2-ARYL-6,8-DIBROMOQUINOLINONES AS SYNTONS FOR THE
SYNTHESES OF POLYSUBSTITUTED 4-ARYL-6-OXOPYRROLO
[3,2,1-ij]QUINOLINES

by

FELIX ADETUNJI OYEYIOLA

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SUPERVISOR: PROFESSOR MJ MPHILELE

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I declare that 2-ARYL-6,8-DIBROMOQUINOLINONES AS SYNTONS FOR THE SYNTHESIS OF POLYSUBSTITUTED 4-ARYL-6-OXOPYRROLO[3,2,1-ij]QUINOLINES 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.
DEDICATED TO ALMIGHTY GOD, THE AUTHOR AND FINISHER OF MY FAITH; MY SUSTENANCE AND MY PROTECTOR, THE ONE WHO IS, WHO WAS AND WHO IS TO COME
ACKNOWLEDGEMENTS

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Abstract

The known 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122 were dehydrogenated using thallium(III) p-tolylsulfonate in dimethoxyethane under reflux to afford the 2-aryl-6,8-dibromoquinolin-4(1H)-ones 136. Palladium-catalyzed Sonogashira cross-coupling of the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones with terminal alkynes in the presence of PdCl$_2$(PPh$_3$)$_2$-CuI (as homogeneous catalyst source) and 10% Pd/C-PPh$_3$-CuI (as heterogeneous catalyst source) catalyst mixture and NEt$_3$ as a base and co-solvent in ethanol under reflux afforded the corresponding 6,8-dialkynyl-2-aryl-2,3-dihydroquinolin-4(1H)-ones 138 and 8-alkynyl-2-aryl-6-bromo-2,3-dihydroquinolin-4(1H)-ones 137, respectively. PdCl$_2$-catalyzed electrophilic cyclization of the 8-alkynyl-2-aryl-6-bromo-2,3-dihydroquinolin-4(1H)-ones in acetonitrile under reflux afforded the 4-aryl-8-bromo-2-phenyl-6H-pyrrolo[3,2,1-ij]quinolin-6-ones 139 or the 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-ones 140 from the 4-phenylethynyl-substituted or 4-alkylethynyl-substituted precursors, respectively. The 2-aryl-6,8-dibromoquinolin-4(1H)-ones 136, turn, subjected to similar homogeneous and heterogeneous palladium catalyst sources using NEt$_3$ as a base in DMF-water mixture under reflux and K$_2$CO$_3$ as a base in dioxane under reflux afforded 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,2,1-ij]quinolines 143 and 2-substituted 4-aryl-8-bromo-6-oxopyrrolo[3,2,1-ij]quinolines 142, respectively. The monoalkynylated 4-aryl-8-bromo-2-phenyl-6H-pyrrolo[3,2,1-ij]quinolin-6-ones 139 and 2-substituted 4-aryl-8-bromo-6-oxopyrrolo[3,2,1-ij]quinolines 142 were subsequently transformed using palladium-catalyzed Suzuki-Miyaura cross-coupling with arylboronic acids in the presence of PdCl$_2$(PPh$_3$)$_2$-PCy$_3$ catalyst mixture and K$_2$CO$_3$ as a base in dioxane-water mixture to afford the corresponding novel 8-substituted 2-phenyl-6H-pyrrolo[3,2,1-ij]quinolin-6-ones 141 and 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,2,1-ij]quinolines 142.
ij]quinolines 144, respectively. All the new compounds were characterized using a combination of $^1$H NMR, $^{13}$C NMR, IR, mass spectroscopic techniques and X-ray crystallography.

**Keywords:** 2-aryl-2,3-dihydroquinolin-4(1H)-ones; 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones; Sonogashira cross-coupling reaction; 8-alkynyl-2-aryl-6-bromo-2,3-dihydroquinolin-4(1H)-ones; 6,8-dialkynyl-2-aryl-2,3-dihydroquinolin-4(1H)-ones; 4-aryl-8-bromo-2-phenyl-6H-pyrrolo[3,2,1-ij]quinolin-6-ones; 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-ones; 2-substituted 4-aryl-8-bromo-6-oxopyrrolo[3,2,1-ij]quinolines; 2-substituted 8-alkynyl 4-aryl-6-oxopyrrolo[3,2,1-ij]quinolines; Suzuki-Miyaura cross-coupling reaction; 8-substituted 2-phenyl-6H-pyrrolo[3,2,1-ij]quinolin-6-ones; 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,2,1-ij]quinolines.
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References
List of abbreviations of palladium catalysts and ligands

1. PdCl$_2$(PPh$_3$)$_2$: dichlorobis(triphenylphosphine)palladium(II)
2. PCy$_3$: tricyclohexyltriphenylphosphine
3. Pd/C: palladium on carbon
4. PdCl$_2$: palladium(II) dichloride
5. PdCl$_2$(PCy$_3$)$_2$: dichlorobis(tricyclohexyl-phosphine)palladium(II)
6. PdCl$_2$(dppf): dichlorobis((1,1’-diphenylphosphino)ferrocene)palladium
7. PPh$_3$: triphenylphosphine
Chapter 1: INTRODUCTION

1.1 General overview

The design and synthesis of furo-, thieno- or pyrrolo-based quinolinones and quinoline derivatives continue to attract considerable attention in organic and medicinal chemistry; because of their wide range of biological properties\(^1\) and some examples have also been found to serve as components of optoelectronic materials. These azoloquinolinones and their quinoline derivatives are characterized by a five-membered heterocyclic ring with a single heteroatom fused to the main framework and they can either be linear or angular depending on the site of the main framework A or B on which the pyrrole, furan or thiophene ring is attached (Figure 1). Linear derivatives comprise of the heterocyclic five-membered ring fused on the b or g face of the main framework. Angular derivatives, on the other hand, have the five-membered heterocyclic ring fused on the c, f or h face of structure A or B. The angular pyrrolo[3,2,1-ij]quinolinones and their pyrrolo[3,2,1-ij]quinoline derivatives have the pyrrole ring attached to N-1 and C-8, encompassing the i and j faces of the framework of generalized structure A or B, respectively (Figure 1). Some of the angular annulated quinolinones and quinoline derivatives bearing a five-membered ring consisting of a single heteroatom have been found to exhibit a variety of biological activities and possessing optoelectronic properties. Some angular furoquinolines, for example, exhibit anticancer properties.\(^2\) Angular thienoquinoline derivatives, on the other hand, are employed as light-emitting diodes,\(^3\) while angular pyrroloquinolinones and their pyrroloquinoline derivatives exhibit antihypertensive,\(^4\) anticonvulsant\(^5\) and antiviral properties.\(^6\)
Furoquinolines are the first examples of angular heteroannulated quinoline derivatives under consideration. The naturally occurring furoquinolines such as Kolbisine and Kokusaginine and their analogues, viz., Pteleatine, Skimmianine and Maculine which are present in a large number of rutaceous plants like Galipea and Esenbeckia are linear.\textsuperscript{7,8} Kolbisine has been found to exhibit antibacterial and antifungal activities against both Salmonella typhi and Candida albicans, respectively.\textsuperscript{9,10} The mechanism of antimicrobial activity of furoquinolines is connected to their ability to bind DNA forming hydrogen bonds using the oxygen atom in the furan ring.\textsuperscript{11} Kokusagine, on the other hand, was found to exhibit antiplasmodial activity against Plasmodium falciparum \textit{in vitro}.\textsuperscript{7,8} (E)-1-[3-(Furo[3,2-c]quinolin-4-ylamino)phenyl]ethanones 1 have been prepared before in the laboratory and are reported to exhibit inhibitory activities on the full panel of National Cancer Institute 60 cancer cell lines with GI\textsubscript{50} < 0.01 μM.\textsuperscript{2}

Another group of heteroannulated compounds are the thienoquinolinones and thienoquinolines, which are characterized by a thiophene ring attached to the main heterocyclic framework. Thienoquinolinones and their quinoline derivatives have not been found in nature and they are
only accessible in the laboratory. Several examples of thieno[2,3-c]quinolinones and thieno[3,2-c]quinolines have been found to exhibit antibacterial,\textsuperscript{12} anticancer\textsuperscript{13} and anti-inflammatory properties.\textsuperscript{14} 4-Oxo-4,5-dihydrothieno[3,2-c]quinoline-7-carboxylic acid 2 for example, exhibit chemotherapeutic properties against poly (ADP-ribose) polymerase and protein kinase C.\textsuperscript{14,15} Rhodamine derivative 3, a benzothienoquinoline analogue, on the other hand, is an optoelectronic component with fluorescence properties.\textsuperscript{3}

The third class of angular annulated quinolinone/quinoline derivatives of relevance to this investigation are the pyrroloquinolinones or pyrroloquinolines, which differ from the previous classes due to the presence of a pyrrole ring attached to the main heterocyclic skeleton. Although there are several angular pyrroloquinolines, the focus in this investigation is on the pyrrolo[3,2,1-ij]quinolinone and pyrrolo[3,2,1-ij]quinoline frameworks in which the pyrrole ring is attached to the N-1 and C-8 positions of the quinolinone or the quinoline scaffold. Pyrrolo[3,2,1-ij]quinoline moiety occurs in a number of alkaloids that have been isolated from the \textit{Crinum} genus of the Amaryllidaceae family.\textsuperscript{16-18} Several examples of these angular heteroannulated quinolones and their quinoline derivatives exhibit anticonvulsant,\textsuperscript{5} anti-inflammatory,\textsuperscript{19,20} antifungal,\textsuperscript{21} antihypertensive,\textsuperscript{4,22} antiviral\textsuperscript{6} and antitumor\textsuperscript{23} activities. 8-Fluoro-4-methylpyrrolo[3,2,1-ij]quinolin-1-ylethylamine 4 and 6-[(dimethylamino)methyl]-4,5,6,8,9,10-hexahydrocyclopenta[4,5]pyrrolo[3,2,1-ij]quinoline 5 exhibit activity as an antiepileptic and an anticonvulsant agent, respectively.\textsuperscript{5,24}
The 4- and 6-oxo pyrrolo[3,2,1-ij]quinolines, on the other hand, have found applications as antifungal,\textsuperscript{25,26} anticancer\textsuperscript{27} and antiviral agents,\textsuperscript{6} and others are inhibitors of protein and DNA synthesis.\textsuperscript{22} \(N\)-(4-Chlorobenzyl)-2-(2-hydroxyethyl)-8-(morpholin-4-ylmethyl)-6-oxo-6-\(H\)-pyrrolo[3,2,1-ij]quinolin-5-carboxamide (PHA-529311) \(6\), for example, has been found to exhibit in-vitro antiviral activities against human herpesvirus DNA polymerases.\textsuperscript{6}

Most of the conventional approaches for the synthesis of angular furo-, thieno- and pyrroloquinolinones and their quinoline derivatives involve several steps that are often low yielding and do not allow further modification to introduce molecular diversity.\textsuperscript{28-30} There is continued effort to develop new and efficient methods for the synthesis of angular heteroannulated quinolinones and their quinoline derivatives bearing alkyl and/or aryl substituents. Some of the methods reported to-date for the synthesis of angular heteroannulated quinolinones and/or their quinoline derivatives are described below.
1.2 Synthesis of heteroannulated quinolinones and quinolines

Although there are several examples of azoloquinolinones and quinolines described in the literature;\(^1\) our interest is on angular derivatives bearing a five-membered heterocyclic ring bearing a single heteroatom, namely: furo-, thieno- and pyrrolo-based quinolinones and quinolines. The methods for the synthesis of angular furo-, thieno- and pyrrolo-based quinolinones and quinolines are described in sequence in the following sections.

1.2.1 Synthesis of furoquinolinones and furoquinolines

Angular furoquinolinones and furoquinoline derivatives are generally prepared through transition metal cross-coupling of appropriately substituted halogenoquinolinones or halogenoquinolines with terminal alkenes\(^3\) and alkynes\(^3\) or the reaction of nucleophiles with appropriately substituted quinolinones or quinolines.\(^3\) A multicomponent approach involving the Aza-Diels-Alder reaction of imines obtained from reaction of aldehydes and amines with furan has also been described in the literature.\(^5\) Oxidative cyclization of the \(N\)-methyl-4-hydroxy-3-(methylbut-2-enyl)quinolin-2-one derivatives 7 with \(m\)-chloroperbenzoic acid in chloroform at room temperature followed by ring closure of the incipient epoxide intermediate 8 with hydrochloric acid or sodium hydroxide, for example, previously afforded a series of disubstituted dihydrofuro[2,3-\(b\)]quinolinones 9 (Scheme 1).\(^4\) These compounds were, in turn, reacted with sodium methoxide in methanol at room temperature to afford the corresponding angular dihydrofuroquinolines 10, which upon dehydration with sulphuric acid at room temperature afforded 8-substituted 2-(1-methylethyl)-5-methyl-4,5-dihydrofuro[3,2-\(c\)]quinolin-4-ones 11 in 75-80% yields. Of interest, is that these angular dihydrofuro[3,2-\(c\)]quinolin-4-one derivatives 11
show promising blocking activities of the voltage-gated potassium channel Kv 1.3, which represents an attractive target for immunosuppression.\textsuperscript{34}

\[
\begin{align*}
\text{7} & \xrightarrow{(i)} \text{8} \\
\text{9} & \xrightarrow{(iii)} \text{10} \\
\text{11} & \xrightarrow{(iv)} \text{12}
\end{align*}
\]

\textit{Reagents and conditions:} (i) \textit{m}-chloroperbenzoic acid, CHCl\textsubscript{3}, r.t.; (ii) 3 M HCl or NaOH; (iii) NaOCH\textsubscript{3}, MeOH, r.t., 20 h; (iv) conc. H\textsubscript{2}SO\textsubscript{4}, r.t., 3-15 min.

**Scheme 1:** Epoxidation, cyclization and dehydration reactions of 7

In another approach, angular furoquinolines were synthesized through the reaction of 2,4-dihydroxyquinoline 12 (a tautomer of 4-hydroxyquinolin-2-one) with chloroacetaldehyde and KI in aqueous KOH under reflux to afford 4-hydroxyfuro[3,2-c]quinoline 13 (Scheme 2).\textsuperscript{2} Chlorination of the latter with POCl\textsubscript{3} in the presence of Et\textsubscript{3}N yielded 4-chlorofuro[3,2-c]quinoline 14, which was then reacted with 3-aminoacetophenone in EtOH/H\textsubscript{2}O mixture (2:1; v/v) in the presence of an acid under reflux to afford the corresponding 1-[3-(furo[3,2-c]quinoline-4-ylamino)phenyl]ethanone 15. Treatment of 15 with NH\textsubscript{2}OH or NH\textsubscript{2}OMe in ethanol under reflux afforded (\textit{E})-1-[3-(furo[3,2-c]quinoline-4-ylamino)phenyl]ethanone oxime.
16a and \((E)-1-\text{3-(furo[3,2-c]quinoline-4-ylamino)phenyl}ethanone\) \text{O-methyl oxime} 16b, respectively. Of interest, is that compounds 16 exhibits anticancer activities.

![Chemical structures](image)

**Reagents and conditions:** (i) ClCH₂CHO, KI, KOH, reflux, 4 h; (ii) POCl₃, Et₃N, 110 °C, 8 h; (iii) 3-aminoacetophenone, conc. HCl, EtOH-H₂O (2:1,v/v), reflux, 40 mins; (iv) NH₂OH HCl or NH₂OMe HCl, EtOH, reflux, 0.5 h

**Scheme 2:** Cycloaddition, chlorination and amination of 2,4-dihydroxyquinoline 12

A high yielding (87-92%) 3-component Aza-Diels-Alder (Poyarov’s) reaction of benzaldehyde derivatives 17, arylamines 18 and 2,3-dihydrofuran in the presence of nano silica chromic acid as a catalyst in tetrahydrofuran at room temperature afforded a mixture of disubstituted \text{trans-} 19 and \text{cis-tetrahydrofuroquinoline isomers} 20 in the ratio 2.5:1 (Scheme 3).\(^{35}\) The reaction involves the generation of imine intermediates \textit{in situ}, which react with the dihydrofuran to furnish the corresponding tetrahydrofuroquinolines with high diastereoselectivity. It was observed that the presence of electron-donating or electron-withdrawing substituents on the reactants have no effect on the reactivity of the imine intermediate and the yield of the products.
Scheme 3: Acid-promoted 3-component reaction of 17 with benzaldehydes and dihydrofuran

In another approach, a three-component-cycloaddition reaction of cyclohexanecarbaldehyde 21, methyl 3-(2-aminophenyl)propionate 22 and ethyl α-(p-nitrophenyl)-α-isocyanoacetate 23 in methanol at room temperature followed by the addition of toluene under reflux to afford 2-alkoxyfuro[2,3-c]quinoline 24 in 89% yield has also been reported (Scheme 4).²⁶

Reagents and conditions: (i) MeOH, 0.5 h, r.t. then toluene, 5 h, reflux

Scheme 4: 3-Component reaction of 21 with methyl 3-(2-aminophenyl)propionate and ethyl α-(p-nitrophenyl)-α-isocyanoacetate
Recently, a series of (E)-3-iodo-2-styrylquinolin-4(1H)-ones 25 was reacted with styrene and its p-methoxy derivative 26 in the presence of Pd(PPh₃)₄ and NEt₃ as a base in MeCN or NMP [N-methyl-2-pyrrolidone] under reflux to afford the (E,E)-2,3-distyrylquinolin-4(1H)-ones 27 in 58-65% yield (Scheme 5). The electrocyclization of the latter in 1,2,4-trichlorobenzene in the presence of catalytic amount of iodine and p-toluenesulfonic acid under reflux in an inert atmosphere afforded a mixture of the disubstituted acridin-9(10H)-ones 28 as the minor product (2-40% yields) and (E)-2-phenyl-4-styrylfuro[3,2-c]quinolines 29 as the major products (36-60% yields), respectively.

Reagents and conditions: (i) Pd(PPh₃)₄, NEt₃, NMP or MeCN, reflux, 3-7 h, N₂(g)
(ii) 1,2,4-Trichlorobenzene, I₂ (10%), p-TsOH (10%), reflux, N₂(g)

Scheme 5: Transition metal-catalyzed Heck cross-coupling of 25 with styrene derivatives
Previously, a series of 2,6-disubstituted 3-iodoquinolin-4(1H)-ones 30a was reacted with terminal alkynes in the presence of Pd(0)-CuI-PPh₃ catalyst mixture and Et₃N as a base in DMF at 80 °C in an inert atmosphere to afford the corresponding 2,6-disubstituted furo[3,2-c]quinolines 31 in 68-85% yield (Scheme 6).³² Treatment of 3-iodo-1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid 30b with terminal alkynes under the same reaction conditions, on the other hand, afforded the 3-alkynylquinoline-4(1H)-ones 32 in 60-70% yield (Scheme 6).³² The difference in reactivity of 2,6-disubstituted 3-iodoquinolin-4(1H)-ones and 3-iodo-1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid is due to the presence of acidic hydrogen in the NH-derivatives, which promotes the metal-mediated cyclization of the tethered alkynyl moiety to afford the furoquinolines in a single-pot operation.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>31</th>
<th>32</th>
</tr>
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<tbody>
<tr>
<td>a: R₁ = CO₂CH₃; R₂ = F; R₃ = -C(OH)Me₂ (83%); R₂ = H; R₃ = -C₆H₅ (67%);</td>
<td>b: R₁ = CO₂CH₃; R₂ = F; R₃ = -CH₂OH (75%); R₂ = H; R₃ = -C₆H₅ (70%);</td>
</tr>
<tr>
<td>c: R₁ = -C₆H₅; R₂ = H; R₃ = -CH₂OH (72%); R₂ = H; R₃ = -C₆H₃(OMe)-m,p (65%);</td>
<td>d: R₂ = H; R₁, R₃ = -C₆H₅ (67%);</td>
</tr>
</tbody>
</table>
Scheme 6: Sonogashira cross coupling of 30 with terminal alkynes

1.2.2 Synthesis of thienoquinolinones and thienoquinolines

A series of thienoquinolinones 35 were prepared via a microwave-assisted tandem Suzuki-Miyaura cross-coupling of methyl 2-bromo-3-thiophene carboxylate 33 and boronic acids 34 in the presence of dichlorobis((1,1’-diphenylphosphino)ferrocene)palladium [PdCl$_2$(dppf)] and NaOAc as a base in DMF at 120 °C (Scheme 7). Functional group transformation of the ester group of compounds 35 into carboxylic group when treated with LiOH in a mixture of MeOH, THF and H$_2$O (1:1:1,v/v) at room temperature afforded the substituted thieno[3,2-c]quinolinones 36 (R$_3$ = CO$_2$H) in 96% yield; and cyano group into amide group when treated with NH$_4$OH at 100 °C, followed by aqueous NaOH at room temperature afforded the substituted thieno[3,2-c]quinolinones 36 (R$_3$ = CONH$_2$) in 32% yield. Of interest, is that compounds 36 were found to act as ATP-competitive inhibitors of protein kinase CK2 with a poly-ADP-ribose polymerase IC$_{50}$ = 0.7 μM.

Reagents and conditions: (i) NaOAc, PdCl$_2$(dppf), anhy. DMF, 120 °C, 10 min.; (ii) R$_3$ = CO$_2$H: LiOH, MeOH, THF, H$_2$O, r.t., 5 h; for R$_3$ = CONH$_2$: NH$_4$OH, 100 °C, 12 h.

Scheme 7: Microwave-assisted Suzuki-Miyaura cross-coupling of 33
Thienoquinolines, on the other hand, are commonly synthesized through either the reaction of the carboxanilides\(^\text{(37)}\) or from thio-Claisen rearrangement of allyl-4-quinolyl sulphides.\(^\text{(38)}\) The carboxanilides are, in turn, prepared by amination of the corresponding benzothiophene halides with aniline derivatives.\(^\text{(37,39)}\) The allyl-4-quinolyl sulphides, on the other hand, can be prepared via alkylation of sodium 4-quinolyl-mercaptides with alkylallyl chlorides.\(^\text{(38)}\) Allyl 4-quinolylsulfides 37, for example, undergo thio-Claisen rearrangement when heated at 200 °C for 2 hours under solvent-free condition to afford the incipient 3-allyl-4(1\(H\))-quinolinethione intermediates 38, which in turn, cyclize to afford 2,3-dihydrothieno[3,2-\(c\)]quinolines 39 in 85-90% yield (Scheme 8).\(^\text{(38)}\)

\[
\begin{align*}
R & \quad \text{(i)} \quad \text{S} \quad \text{H} \quad \text{N} \\
\text{(i)} & \quad \text{Me} \\
\text{37} & \quad \text{(R = H, Alkyl)} \\
\text{38} & \quad \text{(ii)} \\
\text{39} & \quad \text{37 (R = H, Alkyl)} \\
\end{align*}
\]

Condition: 200 °C, 2 h

**Scheme 8:** Solvent-free thermal-promoted cyclization of allyl 4-quinolylsulfides

Merkheimer *et al.* previously reacted 2,4-dichloroquinoline-3-carbonitrile 40 with ethyl mercaptoacetate in an excess of DMF in the presence of triethylamine at room temperature to afford 3-amino-4-chlorothieno[3,2-\(c\)]quinoline-2-carboxylate 41 (Scheme 9).\(^\text{(40)}\) Compound 41 was then subjected to amination with different aliphatic amines in dimethylformamide under reflux to yield the corresponding amino-thienoquinolines 42. The latter were, in turn, sequentially treated with sodium nitrite and sodium azide under acidic condition at -5 °C then at room temperature to convert them into the corresponding 3-azidothienoquinolines 43 in 70-93% yield.
In a cognate study in our laboratory, 6,8-dibromo-4-chloroquinoline-3-carbaldehyde 44 was reacted with methyl mercaptoacetate in the presence of anhydrous K$_2$CO$_3$ as a base in MeCN under reflux to afford methyl[(6,8-dibromothieno[3,2-c]quinoline)]-2-carboxylate 45 in 89% yield (Scheme 10)$^{41}$ Compound 45 was then subjected to the Suzuki-Miyaura cross-coupling with aryl- and arylvinylboronic acids in the presence of dichlorobis(tricyclohexylphosphine)palladium(II) and anhydrous K$_2$CO$_3$ as a base in DMF under reflux to afford novel alkyl[(6,8-diaryltbeno[3,2-c]quinoline)]-2-carboxylates 46 in 65-96% yield. Of interest, is that

<table>
<thead>
<tr>
<th>43</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>Bu</td>
<td>74</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>i-Bu</td>
<td>78</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>c-C$<em>6$H$</em>{11}$</td>
<td>93</td>
</tr>
</tbody>
</table>

Scheme 9: Cycloaddition of 40 and ethyl mercaptoacetate with aliphatic amines
compounds 46 exhibit cytotoxic activities against human breast cancer cell line MCF-7 with LC<sub>50</sub> values < 0.13 μg/mL when compared to nocodazole as a standard.

\[
\begin{array}{c}
\text{Br} & \text{Cl} & \text{O} \\
\text{Br} & \text{Br} & \text{H}
\end{array}
\xrightarrow{(i)}
\begin{array}{c}
\text{Br} & \text{Br} & \text{N} \\
\text{Br} & \text{Br} & \text{S} \\
\text{CO}_2\text{CH}_3
\end{array}
\xrightarrow{(ii)}
\begin{array}{c}
\text{Ar} & \text{Ar} & \text{N} \\
\text{Ar} & \text{Ar} & \text{S} \\
\text{CO}_2\text{CH}_3
\end{array}
\]

46 Ar = -C<sub>6</sub>H<sub>5</sub>, 4-FC<sub>6</sub>H<sub>4</sub>-

4-FC<sub>6</sub>H<sub>4</sub>CH=CH-

*Reagents and conditions:* (i) HSCH<sub>2</sub>CO<sub>2</sub>Me (2.5 equiv.), K<sub>2</sub>CO<sub>3</sub>, MeCN, reflux, 3 h; (ii) ArB(OH)<sub>2</sub> (2.5 equiv.), PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, DMF, reflux, 4 h

**Scheme 10:** Base-promoted conjugate addition-elimination of 44 with methyl mercaptooacetate

A high yielding one-pot synthesis of thienoquinoline 50 involving the initial condensation of 2-bromoaniline 47 with an excess of thiophene-3-carbaldehyde 48 (2 equiv.) in xylene under reflux in an inert atmosphere followed by intramolecular arylation of the *in-situ* generated imine-N-(2-bromophenyl)thiophene intermediate 49 in the presence of Pd(OAc)<sub>2</sub>-PPh<sub>3</sub> catalyst complex using Cs<sub>2</sub>CO<sub>3</sub> as a base in xylene at 130 °C has also been reported in the literature (Scheme 11).<sup>39</sup>

\[
\begin{array}{c}
\text{NH}_2 \\
\text{Br}
\end{array}
\xrightarrow{(i)}
\begin{array}{c}
\text{Br} & \text{N} & \text{S} \\
\text{Br} & \text{S}
\end{array}
\xrightarrow{(ii)}
\begin{array}{c}
\text{N} & \text{S} \\
\text{S} & \text{S}
\end{array}
\]

47

48

49

50 (85%)
Reagents and conditions: (i) xylene, 150 °C, 24 h, argon; (ii) Pd(OAc)$_2$, PPh$_3$, Cs$_2$CO$_3$, xylene, 130 °C, 18 h

Scheme 11: One-pot sequential imination and intramolecular arylation of 48 with 2-bromoaniline

1.2.3 Synthesis of pyrrolo[3,2,1-ij]quinolinones and pyrrolo[3,2,1-ij]quinolines

The pyrrolo[3,2,1-ij]quinolinones and pyrrolo[3,2,1-ij]quinoline moiety can be accessed through two general approaches, involving (i) the construction of a pyrrole ring on to a quinolinone or quinoline framework,$^{5,19,42,43}$ or (ii) construction of a pyridine ring between N-1 and C-7 of an indole moiety.$^{44,45,46}$ Previously, $m$-phenylenediamine and its 4-methyl derivative 51 were condensed with ethyl/methyl acetoacetate at 150 °C to afford methyl-7-aminoquinolin-2-ones 52 (Scheme 12).$^{43}$ The latter were, in turn, treated with sodium nitrite in the presence of an acid at 0 °C followed by heating to yield methyl-7-hydroxyquinolin-2-ones 53 as the products. Compounds 53 were then condensed with allyl bromide in the presence of potassium carbonate in acetone to afford the corresponding 7-O-allyl ethers 54. The latter were, in turn, subjected to Claisen rearrangement in diethylaniline under reflux to produce the corresponding 8-allyl derivatives 55, exclusively. The methyl-7-hydroxy-8-allylquinolin-2-ones 55 were then treated with sodium acetate in acetic anhydride under reflux to furnish 56 followed by halogenation with molecular bromine of the allylic carbon chain at C-8 in acetic acid at room temperature in an addition reaction to yield 57. Compounds 57 were, in turn, cyclized using aqueous KOH in EtOH under reflux to afford 2-methyl-9-hydroxypyrrolo[3,2,1-ij]quinolin-4-ones 58 in 43-55% yield. This approach, however, involves too many steps and in reduced yields of the products.
Reagents and conditions: (i) ethyl/methyl acetoacetate, 150 °C, 48 h; (ii) H$_2$SO$_4$, NaNO$_2$, 0 °C to reflux, 10 min (iii) allyl bromide, K$_2$CO$_3$, acetone, reflux, 5 h; (iv) N,N-diethylaniline, reflux, 3 h; (v) NaOAc, acetic anhydride, reflux, 1 h; (vi) Br$_2$, acetic acid, r.t., 0.5 h; (vii) 5% KOH, EtOH, reflux, 2 h

Scheme 12: Cyclocondensation, acetylation, alkylation and cyclization reactions of 51 with alkylated acetoacetate

In another approach, a nitrile (2-chloro-6-nitrophenylacetonitrile) 59 was treated with 50% H$_2$SO$_4$ at 110 °C to convert the nitrile functional group to an acid derivative 60 (Scheme 13).
The latter was, in turn, reacted with thionyl chloride in dichloroethane at 70 °C for 2 h followed by addition of AlCl₃ and benzene at 60 °C to afford 2-chloro-6-nitrophenylacetophenone 61. Treatment of compound 61 with aqueous acetic acid in the presence of zinc powder at 70 °C followed by heating at 90 °C afforded the indole derivative 62. This indole was reacted with acrylonitrile in the presence of Triton B (10 drops) in dioxane at 70 °C yielded 4-chloro-1-(2-cyanoethyl)-2-phenylindole 63. The cyano group was, in turn, converted to the acid function in aqueous H₂SO₄ at 110 °C to yield 64. The latter was finally reacted with phosphorus pentoxide in xylene under reflux to afford pyrrolo[3,2,1-ij]quinolin-6-one 65.

**Reagents and conditions:** (i) 50% H₂SO₄, 110 °C, 3 h; (ii) SOCl₂, dichloroethane, 70 °C, 2 h, then AlCl₃, benzene, 60 °C, 10 min; (iii) Zinc powder, 80% AcOH, 90 °C, 1 h; (iv) acrylonitrile, Triton B, dioxane, 70 °C, 2 h; (v) P₂O₅, xylene, reflux, 1 h

**Scheme 13:** Oxidation, acetylation, cyclization of 2-chloro-6-nitrophenylnitrile
Previously, 4-nitrobenzyl bromide 66 was reacted with morpholine (which acts as the nucleophile as well as the base) in toluene at below 50 °C to afford morpholinonitrobenzene 67 in 93% yield (Scheme 14). The nitrobenzene was reduced with hydrogen gas in the presence of 5% Pt/C in THF at 60-70 °C to afford aniline derivative 68 in 94% yield. Iodination of the latter with iodine monochloride in dichloromethane-methanol mixture (5:1; v/v) under acidic conditions at 10-15 °C afforded the iodo derivative 69 in 87% yield. Compound 72 was reacted with diethylethoxymethylene malonate (DEEM) in toluene at 120 °C under nitrogen atmosphere to afford the enamine 70 in 74% yield. Acid-promoted ring closure of compound 73 using phosphorus pentoxide in the presence of methane sulfonic acid (MesOH) at 90 °C afforded the quinolin-4(1H)-one derivative 71 in 70% yield. The 8-iodoquinolin-4(1H)-one 71 was subjected to Sonogashira cross-coupling with 3-butyn-1-ol in the presence of PdCl$_2$(PPh$_3$)$_2$-CuI catalyst complex and NEt$_3$ as a base in ethanol under reflux to afford pyrrolo[3,2,1-ij]quinolin-6-one 72 in 76% yield. The amidation of the ester group at C-5 using an excess of 4-chlorobenzylamine in ethylene glycol at 130 °C afforded the 5-amidopyrrolo[3,2,1-ij]quinolin-6-one 73 (74%). Of interest, is that compound 73 was found to inhibit herpesvirus DNA polymerase in human.
Reagents and conditions: (i) morpholine, toluene, <50 °C; (ii) H₂ (g), 5% Pt/C, THF, 60-70 °C, N₂ (g), 2 h; (iii) ICl, AcOH, DCM-MeOH (5:1; v/v), 10-15 °C, 1 h; (iv) DEEM, toluene, 120 °C, N₂ (g); (v) P₂O₅, MsOH, 90 °C, 4 h; (vi) 3-butyn-1-ol, PdCl₂(PPh₃)₂, CuI, NEt₃, EtOH, reflux, N₂ (g), 12-17 h; (vii) 4-chlorobenzylamine, ethylene glycol, 130 °C, N₂ (g), 8 h

Scheme 14: Amidation, reduction, iodination, cyclization, metal-catalyzed cross-coupling of 66

Nakatsuka et al., on the other hand, employed the indole pathway to prepare 4,5-dihydropyrrolo[3,2,1-ij]quinolin-6-ones 76. These authors reacted methyl indole-3-carboxylate 74 with methyl acrylate in the presence of potassium carbonate in dimethylformamide followed by aqueous NaOH to furnish the 3-carboxymethylindole-1-propanoic acid 75 (Scheme 15). The latter was, in turn, cyclized onto the C-7 position when
treated with polyphosphoric acid at 60 °C to afford the 4,5-dihydropyrrolo[3,2,1-ij]quinolin-6-one derivative 76 in 53% yield.

![Chemical structure](image)

Reagents and conditions: (i) methyl acrylate, K$_2$CO$_3$, DMF then NaOH; (ii) PPA, 60 °C, 1.5 h

Scheme 15: Sequential acidification and cyclization of methyl indole-3-carboxylate

In another approach, a series of chalcone intermediates was converted to the corresponding epoxides followed by ring opening and cyclization of the incipient products to afford pyrroloquinolinones.$^{48}$ The main challenge in this investigation was to prepare the desired indole. 7-Cinnamoylindole was first prepared in 53% yield by direct Friedel-Crafts acylation of 4,6-dimethoxy-2,3-phenylindole using cinnamoyl chloride and stannic chloride in benzene in an effort to activate the C-7 position of the indole.$^{48}$ An alternative aldol approach involving acetylation of indole with $N,N$-dimethylacetamide and phosphoryl chloride afforded a mixture of the 7-acetylindole, 2-acetylindole, and the 2,7-diacetylindole in 65%, 20% and 8% yields, respectively.$^{48}$ The condensation of the 7-acetylindole 77 with a series of substituted benzaldehyde derivatives 78 when treated with sodium amide in dry THF at room temperature produced a range of chalcones 79 in 58-95% yield (Scheme 16).$^{48}$ The chalcones were reacted with saturated sodium hydroxide and 30% hydrogen peroxide in aqueous tetrahydrofuran at room temperature to afford the corresponding epoxides 80 in 54-94% yield. Cyclization of the epoxides with saturated potassium hydroxide in aqueous tetrahydrofuran at room temperature...
afforded a range of the 6-oxopyrroloquinoline derivatives 81 in 54-82% yield. This method involves several steps.

\[
\begin{align*}
\text{MeO} & \quad \text{Ph} \\
\text{OMe} & \quad \text{N} \\
\text{Me} & \quad \text{N} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{OH} \\
\text{R}_1 & \quad \text{CHO} \\
\text{R}_2 & \quad \text{R} \\
\text{R}_2 & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{OMe} & \quad \text{Ph} \\
\text{Me} & \quad \text{N} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{Ph} \\
\text{R}_2 & \quad \text{R} \\
\text{R}_2 & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{OMe} & \quad \text{Ph} \\
\text{Me} & \quad \text{N} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{Ph} \\
\text{R}_2 & \quad \text{R} \\
\text{R}_2 & \quad \text{R} \\
\end{align*}
\]

Reagents and conditions: (i) NaNH\(_2\), anhyd. THF, r.t., 0.5 h; (ii) NaOH, H\(_2\)O\(_2\), THF, r.t., 6-8 h; (iii) KOH, THF, r.t., 4 h

Scheme 16: Condensation, epoxidation and cyclization reactions of 77 with aromatic aldehydes

Grandberg has previously subjected 1-amino-1,2,3,4-tetrahydroquinoline 82 and 4-chloro-1-(3,5-dimethylphenyl)butan-1-one 83 to cyclocondensation in ethanol under reflux (Scheme 17).\(^{49}\)

This reaction which involves cyclodehydration and dechloroamination afforded 1-(2-aminoethyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline 84 in 15% yield.
Scheme 17: Cyclocondensation of 82 and 4-chloro-1-(3,5-dimethylphenyl)butan-1-one

6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline 85 was treated with NaNO₂ under acidic conditions at 0 °C followed by reduction with LiAlH₄ in diethyl ether to afford 1-amino-1,2,3,4-tetrahydroquinoline derivative 86 (Scheme 18). The latter was cyclized with 4-chlorobutanal in MeOH-H₂O mixture (9:1; v/v) under reflux isolating the corresponding pyrrolo[3,2,1-ij]quinolin-1-yl ethylamine derivative 87. Of interest, is that compound 87 was found to be a 5-HT₂c receptor agonist with selectivity over 5-HT₂a receptor.

Reagents and conditions: (i) NaNO₂, H₂SO₄, 0-5 °C, then LiAlH₄, diethyl ether; (ii) 4-chlorobutanal, MeOH/H₂O (9:1; v/v), reflux

Scheme 18: Amination and cycloaddition reaction of 85

In another method, quinaldic acids 88 was subjected to successive amidation with thionyl chloride in toluene under reflux followed by bubbling of dimethylamine at room temperature
afforded dimethyl amide intermediates. These intermediates were reduced with hydrogen in the presence of platinum oxide in propanol to afford tetrahydroquinolines 89 (Scheme 1). The latter were treated with sodium nitrite in an acidic medium at 5-10 °C followed by reduction of the N-nitroso compounds with lithium aluminum hydride in ether under reflux, then cooled to 0 °C under alkaline conditions to afford hydrazine intermediates 90. These hydrazine derivatives were, in turn, reacted with cyclic ketones in acetic acid under reflux to afford a series of 1,2,4-trisubstituted cycloalkyl[4,5]pyrrolo[3,2,1-ij]quinolines 91 in 37-75% yield. Of interest, is that compounds 91 were found to exhibit anticonvulsant activity.

Reagents and conditions: (i) SOCl₂, toluene, reflux, 2 h; then Me₂NH, PtO₂, H₂, 2-propanol, r.t.; (ii) NaNO₂, dil. HCl, 5-10 °C, 1 h; then LiAlH₄, ether, reflux, dil. NaOH, 1 h; (iii) acetic acid, reflux, 1 h

Scheme 19: Amidation and cyclocondensation reactions of 88

Another route for the construction of pyrrolo[3,2,1-ij]quinoline framework, which involves the generation and reactions of radicals at the C-7 position of an indole has been described before. Different methods for the synthesis of the C-7 activated indoles have been developed over the
years. A series of C-7 activated indoles, for example, was synthesized from 4,6-dimethoxy-2,3-diphenylindole by treatment with acetyl chloride and stannic chloride in benzene to afford the 7-acetyl indole in 53% yield.\(^{51}\) In another approach, ethyl azidoacetate was condensed with aldehydes to yield the corresponding azidocinnamates followed by thermal decomposition and subsequent Claisen rearrangement in bromobenzene under reflux to afford the 7-allylindoles.\(^{52}\) Despite their importance, the above methods involve several steps and longer reaction time to afford the requisite activated 7-substituted indole. A rapid and convenient method which involves the reaction of three equivalents of vinylmagnesium bromide with 2-bromonitrobenzene to afford the 7-bromoindole in 62% yield has also been reported.\(^{53}\) The N-alkylation of 7-bromoindole 92 to afford the N-alkylated compound 93 in 80% yield, on the other hand, was achieved by reacting it with an excess of bromoalkene in the presence of potassium carbonate as a base in acetone under reflux (Scheme 20).\(^{50}\) Previously, a mixture of 7-bromoindole, bromoalkene, acid chloride and potassium hydroxide in dimethylformamide was reacted at room temperature to afford compound 93 in 87% yield.\(^{54}\) The cyclization of the N-alkylated 7-bromoindole 93 was, in turn, achieved using tributyltin hydride and AIBN (azobisisobutyronitrile) as the radical initiator in refluxing toluene to afford a mixture of products 94 and 95 in the ratio 2:1 in 84% yield.\(^{50}\)

\[
\text{Reagents and conditions: (i) HCCHCH}_2\text{Br (4.5 eq.), K}_2\text{CO}_3 (5 \text{ eq.}, \text{ acetone, reflux, 24 h; or bromoalkene/acid chloride (1.5 eq.), KOH, DMF, r.t., 24 h; (ii) SnBu}_3, \text{ AIBN, toluene, reflux}}
\]

\textbf{Scheme 20: Reaction of 92 with 2-bromoalkene and radical cyclization of the N-alkylated 7-bromoindoles}
The 5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline framework has been found in numerous natural products and has attracted much attention in the effort to discover new drugs.\textsuperscript{17} For example, a series of pyrrolo[3,2,1-ij]quinoline derivatives exhibit histamine and platelet activating factor antagonism.\textsuperscript{19} Moreover, some pyrrolo[3,2,1-ij]quinolines exhibit antifungal activities for rice plants.\textsuperscript{25,26} The 6-oxopyrrolo[3,2,1-ij]quinoline skeleton though uncommon in nature, constitutes the central core of an antiviral agent, \( N-(4\text{-chlorobenzyl})-2\text{-}(2\text{-hydroxyethyl})\text{-8\text{-}(morpholin-4\text{-ylmethyl})\text{-6\text{-oxo-6\text{-H\text{-pyrrolo[3,2,1-ij\text{]quinolin-5\text{-carboxamide (PHA-529311)}}.}\textsuperscript{6} \) The metal catalyzed cross-coupling of quinolinones and quinolines bearing alkynyl substituents tethered to the acidic NH has also been employed for the synthesis of angular pyrrolo[3,2,1-ij]quinolinones/pyrrole[3,2,1-ij]quinolines. Pal \textit{et al.}, for example, previously reacted 8-iodo-6-bromo-1,2,3,4-tetrahydroquinoline \textit{96} with a series of terminal alkynes in the presence of 10% Pd/C-PPh\textsubscript{3}-CuI in water using 2-aminoethanol as a base at 80 °C in an inert atmosphere to afford the cross-coupled products \textit{97} in 51-95% yield (Scheme 21).\textsuperscript{55} The latter were subsequently subjected to intramolecular cyclization with CuI in DMF at 100 °C to afford the corresponding 2-substituted 5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline derivatives \textit{98} in 50-92% yield.

\[
\begin{align*}
\text{Br} & \quad \text{Br} & \quad \text{Br} \\
\text{I} & \quad \text{H} & \quad \text{R} \\
96 & & 97 & & 98
\end{align*}
\]

\text{R} = \text{C}_6\text{H}_5, \text{4-CH}_3\text{C}_6\text{H}_4-, \text{2-NO}_2\text{C}_6\text{H}_4-, \text{-CH}_2\text{CH}_2\text{OH}

\textit{Reagents and conditions: } (i) \text{RC≡CH (3.0 equiv.), 10\% Pd/C, PPh}_3, \text{CuI, 2-aminoethanol (3.0 equiv.), H}_2\text{O, 80 °C, 4-30 h, N}_2(\text{g}); (ii) \text{CuI, DMF, 100 °C, 4-36 h}

\textbf{Scheme 21:} Sequential Sonogashira coupling and cyclization of \textit{96} with terminal alkynes
In another development, a series of 6-substituted 8-iodo-2,3-dihydroquinolin-4(1H)-ones 99 was subjected to Sonogashira cross-coupling with terminal alkynes in the presence of 10% Pd/C-PPh3-CuI catalyst mixture and Et3N as a base in ethanol at 80 °C under nitrogen atmosphere to afford compounds 100 (Scheme 22). The latter were, in turn, subjected to a transitional metal-mediated intramolecular cyclization using PdCl2 as catalyst in MeCN at 80 °C to afford 5-substituted 2,3-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-1-ones 101 in 60-90% yield.

