SYNTHESIS AND TRANSFORMATION OF THE 2,6,8-TRIARYL-2,3-DIHYDROQUINOLIN-4(1*H*)-ONES

by

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I declare that **SYNTHESIS AND TRANSFORMATION OF THE 2,6,8-TRIARYL-2,3-DIHYDROQUINOLIN-4(1*H*)-ONES** is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references

SIGNATURE DATE

(MR F A OYEYIOLA)

THIS WORK IS DEDICATED TO MY LATE PARENTS, PA ADEOTI AND MADAM JOLAADE OYEYIOLA, FOR KINDLING THE FLAME OF KNOWLEDGE; AND MY DARLING WIFE, ADERONKE AND WONDERFUL SONS; ADESOYE, ADEOLUWA AND ADETAYO FOR KEEPING THE FLAME GLOWING

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Abstract

The 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones were prepared *via* acid-catalyzed cyclization of the corresponding 2-aminochalcones, which were in turn, prepared by base-promoted Claisen-Schmidt aldol condensation of 2-aminoacetophenone and benzaldehyde derivatives. The 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones were prepared by reacting 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones with *N*-bromosuccinimide (NBS) in carbon tetrachloride-chloroform mixture at room temperature. The 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones were subjected to palladium-catalyzed Suzuki-Miyaura cross-coupling reaction with arylboronic acid using dichlorobis(triphenylphosphine)palladium(II)-tricycohexylphosphine as catalyst mixture and potassium carbonate as a base in dioxane-water under reflux to afford the corresponding novel 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones in a single-pot operation. The latter were subjected to thallium(III) *p*-tolylsulfonate in dimethoxyethane under reflux to yield the 2,6,8-triarylquinolin-4(1*H*)-ones. The 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones were treated with molecular iodine in refluxing methanol to afford the corresponding 2,6,8-triaryl-4-methoxyquinolines. All the new compounds were characterized using a combination of ^{1}H NMR & ^{13}C NMR spectroscopy, IR and mass spectroscopic techniques.

Keywords: 2-aminochalcones; 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones; 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones; Suzuki-Miyaura cross-coupling reaction; 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones; 2,6,8-triarylquinolin-4(1*H*)-ones; 2,6,8-triaryl-4-methoxyquinolines.

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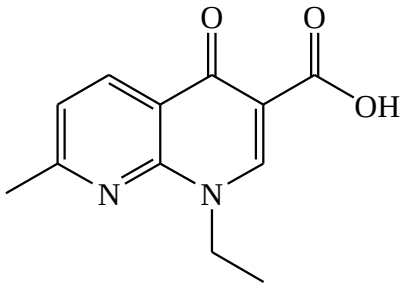
CHAPTER 1 INTRODUCTION

1.1 Background literature

The role and impact of organic synthesis in medicinal chemistry cannot be overemphasized, considering the attention and research efforts devoted to the synthesis of more potent and efficient compounds. Quinolones are one of the groups of heterocyclic compounds that have engendered much interest due to their broad spectrum of biological properties.[1] Their broad spectrum of therapeutic activities include; genitourinary infections,[2] respiratory diseases,[3] sexually transmitted diseases,[4] prostatis and gastroenteritis.[4] Several other quinolones and their quinoline derivatives possess antimitotic,[1] antiplatelet,[4] and chemotherapeutic properties[5] and also serve as components of photographic sensitizers and dyestuffs.[6] The advancement in research has led to improvement in potency and other properties of the quinolones and is best exemplified by the fluoroquinolones. The quinolones can be classified according to their antimicrobial activity.[3,7] Nalidixic acid **1** was the first quinolone to be employed as an antibiotic of limited efficacy,[2,5] with improvement achieved with the fluoroquinolones such as Lomefloxacin **2** and Levofloxacin **3**.[3,6,7]



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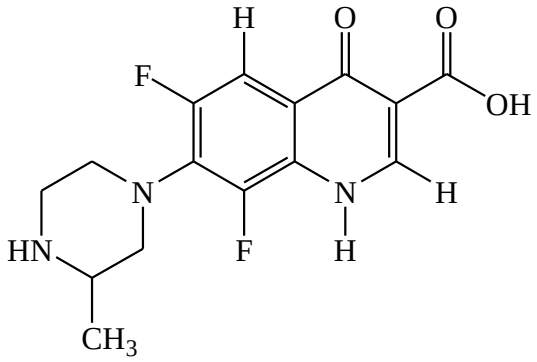

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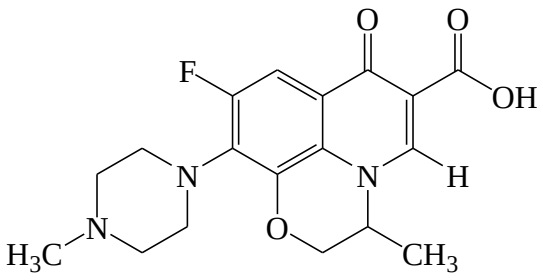
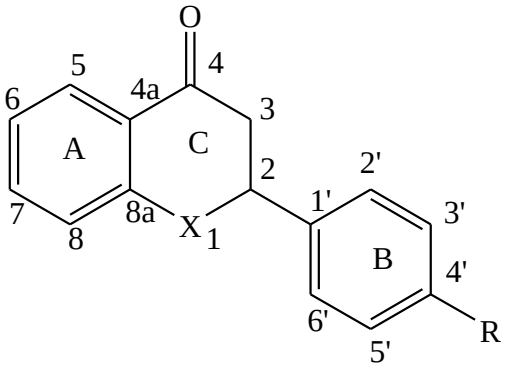


3

Quinolones are known to facilitate the rupturing of bacterial DNA and to culminate in the elimination of such bacteria by inhibiting prokaryotic type II topoisomerases, namely DNA gyrase.[6,7] In a few cases they inhibit topoisomerase IV by direct binding to the bacterial chromosome.[8] The possibility of targeting viral nucleic acids or nucleoprotein-complexes led to several quinolone derivatives being tested for antiviral activity against *Vaccinia* virus and *Papovaviruses*.[9] The evolution of quinolones with limited antimicrobial and antibacterial activity has led to a vast and diverse range of structural modifications of the quinolone unit to enhance potency.[6,10,11] The 2-arylquinolin-4-ones are of interest to us due to their versatility as substrates for further transformation to afford novel derivatives with potential biological activity. The 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones (X = NH), commonly known as azaflavanones, are analogues of flavanones (X = O) and thiaflavanones (X = S), the framework of which consists of a fused benzo ring A and aryl substituent B at position 2 of the heterocyclic ring C as shown by the generalized structure **4**.



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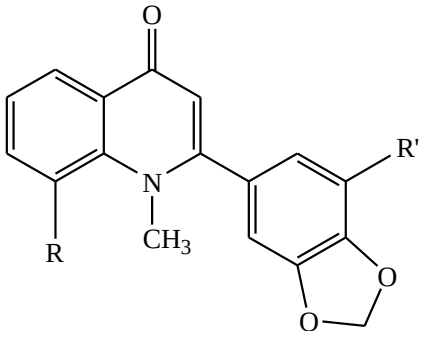
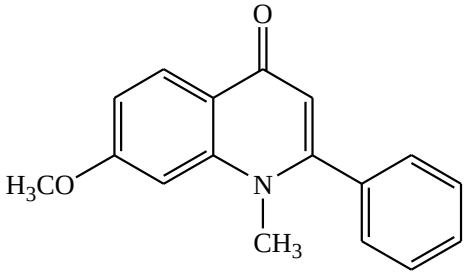
The 2-aryl-4-quinolones and their 2-arylquinoline derivatives are widely distributed in the plant family *Rutaceae*.[12,13] Graveoline (R = R′ = H) **5a**, for example, was first isolated from the plant species *Ruta graveolens*[14,15] and its substituted derivatives, the 3′-methoxygraveoline (R = H, R′ = OMe) **5b** and 3′,8-dimethoxygraveoline (R = R′ = OMe) **5c** were later isolated from the roots of the Brazilian plant species *Esenbeckia grandiflora*.[14-16] Edulein **6**, a 2-phenylquinolin-4-one derivative was isolated from the bark of the Mexican tree *Casimiroa edulis* and the leaves of *Lunasia amara*.[17-19] The isomeric 4-methoxy-2-phenylquinoline **7** (R, R′ = H) and its 4-methoxy-2-(3,4-methylenedioxyphenyl)quinoline analogue **7** (R, R′ = -OCH_2O-) were isolated from the leaves of *Lunasia amara* Blanco of Philippine origin.[18]



5 R = R′ = H (**a**); R = H, R′ = OCH_3 (**b**); R = R′ = OCH_3 (**c**)



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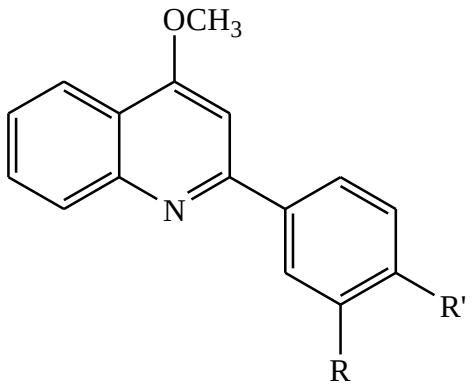


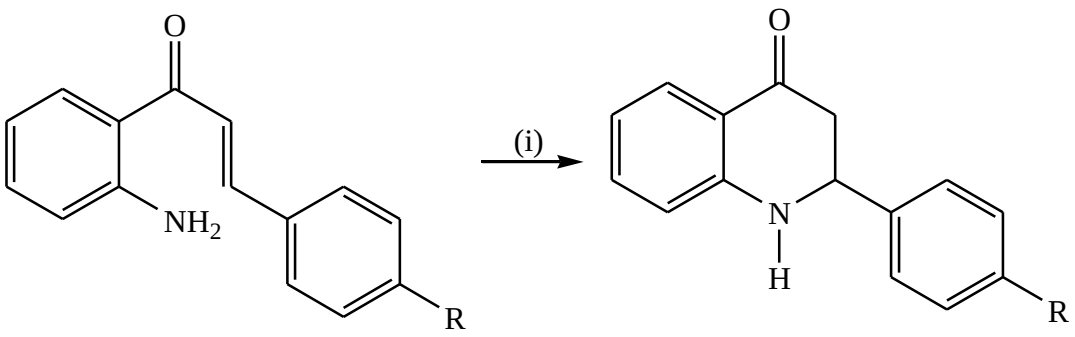
7 R, R′ = H (**a**); R, R′ = -OCH_2O- (**b**)

1.2 Synthesis of 2-aryl-2,3-dihydroquinol-4(1*H*)-ones and 2-arylquinolin-4(1*H*)-one derivatives

The growing interest in the synthesis of 2-aryl-2,3-dihydroquinol-4(1*H*)-ones is due to their application as antibacterials[20,21] and antiplatelet agents,[22] as well as cardiovascular protectors.[23] These diverse activity is attributed to the presence of nitrogen (N-1), a biologically active site which allows for the attachment of different substituents.[24] 2-Aryl-2,3-dihydro-4-quinolones are also useful as intermediates in synthesis to afford highly functionalized quinolones and/or their quinoline derivatives[24,25] with enhanced antitumour and antibacterial properties.[20,26] The *N*-substituted 2-arylquinolin-4(1*H*)-one derivatives, on the other hand, serve as antimalarial agents, immunostimulants and non-nucleoside HIV-1 inhibitors.[27] Although the 2-aryl-4-quinolones and their quinoline derivatives are naturally occurring, the quantity isolated from the plants cannot satisfy the huge demand and commensurate volume required of these biologically important compounds. Hence there is an increased need to develop efficient methods for the synthesis of analogues with increased potency and reduced side effects to address this challenge.

1.2.1 Synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones

The 1-(2-aminophenyl)-3-aryl-2-propen-1-ones **8**, commonly known as 2-aminochalcones, are also naturally occurring compounds found in various plant species such as *Angelica, Glycyrrhiza, Humus* and *Scutellaria.*[28] The 2-aminochalcones are the most common precursors for the synthesis of azaflavanones. The 2-aminochalcones are in turn, readily accessible in the laboratory *via* Claisen-Schmidt condensation of 2-aminoacetophenone with benzaldehyde derivatives.[29a,30,31] Chalcones have been found to inhibit tubulin assembly and angiogenesis, and to induce apostosis, antiestrogenic activity and the reversal of multidrug resistance.[32] They also possess antimitotic activity, as well as anti-infective and anti-inflammatory properties.[33] The 2-aminochalcones are cyclized either under either basic[29a] or acidic conditions[29b,30] to afford the corresponding 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones. A convenient and high yielding method (>90%) for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **9** involves cyclization of the corresponding 2-aminochalcones **8** with orthophosphoric acid in acetic acid under reflux (Scheme 1).[30,31] More recently, 2-aminochalcones **8** were also mixed with silica gel impregnated with sodium hydrogen sulphate and subjected to microwave irradiation to afford the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **9** in high yields (82-96%).[34] A solvent-free cyclization of the 2-aminochalcones in the presence of alumina supported-$CeCl_3.7H_2O$-NaI as catalyst at 70 °C, to afford systems **9** in 86-90% yields, has also been reported.[35] A similar attempt using silica gel instead of alumina yielded the same products, however, in relatively low quantities.[35] A more recent procedure which involves the cyclization of 2-nitrochalcones using iron powder in concentrated hydrochloric acid at 100 °C for 0.5 h to afford the corresponding products **9** in 72-88% yields has also been reported.[36]



8 **9**

Reagents and conditions: (i) H_3PO_4, AcOH, heat, 2 h[30,31] or $NaHSO_4$-SiO_2, MW, 2 min[34]

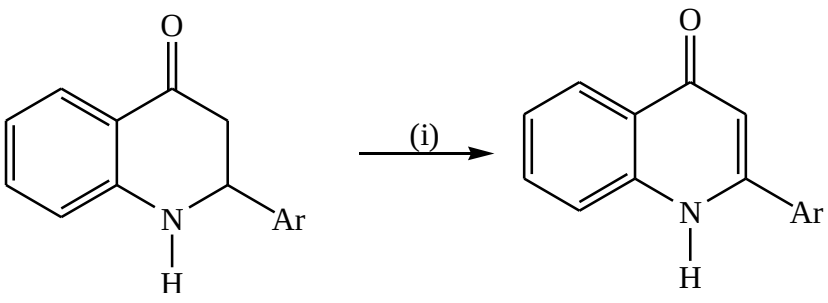
Scheme 1

The heterocyclic ring of the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones represents a suitable framework for further modification that could involve dehydrogenation or oxidative aromatization to afford variously substituted 2-arylquinolin-4(1*H*)-ones or quinoline derivatives.

1.2.2 Synthesis of 2-arylquinolin-4(1*H*)-ones

1.2.2.1 Synthesis of 2-arylquinolin-4(1*H*)-ones *via* dehydrogenation of the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones

The 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **9** have been reported to undergo C2-C3 dehydrogenation with different oxidizing agents such as thallium(III) *p*-tolylsulfonate (TTS) in dimethoxyethane (DME)[37] or iodobenzene diacetate [$PhI(OAc)_2$]-KOH in methanol,[38] to afford the 2-arylquinolin-4(1*H*)-ones **10** (Scheme 2).



9 **10**

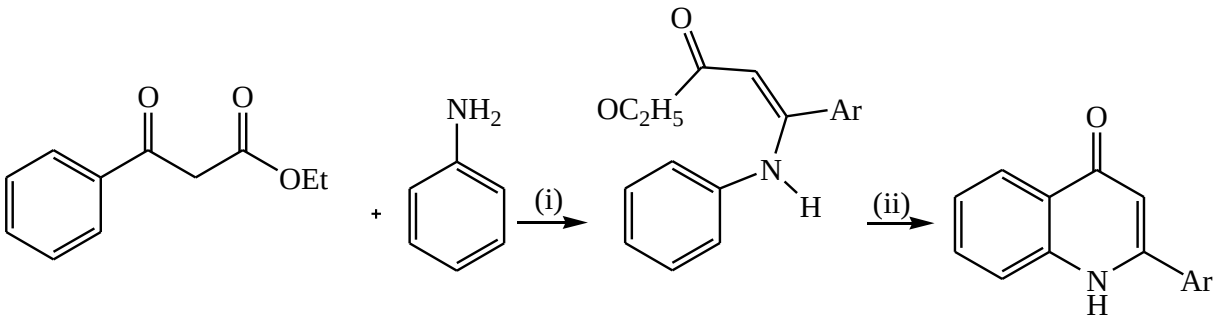
Reagents and conditions: (i) TTS, DME, heat;[37] or $PhI(OAc)_2$, KOH, MeOH, heat[38]

Scheme 2

1.2.2.2 Synthesis of 2-arylquinolin-4(1*H*)-ones *via* tandem condensation-cyclization

Several methods continue to appear in literature describing the synthesis of 2-arylquinolin-4(1*H*)-ones via sequential condensation and cyclization. In earlier methods, anthranilic acid or its ester derivative was heated with the acetal of an alkyl aryl ketone to afford the corresponding 2-arylquinolin-4(1*H*)-ones.[29a] Arylamines were also condensed with an ethyl benzoylacetate derivative in the presence of polyphosphoric acid to afford 2-arylquinolin-4(1*H*)-ones.[39] Anilinoarylidenemalonates derived from carboxymidoyl chlorides were subjected to thermolysis at 170 °C to afford 2-aryl-3-(ethoxycarbonyl)-4-quinolones.[40] Thermolysis of the mono-ethoxycarbonylvinyl derivatives, which were isolated in comparable yields along with the anilinoarylidenemalonates, afforded the 2-aryl-4-quinolones. For example, ethyl benzoylacetate **11** was condensed with aniline **12** in ethanol at 50 °C to afford systems **13** which were, in turn, cyclized at 240-250 °C in diphenyl ether to afford **10** in low to moderate yields (15-50%) (Scheme 3).[41] A series of substituted 2-aryl-4-quinolones was synthesized in moderate to high

yields (16-88%) *via* flash thermolysis of the 1-aryl-5-phenylpyrrole-2,3-diones substituted at the 4-position with cyano or methoxycarbonyl group.[42]

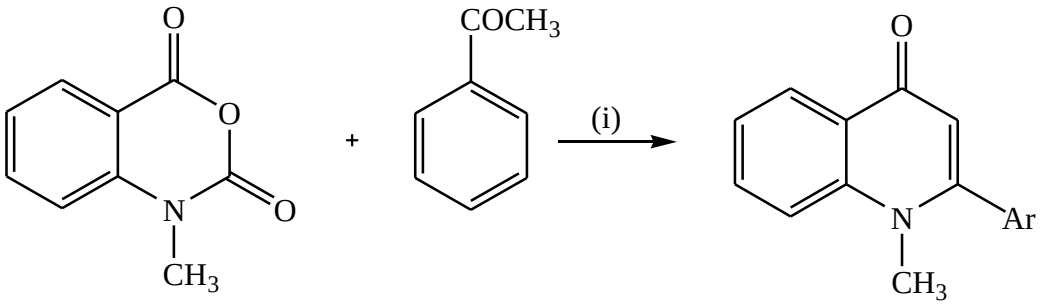


11 **12** **13** **10**

Reagents and conditions: (i) AcOH, EtOH, 50 °C, 24 h; (ii) Diphenyl ether, 240 °C, then 250 °C, 10 min

Scheme 3

A single step reaction, which involves the reaction of *N*-methylisatoic anhydride **14** with acetophenone **15**, using diisopropylamine (DIPA) and *n*-butyllithium (*n*-BuLi) as a base, to produce 2-aryl-1-methylquinolin-4(1*H*)-one **16** in high yields has also been described (Scheme 4).[13,43]

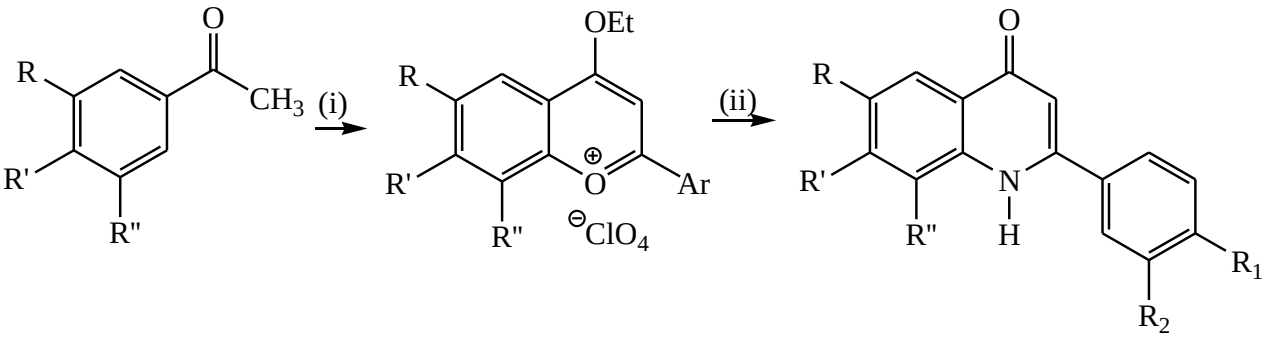


14 **15** **16**

Reagents and conditions: (i) DIPA, *n*-BuLi, THF, -65 °C, 3.5 h

Scheme 4

Direct single-pot acid-catalyzed condensation of substituted aniline derivatives with ethyl benzoylacetate in refluxing toluene also afforded polysubstituted 2-arylquinolin-4(1*H*)-ones.[41,44] Another approach makes use of flavylium salts derived from the reaction of 2-hydroxyacetophenones **17** with aryldehydes in ethyl orthoformate in the presence of potentially explosive perchloric acid.[45] The flavylium salt **18** obtained was then treated with aqueous ammonia to release the 2-aryl-4-quinolone **19** (Scheme 5). A modification of this procedure involves the use of trifluoroacetic acid or trifluoromethanesulfonic acid in ethyl orthoformate or dichloromethane to afford flavylium salts in high yields, but the desired quinolones are isolated in low to moderate yields (18-59%).[45]



17 **18** **19**

R = H, CH_3, *t*-Bu, $NHCOCF_3$ R_1 = H, OH, OCH_3

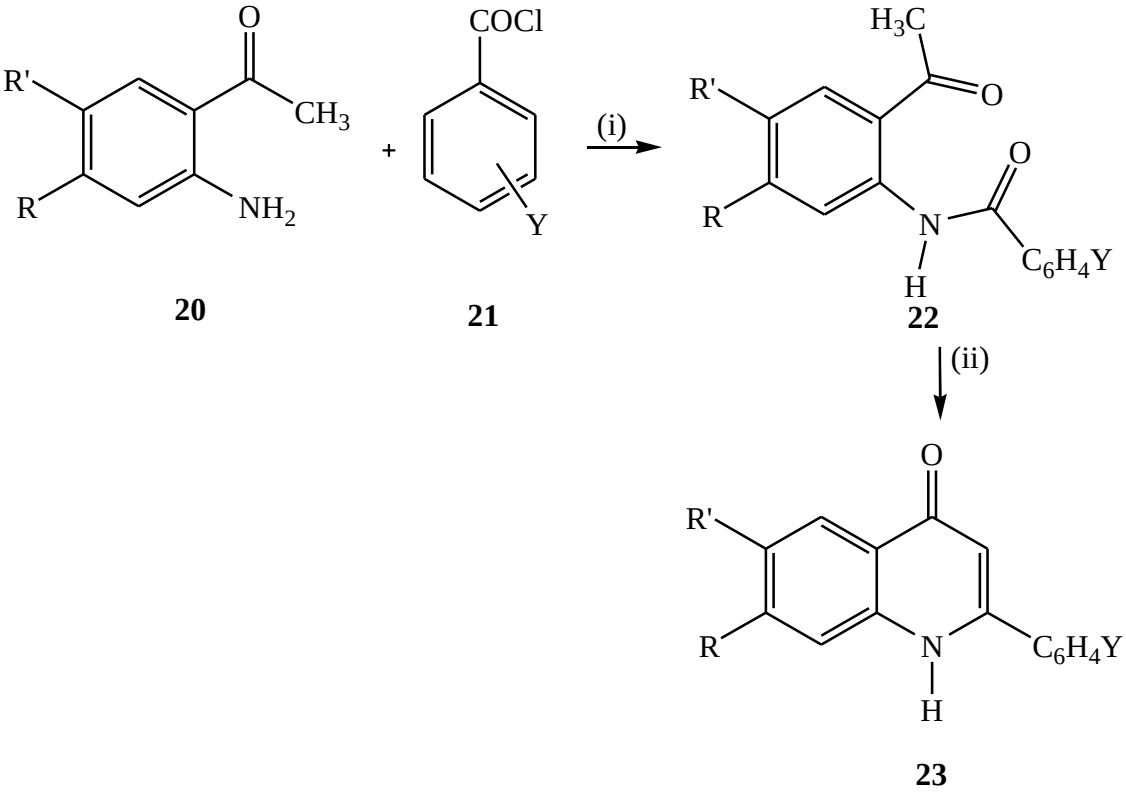
R′ = H; R″ = H, $NHCOCF_3$ R_2 = H, OH, OCH_3

Reagents and conditions: (i) ArCHO, $HClO_4$, $HC(OEt)_3$; (ii) 25% NH_3 (aq)

Scheme 5

In our opinion, the most convenient method for the synthesis of substituted 2-arylquinolin-4(1*H*)-ones reported to-date involves the base-mediated cyclization of *N*-benzoyl-2-aminoacetophenone **22**.[1,46] The latter are in turn, prepared in excellent yields (90-98%) by condensing an appropriately substituted 2-aminoacetophenone **20** with benzoyl chloride

derivatives **21** in the presence of Et_3N in THF. Treatment of systems **22** with *t*-BuOK in *t*-BuOH under reflux afforded the substituted 2-arylquinolin-4(1*H*)-one derivatives **23** in high yield (60-80%) and purity (Scheme 6).



20 **21** **22** **23**

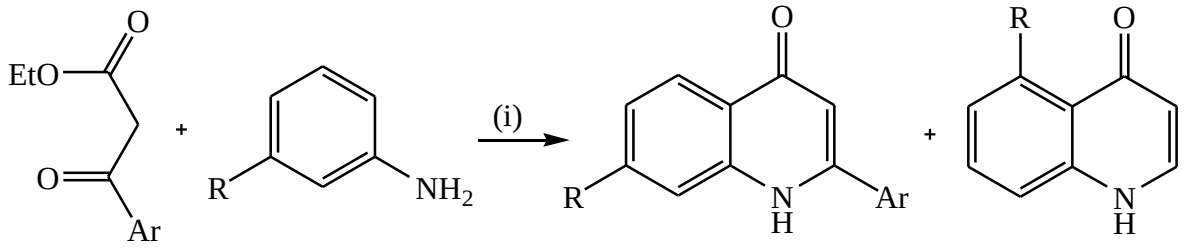
R = R′ = H, OCH_2O; Y = H, F, Cl, OCH_3, -OCH_2O-

Reagents and conditions: (i) Et_3N, THF, 0 °C to rt, 2 h; (ii) *t*-BuOK, *t*-BuOH, reflux, 12 h

Scheme 6

The Conrad-Limpach method is the most common reaction for the synthesis of 3-substituted-4-quinolones involving 2-substituted-β-ketoesters and anilines as starting materials. However, the cyclization step which employs sterically hindered and/or acid-sensitive 2-substituted β-ketoesters usually generates 3-substituted-4-quinolones in poor yields and involves a difficult purification process. For example, when ethyl aroylacetate **24** was reacted with substituted

aniline **25** in the presence of polyphosphoric acid at 260 °C substituted 2-arylquinolin-4(1*H*)-ones **26** and **27** were obtained (Scheme 7). [47a]



24 **25** **26** **27**

Reagents and conditions: (i) PPA, 260 °C

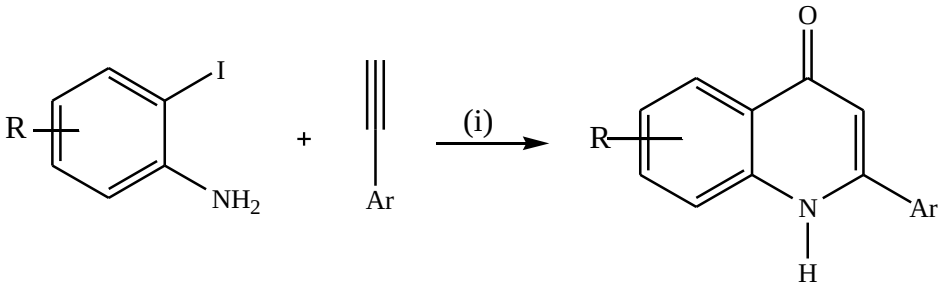
Scheme 7

A short and high yielding synthesis of a series of 2-arylquinolin-4(1*H*)-ones *via* reductive cyclization of 2-nitrochalcones promoted by $TiCl_4$/Zn has been reported.[48] The disadvantage of this route is the non-availability of properly substituted 2-nitroacetophenones. Less traditional methods for the synthesis of 2-arylquinolin-4(1*H*)-ones which make use of transitional metals have also been developed and these are described below.

1.2.3 Synthesis of 2-arylquinolin-4(1*H*)-ones: metal-mediated tandem cyclization approaches

The 2-arylquinolin-4(1*H*)-ones have previously been prepared in moderate to high yields (55-85%) *via* dichlorobis(triphenylphosphine)palladium [$PdCl_2(PPh_3)_2$]-mediated intramolecular cyclization of the corresponding 1-(2-aminophenyl)-3-aryl-2-propen-1-ones in THF.[42,47b] The significant disadvantage of this reaction is the use of stoichiometric quantities of the relatively expensive organometallic reagent and tedious column chromatographic separation of the NH-4-

oxo derivatives that are almost insoluble in many organic solvents. Carbonylations of series of haloanilines and terminal alkynes in the presence of palladium catalyst have also been reported to afford 2-arylquinolin-4(1*H*)-ones in good yields.[49,50] Palladium-catalyzed carbonylation of 2-haloaniline (1.0 eq.) in the presence of terminal acetylenes (2.0 eq.) under CO atmosphere (20 kg/cm^2) at 120 °C resulted in a variety of 2-substituted quinolin-4(1*H*)-ones in moderate to high yields (55-95%).[49] Kalinin *et al*. also reacted *o*-iodoanilines **28** with terminal arylacetylenes **29** in the presence of dichlorobis((1,1′-diphenylphosphino)ferrocene)palladium [$PdCl_2$(dppf)] to afford **30** in good yields (62-85%) (Scheme 8).[50] The reaction proceed well both in diethylamine or tertiary amines and in benzene containing 4 eq. of diethylamine. The drawback of this approach is the use of excessive amounts of carbon monoxide.

