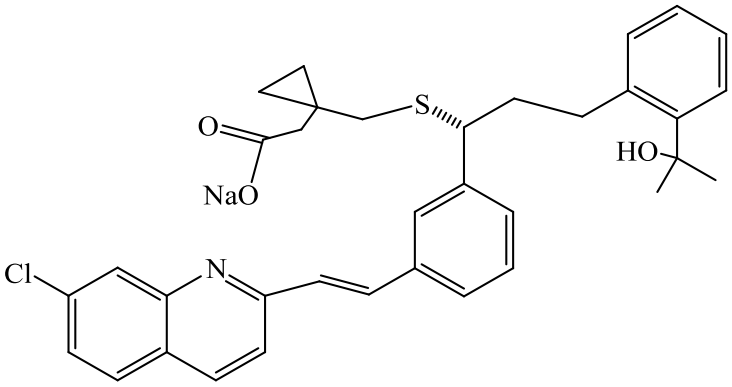
CHAPTER 1: INTRODUCTION

1.1 Background

The synthesis of polysubstituted quinoline derivatives is the focus of a large number of studies because of their wide range of biological applications [1]. The quinoline moiety constitutes the main framework of several natural products such as Montelukast **1** [2] and Skimmianine **2** [3]. Polysubstituted quinolines in particular are very important compounds because of their medicinal applications as antimalarial, anti-inflammatory, antiasthmatic and antibacterial agents and they also have a wide array of industrial applications [4-6]. There is a growing interest in the synthesis of 2-arylquinolines bearing various substituents such as alkenyl, akynyl, aryl or primary amino groups on the 3- and 4-positions of 2-arylquinoline moiety. The 2-arylquinoline derivatives **3a** or **3b** bearing alkynyl or amine group at position 4 of the quinoline ring were synthesized and tested for selectivity in binding to the estrogen receptor β (ER β), which plays an important role in the development, maintenance, and function of the mammalian reproductive system, as well as non-sexual tissues [7].



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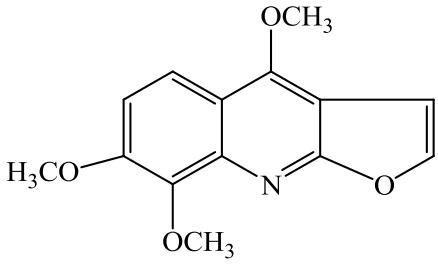

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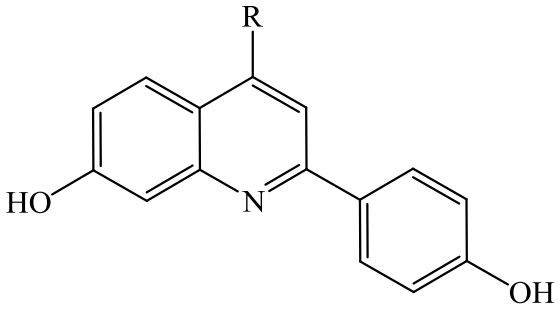
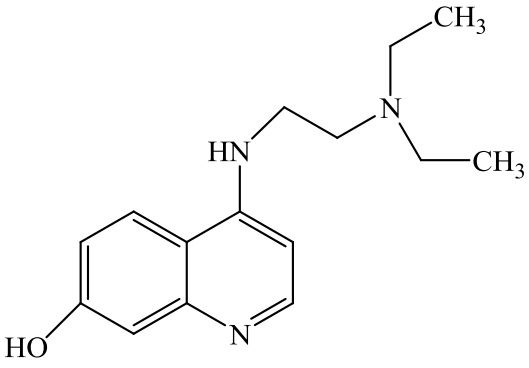


3a R = -C≡CH

b R = NH_2

The primary 4-aminoquinolines also exhibit tyrosine-kinase PDGF-RTK activity [8]. 4-(2-(Diethylamino)ethylamino)quinolin-7-ol **4** containing nitrogen at position 4 exhibits antiplasmodial activity [9]. Polysubstituted quinolines such as 8-hydroxyquinoline and quinoline-8-thiol have been used to produce metal complexes which emit light [10]. 2-(4-Bromo-5-ethylnylthiophen-2-yl)-6-ethynyl-4-phenylquinoline **5** has been applied in sensors and light emitting diodes [11].



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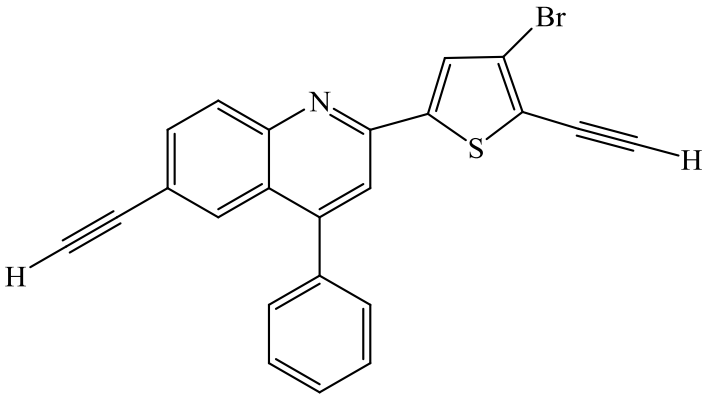
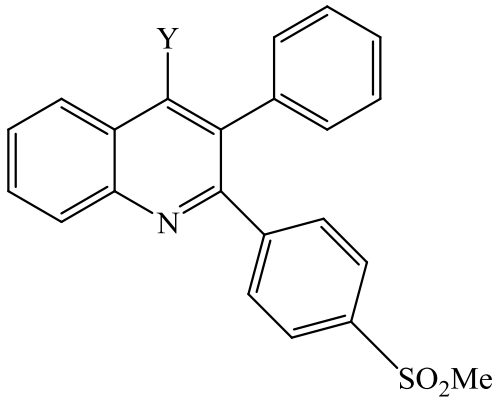


5

The 4-substituted 2,3-diarylquinoline derivatives **6** bearing methylsulfonyl group at the *para*-position of the 2-phenyl ring were synthesized and evaluated as selective cyclooxygenase-2 inhibitors (COX-2) [12] which are important for the treatment of colon cancer and neurological disorders such as Parkinson [13] and Alzheimer diseases [14]. 3,4-Diphenyl-2-(4-methylsulfonyl)phenylquinoline **6a** (R = C_6H_5) 4-amino-2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline **6b** (R = NH_2) and 2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline-4-carboxylic acid **6c** were found to exhibit high potency and selectivity as COX-2 inhibitors [12]. The trend decreases as follows: COOH > H > NH_2 > Me > Ph and this reflects the nature and size of the substituent at C-4 position. Bulky and hydrophobic substituents at C-4 position were found to lead to reduced selectivity due to the lack of hydrogen bonding interaction. 4-Carboxylic acid moiety, on the other hand, promotes hydrogen bonding interaction, which accounts for their high potency and selectivity as COX-2 inhibitors.

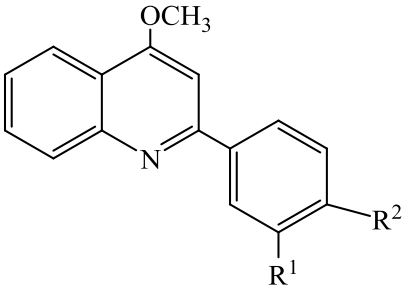


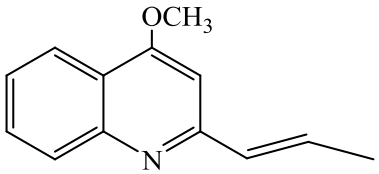
6: Y = Ph (**a**); NH_2 (**b**); CO_2H (**c**); H (**d**) and CH_3 (**e**)

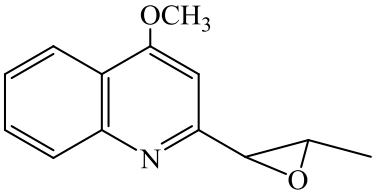
Substituted quinoline derivatives constitute an important chemical unit in a large variety of naturally occurring compounds and are distributed in a wide variety of plants, animals and fungi.

1.2 Natural distribution of polysubstituted quinolines and their biological applications

Substituted quinolines are plant-based alkaloids widely distributed in the plant family *Rutaceae* [15]. The 4-methoxy-2-phenylquinoline **7a** and 4-methoxy-2-(3,4-methylenedioxyphenyl)quinoline **7b**, for example, were isolated from the leaves of *Lunasia amara* Blanco of the Philippine origin and were found to exhibit inhibitory activity against *Mycobacterium tuberculosis* H_{37}Rv [16]. The 4-methoxy-2-(*E*)-prop-1-enylquinoline **8** and 4-methoxy-2-(1,2-*trans*-epoxypropyl)quinoline **9** were isolated from the bark and the leaves of *Galipea longiflora* widely distributed in South America, particularly in the Amazonian forest [17].





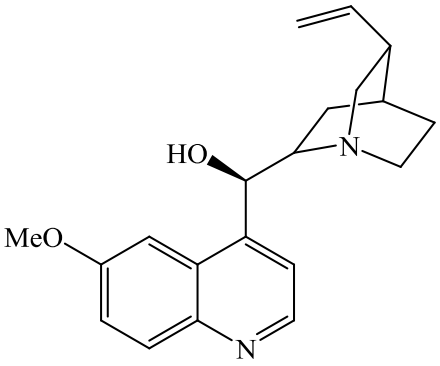


7(**a**) R^1, R^2 = H
(**b**) R^1, R^2 = -OCH2O-

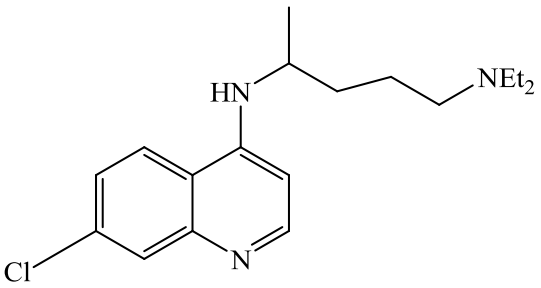
8

9

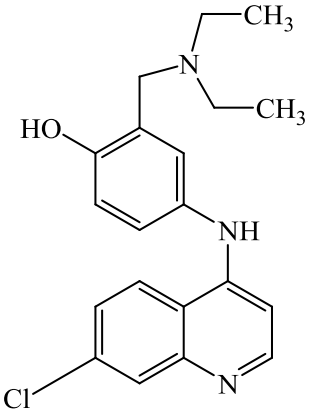
Substituted quinoline derivatives have attracted considerable interest in medicine as anti-malarial [5], anti-leishmanial [3], anti-bacterial, antiasmatic agents and some serve as therapeutic drugs for the treatment of inflammatory diseases [6]. The 4-methoxyquinoline **7a** and **7b** which exhibit antimalarial activity also serve as peptidoleukotriene LTD_4 antagonists [18]. These compounds also exhibit activity against antileishmania, which is a parasitic disease caused by protozoan parasites of the genus Leishmania in tropical and subtropical areas of South America [19,20]. Quinoline derivatives play an important role in the industry and have also been detected in urban air particulates and cigarette smoke [21]. Malaria remains one of the most devastating infectious diseases worldwide and the quinoline-containing compounds have been used in the treatment of malaria, beginning with quinine **10a**. Over the years, modifications of quinine led to the potent 4-aminoquinoline drug chloroquine **10b** as an antimalarial agent [22]. Chloroquine **10b** has become ineffective in many malarial infected areas and as a result, a series of 4-aminoquinoline analogues of chloroquine have been developed to cover a range of potencies in antimalarial activity [5]. For example, amodiaquine **10c**, amopyroquine **10d** and tebuquine **10e** have proven to be superior alternative drugs to chloroquine in areas of high chloroquine resistance [23]. Due to the growing problems with drug resistance, there is a growing need for the design of new and cost-effective drugs for the treatment of malaria [24].



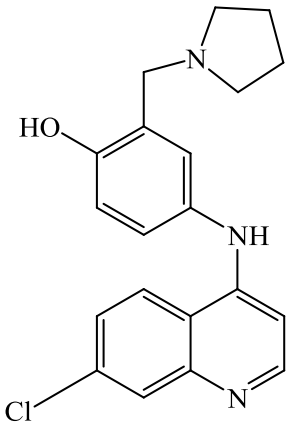
10a



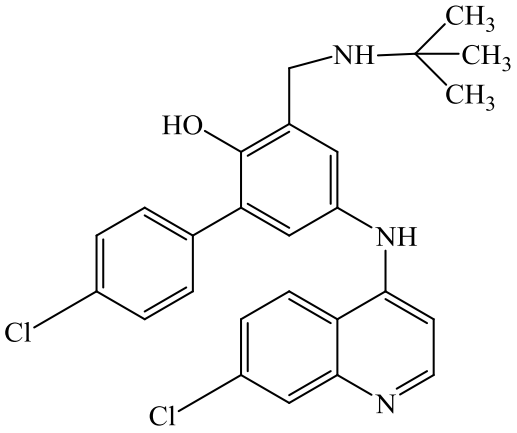
10b



10c



10d



10e

1.3 Known synthetic methods for the preparation of polysubstituted quinoline derivatives

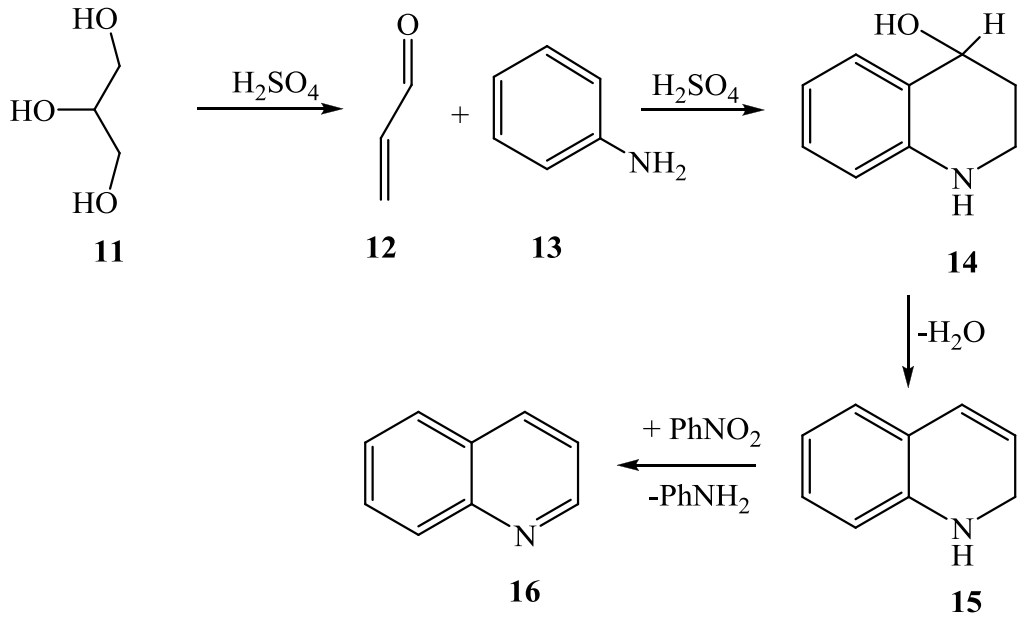
There are several methods described in the literature for the construction of the quinoline ring systems. The well-known classical methods such as Skraup, Friedlander, Doebner-von Miller and Combes are frequently used for the preparation of quinoline backbone. These classical methods which are briefly reviewed below generally make use of nucleophilic primary amines containing

nitrogen donating component as C-C-N unit and electrophilic three carbon unit, usually carbonyl compounds [4,19].

1.3.1 Classical methods for the direct synthesis of polysubstituted quinoline

1.3.1.1 Skraup synthesis of quinolines

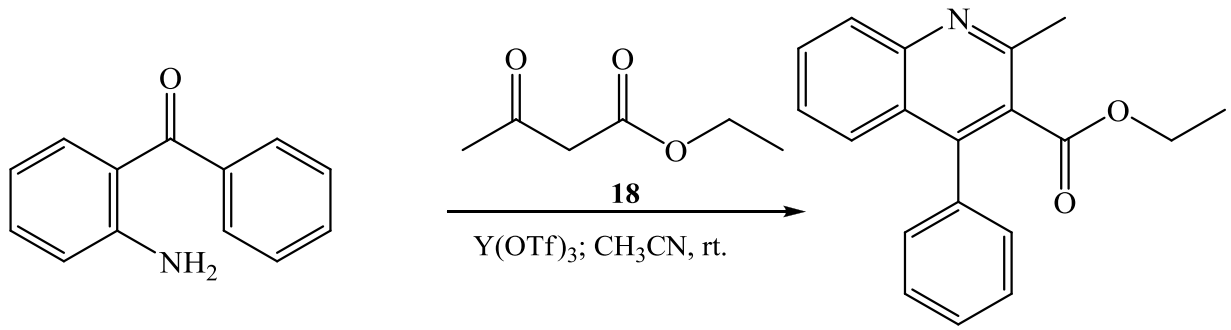
Skraup synthesis involves heating aniline derivatives with glycerol, sulfuric acid and oxidizing agents. Glycerol **11** is dehydrated with sulfuric acid to acrolein **12**, which then reacts with aniline **13** by conjugate addition (Scheme 1). The resulting intermediate is cyclised, oxidized and dehydrated to give quinoline **16.** If aniline bears a *meta*-substituent, there are two different *ortho* positions available for cyclizaton and this often leads to an isomeric mixture of quinoline which is difficult to separate [25].



Scheme 1

1.3.1.2 Friedlander synthesis of substituted quinolines

The Friedlander synthesis is one of the most convenient routes for the synthesis of quinoline scaffold and is also regarded as one of the most simple and straightforward method involving condensation of 2-aminoacetophone with a carbonyl derivatives having α-methylene proton(s). The reaction is promoted by acid, base or heat. Two possible mechanistic pathways have been suggested for the Friedlander reaction; the first involves initial imine formation followed by intramolecular Claisen condensation, while the second reverses the order of the steps [26]. The condensation of 2-aminobenzophenone **17** with ethyl acetoacetate **18** in the presence of yttrium triflate at room temperature resulted in the formation of ethyl 3-carboxylate-2-methyl-4-phenylquinoline **19** in 92% yield (Scheme 2) [27]. Although Friedlander synthesis is quite a versatile method for the synthesis of quinolines, the primary limitation of this method is the preparation and stability of 2-aminobenzaldehyde precursors which are prone to self-condensation [28].

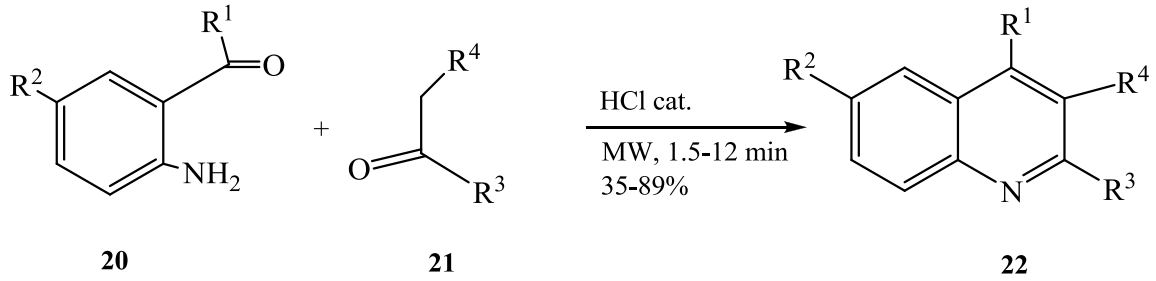


17 **19**

Scheme 2

Muscia and coworkers [29] have used hydrochloric acid (HCl) as a catalyst in the reaction of 2-aminoacetophenones ($R^1 = CH_3$, $R^2 = H$) **20** or benzophenones **20** ($R^1 = Ar$, $R^2 = H$) with a variety of α-methylene-containing ketones and keto-esters **21** under microwave irradiation (400W) to afford

substituted quinolines **22** (Scheme 3). Unlike conventional heating under reflux which takes 6 hours to completion, the microwave conditions afforded the products within 1.5 to 12 min.

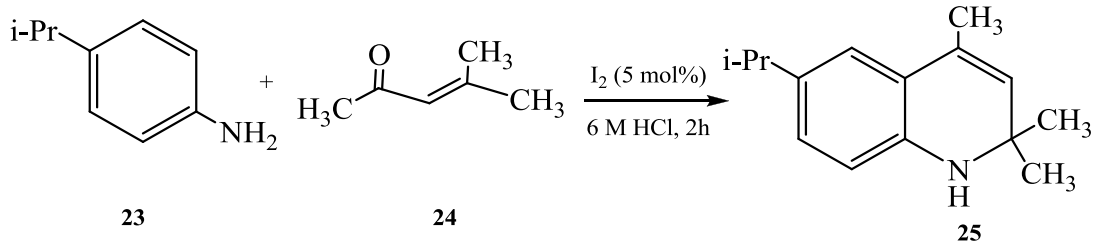


20 **21** **22**

Scheme 3

1.3.1.3 Doebner-von Miller synthesis of quinolines

The Doebner-von Miller synthesis adopts a similar reaction sequence to that of the Skraup synthesis and both are based on the reaction of aromatic amine containing one free *ortho* position with a reagent providing three carbon fragments. The Doebner-von Miller protocol replaced the potentially explosive glycerol with α,β-unsaturated ketone **24** and conducted the reaction by heating with an aromatic amine **23** in the presence of an acid catalyst and iodine to afford 6-isopropyl-2,2,4-trimethyl-1,2-dihydroquinoline **25** (Scheme 4) [30].

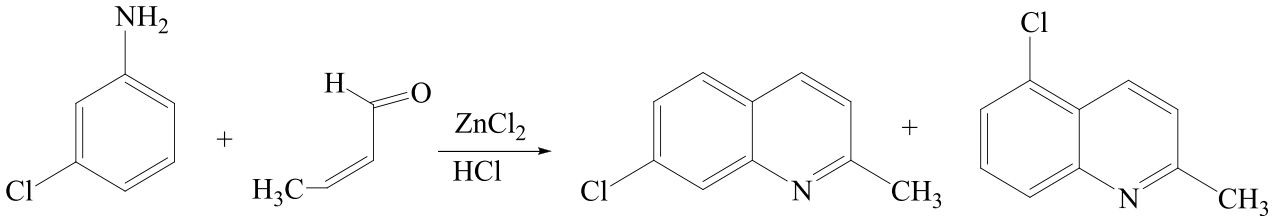


23 **24** **25**

Reagents: (i) I_2 (5%), 6M HCl, heat, 2h

Scheme 4

Zinc chloride with or without hydrochloric acid was used as condensing agent in the reaction of 3-chloroaniline **26** and (*Z*)-but-2-enal **27** to afford mixture 7-chloro-2-methylquinoline **28** and 5-chloro-2-methylquinoline **29** (scheme 5). The mixture is the result of parallel polymerization of α,β-unsaturated aldehydes [31] which is catalyzed by acid and results in a low yields of the product.

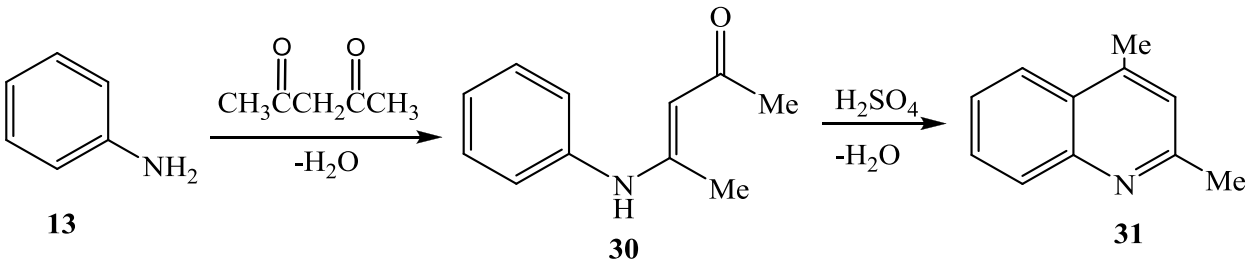


26 **27** **28** (97%) **29** (2.5%)

Scheme 5

1.3.1.4 Combes synthesis of quinolines

The Combes synthesis involves nucleophilic addition of aniline **13** to the carbonyl group of the 1,3-diketone to form enamine intermediate **30** followed by electrophilic aromatic annulations to yield 2,4-dimethylquinoline **31 (**Scheme 6**) [**32**]**.



13 **30** **31**

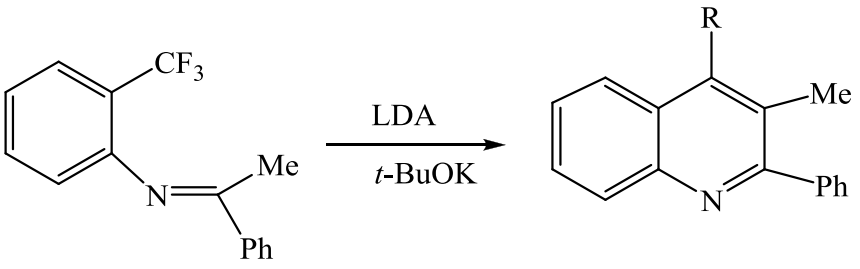
Scheme 6

In this project the synthesis of 2-arylquinoline derivatives bearing alkynyl, aryl or amino at C-3 and/ or C-4 positions of the quinoline moiety to afford 2,3,4-trisubstituted quinoline derivatives with potential biological activity or application in materials was investigated. Unfortunately, the classical methods such as Skraup [13], Doebner-von Miller [30], Friedlander [26] and Combes [32] do not allow for adequate substitution on the quinoline ring. Moreover, these methods have many significant drawbacks ranging from the use of expensive reagent, strong acidic conditions, longer reaction times, high temperatures, difficult work-up steps and environmentally unfriendly reagents. Furthermore, these classical methods cannot be adapted for the incorporation of heteroatom-containing group (O, N or S) at the 4-position, which is usually a requirement for biological activity. As a result, indirect methods involving cyclization reactions or the displacement of a leaving group (e.g., halogen or tosylate group) on the 4-position of the quinoline ring by nucleophile continue to be developed for the synthesis of polysubstituted quinoline derivatives.

1.3.2 Indirect methods for the synthesis of polysubstituted quinolines

1.3.2.1 Cyclization methods

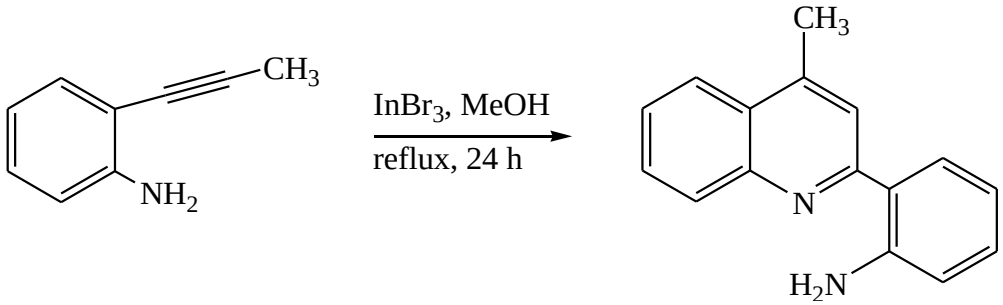
The synthesis of polysubstituted quinoline via cyclization methods continues to attract attention in heterocyclic chemistry [33]. Ketimine **32** derived from 2-trifluoromethylaniline and alkyl or heterophenyl ketones is reported to afford 3-methyl-*N*,*N*-2-triphenylquinolin-4-amine **33a** and 4-*tert*-butoxy-3-methyl-2-phenylquinoline **33b** [34] (Scheme 7). Treatment of **32** with lithium diisopropylamide (LDA) and *tert*-butoxide (*t*-BuOK) under reflux afforded cyclized products **33** in 52-82% yield.



32 **33 a**) R=N(*i*-Pr)$_2$; **b)** R=t-OBu

Scheme 7

Cyclization of 2-ethylnylaniline **34** (1 equiv.) in the presence of tribromolanthanoids (lnBr$_3$) in methanol (MeOH) afforded the 2-(4-methylquinolin-2-yl)aniline **35** in 56-89% yiel (Scheme 8) [35].



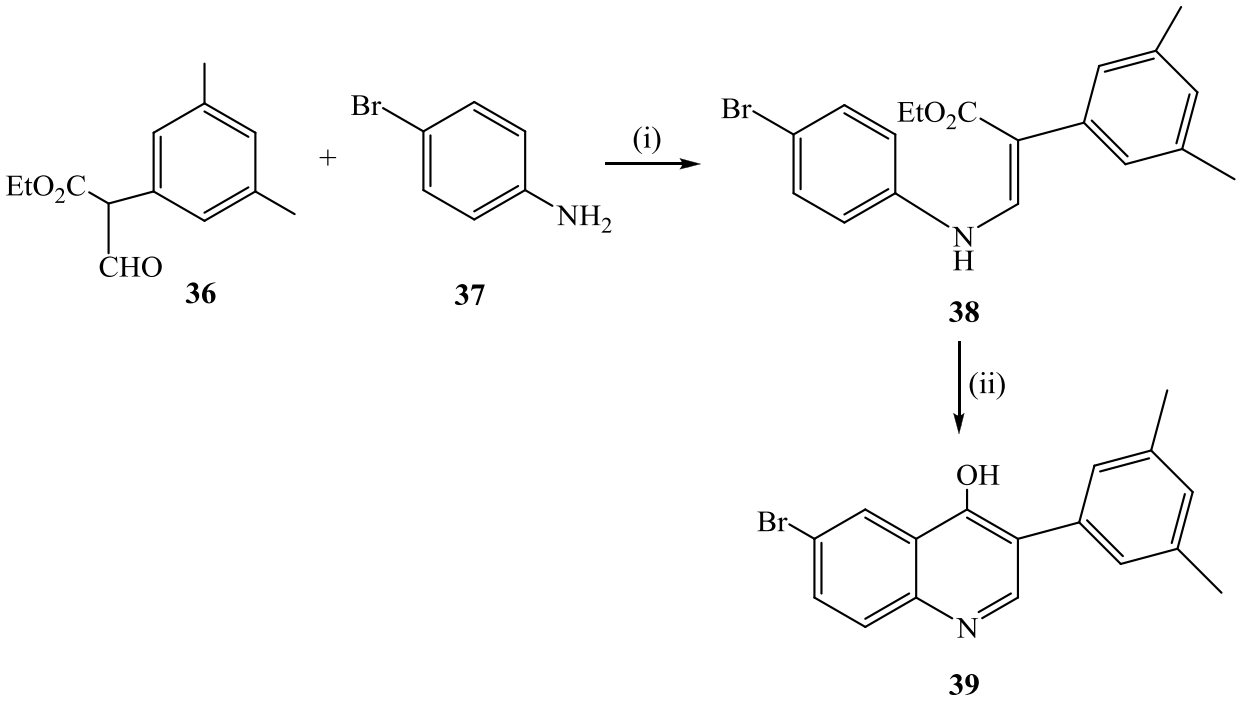
34 **35**

Scheme 8

1.3.2.2 4-Quinolinols or 4-quinolones as precursors

The Conrad-Limpach synthesis is one of the classical methods used for preparation of quinolone or quinolinol derivatives which are important intermediate for the synthesis of substituted quinoline via halogenation and subsequent metal-catalyzed C-C bond formation or displacement of halogen atom by nucleophiles. The Conrad-Limpach synthesis involves condensation of aniline with β-ketoesters followed cyclisation at high temperature to afford quinolone derivatives [36].

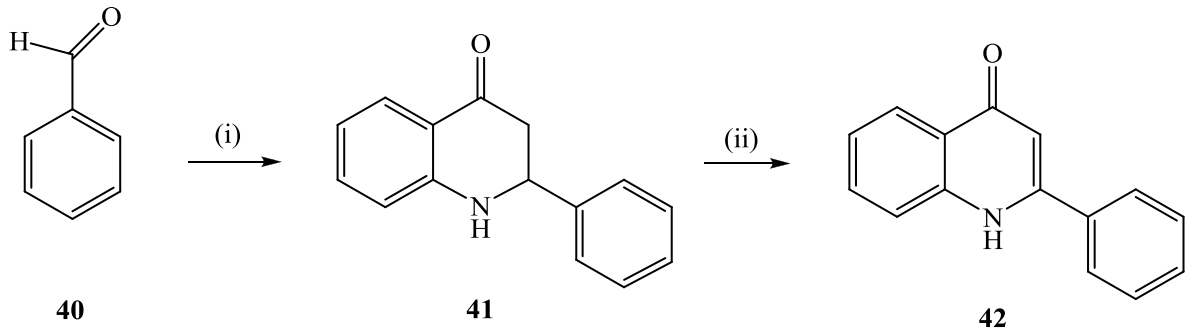
Nolt *et al*. reacted 4-bromoaniline **37** with ethyl 3,5-dimethylbenzoate **36** in THF to afford (*Z*)-ethyl 3-(4-bromophenylamino)-2-(3,5-dimethylphenyl)acrylate **38** which was, in turn, cyclised in diphenylether at 250 °C to afford 6-bromo-3-(3,5-dimethylphenyl)quinolin-4-ol **39** (Scheme 9) [37].



Reagents: (i) THF, 120 °C (ii) diphenylether, 250 °C, 30 min

Scheme 9

Several methods have since been developed for the preparation of 2-arylquinolin-4(1*H*)-ones. *o*-Aminoacetophonone **20** was condensed with benzaldehyde **40** in the presence of L-proline and methanol to afford 2-aryl-1,2,3,4-tetrahydro-4-quinolinones **41** in 85% yield (Scheme 10) [38]. Thallium(III) *p*-tolysulfonate (TTS) in dimethoxy-ethane (DME) or iodobenzene diacetate in methanolic KOH were used to dehydrogenate 2-aryl-1,2,3,4 tetrahydro-4-quinolinones to afford the 2-aryl-4-quinolin-4(1*H*)-ones **42** (Scheme 10) [68,41].

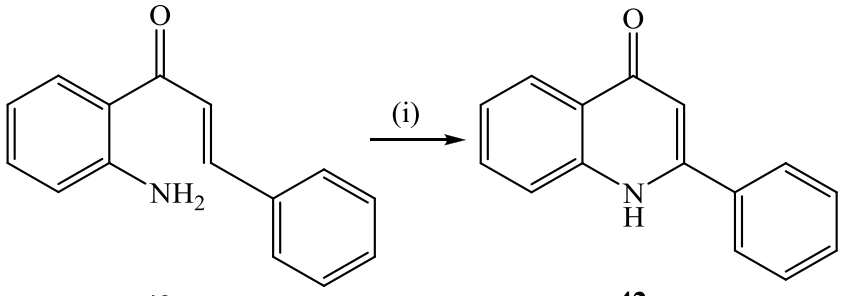


40 **41** **42**

Reagents: (i) L-proline, MeOH, 48 h, rt. (ii) TTS, DME, toluene, heat

Scheme 10

2'-Aminochalcones **43** and their isomeric 2-aryl-1,2,3,4-tetrahydro-4-quinolinone derivatives have also been used as substrates for the synthesis of 2-arylquinolin-4(1*H*)-ones. 2´-Amonichalcones **43** have been found to undergo intramolecular cyclization in THF in the presence of dichloro-bis(triphenylphosphine)palladium(II) to afford the corresponding 2-arylquinolin-4(1*H*)-ones **42** in 55-85% yield (Scheme 11). The main disadvantage of this reaction is the use of stoichiometric amount of the organometallic reagent and column chromatographic separation of the NH-4-oxo derivatives that are sparingly soluble in many organic solvents [68].

