PALLADIUM-CATALYZED HETEROANNULATION OF 2-ARYL-3-IODO-4-(PHENYLAMINO)QUINOLINES AND 4-(*N*,*N*-ALLYLPHENYLAMINO)-2-ARYL-3-IODOQUINOLINES

by

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DECLARATION

Student number: 3507-196-6

I, Lehlohonolo Godfrey Lesenyeho sincerely and solemnly declare that the work:

PALLADIUM-CATALYZED HETEROANNULATION OF 2-ARYL-3-IODO-4-(PHENYLAMINO)QUINOLINES AND 4-(*N*,*N*-ALLYLPHENYLAMINO)-2-ARYL-3-IODOQUINOLINES is my own work and that all the sources that I have used have been indicated and acknowledged by means of references

……. …….

SIGNATURE DATE

(MR. L. G. LESENYEHO)

This thesis is dedicated to my family, Tumelo, Mpho, Tsebo, Tshepo and Kamohelo.

ACKNOWLEDGEMENTS

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ABSTRACT

The previously described 2-aryl-4-chloro-3-iodoquinolines were prepared following literature procedure and in turn converted to the corresponding hitherto unknown 2-aryl-3-iodo-4-(phenylamino)quinoline derivatives using aniline in refluxing ethanol. These 2-aryl-3-iodo-4-(phenylamino)quinolines were reacted with allybromide in ethanol at room temperature to afford 4-(*N*,*N*-allylphenylamino)-2-aryl-3-iodoquinoline derivatives. The 2-aryl-3-iodo-4-(phenylamino)quinoline and 4-(*N*,*N*-allylphenylamino)-2-aryl-3-iodoquinoline derivatives were subjected to metal-catalysed carbon-carbon bond formations. Palladium(0)-copper iodide catalysed Sonogashira cross-coupling of 2-aryl-3-iodo-4-(phenylamino)quinoline with terminal alkynes afforded series of 1,2,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines in a single step operation. On the other hand, the 4-(*N*,*N*-allylphenylamino)-2-aryl-3-iodoquinoline derivatives were found to undergo palladium-catalysed intramolecular Heck reaction to yield the corresponding 1,3,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines. All new compounds were characterized by using a combination of NMR (^{1}H and ^{13}C), IR, mass spectroscopic techniques as well as elemental analysis.

Keywords: 2-Aryl-3-iodo-4-(phenylamino)quinoline; 4-(*N*,*N*-allylphenylamino)-2-aryl-3-iodoquinolines; Sonogashira cross-coupling reaction; intramolecular Heck reaction; 1*H*-pyrrolo[3,2-*c*]quinolines

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CHAPTER 1: INTRODUCTION

1.1 Background information

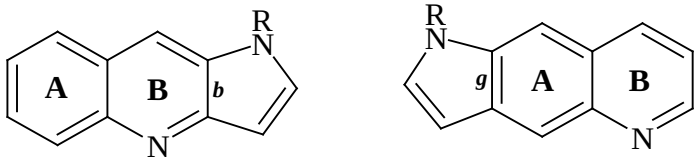
Synthesis of naturally occurring quinoline alkaloids and their analogues have gained a lot of attention in the fields of organic and medicinal chemistry. In search for new therapeutic targets, polynuclear quinolines such as pyrrolo-, furo- and thienoquinolines have become the targets of synthesis because of their broad spectrum of activity against mycobacteria and various parasites. Moreover, hetero-fused quinolines are known to bind to DNA with high affinity, inhibit DNA topoisomerase I, and they also display cytotoxic and antitumor activities[1]. We are currently interested in the synthesis of annulated quinoline derivatives such as pyrroloquinolines. This interest is prompted by the emergence of parasitical and viral strains that are resistant to medicinally important drugs currently in the market.

The challenge in synthesizing the desired polynuclear quinolines such as pyrroloquinolines is that the preformed quinoline moiety must be a suitably functionalized precursor to allow traditional aromatic substitution chemistry, and/or directed metalation methods as well as halogen-metal exchange reactions. Unfortunately, the known classical methods such as Skraup[2], Friedländer[3], Conrad-Limpach[4] and Doebner-von Miller[5] for the synthesis of polysubstituted quinolines bearing alkyl and/ or aryl groups, cannot be adapted for heteroannulation to form polycyclic quinoline derivatives. The most effective methods for the synthesis of pyrroloquinolines involve indirect approach whereby appropriately substituted dihaloquinolines serve as intermediates. Several indirect methods involving dihaloquinolines activated for metal-

catalyzed Csp^2-Csp^2 or Csp^2-Csp bond formation and nucleophilic displacement to form Csp^2-N bonds have been developed for the synthesis of polysubstituted and polynuclear quinolines. In this work, attention is focused on methods that involve nucleophilic displacement of 4-chloro atom from the 2-aryl-4-chloro-3-iodoquinolines by aniline and subsequent metal-catalyzed C-C bond formation to afford pyrroloquinoline derivatives.

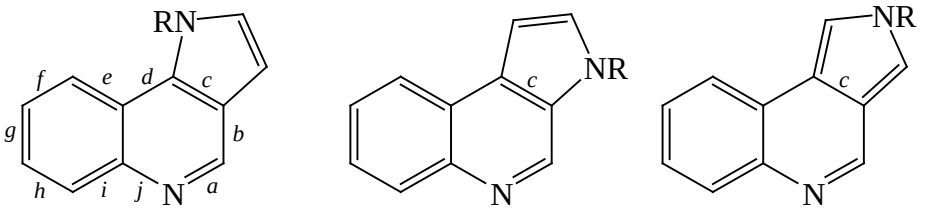
1.2 Description of pyrroloquinoline framework and examples of biologically important derivatives

Quinoline moiety (rings A and B) constitutes the central unit for both polysubstituted quinolines and polynuclear derivatives such as pyrroloquinolines. Pyrroloquinolines are either linear (Fig. 1) or angular tricyclic heterocycles (Fig. 2) with pyrrole and quinoline fragments fused together. A pyrrole ring can be fused to the quinoline framework at different sites on the quinoline ring. Fusion at the *b* (**1**) or *g* (**2**) face of the quinoline moiety gives linear heterocycles, whereas fusion at *a*, *c*, *f* and *h* faces gives angular heterocycles. Other angular isomers include the pyrrole ring attached at the *c* face and fused through C2-C3 of the pyrrole ring to give pyrrolo[2,3-*c*]quinolines **4** and fused through C3-C4 to give pyrrolo[3,4-*c*]quinolines **5** (Fig. 2).



1 **2**

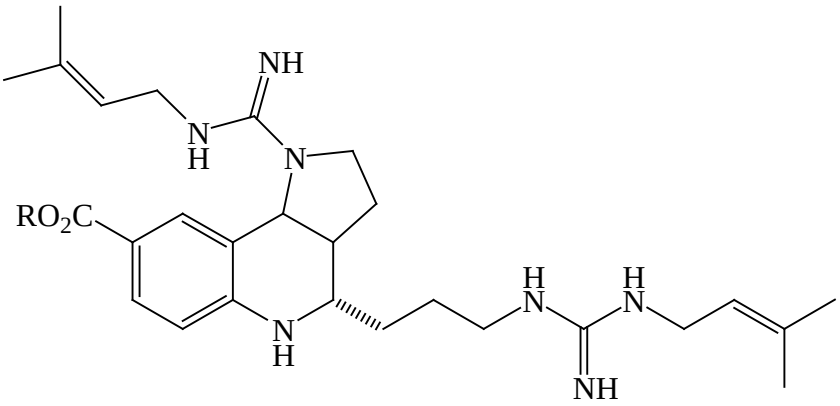
Figure 1: Linear tricylic heterocycles



3 [3,2-*c*] **4** [2,3-*c*] **5** [3,4-*c*]

Figure 2: Angular tricylic heterocycles

In 1995, a group at Merck reported the isolation of two alkaloids from *Martinella iquitosenis*, which they named martinellic acid **6** and martinelline **7** (Fig. 3)[6]. These alkaloids are now known for their biological activity as antagonists of the Bradykinine B_1 and B_2 receptors and for their antibiotic activity against both Gram–positive and Gram–negative bacteria[6,7]. The pyrroloquinolines **6** and **7** were recently isolated from the organic extracts of the roots of a South American plant, *Martinella iquitosenis*[7].



6: Martinellinic acid R = H

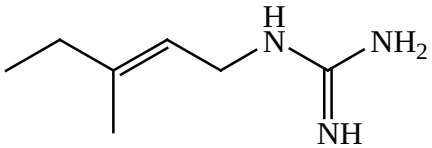
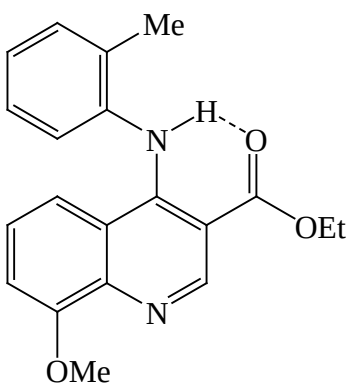
7: Martinelline R = 

Figure 3: Structure of *Martinella iquitosenis*

The focus of this investigation is on the synthesis of angular pyrrolo[3,2-*c*]quinoline derivatives of the generalized structure **3** (Fig. 2) where the pyrrole ring is attached to the *c* face of the quinoline moiety and are fused through C3–C2 of the pyrrole ring. Angular pyrrolo[3,2-*c*]quinoline derivatives were found to possess a wide spectrum of biological activities including antitumor properties[8], gastric (H^+/K^+)–ATPase inhibitor[9], antineoplastic[10] and anti-inflammatory activities[11]. There has been considerable interest in recent years in the gastric (H^+/K^+)–ATPase which is the enzyme responsible for the secretion of acid into the gastric lumen and has thus been viewed as an important target for peptic ulcer therapy[12]. 4-(Arylamino)quinoline **8**, previously described as an antiulcer agent[13] was also found to be a gastric (H^+/K^+)–ATPase inhibitor. Based on the hypothesis that the ester group in 4-(arylamino)quinoline **8** (Fig. 4) is responsible for fixing the conformation of the arylamino group, both by forming a hydrogen bond to the NH and by increasing the conjugation between the nitrogen and the quinoline ring, it is postulated that 1-arylpyrrolo[3,2-*c*]quinolines **9** act as a conformationally restrained analogue of 4-(arylamino)quinoline (Fig. 4)[14]. As a result, Brown *et al.*[12,14] prepared a series of derivatives of 1-arylpyrrolo[3,2-*c*]quinoline derivatives which were found to act as potent inhibitors of the target enzyme in vitro. It has been shown that substitution at the *ortho* position of the aryl ring as well as unsaturation in the 5-membered ring are important for biological activity[12, 14].



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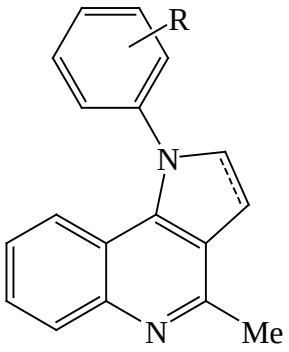

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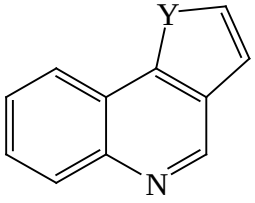
Figure 4: 4-(Arylamino)quinoline and its analogue 1-arylpyrrolo[3,2-*c*]quinoline

1.3 Synthesis and applications of polynuclear analogues

In addition to pyrrolo[3,2-*c*]quinoline derivatives **10** (Y=NR), other heterocyclic analogues such as thieno- (Y=S) and furoquinolines (Y=O) are also described in the literature. Some of these polynuclear derivatives possess interesting biological properties such as antimalarial[15], antiasthmatic[16], antidiabetic[17], antibacterial[18], *in vitro* antifungal[19], antiinflammatory[20], immunosuppressive[21], HIV-1 integrase inhibitory[22], anti-breast cancer[23] and antiproliferative activities[24].



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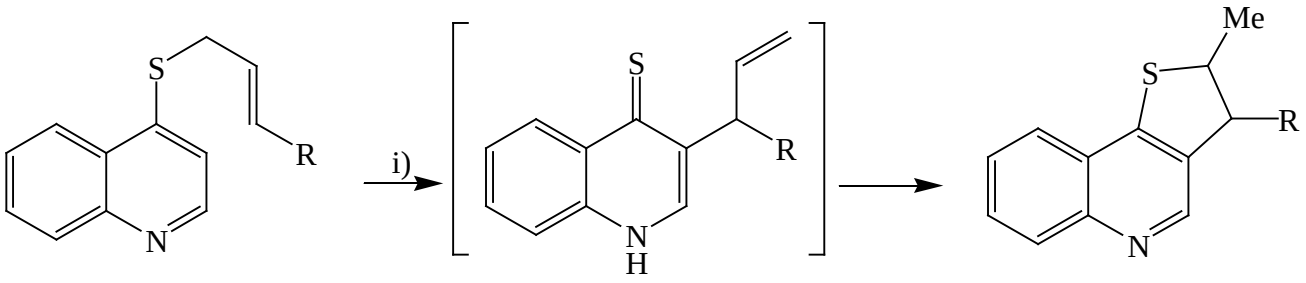
1.3.1 Synthesis and applications of thieno[3,2-*c*]quinoline derivatives (Y=S)

Several thieno[3,2-*c*]quinolines have been found to exhibit antibacterial[18], antifungal[19] and anti-inflammatory activities[20]. These compounds are commonly synthesised by thio-Claisen rearrangement of ally-4-quinolyl sulphides **11**, which is in turn, prepared by alkylation of sodium 4-quinolyl-mercaptide with allyl chloride at room temperature (Scheme 1)[25]. Allyl 4-quinolylsulfide **11** is heated at 200 ºC for 2 hours without solvent or in quinoline to afford 2,3-dihydrothieno[3,2-*c*]quinolines **13** in 85-90% yield. The cyclization reaction proceeds through 3-allyl-4(1*H*)-quinolinethione intermediate **12**.



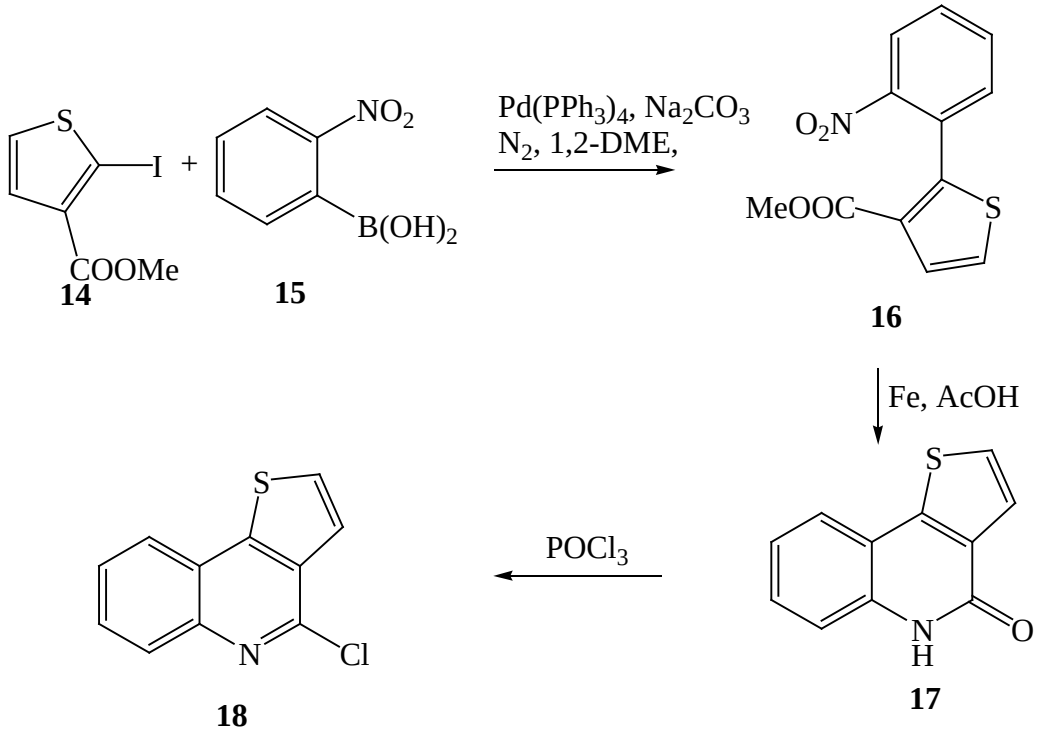
11 (R = H and Alkyl) **12** **13**

Conditions: (i) 200 ºC, 2 h

Scheme 1

Recently, 4-chlorothieno[3,2-*c*]quinoline **18**, prepared as shown in Scheme 2 was used as substrate for the preparation of various chloroquine-type compounds with interesting antimalarial activity against *Plasmodium falciparum*[26]. Methyl 2-iodothiophene-3-carboxylate **14**, used as precursor, was in turn, prepared by treatment of thiophene-3-carboxylic acid with butyllithium at

-78 ºC followed by addition of elemental iodine and subsequent esterification in methanol. The ester **14** was then reacted with 2-nitrophenylboronic acid **15** in the presence of palladium(0)tetrakis(triphenylphosphine) ($Pd(PPh_3)_4$ in dimethylformamide (DMF) to afford methyl 2-(2-nitrophenyl)thiophene-3-carboxylate **16** (Scheme 2). Treatment of **16** with iron in acetic acid afforded a lactam **17**, which was aromatized with phosphoryl chloride ($POCl_3$) to yield 4-chlorothieno[3,2-*c*]quinoline **18**.

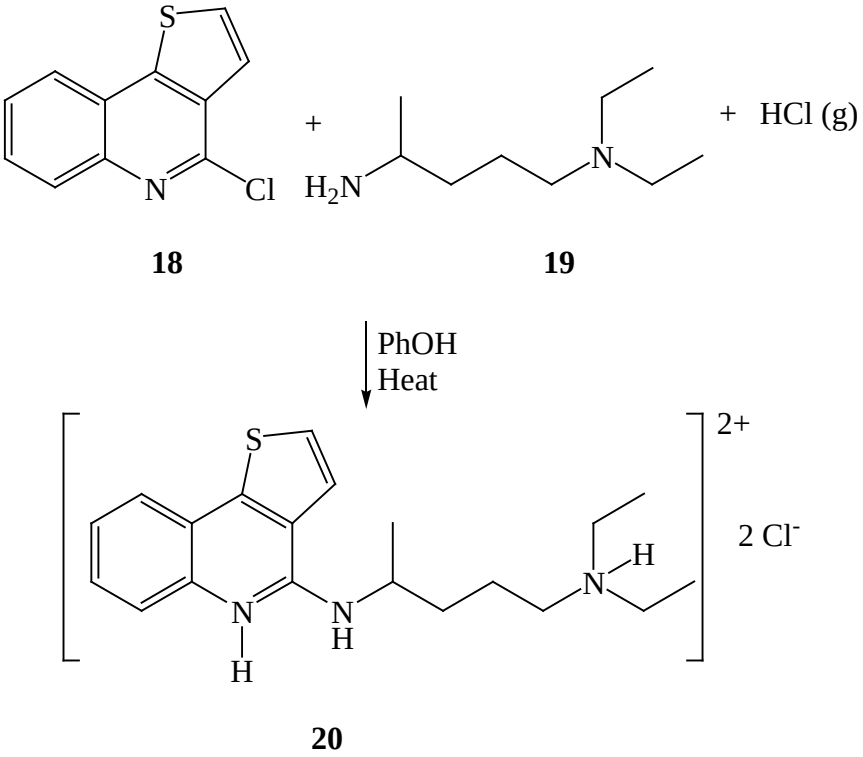


14 **15** **16** **17** **18**

Scheme 2

Thieno[3,2-*c*]quinoline **20,** an analogue of chloroquine, was prepared by treatment of chlorothieno[3,2-*c*]quinoline **18** with *N*,*N*-diethyl-1,4-pentanediamine **19** in phenol under reflux followed by passing gaseous hydrogen chloride through an ethereal solution and was isolated as a dihydrochloride salt **20** (Scheme 3)[26]. The antimalarial activity of compound **20** was tested

against chloroquine sensitive *Plasmodium falciparum* strain 3D7 however, the compound was found to be inactive with IC_{50} value of 8000 µM[27].



18 **19**

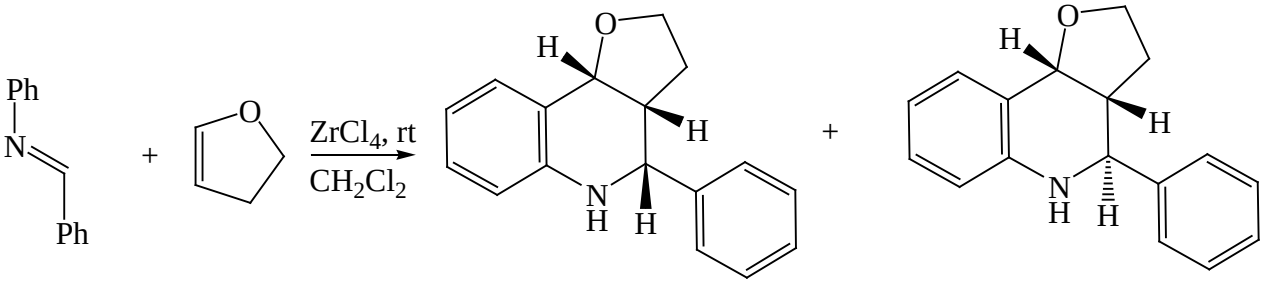
20

Scheme 3

1.3.2 Synthesis and applications of furo[3,2-*c*]quinoline derivatives (Y=O)

Many natural products containing furoquinoline moiety are known to exhibit a wide range of biological activities such as antiasthmatic[16], anti-inflammatory[20] and antiproliferative activities[24]. Among the methods developed to date for the synthesis of furoquinoline derivatives is the Lewis acids catalysed imino Diels-Alder reaction between *N*-benzylideneanilines **21** and nucleophilic olefins **22** (Scheme 4)[28]. The less toxic zirconium tetrachloride ($ZrCl_4$) has been used as catalyst of choice in imino Diels-Alder reaction for the synthesis of furoquinolines. This procedure uses

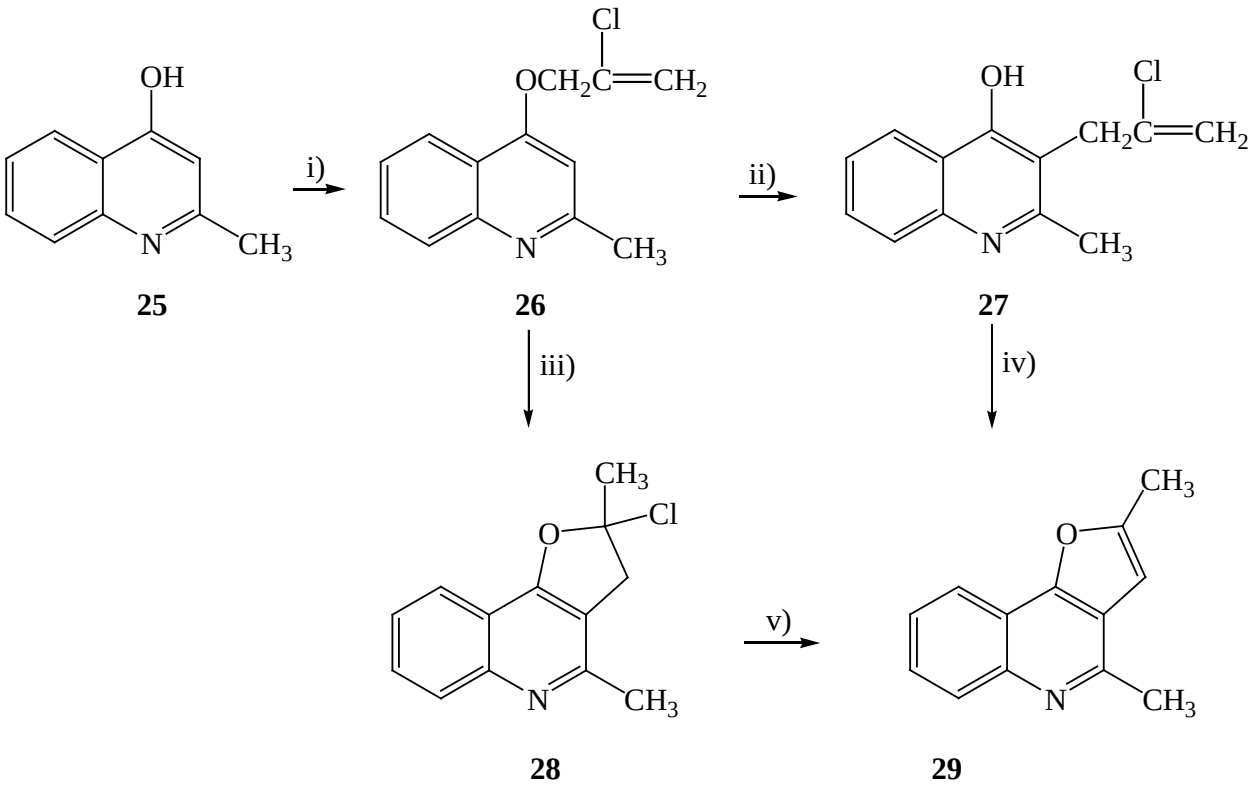
N-benzylideneanilines **21** as dienes and 2,3-dihyrofuran **22** as dienophiles in the presence of $ZrCl_4$ (10%) in dichloromethane to yield a mixture of *endo* **23** and *exo* **24** furo[3,2-*c*]quinolines isomers in 72-97% yield[28]. The use of 2,3-dihyrofuran **22** as dienophile allows for selective synthesis of furo[3,2-*c*]quinolines whereas furan gives a mixture of *endo* and *exo* furo[3,2 -*c*]quinolines and furo[2,3-*c*]quinolines isomers.



21 **22** **23** **24**

Scheme 4

4-Hydroxy-2-methylquinoline **25** was allylated with 2,3-dichloropropene in anhydrous ethanol in the presence of sodium metal to afford 2-methyl-4-(2-chloro-2-propenyloxy)quinoline **26** for synthesis of furo[3,2-*c*]quinoline[29] (Scheme 5). Claisen rearrangement of **26** in boiling ether in the presence of bromobenzene yielded 3-(2-chloro-2-propenyl)-4-hydroxy-2-methylquinoline **27** in 6-7 hours. On heating compound **26** to 180-190 ºC, a small amount (20%) of 2-chloro-2,3-dihydro-2,4-dimethylfuro[3,2-*c*]quinoline **28** was obtained. The latter underwent HCl elimination upon heating in the presence of alcoholic NaOH to afford 2,4-dimethylfuro[3,2-*c*]quinoline **29**. Another route for the synthesis of 2,4-dimethylfuro[3,2-*c*]quinoline **29** involved subjecting compound **27** to sulphuric acid at 25 ºC for 5-6 hours.



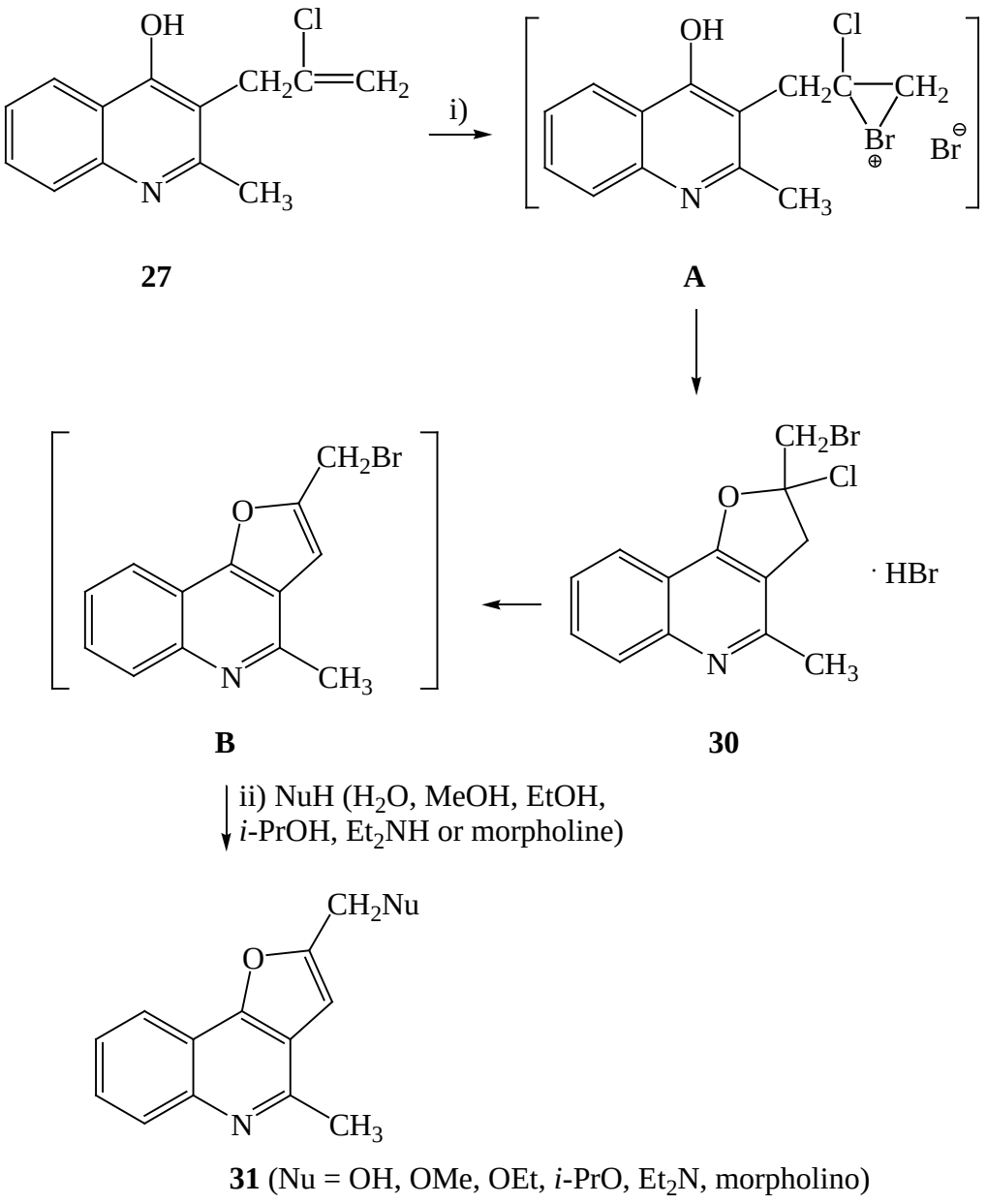
25 **26** **27**

28 **29**

Reagents and conditions: i) CH_3CH_2ONa, $ClCH_2C(Cl)=CH_2$, EtOH, 35-40 ºC, 8-9 h; ii) PhBr, 156 ºC, 6-7 h; iii) Mineral oil, 180-190 ºC, 10 min; iv) conc. H_2SO_4, rt, 5-6 h; v) NaOH, EtOH, reflux, 2 h

Scheme 5

Avetisyan *et al.* [30] later developed a more convenient approach which involves treatment of **27** with a solution of bromine in chloroform at room temperature for 1-2 hours to give 2-bromomethyl-2-chloro-4-methyl-2,3-dihydrofuro[3,2-*c*]quinoline hydrobromide **30** (Scheme 6). The bromomethylfuroquinoline reacted with various nucleophiles to afford the corresponding 2-substituted-4-methylfuro[3,2-*c*]quinoline **31** in 83-98% yield (Scheme 7).

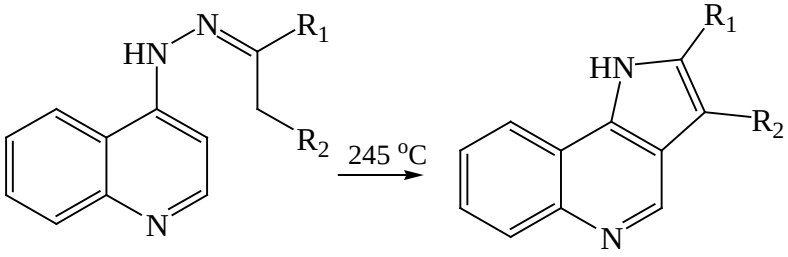


Reagents and conditions: i) 0.5 M Br_2, $CHCl_3$, rt, 1 h; ii) Aqueous-alcoholic solution of alkali for Nu = OH, reflux, 2 h; Sodium alkoxide in corresponding alcohol for Nu = OMe, OEt, i-PrO, reflux, 2 h; Et_2NH, DMF, reflux, 3 h for Nu = Et_2N; morpholine, DMF, pyridine, reflux, 3 h for Nu = morpholino

Scheme 6

1.3.3 Synthesis and applications of pyrrolo[3,2-*c*]quinoline derivatives (Y = NR)

Several methods have been developed for the synthesis of pyrrolo[3,2-*c*]quinoline and these include thermal cyclisation[31,32], Diels–Alder reaction[33], free radical cyclisation[34] and transition metal cyclization[35]. Under thermal cyclisation[31], pyrrolo[3,2-*c*]quinolines **33** were synthesized by refluxing the corresponding 4-quinolylhydrazone **32** in an inert solvent such as ethylene glycol[31] (Scheme 7). However, cyclization of 4-quinolylhydrazone **32** is achieved under acidic conditions and high temperatures leading to decomposition of 4-quinolylhydrazone to 4-aminoquinolines.

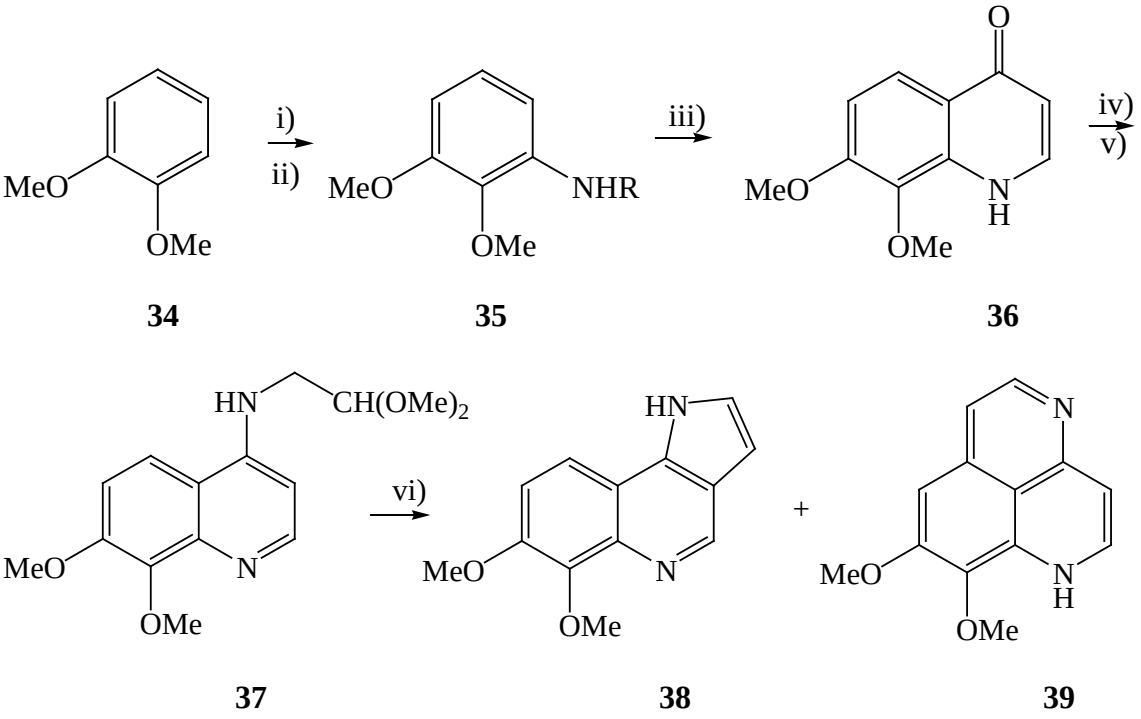


32 **33**

Scheme 7

In another thermal cyclization method, *ortho*-lithiation of 1,2-dimethoxybenzene **34** followed by reaction with trimethylsilylmethyl azide afforded 2,3-dimethoxyaniline **35** (Scheme 8)[32]. Michael addition of 2,3-dimethoxyaniline **35** to methyl propionate in methanol followed by replacement of the methanol with diphenyl ether and thermal cyclization under reflux affords quinolone **36**. Chlorination of quinolone yielded 4-chloroquinoline, which in turn, reacted with the dimethyl acetal of aminoacetaldehyde to afford the key intermediate **37**. Addition of a mixture of trifluoromethanesulfonic acid and antimony pentafluoride in trifluoroacetic acid to

aminoquinoline at 75-80 ºC afforded a mixture of pyrroloquinoline **38** and aaptamine **39** in 33% and 34% yields, respectively.



34 **35** **36**

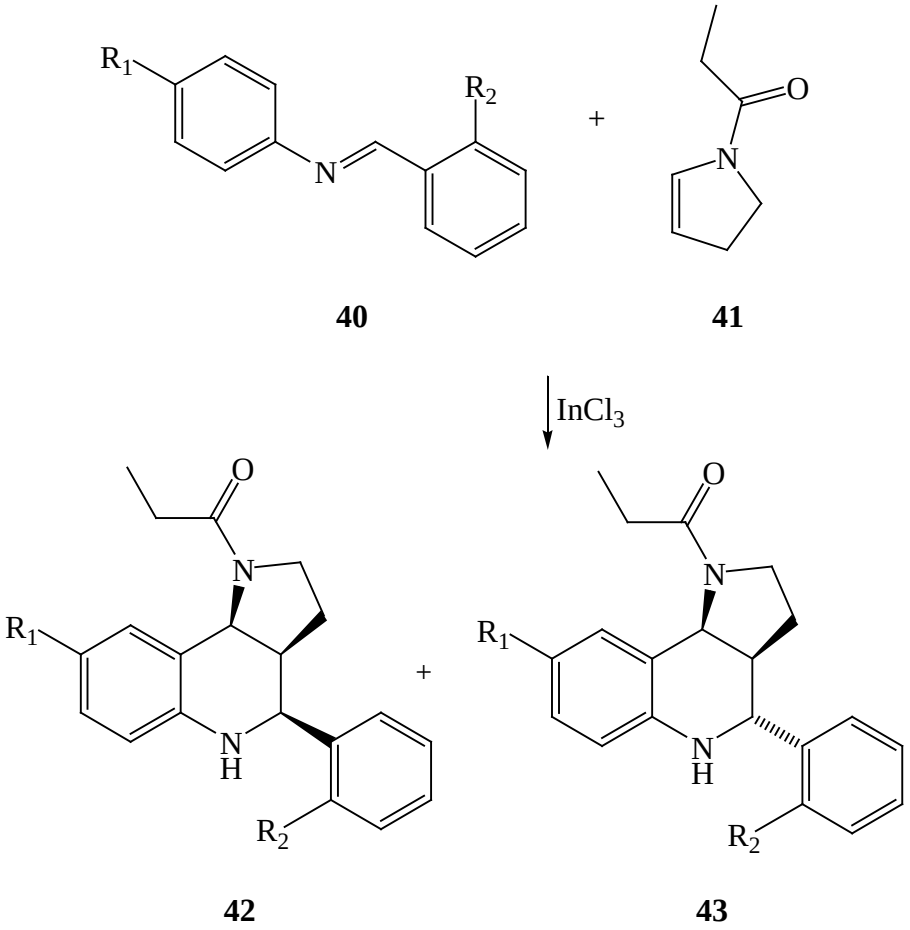
37 **38** **39**

Reagents and conditions: i) *n*-BuLi, $(CH_3)_2O$, 22 ºC, N_2, 18.5 h; ii) $Me_3SiCH_2N_3$, $(CH_3)_2O$, 22 ºC, N_2, 3.5 h; iii) HC≡CCO $_2$Me, MeOH and Ph_2O, N_2, Δ, 96 h; iv) $POCl_3$, N_2, 22 ºC, 24 h; v) $H_2NCH_2CH(OMe)_2$, DMSO, N_2, 95 ºC, 120 h, CF_3SO_3H, SbF_5, CF_3CO_2H, 80 ºC, 3 min.