![Chemical structures](image)

**Reagents and conditions:** (i) RC≡CH, 10% Pd/C, PPh3, CuI, Et3N, EtOH, 80 °C, 2-10 h, N2(g);
(ii) PdCl2, MeCN, 80 °C

**Scheme 22:** Sequential Sonogashira cross-coupling and cyclization of 99

The Sonogashira cross-coupling of 8-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester 102 with terminal alkynes in the presence of 10% Pd/C-PPh3-CuI catalyst complex and Et3N as a base in ethanol at 80 °C under nitrogen atmosphere, on the other hand, afforded 6-oxopyrroloquinolines 103 in 50-95% yield in a single-pot operation (Scheme 23). The in situ metal-mediated cyclization of the tethered alkynyl moiety in this case is attributed to the increased acidity of NH because of the adjacent electron withdrawing α,β-unsaturated carbonyl framework.
Reagents and conditions: (i) RC≡CH, 10% Pd/C, PPh₃, CuI, Et₃N, EtOH, 80 °C, 2-5 h, N₂(g)

Scheme 23: One-pot Sonogashira cross-coupling of 102 with terminal alkynes and subsequent cyclization into 103

Of interest to us within the above classes of azoloquinolinones and their quinoline derivatives, are the angular polycarbo-substituted derivatives based on the 5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline and/or 6-oxopyrrolo[3,2,1-ij]quinoline skeleton and bearing alkyl- and/or aryl-substituents at the C-2, C-4 and C-6 positions. Structure-activity relationship of angular N-heterocyclic derivatives such as the pyrrolo[3,2,1-ij]quinoline scaffold bearing polycarbo substituents have been found to result in a variety of biological properties such as antiviral⁶, antihistamine²⁴ and antifungal²⁵ activities. The choice of the metal-catalyzed cross-coupling approach was based on the ease of displacement of the halogen atom(s) of halogenated quinoline-4-ones by terminal alkynes and the resultant improved yield.⁵⁶,⁵⁷ Since the halogenated 2-aryl-2,3-dihydroquinolin-4(1H)-ones and 2-arylquinolin-4(1H)-ones required as substrates for this investigation are not commercially available, we were required to develop efficient methods for their synthesis in the laboratory. Literature review revealed several methods for their synthesis and these are described in sequence in the sections below.
1.3 Methods for the synthesis of 2-substituted quinolin-4(1H)-ones

The 2-aryl-4-quinolone moiety has been found to serve as a versatile scaffold for further chemical transformation to afford derivatives with a wide variety of biological properties such as antiviral, antitumor and antibacterial activities. Their halogenated derivatives represent suitable substrates for metal-catalyzed carbon-carbon bond formation to afford polycarbono-substituted quinolinones and/ or quinoline derivatives. Alkenylated and alkynylated quinolinones or quinolines in which the appended carbon-containing group is tethered to a heteroatom are capable of undergoing subsequent or in situ heteroannulation to afford novel annulated quinolinones or quinolines. A common strategy for the synthesis of alkenyl- and alkynyl substituted quinin-4(1H)-ones involves the modification of the halogenated quinolin-4(1H)-one moiety via metal-catalyzed cross-coupling reactions. The methods for the synthesis and transformation of 2-aryl-2,3-dihydroquinolin-4(1H)-ones and their quinoline derivatives have been reviewed in detail in the literature before. Selected examples of the methods for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones are briefly discussed below.

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

The 2-aryl-2,3-dihydroquinolin-4(1H)-ones are commonly prepared by acid or base-promoted cyclization of their isomeric 1-(2-aminophenyl)-3-aryl-2-propen-1-ones (2-aminochalcones). The 2-aminochalcones are themselves readily prepared via Claisen-Schmidt condensation of 2-aminoacetophenone with benzaldehyde derivatives in ethanol at room temperature under basic condition. The 2-aminochalcones are subsequently cyclized under either acidic or basic conditions to afford the corresponding 2-aryl-2,3-dihydroquinolin-4(1H)-ones. A convenient approach involves cyclization of with
orthophosphoric acid in acetic acid under reflux to afford the 2-aryl-2,3-dihydroquinolin-4(1H)-ones 105 in high yields (Scheme 24).\(^6\) A microwave-mediated cyclization of the 2-aminochalcones 104 in the presence of silica gel impregnated with NaHSO\(_4\) to afford the 2-substituted 2,3-dihydroquinolin-4(1H)-ones in 82-96% yields has also been reported before.\(^6\)

Another solvent-free and solid-supported method involving the cyclization of 4-substituted 2-aminochalcones in the presence of alumina supported CeCl\(_3\).7H\(_2\)O-NaI as catalyst at 70 °C to afford 2,7-disubstituted 2,3-dihydroquinolin-4(1H)-ones in 86-98% yields has also been reported in the literature.\(^7\) A similar attempt using silica gel in place of alumina afforded the 2-phenyl-2,3-dihydroquinolin-4(1H)-one in relatively lower yield (80%).\(^7\) Silica chloride promoted cyclization of the chalcones under solvent-free conditions also afforded the cyclized products in high yields (Scheme 24).\(^7\) 2-Nitrochalcones has also been cyclized using iron powder in concentrated hydrochloric acid at 100 °C for 0.5 h to afford the corresponding NH-4-oxo derivatives in 72-88% yield.\(^7\) The cyclization in this case is initiated by reduction of the nitro group in the presence of iron under acidic condition and subsequent ring closure.

![Image](image_url)

**Reagents and conditions:** (i) H\(_3\)PO\(_4\), AcOH, reflux, 2 h\(^6\) or SiO\(_2\)Cl, MW, 3-6 min.\(^7\)

**Scheme 24:** Acid-promoted or solvent-free cyclization of 2-aminochalcones into quinolinones

The heterocyclic ring of the 2-aryl-2,3-dihydroquinolin-4(1H)-ones can undergo different degree of unsaturation, for example, via dehydrogenation or aromatization to afford 2arylquinolin-4(1H)-ones or 4-substituted 2arylquinolines, respectively. The methods for the synthesis of 4-quinolinones are described in detail in the sections below.
1.3.2 Methods for the synthesis of 2-substituted quinolin-4(1H)-ones

The methods for the dehydrogenation of the 2-aryl-2,3-dihydroquinolin-4(1H)-ones 105 using thallium(III) p-tolylsulfonate (TTS) in dimethoxyethane (DME) under reflux\textsuperscript{74} or iodosobenzene diacetate [PhI(OAc)\textsubscript{2}] with potassium hydroxide (KOH) as a base in methanol (MeOH)\textsuperscript{75} to afford the potentially tautomic 2-arylquinolin-4(1H)-ones 106 have been described before (Scheme 25).\textsuperscript{74} Tautomeric studies based on IR and NMR spectroscopic and X-ray crystallographic techniques as well as quantum chemical calculations of the equilibria of 2-substituted 4-quinolinols versus 2-substituted 4-quinolinone confirm the sole existence of the NH-4-oxo isomer in the solution and solid states, while the two isomers coexist in the gas phase according to mass spectrometry and quantum chemical calculations.\textsuperscript{76}

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{C}_6\text{H}_4\text{R} & \quad \text{C}_6\text{H}_4\text{R} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

105 (R = H, 3-OCH\textsubscript{3}, 4-OCH\textsubscript{3}, 3,4-OCH\textsubscript{2}O, 4-CH\textsubscript{3}, 4-Cl) 106 (90-96%)

Scheme 25: Dehydrogenation of 2-aryl-2,3-dihydroquinolin-4(1H)-ones

Methods for the direct synthesis of the 2-arylquinolin-4(1H)-ones involving cycloaddition or cyclocondensation reactions as well as metal-mediated approaches have also been described in the literature. Some of the examples of the methods of cycloaddition, cyclocondensation and metal-mediated approaches to the 2-arylquinolin-4(1H)-ones are described in sequence below.

Among the conventional cyclocondensation methods that have been previously reported for the synthesis of 4-quinolones is the Conrad-Limpach approach, which involves condensation of 2-substituted β-ketoesters and arylamines, followed by cyclization at high temperature to afford
quinolinones. However, the use of high temperature results in a viscous tar-like mixture and difficulty in purifying the products. For example, the reaction of ethyl aroylacettes with meta-substituted aniline in polyphosphoric acid at 260 °C afforded a mixture of substituted quinolin-4(1H)-ones albeit in poor yields after tedious purification process. Several other methods for the cyclocondensation of substituted benzoyl acetates with arylamine derivatives or isatoic derivative with acetophenone have also been described before. Ethyl benzoylacette 107 was previously condensed with substituted anilines 108 in ethanol at 50 °C under acidic conditions to afford compounds 109 which were, in turn, cyclized in diphenyl ether at 240-250 °C to afford the substituted 2-phenylquinolin-4-ones 110 in 15-50% yield (Scheme 26).

\[
\begin{align*}
\text{O} & \text{OEt} + \text{NH}_2 \quad \text{(i)} & \text{EtO} & \text{O} \quad \text{(ii)} & \text{O} \\
107 & 108 & 109 & 110 (R = H, 6-F, 6-Cl, 6-CH}_3, 6-OCH}_3) \\
\end{align*}
\]

Reagents and conditions: (i) AcOH, EtOH, 50 °C, 24 h; (ii) diphenyl ether, 240 °C, 0.5 h then 250 °C, 10 min.

**Scheme 26:** Cyclocondensation of ethylbenzoyacetate with substituted aniline

A single step approach involves the condensation of N-methylisatoic anhydride 111 with n-butyllithium (n-BuLi) lithiated enolate of acetophenone 112 in diisopropylamine (DIPA) as a base at -65 °C to produce 2-phenyl-1-methylquinolin-4(1H)-one 113 has also been described (Scheme 27). In another approach, 2-aminoacetophenone was initially condensed with a series of aldehydes followed by selective reduction of the keto functionality using NaBH₃CN to afford the alkylated derivatives. The latter were, in turn, acylated using variously substituted benzoyl
chlorides and the amides produced were cyclized using t-BuOK in refluxing t-BuOH to afford 1-benzyl-2-arylquinolin-4-ones.\textsuperscript{81}

\[
\begin{align*}
\text{N}-methylisatoic anhydride & \quad \text{acetophenone} \\
111 & \quad 112 \quad \xrightarrow{\text{DIPA, } n\text{-BuLi, THF, } -65^\circ \text{C, } 3.5 \text{ h}} \quad 113
\end{align*}
\]

**Scheme 27:** Condensation reaction of \(N\)-methylisatoic anhydride with acetophenone

Previously, the 2,2-dimethyl-5-methylthioalkylidene-1,3-dioxano-4,6-diones 114 were reacted with arylamines 115 in diphenyl ether under reflux to afford the corresponding 2-arylquinolin-4(1H)-ones 117 directly in 67-89\% yield without isolating the incipient intermediates 116 (Scheme 28).\textsuperscript{82}

\[
\begin{align*}
\text{114 (} R = \text{CH}_3, \text{C}_2\text{H}_5, \text{Ph} \text{)} & \quad \text{115 (} X = \text{H, Cl, Br, NO}_2 \text{)} & \quad \text{116} & \quad \text{117}
\end{align*}
\]

*Reagents and conditions:* (i) (C\textsubscript{6}H\textsubscript{5})\textsubscript{2}O, 140 °C, 0.5 h or C\textsubscript{2}H\textsubscript{5}OH, heat, 2-4 h

(ii) (C\textsubscript{6}H\textsubscript{5})\textsubscript{2}O, 250-260 °C, N\textsubscript{2} (g)

**Scheme 28:** Cyclocondensation reaction of 114 with arylamines
Recently, a series of nitrochalcones 118 was subjected to in situ reduction and cyclization in the presence of TiCl₄/Zn in THF at 40 °C to afford the corresponding 2-arylquinolin-4(1H)-ones 106 in 70-88% yield (Scheme 29). In this reaction, titanium is reduced by zinc to low valent titanium which then serve as the catalyst for the reaction. The difference in this reaction is that the cyclized products 106 are partially unsaturated.

\[
\begin{align*}
\text{NO}_2 & \quad \text{C}_6\text{H}_4\text{R} \\
\text{TiCl}_4/\text{Zn, THF} & \quad \text{40°C, 2 h} \\
\text{O} & \quad \text{C}_6\text{H}_4\text{R} \\
118 \quad (\text{R} = 4-\text{F}, 4-\text{Br}, 4-\text{CH}_3, 4-\text{OCH}_3) & \quad 106
\end{align*}
\]

**Scheme 29: Reduction and cyclization of nitrochalcones 118**

Less traditional methods for the synthesis of 2-arylquinolin-4(1H)-ones, which make use of transition metals as catalysts have also been reported in the literature and these are described below.

Palladium-catalyzed Sonogashira cross-coupling and cyclization reaction of iodoanilines 119 with terminal alkynes in the presence of dichlorobis((1,1’-diphenylphosphino)ferrocene)palladium [PdCl₂(dppf)] in diethylamine under CO atmosphere at 120 °C afforded substituted 2-arylquinolin-4(1H)-ones 120 in 62-84% yield (Scheme 30). In another example, palladium-catalyzed reaction of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one and aniline in the presence of Pd(PPh₃)₄ and K₂CO₃ as a base in dioxane under reflux afforded 1,2-diphenylquinolin-4(1H)-one in 75% yield.
The quinolin-4(1H)-one scaffold contains several reactive sites for possible modifications via halogenation, N- or O-alkylation and oxidative aromatization to afford novel substituted quinolinones or quinoline derivatives. The 2-arylquinolin-4(1H)-ones can 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. Aromatization of the 4-quinolone core with phosphorus oxychloride or thionyl chloride yield 4-chloroquinolinones which are essential intermediates for amination or alkoxylation and for cross-coupling. The focus of this discussion, however, is restricted to methods for the transformation of quinolin-4-one moiety to afford halogenated derivatives with potential to undergo sequential and/or one-pot palladium catalyzed cross-coupling reaction with terminal alkenes and alkynes to afford alkenylated or alkynylated quinolinones. For derivatives in which the unsaturated chain is tethered to the heteroatom, there exists a possibility to effect a single-pot or sequential metal-mediated intramolecular cyclization to afford heteroannulated quinolinones or their quinoline derivatives with potential biological properties. The known methods for the halogenation of the 2-aryl-2,3-dihydroquinolin-4(1H)-ones and 2-arylquinolin-4(1H)-ones are described in sequence below.
1.4 Halogenation of 2-aryl-2,3-dihydroquinolin-4(1H)-ones and 2-arylinolin-4(1H)-ones

The halogenation of either the fused benzo or the heterocyclic ring or both rings of the quinolin-4(1H)-one moiety has been reported before and selected examples are described in sequence below.

Halogenated quinolones\textsuperscript{90} and their quinoline derivatives\textsuperscript{91} are useful precursors for carbon-carbon bond formation or nucleophilic substitution to afford a range of polycarbo-substituted\textsuperscript{86,92,93} and/or their annulated derivatives.\textsuperscript{56,57,89} Halogen-containing quinolones are also of particular interest because the halogen plays a crucial role in the compounds’ bioactivity.\textsuperscript{94} Several methods have been reported for the halogenation of the fused benzo-ring of the dihydroquinolin-4(1H)-one framework. Sharma \textit{et al.} previously treated 2-aryl-2,3-dihydroquinolin-4(1H)-ones \textbf{105} with 1.5 equivalent of (dichloriodo)benzene (PhICl\textsubscript{2}) in dichloromethane (DCM) at room temperature to afford the corresponding 2-aryl-6-chloro-2,3-dihydroquinolin-4(1H)-ones \textbf{121} in 53-76\% yield (Scheme 31).\textsuperscript{90}

\begin{equation*}
\textbf{105} \xrightarrow{\text{PhICl}_2, \text{DCM, r.t.}} \textbf{121} \\
(R = \text{H, 4-F, 4-Br, 4-NO}_2, \text{2-OCH}_3)
\end{equation*}

\textbf{Scheme 31}: Halogenation of the fused benzo ring of the 2-aryl-2,3-dihydroquinolin-4(1H)-ones

In another development, treatment of compounds \textbf{105} with an excess of \textit{N}-bromosuccinimide (NBS) in carbon tetrachloride-chloroform mixture at room temperature, on the other hand, afforded the corresponding 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones \textbf{122} in 82-88\% yield (Scheme 32).\textsuperscript{86}
Akinlepally et al. treated 2-aminoacetophenone 123 with molecular bromine in dichloromethane at 0-5 °C to afford the 1-(2-amino-3,5-dibromophenyl)ethanones 124 (Scheme 33). The latter were, in turn, condensed with a variety of benzaldehyde derivatives 125 in ethanol under basic condition at 0-5 °C to afford a series of chalcones 126 followed by cyclization with orthophosphoric acid in acetic acid under reflux to afford the dihaloquinolin-4(1H)-ones 122 in 55-72% yield. In another approach, the authors also isolated the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122 directly from the reaction of compounds 124 with the benzaldehyde derivatives 125 in the presence of L-proline in methanol at 55-60 °C for 48 hours in yields comparable to their preparation via the chalcones (Scheme 33).
A variety of methods have been reported for the halogenation of the quinolin-4(1H)-one moiety. For example, treatment of 2-phenylquinolin-4(1H)-one 127 with an excess of molecular bromine (4.0 eq.) in ethanolic chloroform yielded 2-phenyl-3,6,8-tribromoquinolin-4(1H)-one 128 as the main product (43%) along with smaller quantities of 6,8-dibromo-2-phenylquinolin-4(1H)-one 129 and ethoxyquinoline derivative 130 (Scheme 34). For the halogenation of the potentially tautomeric 2-phenylquinolin-4(1H)-one 127, the ortho-para directing effects of the amino and hydroxyl groups activates the aromatic ring which supports the positions C-3, C-6 and C-8 of compound 127. While the inductive effect of the more electronegative oxygen of the carbonyl moiety also favours the C-3 position hence the mixture of products 128 and 129. The mechanism of formation of 130 presumably involves initial addition of ethanol to the carbonyl group to

\[ R = 4\text{-}F, 4\text{-}Cl, 4\text{-}Br, 4\text{-}NO_2, 4\text{-}CN, 4\text{-}OH, 3\text{-}OH, 4\text{-}(CH_3)_2, 3\text{-}4\text{-}5\text{-}\text{tri-OCH}_3^{-} \]

Reagents and conditions: (i) Br\(_2\), DCM, 0-5 °C, 7 h; (ii) EtOH, NaOH, 0-5 °C, 24 h; (iii) AcOH, H\(_3\)PO\(_4\), 100 °C, 2-3 h; (iv) L-proline, MeOH, 55-60 °C, 48 h

Scheme 33: Dihalogenation of 123 and cyclocondensation with arylaldehydes
afford a hemiacetal, which in turn, would undergo dehydration to yield an enolether derivative followed by dehydrobromination to afford ethoxyquinoline 130.96

\[
\text{Reagents and conditions: (i) Br (4.0 eq.), CHCl}_3, \text{ r.t.}
\]

**Scheme 34:** Bromination of 2-phenylquinolin-4(1H)-one

A series of 2-arylquinolin-4(1H)-ones 131 was treated with pyridinium tribromide (PTB) in acetic acid at room temperature to afford the 3-bromoquinolin-4(1H)-ones 132 (X = Br) in 80-95% yield (Scheme 35).97 The use of molecular iodine and sodium carbonate in THF at room temperature, on the other hand, afforded the 3-iodoquinolin-4(1H)-ones 132 (X = I) in 80-92% yield (Scheme 35).97
Methods that make use of oxidizing agents to promote aromatization of the quinolin-4(1H)-one framework into quinolines have also been developed and a few examples are described in the section below.

### 1.5 Aromatization of 2-arylquinolin-4(1H)-ones into 4-halogenoquinolines

Reagents such as thionyl chloride and phosphoryl chloride have been employed before for the aromatization of the quinolin-4(1H)-one moiety into quinoline. For example, aromatization of a series of substituted 2-arylquinolin-4(1H)-ones 133 ($X = H$) with thionyl chloride in dichloromethane under reflux afforded the corresponding substituted 2-aryl-4-chloroquinoline derivatives 134 in 77-92% yield (Scheme 36).\(^{87}\) The 2-aryl-3-iodoquinolin-4(1H)-ones 133 ($X = I$), on the other hand, were subjected to phosphoryl chloride under reflux to afford a series of 2-aryl-4-chloro-3-iodoquinolines 134 in 55-65% yield (Scheme 36).\(^{88}\)
A great deal of work has been focused on the incorporation of a halogen atom/s onto quinolinones and their quinoline derivatives. The presence of halogen atoms on these N-containing heterocycles enhance their bioactivity and also present a platform for structural elaboration. In recent time, much attention has been focused on these halogenated quinolinones and their quinoline derivatives as suitable candidates for transition metal-catalyzed cross-coupling with terminal alkynes in carbon-carbon bonds formation and subsequent annulation of tethered alkynyl moieties to afford pyrroloquinolinones and pyrroloquinolines. Our interest in the synthesis of polysubstituted angular pyrroloquinolinones and pyrroloquinolines prompted us to investigate the reactivity of the known 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones and the 2-aryl-6,8-dibromoquinolin-4(1H)-ones. Our goal was to prepare a series of polycarboxysubstituted pyrrolo[3,2,1-ij]quinolinones and pyrrolo[3,2,1-ij]quinoline derivatives bearing alkyl and/ or aryl groups at the 2, 4 and 8 positions.

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>R</th>
<th>R₁</th>
<th>% Yield</th>
</tr>
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<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>91</td>
</tr>
<tr>
<td>b</td>
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<td>2-F</td>
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<td>55</td>
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<tr>
<td>e</td>
<td>I</td>
<td>F</td>
<td>H</td>
<td>62</td>
</tr>
<tr>
<td>f</td>
<td>I</td>
<td>Cl</td>
<td>H</td>
<td>65</td>
</tr>
</tbody>
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**Scheme 36**: Aromatization of the 2-arylquinolin-4(1H)-ones into 4-chloroquinolines
1.6 Research hypothesis

Pyrrolo[3,2,1-ij]quinolinone derivatives have been reported to serve as antifungal agents against rice plants\textsuperscript{25} and exhibit antiviral activities on human herpesviruses DNA polymerases.\textsuperscript{6} Pyrrolo[3,2,1-ij]quinoline derivatives, on the other hand, have been found to exhibit inhibitory activity against platelet activating factor and histamine\textsuperscript{19} and as anticonvulsant agents.\textsuperscript{5} Our focus is on the synthesis of 2,4,8-polycarbosubstituted pyrrolo[3,2,1-ij]quinolinones and pyrrolo[3,2,1-ij]quinolines (Figure 2) with $R_2 = \text{aryl}$, bearing alkyl and polyaryl substituents and such compounds cannot be easily accessible through conventional methods.

\begin{figure}[h]
\centering
\includegraphics[width=0.3\textwidth]{structure.png}
\caption{The generalized structure of 2,4,8-trisubstituted 6-oxopyrrolo[3,2,1-ij]quinoline}
\end{figure}

As a result, the indirect method involving the use of 2-aryl-6,8-dibromoquinolin-4(1H)-ones remain the method of choice for the synthesis of the novel polycarbosubstituted pyrrolo[3,2,1-ij]quinolinones and pyrrolo[3,2,1-ij]quinoline derivatives. The preferred choice of transition metal-catalyzed cross-coupling methodology over other conventional approaches takes advantage of the ready availability of transition metal catalysts, transition metal-promoted displacement of halogen atom on the aryl or heteroaryl moiety and the proximity of the tethered nucleophilic heteroatom to promote heteroannulation.\textsuperscript{56,57} In this investigation, we opted for the use of the 2-aryl-6,8-dibromoquinolin-4(1H)-ones as substrates for the proposed initial metal catalyzed $Csp^2-Csp$ bond formation with terminal alkynes and possible subsequent heteroannulation to afford angular pyrrolo[3,2,1-ij]quinolinones and pyrrolo[3,2,1-ij]quinolines.
Our approach to make use of the 2-aryl-6,8-dibromoquinolin-4(1H)-ones as substrates takes advantage of the potential for bromine atoms at positions 6 and 8 to facilitate metal-catalyzed cross-coupling reaction as was observed with the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones cross-coupling with arylboronic acids to afford 2,6,8-triaryl-2,3-dihydroquinolin-4(1H)-ones.\(^8\) Although a similar approach was employed before in the reaction of analogous 6,8-dibromoflavone with methyl acrylate under Heck conditions,\(^9\) 6,8-dichlorotetrahydroquinoline with Grignard reagents,\(^9\) and 2,4-diiodoquinoline with terminal alkynes under Sonogashira conditions\(^10\) the reaction sequence has never been applied to azaflavanones bearing identical halogen atoms. Thus the ease of dihaloquinolin-4-ones to undergo metal-catalyzed carbon-carbon bond formation makes it difficult to easily predict the reactivity of the two bromine atoms in palladium catalyzed Sonogashira cross-coupling with terminal alkynes. The main aim of this investigation is to prepare polycarbosubstituted angular pyrrolo[3,2,1-ij]quinolinones, pyrrolo[3,2,1-ij]quinoline and furo[3,2-c]quinoline derivatives consisting of either quinolin-4(1H)-one or quinoline framework as central core annulated on the i and j faces or the c face with a five-membered ring containing a single heteroatom (X = N, O). The challenge is to determine which of the bromine atoms will be substituted first and whether we can establish a suitable reaction conditions to effect regioselective carbon-carbon bond formation. The other challenge is whether a suitable reaction condition for the one-pot synthesis of the 6,8-dialkynylquinolin-4(1H)-ones can be developed.

1.7 Aims and objectives

The aims and objectives of this investigation are:

(i) To subject the known 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones to dehydrogenation to afford the 2-aryl-6,8-dibromoquinolin-4(1H)-ones
(ii) To subject the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones and the 2-aryl-6,8-dibromoquinolin-4(1H)-ones to transition metal-catalyzed Sonogashira cross-coupling reaction with terminal alkynes as coupling partners using either homogeneous or heterogeneous catalyst.

(iii) To subject the monoalkynyl dihydroquinolin-4(1H)-ones and monoalkynyl quinolin-4(1H)-ones to metal-promoted electrophilic cyclization to furnish pyrrolo[3,2,1-ij]quinolinones and pyrrolo[3,2,1-ij]quinolines.


(v) To halogenate the known 2,6,8-triarylquinolin-4(1H)-ones with molecular iodine to afford the 2,6,8-triaryl-3-iodoquinolin-4(1H)-ones and transform these into 4,6,8-triaryl[furo[3,2-c]quinolines via palladium-promoted Sonogashira coupling reaction with terminal alkynes.

(vi) To evaluate some of the synthesized compounds for antimicrobial activity.
CHAPTER 2: RESULTS AND DISCUSSION

2.0 General Overview

Figure 3 below presents an overview of all the steps undertaken in this investigation to achieve the requisite polycarbosubstituted pyrrolo[3,2,1-ij]quinolinones and pyrrolo[3,2,1-ij]quinolines. The 2-aryl-2,3-dihydroquinolin-4(1H)-ones \textbf{105} were prepared by cyclizing the 1-(2'-aminophenyl)-3-aryl-2-propen-1-one derivatives \textbf{104} using orthophosphoric acid in acetic acid. The 1-(2'-aminophenyl)-3-aryl-2-propen-1-ones were themselves prepared by condensing 2-aminoacetophenone \textbf{123} and benzaldehyde derivatives \textbf{135} in the presence of NaOH in ethanol. Compounds \textbf{105} were, in turn, treated with N-bromosuccinimide in carbon tetrachloride-chloroform mixture (3:2; v/v) to afford the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones \textbf{122}. Dehydrogenation of the latter using thallium(III) \(p\)-tolylsulphonate in dimethoxyethane under reflux afforded 2-aryl-6,8-dibromoquinolin-4(1H)-ones \textbf{136}. Compounds \textbf{122} were then subjected to Sonogashira cross-coupling reaction with terminal alkynes in the presence of 10% palladium on carbon-triphenylphosphate and copper(I) iodide [10% Pd/C-PPh\textsubscript{3}-CuI] catalyst complex and dichlorobis(triphenylphosphine)palladium(II)-copper(I) iodide [PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}-CuI] catalyst mixture and triethylamine (NEt\textsubscript{3}) as a base and co-solvent with ethanol [2:1; v/v] under reflux and inert atmosphere to yield the corresponding site-controlled 8-alkynyl 2-aryl-6-bromo-2,3-dihydroquinolin-4(1H)-ones \textbf{137} and non-selective 6,8-disubstituted-2-aryl-2,3-dihydroquinolin-4(1H)-ones \textbf{138}, respectively. The coupled compounds \textbf{137} were then cyclized in the presence of palladium chloride in acetonitrile under reflux and inert atmosphere to yield 4-aryl-8-bromo-2-phenyl-6\(H\)-4,5-dihydropyrrolo[3,2,1-ij]quinolin-6-ones \textbf{139} and 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-ones \textbf{140}. In a tandem coupling and heteroannulation reaction, the 2-aryl-6,8-dibromoquinolin-4(1H)-ones \textbf{136} were, in turn,
subjected to cross-coupling reaction with terminal alkynes under Sonogashira reaction conditions in the presence of 10% palladium on carbon-triphenyl phosphine-copper(I) iodide (10% Pd/C-PPh₃-CuI) catalyst mixture and potassium carbonate (K₂CO₃) as a base in dioxane-water mixture [3:1; v/v] and dichlorobis(triphenylphosphine)palladium(II)-copper(I) iodide [PdCl₂(PPh₃)₂-CuI] with triethylamine (NEt₃) as a base in DMF/water mixture [4:1; v/v] under reflux and inert atmosphere to afford the corresponding 2-substituted 4-aryl-8-bromo-6-oxopyrrolo[3,2,1-ij]quinolines 142 and 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,2,1-ij]quinolines 143, respectively. The mono-substituted annulated compounds were subjected to further transformation with arylboronic acids as their coupling partners under Suzuki-Miyaura metal-catalyzed cross coupling reaction in the presence of dichlorobis(triphenylphosphine)palladium(II)-tricyclohexylphosphine catalyst mixture using potassium carbonate as a base in dioxane-water mixture [3:1; v/v] under reflux and inert atmosphere to afford a novel series of 2,8-disubstituted 4-aryl-6H-4,5-dihydropyrrolo[3,2,1-ij]quinolin-6-ones 141 and 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,2,1-ij]quinolines 144, respectively. The known 2,6,8-triarylquinolin-4(1H)-ones were treated with molecular iodine and sodium carbonate in THF to afford a series of 2,6,8-triaryl-3-iodoquinolin-4(1H)-ones which were then transformed into 4,6,8-triarylfuro[3,2-c]quinolines via dichlorobis(triphenylphosphine)palladium(II)-copper(I) iodide-promoted Sonogashira coupling reaction with terminal alkynes under alkaline conditions of NEt₃ in DMF under reflux and inert atmosphere. All the prepared products in this investigation were characterized using a combination of ¹H NMR & ¹³C NMR spectroscopy, IR, mass spectrometry and X-ray diffraction techniques.
Figure 3: Generalized scheme depicting reaction pathways followed to prepare the pyrrolo[3,2,1-ij]quinolinones and pyrrolo[3,2,1-ij]quinoline derivatives described in this investigation
2.1 Preparation of Substrates

2.1.1 Synthesis of 1-(2-aminophenyl)-3-aryl-2-propen-1-ones 104a-d

Several methods have been reported in the literature for the synthesis of the 2-aminochalcones, which are important substrates for the synthesis of the isomeric 2-aryl-2,3-dihydroquinolin-4(1H)-ones. The 2-aminochalcones 104 required as precursors in this investigation were prepared by the Claisen-Schmidt aldol condensation of 2-aminoacetophenone 123 and benzaldehyde derivatives 135 in the presence of sodium hydroxide in ethanol at room temperature for 18 hours (Scheme 37). The 1H NMR spectra of compounds 104 reveal the presence of a broad singlet at δ ca. 6.35 ppm, which corresponds to the amino group and a group of proton signals in the region, δ 6.67-7.86 ppm for the aromatic and olefinic protons. The presence of the C=O and NH₂ groups was also confirmed by the corresponding IR absorption bands at ν_max ca. 1628 cm⁻¹ and 3385 cm⁻¹, respectively. Although some of the observed melting point values differ from those reported in the literature, the corresponding 1H NMR and IR spectroscopic data represent closest fit consistent with the assigned structures.
With the aminochalcones in hand, we explored the possibility of cyclization into the isomeric 2,3-dihydroquinolin-4(1H)-ones as described below.

2.1.2 Synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones 105a-d

The 2-aryl-2,3-dihydroquinolin-4(1H)-ones are generally prepared by acid or base-promoted cyclization of the corresponding isomeric 2-aminochalcones 104. In this investigation, we adapted the method described in the literature and subjected the 1-(2-aminophenyl)-3-aryl-2-propen-1-ones 104 to orthophosphoric acid in acetic acid under reflux to afford the corresponding 105 in high yield and purity (Scheme 38). The ¹H NMR spectra of these cyclic derivatives show the presence of diastereotopic methylene protons, which resonate as a set of two doublet of doublets (dd) at δ ca. 2.68 ppm with J = 7.5 and 15.5 Hz and 2.88 ppm with J = 13.2 and 15.5 Hz), a broad singlet (br. s) at δ ca. 4.56 ppm for the N-1 proton, a doublet of
doublets (dd) at δ ca. 4.70 ppm with coupling constant value \( J = 7.5 \) and 9.0 Hz for the H-2 proton as well as a group of signals in the aromatic region δ ca. 6.71-7.85 ppm (Figure 4). Their IR spectra, on the other hand, reveal the presence of intense absorption bands at \( \nu_{\text{max}} \) 1649 cm\(^{-1}\) and 3306 cm\(^{-1}\), which correspond to C=O and N-H groups, respectively.

\[ \text{NH}_2 \quad \text{O} \quad \text{C}_6\text{H}_4\text{R} \quad \text{N} \quad \text{O} \quad \text{C}_6\text{H}_4\text{R} \quad \text{H} \quad \text{H}_3\text{PO}_4, \text{AcOH, 100°C, 2 h} \]

**Scheme 38**: Acid-catalyzed cyclization of 1-(2-aminophenyl)-3-aryl-2-propen-1-ones 104

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>% Yield</th>
<th>Mp °C (Lit. ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>90</td>
<td>147-149 (148-150(^\circ))</td>
</tr>
<tr>
<td>b</td>
<td>F</td>
<td>88</td>
<td>118-120 (116-118(^\circ))</td>
</tr>
<tr>
<td>c</td>
<td>Cl</td>
<td>92</td>
<td>146-148 (146(^\circ))</td>
</tr>
<tr>
<td>d</td>
<td>OMe</td>
<td>90</td>
<td>109-111 (112-114(^\circ))</td>
</tr>
</tbody>
</table>

With compounds 105 in hand, we decided to investigate the possibility to effect bromination on the fused benzo ring as described in the next section.
Figure 4: $^1$H NMR spectrum of compound 105b in CDCl$_3$ at 300 MHz
2.2 Synthesis of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122a-d

Halogenation of the 2-aryl-2,3-dihydroquinolin-4(1H)-ones has been previously effected through the use of dichlororiodobenzene. In this study we subjected the 2-aryl-2,3-dihydroquinolin-4(1H)-ones 105 to N-bromosuccinimide (NBS) (2.5 equivalent) in carbon tetrachloride-chloroform [CCl₄-CHCl₃] mixture [3:2; v/v] at room temperature for 3 h to afford upon column chromatography on silica gel the corresponding 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122 in 83-88% yields (Scheme 39). Incorporation of the two bromine atoms was confirmed by the presence of two sets of doublets at δ ca. 7.71 ppm and 7.95 ppm with coupling constant value \( J = 2.1 \) Hz corresponding to the protons at H-7 and H-5, respectively (Fig. 5). Moreover, the reduced intensity of signals for C-8 and C-6 at δ ca. 120.7 ppm and 147.0 ppm in their \(^{13}\)C NMR spectra confirm the presence of bromine atoms on these nuclei (Fig. 6). Crystals suitable for X-ray diffraction were obtained for 122b by slow evaporation of the ethanol solution. The molecular geometry of compounds 122 was also confirmed independently by the X-ray diffraction data (Figure 7). The compound crystallized in the monoclinic space group P2(1)/n with one molecule in the unit cell (a/Å 13.0752, b/Å 8.0086, c/Å 14.3026, α = γ = 90°, β = 111.8230°). The 2-aryl moiety is not co-planar with the quinolin-4(1H)-one ring as confirmed by the large torsion angle [C(8)-C(9)-C(10)-C(15)] with a value of 82.9° (see Table 1 for selected torsion angles).
Table 1: Selected torsion angles of compound 122b

<table>
<thead>
<tr>
<th>Bond Sequence</th>
<th>Torsion Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-C(9)-C(10)-C(15)</td>
<td>-37.3°</td>
</tr>
<tr>
<td>C(8)-C(9)-C(10)-C(15)</td>
<td>82.9°</td>
</tr>
<tr>
<td>N(1)-C(9)-C(10)-C(11)</td>
<td>146.9°</td>
</tr>
<tr>
<td>C(8)-C(9)-C(10)-C(11)</td>
<td>-92.8°</td>
</tr>
</tbody>
</table>

Scheme 39: Bromination of the 2-aryl-2,3-dihydroquinolin-4(1H)-ones 105

The 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones were found by other authors to exhibit antiproliferative activity against MCF-7 breast cancer cell lines. The presence of two bromine atoms on the fused benzo ring of 122 make these compounds suitable candidates for further transformation through sequential or single-pot metal-catalyzed carbon-carbon bond formation. Also of importance is the potential of the heterocyclic ring of compounds 122 to undergo
different degree of unsaturation via dehydrogenation to yield the 2-aryl-6,8-dibromoquinolin-4(1H)-ones or oxidative aromatization to afford quinoline derivatives.
Figure 5: $^1$H NMR spectrum of $^{122b}$ in CDCl$_3$ at 300 MHz
Figure 6: $^{13}$C NMR spectrum of 122b in CDCl$_3$ at 75 MHz
Figure 7: ORTEP diagram (50% probability level) of compound 122b showing crystallographic numbering. For clarity, hydrogen atoms are not labeled.

We decided to introduce partial unsaturation between the C-2 and C-3 bond of the heterocyclic ring of compounds 122 as described in the next section. The partial unsaturation of the heterocyclic ring provides an additional reactive center at C-3 for possible functionalization and increase the acidity of N-H moiety of the 2-arylquinolin-4(1H)-one framework.

2.3 Synthesis of 2-aryl-6,8-dibromoquinolin-4(1H)-ones 136a-d via dehydrogenation of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones

The 2-aryl-2,3-dihydroquinolin-4(1H)-ones were previously dehydrogenated using thallium(III) $p$-tolylsulfonate (TTS) in dimethoxyethane (DME) under reflux$^{74}$ or iodobenzene diacetate [PhI(OAc)$_2$] with potassium hydroxide (KOH) as a base in methanol (MeOH).$^{75}$ In this study, we
opted for the use of thallium(III) \textit{p}-tolylsulphonate due to the ease of preparation from thallium(III) nitrate and \textit{p}-toluene sulphonic acid.\textsuperscript{74} We treated the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1\textit{H})-ones \textbf{122} with thallium(III) \textit{p}-tolylsulphonate (TTS) in dimethoxyethane (DME) under reflux to afford the corresponding 2-aryl-6,8-dibromoquinolin-4(1\textit{H})-ones \textbf{136} exclusively and in good yields without need for purification by column chromatography (Scheme 40). The $^1$H NMR for these potentially tautomeric compounds reveal the absence of both the aliphatic proton signals present in the spectra of the corresponding substrates and the presence of the olefinic and aromatic signals in the region $\delta$ ca. 7.05-8.30 ppm and a less intense broad singlet significantly downfield at $\delta$ ca. 11.90 ppm for N-H (Figure 8). The $^{13}$C NMR spectra of compounds \textbf{136} also reveal the resonances corresponding to the olefinic signals at $\delta$ ca. 79.6 and 102.3 ppm for C-2 and C-3, respectively (Figure 9). Although, compounds \textbf{136} show potential to coexist in a tautomeric equilibrium with the quinolinol isomer, previous studies have confirmed that only the NH-4-oxo tautomer exists exclusively in solution phase (NMR spectroscopy) and solid state (IR spectroscopy and X-ray diffraction).\textsuperscript{76} The IR absorption bands at $\nu_{\text{max}}$ ca. 3384 cm$^{-1}$ and 1622 cm$^{-1}$ attributed to the N-H and C=O groups, further confirm their quinolin-4(1\textit{H})-one nature.
Reagents and conditions: (i) thallium(III) p-tolylsulphonate, dimethoxyethane, reflux, 0.5 h

**Scheme 40**: Dehydrogenation of the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122

<table>
<thead>
<tr>
<th>136</th>
<th>R</th>
<th>% Yield</th>
<th>Mp °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>86</td>
<td>212-214</td>
</tr>
<tr>
<td>b</td>
<td>F</td>
<td>80</td>
<td>222-224</td>
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<tr>
<td>c</td>
<td>Cl</td>
<td>88</td>
<td>233-235</td>
</tr>
<tr>
<td>d</td>
<td>OMe</td>
<td>82</td>
<td>190-192</td>
</tr>
</tbody>
</table>
Figure 8: $^1$HNMR spectrum of compound 136d in DMSO-$d_6$ at 300 MHz
Figure 9: $^{13}$CNMR spectrum of compound 136d in DMSO-$d_6$ at 75 MHz
With the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones and 2-aryl-6,8-dibromoquinolin-4(1H)-ones in hand, we explored their reactivity in palladium-catalyzed Sonogashira cross-coupling with terminal alkynes.