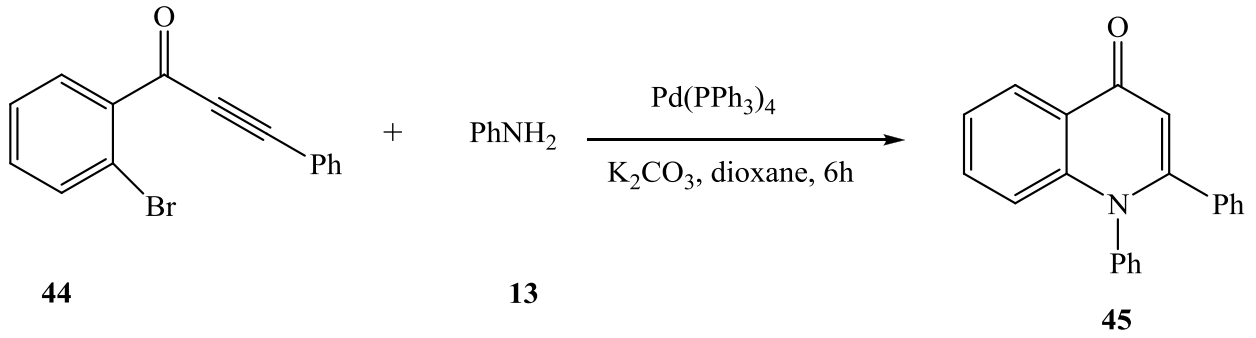


43 **42**

Reagents: (i) $PdCl_2(PPh_3)_2$, THF, heat, 2 h

Scheme 11

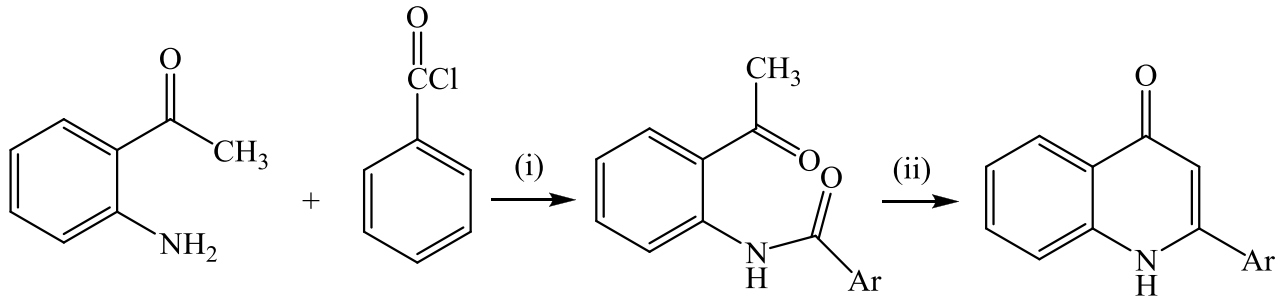
Palladium-catalyzed reaction of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one **44** and aniline **12** in the presence of K_2CO_3 in dioxane afforded 1,2-diphenylquinolin-4(1*H*)-one **45** in 75% (Scheme 12) [39].



44 **13** **45**

Scheme 12

The most convenient and high yielding method reported to-date for the synthesis of 2-arylquinolin-4(1*H*)-ones involves the use of 2-aminoacetophenone **20** and substituted benzoyl chlorides **46** as starting materials [35]. The resulting *N*-benzoyl-2-aminoacetophonones **47** are cyclised under reflux using *t*-BuOK in *t*-BuOH to afford the 2-arylquinolin-4(1*H*)-ones **42** in high yield (60-80%) and purity without the need for column chromatographic separation (Scheme 13) [40,41].



20 **46** **47** **42**

Reagents: (i) NEt_3, THF, 0 °C , rt. 2 h (ii) *t*-BuOK, *t*-BuOH, heat, 20 h

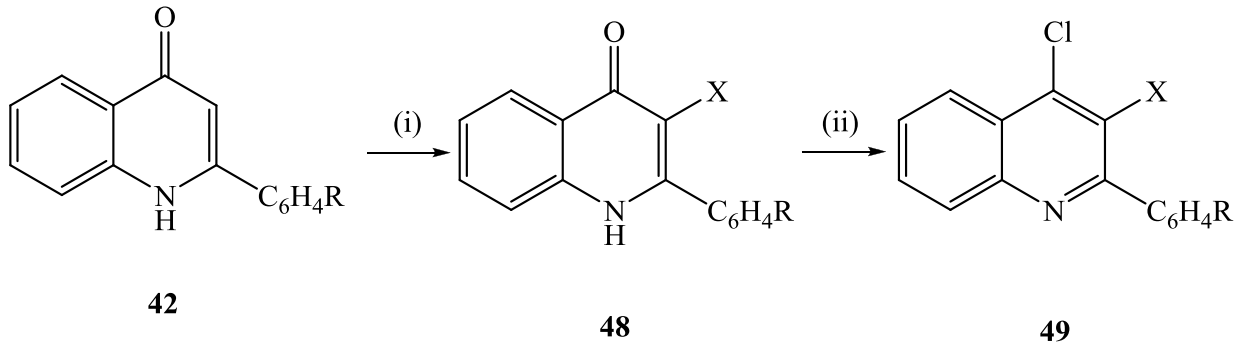
Scheme 13

The 2-arylquinolin-4(1*H*)-ones **42** are versatile synthetic intermediates which contain several reactive centers (positions 1, 3 and 4) for possible fuctionalization and can also enable different degree of unsaturation of the heterocyclic ring. 2-Arylquinolin-4(1*H*)-ones are known to undergo electrophilic substitution with alkyl derivatives to afford *N*-alkylated quinolones or *O*-alkylated quinoline derivatives or a mixture of the two isomers depending on the nature of electrophiles and steric effect

on the quinolone moiety [35]. The α,β-unsaturated framework allows C-3 halogenation to yield 3-halogeno derivatives, which have been shown to undergo metal-catalyzed C-C bond formation to yield a polysubstituted quinolone derivatives [42]. The 4-chloroquinolines which are important intermediates in the synthesis of 2-arylquinolines bearing a heteroatom group in the 4-position are prepared from the 2-arylquinolin-4(1*H*)-one derivatives by aromatization with phosphorus oxychloride ($POCl_3$) under reflux.

1.3.2.3 Methods involving 4-haloquinoline or tosylquinoline derivatives

Halogen-containing quinolines and their derivatives are of significant interest as the halogen atoms play a critical role in a compound's bioactivity, and they provide a further possibility for structural elaboration such as alkynylation, arylation and amination [43]. The use of halogenated derivatives as substrates for the regioselective substitution opens up a facile synthetic approach to diverse classes of polysubstituted aromatic or heteroaromatic compound. Indirect methods involving halogenated quinolines bearing iodine, bromine and/ or chlorine take an advantage of ease of displacement of these atoms by nucleophiles or metal catalysts to afford variously substituted quinoline derivatives that cannot be easily prepared otherwise. The 2-arylquinolin-4(1*H*)-ones **42** were reacted with iodine in the presence of sodium carbonate (Na_2CO_3) in THF to afford 2-aryl-3-iodoquinolin-4(1*H*)-one **48** (X = I) or pyridinium tribromide in acetic acid to afford the analogous 2-aryl-3-bromoquinolin-4(1*H*)-ones **48** (X = Br), respectively (Scheme 14) [44,45,69]. The latter were reacted with $POCl_3$ under reflux to afford the 2-aryl-4-chloro-3-iodoquinoline (X = I) and 2-aryl-3-bromo-4-chloroquinoline (X = Br) **49** in reasonable yields (60-65%) (Scheme 14) [44].

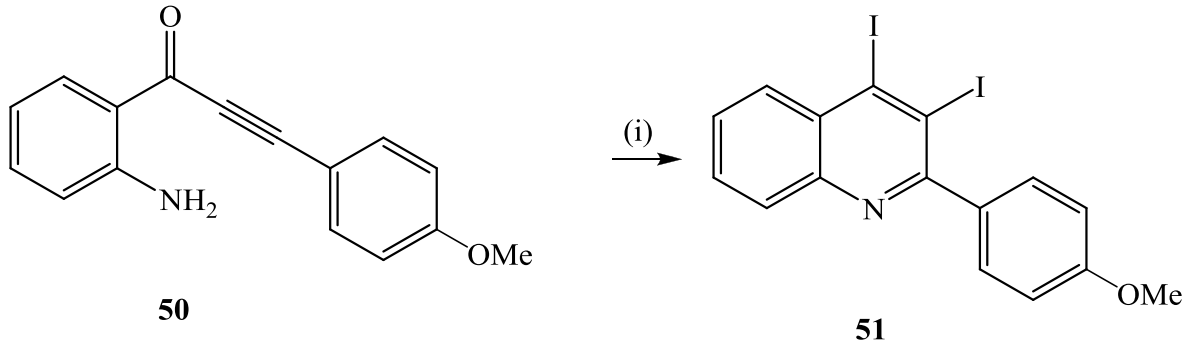


42 **48** **49**

Reagents: (i) I_2, Na_2CO_3, THF (X = I) or $C_5H_5NHBr_3$, AcOH, rt, 2h (X = Br) (ii) $POCl_3$, heat, 2h

Scheme 14

The 3,4-diiodo-2-(4-methoxyphenyl)quinoline **51** was prepared in 34% yield by the reaction of β-(2-aminophenyl)-α,β-ynone **50** with I_2 in the presence of $NaHCO_3$ in CH_3CN (Scheme 15) [46]. The observed result in this case was found to be different from those of the regio-controlled iodoaminocyclization reaction of related derivatives.



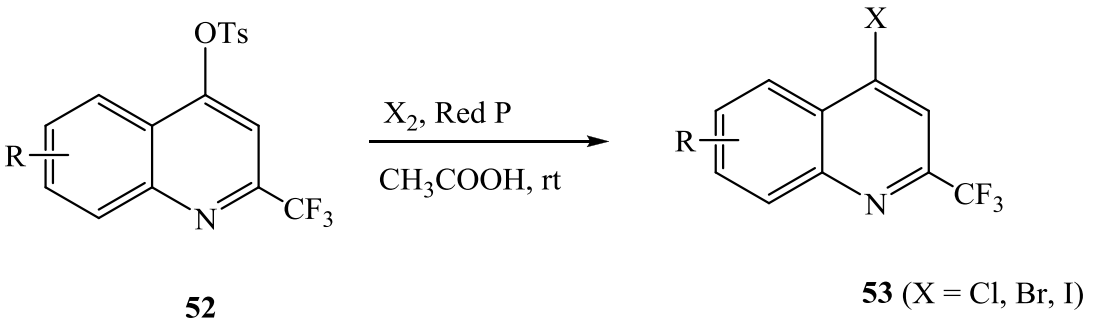
50 **51**

Reagents: (i) I_2, $NaHCO_3$, CH_3CN

Scheme 15

An alternative route that involves the displacement of 4-tosyloxy group from a quinoline moiety of 4-methylbenzenesulfonate-2-(trifluoromethyl)quinolin-4-yl **52** with iodine, bromine or chlorine in the presence of red phosphorous, acetyl chloride and glacial acetic acid in chloroform to afford the 4-haloquinoline derivatives **53** has also been reported (Scheme 16) [47].

Unfortunately, the displacement of tosyloxy group from 4-tosyloxyquinoline by a halogen requires the presence of a highly electron-withdrawing group at C-2 position of the quinoline, e.g, CF_3 [47].



52 **53** (X = Cl, Br, I)

Scheme 16

Organometallic reagents have also been employed on halogenated quinoline derivatives to promote C-C bond formation to afford polysubstituted quinoline derivatives. The order of aryl halide reactivity in carbon-metal halogen insertion is as follows: I > Br > Cl > F and the trend is consistent with the strength of the C-halide bond [48].

1.3.3 Application of organometallic reagents in the synthesis of polysubstituted quinolines

The use of metal-catalyzed cross-coupling reactions for the preparation of alkylated and arylated heteroaromatic compound have become a standard tool for the synthetic chemist. The advantage of cross-coupling reactions is that one can employ a wide range of aromatic substituents and various nucleophiles successively or in one easy step [49]. The carbon-based nucleophiles used include the alkyl, aryl or vinyl derivatives of boron (Suzuki), tin (Stille), zinc (Negishi), silicon (Hiyama) or magnesium (Kumada) [50]. Palladium is known to be more effective in activating sp^2-carbon-halogen bonds and the general mechanism of the catalytic cycle consists of several consecutive elementary steps, namely, (i) oxidative addition, (ii) transmetalation and trans-cis isomerisation and (iv)

reductive elimination [51]. The reaction mechanism of palladium catalyzed cross-coupling has been well studied (Figure 1). The first step in the mechanism involves reduction of the palladium catalyst to the 16-electron species $Pd(0)L_3$, which is then reduced to the 14 electron species $Pd(0)L_2$ **A**. The active palladium(0) species, $Pd(0)L_2$, reacts with arylhalide under oxidative addition to afford the *trans* arylpalladium(II) complex (*trans*-$RPdXL_2$) **B**. The second step is transmetalation, with either CuI (Sonogashira), arylboronic acid (Suzuki) or organostannane (Stille) to form intermediate **C** in which both organic ligands are *trans* oriented and converted to *cis* geometry 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) ctalyst.

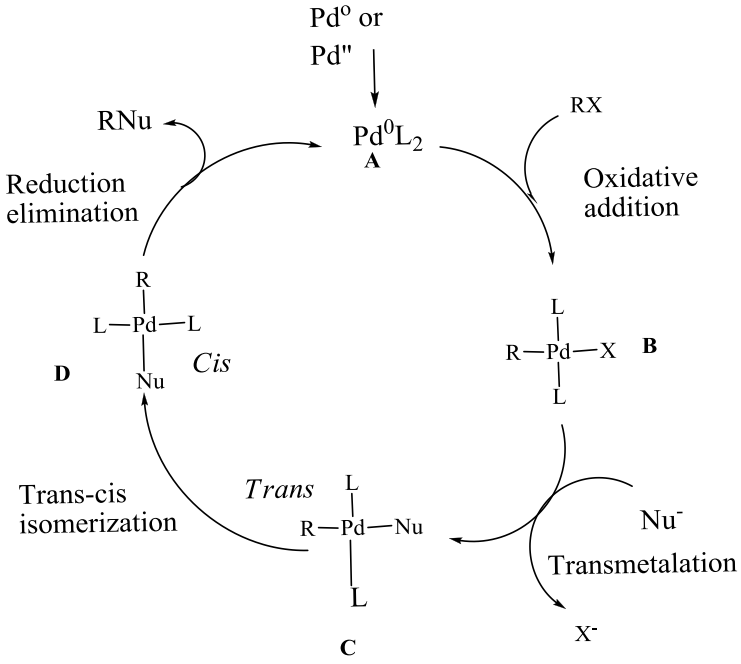
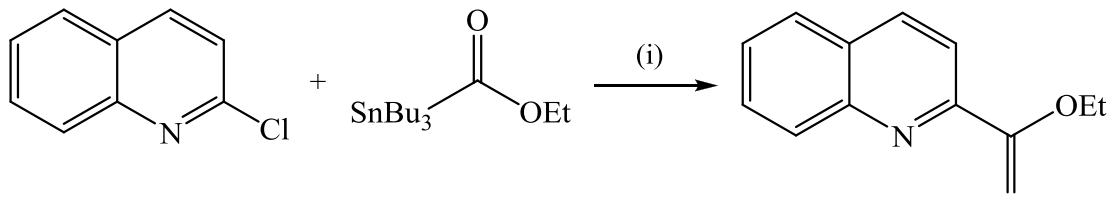


Figure 1: Generalized mechanism for Pd-catalyzed cross-coupling reactions

Selected examples of metal-catalyzed cross-coupling reactions that have been applied in the synthesis and/ or further transformation of quinoline derivatives are discussed below.

1.3.3.1 Application of Stille coupling in quinoline synthesis

The palladium-catalyzed Stille cross-coupling of aryl and vinyl halides/triflates with organostannanes is a powerful and widely used method for the formation of carbon-carbon bonds [52]. The Stille coupling is a reaction of organotin compound with an sp^2-hybridized organic halide catalyzed by palladium complexes, and quinolinyl halides as electrophiles are more prevalent in the Stille coupling reactions. 2-Chloroquinoline **54** was reacted with 1-ethoxy-2-tributylstannylester **55** in the presence of $Pd(dba)_2/PPh_4$ (1:2 equiv) in toluene under reflux to afford 2-(1-ethoxyvinyl)quinoline **56** in 68% yield (Scheme 17) [53].



54 **55** **56**

Reagents: (i) Toluene, 4% $Pd(dba)_2$, 8% PPh_3, reflux, 12h

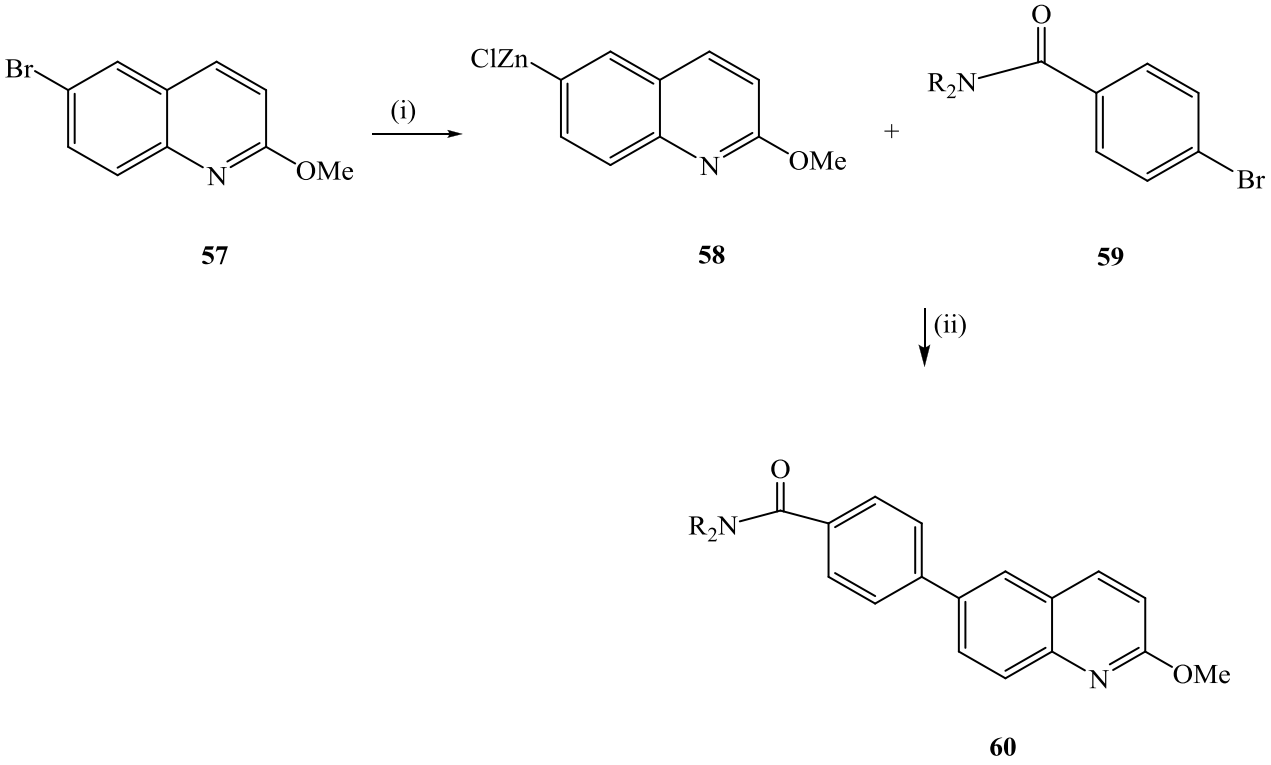
Scheme 17

The main drawback of this reaction is the toxicity of the tin compounds and their low polarity which make them poorly soluble in water.

1.3.3.2 Application of Negishi coupling in quinoline synthesis

The Negishi coupling occurs between organohalides and organozinc compound in the presence of palladium or nickel source as catalyst. Negishi cross-coupling reaction is found to be a versatile and

efficient method for the synthesis if a variety of quinolinyl motif [54]. Halogen-metal exchange on 6-bromo-2-methoxyquinoline **57** using two equivalents of *t*-butylithium and $ZnCl_3$ in THF afforded (2-methoxyquinolin-6-yl)zinc(II) chloride **58 (**Scheme 18**)**. (2-Methoxyquinolin-6-yl)zinc(II) chloride reacted with 4-bromobenzamides **59** in the presence of $Pd(PPh_3)_2$ under reflux to afford 6-[4-(*N*,*N*-diclohexylcarbomoyl)phenyl]-2-methoxyquinoline **60** in 52-83% yield [55].



57 **58** **59** **60**

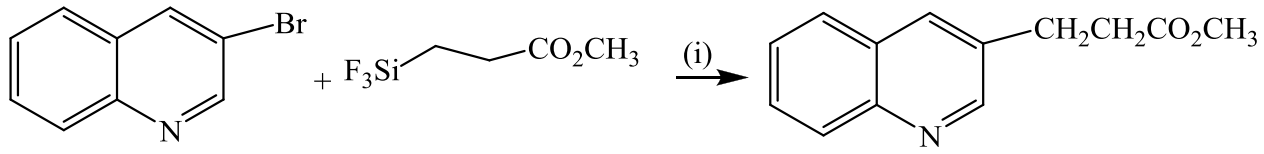
Reagents: (i) *t*-BuLi, THF, $ZnCl_2$, -75 ^oC (ii) $Pd(PPh_3)_4$, reflux, 2 h

Scheme 18

The drawback with this reaction is on the preparation of organozinc reagents.

1.3.3.3 Application of Hiyama coupling in quinoline synthesis

Hiyama coupling is the palladium or nickel-catalyzed cross coupling reaction of organosilanes with organic halides or triflates. The reaction is promoted by activation of C-Si bond with nucleophiles such as F^- or HO^- through formation of a pentacoordinated silicate, which weakens the C-Si bond by enhancing the polarization. The reaction conditions tolerate functional groups in comparison to other strong nucleophilic organometallic reagents. Mahsuhashi *et al.* reported the coupling reaction of 3-bromoquinoline **61** with functionalized alkyltrifluorosilane **62** in the presence of $Pd(PPh_3)_2$ catalyst and tetrabutylammonium fluoride in THF to afford methyl 3-(quinolin-3-yl)propanoate **63** in 65% yield (Scheme 19) [56].



61 **62** **63**

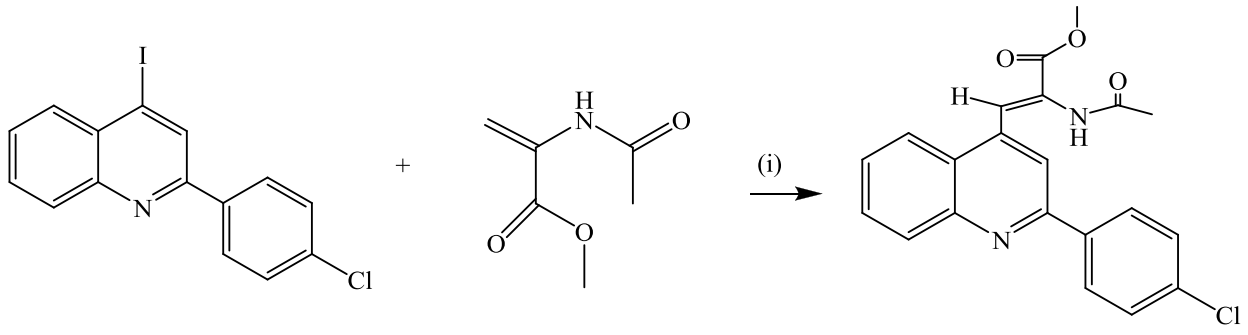
Reagents: (i) 5% $Pd(PPh_3)_4$, *n*-Bu_4NF, THF, 100 °C, 8h

Scheme 19

1.3.3.4 Application of Heck coupling in quinoline synthesis

The Heck reaction involves Pd-catalyzed cross-coupling reaction between organo halides or triflates with alkenes and it can take place by inter- or intra-molecular C-C bond formation. It is a powerful reaction for the preparation of alkenyl- and aryl-substituted alkenes. Only a catalytic amount of a palladium(0) source such as $Pd(PPh_3)_2$, $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$ are commonly used.

Arcadi *et al.*[18] developed a one-step synthesis of the (*Z*)-methyl 2-acetamido-3-(2-(4-chlorophenyl)quinolin-4-yl)acrylate **66** (50%) via Pd-catalyzed intermolecular reaction 4-iodo-2-(4'-chlorophenyl)quinoline **64** with α-acetamidoacrylate **65** (Scheme 20).

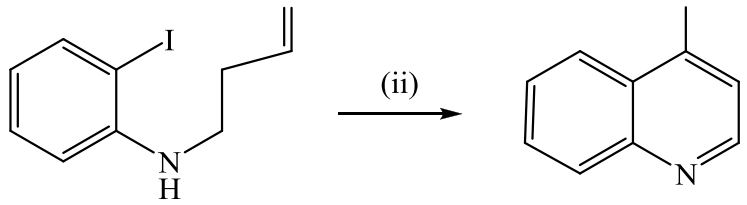


64 **65** **66**

Reagents: AcOK, $Pd(OAc)_3$, DMF, heat, 60 °C

Scheme 20

Larock and Babu, on the other hand, synthesized quinolines and other nitrogen-containing heterocyclicles via intramolecular Heck reaction as shown in Scheme 19 [56]. Intramolecular cyclization of *N*-(but-3-enyl)-2-iodoaniline **67** was effected with 2% $Pd(OAc)_2$, n-Bu_4NCl and Na_2CO_3 in DMF to afford 4-methylquinoline **68** in 92-97% yield (Scheme 21) [57].



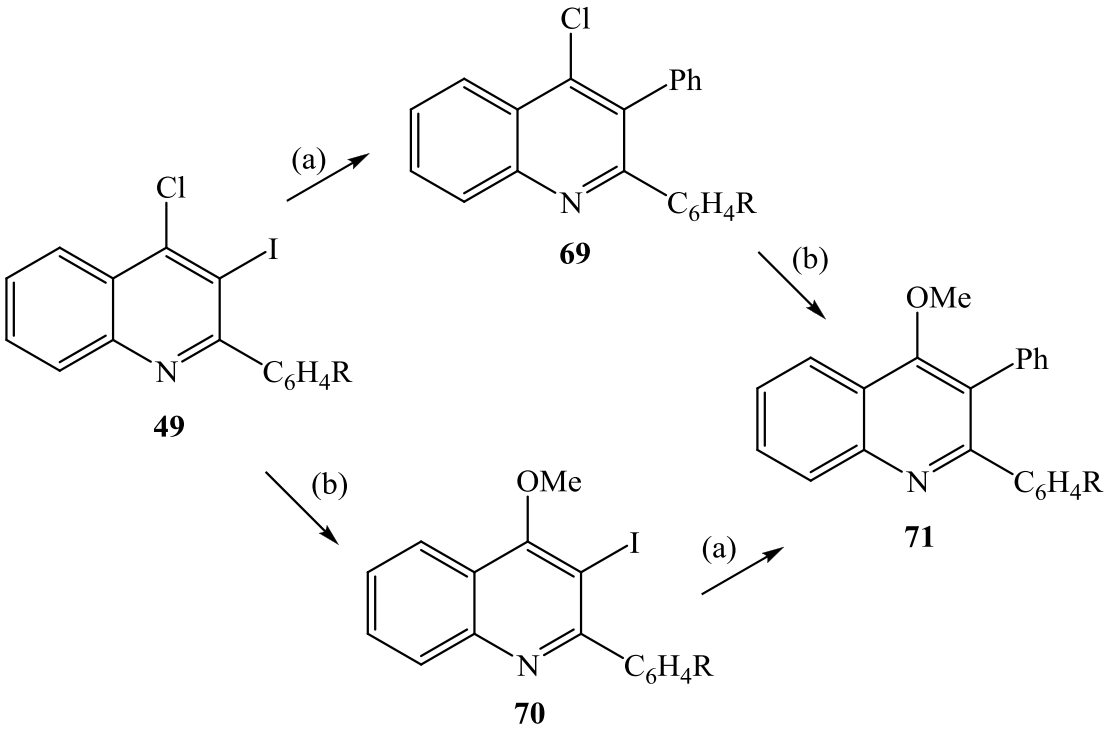
67 **68**

Reagents: 2% $Pd(OAc)_2$, Na_2CO_3, DMF, *n*-Bu_4NCl.

Scheme 21

1.3.3.5 Application of Suzuki coupling in quinoline synthesis

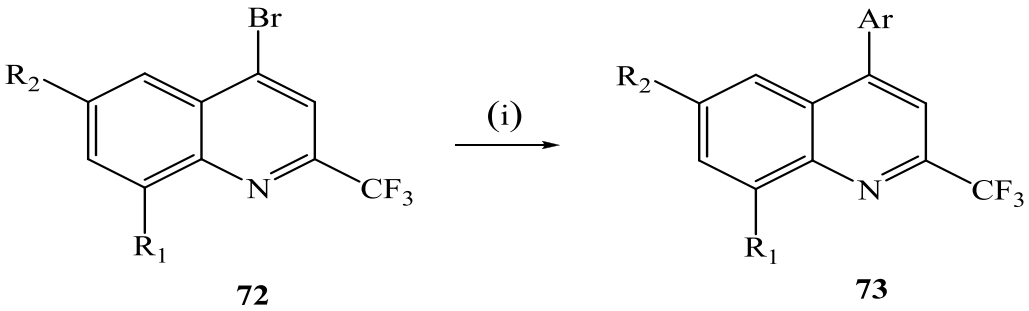
Palladium-catalyzed Suzuki cross-coupling reactions of boranes, boronic esters or boronic acids with aryl halides or pseudo halides to form biaryl derivatives has emerged over many years as an extremely powerful tool in organic synthesi [58]. It is a coupling reaction of organoboron compounds mainly esters or organoboronic acids with organic halides or triflates in the presence of palladium catalyst and a base. Previously in our laboratory, compounds **69** and **71** were prepared via Suzuki-Miyaura cross-coupling from 2-aryl-3-iodo-4-methoxyquinoline **70** and 2-aryl-4-chloro-3-iodoquinoline **49** with phenylboronic acid in DMF (Scheme 22) [59].



Reagents: (a) $Pd(PPh_3)_4$, $PhB(OH)_2$, 2M K_2CO_3, DMF; (b) NaOMe, DMF, heat

Scheme 22

Srikanth *et al*. reported the preparation of arylated quinolines via Suzuki cross-coupling [58]. The reaction involves 4-haloquinoline **72** with various boronic acid derivatives in the presence of palladium acetate in DMF to afford 4-arylated quinoline derivatives **73** (Scheme 23).



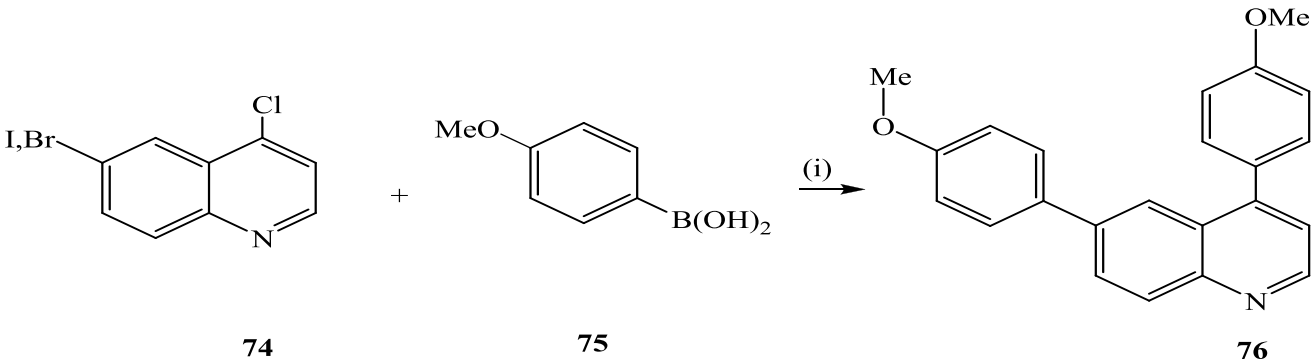
72 **73**

R_1 = H, Br; R_2 = H, CH_3, F, Cl; Ar = $PhB(OH)_2$, $C_4H_5BO_2S$, C_7H_9BO

Reagents: (i) $ArB(OH)_2$, PPh_3, $Pd(OCOCH_3)_2$, DMF

Scheme 23

Beletskaya *et al.* on the other hand, reported the preparation of biaryl quinolines via Suzuki reaction of 6-halo-4-chloroquinolines **74** with 4-methoxyphenylboronic acid (2 equiv) **75** in the presence of $Pd(PPh_3)_4$ and potassium carbonate (K_2CO_3) in dioxane to afford 4,6-bis-(4-methoxyphenyl)quinoline **76** in low yield (12 %) (Scheme 24) [60].



74 **75** **76**

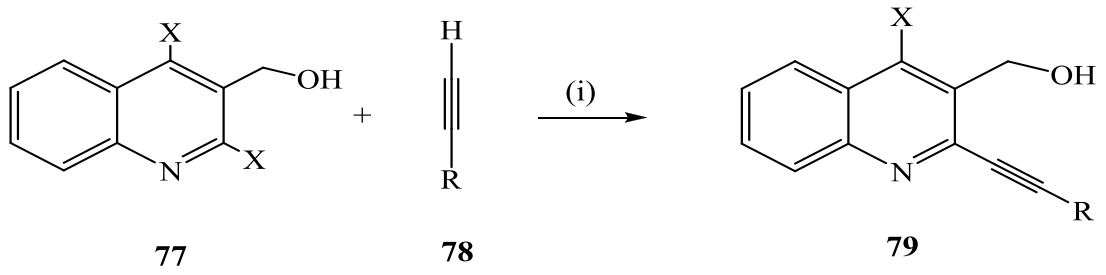
Reagents: (i) $Pd(PPh_3)_4$, K_2CO_3, dioxane, heat, 48 h

Scheme 24

The key advantage of the Suzuki reaction is the high tolerance to most functional groups, the mild conditions under which the reaction is conducted, the relative stability of boronic acids/esters to heat and water, the ease of handling and separation of boron-containing byproducts, and their abundant commercial availability [51].

