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

by

FELIX ADETUNJI OYEYIOLA

Submitted in accordance with the requirements for the degree of

DOCTOR OF PHILOSOPHY

in the subject

CHEMISTRY

at the

UNIVERSITY OF SOUTH AFRICA

SUPERVISOR: PROFESSOR MJ MPHAHLELE

SEPTEMBER 2015

Student number: **46349995**

I declare that **2-ARYL-6,8-DIBROMOQUINOLINONES AS SYNTHONS 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

…… ……...

SIGNATURE DATE

MR F A OYEYIOLA

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

My thanks and gratitude goes to my Supervisor, Professor MJ Mphahlele, for his mentoring and support throughout this project to completion. Financial support from University of South Africa (UNISA) and the National Research Fund (NRF) is acknowledged. I thank Ms Dineo Moema for assisting me with HPLC analysis. The different roles played by the departmental support staff, namely, Ms Shadi Mokiri, Ms Dorcas Molawa and Mr Oupa Tshabalala are also appreciated.

Appreciation from the depth of my heart is due to my wonderful and lovely wife, Dr (Mrs) Aderonke O. Oyeyiola and my children, Adesoye, Adeoluwa and Adetayo for their sacrifice, understanding and support during this project. I recognise the huge impact and the unforgettable life lessons in perseverance, focus and drive by my late parents and grandmother, Pa Gabriel Adeoti and Madam Josephine Jolaade Oyeyiola and Madam Cecelia Olatundun Alayoku in the course of this program. I must not forget Dr (Engr) Pastor Olabisi and Dr (Mrs) Temilola Oluseyi as well as Prof. (Mrs) Kehinde Olayinka and family for their love and support to me and my family during my studies. Drs Popoola and Bisi-Johnson are acknowledged for their immense assistance at the inception of this program.

Special mention must be made of my siblings (Segun, Niyi, Bukola, Damola and Femi) and my in-laws (Shola Olaniyan, Dewunmi Olaniyi, Bimbo Sadiku, Bayo Adedeji and their spouses) as well as Engr Banjo Adedeji (his wife and his company the Nego Construction) for the huge role played in actualising this dream. I must also not fail to recognize the magnanimity of these UNISA alumni; Drs Olumuyiwa Okedeyi (LASU) and Adelowotan (Unilag), for loans at a critical point in the program.

Abstract

The known 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones **122** were dehydrogenated using thallium(III) *p*-tolylsulfonate in dimethoxyethane under reflux to afford the 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones **136**. Palladium-catalyzed Sonogashira cross-coupling of the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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(1*H*)-ones **138** and 8-alkynyl-2-aryl-6-bromo-2,3-dihydroquinolin-4(1*H*)-ones **137**, respectively. $PdCl_2$-catalyzed electrophilic cyclization of the 8-alkynyl-2-aryl-6-bromo-2,3-dihydroquinolin-4(1*H*)-ones in acetonitrile under reflux afforded the 4-aryl-8-bromo-2-phenyl-6*H*-pyrrolo[3,2,1-*ij*]quinolin-6-ones **139** or the 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1*H*)-ones **140** from the 4-phenylethynyl-substituted or 4-alkylethynyl-substituted precursors, respectively. The 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones **136** wturn, subjected to similar homogeneous and heterogeneous palladium catalyst sources using NEt_3 as a base in DMF-water mixture under reflux and K_2CO_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-6*H*-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_2CO_3 as a base in dioxane-water mixture to afford the corresponding novel 8-substituted 2-phenyl-6*H*-pyrrolo[3,2,1-*ij*]quinolin-6-ones **141** and 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,2,1-

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(1*H*)-ones; 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones; Sonogashira cross-coupling reaction; 8-alkynyl-2-aryl-6-bromo-2,3-dihydroquinolin-4(1*H*)-ones; 6,8-dialkynyl-2-aryl-2,3-dihydroquinolin-4(1*H*)-ones; 4-aryl-8-bromo-2-phenyl-6*H*-pyrrolo[3,2,1-*ij*]quinolin-6-ones; 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1*H*)-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-6*H*-pyrrolo[3,2,1-*ij*]quinolin-6-ones; 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,2,1-*ij*]quinolines.

TABLE OF CONTENT

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)

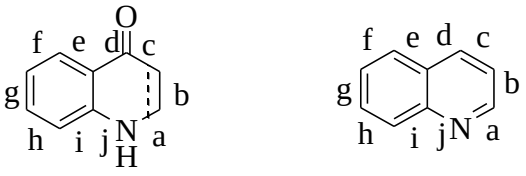
6. $PdCl_2$(dppf): dichlorobis((1,1′-diphenylphosphino)ferrocene)palladium

7. PPh_3: triphenylphosphine

Chapter 1: INTRODUCTION

1.1 General overview

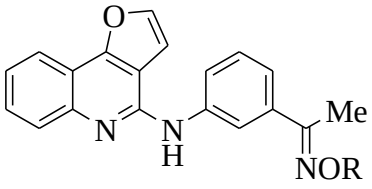
The design and synthesis of furo-, thieno- or pyrrolo-based quinolinones and quinoline derivatives continue to attract considerable attention in organic and medicinal chemistry; because of their wide range of biological properties[1] and some examples have also been found to serve as components of optoelectronic 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]



A **B**

Figure 1: The generalized structures of quinolin-4(1*H*)-one **A** and quinoline **B**

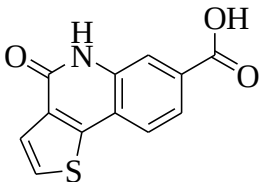
Furoquinolines are the first examples of angular heteroannulated quinoline derivatives under consideration. The naturally occurring furoquinolines such as Kolbisine and Kokusaginine and their analogues, *viz*., Pteleatine, Skimmianine and Maculine which are present in a large number of rutaceous plants like *Galipea* and *Esenbeckia* are linear.[7,8] Kolbisine has been found to exhibit antibacterial and antifungal activities against both *Salmonella typhi* and *Candida albicans*, respectively.[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.[11] Kokusagnine, on the other hand, was found to exhibit antiplasmodial activity against *Plasmodium falciparum in vitro*.[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 $GI_{50} < 0.01$ μM.[2]



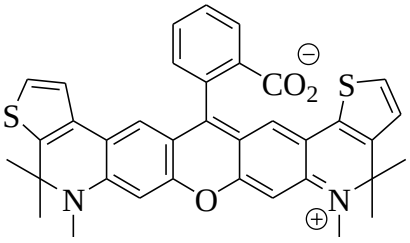
1

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,[12] anticancer[13] and anti-inflammatory properties.[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.[14,15] Rhodamine derivative **3**, a benzothienoquinoline analogue, on the other hand, is an optoelectronic component with fluorescence properties.[3]

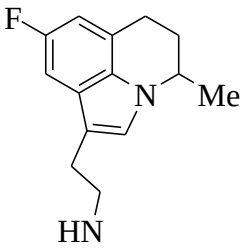


2

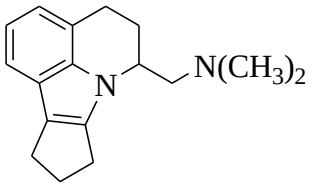


3

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 *Crinum* genus of the Amaryllidaceae family.[16-18] Several examples of these angular heteroannulated quinolones and their quinoline derivatives exhibit anticonvulsant,[5] anti-inflammatory,[19,20] antifungal,[21] antihypertensive,[4,22] antiviral[6] and antitumor[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.[5,24]

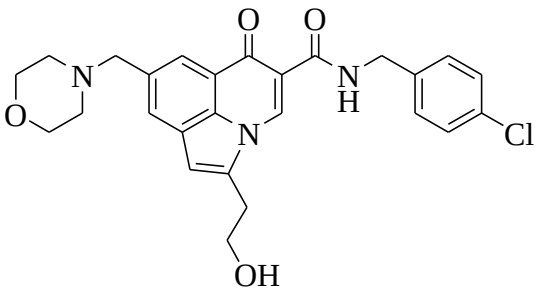


4



5

The 4- and 6-oxo pyrrolo[3,2,1-*ij*]quinolines, on the other hand, have found applications as antifungal,[25,26] anticancer[27] and antiviral agents,[6] and others are inhibitors of protein and DNA synthesis.[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.[6]



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.[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.

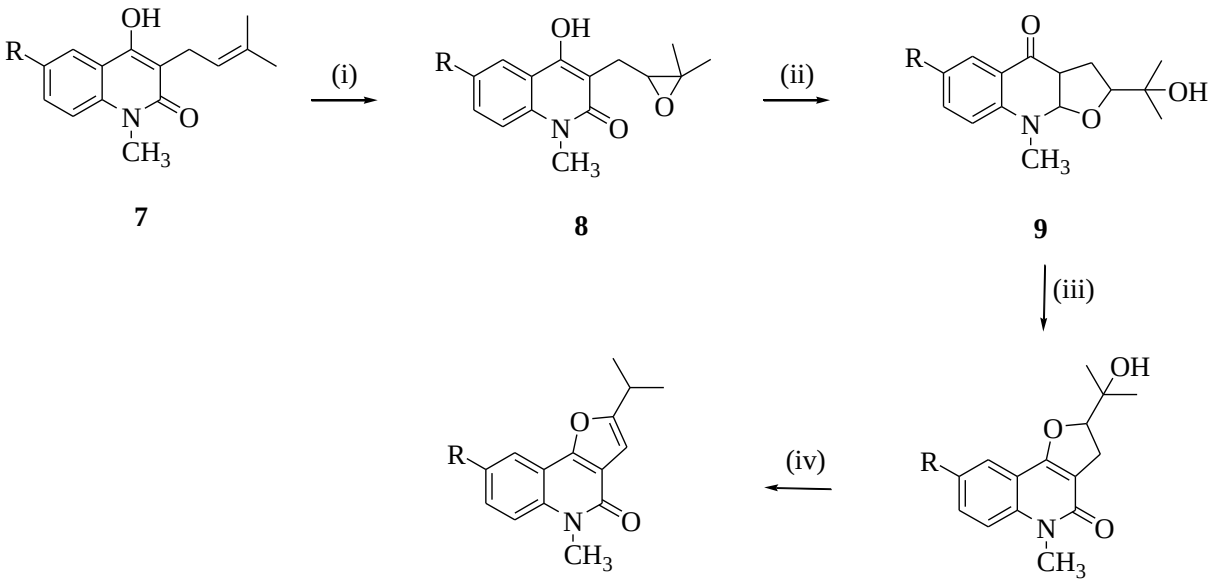
1.2 Synthesis of heteroannulated quinolinones and quinolines

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[31] and alkynes[32] or the reaction of nucleophiles with appropriately substituted quinolinones or quinolines.[33,34] 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.[35,36] 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).[34] 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.[34]



7 **8** **9**

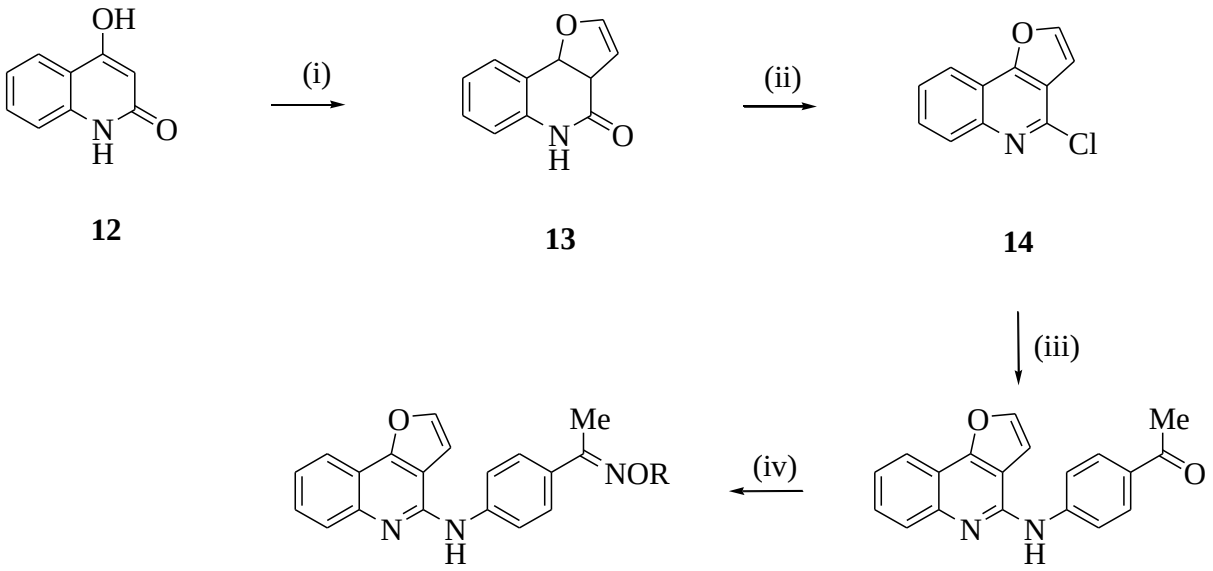
11 (R = H, OCH_3) **10**

Reagents and conditions: (i) *m*-chloroperbenzoic acid, $CHCl_3$, r.t.; (ii) 3 M HCl or NaOH; (iii) $NaOCH_3$, MeOH, r.t., 20 h; (iv) conc. H_2SO_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).[2] Chlorination of the latter with $POCl_3$ in the presence of Et_3N yielded 4-chlorofuro[3,2-*c*]quinoline **14**, which was then reacted with 3-aminoacetophenone in EtOH/H_2O 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_2OH or NH_2OMe in ethanol under reflux afforded (*E*)-1-[3-(furo[3,2-*c*]quinoline-4-ylamino)phenyl]ethanone oxime

16a and (*E*)-1-[3-(furo[3,2-*c*]quinoline-4-ylamino)phenyl]ethanone *O*-methyl oxime **16b**, respectively. Of interest, is that compounds **16** exhibits anticancer activities.



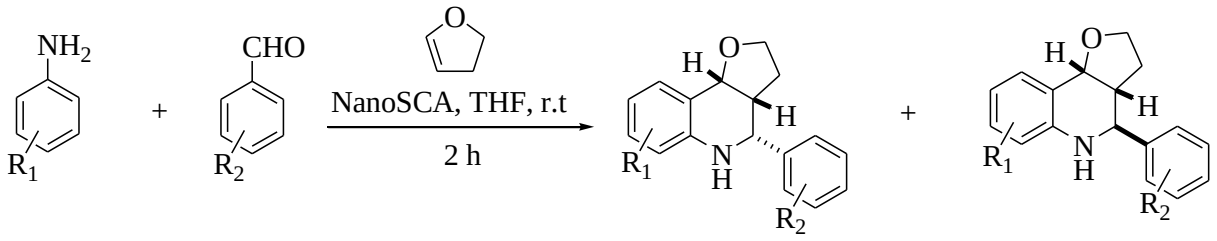
12 **13** **14**

16: R = H (**a**); R = Me (**b**) **15**

Reagents and conditions: (i) $ClCH_2CHO$, KI, KOH, reflux, 4 h; (ii) $POCl_3$, Et_3N, 110 °C, 8 h; (iii) 3-aminoacetophenone, conc. HCl, EtOH-H_2O (2:1,v/v), reflux, 40 mins; (iv) NH_2OH HCl or NH_2OMe 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 *trans*- **19** and *cis*-tetrahydrofuroquinoline isomers **20** in the ratio 2.5:1 (Scheme 3).[35] The reaction involves the generation of imine intermediates *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.

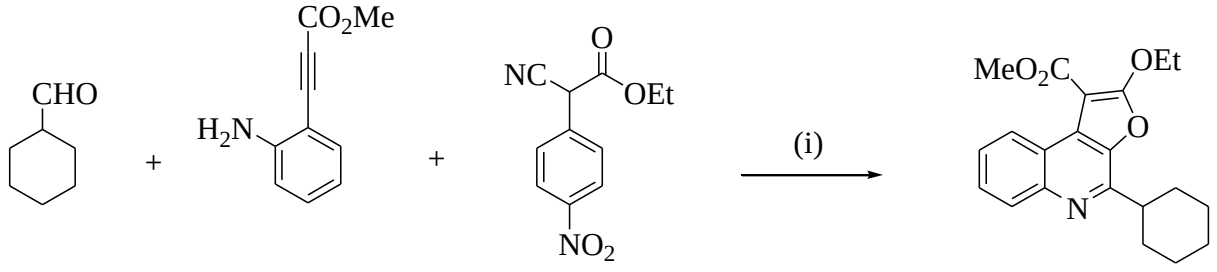


17 **18** **19** **20**

	17	**18**	**19 : 20**	**Yield (%)**
a:	R_1 = H	R_2 = 4-Br	73 : 27	87
b:	R_1 = 4-F	R_2 = 4-Cl	70 : 30	92
c:	R_1 = 4-OMe	R_2 = 4-Cl	80 : 20	91

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).[36]

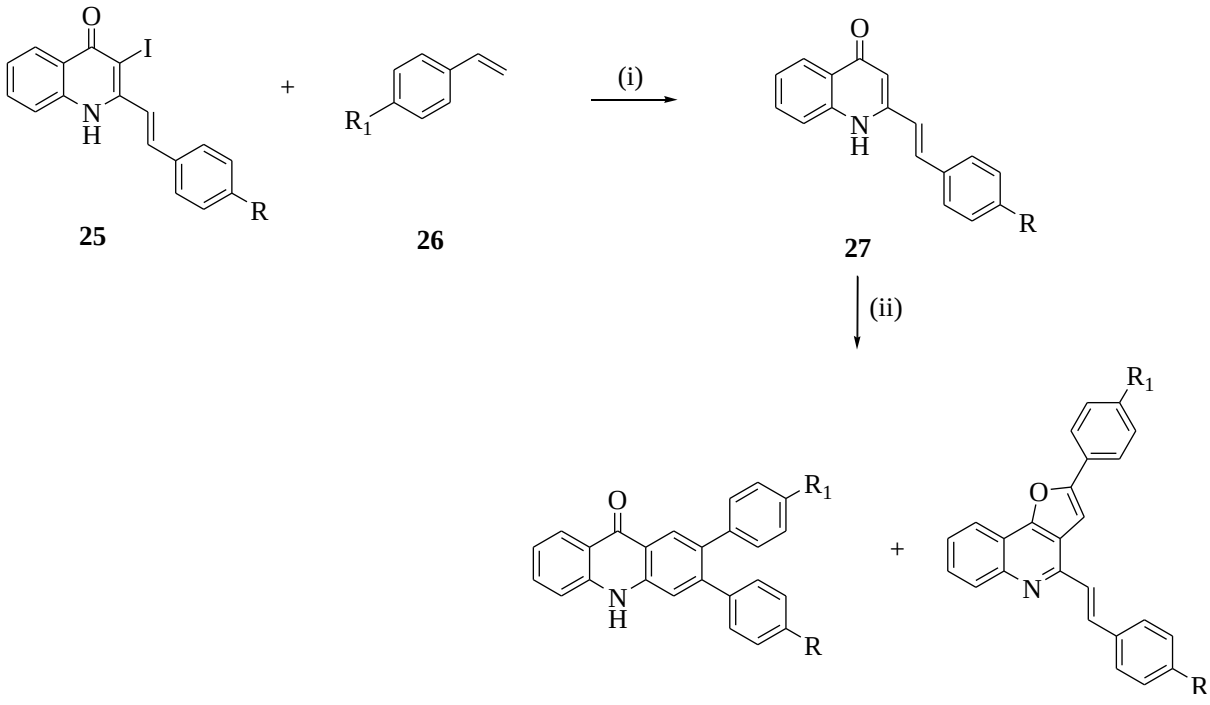


21 **22** **23** **24**

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(1*H*)-ones **25** was reacted with styrene and its *p*-methoxy derivative **26** in the presence of $Pd(PPh_3)_4$ and NEt_3 as a base in MeCN or NMP [*N*-methyl-2-pyrrolidone] under reflux to afford the (*E*,*E*)-2,3-distyrylquinolin-4(1*H*)-ones **27** in 58-65% yield (Scheme 5).[31] 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(10*H*)-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.



25 **26** **27**

R = H, Cl, OMe; R_1 = H, OMe

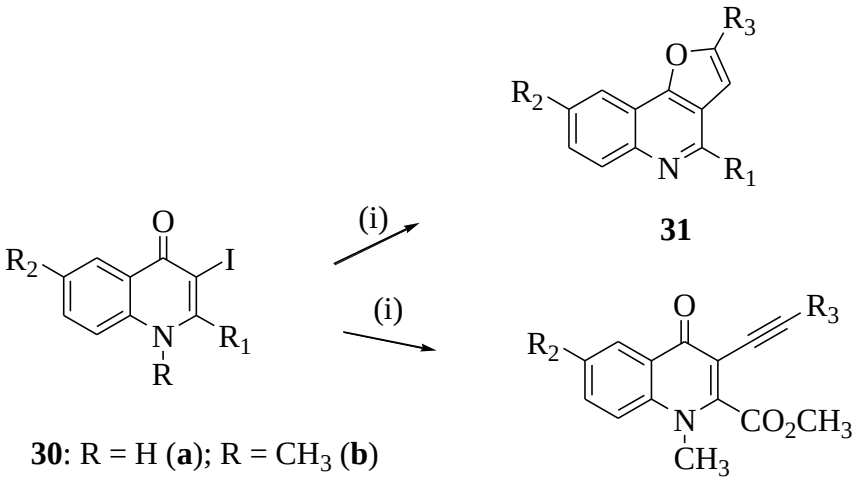
28 **29**

Reagents and conditions: (i) $Pd(PPh_3)_4$, NEt_3, NMP or MeCN, reflux, 3-7 h, N_2(g)

(ii) 1,2,4-Trichlorobenzene, I_2 (10%), *p*-TsOH (10%), reflux, N_2(g)

Scheme 5: Transition metal-catalyzed Heck cross-coupling of **25** with styrene derivatives

Previously, a series of 2,6-disubstituted 3-iodoquinolin-4(1*H*)-ones **30a** was reacted with terminal alkynes in the presence of Pd(0)-CuI-PPh_3 catalyst mixture and Et_3N 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(1*H*)-ones **32** in 60-70% yield (Scheme 6).[32] The difference in reactivity of 2,6-disubstituted 3-iodoquinolin-4(1*H*)-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.



30: R = H (**a**); R = CH_3 (**b**)

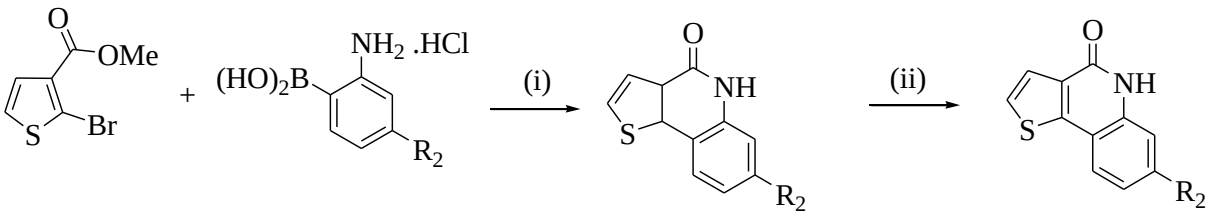
31	**32**
a: R_1 = CO_2CH_3; R_2 = F; R_3 = -C(OH)Me_2 (83%);	R_2 = H; R_3 = -CMe_2OH (60%)
b: R_1 = CO_2CH_3; R_2 = F; R_3 = -CH_2OH (75%);	R_2 = H; R_3 = -C_6H_5 (70%)
c: R_1 = -C_6H_5; R_2 = H; R_3 = -$CH_2)_2OH$ (72%);	R_2 = H; R_3 = -C_6H_3(OMe)-*m.p* (65%)
d: R_2 = H; R_1, R_3 = -C_6H_5 (67%);	

Reagents and conditions: (i) $R_3C{\equiv}CH$, Pd/C, PPh_3, CuI, Et_3N, DMF, 80 °C, 3 h, N_2(g)

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).[14] 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_2O (1:1:1,v/v) at room temperature afforded the substituted thieno[3,2-*c*]quinolinones **36** (R_3 = CO_2H) in 96% yield; and cyano group into amide group when treated with NH_4OH 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.[14]

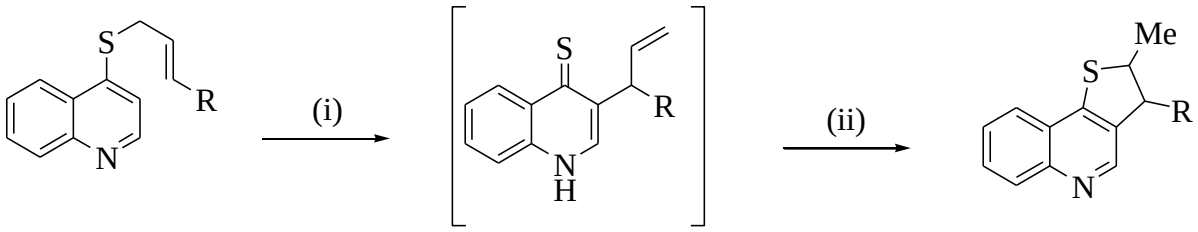


33 **34** (R_2 = CO_2Me, CN) **35** **36** (R_3 = CO_2H, $CONH_2$)

Reagents and conditions: (i) NaOAc, $PdCl_2$(dppf), anhy. DMF, 120 °C, 10 min.; (ii) R_3 = CO_2H: LiOH, MeOH, THF, H_2O, r.t., 5 h; for R_3 = $CONH_2$: NH_4OH, 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[37] or from thio-Claisen rearrangement of allyl-4-quinolyl sulphides.[38] The carboxanilides are, in turn, prepared by amination of the corresponding benzothiophene halides with aniline derivatives.[37,39] The allyl-4-quinolyl sulphides, on the other hand, can be prepared via alkylation of sodium 4-quinolyl-mercaptides with alkylallyl chlorides.[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).[38]

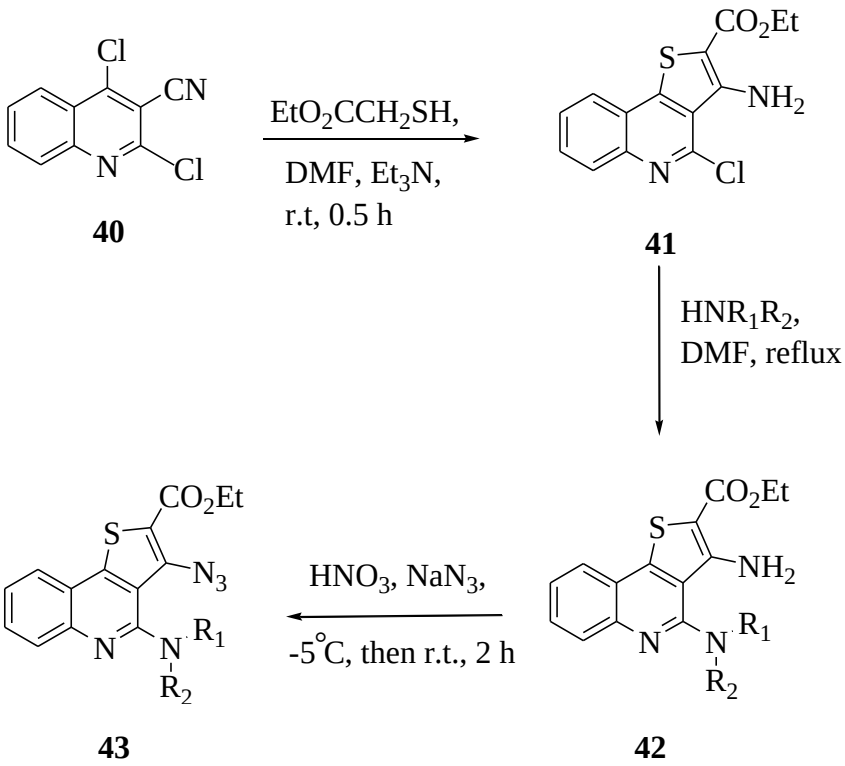


37 (R = H, Alkyl) **38** **39**

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).[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.

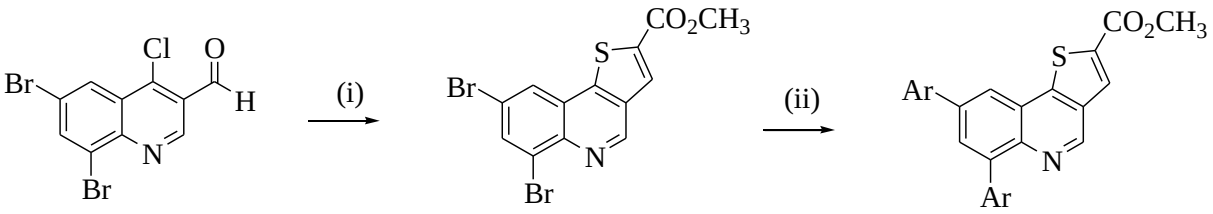


43	R_1	R_2	Yield (%)
a	H	Bu	74
b	H	*i*-Bu	78
c	H	*c*-C_6H_{11}	93

Scheme 9: Cycloaddition of **40** and ethyl mercaptoacetate with aliphatic amines

In a cognate study in our laboratory, 6,8-dibromo-4-chloroquinoline-3-carbaldehyde **44** was reacted with methyl mercapto-acetate in the presence of anhydrous K_2CO_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(tricyclohexyl-phosphine)palladium(II) and anhydrous K_2CO_3 as a base in DMF under reflux to afford novel alkyl[(6,8-diarylthieno[3,2-c]quinoline)]-2-carboxylates **46** in 65-96% yield. Of interest, is that

compounds **46** exhibit cytotoxic activities against human breast cancer cell line MCF-7 with LC_{50} values < 0.13 μg/mL when compared to nocodazole as a standard.

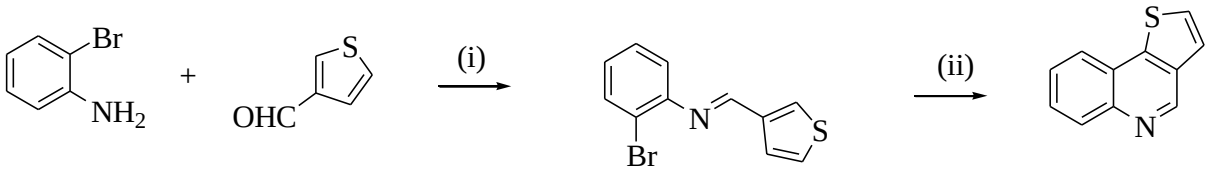


44 **45** (89%) **46** Ar = -C_6H_5, 4-FC_6H_4-, 4-FC_6H_4CH=CH-

Reagents and conditions: (i) $HSCH_2CO_2Me$ (2.5 equiv.), K_2CO_3, MeCN, reflux, 3 h; (ii) $ArB(OH)_2$ (2.5 equiv.), $PdCl_2(PCy_3)_2$, K_2CO_3, DMF, reflux, 4 h

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

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 $Pd(OAc)_2$-PPh_3 catalyst complex using Cs_2CO_3 as a base in xylene at 130 °C has also been reported in the literature (Scheme 11).[39]



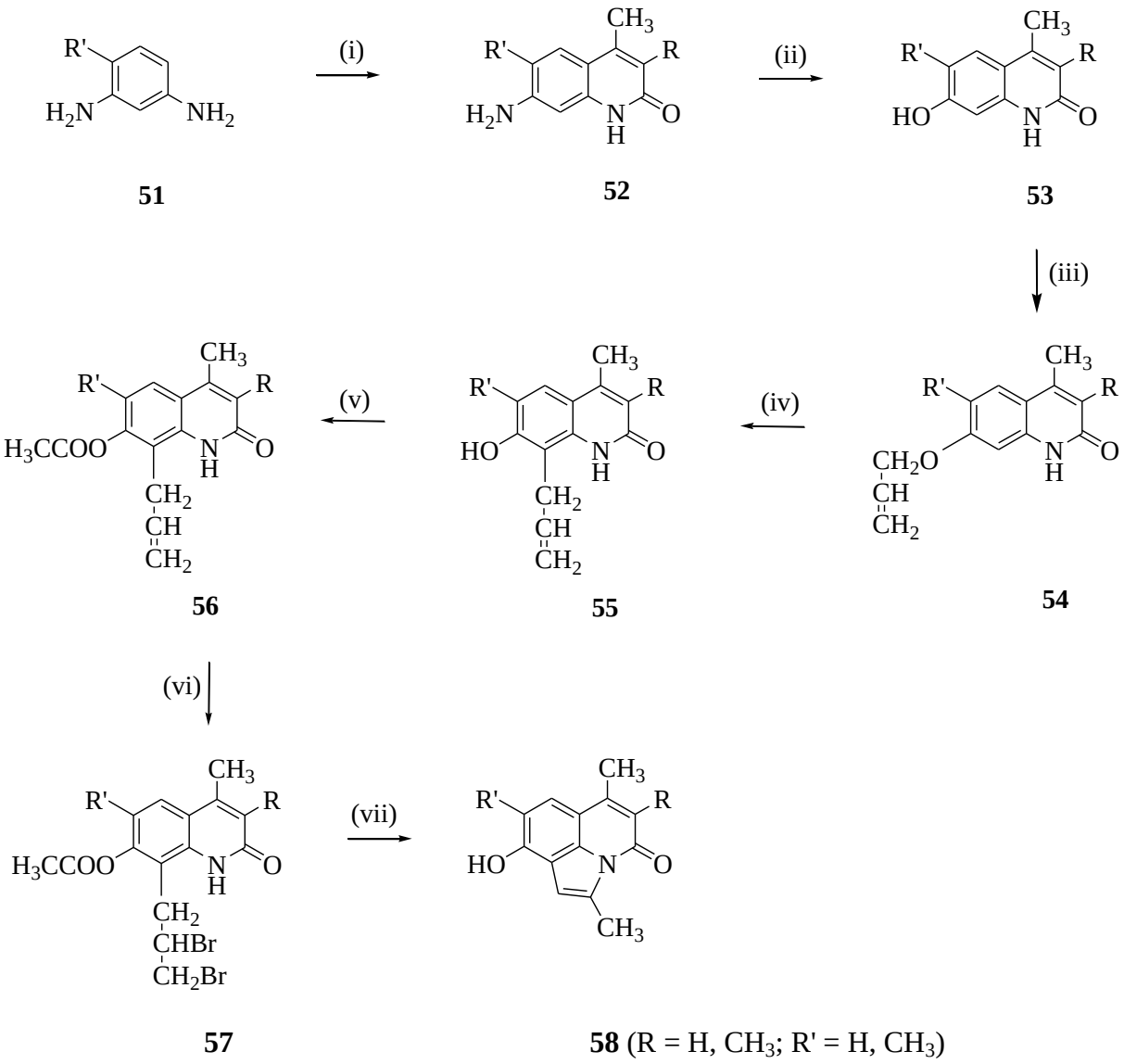
47 **48** **49** **50** (85%)

Reagents and conditions: (i) xylene, 150 °C, 24 h, argon; (ii) $Pd(OAc)_2$, PPh_3, Cs_2CO_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.



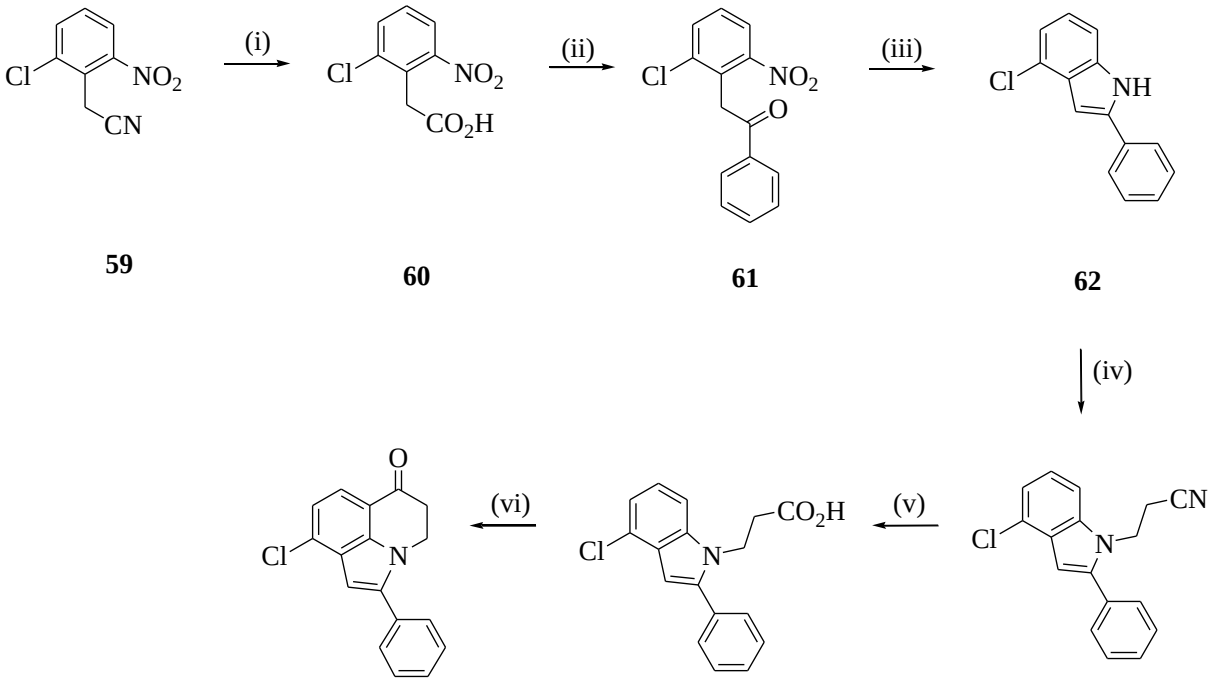
51 **52** **53** **54** **55** **56** **57** **58** (R = H, CH_3; R' = H, CH_3)

Reagents and conditions: (i) ethyl/methyl acetoacetate, 150 °C, 48 h; (ii) H_2SO_4, $NaNO_2$, 0 °C to reflux, 10 min (iii) allyl bromide, K_2CO_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_2SO_4 at 110 °C to convert the nitrile functional group to an acid derivative **60** (Scheme 13).[47]

The latter was, in turn, reacted with thionyl chloride in dichloroethane at 70 °C for 2 h followed by addition of $AlCl_3$ and benzene at 60 °C to afford 2-chloro-6-nitrophenyl)acetophenone **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 H_2SO_4 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**.

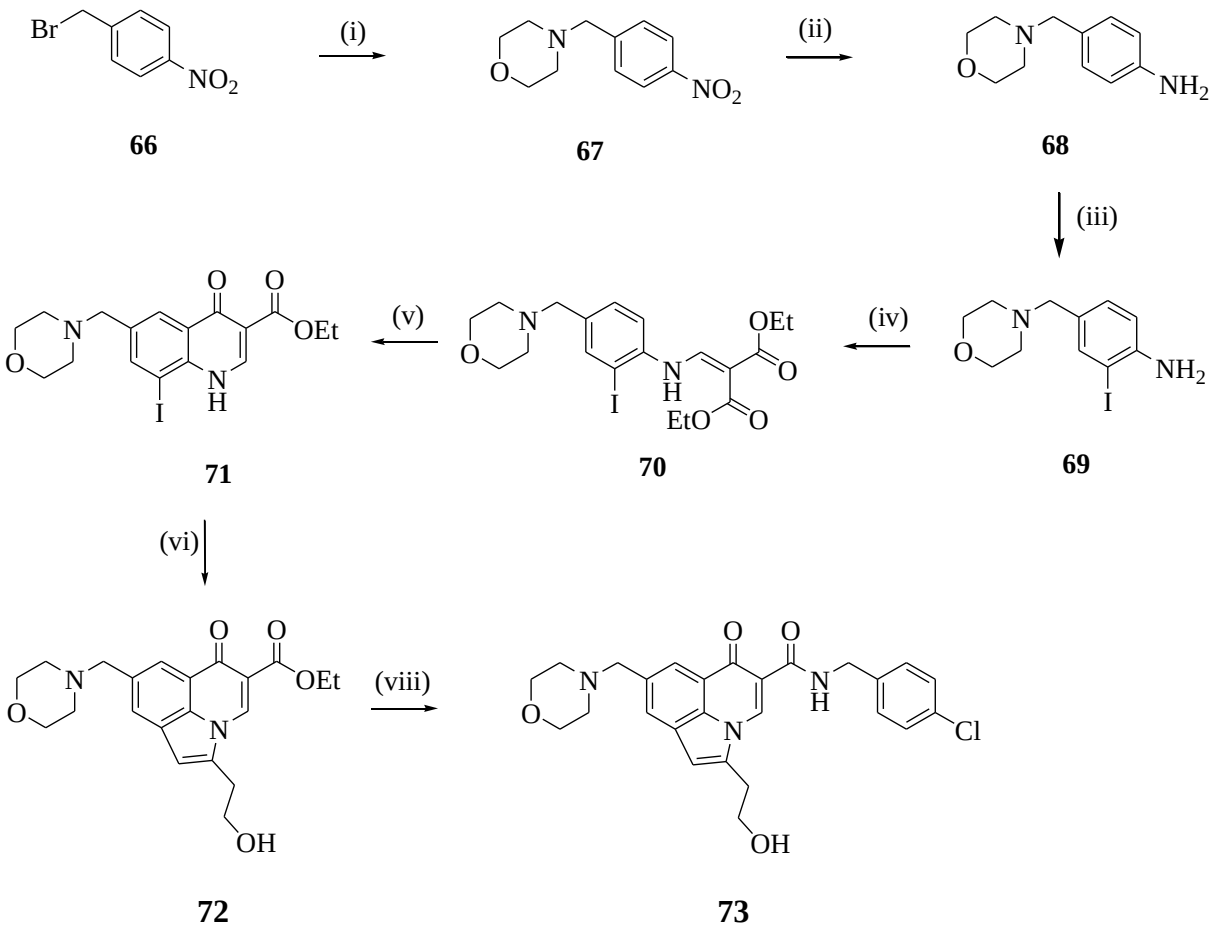


59 **60** **61** **62** **68** **67** **66**

Reagents and conditions: (i) 50% H_2SO_4, 110 °C, 3 h; (ii) $SOCl_2$, dichloroethane, 70 °C, 2 h, then $AlCl_3$, benzene, 60 °C, 10 min; (iii) Zinc powder, 80% AcOH, 90 °C, 1 h; (iv) acrylonitrite, Triton B, dioxane, 70 °C, 2 h; (v) P_2O_5, 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).[6] 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(1*H*)-one derivative **71** in 70% yield. The 8-iodoquinolin-4(1*H*)-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 pomerase in human.[6]

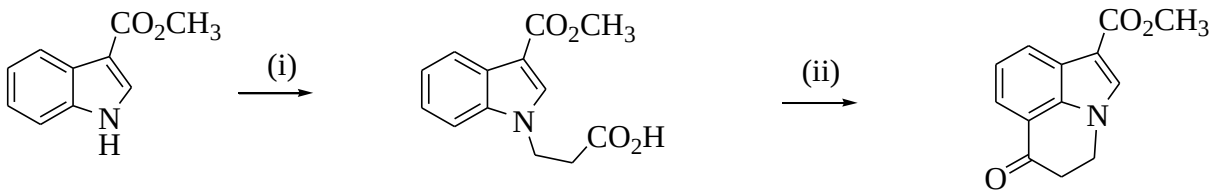


Reagents and conditions: (i) morpholine, toluene, <50 °C; (ii) H_2 (g), 5% Pt/C, THF, 60-70 °C, N_2 (g), 2 h; (iii) ICl, AcOH, DCM-MeOH (5:1; v/v), 10-15 °C, 1 h; (iv) DEEM, toluene, 120 °C, N_2 (g); (v) P_2O_5, MsOH, 90 °C, 4 h; (vi) 3-butyn-1-ol, $PdCl_2(PPh_3)_2$, CuI, NEt_3, EtOH, reflux, N_2 (g), 12-17 h; (vii) 4-chlorobenzylamine, ethylene glycol, 130 °C, N_2 (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**.[44,45] 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).[45] 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.



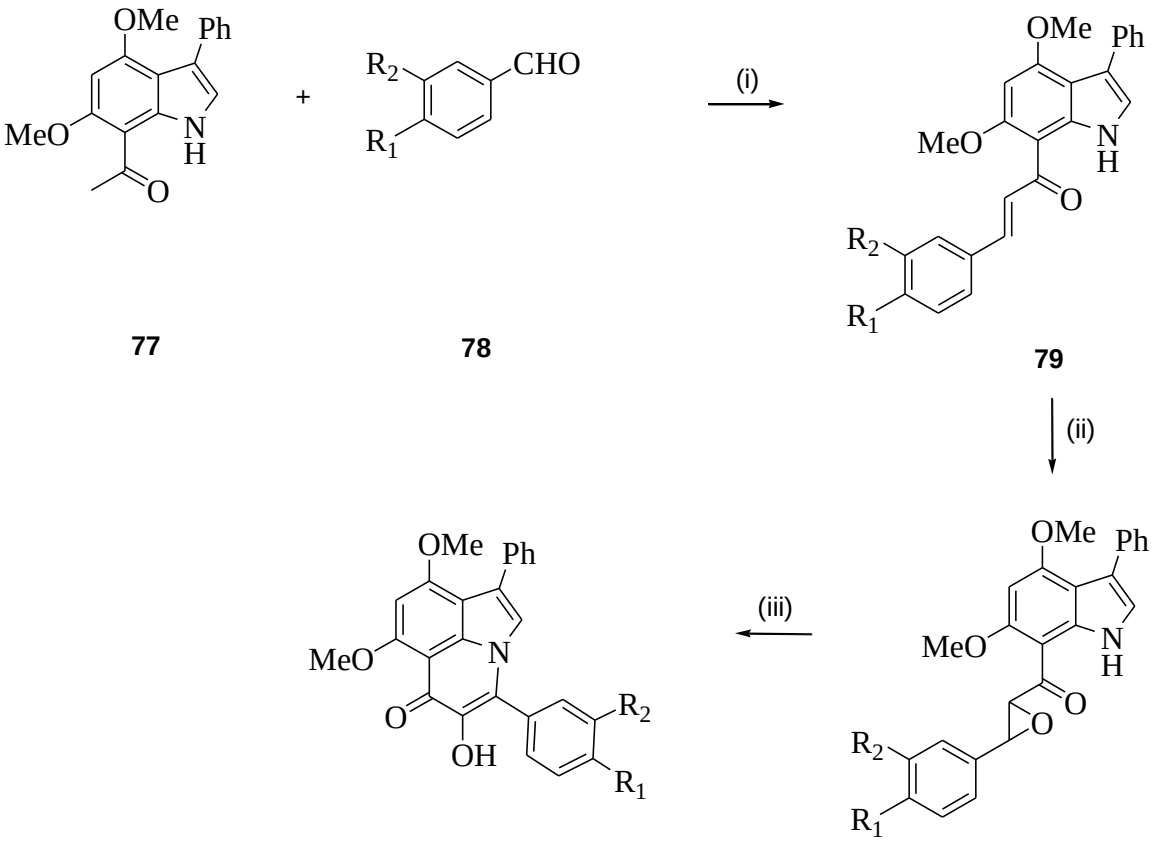
74 **75** **76**

Reagents and conditions: (i) methyl acrylate, K_2CO_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

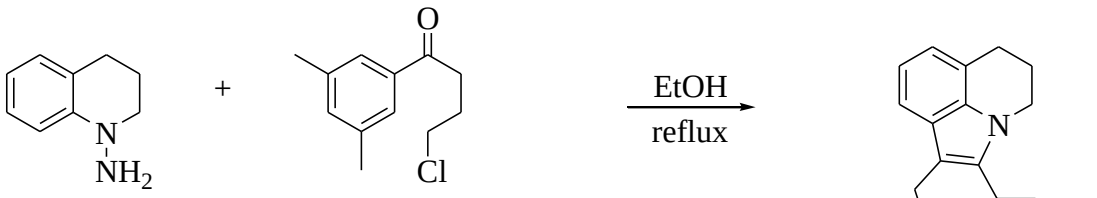
afforded a range of the 6-oxopyrroloquinoline derivatives **81** in 54-82% yield. This method involves several steps.



