

**SYNTHESIS OF 2,3-DIARYL-4-METHOXYQUINOLINES VIA  
PALLADIUM- CATALYZED CROSS COUPLING REACTIONS**

**by**

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I declare that SYNTHESIS OF 2,3-DIARYL-4-METHOXYQUINOLINES VIA  
PALLADIUM-CATALYZED CROSS COUPLING REACTIONS is my own work  
and that all the sources that I have used have been indicated and acknowledged by  
means of references.

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SIGNATURE

(MS V MTSHEMLA)

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DATE

**This thesis is dedicated to my late father, G.T. Mtshemla**

## ACKNOWLEDGEMENTS

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## Abstract

The main objective of this investigation was to study palladium-catalyzed coupling of 2-aryl-4-chloro-3-iodoquinolines with phenyl boronic acid in order to assess the regioselectivity of carbon-carbon bond formation at either C3 or C4. The 2-aryl-4-chloro-3-iodoquinolines were subjected to  $\text{Pd}(\text{PPh}_3)_4$ -catalyzed coupling reaction with phenyl boronic acid in DMF in the presence of 2M sodium carbonate (aq) to afford 2,3-diaryl-4-chloroquinolines. Reaction of 2,3-diaryl-4-chloroquinolines with sodium methoxide in MeOH-DMF mixture under reflux afforded the corresponding 2,3-diaryl-4-methoxyquinoline. An alternative route to the latter involving palladium-catalyzed cross-coupling reaction of 2-aryl-3-iodo-4-methoxyquinolines derived from the reaction of 2-aryl-4-chloro-3-iodoquinolines with sodium methoxide in refluxing methanol-THF mixture was also investigated. The 2,3-diaryl-4-methoxyquinolines were subjected to further studies of chemical transformation with boron tribromide to afford the corresponding 2,3-diarylquinolin-4(1*H*)-ones. All new compounds were characterized using a combination of NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ), IR and mass spectroscopic techniques as well as elemental analysis.

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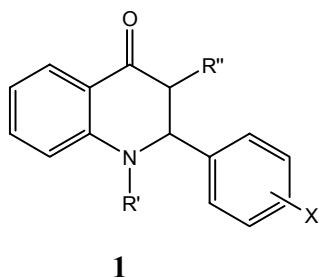


## CHAPTER 1

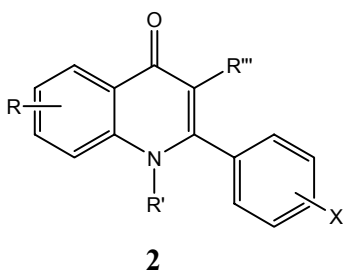
### 1. INTRODUCTION

#### 1.1 General description and sources of 2-arylquinolones and their quinoline derivatives

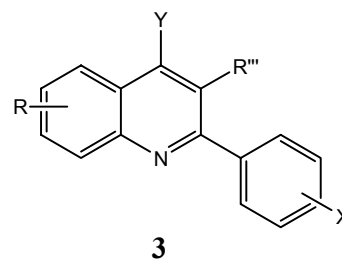
2-Arylquinolon-4-ones are nitrogen-containing analogues of flavanones and flavones, and are characterised by a benzo ring fused to six-membered nitrogen containing heterocyclic ring with an aryl substituent at position 2.<sup>1-3</sup> The heterocyclic ring of quinolones has many reactive sites for possible transformation and can also result in different degree of unsaturation. The heterocyclic ring of 2-aryl-1,2,3,4-tetrahydroquinol-4-ones ( $R'$ ,  $R'' = H$ ) and 2-aryl-2,3-dihydroquinol-4-ones ( $R' = Ac$ ,  $SO_2R$ ,  $R'' = \text{halogen, } OCH_3$ ) can be represented by the general structure **1**. On the other hand, the 2-arylquinolin-4(1*H*)-ones are characterised by  $C_2-C_3$  double bond as shown in generalised structure **2** and can exist in tautomeric equilibrium with the quinolinol isomer. The quinoline derivatives are characterised by fully aromatic heterocyclic ring which can be substituted at 2, 3 or 4 positions as represented by structure **3**. Systems **1** and **2** are structural analogues of flavanones and flavones which have oxygen at position **1** instead of nitrogen.



$R' = H, Ac, SO_2R$

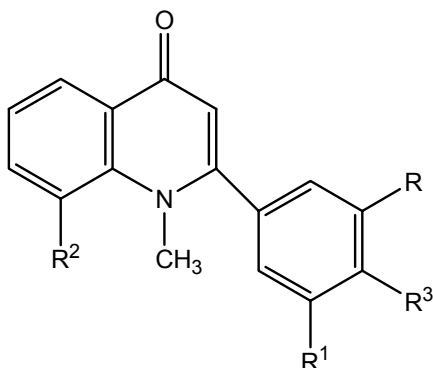


$R' = H, \text{alkyl}$



$Y = \text{Halogen, } NR_2, OR$

Quinolone and quinoline ring systems are distributed in a wide range of natural products, especially in alkaloids obtained from the plant family *Rutacea*.<sup>4</sup> Compounds **4a** and **4b**, for example, were isolated from *Balfourodendron riedelianum* and from the fruit tree *Casimiroa edulis*, respectively.<sup>5,6</sup> The 3'-methoxygraveoline **4c** and 3',8-dimethoxygraveoline **4d** have previously been isolated from the roots of the Brazilian plant *Esenbeckia grandiflora*.<sup>7</sup> Quinolone alkaloid, 1-methyl-2-tetradecylquinolin-4(1*H*)-one **5**, was isolated from the fruits of *Evodia rutaecarpa*.<sup>8</sup>

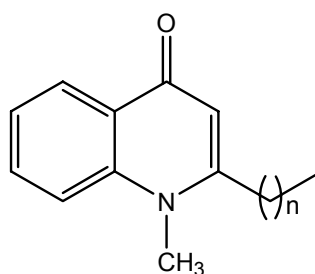


**4a** R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = H

**b** R = OCH<sub>3</sub>, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = H

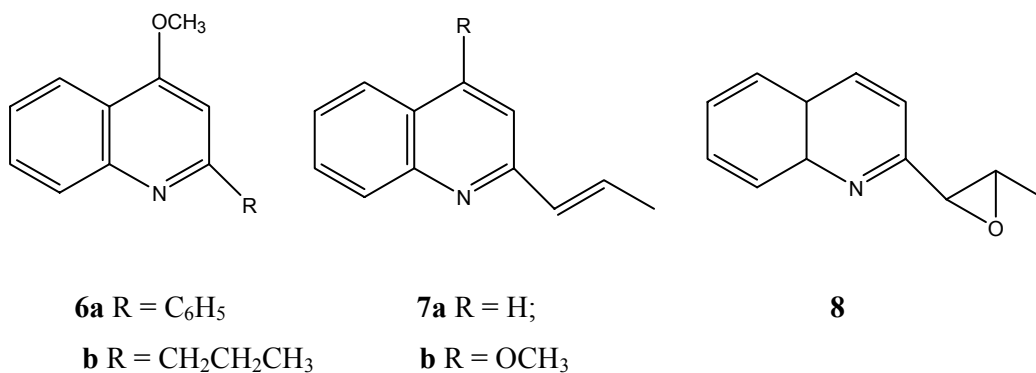
**c** R, R<sup>3</sup> = -OCH<sub>2</sub>O-, R<sup>1</sup> = H, R<sup>2</sup> = OCH<sub>3</sub>

**d** R, R<sup>3</sup> = -OCH<sub>2</sub>O-, R<sup>1</sup>, R<sup>2</sup> = OCH<sub>3</sub>

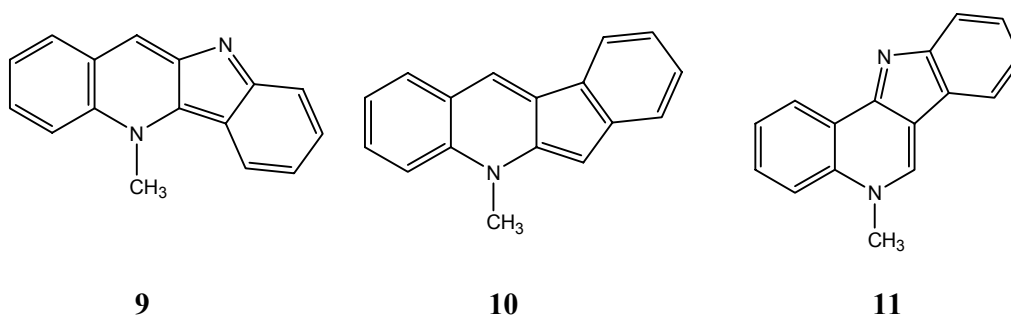


**5** n = 13

Quinoline derivatives are also plant-based compounds. The 4-methoxy-2-phenylquinoline **6a**, for example, was isolated from the leaves of *Lunasia amara*.<sup>6,9</sup> The 2-alkylated derivatives such as 4-methoxy-2-(n-propyl)quinoline **6b**, 2-(*E*)-prop-1'-enylquinoline **7a**, 4-methoxy-2-(*E*)-prop-1-enylquinoline **7b** and 2-(1,2-*trans*-epoxypropyl)-quinoline **8** were isolated from the leaves and also from trunk bark of *Galipea longiflora*.<sup>9</sup>



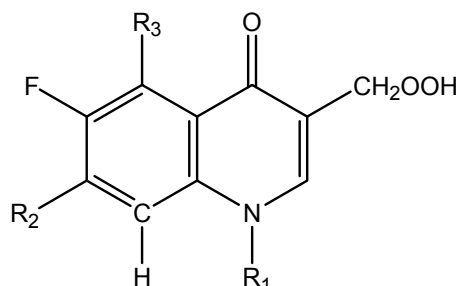
The polycyclic quinoline derivatives cryptolepine **9**, neocryptolepine **10** and isocryptolepine **11** are also constituents of the West African climbing shrub, *Cryptolepis sanguinolenta*.<sup>10</sup>



## 1.2 Medicinal and industrial applications of 2-arylquinolones and their quinoline derivatives

Quinolones and quinoline derivatives are a major class of alkaloids and have remarkable applications in the field of medicinal chemistry.<sup>11</sup> Quinolones are known to possess cytotoxic, antimitotic, antibacterial, and anti-platelet properties and some serve as cardiovascular protectors.<sup>2</sup> The antibacterial properties of norfloxacin **12a** and ciprofloxacin **12b** quinolone are well documented.<sup>12</sup> These systems target the bacterial DNA gyrase and topoisomerase IV, the enzymes essential for DNA replication and transcription.<sup>13</sup> Quinolones that are currently available in the market

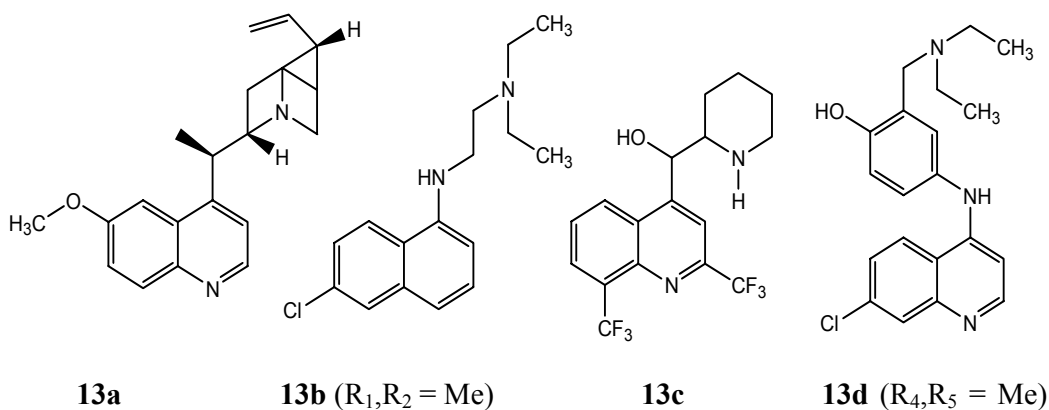
show moderate activity against infections caused by Gram-positive bacteria.<sup>16</sup> 2-Aryl-4-quinolones have also been evaluated for cytotoxic, topoisomerase I and II inhibitory and anti-HIV activities.<sup>12</sup>



**12a** R<sub>1</sub> = ethyl, R<sub>2</sub> = piperazin-1-yl, R<sub>3</sub> = H,

**b** R<sub>1</sub> = cyclopropyl, R<sub>2</sub> = piperazin-1-yl, R<sub>3</sub> = H,

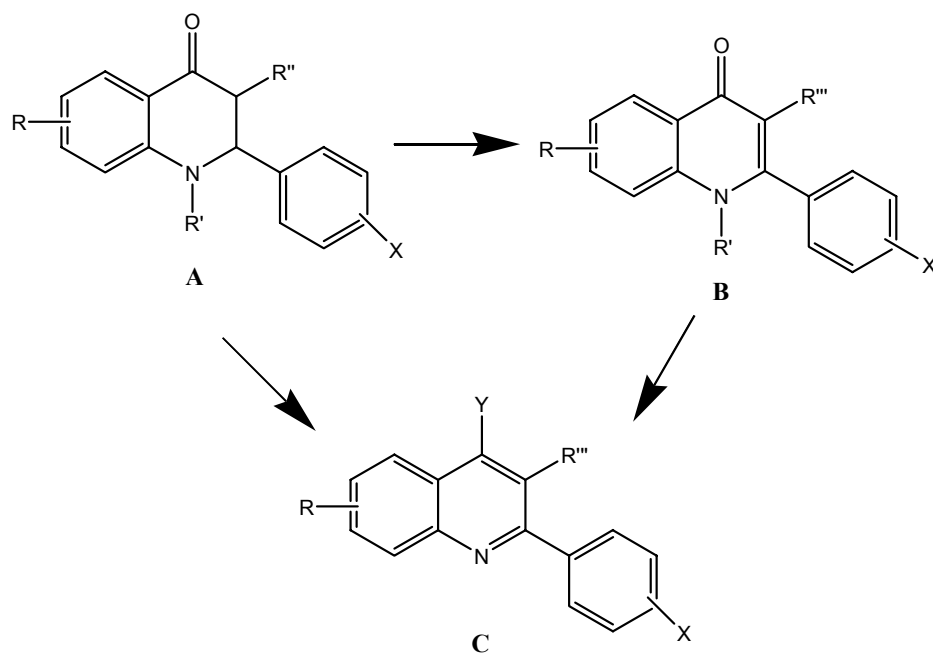
Quinoline alkaloids, such as quinine **13a**, chloroquine **13b**, mefloquine **13c** and amodiaquine **13d** are used as efficient drugs for the treatment of malaria.<sup>14,15</sup> The 8-(diethylamino)hexylamino)-6-methoxy-4-methylquinoline is highly effective against the *Trypanosoma cruzi* an agent of Chaga's disease.<sup>16</sup> The indoloquinoline alkaloids have been used by Ghanaian healers to treat a variety of health disorders. A decoction of the *Cryptolepis sanguinolenta* has been used in the clinical therapy of rheumatism, urinary tract infections, malaria and other disease.<sup>10</sup>



Quinolines are also active components in various industrial antioxidants including dyes, and some are also used for the preparation of nano- and mesostructures with enhanced electronic and photonic properties.<sup>17,18</sup> Quinolones, on the other hand, have been the subject of interest because of their antibacterial, antimitotic and antiplatelet properties.<sup>2</sup> Due to the global rise of drug resistance by malarial parasite, *Plasmodium falciparum*, there is increased interest by bioorganic chemists to design new analogues with increased potency and reduced side effects. The biological and industrial applications of quinolones and their quinoline derivatives have prompted the development of several new methods for their syntheses that are cost-effective and accompanied by improved yields.<sup>19</sup>

### **1.3 Classical methods for the synthesis of 2-aryl-4-quinolones and their 2-arylquinoline derivatives**

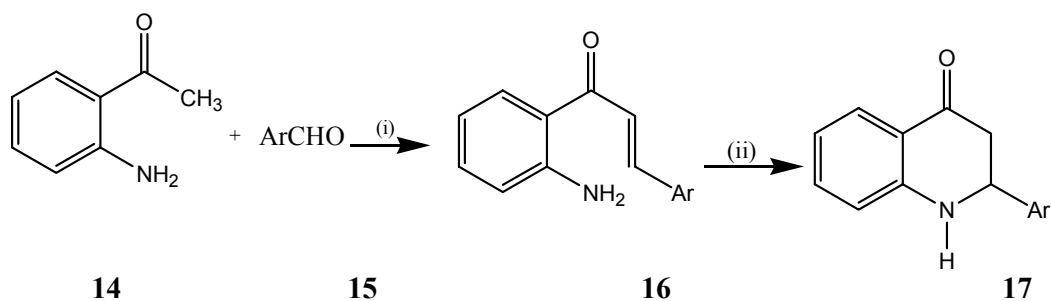
Quinolones and their quinoline derivatives can be interconverted through oxidation and reduction reactions (Fig. A). The 2-aryl-1,2,3,4-tetrahydroquinol-4-ones ( $R' = H$ ) **A** can be transformed into the corresponding 2-arylquinolin-4(1*H*)-ones **B** with unsaturation between C<sub>2</sub>-C<sub>3</sub> position. The latter, in turn, can be converted to fully aromatic quinoline derivatives **C**. Several methods have been developed for the direct oxidation of systems **A** to **C**.



**Figure A:** Interconversion of quinolones and their quinoline derivatives through oxidation and reduction reactions.

### 1.3.1 Synthesis of 2-aryl-1,2,3,4-tetrahydroquinol-4-ones and 2-aryl-2,3-dihydroquinol-4-ones

The 2-aryl-1,2,3,4-tetrahydroquinol-4-ones **17** can be prepared by acid catalysed cyclization of 2'-aminochalcone **16**, which are themselves prepared by Murphy-Watanisn's aldol condensation of 2-aminoacetophenone **14** and substituted benzaldehyde derivatives **15** (Scheme 1).<sup>20,21</sup> A microwave-assisted cyclization of 2-aminochalcones on clay to afford 2,3-dihydroquinolin-4(*1H*)-ones has also been reported.<sup>22,23</sup> The cyclization of 2-aminochalcones using different catalysts supported on either silica or alumina gel represents one of the efficient and rapid method for the synthesis of 2,3-dihydroquinolin-4(*1H*)-ones.<sup>22,23,24</sup>

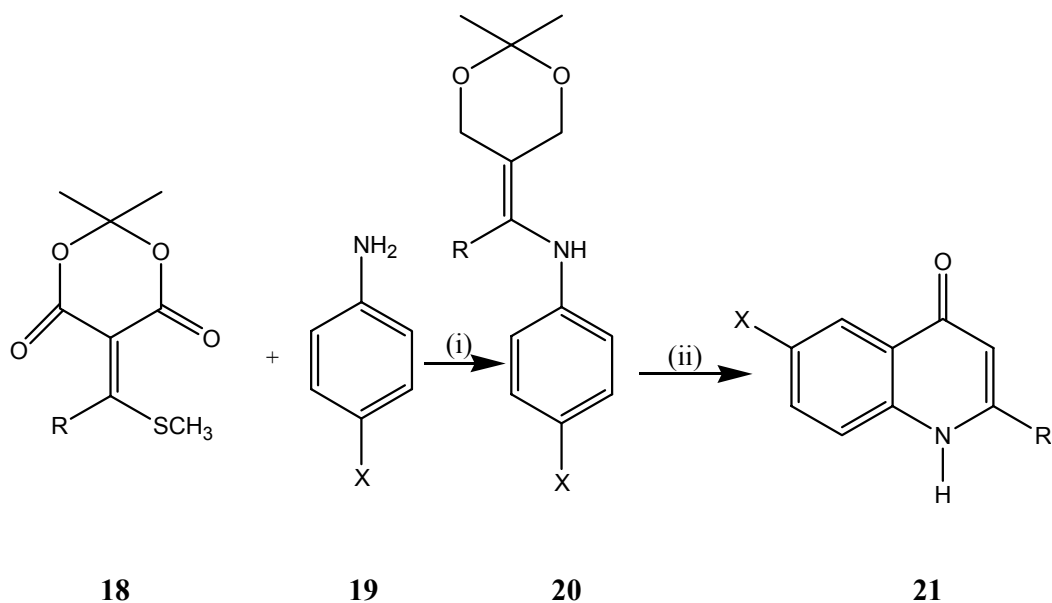


**Reagents:** (i)  $\text{NEt}_3$ , THF,  $0^\circ\text{C}$  to r.t., 2h (ii)  $\text{H}_3\text{PO}_4$ , AcOH, reflux.<sup>21,22,23</sup>

**Scheme 1**

### 1.3.2 Synthesis of 2-arylquinolin-4(1H)-ones

There are several pathways described in literature for the preparation of 2-arylquinolin-4(1H)-ones. In one method, anthranilic acid or its ester is heated with the acetal of an alkyl aryl ketone to yield 2-aryl-4-quinolin-4(1H)-ones.<sup>25,26</sup> The other method involves condensing arylamine with an ethyl arylacetate in the presence of polyphosphoric acid (PPA) or sulphuric acid.<sup>25,26</sup> Both these methods are, however, not suitable for the preparation of 2-aryl-4-quinolones with multiple substituents.<sup>27,28</sup> As a result, more efficient methods for the synthesis of substituted derivatives in relatively higher yields are continuously being developed. The 2-aryl-4-quinolones **21** were previously prepared by the reaction of 2,2-dimethyl-5-methylthioalkylidene-1,3-dioxane-4,6-diones **18** with arylamine **19** in diphenyl ether without isolating intermediate **20** (Scheme 2).<sup>29</sup>



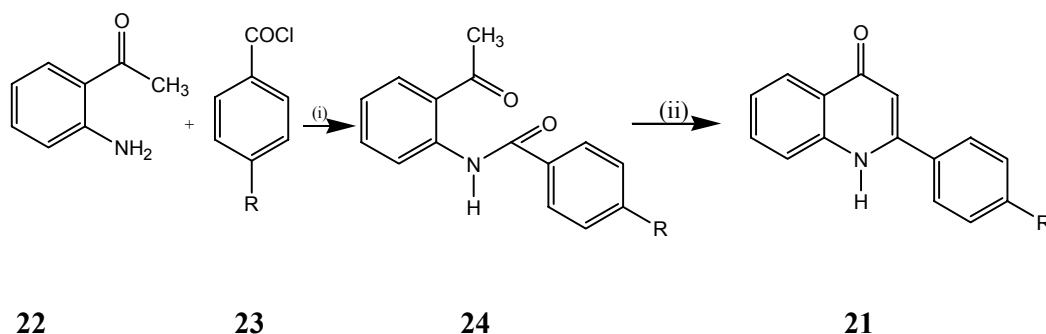
$X = \text{H}, \text{CH}_3, \text{NO}_2, \text{Br}, \text{Cl}; R = \text{CH}_3, \text{Ar}$

**Reagents:** (i)  $(\text{C}_6\text{H}_5)_2\text{O}$ ,  $140^\circ\text{C}$ , 30min or  $\text{C}_2\text{H}_5\text{OH}$ , heat, 2-4 h; (ii)  $(\text{C}_6\text{H}_5)_2\text{O}$ ,  $250\text{-}260^\circ\text{C}$ ,  $\text{N}_2$  (g)

**Scheme 2**

The most convenient method reported to date for the synthesis of **21** involves the use of 2-aminoacetophenones **22** and substituted benzoyl chlorides **23** as starting materials (Scheme 3).<sup>27,28</sup> 3,5-Dimethoxyaniline was reacted with benzoyl chloride derivative in the presence of  $\text{Et}_3\text{N}$  to afford 3,5-dimethoxyphenyl-*N*-phenylamide.<sup>2</sup> Friedel-Crafts acylation with methoxyacetyl chloride in 1,2-dichloroethane and in the presence of stannic chloride ( $\text{SnCl}_4$ ) afford the corresponding *N*-arylamido methoxyacetophenone in 26-42% yield.<sup>1</sup> Cyclization of *N*-arylamido methoxyacetophenone in the presence of *t*-BuOK at  $80^\circ\text{C}$  is reported to afford quinolones in 53-80% yield.

