and improve the binding affinity of the ligand for the Tec SH3 domain. The final class of ligand involves substitution at the 3-position of 2-aminoquinoline, in order to study the potential for the ligand to make a further contact with the protein surface in that region.

The research presented within this thesis conclusively shows that introducing a substituent at either 5- or 7-positions of 2-aminoquinoline does not improve the affinity of the small molecule for the Tec SH3 domain. All of the 6-substituted ligands do however bind to the Tec SH3 domain with far greater affinity, relative to 2-aminoquinoline, and some of these derivatives bind with greater affinity than any previously prepared. The studies performed have also shown that there is the potential to make further interactions with the protein surface by introducing a substituent in the 3-position of the 2-aminoquinoline ligand. The research contained within this thesis will potentially allow for the synthesis of a ligand with a higher affinity for the Tec SH3 domain. This in turn may allow for the unambiguous characterisation of the mode of binding of the ligand to the protein surface by either NMR methods or X-ray crystallography.

# STATEMENT

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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.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Rhiannon Jones, October 2007

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# LIST OF ABBREVIATIONS

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DMAP	<i>N,N</i> -Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
HSQC	Heteronuclear Single Quantum Coherence
LDA	Lithium diisopropyl amide
MPM	Methoxyphenylmethyl (as protecting group)
NBS	<i>N</i> -Bromosuccinimide
PH	Plekstrin Homology
SAR	Structure Activity Relationship
SH2	Src Homology 2
SH3	Src Homology 3
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

# Chapter 1.

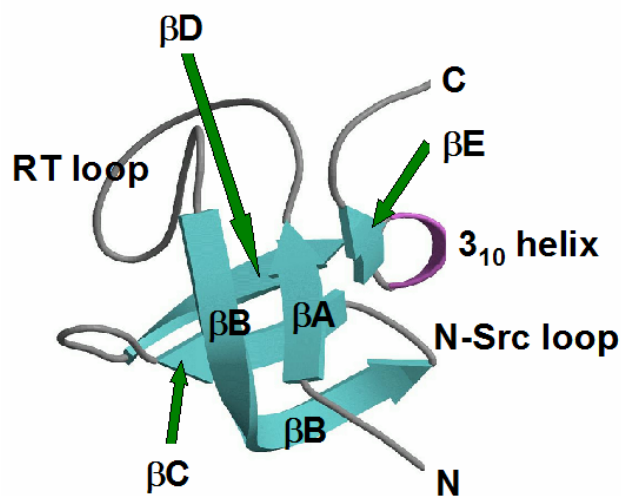
## INTRODUCTION

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### 1.1 The SH3 Domain: Structure and Function

#### 1.1.1. The SH3 Domain

The Src homology 3 (SH3) domain is a small, modular protein domain of approximately 60 amino acids in length which is found in a wide variety of proteins that have a large number of roles and occur across a range of organisms.<sup>1,2</sup> The SH3 domain has been found to bind to proline rich peptide sequences in order to effect their roles, which will be discussed in more detail later. Despite their wide distribution, the general structure of the SH3 domain remains relatively consistent.<sup>1</sup> This general structure can be seen below in a diagram of the *murine* Tec SH3 Domain (Figure 1), the solution structure of which was solved by NMR spectroscopy.<sup>3</sup>



**Figure 1.** Structure of the *murine* Tec SH3 Domain<sup>3</sup>

Five  $\beta$ -strands, which consist largely of hydrophobic residues, make up two  $\beta$ -sheets, with one of the strands shared between the two sheets. These sheets are at right angles to one another and are arranged in such a way that they make up a  $\beta$ -sandwich. There are three variable loops that link the  $\beta$ -strands, the RT, N-Src and distal loops. Only the RT and N-Src loops are shown in Figure 1. The distal loop lies on the opposite face to the region that binds to proline rich peptides, whereas the RT and N-Src loops appear on the same face as this binding region. The region that binds to proline rich ligands, known as the binding site,

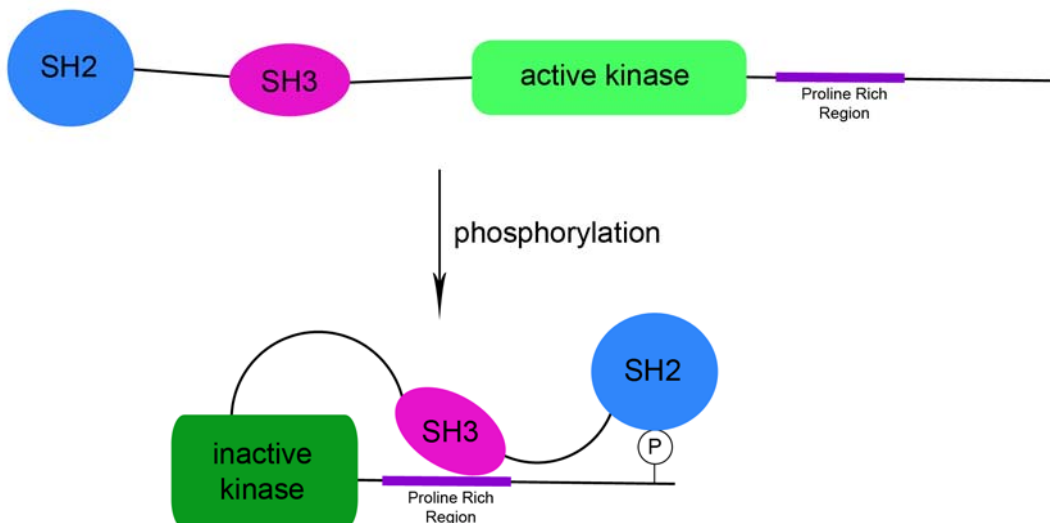


consists of aromatic residues which are highly conserved amongst different SH3 domains.<sup>1-5</sup> In the case of the Tec SH3 domain, the binding site has been found to be a shallow indentation on the surface of the protein.<sup>3</sup>

### 1.1.2. Roles of SH3 Domains

As mentioned previously, SH3 domains have a number of different functions within cellular systems. SH3 domains have been found to be involved in both the regulation of enzyme catalytic activity and in mediating membrane and cytoskeletal interactions.<sup>2</sup> However, one of the major functions of the SH3 domain is to facilitate protein-protein interactions within cellular signalling pathways, by helping to form multiprotein complexes.<sup>2,6</sup>

The SH3 domain function of regulating enzyme activity can be seen within the Src family of protein-tyrosine kinases. A member of this family, c-Src, which contains an SH2, an SH3 and a kinase domain, is found in a number of cell types and is activated during processes that cause cell differentiation and proliferation.<sup>7</sup> In its inactive state, the tyrosine residue, Y527, is phosphorylated and the SH2 domain of the c-Src protein is able to bind to this region. This then brings the SH3 domain within close proximity of a proline rich region, which it can subsequently bind to, thus rendering the kinase inactive (Figure 2).<sup>8</sup>

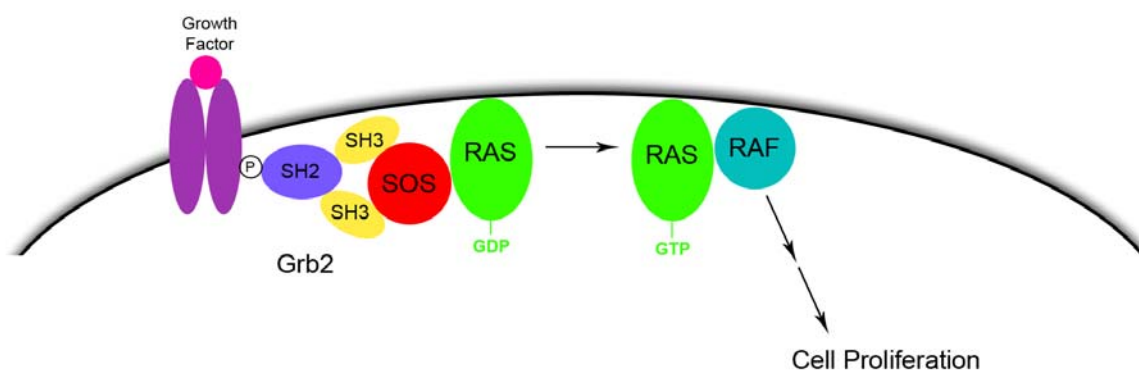


**Figure 2.** Cartoon representation of the role of the SH2 and SH3 domains in the deactivation of c-Src.

Activation is brought about by dephosphorylation of the tyrosine residue, so the SH2 domain is no longer able to bind and the SH3 intramolecular interaction is weakened. The

kinase domain is then able to be activated through the phosphorylation of another tyrosine residue. The SH3 and SH2 domains, now that they are not binding to regions of the Src protein, are able to bind to heterologous ligands. This is thought to localise the Src kinase domain to the region of the cell required for the signalling pathway.<sup>8</sup>

The Grb2 adapter protein is an example of an SH3 domain containing protein that is involved in a cellular signalling pathway. The Grb2 protein, consisting of a Src homology 2 (SH2) domain flanked by an SH3 domain on either side, is found in the Ras pathway, which is an important step in cell proliferation (Figure 3).



**Figure 3.** A cartoon representation of the Ras pathway and the involvement of the SH3 domain within this pathway.<sup>9</sup>

An external signal, such as a growth factor binding to a membrane-bound receptor protein, causes autophosphorylation of a tyrosine residue in the internal region of this trans-membrane protein. The SH2 domain of Grb2 is then able to bind to this phosphorylated tyrosine residue. The Grb2 protein then recruits the SOS protein to the multi-protein complex through interaction of the SH3 binding sites with proline rich regions on SOS. This combination of interactions localises SOS to the cell membrane and places it in the vicinity of membrane-bound Ras, which is then activated. Ras, in turn, can activate further targets, which allows the signal to continue in the same manner, so that it is conveyed to the nucleus where genes involved in cell proliferation are activated.<sup>8-10</sup>

Using the Grb2/Ras pathway as an example, it is easy to see that if this pathway operates without an external stimulus such as the growth factor, the uncontrolled cell proliferation could be involved in diseases such as cancer. If this pathway was blocked, then uncontrolled cell proliferation could be halted, which, in theory, could lead to a cure for the disease. The SH3 domain is one point at which the pathway could be blocked. A small molecule that

binds to the binding site of the SH3 domain with higher affinity than the natural ligand could act as a blocker, by preventing the natural ligand from associating to the multi-protein complex. In the case of Grb2, this would stop the SOS protein from binding to Grb2, which would prevent the rest of the pathway from being activated, thus halting cell proliferation and preventing the manifestation of the disease.

The deregulation of a number of pathways that involve SH3 domains, including the aforementioned Grb2 and Src, have been linked to a number of diseases and therefore the SH3 domain could provide a useful target for drug design (Table 1).

**Table 1.** A number of pathologies associated with SH3 domains and their potential targets for drug design. Table adapted from Dalgarno *et al.*<sup>2</sup>

Pathology	SH3 Target	Reference
AIDS	Lyn	11
	Hck	11
Breast Cancer	Csk	12
	Grb2	13, 14
	Src	15
Cancer	p85	16, 17
	Csk	18
	Grb2	13, 19-21
	Gap	22
Colorectal Cancer	Nck1	23
Huntington's Disease	SH3GL3	24
	p47- <i>phox</i>	25
	p67- <i>phox</i>	25
Leukaemia	CrkL	26
Pre-B-cell Leukaemia	Btk	27
Myelodysplastic Syndrome	Tec	28
Osteoporosis	Src	29, 30

## 1.2 The Tec Family of Protein Tyrosine Kinases

The Tec family of protein tyrosine kinases are SH3 domain containing proteins. Like the Src family, they also contain an SH2 domain and a kinase domain. However, most of the Tec family members also contain two domains that are unique to this family of protein tyrosine kinases. One is a Plekstrin homology (PH) domain, which binds to phosphatidylinositol (3,4,5)-trisphosphate (PIP<sub>3</sub>) and targets the protein to the cell membrane. The other is a Tec homology (TH) domain, which comprises a Zn<sup>2+</sup> binding region and a proline rich region.<sup>31</sup>

Tec family proteins tend to be found in haematopoietic cells and are activated following external stimuli by localisation of the PH domain to the cell membrane, which then leads to phosphorylation of the activation loop in the kinase domain and subsequent autophosphorylation of the SH3 domain. This autophosphorylation alters the affinity of the SH3 domain for different ligands and may even prevent the intracellular association of the SH3 domain with the proline rich regions.<sup>32</sup>

The solution structure of the *murine* Tec SH3 domain was solved by NMR spectroscopy by Pursglove *et al.*<sup>3</sup> Because this protein is from a mouse, it is not a viable target for drug design, however it has been widely studied so its structure and binding site are well characterised and the methods and materials for the preparation of the protein are readily available.<sup>3, 33</sup> Consequently it has the potential to be a good model system for SH3 domain ligand design. The principles that are applied to this system can then be applied to a more viable target once a high affinity ligand has been established and a structure of the ligand-protein complex has been obtained.

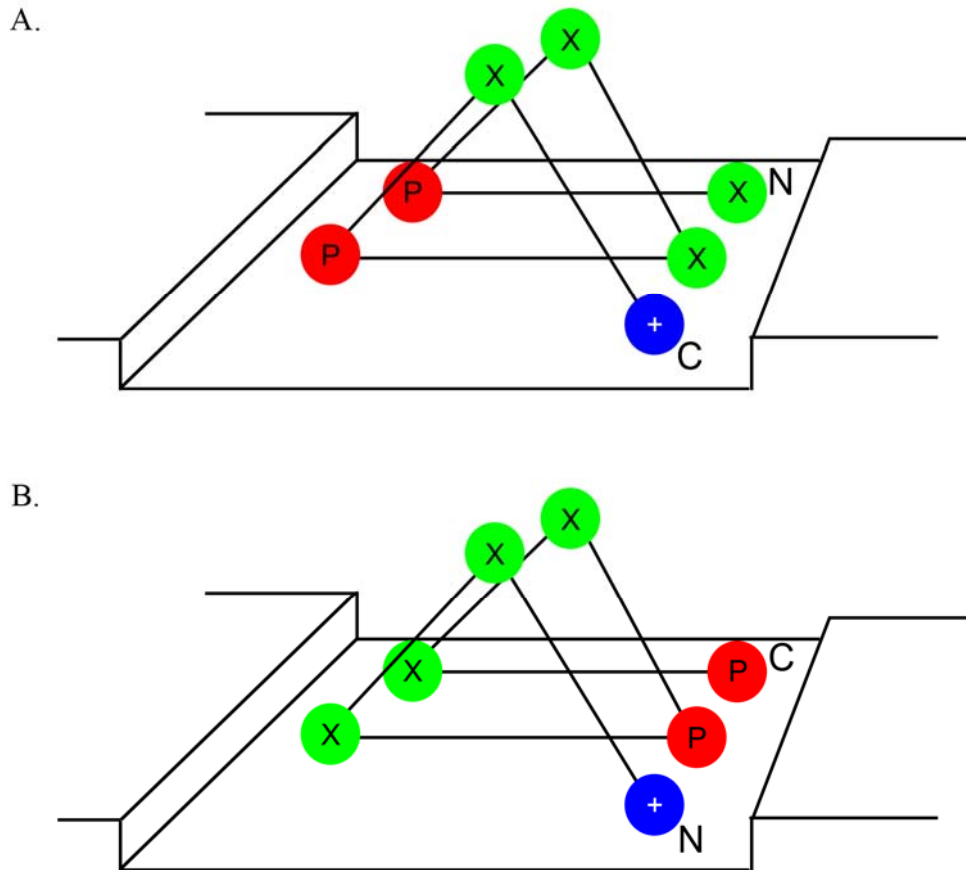
## **1.3 Ligands for the SH3 Domain**

### **1.3.1. Naturally Occurring Ligands**

SH3 domains bind to proline rich regions of peptides with equilibrium dissociation binding constants ( $K_d$ ) of around 1-200  $\mu\text{M}$ , which is indicative of moderate to low binding affinity.<sup>34</sup> The proline rich region tends to contain a core which follows the pattern PpXP, where P is proline, X is any amino acid, but tends to be aliphatic and p can be any amino acid, but has a tendency to be proline.<sup>8</sup> The ligands adopt a polyproline II (PPII) conformation when bound to the SH3 domain, which is a left-handed helix with approximately three residues per turn.<sup>35</sup> This fits ideally into the shallow groove that comprises the binding site of the SH3 domain.<sup>36</sup>

Each of the SH3 domain ligands can be placed in one of two categories, depending on the N-terminal to C-terminal orientation of binding, which is determined by the location of a positive amino acid within the binding site (Figure 4). Ligands containing the motif PXXPX+, where + is a positively charged amino acid, belong to Class I and those with the motif +XXPXXP belong to Class II.<sup>37</sup> The binding site is made up of three binding pockets, the first two of which bind the PXXP core and are comprised of the conserved residues, so

that this pocket remains consistent throughout SH3 domains. The third “specificity pocket” is comprised of the variable residues from the RT and n-Src loops.<sup>37</sup> This pocket binds the positively charged residue and determines the specificity of the ligand for individual SH3 domains.



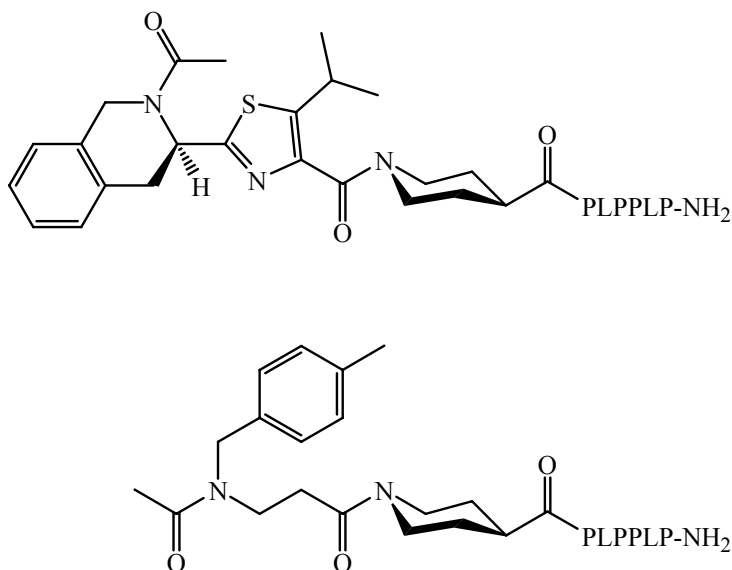
**Figure 4.** Cartoon representation of A. Class I PPII helix ligands, and B. Class II PPII helix ligands binding to the SH3 domain binding site. Figure adapted from Feng *et al.*<sup>38</sup>

### 1.3.2. Novel Peptide-Peptoid Ligands

Despite SH3 domains being attractive targets for drug design, a recent review has labelled them as “undruggable” targets. This is due to the relatively small and featureless binding site, the transient interaction between the protein and its ligand and also the large region of homology between SH3 domains in different proteins that makes specificity challenging.<sup>39</sup>

Nevertheless in recent years there have been a number of advances in finding novel ligands for SH3 domains. The first successes in this area have been from using a traditional Class I

ligand core with the motif PLPPLP linked to novel monomeric units that bind to the specificity pocket (Figure 5).<sup>40, 41</sup>

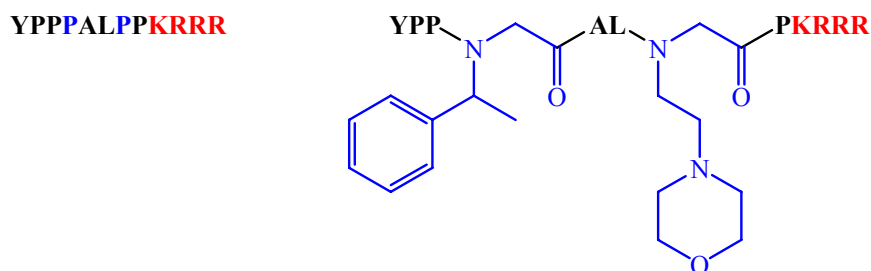


**Figure 5.** Two of the novel ligands with a PLPPLP core that were found to bind to the Src SH3 domain.<sup>40, 41</sup>

These and other similar ligands were shown by NMR methods to bind to the native ligand binding site, including the specificity pocket of the Src SH3 domain, with similar affinity to the native ligand ( $K_d \approx 5\text{-}10 \mu\text{M}$ ). They were also found to be selective for the Src SH3 domain over the SH3 domain of P13K.<sup>40, 41</sup>

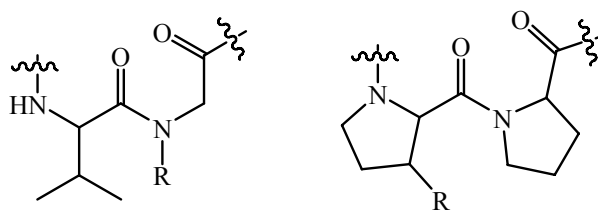
Another study into finding novel ligands for SH3 domains looked into achieving improved affinity through targeting the conserved residues within the binding site, rather than the specificity pocket. It achieved this by replacing the necessary proline residues with *N*-substituted non-naturally occurring amino acids.<sup>34, 42</sup> It was found that by replacing one or both prolines with these peptoid residues, equal or greater affinity than the native ligand could be achieved. It was surmised that the SH3 domain's preference for proline is not due to the properties of the side chain, but because it is the only naturally occurring *N*-substituted amino acid.<sup>34</sup> These efforts in ligand design led to a greater than 100-fold improvement in binding affinity over the native ligand for the Grb2 SH3 domain ( $K_d = 40 \text{ nM}$ ). This ligand also showed selectivity for the Grb2 SH3 domain with a 100-fold selectivity over other SH3 domains including Src and Crk.<sup>34</sup> It was also found that by combining the peptoid substitutions with flanking sequences that bound to the specificity pocket of the SH3 domain, the selectivity for individual SH3 domains could be improved. The ligand shown below in Figure 6 was found to bind to the Crk SH3 domain with

improved affinity over the native ligand ( $K_d = 1.98 \mu\text{M}$ ), but was not found to bind to either the Src or Grb2 SH3 domains.



**Figure 6.** The Crk specific peptide-peptoid ligand compared with the Crk-specific wild-type peptide ligand (left).<sup>42</sup>

More recent research into novel SH3 domain ligands proposed that the preference of the SH3 domain for these peptoid containing ligands may be due to side-chain interaction with the SH3 domain surface rather than the *N*-substitution alone. Therefore a number of ligands containing a  $C^\beta$ -substituted proline adjacent to the site of Nguyen's *N*-substituted residues (Figure 7) were prepared and assessed for binding affinity.<sup>43</sup>



**Figure 7.** The ligands designed by Nguyen *et al.*<sup>34</sup> as compared with the  $C^\beta$ -substituted ligands.<sup>43</sup>

One of the  $C^\beta$ -substituted ligands, with  $R=\text{Me}$ , showed improved affinity by 3-fold for the Grb2 SH3 domain over a decapeptide taken from the native ligand. However, other ligands of this variety showed no binding to the Grb-2 SH3 domain.<sup>43</sup> This would tend to indicate that it is indeed the preference for an *N*-substituted ligand that gives rise to the improved binding affinity for the ligands prepared by Nguyen *et al.* It is possible that the methyl group on the  $C^\beta$ -substituted ligand is, in fact, making an incidental contact which could be explored further.

Although the novel peptide studies have given SH3 domain ligands with high affinity and selectivity and have provided a great deal of information about the mode of ligand binding, they are not practical in terms of drug design for a number of reasons. Peptides are easily broken down within the stomach, by means of stomach acid degradation and non-specific

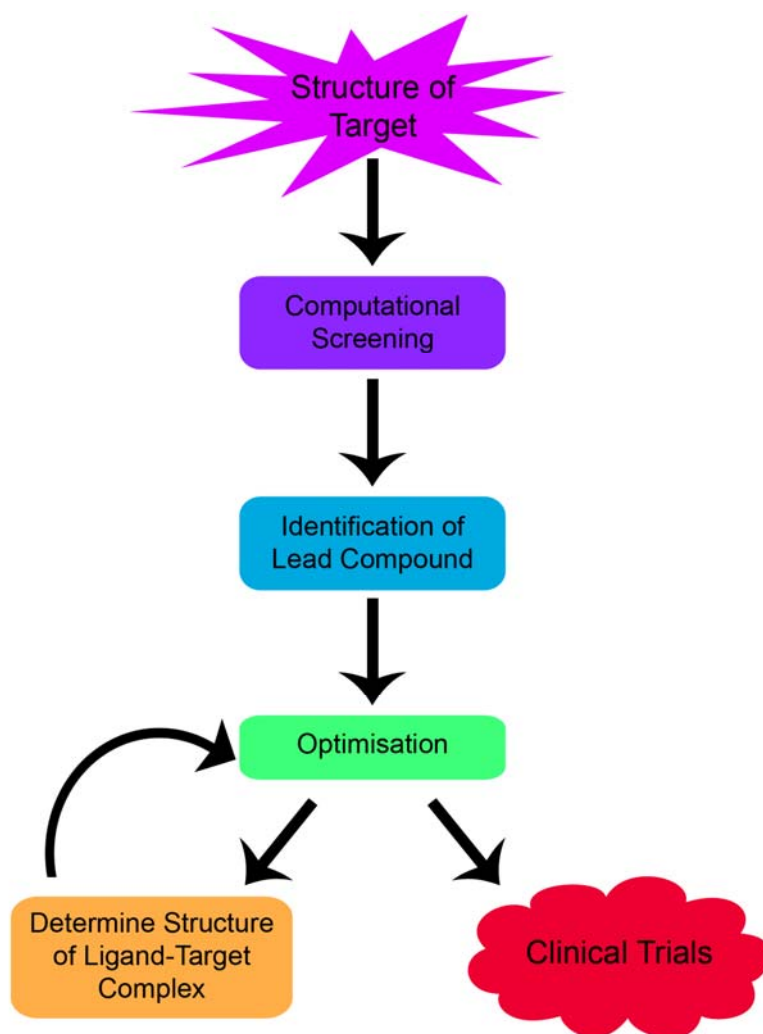
proteases. Therefore a peptide drug needs to be injected in order to have a chance of being effective. However, even if the drug is injected, it could be cleared quite quickly from the body and could potentially cause an immune response. Peptides are also not easily delivered to their respective targets as they are unable to cross the cell membrane. As a result the peptide is not likely to make it to the cellular target in order to effect the response, so a non-peptide ligand is more favourable in terms of drug design.<sup>44</sup>

## **1.4 The Development of Small Molecule Ligands for the Tec SH3 Domain**

### **1.4.1. Strategies Involved in Structure Based Drug Design**

In order to discover a small molecule ligand for the SH3 domain, the tactics of structure based drug design have been employed. This is a process whereby the structure of the target is known and utilised in order to identify a lead compound, which is then refined in order to yield a high affinity ligand. The process shown in Figure 8 has been used to develop small molecule ligands for the Tec SH3 domain.





**Figure 8.** Schematic diagram of the method used for structure based drug design.

The Tec SH3 domain was identified as the target for drug design. As mentioned previously (Section 1.2), the Tec SH3 domain provides an ideal model system for drug design despite being a *murine* protein.

#### 1.4.2. Computational Screening and the Identification of a Lead Compound

The solution structure of the Tec SH3 domain was used in combination with the program LUDI for *in-silico* screenings to discover a lead compound. LUDI recognises binding elements within the binding site of proteins and predicts fragments that will bind to these elements. It then links the fragments with small, simple groups such as CH<sub>2</sub> to give a compound predicted to bind to the ligand.<sup>45</sup> In this case, LUDI predicted 2-aminquinazoline would bind to conserved residues within the binding site of the Tec SH3 domain.<sup>46</sup> 2-Aminoquinazoline was prepared and assayed for binding affinity along with the structurally similar 2-aminoquinoline (Figure 9).



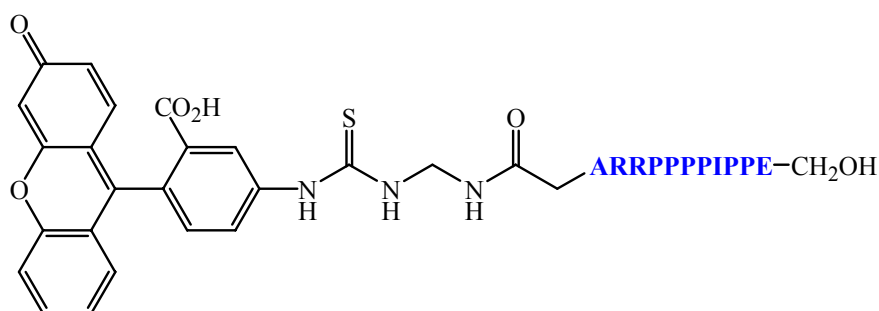
**Figure 9.** 2-Aminoquinazoline, **1** which was predicted to bind to the Tec SH3 domain by *in-silico* screening and structurally similar 2-aminoquinoline, **2**.

Both were found to bind to the Tec SH3 domain, however 2-aminoquinoline was found to bind with higher affinity than 2-aminoquinazoline, so 2-aminoquinoline was identified as the lead compound in these studies. Structure activity relationships could then be investigated and the lead compound optimized to produce a high affinity ligand for the SH3 domain.

### 1.4.3. Assay Methods

#### 1.4.3.A. The Fluorescence Polarisation Assay

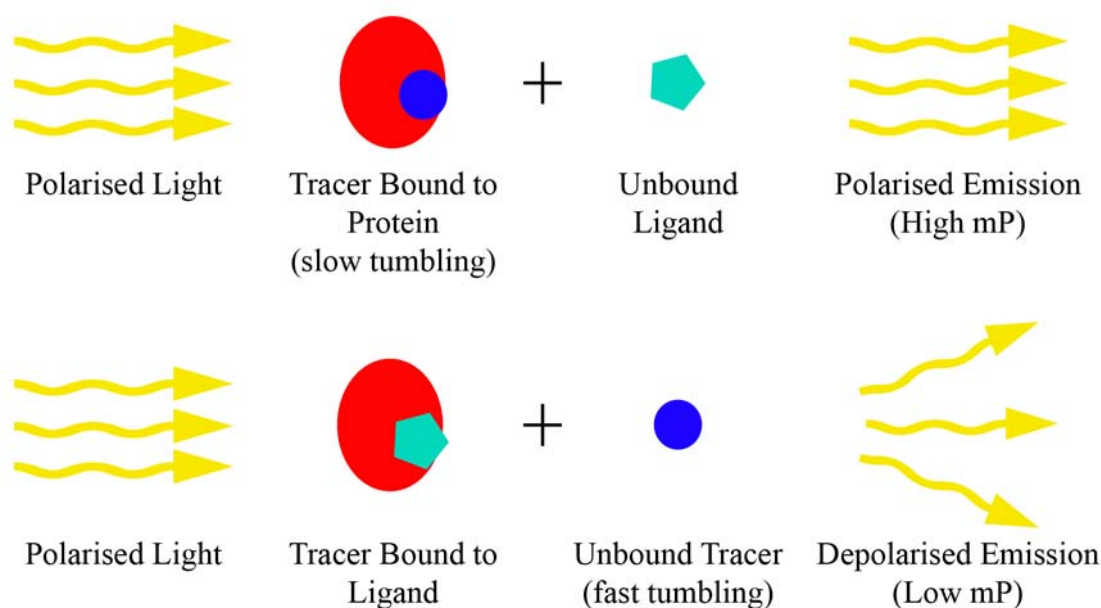
Two methods for determining the binding affinity of a small molecule for the SH3 domain were utilised in this study. The first of these methods was a fluorescence polarisation competition assay. Within this assay, a fluorescently labelled molecule (tracer) binds to a protein in order to measure how much of a competing ligand has bound to the protein, and therefore its binding affinity can be determined. In this fluorescence polarisation assay, the tracer used was FLUORO-PRS-2 (Figure 10). This consisted of a small proline rich peptide ligand, known to bind to Tec SH3, that was then linked to a fluorescent label (fluorescein-5-thiourea) at the N-terminus.



**Figure 10.** Structure of the tracer FLUORO-PRS-2.

The premise behind the fluorescence polarisation assay is that a small molecule is able to tumble rapidly in its photoexcited state, whereas a large molecule tumbles slowly. In this instance, the tracer is considered to be a small molecule. As shown in Figure 11, if the

tracer, when it is not bound to the protein, is irradiated at or near its excitation maximum with polarised light, it will tumble quickly. As a result, the light that it emits will be scattered and is therefore largely depolarised. However, when the tracer is bound to the protein, it is a large complex. Therefore when it is irradiated with polarised light, it will tumble slowly so the light that it emits will be largely polarised.<sup>47</sup> Hence the amount of competing ligand that is bound to the protein can be quantified by how much polarized light is emitted by the tracer. The extent of polarisation is measured in mP, where a low value indicates a depolarised emission and therefore high binding affinity of the competing ligand for the protein and a high value indicates a polarised emission and therefore low binding affinity of the competing ligand for the protein.



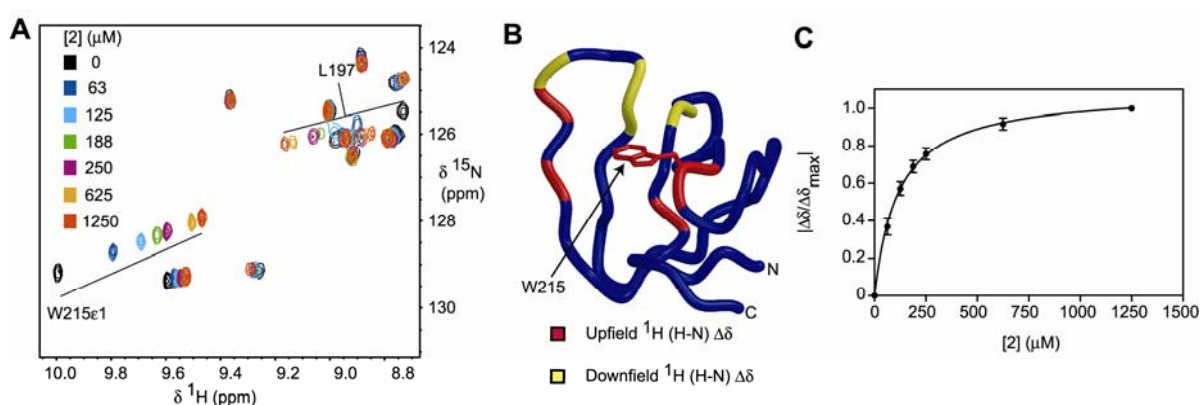
**Figure 11.** Schematic representation of the fluorescence polarisation assay.

The results of the competition assay are then used to plot a curve of mP versus the log of the ligand concentration. The graph gives a standard dose-dependent curve and the  $EC_{50}$  value can be determined by finding the concentration of the ligand at the point of inflection on the curve.

#### 1.4.3.B. The [ $^1H,^{15}N$ ] HSQC NMR Chemical Shift Perturbation Assay

The primary method of assessing the binding affinity of small molecule ligands for the Tec SH3 domain throughout this research was the [ $^1H,^{15}N$ ] HSQC NMR chemical shift perturbation assay. This involves the titration of small molecule ligands into a constant concentration of uniformly  $^{15}N$ -labelled protein solution and acquiring [ $^1H,^{15}N$ ] HSQC NMR spectra after addition of each aliquot of ligand. As the concentration of the ligand

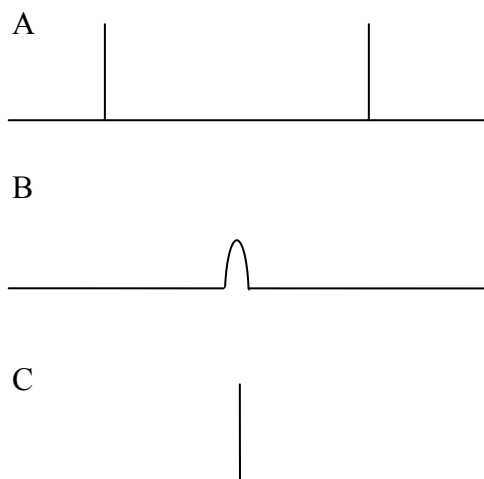
increases, the chemical shifts of the residues involved in binding the small molecule ligand move, so that an average of the bound versus the unbound protein is seen in the spectrum, assuming fast exchange on the NMR timescale. The change in chemical shift for each of the residues that are shifted by a significant amount ( $> \sim 0.1$  ppm) are then averaged and plotted against the concentration of the ligand, using a one site binding model. The resulting binding isotherm is then used to determine the  $K_d$  of the ligand, which is defined as the concentration when 50% of the ligand is bound to the protein. An example of the overlaid spectra from the assay and the binding isotherm is shown below in Figure 12.



**Figure 12.** A. An expansion of several peaks in overlaid HSQC spectra from the assay of **2**. B. Chemical shift mapping of the residues that move in the assay of **2**. C. The binding isotherm derived from the HSQC NMR assay of **2**.<sup>46</sup>

### *Fast, Intermediate and Slow Exchange*

The HSQC NMR assay relies on the protein and protein-ligand complex being in fast exchange with one another so the signals that are seen are an average of the unbound protein and protein bound to ligand. However, when the rate of the exchange between bound and unbound forms slows down, two signals can be seen; one is for the bound protein-ligand complex and one is for the unbound state of the protein. If the rate of exchange is between fast and slow exchange, a phenomenon known as intermediate exchange occurs (Figure 13). This is where the signal may have much lower intensity and may be substantially broadened. During intermediate exchange it is often difficult to analyse the observed signal as it may be so low in intensity that it is lost amongst the noise of the spectrum. Fast, intermediate and slow exchange can also be observed in small molecule NMR spectra if there are two or more available structures that a compound can exchange between (i.e. conformers, rotamers, etc).

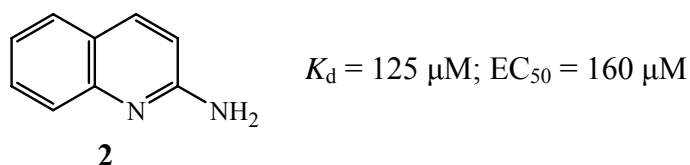


**Figure 13.** Schematic representation of slow exchange (A), intermediate exchange (B) and fast exchange (C).

If the ligand-protein complex enters into slow exchange, the HSQC NMR method cannot be used to determine binding affinity as the average of bound versus unbound chemical shifts will no longer be observed. However, at this rate of exchange between bound and unbound forms, the interaction should be slow enough for a structure of the protein-ligand complex to be determined through intermolecular NOE experiments. So even though the binding affinity cannot be determined, the ultimate aim of the ligand design is to find a ligand that enters into slow exchange with the protein.

#### 1.4.4. Lead Optimisation and Structure Activity Relationship Studies

As stated previously, 2-aminoquinoline, **2**, was identified as the lead compound in the study into finding small molecule ligands for the Tec SH3 domain. It bound to the Tec SH3 domain with moderate affinity (Figure 14).

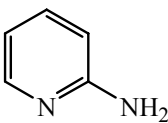
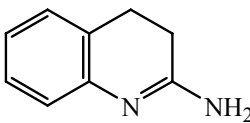
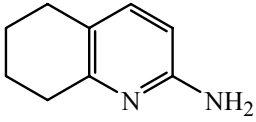
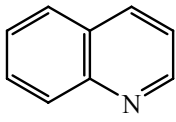
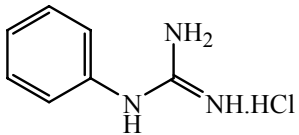
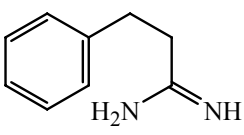


**Figure 14.** The lead compound, **2** and its  $K_d$  and  $EC_{50}$  values.

Various analogues of **2** were subsequently prepared in order to study the binding interaction of the SH3 domain with 2-aminoquinoline. The importance of the heteroaromatic, bicyclic ring structure was determined through binding studies of the analogues **3-8** (Table 2). 2-Aminopyridine, **3**, retains the heteroaromatic character of 2-aminoquinoline and also contains a primary amino group in the same position relative to the heteroatom. Despite this,

**3** bound to the SH3 domain with reduced affinity compared with **2**. This indicated that the bicyclic ring system was of importance. Both **4** and **5** have lost some of their aromatic character but both compounds bind to the Tec SH3 domain with similar affinity to 2-aminoquinoline. Therefore it can be assumed that it is not absolutely necessary for the ring system to be wholly aromatic. **6**, which contains the quinoline but not the amino functionality, does not bind to the Tec SH3 domain, thus indicating that the amino group is of high importance. The guanidine **7** and amidine **8** still contain an amino group in the same region as **2**, however there is a certain amount of flexibility introduced into these two compounds. This flexibility results in loss of binding (as in **8**) or reduced binding (as in **7**). These results show that the minimum structure required for binding appears to be a rigid bicyclic ring system that may be wholly or partly aromatic but must contain an amino group in the 2-position relative to the heteroatom.

**Table 2.** Analogues of 2-aminoquinoline and their binding affinity in comparison with 2-aminoquinoline.

Compound	Binding Affinity	Compound	Binding Affinity
<b>3</b> 	Reduced <sup>46</sup>	<b>4</b> 	Similar <sup>48</sup>
<b>5</b> 	Similar <sup>46</sup>	<b>6</b> 	None <sup>46</sup>
<b>7</b> 	Reduced <sup>48</sup>	<b>8</b> 	None <sup>48</sup>

#### 1.4.5. The Binding Model

A binding model for **2** was formulated based upon chemical shift mapping, following a series of [<sup>1</sup>H,<sup>15</sup>N] HSQC NMR experiments. The largest change in chemical shift upon binding of the ligand occurs in the side chain of tryptophan residue 215 (W215), which undergoes a large <sup>1</sup>H upfield shift.<sup>46</sup> Aspartic acid 196 (D196) also displays a change in chemical shift upon binding. Site directed mutagenesis studies were performed to determine the importance of D196 in the binding of the small molecule ligand to the SH3 domain. Tec SH3 domains with the following mutations were prepared: D196A, D196E, D196N and

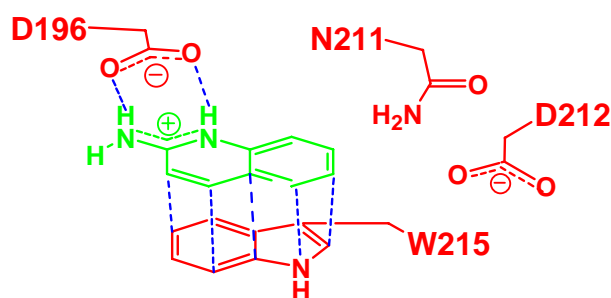
D196T and **2** was unable to bind to any of these mutants. This indicates that a negatively charged, polar group is necessary at the D196 position in order for 2-aminoquinoline to bind to the Tec SH3 domain.<sup>46</sup> It has also been shown through fluorescence polarisation studies that **2** binds with a greater affinity at lowered pH.<sup>49</sup> These results, along with the SAR studies shown above (Section 1.4.4.), led to the hypothesis that the quinoline ring system forms a  $\pi$ - $\pi$  stack with W215 and a salt bridge is formed with D196 (shown in Figure 15).<sup>46</sup>



**Figure 15.** Proposed binding model of 2-aminoquinoline with the Tec SH3 domain and the lead compound.<sup>46</sup>

#### 1.4.6. Substitution at the 6-position of 2-Aminoquinoline

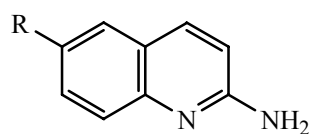
The introduction of substituents on the quinoline ring has been investigated with the aim of improving the binding affinity of the small molecule ligand for the Tec SH3 domain, by making additional contacts with the protein surface. Inspection of the SH3 domain showed the presence of charged amino acid side chains to one side of the binding site (Figure 16). It was hoped that through substitution at the 6-position of 2-aminoquinoline that a hydrogen bond contact could be made between a polar group on the ring substituent and the side chains of asparagine 211 (N211) and aspartate 212 (D212).<sup>46</sup>



**Figure 16.** The charged amino acids that may form a contact with a substituent in the 6-position of **2**.

A number of different compounds containing substituents at the 6-position of 2-aminoquinoline, **9-12** were prepared. A selection of these, along with their binding data, are shown below in Table 3.

**Table 3.** A number of 6-substituted-2-aminoquinoline ligands found to bind to the Tec SH3 domain, and their binding affinities.<sup>46, 50</sup>



	R	$K_d$ ( $\mu\text{M}$ )	$\text{EC}_{50}$ ( $\mu\text{M}$ )
<b>9</b>	$\text{CH}_3$	63	52
<b>10</b>		49	25
<b>11</b>		35	35
<b>12</b>		22	-

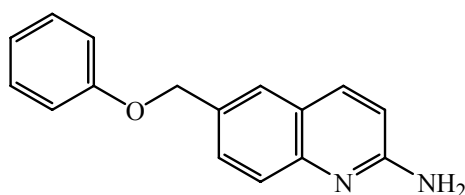
Note:  $K_d$  was determined by NMR,  $\text{EC}_{50}$  was determined by fluorescence polarization spectroscopy.

The increased binding affinity upon substitution at the 6-position of the quinoline ring (**9 – 12**) indicates that there is likely to be an additional interaction with the protein surface taking place (Table 3). However, as both the polar and non-polar substituents increase the binding of the ligand, the interaction is likely to be lipophilic. Further substitution of this ring could improve the interaction with this specific region, and thus significantly increase the binding affinity.

Although the previously prepared 6-substituted 2-aminoquinolines have yielded the highest affinity ligands to date, the acetal substituents are not stable in aqueous conditions.



Obviously this is not ideal for a drug candidate, so it was desirable to find another type of substituent that would be more robust. It was found that introducing a phenoxyethyl substituent in the 6-position of 2-aminoquinoline gave rise to a ligand with similar affinity (Figure 17).<sup>49</sup>



**13**

$K_d = 32 \mu\text{M}$

**Figure 17.** The structure of the 6-phenoxyethyl-2-aminoquinoline and its binding affinity.

#### 1.4.7. Investigating *N*-Substitution

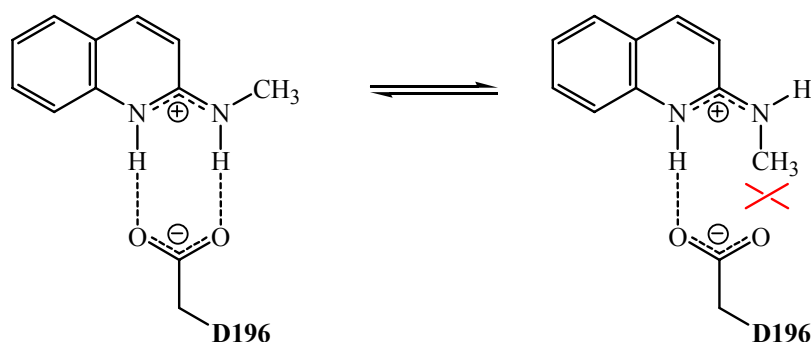
Several *N*-substituted analogues of **2** were synthesised previously and assayed for binding affinity (Table 4) in order to ascertain the importance of the salt bridge and determine whether or not any further contacts could be made with the protein surface.

**Table 4.** *N*-substituted analogues of 2-aminoquinoline along with their binding activities.

	Compound	$K_d$ ( $\mu\text{M}$ )		Compound	$K_d$ ( $\mu\text{M}$ )
<b>14</b>		380 <sup>46</sup>	<b>15</b>		Does Not Bind <sup>46</sup>
<b>16</b>		190 <sup>51</sup>	<b>17</b>		80 <sup>50</sup>

The salt bridge was indeed shown to be of high importance through the binding studies of compounds **14** and **15**. As seen in Table 4, substitution on the amino group results in complete loss of binding (as in **15**) or a reduction in binding affinity (as in **14**). The inability of **15** to bind to the Tec SH3 domain is most likely due to the carbonyl group adjacent to the NH. This would withdraw electron density through resonance, thus reducing the ability of the ligand to make a salt bridge with residue D196. The reason for the reduced binding of **14** is most likely because of the presence of a second conformer. As shown in Figure 18, in one

of the conformations the N-H is facing towards the protein and able to form a salt bridge, whereas, in the other conformation, the methyl group is facing towards D196 and therefore prevents the salt bridge from forming.

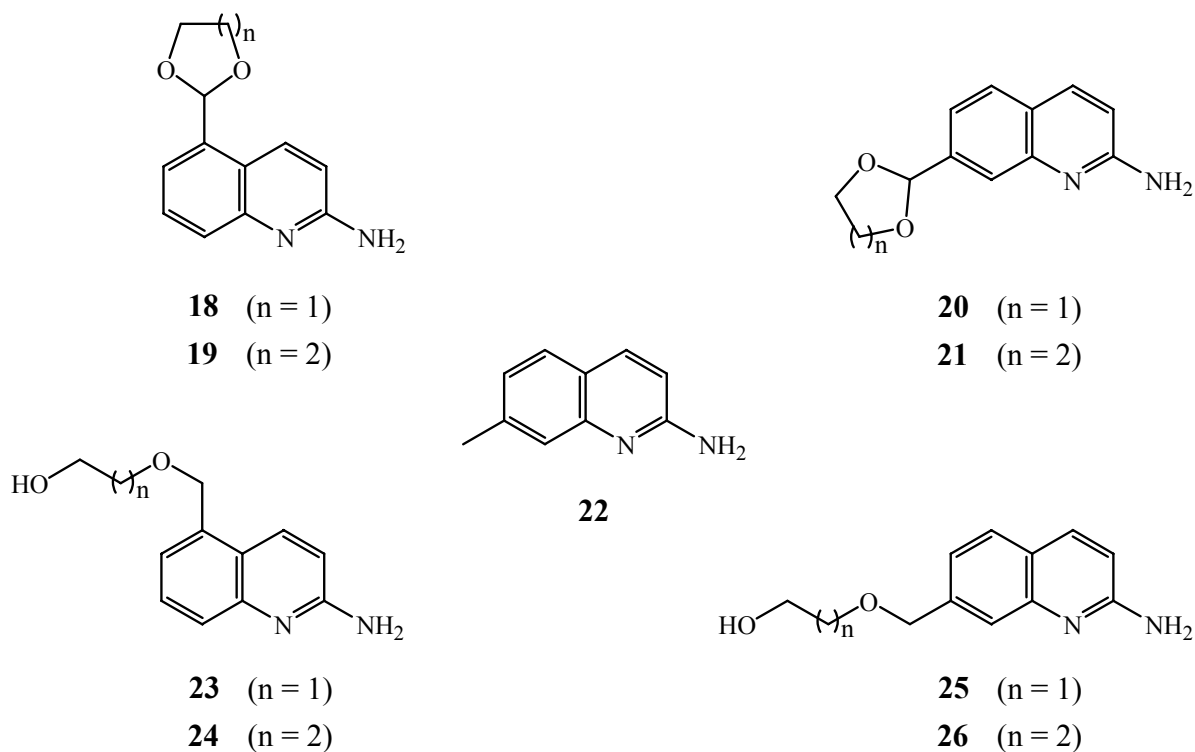


**Figure 18.** The reason for the reduction in binding for the *N*-substituted ligands.

It would appear that this loss of binding can be counteracted by a substitution with a bulky group as in **16** and **17**. When the 2-aminoquinoline is only *N*-substituted (as in **16**), the binding affinity is still less than that of 2-aminoquinoline, however some of the loss in binding was regained, probably due to an interaction occurring between the lipophilic group and the protein surface. When there is also a substitution at the 6-position (as in **17**), the dissociation constant of the new ligand is lower than that of 2-aminoquinoline (i.e. it binds with higher affinity). This is because an additional two contacts are being made with the protein surface, causing the ligand bind more tightly, so that the loss of binding due to the reduction in the ability to form a salt bridge is counteracted.

#### 1.4.8. Substitution at the 5- and 7-Positions of 2-Aminoquinoline

Prior to the commencement of this study, ligands with substituents in the 5- and 7-positions, **18** – **26** (Figure 19) had been prepared in order to determine if further contacts could be made with the protein surface in these regions.<sup>50</sup> Preliminary results indicate that a substituent in the 5-position does not affect the binding affinity and a substituent in the 7-position decreases binding affinity. However, despite the reduction in binding affinity, there would appear to be a further interaction occurring between the protein and possibly one of the oxygen atoms in the acetal (**20** or **21**) or open-chain species (**25** or **26**).<sup>50</sup>



**Figure 19.** Ligands with substituents in the 5- or 7-position.

## 1.5 Aims

### 1.5.1. General Aims

The main aim of the project was to improve the affinity of the 2-aminoquinoline ligand for the Tec SH3 domain. In order for this to be achieved, further substitution at different positions around the ring could be explored. Since including a 6-substituent had provided the most success to date, many more ligands with substitution at the 6-position could also be prepared and assessed for binding affinity.

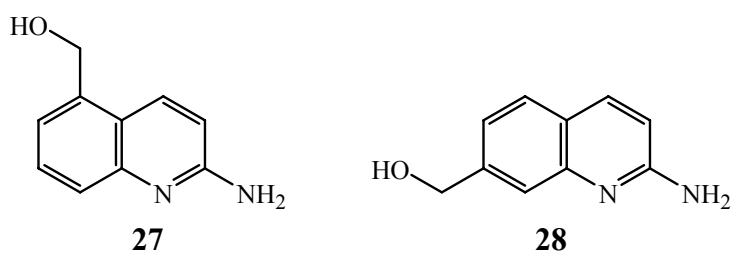
The ultimate aim of this work was to find a ligand that bound with a high enough affinity so that it was in slow exchange with the protein on the NMR timescale. This would mean that the structure of the complex could be solved either through NMR or X-ray crystallographic methods and the binding model could be validated.

### 1.5.2. Synthetic Targets

#### *Substitution at the 5- and 7-Position of 2-Aminoquinoline*

The first aim of this project was to complete the studies of the 5- and 7-substituted-2-aminoquinoline ligands. Binding data was required for 7-substituted ligands that had been

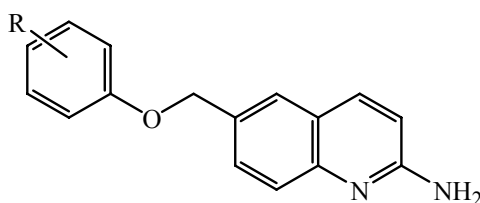
prepared previously and further ligands could be prepared in order to complete these studies. In order to obtain conclusive results for the 5- and 7-substituted analogues of 2-aminoquinoline, **18** – **26**, further studies needed to be done. Firstly [ $^1\text{H}$ ,  $^{15}\text{N}$ ] HSQC NMR assays were required in order to obtain binding data for the 7-substituted ligands, **19-22**, **25** and **26**. Following this, 5- and 7-hydroxymethyl-2-aminoquinolines (**27** and **28**) could be synthesised and their respective binding affinities determined. **28** would give information on whether or not the oxygen atom  $\beta$  to the quinoline ring provides a point of contact with the protein surface.



**Figure 20.** The 5- and 7-hydroxymethyl-2-aminoquinoline target ligands.

#### *Substitution at the 6-Position of 2-Aminoquinoline*

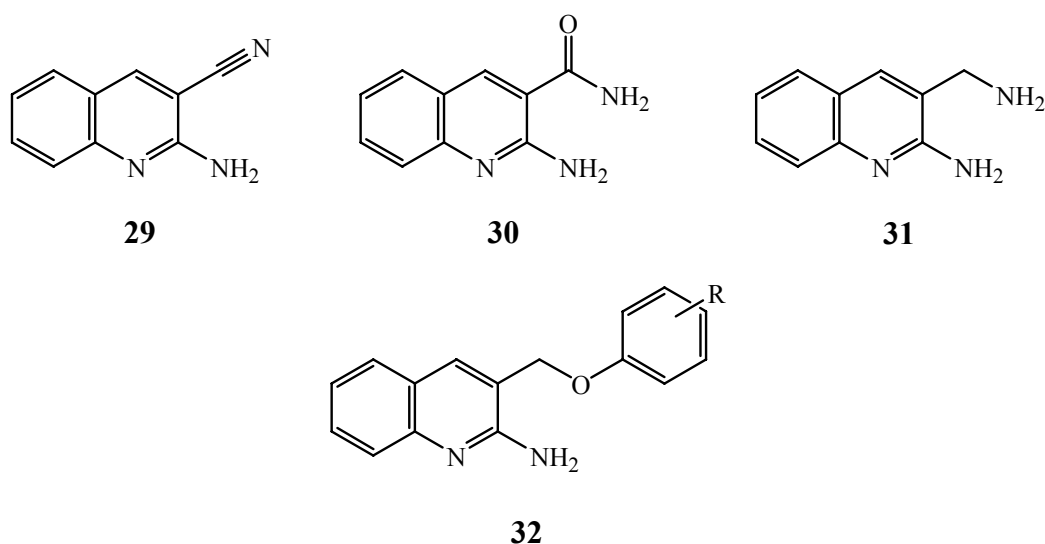
Substitution at the 6-position of 2-aminoquinoline has given rise to the most promising results so far and therefore ligands of this variety should be further explored. Different types of substituted phenoxyethyl groups could be introduced into the 6-position of 2-aminoquinoline (Figure 21). This may provide information on which functional groups are tolerated (i.e. hydrophobic or hydrophilic; electron withdrawing or electron donating) and how to make the interaction between the protein surface and the small molecule ligand stronger.



**Figure 21.** The 6-phenoxyethyl-2-aminoquinoline target ligands.

### *Substitution at the 3-Position of 2-Aminoquinoline*

To acquire further information about the binding site of the small molecule ligand, substitution could be explored at other positions around the quinoline ring to see if further contacts could be made with the surface of the SH3 protein domain. As an interaction occurred between the protein surface and benzylic substituents on the amine in the *N*-substituted ligands, this area could be further investigated.<sup>51</sup> Introducing a substituent in the 3-position of 2-aminoquinoline may allow for a similar contact to be made with the protein surface. Therefore a number of 3-substituted-2-aminoquinolines could be prepared and assayed for binding affinity (Figure 22). There are a number of 2-aminoquinoline compounds with small hydrophilic substituents at the 3-position reported in the literature, so a number of these could be made easily. However, it is more likely that a larger hydrophobic substituent in the 3-position would be required in order to make a contact with the protein surface. Therefore some large aromatic groups could be introduced, using the phenolic coupling strategy that was successful for the 6-position.<sup>49</sup>



**Figure 22.** The 3-substituted-2-aminoquinoline target ligands.

## Chapter 2.

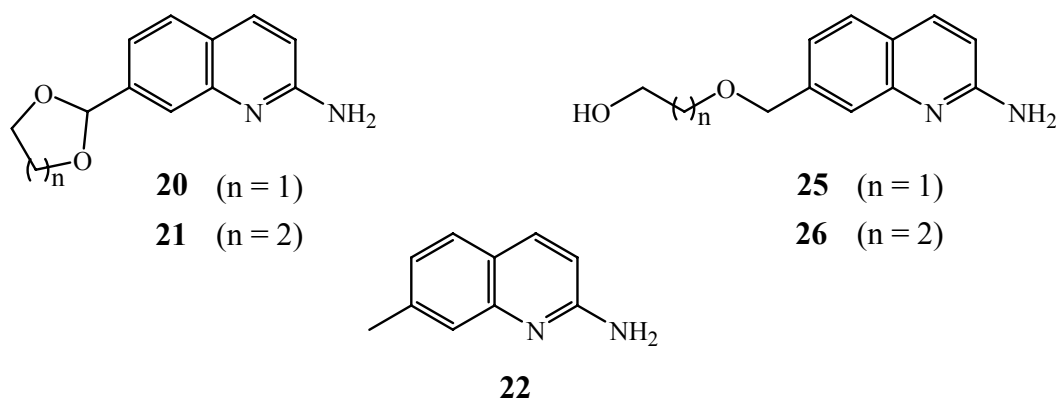
# COMPLETING STUDIES OF 5- AND 7-SUBSTITUTED LIGANDS

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### 2.1 Introduction

A number of 5- and 7-substituted ligands had been synthesised previously,<sup>50</sup> and preliminary results showed that introducing a substituent in either of these positions on the 2-aminoquinoline ring did not improve the affinity of the ligand for the SH3 domain. Although accurate binding data had not been obtained for the 7-substituted ligands, it appeared as though one of the oxygen atoms in the substituents of **25** and **26** might be making a contact with the protein surface. In order to investigate whether this was the case 7-hydroxymethyl-2-aminoquinoline, **28** was prepared and then assayed for binding affinity. The 5-substituted equivalent, **27** was synthesised in order to complete the series of 5-substituted ligands.

Along with the preparation of new ligands, the 5- and 7-substituted series was completed by using the HSQC NMR chemical shift perturbation assay in order to obtain binding data for the previously synthesised 7-substituted 2-aminoquinoline ligands **20-22**, **25** and **26**.

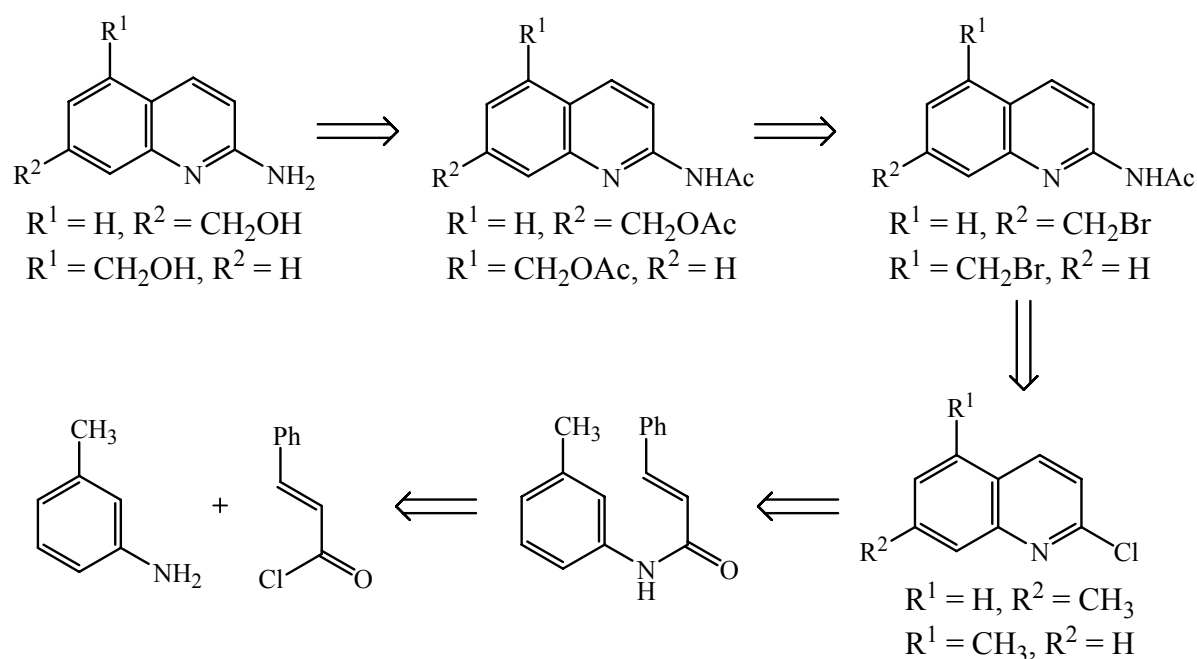


**Figure 23.** The previously prepared 7-substituted ligands.

## 2.2 Synthesis of 5- and 7- Substituted 2- Aminoquinolines

### 2.2.1. General Synthetic Pathway

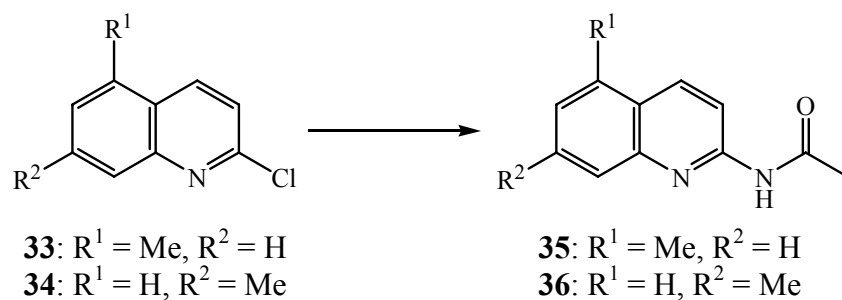
In order to synthesise the new 5- and 7- substituted ligands, the basic pathway shown in Figure 24 was used. The 5- or 7-hydroxymethyl products could be prepared from the appropriately protected acetoxymethyl derivatives that are derived from the bromomethyl substituted quinoline species. These are synthesised from a mixture of the 5- and 7-methyl quinoline species, which can both be obtained from one cinnamanilide.<sup>52, 53</sup> The cinnamanilide is easily prepared from a mixture of *m*-toluidine and cinnamoyl chloride.<sup>54</sup>



**Figure 24.** The retro-synthetic pathway for the synthesis of 5- and 7-substituted 2-aminoquinolines.

### 2.2.2. Synthesis of Hydroxymethyl Substituted 2-Aminoquinolines

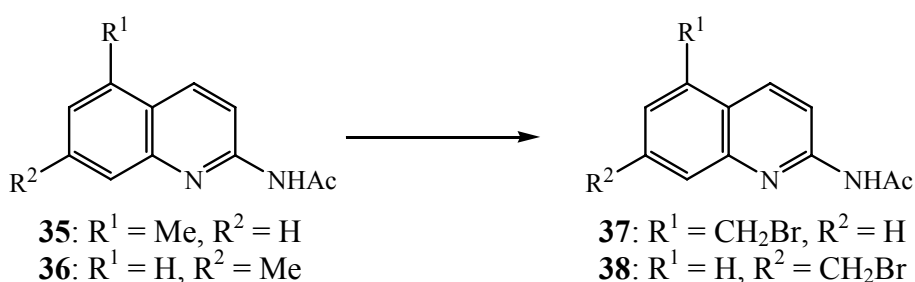
The 5- and 7-methyl substituted 2-chloroquinolines were prepared according to the methods used for the synthesis of previous 5- and 7-substituted ligands.<sup>50</sup> They were then treated with acetamide at a high temperature according to the method of Watanabe *et al.*<sup>50, 55</sup> This is similar to the Kóródi method used in previous studies, however, in this case the reaction was allowed to proceed overnight, which led to the formation of the protected acetamide species as opposed to the amino derivatives (Scheme 1).<sup>46, 50, 56</sup>



**Scheme 1.** Reaction conditions: *acetamide / K<sub>2</sub>CO<sub>3</sub> / 200°C*.

The products **35** and **36** were prepared as an inseparable mixture in a moderate combined yield of 53%. The high resolution mass spectrum was consistent with the molecular mass of the desired products and the low resolution mass spectrum showed a peak at  $m/z$  200 corresponding to  $M^+$ . The IR spectrum of the mixture showed the characteristic C=O peak at  $1709\text{ cm}^{-1}$ . There were some distinctive changes in the  $^1\text{H}$  NMR spectrum upon conversion from the 2-chloroquinoline derivative, such as the appearance of two new acetyl methyl peaks at  $\delta_{\text{H}} = 2.18$  and  $\delta_{\text{H}} = 2.30$ , as well as a downfield peak corresponding to the two NH groups. The signals for the H(3) peaks had shifted downfield due to the deshielding effect of the nearby acetamido-group (c.f. **33** and **34**,  $\delta_{\text{H}} = 7.27\text{-}7.39$  ppm; **35**  $\delta_{\text{H}} = 8.51$  ppm; **36**  $\delta_{\text{H}} = 8.44$  ppm).