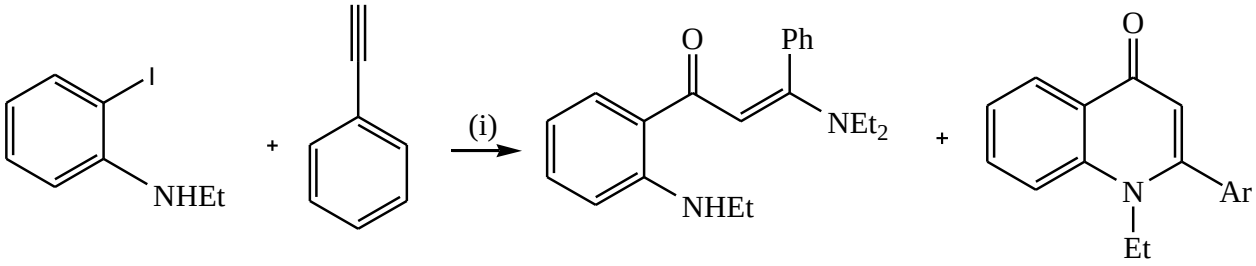


28 **29** **30**

Reagents and conditions: (i) $PdCl_2$(dppf), CO, Et_2NH, 120 °C, 1 h

Scheme 8

Alkylated haloaniline **31** were previously reacted with terminal acetylenes **32** in diethylamine to afford compounds **33** and **34** in 52% and 20% yields, respectively (Scheme 9). Compound **33** was subsequently treated with NaH in THF to afford system **34** in 94% yield.[50] Variously substituted 2-arylquinolin-4(1*H*)-ones were also prepared in high yields (75-97%) through the sequential copper-catalyzed amidation of halophenes, followed by a base-promoted Camps cyclization of the resulting *N*-(2-ketoaryl)amides.[51]



31 **32** **33** **34**

Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, Et_2NH, CO, 120 °C, 6 h.

Scheme 9

A one-pot synthesis of substituted 2-arylquinolin-4(1*H*)-ones *via* sequential Pd-catalyzed amidation of 2-bromoacetophenone derivatives, followed by base-assisted intramolecular cyclization of the resulting intermediates also afforded the substituted 2-arylquinolin-4(1*H*)-ones in good yields (>85%).[52,53] Although effective and high yielding, both the classical and carbonylation pathways are not suitable for the preparation of derivatives bearing alkyl- or aryl-containing substituents on the fused benzo ring, due to unavailability of suitably substituted aniline precursors.[44] Such substituted quinoline derivatives are known to possess electronic, optoelectronic or non-linear optical properties.[54]

1.3 Transformation of 2-arylquinolin-4(1*H*)-ones

The 2-arylquinolin-4(1*H*)-ones represent an attractive platform, allowing for an increase in diversity of substituents around the molecule due to their synthetic accessibility. The 4-quinolone scaffold contains several reactive sites for possible functionalization to yield novel derivatives for further chemical elaboration. The 2-arylquinolin-4(1*H*)-ones have been reported to undergo

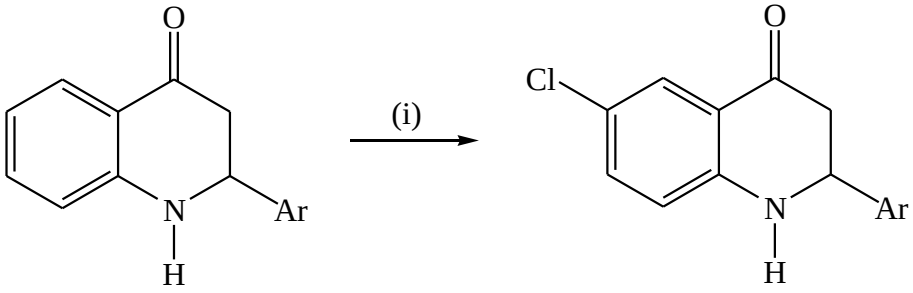
halogenation, *N*- or *O*-alkylation, oxidative aromatization and sequential and one-pot palladium-catalyzed reactions.[42,84] Modifications of the quinolone nucleus through the addition of different substituents at the N-1, C-5, -6, -7 or -8 positions have been found to alter and/or enhance their biological properties.[21,46,55] The 2-arylquinolin-4(1*H*)-ones can also undergo electrophilic substitution with alkyl derivatives to afford *N*- or *O*-alkylated derivatives or a mixture of the two isomers depending on the nature and steric properties of the electrophile used. The oxidative aromatization of the 4-quinolone core with phosphorus oxychloride has yielded 4-chloroquinolines which are essential intermediates in the synthesis of 2-arylquinolines with an heteroatom group in the C-4 position.[42]

1.3.1 Halogenation of the 2-arylquinolin-4(1*H*)-ones

The introduction of a halogen atom onto an aromatic or heteroaromatic ring is used extensively in organic synthesis and medicinal chemistry. The presence of halogen atom/s on the quinolone or quinoline moiety plays an important role in the bioactivity of these compounds and presents an avenue for further structural modification.[56,57] Halogenated quinolones and quinolines are useful precursors in carbon-carbon bond formation or nucleophilic substitution to afford variously substituted quinolones and their quinoline derivatives.[57]

1.3.1.1 Halogenation of the fused benzo ring of the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones and 2-arylquinolin-4(1*H*)-ones

Several methods have been described in the literature for the halogenation of 2-arylquinolones.[58-61] Sharma *et al.* previously treated 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **9** with 1.5 equivalents of (dichloroiodo)benzene ($PhICl_2$) in dichloromethane (DCM) at room temperature in an example of iodine-mediated reaction to afford the corresponding 2-aryl-6-chloro-2,3-dihydroquinolin-4(1*H*)-ones **35** (Scheme 10).[61]

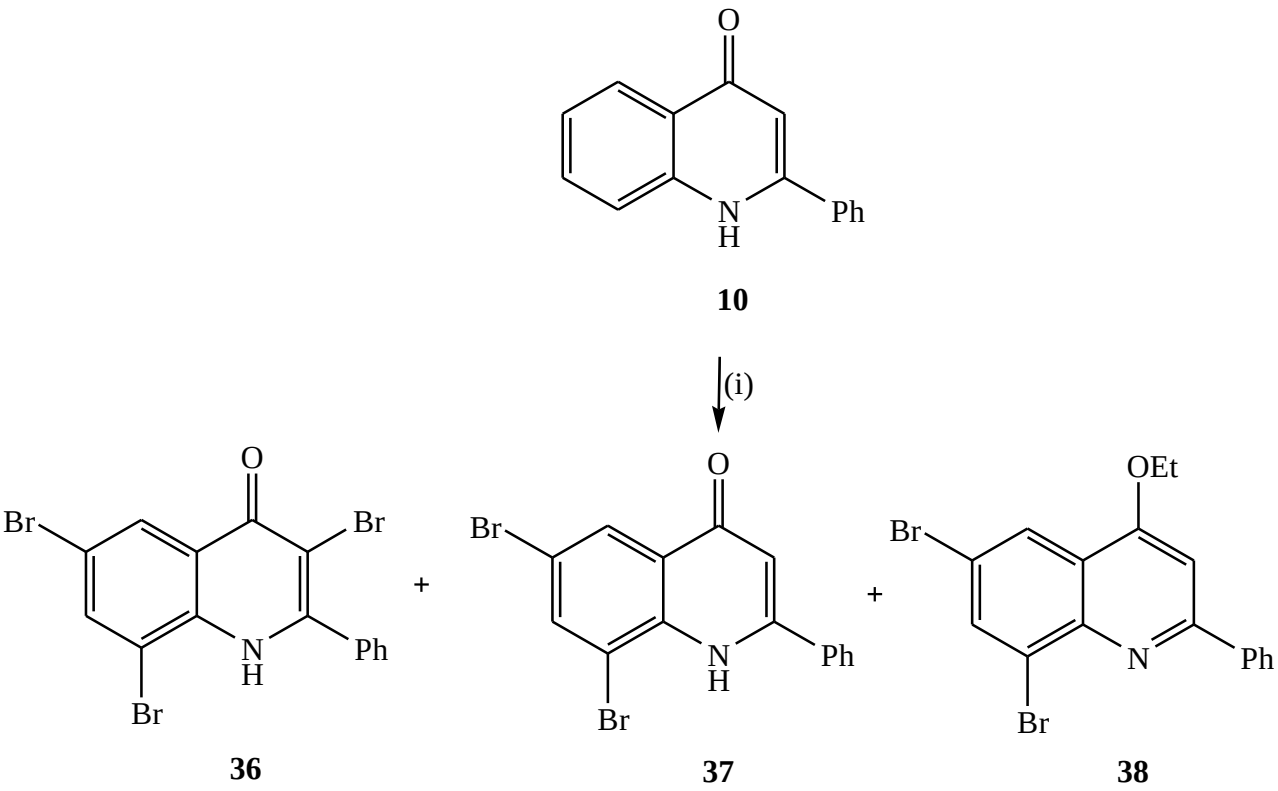


9 **35**

Reagents and conditions: (i) $PhICl_2$, DCM, rt

Scheme 10

Cyclization of 2-aminochalcone with Br_2 (1.0 eq.) in chloroform at room temperature, on the other hand, afforded the 6-bromo derivative in 30% yield.[62] Treatment of **10** with excess Br_2 (4.0 eq.) in chloroform yielded 2-phenyl-3,6,8-tribromoquinolin-4(1*H*)-one **36** as the main product (43%), along with smaller quantities of 6,8-dibromo-2-phenylquinolin-4(1*H*)-one **37** and the ethoxyquinoline derivative **38** (Scheme 11).[62] Formation of the latter was attributed to traces of ethanol present in $CDCl_3$ because the product was not detected or formed when ethanol-free chloroform was used as a solvent in which case only compounds **36** and **37** were isolated.[62]



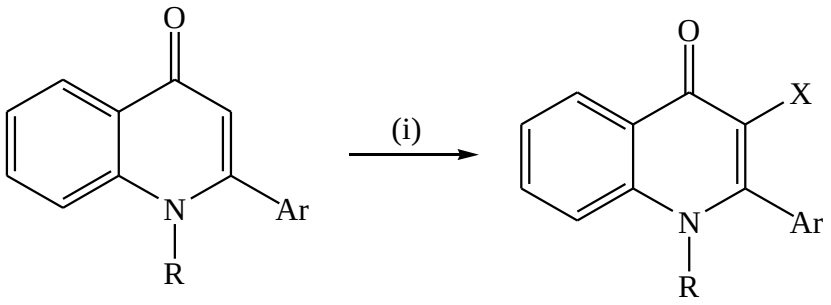
Reagents and conditions: (i) Br_2 (4.0 eq.), $CHCl_3$, rt

Scheme 11

1.3.1.2 C-3 Halogenation of 2-arylquinolin-4(1*H*)-ones

C-3 Bromination of the 2-arylquinolin-4(1*H*)-ones **10** was previously achieved using 2.0 equiv. of pyridinum tribromide in acetic acid at room temperature to afford the 2-aryl-3-bromoquinolin-4(1*H*)-ones **39** (X = Br) (Scheme 12).[63a] Treatment of **10** with molecular iodine (2 eq.) and sodium carbonate (1.5 eq.) in THF at room temperature for 12 h, on the other hand, afforded the corresponding 2-aryl-3-iodoquinolin-4(1*H*)-ones **39** (X = I) (Scheme 12).[63a] A similar reaction involving **10** with an iodine-ammonium cerium nitrate (CAN) (acting as an in-situ oxidant)

mixture in acetonitrile at 70-80 °C also yielded compounds **39** (X = I).[63b] Another route which involves the use of pyridinium tribromide-pyridine mixture in dichloromethane has been described. However, it requires excess reagents and is accompanied by a laborious workup procedure.[63a]



10 (R = H, CH_3) **39**

Reagents and conditions: (i) $C_5H_5NHBr_3$, AcOH, rt, 2 h for X = Br; or I_2, Na_2CO_3, THF, rt, 12 h for X = I

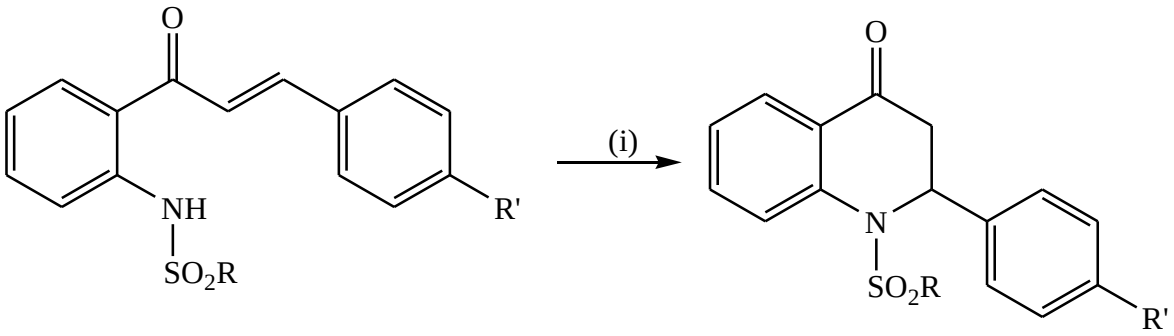
Scheme 12

1.3.2 *N*-substitution of 2-arylquinolin-4(1*H*)-ones

1.3.2.1 *N*-sulfonylation of 2-arylquinolin-4(1*H*)-ones

2-Benzenesulphonamido-4-methoxychalcone **40** was previously treated with aqueous ethanolic sodium hydroxide to afford a benzenesulphonyl derivative **41** (Scheme 13).[30] 2-(Benzenesulfonamido)-α-bromo-β-methoxydihydrochalcone was then cyclized in the presence of

ethanolic potassium hydroxide to afford *cis*-1-(phenylsulfonyl)-3-bromo-2,3-dihydroquinolin-4(1*H*)-one in 32% yield.[29a] Treatment of 2-aminochalcones with methanesulfonyl chloride in pyridine afforded the *N*-methanesulfonylaminochalcones which were, in turn, subjected to base-promoted cyclization in ethanol to afford *N*-methanesulfonylaminoquinolones in appreciable yields (55-75%).[66]



40 **41**

R = Ph; R′ = OMe

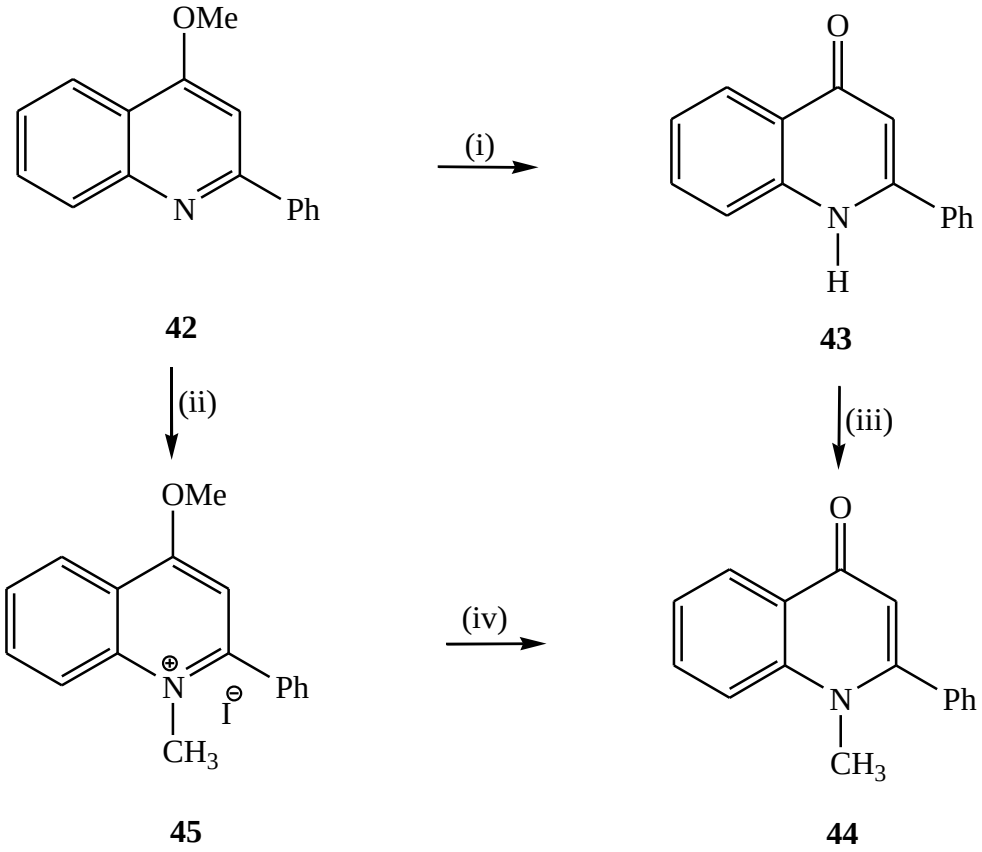
Reagents and conditions: (i) NaOH, EtOH, rt

Scheme 13

1.3.2.2 *N*-alkylation of 2-arylquinolin-4(1*H*)-ones

The potentially tautomeric 4-quinolone moiety enables interconversion between the NH-4-oxo precursors and their *O*- or *N*-methylated derivatives. The reaction of the naturally occurring 4-methoxy-2-phenylquinoline **42** with HCl in methanol under reflux previously afforded 2-phenylquinolin-4(1*H*)-one **43**, which was in turn, treated with dimethyl sulfate under basic conditions to yield *N*-Me-4-oxo derivative **44**.[42] Conversely, compound **42** when heated with

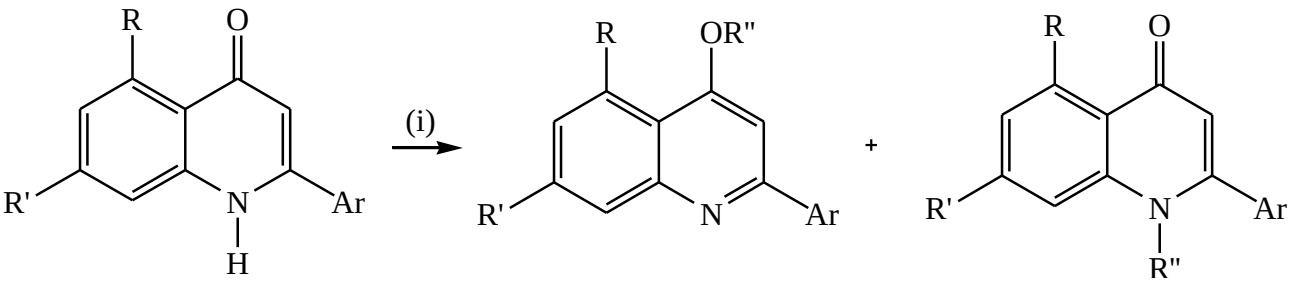
methyl iodide afforded the dimethylated derivative **45**, which yielded the 1-methyl-2-phenylquinoline **44** upon treatment with a base (Scheme 14).[64]



Reagents and conditions: (i) HCl, MeOH, heat; (ii) MeI, heat; (iii) Me_2SO_4, NaOH; (iv) NaOH

Scheme 14

It was observed that the presence of a substituent at the C-5 or C-3 position has a major effect on the regioselectivity of alkylation of the quinolone derivatives. When 5,7-dimethoxy-2-phenylquinolin-4(1*H*)-one **46** was treated with a MeI-K_2CO_3 mixture in DMF, the *O*-methylated derivative **47** was formed as the sole product (Scheme 15).[24] Under similar reaction conditions, 5-hydroxy-7-methoxy-2-phenyl-4-quinolone **46** (R = OH, R′ = OMe), with the potential to form a strong hydrogen bond between the carbonyl oxygen and 5-OH, afforded a mixture of both *O*-**47** and *N*-methylated derivatives **48** in the ratio 9:1 in favour of the *N*-methylated derivative.[43,65]



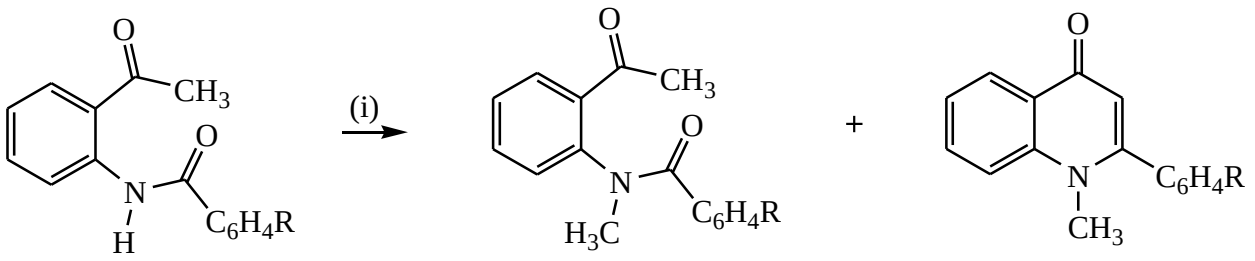
46 **47** **48**

Reagents: (i) K_2CO_3, R″X, DMF[24] or NaH, R″X, THF[43,65]

Scheme 15

1.3.2.3 Direct synthesis of *N*-alkylated 2-arylquinolin-4(1*H*)-ones

The synthesis of 2-aryl-1-methyl-4-quinolones **16**, involving the reaction of lithium enolates of acetophenone derivatives **15** with *N*-methylisatoic anhydride **14**, represents the shortest route reported to-date (Scheme 4).[13,43] Although the reaction is efficient in terms of the yields, the drawback is that each reaction, when using different substrates, has its unique temperature requirements for completion. A direct one-pot synthesis of 2-aryl-1-methylquinolin-4(1*H*)-ones **51**, involving the reaction of *N*-arylamidoacetophenone derivatives **49** with MeI in the presence of NaH in THF to afford 2-aryl-1-methylquinolin-4(1*H*)-ones **51** in moderate yields (51-61%), has also been reported (Scheme 16).[53] The corresponding *N*-methylated arylamidoacetophenone derivatives **50** were only isolated in trace amounts (> 5%).

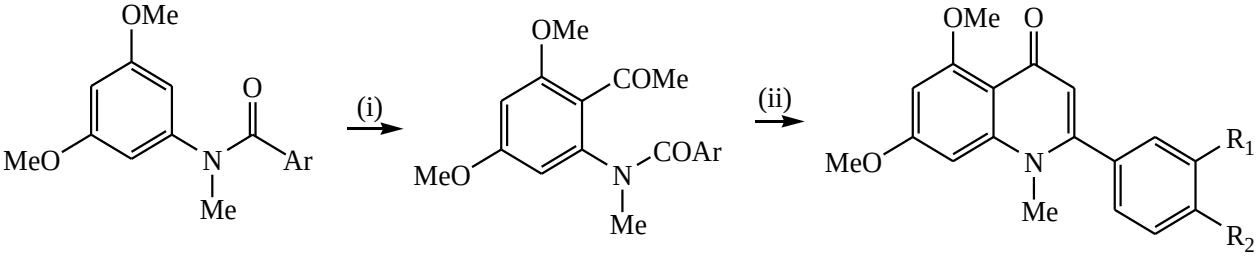


49 **50** **51**

*Reagents and conditions***:** (i) NaH, MeI, THF, rt

Scheme 16

Another example involving stannic chloride ($SnCl_4$)-induced Friedel-Crafts acylation of **52** with methylacetylchloride **(**MeCOCl) in dichloromethane afforded **53**, which upon cyclization with *t*-BuOK in *t*-BuOH yielded the corresponding 2-aryl-1-methylquinolin-4(1*H*)-ones **54** (Scheme 17).[42,99]



52 **53** **54**

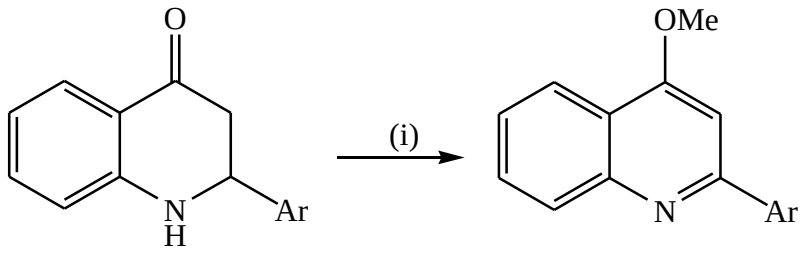
$R_1 = NO_2$, H; R_2 = Cl, OCOMe

Reagents and conditions: (i) MeCOCl, $SnCl_4$, CH_2Cl_2; (ii) *t*-BuOK, *t*-BuOH, 30 °C

Scheme 17

1.3.3 Direct *O*-alkylation *via* oxidative aromatization of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones

The treatment of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **9** with molecular iodine,[67] ferric chloride hexahydrate in methanol[68] or [hydroxyl(tosyloxy)iodo]benzene in trimethyl orthoformate in the presence of perchloric acid as a catalyst under reflux[95] has been reported to afford the corresponding 2-aryl-4-methoxyquinolines **55** (>70%) (Scheme 18).



9 **55**

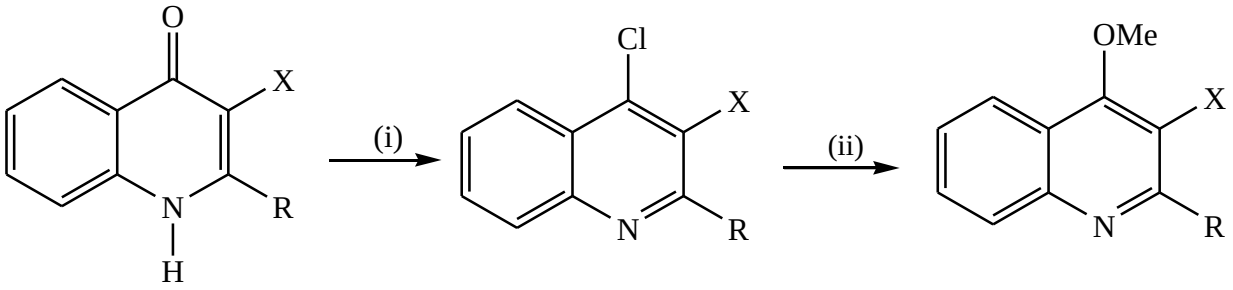
Reagents and conditions: (i) I_2, MeOH;[67] $FeCl_3 \cdot 7H_2O$, MeOH;[68] HTIB, $CH(OR'')_3$, $HClO_4$[95]

Scheme 18

1.3.3.1 Phosphorus oxychloride ($POCl_3$)–mediated aromatization of 2-arylquinolin-4(1*H*)-ones

Phosphorus oxychloride-induced aromatization of the 2-arylquinolin-4(1*H*)-ones **56** under reflux afforded the corresponding 2-aryl-4-chloroquionoline derivatives **57**, which upon treatment with sodium methoxide in THF resulted in the corresponding 4-alkoxyquinoline derivatives **58** (Scheme 19).[69] Series of 2-aryl-3-(bromo/iodo)-4-methoxyquinolines (X = H, Br, I) were also

prepared from the corresponding 2-aryl-4-chloro-3-halogenoquinolines following this procedure.[69]

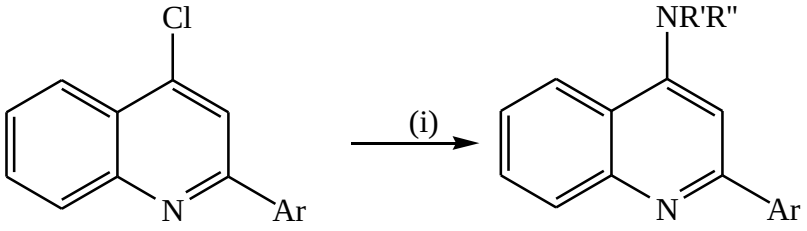


56 **57** **58**

Reagents and conditions: (i) $POCl_3$, heat, 2 h; (ii) NaOMe, THF, heat, 18 h

Scheme 19

Conversely, the reaction of 4-chloroquinolines **59** with ammonia derivatives afforded the 4-aminoquinolines **60** (Scheme 20).[70-72] Amination of 6-bromo-4-chloroquinoline (1.0 eq.) with a small excess of morpholine (1.2 eq.) in refluxing dioxane in the presence of sodium *tert*-butoxide and 2 mol% of palladium catalyst at 100 °C for 7 h, resulted in the formation of 6-amino-4-chloroquinolines (84-94%).[72] The yields of the products and selectivity of the reaction improved in the presence of ligand complexes. The use of morpholine (4 eq.) and prolonged reaction time (24 h) resulted in the isolation of 4,6-diaminoquinoline as the major product (91%).[72]



59 **60** [R′ = H, R″ = Ph; R′, R″ = -$(CH_2)_4$-]

Reagents and conditions: (i) R″NH_2, R′R″NH, heat

Scheme 20

1.4 Applications of organometallic reagents in the synthesis of polysubstituted quinolones

The need to address the limitations of the classical methods in the synthesis of polysubstituted quinolones resulted in the development of metal-catalyzed reactions. Palladium-catalyzed Suzuki-Miyaura,[73] Negishi,[74,75] Stille,[75,76] Heck[77,78] and Sonogashira cross-coupling reactions[79,80] are well developed methods for C-C bond formation and these methods have found important application in the synthesis of polysubstituted quinolones and quinoline derivatives. The mechanism of these reactions commonly involves 3 major steps, namely, (i) oxidative addition; (ii) transmetalation and (iii) reductive elimination (Fig. 1). The first step involves the oxidative addition of the 14 electron complex $Pd(0)L_2$ into the arylhalide to afford the *trans* arylpalladium(II) complex (*trans*-$RPdXL_2$) **B**. The difference in these cross-coupling reactions is in the transmetalation step to afford intermediate **C**. Here, both organic ligands are *trans* oriented and converted to *cis* in a *trans*-*cis* isomerization to complex **D**. Reductive elimination from **D** affords the cross-coupled product with the regeneration of Pd(0) to commence another cycle. The order of reactivity in transition metal-mediated cross-coupling of aryl or heteroarylhalides: I>Br>Cl>F relates to the strength of the Csp^2-halide bond and this allows for selective coupling with bromides or iodides in the presence of chlorides.[97]

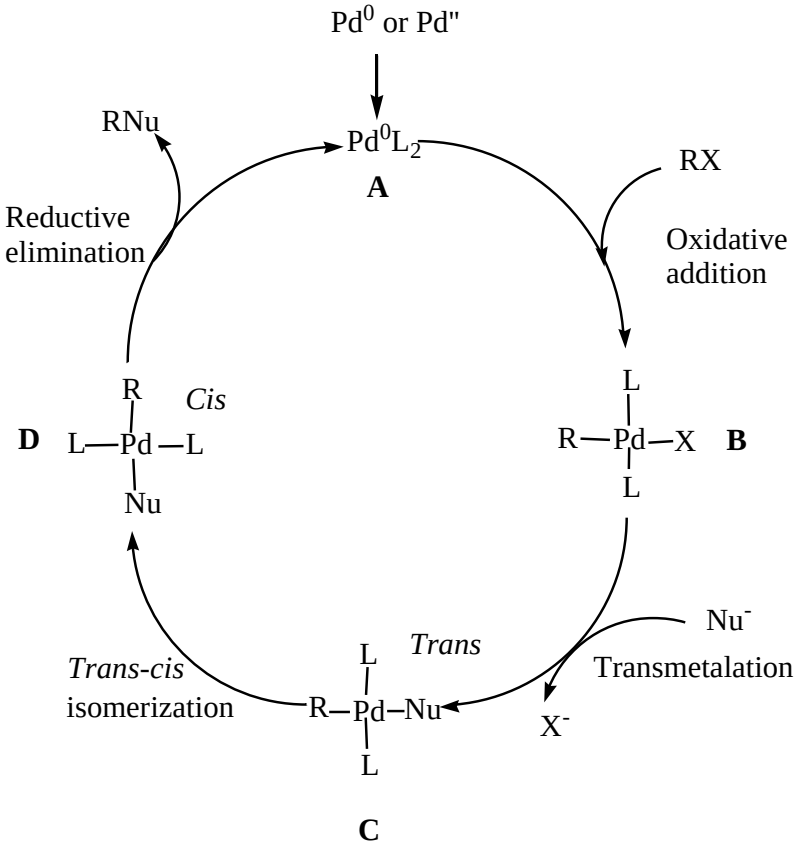


Figure 1: Generalized cycle for palladium-catalyzed cross-coupling

1.4.1 Applications of the Negishi cross-coupling reaction

Negishi coupling involves the reaction of an aryl and vinylhalides/triflates with organozinc reagents to form carbon-carbon bonds.[74] Organozinc reagents can be prepared either by direct reaction of organic halide with zinc or activated zinc, or by transmetalation of the corresponding organolithium or Grignard reagents with a zinc halide. Organic halides, especially iodides and bromides are the most reactive category of electrophiles. However, the use of leaving groups such as acetates and triflates have also been investigated. This method has been employed extensively on haloquinolines to afford polysubstituted quinoline derivatives.[81,89] Transition

metal-catalyzed organozinc reagents have advantages over the conventional reagents because they are synthetically useful, especially for the control of the chemo-, regio- and stereo-selectivity.[74] Moreover, organozinc compounds also tolerate a wide range of functional groups in either or both of the coupling reactants.