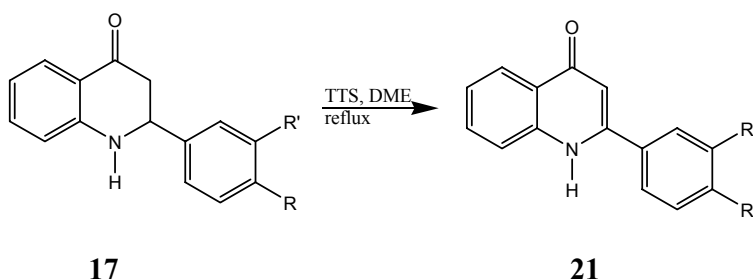




**Reagents:** (i) NEt<sub>3</sub>, THF, 0°C to r.t, 2 h; (ii) *t*-BuOK, *t*-BuOH, heat, 20 h

**Scheme 3**

In another method, thallium(III) *p*-tolylsulphonate (TTS) in dimethoxyethane (DME) was used to dehydrogenate 2-aryl-1,2,3,4-tetrahydro-4-quinolones **17** to 2-aryl-4-quinolones **21** (Scheme 4).<sup>30</sup> 2-Aryl-4-quinolone **21** can also be prepared by exposing acylated 2'-aminoacetophenone to microwave irradiation in the presence of sodium hydroxide.<sup>31</sup>

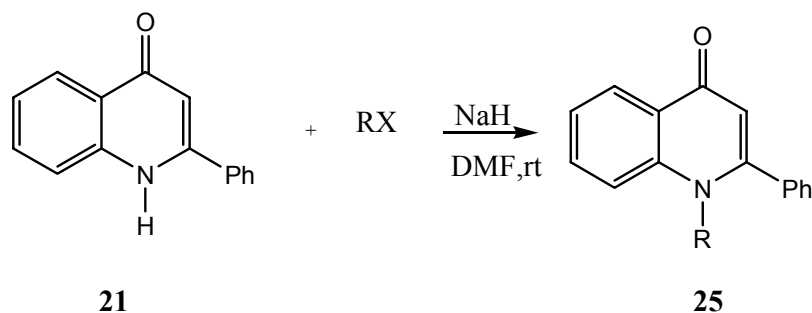


**Scheme 4**

### 1.3.3 Synthesis of *N*-substituted 2-arylquinolin-4-(1*H*)-ones

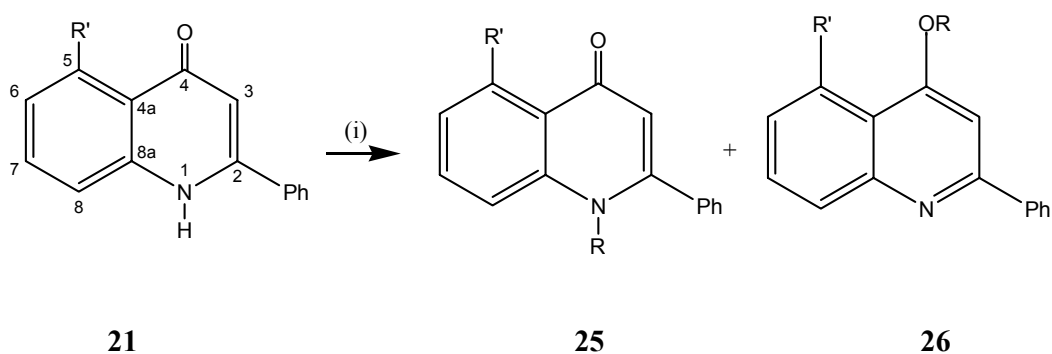
The preparation of *N*-alkylated derivatives was previously achieved by reacting 2-phenyl-1,4-dihydro-4-oxoquinoline with some alkyl halides.<sup>32</sup> *N*-Alkylation of 2-phenyl-4-quinolone in DMF using NaH as base at room temperature was found to proceed smoothly with primary alkyl halides (RX) such as methyl iodide, ethyl iodide, ethyl bromide, *n*-propyl iodide, allyl bromide and benzyl bromide (Scheme 5).

On the other hand, secondary alkyl halides such as iso-propyl iodide lead to relatively lower yields (62%) than primary derivatives whereas *tert*-butyl bromide led to unsatisfactory result.<sup>32</sup>



**Scheme 5**

It was reported by Kuo S.C and coworkers that treatment of system **21** under similar reaction conditions employed in scheme 5 afford a mixture of *N*-methylated **25** and *O*-methylated **26** derivatives in the ratio 2:3 (Scheme 6).<sup>33</sup> Alkylation of system **21** with ethyl or higher alkyl halide, on the other hand, led to the formation of *O*-alkylated **26** derivatives.<sup>34</sup>



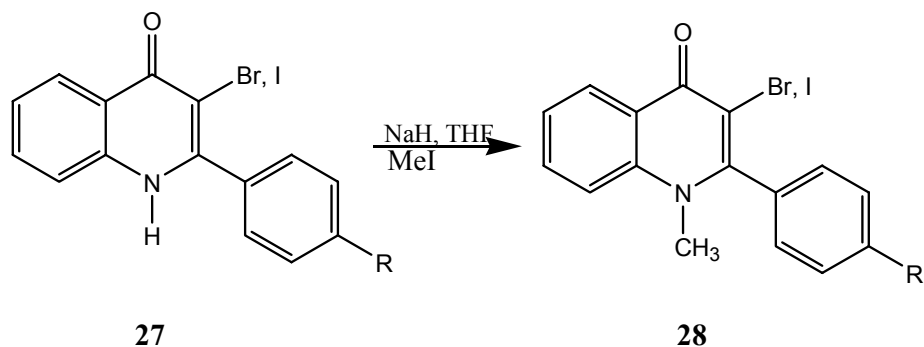
R = -CH<sub>3</sub>, -Et, -CH<sub>2</sub>COOEt, -CH<sub>2</sub>COOH

R' = OH, OCH<sub>3</sub>

**Reagents:** (i) NaH, DMF, Alkyl halide or NaH, THF, Alkyl halide

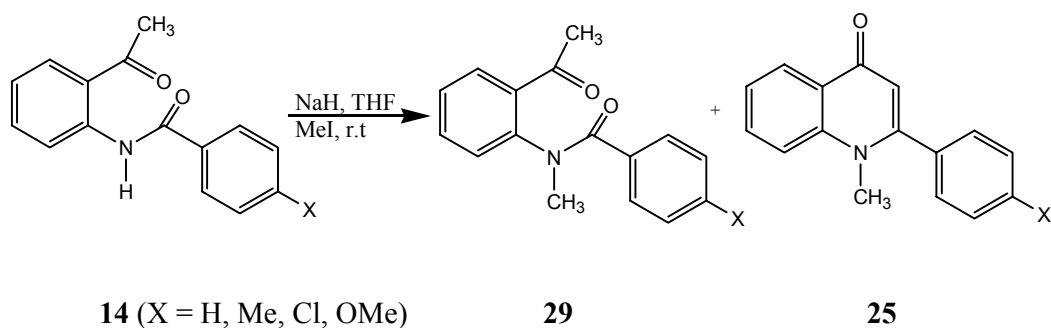
**Scheme 6**

It was observed that the presence of substituent at C-5 or C-3 position has significant effect on the regioselectivity of alkylation of the quinolone derivatives. For instance, if the substituent at C-5 is a hydroxyl group, a mixture of compounds **25** and **26** is formed.<sup>35</sup> On the other hand, only isomer **26** is formed for the 5-methoxy derivative. Formation of a mixture of **25** and **26** is attributed to chelation of the quinolinol isomer with 5-OH or the latter with NH-4-oxo group, which favour tautomeric equilibrium between the NH-4-oxo and its quinolinol isomer. On the other hand, formation of **26** as sole product is presumably the result of predominance of chelation between the hydroxyl groups of quinolinol isomer with 5-OMe group. For the C-3 substituted derivatives such as 3-bromo- and 3-iodoquinolone derivatives **27**, alkylation using sodium hydride-iodomethane mixture in THF afforded 2-aryl-3-halogeno-1-methylquinolin-4(*1H*)-ones **28**, exclusively (Scheme 7).<sup>36,37</sup>



**Scheme 7**

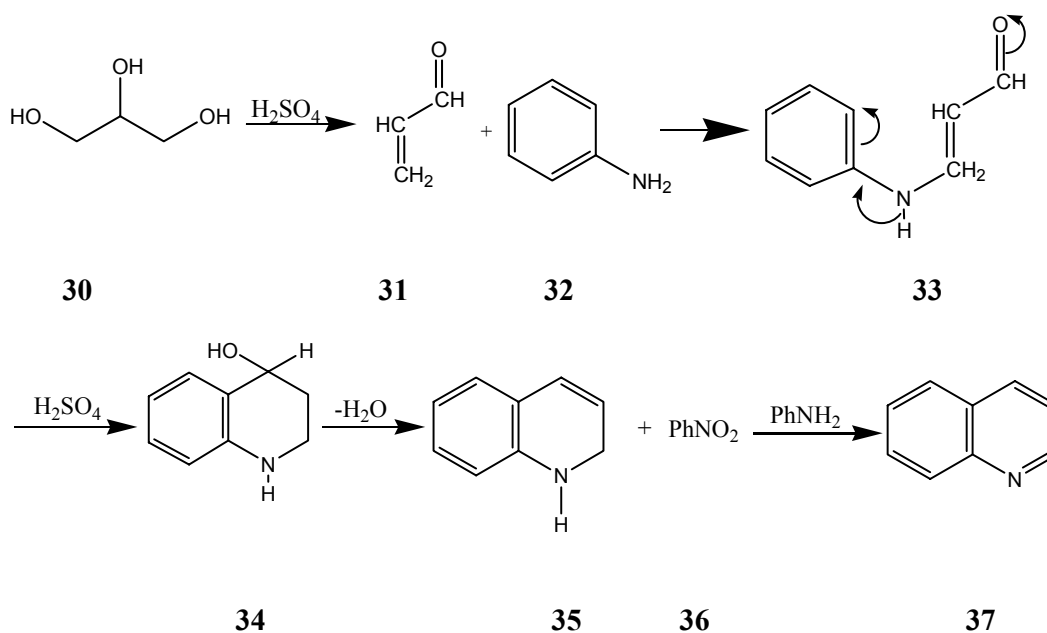
A more convenient method for the synthesis of 2-aryl-1-methylquinolin-4(*1H*)-ones was developed recently in our laboratory, it involves the use of systems **14** as substrates, NaH as base and MeI in THF to afford the expected products **29** (minor) and **25** (major) (Scheme 8).<sup>38</sup>



**Scheme 8**

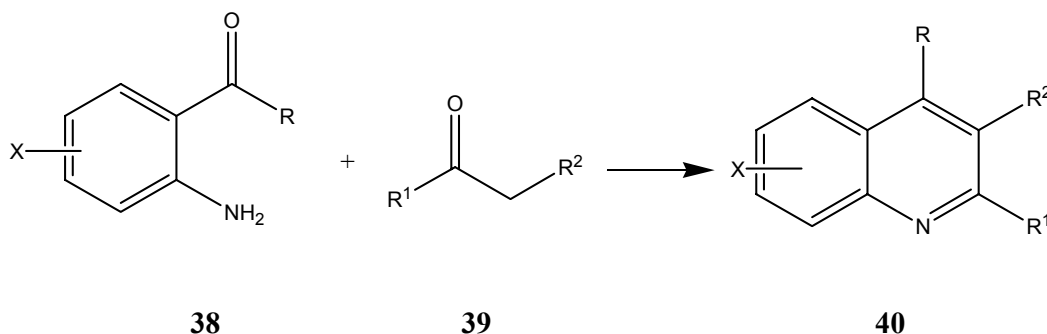
#### 1.3.4 Classical methods for the synthesis of 2-arylquinolines

Several novel methods have been developed for the synthesis of polysubstituted quinoline derivatives. Skraup, Friedländer and Combes reactions are classical methods for the synthesis of polysubstituted quinolines.<sup>39</sup> The Skraup synthesis is performed by heating a mixture of an aromatic amine **32**, glycerol **30**, sulphuric acid and an oxidizing agent together (Scheme 9). Sulphuric acid catalyzes the dehydration of glycerol **30** to acrolein **31** while the oxidizing agent transforms the initially formed 1,2-dihydroquinoline **35** into the fully aromatized heterocyclic quinoline **37**. This reaction requires a large amount of sulphuric acid at temperatures above 150°C and is often violent. Iron (II) sulphate or boric acids are often used often as additives to control the reaction conditions.<sup>39,40</sup>



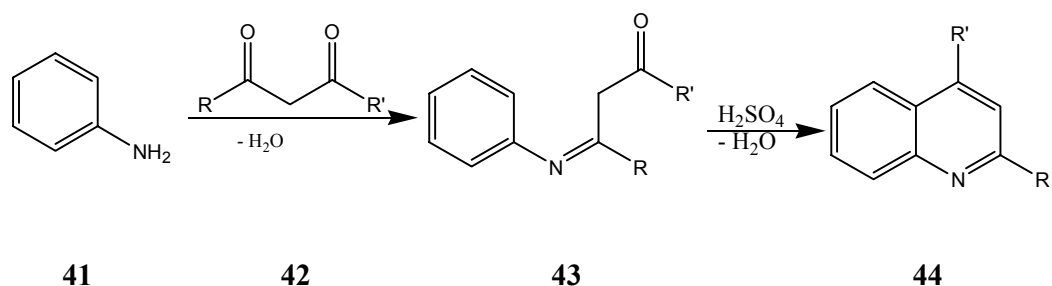
**Scheme 9**

The Friedlander reaction is also one of the most useful methods for the preparation of quinolines.<sup>39,41</sup> In this reaction an aromatic *o*-aminoaldehyde or *o*-aminoketone **38** condenses with an aldehyde or a ketone **39** having a methylene group adjacent the carbonyl moiety, under basic or acidic conditions (Scheme 10). This is considered as one of the most reliable reactions for the synthesis of quinolines. The formation of quinoline derivatives from ketones and *o*-aminoaldehydes is effective under basic conditions whereas the condensation of ketones with *o*-aminoketones is best in acidic media. One of the drawbacks of this reaction is the instability of the 2-aminoarylcarbaldehyde which can readily undergo self condensation.



**Scheme 10**

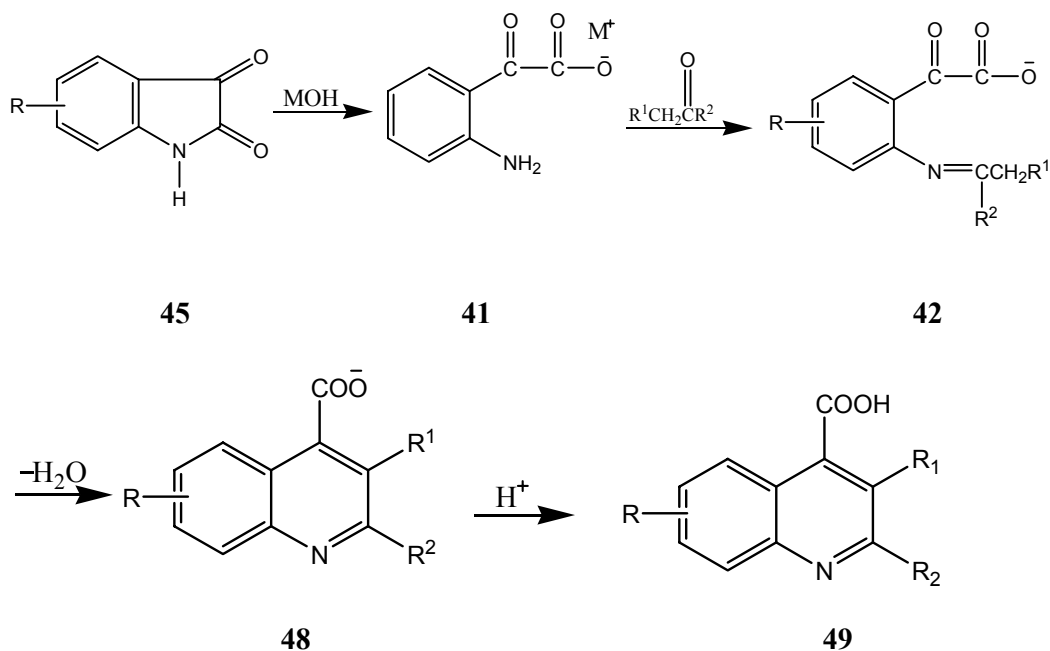
The Combes method involves heating aniline **46** with  $\beta$ -diketones **47** to form substituted quinolines **35** after acid-catalysed ring closure of an intermediate Schiff base **48** (Scheme 11). In this reaction the use of unsymmetrical 1,3-diketones complicates separation process.<sup>39,42</sup>



**Scheme 11**

The classical methods described above are, however, largely restricted to the synthesis of 4-alkyl or aryl substituted quinoline derivatives and cannot be adapted for the synthesis of biologically-relevant derivatives substituted at the 4-position with nitrogen- or oxygen-containing groups.

The Pfitzinger reaction, which involves the reaction of isatin or its derivatives with ketones containing the  $\alpha$ -methylene group in alkaline medium result in the formation of the corresponding 4-carboxyquinoline derivatives (Scheme 12).<sup>39,43,44</sup> This reaction represents the most convenient and simplest method for the synthesis of 4-quinolinecarboxylic acid derivatives.



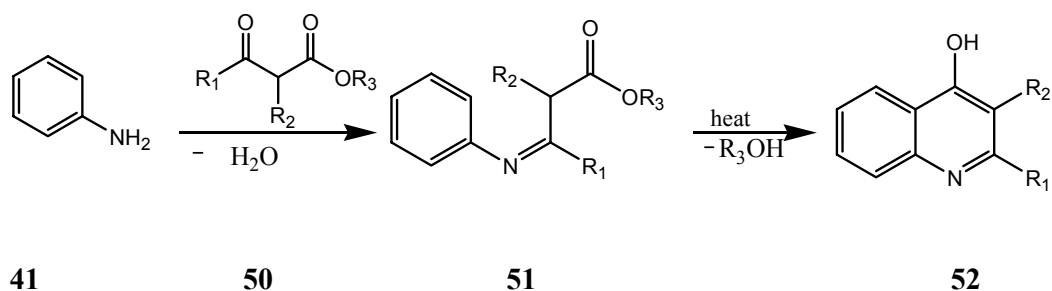
**Scheme 12**

Recent developments in the chemistry of quinoline derivatives have led to establishment of metal-catalysed intra- and intermolecular coupling reactions for the construction of variously substituted quinoline derivatives. These methods compete with the above classical methods for the synthesis of variously substituted quinoline derivatives in terms of efficiency and rapidness.<sup>39</sup>

### 1.3.5 Synthesis of 2-arylquinolines bearing oxygen or nitrogen containing substituent at C-4 Position

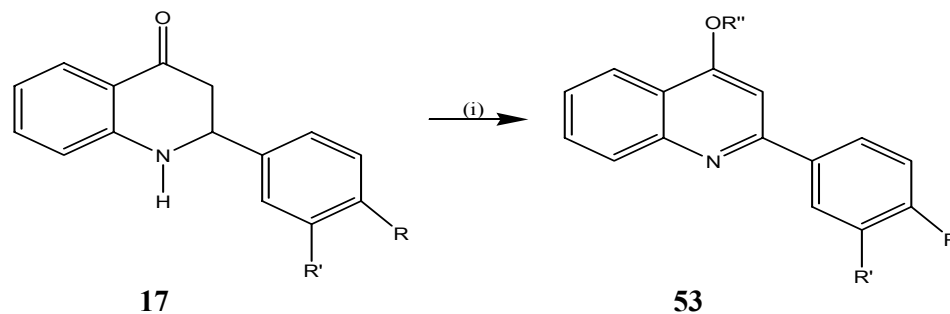
One of the most popular methods for the synthesis of 4-hydroxyquinolines is the Conrad-Limpach methods, which involves the condensation of arylamines with  $\beta$ -ketoesters to afford  $\beta$ -anilinoacrylates. The latter are then cyclised at about 250°C to afford 4-hydroxyquinolines (Scheme 13). The cyclization was previously achieved by heating the ester without a solvent, however, the yields were very moderate. It was reported later by Limpach that the yields of cyclization can be raised from below 30%

up to 95% when inert solvent is used.<sup>45</sup> The 4-hydroxyquinolines may exist in tautomeric equilibrium with the 4-quinolones.