The next step was to synthesise the bromomethyl-substituted quinolines from the mixture of **35** and **36** (Scheme 2).



**Scheme 2.** Reaction conditions: *NBS / benzoyl peroxide / benzene*.

Both **37** and **38** were prepared as an inseparable mixture in a moderate combined yield of 46% in a radical bromination reaction using *N*-bromosuccinimide with benzoyl peroxide as the initiator. The high resolution mass spectrum was consistent with the molecular mass of the desired products and the low resolution mass spectrum gave two peaks corresponding to  $M^+$  (for  $^{79}\text{Br}$   $m/z$  278, for  $^{81}\text{Br}$   $m/z$  280). The  $^1\text{H}$  NMR spectrum showed the characteristic downfield shift for the methyl protons upon conversion from methyl to bromomethyl (see Table 5).



**Table 5.** Comparison of chemical shifts ( $\delta$ , ppm) for the methylene protons of the methyl and bromomethyl substituted compounds **35-38**.

	$\delta_{\text{H}}(\text{CH}_3)$		$\delta_{\text{H}}(\text{CH}_2\text{Br})$
<b>35</b>	2.68	<b>37</b>	4.88
<b>36</b>	2.55	<b>38</b>	4.63

Once the bromomethylquinoline derivatives had been prepared, the acetoxymethyl derivatives **39** and **40** could be synthesised by a simple substitution reaction (Scheme 3).



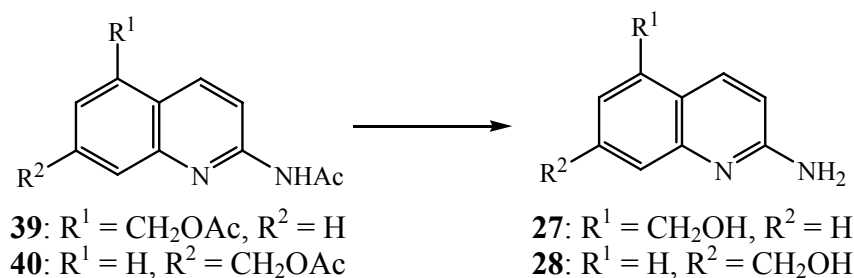
**Scheme 3.** Reaction conditions:  $\text{KOAc} / \text{DMF}$ .

The acetoxymethyl derivatives **39** and **40** were prepared in a good combined yield of 70%. At this stage, the  $R_f$  values of two the regioisomers [c.f. for **39**  $R_f$  0.19 (20% ethyl acetate / dichloromethane) and for **40**  $R_f$  0.15 (20% ethyl acetate / dichloromethane)] were of sufficient difference to allow for separation by flash chromatography. Both of the isomers were of sufficient purity to obtain microanalysis and in each case this showed that the correct product had been obtained with excellent purity. Both isomers also displayed a peak at  $m/z$  258 in their mass spectrum, which corresponds to  $\text{M}^+$ . The  $^1\text{H}$  NMR spectrum for each isomer showed a new acetyl methyl peak (c.f. **39**  $\delta_{\text{H}} = 2.35$ ; **40**  $\delta_{\text{H}} = 2.25$ ) and a downfield shift in the  $\text{CH}_2$  peak of the acetoxymethyl compound compared with that of the bromomethyl compound (see Table 6).

**Table 6.** Comparison of chemical shifts ( $\delta$ , ppm) for the  $\text{CH}_2$  protons of the bromomethyl and acetoxymethyl substituted compounds **37-40**.

	$\delta_{\text{H}}(\text{CH}_2\text{Br})$		$\delta_{\text{H}}(\text{CH}_2\text{OAc})$
<b>37</b>	4.88	<b>39</b>	5.52
<b>38</b>	4.63	<b>40</b>	5.29

The final step in the synthesis of 5- and 7-hydroxymethyl-2-aminoquinoline was the removal of the acyl groups to give the final products **27** and **28** (Scheme 4).



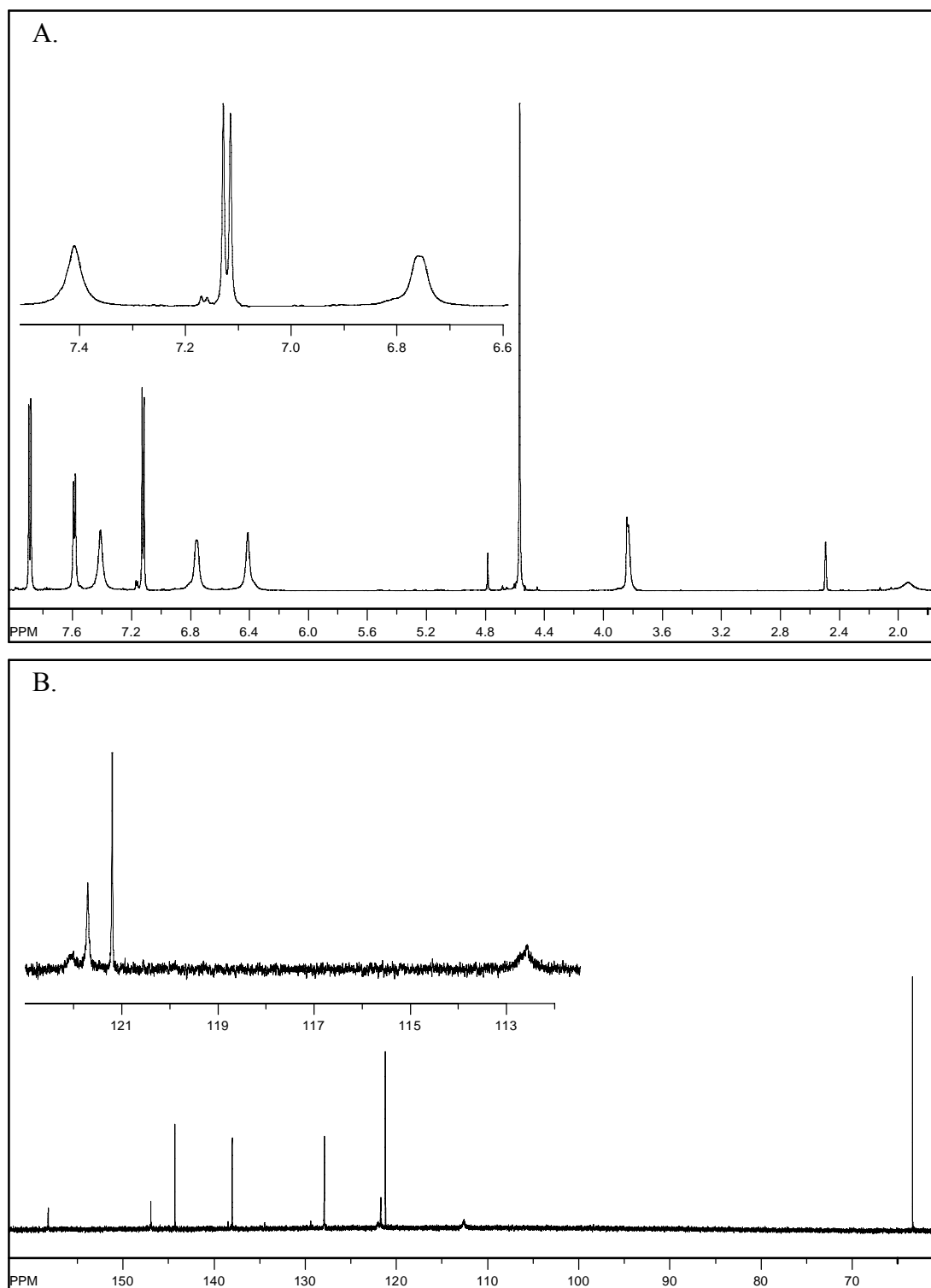
**Scheme 4.** Reaction conditions: K<sub>2</sub>CO<sub>3</sub> / methanol.

The final products were obtained individually in high yield of 93% for **27** and 88% for **28**. The molecular mass of both products was consistent with the high resolution mass spectrum and each low resolution mass spectrum showed a peak at  $m/z$  174 corresponding to M<sup>+</sup>. The IR spectrum for each isomer showed characteristic OH and NH peaks (c.f. for **27** 3467, 3319 and 3203cm<sup>-1</sup>; for **28** 3467, 3317 and 3201cm<sup>-1</sup>). The <sup>1</sup>H NMR spectrum showed the expected upfield shift for H(3) in both isomers (see Table 7). Both H(3) peaks are further upfield than those seen for the 2-chloroquinolines, **33** and **34**. This is due to the shielding from the amino group which is electron donating at H(3) through resonance.

**Table 7.** Comparison of chemical shifts ( $\delta$ , ppm) for H(3) of 2-chloroquinolines **33** and **34**, (quinoline-2-yl)acetamides **39** and **40** and 2-aminoquinolines **27** and **28**.

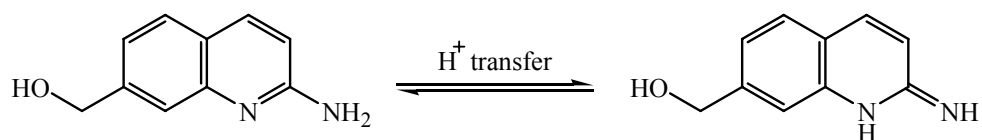
	$\delta_{\text{H}}$ [H(3)]		$\delta_{\text{H}}$ [H(3)]		$\delta_{\text{H}}$ [H(3)]
<b>33</b>	7.27-7.39	<b>39</b>	8.48	<b>27</b>	6.77
<b>34</b>	7.27-7.39	<b>40</b>	8.43	<b>28</b>	6.71

There was some significant line broadening observed in the <sup>1</sup>H NMR spectrum of **28** and the <sup>13</sup>C NMR spectra of both **27** and **28** (Figure 25).



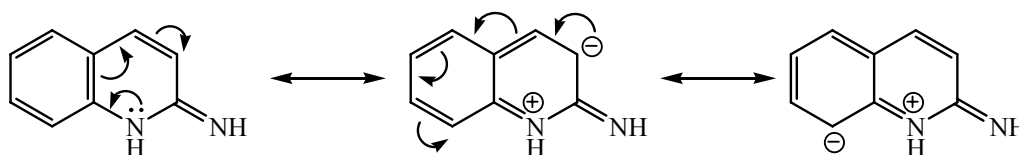
**Figure 25.** A. The  $^1\text{H}$  spectrum of **28** with H(3) and H(8) inset B. The  $^{13}\text{C}$  NMR spectrum of **28** with C(3) and C(8) inset.

The signals that were broadened were those for H(3) and H(8) as well as C(3) and C(8). This is most likely due to the tautomerism between the amino and imino forms (see Figure 26).<sup>57</sup>



**Figure 26.** The tautomerism between amino and imino forms of **28** that occurs to cause the line broadening in the NMR spectra.

In the imino form, C(3) and C(8) are shielded by resonance (Figure 27). Therefore the chemical shift of these signals in the imino form will be different from the chemical shift in the amino form. It is this difference in chemical shift that gives rise to the line broadening.



**Figure 27.** The resonance contributors that shield the nuclei at C(3) and C(8) of the imino form of **28**.

In order for the broadening to occur, the tautomerism must be occurring reasonably slowly relative to the NMR timescale, but not slow enough for the two protons to be observed as separate peaks (i.e. slow exchange). Therefore **27** and **28** are in intermediate exchange with their respective tautomers.

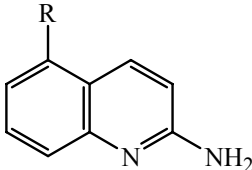
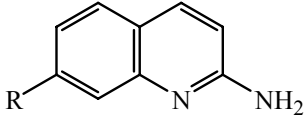
This effect, which has not been observed in the spectra of other 2-aminoquinolines prepared in this study, may be due to a solvent effect. The  $^1\text{H}$  NMR spectrum for **27** was run in  $\text{CDCl}_3$ , whereas the spectra that showed significant line broadening were run using  $\text{d}_6$ -DMSO. There may have been some acid present in the chloroform that might have catalysed the tautomerism, thus allowing it to occur more rapidly so the tautomers were in fast exchange. However, the samples dissolved in  $\text{d}_6$ -DMSO were less likely to have contained acid so as a consequence the tautomerism might have been occurring at a slower rate, thus giving rise to the line broadening. The intermediate exchange may also have been due to solvent viscosity, as  $\text{d}_6$ -DMSO is more viscous than  $\text{CDCl}_3$  and as such might have reduced the rate of interconversion between isomers.

### 2.3 Binding Data for the 5- and 7-Substituted 2-Aminoquinolines

The equilibrium dissociation binding constants of the previously synthesised 7-substituted-2-aminoquinoline ligands **20-22**, **25** and **26** were determined using the  $[^1\text{H}, ^{15}\text{N}]$  HSQC

NMR assay. The two new ligands, **27** and **28** were also assayed for binding ability using this method. The previously synthesised 5-substituted ligands **18**, **19**, **23** and **24** were assessed for their ability to bind to the Tec SH3 domain using a fluorescence polarisation assay.<sup>50</sup> This work was carried out previously, but has been included for comparison. The results of the binding assays are shown below (Table 8).

**Table 8.** The binding data for the 5- and 7-substituted 2-aminoquinoline ligands.

	<b>5-Substituted Ligands</b>		<b>7-Substituted Ligands</b>	
				
<b>R =</b>	<b>EC<sub>50</sub> (μM)</b>	<b>K<sub>d</sub> (μM)</b>	<b>K<sub>d</sub> (μM)</b>	
CH <sub>2</sub> (OCH <sub>2</sub> ) <sub>2</sub>	<b>18</b>	239 ± 39	-	<b>20</b> 207 ± 48
CH <sub>2</sub> (OCH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>	<b>19</b>	269 ± 83	-	<b>21</b> 439 ± 101
CH <sub>3</sub>				<b>22</b> 369 ± 93
CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> OH	<b>23</b>	238 ± 82	-	<b>25</b> 176 ± 44
CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>3</sub> OH	<b>24</b>	254 ± 40	-	<b>26</b> 182 ± 21
CH <sub>2</sub> OH	<b>27</b>	-	76 ± 11	<b>28</b> 195 ± 34

Note: K<sub>d</sub> was determined by NMR, EC<sub>50</sub> was determined by fluorescence polarization spectroscopy.

The 5-substituted ligands synthesised previously, **18**, **19**, **23** and **24** all bind with similar affinity to 2-aminoquinoline (K<sub>d</sub> = 125 μM, EC<sub>50</sub> = 160 μM). Therefore the substituent has little effect on the binding affinity of the ligand for the Tec SH3 domain, which indicates that the sidechains do not interact significantly with the protein surface. This is in accord with the binding model, and indicates that the substituent faces away from the SH3 domain surface, and as a result, is unable to make a contact with any amino acid sidechains. The newly synthesised ligand **27** does, however, have a higher affinity for the SH3 domain than 2-aminoquinoline. There is a hydrogen atom in **27** that can be involved in the formation of a hydrogen bond, whereas the other 5-substituted ligands do not. This suggests that there may be an amino acid side chain in the vicinity that can act as a hydrogen bond acceptor and form a weak hydrogen bond with the ligand.

None of the 7-substituted 2-aminoquinolines have higher affinity for the SH3 domain than the lead compound, **2**; however, some interesting results were obtained from the binding studies. The methyl substituted ligand **22** has a much lower affinity for the SH3 domain than

2. This would appear to indicate that a substituent in the 7-position is not well tolerated. The ligand which contains a 6-membered acetal as a substituent, **21**, has a similar affinity to that of **22**, however **20**, which contains a 5-membered acetal as a substituent, has greater affinity for the protein, but still less than **2**. The acetal may be making a contact with the protein surface, so despite the steric unfavourability of the substituent, the ligand binds with reasonable affinity. The methyl substituted ligand **22** may be unable to make this contact and the larger substituent on **21** may be too bulky to be easily accommodated, despite the additional contact.

Ligands **25** and **26** have more flexible open chain substituents. The binding affinity for each compound has improved upon that of **21**, but is not significantly different from that of the lead compound, **2**. These ligands may make the same contacts as the acetal substituted 2-aminoquinoline ligands **20** and **21** and their flexible sidechains may be more easily accommodated in the binding site of the SH3 domain. The hydroxymethyl substituted ligand **28** has a similar binding affinity to **25** and **26**. This would tend to indicate that the contact that is being made is from the oxygen adjacent to the benzylic carbon for all of the ligands **20**, **21**, **25**, **26** and **28**.

Although the ligands with substitution in the 5- and 7-positions of 2-aminoquinoline have provided interesting information about the binding site for the ligands on the SH3 domain surface, none of them have shown great improvements in binding affinity. Therefore no further investigation into substitution at the 5- and 7-position of 2-aminoquinoline has been pursued.

# Chapter 3.

## 6-SUBSTITUTED 2-AMINOQUINOLINES

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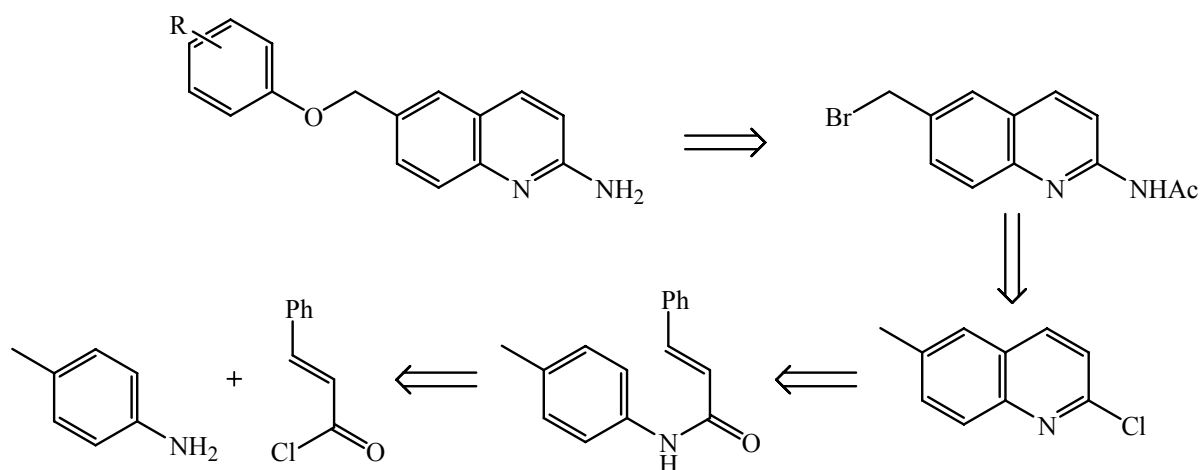
### 3.1 Introduction

It has been shown previously that ligands with substituents in the 6-position of 2-aminoquinoline have improved binding affinity compared to the lead compound, **2**.<sup>46, 50</sup> 6-Phenoxymethyl-2-aminoquinoline has been prepared and shown to bind to the SH3 domain with similar affinity to the highest affinity ligands to date.<sup>49</sup> In order to further improve binding affinity of the small molecule ligand for the Tec SH3 domain, a range of substituted 6-phenoxymethyl-2-aminoquinolines were prepared and assayed for binding affinity.

### 3.2 Synthesis of 6-Substituted-2-Aminoquinolines

#### 3.2.1. General Synthetic Pathway

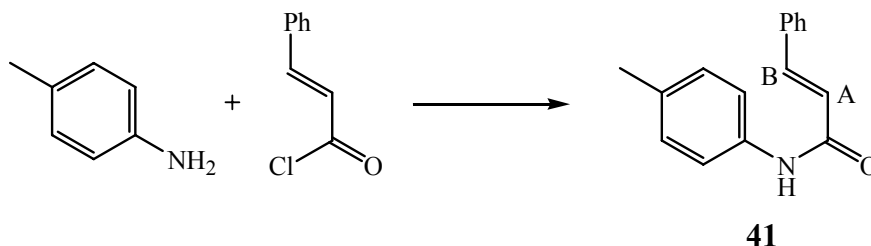
The 6-substituted ligands can be accessed through a similar pathway to the 5- and 7-substituted ligands (Figure 28). The synthetic targets are 6-(phenoxymethyl)-2-aminquinolines, which can be prepared from the appropriately protected 6-(bromomethyl)quinoline. This in turn can be prepared in the same manner as the 5- and 7-substituted derivatives.



**Figure 28.** The retro-synthetic pathway for the synthesis of 6-substituted phenoxymethyl-2-aminoquinolines.

### 3.2.2. Synthesis of 6-Phenoxymethyl-2-aminoquinoline Derivatives

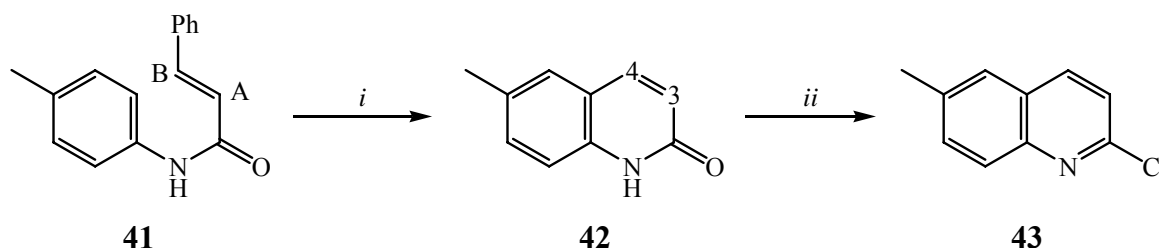
The first step in the synthesis of 6-substituted 2-aminoquinolines was the synthesis of the amide, **41**, using a literature procedure (Scheme 5).<sup>54</sup>



**Scheme 5.** Reaction conditions: *pyridine / DMAP / dichloromethane*.

The reaction proceeded without complication to give a high yield (96%) of the desired product, **41**. The melting point (159-162°C) was consistent with the literature value (162°C)<sup>54</sup> and the IR and <sup>1</sup>H NMR spectra were also diagnostic. The IR spectrum showed a characteristic peak at 1661 cm<sup>-1</sup> that corresponds to a carbonyl amide stretch. The <sup>1</sup>H NMR spectrum of **41** showed a characteristic *E* coupling constant ( $J = 15.6$  Hz) due to the vinyl protons labelled A and B.

The cinnamanilide then underwent a Friedel-Crafts style cyclisation in the presence of aluminium chloride to give rise to the quinolone **42**.<sup>52</sup> This product was subsequently converted to the 2-chloro derivative **43**, by reaction with phosphorus oxychloride (Scheme 6).<sup>53</sup>



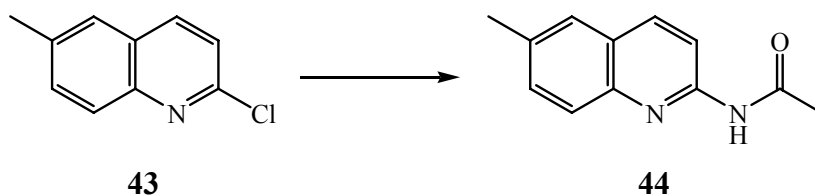
**Scheme 6.** Reaction conditions: *i. AlCl<sub>3</sub>; ii. POCl<sub>3</sub>*.

The <sup>1</sup>H NMR spectrum of **42** showed a change in the coupling constant from  $J_{A,B} = 15.6$  Hz to  $J_{3,4} = 9.6$  Hz for protons 3 and 4, which is consistent with a change in the geometry from *E* to *Z*. This is, in turn, consistent with the formation of the ring structure. The IR spectrum once again showed a peak corresponding to a carbonyl amide group at 1662 cm<sup>-1</sup>.



The next step was carried out without the full purification of **42**. Overall, the pair of reactions proceeded in good yield (66%) over the two steps. The melting point of **43** (112-114°C) was consistent with the literature value (111-114°C).<sup>58</sup> The <sup>1</sup>H NMR spectrum showed a large downfield shift in the signal for H(3) (c.f. **42**  $\delta_{\text{H}} = 6.70$  ppm; **43**  $\delta_{\text{H}} = 7.35$  ppm), which is consistent with the introduction of an electron withdrawing group at C(2). The disappearance of the peak corresponding to a carbonyl stretch in the IR spectrum of **43** is also diagnostic.

Introducing nitrogen in the 2 position of the quinoline ring through an acetamide protecting group, using the method of Watanabe *et al*, was the next step in the reaction series (Scheme 7).<sup>55</sup>

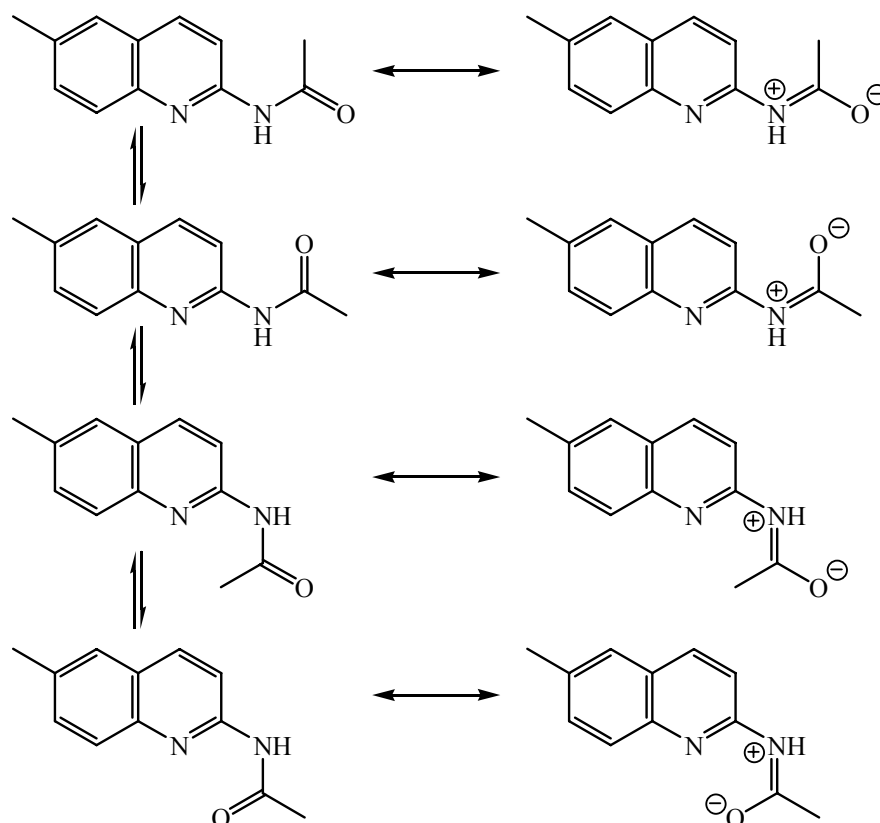


**Scheme 7.** Reaction conditions:  $K_2CO_3$  / acetamide / 200°C.

This reaction proceeded as for the 5- and 7-position in moderate yield (44 %). The melting point of **44** (181-185°C) was consistent with the literature value (181-184°C).<sup>50</sup> The IR spectrum showed a characteristic peak at  $1693\text{ cm}^{-1}$  that corresponds to the carbonyl in the acetamido protecting group. The <sup>1</sup>H NMR spectrum showed some diagnostic changes. A methyl peak appears at  $\delta_{\text{H}} = 2.20$  ppm and a broadened peak corresponding to NH appears at 9.18 ppm. Another change in the <sup>1</sup>H NMR spectrum is that the H(3) peak is shifted downfield due to an anisotropic deshielding from the acetamido group at C(2) (c.f. **43**  $\delta_{\text{H}} = 7.35$  ppm; **44**  $\delta_{\text{H}} = 8.10$  ppm).

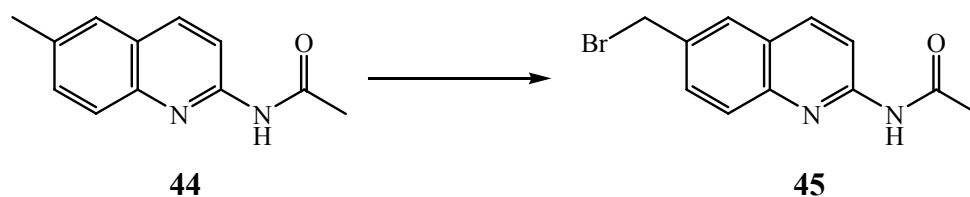
Another interesting feature of the <sup>1</sup>H NMR spectrum of **44** is that the signal due to H(3) is broadened due once again to intermediate exchange. This is also seen in several other quinolin-2-yl acetamides. The exchange broadening occurs because a number of resonance contributors give rise to a partial double bond within the acetamido group (Figure 29). There are four possible conformations of the acetamido group and each of these gives rise to a different chemical environment, and therefore different chemical shift for H(3). The partial double bond character in the acetamido group means that the rotation of the bond that gives

rise to the different conformations, will be occurring slowly and thus **44** enters into intermediate exchange.



**Figure 29.** The resonance contributors that bring about the broadened signal due to H(3) in the  $^1\text{H}$  NMR spectrum of **44**.

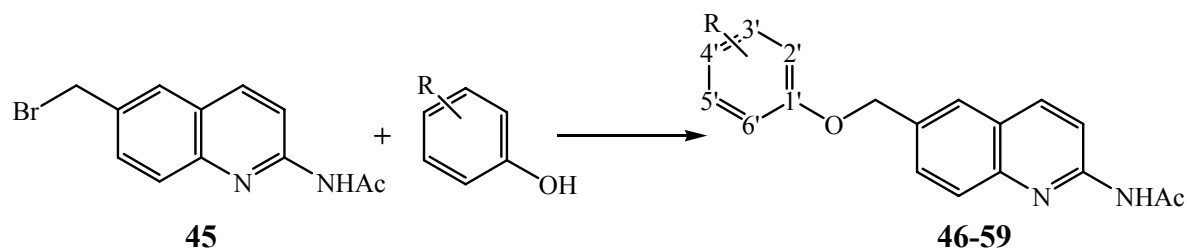
The bromomethyl-substituted quinoline derivative, **45** was synthesised next through a radical bromination reaction (Scheme 8).



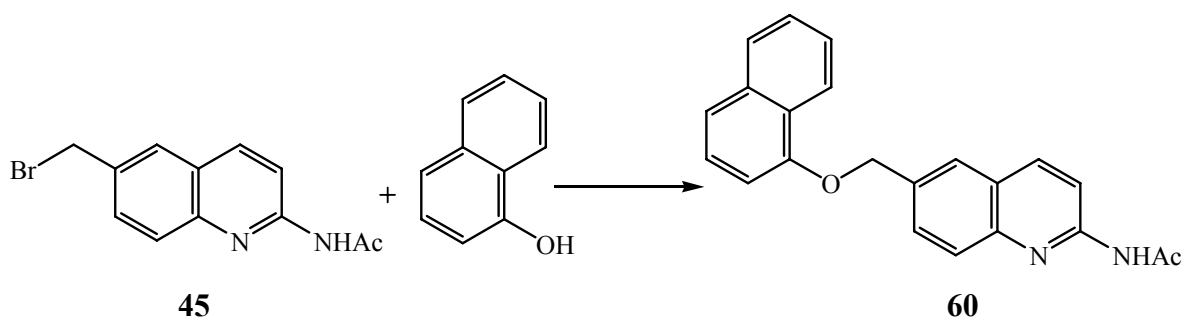
**Scheme 8.** Reaction conditions: *NBS* / *benzoyl peroxide* / *benzene*.

The desired product, **45** was synthesised in good yield (63%) and the melting point (183-186°C) was consistent with the literature melting point (185-187°C).<sup>50</sup> The  $^1\text{H}$  NMR showed downfield shift in the benzylic protons (c.f. **44**  $\delta_{\text{H}} = 2.51$ ; **45**  $\delta_{\text{H}} = 4.65$  ppm) that is characteristic of the introduction of an electron withdrawing group.

It was then possible to convert **45** to the phenolic derivatives **46-60** using a simple substitution reaction (Scheme 9).

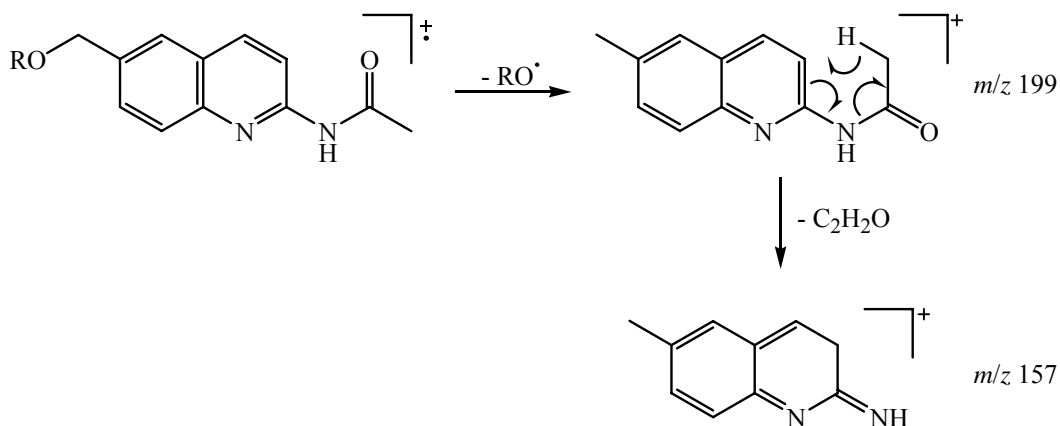


<b>46</b>	<b>47</b>	<b>48</b>	<b>49</b>	<b>50</b>	<b>51</b>	<b>52</b>
R = 4-Me	3-Me	2-Me	4- <i>t</i> -Bu	3- <i>t</i> -Bu	4- <i>i</i> -Pr	2- <i>i</i> -Pr
<b>53</b>	<b>54</b>	<b>55</b>	<b>56</b>	<b>57</b>	<b>58</b>	<b>59</b>
R = 4-MeO	3-MeO	2-NHAc	4-Br	2-Br	4-Cl	2-Cl



**Scheme 9.** Reaction conditions:  $K_2CO_3$  / acetonitrile.

A range of phenoxy-methyl substituted compounds were synthesised in a wide range of yields (22-87%). A high resolution mass spectrum was consistent with the molecular mass of the desired product in each reaction and the low resolution mass spectrum of each of the products, **46-60**, showed characteristic fragmentations. Each of the mass spectra showed a peak corresponding to 199 mass units, which is equivalent to loss of the phenolic group. This daughter ion then underwent a McLafferty style rearrangement to lose  $C_2H_2O$  and give a fragment with a mass of 157 (Figure 30).



**Figure 30.** Cleavages from the mass spectra of **46-60**.

The  $^1\text{H}$  NMR of each of the phenoxyethyl substituted derivatives showed a small downfield shift in the benzylic protons, due to the introduction of phenoxy group (Table 9). The chemical shifts of the methylene protons of **46-60** are in the most part around 5.2 ppm, however when there is an electronegative group in the 2-position of the phenyl ring, there is a small additional downfield shift to around 5.3 ppm. The naphthyl group also causes a similar downfield shift to 5.38 ppm.

**Table 9.** Comparison of chemical shifts ( $\delta$ , ppm) for the benzylic protons of **45-60**.

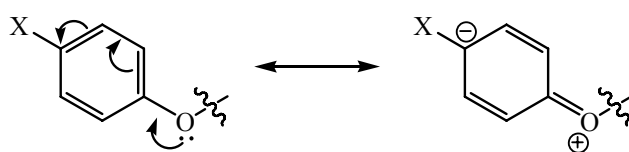
$\delta_{\text{H}}$ ( $\text{CH}_2$ )		$\delta_{\text{H}}$ ( $\text{CH}_2$ )	
<b>45</b>	4.65	<b>53</b>	5.17
<b>46</b>	5.19	<b>54</b>	5.17
<b>47</b>	5.18	<b>55</b>	5.29
<b>48</b>	5.24	<b>56</b>	5.17
<b>49</b>	5.21	<b>57</b>	5.30
<b>50</b>	5.22	<b>58</b>	5.19
<b>51</b>	5.16	<b>59</b>	5.30
<b>52</b>	5.24	<b>60</b>	5.38

A number of trends were observed in the  $^{13}\text{C}$  NMR spectra of each of the phenolic substituents. One of these trends can be seen in the chemical shifts of the signals corresponding to  $\text{C}(4')$  for each of the 4'-substituted phenoxyethyl derivatives (Table 10).

**Table 10.** Comparison of chemical shifts ( $\delta$ , ppm) for C(4') of each of the 4'-substituted (phenoxy)methylquinoline derivatives.

4'-Substituent		$\delta_c$ [C(4')]
Br	<b>56</b>	113.39
Cl	<b>58</b>	126.17
Me	<b>46</b>	130.56
<sup>i</sup> Pr	<b>51</b>	138.86
<sup>t</sup> Bu	<b>49</b>	144.26
MeO	<b>53</b>	154.19

It is not immediately apparent why the substitution of a halogen shifts the signal upfield. This is indeed counter-intuitive as the introduction of a halogen substituent would normally deshield the adjacent nucleus thereby causing a downfield change in chemical shift. However, when examining these results, the effect that the nearby oxygen on the carbon at C(4') must also be considered. This phenolic oxygen would donate electron density to C(4') via resonance (Figure 31).

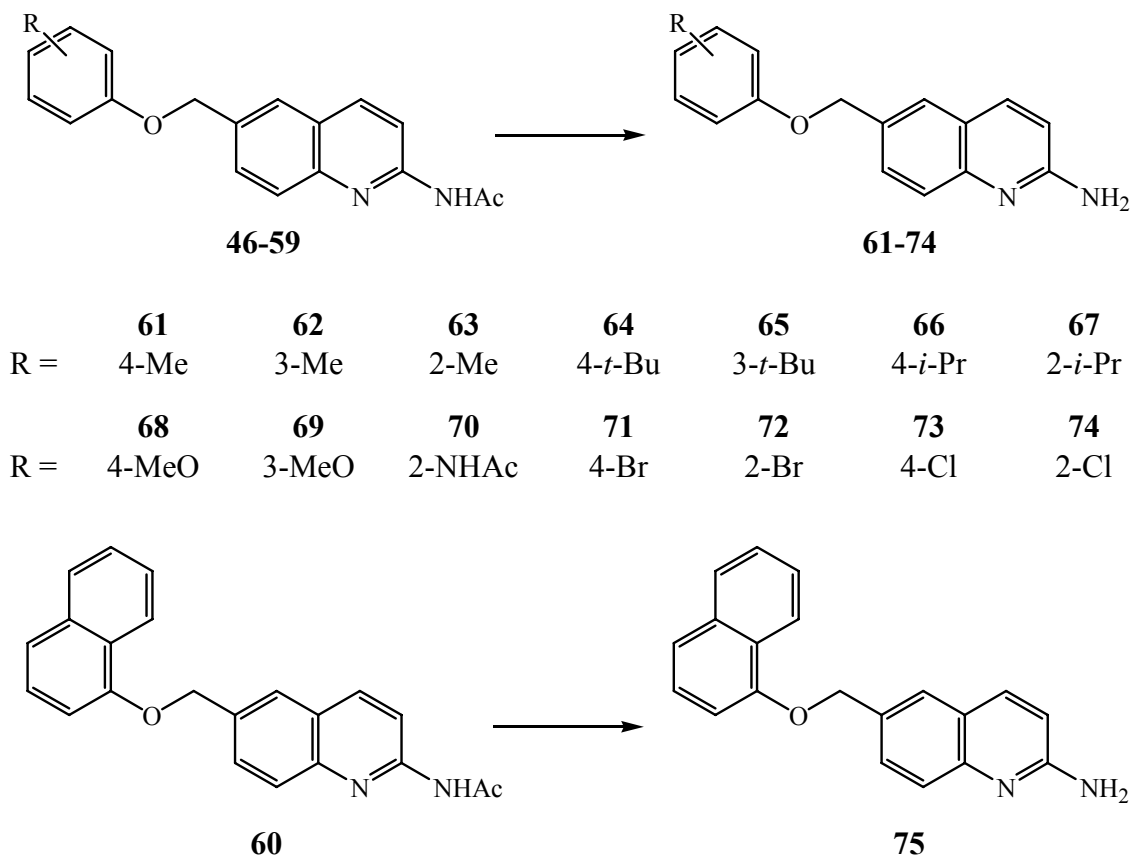


**Figure 31.** The resonance donation of electron density from the phenolic oxygen to C(4').

The donation of electron density from the lone pair on the phenolic oxygen by resonance would shield the carbon at C(4'). As a result, there are two competing effects that can act to either shield or deshield the nucleus at C(4'); the resonance effect from the phenolic oxygen and the inductive effect from the *para* substituent. It is apparent from the chemical shifts shown in Table 10 that the resonance donating effect of the oxygen outweighs the inductive effect for the halogen substituents, as their respective C(4) signals have the most shielded chemical shifts. The chemical shift of the signal corresponding to C(4') in the spectrum of **53** is the most deshielded for all the *para* substituted phenoxy)methyl derivatives. This indicates that the inductive withdrawing effect of the methoxy substituent outweighs the resonance donation from the phenolic oxygen.

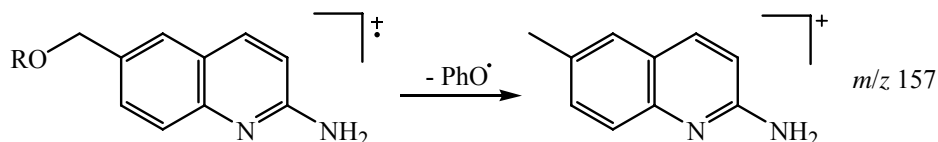
Similar chemical shift comparisons can be made for the NMR spectra of the 3' and 2' substituted (phenoxy)methylquinoline derivatives.

The final step in the synthesis in the 6-substituted ligands was the removal of the acyl group (Scheme 10).



**Scheme 10.** Reaction conditions:  $K_2CO_3$  / methanol.

The deprotection step occurred successfully in every case in good to high yields (71-96%). The structures of the final products were confirmed by microanalysis or high resolution mass spectrometry. The low resolution mass spectra for all 6-substituted ligands show a characteristic fragmentation to give an ion corresponding to  $m/z$  157, which coincides with the loss of the phenolic group as shown in Figure 32.



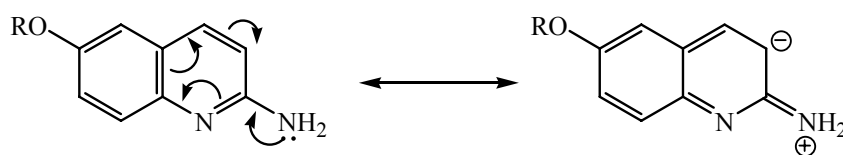
**Figure 32.** The fragmentation that gives rise to the ion corresponding to  $m/z$  157 in the mass spectra of **61-75**.

$^1\text{H}$  NMR spectra for the products show that the chemical shifts of the signals corresponding to the phenolic protons remain unchanged. The signal due to H(4) in the  $^1\text{H}$  NMR spectrum shifts upfield slightly, and the signal due to H(3) undergoes a large upfield shift (Table 11).

**Table 11.** Comparison of chemical shifts ( $\delta$ , ppm) for H(3) and H(4) of **46-60** and **61-75**.

R		$\delta_{\text{H}}$ [H(3)]	$\delta_{\text{H}}$ [H(4)]		$\delta_{\text{H}}$ [H(3)]	$\delta_{\text{H}}$ [H(4)]
4-Me	<b>46</b>	8.45	8.23	<b>61</b>	6.73	7.88
3-Me	<b>47</b>	8.43	8.16	<b>62</b>	6.72	7.87
2-Me	<b>48</b>	8.48	8.27	<b>63</b>	6.73	7.89
4- <sup>t</sup> Bu	<b>49</b>	8.50	8.29	<b>64</b>	6.72	7.87
3- <sup>t</sup> Bu	<b>50</b>	8.44	8.22	<b>65</b>	6.72	7.88
4- <sup>i</sup> Pr	<b>51</b>	8.42	8.14	<b>66</b>	6.72	7.87
2- <sup>i</sup> Pr	<b>52</b>	8.48	8.26	<b>67</b>	6.73	7.69
4-MeO	<b>53</b>	8.43	8.19	<b>68</b>	6.73	7.88
3-MeO	<b>54</b>	8.44	8.16	<b>69</b>	6.73	7.88
2-NHAc	<b>55</b>	8.49	8.24	<b>70</b>	6.76	7.88
4-Br	<b>56</b>	8.44	8.17	<b>71</b>	6.73	7.87
2-Br	<b>57</b>	8.42	8.18	<b>72</b>	6.73	7.89
4-Cl	<b>58</b>	8.45	8.21	<b>73</b>	6.73	7.87
2-Cl	<b>59</b>	8.43	8.20	<b>74</b>	6.73	7.89
naphthyl	<b>60</b>	8.44	8.19	<b>75</b>	6.74	7.90

The upfield shift of the protons at H(3) occurs as a result of the resonance donation from the lone pair of the electrons on the amine group. They would previously have been involved in the partial double bond shown in Figure 29 but upon deprotection of the amine, they become available to donate into the quinoline and hence shield the proton at H(3) (Figure 33).

**Figure 33.** The resonance contributor that shields the proton at H(3) to cause the upfield shift in the  $^1\text{H}$  NMR spectra of **61-75**.

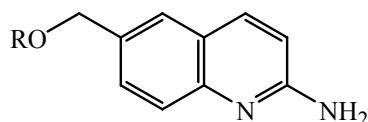
The acetyl methyl signal (typically  $\sim 2.3$  ppm) and also the NH signal (typically  $\sim 9.5$  ppm) from the acetamido group were no longer present in the  $^1\text{H}$  NMR spectra for each of the products. The spectra also showed the appearance of an  $\text{NH}_2$  peak (typically  $\sim 4.8$  ppm).

The acetamido signals (c.f.  $\sim 169$  ppm for  $\text{C}=\text{O}$  and  $\sim 25$  ppm for Me) were similarly no longer present in the  $^{13}\text{C}$  NMR spectra of the products.

### 3.3 Binding Data for the 6-Phenoxymethyl-2-aminoquinoline Derivatives

The binding affinity of each of the 6-substituted ligands was determined using the [ $^1\text{H}$ ,  $^{15}\text{N}$ ] HSQC chemical shift perturbation assay. Each of the ligands bound to the Tec SH3 domain with a higher affinity than the lead compound, **2** (Table 12).

**Table 12.** The binding affinities of 6-substituted phenoxymethyl ligands.



R		$K_d$ ( $\mu\text{M}$ )
4-Me-C <sub>6</sub> H <sub>4</sub>	<b>61</b>	33 $\pm$ 5
3-Me-C <sub>6</sub> H <sub>4</sub>	<b>62</b>	57 $\pm$ 9
2-Me-C <sub>6</sub> H <sub>4</sub>	<b>63</b>	55 $\pm$ 8
4- <i>t</i> Bu-C <sub>6</sub> H <sub>4</sub>	<b>64</b>	21 $\pm$ 4
3- <i>t</i> Bu-C <sub>6</sub> H <sub>4</sub>	<b>65</b>	65 $\pm$ 6
4- <i>i</i> Pr-C <sub>6</sub> H <sub>4</sub>	<b>66</b>	20 $\pm$ 3
2- <i>i</i> Pr-C <sub>6</sub> H <sub>4</sub>	<b>67</b>	53 $\pm$ 10
4-MeO-C <sub>6</sub> H <sub>4</sub>	<b>68</b>	39 $\pm$ 10
3-MeO-C <sub>6</sub> H <sub>4</sub>	<b>69</b>	55 $\pm$ 7
2-NHAc-C <sub>6</sub> H <sub>4</sub>	<b>70</b>	67 $\pm$ 7
4-Br-C <sub>6</sub> H <sub>4</sub>	<b>71</b>	16 $\pm$ 3
2-Br-C <sub>6</sub> H <sub>4</sub>	<b>72</b>	18 $\pm$ 3
4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>73</b>	15 $\pm$ 3
2-Cl-C <sub>6</sub> H <sub>4</sub>	<b>74</b>	16 $\pm$ 2
1-naphthyl	<b>75</b>	37 $\pm$ 7

Several trends are observed in the  $K_d$  values for the 6-substituted-2-aminoquinoline ligands. In regard to the alkyl substituents, **61-67**, it would appear that a substituent in the 4-position is more favourable than in other positions around the ring. It would also appear that a larger substituent, such as the *tert*-butyl or isopropyl groups, are more favoured over the smaller methyl substituent. This trend is also observed for the compounds with a methoxy substituent (**68** and **69**).

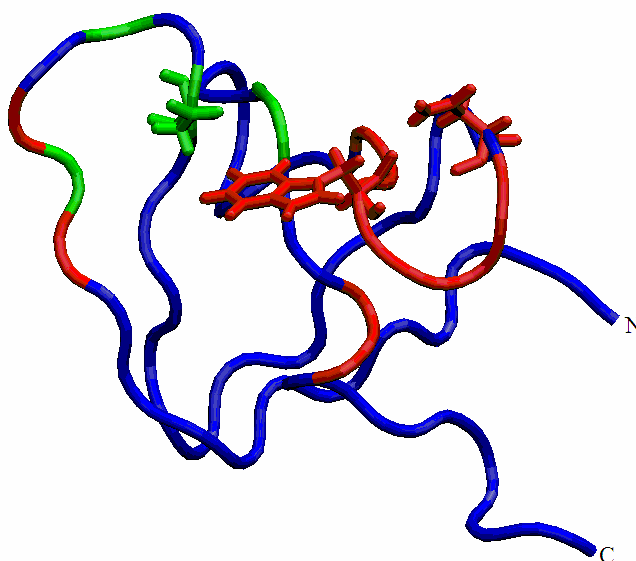
It would appear that the ligands containing inductively withdrawing halogens on the phenoxy group have greater affinity for the Tec SH3 domain than ligands with other substituents. The position of the halogen around the ring doesn't appear to affect the binding



affinity significantly and neither does the identity of the halogen atom. These ligands bind with a 7-8 fold improvement in affinity as compared with the lead compound, **2**. These ligands have the highest affinity of those prepared to date.

### 3.3.1. Chemical Shift Mapping

In order to gain an understanding of the mode of binding of the ligand to the SH3 domain, the residues that undergo changes in chemical shift (defined as  $> \sim 0.1$  ppm on the ) during the chemical shift perturbation assay can be mapped onto the backbone of the protein. This can be seen in Figure 34.



**Figure 34.** Chemical shift mapping of the backbone of the Tec SH3 domain with the 6-substituted ligands where  $\delta_H > \sim 0.1$  ppm for a number of the ligands. Downfield shifts are marked in green and upfield shifts are marked in red.

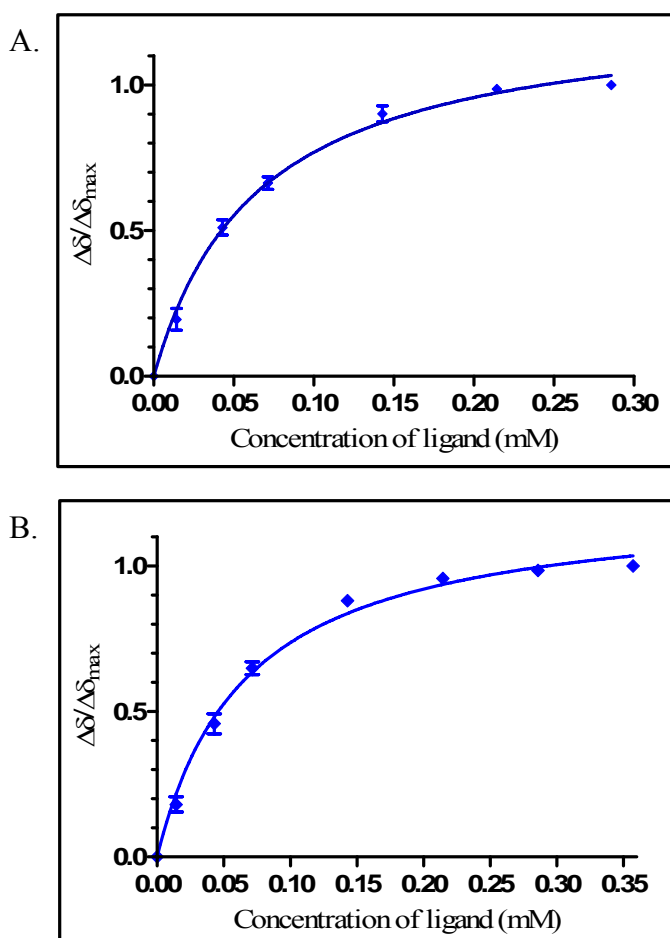
A number of signals corresponding to residues that lie towards the N-terminus from W215, undergo upfield shifts upon addition of the ligand. This is the area in which the phenolic substituent would make contact with the protein surface. These signals do not undergo an upfield chemical shift when 2-aminoquinoline is the ligand.<sup>46</sup> The signal corresponding to the sidechain of the residue N211 also undergoes an upfield chemical shift upon binding of the ligand. This shift has only been observed previously when the substituent in the 6-position is a phoxymethyl group.<sup>49</sup>

### 3.3.2. Potential Problems with $K_d$ Determination

Some difficulties were encountered with the calculation of  $K_d$  values shown above. The first of these is that the solubility of each of the ligands in aqueous solutions was relatively poor. The second problem encountered was that the data obtained from the HSQC NMR chemical shift perturbation assay was not adequately represented by the calculated one-site binding model curve obtained.

#### 3.3.2.A. Problems with Solubility

In preparation for the assay, the ligand was dissolved in  $d_6$ -DMSO and then during the assay this was titrated into a protein solution of 10%  $d_6$ -DMSO in aqueous buffer. A number of the ligands precipitated out of solution at relatively low concentrations. Therefore some of the ligands with lesser affinities were not soluble in concentrations high enough to allow for saturation of the protein to be approached. As an example the equilibrium dissociation binding isotherms for **65** and **70** are shown below (Figure 35).



**Figure 35.** The equilibrium dissociation binding isotherm for: A. **65** and B. **70**. Note that when no error bars are present, the error is too small to be shown.

In these cases, the value of the  $K_d$  is underestimated. The point at which saturation is reached is higher than the current top of the curve, so 50% of the ligand is bound at a higher point on the curve, which gives an increased concentration. As a result the  $K_d$  value would be higher than that observed. Consequently these ligands bind with a lesser affinity than is indicated by the values obtained from the curve-fitting (as determined using GraphPad Prism).<sup>59</sup> The ligands for which this is the case, are shown below in Table 13.

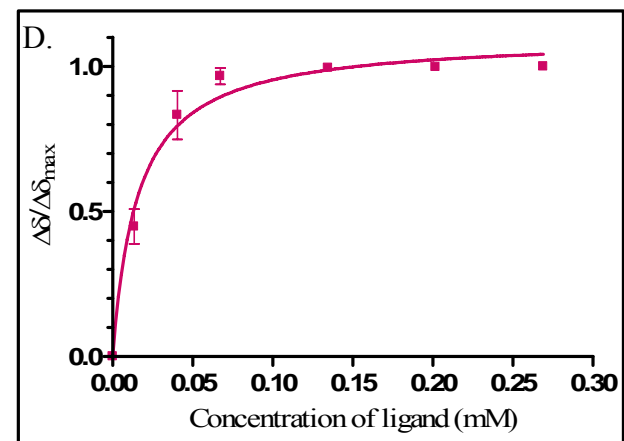
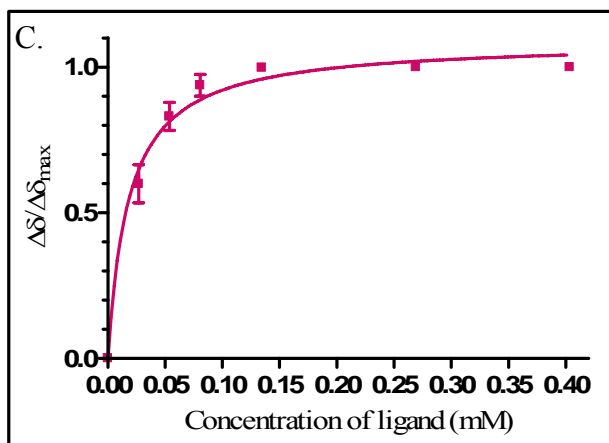
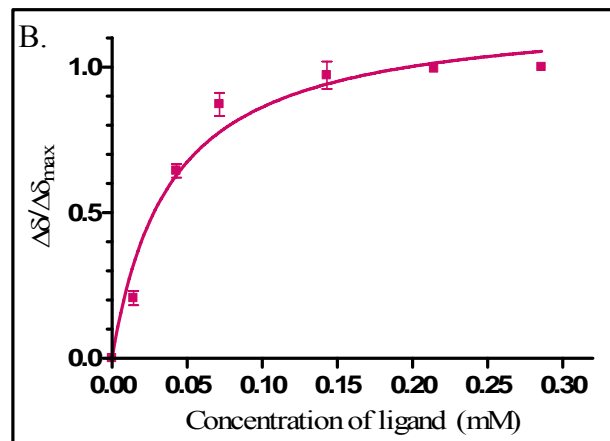
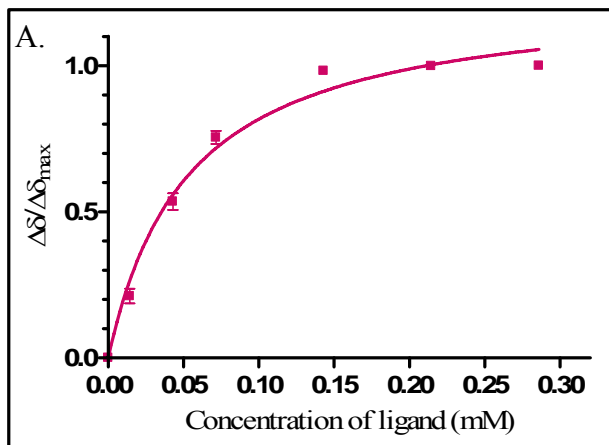
**Table 13.** The 6-substituted ligands that did not reach saturation during the binding assay.

R		* $K_d$ ( $\mu\text{M}$ )
3-Me	<b>62</b>	$57 \pm 9$
2-Me	<b>63</b>	$37 \pm 5$
3- <sup>t</sup> Bu	<b>65</b>	$65 \pm 6$
3-MeO	<b>69</b>	$55 \pm 7$
2-NHAc	<b>70</b>	$67 \pm 7$

\* $K_d$  will be higher than that shown.

### 3.3.2.B. Problems with the Curve Fit

With the exception of the afore-mentioned compounds, the assays of all the 6-substituted ligands approached saturation; as indicated by no change in chemical shift after the last aliquot of small molecule was added during the HSQC NMR chemical shift perturbation assay. However, the calculated equilibrium dissociation binding isotherms did not show this. As illustrated in the binding isotherms shown below, the calculated curves are still rising, thus indicating that saturation has not been approached (Figure 36) and this is not consistent with the data obtained.



**Figure 36.** The equilibrium binding dissociation isotherm for:  
 A. 67; B. 68; C. 72; D. 73.

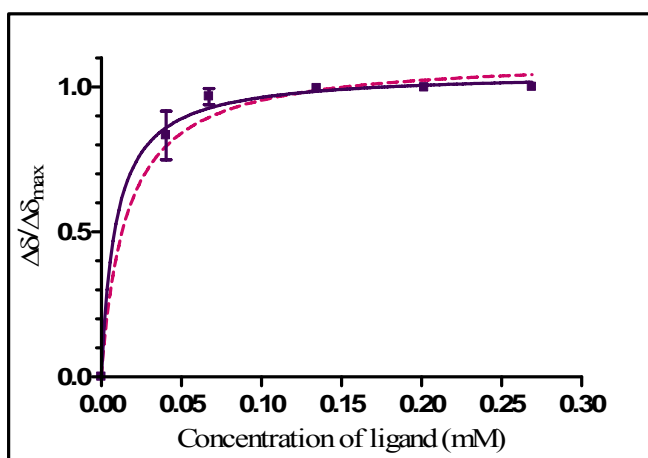
Note that when no error bars are present, the error is too small to be shown.

The equilibrium dissociation constants for these examples are shown in Table 14 accompanied by their respective  $R^2$  and absolute sum of squares values. All  $R^2$  values are close to one and the absolute sum of squares values are low, but despite this, it is apparent that the calculated curves do not adequately fit the data.

**Table 14.** The binding affinities and statistical data for the binding curves of some 6-substituted ligands.

R		$K_d$ ( $\mu\text{M}$ )	$R^2$	Sum of Squares
2- <i>i</i> Pr	<b>67</b>	$53 \pm 10$	0.9872	0.01274
4-MeO	<b>68</b>	$39 \pm 10$	0.9732	0.02710
2-Br	<b>72</b>	$18 \pm 3$	0.9891	0.00883
4-Cl	<b>73</b>	$15 \pm 3$	0.9856	0.01286

At first glance, it would appear that the first data point after the addition of the ligand is problematic. This data point appears to be too low for the curve, thus indicating that change in chemical shift is underestimated. It is possible that this data point is responsible for the inability to fit the curve to the data adequately. If the first data point is removed, then the curve fit is much improved. The binding isotherm for **73** is shown below as an example (Figure 37). A consequence of this improvement in curve fit is that the dissociation constant,  $K_d$  is reduced and therefore the ligands appear to bind with a greater affinity than indicated by the original data. The  $K_d$  in this case is  $9 \pm 2 \mu\text{M}$  (c.f.  $15 \pm 3 \mu\text{M}$  from original data).



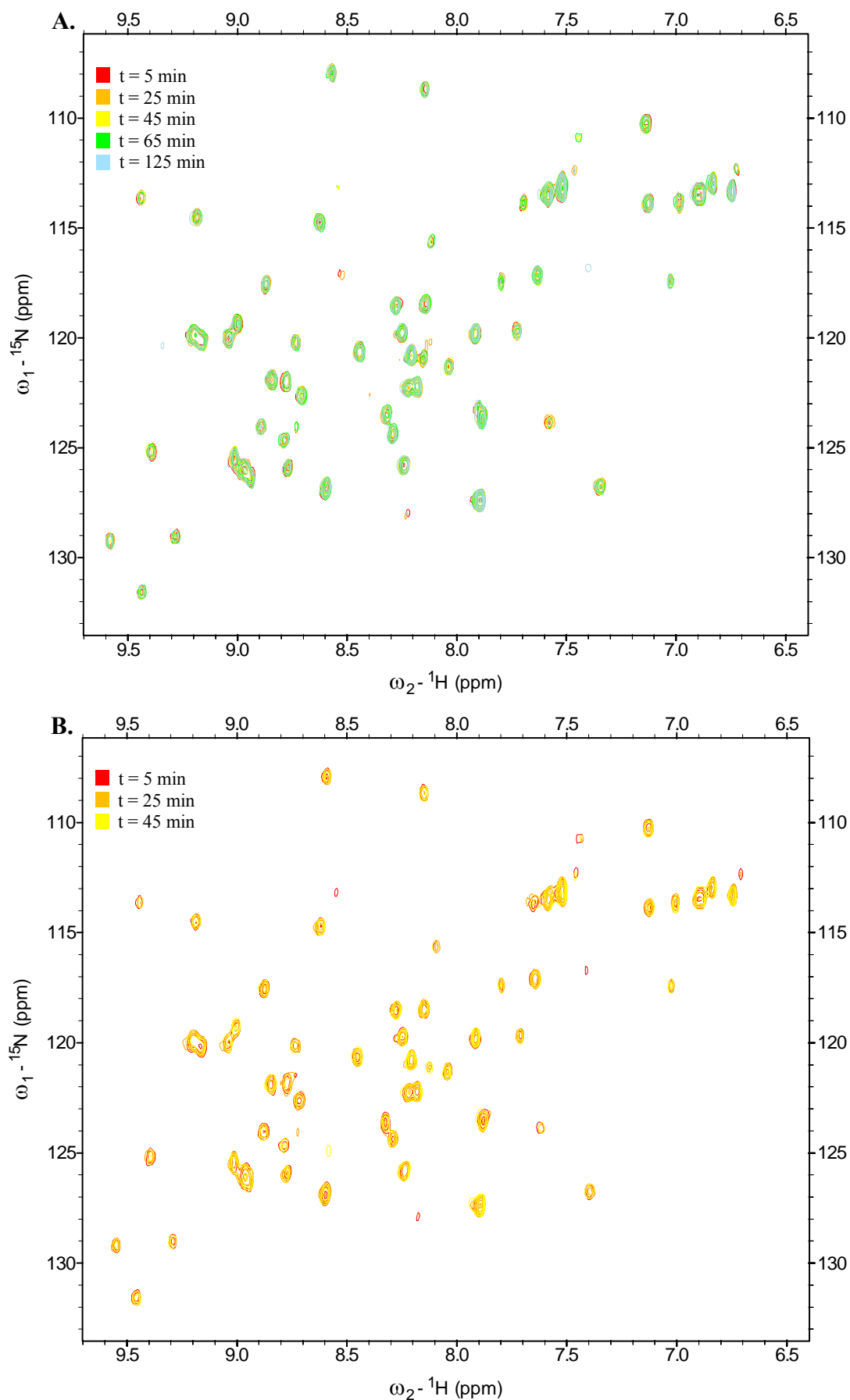
**Figure 37.** The binding isotherm for **73** with the first data point removed. The original curve is shown in pink for comparison.

Note that when no error bars are present, the error is too small to be shown.

However, before the assumption can be made that the first data point is too low for each of the 6-substituted ligands, the possible reasons for this must be considered.