Reagents and conditions: (i) $NaNH_2$, anhyd. THF, r.t., 0.5 h; (ii) NaOH, H_2O_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

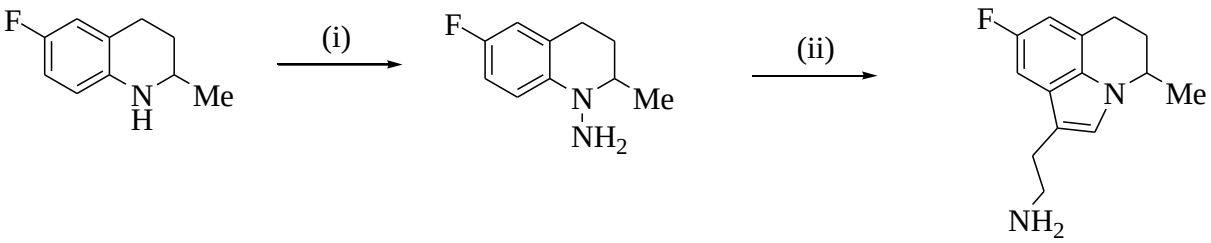
Grandberg has previously subjected 1-amino-1,2,3,4-tetrahydroquinoline **82** and 4-chloro-1-(3,5-dimethylphenyl)butan-1-one **83** to cyclocondensation in ethanol under reflux (Scheme 17).[49] This reaction which involves cyclodehydration and dechloroamination afforded 1-(2-aminoethyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline **84** in 15% yield.



82 **83** **84**

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 $NaNO_2$ under acidic conditions at 0 °C followed by reduction with $LiAlH_4$ in diethyl ether to afford 1-amino-1,2,3,4-tetrahydroquinoline derivative **86** (Scheme 18).[24] The latter was cyclized with 4-chlorobutanal in MeOH-H_2O 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-HT_{2c} receptor agonist with selectivity over 5-HT_{2a} receptor.



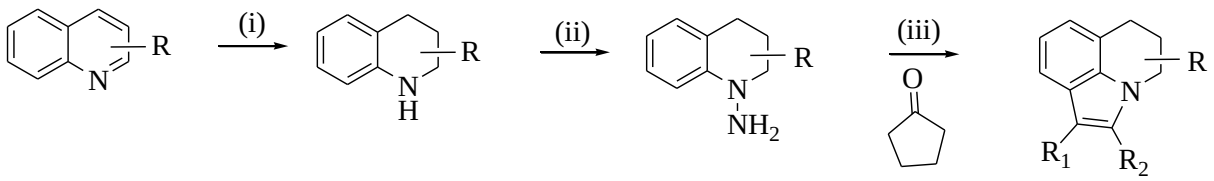
85 **86** **87**

Reagents and conditions: (i) $NaNO_2$, H_2SO_4, 0-5 °C, then $LiAlH_4$, diethyl ether; (ii) 4-chlorobutanal, MeOH/H_2O (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 19).[5] 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.[5]



88 **89** **90** **91**

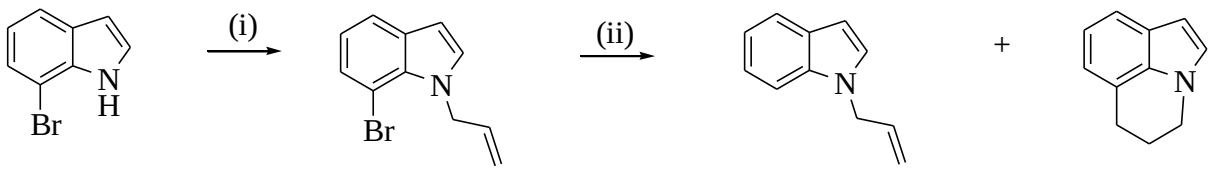
88	**89**	**90**	**91**
a: R = 2-CO_2H	R = 2-$CON(CH_3)_2$	R = 2-$CH_2N(CH_3)_2$	R = 4- or 5-$CH_2N(CH_3)_2$
b: R = 3-CO_2H	R = 3-$CON(CH_3)_2$	R = 3-$CH_2N(CH_3)_2$	R_1, R_2 = -$(CH_2)_{3-6}$

Reagents and conditions: (i) $SOCl_2$, toluene, reflux, 2 h; then Me_2NH, PtO_2, H_2, 2-propanol, r.t.; (ii) $NaNO_2$, dil. HCl, 5-10 °C, 1 h; then $LiAlH_4$, 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.[50] 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 (azobisisibutyronitrile) 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]

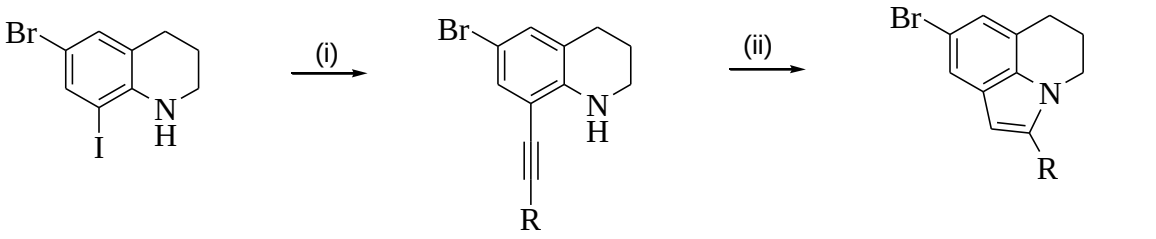


92 **93** **94** **95**

Reagents and conditions: (i) $HCCHCH_2Br$ (4.5 eq.), K_2CO_3 (5 eq.), acetone, reflux, 24 h; or bromoalkene/acid chloride (1.5 eq.), KOH, DMF, r.t., 24 h; (ii) $SnBu_3$, AIBN, toluene, reflux

Scheme 20: Reaction of **92** with 2-bromoalkene and radical cyclization of the *N*-alkylated 7-bromoindoles

The 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline framework has been found in numerous natural product and has attracted much attention in the effort to discover new drugs.[17] For example, a series of pyrrolo[3,2,1-*ij*]quinoline derivatives exhibit histamine and platelet activating factor antagonism.[19] Moreover, some pyrrolo[3,2,1-*ij*]quinolinones exhibit antifungal activities for rice plants.[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-chlorobenzyl)-2-(2-hydroxyethyl)-8-(morpholin-4-ylmethyl)-6-oxo-6-*H*-pyrrolo[3,2,1-*ij*]quinolin-5-carboxamide (PHA-529311).[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 *et al*., for example, previously reacted 8-iodo-6-bromo-1,2,3,4-tetrahydroquinoline **96** with a series of terminal alkynes in the presence of 10% Pd/C-PPh_3-CuI in water using 2-aminoethanol as a base at 80 °C in an inert atmosphere to afford the cross-coupled products **97** in 51-95% yield (Scheme 21).[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-4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives **98** in 50-92% yield.



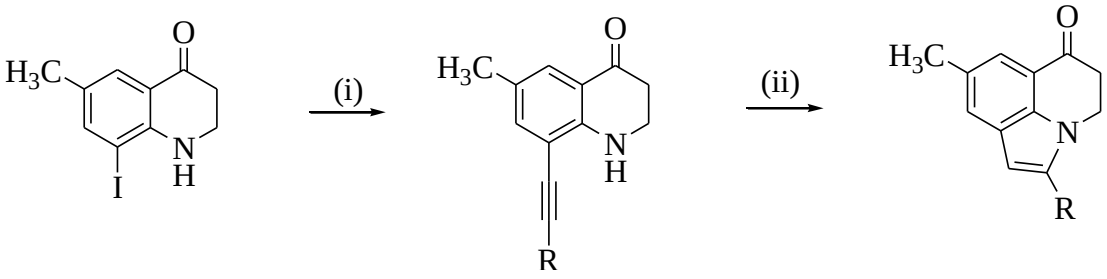
R = -C_6H_5, 4-$CH_3C_6H_4$-, 2-$NO_2C_6H_4$-, -CH_2CH_2OH

96 **97** **98**

Reagents and conditions: (i) RC≡CH (3.0 equiv.), 10% Pd/C, PPh_3, CuI, 2-aminoethanol (3.0 equiv.), H_2O, 80 °C, 4-30 h, N_2(g); (ii) CuI, DMF, 100 °C, 4-36 h

Scheme 21: Sequential Sonogashira coupling and cyclization of **96** with terminal alkynes

In another development, a series of 6-substituted 8-iodo-2,3-dihydroquinolin-4(1*H*)-ones **99** was subjected to Sonogashira cross-coupling with terminal alkynes in the presence of 10% Pd/C-PPh_3-CuI catalyst mixture and Et_3N as a base in ethanol at 80 °C under nitrogen atmosphere to afford compounds **100** (Scheme 22).[56] The latter were, in turn, subjected to a transitional metal-mediated intramolecular cyclization using $PdCl_2$ as catalyst in MeCN at 80 °C to afford 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones **101** in 60-90% yield.



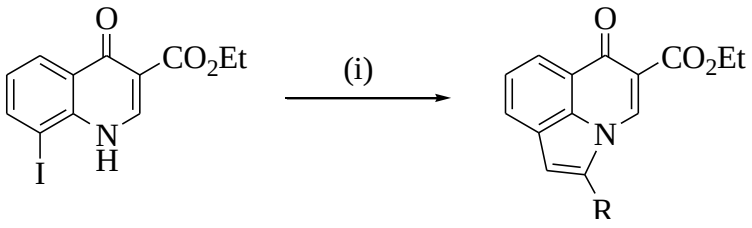
R = -C_6H_5, 4-MeC_6H_4, $(CH_2)_3CN$, $(CH_2)_2OH$

99 **100** **101**

Reagents and conditions: (i) RC≡CH, 10% Pd/C, PPh_3, CuI, Et_3N, EtOH, 80 °C, 2-10 h, N_2(g); ii) $PdCl_2$, 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-PPh_3-CuI catalyst complex and Et_3N 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).[57] 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.



102 **103 (**R = -CH_2OH, -$(CH_2)_2OH$, -$CHOHCH_3$, -$(CH_2)_3CH_3$)

Reagents and conditions: (i) RC≡CH, 10% Pd/C, PPh_3, CuI, Et_3N, EtOH, 80 °C, 2-5 h, N_2(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-4*H*-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 antiviral[6], antihistamine[24] and antifungal[25] 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(1*H*)-ones and 2-arylquinolin-4(1*H*)-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.

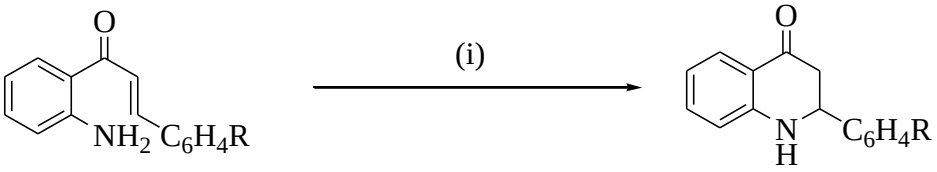
1.3 Methods for the synthesis of 2-substituted quinolin-4(1*H*)-ones

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,[6] antitumor[59,60] and antibacterial[58,61] activities. Their halogenated derivatives represent suitable substrates for metal-catalyzed carbon-carbon bond formation to afford polycarbo-substituted quinolinones[56,62,63] and/ or quinoline derivatives.[64] Alkenylated-[32] and alkynylated[56,57] 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 quinolin-4(1*H*)-ones involves the modification of the halogenated quinolin-4(1*H*)-one moiety *via* metal-catalyzed cross-coupling reactions. The methods for the synthesis and transformation of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones and their quinoline derivatives have been reviewed in detail in the literature before.[65,66,67,68,69] Selected examples of the methods for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones are briefly discussed below.

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

The 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **105** are commonly prepared by acid or base-promoted cyclization of their isomeric 1-(2-aminophenyl)-3-aryl-2-propen-1-ones (2-aminochalcones) **104**. 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.[65,66,67] The 2-aminochalcones **104** are subsequently cyclized under either acidic[67,68] or basic[66] conditions to afford the corresponding 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **105**. A convenient approach involves cyclization of **104** with

orthophosphoric acid in acetic acid under reflux to afford the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **105** in high yields (Scheme 24).[68] 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(1*H*)-ones in 82-96% yields has also been reported before.[69] Another solvent-free and solid-supported method involving the cyclization of 4-substituted 2-aminochalcones in the presence of alumina supported $CeCl_3.7H_2O$-NaI as catalyst at 70 °C to afford 2,7-disubstituted 2,3-dihydroquinolin-4(1*H*)-ones in 86-98% yields has also been reported in the literature.[70] A similar attempt using silica gel in place of alumina afforded the 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one in relatively lower yield (80%).[71] Silica chloride promoted cyclization of the chalcones under solvent-free conditions also afforded the cyclized products in high yields (Scheme 24).[72] 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.[73] 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.



104 R = H, 2-F, 2-Cl, 3-Cl, 4-CH_3, 4-Cl, 4-OCH_3 **105**

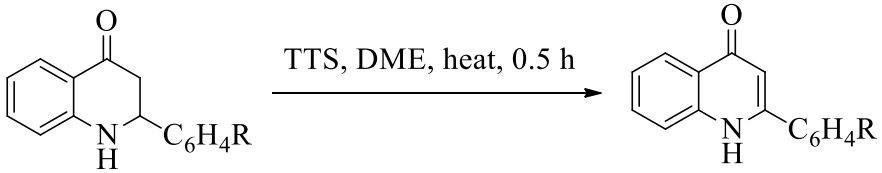
Reagents and conditions: (i) H_3PO_4, AcOH, reflux, 2 h[68] or SiO_2Cl, MW, 3-6 min.[72]

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

The heterocyclic ring of the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones can undergo different degree of unsaturation, for example, via dehydrogenation or aromatization to afford 2-arylquinolin-4(1*H*)-ones or 4-substitued 2-arylquinolines, 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(1*H*)-ones

The methods for the dehydrogenation of the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **105** 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] to afford the potentially tautomeric 2-arylquinolin-4(1*H*)-ones **106** have been described before (Scheme 25).[74] Tautomeric studies based on IR and NMR spectroscopic and X-ray crystallographic techniques as well as quantum chemical calculations of the equilibra 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.[76]



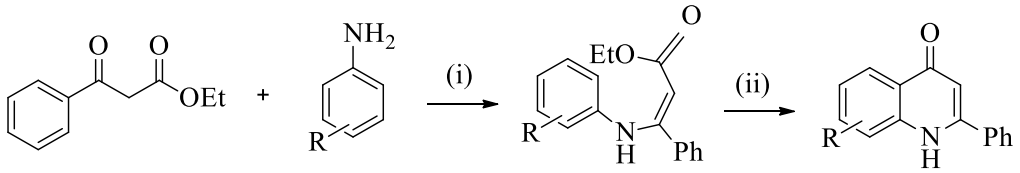
105 (R = H, 3-OCH_3, 4-OCH_3, 3,4-OCH_2O, 4-CH_3, 4-Cl) **106** (90-96%)

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

Methods for the direct synthesis of the 2-arylquinolin-4(1*H*)-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(1*H*)-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.[77] 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 aroylacetates with meta-substituted aniline in polyphosphoric acid at 260 °C afforded a mixture of substituted quinolin-4(1*H*)-ones albeit in poor yields after tedious purification process.[78] Several other methods for the cyclocondensation of substituted benzoyl acetates with arylamine derivatives or isatoic derivative with acetophenone have also been described before. Ethyl benzoylacetate **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).[79]



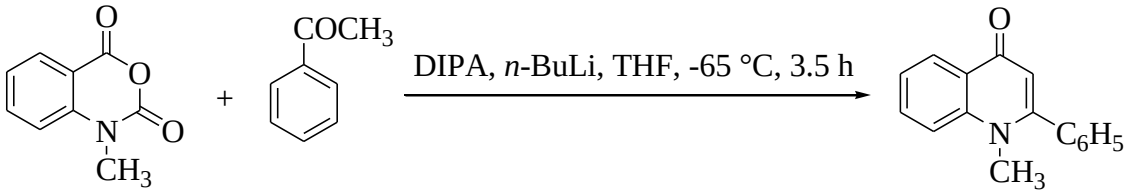
107 **108** **109** **110** (R = H, 6-F, 6-Cl, 6-CH_3, 6-OCH_3)

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(1*H*)-one **113** has also been described (Scheme 27).[80] In another approach, 2-aminoacetophenone was initially condensed with a series of aldehydes followed by selective reduction of the keto functionality using $NaBH_3CN$ to afford the alkylated derivatives. The latter were, in turn, acylated using variously substituted benzoyl

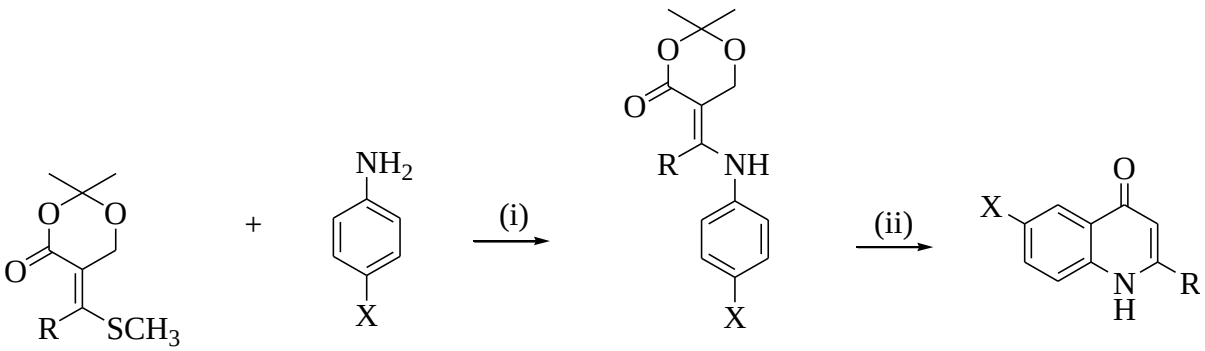
chlorides and the amides produced were cyclized using *t*-BuOK in refluxing *t*-BuOH to afford 1-benzyl-2-arylquinolin-4-ones.[81]



111 **112** **113**

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(1*H*)-ones **117** directly in 67-89% yield without isolating the incipient intermediates **116** (Scheme 28).[82]



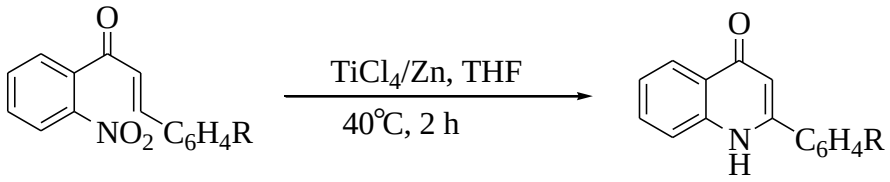
114 (R = CH_3, C_2H_5, Ph) **115** (X = H, Cl, Br, NO_2) **116** **117**

Reagents and conditions: (i) $(C_6H_5)_2O$, 140 °C, 0.5 h or C_2H_5OH, heat, 2-4 h

(ii) $(C_6H_5)_2O$, 250-260 °C, N_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 $TiCl_4$/Zn in THF at 40 °C to afford the corresponding 2-arylquinolin-4(1*H*)-ones **106** in 70-88% yield (Scheme 29).[83] 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.

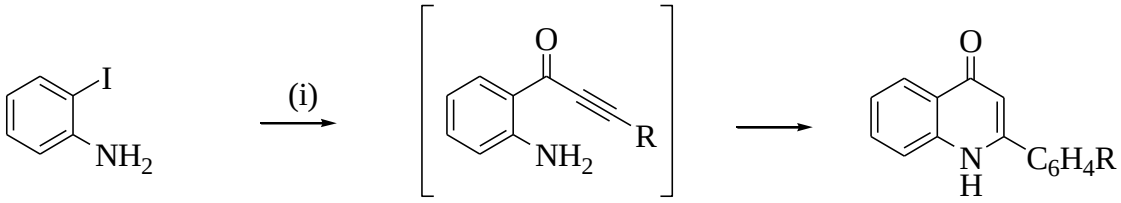


118 (R = 4-F, 4-Br, 4-CH_3, 4-OCH_3) **106**

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

Less traditional methods for the synthesis of 2-arylquinolin-4(1*H*)-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 [$PdCl_2$(dppf)] in diethylamine under CO atmosphere at 120 °C afforded substituted 2-arylquinolin-4(1*H*)-ones **120** in 62-84% yield (Scheme 30).[84] In another example, palladium-catalyzed reaction of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one and aniline in the presence of $Pd(PPh_3)_4$ and K_2CO_3 as a base in dioxane under reflux afforded 1,2-diphenylquinolin-4(1*H*)-one in 75% yield.[85]



119 **120** (R = H, 3-OCH_3, 4-OCH_3)

Reagents and conditions: (i) RC≡CH, $PdCl_2$(dppf), $NHEt_2$, CO (20 atm.), 120 °C, 1 h.

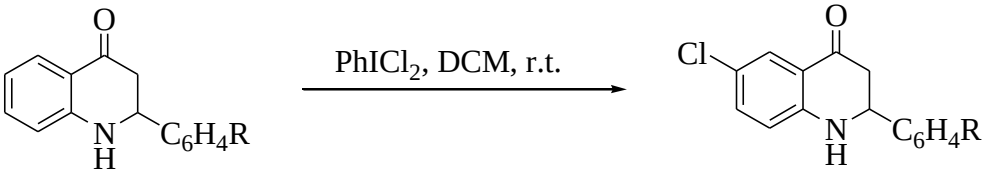
Scheme 30: Transition metal-catalyzed reaction of iodoaniline with terminal alkynes

The quinolin-4(1*H*)-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.[69] The 2-arylquinolin-4(1*H*)-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.[79,86] Aromatization of the 4-quinolone core with phosphorus oxychloride or thionyl chloride yield 4-chloroquinolines which are essential intermediates for amination[87,] or alkoxylation[88] and for cross-coupling.[88,89] 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-[32] or alkynylated quinolinones.[56,57] 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.[2,57,89] The known methods for the halogenation of the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones and 2-arylquinolin-4(1*H*)-ones are described in sequence below.

1.4 Halogenation of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones and 2-arylquinolin-4(1*H*)-ones

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

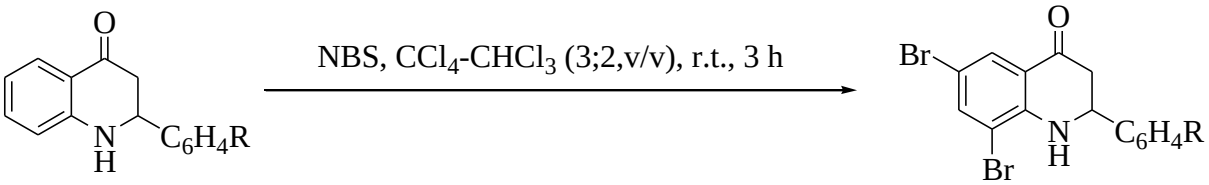
Halogenated quinolones[90] and their quinoline derivatives[91] are useful precursors for carbon-carbon bond formation or nucleophilic substitution to afford a range of polycarbo-substituted[86,92,93] and/ or their annulated derivatives.[56,57,89] Halogen-containing quinolones are also of particular interest because the halogen plays a crucial role in the compounds' bioactivity.[94] Several methods have been reported for the halogenation of the fused benzo-ring of the dihydroquinolin-4(1*H*)-one framework. Sharma *et al.* previously treated 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **105** with 1.5 equivalent of (dichloroiodo)benzene ($PhICl_2$) in dichloromethane (DCM) at room temperature to afford the corresponding 2-aryl-6-chloro-2,3-dihydroquinolin-4(1*H*)-ones **121** in 53-76% yield (Scheme 31).[90]



105 (R = H, 4-F, 4-Br, 4-NO_2, 2-OCH_3) **121**

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

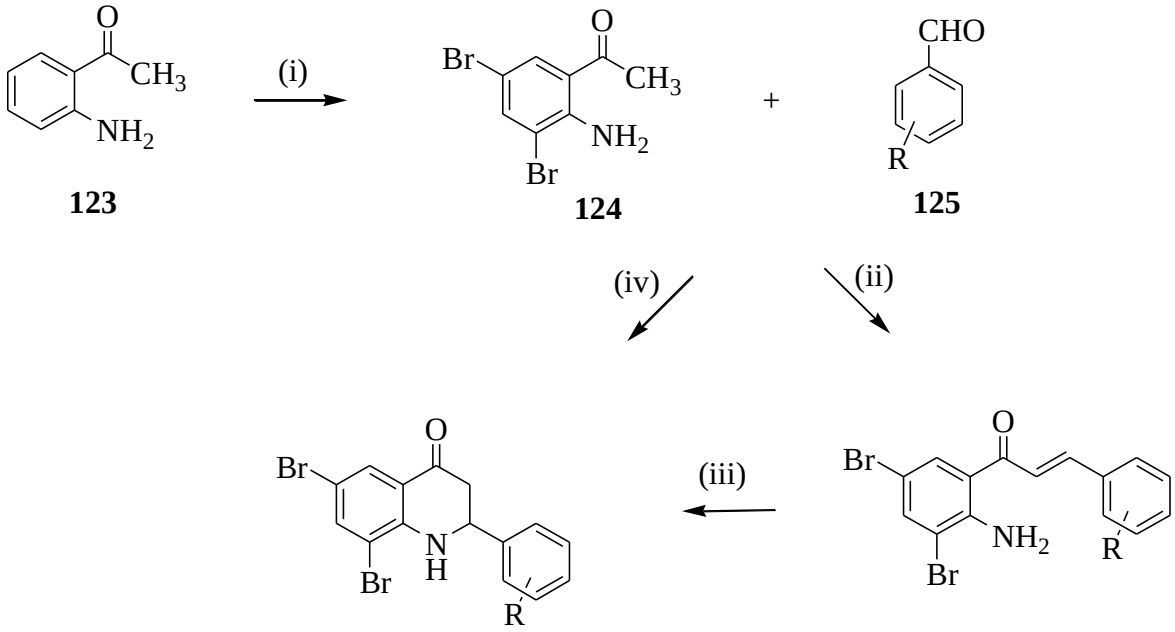
In another development, treatment of compounds **105** with an excess of *N*-bromosuccinimide (NBS) in carbon tetrachloride-chloroform mixture at room temperature, on the other hand, afforded the corresponding 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones **122** in 82-88% yield (Scheme 32).[86]



105 (R = H, 4-F, 4-Cl, 4-OCH_3) **122**

Scheme 32: Dihalogenation of the fused benzo ring of **105**

Akinnepally *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).[94] 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(1*H*)-ones **122** in 55-72% yield. In another approach, the authors also isolated the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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).[94]



123 **124** **125**

R = 4-F, 4-Cl, 4-Br, 4-NO_2, 4-CN, 4-OH, 3-OH, 4-$N(CH_3)_2$, 3,4,5-tri-OCH_3-

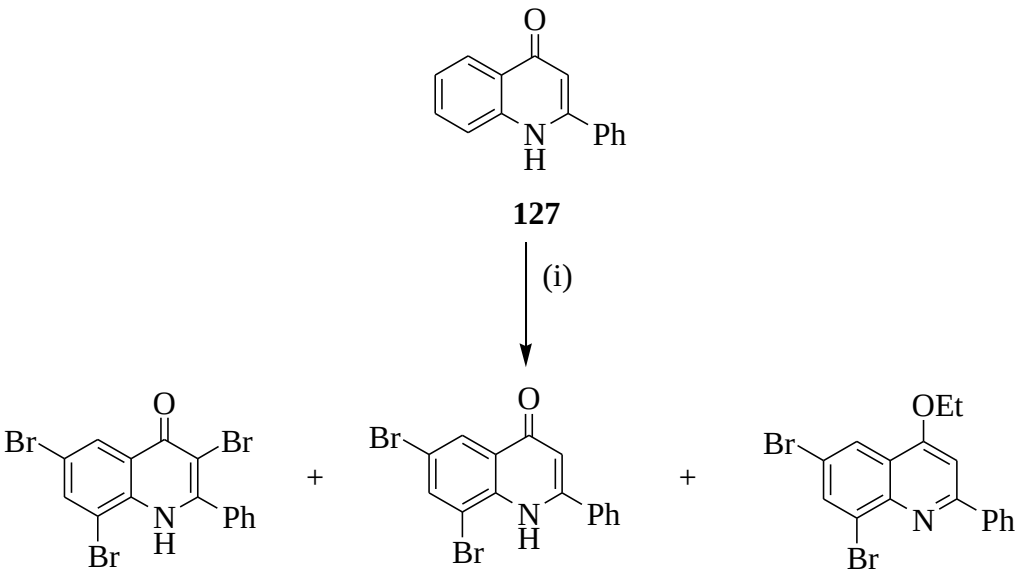
122 **126**

Reagents and conditions: (i) Br_2, DCM, 0-5 °C, 7 h; (ii) EtOH, NaOH, 0-5 °C, 24 h; (iii) AcOH, H_3PO_4, 100 °C, 2-3 h; (iv) L-proline, MeOH, 55-60 °C, 48 h

Scheme 33: Dihalogenation of **123** and cyclocondensation with arylaldehydes

A variety of methods have been reported for the halogenation of the quinolin-4(1*H*)-one moiety. For example, treatment of 2-phenylquinolin-4(1*H*)-one **127** with an excess of molecular bromine (4.0 eq.) in ethanolic chloroform yielded 2-phenyl-3,6,8-tribromoquinolin-4(1*H*)-one **128** as the main product (43%) along with smaller quantities of 6,8-dibromo-2-phenylquinolin-4(1*H*)-one **129** and ethoxyquinoline derivative **130** (Scheme 34).[95] For the halogenation of the potentially tautomeric 2-phenylquinolin-4(1*H*)-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

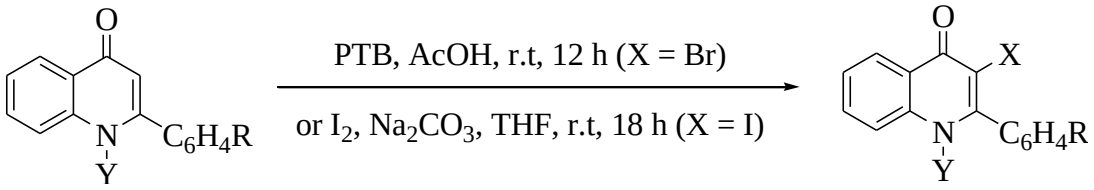
afford a hemiacetal, which in turn, would undergo dehydration to yield an enolether derivative followed by dehydrobromination to afford ethoxyquinoline **130**.[96]



Reagents and conditions: (i) Br (4.0 eq.), $CHCl_3$, r.t.

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

A series of 2-arylquinolin-4(1*H*)-ones **131** was treated with pyridinum tribromide (PTB) in acetic acid at room temperature to afford the 3-bromoquinolin-4(1*H*)-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(1*H*)-ones **132** (X = I) in 80-92% yield (Scheme 35).[97]



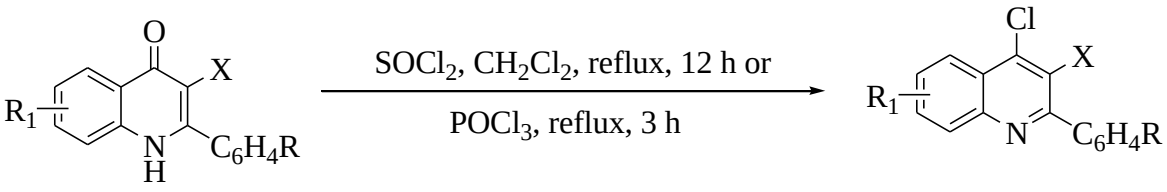
131 (R = H, F, Cl, OCH_3 ; Y = H, CH_3) **132** (X = Br, I)

Scheme 35: C-3 halogenation of 2-arylquinolin-4(1*H*)-ones

Methods that make use of oxidizing agents to promote aromatization of the quinolin-4(1*H*)-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(1*H*)-ones into 4-halogenoquinolines

Reagents such as thionyl chloride and phosphoryl chloride have been employed before for the aromatization of the quinolin-4(1*H*)-one moiety into quinoline. For example, aromatization of a series of substituted 2-arylquinolin-4(1*H*)-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(1*H*)-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]



133 **134**

134	X	R	R_1	% Yield
a	H	H	H	91
b	H	2-F	H	92
c	H	H	6-F	82
d	I	H	H	55
e	I	F	H	62
f	I	Cl	H	65

Scheme 36: Aromatization of the 2-arylquinolin-4(1*H*)-ones into 4-chloroquinolines

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.[86,94] 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.[56,57] 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(1*H*)-ones and the 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones. Our goal was to prepare a series of polycarbosubstituted 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.

1.6 Research hypothesis

Pyrrolo[3,2,1-*ij*]quinolinone derivatives have been reported to serve as antifungal agents against rice plants[25] and exhibit antiviral activities on human herpesviruses DNA polymerases.[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[19] and as anticonvulsant agents.[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 = aryl, bearing alkyl and polyaryl substituents and such compounds cannot be easily accessible through conventional methods.

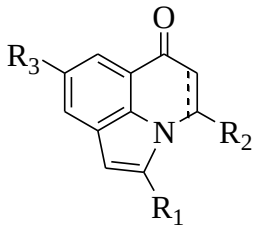


Figure 2: The generalized structure of 2,4,8-trisubstituted 6-oxopyrrolo[3,2,1-*ij*]quinoline

As a result, the indirect method involving the use of 2-aryl-6,8-dibromoquinolin-4(1*H*)-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.[56,57] In this investigation, we opted for the use of the 2-aryl-6,8-dibromoquinolin-4(1*H*)-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(1*H*)-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(1*H*)-ones cross-coupling with arylboronic acids to afford 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones.[86] Although a similar approach was employed before in the reaction of analogous 6,8-dibromoflavone with methyl acrylate under Heck conditions,[98] 6,8-dichlorotetrahydroquinoline with Grignard reagents,[99] and 2,4-diiodoquinoline with terminal alkynes under Sonogashira conditions[100] 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(1*H*)-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(1*H*)-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(1*H*)-ones to dehydrogenation to afford the 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones

(ii) To subject the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones and the 2-aryl-6,8-dibromoquinolin-4(1*H*)-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 monoalkynyldihydroquinolin-4(1*H*)-ones and monoalkynyl quinolin-4(1*H*)-ones to metal-promoted electrophilic cyclization to furnish pyrrolo[3,2,1-*ij*]quinolinones and pyrrolo[3,2,1-*ij*]quinolines.

(iv) To transform the mono-substituted pyrrolo[3,2,1-*ij*]quinolinones and pyrrolo[3,2,1-*ij*]quinolines *via* metal-catalyzed Suzuki-Miyaura cross-coupling reaction with arylboronic acids

(v) To halogenate the known 2,6,8-triarylquinolin-4(1*H*)-ones with molecular iodine to afford the 2,6,8-triaryl-3-iodoquinolin-4(1*H*)-ones and transform these into 4,6,8-triarylfuro[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(1*H*)-ones **105** were prepared by cyclizing the 1-(2′-aminophenyl)-3-aryl-2-propen-1-one derivatives **104** using orthophosphoric acid in acetic acid. The 1-(2′-aminophenyl)-3-aryl-2-propen-1-ones were themselves prepared by condensing 2-aminoacetophenone **123** and benzaldehyde derivatives **135** in the presence of NaOH in ethanol. Compounds **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(1*H*)-ones **122**. Dehydrogenation of the latter using thallium(III) *p*-tolylsulphonate in dimethoxyethane under reflux afforded 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones **136**. Compounds **122** were then subjected to Sonogashira cross-coupling reaction with terminal alkynes in the presence of 10% palladium on carbon-triphenylphosphine and copper(I) iodide [10% Pd/C-PPh_3-CuI] catalyst complex and dichlorobis(triphenylphosphine)palladium(II)-copper(I) iodide [$PdCl_2(PPh_3)_2$-CuI] catalyst mixture and triethylamine (NEt_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(1*H*)-ones **137** and non-selective 6,8-disubstituted-2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **138**, respectively. The coupled compounds **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 **139** and 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydoquinolin-4(1*H*)-ones **140**. In a tandem coupling and heteroannulation reaction, the 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones **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-PPh_3-CuI) catalyst mixture and potassium carbonate (K_2CO_3) as a base in dioxane-water mixture [3:1; v/v] and dichlorobis(triphenylphosphine)palladium(II)-copper(I) iodide [$PdCl_2(PPh_3)_2$-CuI] with triethylamine (NEt_3) 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-disubstitttuted 4-aryl-6*H*-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(1*H*)-ones were treated with molecular iodine and sodium carbonate in THF to afford a series of 2,6,8-triaryl-3-iodoquinolin-4(1*H*)-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 NEt_3 in DMF under reflux and inert atmosphere. All the prepared products in this investigation were characterized using a combination of ^{1}H NMR & ^{13}C NMR spectroscopy, IR, mass spectrometry and X-ray diffraction techniques.

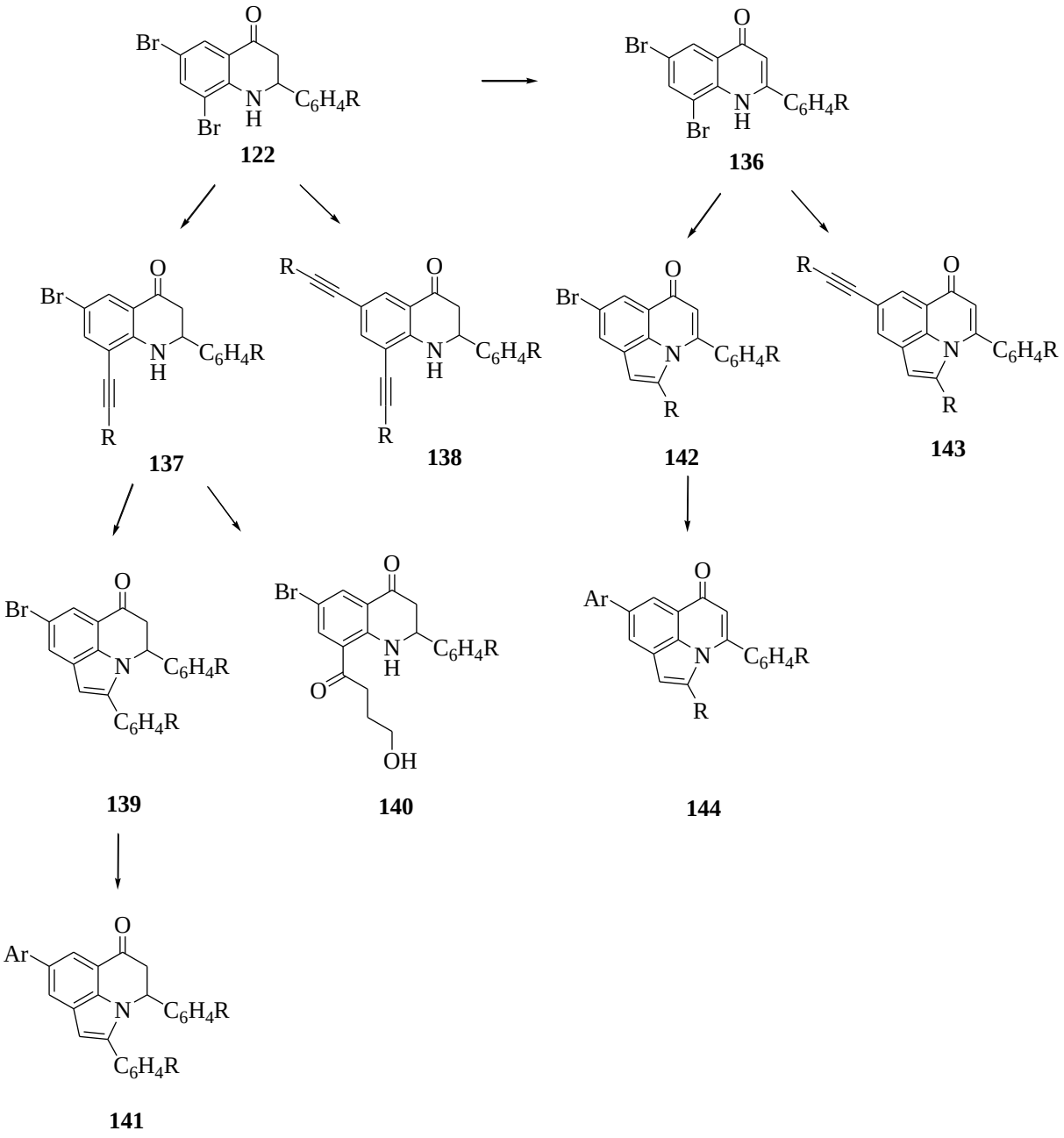
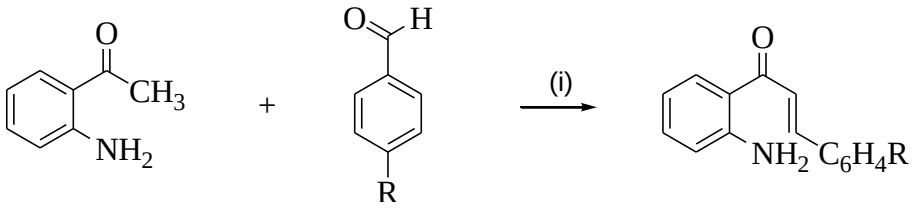


Figure 3: Generalized scheme depicting reaction pathways followed to prepare the pyrrolo[3,2,1-*ij*]quinolinones and pyrrolo[3,2,1-*ij*]quinoline derivatives described in this investigation

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(1*H*)-ones.[65-67,71] 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).[65,66,68] The ^{1}H 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 NH_2 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,[68] the corresponding ^{1}H NMR and IR spectroscopic data represent closest fit consistent with the assigned structures.



123 **135** **104a-d**

104	R	% Yield	Mp °C (Lit. [67])
a	H	99	62-64 (71-72)
b	F	99	108-110 (119-121)
c	Cl	99	99-101 (82-84)
d	OMe	99	91-93 (90-93)

Reagents and conditions: (i) NaOH, ethanol, r.t., 18 h

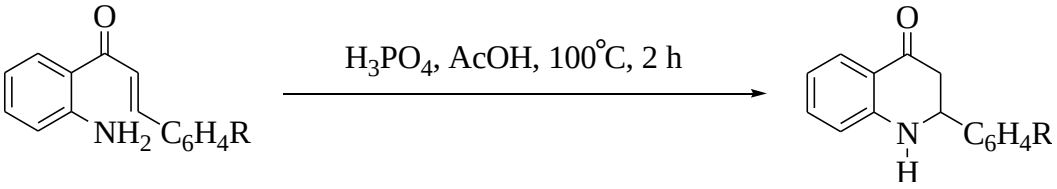
Scheme 37: Condensation of 2-aminoacetophenone with benzaldehyde derivatives

With the aminochalcones in hand, we explored the possibility of cyclization into the isomeric 2,3-dihydroquinolin-4(1*H*)-ones as described below.

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

The 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones are generally prepared by acid or base-promoted cyclization of the corresponding isomeric 2-aminochalcones **104**.[65,66,68-71] In this investigation, we adapted the method described in the literature[65,66,68] 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 ^{1}H 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 ν_{max} 1649 cm^{-1} and 3306 cm^{-1}, which correspond to C=O and N-H groups, respectively.



104 **105**

105	**R**	**% Yield**	**Mp °C (Lit. [ref])**
a	H	90	147-149 (148-150[65])
b	F	88	118-120 (116-118[69])
c	Cl	92	146-148 (146[69])
d	OMe	90	109-111 (112-114[69])

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

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.

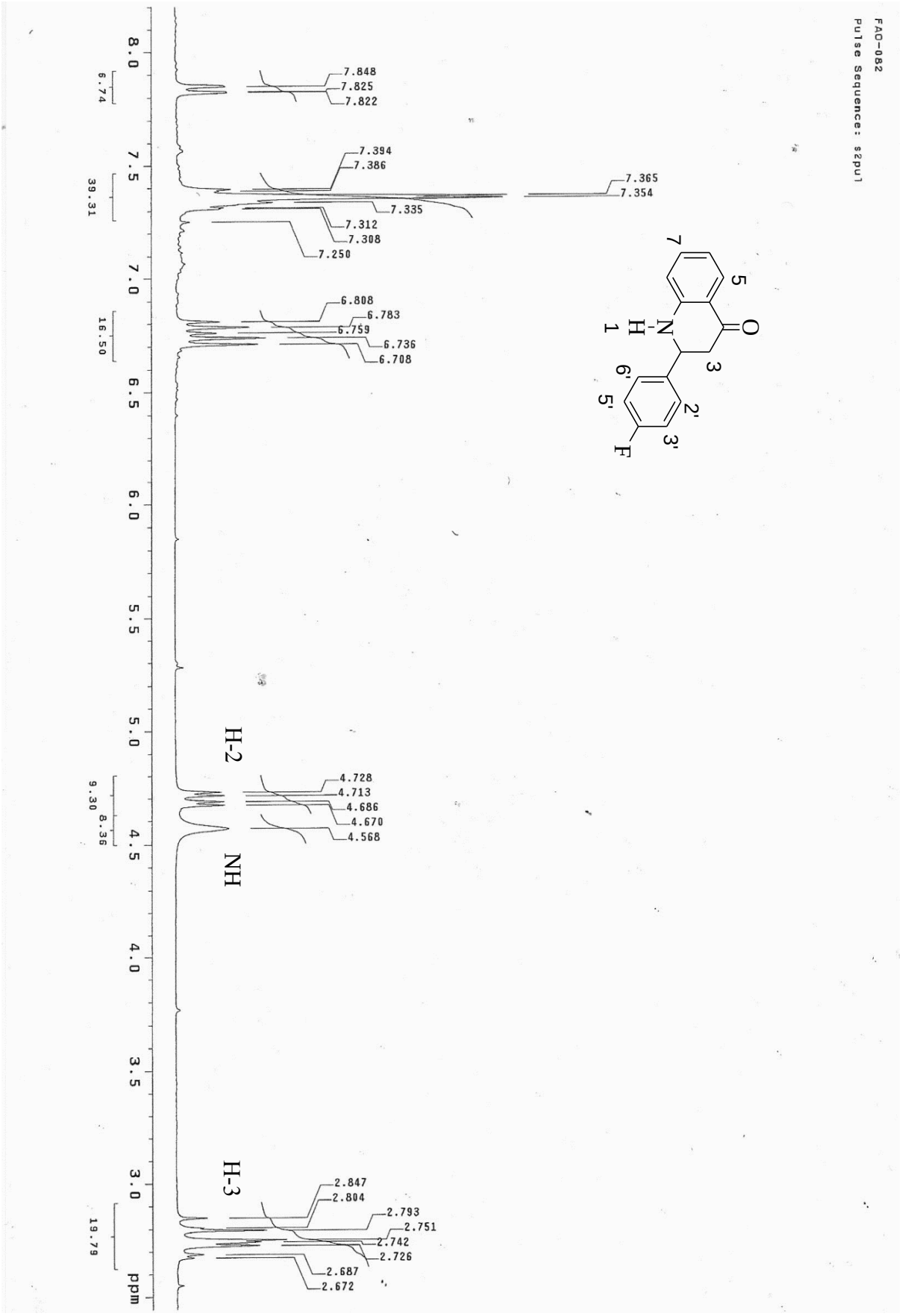


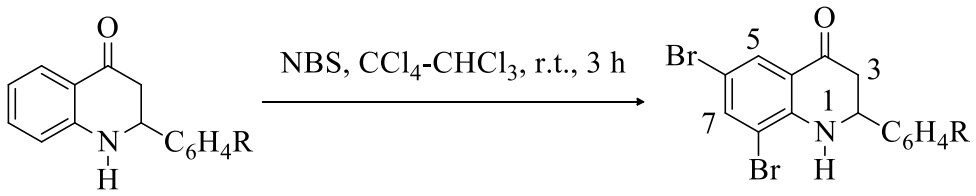
Figure 4: ^{1}H NMR spectrum of compound **105b** in $CDCl_3$ at 300 MHz

2.2 Synthesis of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones 122a-d

Halogenation of the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones has been previously effected through the use of dichloroiodobenzene.[90] In this study we subjected the 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **105** to *N*-bromosuccinimide (NBS) (2.5 equivalent) in carbon tetrachloride-chloroform [CCl_4-$CHCl_3$] 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(1*H*)-ones **122** in 83-88% yields (Scheme 39).[86] 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(1*H*)-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).