**Scheme 13**

Several methods have been reported for the synthesis of 4-alkoxy-2-arylquinolines from 2-aryl-1,2,3,4-tetrahydro-4-quinolones. 2-Aryl-1,2,3,4-tetrahydro-4-quinolones can be converted to 2-aryl-4-methoxyquinolines using either thallium(III) nitrate<sup>46</sup> or hydroxyl(tosyloxy)-iodobenzene<sup>47</sup> in trimethyl orthoformate in the presence of catalytic amount of perchloric acid (Scheme 14). Previously in our group, series of 2-aryl-4-methoxyquinolines were prepared using iodine in refluxing methanol (Scheme 14).<sup>48</sup> In 2004, Kumar and his coworkers employed  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  in methanol to oxidize 2-aryl-1,2,3,4-tetrahydro-4-quinolones to afford the 2-aryl-4-methoxyquinolines.<sup>49</sup>

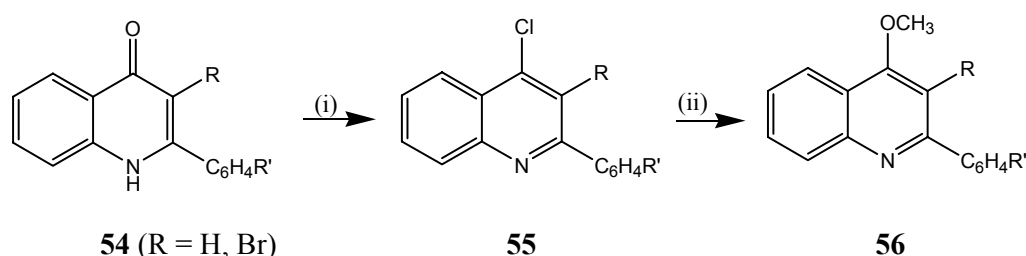


**Reagents:** (i) HTIB,  $\text{CH}(\text{OR}'')_3$ ,  $\text{HClO}_4$ , 1.5h;<sup>47</sup> TTN,  $\text{CH}(\text{OR}'')_3$ ,  $\text{HClO}_4$ , 1h;<sup>46</sup>  $\text{I}_2$ ,  $\text{MeOH}$ <sup>48</sup> or  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /  $\text{EtOH}$ <sup>49</sup>

**Scheme 14**



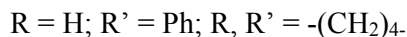
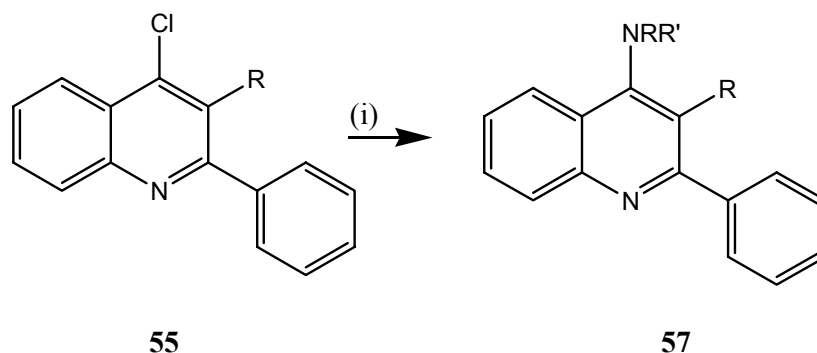
Indirect methods involving the displacement of 4-chloro substituent by alkoxides as nucleophiles have been developed for the synthesis of 4-alkoxyquinolines (Scheme 15).<sup>6,36,37</sup> The NH-4-oxo derivatives **54** are first converted to the corresponding 2-aryl-4-chloroquinoline derivatives **55** using phosphorus oxychloride under reflux and the resulting 4-chloroquinolines are reacted with alkoxide ion to yield the expected 4-alkoxyquinoline derivatives.<sup>6,36,37</sup>



**Reagents:** (i) POCl<sub>3</sub>, reflux, 12h; (ii) NaOMe, MeOH, reflux

**Scheme 15**

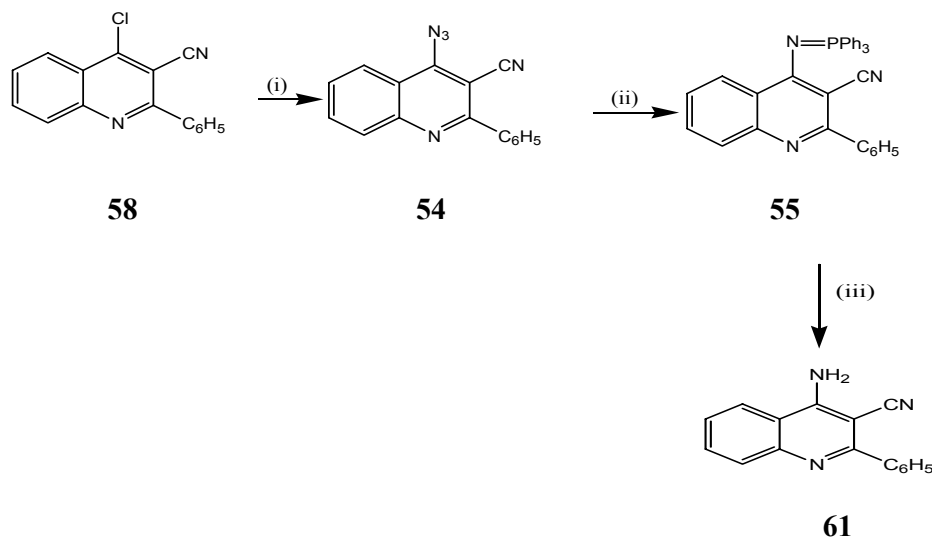
Previously in our laboratory, the 2-aryl-3-bromoquinolin-4(1*H*)-ones **54** (R= Br) were converted to the corresponding 2-aryl-3-bromo-4-chloroquinolines and the latter transformed to the corresponding 2-aryl-3-bromo-4-methoxyquinolines.<sup>50</sup> Although the 2-aryl-3-iodoquinolin-4(1*H*)-ones have been prepared in our laboratory before,<sup>50</sup> they have not been converted to the corresponding 2-aryl-4-chloro-3-iodoquinolines. The ease of displacement of 4-Cl and the potential for iodine to facilitate metal-catalyzed C-C coupling make the 2-aryl-4-chloro-3-iodoquinolines suitable substrates for further studies of transformation. The 4-chloroquinoline derivatives **55** can also be reacted with nitrogen-containing nucleophiles such as ammonia and aniline derivatives to afford compounds **57** (Scheme 16).<sup>51-53</sup>



**Reagents:** (i)  $R'NH_2/RR'NH$

**Scheme 16**

In another development 4-chloroquinoline derivative **58** was reacted with sodium azide in DMF at room temperature to afford 4-azidoquinolines **59** (Scheme 17).<sup>54</sup> It has been shown before that 4-azido-3-cyanoquinoline undergoes Staudinger reaction with triphenylphosphine to afford 4-(triphenylphosphoranylideneamino)quinolin-3-carbonitrile. The latter undergoes hydrolysis with aqueous acetic acid to afford 4-amino-3-cyanoquinolines **61**.<sup>54</sup>



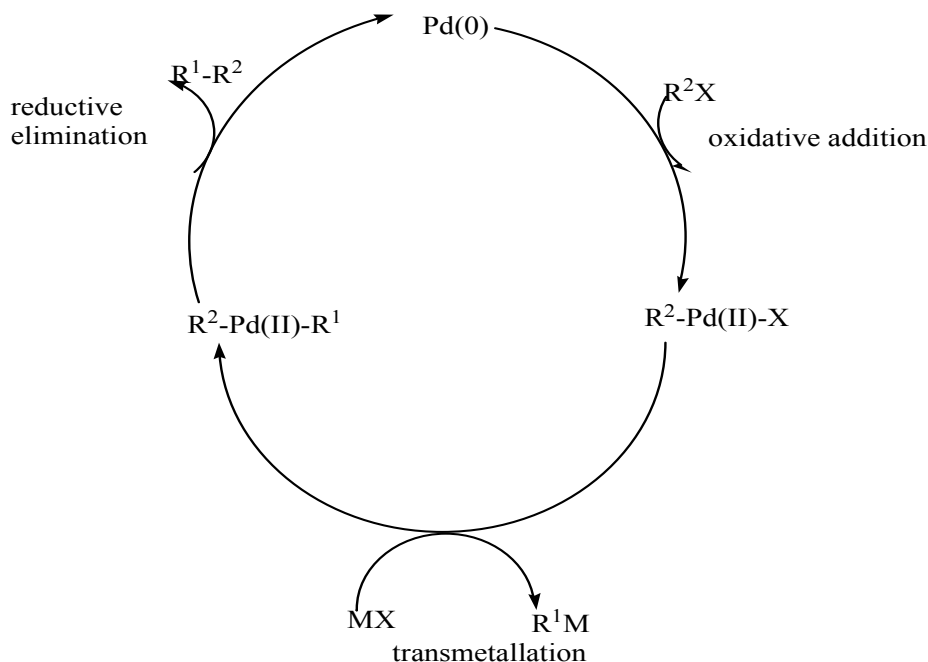
**Reagents:** (i)  $NaN_3$ , DMF, rt, 17 h (ii)  $PPh_3$ , THF, heat (iii) AcOH (aq), heat, 18h

**Scheme 17**

#### **1.4 Application of organometallic reagents in the synthesis of quinoline derivatives**

An organometallic compound is defined as any chemical species containing at least one bond between a carbon atom in an organic molecule and a metal.<sup>55</sup> Metal-catalysed coupling reactions are used for the construction of variously substituted quinoline derivatives.<sup>56</sup> The advantage of coupling reactions is that one can employ a wide range of aromatic substrates and various nucleophiles to prepare a tremendous range of products in one easy step.<sup>57</sup> These methods compete with most of the known methods of quinoline transformation in terms of efficiency and rapidness.

The most commonly used catalytic methods for C-C bond formation are the Kharasch, Negishi, Stille, Heck and Suzuki reactions. These reactions permit the preparation of both symmetrical and unsymmetrical biaryls in a cross-coupling reaction using either nickel or palladium catalysts.<sup>56</sup> The mechanism for cross-coupling reaction is generally a catalytic cycle which can be described in three main steps: oxidative addition, transmetallation and finally reductive elimination as shown in Figure 1 below. The reactions involve similar solvents and catalysts and may require some base to facilitate reductive elimination. The transmetallation is the most characteristic step of the cross-coupling reactions and it requires the presence of a base. A large number of palladium (0) catalysts or precursors can be used for cross-coupling reactions.<sup>56</sup>



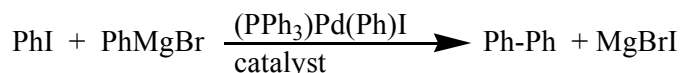
**Figure 1:** A general catalytic cycle for cross-coupling reactions<sup>42</sup>

Aryl chlorides are the most widely used aryl halides for industrial applications. The main drawback of aryl chlorides is the transition metal catalyzed activation and transformation of the inert C-Cl bond in synthetic chemistry.<sup>58</sup> Aryl bromides and iodides are the most reactive, however, they are expensive.<sup>59</sup> In 2003, Tsuyoshi and Mayumi successfully coupled bromopyridines, bromoquinolines, 2-chloropyridines and 2-chloroquinolines via Pd/C catalyzed Suzuki coupling reaction.<sup>60</sup> The order of aryl halides reactivity,  $I > Br > Cl > F$  is coherent with the strength of the C-halide bond.<sup>59</sup>

#### 1.4.1 Kharasch coupling reaction

In the mid to late 1970s the Karasch reaction started to be considered as an important method for the synthesis of biaryls. In general, an arylmagnesium reagent is reacted

with an aryl halide in the presence of a suitable catalyst to yield the biaryl.<sup>56</sup> Kharasch coupling reaction can be demonstrated with the reaction of the halophenyl with phenylmagnesium bromide in the presence of a catalyst to afford the biphenyl in good yield (Scheme 18).

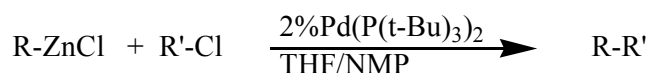


**Scheme 18**

The drawback of this reaction is that functional groups such as aldehydes, ketones, esters and nitro groups become affected due to the polar nature of Grignard reagent.<sup>42</sup>

#### 1.4.2 Negishi coupling reaction

The Negishi coupling reaction is a cross-coupling reaction that uses an arylzinc reagent, aryl halides or triflates and a nickel or palladium catalyst.<sup>56</sup> It represents a powerful method for generating aromatic compounds such as styrene derivatives and biaryls.  $\text{Pd(P(t-Bu)}_3)_2$  is a widely used catalyst for Negishi coupling of aryl- and alkylzinc reagents with aryl and vinyl chlorides (Scheme 19).

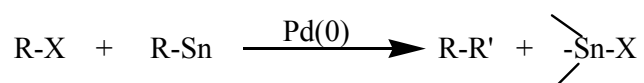


**Scheme 19**

In this reaction functional groups such as aldehydes, ketones, esters and nitro groups undergo coupling with arylzinc reagent.

### 1.4.3 Stille coupling reaction

The Stille reaction began to be used in biaryl synthesis in 1977 and the reaction utilises arylstannes and aryl halides or triflates as the coupling partners (Scheme 20). This reaction involves neutral conditions and can tolerate a wide range of substituents on both coupling partners.

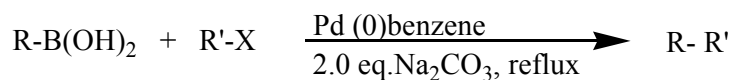


**Scheme 20**

The major drawback of the Stille reaction is the toxicity of the organotin and byproducts.<sup>56</sup>

### 1.4.4 Suzuki coupling reaction

Suzuki coupling reaction is one of the most versatile metal-catalyzed reactions for the selective construction of carbon-carbon bonds.<sup>56</sup> It is a coupling reaction where organoboron compounds mainly organoboronic acids or esters couple with organic halides or triflates in the presence of a palladium catalyst and a base (Scheme 21). The coupling reaction involves mild reaction conditions and the use of readily available wide range of boronic acids that are environmentally safer than the other organometallic reagents. The handling and removal of boron-containing by-products is relatively easy when compared to other organometallic reagents.



**Scheme 21**

This reaction and its modifications have found extensive use in natural product synthesis because the reagents are thermally stable and they tolerate a broad range of functional groups and reaction conditions. Furthermore this reaction leads to the formation of non-toxic products. We are interested in the synthesis of 4-methoxy-2,3-diarylquinolines with potential antimalarial activity, which cannot be easily accessible using classical methods. The 2-aryl-4-chloro-3-iodoquinolines appear to be suitable substrates for the target products. Suzuki cross-coupling reaction represents a method of choice for this purpose.

### 1.5 Aims and Objectives of the investigation

Our research currently focuses on the synthesis and transformation of 2,3,4-trisubstituted quinoline derivatives bearing a heteroatom at the 4-position with potential antimalarial, antibacterial, antihypertensive and antitumor activity. These compounds cannot be easily accessible through the above classical methods for the synthesis of polysubstituted quinolines. Our approach involves the use of palladium-catalyzed Suzuki coupling of 2-aryl-4-chloro-3-iodoquinolines and their 4-methoxyquinoline derivatives as substrates and phenylboronic acid as model for the C–C coupling. Although the 2-aryl-3-iodoquinolin-4(1*H*)-ones are known,<sup>52</sup> their 2-aryl-4-chloro-3-iodoquinolines and 2-aryl-3-iodo-4-methoxyquinoline derivatives have not been prepared before. The ease of displacement of 4-chloro atom by nucleophiles and the potential for iodine to facilitate metal-catalyzed cross-coupling make 2-aryl-4-chloro-3-iodoquinolines and their 4-methoxy derivatives suitable substrates for the synthesis of the requisite 2,3-diaryl-4-methoxyquinolines. 4-Chloropyridine derivatives have been reported to undergo Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed

coupling with aryl boronic acids.<sup>61</sup> This literature observation may bring into play the problem of regioselectivity of C-C bond formation between 2-aryl-4-chloro-3-iodoquinolines and phenyl boronic acid. However, the known order of reactivity in transition metal-catalysed cross coupling of aryl halides,  $I > Br \gg Cl$  can allow selective coupling with bromides or iodides in the presence of chlorides. The question is: Can the 2-aryl-3-iodoquinolines bearing chlorine at the 4-position be prepared and the regioselectivity of C-C bond formation to afford 2,3-diarylquinoline derivatives be established?

The aims and objectives of this investigation are:

- (a) To convert the 2-aryl-3-iodoquinolin-4(1*H*)-ones derivatives into 2-aryl-4-chloro-3-iodoquinolines.
- (b) To prepare the 2-aryl-3-iodo-4-methoxyquinolines from 2-aryl-4-chloro-3-iodoquinolines.
- (c) To assess the regioselectivity of C-C bond formation of the 2-aryl-4-chloro-3-iodoquinolines with phenylboronic acid under standard Suzuki reaction conditions.
- (d) To subject the 2-aryl-3-iodo-4-methoxyquinolines to Suzuki coupling with phenylboronic acid.
- (e) To undertake further chemical transformation of the 2,3-diaryl-4-methoxyquinolines.



## CHAPTER 2

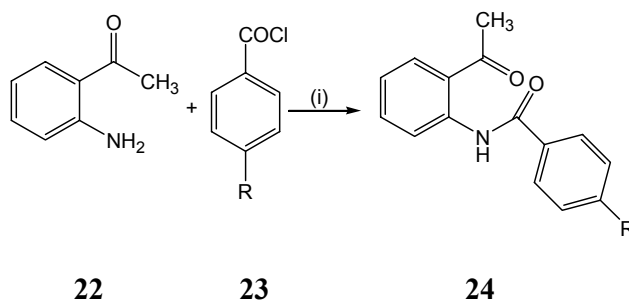
### 2. RESULTS AND DISCUSSION

*N*-benzoyl-2-aminoacetophenone derivatives **24** were prepared by condensing 2-aminoacetophenone **22** and benzoyl chloride derivatives **23** in the presence of NEt<sub>3</sub> in THF. Compounds **24** were converted to 2-aryl-4-quinolone derivatives **21** using *t*-BuOK in *t*-BuOH. Treatment of quinolone derivatives **21** with iodine in the presence of sodium carbonate afforded 2-aryl-3-iodo-4-quinolones **62**. The latter were further treated with phosphoryl chloride to give 2-aryl-4-chloro-3-iodoquinoline derivatives **63**. The conversion of 2-aryl-4-chloro-3-iodoquinoline derivatives **63** into 2-aryl-3-iodo-4-methoxyquinoline derivatives **64** was achieved by treatment with sodium methoxide in methanol-THF mixture under reflux. The 2-aryl-3-iodo-4-chloroquinolines **63** were subjected to Suzuki reaction to afford 2,3-diaryl-4-chloroquinolines **65**. Suzuki coupling reaction conditions were also applied to 2-aryl-3-iodo-4-methoxyquinolines **64** to afford 2,3-diaryl-4-methoxyquinolines **66**. Systems **66** were further demethylated using boron tribromide in dichloromethane to afford 2,3-diarylquinolin-4-(1*H*)-ones. The prepared compounds were characterized using a combination of NMR (<sup>1</sup>H and <sup>13</sup>C), IR and mass spectroscopic techniques and elemental analysis.

#### 2.1 Synthesis of *N*-benzoyl-2-aminoacetophenone derivatives **21**

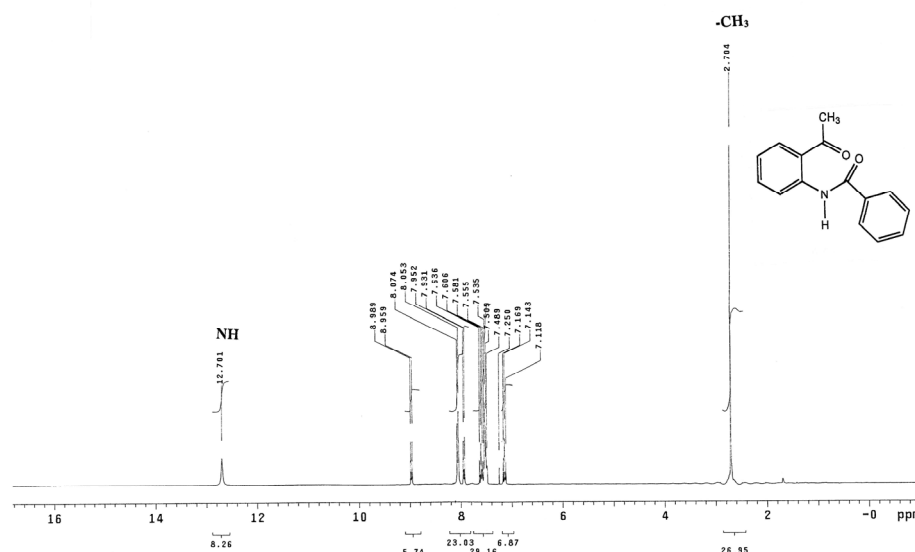
The *N*-benzoyl-2-aminoacetophenone derivatives **24** were prepared by reacting 2-aminoacetophenone **22** with benzoyl chloride derivatives **23** in the presence of NEt<sub>3</sub>

in THF following literature methods (Scheme 22).<sup>62,63</sup> These compounds were found to be analytically pure as confirmed by <sup>1</sup>H NMR and IR spectroscopic data and by comparison with literature data. Their <sup>1</sup>H NMR spectra are characterised by a singlet at  $\delta$  ca. 2.71 ppm corresponding to three hydrogen atoms of the COCH<sub>3</sub>, aromatic proton signals in the region  $\delta$  7.13 - 8.99 ppm and a broad singlet at  $\delta$  12.70 ppm for the NH group (fig. 2). Their IR spectra reveal the presence of two bands at  $\nu_{\text{max}}$  1721 cm<sup>-1</sup> and 3228 cm<sup>-1</sup> corresponding to C=O and N-H groups, respectively. Their melting points compare favourably with those reported in literature.



<b>24</b>	<b>R</b>	% Yield	m.p. °C; (Lit. <sup>ref</sup> )
<b>a</b>	H	72	96-99 (98,5-99) <sup>62</sup>
<b>b</b>	F	80	96-98 (92-95) <sup>63</sup>
<b>c</b>	Cl	71	110-112 (106-109) <sup>63</sup>
<b>d</b>	OMe	63	116-118 (119-121) <sup>62</sup>

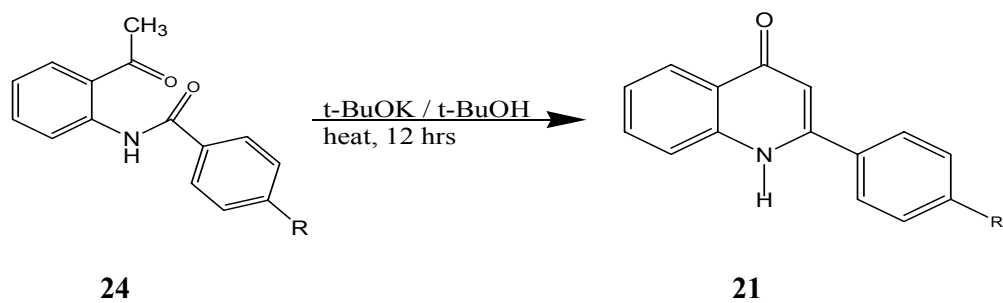
**Scheme 22**



**Figure 2:**  $^1\text{H}$  NMR spectrum of *N*-benzoyl-2-aminoacetophenone derivatives **24a** in  $\text{CDCl}_3$

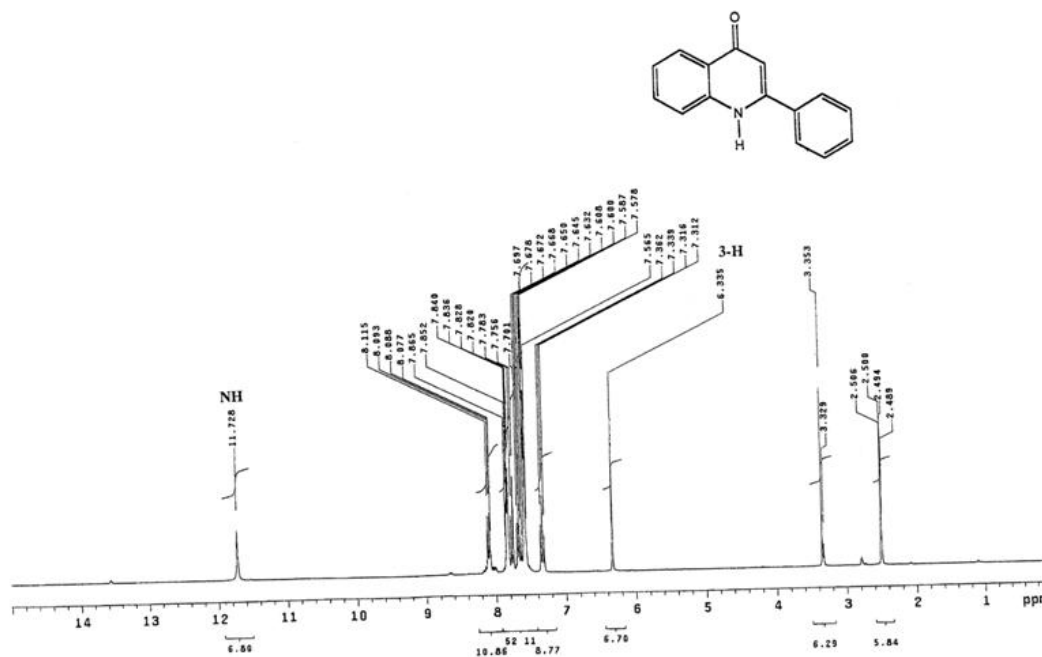
## 2.2 Synthesis of 2-arylquinolin-4(1*H*)-ones **21**

*N*-benzoyl-2-aminoacetophenone derivatives **24** were cyclised to the corresponding quinolone derivatives **21** in the presence of *tert*-BuOK in *tert*-butanol following literature method (Scheme 23).<sup>33,38,63</sup> Compounds **21** are distinguished from the corresponding precursors **24** by the presence of a singlet at  $\delta$  *ca.* 6.30 ppm (3-H) and the absence of a methyl group at  $\delta$  2.70 ppm in their  $^1\text{H}$  NMR spectra (figure 3). Their IR spectra reveal the presence of N-H and C=O bands at about  $\nu_{\text{max}}$  3070 and  $1632\text{ cm}^{-1}$ , respectively. Although their melting points somewhat differ from those reported in literature except for **21b**, their  $^1\text{H}$  NMR and FT-IR spectroscopic data fit well with the assigned structures.



