2-ARYL-6,8-DIBROMO-4-CHLOROQUINAZOLINE AS SCAFFOLD FOR THE SYNTHESIS OF NOVEL 2,6,8-TRIARYL-4-(PHENYLETHYNYL)QUINAZOLINES WITH POTENTIAL PHOTOPHYSICAL PROPERTIES

by

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DECLARATION

Student number: 45312869

I, Hugues Kamdem Paumo sincerely and solemnly declare that the work:

2-ARYL-6,8-DIBROMO-4-CHLOROQUINAZOLINE AS SCAFFOLD FOR THE SYNTHESIS OF NOVEL 2,6,8-TRIARYL-4-(PHENYLETHYNYL)QUINAZOLINES WITH POTENTIAL PHOTOPHYSICAL PROPERTIES is my own work and that all the sources that I have used have been indicated and acknowledged by means of references

…….. ……..

SIGNATURE DATE

(MR. H. KAMDEM PAUMO)

This thesis is dedicated to my parents, Michel Paumo and Therese Tokam.

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ABSTRACT

The 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones were prepared in a single-pot operation by condensing 6,8-dibromoanthranilamide and aryl aldehydes in the presence of molecular iodine in ethanol. Treatment of the 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones with thionylchloride in the presence of dimethylformamide afforded the corresponding 2-aryl-4-chloro-6,8-dibromoquinazolines. Palladium(0)-copper iodide catalysed Sonogashira cross-coupling reaction of 2-aryl-4-chloro-6,8-dibromoquinazolines with terminal alkynes at room temperature afforded series of 2-aryl-6,8-dibromo-4-(alkynyl)quinazolines. Further transformation of the 2-aryl-6,8-dibromo-4-(phenylethynyl)quinazolines *via* Suzuki-Miyaura cross-coupling with arylboronic acids occurred without selectivity to afford the corresponding 2,6,8-triaryl-4-(phenylethynyl)quinazolines. The compounds were characterized using a combination of NMR (^{1}H and ^{13}C) and IR spectroscopic techniques as well as mass spectrometry. The absorption and emission properties of 2,6,8-triaryl-4-(phenylethynyl)quinazolines were determined in solution.

Keywords: 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones; 2-aryl-4-chloro-6,8-dibromoquinazolines; 2-aryl-6,8-dibromo-4-(phenylethynyl)quinazolines; 2,6,8-triaryl-4-(phenylethynyl)quinazolines; Sonogashira cross-coupling reaction; Suzuki-Miyaura cross-coupling reaction; absorption and emission properties

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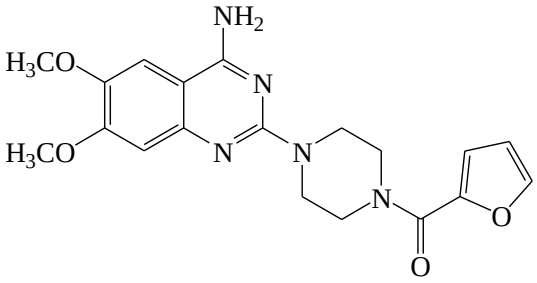
CHAPTER 1 INTRODUCTION

Organic heterocyclic compounds comprise a vast field for the search of new materials possessing diverse applications, such as pharmaceutical products,[1] agrochemical products[2] and organic light-emitting materials.[3,4] Although several methods have been developed for the synthesis of polysubstituted quinazoline derivatives, to our knowledge, there are no derivatives bearing two aryl rings on the fused benzo ring. The main focus of the current investigation is on the design and synthesis of polyaryl substituted quinazolines, in which the electron-deficient quinazoline framework is linked to the 4-phenyl ring via a π-conjugated spacer and to the 2-, 6- and 8-aryl rings directly to afford donor-acceptor systems. It is envisaged that the prepared compounds would exhibit interesting photophysical properties. The challenge in synthesizing the desired tetraaryl substituted quinazolines is that the preformed quinazoline moiety must be suitably functionalized to allow directed metal-catalyzed cross-coupling reactions. In this investigation, attention is focused on methods that involve the use of 2-aryl-6,8-dibromo-4-chloroquinazolines as precursors for sequential metal catalyzed C-C bond formation.

1.1 Structure and application of quinazoline derivatives

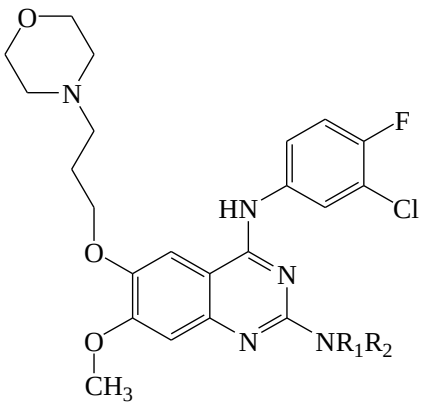
Quinazoline is a compound made up of two fused aromatic rings, that is, the benzene and the pyrimidine ring. It was first prepared by Gabriel in 1903 and isolated from the Chinese plant aseru.[1] The quinazoline scaffold is one of the most encountered moieties in medicinally important compounds with a wide range of biological properties including cardiovascular,[2] anti-cancer,[3] anti-bacterial,[4] anti-malarial[5] and anti-inflammatory activities.[6,7] Prazosin **1**, for

example, was found to possess antihypertensive activity and it is a sympatholytic drug used for the treatment of high blood pressure.[8] In addition, Prazosin is a prototype of several quinazoline based antihypertensive drugs such as Terazosin, Doxazosin and Trimazosin.[4]



1

The study on 4-anilinoquinazoline derivatives as inhibitors of tyrosine kinase activity of epidermal growth factor receptor (EGFR) resulted in the approval of Gefitinib **2** for the treatment of lung cancer.[9] Protein tyrosine kinases are enzymes involved in many cellular processes and are known to be activated in cancer cells to drive tumour growth and progression.[10] Blocking tyrosine kinase activity therefore represents a rational approach to cancer therapy. Erlotinib or Tarceva **3**, a 4-anilinoquinazoline derivative bearing an alkynyl moiety on the aniline ring, is also known as a tyrosine kinase inhibitor which acts on the epidermal growth factor receptor.[9]



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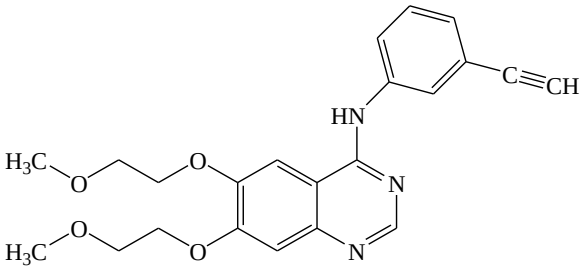
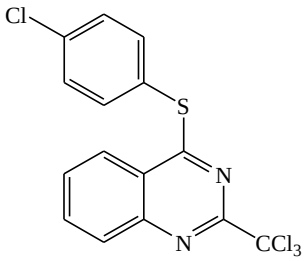


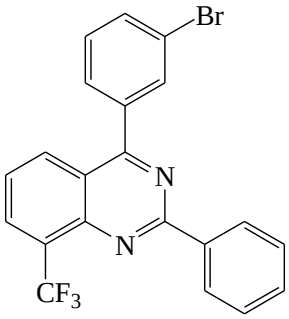
3

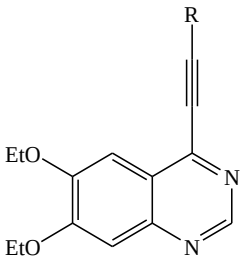
A series of quinazolines bearing a thiophenoxy group at position 4 and a trichloromethyl group at position 2 were synthesized and found to exhibit antiplasmodial activity *in vitro*.[11] 4-(4-Chlorophenylthio)-2-(trichloromethyl)quinazoline **4**, for example, appears to be a new promising candidate for the development of anti-malaria pharmacophores.



4

Biological activity of quinazolines is not only restricted to heteroatom-substituted derivatives. During the course of the exploration of non-anilino quinazoline scaffolds, trisubstituted quinazoline derivatives such as 4-(3-bromophenyl)-8-(trifluoromethyl)-2-phenylquinazoline **5** were prepared as part of a series of liver X receptor modulators.[12] 4-Alkynylquinazolines **6** were found to be potent EGFR tyrosine kinase inhibitors.[13]

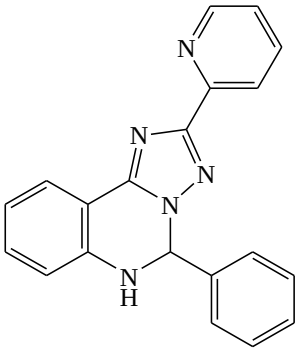




5 **6** (R= Ph, CH_2-O-Ph, $C(Me)_2CH_2Ph$)

Heterocyclic compounds with intramolecular charge transfer properties, on the other hand, have attracted considerable attention for potential applications in organic electroluminescent diodes,[14] organic solar cells,[15,16] polarity probes[17] and nonlinear optics.[18] Polysubstituted quinolines in which an electron acceptor 2-aryl-4-methoxyquinoline framework is linked to

the π-conjugated spacer through positions 6 and 8 to form donor-π-acceptor systems were reported as precursors for compounds with potential photonic or electronic properties.[19] The substitution of a phenyl fragment in stillbene with a nitrogen-containing heterocyclic unit has been established to have a significant effect on their photophysical properties, due to the involvement of the n→π* electronic state.[20] The photophysical properties of 2-styrylquinazolin-4(3*H*)-ones have been reported and these compounds can be regarded as candidates for organic electroluminescent diodes.[21] 5-Phenyl-2-(pyridin-2-yl)-5,6-dihydro[1,2,4]triazolo-[1,5-*c*]-quinazoline **7,** a heteroannulated quinazoline derivative, was found to represent a new class of luminescent compounds in the solid state and in solution.[22] Compound **7** can therefore be recommended as a molecular probe and fluorescent label in microbiological assays.



7

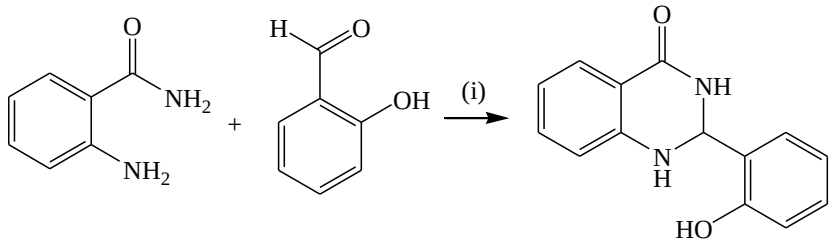
Owing to their diverse applications, the development of methods for the synthesis of quinazoline derivatives has attracted considerable attention over the years. Diverse synthetic approaches towards the construction of quinazoline skeletons have been reported in the literature and the common procedure involves the oxidative aromatization of the corresponding quinazolinone precursors.

1.2 Synthesis of quinazolin-4-one derivatives

The most general method for the synthesis of quinazolinones involves cyclocondensation of anthranilamide derivatives with aldehydes in the presence of various reagents such as *p*-toluenesulfonic acid,[23] sodium bisulfite ($NaHSO_3$),[24] or manganese dioxide (MnO_2),[25] *etc.*

1.2.1 Methods for the synthesis of quinazolin-4(1*H*)-ones

A number of methods for the synthesis of quinazolin-4(1*H*)-ones have been reported in literature including reductive cyclization and metal-mediated reactions. The condensation of anthranilamide **8** with salicyladehyde **9** in the presence of *p*-toluenesulfonic acid (*p*-TsOH) as a catalyst in ethanol at reflux afforded 2-hydroxyphenyl-2,3-dihydroquinazolin-4(1*H*)-one **10** (Scheme 1).[23] *p*-TsOH is an easily available and cheap reagent, which is used as a catalyst to promote the cyclocondensation of anthranilamide derivatives with carbonyl containing compounds.

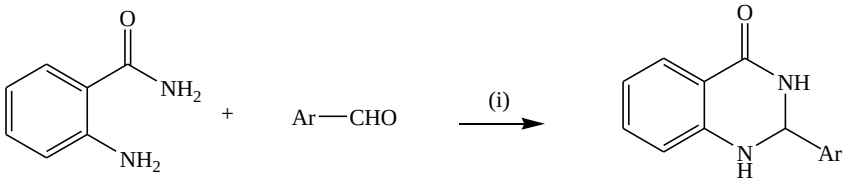


8 **9** **10**

Reagents and conditions: (i) *p*-TsOH, EtOH, reflux, 1 h.

Scheme 1: Synthesis of 2-hydroxyphenyl-2,3-dihydroquinazolin-4(1*H*)-one using *p*-TsOH as a catalyst

Reductive cyclisation of anthranilamide **8** and aldehydes **11** using silica-supported ferric chloride (SiO_2-$FeCl_3$) as catalyst under solvent-free conditions afforded the 2,3-dihydroquinazolin-4(1*H*)-one derivatives **12** (Scheme 2).[26] Iron(III) chloride is a strong Lewis acid which promotes the cyclocondensation.

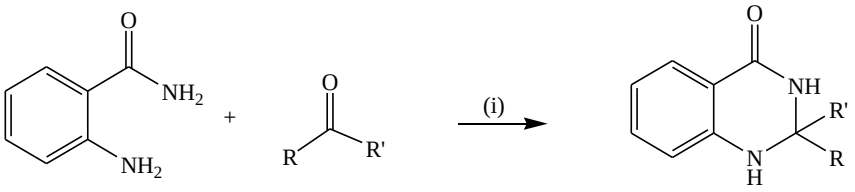


8 **11** **12**

Reagents and conditions: (i) SiO_2-$FeCl_3$, solvent-free, 80 °C.

Scheme 2: SiO_2-$FeCl_3$ catalysed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones under solvent-free conditions

During the course of studies on green chemistry, M. Wang *et al.* developed a new procedure for the synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones **14**, which involves the grinding of anthranilamide **8** with aldehydes or ketones **13** at room temperature in the presence of cerium(IV) ammonium nitrate (CAN) and water. The reaction mixture was later heated at 60 °C until completion of the transformation (Scheme 3).[27] Cerium(IV) ammonium nitrate is a versatile single-electron oxidant that promotes the cyclisation of anthranilamide derivatives with carbonyl containing compounds. The grinding step was found to be essential to increase the surface area and lead to increased yields.

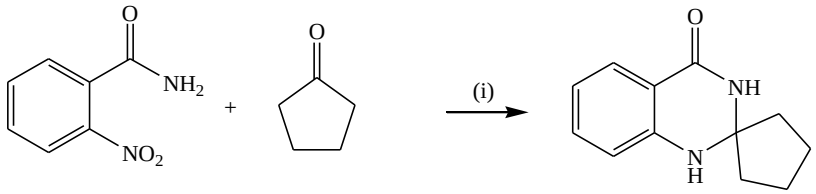


8 **13** **14**

Reagents and conditions: (i) CAN, Grinding.

Scheme 3: CAN-mediated synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

The reaction of *o*-nitrobenzamide **15** and cyclic ketone **16** in the presence of low valent titanium prepared from titanium tetrachloride and zinc powder in anhydrous THF afforded 2,2-polymethylene-2,3-dihydroquinazolin-4(1*H*)-one **17** (Scheme 4).[28] Zinc metal is used to effect the reduction of *o*-nitrobenzamide to *o*-aminobenzamide.[29] Low-valent titanium tetrachloride, on the other hand, activates the carbonyl group to promote cyclocondensation.



15 **16** **17**

Reagents and conditions: (i) $TiCl_4$-Zn, THF.

Scheme 4: Low-valent titanium-promoted synthesis of quinazolin-4(3*H*)-ones

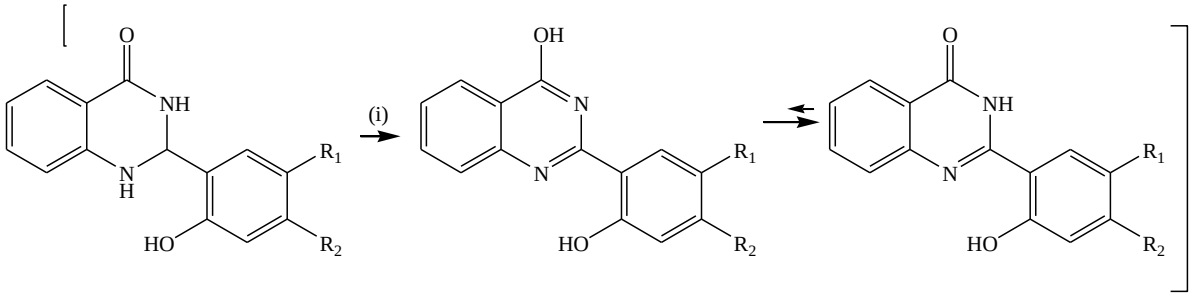
The dihydroquinazolin-4(1*H*)-one core can allow different degrees of unsaturation *via* dehydrogenation or aromatization to afford the corresponding quinazolin-4(3*H*)-ones or the fully aromatic quinazolines.

1.2.2 Methods for the synthesis of quinazolin-4(3*H*)-ones

Tautomeric quinazolin-4(3*H*)-ones can be obtained from the corresponding dihydroquinazolin-4(1*H*)-ones through dehydrogenation using an oxidizing reagent to introduce an unsaturation between N-1 and C-2 of the scaffold. Alternatively, quinazolin-4(3*H*)-ones are prepared directly in a single-pot procedure from anthranilamide derivatives and various carbonyl compounds by oxidative cyclocondensation or transition metal-catalyzed reactions.

1.2.2.1 Indirect methods involving dehydrogenation of quinazolin-4(1*H*)-ones

2-Hydroxyarylquinazolin-4(3*H*)-one derivatives **20,** for example, were prepared by the oxidation of the dihydro derivatives **18** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in ethanol at reflux (Scheme 5).[23] DDQ acts as an oxidizing reagent to introduce an unsaturation between N-1 and C-2. However quinazolin-4-ones were reported to exist in two different forms: the lactam form (major) and the iminol form (minor).[30]

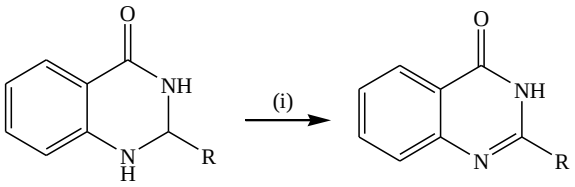


18 **19** (iminol) **20** (lactam)

Reagents and conditions: (i) DDQ, EtOH, reflux.

Scheme 5: Synthesis of 2-hydroxyarylquinazolin-4(3*H*)-ones with DDQ

Similarly, the oxidation of 2,3-dihydroquinazolin-4(1*H*)-ones **21** with iron(III) chloride hexahydrate (2 equiv) as an oxidizing agent, in refluxing water afforded the 2-substituted quinazolin-4(3*H*)-ones **22** in 77 to 92% yield (Scheme 6).[31]



21 **22** (R=H, CH_3, C_6H_5, 4-HOC_6H_4)

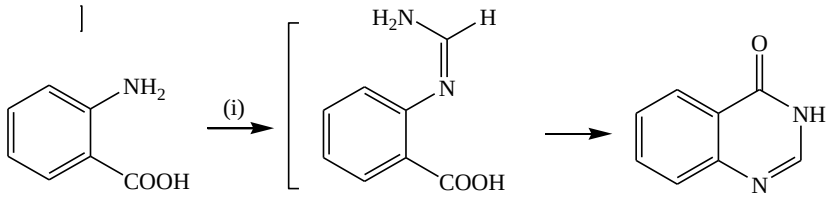
Reagents and conditions: (i) $FeCl_3.6H_2O$, H_2O, reflux.

Scheme 6: Oxidation of 2,3-dihydroquinazolin-4(1*H*)-one with $FeCl_3.6H_2O$

Although effective, the synthesis of quinazolin-4(3*H*)-ones by means of dehydrogenation of the corresponding quinazolin-4(1*H*)-ones involve the use of non-environmentally friendly oxidative reagents in large excess. To minimise the risk of pollution, methods for one-pot synthesis of quinazolin-4(3*H*)-ones continue to appear in the literature.

1.2.2.2 Direct methods for the synthesis of quinazolin-4(3*H*)-ones

The single-pot reaction of 2-aminobenzoic acid **23** with formamide at 150 °C was found to proceed through an *o*-amidine intermediate **24** to afford the quinazolin-4(3*H*)-one **25** in 59% yield (Scheme 7).[32]

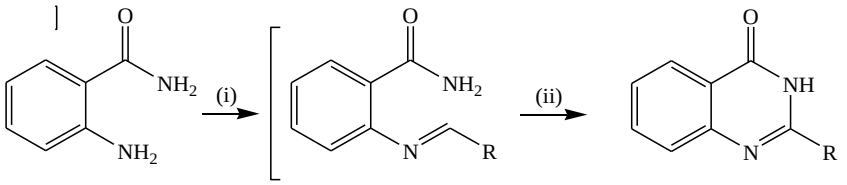


23 **24** **25**

Reagents and conditions: (i) H_2N-CHO, 150 °C, 6 h.

Scheme 7: Single-pot reaction of 2-aminobenzoic acid with formamide

A mixture of anthranilamide **8** and aldehyde derivatives in refluxing ethanol for 3 hours afforded compounds **26** in 82 to 91% yield. The latter were converted within 2 hours to the corresponding quinazolin-4(3*H*)-ones **27** in the presence of copper chloride (3 equiv) in refluxing ethanol (Scheme 8).[33] This procedure has the advantage of using low temperature to achieve complete conversion of anthranilamide. The use of high temperature may produce complex decomposition mixtures.[34]

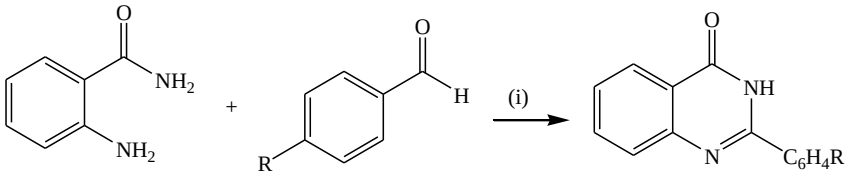


8 **26** **27**

Reagents and conditions: (i) RCHO, EtOH, 78 °C (ii) $CuCl_2$, EtOH, 78 °C.