### ***Investigating Equilibration Time***

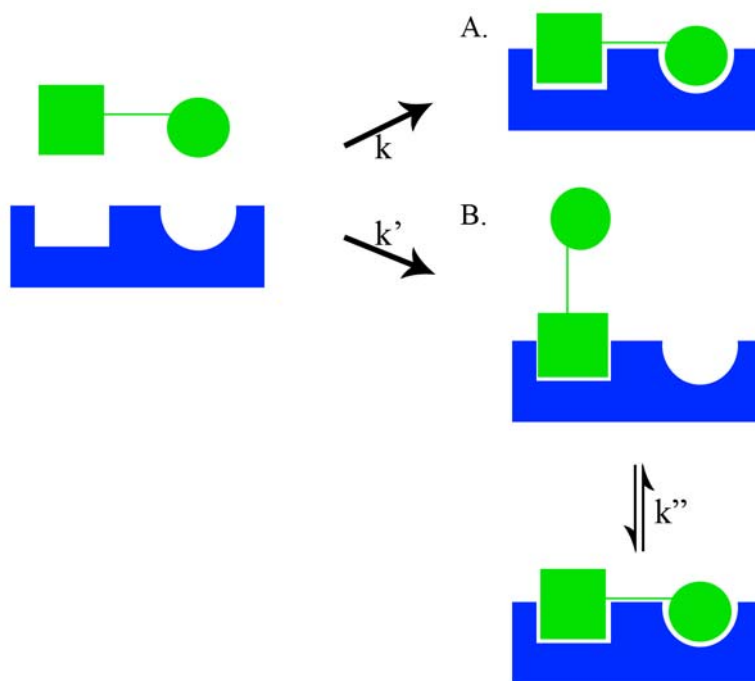
When the HSQC NMR assay is performed, each sample is left to stand for fifteen minutes between the addition of an aliquot of ligand and the acquisition of the NMR spectrum, in order for the protein-ligand complex to equilibrate. However, it is possible that at low ligand concentrations a longer equilibration time is required and equilibrium is therefore not being reached prior to acquiring the NMR spectrum. To test this hypothesis HSQC experiments were conducted with varying equilibration times after the addition of the first two aliquots of small molecule ligand. An aliquot of the ligand was added to the protein and then an HSQC NMR spectrum was acquired after five minutes. Additional spectra were acquired on the same sample after a further 20 minutes, 40 minutes, 60 minutes and 120 minutes. Another aliquot was subsequently added and spectra were acquired at 5 minutes, 25 minutes and 45 minutes. The longer equilibration times did not, however significantly alter the NMR spectra obtained. It can be observed in Figure 38 that there is no variation in the chemical shifts due to changing equilibration time. It would, in fact, appear that the protein-ligand complex reaches equilibrium as soon as the first spectrum is acquired. As a result of this, there is no change in the binding isotherm, which indicates that the problem with curve fit is not a result of equilibration time.



**Figure 38.** Overlay of NMR spectra from the HSQC NMR assay of **73** at varying equilibration times. A. **73** at 0.013 mM; B. **73** at 0.040 mM.

### *Investigating the Curve-Fitting Model*

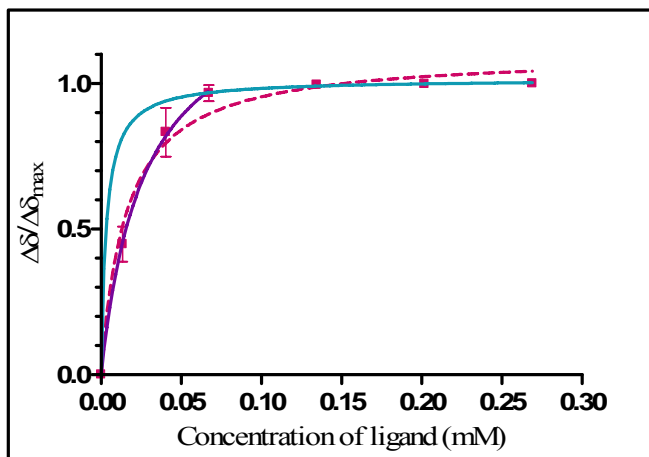
The curve fit used to calculate the equilibrium dissociation binding constants assumes one-site binding. However it is possible that one side of the small molecule ligand binds to the protein before the other side does. For example, the quinoline may form the salt bridge and  $\pi$ - $\pi$  stack first, before the phenol interacts with the protein surface (Figure 39).



**Figure 39.** Cartoon representation of A. one site binding and B. two site binding.

If the binding of the small molecule ligand does follow a two-site binding model, it would bind weakly to begin with and then bind more tightly as the second part of the ligand interacted with the protein surface. If this was the case, then two curves may be seen within the one binding isotherm and this can indeed be seen as illustrated in Figure 40.





**Figure 40.** Binding isotherm of **73** showing the two possible curves that can be drawn through the data. The original curve is shown in pink. The curve that can be drawn through the earlier data points is shown in purple and the curve that can be drawn through the later data points is shown in blue.

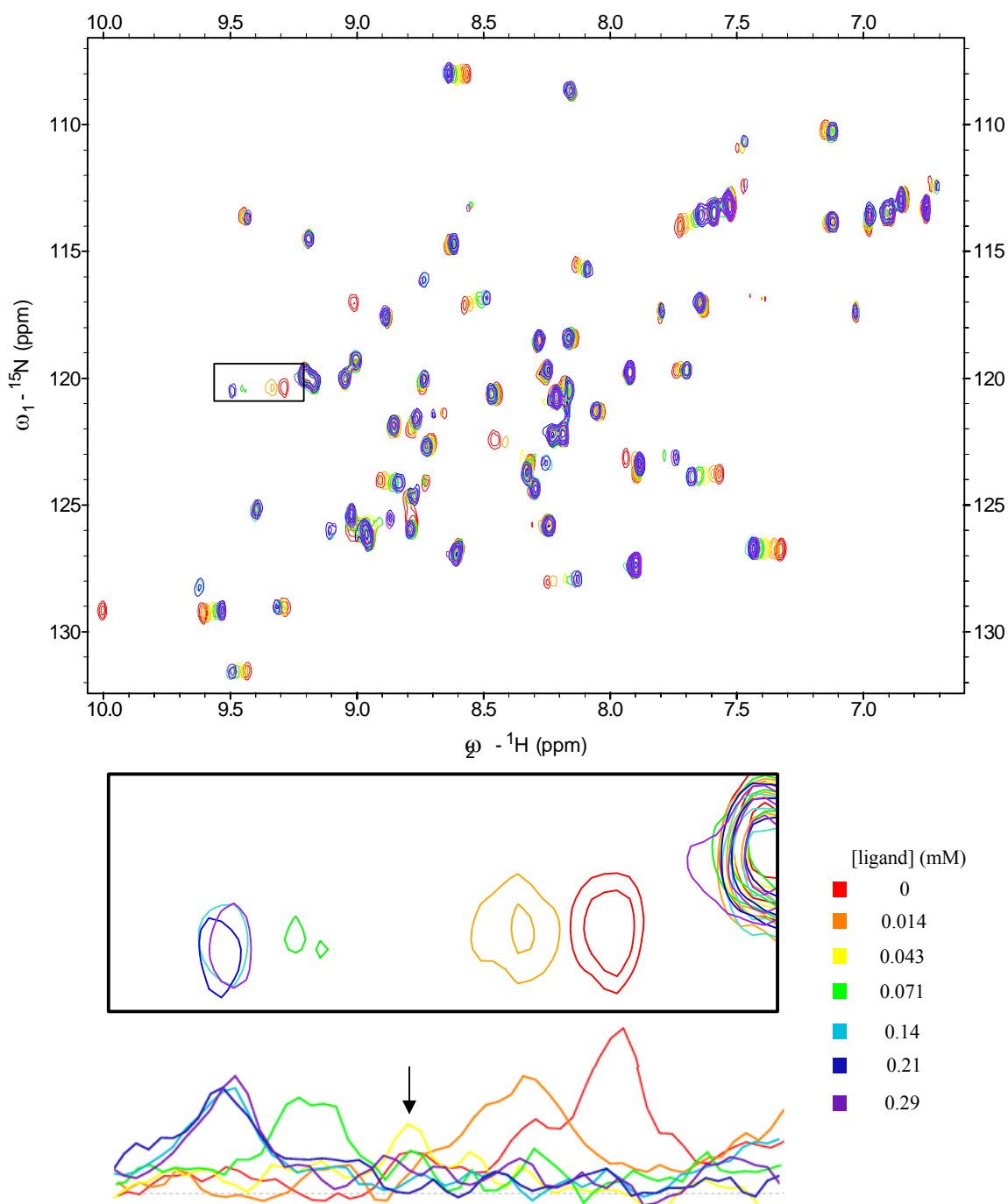
Note that when no error bars are present, the error is too small to be shown.

If two-site binding is the reason behind the curve-fitting problems, a two site binding equation could be used to fit an isotherm to the data and this would result in two dissociation constants. This was attempted using the two site binding curve fitting model from GraphPad Prism, however the resulting isotherm was the same as for the one site binding model.<sup>59</sup> This implies that the curve fitting model is not the cause of the problem with the data although other two-site binding models may need to be explored.

### ***Investigating Intermediate Exchange***

In the assays for all of the 6-substituted ligands, a number of the crosspeaks disappear after the addition of the first aliquot of ligand and then reappear at higher concentrations of the ligand. This is indicative of the ligands and protein complex being in intermediate exchange as discussed earlier (Section 1.4.3.B.). During intermediate exchange, when the peak is very broad, it is sometimes difficult to distinguish the peak from the noise. This can be seen in Figure 41. In the expansion of the overlay of the 1D <sup>1</sup>H spectra, it can be seen that the yellow peak in particular is only just above the level of the noise. In cases such as these it is difficult to assign the centre of the peak. It is also difficult to assign the centre of the peak in instances such as the orange or green peak, where the signal is broadened and one side may be higher than the other. Therefore when the ligand and protein enter intermediate exchange, the  $\Delta\delta$  values may not be precise. In the following example, the spectra obtained after the first second and third aliquots of ligand are added, are in intermediate exchange

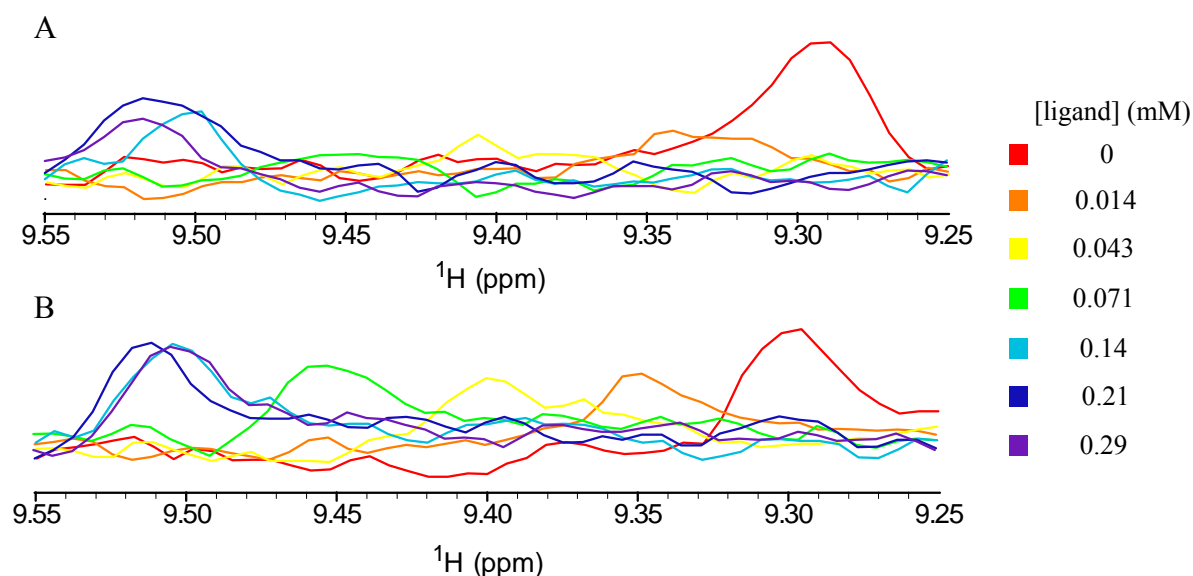
and so consequently may not be precise. This may explain why the curve does not fit the data points – the data points may not truly represent the correct values.



**Figure 41.** Overlay of NMR spectra from the HSQC NMR assay of **67**, with an enlargement of the peak due to Y227 and the  $^1\text{H}$  1D slices for the same peak at different ligand concentrations.

In order to overcome this obstacle, the protein-ligand complex needs to be forced back into fast exchange. This can be done using either a higher temperature or a lower spectrometer frequency. As the ability to run these experiments on a lower frequency spectrometer was not available, forcing the complex into fast exchange using higher temperature was

attempted. This is not ideal as at high temperatures proteins have a tendency to lose their secondary and tertiary structure. A temperature of 35°C, however, should not destabilise the Tec SH3 domain and may be enough to indicate whether a higher temperature would induce fast exchange in the ligand-protein complex. Therefore the HSQC NMR chemical shift perturbation assay was repeated at a temperature of 35°C.



**Figure 42.** Overlay of 1D <sup>1</sup>H traces for Y227 signals from the HSQC NMR assay of **73**  
A. at room temperature and B. at 35°C.

The higher temperature experiment did appear to make a slight improvement upon the intermediate exchange of the protein-ligand complex. Figure 42 shows that the signals for Y227 at low concentrations of the ligand are in intermediate exchange in the spectra acquired at room temperature. The signal after the addition of the first aliquot of ligand is very broad and low (shown in orange). After an increase in temperature, this signal is greater in intensity, and less broad. The signal does however appear to have shifted further downfield by approximately 0.02 ppm, which is a significant change in chemical shift. This would appear to indicate that the intermediate exchange experienced by the ligand-protein complex is causing problems with the assay data.

The signals after the second and third aliquots of ligand are added (shown in yellow and green) are so low in intensity and broad in the spectrum recorded at 25°C that they are indistinguishable from the noise. However they are clearly visible in the higher temperature experiment. Despite their presence at the increased temperature, these signals are still of low intensity and broadened, which indicates that they remain in intermediate exchange. Further increases in temperature are not practical as the protein may not be stable at temperatures

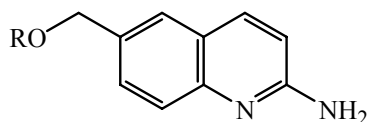
that would be high enough to induce fast exchange. Therefore the intermediate exchange issue cannot be solved by this approach.

Another factor to take into account with the intermediate exchange issue is that there are a number of residues affected by this phenomenon. Because in many cases the signals are difficult to distinguish from the noise, as they are in Figure 42, these residues are unable to be included in the data analysis to produce the binding isotherm. Typically the signals of around five residues are lost due to intermediate exchange during the assay of each of the 6-substituted ligands. The loss of this data would significantly increase the error associated with the  $K_d$  obtained from each assay.

As these ligands are already in intermediate exchange with the protein, a higher field spectrometer may cause the ligand-protein complex to enter slow exchange. This could allow for the characterisation of the binding site of the ligand to the protein surface. If the ligand is in slow exchange with the protein, it would allow intermolecular NOE experiments to be run. This would permit correlations to be made between the ligands and the residues that are nearby the ligand. This would then provide further evidence of the residues with which the ligand is interacting.

### **3.3.3. Revised Binding Constants**

The intermediate exchange experienced by the protein-ligand complex during the HSQC NMR chemical shift perturbation assay appears to introduce additional uncertainty into the early data points of the binding isotherms obtained. As a result, it would appear that intermediate exchange is the reason for the problematic curve-fitting in the binding isotherms for the 6-substituted ligands. By deleting the first one or two data points after the addition of the ligand in the binding isotherm for each of the 6-substituted ligands (as for **73** in Figure 37), the saturation of the protein is better accounted for. The trade off for this is that there is no data for the most important part of the curve, however as a result, the values for  $R^2$  and the absolute sum of squares are much improved. The revised binding constants for the 6-substituted ligands that are in intermediate exchange are shown in Table 15.

**Table 15.** The revised equilibrium dissociation binding constants, and statistical data.

R		Initial $K_d$ ( $\mu\text{M}$ )	Revised $K_d$ ( $\mu\text{M}$ )	$R^2$	Sum of Squares
$\dagger$ 4-Me- $\text{C}_6\text{H}_4$	<b>61</b>	$33 \pm 5$	$23 \pm 4$	0.9988	0.00092
$\dagger$ 3-Me- $\text{C}_6\text{H}_4$	<b>62</b>	$57 \pm 9$	$39 \pm 4$	0.9990	0.00068
$\dagger$ 2-Me- $\text{C}_6\text{H}_4$	<b>63</b>	$55 \pm 8$	$37 \pm 5$	0.9986	0.00100
*4- $t$ Bu- $\text{C}_6\text{H}_4$	<b>64</b>	$21 \pm 4$	$14 \pm 2$	0.9978	0.00172
$\dagger$ 3- $t$ Bu- $\text{C}_6\text{H}_4$	<b>65</b>	$65 \pm 6$	$58 \pm 8$	0.9975	0.00174
*4- $i$ Pr- $\text{C}_6\text{H}_4$	<b>66</b>	$20 \pm 3$	$13 \pm 1$	0.9997	0.00021
$\dagger$ 2- $i$ Pr- $\text{C}_6\text{H}_4$	<b>67</b>	$53 \pm 10$	$34 \pm 9$	0.9943	0.00421
$\dagger$ 4-MeO- $\text{C}_6\text{H}_4$	<b>68</b>	$39 \pm 10$	$15 \pm 1$	0.9997	0.00022
$\dagger$ 3-MeO- $\text{C}_6\text{H}_4$	<b>69</b>	$55 \pm 7$	$40 \pm 4$	0.9985	0.00110
$\dagger$ 2-NHAc- $\text{C}_6\text{H}_4$	<b>70</b>	$67 \pm 7$	$54 \pm 6$	0.9974	0.00196
*4-Br- $\text{C}_6\text{H}_4$	<b>71</b>	$16 \pm 3$	$10 \pm 2$	0.9977	0.00180
*2-Br- $\text{C}_6\text{H}_4$	<b>72</b>	$18 \pm 3$	$12 \pm 3$	0.9963	0.00288
*4-Cl- $\text{C}_6\text{H}_4$	<b>73</b>	$15 \pm 3$	$9 \pm 2$	0.9965	0.00272
*2-Cl- $\text{C}_6\text{H}_4$	<b>74</b>	$16 \pm 2$	$13 \pm 2$	0.9975	0.00189
$\dagger$ 1-naphthyl	<b>75</b>	$37 \pm 7$	$21 \pm 4$	0.9984	0.00117

\*2nd data point deleted;  $\dagger$ 2nd and 3rd data points deleted.

With the revised data to hand, the trend becomes more apparent. The 4-substituted phenolic ligands appear to bind with a higher affinity than their 2- or 3-substituted equivalents. This is most likely because a substituent in the 2- or the 3-position or the phenoxy methyl group would either face towards the protein surface and cause steric clashes or may face away from the protein surface and thus not make any further contacts. A *para* substituent on the other hand, could point further in towards amino acid residues on the protein surface without interfering with the backbone and may allow for further interactions with the protein surface.

### 3.3.4. Conclusions From The Binding Data for the 6-Substituted 2-Aminoquinolines

There were a number of issues that were encountered with the [ $^1\text{H}$ ,  $^{15}\text{N}$ ] HSQC chemical shift perturbation assay. The first issue was that a number of ligands were not soluble enough to reach the point at which the saturation of binding was reached. Consequently the

$K_d$ 's in these cases do not precisely reflect the actual binding affinity. The second problem was that the binding isotherm used to calculate the  $K_d$  of the ligands did not seem to fit the data in many cases. After investigating the issue, it would appear that the fact that the ligands are in intermediate exchange with the protein on the NMR timescale may be affecting the accuracy of the data obtained for the first few data points which in turn may be causing the problem with curve fit.

Despite these issues, it is apparent that all of the 6-substituted ligands bind with higher affinity than the lead compound **2**. A pattern can be seen in the binding affinities of 6-substituted 2-aminoquinolines, which is that ligands containing *para* substituted phenoxyethyl groups bind with greater affinity than their *ortho* or *meta* substituted counterparts. The *para* substituted ligands all bind with approximately 10-fold greater affinity than **2** whereas in general, the *ortho* and *meta* substituted ligands have much weaker binding with only 2 – 4-fold improvement in relation to **2** (the exceptions to this are the halogen substituted derivatives – see below). As this effect can be seen for all the substituents including alkyl, halogen and methoxy, it is likely that this pattern is due to a hydrophobic effect: there may be a hydrophobic contact being made with the protein surface that only a *para* substituent can achieve.

It would also appear that inductively withdrawing substituents on the phenoxyethyl group lead to improved affinities. With regard to the halogen substituents, both the 2- and 4-positions on the phenoxyethyl ring have binding affinity improved by approximately 10-fold as compared to **2**. This may be due to the hydrophobic effect discussed above or there may be a separate effect occurring here that favours an inductively withdrawing group in these positions on the aromatic ring.

# Chapter 4.

## 3-SUBSTITUTED 2-AMINOQUINOLINES

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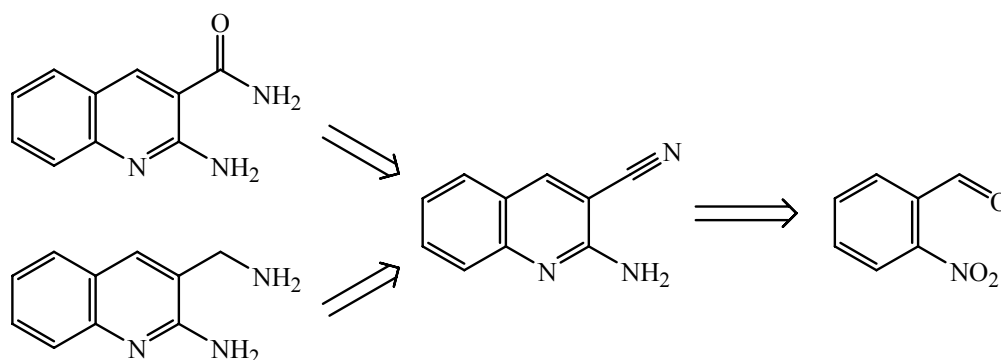
### 4.1 Introduction

The effect of introducing a substituent in the 3-position of 2-aminoquinoline on the binding interaction with the Tec SH3 domain has not yet been investigated. It has, however, been observed that a benzylic substituent on the 2-amino group appears to interact with the protein surface.<sup>50, 51</sup> This indicates that there is potential for a substituent at the 3-position of 2-aminoquinoline to make a similar contact with the Tec SH3 domain. There are a number of literature methods for introducing small substituents at the 3-position of 2-aminoquinoline. These derivatives can be prepared quickly and easily in order to obtain preliminary binding data for ligands containing a substituent at the 3-position of 2-aminoquinoline.

### 4.2 Synthesis of Simple 3-Substituted-2-Aminoquinoline Ligands

#### 4.2.1. General Synthetic Pathway

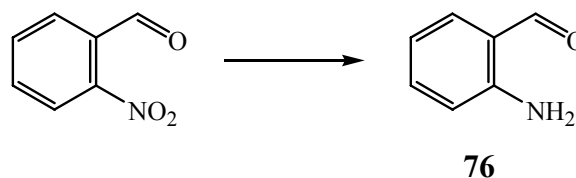
The simple 3-substituted ligands can be accessed through the method outlined in Figure 43. 2-Aminoquinoline-3-carboxamide, **30**, and 2-amino-3-(aminomethyl)quinoline, **31**, can both be prepared from 2-amino-3-cyanoquinoline, **29**, for which 2-nitrobenzaldehyde is the starting point.



**Figure 43.** The retro-synthetic pathway for the synthesis of simple 3-substituted 2-aminoquinolines.

#### 4.2.2. Synthesis of Simple 3-Substituted-2-Aminoquinolines

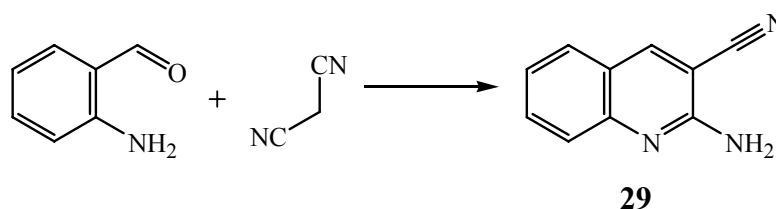
The first step in preparing the simple 3-substituted ligands was the reduction of 2-nitrobenzaldehyde to 2-aminobenzaldehyde, **76**, using the method of Smith and Opie (Scheme 11).<sup>60</sup>



**Scheme 11.** Reaction conditions:  $FeSO_4 \cdot 7H_2O / NH_3$ .

This reaction proceeded in moderate yield (54%), which was consistent with the literature procedure.<sup>60</sup> The IR spectrum showed four peaks above  $3300\text{ cm}^{-1}$  that correspond to the  $NH_2$  group in free and hydrogen bonded forms. The  $^1H$  NMR spectrum also showed the presence of a broad signal at 6.12 ppm which corresponds to an  $NH_2$  group, as well as a sharp peak at 9.87 ppm, which corresponds to the aldehyde group.

The next step was the synthesis of the first ligand, **29**, via reaction of **76** with malononitrile (Scheme 12).<sup>61</sup>

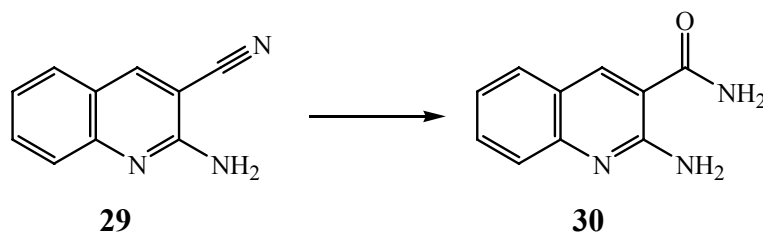


**Scheme 12.** Reaction conditions: *ethanol / pyridine*.

The desired product, **29**, was obtained in good yield (78%). The melting point of **29** (229-230°C) was consistent with the literature (228.5-230°C)<sup>61</sup> and the IR spectrum showed a characteristic peak at  $2227\text{ cm}^{-1}$  that corresponds to a nitrile group. The  $^1H$  NMR spectrum showed the appearance of a singlet at  $\delta_H = 8.32$  ppm, which corresponds to the proton at H(4) as well as the disappearance of the aldehyde signal at  $\delta_H = 9.87$  ppm.

The second ligand, **30**, was prepared from the first ligand via the reaction shown in Scheme 13.<sup>61</sup>

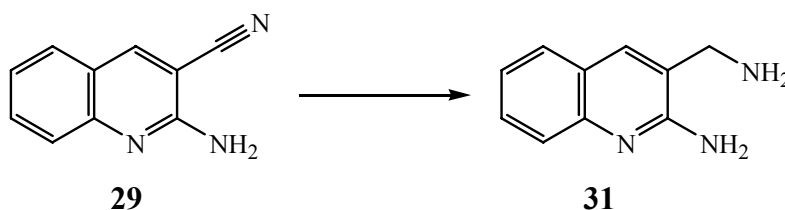




**Scheme 13.** Reaction conditions:  $H_2O_2 / KOH / ethanol$ .

The reaction proceeded in moderate yield (52%). The melting point of the final product (238-241°C) was consistent with the literature value (240-242°C)<sup>61</sup>. The IR spectrum of **30** no longer contained a nitrile peak and also showed the appearance of a strong peak at 1632  $cm^{-1}$  which corresponds to the carbonyl of the amide group. The  $^1H$  NMR spectrum showed two broad peaks corresponding to  $NH_2$  groups ( $\delta_H = 5.88$  ppm and  $\delta_H = 6.53$  ppm).

The third and final ligand, **31**, was also prepared from **29** (Scheme 14).<sup>62, 63</sup>



**Scheme 14.** Reaction conditions:  $NaOH / ethanol / Raney\ nickel$ .

The reaction proceeded in moderate yield (64%) to give the desired product with a slightly broadened melting point (147-155°C) in comparison to the literature melting point (147-149°C)<sup>62</sup>. The  $^1H$  NMR spectrum indicated the presence of a signal corresponding to the  $CH_2$  group at  $\delta_H = 3.99$  ppm. The signal due to H(4) also underwent an upfield shift due to the removal of the electron withdrawing group that deshielded the H(4) nucleus through anisotropy ( $\delta_H = 8.19$  ppm for **30**,  $\delta_H = 7.48-7.67$  ppm for **31**).

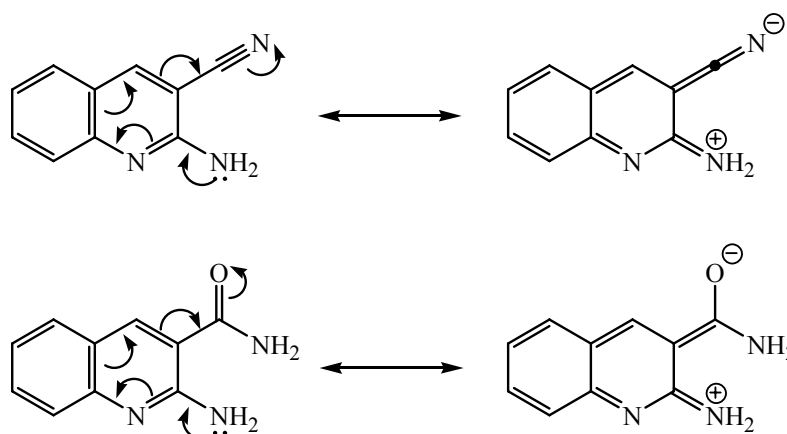
### 4.3 Binding Data for the Simple 3-Substituted-2-Aminoquinoline Ligands

None of the simple 3-substituted ligands prepared bound with high affinity for the Tec SH3 domain (Table 16).

**Table 16.** The equilibrium dissociation binding constants of simple 3-substituted ligands.

	<b>29</b>	<b>30</b>	<b>31</b>
$K_d$ ( $\mu\text{M}$ )	$227 \pm 47$	$279 \pm 12$	$76 \pm 5$

Both **29** and **30** have lesser affinity for the Tec SH3 domain than 2-aminoquinoline. Both of these ligands contain functional groups that withdraw electron density through resonance and as a result the ability of the ligand to become protonated and form a salt bridge with D196 would be reduced (Figure 44).



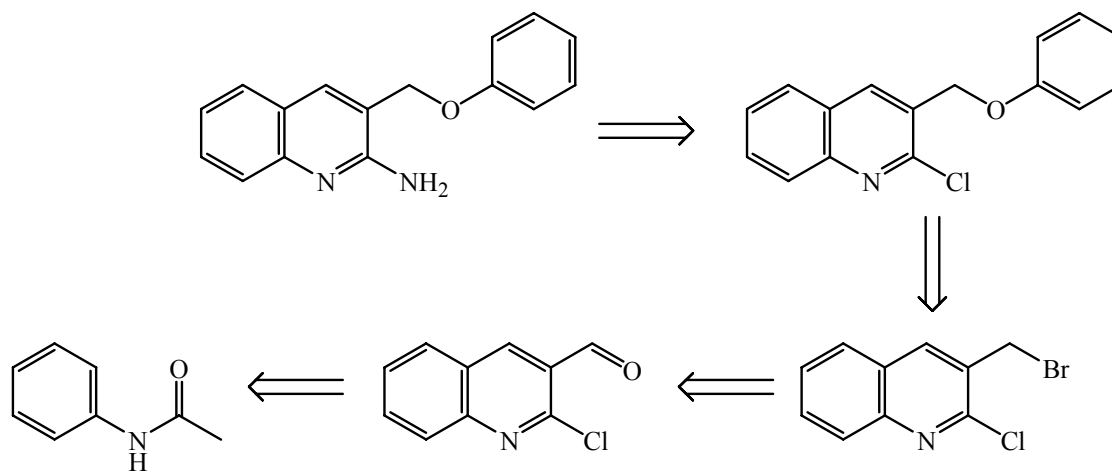
**Figure 44.** The resonance structures that reduce the ability of the ligands to form a salt bridge.

The final ligand, **31** has a slightly improved affinity for the Tec SH3 domain than the lead compound, **2**. This might indicate that there is potential for higher affinity ligands by introducing larger, non-electron withdrawing substituents in the 3-position of 2-aminoquinoline.

## 4.4 Introducing More Complex Substituents in the 3-Position of 2-Aminoquinoline

### 4.4.1. General Synthetic Pathway

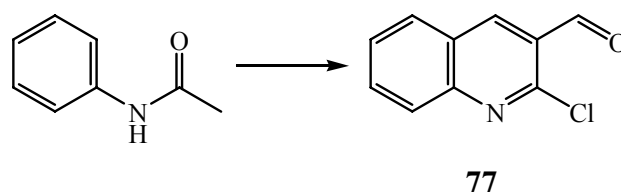
In order to discover if a contact is able to be made with the protein surface by introducing large, non-electron withdrawing substituents in the 3-position of 2-aminoquinoline, phenoxyethyl substitution can once again be utilised. The phenolic substitution reaction can be performed on 2-chloro-3-(bromomethyl)quinoline, **79**. This can be prepared through successive reduction and bromination steps on 3-formyl-2-chloroquinoline, **77**, which in turn can be prepared through a simple literature procedure.<sup>64</sup>



**Figure 45.** The retrosynthetic pathway for the formation of novel 3-substituted ligands.

#### 4.4.2. Synthesis of 3-Phenoxymethyl-2-aminoquinolines

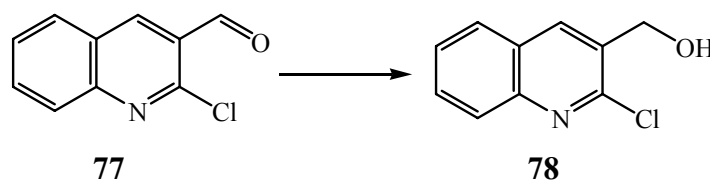
The first step in the synthesis of 3-phenoxymethyl-2-aminoquinoline was the formation of 3-formyl-2-chloroquinoline, **77**, using the method of Meth-Cohn (Scheme 15).<sup>64</sup>



**Scheme 15.** Reaction conditions: *DMF / POCl<sub>3</sub>*.

This reaction proceeded to give the desired product in a reasonable yield (42%). The melting point (147-149°C) was consistent with the literature (148-149°C)<sup>64</sup>. The <sup>1</sup>H NMR spectrum showed a singlet at  $\delta_{\text{H}} = 8.78$  ppm that corresponds to H(4) as well as another singlet at  $\delta_{\text{H}} = 10.58$  ppm that corresponds to the aldehyde functionality.

The next step was the reduction of the aldehyde to the alcohol to give **78** (Scheme 16).

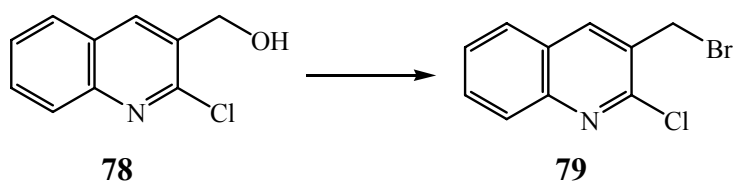


**Scheme 16.** Reaction conditions: *NaBH<sub>4</sub> / ethanol*.

The reaction proceeded in almost quantitative yield (97%). The melting point of the final product was slightly broader (149-157°C) than the literature value (151-152°C).<sup>65</sup> The low

resolution mass spectrum gave a peak at  $m/z$  193 which corresponds to  $M^+$ . The IR spectrum displayed a broad absorbance at  $3410\text{ cm}^{-1}$ , corresponding to an OH peak. The  $^1\text{H}$  NMR spectrum showed the disappearance of the signal corresponding to the aldehyde ( $\delta_{\text{H}} = 10.58\text{ ppm}$ ) and the appearance of a broad signal corresponding to the OH group ( $\delta_{\text{H}} = 2.42\text{ ppm}$ ) and another signal corresponding to the benzylic protons ( $\delta_{\text{H}} = 4.94\text{ ppm}$ ).

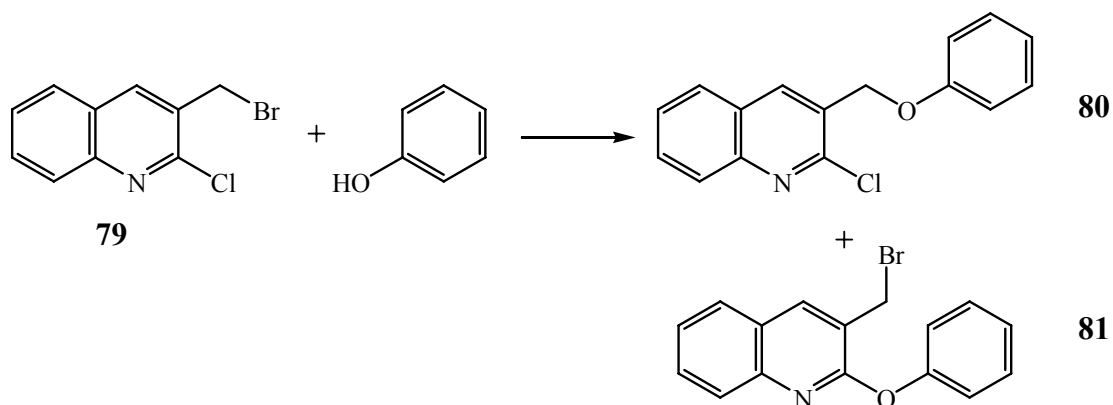
The hydroxymethyl group was then converted to a bromomethyl group, using the method outlined in Scheme 17 to give **79**.



**Scheme 17.** Reaction conditions:  $PBr_3$  / benzene

The bromide, **79**, was isolated in moderate yield (56%). The melting point of **79** ( $122\text{--}125^\circ\text{C}$ ) corresponded to that of the desired product ( $121\text{--}125^\circ\text{C}$ ).<sup>66</sup> The low resolution mass spectrum of the product showed a peak corresponding to  $M^+$  (for  $^{35}\text{Cl}/^{79}\text{Br}$   $m/z$  255, for  $^{35}\text{Cl}/^{81}\text{Br}$  and  $^{37}\text{Cl}/^{79}\text{Br}$   $m/z$  257, for  $^{37}\text{Cl}/^{81}\text{Br}$   $m/z$  259). The  $^1\text{H}$  NMR spectrum showed a slight upfield shift in the signal corresponding to the benzylic protons from  $\delta_{\text{H}} = 4.94\text{ ppm}$  to  $\delta_{\text{H}} = 4.73\text{ ppm}$ , as well as the disappearance of the signal corresponding to the OH group.

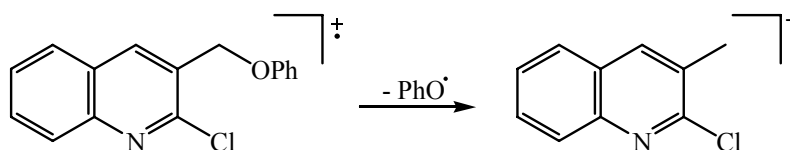
2-Chloro-3-(phenoxyethyl)quinoline could then be prepared through the phenolic substitution reaction shown in Scheme 18.



**Scheme 18.** Reaction conditions:  $K_2CO_3$  / acetonitrile.

The reaction proceeded to give **80** in moderate yield ( $\sim 70\%$  total yield) along with the by-product **81** ( $\sim 20\%$  total yield) formed by 2-substitution, rather than the desired benzylic-

substitution reaction. The two products had a sufficient difference in  $R_f$  to be separated by means of flash column chromatography (c.f. **80**  $R_f$  0.25; **81**  $R_f$  0.28). Although a large number of fractions contained a mixture of the two products, a sufficient amount of each was able to be obtained pure in order to characterise each compound and, in the case of **80**, carry on with the next step in the reaction series. The melting point of the desired product, **80**, (116-118°C) was consistent with that of the expected product (120°C).<sup>67</sup> The low resolution mass spectrum gave a peak corresponding to  $M^{+\bullet}$  (for  $^{37}\text{Cl}$   $m/z$  271, for  $^{35}\text{Cl}$   $m/z$  269), as well as the characteristic fragmentation involving loss of the phenoxy radical that occurs for the 6-phoxymethyl derivatives (Figure 46).

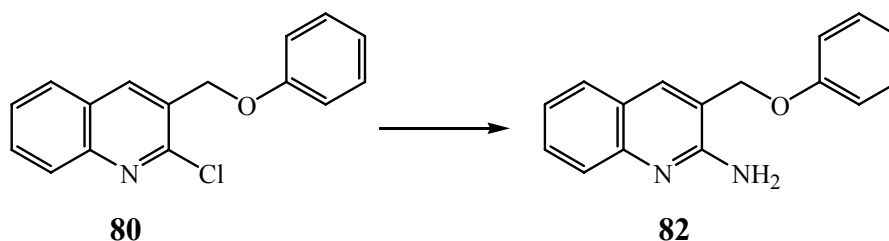


**Figure 46.** The characteristic loss of the phenoxy radical in the mass spectrum of **80**.

The  $^1\text{H}$  NMR spectrum displayed a downfield shift of the benzylic protons (c.f. for **79**  $\delta_{\text{H}} = 4.47$  ppm, for **80**  $\delta_{\text{H}} = 5.27$  ppm) due to the introduction of the phenoxy group and the resultant additional anisotropy.

Both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **81** were very similar to that of **80**. However the structure of the by-product was confirmed by high resolution mass spectrometry. The low resolution mass spectrum gave a peak corresponding to  $M^{+\bullet}$  (for  $^{81}\text{Br}$   $m/z$  315, for  $^{79}\text{Br}$   $m/z$  313) and once again showed the loss of a phenoxy radical.

The final step in the reaction pathway was the Kóródi style amination to give **82**.<sup>56</sup>

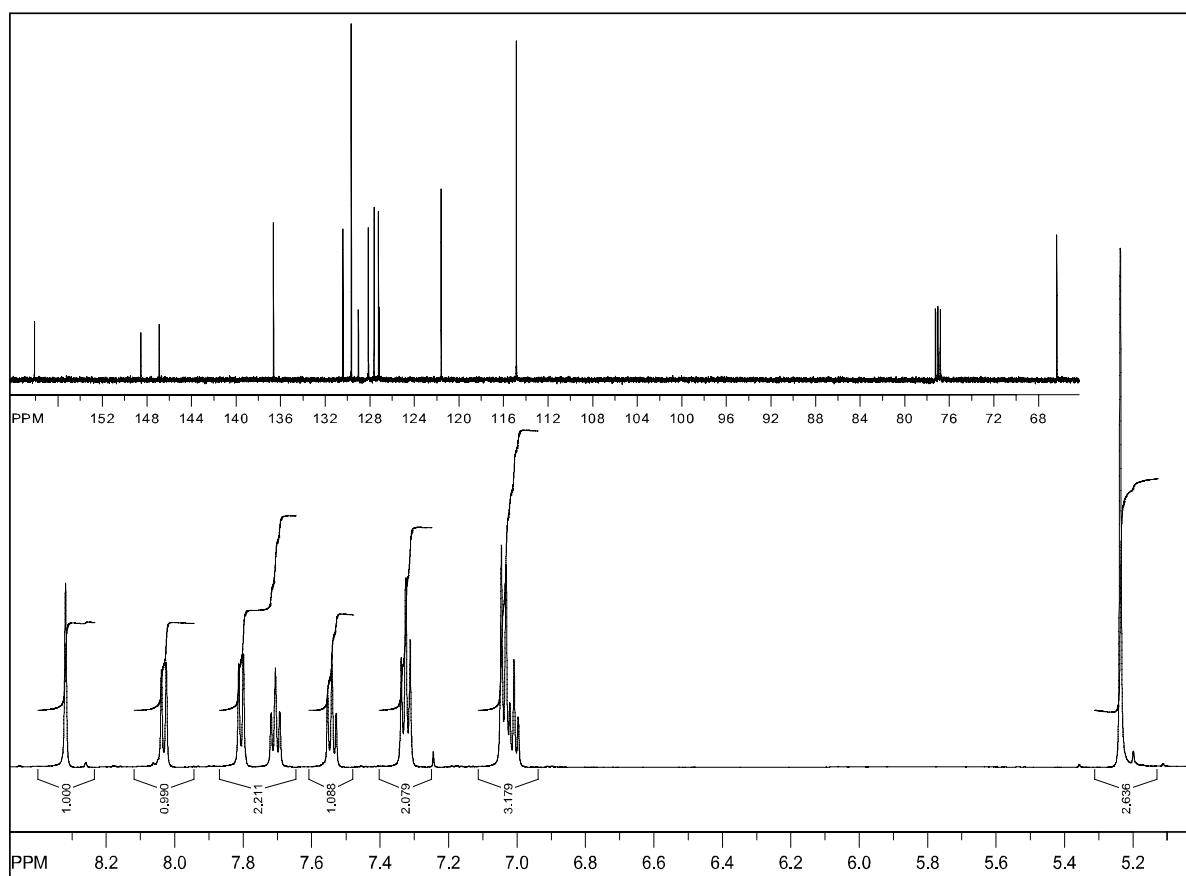


**Scheme 19.** Reaction conditions:  $\text{K}_2\text{CO}_3$  / acetamide / 200°C.

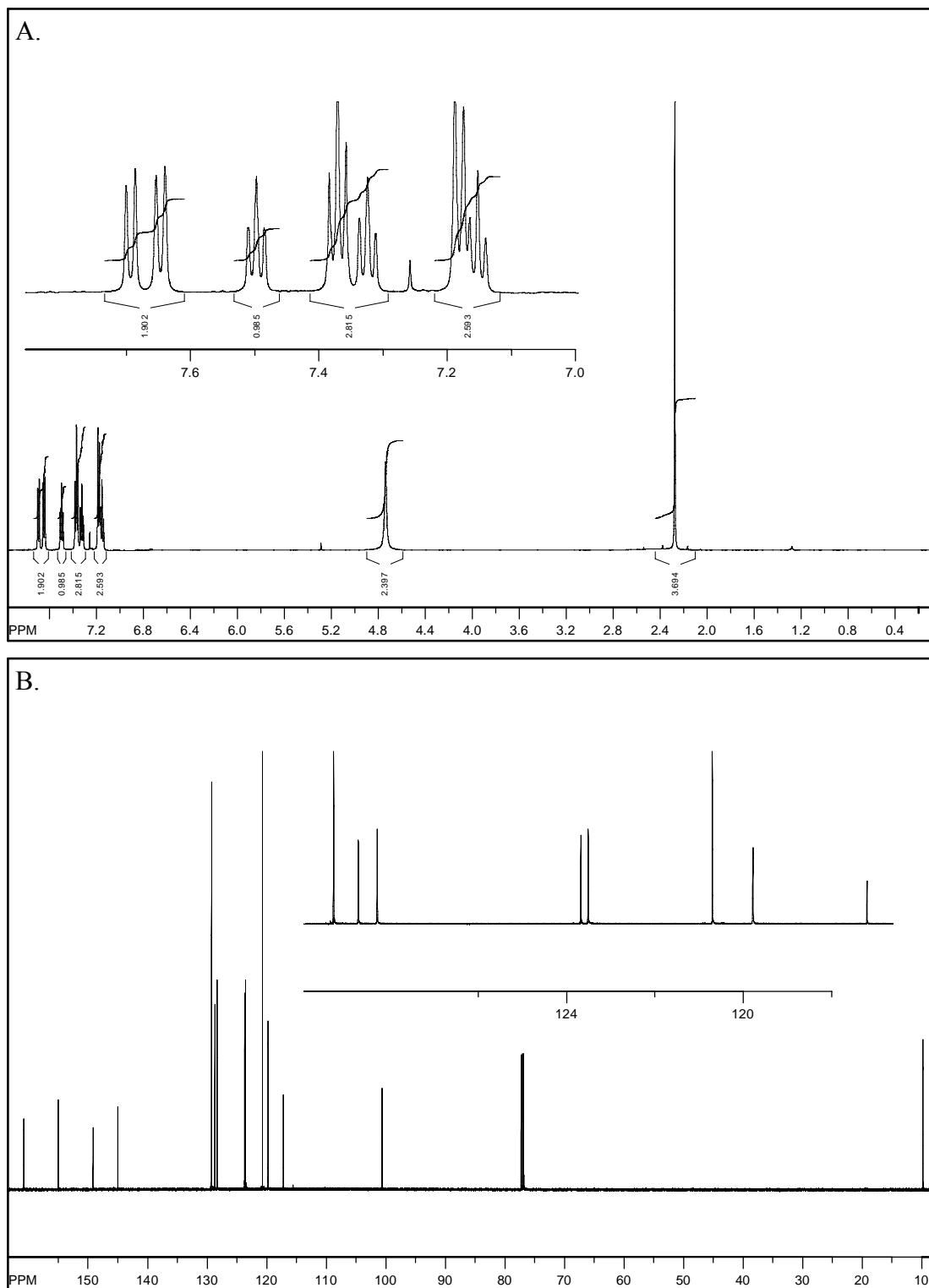
This reaction, however, did not give the desired product, giving instead an unknown product, **83**. In order to ensure that this product was not an anomaly the reaction was

repeated and the same product was obtained. Both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **83** showed significant changes (Figure 48) in comparison to the spectrum of **80** (Figure 47).

The  $^1\text{H}$  NMR spectrum no longer shows the signal corresponding to H(4), which appears at  $\delta_{\text{H}} = 8.35$  ppm in the spectrum of **80**. The spectrum also does not contain the signal corresponding to the benzylic protons ( $\delta_{\text{H}} = 5.27$  ppm for **80**), but shows a signal corresponding to a methyl group at  $\delta_{\text{H}} = 2.52$  ppm. There does appear to be a primary amino group in the final product, as there is a broad signal that integrates to two protons at  $\delta_{\text{H}} = 4.72$  ppm. The  $^{13}\text{C}$  NMR spectrum shows the presence of six quaternary carbons at  $\delta_{\text{C}} = 100.54, 117.14, 144.93, 149.12, 154.92,$  and  $160.76$  ppm. This is one more quaternary carbon than expected, which would tend to indicate that there has been substitution on the quinoline ring. The presence of the methyl group suggests that the phenoxy group has migrated and the disappearance of the H(4) signal, as well as the appearance of an extra quaternary carbon, suggests that the molecule has undergone substitution at C(4). It was thought that the phenoxy group may have migrated to C(4).

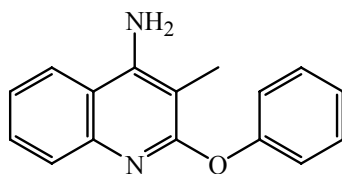


**Figure 47.** The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **80** for comparison with those of **83**, below.



**Figure 48.** A. The  $^1\text{H}$  NMR spectrum and B. the  $^{13}\text{C}$  NMR spectrum of the unknown, **81**, produced from the Kóródi Amination reaction on **80**.

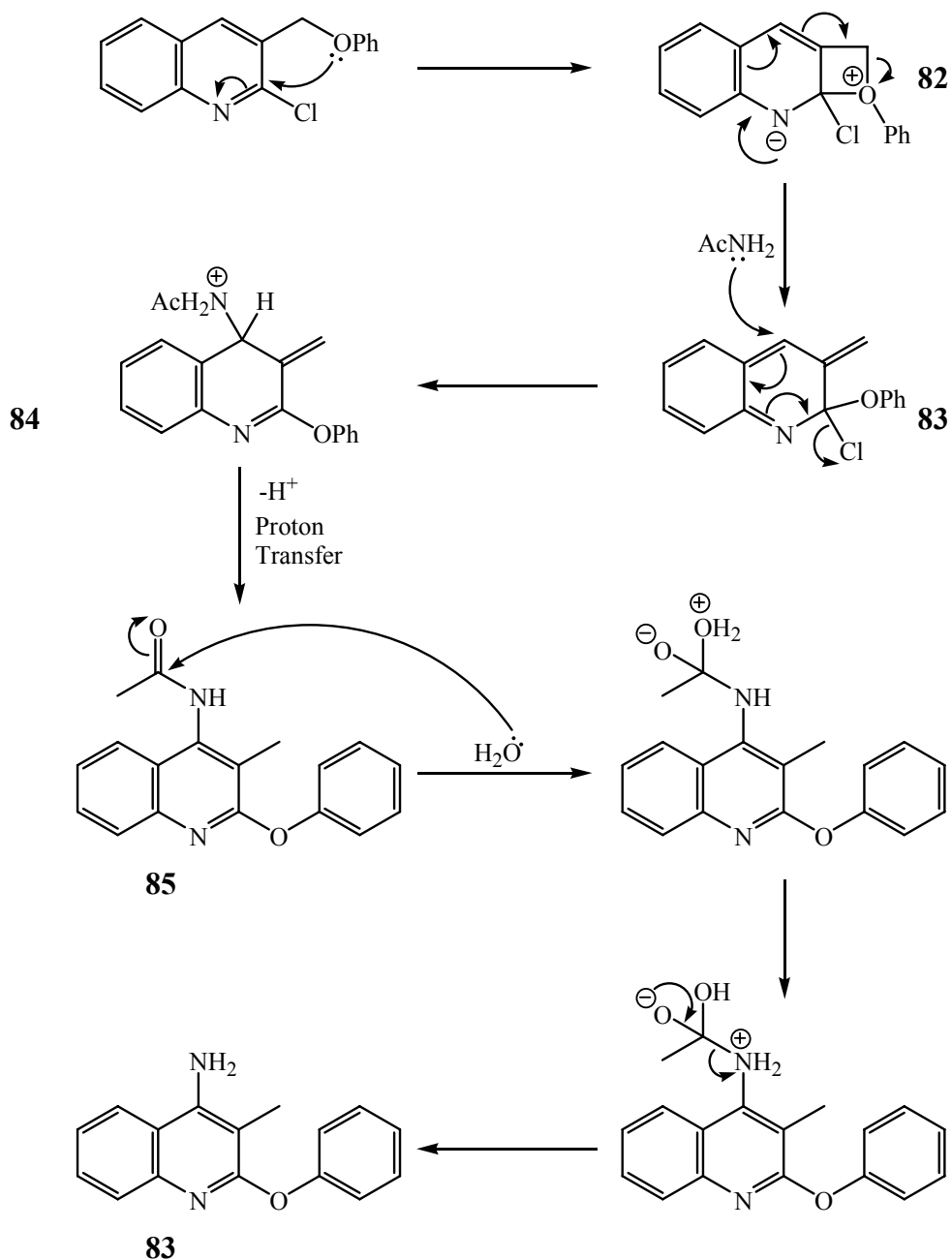
The identity of the product was confirmed by x-ray crystallography (see Appendix 1) and high resolution mass spectrometry. The structure is shown in Figure 49. The phenoxy group has migrated, but not to C(4) as originally thought. Instead it has migrated to C(2) and there is an amino group at C(4).



**Figure 49. 83**, the product obtained from the amination reaction of **80**.

It is not immediately apparent how this product formed from the reaction of **81** with acetamide in basic conditions. Given that the product contains the phenoxy group at the 2-position, the mechanism must account for this migration. It is proposed that this occurs through attack on C(2) by the phenoxy lone pair to bring about a cyclic intermediate, **82**, which then cleaves to give **83**. The final product has an amino group in the 4-position, so it is proposed that the amino functionality is introduced in the form of an acetamide group (as in the Kóródi amination).<sup>56</sup> It is suggested that the acetamide lone pair of electrons attacks C(4) and subsequently causes the chlorine group to leave from C(2) to give the intermediate **84**. Loss of a proton from the acetamide group, followed by a proton transfer, restores aromaticity to result in the intermediate **85**. The starting material has lost HCl by this stage, which would react with the potassium carbonate in the reaction mixture to give carbon dioxide and water. The presence of the water causes hydrolysis of the acetamide group in order to form the final product, **83**. The proposed mechanism is shown in Figure 50.





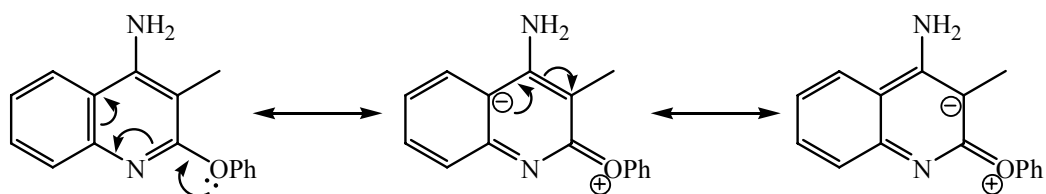
**Figure 50.** Proposed mechanism for the formation of **83**.

The low resolution mass spectrum of the product, **83**, gave a peak at  $m/z$  250, which corresponds to  $\text{M}^+$ . The  $^{13}\text{C}$  NMR spectrum shows a number of characteristic changes in chemical shift (Table 17).

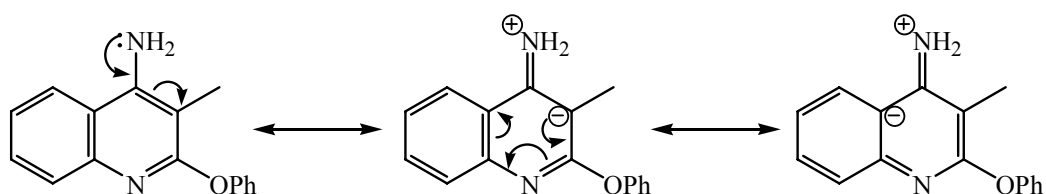
**Table 17.** Significant changes in chemical shift ( $\delta$ , ppm) in the  $^{13}\text{C}$  NMR spectrum upon conversion of **80** to **83**.

C	$\delta_{\text{C}}$ ( <b>80</b> )	$\delta_{\text{C}}$ ( <b>83</b> )
2	148.53	160.76
3	129.00	100.54
4	136.62	149.12
4a	127.14	117.14

There is a large downfield shift in the signal for C(2) upon conversion of the chloro group to a phenoxy group. Obviously the phenoxy substituent is more electron withdrawing by induction than the halogen. The signal corresponding to C(3) undergoes a large upfield shift upon changing from an adjacent phoxymethyl group to a methyl group. This is due to the loss of the inductively withdrawing oxygen and replacement with a weak inductively donating methyl group and also the ability of both the oxygen from the phenoxy group and the nitrogen from the amino group to donate electron density through resonance (Figures 51 and 52). The signal for C(4a) undergoes a small upfield shift. This is also due to the shielding effect of the resonance donation from the amino and phenoxy groups (Figures 51 and 52). There is a downfield shift in the signal that corresponds to C(4) upon the introduction of an amino group. This is due to the inductively withdrawing effect of the adjacent nitrogen atom.



**Figure 51.** The electron donating effect of the phenoxy group on C(3) and C(4a).



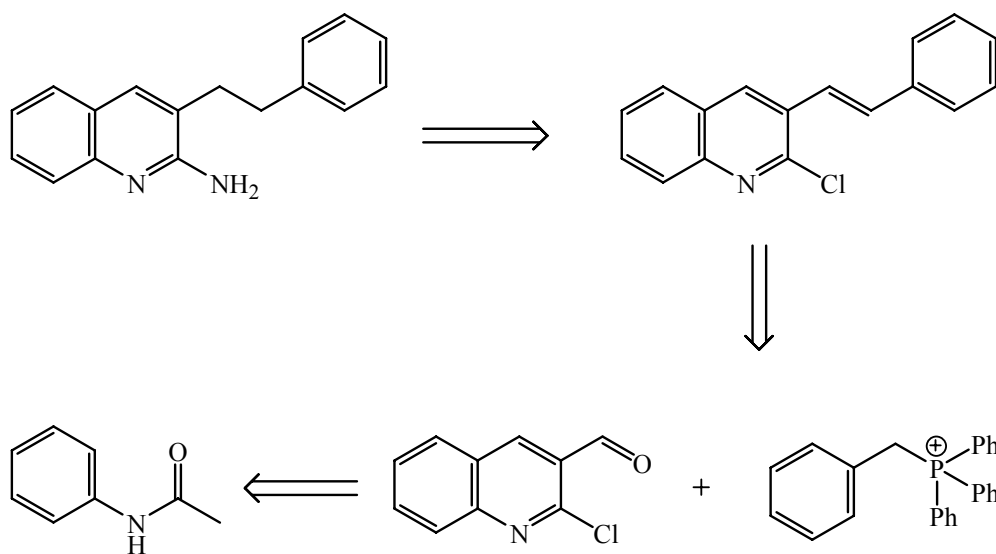
**Figure 52.** The electron donating effect of the amino group on C(3) and C(4a).

## 4.5 Alternative Method for Preparing Ligands with Complex Substitution in the 3-Position

The final, amination step in the synthesis of 3-phenoxyethyl-2-aminoquinoline gave rise to a compound that was not the desired product and was unable to be used as a ligand. Therefore a new method needed to be found for introducing a substituent in this position. The starting material for the phenolic substitution method could be utilised in a Wittig reaction. A benzyl phosphonium salt can be used in the Wittig reaction in order to result in a phenethyl derivative as a substituent in the 3-position of 2-aminoquinoline.

### 4.5.1. General Synthetic Pathway

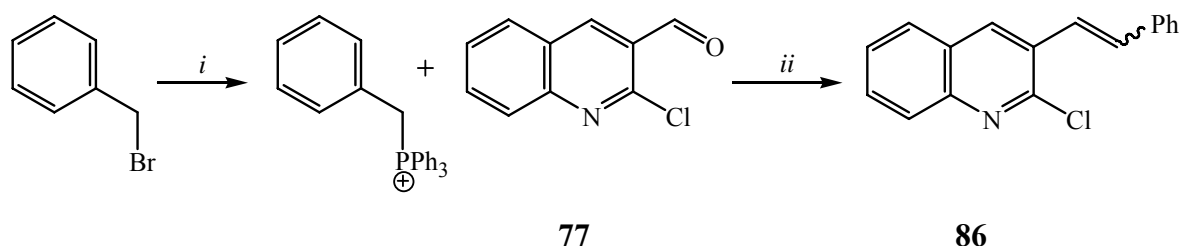
A 3-phenethyl-2-aminoquinoline ligand can be accessed through a short synthetic pathway involving a key Wittig reaction (Figure 53). The desired product is prepared through subsequent reduction and amination steps on a 3-styryl-2-chloro derivative. This can, in turn, be prepared using a Wittig reaction with a benzyl(triphenyl)phosphonium salt and **77**, which can be prepared as for the phenolic substitution pathway.



**Figure 53.** An alternative pathway for the synthesis of novel 3-substituted ligands.

### 4.5.2. Synthesis of 2-Chloro-3-[(*E*)-2-phenylvinyl]quinoline and 2-Chloro-3-[(*Z*)-2-phenylvinyl]quinoline

The benzyl(triphenyl)phosphonium salt was prepared from benzylbromide and triphenylphosphine. The crude phosphonium salt was then deprotonated with potassium *tert*-butoxide and reacted with **77** to give **86** (Scheme 20).<sup>68</sup>

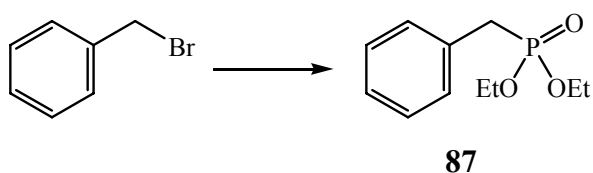


**Scheme 20.** Reaction conditions: *i.* triphenylphosphine / chloroform. *ii.*  $KO^tBu$  / THF.

The reaction proceeded in low yield to give what appeared to be the desired product. However it was unable to be separated from the triphenylphosphonium oxide by-product. While the majority of the by-product was able to be removed through filtration, some still remained in solution and could not be separated through chromatographic methods.

Consequently a new method for introduction of the 3-styryl group was considered. The Horner-Emmons synthesis is similar to the Wittig reaction but in place of a phosphonium salt, a phosphonate anion is reacted with the aldehyde. The by-product is soluble in water, so is easily removed through washing during work up.<sup>69</sup>

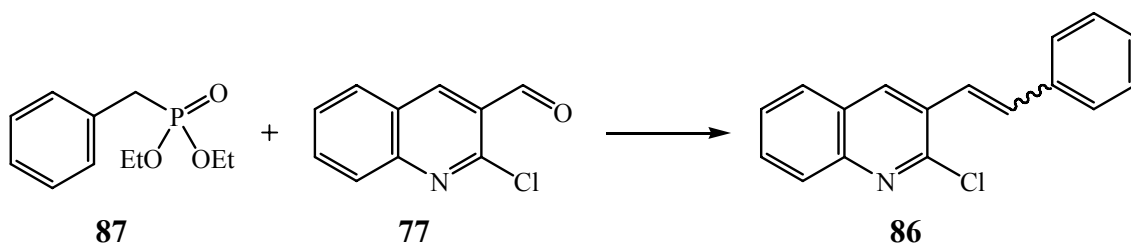
The first step in the Horner-Emmons pathway was the synthesis of the phosphonate, **87**, from benzyl bromide, via a Michaelis-Arbuszov rearrangement (Scheme 21).<sup>70, 71</sup>



**Scheme 21.** Reaction conditions: Triethylphosphite.

The desired product, **87**, was obtained in high yield (97%). The  $^1H$  NMR was consistent with that of the desired product.<sup>71</sup> There was a characteristic doublet at  $\delta_H = 3.15$  ppm with a large coupling constant ( $J_{H,P} = 21.6$  Hz); this signal corresponds to the benzylic protons which couple to the phosphorous atom.