1.3.3.6 Application of Sonogashira coupling in quinoline synthesis

Sonogashira cross-coupling of terminal alkynes with aryl and vinyl halides has attracted more attention for C-C bond formation in organic synthesis. The reaction involves the use of palladium catalyst and CuI as co-catalyst in the presence of a base (e.g. triethylamine) in solvents such as DMF, or dioxane and in some cases in the presence of water as co-solvent. A diversity of aryl halides including electron-deficient heteroaryl chloride have been employed in palladium-catalyzed coupling reactions with terminal alkynes to afford precursors adaptable for the synthesis of fused aromatic heterocycles. (2,4-Dihaloquinolin-3-yl)methanol **77** was reacted with terminal alkyne **78** in dioxane in the presence diisopropylamine or triethylamine and $PdCl_2(PPh_3)_2$-CuI catalytic mixture to afford 2-(alkynyl)- 4-halo-3-methanolquinoline **79** in 74% yield (Scheme 25) [61]. The high reactivity at C-2 versus C-4 when X = Cl is attributed to the increased positive character of the α-carbon of the α,β-unsaturated framework due to the electron-withdrawing effect of the adjacent nitrogen of the quinoline ring. The observed regioselectivity in alkynylation of 2,4-dihaloquinolines (X = I, Br and Cl) is also attributed to the coordination of palladium to nitrogen of quinoline ring resulting in activation of the C-2 position [20].



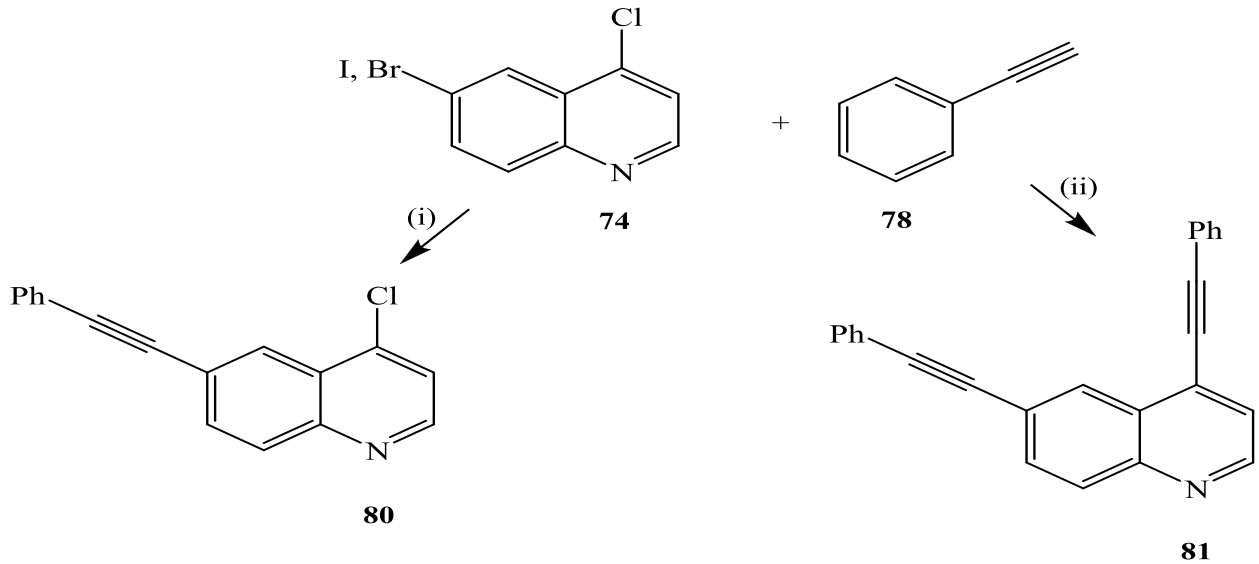
77 **78** **79**

X = I, Br, Cl R = $SiMe_3$, Ph

Reagents: (i) $PdCl_2(PPh_3)_2$, CuI, 1,4-dioxane, 23 °C, H-N(*i*-Pr)$_2$

Scheme 25

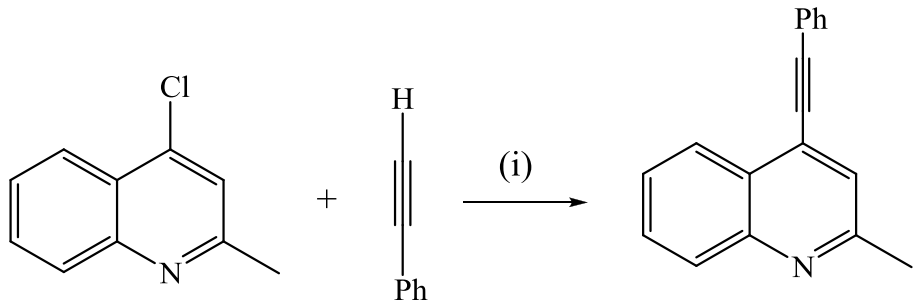
The reaction of 4-chloro-6-haloquinoline **74** with phenylacetylene **78** in dioxane-water in the presence of 2-equiv of triethylamine and $Pd(PPh_3)_4$-CuI catalyst mixture afforded the monoalkynylated derivative, 4-chloro-6-phenylethynylquinoline **80** in 93% yield (Scheme 26) [62]. The 6-bis(phenylethynyl)quinoline **81** was formed in 90% yield by reacting **74** with 2.2 equiv. of phenylacetylene **78** in the presence of 4 equiv. of NEt_3.



Reagents: (i) $Pd(PPh_3)_4$, CuI, 2 equiv NEt_3, dioxane-H_2O (ii) $Pd(PPh_3)_4$, CuI, 4 equiv. NEt_3

Scheme 26

Wolf *et al.* reported the reaction of 4-chloro-2-methylquinoline **82** with phenylacetylene **78** in the presence of palladium phosphinous acid catalyst (POPd), tetra-butylammonium bromide (TBAB) and NaOH in deionized water under reflux to afford 2-methyl-4-phenylethylenylquinoline **83** in 73% yield (Scheme 27) [63].

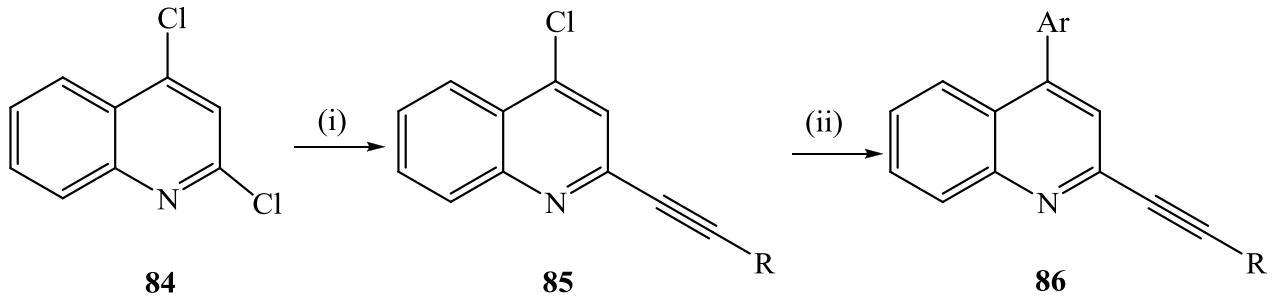


82 **78** **83**

Reagents: (i) POPd, TBAB, NaOH, CuI, H_2O, 5h

Scheme 27

Successive substitution of halogen atoms using electron-deficient heterocycles containing two or more halogens located in positions activated toward metal–catalyzed cross-coupling or nucleophilic attack is of particular interest in organic synthesis. A two step procedure involving successive Sonogashira and Suzuki cross-coupling to afford the 2-alkynyl-4-arylquinoline **86** has been reported by Reddy *et al*. [64]. The first step involved Pd-CuI catalyzed Sonogashira cross-coupling of the 2,4-dichloroquinoline **84** with terminal alkynes to afford 2-alkynyl-4-chloroquinoline **85**. The latter was further subjected to Suzuki cross-coupling with arylboronic acid in the presence of $PdCl_2(PPh_3)_2$, PCy_3 as a ligand and $CsCO_3$ as a base in dioxane-water to afford the 2-alkynyl-4-arylquinoline **86** (Scheme 28).



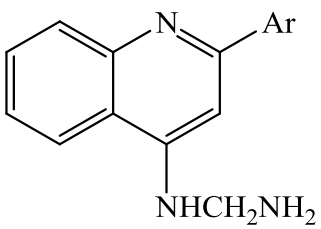
84 **85** **86**

Reagents: H-C≡C-R, Pd/C-PPh_3-CuI, Et_3N, H_2O, 80 °C (ii) $ArB(OH)_2$, $(PPh_3)_2PdCl_2$, PCy_3, $CsCO_3$. dioxane-H_2O, 80 °C.

Scheme 28

1.4 Structure-activity relationship of 2,3,4-trisubstituted quinoline derivatives

Over the last years the structure-activity relationships of substituted quinoline derivatives bearing primary amines, alkynes and aryls have been subjected to extensive study due to their biological importance [65,66]. The amino groups linked to the quinoline framework at position 4 affect the basicity of the ring nitrogen atom of the quinoline and in turn enhance its binding to various receptors in the body [67]. For example, 4-[*N*-(aminomethyl)amino]-2-arylquinolines **87** bind strongly to and stabilize poly(dT·dA·dT) (triplex DNA) and bind weakly to poly- (dA·dT) (duplex DNA) by 4-aminoquinoline interaction strength with the triple-helical DNA structure and suggest that N1 of the quinoline is protonated in the complex with the DNA triplex [66].

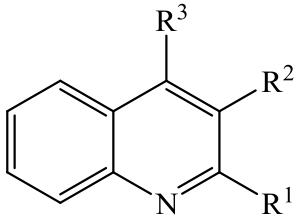


87

The 2-arylquinoline derivatives bearing aliphatic groups such as alkynyl and vinyl at position 4 of quinoline contribute minimal improvement in the estrogen receptor selectivity affinity, whereas phenyl group contribute slight improvement for selectivity [7]. The substituted quinoline derivatives bearing aryl groups have also been reported to act as potent inhibitors of tyrosine kinase PDGF-RTK [8].

1.5 Research problem and hypothesis

Several methods for the synthesis of 2,3,4-substituted quinoline derivatives are well known, but due to their importance in medicine and industry, the development of new methods for the design of more potent derivatives remains an active research area [18]. As pointed out before, our interest is on the synthesis of 2,3,4-trisubstituted quinoline derivatives of the generalized structure **A** (Fig. 2; where R^1 = aryl) bearing various substituents such as alkenyl, akynyl, aryl or primary amino groups at the 3- and/or 4- positions. These compounds cannot be easily accessible through classical methods and as a result the indirect methods involving the use of 2-aryl-4-chloro-3-iodoquinolines remain the method of choice for the synthesis of the target polysubstituted 2-arylquinoline derivatives. The 2-aryl-4-chloro-3-iodoquinolines would enable successive or one pot modification of the C-3 and C-4 positions via metal-catalyzed C-C bond formation reactions including the possibility of nucleophilic displacement of 4-chloro group. Although the 2-aryl-4-chloro-3-iodoquinolines have been prepared before [45], their application in the synthesis of 2-aryl-4-chloro-3-(alkynyl)quinoline and 2-aryl-3,4-bis(alkynyl)quinoline derivatives have not been explored before.



A

Figure 2: Generalized structure of 2,3,4-trisubstituted quinolines

The potential for iodine to facilitate metal-catalyzed cross-coupling reaction and the ease displacement of the activated 4-chloro atom by nucleophiles and its ability to facilitate metal-catalyzed C-C bond formation at the 4-position make 2-aryl-4-chloro-3-iodoquinoline derivatives suitable substrates for the synthesis of 2,3,4-trisubstituted quinolines. The ease of activated chloroquinoline derivatives to undergo metal–catalyzed C–C bond formation makes it difficult to easily predict how different the reactivity of the two Csp^2–halogen bonds in 2-aryl-4-chloro-3-iodoquinolines would be during Pd–catalyzed acetylynation reactions. Since both iodine atom at C-3 and chlorine atom at C-4 can participate efficiently in Pd-catalyzed Sonogashira cross-coupling, a challenge is whether we can establish suitable reaction conditions to effect regioselective C-C bond formation through the replacement of 3-iodo atom to afford 2-aryl-3-(alkynyl)-4-chloroquinoline. The other challenge is whether suitable reaction conditions for the one-pot synthesis of the 3,4-bis(alkynyl)quinolines can be developed. Moreover, the resulting 2-aryl-3-(alkynyl)-4-chloroquinoline should enable further transformation to incorporate alkenyl, alkynyl, aryl or primary amino substituent at the C-4 position.

1.6 Aims and objectives of this investigation

The aim of this work is to compare the reactivity of Csp^2-I and the activated Csp^2-Cl in Sonogashira cross-coupling reaction of 2-aryl-4-chloro-3-iodoquinoline derivatives using terminal alkynes as models for C-C bond formation. The investigation will involve the following major steps or activities:

- Preparation of 2-aryl-4-chloro-3-iodoquinolines as substrates for Csp^2-Csp and Csp^2-Csp^2 bond formation
- Establishment of suitable reaction conditions to effect regioselective monoalkynylation of the 2-aryl-4-chloro-3-iodoquinolines derivatives
- Establishment of reaction conditions to effect one-pot synthesis of dialkynylated derivatives from the 2-aryl-4-chloro-3-iodoquinolines
- To transform the monoalkynylated derivatives to afford 2,3,4-trisubstituted quinoline derivatives via Suzuki cross-coupling and amination reaction, respectively

CHAPTER 2 RESULTS AND DISCUSSION

The *N*-benzoyl-2-aminoacetophonone derivatives **47** were prepared by condensing 2-aminoacetophenone **20** and benzoyl chloride derivatives **46** in the presence of NEt_3 in THF. Compounds **47** were cyclized to 2-aryl-4-quinolone derivatives **42** using *t*-BuOK in *t*-BuOH. The quinolone derivatives were, in turn, subjected to iodine in the presence of sodium carbonate in THF to afford the 2-aryl-3-iodoquinolin-4(*H*)-one derivatives **48**. Treatment of the latter with phosphorus oxychloride in DMF under reflux afforded the corresponding 2-aryl-4-chloro-3-iodoquinoline derivatives **49**. Systems **49** were subjected to Sonogashira cross-coupling to afford the 2-aryl-4-chloro-3-(2-phenylethenyl)quinoline derivatives **87**. The 2-aryl-3,4-bis(2-phenylethyl)quinolines **88** in one pot operation afforded the 2-aryl-4-chloro-3-iodoquinolines **87** with 3-equiv of phenylacetylene under Sonogashira cross-coupling conditions. The 2-aryl-4-chloro-3-(2-phenylethynyl)quinolines **87** were further transformed via Suzuki coupling with *trans*-2-phenylvinylboronic acid or 4-fluorophenylboronic acid to yield the corresponding 3-(2-phenylethynyl)-2,4-diarylquinoline derivatives **89**. On the other hand, the reaction of 2-aryl-3-(phenylethynyl)-4-chloroquinolines with $MeNH_2$ in EtOH under reflux afforded the corresponding 2-aryl-4-(methylamino)-3-(phenylethynyl)quinoline derivatives. The prepared compounds were characterized using a combination of ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopic techniques. Moreover, the structure of the products of successive Sonogashira and Suzuki cross coupling were further confirmed by X-ray crystallography.

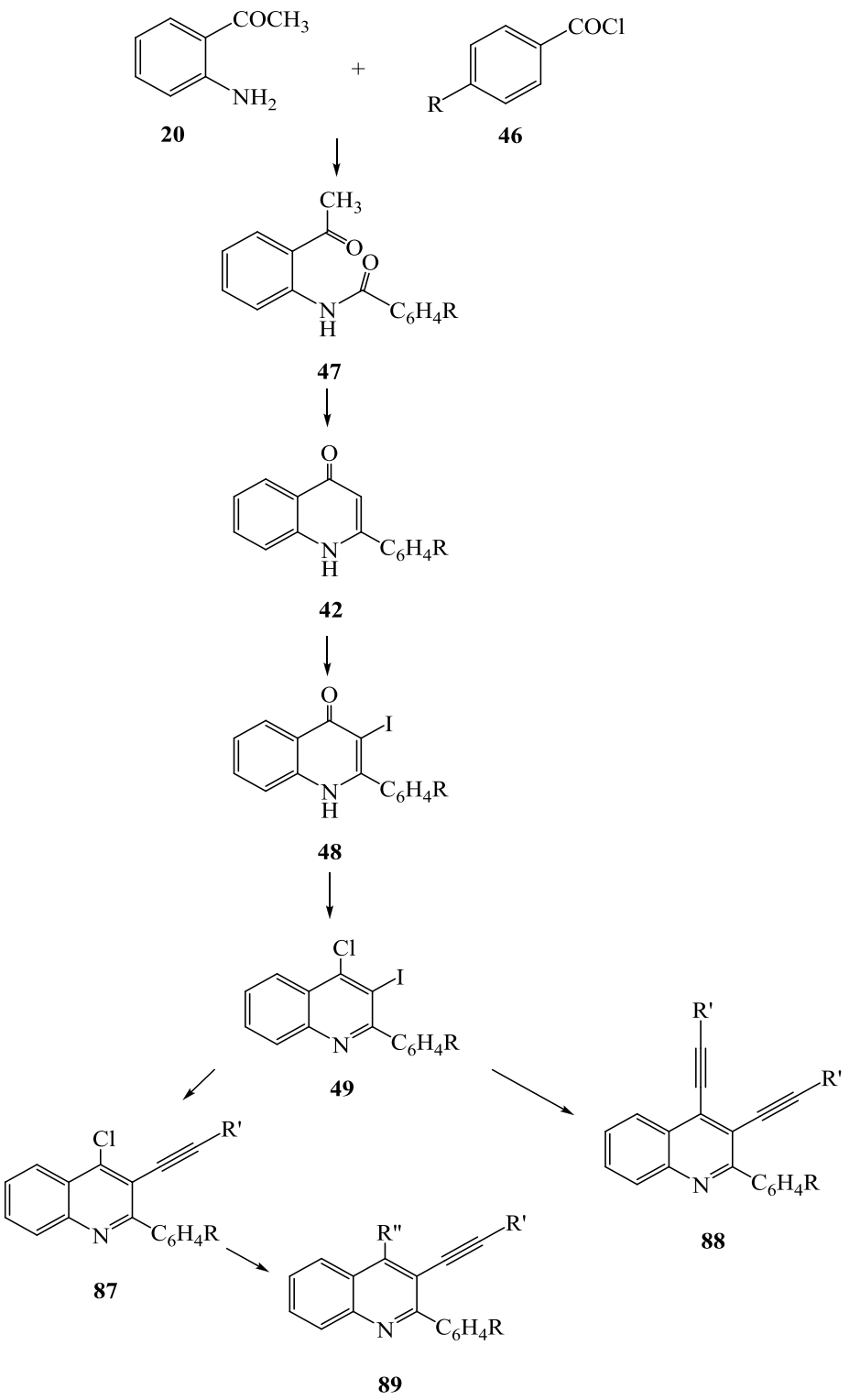
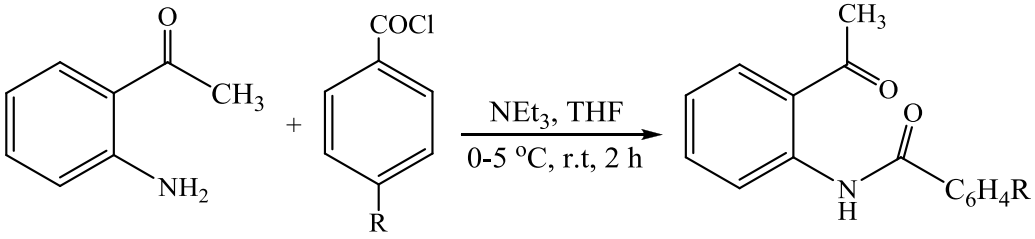


Figure 3: Generalized scheme

2.1 Synthesis of substrates

2.1.1 Synthesis of *N*-benzoyl-aminoacetophone derivatives 47

The *N*-benzoyl-2-aminoacetophonones **47** were prepared by reacting 2-acetoaminophonone **20** with benzoyl chloride derivatives **46** in the presence of NEt_3 in THF were the activated carbonyl of the acid chloride was attack by amine to afford the *N*-benzoyl-2-aminoacetophonones **47** following a literature procedure (Scheme 29) [40,41]. The structure of these compounds was confirmed by ^1H NMR and IR spectroscopic techniques and by comparison with literature data. The ^1H NMR spectra of compounds **47** show the presence of methyl signal at δ *ca*. 2.69 ppm ($COCH_3$) and a broad singlet at δ *ca*. 12.70 ppm for N-H and a group of signals in the aromatic region (Fig. 3). Their IR spectra reveal the presence of C=O absorption band at ν_{max} 1645 cm^{-1} and 1674 cm^{-1} and N-H absorption band at ν_{max} 3209 cm^{-1}. Their ^1H NMR and IR spectroscopic data fit well with the assigned structure and their melting point values compare favourably with those reported in literature.



20 **46** **47**

47	**R**	% Yield	m.p. °C; (Lit. °C) [70]
a	H	99	94-96 (95-99)
b	F	94	83-85 (92-95)
c	Cl	93	108-110 (106-109)
d	OMe	74	117-120 (119-121)

Scheme 29

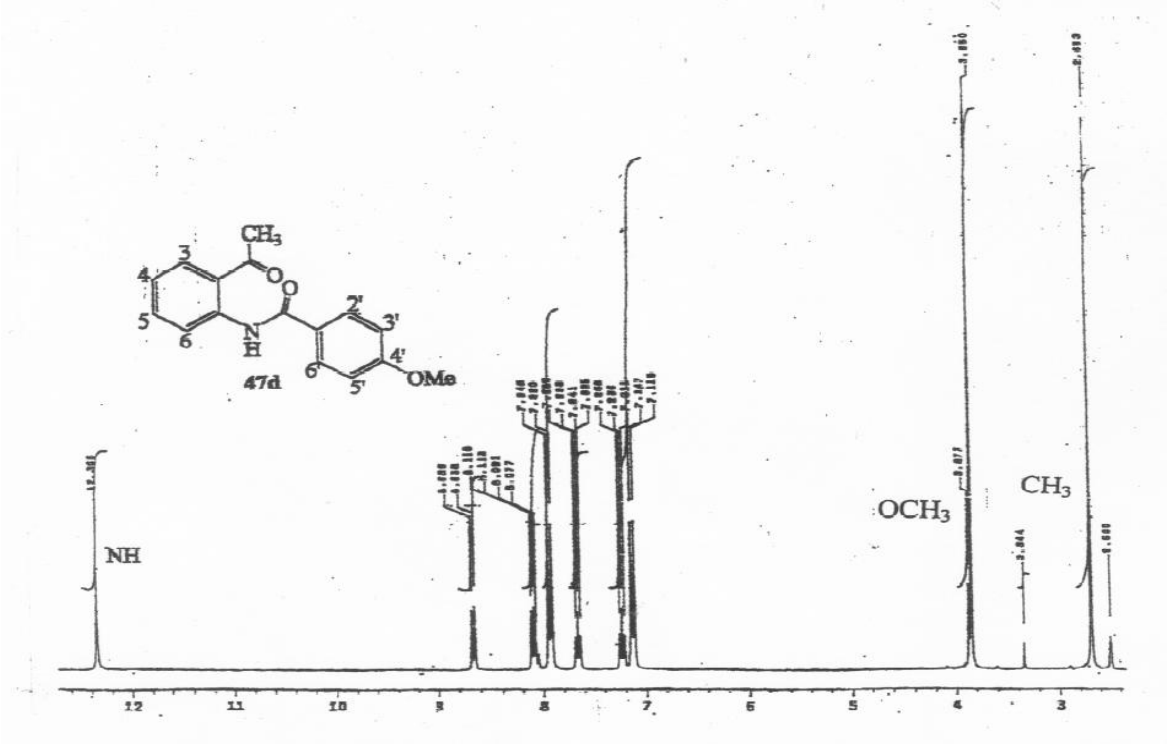


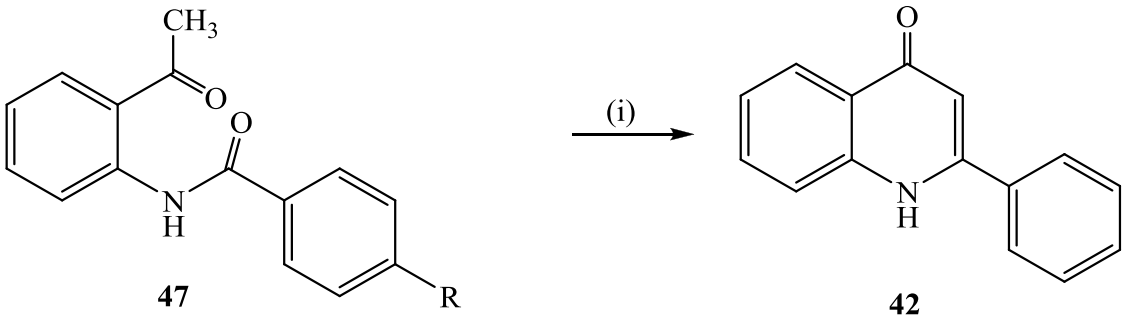
Figure 4: ^{1}H NMR spectrum of *N*-(4-methoxybenzoyl)-2-aminoacetophonone **47d** in DMSO-d_6

2.1.2 Synthesis of 2-arylquinolin-4(1*H*)-one derivatives 42

Several methods for the synthesis of 2-arylquinolin-4(1*H*)-one are well documented. The 2'-amonichalcone was previously cyclized in the presence of stoichiometric amount of $PdCl_2(PPh_3)_2$ in THF to afford the 2-arylquinolin-4(1*H*)-one **42** after column chromatographic separation [68]. The main drawback of this reaction is the use of stoichiometric amount of the more expensive palladium species and column chromatographic separation of the NH-4-oxo products that are almost insoluble in many organic solvents, except DMSO. The *N*-benzoyl-2-aminoacetophenone derivatives **47** were cyclized with *t*-BuOK in *t*-BuOH under reflux to afford the 2-arylquinolin-4(1*H*)-ones **42** in high yield (Scheme 30) [40,41]. The advantage of this method is the use of readily available and easy-to-

handle reagents as well as the high yields and purity of the compounds without the need for column chromatography.

The ^{1}H NMR spectra of compounds **42** (Fig. 4) are distinguished from those of the corresponding precursors by the presence of a singlet δ *ca*. 6.33 ppm which corresponds to 3-H and the absence of intense singlet corresponding to the methyl group at δ *ca*. 2.69 ppm, which is found in the ^{1}H NMR spectra of their precursors. Their NH-4-oxo nature is also confirmed by their IR absorption band for C=O at ν_{max} *ca*. 1625 cm^{-1} and the broad band at ν_{max} *ca*. 3356 cm^{-1} for N-H. The observed melting point values somewhat differ from those describe in the literature except for **42d** and **42b**. The spectroscopic data (^{1}H NMR and IR) for these compounds however are consistent with the assigned structure.



47 **42**

42	**R**	% Yield	m.p. °C; (Lit. °C)[40]
a	H	84	220-221 (240-243)
b	F	74	322-324 (322-325)
c	Cl	87	296-298 (270-273)
d	OMe	77	294-295 (290-293)

Reagents: (i) *tert*-BuOK, *tert*-BuOH, reflux, 12 h.

Scheme 30

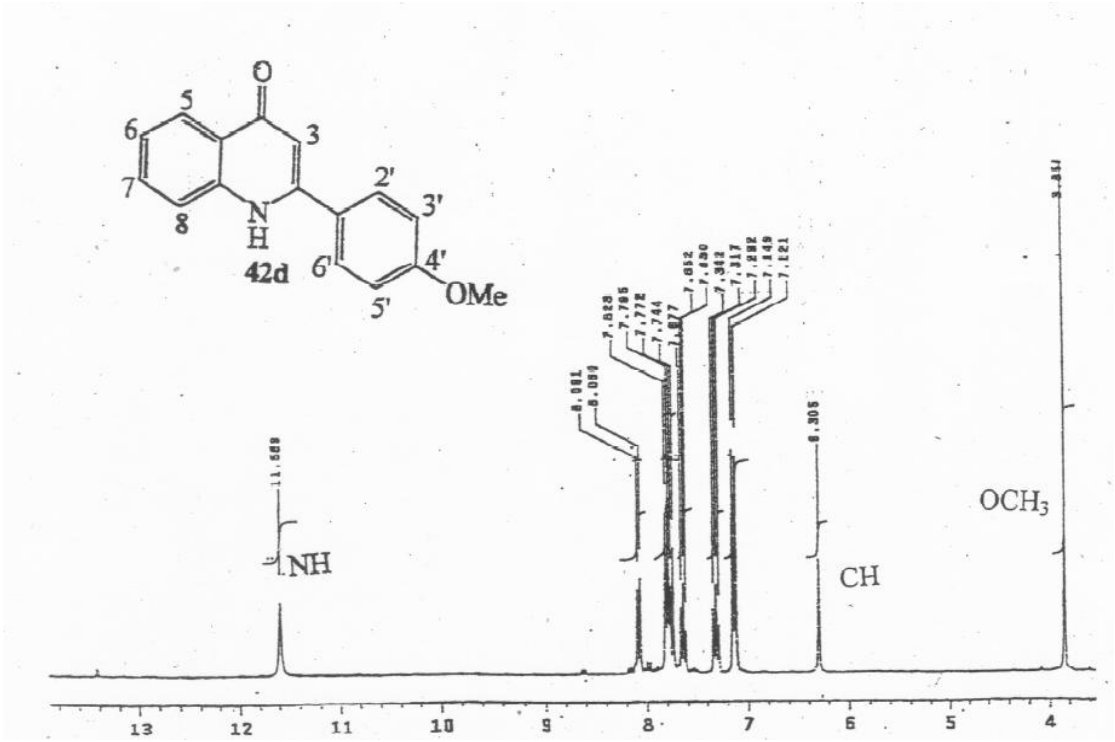
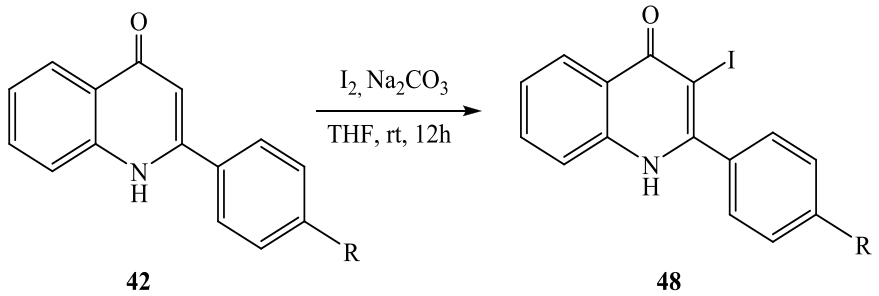


Figure 5: ^{1}H NMR spectrum of 2-(4-methoxyphenyl)quinolin-4(1*H*)-one **42d** in DMSO-d_6

2.1.3 Synthesis of 2-aryl-3-iodoquinolin-4(1*H*)-one derivatives 48

The 2-arylquinolin-4(1*H*)-ones **42** were subjected to iodine and sodium carbonate in THF at room temperature to afford the 2-aryl-3-iodoquinolinone **48** in high yield and purity following a method developed in our laboratory before (Scheme 31) [44]. Their ^{1}H NMR spectra reveal the absence of olefinic proton (3-H) signal at δ *ca*. 6.33 ppm confirming the replacement of this hydrogen atom by iodine atom (Fig. 5). Their IR spectra reveal the presence of C=O absorption band at ν_{max} *ca*. 1626 cm^{-1} and N-H broad band at ν_{max} *ca*. 3377 cm^{-1}, which also confirm their NH-4-oxo nature. Although the observed melting point values differ significantly from those reported in literature, but the spectroscopic data is consistent with the assigned structures.



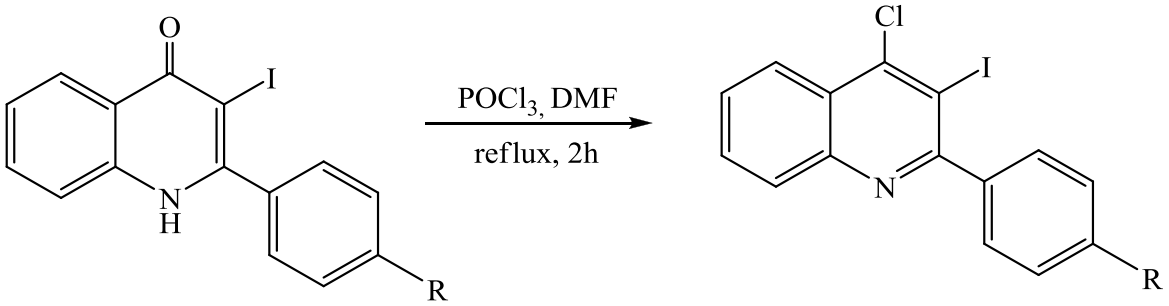
42 **48**

48	**R**	% Yield	m.p. °C; (Lit. °C) [69]
a	H	90	225-228 (284-286)
b	F	73	207-208 (196-198)
c	Cl	93	213-214 (254-256)
d	OMe	73	229-232 (262-264)

Scheme 31

2.1.4 Synthesis of 2-aryl-4-chloro-3-iodoquinoline derivatives 49

The 2-aryl-4-chloro-3-iodoquinoline derivatives **49** were prepared by subjecting the 2-aryl-3-iodoquinolon-4(1*H*)-ones **48** to phosphorus oxychloride in DMF following literature procedure (Scheme 32) [44]. Their ^{1}H NMR spectra lack the broad singlet at δ *ca*. 12.70 ppm (Fig. 6), which corresponds to N-H proton in the NMR spectra of the corresponding substrates. Their IR spectra reveal the absence of both the C=O absorption band and broad band corresponding to N-H and this distinguish their structure from those of the corresponding precursors. Despite the slight difference in melting point values from those described before, their FT-IR and ^{1}H NMR spectroscopic data are consistent with the assigned structures.