N(1)-C(9)-C(10)-C(15)	-37.3°
C(8)-C(9)-C(10)-C(15)	82.9°
N(1)-C(9)-C(10)-C(11)	146.9°
C(8)-C(9)-C(10)-C(11)	-92.8°

Table 1: Selected torsion angles of compound **122b**



105a-d **122a-d**

122	**R**	**% Yield**	**Mp °C**
a	H	85	137-139
b	F	86	126-128
c	Cl	88	145-147
d	OMe	83	149-151

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

The 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones were found by other authors to exhibit antiproliferative activity against MCF-7 breast cancer cell lines.[94] 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.[86] 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(1*H*)-ones or oxidative aromatization to afford quinoline derivatives.

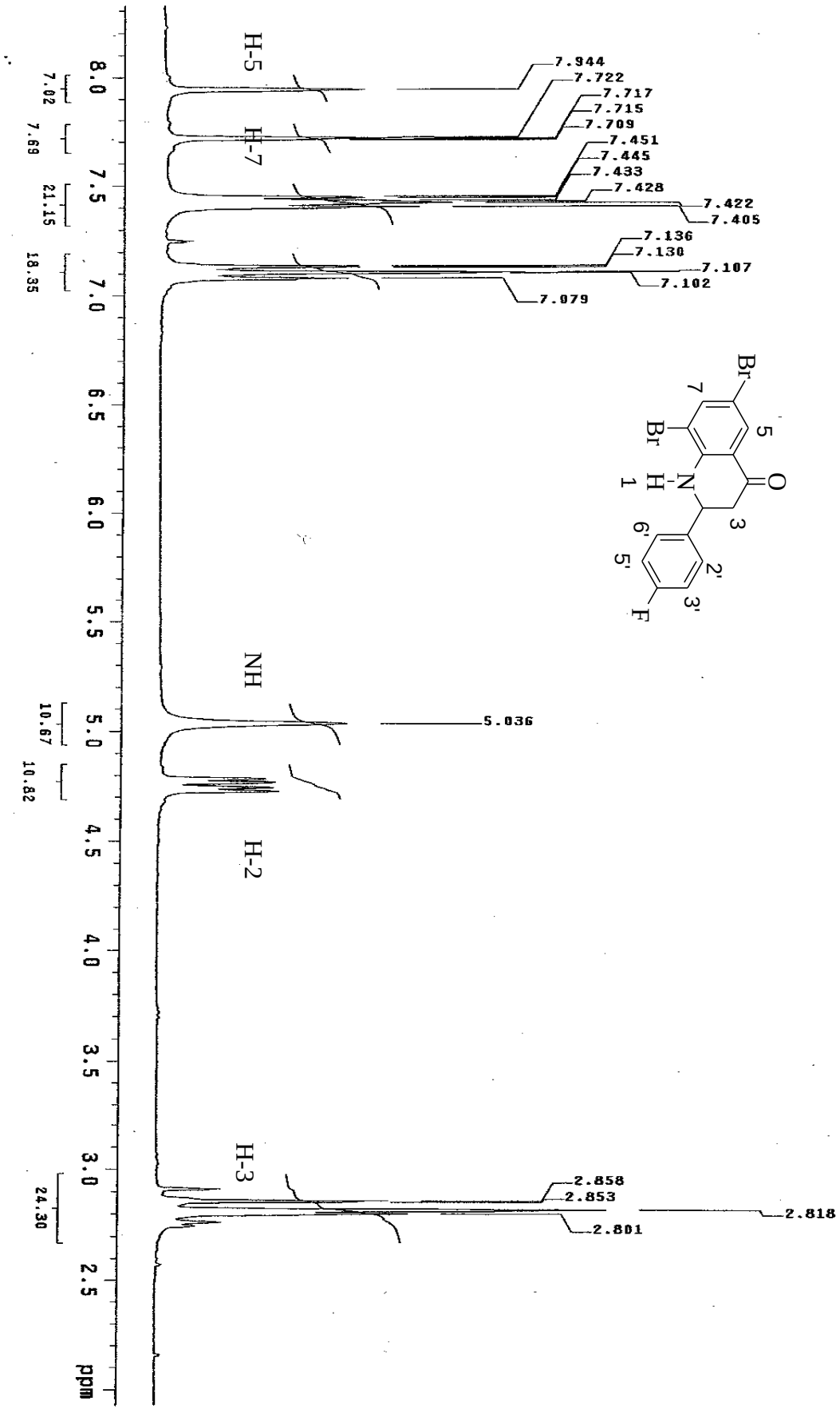


Figure 5: ^{1}H NMR spectrum of **122b** in $CDCl_3$ at 300 MHz

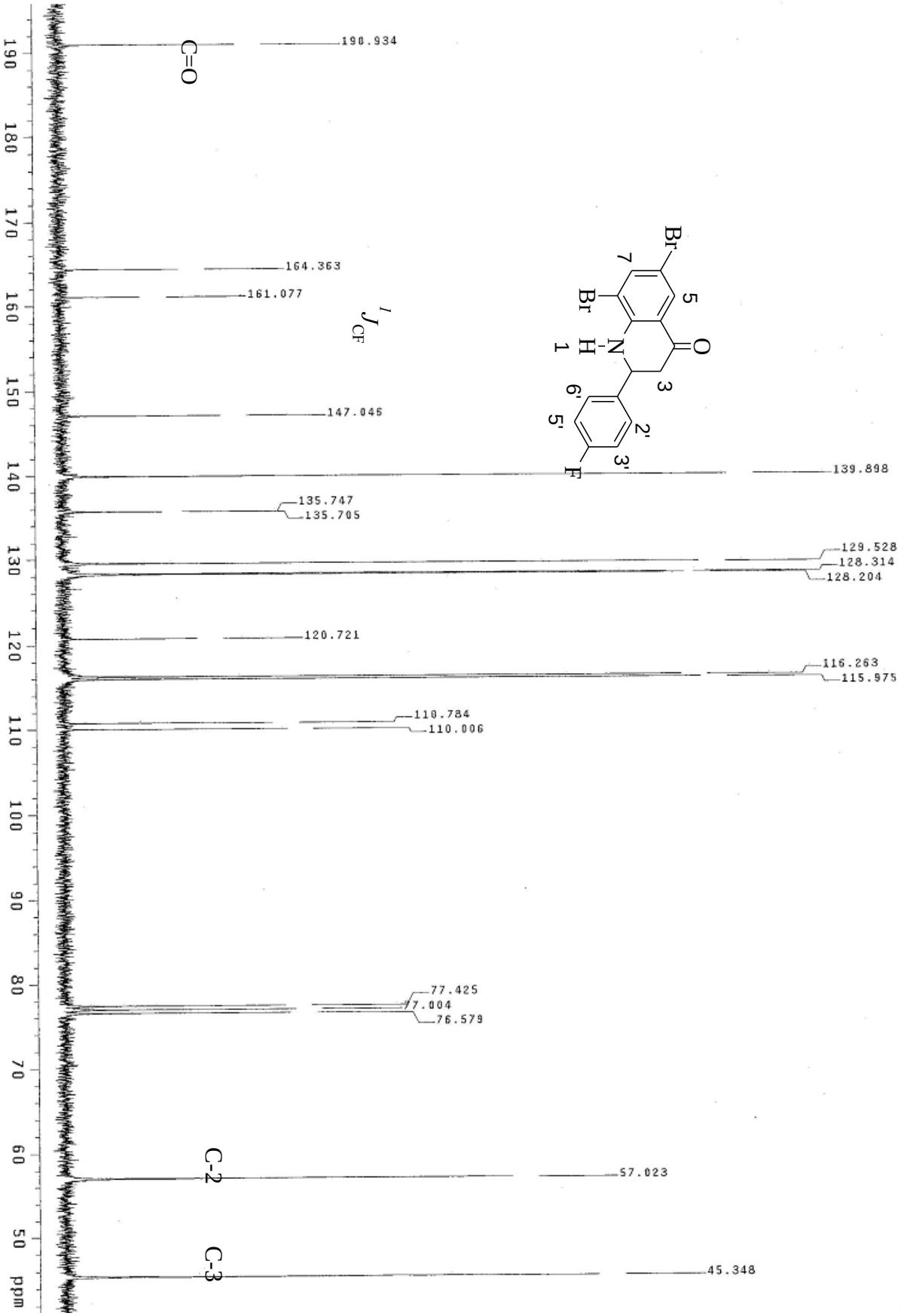


Figure 6: ^{13}C NMR spectrum of **122b** in $CDCl_3$ at 75 MHz

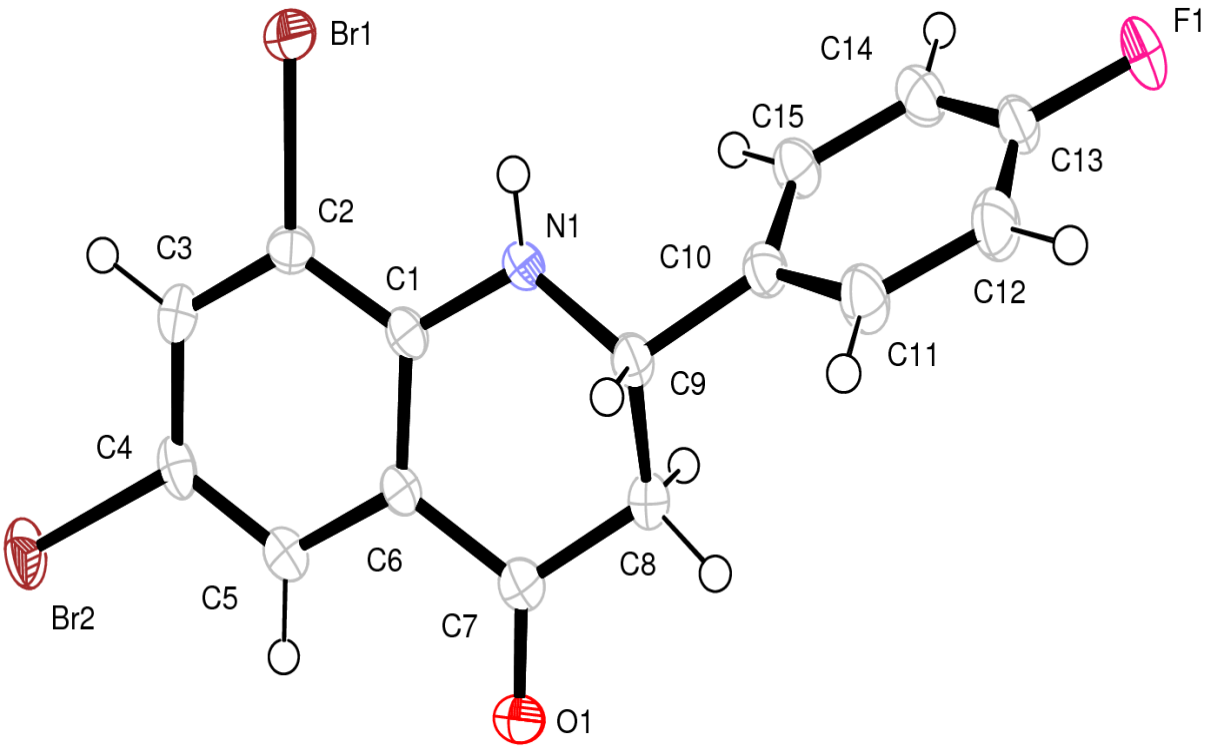


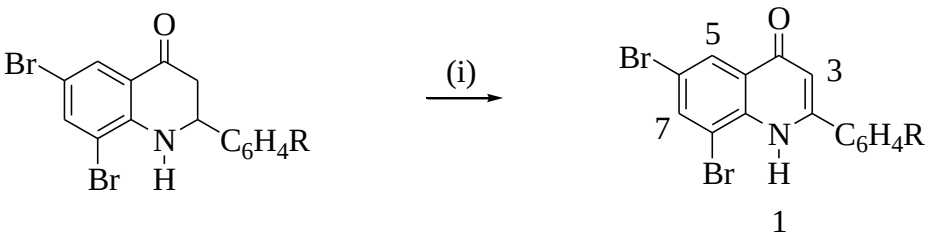
Figure 7: ORTEP diagram (50% probability level) of compound **122b** showing crystallographic numbering. For clarity, hydrogen atoms are not labeled.

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(1*H*)-one framework.

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

The 2-aryl-2,3-dihydroquinolin-4(1*H*)-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) *p*-tolylsulphonate due to the ease of preparation from thallium(III) nitrate and *p*-toluene sulphonic acid.[74] We treated the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones **122** with thallium(III) *p*-tolylsulphonate (TTS) in dimethoxyethane (DME) under reflux to afford the corresponding 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones **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 δ *ca*. 7.05-8.30 ppm and a less intense broad singlet significantly downfield at δ *ca.*11.90 ppm for N-H (Figure 8). The ^{13}C NMR spectra of compounds **136** also reveal the resonances corresponding to the olefinic signals at δ *ca*. 79.6 and 102.3 ppm for C-2 and C-3, respectively (Figure 9). Although, compounds **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).[76] The IR absorption bands at ν_{max} *ca*. 3384 cm^{-1} and 1622 cm^{-1} attributed to the N-H and C=O groups, further confirm their quinolin-4(1*H*)-one nature.



122 **136**

136	**R**	**% Yield**	**Mp °C**
a	H	86	212-214
b	F	80	222-224
c	Cl	88	233-235
d	OMe	82	190-192

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(1*H*)-ones **122**

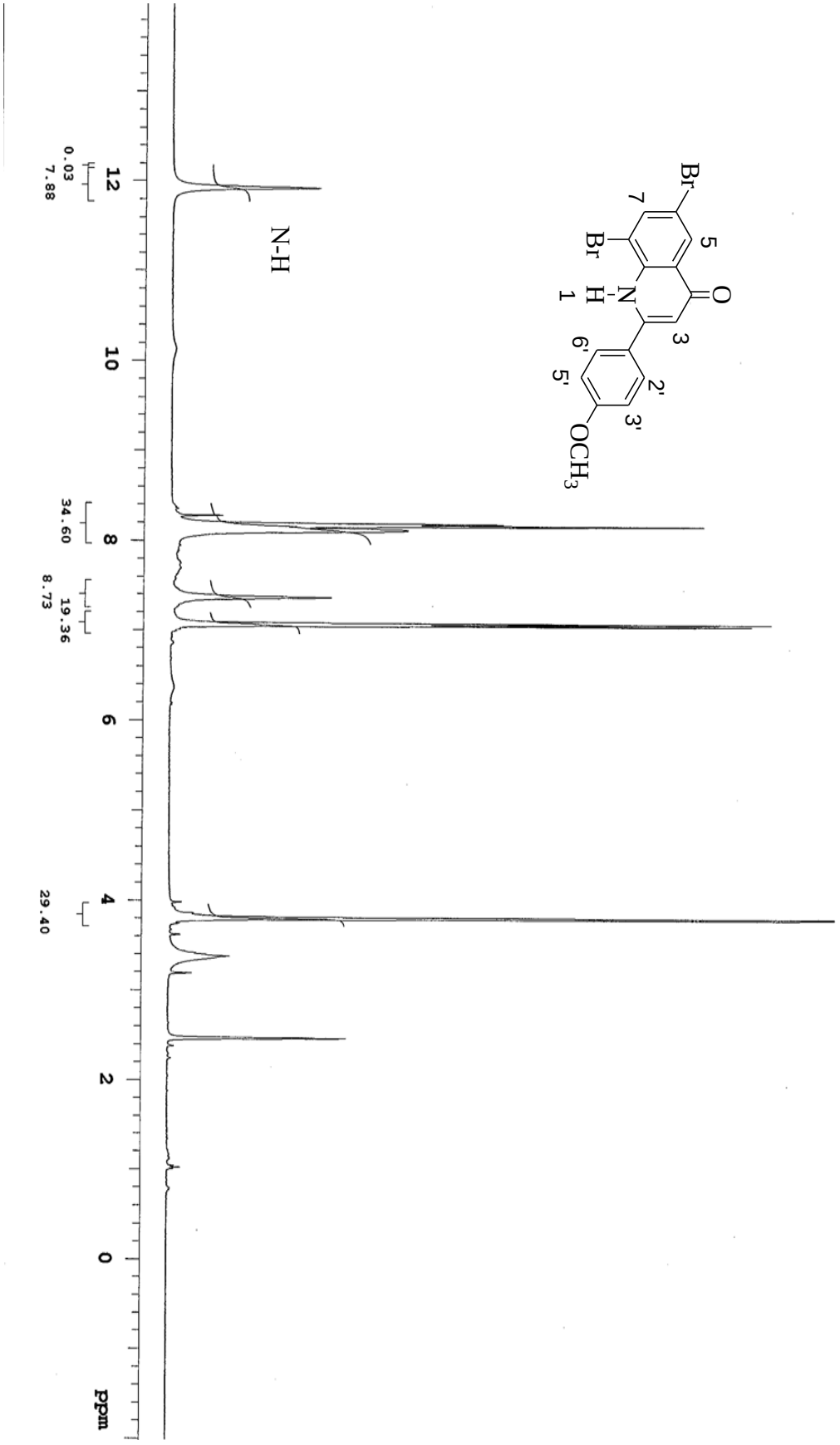


Figure 8: [1]HNMR spectrum of compound **136d** in DMSO-d_6 at 300 MHz

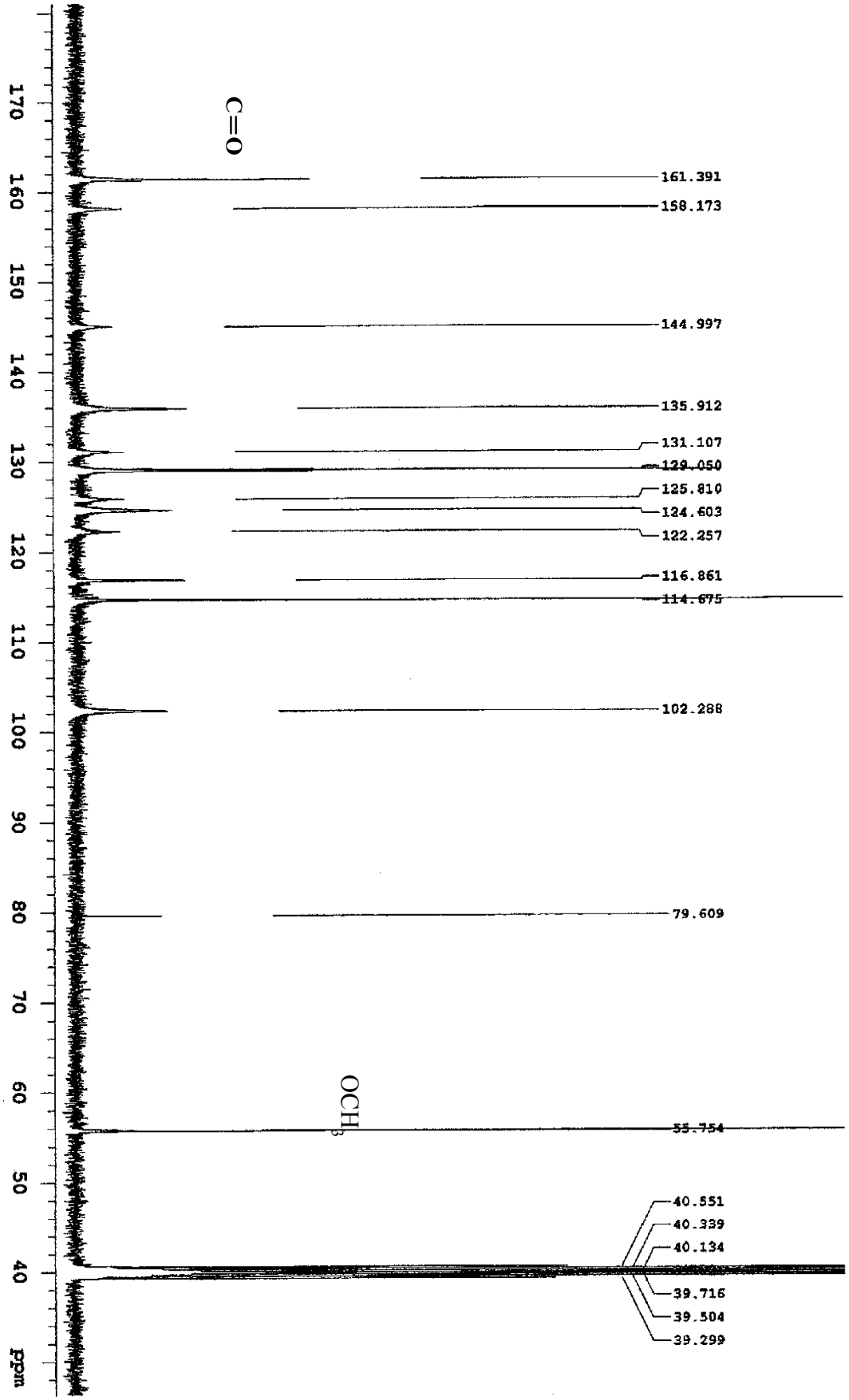


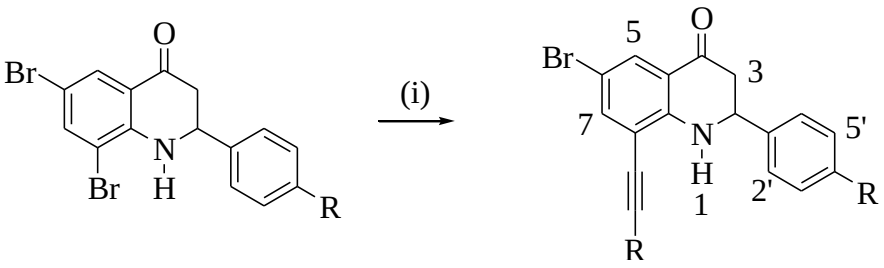
Figure 9: ^{13}CNMR spectrum of compound **136d** in DMSO-d_6 at 75 MHz

With the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones and 2-aryl-6,8-dibromoquinolin-4(1*H*)-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(1*H*)-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.[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(1*H*)-one with phenyl acetylene using 10% Pd/C-PPh_3-CuI catalyst complex with K_2CO_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_3) in place of potassium carbonate (K_2CO_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_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(1*H*)-ones **137a-h** (Scheme 41). Hitherto, 6-chloro-8-iodo-2,3-dihydroquinolin-4(1*H*)-one has been found to undergo palladium-catalyzed Sonogashira cross-coupling in the presence of 10% Pd/C-PPh_3-CuI catalyst complex with phenyl acetylene with ease to afford 8-phenylethynyl-6-chloro-2,3-dihydroquinolin-4(1*H*)-one.[56] The same catalyst complex also promoted C-8 alkynylation of 6-bromo-8-iodoquinolines to afford 8-alkynyl-6-

bromoquinolines.[55] 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.[101] 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)-PdL_2 dxy (HOMO) interaction in the oxidative addition step.[102] 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.[102] The selectivity for heteroaryl halides bearing different halogen atoms depend on the trend in reactivity of the halides: I > Br > Cl >> F,[55,103] as a function of their Ar-X bond strengths ($D_{ph\text{-}X}$ 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.[104] The ^{1}H 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 ^{13}C 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_{max} *ca*. 2201 cm^{-1} which confirms the presence of the C≡C group.



122 **137**

137	**R**	**R'**	**Yield %**	**Mp (°C)**
a	H	-C_6H_5	71	153-155
b	F	-C_6H_5	74	151-152
c	Cl	-C_6H_5	73	155-156
d	OMe	-C_6H_5	78	133-134
e	H	-CH_2CH_2OH	77	129-130
f	F	-CH_2CH_2OH	75	131-132
g	Cl	-CH_2CH_2OH	77	151-152
h	OMe	-CH_2CH_2OH	74	108-110

Reagents and conditions: (i) R'C≡CH, 10% Pd/C, PPh_3, CuI, Et_3N, EtOH, 100 °C, 18 h

Scheme 41: Regioselective alkynylation of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones **122a-d**

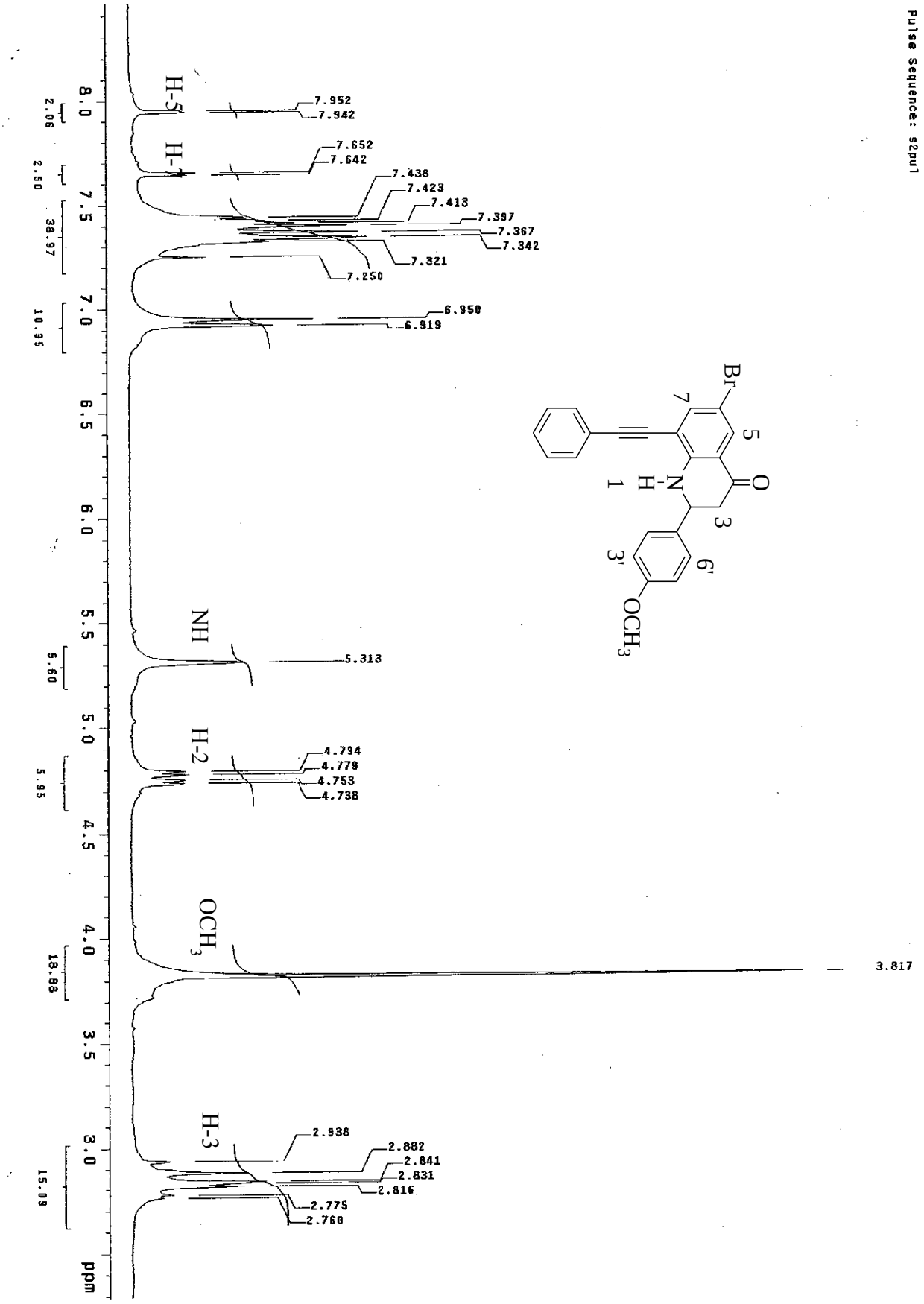


Figure 10: ^{1}H NMR spectrum of compound **140d** in $CDCl_3$ at 300 MHz

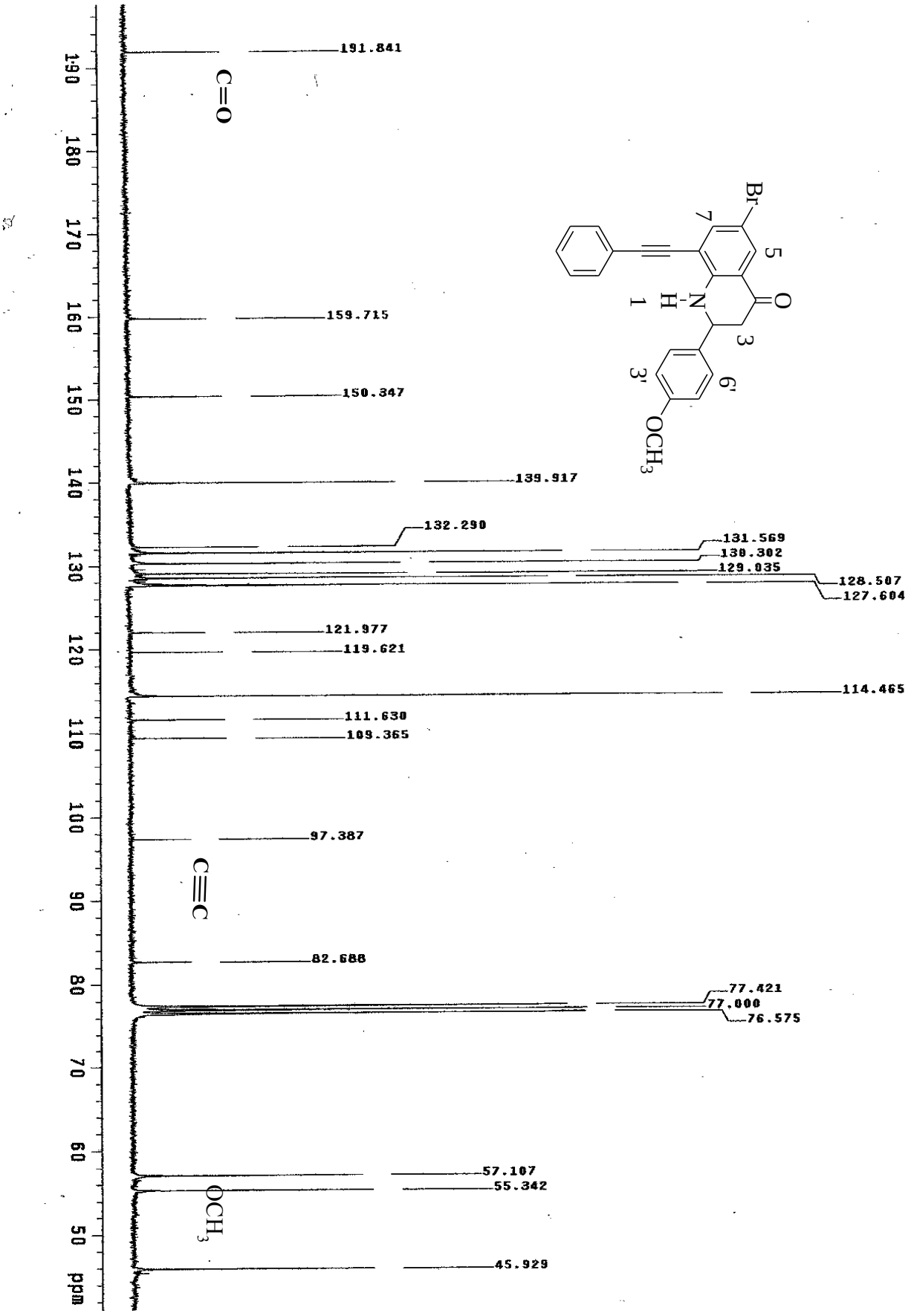


Figure 11: ^{13}C NMR spectrum of compound **140d** in $CDCl_3$ at 75 MHz

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.[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.[107] This allows for palladium to vary the number of electrons between 18 and 14.[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 $Pd(0)(PPh_3))_2Cl^-$ [when generated by reduction of $PdCl_2(PPh_3)_2$] or by acetate ions represented by $Pd(0)(PPh_3)_2(OAc)^-$ [when generated *in situ* in mixtures of $Pd(OAc)_2$ and PPh_3].[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 *via* the palladium-catalyzed Sonogashira cross-coupling.[55.56] The active Pd(0) species generated from the ligated metal (PdL_2) according to the general palladium catalytic cycle,[106] initiate the oxidative addition step on the substrates **122** to give the organopalladium complex **I**. This is followed by an *in situ* formation of the copper acetylide complex resulting in the transmetalation step to afford system **II**. Reductive elimination which involves the regeneration of the palladium species and the products **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 *in situ* and the nitrogen atom in the oxidative addition step to form an organopalladium complex according to the general palladium catalytic cycle.[107]

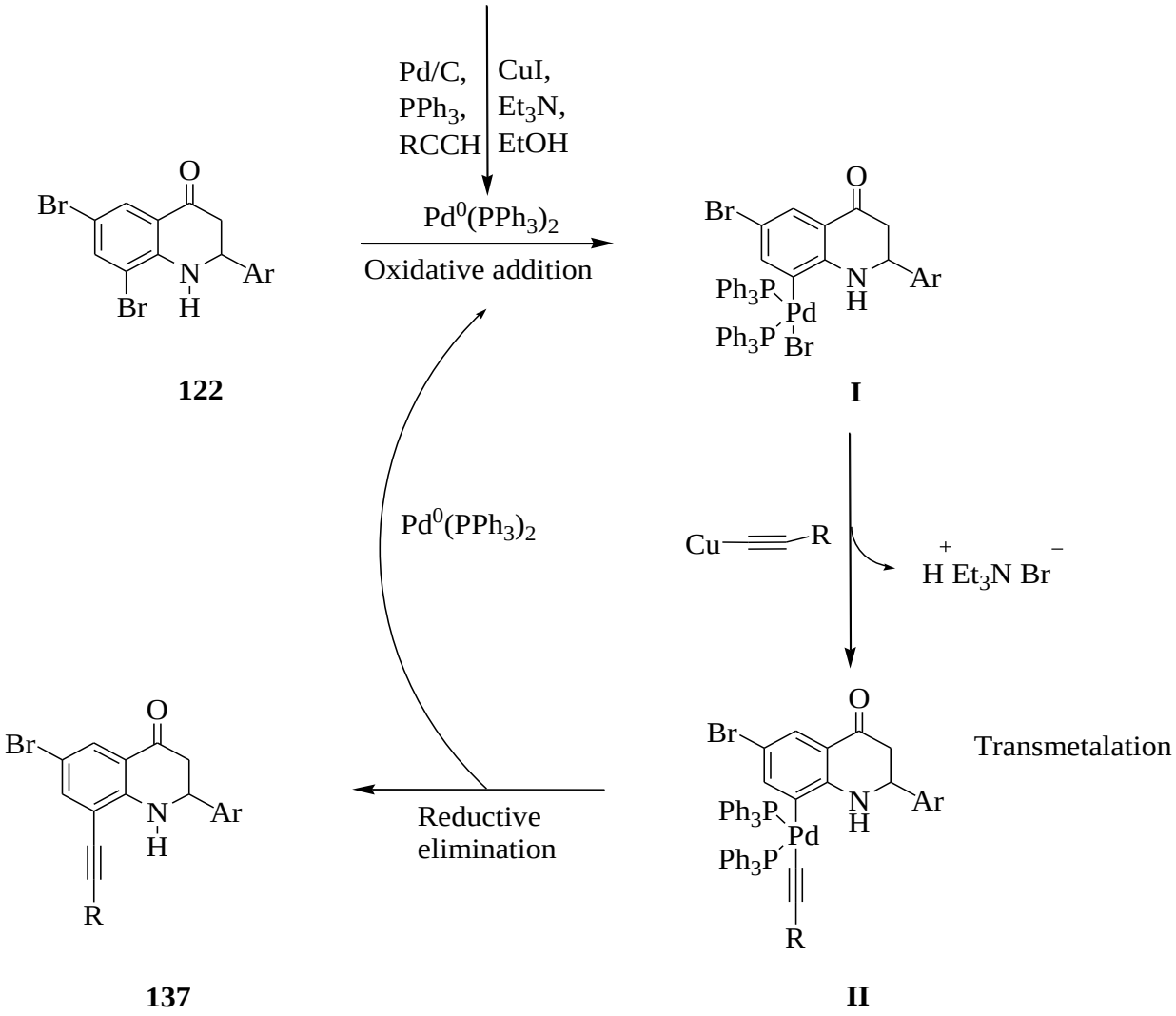
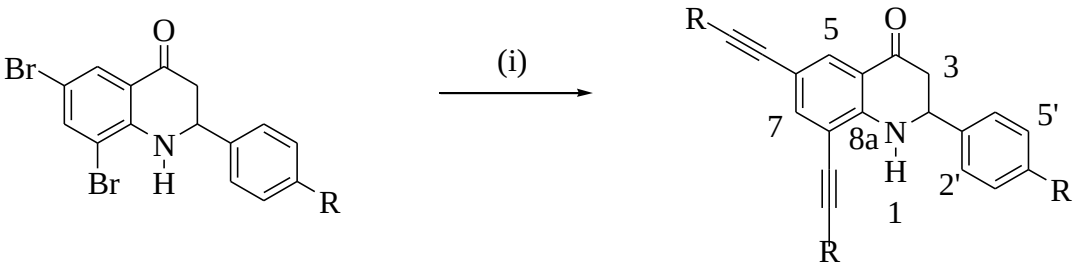


Figure 12: Proposed mechanism for the site-selective cross-coupling of **122**

Encouraged by the regio-selective Sonogashira cross-coupling of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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(1*H*)-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(1*H*)-ones 138a-h

The homogeneous catalyst-assisted cross-coupling of dihaloquinolin-4-ones with aryl substituents[86] and dihaloquinolines with alkynyl substituents[110] has been described before. With these consideration in mind, we explored the versatility of the cross-coupling of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones **122** with terminal acetylenes. We subjected compounds **122** to Sonogashira cross-coupling with terminal alkynes in the presence of $PdCl_2(PPh_3)_2$-CuI catalyst complex in NEt_3/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(1*H*)-ones **138** in a one-pot operation (Scheme 42). The ^{1}H 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 ^{13}C 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 ν_{max} *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 ^{79}Br and ^{81}Br isotopes thus confirm the displacement of the two bromine atoms.



122 **138**

138	**R**	**R'**	**Yield (%)**	**Mp (°C)**
a	H	$-C_6H_5$	76	139-141
b	F	$-C_6H_5$	78	136-138
c	Cl	$-C_6H_5$	76	143-144
d	OMe	$-C_6H_5$	68	142-144
e	H	$-CH_2CH_2OH$	70	127-129
f	F	$-CH_2CH_2OH$	71	115-116
g	Cl	$-CH_2CH_2OH$	69	107-108
h	OMe	$-CH_2CH_2OH$	66	90-92

Reagents and conditions: (i) R'C≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, EtOH, 100 °C, N_2 (g), 8 h

Scheme 42: Non-sequential metal-catalyzed cross-coupling of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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.[109,110] The oxidative addition step leading to the formation of the organopalladium complex has also been identified as vital to the rate of the reaction.[106] Both homogeneous and heterogeneous catalysts generate an active solvated $Pd(0)L_2$ species in the oxidative-addition step. The ligated active metal [$Pd(0)L_2$] 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**.

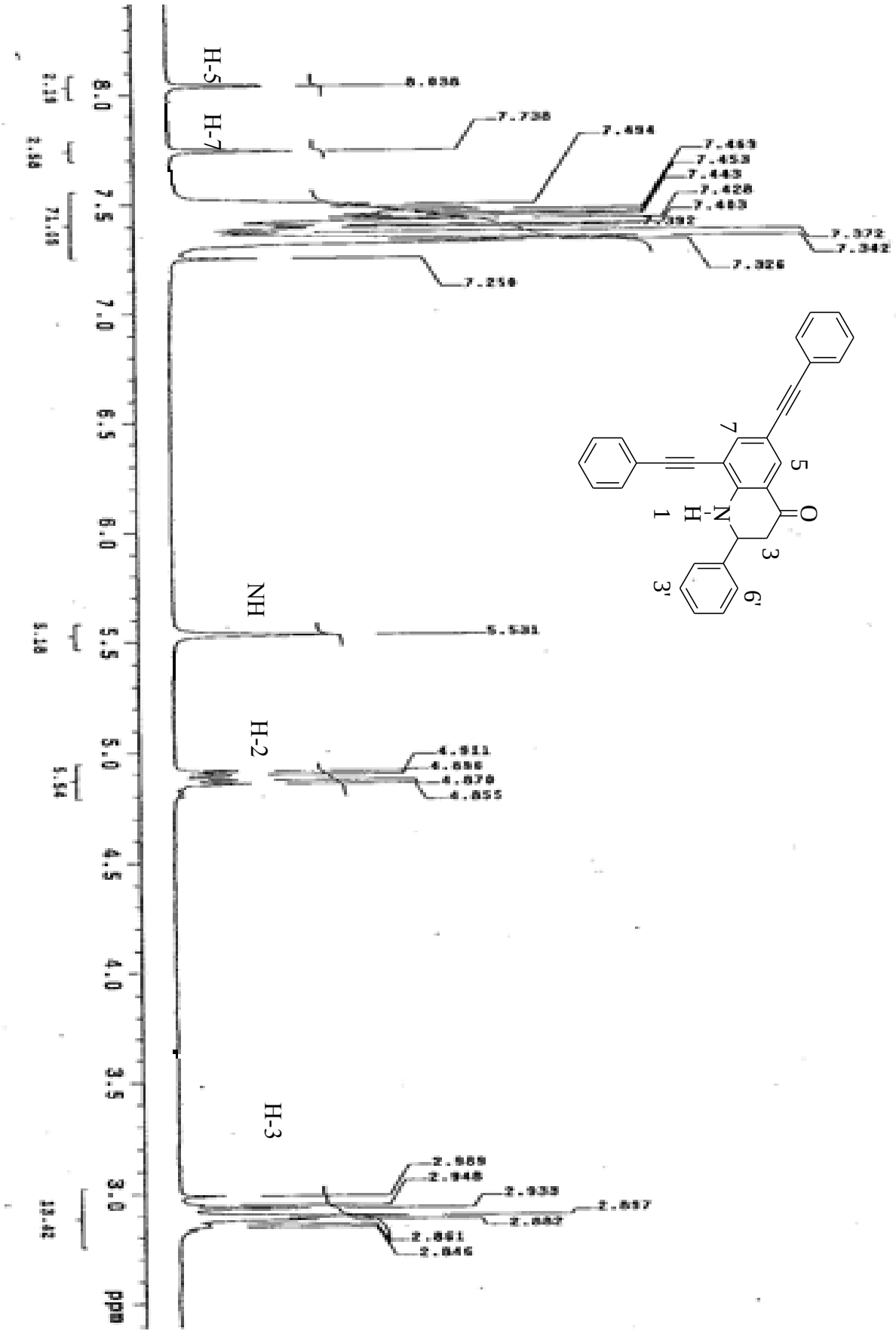


Figure 13: ^{1}H NMR spectrum of compound **138a** in $CDCl_3$ at 300 MHz

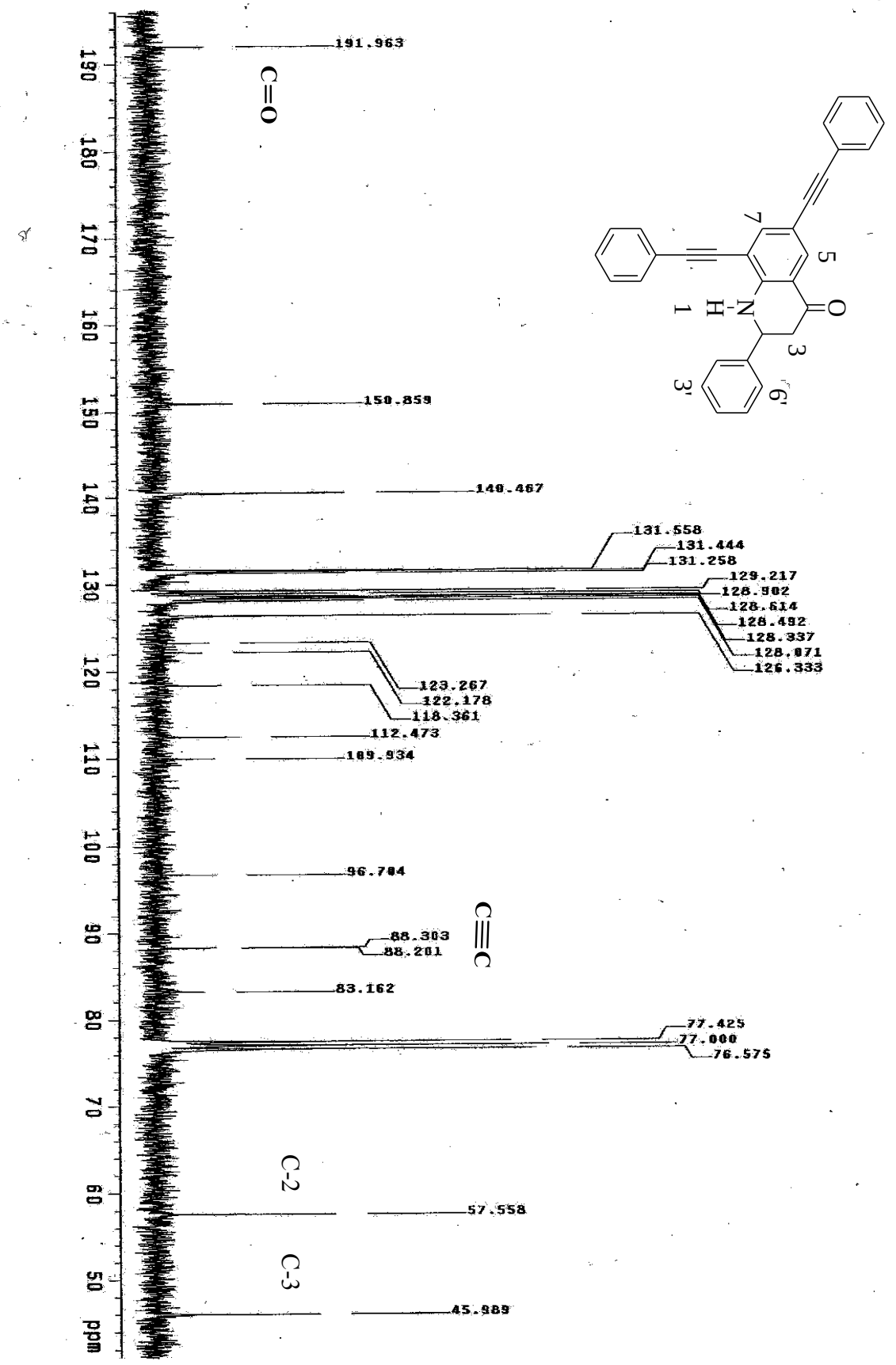


Figure 14: ^{13}C NMR spectrum of **138a** in $CDCl_3$ at 75 MHz

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(1*H*)-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 2nd cross-coupling step. The results are as presented below.