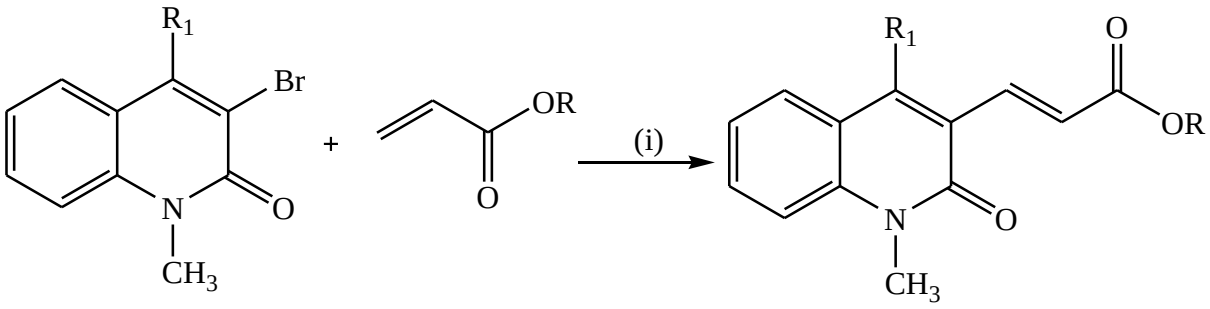
1.4.2 Applications of the Stille cross-coupling reaction

The Stille cross-coupling reaction involves palladium-catalyzed coupling between organostannanes and organic halides. The stannane is usually sp^2 or sp hybridized. However, alkyl-, allyl- or benzyl-stannanes have also been used.[76] The trend in reactivity follows the order: alkynyl > alkenyl > aryl > allyl~benzyl > alkyl. The stille coupling has found many applications in organic synthesis due to the broad scope and good tolerance for many functional groups.[75,76] The major drawback is the toxicity of the tin compounds used, and their low polarity, which makes them poorly soluble in water.[75,76]

1.4.3 Applications of the Heck cross-coupling reaction

The Heck reaction involves cross coupling of an unsaturated halide with an alkene in the presence of a strong base and palladium as catalyst to form a substituted alkene.[77] An aryl, benzyl or vinyl halide or triflate and the alkene which contains at least one proton, for example, acrylate ester or an acrylonitrile are employed as coupling partners. Tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II) and palladium acetate are commonly used as Pd(0) catalyst sources. Triethylamine, potassium

carbonate or sodium acetate are used as bases of choice.[78] Terminal alkenes are good substrates for the Heck reaction and react at the non-substituted carbon. The choice of amine-base and phosphine-ligand has great influence on the selectivity and reactivity in the Heck reaction. For example, palladium-catalyzed reaction of 4-aryl-3-bromoquinolin-2(1*H*)-ones **61** with *n*-butyl acrylate **62** and phosphine ligand, with tetrabutylammonium bromide as an additive afforded 3-alkenyl-4-arylquinolin-2(1*H*)-ones **63** isolated in reasonable yields (60-80%) (Scheme 21).[82]



61 **62** **63**

R = *n*-Bu, R_1 = Ar

Reagents and conditions: (i) $Pd(OAc)_2$ (5mol%), [tri(dimethoxylphenyl)]phosphine, Et_3N, *n*-Bu_4NBr, DMF, 140 °C, 3 h

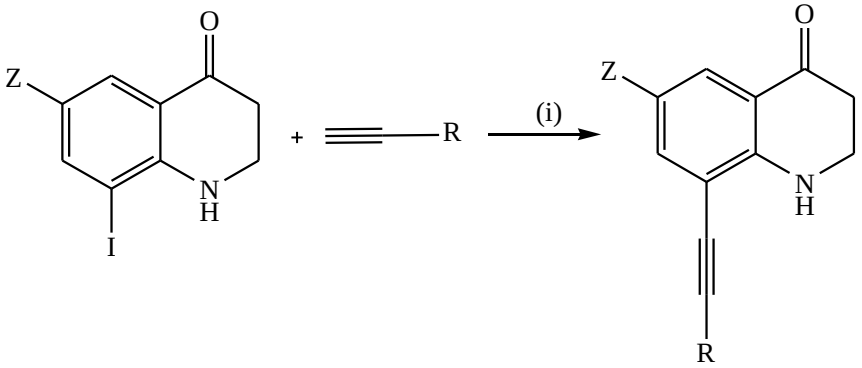
Scheme 21

The advantages of the Heck coupling include, the *trans* selectivity and functional group compatibility.

1.4.4 Applications of the Sonogashira cross-coupling reaction

This reaction involves palladium-catalyzed sp^2-*sp* coupling between aryl or alkenyl halides or triflates and terminal alkynes.[83-85] Palladium-catalyzed alkynylation of aryl or heteroaryl rings

has proved to be a useful method for the C-C bond formation. Typically, the coupling reactions are carried out in the presence of Pd(0) catalyst source and a copper salt as co-catalyst in the presence of an amine base. The use of dihalo derivatives of arenes and hetarenes as substrates for the regioselective introduction of substituents via cross-coupling markedly extends the scope of the method and opens up a facile synthetic approach to diverse classes of di- and polysubstituted aromatic or heteroaromatic compounds.[94] As an example, 6-Substituted-8-iodo-2,3-dihydroquinolin-4(1*H*)-ones **64** were reacted with a series of terminal alkynes **65** in the presence of 10% Pd/C-CuI-PPh_3 catalyst mixture using Et_3N as a base in EtOH at 80 °C to afford a range of alkynylated products **66** in good to excellent yields (60-90%) (Scheme 22).[84] Also, the coupling reaction of 3-iodo-2-phenylquinolin-4(1*H*)-one **67** with 2-methyl-3-butyn-2-ol **68** in the presence of Pd/C-PPh_3 in DMF at 80 °C afforded a mixture of 2-(4-phenylfuro[3,2-c]quinolin-2-yl)-2-ol **69** and **70** in 70% and 11% yield, respectively (Scheme 23).[63b]

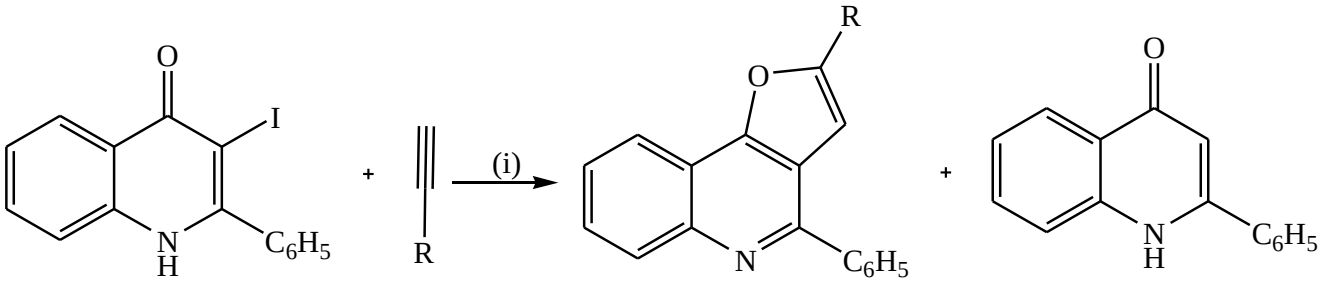


64 **65** **66**

Z = Me, Cl; R= -C_6H_5, *p*-MeC_6H_4-, -$(CH_2)_3CN$, -CMe_3

Reagents and conditions: **(**i) 10% Pd/C, PPh_3, CuI, Et_3N, EtOH, 80 °C

Scheme 22



67 **68** **69** **70**

R= $C(OH)Me_2$

Reagents and conditions: (i) 10% Pd/C, PPh_3, CuI, NEt_3, DMF, heat, 3 h

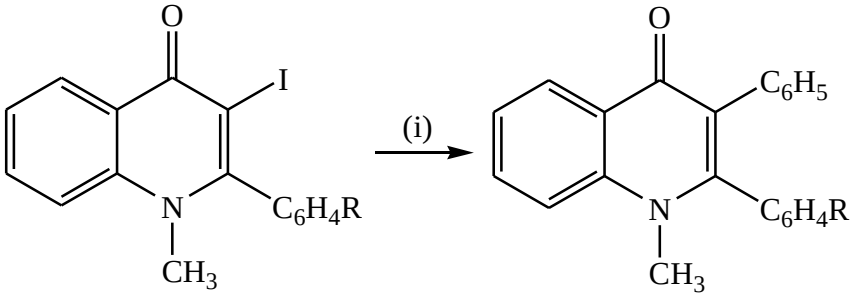
Scheme 23

The advantages for this reaction include functional group compatibility, relatively low temperatures utilized and that the reactions are generally less time consuming.

1.4.5 Applications of the Suzuki-Miyaura cross-coupling reaction

The Suzuki-Miyaura reaction is one of the most versatile methods for the synthesis of both symmetrical and unsymmetrical biaryl derivatives and proceeds best with aryl or heteroaryl iodides or bromides and less so with the corresponding chlorides. Palladium-catalyzed Suzuki-Miyaura cross-coupling involves the reaction of organoboron compounds and carbon electrophiles such as aryl halide or hetaryl halides.[86-88] The reaction is conducted in the presence of palladium catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ and bases such as NaOH, KOH, K_2CO_3, NaOEt, CsOH which activate the weakly nucleophilic boranes, borinates or boronates for the transmetalation step. For example, the reaction involving 2-aryl-3-iodo-1-methylquinolin-

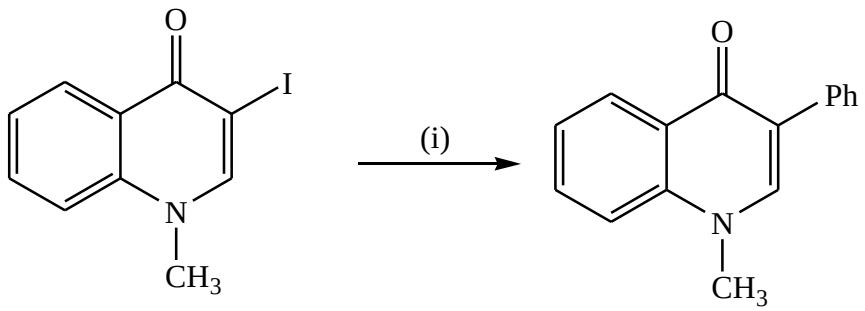
4(1*H*)-ones **71** and phenylboronic acid in the presence of $Pd(PPh_3)_4$ with 2 M Na_2CO_3 in DMF under reflux for 18 h, afforded 2,3-diaryl-1-methylquinolin-4(1*H*)-ones **72** (52-74%) (Scheme 24).[63a] Recently, 3-iodo-1-methylquinolin-4(1*H*)-one **73** was converted to the corresponding 3-phenyl-1-methylquinolin-4(1*H*)-one **74** in 75% yield when treated with phenylboronic acid (1.2 eq.) in the presence of $Pd(OAc)_2$ (10 mol %), PPh_3 (30 mol %) as a ligand and 2 M Na_2CO_3 (2.5 eq.) as a base in DME/EtOH (1.5:1) under microwave irradiation at 70 °C (Scheme 25).[89] The selectivity of Suzuki-Miyaura cross-coupling was demonstrated by the displacement of the iodo atom over the Br atom in the reaction between 1-substituted 6-bromo-3-iodoquinolin-4(1*H*)-ones and a range of arylboronic acids under similar conditions employed in Scheme 25, to afford the corresponding products in moderate to high yields (49-84%).[89]



71 **72**

Reagents and conditions: (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DMF, heat, 18 h

Scheme 24

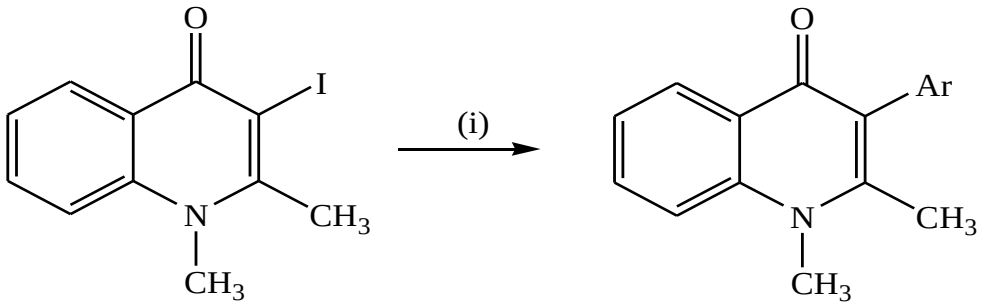


73 **74**

Reagents and conditions: (i) $PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, Na_2CO_3, DME/ EtOH, MW, 70 °C, 5 min

Scheme 25

The versatility of the Suzuki-Miyaura reaction was also demonstrated in the reaction of 3-iodo-1,2-dimethylquinolin-4(1*H*)-one **75** with arylboronic derivatives (1.5 equivalents) in the presence of (dibenzylideneacetone)palladium(II) and 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl (SPHOS) as a ligand and potassium phosphate in toluene to afford 2-aryl-1,2-dimethylquinolin-4(1*H*)-one **76** in 95% yield (Scheme 26).[90]



75 **76**

Reagents and conditions : (i) $ArB(OH)_2$ (1.5 equiv.), $Pd_2(dba)_3$, SPHOS, K_3PO_4, toluene heat, 0.75 h.

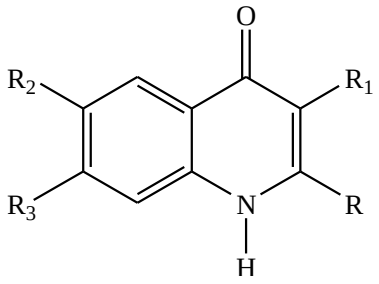
Scheme 26

There is a growing interest in the synthesis of polysubstituted quinolones and their quinoline derivatives bearing aryl, alkenyl and alkynyl groups on the fused benzo and/ or heterocyclic rings. Such groups can be efficiently incorporated via metal-catalyzed C-C bond formation using presynthesized halogenated quinolones or quinoline derivatives as substrates. Our goal is to prepare a series of polysubstituted quinolones and quinoline derivatives bearing aryl groups at the 2-, 6- and 8-positions using 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones as substrates.

1.5 Research Hypothesis and Problem Statement

The quinolin-4(1*H*)-one moiety is prevalent in several natural and synthetic compounds of biological importance (Fig. 2). An array of substituted 2-phenylquinolin-4(1*H*)-ones have been shown to exhibit potent antitumor[91] activity with efficacy comparable to antimitotic[92] natural products such as colchicines, podophyllotoxin and combrestatin A-4.[39,65,94] The 2-arylquinolin-4(1*H*)-ones are also found to serve as antiplatelet agents.[55] The 7-methoxy-2-(4-methoxyphenyl)-6-(5-oxazollyl)quinolin-4(1*H*)-one **A**, for example, serves as an inosine 5′-monophosphate dehydrogenase type II (IMPDH) inhibitor (Fig. 2).[65,94] The other derivatives of 2-arylquinolin-4(1*H*)-ones, such as 3′-methoxy-6,7-(methylenedioxy)-2-phenylquinolin-4(1*H*)-one **B** and 2-(2-fluorophenyl)-6-(1-pyrrolidinyl)quinolin-4(1*H*)-one **C** display strong inhibitory effects on tubulin polymerization with IC_{50} values of 1.0 μM and 0.46 μM, respectively.[46,65,94] Of additionan interest, the 3-ethoxycarbonyl-4-quinolone **D** has previously been identified as a lead compound for ligand binding at the benzodiazepine site of $GABA_A$ receptors.[98] γ-Aminobutyric acid, GABA, is one of the major inhibitory neurotransmitters in the central nervous system. In

terms of anticancer activity, 2-(2′-chlorophenyl)-6,7-methylenedioxyquinolin-4(1*H*)-one **E**[90] and 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones[93] have been found to show strong cytotoxic effects against breast cancer cell lines. Moreover, a series of 1-[(2-hydroxy-ethoxy)methyl]-4(1*H*)quinolone-3-carboxylic acids were evaluated and found to exhibit antiviral activity against herpes simplex virus type 1 (HSV-1) reducing the virus yield by 70-99% at the concentration of 50 μM.[102] Finally, the substituted 4-quinolones have also found important applications in photographic sensitizers,[6] electronic, optoelectronic and non-linear optical material.[54]



Comp	R	R_1	R_2	R_3
A	4- $MeOC_6H_4$-	H	5-oxazolyl	OMe
B	3- $MeOC_6H_4$-	H	-OCH_2O-	-OCH_2O-
C	2-FC_6H_4-	H	1-pyrrolidinyl	H
D	H	-CO_2Et	CF_3	H
E	2-ClC_6H_4-	H	-OCH_2O-	-OCH_2O-

Figure 2: Examples of biologically active derivatives based on quinolin-4(1*H*)-one framework

As demonstrated in the introduction, the quinolin-4(1*H*)-one core is available for functionalization including halogenations, alkylation, alkenylation, alkynylation or arylation. Halogenated quinolones and their quinoline derivatives are getting attention because of the ease of displacement of the halogen atom/s on the aryl or heteroaryl moiety by nucleophiles or metal

catalysts to provide an avenue for further elaboration. From substituted quinolones or quinolines, we became interested in the synthesis of derivatives bearing aryl substituents at the 2-, 6- and 8-positions. To achieve this task we needed the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones as substrates for metal-catalyzed cross-coupling to afford the target compounds. At the outset of this investigation, we were confronted by a challenge to synthesize the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones to serve as precursors for the synthesis of 2-aryl-6,8-dibromo-2,3-dihydroquionolin-4(1*H*)-ones. Our choice of Suzuki-Miyaura cross-coupling reaction was particularly prompted by the ready availability of arylboronic acids. The presence of the acidic NH, however, posed another challenge particularly for the basic conditions employed to effect the Suzuki-Miyaura cross-coupling reactions.

1.6 Aims and Objectives

The main focus of this investigation was to achieve the following aims:

(i) To synthesize the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones using the known 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones as substrates

(ii) To transform the requisite 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones into 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones *via* Suzuki-Miyaura cross-coupling with various arylboronic acids

(iii) To dehydrogenate the 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones to afford the corresponding 2,6,8-triarylquinolin-4(1*H*)-ones

(iv) To effect oxidative aromatization of the 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones to afford the 2,6,8-triaryl-4-methoxyquinolines

CHAPTER 2 RESULTS AND DISCUSSION

Figure 3 below presents a brief overview of all the steps undertaken in this investigation to achieve the set goals. The 1-(2′-aminophenyl)-3-aryl-2-propen-1-one derivatives **8** were prepared by condensing 2-aminoacetophenone **77** and benzaldehyde derivatives **78** in the presence of NaOH in ethanol. Systems **8** were, in turn, cyclized using orthophosphoric acid in acetic acid to afford the corresponding 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **9**. The latter were treated with *N*-bromosuccinimide in carbon tetrachloride to afford the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones **79**. Compounds **79** were, in turn, subjected to Suzuki-Miyaura cross-coupling reaction with arylboronic acids (2.5 equiv.) in the presence of dichlorobis(triphenylphosphine)palladium(II) $[PdCl_2(PPh_3)_2]$-tricyclohexylphosphine (PCy_3) as catalyst complex and potassium carbonate (K_2CO_3) as a base in dioxane-water (3:1, v/v) to afford the corresponding 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones **80**. Dehydrogenation of the latter using thallium(III) *p*-tolylsulphonate in dimethoxyethane under reflux yielded the 2,6,8-triarylquinolin-4(1*H*)-one derivatives **81**. The 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones **80** were also subjected to molecular iodine in methanol to effect oxidative aromatization to afford the corresponding 2,6,8-triaryl-4-methoxyquinoline derivatives **82**. All the prepared products prepared in this investigation were characterized using a combination of ^{1}H NMR & ^{13}C NMR spectroscopy, IR and mass spectroscopic techniques.

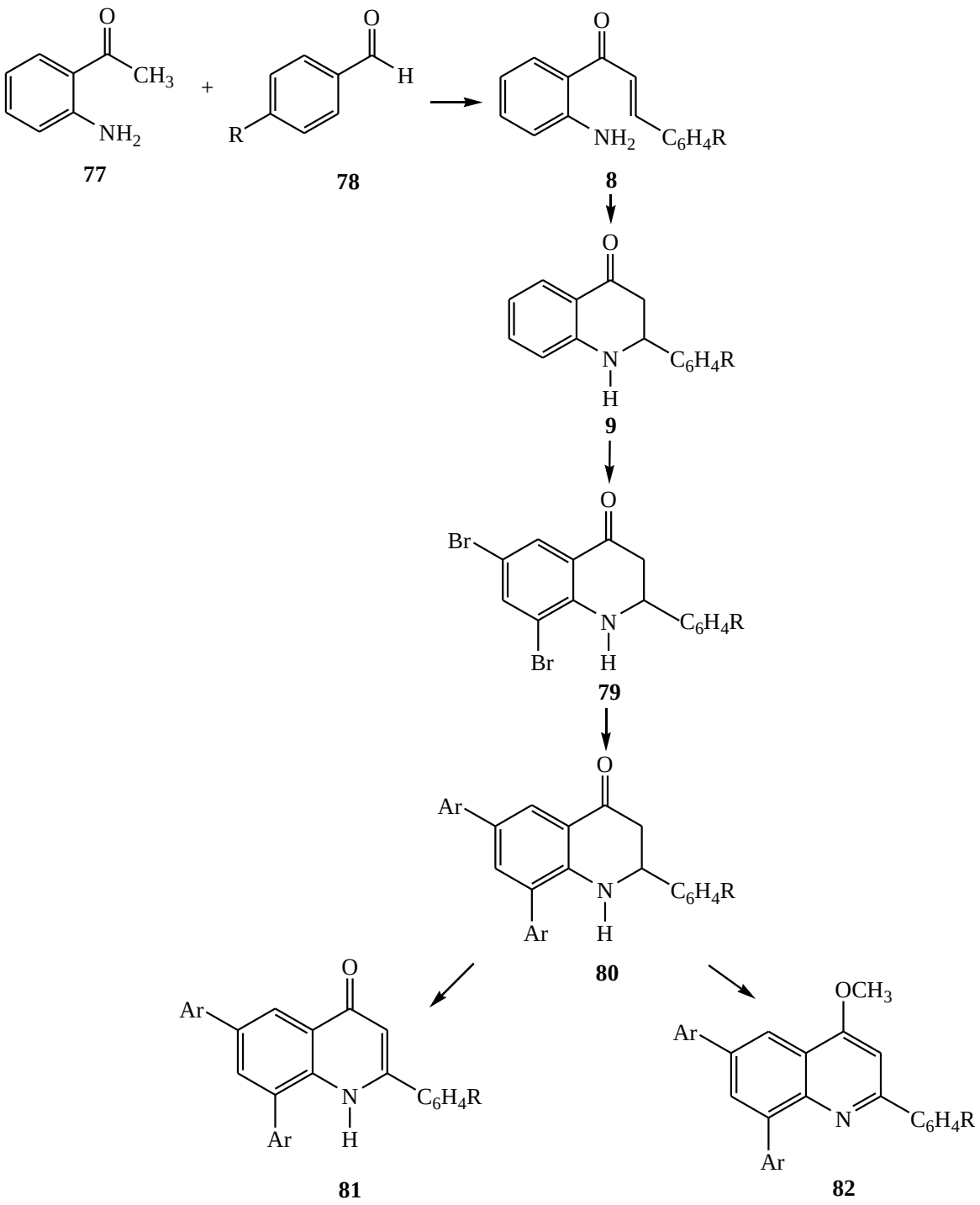
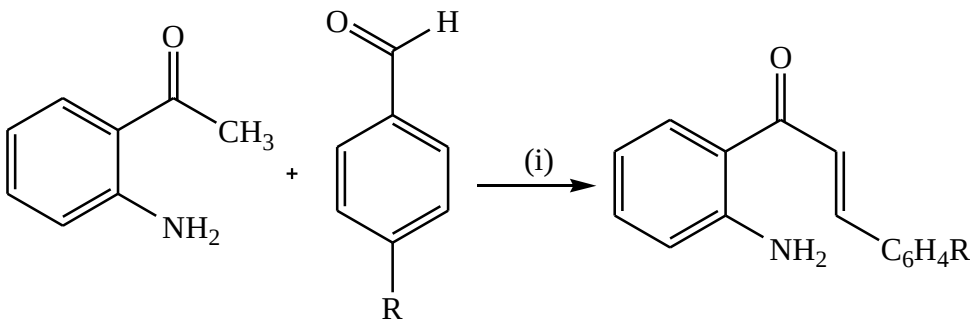


Figure 3: Generalized scheme depicting reaction pathways followed to prepare the compounds described in this investigation

2.1 Preparation of Substrates

2.1.1 Synthesis of 1-(2′-aminophenyl)-3-aryl-2-propen-1-ones 8a-d

Numerous approaches have been reported for the synthesis of the 2-aminochalcones which are important intermediates in the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones. An alternative procedure for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones make use of 2-nitrochalcones as precursors, but gives relatively low yields and requires an additional step.[36] The 2-nitrochalcones themselves are, in turn, prepared by reacting vinylmagnesium bromide with 2-nitrobenzaldehyde in THF, followed by oxidation of the resulting alcohol derivative to afford 1-(2-nitrophenyl)-2-propen-1-one in 71% overall yield.[36] The 2′-nitrochalcones were also prepared in 92-97% yields by reacting 2′-nitroacetophenone with a series of benazaldehyde derivatives in the presence of NaOH in ethanol.[36] In this investigation, we prepared the 1-(2-aminophenyl)-3-aryl-2-propen-1-ones **8** following a previously described method, which involves the Claisen-Schmidt aldol condensation of 2-aminoacetophenone **77** with benzaldehyde derivatives **78** in the presence of NaOH (3 pellets, *ca*. 0.6 g) in ethanol (Scheme 27).[30,31] The ^{1}H NMR spectra of products **8** reveal the presence of a broad singlet at δ *ca*. 6.34 ppm, which corresponds to the amino group and a group of proton signals in the aromatic region, δ 6.66-7.85 ppm. The presence of NH_2 and C=O groups was also confirmed by the corresponding IR absorption bands at ν_{max} *ca*. 3443-3326 cm^{-1} and 1640-1614 cm^{-1}, respectively. Although some of the observed melting point values differ from those reported in the literature,[31] the corresponding ^{1}H NMR and IR spectroscopic data represent closest fit consistent with the assigned structures of compounds **8**.