Scheme 8

In the Diels-Alder method for the synthesis of pyrroloquinoline, indium trichloride was used as a catalyst for the Diels–Alder reaction of imines of aromatic amines **40** with both electron rich and electron deficient alkenes **41** (Scheme 9)[33]. Imines of aromatic amines **40** act as dienes while cyclic enamides **41** act as dienophiles. Hadden *et al.*[33] reacted imine systems **40** with cyclic enamides **41** prepared, in turn, by condensing the corresponding imine with propionyl chloride. The reaction takes place rapidly at room temperature in acetonitrile containing a catalytic amount

of indium trichloride. The limitation of this method is that the reaction leads to a mixture of diastereomeric *endo/exo* cycloadducts in moderate yields (41-50%). Moreover, this reaction is limited to the use of aromatic aldehydes only.



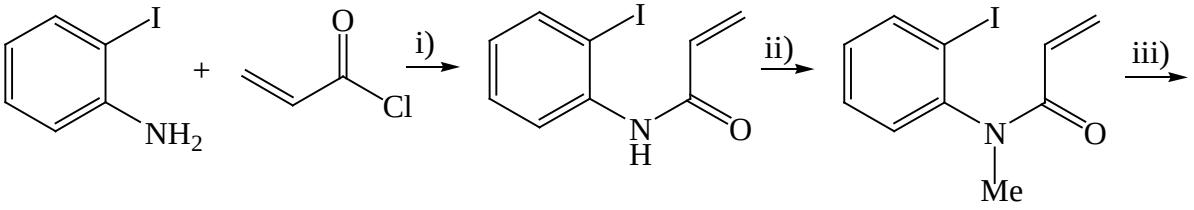
R_1=H, OMe, CO_2Me; R_2=H, NO_2

Reagents and conditions: $InCl_3$, CH_3CN, rt, 0.5 h

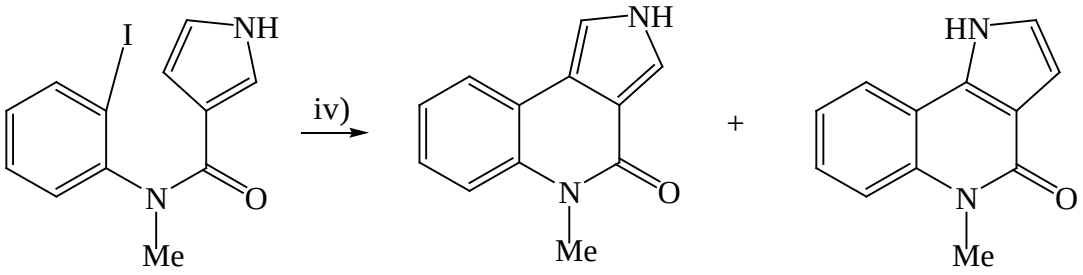
Scheme 9

A free radical mechanism was developed for the synthesis of simple unsubstituted pyrroloquinoline skeleton[6] (Scheme 10). Two equivalents of 2-iodoaniline **44** were reacted with acryloyl chloride **45** to afford *N*-arylacrylamide **46** in 96% yield (Scheme 10). In order to attain

the correct conformation around the amide bond for cyclization, the amide was methylated to give a tertiary amide **47** in 81% yield[33]. Reaction of a tertiary amide **47** with tosylmethylisocyanide ($TsCH_2NC$) afforded a radical cyclization precursor, pyrrole-3-carboxamide **48** in 57% yield. Pyrrole-3-carboxamide **48** was then subjected to reductive radical cyclization with tributyltinhydride (Bu_3SnH) in toluene under refluxing in the presence of azobisisobutyronitrile (AIBN) to yield pyrroloquinolones. This method gives a mixture of two regioisomers **49** and **50** where the aryl radical adds on to the C-2 of the pyrrole ring or to the C-4 of the pyrrole ring.



44 **45** **46** **47**



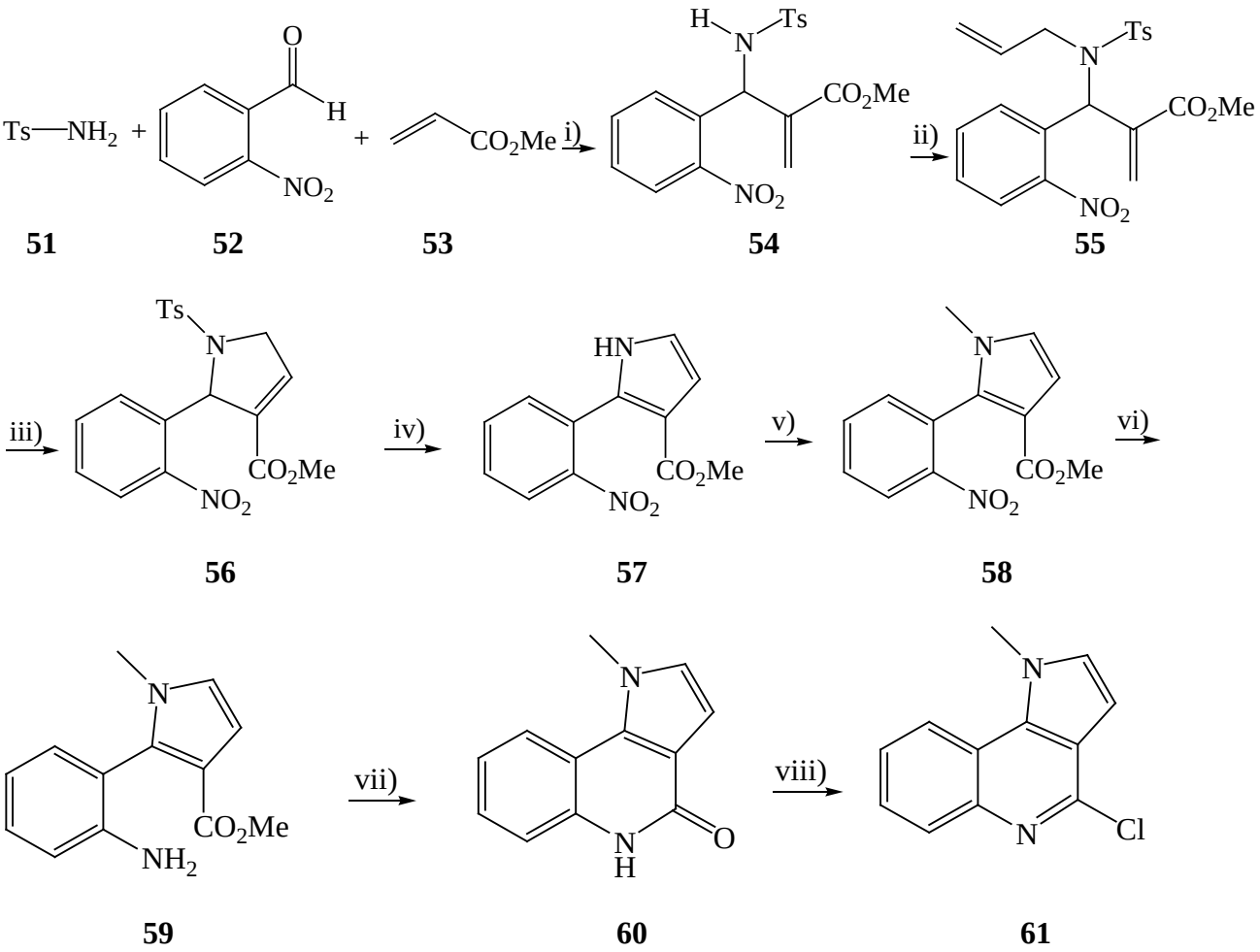
48 **49** **50**

Reagents and conditions: i) $(C_2H_5)_2O$, r.t., 1 h; ii) CH_3I, NaH, THF, rt, 12 h; iii) $TsCH_2NC$, NaH, $(C_2H_5)_2O$, DMSO, KOH, rt, 30 min; iv) Bu_3SnH, AIBN, toluene, 80 ºC, 4 h

Scheme 10

A new approach for the synthesis of substituted pyrroloquinoline derivatives using microwave-assisted chemistry was described by Benakki and coworkers[34] The first step in this strategy

involves the synthesis of the unsaturated β-aminoester **54** through the 3-component one-pot aza-version of the Baylis-Hillman reaction (Scheme 11). The reaction was performed using nitrobenzaldehyde **52** and methylacrylate **53** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), molecular sieves, titanium isopropoxide as a Lewis acid and isopropanol (*i*-PrOH) as solvent to yield a β-aminoester, **54** in 64% yield. The β-aminoester **54** was reacted with allyl bromide in the presence of K_2CO_3 in DMF to afford a diene **55** in 98% yield. The reaction was performed either at room temperature for 12 hours or under microwave irradiation at 100 ºC within 10 minutes without affecting the yield. Diene **55** was subjected to ring-closing metathesis using 4% of the Grubbs second generation catalyst under microwave irradiation at 100 ºC in dichloromethane to give pyrroline **56** in 87% yield (Scheme 11). Cleavage of the tosyl group was achieved using potassium *tert*-butoxide (*t*-BuOK) in DMF at room temperature to give 89% yield of the substituted pyrrole **57**. The pyrrole was reacted with cesium carbonate (Cs_2CO_3) in DMF to afford the protected pyrrole **58** in 98% yield. Reduction of **58** with Pd/C under H_2 atmosphere gave the amine derivative **59** in high yield (98%). Cyclization was carried out by microwave irradiation of a mixture of **59** in *sec*-butanol in the presence of 1% acetic acid for 4 hours at 100 ºC to afford a cyclic amide unit **60** in 98% yield. Compound **60** was subjected to phosphorus oxychloride under microwave irradiation for 15 minutes at 100 ºC to afford imidoyl chloride **61** in appreciable yield 98%.



51 **52** **53** **54** **55**

56 **57** **58**

59 **60** **61**

Reagents and conditions: i) DABCO, TAMIS 4Å, $Ti(OiPr)_4$, *i*-PrOH; ii) Allyl bromide, K_2CO_3, DMF; iii) Grubbs II, CH_2Cl_2, MW, 100 ºC; iv) *t*-BuOK, DMF, v) CH_3I, Cs_2CO_3, DMF vi) H_2, Pd/C, MeOH; vii) CH_3COOH, *sec*-butanol, MW, 100 ºC; viii) $POCl_3$, MW, 100 ºC

Scheme 11

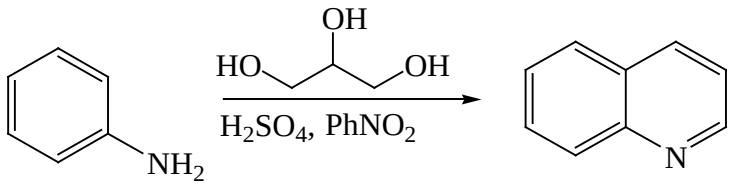
1.4 Classical methods for the synthesis of polysubstituted quinoline derivatives

The structural core of quinoline has generally been synthesized by conventional methods such as Skraup[2], Doebner-von Miller[5], Friedlander[3] and Combes[4] syntheses. These classical methods are

well known and still frequently used for the preparation of pharmaceutical agents, ligands and functional materials bearing a quinoline backbone. The general approaches to quinoline compounds are based on the use of non-heterocyclic precursors. These approaches involve reactions of aromatic primary amines as the nucleophilic nitrogen-donating component and the electrophilic three-carbon unit, usually carbonyl compounds.

1.4.1 The Skraup synthesis

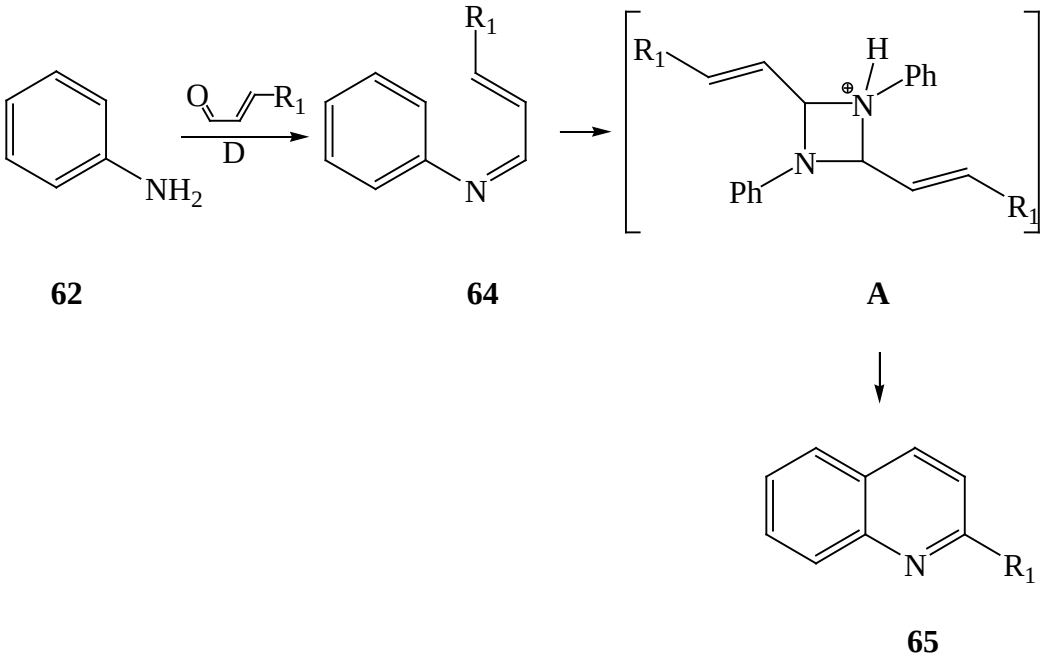
Skraup synthesis developed in 1880 is widely used as a method for the preparation of quinolines and its derivatives[2]. In this method, aniline **62** is heated with glycerol in the presence of sulphuric acid, and an oxidizing agent such as nitrobenzene, which also serves as a solvent[2] (Scheme 12). The mechanism of the Skraup reaction involves initial dehydration of the glycerol to give acrolein, which undergoes a 1,4-addition by the aniline. The resulting β-anilinopropionaldehyde is then cyclized to a dihydroquinoline, which is finally oxidized to give a fully aromatized quinoline **63**. The synthesis is often accompanied by violent reaction and in addition, the yields are variable and very low. The Skraup synthesis is extremely versatile; almost any desired quinoline may be prepared by using the proper combination of aniline and aldehyde, so long as the reagents will survive the hot acid conditions[25].



62 **63**

Scheme 12

Eisch and Dluzniewski[5] studied the mechanism of the Skraup quinoline synthesis and proposed that direct Schiff base might be a critical step in the mechanism. Heating the substrates under the conditions of Skraup synthesis first forms a Schiff base **64** (Scheme 13). Heating a Schiff's base under anhydrous conditions in dimethyl sulfoxide (DMSO) or acetonitrile (CH_3CN) led to a putative diazetidinium cation intermediate **A** which then rearranged rapidly to a 2,4-disubstituted quinoline **65**. The lack of formation of 4-substituted quinoline suggests that the direct cyclization of Schiff's base to 4-substituted is a less favoured pathway.

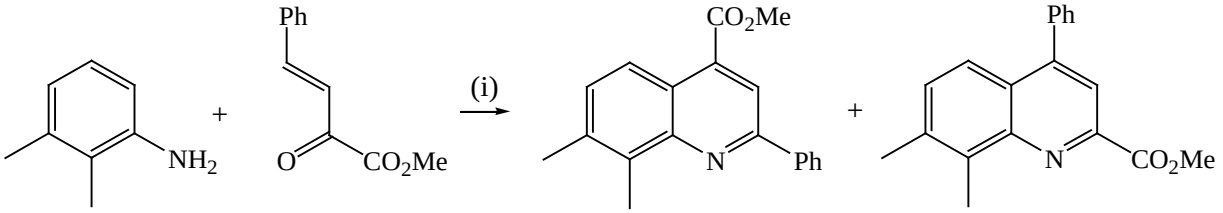


62 **64** **A** **65**

Scheme 13

In order to synthesise 2,4-disubstituted quinolines, Wu *et al.*[35], introduced an electron withdrawing group on the *α,β*-unsaturated carbonyl component **64** which increases the electrophilic reactivity of the Schiff base C-C double bond and facilitates subsequent cyclization (Scheme 14). 2,3-Dimethylaniline **66** was reacted with (3*E*)-2-oxo-4-phenylbuten-3-oatemethyl ester **67** in the presence of hafnium trifluoromethanesulfonate ($Hf(OTf)_4$) in dichloromethane

(CH_2Cl_2) at room temperature for 48 hours to afford a mixture of 2-phenyl-4-carboxyquinoline **68** in 44% yield and 2-carboxy-4-phenylquinoline **69** in 18% yield (Scheme 14).



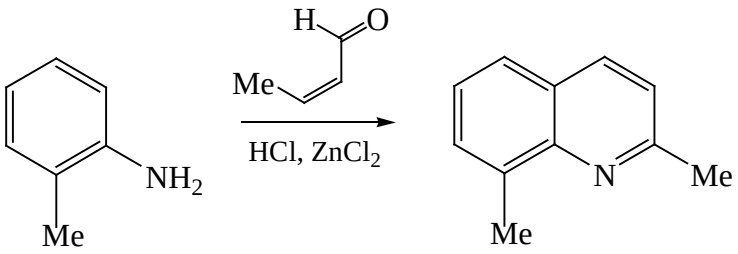
66 **67** **68** **69**

Reagents and Conditions: i) 10% $Hf(OTf)_4$, CH_2Cl_2, rt, 48 h

Scheme 14

1.4.2 The Doebner-von Miller reaction

The classical Skraup and Doebner-von Miller synthesis are very similar; and the latter method involves generating a substituted acrolein and also requires an oxidant. The Doebner–Miller synthesis can be applied to substituted amines **70** with a wide range of substituents that withstand the acidic medium to afford alkyl and/or aryl-substituted quinolines **71** (Scheme 15)[5]. The Doebner–Miller reaction is a process in which the first stage is a crotonic condensation of two molecules of an aldehyde or ketone and results in the formation of an α,β-unsaturated compound. The latter reacts with the aniline **70** to form a Schiff's base. The resulting dihydroquinoline undergoes further oxidation to afford a quinoline derivative[35].



70 **71**

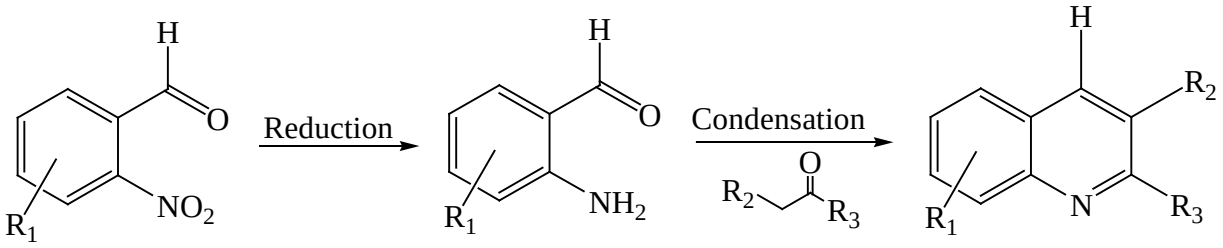
Scheme 15

One serious shortcoming of both Skraup and Doebner–Miller reactions is the laborious procedure for the isolation of the quinoline from the reaction mixture. This is due to parallel polymerization of the α,β-unsaturated aldehydes catalyzed by the acid which results in reduced yields of the product. Investigations in recent decades have therefore been devoted to the search for better conditions for the reactions. It is possible to avoid polymerization of the unsaturated carbonyl compounds if the Doebner–Miller reaction is conducted in a two-phase system consisting of an organic and an aqueous acidic part (e.g., ethanol–sulfuric acid, toluene–6 M HCl, heptane–6 M HCl, xylene–6 M HCl, 1,2-dichloroethane–6 M HCl, toluene–toluenesulfonic acid)[4]. The reactions take place smoothly and with good yields even in the absence of oxidizing agents (47-80%).

1.4.3 The Friedlander reaction

One of the most frequently used pathway to substituted quinoline derivatives **74** is the Friedlander synthesis. This synthesis is usually carried out via a two-step procedure in which reduction of an *o*-nitro aryl aldehyde **72** is followed by condensation with an enolizable carbonyl

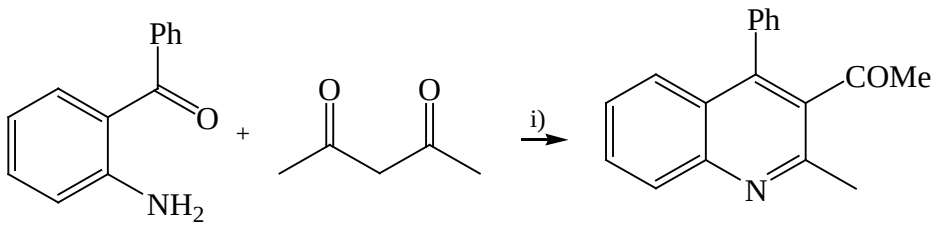
compound in the presence of a Bronsted or Lewis acid catalyst (Scheme 16). It involves acid or base catalyzed condensation between an aromatic 2-aminoaldehyde or ketone **73** with the carbonyl compound containing a reactive α-methylene group followed by a cyclodehydration to afford substituted quinolines **74** (Scheme 16)[3]. It has been reported that drops of concentrated sulfuric acid or 6 mol/L hydrochloric acid can be used as efficient catalysts in the Friedlander condensation procedure. With this method, various structurally different substrates can give the corresponding quinoline products in moderate to high yields.



72 **73** **74**

Scheme 16

More recently, an efficient and rapid approach to quinolines via Friedlander synthesis was developed[36]. The reaction is catalyzed by silica gel supported sodium hydrogen sulfate, $NaHSO_4$-SiO_2, under solvent-free conditions. 2-Aminobenzophenone **75** was reacted with acetylacetone **76** in the presence of a heterogeneous catalyst, $NaHSO_4$-SiO_2, under solvent-free conditions at 100 ºC to afford a substituted quinoline **77** in 87% yield (Scheme 17).



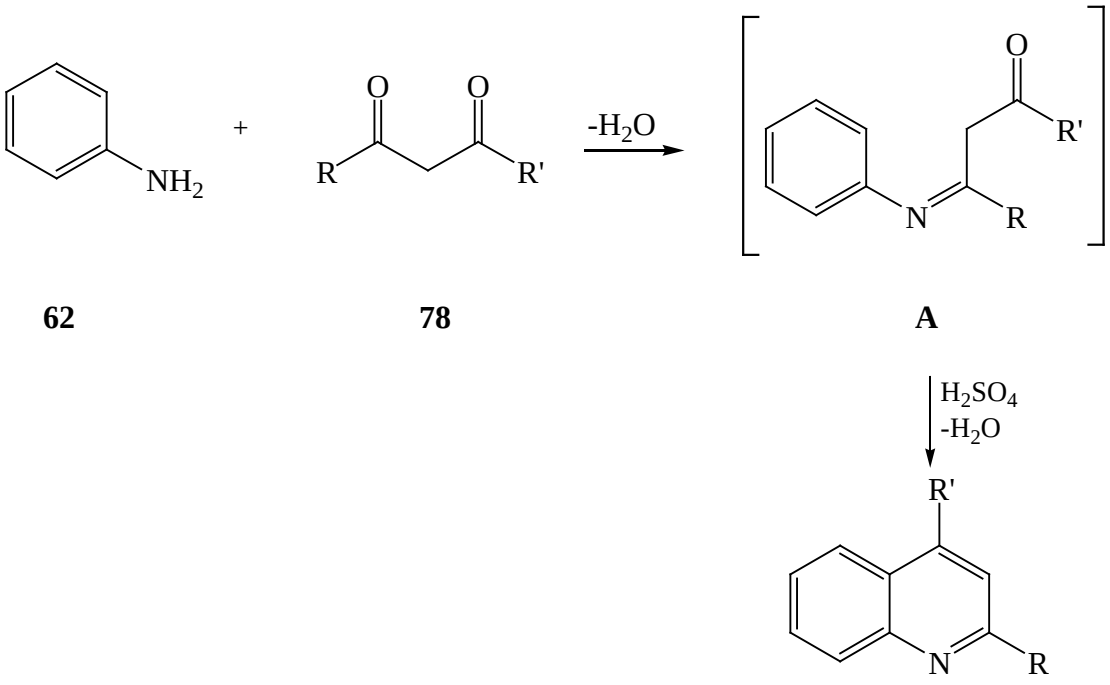
75 **76** **77**

Reagents and conditions: i) $NaHSO_4$-SiO_2, 100 ºC, 1h

Scheme 17

1.4.4 The Combes reaction

The Combes reaction involves condensation of unsubstituted anilines **62** with β-diketones **78** to form a Schiff's base **A** (Scheme 18)[37]. Acid-catalyzed cyclization of an intermediate Schiff base affords a substituted quinoline **79**.



62 **78** **A** **79**

Scheme 18

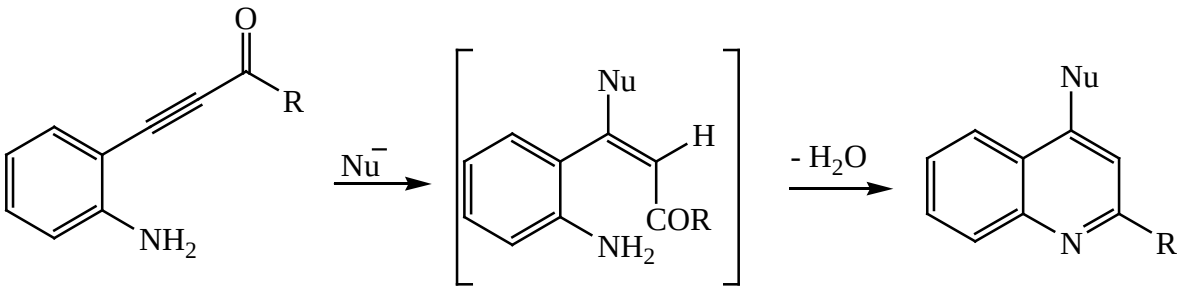
Despite their efficiency in the synthesis of polysubstituted quinolines, the above classical methods for quinoline synthesis do not allow for the adequate diversity and substitution with heteroatom-containing groups on the quinoline ring. Moreover, these methods are only restricted to the synthesis of alkyl and/or aryl substituted quinoline derivatives which cannot be used as substrates for the synthesis of polynuclear quinoline derivatives. The most effective methods for the synthesis of these systems involve carbon-heteroatom bond formation and metal-catalysed carbon-carbon bond formation to afford annulated derivatives. Carbon-heteroatom bond formation can be achieved by indirect methods for the synthesis of the quinoline moiety bearing halogen atoms. Consequently, methods for the indirect synthesis of polysubstituted and polynuclear quinoline derivatives through nucleophilic displacement of halogen followed by metal-catalyzed carbon-carbon bond formation or *vice versa* continue to be developed in literature and these are reviewed below.

1.5 Indirect methods for the synthesis polysubstituted quinolines

1.5.1 Cyclization reactions

Arcadi *et al*[38] previously investigated the synthesis of functionalized quinoline derivatives using α,β-ynones as substrates[38]. This reaction of α,β-ynones with nucleophilic partners provide a versatile new approach to 2,4-disubstituted quinolines through a conjugate addition-cyclization tandem reaction. In this method, β-(2-aminophenyl)-α,β-ynones **80** were reacted with various heteronucleophiles to give 2,4-disubstituted quinolines **81** through tandem nucleophilic addition-annulations reactions (Scheme 19). The reactions were carried out at 60–80 ºC in the presence of

an excess nucleophile or pronucleophile and the 2,4-disubstituted quinolines **81** are isolated in good yields as sole products. Nucleophiles used include MeOH, NaBr, EtSH and PhSH. This method represents a versatile approach to 4-heterosubstituted 2-arylquinolines. Carbonucleophile addition reaction will give 4-alkyl-2-arylquinoline



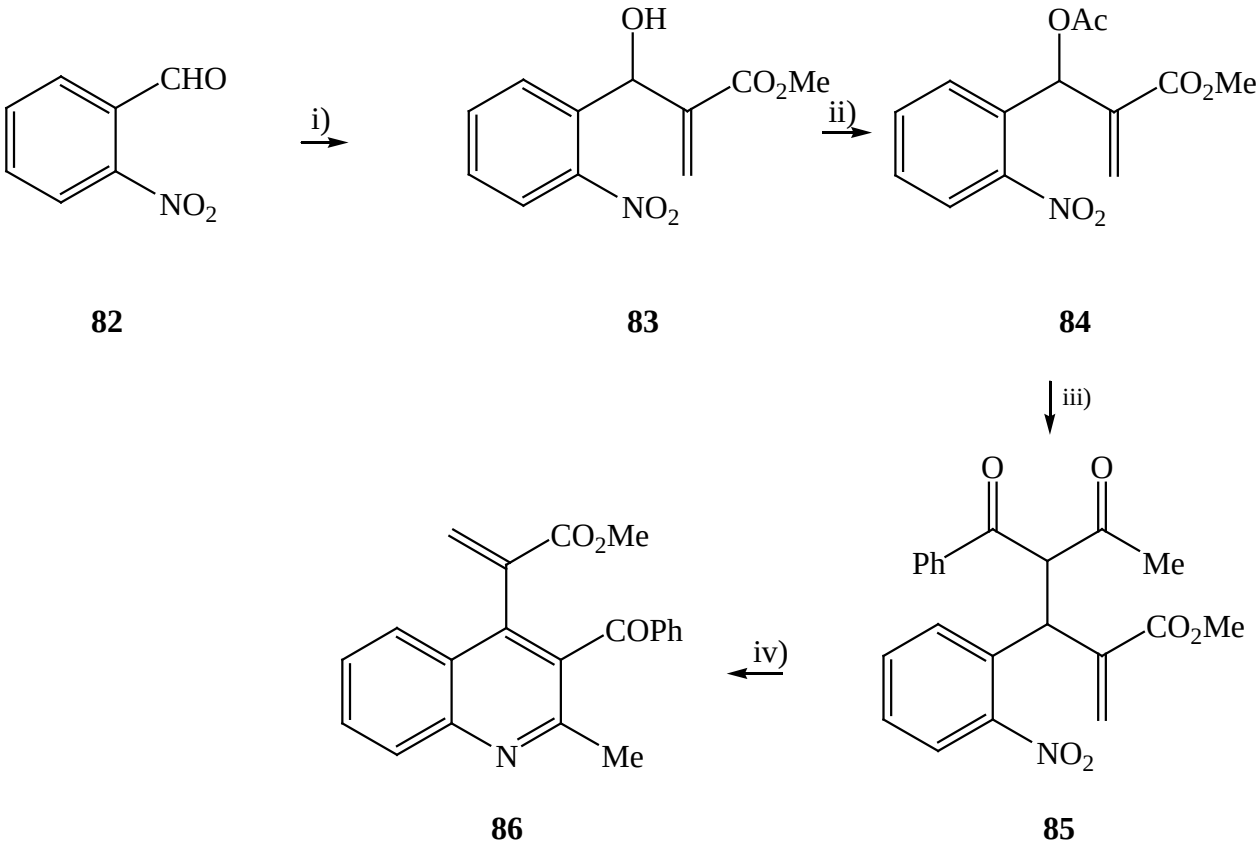
80 **A** **81**

Nu^- = MeO^-, Br^-, EtS^- and PhS^-

Scheme 19

An alternative method to substituted quinoline synthesis involves derivatives of Baylis-Hillman adducts (Scheme 20)[39]. Substrates resulting from the nucleophilic substitution reaction (S_N2) between the acetyl derivatives of Baylis-Hillman adducts of 2-nitrobenzaldehydes **82** and a nucleophile containing a keto group or an ester group represents an interesting carbon framework for the construction of quinoline architecture. Baylis-Hillman adduct **83** (Scheme 20) was reacted with acetyl chloride and pyridine in dichloromethane at room temperature to afford the acetates **84** in good yield (78-84%). S_N2 substitution reaction of benzoyl acetone with the acetate in the presence of DABCO in a THF/H_2O system led to a synthesis of **85** as a diastereoisomeric mixture in good yield (65-85%). The nitro group in **85** was then chemoselectively reduced with anhydrous tin (II) chloride ($SnCl_2$) and this afforded a quinoline **86**. The isolation of quinoline

implied that the $SnCl_2$ had triggered a tandem reaction wherein the reduction of a nitro group was followed by cyclization and subsequent dehydrogenation.



82 **83** **84** **85** **86**

Reagents and conditions: i) $CH_2{=}CHCO_2Me$, DABCO, rt, 15 min to 1h; ii) AcCl, pyridine, CH_2Cl_2, rt, 3h; iii) DABCO, $PhCOCH_2COMe$, THF/H_2O (1:1), rt, 30 min; iv) $SnCl_2$, MeOH, reflux, 1 h

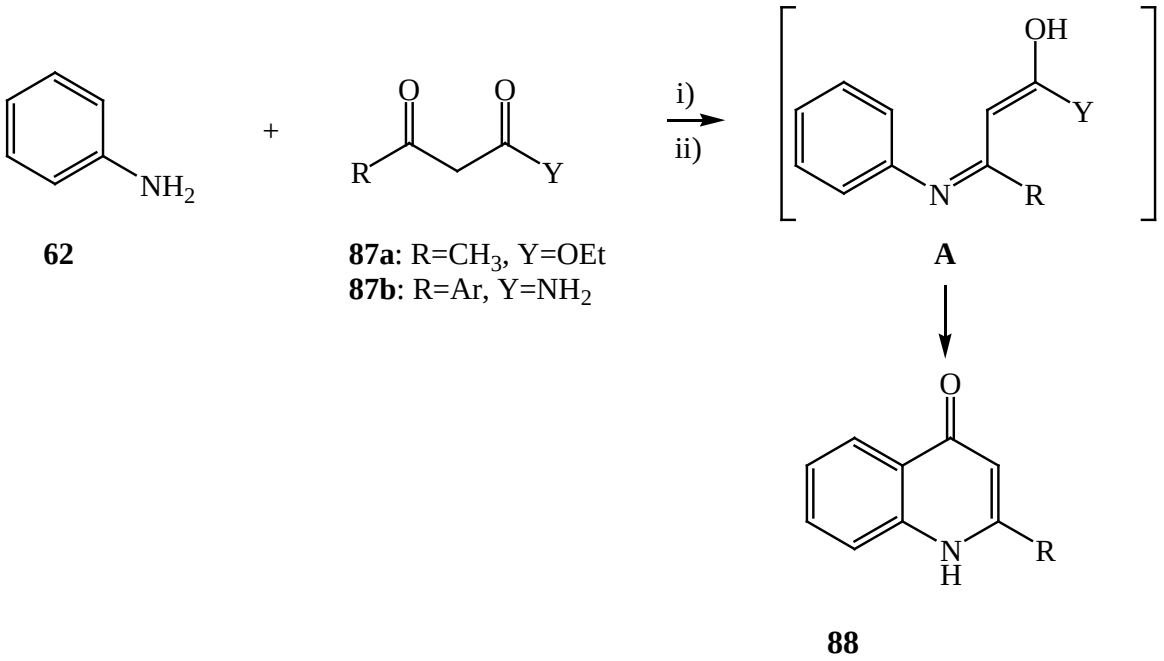
Scheme 20

1.5.2 Synthesis and further transformations of quinolin-4(1*H*)-ones

A common strategy for the synthesis of polysubstituted quinolines involves the construction of a quinoline ring possessing an appropriate substituent at the C-3 and C-4 position. A major

drawback of most of the above classical methods is that once the quinoline ring has been constructed, incorporation of a substituent at C-3 and C-4 through aromatic substitution is difficult. Polysubstituted quinoline derivatives bearing alkyl, aryl and/or heteroatom-containing groups at 2-, 3- and 4- positions are best prepared by modification of the quinolin-4(1*H*)-one moiety through successive reactions involving halogenations reactions followed by nucleophilic displacement and metal-catalysed C-C bond formation or *vice versa*. Perhaps it worths reviewing a few methods for the synthesis of quinolin-4(1*H*)-one derivatives at this stage.

One of the classical methods employed in the synthesis of quinolin-4(1*H*)-one precursors is the Conrad-Limpach synthesis which involves the condensation of β-ketoesters **87a** (R = CH_3, Y = OEt) with an aniline followed by thermal cyclization (Scheme 21)[4]. The use of high temperature results in viscous tars which makes the reaction difficult to separate and purify the products. Modifications of this method incorporate the use of β-ketoamides **87b** (R = Ar, Y = NH_2) and have succeeded in lowering the temperature of the cyclization by employing polyphosphoric acid (Scheme 21).