			5 mol% Pd/C	2.0 mol% $PdCl_2(PPh_3)_2$/C
137	**R**	**R'**	**Yield %**	**Yield %**
a	H	-C_6H_5	73	57
b	F	-C_6H_5	73	59
c	Cl	-C_6H_5	71	57
d	OMe	-C_6H_5	60	50

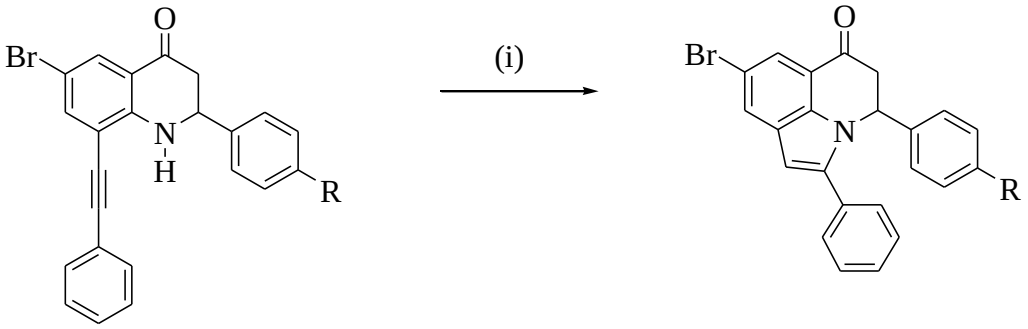
Reagents and conditions: (i) R'C≡CH, 10% Pd/C, PPh_3, CuI, Et_3N, EtOH, 100 °C, N_2 (g), 18 h or (i) R'CCH, $PdCl_2PPh_3$, C, CuI, Et_3N, EtOH, 100 °C, N_2 (g), 48 h

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.[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(1*H*)-ones **137** in hand, we decided to investigate the possibility to effect heteroannulation of 8-alkynylquinolin-4(1*H*)-ones as described in the next section.

2.6 Synthesis of 4-aryl-8-bromo-2-phenyl-6*H*-4,5-dihyropyrrol[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.[56] We adapted the method described in the literature[56] and subjected compounds **137** to intramolecular cyclization in the presence of palladium(II) chloride ($PdCl_2$) in acetonitrile (MeCN) under reflux. We isolated by column chromatography on silica gel the 4-aryl-8-bromo-2-phenyl-6*H*-4,5-dihyropyrrol[3,2,1-*ij*]quinolin-6-ones **139** (Scheme 43). The ^{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 δ *ca*. 3.22 ppm with coupling constant value J_{gem} = 15.0 Hz in the aliphatic region. The second methylene proton resonates as a doublet of doublets at δ *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 δ *ca*. 5.95 ppm with *J* = 7.1 Hz. The singlet at δ *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 δ 7.36-7.40 ppm. The two sets of doublet at δ *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 ^{13}C NMR spectra reveal the absence of the signals in the

region δ *ca*. 82.4-94.5 ppm attributed to the acetylenic carbons. The spectra instead, reveal the presence of signals at δ *ca*. 103.2 and 114.4 ppm which corresponds to the olefinic carbons (C-1 and C-2) and the resonance at δ *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=C and C=O at ν_{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).[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 [N(1)-C(11)-C(18)-C(23)] with a value of 62.5° and [N(1)-C(2)-C(12)-C(17)] with a value of -78.6°, respectively.



137 **139**

139	**R**	**% Yield**	**Mp °C**
a	H	78	169-170
b	F	77	136-137
c	Cl	70	138-139
d	OMe	64	162-163

Reagents and conditions: (i) $PdCl_2$, MeCN, 90 °C, N_2 (g), 2 h

Scheme 43: Intramolecular cyclization of 2-phenyl-8-(2-phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-ones **137a-d**

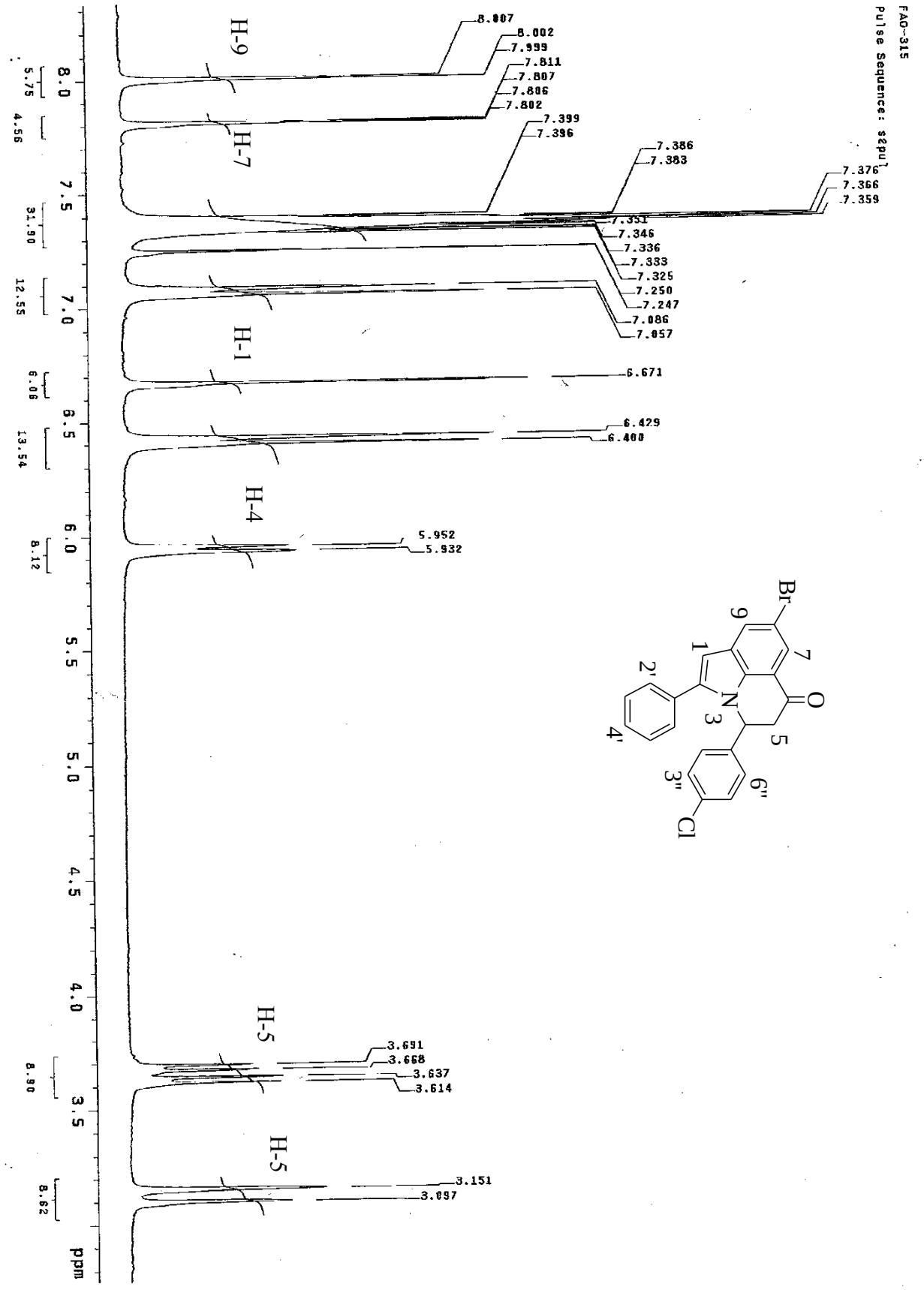


Figure 15: ^{1}H NMR spectrum of compound **139c** in $CDCl_3$ at 300 MHz

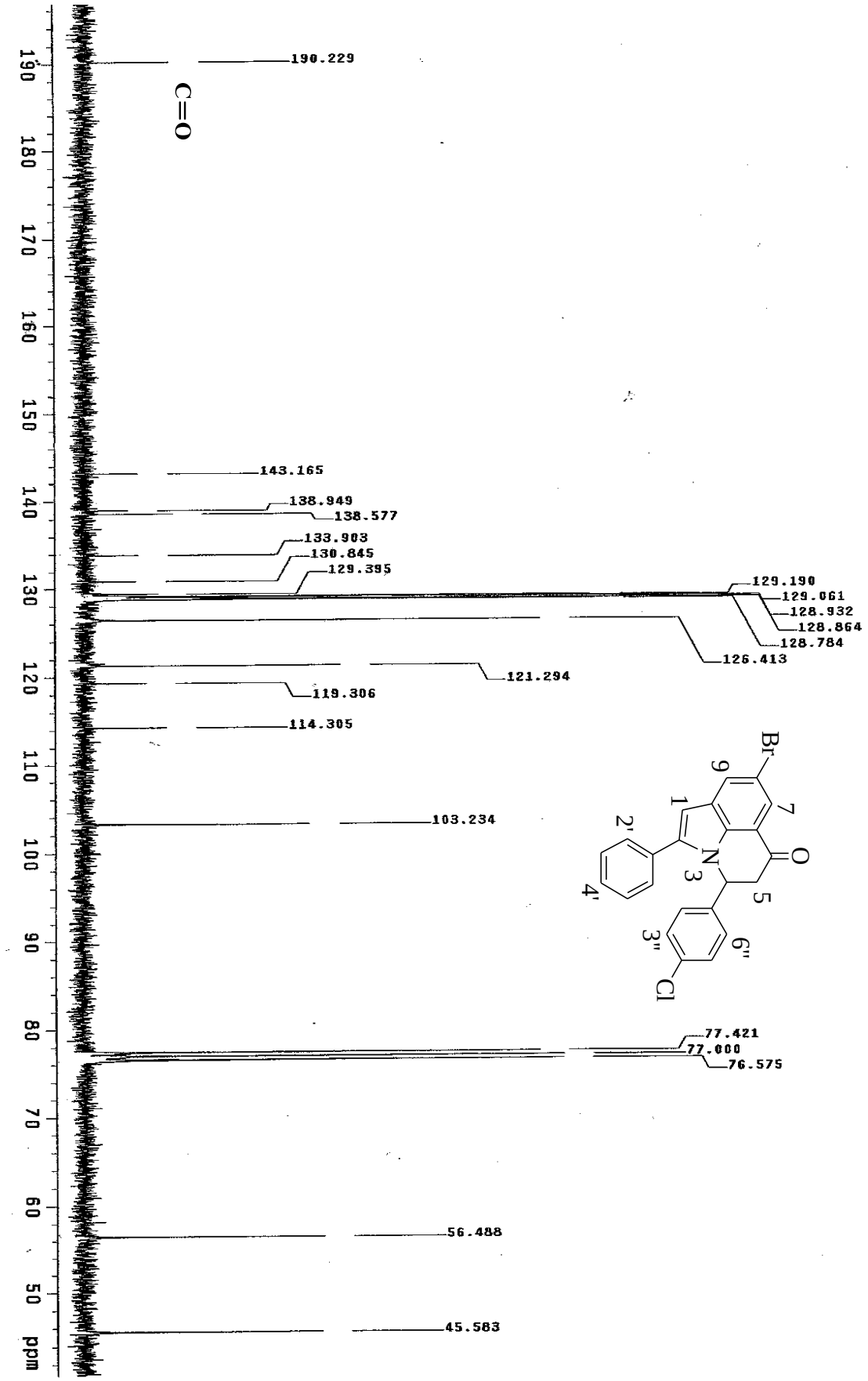


Figure 16: ^{13}C NMR spectrum of compound **139c** in $CDCl_3$ at 75 MHz

Analogous 5,6-dihydropyrrolo[3,2,1-*ij*]quinolines have been reported to exhibit a variety of activity including as anticonvulsant,[5] antitumor,[19] antifungal[25] agents.

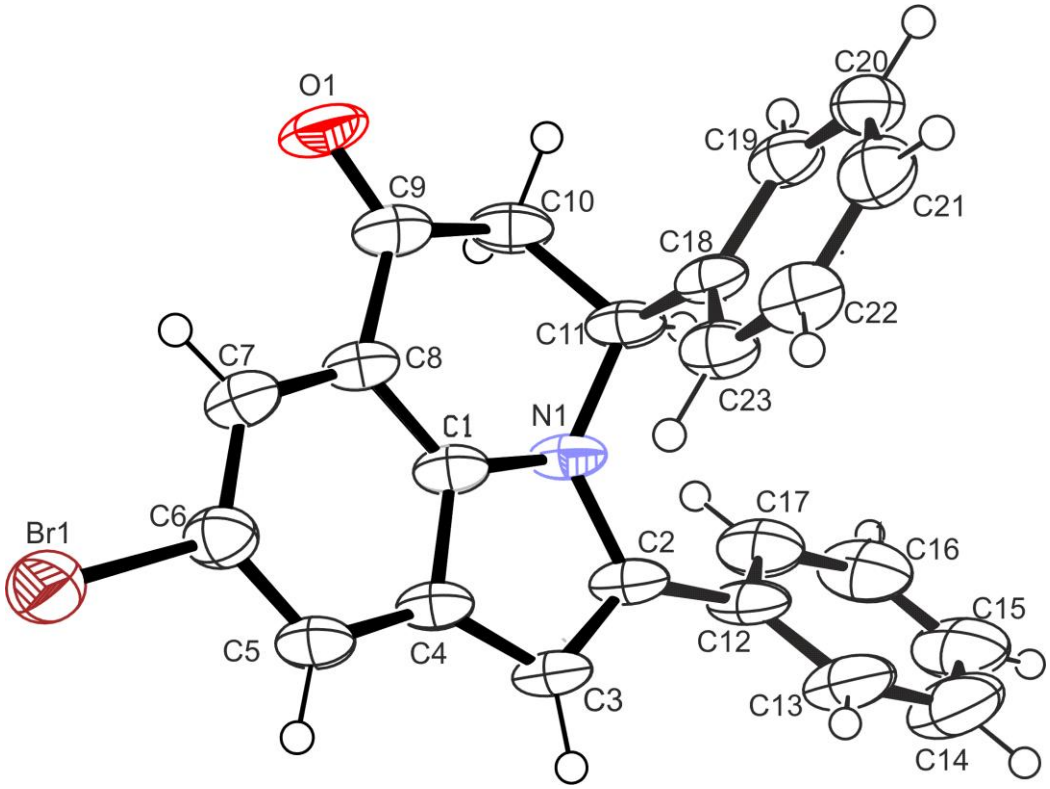
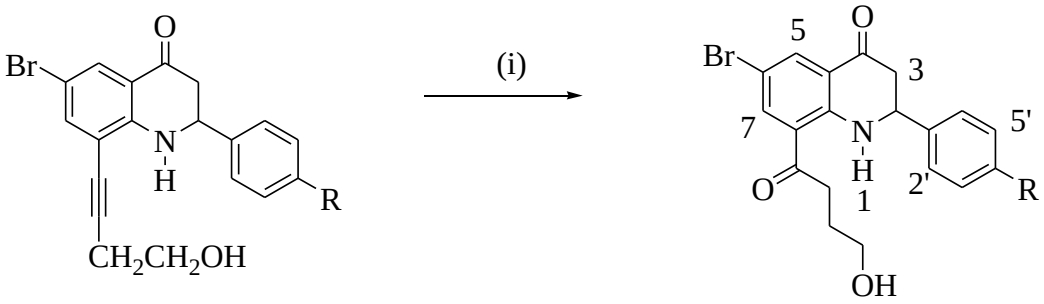


Figure 17: ORTEP diagram (50% probability level) of compound **139a** showing crystallographic numbering. For clarity, hydrogen atoms are not labeled.

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

In a similar fashion as described for compounds **137a-d**, we subjected the aliphatic 8-alkynyldihydroquinolin-4(1*H*)-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 ^{1}H NMR and ^{13}C NMR spectroscopy, IR and mass spectrometry as the corresponding 2-aryl-6-bromo-8-(4-

hydroxybutanoyl)-2,3-dihydroquinolin-4(1*H*)-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 δ *ca*. 1.65 ppm attributed to the signal for the OH group (Figure 18). A quintet at δ *ca*. 1.96 ppm with J = 6.0 and 6.9 Hz correspond to the methylene group; two sets of triplet at δ *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″ (-$CH_2CH_2CH_2OH$), respectively. The NH resonates downfield at δ *ca*. 9.30 ppm as a broad singlet. The ^{13}C NMR spectra reveal the presence of two C=O at δ *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 ν_{max} *ca*. 3347, 3242, 1682, 1646 cm^{-1} corresponding to the OH, NH and the two sets of C=O, respectively.



137e-h **140**

140	**R**	**% Yield**	**Mp °C**
a	H	50	125-127
b	F	58	148-149
c	Cl	50	150-151
d	OMe	54	117-118

Reagents and conditions: (i) $PdCl_2$, MeCN, 90 °C, 6 h

Scheme 44: Palladium-catalyzed oxidation of **137e-h**

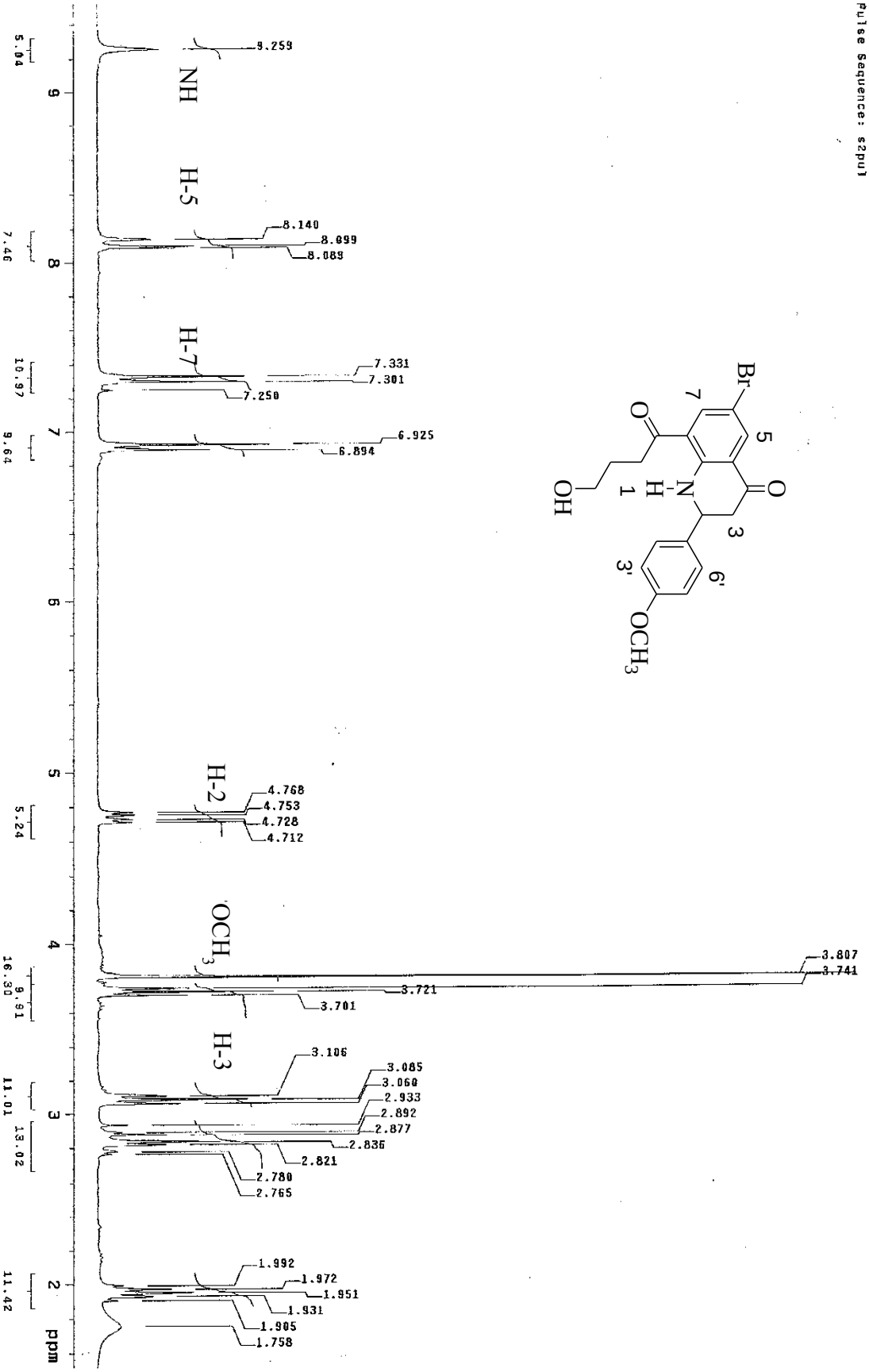


Figure 18: ^{1}H NMR spectrum of compound **140d** in $CDCl_3$ at 300 MHz

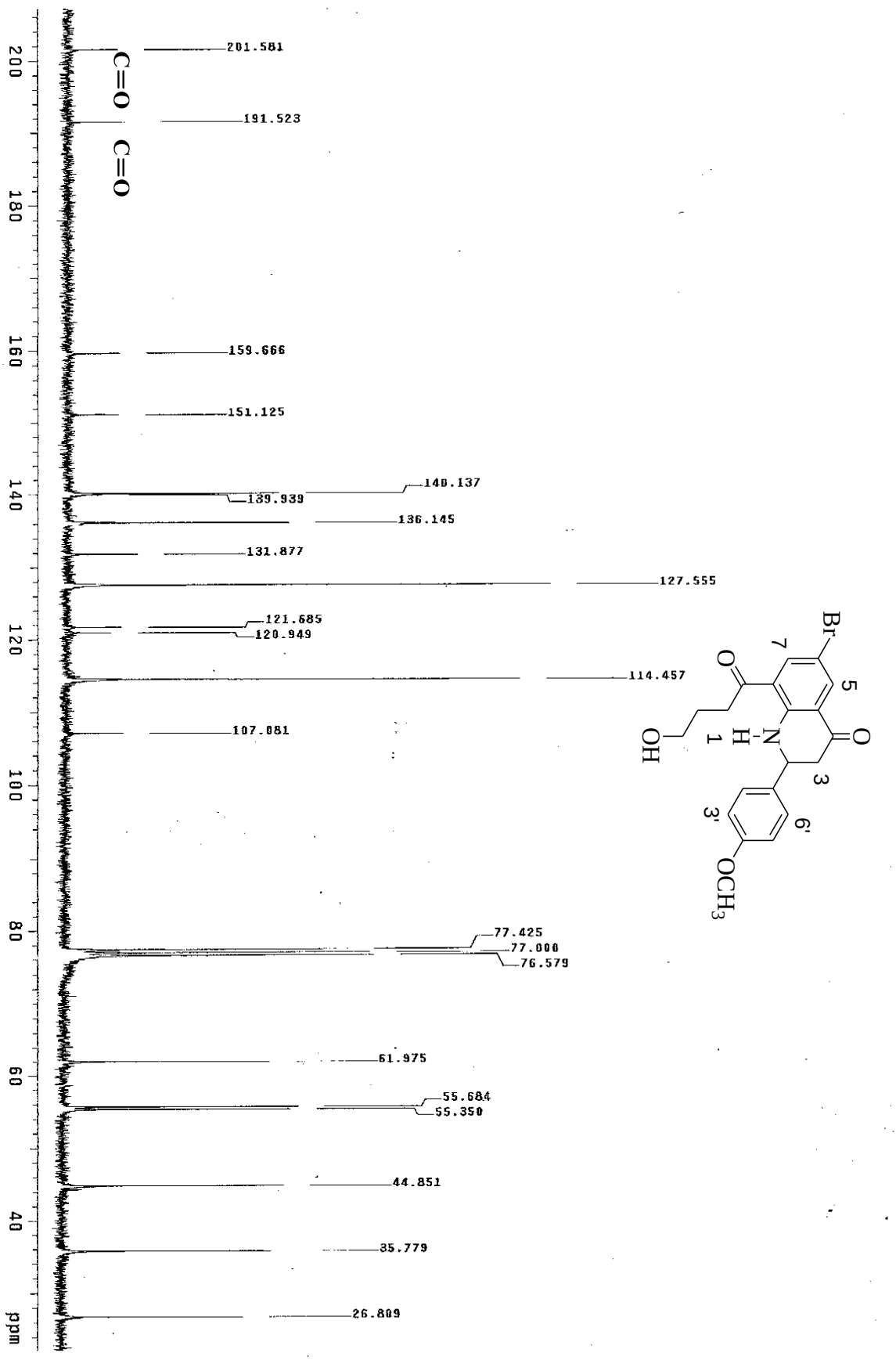


Figure 19: ^{13}CNMR spectrum of compound **140d** in $CDCl_3$ at 75 MHz

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 $PdCl_2$.

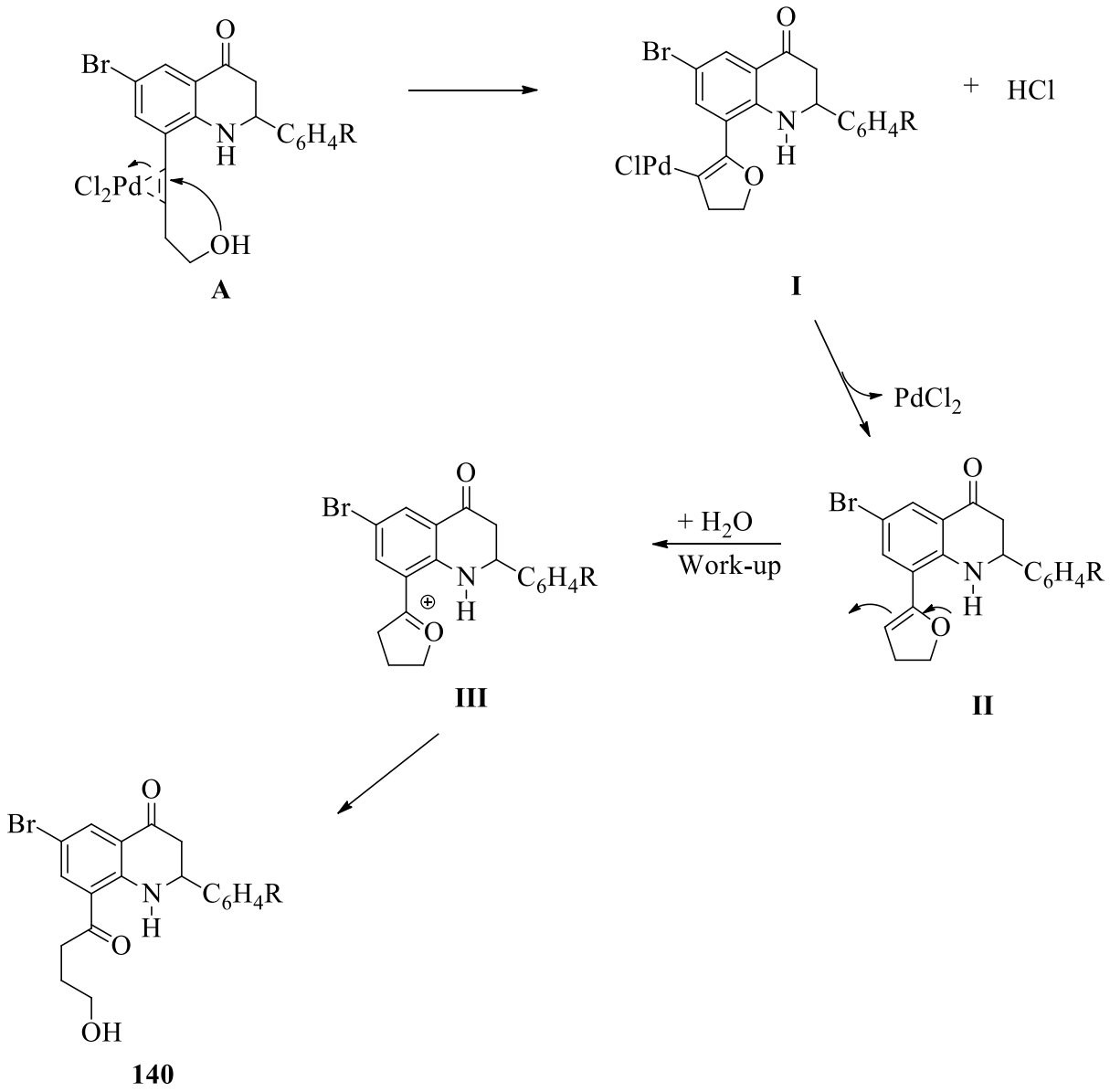
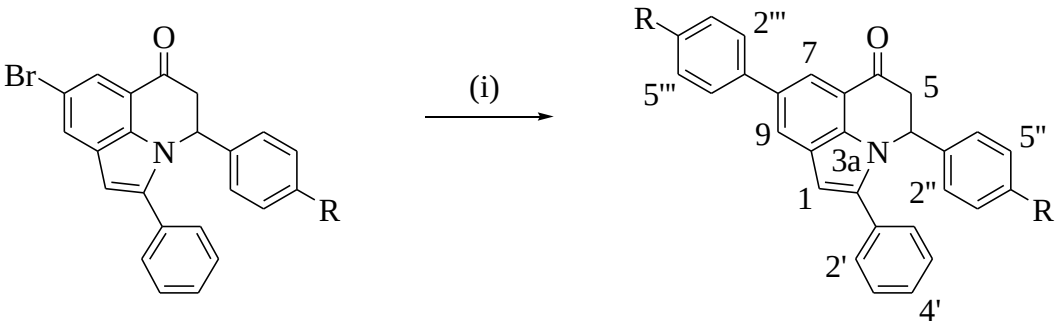


Figure 20: Plausible Mechanism for the Palladium-catalyzed oxidation of **137e-h**

2.8 Synthesis of 8-substituted 4-aryl-2-phenyl-6*H*-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 $PdCl_2(PPh_3)_2$-PCy_3 catalyst complex and K_2CO_3 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 6*H*-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_{gem} = 15.0 Hz and J_{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 ν_{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.



139 **141**

141	**R**	**R'**	**%Yield**	**Mp °C**
a	H	F	67	195-196
b	F	F	78	221-222
c	Cl	F	62	240-241
d	OCH_3	F	66	215-216
e	H	OCH_3	78	170-171
f	Cl	OCH_3	73	158-159

Reagents and conditions: (i) $ArB(OH)_2$, $PdCl_2(PPh_3)_2$, PCy_3, K_2CO_3, dioxane/H_2O, 100 °C, 3 h

Scheme 45: Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of 4-aryl-8-bromo-2-phenyl-6*H*-4,5-dihyropyrrol[3,2,1-*ij*]quinolin-6-ones **139** with arylboronic acids

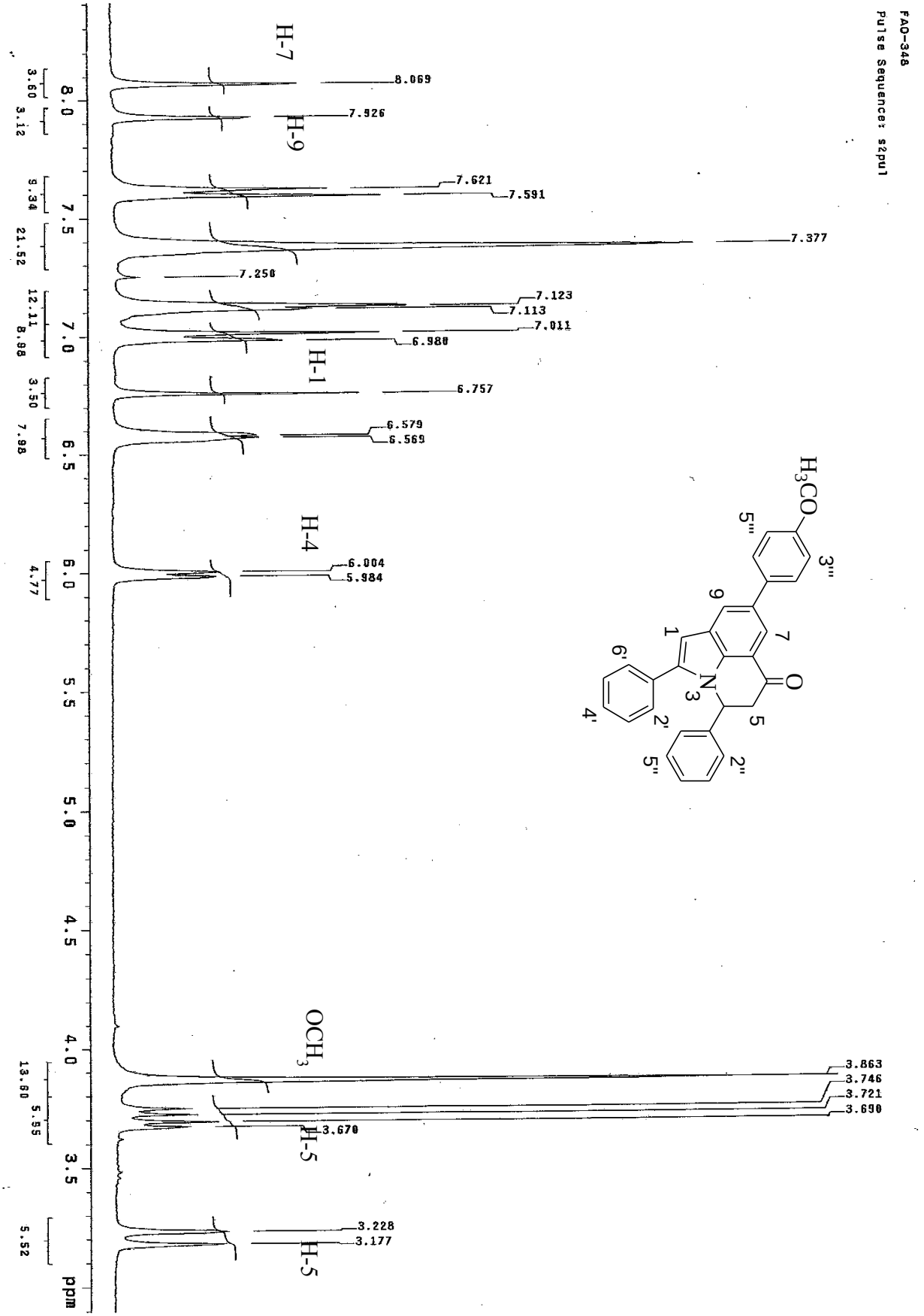


Figure 21: ^{1}H NMR spectrum of compound **141e** in $CDCl_3$ at 300 MHz

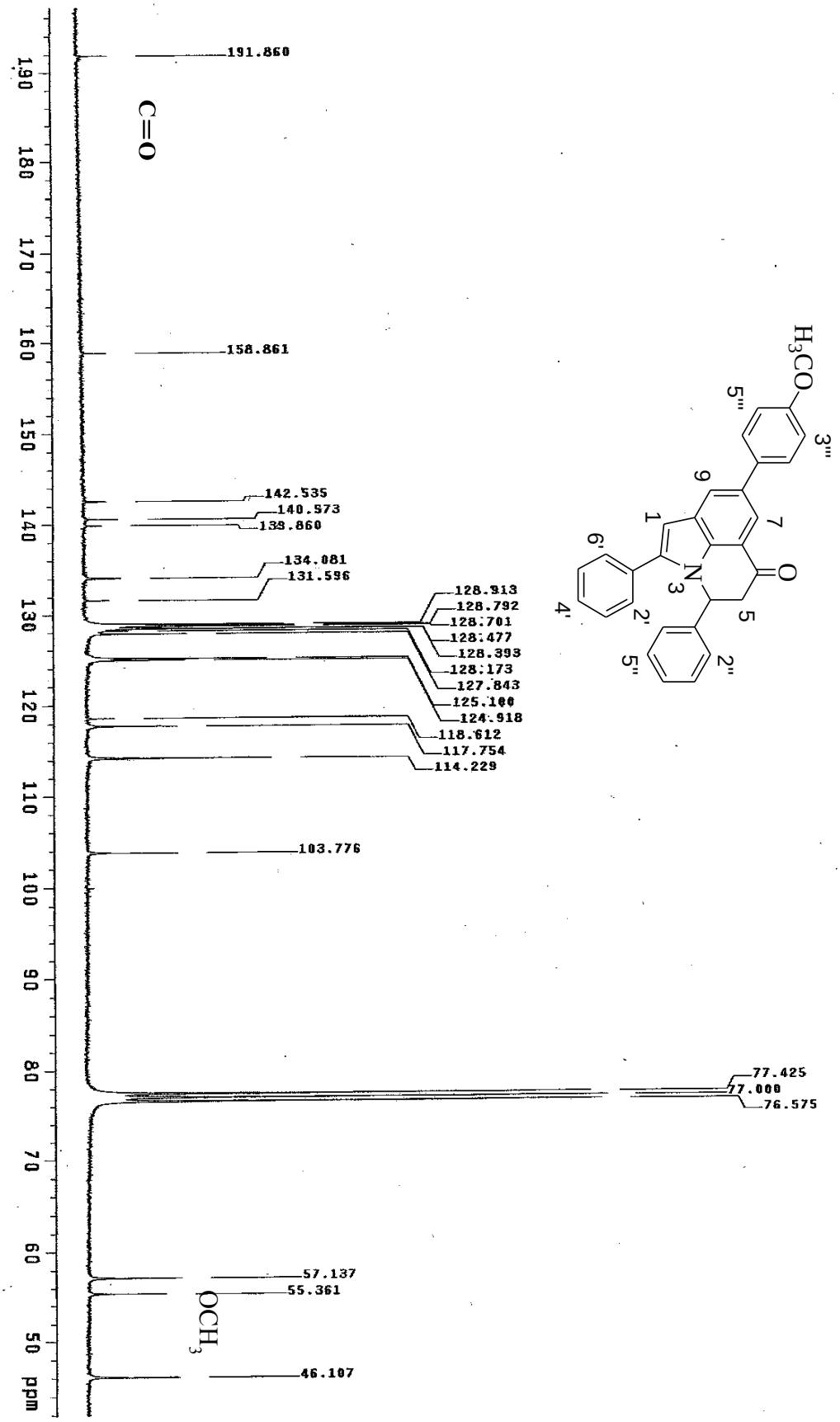
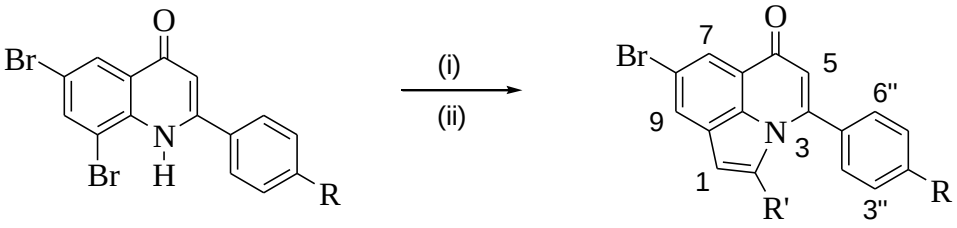


Figure 22: ^{13}C NMR spectrum of compound **141e** in $CDCl_3$ at 75 MHz

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.[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(1*H*)-one **136a** to metal-catalyzed Sonogashira cross-coupling reaction with phenyl acetylene in the presence of Pd/C-CuI-PPh_3 catalyst mixture in DMF/water mixture [4:1; v/v] using Et_3N 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_2CO_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.[107] However, with the use of homogeneous catalyst-$PdCl_2(PPh_3)_2$ and CuI as a co-catalyst with Et_3N as the base in a mixture of DMF/water under reflux, we isolated upon column chromatography a mixture of products with the dialkynylated 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 ^1H 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 C$\underline{H_2}$CH_2OH, respectively. The doublet of doublets at δ *ca*. 3.70 ppm is attributed to the methylene attached to the hydroxyl group. Moreover, the ^{13}C 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 ν_{max} *ca*. 1635 cm^{-1} is for the C=O group; in addition for **142e-h** the stretch for the OH group appear at ν_{max} *ca*. 3415 cm^{-1}.



136 **142**

142	**R**	**R'**	**Yield (%)**	**Mp (°C)**
a	H	-C_6H_5	68	267-269
b	F	-C_6H_5	68	279-281
c	Cl	-C_6H_5	65	286-288
d	OMe	-C_6H_5	62	179-181
e	H	-CH_2CH_2OH	35	144-146
f	F	-CH_2CH_2OH	38	212-214
g	Cl	-CH_2CH_2OH	35	166-168
h	OMe	-CH_2CH_2OH	32	177-179

Reagents and conditions: (i) PhC≡CH, Pd/C, PPh_3, CuI, K_2CO_3, dioxane, 110 °C, 18 h; (ii) HC≡$CHCH_2CH_2OH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF/H_2O, 110 °C, 6 h

Scheme 46: Regioselective Pd-catalyzed tandem Sonogashira cross-coupling/ annulation reaction

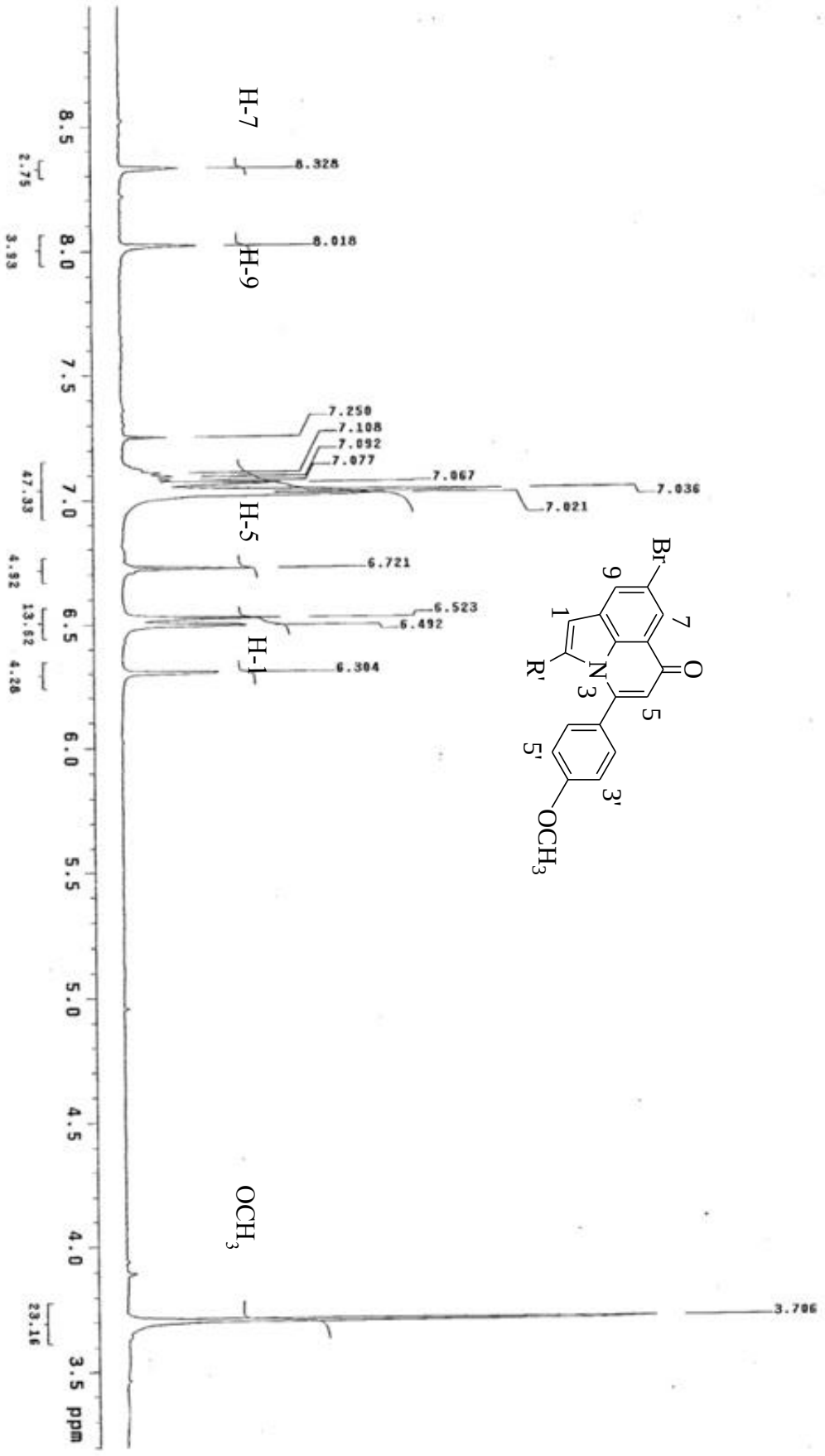


Figure 23: ^{1}H NMR spectrum of compound **142d** in $CDCl_3$ at 300 MHz

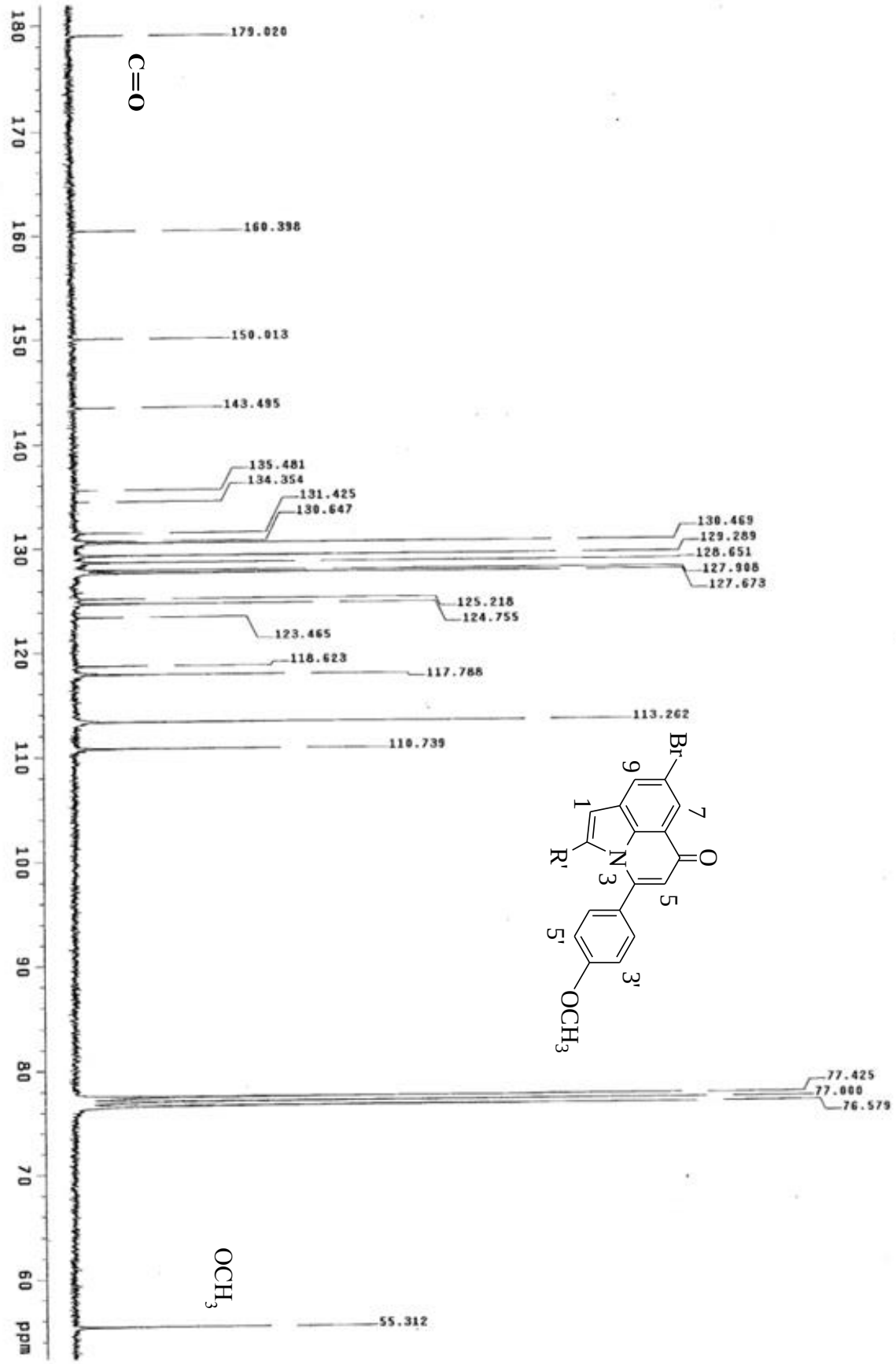
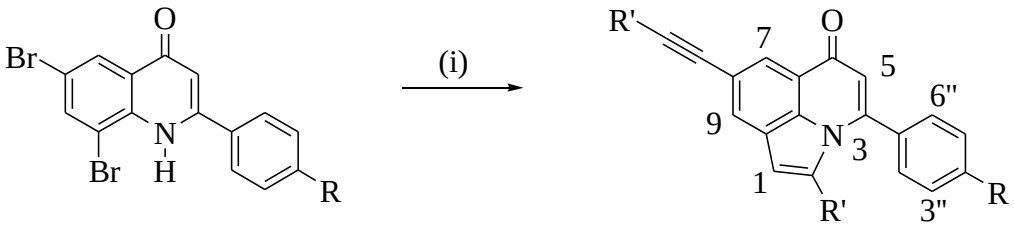


Figure 24: ^{13}C NMR spectrum of compound **142d** in $CDCl_3$ at 75 MHz

2.10 Synthesis of 2,8-disubstituted 4-aryl-6-oxopyrrolo[3,21-*ij*]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(1*H*)-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 alkoxyl carbon atoms in: CH_2CH_2OH', CH_2CH_2OH''', CH_2OH' and CH_2OH''', respectively. The IR spectra reveal absorption bands at ν_{max} *ca*. 2209 and 1637 cm^{-1} confirming the presence of the

C≡C and C=O groups, respectively. And the band at ν_{max} *ca*. 3310 cm^{-1} is due to the OH functional group.