After the phosphonate had been prepared, the Horner-Emmons modification of the Wittig reaction was able to be performed, using sodium hydride as the base, as recommended for benzyl phosphonates (Scheme 22).<sup>72</sup>



**Scheme 22.** Reaction conditions: *NaH* / *DMF*.

The reaction proceeded in moderate yield (57%), to give **86** as a mixture of *E* and *Z* isomers in a ratio of approximately 3:1. High resolution mass spectrometry of the mixture of isomers gave a result consistent with the molecular mass of the desired products. The isomers were inseparable by chromatography, but fractional crystallisation of the mixture (hexane) gave a majority of *E* isomer (>95%) in excellent purity. The identity of pure (*E*)-**86** was confirmed by microanalysis. The low resolution mass spectra of both the mixture and the purified *E* isomer gave a peak at  $m/z$  265, which corresponds to  $M^+$ . The spectra also gave a characteristic peak corresponding to loss of the chlorine atom. The  $^1\text{H}$  NMR spectrum of the two isomeric products showed a number of characteristic signals. The signal corresponding to H(4) is shifted upfield (c.f. for **77**  $\delta_{\text{H}} = 8.78$  ppm; for (*E*)-**86**  $\delta_{\text{H}} = 8.37$  ppm; for (*Z*)-**86**  $\delta_{\text{H}} = 7.94$  ppm). This upfield shift is most likely due to the removal of the anisotropically deshielding carbonyl group. The much larger upfield shift in the *Z* isomer may be due to anisotropy from the  $\pi$  electron cloud of the phenyl group, which could shield H(4), due to the slight skewing of the molecule that might occur in order to fit the phenyl group in this conformation. The  $^1\text{H}$  NMR spectrum of the mixture shows two signals corresponding to H(A) and H(B) for the *Z* isomer and the spectrum of the single isomer shows the two signals corresponding to H(A) and H(B) for the *E* isomer. The coupling constants for these doublets are very characteristic of *E* and *Z* isomers [c.f. for (*E*)-**86**  $J_{\text{A,B}} = 12.4$  Hz; for (*Z*)-**86**  $J_{\text{A,B}} = 16.2$  Hz].

It was thought that the yield of the reaction (57%) might be improved upon by changing the base that was used to form the phosphonate anion. Four bases of differing strength were used in the reaction and the results are shown below in Table 18.

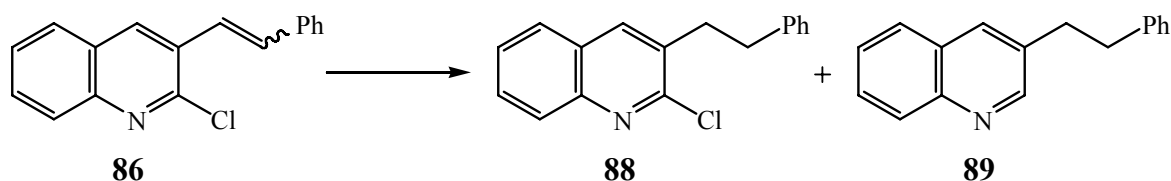
**Table 18.** Yield of **86** obtained using different bases in the Horner-Emmons modification to the Wittig reaction.

Base	Yield of <b>86</b> (%)
NaH	57
KO <sup>t</sup> Bu	-
<i>n</i> -BuLi	35
LDA	-

The reaction using potassium *tert*-butoxide as a base was not successful. There was very little conversion of the starting material to **86** and this was not separated from the reaction mixture. It was therefore apparent that a stronger base was required for the reaction to proceed. The reaction with *n*-butyl lithium proceeded to give the desired product in low yield. It also appeared as though there may be some decomposition occurring at the same time as the reaction. For this reason, a slightly weaker base was trialed, lithium diisopropyl amide. The reaction, however, did not proceed to give the desired product and there were no high yielding products isolated from the reaction mixture. It was thus determined that in this case sodium hydride was the most appropriate base to use for the Horner-Emmons modification to the Wittig reaction.

#### 4.5.3. Synthesis of 3-(2-Phenylethyl)quinolin-2-amine

The first step in the synthesis of 3-(2-phenylethyl)quinolin-2-amine was the reduction of the alkene bond of **86** to give 2-chloro-3-(2-phenylethyl)quinoline, **88** (Scheme 23).

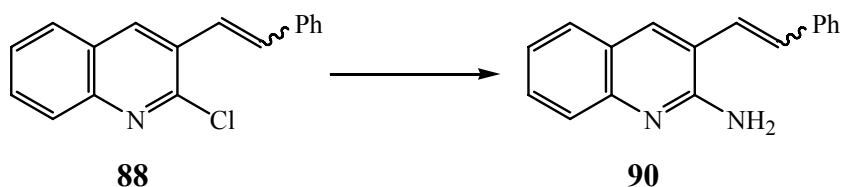


**Scheme 23.** Reaction conditions:  $H_2 / 50 \text{ psi} / Pd-C / EtOH$ .

The reaction proceeded to give the desired product, **88**, in a 2:1 mixture with **86**. These two compounds were unable to be separated, so the product was unable to be characterised. A by-product, the doubly reduced quinoline, **89**, was obtained pure from the reaction in low yield (10%). The high resolution mass spectrum was consistent with the molecular mass of the by-product and the low resolution mass spectrum gave a peak at  $m/z$  233, which corresponds to  $M^+$ . The spectrum also shows a peak at  $m/z$  142, which is consistent with loss of a benzyl radical. The  $^1H$  NMR spectrum of the by-product shows the presence of an

upfield signal due to H(2) ( $\delta_{\text{H}} = 8.79$  ppm). The  $^{13}\text{C}$  NMR spectrum shows a change in the appearance of the peak due to C(2). However there is very little change in the chemical shift of this signal (c.f. for (*E*)-**86**  $\delta_{\text{H}} = 150.21$  ppm; for **89**  $\delta_{\text{H}} = 151.29$ ). The signal corresponding to C(3) is more deshielded (c.f. for (*E*)-**86**  $\delta_{\text{H}} = 130.32$  ppm; for **89**  $\delta_{\text{H}} = 135.22$ ). This may be because the reduction of the double bond has resulted in a loss of a conjugated  $\pi$  system between the quinoline and phenyl ring systems, and therefore a reduction in  $\pi$  electron density around C(3).

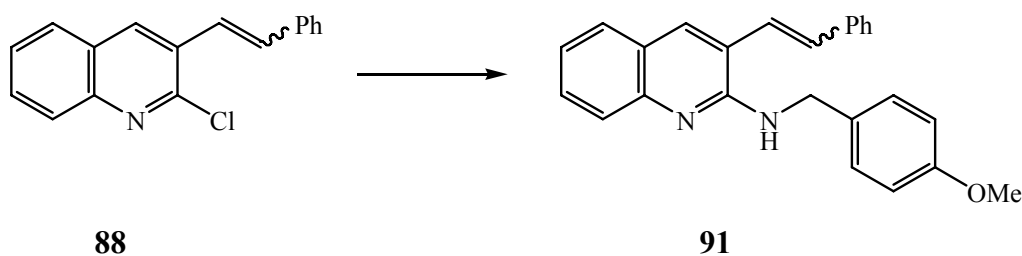
As the reduction of the double bond was not able to be performed using the above method, it was thought that the amination of the 2-position prior to reduction might be more successful. Therefore the Kóródi amination was attempted on **86** (Scheme 24).



**Scheme 24.** Reaction conditions:  $\text{K}_2\text{CO}_3$  / acetamide /  $200^\circ\text{C}$ .

This reaction was performed several times, but on each occasion a large number of products were observed, none of which appeared to be the desired product and no single product predominated. It is possible that the double bond reacted with the acetamide and this caused decomposition of the starting material.

As a result of the previous reactions, it would appear that the synthetic pathway would be best approached by introducing the amino functionality in a protected form that would either stand up to hydrogenation conditions or be cleaved under such conditions to give the free amino group. It was therefore decided that *p*-methoxybenzylamine would be a good choice of protecting group and **91** was prepared using the method outlined in Scheme 25.

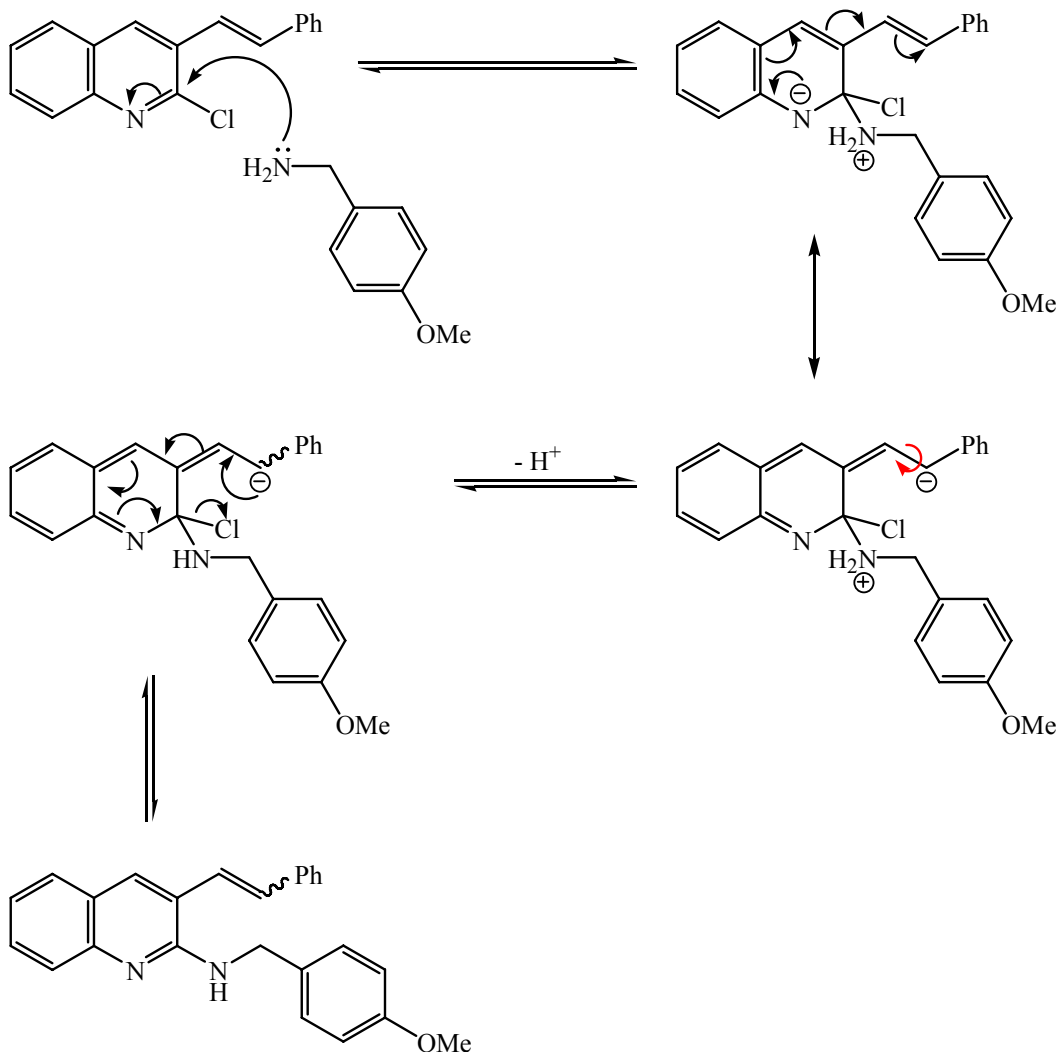


**Scheme 25.** Reaction conditions: *p*-methoxybenzylamine /  $140^\circ\text{C}$ .

This reaction proceeded to give the desired product, **91** as a mixture of *E* and *Z* isomers, in good yield (76%). However the purification of the desired product was difficult as the product streaked on the column whilst using flash chromatography. The addition of triethylamine (0.1%) to the eluting solvent (dichloromethane) minimised the streaking, but it was necessary to repeat the chromatographic procedure several times before a clean product was isolated. A high resolution mass spectrum confirmed that the desired product had been obtained. The low resolution mass spectrum gave a peak at  $m/z$  366, which corresponds to  $M^+$ . A peak at  $m/z$  245, which corresponds to the loss of a *p*-methoxybenzyl radical, was also observed. The IR spectrum of **91** shows two peaks (3688 and 3600  $\text{cm}^{-1}$ ) corresponding to the secondary amino group. The  $^1\text{H}$  NMR spectrum shows a signal corresponding to the methoxy group at  $\delta_{\text{H}} = 3.77$  ppm for (*Z*)-**91** and  $\delta_{\text{H}} = 3.78$  ppm for (*E*)-**91**, as well as a signal at  $\delta_{\text{H}} = 4.62$  ppm for (*E*)-**91** and  $\delta_{\text{H}} = 4.77$  ppm for (*Z*)-**91**, which corresponds to the benzylic protons from the protecting group. There was also a broadened signal at  $\delta_{\text{H}} = 4.95$  ppm for (*E*)-**91** and  $\delta_{\text{H}} = 4.99$  ppm for (*Z*)-**91**, which corresponds to the proton on the secondary amine of the protecting group. The vinylic protons H(A) and H(B) once again show the characteristic coupling constants for *E* and *Z* isomers [c.f. for (*Z*)-**91**  $J_{\text{A,B}} = 12.6$  Hz; for (*E*)-**91**  $J_{\text{A,B}} = 16.2$  Hz]. The  $^{13}\text{C}$  NMR spectrum also shows the presence of the methoxy and benzylic carbons [for (*E*)-**91**  $\delta_{\text{C}} = 55.25$  and 45.30 respectively; for (*Z*)-**91**  $\delta_{\text{C}} = 55.23$  and 45.12 respectively].

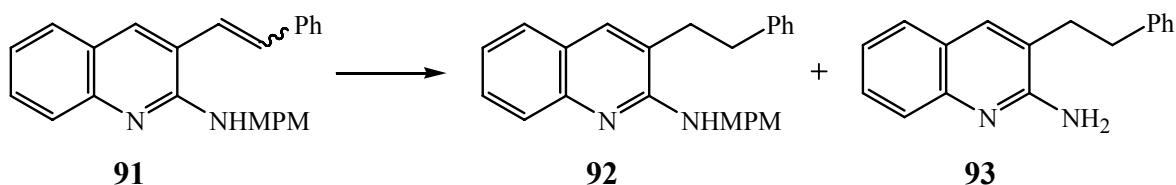
As the *E* and *Z* isomers of **91** were inseparable, in order to prepare an isomerically pure sample of the *E* isomer for characterisation, the above reaction was repeated using the isomerically enriched *E* isomer of **86**, obtained through fractional crystallisation. However upon completion of this reaction, it became apparent that the *Z* isomer was present as well as the *E* isomer, in approximately the same ratio as was obtained for **86** using the Horner-Emmons synthesis. The *p*-methoxybenzylamine must therefore catalyse the isomerisation of the *E* isomer to the *Z* isomer under the experimental conditions. By looking at the reaction mechanism it is easy to see how the isomerisation occurs. The lone pair from the amine attacks **88** at the 2-position to give an intermediate with a negative charge on the quinoyl nitrogen. This negative charge can be delocalised through resonance onto the double bond, which then allows for bond rotation to occur. When the chlorine atom leaves the molecule, the double bond can then reform to give either the *E* or *Z* isomer (Figure 54).





**Figure 54.** The mechanism of *para*-methoxybenzylamine attack that catalyses the isomerisation of the *E* isomer to *Z* isomer.

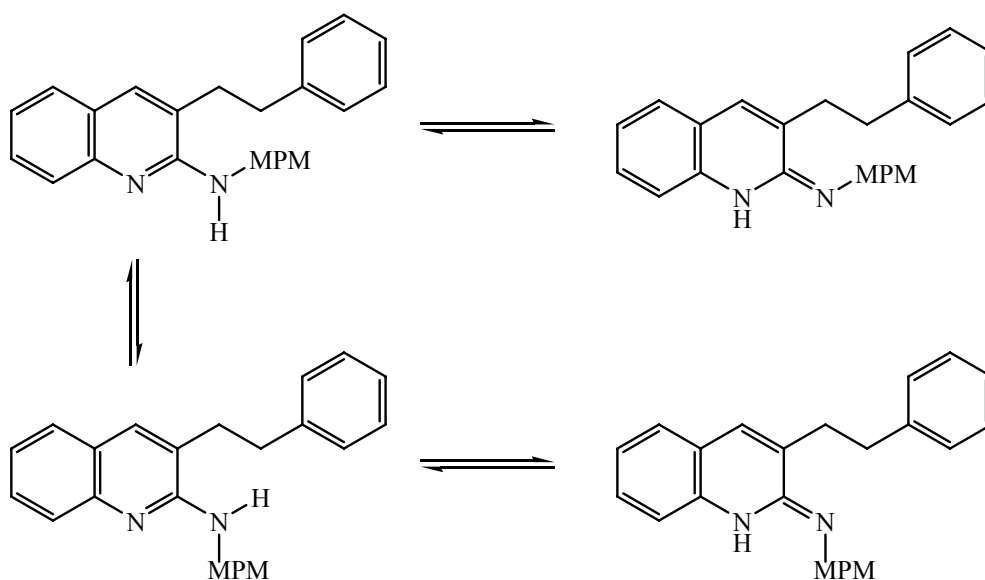
Now that the protected quinoline had been prepared, a hydrogenation could be attempted. It was considered a possibility that the hydrogenation might also cause the protecting group to be removed to leave the reduced 2-aminoquinoline ligand (Scheme 26).



**Scheme 26.** Reaction conditions: *Acetyl Chloride / MeOH / H<sub>2</sub> / 1 atm / Pd-C*.

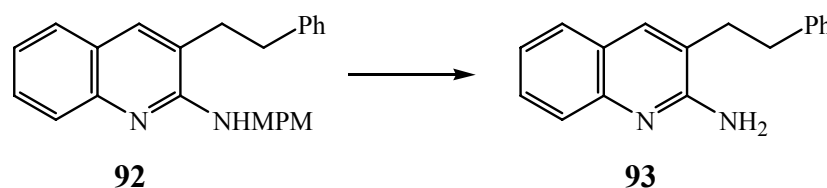
The reaction proceeded to give the reduced, but not deprotected product, **92**, in high yield (80%). There was no evidence for the formation of the deprotected product, **93**, in the reaction mixture after work up. High resolution mass spectroscopy was used to confirm that

**92** had been obtained. The low resolution mass spectrum gave a peak corresponding to  $M^{+}$  at  $m/z$  368 and also a peak that corresponds to the loss of a *p*-methoxy benzyl radical ( $m/z$  247). The  $^1\text{H}$  NMR showed the disappearance of the vinylic signals for both the *E* and *Z* isomers. Instead there are two signals at  $\delta_{\text{H}} = 2.78\text{-}2.80$  ppm and  $2.99\text{-}3.02$  ppm that correspond to the two  $\text{CH}_2$  groups. The signal at H(4) shifts upfield slightly [c.f. for **92**  $\delta_{\text{H}} = 7.60$  ppm; for (*Z*)-**91**  $\delta_{\text{H}} = 7.68$  ppm; for (*E*)-**91**  $\delta_{\text{H}} = 7.90$  ppm]. This is probably due to anisotropic effects. In the  $^{13}\text{C}$  NMR spectrum for **92** the signal for C(1') appears more downfield [c.f. for **92**  $\delta_{\text{C}} = 140.96$  ppm; for (*Z*)-**91**  $\delta_{\text{C}} = 131.96$  ppm; for (*E*)-**91**  $\delta_{\text{C}} = 136.73$  ppm]. The  $^{13}\text{C}$  NMR spectrum also shows the presence of two signals at  $\delta_{\text{C}} = 32.69$  ppm and  $34.36$  which correspond to the two new  $\text{CH}_2$  groups. Again the signal corresponding to C(8a) is significantly broadened in the  $^{13}\text{C}$  NMR spectrum. This could once again be due to the tautomerism that could occur with the amino nitrogen, in a similar fashion to the tautomerism that occurs in **27** (Figure 55).



**Figure 55.** The tautomerism that occurs to cause the line broadening of C(8a) in the  $^{13}\text{C}$  spectrum of **92**.

The final step in the synthesis of 3-(2-phenylethyl)quinolin-2-amine was the deprotection of the *p*-methoxybenzylamine group to give the primary amine in the 2-position (Scheme 27).



**Scheme 27.** Reaction conditions:  $\text{CF}_3\text{COOH}$ .

The desired product, **93**, was obtained in high yield (86%). The molecular mass of the final product was consistent with the result obtained by high resolution mass spectrometry. The low resolution mass spectrum gave a peak corresponding to  $M^{+}$  ( $m/z$  248) and also a peak at  $m/z$  157, which is consistent with loss of a benzyl radical. The  $^1\text{H}$  NMR spectrum showed the disappearance of all the peaks related to the *p*-methoxybenzyl group. The spectrum also showed the presence of two broadened peaks that correspond to the  $\text{NH}_2$  group ( $\delta_{\text{H}} = 3.77$  and 6.19 ppm). There were also a number of changes in the  $^{13}\text{C}$  NMR spectrum upon conversion of **92** to **93** (Table 19).

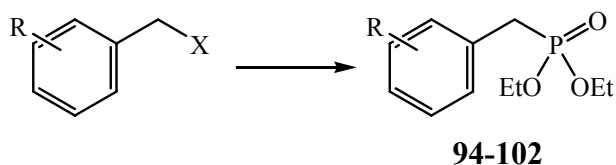
**Table 19.** Significant changes of chemical shift ( $\delta$ , ppm) in the  $^{13}\text{C}$  NMR spectrum upon conversion of **92** to **93**.

C	$\delta_{\text{C}}$ ( <b>92</b> )	$\delta_{\text{C}}$ ( <b>93</b> )
4	134.47	140.58
4a	123.73	121.15
6	122.07	125.29
7	128.61	132.09
8	126.10	118.16
8a	146.80	135.89

Three signals; C(4a), C(8) and C(8a), undergo an upfield shift. The remaining three signals; C(4), C(6), and C(7), undergo a downfield shift. The change in chemical shift for the signals corresponding to C(4), C(8) and C(8a) are quite large ( $>5$  ppm). The change in chemical shift could be attributed to the lack of intermediate exchange in the final product, **93**. There is no broadening in the  $^{13}\text{C}$  NMR of **93** which indicates that there is either no tautomerism occurring or there is rapid interconversion between tautomers, whereas tautomerism is occurring relatively slowly for **92**. This particularly affects C(8a) whose signal shows considerable line broadening in the  $^{13}\text{C}$  NMR of **92**.

#### 4.5.4. Synthesis of Further 3-(2-Phenylethyl)quinolin-2-amine Derivatives

Now that the pathway for the synthesis of 3-(2-phenylethyl)quinolin-2-amine had been established, further ligands of this variety could be prepared using substituted phosphonates. These were prepared through the Michaelis-Arburzov rearrangement with substituted benzyl bromides (Scheme 28).<sup>70, 71</sup>

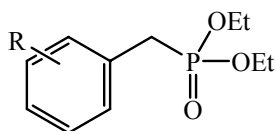


	<b>94</b>	<b>95</b>	<b>96</b>	<b>97</b>	<b>98</b>	<b>99</b>	<b>100</b>	<b>101</b>	<b>102</b>
R =	4-Me	3-Me	2-Me	4- <sup>t</sup> Bu	4-F	3-F	2-F	4-Br	3-Br
X =	Br	Br	Br	Br	Br	Br	Cl	Br	Br

**Scheme 28.** Reaction conditions: *triethylphosphite*.

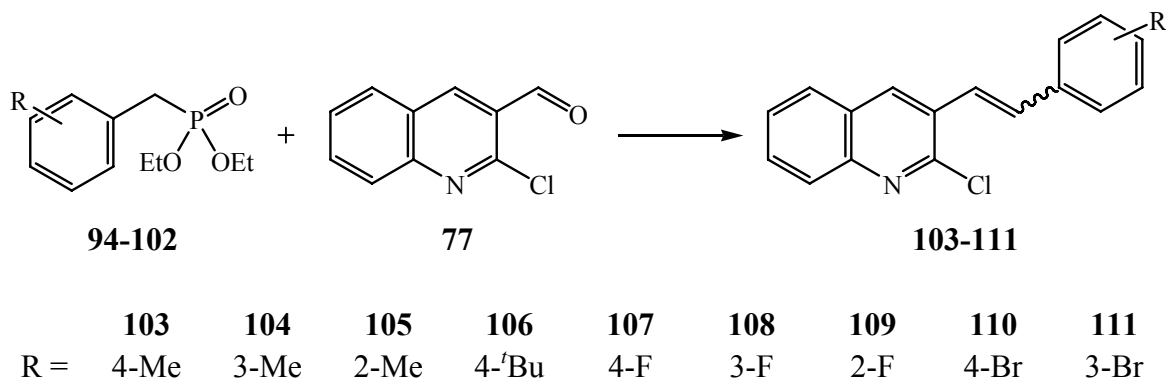
The reactions proceeded to give the desired products in high yield. The <sup>1</sup>H NMR spectra of the reaction products were consistent with that of the desired products. Each of the spectra contained a signal corresponding to the benzylic protons with a large coupling constant, consistent with a proton coupling to an adjacent phosphorus atom (Table 20).

**Table 20.** The details of the benzylic protons from the <sup>1</sup>H NMR spectra of the substituted benzylphosphonates **94-102**.



R		$\delta_{\text{H}}$ (ppm)	$J_{\text{H,P}}$ (Hz)
4-Me	<b>94</b>	3.11	21.4
3-Me	<b>95</b>	3.12	21.6
2-Me	<b>96</b>	3.17	21.9
4- <sup>t</sup> Bu	<b>97</b>	3.12	21.3
4-F	<b>98</b>	3.12	21.2
3-F	<b>99</b>	3.14	21.8
2-F	<b>100</b>	3.21	21.6
3-Br	<b>101</b>	3.09	21.6
2-Br	<b>102</b>	3.11	21.8

The crude phosphonates were then used without further purification in the Horner-Emmons reaction to give the substituted 2-chloro-3-(2-phenylvinyl)quinolines (Scheme 29).



**Scheme 29.** Reaction conditions: *NaH* / *DMF*.

The desired products were obtained from the reactions in moderate yields (32-60%) and high purity. The identity of each of the final products was confirmed by high resolution mass spectroscopy and/or microanalysis. The low resolution mass spectrum gave a peak corresponding to  $M^+$  for each of the final products as well as fragmentation that is consistent with loss of a chlorine radical (Table 21). The mass spectra of **110** and **111** also contain a fragmentation corresponding to loss of bromine ( $m/z$  229).

**Table 21.** The  $M^+$  and first fragmentation from the low resolution mass spectra of **104-111**.

R		$M^+$	$[M - Cl]^+$
Me	<b>103-105</b>	281 / 279	244
<sup>t</sup> Bu	<b>106</b>	323 / 321	306
F	<b>107-109</b>	285 / 283	248
Br	<b>110, 111</b>	347 / 345 / 343	310 / 308

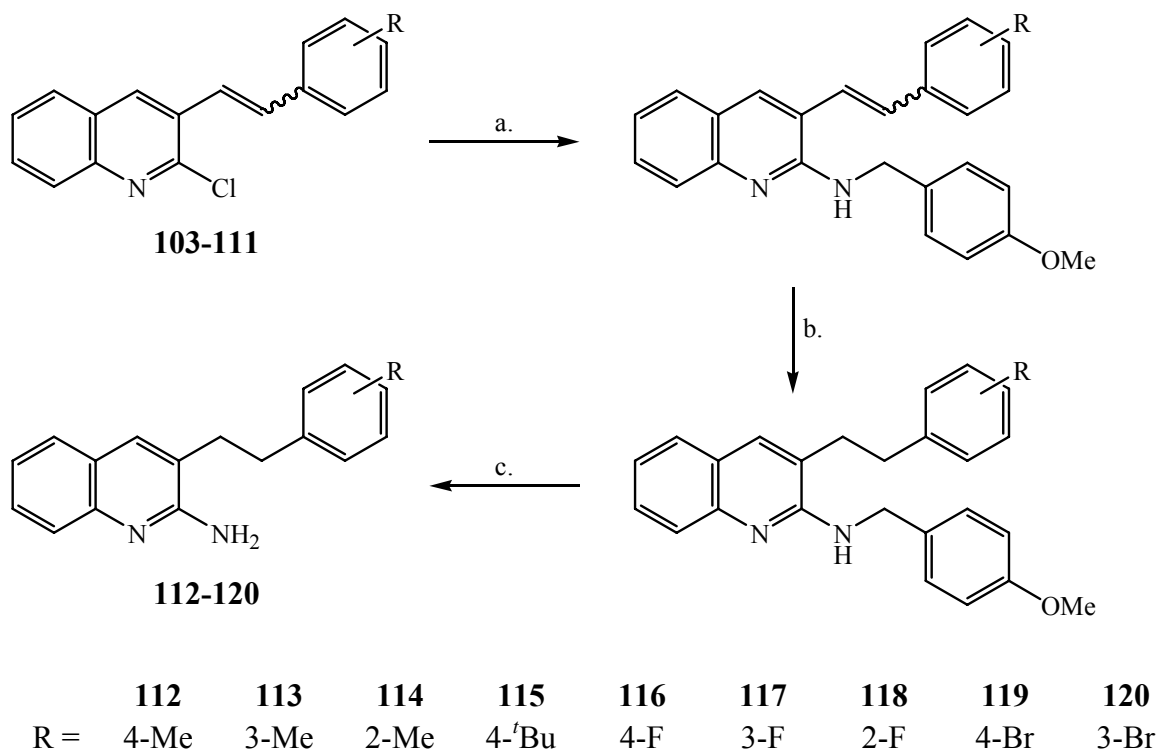
Due to the mixture of isomers in each of the products, it was difficult to fully assign both the  $^1H$  and  $^{13}C$  NMR spectra. Nevertheless, full assignments have been made where possible. The  $^1H$  NMR spectra of the final products showed in each case the presence of both the *E* and *Z* isomer in about a 3:1 ratio. The signals corresponding to H(A) and H(B) in each of the products have the characteristic *E* and *Z* coupling constants (for the *E* isomer, ~16 Hz; for the *Z* isomer, ~12 Hz).

Once again the chemical shift of H(4) in these derivatives has moved upfield in comparison to **77** (Table 22). The chemical shifts for H(4) are similar to those for **86** and the reason for the change in chemical shift would be the same.

**Table 22.** Comparison of chemical shifts for H(4) ( $\delta$ , ppm) between **77** and the 2-chloro-3-(2-phenylvinyl)quinolines **86** and **103-111**.

77		$\delta_{H(4)}$	
		8.78	
R		$\delta_{H(4)}$ (E)	$\delta_{H(4)}$ (Z)
H	<b>86</b>	8.37	7.94
4-Me	<b>103</b>	8.36	7.98-8.00
3-Me	<b>104</b>	8.38	7.97
2-Me	<b>105</b>	8.36	7.67-7.71
4- <sup>t</sup> Bu	<b>106</b>	8.37	7.99-8.02
4-F	<b>107</b>	8.36	7.93
3-F	<b>108</b>	8.36	7.92
2-F	<b>109</b>	8.42	7.86-7.89
4-Br	<b>110</b>	8.36	7.91
3-Br	<b>111</b>	8.37	7.92

The addition of the *p*-methoxybenzylamine protecting group followed next. As it was difficult to purify the protected parent compound **92** and the corresponding reduced species, **93**, the substituted derivatives were carried through to the final ligand species without isolation and purification between steps (Scheme 30).



**Scheme 30.** Reaction conditions: a. *p*-methoxybenzylamine; b. Acetyl Chloride / MeOH / H<sub>2</sub> / Pd-C; c. CF<sub>3</sub>COOH.

The reactions to produce **112-118** proceeded in varying yields over three steps (24-78%). The identity of each of these final products was confirmed by high resolution mass spectroscopy and/or microanalysis. The low resolution mass spectra for **112-118** showed a peak corresponding to  $M^{+\bullet}$  followed by a fragmentation at  $m/z$  157 due to loss of the substituted benzyl radical. The  $^1\text{H}$  NMR spectra for each of the compounds **112-118** gave a broadened signal corresponding to the  $\text{NH}_2$  group. The  $^1\text{H}$  NMR spectra no longer showed signals corresponding to the vinylic protons, but instead showed the appearance of signals due to the protons of the ethylene linker, in the region  $\delta_{\text{H}} = 2.79 - 3.05$  ppm.

The signal corresponding to H(4) for each of the products, **112-118**, underwent an upfield change in chemical shift (Table 23). This is due to the loss of conjugation between the phenyl group and the quinoline ring.

**Table 23.** Comparison of chemical shifts for H(4) ( $\delta$ , ppm) between the phenylvinyl compounds, **103-109** and the phenylethyl compounds, **112-118**.

Phenylvinyl Compounds		Phenylethyl Compounds			
R		$\delta_{\text{H}(4)} (E)$	$\delta_{\text{H}(4)} (Z)$		$\delta_{\text{H}(4)}$
4-Me	<b>103</b>	8.36	7.98-8.00	<b>112</b>	7.64-7.67
3-Me	<b>104</b>	8.38	7.97	<b>113</b>	7.66
2-Me	<b>105</b>	8.36	7.67-7.71	<b>114</b>	7.65-7.68
4- $t$ Bu	<b>106</b>	8.37	7.99-8.02	<b>115</b>	7.65-7.67
4-F	<b>107</b>	8.36	7.93	<b>116</b>	7.61
3-F	<b>108</b>	8.36	7.92	<b>117</b>	7.59
2-F	<b>109</b>	8.42	7.86-7.89	<b>118</b>	7.72

The phenyl carbons for the *para* substituted products show significant changes in chemical shift when the substituent is changed (Table 24).

**Table 24.** Comparison of chemical shifts for the phenyl carbons in the *para* substituted products, **103**, **106** and **107** and the parent compound, **93**.

R		$\delta_{\text{C}} [\text{C}(4')]$	$\delta_{\text{C}} [\text{C}(3') + \text{C}(5')]$	$\delta_{\text{C}} [\text{C}(2') + \text{C}(6')]$	$\delta_{\text{C}} [\text{C}(1')]$
H	<b>93</b>	126.87	128.86	128.38	139.30
Me	<b>112</b>	135.98	129.44	128.39	137.97
$t$ Bu	<b>115</b>	146.47	125.67	128.19	138.03
F	<b>116</b>	161.71	115.58	130.01	136.37

The signals corresponding to C(1'), C(2') and C(6') are virtually unaffected by the change in substituent as there are only small variations in chemical shift. However the signals due to C(4'), C(3') and C(5') undergo quite large chemical shift changes in some instances. In regards to the methyl substituted compound, **112**, there is a downfield change in chemical shift for C(4') relative to **93**, but very little change is observed in the chemical shift of the signal responsible for C(3') and C(5'). A larger downfield change in chemical shift is observed for C(4') in the spectrum of the compound with the *tert*-butyl group in the 4-position, **115**, and an even larger change in chemical shift is observed for the fluoro-substituted compound, **116** (~35 ppm). The large downfield shift for **116** is observed because of the introduction of an electron withdrawing group directly adjacent to this carbon. The signal corresponding to C(3') and C(5') undergoes an upfield change in chemical shift, relative to **93**, upon introduction of the inductively withdrawing fluorine group. However, fluorine has a lone pair of electrons that are able to donate back into the aromatic ring, so these carbons will be shielded through resonance.

The reactions of the bromo-substituted 2-chloro-3-(2-phenylvinyl)quinolines did not give the desired products, but instead gave unknown products **121** and **122**. The <sup>1</sup>H NMR spectra of the products appeared to be of the same compound. The high resolution mass spectra of these two unknown products both had the same exact mass as each other, which also matched the exact mass of the unsubstituted 3-(2-phenylethyl)quinolin-2-amine, **93**. The electron impact low resolution mass spectrum also gave a peak at *m/z* 248, which corresponds to the mass of the parent compound, and also a fragmentation peak at *m/z* 157 that is consistent with the loss of a benzyl radical. A softer ionisation method, LSI, was used to obtain the mass spectra for each of the unknown products, but these gave a peak at *m/z* 249 which corresponds to [M+H]<sup>+</sup> and there was no sign of a higher molecular weight ion. Both mass spectra also showed that there was no bromine present in the products as there were no isotope peaks.

The <sup>1</sup>H NMR spectrum of each of the unknown products, **121** and **122**, contains signals that correspond almost identically with the chemical shifts of H(2') – H(6') in the spectrum of **93** (Table 25). This would appear to indicate that the phenyl ring no longer contains a substituent and this in turn supports the evidence from the mass spectra that there is no longer any bromine atom present in the products.



**Table 25.** Comparison of the chemical shifts ( $\delta$ , ppm) of the phenyl protons in the  $^1\text{H}$  NMR spectra of **93** and unknowns **121** and **122**.

	<b>93</b>	<b>121</b>	<b>122</b>
$\delta_{\text{H}}$ [H(2') + H(6')]	7.17	7.19	7.20
$\delta_{\text{H}}$ [H(3') + H(5')]	7.31	7.29-7.34	7.28
$\delta_{\text{H}}$ [H(4')]	7.24	7.24	7.23

The  $^{13}\text{C}$  NMR spectra also supported the proposal that the bromine substituents had been lost from the phenyl ring. These spectra showed that the signals corresponding to the carbons in the phenyl groups of the two unknowns, **121** and **122**, were all relatively similar and also corresponded to those of the parent compound, **93** (Table 26).

**Table 26.** Comparison of the chemical shifts ( $\delta$ , ppm) of the phenyl carbons in the  $^{13}\text{C}$  NMR spectra of **93** and unknowns **121** and **122**.

	<b>93</b>	<b>121</b>	<b>122</b>
$\delta_{\text{C}}$ [C(1')]	139.30	140.12	140.53
$\delta_{\text{C}}$ [C(2') + C(6')]	128.38	128.38	128.38
$\delta_{\text{C}}$ [C(3') + C(5')]	128.86	128.76	128.67
$\delta_{\text{C}}$ [C(4')]	126.87	126.63	126.46

Despite the similarities in chemical shifts for the phenyl carbons, the signals corresponding to the quinolyl carbons did not seem to correspond very closely at all. There were a number of signals that underwent quite a large change in chemical shift. However these signals corresponded to carbons whose respective signals are quite variable between spectra of other 3-(2-phenylethyl)quinolin-2-amines (Table 27). For example, the chemical shift of C(8a) varies between 149.40 ppm for **115** and 135.89 for **93**, which is a dramatic difference in chemical shift of almost 15 ppm. The chemical shift of C(4) also varies substantially with a difference in chemical shift of around 5 ppm. C(4a) and C(6), however, do not appear to vary a great deal, with one or two exceptions. This variation in chemical shift may be attributable to differing trace amounts of residual TFA from the deprotection reaction.

**Table 27.** Comparison of chemical shifts for the quinolyl carbons in the complex 3-substituted ligands.

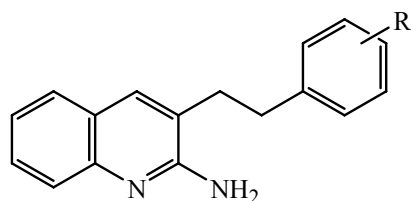
	$\delta_C$ [C(4)]	$\delta_C$ [C(4a)]	$\delta_C$ [C(6)]	$\delta_C$ [C(7)]	$\delta_C$ [C(8)]	$\delta_C$ [C(8a)]
<b>93</b>	140.58	121.15	125.29	132.09	118.16	135.89
<b>121</b>	138.09	122.87	123.95	130.49	122.04	141.50
<b>122</b>	136.81	123.03	123.67	129.65	123.87	144.20
<b>112</b>	135.73	123.13	122.70	129.05	125.53	146.52
<b>113</b>	135.75	122.96	122.72	129.16	125.37	146.18
<b>114</b>	135.94	123.21	122.92	129.24	125.49	146.31
<b>115</b>	135.70	124.50	122.77	129.10	125.53	149.40
<b>116</b>	136.92	123.86	123.40	129.82	124.18	144.49
<b>117</b>	136.74	123.70	123.33	129.79	123.89	144.25
<b>118</b>	137.62	123.28	123.62	130.15	122.91	142.86

The evidence would appear to indicate that the bromine is no longer present on the phenyl ring and there is, in fact, no substituent present on the phenylethyl group at all. As a result, these two unknown products must be equivalent to **93**. It is proposed that the bromine atoms were removed from the products during the hydrogenation step. A  $^{13}\text{C}$  NMR spectrum of a mixture of **93** and **121** showed that only one compound was present and thus confirmed that the bromine atom had been removed.

#### **4.6 Binding Data for the More Complex 3-Substituted 2-Aminoquinoline Ligands**

The binding affinity of each of the complex 3-substituted ligands was determined using the [ $^1\text{H}$ ,  $^{15}\text{N}$ ] HSQC chemical shift perturbation assay. All the ligands prepared bound to the Tec SH3 domain with equal or greater affinity than the lead compound, **2** (Table 28).

**Table 28.** The binding data for the complex 3-substituted 2-aminoquinolines.



R =		$K_d$ ( $\mu\text{M}$ )
H	<b>93</b>	$128 \pm 8$
2-F	<b>118</b>	$95 \pm 17$
3-F	<b>117</b>	$134 \pm 8$
4-F	<b>116</b>	$75 \pm 16$
2-Me	<b>114</b>	$130 \pm 3$
3-Me	<b>113</b>	$84 \pm 5$
4-Me	<b>112</b>	$74 \pm 14$
4- <i>t</i> Bu	<b>115</b>	$40 \pm 7$

The unsubstituted 3-(2-phenylethyl)quinolin-2-amine ligand, **93**, binds to the Tec SH3 domain with approximately the same affinity as **2**. This suggests that the phenylethyl group is not making further contact with the protein surface.

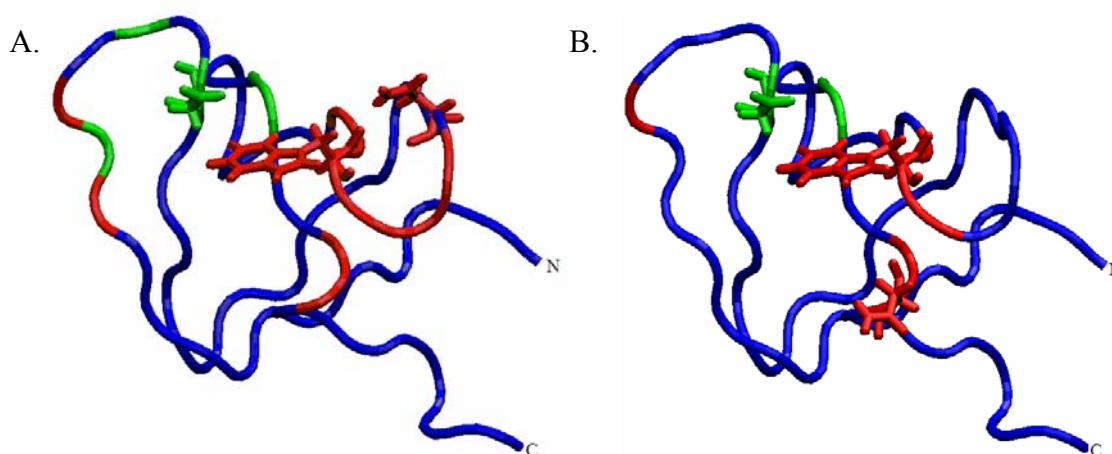
The fluorophenyl substituted ligand, **117**, binds to the Tec SH3 domain in approximately the same affinity as the lead compound, **2**. However, it would appear as though an electron withdrawing group is preferred in the 2- or 4- position of the phenyl group. The 2- and 4-fluoro substituted ligands bind with slightly higher affinities than both **2** and **117**, with equilibrium dissociation binding constants of around 95 and 75  $\mu\text{M}$  respectively.

The 2-methylphenyl compound, **114**, also binds to the Tec SH3 domain in around the same binding affinity as **2** and **93**. The binding affinity of the 3-methyl ligand, **113**, is slightly improved and the 4-methyl ligand, **112**, is improved beyond that ( $K_d = 84$  and  $74 \mu\text{M}$  respectively). The 4-*tert*-butyl substituted ligand, **115**, binds with the greatest affinity of all the 3-substituted ligands. However this ligand does enter into intermediate exchange with the protein, and the results from the 6-substituted ligands in the previous chapter suggest that when a ligand enters into intermediate exchange during the chemical shift perturbation assay, the resulting  $K_d$  is underestimated. Thus the  $K_d$  of **115** may be lower and therefore **115** could bind to the Tec SH3 domain with higher affinity than the  $K_d$  indicates. These results suggest that a bulky group *para* to the ethyl linker on the phenyl ring is desirable. It

is proposed that this large hydrophobic group is making an additional hydrophobic contact with the protein surface.

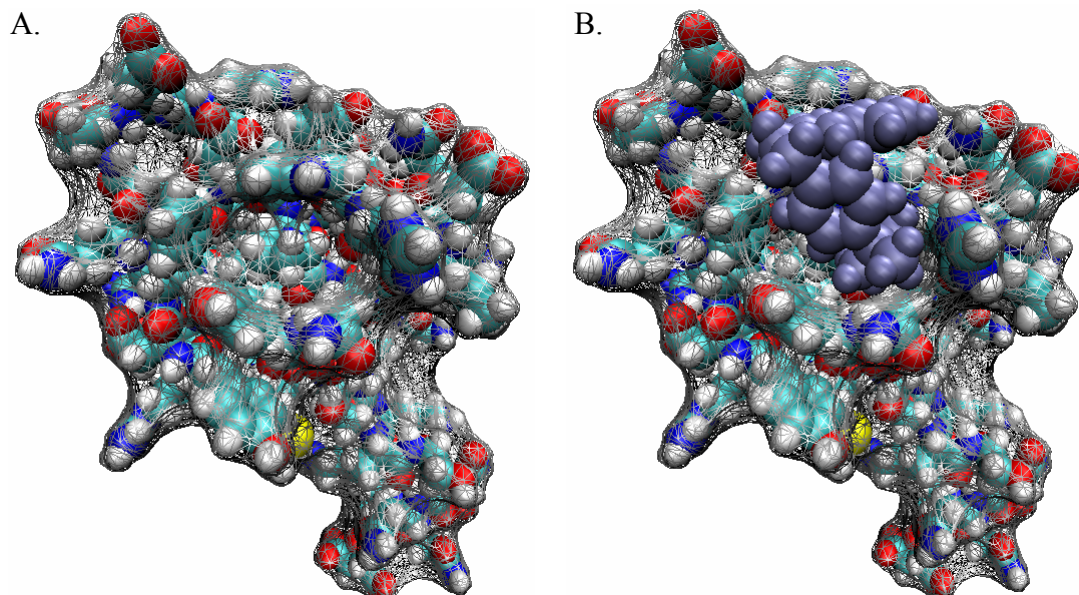
#### 4.6.1. Chemical Shift Mapping

The residues that underwent significant changes in chemical shift upon addition of the complex 3-substituted ligands ( $> \sim 0.1$  ppm at saturation) were mapped onto the protein surface and compared with the map from the 6-substituted ligands (Figure 56). This was carried out in order to see if there were any new residues involved in the binding of the 3-substituted ligands.



**Figure 56.** Chemical shift mapping of the backbone of the Tec SH3 domain with A. the 6-substituted ligands and B. the complex 3-substituted ligands where  $\delta_H > \sim 0.1$  ppm for a number of the ligands. Downfield shifts are marked in green and upfield shifts are marked in red.

It is apparent from these figures that there are fewer residues that shift during the assay of the 3-substituted ligands. There is, however, one residue that appears to shift during the assay of the 3-substituted ligands but does not in the assay of the 6-substituted ligands. This is the side chain of N231. From the figure above it can be seen that this side chain is underneath the W215 side chain. In order for the 3-substituent to interact with the N231 side chain, it must bend around underneath the tryptophan side chain. It can be seen in Figure 57 that there is a shallow indentation below the tryptophan residue that the phenethyl group might fit into.

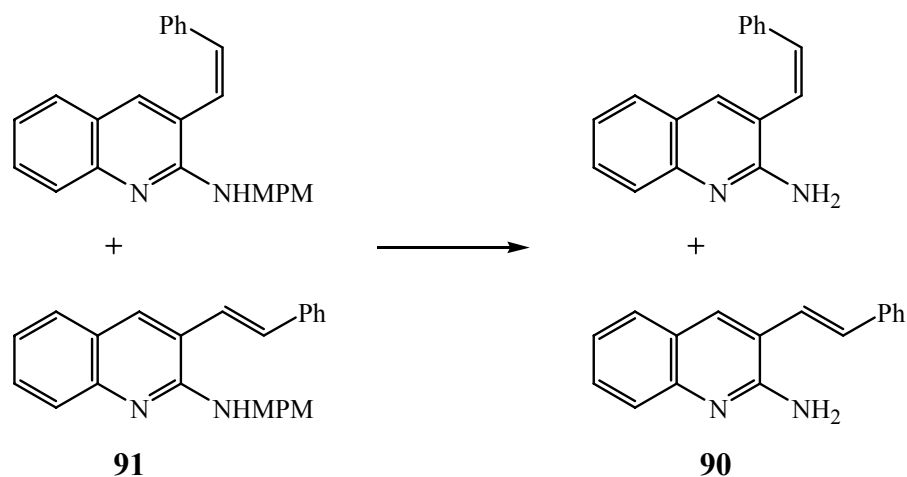


**Figure 57.** A. A graphical representation of the protein surface showing the indentation below W215; B. **115** superimposed on the protein surface to illustrate a possible method of binding.

It is also possible that this is a transferred effect, so the interaction of the ligand with surrounding residues is causing a change in the chemical environment of the sidechain of N231.

#### 4.7 Synthesis of Further Complex 3-Substituted Ligands

An intermediate in the synthesis of 3-(2-phenylethyl)quinolin-2-amine was the protected phenylvinyl species, **91**, that was isolated as a mixture of *E* and *Z* isomers. This intermediate was originally reduced to remove the double bond and then deprotected to give the desired product, **93**. However, **91** could be deprotected at this stage in order to give **90** as a mixture of *E/Z* phenylvinyl 2-aminoquinolines (Scheme 31).



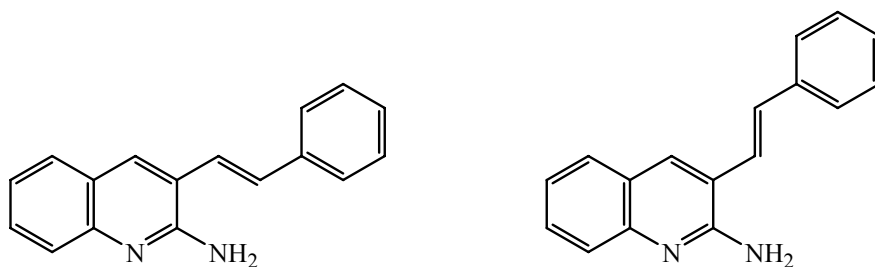
**Scheme 31.** Reaction conditions:  $CF_3COOH$ .

The reaction proceeded to give the desired products, *E*-**90** and *Z*-**90**, in good yield (60%), in a ratio of approximately 5:1. These were unable to be separated through chromatographic methods or fractional crystallisation. The addition of iodine to a solution of the isomers was also unable to change the ratio. However a sample of the product was left in sunlight for several months and, when analysed, was found to have isomerised to >95% *E* isomer. The identity of this product, *E*-**90**, was confirmed by microanalysis and high resolution mass spectrometry gave a result that was consistent with the molecular mass of the desired product. The low resolution mass spectrum of *E*-**90** gave a peak corresponding to  $M^{+\bullet}$  at  $m/z$  246. However it also gave a large peak corresponding to a loss of  $H^{\bullet}$ . A softer ionisation technique, LSI mass spectroscopy, was then used to obtain a mass spectrum. This gave a peak corresponding to  $[MH]^{+\bullet}$  at  $m/z$  247. The  $^1H$  NMR gave a broadened signal at  $\delta_H = 5.33$  ppm, which corresponds to an  $NH_2$  group. This indicates that the deprotection was successful. The signals due to the vinyl protons have a characteristic *E* coupling constant ( $J_{A,B} = 16.2$  Hz).

#### 4.8 Binding Data for Remaining 3-Substituted Ligand

The binding affinity of *N*-(4-methoxybenzyl)-3-[(*E*)-2-phenylvinyl]quinolin-2-amine, *E*-**90** could now be determined using the [ $^1H, ^{15}N$ ] HSQC NMR assay. The *E* isomer binds to the Tec SH3 domain with 4-fold lower affinity than the lead compound, **2** ( $K_d = 410 \pm 20 \mu M$ ). This indicates that the conjugation with the phenyl group is unfavourable. It is possible that the conjugation is withdrawing electron density from the quinoline ring and therefore reducing the ability of the ligand to make the salt bridge with D196 and  $\pi$ - $\pi$  stack with W215. However it is more likely reduction in binding affinity is due to the rigidity that the conjugation gives the ligand. Two conformations are able to be adopted by *E*-**90** (Figure 58)

and in either of these conformations, the substituent may either face away from the protein surface, thereby not improving affinity or it may interfere with the protein backbone, thus reducing the affinity.



**Figure 58.** The two conformations that the *E* isomer of **90** may take.

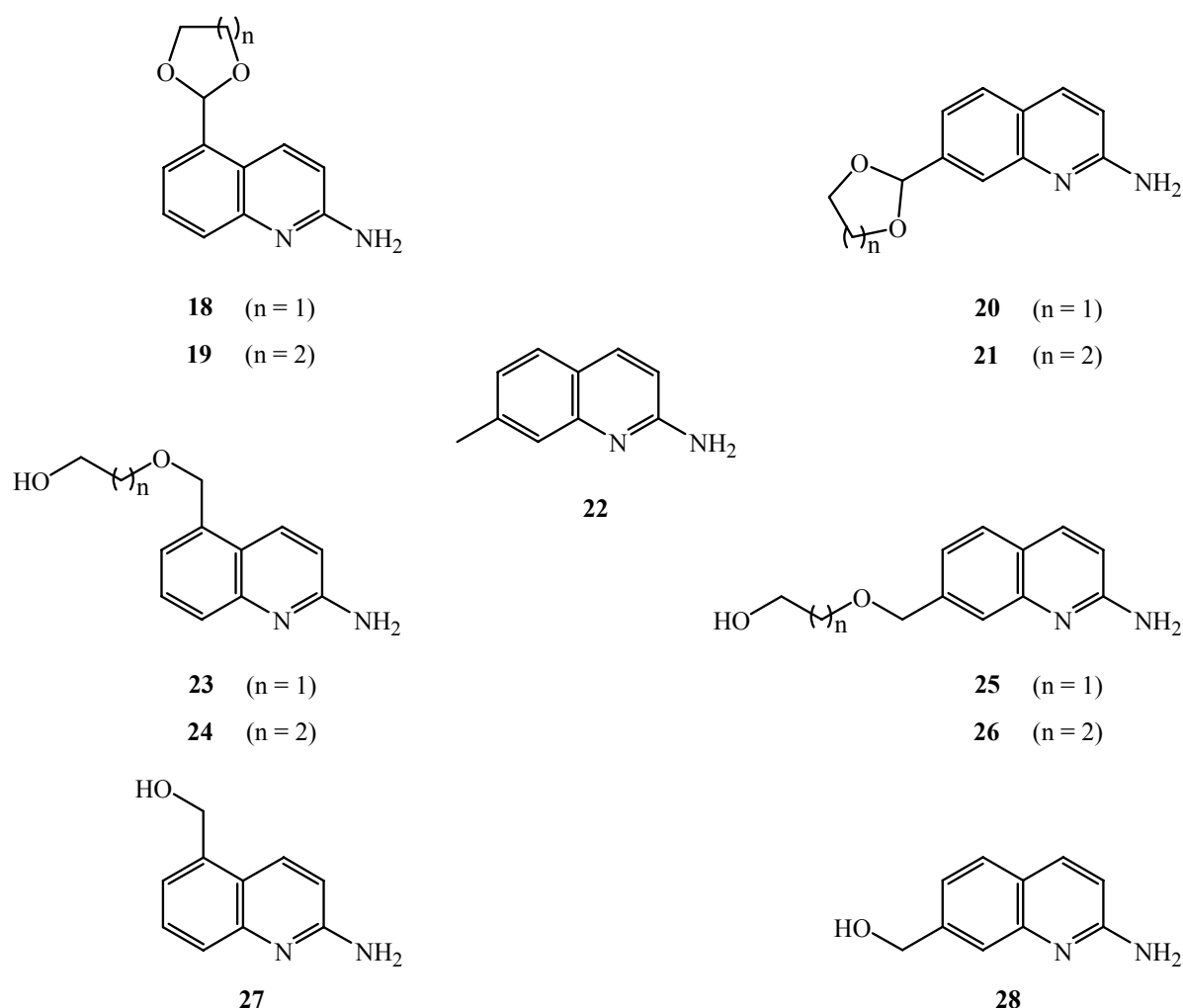
# Chapter 5.

## CONCLUSIONS AND FUTURE DIRECTIONS

### 5.1 The 5- and 7- Positions of 2-Aminoquinoline

#### 5.1.1. Summary and Conclusions

The two 5- and 7-substituted 2-aminoquinoline ligands, **27** and **28**, were successfully prepared using previously established methods.<sup>50</sup> These and other previously prepared 7-substituted ligands (Figure 59) were assayed for binding activity using a [<sup>1</sup>H,<sup>15</sup>N] HSQC chemical shift perturbation assay.



**Figure 59.** The 5- and 7-substituted ligands that were assayed for binding affinity to the Tec SH3 domain.



All of the 7-substituted ligands, **20-22**, **25**, **26** and **28**, were found to bind to the SH3 domain, but with lesser affinity than the lead compound 2-aminoquinoline, **2**. This indicates that a substituent in the 7-position is not tolerated in the binding site. The substituent might be too bulky and therefore not allow the 2-aminoquinoline portion of the ligand to sit in the position that would allow it to make the most effective  $\pi$ - $\pi$  stack and salt bridge with the protein.

The newly synthesised 5-substituted ligand, **27**, bound to the SH3 domain in greater affinity than the previously assayed ligands, which all bound with similar affinity to 2-aminoquinoline. The slight improvement in affinity could be due to a weak hydrogen bond, as the new ligand has the ability to be a hydrogen bond donor, whereas the previous ligands do not have this ability.

The preparation and assay of ligands with substituents in the 5- and 7-position of 2-aminoquinoline has provided some important information about the binding site of the Tec SH3 domain. However no great improvement in binding affinity has been made with any of these ligands. Therefore the study of ligands containing 5- and 7- substitutions does not need to be pursued further.

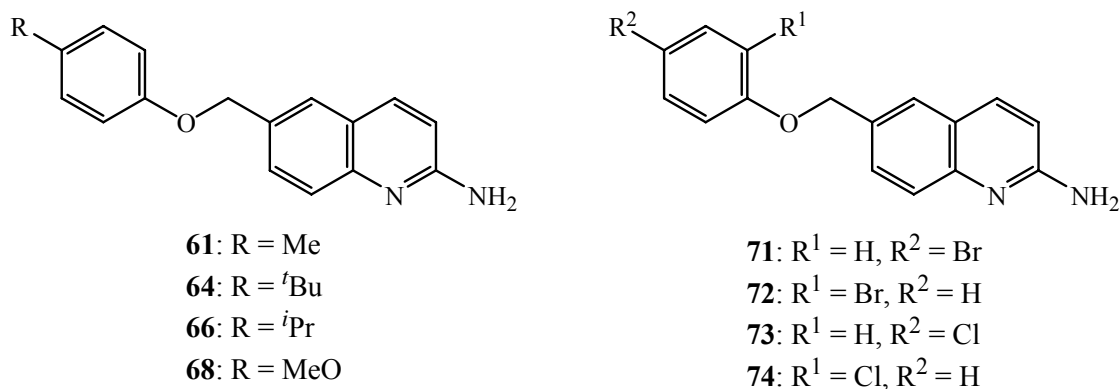
## **5.2 The 6-Position of 2-Aminoquinoline**

### **5.2.1. Summary and Conclusions**

A number of ligands containing a substituted phoxymethyl derivative in the 6-position of **2** were successfully prepared. The [ $^1\text{H}$ ,  $^{15}\text{N}$ ] HSQC chemical shift perturbation assay was used to determine the binding affinity of these ligands for the Tec SH3 domain. All of the prepared ligands bound to the SH3 domain with greater affinity than the lead compound **2**. All of the ligands also entered into intermediate exchange with the protein on the NMR timescale, which caused difficulties with the assay and the resulting binding data. Despite these problems, it would appear that many of these 6-substituted ligands bind with greater affinity than any previously prepared ligand. The ligand with the greatest binding affinity was **73** ( $K_d = 9 \mu\text{M}$ ), with a 13-fold reduction in dissociation constant relative to the lead compound, **2** (Figure 60).

There seems to be a pattern in the binding affinity of the 6-substituted ligands prepared. The ligands with a substituent in the 4-position of the phoxymethyl group (e.g. **61**, **64**, **66** and

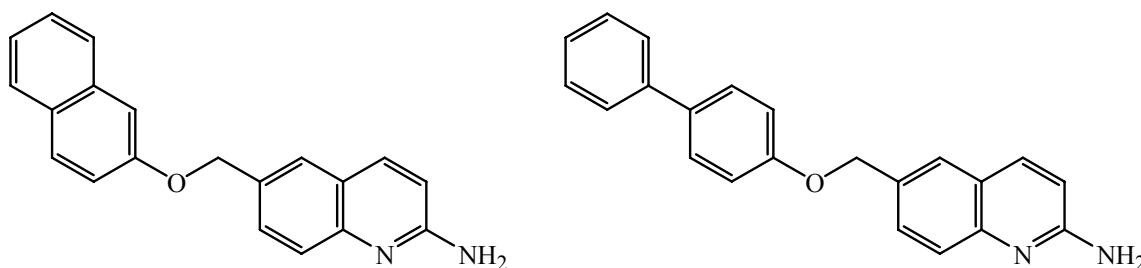
**68**) bind with greater affinity than their 2- or 3-substituted counterparts, perhaps due to a hydrophobic contact being made with the protein surface. Another pattern that seems to be occurring for a different reason is that the inclusion of a halogen substituent in either the 2- or 4-position of the phenoxyethyl group (e.g. **71 – 74**) improves affinity of the ligand by approximately 10-fold in relation to **2**.



**Figure 60.** The highest affinity 6-phenoxyethyl ligands.

### 5.2.2. Proposed Future Work

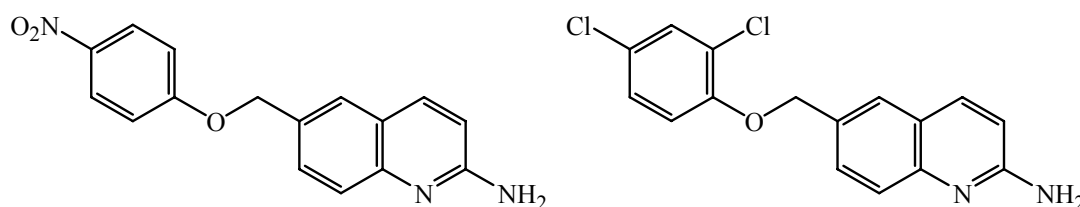
In order to improve binding affinity of the 2-aminoquinoline ligand beyond that of **73**, two methods could be deployed. Firstly, to capitalise on the improvement seen in the binding affinity by including a *para* substituent on the phenoxyethyl group, a range of ligands with large substituents in the 4-position could be prepared, such as those shown in Figure 61, to explore whether a large substituent will make further hydrophobic contacts with the protein surface.



**Figure 61.** Proposed future ligands that contain bulkier substituents in the 4-position of the phenoxyethyl group.

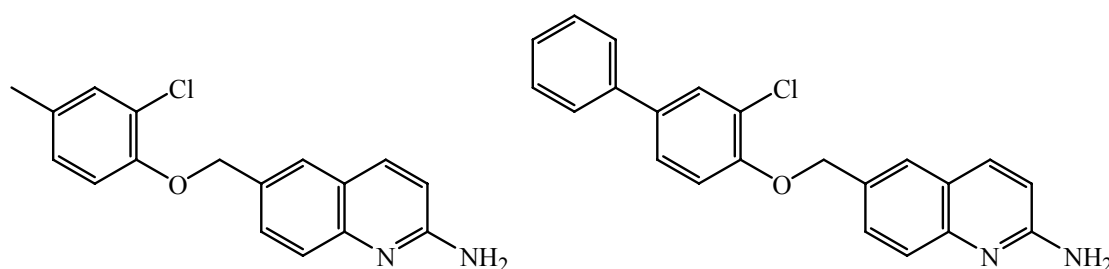
The second method for attempting to improve binding affinity is by preparing ligands with alternative electron withdrawing capabilities. The addition of more than one electron withdrawing substituent on the phenoxyethyl group (Figure 62) would further explore the

improvement in binding affinity seen in the halogenated phenoxyethyl ligands. The introduction of a resonance withdrawing group such as a nitro group in the *para* position (Figure 62) could further explore the hydrophobic versus electron withdrawing effect and also determine whether inductively withdrawing groups are favoured over resonance withdrawing groups.



**Figure 62.** Proposed future ligands containing electron withdrawing substituents on the phenoxyethyl group.

There is also the possibility of combining a substituent in the 4-position with an electron withdrawing group in another position as in Figure 63.



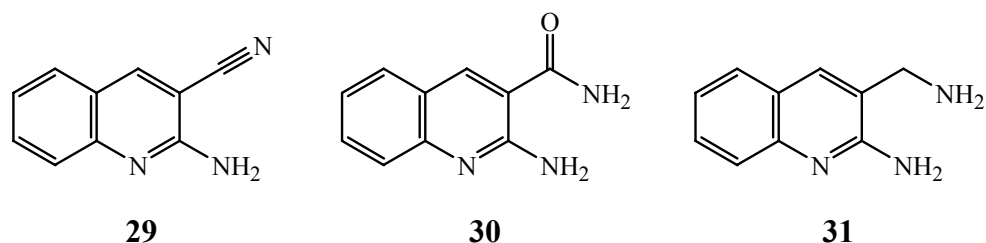
**Figure 63.** Proposed future ligands combining 4-substitution with an electron withdrawing substituent on the phenoxyethyl group.

All of the 6-substituted ligands were observed to be in intermediate exchange with the Tec SH3 domain on the NMR timescale. Therefore it was difficult to determine the exact equilibrium dissociation binding constants for these ligands. In order for the [ $^1\text{H}$ ,  $^{15}\text{N}$ ] HSQC chemical shift perturbation assay to continue to be useful, it is necessary to force the ligands out of intermediate exchange. This could be achieved either through increasing the temperature of the NMR assay or using a lower field strength NMR spectrometer. Either of these solutions will cause the ligand and the protein to be in fast exchange with one another so the signals in the spectrum will give an accurate estimation of bound versus unbound protein.

## 5.3 The 3-Position of 2-Aminoquinoline

### 5.3.1. Summary and Conclusions

A number of simple 3-substituted 2-aminoquinoline ligands were prepared and assayed for binding activity (Figure 64).



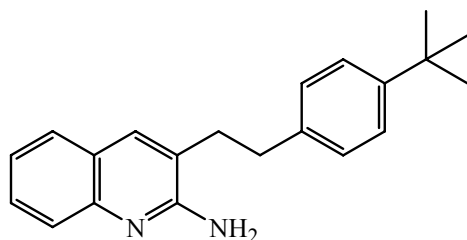
**Figure 64.** The simple 3-substituted ligands that were assayed for binding affinity to the Tec SH3 domain.