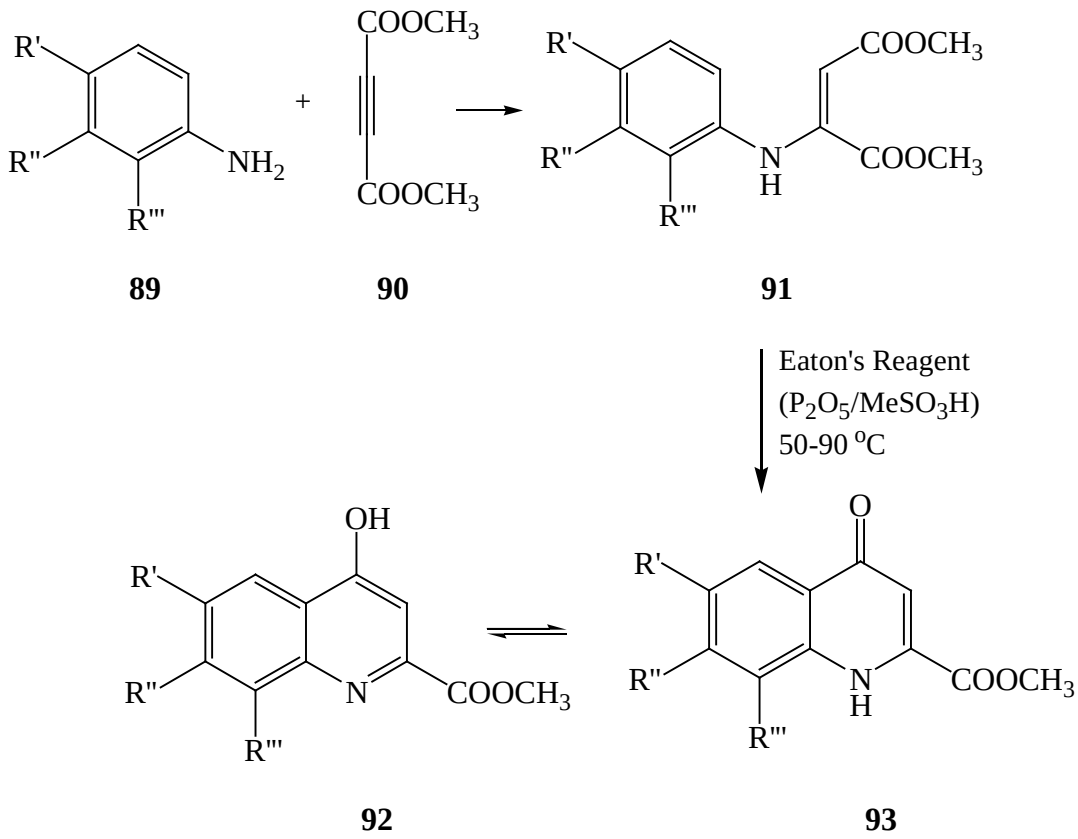


62 **87a**: R=CH_3, Y=OEt; **87b**: R=Ar, Y=NH_2 **A** **88**

Reagents and conditions: i) Ph_2O, 260 ºC if R=CH_3, Y=OEt; ii) Polyphosphoric acid (PPA), 135-150 ºC if R=Ar, Y=NH_2

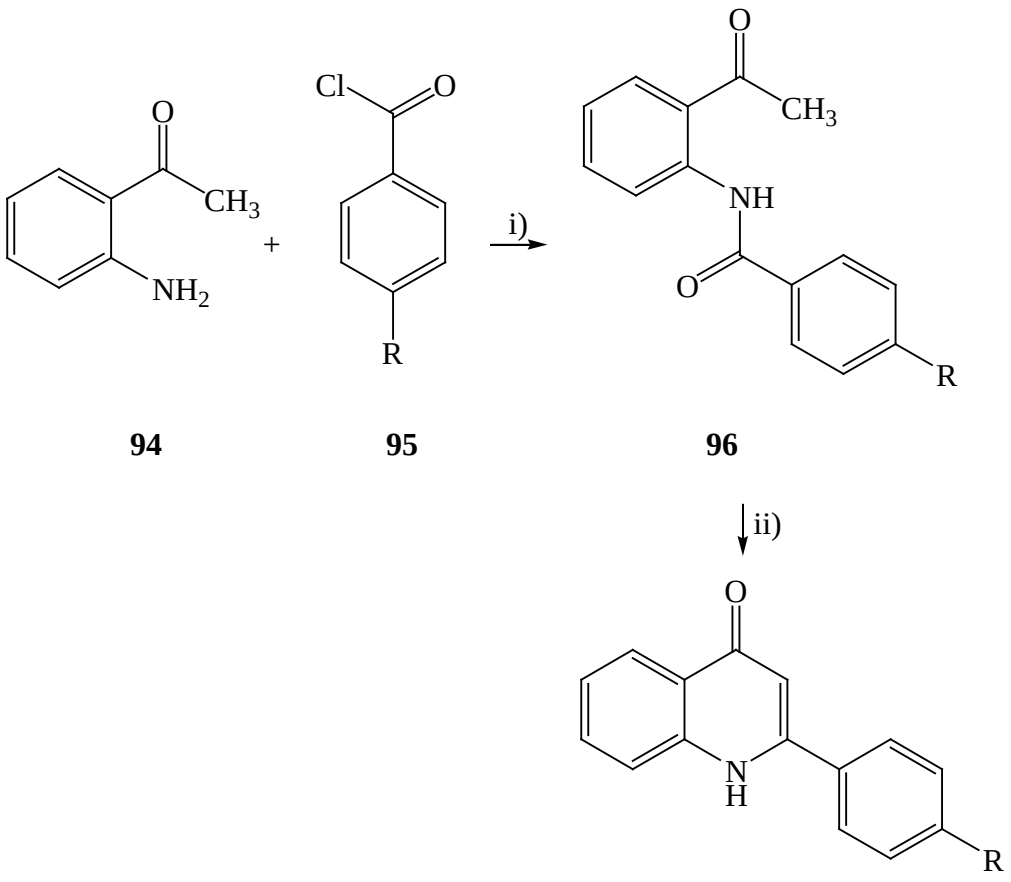
Scheme 21

Recently, milder conditions have been applied in which Eaton's reagent (P_2O_5/$MeSO_3H$) is used as an alternative to polyphosphoric acid to effect cyclization to 4-quinolones at temperatures below 90 ºC (Scheme 22)[40]. Enamines **91** used as substrates are prepared in quantitative yield via condensation of aryl amines **89** with dimethyl acetylenedicarboxylate (DMAD) **90** in alcoholic solvents at temperatures ranging from 25-60 ºC. The new protocol was examined and found to be effective for the cyclization of enamines with various types of substituents, including substrates with electron-withdrawing groups which are typically poor substrates for similar cyclizations. In all cases, Eaton's reagent promoted cyclization at 50 ºC to afford 2-carboxy-4-quinolones **93** in high yields (85-98%) in less than 3 h.



Scheme 22

The most convenient method for the synthesis of 2-substituted quinolin-4(1*H*)-one **97** involves cyclization of *N*-benzoyl-2-aminoacetophenone derivatives **96** in the presence of *t*-BuOK in *t*-BuOH under reflux to yield 2-arylquinolin-4(1*H*)-one derivatives **97** in good yields (Scheme 23)[41]. *N*-benzoyl-2-aminoacetophenone derivatives **96** are in turn synthesized from appropriately substituted 2-aminoacetophenone **94** and a range of benzoyl chloride derivatives **95** in the presence THF and triethylamine (NEt_3) to afford *N*-benzoyl-2-aminoacetophenone derivatives in excellent yields (90-98%).



94 **95** **96**

R=H, F, Cl, OMe **97**

Reagents and conditions: NEt_3, THF, 0 ºC, rt**,** 2 h; ii) *t*-BuOK, *t*-BuOH, reflux, 18 h

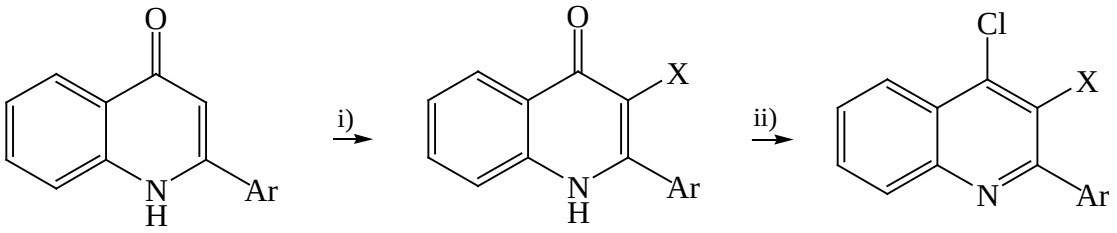
Scheme 23

Hadjeri *et al.*[42] adapted a similar approach and synthesized 5,7-dimethoxy-2-phenyl-4-quinolone from 3,5-dimethoxyaniline. These authors reacted 3,5-dimethoxyaniline with benzoyl chloride in the presence of triethylamine to yield *N*-(3,5-dimethoxyphenyl)benzamide. Friedel-Crafts acylation with acetyl chloride in 1,2-dichloroethane and in the presence of $SnCl_4$ gave *N*-(2-acetyl-3,5-dimethoxyphenyl)benzamide in 58% yield, together with its regioisomer, *N*-(4-acetyl-3,5-dimethoxyphenyl)benzamide (in less than 5% yield). Cyclization of the benzamide in the presence of *t*-BuOK in THF gave quinolone in 83% yield.

Quinolin-4(1*H*)-one derivatives have potential to exist in tautomeric equilibrium with the 4-quinolinol isomers[43]. Spectroscopic studies and X-ray crystallographic techniques reveal that quinolin-4(1*H*)-one systems exist exclusively in solution (NMR) and solid state (IR and X-ray) as the NH-4-oxo derivatives. In the gas phase there is coexistence of the 4-quinolinone and 4-hydroquinoline isomer with the NH-4-oxo isomer which was confirmed by mass spectrometry. The enol form also predominates in systems bearing hydrogen-bond acceptors at the 3-position, such as 4-hydroxyquinoline-3-carboxylic acid derivatives[44], to form six membered ring through hydrogen bonding. In the gas phase there are no solvent-assisted stabilization and intermolecular hydrogen bonds and as a result both tautomers coexist. The predominant 2-aryl-quinolin-4(1*H*)-one isomers are useful for possible functionalization as they contain several reactive centres at positions 1, 3 and 4 and can also enable different degree of unsaturation. C-3 halogenation gives 3-halogeno derivatives, whereas reaction with $POCl_3$ affords aromatization of quinolin-4(1*H*)-one ring to halogenoquinolines[44].

Halogen-containing quinolines are of particular interest because halogens play a crucial role in the compounds' bioactivity and provide an avenue for further structure elaboration[45]. C-3 and C-4 halogenation can be effected on a quinolone derivative through electophilic substitution at C-3 position followed by aromatization with phosphorus oxychloride ($POCl_3$) to afford 3-,4-dihaloquinoline derivatives. The 2-aryl-quinolin-4(1*H*)-one derivatives **98** were reacted with iodine (I_2) in the presence of sodium carbonate (Na_2CO_3) in THF under reflux to afford 2-aryl-3-iodoquinolin-4(1*H*)-ones **98a** (71-90%)[46]. 2-Aryl-quinolin-4(1*H*)-one derivatives **97** were also subjected to pyridinium tribromide ($C_5H_5NHBr_3$) (2 equiv) in glacial acetic acid at room temperature to afford 2-aryl-3-bromoquinolin-4(1*H*)-ones **98b** in high yield. The 2-aryl-3-

halogenoquinolin-4(1*H*)-one derivatives **98** were reacted with excess ($POCl_3$) under reflux to afford the fully aromatized 2-aryl-4-chloro-3-iodoquinoline derivatives **99** in high yield (82-96%)[47].

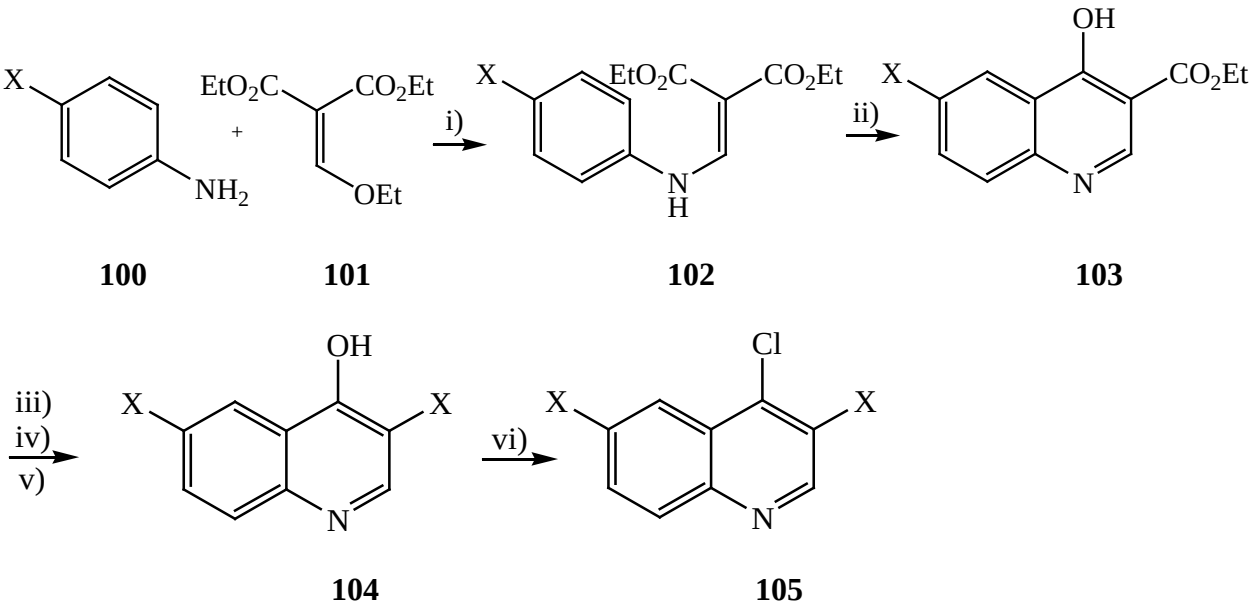


97 **98** X = I **(a)**, Br **(b)** **99**

Reagents and conditions: i) I_2, Na_2CO_3, THF, reflux, 18 h for X = I or $C_5H_5NHBr_3$, AcOH, rt, 2 h for X = Br; ii) $POCl_3$, reflux, 2 h

Scheme 24

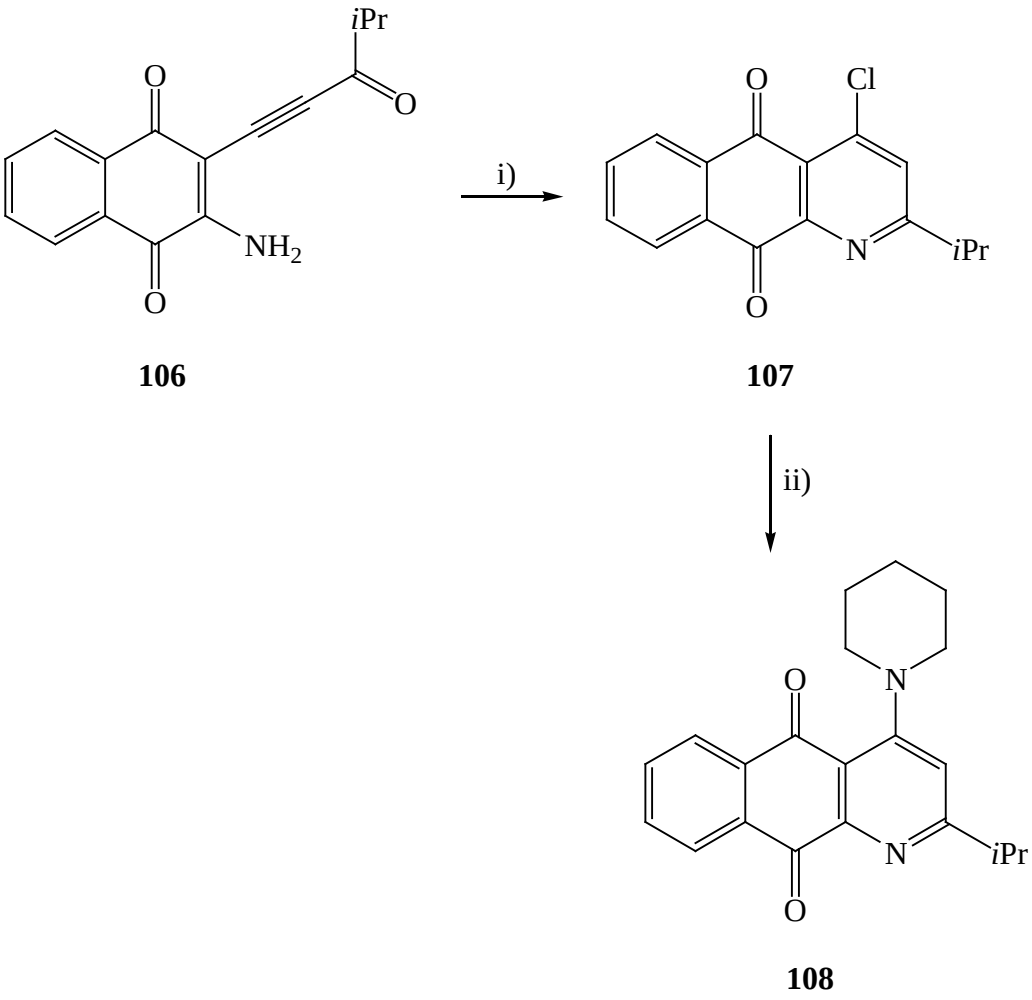
In another method 4-haloaniline **100** was condensed with diethylethoxymethylene malonate **101** with evaporation of ethanol to afford enamines **102** in good yields (Scheme 25)[48]. The latter were cyclized to 4-hydroxyquinolines **103** upon heating at high temperatures (Scheme 25). Saponification in the presence of aqueous NaOH followed by thermal decarboxylation in the presence of diphenyl ether at 250 ºC followed by bromination or iodination at the 3-position with *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) in warm acetic acid to afford 3-,6-dihalo-4-hydroxyquinoline **104** in good yield (88%). Chlorination with $POCl_3$ afforded 3-,4-,6-trihalogenated quinoline **105**. The resulting haloquinolines bear no substituent at the 2-position.



Reagents and conditions: i) 120 ºC, heat, 1 h; ii) 250 ºC, diphenyl ether; iii) 10% aq NaOH; iv) 250 ºC, diphenyl ether; v) NBS or NIS, AcOH, 60 ºC, 2 h; vi) $POCl_3$, reflux

Scheme 25

The pyridine ring of quinoline derivatives has properties of an α,β-unsaturated enamine and this makes C-2 and C-4 positions electrophilic and therefore susceptible to nucleophilic attack. In the case of 2-aryl-4-chloro-3-iodoquinoline derivatives, only the 4-carbon atom is electrophilic and this allows for the easy displacement by heteroatom-containing nucleophilies to afford 4-substituted quinoline derivatives that cannot be accessible via classical methods described earlier[46, 47]. The halogen atom at the 4-position of a quinoline is easily displaced by various hydrocarbon- and heteroatom-containing nucleophiles (Scheme 26)[49]. 4-Haloquinoline-5,8-dione (chlorazaanthraquinone) **107** was reacted with piperidine at 20 ºC to give 2-isopropyl-4-*N*-piperidino-benzo[*g*]quinoline-5,10-dione **108** in good yield (95%)[49]. The reaction proceeded via a one pot cyclization and aromatization to afford 4-chloroquinoline

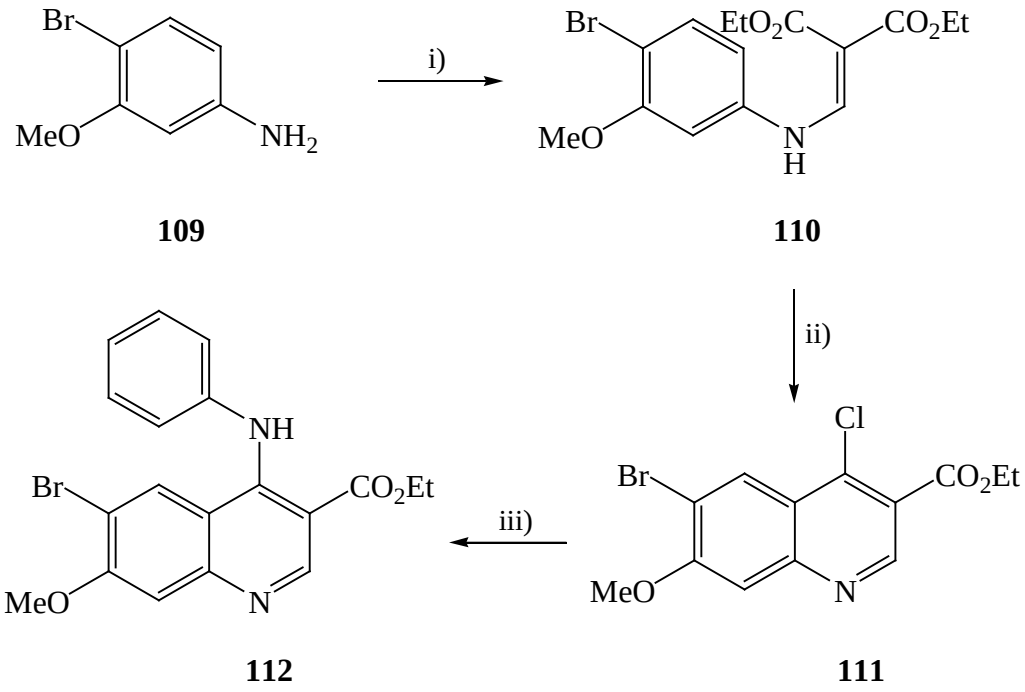


106 **107** **108**

Reagents and conditions: i) HCl, dioxane or $CHCl_3$, 20 ºC, 5-6 h; ii) Piperidine, 20 ºC, 5-6 h

Scheme 26

In another development, 4-chloroquinoline ester derivatives **111** were prepared from 4-bromo-3-methoxyaniline **109** and diethylethoxymethylene malonate in acetonitrile at room temperature to form **110** (Scheme 27). A one-pot cyclization-chlorination of **110** afforded 4-chloroquinoline ester **111**. 4-Chloroquinoline ester **111** was, in turn, reacted with aniline in the presence of acetic acid in ethanol at 80 ºC to afford 4-anilinoquinoline ester **112**[50].

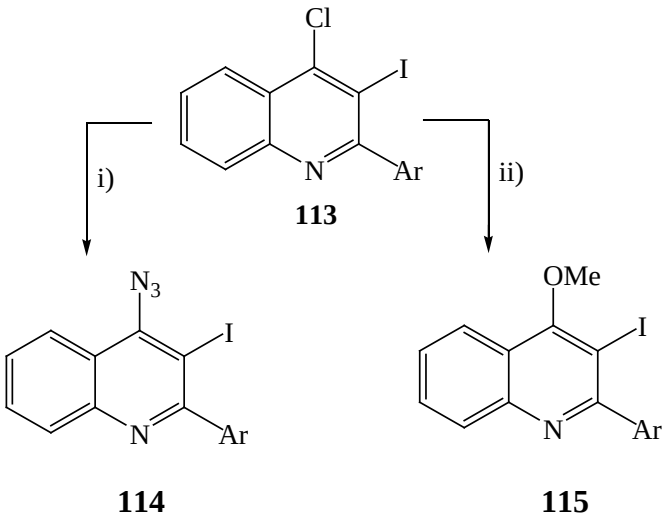


109 **110** **111** **112**

Reagents and conditions: i) Diethylethoxymethylene malonate, CH_3CN, rt; ii) $POCl_3$, PhMe, 100 ºC, aniline, cat. AcOH, EtOH, 80 ºC

Scheme 27

In this work, the approach involving the use of quinolin-4(1*H*)-ones **97** as substrates allows for the functionalization at both C-3 and C-4. Moreover the 2,3-dihaloquinolines allow further derivatization at these positions. For example, 2-aryl-4-chloro-3-iodoquinoline derivatives **99** were reacted with sodium azide (NaN_3) in DMF at room temperature for 48 hours to afford 4-azidoquinoline derivatives **114** in reasonable yields (60-78%) (Scheme 28)[46]. 2-Aryl-4-chloro-3-iodoquinoline derivatives **114** were also reacted with sodium methoxide (NaOMe), in THF, under reflux for 18 hours to afford 4-methoxyquinoline derivatives **115** in reasonable yield (60-75%) (Scheme 28)[47].



Reagents and conditions: i) NaN_3, DMF, rt, 48h; ii) NaOMe, THF, Δ, 18h

Scheme 28

The 3,4-dihaloquinoline derivatives are suitable candidates for successive nucleophilic displacement of Cl by heteroatom-containing nucleophiles and metal-catalyzed C-C bond formation at C-3 to afford 3,4-disubstituted quinoline derivatives with potential to undergo metal-mediated annulations. Moreover, the presence of 4-nitrogen- or oxygen-containing substituent in close proximity with C-3 iodo-substituent can facilitate one-pot C-C bond formation and heteroannulation to afford tricyclic quinoline derivatives. A brief review of these metal-catalyzed C-C bond formation reactions and their application in quinoline chemistry is outlined below.

1.6 Metal-catalysed C-C bond formation using in haloquinoline derivatives as substrates

Cross coupling reactions involve organometallic reagent R-M and an organic compound R'–X, where X is a leaving group and is often catalyzed by a complex transition metal such as nickel or palladium. Metal catalyzed coupling reactions have been used for construction of variously substituted quinoline derivative[51]. The most commonly used methods are Suzuki, Negishi, Stille, Heck and Sonogashira reactions. The mechanisms of these reactions generally involve three main steps, namely (i) oxidative addition, (ii) transmetalation and (iii) reductive elimination and they only differ in the transmetalation step (Fig. 5). The first step involves reduction of the palladium catalyst to active $Pd(0)L_2$ species **A**. The active palladium catalyst is the 14 electron compound $Pd(0)L_2$ which reacts with arylhalide in oxidation addition to afford arylpalladium(II) complex. The complex is *trans*-$RPdXL_2$ **B**. The second step is transmetalation, with either CuI or organostannane forming intermediate **C** in which both organic ligands are *trans* oriented and converted to *cis* in a *trans-cis* isomerization to complex **D**. In the final step, the generated product is released in a reductive elimination with regeneration of Pd(0).

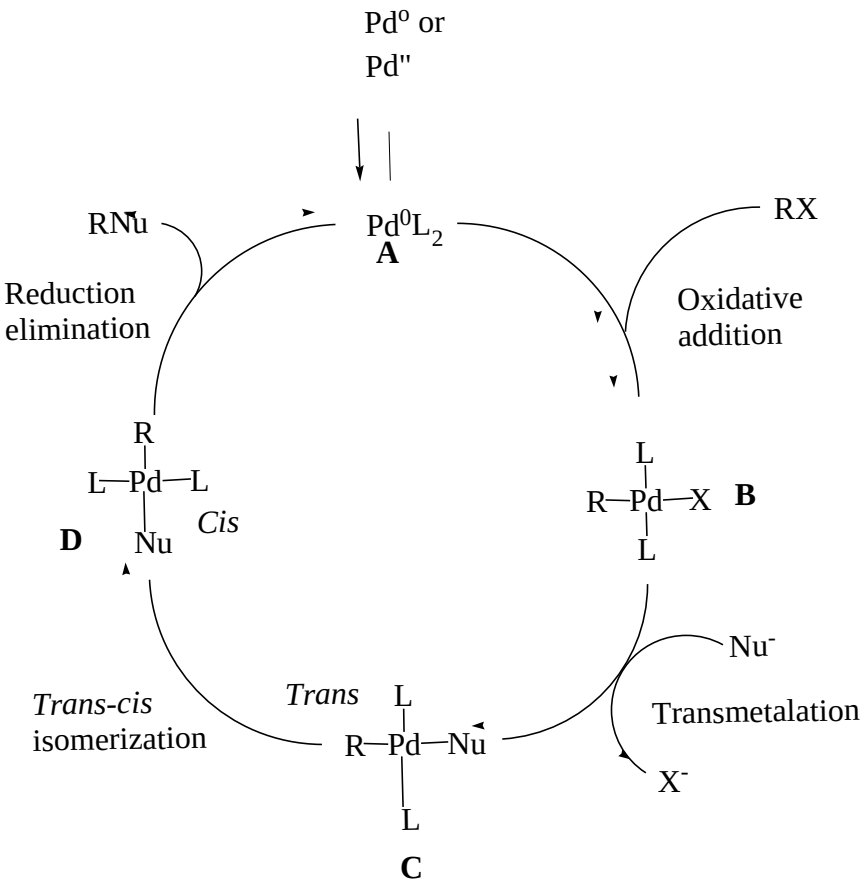
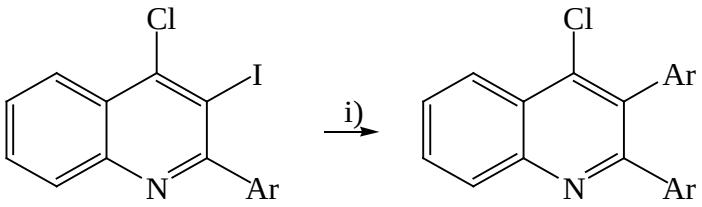


Figure 5: Generalised cycle for palladium-catalyzed cross coupling

1.6.1 Applications of Suzuki coupling reaction in the synthesis of quinoline derivatives

Suzuki cross coupling involves the reaction of organoboron compounds and carbon electrophiles such as aryl halide or hetaryl halides[52]. The broad availability of organoboron compounds and a high functional group tolerance make this method useful. The reaction is conducted in the presence of a palladium catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ and bases such as NaOH, K_2CO_3, NaOEt, KOH, CsOH which activate the weakly nucleophilic boranes, borinates or boronates for the transmetalation step. The Suzuki reaction is one of the versatile procedures for

the synthesis of unsymmetrical biaryl derivatives and proceeds best with aryl or heteroaryl iodides or bromide and either poorly or not at all with the corresponding chlorides. The order of reactivity in transition metal-mediated cross-coupling of aryl halides (order: I > Br > Cl > F)[53] allows selective coupling with bromides or iodides in the presence of chlorides. For example, substrates **99a** were subjected to $Pd(PPh_3)$-catalyzed coupling reactions with phenylboronic acid in DMF in the presence of 2M sodium carbonate to afford 2,3-diaryl-4-chloroquinoline **116** in moderate yield (Scheme 29)[47].



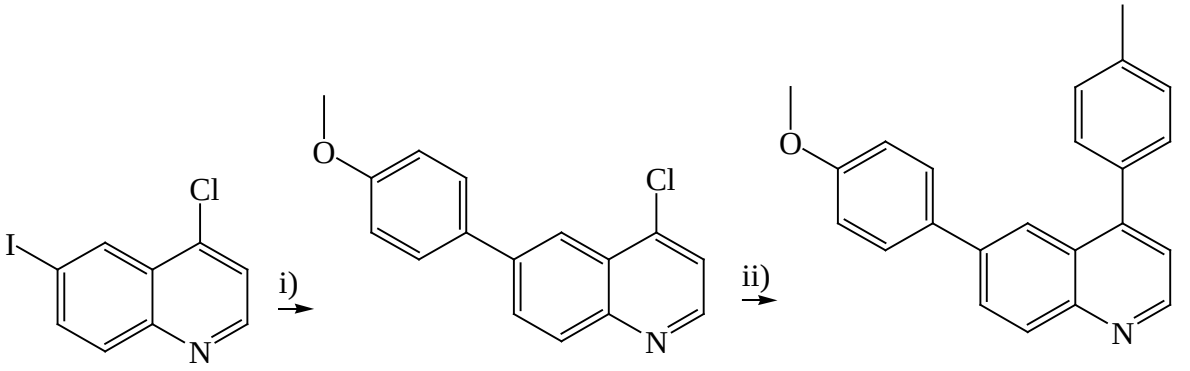
99 **116**

Reagents and conditions: $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3(aq), DMF, reflux, 48 h

Scheme 29

The possibility to perform successive introduction of several substituents into a substrate by means of the cross-coupling reaction considerably extends the prospects of the method and opens a simple synthetic way to versatile classes of aromatic compounds. This approach was used in the synthesis of polyaryl-substituted quinolines (Scheme 30)[54]. Although chlorine at position 4 of the quinoline is more active towards nucleophilic substitution, Suzuki cross-coupling reactions of 6-halo-4-chloroquinolines (X = I, Br) allowed successive replacement of halogens at positions 6 and 4, respectively. For the 6-iodo-4-chloroquinoline **117**, the iodine atom was selectively substituted within 4 hours by 4-anisylboronic acid in the presence of $Pd(PPh_3)_4$ and potassium carbonate in dioxane to afford 6-aryl-4-chloroquinoline **118** (Scheme 30). Subsequent replacement of chlorine

under the same conditions to afford 4,6-diarylquinolie **119** occurred very slowly with very low yields (7%). Improved yields (97%) were however, obtained by the use of dioxane-H_2O (3:1) mixture as a solvent in 4 h. The experimentally found bond dissociation energies or bond strength for phenyl halides (D_{Ph-X}) are 126, 96, 81 and 65, kcal/mol at 298 K for X = F, C1, Br, and I are consistent with the order of reactivity, ArI > ArBr > ArC1 > ArF which results in iodine atom at C-6 position being displaced first followed by the Cl displacement at C-4 position.

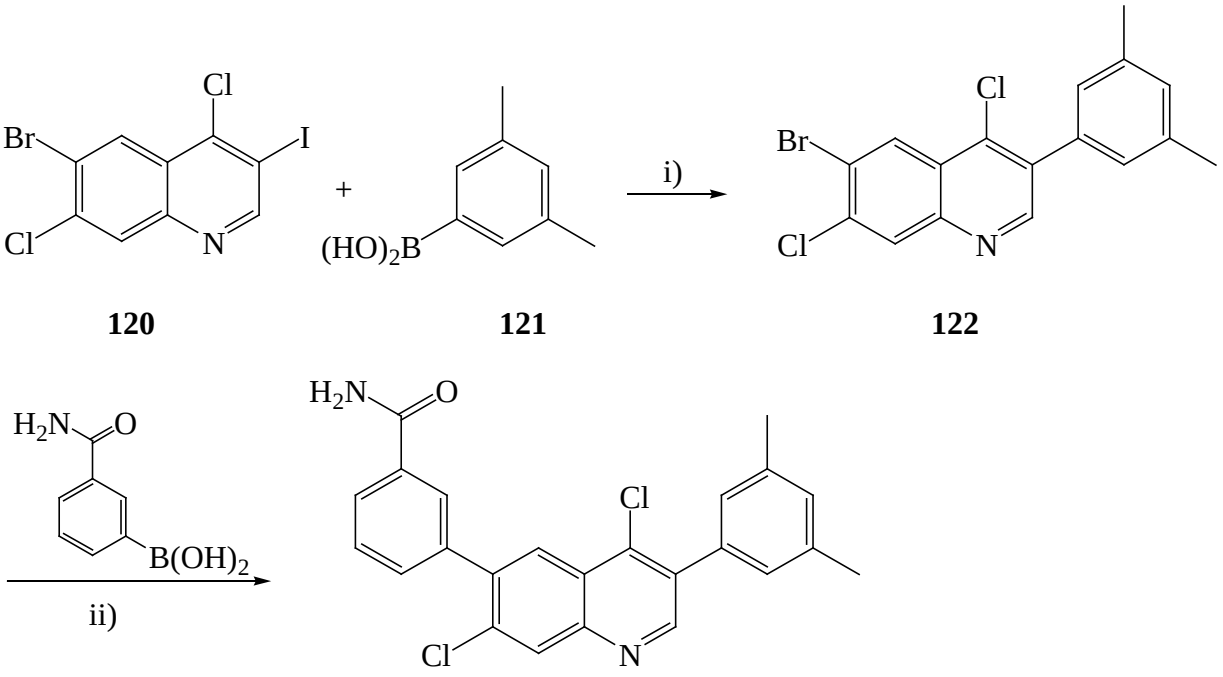


117 **118** **119**

Reagents and conditions: i) 4-methoxyphenylboronic acid, 2 mol% $Pd(PPh_3)_4$, K_2CO_3, dioxane-H_2O, reflux; ii) 4-methylphenylboronic acid, 2 mol% $Pd(PPh_3)_4$, K_2CO_3, dioxane-H_2O, reflux

Scheme 30

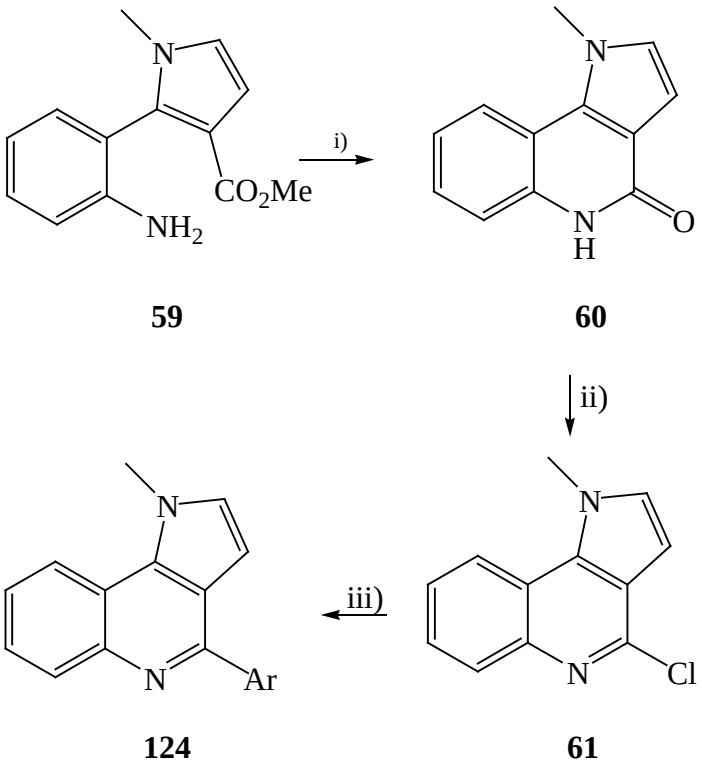
Polyhalogenated quinoline derivative **120** was subjected to successive palladium-catalyzed cross coupling with 3,5-dimethylboronic acid **121** to afford 3-arylsubstituted quinoline derivative **122** and 3,6-diarylquinoline **124** respectively (Scheme 31)[57].



Reagents and conditions: i) Pd(dppf)Cl_2, 1M aq Cs_2CO_3, THF, 35 ºC, 72 h; ii) Pd(dppf)Cl_2, 1M aq Cs_2CO_3, THF, MW, 100 ºC, 15 min

Scheme 31

The precursor for Suzuki coupling, 4-chloro-1-methyl-1*H*-pyrrolo[3,2-*c*]quinoline **61** was obtained by cyclization of 1-methyl-2-(2-aminophenyl)-1*H*-pyrrole-3-carboxylate **59** to give 1-methyl-1*H*-pyrrolo[3,2-c]quinolin-4(5*H*)-one **60** followed by chlorination of an amide to give a imidoyl chloride **58** as a precursor (Scheme 32). Imidoyl chloride was subjected to Suzuki conditions under microwave to afford 4-arylated pyrroloquinoline **124** in good yield (70-91%)[34].