136 **143**

143	**R**	**R'**	**Yield (%)**	**Mp (°C)**
a	H	$-C_6H_5$	67	219-221
b	F	$-C_6H_5$	70	242-244
c	Cl	$-C_6H_5$	68	254-256
d	OMe	$-C_6H_5$	62	235-237
e	H	$-CH_2CH_2OH$	59	190-192
f	F	$-CH_2CH_2OH$	49	227-228
g	Cl	$-CH_2CH_2OH$	60	208-210
h	OMe	$-CH_2CH_2OH$	57	181-182

Reagents and conditions: (i) R'C≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF/H_2O, 100 °C, 4-8 h

Scheme 47: Pd-catalyzed tandem Sonogashira coupling/annulation-dialkynylation reaction

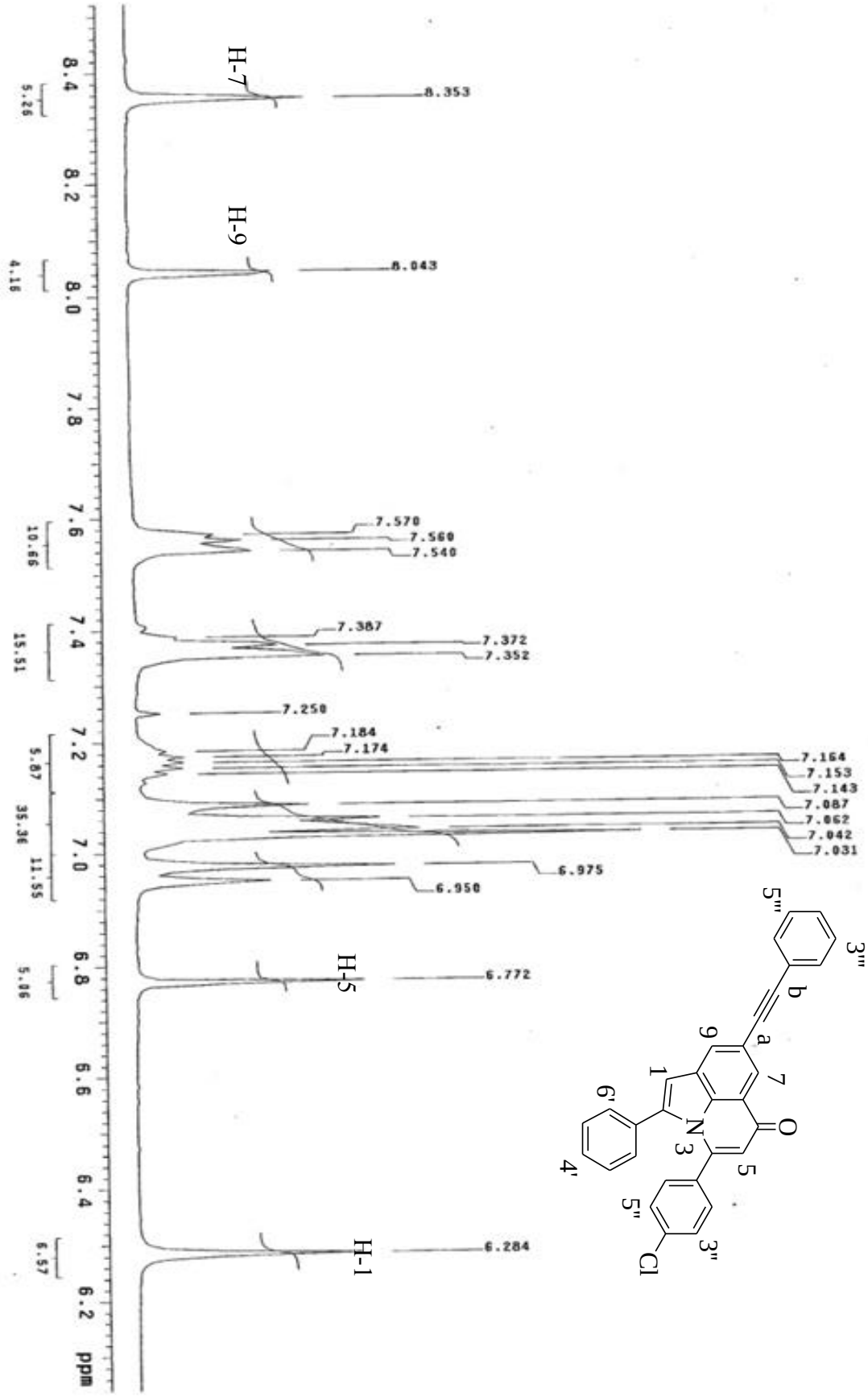


Figure 25: ^{1}H NMR spectrum of compound **143c** in $CDCl_3$ at 300 MHz

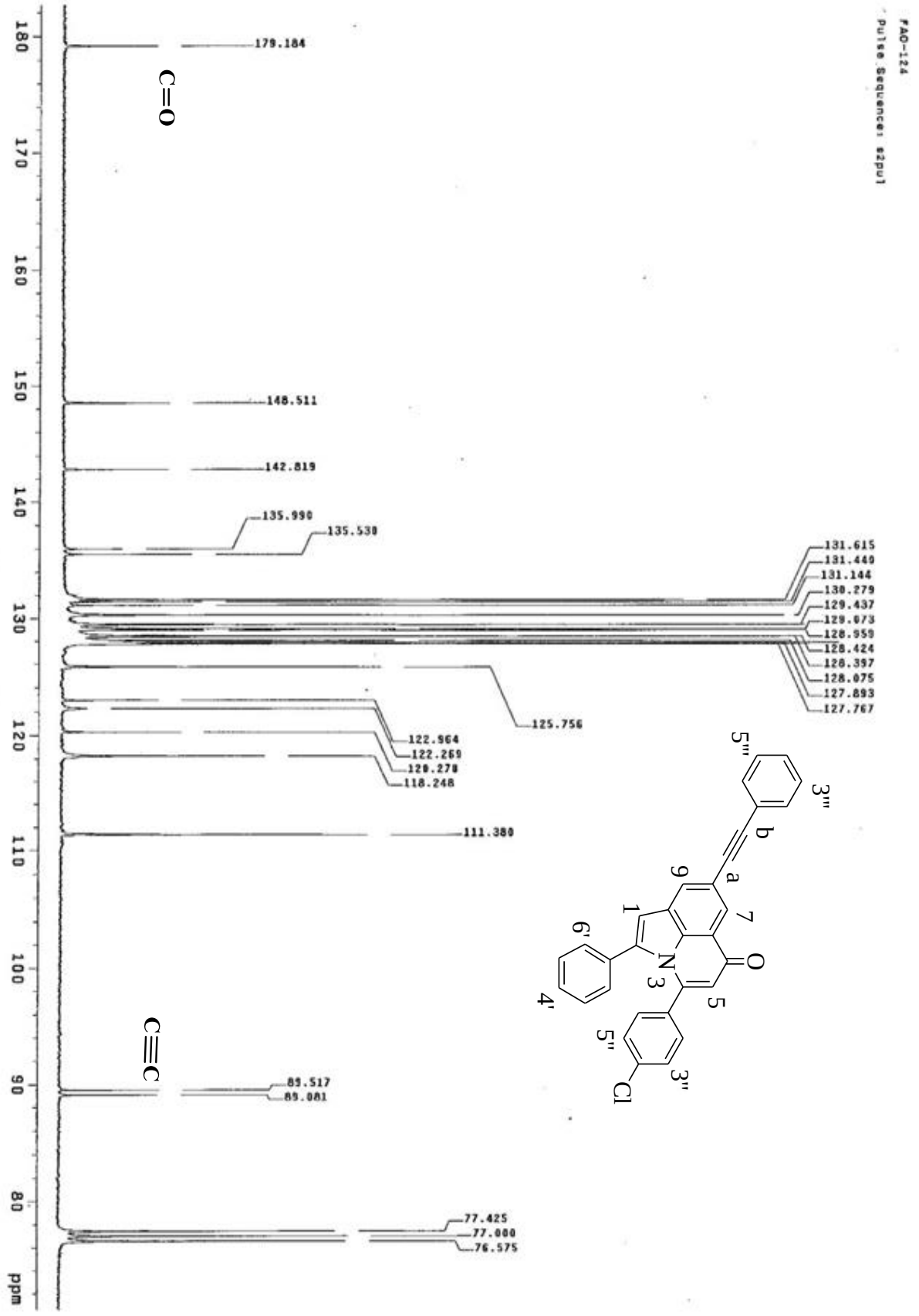
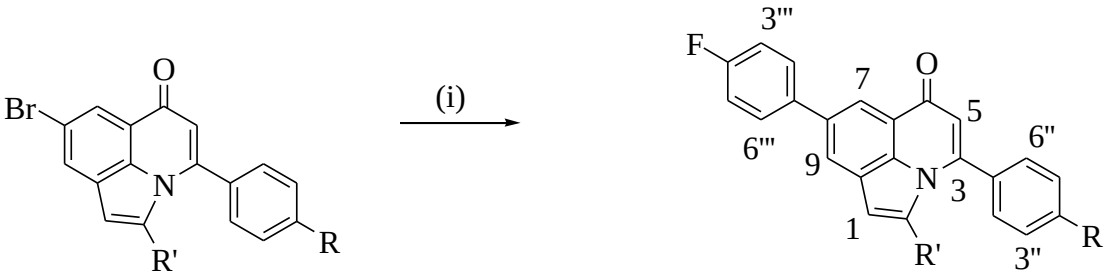


Figure 26: ^{13}C NMR spectrum of compound **143c** in $CDCl_3$ at 75 MHz

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 $PdCl_2(PPh_3)_2$-PCy_3 catalyst complex with K_2CO_3 as a base in dioxane/H_2O 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 ^{1}H 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 ^{13}C 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.



142 **144**

144	**R**	**R'**	**Yield (%)**	**Mp (°C)**
a	H	-C_6H_5	69	238-240
b	F	-C_6H_5	57	270-272
c	Cl	-C_6H_5	62	276-278
d	OCH_3	-C_6H_5	63	232-234
e	H	-CH_2CH_2OH	59	200-202

Reagents and conditions: (i) 4-FPhB$(OH)_2$, $PdCl_2(PPh_3)_2$, PCy_3, K_2CO_3, dioxane/H_2O, 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.

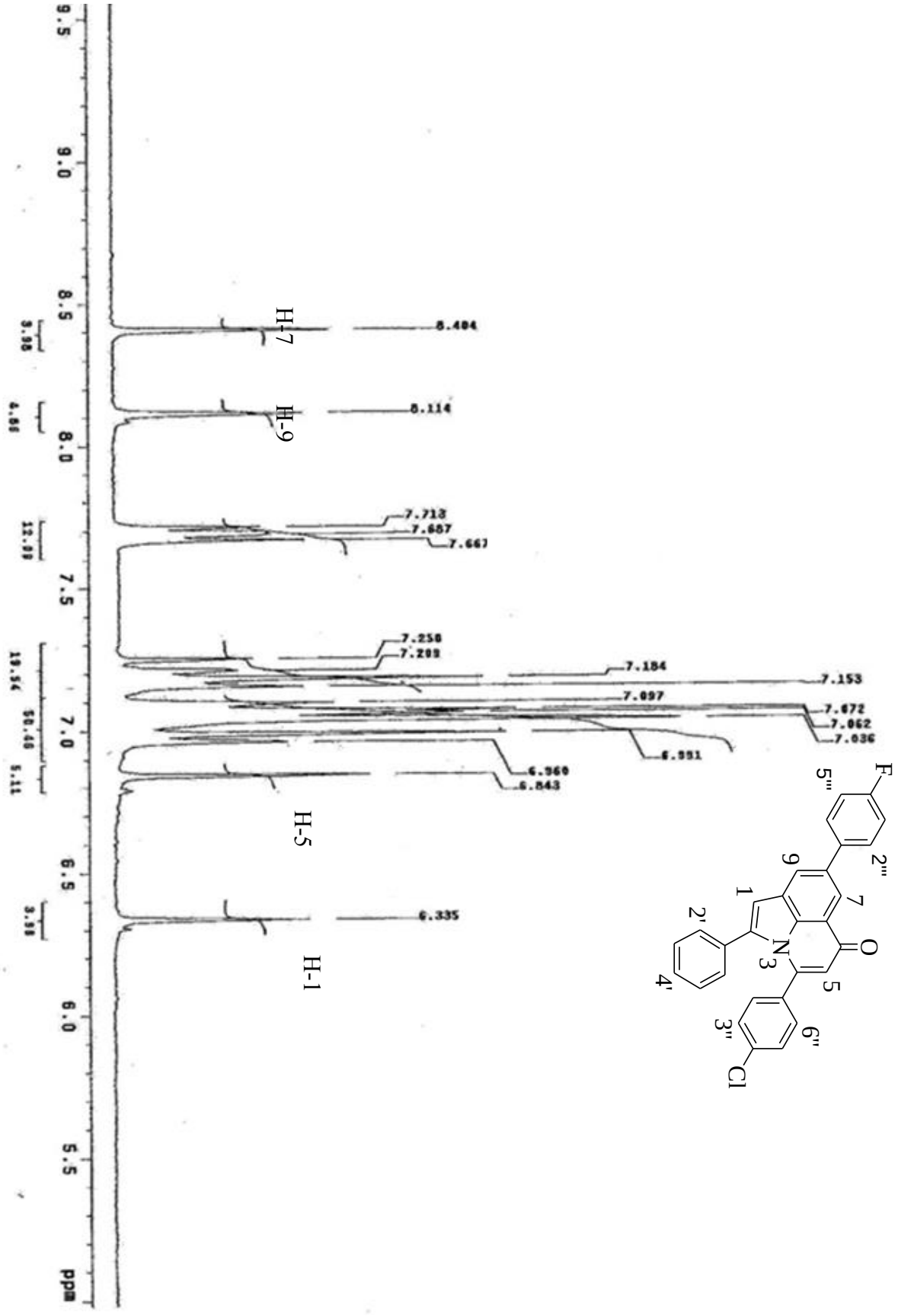


Figure 27: ^{1}H NMR spectrum of compound **144c** in $CDCl_3$ at 300 MHz

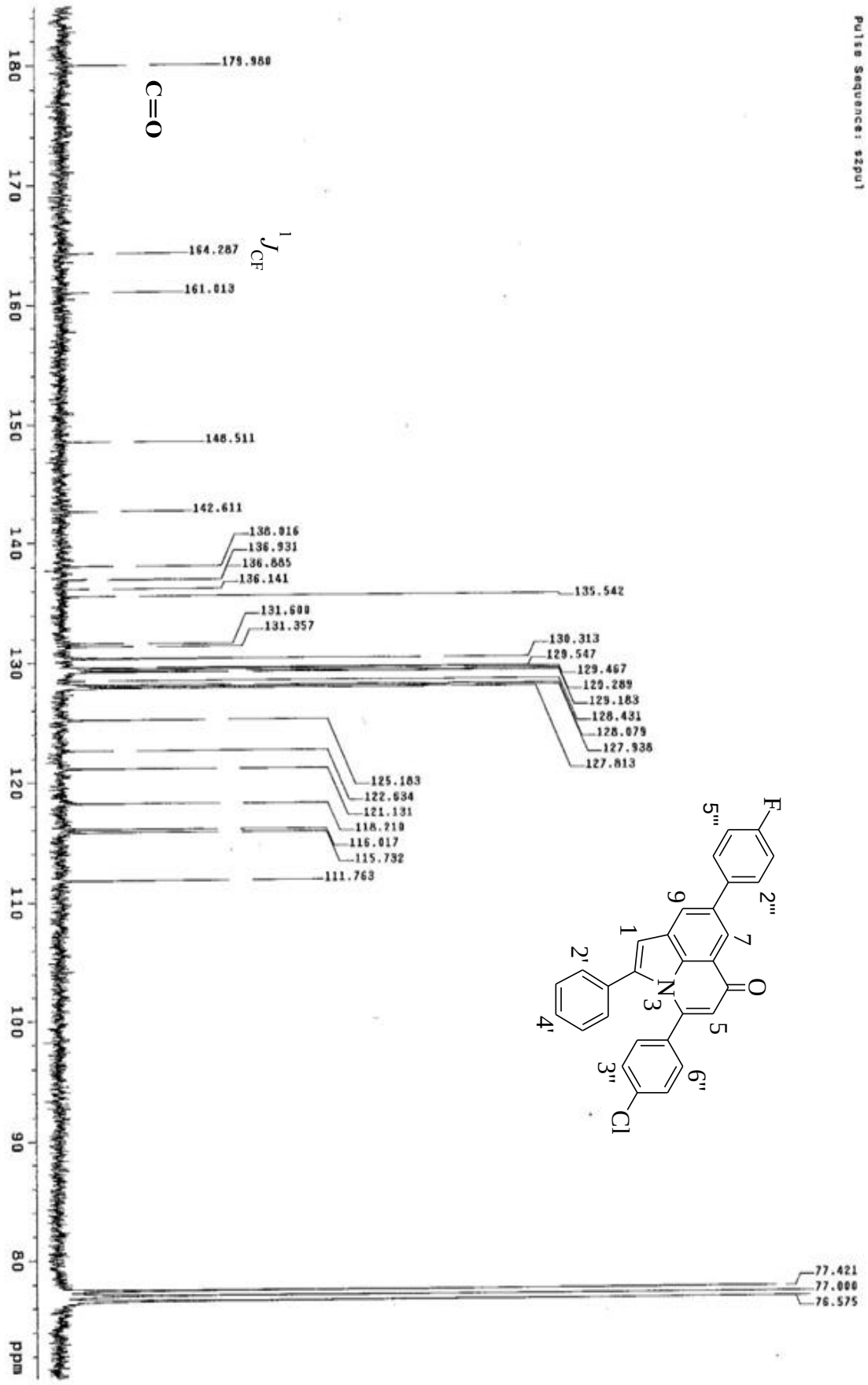
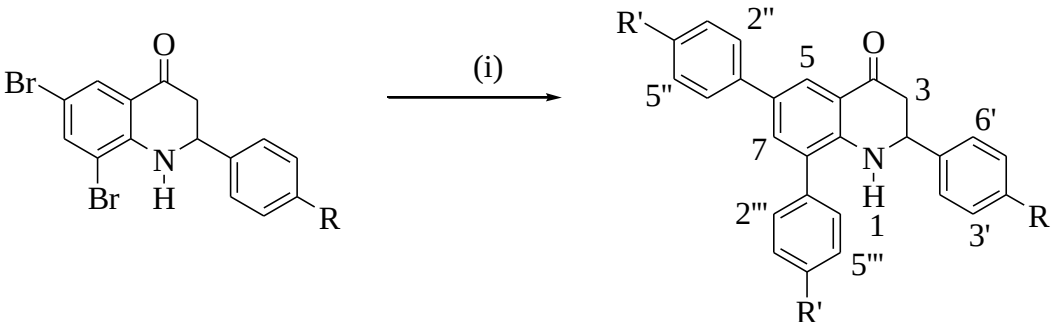


Figure 28: ^{13}C NMR spectrum of compound **144c** in $CDCl_3$ at 75 MHz

2.12 Palladium-catalyzed Suzuki-Miyaura cross-coupling: synthesis of 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones 145a-h

We subjected the 2-aryl-6,8-dibromo-2,3-diydroquinolin-4(1*H*)-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_2CO_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(1*H*)-ones **145a-h** in 75-85% yields. The ^{1}H NMR spectra reveal the two sets of doublet of doublets at δ *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 δ *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 δ *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 ν_{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, α = γ = 90°, β = 99.7100°). The 2-aryl moiety is not co-planar with the quinolin-4(1*H*)-one ring as confirmed by the large torsion angle [C(8)-C(9)-C(10)-C(15)] with a value of 91.70°.



122 **145**

145	**4′-R**	**R′**	**% Yield**	**Mp °C**
a	4′-H	H	85	165-166
b	4′-F	H	84	182-184
c	4′-Cl	H	82	202-204
d	4′-OMe	H	86	194-196
e	4′-H	F	77	167-169
f	4′-F	F	76	176-178
g	4′-Cl	F	78	190-192
h	4′-OMe	F	75	182-184

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

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

Some examples of aryl-substituted quinolin-4(1*H*)-ones have been reported to exhibit antitumor,[87] tubulin inhibitory properties[87] and in vitro activity against erythrocytic stages of multi-drug-resistant isolates and clones of *Plasmodium falciparum*.[112]

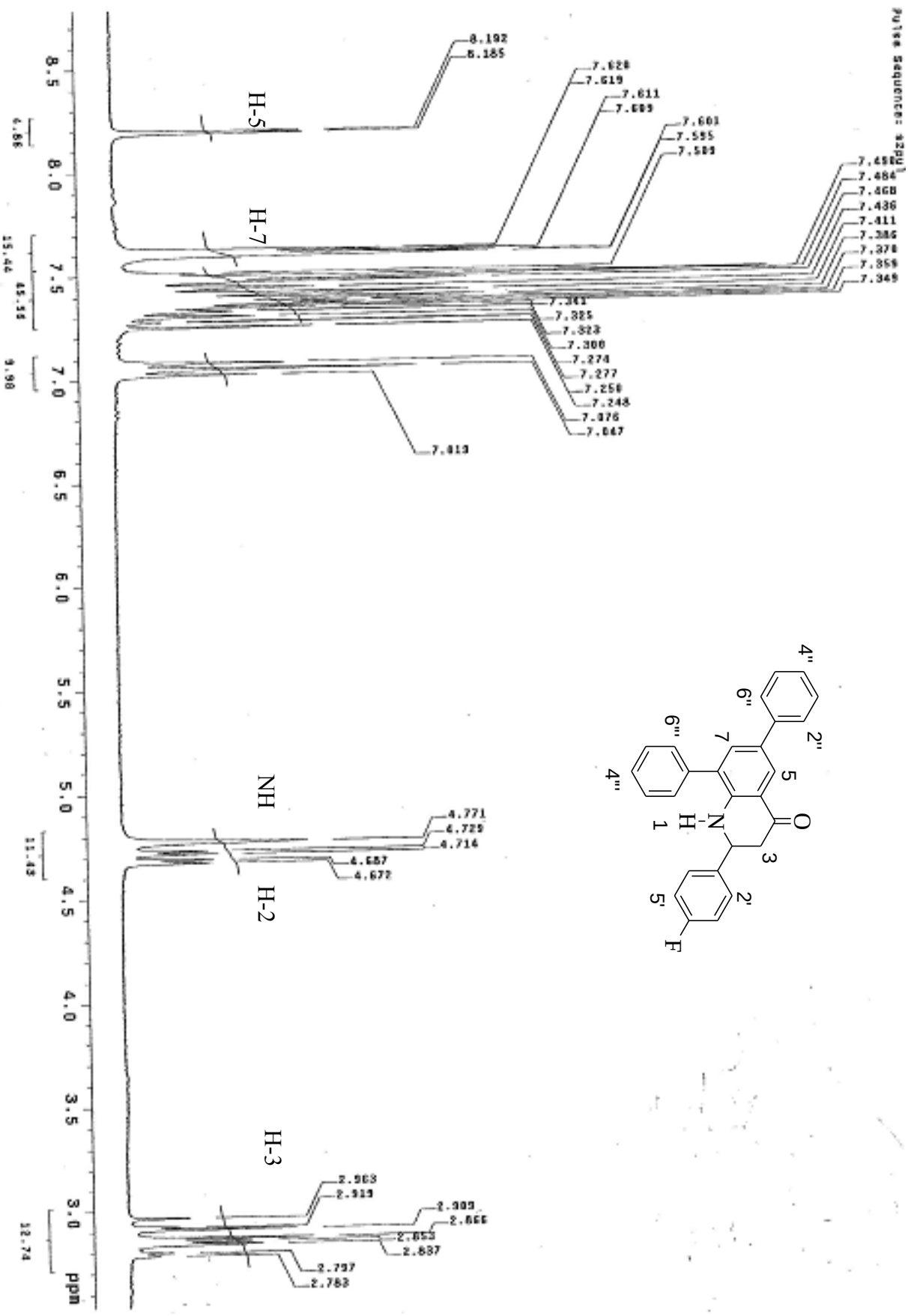


Figure 29: ^{1}H NMR spectrum of compound **145b** in $CDCl_3$ at 300 MHz

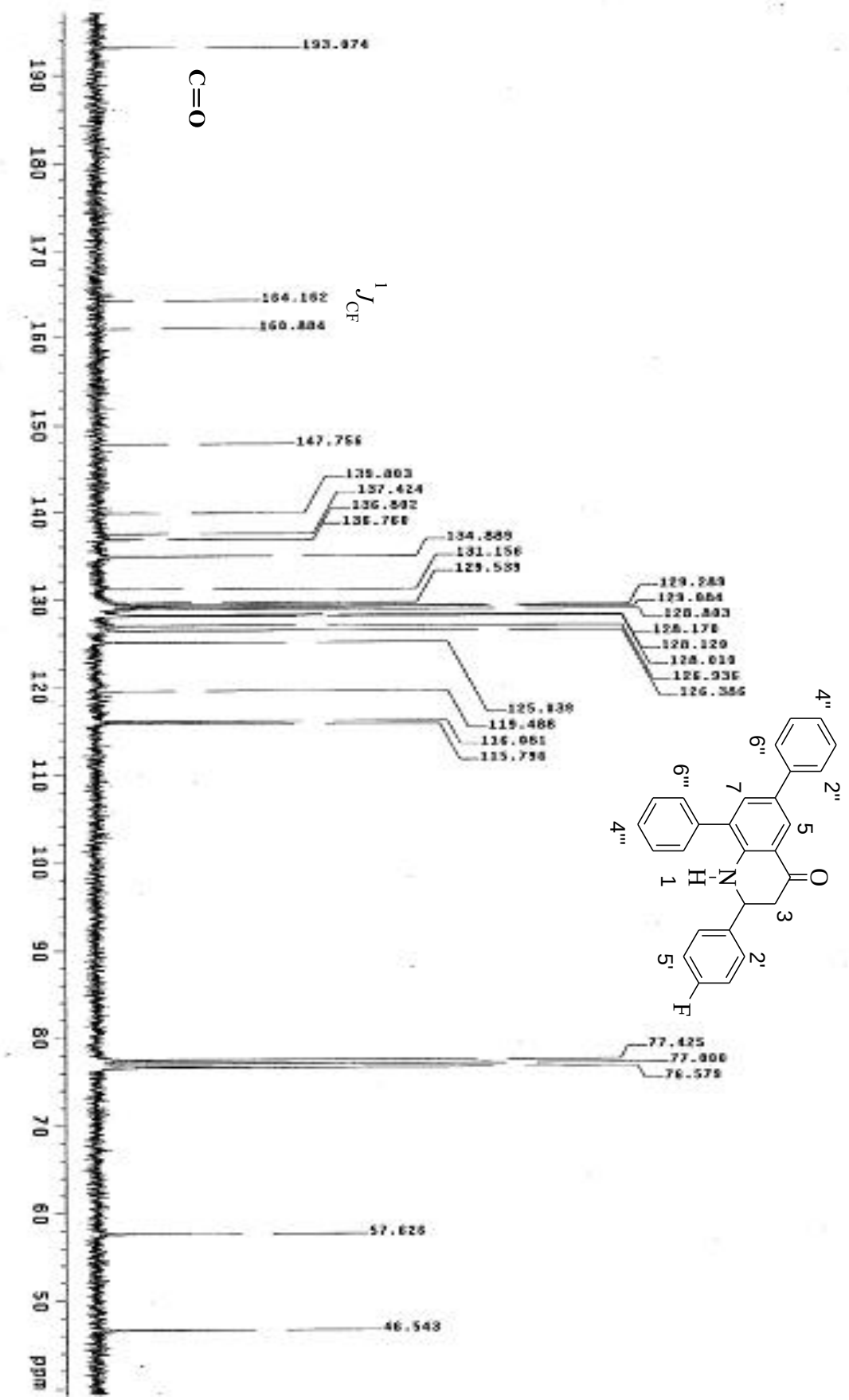


Figure 30: ^{13}C NMR spectrum of compound **145b** in $CDCl_3$ at 75 MHz

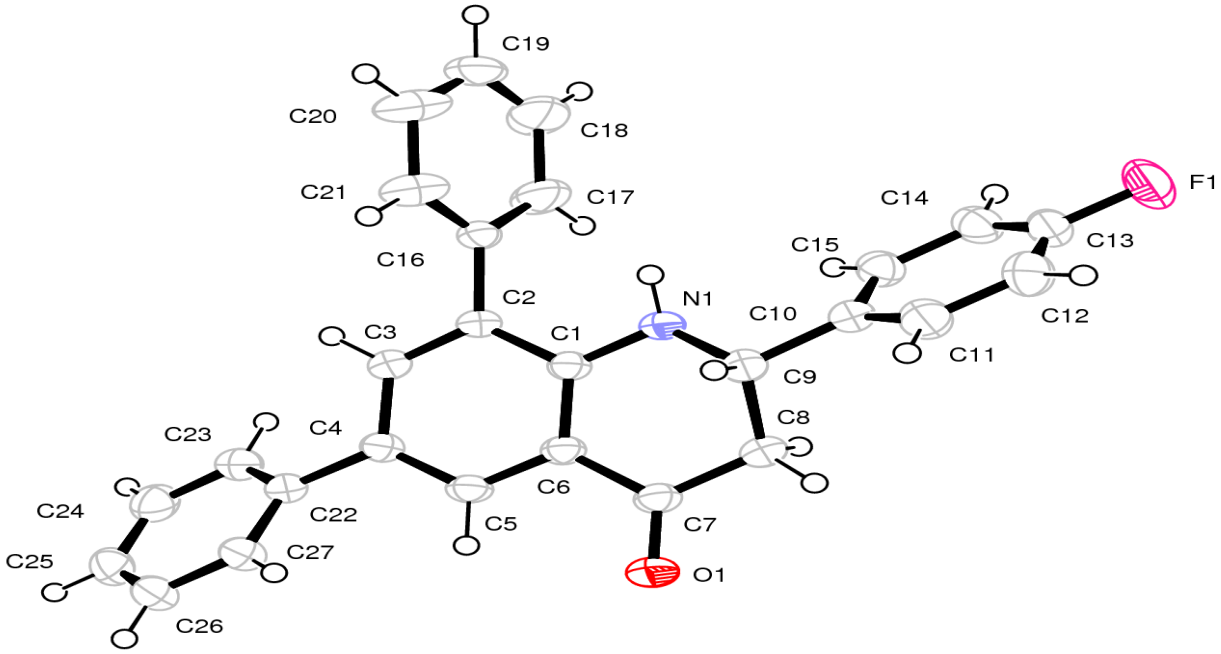
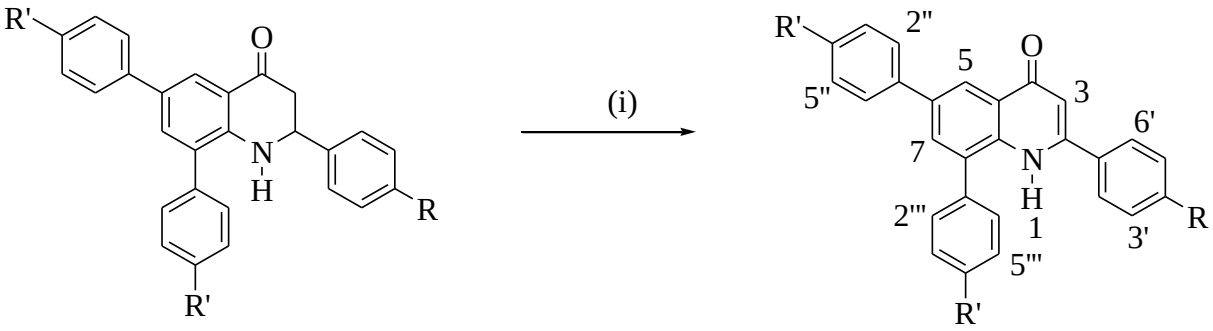


Figure 31: ORTEP diagram (50% probability level) of compound **145b** showing crystallographic numbering. For clarity, hydrogen atoms are not labeled

2.13 Preparation of 2,6,8-triarylquinolin-4(1*H*)-ones 146a-h *via* dehydrogenation of 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones

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 δ *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 δ *ca*. 108.2 and 178.9 ppm, respectively (Figure 33). The IR spectra show absorption bands at ν_{max} *ca*. 3394 and 1644 cm-1 for NH and C=O, respectively.



145 **146**

146	**4′-R**	**R′**	**% Yield**	**Mp °C**
a	4′-H	H	86	242-244
b	4′-F	H	82	237-239
c	4′-Cl	H	83	208-210
d	4′-OMe	H	80	212-214
e	4′-H	F	88	239-242
f	4′-F	F	80	240-242
g	4′-Cl	F	78	225-228
h	4′-OMe	F	75	219-220

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

Scheme 50: Dehydrogenation of 2,6,8-triaryl-2,3-dihydroquinolin-4(1*H*)-ones **145a-h**

With the 2,6,8-triarylquinolin-4(1*H*)-ones in hand, we explore their functionalization taking advantage of the reaction center at C-3 as described in sequence below.

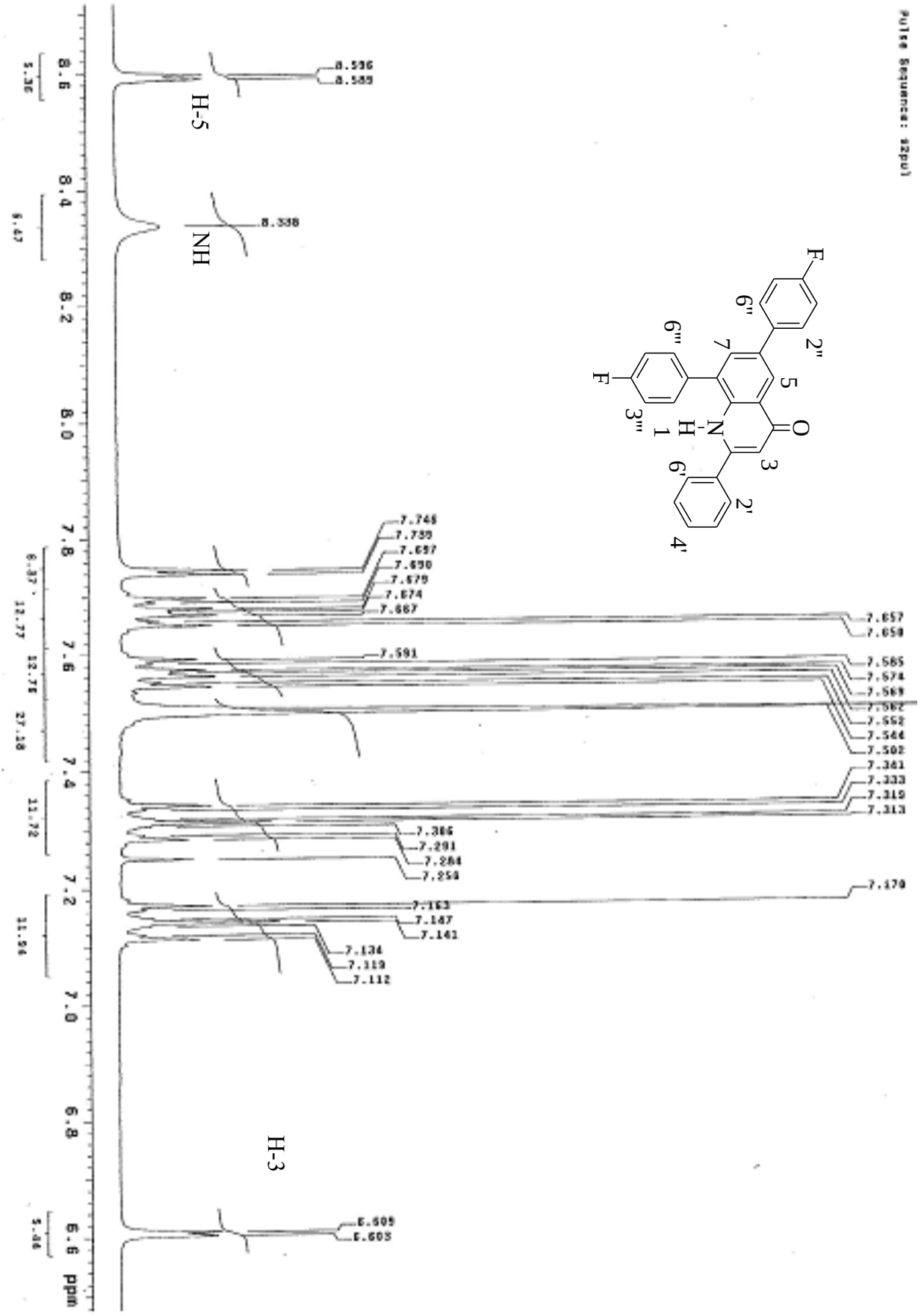


Figure 32: ^{1}H NMR spectrum of compound **146e** in $CDCl_3$ at 300 MHz

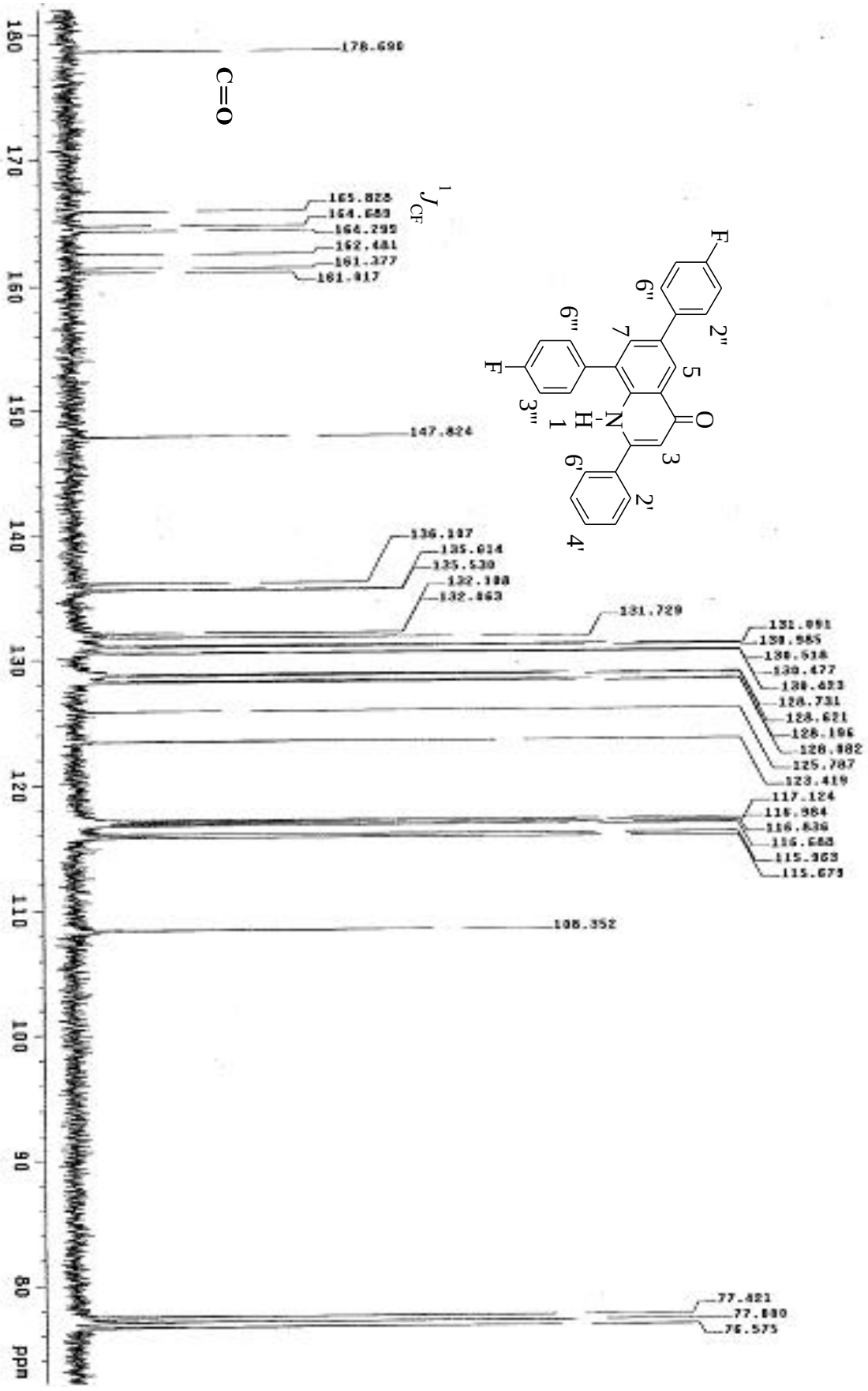
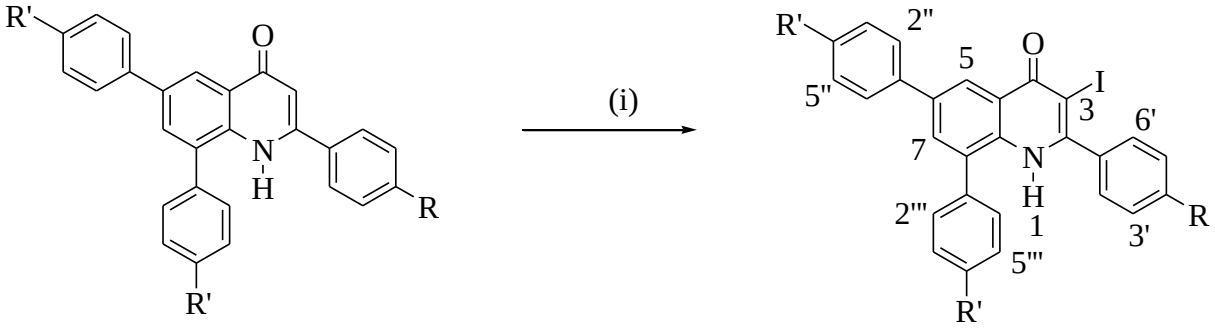


Figure 33: ^{13}C NMR spectrum of compound **146e** in $CDCl_3$ at 75 MHz

2.14 Synthesis of 2,6,8-triaryl-3-iodoquinolin-4(1*H*)-ones 147a-h

We investigated the halogenation of the 2,6,8-triarylquinolin-4(1*H*)-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(1*H*)-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(1*H*)-ones **147** (Scheme 51). The ^{1}H NMR spectra of these compounds consist of two set of doublets at δ *ca*. 7.83 and 8.63 ppm with coupling constant value J = 2.1 Hz and a broad singlet at δ *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 δ *ca*. 86.9 and 174.6 ppm, respectively (Figure 35). Moreover, the IR spectra show absorption at ν_{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.