It was found that those with electron withdrawing capabilities did not bind with greater affinity than **2**. This may be due to the reduction in the ability of the ligand to make a salt bridge with the D196 residue of the SH3 domain. One of the simple 3-substituted 2-aminoquinoline ligands with an aminomethyl substituent, **31**, bound to the Tec SH3 domain with a slight improvement in affinity over the SH3 domain. It was thought that this group might be making a contact with the protein surface.

With this in mind, further 3-substituted 2-aminoquinoline ligands were prepared with larger substituents with the aim of capitalising on this additional contact with the protein surface. The intended ligand, **82** was unable to be synthesised. The precursor, 2-chloro-3-(phoxymethyl)quinoline, **80** was successfully prepared, but the Kóródi amination reaction was unsuccessful and gave an unexpected product, **83**, which was identified by means of X-ray crystallography.

A new synthetic strategy was therefore designed that involved a Wittig reaction. Unfortunately the triphenylphosphine oxide by-product from the bond forming step was unable to be separated from the product. A Horner-Emmons reaction was therefore employed instead which gave a clean product for each of the substrates, which could be carried through to give the final ligands, which were then assayed for binding affinity.

A number of the more complex 3-substituted ligands bound to the Tec SH3 domain in greater affinity than the lead compound **2**. The best of the 3-substituted ligands was **115** ( $K_d = 40 \mu\text{M}$ ; Figure 65).

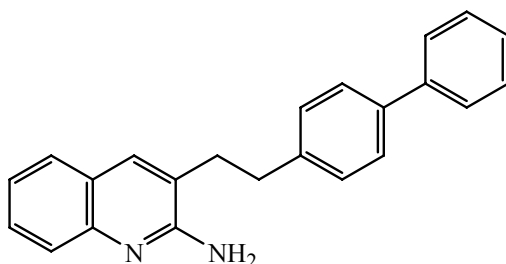


**Figure 65.** The highest affinity 3-substituted ligand, **115**.

It would appear as though a non-conjugated substituent is desirable in the 3-position of 2-aminoquinoline and a large substituent such as a *tert*-butyl group in the 4-position of the phenyl group, as in **115**, is also desirable. The chemical shift mapping appears to indicate that the phenylethyl substituent bends below the quinoline ring and sits in a shallow indentation beneath the W215 residue. Therefore the conjugated system would be unfavourable in this situation and a bulky group in the 4-position would extend further towards residues with which it may be able to interact (the conjugated ligand, **90**, bound to the Tec SH3 domain with lesser affinity than the lead compound **2**). The conjugated system may lead to a decrease in electron density around the quinoline ring which would reduce the ligand's ability to form the salt bridge and  $\pi$ - $\pi$  stack which are necessary for the binding interaction. The rigidity of the conjugated structure may also be undesirable for binding.

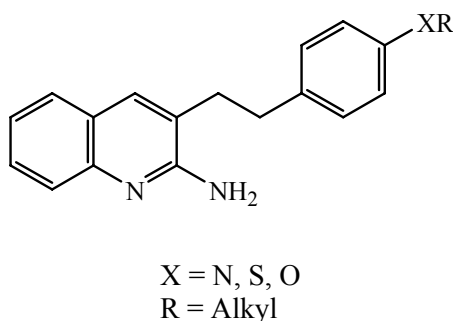
### 5.3.2. Proposed Future Work

Now that it has been established that a further contact can be made through the introduction of a substituent in the 3-position of 2-aminoquinoline, a number of ligands could be prepared in order to explore this additional contact. Firstly a range of ligands with alternative substituents *para* to the ethyl linker on the phenyl ring could be prepared (Figure 66).



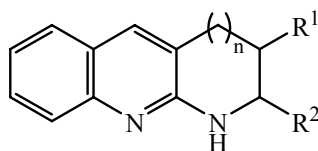
**Figure 66.** Proposed future ligand that involves a bulky substituent in the 3-position of 2-aminoquinoline.

It is possible that the alkyl substituted phenethyl ligands, **112-115** were favoured not because of the bulky nature of the substituent, but because the alkyl substituents on the phenethyl group are mildly electron donating. Therefore substituents with electron donating capabilities could be included in a range of ligands such as those in Figure 67 and these could subsequently be assayed for binding affinity. This would provide more information about the mode of interaction for the 3-substituted ligands.



**Figure 67.** Proposed ligands with resonance electron donating substituents on the phenyl group.

In order to see if the phenethyl group is sitting below W215 and interacting with N231, ligands with a third ring system that would restrict the substituent to the one side of the binding site could be prepared. Ligands such as that in Figure 68 would prevent interaction with the residue at N231, so if the above hypothesis is correct there should be a reduction in binding affinity and chemical shift mapping should show that this residue is unaffected by the binding of the ligand during the NMR assay. This strategy could also be used to capitalise on the improvement in binding affinity seen in *N*-substituted ligands, but without the reduction in binding affinity that comes from the rotation about the amino bond.

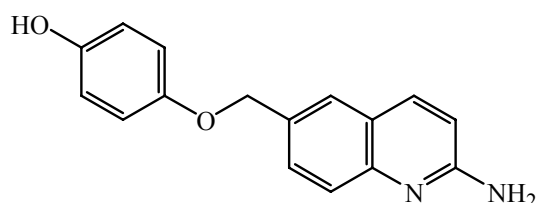


**Figure 68.** Proposed ligand with a constrained ring system.  
n = 0 or 1, R<sup>1</sup> and R<sup>2</sup> = H or Ar.

## 5.4 Proposed Further Studies

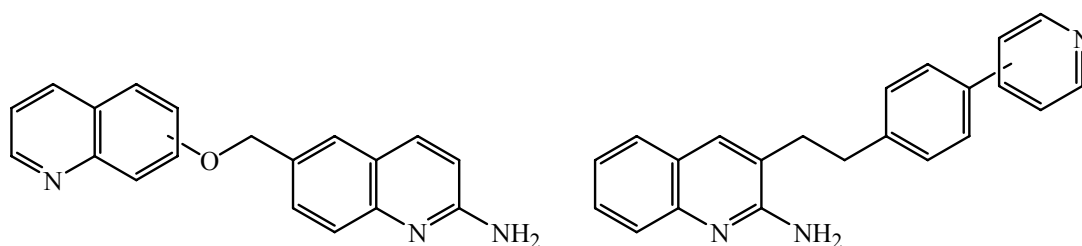
### 5.4.1. Solubility

One of the issues encountered during the assay of a number of the above ligands was lack of water-solubility. Several of the ligands were not sufficiently soluble enough in the protein assay solution to allow saturation of binding to be reached and therefore a precise dissociation binding constant could not be determined. There are a number of ways that this problem could be resolved. One of them would be to add polar hydrophilic groups, such as hydroxy or amino groups to the 2-aminoquinoline ligand (Figure 69).



**Figure 69.** Proposed future ligand with an additional polar group to improve solubility.

There are however difficulties with this method of attempting to improve the solubility of the ligand. Adding polar functional groups to the ligand may in fact interfere with the mode of interaction with the protein binding hence resulting in a reduction in binding affinity. With this in mind, a more effective method of improving water solubility may be to substitute heteroaromatic rings for phenyl groups (Figure 70). This would introduce additional hydrophilicity and minimise changes to the desired structure.



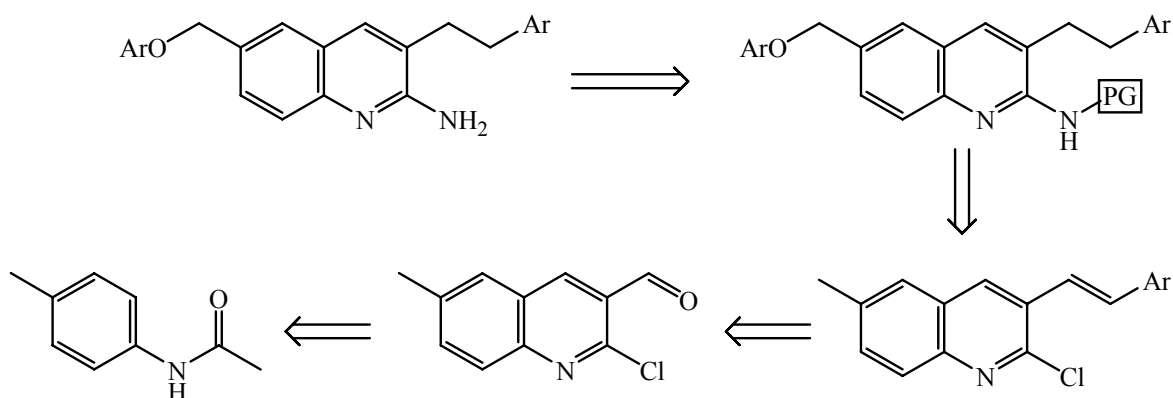
**Figure 70.** Proposed future ligands containing heteroaromatic rings to improve solubility.

Another solution to the solubility issue that could be used either on its own or in conjunction with the above techniques would be to make a salt from the amino group. A simple hydrochloride salt or a maleate salt may improve the solubility of the molecule in the aqueous protein solution for assay, but the salt shouldn't interfere with the binding interaction at all as it will dissociate in solution. The separation and purification of the salt

should not be troublesome either as the product can be purified prior to its conversion to a salt. Therefore this would appear to be a simple and effective means of improving the solubility of the 2-aminoquinoline ligands for the binding assays.

#### 5.4.2. Combining Substituents

Introducing a substituent in the 6-position of 2-aminoquinoline has seen a 13-fold improvement in binding affinity of the ligand for the SH3 domain in comparison to the lead compound, **2**. A substituent at the 3-position has seen a 3-fold improvement in comparison to **2**. Therefore combining 3- and 6-substitution in the same ligand should see an even greater improvement in binding affinity, assuming that this strategy introduces no additional geometric constraints for protein-ligand binding. The simplest way of introducing a substituent into the 3- and 6- position of 2-aminoquinoline is to combine the methods already used for single substitution (Figure 71).



**Figure 71.** Proposed pathway for combining substitution in both the 3- and 6-position of 2-aminoquinoline. PG = Protecting Group.

The combination of 3- and 6-substitution in the one ligand may allow the ligand to bind to the Tec SH3 domain with high enough affinity to allow for full characterisation of the mode of binding through either X-ray crystallography or NMR methods.

#### 5.4.3. Forcing the Ligand and SH3 domain into Slow Exchange

In order to characterise the binding site of the 2-aminoquinoline ligand on the Tec SH3 domain, by NMR the ligand needs to be in slow exchange with the protein-ligand complex. This will happen if a high affinity ligand is found. However if none of the ligands that are prepared bind with high enough affinity such that the protein-ligand complex is in slow exchange on the NMR timescale, it may be possible to force the NMR spectrum into slow



exchange. This could be done either by using a higher field strength NMR spectrometer or decreasing the temperature of solution during the NMR assay. As the samples for the NMR assay contain 10% d<sub>6</sub>-DMSO, a great reduction in temperature is not possible. A reduction in temperature may also reduce the already low solubility of the ligand. Therefore the most feasible way of forcing the ligand-protein complex into slow exchange is to run the [<sup>1</sup>H,<sup>15</sup>N] HSQC chemical shift perturbation assay on an NMR spectrometer with a higher field. A large number of the ligands prepared for the purpose of this thesis are already in intermediate exchange, so any number of these could be used in this attempt to force the ligand into slow exchange.

# Chapter 6.

## EXPERIMENTAL

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### 6.1 General Methods

All commercially available reagents and reagent grade solvents were used without further purification. Dry THF was prepared by distilling over benzophenone and sodium under nitrogen. Where necessary, solvents were dried by the appropriate methods as outlined in *Advanced Practical Organic Chemistry*.<sup>73</sup>

Thin layer chromatograms were run on MERCK aluminium-backed silica gel 60 F<sub>254</sub> plates and visualised under UV light at 254 nm. Preparative thin layer chromatograms were run on MERCK silica gel 60 F<sub>254</sub> plates (20 x 20 cm, 0.25 mm thickness). Flash column chromatography was performed using MERCK silica gel 60 (particle size 0.040 – 0.063 mm) using the guidelines outlined by Still, Kahn and Mitra.<sup>74</sup>

<sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained using either Varian Gemini 2000 Spectrometers (<sup>1</sup>H: 199.954, <sup>13</sup>C: 50.283 MHz; <sup>1</sup>H: 300.13, <sup>13</sup>C: 74.47, <sup>19</sup>F: 282.39 MHz), or a Varian INOVA Spectrometer (<sup>1</sup>H: 599.842, <sup>13</sup>C: 150.842 MHz). All spectra were recorded as solutions in either CDCl<sub>3</sub> using tetramethylsilane as an internal standard, or d<sub>6</sub>-DMSO. The following abbreviations for proton multiplicities are used: s, singlet; d, doublet; t, triplet; sept, septet; br, broad signal; m, multiplet. ‡ Indicates (an) unresolved *J* value(s). <sup>1</sup>H and <sup>13</sup>C Signals were assigned by use of COSY, ROESY, HMQC and HMBC spectra.

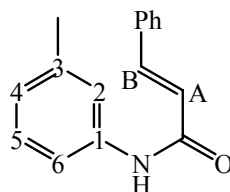
All infrared spectra were obtained using a Perkin Elmer BX FT-IR spectrometer as nujol mulls between sodium chloride plates unless otherwise stated.

All electron impact mass spectra were obtained using a VG ZAB 2HF mass spectrometer at ionisation energy 70 eV at the University of Adelaide or Kratos Concept High Resolution mass spectrometer at the University of Tasmania. All LSIMS and HRMS were performed at the University of Tasmania. All microanalyses were performed at the University of Otago, New Zealand.

## 6.2 Synthetic Procedures

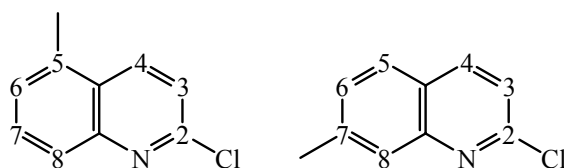
### 6.2.1. 5- and 7-Substituted 2-Aminoquinolines

(2E)-N-(3-methylphenyl)-3-phenylacrylamide (**123**)<sup>50, 54</sup>



Cinnamoyl chloride (20.7 g, 0.124 mol) in dichloromethane (80 mL) was added dropwise over 45 minutes to DMAP (1.5 g, 0.0124 mol), pyridine (10 mL, 0.124 mol) and dichloromethane (25 mL) cooled on ice, under a nitrogen atmosphere. *m*-Toluidine (13.3 mL, 0.124 mol) in dichloromethane (60 mL) was then added dropwise over 30 minutes. The mixture was stirred until the reaction mixture became clear. The solution was diluted with dichloromethane (70 mL) and washed with 5% HCl (3 x 200 mL), 10% NaOH (2 x 200 mL) and H<sub>2</sub>O (1 x 260 mL). The extract was then dried (Na<sub>2</sub>SO<sub>4</sub>) and the dichloromethane was evaporated to give pale yellow crystals (26.2 g, 89%). A small amount of **123** was recrystallised from aqueous ethanol for the purpose of characterization, to give white crystals (m.p. 111-113°C [lit. 114°C]<sup>54</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3251, 3084, 1655, 1613, 1554. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>);  $\delta$ : 2.33 [3H, s, CH<sub>3</sub>], 6.58 [1H, d,  $J_{A,B}$  = 15.5 Hz, H(A)], 6.94 [1H, d,  $J_{4,5}$  = 7.8 Hz, H(4)], 7.22 [1H, dd,  $J_{4,5}$  =  $J_{5,6}$  = 7.8 Hz H(5)], 7.34-7.53 [7H, m, aromatic H + H(6) + H(2)], 7.60 [1H, br, NH], 7.75 [1H, d,  $J_{A,B}$  = 15.5Hz, H(B)].

2-Chloro-5-methylquinoline (**33**) / 2-Chloro-7-methylquinoline (**34**)<sup>50, 52, 53</sup>



**123** (12.2 g, 51.4 mmol) and aluminium chloride (20.6 g, 0.154 mol) were combined in an intimate mixture using a mortar and pestle. The resulting paste was melted with a heat gun to initiate the reaction and then heated at 120°C for an hour. The reaction mixture was allowed to cool to room temperature then placed in an ice water bath. Ice was added to the mixture and the product was extracted with chloroform (3 x 200 mL). The combined organic extracts were then washed with water (1 x 600 mL) and 5% hydrochloric acid (1 x 600 mL). The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed to give a mixture of

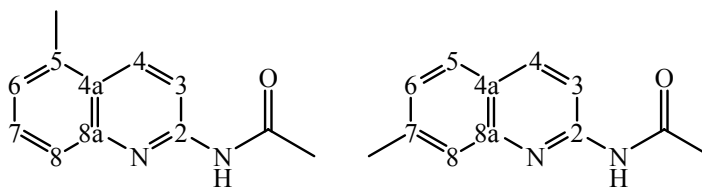
**124** and **125**. No further purification took place prior to the next step.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.47 [3H, s,  $^*\text{CH}_3$ ], 2.58 [3H, s,  $\text{CH}_3$ ], 6.67 [1H, d,  $J_{3,4} = 9.3$  Hz, H(3 $^*$ )], 6.76 [1H, d,  $J_{3,4} = 9.8$  Hz, H(3)], 7.07 [2H, d,  $J = 7.2$  Hz], 7.26-7.48 [5H, m], 7.80 [1H, d,  $J_{3,4} = 9.3$  Hz, H(4 $^*$ )], 8.05 [1H, d,  $J_{3,4} = 9.8$  Hz, H(4)], 12.06 [1H, br,  $^*\text{NH}$ ]. EIMS:  $m/z$ : 159 ( $\text{M}^{+\bullet}$ , 100%), 158 (11), 130 (44).

\* Refers to **125**.

The crude mixture of **124** and **125** was combined with phosphorus oxychloride (48 mL, 0.514 mol) and heated at 60°C for 20 hours. The phosphorus oxychloride was removed by distillation and the resulting solid was added to ice, extracted with ether (3 x 100 mL) and the combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed and the remaining solid was dissolved in dichloromethane then filtered through silica gel to remove any remaining aluminium by-products. The solvent was removed to give a crude mixture of **33** and **34** (7.517 g, 82%), which was carried through to the next reaction without further purification.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.54 [3H, s,  $^*\text{CH}_3$ ], 2.65 [3H, s,  $\text{CH}_3$ ], 7.27-7.39 [4H, m, H(3) + H(3 $^*$ ) + H(6) + H(6 $^*$ )], 7.60 [1H, dd,  $J_{6,7} = 7.0$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.68 [1H, d,  $J_{5,6} = 8.2$  Hz, H(5 $^*$ )], 7.78 [1H, d,  $^5J_{4,8} = 0.8$  Hz, H(8 $^*$ )], 7.86 [1H, d $^\ddagger$ ,  $J_{7,8} = 8.4$  Hz, H(8)], 8.02 [1H, d $^\ddagger$ ,  $J = 8.4$  Hz, H(4 $^*$ )], 8.23 [1H, dd,  $^5J_{4,8} = 0.8$  Hz,  $J_{3,4} = 8.8$  Hz, H(4)].

\* Refers to **34**.

*N*-(5-Methylquinolin-2-yl)acetamide (**35**) / *N*-(7-Methylquinolin-2-yl)acetamide (**36**)<sup>50, 55</sup>

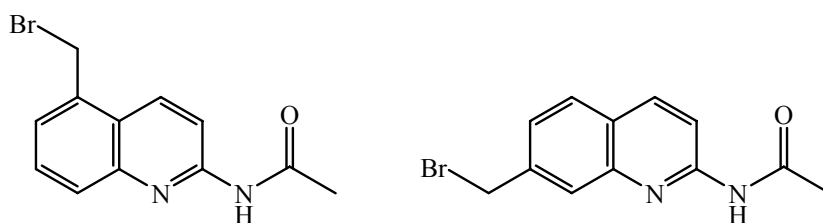


A mixture of **33** and **34** (5.0 g, 28 mmol) was added to potassium carbonate (19.35 g, 0.14 mol) and acetamide (82.7 g, 1.4 mol). The mixture was heated at reflux for 16 hours then added to water (500 mL) and extracted with dichloromethane (3 x 200 mL). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ), the solvent was removed and the resulting crude product was filtered through silica gel (10% ethyl acetate / dichloromethane). This gave rise to the product mixture, **35** and **36** (2.92 g, 52%). HRMS: Found 200.0958;  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}$  requires 200.0950. IR (nujol mull):  $\nu$  ( $\text{cm}^{-1}$ ): 1709, 1661, 1603, 1509.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.18 [3H, s,  $^*\text{COCH}_3$ ], 2.30 [3H, s,  $\text{COCH}_3$ ], 2.55 [3H, s,  $^*\text{CH}_3$ ], 2.68 [3H, s,  $\text{CH}_3$ ], 7.29-7.33 [2H, m, H(6) + H(6 $^*$ )], 7.57 [1H, dd,  $J = 7.1$  Hz,  $J = 8.5$  Hz, H(7)], 7.61 [1H, d,  $^5J_{4,8} =$

0.6 Hz, H(8\*)), 7.67-7.70 [2H, m, H(5\*) + H(8)], 8.18 [1H, dd,  $^5J_{4,8} = 0.6$  Hz,  $J_{3,4} = 9.0$  Hz, H(4\*)], 8.39 [1H, dd,  $^5J_{4,8} = 0.6$  Hz,  $J_{3,4} = 9.3$  Hz, H(4)] 8.44 [1H, d,  $J_{3,4} = 9.0$  Hz, H(3\*)], 8.51 [H, d,  $J_{3,4} = 9.3$  Hz, H(3)], 10.53 [2H, s, \*NH + NH]. EIMS:  $m/z$ : 200 ( $M^+$ , 26%), 158 (67).

\* Refers to **36**.

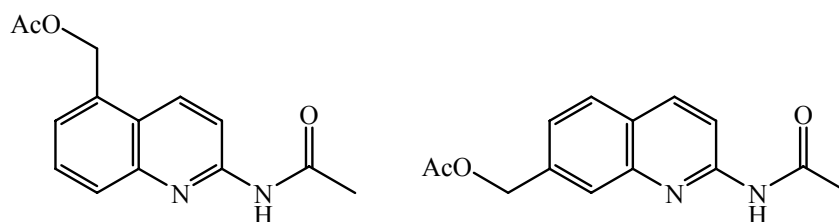
**N-[5-(Bromomethyl)quinolin-2-yl]acetamide (37) / N-[7-(Bromomethyl)quinolin-2-yl]acetamide (38)**<sup>50</sup>



A mixture of **35** and **36** (2.55 g, 12.7 mmol), *N*-bromosuccinimide (2.26 g, 12.7 mmol, 1 equiv.) and benzoyl peroxide (0.31 g, 1.27 mmol, 0.1 equiv.) was added to benzene (8 mL) and heated at reflux for 2.5 hours. The mixture was then allowed to cool and the succinimide was filtered off. The solvent was removed and the resulting crude product was chromatographed over silica gel (15% ethyl acetate / dichloromethane). The products, **37** and **38** (1.64 g, 46%) were isolated from the combined fractions with  $R_f$  of 0.24. HRMS: Found 278.0053;  $C_{12}H_{11}^{79}BrN_2O$  requires 278.0055. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 1663, 1639, 1607, 1580.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$ : 2.23 [6H, s, \*COCH<sub>3</sub> + COCH<sub>3</sub>], 4.63 [2H, s, \*CH<sub>2</sub>Br], 4.88 [2H, s, CH<sub>2</sub>Br], 7.45-7.49 [2H, m, H(6\*) + H(6)], 7.57 [1H, dd,  $J = 7.2$  Hz,  $J = 8.4$  Hz, H(7)], 7.67-7.70 [3H, m, H(5\*) + H(8\*) + H(8)], 8.15 [1H, d,  $J = 8.7$  Hz, H(4\*)], 8.42-8.55 [3H, m, H(3\*) + H(3) + H(4)], 9.28 [1H, s, NH], 9.37 [1H, s, NH]. EIMS:  $m/z$ : 280 ( $M^+$  [ $^{81}Br$ ], 60%), 278 ( $M^+$  [ $^{79}Br$ ], 63%), 238, (36), 236 (39), 199 (100), 157 (65).

\* Refers to **38**.

***N*-[5-(Acetoxymethyl)quinolin-2-yl]acetamide (39) / *N*-[7-(Acetoxymethyl)quinolin-2-yl]acetamide (40)<sup>50</sup>**

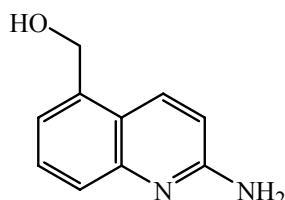


A mixture of **37** and **38** (875 mg, 3.13 mmol) was added to DMF (20 mL) and potassium acetate (614 mg, 6.26 mmol) and stirred for 16 hours at 80°C. The reaction mixture was diluted with ethyl acetate (50 mL), then washed with water (4 x 50 mL) and brine (2 x 50 mL). The organic phase was then dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed. The crude product was chromatographed over silica gel (20% ethyl acetate / dichloromethane) to give **39** (260 mg, 32%), as a cream coloured solid ( $R_f = 0.19$ ; m.p. 140-145°C). Analysis Found: C, 65.04; H, 5.46; N, 10.57%. C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> requires C, 65.11; H, 5.46; N, 10.85%. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3427, 3213, 1727, 1704, 1671, 1602, 1583, 1503. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.11 [3H, s, CH<sub>3</sub>], 2.35 [3H, s, CH<sub>3</sub>], 5.52 [2H, s, CH<sub>2</sub>], 7.50 [1H, d,  $J_{6,7} = 7.2$  Hz, H(6)], 7.63 [1H, dd,  $J_{6,7} = 7.2$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.82 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 8.38 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)], 8.48 [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 9.07 [1H, s, NH]. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$ : 21.00 [CH<sub>3</sub>], 24.79 [CH<sub>3</sub>], 63.79 [CH<sub>2</sub>], 114.92 [C(3)], 124.77 [C(4a)], 126.60 [C(6)], 128.33 [C(8)], 129.55 [C(7)], 132.18 [C(5)], 134.84 [C(4)], 146.81 [C(8a)], 151.39 [C(2)], 169.71 [C=O], 170.83 [C=O]. EIMS:  $m/z$ : 258 (M<sup>+</sup>, 45%), 216 (41), 174 (100), 157 (52).

**40** (210 mg, 26%), was isolated as a white solid ( $R_f = 0.15$ ; m.p. 124-126°C), however some **39** remained as a slight impurity. Analysis Found: C, 65.05; H, 5.35; N, 10.67%. C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> requires C, 65.11; H, 5.46; N, 10.85%. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3483, 3198, 1740, 1706, 1666, 1600, 1579, 1535, 1508. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.15 [3H, s, CH<sub>3</sub>], 2.25 [3H, s, CH<sub>3</sub>], 5.29 [2H, s, CH<sub>2</sub>], 7.42 [1H, dd,  $^4J_{6,8} = 1.2$  Hz,  $J_{5,6} = 8.2$  Hz, H(6)], 7.84 [1H, s<sup>†</sup>, H(8)], 7.85 [1H, d,  $J_{5,6} = 8.2$  Hz, H(5)], 8.17 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)], 8.43 [1H, d,  $J_{3,4} = 9.0$  Hz H(3)], 8.80 [1H, s, NH]. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$ : 21.00 [CH<sub>3</sub>], 24.80 [CH<sub>3</sub>], 65.91 [CH<sub>2</sub>], 114.86 [C(3)], 124.88 [C(8)], 125.84 [C(4a)], 125.95 [C(6)], 128.07 [C(5)], 138.21 [C(7)], 138.56 [C(4)], 146.27 [C(8a)], 151.84 [C(2)], 169.72 [C=O], 170.84 [C=O]. EIMS:  $m/z$ : 258 (M<sup>+</sup>, 70%), 216 (41), 174 (80), 157 (31).

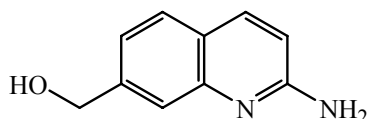
A mixture of **39** and **40** (100 mg, 12%) was also obtained from several overlapping fractions.

### 5-Hydroxymethyl-2-aminoquinoline (**27**)<sup>50</sup>



**39** (80 mg, 0.31 mmol) and potassium carbonate (43 mg, 0.31 mmol) were added to methanol (4 mL) and the resulting solution was stirred at 50°C for 2 hours. The reaction mixture was allowed to cool before the methanol was removed and the resulting solid was chromatographed over silica gel (20% methanol / dichloromethane) to give pure **27** (50 mg, 93%) as a yellow solid ( $R_f = 0.21$ ; m.p. 155-157°C). HRMS: Found 174.0792;  $C_{10}H_{10}N_2O$  requires 174.0793. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3467, 3319, 3203, 1686, 1618, 1564, 1512.  $^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$ : 1.25 [1H, s, OH], 4.91 [2H, s,  $NH_2$ ], 5.03 [2H, s,  $CH_2$ ], 6.77 [1H, d,  $J_{3,4} = 9.2$  Hz, H(3)], 7.26 [1H, d,  $J_{6,7} = 7.0$  Hz, H(6)], 7.51 [1H, dd,  $J_{6,7} = 7.0$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.63 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 8.27 [1H, d,  $J_{3,4} = 9.0$  Hz H(4)].  $^{13}C$  NMR (150MHz,  $d_6$ -DMSO):  $\delta$ : 62.74 [ $CH_2OH$ ], 111.12 [C(3)], 120.29 [C(4a)], 120.58 [C(6)], 123.57 [C(8)], 128.96 [C(7)], 134.28 [C(5)], 138.49 [C(4)], 146.35 [C(8a)], 157.12 [C(2)]. EIMS:  $m/z$ : 174 ( $M^+$ , 100%), 157 (31), 145 (64), 128 (52).

### 7-Hydroxymethyl-2-aminoquinoline (**28**)<sup>50</sup>



As for **27**, using **40** (120mg, 0.46 mmol), potassium carbonate (64 mg, 0.46 mmol) and methanol (5 mL) to give clean **28** (35 mg, 44%), as a yellow solid ( $R_f = 0.15$ ; m.p. 153 – 159°C). HRMS: Found 174.0790;  $C_{10}H_{10}N_2O$  requires 174.0793. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3467, 3317, 3201, 1686, 1624, 1563, 1514.  $^1H$  NMR (600 MHz,  $d_6$ -DMSO):  $\delta$ : 1.93 [1H, br, OH], 3.83 [1H, s, NH], 4.56 [2H, s,  $CH_2$ ], 6.41 [1H, s, NH], 6.75 [1H, br s, H(3)], 7.12 [1H, d,  $J_{5,6} = 8.1$  Hz, H(6)], 7.41 [1H, br s, H(8)], 7.58 [1H, d,  $J_{5,6} = 8.1$  Hz, H(5)], 7.88 [1H, d,  $J_{3,4} = 9.0$  Hz H(4)].  $^{13}C$  NMR (150 MHz,  $d_6$ -DMSO):  $\delta$ : 63.48 [ $CH_2OH$ ], 112.66 [C(3)],

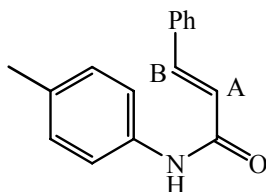
121.29 [C(6) + C(8)], 121.80 [C(4a)], 128.00 [C(5)], 138.11 [C(4)], 144.38 [C(7)], 147.03 [C(8a)], 158.29 [C(2)]. EIMS:  $m/z$ : 174 ( $M^+$ , 100%), 157 (23), 145 (70), 128 (52).

A mixture of **27** and **28** (predominantly **28**; 35 mg, 44%) was also isolated from the crude product.



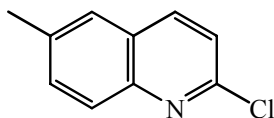
## 6.2.2. 6-Substituted 2-Aminoquinolines

(2E)-N-(4-methylphenyl)-3-phenylacrylamide (**41**)<sup>46, 54</sup>



Cinnamoyl chloride (28.0 g, 0.168 mol) in dichloromethane (120 mL) was added dropwise over 45 minutes to DMAP (2.05 g, 0.0168 mol), pyridine (13.6 mL, 0.168 mol) and dichloromethane (35 mL) cooled on ice, under a nitrogen atmosphere. *p*-Toluidine (18.0 g, 0.168 mol) in dichloromethane (80 mL) was then added dropwise over 45 minutes. The mixture was stirred until the reaction mixture became clear. The solution was diluted with dichloromethane (100 mL) and washed with 5% HCl (2 x 350 mL), 10% NaOH (2 x 350 mL) and H<sub>2</sub>O (1 x 350 mL). The extract was then dried (Na<sub>2</sub>SO<sub>4</sub>) and the dichloromethane was evaporated to give rise to **41** (38.4 g, 96%) as a white solid (m.p. 159-162°C [lit 162°C]<sup>54</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3254, 1661, 1622, 1598, 1541. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>);  $\delta$ : 2.29 [3H, s, CH<sub>3</sub>], 6.61 [1H, d, *J* = 15.6 Hz, H(A)], 7.10 [2H, br d, *J* = 8.0 Hz, H(3) + H(5)] 7.26-7.45 [5H, m, aromatic H], 7.53 [1H br d, *J* = 8.0 Hz, H(2) + H(6)], 7.72 [1H, d, *J* = 15.6 Hz, H(B)], 8.02 [1H, br s, NH].

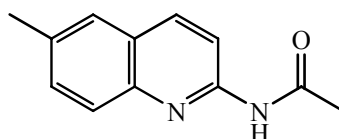
6-Methyl-2-chloroquinoline (**43**)<sup>46, 52, 53, 58</sup>



**41** (16.0 g, 67.4 mmol) and aluminium chloride (26.9 g, 0.202 mol) were combined in an intimate mixture using a mortar and pestle. The resulting mixture was melted with a heat gun to initiate the reaction and then heated at 120°C for an hour. The reaction mixture was allowed to cool to room temperature then placed in an ice water bath. Ice was added and massaged into the reaction mixture. The resulting precipitate was filtered and air dried to give **42** (12.79 g). No further purification took place prior to the next step. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3452, 3278, 1662, 1624, 1563. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.42 [3H, s, CH<sub>3</sub>], 6.70 [1H, d, *J* = 9.6 Hz, H(3)], 7.34-7.35 [3H, m, H(5) + H(7) + H(8)], 7.76 [1H, d, *J* = 9.6 Hz, H(4)], 12.22 [1H, br s, NH]. Crude **42** was combined with phosphorus oxychloride (63

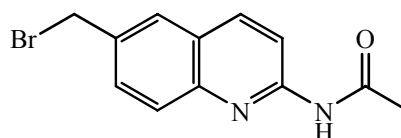
mL, 0.674 mol) and heated at 60°C for 20 hours. The phosphorus oxychloride was removed by distillation and the remaining mixture added to ice. The resulting precipitate was filtered, dried and recrystallised from hexane to give clean **43** (7.88 g, 66%) as cream coloured crystals (m.p. 112-114°C [lit 111-114°C]<sup>58</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 1585, 1566, 1504. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.53 [3H, s, CH<sub>3</sub>], 7.35 [1H, d,  $J$  = 8.6 Hz, H(3)], 7.54-7.58 [2H, m, H(6) + H(5)], 7.92 [1H, d,  $J$  = 9.4 Hz, H(8)], 8.01 [1H, d,  $J$  = 8.6 Hz, H(4)].

**N-(6-Methylquinolin-2-yl)acetamide (44)**<sup>50, 55</sup>



A mixture of **43** (12.0 g, 67.6 mmol), acetamide (200 g, 3.38 mol) and potassium carbonate (46.7 g, 0.34 mol) was heated at reflux for 16 hours. The acetamide was removed by distillation. Water (300 mL) was added to the residue and the resulting solution was extracted with dichloromethane (3 x 300mL). The combined organic extracts were washed with water (1 x 900 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was then removed and the resulting solid was filtered through silica gel (17:3 dichloromethane / ethyl acetate) to give **44** (6.0 g, 44%) as a white solid (m.p. 181-185°C [lit 181-184]<sup>50</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3647, 3213, 1732, 1693, 1660, 1597, 1537, 1491. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.20 [3H, s, COCH<sub>3</sub>], 2.51 [3H, s, CH<sub>3</sub>], 7.49 [1H, dd, <sup>4</sup> $J_{5,7}$  = 2.0 Hz,  $J_{7,8}$  = 8.6 Hz, H(7)], 7.55 [1H, d, <sup>4</sup> $J_{5,7}$  = 2.0 Hz, H(5)], 7.72 [1H, d,  $J_{7,8}$  = 8.6 Hz, H(8)], 8.10 [1H, d,  $J_{3,4}$  = 8.4 Hz, H(4)], 8.38 [1H, br d,  $J_{3,4}$  = 8.4 Hz, H(3)], 9.18 [1H, br s, NH].

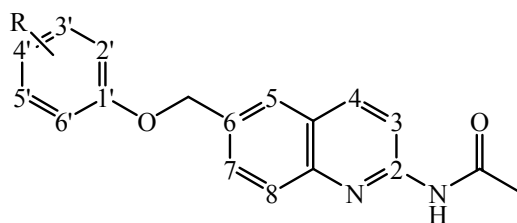
**N-[6-(Bromomethyl)quinolin-2-yl]acetamide (45)**<sup>50</sup>



A mixture of **44** (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 hours. The solution was cooled to room temperature and the benzene was removed. Dichloromethane was added and the resulting solution was washed with 10% sodium bicarbonate solution (3 x 150 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed and the resulting solid was

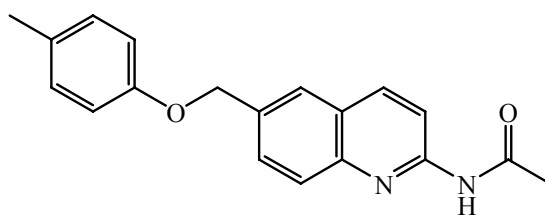
chromatographed over silica gel (17:3 dichloromethane / ethyl acetate) to give **45** (6.64 g, 63%) as a pale brown solid (m.p. 183-186°C [lit 185-187°C]<sup>50</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3237, 1663, 1598, 1581, 1537, 1491. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.27 [3H, s, COCH<sub>3</sub>], 4.65 [2H, s, CH<sub>2</sub>Br], 7.70 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 8.8 Hz, H(7)], 7.78-7.83 [2H, m, H(5) + H(8)], 8.16 [1H, d, J<sub>3,4</sub> = 9.0 Hz, H(4)], 8.44 [1H, br d, J<sub>3,4</sub> = 9.0 Hz, H(3)], 8.62 [1H, br s, NH].

### General Method for Synthesis of N-[6-(Phenoxymethyl)quinolin-2-yl]acetamides



**45** (1 mol. equiv.), a substituted phenol (1.1 mol. equiv.) and potassium carbonate (2 mol. equiv.) were added to acetonitrile and the mixture was heated at reflux until the reaction was complete by TLC. The mixture was then cooled and the solvent was removed. The remaining residue was suspended in ethyl acetate and washed with 10% sodium bicarbonate solution and water (2 x). The organic phase was then dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed. The crude product was chromatographed over silica gel to give rise to the final product.

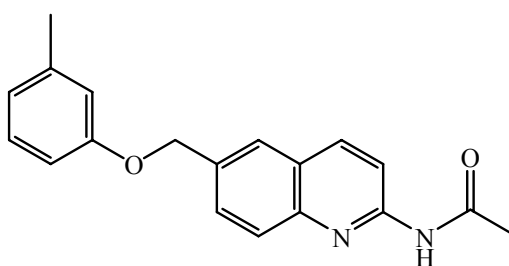
### N-{6-[(4-Methylphenoxy)methyl]quinolin-2-yl}acetamide (**46**)



A mixture of **45** (0.30 g, 1.07 mmol), 4-cresol (0.13 g, 1.18 mmol), potassium carbonate (0.30 g, 2.15 mmol) and acetonitrile (15 mL) were heated as described above for 5 hours. After work up, the crude product was chromatographed over silica gel (20% ethanol / hexane) to give **46** (0.14 g, 43%) as a cream coloured solid (m.p. 160-163°C). HRMS: Found 306.1366; C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub> requires 306.1368. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3384, 3330, 3251, 3066, 1671, 1604, 1579, 1511, 1492. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.29 [6H, s, 2 x

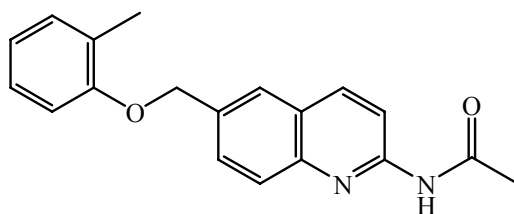
CH<sub>3</sub>], 5.19 [2H, s, CH<sub>2</sub>], 6.89-6.92 [2H, m, H(2') + H(6')], 7.09-7.11 [2H, m, H(3') + H(5')], 7.76 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 9.0 Hz, H(7)], 7.84-7.86 [2H, m, H(5) + H(8)], 8.23 [2H, d, J<sub>3,4</sub> = 9.0 Hz, H(4)], 8.45 [1H, br d, J<sub>3,4</sub> = 9.0 Hz, H(3)], 9.42 [1H, br s, NH]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ: 20.45 [CH<sub>3</sub>], 24.89 [COCH<sub>3</sub>], 69.52 [CH<sub>2</sub>], 114.50 [C(3)], 114.73 [C(2') + C(6')], 125.72 [C(4a)], 125.97 [C(5) + C(8)], 130.00 [C(3') + C(5')], 130.24 [C(7)], 130.56 [C(4')], 135.07 [C(6)], 140.10 [C(4)], 143.76 [C(8a)], 150.89 [C(2)], 156.39 [C(1')], 169.83 [C=O]. EIMS: *m/z*: 306 (M<sup>+</sup>, 2%), 263 (1), 199 (63), 157 (100).

**N-{6-[(3-Methylphenoxy)methyl]quinolin-2-yl}acetamide (47)**



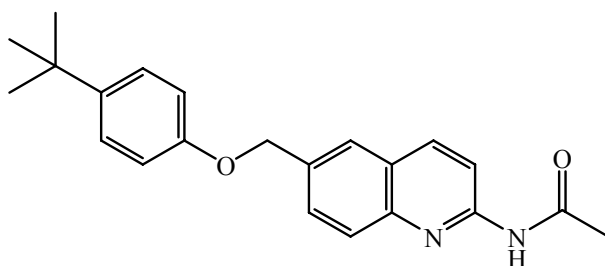
A mixture of **45** (0.50 g, 1.79 mmol), 3-cresol (0.20 mL, 2.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) and acetonitrile (25 mL) were heated as described above for 6 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **47** (0.46 g, 83%) as a pale yellow solid (m.p. 128-130°C). HRMS: Found 306.1369; C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub> requires 306.1368. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3320, 3249, 1672, 1602, 1582, 1547, 1535, 1501. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ: 2.20 [3H, s, CH<sub>3</sub>], 2.33 [3H, s, CH<sub>3</sub>], 5.18 [2H, s, CH<sub>2</sub>], 6.79-6.84 [3H, m, H(2') + H(4') + H(6')], 7.18 [1H, dd, J<sub>4',5'</sub> = J<sub>5',6'</sub> = 7.8 Hz, H(5')], 7.44 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 9.0 Hz, H(7)], 7.82-7.85 [2H, m, H(5) + H(8)], 8.16 [1H, d, J<sub>3,4</sub> = 9.0 Hz, H(4)], 8.43 [1H, br d, J<sub>3,4</sub> = 9.0 Hz, H(3)], 9.29 [1H, s, NH]. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ: 21.63 [CH<sub>3</sub>], 24.88 [COCH<sub>3</sub>], 69.61 [CH<sub>2</sub>], 111.84 [C(2')], 114.87 [C(3)], 115.94 [C(6')], 122.19 [C(4')], 126.07 [C(4a)], 126.15 [C(8)], 127.34 [C(5)], 129.42 [C(5')], 129.73 [C(7)], 134.51 [C(6)], 139.05 [C(4)], 139.76 [C(3')], 145.78 [C(8a)], 151.50 [C(2)], 158.81 [C(1')], 169.67 [C=O]. EIMS: *m/z*: 306 (M<sup>+</sup>, 2%), 263 (2), 199 (63), 157 (100).

**N-{6-[(2-Methylphenoxy)methyl]quinolin-2-yl}acetamide (48)**



A mixture of **45** (0.50 g, 1.79 mmol), 2-cresol (0.20 mL, 2.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) and acetonitrile (25 mL) were heated as described above for 5 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **48** (0.25 g, 46%) as a pale yellow solid (m.p. 127-129°C). HRMS: Found 306.1369; C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub> requires 306.1368. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3199, 3062, 1660, 1607, 1584, 1554, 1496. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.32 [6H, s, 2 x CH<sub>3</sub>], 5.24 [2H, s, CH<sub>2</sub>], 6.90-6.92 [2H, m, H(3') + H(5')], 7.16 [1H, ddd, <sup>4</sup>J<sub>4',6'</sub> = 1.2 Hz, J<sub>3',4'</sub> = J<sub>4',5'</sub> = 7.8 Hz, H(4')], 7.19 [1H, ddd, <sup>5</sup>J<sub>3',6'</sub> = 0.6 Hz, <sup>4</sup>J<sub>4',6'</sub> = 1.2 Hz, J<sub>5',6'</sub> = 7.2 Hz, H(6')], 8.80 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 8.4 Hz, H(7)], 7.87-7.89 [2H, m, H(5) + H(8)], 8.27 [1H, d, J<sub>3,4</sub> = 9.0 Hz, H(4)], 8.48 [1H, br d, J<sub>3,4</sub> = 9.0 Hz, H(3)], 9.79 [1H, br s, NH]. [<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 16.6 [CH<sub>3</sub>], 25.16 [COCH<sub>3</sub>], 69.49 [CH<sub>2</sub>], 111.69 [C(3')], 114.72 [C(3)], 121.21 [C(5')], 125.84 [C(2')], 125.90 [C(5) + C(8)], 127.06 [C(4')], 127.31 [C(4a)], 130.52 [C(7)], 131.13 [C(6')], 135.75 [C(6)], 140.80 [C(4)], 143.26 [C(8a)], 151.02 [C(2)], 156.79 [C(1')], 170.23 [C=O]. EIMS: *m/z*: 306 (M<sup>+</sup>, 1%), 263 (1), 199 (62), 157 (100).

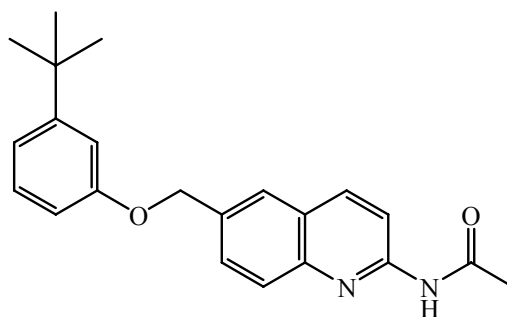
**N-{6-[(4-tert-Butylphenoxy)methyl]quinolin-2-yl}acetamide (49)**



A mixture of **45** (0.50 g, 1.79 mmol), 4-*tert*-butylphenol (0.30 g, 2.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) and acetonitrile (25 mL) were heated as described above for 5 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **49** (0.43 g, 68%) as a white solid (m.p. 155-160°C).

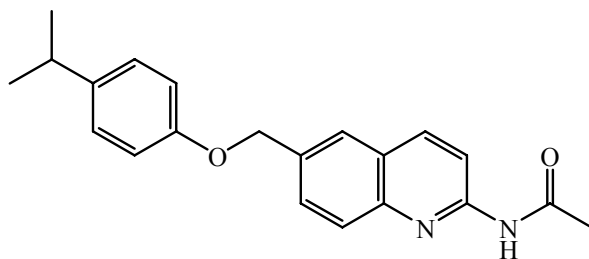
HRMS: Found 348.1829; C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> requires 348.1838. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3245, 3212, 1693, 1675, 1603, 1579, 1542, 1513 1497. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.30 [9H, s, (CH<sub>3</sub>)<sub>3</sub>], 2.34 [3H, s, COCH<sub>3</sub>], 5.21 [2H, s, CH<sub>2</sub>], 6.94-6.96 [2H, m, H(2') + H(6')], 7.32-7.34 [2H, m, H(3') + H(5')], 7.80 [1H, dd, <sup>4</sup>J<sub>4,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 9.0 Hz, H(7)], 7.88 [1H, d, J<sub>7,8</sub> = 9.0 Hz, H(8)], 7.90 [1H, s<sup>‡</sup>, H(5)], 8.29 [1H, d, J<sub>3,4</sub> = 9.6 Hz, H(4)], 8.50 [1H, br d, J<sub>3,4</sub> = 9.6 Hz, H(3)], 10.14 [1H, br s, NH]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 24.94 [COCH<sub>3</sub>], 31.47 [C(CH<sub>3</sub>)<sub>3</sub>], 34.09 [C(CH<sub>3</sub>)<sub>3</sub>], 69.31 [CH<sub>2</sub>], 114.45 [C(2') + C(6')], 114.54 [C(3)], 124.72 [C(8)], 125.46 [C(4a)], 126.03 [C(5)], 126.38 [C(3') + C(5')], 130.94 [C(7)], 135.93 [C(6)], 141.36 [C(4)], 141.82 [C(8a)], 144.26 [C(4')], 150.78 [C(2)], 156.29 [C(1')], 170.25 [C=O]. EIMS: *m/z*: 348 (M<sup>+</sup>, 3%), 305 (1), 199 (81), 157 (100).

**N-{6-[(3-*tert*-Butylphenoxy)methyl]quinolin-2-yl}acetamide (50)**



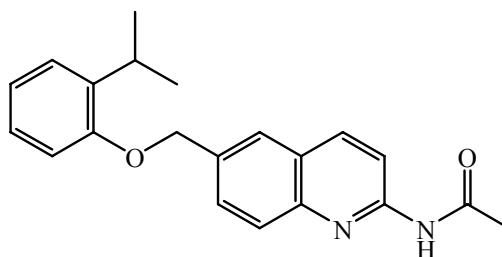
A mixture of **45** (0.50 g, 1.79 mmol), 3-*tert*-butylphenol (0.30 g, 2.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) and acetonitrile (25 mL) were heated as described above for 5 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **50** (0.54 g, 87%) as a white solid (m.p. 114-118°C). HRMS: Found 348.1840; C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> requires 348.1838. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3428, 3249, 3196, 3164, 1706, 1686, 1597, 1579, 1548, 1535, 1493. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.31 [9H, s, (CH<sub>3</sub>)<sub>3</sub>], 2.28 [3H, s, COCH<sub>3</sub>], 5.22 [2H, s, CH<sub>2</sub>], 6.83 [1H, ddd, <sup>4</sup>J<sub>4',6'</sub> = 0.9 Hz, <sup>4</sup>J<sub>2',4'</sub> = 2.4 Hz, J<sub>4',5'</sub> = 8.1 Hz, H(4')], 7.03 [1H, ddd, <sup>4</sup>J<sub>4',6'</sub> = 0.9 Hz, <sup>4</sup>J<sub>2',6'</sub> = 1.8 Hz, J<sub>5',6'</sub> = 7.8 Hz, H(6')], 7.07 [1H, dd, <sup>4</sup>J<sub>2',6'</sub> = 1.8 Hz, <sup>4</sup>J<sub>2',4'</sub> = 2.4 Hz, H(2')], 7.25 [1H, dd, J<sub>5',6'</sub> = 7.8 Hz, J<sub>4',5'</sub> = 8.1 Hz, H(5')], 7.77 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 8.7 Hz, H(7)], 7.85 [1H, d, J<sub>7,8</sub> = 8.7 Hz, H(8)], 7.88 [1H, s<sup>‡</sup>, H(5)], 8.22 [1H, d, J<sub>3,4</sub> = 8.7 Hz, H(4)], 8.44 [1H, br d, J<sub>3,4</sub> = 8.7 Hz, H(3)], 8.79 [1H, br s, NH]. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$ : 25.08 [COCH<sub>3</sub>], 31.48 [C(CH<sub>3</sub>)<sub>3</sub>], 34.96 [C(CH<sub>3</sub>)<sub>3</sub>], 69.68 [CH<sub>2</sub>], 111.15 [C(2')], 113.19 [C(6')], 114.74 [C(3)], 118.68 [C(4')], 126.00 [C(4a)], 126.32 [C(5)], 126.44 [C(8)], 129.26 [C(5')], 130.49 [C(7)], 135.17 [C(6)], 140.15 [C(4)], 145.38 [C(8a)], 151.16 [C(2)], 153.41 [C(3')], 158.64 [C(1')], 169.95 [C=O]. EIMS: *m/z*: 348 (M<sup>+</sup>, 1%), 305 (1), 199 (78), 157 (100).

**N-{6-[(4-Isopropylphenoxy)methyl]quinolin-2-yl}acetamide (51)**



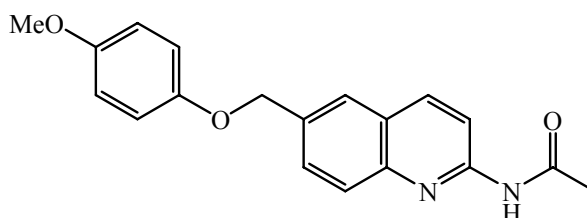
A mixture of **45** (0.50 g, 1.79 mmol), 4-*iso*-propylphenol (0.27 g, 2.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) and acetonitrile (25 mL) were heated as described above for 6 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **51** (0.30 g, 50%) as a cream coloured solid (m.p. 144-149°C). HRMS: Found 334.1682; C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> requires 334.1681. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3229, 3200, 3065, 1665, 1603, 1580, 1544, 1511, 1495. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.22 [6H, d,  $J = 7.2$ , (CH<sub>3</sub>)<sub>2</sub>], 2.20 [3H, s, COCH<sub>3</sub>], 2.86 [1H, sept,  $J = 7.2$  Hz, CH], 5.16 [2H, s, CH<sub>2</sub>], 6.93-6.95 [2H, m, H(2') + H(6')], 7.14-7.16 [2H, s, H(3') + H(5')], 7.70 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 9.0$  Hz, H(7)], 7.81 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 7.82 [1H, d,  $J_{7,8} = 9.0$  Hz, H(8)], 8.14 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)], 8.42 [1H, br s, H(3)], 9.48 [1H, br s, NH]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 24.08 [CH(CH<sub>3</sub>)<sub>2</sub>], 24.67 [COCH<sub>3</sub>], 33.18 [CH(CH<sub>3</sub>)<sub>2</sub>], 69.58 [CH<sub>2</sub>], 114.61 [C(2') + C(6')], 115.30 [C(3)], 125.88 [C(5)], 125.91 [C(4a)], 127.05 [C(8)], 127.27 [C(3') + C(5')], 129.55 [C(7)], 134.36 [C(6)], 138.86 [C(4')], 141.54 [C(4)], 145.52 [C(8a)], 151.31 [C(2)], 156.63 [C(1')], 169.53 [C=O]. EIMS:  $m/z$ : 334 (M<sup>+</sup>, 1%), 199 (71), 157 (100).

**N-{6-[(2-Isopropylphenoxy)methyl]quinolin-2-yl}acetamide (52)**



A mixture of **45** (0.50 g, 1.79 mmol), 2-*iso*-propylphenol (0.27 g, 2.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) and acetonitrile (25 mL) were heated as described above for 5 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **52** (0.37 g, 62%) as a cream coloured solid (m.p. 145-153°C). HRMS: Found 334.1678; C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> requires 334.1681. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3223, 3192, 3105, 1691, 1670, 1598, 1598, 1581, 1536, 1493. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.26 [6H, d,  $J$  = 7.2 Hz, (CH<sub>3</sub>)<sub>3</sub>], 2.31 [3H, s, COCH<sub>3</sub>], 3.44 [1H, sept,  $J$  = 7.2 Hz, CH], 5.24 [2H, s, CH<sub>2</sub>], 6.93 [1H, d,  $J_{5',6'} = 7.8$  Hz, H(6')], 6.98 [1H, dd,  $J_{3',4'} = J_{4',5'} = 7.8$  Hz, H(4')], 7.16 [1H, ddd,  $^4J_{3',5'} = 1.8$  Hz,  $J_{4',5'} = J_{5',6'} = 7.8$  Hz, H(5')], 7.27 [1H, dd,  $^4J_{3',5'} = 1.8$  Hz,  $J_{3',4'} = 7.8$  Hz, H(3')], 7.79 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.87-7.89 [2H, m, H(5) + H(8)], 8.26 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)], 8.48 [1H, br d,  $J_{3,4} = 9.0$  Hz, H(3)], 9.69 [1H, br s, NH]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 22.71 [CH(CH<sub>3</sub>)<sub>2</sub>], 24.89 [COCH<sub>3</sub>], 26.87 [CH(CH<sub>3</sub>)<sub>2</sub>], 69.498 [CH<sub>2</sub>], 111.74 [[C(3')], 114.53 [C(3)], 121.27 [C(5')], 125.67 [C(5) + C(8)], 125.78 [C(4a)], 126.30 [C(6')], 126.59 [C(4')], 130.17 [C(7)], 135.42 [C(6)], 137.36 [C(2')], 140.31 [C(4)], 143.46 [C(8a)], 150.89 [C(2)], 155.59 [C(1')], 169.97 [C=O]. EIMS:  $m/z$ : 334 (M<sup>+</sup>, 1%), 199 (76), 157 (100).

**N-{6-[(4-Methoxyphenoxy)methyl]quinolin-2-yl}acetamide (53)**

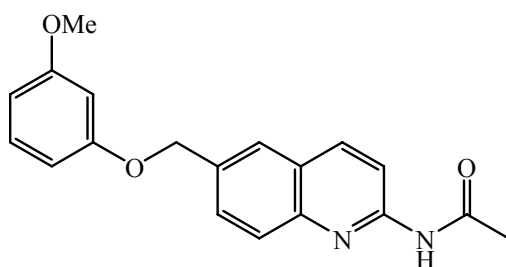


A mixture of **45** (0.30 g, 1.07 mmol), 4-methoxyphenol (0.15 g, 1.21 mmol), potassium carbonate (0.30 g, 2.18 mmol) and acetonitrile (15 mL) were heated as described above for 4 hours. After work up, the crude product was chromatographed over silica gel (50% ethyl



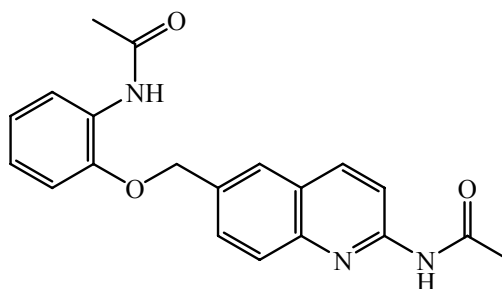
acetate / hexane) to give **53** (0.31 g, 87%) as a white solid (m.p. 153-157°C). HRMS: Found 322.1315; C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> requires 322.1317. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3232, 1666, 1601, 1579, 1511, 1493. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.26 [3H, s, COCH<sub>3</sub>], 3.77 [3H, s, OCH<sub>3</sub>], 5.17 [2H, s, CH<sub>2</sub>], 6.83-6.86 [2H, m, H(3') + H(5')], 6.93-6.96 [2H, m, H(2') + H(6')], 7.73 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 8.4 Hz, H(7)], 7.83 [1H, d, J<sub>7,8</sub> = 8.4 Hz, H(8)], 7.84 [1H, s, H(5)], 8.19 [1H, d, J<sub>3,4</sub> = 9.0 Hz, H(4)], 8.43 [1H, br d, J<sub>3,4</sub> = 9.0 Hz, H(3)], 8.77 [1H, br s, NH]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 24.90 [COCH<sub>3</sub>], 55.70 [OCH<sub>3</sub>], 70.31 [CH<sub>2</sub>], 114.47 [C(3)], 114.73 [C(3') + C(5')], 115.93 [C(2') + C(6')], 125.92 [C(4a)], 125.97 [C(5)], 126.83 [C(8)], 129.88 [C(7)], 134.71 [C(6)], 139.36 [C(4)], 145.01 [C(8a)], 150.96 [C(2)], 152.70 [C(1')], 154.19 [C(4')], 169.41 [C=O]. EIMS: *m/z*: 322 (M<sup>+</sup>, 4%), 199 (65), 157 (100).

#### **N-{6-[(3-Methoxyphenoxy)methyl]quinolin-2-yl}acetamide (54)**



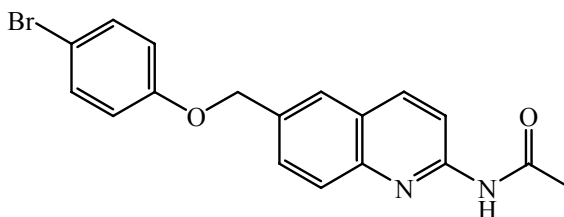
A mixture of **45** (0.40 g, 1.43 mmol), 3-methoxyphenol (0.17 mL, 1.57 mmol), potassium carbonate (0.40 g, 2.90 mmol) and acetonitrile (20 mL) were heated as described above for 2.5 hours. After work up, the crude product was chromatographed over silica gel (50% ethyl acetate / hexane) to give **54** (0.18 g, 39%) as a cream coloured solid (m.p. 118-121°C). HRMS: Found 322.1317; C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> requires 322.1317. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3410, 3236, 3196, 1674, 1614, 1596, 1580, 1537, 1491. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.21 [3H, s, COCH<sub>3</sub>], 3.78 [3H, s, OCH<sub>3</sub>], 5.17 [2H, s, CH<sub>2</sub>], 6.52-6.63 [3H, m, H(2') + H(4') + H(6')], 7.20 [1H, ddd, <sup>5</sup>J<sub>2',5'</sub> = 0.3 Hz, J<sub>4',5'</sub> = J<sub>5',6'</sub> = 8.1 Hz, H(5')], 7.71 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 8.4 Hz, H(7)], 7.82-7.85 [2H, m, H(5) + H(8)], 8.16 [1H, d, J<sub>3,4</sub> = 8.7 Hz, H(4)], 8.44 [1H, br d, J<sub>3,4</sub> = 8.7 Hz, H(3)], 9.28 [1H, br s, NH]. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$ : 24.92 [COCH<sub>3</sub>], 55.42 [OCH<sub>3</sub>], 69.74 [CH<sub>2</sub>], 101.67 [C(2')], 106.93 [C(6')], 107.15 [C(4')], 114.85 [C(3)], 126.12 [C(4a)], 126.17 [C(5)], 127.28 [C(8)], 129.80 [C(7)], 130.14 [C(5')], 134.33 [C(6)], 139.17 [C(4)], 145.62 [C(8a)], 151.45 [C(2)], 159.99 [C(1')], 161.06 [C(3')], 169.71 [C=O]. EIMS: *m/z*: 322 (M<sup>+</sup>, 3%), 199 (63), 157 (100).

**N-(6-{[2-(Acetylamino)phenoxy]methyl}quinolin-2-yl)acetamide (55)**



A mixture of **45** (0.50 g, 1.79 mmol), 2-acetamidophenol (0.15 g, 2.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) and acetonitrile (25 mL) were heated as described above for 5 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **55** (0.15 g, 24%) as a white solid (m.p. 191-201°C). HRMS: Found 349.1426; C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub> requires 349.1426. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3261, 3191, 1672, 1659, 1598, 1584, 1525, 1493. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.16 [3H, s, C(2')COCH<sub>3</sub>], 2.31 [3H, s, COCH<sub>3</sub>], 5.29 [2H, s, CH<sub>2</sub>], 6.95 [1H, dd, <sup>4</sup>J<sub>4',6'</sub> = 1.2 Hz, J<sub>5',6'</sub> = 7.8 Hz, H(6')], 6.98-7.03 [2H, m, H(4') + H(5')], 7.75 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 9.0 Hz, H(7)], 7.82 [1H, s<sup>‡</sup>, H(5)], 7.89 [1H, d, J<sub>7,8</sub> = 9.0 Hz, H(8)], 8.24 [1H, d, J<sub>3,4</sub> = 9.0 Hz, H(4)], 8.37 Hz [1H, dd, <sup>4</sup>J<sub>3',5'</sub> = 1.8 Hz, J<sub>3',4'</sub> = 7.2 Hz, H(3')], 8.49 [1H, br d, J<sub>3,4</sub> = 9.0 Hz, H(3)], 9.21 [1H, br s, NH]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 24.94 [2 x COCH<sub>3</sub>], 70.44 [CH<sub>2</sub>], 111.66 [C(6')], 114.74 [C(3)], 120.39 [C(3')], 121.84 [C(4')], 123.75 [C(5')], 125.69 [C(4a)], 126.40 [C(5) + C(8)], 128.00 [C(2')], 130.19 [C(7)], 134.12 [C(6)], 140.14 [C(4)], 143.89 [C(8a)], 146.81 [C(1')], 151.11 [C(2)], 168.16 [C=O]. EIMS: *m/z*: 349 (M<sup>+</sup>, 3%), 307 (1), 199 (69), 157 (100).

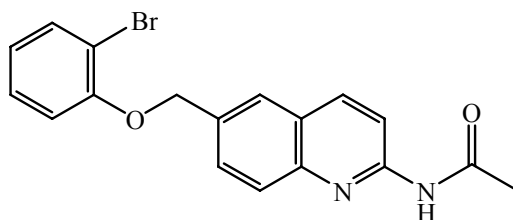
**N-{6-[(4-Bromophenoxy)methyl]quinolin-2-yl}acetamide (56)**



A mixture of **45** (0.50 g, 1.79 mmol), 4-bromophenol (0.34 g, 2.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) and acetonitrile (25 mL) were heated as described above for 6 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **56** (0.23 g, 35%) as a cream coloured solid (m.p. 157-

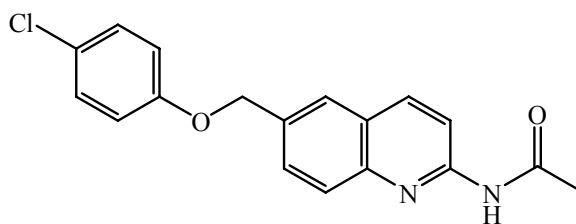
163°C). HRMS: Found 371.0391;  $[C_{18}H_{16}^{79}BrN_2O_2]^+$  requires 371.0390. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3288 3220, 1670, 1600, 1586, 1536, 1488.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 2.24 [3H, s,  $COCH_3$ ], 5.17 [2H, s,  $CH_2$ ], 6.87-6.91 [2H, m, H(2') + H(6')], 7.37-7.40 [2H, m, H(3') + H(5')], 7.70 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.81 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 7.83 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 8.17 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)], 8.44 [1H, br d,  $J_{3,4} = 9.0$  Hz, H(3)], 8.85 [1H, br s, NH].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 24.84 [ $COCH_3$ ], 69.81 [ $CH_2$ ], 113.39 [C(4')], 114.65 [C(3)], 116.68 [C(2') + C(6')], 125.97 [C(4a)], 126.01 [C(5)], 127.35 [C(8)], 129.48 [C(7)], 132.36 [C(3') + C(5')], 133.65 [C(6)], 138.95 [C(4)], 145.65 [C(8a)], 151.22 [C(2)], 157.64 [C(1')], 169.31 [C=O]. EIMS:  $m/z$ : 370 ( $M^+$ , 0.5%), 199 (68), 157 (100). LSIMS:  $m/z$ : 371 ( $M+H^+$ , 100%), 199 (88).