Reagents and conditions: i) CH_3COOH, *sec*-butanol, MW, 100 ºC; ii) $POCl_3$, MW, 100 ºC, iii) $ArB(OH)_2$, Pd catalyst, Cs_2CO_3, dioxane/ H_2O, MW, 100 ºC, 4h

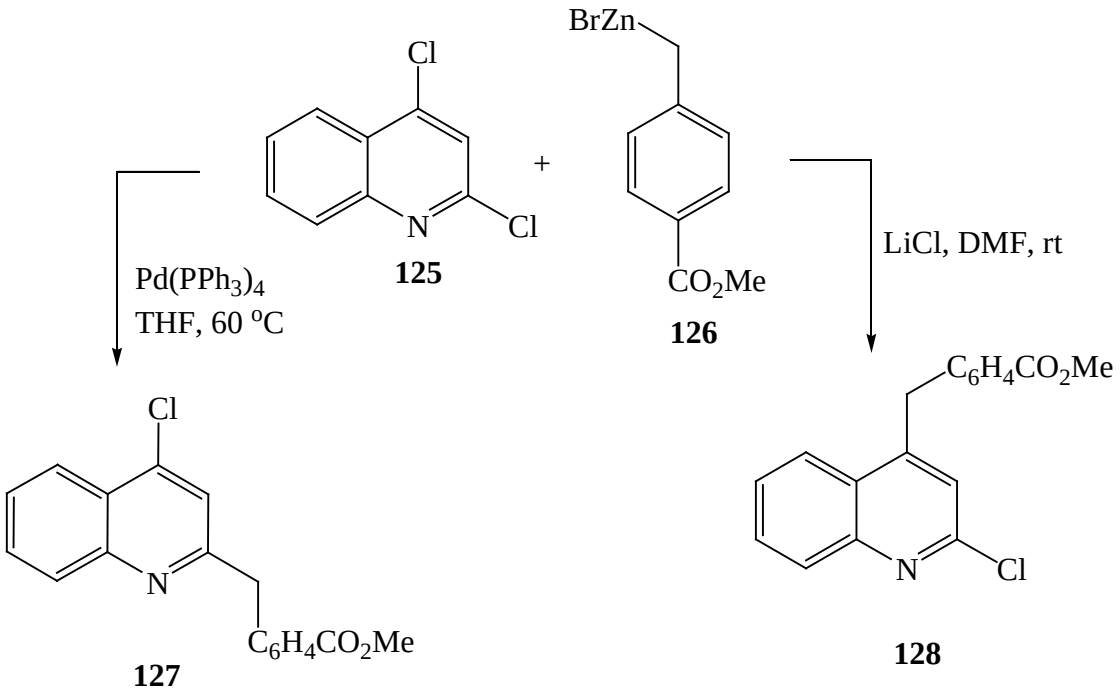
Scheme 32

1.6.2 Applications of Negishi coupling reaction in the synthesis of quinoline derivatives

The palladium-catalyzed Negishi coupling involves the reaction of aryl and vinyl halides/triflates with organozinc reagents for the formation of carbon-carbon bonds. Transition metal-catalyzed organozinc reagents have advantages over the conventional ones because they are synthetically useful, particularly for control of the chemo-, regio- and stereo-selectivity[55]. Organozinc reagents can be prepared either by direct reaction of organic halide with zinc or activated zinc or by transmetallation of the corresponding organolithium or Grignard reagents with a zinc halide. A

wide variety of Ni°, Pd°, Ni^{2+} and Pd^{2+} catalysts have been used for promoting the reactions of organozinc reagents. The most generally used ligands (L) are phosphines. Triphenylphosphine is inexpensive and is a most satisfactory ligand for the desired catalysis. Ni° and Pd° catalysts are considerably less stable than Ni^{2+} and Pd^{2+} catalysts. However, in some cases Ni° and Pd° catalysts are prepared *in situ* by reducing Ni^{2+} and Pd^{2+} catalysts. Organozinc compounds can tolerate a wide range of functional groups in either or both of the coupling partners. Organic halides, especially iodides and bromides, are the most reactive class of electrophiles. However, the use of other leaving groups such as acetates and triflates has also been investigated.

To demonstrate regioselectivity in organozinc coupling reactions, 2,4-dichloroquinoline **125** was reacted with benzyl zinc reagent **126** in the presence of various additives (Scheme 33)[56]. In the first reaction, 2,4-dichloroquinoline **125** was reacted with benzyl zinc **126** in the presence of tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) (0.05 equiv) in THF at 60 ºC to exclusively afford 2-substituted product **127** in 80% yield. In the second reaction, the same reagents **125** and **126** were reacted in the presence of lithium chloride (LiCl) (4 equiv) in DMF at room temperature to afford a 4-substituted quinoline **128**. Selective coupling at the C-2 position is known to be favoured by coordination of palladium to the quinoline nitrogen[56]. On the other hand, halide ions are known to have high affinity for and to coordinate strongly to zinc metal[56]. Thus in a polar solvent such as DMF, which is known to assist in stabilizing ionized transition states and intermediates, LiCl is ionized and the chloride ion, in turn, coordinates to zinc and polarizes C–Zn bond. This coordination promotes transmetalation to the more nucleophilic organolithium reagent that selectively attacks the C-4 position of the quinoline **125** to afford **128**.

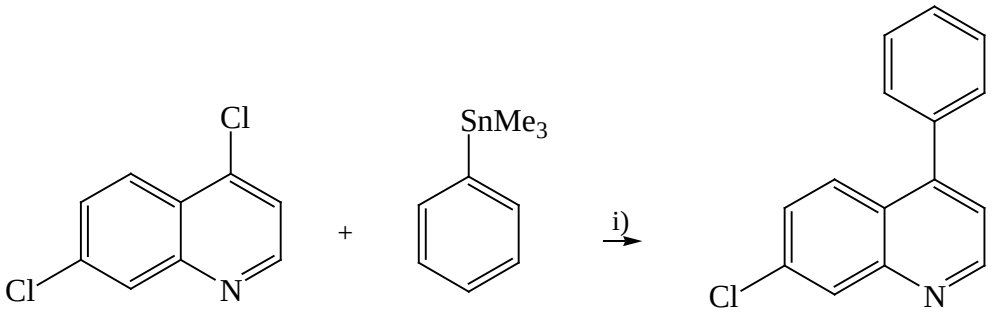


Scheme 33

1.6.3 Applications of Stille coupling reaction in the synthesis of quinoline derivatives

The Stille coupling is the Pd-catalyzed reaction between organostannanes and organic halides, with very few limitations on the R groups. Typically the stannane is sp^2 or sp hybridized (aryl, alkenyl, alkynyl) and also alkyl-, allyl- and benzyl-stannanes are used. The main drawback is the toxicity of the tin compounds used, and their low polarity, which makes them poorly soluble in water. Stannanes are stable, but boronic acids and their derivatives undergo much the same chemistry in what is known as the Suzuki coupling, discussed above. Improvements in the Suzuki coupling lead to the same versatility without the drawbacks of using tin compounds[57].

Wolf and coworkers[58] reported an efficient aqueous C-C bond formation procedure employing commercially available, water-soluble palladium-phosphinous acid complexes [(*t*-Bu)$_2$P(OH)]$_2$PdCl$_2$ (POPd), ([(*t*-Bu)$_2$P(OH)(*t*-Bu)$_2$PO)]-PdCl)$_2$ (POPd1), and [(*t*-Bu)$_2$P(OH)PdCl$_2$]$_2$ (POPd2) in the coupling reaction of aryl chlorides or bromides and phenyltrimethylstannane (Scheme 34). The introduction of palladium-phosphinous acids to aqueous organic catalysis using inexpensive aryl chlorides and bromides provides another entry for the development of coupling procedures utilizing water as the solvent. The stability to air of palladiumphosphinous acid complexes POPd, POPd1, and POPd2 greatly facilitates catalyst handling and operation of the Stille reaction because working under an inert atmosphere is not required. 4,7-Dichloroquinoline **129** was reacted with phenyltrimethylstannane **130** in the presence palladium-phosphinous acid complexes, *N*,*N*-dicyclohexylmethylamine (Cy$_2$NMe) (1.2 equiv) and water at 135-140 ºC afforded 7-chloro-4-phenylquinoline **131** (Scheme 34).



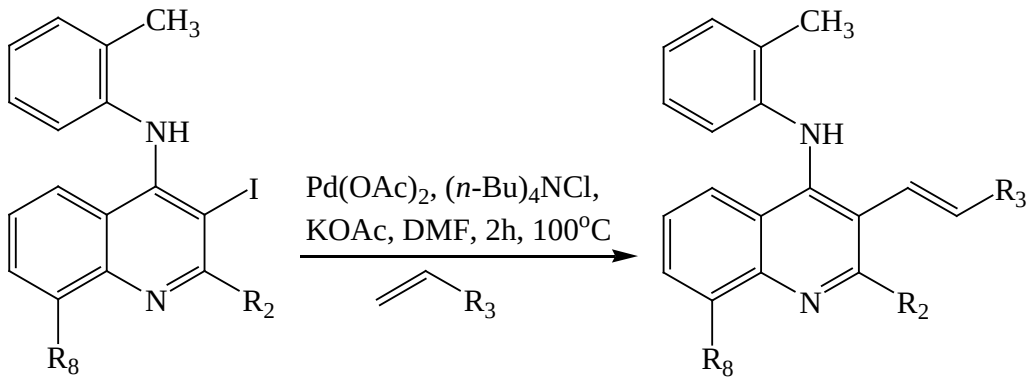
129 **130** **131**

Reagents and conditions: i) 6 mol% Pd catalyst, Cy$_2$NMe, H$_2$O, 135-140 ºC, 24 h

Scheme 34

1.6.4 Applications of Heck coupling reaction in the synthesis of quinoline derivatives

The Heck reaction involves cross coupling of an unsaturated halide with an alkene in the presence of strong base and palladium as catalyst to form a substituted alkene[59]. An aryl, benzyl or vinyl halide or triflate and the alkene which contains at least one proton is often electron deficient for example acrylate ester or an acrylonitrile is employed as coupling partners. $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ are commonly used as catalysts. The bases commonly used include triethylamine, potassium carbonate or sodium acetate. 4-(2-Methylphenylamino)-3-iodoquinoline **132** was subjected to standard Heck reaction conditions in the presence of terminal alkenes to afford 3-vinylquinolines **133** with potential activity (Scheme 35)[13].



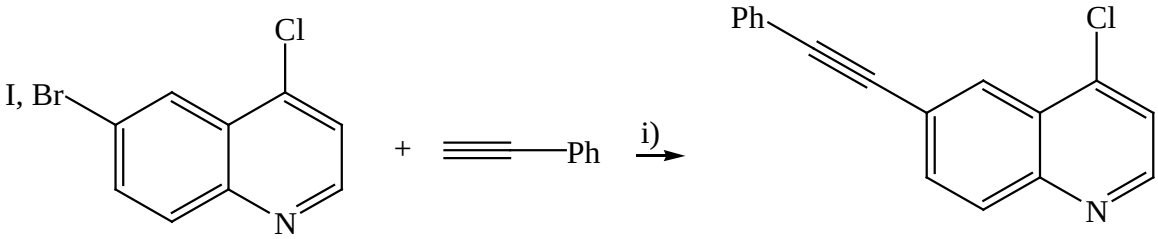
132 **133**

Scheme 35

The advantage for this reaction is the *trans* selectivity and functional group compatibility.

1.6.5 Applications of Sonogashira coupling reaction in the synthesis of quinoline derivatives

Palladium-catalysed alkynylation of aryl or heteroaryl rings has proved to be a powerful method for the C-C bond formation. This reaction involves palladium-catalyzed sp^2-sp coupling between aryl or alkenyl halides or triflates and terminal alkynes[60]. Typically, the coupling reactions are carried out in the presence of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ and a copper salt as co-catalyst in the presence of an amine base. The use of dihalo derivatives of arenes and hetarenes as substrates for the regioselective introduction of substituents *via* cross-coupling markedly extends the scope of the method and opens up a facile synthetic approach to diverse classes of di- and polysubstituted aromatic or heteroaromatic compounds. Conduction of consecutive substitution reactions using electron-deficient heterocycles containing two halogen atoms, one being located in a position activated toward a nucleophilic attack, is of particular interest[61]. Selective monoalkynylation of 4,6-dihaloquinolines **134** was achieved on 4-chloro-6-iodoquinoline using phenylacetylene in THF in the presence of 2 equiv. of Et_3N and a catalytic amount of $Pd(PPh_3)_4$ and CuI to afford the product of iodine replacement **135** in 81% yield (Scheme 36).

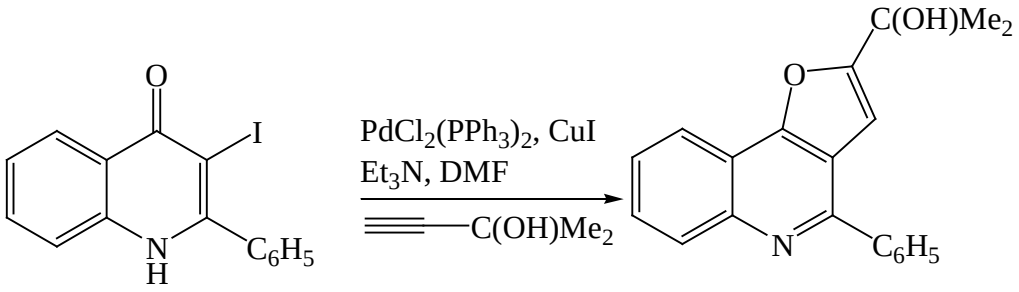


134 **135**

Reagents and conditions: i) $Pd(PPh_3)_4$, CuI, Et_3N, THF

Scheme 36

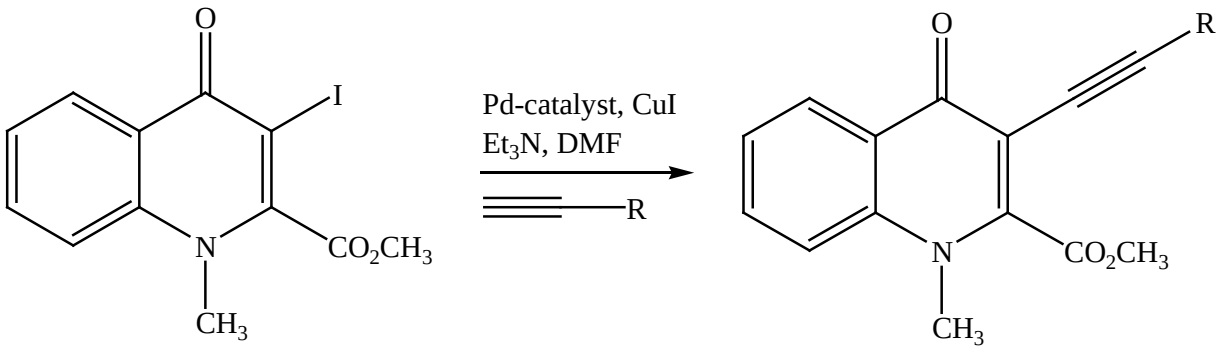
One pot process involving Sonogashira type coupling followed by the electrophilic or transition metal-mediated cyclization of the resulting alkynes possessing a suitable nucleophilic group in proximity to the triple bond has now emerged as a versatile and efficient route to various substituted heterocyclic systems[62]. In the synthesis of furo[3,2-*c*]quinoline **137**, 3-iodo-2-phenyl-1*H*-quinolin-4-one **136** was treated with 2.0 equiv of 2-methyl-3-butyn-2-ol in the presence of $PdCl_2(PPh)_3$ (0.03 equiv), CuI (0.06 equiv) and Et_3N (5 equiv) in DMF under N_2 atmosphere (Scheme 37). Alkyl, aryl hydroxyl groups and other functional groups present in the terminal alkynes are well tolerated.



136 **137**

Scheme 37

In the proposed mechanism for cyclization step, there is activation of the newly formed carbon-carbon triple bond by a metal[62]. When 3-iodo-1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester **138** was treated with terminal alkynes under the same conditions only 3-alkynyl quinolones **139** were isolated (Scheme 38). The cyclization step to afford the furoquinoline in the case of **136** is promoted by the abstraction of the acidic N-H proton by the NEt_3, which leads to intramolecular attack of the transition-metal activated triple bond of the 3-alkynyl moiety by the negatively charged oxygen.

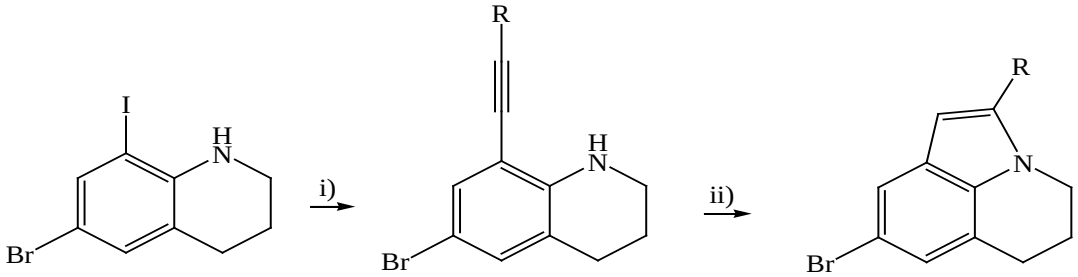


138 **139**

R=C(OH)Me_2, C_6H_5

Scheme 38

In the synthesis of 2-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline **142**[63], 8-iodo-6-bromo-1,2,3,4-tetrahydroquinoline **140** was reacted with a number of terminal alkynes in the presence of 10% Pd/C-CuI-PPh_3 in water at 80 ºC using 2-aminoethanol as a base to afford coupled products **114** in moderate to good yield (50-92%) (Scheme 39). Intramolecular cyclization of alkynes was carried out in the presence of CuI in DMF at 100 ºC for 12 hours to afford cyclized products **142**.

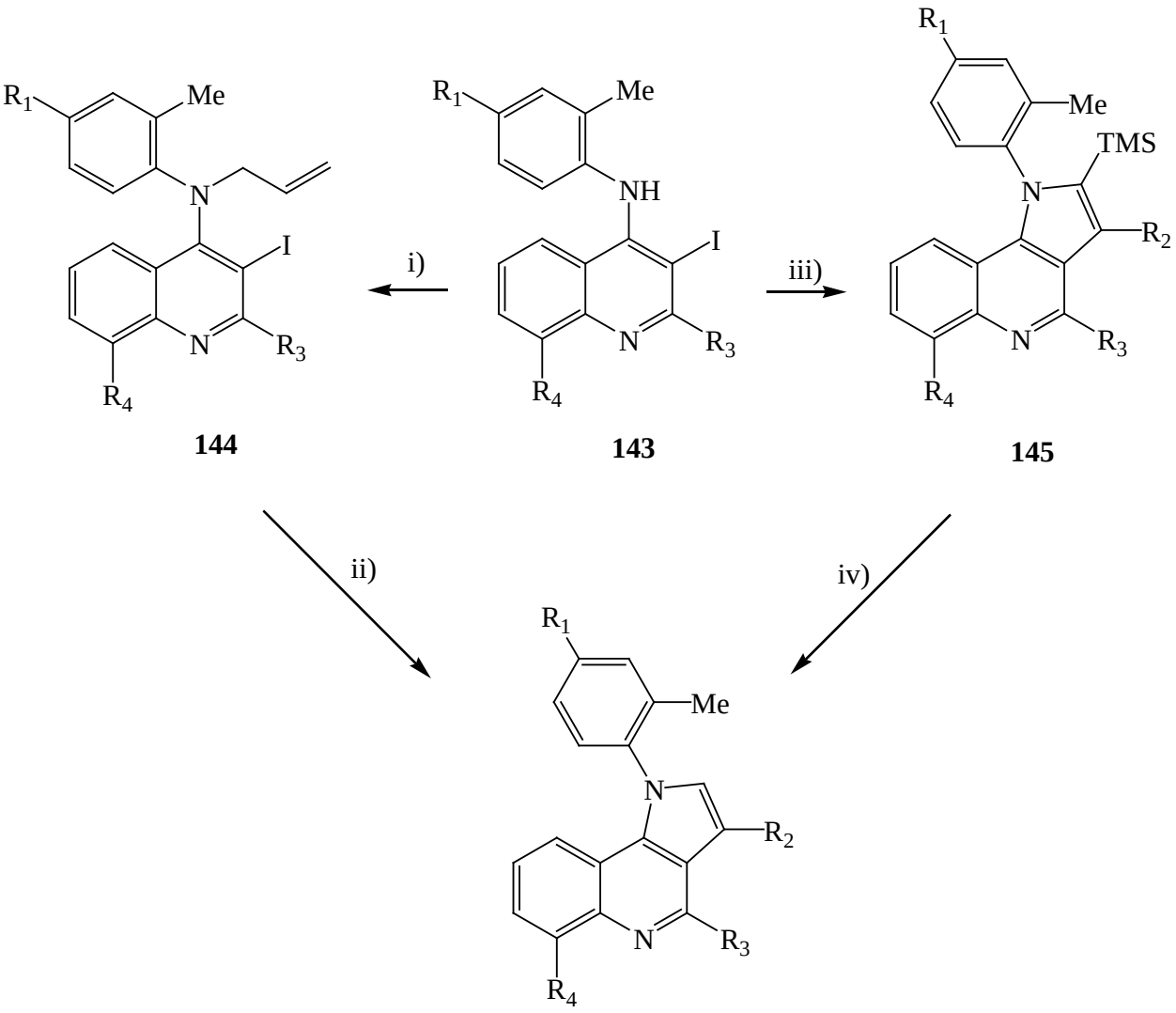


140 **141** **142**

Reagents and conditions: i) Terminal alkyne (3 equiv), Pd/C-CuI-PPh_3 (1:4:2), 2-aminoethanol (3 equiv), H_2O, 80 ºC; ii) CuI, DMF, 100 ºC

Scheme 39

The synthesis of 1-aryl-3-substituted pyrrolo[3,2-*c*]quinolines was previously carried out by two different routes (Scheme 40)[64]. The first route involved intramolecular Heck reaction of 4-(*N*-allyl-*N*-aryl)amino-3-iodoquinoline **144** in the presence of $Pd(OAc)_2$, LiCl, KOAc and HCO_2Na in DMF at 100 ºC to afford 3-alkyl-1-arylpyrrolo[3,2-*c*]quinolines **146** in 55-85% yields. This intramolecular reaction provided only alkyl chains at the C-3 position. The second route involved one-pot intermolecular palladium-catalyzed cross-coupling of the 3-iodo-4-(phenylamino)quinolines **143** with internal alkynes in the presence of $Pd(OAc)_2$, LiCl and KOAc in DMF at 120 ºC followed by heteroannulation to afford the 1-aryl-2-trimethylsilyl-3-substituted pyrrolo[3,2-*c*]quinoline **145**. Desilylation of the latter with trifluoroacetic acid or 1 *N* NaOH in methanol under reflux afforded the 3-alkyl-1-arylpyrrolo[3,2-*c*]quinolines and 1-aryl-3-hydroxyalkylpyrrolo[3,2-*c*]quinolines **146**. A method that would afford systems **146** in a single-pot operation without involving an additional step such as desilylation is required.



Reagents and conditions: i) Allyl halide, NaH, THF, rt; ii) 5% $Pd(OAc)_2$, 1 eq LiCl, 2 eq KOAc, 2 eq HCO_2Na, DMF, 100 ºC; iii) R_2–≡–TMS, 5% $Pd(OAc)_2$, 1 eq LiCl, 2 eq KOAc, DMF, 120 ºC; iv) 1*N* NaOH, CH_3OH, reflux, 1 h

Scheme 40

1.7 Research hypothesis and problem statement

Pyrroloquinoline derivatives are postulated to act as a conformationally restrained analogue of 4-(arylamino)quinoline[12], a gastric (H^+/K^+)–ATPase inhibitor. These substrates are also found to possess biological activity as antitumor agents, acting as DNA intercalators[65]. The planar arrangement of substituents on the pyrroloquinoline moiety makes it possible to interact with tumor cell, thereby inhibiting rapid growth of cancerous cells. The amine substituent on C-4 of the quinoline moiety enhances the binding of substrates to various receptors in the body. The interest in this work is in the syntheses of substituted pyrroloquinolines derivatives, 1,2,4-trisubstituted pyrrolo[3,2-c]quinoline and 1,3,4- trisubstituted pyrrolo[3,2-c]quinoline of the generalized structure (Fig. 5).

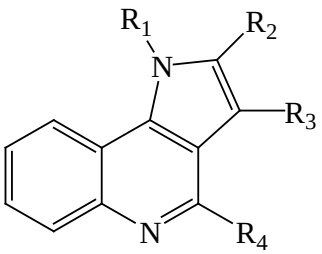


Figure 5: Generalised structure of pyrrolo[3,2-*c*]quinoline

The close proximity of the two reactive centers at C-3 and C-4 to effect possible one-pot Csp^2-C*sp* bond formation and annulation to lead to the target 1,2,4-trisubstituted pyrrolo[3,2-c]quinoline derivatives is used. Two possible routes are envisaged. Route A which makes use of known 2-aryl-4-chloro-3-iodoquinoline to form an alkynyl substituent at C-3 by Sonogashira cross coupling, followed by nucleophilic displacement of Cl by aniline at C-4 to afford 4-anilino-3-alkynyl-2arylquinoline as a precursor for a cyclization step. Literature precedence show that

there is a possibility that the initial Sonogashira cross coupling can occur at both C-3 and C-4 of the quinoline framework to afford a doubly alkynylated substrate. It is believed that control of the conditions and the ease of displacement of iodo atom can ensure coupling only at C-3. Route B, on the other hand, would involve the initial nucleophilic displacement of Cl atom by aniline followed by possible Sonogashira cross-coupling at C-3 and subsequent heteroannulation to form pyrroloquinolines in a one-pot operation. Whereas route A requires one extra cyclisation step with the possibility of forming a dialkynyl-quinoline derivatives route B may lead to annulated derivatives in a one-pot operation.

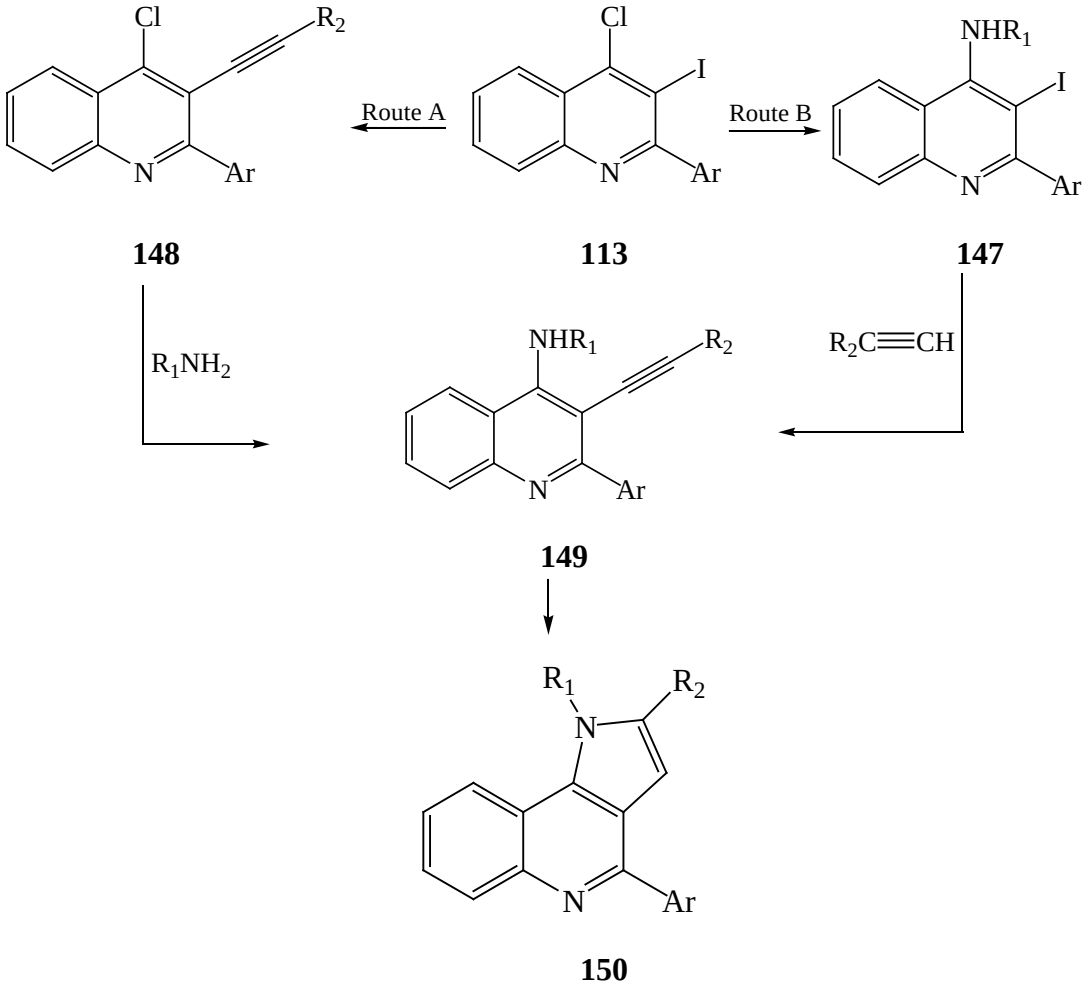


Figure 6: Possible routes for Sonogashira cross coupling reaction

The synthesis of the 1,3,4-trisubstituted pyrrolo[3,2-*c*]quinolines would require the 2-aryl-3-iodo-4-phenylaminoquinoline to be converted to 4-(*N*,*N*-allyphenylamino)-2-aryl-3-iodoquinolines and then subjected to standard intramolecular Heck conditions to afford a tricyclic structures (Fig. 7). The possibility of Csp^2-Csp^2 bond formation involving C-3 and the phenyl carbon of the aniline group to form indolo[3,2-*c*] derivative **153** cannot be ruled out.

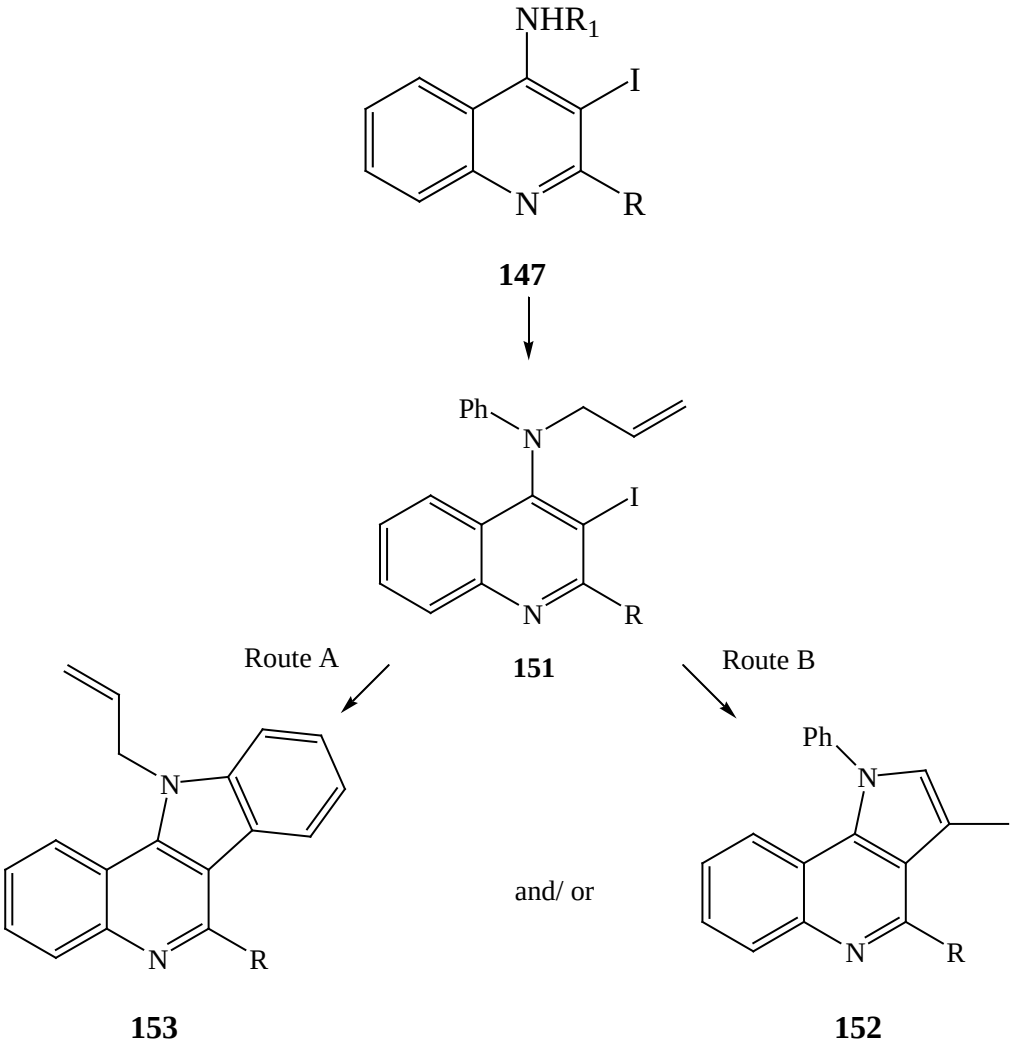


Figure 7: Possible routes for Heck cross-coupling reaction

1.8 Aims and Objectives

With above hypothesis it was decided to investigate the possibility of displacing the chlorine atom at the γ-position of the quinoline ring of the previously described 2-aryl-4-chloro-3-iodoquinolnes to afford the 2-aryl-3-iodo-4-(phenylamino)quinolines with potential to undergo palladium-catalyzed Sonogashira cross-coupling with terminal alkynes. The 4-amino moiety bears a labile proton for possible substitution with allyl bromide to afford the 4-(*N*,*N*-allylphenylamino)quinoline derivatives with potential to undergo intramolecular Heck reaction. The approach to aims and objectives of this project will involve the following activities:

a) To convert 2-aryl-4-chloro-3-iodoquinolines to 2-aryl-3-iodo-4-(phenylamino)quinolines.

b) To prepare 4-(*N*,*N*-allylphenylamino)-2-aryl-3-iodoquinolines from 2-aryl-3-iodo-4-(phenylamino)quinolines.

c) To subject 2-aryl-3-iodo-4-(phenylamino)quinolines to Sonogashira coupling conditions with different terminal alkynes

d) To subject 4-(*N*,*N*-allylphenylamino)-2-aryl-3-iodoquinolines to standard Heck reaction conditions

CHAPTER 2

2. RESULTS AND DISCUSSION

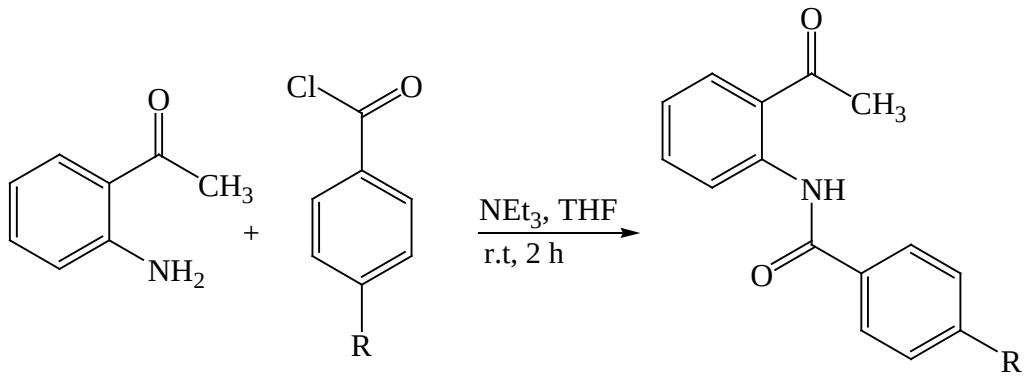
N-benzoyl-2-aminoacetophenone derivatives were prepared by condensing 2-aminoacetophenone and benzoyl chloride derivatives in the presence of NEt_3 in THF. The *N*-benzoyl-2-aminoacetophenones were reacted with *t*-BuOK in *t*-BuOH to afford 2-arylquinolin-4(1*H*)-ones. Treatment of the 2-arylquinolin-4(1*H*)-ones with iodine in the presence Na_2CO_3 afforded the corresponding 2-aryl-3-iodoquinolin-4(1*H*)-ones. The latter were treated with $POCl_3$ to afford the 2-aryl-4-chloro-3-iodoquinolines. The 2-aryl-4-chloro-3-iodoquinolines were, in turn, reacted with aniline in EtOH to afford the 2-aryl-3-iodo-4-phenylaminoquinoline derivatives. The 2-aryl-3-iodo-4-phenylaminoquinoline derivatives were reacted with allyl bromide in the presence of NaH to afford the 4-(*N*,*N*-allyphenylamino)-2-aryl-3-iodoquinoline derivatives.

The aniline derivatives were subjected to Sonogashira cross coupling with terminal alkynes in the presence of $PdCl_2(PPh_3)_2$-CuI catalyst mixture and NEt_3 in DMF to afford the corresponding 1,2,4-trisubstituted pyrrolo[3,2-*c*]quinoline derivatives. 4-(*N*,*N*-allyphenylamino)-2-aryl-3-iodoquinoline derivatives were subjected to Heck reaction in the presence of $PdCl_2(PPh_3)_2$ and NEt_3 in dioxane/H_2O mixture (3:1, v/v) to afford the 1,3,4-trisubstituted pyrrolo[3,2-*c*]quinoline derivatives. The prepared compounds were characterized using a combination of NMR (^1H and ^{13}C), IR, and mass spectroscopic techniques.

2.1 Synthesis of *N*-benzoyl-2-aminoacetophenone derivatives 96

The *N*-benzoyl-2-aminoacetophenone derivatives **96** were prepared by reacting 2-aminoacetophenone **94** with 1.2 equivalents of benzoyl chloride derivatives **95** in the presence of NEt_3 in THF according to the literature method (Scheme 41)[41]. The compounds were characterized by ^1H NMR spectroscopy and the spectral data were found to compare favourably with those reported in literature. ^1H NMR spectra show the presence of a singlet at δ *ca.* 2.71 ppm integrating for three hydrogens and this signal corresponds to methyl group of the $COCH_3$ group. Resonances in the region δ 6.95-8.98 ppm correspond to aromatic protons while an NH proton signal resonates as a broad singlet at δ *ca.* 12.70 ppm.

The melting point values of the prepared compounds also compare well with those reported in the literature[46]. The compounds were prepared in high yield and purity without the use of chromatographic separation.