146 **147**

147	**4′-R**	**R′**	**% Yield**	**Mp °C**
a	4′-H	H	81	219-220
b	4′-F	H	75	225-226
c	4′-Cl	H	74	246-248
d	4′-OMe	H	77	245-247
e	4′-H	F	72	240-241
f	4′-F	F	71	242-244
g	4′-Cl	F	75	251-252
h	4′-OMe	F	75	237-239

Reagents and conditions: (i) I_2, Na_2CO_3, THF, r t, 18 h

Scheme 51: Halogenation of 2,6,8-triarylquinolin-4(1*H*)-ones **146a-h**

Several examples of 2-arylquinolin-4(1*H*)-ones and their analogues have been found to exhibit antitumor[113,114] and antiplatelet properties, and a degree of activity against a variety of cancer.[115] Furthermore, their fluoroquinolone analogues have been reported to possess anti-ischemic activity and serves as cardioprotector.[116]

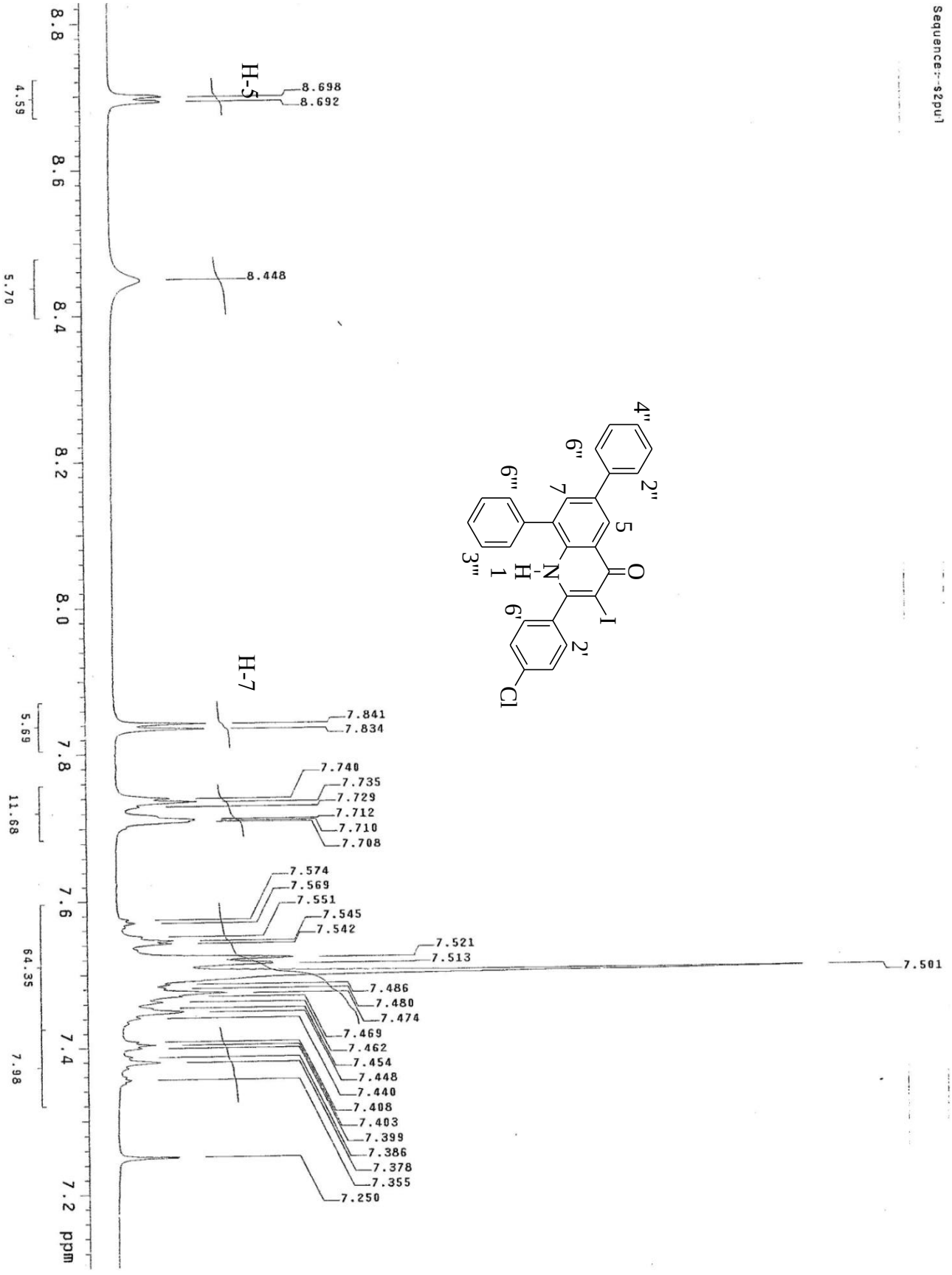


Figure 34: ^{13}C NMR spectrum of compound **147c** in $CDCl_3$ at 300 MHz

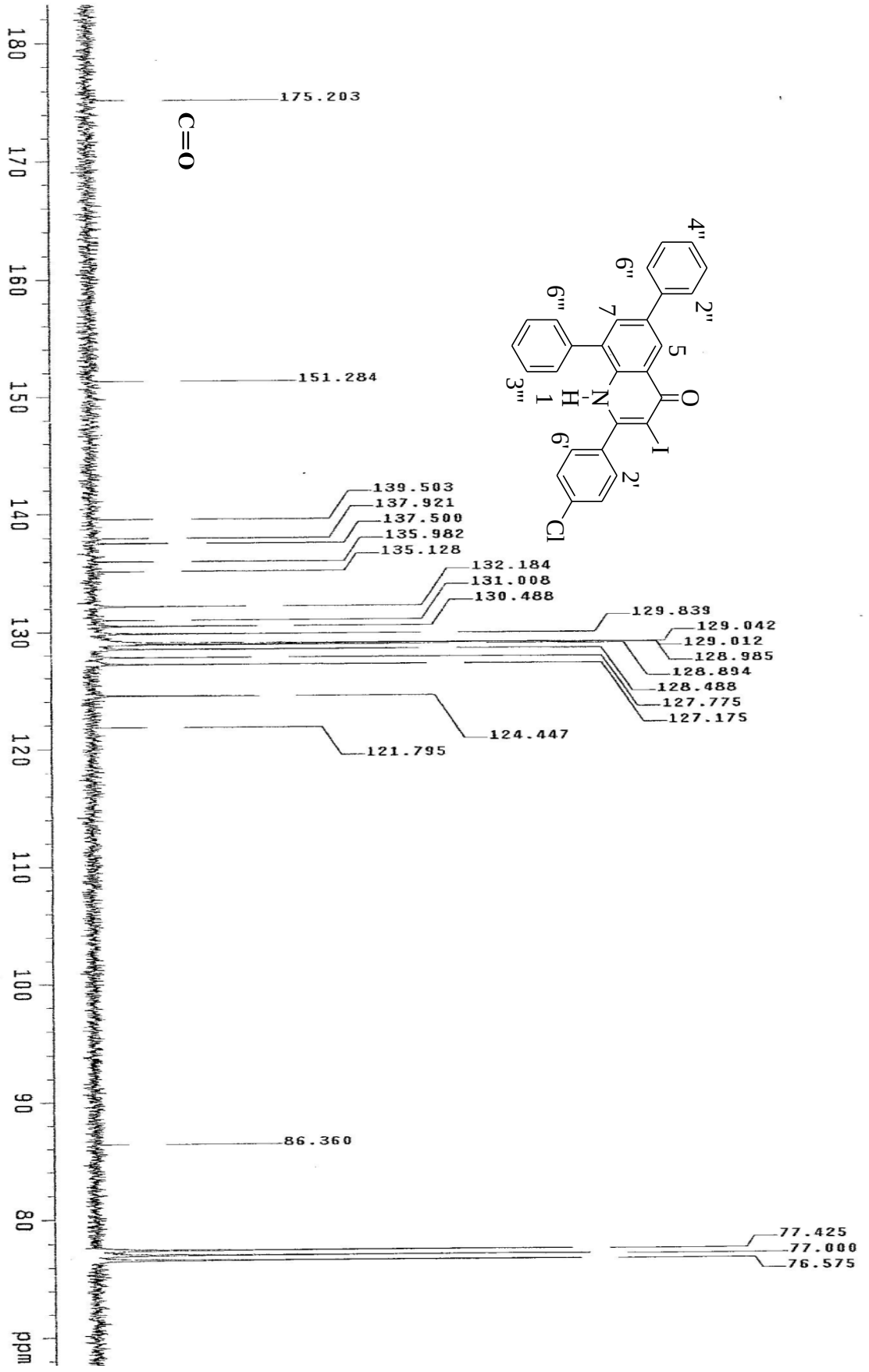
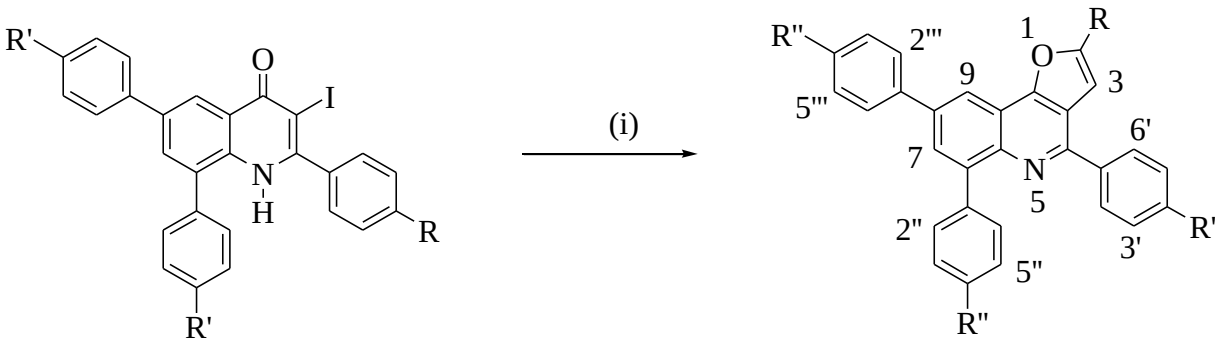


Figure 35: ^{13}C NMR spectrum of compound **147c** in $CDCl_3$ at 75 MHz

2.15 Synthesis of 2,6',8'-trisubstituted 2'-arylfuro[3,2-*c*]quinoline derivatives 148a-i

The potential of the substituted-3-haloquinolin-4(1*H*)-ones to undergo metal-catalyzed alkynylation and subsequent cyclization of the tethered alkynylquinolin-4(1*H*)-ones in close proximity to a nucleophilic heteroatom has been described.[32] To demonstrate the potential of 2,6,8-triaryl-3-iodoquinolin-4(1*H*)-ones **147** in synthesis we subjected compounds **147a-h** to $PdCl_2(PPh_3)_2$-CuI catalyzed Sonogashira cross-coupling with terminal alkynes in the presence of NEt_3 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 ^{1}H 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 ^{13}C 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 ^{127}I isotope, thus confirms the replacement of the iodine atom.



147 **148**

148	**4′-R**	**R″**	**R**	**% Yield**	**Mp °C**
a	4′-H	H	-C_6H_5	67	202-204
b	4′-F	H	-C_6H_5	71	204-205
c	4′-Cl	H	-C_6H_5	68	245-246
d	4′-OMe	H	-C_6H_5	60	200-201
e	4′-H	F	-C_6H_5	74	213-215
f	4′-F	F	-C_6H_5	67	249-250
g	4′-Cl	F	-C_6H_5	62	264-264
h	4′-OMe	F	-C_6H_5	63	221-222
i	4′-H	F	-$CHOHCH_3$	68	245-246

Reagents and conditions: (i) RCCH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 100 °C, 2 h

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

Examples of these classes of annulated compounds have been reported to exhibit anticancer[2] activity. Some of the synthesized compounds were found to exhibit antifungal activity against *C. neoformans* (Table 1).

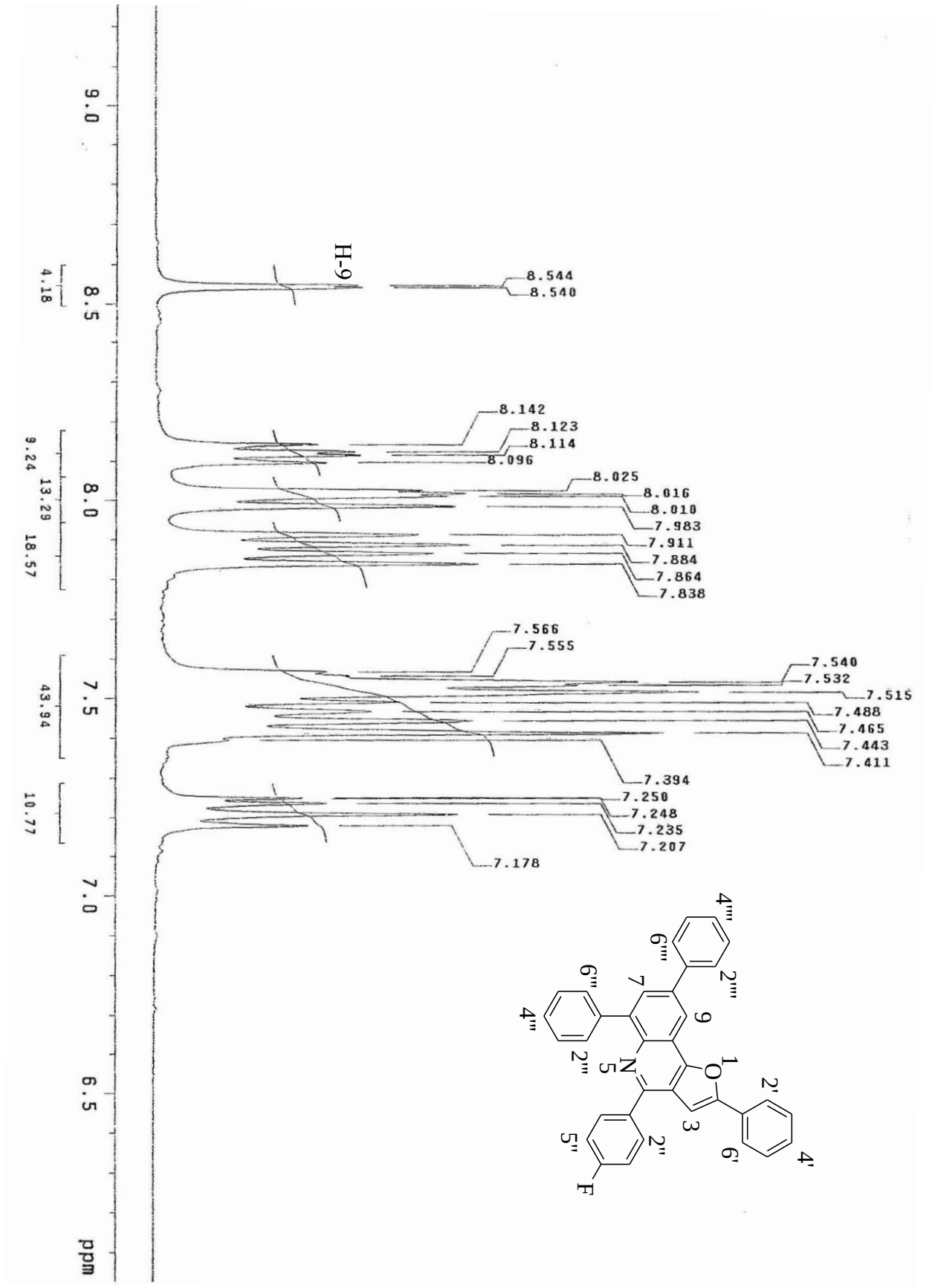


Figure 36: ^{1}H NMR spectrum of compound **148b** in $CDCl_3$ at 300 MHz

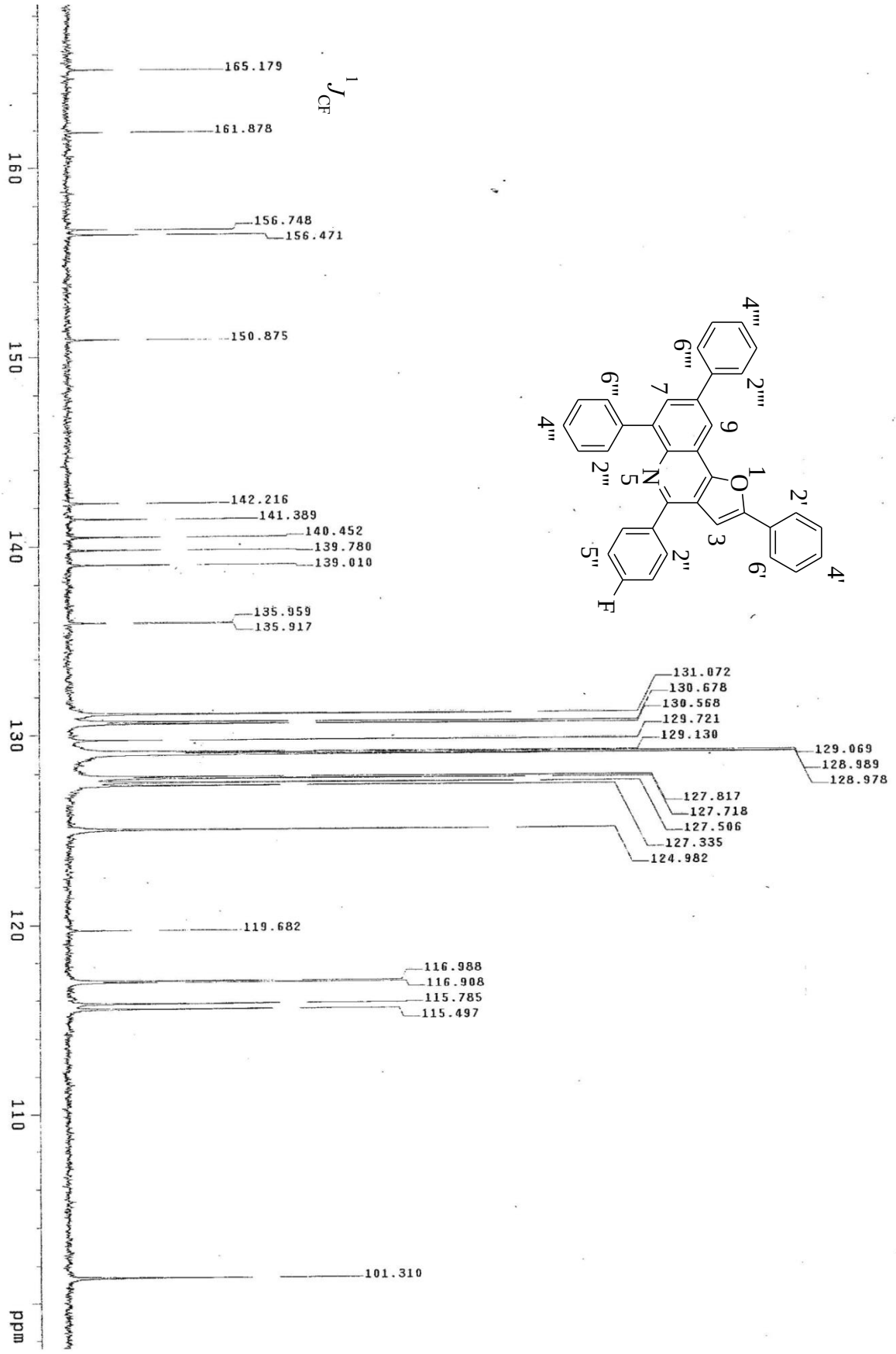


Figure 37: ^{13}C NMR spectrum of compound **148b** in $CDCl_3$ at 75 MHz

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*]quinolines[6] and the furo[3,2-*c*]quinolines[2] 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] antibacterial[22] and antifungal[21,25] 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

Samples	Pathogens					
	E. coli **ATCC 8739**	***E. faecalis*** **ATCC 29212**	***P. aeruginosa*** **ATCC 27858**	***S. aureus*** **ATCC 25923**	***C. albicanss*** **ATCC 10231**	***C. neoforman*** **ATCC 14116**
137b	0.620	0.620	0.156	0.470	>1.25	0.039
137e	0.620	0.620	0.156	0.420	0.039	0.039
137f	0.620	0.620	0.156	0.312	0.078	0.078
137g	0.620	0.620	0.156	0.940	0.312	0.156
137h	0.620	0.620	0.156	0.312	0.078	0.015
138f	0.380	0.620	0.156	0.156	0.078	0.047
138g	0.310	0.380	0.156	0.312	0.078	0.015
139a	0.620	0.620	0.312	0.620	1.250	0.100
139b	0.620	>1.25	0.156	0.312	>1.25	0.078
139c	0.620	>1.25	0.156	0.312	>1.25	0.078
139d	0.620	>1.25	0.156	0.312	1.250	0.078
141e	>1.25	0.620	0.312	0.620	0.620	0.156
142f	0.620	0.470	0.156	>1.25	0.312	0.039
142g	0.620	0.620	0.312	>1.25	ND	0.078
142h	0.620	0.620	0.312	0.620	0.230	0.078
143f	0.620	0.620	0.312	0.620	0.156	0.078
143g	0.620	0.620	0.312	0.620	0.156	0.039
143h	0.620	0.620	0.312	0.620	0.620	0.039
144b	>1.25	0.620	0.312	0.620	ND	0.039
148a	0.620	>2.50	0.620	0.312	0.470	ND
148b	0.620	>2.50	0.620	0.312	0.470	0.312
148c	>2.50	>2.50	>2.50	0.620	0.620 N	ND
148d	0.620	2.50	0.940	0.312	2.50	0.470

Table 1 continues						
148e	0.620	0.620	0.620	0.312	0.156	0.078
148f	>1.25	0.620	0.312	>1.25	>1.25	0.156
148g	>1.25	>1.25	0.156	0.620	0.620	0.078
148h	0.620	0.620	1.25	0.313	0.156	0.156
Ciprofloxacin control µg /ml	0.310	0.310	0.160	0.630		
Negative control	> 1.25	> 1.25	> 1.25	> 1.25	> 1.25	> 1.25
culture control	> 1.25	> 1.25	> 1.25	> 1.25	> 1.25	> 1.25
Amphotericin B µg /ml					2.50	1.25

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.[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.[6,46]

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*.

Chapter 3: CONCLUSION

The reactivity of the substituted dihalogenoquinolin-4(1*H*)-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-PPh_3-CuI catalyst mixture as a heterogenous Pd(0) source, the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones couple with terminal alkynes to afford the corresponding 2-aryl-6-bromo-8-(alkynyl)-2,3-dihydroquinolin-4(1*H*)-ones, exclusively. The use of $PdCl_2(PPh_3)_2$ as Pd(0) source, on the other hand, afforded 2-aryl-6,8-bis(alkynyl)-2,3-dihydroquinolin-4(1*H*)-ones in reasonable yields and high purity. The structures of the compounds were characterized using a combination of ^{1}H and ^{13}C 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(1*H*)-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)-PPh_3 species *in situ*.[118] The homogenous Pd(0)-PPh_3 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 $PdCl_2(PPh_3)_2$ 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(1*H*)-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(1*H*)-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-5*H*-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(1*H*)-ones were found to undergo iodine-promoted halogenation to afford 2,6,8-triaryl-3-iodoquinolin-4(1*H*)-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-triarylfuro[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(1*H*)-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.[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,[2] antihypertensive,[4] anticonvulsant,[5] antiviral,[6] and antifungal[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 *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*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 polycarbosubstituted 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_α 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.

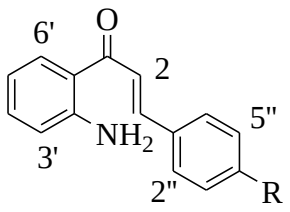
The following abbreviations are used throughout for NMR spectroscopy:

ppm = parts per million

J = coupling constant in Hz; δ = 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



1-(2′-Aminophenyl)-3-aryl-2-propen-1-ones 104a-d

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, $CDCl_3$) δ: 6.34 (2H, s, NH_2), 6.67-6.72 (2H, m, 3′-H and 5′-H), 7.29 (1H, t, *J* 7.2 Hz, 4′-H), 7.37-7.43 (3H, m, 3′′-H, 4′′-H and 5′′-H), 7.59-7.64 (3H, m, 2′′-H, 6′′-H and 6′-H), 7.75 (1H, d, *J* 15.6 Hz, 3-H), 7.86 (1H, d, *J* 15.6 Hz, 2-H); IR (neat): ν_{max} 3443, 3326, 1640, 1614, 1573, 1539, 1495, 1448, 1338, 1206, 1157, 1010, 976, 737, 696, 662 cm^{-1}.

4.1.2 Preparation of 1-(2′-aminophenyl)-3-(4-fluorophenyl)-2-propen-1-one 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, $CDCl_3$) δ: 6.33 (2H, s, NH_2), 6.66-6.72 (2H, m, 3′-H and 5′-H), 7.09 (1H, t, *J* 8.4 Hz, 4′-H), 7.25-7.31 (2H, m, 3′′-H and 5′′-H), 7.50-7.72 (3H, m, 2′′-H, 6′-H, 6′′-H), 7.74 (1H, d, *J* 15.6 Hz, 3-H), 7.84 (1H, d, *J* 15.6 Hz, 2-H); IR (neat):

ν_{max} 3427, 3317, 1646, 1615, 1575, 1541, 1506, 1483, 1445, 1414, 1341, 1266, 1205, 1153,1096, 1007, 978, 847, 824, 770, 739, 657 cm^{-1}.

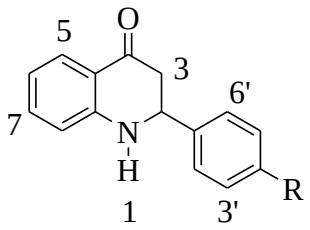
4.1.3 Preparation of 1-(2′-aminophenyl)-3-(4-chlorophenyl)-2-propen-1-one 104c (R = Cl)

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, *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.,[31] 82-84 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.34 (2H, s, NH_2), 6.66-6.71 (2H, m, 3′-H and 5′-H), 7.25-7.38 (3H, m, 3′′-H and 5′′-H, 4′-H), 7.53-7.70 (3H, m, 2′′-H, 6′-H, 6′′-H), 7.74 (1H, d, *J* 15.5 Hz, 3-H), 7.83 (1H, d, *J* 15.5 Hz, 2-H); IR (neat): ν_{max} 3472, 3325, 3034, 1641, 1611, 1568, 1536, 1491, 1446, 1405, 1336, 1292, 1263, 1208, 1156, 1089, 1006, 981, 816, 749, 674, 640 cm^{-1}.

4.1.4 Preparation of 1-(2′-aminophenyl)-3-(4-methoxyphenyl)-3-propen-1-one 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, *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.,[31] 90-93 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.84 (3H, s, $COCH_3$), 6.31 (2H, s, NH_2), 6.66-6.72 (2H, m, 3′-H and 5′-H), 6.92 (2H, dd, *J* 3.0 and 8.7 Hz, 3′′-H and 5′′-H), 7.47-7.74 (4H, m, 2′′-H, 4′-H, 6′-H and 6′′-H), 7.75 (1H, d, *J* 15.5 Hz, 3-H), 7.85 (1H, d, *J* 15.5 Hz, 2-H); IR (neat): ν_{max} 3427, 3306, 2840, 1680, 1639, 1611, 1568, 1535, 1509, 1460, 1423, 1355, 1290, 1251, 1208, 1158, 1022, 981, 827, 801, 683, 655 cm^{-1}.

4.2 Preparation of 2-aryl-2,3-dihydoquinolin-4(1*H*)-ones 105a-d



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

4.2.1 Preparation of 2-phenyl-2,3-dihydroquinolin-4(1*H*)-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 $MgSO_4$. 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); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.70 (1H, ddd, *J* 1.2, 4.5 and 16.5 Hz, 3-H), 2.87 (1H, dd, *J* 13.2 and 16.5 Hz, 3-H), 4.61 (1H, s, N-H), 4.74 (1H, dd, *J* 4.5 and 9.0 Hz, 2-H), 6.71 (1H, d, *J* 8.1 Hz, 8-H), 6.75 (1H, t, *J* 7.5 Hz, 6-H), 7.25-7.46 (6H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H and 7-H), 7.86 (1H, d, *J* 9.3 Hz, 5-H); IR (neat): ν_{max} 3332, 1655, 1604, 1480, 1332, 1303, 1261, 1215, 1154, 1115, 1076, 1024, 999, 915, 765, 699, 617 cm^{-1}.

4.2.2 Preparation of 2-(4-fluorophenyl)-2,3-dihydroquinolin-4(1*H*)-one 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); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.72 (1H,

dd, *J* 4.5 and 16.8 Hz, 3-H), 2.87 (1H, dd, *J* 13.2 and 16.8 Hz, 3-H), 4.53 (1H, s, N-H), 4.71 (1H, dd, *J* 4.5 and 9.0 Hz, 2-H), 6.71 (1H, d, *J* 8.1 Hz, 8-H), 6.78 (1H, t, *J* 7.8 Hz, 6-H), 7.10 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 7.25-7.44 (3H, m, 3′-H, 5′-H and 7-H), 7.85 (1H, d, *J* 8.4 Hz, 5-H); IR (neat): ν_{max} 3299, 1645, 1603, 1505, 1479, 1436, 1355, 1309, 1223, 1154, 1120, 1001, 913, 860, 836, 796, 755, 639 cm^{-1}.

4.2.3 Preparation of 2-(4-chlorophenyl)-2,3-dihydroquinolin-4(1*H*)-one 105c (R = Cl)

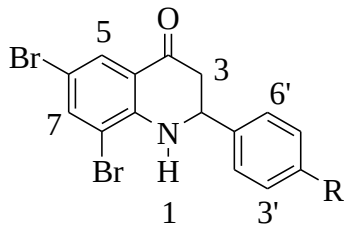
A stirred mixture of **104c** (11.33 g, 44.0 mmol), orthophosphoric acid (30 mL) and glacial acetic acid (30 mL) was treated as described for **105a**. Work-up afforded **105c** as yellow solid (10.42 g, 92%) ; mp 146-148 °C (EtOH), (lit.,[67] 146 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.67 (1H, dd, *J* 4.5 and 16.5 Hz, 3-H), 2.83 (1H, dd, *J* 13.2 and 16.5 Hz, 3-H), 4.57 (1H, s, N-H), 4.70 (1H, dd, *J* 4.5 and 7.5 Hz, 2-H), 6.72 (1H, d, *J* 8.4 Hz, 8-H), 6.78 (1H, t, *J* 7.4 Hz, 6-H), 7.25-7.39 (5H, m, 2′-H, 3′-H, 5′-H, 6′-H and 7-H), 7.84 (1H, d, *J* 8.7 Hz, 5-H); IR (neat): ν_{max} 3306, 1651, 1604, 1508, 1480, 1410, 1326, 1250, 1211, 1151, 1118, 1089, 1015, 916, 825, 764, 685, 647 cm^{-1}.

4.2.4 Preparation of 2-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one 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, $CDCl_3$) δ: 2.67 (1H, dd, *J* 4.5 and 16.5 Hz, 3-H), 2.87 (1H, dd, *J* 13.2 and 16.5 Hz, 3-H), 3.80 (3H, s, $COCH_3$), 4.53 (1H, s, N-H), 4.66 (1H, dd, *J* 4.5 and 9.9 Hz, 2-H), 6.69 (1H, d, *J* 8.4 Hz, 8-H), 6.76 (1H, t, *J* 7.5 Hz, 6-H), 6.90 (2H, d, *J* 6.9 Hz, 2′-H and 6′-H), 7.29-7.37 (3H, m, 3′-H, 5′-H and 7-H), 7.85

(1H, d, *J* 7.8 Hz, 5-H); IR (neat): ν_{max} 3290, 1645, 1603, 1506, 1478, 1362, 1330, 1301, 1244, 1213, 1175, 1153, 1118, 1028, 913, 826, 753, 634 cm^{-1}.

4.3 Preparation of 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones 122a-d



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

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

A mixture of 2-phenyl-2,3-dihydroquinolin-4(1*H*)-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, $CDCl_3$) δ: 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, -C_6H_5), 7.71 (1H, d, *J* 2.1 Hz, 7-H), 7.95 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.3 (C-3), 57.7 (C-2), 109.8 (C-6), 110.8 (C-8), 120.8 (C-4a), 126.5 (C-2′ and C-6′), 128.8 (C-3′ and C-5′), 129.1 (C-5), 129.2 (C-4′), 129.6 (C-7), 139.9 (C-1′), 147.2 (C-8a), 191.1 (C-4); IR (neat): ν_{max} 3375,

1679, 1590, 1482, 1396, 1362, 1323, 1277, 1226, 1155, 1123, 1077, 1001, 882, 846, 757, 702 cm^{-1}.

4.3.2 Preparation of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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%); R_f (toluene) 0.58; mp 127-129 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.78 (1H, dd, *J* 4.5, 16.8 Hz, 3-H), 2.86 (1H, dd, *J* 13.2, 16.8 Hz, 3H), 4.75 (1H, dd, *J* 4.5 and 13.2 Hz, 2-H), 5.03 (1H, s, N-H), 7.10 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 7.43 (2H, dd, *J* 5.4 and 14.1 Hz, 3′-H and 5′-H), 7.71 (1H, d, *J* 2.1 Hz, 7-H), 7.94 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.4 (C-3), 57.0 (C-2), 110.0 (C-6), 110.8 (C-8), 116.1 (d, $^2J_{CF}$ 21.6 Hz, C-3′ and C-5′), 120.7 (C-4a), 128.3 (d, $^3J_{CF}$ 8.3 Hz, C-2′ and C-6′), 129.5 (C-5), 129.8 (C-7), 135.8 (d, $^4J_{CF}$ 3.2 Hz, C-1′), 147.1 (C-8a), 162.8 (d, $^1J_{CF}$ 246.5 Hz, C-4′), 190.9 (C-4); IR (neat): ν_{max} 3363, 1684, 1592, 1509, 1480, 1408, 1360, 1328, 1284, 1225, 1160, 1017, 896, 856, 833, 749 cm^{-1}.

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

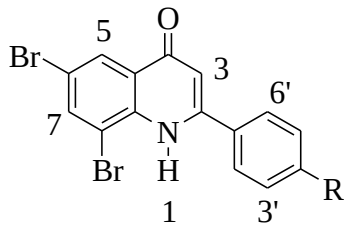
An experimental procedure employed for the synthesis of **122a** was followed using a mixture of **105c** (5.00 g, 19.4 mmol) and *N*-bromosuccinimide (6.91 g, 38.8 mmol) in carbon tetrachloride-chloroform (3:2, v/v; 500 mL); work-up and column chromatography on silica gel afforded **122c**

as light yellow solid (7.09 g, 88%); R_f (toluene) 0.63; mp 145-146 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.78 (1H, dd, *J* 4.5 and 16.5 Hz, 3-H), 2.85 (1H, dd, *J* 13.2 and 16.5 Hz, 3H), 4.76 (1H, dd, *J* 4.5 and 6.3 Hz, 2-H), 5.05 (1H, s, N-H), 7.11 (2H, t, *J* 9.2 Hz, 2′-H and 6′-H), 7.44 (2H, dd, *J* 4.5 and 9.3 Hz, 3′-H and 5′-H), 7.72 (1H, d, *J* 2.4 Hz, 7-H), 7.94 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.2 (C-3), 57.1 (C-2), 110.1 (C-6), 110.8 (C-8), 120.8 (C-4a), 127.9 (C-2′ and C-6′), 129.4 (C-3′ and C-5′), 129.6 (C-5), 134.6 (C-4′), 138.4 (C-7), 140.0 (C-1′), 147.0 (C-8a), 190.8 (C-4); IR (neat): ν_{max} 3375, 1672, 1592, 1483, 1396, 1334, 1280, 1228, 1164, 1089, 1018, 868, 824, 725, 675 cm^{-1}.

4.3.4 Preparation of 2-(4-methoxyphenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-one 122d (R = OCH_3)

An experimental procedure employed for the synthesis of **122a** was followed using a mixture of **105d** (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 **122d** as light yellow solid (6.75 g, 83%); R_f (toluene) 0.40; mp 149-151 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.77 (1H, dd, *J* 4.5 and 16.5 Hz, 3-H), 2.88 (1H, dd, *J* 13.2 and 16.5 Hz, 3H), 3.82 (3H, s, $COCH_3$), 4.71 (1H, dd, *J* 4.5 and 9.0 Hz, 2-H), 5.03 (1H, s, N-H), 6.94 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 7.31 (2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.70 (1H, d, *J* 2.1 Hz, 7-H), 7.95 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.4 (C-3), 54.4 (OCH_3), 57.2 (C-2), 109.8 (C-6), 110.7 (C-8), 114.5 (C-4a), 120.8 (C-2′ and C-6′), 127.8 (C-3′ and C-5′), 129.6 (C-5), 132.0 (C-4′), 139 9 (C-7), 147.3 (C-1′), 159.9 (C-8a), 191.4 (C-4); IR (neat): ν_{max} 3317, 1661, 1596, 1503, 1414, 1348, 1283, 1246, 1203, 1180, 1149, 1026, 962, 880, 809, 787, 737, 704 cm^{-1}.

4.4 Preparation of 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones 136a-d



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

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

A stirred mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-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 $CHCl_3$ (3x100 mL). The combined organic layers were washed with saturated Na_2CO_3 solution (2x15 mL); dried over anhydrous $MgSO_4$ 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; ^{1}H NMR (300 MHz, DMSO-d_6) 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); ^{13}C NMR (75 MHz, DMSO-d_6) 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(1*H*)-one 136b (R = F)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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) ν_{max} 3383, 3064, 1620, 1585, 1540, 1507, 1490, 1447, 1386, 1348, 1223, 1162, 869, 832, 718, 680 cm^{-1}.

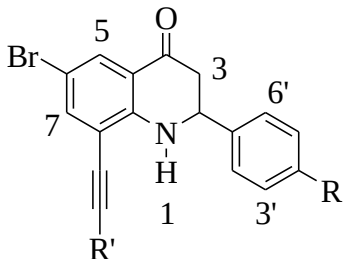
4.4.3 Preparation of 2-(4-chlorophenyl)-6,8-dibromoquinolin-4(1*H*)-one 136c (R = Cl)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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) ν_{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(1*H*)-one 136d (R = OCH_3)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.84 (3H, s, OCH_3), 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); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.8 (OCH_3), 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(1*H*)-ones 137a-h



2-Aryl-8-alkynyl-6-bromo-2,3-dihydroquinolin-4(1*H*)-ones 137a-h

4.5.1 Preparation of 6-bromo-2-phenyl-8-(2-phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one 137a (R = H; R' = -C_6H_5)

A mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one **122a** (0.50 g, 1.3 mmol) 10% Pd/C (0.015 g, 0.01 mmol), PPh_3 (0.013 g, 0.05 mmol) and CuI (0.02 g, 0.13 mmol) in EtOH/NEt_3 (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 $CHCl_3$ (150 mL). The organic solvent was washed with brine (2 x 15 mL), dried over anhydrous $MgSO_4$ 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; R_f (toluene) 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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-4a), 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-8a), 191.6 (C-4); IR (neat) ν_{max} 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 $[C_{23}H_{17}NO^{79}Br]^+$, requires 402.0494.

4.5.2 Preparation of 2-(4-fluorophenyl)-6-bromo-8-(2-phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one 137b (R = F; R' = -C_6H_5)

A stirred mixture of **122b** (0.50 g, 1.2 mmol), 10% Pd/C (0.014 g, 0.01 mmol), PPh_3 (0.013 g, 0.04 mmol), CuI (0.02 g, 0.1 mmol) in EtOH/NEt_3 (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; R_f (toluene) 0.33; ^{1}H NMR (300 MHz, $CDCl_3$) 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', 2", 6' & 6"), 7.66 (1H, d, *J* 2.4 Hz, 7-H), 7.95 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 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, $^3J_{CF}$ 21.6 Hz, C-3' & 5'), 119.7 (C-4a), 121.9 (C-2" & 6"), 128.2 (d, $^2J_{CF}$ 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, $^1J_{CF}$ 3.4 Hz, C-1'), 140.0 (C-7), 150.1 (C-8a), 162.7 (d, $^4J_{CF}$ 246.2 Hz, C-4'), 191.3 (C-4); IR (neat) ν_{max} ν_{max} (neat)3373, 3071, 3028, 2821, 1947, 1681, 1583, 1491, 1477, 1325, 1234, 1156, 881, 837, 754, 747, 672 cm^{-1}; *m/z* (100, MH^+) 420; HRMS (EI): MH^+, found 420.0391. For $[C_{23}H_{16}NOF^{79}Br]^+$, requires 420.0484.

4.5.3 Preparation of 2-(4-chlorophenyl)-6-bromo-8-(2-phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one 137c (R = Cl; R' = -C_6H_5)

A stirred mixture of **122c** (0.50 g, 1.2 mmol), 10% Pd/C (0.014 g, 0.01 mmol), PPh_3 (0.013 g, 0.04 mmol), CuI (0.02 g, 0.1 mmol) in EtOH/NEt_3 (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; R_f (toluene) 0.38; ^{1}H NMR (300

MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 45.7 (C-3), 57.1 (C-2), 82.5 ((C≡α), 97.5 (C≡β), 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) ν_{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(1*H*)-one 137d (R = OCH_3; R' = $-C_6H_5$)

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 °C; R_f (toluene) 0.18; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 45.9 (C-3), 55.3 (OCH_3), 57.1 (C-2), 82.7 ((C≡α), 97.4 (C≡β), 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) ν_{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(1*H*)-one 137e (R = H; R' = -CH_2CH_2OH)

A stirred mixture of **122a** (0.51 g, 1.3 mmol) 10% Pd/C (0.015 g, 0.01 mmol), PPh_3 (0.013 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) in EtOH/NEt_3 (2:1; v/v) (30 mL) and 3-butyn-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. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.89 (1H, t, *J* 5.4 Hz, OH), 2.66 (2H, t, *J* 6.3 Hz, C$\underline{H}_2$CH_2OH), 2.76-2.89 (2H, m, 3-H), 3.76 (2H, dd, *J* 6.0, 6.3 Hz, C$\underline{H}_2$OH), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.7 ($\underline{C}H_2CH_2OH$), 45.7 (C-3), 57.5 ($\underline{C}H_2OH$), 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 $[C_{19}H_{17}NO_2{}^{79}Br]^+$, requires 370.0444.

4.5.6 Preparation of 6-bromo-2-(4-fluorophenyl)-8-(4-hydroxybut-1-yn-1-yl)-2,3-dihydroquinolin-4(1*H*)-one 137f (R = F; R' = -CH_2CH_2OH)

A stirred mixture of **122b** (0.52 g, 1.3 mmol), 10% Pd/C (0.015 g, 0.01 mmol), PPh_3 (0.013 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) in EtOH/NEt_3 (30 mL) and 3-butyn-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. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.60 (1H, t, *J* 5.4 Hz, OH), 2.68 (2H, t, *J* 6.3 Hz, C$\underline{H}_2$CH_2OH), 2.76-

2.89 (2H, m, 3-H), 3.77 (2H, dd, *J* 4.5, 6.3 Hz, C$\underline{H}_2$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 ($\underline{C}H_2CH_2OH$), 45.7 (C-3), 56.9 ($\underline{C}H_2OH$), 60.8 (C-2), 95.7 ((C≡α), 95.8 (C≡β), 109.3 (C-8), 112.0 (C-6), 115.9 (d, $^3J_{CF}$ 21.4 Hz, C-3' & 5'), 119.4 (C-4a), 128.3 (d, $^2J_{CF}$ 8.0 Hz, C-2' & 6'), 129.8 (C-5), 136.2 (d, $^1J_{CF}$ 3.2 Hz, C-1'), 139.7 (C-7), 150.6 (C-8a), 162.6 (d, $^4J_{CF}$ 245.9 Hz, C-4'), 191.5 (C-4); IR (neat) ν_{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 $[C_{19}H_{16}NO_2F^{79}Br]^+$, requires 388.0338.

4.5.7 Preparation of 6-bromo-2-(4-chlorophenyl-8-(4-hydroxybut-1-yn-1-yl)-2,3-dihydroquinolin-4(1*H*)-one 137g (R = Cl; R' = -CH_2CH_2OH)

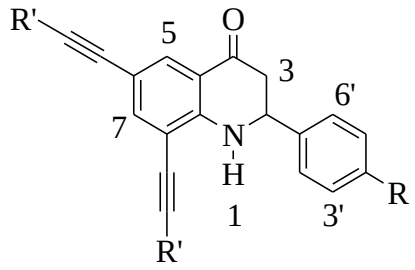
A stirred mixture of **122c** (0.4 g, 0.9 mmol), 10% Pd/C (0.011 g, 0.009 mmol), PPh_3 (0.009 g, 0.03 mmol), CuI (0.018 g, 0.09 mmol) and 3-butyn-1-ol (0. 14 mL, 1.4 mmol) in EtOH/NEt_3 (30 mL), was treated as described for **137c**; work up and column chromatography on silica gel afforded **137g** as 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, C$\underline{H}_2$CH$_2$OH), 2.76-2.89 (2H, m, 3-H), 3.78 (2H, dd, *J* 4.5, 6.3 Hz, C$\underline{H}_2$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 ($\underline{C}H_2CH_2OH$), 45.6 (C-3), 57.0 ($\underline{C}H_2OH$), 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) ν_{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 $[C_{19}H_{16}NO_2Cl^{79}Br]^+$, requires 404.0053.

4.5.8 Preparation of 6-bromo-2-(4-methoxyphenyl-8-(4-hydroxybut-1-yn-1-yl)-2,3-dihydroquinolin-4(1*H*)-one 137h (R = OCH_3; R' = $-CH_2CH_2OH$)

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/NEt_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, $CDCl_3$) δ: 1.57 (1H, t, *J* 5.4 Hz, OH), 2.67 (2H, t, *J* 6.3 Hz, C<u>H</u>$_2$CH_2OH), 2.72-2.91 (2H, m, 3-H), 3.76 (2H, dd, *J* 6.0, 6.3 Hz, C<u>H</u>$_2$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, $CDCl_3$) δ: 23.7 (<u>C</u>H_2CH_2OH), 45.8 (C-3), 55.3 (OCH_3), 57.1 (<u>C</u>H_2OH), 60.8 (C-2), 95.7 ((C≡α), 95.8 (C≡β), 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) ν_{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(1*H*)-ones 138a-h



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

4.6.1 Preparation of 6,8-bis(2-phenylethynyl)-2-phenyl-2,3-dihydroquinolin-4(1*H*)-ones 138a (R = H; R'' = -C_6H_5)

A stirred mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-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_3N (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 $CHCl_3$ (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; R_f (toluene) 0.42; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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) ν_{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 $[C_{31}H_{22}NO]^+$, requires 424.1701.

4.6.2 Preparation of 2-(4-fluorophenyl)-6,8-bis(2-phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one 138b (R = F; R'' = -C_6H_5)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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_3N (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, $CDCl_3$) δ: 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, $CDCl_3$) δ:46.0 (C-3), 56.9 (C-2), 83.1 (C≡α'), 88.2 (C≡α''), 88.4 (C≡β'), 96.8 (C≡β''), 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) ν_{max} 3366, 2215, 1678, 1592, 1499, 1224, 834, 751, 687 cm^{-1}; *m/z* (100, MH^+) 442; HRMS (EI): MH^+, found 442.1599. For $[C_{31}H_{22}NOF]^+$, requires 442.1607.

4.6.3 Preparation of 2-(4-chlorophenyl)-6,8-bis(2-phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one 138c (R = Cl; R'' = -C_6H_5)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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_3N (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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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-4'), 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 $[C_{31}H_{22}NOCl]^+$, requires 458.1312.

4.6.4 Preparation of 2-(4-methoxyphenyl)-6,8-bis(2-phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one 138d (R = OCH_3; R'' = -C_6H_5)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-one **122d** (0.40 g, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.034 g, 0.05 mmol) and CuI (0.10 g, 0.5 mmol) in EtOH/Et_3N (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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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) ν_{max} 3378, 3054, 2956, 2932, 2834, 2208, 1677, 1605, 1592, 1569, 1496, 1441, 1304, 1238, 1176, 1028, 898, 830, 752, 688 cm^{-1}; *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(1*H*)-one 138e (R = H; R' = -CH_2CH_2OH)

A stirred mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-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_3N (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, $CDCl_3$) δ: 1.95 (2H, br s, OH), 2.66-2.71 (4H, m, CH_2CH_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, CH_2CH_2), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.8 ($\underline{C}H_2CH_2OH$), 23.8 ($\underline{C}H_2CH_2OH$), 45.9 (C-3), 57.5 (C-2), 60.9 (CH_2OH), 61.2 (CH_2OH), 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) ν_{max} 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-dihydro quinolin-4(1*H*)-one 138f (R = F; R' = -CH_2CH_2OH)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-one **122b** (0.40 g, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol) and CuI (0.10 g, 0.5 mmol) in EtOH/Et_3N (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; R_f (40% ethyl acetate/toluene) 0.16; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.72 (2H, t, *J* 5.4 Hz, OH), 1.91 (2H, t, *J* 5.4 Hz, $C\underline{H}_2CH_2OH$), 2.62-2.69 (4H, m, CH_2CH_2), 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, $CH_2C\underline{H}_2OH$), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.7 ($\underline{C}H_2CH_2OH$)", 23.7 ($\underline{C}H_2CH_2OH$)'", 45.9 (C-3), 56.9 (C-2), 60.9 (CH_2OH) ", 61.2 (CH_2OH) '", 81.1 (C≡α) ", 85.0 (C≡α) '", 94.7 (C≡β) ", 110.1 (C≡β) '", 112.4 (C-8), 116.0 (d, $^3J_{CF}$ 21.6 Hz, C-3' & 5'), 118.0 (C-6), 128.2 (d, $^2J_{CF}$ 8.0 Hz, C-2' & 6'), 130.8 (C-5), 132.0 (C-4a), 136.3 (d, $^4J_{CF}$

3.2 Hz, C-1'), 140.3 (C-7), 151.0 (C-8a), 162.6 (d, $^{1}J_{CF}$ 245.9 Hz, C-4'), 192.0 (C-4); IR (neat) ν_{max} 3352, 2939, 2878, 2222, 1670, 1601, 1567, 1509, 1491, 1239, 1202, 1037, 1016, 841 cm^{-1}; *m/z* (100, MH^+) 378; HRMS (EI): MH^+, found 378.1509. For $[C_{23}H_{21}NO_3F]^+$ requires 378.1505.