### N-{6-[(2-Bromophenoxy)methyl]quinolin-2-yl}acetamide (57)



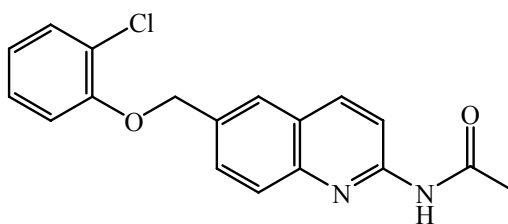
A mixture of **45** (0.50 g, 1.79 mmol), 2-bromophenol (0.34 g, 2.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) and acetonitrile (25 mL) were heated as described above for 5 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **57** (0.32 g, 48%) as a yellow solid (m.p. 138-144°C). HRMS: Found 370.0314;  $C_{18}H_{15}^{79}BrN_2O_2$  requires 370.0317. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3234, 3194, 3105, 1661, 1605, 1582, 1552, 1498.  $^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$ : 2.26 [3H, s,  $COCH_3$ ], 5.30 [2H, s,  $CH_2$ ], 6.87 [1H, ddd,  $^4J_{4',6'} = 1.2$  Hz,  $J_{4',5'} = 7.2$  Hz,  $J_{3',4'} = 7.8$  Hz, H(4')], 6.98 [1H, dd,  $^4J_{4',6'} = 1.2$  Hz,  $J_{5',6'} = 8.4$  Hz, H(6')], 7.25 [1H, ddd,  $^4J_{3',5'} = 1.2$  Hz,  $J_{4',5'} = 7.2$  Hz,  $J_{5',6'} = 8.4$  Hz, H(5')], 7.58 [1H, dd,  $^4J_{3',5'} = 1.2$  Hz,  $J_{3',4'} = 7.8$  Hz, H(3')], 7.77 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.84 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 7.89 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 8.18 [1H, d,  $J_{3,4} = 8.4$  Hz, H(4)], 8.31 [1H, br s, NH], 8.42 [1H, br d,  $J_{3,4} = 8.4$  Hz, H(3)].  $^{13}C$  NMR (50 MHz,  $CDCl_3$ ):  $\delta$ : 24.91 [ $COCH_3$ ], 70.56 [ $CH_2$ ], 112.63 [C(2')], 114.02 [C(6')], 114.45 [C(3)], 122.44 [C(4')], 125.65 [C(5)], 126.12 [C(4a)], 127.74 [C(8)], 128.46 [C(5')], 129.04 [C(7)], 133.50 [C(6)], 133.55 [C(3')], 138.69 [C(4)], 146.24 [C(8a)], 151.05 [C(2)], 154.91 [C(1')], 169.58 [C=O]. EIMS:  $m/z$ : 370 ( $M^+$ , 0.5%), 199 (67), 157 (100).

**N-{6-[(4-Chlorophenoxy)methyl]quinolin-2-yl}acetamide (58)**



A mixture of **45** (0.30 g, 1.07 mmol), 4-chlorophenol (0.15 g, 1.16 mmol), potassium carbonate (0.30 g, 2.18 mmol) and acetonitrile (15 mL) were heated as described above for 5 hours. After work up, the crude product was chromatographed over silica gel (20% ethanol / hexane) to give **58** (0.30 g, 84%) as a yellow solid (m.p.167-170°C). HRMS: Found 326.0813; C<sub>18</sub>H<sub>15</sub><sup>35</sup>ClN<sub>2</sub>O<sub>2</sub> requires 326.0822. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3283 3222, 3060, 1670, 1600, 1580, 1543, 1492. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.28 [1H, s, COCH<sub>3</sub>], 5.19 [1H, s, CH<sub>2</sub>], 6.91-6.95 [2H, m, H(2') + H(6')], 7.24-7.26 [1H, m, H(3') + H(5')], 7.74 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, J<sub>7,8</sub> = 8.4 Hz, H(7)], 7.84 [1H, d, <sup>4</sup>J<sub>5,7</sub> = 1.8 Hz, H(5)], 7.85 [1H, d, J<sub>7,8</sub> = 8.4 Hz, H(8)], 8.21 [1H, d, J<sub>3,4</sub> = 9.0 Hz, H(4)], 8.45 [1H, br d, J<sub>3,4</sub> = 9.0 Hz, H(3)], 9.10 [1H, br s, NH]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 24.88 [COCH<sub>3</sub>], 69.80 [CH<sub>2</sub>], 114.61 [C(3)], 116.17 [C(2') + C(6')], 125.84 [C(4a)], 126.05 [C(5)], 126.17 [C(4')], 126.70 [C(8)], 129.44 [C(3') + C(5')], 129.85 [C(7)], 134.08 [C(6)], 139.60 [C(4)], 144.63 [C(8a)], 151.05 [C(2)], 157.10[C(1')], 169.59 [C=O]. EIMS: *m/z*: 326 (M<sup>+</sup>, 1%), 199 (62), 157 (100).

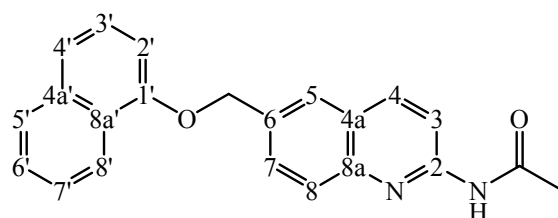
**N-{6-[(2-Chlorophenoxy)methyl]quinolin-2-yl}acetamide (59)**



A mixture of **45** (0.40 g, 1.43 mmol), 2-chlorophenol (0.16 mL, 1.57 mmol), potassium carbonate (0.40 g, 2.90 mmol) and acetonitrile (20 mL) were heated as described above for 5 hours. After work up, the crude product was chromatographed over silica gel (20% ethanol / hexane) to give **59** (0.26 g, 54%) as a pale brown solid (m.p.114-122°C). HRMS: Found 326.0817; C<sub>18</sub>H<sub>15</sub><sup>35</sup>ClN<sub>2</sub>O<sub>2</sub> requires 326.0822. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3239, 3202, 3060, 1661, 1606, 1586, 1553, 1499. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.26 [3H, s, COCH<sub>3</sub>], 5.30 [2H, s, CH<sub>2</sub>], 6.93 [1H, ddd, <sup>4</sup>J<sub>4',6'</sub> = 1.2 Hz, J<sub>3',4'</sub> = J<sub>4',5'</sub> = 7.8 Hz, H(4')], 7.00 [1H, dd,

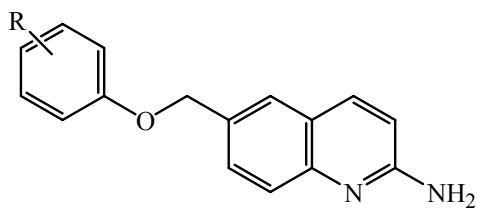
$^4J_{4',6'} = 1.2$  Hz,  $J_{5',6'} = 8.4$  Hz, H(6')], 7.20 [1H, ddd,  $^4J_{3',5'} = 1.8$  Hz,  $J_{4',5'} = 7.8$  Hz,  $J_{5',6'} = 8.4$  Hz, H(5')], 7.41 [1H, dd,  $^4J_{3',5'} = 1.8$  Hz,  $J_{3',4'} = 7.8$  Hz, H(3')], 7.77 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.85 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 7.88 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 8.20 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)], 8.43 [1H, br d,  $J_{3,4} = 9.0$  Hz, H(3)], 8.81 [1H, br s, NH].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 24.94 [COCH<sub>3</sub>], 70.48 [CH<sub>2</sub>], 114.23 [C(6')], 114.54 [C(3)], 122.00 [C(4')], 123.40 [C(2')], 125.74 [C(5)], 125.98 [C(4a)], 127.20 [C(8)], 127.70 [C(5')], 129.32 [C(7)], 130.47 [C(3')], 133.74 [C(6)], 139.98 [C(4)], 145.51 [C(8a)], 151.09 [C(2)], 154.03 [C(1')], 169.32 [C=O]. EIMS:  $m/z$ : 326 ( $\text{M}^+$ , 0.5%), 199 (64), 157 (100).

**N-{6-[(2-Naphthyloxy)methyl]quinolin-2-yl}acetamide (60)**



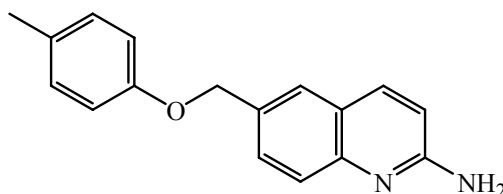
A mixture of **45** (0.60 g, 3.00 mmol), 1-naphthol (0.38 g, 2.61 mmol), potassium carbonate (0.83 g, 6.99 mmol) and acetonitrile (25 mL) were heated as described above for 6 hours. After work up, the crude product was chromatographed over silica gel (10% ethyl acetate / dichloromethane) to give **60** (0.20 g, 22%) as a pale brown solid (m.p. 165-171°C). HRMS: Found 342.1365; C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub> requires 342.1368. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3404, 3303, 1690, 1606, 1579, 1529, 1493.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.25 (3H, s, COCH<sub>3</sub>), 5.38 [2H, s, CH<sub>2</sub>], 6.90 [1H, d,  $J_{2',3'} = 7.2$  Hz, H(2')], 7.36 [1H, dd,  $J_{2',3'} = 7.2$  Hz,  $J_{3',4'} = 8.4$  Hz, H(3')], 7.46 [1H, d,  $J_{3',4'} = 8.4$  Hz, H(4')], 7.47-7.52 [2H, m, H(6') + H(7')], 7.81-7.82 [2H, m, H(5') + H(7)], 7.86 [1H, d,  $J_{7,8} = 9.0$  Hz, H(8)], 7.90 [1H, s, H(5)], 8.19 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)], 8.36 [1H, dd,  $^4J_{6',8'} = 2.4$  Hz,  $J_{7',8'} = 8.4$  Hz, H(8')], 8.44 [1H, br s, H(3)], 9.06 [1H, br s, NH].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 24.84 [COCH<sub>3</sub>], 69.67 [CH<sub>2</sub>], 105.28 [C(2')], 114.57 [C(3)], 120.76 [C(4')], 122.00 [C(8')], 125.35 [C(7')], 125.68 [C(8a')], 125.74 [C(3')], 125.85 [C(5)], 125.94 [C(4a)], 126.50 [C(6')], 126.97 [C(8)], 127.51 [C(5')], 129.70 [C(7)], 134.40 [C(6)], 134.56 [C(4a')], 139.24 [C(4)], 145.175 [(8a)], 151.10 [C(1')], 154.24 [C(2)], 169.46 [C=O]. EIMS:  $m/z$ : 342 ( $\text{M}^+$ , 2%), 199 (58), 157 (100).

**General Method for Synthesis of 6-(Phenoxymethyl)quinolin-2-amines<sup>50</sup>**



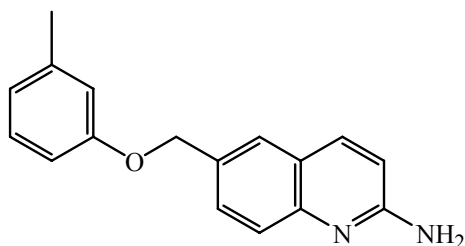
The acetamide protected quinoline (1 mol. equiv) was treated with potassium carbonate (1.5 mol. equiv) in methanol at 60°C for the prescribed length of time. The reaction mixture was then cooled, water was added and the resulting precipitate was filtered and washed with water to afford an analytically pure 2-aminoquinoline.

**6-[(4-Methylphenoxy)methyl]quinolin-2-amine (61)**



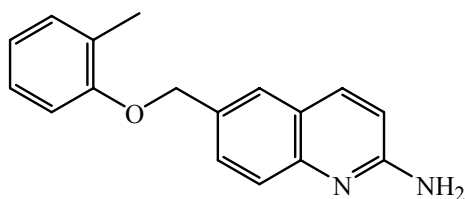
A mixture of **46** (80 mg, 0.26 mmol), potassium carbonate (54 mg, 0.39 mmol) and methanol (3 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **61** (49 mg, 71%) as a cream coloured solid (m.p. 182-194°C). Analysis Found: C, 76.27; H, 6.13; N, 10.38;  $C_{17}H_{16}N_2O \cdot 0.2H_2O$  requires C, 76.21; H, 6.17; N, 10.46%. HRMS: Found 264.1257;  $C_{17}H_{16}N_2O$  requires 264.1263. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3440, 3305, 3130, 1661, 1609, 1583, 1568, 1509, 1494.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 2.29 [3H, s,  $CH_3$ ], 4.81 [2H, br s,  $NH_2$ ], 5.13 [2H, s,  $CH_2$ ], 6.73 [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.89-6.92 [2H, m, H(2') + H(6')], 7.08-7.10 [2H, m, H(3') + H(5')], 7.62 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.68 [1H, s<sup>†</sup>, H(5)], 7.68 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 7.88 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 20.47 [ $CH_3$ ], 70.03 [ $CH_2$ ], 111.86 [C(3)], 114.78 [C(2')], 123.38 [C(4a)], 126.25 [C(5) + C(8)], 129.46 [C(7)], 129.93 [C(3')], 130.24 [C(4')], 131.75 [C(6)], 138.19 [C(4)], 147.21 [C(8a)], 156.68 [C(1')], 156.95 [C(2)]. EIMS:  $m/z$ : 264 ( $M^+$ , 3%), 157 (100).

### 6-[(3-Methylphenoxy)methyl]quinolin-2-amine (62)



A mixture of **47** (150 mg, 0.49 mmol), potassium carbonate (100 mg, 0.74 mmol) and methanol (3 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **62** (101 mg, 77%) as a pale yellow solid (m.p. 138-142°C). Analysis Found: C, 76.90; H, 6.23; N, 10.70; C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O requires C, 77.25; H, 6.10; N, 10.60%. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3437, 3306, 3132, 1662, 1628, 1594, 1567, 1491. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.33 [3H, s, CH<sub>3</sub>], 4.80 [2H, br s, NH<sub>2</sub>], 5.14 [2H, s, CH<sub>2</sub>], 6.72 [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.79 [1H, dd,  $J = 1.2$  Hz,  $J_{4',5'} = 7.8$  Hz, H(4')], 6.81 [1H, d<sup>‡</sup>,  $J_{5',6'} = 7.8$  Hz, H(6')], 6.84 [1H, s<sup>‡</sup>, H(2')], 7.18 [1H, dd,  $J_{4',5'} = J_{5',6'} = 7.8$  Hz, H(5')], 7.61 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 9.0$  Hz, H(7)], 7.67-7.68 [2H, m, H(5) + H(8)], 7.87 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 21.52 [CH<sub>3</sub>], 69.81 [CH<sub>2</sub>], 111.70 [C(6')], 111.86 [C(3)], 115.77 [C(2')], 121.82 [C(4')], 123.41 [C(4a)], 126.26 [C(5)], 126.38 [C(8)], 129.21 [C(5')], 129.38 [C(7)], 131.39 [C(6)], 138.05 [C(4)], 139.55 [C(3')], 147.47 [C(8a)], 157.05 [C(2)], 158.84 [C(1')]. EIMS:  $m/z$ : 264 (M<sup>+</sup>, 4%), 157 (100).

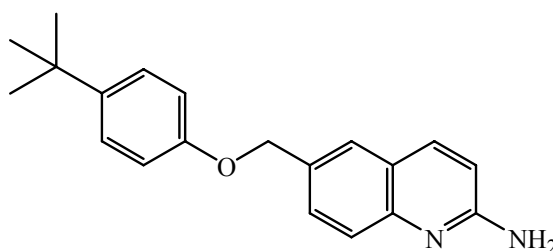
### 6-[(2-Methylphenoxy)methyl]quinolin-2-amine (63)



A mixture of **48** (120 mg, 0.37 mmol), potassium carbonate (82 mg, 0.59 mmol) and methanol (5 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **63** (87 mg, 84%) as a pale yellow solid (149-156°C). Analysis Found: C, 77.09; H, 6.22; N, 10.69; C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O requires C, 77.25; H, 6.10; N, 10.60%. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3439, 3307, 3124, 1662, 1626, 1602, 1590, 1567, 1508, 1495. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.30 [3H, s, CH<sub>3</sub>], 4.80 [2H, br s, NH<sub>2</sub>], 5.17 [2H, s, CH<sub>2</sub>], 6.73 [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.88 [1H, ddd,  $^4J_{4',6'} = 1.2$  Hz,  $J_{3',4'} = J_{4',5'} = 7.2$  Hz, H(4')],

6.92 [1H, d<sup>‡</sup>,  $J_{5,6'} = 8.4$ , H(6')], 7.14-7.18 [2H, m, H(3') + H(5')], 7.64 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.68-7.69 [2H, m, H(5) + H(8)], 7.89 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ: 16.40 [CH<sub>3</sub>], 69.84 [CH<sub>2</sub>], 111.60 [C(6')], 111.85 [C(3)], 120.67 [C(4')] 123.37 [C(4a)], 125.87 [C(5)], 126.25 [C(8)], 126.76 [C(5')], 127.15 [C(2')], 129.20 [C(7)], 130.76 [C(3')], 131.82 [C(6)], 138.15 [C(4)], 147.25 [C(8a)], 156.92 [C(2)], 156.96 [C(1')]. EIMS:  $m/z$ : 264 (M<sup>+</sup>, 2%), 157 (100).

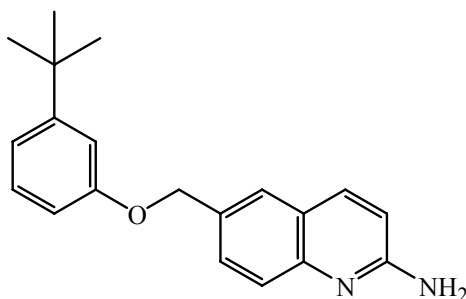
**6-[(4-tert-Butylphenoxy)methyl]quinolin-2-amine (64)**



A mixture of **49** (150 mg, 0.43 mmol), potassium carbonate (90 mg, 0.65 mmol) and methanol (6 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **64** (125 mg, 95%) as a white solid (m.p. 179-183°C). Analysis Found: C, 78.59; H, 7.25; N, 9.20; C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O requires C, 78.40; H, 7.24; N, 9.14%. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3392, 3312, 3102, 1656, 1608, 1571, 1513, 1490. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ: 1.30 [9H, s, (CH<sub>3</sub>)<sub>3</sub>], 4.78 [2H, br s, NH<sub>2</sub>], 5.14 [2H, s, CH<sub>2</sub>], 6.72, [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.93-6.96 [2H, m, H(2') + H(6')], 7.31-7.33 [2H, m, H(3') + H(5')], 7.61 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.68 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 7.68 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 7.87 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ: 31.51 [C(CH<sub>3</sub>)<sub>3</sub>], 34.08 [C(CH<sub>3</sub>)<sub>3</sub>], 69.97 [CH<sub>2</sub>], 111.85 [C(3)], 114.32 [C(2')], 123.42 [C(4a)], 126.26 [C(3')], 126.28 [C(5)], 126.39 [C(8)], 129.42 [C(7)], 131.52 [C(6)], 138.06 [C(4)], 143.67 [C(4')], 147.47 [C(8a)], 156.59 [C(1')], 157.03 [C(2)]. EIMS:  $m/z$ : 306 (M<sup>+</sup>, 3%), 157 (100).

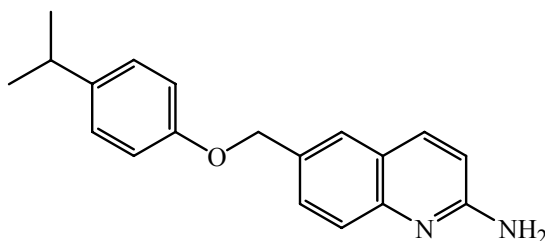


**6-[(3-tert-Butylphenoxy)methyl]quinolin-2-amine (65)**



A mixture of **50** (150 mg, 0.43 mmol), potassium carbonate (90 mg, 0.65 mmol) and methanol (6 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **65** (121 mg, 92%) as a white solid (m.p. 161-164°C). Analysis Found: C, 78.57; H, 7.24; N, 9.20; C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O requires C, 78.40; H, 7.24; N, 9.14%. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3413, 3307, 3156, 1645, 1608, 1575, 1509, 1485. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.30 [9H, s, (CH<sub>3</sub>)<sub>3</sub>], 4.81 [2H, br s, NH<sub>2</sub>], 5.15 [2H, s, CH<sub>2</sub>], 6.72, [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.83 [1H, ddd,  $^4J_{4',6'} = 1.2$  Hz,  $^4J_{2',6'} = 2.4$  Hz,  $J_{5',6'} = 8.4$  Hz, H(6')], 7.01 [1H, ddd,  $^4J_{4',6'} = 1.2$  Hz,  $^4J_{2',4'} = 1.8$  Hz,  $J_{4',5'} = 7.8$  Hz, H(4')], 7.06 [1H, dd,  $^4J_{2',4'} = 1.8$  Hz,  $^4J_{2',6'} = 2.4$  Hz, H(2')], 7.24 [1H, dd,  $J_{4',5'} = 7.8$  Hz,  $J_{5',6'} = 8.4$  Hz, H(5')], 7.63 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.68 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 7.69 [1H, s<sup>‡</sup>, H(5)], 7.88 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 31.29 [C(CH<sub>3</sub>)<sub>3</sub>], 34.75 [C(CH<sub>3</sub>)<sub>3</sub>], 69.93 [CH<sub>2</sub>], 110.89 [C(6')], 111.87 [C(3)], 113.03[C(2')], 118.17 [C(4')], 123.42 [C(4a)], 126.39 [C(8)], 126.44 [C(5)], 128.97 [C(5')], 129.53 [C(7)], 131.40 [C(6)], 138.06 [C(4)], 147.48 [C(8a)], 153.04 [C(3')], 157.05 [C(2)], 158.68 [C(1')]. EIMS:  $m/z$ : 306 (M<sup>+</sup>, 4%), 157 (100).

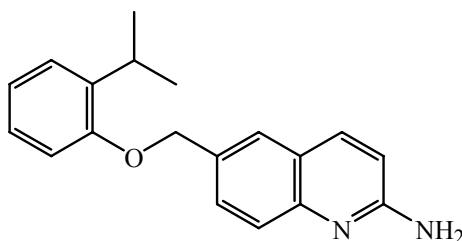
**6-[(4-Isopropylphenoxy)methyl]quinolin-2-amine (66)**



A mixture of **51** (150 mg, 0.45 mmol), potassium carbonate (93 mg, 0.68 mmol) and methanol (6 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **66** (115 mg, 88%) as a white solid (m.p. 179-182°C). Analysis

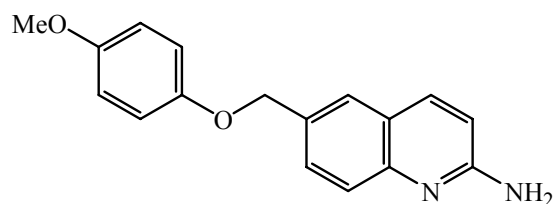
Found: C, 78.21; H, 7.11; 9.62; C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O requires C, 78.05; H, 6.89; N, 9.58%. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3446, 3306, 3140, 1659, 1627, 1609, 1568, 1510, 1494. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.23 [6H, d,  $J = 7.2$  Hz, (CH<sub>3</sub>)<sub>2</sub>], 2.87 [1H, sept,  $J = 7.2$  Hz, CH], 4.77 [2H, br s, NH<sub>2</sub>], 5.13 [1H, s, CH<sub>2</sub>], 6.72, [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.93-6.95 [2H, m, H(2') + H(6')], 7.14-7.17 [2H, m, H(3') + H(5')], 7.61 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.67 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 7.67 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 7.87 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 24.18 [(CH<sub>3</sub>)<sub>2</sub>], 33.28 [CH], 70.02 [CH<sub>2</sub>], 111.84 [C(3)], 114.69 [C(2')], 123.42 [C(4a)], 126.27 [C(5)], 126.40 [C(8)], 127.29 [C(3')], 129.41 [C(7)], 131.52 [C(6)], 138.06 [C(4)], 141.40 [C(4')], 147.48 [C(8a)], 156.92 [C(1')], 157.03 [C(2)]. EIMS:  $m/z$ : 292 (M<sup>+</sup>, 3%), 157 (100).

**6-[(2-Isopropylphenoxy)methyl]quinolin-2-amine (67)**



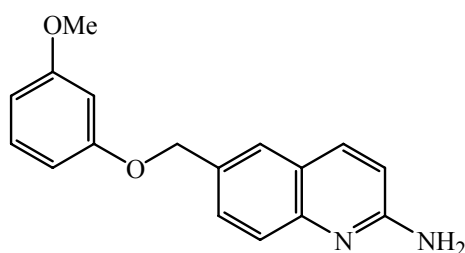
A mixture of **52** (150 mg, 0.45 mmol), potassium carbonate (93 mg, 0.68 mmol) and methanol (6 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **67** (126 mg, 96%) as a cream coloured solid (m.p. 140-142°C). Analysis Found: C, 78.17; H, 6.82; N, 9.70; C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O requires C, 78.05; H, 6.89; N, 9.58%. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3453, 3309, 3130, 1646, 1624, 1606, 1567, 1490. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.25 [6H, d,  $J = 6.6$  Hz, (CH<sub>3</sub>)<sub>2</sub>], 3.43 [1H, sept,  $J = 6.6$  Hz, CH], 4.79 [2H, br s, NH<sub>2</sub>], 5.17 [2H, s, CH<sub>2</sub>], 6.73, [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.94-6.97 [2H, m, H(4') + H(6')], 7.15 [1H, ddd,  $^4J_{3',5'} = 1.8$  Hz,  $J = 7.8$  Hz,  $J = 9.0$  Hz, H(5')], 7.25 [1H, dd,  $^4J_{3',5'} = 1.8$  Hz,  $J_{3',4'} = 8.4$ , H(3')], 7.63 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 9.0$  Hz, H(7)], 7.68 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 7.69 [1H, d,  $J_{7,8} = 9.0$  Hz, H(8)], 7.88 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 22.72 [(CH<sub>3</sub>)<sub>2</sub>], 26.84 [CH], 70.01 [CH<sub>2</sub>], 111.84 [C(6') + C(3)], 120.95 [C(4')] 123.39 [C(4a)], 125.88 [C(5)], 126.16 [C(3')], 126.35 [C(8)], 126.53 [C(5')], 129.17 [C(7)], 131.80 [C(6)], 137.42 [C(2')], 138.06 [C(4)], 147.41 [C(8a)], 155.93 [C(1')], 157.01 [C(2)]. EIMS:  $m/z$ : 292 (M<sup>+</sup>, 3%), 157 (100).

### 6-[(4-Methoxyphenoxy)methyl]quinolin-2-amine (68)



A mixture of **53** (100 mg, 0.31 mmol), potassium carbonate (64 mg, 0.47 mmol) and methanol (5 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **68** (79 mg, 91%) as a white solid (m.p. 185-197°C). Analysis Found: C, 72.09; H, 5.78; N, 9.72;  $C_{17}H_{16}N_2O_2 \cdot 0.2H_2O$  requires C, 71.91; H, 5.82; N, 9.87%. HRMS: Found 280.1211;  $C_{17}H_{16}N_2O_2$  requires 280.1212. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3440, 3305, 3132, 1662, 1628, 1608, 1568, 1509, 1494.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 3.77 [3H, s,  $CH_3$ ], 4.76 [2H, br s,  $NH_2$ ], 5.17 [2H, s,  $CH_2$ ], 6.73 [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.83-6.85 [2H, m, H(3') + H(5')], 6.93-6.95 [2H, m, H(2') + H(6')], 7.61 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.67-7.68 [2H, m, H(5) + H(8)], 7.88 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 55.72 [ $CH_3$ ], 70.71 [ $CH_2$ ], 111.85 [C(3)], 114.68 [C(3')], 115.96 [C(2')], 123.45 [C(4a)], 126.28 [C(8)], 126.40 [C(5)], 129.42 [C(7)], 131.55 [C(6)], 138.07 [C(4)], 147.48 [C(2)], 152.97 [C(4')], 154.03 [C(1')], 157.02 [C(2)]. EIMS:  $m/z$ : 280 ( $M^+$ , 2%), 157 (100).

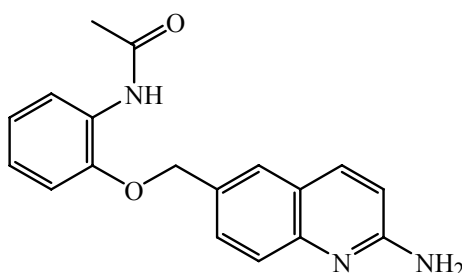
### 6-[(3-Methoxyphenoxy)methyl]quinolin-2-amine (69)



A mixture of **54** (100 mg, 0.31 mmol), potassium carbonate (64 mg, 0.47 mmol) and methanol (5 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **69** (73 mg, 84%) as a cream coloured solid (m.p. 171-173°C). Analysis Found: C, 72.57; H, 5.89; N, 10.05;  $C_{17}H_{16}N_2O_2$  requires C, 72.84; H, 5.75; N, 9.99%. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3433, 3323, 3142, 1661, 1612, 1597, 1565, 1493.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 3.79 [3H, s,  $CH_3$ ], 4.81 [2H, br s,  $NH_2$ ], 5.14 [2H, s,  $CH_2$ ], 6.53 [1H, ddd,  $^4J_{4',6'} = 0.6$  Hz,  $^4J_{2',6'} = 2.4$  Hz,  $J_{5',6'} = 8.4$  Hz, H(6')], 6.58 [1H, dd,  $^4J_{2',4'} = ^4J_{2',6'} = 2.4$

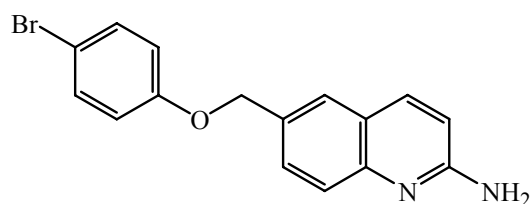
Hz, H(2')), 6.61 [1H, ddd,  $^4J_{4',6'} = 0.6$  Hz,  $^4J_{2',4'} = 2.4$  Hz,  $J_{4',5'} = 8.4$  Hz, H(4')], 6.73, [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 7.19 [1H, dd,  $J_{4',5'} = J_{5',6'} = 8.4$  Hz, H(5')], 7.62 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 9.0$  Hz, H(7)], 7.68-7.69 [2H, m, H(8) + H(5)], 7.88 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 55.28 [ $\text{CH}_3$ ], 69.97 [ $\text{CH}_2$ ], 101.44 [C(2')], 106.66 [C(6')], 106.98 [C(4')], 111.90 [C(3)], 123.40 [C(4a)], 126.36 [C(8)], 126.37 [C(5)], 129.45 [C(7)], 129.92 [C(5')], 131.23 [C(6)], 138.13 [C(4)], 147.37 [C(8a)], 157.03 [C(2)], 160.06 [C(1')], 160.86 [C(3')]. EIMS:  $m/z$ : 280 ( $\text{M}^{+\bullet}$ , 1%), 157 (100).

***N*-{4-[(2-Aminoquinolin-6-yl)methoxy]phenyl}acetamide (70)**



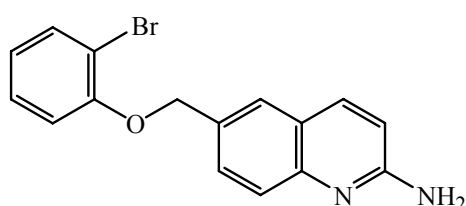
A mixture of **55** (60 mg, 0.17 mmol), potassium carbonate (59 mg, 0.43 mmol, 2.5 equiv) and methanol (4 mL) were heated as described above for 1.5 hours. The work up was carried out with 3 mL of water to give **70** (36 mg, 78%) as a cream coloured solid (m.p. 235-238°C). Analysis Found: C, 70.39; H, 5.80; N, 13.58;  $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$  requires C, 70.34; H, 5.58; N, 13.67%. IR (nujol mull):  $\nu$  ( $\text{cm}^{-1}$ ): 3462, 3292, 3139, 1666, 1648, 1595, 1539, 1488.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.13 [3H, s,  $\text{COCH}_3$ ], 4.79 [2H, br s,  $\text{NH}_2$ ], 5.21 [2H, s,  $\text{CH}_2$ ], 6.76, [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.97-7.03 [3H, m, H(4') + H(5') + H(6')], 7.60 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.64 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 7.71 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 7.75 [1H, br s, NH], 7.88 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)], 8.38 [1H, d $^\ddagger$ ,  $J_{3',4'} = 7.2$ , H(3')].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 24.95 [ $\text{COCH}_3$ ], 70.11 [ $\text{CH}_2$ ], 111.80 [C(6')], 112.11 [C(3)], 119.35 [C(3')], 120.03 [C(4')], 121.59 [C(2')], 123.41 [C(4a)], 123.62 [C(5')], 126.71 [C(8)], 126.74 [C(5)], 129.38 [C(7)], 130.54 [C(6)], 138.00 [C(4)], 147.02 [C(1')], 147.74 [C(8a)], 157.24 [C(2)], 168.14 [C=O]. EIMS:  $m/z$ : 307 ( $\text{M}^{+\bullet}$ , 3%), 289 (31), 247 (12), 157 (100).

### 6-[(4-Bromophenoxy)methyl]quinolin-2-amine (71)



A mixture of **56** (150 mg, 0.40 mmol), potassium carbonate (84 mg, 0.61 mmol) and methanol (6 mL) were heated as described above for 1.5 hours. The work up was carried out with 3 mL of water to give **71** (112 mg, 86%) as a white solid (m.p. 186-189°C). Analysis Found: C, 58.54; H, 4.04; N, 8.51;  $C_{16}H_{13}BrN_2O$  requires C, 58.38; H, 3.98; N, 8.51%. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3438 3305, 3122, 1660, 1627, 1606, 1588, 1567, 1507, 1485.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 4.79 [2H, br s,  $NH_2$ ], 5.12 [2H, s,  $CH_2$ ], 6.73 [1H, d,  $J_{3,4} = 8.7$  Hz, H(3)], 6.87-6.89 [2H, m, H(2') + H(6')], 7.37-7.39 [2H, m, H(3') + H(5')], 7.59 [1H, dd,  $^4J_{5,7} = 2.1$  Hz,  $J_{7,8} = 9.0$  Hz, H(7)], 7.65 [1H, s $^\ddagger$ , H(5)], 7.68 [1H, d,  $J_{7,8} = 9.0$  Hz, H(8)], 7.87 [1H, d,  $J_{3,4} = 8.7$  Hz, H(4)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 70.20 [ $CH_2$ ] 111.97 [C(3)], 113.18 [C(4')], 116.75 [C(2') + C(6')], 123.40 [C(4a)], 126.34 [C(5)], 126.53 [C(8)], 129.26 [C(7)], 130.71 [C(6)], 132.30 [C(3') + C(5')], 138.02 [C(4)], 147.58 [C(8a)], 157.12 [C(2)], 157.87 [C(1')]. EIMS:  $m/z$ : 330 ( $M^+$  [ $^{81}Br$ ], 1%), 328 ( $M^+$  [ $^{79}Br$ ], 1%), 157 (100).

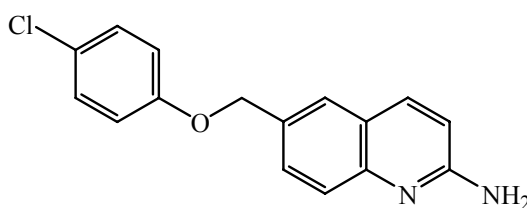
### 6-[(2-Bromophenoxy)methyl]quinolin-2-amine (72)



A mixture of **57** (150 mg, 0.40 mmol), potassium carbonate (84 mg, 0.61 mmol) and methanol (6 mL) were heated as described above for 1.5 hours. The work up was carried out with 3 mL of water to give **72** (118 mg, 89%) as a pale yellow solid (m.p. 182-186°C). Analysis Found: C, 58.54; H, 4.08; N, 8.58;  $C_{16}H_{13}BrN_2O$  requires C, 58.38; H, 3.98; N, 8.51%. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3454, 3304, 3101, 1646, 1608, 1583, 1569, 1493.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 4.76 [2H, br s,  $NH_2$ ], 5.25 [2H, s,  $CH_2$ ], 6.73 [1H, d,  $J_{3,4} = 8.7$  Hz, H(3)], 6.85 [1H, ddd,  $^4J_{4,6'} = 1.2$  Hz,  $J_{4,5'} = 7.2$  Hz,  $J_{3,4'} = 7.8$  Hz, H(4')], 6.98 [1H, dd,  $^4J_{4,6'} = 1.2$  Hz,  $J_{5,6'} = 8.4$  Hz, H(6')], 7.23 [1H, ddd,  $^4J_{3,5'} = 1.2$  Hz,  $J_{4,5'} = 7.2$  Hz,  $J_{5,6'} =$

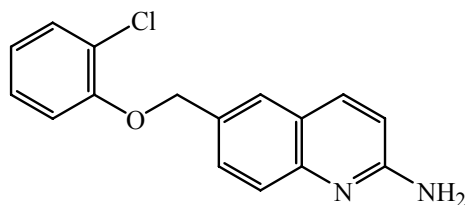
8.4 Hz, H(5')), 7.57 [1H, dd,  $^4J_{3',5'} = 1.2$  Hz,  $J_{3',4'} = 7.8$  Hz, H(3')], 7.65 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 9.0$  Hz, H(7)], 7.68 [1H, d,  $J_{7,8} = 9.0$  Hz, H(8)], 7.73 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 7.89 [1H, d,  $J_{3,4} = 8.7$  Hz, H(4)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 70.85 [ $\text{CH}_2$ ] 111.89 [C(3)], 112.64 [C(2')], 114.15 [C(6')], 122.25 [C(4')], 123.43 [C(4a)], 125.92 [C(5)], 126.45 [C(8)], 128.41 [C(5')], 128.90 [C(7)], 130.76 [C(6)], 133.47 [C(3')], 138.11 [C(4)], 147.53 [C(8a)], 155.07 [C(1')], 157.06 [C(2)]. EIMS:  $m/z$ : 330 ( $\text{M}^+$  [ $^{81}\text{Br}$ ], 1%), 328 ( $\text{M}^+$  [ $^{79}\text{Br}$ ], 1%), 157 (100).

**6-[(4-Chlorophenoxy)methyl]quinolin-2-amine (73)**



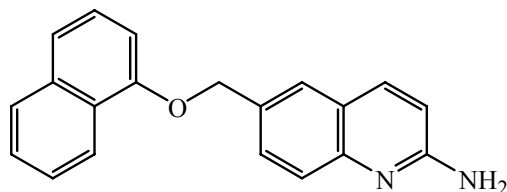
A mixture of **58** (150 mg, 0.45 mmol), potassium carbonate (95 mg, 0.69 mmol) and methanol (6 mL) were heated as described above for 1.5 hours. The work up was carried out with 3 mL of water to give **73** (109 mg, 83%) as a cream coloured solid (m.p. 160-172°C). Analysis Found: C, 67.64; H, 4.79; N, 9.62;  $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}$  requires C, 67.49; H, 4.60; N, 9.84%. IR (nujol mull):  $\nu$  ( $\text{cm}^{-1}$ ): 3439, 3304, 3131, 1660, 1626, 1595, 1568, 1510, 1488.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 4.78 [2H, br s,  $\text{NH}_2$ ], 5.13 [2H, s,  $\text{CH}_2$ ], 6.73 [1H, d,  $J_{3,4} = 8.7$  Hz, H(3)], 6.91-6.94 [2H, m, H(2') + H(6')], 7.23-7.25 [2H, m, H(3') + H(5')], 7.59 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 9.0$  Hz, H(7)], 7.65 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 7.68 [1H, d,  $J_{7,8} = 9.0$  Hz, H(8)], 7.87 [1H, d,  $J_{3,4} = 8.7$  Hz, H(4)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 70.28 [ $\text{CH}_2$ ] 111.96 [C(3)], 116.23 [C(2') + C(6')], 123.40 [C(4a)], 125.88 [C(4')], 126.34 [C(5)], 126.53 [C(8)], 129.27 [C(7)], 129.37 [C(3') + C(5')], 130.77 [C(6)], 138.02 [C(4)], 147.58 [C(8a)], 157.12 [C(2)], 157.37 [C(1')]. EIMS:  $m/z$ : 286 ( $\text{M}^+$  [ $^{37}\text{Cl}$ ], <1%), 284 ( $\text{M}^+$  [ $^{35}\text{Cl}$ ], 1%), 157 (100).

### 6-[(2-Chlorophenoxy)methyl]quinolin-2-amine (74)



A mixture of **59** (150 mg, 0.45 mmol), potassium carbonate (95 mg, 0.69 mmol) and methanol (6 mL) were heated as described above for 1.5 hours. The work up was carried out with 3 mL of water to give **74** (98 mg, 75%) as a cream coloured solid (m.p. 176-186°C). Analysis Found: C, 67.41; H, 4.63; N, 9.83; C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O requires C, 67.49; H, 4.60; N, 9.84%. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3466, 3308, 3129, 1649, 1625, 1588, 1576, 1509, 1493. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 4.76 [2H, br s, NH<sub>2</sub>], 5.25 [2H, s, CH<sub>2</sub>], 6.73 [1H, d,  $J_{3,4}$  = 9.0 Hz, H(3)], 6.91 [1H, ddd,  $^4J_{4',6'} = 1.2$  Hz,  $J_{4',5'} = 7.2$  Hz,  $J_{3',4'} = 7.8$  Hz, H(4')], 7.00 [1H, dd,  $^4J_{4',6'} = 1.2$  Hz,  $J_{5',6'} = 8.4$  Hz, H(6')], 7.18 [1H, ddd,  $^4J_{3',5'} = 1.2$  Hz,  $J_{4',5'} = 7.2$  Hz,  $J_{5',6'} = 8.4$  Hz, H(5')], 7.39 [1H, dd,  $^4J_{3',5'} = 1.2$  Hz,  $J_{3',4'} = 7.8$  Hz, H(3')], 7.64 [1H, dd,  $^4J_{5,7} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.68 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 7.72 [1H, d,  $^4J_{5,7} = 1.8$  Hz, H(5)], 7.89 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 70.85 [CH<sub>2</sub>], 111.89 [C(3)], 114.36 [C(6')], 121.77 [C(4')], 123.40 [C(2')], 123.43 [C(4a)], 125.99 [C(5)], 126.47 [C(8)], 127.65 [C(5')], 128.97 [C(7)], 130.39 [C(3')], 130.78 [C(6)], 138.10 [C(4)], 147.53 [C(8a)], 154.23 [C(1')], 157.06 [C(2)]. EIMS:  $m/z$ : 286 (M<sup>+</sup> [<sup>37</sup>Cl], 1%), 284 (M<sup>+</sup> [<sup>35</sup>Cl], 3%), 157 (100).

### 6-[(2-Naphthyloxy)methyl]quinolin-2-amine (75)



A mixture of **60** (100 mg, 0.29 mmol), potassium carbonate (61 mg, 0.44 mmol) and methanol (5 mL) were heated as described above for 2 hours. The work up was carried out with 4 mL of water to give **75** (76 mg, 86%) as a pale brown solid (m.p. 194-201°C). Analysis Found: C, 79.26; H, 5.49; N, 9.22; C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O.0.2H<sub>2</sub>O requires C, 79.03; H, 5.44; N, 9.22%. HRMS: Found 301.1342; [C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O+H]<sup>+</sup> requires 301.1335. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3451, 3302, 3093, 1646, 1627, 1594, 1576, 1510, 1492. <sup>1</sup>H NMR (600 MHz,

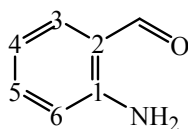
CDCl<sub>3</sub>):  $\delta$ : 4.80 [2H, br s, NH<sub>2</sub>], 5.35 [2H, s, CH<sub>2</sub>], 6.74 [1H, d,  $J_{3,4} = 9.0$  Hz, H(3)], 6.93 [1H, d,  $J_{2,3'} = 7.2$  Hz, H(2')], 7.37 [1H, dd,  $J_{2,3'} = 7.2$  Hz,  $J_{3',4'} = 8.4$  Hz, H(3')], 7.37 [1H, d<sup>†</sup>,  $J_{3',4'} = 8.4$  Hz, H(4')], 7.46-7.51 [2H, m, H(6') + H(7')], 7.72 [2H, m, H(7) + H(8)], 7.76 [1H, s, H(5)], 7.81 [1H, dd,  $J_{5,7'} = 1.8$  Hz,  $J_{5,6'} = 7.8$  Hz, H(5')], 7.90 [1H, d,  $J_{3,4} = 9.0$  Hz, H(4)], 8.36 [1H, ddd,  ${}^4J_{4,8'} = {}^4J_{6,8'} = 1.2$  Hz,  $J_{7,8'} = 7.2$  Hz, H(8')]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 70.10 [CH<sub>2</sub>], 105.29 [C(2')], 111.91 [C(3)], 120.54 [C(4')], 122.18 [C(8')], 123.43 [C(4a)], 125.25 [C(7')], 125.82 [C(3') + C(8a')], 126.18 [C(5)], 126.42 [C(6')<sup>†</sup>], 126.44 [C(8)<sup>†</sup>], 127.46 [C(5')], 129.36 [C(7)], 131.40 [C(6)], 134.57 [C(4a')], 138.11 [C(4)], 147.47 [C(8a)], 154.54 [C(1')], 157.05 [C(2)]. LSIMS:  $m/z$ : 301 ([M+H]<sup>+</sup>, 100%).

<sup>†</sup>Assignments may be reversed.



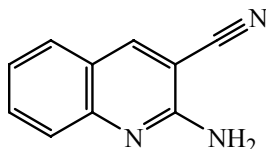
### 6.2.3. 3-Substituted 2-Aminoquinolines

#### 2-Aminobenzaldehyde (**76**)<sup>60</sup>



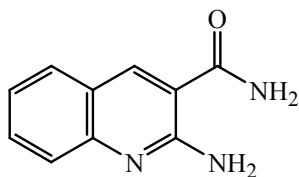
Ferrous sulfate (92 g, 0.331 mol) was dissolved in water (300 mL) and 5% HCl (5 mL) and stirred at room temperature. 2-Nitrobenzaldehyde (5 g, 33.1 mmol) was added, along with concentrated ammonia solution (50 mL). The mixture was heated to 80°C quickly with a heat gun and left to stir for 10 minutes. The mixture was then distilled. The distillate was cooled on ice and the resulting crystals were collected to give **76** (2.15 g, 54%) as a yellow, low-melting solid. IR (nujol mull):  $\nu$  ( $\text{cm}^{-1}$ ): 3461, 3412, 3345, 3301, 1662, 1618, 1593, 1556.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 6.12 [2H, br s,  $\text{NH}_2$ ], 6.65 [1H, dd,  $^3J_{4,6} = 1.2$  Hz,  $J_{5,6} = 8.2$  Hz, H(6)], 6.75 [1H ddd,  $^3J_{4,6} = 1.2$  Hz,  $J_{4,5} = 7.2$  Hz,  $J_{3,4} = 8.0$  Hz, H(4)], 7.32 [1H, ddd,  $^3J_{3,5} = 1.6$  Hz,  $J_{4,5} = 7.2$  Hz,  $J_{5,6} = 8.2$  Hz, H(5)], 7.48 [1H, dd,  $^3J_{3,5} = 1.6$  Hz,  $J_{3,4} = 8.0$  Hz, H(3)], 9.87 [1H, s, CHO].

#### 2-Amino-3-cyanoquinoline (**29**)<sup>61</sup>



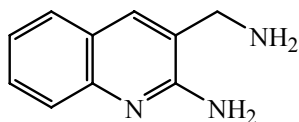
Malononitrile (1.64 g, 24.8 mmol), **76** (3.0 g, 24.8 mmol), ethanol (30 mL) and pyridine (3 drops) were heated at reflux overnight. The reaction mixture was then cooled and the resulting precipitate collected and recrystallised from ethanol to give rise to **29** (3.27 g, 78%) as yellow crystals (m.p. 229-230°C [lit 228.5-230°C]<sup>61</sup>). IR (nujol mull):  $\nu$  ( $\text{cm}^{-1}$ ): 3393, 3317, 3163, 2227, 1654, 1619, 1600, 1562.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 5.45 [2H, br s,  $\text{NH}_2$ ], 7.35 [1H, ddd,  $J = 2.1$  Hz,  $J = 6.0$  Hz,  $J = 8.1$  Hz H(6)], 7.66-7.74 [3H m, H(5) + H(7) + H(8)], 8.32 [1H, s, H(4)].

**2-Aminoquinoline-3-carboxamide (30)** <sup>61</sup>



**29** (0.5 g, 2.96 mmol) and potassium hydroxide (0.21 g, 3.74 mmol) were added to ethanol (10 mL). Hydrogen peroxide (30%, 10 mL) was then added and the reaction mixture was heated at 70°C for 30 minutes. Additional hydrogen peroxide (30%, 2.5 mL) was added and the mixture was heated for a further 30 minutes at 70°C. The reaction mixture was cooled to 0°C and the resulting yellow solid was collected and recrystallised from water to give **30** (290 mg, 52%) as small yellow needles (m.p. 238-241°C [lit 240-242°C]<sup>61</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3412, 3194, 1632, 1565. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 5.88 [2H, br s, NH<sub>2</sub>], 6.53 [2H, br s, NH<sub>2</sub>] 7.18-7.30 [1H, m, H(6)], 7.53-7.66 [3H, m, H(5) + H(7) + H(8)], 8.19 [1H, s, H(4)].

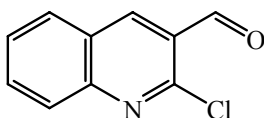
**2-Amino-3-(aminomethyl)quinoline (31)** <sup>62, 63</sup>



**29** (150 mg, 0.887 mmol) was added to ethanol (3.7 mL) followed by activated Raney nickel catalyst (219 mg) and sodium hydroxide solution (3M, 3.7 mL) dropwise. Additional ethanol (3 mL) was then added and the mixture was left to stir for 72 hours, filtered through celite and the solvent was removed. The remaining residue was dissolved in water (10 mL) and concentrated ammonia solution was added until the solution reached pH 10. This was then extracted with dichloromethane (3 x 20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed to give rise to **31** (99 mg, 64%) as a brown solid (m.p. 147-155°C [lit 147-149°C]<sup>62</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3388, 3238, 1622, 1563, 1493. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.03 [2H, br s, NH<sub>2</sub>], 3.99 [2H, s, CH<sub>2</sub>], 6.03 [2H, br s, NH<sub>2</sub>], 7.23 [1H, ddd,  $J$  = 1.2 Hz,  $J$  = 6.8 Hz,  $J$  = 8.0 Hz, H(6)], 7.48-7.67 [4H, m, H(4) + H(5) + H(7) + H(8)].

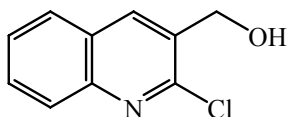
## 6.2.4. Complex 3-Substituted-2-Aminoquinolines

### 2-Chloroquinoline-3-carbaldehyde (**77**)<sup>64</sup>



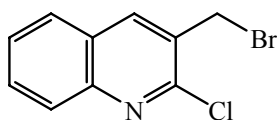
DMF (7.2 mL, 92.5 mmol) was stirred at 0°C and phosphorous oxychloride (24.1 mL, 0.259 mol) was added dropwise. Acetanilide (5.0 g, 37 mmol) was added to the stirring solution, which was then stirred at 0°C until homogeneous. The reaction mixture was heated at 80°C overnight, then cooled and added slowly to ice water (250 mL). The resulting precipitate was collected and recrystallised from ethyl acetate to give **77** (2.97 g, 42%) as bright yellow needles (m.p. 147-149°C [lit 148-149°C]<sup>64</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 1686, 1662, 1615, 1579. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ : 7.66 [1H, ddd,  $J_{6,8} = 1.2$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{5,6} = 8.1$  Hz, H(6)], 7.90 [1H, ddd,  $J_{5,7} = 1.5$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{7,8} = 8.1$  Hz, H(7)], 8.00 [1H, d<sup>‡</sup>,  $J_{5,6} = 8.1$  Hz, H(5)], 8.09 [1H, d<sup>‡</sup>,  $J_{7,8} = 8.1$  Hz, H(8)], 8.78 [1H, s, H(4)], 10.58 [1H, s, CHO].

### (2-Chloroquinolin-3-yl)methanol (**78**)



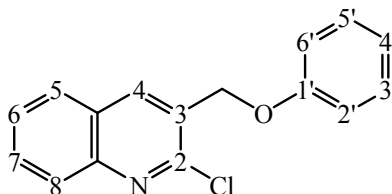
**77** (3.74 g, 19.6 mmol) was dissolved in ethanol (300mL). Sodium borohydride (0.74 g, 19.6 mmol) and water (20 mL) were added and the solution was stirred at room temperature for 1 hour. The ethanol was removed from the reaction mixture and water (150 mL) was added, then the mixture was extracted with dichloromethane (3 x 150 mL). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed to give clean **78** (3.66 g, 97%) as a cream coloured solid (m.p. 149-157°C [lit 151-152°C]<sup>65</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3410, 1590, 1568, 1490. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.42 [1H, br s, OH], 4.94 [2H, d,  $^4J_{CH,4} = 1.0$  Hz, CH<sub>2</sub>], 7.57 [1H, ddd,  $^3J_{6,8} = 1.4$  Hz,  $J_{6,7} = 7.0$  Hz,  $J_{5,6} = 8.0$  Hz, H(6)], 7.73 [1H, ddd,  $^3J_{5,7} = 1.4$  Hz,  $J_{6,7} = 7.0$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.85 [1H, dd<sup>‡</sup>,  $^3J_{5,7} = 1.4$  Hz,  $J_{5,6} = 8.0$  Hz, H(5)], 8.03 [1H, dddd,  $^4J_{4,8} = ^4J_{5,8} = 0.8$  Hz,  $^3J_{6,8} = 1.4$  Hz,  $J_{7,8} = 8.4$  Hz, H(8)], 8.30 [1H, d<sup>‡</sup>,  $^4J_{CH,4} = 1.0$  Hz, H(4)]. EIMS:  $m/z$ : 195 (M<sup>+</sup> [<sup>37</sup>Cl], 27%), 193 (M<sup>+</sup> [<sup>35</sup>Cl], 100), 164 (54), 156 (39), 128 (60).

### 3-(Bromomethyl)-2-chloroquinoline (79)



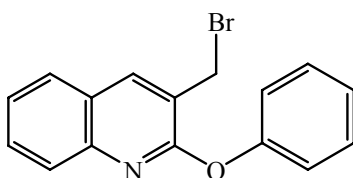
**78** (0.7 g, 3.63 mmol) was dissolved in benzene (1 mL) and stirred at 0°C. Phosphorus tribromide (0.34 mL, 3.63 mmol) was added slowly. The reaction mixture was stirred at room temperature overnight, and then added to water (50 mL). The resulting solution was extracted with dichloromethane (3 x 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed. The remaining solid was recrystallised from hexane to give **79** (520 mg, 56%) as a pale brown solid (m.p. 122-125°C [lit 121-125°C]<sup>66</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 1647, 1616, 1588, 1560, 1489. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 4.73 [2H, s, CH<sub>2</sub>Br], 7.59 [1H, ddd, <sup>4</sup>J<sub>6,8</sub> = 1.2 Hz, J<sub>6,7</sub> = 6.9 Hz, J<sub>5,6</sub> = 8.1 Hz, H(6)], 7.76 [1H, <sup>4</sup>J<sub>5,7</sub> = 1.5 Hz, J<sub>6,7</sub> = 6.9 Hz, J<sub>7,8</sub> = 8.4 Hz, H(7)], 7.83 [1H, dd<sup>‡</sup>, <sup>4</sup>J<sub>5,7</sub> = 1.5 Hz, J<sub>5,6</sub> = 8.1 Hz, H(5)], 8.03 [1H, dddd, <sup>5</sup>J<sub>4,8</sub> = <sup>5</sup>J<sub>5,8</sub> = 0.6 Hz, <sup>4</sup>J<sub>6,8</sub> = 1.2 Hz, J<sub>7,8</sub> = 8.4 Hz, H(8)], 8.26 [1H s<sup>‡</sup>, H(4)]. EIMS: *m/z*: 259 (M<sup>+</sup> [<sup>37</sup>Cl, <sup>81</sup>Br], 4%), 257 (M<sup>+</sup> [<sup>35</sup>Cl, <sup>81</sup>Br], & M<sup>+</sup> [<sup>37</sup>Cl, <sup>79</sup>Br], 13), 255 (M<sup>+</sup> [<sup>35</sup>Cl, <sup>79</sup>Br], 9), 222, (19), 220 (19), 176 (100), 140 (50).

### 2-Chloro-3-(phenoxymethyl)quinoline (80)



**79** (1.5 g, 5.85 mmol), phenol (0.6 g, 6.44 mmol) and potassium carbonate (1.6 g, 11.7 mmol) were added to acetonitrile (80 mL) and the mixture was heated at reflux for 5 hours. The mixture was then cooled and the solvent was removed. Water (200 mL) and dichloromethane (200 mL) were added to the remaining residue. The aqueous phase was acidified to pH1 and the organic phase was separated. The aqueous phase was extracted further with dichloromethane (200 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed. The crude product was chromatographed over silica gel (30% hexane / dichloromethane) to give **80** (315 mg, 20%) as a white solid (R<sub>f</sub> = 0.25; m.p. 116-118°C [lit 120°C]<sup>67</sup>). IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 1598, 1585, 1567, 1494. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 5.27 [2H, s, CH<sub>2</sub>], 7.02-7.08 [3H, m, H(2') + H(4') + H(6')], 7.34-7.37 [2H, m, H(3') + H(5')], 7.57 [1H, dd, <sup>4</sup>J<sub>6,8</sub> = 1.2 Hz, J<sub>6,7</sub> = 7.2 Hz, J<sub>5,6</sub> = 8.4 Hz, H(6)],

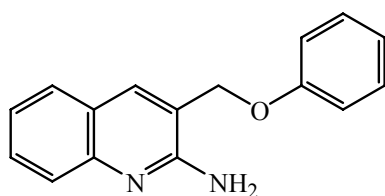
7.74 [1H, dd,  $^4J_{5,7} = 1.2$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.84 [1H, d $^\ddagger$ ,  $J_{5,6} = 8.4$  Hz, H(5)], 8.07 [1H, d $^\ddagger$ ,  $J_{7,8} = 8.4$  Hz, H(8)], 8.35 [1H, s, H(4)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 66.33 [ $\text{CH}_2$ ], 114.82 [ $\text{C}(2')$ ], 121.57 [ $\text{C}(4')$ ], 127.14 [ $\text{C}(4\text{a})$ ], 127.20 [ $\text{C}(6)$ ], 127.60 [ $\text{C}(5)$ ], 128.10 [ $\text{C}(8)$ ], 129.00 [ $\text{C}(3)$ ], 129.64 [ $\text{C}(3')$ ], 130.38 [ $\text{C}(7)$ ], 136.62 [ $\text{C}(4)$ ], 146.87 [ $\text{C}(8\text{a})$ ], 148.53 [ $\text{C}(2)$ ], 158.06 [ $\text{C}(1')$ ]. EIMS:  $m/z$ : 271 ( $\text{M}^+$  [ $^{37}\text{Cl}$ ], 4%), 269 ( $\text{M}^+$  [ $^{35}\text{Cl}$ ], 10%), 178, (32), 176 (100), 140 (32).



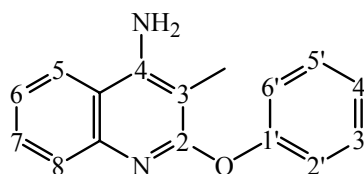
**81** (138 mg, 8%) was also isolated crude from the reaction mixture as a cream coloured solid ( $R_f = 0.28$ ; m.p 112-115°C ). HRMS: Found 313.0103;  $\text{C}_{16}\text{H}_{12}^{79}\text{BrNO}$  requires 313.0102. IR (nujol mull):  $\nu$  ( $\text{cm}^{-1}$ ): 1597, 1584, 1567, 1497.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 5.30 [2H, s,  $\text{CH}_2$ ], 6.97 – 7.09 [3H, m, H(2') + H(4') + H(6')], 7.30-7.40 [2H, m, H(3') + H(5')], 7.55 [1H, ddd,  $^4J_{6,8} = 1.2$  Hz,  $J_{6,7} = 7.0$  Hz,  $J_{5,6} = 8.0$  Hz, H(6)], 7.70 [1H, ddd,  $^4J_{5,7} = 1.6$  Hz,  $J_{6,7} = 7.0$  Hz,  $J_{7,8} = 8.6$  Hz, H(7)], 7.80 [1H, dd,  $^4J_{5,7} = 1.6$  Hz,  $J_{5,6} = 8.0$  Hz, H(5)], 8.05 [1H, d $^\ddagger$ ,  $J_{7,8} = 8.6$  Hz, H(8)], 8.25 [1H, d,  $^5J_{4,8} = 1.0$  Hz, H(4)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 68.25 [ $\text{CH}_2\text{Br}$ ], 114.93 [ $\text{C}(2') + \text{C}(6')$ ], 12.64 [ $\text{C}(4')$ ], 127.34 [ $\text{C}(4\text{a})$ ], 127.39 [ $\text{C}(6)$ ], 127.76 [ $\text{C}(5)$ ], 128.38 [ $\text{C}(8)$ ], 129.07 [ $\text{C}(7)$ ], 129.70 [ $\text{C}(3') + \text{C}(5')$ ], 130.39 [ $\text{C}(3)$ ], 136.12 [ $\text{C}(4)$ ], 141.22 [ $\text{C}(8\text{a})$ ], 147.82 [ $\text{C}(2)$ ], 158.12 [ $\text{C}(1')$ ]. EIMS:  $m/z$ : 315 ( $\text{M}^+$  [ $^{81}\text{Br}$ ], 9%), 313 ( $\text{M}^+$  [ $^{79}\text{Br}$ ], 9%), 222 (98), 220 (100), 176 (44), 140 (73).

A 3:1 mix of **80** : **81** (1.11 g) was also isolated from the experiment.

*Attempted Synthesis of 3-(Phenoxymethyl)-2-aminoquinoline (82)*<sup>56</sup>



**82**



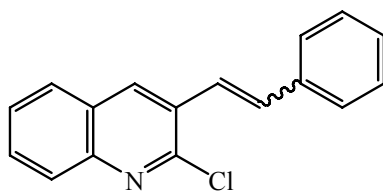
**83**

A mixture of **80** (0.10 g, 0.37 mmol), acetamide (0.44 g, 7.4 mmol) and potassium carbonate (0.26 g, 1.85 mmol) were combined and heated at 200°C for 1 hour. The reaction mixture was allowed to cool to room temperature then water (15 mL) was added to the mixture, which was then extracted with dichloromethane (3 x 15 mL). The combined organic extracts were then washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed to give **83** (80 mg, 85%) as a pale brown solid (m.p. 155-156°C). A small portion was recrystallised (dichloromethane / hexane) for the purpose of characterisation by X-Ray crystallography (see Appendix 1). *X-Ray Crystal Structure Results:* Formula C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O, *M* 250.29, monoclinic, space group *P*2<sub>1</sub>/*c*(#14), *a* 16.8757(8), *b* 5.6530(3), *c* 13.2810(7) Å,  $\beta$  96.210(2), *V* 1259.55(11) Å<sup>3</sup>, *D<sub>c</sub>* 1.320 g cm<sup>-3</sup>, *Z* 4, crystal size 0.184 by 0.154 by 0.096 mm, colour colourless, habit plate, temperature 150(2) Kelvin,  $\lambda$ (MoK $\alpha$ ) 0.71073 Å,  $\mu$ (MoK $\alpha$ ) 0.084 mm<sup>-1</sup>,  $2\theta_{\max}$  61.06, *hkl* range -24 24, -5 8, -18 18, *N* 24485, *N<sub>ind</sub>* 3843(*R<sub>merge</sub>* 0.0704), *N<sub>obs</sub>* 2807(*I* > 2 $\sigma$ (*I*)), *N<sub>var</sub>* 181, residuals\* *R*1(*F*) 0.0418, *wR*2(*F*<sup>2</sup>) 0.1320, GoF(all) 1.327,  $\Delta\rho_{\min,\max}$  -0.333, 0.319 e<sup>-</sup> Å<sup>-3</sup>. HRMS: Found 251.1179; [C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O-H]<sup>+</sup> requires 251.1179. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3492, 3321, 3224, 1631, 1570. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.52 [3H, s, CH<sub>3</sub>], 4.72 [2H, s, NH<sub>2</sub>], 7.11-7.17 [1H, m, H(2') + H(4') + H(6')], 7.30 [1H, ddd, <sup>4</sup>*J*<sub>6,8</sub> = 1.2 Hz, *J*<sub>6,7</sub> = 7.2 Hz, *J*<sub>5,6</sub> = 8.4 Hz, H(6)], 7.33-7.36 [2H, m, H(3') + H(5')], 7.47 [1H, ddd, <sup>4</sup>*J*<sub>5,7</sub> = 1.2 Hz, *J*<sub>6,7</sub> = 7.2 Hz, *J*<sub>7,8</sub> = 8.4 Hz, H(7)], 7.62 [1H, d<sup>‡</sup>, *J*<sub>5,6</sub> = 8.4 Hz, H(5)], 7.67 [1H, d<sup>‡</sup>, *J*<sub>7,8</sub> = 8.4 Hz, H(8)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 9.76 [CH<sub>3</sub>], 100.54 [C(3)], 117.14 [C(4a)], 119.73 [C(5)], 120.65 [C(2')], 123.46 [C(6)], 123.63 [C(4')], 128.24 [C(8)], 128.67 [C(7)], 129.22 [C(3')], 144.93 [C(8a)], 149.12 [C(4)], 154.92 [C(1')], 160.76 [C(2)]. EIMS: *m/z*: 250 (M<sup>+</sup>, 100), 249 (97), 221 (11). LSIMS: *m/z*: 251 ([MH]<sup>+</sup>, 100%).