94 **95** **96**

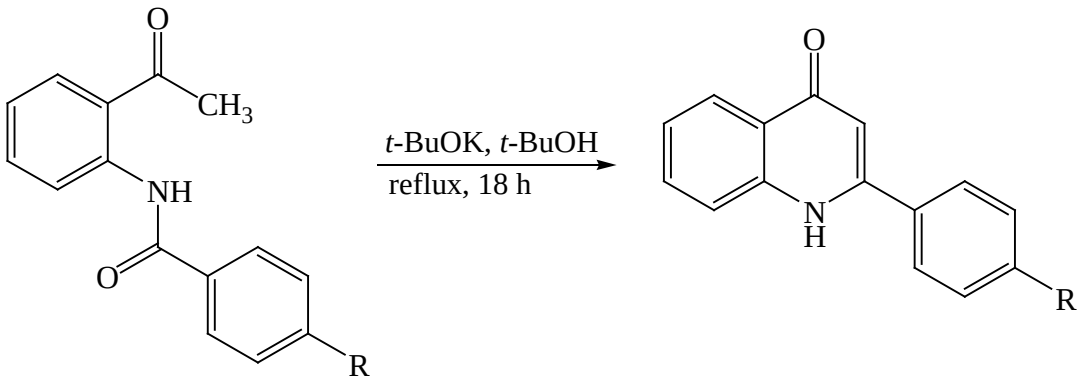
96	4′-R	δ ($COCH_3$)	δ (Aromatic H)	δ (N-H)	% Yield	m.p. ºC; (Lit. ºC) [ref]
a	4′-H	2.72	7.15 – 8.98	12.72	95	96-98; (lit. 98.5-99)[46]
b	4′-F	2.70	7.15 – 8.92	12.65	95	90-92; (lit. 92-95)[46]
c	4′-Cl	2.71	7.16 – 8.98	12.72	97	107-108; (lit. 106-109)[46]
d	4′-OMe	2.72	6.98 – 8.96	12.62	95	118-120; (lit. 119-121)[46]

Scheme 41

2.2 Synthesis of 2-arylquinolin-4(1*H*)-one derivatives 97

In addition to the Conrad Limpach synthesis[4], several other methods for the synthesis of 2-arylquinolin-4(1*H*)-ones have been developed. One of the earlier methods involves heating anthranilic acid with acetal of an alkyl aryl ketone to yield 2-arylquinolin-4(1*H*)-one[66]. Another method involves the condensation of substituted aryl amines with 2,2-dimethyl-5-methylthioalkylidene-1,3-dioxane-4,6-diones, prepared from 2,2-dimethyl-1,3-dioxane-4,6-diones[66]. The reaction is carried out in diphenyl ether or ethanol under reflux to afford 2-alkyl- and 2-arylquinolin-4(1*H*)-ones upon cyclization in diphenyl ether at high temperatures. Other methods make use of transition metals. One method involves palladium-catalyzed intramolecular cyclisation of 2-aminochalcones to afford 2-aryl-4-quinolones **97**[67]. A mixture of 2-aminochalcone and dichloro-bis(triphenylphosphine)palladium(II) in THF and NEt_3 was stirred at 60 ºC under nitrogen atmosphere to afford **97**. Unfortunately, this method requires equimolar amount of the more expensive dichloro-bis(triphenylphosphine)palladium(II). Palladium-catalyzed carbonylation of 2-haloaniline in the presence of terminal alkynes under CO at 120 ºC

for example, afforded 2-substituted quinolin-4(1*H*)-ones[68]. This reaction proceeds well in both secondary (diethylamine) and tertiary amines (triethylamine) and in benzene containing 4 equivalents of diethylamine[68]. The disadvantage with this method is the use of the toxic carbon monoxide. A literature methods that involves the reaction of *N*-benzoyl-2-aminoacetophenone derivatives **96** with *t*-BuOK in *t*-BuOH to afford the cyclized 2-arylquinolin-4(1*H*)-one derivatives **97** was followed (Scheme 42)[41]. This method is high yielding and the pure products are isolated without the need for tedious column chromatographic separations (Table 2).



96 **97**

97	**4′-R**	**δ (3-H)**	**δ (ArH)**	**δ (N-H)**	**% Yield**	**m.p. ºC; (lit. ºC) [ref]**
a	4′-H	6.34	7.34 – 8.10	11.73	90	240-241; (lit. 240-243)[43]
b	4′-F	6.32	7.32 – 8.10	11.76	94	319-320; (lit. 322-325)[43]
c	4′-Cl	6.32	7.32 – 8.10	11.76	96	323-324; (lit. 270-273)[43]
d	4′-OMe	6.32	7.32 – 8.10	11.76	92	294-296; (lit. 290-293)[43]

Scheme 42

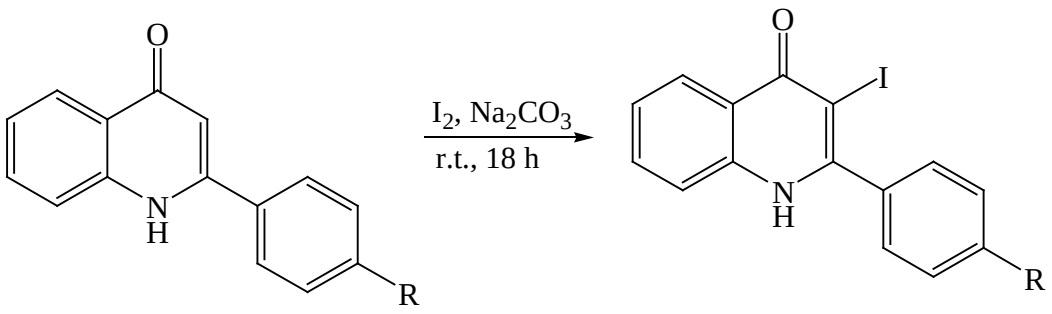
The proton spectra of these compounds also show two singlets at δ *ca.* 6.32 ppm and δ *ca.* 11.76 ppm, which correspond to 3-H and N-H protons, respectively. The absence of methyl proton

signals of $COCH_3$ in the ^1H NMR spectra confirms the structure to be that of the 2-arylquinolin-4(1*H*)-one derivatives. The melting point values are also comparable to those reported in literature for the corresponding compounds[54].

2.3 Synthesis of 2-aryl-3-iodoquinolin-4(1*H*)-one derivatives 98

2-Phenylquinolin-4(1*H*)-one **97** was previously iodinated using iodine-ammonium cerium nitrate mixture in acetonitrile at 70-80 ºC to afford 2-phenyl-3-iodoquinolin-4(1*H*)-one **98a**[62]. The 2-substituted 3-iodo-1-methylquinolin-4(1*H*)-ones were also prepared before via iodocyclization of the dimethylamino systems using iodine in dichloromethane[66]. Previously described method which involves the use of readily available and easy to handle reagents for the iodination of substrates was employed. The 2-arylquinolin-4(1*H*)-ones **97** were reacted with I_2 in the presence of Na_2CO_3 in THF at room temperature to afford the corresponding 2-aryl-3-iodoquinolin-4(1*H*)-ones **98** (Scheme 43)[69]. The analogous 2-aryl-3-bromoquinolin-4(1*H*)-ones **98b** can be prepared from the corresponding 2-arylquinolin-4(1*H*)-ones **97** using pyridinium tribromide in acetic acid at room temperature[69].

The ^1H NMR of products **98** are characterized by the absence of a singlet at δ *ca.* 6.32 ppm for 3-H thus confirming incorporation of iodine atom at the 3 positions of the quinolone ring. The presence of an N-H group was confirmed by a broad singlet at δ *ca.* 12.30 ppm. Although the melting point values of some of the compounds deviated from the literature values, NMR spectral data is consistent with the assigned structure.



97 **98**

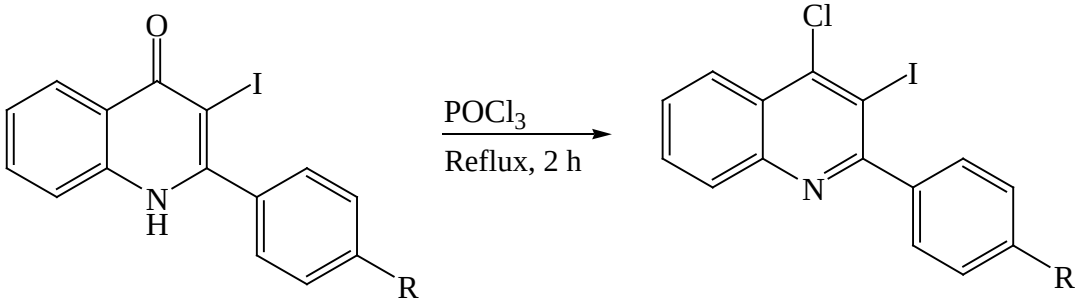
98	**4′-R**	**δ (ArH)**	**δ (N-H)**	**% Yield**	**m.p. °C; (lit. °C) [ref]**
a	4′-H	7.40 – 8.15	12.30	90	282-284; (lit. 284-286)[69]
b	4′-F	7.36 – 8.15	12.32	77	196-197; (lit. 196-198)[69]
c	4′-Cl	7.41 – 8.14	12.30	71	231-233; (lit. 254-256)[69]
d	4′-OMe	7.11 – 8.13	12.20	83	239-241; (lit. 262-264)[69]

Scheme 43

2.4 Synthesis of 2-aryl-4-chloro-3-iodoquinoline derivatives 113

Several methods have been described before for the synthesis of 4-halogenoquinolines. 4-Bromo-3-methoxyaniline and diethylethoxymethylene malonate, for example, were reacted in acetonitrile at room temperature followed by a one-pot cyclization-chlorination to afford 4-chloroquinoline ester (see Scheme 27)[50]. The drawback of this approach is that once these systems have been aromatized, activation at C-3 is difficult. C-4 halogenation was also achieved via tosylation of 4-hydroxy quinoline followed by reaction with I_2 in the presence of red phosphorus in glacial acetic acid at room temperature to afford 4-iodoquinolines in good

yields[70]. Unfortunately, this approach works well with quinoline derivatives bearing a strong electron-withdrawing group such as trifluoromethyl group (CF_3) at the 2-position. One of the most convenient ways of preparing quinoline derivatives activated at position 4 for nucleophilic attack involves the aromatization of the corresponding NH-4-oxo precursors. The literature method that involves aromatization of 2-aryl-3-iodoquinolin-4(1*H*)-one derivatives **98** using $POCl_3$ under reflux to afford the previously described 2-aryl-4-chloro-3-iodoquinoline derivatives **113** was opted for (Scheme 44)[47]. The success of this transformation was confirmed by the absence of N-H peak in the ^{1}H NMR spectra of systems **113** and the presence of the aromatic proton signals in the region δ 7.11–8.30 ppm. Although the melting points differ from those reported, ^{1}H NMR spectroscopic data is consistent with the assigned structures, which confirms the transformation of **98** to **113.** Moreover, the IR spectra of products **113** are characterized by the absence of the C=O stretch found in the spectra of the corresponding substrate.



98 **113**

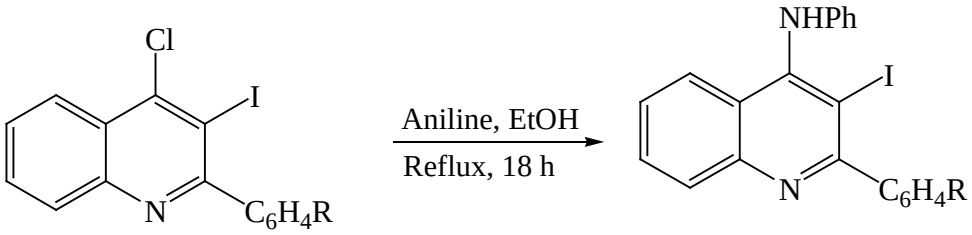
113	**4′-R**	**δ (ArH)**	**% Yield**	**m.p. ºC; (lit. ºC)[ref]**
a	4′-H	7.45 – 8.27	82	254-256; (lit. 150-153)[47]
b	4′-F	7.45 – 8.27	87	180-181; (lit. 176-178)[47]
c	4′-Cl	7.41 – 8.14	96	300-301; (lit. 218-220)[47]
d	4′-OMe	7.11 – 8.13	83	239-241; (lit. 185-187)[47]

Scheme 44

Nucleophilic displacement of 4-chloro atom from 4-chloroquinoline by sodium azide[46], amines[13] and sodium methoxide[47] take advantage of the ease of displacement of the chloro atom at the γ-position (relative to the nitrogen) of the quinoline ring.

2.5 Synthesis of 2-aryl-3-iodo-4-(phenylamino)quinoline derivatives 143

The 2-aryl-4-chloro-3-iodoquinoline derivatives **113** were reacted with aniline in ethanol under reflux to afford the hitherto unknown 2-aryl-3-iodo-4-phenylaminoquinoline derivatives **148** (Scheme 45). The ^{1}H NMR spectra of systems **114** show the presence of a broad singlet at δ *ca*. 6.60 ppm which corresponds to N-H proton of the 4-anilino group.



113 **147**

143	**4′-R**	**δ (N-H)**	**ν_{max} (cm^{-1}) N-H**	**% Yield**	**m.p. °C**
a	4′-H	6.60	3363	86	159-161
b	4′-F	6.62	3368	76	191-192
c	4′-Cl	6.58	3368	77	199-200
d	4′-OMe	6.56	3369	72	210-212

Scheme 45

The aromatic region δ *ca.* 6.86-8.03 ppm shows increased number of proton signals and this confirms the incorporation of the anilino group (Fig. 8). The doublet at δ *ca.* 6.90 ppm which integrates for 2 protons corresponds to the 2-H and 6-H on the newly formed 4-anilino group. Moreover, the ^{13}C NMR spectra show extra peaks due to the presence of phenyl group of the aniline moiety at the 4 positions (see Table 1). The presence of the C*sp*^{2}-I bond is confirmed by the carbon signal δ *ca*. 90.4 ppm and this further confirms that substitution occured at the C-4 position (Fig 9). The accurate calculated *m/z* value represents closest fit consistent with the incorporation of the anilino group. Mass spectrometric data reveal the presence of iodine atom in the molecular ion and the absence of two peaks in the ratio 3:1 which are typical for the chlorine isotopes ^{35}Cl and ^{37}Cl. IR spectra, on the other hand, reveal absorption bands at ν_{max} 3363-3369 cm^{-1} due to an N-H stretch.

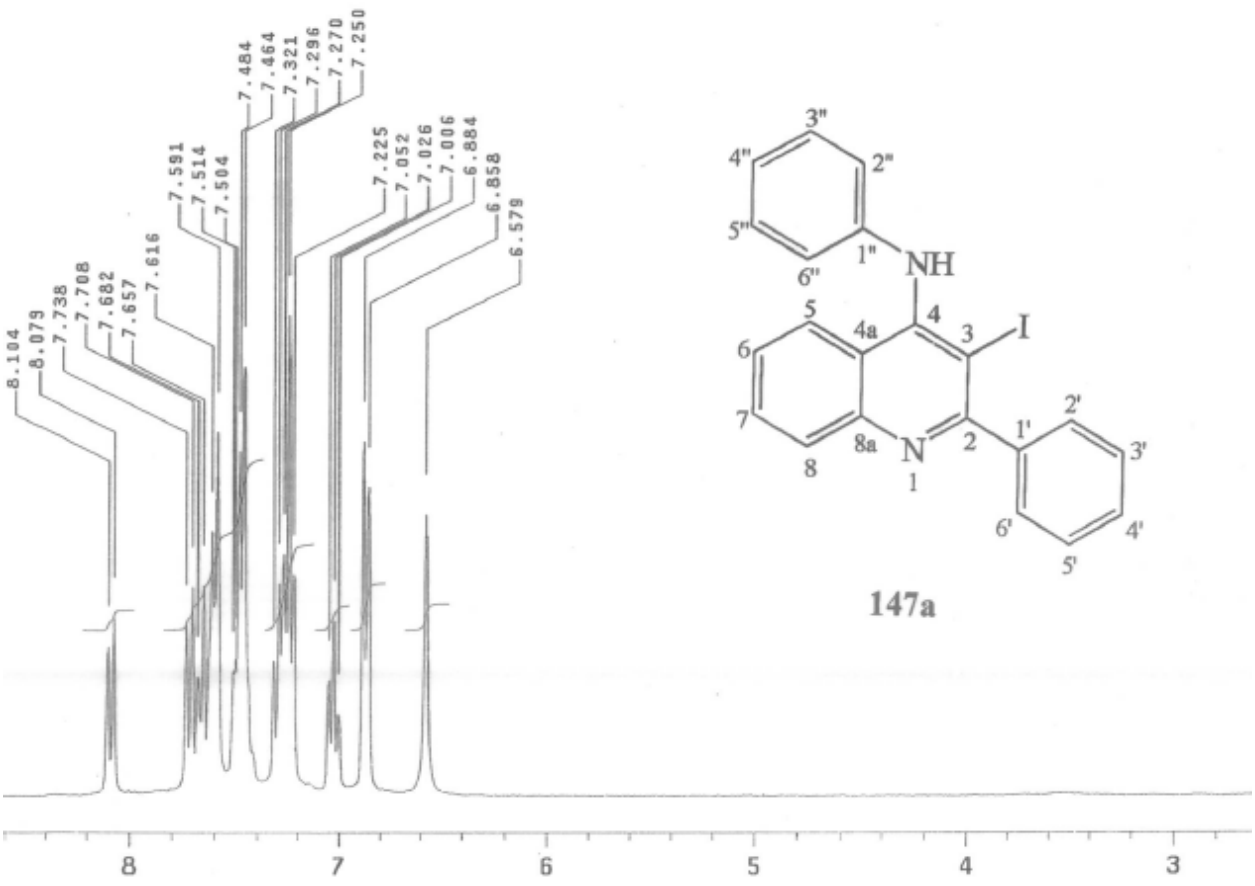


Figure 8: ^{1}H NMR spectrum of 2-phenyl-3-iodo-4-(phenylamino)quinoline **147a**

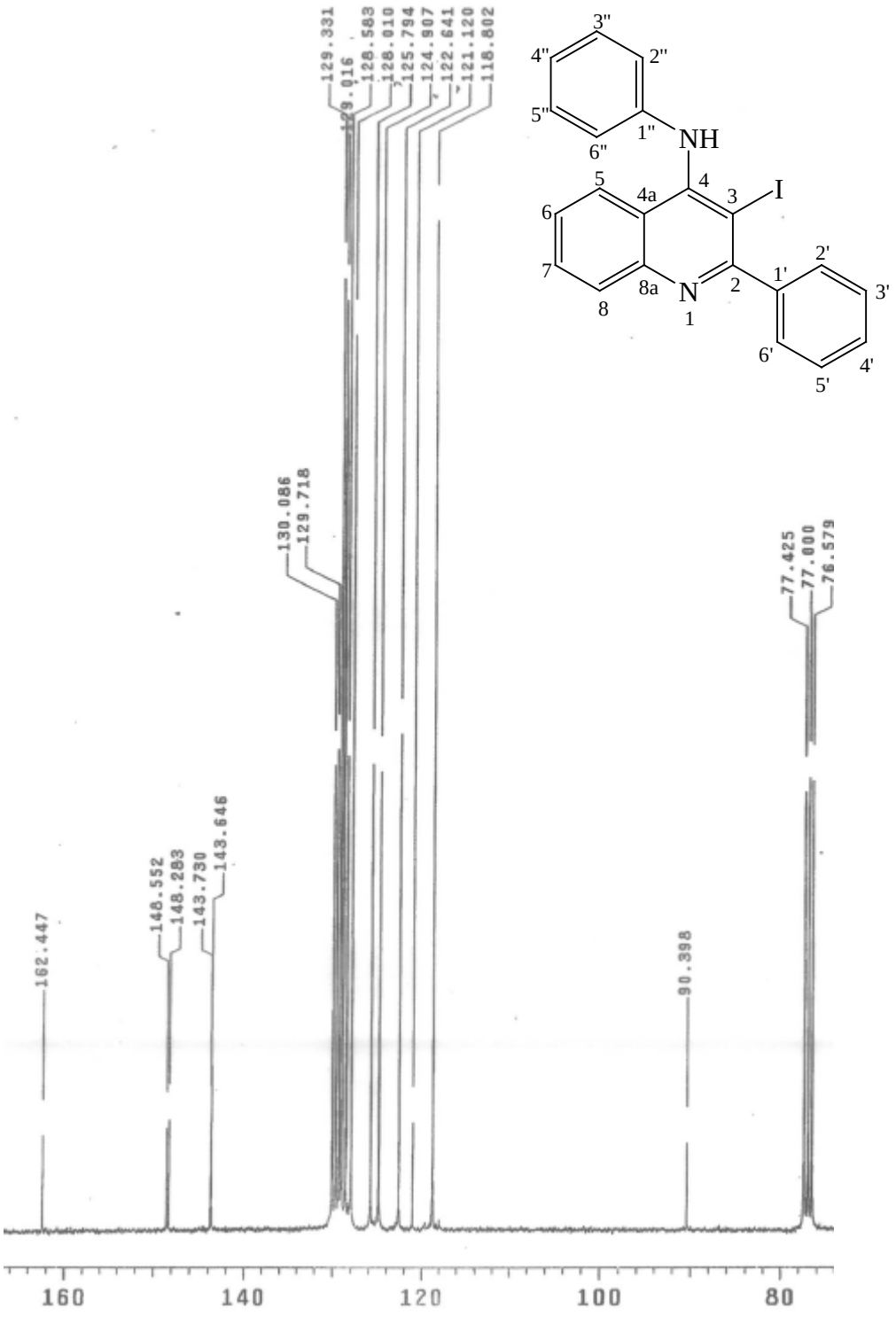
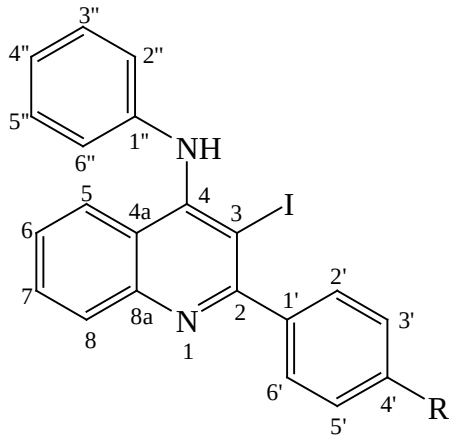


Figure 9: ^{13}C NMR spectra of 2-phenyl-3-iodo-4-(phenylamino)quinoline **147a**

Table 1: ^{13}C NMR chemical shift values of **147** in $CDCl_3$ (at 75 MHz)

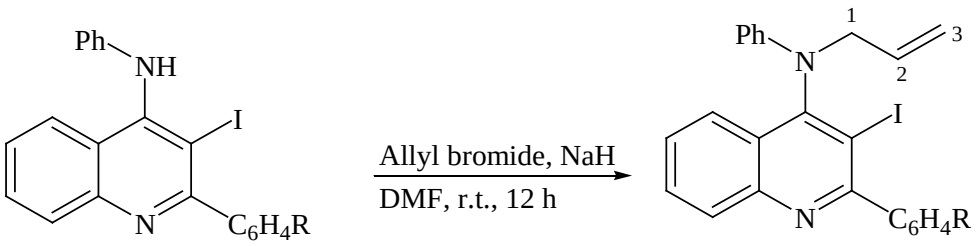


Nucleus	**147a** (R = H)	**147b (**R = F)	**147c** (R = Cl)	**147d (**R = OMe)
C-2	162.45	161.31	161.19	162.08
C-3	90.40	90.16	89.67	91.04
C-4	148.55	148.74	148.76	159.84
C-4a	121.12	121.12	121.06	121.11
C-5	125.79	125.91	125.97	125.67
C-6	128.58	129.72	129.68	129.67
C-7	130.08	130.21	130.25	130.02
C-8	122.64	122.79	122.83	122.52
C-8a	143.73	143.61	143.52	148.52
C-1′	143.65	139.83 ($^4J_{CF}$ 3.24 Hz)	142.04	143.72
C-2′, C-6′	128.01	131.03 ($^3J_{CF}$ 8.25 Hz)	128.26	113.32
C-3′, C-5′	129.02	114.87 ($^2J_{CF}$ 21.60 Hz)	129.37	129.31
C-4′	129.72	163.00 ($^1J_{CF}$ 238.20 Hz)	134.68	136.29
C-1″	148.28	148.31	148.28	148.32
C-2″, C-6″	118.80	118.91	118.94	118.67
C-3″, C-5″	129.33	129.38	130.57	130.57
C-4″	124.91	124.94	124.93	124.90

OCH_3	-	-	-	55.35

2.6 Preparation of 4-(*N*,*N*-allyphenylamino)-2-aryl-3-iodoquinolines 151

The 2-aryl-3-iodo-4-phenylaminoquinolines **149** were reacted with NaH in DMF at room temperature for 20 minutes and then quenched with allyl bromide to afford the 4-(*N*,*N*-allyphenylamino)-2-aryl-3-iodoquinolines **151** in good yields and as sole products (Scheme 46). We did not detect any products resulting from possible *N*-1 alkylation or quartenarization[9]. The ^{1}H NMR spectra of 4-(*N*,*N*-allyphenylamino)-2-aryl-3-iodoquinolines **151** lack a singlet at δ *ca.* 6.60 ppm corresponding to N-H group of the 4-anilino group characteristic of the spectra of the precursors **147** (Fig. 10). Their spectra reveal the presence of signals corresponding to the allyl and vinyl hydrogens (Fig. 10). Although the molecules are achiral, the allylic protons are nonequivalent and resonate as ABX spin system with two sets of doublet of doublets at δ *ca.* 4.31 ppm and 4.54 ppm. The doublet of doublets at δ *ca.* 5.18 ppm and 5.30 ppm correspond to terminal vinyl protons with coupling constants of 10.8 Hz (J_{cis}) and 16.8 Hz (J_{trans}). The vinylic proton at C-2 position of an allyl group resonates as a multiplet at δ *ca.* 6.10 ppm due to coupling to the two diastereotopic allylic protons and the two terminal vinyl protons. Their ^{13}C NMR spectra show sets of signals at δ *ca.* 54.94, 134.20 and 124.45 ppm, which correspond to C-1, C-2 and C-3 of the allyl group, respectively (Fig 11 and Table 2). C-3 of the quinoline resonates at δ *ca.* 99.9 due to the less shielding effect of iodine atom (Fig 11).



147 **151**

151	4′-R	% Yield	m.p. ºC
a	4′-H	67	116-117
b	4′-F	96	160-162
c	4′-Cl	89	119-121
d	4′-OMe	59	110-112

Scheme 46

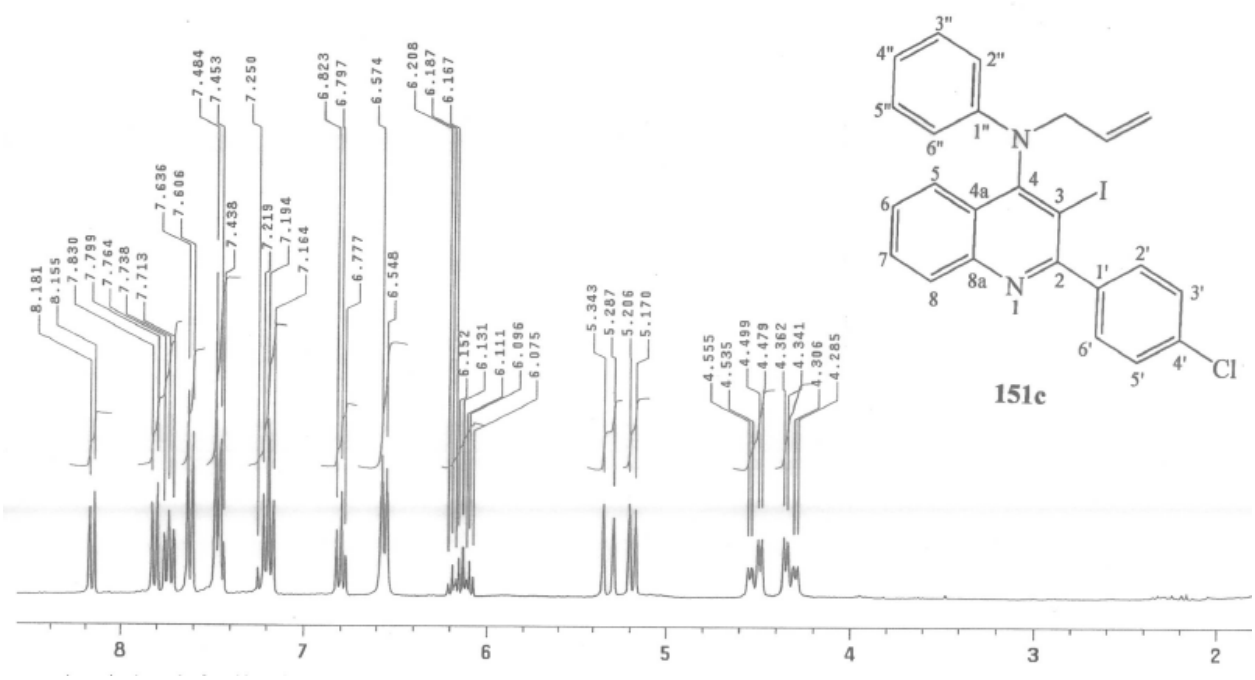


Figure 10: ^{1}H NMR spectrum of 4-(*N*,*N*-allylphenylamino)-2-(4′-chlorophenyl)-3-iodoquinoline **151a**

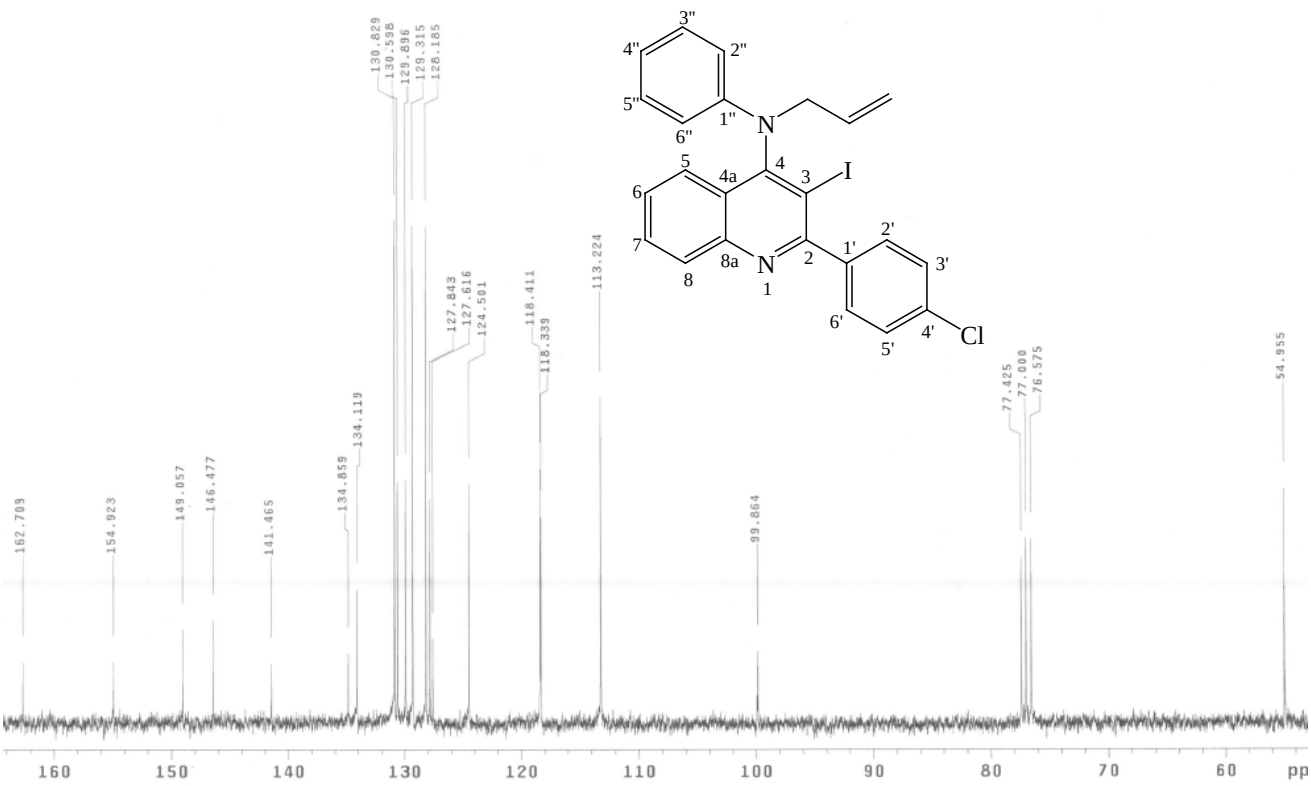
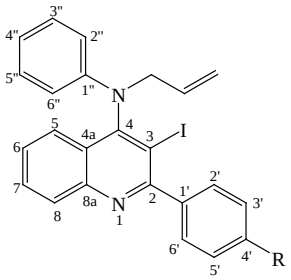


Figure 11: ^{13}C NMR spectrum of 4-(*N*,*N*-allylphenylamino)-2-(4′-chlorophenyl)-3-iodoquinoline **151a**

Table 2: ^{13}C NMR chemical shift values of **151** in $CDCl_3$ (at 75 MHz)



Nucleus	**151a** (R = H)	**151b** (R = F)	**151c** (R = Cl)	**151d** (R = OMe)
$\underline{C}H_2CH{=}CH_2$	54.94	54.96	54.96	54.96
$CH_2\underline{C}H{=}CH_2$	134.20	134.15	134.12	134.12
$CH_2CH{=}\underline{C}H_2$	118.27	118.34	118.34	118.24
C-2	163.98	162.90	162.71	162.71
C-3	100.35	100.25	99.86	100.77
C-4	154.67	154.87	154.92	154.65
C-4a	118.27	118.39	118.41	118.24
C-5	127.53	127.57	127.84	127.35
C-6	127.63	127.77	129.90	127.43
C-7	130.44	130.58	130.60	129.82
C-8	127.58	129.87	127.61	124.45
C-8a	146.53	146.50	146.48	146.54
C-1′	143.16	139.16 ($^4J_{CF}$ 3.38 Hz)	141.47	134.70
C-2′, C-6′	128.72	131.35 ($^3J_{CF}$ 8.48 Hz)	128.19	130.83
C-3′, C-5′	129.27	114.97 ($^2J_{CF}$ 21.6 Hz)	129.32	129.27
C-4′	127.94	161.37 ($^1J_{CF}$ 246.7 Hz)	134.86	130.37
C-1″	149.57	149.03	149.06	149.09
C-2″, C-6″	113.18	113.22	113.22	113.15
C-3″, C-5″	129.91	129.32	130.83	130.87
C-4″	124.45	124.51	124.50	124.93
OCH_3	-	-	-	55.34

With the 4-phenylamino- and 4-(*N*,*N*-allylphenylamino)-2-aryl-3-iodoquinolines in hand, the stage was set to investigate their reactivity in palladium-catalyzed Sonogashira and Heck reactions, respectively.

2.7 A brief description of a generalized mechanism for the palladium-catalyzed Sonogashira cross-coupling reactions.

In most of the palladium catalysed cross coupling reactions, the first step of the catalytic cycle is an oxidative addition of the arylhalide (RX) to the 14-electron complex (Pd^0L_2) **A** to afford a σ-arylpalladium(II) complex, *trans*-$RPdXL_2$ **B** (cycle A, Fig. 10). The second step is a nucleophilic attack on *trans*-$RPdXL_2$. The final product is generated by reductive elimination of a product from a *cis* intermediate **D**.

In the case of Sonogashira reaction, CuI is used as a co-catalyst to react with terminal acetylene and generate copper acetylide (cycle B, Fig. 10). This is followed by the formation of alkynylpalladium(II) derivatives which proceeds to give required coupled products and to regenerate the active Pd species **A**.

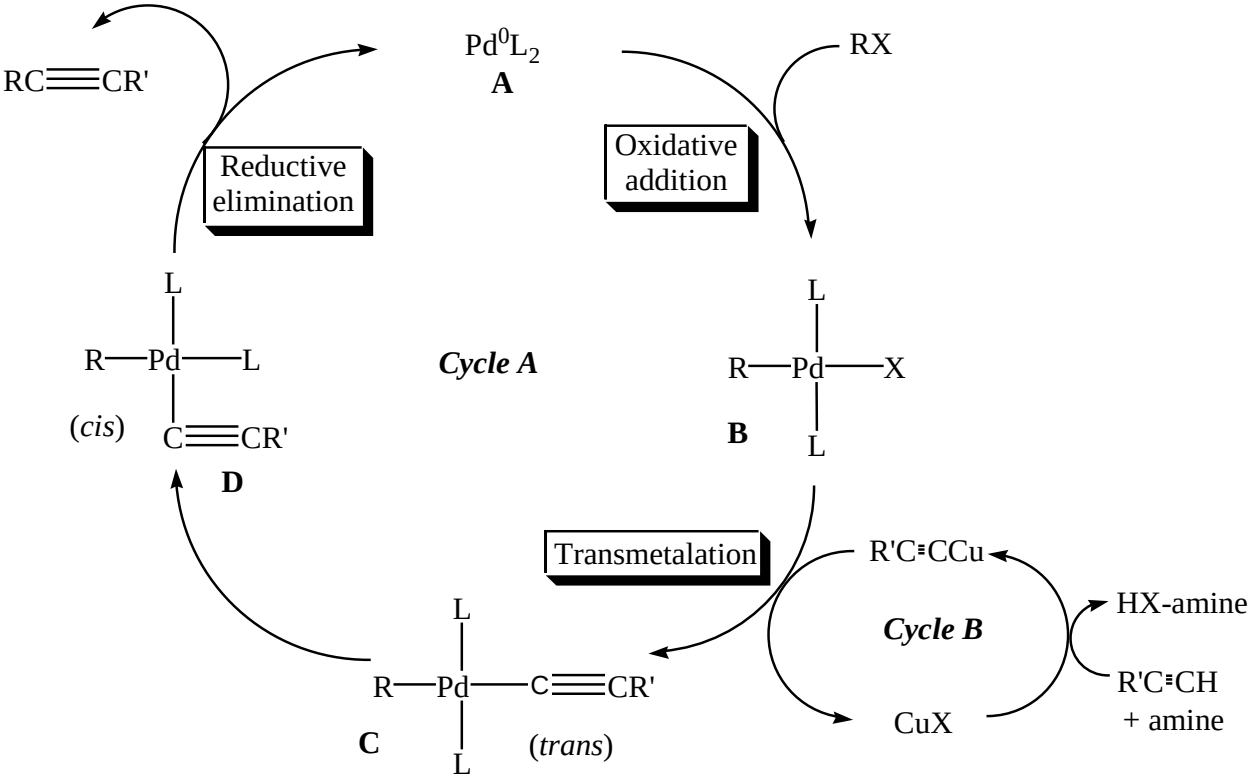


Figure 10: Generalized mechanism of Sonogashira cross coupling

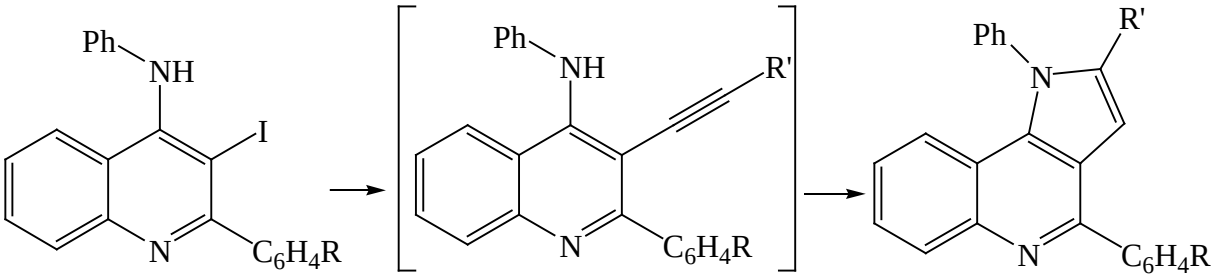
2.7.1 Sonogashira cross-coupling of 2-aryl-3-iodo-4-phenylaminoquinoline derivatives to form 1,2,4-trisubstituted pyrrolo[3,2-*c*]quinoline 150a-j

The 4-anilinoquinolines **147** were reacted with terminal alkynes (phenylacetylene, 3-butyn-2-ol or ethynyltrimethylsilane) in the presence of $PdCl_2(PPh_3)_2$-CuI catalyst mixture and NEt_3 in dioxane/ H_2O (3:1, v/v) at 80 ºC for 2 hours to afford the hitherto unreported 1,2,4-trisubstituted pyrrolo[3,2-*c*]quinoline **150a-j** in one-pot operation (Scheme 47). The ^1H NMR spectra of the products of Sonogashira cross-coupling of **147** with phenylacetylene lack the singlet corresponding to N-H proton found in the NMR spectra of the corresponding substrates and show the presence of a singlet at δ *ca.* 7.29 ppm corresponding to 3-H of the pyrrolo[3,2-

c]quinolines **150a-d** (R′ = Ph). The absence of an N-H stretch at ν_{max} 3363-3368 cm^{-1} in the IR spectra of these compounds, which is found in the spectra of the corresponding precursors also confirmed the structure of the annulated derivative **150a-d** (R′ = Ph).