2.4 Palladium-catalyzed Sonogashira cross-coupling of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones with terminal alkynes

Sonogashira cross-coupling of terminal alkynes in the presence of a palladium catalyst is known to proceed well with aryliodides and arylbromides.\textsuperscript{32,56,57,99} With compounds 122 in hand, we decided to investigate their reactivity in Pd-catalyzed Sonogashira cross-coupling using terminal acetylenes as coupling partners. Initial attempt to effect site-selective cross-coupling of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1H)-one with phenyl acetylene using 10% Pd/C-PPh\textsubscript{3}-CuI catalyst complex with K\textsubscript{2}CO\textsubscript{3} as the base in ethanol under reflux and inert atmosphere after 18 hours led to the recovery of the starting material. However, the use of triethylamine (NEt\textsubscript{3}) in place of potassium carbonate (K\textsubscript{2}CO\textsubscript{3}) resulted in the desired monoalkynyl product 137a in low yield <30% along with the starting material. The yield of compound 137a was improved in ethanol using NEt\textsubscript{3} as a base and co-solvent. We isolated upon column chromatography on silica gel the corresponding compound 137a in high yield (71%) and purity (Scheme 41). The reaction conditions were extended to other dihaloquinolin-4-ones 122 with phenyl acetylene and 3-butyn-1-ol as coupling partners. We isolated in all cases the corresponding 8-alkynyl-2-aryl-8-bromo-2,3-dihydroquinolin-4(1H)-ones 137a-h (Scheme 41). Hitherto, 6-chloro-8-iodo-2,3-dihydroquinolin-4(1H)-one has been found to undergo palladium-catalyzed Sonogashira cross-coupling in the presence of 10% Pd/C-PPh\textsubscript{3}-CuI catalyst complex with phenyl acetylene with ease to afford 8-phenylethynyl-6-chloro-2,3-dihydroquinolin-4(1H)-one.\textsuperscript{56} The same catalyst complex also promoted C-8 alkynylation of 6-bromo-8-iodoquinolines to afford 8-alkynyl-6-
bromoquinolines. In these examples, preferential replacement of the 8-iodo atom over the 6-chloro/bromo atom is observed. However, in this study the observed site-selectivity at the C-8 over C-6 of compounds 122 is attributed to the ortho directing effect of NH in analogy with literature precedent for the dihalogenated fused benzo heterocycles bearing two similar halogen atoms. Furthermore, selectivity of the transition metal-catalyzed cross-coupling reaction of multiple identical halogen atoms bearing heterocycles with similar carbon-halide bond strengths has been found to depend largely on the heterocycle π* (LUMO)-PdL₂ dxy (HOMO) interaction in the oxidative addition step. In addition, the interaction of the orbital formed by the lone pair of electrons on the nitrogen atom with the palladium catalyst further favours the initial substitution of the bromine at the C-8 position. The selectivity for heteroaryl halides bearing different halogen atoms depend on the trend in reactivity of the halides: I > Br > Cl >> F, as a function of their Ar-X bond strengths (D_{ph-X} values 65, 81, 96 and 126 kcal mol⁻¹). Selectivity also depend to a lesser degree on the electronic effect of its position on the heteroaryl moiety. The ¹H NMR spectra of compounds 137 still retained some of the characteristic features observed in the spectra of corresponding substrates with the aliphatic protons at the position H-3 resonating as a doublet and doublet of doublets at δ ca. 2.76 ppm with J_{gem} = 15.0 Hz and at δ ca. 2.89 ppm with J_{vic} = 7.1 and 15.0 Hz. A doublet of doublets at δ ca. 4.75 ppm with J = 7.1 and 9.3 Hz, due to the resonance of the methine proton of the chiral carbon center at the position H-2; a singlet at δ ca. 5.49 ppm correspond to the NH and the two sets of doublet at δ ca. 7.58 ppm and δ ca. 7.90 ppm with coupling constant value J = 2.4 Hz, correspond to the slightly deshielded protons at positions H-7 and H-5, respectively (Figure 10). Their ¹³C NMR spectra reveal the presence of acetylenic carbons at δ ca. 88.7 and 96.7 ppm, respectively (Figure 11). Their IR spectra also show an intense absorption band at ν\text{max} ca. 2201 cm⁻¹ which confirms the presence of the C≡C group.
Reagents and conditions: (i) R'C≡CH, 10% Pd/C, PPh₃, CuI, Et₃N, EtOH, 100 °C, 18 h

Scheme 41: Regioselective alkynylation of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122a-d
Figure 10: $^1$H NMR spectrum of compound 140d in CDCl$_3$ at 300 MHz
Figure 11: $^{13}$C NMR spectrum of compound 140d in CDCl$_3$ at 75 MHz
The efficiency of palladium derives from its ability at zero valent to activate carbon-halogen bonds by an oxidative addition which results in an organopalladium complex prone to react with nucleophiles.\textsuperscript{105,106} For the palladium catalytic cycle, studies have revealed that the ready accessibility of two oxidation states of 0 and +2, and the ease of interconversion due to the filling of the non-bonding orbitals are vital to the efficiency of this metal.\textsuperscript{107} This allows for palladium to vary the number of electrons between 18 and 14.\textsuperscript{108} Furthermore, new reactive anionic palladium(0) complexes species are formed in which Pd(0) is ligated in conjunction with either chloride ions such as Pd(0)(PPh\textsubscript{3})\textsubscript{2}Cl\textsuperscript{−} [when generated by reduction of PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}] or by acetate ions represented by Pd(0)(PPh\textsubscript{3})\textsubscript{2}(OAc)\textsuperscript{−} [when generated \textit{in situ} in mixtures of Pd(OAc)\textsubscript{2} and PPh\textsubscript{3}].\textsuperscript{109} This reactivity of the anionic palladium(0) is evidenced in the oxidative addition of organohalides with a coupling partner such as an acetylenic moiety \textit{via} the palladium-catalyzed Sonogashira cross-coupling.\textsuperscript{55,56} The active Pd(0) species generated from the ligated metal (PdL\textsubscript{2}) according to the general palladium catalytic cycle,\textsuperscript{106} initiate the oxidative addition step on the substrates \textbf{122} to give the organopalladium complex \textbf{I}. This is followed by an \textit{in situ} formation of the copper acetylide complex resulting in the transmetalation step to afford system \textbf{II}. Reductive elimination which involves the regeneration of the palladium species and the products \textbf{137} then take place (Figure 12). Furthermore, the preferential installation of alkynyl substituents at C-8 position over C-6, might be supported by the reported coordination between the 14 electron ligated low valent metal Pd(0) generated \textit{in situ} and the nitrogen atom in the oxidative addition step to form an organopalladium complex according to the general palladium catalytic cycle.\textsuperscript{107}
Figure 12: Proposed mechanism for the site-selective cross-coupling of 122

Encouraged by the regio-selective Sonogashira cross-coupling of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones with terminal alkynes in the presence of a heterogeneous catalyst, we decided to investigate the reactivity of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones with terminal alkynes using a homogeneous catalyst.
2.5 One-pot Sonogashira cross-coupling: synthesis of 6,8-dialkynylated 2-aryl-2,3-dihydroquinolin-4(1H)-ones 138a-h

The homogeneous catalyst-assisted cross-coupling of dihaloquinolin-4-ones with aryl substituents and dihaloquinolines with alkynyl substituents has been described before. With these considerations in mind, we explored the versatility of the cross-coupling of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122 with terminal acetylenes. We subjected compounds 122 to Sonogashira cross-coupling with terminal alkynes in the presence of PdCl₂(PPh₃)₂-CuI catalyst complex in NEt₃/EtOH mixture under reflux and inert atmosphere for 6 hours. We isolated upon column chromatography on silica gel the corresponding 6,8-dialkynyl-2-aryl-2,3-dihydroquinolin-4(1H)-ones 138 in a one-pot operation (Scheme 42). The ¹H NMR spectra of compounds 138 reveal an increase in number of signals in the aromatic region at δ ca. 7.21-7.50 ppm due to the presence of additional phenyl groups in compounds 138a-d (Figure 13). For the alkynyl-substituted derivatives 138e-h, there is a broad singlet at δ ca. 1.80 ppm for the OH and two sets of multiplets at δ ca. 2.62-2.66 ppm and δ ca. 3.77-3.82 ppm attributed to the ethyl chain. Their ¹³C NMR spectra, on the other hand, reveal the presence of resonances attributed to the two sets of acetylenic group at δ ca. 82.2, 86.7, 91.6, 102.9 ppm (Figure 14). Their acetylenic nature was also confirmed by the presence of intense IR absorption band at νmax ca. 2218 cm⁻¹ in their IR spectra. The accurately calculated m/z values for the molecular ions reveal the absence of the almost equal M+ and M+2 peaks typical of molecules containing ⁷⁹Br and ⁸¹Br isotopes thus confirm the displacement of the two bromine atoms.
Reagents and conditions: (i) R'≡C, PdCl₂(PPh₃)₂, CuI, Et₃N, EtOH, 100 °C, N₂ (g), 8 h

Scheme 42: Non-sequential metal-catalyzed cross-coupling of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122a-d with terminal alkynes

It is well known the efficiency and reactivity of a palladium catalyst strongly depends on the precursor of palladium(0) complex. The oxidative addition step leading to the formation of the organopalladium complex has also been identified as vital to the rate of the reaction. Both homogeneous and heterogeneous catalysts generate an active solvated Pd(0)L₂ species in the oxidative-addition step. The ligated active metal [Pd(0)L₂] species formed from the interaction of the ligands (L) with the palladium metal (Pd), is preceded in the case of heterogenous catalyst,
by the initial leaching of palladium particles from the surface of the carbon support into the solvent. The active Pd(0)L$_2$ species then promotes the initial cross-coupling reaction by oxidative addition then transmetalation with the displacement of one bromine atom followed by reductive elimination and re-adsorption of the Pd species onto the carbon support upon completion of a single cross-coupling cycle. This makes it unavailable to couple with the ligand to generate the active species, thus terminating the reaction. The homogeneous pre-catalyst source such as PdCl$_2$(PPh$_3$)$_2$, on the other hand, catalyzes the first cross-coupling cycle with the displacement of one of the bromine atom and upon regeneration the active species of the catalyst is able to facilitate further cross-coupling leading to complete conversion of the substrates to afford compounds 138.
Figure 13: $^1$H NMR spectrum of compound 138a in CDCl$_3$ at 300 MHz
Figure 14: $^{13}$C NMR spectrum of 138a in CDCl$_3$ at 75 MHz
In order to ascertain the effect of the solid support in the cross-coupling reaction, we explored the role and impact of activated charcoal on both the heterogeneous and homogeneous catalysts in the metal-catalyzed cross-coupling of the substrates, 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122. An increase in the amount of 10% Pd/C from 1 to 5 mol% using the same reagents and conditions as described in the monoalkynylation of compounds 122 with terminal acetylene (Scheme 41) still furnished compounds 137. A similar reduction in the amount of PdCl$_2$(PPh$_3$)$_2$ from 5 to 2 mol% (which was the minimum reactive amount to effect the cross-coupling) in combination with activated charcoal (10 mol%) also afforded compounds 137 albeit in lower yields even with the use of an excess of phenyl acetylene and the dialkynylated derivatives as minor products in the ratio 6:1 (determined with the aid of HPLC). We conclude from these trial runs that Pd species released from reductive elimination step becomes adsorbed onto the support. This makes it unavailable to interact with the ligand to regenerate active Pd(0) species for the 2$^{nd}$ cross-coupling step. The results are as presented below.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>5 mol% Pd/C</th>
<th>2.0 mol% PdCl$_2$(PPh$_3$)$_2$/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>137</td>
<td>R</td>
<td>R'</td>
<td>Yield %</td>
</tr>
<tr>
<td>a</td>
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<td>c</td>
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<tr>
<td>d</td>
<td>OMe</td>
<td>-C$_6$H$_5$</td>
<td>60</td>
</tr>
</tbody>
</table>

*Reagents and conditions:* (i) R'C≡CH, 10% Pd/C, PPh$_3$, CuI, Et$_3$N, EtOH, 100 °C, N$_2$ (g), 18 h or (i) R'CCH, PdCl$_2$PPh$_3$, C, CuI, Et$_3$N, EtOH, 100 °C, N$_2$ (g), 48 h
Alkynylated compounds in which the alkynyl group is tethered to the nucleophilic heteroatom are known to undergo heteroannulation in the presence of metal or Lewis acid catalyst with ease.\textsuperscript{56} This heteroannulation strategy represents a versatile and efficient pathway to polynuclear compounds. With the 8-alkynyl-2-aryl-8-bromo-2,3-dihydroquinolin-4(1H)-ones 137 in hand, we decided to investigate the possibility to effect heteroannulation of 8-alkynylquinolin-4(1H)-ones as described in the next section.

2.6 Synthesis of 4-aryl-8-bromo-2-phenyl-6H-4,5-dihyropyrrrol[3,2,1-ij]quinolin-6-ones 139a-d

The installation of the alkynyl group at the C-8 position followed by the electrophilic or metal-promoted cyclization of the resulting alkynylated compound has been described before.\textsuperscript{56} We adapted the method described in the literature\textsuperscript{56} and subjected compounds 137 to intramolecular cyclization in the presence of palladium(II) chloride (PdCl\textsubscript{2}) in acetonitrile (MeCN) under reflux. We isolated by column chromatography on silica gel the 4-aryl-8-bromo-2-phenyl-6H-4,5-dihyropyrrrol[3,2,1-ij]quinolin-6-ones 139 (Scheme 43). The \textsuperscript{1}H NMR spectra of compounds 139 show the absence of the signal for NH present in the spectra of the corresponding substrates. One of the diastereotopic methylene protons, H-5 resonates as a doublet at $\delta$ ca. 3.22 ppm with coupling constant value $J_{gsm} = 15.0$ Hz in the aliphatic region. The second methylene proton resonates as a doublet of doublets at $\delta$ ca. 3.64 ppm with $J_{vic} = 7.1$ and 15.0 Hz. The methine proton, on the other hand, resonates as a doublet at $\delta$ ca. 5.95 ppm with $J = 7.1$ Hz. The singlet at $\delta$ ca. 6.62 ppm is attributed to the olefinic proton at H-1 with the phenyl substituent on C-2 resonating as a multiplet in the region $\delta$ 7.36–7.40 ppm. The two sets of doublet at $\delta$ ca. 7.80 and 8.00 ppm with coupling constant value $J = 1.8$ Hz, on the other hand, correspond to the 7-H and 9-H, respectively (Figure 15). Their \textsuperscript{13}C NMR spectra reveal the absence of the signals in the
region $\delta$ ca. 82.4-94.5 ppm attributed to the acetylenic carbons. The spectra instead, reveal the presence of signals at $\delta$ ca. 103.2 and 114.4 ppm which corresponds to the olefinic carbons (C-1 and C-2) and the resonance at $\delta$ ca. 190.6 ppm for the carbonyl carbon (Figure 16). The IR spectra, on the other hand, reveal the absence of the absorption bands corresponding to NH and C≡C groups present in the spectra of the corresponding precursors. Instead, their IR spectra reveal the presence of the bands corresponding to the C=\tex{C} and C=O at $\nu_{\text{max}}$ ca. 3023 and 1686 cm$^{-1}$, respectively. Crystals suitable for X-ray diffraction were obtained for 139a by slow evaporation of the ethanol solution and the molecular geometry of compounds 139 was also confirmed independently by the X-ray diffraction (Figure 17).\textsuperscript{111} The aryl ring at C(11) and the phenyl ring at C(2) are not co-planar, they are twisted out of plane of the pyrrolo[3,2,1-ij]quinoline-6-one ring with torsional angles $[\text{N(1)-C(11)-C(18)-C(23)}]$ with a value of 62.5° and $[\text{N(1)-C(2)-C(12)-C(17)}]$ with a value of -78.6°, respectively.
Reagents and conditions: (i) PdCl₂, MeCN, 90 °C, N₂ (g), 2 h

**Scheme 43**: Intramolecular cyclization of 2-phenyl-8-(2-phenylethynyl)-2,3-dihydroquinolin-4(1H)-ones 137a-d
Figure 15: $^1$H NMR spectrum of compound 139c in CDCl$_3$ at 300 MHz
Figure 16: $^{13}$C NMR spectrum of compound 139c in CDCl$_3$ at 75 MHz
Analogous 5,6-dihydropyrrolo[3,2,1-ij]quinolines have been reported to exhibit a variety of activity including as anticonvulsant,\textsuperscript{5} antitumor,\textsuperscript{19} antifungal\textsuperscript{25} agents.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure17}
\caption{ORTEP diagram (50\% probability level) of compound 139a showing crystallographic numbering. For clarity, hydrogen atoms are not labeled.}
\end{figure}

### 2.7 Synthesis of 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-ones 140a-d

In a similar fashion as described for compounds 137a-d, we subjected the aliphatic 8-alkynyldihydroquinolin-4(1H)-ones 137e-h to metal-catalyzed intramolecular cyclization in the presence of palladium(II) chloride in acetonitrile under reflux. We however, isolated by column chromatography on silica gel compounds characterized through a combination of \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopy, IR and mass spectrometry as the corresponding 2-aryl-6-bromo-8-(4-
hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-ones 140 (Scheme 44). The $^1$H NMR spectra of compounds 140 reveals the presence of an aliphatic chain at C-8, with a broad singlet at the region $\delta$ ca. 1.65 ppm attributed to the signal for the OH group (Figure 18). A quintet at $\delta$ ca. 1.96 ppm with $J = 6.0$ and 6.9 Hz correspond to the methylene group; two sets of triplet at $\delta$ ca. 3.10 and 3.73 ppm with $J = 6.9$ Hz and $J = 6.3$ Hz for the methylene protons of the aliphatic chain at C-8: H-3″, H-2″ and H-4″ (-CH$_2$CH$_2$CH$_2$OH), respectively. The NH resonates downfield at $\delta$ ca. 9.30 ppm as a broad singlet. The $^{13}$C NMR spectra reveal the presence of two C=O at $\delta$ ca. 191.2 and 201.6 ppm (Figure 19), distinguishing it from the spectra of the corresponding substrates which have a single C=O group. The IR spectra show absorption bands at $\nu_{\text{max}}$ ca. 3347, 3242, 1682, 1646 cm$^{-1}$ corresponding to the OH, NH and the two sets of C=O, respectively.
Reagents and conditions: (i) PdCl$_2$, MeCN, 90 °C, 6 h

Scheme 44: Palladium-catalyzed oxidation of 137e-h
Figure 18: $^1$H NMR spectrum of compound 140d in CDCl$_3$ at 300 MHz
Figure 19: $^{13}$CNMR spectrum of compound 140d in CDCl$_3$ at 75 MHz
The formation of compounds 140a-d from 137e-h under the same condition employed on 137a-d to afford heteroannulated derivatives 139a-d is interesting. We envision in both cases that PdCl$_2$ coordinates with the pi electrons of the triple bond to form the activated intermediate A (Figure 20). In the case of intermediates A derived from phenylacetylene, heteroannulation occurs between the electrophilic carbon and the nucleophilic nitrogen atom which would then afford products 139. The formation of products 140a-d from 137e-h, on the other hand, is presumably the consequence of nucleophilic attack by the hydroxyl group to form a thermodynamically favoured dihydrofuran ring as in structure I with concomitant release of HCl. Regeneration of the catalyst, PdCl$_2$, from I releases dihydrofuran intermediate II. We envisage that the dihydrofuran ring of II becomes protonated during aqueous work-up to form III, which then undergoes ring opening by water to form compounds 140. Despite the fact that our proposed mechanism is necessarily speculative, it represents the best option consistent with the formation of the observed products in the presence of PdCl$_2$. 
Figure 20: Plausible Mechanism for the Palladium-catalyzed oxidation of 137e-h

2.8 Synthesis of 8-substituted 4-aryl-2-phenyl-6H-4,5-dihydroquinolin-6-ones 141a-f

We next focused our attention on the reactivity of the monosubstituted polynuclear compounds 139 in Suzuki-Miyaura cross-coupling with arylboronic acids in the presence of PdCl₂(PPh₃)₂-PCy₃ catalyst complex and K₂CO₃ as a base in dioxane-water mixture under reflux for 3 hours. We isolated upon column chromatography on silica gel the novel 2,4,8-trisubstituted 6H-4,5-
dihydroquinolin-6-ones 141 (Scheme 45). The $^1$H NMR spectra of compounds 141 reveal a set of doublet and a doublet of doublets at δ *ca.* 3.18 and 3.71 ppm with coupling constant values $J_{\text{gem}} = 15.0$ Hz and $J_{\text{vic}} = 7.1$ and 15.0 Hz attributed to the diastereotopic methylene protons at H-5, respectively (Figure 21). The methine proton at H-4 resonates as a doublet at δ *ca.* 5.99 ppm with $J = 7.1$ Hz. The intense singlet at δ *ca.* 7.39 ppm is attributed to the phenyl group at C-2; an increase in the aromatic protons in the region δ *ca.* 6.54-7.58 ppm confirmed the installed aryl ring at position C-8. Their $^{13}$C NMR spectra show an increase of between five to eight peaks due to the resonances of the inserted aryl ring (Figure 22). The presence of the C=O absorption band at $\nu_{\text{max}}$ *ca.* 1678 cm$^{-1}$ was confirmed by IR spectra. The accurately calculated $m/z$ values for the molecular ions and the absence of the M+ and M+2 peaks typical of the $^{79}$Br and $^{81}$Br isotopes thus confirm the displacement of the bromine atom.
**Reagents and conditions:** (i) ArB(OH)$_2$, PdCl$_2$(PPh$_3$)$_2$, PCy$_3$, K$_2$CO$_3$, dioxane/H$_2$O, 100 °C, 3 h

**Scheme 45:** Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of 4-aryl-8-bromo-2-phenyl-6H-4,5-dihydropyrrol[3,2,1-ij]quinolin-6-ones 139 with arylboronic acids
Figure 21: $^1$H NMR spectrum of compound 141e in CDCl$_3$ at 300 MHz
Figure 22: $^{13}$C NMR spectrum of compound 141e in CDCl$_3$ at 75 MHz
2.9 Synthesis of 2-substituted 4-aryl-8-bromo-6-oxopyrrolo[3,2,1-ij]quinolines 142a-h

The versatility of an N-containing heterocycles to undergo palladium-catalyzed one-pot cross-coupling and intramolecular cyclization with terminal alkynes in the synthesis of annulated compounds has been previously demonstrated.\textsuperscript{56,57} In our investigation particularly with the success of the monoalkynylation of compounds 122 we envisage that control of the reaction conditions and the proximity of the C-8 to N-1 might favour the preferential displacement of the bromine atom ortho to the NH and intramolecular cyclization. With this assumption in mind, we subjected 6,8-dibromo-2-phenylquinolin-4(1H)-one 136a to metal-catalyzed Sonogashira cross-coupling reaction with phenyl acetylene in the presence of Pd/C-CuI-PPh\textsubscript{3} catalyst mixture in DMF/water mixture [4:1; v/v] using Et\textsubscript{3}N as a base under reflux for 18 hours and isolated the requisite product 142a in low yield. Varying the reaction conditions, increased yield (68\%) of the product 142a was observed with the use of K\textsubscript{2}CO\textsubscript{3} as a base in dioxane (Scheme 46). The scope of the reaction was explored using various derivatives and terminal aromatic and aliphatic alkynes. However, the phenyl derivatives 142a-d were isolated in 62-68\% yields with poor yields (< 20\%) observed for the aliphatic derivatives 142e-h. Attempt to improve the yields of the aliphatic derivatives by the use of excess terminal alkyne and longer reaction times were unsuccessful as we recovered the starting material mostly unchanged, presumably due to the volatile nature of the aliphatic acetylene and the slow rate determining step of the heterogeneous catalyst employed.\textsuperscript{107} However, with the use of homogeneous catalyst-PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} and CuI as a co-catalyst with Et\textsubscript{3}N as the base in a mixture of DMF/water under reflux, we isolated upon column chromatography a mixture of products with the dialkynyalted aliphatic derivatives as the major products and the monosubstituted products in <40\% yield. The success of this one-pot cross-coupling and heteroannulation was confirmed by the \textsuperscript{1}H NMR spectra of 142a-h with the absence of the signal for the NH, the presence of four sets of singlet at δ ca. 6.23, 6.69, 7.11 and
8.25 ppm corresponding to the methine proton at H-1, H-5, H-9 and H-7, respectively (Figure 23). The increase in the signals in the aromatic region is attributed to the incorporation of the phenyl ring. The signals for the pair of singlet attributed to the proton at H-1 and H-5 appeared slightly upfield due to anisotropic effect, which is due to the internal electromagnetic field of the pi-electrons shielding the protons from the applied magnetic field and interfering with the attendant electronegativity of the carbon atom(s) thereby reducing the effective magnetic field.

The aliphatic derivatives 142e-h exhibit two sets of triplet at δ ca. 1.86 and 2.52 ppm corresponding to the OH and CH₂CH₂OH, respectively. The doublet of doublets at δ ca. 3.70 ppm is attributed to the methylene attached to the hydroxyl group. Moreover, the ¹³C NMR spectra reveal the resonance for the C=O group at δ ca. 178.6 ppm (Figure 24). The absence of the NH was also confirmed by the IR spectra with the lack of the NH absorption stretch while the absorption band at νmax ca. 1635 cm⁻¹ is for the C=O group; in addition for 142e-h the stretch for the OH group appear at νmax ca. 3415 cm⁻¹.
Reagents and conditions: (i) PhC≡CH, Pd/C, PPh₃, CuI, K₂CO₃, dioxane, 110 °C, 18 h;
(ii) HC≡CH₂CH₂OH, PdCl₂(PPh₃)₂, CuI, Et₃N, DMF/H₂O, 110 °C, 6 h

Scheme 46: Regioselective Pd-catalyzed tandem Sonogashira cross-coupling/ annulation reaction
Figure 23: $^1$H NMR spectrum of compound 142d in CDCl$_3$ at 300 MHz
Figure 24: $^{13}$C NMR spectrum of compound 142d in CDCl$_3$ at 75 MHz
2.10 Synthesis of 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,2-1j]quinoline derivatives 143a-h via palladium-catalyzed Sonogashira cross-coupling reaction

We next explored the possibility of dialkynylation utilizing substrates 136a-d. We subjected 2-aryl-6,8-dibromoquinolin-4(1H)-ones 136a-d to Sonogashira cross-coupling with terminal alkynes in the presence of PdCl$_2$(PPh$_3$)$_2$-CuI catalyst mixture in DMF/water mixture [4:1; v/v] under reflux. We isolated upon column chromatography on silica gel compounds 143a-d (Scheme 47). The use of aliphatic alkyne as the coupling partner, however, afforded mixtures of mono- and di-substituted products. Presumably, due to the sequential mode of cross-coupling, with the replacement of the two bromine atoms in turn and the volatility of the low boiling aliphatic alkyne. The $^1$H NMR spectra of compounds 143a-d reveal four sets of singlet at δ ca. 6.17, 6.78, 7.97 and 8.19 ppm corresponding to proton at H-1, H-5, H-9 and H-7, respectively (Figure 25). An increase in the signals by ten (10) in the aromatic region δ ca. 6.93-7.40 ppm confirms the presence of the two phenyl rings. The aliphatic compounds 143e-h show two sets of triplet at δ ca. 2.26 and 2.61 ppm with coupling constant value $J = 6.0$ Hz attributed to the methylene group in the aliphatic chain bearing the triple bond. The pair of doublet of doublets at δ ca. 3.49 and 3.63 ppm with coupling constant values $J = 6.0$ and 7.3 Hz corresponds to the methylene protons attached to the hydroxyl group. Furthermore, another set of triplets at δ ca. 4.68 and 4.98 ppm with coupling constant value $J = 5.9$ Hz is attributed to the OH. The acetylenic nature and carbonyl carbon was confirmed by the $^{13}$C NMR spectra resonance at δ ca. 85.3, 89.2 and 178.7 ppm, due to C≡α, C≡β and C=O, respectively (Figure 26). Compounds 143e-h exhibit further resonances at δ ca. 23.9, 32.7, 59.2 and 60.3 ppm, which correspond to the alkoxy carbon atoms in: CH$_2$CH$_2$OH', CH$_2$CH$_2$OH'''', CH$_2$OH' and CH$_2$OH''', respectively. The IR spectra reveal absorption bands at $\nu_{max}$ ca. 2209 and 1637 cm$^{-1}$ confirming the presence of the
C≡C and C=O groups, respectively. And the band at $\nu_{\text{max}} \text{ ca. } 3310 \text{ cm}^{-1}$ is due to the OH functional group.

\[ \text{Reagents and conditions: (i) } R'\text{C≡CH, PdCl}_2(\text{PPh}_3)_2, \text{ CuI, Et}_3\text{N, DMF/H}_2\text{O, 100 °C, 4-8 h} \]

**Scheme 47:** Pd-catalyzed tandem Sonogashira coupling/annulation-dialkynylation reaction
Figure 25: $^1$H NMR spectrum of compound 143c in CDCl$_3$ at 300 MHz
Figure 26: $^{13}$C NMR spectrum of compound 143c in CDCl$_3$ at 75 MHz
2.11 Synthesis of 2-substituted 4-aryl-8-(4-fluorophenyl)-6-oxopyrrolo[3,2,1-ij]quinoline derivatives 144a-e via Pd-catalyzed Suzuki-Miyaura cross-coupling reaction

Further transformation of the monosubstituted compounds 142a-h via a palladium-promoted Suzuki-Miyaura cross-coupling reaction was also investigated. The 2-substituted 4-aryl-8-bromo-6-oxopyrrolo[3,2,1-ij]quinolines 142a-h were subjected to cross-coupling with fluorophenylboronic acid in the presence of PdCl₂(PPh₃)₂-PCy₃ catalyst complex with K₂CO₃ as a base in dioxane/H₂O mixture [3:1; v/v] under reflux. We isolated upon column chromatography the corresponding trisubstituted 6-oxopyrrolo[3,2,1-ij]quinolines 144 exclusively (Scheme 48). The ¹H NMR spectra of compounds 144a-e reveal an increase in the number of protons in the aromatic region for the installed aryl ring as well as the presence of four sets of singlet at δ ca. 6.33, 6.81, 8.08 and 8.38 ppm corresponding to the methine protons at H-1, H-5, H-9 and H-7 positions, respectively (Figure 27). The ¹³C NMR spectra show the presence of doublets due to the C-F interaction of the 4-fluorophenyl ring with the resonances at δ ca. 115.9, 129.3, 134.3 and 162.7 ppm corresponding to ¹J_CF 245.7 Hz (C-4), ²J_CF 21.4 Hz (C-3 & 5), ³J_CF 8.0 Hz (C-2 & 6) and ⁴J_CF 3.3 Hz (C-1), respectively (Figure 28). The resonance for the C=O appears at δ ca. 180.0 ppm. The IR spectra reveal the presence of the carbonyl group with absorption band at ν_max ca. 1638 cm⁻¹. The accurately calculated m/z of the molecular ions also confirmed the assigned structure.
Reagents and conditions: (i) 4-FPhB(OH)$_2$, PdCl$_2$(PPh$_3$)$_2$, PCy$_3$, K$_2$CO$_3$, dioxane/H$_2$O, 100 °C, 3 h

Scheme 48: Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of compounds 142a-e

Several examples from this class of polysubstituted oxopyrrolo[3,2,1-ij]quinolines have been found to exhibit antifungal,$^{23}$ antiviral$^{25}$ and anticancer$^{26}$ activity.
Figure 27: $^1$H NMR spectrum of compound 144c in CDCl$_3$ at 300 MHz
Figure 28: $^{13}$C NMR spectrum of compound 144c in CDCl$_3$ at 75 MHz
2.12 Palladium-catalyzed Suzuki-Miyaura cross-coupling: synthesis of 2,6,8-triaryl-2,3-dihydroquinolin-4(1H)-ones 145a-h

We subjected the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122a-d to palladium-catalyzed Suzuki-Miyaura cross-coupling with arylboronic acids in the presence of PdCl$_2$(PPh$_3$)$_2$-PCy$_3$ catalyst mixture and K$_2$CO$_3$ as a base in dioxane-water mixture under reflux for 3 hours (Scheme 49). We isolated upon column chromatography the desired 2,6,8-triaryl-2,3-dihydroquinolin-4(1H)-ones 145a-h in 75-85% yields. The $^1$H NMR spectra reveal the two sets of doublet of doublets at $\delta$ ca. 2.80 ppm with $J = 15.5$ Hz and 2.97 ppm with $J = 7.4$ and 15.5 Hz for the methylene protons at H-3 (Figure 29). A doublet of doublets at $\delta$ ca. 4.72 ppm with $J = 4.5$ and 7.4 Hz and a broad singlet at 4.80 ppm, attributed to the H-2 and N-1 protons, respectively. The insertion of the aryl rings at positions C-6 and C-8 were confirmed by the increased signals in the aromatic region at $\delta$ ca. 7.07-8.21 ppm. The $^{13}$C NMR spectra show an increased number of resonances of between eight and sixteen due to the aryl rings (Figure 30). Moreover, the IR spectra show the presence of absorption bands at $\nu_{\text{max}}$ ca. 3380 and 1675 cm$^{-1}$ due to the N-H and C=O, respectively. The accurately calculated $m/z$ values for the molecular ions further confirmed the assigned structures. The compound crystallized in the monoclinic space group P2(1)/c with one molecule in the unit cell (a/Å 13.1620, b/Å 13.8779, c/Å 11.1618, $\alpha = \gamma = 90^\circ$, $\beta = 99.7100^\circ$). The 2-aryl moiety is not co-planar with the quinolin-4(1H)-one ring as confirmed by the large torsion angle [C(8)-C(9)-C(10)-C(15)] with a value of 91.70°.
Reagents and conditions: (i) ArB(OH)$_2$, PdCl$_2$(PPh$_3$)$_2$, PCy$_3$, K$_2$CO$_3$, dioxane-H$_2$O (3:1, v/v), 90 °C, 3 h

**Scheme 49:** Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of 122a-d

Some examples of aryl-substituted quinolin-4(1H)-ones have been reported to exhibit antitumor, tubulin inhibitory properties and in vitro activity against erythrocytic stages of multi-drug-resistant isolates and clones of *Plasmodium falciparum*.112
Figure 29: $^1$H NMR spectrum of compound 145b in CDCl$_3$ at 300 MHz
Figure 30: $\text{^{13}C NMR spectrum of compound 145b in CDCl}_3$ at 75 MHz
We explored the introduction of partial unsaturation in the heterocyclic ring of compounds 145a-h via dehydrogenation and treated these compounds to thallium(III) para tolylsulphonate (TTS) in dimethoxyethane (DME) under reflux and isolated the dehydrogenated derivatives 146a-h exclusively (Scheme 50). The $^1$H NMR show the olefinic proton at C-3 and the N-1 proton resonating downfield as a singlet and broad singlet at $\delta$ ca. 6.57 and 8.37 ppm, respectively (Figure 32). The corresponding $^{13}$C NMR spectra reveal resonance for C-3 and C=O at $\delta$ ca. 108.2 and 178.9 ppm, respectively (Figure 33). The IR spectra show absorption bands at $v_{\text{max}}$ ca. 3394 and 1644 cm$^{-1}$ for NH and C=O, respectively.
With the 2,6,8-triarylquinolin-4(1H)-ones in hand, we explore their functionalization taking advantage of the reaction center at C-3 as described in sequence below.
Figure 32: $^1$H NMR spectrum of compound 146e in CDCl$_3$ at 300 MHz
Figure 33: $^{13}$C NMR spectrum of compound 146e in CDCl$_3$ at 75 MHz
2.14 Synthesis of 2,6,8-triaryl-3-iodoquinolin-4(1H)-ones 147a-h

We investigated the halogenation of the 2,6,8-triarylquinolin-4(1H)-ones 146a-h with focus on the available reactive center with the potential of further transformation via carbon-carbon bond formation due to the ease of displacement of the halogen atom of haloquinolin-4(1H)-ones.\(^{56,86}\)

We adapted a previously reported method\(^{97}\) and treated compounds 146 with molecular iodine in the presence of sodium carbonate in tetrahydrofuran at room temperature to afford the 2,6,8-triaryl-3-iodoquinolin-4(1H)-ones 147 (Scheme 51). The \(^1\)H NMR spectra of these compounds consist of two set of doublets at \(\delta\) ca. 7.83 and 8.63 ppm with coupling constant value \(J = 2.1\) Hz and a broad singlet at \(\delta\) ca. 8.38 ppm for the protons at H-7, H-5 and N-1, respectively (Figure 34). The absence of the singlet at H-3 also confirmed the replacement with iodine. The \(^{13}\)C NMR spectra show the resonance for C-3 and C=O at \(\delta\) ca. 86.9 and 174.6 ppm, respectively (Figure 35). Moreover, the IR spectra show absorption at \(\nu_{\text{max}}\) ca. 3386 and 1762 cm\(^{-1}\) for NH and C=O, respectively. The accurately calculated \(m/z\) value with M+2 peak typical of \(^{127}\)I isotope also confirmed the presence of iodine in the compounds.
Several examples of 2-arylquinolin-4(1H)-ones and their analogues have been found to exhibit antitumor\textsuperscript{113,114} and antiplatelet properties, and a degree of activity against a variety of cancer.\textsuperscript{115} Furthermore, their fluoroquinolone analogues have been reported to possess anti-ischemic activity and serves as cardioprotector.\textsuperscript{116}
Figure 34: $^{13}$C NMR spectrum of compound 147c in CDCl$_3$ at 300 MHz
Figure 35: $^{13}$C NMR spectrum of compound 147c in CDCl$_3$ at 75 MHz
2.15 Synthesis of 2,6',8'-trisubstituted 2'-aryl furo[3,2-c]quinoline derivatives 148a-i

The potential of the substituted-3-haloquinolin-4(1H)-ones to undergo metal-catalyzed alkynylation and subsequent cyclization of the tethered alkynylquinolin-4(1H)-ones in close proximity to a nucleophilic heteroatom has been described. To demonstrate the potential of 2,6,8-triaryl-3-iodoquinolin-4(1H)-ones 147 in synthesis we subjected compounds 147a-h to PdCl₂(PPh₃)₂-CuI catalyzed Sonogashira cross-coupling with terminal alkynes in the presence of NEt₃ as a base in DMF under reflux. We isolated by column chromatography on silica gel the novel polycarbosubstituted furo[3,2-c]quinoline derivatives 148a-i (Scheme 52). The ¹H NMR spectra reveals the absence of signals corresponding to the NH and all the protons were observed in the aromatic region δ ca. 7.04-8.54 ppm (Figure 36). The absence of resonance corresponding to the carbonyl carbon in the ¹³C spectra also confirms the assigned structure (Figure 37). The IR spectra lack the absorption bands for both the NH and C=O groups present in the spectra of the corresponding precursors 148. The accurately calculated m/z values reveal the absence of the M+2 peak typical of ¹²⁷I isotope, thus confirms the replacement of the iodine atom.
Reagents and conditions: (i) RCCH, PdCl₂(PPh₃)₂, CuI, Et₃N, DMF, 100 °C, 2 h

Scheme 52: Pd-catalyzed tandem alkynylation and heteroannulation of 2,6,8-triaryl-3-iodoquinolin-4(1H)-ones 147a-h

Examples of these classes of annulated compounds have been reported to exhibit anticancer² activity. Some of the synthesized compounds were found to exhibit antifungal activity against C. neoformans (Table 1).
Figure 36: $^1$H NMR spectrum of compound 148b in CDCl$_3$ at 300 MHz
Figure 37: $^{13}$C NMR spectrum of compound 148b in CDCl$_3$ at 75 MHz
2.16 Evaluation of antimicrobial activity for compounds 137–139, 141–144 and 148

The antimicrobial activity of the pyrrolo[3,2,1-ij]quinolines,5,20,21 the 6-oxopyrrolo[3,2,1-ij]quinolines6 and the furo[3,2-c]quinolines2 has been investigated by various groups before. The pyrrolo[3,2,1-ij]quinolines, 6-oxopyrrolo[3,2,1-ij]quinolines and furo[3,2-c]quinolines were also reported to exhibit antiviral,6 antitumor,2,23 antihypertensive,4 antibacterial22 and antifungal21,25 activities. As a prelude to annulated heterocycles with potential biological properties, in this investigation we evaluated compounds 137-139, 141-144 and 148 for their potential antimicrobial activity against six pathogens: *Staphylococcus aureus* (ATCC 25923, Gram-positive), *Enterococcus faecalis* (ATCC 29212, Gram-positive), *Escherichia coli* (ATCC 8739, Gram-negative), *Pseudomonas aureginosa* (ATCC 27858, Gram-negative), *Candida albicans* (ATCC 10231, yeast) and *Cryptococcus neoformans* (ATCC 14116, yeast) using the minimum inhibitory concentration (MIC) screening assay. These results are presented in Table 1 below, which gives the mean of the minimum inhibitory concentrations (MIC) results in mg/mL for the six reference organisms tested. Culture controls and negative controls were within limits recommended for the assay. All assays were carried out without any evidence of contamination. Previously, MIC values of 0.064-0.100 mg/mL have been accepted as having clinical relevance.117 None of these compounds exhibited remarkable antibacterial activity against the reference pathogens: *E. coli*, *E. faecalis*, *P. aureginosa* and *S. aureus* as observed in Table 1, as their MIC values are higher than 0.100 mg/mL the upper limit to be acceptable as clinically relevant.
Table 1: Minimum Inhibitory Concentration values for selected synthesized compounds

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Compounds 137e, 137f, 137h, 138f and 138g, on the other hand, were found to exhibit activity against both yeast strains: *C. albicans* and *C. neoformans* with MIC values in the range of 0.039 & 0.039, 0.078 & 0.078, 0.078 & 0.015, 0.078 & 0.047 and 0.078 & 0.015 mg/mL, respectively. The antifungal activity of oxygen atom-containing furoquinolines has previously been attributed to the ease to bind to DNA through hydrogen bonding.\(^6\)\(^,\)\(^46\) We envisage that the presence of oxygen atom and hydroxyl group in some of the compounds synthesized in this investigation (eg., 137-139, 141-144 and 148) would enable them to form hydrogen bonds with DNA and presumably impart the observed antifungal activity.\(^5\)\(^,\)\(^46\)

A minimum inhibitory concentration value of 0.039 mg/mL was exhibited by 137b, 142f, 143g, 143h and 144b against the *C. neoformans* spores. Compounds 139b, 139c, 139d, 142g, 142h, 143f, 148e and 148g, on the other hand, displayed inhibitory activity against *C. neoformans* with MIC value in the region of 0.078 mg/mL. Amongst these compounds, 137h and 138g exhibited the highest activity with minimum inhibition concentration value of 0.015 mg/mL against the *C. neoformans*.  