<b>21</b>	<b>R</b>	<b>%Yield</b>	<b>m.p/ °C; (Lit.<sup>ref</sup>)</b>
<b>a</b>	H	90	260-263 (240-243) <sup>33</sup>
<b>b</b>	F	65	320-323 (322-325) <sup>38</sup>
<b>c</b>	Cl	71	332-335 (270-273) <sup>38</sup>
<b>d</b>	OMe	73	306-309 (290-293) <sup>38</sup>

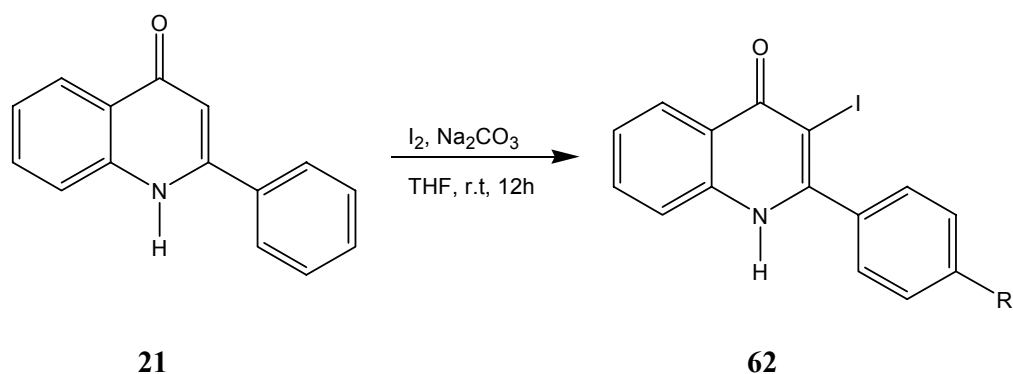
**Scheme 23**



**Figure 3:** <sup>1</sup>H NMR spectrum of 2-phenylquinolin-4(1H)-one **21** in DMSO-*d*<sub>6</sub>

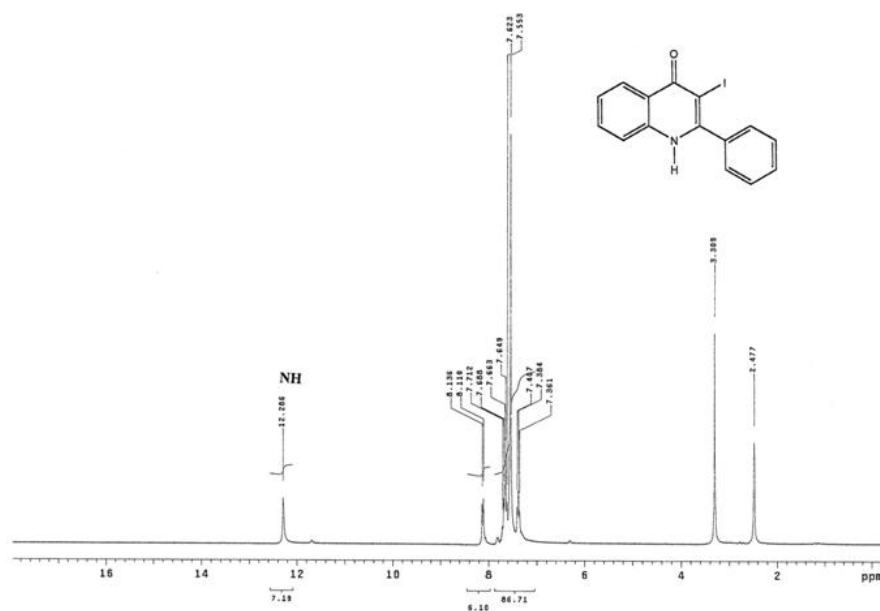
### 2.3 C-3 iodination of 2-arylquinolin-4(1*H*)-ones **62**

The 2-arylquinolin-4(1*H*)-ones **21** were, in turn, subjected to iodine in THF in the presence of sodium carbonate to afford the corresponding 3-iodo-4-quinolones **62** following a method recently developed in our laboratory (Scheme 24).<sup>50</sup> Their IR spectra are characterized by the presence of N-H and C=O bands at  $\nu_{\max}$  3056 and 1625  $\text{cm}^{-1}$ , respectively. Their  $^1\text{H}$  NMR spectra lack the 3-H signal around  $\delta$  6.30 ppm thus confirming the incorporation of iodine atom (Figure 4). Although the observed melting points differ from those reported before, their  $^1\text{H}$  NMR and FT-IR spectroscopic data are consistent with the assigned structures.



<b>62</b>	R	% Yield	m.p. <sup>o</sup> C; (Lit. <sup>ref</sup> )
<b>a</b>	H	67	276-279 (284-286) <sup>50</sup>
<b>b</b>	F	65	226-229 (196-198) <sup>50</sup>
<b>c</b>	Cl	71	205-208 (254-256) <sup>50</sup>
<b>d</b>	OMe	73	225-228 (262-264) <sup>50</sup>

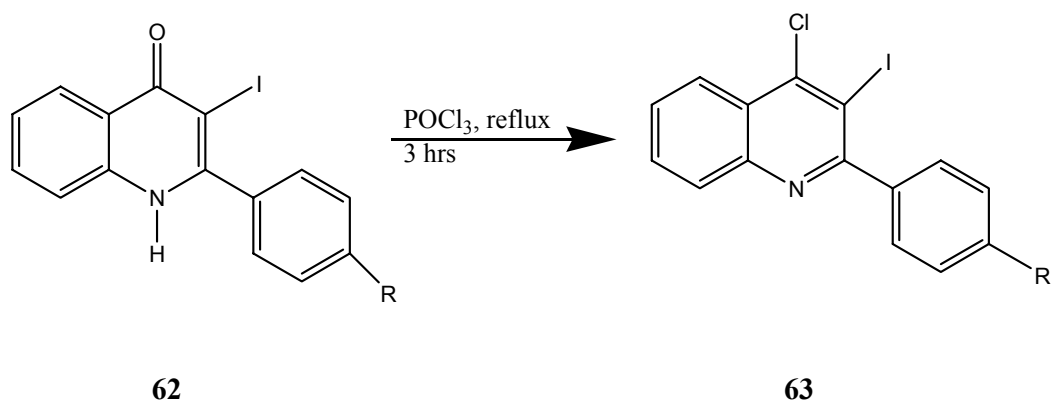
Scheme 24



**Figure 4:**  $^1\text{H}$  NMR spectrum of 3-iodo-2-phenylquinolin-4(1*H*)-one **62a** in  $\text{DMSO-}d_6$

## 2.4 Preparation of 2-aryl-4-chloro-3-iodoquinoline derivatives **63**

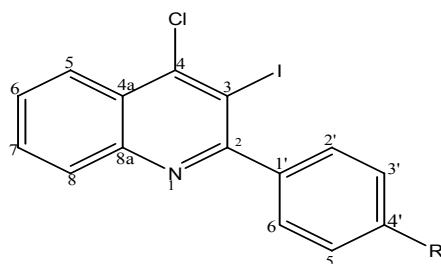
The previously undescribed 2-aryl-4-chloro-3-iodoquinoline derivatives **63** were obtained by subjecting the iodinated products **62** to  $\text{POCl}_3$  under reflux for 3 hours (Scheme 24). Their IR spectra are characterized by the absence of  $\text{C=O}$  and  $\text{N-H}$  bands which are present in the IR spectra of the corresponding substrates **62**. Their  $^1\text{H}$  NMR spectra, on the other hand, are characterized by group of signals in the aromatic region and the absence of  $\text{N-H}$  signal at  $\delta$  ca.12.22 ppm thus confirming their aromatic nature (Figure 5).



<b>63</b>	R	% Yield	m.p. °C
<b>a</b>	H	44	150-152
<b>b</b>	F	62	176-178
<b>c</b>	Cl	65	218-220
<b>d</b>	OMe	56	185-187

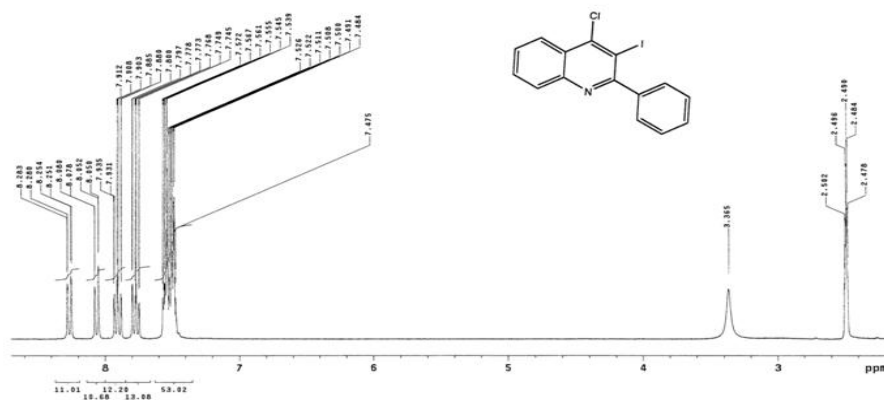
**Scheme 25**

**Table 1:**  $^{13}\text{C}$  NMR chemical shift values of products **63** in  $\text{DMSO-}d_6$  at 75 MHz



nucleus	<b>63a</b> (R = H)	<b>63b</b> (R = F)	<b>63c</b> (R = Cl)	<b>63d</b> (R = OMe)
$\text{OCH}_3$	-	-	-	55.2
C-2	162.3	161.5	161.3	162.0
C-3	99.6	99.3	99.2	98.2
C-4	146.1	146.6	146.5	147.3
C-4a	125.0	124.9	125.0	125.6
C-5	129.0	124.6	131.0	129.6
C-6	128.8	129.3	129.2	128.2
C-7	131.5	131.4	133.4	130.8
C-8	124.2	124.6	124.6	125.1
C-8a	147.1	160.5	146.7	147.7
C-1'	142.8	139.6 (d, $^4J_{\text{CF}}$ 3.5 Hz)	141.9	135.9
C-2', 6'	127.8	131.3 (d, $^3J_{\text{CF}}$ 7.3 Hz)	131.4	130.6
C-3', 5'	129.1	114.6 (d, $^2J_{\text{CF}}$ 21.6 Hz)	127.8	113.0
C-4'	129.2	163.8 (d, $^1J_{\text{CF}}$ 244.8 Hz)	129.3	160.0

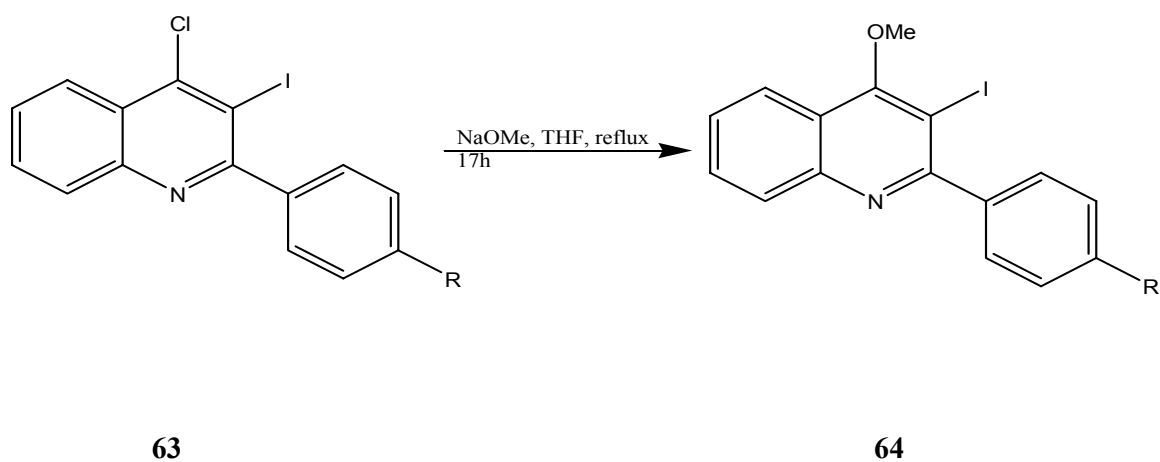




**Figure 5:** <sup>1</sup>H NMR spectrum of 3-iodo-4-chloro-2-phenylquinoline **63a** in DMSO-*d*<sub>6</sub>

## 2.5 Synthesis of 2-aryl-3-iodo-4-methoxyquinoline derivatives **64**

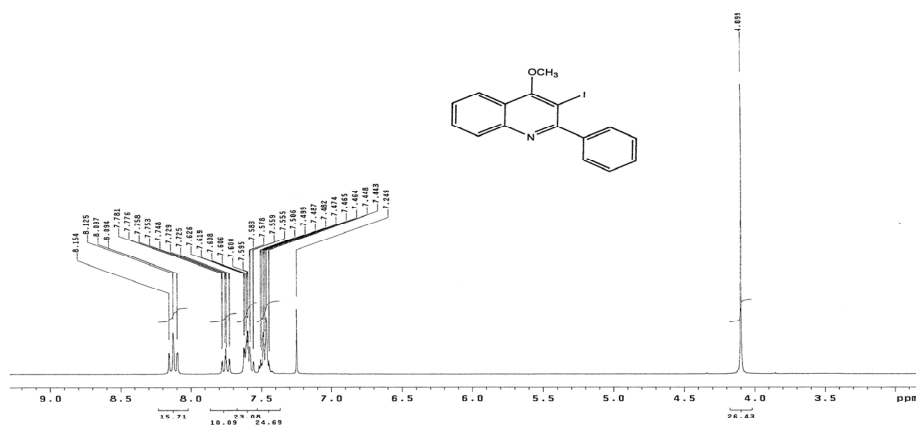
The 2-aryl-3-bromo-4-chloroquinolines were found to react with sodium methoxide in MeOH under reflux to afford the corresponding 2-aryl-3-bromo-4-methoxyquinolines.<sup>37</sup> We took advantage of the known ease of displacement of the 4-Cl by nucleophiles and subjected the 2-aryl-3-iodo-4-chloroquinolines **63** to sodium methoxide in methanol-THF mixture under reflux for 12hrs to afford products **64**. The <sup>1</sup>H NMR spectra of these products are characterised by the presence of an intense peak at  $\delta$  ca. 4.10 ppm corresponding to OCH<sub>3</sub> group (figure 6).



<b>64</b>	R	% Yield	m.p. °C
<b>a</b>	H	53	148-151
<b>b</b>	F	70	153-156
<b>c</b>	Cl	78	200-203
<b>d</b>	OMe	60	167-170

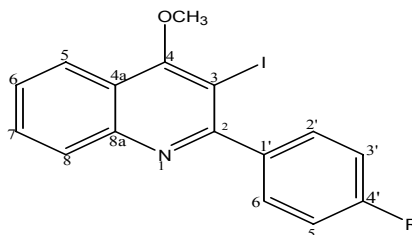
**Scheme 26**

With compounds **63** and **64** in hand, we were ready to investigate palladium catalyzed coupling with phenyl boronic acid as a model to effect metal-catalyzed coupling reaction. One of the challenges of this investigation was to effect the regioselective carbon-carbon formation between phenyl group and C-3 of 2-aryl-4-chloro-3-iodoquinolines **63**.



**Figure 6:**  $^1\text{H}$  NMR spectrum of 3-iodo-4-methoxy-2-phenyl-quinoline **64a** in  $\text{CDCl}_3$

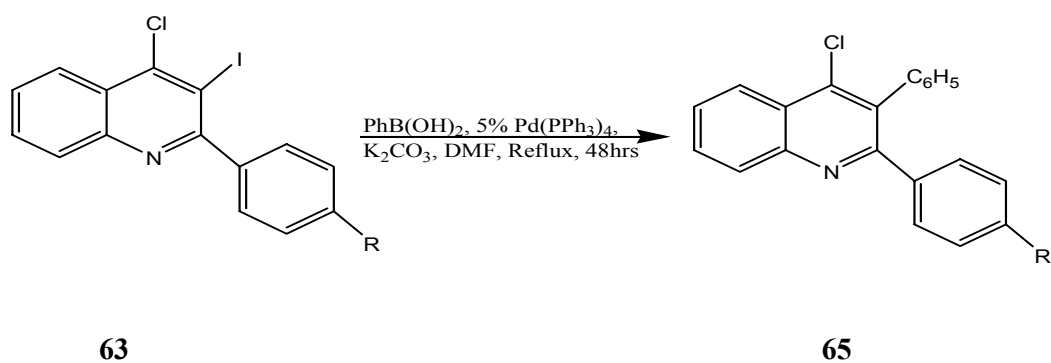
**Table 2:**  $^{13}\text{C}$  NMR chemical shift values (ppm) of systems **64** in  $\text{CDCl}_3$  (at 75MHz)



nucleus	<b>64a</b> (R = H)	<b>64b</b> (R = F)	<b>64c</b> (R = Cl)	<b>64d</b> (R = OMe)
$\text{OCH}_3$	-	-	-	55.4
$\text{OCH}_3$	62.0	62.0	62.0	62.0
C-2	163.1	161.3	161.8	162.6
C-3	88.0	87.8	87.4	88.3
C-4	165.0	164.7	164.9	164.7
C-4a	121.9	114.7	121.9	121.9
C-5	129.0	121.9	129.6	129.5
C-6	127.0	122.7	127.2	126.8
C-7	129.6	129.5	130.7	130.4
C-8	127.9	127.1	128.1	113.2
C-8a	149.1	149.0	149.0	159.9
C-1'	142.6	138.6 (d, $^4J_{\text{CF}}$ 3.4 Hz)	141.0	149.0
C-2', 6'	130.5	131.0 (d, $^3J_{\text{CF}}$ 8.5 Hz)	130.8	130.8
C-3', 5'	122.7	115.0 (d, $^2J_{\text{CF}}$ 21.6 Hz)	122.8	122.5
C-4'	129.2	161.6 (d, $^1J_{\text{CF}}$ 246.8 Hz)	134.8	135.1

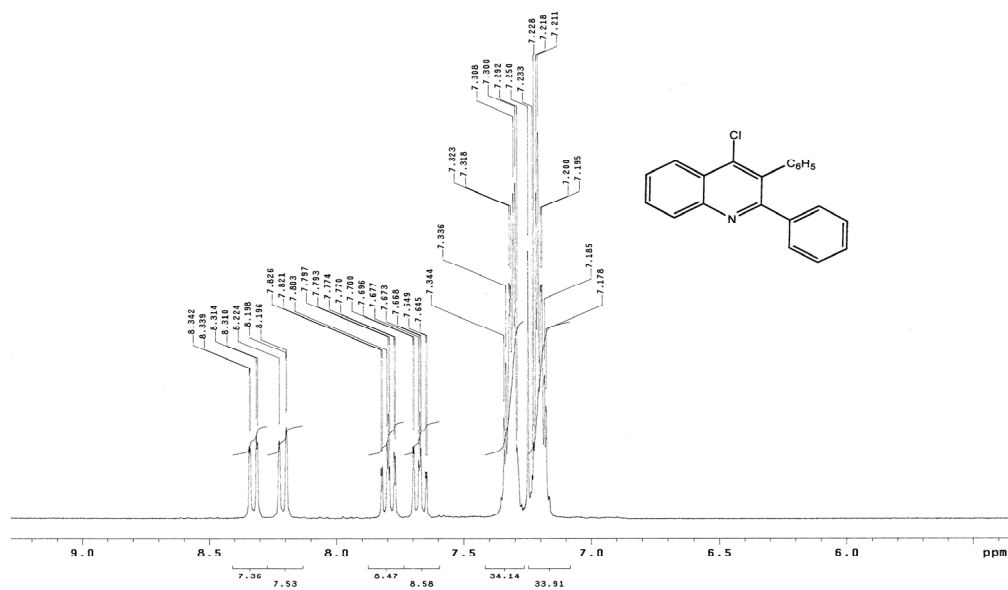
## 2.6 Suzuki coupling reactions of 2-aryl-4-chloroquinoline derivatives **65**

Palladium-catalyzed cross-coupling reactions of arylboronic acid and other organometallic species are known to proceed best with aryl or heteroaryl iodides or bromides. Although aryl chlorides are known to be less reactive, activated derivatives like 4-chloropyridines undergo palladium catalyzed cross-coupling reaction with ease.<sup>65</sup> In 2003 Alexey and his coworkers used 4-chloro-6-iodoquinoline as a model compound for the study of selective cross-coupling reactions. The model compound was subjected to Suzuki reaction conditions and it was found that only iodine atom was replaced.<sup>66</sup> The Cl atom was replaced by subjecting the resulting products to further Suzuki reaction conditions. With this consideration in mind and the key intermediates **63** in hand, we were ready to investigate the introduction of C-3 substituent using phenyl boronic acid as a model system to effect metal-catalyzed cross-coupling reaction. The previously undescribed 3-iodo-4-chloro-2-arylquinoline derivatives **63** were subjected to tetrakis(triphenylphosphine)palladium(0)-catalyzed coupling reaction with phenyl boronic acid in DMF in the presence of 2M sodium carbonate (aq) to afford 2,3-diaryl-4-chloroquinolines **65** (Scheme 27). The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of systems **65** are characterised by the increased number of resonances in the aromatic region confirming incorporation of the phenyl ring (see figure 9). In the <sup>13</sup>C NMR spectra of systems **65** the signal of C-3 at  $\delta$  ca. 127.9 ppm is significantly downfield than that of the corresponding substrates **63**, which resonate at  $\delta$  ca. 99.6 ppm (Table 3).