Scheme 8: Oxidative cyclization of anthranilamide and aldehydes with $CuCl_2$

Mehdi Bakavoli and his group reported the oxidative cyclocondensation of anthranilamide **8** with aromatic aldehydes **28** in the presence of molecular iodine (1.2 equiv) (Scheme 9).[35] Iodine is a Lewis acid that promotes the cyclocondensation and also effects the dehydrogenation.



8 **28** **29**

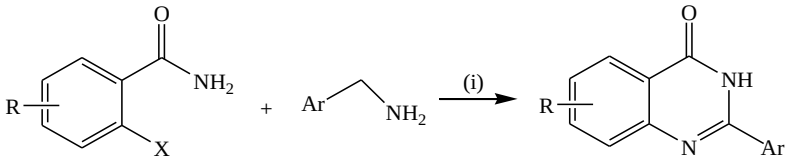
Reagents and conditions: (i) I_2, EtOH, rt.

Scheme 9: Iodine-promoted oxidative cyclization of anthranilamide and aldehydes

Non-classical methods such as transition metal-catalyzed cyclocondensation have also been described in the literature and those are discussed below.

1.2.2.3 Synthesis of quinazolin-4(3*H*)-ones *via* transition metal-catalyzed cyclocondensation

X. Wei *et al*., reported the synthesis of 2-arylsubtituted quinazolin-4(3*H*)-ones **32** by copper(I) bromide catalyzed reaction of halobenzamides **30** and arylmethanamines **31** in the presence of potassium carbonate as a base in DMSO under air as the oxidant at 110 °C (Scheme 10).[36]

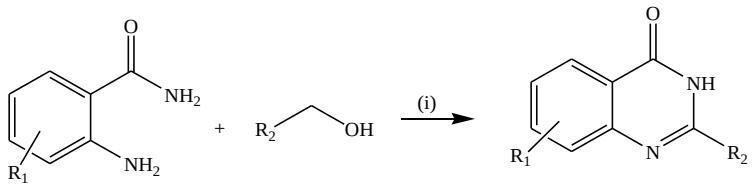


30 (X=I, Br, Cl) **31** **32**

Reagents and conditions: (i) CuBr, K_2CO_3, DMSO, 110 °C, 8 h.

Scheme 10: CuBr catalysed reaction of halobenzamides with arylmethanamines

A one-pot oxidative cyclization of anthranilamides **33** with primary alcohols **34** to afford quinazolin-4(3*H*)-ones **35** was successfully achieved using bis[pentamethylcyclopentadienyl iridium chloride] as a catalyst in refluxing xylene (Scheme 11).[37]

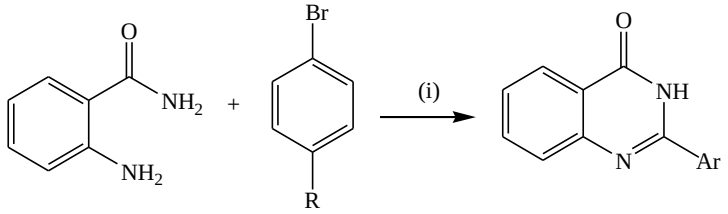


33 **34** **35**

Reagents and conditions: (i) $[CpIrCl_2]_2$, K_2CO_3, xylene, 140 °C, 62 h.

Scheme 11: Iridium-catalyzed one-pot synthesis of quinazolin-4(3*H*)-ones

W. Xiao-Feng *et al.* reported the synthesis of quinazolin-4(3*H*)-ones **37** from 2-aminobenzamide **8** and aryl bromides **36** in the presence of palladium(II) acetate as a source of Pd(0) catalyst, butyldiadamantylphosphine ($BuPAd_2$) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at 120 °C under 10 bar of CO (Scheme 12).[38]



8 **36** **37**

Reagents and conditions: (i) $Pd(OAc)_2$, $BuPAd_2$, DBU, CO, DMF, 120 °C, 16 h.

Scheme 12: Palladium-catalyzed one-pot synthesis of quinazolin-4(3*H*)-ones

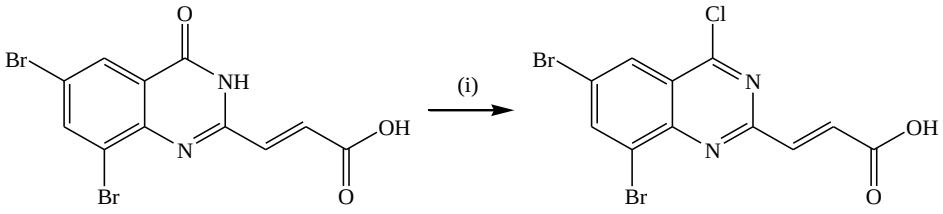
The quinazolin-4(3*H*)-one nucleus is a key intermediate for the preparation of quinazolines through oxidative aromatization.

1.3 Synthesis of quinazolines

Diverse synthetic approaches towards the construction of quinazoline skeleton have been reported in the literature using different starting materials, such as quinazolin-4(3*H*)-ones, *N*-substituted anthranilamides and isatoic anhydride derivatives.

1.3.1 Oxidative-aromatization of quinazolin-4(3*H*)-one derivatives

4-Halogenoquinazolines are important intermediates in the synthesis of substituted quinazolines due to the increased reactivity of the C-X bond towards various nucleophiles. The common method for the preparation of 4-chloroquinazoline derivatives involves oxidative aromatization of the corresponding quinazolin-4(3*H*)-ones using reagents such as thionyl chloride ($SOCl_2$),[39] phosphoryl chloride ($POCl_3$)[40,41] or a combination of phosphorus pentachloride (PCl_5) and phosphoryl chloride ($POCl_3$).[42,43] The synthesis of 3-(6,8-dibromo-4-chloroquinazolin-2-yl)-2-propenoic acid **39**, for example, was achieved *via* the aromatization of the quinazolin-4(3*H*)-one precursor **38** using a mixture of $POCl_3$ and PCl_5 in a boiling water bath (Scheme 13).[42]

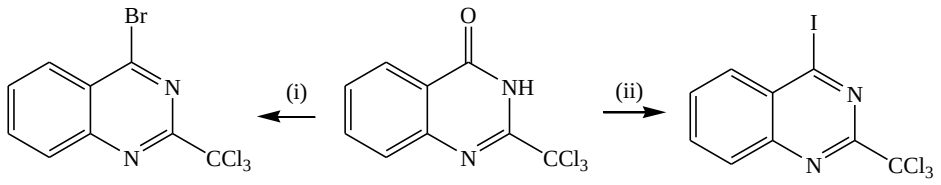


38 **39**

Reagents and conditions: (i) $POCl_3$, PCl_5, 70 °C.

Scheme 13: Oxidative aromatization of quinazolin-4(3*H*)-one **38** with PCl_5 and $POCl_3$

The reaction of 2-trichloromethylquinazolin-4(3*H*)-one **40** with either tetrabutylammonium bromide (TBABr) or tetrabutylammonium iodide (TBAI) in the presence of phosphorus pentoxide (P_2O_5) in toluene, on the other hand, afforded the corresponding brominated or iodinated quinazoline derivatives **41** or **42**, respectively (Scheme 14).[44]



41 **40** **42**

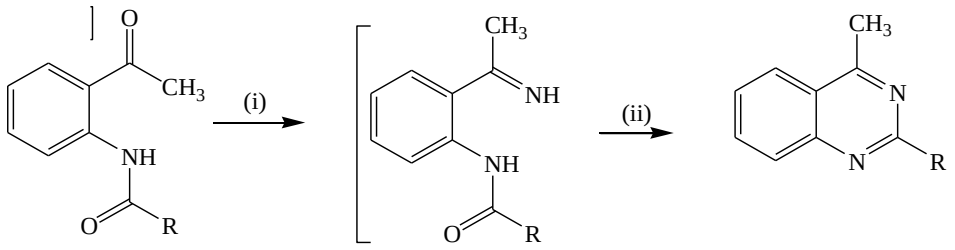
Reagents and conditions: (i) TBABr, P_2O_5, toluene. (ii) TBAI, P_2O_5, toluene.

Scheme 14: Oxidative aromatization of quinazolin-4(3*H*)-one **40** with TBABr or TBAI

In addition to undergoing nucleophilic displacement of the 4-halogeno atom with various heteroatom-containing nucleophiles,[40,41,44] the 4-halogenoquinazolines easily undergo metal-catalyzed cross-coupling to afford carbo-substituted quinazoline derivatives. [46]

1.3.2 Direct synthesis of quinazolines from substituted anthranilamide derivatives

The microwave-assisted reaction of *N*-(2-acetylphenyl)alkylamide **43** and ammonium formate was found to proceed *via* the formation of an imine intermediate **44** to afford the 2,4-dialkyl or -aryl quinazolines **45** in 50 to 65% yield (Scheme 15).[47] During the course of this reaction, ammonium formate is decomposed at high temperature to form ammonia which generates the imine that cyclises in the acid environment due to the presence of excess ammonium formate.

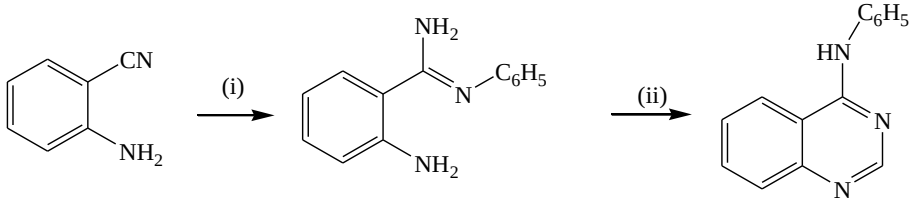


43 **44** **45**

Reagents and conditions: (i) $HCOONH_4$, MW 150 °C, 3 to 9 min (ii) HCOOH.

Scheme 15: Microwave-assisted synthesis of 2,4-disubstitutedquinazolines

The reaction of 2-aminobenzonitrile **46** with aniline in the presence of aluminium chloride afforded 2-amino-*N*-phenylbenzamidine **47**, which upon heating with NaOH in formic acid yielded 4-phenylaminoquinazoline **48** (Scheme 16).[48]

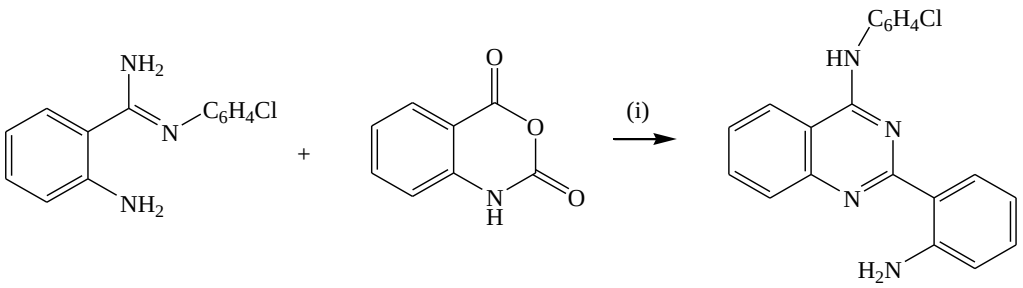


46 **47** **48**

Reagents and conditions: (i) $C_6H_5NH_2$, $AlCl_3$, 180 °C (ii) HCOOH, NaOH, 90 °C, 2 h.

Scheme 16: Synthesis of 4-phenylaminoquinazoline from 2-aminobenzonitrile and aniline

A one-pot cyclisation involving heating of 2-amino-*N*-(3-chlorophenyl)benzamidine **49** with isatoic anhydride **50** in absolute ethanol afforded 2-(2-aminophenyl)-*N*-(3-chlorophenyl)quinazolin-4-amine **51** in 70% yield (Scheme 17).[49]

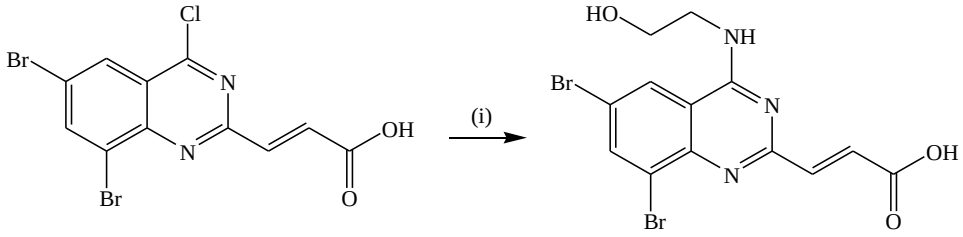


49 **50** **51**

Reagents and conditions: (i) EtOH, 180 °C, 3 h.

Scheme 17: Reaction of 2-amino-3-chlorophenylbenzimidamide with isatoic anhydride

The 4-alkyl/arylaminoquinazolines are also commonly prepared through dechloroamination of the corresponding 4-chloroquinazolines. The condensation of 2-carboxyvinyl-4-chloro-6,8-dibromoquinazoline **38** with ethanolamine in boiling ethanol, afforded the alkyl amino derivative **52** in 72% yield (Scheme 18).[42] The nitrogen atom of the ethanolamine is more nucleophilic than the more electronegative oxygen atom.

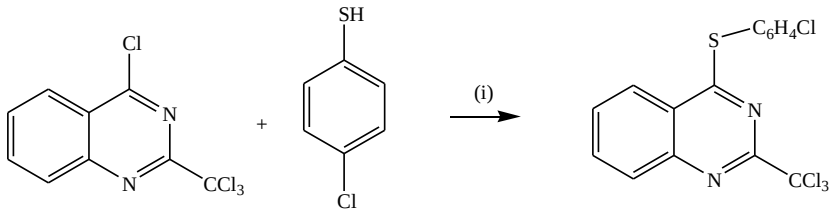


38 **52**

Reagents and conditions: (i) $H_2N(CH_2)_2OH$, EtOH, 80 °C.

Scheme 18: Condensation of 2-carboxyvinyl-4-chloro-6,8-dibromoquinazoline with ethanolamine

The reaction of 4-chloro-2-(trichloromethyl)quinazoline **53** and 4-chlorothiophenol **54** in DMSO under nitrogen atmosphere at room temperature afforded 4-(4-chlorophenylthio)-2-(trichloromethyl)quinazoline **55** in 68% yield (Scheme 19).[11]



53 **54** **55**

Reagents and conditions: (i) NaH, DMSO, N_2, rt, 1 h 20 min.

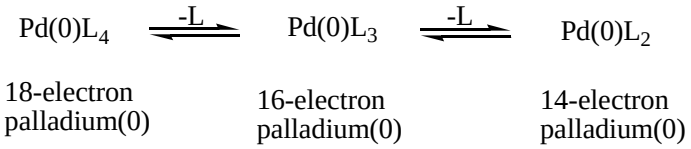
Scheme 19: Preparation of 4-(4-chlorophenylthio)-2-(trichloromethyl)quinazoline

Halogenated quinazolines also constitute important substrates for structural elaboration *via* metal-catalyzed carbon-carbon bond formation to afford novel polysubstituted quinazolines as described below.

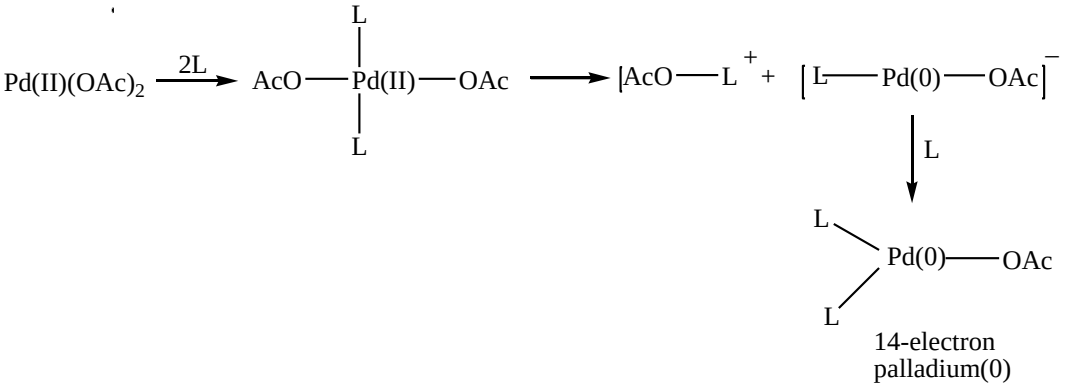
1.3.3 Synthesis of carbo-substituted quinazoline derivatives *via* metal-catalyzed cross-coupling reactions

The development of metal-catalyzed cross-coupling reactions over the past decade has revolutionized the way carbon-carbon bonds are formed. Kumada, Negishi, Suzuki-Miyaura, Stille, and Sonogashira cross-coupling reactions represent powerful synthetic tools for the construction of highly substituted heterocycles.[50] The mechanism for metal-catalyzed cross-coupling usually occurs in three steps, namely, oxidative addition, transmetallation and reductive elimination. In the case of palladium cross coupling reactions, a catalytically active 14-electron

Pd(0) species is first generated from a pre-catalyst, either by ligand dissociation for Pd(0) precursors (Scheme 20) or by palladium reduction for Pd(II) precursors (Scheme 21). A wide range of palladium(0) catalysts or precursors are used for cross-coupling reaction. $Pd(PPh_3)_4$ is most commonly used, but $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ plus PPh_3 or other phosphine ligands are also efficient since they are stable to air and readily reduced to the active Pd(0) complexes with phosphines.[51]



Scheme 20: Palladium ligand dissociation



Scheme 21: Palladium reduction of $Pd(OAc)_2$

The palladium cross-coupling start with oxidative addition of the active palladium(0) catalyst $Pd(0)L_2$ **A** to the aryl halide (Figure 1). During this step, the Csp^2-X bond breaks and a palladium(II) complex *trans*-$R_1Pd(II)L_2X$ **B** bearing both aryl and halide components as ligands. The rate of the oxidative addition is influenced by the reactivity of the aryl halide and the nature of the ligand present in the palladium(0) precursor.[51] An order of reactivity of aryl halides is in

agreement with the C-X bond strengths. Likewise, alkylphosphine ligands are known to increase the electron density of palladium and, in turn, accelerate the oxidative addition step. The palladium(II) complex **B** formed is a 16-electron tetra-coordinated and square-planar species which can undergoes transmetallation *via* ligand exchange process with the aid of a base to formed an organopalladium(II) complex $R_1Pd(II)L_2Nu$ **C** (Figure 1). The organic ligands of compound **C** are *trans* oriented and are converted to *cis* in a *trans-cis* isomerization to form isomer **D**. In the final step, known as reductive elimination, the organopalladium(II) complex *cis*-$R_1Pd(II)L_2Nu$ **D** releases the coupled product and regenerates the catalyst Pd(0). An increase of the electron density at the metal center facilitates the reductive elimination. Alkylphosphine ligands are known to coordinate with palladium and increase its electron density more than arylphosphines.[51] The general catalytic cycle for such reaction can be represented as follows:

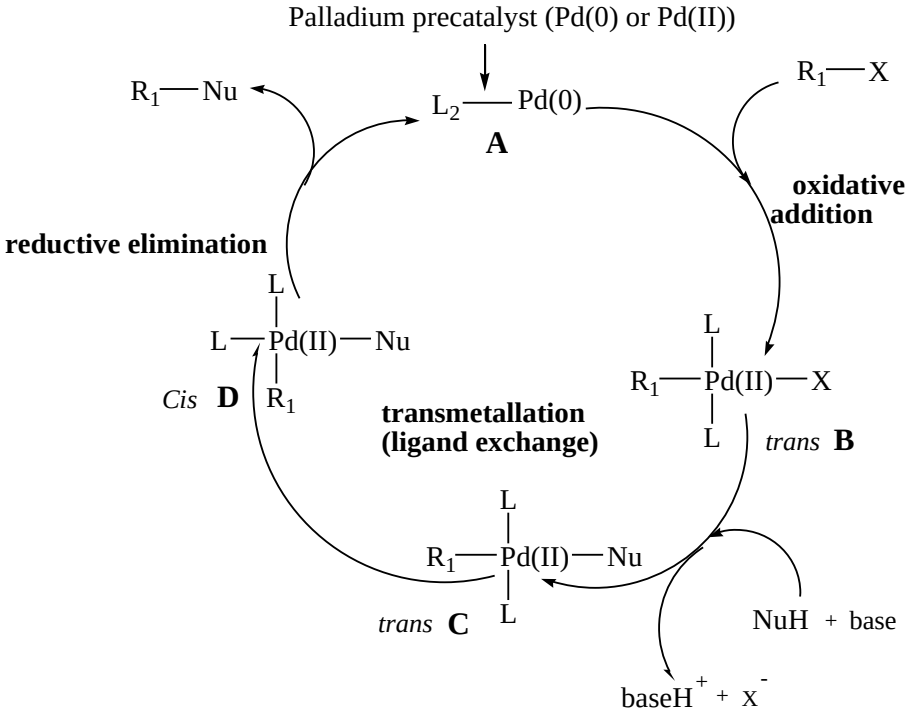
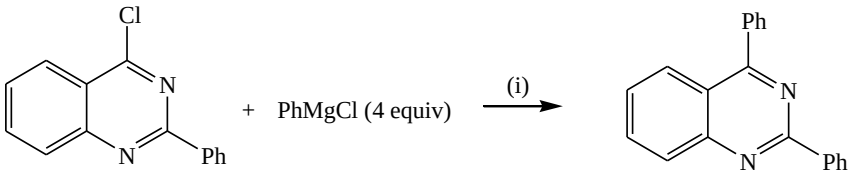


Figure 1: Generalised cycle for palladium-catalysed cross coupling

1.3.3.1 Kumada cross-coupling reaction

The Kumada cross-coupling reaction involves the reaction of an organohalide with an organomagnesium compound (Grignard reagent) to yield the cross-coupled product using a palladium or nickel species as a catalyst. The reaction of 4-chloro-2-phenylquinazoline **56** with phenylmagnesium chloride **57** using anhydrous manganese chloride ($MnCl_2$) or manganese chloride tetrahydrate ($MnCl_2.4H_2O$) in tetrahydrofuran (THF), for example, afforded 2,4-diphenylquinazoline **58** in 71% yield (Scheme 22).[52] The reaction is complete within 1.5 hour because of the α-nitrogen effect that activates the C-4 position of the quinazoline ring.