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Table 1 continues
Chapter 3: CONCLUSION

The reactivity of the substituted dihalogenoquinolin-4(1H)-ones in Sonogashira cross-coupling reaction with terminal alkynes in the presence of homogeneous and heterogeneous catalysts was investigated. In the presence of Pd/C-PPh₃-CuI catalyst mixture as a heterogenous Pd(0) source, the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones couple with terminal alkynes to afford the corresponding 2-aryl-6-bromo-8-(alkynyl)-2,3-dihydroquinolin-4(1H)-ones, exclusively. The use of PdCl₂(PPh₃)₂ as Pd(0) source, on the other hand, afforded 2-aryl-6,8-bis(alkynyl)-2,3-dihydroquinolin-4(1H)-ones in reasonable yields and high purity. The structures of the compounds were characterized using a combination of ¹H and ¹³C NMR spectroscopy, IR and mass spectrometry; and the geometry established by means of single X-ray crystallography. We rationalize that monoalkynylation of the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones to be the consequence of using Pd/C as the Pd(0) source. It is well known that palladium on carbon serves only as a heterogenous source of Pd(0) catalyst for homogenous coupling which involves the initial slow leaching of Pd to interact with the ligand to generate the active Pd(0)-PPh₃ species in situ.¹¹⁸ The homogenous Pd(0)-PPh₃ species then undergoes facile transmetallation with copper acetylide followed by reductive elimination and concomitant re-deposition of Pd onto the support.¹⁰² The re-adsorption onto the solid support presumably immobilizes Pd and makes it unavailable to promote further cross-coupling with the excess terminal alkyne. This assertion was corroborated when we employed a more reactive Pd(II) pre-catalyst as source of active catalyst to explore the role and effect of the presence and absence of activated carbon. The varied amount of PdCl₂(PPh₃)₂ with activated charcoal using the same reagents and conditions still furnished the monoalkynylated products predominantly even with use of excess of phenylacetylene. Dialkynylation was, however, observed as the predominant reaction in the absence of activated carbon under these conditions with traces of the monoalkynylated
derivatives detected (tlc) in the crude reaction mixture. The preponderance of the monoalkynylated derivative using PdCl$_2$(PPh$_3$)$_2$-CuI catalyst complex as Pd(0) source in the presence of activated carbon seems to support our view that the active Pd(0)-PPh$_3$ species becomes adsorbed onto the solid support and becomes unavailable to promote further alkynylation. In the absence of the activated carbon, the active Pd(0)-PPh$_3$ species derived from PdCl$_2$(PPh$_3$)$_2$ becomes available in solution to promote further alkynylation and under these conditions, the dialkynylated product predominates. Conversely, in the presence of Pd/C-PPh$_3$-CuI pre-catalyst mixture as a heterogenous Pd(0) source, the 2-aryl-6,8-dibromoquinolin-4(1H)-ones undergoes one-pot site-selective Sonogashira cross-coupling-heteroannulation with terminal alkynes to afford the corresponding 4-aryl-8-bromo-2-(alkynyl)-6-oxopyrrolo[3,2,1-ij]quinolines. Dialkynylated, 4-aryl-2,8-bis(alkynyl)-6-oxopyrrolo[3,2,1-ij]quinolines were, however, isolated as the predominant products in the presence of PdCl$_2$(PPh$_3$)$_2$ as Pd(0) source.

In both cases, the *in situ* heteroannulation is attributed to the increased acidity of NH and the proximity of the metal activated triple bond of the 8-alkynyl moiety to nitrogen of the incipient 8-alkynyl-2-arylquinolin-4(1H)-ones. The 8-bromo-2,4-diarylpyrrolo derivatives were transformed via palladium-catalyzed Suzuki-Miyaura cross-coupling with arylboronic acids to afford the corresponding 2,4,8-trisubstituted 4,5-dihydro-5H-pyrrolo[3,2,1-ij]quinolin-6-ones and the 2,4,8-trisubstituted 6-oxopyrrolo[3,2,1-ij]quinolines. The known 2,6,8-triarylquinolin-4(1H)-ones were found to undergo iodine-promoted halogenation to afford 2,6,8-triaryl-3-iodoquinolin-4(1H)-ones. The latter, in turn, were subjected to palladium-mediated Sonogashira cross-coupling with terminal alkynes to afford a series of 2-substituted 4,6,8-triarylfluoro[3,2-c]quinolines, exclusively. The tandem coupling-heteroannulation is presumably due to the ease of displacement of the halide by alkynyl moiety and proximity of the nucleophilic heteroatom, oxygen to the tethered alkynyl of the incipient 3-alkynylquinolin-4(1H)-ones.
We conclude that the proximity of the nucleophilic heteroatom in the case of tethered alkynylated derivatives promotes sequential or one-pot intramolecular attack of the metal-activated triple bond to afford heteroannulated compounds. The differences in structure and behaviour of the phenyl acetylene and propargyl alcohol derivatives include the aromatic nature of the phenyl acetylene derivatives while the propargyl alcohol bear an alkyl chain containing hydroxyl group with the attendant potential for hydrogen bonding. Some results from this investigation have since been described in the literature.\textsuperscript{119,120}

Most of the compounds prepared in this study are analogues of the physiologically important pyrrolo[3,2,1-ij]quinolinones, pyrrolo[3,2,1-ij]quinolines and furo[3,2-c]quinolines with a spectrum of applications as: anticancer,\textsuperscript{2} antihypertensive,\textsuperscript{4} anticonvulsant,\textsuperscript{5} antiviral,\textsuperscript{6} and antifungal\textsuperscript{21,25,26} agents. Preliminary antimicrobial susceptible study reveals promising antifungal activity in several of the synthesized compounds. Compounds 137h and 138g exhibited the highest activity with minimum inhibition concentration value of 0.015 mg/mL against the \textit{C. neoformans}. A possible link in structure-activity relation is the presence of hydroxyl groups in addition to the oxygen atom in these compounds which could facilitate binding to DNA through hydrogen bonding.

Future research extending from this study might include:

i. Further functionalization of the heterocyclic ring of the quinolin-4(1\textit{H})one scaffold

ii. Initial halogenation of the 2-aminoacetophenone to afford halogenated aminoacetophenone, with the latter subjected to metal-catalyzed cross-coupling with terminal alkenes and alkynes followed by condensation with benzaldehyde derivatives and cyclization of the incipient chalcones
iii. Comprehensive evaluation of the polycarboxsubstituted pyrroloquinolines and furoquinolines for physiological properties e.g. anticancer and antifungal activities
Chapter 4: EXPERIMENTAL

4.0 GENERAL

Commercially available solvents and 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 and as CDCl$_3$ or DMSO-$d_6$ solution. The chemical shifts were referenced relative to the solvent peaks (δ$_H$ 7.25 or δ$_C$ 77.0 ppm for CDCl$_3$ and δ$_H$ 2.50 or δ$_C$ 40.0 ppm for DMSO-$d_6$) 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 Infrared 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 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. Single X-ray crystal geometry and data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo $K_a$ radiation (50kV, 30mA) using the APEX 2 (Bruker, 2005a) data collection software. The collection method involved ω-scans of width 0.5° and 512x512 bit data frames at the University of Witwatersrand.

The following abbreviations are used throughout for NMR spectroscopy:

ppm = parts per million

$J$ = coupling constant in Hz; $\delta$ = chemical shift values in ppm

s = singlet; br $s$ = broad singlet; $t$ = triplet; $q$ = quartet; $d$ = doublet; $dd$ = doublet of doublets; $m$ = multiplet; $qt$ = quintet
4.1 Preparation of 1-(2-aminophenyl)-3-aryl-2-propen-1-ones 104a-d

\[
\begin{align*}
\text{1-(2'-Aminophenyl)-3-aryl-2-propen-1-ones 104a-d}
\end{align*}
\]

4.1.1 Preparation of 1-(2'-aminophenyl)-3-phenyl-2-propen-1-one 104a (R = H)

A mixture of 2-aminoacetophenone 123 (6.00 g, 44.4 mmol), benzaldehyde 135a (4.71 g, 44.4 mmol) and sodium hydroxide (3 pellets, ca 0.6 g) in ethanol (30 mL) was stirred for 12 hours at room temperature. The mixture was quenched with ice cold water (120 mL) and the precipitate was filtered to afford 104a as orange solid (9.79 g, 99%); mp 62-64 °C (EtOH), (lit., 31 71-72 °C); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 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): \(\nu_{\text{max}}\) 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 104b (R = F)

A mixture of 2-aminoacetophenone 123 (6.00 g, 44.4 mmol), 4-fluorobenzaldehyde 135b (5.51 g, 44.4 mmol) and sodium hydroxide (3 pellets, ca 0.6 g) in ethanol (30 mL) was treated as described for 104a. Work-up afforded 104b as yellow solid (10.59 g, 99%); mp 108-110 °C (EtOH), (lit., 31 119-121 °C); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 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):
\[ \nu_{\text{max}} \] 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 104c (R = Cl)

A mixture of 2-aminoacetophenone 123 (6.00 g, 44.4 mmol), 4-chlorobenzaldehyde 135c (6.24 g, 44.4 mmol) and sodium hydroxide (3 pellets, \textit{ca} 0.6 g) in ethanol (30 mL) was treated as described for 104a. Work-up afforded 104c as yellow solid (11.33 g, 99%); mp 99-101 °C (EtOH), (lit., \textit{31} 82-84 °C); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 6.34 (2H, s, NH\(\text{2}\)), 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): \(\nu_{\text{max}}\) 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 104d (R = OCH\(_3\))

A mixture of 2-aminoacetophenone 123 (6.00 g, 44.4 mmol), 4-methoxybenzaldehyde 135d (6.05 g, 44.4 mmol) and sodium hydroxide (3 pellets, \textit{ca} 0.6 g) in ethanol (30 mL) was treated as described for 104a. Work-up afforded 104d as orange solid (11.10 g, 99%); mp 91-93 °C (EtOH), (lit., \textit{31} 90-93 °C); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 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): \(\nu_{\text{max}}\) 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-dihydroquinolin-4(1H)-ones 105a-d

![Chemical Structure](image)

2-Aryl-2,3-dihydroquinolin-4(1H)-ones 105a-d

4.2.1 Preparation of 2-phenyl-2,3-dihydroquinolin-4(1H)-one 105a (R = H)

A stirred mixture of 104a (9.79 g, 43.9 mmol), orthophosphoric acid (30 mL) and glacial acetic acid (30 mL) was heated under reflux for 2 hours. The mixture was allowed to cool to room temperature, quenched with ice-cold water and then extracted with chloroform (3×100 mL). The combined organic phases were washed with water (3×20 mL) and dried over anhydrous MgSO₄. The salt was filtered off and the solvent was evaporated under reduced pressure to afford 105a as yellow solid (8.81 g, 90%); mp 147-149 °C (EtOH), (lit., 68 148-150 °C); ¹H NMR (300 MHz, CDCl₃) 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): νₘₐₓ 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(1H)-one 105b (R = F)

A stirred mixture of 104b (10.59 g, 43.9 mmol), orthophosphoric acid (30 mL) and glacial acetic acid (30 mL) was treated as described for 105a. Work-up afforded 105b as yellow solid (9.39 g, 88%); mp 118-120 °C (EtOH), (lit., 31 116-118 °C); ¹H NMR (300 MHz, CDCl₃) 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): $\nu_{\text{max}}$ 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(1H)-one 105c (R = Cl)

A stirred mixture of 104c (11.33 g, 44.0 mmol), orthophosphoric acid (30 mL) and glacial acetic acid (30 mL) was treated as described for 105a. Work-up afforded 105c as yellow solid (10.42 g, 92%); mp 146-148 °C (EtOH), (lit.$^{67}$ 146 °C); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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): $\nu_{\text{max}}$ 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(1H)-one 105d (R = OCH$_3$)

A stirred mixture of 104d (11.10 g, 43.9 mmol), orthophosphoric acid (30 mL) and glacial acetic acid (30 mL) was treated as described for 105a. Work-up afforded 105d as yellow solid (9.99 g, 90%); mp 109-111 °C (EtOH), (lit.$^{67}$ 112-114 °C); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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): $\nu_{\text{max}}$ 3290, 1645, 1603, 1506, 1478, 1362, 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(1H)-ones 122a-d

2-Aryl-6,8-dibromo-2,3-dihydroquinolin-4(1H)-ones 122a-d

4.3.1 Preparation of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1H)-one 122a (R = H)

A mixture of 2-phenyl-2,3-dihydroquinolin-4(1H)-one 105a (5.00 g, 22.4 mmol) and N-bromosuccinimide (7.97 g, 44.8 mmol) in carbon tetrachloride: chloroform (3 : 2, v/v; 500 mL) in a round bottomed flask was stirred at room temperature for 3 h. Saturated sodium carbonate (100 mL) was added to the mixture with stirring. The aqueous phase was extracted with chloroform (3×100 mL) and the combined organic phases were washed with brine (2×30 mL), dried over anhydrous MgSO$_4$ and the salt was filtered off. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to afford 122a as light yellow solid (7.25 g, 85%); $R_f$ (toluene) 0.58; mp 137-138 °C (EtOH); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.80 (1H, ddd, $J$ 1.2, 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, $\text{-C}_6\text{H}_5$), 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$_3$) $\delta$: 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): $\nu_{\text{max}}$ 3375,
4.3.2 Preparation of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122b 
(R = F)

An experimental procedure employed for the synthesis of 122a was followed using a mixture of 
105b (5.00 g, 20.7 mmol) and N-bromosuccinimide (7.37 g, 41.4 mmol) in carbon tetrachloride-
chloroform (3 : 2, v/v; 500 mL); work-up and column chromatography on silica gel afforded 122b as light yellow solid (7.10 g, 86%); Rf (toluene) 0.58; mp 127-129 °C (EtOH); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ: 45.4 (C-3), 57.0 (C-2), 110.0 (C-6), 110.8 (C-8), 116.1 (d, 
²JC 21.6 Hz, C-3’ and C-5’), 120.7 (C-4a), 128.3 (d, ³JC 8.3 Hz, C-2’ and C-6’), 129.5 (C-5), 
129.8 (C-7), 135.8 (d, ⁴JC 3.2 Hz, C-1’), 147.1 (C-8a), 162.8 (d, ¹JC 246.5 Hz, C-4”), 190.9 (C-
4); IR (neat): ʋmax 3363, 1684, 1592, 1509, 1480, 1408, 1360, 1328, 1284, 1225, 1160, 1017, 
896, 856, 833, 749 cm⁻¹.

4.3.3 Preparation of 2-(4-chlorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122c 
(R = Cl)

An experimental procedure employed for the synthesis of 122a was followed using a mixture of 
105c (5.00 g, 19.4 mmol) and N-bromosuccinimide (6.91 g, 38.8 mmol) in carbon tetrachloride-
chloroform (3:2, v/v; 500 mL); work-up and column chromatography on silica gel afforded 122c
as light yellow solid (7.09 g, 88%); R\textsubscript{f} (toluene) 0.63; mp 145-146 °C (EtOH); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{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); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{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\textsubscript{max} 3375, 1672, 1592, 1483, 1396, 1334, 1280, 1164, 1089, 1018, 868, 824, 725, 675 cm\textsuperscript{-1}.

4.3.4 Preparation of 2-(4-methoxyphenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1\textsubscript{H})-one

122\textsubscript{d} (R = OCH\textsubscript{3})

An experimental procedure employed for the synthesis of 122\textsubscript{a} was followed using a mixture of 105\textsubscript{d} (5.00 g, 19.8 mmol) and N-bromosuccinimide (7.05 g, 39.6 mmol) in carbon tetrachloride-chloroform (3:2, v/v; 500 mL); work-up and column chromatography on silica gel afforded 122\textsubscript{d} as light yellow solid (6.75 g, 83%); R\textsubscript{f} (toluene) 0.40; mp 149-151 °C (EtOH); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{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\textsubscript{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); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ: 45.4 (C-3), 54.4 (OCH\textsubscript{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\textsubscript{max} 3317, 1661, 1596, 1503, 1414, 1348, 1283, 1246, 1203, 1180, 1149, 1026, 962, 880, 809, 787, 737, 704 cm\textsuperscript{-1}.
4.4 Preparation of 2-aryl-6,8-dibromoquinolin-4(1H)-ones 136a-d

![Chemical structure](image)

2-Aryl-6,8-dibromoquinolin-4(1H)-ones 136a-d

4.4.1 Preparation of 6,8-dibromo-2-phenylquinolin-4(1H)-one 136a (R = H)

A stirred mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1H)-one 122a (1.0 g, 2.6 mmol) and thallium(III) para tolylsulphonate (TTS) (2.87 g, 3.9 mmol) in 1,2-dimethoxyethane (DME) (30 mL) was heated at 100 °C for 30 minutes. The solvent was evaporated from the cooled reaction mixture under reduced pressure; mixed with cold water (50 mL) and the product was extracted into CHCl₃ (3x100 mL). The combined organic layers were washed with saturated Na₂CO₃ solution (2x15 mL); dried over anhydrous MgSO₄ and the salt was filtered off. The organic layer was concentrated under reduced pressure and the crude product was recrystallized in ethanol/ethyl acetate to afford 136a as light yellow solid, (0.86 g, 86%); mp 212-214 °C; ¹H NMR (300 MHz, DMSO-d₆) δ: 7.47 (1H, s, 3-H), 7.57-7.59 (5H, m, Ph-H), 8.19 (1H, s, 7-H), 8.27 (1H, s, 5-H), 12.10 (1H, br s, N-H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 103.0 (C-3), 117.3 (C-6), 122.5 (C-8), 124.7 (C-4a), 127.6 (C-4'), 128.8 (C-2' & 6'), 129.3 (C-3' & 5'), 130.4 (C-1'), 136.1 (C-5), 138.7 (C-7), 145.0 (C-2), 158.4 (C-8a), 161.7 (C-4); IR (neat) ν_max 3386, 3072, 1618, 1574, 1537, 1492, 1456, 1383, 1348, 1222, 920, 869, 769, 734, 692, 683 cm⁻¹.
4.4.2 Preparation of 2-(4-fluorophenyl)-6,8-dibromoquinolin-4(1H)-one 136b (R = F)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122b (1.0 g, 2.5 mmol) and thallium(III) para tolylsulphonate (TTS) (2.74 g, 3.8 mmol) in 1,2-dimethoxyethane (DME) (30 mL) was heated at 100 °C for 30 minutes; work up described for 136a afforded 136b as light yellow solid, (0.80 g, 80%); mp 222-224 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ: 7.27 (1H, s, 3-H), 7.36 (2H, d, $J$ 7.5 Hz, 3' & 5'-H), 7.55 (2H, d, $J$ 7.5 Hz, 2' & 6'-H), 8.21 (1H, s, 7-H), 8.28 (1H, s, 5-H), 12.05 (1H, s, N-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ: 102.8 (C-3), 116.2 (d, $^2$J$_{CF}$ 21.2 Hz, C-3' & 5'), 117.5 (C-6), 122.4 (C-8), 126.0 (C-4a), 129.8 (d, $^3$J$_{CF}$ 8.0 Hz, C-2' & 6'), 130.8 (d, $^4$J$_{CF}$ 3.2 Hz, C-1'), 135.2 (C-5), 136.1 (C-7), 144.9 (C-2), 157.4 (C-8a), 162.3 (d, $^1$J$_{CF}$ 245.4 Hz, C-4'), 165.1 (C-4); IR (neat) $\nu_{max}$ 3383, 3064, 1620, 1585, 1540, 1507, 1490, 1447, 1386, 1348, 1223, 1162, 869, 832, 718, 680 cm$^{-1}$.

4.4.3 Preparation of 2-(4-chlorophenyl)-6,8-dibromoquinolin-4(1H)-one 136c (R = Cl)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122c (1.0 g, 2.4 mmol) and thallium(III) para tolylsulphonate (TTS) (2.63 g, 3.6 mmol) in 1,2-dimethoxyethane (DME) (30 mL) was heated at 100 °C for 30 minutes; work up described for 136a afforded 136c as light yellow solid, (0.88 g, 88%); mp 233-235 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ: 7.36 (1H, s, 3-H), 7.47 (2H, d, $J$ 7.5 Hz, 3' & 5'-H), 7.70 (2H, d, $J$ 7.5 Hz, 2' & 6'-H), 8.20 (1H, s, 7-H), 8.28 (1H, s, 5-H), 11.65 (1H, s, N-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ: 103.0 (C-3), 117.6 (C-6), 122.8 (C-8), 124.8 (C-4a), 126.2 (C-4'), 129.3 (C-2' & 6'), 129.3 (C-3' & 5'), 135.3 (C-1'), 136.2 (C-5), 137.3 (C-7), 145.0 (C-2), 156.9 (C-8a), 160.5 (C-4); IR (neat) $\nu_{max}$ 3383, 3090, 1617, 1589, 1565, 1542, 1491, 1447, 1384, 1328, 1222, 1124, 1093, 1066, 1014, 938, 924, 871, 825, 749, 689 cm$^{-1}$. 
4.4.4 Preparation of 2-(4-methoxyphenyl)-6,8-dibromoquinolin-4(1H)-one 136d (R = OCH₃)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122d (1.0 g, 2.4 mmol) and thallium(III) para tolylsulphonate (TTS) (2.63 g, 3.6 mmol) in 1,2-dimethoxyethane (DME) (30 mL) was heated at 100 °C for 30 minutes; work up described for 136a afforded 136d as light yellow solid, (0.82 g, 82%); mp 190-192 °C; ¹H NMR (300 MHz, DMSO-d₆) δ: 3.84 (3H, s, OCH₃), 6.99 (1H, s, 3-H), 7.06 (2H, d, J 7.5 Hz, 3’ & 5’-H), 7.12 (2H, d, J 7.5 Hz, 2’ & 6’-H), 8.11 (1H, s, 7-H), 8.24 (1H, s, 5-H), 12.01 (1H, s, N-H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 55.8 (OCH₃), 79.6 (C-3), 102.3 (C-6), 114.7 (C-3’ & 5’), 116.9 (C-8), 122.3 (C-4a), 124.6 (C-2’ & 6’), 125.8 (C-1’), 129.1 (C-5), 131.1 (C-7), 135.9 (C-2), 145.0 (C-8a), 158.2 (C-4’), 161.4 (C-4); IR (neat) ν_max 3210, 3059, 3013, 2931, 2840, 1631, 1606, 1565, 1552, 1510, 1488, 1417, 1376, 1302, 1267, 1243, 1186, 1116, 1028, 864, 830, 795, 736, 722, 680 cm⁻¹.

4.5 Preparation of 2-aryl-8-alkynyl-6-bromo-2,3-dihydroquinolin-4(1H)-ones 137a-h

![Chemical Structure](image)
4.5.1 Preparation of 6-bromo-2-phenyl-8-(2-phenylethynyl)-2,3-dihydroquinolin-4(1H)-one 137a (R = H; R' = -C₆H₅)

A mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1H)-one 122a (0.50 g, 1.3 mmol) 10% Pd/C (0.015 g, 0.01 mmol), PPh₃ (0.013 g, 0.05 mmol) and CuI (0.02 g, 0.13 mmol) in EtOH/NEt₃ (2:1; v/v) (30 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 45 minutes. Phenyl acetylene (0.2 mL, 1.9 mmol) was added via a syringe and the mixture was heated under reflux for 18 hours under nitrogen atmosphere. The cooled reaction mixture was evaporated to dryness and the product dissolved in CHCl₃ (150 mL). The organic solvent was washed with brine (2 x 15 mL), dried over anhydrous MgSO₄ and the salt was filtered off. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel to afford the product 137a as yellow solid, (0.37 g, 71%); mp 153–155 °C; Rₜ (toluene) 0.28; ¹H NMR (300 MHz, CDCl₃) δ: 2.82 (1H, d, J 10.7 Hz, 3-H), 2.94 (1H, dd, J 12.2, 15.1 Hz, 3-H), 4.83 (1H, dd, J 4.5, 6.0 Hz, 2-H), 5.37 (1H, s, NH), 7.29–7.48 (10H, m, Ph', Ph''-H), 7.66 (1H, d, J 3.0 Hz, 7-H), 7.96 (1H, d, J 3.0 Hz, 5-H); ¹³C NMR (75 MHz, CDCl₃) δ: 45.8 (C-3), 57.6 (C-2), 82.7 (C≡α), 97.5 (C≡β), 109.5 (C-8), 111.7 (C-6), 119.7 (C-4α), 122.0 (C-2' & 6'), 126.3 (C-2'' & 6''), 128.5 (C-1''), 128.6 (C-4''), 129.1 (C-3' & 5'), 129.2 (C-3'' & 5''), 130.3 (C-5), 131.6 (C-4'), 139.9 (C-7), 140.4 (C-1'), 150.3 (C-8α), 191.6 (C-4); IR (neat) νmax 3364, 3066, 2971, 1890, 1684, 1591, 1509, 1480, 1328, 1284, 1226, 1161, 865, 857, 713 cm⁻¹; m/z (100, MH⁺) 402; HRMS (EI): MH⁺, found 402.0484. For [C₂₃H₁₇NO₇⁹Br]⁺, requires 402.0494.
4.5.2 Preparation of 2-(4-fluorophenyl)-6-bromo-8-(2-phenylethynyl)-2,3-dihydroquinolin-4(1H)-one 137b (R = F; R' = -C₆H₅)

A stirred mixture of 122b (0.50 g, 1.2 mmol), 10% Pd/C (0.014 g, 0.01 mmol), PPh₃ (0.013 g, 0.04 mmol), CuI (0.02 g, 0.1 mmol) in EtOH/NEt₃ (30 mL) and Phenyl acetylene (0.2 mL, 1.8 mmol) was treated as described for 137a; work up and column chromatography on silica gel afforded 137b as yellow solid, (0.33 g, 74%); mp 151-152 °C; Rf (toluene) 0.33; ¹H NMR (300 MHz, CDCl₃) δ: 2.79 (1H, d, J 10.8 Hz, 3'-H), 2.90 (1H, dd, J 12.0, 15.2 Hz, 3''-H), 4.81 (1H, dd, J 5.1, 6.0 Hz, 2'-H), 5.32 (1H, s, NH), 7.11 (2H, t, J 8.4 Hz, 3' & 5'-H), 7.34 (3H, dd, J 2.1, 3.0 Hz, 3'', 4'' & 5''-H), 7.45 (4H, dd, J 2.1, 3.0 Hz, 2'', 6' & 6''), 7.66 (1H, d, J 2.4 Hz, 7-H), 7.95 (1H, d, J 2.4 Hz, 5-H); ¹³C NMR (75 MHz, CDCl₃) δ: 45.9 (C-3), 57.0 (C-2), 82.6 (C≡α), 97.5 (C≡β), 109.7 (C-8), 111.7 (C-6), 116.1 (d, 3JC 21.6 Hz, C-3' & 5'), 119.7 (C-4a), 121.9 (C-2'' & 6''), 128.2 (d, 2JC 8.3 Hz, C-2' & 6'), 128.5 (C-1''), 129.1 (C-4''), 130.3 (C-3'' & 5''), 131.5 (C-5), 136.1 (d, 1JC 3.4 Hz, C-1'), 140.0 (C-7), 150.1 (C-8a), 162.7 (d, 4JC 246.2 Hz, C-4'), 191.3 (C-4); IR (neat) νmax νmax (neat)3373, 3071, 3028, 2821, 1947, 1497, 1583, 1583, 1497, 1477, 1325, 1234, 1156, 881, 837, 754, 747, 672 cm⁻¹; m/z (100, MH⁺) 420; HRMS (EI): MH⁺, found 420.0391. For [C₂₃H₁₆NOF⁷⁹Br]⁺, requires 420.0484.

4.5.3 Preparation of 2-(4-chlorophenyl)-6-bromo-8-(2-phenylethynyl)-2,3-dihydroquinolin-4(1H)-one 137c (R = Cl; R' = -C₆H₅)

A stirred mixture of 122c (0.50 g, 1.2 mmol), 10% Pd/C (0.014 g, 0.01 mmol), PPh₃ (0.013 g, 0.04 mmol), CuI (0.02 g, 0.1 mmol) in EtOH/NEt₃ (30 mL) and Phenyl acetylene (0.2 mL, 1.8 mmol) was treated as described for 137a; work up and column chromatography on silica gel afforded 137c as yellow solid, (0.38 g, 73%); mp 155-156 °C; Rf (toluene) 0.38; ¹H NMR (300
MHz, CDCl$_3$ $\delta$: 2.66 (1H, d, J 10.8 Hz, 3-H), 2.74 (1H, dd, J 12.2, 15.5 Hz, 3-H), 4.65 (1H, dd, J 3.3, 6.9 Hz, 2-H), 5.17 (1H, s, NH), 7.17-7.30 (9H, m, 2', 3', 5', 6' & Ph''-H), 7.52 (1H, d, J 2.4 Hz, 7-H), 7.80 (1H, d, J 2.4 Hz, 5-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 45.7 (C-3), 57.1 (C-2), 82.5 ((C≡$\alpha$), 97.5 (C≡$\beta$), 109.7 (C-8), 111.8 (C-6), 119.7 (C-4a), 121.9 (C-2' & 6'), 127.7 (C-2'' & 6''), 128.1 (C-1''), 128.5 (C-4''), 129.1 (C-3' & 5'), 129.4 (C-3'' & 5''), 130.3 (C-5), 131.6 (C-4'), 138.8 (C-7), 140.0 (C-1'), 150.1 (C-8a), 191.6 (C-4); IR (neat) $\nu_{\text{max}}$ 3357, 3074, 3052, 2838, 1960, 1680, 1584, 1477, 1331, 1273, 1088, 891, 822, 751, 684 cm$^{-1}$; m/z (100, MH$^+$) 436; HRMS (EI): MH$^+$, found 436.0107. For [C$_{23}$H$_{16}$NOF$_{79}$Br]$^+$, requires 436.0104.

4.5.4 Preparation of 2-(4-methoxyphenyl)-6-bromo-8-(2-phenylethynyl)-2,3-dihydroquinolin-4(1H)-one 137d (R = OCH$_3$; R' = -C$_6$H$_5$)

A stirred mixture of 122d (0.30 g, 0.7 mmol), 10% Pd/C (0.01 g, 0.007 mmol), PPh$_3$ (0.009 g, 0.02 mmol), CuI (0.013 g, 0.07 mmol) in EtOH/NEt$_3$ (20 mL) and phenylacetylene (0.12 mL, 1.0 mmol) was treated as described for 137a; work up and column chromatography on silica gel afforded 137d as yellow solid, (0.18 g, 78%); mp 133-134 $^\circ$C; $R_f$ (toluene) 0.18; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.76 (1H, d, J 10.5 Hz, 3-H), 2.91 (1H, dd, J 11.8, 15.0 Hz, 3-H), 3.82 (3H, s, OCH$_3$), 4.77 (1H, dd, J 4.5, 7.8 Hz, 2-H), 5.31 (1H, s, NH), 6.94 (2H, d, J 9.3 Hz, 3' & 5'-H), 7.32-7.44 (7H, m, 2', 6' & Ph''-H), 7.65 (1H, d, J 3.0 Hz, 7-H), 7.95 (1H, d, J 3.0 Hz, 5-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 45.9 (C-3), 55.3 (OCH$_3$), 57.1 (C-2), 82.7 ((C≡$\alpha$), 97.4 (C≡$\beta$), 109.4 (C-8), 111.6 (C-6), 114.5 (C-4a), 119.6 (C-2' & 6''), 122.0 (C-2'' & 6''), 127.6 (C-1''), 128.5 (C-3' & 5'), 129.0 (C-3'' & 5''), 130.3 (C-5), 131.6 (C-4''), 132.3 (C-7), 140.0 (C-1'), 150.3 (C-8a), 159.7 (C-4'), 191.6 (C-4); IR (neat) $\nu_{\text{max}}$ 3617, 3359, 3061, 2964, 2932, 2907, 2840, 2192, 1675, 1582, 1492, 1482, 1235, 830, 749, 690 cm$^{-1}$; m/z (100, MH$^+$) 432; HRMS (EI): MH$^+$, found 432.0599. For [C$_{24}$H$_{19}$NO$_2$$_{79}$Br]$^+$, requires 432.0584.
4.5.5 Preparation of 6-bromo-2-phenyl-8-(4-hydroxybut-1-yn-1-yl)-2,3-dihydroquinolin-4(1H)-one 137e (R = H; R' = -CH₂CH₂OH)

A stirred mixture of 122a (0.51 g, 1.3 mmol) 10% Pd/C (0.015 g, 0.01 mmol), PPh₃ (0.013 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) in EtOH/NEt₃ (2:1; v/v) (30 mL) and 3-butyne-1-ol (0.2 mL, 2.0 mmol) was treated as described for 137a; work up and column chromatography on silica gel afforded 137e as yellow solid, (0.38 g, 77%); mp 129-130 °C; R_f (40% ethyl acetate/toluene) 0.38; Same preparation as above. ¹H NMR (300 MHz, CDCl₃) δ: 1.89 (1H, t, J 5.4 Hz, OH), 2.66 (2H, t, J 6.3 Hz, CH₂CH₂OH), 2.76-2.89 (2H, m, 3-H), 3.76 (2H, dd, J 6.0, 6.3 Hz, CH₂OH), 4.76 (1H, dd, J 4.5, 7.8 Hz, 2-H), 5.48 (1H, s, NH), 7.35-7.46 (5H, m, Ph-H), 7.53 (1H, s, 7-H), 7.90 (1H, s, 5-H); ¹³C NMR (75 MHz, CDCl₃) δ: 23.7 (C₂H₂CH₂OH), 45.7 (C-3), 57.5 (CH₂OH), 60.8 (C-2), 95.7 (C=α), 95.7 (C=β), 109.1 (C-8), 112.0 (C-6), 119.3 (C-4a), 126.4 (C-2′ & 6′), 128.5 (C-3′ & 5′), 129.1 (C-4′), 129.7 (C-5), 139.7 (C-7), 140.4 (C-1′), 150.7 (C-8a), 191.8 (C-4); IR (neat) ν_max 3388, 3081, 2976, 2951, 2905, 2869, 2228, 1677, 1589, 1579, 1492, 1320, 1056, 882, 764, 699 cm⁻¹; m/z (100, MH⁺) 370; HRMS (EI): MH⁺, found 370.0443. For [C₁₉H₁₇NO₂⁺]⁷⁹Br⁺, requires 370.0444.

4.5.6 Preparation of 6-bromo-2-(4-fluorophenyl)-8-(4-hydroxybut-1-yn-1-yl)-2,3-dihydroquinolin-4(1H)-one 137f (R = F; R' = -CH₂CH₂OH)

A stirred mixture of 122b (0.52 g, 1.3 mmol), 10% Pd/C (0.015 g, 0.01 mmol), PPh₃ (0.013 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) in EtOH/NEt₃ (30 mL) and 3-butyne-1-ol (0.2 mL, 2.0 mmol) was treated as described for 137a; work up and column chromatography on silica gel afforded 137f as yellow solid (0.38 g, 75%), mp 131-132 °C; R_f (40% ethyl acetate/toluene) 0.45. ¹H NMR (300 MHz, CDCl₃) δ: 1.60 (1H, t, J 5.4 Hz, OH), 2.68 (2H, t, J 6.3 Hz, CH₂CH₂OH), 2.76-
2.89 (2H, m, 3-H), 3.77 (2H, dd, J 4.5, 6.3 Hz, CH$_2$OH), 4.75 (1H, dd, J 6.0, 6.3 Hz, 2-H), 5.44 (1H, s, NH), 7.08 (2H, t, J 8.6 Hz, 3' & 5'-H), 7.42 (2H, dd, J 3.6, 5.4 Hz, 2' & 6'-H), 7.53 (1H, d, J 2.4 Hz, 7-H), 7.90 (1H, d, J 2.4 Hz, 5-H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 23.7 (CH$_2$CH$_2$OH), 45.7 (C-3), 56.9 (CH$_2$OH), 60.8 (C-2), 95.7 ((C≡α), 95.8 (C≡β), 109.3 (C-8), 112.0 (C-6), 115.9 (d, $^3$J$_{CF}$ 21.4 Hz, C-3' & 5'), 119.4 (C-4a), 128.3 (d, $^2$J$_{CF}$ 8.0 Hz, C-2' & 6'), 129.8 (C-5), 136.2 (d, $^1$J$_{CF}$ 3.2 Hz, C-7), 139.7 (C-6), 162.6 (d, $^4$J$_{CF}$ 245.9 Hz, C-4'), 191.5 (C-4); IR (neat) $\nu_{max}$ 3369, 3067, 2969, 2880, 2821, 2224, 1642, 1588, 1576, 1489, 1321, 1230, 1157, 1052, 886, 835, 731 cm$^{-1}$; m/z (100, MH$^+$) 388; HRMS (EI): MH$^+$, found 388.0348. For [C$_{19}$H$_{16}$NO$_2$F$_7$Br$^+$], requires 388.0338.

4.5.7 Preparation of 6-bromo-2-(4-chlorophenyl)-8-(4-hydroxybut-1-yn-1-yl)-2,3-dihydroquinoline-4(1H)-one 137g (R = Cl; R' = -CH$_2$CH$_2$OH)

A stirred mixture of 122c (0.4 g, 0.9 mmol), 10% Pd/C (0.011 g, 0.009 mmol), PPh$_3$ (0.009 g, 0.03 mmol), CuI (0.018 g, 0.09 mmol) and 3-buten-1-ol (0.14 mL, 1.4 mmol) in EtOH/NEt$_3$ (30 mL), was treated as described for 137c; work up and column chromatography on silica gel afforded 137g as yellow solid, (0.30 g, 77%); mp 151-152 °C; R$_f$ (40% ethyl acetate/toluene) 0.46; $^1$H NMR (300 MHz, CDCl$_3$) δ: 1.56 (1H, t, J 5.4 Hz, OH), 2.69 (2H, t, J 6.3 Hz, CH$_2$CH$_2$OH), 2.76-2.89 (2H, m, 3-H), 3.78 (2H, dd, J 4.5, 6.3 Hz, CH$_2$OH), 4.75 (1H, dd, J 6.0, 6.3 Hz, 2-H), 5.44 (1H, s, NH), 7.39 (4H, s, 2', 3', 5' & 6'-H), 7.54 (1H, d, J 2.4 Hz, 7-H), 7.90 (1H, d, J 2.4 Hz, 5-H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 23.7 (CH$_2$CH$_2$OH), 45.6 (C-3), 57.0 (CH$_2$OH), 60.8 (C-2), 95.7 ((C≡α), 95.9 (C≡β), 109.4 (C-8), 112.0 (C-6), 119.4 (C-4a), 127.9 (C-2' & 6'), 129.3 (C-3' & 5'), 129.8 (C-4'), 134.3 (C-5), 138.9 (C-7), 139.8 (C-1'), 150.5 (C-8a), 191.4 (C-4); IR (neat) $\nu_{max}$ 3360, 3070, 2955, 2884, 2818, 2222, 1643, 1587, 1574, 1485, 1320,
1230, 1199, 1048, 1013, 885, 817, 692 cm\(^{-1}\); \(m/z\) (100, MH\(^+\)) 404; HRMS (EI): MH\(^+\), found 404.0039. For [C\(_{19}\)H\(_{16}\)NO\(_2\)Cl\(^{79}\)Br]\(^+\), requires 404.0053.

4.5.8 Preparation of 6-bromo-2-(4-methoxyphenyl)-8-(4-hydroxybut-1-yn-1-yl)-2,3-dihydroquinolin-4(1H)-one 137h (R = OCH\(_3\); R' = -CH\(_2\)CH\(_2\)OH)

A stirred mixture of **122d** (0.50 g, 1.2 mmol), 10% Pd/C (0.014 g, 0.01 mmol), PPh\(_3\) (0.012 g, 0.04 mmol), CuI (0.023 g, 0.1 mmol) and 3-butyn-1-ol (0.18 mL, 1.8 mmol) in EtOH/NE\(_3\) (30 mL), was treated as described for **137a**; work up and column chromatography on silica gel afforded **137h** as yellow solid (0.36 g, 74%); mp 108-110 °C; \(R_f\) (40% ethyl acetate/toluene) 0.35; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.57 (1H, t, \(J\ 5.4\ Hz\), OH), 2.67 (2H, t, \(J\ 6.3\ Hz\), CH\(_2\)CH\(_2\)OH), 2.72-2.91 (2H, m, 3-H), 3.76 (2H, dd, \(J\ 6.0\), 6.3 Hz, CH\(_2\)OH), 3.82 (3H, s, OCH\(_3\)), 4.71 (1H, dd, \(J\ 4.5\), 9.3 Hz, 2-H), 5.41 (1H, s, NH), 6.93 (2H, d, \(J\ 9.0\ Hz\), 3' & 5'-H), 7.37 (2H, d, \(J\ 9.0\ Hz\), 2' & 6'-H), 7.51 (1H, d, \(J\ 2.4\ Hz\), 7-H), 7.90 (1H, d, \(J\ 2.4\ Hz\), 5'-H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 23.7 (CH\(_2\)CH\(_2\)OH), 45.8 (C-3), 55.3 (OCH\(_3\)), 57.1 (CH\(_2\)OH), 60.8 (C-2), 95.7 \((\text{C=\(\alpha\)})\), 95.8 (C=\(\beta\)), 109.1 (C-8), 111.9 (C-6), 114.3 (C-4a), 119.4 (C-2' & 6'), 127.8 (C-3' & 5'), 129.8 (C-5), 132.3 (C-7), 139.7 (C-1'), 150.8 (C-8a), 159.7 (C-4'), 192.0 (C-4); IR (neat) \(\nu\)\(_{\text{max}}\) 3351, 3047, 2956, 2922, 2854, 2841, 2219, 1646, 1587, 1572, 1490, 1319, 1251, 1231, 1171, 1049, 1037, 891, 830, 730 cm\(^{-1}\); \(m/z\) (100, MH\(^+\)) 400; HRMS (EI): MH\(^+\), found 400.0545. For [C\(_{20}\)H\(_{19}\)NO\(_3\)\(^{79}\)Br]\(^+\), requires 400.0548.
4.6 Preparation of 2-aryl-6,8-dialkynylated 2,3-dihydroquinolin-4(1H)-ones 138a-h

2-Aryl-6,8-dialkynylated-2,3-dihydroquinolin-4(1H)-ones 138a-h

4.6.1 Preparation of 6,8-bis(2-phenylethynyl)-2-phenyl-2,3-dihydroquinolin-4(1H)-ones

138a (R = H; R'' = -C₆H₅)

A stirred mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1H)-one 122a (0.50 g, 1.3 mmol), PdCl₂(PPh₃)₂ (0.045 g, 0.06 mmol) and CuI (0.12 g, 0.6 mmol) in EtOH/Et₃N (30 mL; 2:1; v/v) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 45 minutes. Phenyl acetylene (0.43 mL, 3.9 mmol) was added to the flask via a syringe and the mixture was heated under reflux for 6 hours under nitrogen atmosphere. The solvent was evaporated from the cooled reaction mixture, the product was dissolved in CHCl₃ (200 mL) and washed with brine (2x20 mL). The organic layer was dried over anhydrous magnesium sulphate, the salt was filtered off and the solvent concentrated. The crude product was purified by column chromatography on a silica gel column to afford 138a as yellow solid (0.42 g, 76%); mp 139-141 °C; R₇ (toluene) 0.42; ¹H NMR (300 MHz, CDCl₃) δ: 2.85 (1H, d, J 10.8 Hz, 3-H), 2.96 (1H, dd, J 12.2, 16.6 Hz, 3-H), 4.88 (1H, dd, J 4.5, 7.8 Hz, 2-H), 5.53 (1H, s, NH), 7.33-7.49 (15H, m, Ph', Ph" & Ph"'-H), 7.74 (1H, s, 7-H), 8.04 (1H, s, 5-H); ¹³C NMR (75 MHz, CDCl₃) δ: 46.0 (C-3), 57.6 (C-2), 83.2 (C=α'), 88.2 (C=α''), 88.3 (C=β'), 96.7 (C=β''), 109.9 (C-8), 112.5 (C-6), 118.4 (C-4a), 122.2 (C-2' & 6'), 123.3 (C-2'' & 6''), 126.3 (C-2''' & 6''''), 128.1 (C-3' & 5'), 128.3 (C-3'' & 5''), 128.9 (C-3''' & 5'''), 129.2 (C-1'), 131.3 (C-1''
& 1''), 131.4 (C-4'), 131.6 (C-4'' & 4'''), 138.8 (C-5), 140.5 (C-7), 150.6 (C-8a) 192.0 (C-4); IR (neat) \( \nu_{\text{max}} \) 3401, 2206, 1671, 1606, 1592, 1569, 1513, 1489, 1244, 1211, 893, 753, 688 cm\(^{-1}\); \( m/z \) (100, MH\(^+\)) 424; HRMS (EI): MH\(^+\), found 424.1696. For [C\(_{31}\)H\(_{22}\)NO\(_{2}\)]\(^+\), requires 424.1701.