77 **78** **8a-d**

8	**R**	**% Yield**	**Mp °C (Lit. [31])**
a	H	99	62-64 (71-72)
b	F	99	108-110 (119-121)
c	Cl	99	99-101 (82-84)
d	OMe	99	91-93 (90-93)

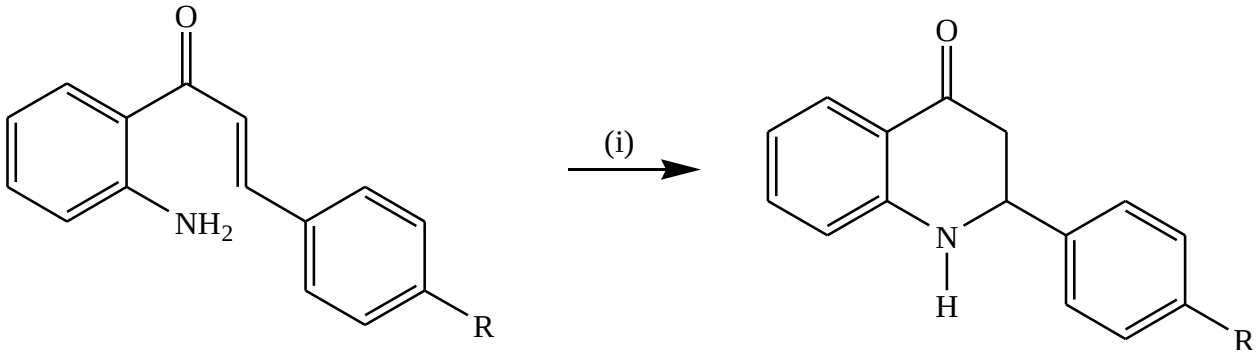
Reagents and conditions: (i) NaOH, ethanol, rt, 18 h

Scheme 27: Condensation of 2-aminoacetophenone with benzaldehyde derivatives

2.1.2 Synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones 9a-d

Several methods have been described in the literature for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones.[34,42] The 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **9** in this study were prepared in high yield and purity by reacting the corresponding 1-(2-aminophenyl)-3-aryl-2-propen-1-ones **8** with orthophosphoric acid in acetic acid, following literature method (Scheme 28).[31,34] Their ^{1}H NMR spectra show the presence of diastereotopic methylene protons, which resonate as a set of two doublets (dd) at δ *ca.* 2.68 ppm (*J* 4.5 and 16.5 Hz) and 2.88 ppm (*J* 13.2

and 16.5 Hz), a broad singlet at δ *ca*. 4.56 ppm for the N-1 proton, a doublet of doublets at δ *ca*. 4.70 ppm (*J* 4.5 and 9.0 Hz) for the C-2 proton as well as a group of signals in the aromatic region δ *ca*. 6.71-7.85 ppm. The IR spectra, on the other hand, revealed the presence of intense absorption bands at ν_{max} 1649 cm^{-1} and 3306 cm^{-1}, which correspond to C=O and N-H groups, respectively.



8 **9**

9	**R**	**% Yield**	**Mp °C (Lit. [ref])**
a	H	82	147-149 (148-150[34])
b	F	85	118-120 (116-118[31])
c	Cl	88	146-148 (146[31])
d	OMe	80	109-111 (112-114[31])

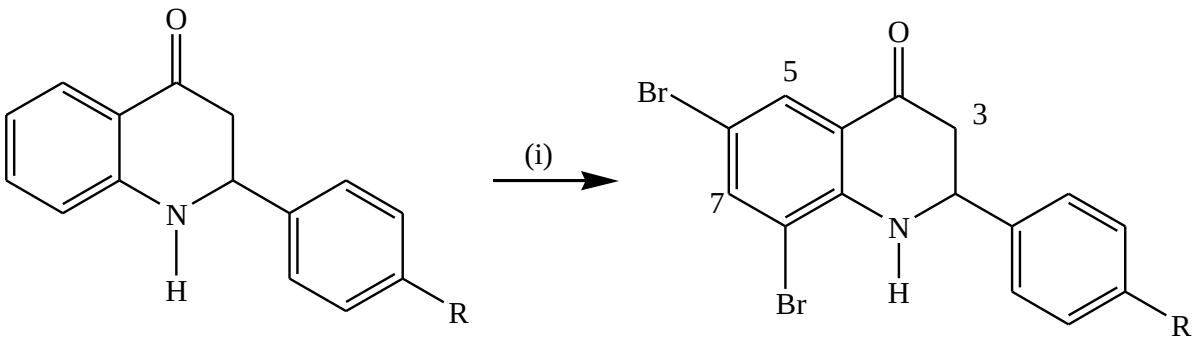
Reagents and conditions: (i) H_3PO_4, AcOH, 90-100 °C, 2 h.

Scheme 28: Acid-catalyzed cyclization of 1-(2-aminophenyl)-3-aryl-2-propen-1-ones

2.2 Synthesis of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones 79a-d

Several methods for the synthesis of dihalogenated quinolones and their quinoline derivatives have been described before.[57,61,62] The prepared derivatives either contain similar or different

halogen atoms at various positions of the fused benzo ring and/or the heterocyclic ring. In this investigation we required the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones **79** to serve as substrates for Pd-catalyzed Suzuki-Miyaura cross-coupling. We first subjected systems **9** to *N*-bromosuccinimide (NBS) (2.5 equiv.) in carbon tetrachloride at room temperature for 12 h to afford the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones **79** in moderate yields (50-66%) (Scheme 29). Improved yields (63-75%) were, however, observed when a mixture of CCl_4-$CHCl_3$ (3:2) was used as solvent and the reaction in this case was found to be complete within 3 h (tlc monitoring). The ^{1}H NMR spectral data of systems **79** show the presence of diastereotopic methylene protons, which resonate as a set of two doublet of doublets at δ *ca*. 2.80 ppm (*J* 4.5 and 16.5 Hz) and δ *ca*. 2.90 ppm (*J* 13.2 and 16.5 Hz), a doublet of doublets at δ *ca*. 4.75 ppm (*J* 4.5 and 13.2 Hz) for the methine proton (C-2) and a broad singlet at δ *ca.* 5.05 ppm for the N-H. Incorporation of the two bromine atoms on the fused benzo ring was confirmed in all cases by the two sets of doublets at δ *ca*. 7.71 ppm (*J* 2.1 Hz) and 7.95 ppm (*J* 2.1 Hz) corresponding to the protons at C-7 and C-5, respectively (Fig. 4). The ^{13}C NMR spectral data of compounds **79** also reveal the resonances corresponding to C-3, C-2 and C-4 (C=O) at δ ca. 45.3, 57.2 ppm and 191.1 ppm respectively (Table 1 and Fig. 5). Moreover, the IR absorption bands at ν_{max} ca. 3358 cm^{-1} and 1647 cm^{-1} confirm the presence of the N-H and C=O groups, respectively. The accurately calculated *m/z* values for the molecular ions confirm the presence of two bromine atoms corresponding to the ^{79}Br isotope.



9 **79a-d**

79	R	% Yield	Mp °C
a	H	70	137-138
b	F	75	126-129
c	Cl	68	145-147
d	OMe	63	149-151

Reagents and conditions: (i) NBS, CCl_4-$CHCl_3$, rt, 3 h

Scheme 29: Bromination of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones

Upon conclusion of this work, we came across a recently published paper describing an alternative method for the synthesis of systems **79**,[93] in which 2-aminoacetophenone **8** was first treated with bromine in dichloromethane at 0-5 °C for 7 h to afford a mixture of 1-(2-amino-3,5-dibromophenyl)ethanone (as the major product) and 1-(2-amino-5-bromophenyl)ethanone.[93] The 1-(2-amino-3,5-dibromophenyl)ethanone was, in turn, reacted with benzaldehyde derivatives in the presence of sodium hydroxide in absolute ethanol at 0-5 °C for 35-40 h to afford the chalcones in analogy with preparation of **8** from **77** and **78** (see Scheme 27). The latter were then cyclized using orthophosphoric acid in acetic acid to afford 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones **79** (58-67%).[93] The azaflavanones were also prepared in a one-pot operation involving the

use of equimolar amounts of 1-(2-amino-3,5-dibromophenyl)ethanone and benzaldehyde derivatives in methanol at 55-60 °C in the presence of *L*-proline (30 mol%) for 48 h.[93]

Table 1: ^{13}C NMR Chemical shift values of **79a-d** in $CDCl_3$ (at 75 MHz)

Nucleus	**79a (R = H)**	**79b (R = F)**	**79c (R = Cl)**	**79d (R =OMe)**
OCH_3	_	_	_	54.4
C-2	57.7	57.0	57.1	57.2
C-3	45.3	45.4	45.2	45.4
C-4	191.1	190.9	190.8	191.4
C-4a	120.8	120.7	120.8	114.5
C-5	129.1	129.5	129.6	129.6
C-6	109.8	110.0	110.1	109.8
C-7	129.6	135.7	138.4	139.9
C-8	110.8	116.0	110.8	110.7
C-8a	147.2	147.1	147.0	159.9
C-1′	139.9	135.8 (d, $^4J_{CF}$ 3.2 Hz)	140.0	147.3
C-2′ & C-6′	126.5	128.3 (d, $^3J_{CF}$ 8.3 Hz)	127.9	120.8
C-3′ & C-5′	128.8	116.1 (d,$^2J_{CF}$ 21.6 Hz)	129.4	127.8
C-4′	129.2	162.8 (d, $^1J_{CF}$ 246.5 Hz)	134.6	132.0

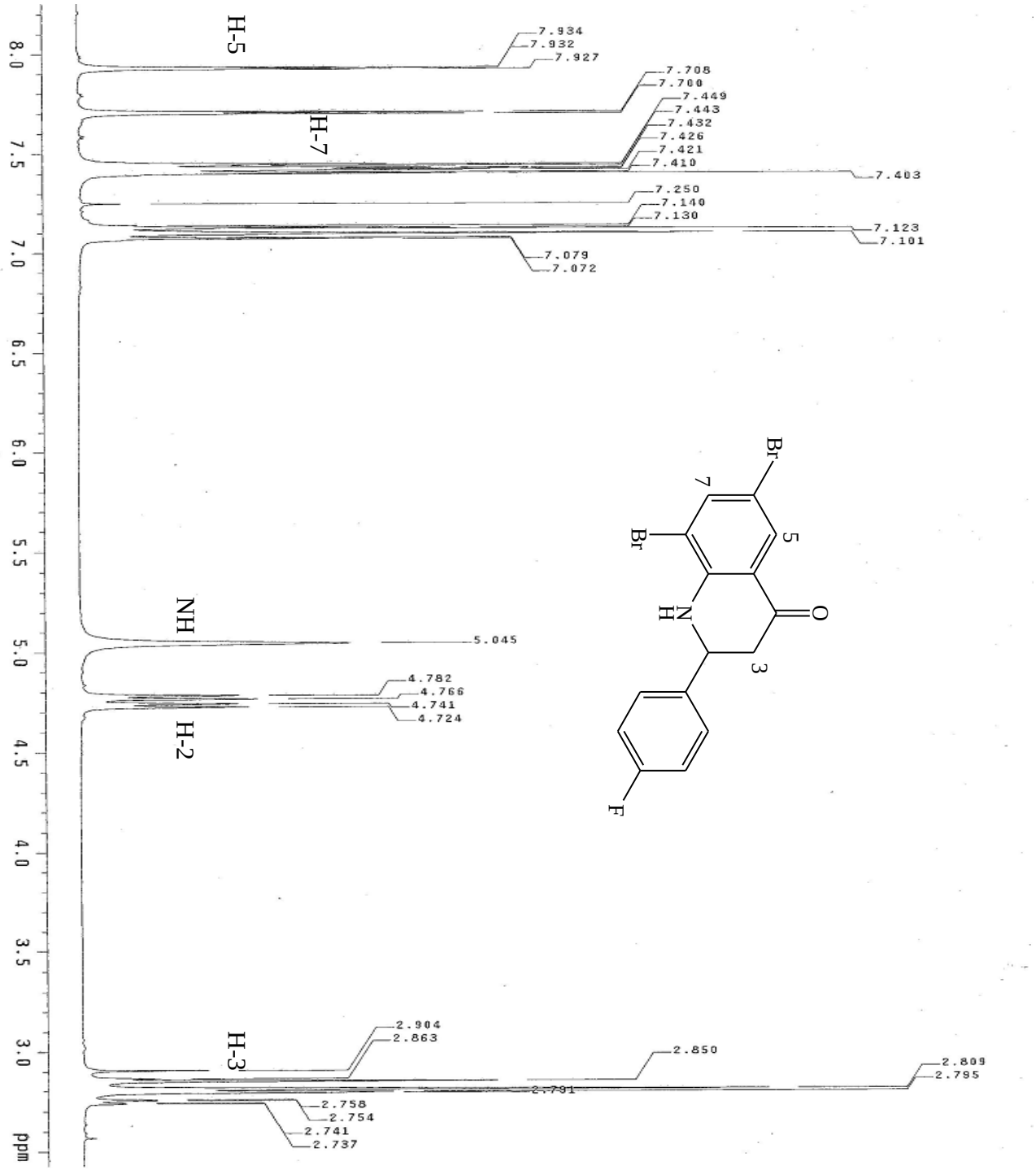


Figure 4: ^{1}H NMR spectrum of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-one **79b** in $CDCl_3$

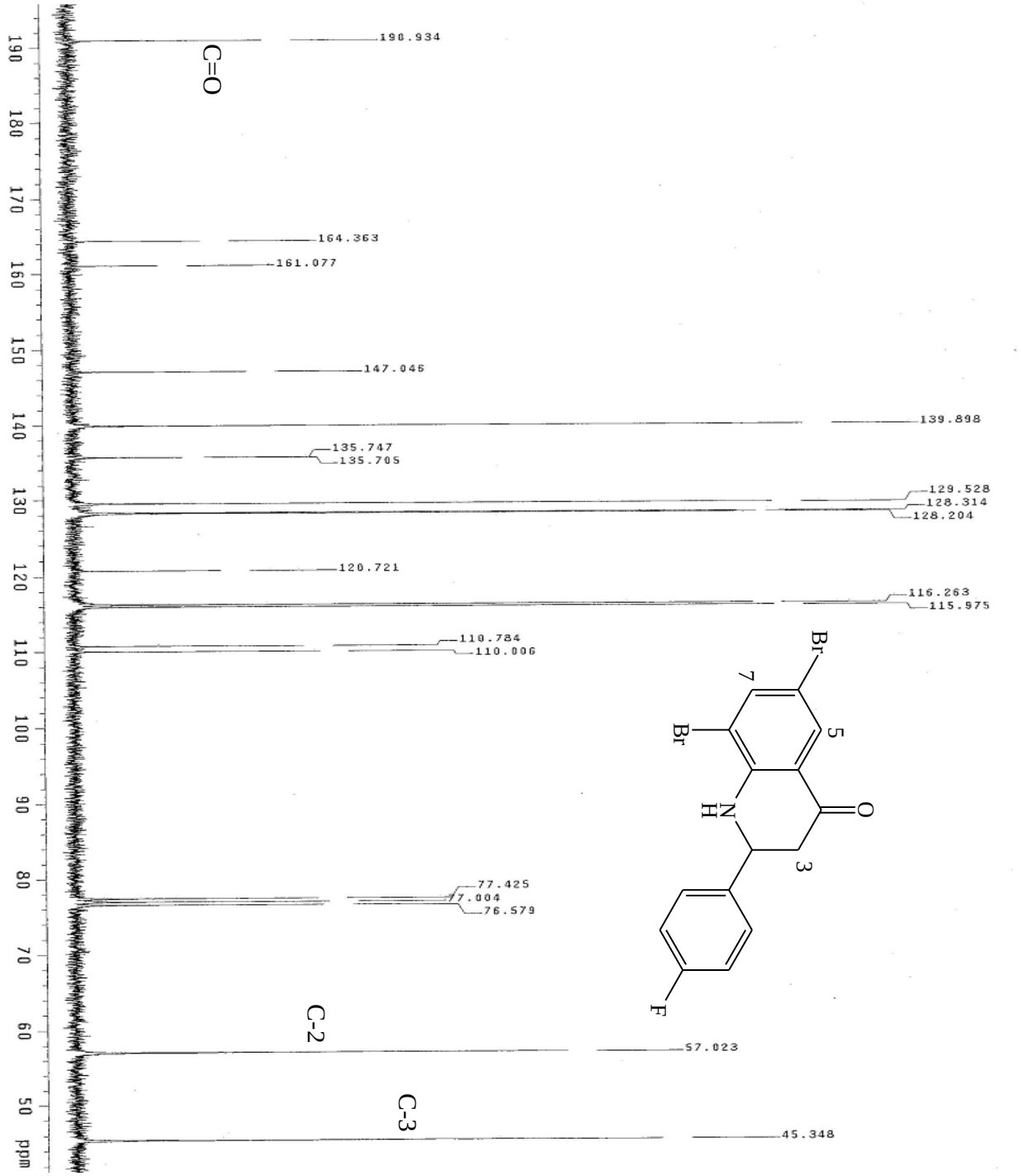


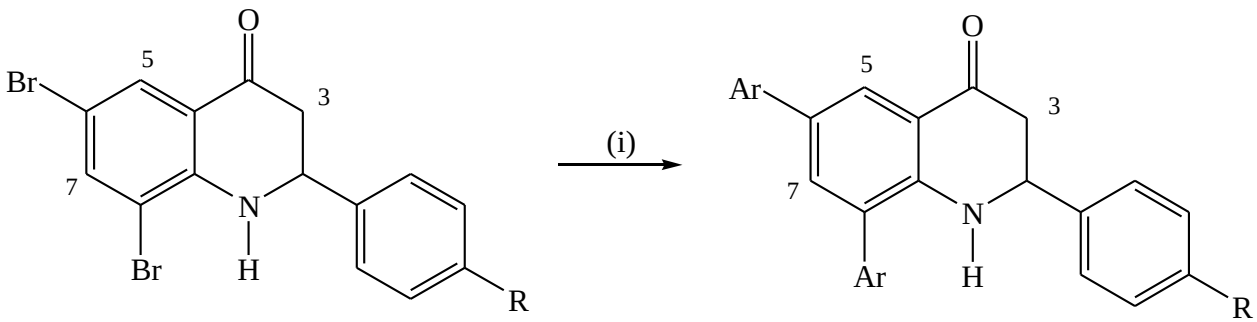
Figure 5: ^{13}C NMR spectrum of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-one **79b** in $CDCl_3$

Several examples from this class of compounds have been found to exhibit anticancer,[93] antimitotic and antitumor properties.[94] For example, the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones were found to exhibit antiproliferative activity against MCF-7 breast cancer cell lines.[93] An analogue of compounds **79** was also found to exhibit *in vitro* inhibition of human tumor cell lines.[94] Thus, systems **79** represent suitable candidates for biological activity studies and for further transformation. The two bromine atoms on the fused benzo ring of systems **79**, for example, can be displaced sequentially or in a single-pot operation through metal-catalyzed alkylation, arylation, alkenylation or alkynylation.[65,80,95] Moreover, the heterocyclic ring of systems **79** can also enable further transformation by introducing partial unsaturation between C-2 and C-3 or full aromatization to afford quinoline derivatives.

2.3 Synthesis of 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones *via* palladium-catalyzed Suzuki-Miyaura cross coupling reaction (80a-h)

With compounds **79** in hand, we opted for the introduction of the aryl moiety at positions 6 and 8 *via* the Suzuki-Miyaura cross-coupling with arylboronic acids. The choice of Suzuki-Miyaura cross-coupling method over Kumada or Negishi cross-coupling reactions was based on the ready availability of organoboronic acids and the high functional group tolerance of the reaction conditions.[86] We first reacted 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one **79a** with phenylboronic acid (1.0 or 2.5 equiv.) in the presence of $Pd(PPh_3)_4$ and 2 M K_2CO_3 as a base in DMF at 90-95 °C. We recovered the starting material unchanged after 48 h. Next, system **79a** was reacted with phenylboronic acid (1.0 equiv.) in the presence of dichlorobis(triphenylphosphine)palladium(II)-tricyclohexylphosphine [$PdCl_2(PPh_3)_2$-PCy_3]

catalyst complex and potassium carbonate (K_2CO_3) as a base in dioxane-H_2O (3:1, v/v) at 80-90 °C for 12 hours. We isolated by column chromatography on silica gel the 2,6,8-triphenyl-2,3-dihydroquinolin-4(1*H*)-one **80a** in 40% yield and the starting material in substantial quantity due to incomplete conversion. Compound **80a** was isolated in high yield and purity by column chromatography on silica gel when 2.5 equiv. of phenylboronic acid was used (Scheme 30). The reaction conditions were extended to other substituted derivatives **80** with phenylboronic and 4-fluorophenylboronic acids as coupling partners. We isolated in all cases the corresponding novel 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-one derivatives **80a-h** in a single-pot operation (Scheme 30). The ^{1}H NMR spectra of products **80a-h** show the two sets of doublet of doublets (dd) in the region δ *ca*. 2.79 ppm (*J* 4.5 and 16.3 Hz) and 2.98 ppm (*J* 13.1 and 16.3 Hz) for the C-3 protons, a doublet of doublets at δ *ca*. 4.70 ppm (*J* 4.5 and 8.7 Hz) and a broad singlet at 4.79 ppm, corresponding to the C-2 proton and N-H, respectively. Increased peaks (2:10) were observed in the aromatic region of the compounds **80a-d** at δ *ca*. 7.11-8.20 ppm thus confirming the incorporation of the two aryl groups (Fig. 6). The ^{13}C NMR spectral data show increased number of resonances for the aromatic carbon, and chemical shifts corresponding to C-3, C-2 and C-4 at δ *ca*. 46.3, 58.3 and 193.3 ppm, respectively (Fig. 7). The ^{13}C NMR spectra of compounds **80e-h** show a set of doublets typical of Csp^2–F coupling interaction with coupling constant values $^1J_{CF}$ 240-248, $^2J_{CF}$ 21.3-21.6, $^3J_{CF}$ 7.5-8.3 and $^4J_{CF}$ 3.0-3.8 Hz, respectively. The IR spectra, on the other hand, reveal the presence of absorption bands at ν_{max} 1675 cm^{-1} and 3380 cm^{-1} which correspond to the C=O and N-H functional groups, respectively. Finally, the accurately calculated *m/z* values represent closest fit consistent with the displacement of the bromine atoms by the aryl groups.



79 **80**

80	**4′-R**	**6, 8-Ar**	**% Yield**	**Mp °C**
a	4′-H	-C_6H_5	72	165-166
b	4′-F	-C_6H_5	62	182-184
c	4′-Cl	-C_6H_5	71	202-204
d	4′-OMe	-C_6H_5	62	194-196
e	4′-H	4-FC_6H_4 -	66	167-169
f	4′-F	4-FC_6H_4-	65	176-178
g	4′-Cl	4-FC_6H_4-	52	190-192
h	4′-OMe	4-FC_6H_4-	66	182-184

Reagents and conditions: (i) $ArB(OH)_2$, $PdCl_2(PPh_3)_2$, PCy_3, K_2CO_3, dioxane-H_2O (3:1, v/v), 85-90 °C, 12 h

Scheme 30: Pd-catalyzed Suzuki-Miyaura cross-coupling reaction on 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones

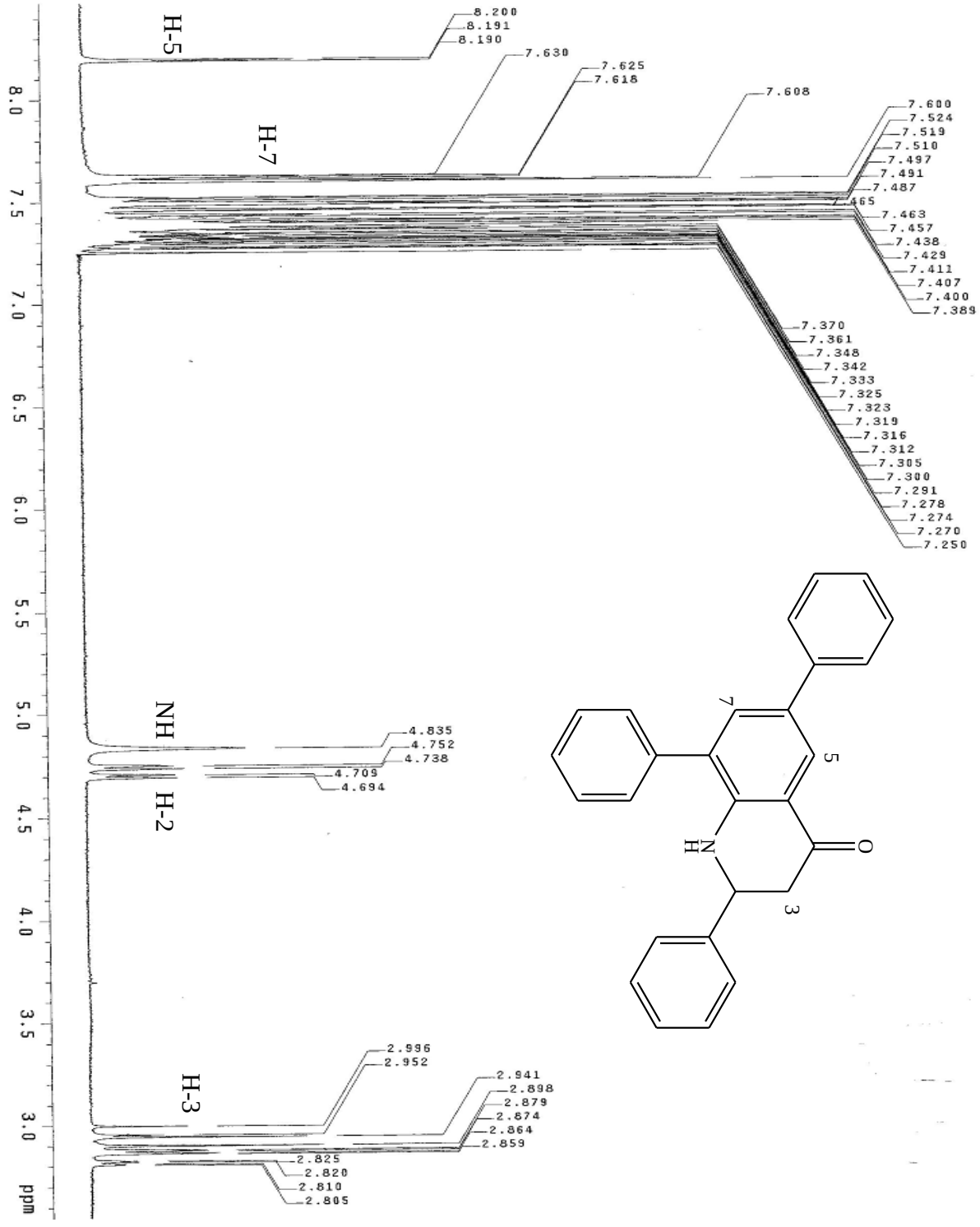


Figure 6: ^{1}H NMR spectrum of 2,6,8-trisphenyl-2,3-dihydroquinolin-4(1*H*)-one **80a** in $CDCl_3$

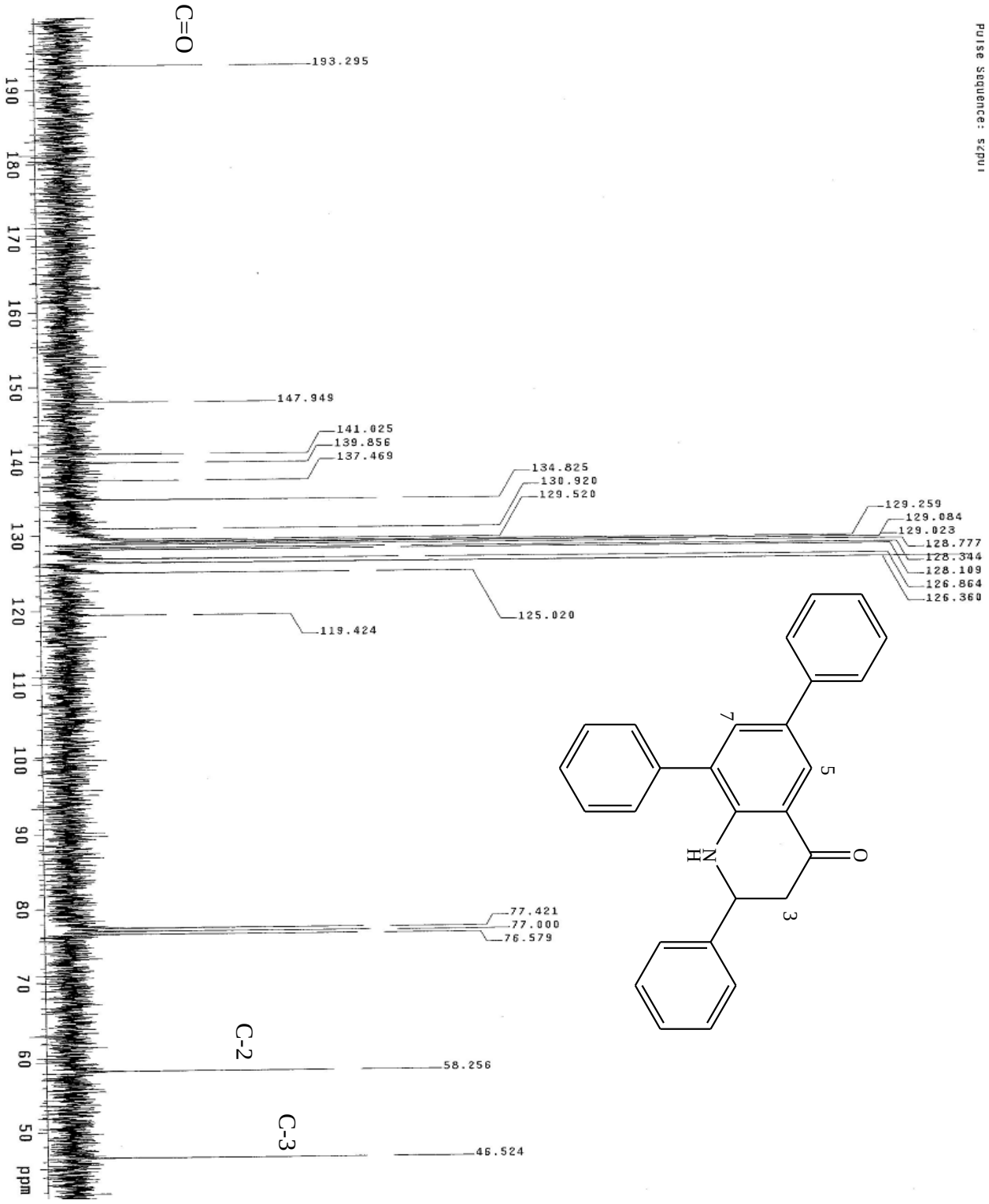
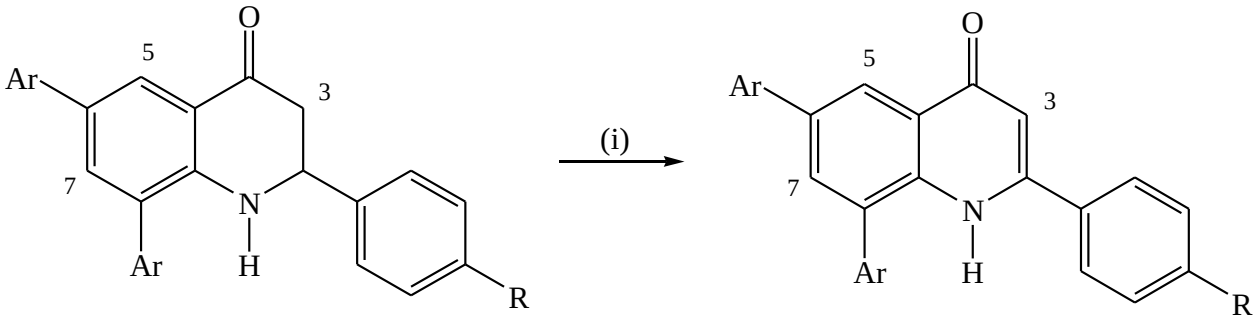


Figure 7: ^{13}C NMR spectrum of 2,6,8-trisphenyl-2,3-dihydroquinolin-4(1*H*)-one **80a** in $CDCl_3$

Arylsubstituted quinolin-4-ones have been found to exhibit antitumor[94] and tubulin polymerization inhibitory activity.[94] They have also been subjected to *in vitro* assays against erythrocytic stages of multidrug-resistant isolates and clones of *P. falciparum.*[90]

2.4 Dehydrogenation of systems 82 to afford 2,6,8-triarylquinolin-4(1*H*)-ones 81a-h

Dehydrogenation of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **9** was previously effected using iodobenzene diacetate under basic conditions in methanol[61] or thallium(III) *p*-tolylsulfonate (TTS) in dimethoxyethane (DME) under reflux.[71] In this investigation, we opted for the use of TTS due to the ease of its preparation and treated compounds **80** with TTS in DME under reflux for 0.5 hour (Scheme 31). In this manner, we isolated the 2,6,8-triarylquinolin-4(1*H*)-ones **81a-h** in very good yields and purity. The C-3 and N-1 protons of systems **81** resonate in the aromatic region of their ^{1}H NMR spectra at δ *ca*. 6.50 and 8.45 ppm as a singlet and a broad singlet, respectively (Fig. 8). The corresponding C-3 and C-2 nuclei resonate at δ *ca*. 108.1 and 113.7 ppm, respectively. C-F couplings were observed in compounds having carbon atoms attached to fluorine atoms (Fig. 9). Finally, their IR spectra show absorption bands for C=O and N-H groups at ν_{max} *ca*. 1662 and 3566 cm^{-1}, respectively.