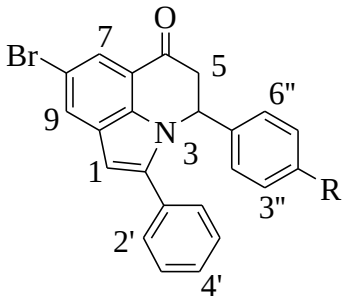
4.6.7 Preparation of 2-(4-chlorophenyl)-6,8-bis(4-hydroxybut-1-yn-1-yl)-2,3-dihydro quinolin-4(1*H*)-one 138g (R = Cl; R' = -CH_2CH_2OH)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-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_3N (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, $CDCl_3$) δ: 1.27 (1H, t, *J* 5.4 Hz, OH), 1.27 (1H, t, *J* 5.4 Hz, OH), 1.88 (2H, t, *J* 6.3 Hz, $C\underline{H}_2CH_2OH$) ", 2.53 (2H, t, *J* 6.3 Hz, $C\underline{H}_2CH_2OH$) '", 2.66 (2H, dd, *J* 4.5, 6.3 Hz, CH_2OH), 2.71 (1H, d, *J* 10.8 Hz, 3-H), 2.89 (1H, dd, *J* 12.3, 16.8 Hz, 3-H), 4.78 (1H, dd, *J* 6.0, 6.3 Hz, 2-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, $CDCl_3$) δ: 23.5 ($\underline{C}H_2CH_2OH$)", 23.7 ($\underline{C}H_2CH_2OH$)'", 45.7 (C-3), 56.9 (C-2), 60.7 (CH_2OH) ", 60.9 (CH_2OH) '", 81.0 (C≡α) ", 85.1 (C≡α) '", 94.9 (C≡β) ", 101.2 (C≡β) '", 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) ν_{max} 3341, 3277, 2929, 2856, 2226, 1659, 1601, 1489, 1277, 1239, 1206, 1041, 1016, 907, 827 cm^{-1}; *m/z* (100, MH^+) 394; HRMS (EI): MH^+, found 394.1212. For $[C_{23}H_{21}NO_3Cl]^+$ requires 394.1210.

4.6.8 Preparation of 2-(4-methoxyphenyl)-6,8-bis(4-hydroxybut-1-yn-1-yl)-2,3-dihydro quinolin-4(1*H*)-one 138h (R = OCH_3; R' = $-CH_2CH_2OH$)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-one **122d** (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_3N (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; R_f (40% ethyl acetate/toluene) 0.12; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.85 (2H, br s, OH), 2.60-2.66 (4H, m, CH_2CH_2), 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, CH_2CH_2), 3.80 (3H, s, OCH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.5 ($\underline{C}H_2CH_2OH$)", 23.8 ($\underline{C}H_2CH_2OH$)"', 45.9 (C-3), 55.4 (OCH_3), 57.0 (C-2), 60.9 (CH_2OH) ", 61.2 (CH_2OH) "', 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) ν_{max} 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-6*H*-pyrrolo[3,2,1-*ij*]quinolin-6-ones 139a-d



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

4.7.1 Preparation of 8-bromo-2,4-diphenyl-4,5-dihydro-6*H*-pyrrolo[3,2,1-*ij*]quinolinone 139a (R = H)

A mixture of **137a** (0.32 g, 0.7 mmol) and $PdCl_2$ (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 $CHCl_3$ (100 mL). The organic solvent was washed with brine, dried over anhydrous $MgSO_4$ 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; R_f (toluene) 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.18 (1H, d, *J* 13.8 Hz, 5-H *trans*), 3.65 (1H, dd, *J* 6.8, 9.3 Hz, 5-H *cis*), 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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) ν_{max} 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 $[C_{23}H_{17}NO^{79}Br]^+$, requires 402.0494.

4.7.2 Preparation of 8-bromo-4-(4-fluorophenyl)-2-phenyl-4,5-dihydro-6*H*-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. 007g, 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, $^2J_{CF}$ 21.6 Hz, C-3" & 5"), 119.3 (C-9a), 121.2 (C-1), 126.7 (d, $^3J_{CF}$ 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, $^4J_{CF}$ 3.2 Hz, C-1"), 138.9 (C-1'), 143.2 (C-3a), 162.2 (d, $^1J_{CF}$ 245.6 Hz, C-4"), 190.4 (C-6); IR (neat) ν_{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 $[C_{23}H_{16}NOF^{79}Br]^+$, requires 420.0399.

4.7.3 Preparation of 8-bromo-4-(4-chlorophenyl)-2-phenyl-4,5-dihydro-6*H*-pyrrolo[3,2,1-*ij*]quinolinone 139c (R = Cl)

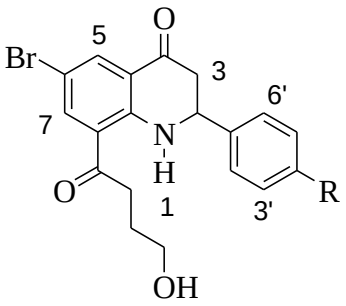
A mixture of **137c** (0.30 g, 0.6 mmol) and $PdCl_2$ (0.006 g, 0.03 mmol) in MeCN (15 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for 3 h. work up and column chromatography on silica gel described for **139a** afforded **139c** as yellow solid (0.21 g, 70%); mp 138-139 °C; R_f (toluene) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $[C_{23}H_{16}NOCl^{79}Br]^+$, requires 436.0104.

4.7.4 Preparation of 8-bromo-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-6*H*-pyrrolo[3,2,1-*ij*]quinolinone 139d (R = OCH_3)

A mixture of **137d** (0.3 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 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; R_f (toluene) 0.26; ^{1}H NMR (300 MHz, $CDCl_3$) 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, OCH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.9 (C-5), 55.1 (OCH_3), 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) ν_{max} 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 $[C_{24}H_{19}NO_2{}^{79}Br]^+$, requires 432.0599.

4.8 Preparation of 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1*H*)-ones 140a-d



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

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

A mixture of **137e** (0.30 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

8 h. The cooled reaction mixture was evaporated to dryness and the product dissolved in $CHCl_3$ (100 mL). The organic solvent was washed with brine, dried over anhydrous $MgSO_4$ 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; R_f (20% ethyl acetate/toluene) 0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.64 (1H, s, OH), 1.96 [2H, qt, *J* 6.0, 7.8 Hz, 8-(3yl-$CH_2C\underline{H}_2CH_2$)], 2.83-2.96 (2H, m, 3-H), 3.10 (2H, t, *J* 6.9 Hz, 8-2yl-CH_2), 3.73 (2H, t, *J* 6.0 Hz, 8-4yl-CH_2), 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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) ν_{max} 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 $[C_{19}H_{19}NO_3{}^{79}Br]^+$; requires 386.0392.

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

A stirred mixture of **137f** (0.30 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 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; R_f (20% ethyl acetate/toluene) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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, $^2J_{CF}$ 21.4 Hz, C-3' & 5'), 121.0 (C-4a), 121.7 (C-8), 128.1 (d, $^3J_{CF}$ 8.3 Hz, C-2' & 6'), 135.7 (d, $^4J_{CF}$ 3.0 Hz, C-1'), 136.2 (C-5), 140.2 (C-7), 151.0 (C-8a), 162.6 (d, $^1J_{CF}$ 245.9 Hz, C-4'), 191.0 (C-4), 201.7 (C-1yl); IR (neat) ν_{max} 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 $[C_{19}H_{18}NO_3F^{79}Br]^+$, requires 406.0436.

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

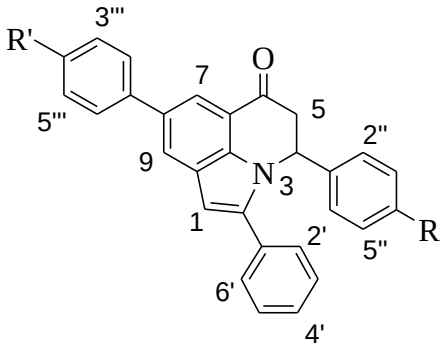
A stirred mixture of **137g** (0.50 g, 1.6 mmol) and $PdCl_2$ (0. 014 g, 0.08 mmol) in MeCN (25 mL) in a three-necked round bottom flask equipped with a stirrer, condenser and rubber septum was purged with nitrogen gas for 20 minutes, then heated at 90 °C under nitrogen gas atmosphere for 8 h. Treated 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; R_f (20% ethyl acetate/toluene) 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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) ν_{max} 3374, 3301, 2962, 2934, 2904, 2869, 1686, 1644, 1563, 1485, 1398,

1325, 1228, 1122, 1088, 116, 891, 851, 640 cm^{-1}; *m/z* (100, MH^+) 422; HRMS (EI): MH^+, found 422.0159. For $[C_{19}H_{18}NO_3Cl^{79}Br]^+$, requires 422.0139.

4.8.4 Preparation of 6-bromo-2-(4-methoxyphenyl)-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1*H*)-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; ^1H NMR (300 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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) ν_{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 $[C_{20}H_{21}NO_4{}^{79}Br]^+$, reqiures 416.0494.

4.9 Preparation of 8-substituted 4-aryl-2-phenyl-4,5-dihydro-6*H*-pyrrolo[3,2,1-*ij*]quinolin-6-ones 141a-f



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

4.9.1 Preparation of 8-(4-fluorophenyl)-2,4-diphenyl-4,5-dihydro-6*H*-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), $PdCl_2(PPh_3)_2$ (0.01g, 0.01 mmol), PCy_3 (0.01 g, 0.03 mmol) and K_2CO_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. The cooled reaction mixture was mixed with cold water (20 mL) and the product was extracted into $CHCl_3$ (3x30 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ 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; R_f (20% ethyl acetate/toluene) 0.78; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.22 (1H, d, *J* 16.2 Hz, 5-H *trans*), 3.73 (1H, dd, *J* 6.9, 9.3 Hz, 5-H *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); ^{13}C NMR (75 MHz, $CDCl_3$) δ:

46.0 (C-5), 57.1 (C-4), 103.8 (C-8), 115.6 (d, $^{2}J_{CF}$ 21.3 Hz, C-3''' & 5'''), 117.8 (C-6a), 118.6 (C-2' & 6'), 125.1 (d, $^{3}J_{CF}$ 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, $^{4}J_{CF}$ 3.0 Hz, C-1'''), 140.0 (C-4'), 140.4 (C-4''), 142.8 (C-10a), 162.2 (d, $^{1}J_{CF}$ 244.4 Hz, C-4'''), 191.8 (C-6); IR (neat) ν_{max} 3062, 3027, 2976, 2910, 1667, 1599, 1512, 1467, 1451, 1320, 1297, 1251, 1215, 1160, 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-6*H*-pyrrolo[3,2,1-*ij*]quinolinone 141b (R = F, R' = F)

A mixture of **139b** (0.15 g, 0.3 mmol), 4-$FC_6H_4B(OH)_2$ (0.06 g, 0.4 mmol), $PdCl_2(PPh_3)_2$ (0.01g, 0.01 mmol), PCy_3 (0.01 g, 0.03 mmol) and K_2CO_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, $CDCl_3$) δ: 3.17 (1H, d, *J* 16.8 Hz, 5-H *trans*), 3.72 (1H, dd, *J* 7.5, 9.3 Hz, 5-H *cis*), 6.00 (1H, d, *J* 6.0 Hz, 4-H), 6.52 (2H, dd, *J* 3.0, 5.4 Hz, 3''' & 5'''-H), 6.68 (1H, s, 1-H), 6.80 (2H, t, *J* 9.3 Hz, 3'' & 5''-H), 7.14 (2H, t, *J* 9.3 Hz, 2'' & 6''-H), 7.39 (5H, s, Ph'-H), 7.62 (2H, dd, *J* 3.0, 5.4 Hz, 2''' & 6'''-H), 7.91 (1H, d, *J* 1.8 Hz, 9-H), 8.05 (1H, d, *J* 1.8 Hz, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.0 (C-5), 56.6 (C-4), 104.0 (C-8), 115.7 (d, $^{2}J_{CF}$ 21.3 Hz, C-3''' & 5'''), 115.9 (d, $^{2}J_{CF}$ 21.3 Hz, C-3'' & 5''), 118.0 (C-10), 118.5 (C-6a), 125.3 (C-1), 126.8 (d, $^{3}J_{CF}$ 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, $^{3}J_{CF}$ 8.0 Hz, C-2'' & 6''), 131.4 (C-2), 135.6 (C-1'), 136.2 (d, $^{4}J_{CF}$ 3.5 Hz, C-1''), 137.6 (d, $^{4}J_{CF}$ 3.5 Hz, C-1'''),

139.9 (C-4'), 142.7 (C-10a), 162.2 (d, $^{1}J_{CF}$ 245.2 Hz, C-4"), 162.3 (d, $^{1}J_{CF}$ 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, 944, 890, 835, 758, 747, 619 cm^{-1}; *m/z* (100, MH^{+}) 436; HRMS (EI): MH^{+}, found 436.1513. For, $[C_{29}H_{20}NOF_2]^{+}$, requires 436.1518.

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

A mixture of **139c** (0.08 g, 0.1 mmol), 4-$FC_6H_4B(OH)_2$ (0.03 g, 0.2 mmol), $PdCl_2(PPh_3)_2$ (0.005g, 0.005 mmol), PCy_3 (0.005 g, 0.01 mmol) and K_2CO_3 (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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.0 (C-5), 56.6 (C-4), 104.1 (C-8), 114.0 (C-10), 115.6 (d, $^{2}J_{CF}$ 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, $^{3}J_{CF}$ 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, $^{4}J_{CF}$ 3.2 Hz, C-1'"), 137.9 (C-1"), 138.9 (C-4'), 139.9 (C-4"), 142.7 (C-10a), 162.3 (d, $^{1}J_{CF}$ 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-6*H*-pyrrolo[3,2,1-*ij*]quinolinone 141d (R = OCH_3, R' = F)

A mixture of **139d** (0.10 g, 0.2 mmol), 4-$FC_6H_4B(OH)_2$ (0.04 g, 0.3 mmol), $PdCl_2(PPh_3)_2$ (0.008g, 0.01 mmol), PCy_3 (0.007 g, 0.02 mmol) and K_2CO_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, $^2J_{CF}$ 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, $^3J_{CF}$ 8.0 Hz, C-2"' & 6"'), 131.6 (C-9), 132.5 (C-2), 133.3 (C-1' & 1"), 137.7 (d, $^4J_{CF}$ 3.2 Hz, C-1"'), 139.9 (C-4'), 142.7 (C-10a), 159.0 (C-4"), 162.3 (d, $^1J_{CF}$ 244.2 Hz, C-4"'), 192.0 (C-6); IR (neat) ν_{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 $[C_{30}H_{23}NO_2F]^+$, requires 448.1710.

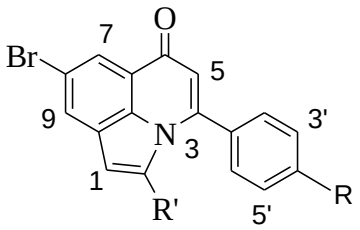
4.9.5 Preparation of 8-(4-methoxyphenyl)-2,4-diphenyl-4,5-dihydro-6*H*-pyrrolo[3,2,1-*ij*]quinolinone 141e (R = H, R' = OCH_3)

A mixture of **139a** (0.15 g, 0.4 mmol.), 4-OMePhB$(OH)_2$ (0. 07 g, 0.4 mmol.), $PdCl_2(PPh_3)_2$ (0.013g, 0.02 mmol), PCy_3 (0.01 g, 0.2 mmol) and K_2CO_3 (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; R_f (20% ethyl acetate/toluene) 0.77; ^{1}H NMR (300 MHz, $CDCl_3$) 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, OCH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.1 (C-5), 55.4 (OCH_3), 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) ν_{max} 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, $[C_{30}H_{24}NO_2]^+$, requires 430.1807.

4.9.6 Preparation of 4-(4-chlorophenyl)-8-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-6*H*-pyrrolo[3,2,1-*ij*]quinolinone 141f (R = Cl, R' = OCH_3)

A mixture of **139c** (0.10 g, 0.2 mmol), 4-OMePhB$(OH)_2$ (0.04 g, 0.2 mmol), $PdCl_2(PPh_3)_2$ (0.007g, 0.01 mmol), PCy_3 (0.005 g, 0.02 mmol) and K_2CO_3 (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; R_f (20% ethyl acetate/toluene) 0.80; ^{1}H NMR (300 MHz, $CDCl_3$) 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, OCH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.9 (C-5), 55.4 (OCH_3), 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) ν_{max} 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 $[C_{30}H_{23}NO_2Cl]^+$, requires 464.1417.

4.10 Preparation of 2-substituted 4-aryl-8-bromo-6-oxopyrrolo[3,2,1-*ij*]quinoline derivatives 142a-h



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' = -C_6H_5)

A stirred mixture of 6,8-dibromo-2-phenylqunolin-4(1*H*)-one **136a** (0.25 g, 0.7 mmol), 10% Pd/C (0.008 g, 0.007 mmol), PPh_3 (0.007 g, 0.03 mmol), CuI (0.013 g, 0.07 mmol) and Et_3N (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 $CHCl_3$ (3x60 mL). The combined organic layers were washed with brine (2x10 mL), dried with anhydrous $MgSO_4$ 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; R_f 0.37 (20% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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): $\nu_{(max)}$ 3080, 3057, 1635, 1613, 1590, 1456, 1349,1267, 996, 875, 841, 757, 692,

661 cm^{-1}; *m/z* (100, M+H) 400; HRMS (ES): MH^+, found 400.0337. Calculated for $[C_{23}H_{15}{}^{79}BrNO]^+$: requires, 400.0327.

4.10.2 Preparation of 8-bromo-4-(4-fluorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1-*ij*]quinoline 142b (R = F; R' = -C_6H_5)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromoqunolin-4(1*H*)-one **136b** (0.25 g, 0.6 mmol), 10% Pd/C (0.007 g, 0.006 mmol), PPh_3 (0.006 g, 0.02 mmol), CuI (0.013 g, 0.06 mmol) and Et_3N (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; R_f 0.48 (20% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 110.8 (C-5), 114.8 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 8.8 Hz, C-2' & 6'), 129.4 (2-Ph, C-1), 130.6 (C-7), 131.0 (d, $^4J_{CF}$ 3.7 Hz, C-1'), 131.7 (C-9), 135.4 (C-2), 143.2 (C-4), 148.9 (C-3a), 163.1 (d, $^1J_{CF}$ 249.2 Hz, C-4'), 178.8 (C-6); IR (neat): $\nu_{(max)}$ 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 $[C_{23}H_{14}F^{79}BrNO]^+$: 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' = -C_6H_5)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromoqunolin-4(1*H*)-one **136c** (0.25 g, 0.6 mmol), 10% Pd/C (0.007 g, 0.006 mmol), PPh_3 (0.006 g, 0.02 mmol), CuI (0.013 g, 0.06 mmol) and Et_3N (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; R_f 0.54 (20% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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): $\nu_{(max)}$ 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 $[C_{23}H_{14}Cl^{79}BrNO]^+$: requires, 435.0869.

4.10.4 Preparation of 8-bromo-4-(4-methoxyphenyl)-2-phenyl-6-oxopyrrolo[3,2,*ij*]quinoline 142d (R = OCH_3; R' = -C_6H_5)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromoqunolin-4(1*H*)-one **136d** (0.25 g, 0.6 mmol), 10% Pd/C (0.007 g, 0.006 mmol), PPh_3 (0.006 g, 0.02 mmol), CuI (0.013 g, 0.06 mmol) and Et_3N (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; R_f 0.20

(20% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.71 (3H, s, OCH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3 (OCH_3), 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): $\nu_{(max)}$ 3079, 3055, 2996, 2933, 2834, 1636, 1600, 1505, 1459, 1399, 1269, 1175, 828, 759, 691 cm^{-1}; *m/z* (100, M+H) 430; HRMS (ES): MH^+, found 430.0443. Calculated for $[C_{24}H_{17}{}^{79}BrNO_2]^+$: 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' = -CH_2CH_2OH)

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_3N (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 $CHCl_3$ (3x60 mL). The combined organic layers were washed with brine (2x10 mL), dried with anhydrous $MgSO_4$ 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; R_f 0.25 (50% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.74 (1H, t, *J* 5.4 Hz, OH), 2.37 (2H, t, *J* 6.2 Hz, C$\underline{H}_2$$CH_2$), 3.66 (2H, dd, *J* 4.5, 6.2 Hz, C$\underline{H}_2$OH), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.2 (CH_2), 60.4 (CH_2OH), 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): $\nu_{(max)}$ 3484, 3150, 3063, 2922, 1633, 1588, 1461, 1408, 1276, 1223, 1066, 1046, 1002, 885, 850, 775, 703, 669 cm^{-1}; *m/z* (100, M+H) 368; HRMS (ES): MH^+, found 368.0285. Calculated for $[C_{19}H_{15}{}^{79}BrNO_2]^+$: 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' = -CH_2CH_2OH)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromoquinolin-4(1*H*)-one **136b** (0.56 g, 1.4 mmol), $PdCl_2(PPh_3)_2$ (0.06 g, 0.07 mmol), CuI (0.028 g, 0.1 mmol) and Et_3N (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; R_f 0.30 (50% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.80 (1H, t, *J* 5.4 Hz, OH), 2.83 (2H, t, *J* 6.0 Hz, C$\underline{H}_2$CH_2), 3.71 (2H, dd, *J* 3.0, 6.3 Hz, C$\underline{H}_2$OH), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.7 (C$\underline{H}_2$CH_2), 59.1 C$\underline{H}_2$OH), 108.7 (C-5), 116.3 (d, $^2J_{CF}$ 21.9 Hz, C-3' & 5'), 117.8 (C-2), 118.1 (C-8), 122.6 (C-1) 128.5 (d, $^3J_{CF}$ 8.0 Hz, C-2' & 6'), 130.4 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 245.9 Hz, C-4'), 177.7 (C-6); IR (neat): $\nu_{(max)}$ 3351, 3058, 2955, 2925, 1632, 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 $[C_{19}H_{14}F^{79}BrNO_2]^+$: 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' = -CH_2CH_2OH)

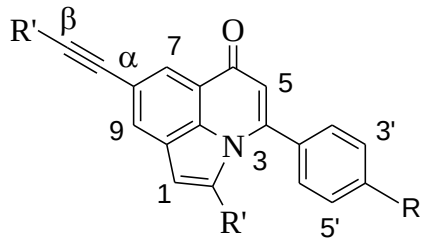
A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromoquinolin-4(1*H*)-one **136c** (0.4 g, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.034 g, 0.05 mmol), CuI (0.02 g, 0.1 mmol) and Et_3N (0.6 mL, 4.0 mmol) in DMF/water (30 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.30 mL, 3.0 mmol) was added and the mixture 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; R_f 0.32 (50% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.83 (1H, broad s, OH), 2.40 (2H, t, *J* 6.2 Hz, C$\underline{H}_2$CH_2), 3.73 (2H, br s, C$\underline{H}_2$OH), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.3 ($\underline{C}H_2CH_2$), 60.2 ($\underline{C}H_2OH$), 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): $\nu_{(max)}$ 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 $[C_{19}H_{14}{}^{79}ClBrNO_2]^+$: 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 = OCH_3; R' = -CH_2CH_2OH)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromoquinolin-4(1*H*)-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_3N (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; R_f 0.16 (50% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.05 (1H, t, *J* 4.5 Hz, OH), 2.47 (2H, t, *J* 6.0 Hz, C<u>H</u>$_2$CH$_2$), 3.72 (2H, dd, *J* 4.5, 6.0 Hz, C<u>H</u>$_2$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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.4 (<u>C</u>H$_2$CH$_2$), 55.4 (OCH_3), 60.3 (<u>C</u>H$_2$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_6H_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_3N (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 $CHCl_3$ (3x50 mL). The combined organic layers were washed with brine (2x20 mL); dried with anhydrous $MgSO_4$ 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; R_f 0.70 (20% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C 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): $\nu_{(max)}$ 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 $[C_{31}H_{20}NO]^+$: 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' = -C_6H_5)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromoquinolin-4(1*H*)-one **136b** (0.56 g, 1.4 mmol), $PdCl_2(PPh_3)_2$ (0.06 g, 0.07 mmol), CuI (0.028 g, 0.1 mmol) and Et_3N (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; R_f 0.30 (50% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 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): $\nu_{(max)}$ 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-*ij*]quinoline 143c (R = Cl; R' = -C_6H_5)

A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromoquinolin-4(1*H*)-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_3N (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"), 123.0 (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'),

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): $\nu_{(max)}$ 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' = $-C_6H_5$)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromoquinolin-4(1*H*)-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_3N (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); ^1H NMR (300 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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): $\nu_{(max)}$ 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' = -CH_2CH_2OH)

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_3N (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 $CHCl_3$ (3x60 mL). The combined organic layers were washed with brine (2x10 mL), dried with anhydrous $MgSO_4$ 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; R_f 0.20 (50% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.18 (2H, t, *J* 6.0 Hz, C$\underline{H}_2$CH_2'), 2.61 (2H, t, *J* 6.0 Hz, C$\underline{H}_2$CH_2'"), 3.47 (2H, dd, *J* 6.0, 6.3 Hz, C$\underline{H}_2$OH'), 3.63 (2H, dd, *J* 6.0, 6.3 Hz, C$\underline{H}_2$OH'"), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C$\underline{H}_2$CH_2'), 32.6 (C$\underline{H}_2$CH_2'"), 59.2 (C$\underline{H}_2$OH'), 60.3 (C$\underline{H}_2$OH'"), 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): $\nu_{(max)}$ 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 $[C_{23}H_{20}NO_3]^+$: 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' = -CH_2CH_2OH)

A stirred mixture of 2-(4-fluorophenyl)-6,8-dibromoquinolin-4(1*H*)-one **136b** (0.56 g, 1.4 mmol), $PdCl_2(PPh_3)_2$ (0.06 g, 0.07 mmol), CuI (0.028 g, 0.1 mmol) and Et_3N (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; R_f 0.24 (50% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.19 (2H, t, *J* 6.0 Hz, C$\underline{H}_2$CH_2'), 2.61 (2H, t, *J* 6.0 Hz,C$\underline{H}_2$CH_2'"), 3.50 (2H, dd, *J* 6.0, 7.8 Hz, C$\underline{H}_2$OH'), 3.64 (2H, dd, *J* 6.0, 7.8 Hz, C$\underline{H}_2$OH'"), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 ($\underline{C}H_2CH_2$'), 32.7 ($\underline{C}H_2CH_2$'"), 59.2 ($\underline{C}H_2$OH'), 60.3 ($\underline{C}H_2$OH'"), 81.5 (C≡α), 89.0 (C≡β), 109.1 (C-5), 116.3 (d, $^2J_{CF}$ 21.7 Hz, C-3" & 5"), 117.9 (C-8), 121.9 (C-9a), 123.7 (C-1), 128.7 (d, $^3J_{CF}$ 8.0 Hz, C-2" & 6"), 130.2 (C-6a), 130.5 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 246.2 Hz, C-4"), 178.1 (C-6); IR (neat): $\nu_{(max)}$ 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 $[C_{23}H_{19}FNO_3]^+$: 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' = -CH_2CH_2OH)

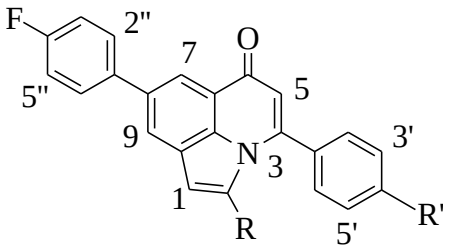
A stirred mixture of 2-(4-chlorophenyl)-6,8-dibromoquinolin-4(1*H*)-one **136c** (0.40 g, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.034 g, 0.05 mmol), CuI (0.020 g, 0.1 mmol) and Et_3N (0.5 mL, 3.9 mmol) in DMF/water (30 mL) was purged with argon for 1 h. 3-Butyn-1-ol (0.3 mL, 2.9 mmol) was added and the mixture 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; R_f 0.25 (50% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.10 (2H, t, *J* 6.0 Hz, C$\underline{H}_2$CH_2'), 2.60 (2H, t, *J* 6.0 Hz, C$\underline{H}_2$CH_2'"), 3.51 (2H, dd, *J* 6.0, 7.8 Hz, C$\underline{H}_2$OH'), 3.63 (2H, dd, *J* 6.0, 7.8 Hz, C$\underline{H}_2$OH'"), 4.71 (1H, t, *J* 5.4 Hz, OH'), 4.98 (1H, t, *J* 5.4 Hz, OH'"), 6.04 (1H, s, 1-H), 6.78 (1H, s, 5-H), 7.64 (2H, t, *J* 7.5 Hz, 3" & 5"-H), 7.65 (2H, dd, *J* 7.5 Hz, 2" & 6"-H), 7.88 (1H, s, 9-H), 7.98 (1H, s, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C$\underline{H}_2$CH_2'), 32.7 (C$\underline{H}_2$CH_2'"), 59.2 (C$\underline{H}_2$OH'), 60.3 (C$\underline{H}_2$OH'"), 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): $\nu_{(max)}$ 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 $[C_{23}H_{19}ClNO_3]^+$: 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 = OCH_3; R' = -CH_2CH_2OH)

A stirred mixture of 2-(4-methoxyphenyl)-6,8-dibromoquinolin-4(1*H*)-one **136d** (0.50 g, 1.2 mmol), $PdCl_2(PPh_3)_2$ (0.043 g, 0.06 mmol), CuI (0.023 g, 0.1 mmol) and Et_3N (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); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.57 (2H, t, *J* 6.3 Hz, C$\underline{H}_2$CH$_2$'), 2.60 (2H, t, *J* 6.3 Hz, C$\underline{H}_2$CH$_2$'"), 3.49 (2H, d, *J* 4.5 Hz, C$\underline{H}_2$OH'), 3.63 (2H, d, *J* 4.5 Hz, C$\underline{H}_2$OH'"), 3.85 (3H, s, OCH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C$\underline{H}_2$CH$_2$'), 32.8 (C$\underline{H}_2$CH$_2$'"), 55.9 (OCH_3), 59.2 (C$\underline{H}_2$OH'), 60.3 (C$\underline{H}_2$OH'"), 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): $\nu_{(max)}$ 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 $[C_{24}H_{22}NO_4]^+$: 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 = -C_6H_5; 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), $PdCl_2(PPh_3)_2$ (0.013 g, 0.02 mmol), PCy_3 (0.011 g, 0.04 mmol) and K_2CO_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. The cooled reaction mixture was mixed with cold water (20 mL) and the product was extracted into $CHCl_3$ (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; R_f (20% ethyl acetate/hexane) 0.64; ^{1}H NMR (300 MHz, $CDCl_3$) δ: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 111.8 (C-5), 115.9 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 8.0 Hz, C-2"' & 6"'),129.2 (C-9), 129.6 (C-1), 130.1 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 245.3 Hz, C-4"'), 180.1 (C-6); IR (neat): $\nu_{(max)}$ 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 $[C_{29}H_{19}FNO]^+$: requires, 416.1451.

4.12.2 Preparation of 4,8-bis(4-fluorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1-*ij*]quinoline 144b (R = -C_6H_5; 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_2CO_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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 111.8 (C-5), 114.9 (d, $^2J_{CF}$ 21.6 Hz, C-3" & 5"), 115.4 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 8.0 Hz, C-2" & 6"), 129.3 (d, $^3J_{CF}$ 8.0 Hz, C-2"' & 6"'), 129.4 (C-4'), 129.5 (C-8), 131.1 (d, $^4J_{CF}$ 3.2 Hz, C-1") 131.2 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 247.5 Hz, C-4"), 163.1 (d, $^1J_{CF}$ 247.5 Hz, C-4"), 180.0 (C-6); IR (neat): $\nu_{(max)}$ 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 $[C_{29}H_{18}F_2NO]^+$: requires, 434.1356.

4.12.3 Preparation of 4-(4-chloropheenyl)-8-(4-fluorophenyl)-2-phenyl-6-oxopyrrolo[3,2,1-*ij*]quinoline derivative 144c (R = -C_6H_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 K_2CO_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 **144c** as light yellow solid, (0.096 g, 62%); mp 276-278 °C; R_f 0.68 (20% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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): $\nu_{(max)}$ 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 $[C_{29}H_{18}FClNO]^+$: 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 = -C_6H_5; R' = OCH_3)

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), $PdCl_2(PPh_3)_2$ (0.013 g, 0.02 mmol), PCy_3 (0.010 g, 0.03 mmol) and K_2CO_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 **144d** as light yellow solid, (0.116 g, 63%); mp 232-234 °C; R_f 0.48 (20% ethyl acetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.71 (3H, s, OCH_3), 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*

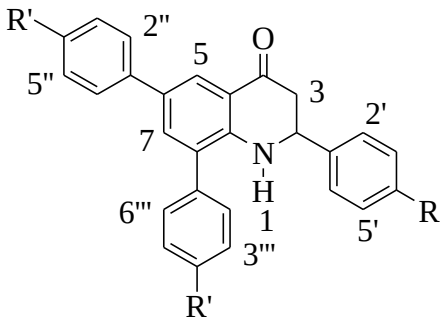
3.0, 6.0 Hz, 2''' & 6'''), 8.09 (1H, s, 9-H), 8.41 (1H, s, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3 (OCH_3), 111.7 (C-5), 113.2 (C-3' & 5'), 115.8 (d, $^2J_{CF}$ 21.4 Hz, C-3''' & 5'''), 117.8 (C-2), 121.0 (C-9a), 122.6 (C-8), 124.9 (C-2' & 6"), 125.5 (C-4'), 127.6 (C-2' & 6'), 127.7 (C-3' & 5'), 128.4 (C-6), 129.3 (d, $^3J_{CF}$ 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, $^4J_{CF}$ 3.4 Hz, C-1'''), 137.8 (C-1'), 142.9 (C-4), 149.8 (C-3a), 160.3 (C-4"), 162.6 (d, $^1J_{CF}$ 245.3 Hz, C-4'''), 180.2 (C-6); IR (neat): $\nu_{(max)}$ 3080, 3052, 2960, 2931, 2836, 1636, 1597, 1507, 1461, 1401, 1286, 1246, 1201, 1179, 1035, 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_2CH_2OH; 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_2CO_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, C$\underline{H}_2$$CH_2$), 3.68 (2H, q, *J* 4.5, 6.0 Hz, C$\underline{H}_2$OH), 6.24 (1H, s, 1-H), 6.72 (1H, s, 5-H), 7.16 (2H, t, *J* 8.4 Hz, 3" & 5"-H), 7.49-7.56 (5H, m, Ph'-H), 7.64 (2H, dd, *J* 3.6, 6.0 Hz, 2" & 6"), 7.97 (1H, s, 9-H), 8.29 (1H, s, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.2 (C$\underline{H}_2$$CH_2$), 60.5 (C$\underline{H}_2$OH), 109.9 (C-5), 115.9 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 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, $^4J_{CF}$ 3.2 Hz, C-1"), 137.0

(C-4'), 140.5 (C-4), 148.9 (C-3a), 162.6 (d, $^{1}J_{CF}$ 245.3 Hz, C-4"), 179.8 (C-6); IR (neat): $\nu_{(max)}$ 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(1*H*)-ones 145a-h



2,6,8-Triaryl-2,3-dihydroquinolin-4(1*H*)-ones 145a-h

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

A stirred mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-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, $CDCl_3$) δ: 2.84 (1H, ddd, *J* 1.5, 4.5 and 16.3 Hz, 3-H), 2.95 (1H, dd, *J* 13.1 and 16.3 Hz, 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, 4′′′-H, 5′-H, 5′′-H, 5′′′-H, 6′-H and 6′′-H), 7.60-7.63 (3H, m, 2′′′-H, 6′′′-H and 7-H), 8.21 (1H, d, *J* 3.0 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.5 (C-3), 58.3 (C-2), 115.6 (C-8), 119.4 (C-4a), 125.0 (C-2′ and C-6′), 126.4 (C-6), 126.9 (C-4′′), 128.1 (C-2′′ and C-6′′), 128.3 (C-2′′′ and C-6′′′), 128.8 (C- 4′′′), 129.0 (C-3′ and C-5′), 129.1 (C-3′′′ and C-5′′′), 129.3 (C-3′′ and C-5′′), 129.5 (C-5), 130.9 (C-7), 134.8 (C-4′), 137.5 (C-1′), 139.9 (C-1′′′), 141.0 (C-1′′), 148.0 (C-8a), 193.3 (C-4); IR (neat): ν_{max} 3380, 2134, 2098, 1675, 1600, 1575, 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(1*H*)-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_2CO_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, $CDCl_3$) δ: 2.82 (1H, ddd, *J* 1.5, 4.5 and 16.3 Hz, 3-H), 2.92 (1H, dd, *J* 12.9 and 16.3 Hz, 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, 3′′′-H, 4′′-H, 4′′′-H, 5′-H, 5′′-H, 5′′′-H, 6′-H), 7.60-7.63 (3H, m, 2′′-H and 6′′-H, 7-H), 8.20 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.5 (C-3), 57.6 (C-2), 115.8 (C-8), 116.0 (d, $^{2}J_{CF}$ 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, $^{3}J_{CF}$ 8.3 Hz, C-2′ and C-6′), 128.2 (C-4′′′), 129.1 (C-

3‴ and C-5‴), 129.3 (C-3″ and C-5″), 129.5 (C-5), 131.2 (C-7), 136.8 (d, $^{4}J_{CF}$ 3.0 Hz, C-1′), 137.4 (C-1‴), 139.8 (C-1″), 147.8 (C-8a), 162.5 (d, $^{1}J_{CF}$ 246.0 Hz, C-4′), 193.1 (C-4); IR (neat): ν_{max} 3381, 3056, 2923, 2652, 2113, 1681, 1600, 1481, 1350, 1321, 1270, 1232, 1157, 905, 868 cm^{-1}.

4.13.3 Preparation of 2-(4-chlorophenyl)-6,8-bisphenyl-2,3-dihydroquinolin-4(1*H*)-one 145c (R = Cl, R′ = 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_2CO_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, $CDCl_3$) δ: 2.87 (1H, dd, *J* 4.5 and 16.2 Hz, 3-H), 2.91 (1H, dd, *J* 12.3 and 16.2 Hz, 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, 3‴-H, 4″-H, 4‴-H, 5′-H, 5″-H, 5‴-H, 6″-H, and 7-H), 8.18 (1H, d, *J* 2.7 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.3 (C-3), 57.6 (C-2), 115.1 (C-8), 119.5 (C-4a), 125.0 (C-2′ and C-6′), 126.4 (C-6), 127.0 (C-4″), 127.8 (C-2″ and C-6″), 128.2 (C-2‴ and C-6‴), 128.8 (C-4‴), 129.1 (C-3′ and C-5′), 129.3 (C-3‴ and C-5‴), 129.6 (C-3″ and C-5″), 131.2 (C-5), 134.1 (C-7), 134.9 (C-4′), 137.4 (C-1′), 139.5 (C-1‴), 139.8 (C-1″), 147.7 (C-8a), 192.9 (C-4); IR (neat): ν_{max} 3744, 3373, 2086, 1666, 1611, 1479, 1409, 1358, 1312, 1274, 1231, 1143, 1086, 897, 865 cm^{-1}.

4.13.4 Preparation of 6,8-bisphenyl-2(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one 145d (R = OCH_3, 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), $PdCl_2(PPh_3)_2$ (0.085 g, 0.1 mmol), PCy_3 (0.068 g, 0.2 mmol) and K_2CO_3 (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%); R_f (30% ethyl acetate/ hexane) 0.63; mp 194-196 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.80 (1H, ddd, *J* 1.5, 4.5 and 16.2 Hz, 3-H), 2.93 (1H, dd, *J* 12.3 and 16.2 Hz, 3-H), 3.79 (3H, s, $COCH_3$), 4.66 (1H, dd, *J* 4.5 and 9.6 Hz, 2-H), 4.78 (1H, s, N-H), 6.89 (2H, d, *J* 9.0 Hz, 2′′′-H and 6′′′-H), 7.25-7.51 (10H, m, 2′-H, 3′-H, 3′′-H,3′′′-H, 4′′-H, 4′′′-H, 5′-H, 5′′-H, 5′′′-H, 6′-H), 7.59-7.63 (3H, m, 2′′-H and 6′′-H, 7H), 8.19 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.6 (C-3), 55.0 (OCH_3), 57.7 (C-2), 114.3 (C-8), 119.4 (C-4a), 125.0 (C-2′ and C-6′), 126.4 (C-6), 126.8 (C-4′′), 127.6 (C-2′′ and C-6′′), 128.1 (C-2′′′ and C-6′′′), 128.8 (C-4′′′), 129.1 (C-3′ and C-5′), 129.2 (C-3′′′ and C-5′′′), 129.5 (C-3′′ and C-5′′), 130.8 (C-5), 133.0 (C-7), 134.8 (C-4′), 137.5 (C-1′), 139.9 (C-1′′′), 148.0 (C-1′′), 159.5 (C-8a), 193.5 (C-4); IR (neat): ν_{max} 3744, 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(1*H*)-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), $PdCl_2(PPh_3)_2$ (0.09 g, 0.1 mmol), PCy_3 (0.073 g, 0.2 mmol) and K_2CO_3 (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%);

R_f (30% ethyl acetate/ hexane) 0.70; mp 167-169 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.84 (1H, ddd, *J* 1.5, 4.5 and 16.2 Hz, 3-H), 2.94 (1H, dd, *J* 12.9 and 16.2 Hz, 3-H), 4.71 (1H, t, *J* 8.0 Hz, 2-H), 4.74 (1H, s, N-H), 7.07-7.19 (4H, m, 2′-H, 3′-H, 5′-H, 6′-H), 7.32-7.39 (5H, m, 2″-H, 3″-H, 4′-H, 5″-H, 6″), 7.43-7.58 (5H, m, 2‴-H, 3‴-H, 5‴-H, 6‴-H, 7-H), 8.13 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.4 (C-3), 58.2 (C-2), 115.6 (d, $^2J_{CF}$ 21.4 Hz, C-3″ and C-5″), 115.8 (d, $^2J_{CF}$ 21.4 Hz, C-3‴ and C-5‴), 119.5 (C-4a), 125.0 (C-2′ and C-6′), 126.3 (C-6), 128.1 (C-8), 129.0 (C-5), 129.1 (C-3′ and C-5′), 130.1 (C-7), 130.8 (d, $^3J_{CF}$ 7.5 Hz, C-2‴ and C-6‴), 130.9 (d, $^3J_{CF}$ 7.5 Hz, C-2″ and C-6″), 133.2 (C-4′), 134.6 (d, $^4J_{CF}$ 3.0 Hz, C-1‴), 135.9 (d, $^4J_{CF}$ 3.0 Hz, C-1″), 140.8 (C-1′), 147.9 (C-8a), 162.2 (d, $^1J_{CF}$ 240 Hz, C-4‴), 162.6 (d, $^1J_{CF}$ 247.5 Hz, C-4″), 193.1 (C-4); IR (neat): ν_{max} 3376, 2924, 2853, 1669, 1603, 1482, 1360, 1220, 1144, 1014, 903, 832, 765, 701,602 cm^{-1}.

4.13.6 Preparation of 2,6,8-tris(4-fluorophenyl)-2,3-dihydroquinolin-4(1*H*)-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), $PdCl_2(PPh_3)_2$ (0.088 g, 0.1 mmol), PCy_3 (0.070 g, 0.2 mmol) and K_2CO_3 (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%); R_f (30% ethyl acetate/ hexane) 0.70; mp 176-178 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 2.81 (1H, ddd, *J* 1.5, 4.5 and 16.2 Hz, 3-H), 2.91 (1H, dd, *J* 12.9 and 16.2 Hz, 3-H), 4.64 (1H, s, N-H), 4.69 (1H, dd, *J* 4.5 and 7.8 Hz, 2-H), 7.02-7.10 (4H, m, 2′-H, 3′-H, 5′-H, 6′-H), 7.12-7.20 (2H, m, 3″-H and 5″-H), 7.36 (2H, dd, *J* 3.6 and 5.3 Hz, 2″-H and 6″-H), 7.46 (2H, dd, *J* 3.0 and 5.4 Hz, 3‴-H and 5‴-H), 7.50-7.57 (3H, m, 2‴-H and 6‴-H, 7-H), 8.12 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.4 (C-3), 57.6 (C-2), 115.8 (C-8), 116.0 (d, $^2J_{CF}$ 21.6 Hz, C-3′ and C-5′),

116.0 (d, $^{2}J_{CF}$ 21.4 Hz, C-3″ and C-5″), 116.0 (d, $^{2}J_{CF}$ 21.4 Hz, C-3‴ and C-5‴), 119.5 (C-4a), 125.3 (C-6), 128.0 (d, $^{3}J_{CF}$ 7.5 Hz, C-2′ and C-6′),129.0 (C-5), 130.9 (d, $^{3}J_{CF}$ 7.5 Hz, C-2″ and C-6″), 133.2 (d, $^{3}J_{CF}$ 8.3 Hz, C-2‴ and C-6‴), 133.3 (C-4′), 134.7 (C-7), 135.7 (d, $^{4}J_{CF}$ 3.0 Hz, C-1″), 135.8 (d, $^{4}J_{CF}$ 3.0 Hz, C-1‴), 136.6 (d, $^{4}J_{CF}$ 3.0 Hz, C-1′), 147.7, (C-8a), 162.2 (d, $^{1}J_{CF}$ 240.0 Hz, C-4″), 162.2 (d, $^{1}J_{CF}$ 240.0 Hz, C-4‴), 162.6 (d, $^{1}J_{CF}$ 247.5 Hz, C-4′), 193.0 (C-4); IR (neat): ν_{max} 3390, 3069, 2114, 1682, 1603, 1490, 1356, 1319, 1218, 1157, 1095, 1016, 909, 835, 804cm^{-1}.

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

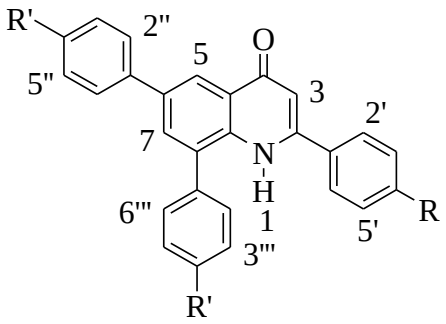
An experimental procedure employed for the synthesis of **145a** was followed using a mixture of **122c** (1.0 g, 2.4 mmol), $ArB(OH)_2$ (0.85 g, 6.0 mmol), $PdCl_2(PPh_3)_2$ (0.084 g, 0.1 mmol), PCy_3 (0.067 g, 0.2 mmol) and K_2CO_3 (0.75 g, 5.3 mmol) in dioxane-water (50 mL); work-up and column chromatography 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* 12.6 and 16.3 Hz, 3-H), 4.64 (1H, s, N-H), 4.69 (1H, dd, *J* 4.5 and 7.5 Hz, 2-H), 7.07-7.19 (4H, m, 2′-H, 3′-H, 5′-H, 6′-H), 7.33 (4H, t, *J* 9.6 Hz, 2″-H, 3″-H, 5″-H and 6″-H), 7.43-7.56 (5H, m, 2‴-H, 3‴-H, 5‴-H, 6‴-H, 7-H), 8.12 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.2 (C-3), 57.6 (C-2), 115.9 (d, $^{2}J_{CF}$ 21.3 Hz, C-3‴ and C-5‴), 116.2 (d, $^{2}J_{CF}$ 21.3 Hz, C-3″ and C-5″), 119.6 (C-4a), 125.0 (C-6), 127.7 (C-8), 127.9 (d, $^{3}J_{CF}$ 7.5 Hz, C-2‴and C-6‴), 130.4 (C-5), 130.9 (d, $^{3}J_{CF}$ 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, $^{4}J_{CF}$ 3.0 Hz, C-1‴), 135.8 (d, $^{4}J_{CF}$ 3.0 Hz, C-1″), 139.3 (C-1′), 147.6 (C-8a), 162.3 (d, $^{1}J_{CF}$ 244.5 Hz, C-4‴), 162.6 (d, $^{1}J_{CF}$ 247.5 Hz, C-4″), 192.7

(C-4); IR (neat): ν_{max} 3392, 2846, 2625, 1678, 1603, 1577, 1487, 1406, 1354, 1320, 1231, 1163, 1014, 908, 834, 761, 732 cm^{-1}.