56 **57** **58**

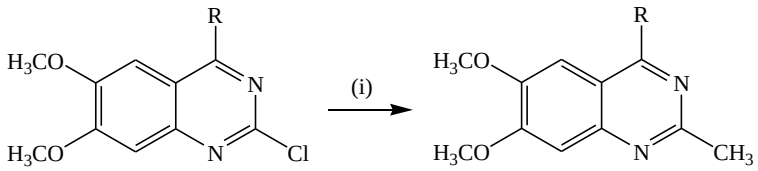
Reagents and conditions: (i) $MnCl_2$ or $MnCl_2.4H_2O$, THF, 0 °C 1.5 h.

Scheme 22: Manganese-catalyzed cross-coupling of 4-chloro-2-phenylquinazoline with phenylmagnesium chloride

The mild reaction conditions as well as the lower cost of manganese chloride, as compared to palladium or nickel salts, render this transformation an attractive alternative for the synthesis of carbo-substituted heterocycles. However, due to the high nucleophilicity of Grignard reagents, limited functional groups can be tolerated on both of the coupling partners and this makes the Kumada cross-coupling less applicable.

1.3.3.2 Negishi cross-coupling reaction

The Negishi cross-coupling is the reaction between an organohalide with an organozinc compound in the presence of a palladium or nickel catalyst.[53] The alkylation at C-2 position of 4-substituted 2-chloro-6,7-dimethoxyquinazoline **59** was achieved *via* Negishi cross-coupling with methyl lithium and zinc(II) chloride using tetrakis(triphenylphosphine) palladium(0) [$Pd(PPh_3)_4$] as a catalyst in dioxane to afford the coupled product **60** (Scheme 23).[54]



59 **60**

Reagents and conditions: (i) MeLi, $ZnCl_2$, $Pd(PPh_3)_4$, dioxane.

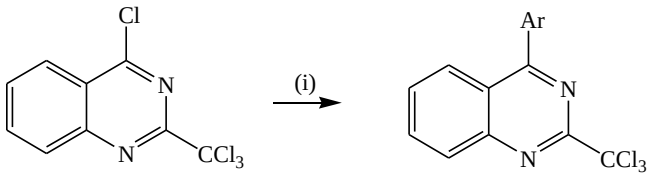
Scheme 23: Palladium-catalyzed cross-coupling of 4-substituted 2-chloro-6,7-dimethoxyquinazoline **59** with MeLi and $ZnCl_2$

The main drawbacks of organozinc reagents are their incompatibility with a number of functional groups and their sensitivity to water and air.

1.3.3.3 Suzuki-Miyaura cross-coupling reaction

Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction between organoboron compounds and organic halides or triflates is a general and efficient method for the formation of Csp^2–Csp^2 bonds.[55] This cross-coupling reaction has several advantages including

functional group compatibility, low toxicity of reagents and intermediates, easy availability of boron derivatives, high thermal stability and good tolerance toward oxygen and aqueous solvents.[56] The reaction has a wide application in organic syntheses, material and medicinal chemistry and it is still an area of intense research. P. Verhaeghe *et al.* subjected 4-chloro-2-trichloromethylquinazoline **61** to Suzuki cross-coupling with arylboronic acids (2.5 equiv) in the presence of $Pd(OAc)_2$ in DMF to afford the corresponding 4-aryl-2-trichloromethylquinazolines **62** in 50 to 65% yield (Scheme 24).[57] Compounds **62** were found to exhibit antiplasmodial activity.

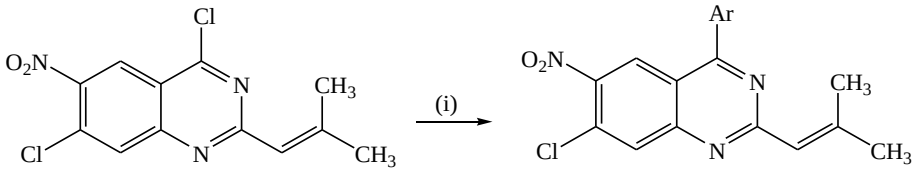


61 **62** (Ar = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4)

Reagents and Conditions: (i) $ArB(OH)_2$ (2.5 equiv), Cs_2CO_3, $Pd(OAc)_2$, DMF, reflux, 2 h.

Scheme 24: Suzuki-Miyaura cross-coupling of 4-aryl-2-trichloromethylquinazolines

The Suzuki-Miyaura cross-coupling of 4,7-dichloro-2-(2-methylprop-1-enyl)-6-nitro quinazoline **63** with arylboronic acids (1.5 equiv), Na_2CO_3 and $Pd(PPh_3)_4$ in DME-ethanol (9:1, v/v) under microwave irradiation afforded the monosubstituted C-4 products **64** exclusively in 48 to 63% yield (Scheme 25).[56] In the case of the 4-methoxy derivative, the monosubstituted C-4 product was obtained using 1.2 equivalents of the 4-methoxyphenylboronic acid. The use of 1.5 equivalents of the electron rich 4-methoxyphenylboronic acid, on the other hand, afforded the monosubstituted product **64** in 45% yield and the disubstituted product in 15% yield. The latter was obtained as the only product when using 4 equivalents of the 4-methoxyphenylboronic acid.

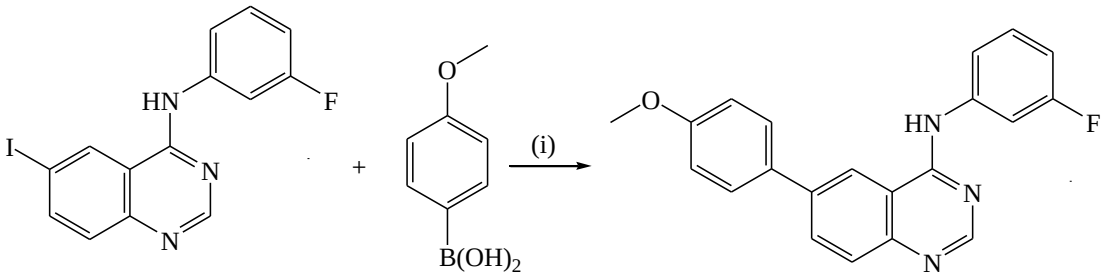


63 **64**

Reagents and Conditions: (i) $ArB(OH)_2$ (4 equiv), Na_2CO_3, $Pd(PPh_3)_4$, DME/ethanol (9:1, v/v), MW (300 W), 80 °C, 3 h.

Scheme 25: Suzuki-Miyaura cross-coupling of 4,7-diarylquinazolines

The Suzuki cross-coupling reaction of *N*-(3-fluorophenyl)-6-iodoquinazolin-4-amine **65** with 4-methoxyphenylboronic acid **66** using $Pd(OAc)_2$ as a catalyst and Cs_2CO_3 as a base in aqueous dioxane led to *N-(*3-fluorophenyl)-6-(4-methoxyphenyl)quinazolin-4-amine **67** in 70% yield (Scheme 26).[58]



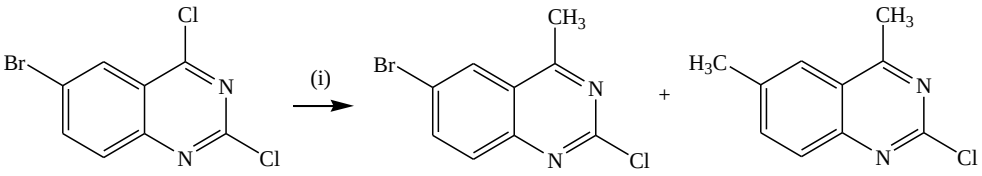
65 **66** **67**

Reagents and Conditions: (i) Cs_2CO_3, $Pd(OAc)_2$, dioxane-water (3:1, v/v), reflux 30 min.

Scheme 26: The Suzuki cross-coupling reaction of *N*-(3-fluorophenyl)-6-iodoquinazolin-4-amine

1.3.3.4 Stille cross-coupling reaction

The Stille cross-coupling involves a cross-coupling between organostannanes and organic halides in the presence of Pd catalyst.[59] Attempts to achieve monosubstitution via the Stille cross-coupling of 6-bromo-2,4-dichloroquinazoline **68** with trimethylalane (1.2 equiv) in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] as a catalyst resulted in mixture of both the C-4 **69** (47% yield) and C-6 **70** (16% yield) cross-coupled products (Scheme 27).[60]



68 **69** **70**

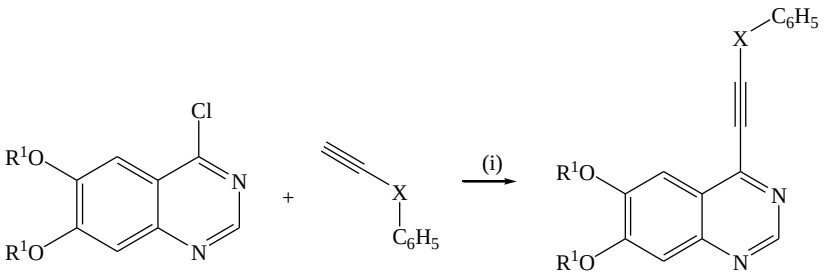
Reagents and Conditions: (i) $Al(CH_3)_3$, $Pd(PPh_3)_4$, THF, reflux.

Scheme 27: Regioselective alkylation of 6-bromo-2,4-dichloroquinazoline

1.3.3.5 Sonogashira cross-coupling reaction

The Sonogashira coupling reaction of aryl halides with terminal acetylenes provides an effective route for C*sp*-C*sp*^{2} bond formation to afford arylalkynes and conjugated enynes.[61] The reaction is widely applied as a key step in natural product synthesis and the preparation of molecular organic materials.[62] The use of both palladium and copper catalyst results in the increased reactivity of the reagents and the ability of the reaction to be carried out at room temperature. The alkynylation of 4-chloroquinazoline **71** with various terminal alkynes **72** (1.5 equiv) was achieved in the presence of palladium catalyst, with copper(I) iodide as a co-

catalyst and triethylamine (Et_3N) as a base in DMF to afford the 4-alkynylquinazolines **73** as new scaffolds for potent epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (Scheme 28).[62]

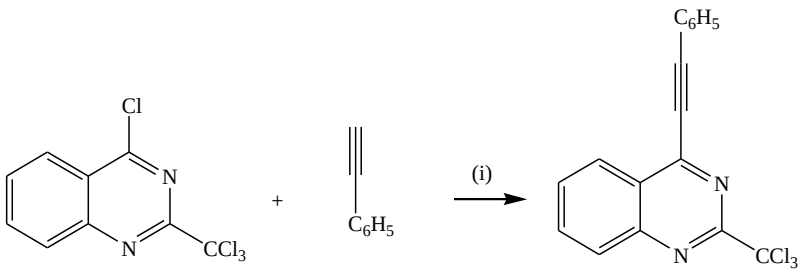


71 **72** **73** (X= -$(CH_2)_2$-, 4- ClC_6H_4-, -CH_2O-)

Reagents and conditions: Et_3N, $Pd(PPh_3)_4$, CuI, DMF, rt.

Scheme 28: Sonogashira cross-coupling of 6,7-disubtituted-4-chloroquinazoline

Attempted Sonogashira cross-coupling reaction between 4-chloro-2-trichloromethyl-quinazoline **61** and phenylacetylene **74** using triethylamine as a base, tetrakis(triphenyl-phosphine)palladium(0) [$Pd(PPh_3)_4$] as a source of a reactive Pd(0) species and copper(I) iodide (CuI) as a co-catalyst in THF under nitrogen atmosphere did not afford the expected cross-coupled product.[44] The presence of the trichloromethyl group at position 2 was found to complicate the outcome of this reaction. The use of cesium carbonate (Cs_2CO_3) as a base and palladium(II) acetate [$Pd(OAc)_2$] as a catalyst in dimethylformamide (DMF), on the other hand, afforded the cross-coupled product **75** in low yield (15%) along with other undesirable products (Scheme 29).[44]

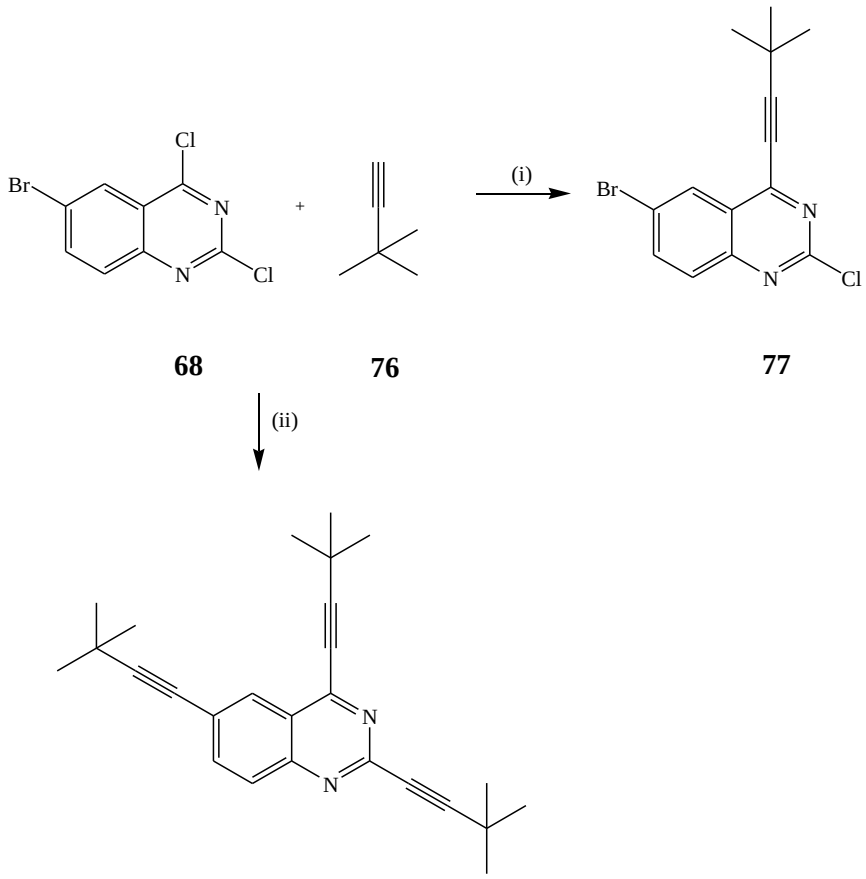


61 **74** **75**

Reagents and conditions: (i) Cs_2CO_3, $Pd(OAc)_2$, CuI, DMF, N_2, rt, 3 h.

Scheme 29: Sonogashira cross-coupling reaction of 4-chloro-2-trichloromethylquinazoline

The selective mono-alkynylation of 6-bromo-2,4-dichloroquinazoline **68** with *tert*-butyl acetylene **76** in the presence of bis(tryphenylphosphine)palladium(II) dichloride [$PdCl_2(PPh_3)_2$] and copper(I) iodide as catalyst complex and triethylamine as a base in THF at room temperature afforded the C-4 substituted product **77** in 67% yield (Scheme 30).[63] The selectivity of Pd-catalyzed cross-coupling favours C-4 substitution due to α-nitrogen effect. On the other hand, heating the reaction mixture of 6-bromo-2,4-dichloroquinazoline with *tert*-butyl acetylene at 65 °C afforded the trisalkynylated derivative **78** in 54% yield (Scheme 30).[63]



68 **76** **77**

78

Reagents and conditions: (i) Et_3N, $PdCl_2(PPh_3)_2$, CuI, THF, 20 h, rt. (ii) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 20 h, 65 °C.

Scheme 30: Sonogashira cross-coupling reaction of 6-bromo-2,4-dichloroquinazoline

1.4 Research objectives

During our research on the development of polysubstituted heterocycles, we became interested in the synthesis of 2,4,6,8-tetrasubstituted quinazolines in which the electron-deficient quinazoline framework is linked at C-4 to an aryl ring *via* π-conjugated spacer and directly at C-2, C-6 and C-8 to aryl rings to form donor-acceptor systems. Organic compounds with intramolecular charge transfer properties have potential applications in

organic electroluminescent diodes,[14] organic solar cells,[15,16] polarity probes[64] and nonlinear optics.[65] A broad variety of donor-acceptor compounds with different configurations have been extensively developed because their absorption spectra and energy gaps can be tuned by controlling the intramolecular charge transfer from the electron donors to the electron acceptor.[19] We envisioned that the 2-aryl-6,8-dibromo-4-chloroquinazolines represent suitable candidates for sequential Pd-catalyzed Sonogashira and Suzuki cross-coupling to afford the requisite polysubstituted quinazolines with potential photophysical properties. The main objectives of this investigation are to:

(i) effect direct one-pot synthesis of the 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones using 3,5-dibromoanthranilamide and substituted benzaldehydes as substrates,

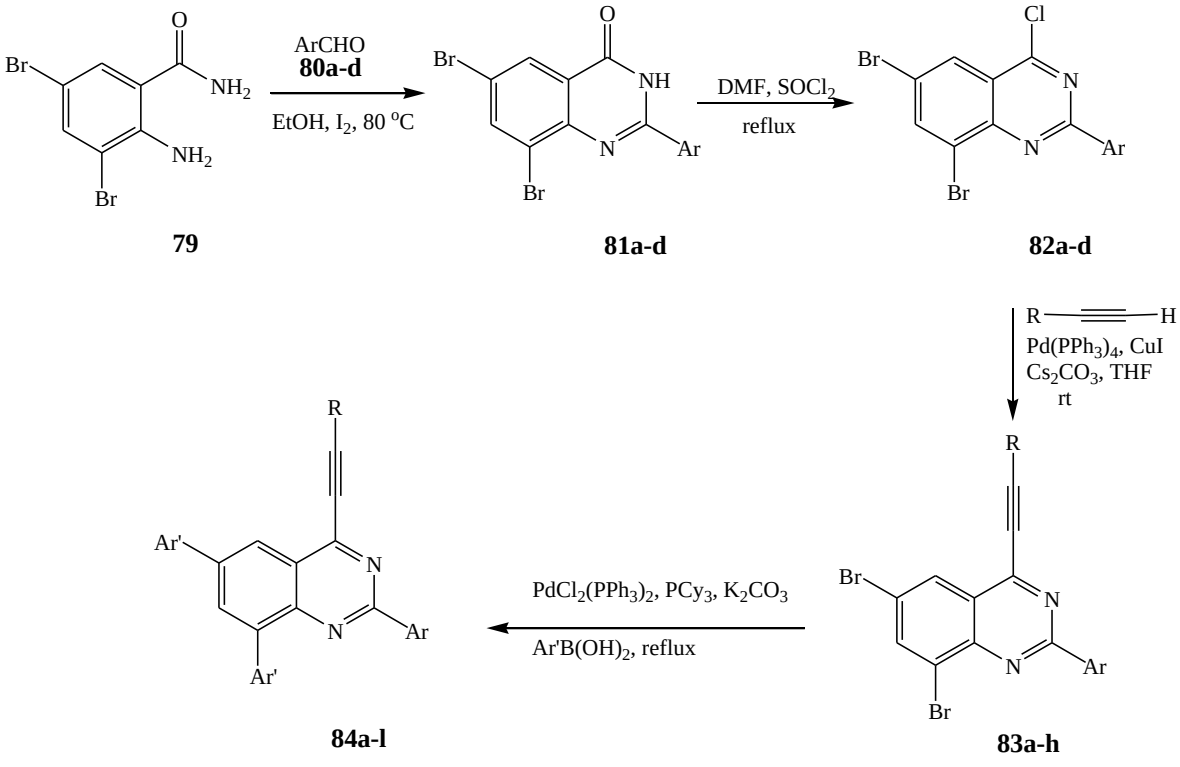
(ii) prepare the corresponding 2-aryl-6,8-dibromo-4-chloroquinazolines *via* oxidative-aromatization of the 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones,

(iii) subject the 2-aryl-6,8-dibromo-4-chloroquinazolines to sequential palladium catalyzed Sonogashira and Suzuki-Miyaura cross coupling reactions, and

(iv) to study the absorption and emission properties of the resultant 2,4,6,8-tetrasubstituted quinazolines using UV-Vis and fluorescence spectroscopic techniques.

CHAPTER 2 RESULTS AND DISCUSSION

Brief overviews of all the reaction steps undertaken in this investigation are summarized in scheme 31. The 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones **81a-d** were prepared by condensing 6,8-dibromoanthranilamide **79** and benzaldehyde derivatives **80a-d** in the presence of molecular iodine in ethanol at 80 °C. Treatment of 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones **81a-d** with thionyl chloride in the presence of DMF afforded the corresponding 2-aryl-4-chloro-6,8-dibromoquinazolines **82a-d**. The latter were, in turn, subjected to Sonogashira cross-coupling reaction with terminal alkynes in the presence of $Pd(PPh_3)_4$-CuI catalyst mixtures and Cs_2CO_3 as a base in THF at room temperature to afford novel 2-aryl-6,8-dibromo-4-(alkynyl)quinazolines **83a-h**.