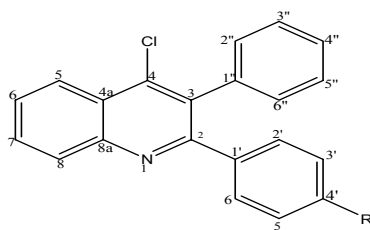
<b>65</b>	R	% Yield	m.p/ <sup>o</sup> C
<b>a</b>	H	48	116-118
<b>b</b>	F	54	120-122
<b>c</b>	Cl	42	145-148
<b>d</b>	OMe	47	110-112

**Scheme 27**



**Figure 7:** <sup>1</sup>H NMR spectrum of 4-chloro-2,3-diphenylquinoline **65a** in CDCl<sub>3</sub>

**Table 3:**  $^{13}\text{C}$  NMR chemical shift values (ppm) of systems **65** in DMSO- $d_6$  (at 75MHz)



nucleus	<b>65a</b> (R = H)	<b>65b</b> (R = F)	<b>65c</b> (R = Cl)	<b>65d</b> (R = OMe)
OCH <sub>3</sub>	—	—	—	55.1
C-2	159.2	160.9	157.8	159.4
C-3	127.9	127.8	127.9	127.6
C-4	141.9	147.5	138.6	141.8
C-4a	125.4	125.4	125.5	125.2
C-5	130.3	130.2	130.4	129.7
C-6	129.0	130.4	129.8	128.1
C-7	137.0	136.9	136.8	130.7
C-8	124.6	124.7	124.7	124.6
C-8a	147.6	158.0	147.6	147.6
C-1'	140.2	142.0(d, $^4J_{\text{CF}}$ 2.9Hz)	142.1	137.3
C-1''	127.9	127.8	127.9	132.8
C-4'	133.0	164.1(d, $^1J_{\text{CF}}$ 246.8Hz)	134.2	158.6
C-4''	127.6	127.7	132.7	131.2
C-2',6'	129.7	129.8(d, $^3J_{\text{CF}}$ 8.3Hz)	127.9	130.2
C-2'',6''	127.7	127.8	131.1	127.3
C-3',5'	130.7	114.7 (d, $^2J_{\text{CF}}$ 21.6 Hz)	128.2	113.1
C-3'',5''	128.0	128.1	130.6	130.7

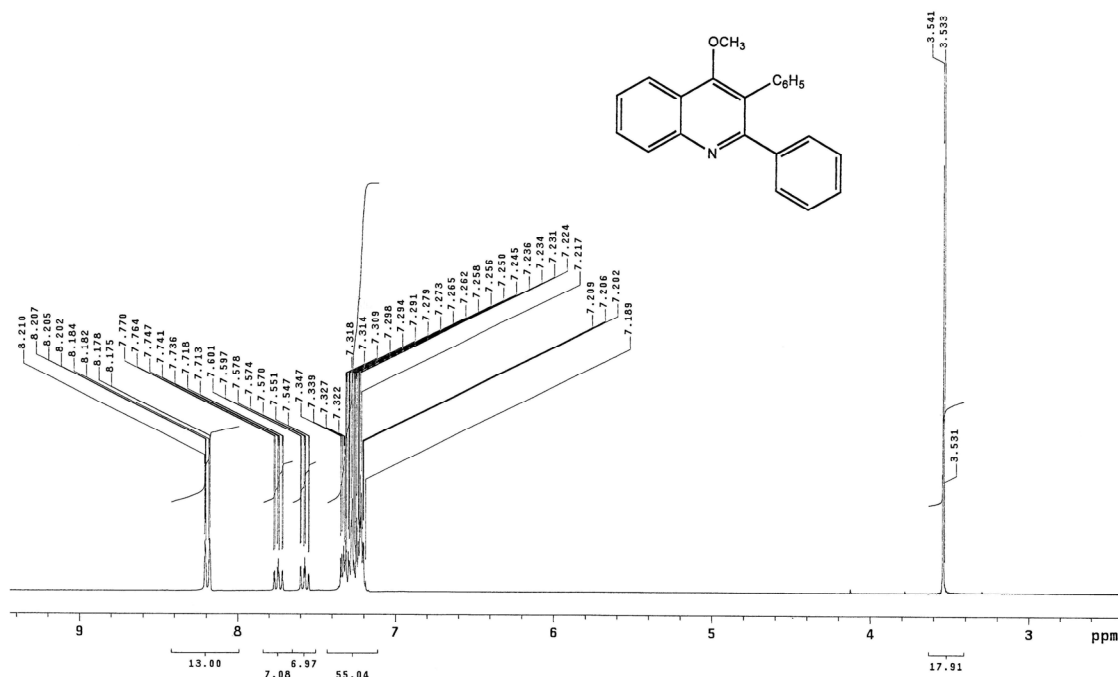
## 2.7 Suzuki coupling reaction of 2-aryl-3-iodo-4-methoxyquinoline derivatives

The known ease of displacement of a halogen atom at the  $\gamma$  position of quinoline nucleus by nucleophiles prompted us to replace Cl with methoxy group. The 4-methoxy-2,3-diarylquinoline derivatives **66** were obtained by subjecting a mixture of **65** and sodium methoxide in methanol-DMF mixture under reflux for 17hrs (Scheme 28). These products are easily distinguished from the corresponding substrates by the presence of an intense peak in their  $^1\text{H}$  NMR spectra at  $\delta$  *ca* 4.10 ppm corresponding to  $\text{OCH}_3$  (figure 8). The  $^{13}\text{C}$  NMR spectra of system **66** are further distinguished from those of their precursors **63** by the presence of a methoxy peak at  $\delta$  *ca* 62.1 ppm (Table 4). This also serves as retrospective confirmation that phenyl group replaced iodine at C-3 position of **63** (see scheme 25).

**Reagents:** (i) NaOMe, DMF, heat, 18h; (ii) PhB(OH)<sub>2</sub>, 5% Pd(PPh<sub>3</sub>)<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, DMF, heat, 48h

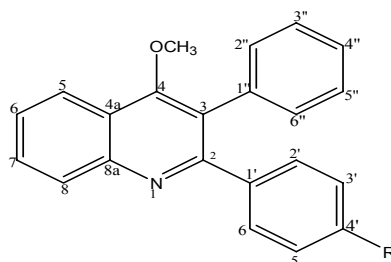
## Scheme 28

Although not observed, coupling of 2,3-diaryl-4-chloroquinolines with phenylboronic acid cannot be ruled out. Reaction conditions for Suzuki coupling reaction can be optimized or microwave conditions used to improve the yields. The 4-methoxy-2,3-diarylquinoline derivatives **66** were also synthesised from 4-methoxyquinoline derivatives **64** using phenylboronic acid in DMF in the presence of 2M potassium carbonate (aq). Analytical data of compounds **66** prepared from **64** compared favourably with those derived from **65**.



**Figure 8:** <sup>1</sup>H NMR spectrum of 4-methoxy-2,3-diphenylquinoline **66a** in CDCl<sub>3</sub>

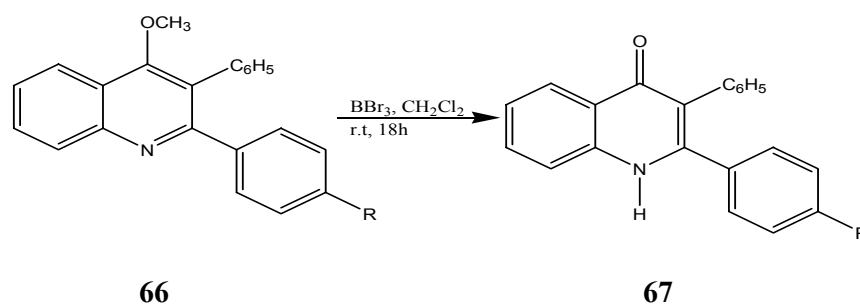


**Table 4:**  $^{13}\text{C}$  NMR chemical shift values (ppm) of **66** in  $\text{CDCl}_3$  (at 75MHz)

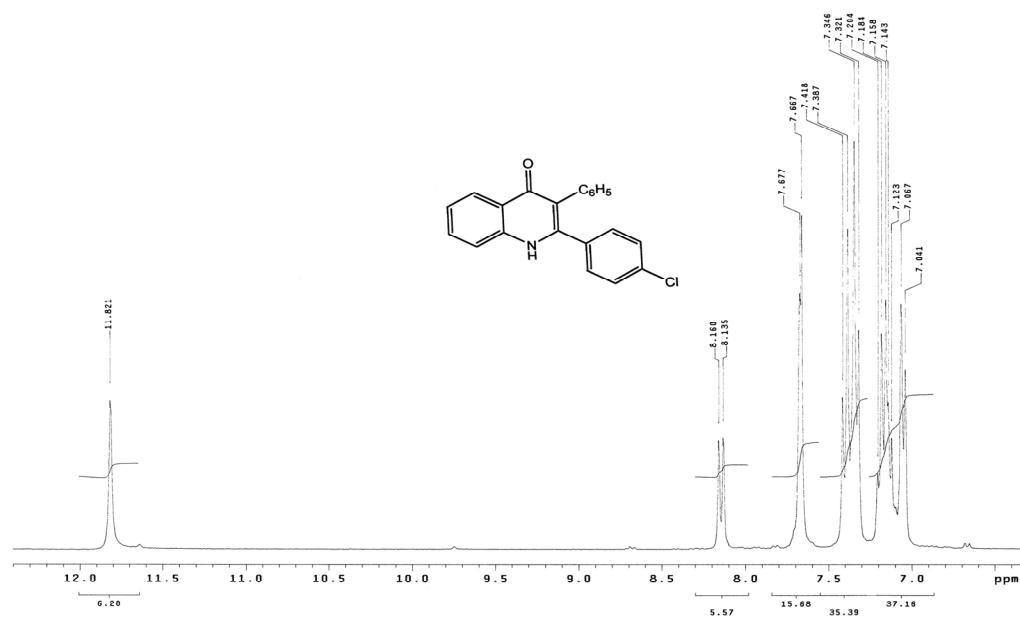
nucleus	<b>66a</b> (R= H)	<b>66b</b> (R = F)	<b>66c</b> (R = Cl)	<b>66d</b> (R = OMe)
OCH <sub>3</sub>	61.3	61.2	61.3	55.1; 61.2
C-2	159.2	159.2	159.1	159.2
C-3	135.1	124.7	122.3	122.2
C-4	161.5	161.1	161.5	161.2
C-4a	126.3	126.4	126.5	126.1
C-5	125.3	125.3	125.2	125.4
C-6	122.8	122.7	122.8	122.5
C-7	133.8	131.6	133.9	133.0
C-8	129.5	129.5	129.5	129.8
C-8a	149.0	148.7	148.7	148.8
C-1'	142.6	136.6 (d, $^4J_{\text{CF}}$ 2.9 Hz)	138.9	128.1
C-1''	135.1	135.3	135.1	135.6
C-4'	130.0	164.0 (d, $^1J_{\text{CF}}$ 245.8 Hz)	130.0	129.5
C-4''	127.4	127.3	127.4	127.1
C-2',6'	131.2	131.0 (d, $^3J_{\text{CF}}$ 8.3 Hz)	131.2	131.0
C-2'',6''	130.9	130.6	130.9	131.0
C-3',5'	128.2	114.6 (d, $^2J_{\text{CF}}$ 21.6 Hz)	128.2	113.1
C-3'',5''	127.9	127.8	127.9	127.1

### 2.8.1 Synthesis of 2,3-diarylquinolin-4(1*H*)-ones derivatives **67** via demethylation of 2,3-diaryl-4-methoxyquinolines

Aryl ethers are known to be easily demethylated using either HBr or BBr<sub>3</sub>.<sup>67</sup> The problem with HBr is that it can attack the C-C double bond leading to various side products.<sup>67</sup> On the other hand, BBr<sub>3</sub> is a Lewis acid which only promotes demethylation. In our case, we subjected compounds **66** to boron tribromide in dichloromethane to afford 2,3-diarylquinolin-4(1*H*)-ones **67** in high yield and purity. Demethylation of **66d** led to a complicated mixture of products lacking methyl signal in the proton spectrum. The <sup>1</sup>H NMR spectra of **67a-c** (figure 9) are characterised by the absence of an intense peak at  $\delta$  ca. 4.10 ppm, which is found in the spectra of the corresponding precursors. Their <sup>1</sup>H NMR spectra also reveal the presence of NH signal at  $\delta$  ca 11.4 ppm. The carbonyl carbon resonates at  $\delta$  ca 177.7 ppm (C=O) in their <sup>13</sup>C NMR spectra, which further confirm the quinolone nature of products **67** (Table 5). The IR spectra of products **67** reveal the presence of absorption bands at  $\nu_{\text{max}}$  1631.3 cm<sup>-1</sup> and  $\nu_{\text{max}}$  3200 cm<sup>-1</sup> corresponding to the C=O and NH, respectively.



<b>67</b>	R	% Yield	m.p/ <sup>o</sup> C
<b>a</b>	H	58	342-344
<b>b</b>	F	53	385-387
<b>c</b>	Cl	63	388-390



**Figure 9:**  $^1\text{H}$  NMR spectrum of 2-(4'-Chlorophenyl)-3-phenylquinolin-4(1H)-one **67c** in  $\text{DMSO}-d_6$

**Table 5:**  $^{13}\text{C}$  NMR chemical shift values (ppm) of **67** in DMSO- $d_6$  (at 75MHz)

nucleus	<b>67a</b> (R= H)	<b>67b</b> (R = F)	<b>67c</b> (R = Cl)
C-2	148.4	160.5	149.6
C-3	120.4	120.6	133.3
C-4	175.4	175.3	185.3
C-4a	135.1	135.6	157.3
C-5	125.3	125.3	134.6
C-6	123.1	123.2	130.6
C-7	131.7	147.5	141.8
C-8	118.4	118.4	128.4
C-8a	131.6	131.9	157.3
C-1'	124.6	131.8 (d, $^3J_{\text{CF}}$ 4.3 Hz)	144.0
C-1''	135.7	135.6	145.4
C-4'	128.9	163.8 (d, $^1J_{\text{CF}}$ 245.0 Hz)	143.7
C-4''	125.9	125.3	136.1
C-2',6'	139.6	139.6 (d, $^4J_{\text{CF}}$ 3.6 Hz)	138.1
C-2'',6''	127.2	127.3	137.3
C-3',5'	128.0	115.0 (d, $^2J_{\text{CF}}$ 21.7 Hz )	141.7
C-3'',5''	129.5	126.0	141.4

Demethylation of **66** represents a convenient method for the synthesis of 2,3-diarylquinolin-4(1*H*)-ones of potential biological interest that can be obtained only with difficulty otherwise.

All low and high resolution mass spectra of the quinoline derivatives **63-66** and quinolone **67** are characterized by the molecular ion as the base peak (see appendix). The daughter fragments resulting from the molecular ion are less intense (< 20%) and show no consistent pattern of fragmentation in each series. The experimentally determined accurate *m/z* values, nevertheless represents in each case closest fit consistent with the assigned structures.

## CHAPTER 3

### 3. CONCLUSIONS

In the first part of this investigation we managed to effect C3-Ph bond formation with the displacement of iodine by phenyl group. This further demonstrates the ease of displacement of iodine over chlorine in palladium-catalyzed cross-coupling reaction. The 4-Cl atom was, in turn, easily displaced by  $^-OCH_3$  to afford 2,3-diaryl-4-methoxyquinoline derivatives that cannot be easily prepared using renowned classical methods for the synthesis of polysubstituted quinolines. In an alternative route, we used 2-aryl-3-iodo-4-methoxyquinolines to effect palladium-catalyzed cross-coupling with phenyl boronic acid to afford 2,3-diaryl-4-methoxyquinoline derivatives in reasonable yields. This appears to be a better route than one from 2-aryl-4-chloro-3-iodoquinoline derivatives due to the observed incomplete conversion of 2-aryl-4-chloro-3-iodoquinolines to 2,3-diaryl-4-chloroquinolines. Further modification of the 2,3-diaryl-4-methoxyquinolines involving demethylation afforded 2,3-diarylquinolin-4(1*H*)-ones of potential biological interest that can be obtainable only with difficulty otherwise. Our results demonstrate the synthetic importance of 2-aryl-4-chloroquinolines in the synthesis of 2,3,4-trisubstituted quinolines.

Future research extending from this investigation is expected to include the following:

- Displacement of Cl in 2-aryl-4-chloro-3-iodoquinolines with  $N_3^-$  ion to afford 2-aryl-4-azido-3-iodoquinoline derivatives.
- Chemoselective reduction of the azide group without removal of halogen atoms via Staudinger reaction with triphenylphosphine.
- Suzuki coupling of 2-aryl-4-azido-3-iodoquinoline derivatives
- Application of other metal catalyzed coupling reactions such as Sonagashira or Heck reaction on 2-aryl-4-chloro-3-iodoquinolines and 2-aryl-4-azido-3-iodoquinolines.

In conclusion, the results of this investigation represent another example of the use of 4-chloroquinolines in the synthesis of variously substituted quinoline derivatives. The results of this investigation have since been submitted for possible publication.

## CHAPTER 4

### 4. EXPERIMENTAL

#### 4.1 General

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected.  $^1\text{H}$  NMR spectra were obtained on a Varian Mercury 300MHz NMR spectrometer using  $\text{CDCl}_3$  or  $\text{DMSO-d}_6$  as solvents. IR spectra were recorded with a Digilab FTS 7000 Series Digilab Win-IR Pro FTIR Spectrometer using a nitrogen cooled germanium crystal detector. Merck silica gel was used for the thin layer chromatography and column chromatography was performed on silica gel. Low and high-resolution mass spectra were recorded at an ionisation potential of 70eV using Micromass Autospec-TOF (double focusing high resolution) instrument (University of North West). Elemental (C, H, N) analyses were performed at the University of Cape Town.

#### 4.2 Preparation of *N*-benzoyl-2-aminoacetophenone derivatives 24

##### 4.2.1 Preparation of *N*-benzoyl-2-aminoacetophenone 24a

Benzoyl chloride **23a** (4.6 ml, 39.8 mmol) was added drop-wise to a mixture of 2-aminoacetophenone **22** (6.0 g, 44.4 mmol) and triethylamine (12.33 g, 119.5 mmol) in THF (60 ml) at 0°C. After 30 minutes at 0°C the mixture was allowed to warm to room temperature, stirred for 2 hours and then poured into ice-cold water (100 ml).



The resulting precipitate was filtered and then dissolved in chloroform (50 ml). The solution was washed with water and the organic layer was separated and dried over anhydrous sodium sulphate. The salt was filtered off and the solvent was evaporated under reduced pressure to afford **24a**, solid (6.34 g, 72%), m.p. 96.7-99.7°C (lit.<sup>62</sup> 98.5-99°C); <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 2.70 (3H, s, COCH<sub>3</sub>), 7.12 – 7.64 (1H, t, *J* 7.5 Hz, 4-H), 7.49-7.64 (4H, m, 3'-H, 4'-H, 5'-H, and 5-H), 7.93-8.07 (3H, dd, *J* 7.5 and 6.9 Hz, 2'-H, 6'-H and 3-H), 8.96-8.99 (1H, d, *J* 8.4 Hz, 6-H), 12.70 (1H, s, NH);  $\nu_{\text{max}}/\text{cm}^{-1}$  760.0, 962.9, 1242.2, 1446.6, 1533.4, 643.3, 1672.9, 3121.1.

#### 4.2.2 Preparation of *N*-(4-fluorobenzoyl)-2-aminoacetophenone **24b**

A mixture of **22** (6.0 g, 44.4 mmol), triethylamine (12.33 g, 119.5 mmol) and 4-fluorobenzoyl chloride **23b** (4.7 ml, 39.8 mmol) in THF (60 ml) was treated as for the synthesis of **24a** to afford **24b**, solid (7.61 g, 80%), m.p 96.7-98.2°C (lit.<sup>63</sup> 92-95°C); <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 2.72 (3H, s, COCH<sub>3</sub>), 7.17 (2H, m, 4-H and 5-H), 7.62 (2H, dt, *J* 1.2 and 7.8 Hz, 3'-H and 5'-H), 7.96 (1H, dd, *J* 1.5 and 8.0 Hz, 3-H), 8.05-8.10 (2H, m, 2'-H and 6'-H), 8.95 (1H, dd, *J* 8.3 Hz, 6-H), 12.70 (1H, s, NH);  $\nu_{\text{max}}/\text{cm}^{-1}$  750.2, 846.7, 1163.1, 1231.2, 1448.5, 1504.4, 1588.8, 1649.1, 1671.8, 3187.8.

#### 4.2.3 Preparation of *N*-(4-chlorobenzoyl)-2-aminoacetophenone **24c**

A mixture of **22** (6.0 g, 44.4 mmol), triethylamine (12.33 g, 119.5 mmol) and 4-chlorobenzoyl chloride **23c** (5.1 ml, 39.8 mmol) in THF (60 ml) treated as for the synthesis of **24a** to afford **24c**, solid (7.01 g, 69%), m.p 110-112.5°C (lit.<sup>63</sup> 106-

109°C);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 2.71 (3H, s,  $\text{COCH}_3$ ), 7.17 (1H, dt,  $J$  1.5 and 7.8 Hz, 4-H), 7.46-7.51 (1H, m, 5-H), 7.61 (2H, dt,  $J$  1.5 and 8.5 Hz, 3'-H and 5'-H), 7.94-8.08 (3H, m, 2'-H, 6'-H and 3-H), 8.93 (1H, dd,  $J$  1.5 and 8.0 Hz, 6-H), 12.72 (1H, s, NH);  $\nu_{\text{max}}/\text{cm}^{-1}$  744.1, 1010.7, 1244.1, 1316.1, 1448.5, 1533.4, 1587.8, 1647., 1669.4, 3226.5.

#### 4.2.4 Preparation of *N*-(4-methoxybenzoyl)-2-aminoacetophenone **24d**

A mixture of **22** (6.0 g, 44.4 mmol), triethylamine (12.33 g, 119.5 mmol) and 4-methoxybenzoyl chloride **23d** (6.79 g, 39.8 mmol) in THF (60 ml) was treated as for the synthesis of **24a** to afford **24d**, solid (7.49 g, 63%), m.p 116-118.8°C (lit.<sup>62</sup> 119-121°C);  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 2.71 (3H, s,  $\text{COCH}_3$ ), 3.87 (3H, s,  $\text{OCH}_3$ ), 6.95-7.02 (2H, m, 3'-H and 5'-H), 7.10-7.16 (1H, t,  $J$  7.5 Hz, 4-H), 7.57-7.63 (1H, dt,  $J$  7.9 Hz, 5-H), 7.93-8.05 (3H, m, 3-H, 2'-H and 6'-H), 8.97 (1H, d,  $J$  8.7 Hz, 6-H), 12.63 (1H, s, NH);  $\nu_{\text{max}}/\text{cm}^{-1}$  758.0, 1018.4, 1158.4, 1188.1, 1249.9, 1313.5, 1508.3, 1604.8, 1644.9, 1669.0, 3225.0.

#### 4.3 Preparation of 2-arylquinolin-4(1*H*)-one derivatives **21**

##### 4.3.1 Preparation of 2-phenylquinolin-4(1*H*)-one **21a**

A stirred mixture of *N*-benzoyl-2-aminoacetophenone **24a** (3.00 g, 12.6 mmol) and potassium *tert*-butoxide (1M in *tert*-butanol; 25.0 ml, 25.0 mmol) in *tert*-butanol (24 ml) was heated under reflux for 20 hours. The mixture was allowed to cool to room temperature and then poured into aqueous ammonium chloride solution (60 ml) to

form a precipitate. The precipitate was collected, washed sequentially with water and ice-cold ethanol and then dried in an oven to afford **21a**, solid (2.50 g, 90%), m.p 237-239°C (lit.<sup>33</sup> 240-243°C); <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) 6.33 (1H, s, 3-H), 7.33 (1H, t, *J* 6.9 Hz, 6-H), 7.59 (2H, t, *J* 3.9 Hz, 2'-H and 6'-H), 7.67 (1H, t, *J* 6.9 Hz, 7-H), 7.76 (1H, d, *J* 8.1 Hz, 8-H), 7.83 (2H, d, *J* 3.6 Hz, 3'-H and 5'-H), 8.09 (1H, d, *J* 8.1 Hz, 5-H), 11.71 (1H, s, NH);  $\nu_{\max}/\text{cm}^{-1}$  754.9, 767.7, 839.0, 1253.7, 1471.2, 1499.0, 1545.0, 1581.6, 1629.8, 2969.2, 3066.8, 3090.2, 3259.

#### 4.3.2 Preparation of 2-(4-fluorophenyl)quinolin-4(1*H*)-one **21b**

A procedure employed for the synthesis of **21a** was followed using a mixture of *N*-(4-fluorobenzoyl)-2-aminoacetophenone **24b** (3.00 g, 11.7 mmol) and potassium *tert*-butoxide (1M in *tert*-butanol; 23.2 ml, 23.2 mmol) in *tert*-butanol (24 ml). Work up afforded **21b**, solid (2.40 g, 86%), m.p 320- 323°C (lit.<sup>38</sup> 322-325°C ); <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) 6.32 (1H, s, 3-H), 7.33 (1H, t, *J* 7.3 Hz, 7-H), 7.43 (2H, t, *J* 8.5 Hz, 3'-H and 5'-H), 7.67 (1H, t, *J* 6.9 Hz, 6-H), 7.74 (1H, d, *J* 8.1 Hz, 8-H), 7.90 (2H, t, *J* 6.3 Hz, 2'-H and 6'-H), 8.09 (1H, d, *J* 7.9 Hz, 5-H), 11.71 (1H, s, NH);  $\nu_{\max}/\text{cm}^{-1}$  763.7, 794.8, 827.5, 1229.0, 1503.6, 1547.7, 1591.3, 1631.8, 2972.6, 3068.7, 3258.0.