80 **81**

81	**4′-R**	**6, 8-Ar**	**% Yield**	**Mp °C**
a	4′-H	-C_6H_5	65	242-244
b	4′-F	-C_6H_5	60	237-239
c	4′-Cl	-C_6H_5	55	208-210
d	4′-OMe	-C_6H_5	55	212-214
e	4′-H	4-FC_6H_4-	90	239-242
f	4′-F	4-FC_6H_4-	65	240-242
g	4′-Cl	4-FC_6H_4-	71	225-228
h	4′-OMe	4-FC_6H_4-	65	219-220

Reagents and conditions: (i) TTS, DME, heat, 0.5 h.

Scheme 31: Dehydrogenation of 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones

Series of 2-arylquinolin-4(1*H*)-ones and their analogues have been found to exhibit activity against different types of cancer[47a] and also exhibit antiplatelet,[55] antitumor and antimitotic properties.[65,94,106] In addition, their fluoroquinolone analogues have been reported to exhibit antiischemic activity and potent cardioprotective effect.[105]

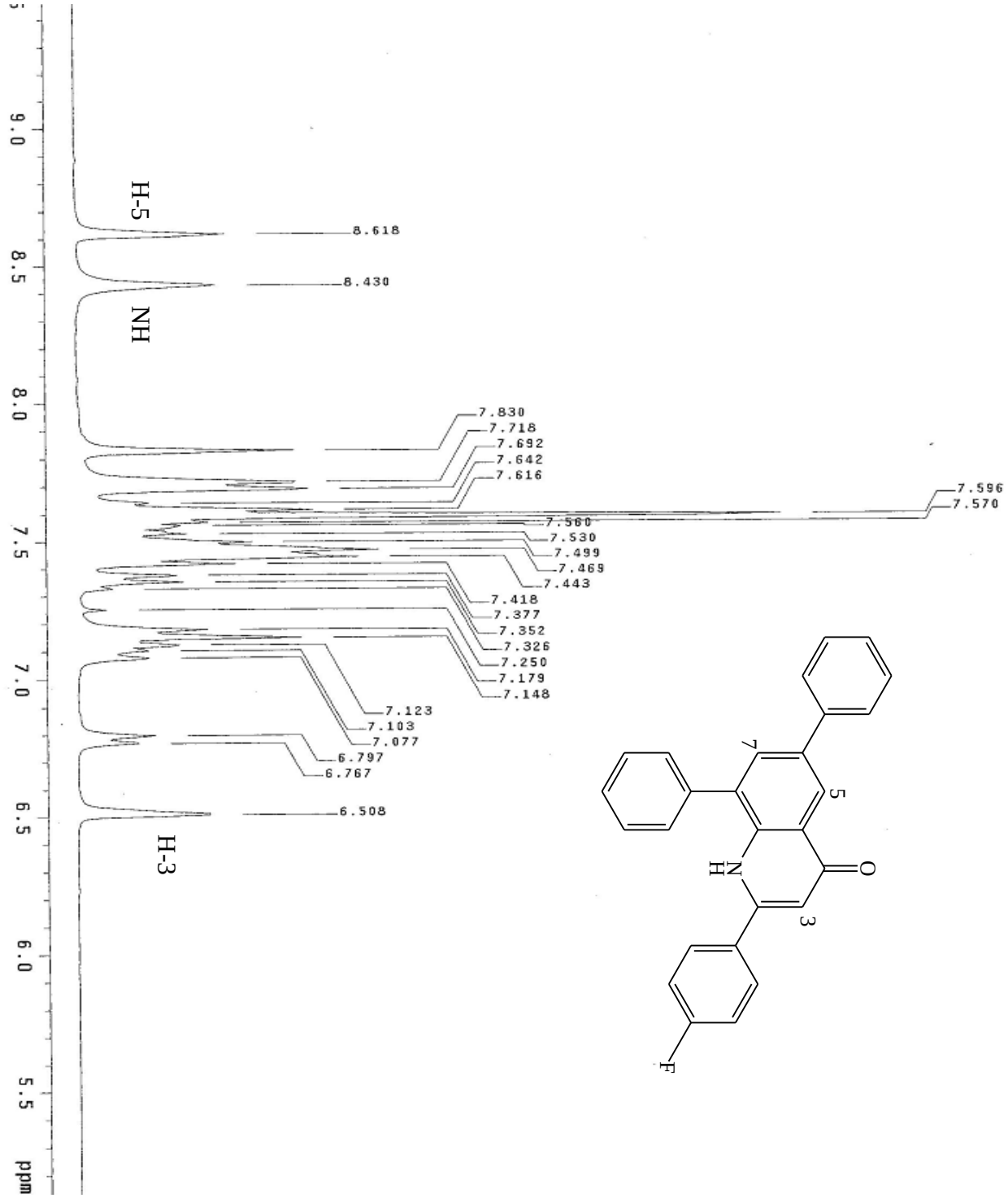


Figure 8: ^{1}H NMR spectrum of 2-(4-fluorophenyl)-6,8-diphenylquinolin-4(1*H*)-one **81b** in $CDCl_3$

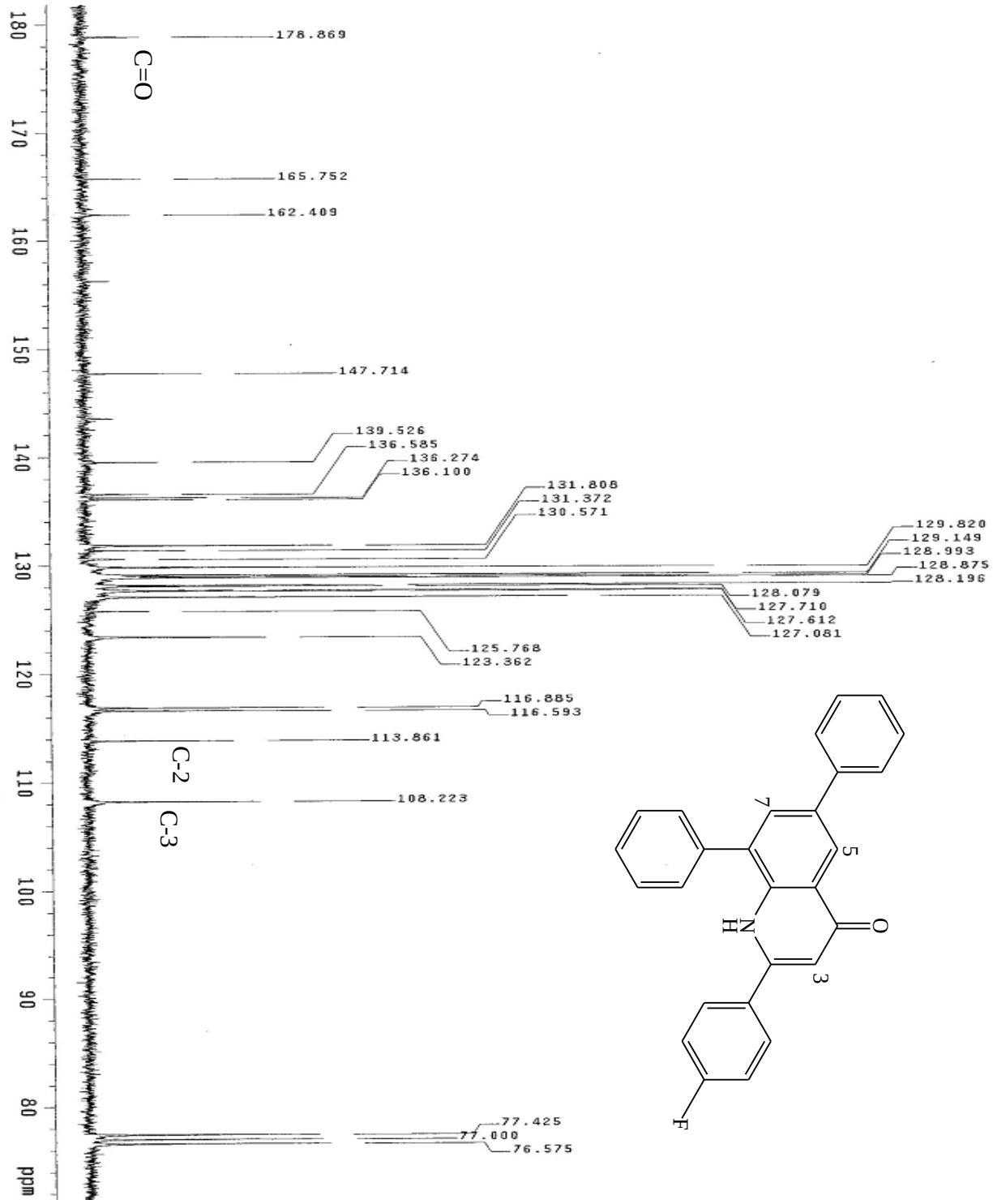
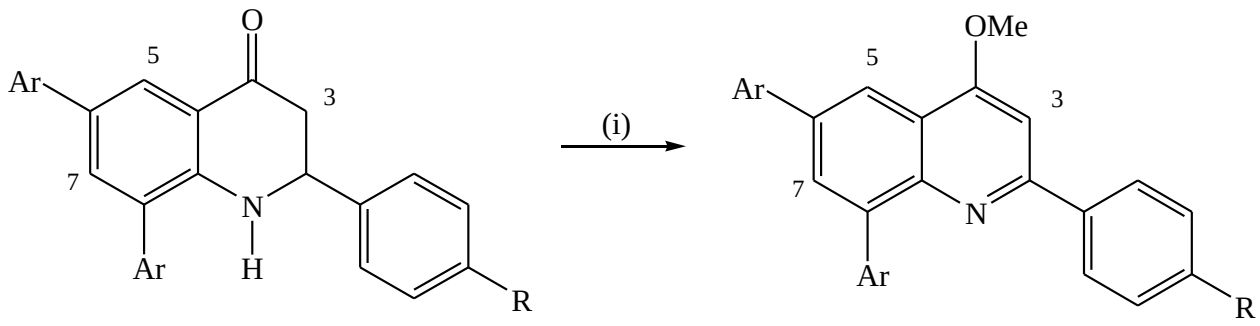


Figure 9: ^{13}C NMR spectrum of 2-(4-fluorophenyl)-6,8-diphenylquinolin-4(1*H*)-one **81b** in $CDCl_3$

2.5 Oxidative aromatization of 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones

The possibility to effect oxidative aromatization of compounds **80** to afford 4-alkoxyquinoline derivatives with potential antimalarial activity was also investigated. The analogous compounds **9** were previously transformed to the 4-alkoxylquinolines using manganese acetate or cerium ammonium nitrate in methanol,[68] copper(II) acetate-manganese(III) acetate[68] or $FeCl_3 \cdot 6H_2O$ in methanol.[68] An indirect, but certain to succeed, approach involves the use of phosphoryl chloride to aromatize the quinolin-4(1*H*)-ones to yield the 4-chloroquinolines which are then subjected to dechloromethoxylation.[69] Molecular iodine in methanol,[67] thallium(III) nitrate[96] or [hydroxyl(tosyloxy)iodo]benzene in trimethylorthoformate in the presence of perchloric acid[95] have also been used to effect direct oxidative aromatization of the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones. Iodine in methanol mixture involves relatively mild conditions and the reagents are relatively inexpensive and efficient. We thus opted for these reaction conditions and subjected the 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones **80** to molecular iodine (2.0 eq.) in methanol under reflux for 2 hours to afford products **82a-h** in good yields and purity (Scheme 32). The ^{1}H NMR spectral data of the derivatives **82a-h** are characterized by the absence in the aliphatic region of the signals usually corresponding to protons attached to N-1, C-3 and C-2. The methoxy protons resonate as an intense singlet at δ *ca*. 4.15 ppm and other signals resonate in the aromatic region δ *ca*. 7.11-8.42 ppm (Fig. 10). Their ^{13}C NMR spectral data also reveal the presence of a methoxy carbon signal at δ *ca*. 55.7 ppm and C-F couplings were also observed between carbon and fluorine atoms (Fig. 11). Their IR spectra lack the absorption bands for N-H and C=O functionalities present in the spectra of the corresponding precursors, thus confirming the assigned structure for compounds **82**.



80 **82**

82	**4′-R**	**6, 8-Ar**	**% Yield**	**Mp °C**
a	H	-C_6H_5	82	221-223
b	F	-C_6H_5	78	210-212
c	Cl	-C_6H_5	97	231-233
d	OMe	-C_6H_5	88	196-198
e	H	4-FC_6H_4-	88	231-233
f	F	4-FC_6H_4-	68	197-199
g	Cl	4-FC_6H_4-	88	236-238
h	OMe	4-FC_6H_4-	78	171-173

Reagents and conditions: (i) Iodine, Methanol, heat, 2 h

Scheme 32: Oxidative aromatization of 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones

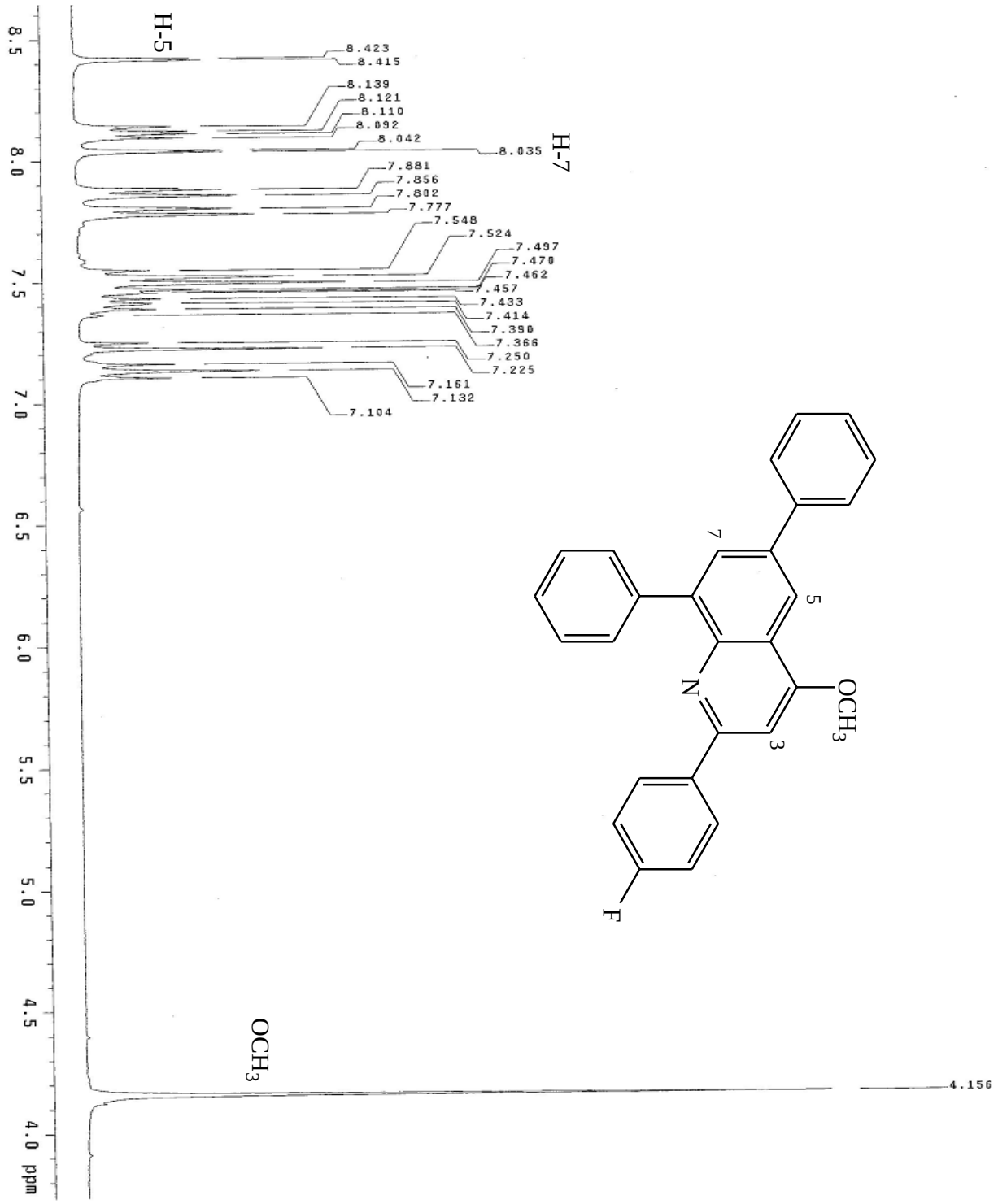


Figure 10: ^{1}H NMR spectrum of 2-(4-fluorophenyl)-6,8-diphenyl-4-methoxyquinoline **82b** in $CDCl_3$

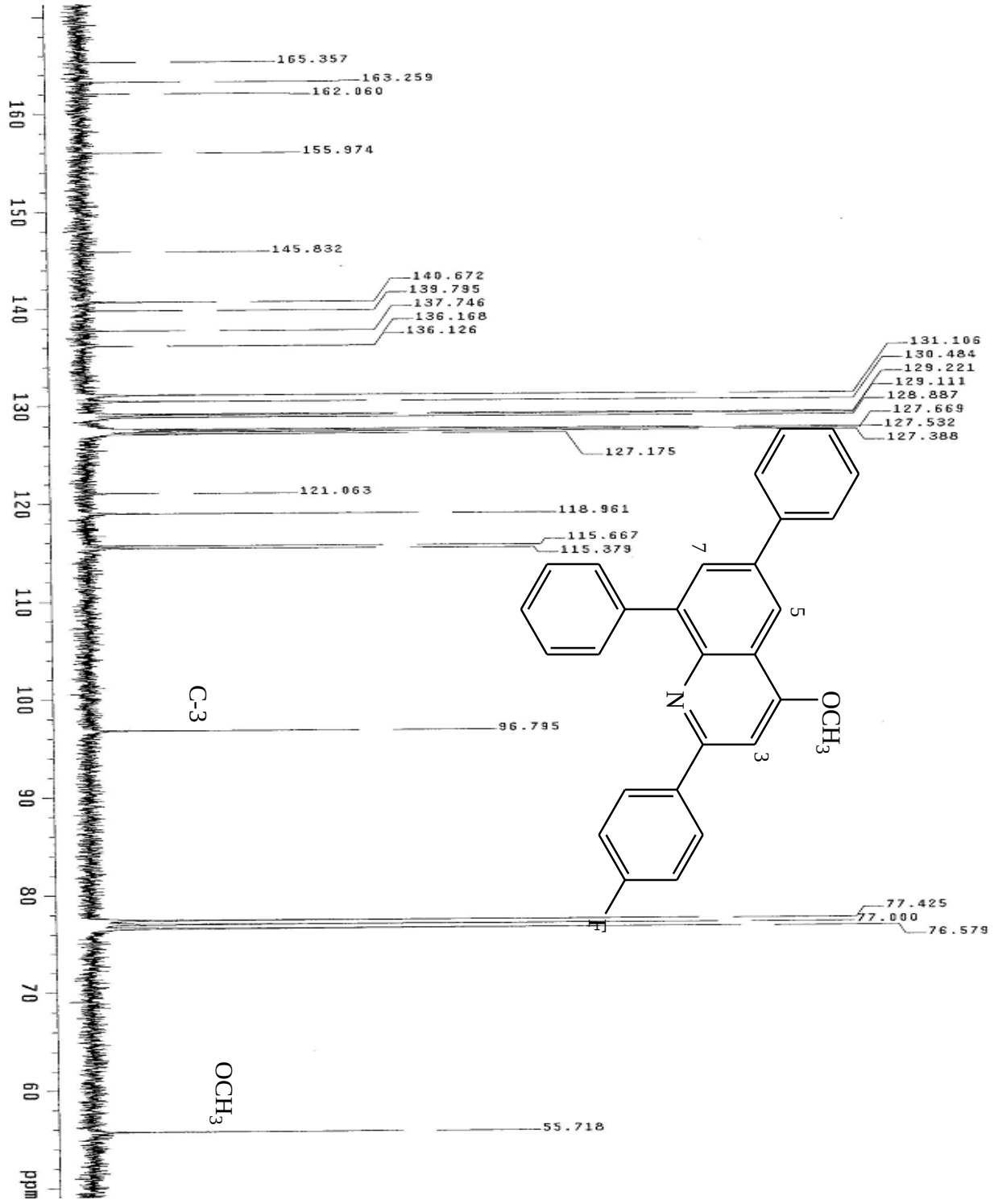


Figure 11: ^{13}C NMR spectrum of 2-(4-fluorophenyl)-6,8-diphenyl-4-methoxyquinoline **82b** in $CDCl_3$

The mechanism for the oxidative aromatization of 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones **80** is proposed in Fig. 12. The first step presumably involves formation of a hemiacetal **I**. This is probably followed by dehydration to afford an enolether derivative **II**. We envision the last step to involve the dehydroiodination of the enolether **II** to afford a fully aromatic derivative **82**.

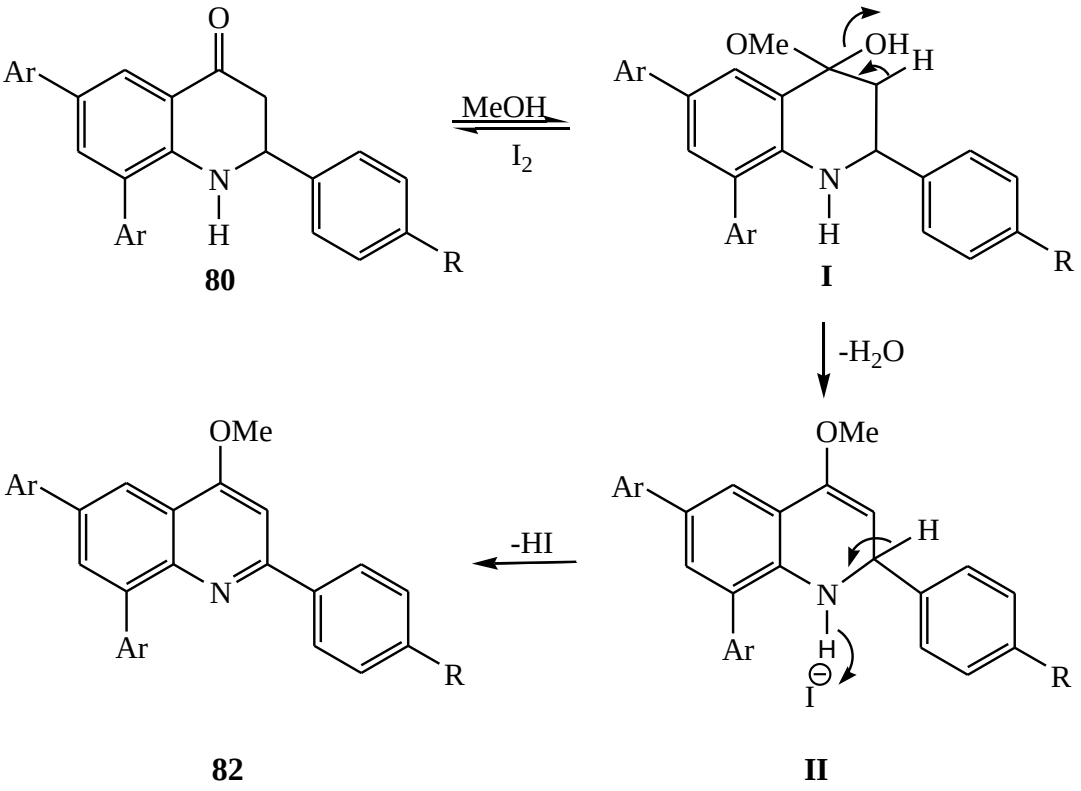


Figure 12: Proposed mechanistic pathway for the oxidative aromatization reactions

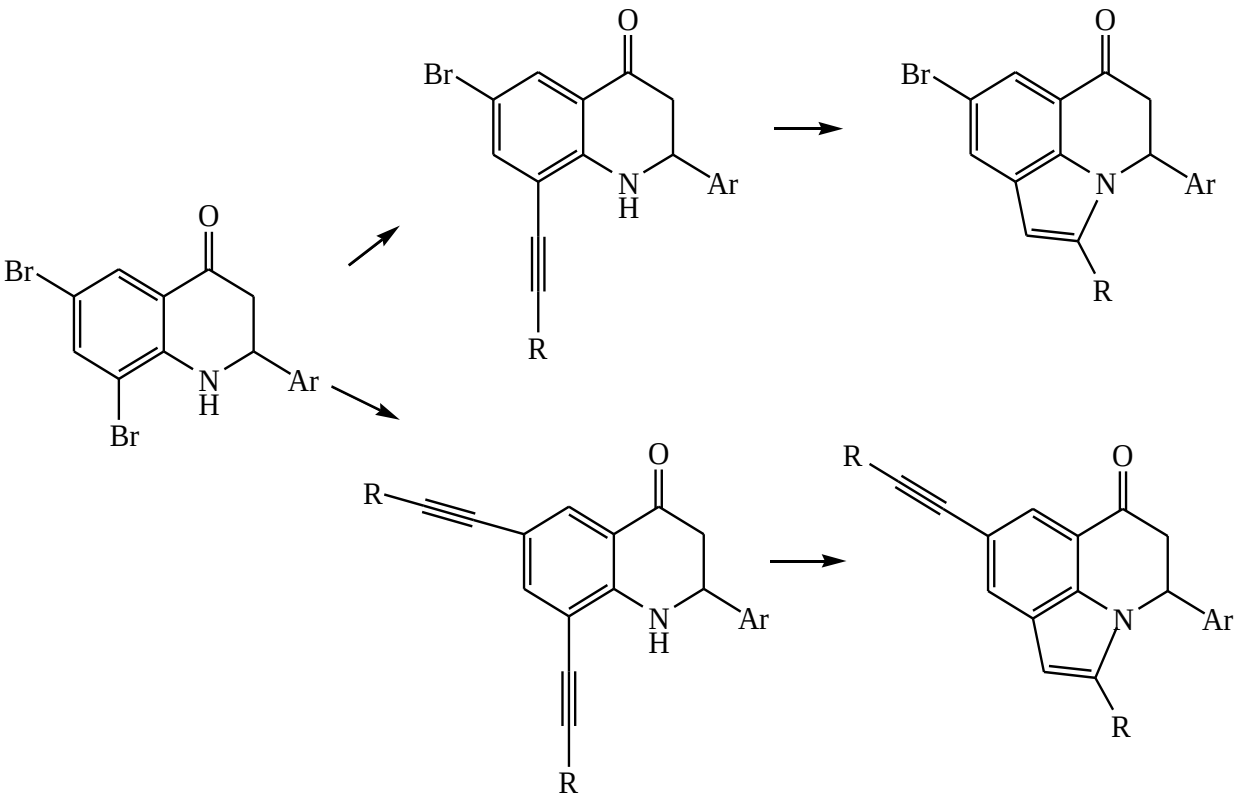
The quinoline moiety is present in many classes of biologically active compounds and the analogues of systems **82** have been found to serve as antibacterials,[6,7] HIV integrase inhibitors,[27,102] anticonvulsant and antiproliferative agents.[103] A series of 4-substituted 8-aryl-2-methylquinolines were also found to be highly potent antagonists for the human corticotrophin-releasing factor (CRF_1) receptor,[104] and others exhibited antiplatelet[107] and antihelmintic activities.[108]

CHAPTER 3 CONCLUSION

NBS-promoted bromination of the 2-aryl-2,3-dihydroquionolin-4(1*H*)-ones afforded the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones in reasonable yields and high purity. The 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones were, in turn, subjected to palladium-catalyzed Suzuki-Miyaura cross-coupling with arylboronic acids to afford a range of novel 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones in a single-pot operation and without selectivity. The latter were dehydrogenated to the corresponding 2,6,8-triarylquinolin-4(1*H*)-ones using thallium(III) *p*-tolylsulfonate in dimethoxyethane. The 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones were also subjected to oxidative aromatization using iodine in methanol under reflux to afford the 2,6,8-triaryl-4-methoxyquinolines. The results described in this investigation have since been published.[109]

The compounds prepared in this investigation are analogues of the medicinally important quinolones and quinoline derivatives with diverse applications including; cancer chemotherapies,[5] antiviral therapies,[9] antimicrobial[3,7] and antimalarial agents,[27,90] tubulin polymerization inhibitors,[94] anti-tumor agents,[94] and for antiallergy treatments.[100,101] Moreover, the prepared compounds bear several reactive centers for further chemical transformations to afford novel derivatives as follows:

(i) Further elaboration of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones *via* mono and/ or sequential Pd-catalyzed Sonogashira cross-coupling and subsequent metal-catalyzed annulation of the resulting tethered alkynylated derivatives



(ii) Elaboration of the 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones *via* sequential or single-pot multiple cross-coupling using other Pd-catalyzed cross-coupling methods separately or in combination

(iii) C-3 Halogenation (X = Br, I) of the 2,6,8-trisubstituted quinolin-4(1*H*)-ones followed by sequential/ site-selective metal-catalyzed C-C bond formation

(iv) Possible annulation of the resulting 3-halogeno-2,6,8-trisubstituted quinolin-4(1*H*)-ones *via* Sonogashira cross-coupling when terminal alkynes are used as coupling partners

(v) Evaluation of the prepared novel compounds for anti-tumour and/or anti-microbial properties

CHAPTER 4: EXPERIMENTAL

4.1 GENERAL

Solvents and commercially available reagents were used as supplied or purified by conventional methods before use. Melting points were determined on a Stuart melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Mercury 300 MHz Spectrometer as $CDCl_3$ solutions and the chemical shifts are referenced relative to the residual proton signal in the solvent (δ_H 7.25 or δ_C 77.0 ppm) and are expressed in parts per million (ppm). The IR spectra were recorded as powders on a Digilab FTS 7000 series Win-Pro Fourier Transform Infra Red Spectrometer equipped with a nitrogen cooled germanium crystal detector. Merck silica gel 60 F_{254} plates were used for thin layer chromatography (tlc) and the powder 90% (0.0063-0.10mm) and flow time <80s/10cm was used as stationary phase for column chromatography. High and low resolution mass spectra were recorded on a Waters API Q-TOF Ultima mass spectrometer at the University of Stellenbosch.