79 **81a-d** **82a-d**

84a-l **83a-h**

Scheme 31: Generalized scheme illustrates reaction pathways followed to prepare the compounds described in this investigation

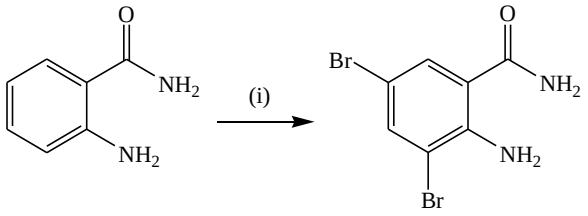
The 2-aryl-6,8-dibromo-4-(phenylethynyl) quinazolines **83a-d** were subjected to Suzuki-Miyaura cross-coupling with arylboronic acids in the presence of $PdCl_2(PPh_3)_2$-PCy_3 catalyst complex and K_2CO_3 in dioxane-water (3:1, v/v) to afford the corresponding 2,6,8-triaryl-4-(phenylethynyl)quinazolines **84a-l**.

2.1 Synthesis of substrates

2.1.1 Synthesis of 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones

The first requirement of this investigation was to synthesize the 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones **81a-d** to be used as substrates for the 2-aryl-6,8-dibromo-4-chloroquinazolines **82a-d**. The quinazolin-4(3*H*)-one scaffold is generally accessible *via* dehydrogenation of the corresponding 2,3-dihydroquinazolin-4(1*H*)-one precursors using oxidants such as $KMnO_4$,[66] $CuCl_2$[67] and DDQ[68] in stoichiometric quantities or in large excess. The 2-substituted quinazolin-4(3*H*)-ones have also been synthesized directly from anthranilamide and aldehydes using $NaHSO_3$,[69] DDQ,[23] or I_2[35] as catalysts. In order to synthesize the required 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones, we needed 2-amino-3,5-dibromobenzamide **79** as a precursor. 3,5-Dibromoanthranilamide analogue was previously prepared by reacting anthranilic acid with bromine in glacial acetic acid.[70] However, because of the lack of selectivity of bromine, this reaction results in a mixture of mono- and dibromoanthranilic acids. The reaction of 2-aminobenzamide **8** with *N*-bromosuccinimide (NBS) in chloroform at room temperature afforded 2-amino-3,5-dibromobenzamide **79** in 70% yield (Scheme 32). The amino group is a strong *ortho/para* director and this effect is relatively reinforced by the presence of the strong electron withdrawing amide group thus

activating both positions 3 and 5 for attack by the electrophilic bromide ion. The ^{1}H NMR spectrum of compound **79** reveals the presence of a singlet at δ *ca.* 6.77 ppm integrating for two hydrogen atoms and corresponding to the protons of amino group (Figure 2). The singlets at δ *ca* 7.72 ppm and δ *ca* 7.77 ppm correspond to 4-H and 6-H, respectively. The amide protons resonate at δ *ca* 7.47 ppm and 8.05 ppm. This non-equivalence between the two amide protons is due to the presence of an intramolecular hydrogen bond between the proton (H_a) at 8.05 ppm and the amine nitrogen in analogy with the literature precedent on the 2-aryliminocoumarin-3-carboxamides.[71]



8 **79**

Reagents and conditions: (i) NBS (2 equiv), $CHCl_3$, rt, 3 h.

Scheme 32: Bromination of 2-aminobenzamide with NBS

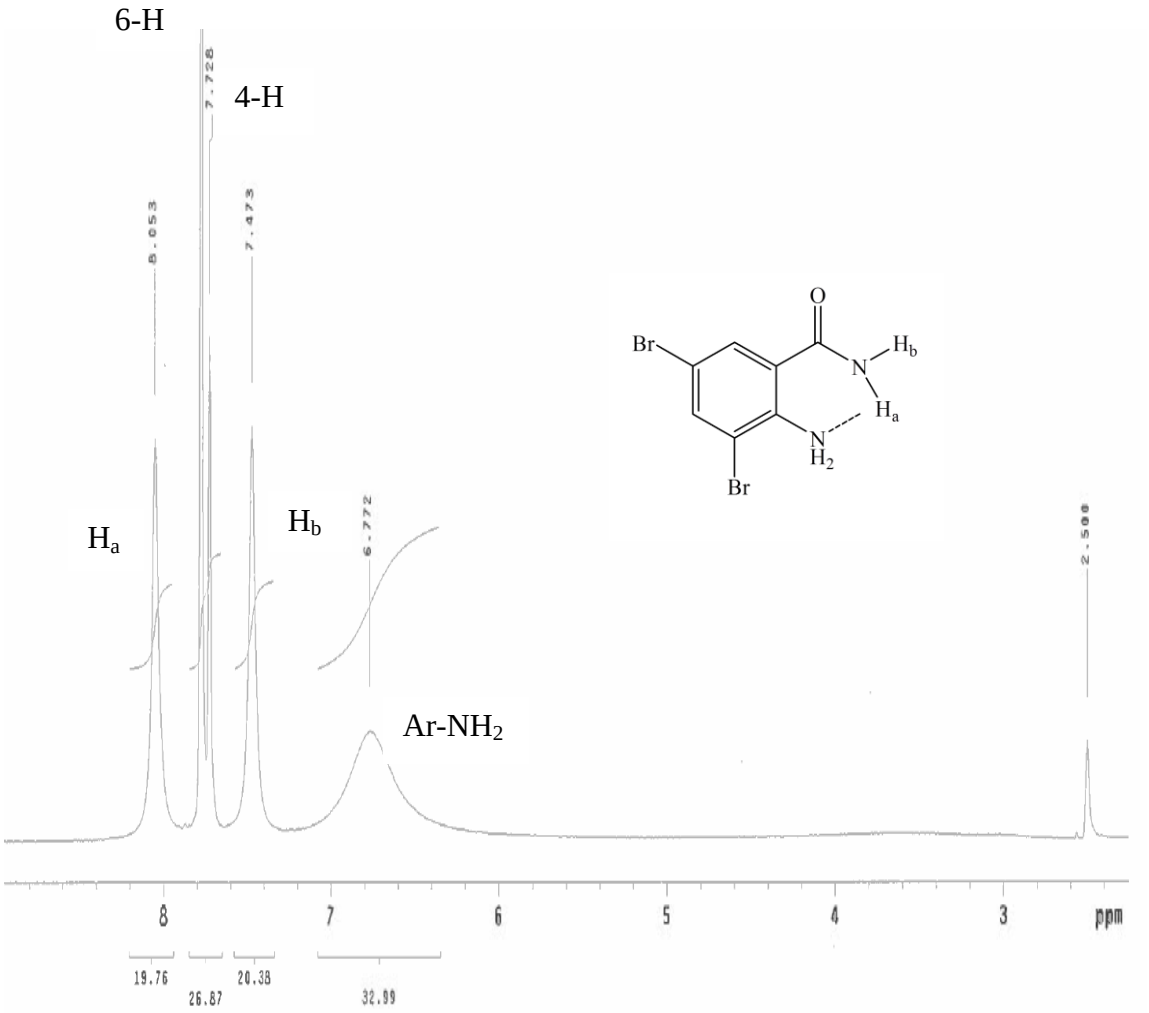
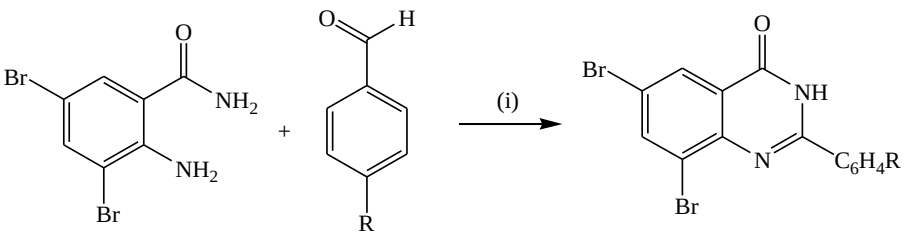


Figure 2: ^{1}H NMR spectrum of **79** in DMSO-d_6 at 300 MHz

With 3,5-dibromoanthranilamide **79** in hand, we decided to investigate the possibility of synthesizing 2-aryl-6,8-dibroquinazolin-4(3*H*)-ones *via* one-pot cyclocondensation and dehydrogenation with benzaldehyde derivatives. Compounds **81a-d** were prepared in a single-pot operation by the oxidative cyclocondensation of 2-amino-3,5-dibromobenzamide **79** with benzaldehyde derivatives **80a-d** in the presence of molecular iodine (2 equiv) in absolute ethanol at 80 °C (Scheme 33). Molecular iodine in this case serves as a catalyst to

effect the cyclocondensation and as an oxidant to introduce dehydrogenation. The prepared compounds **81a-d** were characterized using ^{1}H NMR, IR, and mass spectroscopic techniques. Because of a poor solubility of **81a-d** in DMSO-d_6 we were not able to obtain their ^{13}C NMR spectra. The ^{1}H NMR spectra of products **81a-d** reveal the presence of a singlet at δ *ca.* 12.94 ppm corresponding to the N-H proton, and resonances in the region δ 7.11−8.39 ppm for the aromatic protons (Figure 3). Their amide nature is also confirmed by the presence of IR bands in the region ν_{max} 1660−1680 cm^{-1} and ν_{max} 1550−1595 cm^{-1} corresponding to C=O and C-N, respectively. The accurate calculated *m/z* values in each case are consistent with the observed molecular weight of the assigned structure.



79 **80** **81a-d**

81	**R**	**ν_{max} C=O (cm^{-1})**	**ν_{max} C−N (cm^{-1})**	**% Yield**	**mp. (ºC)**
a	4-H	1666	1592	80	332−335
b	4-F	1676	1583	89	> 345
c	4-Cl	1672	1558	94	> 345
d	4-OCH$_3$	1663	1556	89	302−304

Reagents and conditions: (i) I_2 (2 equiv), EtOH, 80 °C, 7 h.

Scheme 33: Iodine-promoted oxidative cyclocondensation of 2-amino-3,5-dibromobenzamide with aldehydes

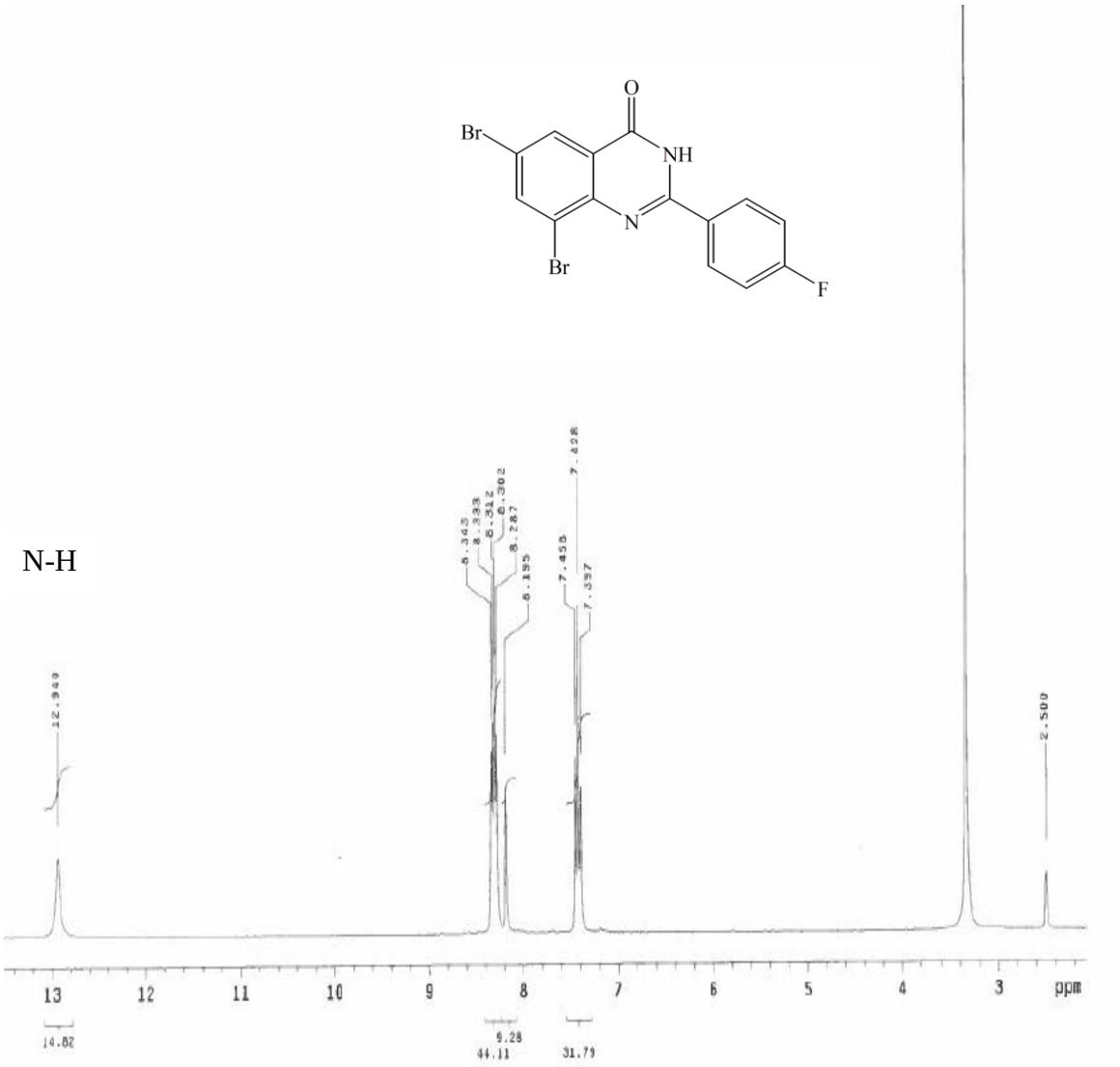
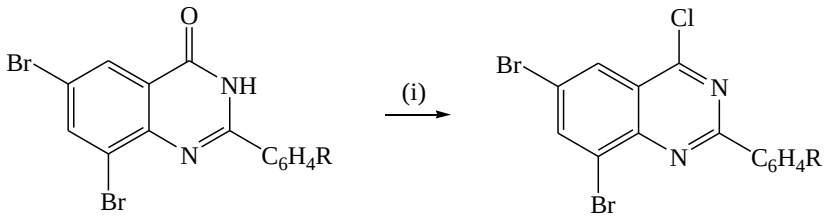


Figure 3: ^{1}H NMR spectrum of **81b** in DMSO-d_6 at 300 MHz

2-Phenyl-6,8-dibromoquinazolin-4(3*H*)-one **81a** was previously found to exhibit antibacterial and antiinflammatory properties.[72] Moreover, the 2-substituted 6,8-dibromoquinazolin-4(3*H*)-ones were reported as starting materials for the synthesis of a series of 2,4-disubstituted quinazolines as antibacterial and antifungal agents.[73] Compounds **81a-d** represents suitable scaffolds for further dehydrogenation to afford the fully aromatic quinazoline derivatives.

2.1.2 Synthesis of 2-aryl-4-chloro-6,8-dibromoquinazolines

Several methods have been described for the synthesis of 4-chloroquinazolines *via* oxidative aromatization of the quinazolin-4(3*H*)-ones. 4-Chloro-5,7-difluoroquinazoline, for instance, was prepared following the condensation of 5,7-difluoroquinazolin-4(3*H*)-one in an excess of phosphoryl chloride ($POCl_3$) in the presence of tertiary amine as a catalyst.[74] Attempted oxidative aromatization of compounds **81a-d** with $POCl_3$, $POCl_3$−amine or $POCl_3$−DMF mixtures under reflux led to incomplete conversion (tlc monitoring) to the requisite 4-chloroquinazolines. The 4-chloroquinazolines **82a-d** were prepared with thionyl chloride in the presence of trace amounts of DMF under reflux for 2 h (Scheme 34).[39] The success of this transformation was confirmed by the absence of an N-H signal in the ^{1}H NMR spectra of compounds **82a-d** and the presence of additional aromatic proton signals in the region δ 7.08−8.28 ppm (Figure 4). Moreover, the IR spectra of products **82a-d** are characterized by the absence of the C=O stretch found in the spectra of the corresponding substrates.



81a-d **82a-d**

82	R	% Yield	mp. (°C)
a	4-H	96	186-187
b	4-F	81	206-208
c	4-Cl	77	239-240
d	4-OCH_3	77	200-202

Reagents and conditions: (i) $SOCl_2$, DMF, 120 °C, 2 h.

Scheme 34: Oxidative aromatization of 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones

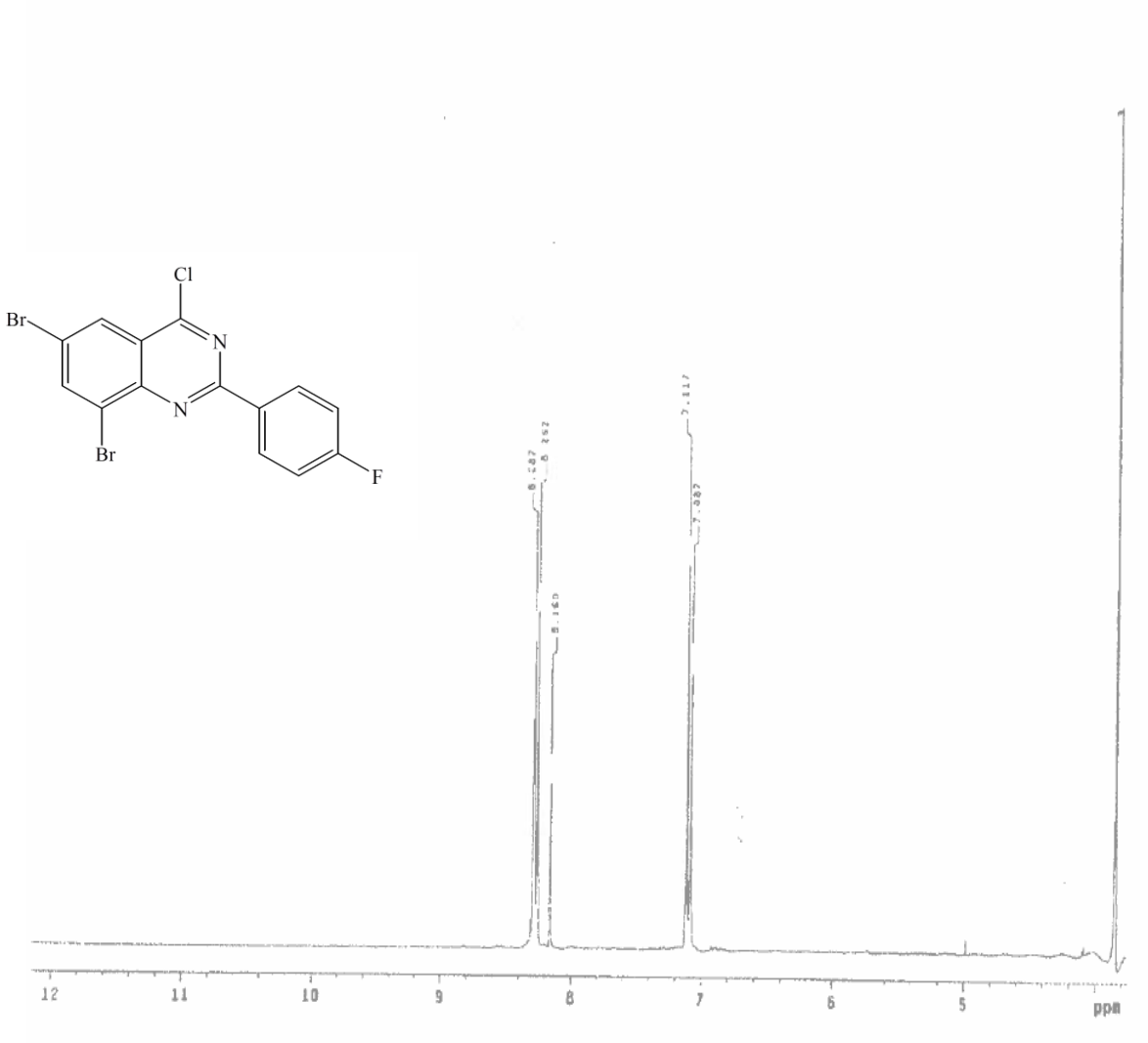


Figure 4: ^{1}H NMR spectrum of **82b** in $CDCl_3$ at 300 MHz

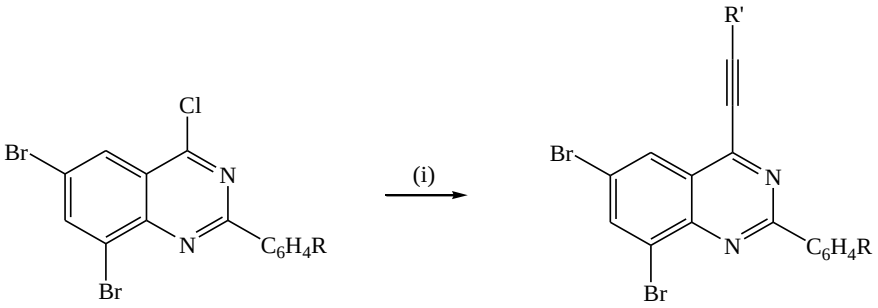
It is well known in the literature that the C-4 position of the quinazoline moiety is highly electrophilic due to the α-nitrogen effect.[56] The reaction of 4-chloroquinazoline derivatives with hydrazine hydrate and subsequent condensation with different aromatic aldehydes furnished a series of fused 5-substituted-[1,2,4]triazoloquinazoline derivatives.[42] Likewise, interaction of 6,8-dibromo-4-chloro-2-methylquinazoline with acetyl acetone in boiling ethanol in the presence of sodium ethoxide as a catalyst afforded 6,8-dibromo-2-methyl-4-(diacetylmethyl)quinazoline.[73]

Moreover, compounds **82** represent suitable candidates for further transformation *via* metal catalyzed cross-coupling due to the presence of halogens at positions 4, 6 and 8. In this investigation, we focused our attention on the reactivity of compounds **82a-d** in Sonogashira cross-coupling with terminal alkynes as models for C*sp*^{2}–C*sp* bond formation.