48 **49**

49	**R**	% Yield	m.p. °C; (Lit. °C) [44]
a	H	50	145-146 (150-153)
b	F	89	159-162(176-178)
c	Cl	63	213-214 (218-220)
d	OMe	49	181-182 (185-187)

Scheme 32

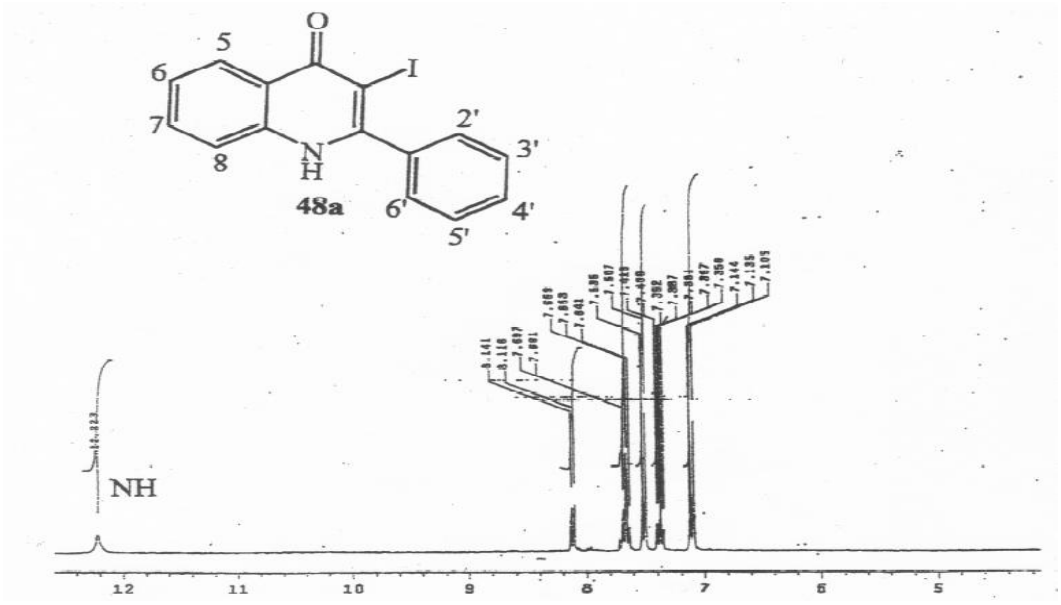


Figure 6: ^{1}H NMR spectrum of 3-iodo-2-phenylquinolin-4(1*H*)-one **48a** in DMSO-d_6

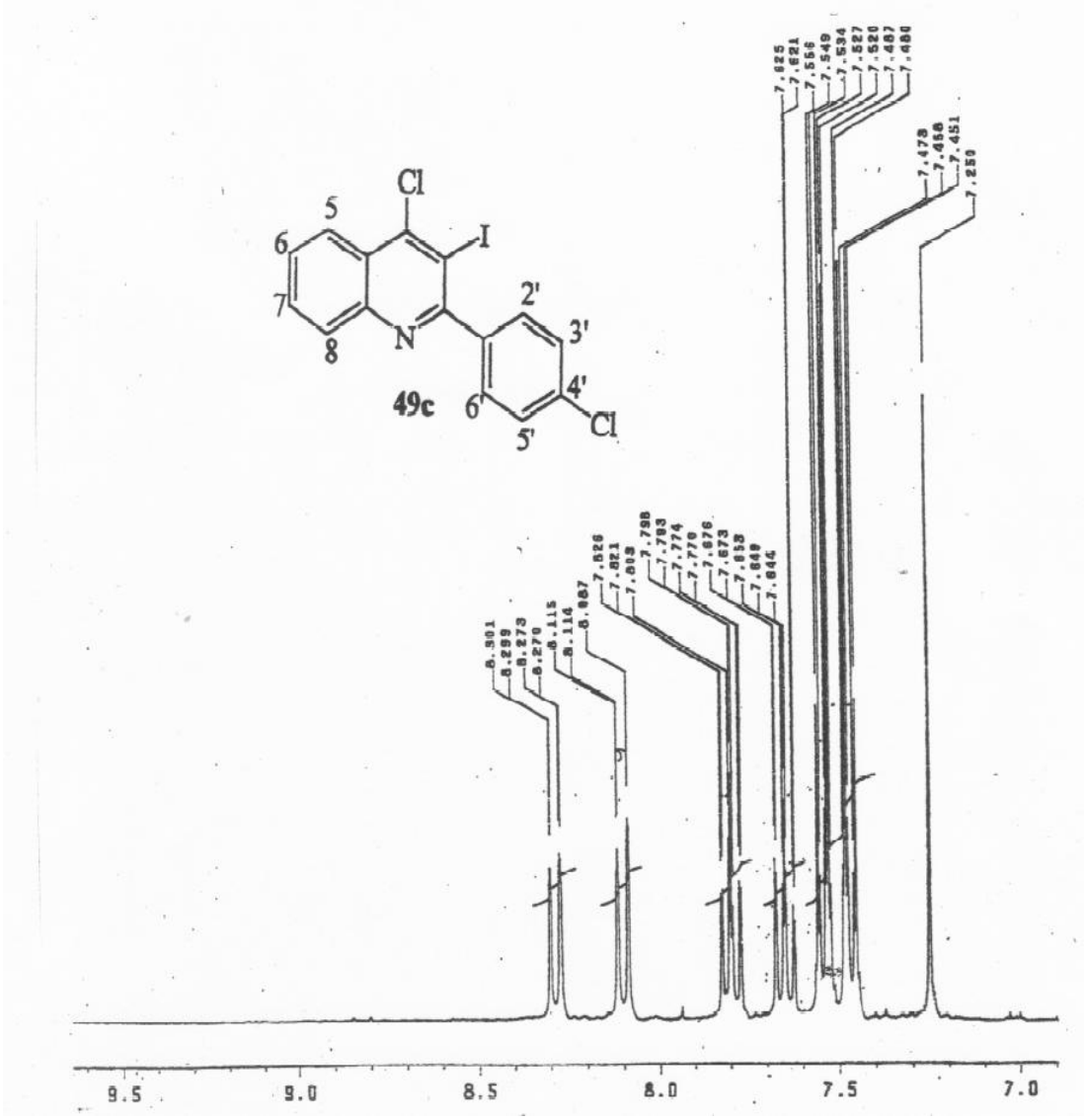


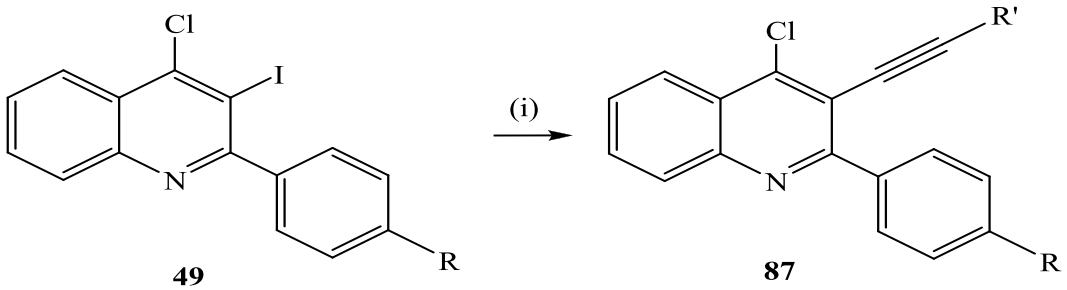
Figure 7: ^{1}H NMR spectrum of 2-(4-chlorophenyl)-4-chloro-3-iodoquinoline **49c** in $CDCl_3$

Palladium catalyzed cross-coupling reactions have become an important tool in the promotion of C-C bond formation to afford alkenylated, alkynylated and/ or arylated heteroaromatic compounds. In this investigation we employed Sonogashira and Suzuki cross-coupling reaction on the 2-aryl-4-chloro-3-iodoquinolines to afford novel 2,3,4-trisubstituted quinoline derivatives.

2.2 Regioselective synthesis of 2-aryl-4-chloro-3-(alkynyl)quinoline derivatives 87

Sonogashira cross-coupling of terminal alkynes is known to proceed well with aryl iodides or aryl bromides. Although aryl chlorides are known to be less reactive, the activated derivatives such as 2,4-dichloroquinoline have been found to undergo palladium-catalyzed Sonogashira cross-coupling reaction with ease to afford the 2-alkynyl-4-arylquinolines [64]. Baletskaya and co-workers reported the results of Sonogashira cross-coupling reaction of 4-chloro-6-iodoquinoline with phenylacetylene [62]. In all cases the authors observed preferential replacement of iodine atom over that of the 4-chlorine atom. The dialkynylated derivatives were isolated in high yields when excess of phenylacetylene was used [64]. This literature observation makes it difficult to predict how the reactivity of the adjacent Csp^2–I versus the activated Csp^2–Cl bond in systems **49** would differ in metal-catalyzed reactions. With this consideration in mind, we first subjected the 2-aryl-4-chloro-3-iodoquinoline **49** to the Sonogashira cross-coupling reaction with phenylacetylene or 3-butyn-2-ol in the presence of $PdCl_2(PPh_3)_2$–CuI catalyst mixture and triethylamine as a base in dioxane (Scheme 33). The reaction afforded the 2-aryl-4-chloro-3-(alkynyl)quinoline derivatives **87** in low yield after 18 hours when phenylacetylene was used as a coupling partner. The use of DMF as solvent on the other hand, resulted in a mixture of mono- and bis(alkynylated) in low yields. The yield for the monosubstituted derivatives in both cases was improved when NEt_3 was used as a base and solvent (Scheme 33). The ^{1}H NMR spectra of 2-aryl-4-chloro-3-(2-phenylethynyl)quinoline derivatives **87a-d** show an increased number of aromatic proton signals in the region δ *ca*. 7.31-7.44 ppm (Fig. 7). The ^{13}C NMR spectra of systems of **87** also reveal the presence of ethynyl carbon signals at δ *ca*. 85.55 ppm and 100.55 ppm (Table 1). Their alkynyl nature is also confirmed by a weak IR absorption band at ν_{max} *ca*. 2214 cm^{-1}. The ^{1}H NMR spectra of 2-aryl-4-chloro-3-(3-hydroxybutynyl)quinoline

derivatives, on the other hand, show the methyl proton signal at δ *ca*. 1.47 ppm and the OH signal at δ *ca*. 1.90 ppm as well as a quartet at δ *ca*. 4.71 ppm corresponding to the methine proton (Fig. 8). The ^{13}C NMR spectra of **87e-h** also show the presence of carbon signals of the butynyl group at δ *ca*. 79.75 ppm and 102.18 ppm (Table 2). The presence of the OH group is also confirmed by a broad IR absorption band at ν_{max} *ca*. 3298 cm^{-1}. The accurate calculated m/z values represent in each case closest fit consistent with the incorporation of the alkynyl moiety. Moreover, mass spectrometric data reveal the absence of iodine atom in the molecular ion and the presence of the 4-chloro atom as exemplified by molecular ion peaks in the ratio 3:1, which confirms the presence of chlorine isotopes ^{35}Cl and ^{37}Cl.



87	**R**	**R′**	%yield dioxane	%yield NEt_3	m.p.° C
a	H	Ph	54	74	145-148
b	F	Ph	57	64	175-178
c	Cl	Ph	49	67	179-180
d	OMe	Ph	44	70	120-122
e	H	$CH(OH)CH_3$	50	64	106-110
f	F	$CH(OH)CH_3$	62	61	152-155
g	Cl	$CH(OH)CH_3$	61	66	168-170
h	OMe	$CH(OH)CH_3$	60	65	120-124

Reagents: (i) $PdCl_2(PPh_3)_2$, CuI, NEt_3 or dioxane, reflux, 80 ºC, 2 h

Scheme 33

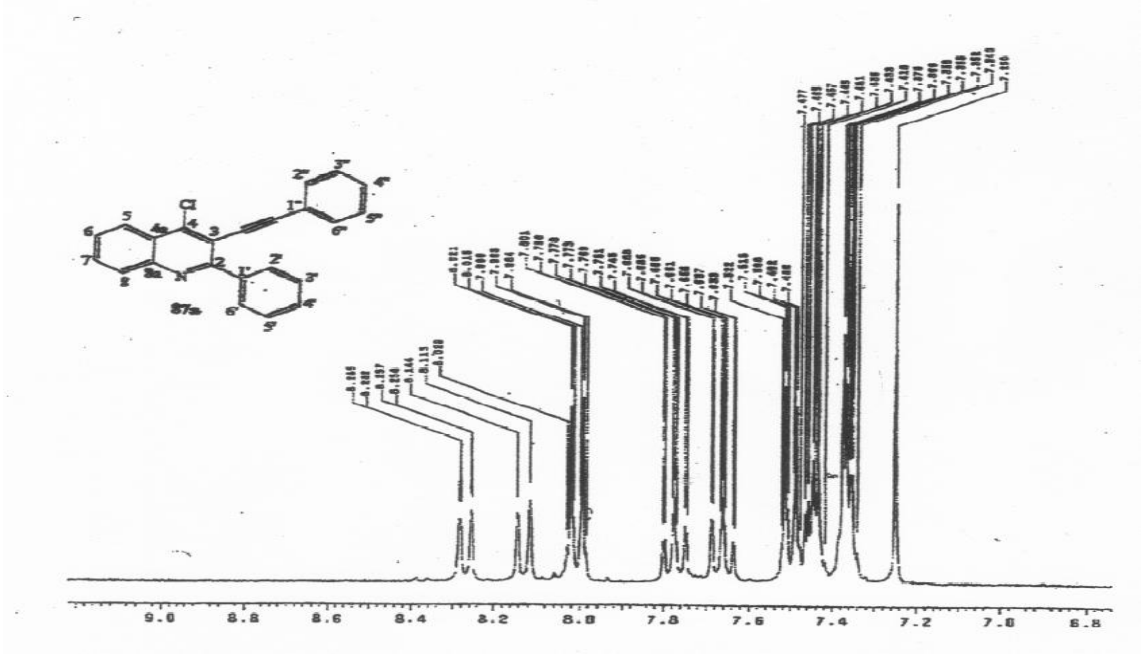


Figure 8: ^{1}H NMR spectrum of 4-chloro-3-(2-phenylethynyl)-2-phenylquinoline **87a** in $CDCl_3$

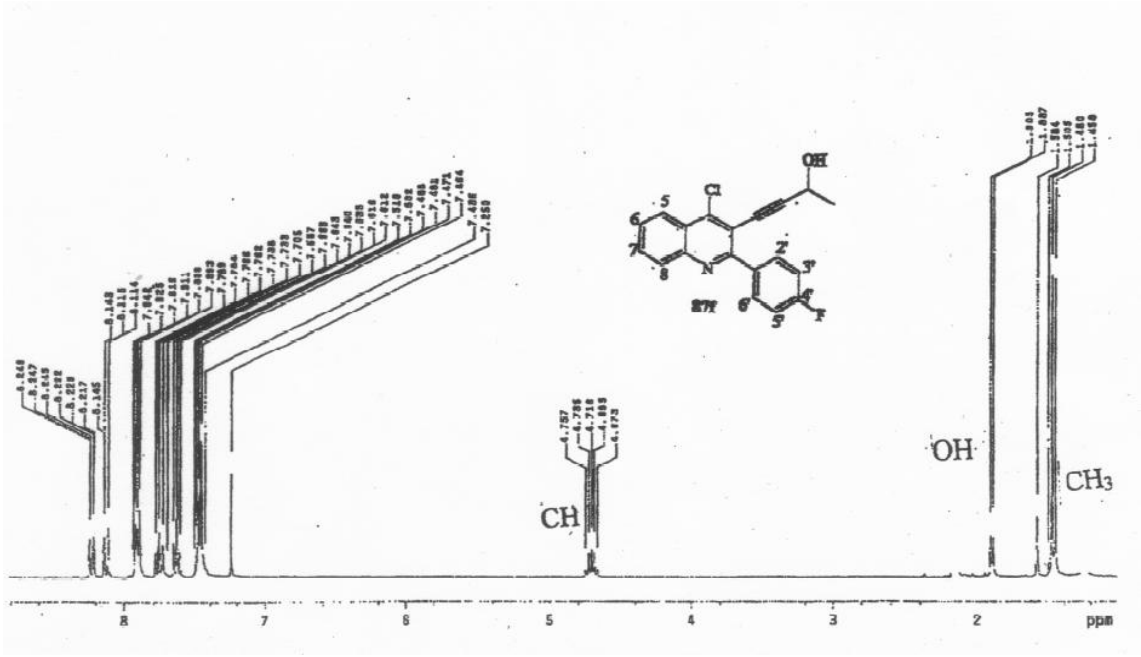
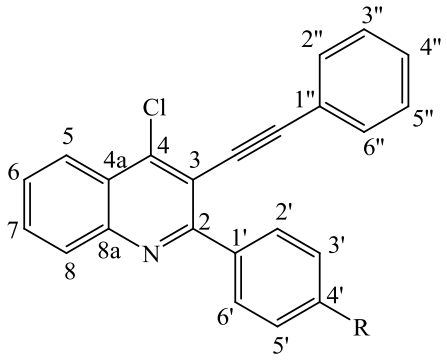


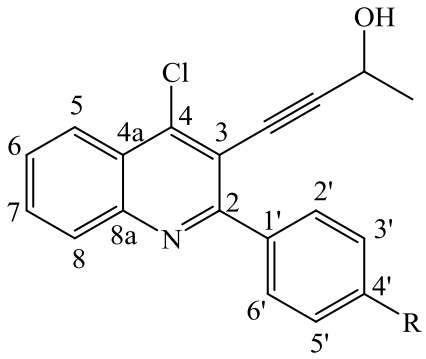
Figure 9: ^{1}H NMR spectrum of 2-(4-fluorophenyl)-4-chloro-3-(3-hydroxybutynyl)quinoline **87f** in $CDCl_3$

Table 1: ^{13}C NMR chemical shift values (ppm) of systems **87a-d** in $CDCl_3$ (at 75 MHz)



Nucleus	**87a** (R = H)	**87b** (R = F)	**87c** (R = Cl)	**87d** (R = OMe)
OCH_3	-	-	-	55.1
-**C**≡C-Ph	85.55	85.33	85.18	85.77
-C≡**C**-Ph	100.55	100.63	100.78	100.37
C-2	159.77	161.84	158.26	160.59
C-3	116.40	116.12	116.07	116.10
C-4	145.08	146.72	145.45	145.21
C-4a	122.71	122.48	122.46	122.77
C-5	125.36	124.33	124.38	124.33
C-6	129.24	127.94	129.14	127.59
C-7	130.80	130.90	130.00	130.74
C-8	130.01	129.86	129.94	129.84
C-8a	146.87	158.44	146.79	146.89
C-1′	139.53	135.51 (d, $^4J_{CF}$ 2.8 Hz)	137.88	132.06
C-1″	124.84	124.75	124.86	124.60
C-4′	127.88	165.15 (d, $^1J_{CF}$247.6 Hz)	128.09	159.10
C-4″	129.96	129.07	129.09	128.95
C-2′, 6′	127.94	131.62 (d, $^3J_{CF}$ 8.8 Hz)	128.50	131.17
C-2″, 6″	131.54	131.47	135.46	131.56
C-3′, 5′	129.60	114.90 (d, $^2J_{CF}$ 21.3 Hz)	131.51	113.34
C-3″, 5″	128.40	128.48	128.15	128.4

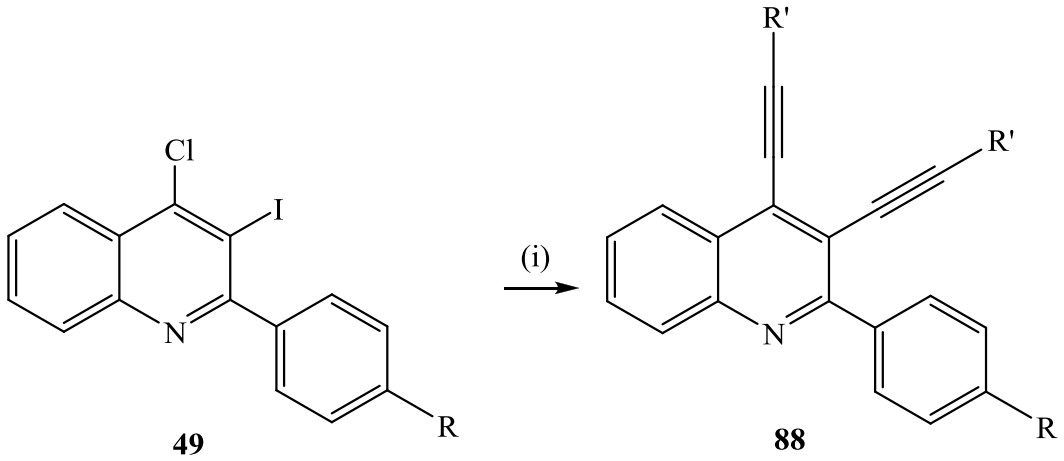
Table 2: ^{13}C NMR chemical shift values (ppm) of systems **87e-h** in $CDCl_3$ (at 75 MHz)



Nucleus	**87e** (R = H)	**87f** (R = F)	**87g** (R = Cl)	**87g** (R = OMe)
CH_3	23.73	23.79	23.78	23.74
-**C**H(OH)CH_3	58.98	58.94	58.94	58.82
OCH_3	-	-	-	55.32
-**C**≡C-Ph	79.75	79.76	79.62	79.97
-C≡**C**-Ph	102.18	102.32	102.43	102.18
C-2	159.81	158.55	158.33	160.51
C-3	115.60	115.38	115.29	115.32
C-4	145.56	145.85	1145.93	145.63
C-4a	124.65	124.63	124.64	124.34
C-5	124.36	124.38	124.38	124.23
C-6	129.27	128.02	128.13	127.54
C-7	130.98	131.10	131.14	130.82
C-8	129.95	129.85	129.89	129.66
C-8a	146.86	146.82	146.83	146.79
C-1′	139.35	135.35 (d, $^4J_{CF}$ 3.2 Hz)	137.65	131.71
C-4′	128.18	163.48 (d, $^1J_{CF}$ 247.8 Hz)	135.48	159.06
C-2′, 6′	129.48	131.53 (d, $^3J_{CF}$ 8.6 Hz)	130.92	131.05
C-3′, 5′	127.91	114.91 (d, $^2J_{CF}$ 21.7 Hz)	128.13	113.21

2.3 One-pot synthesis of 2-aryl-3,4-bis(alkynyl)quinoline derivatives 88

Beletskaya *et al*. [62] only isolated the dialkynylated quinolines from the 4,6-bis(phenylethynyl)quinoline **81** when 2.2 equiv. of phenylacetylene and 4 equiv. of NEt_3 in dioxane-water were employed. We followed a similar strategy and subjected substrates **49** to excess of terminal acetylene. The 2-aryl-4-chloro-3-iodoquinolines **49** were treated with phenylacetylene or 3-butyn-2-ol at 80 °C for 12 hours in the presence of $PdCl_2(PPh_3)_2$-CuI catalyst mixture and NEt_3 in dioxane-H_2O (3:1, v/v) to afford the 2-aryl-3,4-bis(alkynyl)quinolines **88** (Scheme 34).



88	**R**	**R′**	**%** Yield	m.p. °C
a	H	Ph	72	184-187
b	F	Ph	67	153-156
c	Cl	Ph	84	162-164
d	OMe	Ph	79	134-137
e	H	$CH(OH)CH_3$	16	98-100
F	Cl	$CH(OH)CH_3$	90	162-164
g	OMe	$CH(OH)CH_3$	47	100-106

Reagents: (i) $PdCl_2(PPh_3)_2$, CuI, NEt_3, dioxane-H_2O, 80^oC, 12h

Scheme 34

The ^{1}H NMR spectra of 2-aryl-3,4-bis(2-phenylethynyl)quinolines **88a-d** show an increase of proton signals in the aromatic region δ *ca*. 7.33-7.54 ppm confirming incorporation of two phenyl rings (Fig. 9). The ^{13}C NMR spectra of systems **88a-d** reveal the presence of two set of singlets for the carbon atoms of the ethynyl group at δ *ca*. 85.31, 87.82 and 99.35, 103.03 ppm (Table 3). The presence of alkynyl group was also confirmed by IR spectroscopy with sharp absorption band in the region ν_{max} *ca*. 2201-2214 cm^{-1}. The ^{1}H NMR spectra of the 2-aryl-3,4-bis(3-hydroxybutynyl)quinolines **88e-g** show two sets of doublets at δ *ca*.1.48 ppm for the two methyl groups, a broad singlet at δ *ca*. 2.03 ppm for 2-(OH) and two quartets at δ *ca*. 4.54 and 4.73 ppm corresponding to methine protons of the two 1-hydroxybutynyl group, respectively (Fig. 10). The incorporation of the two butynyl groups is also confirmed by the presence of carbon signals of the at δ *ca*. 69.62, 78.56, 80.32 and 102.43 in ^{13}C NMR spectra of systems **88e-g** (Table 4). The presence of the 2-(OH) group is also confirmed by a broad IR absorption band at ν_{max} *ca*. 3264 cm^{-1}.

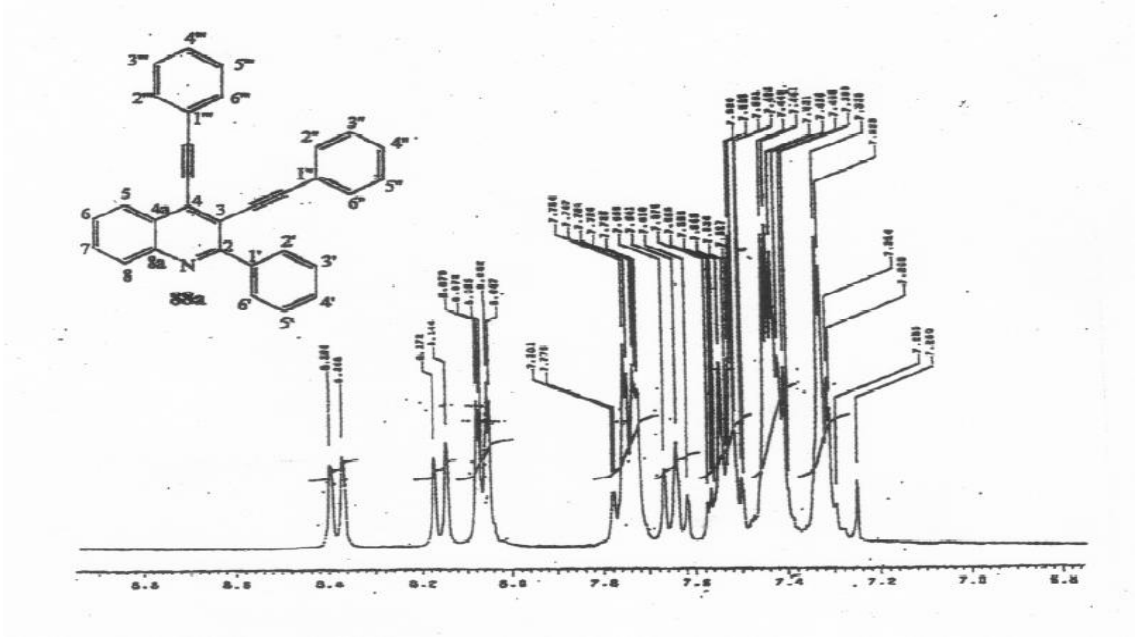
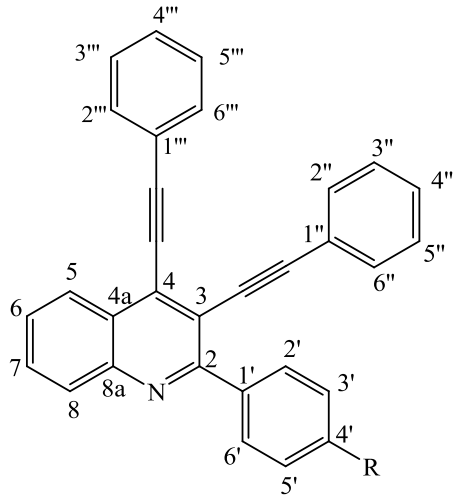


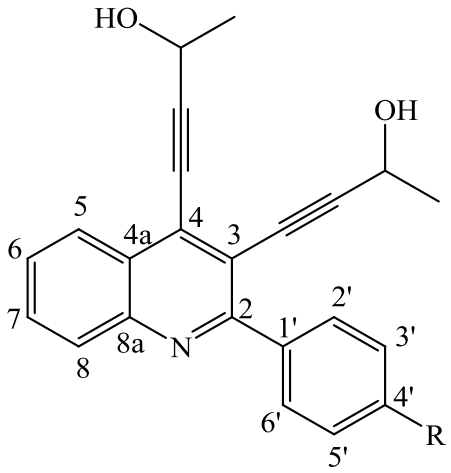
Figure 10: ^{1}H NMR spectrum of 3,4-(2-phenylethynyl)-2-phenylquinoline **88a** in $CDCl_3$

Table 3: ^{13}C NMR chemical shift values (ppm) of system **88a-d** in $CDCl_3$ (at 75 MHz)



Nucleus	**88a** (R = H)	**88b** (R = F)	**88c** (R = Cl)	**88d** (R = OMe)
OCH_3	-	-	-	55.36
-**C**≡C-Ph	85.31 & 87.83	73.86 & 81.52	85.31& 87.83	85.38 & 88.06
-C≡**C**-Ph	99.35 & 103.33	85.32 & 100.65	99.35 & 103.3	99.18 & 102.88
C-2	159.28	158.51	159.28	160.39
C-3	118.27	116.16	118.27	113.27
C-4	133.06	145.32	133.06	158.51
C-4a	122.51	122.50	122.51	125.65
C-5	125.90	124.38	125.90	125.81
C-6	127.52	127.99	127.52	129.39
C-7	129.97	130.96	129.97	130.29
C-8	129.48	129.89	129.48	129.75
C-8a	146.31	145.32	146.31	146.31
C-1′	139.75	135.55 (d, $^4J_{CF}$ 3.2 Hz)	139.75	132.28
C-1″	123.09	121.75	123.09	122.50
C-1‴	123.09	124.80	123.09	123.13
C-4′	133.06	163.59 (d, $^1J_{CF}$247.4 Hz)	130.41	158.51
C-4″	128.75	129.11	128.75	127.19
C-4‴	128.75	129.11	128.75	128.38
C-2′, 6′	129.61	131.63 (d, $^3J_{CF}$ 8.6 Hz)	129.61	131.96
C-2″, 6″	131.42	129.20	131.42	131.40
C-2‴, 6‴	132.06	131.50	132.06	131.12
C-3′, 5′	127.92	114.94 (d, $^2J_{CF}$ 21.6 Hz)	127.92	117.96
C-3″, 5″	128.63	128.49	128.63	128.56
C-3‴, 5‴	128.41	128.49	128.41	128.68

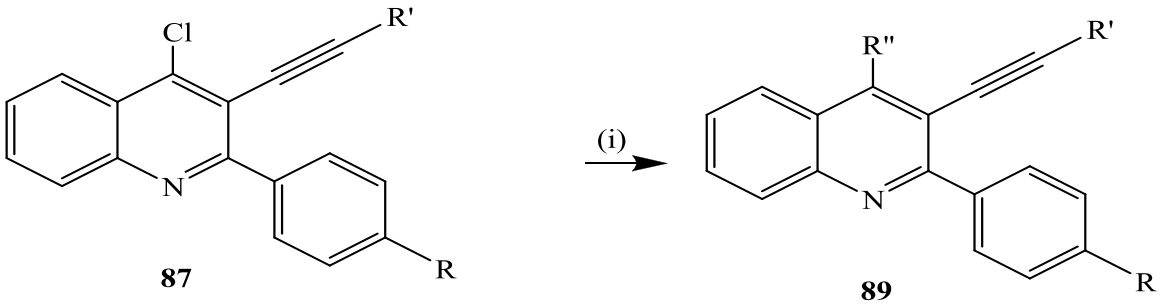
Table 4: ^{13}C NMR chemical shift values (ppm) of system **88e-g** in $CDCl_3$ (at 75 MHz)



Nucleus	**88e** (R = H)	**88f** (R = Cl)	**88g** (R = OMe)
CH_3	23.71& 23.78	23.77 & 23.88	23.73 & 23.80
-**C**H(OH)CH_3	58.90 & 58.98	58.63 & 58.93	58.37 & 58.79
OCH_3	-	-	55.32
-**C**≡C-Ph	69.62 & 78.56	68.03 & 79.61	67.03 & 79.91
-C≡**C**-Ph	80.32 & 102.43	81.20 & 102.46	81.23 & 102.21
C-2	158.33	158.35	160.49
C-3	115.29	115.31	115.35
C-4	145.93	145.93	145.68
C-4a	124.64	124.69	124.69
C-5	124.38	124.38	124.22
C-6	128.87	128.13	127.56
C-7	131.54	131.17	130.86
C-8	129.89	129.86	129.57
C-8a	146.83	146.81	146.71
C-1′	137.65	137.63	131.62
C-4′	135.48	135.49	159.10
C-2′, 6′	130.92	130.92	131.06
C-3′, 5′	127.13	128.13	113.21

2.4 Suzuki cross-coupling of 2-aryl-4-chloro-3-(alkynyl)quinoline derivatives 87

Suzuki cross-coupling of boronic acid derivatives are also known to proceed well with aryl iodides or aryl bromides and to some extend with activated aryl- or heteroaryl chlorides [64]. In order to prepare the 2,4-diaryl-3-(alkynyl)quinoline **89** we subjected the 2-aryl-4-chloro-3-(alkynyl)quinolines **87** under Suzuki cross-coupling reaction with arylboronic acids (4-flourophenyl boronic acid and *trans*-vinylphenylboronic acid) in the presence of $PdCl_2(PPh_3)_2$ as a catalyst, K_2CO_3 as a base and PCy_3 as a ligand in dioxane-water (3:1 v/v) (Scheme 34). The reaction failed to take place in the absence of PCy_3 ligand indicating the importance of alkylphosphine ligands in activating palladium towards oxidative addition to R-X [64]. Both 4-flourophenyl boronic acid and *trans*-vinylphenylboronic acid participated well in the coupling reaction without affecting the alkynyl substituents at position 3 of compound **87.**



89	**R**	**R′**	**R″**	% yield	m.p ^{o}C
a	H	Ph	-CH=CH-Ph	92	183-185
b	F	Ph	-CH=CH-Ph	50	161-163
c	OMe	Ph	-CH=CH-Ph	55	128-129
d	F	$CH(OH)CH_3$	-CH=CH-Ph	50	105-108
e	H	Ph	PhF	74	147-149
F	OMe	Ph	PhF	62	166-167

Reagents: $PdCl_2(PPh_3)_2$, K_2CO_3, PCy_3, dioxane-water, 18 h

Scheme 35

The ^{1}H NMR spectra of the 2-aryl-4-(4-*trans*-vinylphenyl)-3-(alkynyl)quinolines **89a-d** show an increase of proton signals in the aromatic region confirming incorporation of vinylphenyl group (Fig. 11). The ^{1}H NMR spectra of 2-aryl-4-(4-fluorophenyl)-3-(alkynyl)quinolines **89e-f**, on the other hand, show an increase of proton signals in the aromatic region confirming incorporation of the vinylphenyl.