The following abbreviations are used throughout for NMR spectral data:

ppm = parts per million

J = coupling constant in Hz

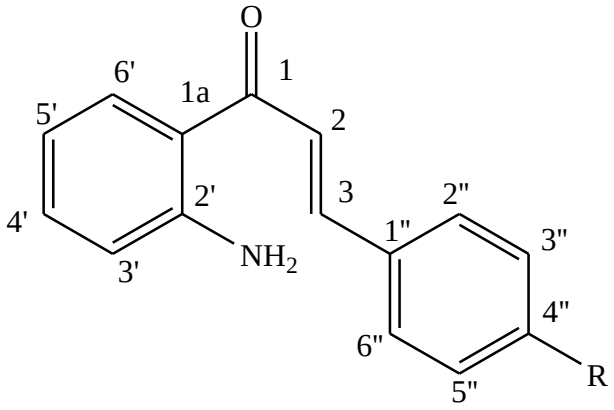
δ = chemical shift values in ppm

s = singlet, br s = broad singlet

d = doublet, dd = doublet of doublets

t = triplet, q = quartet, m = multiplet

4.1 Preparation of 1-(2′-aminophenyl)-3-aryl-2-propen-1-ones 8a-d



1-(2′-Aminophenyl)-3-aryl-2-propen-1-ones 8a-d

4.1.1 Preparation of 1-(2′-aminophenyl)-3-phenyl-2-propen-1-one 8a (R = H)

A mixture of 2-aminoacetophenone **77** (4.00 g, 29.6 mmol), benzaldehyde **78a** (3.14 g, 29.6 mmol) and sodium hydroxide (3 pellets, *ca.* 0.6 g) in ethanol (20 mL) was stirred for 12 hours at room temperature. The mixture was quenched with an ice cold water (100 mL) and the precipitate was filtered to afford **8a** as an orange solid (6.53 g, 99%); mp 62-64 °C (EtOH), (lit.,[31] 71-72 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.34 (2H, s, NH_2), 6.67-6.72 (2H, m, 3′-H and 5′-H), 7.29 (1H, t, *J* 7.2 Hz, 4′-H), 7.37-7.43 (3H, m, 3′′-H, 4′′-H and 5′′-H), 7.59-7.64 (3H, m, 2′′-H, 6′′-H and 6′-H), 7.75 (1H, d, *J* 15.6 Hz, 3-H), 7.86 (1H, d, *J* 15.6 Hz, 2-H); IR (neat): ν_{max} 3443, 3326, 1640, 1614, 1573, 1539, 1495, 1448, 1338, 1206, 1157, 1010, 976, 737, 696, 662 cm^{-1}.

4.1.2 Preparation of 1-(2′-aminophenyl)-3-(4-fluorophenyl)-2-propen-1-one 8b (R = F)

A mixture of 2-aminoacetophenone **77** (4.00 g, 29.6 mmol), 4-fluorobenzaldehyde **78b** (3.67 g, 29.6 mmol) and sodium hydroxide (3 pellets, *ca.* 0.6 g) in ethanol (20 mL) was treated as described for **8a**; work-up afforded **8b** as a yellow solid (7.06 g, 99%); mp 108-110 °C (EtOH), (lit.,[31] 119-121 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.33 (2H, s, NH_2), 6.66-6.72 (2H, m, 3′-H and 5′-H), 7.09 (1H, t, *J* 8.4 Hz, 4′-H), 7.25-7.31 (2H, m, 3′′-H and 5′′-H), 7.50-7.72 (3H, m, 2′′-H, 6′-H, 6′′-H), 7.74 (1H, d, *J* 15.6 Hz, 3-H), 7.84 (1H, d, *J* 15.6 Hz, 2-H); IR (neat): ν_{max} 3427, 3317, 1646, 1615, 1575, 1541, 1506, 1483, 1445, 1414, 1341, 1266, 1205, 1153,1096, 1007, 978, 847, 824, 770, 739, 657 cm^{-1}.

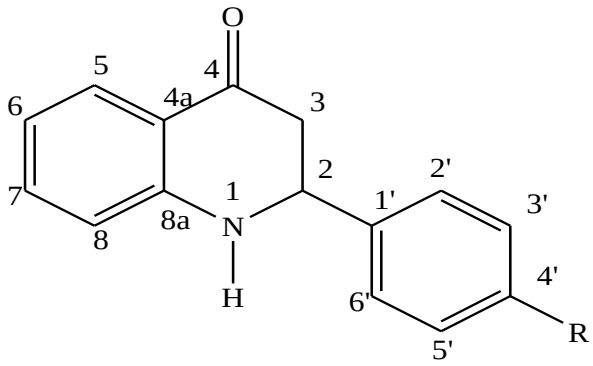
4.1.3 Preparation of 1-(2′-aminophenyl)-3-(4-chlorophenyl)-2-propen-1-one 8c (R = Cl)

A mixture of 2-aminoacetophenone **77** (4.00 g, 29.6 mmol), 4-chlorobenzaldehyde **78c** (4.16 g, 29.6 mmol) and sodium hydroxide (3 pellets, *ca.* 0.6 g) in ethanol (20 mL) was treated as described for **8a**; work-up afforded **8c** as a yellow solid (7.60 g, 99%); mp 99-101 °C (EtOH), (lit.,[31] 82-84 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.34 (2H, s, NH_2), 6.66-6.71 (2H, m, 3′-H and 5′-H), 7.25-7.38 (3H, m, 3′′-H and 5′′-H, 4′-H), 7.53-7.70 (3H, m, 2′′-H, 6′-H, 6′′-H), 7.74 (1H, d, *J* 15.5 Hz, 3-H), 7.83 (1H, d, *J* 15.5 Hz, 2-H); IR (neat): ν_{max} 3472, 3325, 3034, 1641, 1611, 1568, 1536, 1491, 1446, 1405, 1336, 1292, 1263, 1208, 1156, 1089, 1006, 981, 816, 749, 674, 640 cm^{-1}.

4.1.4 Preparation of 1-(2′-Aminophenyl)-3-(4-methoxyphenyl)-3-propen-1-one 8d (R = OCH_3)

A mixture of 2-aminoacetophenone **77** (4.00 g, 29.6 mmol), 4-methoxybenzaldehyde **78d** (4.03 g, 29.6 mmol) and sodium hydroxide (3 pellets, *ca.* 0.6 g) in ethanol (20 mL) was treated as described for **8a**; work-up afforded **8d** as an orange solid (7.40 g, 99%); mp 91-93 °C (EtOH), (lit.,[31] 90-93 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.84 (3H, s, $COCH_3$), 6.31 (2H, s, NH_2), 6.66-6.72 (2H, m, 3′-H and 5′-H), 6.92 (2H, dd, *J* 3.0 and 8.7 Hz, 3′′-H and 5′′-H), 7.47-7.74 (4H, m, 2′′-H, 4′-H, 6′-H and 6′′-H), 7.75 (1H, d, *J* 15.5 Hz, 3-H), 7.85 (1H, d, *J* 15.5 Hz, 2-H); IR (neat): ν_{max} 3427, 3306, 2840, 1680, 1639, 1611, 1568, 1535, 1509, 1460, 1423, 1355, 1290, 1251, 1208, 1158, 1022, 981, 827, 801, 683, 655 cm^{-1}.

4.2 Preparation of 2-aryl-2,3-dihydoquinolin-4(1*H*)-ones 9a-d



2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones 9a-d

4.2.1 Preparation of 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one 9a (R = H)

A stirred mixture of **8a** (3.00 g, 13.5 mmol), orthophosphoric acid (15 mL) and glacial acetic acid (15 mL) was heated under reflux for 2 hours. The mixture was allowed to cool to room temperature, quenched with an ice-cold water and then extracted with chloroform. The combined organic phases were washed with water (3×40 mL) and dried over anhydrous $MgSO_4$. The salt was filtered off and the solvent was evaporated under reduced pressure to afford **9a** as a yellow solid (2.45 g, 82%); mp 147-149 °C (EtOH), (lit.,[34] 148-150 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.70 (1H, ddd, *J* 1.2, 4.5 and 16.5 Hz, 3-H), 2.87 (1H, dd, *J* 13.2 and 16.5 Hz, 3-H), 4.61 (1H, s, N-H), 4.74 (1H, dd, *J* 4.5 and 9.0 Hz, 2-H), 6.71 (1H, d, *J* 8.1 Hz, 8-H), 6.75 (1H, t, *J* 7.5 Hz, 6-H), 7.25-7.46 (6H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H and 7-H), 7.86 (1H, d, *J* 9.3 Hz, 5-H); IR (neat): ν_{max} 3332, 1655, 1604, 1480, 1332, 1303, 1261, 1215, 1154, 1115, 1076, 1024, 999, 915, 765, 699, 617 cm^{-1}.

4.2.2 Preparation of 2-(4-fluorophenyl)-2,3-dihydroquinolin-4(1*H*)-one 9b (R = F)

A stirred mixture of **8b** (3.00 g, 12.5 mmol), orthophosphoric acid (15 mL) and glacial acetic acid (15 mL) was treated as described for **8a**; work-up afforded **9b** as a yellow solid (2.55 g, 85%); mp 118-120 °C (EtOH), (lit.,[31] 116-118 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.72 (1H, dd, *J* 4.5 and 16.8 Hz, 3-H), 2.87 (1H, dd, *J* 13.2 and 16.8 Hz, 3-H), 4.53 (1H, s, N-H), 4.71 (1H, dd, *J* 4.5 and 9.0 Hz, 2-H), 6.71 (1H, d, *J* 8.1 Hz, 8-H), 6.78 (1H, t, *J* 7.8 Hz, 6-H), 7.10 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 7.25-7.44 (3H, m, 3′-H, 5′-H and 7-H), 7.85 (1H, d, *J* 8.4 Hz, 5-H); IR

(neat): ν_{max} 3299, 1645, 1603, 1505, 1479, 1436, 1355, 1309, 1223, 1154, 1120, 1001, 913, 860, 836, 796, 755, 639 cm^{-1}.

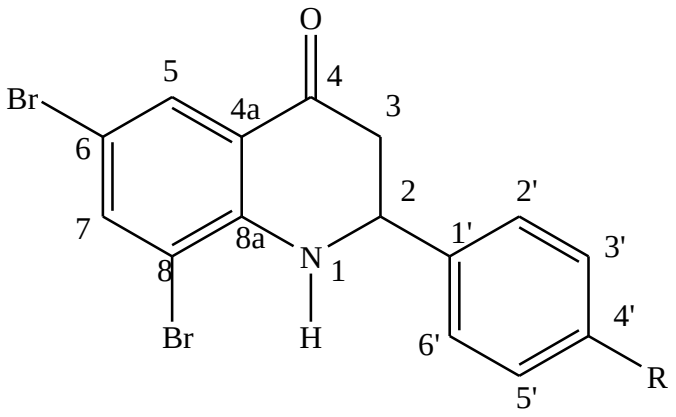
4.2.3 Preparation of 2-(4-chlorophenyl)-2,3-dihydroquinolin-4(1*H*)-one 9c (R = Cl)

A stirred mixture of **8c** (3.00 g, 11.7 mmol), orthophosphoric acid (15 mL) and glacial acetic acid (15 mL) was treated as described for **8a**; work-up afforded **9c** as a yellow solid (2.64 g, 88%); mp 146-148 °C (EtOH), (lit.,[31] 146 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.67 (1H, dd, *J* 4.5 and 16.5 Hz, 3-H), 2.83 (1H, dd, *J* 13.2 and 16.5 Hz, 3-H), 4.57 (1H, s, N-H), 4.70 (1H, dd, *J* 4.5 and 7.5 Hz, 2-H), 6.72 (1H, d, *J* 8.4 Hz, 8-H), 6.78 (1H, t, *J* 7.4 Hz, 6-H), 7.25-7.39 (5H, m, 2′-H, 3′-H, 5′-H, 6′-H and 7-H), 7.84 (1H, d, *J* 8.7 Hz, 5-H); IR (neat): ν_{max} 3306, 1651, 1604, 1508, 1480, 1410, 1326, 1250, 1211, 1151, 1118, 1089, 1015, 916, 825, 764, 685, 647 cm^{-1}.

4.2.4 Preparation of 2-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one 9d (R = OCH_3)

A stirred mixture of **8d** (3.00 g, 11.9 mmol), orthophosphoric acid (15 mL) and glacial acetic acid (15 mL) was treated as described for **8a**; work-up afforded **9d** as a yellow solid (2.40 g, 80%); mp 109-111 °C (EtOH), (lit.,[31] 112-114 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.67 (1H, dd, *J* 4.5 and 16.5 Hz, 3-H), 2.87 (1H, dd, *J* 13.2 and 16.5 Hz, 3-H), 3.80 (3H, s, $COCH_3$), 4.53 (1H, s, N-H), 4.66 (1H, dd, *J* 4.5 and 9.9 Hz, 2-H), 6.69 (1H, d, *J* 8.4 Hz, 8-H), 6.76 (1H, t, *J* 7.5 Hz, 6-H), 6.90 (2H, d, *J* 6.9 Hz, 2′-H and 6′-H), 7.29-7.37 (3H, m, 3′-H, 5′-H and 7-H), 7.85 (1H, d, *J* 7.8 Hz, 5-H); IR (neat): ν_{max} 3290, 1645, 1603, 1506, 1478, 1362, 1330, 1301, 1244, 1213, 1175, 1153, 1118, 1028, 913, 826, 753, 634 cm^{-1}.

4.3 Preparation of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones 79a-d



2-Aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones 79a-d

4.3.1 Preparation of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one 79a (R = H)

A mixture of 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one **9a** (1.00 g, 4.5 mmol) and *N*-bromosuccinimide (1.99 g, 11.2 mmol) in a carbon tetrachloride:chloroform mixture (CCl_4:$CHCl_3$), (3 : 2, v/v, 50 mL) in a round bottomed flask was stirred at room temperature for 3 h. Saturated sodium carbonate (100 mL) was then added to the mixture with stirring. The aqueous phase was extracted with chloroform (3×30 mL) and the combined organic phases were washed with brine (2×30 mL), filtered and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to afford **79a** as a light yellow solid (1.20 g, 70%); R_f (toluene) 0.58; mp 137-138 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.80 (1H, dd, *J* 4.5, 16.5 Hz, 3-H), 2.90 (1H, dd, *J* 13.2, 16.5 Hz, 3H), 4.77 (1H, dd, *J* 4.5 and 13.2 Hz, 2-H), 5.10 (1H, s, N-H), 7.35-7.46 (5H, m, -C_6H_5), 7.71 (1H, d, *J* 2.1 Hz, 7-H), 7.95 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.3 (C-3), 57.7 (C-2), 109.8 (C-6), 110.8 (C-8), 120.8 (C-4a), 126.5 (C-2′ and C-6′), 128.8 (C-3′

and C-5′), 129.1 (C-5), 129.2 (C-4′), 129.6 (C-7), 139.9 (C-1′), 147.2 (C-8a), 191.1 (C-4); IR (neat): ν_{max} 3375, 1679, 1590, 1482, 1396, 1362, 1323, 1277, 1226, 1155, 1123, 1077, 1001, 882, 846, 757, 702 cm^{-1}; *m/z* (100, M+H) 380; HRMS (ES): MH^+, found: 379.9109. For $[C_{15}H_{11}{}^{79}Br_2NO]^+$: requires, 379.9187.

4.3.2 Preparation of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-one 79b (R = F)

An experimental procedure employed for the synthesis of **79a** was followed using a mixture of **9b** (1.00 g, 4.2 mmol) and *N*-bromosuccinimide (1.85 g, 10.4 mmol) in CCl_4:$CHCl_3$ (50 mL); work-up and column chromatography on silica gel afforded **79b** as a light yellow solid (1.25 g, 75%); R_f (toluene) 0.58; mp 127-129 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.78 (1H, dd, *J* 4.5, 16.8 Hz, 3-H), 2.86 (1H, dd, *J* 13.2, 16.8 Hz, 3H), 4.75 (1H, dd, *J* 4.5 and 13.2 Hz, 2-H), 5.03 (1H, s, N-H), 7.10 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 7.43 (2H, dd, *J* 5.4 and 14.1 Hz, 3′-H and 5′-H), 7.71 (1H, d, *J* 2.1 Hz, 7-H), 7.94 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.4 (C-3), 57.0 (C-2), 110.0 (C-6), 110.8 (C-8), 116.1 (d, $^2J_{CF}$ 21.6 Hz, C-3′ and C-5′), 120.7 (C-4a), 128.3 (d, $^3J_{CF}$ 8.3 Hz, C-2′ and C-6′), 129.5 (C-5), 129.8 (C-7), 135.8 (d, $^4J_{CF}$ 3.2 Hz, C-1′), 147.1 (C-8a), 162.8 (d, $^1J_{CF}$ 246.5 Hz, C-4′), 190.9 (C-4); IR (neat): ν_{max} 3363, 1684, 1592, 1509, 1480, 1408, 1360, 1328, 1284, 1225, 1160, 1017, 896, 856, 833, 749 cm^{-1}; *m/z* (100, M+H) 398; HRMS (ES): MH^+, found: 397.9200. For $[C_{15}H_{10}{}^{79}Br_2FNO]^+$: requires, 397.9093.

4.3.3 Preparation of 2-(4-chlorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-one 79c (R = Cl)

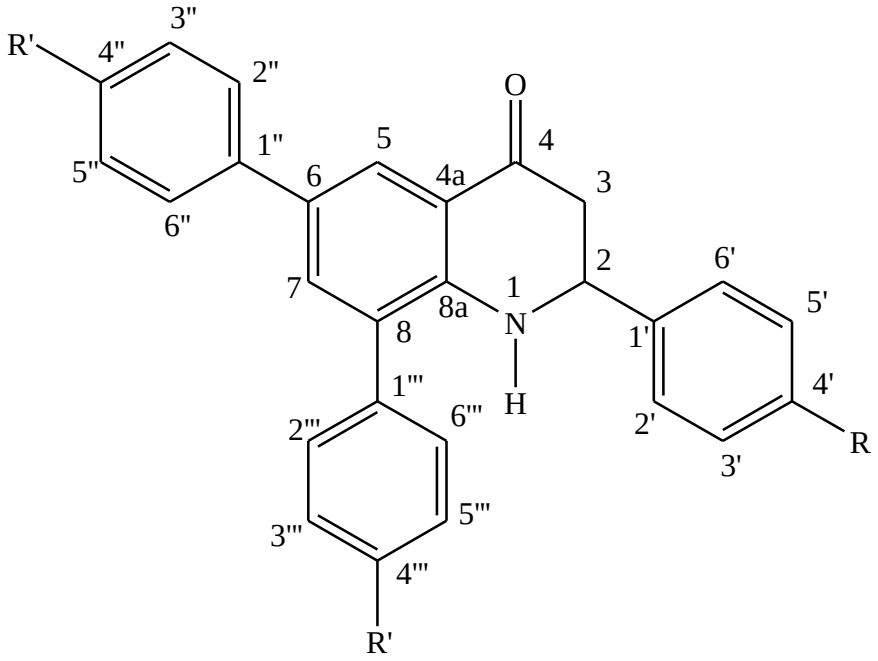
An experimental procedure employed for the synthesis of **79a** was followed using a mixture of **9c** (1.00 g, 3.9 mmol) and *N*-bromosuccinimide (1.73 g, 9.7 mmol) in CCl_4:$CHCl_3$ (50 mL); work-up and column chromatography on silica gel afforded **79c** as a light yellow solid (1.10 g, 68%); R_f (toluene) 0.63; mp 145-146 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.78 (1H, dd, *J* 4.5 and 16.5 Hz, 3-H), 2.85 (1H, dd, *J* 13.2 and 16.5 Hz, 3H), 4.76 (1H, dd, *J* 4.5 and 6.3 Hz, 2-H), 5.05 (1H, s, N-H), 7.11 (2H, t, *J* 9.2 Hz, 2′-H and 6′-H), 7.44 (2H, dd, *J* 4.5 and 9.3 Hz, 3′-H and 5′-H), 7.72 (1H, d, *J* 2.4 Hz, 7-H), 7.94 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.2 (C-3), 57.1 (C-2), 110.1 (C-6), 110.8 (C-8), 120.8 (C-4a), 127.9 (C-2′ and C-6′), 129.4 (C-3′ and C-5′), 129.6 (C-5), 134.6 (C-4′), 138.4 (C-7), 140.0 (C-1′), 147.0 (C-8a), 190.8 (C-4); IR (neat): ν_{max} 3375, 1672, 1592, 1483, 1396, 1334, 1280, 1228, 1164, 1089, 1018, 868, 824, 725, 675 cm^{-1}; *m/z* (100, M+H) 414; HRMS (ES): MH^+, found: 413.8835. For $[C_{15}H_{10}{}^{35}Cl^{79}Br2NO]^+$: requires, 413.8797.

4.3.4 Preparation of 2-(4-methoxyphenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-one 79d (R = OCH_3)

An experimental procedure employed for the synthesis of **79a** was followed using a mixture of **9d** (1.00 g, 4.0 mmol) and *N*-bromosuccinimide (1.76 g, 9.9 mmol) in CCl_4:$CHCl_3$ (50 mL); work-up and column chromatography on silica gel afforded **79d** as a light yellow solid (1.03 g, 63%); R_f (toluene) 0.40; mp 149-151 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.77 (1H, dd, *J*

4.5 and 16.5 Hz, 3-H), 2.88 (1H, dd, *J* 13.2 and 16.5 Hz, 3H), 3.82 (3H, s, $COCH_3$), 4.71 (1H, dd, *J* 4.5 and 9.0 Hz, 2-H), 5.03 (1H, s, N-H), 6.94 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 7.31 (2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.70 (1H, d, *J* 2.1 Hz, 7-H), 7.95 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.4 (C-3), 54.4 (OCH_3), 57.2 (C-2), 109.8 (C-6), 110.7 (C-8), 114.5 (C-4a), 120.8 (C-2′ and C-6′), 127.8 (C-3′ and C-5′), 129.6 (C-5), 132.0 (C-4′), 139 9 (C-7), 147.3 (C-1′), 159.9 (C-8a), 191.4 (C-4); IR (neat): ν_{max} 3317, 1661, 1596, 1503, 1414, 1348, 1283, 1246, 1203, 1180, 1149, 1026, 962, 880, 809, 787, 737, 704 cm^{-1}; *m/z* (100, M+H) 412; HRMS (ES): MH^+, found: 411.9372. For $[C_{16}H_{13}{}^{79}Br_2NO_2]^+$: requires, 411.9293.

4.4 Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions 80a-h



2,6,8-Triaryl-2,3-dihydroquinolin-4(1*H*)-ones 80a-h

4.4.1 Preparation of 2,6,8-trisphenyl-2,3-dihydroquinolin-4(1*H*)-one 80a (R, R′ = H)

A stirred mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one **79a** (0.40 g, 1.1 mmol), phenylboronic acid (0.32 g, 2.6 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.037 g, 0.05 mmol), tricyclohexylphosphine (0.029 g, 0.1 mmol) and potassium carbonate (0.32 g, 2.3 mmol) in dioxane-water (3:1, v/v; 20 mL), in a 2-necked round bottomed flask equipped with a stirrer bar, rubber septum and a condenser was degassed for 20 min with nitrogen gas. A balloon filled with nitrogen gas was then connected to the top of the condenser and the mixture was heated at 85-90 °C for 18 h. The mixture was then allowed to cool to room temperature and then poured into an ice-cold water (40 mL). The product was extracted into chloroform (3×30 mL) and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The salt was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **80a** as a yellow solid (0.28 g, 72%); R_f (30% ethyl acetate/ hexane) 0.75; mp 165-166 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.84 (1H, ddd, *J* 1.5, 4.5 and 16.3 Hz, 3-H), 2.95 (1H, dd, *J* 13.1 and 16.3 Hz, 3H), 4.72 (1H, dd, *J* 4.5 and 8.7 Hz, 2-H), 4.84 (1H, s, N-H), 7.25-7.52 (13H, m, 2′-H, 2′′-H, 3′-H, 3′′-H, 3′′′-H, 4′-H, 4′′-H, 4′′′-H, 5′-H, 5′′-H, 5′′′-H, 6′-H and 6′′-H), 7.60-7.63 (3H, m, 2′′′-H, 6′′′-H and 7-H), 8.21 (1H, d, *J* 3.0 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.5 (C-3), 58.3 (C-2), 115.6 (C-8), 119.4 (C-4a), 125.0 (C-2′ and C-6′), 126.4 (C-6), 126.9 (C-4′′), 128.1 (C-2′′ and C-6′′), 128.3 (C-2′′′ and C-6′′′), 128.8 (C- 4′′′), 129.0 (C-3′ and C-5′), 129.1 (C-3′′′ and C-5′′′), 129.3 (C-3′′ and C-5′′), 129.5 (C-5), 130.9 (C-7), 134.8 (C-4′), 137.5 (C-1′), 139.9 (C-1′′′), 141.0 (C-1′′), 148.0 (C-8a), 193.3 (C-4); IR (neat): ν_{max} 4861, 3380, 2134, 2098, 1675,

1600, 1575, 1474, 1315, 1269, 1234, 1142, 1073, 1030, 901 cm^{-1}; *m/z* (100, M+H) 376; HRMS (ES): MH^+, found: 376.1685. For $[C_{27}H_{21}NO]^+$: requires, 376.1623.

4.4.2 Preparation of 2-(4-fluorophenyl)-6,8-bisphenyl-2,3-dihydroquinolin-4(1*H*)-one 80b (R = F, R′ = H)

An experimental procedure employed for the synthesis of **80a** was followed using a mixture of **79b** (0.40 g, 1.0 mmol), $PhB(OH)_2$ (0.31 g, 2.5 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), PCy_3 (0.028 g, 0.1 mmol), and K_2CO_3 (0.305 g, 2.2 mmol) in dioxane-water (20 mL); work-up and column chromatography on silica gel afforded **80b** as a yellow solid (0.24 g, 62%); R_f (30% ethyl acetate/ hexane) 0.75; mp 182-185 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.82 (1H, ddd, *J* 1.5, 4.5 and 16.3 Hz, 3-H), 2.92 (1H, dd, *J* 12.9 and 16.3 Hz, 3H), 4.70 (1H, dd, *J* 4.5 and 8.1 Hz, 2-H), 4.77 (1H, s, N-H), 7.06 (2H, t, *J* 8.7 Hz, 2′′′-H and 6′′′-H), 7.26-7.51 (10H, m, 2′-H, 3′-H, 3′′-H, 3′′′-H, 4′′-H, 4′′′-H, 5′-H, 5′′-H, 5′′′-H, 6′-H), 7.60-7.63 (3H, m, 2′′-H and 6′′-H, 7-H), 8.20 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.5 (C-3), 57.6 (C-2), 115.8 (C-8), 116.0 (d, $^2J_{CF}$ 21.8 Hz, C-3′ and C-5′), 119.5 (C-4a), 125.0 (C-2′′ and C-6′′), 126.4 (C-6), 126.9 (C-4′′), 128.0 (C-2′′′ and C-6′′′), 128.1 (d, $^3J_{CF}$ 8.3 Hz, C-2′ and C-6′), 128.2 (C-4′′′), 129.1 (C-3′′′ and C-5′′′), 129.3 (C-3′′ and C-5′′), 129.5 (C-5), 131.2 (C-7), 136.8 (d, $^4J_{CF}$ 3.0 Hz, C-1′), 137.4 (C-1′′′), 139.8 (C-1′′), 147.8 (C-8a), 162.5 (d, $^1J_{CF}$ 246.0 Hz, C-4′), 193.1 (C-4); IR (neat): ν_{max} 3381, 3056, 2923, 2652, 2113, 1681, 1600, 1481, 1350, 1321, 1270, 1232, 1157, 905, 868 cm^{-1}; *m/z* (100, M+H) 394; HRMS (ES): MH^+, found: 394.1599. For $[C_{27}H_{20}FNO]^+$: requires, 394.1529.