^{1}H NMR spectra of 4-aryl-2-(1-hydroxyethyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines **150e-g** (R′ = $CH(OH)CH_3$), on the other hand, reveal a doublet at δ *ca.* 1.56 ppm, a broad singlet at δ *ca.* 1.98 ppm, a quartet at δ *ca.* 4.70 ppm and a singlet at δ *ca.* 6.94 ppm corresponding to CH_3, OH, 1-H of 1-hydroxyethyl group and 3-H, respectively (Fig. 12, pg. 77). Their ^{13}C NMR spectra reveal corresponding signals for the 1-hydroxyethyl group at δ *ca.* 22.73 ppm and at δ *ca.* 62.09 ppm for both CH_3 and C-1 (Fig. 13, pg. 78). Their IR spectra show broad absorption bands in the region ν_{max} 3176-3389 cm^{-1}, which correspond to the OH group of the 1-hydroxyethyl group.

The ^{1}H NMR spectra for 4-aryl-2-(trimethylsilyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines **150h-j** (R′ = $Si(CH_3)_3$), on the other hand, reveal a singlet at δ *ca*. 0.07 ppm integrating for 9 protons of the trimethylsilyl group. The presence of the 3-H is evidenced by a singlet at δ *ca.* 7.00 ppm with the corresponding ^{13}C NMR signal at δ *ca.* 114.4 ppm. IR spectra also show very strong absorption bands at ν_{max} *ca.* 840 cm^{-1} and at ν_{max} *ca.* 760 cm^{-1} corresponding to Si-CH_3 rocking and Si-C stretch vibrations respectively. The accurate calculated m/z values in all cases are consistent with the observed molecular weight of the assigned structure (see experimental section). The observed result supports the argument that the one-pot heteroannulation of **147** proceeds through a 3-alkynylated 2-aryl-4-phenylaminoquinoline intermediate **A**, followed by nucleophilic attack of nitrogen on the metal-activated triple bond to afford **150**.



147 **A** **150**

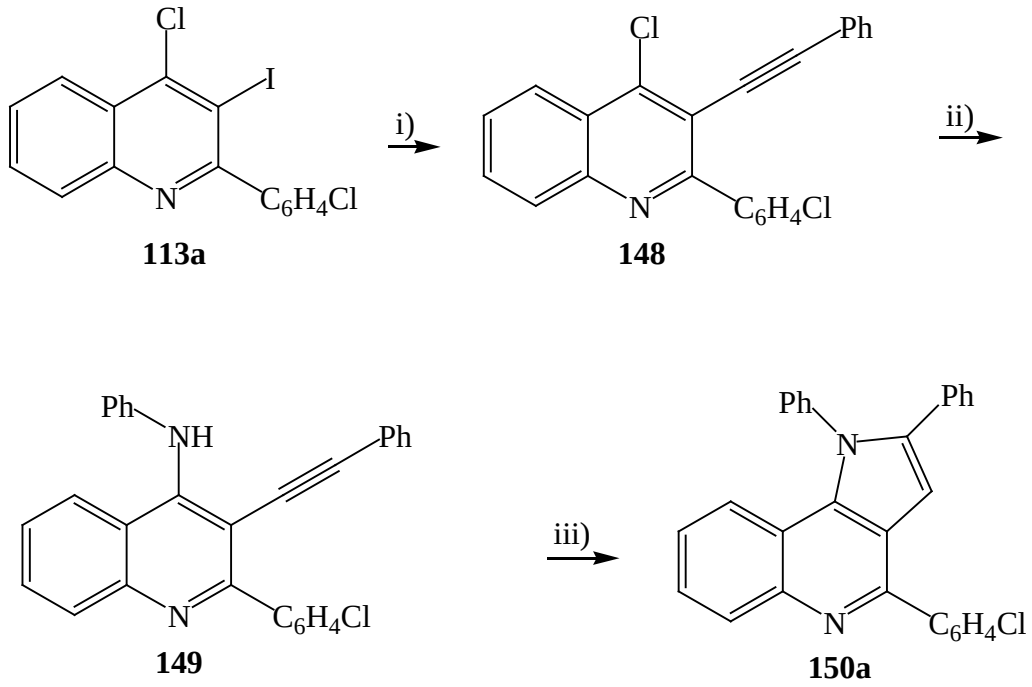
150	**4′-R**	**R′**	**% Yield**	**m.p. ºC**
a	4′-H	-Ph	59	210-212
b	4′-F	-Ph	58	159-160
c	4′-Cl	-Ph	53	165-167
d	4′-OMe	-Ph	64	154-156
e	4′-H	$-CH(OH)CH_3$	62	183-185
f	4′-Cl	$-CH(OH)CH_3$	59	202-204
g	4′-OMe	$-CH(OH)CH_3$	61	221-222
h	4′-H	$-Si(CH_3)_3$	68	163-165
i	4′-F	$-Si(CH_3)_3$	65	185-187
j	4′-OMe	$-Si(CH_3)_3$	60	153-155

Reagents and conditions: HC≡CR′, $PdCl_2(PPh_3)_2$, CuI, NEt_3, dioxane/ H_2O (3:1, v/v), 80 ºC, 2h

Scheme 47

The experimental simplicity and tolerance to a broad range of functional groups have made this reaction one of the most convenient and versatile methods for the synthesis of functionalized polysubstituted and polynuclear quinolines without the use of protection/deprotection chemistry. To confirm possible participation of the 3-alkynylated intermediate **A** implicated in the proposed mechanism for the heteroannulation (Scheme 47), we subjected **113a** to Sonogashira cross-coupling

with phenylacetylene to afford 4-chloro-2-phenyl-3-(phenylethynyl)quinoline **148** (Scheme 48). The accurate calculated *m/z* value represents closest fit consistent with the incorporation of the alkynyl moiety and the absence of iodine atom in the molecular ion. The presence of the 4-chloro atom in the molecular ion is confirmed in all cases by two prominent peaks in the ratio 3:1 which are typical for the chlorine isotopes ^{35}Cl and ^{37}Cl. Compound **148** was, in turn, reacted with aniline in refluxing ethanol to yield 2-phenyl-4-(phenylamino)-3-(phenylethynyl)quinoline **149**. The latter was subjected to similar reaction conditions applied to **113** to afford **150a**.



113a **148** **149** **150a**

Reagents and conditions: $PdCl_2(PPh_3)_2$, CuI, NEt_3, 80 ºC, 18 h; ii) Aniline, EtOH, reflux, 18 h; iii), CuI, NEt_3, dioxane/ H_2O (3:1, v/v), 80 ºC, 3 h

Scheme 48

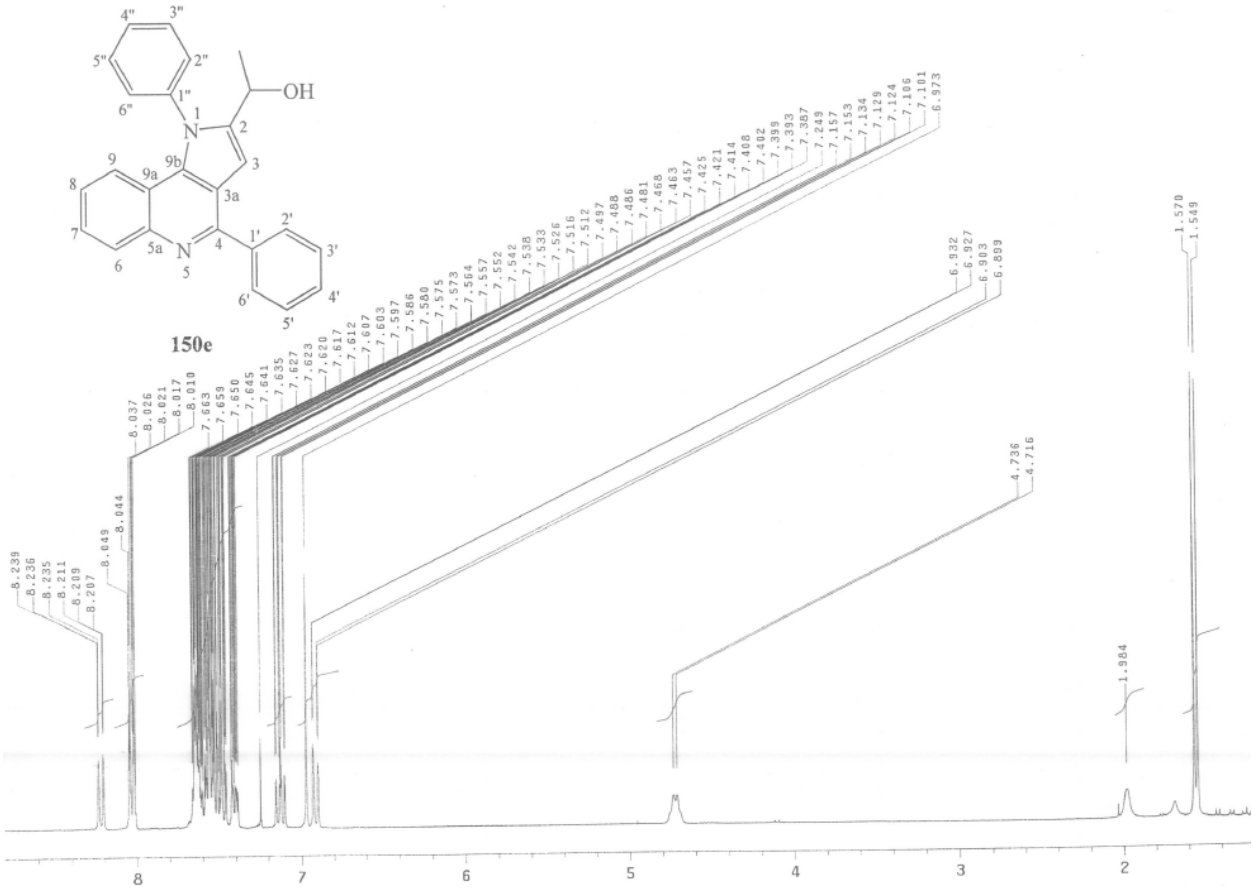


Figure 12: ^{1}H NMR spectrum of 2-(1-hydroxyethyl)-1,4-diphenyl-1*H*-pyrrolo[3,2-*c*]quinolines **150e**

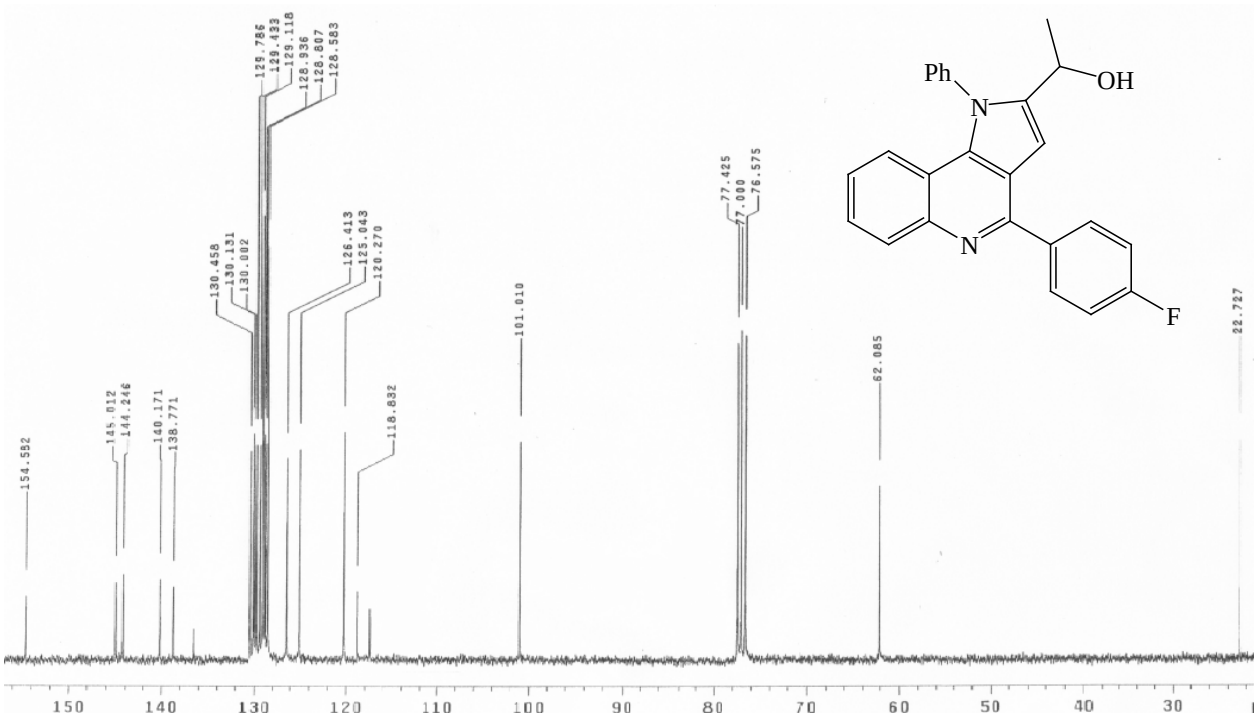


Figure 13: ^{13}C NMR spectrum of 2-(1-hydroxyethyl)-1,4-diphenyl-1*H*-pyrrolo[3,2-*c*]quinolines **150e**

2.8 A brief description of a generalized mechanism for the palladium-catalyzed Heck cross-coupling reactions.

Palladium-catalyzed Heck coupling reaction of aryl halides and activated alkenes in the presence of a base may occur via inter- or intramolecular pathways. The basic mechanism for the Heck reaction of aryl halides or triflates involves initial oxidative addition of the halide substrate into the Pd(0) catalyst **A** to give a Pd(II) species **B** (Fig. 12). Coordination and *syn*-insertion of the alkene substrate affords another Pd(II) intermediate **C**, which readily undergoes β-elimination to provide the Heck product. The cycle is complete with the regeneration of the Pd(0) species **A** by reductive elimination of HX from the Pd(II) species **D** generated by the preceding β-elimination.

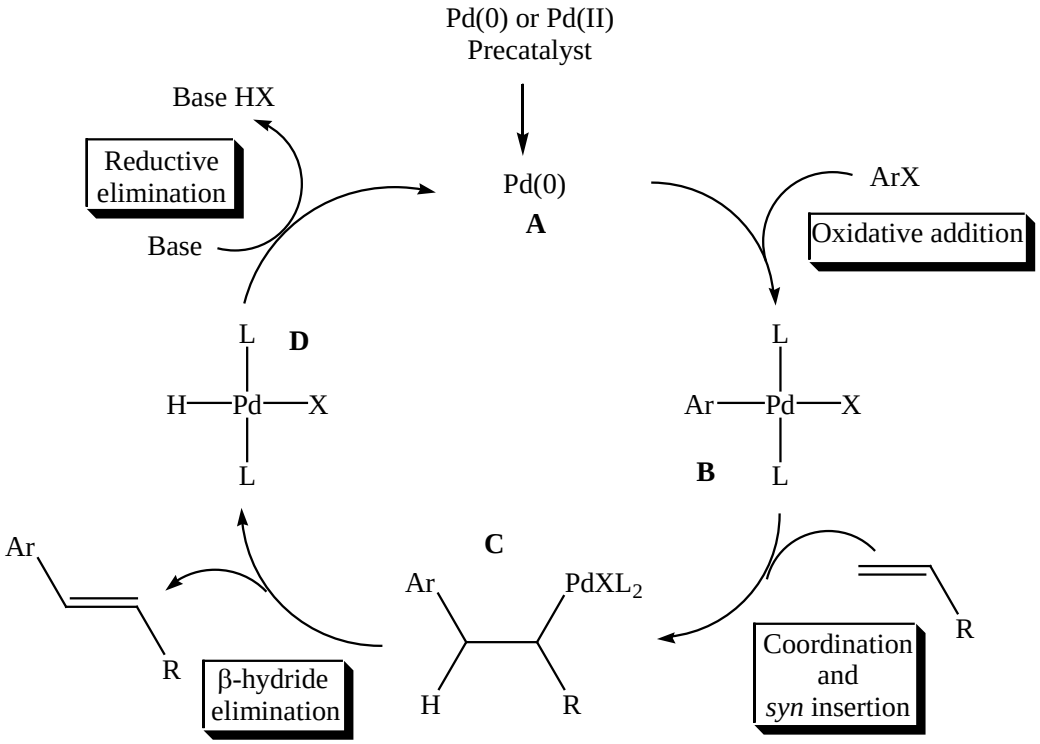
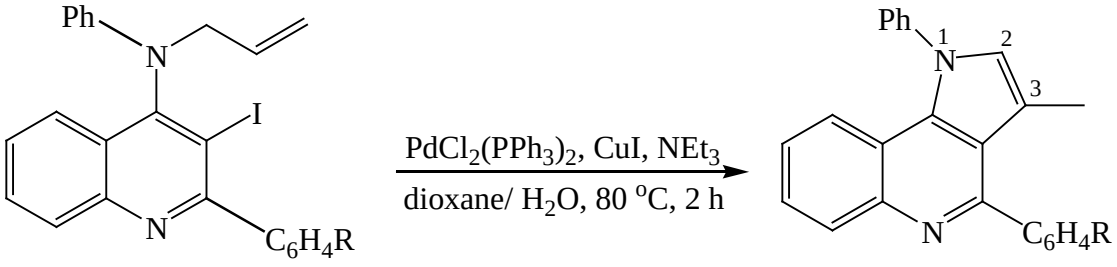


Figure 12: Generalized mechanism of the Heck cross-coupling

2.8.1 Heck cross coupling of 4-(*N,N*-allyphenylamino)-2-aryl-3-iodoquinolines derivatives 151 to afford 152

The Heck reaction of 4-anilino-3-iodoquinoline with various substituted vinyl derivatives to afford the 4-(phenylamino)-3-vinylquinolines as sole products with no cyclisation products detected or isolated[13]. We required a method for the synthesis of variously substituted 1,3,4-trisubstituted pyrrolo[3,2-*c*]quinolines. With the 4-(*N,N*-allyphenylamino)-2-aryl-3-iodoquinolines **151** in hand, we investigated the possibility of intramolecular Heck cyclization in the presence of $PdCl_2(PPh_3)_2$-CuI catalyst mixture and NEt_3 as base in dioxane/ H_2O (3:1, v/v) at 80 ºC for 2 hours. The corresponding 1,3,4-trisubstituted pyrrolo[3,2-*c*]quinoline **152** was

isolated (Scheme 48). The ^{1}H NMR spectra of products **152** lack the singlet corresponding to N-H proton and reveal the presence of singlets at δ *ca.* 1.94 ppm and 7.00 ppm, which correspond to methyl protons and a proton at position 2 of 1,3,4-trisubstituted pyrrolo[3,2-*c*]quinolines **151** (Fig. 14). ^{13}C NMR spectra reveal a signal at δ *ca.* 12.54 ppm, which corresponds to the methyl carbon at position 3 (Fig. 15). The accurate calculated m/z values in each case are consistent with the observed molecular weight of the assigned structure. The analogous 1,3,4-trisubstituted pyrrolo[3,2-*c*]quinolines **152** bearing a methyl group at the 4-position were prepared before via intermolecular palladium-catalyzed heteroannulation of 4-anilino-3-iodoquinoline with 1-trimethylsilyl alkynes followed by desilylation of corresponding 2-trimethylsilylpyrrolo[3,2-c]quinoline using trifluoroacetic acid (see Scheme 40 on page51)[64]. Moreover the authors also prepared those 1,3,4-trisubstituted pyrrolo[3,2-*c*]quinolines via the Heck reaction of 4-(*N*-allyl-*N*-aryl)amino-3-iodoquinolines. Although this method does not require a desilylation step, it provides products with limited functional groups and selective allylation is difficult due to quaternarization[9, 12].



151 **152**

152	4′-R	m/z	% Yield	m.p. ^{o}C
a	4′-H	335.15	76	139-141
b	4′-F	353.14	75	123-125
c	4′-Cl	369.12	81	166-167
d	4′-OMe	365.17	74	175-177

Scheme 49

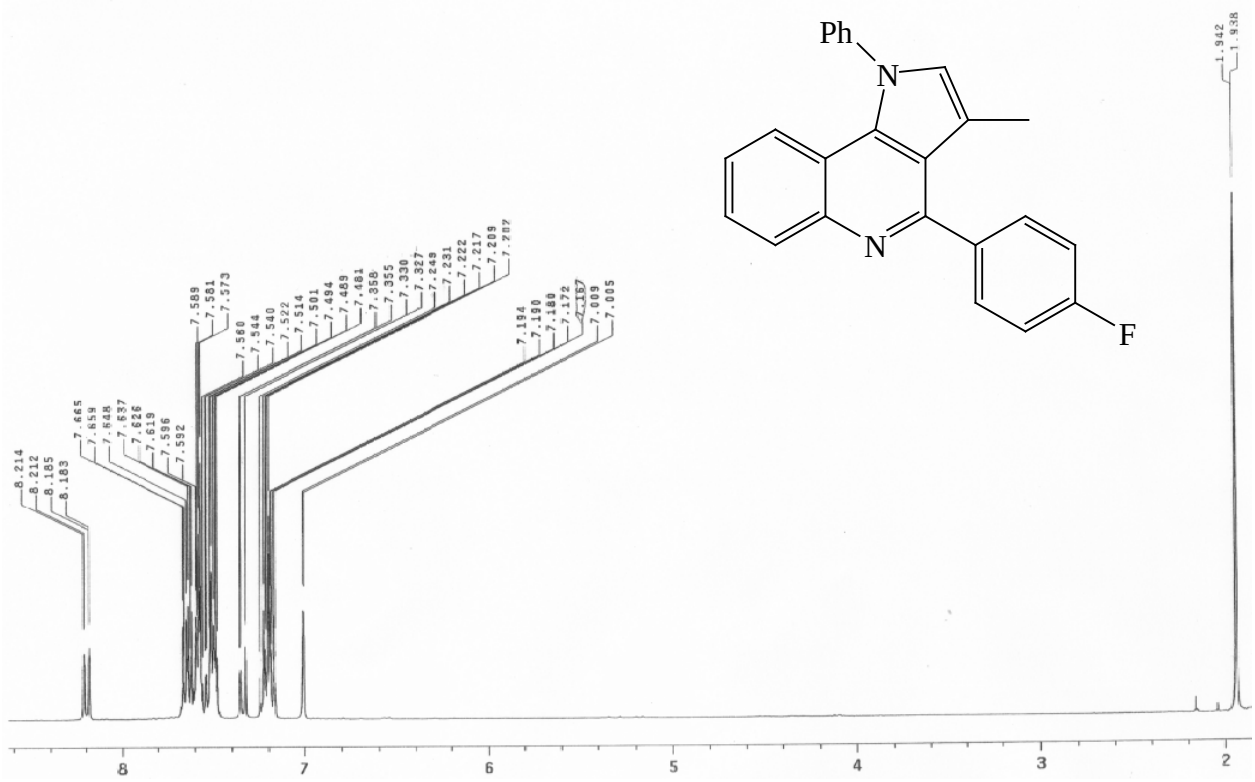


Figure 14: ^{1}H NMR spectrum of 4-(4′-fluorophenyl)-3-(methyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines **152b** in $CDCl_3$

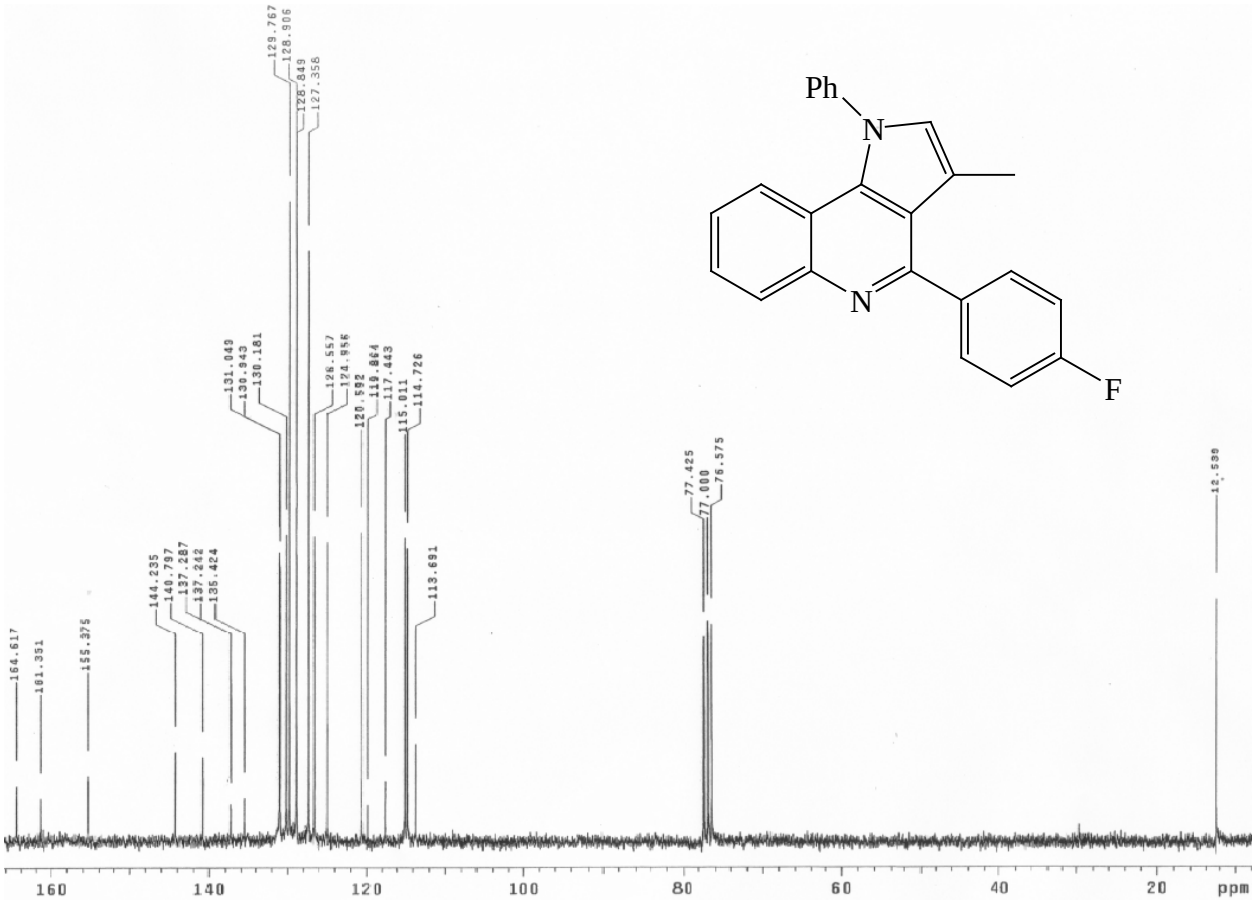


Figure 15: ^{13}C NMR spectrum of 4-(4′-fluorophenyl)-3-(methyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines **152b** in $CDCl_3$

Gengan *et al.*[71] previously subjected the analogous 4-anilino-3-iodo-2-methylquinoline to triphenylphosphine and sodium carbonate in the presence of palladium acetate and tricaprylyl methyl ammonium chloride under microwave irradiation at 80 ºC. These authors isolated the 6-methyl-11*H*-indolo[3,2-*c*]quinoline formed through cyclisation of the phenyl group of the anilino moiety with C-3. We did not detect or isolate the isomeric indolo[3,2-*c*]quinoline derivatives resulting from possible cyclization involving the phenyl ring of the aniline moiety (see structure **153** in Fig. 7, pg. 54).

CHAPTER 3 CONCLUSION

Nucleophilic substitution at 4 position of 2-aryl-4-chloro-3-iodoquinoline was effected by the displacement of Cl atom with aniline to afford 2-aryl-3-iodo-4-(phenylamino)quinoline. Allylation of 2-aryl-3-iodo-4-(phenylamino)quinoline was selectively achieved at the nitrogen of the anilino group using allyl bromide to afford 4-(*N*,*N*-allyphenylamino)-2-aryl-3-iodo-quinolines. The 2-aryl-3-iodo-4-(phenylamino)quinolines were subjected to Sonogashira cross-coupling using different terminal acetylenes such as phenylacetylene, 3-butyn-2-ol and ethynyltrimethylsilane to afford a range of 1,2,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines. Iodine at C-3 position was displaced by terminal acetylenes, followed by cyclisation to afford 1,2,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines in one step operation. The annulation sequence was confirmed by an alternative route which involves subjecting 2-aryl-4-chloro-3-iodoquinoline to Sonogashira cross-coupling to afford 3-alkynylated-4-chloroquinoline, followed by nucleophilic substitution of chloro atom by aniline. The last step involves cyclisation of 3-alkynylated-4-(phenylamino)quinoline to afford 1,2,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines. The former route appears to be a better route than the alternative route as an extra cyclisation step is required. 4-(*N*,*N*-Allyphenylamino)-2-aryl-3-iodo-quinolines were subjected to intramolecular Heck reaction conditions to afford 1,3,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines in one-pot synthesis.

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

- Application of Sonogashira reaction conditions to 2-aryl-3-iodoquinoline derivatives substituted with oxygen- or sulphur-containing groups at the C-4 position to afford furo- or thieno[3,2-*c*]quinolines.
- Subjecting the 2-aryl-3-iodo-4-(phenylamino)quinolines to Suzuki cross-coupling with various aryl boronic acid derivatives to afford the primary 4-aminoquinoline derivatives.
- Subjecting 4-anilino-3-iodoquinolines to Sonogashira cross-coupling with 1,2-substituted acetylenes to afford 1,2,3,4-tetrasubstituted pyrrolo-, furo- and thieno[3,2-*c*]quinolines.
- Further functionalisation of the C2-C3 unsaturated moiety of the 1,2,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines and 1,3,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines.
- Desilylation of 4-aryl-2-(trimethylsilyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines followed by addition of other functional groups across C2-C3 double bond
- Further derivatisation of the OH group in 4-aryl-2-(1-hydroxyethyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines.
- Testing the substituted pyrrolo[3,2-*c*]quinolines for inhibitory effects on gastric H^+/K^+ ATPase.

In conclusion, the results of this investigation represent another application of the 2-aryl-4-chloro-3-iodoquinolines in the synthesis of polysubstituted and polynuclear quinolines. The results of this investigation have since been published as a full paper[72].

CHAPTER 4 EXPERIMENTAL

4.1 General

Solvents and commercially available reagents were used as they supplied or purified by conventional methods before use. All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a varian mercury 300 MHz NMR spectrometer using $CDCl_3$ or DMSO-d_6 as solvents and the chemical shifts are recorded relative to the solvent peaks expressed in parts per million (ppm) (δ_H 7.25 or δ_C 77.0 ppm for $CDCl_3$ and δ_H 2.50 or δ_C 40.0 ppm for DMSO-d_6).

IR spectra were recorded with a Digilab FTS 7000 Series Digilab Win-IR Pro FTIR spectrometer using nitrogen cooled germanium crystal detector. Thin Layer Chromatography (TLC) was carried out on silica gel plates Merck silica gel 60 F_{254} as stationary phase. Low and high resolution mass spectra were recorded using Waters API Q-TOF Ultima instrument (Stellenbosch University). The following abbreviations are used:

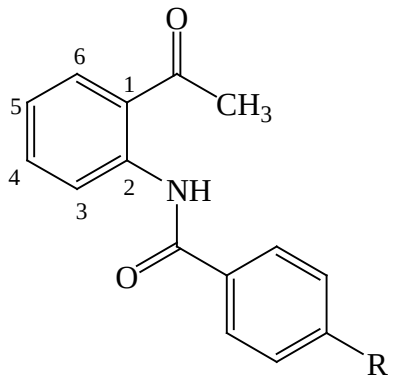
ppm = part per million

J = coupling constant values in Hz

δ = chemical shift values in ppm

s = singlet; br s = broad singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; m = multiplets

4.2 Preparation of *N*-benzoyl-2-aminoacetophenone derivatives 96a-d



N-benzoyl-2-aminoacetophenone

4.2.1 Preparation of *N*-benzoyl-2-aminoacetophenone 96a (4′-R = H)

Benzoyl chloride **95a** (4.36 mL, 31.08 mmol) was added dropwise to a mixture of 2-aminoacetophenone **94** (3.50 g, 25.94 mmol) and triethylamine (7.20 mL, 51.88 mmol) in THF (50 ml) at 0 ºC. After 30 minutes at 0 ºC, the mixture was stirred at room temperature for 2 hours. The mixture was then poured into ice-cold water. The resulting precipitate was filtered and then dissolved in chloroform. The solution was washed with water and the organic layer was separated and dried over anhydrous magnesium sulphate. The salt was filtered off and the solvent removed under reduced pressure to afford **96a** as a solid (5.90 g, 95%); m.p. 96-98 ºC (lit.[46] 96-98 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.72 (3H, s, $COCH_3$), 7.15 (1H, t, *J* 7.5 Hz, 4-H), 7.48-7.70 (4H, m, 3′-H, 4′-H, 5′-H and 5-H), 7.92-7.98 (1H, d, *J* 7.5 Hz, 3-H), 8.05 (2H, d, *J* 7.5 Hz 2′-H and 6′-H), 8.98 (1H, d, *J* 8.4 Hz 6-H), 12.72 (1H, br s, N-H).

4.2.2 Preparation of *N*-(4-fluorobenzoyl)-2-aminoacetophenone 96b (4′-R = F)

A mixture of **94** (3.50 g, 25.94 mmol), triethylamine (7.20 mL, 51.88 mmol) and 4-fluorobenzoyl chloride **95b** (4.91 g, 31.08 mmol) in THF (50 mL) was treated as for the synthesis of **96a**. Work-up and solvent evaporation afforded **96b** as a solid (6.32 g, 95%); m.p. 90-92 ºC (lit.[46] 90-92 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.70 (3H, s, $COCH_3$), 7.15-7.24 (3H, m, 3′-H and 5′-H, 3-H), 7.61 (1H, t, *J* 8.1 Hz, 4-H), 7.95 (1H, d, *J* 8.0 Hz, 3-H), 8.05 (2H, d, *J* 8.0 Hz, 2′-H and 6′-H), 8.92 (1H, d, *J* 8.3 Hz, 6-H), 12.65 (1H, br s, N-H).

4.2.3 Preparation of *N*-(4-chlorobenzoyl)-2-aminoacetophenone 96c (4′-R = Cl)

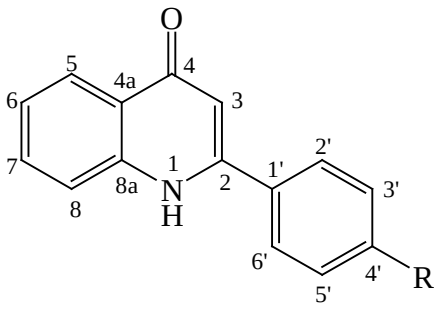
A mixture of **94** (3.50 g, 25.94 mmol), triethylamine (7.20 mL) and 4-chlorobenzoyl chloride **95c** (5.37 g, 31.08 mmol) in THF (50 mL) was treated as for the synthesis of **96a** to afford. Work-up and solvent evaporation afforded **96c** as a solid (6.85 g, 97%); m.p. 107-108 ºC (lit.[46] 107-108 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.71 (3H, s, $COCH_3$), 7.16 (1H, t, *J* 8.2 Hz, 4-H), 7.48 (2H, d, *J* 8.2 Hz , 3′-H and 5′-H), 7.61(1H, t, *J* 8.2 Hz , 5-H), 7.95 (2H, d, *J* 7.9 Hz 2′-H and 6′-H), 7.99 (1H, d, *J* 8.1 Hz, 3-H), 8.98 (1H, d, *J* 8.2 Hz, 6-H), 12.72 (1H, br s, N-H).

4.2.4 Preparation of *N*-(4-methoxybenzoyl)-2-aminoacetophenone 96d (4′-R = OCH_3)

A mixture of **94** (3.50 g, 25.94 mmol), triethylamine (7.20 mL, 51.88 mmol) and 4-methoxybenzoyl chloride **95d** (5.32 g, 31.08 mmol) in THF (50 mL) was treated as for the synthesis of **96a**. Work-up and solvent evaporation afforded **96d** as a solid (6.63 g, 95%); m.p.

119-121 ºC (lit.[46] 118-120 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.72 (3H, s, $COCH_3$), 3.89 (3H, s, OCH_3), 6.98 (2H, d, *J* 7.8 Hz, 3′-H and 5′-H), 7.16 (1H, t, *J* 7.9 Hz, 4-H), 7.59 (1H, t, *J* 8.0 Hz, 5-H), 7.94 (1H, d, *J* 8.0 Hz, 3-H), 8.04 (2H, d, *J* 8.2 Hz, 2′-H and 6′-H), 8.96 (1H, d, *J* 8.1 Hz, 6-H), 12.62 (1H, br s, N-H).

4.3 Preparation of 2-arylquinolin-4(1*H*)-one derivatives 97a-d



2-Arylquinolin-4(1*H*)-one

4.3.1 Preparation of 2-phenylquinolin-4(1*H*)-one 97a (4′-R = H)

A stirred mixture of **96a** (12.14 g, 50.79 mmol) and potassium *tert*-butoxide (1M solution in 2-methyl-2-propanol; 112 mL, 112 mmol) in *tert*-butanol (60 mL) was heated under reflux for 12 hours. The mixture was allowed to cool to room temperature and poured into an ice-cold saturated aqueous ammonium chloride solution. The precipitate was collected and washed several times with water and then with ice-cold ethanol (10 mL). The precipitate was dried in an oven at 80 ºC to afford **97a** as a solid (10.10, 90%); m.p. 240-241 ºC (EtOH) (lit.[43] 240-243 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.34 (1H, s, 3-H), 7.34 (1H, t, *J* 7.5 Hz,7-H), 7.59 (2H, t, *J*

8.0 Hz, 2′-H and 6′-H), 7.67 (1H, t, *J* 8.2 Hz, 6-H), 7.77 (1H, d, *J* 8.1 Hz, 8-H), 7.82-7.85 (2H, m, 3′-H and 5′-H), 8.10 (1H, d, *J* 8.1, 5-H), 11.73 (1H, br s, N-H).

4.3.2 Preparation of 2-(4′-fluorophenyl)phenylquinolin-4(1*H*)-one 97b (4′-R = F)

A procedure employed for the synthesis of **97a** was followed using a mixture of **96b** (13.47 g, 52.41 mmol) and 1M potassium *tert*-butoxide (105 mL, 105 mmol). Work up afforded a solid **97b** (11.77 g, 94%); m.p. 319-320 ºC (EtOH) (lit.[43] 322-325 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.29 (1H, s, 3-H), 7.35 (1H, t, *J* 7.2 Hz, 7-H), 7.60 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 7.70 (1H, t, *J* 7.1 Hz, 6-H), 7.77 (1H, d, *J* 8.1 Hz, 8-H), 7.80-7.93 (2H, m, 3′-H and 5′-H), 8.12 (1H, d, *J* 8.1 Hz, 5-H), 11.69 (1H, br s, N-H).