#### 4.3.3 Preparation of 2-(4-chlorophenyl)quinolin-4(1*H*)-one **21c**

A procedure employed for the synthesis of **21a** was followed using a mixture of *N*-(4-chlorobenzoyl)-2-aminoacetophenone **24c** (3.00 g, 11.0 mmol) and potassium *tert*-butoxide (1M in *tert*-butanol; 21.9 ml, 21.9 mmol) in *tert*-butanol (24 ml). Work up afforded **21c**, solid (2.68 g, 96%), m.p 332- 335°C (lit.<sup>38</sup> 270-273 °C); <sup>1</sup>H NMR

(300MHz, DMSO- $d_6$ ) 6.35 (1H, s, 3-H), 7.34 (1H, t,  $J$  7.2 Hz, 7-H), 7.64-7.70 (3H, m, 3'-H, 5'-H and 6-H), 7.76 (1H, d,  $J$  8.1 Hz, 8-H), 7.87 (2H, d,  $J$  8.1 Hz, 2'-H and 6'-H), 8.09 (1H, d,  $J$  8.1 Hz, 5-H), 11.71 (1H, s, NH) ;  $\nu_{\max}/\text{cm}^{-1}$  763.7, 794.8, 827.5, 1229.0, 1503.6, 1547.3, 1547.7, 1591.3, 1631.8, 1972.6, 3068.7, 3238.0.

#### 4.3.4 Preparation of 2-(4-methoxyphenyl)quinolin-4(1H)-one **21d**

A procedure employed for the synthesis of **21a** was followed using a mixture of *N*-(4-methoxybenzoyl)-2-aminoacetophenone **24d** (3.00 g, 11.2 mmol) and potassium *tert*-butoxide (1M in *tert*-butanol; 22.2 ml, 22.2 mmol) in *tert*-butanol (24 ml). Work up afforded **21d**, solid (2.50 g, 89%), m.p 306- 309°C (lit.<sup>38</sup> 290-293°C);  $^1\text{H}$  NMR (300MHz, DMSO- $d_6$ ) 3.85 (3H, s, OCH<sub>3</sub>), 6.30 (1H, s, 3-H), 7.13 (2H, d,  $J$  6.9 Hz, 2'-H and 6'-H), 7.31 (1H, t,  $J$  7.6 Hz, 6-H), 7.65 (1H, t,  $J$  7.0 Hz, 7-H), 7.75 (1H, d,  $J$  8.4 Hz, 8-H), 7.80 (2H, d,  $J$  8.4 Hz, 3'-H and 5'-H), 8.07 (1H, d,  $J$  8.1 Hz, 6-H), 11.58 (1H, s, NH);  $\nu_{\max}/\text{cm}^{-1}$  752.2, 801.8, 1028.1, 1244.1, 1503.4, 1543.1, 1580.7, 1631.8, 2986.7, 3076.8, 3101.5, 3259.1.

#### 4.4 Preparation of 2-aryl-3-iodoquinolin-4(1H)-one derivatives **62**

##### 4.4.1 Preparation of 3-iodo-2-phenylquinolin-4(1H)-one **62a**

A stirred mixture of **21a** (2.00 g, 9.1 mmol), iodine (3.45 g, 13.6 mmol,) and sodium carbonate (1.92 g, 18.1 mmol) in THF (35 ml) was stirred at room temperature for 12 hours. After 12 hours, the reaction mixture was poured into ice-cold sodium thiosulphate solution. The precipitate was filtered, washed with water and

recrystallized from ethanol to afford **62a**, solid (2.09g, 67%); m.p 276-279°C (lit.<sup>50</sup> 284-286°C); <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>), 7.40 (1H, t, *J* 7.8 Hz, 7-H), 7.66 (7H, m, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H, 6-H and 8-H), 8.14 (1H, d, *J* 8.1 Hz, 5-H), 12.31 (1H, s, NH);  $\nu_{\text{max}}/\text{cm}^{-1}$  755.6, 869.7, 1350.2, 1468.3, 1490.5, 1539.5, 1566.2, 1624.8, 2899.0, 3056.2, 3361.9.

#### 4.4.2 Preparation of 2-(4'-fluorophenyl)-3-iodoquinolin-4-(1*H*)-one **62b**

A procedure employed for the synthesis of **62a** was followed using a mixture of 2-(4-fluorophenyl)quinolin-4(1*H*)-one **21b** (2.00 g, 8.4 mmol), iodine (3.19 g, 12.6 mmol) and sodium carbonate (1.77 g, 16.7 mmol) in THF (35 ml). Work-up afforded **62b**, solid (1.98 g, 65%), m.p 226-229°C (lit.<sup>50</sup> 196-198°C); <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) 7.43 (3H, m, 3'-H, 5'-H and 7-H), 7.67 (4H, m, 2'-H, 6'-H, 6-H and 8-H), 8.14 (1H, d, *J* 8.1 Hz, 5-H), 12.32 (1H, s, NH);  $\nu_{\text{max}}/\text{cm}^{-1}$  754.7, 8180.0, 1157.8, 1224.8, 1466.3, 1492.9, 1535.3, 1622.1, 2924.7, 3063.1, 3414.4.

#### 4.4.3 Preparation of 2-(4'-chlorophenyl)-3-iodoquinolin-4-(1*H*)-one **62c**

A procedure employed for the synthesis of **62a** was followed using a mixture of 2-(4-chlorophenyl)quinolin-4(1*H*)-one **21c** (2.00 g, 7.8 mmol), iodine (2.99 g, 11.8 mmol) and sodium carbonate (1.66 g, 15.7 mmol) in THF (35 ml). Work-up afforded **62c**, solid (2.13 g, 71%); m.p 205-208°C (lit.<sup>50</sup> 254-256°C); <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) 7.41 (1H, t, *J* 7.7 Hz, 7-H), 7.59-7.74 (6H, m, 2'-H, 3'-H, 5'-H, 6'-H, and 6-H and 8-H), 8.14 (1H, m, 5-H), 12.33 (1H, s, NH);  $\nu_{\text{max}}/\text{cm}^{-1}$  758.6, 995.7, 1090.0, 1165.2, 1487.4, 1539.5, 1626.2, 2900.8, 3060.6, 3401.0.

#### 4.4.4 Preparation of 2-(4-methoxyphenyl)-3-iodoquinolon-4-(1*H*)-one **62d**

A procedure employed for the synthesis of **62a** was followed using a mixture of 2-(4-methoxyphenyl)quinolin-4(1*H*)-one **21d** (2.00 g, 7.97 mmol), iodine (3.00 g, 12.0 mmol) and sodium carbonate (1.69 g, 15.94 mmol,) in THF (35 ml). Work-up afforded **62d**, solid (2.20g, 73.3%), m.p 225-228°C (lit.<sup>50</sup> 262-264°C); <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) 3.85 (3H, s, OCH<sub>3</sub>) 7.12 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H), 7.39 (1H, t, *J* 7.5 Hz, 7-H), 7.52 (2H, d, *J* 9.0 Hz, 2'-H and 6'-H), 7.68 (2H, m, 6-H and 8-H), 8.13 (1H, d, *J* 8.1 Hz, 5-H), 12.22 (1H, s, NH);  $\nu_{\max}$ / cm<sup>-1</sup> 759.8, 1024.2, 1178.9, 1253.6, 1467.8, 1544.3, 1624.1, 2929.9, 3061.3, 3390.7.

#### 4.5 Preparation of 2-aryl-4-chloro-3-iodoquinoline derivatives **63**

##### 4.5.1 Preparation of 4-chloro-3-iodo-2-phenyl-quinoline **63a**

A stirred suspension of **62a** (2.00 g, 5.8 mmol) in POCl<sub>3</sub> (15 ml) was heated under reflux for 3 hours. The mixture was allowed to cool and then poured into an ice-cold 25% ammonium solution. The precipitate was filtered, washed with water and recrystallised from a mixture of ethyl acetate and acetic acid (4:1, v/v) to afford **63a**, solid (1.45g, 73%); m.p 148-151°C; <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) 7.48-7.57 (5H, m, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H), 7.75-7.80 (1H, dt, *J* 1.5 and 7.2 Hz, 7-H), 7.88-7.94 (1H, dt, *J* 1.2 and 7.8 Hz, 6-H), 8.05-8.08 (1H, dd, *J* 0.9 and 8.4 Hz, 8-H), 8.25-8.28 (1H, dd, *J* 1.2 and 7.95 Hz, 5-H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 99.6 (C-3), 124.2 (C-8), 125.0 (C-4a), 127.8 (C-2',6'), 128.8 (C-6), 129.0 (C-5), 129.1 (C-3',5'),

129.2 (C-4'), 131.5 (C-7), 142.8 (C-1'), 146.1 (C-4), 147.1 (C-8a), 162.3 (C-2);  $\nu_{\max}/\text{cm}^{-1}$  762, 845, 1026, 1088, 1339, 1555; MS (EI):  $m/z$  365 ( $M^+$ , 89), 238 (100), 220 (69), 203 (58); HRMS (EI) calculated for  $C_{15}H_{11}ClIN$ : 364.9477. Found: 364.9468. *Anal.* Calcd. for  $C_{15}H_{11}ClIN$ : C, 48.96; H, 2.99; N, 3.80. Found: C, 48.91; H, 2.49; N, 3.16.

#### 4.5.2 Preparation of 4-chloro-3-iodo-2-(4-fluorophenyl)quinoline 63b

A procedure employed for the synthesis of **63a** was followed using a mixture of 2-(4-fluorophenyl)-3-iodoquinolin-4-(1*H*)-one **62b** (1.98 g, 5.4 mmol) and  $POCl_3$  (15 ml). Work up afforded **63b**, solid (1.69g, 85%); m.p (153-156°C),  $^1H$  NMR (300MHz,  $DMSO-d_6$ ) 7.30-7.36 (2H, dt,  $J$  2.1 and 9Hz, 3'-H and 5'-H), 7.59-7.65 (1H, dt,  $J$  1.5 and 7.5Hz, 2'-H and 6'-H), 7.75-7.80 (1H, dt,  $J$  1.2 and 6.0 Hz, 7-H), 7.88-7.93 (1H, dt,  $J$  1.2 and 7.2Hz, 6-H), 8.05-8.08 (1H, d,  $J$  8.1 Hz, 8-H), 8.26 (1H, dt,  $J$  0.9 and 8.5 Hz, 5-H);  $^{13}C$  NMR (75 MHz,  $DMSO-d_6$ ) 99.3 (C-3), 114.6 (d,  $^2J_{CF}$  21.6 Hz, C-3' and C-5'), 124.6 (C-5), 124.6 (C-8), 124.9 (C-4a), 129.3 (C-6), 131.3 (d,  $^3J_{CF}$  8.3 Hz, C-2' and C-6'), 131.4 (C-7), 139.6 (d,  $^4J_{CF}$  3.5 Hz, C-1'), 146.6 (C-4), 161.5 (C-2), 163.8 (d,  $^1J_{CF}$  244.8 Hz, C-4');  $\nu_{\max}/\text{cm}^{-1}$  757.8, 827.6, 1218.9, 1342.6, 1508.0, 1596.6; MS (EI)  $m/z$  383 ( $M^+$ , 97), 256 (100), 221 (78); HRMS (EI) calculated for  $C_{15}H_{10}ClFIN$ : 382.9374. Found 382.9368. *Anal.* Calcd. for  $C_{15}H_{10}ClFIN$ : C, 46.68; H, 2.59; N, 3.63. Found: C, 47.22; H, 2.12; N, 3.55.

#### 4.5.3 Preparation of 4-chloro-2-(4-chlorophenyl)-3-iodoquinoline 63c

A procedure employed for the synthesis of **63a** was followed using a mixture of 2-(4-chlorophenyl)-3-iodoquinolon-4-(1*H*)-one **62c** (2.0 g, 5.3 mmol) and POCl<sub>3</sub> (15 ml). Work up afforded **63c**, solid (1.60 g, 80%); m.p 200-203°C; <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) 7.56-7.62 (4H, m, 2'-H, 3'-H, 5'-H and 6'-H), 7.76-7.81 (1H, dt, *J* 7.2 Hz, 7-H), 7.89-7.94 (1H, t, *J* 7.2 Hz, 6-H), 8.06-8.09 (1H, d, *J* 8.4 Hz, 8-H); 8.25-8.28 (1H, d, *J* 8.4 Hz, 5-H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 99.2 (C-3), 124.6 (C-8), 125.0 (C-4a), 127.8 (C-3',5'), 129.2 (C-6), 129.3 (C-4'), 131.0 (C-5), 131.4 (C-2',6'), 133.4 (C-7), 141.9 (C-1'), 146.5 (C-4), 146.7 (C-8a), 161.3 (C-2); IR (neat):  $\nu_{\text{max}}$ / cm<sup>-1</sup> 756, 822, 1092, 1247, 1342, 1473, 1605; MS (EI) *m/z* 399 (M<sup>+</sup>, 62), 273 (100), 238 (72), 219 (66), 160 (21), 128 (24), 101 (21), 64 (33); HRMS (EI) calculated for C<sub>15</sub>H<sub>8</sub>Cl<sub>2</sub>IN: 398.9100. Found: 398.9061 *Anal.* Calcd. for C<sub>15</sub>H<sub>8</sub>Cl<sub>2</sub>IN: C, 44.99; H, 1.99; N, 3.49. Found: C, 44.80; H, 1.97; N, 3.41.

#### 4.5.4 Preparation of 4-chloro-3-iodo-2-(4-methoxyphenyl)quinoline 63d

A procedure employed for the synthesis of **63a** was followed using a mixture of 2-(4-methoxyphenyl)-3-iodoquinolon-4-(1*H*)-one **62d** (2.0 g, 5.1 mmol) and POCl<sub>3</sub> (15 ml). Work up afforded **63d**, solid (1.73 g, 87.%); m.p 269-272°C; <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) 3.87 (3H, s, OCH<sub>3</sub>), 6.99-7.02 (2H, dd, *J* 3.0 and 9.0 Hz, 3'-H and 5'-H), 7.55-7.64 (2H, dd, *J* 2.1 and 6.3 Hz, 2'-H and 6'-H), 7.74-7.79 (1H, dt, *J* 1.2 and 7.5 Hz, 6-H), 8.08-8.11 (1H, d, *J* 8.4 Hz, 8-H), 8.25-8.28 (1H, dd, *J* 0.9 and 8.8 Hz, 5-H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 55.2 (COMe), 98.2 (C-3), 113.0 (C-3',5'), 125.1 (C-8), 125.6 (C-4a'), 128.2 (C-6), 129.6 (C-5), 130.6 (C-2',6'), 130.8 (C-7), 135.9 (C-



1'), 147.3 (C-4), 147.7 (C-8a), 160.0 (C-4'), 162.0 (C-2);  $\nu_{\max}/\text{cm}^{-1}$  759.6, 823.6, 1030.0, 1176.9, 1245.9, 1510.8, 1606.1; MS (EI):  $m/z$  395 ( $M^+$ , 6), 269 (100), 254 (69), 191 (24), 162 (27), 127 (32) HRMS (EI) calculated for  $C_{16}H_{11}ClINO$ : 394.9568. Found: 394.9574. *Anal.* Calcd. for  $C_{16}H_{11}ClINO$ : C, 48.53; H, 2.78; N, 3.54. Found: C, 48.24; H, 2.68; N, 3.71.

## 4.6 Preparation of 2-aryl-3-iodo-4-methoxyquinoline derivatives **64**

### 4.6.1 Preparation of 3-iodo-4-methoxy-2-phenylquinoline **64a**

A stirred mixture of 2-aryl-4-chloro-3-iodoquinoline **63a** (0.50 g, 1.37 mmol) and sodium methoxide solution (0.5M solution in methanol; 0.16 g, 3.01 mmol, 6.02 ml) in THF (6.85 ml) was refluxed for 18 hours. The mixture was allowed to cool to room temperature and then quenched with ice-cold water. The product was extracted into chloroform and the combined chloroform extracts were dried ( $MgSO_4$ ), filtered and evaporated under reduced pressure. The residue was purified by column chromatography (1:4 ethyl acetate-hexane, v/v) and recrystallized to afford **64a** as solid (0.26 g, 53%) m.p (153-155°C);  $^1H$ NMR (300MHz,  $CDCl_3$ ) 4.10 (3H, s,  $OCH_3$ ), 7.44-7.52 (3H, m, 2'-H, 3'-H and 4'-H), 7.56-7.63 (3H, m, 6-H, 6'-H and 7-H), 7.75 (1H, t,  $J$  1.5 and 7.7 Hz, 5'-H), 8.10 (2H, t,  $J$  9.0 Hz, 8-H and 5-H);  $^{13}C$  NMR (75MHz,  $CDCl_3$ ) 62.0 ( $OCH_3$ ), 88.0 (C-3), 121.9 (C-4a), 122.7 (C-3',5'), 127.0 (C-6), 127.9 (C-8), 129.0 (C-5), 129.6 (C-7), 130.5 (C-2',6'), 142.6 (C-1'), 149.1 (C-8a), 163.1 (C-2), 165.0 (C-4);  $\nu_{\max}/\text{cm}^{-1}$  763.6, 894.0, 979.9, 1072.0, 1360.8, 1485.0, 1565.9; MS (EI)  $m/z$  361 ( $M^+$ , 100), 331 (30), 204 (35), 190 (20); HRMS (EI)

calculated for C<sub>16</sub>H<sub>12</sub>INO: 360.9964. Found: 360.9964. *Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>INO: C, 53.15; H, 3.32; N, 3.87. Found: C, 52.87; H, 3.29; N, 3.57.

#### 4.6.2 Preparation of 2-(4'-fluorophenyl)-3-iodo-4-methoxyquinoline **64b**

The experimental procedure employed for the synthesis of **64a** was followed using a mixture of 4-chloro-2-(4-fluorophenyl)-3-iodoquinoline **63b** (0.50 g, 1.30 mmol) and sodium methoxide solution (0.5M solution in methanol, 0.15 g, 2.86 mmol, 5.70 ml) in THF (6.50 ml). Work up afforded **64b** as solid (0.35 g, 70%), mp 140-142°C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 4.10 (3H, s, OCH<sub>3</sub>), 7.17 (2H, t, *J* 8.9 Hz, 3'-H and 5'-H), 7.55-7.65 (3H, m, 6-H, 7-H and 8-H), 7.76 (1H, dt, *J* 1.2 and 7.8 Hz, 2'-H), 8.09-8.14 (2H, m, 6'-H and 5-H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 62.0 (OCH<sub>3</sub>), 87.8 (C-3), 114.7 (C-4a), 115.0 (d, <sup>2</sup>*J*<sub>CF</sub> 21.6 Hz, C-3' and 5'), 121.9 (C-5), 122.7 (C-6), 127.1 (C-8), 129.5 (C-7), 131.0 (d, <sup>3</sup>*J*<sub>CF</sub> 8.5 Hz, C-2' and C-6'), 138.6 (d, <sup>4</sup>*J*<sub>CF</sub> 3.4 Hz, C-1'), 149.0 (C-8a), 161.3 (C-2), 161.6 (d, <sup>1</sup>*J*<sub>CF</sub> 246.8 Hz, C-4'), 164.7 (C-4); *v*<sub>max</sub>/ cm<sup>-1</sup> 767.7, 831.3, 981.6, 1075.3, 1217.6, 1363.7, 1487.5, 1508.6, 1570.1, 1599.0; MS (EI) *m/z* 379 (M<sup>+</sup>, 100), 349 (26), 222 (31), 208 (21); HRMS (EI) calculated for C<sub>16</sub>H<sub>11</sub>FINO: 378.9866. Found: 378.9869. *Anal.* Calcd. for C<sub>16</sub>H<sub>11</sub>FINO: C, 50.66; H, 2.90; N, 3.69. Found: C, 50.00; H, 2.40; N, 3.52.

#### 4.6.3 Preparation of 2-(4'-chlorophenyl)-3-iodo-4-methoxyquinoline **64c**

The experimental procedure employed for the synthesis of **64a** was followed using a mixture of 4-chloro-2-(4-chlorophenyl)-3-iodoquinoline **63c** (0.50 g, 1.25 mmol) and sodium methoxide solution (0.5M solution in methanol; 0.15 g, 2.75 mmol, 5.50 ml) in THF (6.25 ml). Work up afforded **64c** as solid (0.38 g, 78%) m.p 178-180°C; <sup>1</sup>HNMR (300MHz, CDCl<sub>3</sub>) 4.10 (3H, s, OCH<sub>3</sub>), 7.46 (2H, d, *J* 7.8 Hz, 3'-H and 5'-H), 7.58 (2H, d, *J* 7.8 Hz, 6-H, 7-H and 2'-H), 7.76 (1H, dt, *J* 1.2 and 7.8 Hz, 6'-H), 8.09-8.13 (2H, m, 8-H and 5-H); <sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>) 62.0 (OCH<sub>3</sub>), 87.4 (C-3), 121.9 (C-4a), 122.8 (C-2', 6'), 127.2 (C-6), 128.1 (C-8), 129.6 (C-5), 130.7 (C-7), 130.8 (C-2',6'), 134.8 (C-4'), 141.0 (C-1'), 149.0 (C-8a), 161.8 (C-2), 164.9 (C-4),  $\nu_{\max}/\text{cm}^{-1}$  756.6, 823.7, 1089.8, 1341.3, 1533.7, 1556.9; MS (EI) *m/z* 395 (M<sup>+</sup>, 100), 379 (28), 366 (31), 190 (21); HRMS (EI) calculated for C<sub>16</sub>H<sub>11</sub>ClINO: 394.9596. Found: 394.9574. *Anal.* Calcd. for C<sub>16</sub>H<sub>11</sub>ClINO: C, 48.53; H, 2.78; N, 3.54. Found: C, 48.63; H, 2.79; N, 2.33

#### 4.6.4 Preparation of 3-iodo-4-methoxy-2-(4'-methoxyphenyl)quinoline **64d**

##### **64d**

The experimental procedure employed for the synthesis of **64a** was followed using a mixture of 4-chloro-3-iodo-2-(4-methoxyphenyl)quinoline **63d** (0.50 g, 1.27 mmol) and sodium methoxide solution (0.5M solution in methanol, 0.15 g, 2.79 mmol, 5.60 ml) in THF (6.35 ml). Work up afforded **64d** as solid (0.30 g, 60%) m.p 167-170°C <sup>1</sup>HNMR (300MHz, CDCl<sub>3</sub>) 3.88 (3H, s, 4'-OCH<sub>3</sub>), 4.09 (3H, s, 4-OCH<sub>3</sub>), 7.00 (2H, d,

*J* 8.7 Hz, 3'-H and 5'-H), 7.53-7.62 (3H, m, 2'-H, 6'-H and 7-H), 7.74 (1H, dt, *J* 1.2 and 7.5 Hz, 6-H), 8.07-8.14 (2H, m, 5-H and 8-H); <sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>): 55.4 (OCH<sub>3</sub>), 62.0 (OCH<sub>3</sub>), 88.3 (C-3), 113.2 (C-8), 121.9 (C-4a), 122.5 (C-3',5'), 126.8 (C-6), 128.1 (C-8), 129.6 (C-5), 130.7 (C-7), 130.8 (C-2',6'), 135.1 (C-4'), 149.0 (C-1'), 159.9 (C-8a), 162.6 (C-2), 164.7 (C-4);  $\nu_{\text{max}}$ / cm<sup>-1</sup> 767.7, 827.9, 1242.2, 1361.7, 1510.3, 1568.6, 1606.7; MS (EI) *m/z* 391 (M<sup>+</sup>, 100), 361 (25); HRMS (EI) calculated for C<sub>17</sub>H<sub>14</sub>INO<sub>2</sub>: 391.0069. Found: 391.0086. *Anal.* Calcd. for C<sub>17</sub>H<sub>14</sub>INO<sub>2</sub>: C, 52.15; H, 3.58; N, 3.58. Found: C, 51.74; H, 3.45; N, 3.00.