4.4.3 Preparation of 2-(4-chlorophenyl)-6,8-bisphenyl-2,3-dihydroquinolin-4(1*H*)-one 80c (R = Cl, R′ = H)

An experimental procedure employed for the synthesis of **80a** was followed using a mixture of **79c** (0.40 g, 1.0 mmol), $PhB(OH)_2$ (0.29 g, 2.4 mmol), $PdCl_2(PPh_3)_2$ (0.034 g, 0.05 mmol), PCy_3 (0.027 g, 0.1 mmol) and K_2CO_3 (0.29 g, 2.1 mmol) in dioxane-water (20 mL); work-up and column chromatography on silica gel afforded **80c** as a yellow solid (0.28 g, 71%); R_f (30% ethyl acetate/ hexane) 0.75; mp 202-204 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.87 (1H, dd, *J* 4.5 and 16.2 Hz, 3-H), 2.91 (1H, dd, *J* 12.3 and 16.2 Hz, 3H), 4.70 (1H, dd, *J* 4.5 and 7.5 Hz, 2-H), 4.77 (1H, s, N-H), 7.25-7.33 (4H, m, 2′-H, 2‴-H, 6′-H, 6‴-H), 7.35-7.51 (8H, m, 2′′-H, 3′-H, 3′′-H, 3‴-H, 4′′-H, 4‴-H, 5′-H, 5′′-H, 5‴-H, 6′′-H, and 7-H), 8.18 (1H, d, *J* 2.7 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.3 (C-3), 57.6 (C-2), 115.1 (C-8), 119.5 (C-4a), 125.0 (C-2′ and C-6′), 126.4 (C-6), 127.0 (C-4′′), 127.8 (C-2′′ and C-6′′), 128.2 (C-2‴ and C-6‴), 128.8 (C-4‴), 129.1 (C-3′ and C-5′), 129.3 (C-3‴ and C-5‴), 129.6 (C-3′′ and C-5′′), 131.2 (C-5), 134.1 (C-7), 134.9 (C-4′), 137.4 (C-1′), 139.5 (C-1‴), 139.8 (C-1′′), 147.7 (C-8a), 192.9 (C-4); IR (neat): ν_{max} 3744, 3373, 2086, 1666, 1611, 1479, 1409, 1358, 1312, 1274, 1231, 1143, 1086, 897, 865 cm^{-1}; *m/z* (100, M+H) 410; HRMS (ES): MH^+, found: 410.1300. For $[C_{27}H_{20}{}^{35}ClNO]^+$: requires, 410.1233.

4.4.4 Preparation of 6,8-bisphenyl-2(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one 80d (R = OCH_3, R′ = H)

An experimental procedure employed for the synthesis of **80a** was followed using a mixture of **79d** (0.40 g, 1.0 mmol), $PhB(OH)_2$ (0.29 g, 2.4 mmol), $PdCl_2(PPh_3)_2$ (0.034 g, 0.05 mmol), PCy_3 (0.027 g, 0.1 mmol) and K_2CO_3 (0.30 g, 2.1 mmol) in dioxane-water (20 mL); work-up and column chromatography on silica gel afforded **80d** as a yellow solid (0.24 g, 62%); R_f (30% ethyl acetate/ hexane) 0.63; mp 194-196 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.80 (1H, ddd, *J* 1.5, 4.5 and 16.2 Hz, 3-H), 2.93 (1H, dd, *J* 13.2 and 16.2 Hz, 3-H), 3.79 (3H, s, $COCH_3$), 4.66 (1H, dd, *J* 4.5 and 9.6 Hz, 2-H), 4.78 (1H, s, N-H), 6.89 (2H, d, *J* 9.0 Hz, 2′′′-H and 6′′′-H), 7.25-7.51 (10H, m, 2′-H, 3′-H, 3′′-H,3′′′-H, 4′′-H, 4′′′-H, 5′-H, 5′′-H, 5′′′-H, 6′-H), 7.59-7.63 (3H, m, 2′′-H and 6′′-H, 7H), 8.19 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.6 (C-3), 55.0 (OCH_3), 57.7 (C-2), 114.3 (C-8), 119.4 (C-4a), 125.0 (C-2′ and C-6′), 126.4 (C-6), 126.8 (C-4′′), 127.6 (C-2′′ and C-6′′), 128.1 (C-2′′′ and C-6′′′), 128.8 (C-4′′′), 129.1 (C-3′ and C-5′), 129.2 (C-3′′′ and C-5′′′), 129.5 (C-3′′ and C-5′′), 130.8 (C-5), 133.0 (C-7), 134.8 (C-4′), 137.5 (C-1′), 139.9 (C-1′′′), 148.0 (C-1′′), 159.5 (C-8a), 193.5 (C-4); IR (neat): ν_{max} 3744, 2359, 1881, 1675, 1607, 1509, 1478, 1347, 1300, 1240, 1171, 1143, 1107, 1036, 901 cm^{-1}; *m/z* (100, M+H) 406; HRMS (ES): MH^+, found: 406.1790. For $[C_{28}H_{23}NO_2]^+$: requires, 406.1729.

4.4.5 Preparation of 6,8-bis(4-fluorophenyl)-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one 80e (R = H, R′ = F)

An experimental procedure employed for the synthesis of **80a** was followed using a mixture of **79a** (0.40 g, 1.1 mmol), 4-fluorophenylboronic acid (0.37 g, 2.6 mmol), $PdCl_2(PPh_3)_2$ (0.036 g, 0.05 mmol), PCy_3 (0.029 g, 0.1 mmol) and K_2CO_3 (0.32 g, 2.3 mmol) in dioxane-water (20 mL); work-up and column chromatography on silica gel afforded **82e** as a yellow solid (0.28 g, 66%); R_f (30% ethyl acetate/ hexane) 0.70; mp 167-169 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.84 (1H, ddd, *J* 1.5, 4.5 and 16.2 Hz, 3-H), 2.94 (1H, dd, *J* 12.9 and 16.2 Hz, 3-H), 4.71 (1H, t, *J* 8.0 Hz, 2-H), 4.74 (1H, s, N-H), 7.07-7.19 (4H, m, 2′-H, 3′-H, 5′-H, 6′-H), 7.32-7.39 (5H, m, 2″-H, 3″-H, 4′-H, 5″-H, 6″), 7.43-7.58 (5H, m, 2‴-H, 3‴-H, 5‴-H, 6‴-H, 7-H), 8.13 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.4 (C-3), 58.2 (C-2), 115.6 (d, $^2J_{CF}$ 21.4 Hz, C-3″ and C-5″), 115.8 (d, $^2J_{CF}$ 21.4 Hz, C-3‴ and C-5‴), 119.5 (C-4a), 125.0 (C-2′ and C-6′), 126.3 (C-6), 128.1 (C-8), 129.0 (C-5), 129.1 (C-3′ and C-5′), 130.1 (C-7), 130.8 (d, $^3J_{CF}$ 7.5 Hz, C-2‴ and C-6‴), 130.9 (d, $^3J_{CF}$ 7.5 Hz, C-2″ and C-6″), 133.2 (C-4′), 134.6 (d, $^4J_{CF}$ 3.0 Hz, C-1‴), 135.9 (d, $^4J_{CF}$ 3.0 Hz, C-1″), 140.8 (C-1′), 147.9 (C-8a), 162.2 (d, $^1J_{CF}$ 240 Hz, C-4‴), 162.6 (d, $^1J_{CF}$ 247.5 Hz, C-4″), 193.1 (C-4); IR (neat): ν_{max} 3376, 2924, 2853, 1669, 1603, 1482, 1360, 1220, 1144, 1014, 903, 832, 765, 701,602 cm^{-1}; *m/z* (100, M+H) 412; HRMS (ES): MH^+, found: 412.1492. For $[C_{27}H_{19}F_2NO]^+$: requires, 412.1435.

4.4.6 Preparation of 2,6,8-tris(4-fluorophenyl)-2,3-dihydroquinolin-4(1*H*)-one 80f (R = F, R′ = F)

An experimental procedure employed for the synthesis of **80a** was followed using a mixture of **79b** (0.40 g, 1.0 mmol), $ArB(OH)_2$ (0.35 g, 2.5 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), PCy_3 (0.028 g, 0.1 mmol) and K_2CO_3 (0.304 g, 2.2 mmol) in dioxane-water (20 mL); work-up and column chromatography on silica gel afforded **80f** as a yellow solid (0.28 g, 65%); R_f (30% ethyl acetate/ hexane) 0.70; mp 176-178 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 2.81 (1H, ddd, *J* 1.5, 4.5 and 16.2 Hz, 3-H), 2.91 (1H, dd, *J* 12.9 and 16.2 Hz, 3-H), 4.64 (1H, s, N-H), 4.69 (1H, dd, *J* 4.5 and 7.8 Hz, 2-H), 7.02-7.10 (4H, m, 2′-H, 3′-H, 5′-H, 6′-H), 7.12-7.20 (2H, m, 3″-H and 5″-H), 7.36 (2H, dd, *J* 3.6 and 5.3 Hz, 2″-H and 6″-H), 7.46 (2H, dd, *J* 3.0 and 5.4 Hz, 3‴-H and 5‴-H), 7.50-7.57 (3H, m, 2‴-H and 6‴-H, 7-H), 8.12 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.4 (C-3), 57.6 (C-2), 115.8 (C-8), 116.0 (d, $^2J_{CF}$ 21.6 Hz, C-3′ and C-5′), 116.0 (d, $^2J_{CF}$ 21.4 Hz, C-3″ and C-5″), 116.0 (d, $^2J_{CF}$ 21.4 Hz, C-3‴ and C-5‴), 119.5 (C-4a), 125.3 (C-6), 128.0 (d, $^3J_{CF}$ 7.5 Hz, C-2′ and C-6′),129.0 (C-5), 130.9 (d, $^3J_{CF}$ 7.5 Hz, C-2″ and C-6″), 133.2 (d, $^3J_{CF}$ 8.3 Hz, C-2‴ and C-6‴), 133.3 (C-4′), 134.7 (C-7), 135.7 (d, $^4J_{CF}$ 3.0 Hz, C-1″), 135.8 (d, $^4J_{CF}$ 3.0 Hz, C-1‴), 136.6 (d, $^4J_{CF}$ 3.0 Hz, C-1′), 147.7, (C-8a), 162.2 (d, $^1J_{CF}$ 240.0 Hz, C-4″), 162.2 (d, $^1J_{CF}$ 240.0 Hz, C-4‴), 162.6 (d, $^1J_{CF}$ 247.5 Hz, C-4′), 193.0 (C-4); IR (neat): ν_{max} 3390, 3069, 2114, 1682, 1603, 1490, 1356, 1319, 1218, 1157, 1095, 1016, 909, 835, 804cm^{-1}; *m/z* (100, M+H) 430 cm^{-1}; HRMS (ES): MH^+, found: 430.1421. For $[C_{27}H_{18}F_3NO]^+$: requires, 430.1340.

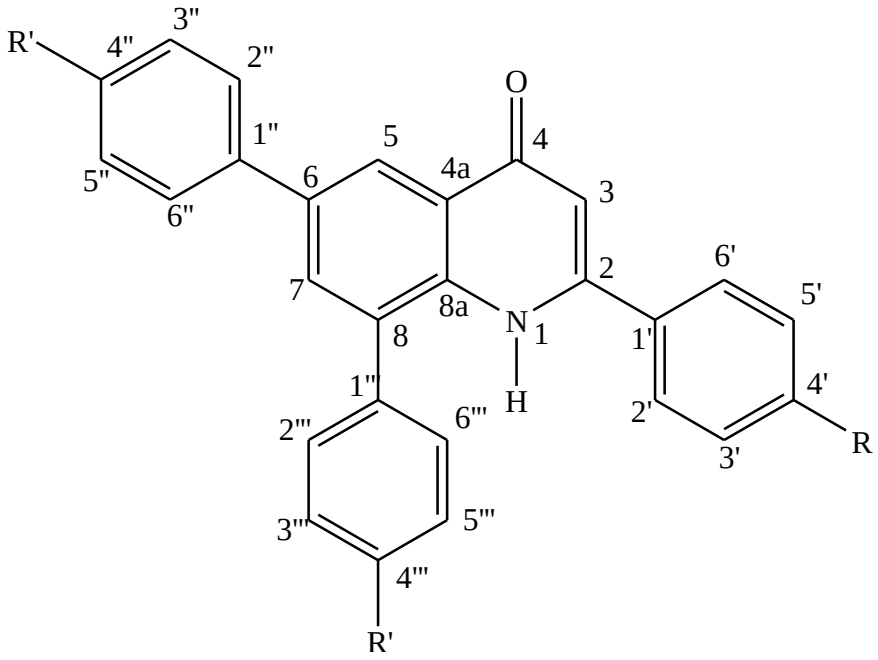
4.4.7 Preparation of 6,8-bis(4-fluorophenyl)-2(4-chlorophenyl)-2,3-dihydroquinolin-4(1*H*)-one 80g (R = Cl, R′ = F)

An experimental procedure employed for the synthesis of **80a** was followed using a mixture of **79c** (0.40 g, 1.0 mmol), $ArB(OH)_2$ (0.34 g, 2.4 mmol), $PdCl_2(PPh_3)_2$ (0.034 g, 0.05 mmol), PCy_3 (0.027 g, 0.1 mmol) and K_2CO_3 (0.30 g, 2.1 mmol) in dioxane-water (20 mL); work-up and column chromatography on silica gel afforded **80g** as a yellow solid (0.23 g, 52%); R_f (30% ethyl acetate/ hexane) 0.70; mp 190-192 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.62 (1H, dd, *J* 4.5 and 16.3 Hz, 3-H), 2.90 (1H, dd, *J* 12.6 and 16.3 Hz, 3-H), 4.64 (1H, s, N-H), 4.69 (1H, dd, *J* 4.5 and 7.5 Hz, 2-H), 7.07-7.19 (4H, m, 2′-H, 3′-H, 5′-H, 6′-H), 7.33 (4H, t, *J* 9.6 Hz, 2″-H, 3″-H, 5″-H and 6″-H), 7.43-7.56 (5H, m, 2‴-H, 3‴-H, 5‴-H, 6‴-H, 7-H), 8.12 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.2 (C-3), 57.6 (C-2), 115.9 (d, $^2J_{CF}$ 21.3 Hz, C-3‴ and C-5‴), 116.2 (d, $^2J_{CF}$ 21.3 Hz, C-3″ and C-5″), 119.6 (C-4a), 125.0 (C-6), 127.7 (C-8), 127.9 (d, $^3J_{CF}$ 7.5 Hz, C-2‴and C-6‴), 130.4 (C-5), 130.9 (d, $^3J_{CF}$ 8.3 Hz, C-2″ and C-6″), 131.0 (C-3′ and C-5′), 133.1 (C-7), 134.2 (C-4′), 134.7 (d, $^4J_{CF}$ 3.0 Hz, C-1‴), 135.8 (d, $^4J_{CF}$ 3.0 Hz, C-1″), 139.3 (C-1′), 147.6 (C-8a), 162.3 (d, $^1J_{CF}$ 244.5 Hz, C-4‴), 162.6 (d, $^1J_{CF}$ 247.5 Hz, C-4″), 192.7 (C-4); IR (neat): ν_{max} 3392, 2846, 2625, 1678, 1603, 1577, 1487, 1406, 1354, 1320, 1231, 1163, 1014, 908, 834, 761, 732 cm^{-1}; *m/z* (100, M+H) 446; HRMS (ES): MH^+, found 446.1101. For $[C_{27}H_{18}{}^{35}ClF_2NO]^+$: requires, 446.1045.

4.4.8 Preparation of 6,8-bis(4-fluorophenyl)-2(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one 80h (R = OCH_3, R′ = F)

An experimental procedure employed for the synthesis of **80a** was followed using a mixture of **79d** (0.40 g, 1.0 mmol), $ArB(OH)_2$ (0.34 g, 2.4 mmol), $PdCl_2(PPh_3)_2$ (0.034 g, 0.05 mmol), PCy_3 (0.027 g, 0.1 mmol) and K_2CO_3 (0.295 g, 2.1 mmol) in dioxane-water (20 mL); work-up and column chromatography on silica gel afforded **80h** as a yellow solid (0.28 g, 66%); R_f(30% ethyl acetate/ hexane) 0.64; mp 182-184 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.80 (1H, dd, *J* 4.5 and 16.8 Hz, 3-H), 2.90 (1H, dd, *J* 12.6 and 16.8 Hz, 3-H), 3.80 (3H, s, $COCH_3$), 4.62-4.68 (2H, m, 2-H and N-H), 6.89 (2H, d, *J* 7.5 Hz, 3′-H and 5′-H), 7.06-7.17 (4H, m, 2′-H, 3′′-H, 5′′-H, 6′-H), 7.30 (2H, d *J* 9.0Hz, 2′′-H and 6′′-H), 7.42-7.57 (5H, m, 2′′′-H, 3′′′-H,5′′′-H, 6′′′-H and 7-H), 8.12 (1H, d, *J* 3.0 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.5 (C-3), 55.1 (OCH_3), 57.7 (C-2), 114.4 (C-4a), 115.8 (d, $^2J_{CF}$ 21.4 Hz, C-3′′′ and C-5′′′), 116.2 (d, $^2J_{CF}$ 21.4 Hz,(C-3′′ and C-5′′), 119.5 (C-8), 127.9 (d, $^3J_{CF}$ 7.5 Hz, C-2′′′ and C-6′′′), 128.5 (C-2′ and C-6′), 130.0 (C-5), 130.9 (d, $^3J_{CF}$ 8.3 Hz, C-2′′ and C-6′′), 131.0 (C-3′ and C-5′)), 132.8 (C-7), 133.3 (d, $^4J_{CF}$ 3.8 Hz, C-1′′′), 135.9 (d, $^4J_{CF}$ 3.0 Hz, C-1′′), 148.0 (C-8a), 162.2 (d, $^1J_{CF}$ 244.5 Hz, C-4′′′), 162.5 (d, $^1J_{CF}$ 246.8 Hz C-4′′), 193.4 (C-4); IR (neat): ν_{max} 3402, 2123, 1887, 1676, 1609, 1509, 1484, 1349, 1304, 1220, 1153, 1028, 908, 830, 787 cm^{-1}; *m/z* (100, M+H) 442; HRMS (ES): MH^+, found 442.1546. For $[C_{28}H_{21}F_2NO_2]^+$: requires, 442.1540.

4.5 Preparation of 2,6,8-triphenylquinolin-4(1*H*)-ones 81a-h



2,6,8-Triphenylquinolin-4(1*H*)-ones 81a-h

4.5.1 Preparation of 2,6,8-trisphenylquinolin-4(1*H*)-one 81a (R = H, R′ = H)

A stirred mixture of **80a** (0.40 g, 1.1 mmol) and thallium(III) *p*-tolylsulphonate (TTS) (0.85 g, 1.2 mmol) in dimethoxyethane (DME) (15 mL) was heated under reflux for 0.5 h. The mixture was allowed to cool to room temperature and poured into cold water (50 mL). The precipitate was filtered and dissolved in chloroform (40 mL). The organic phase was washed sequentially with Na_2CO_3 solution (2×50 mL) and cold water (2×50 mL). The product was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford **81a** as a white solid (0.26 g, 65%); R_f (ethyl acetate) 0.56; mp 242-244 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.61 (1H, d, *J* 7.5 Hz, 3-H), 6.78 (1H, d, *J* 2.1 Hz, 4′′-H), 7.11 (2H, d, *J* 8.1 Hz,

2′′′-H and 6′′′-H), 7.37 (1H, t, *J* 7.2 Hz, 4′-H), 7.44-7.64 (10H, m, 2′-H, 3′-H and 5′-H, 3′′-H and 5′′-H, 3′′′-H and 5′′′-H, 4′′′-H, 6′-H, 6′′′-H), 7.75 (2H, d, *J* 7.2 Hz, 2′′-H and 6′′-H), 7.85 (1H, s, 7-H), 8.51 (1H, br s, N-H), 8.66 (1H, s, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.3 (C-3), 116.9 (C-8), 123.4 (C-2′ and C-6′), 125.9 (C-6), 127.6 (C-4′′), 127.7 (C-4′′′), 128.9 (C-2′′ and C-6′′), 129.0 (C-2′′′ and C-6′′′), 129.2 (C-3′ and C-5′), 129.6 (C-3′′ and C-5′′), 129.8 (C-3′′′ and C-5′′′), 130.7 (C-5), 131.4 (C-4a), 131.8 (C-7), 136.2 (C-4′), 136.3 (C-1′), 136.5 (C-1′′), 139.6 (C-1′′′), 143.5 (C-2), 148.7 (C-8a), 179.0 (C-4); IR (neat): ν_{max} 3398, 3056, 2962,1626, 1591, 1492, 1382, 1290, 1246, 1181, 1076, 931, 897, 844, 759, 695, 653, 622 cm^{-1}; *m/z* (100, M+H) 374; HRMS (ES): MH^+, found 374.1530. For $[C_{27}H_{20}NO]^+$: requires, 374.1467.

4.5.2 Preparation of 2-(4-fluorophenyl)-6,8-bisphenylquinolin-4(1*H*)-one 81b (R = F, R′ = H)

A stirred mixture of **80b** (0.40 g, 1.0 mmol) and TTS (0.81 g, 1.1 mmol) in DME (15 mL); work-up employed for the synthesis of **81a** was followed and afforded **81b** as a yellowish orange solid (0.24 g, 60%); R_f (ethyl acetate) 0.65; mp 237-239 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.51 (1H, d, *J* 9.0 Hz, 3-H), 6.78 (1H, d, *J* 3.0 Hz, 4′′-H), 7.08-7.18 (2H, m, 2′′′-H and 6′′′-H), 7.33-7.64 (10H, m, 2′-H and 6′-H, 3′-H and 5′-H, 3′′-H and 5′′-H, 3′′′-H and 5′′′-H, 4′′′-H, 7-H), 7.69-7.83 (2H, m, 2′′-H and 6′′-H), 8.43 (1H, br s, N-H), 8.62 (1H, s, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.2 (C-3), 113.9 (C-8), 116.7 (d, $^2J_{CF}$ 22.5 Hz, C-3′ and C-5′), 125.8 (C-6), 127.1 (C-4′′), 127.7 (d, $^3J_{CF}$ 7.5 Hz, C-2′ and C-6′), 128.1 (C-2′′ and C-6′′), 128.2 (C-2′′′ and C-6′′′), 128.9 (C-4′′′), 129.0 (C-3′′ and C-5′′), 129.2 (C-3′′′and C-5′′′), 129.8 (C-5), 130.6 (C-4a), 131.8

(C-7), 136.3 (d, $^{4}J_{CF}$ 3.0 Hz, C-1′), 136.6 (C-1″), 139.5 (C-1‴), 143.1 (C-2), 147.7 (C-8a), 164.1 (d, $^{1}J_{CF}$ 250.5 Hz, C-4′), 178.9 (C-4); IR (neat): ν_{max} 3381, 3056, 2923, 2652, 2113, 1681, 1600, 1481, 1350, 1321, 1270, 1232, 1157, 905, 868 cm^{-1}; *m/z* (100, M+H) 392; HRMS (ES): MH^{+}, found: 392.1465. For $[C_{27}H_{18}FNO]^{+}$: requires, 392.1372.

4.5.3 Preparation of 2-(4-chlorophenyl)-6,8-bisphenylquinolin-4(1*H*)-one 81c (R = Cl, R′ = H)

A stirred mixture of **80c** (0.40 g, 1.0 mmol) and TTS (0.78 g, 1.1 mmol) in DME (15 mL); work-up employed for the synthesis of **81a** was followed and afforded **81c** as a light orange solid (0.22 g, 55%); R_f (ethyl acetate) 0.72; mp 208-210 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.57 (1H, d, *J* 7.8 Hz, 3-H), 6.79 (1H, d, *J* 3.0 Hz, 4″-H), 7.10 (2H, d, *J* 9.3 Hz, 2‴-H and 6‴-H), 7.34-7.51 (5H, m, 2′-H and 6′-H, 3′-H and 5′-H, 4‴-H), 7.54-7.64 (4H, m, 3″-H, 3‴-H, 5″-H, 5‴-H), 7.74 (2H, d, *J* 7.5 Hz, 2″-H and 6″-H), 7.85 (1H, s, 7-H), 8.42 (1H, br s, N-H), 8.65 (1H, s, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.4 (C-3), 113.9 (C-8), 123.5 (C-2′and C-6′), 125.9 (C-6), 127.7 (C-4″), 127.8 (C-4‴), 128.9 (C-2″ and C-6″), 129.1 (C-2‴ and C-6‴), 129.2 (C-3′ and 5′), 129.9 (C-3″ and C-5″), 129.9 (C-3‴ and C-5‴), 131.4 (C-5), 131.9 (C-4a), 132.9 (C-7), 136.2 (C-4′), 136.3 (C-1′), 136.8 (C-1″), 139.6 (C-1‴), 144.1 (C-2), 147.5 (C-8a), 179.0 (C-4); IR (neat): ν_{max} 3744, 3373, 2086, 1666, 1611, 1479, 1358, 1312, 1274, 1231, 1143, 1086, 897, 865 cm^{-1}; *m/z* (100, M+H) 408; HRMS (ES): MH^{+}, found: 408.1148. For $[C_{27}H_{18}{}^{35}ClNO]^{+}$: requires, 408.1147.

4.5.4 Preparation of 2(4-methoxyphenyl)-6,8-bisphenylquinolin-4(1*H*)-one 81d (R = OCH_3, R′ = H)

A stirred mixture of **80d** (0.40 g, 1.0 mmol) and TTS (0.79 g, 1.1 mmol) in DME (15 mL); work-up employed for the synthesis of **81a** was followed and afforded **81d** as a white solid (0.22g, 55%); R_f (ethyl acetate) 0.47; mp 212-214 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (3H, s, $COCH_3$), 6.59 (1H, d, *J* 8.4 Hz, 3-H), 6.99 (1H, d, *J* 2.1 Hz, 4′′-H), 7.36 (2H, d, *J* 7.7 Hz, 2′′′-H and 6′′′-H), 7.44 (2H, d, *J* 7.8 Hz, 2′-H and 6′-H), 7.45 (2H, d, *J* 8.7 Hz, 3′-H and 5′-H), 7.51-7.64 (5H, m, 3′′-H, 3′′′-H, 4′′′-H, 5′′-H, 5′′′-H), 7.74 (2H, d, *J* 7.5 Hz, 2′′-H and 6′′-H), 7.84 (1H, d, *J* 2.1 Hz, 7-H), 8.45 (1H, br s, N-H), 8.66 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.5 (OCH_3), 107.5 (C-3), 115.0 (C-8), 123.5 (C-2′ and C-6′), 125.8 (C-6), 127.2 (C-4′′), 127.5 (C-4′′′), 128.9 (C-2′′ and C-6′′), 128.9 (C-2′′′ and C-6′′′), 129.2 (C-3′ and C-5′), 129.7 (C-3′′ and C-5′′), 129.8 (C-3′′′ and C-5′′′), 130.1 (C-5), 131.3 (C-4a), 131.7 (C-7), 136.1 (C-4′), 136.2 (C-1′), 136.5 (C-1′′), 139.7 (C-1′′′), 144.2 (C-2), 148.5 (C-8a), 179.0 (C-4); IR (neat): ν_{max} 3744, 1881, 1675, 1607, 1509, 1478, 1347, 1300, 1240, 1171, 1143, 1107, 1036, 901 cm^{-1}; *m/z* (100, M+H) 404; HRMS (ES): MH^+, found: 404.1634. For $[C_{28}H_{21}NO_2]^+$: requires, 404.1572.

4.5.5 Preparation of 6,8-bis(4-fluorophenyl)-2-phenylquinolin-4(1*H*)-one 81e (R = H, R′= F)

A stirred mixture of **80e** (0.40 g, 1.0 mmol) and TTS (0.78 g, 1.1 mmol) in DME (15 mL); work-up employed for **81a** was followed and afforded **81e** as a solid (0.36 g, 90%); R_f (ethyl acetate) 0.75; mp 239-242 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.61 (1H, d, *J* 8.7 Hz, 3-H), 7.14

(2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.31 (2H, t, *J* 8.6 Hz, 3″-H and 5″-H), 7.50-7.55 (5H, m, 2′-H and 6′-H, 3″-H and 5″-H, 4′-H), 7.57 (2H, t, *J* 8.7 Hz, 2‴-H and 6‴-H), 7.68 (2H, t, *J* 8.7 Hz, 2″-H and 6″-H), 7.74 (1H, d, *J* 2.1 Hz, 7-H), 8.34 (1H, br s, N-H), 8.59 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.4 (C-3), 115.8 (d, $^2J_{CF}$ 21.8 Hz, C-3″ and C-5″), 117.0 (d, $^2J_{CF}$ 21.8 Hz, C-3‴ and C-5‴), 123.5 (C-8), 125.9 (C-2′ and C-6′), 126.1 (C-6), 128.8 (d, $^3J_{CF}$ 8.3 Hz, C-2″ and C-6″), 129.7 (C-3′ and C-5′), 130.4 (C-5), 130.9 (C-4a), 131.0 (d, $^3J_{CF}$ 8.3 Hz, C-2‴ and C-6‴),131.7 (C-7), 132.2 (d, $^4J_{CF}$ 3.0 Hz, C-1″), 134.3 (C-1′), 135.7 (d, $^4J_{CF}$ 3.8 Hz, C-1‴), 136.2 (C-2), 148.8 (C-8a), 162.6 (d, $^1J_{CF}$ 245.3 Hz, C-4″), 166.0 (d, $^1J_{CF}$ 254.3 Hz, C-4‴), 178.8 (C-4); IR (neat): ν_{max} 3405, 2924, 2161, 1628, 1584, 1495, 1460, 1373, 1218, 1158, 1098, 1035, 882, 834, 768, 695, 628 cm^{-1}; *m/z* (100, M+H) 410; HRMS (ES): MH$^+$, found: 410.1343. For $[C_{27}H_{17}F_2NO]^+$: requires, 410.1278.