2.2 Sonogashira cross-coupling of 2-aryl-4-chloro-6,8-dibromoquinazolines

The choice of Sonogashira cross-coupling is based on the fact that this reaction occurs under mild conditions and can tolerate various functional groups. At first we reacted 4-chloro-6,8-dibromo-2-phenylquinazoline **82a** with phenylacetylene (1.2 equiv) using tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] as a Pd(0) source, copper(I) iodide (CuI) as co-catalyst and Cs_2CO_3 as a base in DMF under nitrogen atmosphere at room temperature for 3 hours in analogy with previous literature procedure.[44] We recovered the starting material **82a**. We then reacted **82a** with phenylacetylene (1.2 equiv) in the presence of $Pd(PPh_3)_4$, CuI and Cs_2CO_3 in THF under nitrogen atmosphere at room temperature for 24 hours. Compound **83a** was isolated in 59% yield and the reaction conditions were extended to other derivatives using phenylacetylene, 2-ethynylpyridine, and 3-butyn-2-ol as coupling partners to afford product **83b-h** (Scheme 35). The ^{1}H NMR spectra of compounds **83a-h** reveal two singlets at δ *ca.* 8.28 and 8.47 ppm corresponding to 5-H and 7-H, respectively (Figure 5). The ^{1}H NMR spectrum of **83h** is also characterised by the presence of a doublet at δ *ca.* 1.70 ppm, a singlet at δ *ca.* 2.35 ppm, and a quartet at δ *ca.* 4.94 ppm corresponding to CH_3, OH and CH of the 1-hydroxyethyl group, respectively. The ^{13}C NMR spectra of **80a-h** show, as expected, an increased number of resonances and the alkyne carbons resonating at δ *ca*. 84.9 ppm (≡C−R'), and 99.0 ppm (C(4)−C≡) respectively (Figure 6). Likewise, their IR

spectra reveal the presence of an intense absorption band at ν_{max} 2210 cm^{-1} which corresponds to the C–C triple bond (Figure 7). The accurately calculated *m/z* values in all cases confirm the replacement of the 4-Cl due to the absence of peaks attributed to the chlorine isotopes (*m/z* 35 and 37). On the other hand, the appearance of Br isotopes (*m/z* 79 and 81) peaks confirmed the presence of two bromine atoms.



82a-d **83a-h**

83	R	R'	ν_{max} C≡C (cm^{-1})	% Yield	mp. (°C)
a	4-H	-C_6H_5	2215	59	186-187
b	4-F	-C_6H_5	2210	72	206-208
c	4-Cl	-C_6H_5	2209	70	239-240
d	4-OCH_3	-C_6H_5	2210	71	200-202
e	4-H	2-pyridyl-	2228	65	207-209
f	4-F	2-pyridyl-	2219	67	216-218
g	4-OCH_3	2-pyridyl-	2221	55	204-206
h	4-H	-CH(OH)CH_3	2221	56	162-165

Reagents and conditions: (i) R′C≡CH, $Pd(PPh_3)_4$, CuI, Cs_2CO_3, THF, rt, 24 h.

Scheme 35: Sonogashira cross-coupling of 2-aryl-4-chloro-6,8-dibromoquinazolines with terminal akynes

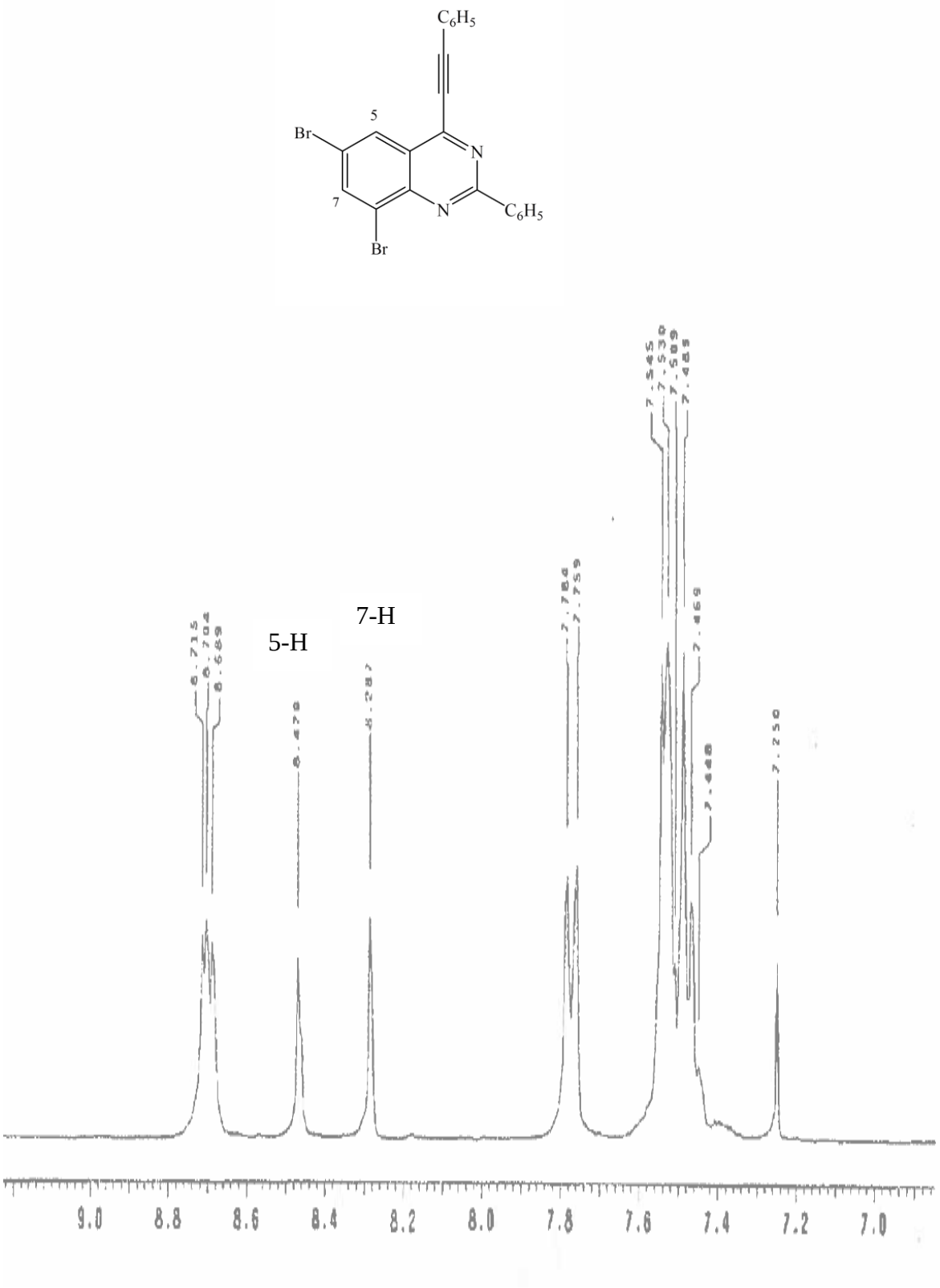


Figure 5: ^{1}H NMR spectrum of **83a** in $CDCl_3$ at 300 MHz

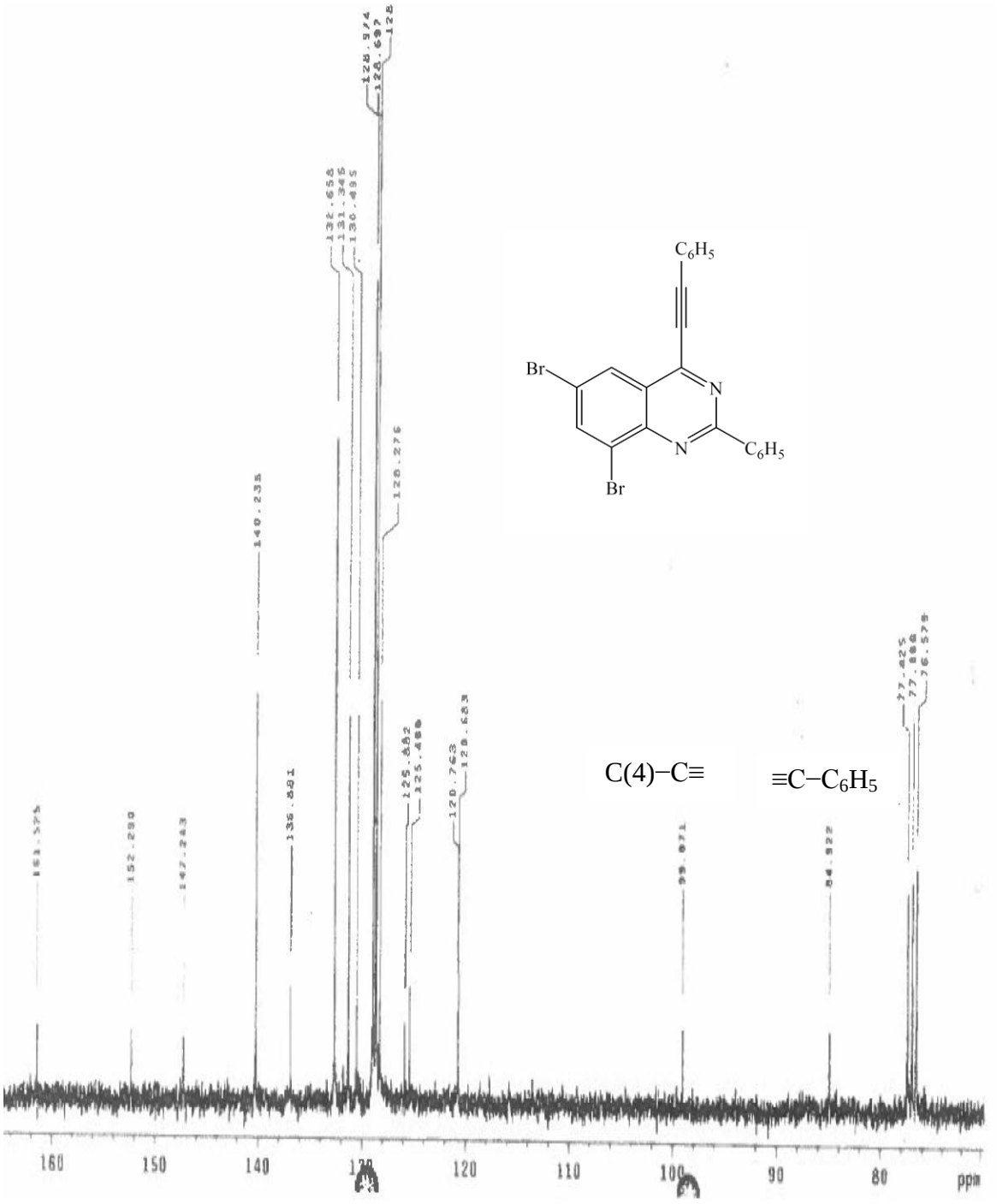


Figure 6: ^{13}C NMR spectrum of **83a** in $CDCl_3$ at 75 MHz

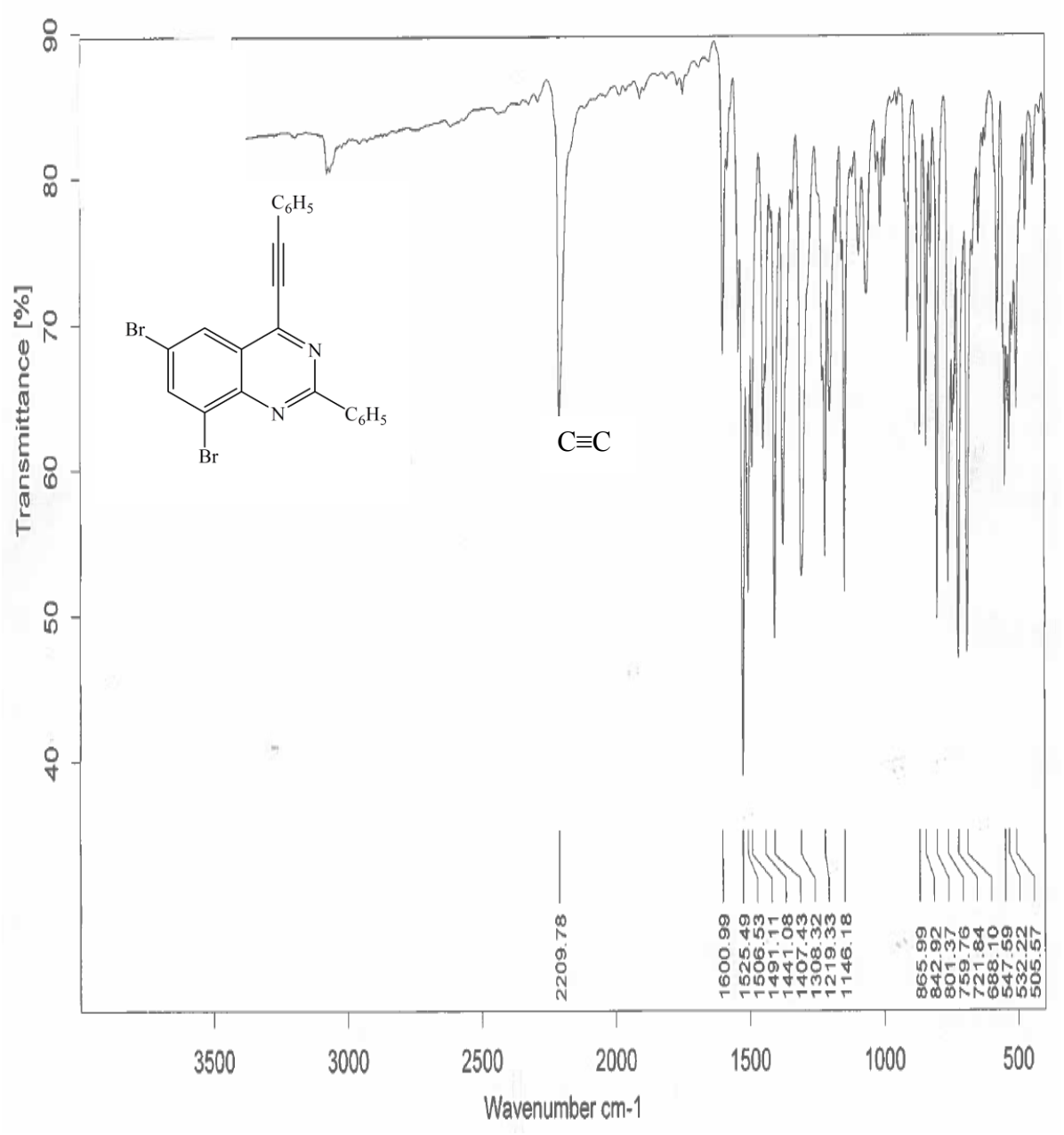


Figure 7: IR spectrum of **83a**

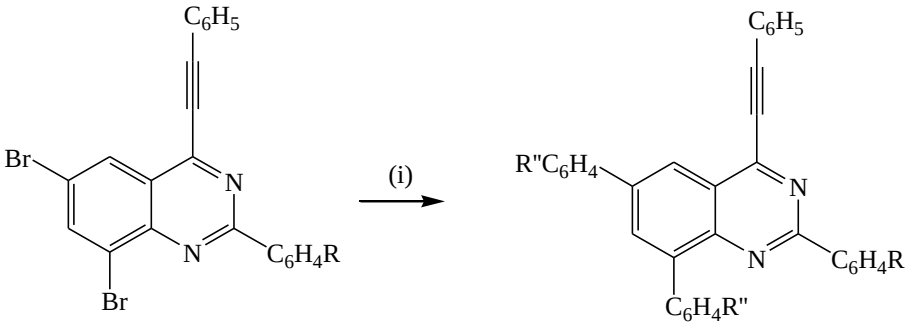
Several examples of 2-substituted quinazolines bearing an alkynyl substituent at the C-4 position have been reported to exhibit excellent epidermal growth factor receptor (EGFR) activity.[12] The two bromine atoms on the fused benzo ring in compounds **83** makes them

suitable candidates for subsequent elaboration *via* metal-catalyzed cross-coupling. We decided to investigate the reactivity of compounds **83** in palladium catalyzed Suzuki-Miyaura cross-coupling with arylboronic acids.

2.3 Suzuki cross-coupling of 2-aryl-6,8-dibromo-4-(phenylethynyl)quinazolines

The displacement of halogen atoms on dihalogenated heterocyclic compounds bearing different halogens *via* cross-coupling reactions is known to follow the trend: I > Br > Cl.[75] The C-X bond dissociation energies decrease down the halogen group with the electronegativity. In the case of dihalogenated heterocycles bearing the same halogen atoms, the challenge is to study the reactivity of both halogens in a cross-coupling reaction. Suzuki cross-coupling of 6,8-dibromo-4-methoxy-2-phenylquinoline, for example, with arylvinylboronic acid (1 equiv) using $Pd(PPh_3)_4$ as Pd(0) source, led to the recovery of the starting material.[19] The reaction failure was attributed to the inhibiting role of the extra PPh_3 generated from the ligand exchange between $Pd(PPh_3)_4$ and the solvent. However, the use of dichlorobis(triphenylphosphine)palladium(II) [$PdCl_2(PPh_3)_2$] afforded the doubly coupled product and the starting material. The double coupled product, on the other hand, was obtained as a sole product with an excess of arylvinylboronic acid (2.5 equiv) in the presence of $PdCl_2(PPh_3)_2$-tricyclohexylphosphine catalyst complex.[19] Prompted by the above result, we decided to investigate the reactivity of the two bromine atoms of the 2-aryl-6,8-dibromo-4-(phenylethynyl)quinazolines **83** *via* Suzuki cross-coupling with arylboronic acids. At first we reacted compounds **83a** with phenylboronic acid (1.5 equiv) using $PdCl_2(PPh_3)_2$-PCy_3 as catalyst complex and K_2CO_3 as a base in dioxane under reflux. After 4 hours we isolated by column chromatography on silica gel, the 2,6,8-triphenyl-4-(phenylethynyl)quinazoline **84a**

in 30% along with the starting material. This observation was found to compare with the previous literature data for the analogous 2-aryl-6,8-dibromo-4-methoxyquinolines.[19] We then opted for the use of an excess arylboronic acid (2.5 equiv) on compounds **83a-d** and we isolated the corresponding 2,6,8-triaryl-4-(phenylethynyl)quinazolines **84a-l** in 57−78% yield (Scheme 36). The prepared compounds **84a-l** were characterized using a combination of NMR (^{1}H and ^{13}C), IR and mass spectroscopic techniques. The ^{1}H NMR spectra of products **84a-l** show an increase number of proton signals in the aromatic region δ *ca.* 6.86−8.03 ppm (Figure 8). The ^{13}C NMR spectra also show an increase in the number of peaks in the aromatic region corresponding, in each case, to double aryl substitution on the fused benzo ring (Figure 9). Moreover, the absence of Br isotope peaks further confirms double aryl substitution.



83a-d **84a-l**

84	**R′′**	**R**	**% Yield**	**mp. (°C)**
a	4-H	4-H	71	184-186
b	4-H	4-F	57	250-252
c	4-H	4-Cl	78	246-248
d	4-H	4-OCH_3	68	220-223
e	4-F	4-H	66	228-230
f	4-F	4-F	76	255-257
g	4-F	4-Cl	75	243-245
h	4-F	4-OCH_3	65	211-213
i	4-OCH_3	4-H	69	209-212
j	4-OCH_3	4-F	62	236-239
k	4-OCH_3	4-Cl	76	233-235
l	4-OCH_3	4-OCH_3	60	237-239

Reagents and conditions: (i) Ar′′$B(OH)_2$, $PdCl_2(PPh_3)_2$, PCy_3, K_2CO_3, dioxane-H_2O (3:1, v/v), 2 h.