### 4.6.2 Preparation of 2-(4-fluorophenyl)-6,8-bis(2-phenylethynyl)-2,3-dihydroquinolin-4(1H)-one 138b (R = F; R'' = -C\(_6\)H\(_5\))

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122b (0.50 g, 1.2 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.044 g, 0.06 mmol) and CuI (0.12 g, 0.6 mmol) in EtOH/Et\(_3\)N (30 mL; 2:1) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was degassed with nitrogen gas for 45 minutes. Phenyl acetylene (0.41 mL, 3.8 mmol) was added via a syringe and was treated as described for 138a; work up and column chromatography on silica gel afforded 138b as yellow solid (0.43 g, 78%); mp 136-138 °C; \( R_f \) (toluene) 0.48; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 2.82 (1H, d, \( J \) 10.8 Hz), 2.93 (1H, dd, \( J \) 12.4, 16.8 Hz, 3-H), 4.87 (1H, dd, \( J \) 4.5, 7.5 Hz, 2-H), 5.47 (1H, s, NH), 7.11 (2H, t, \( J \) 9.3 Hz, 3' & 5'-H), 7.34 (5H, s, Ph-H), 7.44 (5H, s, Ph-H), 7.48 (2H, dd, \( J \) 4.5, 9.3 Hz, 2' & 6'-H), 7.74 (1H, s, 7-H), 8.03 (1H, s, 5-H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \): 46.0 (C-3), 56.9 (C-2), 83.1 (C≡\( \alpha \)), 88.2 (C≡\( \alpha'' \)), 88.4 (C≡\( \beta \)), 96.8 (C≡\( \beta'' \)), 109.9 (C-8), 112.6 (C-6), 116.1 (d, \( J_{CF} \) 21.4 Hz, C-3' & 5'), 118.3 (C-4a), 122.1 (C-2'' & 6''), 123.3 (C-2''' & 6''''), 128.1 (d, \( J_{CF} \) 8.0 Hz, C-2' & 6'), 128.3 (C-3'' & 5''), 128.5 (C-3''' & 5'''), 128.9 (C-1''), 129.1 (C-1''), 130.2 (C-4''), 131.2 (C-4'''), 136.2 (d, \( J_{CF} \) 3.2 Hz, C-1'), 139.9 (C-5), 140.5 (C-7), 150.6 (C-8a), 162.6 (d, \( J_{CF} \) 247.5 Hz, C-4'), 191.6 (C-4); IR (neat) \( \nu_{\text{max}} \) 3366, 2215, 1678, 1592, 1499, 1224, 834, 751, 687 cm\(^{-1}\); \( m/z \) (100, MH\(^+\)) 442; HRMS (EI): MH\(^+\), found 442.1599. For [C\(_{31}\)H\(_{22}\)NO\(_{2}\)]\(^+\), requires 442.1607.
4.6.3 Preparation of 2-(4-chlorophenyl)-6,8-bis(2-phenylethynyl)-2,3-dihydroquinolin-4(1H)-one 138c (R = Cl; R'' = -C₆H₅)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122c (0.50 g, 1.2 mmol), PdCl₂(PPh₃)₂ (0.042 g, 0.06 mmol) and CuI (0.12 g, 0.6 mmol) in EtOH/Et₃N (30 mL; 2:1) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 45 minutes. Phenyl acetylene (0.40 mL, 3.6 mmol) was added via a syringe and was treated as described for 138a; work up and column chromatography on silica gel afforded 138c as yellow solid (0.42 g, 76%); mp 143-144 °C; R_f (toluene) 0.50; ¹H NMR (300 MHz, CDCl₃) δ: 2.82 (1H, d, J 10.8 Hz, 3'-H), 2.94 (1H, dd, J 12.3, 16.9 Hz, 3'-H), 4.86 (1H, dd, J 4.5, 6.0 Hz, 2'-H), 5.47 (1H, s, NH), 7.33-7.75 (14H, m, 2', 3',5', 6', Ph'' & Ph'''-H), 7.75 (1H, s, 7'-H), 8.03 (1H, s, 5'-H); ¹³C NMR (75 MHz, CDCl₃) δ:46.0 (C-3), 57.0 (C-2), 83.1 (C≡α'), 88.1 (C≡α''), 88.4 (C≡β'), 96.9 (C≡β''), 110.0 (C-8), 112.8 (C-6), 118.4 (C-4a), 122.1 (C-2' & 6'), 123.3 (C-2'' & 6''), 127.8 (C-2''' & 6''''), 128.1 (C-3' & 5'), 128.4 (C-3'' & 5''), 128.5 (C-3''' & 5'''), 129.0 (C-1'), 129.4(C-1''), 131.2 (C-1'''), 131.5 (C-1''), 131.6 (C-4'), 134.4 (C-4'''), 138.9 (C-5), 140.5 (C-7), 150.6 (C-8a) 191.5 (C-4); IR (neat) ν_max 3379, 2206, 1681, 1591, 1504, 1488, 1237, 1087, 1011, 890, 825, 763, 752, 690 cm⁻¹; m/z (100, MH⁺) 458; HRMS (EI): MH⁺, found 458.1292. For [C₃₁H₂₂NOCl]+, requires 458.1312.

4.6.4 Preparation of 2-(4-methoxyphenyl)-6,8-bis(2-phenylethynyl)-2,3-dihydroquinolin-4(1H)-one 138d (R = OCH₃; R'' = -C₆H₅)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122d (0.40 g, 1.0 mmol), PdCl₂(PPh₃)₂ (0.034 g, 0.05 mmol) and CuI (0.10 g, 0.5 mmol) in EtOH/Et₃N (30 mL; 2:1) in a three-necked round bottom flask equipped with a stirrer, condenser
and rubber septum was purged with nitrogen gas for 45 minutes. Phenyl acetylene (0.32 mL, 2.9 mmol) was added via a syringe and treated as described for 138a; work up and column chromatography on silica gel afforded 138d as yellow solid (0.30 g, 68%); mp 142-144 °C; $R_f$ (toluene) 0.14; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.77 (1H, d, $J$ 10.8 Hz, 3-H), 2.95 (1H, dd, $J$ 12.2, 16.7 Hz, 3-H), 3.82 (3H, s, OCH$_3$), 4.83 (1H, dd, $J$ 4.2, 8.4 Hz, 2-H), 5.47 (1H, s, NH), 6.95 (2H, d, $J$ 9.0 Hz, 3' & 5'-H), 7.33 (2H, dd, $J$ 2.1, 4.2 Hz, 2' & 6'-H), 7.38-7.51 (10H, m, Ph'' & Ph'''-H), 7.73 (1H, d, $J$ 1.5 Hz, 7-H), 8.04 (1H, d, $J$ 1.5 Hz, 5-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 44.1 (C-3), 55.4 (OCH$_3$), 57.0 (C-2), 83.1 (C=α'), 88.1 (C=α''), 88.4 (C=β'), 96.6 (C=β''), 110.0 (C-8), 112.4 (C-6), 114.5 (C-4a), 122.1 (C-2' & 6'), 123.3 (C-2'' & 6''), 127.8 (C-2''' & 6'''), 128.1 (C-3' & 5'), 128.4 (C-3'' & 5''), 128.5 (C-3''' & 5'''), 129.0 (C-1'), 129.4 (C-1''), 131.2 (C-1'''), 131.6 (C-4''), 134.4 (C-4''), 138.9 (C-5), 140.5 (C-7), 150.6 (C-8a), 159.7 (C-4'), 191.5 (C-4); IR (neat) $\nu_{\text{max}}$ 3378, 3054, 2956, 2932, 2834, 2208, 1677, 1605, 1592, 1569, 1548; m/z (100, MH$^+$) 454; HRMS (EI): MH$^+$, found 454.1809. For [C$_{32}$H$_{24}$NO$_2$]$^+$, requires 454.1807.

4.6.5 Preparation of 6,8-bis(4-hydroxybut-1-yn-1-yl)-2-phenyl-2,3-dihydroquinolin-4(1H)-one 138e (R = H; R' = -CH$_2$CH$_2$OH)

A stirred mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1H)-one 122a (0.50 g, 1.3 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.045 g, 0.06 mmol) and CuI (0.12 g, 0.6 mmol) in EtOH/Et$_3$N (30 mL; 2:1) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 45 minutes. 3-Butyn-1-ol (0.43 mL, 3.9 mmol) was added via a syringe and was treated as described for 138a; work up and column chromatography afforded 138e as yellow solid (0.33 g, 70%); mp 127-129 °C; $R_f$ (40% ethyl acetate/toluene) 0.16; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 1.95 (2H, br s, OH), 2.66-2.71 (4H, m, CH$_2$CH$_2$), 2.81 (1H, d, $J$ 10.8
Hz, 3-H), 2.92 (1H, dd, J 12.3, 16.8 Hz, 3-H), 3.77-3.82 (4H, m, CH₂CH₂), 4.81 (1H, dd, J 6.0, 6.3 Hz, 2-H), 5.60 (1H, s, N-H), 7.38-7.47 (5H, m, Ph-H), 7.50 (1H, s, 7-H), 7.88 (1H, s, 5-H);

¹³C NMR (75 MHz, CDCl₃) δ: 23.8 (CH₂CH₂OH), 23.8 (CH₂CH₂OH), 45.9 (C-3), 57.5 (C-2), 60.9 (CH₂OH), 61.2 (CH₂OH), 81.2 (C=α "), 85.0 (C=α "", 94.7 (C=β "), 110.1 (C=β "", 112.2 (C-8), 118.1 (C-6), 125.8 (C-4a), 126.5 (C-2' & 6'), 128.6 (C-3' & 5'), 129.1 (C-4'), 130.8 (C-5), 140.4 (C-7), 140.6 (C-1'), 151.1 (C-8a), 192.2 (C-4); IR (neat) νmax 3430, 3400, 3351, 3060, 2923, 2880, 2225, 1666, 1599, 1569, 1492, 1313, 1237, 1204, 1043, 897, 752, 701, 686 cm⁻¹.

4.6.6 Preparation of 2-(4-fluorophenyl)-6,8-bis(4-hydroxybut-1-yn-1-yl)-2,3-dihydroquinolin-4(1H)-one 138f (R = F; R' = -CH₂CH₂OH)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122b (0.40 g, 1.0 mmol), PdCl₂(PPh₃)₂ (0.035 g, 0.05 mmol) and CuI (0.10 g, 0.5 mmol) in EtOH/Et₃N (30 mL; 2:1) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 45 minutes. 3-Butyn-1-ol (0.30 mL, 3.0 mmol) was added via a syringe and treated as described for 138a; work up and column chromatography on silica gel afforded 138f as yellow solid (0.27 g, 71%); mp 115-116 °C; Rf (40% ethyl acetate/toluene) 0.16; ¹H NMR (300 MHz, CDCl₃) δ: 1.72 (2H, t, J 5.4 Hz, OH), 1.91 (2H, t, J 5.4 Hz, CH₂CH₂OH), 2.62-2.69 (4H, m, CH₂CH₂), 2.78 (1H, d, J 10.8 Hz, 3-H), 2.89 (1H, dd, J 12.3, 16.8 Hz, 3-H), 3.77 (2H, t, J 5.4 Hz, CH₂CH₂OH), 4.78 (1H, dd, J 4.8, 7.2 Hz, 2-H), 5.53 (1H, s, N-H), 7.09 (2H, t, J 8.7 Hz, 3' & 5'-H), 7.43 (2H, dd, J 3.3, 5.4 Hz, 2' & 6'-H), 7.48 (1H, d, J 1.8 Hz, 7-H), 7.85 (1H, d, J 1.8 Hz, 5-H); ¹³C NMR (75 MHz, CDCl₃) δ: 23.7 (CH₂CH₂OH)", 23.7 (CH₂CH₂OH)"", 45.9 (C-3), 56.9 (C-2), 60.9 (CH₂OH) "", 61.2 (CH₂OH) "", 81.1 (C=α "), 85.0 (C=α "", 94.7 (C=β "), 110.1 (C=β "", 112.4 (C-8), 116.0 (d, ³JCF 21.6 Hz, C-3' & 5'), 118.0 (C-6), 128.2 (d, ²JCF 8.0 Hz, C-2' & 6'), 130.8 (C-5), 132.0 (C-4a), 136.3 (d, ⁴JCF
3.2 Hz, C-1'), 140.3 (C-7), 151.0 (C-8α), 162.6 (d, \(^1J_{CF} 245.9 \text{ Hz}, \text{C-4}')\), 192.0 (C-4); IR (neat) 
\(\nu_{\text{max}}\) 3352, 2939, 2878, 2222, 1670, 1601, 1567, 1509, 1491, 1239, 1202, 1037, 1016, 841 \text{ cm}^{-1} ; 
\(m/z\) (100, MH\(^+\)) 378; HRMS (EI): MH\(^+\), found 378.1509. For [C\(_{23}\)H\(_{21}\)NO\(_3\)F]\(^+\) requires 378.1505.

4.6.7 Preparation of 2-(4-chlorophenyl)-6,8-bis(4-hydroxybut-1-yn-1-yl)-2,3-dihydro quinolin-4(1H)-one 138g (R = Cl; R' = -CH\(_2\)CH\(_2\)OH)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122c (0.50 g, 1.2 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.042 g, 0.06 mmol) and CuI (0.12 g, 0.6 mmol) in EtOH/Et\(_3\)N (30 mL; 2:1) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 45 minutes. 3-Butyn-1-ol (0.35 mL, 3.6 mmol) was added via a syringe and treated as described for 138a; work up and column chromatography on silica gel afforded 138g as yellow solid (0.32 g, 69%); mp 107-108 °C; \(R_f\) (40% ethyl acetate/toluene) 0.18; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.27 (1H, t, \(J 5.4 \text{ Hz}, \text{OH})\), 1.27 (1H, t, \(J 5.4 \text{ Hz}, \text{OH})\), 1.88 (2H, t, \(J 6.3 \text{ Hz}, \text{CH}_2\text{CH}_2\text{OH})\), 2.53 (2H, t, \(J 6.3 \text{ Hz}, \text{CH}_2\text{CH}_2\text{OH})\), 2.66 (2H, dd, \(J 4.5, 6.3 \text{ Hz}, \text{CH}_2\text{OH})\), 2.71 (1H, d, \(J 10.8 \text{ Hz}, 3-\text{H})\), 2.89 (1H, dd, \(J 12.3, 16.8 \text{ Hz}, 3-\text{H})\), 4.78 (1H, dd, \(J 6.0, 6.3 \text{ Hz}, 2-\text{H})\), 5.55 (1H, s, N-H), 7.39 (4H, s, 2', 3', 5', 6'-H), 7.48 (1H, s, 7-H), 7.85 (1H, s, 5-H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 23.5 (CH\(_2\)CH\(_2\)OH)\), 23.7 (CH\(_2\)CH\(_2\)OH)\), 45.7 (C-3), 56.9 (C-2), 60.7 (CH\(_2\)OH)\), 60.9 (CH\(_2\)OH)\), 81.0 (C\(=\alpha\))\), 85.1 (C\(=\alpha\))\), 94.9 (C\(=\beta\))\), 101.2 (C\(=\beta\))\), 112.5 (C-8), 118.0 (C-6), 127.9 (C-4a), 129.2 (C-2' & 6'), 130.7 (C-3' & 5'), 132.0 (C-4'), 134.2 (C-5), 139.0 (C-7), 140.4 (C-1'), 150.9 (C-8a), 191.8 (C-4); IR (neat) \(\nu_{\text{max}}\) 3341, 3277, 2929, 2856, 2226, 1659, 1601, 1489, 1277, 1239, 1206, 1041, 1016, 907, 827 \text{ cm}^{-1} ; 
\(m/z\) (100, MH\(^+\)) 394; HRMS (EI): MH\(^+\), found 394.1212. For [C\(_{23}\)H\(_{21}\)NO\(_3\)Cl]\(^+\) requires 394.1210.
4.6.8 Preparation of 2-(4-methoxyphenyl)-6,8-bis(4-hydroxybut-1-yn-1-yl)-2,3-dihydroquinolin-4(1H)-one 138h (R = OCH₃; R' = -CH₂CH₂OH)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1H)-one 122d (0.50 g, 1.2 mmol), PdCl₂(PPh₃)₂ (0.042 g, 0.06 mmol) and CuI (0.12 g, 0.6 mmol) in EtOH/Et₃N (30 mL; 2:1) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 45 minutes. 3-Butyn-1-ol (0.35 mL, 3.6 mmol) was added via a syringe and treated as described for 138a; work up and column chromatography on silica gel afforded 138h as yellow solid (0.31 g, 66%); mp 88-90 °C; Rₚ (40% ethyl acetate/toluene) 0.12; ¹H NMR (300 MHz, CDCl₃) δ: 1.85 (2H, br s, OH), 2.60-2.66 (4H, m, CH₂CH₂), 2.74 (1H, d, J 10.8 Hz, 3-H), 2.86 (1H, dd, J 12.3, 16.8 Hz, 3-H), 3.74 (4H, dd, J 5.4, 6.3 Hz, CH₂CH₂), 3.80 (3H, s, OCH₃), 4.69 (1H, dd, J 5.4, 6.0 Hz, 2-H), 5.55 (1H, s, N-H), 6.91 (2H, d, J 6.3 Hz, 3' & 5'-H), 7.44 (2H, dd, J 3.0, 6.0 Hz, 2' & 6'-H), 7.68 (1H, d, J 1.5 Hz, 7-H), 7.85 (1H, d, J 1.5 Hz, 5-H); ¹³C NMR (75 MHz, CDCl₃) δ: 23.5 (CH₂CH₂OH), 23.8 (CH₂CH₂OH), 45.9 (C-3), 55.4 (OCH₃), 57.0 (C-2), 60.9 (CH₂OH), 61.2 (CH₂OH), 94.9 (C≡α), 110.1 (C≡α), 112.1 (C≡β), 114.4 (C≡β), 118.0 (C-8), 127.7 (C-6), 130.7 (C-4a), 130.8 (C-2' & 6'), 132.1 (C-3' & 5'), 132.5 (C-5), 140.3 (C-7), 140.4 (C-1'), 151.5 (C-8a), 159.7 (C-4'), 192.5 (C-4); IR (neat) νₘₐₓ 3336, 3300, 3234, 3031, 2953, 2933, 2905, 2868, 2835, 2234, 1650, 1602, 1566, 1492, 1280, 1237, 1182, 1027, 900, 827, 723 cm⁻¹.
4.7 Preparation of 4-aryl-8-bromo-2-phenyl-2,3-dihydro-6H-pyrrolo[3,2,1-ij]quinolin-6-ones 139a-d

4-Aryl-8-bromo-2-phenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolin-6-ones 139a-d

4.7.1 Preparation of 8-bromo-2,4-diphenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolinone

139a (R = H)

A mixture of 137a (0.32 g, 0.7 mmol) and PdCl₂ (0.007 g, 0.03 mmol) in MeCN (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for 3 h. The cooled reaction mixture was evaporated to dryness and the product dissolved in CHCl₃ (100 mL). The organic solvent was washed with brine, dried over anhydrous MgSO₄ and the salt was filtered off. The organic layer was concentrated and the crude product was purified by column chromatography on silica gel column to afford 139a as yellow solid (0.25 g, 78%); mp 169-170 °C; Rₚ (toluene) 0.34; ¹H NMR (300 MHz, CDCl₃) δ: 3.18 (1H, d, J 13.8 Hz, 5-Htrans), 3.65 (1H, dd, J 6.8, 9.3 Hz, 5-Hcis), 5.97 (1H, d, J 6.3 Hz, 4-H), 6.50 (2H, d, J 7.8 Hz, 3'' & 5''-H), 6.67 (1H, s, 1-H), 7.08-7.12 (3H, m, 2'', 4'', 6''-H), 7.36 (5H, s, Ph'-H), 7.80 (1H, s, 9-H), 8.00 (1H, s, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 45.8 (C-5), 57.0 (C-4), 102.9 (C-8), 114.1 (C-6a), 119.4 (C-9a), 121.1 (C-1), 124.9 (C-2'' & 6''), 128.0 (C-2’ & 6’), 128.5 (C-4’), 128.7 (C-3'' & 5''), 128.8 (C-3’ & 5’), 128.8 (C-7), 129.0 (C-4’), 129.3 (C-9), 131.0 (C-2), 139.0 (C-1’), 140.1 (C-1’’), 143.2 (C-3a), 190.6 (C-6); IR (neat) νmax 3074, 3027, 3002, 2940, 2922, 1683,
1577, 1460, 1445, 1369, 1315, 1300, 1254, 1111, 870, 754, 693, 675 cm$^{-1}$; $m/z$ (100, MH$^+$) 402; HRMS (EI): MH$^+$, found 402.0491. For [C$_{23}$H$_{17}$NO$_7$Br]$^+$, requires 402.0494.

4.7.2 Preparation of 8-bromo-4-(4-fluorophenyl)-2-phenyl-4,5-dihydro-6H-pyrrolo[3,2,1-$ij$]quinolin-6-one 139b (R = F)

A mixture of 137b (0.35 g, 0.8 mmol) and PdCl$_2$ (0.007 g, 0.04 mmol) in MeCN (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for 3 h. work up and column chromatography on silica gel described for 139a afforded 139b as yellow solid (0.27 g, 77%); mp 136-137 °C; R$_f$ (toluene) 0.35; $^1$H NMR (300 MHz, CDCl$_3$) δ: 3.13 (1H, dd, $J$ 1.5, 14.7 Hz, 5-H trans), 3.63 (1H, dd, $J$ 7.0, 9.3 Hz, 5-H cis), 5.95 (1H, d, $J$ 6.3 Hz, 4-H), 6.45 (2H, t, $J$ 8.6 Hz, 3¨ & 5¨-H), 6.66 (1H, s, 1-H), 6.79 (2H, d, $J$ 8.6 Hz, 2¨ & 6¨-H), 7.36-7.39 (5H, m, Ph'-H), 7.81 (1H, d, $J$ 1.5 Hz, 9-H), 8.00 (1H, d, $J$ 1.5 Hz, 7-H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 45.7 (C-5), 56.5 (C-4), 103.2 (C-8), 114.2 (C-6a), 115.9 (d, $^2$J$_{CF}$ 21.6 Hz, C-3¨ & 5¨), 119.3 (C-9a), 121.2 (C-1), 126.7 (d, $^3$J$_{CF}$ 8.0 Hz, C-2¨ & 6¨), 128.8 (C-4¨), 128.8 (C-2¨ & 6´), 128.9 (C-3´ & 5´), 129.0 (C-7), 129.4 (C-9), 130.9 (C-2), 135.9 (d, $^4$J$_{CF}$ 3.2 Hz, C-1¨), 138.9 (C-1´), 143.2 (C-3a), 162.2 (d, $^1$J$_{CF}$ 245.6 Hz, C-4¨), 190.4 (C-6); IR (neat) $\nu_{\text{max}}$ 3111, 3068, 3037, 2985, 2921, 1689, 1600, 1504, 1438, 1250, 1222, 1095, 873, 818, 756, 696 cm$^{-1}$; $m/z$ (100, MH$^+$) 420; HRMS (EI): MH$^+$, found 420.0388. For [C$_{23}$H$_{16}$NOF$_7$Br]$^+$, requires 420.0399.
4.7.3 Preparation of 8-bromo-4-(4-chlorophenyl)-2-phenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolinone 139c (R = Cl)

A mixture of 137c (0.30 g, 0.6 mmol) and PdCl₂ (0.006 g, 0.03 mmol) in MeCN (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for 3 h. work up and column chromatography on silica gel described for 139a afforded 139c as yellow solid (0.21 g, 70%); mp 138-139 °C; Rₖ (toluene) 0.45; ¹H NMR (300 MHz, CDCl₃) δ: 3.13 (1H, d, J 16.2 Hz, 5-H trans), 3.65 (1H, dd, J 6.8, 9.3 Hz, 5-H cis), 5.94 (1H, d, J 6.0 Hz, 4-H), 6.42 (2H, d, J 8.7 Hz, 3'' & 5''-H), 6.67 (1H, s, 1-H), 7.07 (2H, d, J 8.7 Hz, 2'' & 6''-H), 7.33-7.40 (5H, m, Ph'-H), 7.81 (1H, d, J 2.4 Hz, 9-H), 8.00 (1H, d, J 2.4 Hz, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 45.6 (C-5), 56.5 (C-4), 103.2 (C-8), 114.3 (C-6a), 119.3 (C-9a), 121.3 (C-1), 126.4 (C-2' & 6'), 128.8 (C-2'' & 6''), 128.9 (C-4''), 129.0 (C-3' & 5'), 129.1 (C-3'' & 5''), 129.2 (C-7), 129.4 (C-4'), 130.8 (C-9), 133.9 (C-2), 138.6 (C-1'), 138.9 (C-1''), 143.2 (C-3a), 190.2 (C-6); IR (neat) ν_max 3114, 3070, 3025, 2983, 2917, 1687, 1584, 1486, 1437, 1304, 1250, 1205, 1102, 1091, 873, 815, 750, 696 cm⁻¹; m/z (100, MH⁺) 436; HRMS (EI): MH⁺, found 436.0103. For [C₂₃H₁₆NOClBr]⁺, requires 436.0104.

4.7.4 Preparation of 8-bromo-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolinone 139d (R = OCH₃)

A mixture of 137d (0.3 g, 0.6 mmol) and PdCl₂ (0.006 g, 0.03 mmol) in MeCN (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for 3 h. work up and column chromatography on silica gel described for 139a afforded 139d as
yellow solid (0.21 g, 65%); mp 162-163 °C; Rf (toluene) 0.26; ¹H NMR (300 MHz, CDCl₃) δ: 3.45 (1H, d, J 15.3 Hz, 5-H trans), 3.62 (1H, dd, J 7.8, 9.0 Hz, 5-H cis), 3.67 (3H, s, OCH₃), 5.92 (1H, d, J 6.0 Hz, 4-H), 6.43 (2H, d, J 7.5 Hz, 3” & 5”-H), 6.56 (1H, s, 1-H), 6.64 (2H, d, J 7.5 Hz, 2” & 6”-H), 7.37 (5H, m, Ph'-H), 7.80 (1H, d, J 1.8 Hz, 9-H), 7.98 (1H, d, J 1.8 Hz, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 45.9 (C-5), 55.1 (OCH₃), 56.6 (C-4), 102.9 (C-8), 114.0 (C-6a), 114.3 (C-9a), 121.3 (C-1), 126.4 (C-2’ & 6’), 128.8 (C-2” & 6”), 129.0 (C-3’ & 5’), 129.1 (C-3” & 5”), 129.2 (C-7), 129.4 (C-4’), 130.8 (C-9), 133.9 (C-2), 138.6 (C-1’), 138.9 (C-1”), 143.2 (C-3a), 159.1 (C-4”), 190.9 (C-6); IR (neat) νmax 3079, 2986, 2958, 2926, 2896, 2831, 1685, 1582, 1512, 1462, 1441, 1247, 1181, 1108, 1028, 869, 825, 808, 754, 701 cm⁻¹; m/z (100, MH⁺) 432; HRMS (EI): MH⁺, found 432.0596. For [C₂₄H₁₉NO₂⁷⁹Br⁺], requires 432.0599.

4.8 Preparation of 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-ones

140a-d

2-Aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-ones 140a-d

4.8.1 Preparation of 6-bromo-2-phenyl-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-one 140a (R = H)

A mixture of 137e (0.30 g, 0.8 mmol) and PdCl₂ (0.007 g, 0.04 mmol) in MeCN (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for
8 h. The cooled reaction mixture was evaporated to dryness and the product dissolved in CHCl₃ (100 mL). The organic solvent was washed with brine, dried over anhydrous MgSO₄ and the salt was filtered off. The organic layer was concentrated and the crude product was purified by column chromatography on a silica gel to afford 140a as yellow solid, (0.16 g, 50%); mp 125-127 °C; Rᶠ (20% ethyl acetate/toluene) 0.25; ¹H NMR (300 MHz, CDCl₃) δ: 1.64 (1H, s, OH), 1.96 [2H, qt, J 6.0, 7.8 Hz, 8-(3yl-CH₂CH₃CH₂)], 2.83-2.96 (2H, m, 3-H), 3.10 (2H, t, J 6.9 Hz, 8-2yl-CH₂), 3.73 (2H, t, J 6.0 Hz, 8-4yl-CH₂), 4.81 (1H, dd, J 6.0, 6.3 Hz, 2-H), 7.35-7.41 (5H, m, Ph-H), 8.11 (1H, d, J 3.0 Hz, 7-H), 8.16 (1H, d, J 3.0 Hz, 5-H), 9.35 (1H, s, NH); ¹³C NMR (75 MHz, CDCl₃) δ: 26.8 (C-3yl), 35.8 (C-2yl), 44.8 (C-3), 56.3 (C-2), 62.0 (C-4yl), 107.2 (C-6), 121.0 (C-4a), 121.7 (C-8), 126.3 (C-4'), 128.6 (C-2' & 6'), 129.2 (C-3' & 5'), 136.2 (C-5), 139.9 (C-1'), 140.2 (C-7), 151.2 (C-8a), 191.3 (C-4), 201.6 (C-1yl); IR (neat) νₘₐₓ 3354, 3292, 2960, 2932, 2899, 2873, 2841, 1669, 1651, 1592, 1570, 1493, 1402, 1246, 1228, 1210, 1134, 1039, 1018, 885, 832 cm⁻¹; m/z (100, MH⁺) 386; HRMS (EI): MH⁺, found 386.0380. For [C₁₉H₁₉NO₃⁺] requires 386.0392.

4.8.2 Preparation of 6-bromo-2-(4-fluorophenyl)-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-one 140b (R = F)

A stirred mixture of 137f (0.30 g, 0.8 mmol) and PdCl₂ (0. 007 g, 0.04 mmol) in MeCN (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for 8 h. Treated as described for 140a; work up and column chromatography on silica gel afforded 140b as yellow solid (0.18 g, 58%); mp 148-149 °C; Rᶠ (20% ethyl acetate/toluene) 0.30; ¹H NMR (300 MHz, CDCl₃) δ: 1.59 (1H, br s, OH), 1.96 (2H, qt, J 6.0, 6.9 Hz, 3yl-H), 2.81-2.87 (2H, m, 3-H), 3.10 (2H, t, J 6.9 Hz, 2yl-H), 3.73 (2H, t, J 6.3 Hz, 4yl-H), 4.80 (1H, t, J 8.4 Hz, 2-
H), 7.09 (2H, t, J 8.4 Hz, 3' & 5'-H), 7.39 (2H, dd, J 3.3, 4.5 Hz, 2' & 6'-H), 8.12 (1H, s, 7-H), 8.16 (1H, s, 5-H), 9.31 (1H, s, NH); 13C NMR (75 MHz, CDCl3) δ: 26.8 (C-3yl), 35.8 (C-2yl), 44.9 (C-3), 55.7 (C-2), 62.0 (C-4yl), 107.4 (C-6), 116.2 (d, 2JCF 21.4 Hz, C-3' & 5'), 121.0 (C-4a), 121.7 (C-8), 128.1 (d, 3JCF 8.3 Hz, C-2' & 6'), 135.7 (d, 4JCF 3.0 Hz, C-1'), 136.2 (C-5), 140.2 (C-7), 151.0 (C-8a), 162.6 (d, 1JCF 245.9 Hz, C-4'), 191.0 (C-4), 201.7 (C-1yl); IR (neat) νmax 3375, 3300, 2940, 2911, 2869, 1687, 1643, 1586, 1561, 1480, 1219, 1205, 1119, 1038, 1019, 938, 889, 857, 831, 738, 642 cm⁻¹; m/z (100, MH⁺) 406; HRMS (EI): MH⁺, found 406.0454. For [C₁₉H₁₈NO₃F⁷⁹Br]⁺, requires 406.0436.

4.8.3 Preparation of 6-bromo-2-(4-chlorophenyl)-8-(4-hydroxybutanoyl)-2,3-
dihydroquinolin-4(1H)-one 140c (R = Cl)

A stirred mixture of 137g (0.50 g, 1.6 mmol) and PdCl₂ (0.014 g, 0.08 mmol) in MeCN (25 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for 8 h. Treated as described for 140a; work up and column chromatography on silica gel afforded 140c as yellow solid (0.254 g, 50%); mp 150-151 °C; Rf (20% ethyl acetate/toluene) 0.34; 1H NMR (300 MHz, CDCl₃) δ: 1.59 (1H, br s, OH), 1.96 (2H, qt, J 6.0. 6.3 Hz, 3yl-H), 2.84-2.95 (2H, m, 3-H), 3.10 (2H, t, J 6.9 Hz, 2yl-H), 3.74 (2H, d, J 6.0 Hz, 4yl-H), 4.79 (1H, t, J 8.4 Hz, 2-H), 7.20 (2H, d, J 7.5 Hz, 3' & 5'-H), 7.35 (2H, dd, J 3.0, 4.5 Hz, 2' & 6'-H), 7.38 (1H, s, 7-H), 8.14 (1H, s, 5-H), 9.33 (1H, s, NH); 13C NMR (75 MHz, CDCl₃) δ: 26.8 (C-3yl), 35.8 (C-2yl), 44.7 (C-3), 55.7 (C-2), 62.0 (C-4yl), 107.5 (C-6), 121.0 (C-4a), 121.7 (C-8), 127.7 (C-4'), 129.4 (C-2' & 6'), 134.4 (C-3' & 5'), 136.2 (C-5), 138.5 (C-1'), 140.2 (C-7), 151.0 (C-8a), 190.8 (C-4), 201.8 (C-1yl); IR (neat) νmax 3374, 3301, 2962, 2934, 2904, 2869, 1686, 1644, 1563, 1485, 1398,
1325, 1228, 1122, 1088, 891, 851, 640 cm\(^{-1}\); \(m/z\) (100, MH\(^{+}\)) 422; HRMS (EI): MH\(^{+}\), found 422.0159. For [C\(_{19}\)H\(_{18}\)NO\(_3\)Cl\(^{79}\)Br]\(^{+}\), requires 422.0139.

4.8.4 Preparation of 6-bromo-2-(4-methoxyphenyl)-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1H)-one 140d (R = OCH\(_3\))

A stirred mixture of 137h (0.23 g, 0.6 mmol) and PdCl\(_2\) (0.006 g, 0.03 mmol) in MeCN (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for 8 h. Treated as described for 140a; work up and column chromatography on silica gel afforded 140d as yellow solid (0.13 g, 54%); mp 117-118 °C; R\(_f\) (20% ethyl acetate/toluene) 0.19; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.76 (1H, br s, OH), 1.95 (2H, qt, \(J\) 6.0, 6.3 Hz, 3yl-H), 2.77-2.93 (2H, m, 3-H), 3.09 (2H, t, \(J\) 6.3 Hz, 2yl-H), 3.72 (2H, t, \(J\) 6.0 Hz, 4yl-H), 3.81 (3H, s, OCH\(_3\)), 4.74 (1H, dd, \(J\) 4.5, 7.5 Hz, 2-H), 6.92 (2H, d, \(J\) 9.0 Hz, 3’ & 5’-H), 7.32 (2H, d, \(J\) 9.0 Hz, 2’ & 6’-H), 8.10 (1H, s, 7-H), 8.14 (1H, s, 5-H), 9.26 (1H, s, N-H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 26.8 (C-3yl), 35.8 (C-2yl), 44.9 (C-3), 55.4 (OCH\(_3\)), 55.7 (C-2), 62.0 (C-4yl), 107.1 (C-6), 114.5 (C-3’ & 5’), 121.0 (C-4a), 121.7 (C-8), 127.6 (C-2’ & 6’), 136.1 (C-5), 139.9 (C-1’), 140.1 (C-7), 151.1 (C-8a), 159.7 (C-4’), 191.5 (C-4), 201.6 (C-1yl); IR (neat) \(\nu_{\text{max}}\) 3286, 3074, 2936, 2875, 2840, 1687, 1646, 1563, 1484, 1247, 1122, 1022, 832, 646 cm\(^{-1}\); \(m/z\) (100, MH\(^{+}\)) 416; HRMS (EI): MH\(^{+}\), found 416.0497. For [C\(_{20}\)H\(_{21}\)NO\(_4\)\(^{79}\)Br]\(^{+}\), requires 416.0494.
4.9 Preparation of 8-substituted 4-aryl-2-phenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolin-6-ones 141a-f

8-Substituted 4-aryl-2-phenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolinones 141a-f

4.9.1 Preparation of 8-(4-fluorophenyl)-2,4-diphenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolinone 141a (R = H, R' = F)

A mixture of 139a (0.15 g, 0.3 mmol), 4-FPhB(OH)₂ (0.06 g, 0.4 mmol), PdCl₂(PPh₃)₂ (0.01g, 0.01 mmol), PCy₃ (0.01 g, 0.03 mmol) and K₂CO₃ (0.1 g, 0.7 mmol) in dioxane/water (3:1;v/v) (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 0.5 h. The mixture was then heated at 100 °C for 3 h. The cooled reaction mixture was mixed with cold water (20 mL) and the product was extracted into CHCl₃ (3x30 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO₄ and the salt was filtered off. The organic solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel to afford 141a as yellow solid, (0.103 g, 67%); mp 195-196 °C; Rₗ (20% ethyl acetate/toluene) 0.78; ¹H NMR (300 MHz, CDCl₃) δ: 3.22 (1H, d, J 16.2 Hz, 5-Hₗ trans), 3.73 (1H, dd, J 6.9, 9.3 Hz, 5-Hₗ cis), 6.00 (1H, d, J 6.9 Hz, 4-H), 6.57 (2H, dd, J 1.8, 5.4 Hz, 3‴ & 5‴-H), 6.77 (1H, d, J 1.8 Hz, 1-H), 7.12-7.17 (5H, m, Ph'-H), 7.38 (5H, s, Ph"-H), 7.63 (2H, dd, J 1.8, 5.4 Hz, 2″ & 6″-H), 7.91 (1H, d, J 1.8 Hz, 9-H), 8.06 (1H, d, J 1.8 Hz, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ:
46.0 (C-5), 57.1 (C-4), 103.8 (C-8), 115.6 (d, $^2J_{CF}$ 21.3 Hz, C-3'' & 5''), 117.8 (C-6a), 118.6 (C-2' & 6'), 125.1 (d, $^3J_{CF}$ 8.0 Hz, C-2'' & 6''), 127.9 (C-2' & 6'), 128.2 (C-1), 128.5 (C-3' & 5'), 128.7 (C-3'' & 5''), 128.8 (C-7), 128.8 (C-9), 128.9 (C-2), 131.4 (C-1'), 133.4 (C-1''), 137.7 (d, $^4J_{CF}$ 3.0 Hz, C-1''), 140.0 (C-4'), 140.4 (C-4''), 142.8 (C-10a), 162.2 (d, $^1J_{CF}$ 244.4 Hz, C-4''), 191.8 (C-6); IR (neat) $\nu_{max}$ 3062, 3027, 2976, 2910, 1667, 1599, 1512, 1467, 1451, 1320, 1297, 1251, 1215, 889, 835, 807, 756, 693, 637 cm$^{-1}$; $m/z$ (100, MH$^+$) 418; HRMS (EI): MH$^+$, found 418.1607. For, [C$_{29}$H$_{21}$NOF]$^+$, requires 418.1606.

4.9.2 Preparation of 4,8-bis(4-fluorophenyl)-2-phenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolinone 141b (R = F, R' = F)

A mixture of 139b (0.15 g, 0.3 mmol), 4-FC$_3$H$_4$B(OH)$_2$ (0.06 g, 0.4 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.01 g, 0.01 mmol), PCy$_3$ (0.01 g, 0.03 mmol) and K$_2$CO$_3$ (0.1 g, 0.7 mmol) in dioxane/water (3:1;v/v) (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 0.5 h. The mixture was then heated at 100 °C for 3 h. Treated as described for 141a; work up and column chromatography on silica gel afforded 141b as yellow solid, (0.118 g, 78%); mp 221-222 °C; $R_f$ (20% ethyl acetate/toluene) 0.80; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 3.17 (1H, d, $^2J_{CH}$ 16.8 Hz, 5-H trans), 3.72 (1H, dd, $^1J_{CH}$ 7.5, 9.3 Hz, 5-H cis), 6.00 (1H, d, $^2J_{CH}$ 6.0 Hz, 4-H), 6.52 (2H, dd, $^1J_{CH}$ 3.0, 5.4 Hz, 3'' & 5''-H), 6.68 (1H, s, 1-H), 6.80 (2H, t, $^2J_{CH}$ 9.3 Hz, 3'' & 5'-H), 7.14 (2H, t, $^1J_{CH}$ 9.3 Hz, 2'' & 6''-H), 7.39 (5H, s, Ph'-H), 7.62 (2H, dd, $^1J_{CH}$ 3.0, 5.4 Hz, 2'' & 6''-H), 7.91 (1H, d, $^2J_{CH}$ 1.8 Hz, 9-H), 8.05 (1H, d, $^1J_{CH}$ 1.8 Hz, 7-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 46.0 (C-5), 56.6 (C-4), 104.0 (C-8), 115.7 (d, $^2J_{CF}$ 21.3 Hz, C-3'' & 5''), 115.9 (d, $^2J_{CF}$ 21.3 Hz, C-3' & 5'), 118.0 (C-10), 118.5 (C-6a), 125.3 (C-1), 126.8 (d, $^3J_{CF}$ 8.0 Hz, C-2'' & 6''), 128.3 (C-2' & 6'), 128.7 (C-3' & 5'), 128.8 (C-7), 128.8 (C-9), 128.9 (d, $^3J_{CF}$ 8.0 Hz, C-2'' & 6''), 131.4 (C-2), 135.6 (C-1'), 136.2 (d, $^4J_{CF}$ 3.5 Hz, C-1''), 137.6 (d, $^4J_{CF}$ 3.5 Hz, C-1'')}
139.9 (C-4'), 142.7 (C-10a), 162.2 (d, J_CF 245.2 Hz, C-4''), 162.3 (d, J_CF 245.2 Hz, C-4''), 191.5 (C-6); IR (neat) ν_max 3066, 2978, 2906, 1668, 1599, 1510, 1407, 1378, 1320, 1224, 1214, 1161, 1116, 1011, 494, 890, 835, 758, 747, 619 cm⁻¹; m/z (100, MH⁺) 436; HRMS (EI): MH⁺, found 436.1513. For, [C₉H₂₀NOF₂]⁺, requires 436.1518.