#### 4.7 Preparation of 4-chloro-2,3-diaryl-4-chloroquinoline derivatives **65**

##### 4.7.1 Preparation of 4-chloro-2,3-diphenylquinoline **65a**

The 4-chloro-2,3-diphenylquinoline **65a** was obtained by combining a mixture of **63a** (0.65 g, 1.78 mmol), phenyl boronic acid (0.26 g, 2.14 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.10 g, 0.09 mmol, 5% mmol) in a two necked flask equipped with a stirrer bar, rubber septum and a condenser was degassed with argon for 10 minutes. The two-necked flask was filled with DMF (8.90 ml) and aqueous 2M Na<sub>2</sub>CO<sub>3</sub> (3.56 ml) using a syringe and was further degassed with argon for 10 minutes. The mixture was refluxed at 80-90 under argon atmosphere for 48 hours. The mixture was allowed to cool and then quenched with ice-cold H<sub>2</sub>O. The resulting product was extracted into chloroform and the combined organic phase were washed with brine, dried over anhydrous Mg<sub>2</sub>SO<sub>4</sub> and then evaporated under reduced pressure. The residue was purified by column chromatography (10:1 hexane-EtOAc) to afford the 2,3-diaryl-4-

chloroquinoline **65a** as solid (0.27 g, 48%), mp 116-118°C (ethanol)  $^1\text{H}$  NMR (300MHz, DMSO- $d_6$ ) 7.17-7.24 (5H, m, 2''-H, 3''-H, 4''-H, 5''-H and 6''-H), 7.29-7.34 (5H, m, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H), 7.67 (1H, dt,  $J$  1.2 and 7.8 Hz, 7-H), 7.80 (1H, dt,  $J$  1.2 and 7.8, 6-H), 8.21 (2H, d,  $J$  0.6 and 8.4 Hz, 5-H and 8-H);  $^{13}\text{C}$  NMR (75MHz, DMSO- $d_6$ ) 124.6 (C-8), 125.4 (C-4a), 127.6 (C-4''), 127.7 (C-2'', 6''), 127.9 (C-3), 127.9 (C-1''), 128.0 (C-3'', 5''), 129.0 (C-6), 129.7 (C-2', 6'), 130.3 (C-5), 130.7 (C-3', 5'), 133.0 (C-4'), 137.0 (C-7), 140.2 (C-1') 141.9 (C-4), 147.6 (C-8a), 159.2 (C-2);  $\nu_{\text{max}}/\text{cm}^{-1}$  757, 848, 986, 1028, 1076, 1333, 1474, 1549, 3056; MS (EI)  $m/z$  345 ( $\text{M}^+$ , 70), 344 (100); HRMS (EI) calculated for  $\text{C}_{21}\text{H}_{14}\text{ClN}$ : 315.1294. Found: 315.1294. *Anal.* Calcd. for  $\text{C}_{21}\text{H}_{14}\text{ClN}$ : C, 79.80; H, 4.43; N, 4.43. Found: C, 73.54; H, 4.45; N, 3.16

#### 4.7.2 Preparation of 4-chloro-2-(4'-fluorophenyl)-3-arylquinoline **65b**

The experimental procedure employed for the synthesis of **65a** was followed using a mixture of 3-iodo-4-chloro-2-(4-fluorophenyl)quinoline **63b** (0.65 g, 1.69 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (0.10 g, 0.08 mmol), 2M sodium carbonate (3.38 ml) and phenylboronic acid (0.25 g, 2.03 mmol) in DMF (8.45 ml). Work up afforded **65b** as solid (0.31 g, 54%), mp 120-122°C (ethanol)  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 6.90 (2H,  $J$  8.7Hz, 2''-H and 6''-H), 7.19 (2H, m, 3''-H and 5''-H), 7.28-7.35 (5H, m, 4''-H, 2'-H, 3'-H, 5'-H and 6'-H), 7.68 (1H, dt,  $J$  1.2 and 7.8 Hz, 7-H), 7.80 (1H, dt,  $J$  1.2 and 7.8 Hz, 6-H), 8.19 (1H, d,  $J$  8.4 Hz, 8-H), 8.32 (1H, d,  $J$  7.8 Hz, 5-H);  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ ) 114.7 (d,  $^2J_{\text{CF}}$  21.6 Hz, C-3', 5'), 124.7 (C-8), 125.4 (C-4a), 127.7 (C-4''), 127.8 (C-1''), 127.8 (C-3), 127.8 (C-2'', 6''), 128.1 (C-3'', 5''), 129.8 (d,  $^3J_{\text{CF}}$  8.3Hz, C-2', 6'), 130.2 (C-5), 130.4 (C-6), 136.9 (C-7), 142.0 (d,  $^4J_{\text{CF}}$  2.9 Hz, C-1'), 147.5 (C-4), 158.0

(C-8a), 160.9 (C-2), 164.1 (d,  $^1J_{\text{CF}}$  246.8 Hz, C-4');  $\nu_{\text{max}}/\text{cm}^{-1}$  757, 848, 1219, 1342, 1506, 1597, 3059; MS (EI)  $m/z$  333 ( $\text{M}^+$ , 2), 314 (100); HRMS (EI) calculated for  $\text{C}_{21}\text{H}_{13}\text{ClFN}$ : 333.0721. Found: 333.0694. *Anal.* Calcd. for  $\text{C}_{21}\text{H}_{13}\text{ClFN}$ : C, 75.50; H, 3.89; N, 4.19. Found: C, 73.55; H, 3.35; N, 3.83

#### 4.7.3 Preparation of 4-chloro-2-(4'-chlorophenyl)-3-phenylquinoline **65c**

The experimental procedure employed for the synthesis of **65a** was followed using a mixture of 3-iodo-4-chloro-2-(4'-chlorophenyl)quinoline **63c** (0.65 g, 0.25 mmol), Pd ( $\text{PPh}_3$ )<sub>4</sub> (0.10 g, 0.08 mmol %), 2M sodium carbonate (3.38 ml) and phenylboronic acid (0.25 g, 2.03 mmol) in DMF (8.45 ml). Work up afforded **65c** as solid (0.24 g, 42%), m.p 145-148°C (ethanol);  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 7.16-7.21 (4H,m, 2''-H, 3''-H, 5''-H and 6''-H), 7.26-7.29 (2H, m, 2'-H and 6'-H), 7.31-7.37 (3H, m, 3'-H, 4''-H and 5'-H), 7.68 (1H, dt,  $J$  1.2 and 7.8 Hz, 7-H), 7.80 (1H, dt,  $J$  1.5 and 7.8 Hz, 6-H), 8.19 (1H, dd,  $J$  0.9 and 8.7 Hz, 8-H), 8.32 (1H, dd,  $J$  1.2 and 8.4 Hz, 5-H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 124.7 (C-8), 125.5 (C-4a), 127.9 (C-1''), 127.9 (C-3), 127.9 (C-2',6'), 128.2 (C-3',5'), 129.8 (C-6), 130.4 (C-5), 130.6 (C-3'',5''), 131.1 (C-2'',6''), 132.7 (C-4''), 132.8 (C-1'), 134.2 (C-4'), 136.8 (C-7), 138.6 (C-4), 142.1 (C-1'), 147.6 (C-8a), 157.8 (C-2);  $\nu_{\text{max}}/\text{cm}^{-1}$  754, 826, 1086, 1339, 1550, 3063; MS (EI)  $m/z$  349 ( $\text{M}^+$ , 84); HRMS (EI) calculated for  $\text{C}_{21}\text{H}_{13}\text{Cl}_2\text{N}$ : 349.0425. Found: 349.0426. *Anal.* Calcd. for  $\text{C}_{21}\text{H}_{13}\text{Cl}_2\text{N}$ : C, 71.95; H, 3.71; N, 3.99. Found: C, 76.49; H, 4.74; N, 3.45.

#### 4.7.4 Preparation of 4-chloro-2-(4'-methoxyphenyl)-3-phenylquinoline

##### 65d

The experimental procedure employed for the synthesis of **65a** was followed using a mixture of 3-iodo-4-chloro-2-(4'-methoxyphenyl)quinoline **63d** (0.65 g, 1.65 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.10 g, 0.08 mmol), 2M sodium carbonate (3.30 ml) and phenylboronic acid (0.24 g, 1.98 mmol) in DMF (8.25 ml). Work up afforded **65d** as solid (0.27 g, 47%) m.p 110-112°C (ethanol); <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 3.76 (3H, s, 4'-OCH<sub>3</sub>), 6.73 (2H, d, *J* 9.0 Hz, 2''-H and 6''-H), 7.19-7.23 (2H, m, 3''-H and 5''-H), 7.26-7.34 (5H, m, 4''-H, 2'-H, 6'-H, 3'-H and 5'-H), 7.64 (1H, dt, *J* 1.2 and 7.8 Hz, 7-H), 7.78 (1H, dt, *J* 1.2 and 7.8 Hz, 6-H), 8.19 (1H, dd, *J* 0.6 and 8.7 Hz, 8-H), 8.30 (1H, dd, *J* 0.6 and 8.4 Hz, 5-H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 55.1 (OCH<sub>3</sub>), 113.1 (C-3',5'), 124.6 (C-8), 125.2 (C-4a), 127.3 (C-2'',6''), 127.6 (C-3), 128.1 (C-6), 129.7 (C-5), 130.2 (C-2',6'), 130.7 (C-7), 131.2 (C-4''), 132.8 (C-1''), 137.3 (C-1'), 141.8 (C-4), 147.6 (C-8a), 158.6 (C-4'), 159.4 (C-2);  $\nu_{\max}/\text{cm}^{-1}$  746, 833, 1027, 1176, 1242, 1513, 1605, 3063; MS (EI) *m/z* 344 (M<sup>+</sup>, 100); HRMS (EI) calculated for C<sub>22</sub>H<sub>16</sub>ClNO: 345.0842. Found: 344.0797. *Anal.* Calcd. for C<sub>22</sub>H<sub>16</sub>ClNO: C, 76.49; H, 4.74; N, 3.45. Found: C, 76.49; H, 4.74; N, 3.45.

#### 4.8. A Preparation of 2,3-aryl-4-methoxyquinoline derivatives 66

##### 4.8.1 Preparation of 4-methoxy-2,3-diphenylquinoline 66a

A mixture of 4-chloro-2,3-diphenylquinoline **65a** (0.50 g, 1.58 mmol) and sodium methoxide (0.5M in MeOH, 2.38 mmol, 4.8ml) in DMF (10ml) was heated under

reflux for 18 hours. The mixture was allowed to cool and quenched with ice-cold water. The product was extracted into chloroform and the combined organic phases were washed with brine, dried (MgSO<sub>4</sub>), filtered and then evaporated under reduced pressure. The residue was purified by column chromatography (3:2 hexane:ethyl acetate, v/v) to afford the 4-methoxy-2,3-diphenylquinoline **66a** as solid (0.27 g, 55 %), mp 132-134°C (ethanol); <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>), 3.54 (3H, s, OCH<sub>3</sub>), 7.20-7.35 (10H, m, 2''-H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H, 3''-H, 4''-H, 5''-H, and 6''-H), 7.57 (1H, t, *J* 1.5 and 7.5 Hz, 7-H), 7.74 (1H, t, *J* 1.5 and 7.8 Hz, 6-H), 8.17-8.22 (2H, m, 8-H and 5-H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 61.3 (OCH<sub>3</sub>), 122.3, 122.8 (C-6), 125.3 (C-5), 126.3 (C-4a), 127.4 (C-4''), 127.9 (C-3'', 5''), 128.2 (C-3', 5'), 129.5 (C-8), 130.0 (C-4'), 130.9 (C-2'', 6''), 131.2 (C-2', 6'), 133.8 (C-7), 135.1 (C-1''), 142.6 (C-1'), 149.0 (C-8a), 159.2 (C-2), 161.5 (C-4);  $\nu_{\text{max}}$ / cm<sup>-1</sup> 760, 876, 984, 1065, 1360, 1483, 1575, 3059. *Anal.* Calcd. for C<sub>22</sub>H<sub>17</sub>NO: C, 84.78; H, 5.46; N, 4.50. Found: C, 83.50; H, 5.65; N, 4.13.

#### 4.8.2 Preparation of 2-(4'-fluorophenyl)-4-methoxy-3-phenylquinoline **66b**

The experimental procedure employed for the synthesis of **66a** was followed using a mixture of 4-chloro-2-(4'-fluorophenyl)-3-phenylquinoline **65b** (0.45 g, 1.36 mmol) and sodium methoxide (0.5M in MeOH, 2.04 mmol, 4.1ml) in DMF (10 ml). Work up afforded **66b** as solid (0.26 g, 58%), m.p 123-125°C (ethanol); <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 3.54 (3H, s, OCH<sub>3</sub>), 6.90 (2H, t, *J* 8.7 Hz, 2''-H and 6''-H), 7.19-7.33 (7H, m, 2'-H, 3'-H, 5'-H, 6'-H, 3''-H, 4''-H and 5''-H), 7.58 (1H, dt, *J* 1.2 and 7.7 Hz, 7-H), 7.75 (1H, dt, *J* 1.2 and 7.8 Hz, 6-H), 8.17 (1H, d, *J* 8.4 Hz, 8-H), 8.19 (1H, dd, *J* 1.2 and 8.3 Hz, 5-H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 61.2 (OCH<sub>3</sub>), 114.6 (d, <sup>2</sup>*J*<sub>CF</sub> 21.6 Hz,



C-3',5'), 122.7 (C-6), 124.7 (C-3), 125.3 (C-5), 126.4 (C-4a), 127.3 (C-4''), 127.8 (C-3'',5''), 129.5 (C-8), 130.6 (C-2'',6''), 131.0 (d,  $^3J_{\text{CF}}$  8.3Hz, C-2',C-6'), 131.6 (C-7), 135.3 (C-1''), 136.6 (d,  $^4J_{\text{CF}}$  2.9 Hz, C-1') 148.7 (C-8a), 159.2 (C-2), 161.1 (C-4), 164.0 (C-4', d,  $^1J_{\text{CF}}$  245.8 Hz);  $\nu_{\text{max}}/\text{cm}^{-1}$  765, 891, 988, 1069, 1394, 1474, 1594, 3057. *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{16}\text{NOF}$ : C, 80.23; H, 4.90; N, 4.25. Found: C, 80.37; H, 4.77; N, 4.34.

#### 4.8.3 Preparation of 2-(4-chlorophenyl)-4-methoxy-3-phenylquinoline 66c

The experimental procedure employed for the synthesis of **66a** was followed using a mixture of 4-chloro-2-(4'-chlorophenyl)-3-phenylquinoline **65c** (0.50 g, 1.42 mmol) and sodium methoxide (0.5M in MeOH, 2.14mmol, 4.3ml) in DMF (10 ml). Work up afforded **66c** as solid (0.29 g, 60%), m.p 133-135°C (EtOH);  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 3.54 (3H, s,  $\text{OCH}_3$ ), 7.16-7.34 (9H, m, 2'-H, 6'-H, 3'-H, 5'-H, 2''-H, 3''-H, 4''-H, 5''-H and 6''-H), 7.58 (1H, dt,  $J$  1.2 and 7.8 Hz, 7-H), 7.74 (1H, dt,  $J$  1.5 and 7.8 Hz, 6-H), 8.16 (1H, dd,  $J$  0.9 and 8.2 Hz, 8-H), 8.18 (1H,  $J$  0.9 and 8.4 Hz, 5-H);  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ ) 61.3 ( $\text{OCH}_3$ ), 122.3 (C-3), 122.8 (C-6), 125.2 (C-5), 126.5 (C-4a), 127.4 (C-4''), 127.9 (C-3'',5''), 128.2 (C-3',5'), 129.5 (C-8), 130.0 (C-4'), 130.9 (C-2'',6'') 131.2 (C-2',6'), 133.9 (C-7), 135.1 (C-1''), 138.9 (C-1'), 148.7 (C-8a), 159.1 (C-2), 161.5 (C-4);  $\nu_{\text{max}}/\text{cm}^{-1}$  758, 876, 986, 1065, 1360, 1486, 1563, 3057; MS (EI)  $m/z$  346 ( $\text{M}^+$ , 50), 345 (72), 344 (100); HRMS (EI) calculated for  $\text{C}_{22}\text{H}_{16}\text{NO}^{35}\text{Cl}$ : 345.9955. Found: 346.0004. *Anal* Calcd. for  $\text{C}_{22}\text{H}_{16}\text{NO}^{35}\text{Cl}$ : C, 76.41; H, 4.66; N, 4.05. Found: C, 76.32; H, 4.56; N, 4.01.

#### 4.8.4 Preparation of 4'-methoxy-2-(4'-methoxyphenyl)-3-phenylquinoline

##### 66d

The experimental procedure employed for the synthesis of **66a** was followed using a mixture of 4-chloro-2-(4'-methoxyphenyl)-3-phenylquinoline **65d** (0.45 g, 1.30 mmol) and sodium methoxide (0.5M in MeOH, 1.95 mmol, 3.9 ml) in DMF (10 ml). Work up afforded **66c** as solid (0.29 g, 65%), mp 135-137°C (ethanol); <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): 3.53 (3H, s, 4-OCH<sub>3</sub>), 3.77 (3H, s, 4'-OCH<sub>3</sub>), 6.74-6.76 (2H, d, *J* 9.0 Hz, 2''-H and 6''-H), 7.24-7.33 (7H, m, 2'-H, 3'-H, 5'-H, 6'-H, 3''-H, 4''-H and 5''-H), 7.53-7.58 (1H, m, 7-H), 7.70-7.76 (1H, dt, *J* 1.5 and 7.8 Hz, 6-H), 8.16-8.18 (2H, m, 8-H and 5-H) <sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>): 55.1 (OCH<sub>3</sub>), 61.2 (OCH<sub>3</sub>), 122.2 (C-3), 122.5 (C-6), 125.4 (C-5), 126.1 (C-4a), 127.1 (C-4''), 127.9 (C-3'',5''), 113.1 (C-3',5'), 129.5 (C-8), 130.0 (C-4'), 131.0 (C-2'',6''), 131.0 (C-2',6'), 133.6 (C-7), 135.6 (C-1''), 138.9 (C-1'), 148.8 (C-8a), 159.2 (C-2), 161.2 (C-4);  $\nu_{\max}$ / cm<sup>-1</sup> 758, 882, 986, 1069, 1360, 1485, 1580, 3048; MS (EI) *m/z*; 341 (M<sup>+</sup>, 86), 340 (100), 325 (28), 69 (42), 28 (52). HRMS (EI) calculated for C<sub>23</sub>H<sub>19</sub>NO<sub>2</sub>: 340.1338. Found: 340.1341. *Anal.* Calcd. for C<sub>23</sub>H<sub>19</sub>NO<sub>2</sub>: C, 80.92; H, 5.61; N, 4.10. Found: C, 81.01; H, 5.80; N, 3.97.

#### 4.8.B Alternative route for the preparation of 2,3-aryl-4-methoxyquinoline derivatives 66

##### 4.8.5 Preparation of 4-methoxy-2,3-diphenylquinoline 66a

A mixture of 3-iodo-4-methoxy-2-arylquinoline **64a** (0.50 g, 1.39 mmol), phenyl boronic acid (0.20 g, 1.67 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.08 g, 0.07 mmol) in a two-necked

flask equipped with a stirrer bar, rubber septum and a condenser was flushed with argon for 10 minutes. The flask was filled through a syringe with DMF (10 ml) and aqueous 2M K<sub>2</sub>CO<sub>3</sub> (2.78 ml) and bubbled with argon for 10 minutes. A balloon filled with argon gas was connected to the top of the condenser and the mixture was refluxed at 80-90°C for 18 hours. The mixture was allowed to cool and then quenched with ice-cold water. The product was extracted into chloroform and the combined organic phases were washed with brine, dried (MgSO<sub>4</sub>), filtered and then evaporated under reduced pressure. The residue was purified by column chromatography (15:1 hexane:ethyl acetate, v/v) to afford the 4-methoxy-2,3-diphenylquinoline **66a** as solid (0.36 g, 85 %).

#### 4.8.6 Preparation of 2-(4'-fluorophenyl)-4-methoxy-3-phenylquinoline

##### **66b**

The experimental procedure employed for the synthesis of **66a** was followed using a mixture of 3-iodo-2-(4'-fluorophenyl)-4-methoxyquinoline **64b** (0.50 g, 1.32 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.08 g, 0.07 mmol), sodium carbonate (2.64 ml) and phenylboronic acid (0.19 g, 1.58 mmol) in DMF (10 ml). Work up afforded **66b** as solid (0.34 g, 79%).

#### 4.8.7 Preparation of 2-(4-chlorophenyl)-4-methoxy-3-phenylquinoline **66c**

The experimental procedure employed for the synthesis of **66a** was followed using a mixture of 3-iodo-2-(4'-chlorophenyl)-4-methoxyquinoline **64c** (0.50 g, 1.26 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.07 g, 0.06 mmol), sodium carbonate (2.52 ml.) and phenylboronic acid (0.18 g, 1.51 mmol) in DMF (10 ml). Work up afforded **66c** as solid (0.35 g, 80 %)

#### 4.8.8 Preparation of 4'-methoxy-2-(4'-methoxyphenyl)-3-phenylquinoline

##### 66d

The experimental procedure employed for the synthesis of **66a** was followed using a mixture of 3-iodo-4-methoxy-2-(4'-methoxyphenyl) quinoline **64d** (0.50 g, 1.28 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.07 g, 0.06 mmol), sodium carbonate (2.56 ml.) and phenylboronic acid (0.19 g, 1.54 mmol) in DMF (6.40 ml). Work up afforded **66d** as solid (0.36g, 83 %).

#### 4.9 Preparation of 2,3-diarylquinolin-4(1H)-one derivatives 67

##### 4.9.1 Preparation of 2,3-diphenylquinolin-4(1H)-one 67a

A stirred solution of 4-methoxy-2,3-diphenylquinoline **66a** (0.20 g, 0.64 mmol) in dichloromethane (3.20 ml) at 0°C was treated drop wise with boron tribromide (0.24 g, 0.96 mmol). The mixture was then allowed to warm to room temperature and stirred at this temperature for 24 hours. The mixture was cooled to 0°C and quenched with ice-cold water. The mixture was diluted with dichloromethane and the organic solution was dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The residue was purified by column chromatography to afford **67a** as solid (0.11 g, 58%), mp 342-344°C; <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 7.03-7.16 (5H, m, 2''-H and 6''-H, 3''-H, 5''-H and 4''-H), 7.29-7.36 (6H, m, 2'-H 6'-H, 4'-H, 6-H, 7-H and 8-H), 7.62-7.68 (2H, t, *J* 8.4 Hz, 3'-H and 5'-H), 8.13-8.15 (1H, d, *J* 8.4Hz, 5-H), 11.8 (1H, s, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 118.4 (C-8), 123.1 (C-6), 124.6 (C-1'), 125.3 (C-5),

125.9 (C-4''), 127.2 (C-2'',6''), 128.0 (C-3',5'), 128.9 (C-4'), 129.5 (C-3'',5''), 131.6 (C-8a), 135.1 (C-4a), 135.7 (C-1''), 139.6 (C-2',6'), 148.4 (C-2), 175.4 (C-4);  $\nu_{\max}/\text{cm}^{-1}$  756.0, 1351.0, 1515.0, 1553.0, 1622.0 (C=O), 3100.0; MS (EI)  $m/z$  297 ( $M^+$ , 43), 296 (100), 69 (35), 57 (26), 43 (27), 41 (24), 28 (36). HRMS (EI) calculated for  $C_{21}H_{15}NO$ : 297.12. Found: 296.1052.