Scheme 36: Suzuki cross-coupling reaction of 2-aryl-6,8-dibromo-4-(phenylethynyl) quinazolines with arylboronic acids

Youssef Kabri *et al* in a recent publication also describe the synthesis of 2,4,6,8-tetrasubstitutedquinazolines *via* microwave-assisted consecutive bis-S_NAr/bis-Suzuki-Miyaura cross-coupling reactions of the 6,8-dibromo-2,4-dichloroquinazoline.[76]

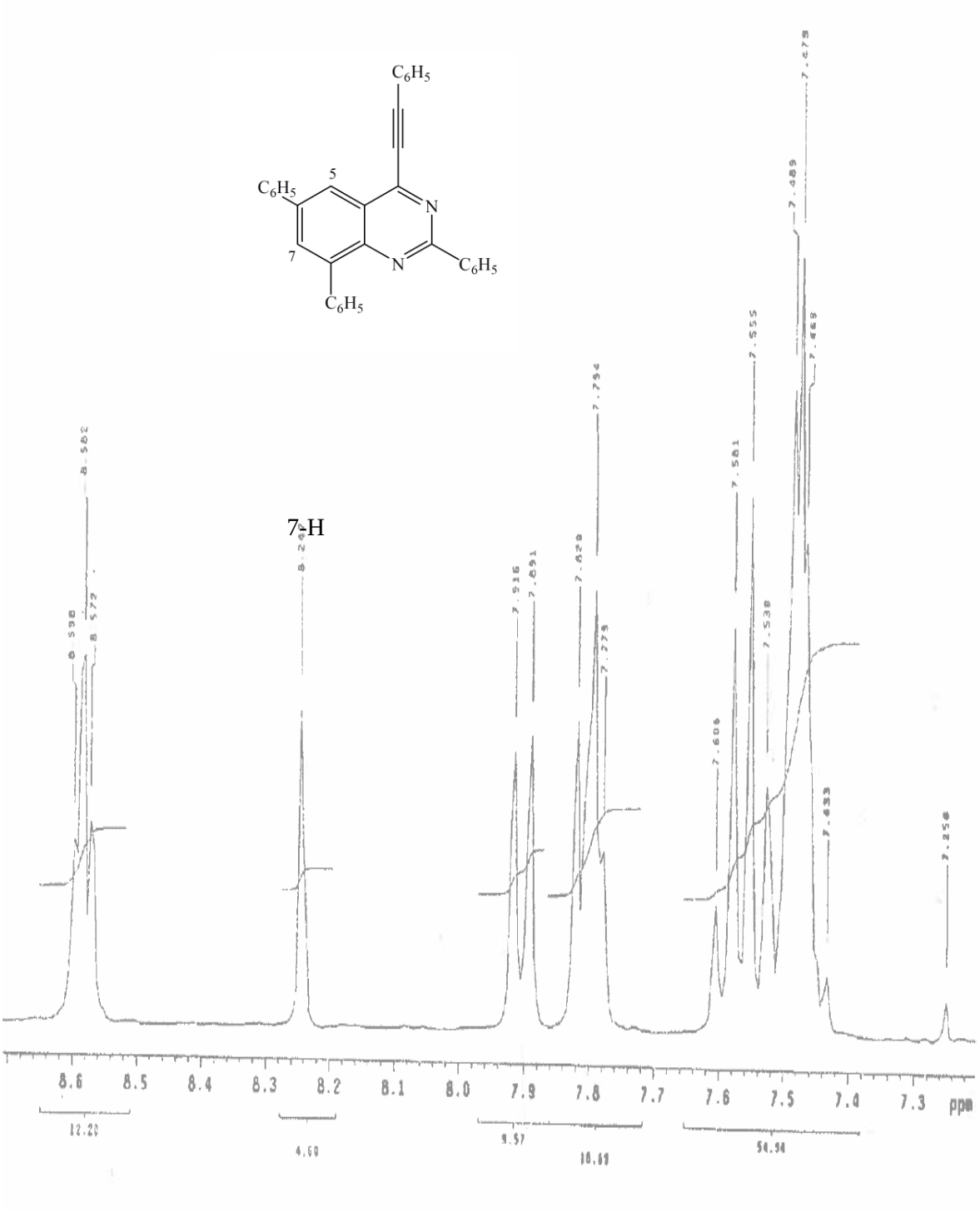


Figure 8: ^1H NMR spectrum of **84a** in $CDCl_3$ at 300 MHz

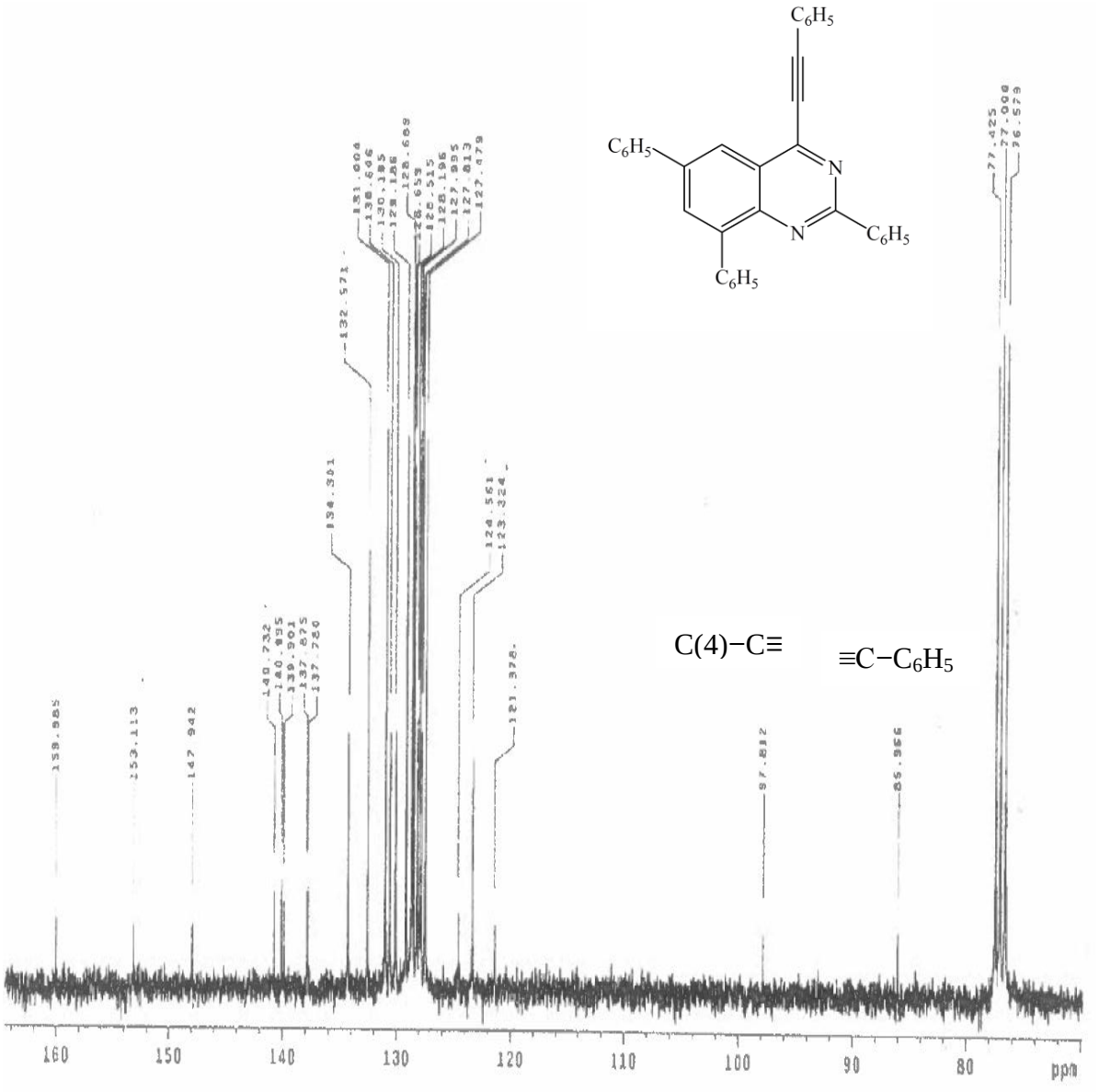


Figure 9: ^{13}C NMR spectrum of **84a** in $CDCl_3$ at 75 MHz

2,6,8-Triaryl-4-(phenylethynyl)quinazolines **84a-l** comprise an electron-deficient quinazoline framework as an electron-acceptor linked directly to aryl rings or through the alkyne bridge to form donor-acceptor systems. We decided to determine the absorption and emission properties of compounds **84a-l** in solvents of different polarity.

2.4 Photophysical property studies of 2,6,8- triaryl-4-(phenylethynyl)quinazolines

The absorption properties of compounds **84a-l** were measured in chloroform (Figure 10-12) and methanol-chloroform (1:1, v/v) (Figure 13-15), whereas their emission properties were determined in chloroform (Figure 16-18) and DMF (Figure 19-21). Quantum yield and Stokes shift calculations to establish the effect of substituents on the absorption and emission properties of these polysubstituted quinazolines were also reported (Table 1).

2.4.1 Absorption properties of 2,6,8-triaryl-4-(phenylethynyl)quinazolines

Compounds **84a-l** are characterized by intense absorption bands in the region λ 270−300 nm in $CHCl_3$ which are due to $\pi \rightarrow \pi^*$ transition, attributed to the conjugated quinazoline ring. In the case of phenyl derivatives **84a-d**, the sharp peak observed for **84a** and **84b** is probably due to the presence of the less electron donating 2-phenyl or 2-(4-fluorophenyl) group as compared to **84c** and **84d** bearing a strong electron withdrawing 2-(4-chlorophenyl) and electron donating 2-(4-methoxyphenyl) groups respectively. However, the intensity of their absorption peaks decrease with the strong resonance effect of the aryl substituent at position 2: **84a > 84b > 84c** and **84d** (Figure 10). A combination of the less electron donating 2-(4-chlorophenyl) or 2-phenyl group and the relatively electron donating 4-fluorophenyl group at positions 6 and 8 enhance the absorptivities for **84g** and **84e**, respectively (Figure 11). A strong electron donating 4-methoxyphenyl group at positions 6 and 8 seems to increase the electron density of the quinazoline ring for **84j** and **84k** (Figure 12) whereas the same group at position 2 decreases the electron density for **84d**, **84h** and **84l**. On the other hand, the strong electron donating 4-methoxyphenyl group is also responsible for a blue shift observed

in solutions of compounds **84**. Therefore, the strong electron donating group has a considerable effect on the conjugation of the π electron of the quinazoline scaffold.

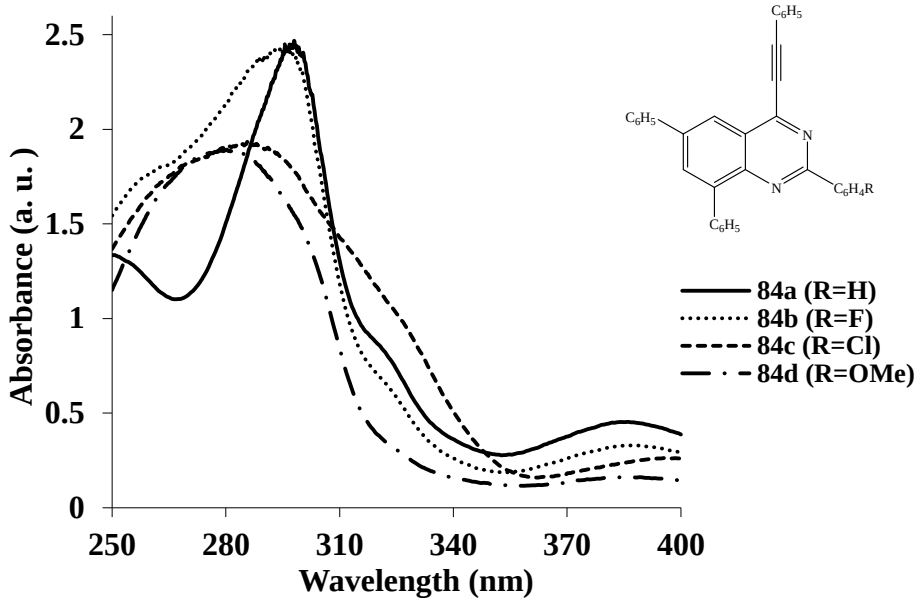


Figure 10: UV-Vis spectra of **84a-d** in $CHCl_3$ (2.2×10^{-5} mol/l)

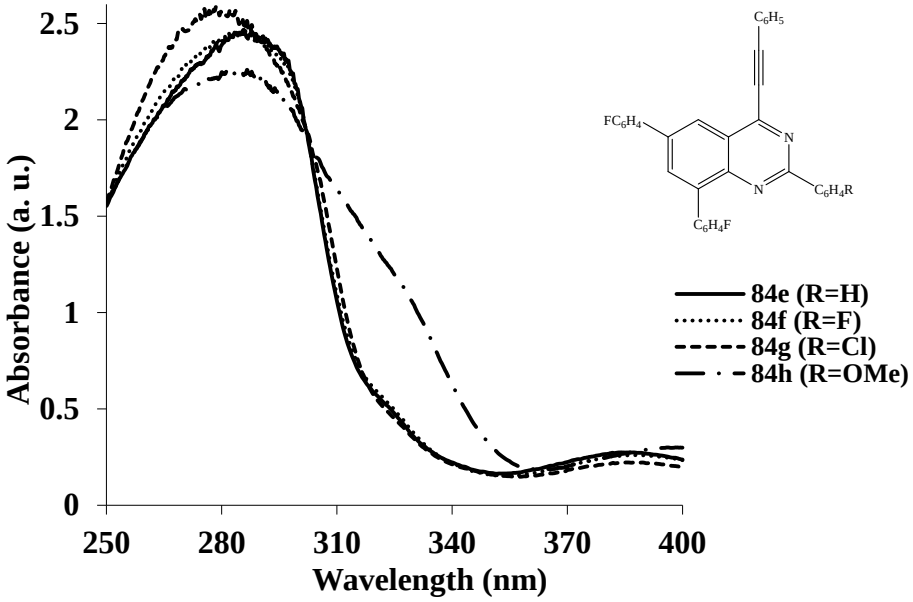


Figure 11: UV-Vis spectra of **84e-h** in $CHCl_3$ (2.2×10^{-5} mol/l)

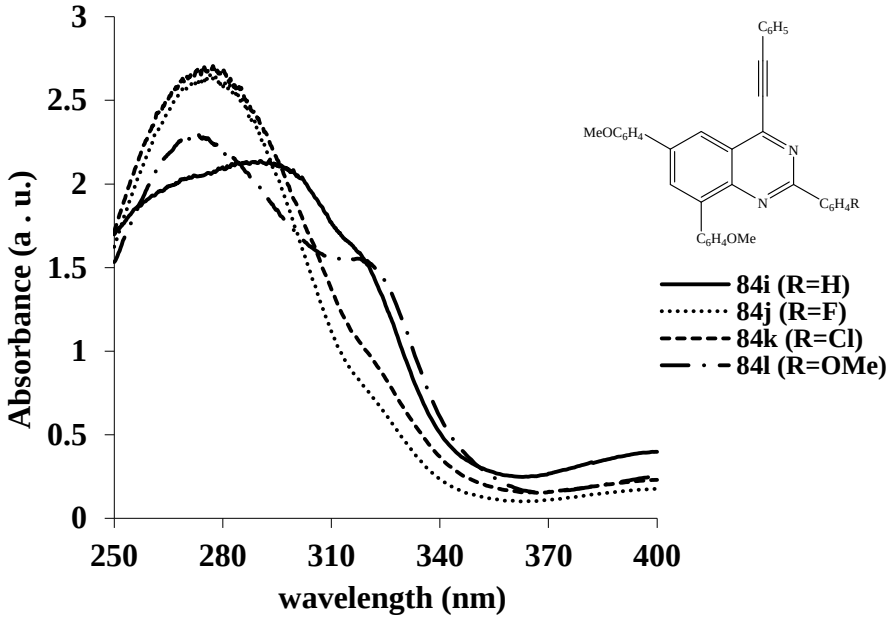


Figure 12: UV-Vis spectra of **84i-l** in $CHCl_3$ (2.2×10^{-5} mol/l)

Solvent effects on absorption spectra of compounds **84** have also been studied. In this investigation, we opted for a mixture methanol-chloroform (1:1, v/v) because of the poor solubility of these compounds in methanol. Solutions of compounds **84** are characterised by single absorption bands in the region λ 296−318 nm. The absorption spectra of compounds **84** in methanol-chloroform solution are red shifted with lower intensities as compared to solutions of these compounds in chloroform. This observation indicates the relatively strong interaction between N-1 of the quinazoline receptor and the polar protic methanol sovent in a form of hydrogen-bonding. In addition, the spectral shifts of compounds **84d**, **84h** and **84l** bearing a methoxy group are also attributed to hydrogen-bonding between oxygen of the donor 4-phenylmethoxy group with methanol (Figure 13, 14 and 15). The longest wavelength is observed for compound **84l** bearing the strong electron donating 4-methoxyphenyl group at positions 2, 6 and 8 (Figure 15). In the case of phenyl derivatives **84a-d** or 4-methoxyphenyl derivatives **84i-l**, the broad band observed in **84c** and **84k** is due to the strong electron

withdrawing 4-chlorophenyl group at position 2 (Figure 13 and 15). Consequently, the solvent effect on absorption spectra of compounds **84** strongly depend on the nature of the substituent on the aryl groups.

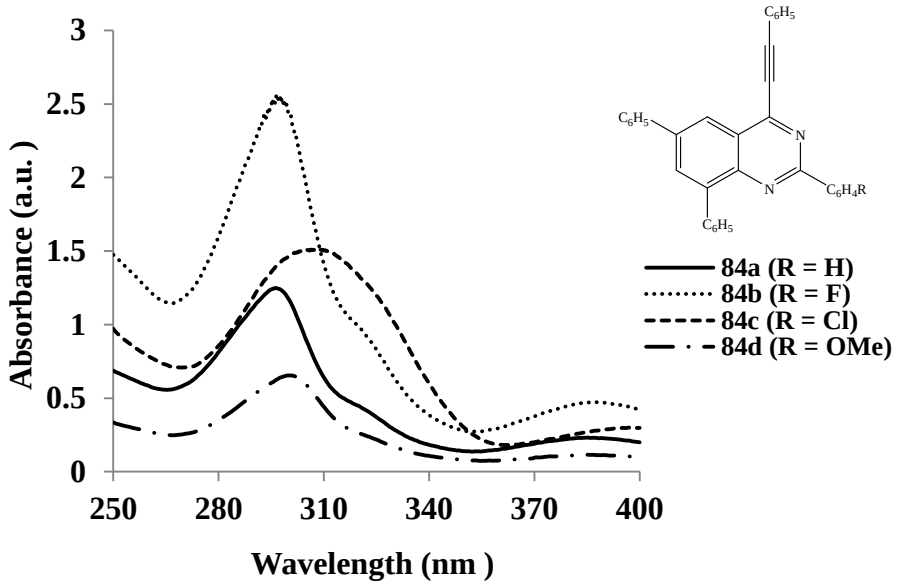


Figure 13: UV-Vis spectra of **84a-d** in MeOH-$CHCl_3$ (2.2×10^{-5} mol/l)

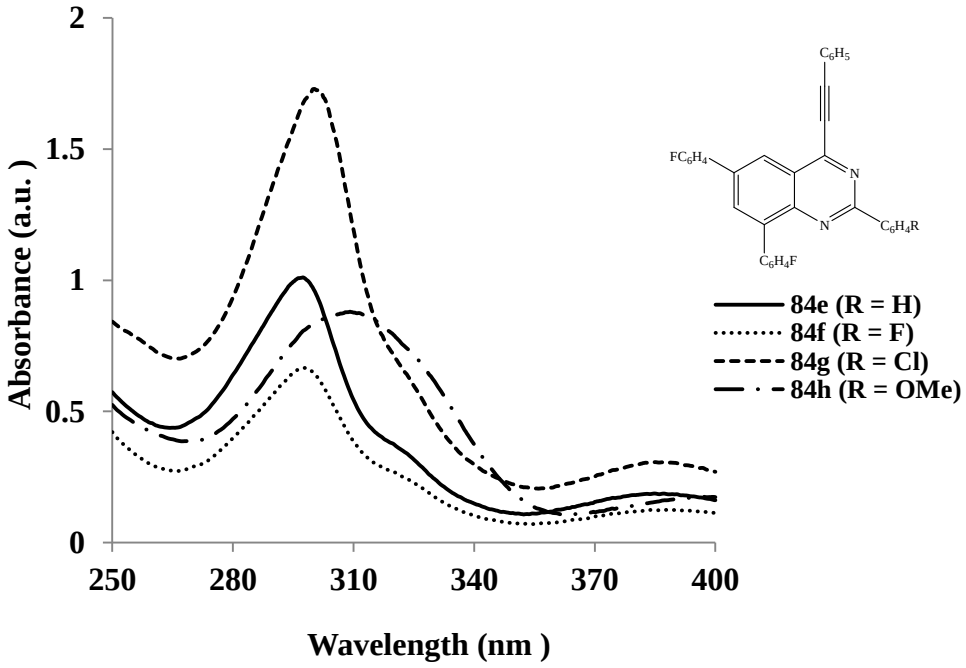


Figure 14: UV-Vis spectra of **84e-h** in MeOH-$CHCl_3$ (2.2×10^{-5} mol/l)

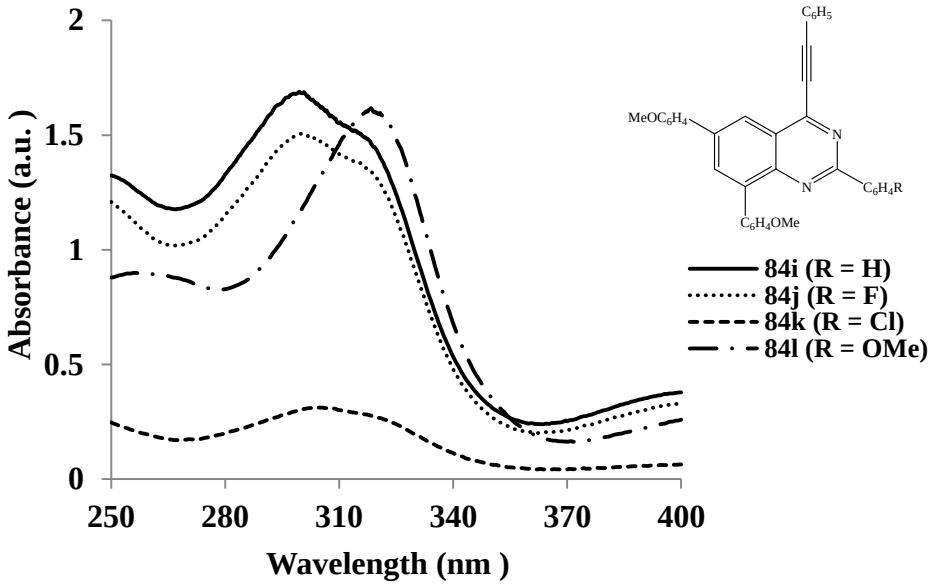


Figure 15: UV-Vis spectra of **84i-l** in MeOH-$CHCl_3$ (2.2×10^{-5} mol/l)

2.4.2 Emission properties of 2,6,8-triaryl-4-(phenylethynyl)quinazolines

In order to investigate the emission properties of compounds **84a-l,** the photoluminescence spectra of these compounds were obtained at room temperature in the non-polar chloroform (Figure 16-18) and in the strongly polar DMF (Figure 19-21) at the excitation wavelengths λ_{ex} = 380 nm and 400 nm, respectively. The spectra of compounds **84a-l** show similar pattern and are characterized by single emission band in the region λ 450−480 nm in $CHCl_3$ and 450−500 nm in DMF. This observation is due to π→π* transition attributed to the conjugated quinazoline ring system. In $CHCl_3$ compounds **84a**, **84e** and **84i** bearing the relatively less electron donating 2-phenyl group exhibit relatively reduced emission intensities reflecting the following trend: **84i > 84e > 84a**. This trend reflects the conjugative effect of the aryl group at positions 6 and 8. Moreover, Stokes shift and fluorescence quantum yield display the same trend (Table 1). The strong electron donating 2-(4-methoxyphenyl) group seems to enhance the

emission intensities of **84d**, **84h** and **84l** as compared to the moderately donating 2-(4-fluorophenyl) (Figure 16, 17, 18). Nevertheless, in the case of 4-fluorophenyl derivatives, a strong electron donating group at position 2 causes a bathochromic shift for solutions of compounds **84**.