4.9.3 Preparation of 4-(4-chlorophenyl)-8-(4-fluorophenyl)-2-diphenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolinone 141c (R = Cl, R' = F)

A mixture of 139c (0.08 g, 0.1 mmol), 4-FC₆H₄B(OH)₂ (0.03 g, 0.2 mmol), PdCl₂(PPh₃)₂ (0.005g, 0.005 mmol), PCy₃ (0.005 g, 0.01 mmol) and K₂CO₃ (0.05 g, 0.3 mmol) in dioxane/water (3:1, v/v; 10 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 0.5 h. The mixture was then heated at 100 °C for 3 hours under nitrogen atmosphere. Treated as described for 141a; work up and column chromatography on silica gel afforded 141c as yellow solid, (0.050 g, 62%); mp 240-241 °C; R_f (20% ethyl acetate/toluene) 0.85; ¹H NMR (300 MHz, CDCl₃) δ: 3.16 (1H, d, J 16.5 Hz, 5-H trans), 3.71 (1H, dd, J 6.6, 9.9 Hz, 5-H cis), 5.98 (1H, d, J 5.7 Hz, 4-H), 6.48 (2H, d, J 8.7 Hz, 3'' & 5''-H), 6.77 (1H, s, 1-H), 7.07 (2H, t, J 8.7 Hz, 2'' & 6''-H), 7.15 (2H, t, J 9.0 Hz, 3'' & 5''-H), 7.39 (5H, s, Ph'-H), 7.62 (2H, dd, J 3.6, 5.4 Hz, 2'' & 6''-H), 7.90 (1H, d, J 1.5 Hz, 9-H), 8.06 (1H, d, J 1.5 Hz, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 46.0 (C-5), 56.6 (C-4), 104.1 (C-8), 114.0 (C-10), 115.6 (d, J_CF 21.3 Hz, C-3'' & 5''), 118.0 (C-6a), 118.5 (C-2' & 6'), 125.3 (C-1), 126.5 (C-2'' & 6''), 128.3 (C-3' & 5'), 128.7 (C-3'' & 5''), 128.8 (d, J_CF 8.0 Hz, C-2'' & 6''), 129.1 (C-7), 131.3 (C-9), 133.6 (C-2), 133.8 (C-1'), 137.6 (d, J_CF 3.2 Hz, C-1''), 137.9 (C-1''), 138.9 (C-4'), 139.9 (C-4''), 142.7 (C-10a), 162.3 (d, J_CF 244.4 Hz, C-4''), 191.4 (C-6); IR (neat) ν_max 3065, 2972, 2906, 1668, 1599, 1513, 1492, 1469, 1408, 1321, 1295, 1247, 1215,
1118, 1098, 1012, 944, 890, 836, 803, 744, 697 cm$^{-1}$; $m/z$ (100, MH$^+$) 452; HRMS (EI): MH$^+$, found 452.1217. For, [C$_{29}$H$_{20}$NOFCl]$^+$, requires 452.1213.

4.9.4 Preparation of 8-(4-fluorophenyl)-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-6H-pyrrolo[3,2,1-$	ext{-}$]quinolinone 141d (R = OCH$_3$, R' = F)

A mixture of 139d (0.10 g, 0.2 mmol), 4-FC$_6$H$_4$B(OH)$_2$ (0.04 g, 0.3 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.008 g, 0.01 mmol), PCy$_3$ (0.007 g, 0.02 mmol) and K$_2$CO$_3$ (0.09 g, 0.5 mmol) in dioxane/water (3:1, v/v; 15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 0.5 h. The mixture was then heated at 100 °C for 3 hours under nitrogen atmosphere. Treated as described for 141a; work up and column chromatography on silica gel afforded 141d as yellow solid, (0.068 g, 66%); mp 215-216 °C; $R_f$ (20% ethyl acetate/toluene) 0.73; $^1$H NMR (300 MHz, CDCl$_3$) δ: 3.18 (1H, d, $J$ 16.8 Hz, 5-H trans), 3.68 (3H, s, OCH$_3$), 3.69 (1H, dd, $J$ 6.0, 9.0 Hz, 5-H cis), 5.97 (1H, d, $J$ 7.8 Hz, 4-H), 6.50 (2H, d, $J$ 7.8 Hz, 3'' & 5''-H), 6.64 (2H, d, $J$ 9.3 Hz, 3'' & 5''-H), 6.76 (1H, s, 1-H), 7.15 (2H, t, $J$ 8.4 Hz, 2'' & 6''-H), 7.40 (5H, s, Ph'-H), 7.63 (2H, dd, $J$ 3.0, 5.4 Hz, 2'' & 6''-H), 7.90 (1H, d, $J$ 1.5 Hz, 9-H), 8.05 (1H, d, $J$ 1.5 Hz, 7-H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 46.2 (C-5), 55.1 (OCH$_3$), 56.7 (C-4), 104.1 (C-8), 114.2 (C-10), 115.7 (d, $^3$J$_{CF}$ 21.4 Hz, C-3'' & 5''), 117.8 (C-6a), 118.6 (C-2' & 6'), 125.1 (C-1), 126.3 (C-2'' & 6''), 128.5 (C-3' & 5'), 128.8 (C-7), 128.9 (d, $^3$J$_{CF}$ 8.0 Hz, C-2'' & 6''), 131.6 (C-9), 132.5 (C-2), 133.3 (C-1' & 1''), 137.7 (d, $^4$J$_{CF}$ 3.2 Hz, C-1''), 139.9 (C-4'), 142.7 (C-10a), 159.0 (C-4''), 162.3 (d, $^1$J$_{CF}$ 244.2 Hz, C-4''), 192.0 (C-6); IR (neat) $v_{max}$ 3079, 2995, 2954, 2931, 2834, 1662, 1600, 1512, 1467, 1410, 1298, 1247, 1215, 1181, 1114, 1035, 1012, 944, 889, 835, 748, 699 cm$^{-1}$; $m/z$ (100, MH$^+$) 448; HRMS (EI): MH$^+$, found 448.1715. For [C$_{30}$H$_{23}$NO$_2$F]$^+$, requires 448.1710.
4.9.5 Preparation of 8-(4-methoxyphenyl)-2,4-diphenyl-4,5-dihydro-6H-pyrrolo[3,2,1-
ij]quinolinone 141e (R = H, R’ = OCH₃)

A mixture of 139a (0.15 g, 0.4 mmol.), 4-OMePhB(OH)₂ (0.07 g, 0.4 mmol.), PdCl₂(PPh₃)₂ (0.013 g, 0.02 mmol), PCy₃ (0.01 g, 0.2 mmol) and K₂CO₃ (0.13 g, 1.0 mmol) in dioxane/water (3:1, v/v; 15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 0.5 h. The mixture was then heated at 100 °C for 3 hours under nitrogen atmosphere. Treated as described for 141a; work-up and column chromatography afforded 141e as yellow solid, (0.10 g, 78%); mp 170-171 °C; Rf (20% ethyl acetate/toluene) 0.77; ¹H NMR (300 MHz, CDCl₃) δ: 3.21 (1H, d, J 15.3 Hz, 5-H trans), 3.72 (1H, dd, J 6.0, 9.3 Hz, 5-H cis), 3.86 (3H, s, OCH₃), 5.99 (1H, d, J 6.0 Hz, 4-H), 6.58 (2H, d, J 3.0 Hz, 3" & 5"-H), 6.76 (1H, s, 1-H), 7.00 (2H, d, J 9.0 Hz, 3" & 5"-H), 7.12 (3H, d, J 3.0 Hz, 2", 4" 6"-H), 7.38 (5H, s, Ph'-H), 7.61(2H, d, J 9.0 Hz, 2" & 6"-H), 7.93 (1H, s, 9-H), 8.07 (1H, s, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 46.1 (C-5), 55.4 (OCH₃), 57.1 (C-4), 103.8 (C-8), 114.2 (C-10), 117.8 (C-6a), 118.6 (C-2' & 6'), 124.9 (C-1), 125.1 (C-2" & 6"), 127.8 (C-2" " & 6"), 128.2 (C-3' & 5'), 128.4 (C-3" & 5"), 128.4 (C-3" & 5"'), 128.5 (C-7), 128.7 (C-9), 128.8 (C-4"'), 128.9 (C-4"), 131.6 (C-2), 134.1 (C-1"), 139.9 (C-1"'), 140.6 (C-1"'), 142.5 (C-10a), 158.9 (C-4"'), 191.9 (C-6); IR (neat) νₘₐₓ 3079, 2986, 2959, 2926, 2897, 2832, 1686, 1609, 1512, 1462, 1441, 1371, 1319, 1248, 1182, 1108, 1029, 869, 825, 808, 768, 754, 701 cm⁻¹; m/z (100, MH⁺) 430; HRMS (EI): MH⁺, found 430.1815. For, [C₃₀H₂₄NO₂]⁺, requires 430.1807.
4.9.6 Preparation of 4-(4-chlorophenyl)-8-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolinone 141f (R = Cl, R' = OCH₃)

A mixture of 139c (0.10 g, 0.2 mmol), 4-OMePhB(OH)₂ (0.04 g, 0.2 mmol), PdCl₂(PPh₃)₂ (0.007g, 0.01 mmol), PCy₃ (0.005 g, 0.02 mmol) and K₂CO₃ (0.05 g, 0.4 mmol) in dioxane/water (3:1, v/v; 15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 0.5 h. The mixture was then heated at 100 °C for 3 hours under nitrogen atmosphere. Treated as described for 141a; work-up and column chromatography afforded 141f as yellow solid, (0.078 g, 73%); mp 158-159 °C; Rₜ (20% ethyl acetate/toluene) 0.80; ¹H NMR (300 MHz, CDCl₃) δ: 3.15 (1H, d, J 16.2 Hz, 5'-H trans), 3.71 (1H, dd, J 7.0, 9.3 Hz, 5'-H cis), 3.86 (3H, s, OCH₃), 5.97 (1H, d, J 6.6 Hz, 4'-H), 6.49 (2H, d, J 8.4 Hz, 3'' & 5''-H), 6.76 (1H, s, 1-H), 7.00 (2H, d, J 8.4 Hz, 3'' & 5''-H), 7.08 (2H, d, J 8.4 Hz, 2'' & 6''-H), 7.38 (5H, s, Ph'-H), 7.60 (2H, d, J 8.4 Hz, 2'' & 6''-H), 7.93 (1H, d, J 1.5 Hz, 9-H), 8.07 (1H, d, J 1.5 Hz, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 45.9 (C-5), 55.4 (OCH₃), 56.6 (C-4), 104.0 (C-8), 114.3 (C-10), 117.9 (C-6a), 118.5 (C-2' & 6'), 125.1 (C-1), 126.6 (C-2'' & 6''), 128.2 (C-2'' & 6''), 128.4 (C-3' & 5'), 128.6 (C-3'' & 5''), 128.7 (C-3'' & 5''), 128.8 (C-7), 129.1 (C-9), 131.4 (C-4'), 133.7 (C-4''), 134.0 (C-2), 134.3 (C-1'), 139.0 (C-1''), 139.7 (C-1''), 142.5 (C-10a), 158.9 (C-4''), 191.5 (C-6); IR (neat) νₘₐₓ 3032, 2990, 2957, 2927, 2901, 2831, 1665, 1594, 1469, 1444, 1247, 1223, 1180, 1113, 1093, 1012, 828, 810, 755, 698 cm⁻¹; m/z (100, MH⁺) 464; HRMS (EI): MH⁺, found 464.1401. For [C₃₀H₂₃NO₂Cl]⁺, requires 464.1417.
4.10 Preparation of 2-substituted 4-aryl-8-bromo-6-oxopyrrolo[3,2,1-ij]quinoline derivatives 142a-h

![Chemical Structure](image)

2-Substituted 4-aryl-8-bromo-6-oxopyrrolo[3,2,1-ij]quinolines 142a-h

4.10.1 Preparation of 8-bromo-2,4-diphenyl-6-oxopyrrolo[3,2,1-ij]quinoline 142a (R = H; R' = -C₆H₅)

A stirred mixture of 6,8-dibromo-2-phenylquinolin-4(1H)-one 136a (0.25 g, 0.7 mmol), 10% Pd/C (0.008 g, 0.007 mmol), PPh₃ (0.007 g, 0.03 mmol), CuI (0.013 g, 0.07 mmol) and Et₃N (0.24 mL, 1.8 mmol) in dioxane (20 mL) was purged for 1 h. Phenyl acetylene (0.14 mL, 1.3 mmol) was added and the mixture was heated at 110 °C for 18 h. The cooled reaction mixture was filtered through celite bed to get rid of the carbon, mixed with water (50 mL) and the product was extracted into CHCl₃ (3x60 mL). The combined organic layers were washed with brine (2x10 mL), dried with anhydrous MgSO₄ and the salt filtered off. The solvent was concentrated under reduced pressure and the crude product was purified on a silica gel column to afford the pure product 142a as yellow solid, (0.18 g, 68%); mp 267-269 °C; Rₜ 0.37 (20% ethyl acetate/ hexane); ¹H NMR (300 MHz, CDCl₃) δ: 6.32 (1H, s, 1-H), 6.73 (1H, s, 5-H), 6.96-7.15 (10H, m, Ph'-H & 2-Ph-H), 8.04 (1H, s, 9-H), 8.34 (1H, s, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 110.8 (C-5), 118.2 (C-8), 123.4 (C-1), 124.8 (C-9a), 127.7 (C-4'), 127.8 (2-Ph, C-4), 128.1 (C-6a), 128.4 (C-2' & 6'), 128.8 (2-Ph, C-2 & 6), 129.0 (C-3' & 5'), 129.2 (2-Ph, C-3 & 5), 129.4 (C-1'), 130.7 (C-7), 131.2 (C-9), 132.9 (C-2), 135.5 (2-Ph, C-1), 143.5 (C-4), 150.0 (C-3a), 179.0 (C-6); IR (neat): ν̃(max) 3080, 3057, 1635, 1613, 1590, 1456, 1349,1267, 996, 875, 841, 757, 692,
4.10.2 Preparation of 8-bromo-4-(4-fluorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1- ij]quinoline

142b (R = F; R' = -C₆H₅)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromoquinolin-4(1H)-one 136b (0.25 g, 0.6 mmol), 10% Pd/C (0.007 g, 0.006 mmol), PPh₃ (0.006 g, 0.02 mmol), CuI (0.013 g, 0.06 mmol) and Et₃N (0.24 mL, 1.8 mmol) in dioxane (20 mL) was purged for 1 h. Phenyl acetylene (0.14 mL, 1.3 mmol) was added and the mixture was heated at 100 °C for 18 h; work up employed for 142a was adopted to afford 142b as light yellow solid, (0.18 g, 68%); mp 279-281 °C; Rₛ 0.48 (20% ethyl acetate/ hexane); ¹H NMR (300 MHz, CDCl₃) δ: 6.29 (1H, s, 1-H), 6.67 (1H, s, 5-H), 6.70 (2H, dd, J 2.4, 6.6 Hz, 3' & 5'-H), 7.00-7.14 (5H, m, 2-Ph-H), 7.17 (2H, dd, J 2.4, 6.6 Hz, 2' & 6'-H), 8.04 (1H, d, J 1.8 Hz, 9-H), 8.34 (1H, d, J 1.8 Hz, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 110.8 (C-5), 114.8 (d, ²Jₐ₁ 22.0 Hz, C-3' & 5'), 118.3 (C-8), 118.8 (C-1), 123.4 (C-9a), 124.9 (2Ph, C-4), 127.8 (C-6a), 128.3 (2-Ph, C-2 & 6), 128.9 (2-Ph, C-3 & 5), 129.1 (d, ³Jₐ₁ 8.8 Hz, C-2' & 6'), 129.4 (2-Ph, C-1), 130.6 (C-7), 131.0 (d, ⁴Jₐ₁ 3.7 Hz, C-1'), 131.7 (C-9), 135.4 (C-2), 143.2 (C-4), 148.9 (C-3a), 163.1 (d, ¹Jₐ₁ 249.2 Hz, C-4'), 178.8 (C-6); IR (neat) ν (max) 3060, 3044, 1637, 1610, 1592, 1505, 1459, 1349, 1267, 998, 880, 839, 761, 697, 659 cm⁻¹; m/z (100, M+H) 418; HRMS (ES): MH⁺, found 418.0248. Calculated for [C₂₃H₁₄F₇BrNO]⁺: requires, 418.0243.
4.10.3 Preparation of 8-bromo-4-(4-chlorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline

142c (R = Cl; R' = -C₆H₅)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromoquinolin-4(1H)-one 136c (0.25 g, 0.6 mmol), 10% Pd/C (0.007 g, 0.006 mmol), PPh₃ (0.006 g, 0.02 mmol), CuI (0.013 g, 0.06 mmol) and Et₃N (0.24 mL, 1.8 mmol) in dioxane (20 mL) was purged for 1 h. Phenyl acetylene (0.14 mL, 1.3 mmol) was added and the mixture was heated at 100 °C for 18 h; work up employed for 142a was adopted to afford 142c as light yellow solid, (0.17 g, 65%); mp 286-288 °C; Rᵢ 0.54 (20% ethyl acetate/ hexane); ¹H NMR (300 MHz, CDCl₃) δ: 6.29 (1H, s, 1-H), 6.74 (1H, s, 5-H), 6.95-7.20 (9H, m, 2', 3', 5' & 6'-H and 2-Ph-H), 8.04 (1H, d, J 1.8 Hz, 9-H), 8.33 (1H, d, J 1.8 Hz, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 110.8 (C-5), 118.2 (C-8), 118.9 (C-1), 123.4 (C-9a), 124.9 (C-4'), 127.9 (2-Ph, C-4), 128.0 (C-6a), 128.3 (C-2' & 6'), 129.0 (2-Ph, C-2 & 6), 129.4 (C-3' & 5'), 129.5 (2-Ph, C-3 & 5), 130.3 (C-1'), 130.7 (C-7), 131.0 (C-9), 131.3 (C-2), 135.7 (2-Ph, C-1), 143.2 (C-4), 148.7 (C-3a), 178.8 (C-6); IR (neat): νₘₐₓ 3060, 3025, 1636, 1616, 1593, 1487, 1454, 1346, 1280, 1265, 1001, 878, 828, 760, 679 cm⁻¹; m/z (100, M+H) 435; HRMS (ES): MH⁺, found 435.0922. Calculated for [C₂₃H₁₄Cl²⁹BrNO]⁺: requires, 435.0869.

4.10.4 Preparation of 8-bromo-4-(4-methoxyphenyl)-2-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline

142d (R = OCH₃; R' = -C₆H₅)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromoquinolin-4(1H)-one 136d (0.25 g, 0.6 mmol), 10% Pd/C (0.007 g, 0.006 mmol), PPh₃ (0.006 g, 0.02 mmol), CuI (0.013 g, 0.06 mmol) and Et₃N (0.24 mL, 1.8 mmol) in dioxane (20 mL) was purged for 1 h. Phenyl acetylene (0.14 mL, 1.3 mmol) was added and the mixture was heated at 100 °C for 18 h; work up employed for 142a was adopted to afford 142d as light yellow solid, (0.16 g, 62%); mp 179-181 °C; Rᵢ 0.20
(20% ethyl acetate/ hexane); 1H NMR (300 MHz, CDCl3) δ: 1H NMR (300 MHz, CDCl3) δ: 3.71 (3H, s, OCH3), 6.30 (1H, s, 1-H), 6.51 (2H, d, J 8.4 Hz, 3’ & 5’-H), 6.72 (1H, s, 5-H), 7.02-7.11 (7H, m, 2’ & 6’-H and 2-Ph-H), 8.02 (1H, s, 9-H), 8.33 (1H, s, 7-H); 13C NMR (75 MHz, CDCl3) δ: 55.3 (OCH3), 110.7 (C-5), 117.8 (C-8), 118.6 (C-1), 123.5 (C-9a), 124.8 (2-Ph, C-4), 125.2 (C-6a), 127.7 (C-2’ & 6’), 127.9 (2-Ph, C-2 & 6), 128.7 (C-3’ & 5’), 129.3 (2-Ph, C-3 & 5), 130.5 (C-1’), 130.6 (C-7), 131.4 (C-9), 134.4 (C-2), 135.5 (2-Ph, C-1), 143.5 (C-4), 150.0 (C-3a), 160.4 (C-4’), 179.0 (C-6); IR (neat): ν(max) 3079, 3055, 2996, 2933, 2834, 1636, 1600, 1505, 1459, 1399, 1269, 828, 759, 691 cm⁻¹; m/z (100, M+H) 430; HRMS (ES): MH⁺, found 430.0443. Calculated for [C24H17BrNO2]⁺: requires, 430.0443.

4.10.5 Preparation of 6-bromo-2-(2-hydroxyethyl)-4-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline

142e (R = H; R’ = -CH2CH2OH)

A stirred mixture of 6,8-dibromo-2-phenylquinolin-4(1H)-one 136a (0.4 g, 1.1 mmol), PdCl2(PPh3)2 (0.04 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) and Et3N (0.6 mL, 4.2 mmol) in DMF/water (30 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.30 mL, 3.2 mmol) was added and the mixture was heated at 110 °C for 6 h. The cooled reaction mixture was mixed with water (50 mL) and the product was extracted into CHCl3 (3x60 mL). The combined organic layers were washed with brine (2x10 mL), dried with anhydrous MgSO4 and the salt filtered off. The solvent was concentrated under reduced pressure and the crude product was purified on a silica gel column to afford the pure product 142e as yellow solid, (0.13 g, 35%); mp 144-146 °C; Rf 0.25 (50% ethyl acetate/ hexane); 1H NMR (300 MHz, CDCl3) δ: 1.74 (1H, t, J 5.4 Hz, OH), 2.37 (2H, t, J 6.2 Hz, CH2CH2), 3.66 (2H, dd, J 4.5, 6.2 Hz, CH2OH), 6.19 (1H, s, 1-H), 6.64 (1H, s, 5-H), 7.50-7.54 (5H, m, ph-H), 7.90 (1H, s, 9-H), 8.18 (1H, s, 7-H); 13C NMR (75 MHz, CDCl3) δ: 32.2 (CH2), 60.4 (CH2OH), 109.0 (C-5), 118.1 (C-2), 118.6 (C-6a), 122.9 (C-1), 124.1
(C-2' & 6'), 128.3 (C-3' & 5'), 128.7 (C-1'), 128.8 (C-9a), 130.3 (C-4'), 130.5 (C-6a), 130.9 (C-7), 133.7 (C-9), 141.3 (C-4), 149.1 (C-3a), 178.6 (C-6); IR (neat): ν(max) 3484, 3150, 3063, 2922, 1633, 1588, 1461, 1408, 1276, 1066, 1046, 1002, 885, 850, 775, 703, 669 cm⁻¹; m/z (100, M+H) 368; HRMS (ES): MH⁺, found 368.0285. Calculated for \([C_{19}H_{15}^{79}\text{BrNO}_2]^+\): requires, 368.0286.

4.10.6 Preparation of 6-bromo-4-(4-fluorophenyl)-2-(2-hydroxyethyl)-6-oxopyrrolo[3,2,1-\(ij\)]quinoline 142f (R = F; R' = -CH₂CH₂OH)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromoquinolin-4(1H)-one 136b (0.56 g, 1.4 mmol), PdCl₂(PPh₃)₂ (0.06 g, 0.07 mmol), CuI (0.028 g, 0.1 mmol) and Et₃N (0.8 mL, 5.5 mmol) in DMF/water (30 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.4 mL, 4.2 mmol) was added and the mixture was heated at 110 °C for 6 h; work up employed for 142e was adopted to afford 142f as light yellow solid, (0.19 g, 38%); mp 212-214 °C; Rf 0.30 (50% ethyl acetate/hexane); \(^1\)H NMR (300 MHz, CDCl₃) δ: 1.80 (1H, t, J 5.4 Hz, OH), 2.83 (2H, t, J 6.0 Hz, CH₂CH₂), 3.71 (2H, dd, J 3.0, 6.3 Hz, CH₂OH), 6.16 (1H, s, 1-H), 6.66 (1H, s, 5-H), 7.41 (2H, t, J 9.0 Hz, 3' & 5'-H), 7.74 (2H, dd, J 3.0, 6.0 Hz, 2' & 6'-H), 7.90 (1H, s, 9-H), 8.15 (1H, s, 7-H); \(^1^3\)C NMR (75 MHz, CDCl₃) δ: 32.7 (CH₂CH₂), 59.1 (CH₂OH), 108.7 (C-5), 116.3 (d, 2J₇F 21.9 Hz, C-3' & 5'), 117.8 (C-2), 118.1 (C-8), 122.6 (C-1) 128.5 (d, 3J₇F 8.0 Hz, C-2' & 6'), 130.4 (d, 4J₇F 3.2 Hz, C-1'), 131.8 (C-9a), 131.9 (C-6a), 132.1 (C-7), 134.9 (C-9), 143.5 (C-4), 149.1 (C-3a), 163.6 (d, 1J₇F 245.9 Hz, C-4'), 177.7 (C-6); IR (neat): ν(max) 3351, 3058, 2955, 2925, 2632, 1580, 1505, 1465, 1416, 1275, 1217, 1162, 1048, 1002, 875, 845, 791, 766, 691, 659 cm⁻¹; m/z (100, M+H) 386; HRMS (ES): MH⁺, found 386.0196. Calculated for \([C_{19}H_{14}F^{79}\text{BrNO}_2]^+\): requires, 386.0192.
4.10.7 Preparation of 6-bromo-4-(4-chlorophenyl)-2-(2-hydroxyethyl)-6-oxopyrrolo[3,2,1-ij]quinoline 142g (R = Cl; R' = -CH₂CH₂OH)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromoquinolin-4(1H)-one 136e (0.4 g, 1.0 mmol), PdCl₂(PPh₃)₂ (0.034 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) and Et₃N (0.6 mL, 4.0 mmol) in DMF/water (30 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.30 mL, 3.0 mmol) was added and the mixture was heated at 110 °C for 6 h; work up employed for 142e was adopted to afford 142g as light yellow solid, (0.134 g, 35%); mp 166-168 °C; Rf 0.32 (50% ethyl acetate/hexane); ¹H NMR (300 MHz, CDCl₃) δ: 1.83 (1H, broad s, OH), 2.40 (2H, t, J 6.2 Hz, CH₂CH₂), 3.73 (2H, br s, CH₂OH), 6.14 (1H, s, 1-H), 6.66 (1H, s, 5-H), 7.50 (4H, d, J 7.7 Hz, 2', 3', 5' & 6'-H), 7.90 (1H, s, 9-H), 8.15 (1H, s, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 32.3 (CH₂CH₂), 60.2 (CH₂OH), 109.2 (C-5), 118.2 (C-1), 118.7 (C-8), 122.7 (C-2), 124.0 (C-2' & 6'), 128.4 (C-3' & 5'), 129.2 (C-1'), 130.1 (C-9a), 130.9 (C-4'), 132.1 (C-6a), 135.0 (C-7), 136.7 (C-9), 141.3 (C-4), 147.9 (C-3a), 178.4 (C-6); IR (neat): ν(max) 3444, 3059, 2956, 2901, 1639, 1589, 1573, 1460, 1412, 1344, 1281, 1219, 1085, 1051, 1019, 999, 971, 879, 832, 767, 730, 701, 657 cm⁻¹; m/z (100, M+H) 402; HRMS (ES): MH⁺, found 401.9884. Calculated for [C₁₉H₁₄⁷⁹ClBrNO₂]⁺: requires, 401.9896.

4.10.8 Preparation of 6-bromo-4-(4-methoxyphenyl)-2-(2-hydroxyethyl)-6-oxopyrrolo[3,2,1-ij]quinoline 142h (R = OCH₃; R' = -CH₂CH₂OH)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromoquinolin-4(1H)-one 136d (0.5 g, 1.2 mmol), PdCl₂(PPh₃)₂ (0.04 g, 0.06 mmol), CuI (0.02 g, 0.1 mmol) and Et₃N (0.5 mL, 3.6 mmol) in DMF/water (30 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.35 mL, 3.6 mmol) was added and the mixture was heated at 110 °C for 6 h; work up employed for 142e was adopted to
afford 142h as light yellow solid, (0.152 g, 32%); mp 177-179 °C; Rf 0.16 (50% ethyl acetate/hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.05 (1H, t, \(J\) 4.5 Hz, OH), 2.47 (2H, t, \(J\) 6.0 Hz, CH\(_2\)CH\(_2\)), 3.72 (2H, dd, \(J\) 4.5, 6.0 Hz, CH\(_2\)OH), 3.91 (3H, s, OCH\(_3\)), 6.17 (1H, s, 1-H), 6.66 (1H, s, 5-H), 7.02 (2H, t, \(J\) 5.7 Hz, 3' & 5'-H), 7.40 (2H, t, \(J\) 5.7 Hz, 2' & 6'-H), 7.89 (1H, s, 9-H), 8.15 (1H, s, 7-H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 32.4 (CH\(_2\)CH\(_2\)), 55.4 (OCH\(_3\)), 60.3 (CH\(_2\)OH), 109.1 (C-5), 114.1 (C-1), 118.2 (C-8), 118.4 (C-2), 122.7 (C-2' & 6'), 123.9 (3' & 5'), 125.8 (C-1'), 128.2 (C-9a), 130.1 (C-6a), 130.9 (C-7), 135.0 (C-9), 141.5 (C-4), 149.2 (C-3a), 161.0 (C-4'), 178.7 (C-6); IR (neat): \(\nu\) (max) 3380, 3062, 2926, 2842, 2220, 1633, 1602, 1582, 1527, 1507, 1463, 1409, 1247, 1218, 1149, 1046, 1024, 1003, 989, 838, 801, 775, 719, 692, 661 cm\(^{-1}\); \(m/z\) (100, M+H) 398; HRMS (ES): MH\(^+\), found 398.0386. Calculated for \([C_{20}H_{17}^{79}BrNO_3]^+\): requires, 398.0392.

4.11 Preparation of 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,2,1-\(ij\)]quinoline derivatives

143a-h

2,8-Disubstituted 4-aryl-6-oxopyrrolo[3,2,1-\(ij\)]quinolines 143a-h

4.11.1 Preparation of 2,4-diphenyl-8-(2-phenylethynyl)-6-oxopyrrolo[3,2,1-\(ij\)]quinoline 143a

(R = H; R' = -C\(_6\)H\(_5\))

A stirred mixture of 6,8-dibromo-2-phenylquinolin-4(1\(H\))-one 136a (0.4 g, 1.1 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.04 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) and Et\(_3\)N (0.6 mL, 4.2 mmol) in DMF/water (30 mL) was purged with argon for 1 h. Phenyl acetylene (0.35 mL, 3.2 mmol) was
added and the mixture was stirred at 110 °C for 5 h. The cooled reaction mixture was mixed with cold water (50 mL) and the product was extracted into CHCl₃ (3×50 mL). The combined organic layers were washed with brine (2×20 mL); dried with anhydrous MgSO₄ and the salt was filtered off. The organic solvent was concentrated under reduced pressure and the concentrate was purified on a silica gel column to afford the pure product 143a as yellow solid, (0.29 g, 67%); mp 219-221 °C; Rf 0.70 (20% ethyl acetate/hexane); ¹H NMR (300 MHz, CDCl₃) δ: 6.34 (1H, s, 1-H), 6.78 (1H, s, 5-H), 6.97-7.17 (10H, m, Ph'-H & Ph'''-H), 7.37 (3H, dd, J 1.6, 5.1 Hz, 3'', 4'' & 5''-H), 7.58 (2H, dd, J 1.6, 5.1 Hz, 2'' & 6''-H), 8.08 (1H, s, 9-H), 8.42 (1H, s, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 89.2 (C≡2), 89.4 (C≡1), 111.4 (C-5), 113.3 (C-8), 118.4 (C-1), 120.2 (C-9a), 122.4 (C-4''), 123.1 (C-4''), 125.8 (C-4'), 127.6 (C-6a), 127.7 (C-2'' & 6''), 128.0 (C-2'' & 6''), 128.4 (C-2' & 6'), 129.0 (C-3'' & 5''), 129.1 (C-3'' & 5''), 129.2 (C-3' & 5'), 129.3 (C-7), 131.4 (C-1''), 131.5 (C-1''), 131.6 (C-2), 133.0 (C-9), 136.2 (C-1'), 143.1 (C-3a), 149.9 (C-4), 179.4 (C-6); IR (neat): ν (max) 3056, 3032, 2205, 1630, 1601, 1492, 1452, 1405, 1264, 1193, 886, 845, 756, 699, 689 cm⁻¹; m/z (100, M+H) 422; HRMS (ES): MH⁺, found 422.1552. Calculated for [C₃₁H₂₀NΟ]⁺: requires, 422.1467.

4.11.2 Preparation of 4-(4-fluorophenyl)-2-phenyl-8-(2-phenylethynyl)-6-oxopyrrolo[3,2,1-ij]quinoline 143b (R = F; R' = -C₆H₅)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromoquinolin-4(1H)-one 136b (0.56 g, 1.4 mmol), PdCl₂(PPh₃)₂ (0.06 g, 0.07 mmol), CuI (0.028 g, 0.1 mmol) and Et₃N (0.8 mL, 5.5 mmol) in DMF/water (30 mL) was purged with argon for 1 h. Phenyl acetylene (0.4 mL, 4.2 mmol) was added and the mixture was heated at 110 °C for 6 h; work up and column chromatography on silica gel employed for 143a afforded 143b as light yellow solid, (0.41 g, 70%); mp 242-244 °C; Rf 0.30 (50% ethyl acetate/hexane); ¹H NMR (300 MHz, CDCl₃) δ: 6.30 (1H, s, 1-H), 6.70 (2H,
t, J 8.4 Hz, 3'' & 5''-H), 6.79 (1H, s, 5-H), 7.04 (3H, t, J 2.7 Hz, 3', 4' & 5'-H), 7.13 (2H, dd, J 2.4, 5.6 Hz, 2'' & 6''-H), 7.36-7.40 (4H, m, 2' & 6' and 3''' & 5'''-H), 7.56-7.59 (3H, m, 2'', 4'' & 6''-H), 8.08 (1H, s, 9-H), 8.40 (1H, s, 7-H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 89.1 (C≡2), 89.5 (C≡1), 111.5 (C-5), 114.8 (d, $^2$J$_{CF}$ 22.0 Hz, C-3'' & 5''), 118.4 (C-8), 120.3 (C-1), 122.4 (C-9a), 123.0 (C-4''), 125.9 (C-4'), 127.8 (C-6a), 128.2 (C-1''), 128.4 (C-2'' & 6''), 129.0 (C-2' & 6'), 129.1 (C-3'' & 5''), 129.2 (C-3' & 5'), 129.4 (C-7), 131.0 (d, $^3$J$_{CF}$ 8.6 Hz, C-2'' & 6''), 131.2 (d, $^4$J$_{CF}$ 3.4 Hz, C-1''), 131.3 (C-2), 131.4 (C-9), 136.1 (C-1'), 142.9 (C-4), 148.7 (C-3a), 163.1 (d, $^1$J$_{CF}$ 249.0 Hz, C-4'), 179.3 (C-6); IR (neat): ν(max) 3058, 2198, 1633, 1605, 1490, 1459, 1416, 1359, 1265, 1222, 1142, 836, 760, 693, 659 cm$^{-1}$; m/z (100, M+H) 440; HRMS (ES): MH$^+$, found 440.1462. Calculated for [C$_{31}$H$_{19}$FNO]+: requires, 440.1372.

4.11.3 Preparation of 4-(4-chlorophenyl)-2-phenyl-8-(2-phenylethynyl)-6-oxopyrrolo[3,2,1-i]quinoline 143c (R = Cl; R' = -C$_6$H$_5$)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromoquinolin-4(1H)-one 136c (0.4 g, 1.0 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.04 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) and Et$_3$N (0.5 mL, 3.9 mmol) in DMF/water (30 mL) was purged with argon for 1 h. Phenyl acetylene (0.32 mL, 2.9 mmol) was added and the mixture was heated at 110 °C for 5 h; work up and column chromatography on silica gel employed for 143a afforded 143c as yellow solid, (0.30 g, 68%); mp 254-256 °C; R$_f$ 0.80 (20% ethyl acetate/ hexane); $^1$H NMR (300 MHz, CDCl$_3$) δ: 6.28 (1H, s, 1-H), 6.77 (1H, s, 5-H), 6.97 (2H, d, J 7.5 Hz, 3'' & 5''-H), 7.03-7.09 (5H, m, Ph'-H), 7.14-7.18 (3H, m, 3'', 4'' & 5'''-H), 7.34-7.38 (2H, m, 2'' & 6''-H), 7.56 (2H, dd, J 3.0, 6.0 Hz, 2'' & 6''-H), 8.04 (1H, s, 9-H), 8.35 (1H, s, 7-H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 89.1 (C≡2), 89.5 (C≡1), 111.4 (C-5), 113.2 (C-8), 118.2 (C-1), 120.3 (C-9a), 122.3 (C-4''), 125.8 (C-4'), 127.8 (C-6a), 127.9 (C-2' & 6'), 128.1 [C-2 & 6(phenyl-1-ethynyl)], 128.4 [C-2 & 6(phenylprop-1-ene)], 129.0 (C-3' & 5'), 171
129.1 [C-3 & 5(phenyl-1-ethynyl)], 129.4130.3 [C-3 & 5 (phenylprop-1-ene)], 130.3 (C-5), 131.1 (C-1''), 131.4 (C-1'''), 131.6 [C-8-(2-yl)], 135.5 (C-7), 136.0 [C-1(phenylprop-1-ene)], 142.8 (C-2), 148.5 (C-8a), 179.2 (C-4); IR (neat): \(\nu_{(\text{max})}\) 3080, 2196, 1634, 1594, 1486, 1461, 1262, 1009, 883, 827, 752, 685 cm\(^{-1}\); \(m/z\) (100, M+H) 456.5; HRMS (ES): MH\(^+\), found 456.1156. Calculated for [C\(_{31}\)H\(_{19}\)ClNO]\(^+\): requires, 456.1077.

4.11.4 Preparation of 4-(4-methoxyphenyl)-2-phenyl-8-(2-phenylethynyl)-6-oxopyrrolo[3,2,1-ij]quinoline 143d (R = OCH\(_3\); R' = -C\(_6\)H\(_5\))

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromoquinolin-4(1H)-one 136d (0.5 g, 1.2 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.04 g, 0.06 mmol), CuI (0.02 g, 0.1 mmol) and Et\(_3\)N (0.7 mL, 4.9 mmol) in DMF/water (30 mL) was purged with argon for 1 h. Phenyl acetylene (0.41 mL, 3.7 mmol) was added and the mixture was stirred at 110 °C for 12 h; work up and column chromatography on silica gel employed for 143a afforded 143d as yellow solid, (0.34 g, 62%); mp 235-237 °C; \(R_f\) 0.34 (30% ethyl acetate/ hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 3.71 (3H, s, OCH\(_3\)), 6.32 (1H, s, 1-H), 6.52 (2H, dd, \(J\) 2.7, 4.8 Hz, 3'' & 5''-H) 6.81 (1H, s, 5-H), 7.03-7.11 (8H, m, 2'', 4'' & 6''-H and 2-Ph'), 7.38 (2H, dd, \(J\) 1.8, 3.0 Hz, 3'' & 5''-H), 7.58 (2H, dd, \(J\) 1.8, 3.0 Hz, 2'' & 6''-H), 8.09 (1H, d, \(J\) 1.5 Hz, 9-H), 8.42 (1H, d, \(J\) 1.5 Hz, 7-H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 55.3 (OCH\(_3\)), 89.2 (C=2), 89.4 (C=1), 111.5 (C-5), 113.2 (C-8), 117.9 (C-1), 120.2 (C-9a), 122.2 (C-4''), 123.0 (C-4'), 125.2 (C-6a), 125.7 (C-1'''), 127.6 (C-2'' & 6''), 127.8 (C-2'' & 6''), 128.4 (C-2' & 6'), 128.8 (C-3'' & 5''), 128.9 (C-3' & 5'), 129.0 (C-3'' & 5''), 129.3 (C-7), 130.3 (C-1''), 130.5 (C-2), 131.5 (C-9), 136.1 (C-1''), 143.2 (C-3a), 150.1 (C-4), 160.4 (C-4''), 179.3 (C-6); IR (neat): \(\nu_{(\text{max})}\) 3058, 3009, 2895, 2837, 2190, 1633, 1605, 1505, 1459, 1395, 1296, 1246, 1176, 1024, 917, 834, 753, 689 cm\(^{-1}\); \(m/z\) (100, M+H) 452; HRMS (ES): MH\(^+\), found 452.1653. Calculated for [C\(_{32}\)H\(_{22}\)NO\(_2\)]\(^+\): requires, 452.1651.
4.11.5 Preparation of 2-(2-hydroxyethyl)-8-(4-hydroxy-2-methylbut-1-en-1-yl)-2-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline 143e (R = H; R' = -CH₂CH₂OH)

A stirred mixture of 6,8-dibromo-2-phenylquinolin-4(1H)-one 136a (0.4 g, 1.1 mmol), PdCl₂(PPh₃)₂ (0.04 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) and Et₃N (0.6 mL, 4.2 mmol) in DMF/water (30 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.30 mL, 3.2 mmol) was added and the mixture was heated at 110 °C for 6 h. The cooled reaction mixture was mixed with water (50 mL) and the product was extracted into CHCl₃ (3x60 mL). The combined organic layers were washed with brine (2x10 mL), dried with anhydrous MgSO₄ and the salt filtered off. The solvent was concentrated under reduced pressure and the crude product was purified on a silica gel column to afford the pure product 143e as yellow solid, (0.22 g, 59%); mp 190-192 °C; Rₚ 0.20 (50% ethyl acetate/ hexane); ᵃ¹H NMR (300 MHz, CDCl₃) δ: 2.18 (2H, t, J 6.0 Hz, CH₂CH₂'), 2.61 (2H, t, J 6.0 Hz, CH₂CH₂''), 3.47 (2H, dd, J 6.0, 6.3 Hz, CH₂OH'), 3.63 (2H, dd, J 6.0, 6.3 Hz, CH₂OH''), 4.66 (1H, t, J 6.3 Hz, OH), 4.98 (1H, t, J 6.3 Hz, OH), 6.03 (1H, s, 1-H), 6.78 (1H, s, 5-H), 7.53-7.66 (5H, m, Ph'-H), 7.88 (1H, s, 9-H), 7.98 (1H, s, 7-H); ᵃ¹C NMR (75 MHz, CDCl₃) δ: 23.9 (CH₂CH₂'), 32.6 (CH₂CH₂''), 59.2 (CH₂OH'), 60.3 (CH₂OH''), 81.5 (C≡α), 88.9 (C≡β), 109.2 (C-5), 117.6 (C-8), 120.1 (C-4''), 121.9 (C-9a), 123.7 (C-1), 128.7 (C-6a), 129.2 (C-3'', & 5''), 129.3 (C-2'' & 6''), 130.2 (C-1''), 132.1 (C-2'), 132.6 (C-7), 135.2 (C-9), 143.0 (C-4), 149.9 (C-3a), 178.1 (C-6); IR (neat): ν(max) 3495, 3448, 3356, 3219, 2937, 2888, 2214, 1658, 1630, 1565, 1466, 1411, 1357, 1271, 1212, 1175, 1065, 1026, 854, 775, 713, 655, 626; m/z (100, M+H) 358; HRMS (ES): MH⁺, found 358.1440. Calculated for [C₂₃H₂₀N₃]⁺: requires, 358.1443.
4.11.6 Preparation of 4-(4-fluorophenyl)-2-(2-hydroxyethyl)-8-(4-hydroxy-2-methylbut-1-en-1-yl)-6-oxopyrrolo[3,2,1-ij]quinoline 143f (R = F; R' = -CH₂CH₃OH)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromoquinolin-4(1H)-one 136b (0.56 g, 1.4 mmol), PdCl₂(PPh₃)₂ (0.06 g, 0.07 mmol), CuI (0.028 g, 0.1 mmol) and Et₃N (0.8 mL, 5.5 mmol) in DMF/water (40 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.4 mL, 4.2 mmol) was added and the mixture was heated at 110 °C for 6 h; work up and column chromatography on silica gel employed for 143e afforded 143f as light yellow solid, (0.26 g, 49%); mp 227-228 °C; Rf 0.24 (50% ethyl acetate/ hexane); ¹H NMR (300 MHz, CDCl₃) δ: 2.19 (2H, t, J 6.0 Hz, CH₂CH₂′), 2.61 (2H, t, J 6.0 Hz, CH₂CH₂′′), 3.50 (2H, dd, J 6.0, 7.8 Hz, CH₂OH′), 3.64 (2H, dd, J 6.0, 7.8 Hz, CH₂OH′′), 4.69 (1H, t, J 6.0 Hz, OH′′′), 4.98 (1H, t, J 6.0 Hz, OH′′), 6.03 (1H, s, 1-H), 6.77 (1H, s, 5-H), 7.41 (2H, t, J 9.0 Hz, 3′ & 5′-H), 7.65 (2H, dd, J 3.0, 5.4 Hz, 2′ & 6′-H), 7.88 (1H, s, 9-H), 7.98 (1H, s, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 23.9 (CH₂CH₂′), 32.7 (CH₂CH₂′′), 59.2 (CH₂OH′), 60.3 (CH₂OH′′), 81.5 (C≡α), 89.0 (C≡β), 109.1 (C-5), 116.3 (d, ²J₉ 21.7 Hz, C-3′ & 5′), 117.9 (C-8), 121.9 (C-9a), 123.7 (C-1), 128.7 (d, ³J₉ 8.0 Hz, C-2′ & 6′), 130.2 (C-6a), 130.5 (d, ⁴J₉ 3.2 Hz, C-1′), 131.9 (C-2), 132.0 (C-7), 135.2 (C-9), 142.9 (C-4), 148.9 (C-3a), 163.6 (d, ⁵J₉ 246.2 Hz, C-4′′), 178.1 (C-6); IR (neat): ν (max) 3264, 2932, 2885, 2218, 1636, 1599, 1504, 1466, 1418, 1290, 1226, 1064, 1038, 1001, 847, 810, 657 cm⁻¹; m/z (100, M+H) 376; HRMS (ES): MH⁺, found 376.1357. Calculated for [C₂₃H₁₉FNO₃]⁺: requires, 376.1349.
4.11.7 Preparation of 4-(4-chlorophenyl)-2-(2-hydroxyethyl)-8-(4-hydroxy-2-methylbut-1-en-1-yl)-6-oxopyrrolo[3,2,1-ij]quinoline 143g (R = Cl; R' = -CH₂CH₂OH)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromoquinolin-4(1H)-one 136c (0.40 g, 1.0 mmol), PdCl₂(PPh₃)₂ (0.034 g, 0.05 mmol), CuI (0.020 g, 0.1 mmol) and Et₃N (0.5 mL, 3.9 mmol) in DMF/water (30 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.3 mL, 2.9 mmol) was added and the mixture was heated at 110 °C for 6 h; work up and column chromatography on silica gel employed for 143e afforded 143g as light yellow solid, (0.23 g, 60%); mp 208-210 °C; Rf 0.25 (50% ethyl acetate/ hexane); ¹H NMR (300 MHz, CDCl₃) δ: 2.10 (2H, t, J 6.0 Hz, CH₂CH₂'), 2.60 (2H, t, J 6.0 Hz, CH₂CH₂''), 3.51 (2H, dd, J 6.0, 7.8 Hz, CH₂OH'), 3.63 (2H, dd, J 6.0, 7.8 Hz, CH₂OH''), 4.71 (1H, t, J 5.4 Hz, OH'), 4.98 (1H, t, J 5.4 Hz, OH''), 6.04 (1H, dd, J 6.0, 7.8 Hz, CH₂OH''), 6.78 (1H, t, J 7.5 Hz, CH₂OH'), 7.64 (2H, t, J 7.5 Hz, 3'' & 5''), 7.65 (2H, dd, J 7.5 Hz, 2" & 6''), 7.88 (1H, s, 1-H), 6.78 (1H, s, 5-H), 7.64 (2H, t, J 7.5 Hz, 3'' & 5''), 7.65 (2H, dd, J 7.5 Hz, 2" & 6''), 7.88 (1H, s, 9-H), 7.98 (1H, s, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 23.9 (CH₂CH₂'), 32.7 (CH₂CH₂''), 59.2 (CH₂OH'), 60.3 (CH₂OH''), 81.4 (C≡α), 89.0 (C≡β), 109.1 (C-5), 117.8 (C-8), 120.2 (C-4''), 121.8 (C-9a), 123.7 (C-1), 128.7 (C-6a), 129.2 (C-3'' & 5''), 130.2 (C-2'' & 6''), 131.4 (C-1''), 132.2 (C-2), 132.9 (C-7), 135.5 (C-9), 142.8 (C-4), 148.6 (C-3a), 178.1 (C-6); IR (neat): ν(max) 3369, 3058, 2935, 2882, 2842, 2220, 1634, 1606, 1586, 1507, 1462, 1408, 1276, 1247, 1221, 1179, 1120, 1025, 1003, 837, 771, 722, 693, 661 cm⁻¹; m/z (100, M+H) 392; HRMS (ES): MH⁺, found 392.1063. Calculated for [C₂₃H₁₉ClNO₃]⁺: requires, 392.1053.