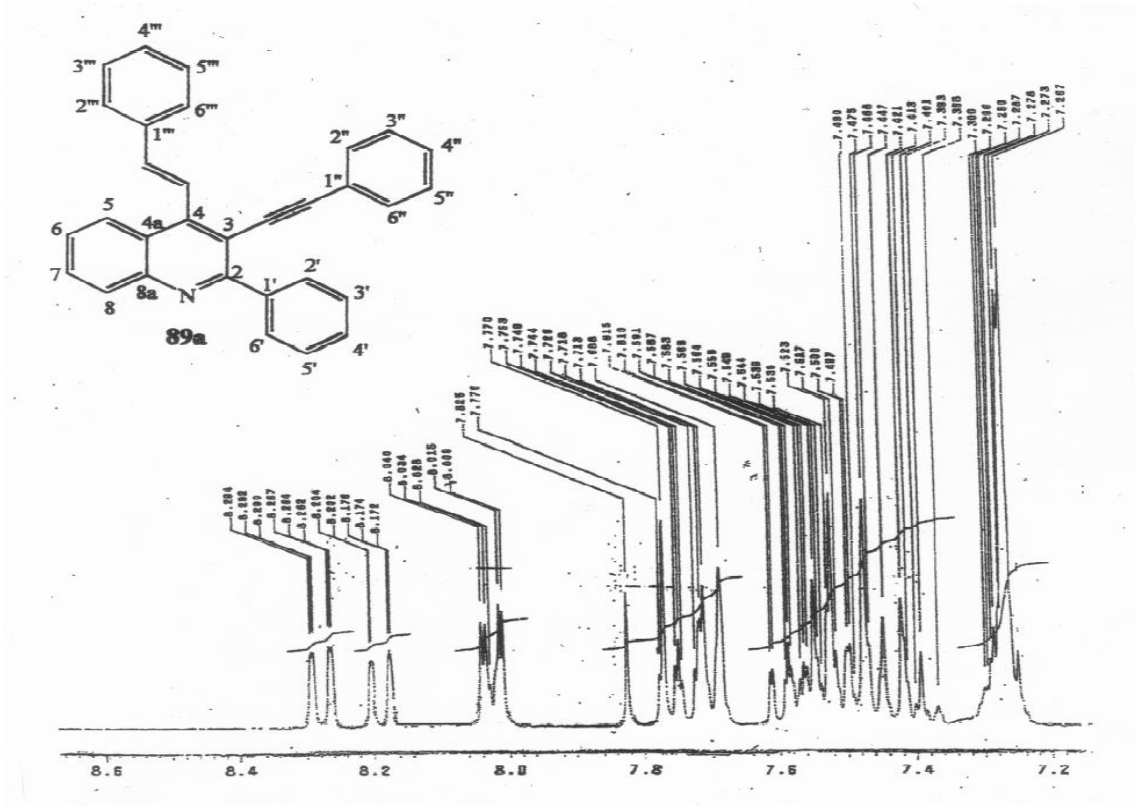


Figure 11: ^{1}H NMR spectrum of 4-(phenylethenyl)-3-(2-phenylethynyl)-2-phenylquinoline **89a** in $CDCl_3$

The ^{13}C NMR spectra of systems **89a-d** reveal the presence of vinyl signals at δ *ca*. 128.53 and 138.79 ppm (Table 5). The presence of vinyl group was also confirmed by IR spectroscopy with absorption band in the region ν_{max} *ca* 3023 cm-1. The ^{13}C NMR spectra of systems **89e-f**, on the other hand, reveal four sets of doublets at δ *ca*. 115.26, 131.97, 132.92 and 162.80 ppm, which correspond to carbon atoms bearing fluorine atom in systems **89e-f**, respectively (Table 6).

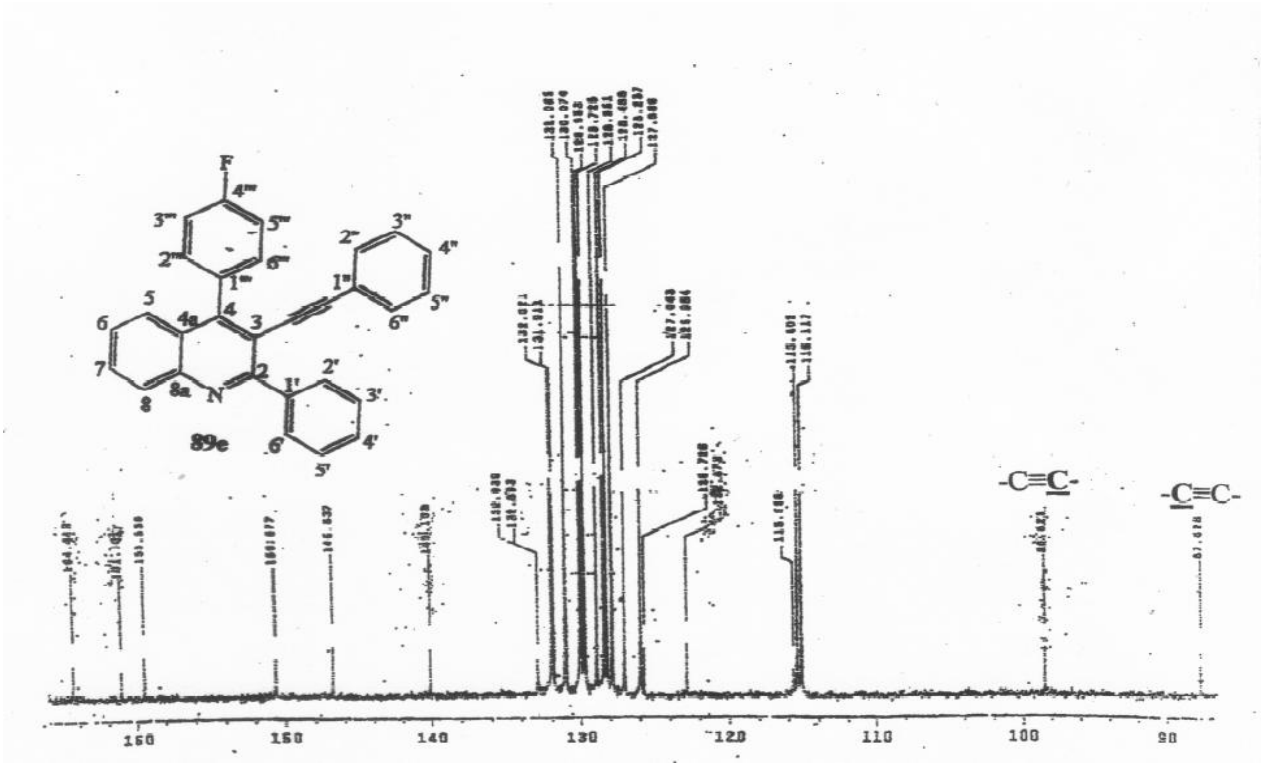
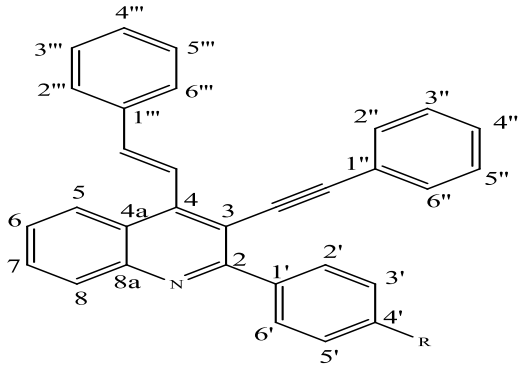


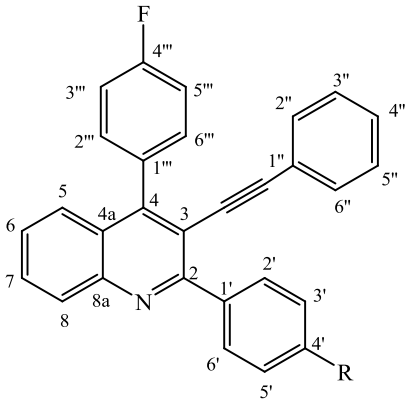
Figure 12: ^{13}C NMR spectrum of 4-(4-fluorophenyl)-3-(2-phenylethynyl)-2-phenylquinoline **89e** in $CDCl_3$

Table 5: ^{13}C NMR chemical shift values (ppm) of system **89a-d** in $CDCl_3$ (at 75 MHz)



Nucleus	**88a** (R=H)	**88b** (R=F)	**88c** (R=OMe)	**88d** (R = F)
OCH_3	-	-	55.40	
CH_3				23.21
-**C**H(OH)CH_3				58.81
-**C**H=CH-	128.53	127.03	126.64	126.99
-CH=**C**H-	138.79	138.93	138.60	138.82
-**C**≡C-Ph	87.90	87.66	88.08	81.77
-C≡**C**-Ph	99.86	99.94	99.70	101.66
C-2	160.02	158.75	160.22	158.62
C-3	114.10	113.86	113.85	113.27
C-4	146.66	146.93	146.97	147.54
C-4a	123.13	122.92	123.15	124.55
C-5	123.40	123.26	123.51	123.14
C-6	125.01	125.05	124.51	125.05
C-7	129.96	130.11	129.89	131.49
C-8	130.28	130.16	130.07	131.60
C-8a	146.94	146.87	146.83	146.90
C-1′	140.35	136.36 (d, $^4J_{CF}$ 3.1 Hz)	132.83	136.12 (d, $^4J_{CF}$ 3.2 Hz)
C-1″	124.78	124.74	124.51	136.46
C-1‴	136.75	136.34	136.76	-
C-4′	128.78	163.30 (d, $^1J_{CF}$ 247.4 Hz)	159.21	163.24 (d, $^1J_{CF}$ 247.0 Hz)
C-4″	128.78	128.84	128.91	128.85
C-4‴	126.94	128.67	128.50	-
C-2′ ,6′	126.94	131.65 (d, $^3J_{CF}$ 8.3 Hz)	131.89	131.96 (d, $^3J_{CF}$ 8.6 Hz)
C-2″, 6″	131.19	131.15	128.39	131.12
C-2‴, 6‴	128.95	128.45	131.89	-
C-3′, 5′	129.68	114.32 (d, $^2J_{CF}$ 21.5 Hz)	113.23	114.71 (d, $^2J_{CF}$ 21.5 Hz)
C-3″, 5″	127.84	126.93	126.89	128.93
C-3‴, 5‴	128.36	128.96	128.91	-

Table 6: ^{13}C NMR chemical shift values (ppm) of system **89e-f** in $CDCl_3$ (at 75 MHz)



Nucleus	**89e** (R = H)	**88f** (R = OMe)
OCH_3	-	55.43
-**C**≡C-Ph	87.63	87.89
-C≡**C**-Ph	98.53	98.43
C-2	159.958	160.40
C-3	115.66	113.28
C-4	150.68	150.84
C-4a	125.73	146.89
C-5	125.95	125.93
C-6	127.04	126.76
C-7	129.97	129.80
C-8	130.07	130.01
C-8a	146.84	146.89
C-1′	140.10	132.67
C-1″	122.87	122.95
C-1‴	132.92 (d, $^4J_{CF}$ 3.5 Hz)	133.05 (d, $^4J_{CF}$ 3.5 Hz)
C-4′	128.49	158.85
C-4″	128.98	128.47
C-4‴	162.80 (d, $^1J_{CF}$ 246.1 Hz)	162.76 (d, $^1J_{CF}$ 246.2 Hz)
C-2′ ,6′	127.87	131.07
C-2″, 6″	131.07	131.25
C-2‴, 6‴	131.97 (d, $^3J_{CF}$ 8.3 Hz)	131.94 (d, $^4J_{CF}$ 7.8 Hz)
C-3′, 5′	129.73	113.28
C-3″, 5″	128.26	128.28
C-3‴, 5‴	115.26 (d, $^2J_{CF}$ 21.4 Hz)	115.23 (d, $^2J_{CF}$ 21.6 Hz)

The structure of the products of successive Sonogashira and Suzuki cross coupling reaction was further confirmed by X-ray crystallography. Single crystals of the 4-(phenylethenyl)-3-(2-phenylethynyl)-2-phenylquinoline **89a** (Fig. 12) suitable for X-ray crystallographic analysis were obtained by slow evaporation of the ethanol solution. The compound crystallizes in the monoclinic space group P2(1)/n with one molecule in the unit cell (a/Å 7.4452, b/ Å 18.2686, c/ Å 16.1705, $\alpha = \gamma = 90^{o}$, $\beta = 97.746^{o}$). The 2-aryl ring is not co-planar with quinoline ring as confirmed by the large torsion angle (C(2′)-C(1′)-C(2)-C(3)) with a value 48.2º (see Table 7 for torsion angles) presumably due to possible steric interaction with the alkynyl moiety at the position 3. The *trans* arrangement of the vinylphenyl group at 4 position is retained with torsion angle C(4)-C(17)-C(18)-C(19) = -175.95º. The phenyl ring of this vinylphenyl moiety is slightly deformed out of co-planarity with torsion angle value of -13.4º for (C(17)-C(18)-C(20)-C(24)).

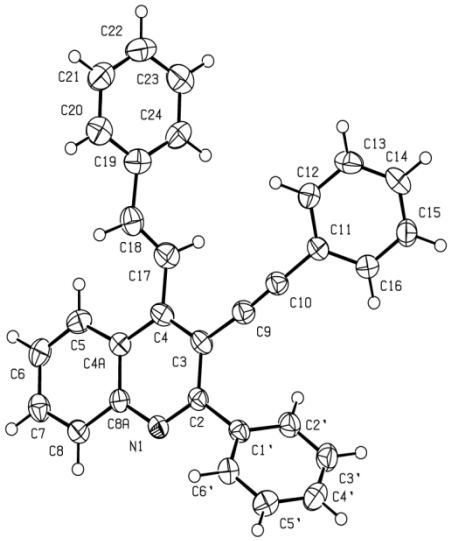


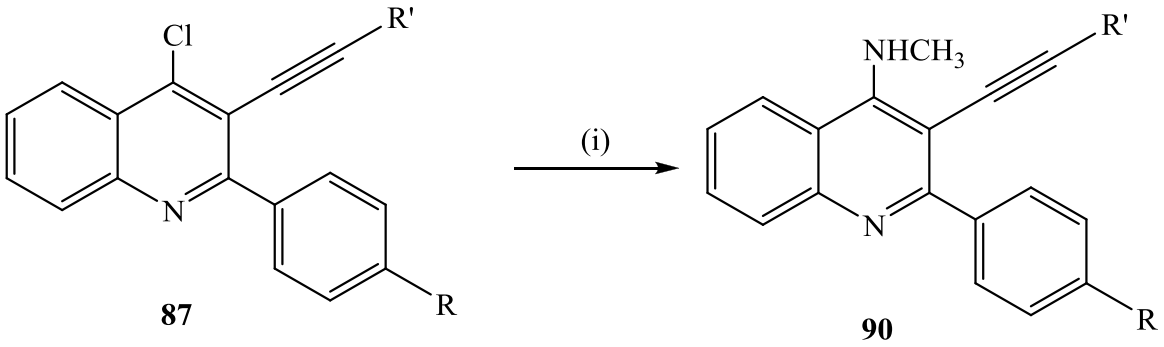
Figure 13: X-ray crystal structure of the 2-aryl-3-(2-phenylethynyl)-4-phenylethenylquinoline **89a**

Table 7: Selected torsion angles [º] for 2-aryl-3-(2-phenylethynyl)-4-phenylethenylquinoline **89a**

Torsion angles [º]	
C(6)-C(1)-C(2)-N(1)	44.6º
C(2')-C(1')-C(2)-C(3)	48.2º
C(4A)-C(4)-C(17)-(18)	-45.6
C(17)-C(18)-C(20)-C(24)	-13.4
C(4)-C(17)-C(18)-C(19)	-175.95

2.5 Amination of 2-aryl-4-chloro-3-(alkynyl)quinoline derivatives 87

The 2-aryl-4-chloro-3-(alkynyl)quinolines **87** were transformed to the corresponding 2-aryl-3-(alkynyl)-4-(methylamino)quinolines **90** with methylamine in ethanol under reflux for 18 hours in good yields (Scheme 35).



90	**R**	**R'**	% yield	m.p ^{o}C
a	H	Ph	73	158-160
b	Cl	Ph	58	176-179
c	OMe	Ph	58	130-133
d	Cl	$CH(OH)CH_3$	61	183-184

Reagents: (i) NH_2CH_3, EtOH, 18h.

Scheme 36

The ^{1}H NMR spectra of systems **90** show the doublet at δ *ca* 3.57 ppm corresponding to methyl group and singlet at δ *ca* 5.68 ppm corresponding to NH (Fig. 12). The ^{13}C NMR spectra of systems **90** reveal the presence of methyl group at δ *ca* 35.65 ppm (Table 8). The presence of the amine group is further confirmed by the IR spectroscopy with broad absorption band at ν_{max} *ca* 3356 cm-1.

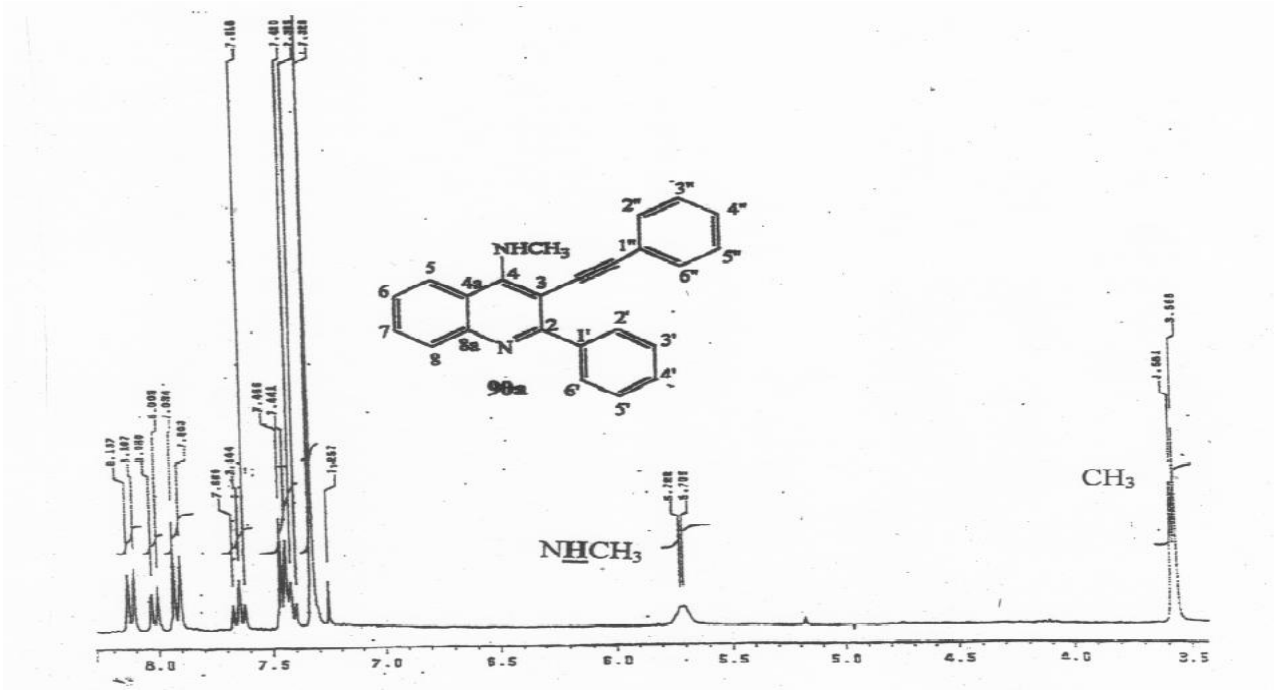
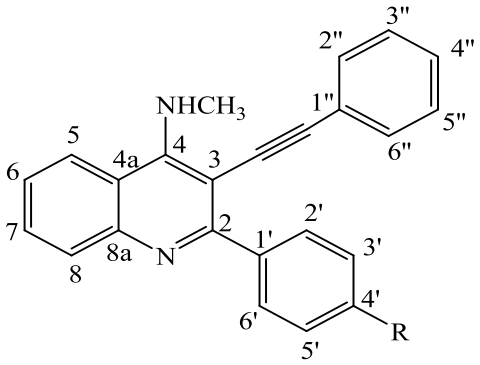


Figure 14: ^{1}H NMR spectrum of 4-(methylamino)-3-(2-phenylethynyl)-2-phenylquinoline **90a** in $CDCl_3$

Table 8: ^{13}C NMR chemical shift values (ppm) of system **90a-d** in $CDCl_3$ (at 75 MHz)



Nucleus	**90a** (R = H)	**90b** (R = Cl)	**90c** (R = OMe)	**90d** (R = Cl)
CH_3	35.65	35.65	35.78	35.65
OCH_3	-	-	55.38	-
-CH(OH)CH_3	-	-	-	58.81
-**C**≡C-Ph	86.23	85.83	86.32	85.83
-C≡**C**-Ph	99.44	93.23	98.63	99.28
C-2	160.50	159.01	158.26	159.01
C-3	95.95	99.62	99.38	99.63
C-4	154.68	154.79	154.79	154.01
C-4a	117.68	117.61	117.61	117.61
C-5	122.69	122.73	122.83	122.73
C-6	124.49	124.64	124.27	124.64
C-7	129.77	129.94	129.94	129.94
C-8	130.38	130.31	130.31	130.31
C-8a	148.08	148.04	148.04	148.04
C-1′	140.83	139.24	139.24	139.24
C-1″	123.36	123.10	123.38	123.10
C-4′	128.12	134.53	134.53	134.53
C-4″	128.29	128.12	128.12	128.12
C-2′, 6′	129.43	130.75	130.75	130.75
C-2″, 6″	130.74	130.90	130.90	130.90
C-3′, 5′	128.36	128.36	113.15	128.36
C-3″, 5″	127.74	127.91	127.91	127.91

CHAPTER 3 CONCLUSIONS

The results described in this investigation represent another example showing the application of the 2-aryl-4-chloro-3-iodoquinolines in the synthesis of polysubstituted quinoline derivatives. Reaction conditions were optimized for regioselective monoalkynylation and one-pot dialkynylation of 2-aryl-4-chloro-3-iodoquinolines. Further transformation of the 2-aryl-3-(alkynyl)-4-chloroquinoline **87** via Suzuki cross-coupling reaction with boronic acid derivatives (e.g., 4-flourophenylboronic acid and *trans*-vinylphenylboronic acid) in the presence of Pd-CuI catalytic mixture and PCy_3 as a ligand afforded the 2,4-diaryl-3-(alkynyl)quinolines in moderate to high yields. The observed results of Sonogashira cross-coupling further confirm that for the presynthesized dihaloquinolines, iodine atom at any position is always displaced preferentially over activated chlorine atom.

Amination of 2-aryl-3-(alkynyl)-4-chloroquinoline with methylamine afforded the 2-aryl-3-(alkynyl)-4-(methylamino)quinoline derivatives and this reflects the ease of displacement of 4-chloro atom by nucleophiles to afford derivatives with potential biological activity.

In summary, the results described in this investigation demonstrate the potential of the 2-aryl-4-chloro-3-iodoquinoline in the synthesis of 2,3,4-trisubstituted quinoline derivatives that can serve as building blocks for more complex compounds with biological applications or applications in materials. Moreover, the monoalkynylated products and the primary 4-aminoquinolines prepared in this investigation can be subjected to further studies of chemical transformation.

Future research extending from this investigation will include the following:

- Cyclization of 2-aryl-3-(alkynyl)-4-(methylamino)quinoline with I_2 (iodocyclization) or Pd/Cu-I catalytic mixture to afford (1*H*)-pyrrolo[3,2-c]quinoline derivatives with potential biological application
- One-pot Pd-PCy_3 catalyzed Suzuki cross-coupling of the 2-aryl-4-chloro-3-iodoquinoline with boronic acid derivatives to afford 2,3,4-triarylquinoline derivatives
- Dechloromethoxylation to afford 2-aryl-3-iodo-4-methoxyquinoline and subsequence displacement of iodo-atom via Sonogashira type reaction to afford either the 2-alkynylated quinolines or their 2,4-diphenylfuro[3,2-*c*]quinoline derivatives in a single-pot operation.

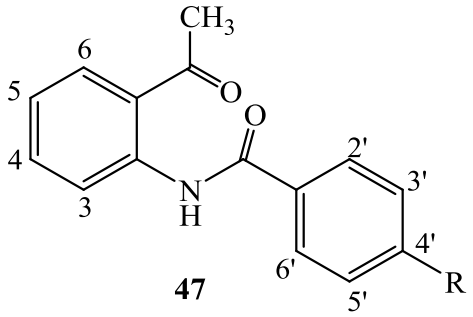
CHAPTER 4 EXPERIMENTAL

4.1 General

All melting points were determined on a Stuart SMP3 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 and δ_C 77.0 ppm for $CDCl_3$ or δ_H 2.50 and δ_C 40.0 ppm for DMSO-d_6).

IR spectra were recorded neat on a Digilab FTS 7000 series Digilab Win-IR Pro FTIR spectrometer using a nitrogen cooled germanium crystal detector. Merck silica gel was used for the thin layer chromatography and column chromatography. Low and high-resolution mass spectra were recorded at the University of Stellenbosch using Waters API Q-TOF Ultima instrument.

4.2 Preparation of *N*-benzoyl-2-aminoacetophenone derivatives 47.



47

N-benzoyl-2-aminoacetophenones **47a-d**

4.2.1 Preparation of *N*-benzoyl-2-aminoacetophenone 47a (R = H)

Benzoyl chloride **46a** (4.10 mL, 35.45 mmol) was added drop-wise to a mixture of 2-aminoacetophenone **20** (4.00 g, 29.59 mmol) and triethylamine (8.20 mL, 59.18 mmol) in THF (70 mL) at 0 ºC. After 30 minutes at 0 ºC, the mixture was stirred at room temperature for 2 hours and then poured into ice-cold water (100 mL). The resulting precipitate was filtered and then dissolved in chloroform (30 mL). The solution was washed with water and the organic layer was separated and dried over anhydrous Mg_2SO_4. The salt was filtered off and the solvent was evaporated under reduced pressure to afford **47a** as a solid (6.45 g, 99%), m.p. 94-96 ºC (lit. [70] 95-99 ºC); ^{1}H MNR (300 MHz, DMSO-d_6) 2.69 (3H, s, $COCH_3$), 7.26 (1H, t, *J* 7.5 Hz, 4-H), 7.48-7.71 (4H, m, 3'-H and 5'-H, 4'-H, 5-H), 7.96 (2H, dd, *J* 1.8 and 6.6 Hz, 2′-H and 6′-H) 8.11 (1H, d, *J* 8.4 Hz, 3-H), 8.67 (1H, d, *J* 8.4 Hz, 6-H), 12.70 (1H, s, NH); ν_{max}/cm^{-1} 763, 962, 1246, 1423, 1645, 1674, 3209.

4.2.2 Preparation of *N*- (4-fluorobenzoyl)-2-aminoacetophonone 47b (R = F)

A mixture of 2-aminoacetophonone **20** (4.00 g, 29.59 mmol), triethylamine (8.20 mL, 59.18 mmol), and 4-fluorobenzoyl chloride **46b** (4.10 mL, 35.45 mmol) in THF (70 mL) was treated as for the

synthesis of **47a** afforded **47b** as a solid (3.75 g, 94%), m.p. 83-85 ºC (lit. [70] 92-95 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 2.68 (3H, s, $COCH_3$), 7.26 (1H, t, *J* 7.5 Hz , 4-H), 7.43 (2H, t, *J* 8.1 Hz, 3'-H and 5'-H), 7.67 (1H, t, *J* 8.4 Hz, 5-H), 8.04 (2H, dt, *J* 2.4 and 6.0 Hz, 2'-H and 6'-H,), 8.09 (1H, d, *J* 6.6 Hz, 3-H), 8.60 (1H, d, *J* 8.4 Hz, 6-H) 12.33 (1H, s, NH); ν_{max}/cm^{-1} 754, 850, 1166, 1246, 1449, 1506, 1590, 1651, 1671, 3169.

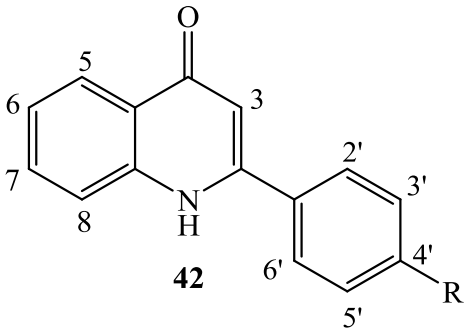
4.2.3 Preparation of *N*- (4-chlorobenzoyl)-2-aminoacetophonone 47c (R = Cl)

A mixture of 2-aminoacetophonone **20** (4.00 g, 35.45 mmol), triethylamine (8.20 mL, 59.18 mmol), and 4-chlorobenzoyl chloride **46c** (4.50 mL, 35.45 mmol) in THF (70 mL) was treated as for the synthesis of **47a** to afford **47c** as a solid (7.50 g, 93%), m.p. 108-110 ºC (lit. [70]. 106-109 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 2.69 (3H, s, COCH3), 7.28 (1H, t, *J* 7.5 Hz, 4-H), 7.67-7.71 (3H, m, 3'-H, 5'-H and 5-H), 7.97 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 8.11 (1H, dd, *J* 1.5 and 6.9 Hz, 3-H), 8.59 (1H, d, *J* 8.4 Hz, 6-H) 12.34 (1H, s, NH); 7 ν_{max}/cm^{-1} 57, 1013, 1316, 1450, 1535, 1588,1648, 1669, 3228.

4.2.4 Preparation of *N*- (4-methoxybenzoyl)-2-aminoacetophonone 47d (R = OMe)

A mixture of 2-aminoacetophonone **20** (4.00 g, 29.59 mmol), triethylamine (8.20 mL, 59.18 mmol), and 4-methoxybenzoyl chloride **46d** (5.94 g, 35.45 mmol) in THF (70 mL) was treated as for **47a** to afford **47d** as a solid (7.45 g, 93%), m.p. 117-120 ºC (lit. [70] 119-121 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 2.69 (3H, s, $COCH_3$), 3.85 (3H, s, OCH_3) 7.13 (2H, d, *J* 8.4, 3'-H and 5'-H), 7.24 (1H, t, *J* 7.5 Hz, 4-H), 7.66 (1H, dt, *J* 1.8 and 8.4 Hz, 5-H), 7.93 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 8.11 (1H, dt, *J* 1.8 and 8.4 Hz, 3-H), 8.67 (1H, d, *J* 8.4 Hz, 6-H) 12.35 (1H, s, NH); ν_{max}/cm^{-1} 759, 1020, 1158, 1188, 1251, 1314, 1509, 1605,1644, 1787, 3227

4.3 Preparation of 2-arylquinolin-4(1*H*)-one derivatives 42.



42

2-Arylquinolin-4(1*H*)-ones **42a-d**

4.3.1 Preparation of 2-phenylquinolin-4(1*H*)-one 42a (R = H)

A stirred mixture of *N*-benzoyl-2-aminoacetophonone **47a** (6.45 g, 29.92 mmol) and 1M potassium *tert*-butoxide (59.60 mL, 59.59 mmol) in *tert*-butanol (20 mL) was heated under reflux for 18 hours. The mixture was allowed to cool to room temperature and was poured into aqueous ammonium chloride solution (100 mL) to form a precipitate. The precipitate was collected, washed sequentially with water and ice-cold ethanol and then dried in an oven to afford **42a** as a solid (5.53 g, 84%), m.p. 220-221 ºC (lit. [40] 240-243 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) 6.33 (1H, s, 3-H), 7.32 (1H, t, *J* 8.1 Hz, 6-H), 7.41-7.47 (2H, m, 3'-H and 5'-H), 7.67 (1H, dt, *J* 1.5 and 8.4 Hz, 7-H), 7.75 (1H, d, *J* 7.5 Hz, 8-H), 7.91 (2H, dt, *J* 3.3 and 9.3 Hz, 2'-H and 6'-H), 8.09 (1H, m, 4'-H), 8.60 (1H, d, *J* 7.8 Hz, 5-H), 11.72 (1H, s, N-H); ν_{max}/cm^{-1} 753, 769, 810, 1252, 1469, 1498, 1545, 1578, 1637, 2339, 2965, 3062.

4.3.2 Preparation of 2-(4-fluorophenyl)quinolin-4-(1*H*)-one 42b (R = F)

A procedure employed for the synthesis of **42a** was followed using a mixture of *N*-(4-fluorobenzoyl)-2-aminoacetophenone **47b** (6.40 g, 24.89 mmol) and 1M potassium *tert*-butoxide (49.80 mL, 49.78 mmol) in *tert*-butanol (20 mL). Work up afforded **42b** as a solid (4.43 g, 74%), m.p. 296-298 ºC (lit. [40] 322-325 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 6.32 (1H, s, 3-H), 7.34 (1H, t, *J* 7.5 Hz, 6-H), 7.44 (1H, t, *J* 8.4 Hz, 7-H), (2H, dt, *J* 1.5 and 8.4 Hz, 3'-H and 5'-H), 7.76 (1H, dt, *J* 8.4 Hz, 8-H), 7.91 (2H, t, *J* 8.4 Hz, 2'-H and 6'-H) 8.09 (1H, dd, *J* 1.5 and 8.4, 8-H), 8.60 (1H, d, *J* 7.5 Hz, 5-H), 11.72 (1H, s, N-H); ν_{max}/cm^{-1} 753, 803, 1018, 1246, 1505, 1547, 1582, 1635, 2813, 3093.

4.3.3 Preparation of 2-(4-chlorophenyl)quinolin-4-(1*H*)-one 42c (R = Cl)

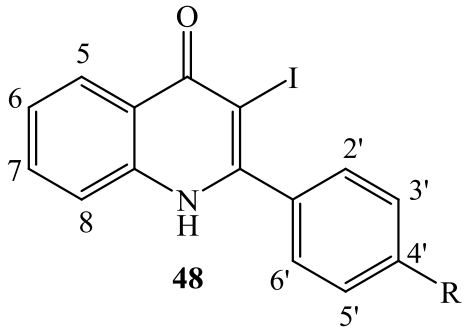
A procedure employed for the synthesis of **42a** was followed using a mixture of *N*-(4-chlorobenzoyl)-2-aminoacetophenone **47c** (7.50 g, 27.41 mmol) and 1M potassium *tert*-butoxide (54.80 mL, 54.82 mmol) in *tert*-butanol (20 ml). Work up afforded **42c** as a solid (5.94 g, 87.8%), m.p. 322-324 ^{o}C (lit. [40] 270-273 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 6.33 (1H, s, 3-H), 7.31 (1H, t, *J* 7.5 Hz, 6-H), 7.60-7.67 (2H, m, 2'-H and 6'-H), 7.68 (1H, t, *J* 8.1 Hz, 7-H), 7.86 (2H, m, 3'-H and 5'-H), 8.07 (1H, d, *J* 7.5 Hz, 8-H), 8.56 (1H, d, *J* 8.4 Hz, 5-H), 11.84 (1H, s, N-H); ν_{max}/cm^{-1} 762, 810, 1014,1092, 1252, 1440, 1545, 1576, 1637, 2965, 3064.