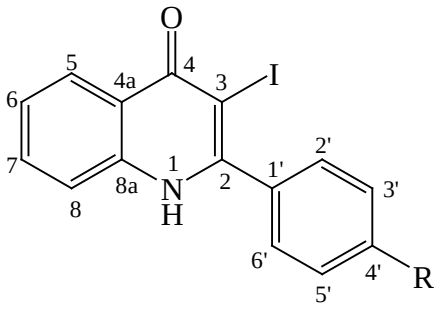
4.3.3 Preparation of 2-(4′-chlorophenyl)phenylquinolin-4(1*H*)-one 97c (4′-R = Cl)

A procedure employed for the synthesis of **97a** was followed using a mixture of **96c** (14.11 g, 51.59 mmol and 1M potassium *tert*-butoxide (103 mL, 103 mmol). Work up afforded **97c** as a solid (12.65, 96%); m.p. 323-324 ºC (EtOH) (lit.[43] 270-273 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.32 (1H, s, 3-H), 7.32 (1H, t, *J* 7.5 Hz, 7-H), 7.59 (2H, t, *J* 7.2 Hz, 2′-H and 6′-H), 7.68 (1H, t, *J* 8.1 Hz, 6-H), 7.77 (1H, d, *J* 8.1 Hz, 8-H), 7.89-7.93 (2H, m, 3′-H and 5′-H), 8.10 (1H, d, *J* 8.0 Hz, 5-H), 11.76 (1H, br s, N-H).

4.3.4 Preparation of 2-(4′-methoxyphenyl)phenylquinolin-4(1*H*)-one 97d (4′-R = OCH_3)

A procedure employed for the synthesis of **97a** was followed using a mixture of **96d** (10.86 g, 40.37 mmol) and 1M potassium *tert*-butoxide (81 mL, 81 mmol). Work up afforded **97d** as a solid (9.32 g, 92%); m.p. 294-296 ºC (EtOH) (lit.[43] 290-293 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.94 (3H, s, OCH_3), 6.32 (1H, s, 3-H), 7.33 (1H, t, *J* 8.7 Hz, 7-H), 7.58 (2H, t, *J* 8.2 Hz, 2′-H and 6′-H), 7.69 (1H, t, *J* 8.1 Hz, 6-H), 7.80 (1H, d, *J* 8.4 Hz, 8-H), 7.88-7.93 (2H, m, 3′-H and 5′-H), 8.11 (1H, d, *J* 8.2 Hz, 5-H), 11.72 (1H, br s, N-H).

4.4 Preparation of 2-aryl-3-iodoquinolin-4(1*H*)-one derivatives 98a-d



2-Aryl-3-iodoquinolin-4(1*H*)-one

4.4.1 Preparation of 3-iodo-2-phenylquinolin-4(1*H*)-one 98a (4′-R = H)

A mixture of **97a** (2.50 g, 11.31 mmol), iodine (4.27 g, 16.81 mmol) and sodium carbonate (1.78 g, 16.95 mmol) in THF (60 mL) was stirred at room temperature for 12 hours and poured into saturated ice-cold aqueous sodium thiosulphate solution. The precipitate was collected, washed with water and dried. The crude solid was recrystallised to afford **98a** as a solid (3.13 g, 90%);

m.p. 282-284 ºC (EtOH) (lit.[69] 284-286 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.40 (1H, t, *J* 8.1 Hz, 7-H), 7.54-7.72 (7H, m, 2′-H and 6′-H, 3′-H and 5′-H, 4′-H, 6-H, 8-H), 8.15 (1H, d, *J* 8.1 Hz, 5-H), 12.30 (1H, br s, N-H).

4.4.2 Preparation of 2-(4′-fluorophenyl)-3-iodoquinolin-4(1*H*)-one 98b (4′-R = F)

The experimental procedure employed for the synthesis of **98a** was followed using a mixture of **97b** (3.00 g, 12.60 mmol), iodine (4.76 g, 18.90 mmol) and sodium carbonate (2.01 g, 18.90 mmol) in THF (60 mL). Work-up and recrystallisation afforded **98b** as a solid (3.53 g, 77%); m.p. 196-197 ºC (EtOH) (lit.[69] 196-198 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.36-7.47 (3H, m, 3′-H and 5′-H, 7-H), 7.63-7.74 (4H, m, 2′-H and 6′-H, 6-H, 8-H), 8.15 (1H, d, *J* 7.8 Hz, 5-H), 12.32 (1H, br s, N-H).

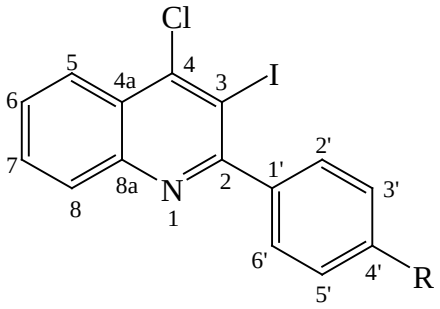
4.4.3 Preparation of 2-(4′-chlorophenyl)-3-iodoquinolin-4(1*H*)-one 98c (4′-R = Cl)

The experimental procedure employed for the synthesis of **98a** was followed using a mixture of **97c** (3.00 g, 12.58 mmol), iodine, (4.45 g, 18.0 mmol) and sodium carbonate (1.50 g, 18.0 mmol) in THF (60 mL). Work-up and recrystallisation afforded **98c** as a solid (3.25 g, 71%); m.p. 231-233 ºC (EtOH) (lit.[69] 231-233 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.41 (1H, t, *J* 7.2 Hz, 7-H), 7.59-7.74 (6H, m, 2′-H and 6′-H, 3′-H and 5′-H, 6-H, 8-H), 8.14 (1H, d, *J* 7.8 Hz, 5-H), 12.30 (1H, br s, N-H).

4.4.4 Preparation of 3-iodo-2-(4′-methoxyphenyl)quinolin-4(1*H*)-one 98d (4′-R = OCH_3)

The experimental procedure employed for the synthesis of **98a** was followed using a mixture of **97d** (2.50 g, 9.96 mmol), iodine, (5.06 g, 19.92 mmol) and sodium carbonate (1.58 g, 14.94 mmol) in THF (60 mL). Work-up and recrystallisation afforded **98d** as a solid (3.72 g, 82%), m.p. 239-241 ºC (EtOH) (lit.[67] 239-241 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.90 (3H, s, OCH_3), 7.11 (2H, d, *J* 7.2 Hz, 3′-H and 5′-H), 7.38 (1H, t, *J* 8.4 Hz, 7-H), 7.52 (2H, d, 2′-H and 6′-H), 7.64-7.72 (2H, m, 6-H and 8-H), 8.13 (1H, d, *J* 8.4 Hz, 5-H), 12.20 (1H, br s, N-H).

4.5 Preparation of 2-aryl-4-chloro-3-iodoquinoline derivatives 113a-d



2-Aryl-4-chloro-3-iodoquinoline

4.5.1 Preparation of 4-chloro-3-iodo-2-phenylquinoline 113a (4′-R = H)

A stirred suspension of **98a** (10.10 g, 25.5 mmol), in $POCl_3$ (50 mL) was heated under reflux for 2 hours. The mixture was allowed to cool to room temperature and slowly poured into an ice-

cold 25% ammonia solution. The resulting precipitate was filtered, washed with water, dried and recrystallised to afford **113a** as a solid (8.25 g, 82%); m.p. 254-256 ºC (EtOH) (lit.[47] 150-153 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.52 (3H, m, 3′-H and 5′-H, 4′-H), 7.56-7.59 (2H, m, 2′-H and 6′-H), 7.64 (1H, t, *J* 7.2 Hz, 7-H), 7.79 (1H, t, *J* 7.5 Hz, 6-H), 8.12 (1H, d, *J* 7.5 Hz, 8-H), 8.27 (1H, d, *J* 7.6 Hz, 5-H).

4.5.2 Preparation of 4-chloro-2-(4′-fluorophenyl)-3-iodoquinoline 113b (4′-R = F)

An experimental procedure employed for the synthesis of **113a** was followed using a suspension of **98b** (9.59 g, 24.1 mmol) in $POCl_3$ (50 mL). Work-up and recrystallisation afforded **113b** as a solid (8.70 g, 87%), m.p. 180.6-181 ºC (EtOH) (lit.[47] 176-178 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.48 (3H, m, 3′-H and 5′-H, 6′-H), 7.50-7.59 (2H, m, 2′-H and 6′-H), 7.64 (1H, t, *J* 7.8 Hz, 7-H), 7.80 (1H, t, *J* 7.5 Hz, 6-H), 8.08 (1H, d *J* 8.1 Hz, 8-H), 8.25 (1H, d, *J* 8.5 Hz, 5-H).

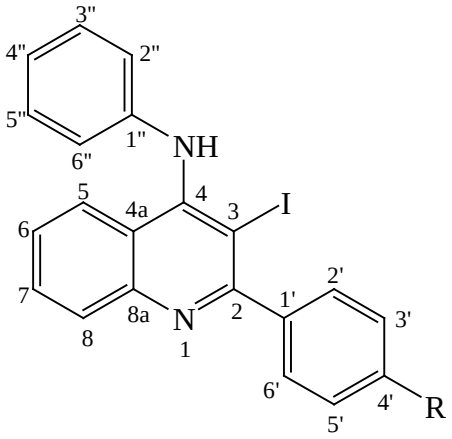
4.5.3 Preparation of 4-chloro-2-(4′-chlorophenyl)-3-iodoquinoline 113c (4′-R = Cl)

An experimental procedure employed for the synthesis of **113a** was followed using a suspension of **98c** (11.13 g, 29.1 mmol) in $POCl_3$ (50 mL) Work-up and recrystallisation afforded **113c** as a solid (12.20 g, 96%), m.p. 300-301 ºC (EtOH) (lit.[47] 218-220 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46-7.52 (3H, m, 3′-H and 5′-H, 6′-H), 7.57-7.60 (2H, m, 2′-H and 6′-H), 7.66 (1H, t, *J* 7.2 Hz, 7-H), 7.77 (1H, t, *J* 8.0 Hz, 6-H), 8.10 (1H, d, *J* 8.2 Hz, 8-H), 8.25 (1H, d, *J* 8.0 Hz, 5-H).

4.5.4 Preparation of 4-chloro-3-iodo-2-(4′-methoxyphenyl)quinoline 113d (4′-R = OCH_3)

An experimental procedure employed for the synthesis of **113a** was followed using a suspension of **98d** (11.13 g, 29.1 mmol) in $POCl_3$ (50 mL). Work-up and recrystallisation afforded **113d** as a solid (10.82 g, 94%); m.p. 265-268 ºC (EtOH) (lit.[47] 185-187 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (3H, s, OCH_3), 7.40-7.51 (3H, m, 3′-H and 5′-H, 6′-H), 7.59-7.62 (2H, m, 2′-H and 6′-H), 7.67 (1H, t, *J* 7.2 Hz, 7-H), 7.82 (1H, t, *J* 8.0 Hz, 6-H), 8.15 (1H, d, *J* 8.2 Hz, 8-H), 8.30 (1H, d, *J* 8.0 Hz, 5-H).

4.6 Preparation of 2-aryl-3-iodo-4-(phenylamino)quinoline derivatives 147a-d



2-Aryl-3-iodo-4-(phenylamino)quinoline **147**

4.6.1 Preparation of 3-iodo-2-phenyl-4-(phenylamino)quinoline 147a (4′-R = H)

A mixture of **113a** (2.50g, 6.84 mmol) and aniline (3.18 g, 34.20 mmol) in ethanol (50 mL) was heated under reflux for 12 hours. The mixture was allowed to cool to room temperature and

added to ice-cold water. The resulting precipitate was filtered, washed with water and dried. The crude product was recrystallised to afford **147a** as a yellow solid (2.58 g, 86%); m.p. 159-161 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.58 (1H, s, N-H), 6.84 (2H, d, *J* 7.8 Hz, N-Ph 2″-H and 6″-H), 7.03 (1H, t, *J* 6.0 Hz, 7-H), 7.14-7.32 (3H, m, 3′-H, 4′-H, 5′-H), 7.45-7.52 (3H, m, 6-H, 2′-H, 6′-H), 7.59-7.69 (3H, m, N-Ph, 3″-H, 4″-H, 5″-H), 7.70 (1H, d, *J* 8.4 Hz, 8-H), 8.27 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 90.40 (C-3), 118.80 (N-Ph, C-2″ and C-6″), 121.12 (C-4a), 122.64 (C-8), 124.91 (N-Ph, C-4″), 125.79 (C-5), 128.01 (C-2′ and C-6′), 128.58 (C-6), 129.02 (C-3′ and C-5′), 129.33 (N-Ph, C-3″ and C-5″), 129.72 (C-4′), 130.08 (C-7), 143.65 (C-1′), 143.73 (C-8a), 148.28 (N-Ph, C-1″), 148.55 (C-4), 162.45 (C-2); ν_{max} (neat)/cm^{-1} 3363, 3056, 1599, 1564, 1486, 1400, 1263, 1236, 1073, 1026, 929; *m/z* (100, M+H) 423; HRMS (ES): MH^+ calcd for $[C_{21}H_{16}IN_2]^+$: 423.0359, found: 423.0360.

4.6.2 Preparation of 2-(4′-fluorophenyl)-3-iodo-4-(phenylamino)quinoline 147b (4′-R = F)

An experimental procedure employed for the synthesis of **147a** was followed using a mixture of **113b** (0.73g, 1.90 mmol) and aniline (0.35 g, 3.76 mmol) in ethanol (50 mL) Work-up and recrystallisation afforded **147b** as a solid (0.64 g, 76%); m.p. 191-192 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.53 (1H, s, N-H), 6.83 (2H, d, *J* 7.8 Hz, N-Ph, 2″-H and 6″-H), 7.06 (1H, t, *J* 6.0 Hz, 7-H), 7.23-7.32 (3H, m, 3′-H, 4′-H, 5′-H), 7.40-7.49 (3H, m, 6-H, 2′-H, 6′-H), 7.62-7.70 (3H, m, N-Ph, 3″-H, 4″-H, 5″-H), 7.72 (1H, d, *J* 8.4 Hz, 8-H), 8.25 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 90.16 (C-3), 114.87 (d, $^{2}J_{CF}$ 21.6 Hz, C-3′ and C-5′), 118.91 (N-Ph, C-2″ and C-6″), 121.12 (C-4a), 122.79 (C-8), 124.94 (N-Ph, C-4″), 125.91 (C-5), 129.38 (N-Ph, C-3″ and C-5″), 129.72 (C-6), 130.21 (C-7), 131.03 (d, $^{3}J_{CF}$ 8.25 Hz, C-2′ and C-6′), 139.83 (d,

$^{4}J_{CF}$ 3.24 Hz, C-1′), 143.61 (C-8a), 148.31 (N-Ph, C-1″), 148.74 (C-4), 161.31 (C-2), 163.00 (d, $^{1}J_{CF}$ 238.20 Hz, C-4′); ν_{max} (neat)/cm^{-1} 3368, 3068, 1599, 1567, 1511, 1485, 1399, 1231, 1217, 1154, 925, 853, 762; *m/z* (100, M+H) 441; HRMS (ES): MH^+ calcd for $[C_{21}H_{15}FIN_2]^+$: 441.2600, found: 441.0285.

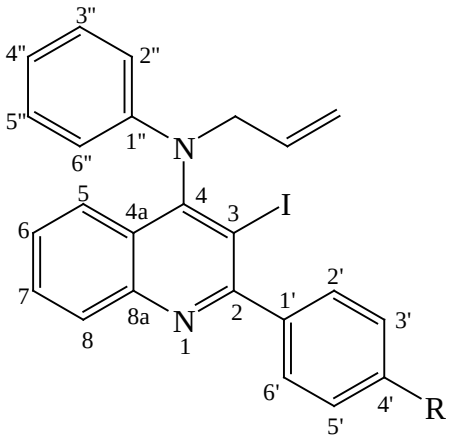
4.6.3 Preparation of 2-(4′-chlorophenyl)-3-iodo-4-(phenylamino)quinoline 147c (4′-R = Cl)

An experimental procedure employed for the synthesis of **147a** was followed using a mixture of **113c** (1.00g, 2.50 mmol) and aniline (0.50 g, 5.37 mmol) in ethanol (50 mL). Work-up and recrystallisation afforded **147c** as a solid (0.88 g, 77%); m.p. 199-200 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.59 (1H, s, N-H), 6.86 (2H, d, *J* 7.5 Hz, N-Ph H-2 and H-6), 7.04 (1H, t, *J* 7.5 Hz, 7-H), 7.23-7.33 (3H, m, 3′-H, 4′-H, 5′-H), 7.45-7.52 (3H, m, 6-H, 2′-H, 6′-H), 7.59-7.69 (3H, m, N-Ph, H-3, H-4, H-5), 7.72 (1H, d, *J* 8.4 Hz, 8-H), 8.27 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 89.67 (C-3), 118.94 (N-Ph, C-2″ and C-6″), 121.06 (C-4a), 122.83 (C-8), 124.93 (N-Ph, C-4″), 125.97 (C-5), 128.26 (C-2′ and C-6′), 129.37 (C-3′ and C-5′), 129.68 (C-6), 130.25 (C-7), 130.57 (N-Ph, C-3″ and C-5″), 134.68 (C-4′), 142.04 (C-1′), 143.52 (C-8a), 148.28 (N-Ph, C-1″), 148.76 (C-4), 161.19 (C-2); ν_{max} (neat)/cm^{-1} 3368, 3071, 1600, 1567, 1486, 1397, 1260, 1233, 1089, 1013, 924, 826; *m/z* (100, M+H) 456; HRMS (ES): MH^+ calcd for $[C_{21}H_{15}ClIN_2]^+$: 456.9969, found: 456.9983.

4.6.4 Preparation of 3-iodo-2-(4′-methoxyphenyl)--4-(phenylamino)quinoline 147d (4′-R = OCH_3)

An experimental procedure employed for the synthesis of **147a** was followed using a mixture of **113d** (0.76g, 1.92 mmol) and aniline (0.36 g, 3.84 mmol) in ethanol (50 mL). Work-up and recrystallisation afforded **147d** as a solid (0.62 g, 72%); m.p. 210-212 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.88 (3H, s, OCH_3), 6.56 (1H, s, N-H), 6.84 (2H, d, *J* 7.8 Hz, N-Ph H-2 and H-6), 7.00-7.05 (3H, m, 7-H, H-2′ and H-6′), 7.23-7.31(3H, m, 3′-H, 4′-H, 5′-H), 7.57-7.68 (4H, m, N-Ph, H-3, H-4, H-5, H-6), 7.71 (1H, d, *J* 8.1 Hz, 8-H), 8.09 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.35 (OCH_3), 91.04 (C-3), 113.32 (C-2′ and C-6′), 118.67 (N-Ph, C-2″ and C-6″), 121.11 (C-4a), 122.52 (C-8), 124.90 (N-Ph, C-4″), 125.67 (C-5), 129.31 (C-3′ and C-5′), 129.67 (C-6), 130.02 (C-7), 130.57 (N-Ph, C-3″ and C-5″), 136.29 (C-4′), 143.72 (C-1′), 148.32 (N-Ph, C-1″), 148.52 (C-8a), 159.84 (C-4), 162.08 (C-2); ν_{max} (neat)/cm^{-1} 3369, 3066, 1567, 1486, 1397, 1260, 1233, 1089, 1013, 924, 826; *m/z* (100, M+H) 453; HRMS (ES): MH^+ calcd for $[C_{22}H_{18}IN_2O]^+$: 453.2955, found: 453.0451.

4.7 Preparation of 4-(*N,N*-allyphenylamino)-2-aryl-3-iodoquinolines 151a-d



4-(*N,N*-Allyphenylamino)-2-aryl-3-iodoquinolines

4.7.1 Preparation of 4-(*N,N*-allyphenylamino)-3-iodo-2-phenylquinolines 151a (R = H)

A mixture of **147a** (1.98g, 4.69 mmol) and NaH (0.22 g, 9.00 mmol) in DMF (40 mL) was stirred at room temperature for 20 minutes. Allyl bromide (1.12 g, 9.00 mmol) was added to the mixture and stirred at room temperature for 12 hours. The reaction mixture was poured into ice-cold water and extracted with chloroform. The chloroform layer was dried over $MgSO_4$, filtered and solvent removed under reduced pressure to afford crude, yellow oil. The crude product was purified by column chromatography to afford **151a** as a yellow solid (1.46 g, 67%); R_f (10% ethyl acetate/ hexane) 0.75; m.p. 116.8-117.1 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.44 (2H, dd, *J* 7.8 and 6.0, -C*H*$_2$CH=CH$_2$), 5.25 (2H, d, *J* 7.8 Hz, CH$_2$CH=C*H*$_2$), 6.09-6.23(1H, m, -CH$_2$C*H*=CH$_2$), 6.58 (2H, d, *J* 7.8 Hz, N-Ph 2″-H and 6″-H), 6.80 (1H, t, *J* 6.0 Hz, 7-H), 7.20 (1H, t, *J* 7.5 Hz, 6-H), 7.43-7.54 (2H, m, N-Ph, 4″-H and 4′-H), 7.66 (2H, d, *J* 6.0 Hz, 2′-H and 6′-H), 7.73 (4H, t, *J* 7.5 Hz, N-Ph, 3″-H, 5″-H and 3″-H ′, 5′-H), 7.82 (1H, d, *J* 7.8 Hz, 8-H),

8.20 (1H, d, *J* 7.5 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 54.94 (-$\underline{C}H_2CH{=}CH_2$), 100.35 (C-3), 113.18 (N-Ph, C-2″ and C-6″), 118.27 (N-Ph, C-4″ and C-4a), 124.45 (-$CH_2CH{=}\underline{C}H_2$), 127.53 (C-5), 127.63 (C-6), 127.94 (C-4′), 128.72 (C-2′ and C-6′), 129.27 (C-3′ and C-5′), 129.91 (N-Ph, C-3″ and C-5″), 130.44 (C-7), 134.20 (-$CH_2\underline{C}H{=}CH_2$), 143.16 (C-1′), 146.53 (C-8a), 149.04 (N-Ph, C-1″), 154.67 (C-4), 163.98 (C-2); ν_{max} (neat)/cm^{-1} 3057, 1598, 1558, 1498, 1481, 1392, 1341, 1296, 1242, 922; *m/z* (100, M+H) 463; HRMS (ES): MH^+ calcd for $[C_{24}H_{20}IN_2]^+$: 463.0671, found: 463.0675.

4.7.2 Preparation of 4-(*N*,*N*-allyphenylamino)-2-(4′-fluorophenyl)-3-iodoquinolines 151b (R = F)

An experimental procedure employed for the synthesis of **151a** was followed using a mixture of **147b** (1.12g, 2.50 mmol), NaH (0.12 g, 5.00 mmol) and allyl bromide (0.60 g, 5.00 mmol) in DMF (40 mL). Work-up and column chromatography afforded **151b** as a solid (1.15 g, 96%); R_f (10% ethyl acetate/ hexane) 0.76; m.p. 160.0-162.1 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.41 (2H, dd, J 7.8 and 6.0, -C$\underline{H}_2CH{=}CH_2$), 5.24 (2H, d, *J* 7.8 Hz, -$CH_2CH{=}C\underline{H}_2$,); 6.07-6.20 (1H, m, -$CH_2C\underline{H}{=}CH_2$), 6.55 (2H, d, *J* 7.8 Hz, N-Ph, 2″-H and 6″-H), 6.79 (1H, t, *J* 6.0 Hz, 7-H), 7.14-7.21 (4H, m, N-Ph, H-4″ and 3-H″, 5-H″, 4′-H), 7.45 (1H, t, *J* 7.5 Hz, 6-H), 7.63-7.82 (4H, m, 2′-H and 6′-H, 3′-H and 5′-H), 8.20 (1H, d, *J* 7.5 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 54.96 (-$\underline{C}H_2CH{=}CH_2$), 100.25 (C-3), 113.22 (N-Ph, C-2″ and C-6″), 114.97 (d, $^2J_{CF}$ 21.6, C-3′ and C-5′), 118.34 (-$CH_2CH{=}\underline{C}H_2$), 118.39 (C-4a), 124.51 (N-Ph, C-4″), 127.57 (C-5), 127.77 (C-6), 129.32 (N-Ph, C-3″ and C-5″), 129.87 (C-8), 130.58 (C-7), 131.35 (d, $^3J_{CF}$ 8.48 Hz, C-2′ and C-6′), 134.15 (-$CH_2\underline{C}H{=}CH_2$), 139.16 (d, $^4J_{CF}$ 3.38 Hz, C-1′), 146.50 (C-8a), 149.03 (N-Ph,

C-1″), 154.87 (C-4), 161.37 (d, $^{1}J_{CF}$ 246.67 Hz, C-4′), 162.90 (C-2); ν_{max} (neat)/cm^{-1} 3061, 1596, 1559, 1498, 1481, 1394, 1295, 1247, 1232, 1211, 1158, 990, 936, 838; *m/z* (100, M+H) 481; HRMS (ES): MH^+ calcd for $[C_{24}H_{19}FIN_2]^+$: 481.0577, found: 481.0597.

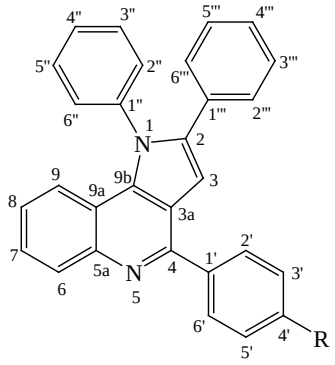
4.7.3 Preparation of 4-(*N*,*N*-allyphenylamino)-2-(4′-chlorophenyl)-3-iodoquinolines 151c (R = Cl)

An experimental procedure employed for the synthesis of **151a** was followed using a mixture of **147c** (1.73 g, 3.70 mmol), NaH (0.185g, 7.40 mmol) and allyl bromide (0.44 g, 7.40 mmol) in DMF (40 mL). Work-up and column chromatography afforded **151c** as a solid (1.63 g, 89%); R_f (10% ethyl acetate/hexane) 0.82; m.p. 119.5-121.7 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.48 (2H, dd, *J* 7.8 and 6.0, -C$\underline{H}_2$CH═CH_2), 5.30 (2H, d, *J* 7.8 Hz, -CH_2CH═C$\underline{H}_2$), 6.11-6.20 (1H, m, -CH_2C$\underline{H}$═CH_2) 6.52 (2H, d, *J* 7.8 Hz, N-Ph 2″-H and 6″-H), 6.79 (1H, t, *J* 6.0 Hz, 7-H), 7.10-7.28 (4H, m, N-Ph, 4″-H-4 and 3″-H, 5″-H, H-4′), 7.45 (1H, t, *J* 7.5 Hz, 6-H), 7.63-7.82 (4H, m, 2′-H and 6′-H, 3′-H and 5′-H), 8.20 (1H, d, *J* 7.5 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 54.96 (-$\underline{C}$$H_2$CH═$CH_2$, C-1), 99.86 (C-3), 113.22 (N-Ph, C-2″ and C-6″), 118.34 (-CH_2CH═$\underline{C}$$H_2$), 118.41 (C-4a), 124.50 (N-Ph, C-4″), 127.61 (C-8), 127.84 (C-5), 128.19 (C-2′ and C-6′), 129.32 (C-3′ and C-5′), 129.90 (C-6), 130.60 (C-7), 130.83 (C-3″ and C-5″), 134.12 (-$CH_2$$\underline{C}$H═$CH_2$, C-2), 134.86 (C-4′), 141.47 (C-1′), 146.48 (C-8a), 149.06 (N-Ph, C-1″), 154.92 (C-4), 162.71 (C-2); ν_{max} (neat)/cm^{-1} 3054, 1596, 1557, 1498, 1481, 1393, 1305, 1239, 1095, 1013, 925, 835; *m/z* (100, M+H) 497; HRMS (ES): MH^+ calcd for $[C_{24}H_{19}ClIN_2]^+$: 497.0281, found: 497.0263.

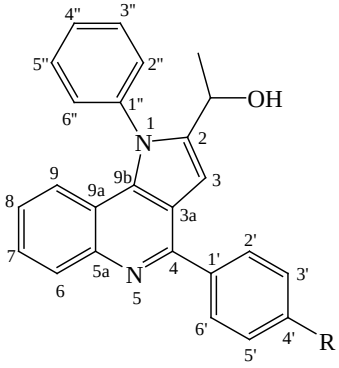
4.7.4 Preparation of 4-(*N*,*N*-allyphenylamino)-3-iodo-2-(4′-methoxyphenyl)quinolines 147d (R = OCH_3)

An experimental procedure employed for the synthesis of **151a** was followed using a mixture of **147d** (1.60 g, 3.50 mmol), NaH (0.17g, 7.00 mmol) and allyl bromide (0.84 g, 7.00 mmol) in DMF (40 mL). Work-up and column chromatography afforded **151d** as a solid. (1.02 g, 59%); R_f (10% ethyl acetate/hexane) 0.78; m.p. 109.8-112.4 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.88 (3H, s, OCH_3), 4.42 (2H, dd, J 7.8 and 6.0, -C$\underline{H}_2$CH═CH_2), 5.24 (2H, d, *J* 7.8 Hz, -CH_2CH═C$\underline{H}_2$), 6.08-6.22 (1H, m, -CH_2C$\underline{H}$═CH_2) 6.59 (2H, d, *J* 9.3 Hz, N-Ph, 2″-H and 6″-H), 6.79 (1H, t, *J* 6.0 Hz, 7-H), 7.02 (2H, d, *J* 9.0 Hz, 2′-H and 6′-H), 7.19 (2H, t, *J* 7.5 Hz, N-Ph, 3″-H and 6″-H), 7.43 (1H, t, *J* 7.5 Hz, 6-H), 7.63-7.81 (4H, m, N-Ph, 4″-H and 8-H, 3′-H and 5′-H), 8.17 (1H, d, *J* 9.3 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 54.96 (-$\underline{C}H_2$CH═CH_2), 55.34 (OCH_3), 100.77 (C-3), 113.15 (N-Ph, C-2″ and C-6″), 118.24 (-CH_2CH═$\underline{C}H_2$ and C-4a), 124.45 (C-8), 124.93 (N-Ph, C-4″), 127.35 (C-5), 127.43 (C-6), 129.27 (C-3′ and C-5′), 129.82 (C-7), 130.37 (C-4′), 130.87 (N-Ph, C-3″ and C-5″), 130.83 (C-2′ and C-6′), 134.12 (-$CH_2\underline{C}$H═CH_2), 134.70 (C-1’), 146.54 (C-8a), 149.09 (N-Ph, C-1″), 154.65 (C-4), 162.71 (C-2); ν_{max} (neat)/cm^{-1} 3060, 2300, 1597, 1557, 1512, 1498, 1478, 1392, 1340, 1250, 1172, 1029, 928, 832; *m/z* (100, M+H) 493; HRMS (ES): MH^+ calcd for $[C_{25}H_{22}IN_2O]^+$: 493.0777, found: 493.0590.

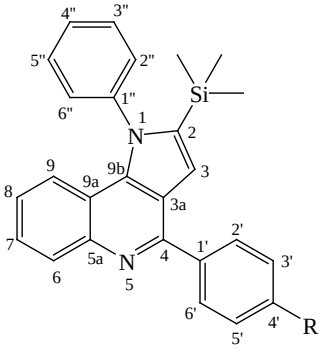
4.8 Preparation of 1,2,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines 150a-j



150a-d



150e-g



150h-j

4.8.1 Preparation of 1,2,4-triphenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150a (R = H)

A mixture of **147a** (0.22 g, 0.474 mmol), CuI (0.005 g, 0.024 mmol) and $PdCl_2(PPh_3)_2$ (0.017 g, 0.024 mmol) in dioxane/ H_2O (3:1 v/v) (20 mL) was purged with N_2. Triethylamine (0.26 mL, 1.90 mmol) was added with a syringe to the mixture, followed by the addition of phenylacetylene (0.054 mL, 0.569 mmol). The mixture was refluxed at 80 ºC for 2 hours under nitrogen atmosphere. The mixture was poured into ice-cold water and extracted with chloroform. The chloroform layer was dried over $MgSO_4$, filtered and solvent removed under reduced pressure to afford crude product. The crude product was purified by column chromatography to afford **150a** as a solid (0.11 g, 59%); R_f (20% ethyl acetate/ hexane) 0.90; m.p. 210-212 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.10-7.23 (10H, m, 3-H, 3′-H, 4′-H, 5′-H, (2-Ph, 3‴, 4‴, 5‴), (N-Ph, 4″-H, 2″-H, 6″-H), 7.43-7.60 (7H, m, H-6, N-Ph, 3″-H, 5″-H, (2-Ph, 2‴-H, 6‴-H), H-7, H-8), 8.11 (2H, d, *J* 8.4 Hz, 2′-H and 6′-H), 8.26 (1H, d, *J* 8.4 Hz, 9-H); ^{13}C NMR (75

MHz, $CDCl_3$) δ: 104.70 (C-3), 117.60 (C-3a), 119.51 (C-9a), 120.40 (N-Ph, C-4″), 125.00 (C-9), 126.31 (C-8), 127.65 (C-4′), 128.08 (N-Ph, C-2″ and C-6″), 128.58 (2-Ph, C-2‴ and C-6‴) 128.81 (2-Ph, C-4‴), 129.14 (2-Ph, C-3‴ and C-5‴), 129.29 (C-8), 129.41 (N-Ph, C-3″ and C-5″), 130.61 (C-7), 131.90 (C-2), 136.60 (C-1′), 139.47 (N-Ph, C-1″), 140.27 (C-9b), 141.20 (2-Ph, C-1‴), 145.14 (C-5a), 154.44 (C-4); ν_{max} (neat)/cm^{-1} 3061, 1596, 1556, 1498, 1480, 1454, 1440, 1370, 1348, 1313, 1246, 1072, 1027, 933, 807, 748, 759; *m/z* (100, M+H) 397; HRMS (ESI^+) *m/z* calcd for $[C_{29}H_{21}N_2]^+$: 397.1705, found: 397.1697.

4.8.2 Preparation of 4-(4′-fluorophenyl)-1,2-diphenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150b (R = F)

An experimental procedure employed for the synthesis of **150a** was followed using a mixture of **147b (**0.22 g, 0.56 mmol), CuI (0.044 g, 0.022 mmol), $PdCl_2(PPh_3)_2$ (0.017 g, 0.024 mmol), triethylamine (0.25 mL, 1.82 mmol) and phenylacetylene (0.059 mL, 0.545 mmol) in dioxane/ H_2O (3:1) (20 mL). Work-up and column chromatography afforded **150b** as a solid (0.11 g, 59%); R_f (20% ethyl acetate/ hexane) 0.94; m.p. 159-160 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.10-7.23 [(10H, m, 3-H, 3′-H, 4′-H, 5′-H, (2-Ph, 3‴-H, 4‴-H, 5‴-H), (N-Ph, 4″-H, 2″-H, 6″-H)], 7.43-7.60 (7H, m, 6-H, (N-Ph, 3″-H, 5″-H), (2-Ph, 2‴-H, 6‴-H), H-7, H-8), 8.11 (2H, d, J 8.4 Hz, 2′-H and 6′-H), 8.26 (1H, d, J 8.4 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.70 (C-3), 117.60 (C-3a), 119.51 (C-9a), 120.40 (N-Ph, C-4″), 125.00 (C-9), 126.31 (C-8), 127.65 (C-4′), 128.08 (N-Ph, C-2″ and C-6″), 128.58 (2-Ph, C-2‴ and C-6‴) 128.81 (2-Ph, C-4‴), 129.14 (2-Ph, C-3‴ and C-5‴), 129.29 (C-8), 129.41 (N-Ph, C-3″ and C-5″), 130.61 (C-7), 131.90 (C-2), 136.60 (C-1′), 139.47 (N-Ph, C-1″), 140.27 (C-9b), 141.20 (2-Ph, C-1‴), 145.14 (C-5a), 154.44

(C-4); ν_{max} (neat)/cm^{-1} 3064, 1595, 1491, 1450, 1372, 1352, 1315, 1089, 1013, 932, 848, 830, 784; *m/z* (100, M+H) 415; HRMS (ES): MH^+ calcd for $[C_{29}H_{20}FN_2]^+$: 415.1611, found: 415.1602.

4.8.3 Preparation of 4-(4′-chlorophenyl)-1,2-diphenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150c (R = Cl)

An experimental procedure employed for the synthesis of **150a** was followed using a mixture of **147c (**0.24 g, 0.454 mmol), CuI (0.0043 g, 0.022 mmol), $PdCl_2(PPh_3)_2$ (0.017 g, 0.024 mmol), triethylamine (0.25 mL, 1.82 mmol) and phenylacetylene (0.059 mL, 0.545 mmol) in dioxane/ H_2O (3:1) (20 mL). Work-up and column chromatography afforded **150c** as a solid (0.11 g, 58%); R_f (20% ethyl acetate/ hexane) 0.93; m.p. 159-160 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.06-7.23 (9H, m, 3-H, 3′-H, 5′-H, (2-Ph, 3‴-H, 4‴-H, 5‴-H), (N-Ph, 4″-H, 2″-H, 6″-H), 7.42-7.56 (7H, m, 6-H, N-Ph, 3-H, 5-H, (2-Ph, 2‴-H, 6‴-H), 7-H, 8-H), 8.07 (2H, d, *J* 8.4 Hz, 2′-H and 6′-H), 8.23 (1H, d, *J* 8.4 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.26 (C-3), 117.59 (C-3a), 119.25 (C-9a), 120.42 (N-Ph, C-4″), 125.21 (C-9), 126.46 (C-8), 128.12 (N-Ph, C-2″ and C-6″), 128.78 (2-Ph, C-2‴ and C-6‴) 129.40 (2-Ph, C-4‴), 129.49 (2-Ph, C-3‴ and C-5‴), 129.77 (C-8), 130.45 (N-Ph, C-3″ and C-5″), 130.61 (C-7), 131.90 (C-2),134.88 (C-4′), 136.66 (C-1′), 138.69 (N-Ph, C-1″), 139.34 (C-9b), 141.42 (2-Ph, C-1‴), 145.02 (C-5a), 153.04 (C-4); ν_{max} (neat)/cm^{-1} 3054, 2359, 1594, 1491, 1450, 1371, 1353, 1314, 1246, 1089, 1013, 931, 848, 832, 789; *m/z* (100, M+H) 431; HRMS (ES): MH^+ calcd for $[C_{29}H_{20}ClN_2]^+$: 431.1315, found: 431.1321.