4.11.8 Preparation of 4-(4-methoxyphenyl)-2-(2-hydroxyethyl)-8-(4-hydroxy-2-methylbut-1-en-1-yl)-6-oxopyrrolo[3,2,1-ij]quinoline 143h (R = OCH₃; R' = -CH₂CH₂OH)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromoquinolin-4(1H)-one 136d (0.50 g, 1.2 mmol), PdCl₂(PPh₃)₂ (0.043 g, 0.06 mmol), CuI (0.023 g, 0.1 mmol) and Et₃N (0.5 mL, 4.9
mmol) in DMF/water (35 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.4 mL, 3.7 mmol) was added and the mixture was heated at 110 °C for 6 h; work up and column chromatography on silica gel employed for 143e afforded 143h as light yellow solid, (0.27 g, 57%); mp 181-182 °C; R_f 0.10 (50% ethyl acetate/ hexane); ^1H NMR (300 MHz, CDCl3) δ: 2.57 (2H, t, J 6.3 Hz, CH2CH'), 2.60 (2H, t, J 6.3 Hz, CH2CH''), 3.49 (2H, d, J 4.5 Hz, CH2OH'), 3.63 (2H, d, J 4.5 Hz, CH2OH''), 3.85 (3H, s, OCH3), 4.67 (1H, s, OH'), 4.97 (1H, s, OH''), 6.00 (1H, s, 1-H), 6.77 (1H, s, 5-H), 7.09 (2H, d, J 8.7 Hz, 3'' & 5''-H), 7.57 (2H, d, J 8.7 Hz, 2'' & 6''-H), 7.86 (1H, s, 9-H), 7.96 (1H, s, 7-H); ^13C NMR (75 MHz, CDCl3) δ: 23.9 (CH2CH'), 32.8 (CH2CH''), 55.9 (OCH3), 59.2 (CH2OH'), 60.3 (CH2OH''), 81.5 (C≡α), 88.8 (C≡β), 109.1 (C-5), 114.5 (C-8), 120.0 (C-9a), 121.8 (C-1), 123.6 (C-6a), 126.2 (C-3'' & 5''), 126.7 (C-2'' & 6''), 128.5 (C-1''), 130.2 (C-2), 130.8 (C-7), 135.3 (C-9), 143.0 (C-4), 149.9 (C-3a), 160.9 (C-4''), 178.2 (C-6); IR (neat): ν(max) 3250, 3196, 3076, 2936, 2882, 2841, 2221, 1635, 1600, 1507, 1462, 1409, 1281, 1246, 1211, 1178, 1057, 1032, 843, 771, 722, 693, 661 cm⁻¹; m/z (100, M+H) 388; HRMS (ES): MH⁺, found 388.1557. Calculated for [C24H22NO4]⁺: requires, 388.1549.

4.12 Preparation of 2-substituted 4-aryl-8-(4-fluorophenyl)-6-oxopyrrolo[3,2,1-ij]quinoline derivatives 144a-e

2-Substituted 4-aryl-8-(4-fluorophenyl)-6-oxopyrrolo[3,2,1-ij]quinolines 144a-e
4.12.1 Preparation of 8-(4-fluorophenyl)-2,4-diphenyl-6-oxopyrrolo[3,2,1-ij]quinoline 144a

(R = -C₆H₅; R' = H)

A stirred mixture of 8-bromo-2,4-diphenyl-6-oxopyrrolo[3,2,1-ij]quinoline 142a (0.15 g, 0.4 mmol), 4-FPhB(OH)₂ (0.063 g, 0.5 mmol), PdCl₂(PPh₃)₂ (0.013 g, 0.02 mmol), PCy₃ (0.011 g, 0.04 mmol) and K₂CO₃ (0.1 g, 0.8 mmol) in dioxane/water (3:1, v/v; 15 mL) was degassed under argon for 0.5 h. The mixture was then stirred at 100 °C for 3 h. The cooled reaction mixture was mixed with cold water (20 mL) and the product was extracted into CHCl₃ (3x30 mL). The combined organic layers were washed with brine (2x10 mL), dried and the salt was filtered off. The organic solvent was evaporated under reduced pressure and the crude product was purified on a silica gel column to afford 144a as yellow solid, (0.107 g, 69%); mp 238-240 °C; Rₚ (20% ethyl acetate/hexane) 0.64; ¹H NMR (300 MHz, CDCl₃) δ: ¹H NMR (300 MHz, CDCl₃) δ: 6.38 (1H, s, 1-H), 6.84 (1H, s, 5-H), 7.00-7.22 (8H, m, 3'', 4'' & 5''-H and 2-Ph'-H), 7.70 (2H, dd, J 3.0, 5.4 Hz, 2'' & 6''-H), 8.10 (1H, s, 9-H), 8.41 (1H, s, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 111.8 (C-5), 115.9 (d, ²JC₆F 21.4 Hz, C-3'' & 5''), 118.3 (C-2), 121.0 (C-3' & 5'), 122.6 (C-9a), 125.0 (C-3'' & 5''), 127.4 (C-2' & 6'), 127.6 (C-2'' & 6''), 127.7 (C-4'), 127.9 (C-4), 128.4 (C-8), 129.1 (d, ³JC₆F 8.0 Hz, C-2'' & 6''), 129.2 (C-9), 129.6 (C-1), 130.1 (d, ⁴JC₆F 3.2 Hz, C-1'''), 131.6 (C-7), 133.2 (C-6a), 136.2 (C-1''), 137.0 (C-4''), 137.8 (C-1'), 142.9 (C-4), 149.9 (C-3a), 162.6 (d, ¹JC₆F 245.3 Hz, C-4''), 180.1 (C-6); IR (neat): ν(max) 3056, 2956, 2923, 2853, 1639, 1598, 1465, 1407, 1288, 1225, 1165, 996, 839, 755, 697 cm⁻¹; m/z (100, M+H) 416; HRMS (ES): MH⁺, found 416.1462. Calculated for [C₂₉H₁₉FNO]⁺: requires, 416.1451.
4.12.2 Preparation of 4,8-bis(4-fluorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline 144b
\( \text{R} = -C_6H_5; \text{R'} = F \)

A stirred mixture of 8-bromo-4-(4-fluorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline 142b (0.15 g, 0.4 mmol), 4-FPhB(OH)\(_2\) (0.060 g, 0.4 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.012 g, 0.02 mmol), PCy\(_3\) (0.010 g, 0.04 mmol) and K\(_2\)CO\(_3\) (0.1 g, 0.8 mmol) in dioxane/water (3:1, v/v; 15 mL) was degassed under argon for 0.5 h. The mixture was then stirred at 100 °C for 3 h; work up and column chromatography on silica gel employed for 144a afforded 144b as light yellow solid, (0.085 g, 57%); mp 270-272 °C; R\(_f\) 0.68 (20% ethyl acetate/ hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 6.34 (1H, s, 1-H), 6.71 (2H, t, \(J = 9.2\) Hz, 3" & 5"-H), 6.84 (1H, s, 5-H), 7.05 (4H, t, \(J = 3.0\) Hz, 2"', 3"', 5''' & 6'''-H), 7.12-7.21 (5H, m, Ph'-H), 7.70 (2H, t, \(J = 9.2\) Hz, 2" & 6"-H), 8.11 (1H, s, 9-H), 8.41 (1H, s, 7-H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 111.8 (C-5), 114.9 (d, \(J_{CF} = 21.6\) Hz, C-3" & 5"), 115.4 (d, \(J_{CF} = 21.6\) Hz, C-3"" & 5""), 118.3 (C-1), 121.1 (C-7), 122.6 (C-6a), 125.1 (C-9), 127.8 (C-2' & 6'), 128.1 (C-3' & 5'), 129.3 (d, \(J_{CF} = 8.0\) Hz, C-2" & 6"), 129.3 (d, \(J_{CF} = 8.0\) Hz, C-2"" & 6""), 129.4 (C-4'), 129.5 (C-8), 131.1 (d, \(J_{CF} = 3.2\) Hz, C-1") 131.2 (d, \(J_{CF} = 3.2\) Hz, C-1"'), 131.5 (C-1'), 136.2 (C-2), 138.0 (C-9a), 142.7 (C-3a), 148.7 (C-4), 162.7 (d, \(J_{CF} = 247.5\) Hz, C-4"), 163.1 (d, \(J_{CF} = 247.5\) Hz, C-4""), 180.0 (C-6); IR (neat): \(v_{(max)}\) 3062, 1639, 1598, 1503, 1464, 1417, 1290, 1270, 1225, 1167, 996, 835, 808, 759, 698 cm\(^{-1}\); m/z (100, M+H) 434; HRMS (ES): MH\(^+\), found 434.1357. Calculated for [C\(_{29}\)H\(_{18}\)F\(_2\)NO\(^+\)]: requires, 434.1356.

4.12.3 Preparation of 4-(4-chlorophenyl)-8-(4-fluorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline derivative 144c (R = -C\(_6\)H\(_5\); R' = Cl)

A stirred mixture of 8-bromo-4-(4-chlorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline 142c (0.15 g, 0.3 mmol), 4-FPhB(OH)\(_2\) (0.060 g, 0.4 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.012 g, 0.02 mmol), PCy\(_3\)
(0.010 g, 0.03 mmol) and K₂CO₃ (0.1 g, 0.8 mmol) in dioxane/water (3:1,v/v; 15 mL) was degassed under argon for 0.5 h. The mixture was then stirred at 100 °C for 3 h; work up and column chromatography on silica gel employed for 144a afforded 144c as light yellow solid, (0.096 g, 62%); mp 276-278 °C; Rf 0.68 (20% ethyl acetate/ hexane); ¹H NMR (300 MHz, CDCl₃) δ: 6.34 (1H, s, 1-H), 6.84 (1H, s, 5-H), 6.96-7.10 (9H, m, 2', 3', 5', 6' & Ph'-H), 7.18 (2H, t, J 8.4 Hz, 3'' & 5''-H), 7.69 (2H, dd, J 3.0, 6.9 Hz, 2'' & 6''-H), 8.11 (1H, s, 9-H), 8.40 (1H, s, 7-H); ¹³C NMR (75 MHz, CDCl₃) δ: 111.8 (C-5), 115.9 (d, ²J_CF 21.4 Hz, C-3'' & 5''), 118.2 (C-2), 121.1 (C-3' & 5'), 122.6 (C-9a), 125.2 (C-3'' & 5''), 127.8 (C-2' & 6'), 127.9 (C-2'' & 6''), 128.1 (C-4'), 128.4 (C-8), 129.3 (d, ³J_CF 8.0 Hz, C-2'' & 6''), 129.5 (C-9), 129.5 (C-1), 131.4 (C-7), 131.6 (C-6a), 135.5 (C-1'), 136.1 (C-1'), 136.9 (d, ⁴J_CF 3.5 Hz, C-1'''), 138.0 (C-4''), 142.6 (C-4), 148.5 (C-3a), 162.7 (d, ¹J_CF 245.3 Hz, C-4''), 180.0 (C-6); IR (neat): ν(max) 3062, 1639, 1593, 1487, 1463, 1413, 1286, 1268, 1230, 1167, 1089, 997, 843, 829, 760, 697 cm⁻¹; m/z (100, M+H) 450; HRMS (ES): MH⁺, found 450.1052. For [C₂₉H₁₈FClNO]⁺: requires, 450.1061.

4.12.4 Preparation of 4-(4-methoxyphenyl)-8-(4-fluorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline derivative 144d (R = -C₆H₅; R' = OCH₃)

A stirred mixture of 8-bromo-4-(4-methoxyphenyl)-2-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline 142d (0.16 g, 0.4 mmol), 4-FPhB(OH)₂ (0.062 g, 0.4 mmol), PdCl₂(PPh₃)₂ (0.013 g, 0.02 mmol), PCy₃ (0.010 g, 0.03 mmol) and K₂CO₃ (0.1 g, 0.8 mmol) in dioxane/water (3:1,v/v; 15 mL) was degassed under argon for 0.5 h. The mixture was then stirred at 100 °C for 3 h; work up and column chromatography on silica gel employed for 144a afforded 144d as light yellow solid, (0.116 g, 63%); mp 232-234 °C; Rf 0.48 (20% ethyl acetate/ hexane); ¹H NMR (300 MHz, CDCl₃) δ: 3.71 (3H, s, OCH₃), 6.35 (1H, s, 1-H), 6.52 (2H, d, J 7.5 Hz, 3'' & 5''-H), 6.83 (1H, s, 5-H), 7.05-7.09 (7H, m, 3'' & 5'' and Ph'-H), 7.18 (2H, t, J 9.2 Hz, 2'' & 6''-H), 7.69 (2H, dd, J
3.0, 6.0 Hz, 2'' & 6''), 8.09 (1H, s, 9-H), 8.41 (1H, s, 7-H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 55.3 (OCH$_3$), 111.7 (C-5), 113.2 (C-3' & 5'), 115.8 (d, $^2$J$_{CF}$ 21.4 Hz, C-3'' & 5''), 117.8 (C-2), 121.0 (C-9a), 122.6 (C-8), 124.9 (C-2' & 6''), 125.5 (C-4'), 127.6 (C-2' & 6'), 127.7 (C-3' & 5'), 128.4 (C-6), 129.3 (d, $^3$J$_{CF}$ 8.3 Hz, C-2'' & 6''), 129.3 (C-6a), 129.5 (C-1), 130.5 (C-7), 131.8 (C-9), 136.2 (C-1''), 137.1 (d, $^4$J$_{CF}$ 3.4 Hz, C-1'''), 137.8 (C-1'), 142.9 (C-4), 149.8 (C-3a), 160.3 (C-4''), 162.6 (d, $^1$J$_{CF}$ 245.3 Hz, C-4''), 180.2 (C-6); IR (neat): ν (max) 3080, 3052, 2960, 2931, 2836, 1636, 1597, 1507, 1461, 1401, 135, 999, 831, 758, 692 cm$^{-1}$; m/z (100, M+H) 446; HRMS (ES): MH$^+$, found 446.1562. Calculated for [C$_{30}$H$_{21}$FNO$_2$]$^+$: requires, 446.1556.

4.12.5 Preparation of 2-(2-hydroxyethyl)-8-(4-fluorophenyl)-4-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline derivatives 144e (R = -CH$_2$CH$_2$OH; R' = H)

A stirred mixture of 6-bromo-2-(2-hydroxyethyl)-4-phenyl-6-oxopyrrolo[3,2,1-ij]quinoline 142e (0.10 g, 0.3 mmol), 4-FPhB(OH)$_2$ (0.046 g, 0.3 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.010 g, 0.01 mmol), PCy$_3$ (0.008 g, 0.03 mmol) and K$_2$CO$_3$ (0.08 g, 0.6 mmol) in dioxane/water (3:1,v/v; 12 mL) was degassed under argon for 0.5 h. The mixture was then stirred at 100 °C for 3 h; work up and column chromatography on silica gel employed for 144a afforded 144e as light yellow solid, (0.058 g, 59%); mp 200-202 °C; R$_f$ 0.27 (20% ethyl acetate/ hexane); $^1$H NMR (300 MHz, CDCl$_3$) δ: 1.61 (1H, s, OH), 2.40 (2H, t, J 6.0 Hz, CH$_2$CH$_2$), 3.68 (2H, q, J 4.5, 6.0 Hz, CH$_2$OH), 6.24 (1H, s, 1-H), 6.72 (1H, s, 5-H), 7.16 (2H, t, J 8.4 Hz, 3'' & 5''-H), 7.49-7.56 (5H, m, Ph'-H), 7.64 (2H, dd, J 3.6, 6.0 Hz, 2'' & 6''), 7.97 (1H, s, 9-H), 8.29 (1H, s, 7-H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 32.2 (CH$_2$CH$_2$), 60.5 (CH$_2$OH), 109.9 (C-5), 115.9 (d, $^2$J$_{CF}$ 21.4 Hz, C-3'' & 5''), 118.1 (C-1), 120.3 (C-9a), 122.1 (C-8), 124.5 (C-3' & 5'), 128.8 (C-2' & 6'), 129.1 (d, $^3$J$_{CF}$ 8.0 Hz, C-2'' & 6''), 129.7 (C-6a), 130.2 (C-7), 133.9 (C-9), 135.8 (C-1'), 136.1 (d, $^4$J$_{CF}$ 3.2 Hz, C-1''), 137.0
(C-4'), 140.5 (C-4), 148.9 (C-3a), 162.6 (d, $^1J_{CF}$ 245.3 Hz, C-4''), 179.8 (C-6); IR (neat): $\nu_{(\text{max})}$ 3415, 3080, 3062, 3046, 1634, 1583, 1467, 1413, 1356, 1269, 1221, 1162, 1069, 1047, 998, 898, 835, 773, 709, 652 cm$^{-1}$; m/z (100, M+H) 384; HRMS (ES): MH$^+$, found 384.1406. Calculated for [C$_{25}$H$_{19}$FNO$_2$]$^+$: requires, 384.1400.

4.13 Preparation of 2,6,8-triaryl-2,3-dihydroquinolin-4(1H)-ones 145a-h

\[
\begin{align*}
\text{2,6,8-Triaryl-2,3-dihydroquinolin-4(1H)-ones 145a-h}
\end{align*}
\]

4.13.1 Preparation of 2,6,8-trisphenyl-2,3-dihydroquinolin-4(1H)-one 145a (R, R' = H)

A stirred mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1H)-one 122a (1.0 g, 2.6 mmol), phenylboronic acid (0.80 g, 6.6 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.092 g, 0.1 mmol), tricyclohexylphosphine (0.073 g, 0.2 mmol) and potassium carbonate (0.79 g, 5.7 mmol) in dioxane-water (3:1, v/v; 50 mL), in a 2-necked round bottomed flask equipped with a stirrer bar, rubber septum and a condenser was degassed for 30 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 3 h. The mixture was then allowed to cool to room temperature and then poured into cold water (100 mL). The product was extracted into chloroform (3×60 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 145a as yellow solid (0.84 g, 85%); $R_f$
(30% ethyl acetate/ hexane) 0.75; mp 165-166 °C (EtOH); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 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, 3-H), 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, 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\(_3\)) \(\delta\): 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): \(\nu_{max}\) 3380, 2134, 2098, 1675, 1600, 1571, 1474, 1315, 1269, 1234, 1142, 1073, 1030, 901 cm\(^{-1}\).

4.13.2 Preparation of 2-(4-fluorophenyl)-6,8-bisphenyl-2,3-dihydroquinolin-4(1H)-one

145b (R = F, R′ = H)

An experimental procedure employed for the synthesis of 145a was followed using a mixture of 122b (1.0 g, 2.5 mmol), PhB(OH)\(_2\) (0.77 g, 6.3 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.088 g, 0.1 mmol), PCy\(_3\) (0.07 g, 0.2 mmol), and K\(_2\)CO\(_3\) (0.76 g, 5.5 mmol) in dioxane-water (50 mL); work-up and column chromatography on silica gel afforded 145b as yellow solid (0.89 g, 84%); \(R_f\) (30% ethyl acetate/ hexane) 0.75; mp 182-184 °C (EtOH); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 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, 3-H), 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, 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\(_3\)) \(\delta\): 46.5 (C-3), 57.6 (C-2), 115.8 (C-8), 116.0 (d, \(J_{CF}\ 21.8\) 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, \(J_{CF}\ 8.3\) Hz, C-2′ and C-6′), 128.2 (C-4‴″), 129.1 (C-
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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): $\nu_{\text{max}}$ 3381, 3056, 2923, 2652, 2113, 1681, 1600, 1481, 1350, 1321, 1270, 1232, 1157, 905, 868 cm$^{-1}$.

4.13.3 Preparation of 2-(4-chlorophenyl)-6,8-bisphenyl-2,3-dihydroquinolin-4(1H)-one

$^{145c}$ ($R = \text{Cl}$, $R' = \text{H}$)

An experimental procedure employed for the synthesis of $^{145a}$ was followed using a mixture of $^{122c}$ (1.0 g, 2.4 mmol), PhB(OH)$_2$ (0.73 g, 6.0 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.084 g, 0.1 mmol), PCy$_3$ (0.067 g, 0.2 mmol) and K$_2$CO$_3$ (0.73 g, 5.3 mmol) in dioxane-water (50 mL); work-up and column chromatography on silica gel afforded $^{145c}$ as yellow solid (0.81 g, 82%); $R_f$ (30% ethyl acetate/ hexane) 0.75; mp 202-204 °C (EtOH); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.87 (1H, dd, $J$ 4.5 and 16.2 Hz, 3-H), 2.91 (1H, dd, $J$ 12.3 and 16.2 Hz, 3-H), 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, 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$_3$) $\delta$: 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): $\nu_{\text{max}}$ 3744, 3373, 2086, 1666, 1611, 1479, 1409, 1358, 1312, 1274, 1231, 1143, 1086, 897, 865 cm$^{-1}$.  


4.13.4 Preparation of 6,8-bisphenyl-2(4-methoxyphenyl)-2,3-dihydroquinolin-4(1H)-one

145d (R = OCH₃, R′ = H)

An experimental procedure employed for the synthesis of 145a was followed using a mixture of 122d (1.0 g, 2.4 mmol), PhB(OH)₂ (0.73 g, 6.0 mmol), PdCl₂(PPh₃)₂ (0.085 g, 0.1 mmol), PCy₃ (0.068 g, 0.2 mmol) and K₂CO₃ (0.30 g, 2.1 mmol) in dioxane-water (50 mL); work-up and column chromatography on silica gel afforded 145d as yellow solid (0.83 g, 86%); Rᵢ (30% ethyl acetate/ hexane) 0.63; mp 194-196 °C (EtOH); ¹H NMR (300 MHz, CDCl₃) δ: 2.80 (1H, ddd, J 1.5, 4.5 and 16.2 Hz, 3- H), 2.93 (1H, dd, J 12.3 and 16.2 Hz, 3-H), 3.79 (3H, s, COCH₃), 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, 4”'-H, 4’’-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); ¹³C NMR (75 MHz, CDCl₃) δ: 46.6 (C-3), 55.0 (OCH₃), 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): νmax 3744, 3390, 2359, 1881, 1675, 1607, 1509, 1478, 1347, 1300, 1240, 1171, 1143, 1107, 1036, 901 cm⁻¹.

4.13.5 Preparation of 6,8-bis(4-fluorophenyl)-2-phenyl-2,3-dihydroquinolin-4(1H)-one

145e (R = H, R’ = F)

An experimental procedure employed for the synthesis of 145a was followed using a mixture of 122a (1.0 g, 2.6 mmol), 4-fluorophenylboronic acid (0.93 g, 6.5 mmol), PdCl₂(PPh₃)₂ (0.09 g, 0.1 mmol), PCy₃ (0.073 g, 0.2 mmol) and K₂CO₃ (0.80 g, 5.8 mmol) in dioxane-water (50 mL); work-up and column chromatography on silica gel afforded 145e as yellow solid (0.82 g, 77%);
Rf (30% ethyl acetate/ hexane) 0.70; mp 167-169 °C (EtOH); 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75 MHz, CDCl3) δ: 46.4 (C-3), 58.2 (C-2), 115.6 (d, 2JCF 21.4 Hz, C-3'' and C-5''), 115.8 (d, 2JCF 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, 3JCF 7.5 Hz, C-2''' and C-6'''), 130.9 (d, 3JCF 7.5 Hz, C-2'' and C-6''), 133.2 (C-4'), 134.6 (d, 4JCF 3.0 Hz, C-1'''), 135.9 (d, 4JCF 3.0 Hz, C-1''), 140.8 (C-1'), 147.9 (C-8a), 162.2 (d, 1JCF 240 Hz, C-4''), 162.6 (d, 1JCF 247.5 Hz, C-4''), 193.1 (C-4); IR (neat): υmax 3376, 2924, 2853, 1669, 1603, 1482, 1360, 1220, 1144, 1014, 903, 832, 765, 701, 602 cm⁻¹.

4.13.6 Preparation of 2,6,8-tris(4-fluorophenyl)-2,3-dihydroquinolin-4(1H)-one 145f (R = F, R' = F)

An experimental procedure employed for the synthesis of 145a was followed using a mixture of 122b (1.0 g, 2.5 mmol), ArB(OH)₂ (0.88 g, 6.3 mmol), PdCl₂(PPh₃)₂ (0.088 g, 0.1 mmol), PCy₃ (0.070 g, 0.2 mmol) and K₂CO₃ (0.76 g, 5.5 mmol) in dioxane-water (50 mL); work-up and column chromatography on silica gel afforded 148f as yellow solid (0.82 g, 76%); Rf (30% ethyl acetate/ hexane) 0.70; mp 176-178 °C (EtOH); 1H NMR (300 MHz, CDCl₃) 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); 13C NMR (75 MHz, CDCl₃) δ: 46.4 (C-3), 57.6 (C-2), 115.8 (C-8), 116.0 (d, 2JCF 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”), 136.6 (d, $^4J_{CF}$ 3.0 Hz, C-1’”), 138.3 (C-3”’ and C-5”’), 116.2 (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-3’), 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

4.13.7 Preparation of 6,8-bis(4-fluorophenyl)-2(4-chlorophenyl)-2,3-dihydroquinolin-4(1H)-one 145g (R = Cl, R’ = F)

An experimental procedure employed for the synthesis of 145a was followed using a mixture of 122c (1.0 g, 2.4 mmol), ArB(OH)$_2$ (0.85 g, 6.0 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.084 g, 0.1 mmol), PCy$_3$ (0.067 g, 0.2 mmol) and K$_2$CO$_3$ (0.75 g, 5.3 mmol) in dioxane-water (50 mL); work-up and column chromatography on silica gel afforded 145g as yellow solid (0.86 g, 78%); 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, $^J_{4,5}$ 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, m, 2′′-H, 3′′-H, 5′′-H, 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”’), 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): $v_{\text{max}}$ 3392, 2846, 2625, 1678, 1603, 1577, 1487, 1406, 1354, 1320, 1231, 1163, 1014, 908, 834, 761, 732 cm$^{-1}$.

### 4.13.8 Preparation of 6,8-bis(4-fluorophenyl)-2(4-methoxyphenyl)-2,3-dihydroquinolin-4(1H)-one 145h ($R = \text{OCH}_3$, $R' = \text{F}$)

An experimental procedure employed for the synthesis of 145a was followed using a mixture of 122d (1.0 g, 2.4 mmol), ArB(OH)$_2$ (0.85 g, 6.0 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.084 g, 0.1 mmol), PCy$_3$ (0.067 g, 0.2 mmol) and K$_2$CO$_3$ (0.295 g, 2.1 mmol) in dioxane-water (50 mL); work-up and column chromatography on silica gel afforded 145h as yellow solid (0.80 g, 75%); $R_f$ (30% ethyl acetate/ hexane) 0.64; mp 182-184 °C (EtOH); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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, 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$_3$) $\delta$: 46.5 (C-3), 55.1 (OCH$_3$), 57.7 (C-2), 114.4 (C-4a), 115.8 (d, $^2J_{\text{CF}}$ 21.4 Hz, C-3''' and C-5'''), 116.2 (d, $^2J_{\text{CF}}$ 21.4 Hz,(C-3'' and C-5'''), 119.5 (C-8), 127.9 (d, $^3J_{\text{CF}}$ 7.5 Hz, C-2'' and C-6'''), 128.5 (C-2' and C-6'), 130.0 (C-5), 130.9 (d, $^3J_{\text{CF}}$ 8.3 Hz, C-2'' and C-6'''), 131.0 (C-3' and C-5'), 132.8 (C-7), 133.3 (d, $^4J_{\text{CF}}$ 3.8 Hz, C-1''), 135.9 (d, $^4J_{\text{CF}}$ 3.0 Hz, C-1''), 148.0 (C-8a), 162.2 (d, $^1J_{\text{CF}}$ 244.5 Hz, C-4''), 162.5 (d, $^1J_{\text{CF}}$ 246.8 Hz C-4''), 193.4 (C-4); IR (neat): $v_{\text{max}}$ 3402, 2123, 1887, 1676, 1609, 1509, 1484, 1349, 1304, 1220, 1153, 1028, 908, 830, 787 cm$^{-1}$. 

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4.14 Preparation of 2,6,8-triphenylquinolin-4(1H)-ones 146a-h

\[ \text{R'} \]

\[ \text{R} \]

2,6,8-Triphenylquinolin-4(1H)-ones 146a-h

4.14.1 Preparation of 2,6,8-triphenylquinolin-4(1H)-one 146a (R = H, R' = H)

A stirred mixture of 145a (0.80 g, 2.1 mmol) and thallium(III) p-tolylsulphonate (TTS) (1.71 g, 2.3 mmol) in dimethoxylethane (DME) (25 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 (100 mL). The organic phase was washed sequentially with \( \text{Na}_2\text{CO}_3 \) solution (2×20 mL) and cold water (2×20 mL). The product was dried over anhydrous MgSO\(_4\), filtered and the solvent was evaporated under reduced pressure and recrystallized from ethanol to afford 146a as white solid (0.69 g, 86%); mp 242-244 °C (EtOH); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta: \) 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, 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\(_3\)) \( \delta: \) 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\text{max} 3398, 3056, 2962, 1626, 1591, 1492, 1290, 1246, 1181, 1076, 844, 759, 695, 653, 622 cm\(^{-1}\).

4.14.2 Preparation of 2-(4-fluorophenyl)-6,8-bisphenylquinolin-4(1H)-one 146b (R = F, R’ = H)

A stirred mixture of 145b (0.80 g, 2.0 mmol) and TTS (1.63 g, 2.2 mmol) in DME (25 mL); work-up employed for the synthesis of 146a was followed and afforded 146b as yellowish orange solid (0.66 g, 82%); 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, \(^2\)J\text{CF} 22.5 Hz, C-3’ and C-5’), 125.8 (C-6), 127.1 (C-4’’), 127.7 (d, \(^3\)J\text{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\text{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\text{CF} 250.5 Hz, C-4’), 178.9 (C-4); IR (neat): ν\text{max} 3381, 3056, 2923, 2652, 2113, 1681, 1600, 1481, 1350, 1321, 1270, 1232, 1157, 905, 868 cm\(^{-1}\).

4.14.3 Preparation of 2-(4-chlorophenyl)-6,8-bisphenylquinolin-4(1H)-one 146c (R = Cl, R’ = H)

A stirred mixture of 145c (0.80 g, 2.0 mmol) and TTS (1.56 g, 2.1 mmol) in DME (25 mL); work-up and column chromatography on silica gel employed for 146a afforded 146c as light orange solid (0.66 g, 83%); mp 208-210 °C (EtOH); \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ: 6.57 (1H, d,
19.0 Hz, 3'-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, 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); 13C NMR (75 MHz, CDCl₃) 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, 1274, 1143, 1086, 897, 865 cm⁻¹.

4.14.4 Preparation of 2(4-methoxyphenyl)-6,8-bisphenylquinolin-4(1H)-one 146d (R = OCH₃, R' = H)

A stirred mixture of 145d (0.80 g, 2.0 mmol) and TTS (1.62 g, 2.2 mmol) in DME (25 mL); work-up and column chromatography on silica gel employed for the 146a afforded 146d as white solid (0.64 g, 80%); mp 212-214 °C (EtOH); 1H NMR (300 MHz, CDCl₃) δ: 3.85 (3H, s, COCH₃), 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); 13C NMR (75 MHz, CDCl₃) δ: 55.5 (OCH₃), 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'''), 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'), 136.1.
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 3374, 1881, 1675, 1607, 1509, 1478, 1347, 1300, 1240, 1171, 1143, 1107, 1036, 901 cm⁻¹.

4.14.5 Preparation of 6,8-bis(4-fluorophenyl)-2-phenylquinolin-4(1H)-one 146e (R = H, R’ = F)

A stirred mixture of 145e (0.80 g, 1.9 mmol) and TTS (1.56 g, 2.1 mmol) in DME (25 mL); work-up and column chromatography on silica gel employed for 146a afforded 146e as off-white solid (0.70 g, 88%); mp 239-242 °C (EtOH); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ: 108.4 (C-3), 115.8 (d, J_CF 21.8 Hz, C-3’’ and C-5’’’), 117.0 (d, J_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, J_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, J_CF 8.3 Hz, C-2’’’ and C-6’’’), 132.2 (d, J_CF 3.0 Hz, C-1’’’), 134.3 (C-1’), 135.7 (d, J_CF 3.8 Hz, C-1’’’), 136.2 (C-2), 148.8 (C-8a), 162.6 (d, J_CF 245.3 Hz, C-4’’), 166.0 (d, J_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.

4.14.6 Preparation of 2,6,8-tris(4-fluorophenyl)quinolin-4(1H)-one 146f (R = F, R’ = F)

A stirred mixture of 145f (0.80 g, 1.9 mmol) and TTS (1.49 g, 2.1 mmol) in DME (25 mL); work-up and column chromatography on silica gel employed for 146a afforded 146f as light yellow solid (0.64 g, 80%); mp 240-242 °C (EtOH); ¹H NMR (300 MHz, CDCl₃) 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$_3$) $\delta$: 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, $^3J_{CF}$ 8.3 Hz, C-2'' and C-6''), 130.5 (d, $^3J_{CF}$ 7.5 Hz, C-2''' and C-6'''), 130.5 (C-4a), 131.0 (d, $^3J_{CF}$ 7.5 Hz, C-2' and C-6'), 131.7 (C-7), 132.1 (d, $^4J_{CF}$ 3.8 Hz, C-1'), 132.1 (d, $^4J_{CF}$ 3.8 Hz, C-1'''), 135.6 (d, $^4J_{CF}$ 3.8 Hz, C-1'), 136.1 (C-2), 147.8 (C-8a), 162.7 (d, $^1J_{CF}$ 246.0 Hz, C-4''), 163.0 (d, $^1J_{CF}$ 248.3 Hz, C-4''), 164.2 (d, $^1J_{CF}$ 251.3 Hz, C-4'), 178.7 (C-4); IR (neat): $\nu_{max}$ 3406, 1627, 1591, 1497, 1237, 1164, 1107, 1021, 894, 839, 809, 726 cm$^{-1}$.

4.14.7 Preparation of 2-(4-chlorophenyl)-6,8-bis(4-fluorophenyl)quinolin-4(1H)-one 146g

(R = Cl, R' = F)

A stirred mixture of 145g (0.80 g, 1.8 mmol) and TTS (1.44 g, 2.0 mmol) in DME (25 mL); work-up and column chromatography on silica gel employed for 146a afforded 146g as orange solid (0.62 g, 78%); mp 225-228 °C (EtOH); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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$_3$) $\delta$: 108.5 (C-3), 115.9 (d, $^2J_{CF}$ 21.0 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'), 127.4 (C-6), 128.7 (d, $^3J_{CF}$ 7.5 Hz, C-2''' and C-6''), 130.0 (C-3' and C-5'), 130.5 (C-5), 192
131.0 (4a), 131.1 (d, $^3J_{CF}$ 8.3 Hz, C-2’’’ and C-6’’’), 131.8 (C-4a), 132.1 (d, $^4J_{CF}$ 3.8 Hz, C-1’’’),
132.8 (C-7), 135.6 (d, $^4J_{CF}$ 3.8 Hz, C-1’’’), 136.1 (C-4’), 137.2 (C-2), 147.6 (C-8a), 162.7 (d, $^1J_{CF}$
245.3 Hz, C-4’’), 163.1 (d, $^1J_{CF}$ 248.3 Hz, C-4’’’), 178.8 (C-4’); IR (neat): $\nu_{max}$ 3400, 1624, 1601,
1490, 1380, 1297, 1224, 1158, 1094, 1013, 942, 884, 828, 766, 725 cm$^{-1}$.

4.14.8 Preparation of 2-(4-methoxyphenyl)-6,8-bis(4-fluorophenyl)quinolin-4(1H)-one

$^{146h}$ ($R = \text{OCH}_3, R’ = F$)

A stirred mixture of $^{145h}$ (0.80 g, 1.8 mmol) and TTS (1.45 g, 2.0 mmol) in DME (25 mL);
work-up and column chromatography on silica gel employed for $^{146a}$ afforded $^{146h}$ as orange
solid (0.60 g, 75%); mp 219–220 °C (EtOH); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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’ 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$_3$) $\delta$: 55.5 (OCH$_3$), 107.5 (C-3),
115.8 (d, $^2J_{CF}$ 21.0 Hz, C-3’’ and C-5’’), 116.9 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 7.5 Hz, C-2’’ and C-6’’’), 131.1 (d,
$^3J_{CF}$ 8.3 Hz, C-2’’’ and C-6’’’), 131.5 (C-4a), 131.7 (C-7), 132.3 (d, $^4J_{CF}$ 3.0 Hz, C-1’’’), 135.7 (d,
$^4J_{CF}$ 3.8 Hz, C-1’’’), 135.4 (C-1’), 136.2 (C-2), 148.5 (C-8a), 161.7 (C-4’), 162.6 (d, $^1J_{CF}$ 246.0
Hz, C-4’’), 163.0 (d, $^1J_{CF}$ 243.8 Hz, C-4’’’), 178.8 (C-4’); IR (neat): $\nu_{max}$ 3413, 1628, 1582, 1508,
1501, 1223, 1158, 827, 765 cm$^{-1}$.
4.15 Preparation of 2,6,8-triaryl-3-iodoquinolin-4(1H)-ones 147a-h

\[
\begin{align*}
R' & \quad 2'' & 5'' & 1 & 3 & 6' \\
5'' & 7 & & H & I & 1 \\
2'' & & 5'' & & & R
\end{align*}
\]

2,6,8-Triaryl-3-iodoquinolin-4(1H)-ones 147a-h

4.15.1 Preparation of 2,6,8-triphenyl-3-iodoquinolin-4(1H)-one 147a (R, R' = H)

A mixture of 146a (0.50 g, 1.3 mmol), I\(_2\) (0.68 g, 2.7 mmol) and Na\(_2\)CO\(_3\) (0.21 g, 2.0 mmol) in THF (20 mL) was stirred at room temperature for 18 hours. The mixture was quenched with saturated sodium thiosulphate solution and the precipitate was collected by filtration and washed with ice-cold water. The crude product was recrystallized in ethanol to afford 147a as light brown solid, (0.48 g, 81%); mp 219-220 °C (EtOH); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.39 (2H, d, \(J\ 7.5\ Hz,\ 3'\ and\ 5'-H\)), 7.44-7.57 (11H, m, 4', Ph''- and Ph'''-H), 7.72 (2H, d, \(J\ 7.5\ Hz,\ 2'\ and\ 6'-H\)), 7.84 (1H, d, \(J\ 2.1\ Hz,\ 7-H\)), 8.45 (1H, s, N-H), 8.70 (1H, d, \(J\ 2.1\ Hz,\ 5-H\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 86.4 (C-3), 121.8 (C-8), 124.4 (C-6), 127.2 (C-4''), 127.8 (C-4'''), 128.5 (C-4'), 128.9 (C-2'' & 6''), 129.0 (C-2'' & 6''), 129.0 (C-2' & 6'), 129.1 (C-3'' & 5'), 129.8 (C-3'' & 5''), 130.5 (C-3' & 5'), 131.0 (C-5), 132.1 (C-4a), 135.1 (C-7), 136.0 (C-1'), 137.5 (C-1''), 137.9 (C-1''), 139.5 (C-8), 151.3 (C-2), 175.2 (C-4); IR (neat): \(v_{\text{max}}\) 3395, 3057, 1736, 1557, 1476, 1441, 1236, 1176, 1023, 892, 761, 654 cm\(^{-1}\); \(m/z\) (100, M+H) 500; HRMS (ES): MH\(^+\); found 500.0411. For [C\(_{27}\)H\(_{19}\)INO\(^+\]): requires 500.0339.
4.15.2 Preparation of 2-(4-fluorophenyl)-6,8-diphenyl-3-idoquinolin-4(1H)-one 147b (R = F; R' = H)

A mixture of 146b (0.50 g, 1.3 mmol), I₂ (0.65 g, 2.6 mmol) and Na₂CO₃ (0.20 g, 1.9 mmol) in THF (20 mL) was stirred at room temperature for 18 hours; work-up as described for 147a afforded 147b as light brown solid (0.45 g, 75%); mp 225-226 °C (EtOH); ¹H NMR (300 MHz, CDCl₃) δ: 7.18 (2H, d, J 7.2 Hz, 3’ & 5’-H), 7.36-7.58 (10H, m, Ph'' & Ph'''-H), 7.72 (2H, d, J 7.2 Hz, 2' & 6’-H), 7.84 (1H, d, J 2.1 Hz, 7-H), 8.40 (1H, s, N-H), 8.68 (1H, d, J 2.1 Hz, 5-H); ¹³C NMR (75 MHz, CDCl₃) δ: 86.6 (C-3), 116.1 (d, ²JCF 21.9 Hz, C-3’ & 5’), 121.7 (C-8), 124.4 (C-6), 127.1 (C-4’), 127.8 (C-4’’), 129.0 (C-2” & 6’’), 129.0 (C-2” & 6’’), 129.1 (C-3” & 5’), 129.9 (C-3” & 5’), 130.7 (d, ³JCF 8.9 Hz, C-2’ & 6’), 131.0 (C-5), 132.2 (C-4a), 133.9 (d, ⁴JCF 3.4 Hz, C-1’), 135.1 (C-7), 135.9 (C-1”), 137.6 (C-1”), 139.4 (C-8a), 150.3 (C-2), 163.7 (d, ¹JCF 250.7 Hz, C-4’), 175.1 (C-4); IR (neat): υ_max 3396, 3055, 1734, 1588, 1480, 1394, 1223, 1157, 837, 760, 696, 611 cm⁻¹; m/z (100, M+H) 518; HRMS (ES): MH⁺; found 518.0411. For [C₂₇H₁₈FINO]⁺: requires 518.0339.