4.3.4 Preparation of 2-(4-methoxyphenyl)quinolin-4-(1*H*)-one 42d (R = OMe)

A procedure employed for the synthesis of **42a** was followed using a mixture of *N*-(4-chlorobenzoyl)-2-aminoacetophenone **47d** (7.45 g, 27.41 mmol) and 1M potassium *tert*-butoxide (54.80 mL, 54.82 mmol) in *tert*-butanol (20 mL). Work up afforded **42d** as a solid (5.32 g, 77%), m.p. 294-295 ºC (lit. [40] 290-297.3 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 3.85 (3H, s, OCH_3), 6.31 (1H, s, 3-H), 7.14 (2H,

d, *J* 8.4 Hz, 3'-H, 5'-H), 7.32 (1H, t, *J* 7.5 Hz, 6-H), 7.65 (1H, t, *J* 7.5 Hz, 7-H), 7.74-7.82 (3H, m, 2'-H and 6'-H, 8-H), 8.09 (1H, d, *J* 7.5 Hz, 5-H), 11.59 (1H, s, N-H); ν_{max}/cm^{-1} 753, 828, 1092, 1254, 1543, 1580, 1640, 2965, 3065, 3256.

4.4 Preparation of 2-aryl-3-iodoquinolon-(1*H*)-one derivatives 48



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2-Aryl-3-iodoquinolon-(1*H*)-ones **48a-d**

4.4.1 Preparation of 3-iodo-2-phenylquinolin-4-(1*H*)-ones 48a (R = H)

A stirred mixture of 2-phenylquinolin-4(1*H*)-one **42a** (5.00 g, 22.61 mmol), iodine (11.47 g, 45.22 mmol) and sodium carbonate (3.60 g, 33.92 mmol) in THF (70 mL) was stirred at room temperature for 12 hours. The reaction mixture was poured into ice-cold sodium thiosulphate solution. The precipitate was filtered, washed with water and to dried in an oven to afford **48a** as a solid (4.13 g, 53%), m.p. 225-228 ºC (lit. [68] 284-286 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 7.39 (1H, t, *J* 6.6 Hz, 6-H), 7.57-7.74 (7H, m, 2'-H and 6'-H, 3'-H and 5'-H, 4'-H, 6-H, 8-H), 8.15 (1H, d, *J* 7.5 Hz, 5-H), 12.31 (1H, s, N-H); ν_{max}/cm^{-1} 757, 835, 1155, 1225, 1469, 1495, 1537, 1627, 2910, 3057, 3372.

4.4.2 Preparation of 2-(4-fluorophenyl)-3-iodoquinolin-4-(1*H*)-one 48b (R = F)

A procedure employed for the synthesis of **48a** was followed using a mixture of 2-(4-fluorophenyl)quinolin-(1*H*)-one **42b** (4.00 g, 16.73 mmol), iodine (8.49 g, 33.45 mmol) and sodium carbonate (2.66 g, 25.10 mmol) in THF (70 mL). Work up afforded **48b** as a solid (5.51 g, 73%), m.p. 207-208 ºC (lit. [69] 196-198 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 7.33-7.42 (3H, m, 3'-H and 5'-H, 7-H), 7.55-7.71 (4H, m, 2'-H and 6'-H, 6-H, 8-H), 8.16 (1H, d, *J* 5.1 Hz, 5-H), 12.31 (1H, s, N-H); ν_{max}/cm^{-1} 758, 818, 1155, 1225, 1470, 1495, 1537, 1627, 2909, 3375.

4.4.3 Preparation of 2-(4-chlorophenyl)-3-iodoquinolin-4-(1*H*)-one 48c (R = Cl)

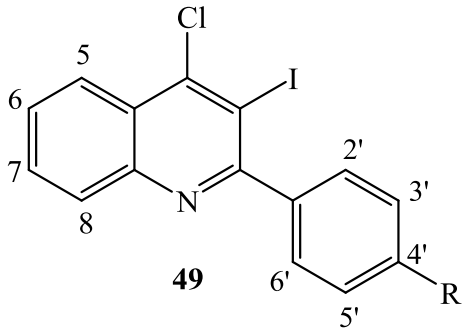
A procedure employed for the synthesis of **48a** was followed using a mixture of 2-(4-chlorophenyl)quinolin-(1*H*)-one **42c** (5.00 g, 19.56 mmol), iodine (9.93 g, 39.12 mmol) and sodium carbonate (3.11 g, 29.34 mmol) in THF (70 mL). Work up afforded **48c** as a solid (8.02 g, 93%), m.p. 213-214 ºC (lit. [69] 254-256 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 7.41 (1H, t, *J* 7.5 Hz, 6-H), 7.62-7.74 (6H, m, 2'-H and 6'-H, 3'-H and 5'-H, 7-H, 8-H), 8.14 (1H, d, *J* 7.5 Hz, 5-H), 12.32 (1H, s, N-H); ν_{max}/cm^{-1} 822, 1094, 1351, 1537, 1627, 2912, 3061, 3387.

4.4.4 Preparation of 2-(4-methoxyphenyl)-3-iodoquinolin-4-(1*H*)-one 48d (R = OMe)

procedure employed for the synthesis of **48a** was followed using a mixture of 2-(4-methoxyphenyl)quinolin-(1*H*)-one **42d** (5.00 g, 20.19 mmol), iodine (10.17 g, 39.82 mmol) and sodium carbonate (3.17, 29,87 mmol) in THF (70 mL). Work up afforded **48d** as a solid (10.41 g, 73%), m.p. 229-232 ºC (lit. [69] 262-264 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) 3.85 (3H, s, OCH_3), 7.12 (2H, d, *J* 9.0 Hz, 3'-H and 5'-H), 7.39 (1H, t, *J* 8.4 Hz, 6-H),7.67 (1H, t, *J* 8.4 Hz, 7-H), 7.93

(2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 8.10 (1H, d, *J* 7.5 Hz, 8-H), 8.67 (1H, d, *J* 8.4 Hz, 5-H), 12.35 (1H, s, N-H); ν_{max}/cm^{-1} 759, 1027, 1177, 1248, 1462, 1512, 1610, 2910, 3058, 3492.

4.5 Preparation of 2-aryl-4-chloro-3-iodoquinoline derivatives 49.



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2-Aryl-4-chloro-3-iodoquinolines **49a-d**

4.5.1 Preparation of 4-chloro-3-iodo-2-phenylquinoline 49a (R = H)

A stirred suspension of **48a** (3.00 g, 12.54 mmol) and $POCl_3$ (15 mL) in DMF (45 mL) was heated under reflux for 2 hours. The mixture was allowed to cool and then poured slowly and dropwise into ice-cold ammonia solution. The precipitate was filtered, and then extracted with chloroform. Dried over Mg_2SO_4 and the solvent was evaporated under reduced pressure to afford **49a** as a solid (1.55 g, 50%), m.p. 145-146 ºC (lit. [44] 150-153 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) 7.45-7.52 (2H, m, 3'-H, and 5'-H, 4'-H), 7.56-7.52 (2H, m, 2'-H and 6'-H), 7.63 (1H, dt, *J* 1.5 and 7.8 Hz, 6-H), 7.78 (1H, dt, *J* 1.5 and 5.7 Hz, 7-H) 8.12 (1H, d, *J* 9.0 Hz, 8-H), 8.29 (1H, d, *J* 9.9 Hz, 5-H); ν_{max}/cm^{-1} 763, 835, 1097, 1343, 1554.

4.5.2 Preparation of 4-chloro-3-iodo-2-(4-fluorophenyl)quinoline 49b (R = F)

A procedure employed for the synthesis of **49a** was followed using a mixture of 2-(4-fluorophenyl)-3-iodoquinolin-4-(1*H*)-one **48b** (4.22 g, 11.67 mmol) and $POCl_3$ (25 mL) in DMF (60 mL). Work up afforded **49b** as a solid (3.81 g; 89%), m.p. 159-162 ºC (lit. [44] 176-178 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) 7.47-7.66 (5H, m, 3'-H and 5'-H, 2'-H and 6'-H, 6-H), 7.79 (1H, t, *J* 7.5 Hz, 7-H), 8.12 (1H, d, *J* 7.8 Hz, 8-H), 8.29 (1H, d, *J* 7.8 Hz, 5-H); ν_{max}/cm^{-1} 758, 828, 1219, 1342, 1508, 1597.

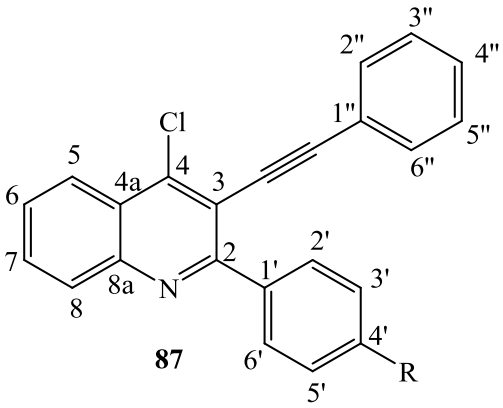
4.5.3 Preparation of 4-chloro-3-iodo-2-(4-chlorophenyl)quinoline 49c (R = Cl)

A procedure employed for the synthesis of **49a** was followed using a mixture of 2-(4-chlorophenyl)-3-iodoquinolin-4-(1*H*)-one **48c** (3.00 g, 10.92 mmol) and $POCl_3$ (15 mL) in DMF (45 mL). Work up afforded **49c** as a solid (2.00 g, 63%), m.p. 213-214 ºC (lit. [44] 218-220 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) 7.45-7.55 (4H, m, 3'-H and 5'-H, 2'-H and 6'-H), 7.65 (1H, dt, *J* 1.2 and 8.1 Hz, 6-H), 7.798 (1H, dt, *J* 1.2 and 8.4 Hz, 7-H), 8.10 (1H, d, *J* 9.0 Hz, 8-H), 8.29 (1H, d, *J* 9.3 Hz, 5-H); ν_{max}/cm^{-1} 825, 1090, 1344, 1474, 1559.

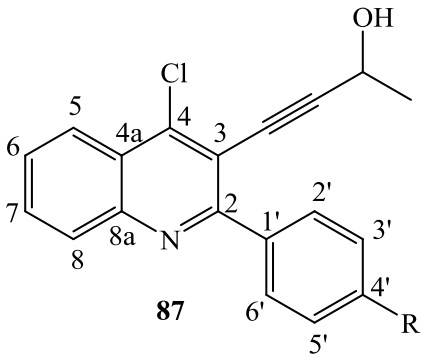
4.5.4 Preparation of 4-chloro-3-iodo-2-(4-methoxyphenyl)quinoline 49d (R = OMe)

A procedure employed for the synthesis of **49a** was followed using a mixture of 2-(4-methoxyphenyl)-3-iodoquinolin-4-(1*H*)-one **48d** (3.00 g, 11.15 mmol) and $POCl_3$ (15 mL) in DMF (45 mL). Work up afforded **49d** as a solid (1.00 g, 49%), m.p. 181-182 ºC (lit. [44] 185-187 ºC) ^{1}H NMR (300 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 7.00 (2H, d, *J* 7.5 Hz, 2'-H and 6'-H), 7.55-7.64 (3H, m, 3'-H 5'-H and 6-H), 7.77 (1H, t, *J* 7.5 Hz, 7-H), 8.10 (1H, d, *J* 9.0 Hz, 8-H), 8.26 (1H, d, *J* 9.0 Hz, 5-H); ν_{max}/cm^{-1} 759,825, 1032, 1175, 1254, 1518.

4.6 Preparation of 2-aryl-4-chloro-3-(alkynyl)quinoline derivatives 87



2-Aryl-4-Chloro-3-(2-phenylethynyl)-quinolines **87a-d**



2-Aryl-4-chloro-3-(3- hydroxybutynyl)-quinolines **87e-h**

4.6.1 Preparation of 4-chloro-3-(2-phenylethynyl)-2-phenylquinoline 87a (R = H)

The stirred mixture of 4-chloro-3-iodo-2-phenylquinoline **49a** (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 **87a** as a solid (0.69 g, 74%), m.p. 145-148 ºC, R_f (10% EtOAc-hexane) 0.44; ^{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", 5"), 128.96 (C-4"), 129.24 (C-6), 129.60 (C-3', 5'), 130.01 (C-8), 130.80 (C-7), 131.54 (C-2", 6"), 139.53 (C-1'), 145.08 (C-4), 146.87 (C-8a), 159.77 (C-2); ν_{max}/cm^{-1} 823, 1087, 1343, 14.47, 1595, 3057; *m/z* (100, MH^+) 340; HRMS (ES): MH^+, found 340.0888. [$C_{23}H_{15}N^{35}Cl^+$] required 340.0893.

4.6.2 Preparation of 4-chloro-2-(4-fluorophenyl)-3-(2-phenylethynyl)-quinoline 87b (R = F)

A procedure employed for the synthesis of **87a** was followed using a mixture of 4-chloro-3-iodo-2-(4-fluorophenyl)quinoline **49b** (0.50 g, 1.303 mmol), $PdCl_2(PPh_3)_2$ (0.046 g, 0.065 mmol), CuI (0.012 g, 0.065 mmol) and phenylacetylene (0.20 mL, 1.56 mmol) in Et_3N (10 mL). Work up and column chromatography afforded **87b** as a solid (0.30 g, 64%), m.p. 175-178 ºC. R_f (10% EtOAc-hexane) 0.42; ^1H NMR (300 MHz, $CDCl_3$) 7.19-7.44 (7H, m, 3'-H and 5'-H, 3"-H and 5"- H, 2"-H and 6"-H, 4"-H), 7.65 (1H, t, *J* 8.1 Hz, 6-H), 7.77 (1H, t, *J* 8.4 Hz, 7-H), 8.05 (2H, t, *J* 8.2 Hz, 2'-H and 6'-H), 8.13 (1H, d, *J* 8.4 Hz, 8-H), 8.27 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 85.33 (-**C**≡C-Ph), 100.63 (-C≡**C**-Ph), 114.90 (d, $^2J_{CF}$ 21.3 Hz, C-3', 5'), 116.12 (C-3), 122.48 (C-4a), 124.33 (C-5), 124.75 (C-1"), 127.94 (C-6), 128.45 (C-3", 5"), 129.07 (C-4"), 129.86 (C-8), 130.90 (C-7), 131.47 (C-2", 6"), 131.62 (d, $^3J_{CF}$ 8.8 Hz, C-2', 6'), 135.51 (d, $^4J_{CF}$ 2.8 Hz, C-1′), 146.72 (C-4), 158.44 (C-8a), 161.84 (C-2), 165.15 ($^1J_{CF}$ 247.6 Hz, C-4'); ν_{max}/cm^{-1} 757, 837, 1153, 1231, 1512, 1559, 1601, 3064; *m/z* (100, MH^+) 358; HRMS (ES): MH^+, found 358.0786. [$C_{23}H_{14}NF^{35}Cl^+$] required 358.0799.

4.6.3 Preparation of 4-chloro-2-(4-chlorophenyl)-3-(2-phenylethynyl)quinoline 87c (R = Cl)

A procedure employed for the synthesis of **87a** was followed using a mixture of 4-chloro-3-iodo-2-(4-chlorophenyl)quinoline **49c** (0.40 g, 1.00 mmol), $PdCl_2(PPh_3)_2$, (0.035 g, 0.05 mmol), CuI (0.011 g, 0.05 mmol) and phenylacetylene (0.20 mL, 1.20 g) in Et_3N (10 mL). Work up and column

chromatography afforded **87c** as a solid (0.25 g, 67%), m.p. 179-180 °C, R_f (10% EtOAc-hexane) 0.69; ^{1}H NMR (300 MHz, $CDCl_3$), 7.34-7.39 (3H, m, 3''-H, 4''-H and 5''-H), 7.42-7.52 (4H, m, 2''-H and 6''-H, 3'-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), 8.01 (1H, d, *J* 8.4 Hz, 8-H), 8.13 (2H, d, *J* 8.2 Hz, 2'-H and 6'-H), 8.27 (1H, dd, *J* 0.9 and 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 85.18 (-**C**≡C-Ph), 100.78(-C≡**C**-Ph), 116.07 (C-3), 122.46 (C-4a), 124.38 (C-5), 124.86 (C-1''), 128.09 (C-4''), 128.15 (C-3'', 5''), 128.50 (C-2', 6'), 129.14 (C-6), 129.94 (C-7), 130.97 (C-8), 131.04 (C-3', 5'), 131.51 (C-2'', 6''),135.46 (C-4'), 137.88 (C-1'), 145.42 (C-4), 146.79 (C-8a), 158.26 (C-2); ν_{max}/cm^{-1} 823, 1087, 1472, 1491, 1560, 1595, 3056; *m/z* (100, MH^+) 374; HRMS (ES): MH^+, found 374.0500. [$C_{23}H_{14}N^{35}Cl_2^+$] required 374.0503.

4.6.4 Preparation of 4-chloro-2-(4-methoxyphenyl)-3-(2-phenylethynyl)quinoline 87d (R = OMe)

A procedure employed for the synthesis of **87a** was followed using a mixture of 4-chloro-3-iodo-2-(4-methoxyphenyl)quinoline **49c** (0.52 g, 1.370 mmol) $PdCl_2(PPh_3)_2$, (0.048 g, 0.069 mmol), CuI (0.01 g, 0.069 mmol) and phenylacetylene (0.20 mL, 1.64 mmol) in Et_3N (10 mL). Work up and column chromatography afforded **87d** as a solid (0.34 g, 70%), m.p. 120-122 °C, R_f (10% EtOAc-hexane) 0.31; ^{1}H NMR (300 MHz, $CDCl_3$) 3.90 (3H, s, OCH_3), 7.05 (2H, d, *J* 9.3 Hz, 3'-H and 5'-H), 7.34-7.36 (3H, m, 3'-H, 4''-H and 5''-H), 7.46-7.49 (2H, m, 2''-H and 6''-H), 7.62 (1H, dt, *J* 1.5 and 7.8 Hz, 6-H), 7.75 (1H, dt, *J* 1.5 and 7.8 Hz, 7-H), 8.05 (2H, d, *J* 9.3 Hz, 2'-H and 6'-H), 8.12 (1H, td, *J* 0.6 and 9.3 Hz, 8-H), 8.24 (1H, td, *J* 0.6 and7.8 Hz, 5-H); ^{13}C NMR (75MHz, $CDCl_3$) 55.42 (OCH_3), 85.77 (-**C**≡C-Ph), 100.37(-C≡**C**-Ph), 113.34 (C-3', 5'), 116.10 (C-3), 122.77 (C-4a), 124.33 (C-5), 124.60 (C-1′), 127.59 (C-6), 128.42 (C-3'', 5''), 128.95 (C-4''), 129.84 (C-8), 130.74 (C-7), 131.17 (C-2', 6'), 131.56 (C-2'', 6''), 132.06 (C-1'), 145.21 (C-4), 146.89 (C-8a), 159.10 (C-4'), 160.59 (C-2);

ν_{max}/cm^{-1} 824, 1176, 1246, 1514, 1607, 2203, 3055; *m/z* (100, MH^+) 370; HRMS (ES): MH^+, found 370.1012. [$C_{24}H_{17}N^{35}ClO^+$] required 370.0999.

4.6.5 Preparation of 4-chloro-3-(3-hydroxybutynyl)-2-phenylquinoline 87e (R = H)

A procedure employed for the synthesis of **87a** was followed using a mixture of 4-chloro-3-iodo-2-phenylquinoline **49a** (0.30 g, 0.82 mmol), 3-butyn-2-ol (0.10 mL, 0.98 mmol), CuI (0.01 g, 0.014 mmol), and $PdCl_2(PPh_3)_2$ (0.03 g, 0.041 mmol) in Et_3N (8 mL) wake up and column chromatography afforded **87e** as a solid (0.16 g, 64%), m.p. 106-110 ºC, R_f (30% EtOAc-hexane) 0.53; ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.6 Hz, CH_3), 1.90 (1H, d, *J* 5.4 Hz, OH), 4.72 (1H, q, *J* 6.3 Hz, C**H**(OH)CH_3), 7.46-7.50 (3H, m, 3'-H and 5'- H,4′-H), 7.64 (1H, dt, *J* 1.2 and 8.1 Hz, 6-H), 7.76 (1H, dt, *J* 1.5 and 8.1 Hz, 7-H), 7.90 (2H, dt, *J* 1.8 and 7.8 Hz, 2'-H and 6'-H), 8.13 (1H, dd, *J* 0.6 and 9.3 Hz, 8-H), 8.22 (1H, td, *J* 0.9 and 9.6 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.73 (CH_3), 58.98 (**C**H(OH)CH_3), 79.75 (-**C**≡C-Ph), 102.18 (-C≡**C**-Ph), 115.60 (C-3), 124.36 (C-5), 124.65 (C-4a), 127.91 (C-3', 5'),128.18 (C-4'),129.27 (C-6), 129.48 (C-2', 6'), 129.95 (C-7), 130.98(C-8), 139.35 (C-1'), 145.56 (C-4), 146.89 (C-8a), 159.81 (C-2); ν_{max}/cm^{-1} 834, 1067, 1343, 1476, 1562, 3066, 3225; *m/z* (100, MH^+) 308; HRMS (ES): MH^+, found 308.0852. [$C_{19}H_{15}NO^{35}Cl^+$] required 308.0842.

4.6.6 Preparation of 4-chloro-2-(4-fluorophenyl)-3-(3-hydroxybutynyl)-quinoline 87f (R = F)

A procedure employed for the synthesis of **87a** was followed using a mixture of 4-chloro-3-iodo-2-(4-fluorophenyl)quinoline **49b** (0.25 g, 0.65 mmol), $PdCl_2(PPh_3)_2$ (0.023 g, 0.033 mmol), CuI (0.01 g, 0.033 mmol) and 3-buty-2-ol (0.10 mL, 0.78 mmol) in Et_3N (10 mL). Work up and column chromatography afforded **87f** as a solid (0.13 g, 61%), m.p. 152-155 °C, R_f (30% EtOAc-hexane) 0.59; ^{1}H NMR (300 MHz, $CDCl_3$) 1.49 (3H, d, *J* 6.6 Hz, CH_3), 2.01 (1H, d, *J* 5.4 Hz, OH), 4.75 (1H,

q, *J* 6.6 Hz, C**H**(OH)CH_3), 7.17 (2H, t, *J* 9.0 Hz, 3'-H and 5'- H), 7.65 (1H, dt, *J* 1.2 and 8.1 Hz, 6-H), 7.77 (1H, dt, *J* 1.2 and 8.4 Hz, 7-H), 7.91- 7.95 (2H, m, 2'-H and 6'-H), 8.11 (1H, dd, *J* 0.3 and 8.1 Hz, 8-H), 8.22 (1H, dd, *J* 0.9 and 9.3 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.79 (CH_3), 58.94 (**C**H(OH)CH_3), 79.76 (-**C**≡C-Ph), 102.32 (-C≡**C**-Ph), 114.91 (d, $^2J_{CF}$ 21.7 Hz, C-3',5') 115.38 (C-3), 124.38 (C-5), 124.63 (C-4a), 128.02 (C-6), 129.85 (C-8), 131.10 (C-7), 131.53 ($^3J_{CF}$ 8.6 Hz, C-2', 6'), 135.35 ($^4J_{CF}$ 3.2 Hz, C- 1'), 145.85 (C-4), 146.82 (C-8a), 158.55 (C-2), 163.48 (d, $^1J_{CF}$ 247.8 Hz, C-4'); ν_{max}/cm^{-1} 756, 832, 1226, 1341, 1513, 1601, 2980, 3298; *m/z* (100, MH^+) 326; HRMS (ES): MH^+, found 326.0763. [$C_{19}H_{14}FNO^{35}Cl^+$] required 326.0748.

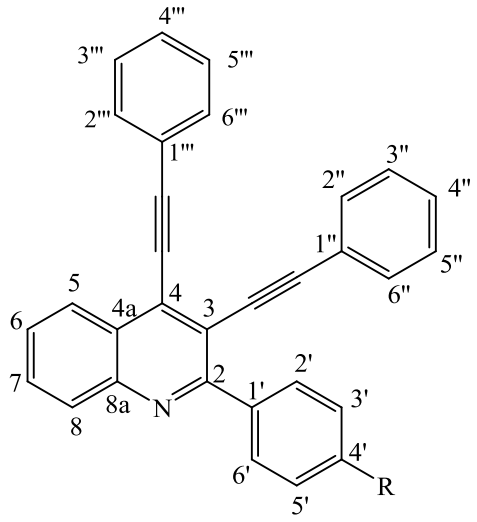
4.6.7 Preparation of 4-chloro-2-(4'-chlorophenyl)-3-(3'-hydroxybutyn-1-yl)-quinoline 87g (R = Cl)

The similar procedure employed for the synthesis of **87a** was followed using a mixture of 4-chloro-3-iodo-2-(4-chlorophenyl)quinoline **49c** (0.25 g, 0.63 mmol), $PdCl_2(PPh_3)_2$ (0.022 g, 0.031 mmol), CuI (0.01 g, 0.031 mmol) and 3-Buty-2-ol (0.10 mL, 0.75 mmol) in Et_3N (10 ml). Work up and column chromatography afforded **87g** as solid (0.14 g, 66%), m.p. 168-172 °C, R_f (30% EtOAc-hexane) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$) 1.51 (3H, d, *J* 6.0 Hz, CH_3), 1.91 (1H, d, *J* 4.8 Hz, OH), 4.75 (1H, q, *J* 6.3 Hz, -C**H**(OH)CH_3), 7.46 (2H, d, *J* 7.8 Hz, 3'-H and 5'- H), 7.65 (1H, dt, *J* 1.5 and 7.5 Hz, 6-H), 7.77 (1H, dt, *J* 1.5 and 6.0 Hz, 7-H), 7.89 (2H, d, *J* 7.5 Hz, 2'-H and 6'-H), 8.11 (1H, d, *J* 9.3 Hz, 8-H), 8.23 (1H, dd, *J* 0.9 and 7.8 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.78 (CH_3), 58.94 (**C**H(OH)CH_3), 79.62 (-**C**≡C-Ph), 102.43 (-C≡**C**-Ph), 115.29 (C-3), 124.38 (C-5), 124.64 (C-4a), 128.13 (C-3', 5' and C-6), 129.89 (C-7), 130.92 (C-2', 6'), 131.14 (C-8), 135.48 (C-4'), 137.65 (C- 1'), 145.93 (C-4), 146.83 (C-8a), 158.33 (C-2); ν_{max}/cm^{-1} 753, 824, 1340, 1473, 1595, 2980, 3303; *m/z* (100, MH^+) 342; HRMS (ES): MH^+, found 342.0454. [$C_{19}H_{14}NO^{35}Cl_2^+$] required 342.0452.

4.6.8 Preparation of 4-chloro-2-(4-methoxyphenyl)-3-(3-hydroxybutynyl)-quinoline 87h (R = OMe)

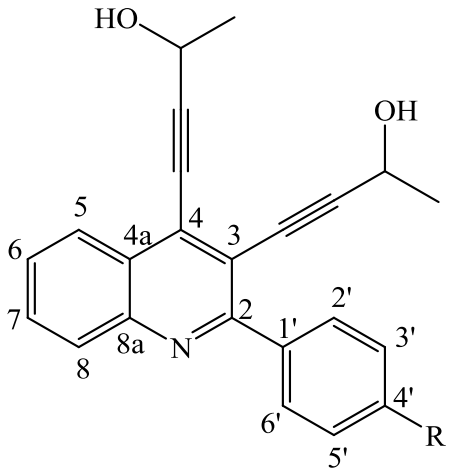
A procedure employed for the synthesis of **88a** was followed using a mixture of 4-chloro-3-iodo-2-(4-fluorophenyl)quinoline **49d** (0.40 g, 1.01 mmol), $PdCl_2(PPh_3)_2$ (0.036 g, 0.051 mmol), CuI (0.01 g, 0.051 mmol) and 3-Buty-2-ol (0.10 ml, 1.21 mmol) in Et_3N (10 mL). Work up and column chromatography afforded **87h** as a solid (0.20 g, 65%), m.p. 118-121 °C, R_f (30% EtOAc-hexane) 0.42; ^{1}H NMR (300 MHz, $CDCl_3$) 1.50 (3H, d, *J* 6.6 Hz, CH_3), 2.16 (1H, d, *J* 5.7 Hz, OH), 3.86 (3H, s, OCH_3), 4.75 (1H, q, *J* 6.6 Hz, -C**H**(OH)CH_3), 7.46 (2H, d, *J* 9.0 Hz, 3′-H and 5′- H), 7.65 (1H, dt, *J* 1.5 and 8.4 Hz, 6-H), 7.77 (1H, dt, *J* 1.5 and 8.4 Hz, 7-H), 7.92 (2H, d, *J* 8.7 Hz, 2′-H and 6′-H), 8.10 (1H, dd, *J* 0.3 and 8.1 Hz, 8-H), 8.18 (1H, dd, *J* 0.3 and 9.9 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.74 (CH_3), 55.32 (OCH_3), 58.82 (OH), 79.97 (-**C**≡C-Ph), 102.18 (-C≡**C**-Ph), 113.21 (C-3', 5'), 115.32 (C-3), 124.23 (C-5), 124.34 (C-4a), 127.54 (C-6), 129.66 (C-8),130.82 (C-7), 131.05 (C-2', 6'), 131.71 (C-1'), 145.63 (C- 4), 146.79 (C-8a), 159.06 (C-4'), 160.51 (C-2); ν_{max}/cm^{-1} 824, 1174, 1253, 1343, 1516, 1607, 2929, 3176; *m/z* (100, MH^+) 338; HRMS (ES): MH^+, found 338.0953. [$C_{20}H_{17}NO_2{}^{35}Cl^+$] required 338.0948.

4.7 Preparation of 2-aryl-3,4-bis(alkynyl)quinoline derivatives 88



2-Aryl-3,4-bis(2-phenylethynyl)quinolines

88a-d



2-Aryl-3,4-bis(3-hydroxybutynl)quinolines

88e-g

4.7.1 Preparation of 2-aryl-3,4-bis(2-phenylethynyl)quinoline 88a (R = H)

The stirred mixture of 4-chloro-3-iodo-2-phenylquinoline **49a** (0.15 g, 0.41 mmol), phenylacetylene (0.2 mL, 1.03 mmol), CuI (0.04 g, 0.021 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.021 mmol) and Et_3N (0.12 mL, 1.20 mmol) in 3:1 dioxane-water (10 ml) in a flask equipped with a reflux condenser was flushed with nitrogen. The reaction mixture was heated at 80 °C under nitrogen atmosphere for 18 hours. The mixture was allowed to cool and then quenched with ice-cold water. The resulting precipitate was extracted with ethylacetate and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to afford **88a** as a solid (0.12g, 72%), m.p. 184-185 °C, R_f (10% EtOAc-hexane) 0.44; ^{1}H NMR (300 MH z, $CDCl_3$) 7.31-7.33 (3H, m, 3″-H, 5″-H and 4″-H), 7.33-7.45 (5H, m, 2″-H and 6″-H, 2‴-H and 6‴-H, 4′-H), 7.50-7.58 (3H, m, 3‴-H and 5‴-H, 4‴-H), 7.64 (1H, t, *J* 8.4 Hz, 6-H), 7.72-7.78 (3H, m, 3´-H, 5´-H and 7-H), 8.06 (2H, dd, *J* 2.1 and 1.5 Hz, 2´-H and 6´-H), 8.16 (1H, d, *J* 8.4 Hz, 8-H), 8.38 (1H, d, *J* 8.4 Hz, 5-H);

^{13}C NMR (75 MHz, $CDCl_3$) 85.31 and 87.83 (-**C**≡C-Ph), 99.35 and 103.33 (-C≡**C**-Ph), 118.27 (C-3), 122.51 (C-4a), 123.09 (C-1″, 1‴), 125.90 (C-5), 127.52 (C-6), 127.92 (C-3′, 5′), 128.41 (C-3‴, 5‴), 128.63 (C-3″, 5″), 128.75 (C-4″, 4‴), 129.48 (C-7), 129.61 (C-2′, 6′), 129.97 (C-8), 130.41 (C-4′), 131.42 (C-2″, 6″), 132.06 (C-2‴, 6‴), 133.06 (C-4), 139.75 (C-1′), 146.31 (C-8a), 159.28 (C-2); ν_{max}/cm^{-1} 822, 1234, 1350, 1474, 1562, 2212, 3052; *m/z* (100, MH^+) 406; HRMS (ES): MH^+, found 406.1590. [$C_{31}H_{20}N^+$] required 406.1596.

4.7.2 Preparation of 3,4-bis(2-phenylethynyl)-2-(4-fluorophenyl)quionoline 88b(R = F)

The experimental procedure employed for the synthesis of **88a** was followed using a mixture of 4-chloro-3-iodo-2-(4-fluorophenyl)quinoline **49b** (0.15 g, 0.39 mmol), $PdCl_2(PPh_3)_2$ (0.02 g, 0.020 mmol), CuI (0.004 g, 0.020 mmol), phenylacetylene (0.20 mL, 0.98 mmol) and Et_3N (0.2 mL, 1.17 mmol) in 3:1 dioxane-water (10 ml).Workup and column chromatography afforded **89b**, as a solid (0.11 g, 67%), m.p. 153-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$), 7.20 (2H, m, 3′-H and 5′-H), 7.33-7.39 (6H, m, 3″-H and 5″-H, 3‴-H and 5‴-H, 4″-H and 4‴-H), 7.42-7.46 (2H, dd, *J* 2.4 and 6.0 Hz, 2″-H and 6″-H), 7.51-7.54 (2H, dd, *J* 2.4 and 1.8 Hz, 2‴-H, 6‴-H), 7.6,6 (1H, t, *J* 8.4 Hz, 6-H), 7.77 (1H, t, *J* 8.4 Hz, 7-H), 8.02-8.06 (2H, m, 2′-H and 6′-H), 8.13 (1H, d, *J* 8.4 Hz), 8.27 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 73.86 and 81.52 (-**C**≡C-Ph), 85.32 and 100.65 (-C≡**C**-Ph), 114.94 (d, $^2J_{CF}$ 21.6 Hz, C-3',5'), 116.16 (C-3), 121.75 (C-1″), 122.50 (C-4a), 124.38 (C-5), 124.80 (C-1‴), 127.99 (C-6), 128.43 (C-3″, 5″), 128.49 (C-3‴,5‴)129.11 (C-4″, 4‴), 129.20 (C-2″, 6″), 129.89 (C-7), 130.96 (C-8), 131.50 (C-2‴, 6‴), 131.63 ($^3J_{CF}$ 8.6 Hz, C-2', 6'), 132.49 (C-2″, 6″), 135.55 ($^4J_{CF}$ 3.2 Hz, C- 1'), 145.32 (C-4), 146.76 (C-8a), 158.51 (C-2), 163.59 (d, $^1J_{CF}$ 247.4 Hz, C-4'); ν_{max}/cm^{-1} 827, 1227, 1343, 1511, 1599, 2214, 3050; *m/z* (100, MH^+) 424; HRMS (ES): MH^+, found 424.1501. [$C_{31}H_{19}FN^+$] required 424.1553.