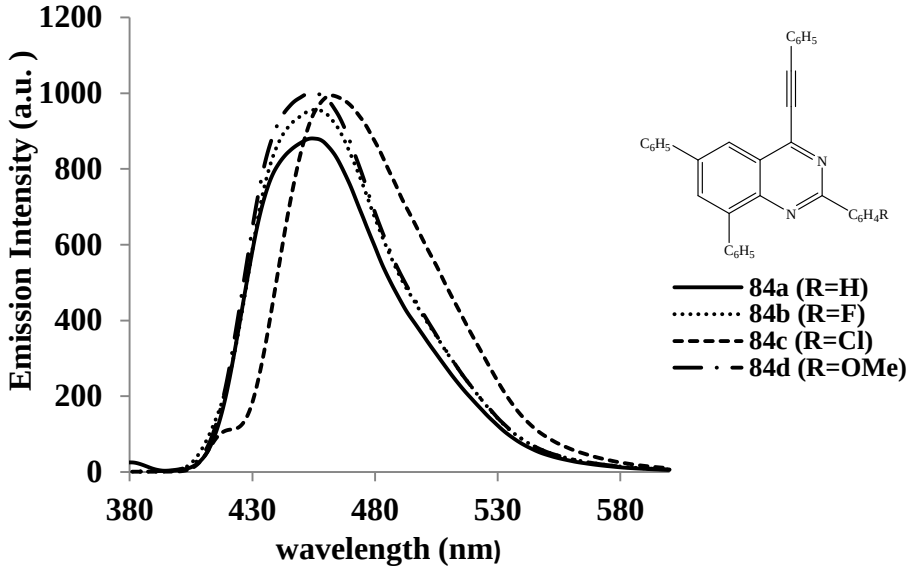


Figure 16: Emission spectra of **84a-d** in $CHCl_3$ (2.2×10^{-5} mol/l)

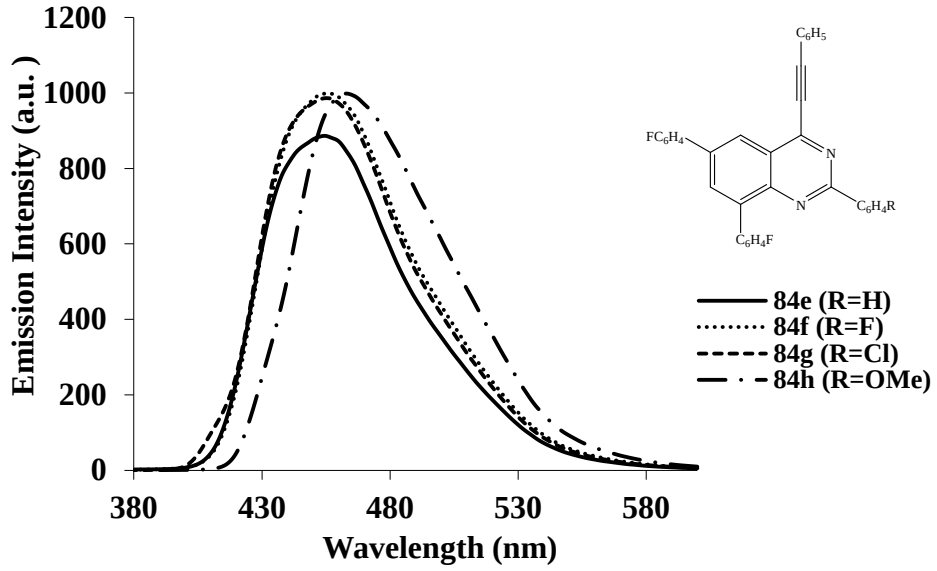


Figure 17: Emission spectra of **84e-h** in $CHCl_3$ (2.2×10^{-5} mol/l)

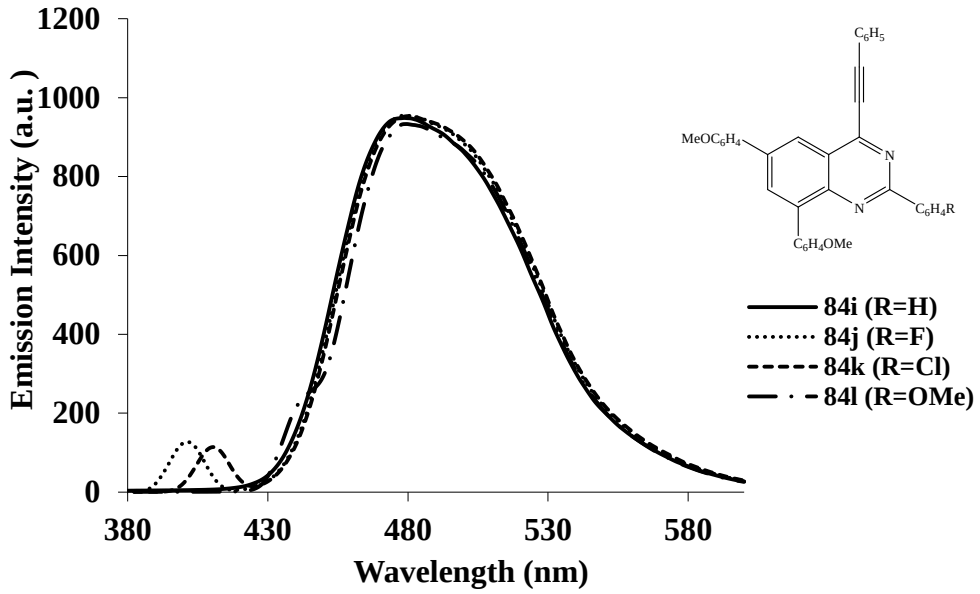


Figure 18: Emission spectra of **84i-l** in $CHCl_3$ (2.2×10^{-5} mol/l)

In the case of phenyl derivatives, the strong electron withdrawing 4-chlorophenyl group at position 2 causes a red shift in solutions of compounds **84**. In DMF, a combination of the strong electron donating 2-(4-methoxyphenyl) group and the relatively less electron donating phenyl group at positions 6 and 8 of the benzo ring reduce the emission intensity of **84d** as compared to **84h** and **84l** bearing the moderately and strongly electron donating 4-fluorophenyl and 4-methoxyphenyl groups at positions 6 and 8, respectively. This observation can be attributed to the π-electron delocalization into the quinazoline ring caused by the electrons donating aryl substituents at positions 6 and 8. In the case of 4-methoxy derivatives **84i-l**, the intensities of emission maxima seem to be influenced by the conjugative effect of the substituent 2-aryl group reflecting the following trend **84l** > **84i** > **84j** > **84k** (Figure 21). The emission spectra of compounds **84a-l** in a strongly polar DMF exhibit lower intensities and are red shifted as compared to solution of the same compounds in $CHCl_3$.

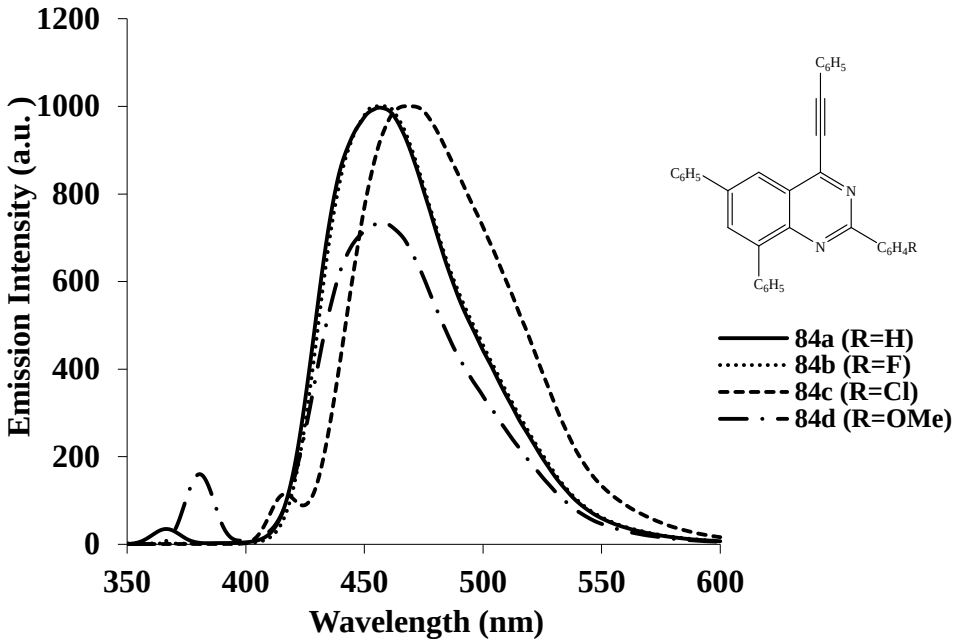


Figure 19: Emission spectra of **84a-d** in DMF (2.2×10^{-5} mol/l)

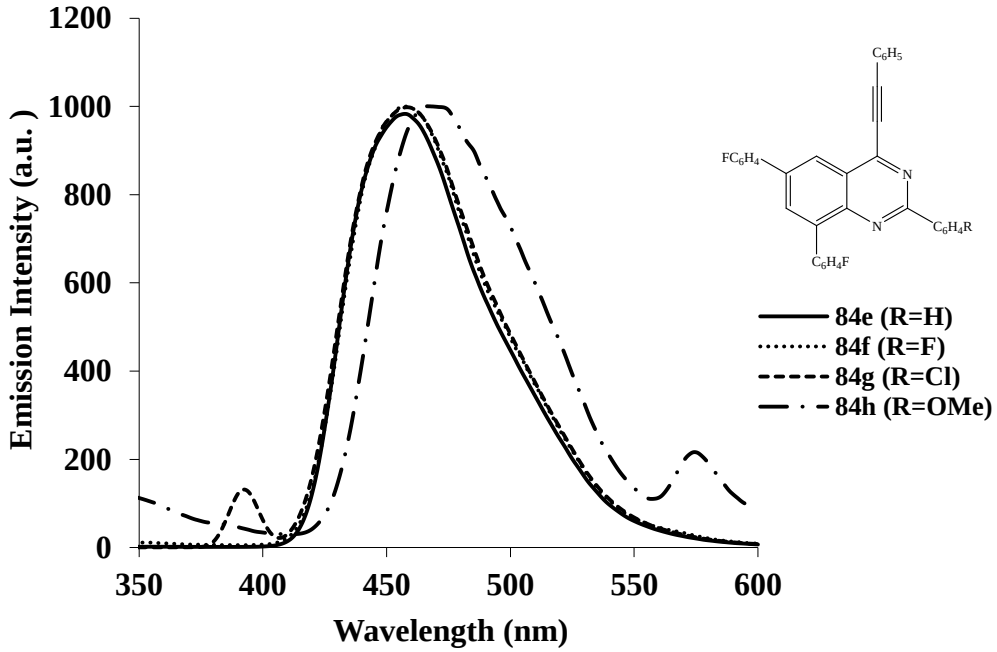


Figure 20: Emission spectra of **84e-h** in DMF (2.2×10^{-5} mol/l)

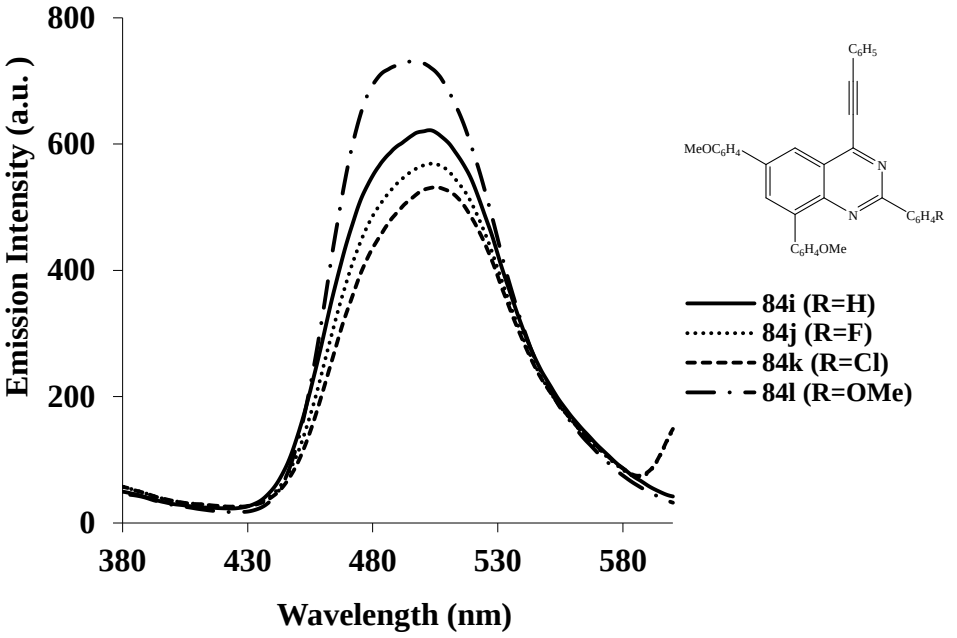
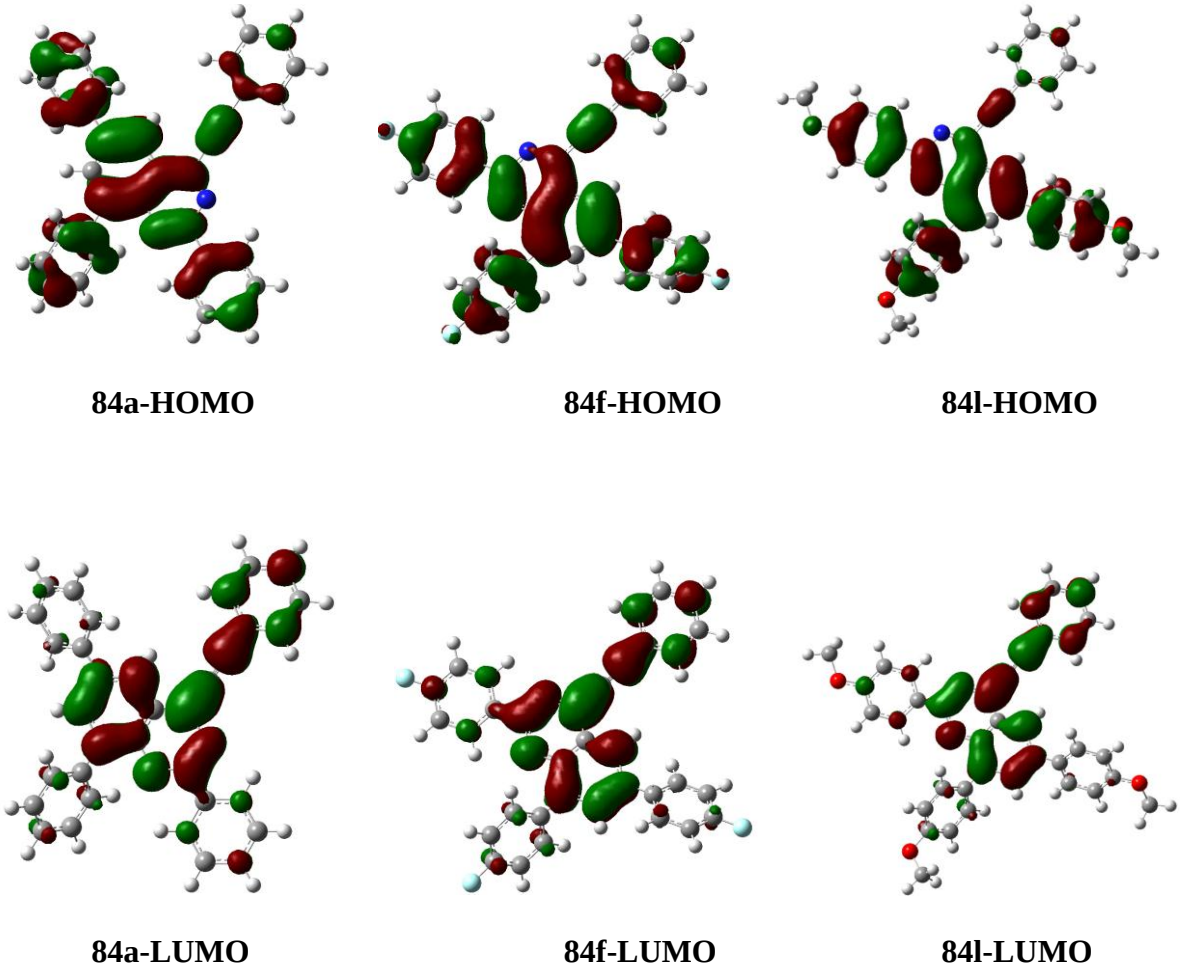


Figure 21: Emission spectra of **84i-l** in DMF (2.2×10^{-5} mol/l)

The attachment of the electron donating 4-methoxyphenyl/4-trifluoromethylphenyl group at positions 1, 3, 5 and 9 of the electron deficient pyrene framework, for example, was found to lower the energy gap between the highest occupied and lowest unoccupied molecular orbitals (HOMO-LUMO) as compared to the phenyl group.[77] The calculated energy gaps were 3.40 eV and 3.43 eV for the 4-methoxyphenyl/4-trifluoromethylphenyl and phenyl derivatives, respectively.[77] The energy needed for the transition state electrons in the case of 4-methoxyphenyl/4-trifluoromethylphenyl derivative is reduced and the emission spectra shift to longer wavelength. Based on this literature precedent, we attribute the red shift observed for compounds **84e-l** bearing the strongly or moderately electron donating 4-methoxyphenyl or 4-fluorophenyl group at positions 6 and 8 of the electron deficient quinazoline core to be due to the decrease in the HOMO-LUMO energy gap. To further understand the electronic properties of compounds **84a-l**, density functional theory (DFT) calculations at B3LYP/6-31G* level[78] were carried out using Gaussian 09 for the geometry

optimization.[79] ZINDO/S calculations were performed in chloroform for the optimized configuration. The lowest-energy absorption transition at 373 nm in **84a,** chosen as a representative model was best characterized by a transition from the HOMO to the LUMO. The optimized structures and orbital distributions of the HOMO and LUMO of **84a**, **84f** and **84l** are shown in figure 22. The HOMO levels mainly involved contributions of the π-orbitals from the entire quinazoline while the LUMO move toward the quinazoline-based moiety as an electron acceptor representing the π*-orbitals.