\*  $R1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$  for  $F_o > 2\sigma(F_o)$ ;  $wR2 = \frac{(\sum w(F_o^2 - F_c^2)^2 / \sum (wF_c^2)^2)^{1/2}}$  all reflections

$w = 1 / [\sigma^2(F_o^2) + (0.03P)^2 + 0.5P]$  where  $P = (F_o^2 + 2F_c^2) / 3$

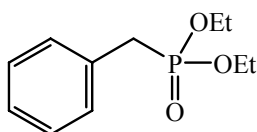
### Attempted Synthesis of 2-Chloro-3-[2-phenylvinyl]quinoline (**86**) via a Wittig Reaction



Triphenylphosphine (5.8 g, 22.1 mmol) was dissolved in chloroform (8 mL) and benzyl bromide (2.6 mL, 22.1 mmol) was added to the solution. The reaction mixture was then stirred under nitrogen for 2 hours. The resulting precipitate was collected by vacuum filtration to give the crude benzyl(triphenyl)phosphonium salt (9.26 g, 97%), which was used without further purification.

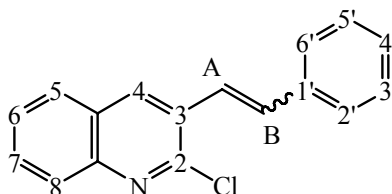
Potassium *tert*-butoxide (1.3 g, 23.2 mmol) was dissolved in THF (30 mL). Benzyl(triphenyl)phosphonium bromide (5.0 g, 11.6 mmol) was added and the mixture was stirred under nitrogen for 2 hours. **77** (2.21 g, 11.6 mmol) in THF (25 mL) was added dropwise and the reaction mixture was stirred under nitrogen for 24 hours. Hexane (50 mL) was added, the reaction mixture was stirred and the resulting precipitate was removed by vacuum filtration. The solvent was then removed from the filtrate to give crude **86** (0.83 g, 27%). This was then chromatographed over silica gel (10% hexane / dichloromethane) to give still crude **86** (0.14g, 5%).

### Diethyl benzylphosphonate (**87**)<sup>71</sup>



Benzyl bromide (3.04 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were heated at reflux for 3 hours. The crude product was then distilled under reduced pressure (b.p. 90-95°C @ 0.14 mmHg) to give **87** (3.88 g, 96%) as a clear, colourless oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3467, 3064, 3032, 2983, 2909, 1604, 1558, 1541, 1496, 1456. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.24 [6H, t, *J* = 7.0, 2 x CH<sub>3</sub>], 3.15 [2H, d, *J*<sub>H,P</sub> = 21.6 Hz, PCH<sub>2</sub>], 3.93-4.08 [4H, m, 2 x CH<sub>2</sub>], 7.26-7.32 [5H, m, aromatic H].

**2-Chloro-3-[(E)-2-phenylvinyl]quinoline / 2-Chloro-3-[(Z)-2-phenylvinyl]quinoline**  
(86)



Sodium hydride (80% in paraffin oil; 0.38 g, 12.5 mmol), was stirred in DMF (4 mL) under an atmosphere of nitrogen. **87** (2.37 g, 10.4 mmol) in DMF (4 mL) was added dropwise, followed by **77** (2.0 g, 10.4 mmol) in DMF (20 mL). The reaction mixture was stirred for 1 hour at 60°C, then added to ice water. The resulting precipitate was filtered to give the crude product which was chromatographed over silica gel (20% hexane / dichloromethane) to give **86** (1.57 g, 57%) as a mixture of *E/Z* isomers ( $R_f = 0.42$ ). HRMS: Found 265.0655;  $C_{17}H_{12}^{35}ClN$  requires 265.0658. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 1630, 1559, 1582.  $^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$ : 6.73 [1H, d,  $J = 12.4$  Hz, \*H( $\dagger$ A)], 6.87 [1H, d,  $J = 12.4$  Hz, \*H( $\dagger$ B)], 7.15-7.73 [m], 7.84 [1H, dd,  $J = 1.2$  Hz,  $J = 7.8$  Hz, H(5)], 7.94 [1H, s, \*H(4)], 8.00 [1H, dd,  $J = 0.6$  Hz,  $J = 8.6$  Hz, H(8)], 8.37 [1H, s, H(4)]. EIMS:  $m/z$ : 265 ( $M^+$ , 33), 230 (100), 202 (16).

\*refers to *Z* isomer

$\dagger$ assignments may be reversed

A portion of **86** was purified by fractional crystallisation (hexane) to give >95% *E* isomer as yellow crystals (117-118°C). Analysis Found: C, 76.90; H, 4.55; N, 5.28;  $C_{17}H_{12}ClN$  requires C, 76.84; H, 4.55; N, 5.27%. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 1630, 1584, 1488.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 7.19 [1H, d,  $J_{A,B} = 16.2$  Hz, H(B)], 7.33 [1H, tt,  $^4J_{2'/6',4'} = 1.2$  Hz,  $J_{3'/5',4'} = 7.2$  Hz, H(4')], 7.41 [1H, dd,  $J_{2'/6',3'/5'} = J_{3'/5',4'} = 7.2$  Hz, H(3') + H(5')], 7.52 [1H, d,  $J_{A,B} = 16.2$  Hz, H(A)], 7.55 [1H, ddd,  $^4J_{6,8} = 1.2$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{5,6} = 7.8$  Hz, H(6)], 7.59 [1H, dd,  $^4J_{2'/6',4'} = 1.2$  Hz,  $J_{2'/6',3'/5'} = 7.2$  Hz, H(2') + H(6')], 7.69 [1H, ddd,  $^4J_{5,7} = 1.2$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.84 [1H, d $\ddagger$ ,  $J_{5,6} = 7.8$  Hz, H(5)], 8.00 [1H, d $\ddagger$ ,  $J_{7,8} = 8.4$  Hz, H(8)], 8.37 [1H, s, H(4)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 123.49 [C(A)], 126.98 [C(6)], 127.25 [C(2') + C(6')], 127.51 [C(4a) + C(5)], 128.29 [C(8)], 128.57 [C(4')], 128.84 [C(3') + C(5')], 130.18 [C(7)], 130.32 [C(3)], 133.26 [C(B)], 133.68 [C(4)], 136.55 [C(1')], 146.80 [C(8a)], 150.21 [C(2)]. EIMS:  $m/z$ : 265 ( $M^+$ , 36%), 230 (100), 202 (15).



***Attempted Optimisation of 2-Chloro-3-[(E)-2-phenylvinyl]quinoline / 2-Chloro-3-[(Z)-2-phenylvinyl]quinoline (86) Number 1***

Potassium *tert*-butoxide (0.35 g, 3.1 mmol), was stirred in THF (10 mL) under an atmosphere of nitrogen. A solution of **87** (0.71 g, 3.1 mmol) in THF (5 mL) was added dropwise, followed by **77** (0.60 g, 3.1 mmol) in THF (10 mL). The reaction mixture was stirred for 72 hours at room temperature, then added to ice water (30 mL). Water (50 mL) was added and the resulting solution was extracted with dichloromethane (2 x 50 mL). The crude product consisted mainly of **77**, so isolation of the product was not attempted.

***Attempted Optimisation of 2-Chloro-3-[(E)-2-phenylvinyl]quinoline / 2-Chloro-3-[(Z)-2-phenylvinyl]quinoline (86) Number 2***

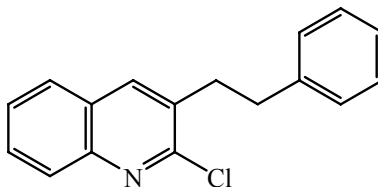
A solution of **87** (1.14 g, 15.0 mmol) was stirred in THF (10 mL) at -78°C under nitrogen. *N*-butyl lithium was then added and the resulting mixture was stirred for 15 minutes. A solution of **77** (1.0 g, 5.2 mmol) in THF (20 mL) was then added dropwise. The resulting solution was stirred at 0°C for 1 hour then warmed to room temperature and stirred for 5 hours. Saturated ammonium chloride solution (10 mL) was added dropwise and this was added to additional ammonium chloride (30 mL). The resulting solution was extracted with ether (3 x 30 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed. The resulting residue was chromatographed over silica gel (20% hexane / dichloromethane) to give **86** (0.45 g, 35%) as a mixture of *E/Z* isomers.

***Attempted Optimisation of 2-Chloro-3-[(E)-2-phenylvinyl]quinoline / 2-Chloro-3-[(Z)-2-phenylvinyl]quinoline (86) Number 3***

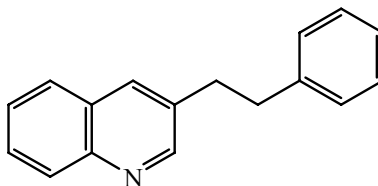
Diisopropylamine (0.18 mL, 1.3 mmol) was added to (THF (5 mL) whilst stirring at -78°C. *n*-Butyllithium was added dropwise and the resulting solution was warmed to -20°C slowly. This solution was subsequently cooled to -78°C and **87** (0.30 g, 1.3 mmol) in THF (1 mL) was added dropwise. The reaction mixture was warmed to 0°C slowly, then stirred again at -78°C. **77** (0.25 g, 1.3 mmol) in THF (5 mL) was added dropwise and the solution was once again warmed to 0 °C and stirred for 5 hours. The reaction mixture was then stirred at room temperature for 1 hour. Ammonium chloride (5 mL) was added dropwise and the resulting solution was added to additional ammonium chloride (10 mL). This solution was then extracted with ether (3 x 30 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and

the solvent was removed. The crude product did not appear to contain any of the desired product, so purification was not attempted.

**2-Chloro-3-(2-phenylethyl)quinoline (88)**



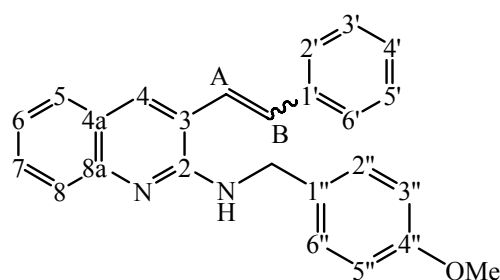
**86** (200 mg, 0.75 mmol) was dissolved in ethanol (25 mL) and palladium on carbon was added. The solution was stirred under pressure (50 psi) in an atmosphere of hydrogen for 2.5 hours then filtered through celite. The solvent was removed and the resulting solid was chromatographed over silica gel (2:1 hexane/ethyl acetate). A 2:1 mixture of **86** and **88** (150 mg) was isolated as a yellow solid ( $R_f$  0.53), which was unable to be separated.



A small amount of **89** (20 mg, 10%) was also isolated ( $R_f$  0.25) as a yellow oil. HRMS: Found 233.1204;  $C_{17}H_{15}N$  requires 233.1204. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 1705, 1658, 1602, 1494.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 3.02-3.15 [4H, m, 2 x  $CH_2$ ], 7.17-7.22 [3H, m, H(2') + H(4') + H(6')], 7.27-7.30 [2H, dd,  $J_{3',4'/4',5'} = J_{2',3'/5',6'} = 7.2$  Hz, H(3') + H(5')], 7.54 [1H, ddd,  $^4J_{6,8} = 1.2$  Hz,  $J_{6,7} = 6.9$  Hz,  $J_{5,6} = 7.8$  Hz, H(6)], 7.68 [1H, ddd,  $^4J_{5,7} = 1.2$  Hz,  $J_{6,7} = 6.9$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.76 [1H, dd,  $^4J_{5,7} = 1.2$  Hz,  $J_{5,6} = 7.8$  Hz, H(5)], 7.91 [1H, d,  $^4J_{2,4} = 1.8$  Hz, H(4)], 8.13 [1H, d $^\ddagger$ ,  $J_{7,8} = 8.4$  Hz, H(8)], 8.79 [1H, d,  $^4J_{2,4} = 1.8$  Hz, H(2)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 35.07 [ $CH_2$ ] 37.38 [ $CH_2$ ], 126.28 [C(4')], 126.85 [C(6)], 127.37 [C(5)], 128.15 [C(8)], 128.44 [C(4a)], 128.49 [C(3') + C(5')], 128.51 [C(2') + C(6')], 129.08 [C(7)], 134.33 [C(4)], 135.22 [C(3)], 140.63 [C(1')], 146.04 [C(8a)], 151.29 [C(2)]. EIMS:  $m/z$ : 233 ( $M^+$ , 49%), 142 (100), 115 (36), 91 (32).

*N*-(4-Methoxybenzyl)-3-[(*E*)-2-phenylvinyl]quinolin-2-amine /

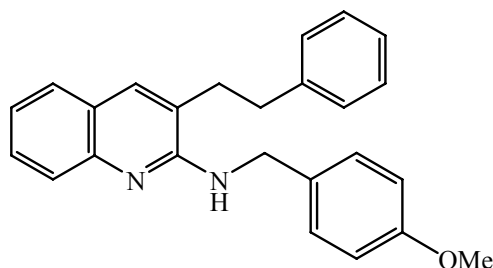
*N*-(4-Methoxybenzyl)-3-[(*Z*)-2-phenylvinyl]quinolin-2-amine (**91**)



**86** (200 mg, 0.75 mmol) and *p*-methoxybenzylamine were stirred together at 140°C overnight. The *p*-methoxybenzylamine was removed under reduced pressure and the resulting oil was chromatographed over silica gel (0.1% triethylamine in dichloromethane) to give clean **91** (210 mg, 76%) as a low melting solid. HRMS: Found 366.1728; C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O requires 366.1732. IR (dichloromethane):  $\nu$  (cm<sup>-1</sup>): 3688, 3600, 3446, 3054, 3032, 2936, 2839, 1615, 1568, 1512, 1488. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 3.77 [3H, s, \*CH<sub>3</sub>], 3.78 [3H, s, CH<sub>3</sub>], 4.62 [2H, d,  $J_{\text{NH,CH}_2}$  = 5.4 Hz, CH<sub>2</sub>], 4.77 [2H, d,  $J_{\text{NH,CH}_2}$  = 4.8 Hz, \*CH<sub>2</sub>], 4.95 [1H, br s<sup>‡</sup>, NH], 4.99 [1H, br s<sup>‡</sup>, \*NH], 6.47 [1H, dd,  $J$  = 1.2 Hz,  $J_{\text{A,B}}$  = 12.6 Hz, \*H(A)], 6.74 [1H, d,  $J_{\text{A,B}}$  = 12.6 Hz, \*H(B)], 6.77-6.78 [2H, m, \*H(3'') + \*H(5'')], 6.86-6.88 [2H, m, H(3'') + H(5'')], 7.02 d,  $J_{\text{A,B}}$  = 16.2 Hz, H(A)], 7.07-7.09 [3H, m, H(B) + \*H(2'') + H(6'')], 7.17-7.20 [5H, m, \*H(2') + \*H(3') + \*H(4') + \*H(5') + H(6')], 7.21-7.24 [3H, m, H(3') + H(5') + H(6)], 7.28 [1H, dd,  $J$  = 7.2 Hz,  $J$  = 7.8 Hz, \*H(6)], 7.31-7.37 [4H, m, H(2'') + H(4') + H(6'') + \*H(7)], 7.48-7.53 [5H, m, H(2') + \*H(5) + H(6') + H(7) + \*H(8)], 7.62 [1H, dd,  $J$  = 1.2 Hz,  $J$  = 7.8 Hz, H(5)], 7.68 [1H, s, \*H(4)], 7.75 [1H, d,  $J$  = 8.4 Hz, H(8)], 7.90 [1H, s, \*H(4)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 45.12 [\*CH<sub>2</sub>], 45.30 [CH<sub>2</sub>], 55.23 [\*OCH<sub>3</sub>], 55.25 [OCH<sub>3</sub>], 113.84 [\*C(3'') + \*C(5'')], 114.00 [C(3'') + C(5'')], 121.26, 122.02, 122.05, 122.38, 122.53 [C(A)], 123.27 [\*C(4a)], 123.78 [C(4a)], 124.20 [\*C(A)], 126.11 [\*C(8)], 126.22 [C(8)], 126.70, 127.30 [\*C(5)], 127.36 [C(5)], 128.00, 128.25, 128.41, 128.74, 128.76, 129.24 [C(7)], 129.51, 129.66, 131.50 [\*C(1'')], 131.72 [C(1'')], 131.96 [\*C(1')], 133.58 [C(4)], 133.79 [C(B)], 134.33 [\*C(B)], 135.73, 135.82 [\*C(4)], 136.73 [C(1')], 147.54 [\*C(8a) + C(8a)], 153.69 [\*C(2)], 154.33 [C(2)], 158.72 [C(4'')], 158.89 [\*C(4'')]. EIMS:  $m/z$ : 366 (M<sup>+</sup>, 36%), 245 (100), 169 (50).

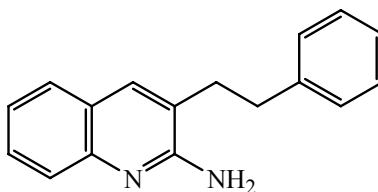
\*refers to *Z* isomer.

**N-(4-Methoxybenzyl)-3-(2-phenylethyl)quinolin-2-amine (92)**



**91** (680 mg, 1.86 mmol) was stirred in methanol (12 mL) and acetyl chloride (0.13 mL, 1.85 mmol) was added slowly. A catalytic amount of palladium on carbon was added and the flask filled with H<sub>2</sub> gas. The reaction mixture was stirred at room temperature for 2 hours then filtered through celite. The resulting crude product was chromatographed over silica gel to give **92** (540 mg, 80%) as a yellow low melting solid. HRMS: Found 368.1884; C<sub>25</sub>H<sub>24</sub>N<sub>2</sub>O requires 368.1889. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3435, 3282, 1637, 1600, 1566, 1505. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.78-2.80 [2H, m, CH<sub>2</sub>], 2.99-3.02 [2H, m, CH<sub>2</sub>], 3.80 [3H, s, CH<sub>3</sub>], 4.67 [1H, br s<sup>‡</sup>, NH], 4.73 [2H, d,  $J_{\text{CH}_2/\text{NH}} = 4.8$  Hz, CH<sub>2</sub>], 6.86-6.89 [2H, m, H(3'') + H(5'')], 7.14-7.16 [2H, m, H(2') + H(6')], 7.19-7.22 [2H, m, H(4') + H(6)], 7.25-7.28 [2H, m, H(3') + H(5')], 7.32-7.34 [2H, m, H(2'') + H(6'')], 7.50 [1H, ddd,  $^4J_{5,7} = 1.2$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{7,8} = 8.1$  Hz, H(7)], 7.55 [1H, dd,  $^4J_{5,7} = 1.2$  Hz,  $J_{5,6} = 7.8$  Hz, H(5)], 7.60 [1H, s, H(4)], 7.75 [1H, d<sup>‡</sup>,  $J_{7,8} = 8.1$  Hz, H(8)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 32.69 [CH<sub>2</sub>], 34.36 [CH<sub>2</sub>], 45.34 [NHCH<sub>2</sub>], 55.28 [OCH<sub>3</sub>], 114.00 [C(3'') + C(5'')], 122.07 [C(6)], 122.90 [C(3)], 123.73 [C(4a)], 126.10 [C(8)], 126.32 [C(4')], 126.85 [C(5)], 128.36 [C(2')], 128.57 [C(3')], 128.61 [C(7)], 129.45 [C(2'') + C(6'')], 131.82 [C(1'')], 134.47 [C(4)], 140.96 [C(1')], 146.80 [C(8a)], 154.97 [C(2)], 158.90 [C(4'')]. EIMS:  $m/z$ : 368 (M<sup>+</sup>, 100), 247 (70), 157 (56).

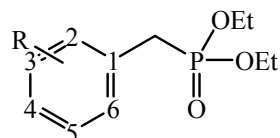
**3-(2-Phenylethyl)quinolin-2-amine (93)**



**92** (120 mg, 0.33 mmol) was stirred in trifluoroacetic acid (2 mL) at 60°C for one hour. The trifluoroacetic acid was then removed under reduced pressure. The resulting residue was dissolved in dichloromethane (20 mL) and stirred. The dichloromethane was removed under

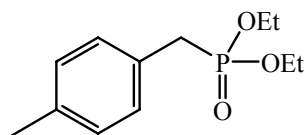
reduced pressure and the above process was repeated until all traces of trifluoroacetic acid were gone by NMR. The resulting residue was then chromatographed over silica gel (7% ethanol in dichloromethane) to give clean **93** (70 mg, 86%) as a yellow solid (m.p. 161-164°C). HRMS: Found 248.1311; C<sub>17</sub>H<sub>16</sub>N<sub>2</sub> requires 248.1313. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3351, 3068, 1683, 1606, 1575, 1508. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.95-2.98 [2H, m, H(A)], 3.06-3.08 [2H, m, H(B)], 3.77 [1H, br s, NH], 6.19 [1H, br s, NH], 7.17 [2H, dd, <sup>4</sup>J<sub>2',4'/4',6'</sub> = 1.2 Hz, J<sub>2',3'/5',6'</sub> = 7.2 Hz, H(2') + H(6')], 7.24 [1H, tt, <sup>4</sup>J<sub>2',4',6'</sub> = 1.2 Hz, J<sub>3',4',5'</sub> = 7.2 Hz, H(4')], 7.31 [2H, dd, J<sub>2',3'/5',6'</sub> = J<sub>3',4'/4',5'</sub> = 7.2 Hz, H(3') + H(5')], 7.40 [1H, ddd, <sup>4</sup>J<sub>6,8</sub> = 1.2 Hz, J<sub>6,7</sub> = 7.2 Hz, J<sub>5,6</sub> = 8.4 Hz, H(6)], 7.59 [1H, dd, <sup>4</sup>J<sub>5,7</sub> = 1.2 Hz, J<sub>5,6</sub> = 8.4 Hz, H(5)], 7.66 [1H, <sup>4</sup>J<sub>5,7</sub> = 1.2 Hz, J<sub>6,7</sub> = 7.2 Hz, J<sub>7,8</sub> = 8.4 Hz, H(7)], 7.75 [1H, s, H(4)], 7.87 [1H, d<sup>‡</sup>, J<sub>7,8</sub> = 8.4 Hz, H(8)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ : 31.35 [C(A)], 33.62 [C(B)], 118.16 [C(8)], 121.15 [C(4a)], 123.83 [C(3)], 125.29 [C(6)], 126.87 [C(4')], 127.49 [C(5)], 128.38 [C(2') + C(6')], 128.86 [C(3') + C(5')], 132.09 [C(7)], 135.89 [C(8a)], 139.30 [C(1')], 140.58 [C(4)], 154.51 [C(2)]. EIMS: *m/z*: 248 (M<sup>+</sup>, 37), 157 (100), 130 (20), 91 (2).

### General Method for Synthesis of Phosphonates<sup>71</sup>



Benzyl halide (1 mol. equiv.) and triethylphosphite (2 mol. equiv) were heated at reflux for the prescribed amount of time. Excess triethyl phosphite was then removed under reduced pressure to give the desired product, which was used without further purification.

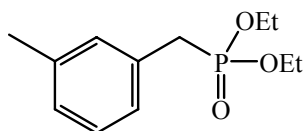
### Diethyl 4-methylbenzylphosphonate (**94**)



4-Methylbenzyl bromide (3.29 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were reacted as described above to give **94** (4.73 g, >100%) as a clear, colourless oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3465, 2983, 2911, 1647, 1516, 1479, 1445. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.25 [6H, t, *J* = 7.0, 2 x CH<sub>3</sub>], 2.32 [3H, s, CH<sub>3</sub>], 3.11 [2H, d, *J*<sub>H,P</sub> = 21.4 Hz,

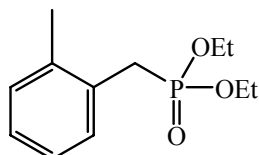
PCH<sub>2</sub>], 3.93-4.09 [4H, m, 2 x CH<sub>2</sub>], 7.10 [2H, d,  $J_{2,3/5,6} = 8.1$  Hz, H(3) + H(5)], 7.19 [2H, dd,  $^4J_{P,2/6} = 2.1$  Hz,  $J_{2,3/5,6} = 8.1$  Hz, H(2) + H(6)].

***Diethyl 3-methylbenzylphosphonate (95)***



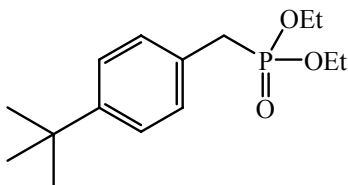
3-Methylbenzyl bromide (3.29 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were reacted as described above to give **95** (4.70 g, >100%) as a clear, colourless oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3467, 2983, 2910, 1647, 1609, 1490, 1445. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.25 [6H, t,  $J = 6.9$ , 2 x CH<sub>3</sub>], 2.33 [3H, s, CH<sub>3</sub>], 3.12 [2H, d,  $J_{H,P} = 21.6$ , PCH<sub>2</sub>], 3.96-4.06 [4H, m, 2 x CH<sub>2</sub>], 7.04-7.11 [3H, m, H(2) + H(4) + H(6)] 7.20 [1H, dd,  $J_{4,5} = J_{5,6} = 7.5$  Hz, H(5)].

***Diethyl 2-methylbenzylphosphonate (96)***



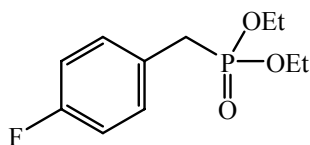
2-Methylbenzyl bromide (3.29 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were reacted as described above to give **96** (4.77 g, >100%) as a clear, colourless oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3468, 2982, 2908, 1653, 1495, 1466, 1444. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.23 [6H, t,  $J = 7.2$ , 2 x CH<sub>3</sub>], 2.39 [3H, s, CH<sub>3</sub>], 3.17 [2H, d,  $J_{H,P} = 21.9$  Hz, PCH<sub>2</sub>], 3.94-4.04 [4H, m, 2 x CH<sub>2</sub>], 7.12-7.15 [3H, m, 3 x CH] 7.25-7.27 [1H, m, CH].

### Diethyl 4-*tert*-butylbenzylphosphonate (97)



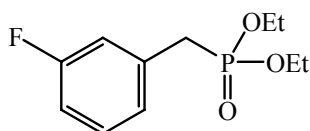
4-*tert*-Butylbenzyl bromide (4.04 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were reacted as described above to give **97** (5.85 g, >100%) as a clear, colourless oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3468, 2964, 2907, 2870, 1512, 1475, 1444. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.24 [6H, t,  $J$  = 7.2, 2 x CH<sub>3</sub>], 1.30 [9H, s, C(CH<sub>3</sub>)<sub>3</sub>], 3.12 [2H, d,  $J_{\text{H,P}}$  = 21.3 Hz, PCH<sub>2</sub>], 3.93-4.07 [4H, m, 2 x CH<sub>2</sub>], 7.22 [2H, dd,  $^4J_{\text{P,2/6}}$  = 2.4 Hz,  $J_{2,3/5,6}$  = 8.3 Hz, H(2) + H(6)], 7.52 [2H, d,  $J_{2,3/5,6}$  = 8.3 Hz, H(3) + H(5)].

### Diethyl 4-fluorobenzylphosphonate (98)



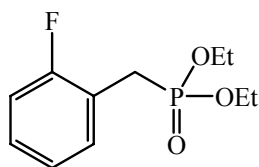
4-Fluorobenzyl bromide (3.36 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were reacted as described above to give **98** (4.84 g, >100%) as a clear, pale yellow oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3461, 2984, 2910, 1603, 1511, 1445. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.26 [6H, t,  $J$  = 7.8, 2 x CH<sub>3</sub>], 3.12 [2H, d,  $J_{\text{H,P}}$  = 21.2 Hz, PCH<sub>2</sub>], 3.87-4.10 [4H, m, 2 x CH<sub>2</sub>], 7.00 [2H, dd,  $J_{\text{F,3/5}}$  =  $J_{2,3/5,6}$  = 8.7 Hz, H(3) + H(5)], 7.23-7.31 [2H, m, H(2) + H(6)].

### Diethyl 3-fluorobenzylphosphonate (99)



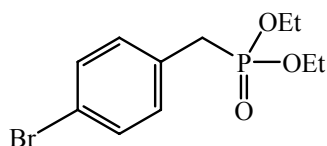
3-Fluorobenzyl bromide (3.36 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were reacted as described above to give **99** (4.48 g, >100%) as a clear, colourless oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3467, 2984, 2910, 1613, 1590, 1488, 1448. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.26 [6H, t,  $J$  = 7.0, 2 x CH<sub>3</sub>], 3.14 [2H, d,  $J_{\text{H,P}}$  = 21.8, PCH<sub>2</sub>], 3.95-4.12 [4H, m, 2 x CH<sub>2</sub>], 6.89-7.12 [3H, m, H(2) + H(5) + H(6)] 7.28 [1H, m, H(4)].

**Diethyl 2-fluorobenzylphosphonate (100)**



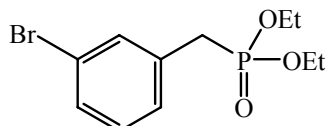
2-Fluorobenzyl chloride (3.36 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were reacted as described above to give **100** (4.11 g, 94%) as a clear, pale yellow oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3466, 2985, 2911, 1647, 1586, 1496, 1456. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.26 [6H, t,  $J = 7.0$ , 2 x CH<sub>3</sub>], 3.21 [2H, d,  $J_{H,P} = 21.6$ , PCH<sub>2</sub>], 3.98-4.15 [4H, m, 2 x CH<sub>2</sub>], 7.00-7.42 [4H, m, H(3) + H(4) + H(5) + H(6)].

**Diethyl 4-bromobenzylphosphonate (101)**



4-Bromobenzyl bromide (4.43 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were reacted as described above to give **101** (5.87 g, >100%) as a clear, colourless oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3468, 2983, 2909, 1654, 1488, 1444, 1406. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.25 [6H, t,  $J = 7.2$ , 2 x CH<sub>3</sub>], 3.09 [2H, d,  $J_{H,P} = 21.6$ , PCH<sub>2</sub>], 3.95-4.10 [4H, m, 2 x CH<sub>2</sub>], 7.14-7.22 [2H, m, H(2) + H(6)], 7.41-7.45 [2H, m, H(3) + H(5)].

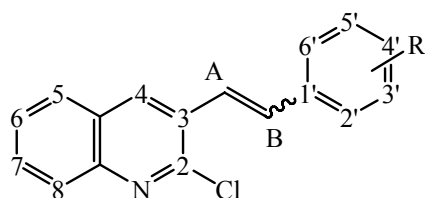
**Diethyl 3-bromobenzylphosphonate (102)**



3-Bromobenzyl bromide (4.43 g, 17.8 mmol) and triethyl phosphite (5 mL, 35.6 mmol) were reacted as described above to give **102** (6.09 g, >100%) as a clear, pale yellow oil. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3448, 2981, 2907, 1654, 1592, 1569, 1474, 1428. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ : 1.26 [6H, t,  $J = 7.0$ , 2 x CH<sub>3</sub>], 3.11 [2H, d,  $J_{H,P} = 21.8$ , PCH<sub>2</sub>], 3.96-4.11 [4H, m, 2 x CH<sub>2</sub>], 7.17-7.27 [2H, m, H(4) + H(5)], 7.34-7.45 [2H, m, H(2) + H(6)].



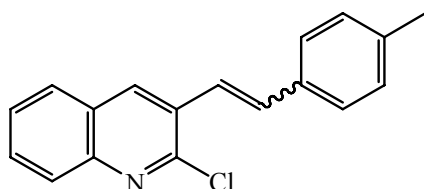
**General Method for Synthesis of 2-Chloro-3-(2-phenylvinyl)quinolines via a Horner-Emmons Reaction**



Sodium hydride (80% in paraffin oil; 0.17 g, 5.49 mmol, 1.5 mol. equiv) was stirred in DMF (1 mL) under an atmosphere of nitrogen. The phosphonate (3.66 mmol, 1 mol. equiv.) in DMF was added dropwise followed by **77** (0.70 g, 3.66 mmol, 1 mol. equiv) in DMF. The reaction mixture was stirred for 2.5 hours at 60°C, then added to ice water. The DMF/water was decanted from the resulting precipitate, which was then dissolved in dichloromethane (50 mL) and washed with water (30 mL). The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed to give the crude product, which was then chromatographed over silica gel to give the final product as a mixture of *E/Z* isomers.

**2-Chloro-3-[(E)-2-(4-methylphenyl)vinyl]quinoline /**

**2-Chloro-3-[(Z)-2-(4-methylphenyl)vinyl]quinoline (**103**)**



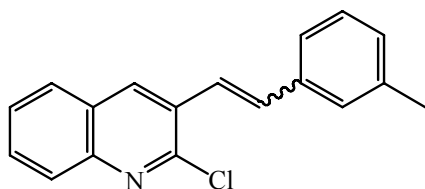
**103** was prepared via the above method, **94** (0.78 g). After work up, the crude product was chromatographed over silica gel (30% hexane / dichloromethane) to give **103** (0.40 g, 44%) as a yellow solid. Analysis Found: C, 75.55; H, 5.13; N, 4.87;  $\text{C}_{18}\text{H}_{14}\text{ClN}\cdot 0.3\text{H}_2\text{O}$  requires C, 75.65; H, 5.17; N, 4.90%. HRMS: Found 279.0811;  $\text{C}_{18}\text{H}_{14}^{35}\text{ClN}$  requires 279.0815. IR (dichloromethane):  $\nu$  ( $\text{cm}^{-1}$ ): 3065, 3048, 2980, 2925, 1698, 1629, 1610, 1583, 1565, 1512, 1488.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.27 [3H, s,  $^*\text{CH}_3$ ], 2.39 [3H, s,  $\text{CH}_3$ ], 6.67 [1H, d,  $J_{\text{A,B}} = 12.0$  Hz,  $^*\text{H}(\text{A})$ ], 6.82 [1H, d,  $J_{\text{A,B}} = 12.0$  Hz,  $^*\text{H}(\text{B})$ ], 6.98-6.99 [2H, m,  $^*\text{H}(3')$  +  $^*\text{H}(5')$ ], 7.07-7.09 [2H, m,  $^*\text{H}(2')$  +  $^*\text{H}(6')$ ], 7.17 [1H, d,  $J_{\text{A,B}} = 16.8$  Hz, H(B)], 7.21-7.22 [2H, m, H( $3'$ ) + H( $5'$ )], 7.45-7.49 [5H, m, H(A) + H( $2'$ ) + H( $6'$ ) +  $^*\text{H}(6)$  +  $^*\text{H}(8)$ ], 7.53-7.57 [2H, m,  $^*\text{H}(5)$  + H( $6$ )], 7.66-7.70 [2H, m, H( $7$ ) +  $^*\text{H}(7)$ ], 7.83 [1H, ddd,  $J = 0.6$  Hz,  $J =$

1.2 Hz,  $J_{5,6} = 8.4$  Hz, H(5)], 7.98-8.00 [2H, m, \*H(4) + H(8)], 8.36 [1H, s, H(4)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 21.18 [\*CH<sub>3</sub>], 21.32 [CH<sub>3</sub>], 122.45 [C(A)], 124.50 [\*C(A)], 126.91 [C(2') + C(6')], 127.20 [C(6) + \*C(6)], 127.47 [C(5) + \*C(5)], 127.56 [C(4a) + \*C(4a)], 128.20 [\*C(8)], 128.27 [C(8)], 128.77 [\*C(3') + \*C(5')], 129.16 [\*C(2') + \*C(6')], 129.55 [C(3') + C(5')], 130.06 [C(7)], 130.20 [\*C(7)], 130.26 [\*C(3)], 130.50 [C(3)], 132.82 [\*C(1')], 133.20 [C(B)], 133.30 [\*C(B)], 133.45 [C(4)], 133.82 [C(1')], 137.62 [\*C(4')], 138.30 [\*C(4)], 138.66 [C(4')], 146.70 [C(8a)], 146.79 [\*C(8a)], 150.24 [C(2)], 150.61 [\*C(2)]. EIMS:  $m/z$ : 281 ( $\text{M}^+$  [ $^{37}\text{Cl}$ ], 20%), 279 ( $\text{M}^+$  [ $^{35}\text{Cl}$ ], 58), 244 (100).

\*refers to Z isomer.

**2-Chloro-3-[(E)-2-(3-methylphenyl)vinyl]quinoline /**

**2-Chloro-3-[(Z)-2-(3-methylphenyl)vinyl]quinoline (104)**



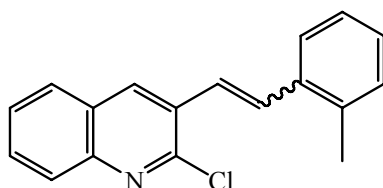
**104** was prepared via the above method, using **95** (0.78 g). After work up, the crude product was chromatographed over silica gel (30% hexane / dichloromethane) to give **104** (0.29 g, 32%) as a pale yellow solid. Analysis Found: C, 77.07; H, 5.16; N, 5.01;  $\text{C}_{18}\text{H}_{14}\text{ClN}$  requires C, 77.28; H, 5.04; N, 5.01%. IR (dichloromethane):  $\nu$  ( $\text{cm}^{-1}$ ): 3064, 3047, 2981, 2924, 2866, 1698, 1631, 1602, 1584, 1564, 1488.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.22 [3H, s, \*CH<sub>3</sub>], 2.41 [3H, s, CH<sub>3</sub>], 6.72 [1H, dd,  $J = 0.9$  Hz,  $J_{\text{A,B}} = 12.0$  Hz, \*H(A)], 6.83 [1H, d,  $J_{\text{A,B}} = 12.0$  Hz, \*H(B)], 6.97 [1H, d,  $J_{4',5'} = 7.8$  Hz, \*H(4')], 7.00 [1H, d,  $J_{5',6'} = 7.8$  Hz, \*H(6')], 7.04-7.06 [2H, m, \*H(2') + \*H(5')], 7.15 [1H, d,  $J_{5',6'} = 7.5$  Hz, H(6')], 7.18 [1H, d,  $J_{\text{A,B}} = 16.2$  Hz, H(B)], 7.30 [1H, dd,  $J_{5',6'} = 7.5$  Hz,  $J_{4',5'} = 7.8$  Hz, H(5')], 7.40 [1H, d,  $J_{4',5'} = 7.8$  Hz, H(4')], 7.41 [1H, s, H(2')], 7.46 [1H, ddd,  $J_{6,8} = 1.2$  Hz,  $J = 6.9$  Hz,  $J = 8.4$  Hz, \*H(6)], 7.52 [1H, d,  $J_{\text{A,B}} = 16.2$  Hz, H(A)], 7.54-7.57 [3H, m, \*H(5) + H(6) + \*H(8)], 7.66 [2H, m, \*H(7) + H(7)], 7.84 [1H, ddd,  $J_{5,7} = J_{5,8} = 0.6$  Hz,  $J_{5,6} = 8.4$  Hz, H(5)], 7.97 [1H, s, \*H(4)], 8.00 [1H, dd,  $J_{5,8} = 0.6$  Hz,  $J_{7,8} = 7.8$  Hz, H(8)], 8.38 [1H, s, H(4)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 21.30 [\*CH<sub>3</sub>], 21.42 [CH<sub>3</sub>], 123.30 [C(A)], 124.25 [C(4')], 125.10 [\*C(A)], 125.75 [\*C(4')], 126.95 [\*C(6)], 127.25 [C(6)], 127.47 [\*C(5)], 127.52 [C(5)], 127.56 [\*C(4a) + C(4a)], 127.60 [C(2')], 128.21 [\*C(5')], 128.31 [C(8)], 128.33 [\*C(8)], 128.49 [\*C(6')], 128.74 [C(5')], 129.42 [C(6')], 129.66 [\*C(2')], 130.03 [\*C(3)], 130.15

[C(7)], 130.25 [\*C(7)], 130.45 [C(3)], 133.42 [C(B)], 133.51 [\*C(B)], 133.64 [C(4)], 135.72 [\*C(1')], 136.52 [C(1')], 138.15 [\*C(3')], 138.39 [\*C(4)], 138.47 [(3')], 146.80 [\*C(8a) + C(8a)], 150.26 [C(2)], 150.64 [\*C(2)]. EIMS:  $m/z$ : 281 ( $M^{+}$  [ $^{37}\text{Cl}$ ], 12%), 279 ( $M^{+}$  [ $^{35}\text{Cl}$ ], 36), 244 (100).

\*refers to *Z* isomer.

**2-Chloro-3-[(E)-2-(2-methylphenyl)vinyl]quinoline /**

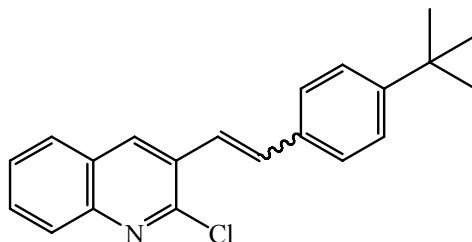
**2-Chloro-3-[(Z)-2-(2-methylphenyl)vinyl]quinoline (105)**



**105** was prepared via the above method, using **96** (0.78 g). After work up, the crude product was chromatographed over silica gel (30% hexane / dichloromethane) to give **105** (0.54 g, 60%) as a pale yellow solid. Analysis Found: C, 77.28; H, 5.16; N, 5.00;  $\text{C}_{18}\text{H}_{14}\text{ClN}$  requires C, 77.28; H, 5.04; N, 5.01%. IR (nujol mull):  $\nu$  ( $\text{cm}^{-1}$ ): 1629, 1579, 1486.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.31 [3H, s, \* $\text{CH}_3$ ], 2.49 [3H, s,  $\text{CH}_3$ ], 6.87 [1H, dd,  $J = 0.6$  Hz,  $J_{\text{A,B}} = 12.0$  Hz, \*H(A)], 6.95-6.96 [2H, m, \*C(B) + \*C(5')], 7.02 [1H,  $\text{d}^\ddagger$ ,  $J_{5',6'} = 7.8$  Hz, \*H(6')], 7.12 [1H, ddd,  $^4J_{4',6'} = 1.2$  Hz,  $J_{3',4'} = 7.2$  Hz,  $J_{4',5'} = 7.8$  Hz, \*H(4')], 7.19 [1H, d,  $J_{3',4'} = 7.2$  Hz, \*H(3')], 7.12-7.28 [3H, m, H(3') + H(4') + H(5')], 7.40 [3H, m, H(A) + H(B) + \*H(6)], 7.56 [1H, ddd,  $^4J_{6,8} = 0.9$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{5,6} = 8.4$  Hz, H(6)], 7.64 [1H, ddd,  $^4J_{5,7} = 2.1$  Hz,  $J_{6,7} = 6.3$  Hz,  $J_{7,8} = 8.4$  Hz, \*H(7)], 7.67-7.71 [3H, m, \*H(4) + H(6') + H(7)], 7.85-7.87 [2H, m, \*H(5) + H(5)], 7.95 [1H, dd,  $^4J_{6,8} = 0.6$  Hz,  $J_{7,8} = 8.4$  Hz, \*H(8)], 8.01 [ddd,  $^5J_{4,8} = 0.6$  Hz,  $^4J_{6,8} = 0.9$  Hz,  $J_{7,8} = 8.4$  Hz, H(8)], 8.36 [1H,  $\text{s}^\ddagger$ , H(4)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 19.83 [\* $\text{CH}_3$ ], 19.96 [ $\text{CH}_3$ ], 124.92 [C(A)], 125.86 [\*C(A) + \*C(5')], 125.95 [C(6')], 126.41 [C(5')], 126.86 [\*C(6)], 127.25 [C(6)], 127.52 [\*C(5)], 127.54 [C(5)], 127.72 [\*C(4')], 128.10 [\*C(8)], 128.32 [C(8)], 128.45 [C(4')], 128.82 [\*C(6')], 129.54 [\*C(3) + C(3)], 130.18 [C(7)], 130.33 [\*C(7)], 130.58 [C(3')], 130.70 [\*C(3')], 131.18 [C(B)], 132.90 [\*C(B)], 133.84 [C(4)], 135.30 [\*C(1')], 135.64 [C(1')], 136.16 [C(2')], 138.18 [\*C(2')], 138.26 [\*C(4)], 146.60 [\*C(8a)], 146.83 [C(8a)], 150.27 [C(2)], 150.60 [\*C(2)]. EIMS:  $m/z$ : 281 ( $M^{+}$  [ $^{37}\text{Cl}$ ], 25%), 279 ( $M^{+}$  [ $^{35}\text{Cl}$ ], 74), 244 (100).

\*refers to *Z* isomer.

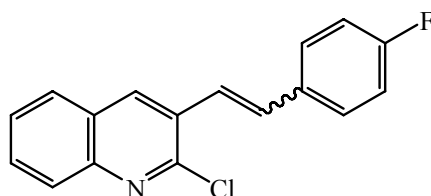
**2-Chloro-3-[(E)-2-(4-tert-butylphenyl)vinyl]quinoline /**  
**2-Chloro-3-[(Z)-2-(4-tert-butylphenyl)vinyl]quinoline (106)**



**106** was prepared via the above method, using **97** (0.92 g). After work up, the crude product was chromatographed over silica gel (30% hexane / dichloromethane) to give **106** (0.42 g, 40%) as a cream coloured solid. Analysis Found: C, 77.29; H, 6.33; N, 4.22;  $C_{21}H_{20}ClN \cdot 0.25H_2O$  requires C, 77.29; H, 6.33; N, 4.29%. HRMS: Found 321.1290;  $C_{21}H_{20}^{35}ClN$  requires 321.1284. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 1629, 1579, 1486.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 1.26 [9H, s,  $*C(CH_3)_3$ ], 1.36 [9H, s,  $C(CH_3)_3$ ], 6.68 [1H, dd,  $J = 0.9$  Hz,  $J_{A,B} = 12.4$  Hz,  $*H(A)$ ], 6.82 [1H, d,  $J_{A,B} = 12.4$  Hz,  $*H(B)$ ], 7.12-7.14 [2H, m,  $*H(2')$  +  $*H(6')$ ], 7.18-7.22 [3H, m,  $H(B)$  +  $*H(3')$  +  $*H(5')$ ], 7.43-7.59 [8H, m,  $H(A)$  +  $H(2')$  +  $H(3')$  +  $H(5')$  +  $*H(5)$  +  $H(6')$  +  $*H(6)$  +  $H(6)$ ], 7.68-7.70 [2H, m,  $*H(7)$  +  $H(7)$ ], 7.84 [1H, ddd,  $J = 0.6$  Hz,  $^4J_{5,7} = 1.2$  Hz,  $J_{5,6} = 8.4$  Hz,  $H(5)$ ], 7.99-8.02 [3H, m,  $*H(4)$  +  $*H(8)$  +  $H(8)$ ], 8.37 [1H, s,  $H(4)$ ].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 31.17 [ $*C(CH_3)_3$ ], 31.24 [ $C(CH_3)_3$ ], 34.58 [ $*C(CH_3)_3$ ], 34.74 [ $C(CH_3)_3$ ], 122.76 [ $C(A)$ ], 124.54 [ $*C(A)$ ], 125.40 [ $*C(3')$  +  $*C(5')$ ], 125.80 [ $C(3')$  +  $C(5')$ ], 126.77 [ $C(2')$  +  $C(6')$ ], 126.94 [ $C(4a)$ ], 127.05 [ $*C(4a)$ ], 127.22 [ $*C(6)$  +  $C(6)$ ], 127.49 [ $C(5)$ ], 127.59 [ $*C(5)$ ], 128.25 [ $*C(8)$ ], 128.31 [ $C(8)$ ], 128.62 [ $*C(2')$  +  $*C(6')$ ], 130.08 [ $C(7)$ ], 130.20 [ $*C(7)$ ], 130.37 [ $*C(3)$ ], 130.56 [ $C(3)$ ], 132.84 [ $*C(1')$ ], 133.11 [ $C(B)$ ], 133.18 [ $*C(B)$ ], 133.49 [ $C(4)$ ], 133.85 [ $C(1')$ ], 138.30 [ $*C(4)$ ], 146.75 [ $C(8a)$ ], 146.84 [ $*C(8a)$ ], 150.28 [ $C(2)$ ], 150.68 [ $*C(2)$ ], 150.96 [ $*C(4')$ ], 151.93 [ $C(4')$ ]. EIMS:  $m/z$ : 323 ( $M^{+\bullet}$  [ $^{37}Cl$ ], 22%), 321 ( $M^{+\bullet}$  [ $^{35}Cl$ ], 65), 308 (37), 306 (100), 270 (46).

\*refers to Z isomer.

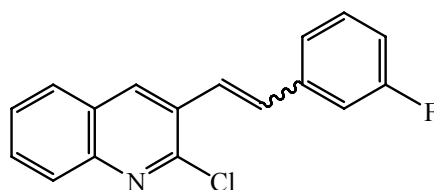
**2-Chloro-3-[(E)-2-(4-fluorophenyl)vinyl]quinoline /**  
**2-Chloro-3-[(Z)-2-(4-fluorophenyl)vinyl]quinoline (107)**



**107** was prepared via the above method, using **98** (0.90 g). After work up, the crude product was chromatographed over silica gel (20% hexane / dichloromethane) to give **107** (0.36 g, 39%) as a cream coloured solid. HRMS: Found 283.0564;  $C_{17}H_{11}^{35}ClFN$  requires 283.0564. IR (dichloromethane):  $\nu$  ( $cm^{-1}$ ): 3047, 1633, 1602, 1584, 1564, 1509, 1488.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 6.73 [1H, d,  $J_{A,B} = 12.0$  Hz, \*H(A)], 6.82 [1H, d,  $J_{A,B} = 12.0$  Hz, \*H(B)], 6.87-6.90 [2H, m, \*H(3') + \*H(5')], 7.08-7.12 [2H, m, H(3') + H(5')], 7.15-7.17 [3H, m, H(B) + \*H(2') + \*H(6')], 7.44 [1H, d,  $J_{A,B} = 16.2$  Hz, H(A)], 7.48 [1H, ddd,  $J = 1.2$  Hz,  $J = 6.9$  Hz,  $J = 8.4$  Hz, \*H(6)], 7.55-7.58 [5H, m, H(2') + \*H(5) + H(6') + H(6) + \*H(8)], 7.68-7.71 [2H, m, \*H(7) + H(7)], 7.84 [1H, d,  $J_{5,6} = 8.4$  Hz, H(5)], 7.93 [1H, s, \*H(4)], 8.00 [1H, d,  $J_{7,8} = 8.4$  Hz, H(8)], 8.36 [1H, s, H(4)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 115.52 [d,  $^2J_{C,F} = 21.9$  Hz, \*C(3') + \*C(5')], 115.87 [d,  $^2J_{C,F} = 21.9$  Hz, C(3') + C(5')], 123.32 [C(A)], 125.35 [\*C(A)], 126.93 [\*C(4a)], 127.10 [C(4a)], 127.31 [\*C(6) + C(6)], 127.45 [\*C(5)], 127.51 [C(5)], 128.24 [\*C(8)], 128.33 [C(8)], 128.60 [d,  $^3J_{C,F} = 8.1$  Hz, C(2') + C(6')], 130.19 [C(3)], 130.26 [\*C(7) + C(7)], 130.43 [\*C(3)], 130.57 [d,  $^3J_{C,F} = 8.3$  Hz, \*C(2') + \*C(6')], 132.01 [C(B)], 132.20 [\*C(B)], 132.80 [d,  $^4J_{C,F} = 3.3$  Hz, \*C(1') + C(1')], 133.66 [C(4)], 133.35 [\*C(4)], 146.84 [\*C(8a) + C(8a)], 150.15 [\*C(2) + C(2)], 162.88 [d,  $^1J_{C,F} = 248.1$  Hz, \*C(4') + C(4')]. EIMS:  $m/z$ : 285 ( $M^+ [^{37}Cl]$ , 15%), 283 ( $M^+ [^{35}Cl]$ , 45), 248 (100).

\*refers to Z isomer.

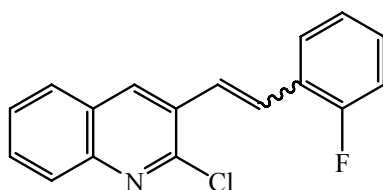
**2-Chloro-3-[(E)-2-(3-fluorophenyl)vinyl]quinoline /**  
**2-Chloro-3-[(Z)-2-(3-fluorophenyl)vinyl]quinoline (108)**



**108** was prepared via the above method, using **99** (0.90 g). After work up, the crude product was chromatographed over silica gel (20% hexane / dichloromethane) to give **108** (0.38 g, 42%) as a pale yellow solid. Analysis Found: C, 71.80; H, 4.06; N, 4.83;  $C_{17}H_{11}ClFN$  requires C, 71.96; H, 3.91; N, 4.94%. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 1629, 1606, 1581, 1487.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 6.78 [1H, d,  $J_{A,B} = 12.0$  Hz, \*H(A)], 6.82 [1H, d,  $J_{A,B} = 12.0$  Hz, \*H(B)], 6.88-6.90 [2H, m, \*C(2') + \*C(4')], 6.94 [1H, d $^\ddagger$ ,  $J_{6',5'} = 7.8$  Hz, \*H(6')], 7.02 [1H, dddd,  $^4J_{2',4'} = 1.2$  Hz,  $^4J_{4',6'} = 2.4$  Hz,  $J_{4',5'} = 7.2$  Hz,  $J_{H,F} = 8.4$  Hz, H(4')], 7.13-7.16 [2H, m, H(B) + \*H(5')], 7.28 [1H, ddd,  $^4J_{2',4'} = 1.2$  Hz,  $^4J_{2',6'} = 1.8$  Hz,  $J_{H,F} = 9.6$  Hz, H(2')], 7.34-7.38 [2H, m, H(5') + H(6')], 7.48 [1H, ddd,  $^4J_{6,8} = 1.2$  Hz,  $J = 7.2$  Hz,  $J = 8.4$  Hz, \*H(6)], 7.52 [1H, d,  $J_{A,B} = 16.2$  Hz, H(A)], 7.55-7.57 [2H, m, \*H(5) + H(6)], 7.68-7.72 [2H, m, \*H(7) + H(7)], 7.83 [2H, m, H(5) + \*H(8)], 7.92 [1H, s, \*H(4)], 8.00 [1H, dd,  $^4J_{6,8} = 0.6$  Hz,  $J_{7,8} = 8.4$  Hz, H(8)], 8.36 [1H, s, H(4)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 113.34 [d,  $^2J_{C,F} = 21.9$  Hz, C(2')], 114.61 [d,  $^2J_{C,F} = 21.3$  Hz, \*C(4')], 115.36 [d,  $^2J_{C,F} = 21.3$  Hz, C(4')], 115.54 [d,  $^2J_{C,F} = 21.3$  Hz, \*C(2')], 122.85 [d,  $^4J_{C,F} = 2.7$  Hz, C(6')], 124.56 [d,  $^4J_{C,F} = 2.7$  Hz, \*C(6')], 124.86 [C(A)], 126.59 [\*C(A)], 126.87, 127.11 [\*C(6)], 127.35 [C(6)], 127.42, 127.47 [\*C(5)], 127.56 [C(5)], 128.24 [\*C(8)], 128.32 [C(8)], 129.82 [C(3)], 129.97 [\*C(3)], 130.30 [d,  $^3J_{C,F} = 8.7$  Hz, \*C(5') + C(5')], 130.41 [C(7)], 130.49 [\*C(7)], 131.95 [d,  $^4J_{C,F} = 2.7$  Hz, C(B)], 132.09 [d,  $^4J_{C,F} = 2.3$  Hz, \*C(B)], 133.95 [C(4)], 138.41 [\*C(1')], 138.82 [C(1')], 138.87 [\*C(4)], 146.95 [\*C(8a) + C(8a)], 150.10 [\*C(2) + C(2)], 163.16 [d,  $^1J_{C,F} = 244.8$  Hz, \*C(3') + C(3')]. EIMS:  $m/z$ : EIMS:  $m/z$ : 285 ( $M^{+}$  [ $^{37}Cl$ ], 12%), 283 ( $M^{+}$  [ $^{35}Cl$ ], 34), 248 (100).

\*refers to Z isomer.

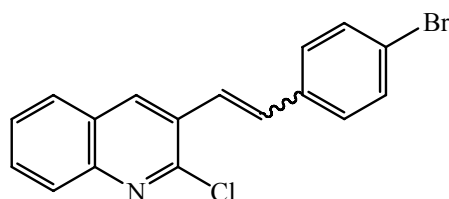
**2-Chloro-2-[(E)-2-(3-fluorophenyl)vinyl]quinoline /**  
**2-Chloro-2-[(Z)-2-(3-fluorophenyl)vinyl]quinoline (109)**



**109** was prepared via the above method, using **100** (0.90 g). After work up, the crude product was chromatographed over silica gel (30% hexane / dichloromethane) to give **109** (0.43 g, 47%) as a pale yellow solid. HRMS: Found 283.0564;  $C_{17}H_{11}^{35}ClFN$  requires 283.0564. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 1625, 1584, 1562, 1487.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 6.85-6.93 [4H, m, \*H(A) + \*H(B) + \*H(3') + H(5')], 7.07 [1H, ddd,  $J = 1.8$  Hz,  $J = 7.2$  Hz,  $J = 7.8$  Hz, \*H(4')], 7.11-7.22 [2H, m, H(3') + \*H(6')], 7.91-7.33 [1H, m, H(6')], 7.38 [1H, d,  $J_{A,B} = 16.2$  Hz, H(B)], 7.44-7.64 [5H, m, H(A) + H(4') + H(5') + \*H(6) + H(6)], 7.66-7.73 [3H, m, \*H(5) + \*H(7) + H(7)], 7.86-7.89 [3H, m, \*H(4) + H(5) + \*H(8)], 8.00 [1H, d,  $J_{7,8} = 7.2$  Hz, H(8)], 8.42 [1H, s, H(4)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 115.07 [d,  $^2J_{C,F} = 22.35$ , \*C(3')], 115.67 [d,  $^2J_{C,F} = 21.9$  Hz, C(3')], 123.89 [\*C(5')], 123.95 [C(5')], 124.41 [\*C(4a)], 124.54 [C(4a)], 125.33 [C(B)], 125.64 [C(A)], 126.09, 126.75, 126.93, 127.02, 127.15, 127.18, 127.33, 127.38, 127.51, 127.57, 127.64, 128.21, 128.33, 128.57 [d,  $^3J_{C,F} = 8.1$  Hz, \*C(6')], 129.87 [d,  $^3J_{C,F} = 8.25$  Hz, C(6')], 130.19, 130.26, 130.38, 134.03 [C(4)], 138.04 [\*C(4)], 146.91 [\*C(8a)], 146.98 [C(8a)], 150.17 [C(2)], 150.42 [\*C(2)], 160.33 [d,  $^1J_{C,F} = 246.9$  Hz, \*C(2)], 160.60 [d,  $^1J_{C,F} = 249.3$  C(2)]. EIMS:  $m/z$ : 285 ( $M^+$  [ $^{37}Cl$ ], 18%), 283 ( $M^+$  [ $^{35}Cl$ ], 49), 248 (100).

\*refers to Z isomer.

**2-Chloro-3-[(E)-2-(4-bromophenyl)vinyl]quinoline /**  
**2-Chloro-3-[(Z)-2-(4-bromophenyl)vinyl]quinoline (110)**

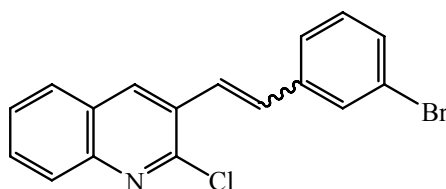


**110** was prepared via the above method, using **101** (1.12 g). After work up, the crude product was chromatographed over silica gel (20% hexane / dichloromethane) to give **110**

(0.63 g, 50%) as a pale yellow solid. HRMS: Found 342.9756;  $C_{17}H_{11}^{79}Br^{35}ClN$  requires 342.9763. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 1616, 1584, 1485.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 6.76 [1H, d,  $J_{A,B} = 11.4$  Hz, \*H(A)], 6.77 [1H, d,  $J_{A,B} = 11.4$  Hz, \*H(B)], 7.03-7.05 [2H, m, \*H(2') + \*H(6')], 7.12 [1H, d,  $J_{A,B} = 16.2$  Hz, H(B)], 7.30-7.31 [2H, m, \*H(3') + \*H(5')], 7.43-7.45 [2H, m, H(2') + H(6')], 7.47-7.53 [5H, m, H(A), H(3') + H(5') + \*H(6) + \*H(8)], 7.54-7.59 [2H, m, \*H(5) + H(6)], 7.68-7.71 [2H, m, \*H(7) + H(7)], 7.83 [1H, dd,  $J = 1.2$  Hz,  $J = 7.8$  Hz, H(5)], 7.91 [1H, s, \*H(4)], 7.99 [1H, dd,  $J = 0.6$  Hz,  $J = 7.8$  Hz, H(8)], 8.36 [1H, s, H(4)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 121.67 [\*C(3)], 122.47 [C(3)], 124.22 [C(A)], 126.16 [\*C(A)], 126.89 [\*C(4a)], 127.14 [C(4a)], 127.35 [C(6)], 127.46 [\*C(6)], 127.51 [\*C(5)], 127.54 [C(5)], 128.25 [\*C(8)], 128.34 [C(8)], 128.40 [C(2') + C(6')], 129.60 [\*C(4')], 129.96 [C(4')], 130.37 [C(7)], 130.43 [\*C(2') + \*C(6')], 130.51 [\*C(7)], 131.67 [\*C(3') + \*C(5')], 131.92 [C(B)], 132.00 [C(3') + C(6')], 132.08 [\*C(B)], 133.82 [C(4)], 134.67 [\*C(1')], 135.49 [C(1')], 138.30 [\*C(A)], 146.91 [C(8a)], 146.92 [\*C(8a)], 150.08 [C(2)], 150.37 [\*C(2)]. EIMS:  $m/z$ : 347 ( $M^+$  [ $^{81}Br,^{37}Cl$ ], 7%), 345 ( $M^+$  [ $^{81}Br,^{35}Cl$ ], &  $M^+$  [ $^{79}Br,^{37}Cl$ ], 25) 343 ( $M^+$  [ $^{79}Br,^{35}Cl$ ], 21), 310 (18), 308 (19), 229 (100). \*refers to Z isomer.

**2-Chloro-3-[(E)-2-(4-bromophenyl)vinyl]quinoline /**

**2-Chloro-3-[(Z)-2-(4-bromophenyl)vinyl]quinoline (111)**



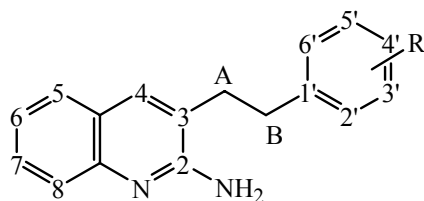
**111** was prepared via the above method, using **102** (1.12 g). After work up, the crude product was chromatographed over silica gel (20% hexane / dichloromethane) to give **111** (0.50 g, 40%) as a cream coloured solid. Analysis Found: C, 59.30; H, 3.31; N, 3.98;  $C_{17}H_{11}BrClN$  requires C, 59.25; H, 3.22; N, 4.06%. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 1621, 1582, 1564, 1486.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 6.79 [1H, d,  $J_{A,B} = 12.0$  Hz, \*H(A)], 6.80 [1H, d,  $J_{A,B} = 12.0$  Hz, \*H(A)], 7.01 [1H, dd,  $J_{4',5'} = J_{5',6'} = 7.8$  Hz, \*H(5')], 7.06 [1H, ddd,  $^4J_{2',6'} = 1.5$  Hz,  $^4J_{4',6'} = 2.4$  Hz,  $J_{5',6'} = 7.8$  Hz, \*H(6')], 7.12 [1H, d,  $J_{A,B} = 16.2$  Hz, H(B)], 7.28 [1H, dd,  $J = 7.8$  Hz,  $J = 8.4$  Hz, H(5')], 7.32 [1H, ddd,  $^4J_{2',4'} = 1.5$  Hz,  $^4J_{4',6'} = 2.4$  Hz,  $J_{4',5'} = 7.8$  Hz, \*H(4')], 7.39 [1H, dd,  $^4J_{2',4'} = ^4J_{2',6'} = 1.5$  Hz, \*H(2')], 7.45-7.59 [7H, m, H(B) + H(4') + \*H(5) + H(6) + \*H(6') + H(6') + \*H(7')], 7.69-7.74 [3H, m, H(2') + H(7) + \*H(8)],



7.85 [1H, ddd,  $^5J_{5,8} = 0.9$  Hz,  $^4J_{5,7} = 1.2$  Hz,  $J_{5,6} = 7.8$  Hz, H(5)], 7.92 [1H, s, \*H(4)], 8.01 [1H, ddd,  $^5J_{5,8} = 0.9$  Hz,  $^4J_{6,8} = 1.8$  Hz,  $J_{7,8} = 8.4$  Hz, H(8)], 8.37 [1H, s, H(4)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 122.60 [\*C(3)], 123.04 [C(3)], 125.56 [C(6')], 126.81 [\*C(A)], 126.86 [\*C(6')], 127.16, 127.21, 127.38 [C(6)], 127.38 [\*C(6)], 127.51 [\*C(5)], 127.59 [C(5)], 128.26, 128.37 [C(8)], 129.31 [129.81, 129.83, 129.95, 130.34 [C(5')], 130.47 [C(2')], 130.54, 130.69, 131.37, 131.64 [C(B)], 131.77 [\*C(B)], 131.88 [\*C(2')], 134.03 [C(4)], 137.96 [\*C(1')], 138.41 [\*C(4)], 138.70 [C(1')], 146.96 [\*C(8a)], 147.01 [C(8a)], 150.13 [C(2)], 150.37 [\*C(2)]. EIMS:  $m/z$ : 347 ( $\text{M}^+$  [ $^{81}\text{Br}$ ,  $^{37}\text{Cl}$ ], 9%), 345 ( $\text{M}^+$  [ $^{81}\text{Br}$ ,  $^{35}\text{Cl}$ ], &  $\text{M}^+$  [ $^{79}\text{Br}$ ,  $^{37}\text{Cl}$ ], 34) 343 ( $\text{M}^+$  [ $^{79}\text{Br}$ ,  $^{35}\text{Cl}$ ], 28), 310 (33), 308 (34), 229 (100).