4.7.3 Preparation of 2-(4-chlorophenyl)-3,4-bis(2-phenylethyn-1-yl)quinoline 88c (R = Cl)

The experimental procedure employed for the synthesis of **88a** was followed using a mixture of 4-chloro-3-iodo-2-(4-chlorophenyl)quinoline **49c** (0.15 g, 0.38 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.018 mmol), CuI (0.004 g, 0.018 mmol) and phenylacetylene (0.10 mL, 0.95 mmol), Et_3N (0.20 ml, 1.14 mmol) in 3:1 dioxane-water (10 mL). Workup and column chromatography afforded **88c** as a solid (0.14 g, 85%), m.p. 162-164 °C, R_f (10% EtOAc-hexane) 0.46; ^{1}H NMR (300 MHz, $CDCl_3$) 7.33-7.37 (3H, m, 3″-H, 5″-H and 4″-H), 7.41-7.43 (5H, m, 2″-H and 6″-H, 2‴-H and 6‴-H, 6-H), 7.51 (2H, d, *J* 11.1 Hz, 3′-H and 5′-H), 7.65 (1H, t, *J* 6.9 Hz, 7-H), 7.71-7.78 (3H, m, 3‴-H, 5‴-H and 4‴-H), 8.03-8.06 (2H, m, 2′-H and 6′-H), 8.13 (1H, d, *J* 8.4 Hz, 8-H), 8.38 (1H, d, *J* 9.3 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 85.31 and 87.83 (-**C**≡C-Ph), 99.35 and 103.33 (-C≡**C**-Ph), 118.27 (C-3), 122.51 (C-4a), 123.09 (C-1″, 1‴), 125.90 (C-5),127.52(C-6), 127.92 (C-3′, 5′), 128.41 (C-3‴, 5‴), 128.63 (C-3″, 5″), 128.75 (C-4″, 4‴), 129.48 (C-7), 129.61 (C-2′, 6′), 129.97 (C-8), 130.41 (C-4′), 131.42 (C-2″, 6″), 132.06 (C-2‴, 6‴), 133.06 (C-4), 139.75 (C-1′), 146.31 (C-8a), 159.28 (C-2); ν_{max}/cm^{-1} 827, 1087, 1492, 1596, 2204, 3056; *m/z* (100, MH^+) 440; HRMS (ES): MH^+, found 440.1227. $[C_{31}H_{19}N^{35}Cl^+]$ required 440.1206.

4.7.4 Preparation of 2-(4-methoxyphenyl)-3,4-bis(2-phenylethynyl)quinoline 88d (R = OMe)

The experimental procedure employed for the synthesis of **88a** was followed using a mixture of 4-chloro-3-iodo-2-(4-methoxyphenyl)quinoline **49d** (0.15 g, 0.38 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.018 mmol), CuI (0.004 g, 0.0018 mmol) and phenylacetylene (0.1 mL, 0.95 mmol), Et_3N (0.2 mL, 1.14 mmol) in 3:1dioxane- water (10 mL). Workup and column chromatograph afforded **88d** as a solid (0.13 g, 79%), m.p. 134-137 °C, R_f (10% EtOAc-hexane) 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) 3.90 (3H, s, OCH_3), 7.07(2H, d, *J* 6.9 Hz, 3′-H and 5′-H), 7.31-7.34 (3H, m, 3″-H and 5″-H, 4″-H), 7.41-

7.49 (5H, m, 2″-H and 6″-H, 2‴-H and 6‴-H, 6-H), 7.61 (1H, t, *J* 8.1 Hz, 7-H), 7.71-7.76 (3H, 3‴ and 5‴-H, 4‴-H), 8.10-8.14 (3H, m, 2′-H and 6′-H, 8-H), 8.34 (1H, d, *J* 9.0 Hz 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 55.36 (OCH_3), 85.38 and 88.06 (-**C**≡C-Ph), 99.18 and 102.88 (-C≡**C**-Ph), 113.27 (C-3), 117.96 (C-3′, 5′), 122.50 (C-1″), 123.13 (C-1‴), 125.65 (C-4a), 125.81 (C-6), 127.19 (C-4″), 128.38 (C-4‴), 128.56 (C-3″, 5″), 128.68 (C-3‴, 5‴), 129.39 (C-5), 129.75 (C-7), 130.29 (C-8), 131.12 (C-2‴, 6‴), 131.40 (C-2″, 6″), 131.96 (C-2′, 6′), 132.28 (C-1′), 133.14 (C-4), 146.31 (C-8a), 158.51 (C-4′),160.39 (C-2); ν_{max}/cm^{-1} 823, 1246, 1491, 1515, 1608, 2330, 3055; *m/z* (100, MH^+) 436; HRMS (ES): MH^+, found 436.1700. [$C_{32}H_{22}NO^+$] required 436.1701.

4.7.5 Preparation of 2-aryl-3,4-bis(3-hydroxybutynyl)quinoline 88e (R = H)

The experimental procedure employed for the synthesis of **88a** was followed using 4-chloro-3-iodo-2-phenylquinoline **49a** (0.20 g, 0.55 mmol), 3-butyn-2-ol (0.10 mL, 1.38 mmol), CuI (0.005 g, 0.027 mmol), $PdCl_2(PPh_3)_2$ (0.02 g, 0.027 mmol), Et_3N (0.23 mL, 1.64 mmol) in 3:1 dioxane-water (20 mL) Workup and column chromatography afforded **88e** as a solid to afford (0.03g, 16%), m.p. 98-100 °C, R_f (30% EtOAc-hexane) 0.47; ^{1}H NMR (300 MHz $CDCl_3$) 1.44 (6H, dd, *J* 6.6 and 6.6 Hz, CH_3), 2.03 (2H, s, OH), 4.56 (1H, q, *J* 6.6 Hz, -C**H**(OH)CH_3), 4.69 (1H, q, *J* 6.9 Hz, -C**H**(OH)CH_3),7.46-7.49 (3H, m, 3′-H and 5′- H, 4′-H), 7.64 (1H, t, *J* 8.4 Hz, 6-H), 7.76 (1H, t, *J* 6.9 Hz, 7-H), 7.88-7.920 (2H, m, 2′-H and 6′-H), 8.13 (1H, d, *J* 9.6 Hz, 8-H), 8.23 (1H, d, *J* 9.9 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.71 and 23.78 (CH_3), 58.90 and 58.98 (-CH(OH)CH_3), 69.62 and 78.56 (-**C**≡C-Ph), 80.32 and 102.43 (-C≡**C**-Ph),115.29 (C-3), 124.38 (C-5), 124.64 (C-4a), 127.13 (C-3′, 5′), 128.87 (C-6), 129.89 (C-7), 130.92 (C-2′, 6′), 131.54 (C-8), 135.48 (C-4′), 137.65 (C- 1’), 145.93 (C-4), 146.83 (C-8a), 158.33 (C-2); ν_{max}/cm^{-1} 834, 917, 1106, 1344, 1477, 1562, 2983, 3264; *m/z* (100, MH^+) 338; HRMS (ES): MH^+, found 338.100. [$C_{23}H_{20}NO_2^+$] required 338.101.

4.7.6 Preparation of 2-(4-chlorophenyl)-3,4-bis(3-hydroxybutynyl)quinoline 88f (R = Cl)

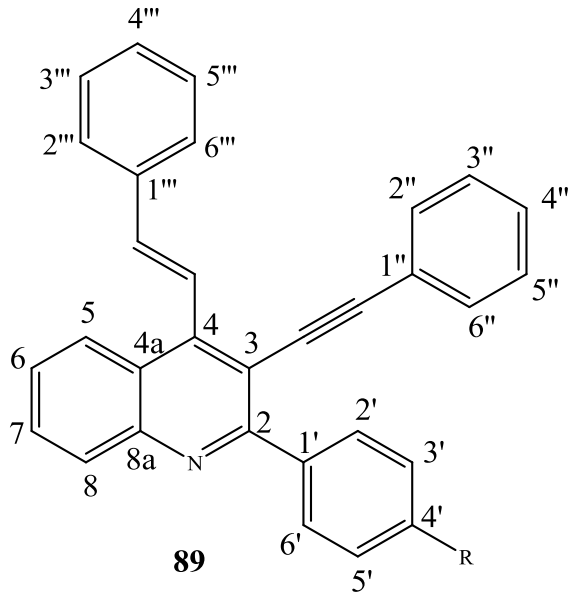
The experimental procedure employed for the synthesis of **88a** was followed using a mixture of 4-chloro-3-iodo-2-(4-chlorophenyl)quinoline **49c** (0.60 g, 1.50 mmol), $PdCl_2(PPh_3)_2$ (0.053 g, 0.075 mmol), CuI (0.014 g, 0.075 mmol) and 3-butyn-2-ol (0.1mL, 3.75 mmol) , Et_3N (0.1 mL, 1.14 mmol) in 3:1 dioxane-water (20 ml). Workup and column chromatography afforded **88f** as a solid (0.50 g, 90%), m.p. 162-164 °C; R_f (30% EtOAc-hexane) 0.59; ^{1}H NMR (300 MHz $CDCl_3$) 1.49 (6H, dd, *J* 6.6 and 6.6 Hz, CH_3), 1.86 (2H, dd,*J* 5.4 and 5.4 Hz, OH), 4.592 (1H, q, *J* 6.3 Hz, -C**H**(OH)CH_3), 4.754 (1H, q, *J* 6.6 Hz, -C**H**(OH)CH_3),7.46 (2H, d, *J* 8.7 Hz, 3′-H and 5′- H,), 7.65 (1H, t, *J* 8.4 Hz, 6-H), 7.77 (1H, t, *J* 8.1 Hz, 7-H), 7.90 (2H, d, *J* 9.0 Hz, 2′-H and 6′-H), 8.11 (1H, d, *J* 8.7 Hz, 8-H), 8.24 (1H, d, *J* 9.9 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.77 and 23.88 (CH_3), 58.63 and 58.93 (OH), 68.03 and 79.61 (-**C**≡C-Ph), 81.20 and 102.46 (-C≡**C**-Ph),115.31 (C-3), 124.38 (C-5), 124.69 (C-4a), 128.13 (C-3′, 5′ and C-6),129.86 (C-7),130.92 (C-2′, 6′), 131.17 (C-8), 135.49 (C-4′), 137.63 (C- 1′), 145.93 (C-4), 146.81 (C-8a), 158.35 (C-2); ν_{max}/cm^{-1} 824, 1087, 1473, 1560, 2981, 3380; *m/z* (100, MH^+) 376; HRMS (ES): MH^+, found 376.1207. [$C_{23}H_{19}NO_2{}^{35}Cl^+$] required 376.1211.

4.7.7 Preparation of 2-(4-methoxyphenyl)-3,4-bis(3-hydroxybutynyl)quinoline 88g (R = OMe)

The experimental procedure employed for the synthesis of **88a** was followed using a mixture of 4-chloro-3-iodo-2-(4-methoxyphenyl)quinoline **49d** (0.18 g, 0.455 mmol), $PdCl_2(PPh_3)_2$ (0.016 g, 0.0228 mmol), CuI (0.004 g, 0.0228 mmol) and 3-butyn-2-ol (0.1 mL, 1.14 mmol) , NEt_3 (0.2 mL, 1.37 mmol) in 3:1 dioxane-water (20 mL). Workup and column chromatography afforded **88g** as a solid (0.08 g, 47%), m.p. 100-106 °C; R_f (30% EtOAc-hexane) 0.50; ^{1}H NMR (300 MHz $CDCl_3$) 1.43-1.52 (6H, dd, *J* 6.6 and 6.6 Hz, CH_3), 2.03 (2H, OH), 3.87 (3H, s, OCH_3), 4.54 (1H, q, *J* 6.6 Hz, -C**H**(OH)CH_3), 4.72 (1H, q, *J* 6.6 Hz, -C**H**(OH)CH_3), 6.99 (2H, d, *J* 8.7 Hz, 3′-H and 5′- H,), 7.57

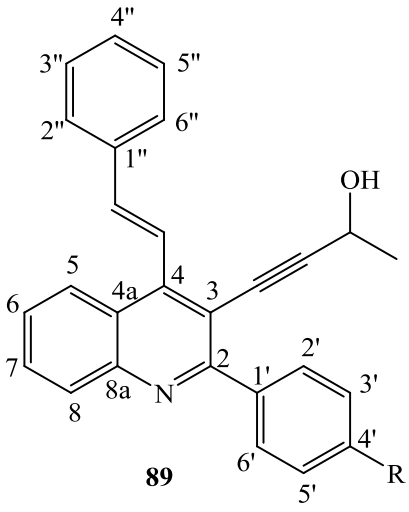
(1H, t, *J* 8.1 Hz, 6-H), 7.73 (1H, t, *J* 7.5 Hz, 7-H), 7.92 (2H, d, *J* 8.7 Hz, 2′-H and 6′-H), 8.10 (1H, d, *J* 8.4 Hz, 8-H), 8.20 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.73 and 23.80 (CH_3), 55.32 (OCH_3), 58.37 and 58.79 (OH), 67.03 and 79.91 (-**C**≡C-Ph), 81.23 and 102.21 (-C≡**C**-Ph),113.21 (C-3′, 5′), 115.35 (C-3), 124.69 (C-4a), 124.22 (C-6),127.56 (C-5), 129.57 (C-7) 130.86 (C-8), 131.06 (C-2′, 6′), 131.62 (C- 1′), 145.68 (C-4), 146.71 (C-8a), 159.10 (C-4′), 160.49 (C-2); ν_{max}/cm^{-1} 826, 1176, 1254, 1516, 1607, 2229, 2980, 3214; *m/z* (100, MH^+) 375; HRMS (ES): MH^+, found 375.1227. [$C_{23}H_{22}NO_2^+$] required 375.1230.

4.8 Preparation of 2-aryl-3-(alkynyl)-4-phenylethenylquinoline derivatives 89



89

2-Aryl-3-(alkynyl)-4-phenylethenylquinolines **89a-c**



89

2-Aryl-3-(3-hydroxybutynyl)-4-phenylethenylquinoline **89d**

4.8 1 Preparation of 2-aryl-3-(2-phenylethynyl)-4-phenylethenylquinoline 89a (R = H)

The stirred mixture of 4-chloro-3-(2-phenylethynyl)-2-phenylquinoline **87a** (0.10 g, 0.29 mmol), *trans*-2-phenylvinylboronic acid (0.05 g, 0.35 mmol), K_2CO_3 (0.081 g, 0.59 mmol), tricyclohexylphosphine (0.01 g, 0.029 mmol) and $Pd(PPh_3)_4$ (0.02 g, 0.002 mmol) in 3:1 dioxane-water (20 mL) in a flask equipped with a reflux condenser was flushed with nitrogen. The reaction mixture was heated at 80 °C under nitrogen atmosphere for 18 hours. The mixture was allowed to cool and then quenched with ice-cold water, and extracted with chloroform and dried over Mg_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to afford **89a** as a solid (0.11g, 92%), m.p. 183-185 °C, R_f (30% EtOAc-hexane) 0.63; ^{1}H NMR (300 MHz $CDCl_3$) 7.27-7.30 (5H, m, 3″-H and 5″-H, 3‴-H and 5‴-H, 4‴-H), 7.37-7.62 (8H, m, 3′-H and 5′-H, 2″-H and 6″-H, 2‴-H and 6‴-H, 4′-H, 4″-H), 7.69-7.83 (4H, m, 6-H, 7-H, -C**H**=C**H**-), 8.02 (2H, dd, *J* 1.8 and 1.8, 2′-H and 6′-H), 8.19 (1H, dd, *J* 1.2 and 8.7 Hz, 8-H), 8.29 (1H, td, *J* 1.2 and 9.6 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 87.90 (-**C**≡C-Ph), 99.86 (-C≡**C**-Ph), 114.10 (C-3), 123.13 (C-4a), 123.40 (C-5), 124.781 (C-1″), 125.01 (C-6), 126.94 (C-2′, 6′, 4‴), 127.84 (C-3", 5"), 128.36 (C-3‴, 5‴), 128.53 (-**C**H=CH-), 128.53 (C-4′, 4″), 128.95 (C-2‴, 6‴), 129.68 (C-3', 5'), 129.96 (C-7), 130.28 (C-8), 131.19 (C-2", 6"), 136.75 (C-1‴), 138.79 (-CH=**C**H-), 140.35 (C-1'), 146.66 (C-4), 146.94 (C-8a), 160.02 (C-2); ν_{max}/cm^{-1} 833, 1158, 1224, 1510, 1599, 2927, 3057; *m/z* (100, MH^+) 408; HRMS (ES): MH^+, found 408.1735. [$C_{31}H_{22}N^+$] required 408.1735.

4.8.2 Preparation of 2-(4-fluorophenyl)-3-(2-phenylethynyl)-4-phenylethenylquinoline 89b (R = F)

The experimental procedure employed for the synthesis of **88a** was followed using a mixture of 4-chloro-2-(4-fluorophenyl)-3-(2-phenylethynyl)quinoline **87b (**0.09 g, 0.25 mmol), *trans*-2-

phenylvinylboronic acid (0.045 g, 0.30 mmol), K_2CO_3 (0.07 g, 0.50 mmol), tricyclohexylphosphine (0.01 g, 0.025 mmol), $Pd(PPh_3)_4$ (0.02 g, 0.001 mmol) in 3:1 dioxane-water (20 mL) Workup and column chromatography afforded **88b** as a solid (0.05 g, 50%), m.p. 161-163 °C, R_f (30% EtOAc-hexane) 0.82; ^{1}H NMR (300 MHz, $CDCl_3$) 7.19-7.28 (7H, m, 3'-H and 5'-H, 3'''-H and 5'''-H, 4'''-H, -C**H**=C**H**), 7.39-7.48 (4H, m, 3''-H and 5''-H, 4''-H, 6-H), 7.58 (1H, t, *J* 8.4 Hz, 7-H), 7.67-7.80 (4H, m, 2''-H and 6''-H, 2'''-H and 6'''-H), 8.03 (2H, dt, *J* 3.6 and 8.4 Hz, 2'-H and 6'-H), 8.15 (1H, d, *J* 8.4 Hz, 8-H), 8.26 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 87.66 (-**C**≡C-Ph), 99.94 (-C≡**C**-Ph), 113.86 (C-3), 114.32 (d, $^2J_{CF}$ 21.5 Hz, C-3',5'), 122.92 (C-4a), 123.26 (C-5), 124.74 (C-1''), 125.05 (C-6), 126.93 (C-3'', 5''), 127.03 (-**C**H=CH-), 128.45 (C-2''', 6'''), 128.67 (C-4'''), 128.84 (C-4''), 128.96 (C-3''', 5'''), 130.11 (C-8), 130.16 (C-7) 131.15 (C-2'',6''), 131.65 (d, $^3J_{CF}$ 8.25 Hz, C-2', 6'), 136.36 (d, $^4J_{CF}$ 3.1 Hz, C-1'), 136.34 (C-1'''), 138,93 (-CH=**C**H-), 146.87 (C-8a), 146,93 (C-4), 158.75 (C-2), 163.30 (d, $^1J_{CF}$ 246.45 Hz, C-4'); ν_{max}/cm^{-1} 841, 1230, 1510, 1601, 2979,3023, 3064; *m/z* (100, MH^+) 426; HRMS (ES): MH^+, found 426.1638. [$C_{31}H_{21}FN^+$] required 426.1638.

4.8.3 Preparation of 2-(4-methoxyphenyl)-3-(2-phenylethynyl)-4-phenyenylquinoline 89c (R = OMe)

The experimental procedure employed for the synthesis of **89a** was followed using a mixture of 4-chloro-2-(4-methoxyphenyl)-3-(2-phenylethynyl)quinoline **87c (**0.10 g, 0.27 mmol), *trans*-2-phenylvinylboronic acid (0.05 g, 0.32 mmol), K_2CO_3 (0.075 g, 0.54 mmol), tricyclohexylphosphine (0.01 g, 0.027 mmol), $Pd(PPh_3)_4$ (0.02 g, 0.001 mmol) in 3:1 dioxane-water (20 mL) Workup and column chromatography afforded **89c** as a solid (0.05 g, 55%), m.p. 128-129 °C, R_f (30% EtOAc-hexane) 0.46; ^{1}H NMR (300 MHz $CDCl_3$) 3.91 (1H, s, OCH_3), 7.06 (2H, d, *J* 6.9 Hz, 3'-H and 5'-H), 7.29-7.33 (5H, m, 3'''-H and 5'''-H, 4'''-H -C**H**=C**H**-), 7.38-7.48 (4H, m, 3''-H and 5''-H, 4''-H, 6-H),

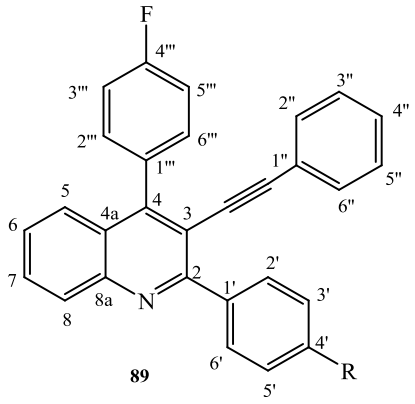
7.54 (1H, dt, *J* 1.5 and 8.4 Hz, 7-H), 7.67-7.80 (4H, m, 2''-H and 6''-H, 2'''-H and 6'''-H), 8.05 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 8.15 (1H, dd, *J* 0.9 and 9.0 Hz, 8-H) , 8.23 (1H, dd, *J* 0.9 and 9.3 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 55.40 ($COCH_3$), 88.08 (-**C**≡C-Ph), 99.70 (-C≡**C**-Ph), 113.23 (C-3', 5'), 113.85 (C-3), 123.15 (C-4a), 123.51 (C-5), 124.51 (C-1''), 124.99 (C-6), 126.64 (-**C**H=CH-), 126.89 (C-3'',5''), 128.39 (C-2'', 6''), 128.50 (C-4'''), 128.913 (C-4''), 128.91 (C-3''', 5'''), 129.89 (C-7), 130.07 (C-8), 131.89 (C-2', 6', 2''', 6''',), 132.83 (C-1'), 136.71 (C-1'''), 138.60 (-CH=**C**H-), 146.83 (C-8a), 146.97 (C-4), 159.21 (C-4'), 160.22 (C-2); ν_{max}/cm^{-1} 836, 1176, 1251, 1514, 1607, 2834, 3060; *m/z* (100, MH^+) 438; HRMS (ES): MH^+, found 438.1847. [$C_{32}H_{24}NO^+$] required 438.1844.

4.8.4 Preparation of 2-(4-fluorophenyl)-3-(3-hydroxybutynyl)-4-phenylethenylquinoline 89d (R = F)

The experimental procedure employed for the synthesis of **89a** was followed using a mixture of 4-chloro-2-(4-fluorophenyl)-3-(3-hydroxybutynyl)quinoline **87f (**0.19 g, 0.56 mmol), *trans*-2-phenylvinylboronic acid (0.10 g, 0.68 mmol), K_2CO_3 (0.16 g, 1.13 mmol), tricyclohexylphosphine (0.002 g, 0.056 mmol), $Pd(PPh_3)_4$ (0.033 g, 0.028 mmol) in 3:1 dioxane-water (20 mL) Workup and column chromatography afforded **89d** as a solid (0.1 g, 50%), m.p. 105-108 °C, R_f (30% EtOAc-hexane) 0.46; ^{1}H NMR (300 MHz $CDCl_3$) 1.39 (3H, d, *J* 6.6 Hz, CH_3), 2.08 (1H, d, *J* 3.0 Hz, OH), 4.63 (1H, q, *J* 6.0 Hz, -C**H**(OH)CH_3), 7.14 (2H, t, *J* 8.7 Hz, 3'-H and 5'-H), 7.28-7.45 (4H, m, 3''-H and 5''-H, 4''-H, -C**H**=CH-), 7.51-7.62 (4H, m, 2''-H and 6''-H, 6-H, -CH=C**H**-), 7.71 (1H, dt, *J* 1.5 and 8.4 Hz, 7-H), 7.93 (2H, dt, *J* 4.8 and 5.4 Hz, 2'-H and 6'-H), 8.12 (1H, dd, *J* 0.6 and 8.4 Hz, 8-H), 8.19 (1H, dd, *J* 0.6 and 8.7 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.21 (CH_3), 58.81 (-**C**H(OH)CH_3), 81.77 (-**C**≡C-Ph), 101.66 (-C≡**C**-Ph), 113.137 (C-3), 114.71 (d, $^2J_{CF}$ 21.6 Hz, C-3',5'), 123.14 (C-5), 124.55 (C-4a), 125.05 (C-6), 126.90 (C-2'', 6''), 126.99 (-**C**H=CH-), 128.85 (C-4''),

128.93 (C-3",5"), 130.11 (d, $^{3}J_{CF}$ 8.6 Hz, C-2', 6'), 131.49 (C-7), 131.60 (C-8), 136.12 (d, $^{4}J_{CF}$ 3.2 Hz, C-1'), 136.46 (C-1"), 138.82 (-CH=**C**H-), 146.90 (C-8a), 147.54 (C-4), 158.62 (C-2), 163.24 (d, $^{4}J_{CF}$ 246.98 Hz, C-4'); ν_{max}/cm^{-1} 841, 1230, 1510, 1601, 2979, 3064; *m/z* (100, MH^{+}) 394; HRMS (ES): MH^{+}, found 394.1596. [$C_{27}H_{21}FON^{+}$] required 394.1594.

4.8.5 Preparation of 4-(4-fluorophenyl)-3-(2-phenylethynyl)-2-phenylquinoline 89e (R = H)



89

2-Aryl-4-(fluorophenyl)-3-(2-phenyiethynyl)quinolines **89e-f**

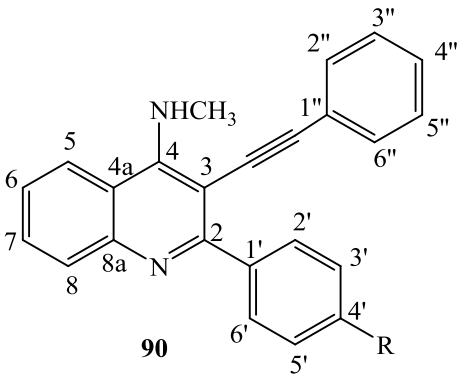
The experimental procedure employed for the synthesis of **89a** was followed using a mixture of 4-chloro-3-(2-phenylethynyl)-2-phenylquinoline **87a** (0.15 g, 0.44 mmol), 4-fluorophenylboronic acid (0.074 g, 0.53 mmol), K_2CO_3 (0.12 g, 0.88 mmol), tricyclohexylphosphine (0.012 g, 0.044 mmol) and $Pd(PPh_3)_4$ (0.026 g, 0.022 mmol) in 3:1 dioxane-water (20 mL), wakeup and column chromatography to afford **89e** as a solid (0.13 g, 74%), m.p. 147-149 °C. R_f (30% EtOAc-hexane) 0.79; ^{1}H NMR (300 MHz $CDCl_3$) 6.99 (2H, dd, *J* 1.5 and 9.3 Hz, 3'''-H and 5'''-H), 7.21-7.34 (5H, m, 2'''-H and 6'''-H, 3"-H and 5"-H, 4"-H), 7.45-7.62 (7H, m, 3'-H and 5'-H, 2"-H and 6"-H, 6-H, 8-H),7.72 (1H, dt, *J* 1.5 and 8.4 Hz, 7-H), 8.05 (2H, td, *J* 1.2 and 8.1 Hz, 2'-H and 6'-H), 8.20 (1H, d, *J* 8.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 87.63 (-**C**≡C-Ph), 98.53 (-C≡**C**-Ph), 115.26 (d, $^{2}J_{CF}$ 21.4 Hz, C-3''', 5'''), 115.66 (C-3), 122.87 (C-1"), 125.73 (C-4a), 125.95 (C-5), 127.04 (C-6), 127.87 (C-2',

6'), 128.26 (C-3", 5"), 128.49 (C-4'), 128.95 (C-4"), 129.73 (C-3', 5'), 129.95 (C-7), 130.07 (C-8), 131.07 (C- 2", 6"), 131.97 (d, $^{3}J_{CF}$ 8.25 Hz, C-2"', 6"'), 132.92 (d, $^{4}J_{CF}$ 3.45 Hz, C-1"'), 140.10 (C-1'), 146.84 (C-8a), 150.68 (C-4), 159.56 (C-2), 162.80 (d, $^{1}J_{CF}$ 246.08 Hz, C-4"'); ν_{max}/cm^{-1} ; 971, 1446, 1488, 1596, 1635, 2361, 3056; *m/z* (100, MH^{+}) 400; HRMS (ES): MH^{+}, found 400.1516. $[C_{29}H_{19}FN^{+}]$ required 400.1502.

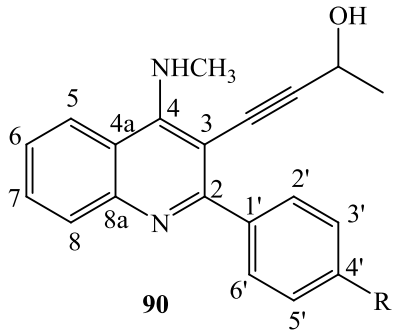
4.8.6 Preparation of 4-(4-fluorophenyl)-2-(4-methoxyphenyl)-3-(2-phenyletynyl)quinoline derivatives 89f (R = OMe)

The experimental procedure employed for the synthesis of **89a** was followed using a mixture of 4-chloro-2-(4-methoxyphenyl)-3-(2-phenylethyn-1-yl)-quinoline **87c (**0.07 g, 0.19 mmol), 4-fluorophenylboronic acid (0.034 g, 0.23 mmol), K_2CO_3 (0.052 g, 0.38 mmol), tricyclohexyl-phosphine (0.01 g, 0.019 mmol) and $Pd(PPh_3)_4$ (0.01 g, 0.010 mmol) in 3:1 dioxane-water (20 mL) Workup and column chromatography afforded **92b** as a solid (0.05 g, 62%), m.p. 166-167 °C, R_f (30% EtOAc-hexane) 0.79; ^{1}H NMR (300 MHz $CDCl_3$) 3.91 (1H, s, OCH_3), 7.05-7.08 (4H, m, 3'-H and 5'-H, 3"'-H and 5"'-H), 7.23-7.31 (5H, m, 2"'-H and 6"'-H, and 3"-H and 5"-H, 4"-H), 7.42-7.59 (4H, m, 2"-H and 6"-H, 6-H, 8-H), 7.71 (1H, t, *J* 7.8 Hz, 7-H), 8.08 (2H,d, *J* 8.4 Hz, 2'-H and 6'-H), 8.18 (1H, d, *J* 8.7 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 55.43 (OCH_3), 87.89 (-**C**≡C-Ph), 98.43 (-C≡**C**-Ph), 113.28 (C-3), 115.23 (d, $^{2}J_{CF}$ 21.6 Hz, C-3"', 5"'), 122.95 (C-1"), 125.54 (C-4a), 125.93 (C-5), 126.76 (C-6), 128.28 (C-3", 5"), 128.47 (C-4"), 129.80 (C-7), 130.01 (C-8), 131.07 (C-2', 6'), 131.25 (C-2", 6"), 131.94 (d, $^{3}J_{CF}$ 7.79 Hz, C-2"', 6"'), 132.67 (C-1'), 133.05 (d, $^{4}J_{CF}$ 3.45 Hz, C-1"'), 146.89 (C-8a), 150.84 (C-4), 158.85 (C-4'), 160.40 (C-2), 162.76 (d, $^{1}J_{CF}$ 246.15 Hz, C-4"'); ν_{max}/cm^{-1} 830, 1227, 1513, 1603, 2837, 3054; *m/z* (100, MH^{+}) 430; HRMS (ES): MH^{+}, found 430.1602. $[C_{30}H_{21}FNO^{+}]$ required 430.1607.

4.9 Preparation of 2-aryl-4-(methylamino)-3-(alkynyl)quinoline derivatives 90



2-Aryl-4-(methylamino)-3-(phenylethynyl)quinolines **90a-c**



2-Aryl-3-(3-hydroxybutynly)-4-(methylamino)quinoline **90d**

4.9.1 Preparation of 4-(methylamino)-3-(2-phenylethynyl)-2-phenylquinoline 90a (R = H)

A mixture of 4-chloro-3-(2-phenylethynyl)-2-phenylquinoline **87a** (0.25 g, 0.74 mmol), and $MeNH_2$ (0.049 mL, 1.47 mmol) in EtOH (40 mL) was stirred under reflux for 18 hours. The reaction mixture was allowed to cool and ethanol was evaporated under reduced pressure, and then taken into chloroform, dried over Mg_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography to afford **90a** as a solid (0.18 g, 73%), m.p. 158-160 °C, R_f (30% EtOAc-hexane) 0.29; ^{1}H NMR (300 MHz, $CDCl_3$) 3.57 (3H, d,*J* 3.6 Hz. CH_3), 5.68 (1H, s, N**H**CH_3), 7.29 (5H, s, 3'-H and 5'-H, 3''-H and 5''-H, 4''-H), 7.38-7.50 (4H, m, 2''-H and 6''-H, 4'-H, 6-H), 7.63 (1H, dt, *J* 1.5 and 8.4 Hz, 7-H), 7.92 (2H, dd, *J* 1.5 and 8.1 Hz, 2'-H and 6'-H), 8.04 (1H, d, *J* 8.4 Hz, 8-H), 8.12 (1H, d, *J* 8.4 Hz. 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 35.65 (CH_3), 86.23 (-**C**≡C-Ph), 99.44 (-C≡**C**-Ph), 99.95 (C-3), 117.68 (C-4a), 122.69 (C-5), 123.36 (C-1''), 124.49 (C-6), 127.74 (C-3'', 5''), 128.12 (C-4'), 128.36 (C-3', 5'), 128.49 (C-4''), 129.43 (C-2', 6'), 129.77 (C-7), 130.38 (C-8), 130.74 (C-2'', 6''), 140.83 (C-1'), 148.08 (C-8a), 154.68 (C-4), 160.50 (C-2); ν_{max}/cm^{-1}

904, 1390, 1527, 1561, 2200, 3054, 3356; *m/z* (100, MH^+) 335; HRMS (ES): MH^+, found 335.1545. [$C_{24}H_{19}N_2^+$] required 335.1548.