#### 4.9.2 Preparation of 2-(4'-fluorophenyl)-3-phenyl-4-quinolone **67b**

The experimental procedure employed for the synthesis of **67a** was followed using a mixture of 2-(4'-fluorophenyl)-4-methoxy-3-phenylquinoline **66b** (0.20 g, 0.61 mmol) and boron tribromide (0.23 g, 0.91 mmol) in dichloromethane (3.05 ml). Work up afforded **67b** as solid (0.10 g, 53%) mp 385-387°C;  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 7.03-7.20 (5H, m, 2''-H, 6''-H, 3'-H, 5''H and 4''H), 7.34-7.39 (6H, m, 2'-H, 6'-H, 4'-H, 6-H, 7-H and 8-H), 7.66-7.68 (2H, d,  $J$  8.4 Hz, 3'-H and 5'-H), 8.12-8.16 (1H, d,  $J$  8.4Hz, 5-H), 11.8 (1H, s, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 115 (d,  $^2J_{\text{CF}}$  21.7 Hz, C-3',5'), 118.4 (C-8), 120.6 (C-3), 123.2 (C-6), 125.3 (C-5), 125.3 (C-4''), 126.0 (C-3'',5''), 131.8 (C-1'), 131.9 (d,  $^3J_{\text{CF}}$  8.6Hz, C-8a), 135.6 (C-1''), 139.6 (d,  $^4J_{\text{CF}}$  3.6Hz, C-2',6'), 147.5 (C-7), 160.5 (C-2), 163.8 (d,  $^1J_{\text{CF}}$  245.0 Hz, C-4') 175.3 (C-4);  $\nu_{\max}/\text{cm}^{-1}$  760.0, 835.0, 1217.0, 1381.0, 1491.0, 1510.0, 1552.0, 1625.0, 2992.0, 3074.0; MS (EI)  $m/z$  315 ( $M^+$ , 70), 314 (100); HRMS (EI) calculated for  $C_{21}H_{14}\text{NOF}$ : 315.1059. Found: 315.1057. *Anal.* Calcd. for  $C_{21}H_{14}\text{NOF}$ : C, 79.99; H, 4.48; N, 4.44. Found: C, 79.63; H, 4.48; N, 4.44.

### 4.9 .3 Preparation of 2-(4'-chlorophenyl)-3-phenyl-4-quinolone 67c

The experimental procedure employed for the synthesis of **67a** was followed using a mixture of 2-(4'-chlorophenyl)-4-methoxy-3-phenylquinoline **66c** (0.20 g, 0.58 mmol) and boron tribromide (0.22 g, 0.87 mmol) in dichloromethane (2.90ml). Work up afforded **67c** as solid (0.12 g, 63%) mp 388-390°C, <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 7.04-7.20 (5H, m, 2''-H and 6''-H and 3''-H, 5''-H, and 4''-H), 7.32-7.41 (6H, m, 2'H, 6'H, 4'H, 6-H, 7-H and 8-H), 7.66-7.67 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 8.13-8.16 (1H, d, *J* 8.4Hz, 5-H), 11.8 (1H, s, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 128.4 (C-8), 130.6 (C-6), 133.3 (C-3), 134.6 (C-5), 136.1 (C-4''), 137.3 (C-2'',6''), 138.1 (C-2',6'), 141.4 (C-3'',5''), 141.7 (C-3',5'), 141.8 (C-7), 143.7(C-4'), 144.0 (C-1'), 145.4 (C-1''), 157.3 (C-8a), 149.6 (C-2), 157.3 (C-4a), 185.3 (C-4); *v*<sub>max</sub>/ cm<sup>-1</sup> 756.0, 826.0, 1213.0, 1383.0, 1485.0, 1515.0, 1552.0, 1622.0, 2991.0, 3064.0; MS (EI) *m/z* 332 (40), 331 (45), 330 (100), 69 (37). *Anal.* Calcd for C<sub>21</sub>H<sub>14</sub>NO<sup>35</sup>Cl: C, 76.02; H, 4.25; N, 4.22. Found: C, 75.96; H, 4.39; N, 4.09.

## References

1. C. Beney, M. Hadjeri, A.M. Mariotte, A. Boumendjel, *Tetrahedron Lett.*, **2000**, 41, 7037-7039.
2. M. Hadjeri, A.M. Mariotte, A. Boumendjel, *Chem. Pharm. Bull.*, **2001**, 49, 1352-1355.
3. M.J. Mphahlele, M.R.C. Mabusela, *S. Afr. J. Chem.*, **1999**, 52, 157-160.
4. G.M. Coppola, *J. Heterocyclic Chem.*, **1982**, 727-731.
5. F. Sondheimer, A. Meisels, *J. Org. Chem.*, **1958**, 23, 762-763.
6. S. Goodwin, A.F. Smith, A.A. Velasquez, E.C. Horning, *J. Am. Chem. Soc.*, **1959**, 81, 6209-6213.
7. J.K. Oyama, I.T. Oyakuni, K.T. Agahara, *Chem. Pharm. Bull.*, **1999**, 47, 1038-1039.
8. J.P. Michael, *Nat. Prod. Rep.*, **2004**, 21, 650-668.
9. J.P. Michael, *J. Nat. Prod. Rep.*, **1997**, 14, 605-618.
10. D.E. Bierer, D.M. Fort, C.D. Mendez, J. Luo, P.A. Imbach, L.G. Dubengo, S.D. Jolad, R.E. Gerber, J. Litvak, Q. Lu, P. Zhang, M.J. Reed, N. Waldeck, R.C. Bruening, B.K. Noamesi, R.F. Hector, T.J. Carlson, S.R. King, *J. Med. Chem.*, **1998**, 41, 894-901.
11. C. Theeraladanon, M. Arisawa, A. Nishida, M. Nakagawa, *Tetrahedron*, **2004**, 60, 3017-3075.
12. H.-J. Zeiler, *Antimicrobial Agents and Chemotherapy*, **1985**, 524-527.
13. D.C. Hopper, J.S. Wolfson in *Mechanism of quinolones action and bacterial killing*, 2nd Ed. 1993, 53-57.
14. I. Novak, *J. Org. Chem.*, **2004**, 69, 5005-5010.

15. F. Palacios, J. Vicario, J.M. de los Santos, D. Aparicio, *Heterocycles.*, **2006**, 70, 261-270.
16. E. Chiari, A.B. Oliveira, M.A.F. Prado, R.J. Alves, L.M.C. Galvao, F.G. Araujo, *Antimicrob. Agents. Chemother.*, **1996**, 40, 613.
17. K. Aggarwal, S.A. Jenekhe, *Macromolecules*, **1991**, 24, 6806.
18. S.A Jenekhe, L. Lu, M.M. Alam, *Macromolecules*, **2001**, 34, 7315.
19. V. R Solomon, W.Haq, K. Srivastava, S K. Puri, , S. B. Katti, *J. Med. Chem.*, **2007**, 50, 394-398.
20. J.A. Donnelly, D.F. Farrell, *J. Org. Chem.*, **1990**, 55, 1757-1761.
21. J.A. Donnelly, D.F.Farrell, *Tetrahedron*, **1990**, 46, 885-894.
22. N. Ahmed, J.E. van Lier, *Tetrahedron Lett.*, **2007**, 48, 13-15.
23. K.H. Kumar, D. Muralidharan, *Synthesis*, **2004**, 1, 63-68.
24. K.H. Kumar, P.T. Perumal, *Can. J. Chem.*, **2006**, 84, 12079-1083.
25. K. Desai, C.M. Desai, *Indian J. Chem.*, **1967**, 5, 170-171.
26. R.C. Fuson, D. M. Burness, *J. Chem.Soc.*, **1946**, 68, 1270-1273.
27. M.J. Mphahlele, A.M. El-Nahas, *J. Mol. Struct.*, **2004**, 688, 129-136.
28. L. Leping, H.-K. Wang, *J. Med. Chem.*, **1994**, 37, 1126-1135.
29. B. Chen, X.H. Huang, J. Wang, *Synthesis*, **1987**, 482-483.
30. O.V Singh, R.S. Kapil, *Synth. Commun.*, **1993**, 23, 3,277-283.
31. D. Ding, X. Li, X. Wang, Y. Du, J. Shen, *Tetrahedron Lett.*, **2006**, 47, 6997-6999.
32. S.C. Shim, S.A. Chae, D.Y. Lee, H.S. Lim, V.N. Kalinin, *J. Chem. Soc.*, **1994**, 38, 774-775.

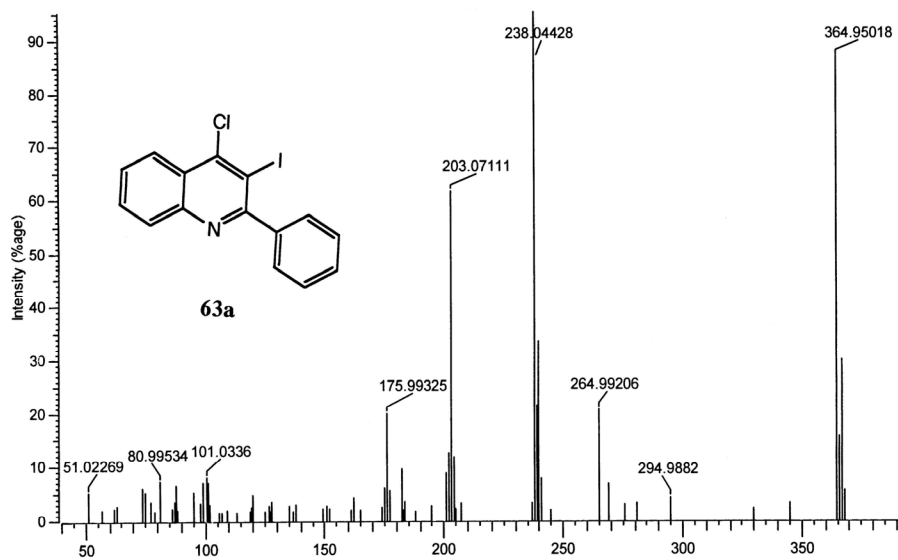


33. S.C. Kuo, H.Z. Lee, J.P. Juang, Y.T. Lin, T.S. Wu, J.J. Chang, D. Lednicer, K.D. Paull, C.M. Lin, E. Hamel, K.H. Lee, *J. Med. Chem.*, **1993**, 36, 1146-1156.
34. T.C. Ko, M.J. Hour, J.C. Lien, C.M. Teng, K.H. Lee, S.C. Kuo, L.J. Huang, *Biorg. Med. Chem. Lett.*, **2001**, 11, 279-282.
35. H. Mohamed, M. Anne-Marie, B. Ahcene, *Chem. Pharm Bull.*, **2001**, 49, 1352-1355.
36. M.J. Mphahlele, *J. Chem. Res. (S)*, **2002**, 196-198.
37. M.J. Mphahlele, M.A. Fernandes, H. Ottosson, A.M. El-Nahas, S.M. Ndlovu, H.M. Sithole, B.S. Dladla, *J. Chem. Soc., Perkin Trans. 2*, **2002**, 2159-2164.
38. M.J. Mphahlele, A.M. El-Nahas, *J. Mol. Struct.*, **2004**, 688, 129-136.
39. R.H.F. Manske, *Chem. Rev.*, **1942**, 30, 113-144.
40. S.A. Yamashkin, E.A. Oreshkina, *Chem. Heterocycl. Compd.*, **2006**, 42, 701-718.
41. J. Wu, H.G. Xia and K. Gao, *Org. Biomol. Chem.*, **2006**, 4, 126-129.
42. F.W. Bergstrom, *Chem. Rev.*, **1944**, 35, 156.
43. M.G.-A. Shvekhgeimer, N.N. Kondrashova, *Chem. Heterocycl. Compd.*, **2002**, 38, 253-254.
44. M.G.-A. Shvekhgeimer, *Chem. Heterocycl. Compd.*, **2004**, 40, 257-294.
45. L. Limpach, *Ber.*, **1931**, 64B, 970-971.
46. O.V. Sing, R.S. Kapil, *Synlett.*, **1992**, 751-752.
47. R.S. Varma, D. Kumar, *Tetrahedron Lett.*, **1998**, 39, 9114-9116.
48. M.J. Mphahlele, F.K. Mogamisi, M. Tsanwani, S.M. Hlatshwayo, R.M. Mampa, *J. Chem. Res.(S)*, **1999**, 706-707.

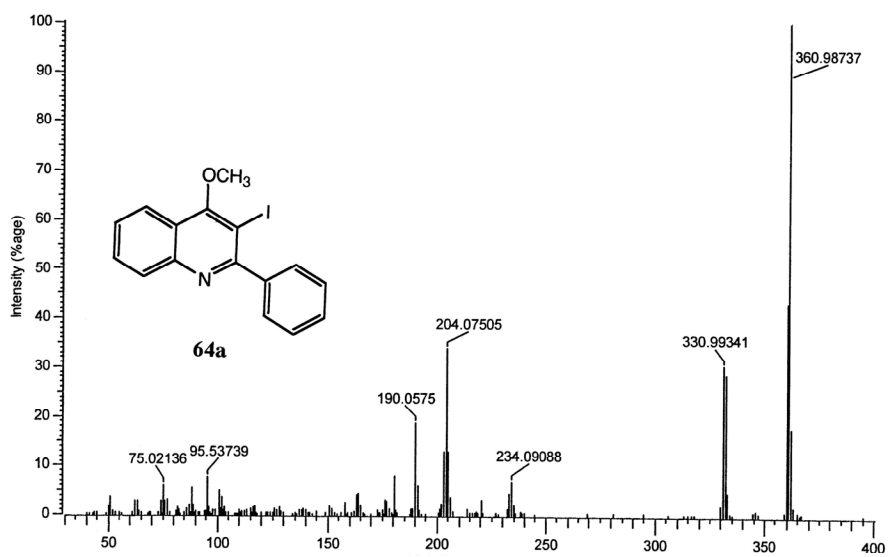
49. K.H. Kumar, D. Muralidharan, P.T. Perumal, *Tetrahedron Lett.*, **2004**, 45, 7903-7906.
50. M.J. Mphahlele, M. Nwamadi, P. Mabeta, *J. Heterocycl. Chem.*, **2006**, 43, 255-260.
51. R.M. Peck, *J. Org. Chem.*, **1963**, 28, 1998-2000.
52. P.C. Anderson, B. Staskun, *J. Org. Chem.*, **1965**, 30, 3033-3037.
53. C. Wolf, R Lerebours, *J. Org. Chem.*, **2003**, 68, 7077-7084.
54. R.A. Mekheir, G.H.M. Elgemeie, T. Kappe, *J. Chem. Res.*, **2005**, 82, 82-85.
55. A. Salzer, *Pure. Appl. Chem.*, **1999**, 71, 1557-1585.
56. S.P. Stanforth, *Tetrahedron*, **1998**, 54, 263-303.
57. D. Alberico, M.E. Scott, M. Lautens, *Chem. Rev.*, **2007**, 107, 174-238.
58. A. Sekiya, N. Ishikawa, *J. Organomet. Chem.*, **1976**, 118-349.
59. V. Vladimir, A. Howard, *Chem. Rev.*, **1994**, 94, 1047-1062.
60. T. Tsuyoshi, N. Mayumi, *J. Org. Chem.*, **2003**, 68, 9412-9415.
61. A.V. Tsvetkov, G.V. Latyshev, N.V. Lukashev, I.P. Beletskaya, *Tetrahedron Lett.*, **2002**, 43, 7267-7270.
62. G.W. Gribble, F.P. Bousquet, *Tetrahedron*, **1971**, 27, 3785-3794.
63. F. McCarpa, P.V. Long, *Tetrahedron Lett.*, **1981**, 22, 3009-3012.
64. L. Li, H.K. Wang, S.C. Kuo, T.C. Wu, D. Lednicer, C.M. Lin, E. Hamel, K.H. Lee, *J. Med. Chem.*, **1994**, 37, 3400-3407.
65. G.C. Fu, A.F. Littke, *Angew. Chem. Int. Ed.*, **2002**, 41, 4176-4211.
66. A.V. Tsvetkov, G.V. Latyshev, N.V. Lukashev, I. P. Beletskaya, *Tetrahedron Lett.*, **2002**, 43, 7267-7270.
67. K. Jones, X Roset, S Rossiter, P. Whitfield, *Org. Biomol. Chem.*, **2003**, 1, 4380-4383.

## APPENDIX

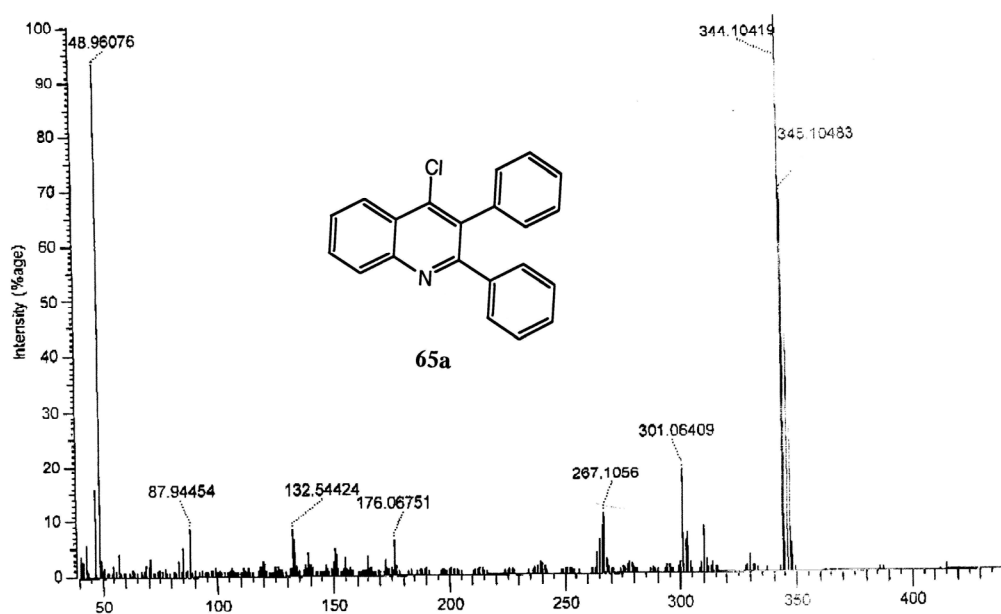
Mass spectra of compounds **63a**, **64a**, **65a**, **66c** and **67a**



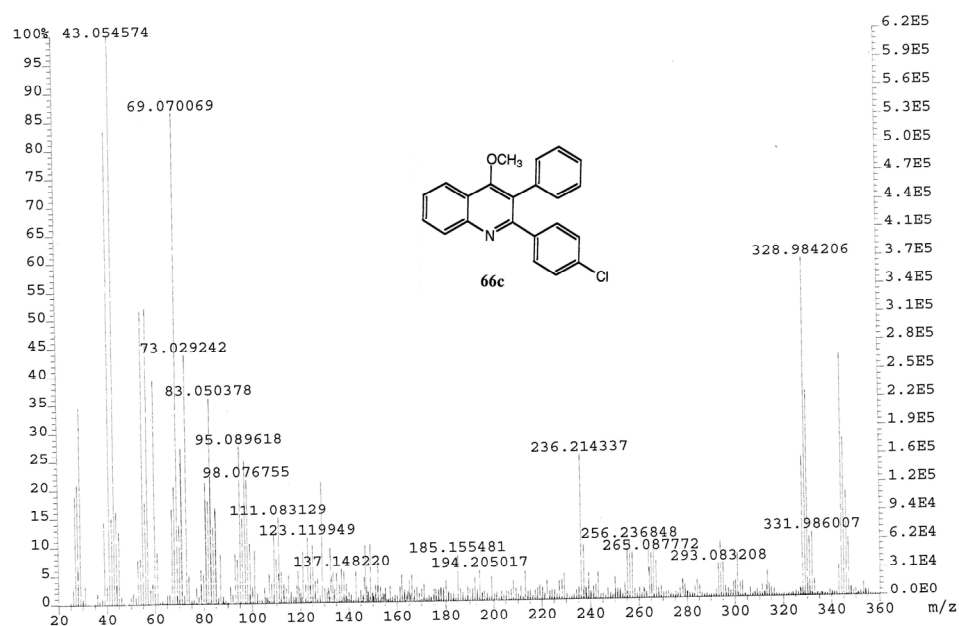
**Figure 13:** Mass spectrum of 4-chloro- 3-iodo-2-phenyl quinoline **63a**



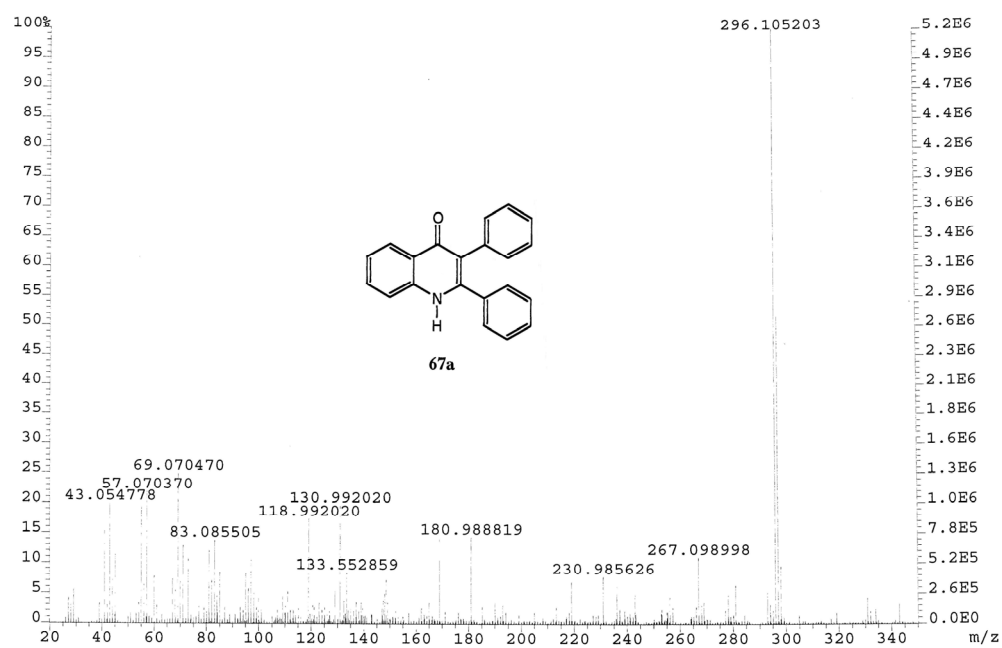
**Figure 14:** Mass spectrum of 3-iodo-4-methoxy-2-phenylquinoline **64a**



**Figure 15:** Mass spectrum of 4-chloro-2,3-diphenylquinoline **65a**



**Figure 16:** Mass spectrum of 2-(4-chlorophenyl)-4-methoxy-3-phenylquinoline **66c**



**Figure 17:** Mass spectrum of 2,3-diphenylquinolin-4-(1*H*)-one **67a**