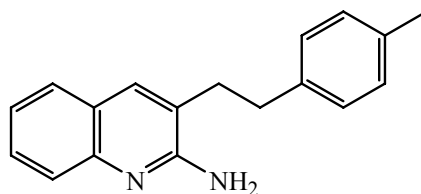
\*refers to Z isomer.

### General Method for the Synthesis of 3-(2-Phenylethyl) quinolin-2-amines



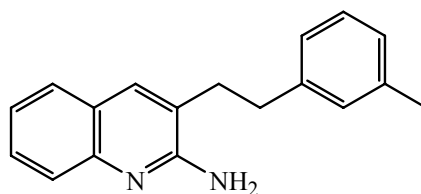
A 2-chloro-3-phenethylquinoline derivative (1 equiv) was stirred in *p*-methoxybenzyl amine (20 equiv) at 140°C overnight. The *p*-methoxybenzyl amine was then removed under reduced pressure. The resulting residue was then added to methanol and stirred at room temperature. Acetyl chloride (1 equiv) was added slowly followed by a catalytic amount of palladium on carbon (0.1%). The flask was flooded with  $\text{H}_2$  gas and the reaction was stirred at room temperature for 2 hours. The reaction mixture was then filtered through celite and chromatographed through silica gel. The resulting crude product was stirred in trifluoroacetic acid for 1 hour at 60°C. The trifluoroacetic acid was then removed under reduced pressure and the resulting residue was dissolved in dichloromethane. The dichloromethane was removed and this process was repeated until all traces of trifluoroacetic acid were gone by  $^{19}\text{F}$  NMR. The resulting crude product was chromatographed through silica gel to afford the desired 3-phenyl-2-aminoquinoline derivative.

### 3-[2-(4-methylphenyl)ethyl]quinolin-2-amine (112)



**112** was prepared via the above method, using **103** (200 mg, 0.72 mmol) and *p*-methoxybenzylamine (1.87 mL, 14.3 mmol) to give crude **126**. This was then reacted via the above method with acetyl chloride (51  $\mu$ L, 0.72 mmol) and palladium catalyst in methanol (5 mL). Work up and chromatography (2% triethylamine in dichloromethane) afforded crude **127**. This was then reacted via the above method with trifluoroacetic acid (3 mL). Work up and chromatography (5% ethanol in dichloromethane) gave rise to clean **112** (90 mg, 48%) as a cream coloured solid (m.p. 120-135°C). Analysis Found: C, 80.87; H, 7.00; N, 10.34.  $C_{18}H_{18}N_2 \cdot 0.33H_2O$  requires C, 80.56; H, 7.01; N, 10.44%. HRMS: Found 262.1470;  $C_{18}H_{18}N_2$  requires 262.1470. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3448, 3301, 3127, 1648, 1618, 1568, 1514, 1500.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$ : 2.31 [3H, s,  $CH_3$ ], 2.79-3.00 [4H, m,  $2 \times CH_2$ ], 5.02 [2H, br s,  $NH_2$ ], 7.06-7.12 [4H, m,  $H(2'') + H(3'') + H(5'') + H(6'')$ ], 7.22 [1H, ddd,  $^4J_{6,8} = 0.9$  Hz,  $J_{6,7} = 6.9$  Hz,  $J_{5,6} = 8.1$  Hz,  $H(6)$ ], 7.50 [1H, ddd,  $^4J_{5,7} = 1.2$  Hz,  $J_{6,7} = 6.9$  Hz,  $J_{7,8} = 8.4$  Hz,  $H(7)$ ], 7.56 [1H, dd,  $^4J_{5,7} = 1.2$  Hz,  $J_{5,6} = 8.1$  Hz,  $H(5)$ ], 7.64-7.67 [2H, m,  $H(4) + H(8)$ ].  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$ : 21.17 [ $CH_3$ ], 33.33 [ $CH_2$ ], 34.10 [ $CH_2$ ], 122.70 [ $C(6)$ ], 123.13 [ $C(4a)$ ], 124.48 [ $C(3)$ ], 125.53 [ $C(8)$ ], 127.16 [ $C(5)$ ], 128.39 [ $C(2'') + C(6'')$ ], 129.05 [ $C(7)$ ], 129.44 [ $C(3'') + C(5'')$ ], 135.73 [ $C(4)$ ], 135.98 [ $C(4')$ ], 137.97 [ $C(1'')$ ], 146.52 [ $C(8a)$ ], 156.46 [ $C(2)$ ]. EIMS:  $m/z$ : 262 ( $M^+$ , 32%), 157 (100), 130 (16), 105 (12).

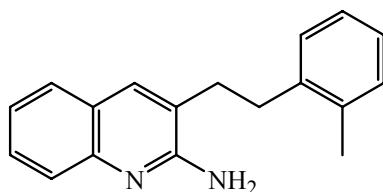
### 3-[2-(3-methylphenyl)ethyl]quinolin-2-amine (113)



**113** was prepared via the above method, using **104** (200 mg, 0.72 mmol) and *p*-methoxybenzylamine (1.87 mL, 14.3 mmol) to give crude **128**. This was then reacted via the above method with acetyl chloride (51  $\mu$ L, 0.72 mmol) and palladium catalyst in

methanol (5 mL). Work up and chromatography (2% triethylamine in dichloromethane) afforded crude **129**. This was then reacted via the above method with trifluoroacetic acid (3 mL). Work up and chromatography (5% ethanol in dichloromethane) gave rise to clean **113** (45 mg, 24%) as a cream coloured solid (m.p. 104-108°C). Analysis Found: C, 80.72; H, 6.80; N, 10.46.  $C_{18}H_{18}N_2 \cdot 0.33H_2O$  requires C, 80.56; H, 7.01; N, 10.44%. HRMS: Found 262.1471;  $C_{18}H_{18}N_2$  requires 262.1470. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3444, 3294, 3155, 1641, 1608, 1588, 1568, 1500.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 2.33 [3H, s,  $CH_3$ ], 2.86-2.88 [2H, m,  $CH_2$ ], 2.99-3.02 [2H, m,  $CH_2$ ], 4.88 [2H, br s,  $NH_2$ ], 7.02 [1H, d,  $J_{6',5'} = 7.2$  Hz, H(6')], 7.04-7.05 [2H, m, H(2') + H(4')], 7.20 [1H, dd,  $J_{5',6'} = 7.2$  Hz,  $J_{4',5'} = 7.8$  Hz, H(5')], 7.25 [1H, ddd,  $^4J_{6,8} = 1.2$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{5,6} = 7.8$  Hz, H(6)], 7.52 [1H, ddd,  $^4J_{5,7} = 1.2$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{7,8} = 7.8$  Hz, H(7)], 7.59 [1H, dd,  $^4J_{5,7} = 1.2$  Hz,  $J_{5,6} = 7.8$  Hz, H(5)], 7.66 [1H, s, H(4)], 7.67 [1H, d $^\ddagger$ ,  $J_{7,8} = 7.8$  Hz, H(8)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 21.37 [ $CH_3$ ], 33.17 [ $CH_2$ ], 34.41 [ $CH_2$ ], 122.72 [C(6)], 122.96 [C(4a)], 124.35 [C(3)], 125.35 [C(6')], 125.37 [C(8)], 126.99 [C(4')], 127.11 [C(5)], 128.54 [C(5')], 129.01 [C(2')], 129.16 [C(7)], 135.75 [C(4)], 138.26 [C(1')], 140.83 [C(3')], 146.18 [C(8a)], 156.07 [C(2)]. EIMS:  $m/z$ : 262 ( $M^+$ , 40%), 157 (100), 130 (20), 105 (5).

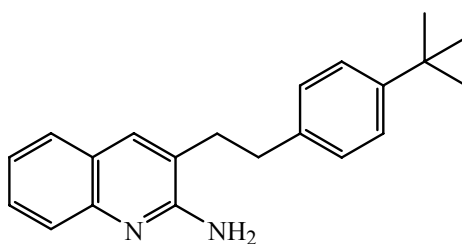
### 3-[2-(-2methylphenyl)ethyl]quinolin-2-amine (114)



**114** was prepared via the above method, using **105** (200 mg, 0.72 mmol) and *p*-methoxybenzylamine (1.87 mL, 14.3 mmol) to give crude **130**. This was then reacted via the above method with acetyl chloride (51  $\mu$ L, 0.72 mmol) and palladium catalyst in methanol (5 mL). Work up and chromatography (2% triethylamine in dichloromethane) afforded crude **131**. This was then reacted via the above method with trifluoroacetic acid (3 mL). Work up and chromatography (5% ethanol in dichloromethane) gave rise to clean **114** (95 mg, 51%) as a pale brown solid (m.p. 138-145°C). Analysis Found: C, 80.45; H, 6.76; N, 10.42.  $C_{18}H_{18}N_2 \cdot 0.33H_2O$  requires C, 80.56; H, 7.01; N, 10.44%. HRMS: Found 262.1466;  $C_{18}H_{18}N_2$  requires 262.1470. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3446, 3295, 3114, 1646, 1615, 1568, 1499.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$ : 2.30 [3H, s,  $CH_3$ ], 2.80-3.05 [4H, m, 2x $CH_2$ ], 4.96 [2H, br s,  $NH_2$ ], 7.14-7.18 [4H, m, H(3') + H(4') + H(5') + H(6')], 7.25 [1H,

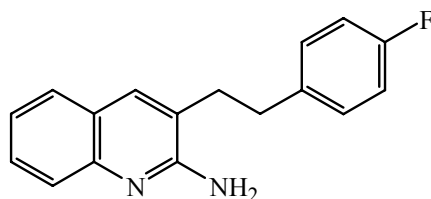
ddd,  $^4J_{6,8} = 1.2$  Hz,  $J_{6,7} = 6.9$  Hz,  $J_{5,6} = 8.0$  Hz, H(6)], 7.52 [1H, ddd,  $^4J_{5,7} = 1.2$  Hz,  $J_{6,7} = 6.9$  Hz,  $J_{7,8} = 8.7$  Hz, H(7)], 7.58 [1H, dd,  $^4J_{5,7} = 1.2$  Hz,  $J_{5,6} = 8.0$  Hz, H(5)], 7.65-7.68 [2H, m, H(4) + H(8)].  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 19.49 [ $\text{CH}_3$ ], 31.92 [ $\text{CH}_2$ ], 32.02 [ $\text{CH}_2$ ], 122.92 [C(6)], 123.21 [C(4a)], 124.48 [C(3)], 125.49 [C(8)], 126.46 [C(5')], 126.72 [C(4')], 127.18 [C(5)], 128.99 [C(6')], 129.24 [C(7)], 130.63 [C(3')], 135.94 [C(4)], 136.03 [C(1')], 139.25 [C(2')], 146.31 [C(8a)], 156.34 [C(2)]. EIMS:  $m/z$ : 262 ( $\text{M}^+$  28%), 157 (100), 130 (20), 105 (9).

### 3-[2-(4-tert-Butylphenyl)ethyl]quinolin-2-amine (115)



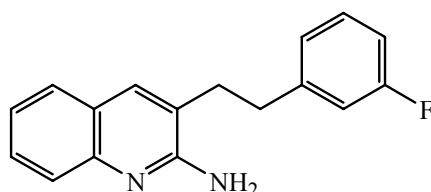
**115** was prepared via the above method, using **106** (250 mg, 0.78 mmol) and *p*-methoxybenzylamine (2.0 mL, 15.6 mmol) to give crude **132**. This was then reacted via the above method with acetyl chloride (55  $\mu\text{L}$ , 0.78 mmol) and palladium catalyst in methanol (5 mL). Work up and chromatography (2% ethanol in dichloromethane) afforded crude **133**. This was then reacted via the above method with trifluoroacetic acid (3 mL). Work up and chromatography (5% ethanol in dichloromethane) gave rise to clean **115** (120 mg, 51%) as a cream coloured solid (m.p. 130-136°C). Analysis Found: C, 82.49; H, 7.78; N, 9.12.  $\text{C}_{21}\text{H}_{24}\text{N}_2$  requires C, 82.85; H, 7.95; N, 9.20%. IR (nujol mull):  $\nu$  ( $\text{cm}^{-1}$ ): 3444, 3300, 3121, 1648, 1618, 1568, 1499.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 1.31 [9H, s, 3 x  $\text{CH}_3$ ], 2.82-2.87 [2H, m,  $\text{CH}_2$ ] 2.97-3.03 [2H, m,  $\text{CH}_2$ ], 5.01 [2H, br s,  $\text{NH}_2$ ], 7.14-7.16 [2H, m, H(2') + H(6')], 7.23 [1H, ddd,  $^4J_{6,8} = 1.2$  Hz,  $J_{6,7} = 6.9$  Hz,  $J_{5,6} = 8.1$  Hz, H(6)], 7.31-7.34 [2H, m, H(3') + H(5')], 7.51 [1H, ddd,  $^4J_{5,7} = 1.2$  Hz,  $J_{6,7} = 6.9$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.57 [1H, dd,  $^4J_{5,7} = 1.2$  Hz,  $J_{5,6} = 8.1$  Hz, H(5)], 7.65-7.67 [2H, m, H(4) + H(8)].  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 31.55 [ $\text{C}(\text{CH}_3)_3$ ], 33.19 [ $\text{CH}_2$ ], 33.98 [ $\text{CH}_2$ ], 34.57 [ $\text{C}(\text{CH}_3)_3$ ], 122.77 [C(6)], 123.21 [C(3)], 124.50 [C(4a)], 125.53 [C(8)], 125.67 [C(3') + C(5')], 127.17 [C(5)], 128.19 [C(2') + C(6')], 129.10 [C(7)], 135.70 [C(4)], 138.03 [C(1')], 146.47 [C(4')], 149.40 [C(8a)], 156.42 [C(2)]. EIMS:  $m/z$ : 304 ( $\text{M}^+$  35%), 157(100), 147 (21), 130 (14).

### 3-[2-(4-Fluorophenyl)ethyl]quinolin-2-amine (116)



**116** was prepared via the above method, using **107** (250 mg, 0.94 mmol) and *p*-methoxybenzylamine (2.5 mL, 18.8 mmol) to give crude **134**. This was then reacted via the above method with acetyl chloride (67  $\mu$ L, 0.94 mmol) and palladium catalyst in methanol (5 mL). Work up and chromatography (1% ethyl acetate and 1% triethylamine in dichloromethane) afforded crude **135**. This was then reacted via the above method with trifluoroacetic acid (5 mL). Work up and chromatography (5% ethanol in dichloromethane) gave rise to clean **116** (130 mg, 52%) as a yellow solid (m.p. 134-141°C). HRMS: Found 266.1215; C<sub>17</sub>H<sub>15</sub>FN<sub>2</sub> requires 266.1219. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3438, 3350, 3295, 3133, 1683, 1644, 1618, 1599, 1570, 1508, 1501. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.83-2.88 [2H, m, CH<sub>2</sub>], 2.98-3.03 [2H, m, CH<sub>2</sub>], 5.65 [2H, br s, NH<sub>2</sub>], 6.92-7.00 [2H, m, H(3') + H(5')], 7.09-7.15 [2H, m, H(2') + H(6')], 7.27 [1H, ddd, <sup>4</sup>J<sub>6,8</sub> = 0.9 Hz, *J* = 7.2 Hz, *J* = 7.8 Hz, H(6)], 7.51-7.57 [2H, m, H(5) + H(7)], 7.61 [1H, s, H(4)], 7.68 [1H, dd, <sup>4</sup>J<sub>6,8</sub> = 0.9 Hz, *J*<sub>7,8</sub> = 8.1 Hz, H(8)]. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ : 33.02 [CH<sub>2</sub>], 33.53 [CH<sub>2</sub>], 115.58 [d, <sup>2</sup>J<sub>C,F</sub> = 21.1 Hz, C(3') + C(5')], 122.92 [C(3)], 123.40 [C(6)], 123.86 [C(4a)], 124.18 [C(8)], 127.30 [C(5)], 129.82 [C(7)], 130.01 [d, <sup>3</sup>J<sub>C,F</sub> = 7.7 Hz, C(2') C(6')], , 136.37 [d, <sup>4</sup>J<sub>C,F</sub> = 3.1 Hz, C(1')], 136.92 [C(4)], 144.49 [C(8a)], 155.93 [C(2)], 161.71 [d, <sup>1</sup>J<sub>C,F</sub> = 242.7 Hz, C(4')]. EIMS: *m/z*: 266 (M<sup>+</sup> 22 %), 157 (100), 130 (28), 102 (5).

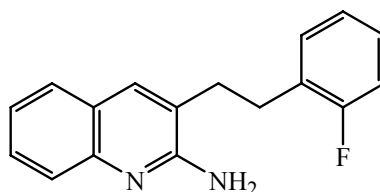
### 3-[2-(3-Fluorophenyl)ethyl]quinolin-2-amine (117)



**117** was prepared via the above method, using **108** (250 mg, 0.94 mmol) and *p*-methoxybenzylamine (2.5 mL, 18.8 mmol) to give crude **136**. This was then reacted via the above method with acetyl chloride (67  $\mu$ L, 0.94 mmol) and palladium catalyst in methanol (5 mL). Work up and chromatography (1% ethyl acetate and 1% triethylamine in

dichloromethane) afforded crude **137**. This was then reacted via the above method with trifluoroacetic acid (5 mL). Work up and chromatography (5% ethanol in dichloromethane) gave rise to clean **117** (200 mg, 78%) as a pale yellow solid (m.p. 119-125°C). HRMS: Found 66.1218; C<sub>17</sub>H<sub>15</sub>FN<sub>2</sub> requires 266.1219. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3446, 3346, 3300, 3118, 1683, 1648, 1619, 1587, 1570, 1489. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.81-2.86 [2H, m, CH<sub>2</sub>], 2.97-3.02 [2H, m, CH<sub>2</sub>], 5.90 [2H, br s, NH<sub>2</sub>], 6.86-6.94 [3H, m, H(2') + H(4') + H(6')], 7.17-7.27 [2H, m, H(5') + H(6)], 7.48-7.55 [2H, m, H(5) + H(7)], 7.59 [1H, s, H(4)], 7.67 [1H, d<sup>†</sup>,  $J_{7,8} = 8.1$  Hz, H(8)]. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ : 32.33 [CH<sub>2</sub>], 33.85 [CH<sub>2</sub>], 113.41 [d, <sup>2</sup> $J_{C,F} = 21.1$  Hz, C(4')], 115.36 [d, <sup>2</sup> $J_{C,F} = 20.8$  Hz, C(2')], 122.86 [C(3)], 123.33 [C(6)], 123.70 [C(4a)], 123.89 [C(8)], 124.23 [d, <sup>4</sup> $J_{C,F} = 2.9$  Hz, C(6')], 127.28 [C(5)], 129.79 [C(7)], 130.19 [d, <sup>3</sup> $J_{C,F} = 8.3$  Hz, C(5')], 136.74 [C(4)], 143.25 [d, <sup>3</sup> $J_{C,F} = 7.1$  Hz, C(1')], 144.25 [C(8a)], 155.93 [C(2)], 163.07 [d, <sup>1</sup> $J_{C,F} = 244.4$  Hz, C(3')]. EIMS:  $m/z$ : 266 (M<sup>+</sup> 28), 157 (100), 130 (19), 109 (2).

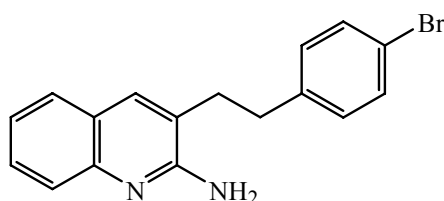
### 3-[2-(2-Fluorophenyl)ethyl]quinolin-2-amine (**118**)



**118** was prepared via the above method, using **109** (250 mg, 0.94 mmol) and *p*-methoxybenzylamine (2.5 mL, 18.8 mmol) to give crude **138**. This was then reacted via the above method with acetyl chloride (67  $\mu$ L, 0.94 mmol) and palladium catalyst in methanol (5 mL). Work up and chromatography (1% ethyl acetate and 1% triethylamine in dichloromethane) afforded crude **139**. This was then reacted via the above method with trifluoroacetic acid (5 mL). Work up and chromatography (5% ethanol in dichloromethane) gave rise to clean **118** (150 mg, 60%) as a cream coloured solid (m.p. 153-161°C). HRMS: Found 266.1220; C<sub>17</sub>H<sub>15</sub>FN<sub>2</sub> requires 266.1219. IR (nujol mull):  $\nu$  (cm<sup>-1</sup>): 3493, 3367, 3311, 3120, 1686, 1647, 1607, 1583, 1568, 1492. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ : 2.88-2.90 [2H, m, H(A)], 3.02-3.05 [2H, m, H(B)], 6.16 [2H, br s, NH<sub>2</sub>], 7.04 [1H, ddd, <sup>4</sup> $J_{3',5'} = 1.3$  Hz,  $J_{3',4'} = 8.1$  Hz,  $J_{3',F} = 10.6$  Hz, H(3')], 7.06 [1H, ddd, <sup>4</sup> $J_{3',5'} = 1.3$  Hz,  $J_{4',5'} = 7.4$  Hz,  $J_{5',6'} = 7.9$  Hz, H(5')], 7.17 [1H, ddd, <sup>4</sup> $J_{4',6'} = 1.9$  Hz,  $J_{6',F} = J_{5',6'} = 7.9$  Hz, H(6')], 7.21 [1H, dddd, <sup>4</sup> $J_{4',6'} = 1.9$  Hz, <sup>4</sup> $J_{4',F} = 5.4$  Hz,  $J_{4',5'} = 7.4$  Hz,  $J_{3',4'} = 8.1$  Hz, H(4')], 7.29 [1H, ddd, <sup>4</sup> $J_{6,8} = 1.2$  Hz,  $J_{6,7} = 7.0$  Hz,  $J_{5,6} = 8.0$  Hz, H(6)], 7.56 [1H, ddd, <sup>4</sup> $J_{5,7} = 1.5$  Hz,  $J_{6,7} = 7.0$  Hz,  $J_{7,8} =$

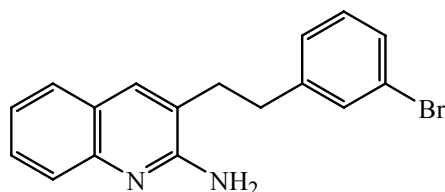
8.5 Hz, H(7)] 7.58 [1H, dd,  $^4J_{5,7} = 1.5$  Hz,  $J_{5,6} = 8.0$  Hz, H(5)], 7.72 [1H, s, H(4)], 7.73 [1H, dd,  $^4J_{6,8} = 1.2$  Hz  $J_{7,8} = 8.5$  Hz, H(8)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 28.22 [d,  $^3J_{\text{C,F}} = 2.1$  Hz, C(B)], 31.64 [d,  $^4J_{\text{C,F}} = 1.2$  Hz, C(A)], 115.49 [d,  $^2J_{\text{C,F}} = 22.0$  Hz, C(3')], 122.91 [C(8)], 123.06 [C(3)], 123.28 [C(4a)], 123.62 [C(6)], 124.35 [d,  $^4J_{\text{C,F}} = 3.5$  Hz, C(5')], 127.16 [C(5)], 127.21 [d,  $^2J_{\text{C,F}} = 15.8$  Hz, C(1')], 128.45 [d,  $^3J_{\text{C,F}} = 8.3$  Hz, C(4')], 130.15 [C(7)], 130.61 [d,  $^3J_{\text{C,F}} = 5.0$  Hz, C(6')], 137.62 [C(4)], 142.86 [C(8a)], 155.43 [C(2)], 161.17 [d,  $^1J_{\text{C,F}} = 244.7$  Hz, C(2')]. EIMS:  $m/z$ : 266 ( $\text{M}^+ - 29$ ), 157 (100), 130 (16), 109 (3).

### Attempted Synthesis of 3-[2-(4-Bromophenyl)ethyl]quinolin-2-amine (119)



The above method, was used in the attempt to prepare **119**, using **110** (300 mg, 0.87 mmol) and *p*-methoxybenzylamine (2.3 mL, 17.4 mmol) to give crude **140**. This was then reacted via the above method with acetyl chloride (62  $\mu\text{L}$ , 0.87 mmol) and palladium catalyst in methanol (5 mL). Work up and chromatography (1% ethyl acetate and 1% triethylamine in dichloromethane) afforded crude **141**. This was then reacted via the above method with trifluoroacetic acid (5 mL). Work up and chromatography (5% ethanol in dichloromethane) gave rise to a product that appeared to be consistent with **93** (100 mg, 47%) as a cream coloured solid (m.p. 141-150°C). HRMS: Found 248.1312;  $\text{C}_{17}\text{H}_{16}\text{N}_2$  requires 248.1313. IR (nujol mull):  $\nu$  ( $\text{cm}^{-1}$ ): 3444, 3351, 3120, 1683, 1646, 1618, 1570, 1499.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.91-2.94 [2H, m, H(A)], 3.05-3.07 [2H, m, H(B)], 6.51 [2H, br s,  $\text{NH}_2$ ], 7.19 [2H, dd,  $^4J_{2',4'/4',6'} = 1.2$  Hz,  $J_{2',3'/5',6'} = 7.8$  Hz, H(2') + H(6')], 7.24 [1H, tt,  $^4J_{2',4',6'} = 1.2$  Hz,  $J_{3',4',5'} = 7.2$  Hz, H(4')], 7.29-7.34 [3H, m, H(3') + H(5') + H(6)], 7.58-7.60 [2H, m, H(5) + H(7)], 7.72 [1H, s, H(4)], 7.76 [1H, d $^\ddagger$ ,  $J_{7,8} = 7.8$  Hz, H(8)].  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 32.33 [C(A)], 34.10 [C(B)], 122.04 [C(8)], 122.87 [C(4a)], 123.87 [C(3)], 123.95 [C(6)], 126.63 [C(4')], 127.23 [C(5)], 128.38 [C(2') + C(6')], 128.76 [C(3') + C(5')], 130.49 [C(7)], 138.09 [C(4)], 140.12 [C(1')], 141.50 [C(8a)], 155.31 [C(2)]. EIMS:  $m/z$ : 248 ( $\text{M}^+ - 26$ ), 171 (2), 169 (2), 157 (100), 130 (19). LSIMS:  $m/z$ : 249 ( $[\text{MH}]^+ - 100\%$ ).

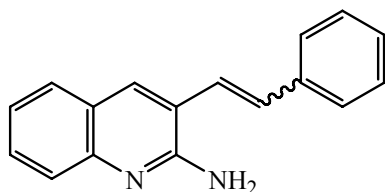
*Attempted Synthesis of 3-[2-(3-Bromophenyl)ethyl]quinolin-2-amine (120)*



The above method, was used in the attempt to prepare **120**, using **111** (300 mg, 0.87 mmol) and *p*-methoxybenzylamine (2.3 mL, 17.4 mmol) to give crude **142**. This was then reacted via the above method with acetyl chloride (62  $\mu$ L, 0.87 mmol) and palladium catalyst in methanol (5 mL). Work up and chromatography (1% ethyl acetate and 1% triethylamine in dichloromethane) afforded crude **143**. This was then reacted via the above method with trifluoroacetic acid (5 mL). Work up and chromatography (5% ethanol in dichloromethane) gave rise to a product that appeared to be consistent with **93** (270 mg, >100%) as a cream coloured solid (m.p. 121-123°C). HRMS: Found 248.1313;  $C_{17}H_{16}N_2$  requires 248.1313. IR (nujol mull):  $\nu$  ( $cm^{-1}$ ): 3463, 3351, 3305, 3110, 1683, 1649, 1616, 1569, 1500.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$ : 2.88-2.91 [2H, m, H(A)], 3.03-3.06 [2H, m, H(B)], 5.63 [2H, br s,  $NH_2$ ], 7.20 [2H, dd,  $^4J_{2',4',6'} = 1.2$  Hz,  $J_{2',3'/5',6'} = 7.8$  Hz, H(2') + H(6')], 7.23 [1H, tt,  $^4J_{2',4',6'} = 1.2$  Hz,  $J_{3',4',5'} = 7.2$  Hz, H(4')], 7.28 [1H, ddd,  $^4J_{6,8} = 1.2$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{5,6} = 7.8$  Hz, H(6)], 7.30 [2H, ddd,  $J_{3',4',5'} = 7.2$  Hz,  $J_{2',3'/5',6'} = 7.8$  Hz, H(3') + H(5')], 7.55 [1H,  $^4J_{5,7} = 1.2$  Hz,  $J_{6,7} = 7.2$  Hz,  $J_{7,8} = 8.4$  Hz, H(7)], 7.57 [1H, dd,  $^4J_{5,7} = 1.2$  Hz,  $J_{5,6} = 7.8$  Hz, H(5)], 7.68 [1H, s, H(4)], 7.70 [1H,  $d^\ddagger$ ,  $J_{7,8} = 8.4$  Hz, H(8)].  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ):  $\delta$ : 32.73 [C(A)], 34.27 [C(B)], 123.03 [C(4a)], 123.25 [C(3)], 123.67 [C(6)], 123.87 [C(8)], 126.46 [C(4')], 127.09 [C(5)], 128.38 [C(2') + C(6')], 128.67 [C(3') + C(5')], 129.65 [C(7)], 136.81 [C(4)], 140.53 [C(1')], 144.23 [C(8a)], 155.72 [C(2)]. EIMS:  $m/z$ : 248 ( $M^+$  27), 171 (2), 169 (2), 157 (100), 130 (20). LSIMS:  $m/z$ : 249 ( $[MH]^+$  100%).



*Attempted Synthesis of 3-[(E)-2-Phenylvinyl]quinolin-2-amine /  
3-[(Z)-2-Phenylvinyl]quinolin-2-amine (90)*



**86** (250 mg, 0.94 mmol), acetamide (1.11 g, 18.8 mmol), and potassium carbonate (650 mg, 4.71 mmol) were heated at 200°C for 2 hours. Water (20 mL) was added and the resulting solution was extracted with dichloromethane (3x 20 mL). The combined extracts were dried (NaSO<sub>4</sub>) and the solvent was removed. The residue that remained was chromatographed through silica (5% ethanol in dichloromethane), however the desired product was unable to be obtained from the mixture.

*3-[(E)-2-Phenylvinyl]quinolin-2-amine / 3-[(Z)-2-Phenylvinyl]quinolin-2-amine (90)*

**91** (100 mg, 0.27 mmol) was stirred in trifluoroacetic acid (2 mL) at 60°C for one hour. The trifluoroacetic acid was then removed under reduced pressure. The resulting residue was dissolved in dichloromethane (20 mL) and stirred. The dichloromethane was removed under reduced pressure and the above process was repeated until all traces of trifluoroacetic acid were gone by <sup>19</sup>F NMR. The resulting residue was then chromatographed over silica gel (5% ethanol in dichloromethane) to give clean **90** (40 mg, 60%) as a mixture of *Z* and *E* isomers. A small portion was left in the sun for several months and when retrieved, majority *E* isomer was present (m.p. 155-170°C). Analysis Found: C, 78.99; H, 5.73; N, 10.38. C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>·0.75H<sub>2</sub>O requires C, 78.59; H, 6.01; N, 10.78%. HRMS: Found 247.1228; [C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>+H]<sup>+</sup> requires 247.1230. IR (nujol mull): ν (cm<sup>-1</sup>): 3460, 3308, 3114, 1649, 1563, 1492. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ: 5.33 [2H, br s, NH<sub>2</sub>], 7.11 [1H, d, J<sub>A,B</sub> = 16.2 Hz, H(B)], 7.14 [1H, d, J<sub>A,B</sub> = 16.2 Hz, H(A)], 7.28 [1H, dd, J = 7.2 Hz, J = 7.8 Hz, H(6)], 7.32 [1H, t, J<sub>3',4',5'</sub> = 7.5 Hz, H(4')], 7.39 [2H, dd, J<sub>3',4',5'</sub> = 7.5 Hz, J<sub>2',3'/5',6'</sub> = 7.8 Hz, H(3') + H(5')], 7.53-7.56 [3H, m, H(2') + H(6') + H(7)], 7.65-7.69 [2H, m, H(5) + H(8)], 8.02 [1H, s, H(4)]. <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ: 121.66 [C(3)], 122.24 [C(A)], 123.25 [C(6)], 124.15 [C(4a)], 124.94 [C(8)], 126.75 [C(2') + C(6')], 127.53 [C(5)], 128.43 [C(4')], 128.85 [C(3') + C(5')], 129.85 [C(7)], 133.76 [C(B)], 134.53 [C(4)], 136.61 [C(1')], 146.02

[C(8a)], 155.17 [C(2)]. EIMS:  $m/z$ : 246 ( $M^{+}$  84%), 245 (100), 169 (78). LSIMS:  $m/z$ : 247 ( $[MH]^{+}$  100%).

## **6.3 Protein Methods**

### **6.3.1. Solutions**

Throughout this section water refers to Milli-Q water at 18.2 m $\Omega$ .

#### ***Luria Broth***

Bacto-tryptone (10 g), yeast extract (5 g) and sodium chloride (10 g) were dissolved in water (to 1 L) and the solution was adjusted to pH 7.0, then autoclaved.

#### ***Minimal A Medium (Min A)***

Dipotassium hydrogen phosphate (10.5 g), potassium dihydrogen phosphate (4.5 g), trisodium citrate (1.0 g) and  $^{15}\text{N}$ -ammonium chloride (0.81 g) were dissolved in water (to 1 L) and the solution was adjusted to pH 7.0, then autoclaved. Just prior to culture, solutions of magnesium sulfate (1M, 0.8 mL), glucose (20%, w/v, 10.0 mL) and thiamine (1 w/v, 0.5 mL) that had been filtered through 0.45  $\mu\text{m}$  nitrocellulose membranes were added to the Min A solution.

#### ***Tris Buffered Saline (TBS)***

Tris(hydroxymethyl)aminomethane (Tris), sodium chloride were dissolved in water to a final concentration of 25 mM and 150 mM respectively. The resulting solution was adjusted to pH 8.0 and filtered through 0.45  $\mu\text{m}$  nitrocellulose membrane.

#### ***TTBS***

Triton X (0.1% v/v) was dissolved in TBS and filtered through 0.45  $\mu\text{m}$  nitrocellulose membrane.

### 6.3.2. Protein Preparation

#### *Preparation of Uniformly <sup>15</sup>N Labelled Tec GST-SH3 Protein*<sup>33</sup>

A previously prepared sample of Escherichia coli (E coli) strain BL21-DE3 transfected with p-Gex 4T-2 expression vector containing regions of cDNA encoding for amino acids 181-245 of the Mouse Tec IV sequence (corresponding to the SH3 domain) that is connected to Glutathione-S-Transferase (GST) by a thrombin site, was used.<sup>33</sup> This was cultured overnight in LB medium and ampicillin (0.1 mg/mL) and then diluted into Min A medium and ampicillin (0.1 mg/mL). This was then incubated at 37°C until the medium reached an optical density of 0.6 at 600 nm. Protein expression was then induced through the addition of isopropyl-β-D-thiogalactopyranoside (IPTG) solution (100 mM) to final concentration of 0.2 mM. The medium was incubated for a further 2 hours, after which the cultures were spun in a centrifuge at 10 000 rpm at 4°C for 15 minutes. The supernatant was then discarded and the pellets frozen at -20°C until required.

The pellets were resuspended in TTBS (40 mL) and phenylmethylsulfonyl fluoride (PMSF) in ethanol (100mM) was added to a final concentration of 1 mM. The cells were then lysed under pressure and the lysate was spun in a centrifuge at 10 000 rpm at 4°C for 10 minutes. The supernatant was filtered through a 0.45 μM nitrocellulose filter.

#### *Purification of Uniformly <sup>15</sup>N Labelled Tec GST-SH3 Protein*

The GST-SH3 fusion protein was purified using an 8 x 2.5 cm id Pharmacia column packed with agarose/glutathione (Zymatrix), attached to a Pharmacia Fast Protein Liquid Chromatography System. The column was equilibrated with TBS and then TTBS, at a flow rate of 3 mL/minute. The protein was then loaded on the column and the column was washed with TTBS until all of the lysate had been eluted from the column. The column was then washed with TBS. Reduced glutathione in TBS was then used to elute the GST-SH3 fusion protein from the column. Sodium azide was added to the protein to a final concentration of 0.01% w/v and the protein was stored at 4°C.

#### *Thrombin Digestion and Purification of Tec SH3 Protein*

The purified GST-SH3 fusion protein was diluted to a concentration of ~1.5 mg/mL. Thrombin (Sigma T 9681, 2.5 units/mg GST-SH3), calcium chloride (to final concentration

of 2.5 mM) and sodium azide (to final concentration of 0.01% w/v) were added to the protein solution. The mixture was incubated at room temperature for 48 hours.

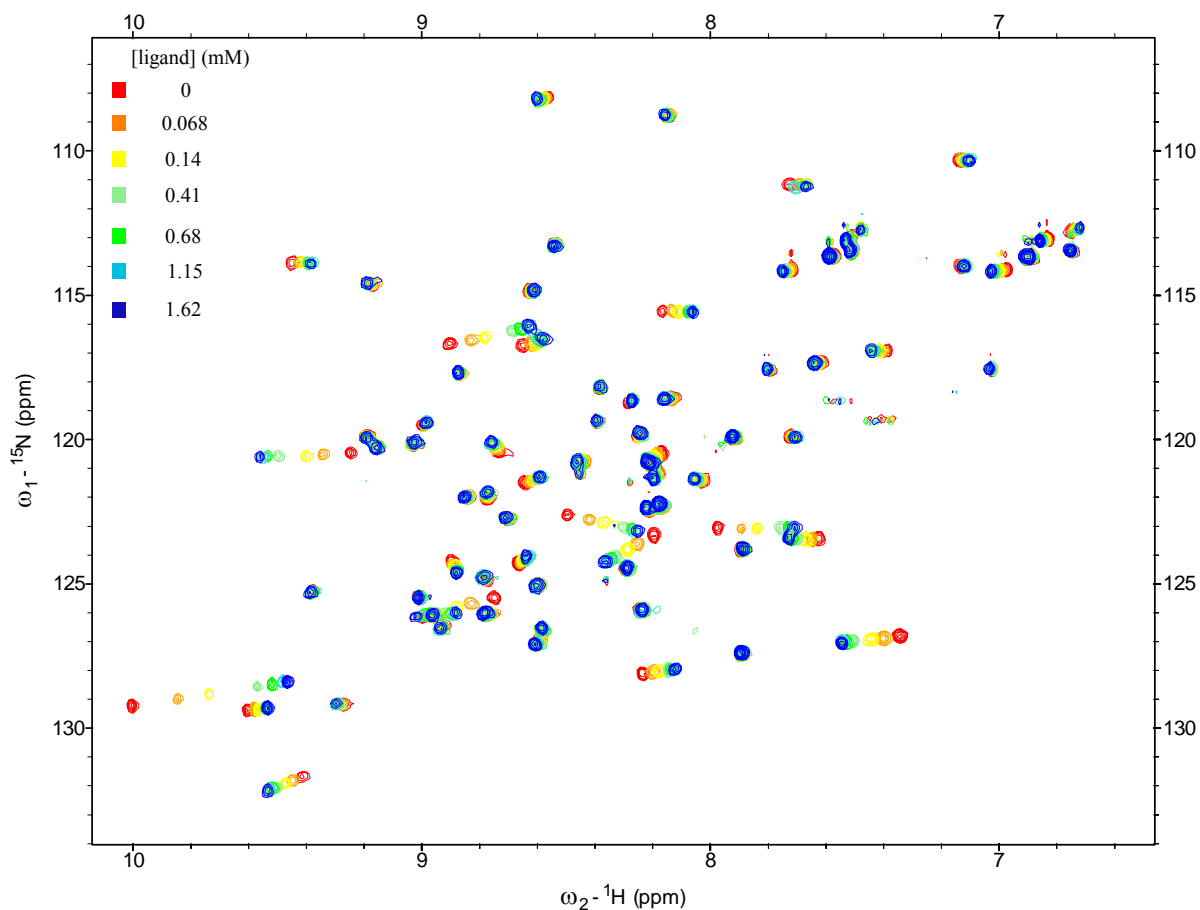
The protein solution was then concentrated to 3 mL by ultrafiltration using a 3 kDa MWCO membrane then filtered through a 0.45 µm nitrocellulose membrane. Size exclusion chromatography was then performed on the resulting solution using a 60 x 2.5 cm id Pharmacia column packed with Superdex G-75 (Pharmacia) attached to a Pharmacia FPLC system. The column was washed with water and equilibrated with TBS overnight. The concentrated protein solution was loaded onto the column and eluted at 1 mL/minute. Fractions containing purified SH3 were combined and concentrated by ultrafiltration using a 3 kDa MWCO membrane. The resulting concentrated solution was then exchanged into a solution of disodium hydrogen phosphate (12 mM, pH ~6.6) using a PD10 de-salting chromatography column. The resultant solution was used as stock for the [<sup>1</sup>H,<sup>15</sup>N] HSQC NMR chemical shift perturbation assay.

### 6.3.3. The [<sup>1</sup>H,<sup>15</sup>N] HSQC NMR Chemical Shift Perturbation Assay<sup>46</sup>

NMR spectra were obtained using a Varian INOVA 600 Spectrometer (3 RF channels), equipped with a 5 mm <sup>1</sup>H{<sup>13</sup>C/<sup>15</sup>N} inverse triple resonance PFG probe with z-axis gradients. Sensitivity enhanced [<sup>1</sup>H,<sup>15</sup>N]-Heteronuclear Single Quantum Coherence (HSQC) spectra were recorded at 25°C with 32 t<sub>1</sub> increments at spectral widths of 8000 and 2000 Hz in F1 and F2 respectively.<sup>46</sup>

A solution of the uniformly <sup>15</sup>N labelled Tec SH3 domain (~0.13 mM) in Na<sub>2</sub>HPO<sub>4</sub> (10mM), D<sub>2</sub>O (10% v/v), d<sub>6</sub>-DMSO (10% v/v), NaN<sub>3</sub> (0.01 % w/v) to a total volume of 550 µL and pH ~6.6 was prepared. Stock solutions of the ligands were prepared by dissolving the ligand in d<sub>6</sub>-DMSO.

A spectrum of the protein without any ligand added was first recorded. Then the ligand was titrated into the protein solution at varying concentrations of 0.1 to 3 molar equivalents of the protein in 2 µL aliquots. This was repeated until either there was little to no change in the spectrum or the ligand was no longer soluble in the protein solution. An example of an overlay of the HSQC Spectra from the assay of **23** is shown in Figure 72.



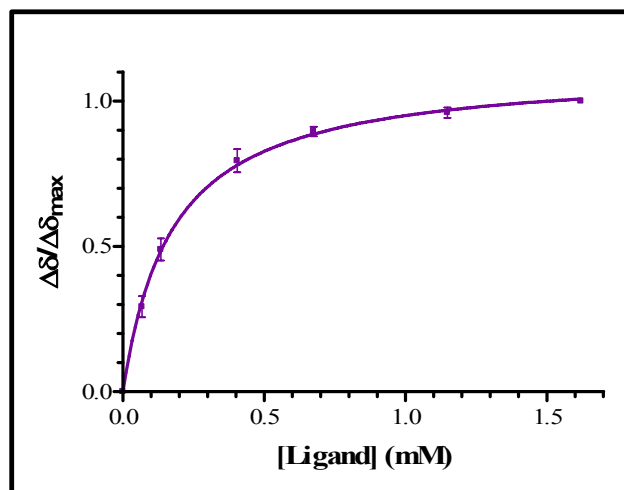
**Figure 72.** The overlay of the  $[^1\text{H}, ^{15}\text{N}]$  HSQC NMR spectra from the chemical shift perturbation assay of **23**.

The NMR spectra were then analysed using SPARKY.<sup>75</sup> Chemical shifts of the signals for the amino acids that had shifted significantly in the  $\delta_{\text{H}}$  direction (usually  $\Delta\delta_{\text{max}} > 0.09$  ppm, where  $\Delta\delta_{\text{max}}$  was the maximum change in chemical shift for the one signal) were recorded. These were then used to calculate  $\Delta\delta = \delta_{\text{L}} - \delta_0$  values where  $\delta_{\text{L}}$  is  $\delta_{\text{H}}$  for the protein in the presence of the ligand at a given concentration  $[\text{L}]$ , and  $\delta_0$  is  $\delta_{\text{H}}$  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 so that the each of the residues could be compared. These values were then averaged over all the residues and Graphpad Prism was used to plot these values against the concentration of the ligand using a one-site hyperbola binding model to give a  $K_{\text{d}} \pm$  standard error.<sup>59</sup> The data from the assay of **23** is shown below as an example (Table 29 and Figure 73).

[ <b>23</b> ] (mM)	$\Delta\delta$ <sup>1</sup> H (H-N) (ppm)												
	A191	A218	D196	H193	H195	L197	Q190	S230	T192	W215	W215 (sc)	W216	Y227
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.68	0.059	0.032	0.023	0.058	0.035	0.079	0.035	0.086	0.075	0.077	0.156	0.027	0.097
0.14	0.098	0.058	0.042	0.091	0.054	0.132	0.058	0.140	0.122	0.128	0.264	0.053	0.156
0.41	0.163	0.088	0.076	0.135	0.088	0.212	0.096	0.218	0.222	0.201	0.431	0.087	0.249
0.68	0.183	0.106	0.094	0.152	0.094	0.239	0.101	0.244	0.248	0.224	0.483	0.097	0.285
1.15	0.198	0.112	0.102	0.159	0.099	0.261	0.110	0.257	0.270	0.235	0.522	0.107	0.304
1.62	0.202	0.120	0.106	0.170	0.105	0.274	0.111	0.269	0.277	0.245	0.537	0.113	0.312

[ <b>23</b> ] (mM)	$\Delta\delta/\Delta\delta_{\max}$ <sup>1</sup> H (H-N) (ppm)													Avg	Std Dev	
	A191	A218	D196	H193	H195	L197	Q190	S230	T192	W215	W215 (sc)	W216	Y227			
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.68	0.292	0.267	0.217	0.034	0.333	0.288	0.315	0.320	0.271	0.314	0.291	0.239	0.311	0.292	0.036	
0.14	0.485	0.483	0.396	0.535	0.514	0.481	0.523	0.520	0.440	0.522	0.492	0.469	0.500	0.489	0.038	
0.41	0.807	0.733	0.717	0.794	0.838	0.774	0.865	0.810	0.801	0.820	0.803	0.770	0.798	0.795	0.040	
0.68	0.906	0.883	0.887	0.894	0.895	0.872	0.910	0.907	0.895	0.914	0.899	0.858	0.913	0.895	0.017	
1.15	0.980	0.933	0.962	0.935	0.943	0.953	0.991	0.955	0.975	0.959	0.972	0.947	0.974	0.960	0.018	
1.62	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	

**Table 29.** The change in chemical shifts for all the residues whose corresponding signals shift significantly ( $> \sim 0.1$  ppm) during the assay of **23** (above) and the normalised values and averages for the same assay (below).



**Figure 73.** The binding isotherm created from the data in Table 29 that was used to calculate the equilibrium dissociation binding constant of **23**. Error bars are set at 1 standard deviation.

The chemical shift mapping of the residues whose signals shift during the assay and therefore the residues involved in binding was performed using VMD – Visual Molecular Dynamics.<sup>76</sup>

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## Appendix 1. X-Ray Crystal Structure Data for 3-Methyl-2-phenoxy-4-aminoquinoline (83)

A colourless plate like crystal was attached with Exxon Paratone N, to a short length of fibre supported on a thin piece of copper wire inserted in a copper mounting pin. The crystal was quenched in a cold nitrogen gas stream from an Oxford Cryosystems Cryostream. A APEXII-FR591 diffractometer employing graphite monochromated MoK $\alpha$  radiation generated from a rotating anode was used for the data collection. Cell constants were obtained from a least squares refinement against 7152 reflections located between 6 and 61° 2 $\theta$ . Data were collected at 150(2) Kelvin with  $\omega+\phi$  scans to 61° 2 $\theta$ . The data integration and reduction were undertaken with SAINT and XPREP<sup>1</sup>, and subsequent computations were carried out with the WinGX<sup>2</sup> and XTAL<sup>3</sup> graphical user interfaces.

The structure was solved in the space group  $P2_1/c$ (#14) by direct methods with SIR97<sup>4</sup>, and extended and refined with SHELXL-97.<sup>5</sup> The non-hydrogen atoms were modelled with anisotropic displacement parameters, and in general a riding atom model was used for the hydrogen atoms. The amine hydrogen atoms were located and modelled with isotropic displacement parameters. Adjacent molecules are linked by amine-pyridyl hydrogen bonds (see Table A7). An ORTEP<sup>6</sup> depiction of the molecule with 50% displacement ellipsoids is provided in Figure A1.

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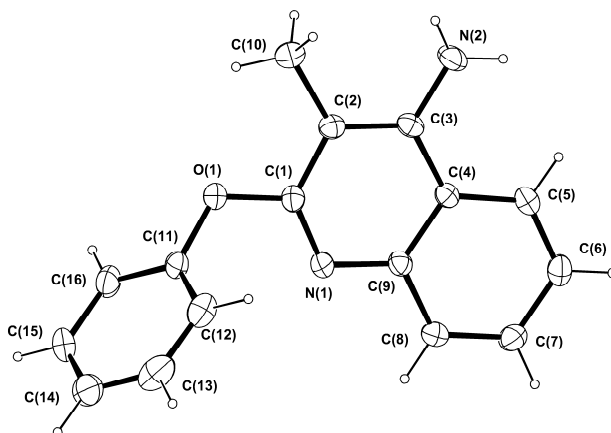


Figure A1: Atom numbering for 3-methyl-2-phenoxy-4-aminoquinoline (83).

**Table A1:** Crystal Structure Parameters for **83**

Formula of the Refinement Model	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O
Model Molecular Weight	250.29
Crystal System	monoclinic
Space Group	<i>P</i> 2 <sub>1</sub> / <i>c</i> (#14)
<i>a</i>	16.8757(8) Å
<i>b</i>	5.6530(3) Å
<i>c</i>	13.2810(7) Å
$\beta$	96.210(2)°
<i>V</i>	1259.55(11) Å <sup>3</sup>
<i>D</i> <sub>c</sub>	1.320 g cm <sup>-3</sup>
<i>Z</i>	4
Crystal Size	0.184 × 0.154 × 0.096 mm
Crystal Colour	colourless
Crystal Habit	plate
Temperature	150(2) Kelvin
$\lambda$ (MoK $\alpha$ )	0.71073 Å
$\mu$ (MoK $\alpha$ )	0.084 mm <sup>-1</sup>
$2\theta_{\max}$	61.06°
<i>hkl</i> range	-24 24, -5 8, -18 18
<i>N</i>	24485
<i>N</i> <sub>ind</sub>	3843( <i>R</i> <sub>merge</sub> 0.0704)
<i>N</i> <sub>obs</sub>	2807( <i>I</i> > 2 $\sigma$ ( <i>I</i> ))
<i>N</i> <sub>var</sub>	181
Residuals* <i>R</i> 1( <i>F</i> ), <i>wR</i> 2( <i>F</i> <sup>2</sup> )	0.0418, 0.1320
GoF(all)	1.327
Residual Extrema	-0.333, 0.319 e <sup>-</sup> Å <sup>-3</sup>

\*  $R1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$  for  $F_o > 2\sigma(F_o)$ ;  $wR2 = \frac{(\sum w(F_o^2 - F_c^2)^2 / \sum (wF_c^2)^2)^{1/2}}$  all reflections  
 $w = 1 / [\sigma^2(F_o^2) + (0.03P)^2 + 0.5P]$  where  $P = (F_o^2 + 2F_c^2) / 3$

**Table A2.** Non-Hydrogen Atom Coordinates, Isotropic Thermal Parameters and Occupancies

atom	x	y	z	$U_{eq}(\text{Å}^2)$	Occ
O(1)	0.30336(7)	0.5811(2)	0.30788(8)	0.0305(3)	1
N(1)	0.21677(7)	0.8944(2)	0.27671(9)	0.0216(3)	1
N(2)	0.14589(9)	0.7916(3)	0.56768(10)	0.0269(3)	1
C(1)	0.24694(8)	0.7313(3)	0.33952(11)	0.0207(3)	1
C(2)	0.22668(8)	0.6831(3)	0.43781(10)	0.0196(3)	1
C(3)	0.16913(8)	0.8264(3)	0.47322(10)	0.0188(3)	1
C(4)	0.13335(8)	1.0109(3)	0.40895(10)	0.0178(3)	1
C(5)	0.07571(8)	1.1714(3)	0.43848(11)	0.0216(3)	1
C(6)	0.04541(8)	1.3484(3)	0.37518(12)	0.0241(3)	1
C(7)	0.07133(9)	1.3728(3)	0.27853(12)	0.0257(3)	1
C(8)	0.12722(9)	1.2207(3)	0.24777(11)	0.0239(3)	1
C(9)	0.15982(8)	1.0373(3)	0.31167(10)	0.0187(3)	1
C(10)	0.26426(9)	0.4830(3)	0.50033(12)	0.0257(3)	1
C(11)	0.34962(8)	0.6545(3)	0.23298(11)	0.0211(3)	1
C(12)	0.39535(9)	0.8579(3)	0.24398(13)	0.0285(3)	1
C(13)	0.44674(9)	0.9079(3)	0.17227(16)	0.0372(4)	1
C(14)	0.45183(11)	0.7580(4)	0.09113(16)	0.0426(5)	1
C(15)	0.40540(12)	0.5569(3)	0.08100(14)	0.0386(4)	1
C(16)	0.35392(9)	0.5033(3)	0.15248(12)	0.0272(3)	1

**Table A3.** Hydrogen Atom Coordinates, Isotropic Thermal Parameters and Occupancies

atom	x	y	z	$U_{eq}(\text{Å}^2)$	Occ
H(2NA)	0.1761(12)	0.712(4)	0.6129(16)	0.038(5)	1
H(2NB)	0.1096(13)	0.888(4)	0.5892(16)	0.047(6)	1
H(5)	0.0581	1.1563	0.5021	0.026	1
H(6)	0.0077	1.4523	0.3961	0.029	1
H(7)	0.0505	1.4924	0.2354	0.031	1
H(8)	0.1440	1.2386	0.1837	0.029	1
H(10A)	0.2236	0.3748	0.5164	0.039	1
H(10B)	0.2917	0.5446	0.5618	0.039	1
H(10C)	0.3014	0.4017	0.4627	0.039	1
H(12)	0.3917	0.9590	0.2985	0.034	1
H(13)	0.4781	1.0436	0.1788	0.045	1
H(14)	0.4866	0.7927	0.0433	0.051	1
H(15)	0.4086	0.4568	0.0260	0.046	1
H(16)	0.3228	0.3672	0.1461	0.033	1



**Table A4.** Anisotropic Thermal Parameters ( $\text{\AA}^2$ )

atom	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
O(1)	0.0387(6)	0.0245(6)	0.0313(6)	0.0119(5)	0.0174(5)	0.0060(5)
N(1)	0.0261(6)	0.0213(6)	0.0179(6)	0.0040(5)	0.0052(4)	-0.0004(5)
N(2)	0.0301(7)	0.0347(8)	0.0165(6)	0.0038(6)	0.0058(5)	0.0039(6)
C(1)	0.0223(6)	0.0194(7)	0.0209(7)	0.0015(5)	0.0043(5)	-0.0024(5)
C(2)	0.0211(6)	0.0193(7)	0.0179(6)	-0.0014(5)	0.0002(5)	0.0003(5)
C(3)	0.0195(6)	0.0220(7)	0.0148(6)	-0.0041(5)	0.0010(5)	-0.0010(5)
C(4)	0.0179(6)	0.0195(7)	0.0157(6)	-0.0024(5)	0.0014(5)	-0.0023(5)
C(5)	0.0205(6)	0.0252(8)	0.0196(6)	-0.0016(6)	0.0048(5)	-0.0037(6)
C(6)	0.0213(6)	0.0225(8)	0.0290(7)	0.0016(6)	0.0053(6)	-0.0037(6)
C(7)	0.0261(7)	0.0230(8)	0.0283(8)	0.0039(6)	0.0040(6)	0.0051(6)
C(8)	0.0272(7)	0.0253(8)	0.0200(7)	0.0026(6)	0.0052(5)	0.0035(6)
C(9)	0.0207(6)	0.0191(7)	0.0163(6)	-0.0009(5)	0.0025(5)	-0.0017(5)
C(10)	0.0277(7)	0.0249(8)	0.0241(7)	0.0014(6)	0.0009(6)	0.0042(6)
C(11)	0.0199(6)	0.0214(7)	0.0223(7)	0.0054(5)	0.0033(5)	0.0009(6)
C(12)	0.0273(7)	0.0246(8)	0.0320(8)	0.0019(6)	-0.0046(6)	-0.0044(7)
C(13)	0.0210(7)	0.0282(9)	0.0618(12)	-0.0013(6)	0.0022(7)	0.0087(9)
C(14)	0.0349(9)	0.0392(11)	0.0586(12)	0.0139(8)	0.0274(9)	0.0156(9)
C(15)	0.0507(11)	0.0319(10)	0.0370(10)	0.0137(8)	0.0222(8)	-0.0021(8)
C(16)	0.0310(8)	0.0201(8)	0.0311(8)	0.0023(6)	0.0065(6)	-0.0047(6)

**Table A5.** Non Hydrogen Bond Lengths ( $\text{\AA}$ )

atom	atom	Distance	atom	atom	Distance
O(1)	C(1)	1.3751(17)	O(1)	C(11)	1.3926(17)
N(1)	C(1)	1.3088(19)	N(1)	C(9)	1.3743(18)
N(2)	C(3)	1.3685(18)	C(1)	C(2)	1.4114(19)
C(2)	C(3)	1.386(2)	C(2)	C(10)	1.502(2)
C(3)	C(4)	1.439(2)	C(4)	C(5)	1.4161(19)
C(4)	C(9)	1.4198(18)	C(5)	C(6)	1.370(2)
C(6)	C(7)	1.407(2)	C(7)	C(8)	1.371(2)
C(8)	C(9)	1.413(2)	C(11)	C(16)	1.377(2)
C(11)	C(12)	1.384(2)	C(12)	C(13)	1.385(2)
C(13)	C(14)	1.381(3)	C(14)	C(15)	1.379(3)
C(15)	C(16)	1.388(2)			

*Symmetry Operators*

- (1)  $x, y, z$                       (2)  $-x, y+1/2, -z+1/2$                       (3)  $-x, -y, -z$   
(4)  $x, -y-1/2, z-1/2$

**Table A6.** Non Hydrogen Bond Angles ( ° )

atom	atom	atom	angle
C(1)	O(1)	C(11)	119.63(12)
C(1)	N(1)	C(9)	115.91(12)
N(1)	C(1)	O(1)	118.35(12)
N(1)	C(1)	C(2)	127.53(13)
O(1)	C(1)	C(2)	114.10(12)
C(3)	C(2)	C(1)	116.73(13)
C(3)	C(2)	C(10)	121.48(13)
C(1)	C(2)	C(10)	121.78(13)
N(2)	C(3)	C(2)	120.53(14)
N(2)	C(3)	C(4)	120.31(13)
C(2)	C(3)	C(4)	119.16(12)
C(5)	C(4)	C(9)	118.55(13)
C(5)	C(4)	C(3)	123.84(12)
C(9)	C(4)	C(3)	117.58(12)
C(6)	C(5)	C(4)	121.32(13)
C(5)	C(6)	C(7)	119.96(14)
C(8)	C(7)	C(6)	120.15(14)
C(7)	C(8)	C(9)	121.12(13)
N(1)	C(9)	C(8)	118.01(12)
N(1)	C(9)	C(4)	123.09(13)
C(8)	C(9)	C(4)	118.90(13)
C(16)	C(11)	C(12)	121.48(14)
C(16)	C(11)	O(1)	116.77(14)
C(12)	C(11)	O(1)	121.44(14)
C(11)	C(12)	C(13)	118.74(16)
C(14)	C(13)	C(12)	120.51(17)
C(15)	C(14)	C(13)	119.96(16)
C(14)	C(15)	C(16)	120.30(17)
C(11)	C(16)	C(15)	119.01(16)

*Symmetry Operators*

(1) x, y, z

(4) x, -y-1/2, z-1/2

(2) -x, y+1/2, -z+1/2

(3) -x, -y, -z

**Table A7.** Torsion Angles (°)

atom	atom	atom	atom	angle
C(9)	N(1)	C(1)	O(1)	179.07(12)
C(9)	N(1)	C(1)	C(2)	1.3(2)
C(11)	O(1)	C(1)	N(1)	25.5(2)
C(11)	O(1)	C(1)	C(2)	-156.39(13)
N(1)	C(1)	C(2)	C(3)	-1.1(2)
O(1)	C(1)	C(2)	C(3)	-178.99(13)
N(1)	C(1)	C(2)	C(10)	177.60(15)
O(1)	C(1)	C(2)	C(10)	-0.3(2)
C(1)	C(2)	C(3)	N(2)	179.91(13)
C(10)	C(2)	C(3)	N(2)	1.2(2)
C(1)	C(2)	C(3)	C(4)	0.62(19)
C(10)	C(2)	C(3)	C(4)	-178.10(13)
N(2)	C(3)	C(4)	C(5)	2.5(2)
C(2)	C(3)	C(4)	C(5)	-178.20(13)
N(2)	C(3)	C(4)	C(9)	-179.74(13)
C(2)	C(3)	C(4)	C(9)	-0.45(19)
C(9)	C(4)	C(5)	C(6)	0.3(2)
C(3)	C(4)	C(5)	C(6)	177.99(14)
C(4)	C(5)	C(6)	C(7)	0.2(2)
C(5)	C(6)	C(7)	C(8)	-0.4(2)
C(6)	C(7)	C(8)	C(9)	0.0(2)
C(1)	N(1)	C(9)	C(8)	178.10(13)
C(1)	N(1)	C(9)	C(4)	-1.0(2)
C(7)	C(8)	C(9)	N(1)	-178.72(14)
C(7)	C(8)	C(9)	C(4)	0.4(2)
C(5)	C(4)	C(9)	N(1)	178.52(13)
C(3)	C(4)	C(9)	N(1)	0.7(2)
C(5)	C(4)	C(9)	C(8)	-0.6(2)
C(3)	C(4)	C(9)	C(8)	-178.45(13)
C(1)	O(1)	C(11)	C(16)	-129.58(15)
C(1)	O(1)	C(11)	C(12)	56.74(19)
C(16)	C(11)	C(12)	C(13)	-0.4(2)
O(1)	C(11)	C(12)	C(13)	172.99(14)
C(11)	C(12)	C(13)	C(14)	0.3(2)
C(12)	C(13)	C(14)	C(15)	0.1(3)
C(13)	C(14)	C(15)	C(16)	-0.5(3)
C(12)	C(11)	C(16)	C(15)	0.0(2)
O(1)	C(11)	C(16)	C(15)	-173.67(14)
C(14)	C(15)	C(16)	C(11)	0.4(3)

*Symmetry Operators*

(1) x, y, z

(4) x, -y-1/2, z-1/2

(2) -x, y+1/2, -z+1/2

(3) -x, -y, -z

**Table A8.** Hydrogen Bond Geometry

Donor	Hydrogen	Acceptor	D-H( Å)	H-A( Å)	D-A( Å)	DHA Angle( °)
N(2)	H(2NA)	N(1) 4_576	0.87(2)	2.29(2)	3.0862(18)	152.1(18)

*Symmetry Operators*

(1) x, y, z	(2) -x, y+1/2, -z+1/2	(3) -x, -y, -z
(4) x, -y-1/2, z-1/2		

**Table A9.** Hydrogen Bond Lengths ( Å)

atom	atom	Distance	atom	atom	Distance
N(2)	(2NA)	0.87(2)	N(2)	H(2NB)	0.89(2)
C(5)	H(5)	0.9300	C(6)	H(6)	0.9300
C(7)	H(7)	0.9300	C(8)	H(8)	0.9300
C(10)	H(10A)	0.9600	C(10)	H(10B)	0.9600
C(10)	H(10C)	0.9600	C(12)	H(12)	0.9300
C(13)	H(13)	0.9300	C(14)	H(14)	0.9300
C(15)	H(15)	0.9300	C(16)	H(16)	0.9300

*Symmetry Operators*

(1) x, y, z	(2) -x, y+1/2, -z+1/2	(3) -x, -y, -z
(4) x, -y-1/2, z-1/2		

**Table A10.** Hydrogen Bond Angles ( ° )

atom	atom	atom	angle
C(3)	N(2)	H(2NA)	120.1(13)
C(3)	N(2)	H(2NB)	118.8(14)
H(2NA)	N(2)	H(2NB)	118.0(19)
C(6)	C(5)	H(5)	119.3
C(4)	C(5)	H(5)	119.3
C(5)	C(6)	H(6)	120.0
C(7)	C(6)	H(6)	120.0
C(8)	C(7)	H(7)	119.9
C(6)	C(7)	H(7)	119.9
C(7)	C(8)	H(8)	119.4
C(9)	C(8)	H(8)	119.4
C(2)	C(10)	H(10A)	109.5
C(2)	C(10)	H(10B)	109.5
H(10A)	C(10)	H(10B)	109.5
C(2)	C(10)	H(10C)	109.5
H(10A)	C(10)	H(10C)	109.5
H(10B)	C(10)	H(10C)	109.5
C(11)	C(12)	H(12)	120.6
C(13)	C(12)	H(12)	120.6
C(14)	C(13)	H(13)	119.7
C(12)	C(13)	H(13)	119.7
C(15)	C(14)	H(14)	120.0
C(13)	C(14)	H(14)	120.0
C(14)	C(15)	H(15)	119.8
C(16)	C(15)	H(15)	119.8
C(11)	C(16)	H(16)	120.5
C(15)	C(16)	H(16)	120.5

*Symmetry Operators*

(1) x, y, z

(4) x, -y-1/2, z-1/2

(2) -x, y+1/2, -z+1/2

(3) -x, -y, -z