4.13.8 Preparation of 6,8-bis(4-fluorophenyl)-2(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one 145h (R = OCH_3, R′ = 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_2CO_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, $CDCl_3$) δ: 2.80 (1H, dd, *J* 4.5 and 16.8 Hz, 3-H), 2.90 (1H, dd, *J* 12.6 and 16.8 Hz, 3-H), 3.80 (3H, s, $COCH_3$), 4.62-4.68 (2H, m, 2-H and N-H), 6.89 (2H, d, *J* 7.5 Hz, 3′-H and 5′-H), 7.06-7.17 (4H, m, 2′-H, 3′′-H, 5′′-H, 6′-H), 7.30 (2H, d *J* 9.0Hz, 2′′-H and 6′′-H), 7.42-7.57 (5H, m, 2′′′-H, 3′′′-H,5′′′-H, 6′′′-H and 7-H), 8.12 (1H, d, *J* 3.0 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.5 (C-3), 55.1 (OCH_3), 57.7 (C-2), 114.4 (C-4a), 115.8 (d, $^2J_{CF}$ 21.4 Hz, C-3′′′ and C-5′′′), 116.2 (d, $^2J_{CF}$ 21.4 Hz,(C-3′′ and C-5′′), 119.5 (C-8), 127.9 (d, $^3J_{CF}$ 7.5 Hz, C-2′′′ and C-6′′′), 128.5 (C-2′ and C-6′), 130.0 (C-5), 130.9 (d, $^3J_{CF}$ 8.3 Hz, C-2′′ and C-6′′), 131.0 (C-3′ and C-5′)), 132.8 (C-7), 133.3 (d, $^4J_{CF}$ 3.8 Hz, C-1′′′), 135.9 (d, $^4J_{CF}$ 3.0 Hz, C-1′′), 148.0 (C-8a), 162.2 (d, $^1J_{CF}$ 244.5 Hz, C-4′′′), 162.5 (d, $^1J_{CF}$ 246.8 Hz C-4′′), 193.4 (C-4); IR (neat): ν_{max} 3402, 2123, 1887, 1676, 1609, 1509, 1484, 1349, 1304, 1220, 1153, 1028, 908, 830, 787 cm^{-1}.

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



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

4.14.1 Preparation of 2,6,8-triphenylquinolin-4(1*H*)-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 dimethoxyethane (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 Na_2CO_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, $CDCl_3$) δ: 6.61 (1H, d, *J* 7.5 Hz, 3-H), 6.78 (1H, d, *J* 2.1 Hz, 4′′-H), 7.11 (2H, d, *J* 8.1 Hz, 2′′′-H and 6′′′-H), 7.37 (1H, t, *J* 7.2 Hz, 4′-H), 7.44-7.64 (10H, m, 2′-H, 3′-H and 5′-H, 3′′-H and 5′′-H, 3′′′-H and 5′′′-H, 4′′′-H, 6′-H, 6′′′-H), 7.75 (2H, d, *J* 7.2 Hz, 2′′-H and 6′′-H), 7.85 (1H, s, 7-H), 8.51 (1H, br s, N-H), 8.66 (1H, s, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.3 (C-3), 116.9 (C-8), 123.4 (C-2′ and C-6′), 125.9 (C-6), 127.6 (C-4′′), 127.7 (C-4′′′), 128.9 (C-2′′ and C-6′′), 129.0 (C-2′′′ and C-6′′′), 129.2 (C-3′ and C-5′), 129.6 (C-3′′ and C-5′′), 129.8 (C-3′′′ and C-5′′′), 130.7 (C-5), 131.4 (C-4a), 131.8 (C-7), 136.2 (C-4′), 136.3 (C-1′), 136.5 (C-

1″), 139.6 (C-1‴), 143.5 (C-2), 148.7 (C-8a), 179.0 (C-4); IR (neat): ν_{max} 3398, 3056, 2962,1626, 1591, 1492, 1382, 1290, 1246, 1181, 1076, 931, 897, 844, 759, 695, 653, 622 cm^{-1}.

4.14.2 Preparation of 2-(4-fluorophenyl)-6,8-bisphenylquinolin-4(1*H*)-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, $^2J_{CF}$ 22.5 Hz, C-3′ and C-5′), 125.8 (C-6), 127.1 (C-4″), 127.7 (d, $^3J_{CF}$ 7.5 Hz, C-2′ and C-6′), 128.1 (C-2″ and C-6″), 128.2 (C-2‴ and C-6‴), 128.9 (C-4‴), 129.0 (C-3″ and C-5″), 129.2 (C-3‴and C-5‴), 129.8 (C-5), 130.6 (C-4a), 131.8 (C-7), 136.3 (d, $^4J_{CF}$ 3.0 Hz, C-1′), 136.6 (C-1″), 139.5 (C-1‴), 143.1 (C-2), 147.7 (C-8a), 164.1 (d, $^1J_{CF}$ 250.5 Hz, C-4′), 178.9 (C-4); IR (neat): ν_{max} 3381, 3056, 2923, 2652, 2113, 1681, 1600, 1481, 1350, 1321, 1270, 1232, 1157, 905, 868 cm^{-1}.

4.14.3 Preparation of 2-(4-chlorophenyl)-6,8-bisphenylquinolin-4(1*H*)-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,

J 7.8 Hz, 3-H), 6.79 (1H, d, *J* 3.0 Hz, 4′′-H), 7.10 (2H, d, *J* 9.3 Hz, 2′′′-H and 6′′′-H), 7.34-7.51 (5H, m, 2′-H and 6′-H, 3′-H and 5′-H, 4′′′-H), 7.54-7.64 (4H, m, 3′′-H, 3′′′-H, 5′′-H, 5′′′-H), 7.74 (2H, d, *J* 7.5 Hz, 2′′-H and 6′′-H), 7.85 (1H, s, 7-H), 8.42 (1H, br s, N-H), 8.65 (1H, s, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.4 (C-3), 113.9 (C-8), 123.5 (C-2′and C-6′), 125.9 (C-6), 127.7 (C-4′′), 127.8 (C-4′′′), 128.9 (C-2′′ and C-6′′), 129.1 (C-2′′′ and C-6′′′), 129.2 (C-3′ and 5′), 129.9 (C-3′′ and C-5′′), 129.9 (C-3′′′ and C-5′′′), 131.4 (C-5), 131.9 (C-4a), 132.9 (C-7), 136.2 (C-4′), 136.3 (C-1′), 136.8 (C-1′′), 139.6 (C-1′′′), 144.1 (C-2), 147.5 (C-8a), 179.0 (C-4); IR (neat): ν_{max} 3744, 3373, 2086, 1666, 1611, 1479, 1358, 1312, 1274, 1231, 1143, 1086, 897, 865 cm^{-1}.

4.14.4 Preparation of 2(4-methoxyphenyl)-6,8-bisphenylquinolin-4(1*H*)-one 146d (R = OCH_3, 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); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (3H, s, $COCH_3$), 6.59 (1H, d, *J* 8.4 Hz, 3-H), 6.99 (1H, d, *J* 2.1 Hz, 4′′-H), 7.36 (2H, d, *J* 7.7 Hz, 2′′′-H and 6′′′-H), 7.44 (2H, d, *J* 7.8 Hz, 2′-H and 6′-H), 7.45 (2H, d, *J* 8.7 Hz, 3′-H and 5′-H), 7.51-7.64 (5H, m, 3′′-H, 3′′′-H, 4′′′-H, 5′′-H, 5′′′-H), 7.74 (2H, d, *J* 7.5 Hz, 2′′-H and 6′′-H), 7.84 (1H, d, *J* 2.1 Hz, 7-H), 8.45 (1H, br s, N-H), 8.66 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.5 (OCH_3), 107.5 (C-3), 115.0 (C-8), 123.5 (C-2′ and C-6′), 125.8 (C-6), 127.2 (C-4′′), 127.5 (C-4′′′), 128.9 (C-2′′ and C-6′′), 128.9 (C-2′′′ and C-6′′′), 129.2 (C-3′ and C-5′), 129.7 (C-3′′ and C-5′′), 129.8 (C-3′′′ and C-5′′′), 130.1 (C-5), 131.3 (C-4a), 131.7 (C-7), 136.1 (C-4′),

136.2 (C-1′), 136.5 (C-1′′), 139.7 (C-1′′′), 144.2 (C-2), 148.5 (C-8a), 179.0 (C-4); IR (neat): ν_{max} 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(1*H*)-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); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.61 (1H, d, *J* 8.7 Hz, 3-H), 7.14 (2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.31 (2H, t, *J* 8.6 Hz, 3′′-H and 5′′-H), 7.50-7.55 (5H, m, 2′-H and 6′-H, 3′′-H and 5′′-H, 4′-H), 7.57 (2H, t, *J* 8.7 Hz, 2′′′-H and 6′′′-H), 7.68 (2H, t, *J* 8.7 Hz, 2′′-H and 6′′-H), 7.74 (1H, d, *J* 2.1 Hz, 7-H), 8.34 (1H, br s, N-H), 8.59 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.4 (C-3), 115.8 (d, $^{2}J_{CF}$ 21.8 Hz, C-3′′ and C-5′′), 117.0 (d, $^{2}J_{CF}$ 21.8 Hz, C-3′′′ and C-5′′′), 123.5 (C-8), 125.9 (C-2′ and C-6′), 126.1 (C-6), 128.8 (d, $^{3}J_{CF}$ 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, $^{3}J_{CF}$ 8.3 Hz, C-2′′′ and C-6′′′),131.7 (C-7), 132.2 (d, $^{4}J_{CF}$ 3.0 Hz, C-1′′), 134.3 (C-1′), 135.7 (d, $^{4}J_{CF}$ 3.8 Hz, C-1′′′), 136.2 (C-2), 148.8 (C-8a), 162.6 (d, $^{1}J_{CF}$ 245.3 Hz, C-4′′), 166.0 (d, $^{1}J_{CF}$ 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(1*H*)-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); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.52 (1H, d,

J 8.7 Hz, 3-H), 7.14 (2H, t, *J* 9.0 Hz, 3′-H and 5′-H), 7.18 (2H, t, *J* 9.0 Hz, 3′′-H and 5′′-H), 7.31 (2H, t, *J* 9.0 Hz, 3′′′-H and 5′′′-H), 7.48 (2H, t, *J* 7.5 Hz, 2′-H and 6′-H), 7.56 (2H, t, *J* 7.5 Hz, 2′′-H and 6′′-H), 7.66 (2H, t, *J* 7.5 Hz, 2′′′-H and 6′′′-H), 7.74 (1H, d, *J* 2.4 Hz, 7-H), 8.25 (1H, br s, N-H), 8.57 (1H, d, *J* 2.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.4 (C-3), 115.8 (d, $^2J_{CF}$ 21.0 Hz, C-3′′ and C-5′′), 116.8 (d, $^2J_{CF}$ 21.8 Hz, C-3′′′ and C-5′′′), 117.0 (d, $^2J_{CF}$ 21.0 Hz, C-3′ and C-5′), 123.4 (C-8), 128.1 (C-6), 128.2 (C-5), 128.7 (d, $^3J_{CF}$ 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): ν_{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(1*H*)-one 146g (R = Cl, R′ = F)

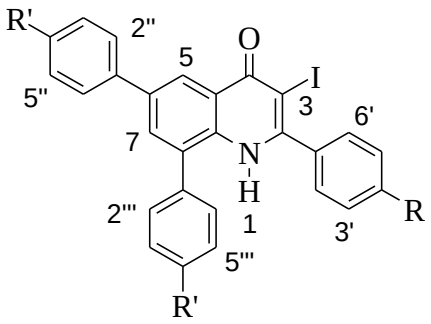
A stirred mixture of **145g** (0.80 g, 1.8 mmol) and TTS (1.44 g, 2.0 mmol) in DME (25 mL); work-up and column chromatography on silica gel employed for **146a** afforded **146g** as orange solid (0.62 g, 78%); mp 225-228 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.56 (1H, d, *J* 8.7 Hz, 3-H), 7.15 (2H, t, *J* 8.7 Hz, 3′-H and 5′-H), 7.31 (2H, t, *J* 8.7 Hz, 3′′-H and 5′′-H), 7.43 (2H, d, *J* 9.0 Hz, 2′′′-H and 6′′′-H), 7.48 (2H, d, *J* 9.0 Hz, 3′′′-H and 5′′′-H), 7.55 (2H, t, *J* 8.7 Hz, 2′-H and 6′-H), 7.68 (2H, t, *J* 8.7 Hz, 2′′-H and 6′′-H), 7.75 (1H, d, *J* 2.1 Hz, 7-H), 8.24 (1H, br s, N-H), 8.59 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.5 (C-3), 115.9 (d, $^2J_{CF}$ 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),

131.0 (4a), 131.1 (d, $^{3}J_{CF}$ 8.3 Hz, C-2‴ and C-6‴), 131.8 (C-4a), 132.1(d, $^{4}J_{CF}$ 3.8 Hz, C-1″), 132.8 (C-7), 135.6 (d, $^{4}J_{CF}$ 3.8 Hz, C-1‴), 136.1 (C-4′), 137.2 (C-2), 147.6 (C-8a), 162.7 (d, $^{1}J_{CF}$ 245.3 Hz, C-4″), 163.1 (d, $^{1}J_{CF}$ 248.3 Hz, C-4‴), 178.8 (C-4); IR (neat): ν_{max} 3400, 1624, 1601, 1490, 1380, 1297, 1224, 1158, 1094, 1013, 942, 884, 828, 766, 725 cm^{-1}.

4.14.8 Preparation of 2-(4-methoxyphenyl)-6,8-bis(4-fluorophenyl)quinolin-4(1*H*)-one 146h (R = 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, $CDCl_3$) δ: 3.85 (3H, s, $COCH_3$), 6.56 (1H, d, *J* 8.7 Hz, 3-H), 7.00 (2H, d, *J* 9.3 Hz, 3′ and 5′-H), 7.14 (2H, t, *J* 9.2 Hz, 3″-H and 5″-H), 7.31 (2H, t, *J* 9.2 Hz, 3‴-H and 5‴-H), 7.43 (2H, d, *J* 9.2 Hz, 2′-H and 6′-H), 7.57 (2H, t, *J* 7.8 Hz, 2″-H and 6″), 7.67 (2H, t, *J* 7.8 Hz, 2‴-H and 6‴-H), 7.73 (1H, s, 7-H), 8.28 (1H, s, N-H), 8.59 (1H, s, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.5 (OCH_3), 107.5 (C-3), 115.8 (d, $^{2}J_{CF}$ 21.0 Hz, C-3″ and C-5″), 116.9 (d, $^{2}J_{CF}$ 21.8 Hz, C-3‴and C-5‴), 123.5 (C-8), 125.8 (C-2′ and C-6′), 126.4 (C-6), 127.4 (C-5), 128.8 (d, $^{3}J_{CF}$ 7.5 Hz, C-2″ and C-6″), 131.1 (d, $^{3}J_{CF}$ 8.3 Hz, C-2‴ and C-6‴), 131.5 (C-4a), 131.7 (C-7), 132.3 (d, $^{4}J_{CF}$ 3.0 Hz, C-1″), 135.7 (d, $^{4}J_{CF}$ 3.8 Hz, C-1‴), 135.4 (C-1′), 136.2 (C-2), 148.5 (C-8a), 161.7 (C-4′), 162.6 (d, $^{1}J_{CF}$ 246.0 Hz, C-4″), 163.0 (d, $^{1}J_{CF}$ 243.8 Hz, C-4‴), 178.8 (C-4); IR (neat): ν_{max} 3413, 1628, 1582, 1508, 1501, 1223, 1158, 827, 765 cm^{-1}.

4.15 Preparation of 2,6,8-triaryl-3-iodoquinolin-4(1*H*)-ones 147a-h



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

4.15.1 Preparation of 2,6,8-triphenyl-3-iodoquinolin-4(1*H*)-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_2CO_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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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): ν_{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-iodoquinolin-4(1*H*)-one 147b (R = F; R' = H)

A mixture of **146b** (0.50 g, 1.3 mmol), I_2 (0.65 g, 2.6 mmol) and Na_2CO_3 (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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 86.6 (C-3), 116.1 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 8.9 Hz, C-2' & 6'), 131.0 (C-5), 132.2 (C-4a), 133.9 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 250.7 Hz, C-4'), 175.1 (C-4); IR (neat): ν_{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 $[C_{27}H_{18}FINO]^+$: requires 518.0339.

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

A mixture of **146c** (0.50 g, 1.2 mmol), I_2 (0.62 g, 2.5 mmol) and Na_2CO_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 **147c** as light brown solid (0.47 g, 74%); mp 246-248 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 86.5 (C-3), 121.8 (C-8), 124.4 (C-6), 127.2 (C-4''), 127.8 (C-4'''),

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): ν_{max} 3382, 3055, 1780, 1586, 1508, 1491, 1481, 1215, 1161, 1087, 1038, 1014, 940, 897, 829, 766 cm^{-1}; *m/z* (100, M+H) 534; HRMS (ES): MH^+; found 534.0123. For $[C_{27}H_{18}ClINO]^+$: requires 534.0043.

4.15.4 Preparation of 2-(4-methoxyphenyl)-6,8-diphenyl-3-iodoquinolin-4(1*H*)-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_2CO_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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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): ν_{max} 3377, 3050, 1784, 1595, 1505, 1478, 1221, 1157, 1026, 898, 786, 622, 610 cm^{-1}; *m/z* (100, M+H) 530; HRMS (ES): MH^+; found 530.0623. For $[C_{28}H_{21}INO_2]^+$: requires 530.0539.

4.15.5 Preparation of 6,8-bis(4-fluorophenyl)-3-iodo-2-phenylquinolin-4(1*H*)-one 147e (R = H; R' = F)

A mixture of **146e** (0.50 g, 1.2 mmol), I_2 (0.62 g, 2.4 mmol) and Na_2CO_3 (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); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.16 (2H, t, *J* 8.4 Hz, 3''' & 5'''-H), 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); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 86.4 (C-3), 115.9 (d, $^2J_{CF}$ 21.4 Hz, C-3'' & 5''), 117.0 (d, $^2J_{CF}$ 21.4 Hz, C-3''' & 5'''), 121.7 (C-8), 124.4 (C-6), 128.4 (C-4'), 128.8 (d, $^3J_{CF}$ 8.0 Hz, C-2'' & 6''), 130.1 (C-4a), 130.6 (C-5), 130.9 (d, $^3J_{CF}$ 8.0 Hz, C-2''' & 6'''), 131.7 (d, $^4J_{CF}$ 3.4 Hz, C-1''), 132.0 (C-2' & 6'), 135.1 (C-3' & 5'), 135.5 (d, $^4J_{CF}$ 3.4 Hz, C-1'''), 136.5 (C-1'), 137.8 (C-7), 151.4 (C-8a), 162.7 (d, $^1J_{CF}$ 247.2 Hz, C-4''), 163.0 (d, $^1J_{CF}$ 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 $[C_{27}H_{17}F_2INO]^+$: requires 536.0245.

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

A mixture of **146f** (0.50 g, 1.2 mmol), I_2 (0.59 g, 2.3 mmol) and Na_2CO_3 (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); ^{1}H NMR (300 MHz, DMSO-d_6) 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),

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-1'), 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): ν_{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(1*H*)-one 147g (R = Cl; R' = F)

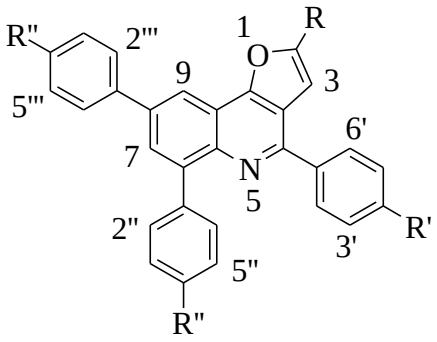
A mixture of **146g** (0.50 g, 1.1 mmol), I_2 (0.57 g, 2.3 mmol) and Na_2CO_3 (0.18 g, 1.7 mmol) in THF (20 mL) was stirred at room temperature for 18 hours; work-up as described for **147a** afforded **147g** as light brown solid (0.48 g, 75%); mp 251-252 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 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): ν_{max} 3382, 3055, 1781, 1586, 1507, 1492,

1481, 1215, 1161, 1087, 1014, 897, 828, 783, 766 cm^{-1}; *m/z* (100, M+H) 570; HRMS (ES): MH^+; found, 569.9911. For $[C_{27}H_{16}F_2ClINO]^+$: requires, 569.9855.

4.15.8 Preparation of 6,8-bis(4-fluorophenyl)-2-(4-methoxyphenyl)-3-iodoquinolin-4(1*H*)-one 147h (R = OCH_3; R' = F)

A mixture of **146h** (0.50 g, 1.1 mmol), I_2 (0.57 g, 2.3 mmol) and Na_2CO_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 **147h** as light brown solid (0.48 g, 75%); mp 237-239 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.82 (3H, s, OCH_3), 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 H, 7-H), 8.39 (1H, s, N-H), 11.0 (1H, d, *J* 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.9 (OCH_3), 87.1 (C-3), 113.9 (C-8), 116.3 (d, $^2J_{CF}$ 21.3 Hz, C-3'' & 5''), 116.4 (d, $^2J_{CF}$ 21.3 Hz, C-3''' & 5'''), 122.8 (d, $^3J_{CF}$ 8.3 Hz, C-2'' & 6''), 129.4 (d, $^3J_{CF}$ 8.3 Hz, C-2''' & 6'''), 130.9 (C-6), 131.4 (C-3' & 5'), 132.5 (C-2' & 6'), 134.0 (d, $^4J_{CF}$ 3.0 Hz, C-1''), 134.0 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 243.3 Hz, C-4''), 162.8 (d, $^1J_{CF}$ 243.3 Hz, C-4'''), 174.3 (C-4); IR (neat): ν_{max} 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 $[C_{28}H_{19}F_2INO_2]^+$: requires, 566.0350.

4.16 Preparation of 2,6',8'-trisubstituted 2'-arylfuro[3,2-c]quinoline derivatives 148a-i



2,6',8'-Trisubstituted 2'-arylfuro[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; ^{1}H 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); ^{13}C 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"), 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): ν_{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_6H_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_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; 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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 101.3 (C-9a), 115.9 (d, $^2J_{CF}$ 21.4 Hz, C-3' & 5'), 116.9 (C-3), 119.7 (3a), 125.0 (d, $^3J_{CF}$ 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''), 129.0 (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, $^4J_{CF}$ 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, $^1J_{CF}$ 247.6 Hz, C-4'); IR (neat): ν_{max} 3052, 3033, 1600, 1485, 1366, 1227, 1154, 1012, 842, 793, 757, 691, 616 cm^{-1};

m/z (100, M+H) 492; HRMS (ES): MH^+, found: 492.1764. For $[C_{35}H_{23}FNO]^+$: requires, 492.1758.

4.16.3 Preparation of 2,6,8-triphenyl-4-(4-chlorophenyl)furo[3,2-*c*]quinoline 148c (R = C_6H_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_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 (0.12 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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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): ν_{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 = C_6H_5; R'' = H; R' =OCH_3)

A mixture of **147d** (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 (0.12 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; R_f(10% ethyl acetate/ hexane) 0.42; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.89 (3H, s, OCH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.4 (OCH_3), 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): ν_{max} 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 $[C_{36}H_{26}NO_2]^+$: requires, 504.1964.

4.16.5 Preparation of 6,8-bis(4-fluorophenyl)-2,4-diphenylfuro[3,2-*c*]quinoline 148e (R = C_6H_5; 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_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; 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 R_f (10% ethyl acetate/ hexane) 0.58; ^{1}H NMR (300 MHz, DMSO-d_6) 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); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 101.6 (C-9a), 114.6 (d, $^2J_{CF}$ 21.3 Hz, C-3" & 5"), 115.9 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 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, $^3J_{CF}$ 8.0 Hz, C-2"' & 6"'), 135.6 (d, $^4J_{CF}$ 3.2 Hz, C-1"), 136.5 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 245.3 Hz, C-4"), 162.8 (d, $^1J_{CF}$ 245.3 Hz, C-4"'); IR (neat): ν_{max} 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 $[C_{35}H_{22}F_2NO]^+$: requires, 510.1669.

4.16.6 Preparation of 4,6,8-tris(4-fluorophenyl)-2-phenylfuro[3,2-*c*]quinoline 148f (R = C_6H_5; R', R'' = F)

A mixture of **147f** (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; work up and column chromatography on silica gel as describeed for **148a** afforded **148f** as pale yellow solid, (0.18 g, 67%); mp 249-250 °C R_f (10% ethyl acetate/ hexane) 0.63; ^{1}H NMR (300 MHz, DMSO-d_6) 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), 7.80-789 (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); ^{13}C NMR (75 MHz, DMSO-d_6) 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 $[C_{35}H_{21}F_3NO]^+$: requires, 528.1575.

4.16.7 Preparation of 6,8-bis(4-fluorophenyl)-4-(4-chlorophenyl)-4-phenylfuro[3,2-*c*]quinoline 148g (R = C_6H_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_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; 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) δ: 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) δ: 101.2 (C-9a), 114.7 (d, $^2J_{CF}$ 21.4 Hz, C-3'' & 5''), 115.9 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 8.0 Hz, C-2'' & 6''), 132.6 (d, $^3J_{CF}$ 8.0 Hz, C-2''' & 6'''), 135.5 (d, $^4J_{CF}$ 3.2 Hz, C-1''), 136.5 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 245.0 Hz, C-4''), 162.8 (d, $^1J_{CF}$ 245.0 Hz, C-4'''); IR (neat): ν_{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 $[C_{35}H_{21}F_2ClNO]^+$: requires, 544.1280.

4.16.8 Preparation of 6,8-bis(4-fluorophenyl)-4-(4-methoxyphenyl)-4-phenylfuro[3,2-*c*]quinoline 148h (R = C_6H_5; R'' = F; R' = OCH_3)

A mixture of **147h** (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; 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 R_f (10% ethyl acetate/ hexane) 0.40; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.91 (3H, s, OCH_3), 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); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.4 (OCH_3), 101.7 (C-9a), 114.6 (d, $^2J_{CF}$ 21.4 Hz, C-3'' & 5''), 115.9 (d, $^2J_{CF}$ 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), 128.5 (2-Ph: C-4), 129.0 (C-7), 129.1 (d, $^3J_{CF}$ 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, $^3J_{CF}$ 8.0 Hz, C-2''' & 6'''), 135.7 (d, $^4J_{CF}$ 3.5 Hz, C-1''), 136.6 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 245.8 Hz, C-4''), 162.8 (d, $^1J_{CF}$ 245.8 Hz, C-4'''); IR (neat): ν_{max} 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 $[C_{36}H_{24}F_2NO_2]^+$: 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_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 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) δ: 1.90 (3H, d, *J* 6.6 Hz, C$\underline{H}_3$OH), 2.41 (1H, d, *J* 5.4 Hz, H-O$\underline{H}$), 5.34 (1H, t, *J* 5.7 Hz, $\underline{H}$-OH), 7.25-7.39 (4H, m, 4-Ph: 3, 4, 5-H), 7.58-7.69 (4H, m, 3", 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) δ: 21.7 (CH_3OH), 64.1 (CHOH), 102.5 (C-3), 114.6 (d, $^2J_{CF}$ 21.4 Hz, C-3" & 5"), 115.8 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 8.0 Hz, C-2" & 6"), 129.4 (C-3' & 5'), 132.7 (d, $^3J_{CF}$ 8.0 Hz, C-2"' & 6"'), 135.6 (d, $^4J_{CF}$ 3.0 Hz, C-1"), 136.4 (d, $^4J_{CF}$ 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, $^1J_{CF}$ 247.5 Hz, C-4"), 162.8 (d, $^1J_{CF}$ 247.5 Hz, C-4"'); IR (neat): ν_{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 $[C_{31}H_{22}F_2NO_2]^+$: requires, 478.1619.

4.17 Antimicrobial susceptiblity 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 *Crytococcus neoformans* (ATCC 14116, yeast).

The minimum inhibitory concentrations were determined using the INT microwell method (NCCLS, 2003). The synthesiszed 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 x 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.

References

1. Abass, M. *Heterocycles* **2005**, 65, 901-965.
2. Chen, Y-L; Chen, I-L; Wang, T-C; Han, C-H; Tzeng, C-C. *Eur. J. Med. Chem*. **2005**, 40, 928-934.
3. Liu, J; Diwu, Z; Leung, W-Y; Lu, Y; Patch, B; Haugland, P. *Tetrahedron Lett*. **2003**, 44, 4355-4359.
4. Johnson, JA; Gray, MO; Chen, CH; Mochly-Rosen, D. *J. Biol. Chem*. **1996**, 271, 24962-24966.
5. Stanton, JL; Ackerman, MH. *J. Med. Chem*. **1983**, 26, 986-989.
6. Dorrow, RL; Herrinton, PM; Hohler, RA; Maloney, MT; Mauragis, MA; McGhee, WE; Moeslein, JA; Strohbach, JW; Veley, MF. *Org. Proc. Res. & Dev*. **2006**, 10, 493-499.
7. Wansi, JD; Hussain, H; Tcho, AT; Kouam, SF; Specht, S; Sarite, SR; Hoeraul, A; Krohn, K. *Phytother. Res*. **2010**, 24, 775-777.
8. Biavatti, MW; Vieira, PC; da Silva, MGF; Fernandes, JB; Victor, SR; Pagnocca, FC; Albuquerque, S; Caracelli, I; Zukerman-Schpector, J. *J. Braz. Chem. Soc*. **2002**, 13, 66-70.
9. Kuete, V; Wansi, JD; Mbaveng, AT; Kana Sop, MM; Tcho Tadjong, A; Penlap Beng, V; Etoa, F-X; Wandji, J; Marion Meyer, JJ; Lall, N. *S. Afr. J. Bot*. **2008**, 74, 572-576.
10. Almeida, R; Penaflor, M; Simote, S; Bueno, O; Hebling, M; Pagnocca, F; Fernandes, J; Vieira, P; da Silva, M. *Bioassay Org. Br*. **2007**, 2, 1-8.
11. Hanawa, F; Fokialakis, N; Skaltsounis, AL. *Planta Med*. **2004**, 70, 531-535.
12. Castrillo, A; Pennington, DJ; Otto, F; Parker, PJ; Owen, MJ; Bosca, L. *J. Exp. Med*. **2001**, 194, 1231-1242.
13. Jarak, I; Kralj, M; Suman, L; Pavlovic, G; Dogan, J; Piantaninda, I; Zinic, M; Pavelic, K; Karminski-Zamola, G. *J. Med. Chem*. **2005**, 48, 2346-2360.

14. Pierre, F; Chua, CC; O'Brien, SE; Siddiqui-Jain, A; Bourbon, P; Haddach, M; Michaux, J; Nagasawa, J; Scwaebe, MK; Stefan, E; Vialettes, A; Whitten, JP; Chen, TK; Darjania, L; Stansfield, R; Anderes, K; Bliesath, J; Drygin, D; Ho, C; Omori, M; Proffitt, C; Streiner, N; Trent, K; Rice, WG; Ryckman, DM. *J. Med. Chem*. **2011**, 54, 635-654.

15. Rechfeld, F; Gruber, P; Kirchmair, J; Boehler, M; Hauser, N; Hechenberger, G; Garczarczyk, D; Lapa, GB; Preobrazhenskaya, MN; Goekjian, P; Langer, T; Hofmann, J. *J. Med. Chem.* **2014**, 57, 3235-3246.

16. *The Alkaloids Chemistry and Physiology* ed. Manske, RHF. Academic Press, London, **1960**, vol. 6, pp 312-327.

17. Black, DSC; Kumar, N. *Org. Prep. Proced. Int*. **1991**, 23, 67-92.

18. Ghosal, S; Saini, KS; Razdan, S. *Phytochemistry* **1985**, 24, 2141-2156.

19. Paris, D; Cottin, M; Demonchaux, P; Augert, G; Dupassieux, P; Lenoir, P; Peck, MJ; Jasserand, D. *J. Med. Chem*. **1995**, 38, 669-685.

20. McClean, S; Costelloe, C; Denny, WA; Searcey, M; Wakelin, L.P.G. *Anticancer Drug Des*. **1999**, 14, 187-204.

21. Gourdie, TA; Valu, KK; Gravatt, GL; Boritzki, TR; Baguley, BC; Wakelin, LPG; Wilson, WR; Woodgate, PD; Denny, WA. *J. Med. Chem*. **1990**, 33, 1177-1186.

22. Kohn, KW; Or, A; O'Connor, PM; Guziec, LJ; Guziec, FS. *J. Med. Chem*. **1994**, 37, 67-72

23. Wijngaarden, I; Haminga, D; van Hes, R; Standaar, PJ; Tipker, J; Tulp, MTM; Mol, F; Olivier, B; de Jong, A. *J. Med. Chem*. **1993**, 36, 3693-3699.

24. Isaac, M; Slassi, A; O'Brien, A; Edwards, L; MacLean, N; Bueschkens, D; Lee, DKH; McCallum, K; De Lanooy, I; Demchyshyn, L; Kamboj, R. *Bioorg. Med. Chem. Lett*. **2000**, 10, 919-921.

25. Bass, RJ; Koch, RC; Richards, HC; Thorpe, JE. *J. Agric. Food Chem*. **1981**, 29, 576-579.

26. Kappe, CO; Kappe, T. *J. Heterocyclic Chem*. **1989**, 26, 1555-1560.

27. Matesic, L; Locke, JM; Vine, K; Ranson, M; Bremner, JB. *Tetrahedron* **2012**, 68, 6810-6819.

28. Schroter, S; Stock, C; Bach, T. *Tetrahedron* **2005**, 2245-2267.

29. Larock, RC, *Pure Appl. Chem*. **1999**, 71, 1435-1442.

30. Hallas, G; Taylor, DC. *J. Chem. Soc*. **1964**, 293, 1518-1521.

31. Rocha, DHA; Pinto, DCGA; Silva, AMS. *Tetrahedron* **2015**, XXX, 1-5.

32. Venkataram, S; Barange, DK; Pal, M. *Tetrahedron Lett*. **2006**, 47, 7317-7322.

33. Avetisyan, AA; Aleksanyan, IL; Sargsyan, KS. *Russ. J. Org. Chem*. **2007**, 43, 426-428.

34. Butenschon, I; Moller, K; Hansel, W. *J. Med. Chem*. **2001**, 44, 1249-1256.

35. Gharib, A; Jahangir, M. *Org. Chem. Inter*. **2013**, 1-7.

36. Bouma, MJ; Masson, G; Zhu, J. *Eur. J. Org. Chem*. **2012**, 475-479.

37. Jarak, I; Kralj, M; Suman, L; Pavlovic, G; Dogan, J; Piantaninda, I; Zinic, M; Pavelic, K; Karminski-Zamola, G. *J. Med. Chem*. **2005**, 48, 2346-2360.

38. Makisumi, Y; Murabayashi, A. *Tetrahedron Lett*. **1969**, 10, 1971-1974.

39. Beydoun, K; Doucet, H. *Eur. J. Org. Chem*. **2012**, 6745-6751.

40. Mekheimer, RA; Abdel Hameed, AM; Sadek, KU. *Arkivoc* **2008**, 16, 144-153.

41. Mphahlele, MJ; Maluleka, MM; Makhafola, TJ; Mabeta, P, *Molecules* **2014**, 19, 18527-18542.

42. Marchand, P; Puget, A; Le Baut, G; Eming, P; Czech, M; Gunther, E. *Tetrahedron* **2005**, 61, 4035-4041.

43. Chilin, A; Rodighiero, P; Pastorini, G; Guiotto, A. *J. Org. Chem*. **1991**, 56, 980-983.

44. Nakatsuka, S; Masuda, T; Goto, T. *Tetrahedron Lett*. **1986**, 27, 6245-6248.

45. Nakatsuka, S; Asano, O; Goto, T. *Heterocycles* **1986**, 24, 2109-2110.

46. Sammes, PG; Weedon, AC. *J. Chem. Soc*. Perkin Trans. I, **1979**, 3053-3055.

47. Nishijima, K; Shinkawa, T; Ito, M; Nishida, H; Yamamoto, I; Onuki, Y; Inaba, H; Miyano, S, *Eur. J. Med. Chem*. **1998**, 33, 763-774.

48. Black, DSC; Kumar, N; Mitchell, PSR. *J. Org. Chem*. **2002**, 67, 2464-2473.

49. Grandberg, II. *Zhurnal Org. Khim*. **1989**, 19, 2439-2452.

50. Dobbs, AP; Jones, K; Veal, KT. *Tetrahedron Lett*. **1997**, 38, 5379-5382.

51. Black, DSC; Deb-Das, RB; Kumar, N. *Aus. J. Chem*. **1992**, 45, 1051-1056.

52. Moody, CJ. *J. Chem. Soc*., *Perkin Trans. 1* **1984**, 1333-1337.

53. Bartoli, G; Palmieri, G; Bosco, M; Dalpozzo, R. *Tetrahedron Lett*. **1989**, 30, 2129-2132.

54. Ziegler, FE; Jeroncic, LO. *J. Org. Chem*. **1991**, 56, 3479-3486.

55. Layek, M; Dhanunjaya Rao, AV; Gajare, V; Kalita, D; Barange, DK; Islam, A; Mukkanti, K; Pal, M. *Tetrahedron Lett*. **2009**, 50, 4878-4881.

56. Layek, M; Appi, RM; Rao, DAV; Alvala, M; Arunasree, MK; Islam, A; Mukkanti, K; Iqbal, J; Pal, M. *Org. Biomol. Chem*. **2011**, 9, 1004-1007.

57. Layek, M; Gajare, V; Kalita, D; Islam, A; Mukkanti, K; Pal, M. *Tetrahedron Lett*. **2009**, 50, 3867-3871.

58. Richter, S; Parolin, C; Palumbo, M; Palu, G. *Curr. Drug Targ. Inf. Dis*. **2004**, 4, 111-116.

59. Xia, Y; Yang, Z-U; Xia, P; Bastow, KF; Tachibana, Y; Kuo, S-C; Hamel, E; Hackl, T; Lee, K-H. *J. Med. Chem*. **1998**, 41, 1155-1162.

60. Huang, L.-J; Hsieh, M.-C; Teng, C.-M; Lee, K.-H; Kuo, S.-C. *Bioorg. Med. Chem*. **1998**, 6, 1657-1662.

61. Andriole, VT. *Clin. Inf. Dis*. **2005**, 41, 113-119.

62. d'A Lucero, B; Gomes, CRB; Frughulletti, ICPP; Faro, LV; Alvarenga, L; de Souza, MCVB; de Souza, TML; Ferreira, VF. *Bioorg. Med. Chem. Lett*. **2006**, 16, 1010-1013.

63. Mugnaini, C; Falciani, C; De Rosa, M; Brizzi, A; Pasquini, S; Corelli, F. *Tetrahedron* **2011**, 67, 5776-5783.

64. de la Cruz, A; Elguero, J; Goya, P; Martinez, A. *Tetrahedron* **1992**, 48, 6135-6150.

65. Donnelly, JA; Farrell, DF. *J. Org. Chem*. **1990**, 55, 1757-1761.

66. Donnelly, JA; Farrell, DF. *Tetrahedron* **1990**, 46, 885-894.

67. Park, MS; Lee, JI. *Bull. Kor. Chem. Soc*. **2004**, 25, 1269-1272.

68. Kaye, PT; Mphahlele, MJ. *S. Afr. J. Chem*. **1994**, 47, 21-25.

69. Boteva, AA; Krasnykh, OP. *Chem. Heterocyclic Compd*. **2009**, 45, 757-785.

70. Kumar, KH; Perumal, PT. *Can. J. Chem*. **2006**, 84, 1079-1083.

71. Ahmed, N; van Lier, JE. *Tetrahedron Lett*. **2007**, 48, 13-15.

72. Muthukrishnan, M; Mujahid, M; Punitharasu, V; Dnyaneshwar, DA. *Synth. Comm*. **2010**, 40, 1391-1398.

73. Bunce, RA; Nammalwar, B. *J. Heterocyclic Chem*. **2011**, 48, 613-619.

74. Singh, OV; Kapil, S. *Synth. Comm*. **2011**, 23, 277-283.

75. Lee, JI; Youn, JS. *Bull. Kor. Chem. Soc*. **2008**, 29, 1853-1856.

76. Mphahlele, MJ; El-Nahas, AM. *J. Mol. Struct*. **2004**, 688, 129-136.

77. Kouznetsov, VV; Vargas-Mendez, LY; Melendez-Gomez, CM. *Curr. Org. Chem*. **2005**, 9, 141-161.

78. Sato, S; Kubota, Y; Kumagai, H; Kumazawa. T; Matsuba, S; Kitamura, N; Onodera, JI; Suzuki, M. *Heterocycles* **2000**, 53, 1523-1532.

79. Kuo, S-C; Lee, HZ; Juang, JP; Lin, YT; Wu, TS; Chang, JJ; Lednicer, D; Paull, KD; Lin, CM; Hamel, E; Lee, KH. *J. Med. Chem*. **1993**, 36, 1146-1156.

80. Mphahlele, MJ. *J. Heterocyclic Chem*. **2010**, 47, 1-13.

81. Coppola, GM. *J. Heterocyclic Chem*. **1982**, 19, 727-731.

82. Niedzinski, EJ; Lashley, MR; Nantz, MH. *Heterocycles* **2001**, 55, 623-626.

83. Sun, F; Zhao, X; Shi, D. *Tetrahedron Lett*. **2011**, 52, 5633-5635.

84. Kalinin, VN; Shostakovsky, NV; Ponomaryov, AB. *Tetrahedron Lett*. **1992**, 33, 373-376.

84. Zhao, T; Xu, B. *Org. Lett*. **2010**, 42, 212-215.

85. Seixas, RSGR; Silva, AMS; Alkorta, I; Elguero, J. *Monatsh Chem*. **2011**, 142, 731-742.

86. Mphahlele, MJ; Oyeyiola, FA. *Tetrahedron* **2011**, 67, 6819-6825.

87. Tsai, J-Y; Chang, C-S; Huang, Y-F; Chen, H-S; Lin, S-K; Wong, FF; Huang, LJ; Kuo, S-C. *Tetrahedron* **2008**, 64, 11751-11755.

88. Mphahlele, MJ; Mtshemla, V. *J. Chem. Res*. **2008**, 437-440.

89. Mphahlele, MJ; Lesenyeho, LG; Makelane, HR. *Tetrahedron* **2010**, 66, 6040-6046.

90. Sharma, D; Ranjan, P; Prakash, O. *Synth. Comm*. **2009**, 39, 596-603.

91. Bellina, F; Rossi, R. *Tetrahedron* **2009**, 65, 10269-10310.

92. Mphahlele, MJ; Mtshemla, V. *J. Heterocyclic Chem*. **2008**, 45, 1343-1350.

93. Mphahlele, MJ; Mphahlele, MM. *Tetrahedron* **2011**, 67, 4689-4695.

94. Bheemanapalli, LN; Kaur, A; Arora, R; Sangeeta; Akinnepally, RR. *Med. Chem. Res*. **2012**, 21, 1741-1750.

95. Janszo, G; Philbin, EM. *Tetrahedron Lett*. **1971**, 33, 3075-3076.

96. Mphahlele, MJ; Mogamisi, FK; Tsanwani, S; Hlatshwayo, SM; Mampa, RM. *J. Chem. Res*. **1999**, 706-707.

97. Mphahlele, MJ; Nwamadi, MS; Mabeta, P. *J. Heterocyclic Chem*. **2006**, 43, 255-260.

98. Dahlen, K; Wallen, EAA; Grotli, M; Luthman, K. *J. Org. Chem*. **2006**, 71, 6863-6871.

99. Konishi, H; Itoh, T; Manabe, K. *Chem. Pharm. Bull*. **2010**, 58, 1255-1258.

100. Reddy, EA; Islam, A; Mukkanti, K; Venkanna, B; Bhowmik, DR; Pal, M. *Beilstein J. Org. Chem.* **2009**, 5, 1-8.

101. Garcia, Y; Schoenebeck, F; Legault, CY; Merlic, CA; Houk, KN. *J. Am. Chem. Soc.* **2009**, 131, 6632-6639.

102. Reddy, EA; Barange, DK; Islam, A; Mukkanti, K; Pal, M. *Tetrahedron* **2008**, 64, 7143-7150.

103. Gil-Molto, J; Karlstrom, S; Najera, C. *Tetrahedron* **2005**, 61, 12168-12173.

104. Grushin, VV; Alper, H. *Chem. Rev*. **1994**, 94, 1047-1062.

105. Larock, RC; Tia, Q. *J. Org. Chem*. **1998**, 63, 2002-2009.

106. Nakamura, I; Yamamoto, Y. *Chem. Rev*. **2004**, 104, 2177-2198.

107. Alberico, D; Scott, ME; Lautens, M. *Chem. Rev*. **2007**, 107, 174-238.

108. Barnard, C. *Plat. Met. Rev*. **2008**, 52, 38-45.

109. Sonogashira, K; Tohda, Y; Hagihara, N. *Tetrahedron Lett*. **1975**, 16, 4467-4470.

110. Reddy, EA; Islam, A; Mukkanti, K; Venu, BK; Pal, M. *J. Braz. Chem. Soc*. **2010**, 21, 1681-1687.

111. CCDC 972588 contains the cif file for 142a and the data can be obtained free of charge from the Cambridge Crystallographic Data Centre through www.ccdc.cam.ac.uk/data_request/cif.

112. Cross, RM; Manetsch, R, *J. Org. Chem*. **2010**, 75, 8654-8657.

113. Pain, C; Celanire, S; Guillaumet, G; Joseph, B. *Tetrahedron* **2003**, 59, 9627-9633.

114. An, Z-Y; Yan, YY; Peng, D; Ou, T-M; Tan, J-H; Huang, S-L; An, L-K; Gu, L-Q; Huang, Z-S. *Eur. J. Med. Chem*. **2010**, 45, 3895-3903.

115. Xia, Y; Yang, Z-Y; Xia, P; Bastow, KF; Nakanishi, Y; Nampothiri, P; Hamel, E; Brossi, A; Lee, K-H, *Bioorg. Med. Chem. Lett*. **2003**, 13, 2891-2896.

116. Park, C-H, Lee, J; Jung, HW; Kim, MJ; Lim, SH; Yeo, HT; Choi, EC; Yoon, EJ; Kim, KW; Cha, JH; Kim, S-H; Chang, D-J; Kwon, D-Y; Li, F; Suh, YG. *Bioorg. Med. Chem*. **2007**, 15, 6517-6526.

117. Chung, PY; Navaratnam, P; Chung, LY. *Annals. Clin. Microb. Antimicrob*. **2011**, 10, 1-6.

118. Chen, J-S.; Vasiliev, AN; Panarello, AP; Khinast, JG. *Appl. Cat. A* **2007**, *325*, 76-86.

119. Mphahlele, MJ; Oyeyiola, FA. *J. Chem. Res*. **2014**, 38, 535-538

120. Mphahlele, MJ; Oyeyiola, FA. *Turk. J. Chem*. **2015**, 39, 1216-1231