4.8.4 Preparation of 4-(4′-methoxyphenyl)-1,2-diphenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150d (R = OCH_3)

An experimental procedure employed for the synthesis of **150a** was followed using a mixture of **147d (**0.25 g, 0.454 mmol), CuI (0.0043 g, 0.022 mmol), $PdCl_2(PPh_3)_2$ (0.017 g, 0.024 mmol), triethylamine (0.25 mL, 1.82 mmol) and phenylacetylene (0.059 mL, 0.545 mmol) in Dioxane/ H_2O (3:1) (20 mL). Work-up and column chromatography afforded **150d** as a solid (0.11 g, 58%); R_f (20% ethyl acetate/ hexane) 0.78; m.p. 159-160 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11-7.25 (10H, m, 3-H, 3′-H, 4′-H, 5′-H, (2-Ph, 3‴-H, 4‴-H, 5‴-H), (N-Ph, 4″-H, 2″-H, 6″-H), 7.43-7.60 (7H, m, 6-H, (N-Ph, 3″-H, 5″-H), (2-Ph, 2-H, 6-H), 7-H, 8-H), 8.11 (2H, d, J 8.4 Hz, 2′-H and 6′-H), 8.26 (1H, d, J 8.4 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.70 (C-3), 117.60 (C-3a), 119.51 (C-9a), 120.40 (N-Ph, C-4″), 125.00 (C-9), 126.31 (C-8), 127.65 (C-4′), 128.08 (N-Ph, C-2″ and C-6″), 128.58 (2-Ph, C-2‴ and C-6‴) 128.81 (2-Ph, C-4‴), 129.14 (2-Ph, C-3‴ and C-5‴), 129.29 (C-8), 129.41 (N-Ph, C-3″ and C-5″), 130.61 (C-7), 131.90 (C-2), 136.60 (C-1′), 139.47 (N-Ph, C-1″), 140.27 (C-9b), 141.20 (2-Ph, C-1‴), 145.14 (C-5a), 154.44 (C-4); ν_{max} (neat)/cm^{-1} 3061, 2961, 2837, 1605, 1501, 1481, 1449, 1372, 1350, 1246, 1172, 1028, 832, 791, 783; *m/z* (100, M+H) 427; HRMS (ES): MH^+ calcd for $[C_{30}H_{23}N_2O]^+$: 427.1810, found: 427.1831.

4.8.5 Preparation of 2-(1-hydroxyethyl)-1,4-diphenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150e (R = H)

An experimental procedure employed for the synthesis of **150a** was followed using a mixture of **147a (**0.25 g, 0.59 mmol), CuI (0.0053 g, 0.03 mmol), $PdCl_2(PPh_3)_2$ (0.021 g, 0.03 mmol), triethylamine (0.33 mL, 2.36 mmol) and 3-butyn-2-ol (0.055 mL, 0.71 mmol) in DMF (20 mL). Work-up and column chromatography afforded **150e** as a solid (0.13g, 62%); R_f (30% ethyl acetate/ hexane) 0.44; m.p. 182.7-184.7 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.56 (3H, d, *J* 6.3 Hz, CH_3), 1.98 (1H, s, OH), 4.70- 4.77 (1H, q, *J* 6.6 Hz, C*H*(OH)CH_3), 6.91(1H, d, *J* 7.2 Hz, 6-H), 6.97 (1H, s, 3-H), 7.13 (1H, t, *J* 6.9 Hz, 8-H), 7.39-7.66 (9H, m, (N-Ph, 2″-H, 3″-H, 4″-H, 5″-H, 6″-H), 3′-H, 4′-H and 5′-H, 7-H), 8.03 (2H, d, *J* 9.6 Hz, 2′-H and 6′-H), 8.22 (1H, d, *J* 8.1 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.73 (CH_3), 62.09 (*C*H(OH)CH_3), 101.01 (C-3), 118.32 (C-3a), 120.27 (C-9a), 125.04 (N-Ph, C-4″), 126.41 (C-9), 128.58 (N-Ph, C-2″ and C-3″), 128.81 (C-8), 128.94 (C-3′), 129.12 (C-2′ and C-6′), 129.43 (C-6), 129.79 (C-7), 130.00 (C-3′ and C-5′), 130.13 (N-Ph, C-3″ and C-5″), 130.46 (C-2), 138.77 (C-1′), 140.17 (C-9b), 144.25 (C-5a), 145.01 (N-Ph, C-1″), 154.58 (C-4); ν_{max} (neat)/cm^{-1} 3389, 3060, 2972, 1595, 1556, 1494, 1454, 1440, 1364, 1320, 1294, 1116, 1092, 1071, 1020, 938, 943, 895, 817, 785; *m/z* (100, M+H) 365; HRMS (ES): MH^+ calcd for $[C_{25}H_{21}N_2O]^+$: 365.1654, found: 365.1662.

4.8.6 Preparation of 4-(4′-chlorophenyl)-2-(1-hydroxyethyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150f (R = Cl)

An experimental procedure employed for the synthesis of **150a** was followed using a mixture of **147c** (0.20 g, 0.44 mmol), CuI (0.0042 g, 0.022 mmol), $PdCl_2(PPh_3)_2$ (0.016 g, 0.022 mmol), triethylamine (0.25 mL, 1.75 mmol) and 3-butyn-2-ol (0.041 mL, 0.53 mmol) in DMF (20 mL). Work-up and column chromatography afforded **150f** as a solid (0.10g, 59%); R_f (30% ethyl acetate/ hexane) 0.47; m.p. 202.3-203.5 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.56 (3H, d, *J* 6.6 Hz, CH_3), 1.98 (1H, s, OH), 3.90 (3H, s, CH_3), 4.72 (1H, q, *J* 6.6 Hz, C*H*(OH)CH_3, 1-H), 6.90 (1H, d, *J* 7.5 Hz, 6-H), 6.98 (1H, s, 3-H), 7.07-7.14 (1H, t, *J* 6.9 Hz, 8-H), 7.39-7.66 (9H, m, (N-Ph, 2″-H, 3″-H, 4″-H, 5″-H, 6″-H), 3′-H, 4′-H and 5′-H, 7-H), 8.03 (2H, d, *J* 9.6Hz, 2′-H and 6′-H), 8.22 (1H, d, *J* 8.1 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.73 (CH_3), 62.09 (C*H*(OH)CH_3, C-1), 101.01 (C-3), 118.32 (C-3a), 120.27 (C-9a), 125.04 (N-Ph, C-4″), 126.41 (C-9), 128.58 (N-Ph, C-2″ and C-3″), 128.81 (C-8), 128.94 (C-3′), 129.12 (C-2″ and C-6″), 129.43 (C-6), 129.79 (C-7), 130.00 (C-3′ and C-5′), 130.13 (N-Ph, C-3″ and C-5″), 130.46 (C-2), 138.77 (C-1′), 140.17 (C-9b), 144.25 (C-5a), 145.01 (N-Ph, C-1″), 154.58 (C-4); ν_{max} (neat)/cm^{-1} 3210, 3072, 2978, 2931, 2849, 1595, 1567, 1499, 1444, 1371, 1354, 1310, 1289, 1249, 1126, 1102, 1087, 1009, 941, 898, 834, 809, 784; *m/z* (100, M+H) 399; HRMS (ES): MH^+ calcd for $[C_{25}H_{20}ClN_2O]^+$: 399.1264, found: 399.1251.

4.8.7 Preparation of 2-(1-hydroxyethyl)-4-(4′-methoxyphenyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150g (R = OCH_3)

An experimental procedure employed for the synthesis of **150a** was followed using a mixture of **147d (**0.25 g, 0.59 mmol), CuI (0.0053 g, 0.03 mmol), $PdCl_2(PPh_3)_2$ (0.021 g, 0.03 mmol), triethylamine (0.33 mL, 2.36 mmol) and 3-butyn-2-ol (0.055 mL, 0.71 mmol) in DMF (20 mL). Work-up and column chromatography afforded **150g** as a solid (0.13 g, 62%); R_f (30% ethyl acetate/ hexane) 0.27; m.p. 182.7-184.7 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.56 (3H, d, *J* 6.6 Hz, CH_3), 1.98 (1H, s, OH), 3.90 (3H, s, CH_3), 4.72 (1H, q, *J* 6.6 Hz, C*H*(OH)CH_3), 6.90 (1H, d, *J* 7.5 Hz, 6-H), 6.98 (1H, s, 3-H), 7.07-7.14 (1H, t, *J* 6.9 Hz, 8-H), 7.39-7.66 (9H, m, (N-Ph, 2″-H, 3″-H, 4″-H, 5″-H, 6″-H), 3'-H, 4'-H and 5'-H, 7-H), 8.03 (2H, d, *J* 9.6Hz, 2'-H and 6'-H), 8.22 (1H, d, *J* 8.1 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.73 (CH_3), 62.09 (C*H*(OH)CH_3), 101.01 (C-3), 118.32 (C-3a), 120.27 (C-9a), 125.04 (N-Ph, C-4″), 126.41 (C-9), 128.58 (N-Ph, C-2″ and C-3″), 128.81 (C-8), 128.94 (C-3′), 129.12 (C-2′ and C-6′), 129.43 (C-6), 129.79 (C-7), 130.00 (C-3″ and C-5″), 130.13 (N-Ph, C-3′ and C-5′), 130.46 (C-2), 138.77 (C-1′), 140.17 (C-9b), 144.25 (C-5a), 145.01 (N-Ph, C-1″), 154.58 (C-4); ν_{max} (neat)/cm^{-1} 3176, 3065, 2970, 2931, 2835, 1606, 1501, 1440, 1365, 1301, 1244, 1171, 1111, 1077, 1033, 943, 890, 835, 782, 760; *m/z* (100, M+H) 395; HRMS (ES): MH^+ calcd for $[C_{26}H_{23}N_2O_2]^+$: 395.1760, found: 395.1743.

4.8.8 Preparation of 2-(trimethylsilyl)-1,4-diphenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150h (R = H)

An experimental procedure employed for the synthesis of **150a** was followed using a mixture of **147a (**0.15 g, 1.185 mmol), CuI (0.011 g, 0.059 mmol), $PdCl_2(PPh_3)_2$ (0.041 g, 0.059 mmol), triethylamine (0.33 mL, 2.36 mmol) and ethynyltrimethylsilane (0.14 g, 1.42 mmol) in DMF (20 mL). Work-up and column chromatography afforded **150h** as a solid (0.04g, 68%); R_f (20% ethyl acetate/ hexane) 0.87; m.p. 163.3.7-164.6 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.07 (9H, s, Si(C$\underline{H}_3$)$_3$, 6.98 (1H, d, *J* 7.8 Hz, H-6), 7.10-7.14 (2H, m, 3-H, 4′′-H), 7.14 (1H, s, 3-H), 7.47-7.66 (9H, m, 3′-H, 4′-H, 5′-H, 2′′-H, 3′′-H, 5′′-H, 6′′-H, 7-H, 8-H), 8.07 (2H, d, *J* 7.5 Hz, 2'-H and 6'-H), 8.23 (1H, d, *J* 9.3 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 0.012 (Si($\underline{C}$H$_3$)$_3$), 114.40 (C-3), 117.65 (C-2), 119.93 (C-3a), 120.48 (N-Ph, C-4′′), 124.93 (C-9), 126.49 (C-8), 128.59 (N-Ph, C-2′′ and C-6′′), 128.75 (C-4′), 129.17 (C-3′ and C-5′), 129.38 (C-2′ and C-6′), 129.67 (N-Ph, C-6′′, C-3′′ and C-5′′), 130.41 (C-7), 139.17 (C-9a), 140.42 (C-1′), 141.62 (C-9b), 142.77 (N-Ph, C-1′′), 145.12 (C-5a), 154.67 (C-4); ν_{max} (neat)/cm^{-1} 3060, 2960, 1598, 1562, 1515, 1500, 1429, 1372, 1320, 1303, 1247, 1101, 980, 938, 838, 814, 781, 754; *m/z* (100, M+H) 393; HRMS (ES): MH$^+$ calcd for $[C_{26}H_{25}N_2Si]^+$: 393.1787, found: 393.1789.

4.8.9 Preparation of 4-(4′-fluorophenyl)-2-(trimethylsilyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150i (R = F)

An experimental procedure employed for the synthesis of **150a** was followed using a mixture of **147c** (0.15 g, 1.185 mmol), CuI (0.011 g, 0.059 mmol), $PdCl_2(PPh_3)_2$ (0.041 g, 0.059 mmol),

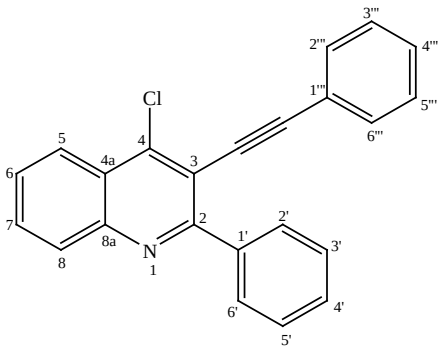
triethylamine (0.33 mL, 2.36 mmol) and ethynyltrimethylsilane (0.14 g, 1.42 mmol) in DMF (20 mL) Work-up and column chromatography afforded **150i** as a solid (0.041 g, 68%); R_f (20% ethyl acetate/ hexane) 0.91; m.p. 163.3.7-164.6 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.072 (9H, s, Si(C$\underline{H}_3$)$_3$), 6.98 (1H, d, *J* 8.4 Hz, 6-H), 7.10-7.16 (2H, m, 3-H, 4″-H), 7.24-7.66 (8H, m, 3′-H, 5′-H, 2″-H, 3″-H, 5″-H, 6″-H, 7-H, 8-H), 8.07 (2H, d, *J* 7.5 Hz, 2'-H and 6'-H), 8.05-8.09 (2H, m, 2'-H and 6'-H), 8.20 (1H, d, *J* 7.5 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 0.331 (Si($\underline{C}$H$_3$)$_2$), 114.06 (C-3), 115.39 (d, $^2J_{CF}$ 21.38 Hz, C-3′ and C-5′), 117.59 (C-2), 119.74 (C-3a), 120.48 (N-Ph, C-4″), 125.00 (C-9), 126.57 (C-8), 129.33 (N-Ph, C-2″ and C-6″), 129.68 (N-Ph, C-3″ and C-5″), 129.73 (C-6), 130.33 (C-7), 130.86 (d, $^3J_{CF}$ 8.25 Hz, C-2′ and C-6′), 136.56 (d, $^4J_{CF}$ 2.85 Hz, C-1′), 141.51 (C-9a), 142.95 (C-9b), 145.04 (N-Ph, C-1″), 153.49 (C-5a), 161.68 (d, $^1J_{CF}$ 240 Hz, C-4′); ν_{max} (neat)/cm^{-1} 3071, 2969, 1597, 1562, 1501, 1450, 1428, 1371, 1301, 1247, 1221, 1155, 1096, 977, 933, 834, 788, 754; *m/z* (100, M+H) 411; HRMS (ES): MH$^+$ calcd for [$C_{26}H_{24}FN_2Si$]$^+$: 411.1693, found: 411.1685.

4.8.10 Preparation of 4-(4′-methoxyphenyl)-2-(trimethylsilyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150j (R = OCH_3)

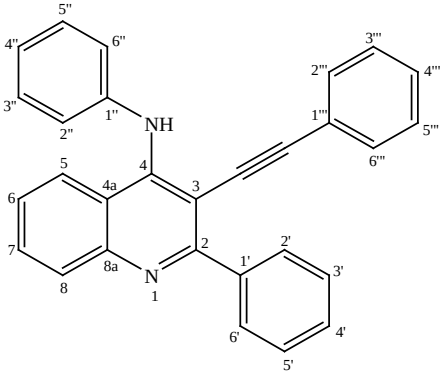
An experimental procedure employed for the synthesis of **150a** was followed using a mixture of **147d** (0.5 g, 1.45 mmol), CuI (0.011 g, 0.059 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.059 mmol), triethylamine (0.33 mL, 2.36 mmol) and ethynyltrimethylsilane (0.14 g, 1.42 mmol) in DMF (20 mL) to afford **150j** as a solid (0.04 g, 68%); R_f (20% ethyl acetate/ hexane) 0.75; m.p. 163.7-164.6 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.07 (9H, s, Si(C$\underline{H}_3$)$_3$), 3.91 (3H, s, OCH_3); 6.96 (1H, d, *J* 8.4 Hz, 6-H), 7.10-7.15 (4H, m, 3-H, 4″-H, 3′-H and 5′-H), 7.45-7.51 (3H, m, 7-H,

3″-H, 5″-H), 7.45-7.51 (3H, m, 2″-H, 6″-H, 8-H), 8.05 (2H, d, *J* 6.6, 2'-H and 6'-H); 8.20 (1H, d, *J* 8.4 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 0.012 ($Si(\underline{C}H_3)_3$, 55.60 (OCH_3); 114.02 (C-3′ and C-5′); 114.46 (C-3), 117.53 (C-2), 119.81 (C-3a), 120.46 (C-9); 124.66 (C-8), 126.44 (C-6 and C-4″), 129.38 (C-2″ and C-6″), 129.65 (C-2′ and C-6′), 130.23 (C-7), 130.48 (C-3″ and C-5″), 133.09 (C-9a), 139.16 (C-1′), 141.65 (C-9b), 142.60 (C-1″), 145.16 (C-5a), 154.26 (C-4), 160.26 (C-4′); ν_{max} (neat)/cm^{-1} 3064, 2965, 2903, 2835, 1608, 1509, 1447, 1430, 1375, 1307, 1249, 1174, 1101, 1035, 981, 935, 840, 763; *m/z* (100, M+H) 423; HRMS (ESI): MH^+ calcd for $[C_{27}H_{27}N_2OSi]^+$: 423.1893, found: 423.1871.

4.8.11 Alternative synthesis of 1,2,4-trisubstituted 1*H*-pyrrolo[3,2-*c*]quinolines 150



148



149

a) Synthesis of 4-Chloro-2-phenyl-3-(phenylethynyl)quinoline 148

The stirred mixture of **113a** (1.00 g, 2.736 mmol), phenylacetylene (0.40 mL, 3.30 mmol), CuI (0.03 g, 0.14 mmol), and $PdCl_2(PPh_3)_2$ (0.10 g, 0.14 mmol) in triethylamine (10 mL) was flushed with nitrogen in a flask equipped with a reflux condenser. The reaction mixture was

heated at 80 °C under nitrogen atmosphere for 2 hours. The mixture was allowed to cool and then quenched with ice-cold water. The resulting product was extracted with ethyl acetate, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography to afford **148** as a solid (0.69 g, 74%); R_f (10% EtOAc-hexane) 0.44; m.p. 145-148 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) 7.31-7.36 (3H, m, 3'''-H, 4'''- H and 5'''-H), 7.40-7.44 (2H, m, 2'''-H, and 6'''-H), 7.49-7.56 (3H, m, 3'-H, 4'-H and 5'-H), 7.66 (1H, dt, *J* 1.5 and 8.1 Hz, 6-H), 7.77 (1H, dt, *J* 1.8 and 8.4 Hz, 7-H), 8.00-8.04 (2H, m, 2'-H and 6'-H), 8.15 (1H, dd, *J* 0.6 and 9.0 Hz, 8-H), 8.27 (1H, dd, *J* 1.5 and 9.9 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 85.55 (-**C**≡C-Ph), 100.55 (-C≡**C**-Ph), 116.40 (C-3), 122.71 (C-4a), 124.36 (C-5), 124.84 (C-1'''), 127.88 (C-4'), 127.94 (C-2', 6'), 128.40 (C-3''' and C-5'''), 128.96 (C-4'''), 129.24 (C-6), 129.60 (C-3' and C-5'), 130.01 (C-8), 130.80 (C-7), 131.54 (C-2''' and C-6'''), 139.53 (C-1'), 145.08 (C-4), 146.87 (C-8a), 159.77 (C-2); ν_{max}/cm^{-1} 3057, 1595, 1447, 1343, 1087,823; *m/z* (100, M+H) 340; HRMS (ESI): MH^+ calcd for $[C_{23}H_{14}N^{35}Cl]^+$: 339.69, found: 340.0888.

b) Synthesis of 2-Phenyl-4-(phenylamino)-3-(phenylethynyl)quinoline 149

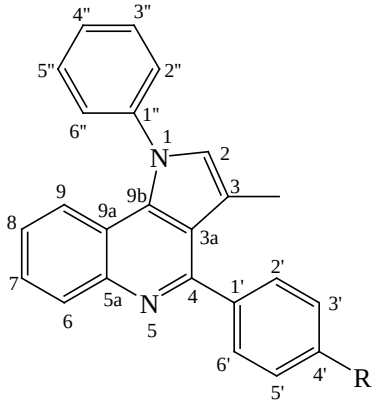
A mixture of **148** (0.18 g, 0.53 mmol) and aniline (0.05 g, 0.53 mmol) in ethanol (20 mL) was heated at 80 ºC for 18 hours and then evaporated under reduced pressure. The residue was acidified with 2M HCl and then extracted into chloroform. The organic solution was washed with saturated solution of Na_2CO_3, water and then dried over $MgSO_4$. The salt was filtered off and the organic solution was evaporated under reduced pressure. The residue was purified by column chromatography to afford **149** as a solid (0.09 g, 45 %), R_f (30% ethyl acetate/hexane) 0.57; m.p. 175–176 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.06 (2H, d, *J* 7.8 Hz, 3′′-H and

5″-H), 7.09 (1H, t, *J* 7.5 Hz, 6-H), 7.14 (1H, s, N-H), 7.20–7.33 (8H, m, 4″-H, 2″-H, 6″-H, 3′-H and 5′-H, 3‴-H and 5‴-H, 7-H), 7.46–7.55 (3H, m, 2‴ and 6‴-H, 4‴-H), 7.64 (1H, dt, *J* 1.5 and 7.5 Hz, 4′-H), 7.70 (1H, d, *J* 8.4 Hz, 8-H), 8.04 (2H, dd, *J* 1.5 and 7.5 Hz, 2′-H and 6′-H), 8.11 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 85.1 (-**C**≡C-Ph), 101.3 (-C≡**C**-Ph), 104.9 (C-3), 119.2 (C-4a), 120.3 (C-2″ and C-6″), 122.8 (C-1‴), 123.2 (C-8), 124.4 (C-4″), 125.2 (C-5), 127.9 (C-2′ and C-6′), 128.3 (C-3‴ and C-5‴), 128.5 (C-6), 128.8 (C-4′), 129.2 (C-3′ and C-5′), 129.5 (C-3″ and C-5″), 130.0 (C-4‴), 130.3 (C-7), 131.1 (C-2‴ and C-6‴), 140.3 (C-1′), 143.3 (C-8a), 147.9 (C-1″), 149.0 (C-4), 160.1 (C-2); ν_{max} (neat) /cm^{-1} 3225, 3182, 1599, 1560, 1529, 1485, 1400, 1354,1261; *m/z* (100, M+H) 397; HRMS (ESI): MH^+ calcd for $[C_{29}H_{21}N_2]^+$: 397.1705, found: 397.1695.

c) Synthesis of 1,2,4-triphenyl-1*H*-pyrrolo[3,2-*c*]quinolines 150a (R = H)

A mixture of **149** (0.08 g, 0.20 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.01 mmol). CuI (0.02 g, 0.01 mmol) and triethylamine (0.1 mL, 0.06 mmol) in dioxane–water (3:1, v/v; 20 mL) was treated as described for the synthesis of systems **150**. Work-up and column chromatography afforded **150a** as a solid (0.04 g, 55 %).

4.9 Intramolecular Heck reaction of 4-(*N*,*N*-allyphenylamino)-2-aryl-3-iodoquinolines 151 to afford 152a-d



4-Aryl-3-(methyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines

4.9.1 Preparation of 3-(methyl)-1,4-diphenyl-1*H*-pyrrolo[3,2-*c*]quinolines 152a (R = H)

A mixture of **151a (**0.20 g, 0.43 mmol), CuI (0.0041 g, 0.022 mmol) and $PdCl_2(PPh_3)_2$ (0.015 g, 0.022 mmol) in DMF (20 mL) was purged with N_2. Triethylamine (0.24 mL, 1.73 mmol) was added to the mixture with a syringe. The mixture was refluxed at 80 ^oC for 2 hours under nitrogen atmosphere. The mixture was poured into ice-cold water and extracted with chloroform. The chloroform layer was dried over $MgSO_4$, filtered and solvent removed under reduced pressure. The crude product was purified by column chromatography to afford **152a** as a solid (0.11 g, 76%); R_f (20% ethyl acetate/ hexane) 0.75, m.p. 138-140 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.92 (3H, s, CH_3); 7.00 (1H, s, 2-H), 7.19 (1H, t, *J* 7.2 Hz, 7-H), 7.35 (1H, d, *J* 8.7 Hz, 6-H), 7.47-7.67 (11H, m, 2′-H and 6′-H, 3′-H and 5′-H, 4′-H, 8-H, 2″-H and 6″-H, 3″-H and 5″-H, 4″-H), 8.23 (1H, d, *J* 8.4 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.42 (CH_3); 113.95 (C-3); 117.44 (C-3a), 119.88 (C-9a), 120.57 (C-2), 124.83 (C-4″); 126.47 (C-9), 127.36

(C-2″ and C-6″), 127.89 (C-2′ and C-6′), 128.20 (C-8), 128.71 (C-4′), 128.84 (C-6), 129.16 (C-3′ and C-5′), 129.74 (C-3″ and C-5″), 130.21 (C-7), 135.34 (C-1′), 140.86 (C-9b), 141.11 (C-1″), 144.23 (C-5a), 156.51 (C-4); ν_{max} (neat)/cm^{-1} 3061, 2970, 2931, 1596, 1557, 1497, 1433, 1370, 1300, 1205, 1126, 1027, 976, 790; *m/z* (100, M+H) 335; HRMS (ES): MH^+ calcd for $[C_{24}H_{19}N_2]^+$: 335.1548, found: 335.1549.

4.9.2 Preparation of 4-(4′-fluorophenyl)-3-(methyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines 152b (R = F)

An experimental procedure employed for the synthesis of **152a** was followed using a mixture of **151b (**0.21 g, 0.42 mmol), CuI (0.004 g, 0.021 mmol), $PdCl_2(PPh_3)_2$ (0.015 g, 0.021 mmol), triethylamine (0.23 mL, 1.67 mmol) in DMF (20 mL). Work-up and column chromatography afforded **152b** as a solid (0.11g, 75%); R_f (20% ethyl acetate/ hexane) 0.81; m.p. 123.4-124.6 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.94 (3H, s, CH_3); 7.01 (1H, s, 2-H), 7.17-7.23 (4H, m, 3′-H and 5′-H, 8-H, 4″-H), 7.34 (1H, d, *J* 8.4 Hz, 6-H), 7.48-7.67 (7H, m, 2′-H and 6′-H, 7-H, 2″-H and 6″-H, 3″-H and 5″-H), 8.20 (1H, d, *J* 8.4 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.54 (CH_3), 113.69 (C-3), 114.87 (d, $^2J_{CF}$ 21.38 Hz, C-3′ and C-5′), 117.44 (C-3a), 119.86 (C-9a), 120.59 (C-2); 124.95 (C-4″), 126.56 (C-9), 127.36 (C-2″ and C-6″), 128.85 (C-8), 128.91 (C-6), 129.77 (C-3″ and C-5″), 130.18 (C-7), 131.00 (d, $^3J_{CF}$ 7.95 Hz, C-2′ and C-6′), 135.42 (C-9b), 137.26 (d, $^4J_{CF}$ 3.38 Hz, C-1′), 140.80 (C-1″), 144.23 (C-5a), 155.37 (C-4), 162.98 (d, $^1J_{CF}$ 244.95 Hz, C-4′); ν_{max} (neat)/cm^{-1} 3063, 2926, 1600, 1557, 1499, 1434, 1371, 1345, 1308, 1219, 1154, 977, 839, 761; *m/z* (100, M+H) 353; HRMS (ES): MH^+ calcd for $[C_{24}H_{18}FN_2]^+$: 353.1454, found: 353.1449.

4.9.3 Preparation of 4-(4′-chlorophenyl)-3-(methyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines 152c (R = Cl)

An experimental procedure employed for the synthesis of **152a** was followed using a mixture of **151c (**0.24 g, 0.40 mmol), CuI (0.004 g, 0.020 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.020 mmol), triethylamine (0.22 mL, 1.61 mmol) in DMF (20 mL). Work-up and column chromatography afforded **152c** as a solid (0.12g, 81%); R_f (20% ethyl acetate/ hexane) 0.85; m.p. 165.9-167.0 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.95 (3H, s, CH_3); 7.01 (1H, s, 2-H), 7.20 (1H, t, *J* 8.4 Hz, 7-H), 7.34 (1H, d, *J* 8.4 Hz, 6-H), 7.48-7.62 (10H, m, 2′-H and 6′-H, 3′-H and 5′-H, 8-H, 2″-H and 6″-H, 3″-H and 5″-H, 4″-H), 8.19 (1H, d, *J* 8.1 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.64 (CH_3); 113.58 (C-3); 117.44 (C-3a), 119.71 (C-9a), 120.60 (C-2), 125.04 (C-4″); 126.60 (C-9), 127.36 (C-2″ and C-6″), 128.14 (C-2′ and C-6′), 128.89 (C-8), 128.92 (C-4′), 129.78 (C-3′ and C-5′), 130.20 (C-6), 130.64 (C-3″ and C-5″), 134.32 (C-7), 135.46 (C-1′), 139.63 (C-9b), 140.76 (C-1″), 144.22 (C-5a), 155.12 (C-4); ν_{max} (neat)/cm^{-1} 3066, 2964, 2927, 1597, 1557, 1489, 1433, 1371, 1305, 1206, 1126, 1085, 1015, 976, 858, 825, 782; *m/z* (100, M+H) 369; HRMS (ES): MH^+ calcd for $[C_{24}H_{18}ClN_2]^+$: 369.1158, found: 369.1168.

4.9.4 Preparation of 4-(4′-methoxyphenyl)-3-(methyl)-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinolines 152d (R = OCH_3)

An experimental procedure employed for the synthesis of **152a** was followed using a mixture of **151d** (0.22 g, 0.41 mmol), CuI (0.0039 g, 0.020 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.020 mmol), triethylamine (0.23 mL, 1.62 mmol) in DMF (20 mL). Work-up and column chromatography

afforded **152d** as a solid (0.11g, 74%); R_f (20% ethyl acetate/ hexane) 0.58; m.p. 175.4-177.2 ºC (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.97 (3H, s, CH_3); 3.89 (3H, s, OCH_3), 6.99 (1H, s, 2-H), 7.04 (2H, d, *J* 9.0 Hz, 2′-H and 6′-H) 7.17 (1H, t, *J* 7.2 Hz, 7-H), 7.33 (1H, d, *J* 8.4 Hz, 6-H), 7.47-7.63 (8H, m, 3′-H and 5′-H, 8-H, 2″-H and 6″-H, 3″-H and 5″-H, 4″-H), 8.20 (1H, d, *J* 8.4 Hz, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.65 (CH_3), 55.36 (OCH_3), 113.34 (C-2′ and C-6′)114.01 (C-3); 117.37 (C-3a), 120.03 (C-9a), 120.55 (C-2), 124.65 (C-4″); 126.39 (C-9), 127.36 (C-2″ and C-6″), 128.66 (C-8), 128.79 (C-4′), 129.72 (C-3″ and C-5″), 130.17 (C-6), 130.52 (C-3′ and C-5′), 133.32 (C-7), 135.38 (C-1′), 140.93 (C-9b), 144.36 (C-1″), 156.28 (C-5a), 159.77 (C-4); ν_{max} (neat)/cm^{-1} 3010, 2965, 2926, 1608, 1557, 1497, 1457, 1434, 1370, 1303, 1246, 1170, 1128, 1030, 975, 825, 766; *m/z* (100, M+H) 365; HRMS (ES): MH^+ calcd for $[C_{25}H_{21}N_2O]^+$: 365.1654, found: 365.1670.

CHAPTER 5 REFERENCES

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APPENDIX

Mass spectra of **147a**, **151a**, **150a** and **152a**

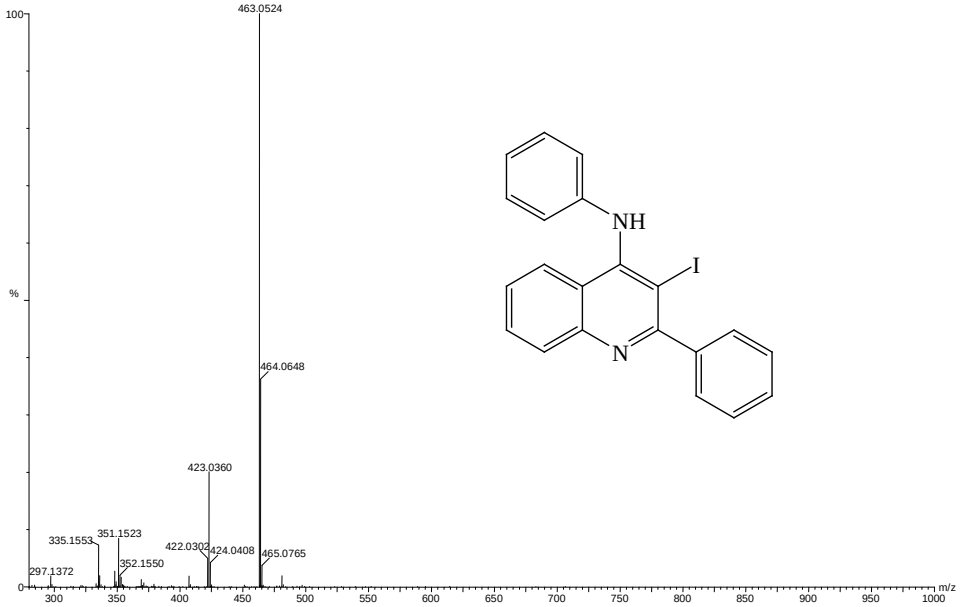

Figure 14: Mass spectrum of 3-iodo-2-phenyl-4-(phenylamino)quinoline **147a**

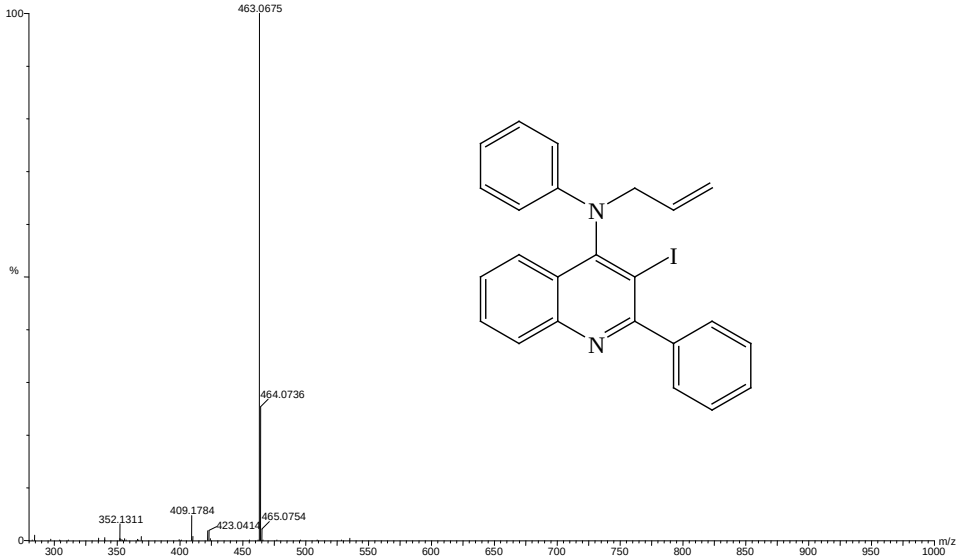

Figure 15: Mass spectrum of 4-(*N*,*N*-allyphenylamino)-3-iodo-2-phenylquinolines **151a**

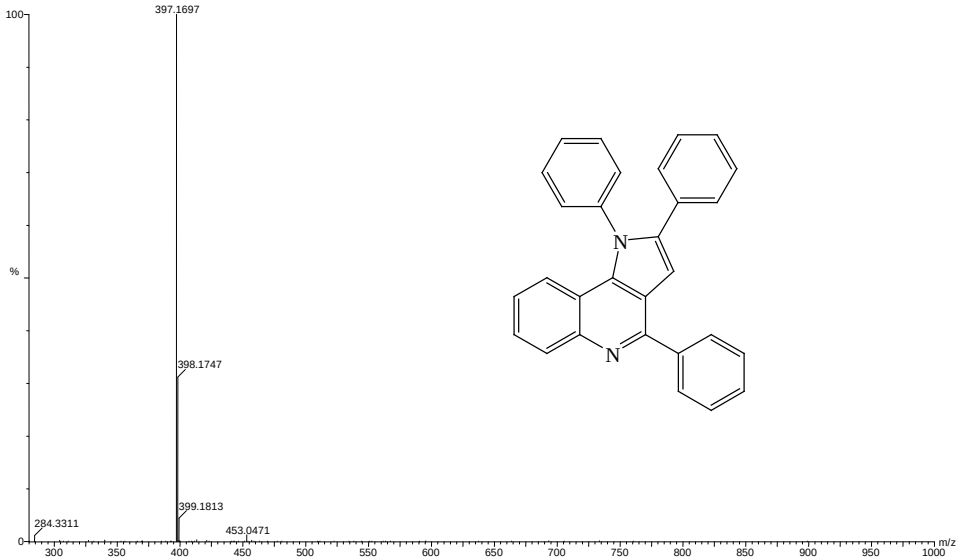

Figure 16: Mass spectrum of 1,2,4-triphenyl-1*H*-pyrrolo[3,2-*c*]quinolines **150a**

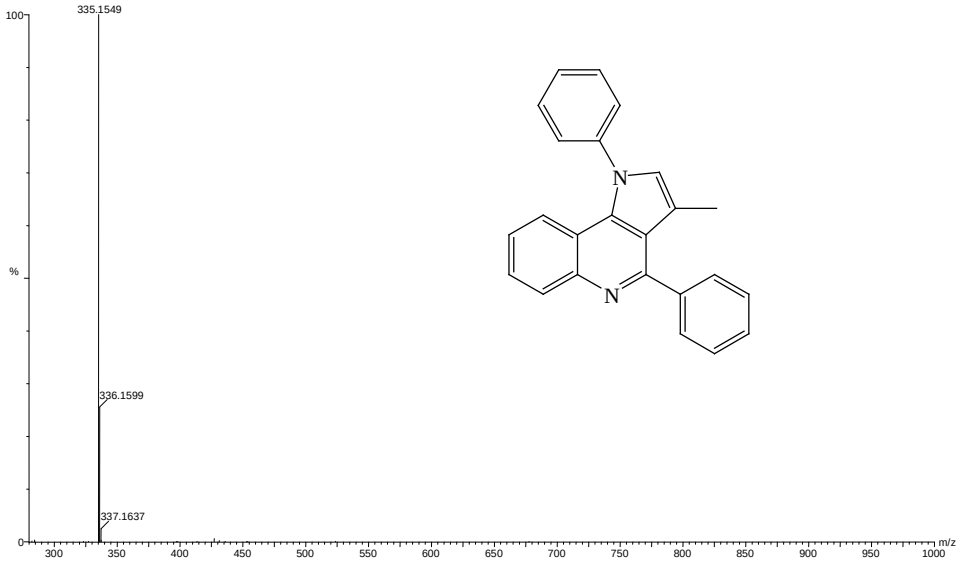

Figure 17: Mass spectrum of 3-(methyl)-1,4-diphenyl-1*H*-pyrrolo[3,2-*c*]quinolines **152a**