4.5.6 Preparation of 2,6,8-tris(4-fluorophenyl)quinolin-4(1*H*)-one 81f (R = F, R′ = F)

A stirred mixture of **80f** (0.40 g, 0.9 mmol) and TTS (0.75 g, 1.0 mmol) in DME (15 mL); work-up employed for **81a** was followed and afforded **81f** as a solid (0.26 g, 65%); R_f (ethyl acetate) 0.81; mp 240-242 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.52 (1H, d, *J* 8.7 Hz, 3-H), 7.14 (2H, t, *J* 9.0 Hz, 3′-H and 5′-H), 7.18 (2H, t, *J* 9.0 Hz, 3″-H and 5″-H), 7.31 (2H, t, *J* 9.0 Hz, 3‴-H and 5‴-H), 7.48 (2H, t, *J* 7.5 Hz, 2′-H and 6′-H), 7.56 (2H, t, *J* 7.5 Hz, 2″-H and 6″-H), 7.66 (2H, t, *J* 7.5 Hz, 2‴-H and 6‴-H), 7.74 (1H, d, *J* 2.4 Hz, 7-H), 8.25 (1H, br s, N-H), 8.57 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.4 (C-3), 115.8 (d, $^2J_{CF}$ 21.0 Hz, C-3″ and C-5″), 116.8 (d, $^2J_{CF}$ 21.8 Hz, C-3‴ and C-5‴), 117.0 (d, $^2J_{CF}$ 21.0 Hz, C-3′ and C-5′), 123.4 (C-8),

128.1 (C-6), 128.2 (C-5), 128.7 (d, $^{3}J_{CF}$ 8.3 Hz, C-2″ and C-6″), 130.5 (d, $^{3}J_{CF}$ 7.5 Hz, C-2‴ and C-6‴), 130.5 (C-4a), 131.0 (d, $^{3}J_{CF}$ 7.5 Hz, C-2′ and C-6′), 131.7 (C-7), 132.1 (d, $^{4}J_{CF}$ 3.8 Hz, C-1″), 132.1 (d, $^{4}J_{CF}$ 3.8 Hz, C-1‴), 135.6 (d, $^{4}J_{CF}$ 3.8 Hz, C-1′), 136.1 (C-2), 147.8 (C-8a), 162.7 (d, $^{1}J_{CF}$ 246.0 Hz, C-4″), 163.0 (d, $^{1}J_{CF}$ 248.3 Hz, C-4‴), 164.2 (d, $^{1}J_{CF}$ 251.3 Hz, C-4′), 178.7 (C-4); IR (neat): ν_{max} 3406, 1627, 1591, 1497, 1237, 1164, 1107, 1021, 894, 839, 809, 726 cm^{-1}; *m/z* (100, M+H) 428; HRMS (ES): MH^{+}, found: 428.1252. For $[C_{27}H_{16}F_3NO]^{+}$: requires, 428.1184.

4.5.7 Preparation of 2-(4-chlorophenyl)-6,8-bis(4-fluorophenyl)quinolin-4(1*H*)-one 81g (R = Cl, R′ = F)

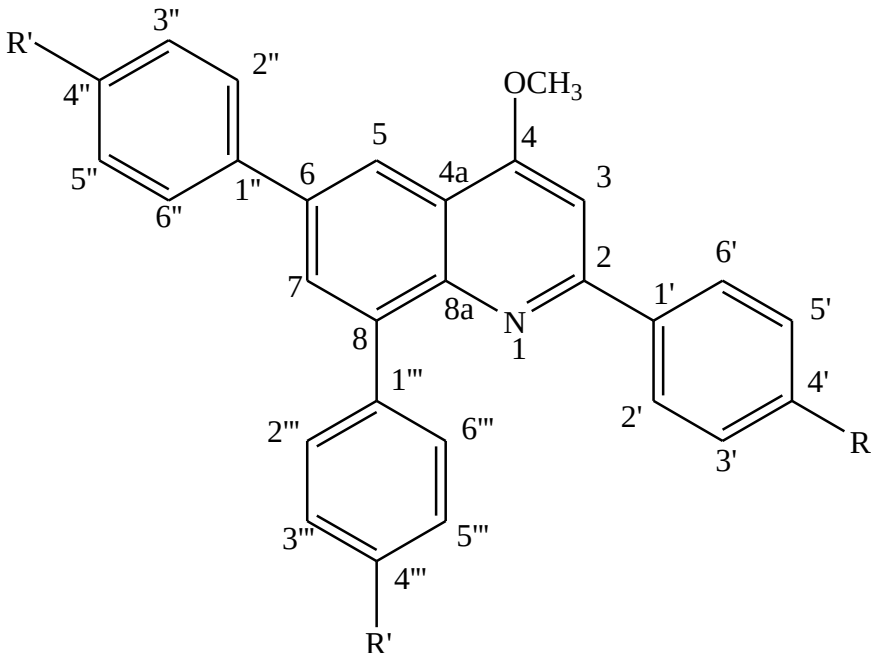
A stirred mixture of **80g** (0.40 g, 0.9 mmol) and TTS (0.72 g, 0.9 mmol) in DME (15 mL); work-up employed for **81a** was followed to afford **81g** as an orange solid (0.28 g, 71%); R_f (ethyl acetate) 0.83; mp 225-228 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.56 (1H, d, *J* 8.7 Hz, 3-H), 7.15 (2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.31 (2H, t, *J* 8.7 Hz, 3″-H and 5″-H), 7.43 (2H, d, *J* 9.0 Hz, 2‴-H and 6‴-H), 7.48 (2H, d, *J* 9.0 Hz, 3‴-H and 5‴-H), 7.55 (2H, t, *J* 8.7 Hz, 2′-H and 6′-H), 7.68 (2H, t, *J* 8.7 Hz, 2″-H and 6″-H), 7.75 (1H, d, *J* 2.1 Hz, 7-H), 8.24 (1H, br s, N-H), 8.59 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.5 (C-3), 115.9 (d, $^{2}J_{CF}$ 21.0 Hz, C-3″ and C-5″), 117.0 (d, $^{2}J_{CF}$ 21.8 Hz, C-3‴ and C-5‴), 123.5 (C-8), 125.9 (C-2′ and C-6′), 127.4 (C-6), 128.7 (d, $^{3}J_{CF}$ 7.5 Hz, C-2″ and C-6″), 130.0 (C-3′ and C-5′), 130.5 (C-5), 131.0 (4a), 131.1 (d, $^{3}J_{CF}$ 8.3 Hz, C-2‴ and C-6‴), 131.8 (C-4a), 132.1(d, $^{4}J_{CF}$ 3.8 Hz, C-1″), 132.8 (C-7), 135.6 (d, $^{4}J_{CF}$ 3.8 Hz, C-1‴), 136.1 (C-4′), 137.2 (C-2), 147.6 (C-8a), 162.7 (d, $^{1}J_{CF}$ 245.3

Hz, C-4″), 163.1 (d, $^{1}J_{CF}$ 248.3 Hz, C-4‴), 178.8 (C-4); IR (neat): ν_{max} 3400, 1624, 1601, 1490, 1380, 1297, 1224, 1158, 1094, 1013, 942, 884, 828, 766, 725 cm^{-1}; *m/z* (100, M+H) 444; HRMS (ES): MH^{+}, found: 444.0957. For $[C_{27}H_{16}{}^{35}ClF_2NO]^{+}$: requires, 444.0888.

4.5.8 Preparation of 2-(4-methoxyphenyl)-6,8-bis(4-fluorophenyl)quinolin-4(1*H*)-one 81h (R = OCH_3, R′ = F)

A stirred mixture of **80h** (0.40 g, 0.9 mmol) and TTS (0.73 g, 1.0 mmol) in DME (15 mL); work-up employed for **81a** was followed to afford **81h** as an orange solid (0.26 g, 65%); R_f (ethyl acetate) 0.61; mp 219-220 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (3H, s, $COCH_3$), 6.56 (1H, d, *J* 8.7 Hz, 3-H), 7.00 (2H, d, *J* 9.3 Hz, 3′-H and 5′-H), 7.14 (2H, t, *J* 9.2 Hz, 3″-H and 5″-H), 7.31 (2H, t, *J* 9.2 Hz, 3‴-H and 5‴-H), 7.43 (2H, d, *J* 9.2 Hz, 2′-H and 6′-H), 7.57 (2H, t, *J* 7.8 Hz, 2″-H and 6″), 7.67 (2H, t, *J* 7.8 Hz, 2‴-H and 6‴-H), 7.73 (1H, s, 7-H), 8.28 (1H, s, N-H), 8.59 (1H, s, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.5 (OCH_3), 107.5 (C-3), 115.8 (d, $^{2}J_{CF}$ 21.0 Hz, C-3″ and C-5″), 116.9 (d, $^{2}J_{CF}$ 21.8 Hz, C-3‴and C-5‴), 123.5 (C-8), 125.8 (C-2′ and C-6′), 126.4 (C-6), 127.4 (C-5), 128.8 (d, $^{3}J_{CF}$ 7.5 Hz, C-2″ and C-6″), 131.1 (d, $^{3}J_{CF}$ 8.3 Hz, C-2‴ and C-6‴), 131.5 (C-4a), 131.7 (C-7), 132.3 (d, $^{4}J_{CF}$ 3.0 Hz, C-1″), 135.7 (d, $^{4}J_{CF}$ 3.8 Hz, C-1‴), 135.4 (C-1′), 136.2 (C-2), 148.5 (C-8a), 161.7 (C-4′), 162.6 (d, $^{1}J_{CF}$ 246.0 Hz, C-4″), 163.0 (d, $^{1}J_{CF}$ 243.8 Hz, C-4‴), 178.8 (C-4); IR (neat): ν_{max} 3413, 1628, 1582, 1508, 1501, 1223, 1158, 827, 765 cm^{-1}; *m/z* (100, M+H) 440; HRMS (ES): MH^{+}, found: 440.1300. For $[C_{28}H_{19}F_2NO_2]^{+}$: requires, 440.1384.

4.6 Preparation of 2,6,8-triphenyl-4-methoxyquinolines 82a-h



2,6,8-Triphenyl-4-methoxyquinolines 82a-h

4.6.1 Preparation of 2,6,8-trisphenyl-4-methoxyquinoline 82a (R = H, R′ = H)

A stirred mixture of **80a** (0.5 g, 1.3 mmol) and I_2 (0.68 g, 2.7 mmol) in MeOH (30 mL) was heated under reflux for 2 h. The mixture was allowed to cool to room temperature and then quenched with an ice cold water (30 mL) followed by saturated $Na_2S_2O_3$ (20 mL) to decompose the unreacted I_2. The aqueous phase was extracted with $CHCl_3$ (3×30 mL) and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The salt was filtered off and the solvent was evaporated under reduced pressure to afford **82a** as a white solid (0.43 g, 82%); R_f (toluene) 0.65; mp 221-223 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.16 (3H, s, $COCH_3$), 7.30 (1H, s, 3-H), 7.39-7.55 (9H, m, 2′′′-H and 6′′′-H, 3′-H and 5′-H, 3′′′-H and 5′′′-H, 4′-H, 4′′-H, 4′′′-H), 7.80 (2H, d, *J* 7.5 Hz, 3′′-H and 5′′-H), 7.91 (2H, d, *J* 7.5 Hz, 2′′-H and 6′′-

H), 8.05 (1H, d, *J* 1.8 Hz, 7-H), 8.15 (2H, d, *J* 8.1 Hz, 2′-H and 6′-H), 8.43 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.7 (OCH_3), 97.2 (C-3), 115.3 (C-3′ and C-5′), 116.0 (C-4a), 121.2 (C-5), 127.4 (C-4″), 127.4 (C-4‴), 127.5 (C-2″ and C-6″), 127.6 (C-2‴ and C-6‴), 128.3 (C-7), 128.6 (C-2′ and C-6′), 128.9 (C-3″ and C-5″), 129.3 (C-3‴ and C-5‴), 130.4 (C-1′), 131.2 (C-8), 139.9 (C-6), 140.0 (C-1″), 140.8 (C-1‴), 145.9 (C-8a), 157.1 (C-2), 158.6 (C-4′), 163.2 (C-4); IR (neat): ν_{max} 2030, 1592, 1486, 1363, 1219, 1103, 1004, 903, 835, 768, 692, 658, 626 cm^{-1}; *m/z* (100, M+H) 388; HRMS (ES): MH^+, found: 388.1709. For $[C_{28}H_{22}NO]^+$: requires, 388.1623.

4.6.2 Preparation of 2-(4-fluorophenyl)-6,8-diphenyl-4-methoxyquinoline 82b (R = F, R′ = H)

A stirred mixture of **80b** (0.50 g, 1.3 mmol) and I_2 (0.65 g, 2.5 mmol) in MeOH (30 mL); work-up as described for **82a** afforded **82b** as a light brown solid (0.40 g, 78%); R_f (toluene) 0.75; mp 210-212 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.16 (3H, s, $COCH_3$), 7.13 (2H, t, *J* 8.6 Hz, 3′-H and 5′-H), 7.23 (1H, s, 3-H), 7.37-7.55 (6H, m, 2‴-H and 6‴-H, 3‴-H and 5‴-H, 4″-H, 4‴-H), 7.79 (2H, d, *J* 7.5 Hz, 3″-H and 5″-H), 7.87 (2H, d, *J* 7.5 Hz, 2″-H and 6″-H), 8.04 (1H, d, *J* 2.1 Hz, 7-H), 8.12 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 8.42 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.7 (OCH_3), 96.8 (C-3), 115.5 (d, $^2J_{CF}$ 21.8 Hz, C-3′ and C-5′), 115.7 (C-4a), 121.1 (C-5), 127.2 (C-4″), 127.4 (C-4‴), 127.5 (C-2″ and C-6″), 127.7 (C-2‴ and C-6‴), 128.9 (C-7), 129.1 (d, $^3J_{CF}$ 8.3 Hz, C-2′ and C6′), 129.2 (C-3″ and C-5″), 129.2 (C-3‴ and C-5‴), 131.1 (C-8), 136.2 (d, $^4J_{CF}$ 3.0 Hz, C-1′), 139.8 (C-6), 139.8 (C-1″), 140.7 (C-

1′′′), 145.8 (C-8a), 156.0 (C-2), 163.3 (C-4), 163.7 (d, $^{1}J_{CF}$ 247.5 Hz, C-4′); IR (neat): ν_{max} 1589, 1484, 1440, 1365, 1292, 1219, 1154, 1103, 994, 904, 894, 825, 765, 699, 615 cm^{-1}; *m/z* (100, M+H) 406; HRMS (ES): MH^{+}, found: 406.1606. For $[C_{28}H_{21}FNO]^{+}$: requires, 406.1529.

4.6.3 Preparation of 2-(4-chlorophenyl)-6,8-diphenyl-4-methoxyquinoline 82c (R = Cl)

A stirred mixture of **80c** (0.50 g, 1.2 mmol) and I_2 (0.62 g, 2.4 mmol) in MeOH (30 mL); work-up as described for **82a** afforded **82c** as a light yellow solid (0.50 g, 97%); R_f (toluene) 0.83; mp 231-233 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.14 (3H, s, $COCH_3$), 7.22 (1H, s, 3-H), 7.40-7.55 (8H, m, 2′′′-H and 6′′′-H, 3′-H and 5′-H, 3′′′-H and 5′′′-H, 4′′-H, 4′′′-H), 7.79 (2H, d, *J* 8.4 Hz, 3′′-H and 5′′-H), 7.87 (2H, d, *J* 8.4 Hz, 2′′-H and 6′′-H), 8.06 (2H, d, *J* 8.4 Hz, 2′-H and 6′-H), 8.07 (1H, d, *J* 2.4 Hz, 7-H), 8.42 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 55.7 (OCH_3), 96.8 (C-3), 115.6 (C-3′ and C-5′), 116.0 (C-4a), 121.2 (C-5), 127.1 (C-4′′), 127.4 (C-4′′′), 127.6 (C-2′′ and C-6′′), 127.7 (C-2′′′ and C-6′′′), 128.6 (C-7), 128.8 (C-2′ and C-6′), 128.9 (C-3′′ and C-5′′), 130.5 (C-3′′′ and C-5′′′), 131.1 (C-1′), 135.3 (C-8), 139.7 (C-6), 140.6 (C-1′′), 140.7 (C-1′′′), 145.8 (C-8a), 155.7 (C-2), 158.9 (C-4′), 163.3 (C-4); IR (neat): ν_{max} 1590, 1483, 1437, 1358, 1302, 1218, 1094, 1003, 900, 824, 760, 698, 637 cm^{-1}; *m/z* (100, M+H) 422; HRMS (ES): MH^{+}, found: 422.1296. For $[C_{28}H_{21}{}^{35}ClNO]^{+}$: requires, 422.1233.

4.6.4 Preparation of 2-(4-methoxyphenyl)-6,8-diphenyl-4-methoxyquinoline 82d (R = OCH_3, R′ = H)

A stirred mixture of **80d** (0.50 g, 1.2 mmol) and I_2 (0.63 g, 2.5 mmol) in MeOH (30 mL); work-up as described for **82a** afforded **82d** as a white solid (0.45 g, 88%); R_f (toluene) 0.41; mp 196-198 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (3H, s, 4-$COCH_3$), 4.14 (3H, s, 4′-$COCH_3$), 6.98 (2H, d, *J* 9.3 Hz, 3′-H and 5′-H), 7.22 (1H, s, 3-H), 7.36-7.59 (6H, m, 2′′′-H and 6′′′-H, 3′′′-H and 5′′′-H, 4′′-H, 4′′′-H), 7.79 (2H, d, *J* 7.2 Hz, 3′′-H and 5′′-H), 7.89 (2H, d, *J* 8.7 Hz, 2′′-H and 6′′-H), 8.02 (1H, d, *J* 2.1 Hz, 7-H), 8.09 (2H, d, *J* 8.7 Hz, 2′-H and 6′-H), 8.40 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3 (4′-$COCH_3$), 55.6 (4-$COCH_3$), 95.6 (C-3), 114.0 (C-3′ and C-5′), 115.9 (C-4a), 120.9 (C-5), 127.0 (C-4′′), 127.3 (C-4′′′), 127.4 (C-2′′ and C-6′′), 127.6 (C-2′′′ and C-6′′′), 128.7 (C-7), 128.8 (C-2′ and C-6′), 130.3 (C-3′′ and C-5′′), 131.2 (C-3′′′ and C-5′′′), 132.7 (C-1′), 137.3 (C-8), 139.9 (C-6), 140.5 (C-1′′), 140.5 (C-1′′′), 145.9 (C-8a), 156.7 (C-2), 160.7 (C-4′), 163.0 (C-4); IR (neat): ν_{max} 1591, 1507, 1484, 1457, 1435, 1366, 1290, 1253, 1217, 1168, 1098, 1027, 1002, 900, 885, 825, 758, 697, 614 cm^{-1}; *m/z* (100, M+H) 418; HRMS (ES): MH^+, found: 418.1816. For $[C_{29}H_{24}NO_2]^+$: requires, 418.1729.

4.6.5 Preparation of 6,8-bis(4-fluorophenyl)-4-methoxy-2-phenylquinoline 82e (R = H, R′ = F)

A stirred mixture of **80e** (0.50 g, 1.2 mmol) and I_2 (0.62 g, 2.4 mmol) in MeOH (30 mL); work-up as described for **82a** afforded **82e** as a solid (0.45 g, 88%); R_f (toluene) 0.79; mp 231- 233 °C

EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.17 (3H, s, $COCH_3$), 7.17 (2H, d, *J* 8.4 Hz, 2′′-H and 6′′-H), 7.22 (2H, d, *J* 8.4 Hz, 3′′-H and 5′′-H), 7.30 (1H, s, 3-H), 7.46 (3H, dd, *J* 7.2 and 9.2 Hz, 3′′′-H and 5′′′-H, 4′-H), 7.73 (2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.85 (2H, t, *J* 8.7 Hz, 2′′′-H and 6′′′-H), 7.93 (1H, d, *J* 2.1 Hz, 7-H), 8.12 (2H, d, *J* 8.4 Hz, 2′-H and 6′-H), 8.36 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.8 (OCH_3), 97.3 (C-3), 114.6 (d, $^{2}J_{CF}$ 21.0 Hz, C-3′′ and C-5′′), 115.8 (d, $^{2}J_{CF}$ 21.8 Hz, C-3′′′ and C-5′′′), 118.9 (C-4a), 121.2 (C-5), 127.3 (C-7), 128.7 (C-2′ and C-6′), 128.9 (C-3′ and C-5′), 129.0 (d, $^{3}J_{CF}$ 7.5 Hz, C-2′′ and C-6′′), 129.5 (d, $^{3}J_{CF}$ 8.3 Hz, C-2′′′ and C-6′′′), 132.6 (C-4′), 132.7 (C-8), 135.6 (d, $^{4}J_{CF}$ 3.8 Hz, C-1′′), 136.7 (C-1′), 136.8 (C-6), 139.8 (d, $^{4}J_{CF}$ 5.3 Hz, C-1′′′), 145.7 (C-8a), 157.3 (C-2), 162.4 (d, $^{1}J_{CF}$ 244.5 Hz, C-4′′), 162.6 (d, $^{1}J_{CF}$ 245.3 Hz, C-4′′′), 163.1 (C-4); IR (neat): ν_{max} 1598, 1509, 1486, 1363, 1219, 1159, 1102, 1004, 901, 832, 772, 694, 650 cm^{-1}; *m/z* (100, M+H) 424; HRMS (ES): MH^{+}, found: 424.1519. For $[C_{28}H_{20}F_2NO]^{+}$: requires, 424.1453.

4.6.6 Preparation of 2,6,8-tris(4-fluorophenyl)-4-methoxyquinoline 82f (R = F, R′ = F)

A stirred mixture of **80f** (0.50 g, 1.2 mmol) and I_2 (0.59 g, 2.3 mmol) in MeOH (30 mL); work-up as described for **82a** afforded **82f** as a solid (0.35 g, 68%); R_f (toluene) 0.84; mp 197- 199 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.16 (3H, s, $COCH_3$), 7.15 (2H, t, *J* 8.7 Hz, 2′′-H and 6′′-H), 7.21 (2H, t, *J* 8.7 Hz, 3′′-H and 5′′-H), 7.23 (2H, t, *J* 8.7 Hz, 3′′′-H and 5′′′-H), 7.24 (1H, s, 3-H), 7.73 (2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.82 (2H, t, *J* 8.7 Hz, 2′′′-H and 6′′′-H), 7.93 (1H, d, *J* 2.1 Hz, 7-H), 8.09 (2H, t, *J* 8.7 Hz, 2′-H and 6′-H), 8.35 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.7 ($COCH_3$), 96.9 (C-3), 114.6 (d, $^{2}J_{CF}$ 21.0 Hz, C-3′′ and C-5′′), 115.6

(d, $^{2}J_{CF}$ 21.8 Hz, C-3′′′ and C-5′′′), 115.7 (C-4a),115.9 (C-8), 118.9 (C-5), 121.1 (C-7), 128.9 (d, $^{3}J_{CF}$ 8.3 Hz, C-2′′ and C-6′′), 129.1 (d, $^{3}J_{CF}$ 8.3 Hz, C-2′′′ and C-6′′′), 130.0 (d, $^{2}J_{CF}$ 21.0 Hz, C-3′ and C-5′), 132.6 (d, $^{3}J_{CF}$ 7.5 Hz, C-2′ and C-6′), 135.6 (d, $^{4}J_{CF}$ 3.8 Hz, C-1′′), 136.0 (d, $^{4}J_{CF}$ 3.0 Hz, C-1′′′), 136.7 (d, $^{4}J_{CF}$ 4.5 Hz, C-1′), 139.7 (C-6), 145.6 (C-8a), 156.1 (C-2), 162.4 (d, $^{1}J_{CF}$ 244.5 Hz, C-4′), 162.6 (d, $^{1}J_{CF}$ 246.0 Hz, C-4′′), 163.2 (C-4), 163.8 (d, $^{1}J_{CF}$ 247.5 Hz, C-4′′′); IR (neat): ν_{max} 1586, 1509, 1491, 1374, 1302, 1216, 1155, 1104, 1001, 902, 819,724 cm^{-1}; *m/z* (100, M+H) 442; HRMS (ES): MH^{+}, found: 442.1404. For $[C_{28}H_{19}F_{3}NO]^{+}$: requires, 442.1340.

4.6.7 Preparation of 2-(4-chlorophenyl)-6,8-di(4-fluorophenyl)-4-methoxyquinoline 82g (R = Cl)

A stirred mixture of **80g** (0.50 g, 1.1 mmol) and I_2 (0.57 g, 2.2 mmol) in MeOH (30 mL); work-up as described for **82a** afforded **82g** as a solid (0.45 g, 88%); R_f (toluene) 0.86; mp 236-238 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.16 (3H, s, $COCH_3$), 7.15 (2H, d, *J* 8.4 Hz, 2′′-H and 6′′-H), 7.22 (2H, d, *J* 8.4 Hz, 3′′-H and 5′′-H), 7.24 (1H, s, 3-H), 7.43 (2H, d, *J* 8.4 Hz, 3′′′-H and 5′′′-H), 7.73 (2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.81 (2H, t, *J* 8.7 Hz, 2′′′-H and 6′′′-H), 7.93 (1H, d, *J* 2.1 Hz, 7-H), 8.04 (2H, d, *J* 8.7 Hz, 2′-H and 6′-H), 8.35 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.8 ($COCH_3$), 97.0 (C-3), 114.6 (d, $^{2}J_{CF}$ 21.0 Hz, C-3′′ and C-5′′), 115.8 (d, $^{2}J_{CF}$ 21.0 Hz, C-3′′′ and C-5′′′), 118.9 (C-4a), 121.2 (C-5), 128.5 (C-7), 128.9 (C-2′ and C-6′), 129.0 (C-3′ and C-5′), 129.1 (d, $^{3}J_{CF}$ 8.3 Hz, C-2′′ and C-6′′), 130.1 (C-4′), 132.6 (d, $^{3}J_{CF}$ 7.5 Hz, C-2′′′ and C-6′′′), 135.5 (d, $^{4}J_{CF}$ 3.0 Hz, C-1′′), 136.7 (d, $^{4}J_{CF}$ 3.0 Hz, C-1′′′), 136.9 (C-1′), 138.2 (C-8), 139.8 (C-6), 145.7 (C-8a), 156.0 (C-2), 162.4 (d, $^{1}J_{CF}$ 244.5 Hz, C-4′′), 162.7 (d,

$^{1}J_{CF}$ 246.0 Hz, C-4′′′), 163.3 (C-4); IR (neat): ν_{max} 1512, 1480, 1352, 1234, 1212, 1156, 1094, 1012, 889, 819, 764, 718, 662, 636 cm^{-1}; *m/z* (100, M+H) 458; HRMS (ES): MH^{+}, found: 458.1135. For $[C_{28}H_{19}F_2{}^{35}ClNO]^{+}$: requires, 458.1045.

4.6.8 Preparation of 6,8-bis(4-fluorophenyl)-4-methoxy-2-(4-methoxyphenyl)quinoline 82h (R = OCH_3, R′ = F)

A stirred mixture of **80h** (0.50 g, 1.1 mmol) and I_2 (0.58 g, 2.3 mmol) in MeOH (30 mL); work-up as described for **82a** afforded **82h** as a solid (0.40 g, 78%); R_f (toluene) 0.56; mp 171- 173 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.86 (3H, s, 4′-$COCH_3$), 4.13 (3H, s, 4-$COCH_3$), 6.99 (2H, d, *J* 8.7 Hz, 3′′-H and 5′′-H), 7.14-7.24 (5H, m, 2′′-H and 6′′-H, 3′′′-H and 5′′′-H, 3-H), 7.72 (2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.84 (2H, t, *J* 8.7 Hz, 2′′′-H and 6′′′-H), 7.90 (1H, d, *J* 1.8 Hz, 7-H), 8.07 (2H, d, *J* 8.7 Hz, 2′-H and 6′-H), 8.32 (1H, d, *J* 1.8 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.4 (4-$COCH_3$), 55.7 (4′-$COCH_3$), 96.7 (C-3), 114.2 (d, $^{2}J_{CF}$ 21.0 Hz, C-3′′ and C-5′′), 115.7 (d, $^{2}J_{CF}$ 21.8 Hz, C-3′′′ and C-5′′′), 118.9 (C-4a), 120.9 (C-5), 128.6 (C-7), 128.8 (C-2′ and C-6′), 128.9 (C-3′ and C-5′), 129.0 (d, $^{3}J_{CF}$ 8.3 Hz, C-2′′ and C-6′′), 132.6 (d, $^{3}J_{CF}$ 7.5 Hz, C-2′′′ and C-6′′′), 132.6 (C-4′), 132.7 (C-8), 135.7 (d, $^{4}J_{CF}$ 3.0 Hz, C-1′′), 136.3 (C-1′), 136.8 (d, $^{4}J_{CF}$ 3.0 Hz, C-1′′′), 139.5 (C-6), 145.7 (C-8a), 156.8 (C-2), 162.3 (d, $^{1}J_{CF}$ 244.5 Hz, C-4′′), 162.6 (d, $^{1}J_{CF}$ 245.3 Hz, C-4′′′), 163.0 (C-4); IR (neat): ν_{max} 1598, 1508, 1486, 1438, 1373, 1296, 1251, 1218, 1159, 1099, 1033, 1001, 902, 826, 636 cm^{-1}; *m/z* (100, M+H) 454; HRMS (ES): MH^{+}, found: 454.1608. For $[C_{29}H_{22}F_2NO_2]^{+}$: requires, 454.1540.

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