4.9.2 Preparation of 2-(4-chlorophenyl)-4-(methylamino)-3-(2-phenylethynyl)quinoline 90b (R = Cl)

The procedure employed for the synthesis of **90a** was followed using a mixture of 4-chloro-2-(4-chlorophenyl)-3-(2-phenylethynyl)quinoline **87b** (0.07 g, 0.19 mmol) and $MeNH_2$ (0.012 mL, 0.37 mmol) in EtOH (40 mL).work up and column chromatography afforded **90b** as a solid (0.04 g, 58%), m.p. 176- 179 °C, R_f (30% EtOAc-hexane) 0.46; ^{1}H NMR (300 MHz $CDCl_3$) 3.57 (3H, d, *J* 4.5 Hz, CH_3), 5.71 (1H, s, N**H**CH_3), 7.33 (5H, s, 2''-H and 6''-H. 3''-H and 5''-H, 4''-H), 7.43 (3H, dd, *J* 7.5 and 7.5 Hz, 3'-H and 5'-H, 6-H), 7.64 (1H, t, *J* 7.8 Hz, 7-H), 7.92 (2H, d, *J* 9.3 Hz, 2'-H and 6'-H), 8.02 (1H, d, *J* 7.5 Hz, 8-H), 8.12 (1H, d, *J* 9.0 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 35.65 (CH_3), 85.83 (-**C**≡C-Ph), 98.23 (-C≡**C**-Ph), 99.62 (C-3), 117.61 (C-4a), 122.73 (C-5), 123.10 (C-1''), 124.64 (C-6), 127.91 (C-3'', 5''), 128.12 (C-4''), 128.36 (C-3', 5'), 129.94 (C-7), 130.31 (C-8) 130.75 (C-2', 6'), 130.90 (C-2'', 6''), 134.53 (C-4'), 139.24 (C-1'), 148.04 (C-8a), 154.79 (C-4), 159.01 (C-2); ν_{max}/cm^{-1} 820, 1261, 1523, 1571, 2201, 2933, 3064; *m/z* (100, MH^+) 369; HRMS (ES): MH^+, found 369.1154. [$C_{24}H_{18}N_2{}^{35}Cl^+$] required 369.1154.

4.9.3 Preparation of 2-(4-methoxyphenyl)-4-(methylamino)-3-(2-phenylethynyl)quinoline 90c (R = OMe)

The procedure employed for the synthesis of **90a** was followed using a mixture of 4-chloro-2-(4-methoxyphenyl)-3-(2-phenylethyn-1-ly)quinoline **87d** (0.26 g, 0.38 mmol) and $MeNH_2$ (0.047 mL, 0.76 mmol) in EtOH (40 mL). Workup and column chromatography afforded **90c** as a solid (0.14 g,

58%), m.p. 130-133 °C, R_f (30% EtOAc-hexane) 0.20; ^{1}H NMR (300 MHz $CDCl_3$) 3.55 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 5.70 (1H, s, N**H**CH_3), 7.00 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.30-7.52 (6H, m, 2"-H and 6"-H. 3"-H and 5"-H, 4"-H, 6-H), 7.62 (1H, t, *J* 8.4 Hz, 7-H), 7.95 (2H, d, *J* 9.0 Hz, 2'-H and 6'-H), 8.02 (1H, d, *J* 8.4 Hz, 8-H), 8.11 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 35.78 (CH_3), 55.38 (OCH_3), 86.32 (-**C**≡C-Ph), 98.63 (-C≡**C**-Ph), 99.38 (C-3), 113.15 (C-3', 5'), 117.61 (C-4a), 122.83 (C-5), 123.38 (C-1"), 124.27 (C-6), 127.91 (C-3", 5"), 128.12 (C-4"), 129.94 (C-7), 130.31 (C-8) 130.75 (C-2', 6'), 130.90 (C-2", 6"), 134.53 (C-4'), 139.24 (C-1'), 148.04 (C-8a), 154.79 (C-4), 159.01 (C-2); ν_{max}/cm^{-1} 836, 1247, 1515, 1568, 1606, 2198, 2934, 3388; *m/z* (100, MH^+) 365; HRMS (ES): MH^+, found 365.16544. [$C_{25}H_{21}N_2O^+$] required 365.1654.

4.9.4 Preparation of 2-(4-chlorophenyl)-3-(3-hydroxybutynly)-4-(methylamino)quinoline 90d (R = Cl)

The procedure employed for the synthesis of **90a** was followed using a mixture of 4-chloro-2-(4-chorophenyl)-3-(3-hydroxybutynyl)quinoline **87g** (0.05 g, 0.14 mmol), and $MeNH_2$ (0.024 mL, 0.71 mmol) in EtOH (40 mL), workup and column chromatography afforded **90d** as a solid (0.03 g, 61%), m.p. 183-184 °C, R_f (30% EtOAc-hexane) 0.10; ^{1}H NMR (300 MHz $CDCl_3$) 1.45 (3H, d, *J* 6.6), 159 (1H, s, OH), 3.49 (3H, s, CH_3),4.69 (1H, q, *J* 6.6 Hz, -C**H**(OH)CH_3), 5.62 (1H, s, N**H**CH_3), 7.37-7.42 (3H, m, 3'-H and 5'-H, 6-H), 7.63 (1H, dt, *J* 1.2 and 8.4 Hz, 7-H), 7.78 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 7.99 (1H, dd, *J* 0.3 and 8.5 Hz, 8-H), 8.12 (1H, dd, *J* 0.6 and 7.8 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 35.65 (CH_3), 58.81 (-**C**H(OH)CH_3), 85.83 (-**C**≡C-Ph), 99.28 (-C≡**C**-Ph), 99.63 (C-3), 117.61 (C-4a), 122.73 (C-5), 123.10 (C-1"), 124.64 (C-6), 127.91 (C-3", 5"), 128.12 (C-4"), 128.36 (C-3', 5'), 129.94 (C-7), 130.31 (C-8) 130.75 (C-2', 6'), 130.90 (C-2", 6"), 134.53 (C-4'), 139.24 (C-1'), 148.04

(C-8a), 154.79 (C-4), 159.01 (C-2); ν_{max}/cm^{-1} 829, 1085, 1522, 1568, 2213, 2962, 3145, 3289; *m/z* (100, MH^+) 337; HRMS (ES): MH^+, found 337.1122. [$C_{20}H_{18}N_2O^{35}Cl^+$] required 337.1108.

4.10 X-ray Crystal structure solution and refinement

Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50kV, 30mA) using the APEX 2 [71] data collection software. The collection method involved ω-scans of width 0.5° and 512x512 bit data frames. Data reduction was carried out using the program *SAINT+* [72]. The crystal structure was solved by direct methods using *SHELXTL* [73]. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL, PLATON [74] and ORTEP-3 [75].

Table 9: Crystal data and structure refinement for 4-(phenylethenyl)-3-(2-phenylethynyl)-2-phenylquinoline.

Identification code	10m_unisa4_h19m_0s	
Empirical formula	$C_{31}H_{21}N$	
Formula weight	407.49	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.4452(4) Å	α= 90°.
	b = 18.2686(9) Å	β= 97.746(2)°.
	c = 16.1705(7) Å	γ = 90°.
Volume	2179.34(18) $Å^3$	
Z	4	
Density (calculated)	1.242 Mg/m^3	
Absorption coefficient	0.071 mm^{-1}	
F(000)	856	
Crystal size	0.47 x 0.27 x 0.22 mm^3	
Theta range for data collection	1.69 to 27.00°.	
Index ranges	-9<=h<=9, -23<=k<=23, -20<=l<=16	
Reflections collected	16609	
Independent reflections	4761 [R(int) = 0.0430]	
Completeness to theta = 27.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4761 / 47 / 289	
Goodness-of-fit on F^2	1.012	
Final R indices [I>2sigma(I)]	R1 = 0.0503, wR2 = 0.1264	
R indices (all data)	R1 = 0.0863, wR2 = 0.1394	
Largest diff. peak and hole	0.659 and -0.325 $e.Å^{-3}$	

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73. Bruker (1999), SHELXTL. Version 5.1. (includes XS, XL, XP, XSHELL) Bruker AXS Inc., Madison, Wisconsin, USA.

74. Farrugia, L. J. *J. Appl. Cryst*. **1997**, *30*, 565.

75. Spek, A. L. *J. Appl. Cryst.* **2003**, *36*, 7-13.

APPENDIX

Mass spectra of compounds **87e, 88a, 89a, 90a**

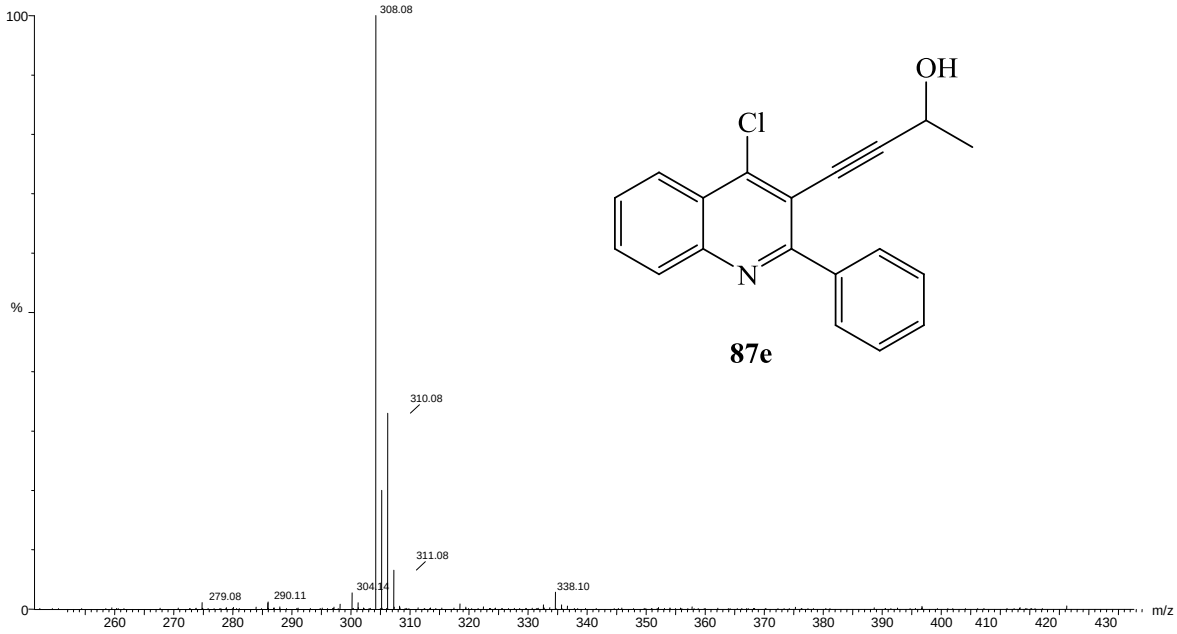

Figure 15: Mass spectrum of 4-chloro-3-(3-hydroxybutynyl)-2-phenylquinoline **87e**

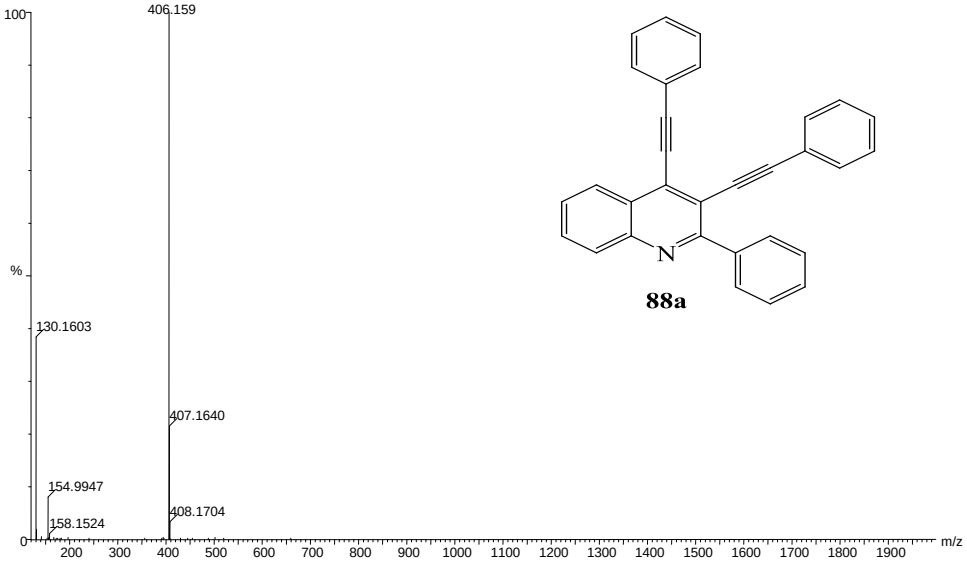

Figure 16: Mass spectrum of 3,4-bis(2-phenylethynyl)-2-phenylquinoline **88a**

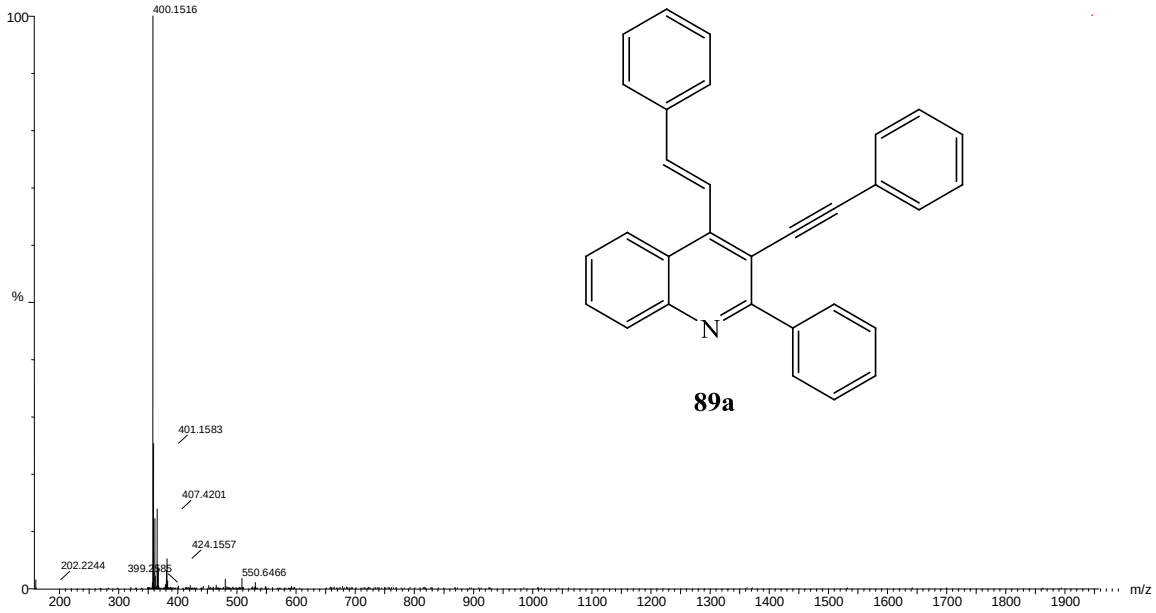

Figure 17: Mass spectrum of 4-(phenylethenyl)-3-(2-phenylethynyl)-2-phenylquinoline **89a**

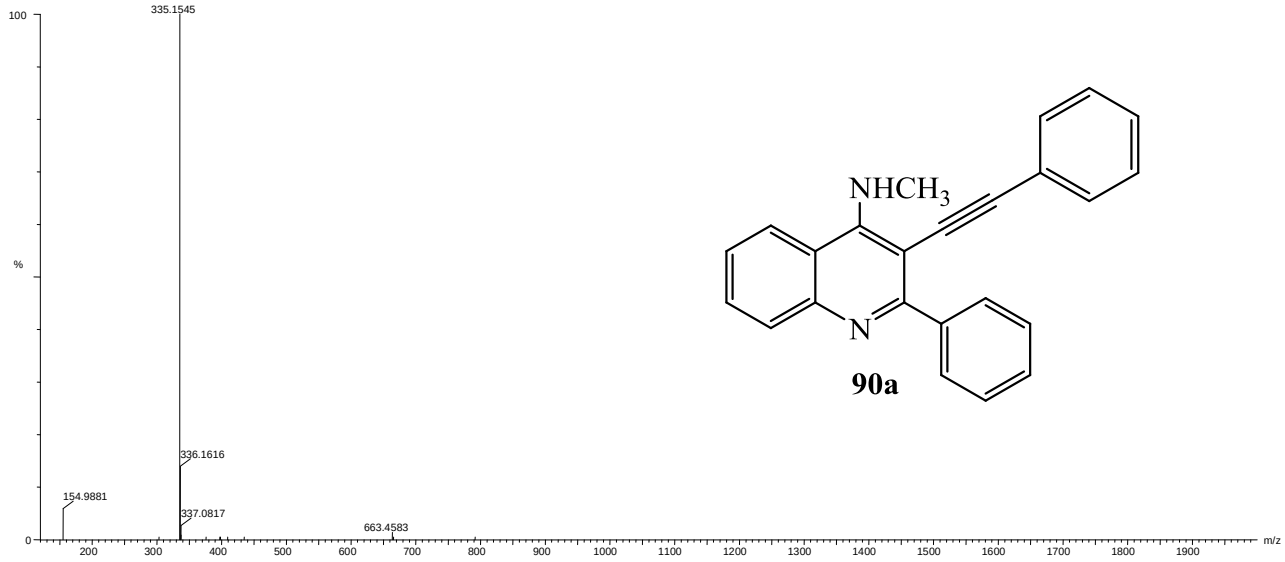

Figure 18: Mass spectrum of 4-(methylamine)-3-(2-phenylethynyl)quinoline **90a**

X-Ray Crystallographic Data

Table10: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 4-(phenylethenyl)-3-(2-phenylethynyl)-2-phenylquinoline U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1')	1276(2)	1757(1)	3550(1)	32(1)
C(2')	2144(3)	2434(1)	3616(1)	41(1)
C(2)	1637(2)	1197(1)	4219(1)	31(1)
C(3)	1619(2)	1370(1)	5077(1)	33(1)
C(3')	1883(3)	2933(1)	2965(1)	47(1)
C(4)	1985(2)	828(1)	5676(1)	35(1)
C(4')	764(3)	2763(1)	2243(1)	47(1)
C(4A)	2452(2)	114(1)	5414(1)	32(1)
C(5)	2995(2)	-475(1)	5963(1)	40(1)
C(5')	-114(3)	2093(1)	2167(1)	44(1)
C(6')	148(2)	1597(1)	2813(1)	38(1)
C(6)	3410(2)	-1144(1)	5664(1)	42(1)
C(7)	3325(2)	-1265(1)	4808(1)	42(1)
C(8)	2855(2)	-710(1)	4260(1)	38(1)
C(8A)	2426(2)	-11(1)	4546(1)	31(1)
C(9)	1123(2)	2085(1)	5341(1)	37(1)
C(10)	750(2)	2662(1)	5627(1)	36(1)
C(11)	408(2)	3359(1)	5990(1)	33(1)
C(12)	-419(3)	3404(1)	6710(1)	43(1)
C(13)	-695(3)	4077(1)	7063(1)	47(1)
C(14)	-117(3)	4710(1)	6708(1)	45(1)
C(15)	711(3)	4665(1)	6002(1)	43(1)
C(16)	955(3)	3999(1)	5638(1)	40(1)
C(17)	1919(3)	1026(1)	6558(1)	44(1)
C(18)	1177(3)	645(1)	7091(1)	46(1)
C(19)	1013(3)	868(1)	7965(1)	43(1)
C(20)	-120(3)	459(1)	8393(1)	48(1)
C(21)	-335(3)	619(1)	9191(1)	52(1)
C(22)	601(3)	1185(1)	9613(1)	54(1)
C(23)	1754(3)	1609(1)	9205(1)	53(1)
C(24)	1951(3)	1450(1)	8377(1)	46(1)
N(1)	1995(2)	529(1)	3962(1)	33(1)

Table 11: Bond lengths [Å] and angles [°] for 4-(phenylethenyl)-3-(2-phenylethynyl)-2-phenylquinoline.

C(1')-C(6')	1.392(2)
C(1')-C(2')	1.393(2)
C(1')-C(2)	1.488(2)
C(2')-C(3')	1.387(3)
C(2')-H(2')	0.9500
C(2)-N(1)	1.327(2)
C(2)-C(3)	1.424(2)
C(3)-C(4)	1.387(2)
C(3)-C(9)	1.438(2)
C(3')-C(4')	1.375(3)
C(3')-H(3')	0.9500
C(4)-C(4A)	1.429(2)
C(4)-C(17)	1.477(3)
C(4')-C(5')	1.386(3)
C(4')-H(4')	0.9500
C(4A)-C(5)	1.419(2)
C(4A)-C(8A)	1.419(2)
C(5)-C(6)	1.365(3)
C(5)-H(5)	0.9500
C(5')-C(6')	1.377(2)
C(5')-H(5')	0.9500
C(6')-H(6')	0.9500
C(6)-C(7)	1.395(3)
C(6)-H(6)	0.9500
C(7)-C(8)	1.361(2)
C(7)-H(7)	0.9500
C(8)-C(8A)	1.410(2)
C(8)-H(8)	0.9500
C(8A)-N(1)	1.373(2)
C(9)-C(10)	1.199(2)
C(10)-C(11)	1.438(2)
C(11)-C(16)	1.386(2)
C(11)-C(12)	1.390(2)
C(12)-C(13)	1.383(3)
C(12)-H(12)	0.9500
C(13)-C(14)	1.385(3)
C(13)-H(13)	0.9500
C(14)-C(15)	1.371(3)
C(14)-H(14)	0.9500
C(15)-C(16)	1.373(2)
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
C(17)-C(18)	1.289(3)
C(17)-H(17)	0.9500
C(18)-C(19)	1.492(3)
C(18)-H(18)	0.9500
C(19)-C(20)	1.381(3)
C(19)-C(24)	1.391(3)
C(20)-C(21)	1.354(3)
C(20)-H(20)	0.9500
C(21)-C(22)	1.375(3)
C(21)-H(21)	0.9500

C(22)-C(23)	1.387(3)
C(22)-H(22)	0.9500
C(23)-C(24)	1.397(3)
C(23)-H(23)	0.9500
C(24)-H(24)	0.9500
C(6')-C(1')-C(2')	118.23(17)
C(6')-C(1')-C(2)	120.43(15)
C(2')-C(1')-C(2)	121.21(16)
C(3')-C(2')-C(1')	120.58(18)
C(3')-C(2')-H(2')	119.7
C(1')-C(2')-H(2')	119.7
N(1)-C(2)-C(3)	122.59(16)
N(1)-C(2)-C(1')	115.35(15)
C(3)-C(2)-C(1')	122.05(15)
C(4)-C(3)-C(2)	119.64(16)
C(4)-C(3)-C(9)	118.37(16)
C(2)-C(3)-C(9)	121.88(16)
C(4')-C(3')-C(2')	120.22(18)
C(4')-C(3')-H(3')	119.9
C(2')-C(3')-H(3')	119.9
C(3)-C(4)-C(4A)	118.52(16)
C(3)-C(4)-C(17)	118.11(16)
C(4A)-C(4)-C(17)	123.35(16)
C(3')-C(4')-C(5')	119.93(18)
C(3')-C(4')-H(4')	120.0
C(5')-C(4')-H(4')	120.0
C(5)-C(4A)-C(8A)	117.52(16)
C(5)-C(4A)-C(4)	124.56(16)
C(8A)-C(4A)-C(4)	117.90(15)
C(6)-C(5)-C(4A)	121.08(17)
C(6)-C(5)-H(5)	119.5
C(4A)-C(5)-H(5)	119.5
C(6')-C(5')-C(4')	119.84(19)
C(6')-C(5')-H(5')	120.1
C(4')-C(5')-H(5')	120.1
C(5')-C(6')-C(1')	121.20(17)
C(5')-C(6')-H(6')	119.4
C(1')-C(6')-H(6')	119.4
C(5)-C(6)-C(7)	120.76(17)
C(5)-C(6)-H(6)	119.6
C(7)-C(6)-H(6)	119.6
C(8)-C(7)-C(6)	120.12(18)
C(8)-C(7)-H(7)	119.9
C(6)-C(7)-H(7)	119.9
C(7)-C(8)-C(8A)	120.70(17)
C(7)-C(8)-H(8)	119.7
C(8A)-C(8)-H(8)	119.7
N(1)-C(8A)-C(8)	117.83(15)
N(1)-C(8A)-C(4A)	122.40(15)
C(8)-C(8A)-C(4A)	119.77(16)
C(10)-C(9)-C(3)	174.61(19)
C(9)-C(10)-C(11)	176.8(2)
C(16)-C(11)-C(12)	118.83(16)
C(16)-C(11)-C(10)	120.06(16)
C(12)-C(11)-C(10)	121.09(16)
C(13)-C(12)-C(11)	120.38(17)

C(13)-C(12)-H(12)	119.8
C(11)-C(12)-H(12)	119.8
C(12)-C(13)-C(14)	119.90(18)
C(12)-C(13)-H(13)	120.1
C(14)-C(13)-H(13)	120.1
C(15)-C(14)-C(13)	119.67(18)
C(15)-C(14)-H(14)	120.2
C(13)-C(14)-H(14)	120.2
C(14)-C(15)-C(16)	120.69(18)
C(14)-C(15)-H(15)	119.7
C(16)-C(15)-H(15)	119.7
C(15)-C(16)-C(11)	120.51(18)
C(15)-C(16)-H(16)	119.7
C(11)-C(16)-H(16)	119.7
C(18)-C(17)-C(4)	125.93(19)
C(18)-C(17)-H(17)	117.0
C(4)-C(17)-H(17)	117.0
C(17)-C(18)-C(19)	125.73(19)
C(17)-C(18)-H(18)	117.1
C(19)-C(18)-H(18)	117.1
C(20)-C(19)-C(24)	118.35(18)
C(20)-C(19)-C(18)	117.43(19)
C(24)-C(19)-C(18)	124.20(18)
C(21)-C(20)-C(19)	121.3(2)
C(21)-C(20)-H(20)	119.3
C(19)-C(20)-H(20)	119.3
C(20)-C(21)-C(22)	121.2(2)
C(20)-C(21)-H(21)	119.4
C(22)-C(21)-H(21)	119.4
C(21)-C(22)-C(23)	119.31(19)
C(21)-C(22)-H(22)	120.3
C(23)-C(22)-H(22)	120.3
C(22)-C(23)-C(24)	119.4(2)
C(22)-C(23)-H(23)	120.3
C(24)-C(23)-H(23)	120.3
C(19)-C(24)-C(23)	120.46(19)
C(19)-C(24)-H(24)	119.8
C(23)-C(24)-H(24)	119.8
C(2)-N(1)-C(8A)	118.84(14)

Symmetry transformations used to generate equivalent atoms:

Table 12: Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 4-(phenylethenyl)-3-(2-phenylethynyl)-2-phenylquinoline. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1')	30(1)	31(1)	37(1)	-5(1)	9(1)	1(1)
C(2')	41(1)	38(1)	44(1)	-5(1)	10(1)	-7(1)
C(2)	27(1)	31(1)	35(1)	-3(1)	4(1)	-4(1)
C(3)	28(1)	33(1)	37(1)	-6(1)	-1(1)	0(1)
C(3')	50(1)	35(1)	60(1)	0(1)	21(1)	-6(1)
C(4)	30(1)	39(1)	34(1)	-6(1)	0(1)	1(1)
C(4')	48(1)	43(1)	53(1)	14(1)	19(1)	7(1)
C(4A)	25(1)	34(1)	35(1)	-1(1)	2(1)	0(1)
C(5)	38(1)	47(1)	35(1)	4(1)	5(1)	3(1)
C(5')	39(1)	50(1)	42(1)	4(1)	4(1)	4(1)
C(6')	37(1)	33(1)	44(1)	0(1)	4(1)	-2(1)
C(6)	41(1)	37(1)	48(1)	11(1)	4(1)	5(1)
C(7)	40(1)	32(1)	54(1)	-1(1)	9(1)	5(1)
C(8)	42(1)	34(1)	39(1)	-4(1)	8(1)	-1(1)
C(8A)	29(1)	30(1)	34(1)	0(1)	3(1)	-2(1)
C(9)	38(1)	37(1)	33(1)	-1(1)	0(1)	0(1)
C(10)	40(1)	36(1)	32(1)	-1(1)	1(1)	1(1)
C(11)	31(1)	32(1)	35(1)	-3(1)	1(1)	2(1)
C(12)	48(1)	39(1)	42(1)	1(1)	9(1)	-8(1)
C(13)	43(1)	61(1)	39(1)	-13(1)	12(1)	-5(1)
C(14)	45(1)	39(1)	48(1)	-15(1)	0(1)	4(1)
C(15)	52(1)	32(1)	45(1)	3(1)	1(1)	-4(1)
C(16)	44(1)	39(1)	37(1)	-1(1)	10(1)	-1(1)
C(17)	42(1)	46(1)	42(1)	-2(1)	1(1)	3(1)
C(18)	42(1)	40(1)	54(1)	0(1)	0(1)	1(1)
C(19)	37(1)	51(1)	38(1)	2(1)	1(1)	12(1)
C(20)	40(1)	49(1)	54(1)	2(1)	7(1)	8(1)
C(21)	54(1)	53(1)	52(1)	10(1)	16(1)	9(1)
C(22)	63(1)	64(2)	36(1)	5(1)	11(1)	20(1)
C(23)	54(1)	49(1)	51(1)	-4(1)	-5(1)	10(1)
C(24)	44(1)	50(1)	46(1)	13(1)	10(1)	5(1)
N(1)	33(1)	30(1)	35(1)	-3(1)	4(1)	-2(1)

Table 13: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 4-(phenylethenyl)-3-(2-phenylethynyl)-2-phenylquinoline.

	x	y	z	U(eq)
H(2')	2922	2555	4112	49
H(3')	2479	3394	3017	56
H(4')	594	3105	1796	56
H(5)	3070	-403	6549	48
H(5')	-896	1976	1671	52
H(6')	-451	1137	2756	46
H(6)	3761	-1532	6043	51
H(7)	3595	-1736	4607	50
H(8)	2816	-794	3678	45
H(12)	-795	2970	6961	51
H(13)	-1282	4105	7549	56
H(14)	-292	5173	6952	54
H(15)	1119	5098	5762	52
H(16)	1503	3977	5141	48
H(17)	2474	1474	6748	52
H(18)	692	181	6912	55
H(20)	-761	57	8122	57
H(21)	-1147	335	9465	63
H(22)	460	1284	10177	65
H(23)	2404	2004	9486	63
H(24)	2731	1741	8093	55

Table 14: Torsion angles [°] for 4-(phenylethenyl)-3-(2-phenylethynyl)-2-phenylquinoline.

C(6')-C(1')-C(2')-C(3')	0.1(3)
C(2)-C(1')-C(2')-C(3')	175.86(17)
C(6')-C(1')-C(2)-N(1)	44.6(2)
C(2')-C(1')-C(2)-N(1)	-131.06(17)
C(6')-C(1')-C(2)-C(3)	-136.13(17)
C(2')-C(1')-C(2)-C(3)	48.2(2)
N(1)-C(2)-C(3)-C(4)	-0.1(3)
C(1')-C(2)-C(3)-C(4)	-179.29(16)
N(1)-C(2)-C(3)-C(9)	-176.21(16)
C(1')-C(2)-C(3)-C(9)	4.6(3)
C(1')-C(2')-C(3')-C(4')	-0.2(3)
C(2)-C(3)-C(4)-C(4A)	2.8(2)
C(9)-C(3)-C(4)-C(4A)	179.08(15)
C(2)-C(3)-C(4)-C(17)	-178.84(16)
C(9)-C(3)-C(4)-C(17)	-2.6(2)
C(2')-C(3')-C(4')-C(5')	0.4(3)
C(3)-C(4)-C(4A)-C(5)	174.83(16)
C(17)-C(4)-C(4A)-C(5)	-3.4(3)
C(3)-C(4)-C(4A)-C(8A)	-3.1(2)
C(17)-C(4)-C(4A)-C(8A)	178.60(16)
C(8A)-C(4A)-C(5)-C(6)	-2.4(3)
C(4)-C(4A)-C(5)-C(6)	179.62(17)
C(3')-C(4')-C(5')-C(6')	-0.5(3)
C(4')-C(5')-C(6')-C(1')	0.5(3)
C(2')-C(1')-C(6')-C(5')	-0.3(3)
C(2)-C(1')-C(6')-C(5')	-176.05(17)
C(4A)-C(5)-C(6)-C(7)	0.5(3)
C(5)-C(6)-C(7)-C(8)	1.2(3)
C(6)-C(7)-C(8)-C(8A)	-0.9(3)
C(7)-C(8)-C(8A)-N(1)	178.86(16)
C(7)-C(8)-C(8A)-C(4A)	-1.1(3)
C(5)-C(4A)-C(8A)-N(1)	-177.27(15)
C(4)-C(4A)-C(8A)-N(1)	0.8(2)
C(5)-C(4A)-C(8A)-C(8)	2.7(2)
C(4)-C(4A)-C(8A)-C(8)	-179.21(15)
C(16)-C(11)-C(12)-C(13)	0.3(3)
C(10)-C(11)-C(12)-C(13)	178.31(17)
C(11)-C(12)-C(13)-C(14)	-1.2(3)
C(12)-C(13)-C(14)-C(15)	0.7(3)
C(13)-C(14)-C(15)-C(16)	0.7(3)
C(14)-C(15)-C(16)-C(11)	-1.6(3)
C(12)-C(11)-C(16)-C(15)	1.0(3)
C(10)-C(11)-C(16)-C(15)	-176.94(17)
C(3)-C(4)-C(17)-C(18)	136.2(2)
C(4A)-C(4)-C(17)-C(18)	-45.6(3)
C(4)-C(17)-C(18)-C(19)	-175.95(17)
C(17)-C(18)-C(19)-C(20)	167.84(19)
C(17)-C(18)-C(19)-C(24)	-13.4(3)
C(24)-C(19)-C(20)-C(21)	0.6(3)
C(18)-C(19)-C(20)-C(21)	179.39(18)
C(19)-C(20)-C(21)-C(22)	-1.6(3)
C(20)-C(21)-C(22)-C(23)	1.5(3)
C(21)-C(22)-C(23)-C(24)	-0.5(3)
C(20)-C(19)-C(24)-C(23)	0.5(3)

C(18)-C(19)-C(24)-C(23)	-178.25(18)
C(22)-C(23)-C(24)-C(19)	-0.5(3)
C(3)-C(2)-N(1)-C(8A)	-2.3(2)
C(1')-C(2)-N(1)-C(8A)	176.98(14)
C(8)-C(8A)-N(1)-C(2)	-178.08(15)
C(4A)-C(8A)-N(1)-C(2)	1.9(2)

Symmetry transformations used to generate equivalent atoms:

ORTEP Diagram (50% probability level):