4.15.3 Preparation of 2-(4-chlorophenyl)-6,8-diphenyl-3-idoquinolin-4(1H)-one 147c (R = Cl; R' = H)

A mixture of 146c (0.50 g, 1.2 mmol), I₂ (0.62 g, 2.5 mmol) and Na₂CO₃ (0.20 g, 1.8 mmol) in THF (20 mL) was stirred at room temperature for 18 hours; work-up as described for 147a afforded 147c as light brown solid (0.47 g, 74%); mp 225-226 °C (EtOH); ¹H NMR (300 MHz, CDCl₃) δ: 7.39 (2H, t, J 7.2 Hz, 3’ & 5’-H), 7.44-7.58 (10H, m, Ph'' & Ph'''-H), 7.72 (2H, d, J 7.2 Hz, 2’ & 6’-H), 7.84 (1H, d, J 2.1 Hz, 7-H), 8.38 (1H, s, N-H), 8.69 (1H, d, J 2.1 Hz, 5-H); ¹³C NMR (75 MHz, CDCl₃) δ: 86.5 (C-3), 121.8 (C-8), 124.4 (C-6), 127.2 (C-4’), 127.8 (C-4’’), 195
129.0 (C-4'), 129.1 (C-2" & 6''), 129.3 (C- 2" & 6''), 129.9 (C-3" & 5''), 129.9 (C-3'' & 5''), 131.0 (C-2' & 6'), 132.3 (C-3' & 5'), 135.1 (C-5), 135.9 (C-4a), 136.2 (C-7), 136.8 (C-1'), 137.7 (C- 1''), 137.9 (C-1''), 139.4 (C-8a), 150.1 (C-2), 175.1 (C-4); IR (neat): \( \nu_{\text{max}} \) 3382, 3055, 1780, 1586, 1508, 1586, 1508, 1491, 1481, 1215, 1161, 1087, 1038, 1014, 940, 897, 829, 766 \text{ cm}^{-1}; m/z (100, M+H) 534; HRMS (ES): MH\(^+\); found 534.0123. For \([\text{C}_{27}\text{H}_{18}\text{ClINO}]^+\): requires 534.0043.

4.15.4 Preparation of 2-(4-methoxyphenyl)-6,8-diphenyl-3-iodoquinolin-4(1H)-one 147d (R = OCH\(_3\); R' = H)

A mixture of 146d (0.50 g, 1.2 mmol), I\(_2\) (0.62 g, 2.5 mmol) and Na\(_2\)CO\(_3\) (0.20 g, 1.8 mmol) in THF (20 mL) was stirred at room temperature for 18 hours; work-up as described for 147a afforded 147d as light brown solid (0.51 g, 77%); mp 245-247 °C (EtOH); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 3.86 (3H, s, OCH\(_3\)), 6.98 (2H, t, \( J \) 7.2 Hz, 3' & 5'-H), 7.38-7.55 (10H, m, Ph'' & Ph'''-H), 7.72 (2H, d, \( J \) 7.2 Hz, 2' & 6'-H), 7.83 (1H, d, \( J \) 2.1 Hz, 7-H), 8.43 (1H, s, N-H), 8.69 (1H, d, \( J \) 2.1 Hz, 5-H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \): 54.4 (OCH\(_3\)), 85.4 (C-3), 112.9 (C-8), 121.0 (C-6), 122.6 (C- 4''), 126.0 (C- 4''), 126.7 (C-2" & 6''), 127.7 (C-2" & 6''), 128.0 (C-2' & 6'), 128.2 (C-3" & 5'), 128.5 (C-3" & 5''), 129.3 (C-3' & 5'), 129.4 (C-5), 130.8 (C-4a), 131.1 (C-7), 134.6 (C-1'), 135.5 (C-1''), 136.0 (C-1''), 138.5 (C-8a), 151.1 (C-2), 159.9 (C-4'), 173.9 (C-4); IR (neat): \( \nu_{\text{max}} \) 3377, 3050, 1784, 1595, 1505, 1478, 1221, 1157, 1026, 898, 786, 622, 610 \text{ cm}^{-1}; m/z (100, M+H) 530; HRMS (ES): MH\(^+\); found 530.0623. For \([\text{C}_{28}\text{H}_{21}\text{NO}_2]^+\): requires 530.0539.
4.15.5 Preparation of 6,8-bis(4-fluorophenyl)-3-iodo-2-phenylquinolin-4(1H)-one 147e (R = H; R’ = F)

A mixture of 146e (0.50 g, 1.2 mmol), I₂ (0.62 g, 2.4 mmol) and Na₂CO₃ (0.19 g, 1.8 mmol) in THF (20 mL) was stirred at room temperature for 18 hours; work-up as described for 147a afforded 147e as light brown solid (0.47 g, 72%); mp 240-241 °C (EtOH); ¹H NMR (300 MHz, DMSO-d₆) δ: 7.16 (2H, t, J 8.4 Hz, 3''' & 5'''); 7.25 (2H, t, J 8.4 Hz, 3'' & 5''); 7.49-7.52 (7H, m, 2''' & 6'''-H and Ph'-H), 7.63-7.68 (2H, t, J 8.4 Hz, 2'' & 6''-H), 7.75 (1H, d, J 2.1 Hz, 7-H), 8.35 (1H, s, N-H), 8.61 (1H, d, J 2.1 Hz, 5-H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 86.4 (C-3), 115.9 (d, 2JCF 21.4 Hz, C-3'' & 5''), 117.0 (d, 2JCF 21.4 Hz, C-3''' & 5''), 121.7 (C-8), 124.4 (C-6), 128.4 (C-4'), 128.8 (d, 3JCF 8.0 Hz, C-2'' & 6''), 130.1 (C-4a), 130.6 (C-5), 130.9 (d, 3JCF 8.0 Hz, C-2'' & 6''), 131.7 (d, 4JCF 3.4 Hz, C-1''), 132.0 (C-2' & 6'), 135.1 (C-3' & 5'), 135.5 (d, 4JCF 3.4 Hz, C-1''), 136.5 (C-1'), 137.8 (C-7), 151.4 (C-8a), 162.7 (d, 1JCF 247.2 Hz, C-4''), 163.0 (d, 1JCF 247.2 Hz, C-4''), 175.0 (C-4); IR (neat): ν max 3399, 3047, 1782, 1589, 1557, 1481, 1388, 1216, 1159, 1038, 1012, 898, 828, 783, 699, 647, 607 cm⁻¹; m/z (100, M+H) 536; HRMS (ES): MH⁺; found 536.0320. For [C₂₇H₁₇F₂INO]⁺: requires 536.0245.

4.15.6 Preparation of 2,6,8-tris(4-fluorophenyl)-3-iodoquinolin-4(1H)-one 147f (R = F; R’ = F)

A mixture of 146f (0.50 g, 1.2 mmol), I₂ (0.59 g, 2.3 mmol) and Na₂CO₃ (0.19 g, 1.8 mmol) in THF (20 mL) was stirred at room temperature for 18 hours; work-up as described for 147a afforded 147f as light brown solid (0.47 g, 71%); mp 242-244 °C (EtOH); ¹H NMR (300 MHz, DMSO-d₆) δ: 7.14-7.28 (6H, m, 3', 3'', 3'''', 5', 5'' & 5'''-H), 7.49 (4H, dd, J 3.6, 5.4 Hz, 2'', 2''', 6'' & 6'''-H), 7.69 (2H, dd, J 3.0, 5.4 Hz, 2' & 6'-H), 7.75 (1H, d, J 2.1 Hz, 7-H), 8.26 (1H, s, N-H), 197
8.62 (1H, d, J 2.1 Hz, 5-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ: 87.4 (C-3), 115.7 (d, $^2$J$_{CF}$ 21.4 Hz, C-3" & 5"), 116.4 (d, $^2$J$_{CF}$ 21.4 Hz, C-3" & 5"), 116.5 (d, $^2$J$_{CF}$ 21.4 Hz, C-3' & 5'), 122.8 (C-8), 129.4 (d, $^3$J$_{CF}$ 8.3 Hz, C-2" & 6"), 132.3 (d, $^3$J$_{CF}$ 8.3 Hz, C-2" & 6"), 132.3 (d, $^3$J$_{CF}$ 8.3 Hz, C-2' & 6').

132.7 (C-6), 134.0 (C-4a), 135.2 (C-5), 135.5 (d, $^4$J$_{CF}$ 3.0 Hz, C-1"), 135.5 (d, $^4$J$_{CF}$ 3.0 Hz, C-1''), 135.8 (d, $^4$J$_{CF}$ 3.0 Hz, C-2'), 135.8 (d, $^4$J$_{CF}$ 3.0 Hz, C-3'), 135.9 (C-3" & 5''), 136.6 (C-7), 147.1 (C-2), 153.2 (C-8a), 162.6 (d, $^1$J$_{CF}$ 243.7 Hz, C-4''), 162.8 (d, $^1$J$_{CF}$ 243.7 Hz, C-4''), 163.3 (d, $^1$J$_{CF}$ 243.7 Hz, C-4'''), 174.3 (C-4);

IR (neat): $\nu_{max}$ 3381, 3066, 1780, 1589, 1503, 1481, 1218, 1158, 1097, 1040, 1014, 897, 839, 811, 797, 784, 618, 608 cm$^{-1}$; m/z (100, M+H) 554; HRMS (ES): MH$^+$; found, 554.0242.

For $[C_{27}H_{16}F_3INO]^+$: requires, 554.0150.

4.15.7 Preparation of 6,8-bis(4-fluorophenyl)-2-(4-chlorophenyl)-3-iodoquinolin-4(1H)-one

147g (R = Cl; R' = F)

A mixture of 146g (0.50 g, 1.1 mmol), I$_2$ (0.57 g, 2.3 mmol) and Na$_2$CO$_3$ (0.18 g, 1.7 mmol) in THF (20 mL) was stirred at room temperature for 18 hours; work-up as described for 147a afforded 147g as light brown solid (0.48 g, 75%); mp 251-252 °C (EtOH); $^1$H NMR (300 MHz, DMSO-$d_6$) δ: 7.33 (4H, dd, J 3.0, 5.4 Hz, 3'', 3''', 5'' & 5'''-H), 7.59 (4H, s, 2'', 2''', 6'' & 6'''-H), 7.72-7.76 (2H, dd, J 3.0, 5.4 Hz, 3 & 5'-H), 7.87 (2H, t, J 6.6 Hz, 2' & 6'-H), 7.89 (1H, d, J 2.1 Hz, 7-H), 8.41 (1H, d, J 2.1 Hz, 5-H), 11.15 (1H, s, N-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ: 87.2 (C-3), 116.3 (d, $^2$J$_{CF}$ 21.4 Hz, C-3" & 5"), 116.4 (d, $^2$J$_{CF}$ 21.4 Hz, C-3" & 5"), 122.8 (C-8), 128.7 (C-6), 129.2 (d, $^3$J$_{CF}$ 8.3 Hz, C-2" & 6"), 129.4 (d, $^3$J$_{CF}$ 8.3 Hz, C-2" & 6"), 131.8 (C-4'), 132.3 (d, $^4$J$_{CF}$ 3.0 Hz, C-1''), 132.7 (C-4a), 133.9 (d, $^4$J$_{CF}$ 3.0 Hz, C-1''), 135.0 (C-5), 135.5 (C-2' & 6'), 135.8 (C-3' & 5'), 136.5 (C-5), 137.5 (C-7), 152.9 (C-8a), 162.6 (d, $^1$J$_{CF}$ 243.4 Hz, C-4''), 162.8 (d, $^1$J$_{CF}$ 243.4 Hz, C-4''), 174.2 (C-4); IR (neat): $\nu_{max}$ 3382, 3055, 1781, 1586, 1507, 1492,
4.15.8 Preparation of 6,8-bis(4-fluorophenyl)-2-(4-methoxyphenyl)-3-iodoquinolin-4(1H)-one 147h (R = OCH₃; R' = F)

A mixture of 146h (0.50 g, 1.1 mmol), I₂ (0.57 g, 2.3 mmol) and Na₂CO₃ (0.18 g, 1.7 mmol) in THF (20 mL) was stirred at room temperature for 18 hours; work-up as described for 147a afforded 147h as light brown solid (0.48 g, 75%); mp 237-239 °C (EtOH); ¹H NMR (300 MHz, DMSO-d₆) δ: 3.82 (3H, s, OCH₃), 7.06 (2H, d, J 7.8 Hz, 3'' & 5''-H), 7.35 (4H, dd, J 3.6, 5.4 Hz, 2'', 3'' 5'' & 6''-H), 7.50 (2H, d, J 7.5 Hz, 2'' & 6''-H), 7.75-7.84 (4H, m, 2', 3', 5' & 6'-H), 7.86 (1H, d, J 2.1 Hz, 7-H), 8.39 (1H, s, N-H), 11.0 (1H, d, J 2.1 Hz, 5-H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 55.9 (OCH₃), 87.1 (C-3), 113.9 (C-8), 116.3 (d, ²JCF 21.3 Hz, C-3'' & 5''), 116.4 (d, ²JCF 21.3 Hz, C-3'' & 5''), 122.8 (d, ³JCF 8.3 Hz, C-2'' & 6''), 129.4 (d, ³JCF 8.3 Hz, C-2'' & 6''), 130.9 (C-6), 131.4 (C-3' & 5'), 132.5 (C-2' & 6'), 134.0 (d, ⁴JCF 3.0 Hz, C-1''), 134.0 (d, ⁴JCF 3.0 Hz, C-1''), 135.4 (C-4a), 135.9 (C-5), 136.5 (C-7), 153.7 (C-8a), 160.8 (C-4'), 162.6 (d, ¹JCF 243.3 Hz, C-4''), 162.8 (d, ¹JCF 243.3 Hz, C-4''), 174.3 (C-4); IR (neat): νₘₐₓ 3377, 3050, 1720, 1569, 1507, 1480, 1221, 1174, 1158, 1108, 1027, 834, 788, 623 cm⁻¹; m/z (100, M+H) 566; HRMS (ES): MH⁺; found, 566.0438. For [C₂₈H₁₉F₂INO₂]⁺: requires, 566.0350.
4.16 Preparation of 2,6',8'-trisubstituted 2'-arylfuoro[3,2-c]quinoline derivatives 148a-i

2,6',8'-Trisubstituted 2'-arylfuoro[3,2-c]quinolines 148a-i

4.16.1 Preparation of 2,4,6,8-tetraphenyl-furo[3,2-c]quinoline 148a (R = C_6H_5; R', R'' = H)

A mixture of 147a (0.30 g, 0.6 mmol), PdCl_2(PPh_3)_2 (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et_3N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added phenyl acetylene (0.13 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere. The mixture was cooled to room temperature and diluted with cold water (50 mL) and the product was taken up into CHCl_3 (3x50 mL). The combined organic layers were washed with water (2x20 mL), dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford 148a as pale yellow solid, (0.18 g, 67%); mp 202-204 °C; R_f (10% ethyl acetate/ hexane) 0.72; ^1H NMR (300 MHz, CDCl_3) δ: 7.39-7.60 (12H, m, 4', Ph'', Ph'''-H & 2'-Ph: 4-H), 7.87 (2H, d, J 8.7 Hz, 2-Ph: 3 & 5-H), 7.94 (2H, d, J 8.7 Hz, 3' & 5'-H), 8.00 (2H, d, J 8.7 Hz, 2-Ph: 2 & 6-H), 8.02 (1H, d, J 2.1 Hz, 7-H), 8.15 (2H, d, J 8.7 Hz, 2' & 6'-H), 8.58 (1H, d, J 2.1 Hz, 9-H); ^13C NMR (75 MHz, CDCl_3) δ: 101.6 (C-9a), 117.0 (C-3), 120.0 (C-3a), 125.0 (2-Ph: C-2 & 6), 127.3 (C-4'), 127.5 (C-9), 127.7 (C-4''), 127.8 (C-4'''), 128.7 (C-2' & 6'), 128.9 (C-2'' & 6''), 129.0 (C-3' & 5'), 129.1 (C-3'' & 5''), 129.2 (C-
3'' & 5''), 129.5 (2Ph: C-4), 129.9 (C-7), 131.1 (2-Ph: C-1), 139.0 (C-8), 139.7 (C-1'), 139.8 (C-1''), 139.8 (C-1'''), 140.6 (C-6), 141.5 (C-8), 142.3 (C-5a), 152.1 (C-2), 156.4 (C-4), 156.8 (C-1a); IR (neat): \( \nu_{\text{max}} \) 3069, 3053, 3032, 1590, 1482, 1365, 1091, 1010, 943, 874, 835, 791, 756, 737, 690, 643, 605 cm\(^{-1} \); \( m/z \) (100, M+H) 474; HRMS (ES): MH\(^+\), found: 474.1859. For \([C_{35}H_{24}NO]^+\): requires, 474.1858.

4.16.2 Preparation of 2,6,8-triphenyl-4-(4-fluorophenyl)furo[3,2-c]quinoline 148b (R = C\(_6\)H\(_5\); R'' = H; R' = F)

A mixture of 147b (0.30 g, 0.6 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et\(_3\)N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added phenyl acetylene (0.13 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere; work up and column chromatography on silica gel as described for 148a afforded 148b as pale yellow solid, (0.21 g, 71%); mp 204-205 °C \( R_f \) (10% ethyl acetate/ hexane) 0.78; \(^1\)H NMR (300 MHz, CDCl\(_3\) \( \delta \): 7.21 (2H, dd, \( J = 3.9, 8.7 \) Hz, 3' & 5'-H), 7.39-7.57 (10H, m, 3-H, 3'', 4'', 5'', Ph''', 2-Ph: 4-H), 7.87 (4H, dd, \( J = 6.0, 8.1 \) Hz, 2'' & 6'' and 2-Ph: 3 & 5-H), 8.00 (3H, dd, \( J = 4.5, 9.9 \) Hz, 7-H and 2-Ph: 2 & 6-H), 8.12 (2H, dd, \( J = 2.7, 5.7 \) Hz, 2' & 6'-H), 8.54 (1H, dd, \( J = 2.1 \) Hz, 9-H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\) \( \delta \): 101.3 (C-9a), 115.9 (d, \( J_{CF} = 21.4 \) Hz, C-3' & 5'), 116.9 (C-3), 119.7 (3a), 125.0 (d, \( J_{CF} = 8.0 \) Hz, C-2' & 6'), 127.3 (2-Ph: C-2 & 6), 127.5 (C-9), 127.7 (C-4''), 127.8 (C-4''), 129.0 (C-2'' & 6''), 129.1 (2-Ph: C-3 & 5), 129.1 (2-Ph: C-4), 129.7 (C-7), 130.6 (C-3'' & 5''), 130.7 (C-3'' & 5'''), 131.1 (2-Ph: C-1), 135.9 (d, \( J_{CF} = 3.2 \) Hz, C-1'), 139.0 (C-6), 139.8 (C-1''), 140.5 (C-1'''), 141.4 (C-8), 142.2 (C-5a), 150.9 (C-2), 156.5 (C-4), 156.7 (C-1a), 163.5 (d, \( J_{CF} = 247.6 \) Hz, C-4'); IR (neat): \( \nu_{\text{max}} \) 3052, 3033, 1600, 1485, 1366, 1227, 1154, 1012, 842, 793, 757, 691, 616 cm\(^{-1} \);
\[ m/z (100, M+H) 492; \text{HRMS (ES): } MH^+, \text{ found: 492.1764. For } [C_{35}H_{23}FNO]^+: \text{ requires, 492.1758.} \]

4.16.3 Preparation of 2,6,8-triphenyl-4-(4-chlorophenyl)furo[3,2-c]quinoline 148c (R = C\(_6\)H\(_5\); R'' = H; R' = Cl)

A mixture of 147c (0.30 g, 0.6 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et\(_3\)N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added phenyl acetylene (0.12 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere; work up and column chromatography on silica gel as described for 148a afforded 148c as pale yellow solid, (0.20 g, 68%); mp 245-246 °C; R\(_f\) (10% ethyl acetate/ hexane) 0.78; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.43-7.55 (12H, m, 3-H, 2-Ph: 4-H, Ph'' and Ph'''-H), 7.88 (4H, dd, J 1.5, 8.9 Hz, 3' & 5'-H and 2-Ph: 3 & 5-H), 8.02 (4H, dd, J 1.5, 8.9 Hz, 2' & 6'-H and 2-Ph: 2 & 6-H), 8.09 (1H, d, J 2.1 Hz, 7-H), 8.56 (1H, d, J 2.1 Hz, 9-H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 101.2 (C-9a), 117.0 (C-3), 119.7 (C-3a), 125.0 (2-Ph: C-2 & 6), 127.4 (C-4'), 127.5 (C-9), 127.7 (C-4''), 127.9 (C-4''''), 128.9 (C-2' & 6'), 129.0 (C-2'' & 6''), 129.0 (C-2''' & 6'''), 129.1 (C-3' & 5'), 129.2 (C-3'' & 5''), 129.2 (C-3'''' & 5'''), 129.7 (2-Ph: C-4), 130.1 (C-7), 131.1 (2-Ph: C-1), 135.3 (C-1'), 138.2 (C-1''), 139.7 (C-1'''), 140.4 (C-6), 141.2 (C-8), 142.2 (C-5a), 150.7 (C-2), 156.6 (C-4), 156.8 (C-1a); IR (neat): \(v_{\text{max}}\) 3069, 3053, 3032, 1590, 1482, 1365, 1091, 1010, 873, 835, 791, 756, 737, 690, 643, 604 cm\(^{-1}\); m/z (100, M+H) 508; HRMS (ES): MH\(^+\), found: 508.1479. For [C\(_{35}\)H\(_{23}\)ClNO]\(^+\): requires, 508.1468.
4.16.4 Preparation of 2,6,8-triphenyl-4-(4-methoxyphenyl)furo[3,2-c]quinoline 148d (R = C₆H₅; R'' = H; R' = OCH₃)

A mixture of 147d (0.30 g, 0.6 mmol), PdCl₂(PPh₃)₂ (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et₃N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added phenyl acetylene (0.12 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere; work up and column chromatography on silica gel as described for 148a afforded 148d as pale yellow solid, (0.18 g, 60%); mp 200-201 °C; Rf (10% ethyl acetate/ hexane) 0.42; ¹H NMR (300 MHz, CDCl₃) δ: 3.89 (3H, s, OCH₃), 7.07 (2H, d, J 8.7 Hz, 3' & 5'-H), 7.39-7.56 (10H, m, 3-H, 3'', 4'', 5'', Ph''' and 2-Ph: 4-H), 7.87 (2H, d, J 8.7 Hz, 2-Ph: 3 & 5-H), 7.94 (2H, d, J 8.7 Hz, 2'' & 6''-H), 8.00 (2H, d, J 8.7 Hz, 2-Ph: 2 & 6-H), 8.02 (1H, d, J 2.1 Hz, 7-H), 8.12 (2H, d, J 8.7 Hz, 2' & 6'-H), 8.56 (1H, d, J 2.1 Hz, 9-H); ¹³C NMR (75 MHz, CDCl₃) δ: 55.4 (OCH₃), 101.7 (C-3), 114.1 (C-3a), 116.8 (2-Ph: C-2 & 6), 117.0 (C-9), 119.6 (C-4''), 124.9 (C-4''), 127.2 (C-2' & 6'), 127.5 (C-2'' & 6''), 127.7 (C-2'' & 6''), 127.7 (C-3' & 5'), 129.0 (C-3'' & 5''), 129.0 (C-3''' & 5'''), 129.9 (2-Ph: C-4), 130.2 (C-7), 131.1 (2-Ph: C-1), 132.5 (C-1'), 138.8 (C-1''), 139.9 (C-1'''), 140.6 (C-6), 141.2 (C-8), 142.3 (C-5a), 151.7 (C-2), 156.2 (C-4), 156.7 (C-1a), 160.6 (C-4'); IR (neat): νmax 3047, 3003, 2959, 2836, 1603, 1482, 1366, 1303, 1246, 1171, 1032, 945, 836, 795, 758, 744, 698, 616 cm⁻¹; m/z (100, M+H) 504; HRMS (ES): MH⁺, found: 504.1970. For [C₃₆H₂₆NO₂]⁺: requires, 504.1964.
4.16.5 Preparation of 6,8-bis(4-fluorophenyl)-2,4-diphenylfuro[3,2-c]quinoline 148e (R = C₆H₅; R' = H; R'' = F)

A mixture of 147e (0.30 g, 0.6 mmol), PdCl₂(PPh₃)₂ (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et₃N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added phenyl acetylene (0.13 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere; work up and column chromatography on silica gel as described for 148a afforded 148e as pale yellow solid, (0.21 g, 74%); mp 213-215 °C Rf (10% ethyl acetate/ hexane) 0.58; ¹H NMR (300 MHz, DMSO-d₆) δ: 7.18-7.24 (4H, m, 3' & 5' and 2-Ph: 3 & 5-H), 7.39-7.57 (7H, m, 2', 3, 4'', 4''' and 2-Ph: 2, 4, 6-H), 7.82 (2H, dd, J 2.7, 6.0 Hz, 3'' & 5''-H), 7.88 (2H, dd, J 2.7, 6.0 Hz, 3'' & 5''-H), 7.91 (1H, d, J 2.1 Hz, 7-H), 7.99 (2H, d, J 8.1 Hz, 2'' & 6''-H), 8.11 (2H, d, J 8.1 Hz, 2'' & 6''-H), 8.47 (1H, d, J 2.1 Hz, 9-H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 101.6 (C-9a), 114.6 (d, ²JCF 21.3 Hz, C-3'' & 5''), 115.9 (d, ²JCF 21.3 Hz, C-3'' & 5''), 116.9 (C-3), 117.0 (C-3a), 120.1 (2-Ph: C-2 & 6), 125.0 (C-9), 128.6 (C-4'), 128.8 (d, ³JCF 8.0 Hz, C-2'' & 6''), 129.0 (2-Ph: C-4), 129.1 (C-7), 129.2 (2-Ph: C-3 & 5), 129.4 (C-2' & 6'), 129.8 (C-3' & 5'), 132.7 (d, ³JCF 8.0 Hz, C-2'' & 6''), 133.5 (d, ⁴JCF 3.2 Hz, C-1''), 136.5 (d, ⁴JCF 3.2 Hz, C-1''), 137.9 (2-Ph: C-1), 139.6 (C-1'), 139.7 (C-6), 140.5 (C-8), 142.1 (C-5a), 152.2 (C-2), 156.5 (C-4), 156.6 (C-1a), 162.5 (d, ¹JCF 245.3 Hz, C-4''), 162.8 (d, ¹JCF 245.3 Hz, C-4''); IR (neat): vmax 3051, 1600, 1509, 1485, 1366, 1225, 1157, 1012, 945, 830, 758, 738, 690, 646 cm⁻¹; m/z (100, M+H) 510; HRMS (ES): MH⁺, found: 510.1663. For [C₅H₂₂F₂NO]⁺: requires, 510.1669.
4.16.6 Preparation of 4,6,8-tris(4-fluorophenyl)-2-phenylfuro[3,2-c]quinoline 148f (R = C₆H₅; R', R'' = F)

A mixture of 147f (0.30 g, 0.6 mmol), PdCl₂(PPh₃)₂ (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et₃N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added phenyl acetylene (0.13 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere; work up and column chromatography on silica gel as described for 148a afforded 148f as pale yellow solid, (0.18 g, 67%); mp 249-250 °C (Rf (10% ethyl acetate/ hexane) 0.63; ¹H NMR (300 MHz, DMSO-d₆) δ: 7.20-7.27 (6H, m, 3, 3'' & 5''' and 2-Ph: 3, 4 & 5-H), 7.45 (2H, dd, J 0.9, 6.9 Hz, 2'' & 6'''-H), 7.54 (2H, dd, J 0.9, 6.9 Hz, 2'' & 6'''-H), 7.80-7.89 (4H, m, 3'' & 5''' and 2-Ph: 2 & 6-H), 7.93 (1H, d, J 1.8 Hz, 7-H), 8.02 (2H, d, J 8.1 Hz, 3' & 5'-H), 8.12 (2H, d, J 8.1 Hz, 2' & 6'-H), 8.51 (1H, d, J 1.8 Hz, 9-H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 101.3 (C-9a), 114.6 (d, ²J_CF 21.4 Hz, C-3'' & 5''), 115.7 (d, ²J_CF 21.4 Hz, C-3'' & 5''), 115.9 (d, ²J_CF 21.4 Hz, C-3' & 5'), 116.9 (C-3a), 119.8 (2-Ph: C-2 & 6), 125.0 (C-9), 128.7 (C-4'), 129.1 (d, ³J_CF 8.3 Hz, C-2' & 6'), 129.2 (d, ⁴J_CF 3.2 Hz, C-1'), 129.6 (2-Ph: C-3 & 5), 130.1 (2-Ph: C-3 & 5), 130.6 (d, ³J_CF 8.3 Hz, C-2'' & 6''), 132.6 (d, ³J_CF 8.3 Hz, C-2'' & 6''), 135.5 (d, ⁴J_CF 3.2 Hz, C-1''), 135.7 (d, ⁴J_CF 3.2 Hz, C-1''), 136.4 (2-Ph: C-1), 136.5 (C-7), 137.9 (C-6), 140.4 (C-8), 142.0 (C-5a), 151.0 (C-2), 155.9 (C-4), 156.6 (C-1a), 162.5 (d, ¹J_CF 246.0 Hz, C-4''), 162.8 (d, ¹J_CF 246.0 Hz, C-4''), 163.6 (d, ¹J_CF 246.0 Hz, C-4''); IR (neat): ν_max 3049, 1602, 1509, 1485, 1366, 1227, 1154, 1011, 946, 868, 820, 803, 756, 688 cm⁻¹; m/z (100, M+H) 528; HRMS (ES): MH⁺, found: 528.1577. For [C₃₅H₂₁F₃NO]⁺: requires, 528.1575.
4.16.7 Preparation of 6,8-bis(4-fluorophenyl)-4-(4-chlorophenyl)-4-phenylfuro[3,2-

\(c\)\)quinoline 148g (R = \(\text{C}_6\text{H}_5\); R'' = F; R' = Cl)

A mixture of 147g (0.30 g, 0.6 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et\(_3\)N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added phenyl acetylene (0.13 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere; work up and column chromatography on silica gel as described for 148a afforded 148g as pale yellow solid, (0.18 g, 62%); mp 263-264 °C \(R_f\) (10% ethyl acetate/ hexane) 0.63; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 7.18-7.26 (4H, m, 3'' & 5'' and 2-Ph: 3 & 5-H), 7.44 (2H, dd, J 6.9, 7.8 Hz, 3' & 5'), 7.53 (4H, dd, J 6.3, 8.4 Hz, 3'' & 5'' and 2'' & 6''), 7.79-7.88 (4H, dd, J 3.3, 5.4 Hz, 3 and 2-Ph: 2, 4, 6-H), 7.93 (1H, d, J 2.1 Hz, 7-H), 8.04 (4H, dd, J 8.1, 8.4 Hz, 2' & 6' and 2'' & 6''-H), 8.51 (1H, d, J 2.1 Hz, 9-H); \(^13\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\): 101.2 (C-9a), 114.7 (d, \(^2\)J\(_{\text{CF}}\) 21.4 Hz, C-3'' & 5''), 115.9 (d, \(^2\)J\(_{\text{CF}}\) 21.4 Hz, C-3'' & 5''), 116.9 (C-3), 117.0 (C-3a), 119.9 (2-Ph: C-2 & 6), 125.0 (C-9), 128.4 (C-4'), 128.8 (2-Ph: C-4), 129.0 (C-7), 129.1 (2-Ph: C-3 & 5), 129.1 (C-3' & 5'), 129.6 (C-2' & 6'), 130.0 (C-4'), 132.6 (d, \(^3\)J\(_{\text{CF}}\) 8.0 Hz, C-2'' & 6''), 132.6 (d, \(^3\)J\(_{\text{CF}}\) 8.0 Hz, C-2'' & 6''), 135.5 (d, \(^4\)J\(_{\text{CF}}\) 3.2 Hz, C-1''), 136.5 (d, \(^4\)J\(_{\text{CF}}\) 3.2 Hz, C-1''), 138.1 (C-1'), 138.2 (C-6), 140.5 (C-8), 142.1 (C-5a), 150.9 (C-2), 156.7 (C-4), 156.8 (C-1a), 162.5 (d, \(^1\)J\(_{\text{CF}}\) 245.0 Hz, C-4''), 162.8 (d, \(^1\)J\(_{\text{CF}}\) 245.0 Hz, C-4''); IR (neat): \(\nu_{\text{max}}\) 3044, 2923, 2852, 1602, 1510, 1484, 1363, 1223, 1157, 1093, 1010, 944, 820, 741, 682, 641 cm\(^{-1}\); \(m/z\) (100, M+H) 544; HRMS (ES): MH\(^+\), found: 544.1279. For [C\(_{35}\)H\(_{21}\)F\(_2\)ClNO]\(^+\): requires, 544.1280.
4.16.8 Preparation of 6,8-bis(4-fluorophenyl)-4-(4-methoxyphenyl)-4-phenylfuro[3,2-c]quinoline 148h (R = C₆H₅; R'' = F; R' = OCH₃)

A mixture of 147h (0.30 g, 0.6 mmol), PdCl₂(PPh₃)₂ (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et₃N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added phenyl acetylene (0.13 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere; work up and column chromatography on silica gel as described for 148a afforded 148h as pale yellow solid, (0.18 g, 63%); mp 221-222 °C Rf (10% ethyl acetate/ hexane) 0.40; ¹H NMR (300 MHz, DMSO-d₆) δ: 3.91 (3H, s, OCH₃), 7.08 (2H, d, J 8.7 Hz, 3''' & 5'''-H), 7.19-7.26 (4H, m, 2Ph: 2, 3, 5, 6-H), 7.40-7.55 (4H, m, 3, 3'' & 5'' and 2-Ph: 4-H), 7.81 (2H, dd, J 3.3, 6.0 Hz, 3' & 5'-H), 7.87 (2H, dd, J 3.3, 6.0 Hz, 2' & 6'-H), 7.92 (1H, d, J 2.1 Hz, 7-H), 8.02 (2H, d, J 8.7 Hz, 2'' & 6''-H), 8.11 (2H, d, J 8.7 Hz, 2'' & 6''-H), 8.49 (1H, d, J 2.1 Hz, 9-H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 55.4 (OCH₃), 101.7 (C-9a), 114.6 (d, ²JCF 21.4 Hz, C-3'' & 5''), 115.9 (d, ²JCF 21.4 Hz, C-3'' & 5''), 116.9 (C-3), 117.0 (C-3a), 119.9 (2-Ph: C-2 & 6), 125.0 (C-9), 128.5 (2-Ph: C-4), 129.0 (C-7), 129.1 (d, ³JCF 8.0 Hz, C-2'' & 6''), 129.8 (2-Ph: C-3 & 5), 130.2 (C-2' & 6'), 132.4 (C-3' & 5'), 132.7 (d, ³JCF 8.0 Hz, C-2'' & 6''), 135.7 (d, ⁴JCF 3.5 Hz, C-1''), 136.6 (d, ⁴JCF 3.5 Hz, C-1''), 137.6 (C-1'), 138.2 (C-6), 140.2 (C-8), 142.1 (C-5a), 151.9 (C-2), 156.4 (C-4), 156.6 (C-1a), 160.7 (C-4'), 162.4 (d, ¹JCF 245.8 Hz, C-4''), 162.8 (d, ¹JCF 245.8 Hz, C-4''); IR (neat): νmax 3044, 2923, 2852, 1602, 1510, 1484, 1363, 1299, 1223, 1157, 1093, 1010, 944, 820, 741, 682, 641 cm⁻¹; m/z (100, M+H) 540; HRMS (ES): MH⁺, found: 540.1766. For [C₃₆H₂₄F₂NO₂⁺]: requires, 540.1775.
4.16.9 Preparation of 2-(2-hydroxyethyl)-6,8-bis(4-fluorophenyl)-4-phenylfuro[3,2-
c]quinoline 148i (R = -CHOHCH\(_3\); R' = H; R'' = F)

A mixture of 147e (0.30 g, 0.6 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.02 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol) and Et\(_3\)N (0.34 mL, 2.4 mmol) in DMF (20 mL) in a three-necked round bottomed flask equipped with stirrer, condenser and rubber septum was stirred under argon for 1 hour. To this mixture was added 3-butyn-2-ol (0.12 mL, 1.2 mmol) slowly via a syringe and the mixture was stirred at 100 °C for 2 hours under argon atmosphere; work up and column chromatography on silica gel as described for 148a afforded 148i as pale yellow solid, (0.20 g, 68%); mp 245-246 °C; R\(_f\) (10% ethyl acetate/ hexane) 0.78; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 1.90 (3H, d, \(J_6.6\) Hz, CH\(_3\)OH), 2.41 (1H, d, \(J_5.4\) Hz, H-OH), 5.34 (1H, t, \(J_5.7\) Hz, H-OH), 7.25-7.39 (4H, m, 4-Ph: 3, 4, 5-H), 7.58-7.69 (4H, m, 3'', 5'' & 5'''-H), 7.92 (2H, dd, \(J_3.6, 5.4\) Hz, 2'' & 6''-H), 8.02 (2H, dd, \(J_3.6, 5.4\) Hz, 2'' & 6''-H), 8.06 (1H, d, \(J_2.1\) Hz, 7-H), 8.20 (2H, dd, \(J_1.5, 6.6\) Hz, 2' & 6'-H), 8.57 (1H, d, \(J_2.1\) Hz, 9-H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\): 21.7 (CH\(_3\)OH), 64.1 (CHOH), 102.5 (C-3), 114.6 (d, \(J_{CF} 21.4\) Hz, C-3'' & 5''), 115.8 (d, \(J_{CF} 21.4\) Hz, C-3'' & 5''''), 116.9 (C-9a), 118.9 (C-3a), 128.4 (C-4'), 128.6 (C-2' & 6'), 128.7 (C-9), 128.9 (C-7), 129.0 (d, \(J_{CF} 8.0\) Hz, C-2'' & 6''), 129.4 (C-3' & 5'), 132.7 (d, \(J_{CF} 8.0\) Hz, C-2'' & 6'''), 135.6 (d, \(J_{CF} 3.0\) Hz, C-1'), 136.4 (d, \(J_{CF} 3.0\) Hz, C-1''), 137.8 (C-6), 139.5 (C-1'), 140.4 (C-8), 142.1 (C-5a), 152.3 (C-2), 156.7 (C-4), 157.0 (C-1a), 162.4 (d, \(J_{CF} 247.5\) Hz, C-4''), 162.8 (d, \(J_{CF} 247.5\) Hz, C-4''); IR (neat): \(v_{max}\) 3408, 3044, 2923, 2852, 1604, 1512, 1484, 1366, 1299, 1223, 1160, 1096, 1010, 940, 820, 742, 684, 646 cm\(^{-1}\); \(m/z\) (100, M+H) 478; HRMS (ES): MH\(^+\), found: 478.1623. For [C\(_{31}\)H\(_{22}\)F\(_2\)NO\(_2\)]\(^+\): requires, 478.1619.
4.17 Antimicrobial susceptibility evaluation of selected synthesized compounds

The antimicrobial screening of several of the synthesized compounds was undertaken, using the minimum inhibitory concentration (MIC) screening assay against six reference pathogens: *Staphylococcus aureus* (ATCC 25923, Gram-positive), *Enterococcus faecalis* (ATCC 29212, Gram-positive), *Escherichia coli* (ATCC 8739, Gram-negative), *Pseudomonas aureginosa* (ATCC 27858, Gram-negative), *Candida albicans* (ATCC 10231, yeast) and *Cryptococcus neoformans* (ATCC 14116, yeast).

The minimum inhibitory concentrations were determined using the INT microwell method (NCCLS, 2003). The synthesized compounds were diluted in acetone so that starting concentrations of 5.00 mg/mL were introduced into the first well of a microtitre plate. The starting concentrations were diluted two-fold in each successive serial dilution. Where necessary, further dilutions were performed so that valid endpoint MIC values could be determined. Positive antimicrobial controls, ciprofloxacin for bacteria at starting stock concentrations of 10.00 μg/mL and amphotericin B for the yeasts at a starting concentration of 100 μg/mL were included in each assay to confirm antimicrobial susceptibility. Negative controls of acetone were included to evaluate the effect of the solvent on the growth of test micro-organisms. A broth control (media incubated without test organism) was included to confirm sterility. Cultures were streaked out onto Tryptone Soya agar to confirm purity. Bacterial cultures were grown overnight at 37 C, diluted 1:100 and 100 μL inoculated into all wells at approximate inoculum concentrations of $1 \times 10^6$ colony forming units/mL. Incubation followed for 24 hours for bacterial and 37 C for 48 hours for the yeasts. After incubation, a 0.40 mg/mL *p*-iodonitrotetrazolium violet solution was transferred into all inoculated wells (40 μL) and examined to determine a colour change in relation to concentration of microbial growth. Tests
were performed at least in duplicate and in triplicate where results varied by more than one dilution factor.
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