84a-HOMO **84f-HOMO** **84l-HOMO**

84a-LUMO **84f-LUMO** **84l-LUMO**

Figure 22: Computed molecular orbital of **84a, 84f** and **84l**

84	**λ_{max} (nm) $CHCl_3$**	**λ_{max} (nm) CH_3OH-$CHCl_3$ (1:1, v/v)**	**Molar Extinction Coefficient (ε) $dm^3Mol^{-1}cm^{-1}$**	**λ_{em} (nm) $CHCl_3$**	**Stokes shift**	**Quantum yields [a] Φ**	**λ_{em} (nm) DMF**
a	298	296.2	11.216×10^3	454.5	156.5	0.071	456.5
b	295.6	297.7	11.163×10^3	455	159.4	0.078	459
c	285.7	307.6	8.798×10^3	462.5	176.8	0.102	467
d	280.3	299.8	8.601×10^3	455	174.7	0.105	458
e	285.7	297.4	11.216×10^3	454.5	168.8	0.071	457.5
f	284.5	297.7	11.181×10^3	456	171.5	0.081	457
g	278.5	300.1	11.754×10^3	455	176.5	0.076	458.5
h	286.6	309.1	10.271×10^3	463	176.4	0.088	466.5
i	292.9	299.5	9.725×10^3	478.5	185.6	0.088	503
j	276.4	300.4	12.063×10^3	479	202.6	0.072	504.5
k	276.7	303.7	12.268×10^3	480	203.3	0.070	505.5
l	273.4	318.4	10.422×10^3	479.5	206.1	0.081	496

(a) Obtained by calculation, based on quinine sulfate in H_2SO_4 0.5 M as the standard

Table 1: The absorption and emission data for compounds **84a-l**

CHAPTER 3 CONCLUSION

A single-pot iodine-mediated cyclocondensation of 2-amino-3,5-dibromobenzamide and subsequent dehydrogenation of the intermediate 2-aryl-6,8-dibromoquinazolin-4(1*H*)-one in ethanol to afford 2-aryl-6,8-dibromoquinazolin-4(3*H*)-one derivatives has been achieved. Molecular iodine serves as a Lewis acid to effect the cyclocondensation and at the same time acts as an oxidant to promote the dehydrogenation step. The oxidative aromatization of 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones was achieved using thionyl chloride in the presence of DMF to afford novel 2-aryl-4-chloro-6,8-dibromoquinazolines. However, oxidative aromatization of 2-aryl-6,8-dibromoquinazolin-4(3*H*)-ones with $POCl_3$, $POCl_3$-tertiary amine or $POCl_3$-DMF mixture resulted in incomplete conversion. Selective alkynylation of the 2-aryl-4-chloro-6,8-dibromoquinazolines was achieved *via* Sonogashira cross-coupling with alkyne derivatives to afford novel 2-aryl-6,8-dibromo-4-(alkynyl)quinazolines. The C-4 position of 2-aryl-4-chloro-6,8-dibromoquinazolines is highly activated due to α-nitrogen effect. The Suzuki-Miyaura cross-coupling of 2-aryl-6,8-dibromo-4-(phenylethynyl)quinazolines with arylboronic acids occurs without selectivity to afford the corresponding novel 2,6,8-triaryl-4-(phenylethynyl)quinazoline derivatives. The lack of selectivity is presumably the consequence of comparable C(6)-Br and C(8)-Br bond strengths[80] as was observed with analogous 2-aryl-6,8-dibromo-4-methoxyquinolines.[19] The absorption and emission properties of compounds **84a-l** prepared in this investigation showed strong correlation with the substituent on the 2-, 6- and 8-aryl groups. The absorption spectra of solutions of these compounds in a polar protic methanol-chloroform mixture were characterized by bathochromic and hypsochromic shift as compared to solutions of these compounds in non-polar chloroform due to hydrogen bonding with methanol. The solutions of 2,6,8-triaryl-4-(phenylethynyl)quinazoline exhibited intense emission in non-polar chloroform

and polar aprotic dimethylformamide. The prepared 2,6,8-triaryl-4-(phenylethynyl)quinazolines **84a-l** can be used as substrates for possible coordination with metals such as palladium[81] or iridium[82] because analogous metal complexes have applications in materials and medicinal chemistry. Palladium(II) complexes of 8-aminoquinoline analogues, for example, were found to interact with extracellular protein responsible for the blood acidity and pressure.[81] an iridium complex containing a phenyl quinazoline ligand, on the other hand, has found application in polymer light-emitting diodes.[82] The molecular architecture of the compounds makes them suitable candidates for further studies of chemical transformation and for application in materials reseach. Future research extending from this investigation could include the following:

- Subjecting the 2-aryl-6,8-dibromo-4-(phenylethynyl)quinazolines to Heck, Suzuki or Sonogashira cross-coupling with aryl alkenes, arylvinylboronic acids or aryl alkynes, respectively, to afford polyaryl substituted quinazolines, in which the quinazoline core is linked to aryl rings *via* π-conjugated spacers.
- Synthesis and electrophosphorescence studies of iridium complexes containing 2,6,8-triaryl-4-(phenylethynyl)quinazolines ligands as a prelude to compounds with potential application in light-emitting diodes[82]
- Synthesis of 2,6,8-triaryl-4-(phenylethynyl)quinazolines palladium(II) complexes with potential biological activities in analogy with palladium(II) complexes of 8-aminoquinoline [81]

In conclusion, the results of this investigation represent an application of the 2-aryl-6,8-dibromo-4-chloroquinazoline in the synthesis of polysubstituted quinazolines. The preliminary photophysical properties of compounds **84** serve as a prelude to compounds with potential electronic properties. The synthesis of the compounds prepared in this investigation

and the result of photophysical (absorption and emission) property studies of compounds **84** have since been published.[83]

CHAPTER 4 EXPERIMENTAL

4.1 General

Reagents and solvents were used as supplied or purified by conventional methods. All melting points reported were determined on a Stuart melting point apparatus. Merk silica gel 60 F254 plates were used for thin-layer chromatography and the powder 90% (0.0063-0.10 mm) and flow time < 80 s / 10 cm was used as stationary phase for column chromatography. IR spectra were recorded as powders on a Bruker Vertex 70 FTIR. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Mercury 300 MHz spectrometer. High and low resolution mass spectra were recorded on a Waters API Q-TOF Ultima mass spectrometer at the University of Stellenbosch. Absorption spectra were recorded on a CECIL CE9500 spectrophotometer and fluorescence spectra on a Perkin Elmer LS55 spectrometer. The quantum efficiencies of fluorescence (Φ_x) were obtained with the following equation:

$$\Phi_x = \Phi_{st} * (F_x/F_{st}) * (A_{st}/A_x) * (n_x^2/n_{st}^2)$$

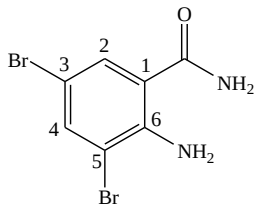
F denotes the area under the fluorescence band ($F = {}^{a}I_{fl}(\lambda)$, where $I_{fl}(\lambda)$ is the fluorescence intensity at each emission wavelength), A denotes the absorbance at the excitation wavelength, and *n* is the refractive index of the solvent.[84]

The following abbreviations are used throughout for NMR spectral data:

ppm = parts per million; *J* = coupling constant in Hz; δ = chemical shift values in ppm.

Splitting patterns: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet

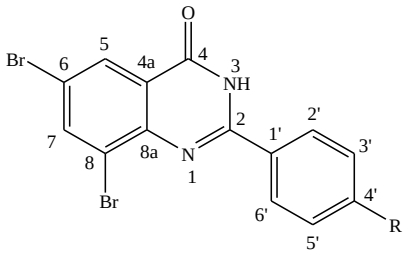
4.2 Preparation of 2-amino-3,5-dibromobenzamide 79



79

A mixture of 2-aminobenzamide **8** (5.00 g, 36.7 mmol) and *N*-bromosuccinimide (14.23 g; 80.0 mmol) in $CHCl_3$ was stirred at room temperature for 3 hours. After completion of the reaction which was monitored by thin-layer chromatography (TLC) using dichloromethane as mobile phase, the resulting precipitate was filtered and washed with cold ethanol to afford **79** as an orange solid (7.51 g, 70%), mp. 215−218 °C; IR (neat): ν_{max} 541, 644, 860, 1240, 1602, 1641, 3181, 3325, 3369 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 6.77 (2H, s, NH_2), 7.47 (1H, s, NH_a), 7.72 (1H, s, ArH), 7.77 (1H, s, ArH), 8,05 (1H, s, NH_b); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 105.4 (C-5), 110.8 (C-3), 117.3 (C-4), 131.2 (C-2), 137.2 (C-1), 146.5 (C-6), 169.7 (C(1)-C) ; m/z (100, MH^+) 293; HRMS (ES): MH^+, found 292.8928. $C_7H_7N_2O^{79}Br_2^+$ requires 292.8925.

4.3 Preparation of 2-aryl-6,8-dibromoquinazolin-4(3*H*)-one derivatives 81a-d



81a-d

4.3.1 Preparation of 6,8-dibromo-2-phenylquinazolin-4(3*H*)-one 81a (4´-R=H)

A stirred mixture of **79** (1.00 g, 3.3 mmol), iodine (1.90 g, 6.7 mmol) and benzaldehyde **80a** (0.43 g, 4.0 mmol) in absolute ethanol (100 ml) was heated under reflux for 7 hours. After completion of the reaction which was monitored by TLC using dichloromethane as mobile phase, water (100 ml) was added to the reaction mixture and the resulting precipitate was filtered and washed with aqueous sodium thiosulfate. The solid obtained was recrystallized from acetonitrile to afford **81a** as a white solid (1.06 g, 80%), mp. 332−335 °C; IR (neat): ν_{max} 690, 737, 1562, 1600, 1666, 3092, 3167 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.58−7.61 (3H, m, ArH), 8.23−8.26 (3H, m, ArH), 8.39 (1H, s, Ar), 12.54 (1H, s, NH); m/z (100, MH^+) 379; HRMS (ES): MH^+, found 378.9087. $C_{14}H_9N_2O^{79}Br_2^+$ requires 378.9082.

4.3.2 Preparation of 6,8-dibromo-2-(4-fluorophenyl)quinazolin-4(3*H*)-one 81b (4´-R=F)

An experimental procedure employed for the preparation of **81a** was followed using a mixture of 2-amino-3,5-dibromobenzamide **79** (1.00 g, 3.3 mmol), iodine (1.90 g, 6.7 mmol), 4-fluorobenzaldehyde **80b** (0.50 g, 4 mmol) in absolute ethanol (100 ml). Work-up and

recrystalization afforded **81b** as a white solid (1.20 g, 89%), mp. > 345 °C; IR (neat): ν_{max} 722, 794, 836, 1236, 1583, 1676, 3162 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 7.42 (2H, t, *J* 9.3 Hz, ArH), 8.19 (1H, s, ArH), 8.28−8.34 (3H, m, ArH), 12.94 (1H, s, NH); m/z (100, MH^+) 397; HRMS (ES): MH^+, found 396.8975. $C_{14}H_8N_2OF^{79}Br_2^+$ requires 396.8987.

4.3.3 Preparation of 6,8-dibromo-2-(4-chlorophenyl)quinazolin-4(3*H*)-one 81c (4´-R=Cl)

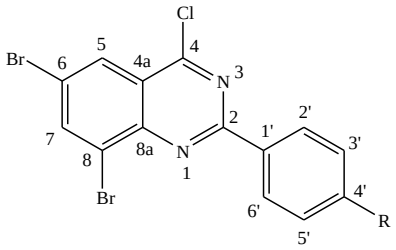
An experimental procedure employed for the preparation of **81a** was followed using a mixture of 2-amino-3,5-dibromobenzamide **79** (1.00 g, 3.3 mmol), iodine (1.90 g, 6.7 mmol), 4-chlorobenzaldehyde **80c** (0.56 g, 4.00 mmol) in absolute ethanol (100 ml). Work-up and recrystalisation afforded **81c** as a white solid (1.37 g, 94%), mp. > 345 °C; IR (neat): ν_{max} 695, 728, 793, 1558, 1601, 1672, 3154 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 7.65 (2H, d, *J* 9.3 Hz, ArH), 8,19 (1H, s, ArH), 8.27 (2H, d, *J* 9.3 Hz, ArH), 8.34 (1H, s, ArH), 12.98 (1H, s, NH); m/z (100, MH^+) 413; HRMS (ES): MH^+, found 412.8683. $C_{14}H_8N_2O^{35}Cl^{79}Br_2^+$ requires 414.8692.

4.3.4 Preparation of 6,8-dibromo-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one 81d (4´-R=OCH_3)

An experimental procedure employed for the preparation of **81a** was followed using a mixture of 2-amino-3,5-dibromobenzamide **79** (1.00 g, 3.3 mmol), iodine (1.90 g, 6.7 mmol), 4-methoxybenzaldehyde **80d** (0.54 g, 4.0 mmol) in absolute ethanol (100 ml). Work-up and recrystalisation afforded **81d** as a white solid (1.28 g, 89%), mp. 302−304 °C; IR (neat): ν_{max} 792, 851, 873, 1253, 1556, 1602, 1663, 3167 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.85

(3H, s, CH_3), 7.11 (2H, d, *J* 9.3 Hz, ArH), 8.17 (1H, s, ArH), 8.25−8.31 (3H, m, ArH), 12.73 (1H, s, ArH); m/z (100, MH^+) 409; HRMS (ES): MH^+, found 408.9190. $C_{15}H_{11}N_2O_2{}^{79}Br_2{}^+$ requires 408.9187.

4.4 Preparation of 2-aryl-4-chloro-6,8-dibromoquinazoline derivatives 82a-d



82a-d

4.4.1 Preparation of 6,8-dibromo-4-chloro-2-phenylquinazoline 82a (4'-R=H)

DMF (1 ml) was added dropwise at room temperature to a stirred mixture of **81a** (1.00 g, 2.6 mmol) and thionyl chloride (30 ml). The reaction mixture was stirred under reflux for 2 hours and then allowed to cool to room temperature. Ice-cold water was added to the reaction and the mixture was extracted with chloroform. The organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford **82a** as a white solid (0.99 g, 96%), mp. 185−188 °C; IR(neat) ν_{max} 685, 705, 1297, 1331, 1551, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.51−7.56 (3H, m, ArH), 8.30 (1H, d, *J* 2.1 Hz, ArH), 8.36 (1H, d, *J* 2.1 Hz, ArH), 8.61−8.65 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 121.2 (C-4a), 123.9 (C-6), 125.6 (C-5), 127.6 (C-8), 128.7 (C-2′ and C-6′), 129.0 (C-3′ and C-5′), 131.8 (C-4′), 135.7 (C-1′), 140.9 (C-7), 148.1 (C-8a), 160.6 (C-4), 161.6 (C-2); m/z (100, MH^+) 397; HRMS (ES): MH^+, found 396.8733. $C_{14}H_8N_2{}^{35}Cl^{79}Br_2{}^+$ requires 396.8743.

4.4.2 Preparation of 6,8-dibromo-4-chloro-2-(4-fluorophenyl)quinazoline 82b (4′-R=F)

A procedure for the preparation of **82a** was followed using a mixture of **81b** (1.00 g, 2.4 mmol), thionyl chloride (30 ml) and DMF (1 ml). Work-up afforded **82b** as a white solid (0.84 g, 81%), mp. 206−208 °C; IR (neat) ν_{max} 721, 769, 848, 1215, 1300, 1332, 1585, 1597 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19 (2H, t, *J* 8.7 Hz, ArH), 8.30 (1H, d, *J* 2.1 Hz, ArH), 8.35 (1H, d, *J* 2.1 Hz, ArH), 8.63 (2H, t, *J* 8.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 115.8 (d, $^{2}J_{CF}$ 21.7 Hz, C-3′ and C-5′), 121.3 (C-4a), 123.8 (C-6), 125.5 (C-5), 127.6 (C-8), 131.3 (d, $^{3}J_{CF}$ 8.3 Hz, C-2′ and C-6′), 132.0 (d, $^{4}J_{CF}$ 3.2 Hz, C-1′), 141.0 (C-7), 148.1 (C-8a), 159.6 (C-4), 161.6 (C-2), 165.3 (d, $^{1}J_{CF}$ 251.2 Hz, C-4′); m/z (100, MH^+) 415; HRMS (ES): MH^+, found 414.8641. $C_{14}H_7N_2F^{35}Cl^{79}Br_2^+$ requires 414.8649.

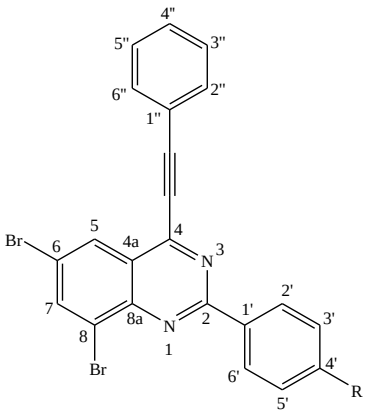
4.4.3 Preparation of 6,8-dibromo-4-chloro-2-(4-chlorophenyl)quinazoline 82c (4′-R=Cl)

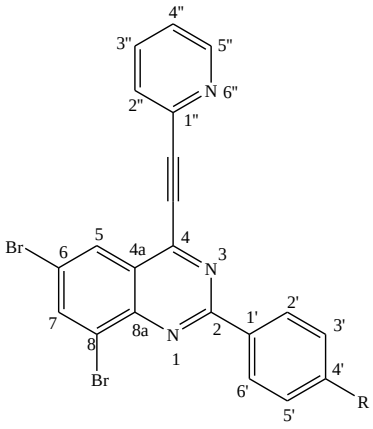
A procedure for the preparation of **82a** was followed using a mixture of **81c** (1.00 g, 2.4 mmol), thionyl chloride (30 ml) and DMF (1 ml). Work-up afforded **82c** as a white solid (0.80 g, 77%), mp. 239−240 °C; IR(neat) ν_{max} 734, 786, 867, 1298, 1333, 1553, 1578 cm^{-1}; (300 MHz, $CDCl_3$) δ: 7.50 (2H, t, *J* 7.8 Hz, ArH), 8.31 (1H, d, *J* 2.1 Hz, ArH), 8.36 (1H, d, *J* 2.1 Hz, ArH), 8.57 (2H, d, *J* 7.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 121.6 (C-4a), 124.1 (C-6), 125.6 (C-5), 127.7 (C-8), 129.1 (C-2′ and C-6′), 130.3 (C-3′ and C-5′), 134.4 (C-1′), 138.2 (C-4′), 141.1 (C-7), 148.1 (C-8a), 159.7 (C-4), 161.8 (C-2); m/z (100, MH^+) 431; HRMS (ES): MH^+, found 430.8339. $C_{14}H_7N_2{}^{35}Cl_2{}^{79}Br_2^+$ requires 430.8353.

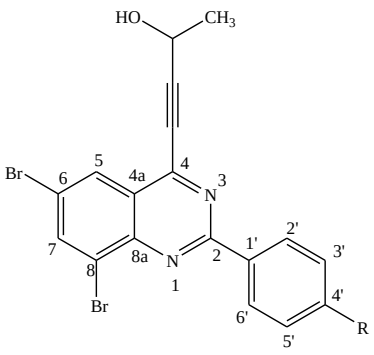
4.4.4 Preparation of 6,8-dibromo-4-chloro-2-(4-methoxyphenyl)quinazoline 82d (4′-R=OCH_3)

A procedure for the preparation of **82a** was followed using a mixture of **81d** (1.00 g, 2.4 mmol), thionyl chloride (30 ml) and DMF (1 ml). Work-up afforded **82d** as a yellow solid (1.02 g, 91%), mp. 200−202 °C; IR(neat) ν_{max} 728, 766, 1026, 1297, 1335, 1554,1583, 1607 cm^{-1}; (300 MHz, $CDCl_3$) δ: 3.89 (3H, s, CH_3), 7.00 (2H, d, *J* 8.7 Hz, ArH), 8.25 (1H, d, *J* 2.1 Hz, ArH), 8.30 (1H, d, *J* 2.1 Hz, ArH), 8.56 (2H, d, *J* 8.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.4 (OCH_3), 114.1 (C-3′ and C-5′), 120.5 (C-4a), 123.6 (C-6), 125.3 (C-5), 127.6 (C-8), 128.5 (C-2′ and C-6′), 130.9 (C-1′), 140.8 (C-7), 148.2 (C-8a), 160.5 (C-4), 161.4 (C-4′), 162.8 (C-2); m/z (100, MH^+) 427; HRMS (ES): MH^+, found 426.8841. $C_{15}H_{10}N_2O^{35}Cl^{79}Br_2^+$ requires 426.8848.

4.5 Preparation of 2-aryl-6,8-dibromo-4-(alkynyl)quinazoline derivatives 83a-h







83a-d (R=H, F, Cl, OCH_3) **83e-g** (R=H, F, OCH_3) **83h** (R=H)

4.5.1 Preparation of 6,8-dibromo-2-phenyl-4-(phenylethynyl)quinazoline 83a (4′-R=H)

A mixture of **82a** (0.50 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol), CuI (0.01 g, 0.06 mmol) and Cs_2CO_3 (0.60 g, 1.7 mmol) in THF (30 ml) was purged with argon gas. Phenyl acetylene (0.14 g, 1.4 mmol) was added using a syringe. The reaction mixture was stirred at room temperature for 24 hours. Water was then added and the mixture was extracted with chloroform. The organic layer was washed with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel to afford **83a** as a yellow solid (0.35 g, 59%), R_f (petroleum ether, toluene 1/1) 0.58, mp. 192−195 °C; IR (neat): ν_{max} 678, 730, 752, 777, 1525, 1670, 2215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 744−7.49 (6H, m, ArH), 7.77 (2H, d, *J* 7.5 Hz, ArH), 8.28 (1H, s, ArH), 8.47 (1H, s, ArH), 8.70 (2H, t, *J* 3.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 84.9 (Ph-C≡), 99.1 (C(4)-C≡), 120.7 (C-6), 120.8 (C-1″), 125.4 (C-4a), 125.9 (C-8), 128.3 (C-2′ and C-6′), 128.6 (C-3″ and C-5″), 128.7 (C-4″), 129.0 (C-4′), 130.5 (C-5), 131.3 (C-1′), 132.7 (C-3′ and C-5′), 136.9 (C-2″ and C-6″), 140.2 (C-7), 147.2 (C-8a), 152.3 (C-4), 161.5 (C-2); m/z (100, MH^+) 463; HRMS (ES): MH^+, found 462.9435. $C_{22}H_{13}N_2{}^{79}Br_2{}^+$ requires 462.9445.

4.5.2 Preparation of 6,8-dibromo-2-(4-fluorophenyl)-4-(phenylethynyl)quinazoline 83b (4′-R=F)

An experimental procedure employed for the preparation of **83a** was followed using a mixture of **82b** (0.50 g, 1.2 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol), CuI (0.01 g, 0.06 mmol), Cs_2CO_3 (0,60 g, 1.7 mmol) and phenyl acetylene (0.14 g, 1.4 mmol) in THF (30 ml). Work-up and

column chromatography afforded **83b** as a yellow solid (035 g, 59%), R_f (petroleum ether, toluene 1/1) 062, mp. 217−220 °C; IR (neat): ν_{max} 683, 753, 802, 872, 1527, 1601, 2210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.20 (2H, t, *J* 7.8 Hz, ArH), 7.45−749 (3H, m, ArH), 7.77 (2H, d, *J* 6 Hz, ArH), 8.29 (1H, s, ArH), 8.46 (1H, s, ArH), 8.71 (2H, dd, *J* 9.3, 6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 84.8 (Ph-C≡), 99.3 (C(4)-C≡), 115.6 (d, $^2J_{CF}$ 21.6 Hz, C-3' and C-5′), 120.6 (C-6), 120.7 (C-1″), 125.3 (C-4a), 125.7 (C-8), 128.3 (C-3″ and C-5″), 128.5 (C-4″), 130.6 (C-2″ and C-6″), 131.2 (d, $^3J_{CF}$ 8.8 Hz, C-2′ and C-6′), 132.7 (C-5), 133.1 (d, $^4J_{CF}$ 3.4 Hz, C-1′), 140.4 (C-7), 147.2 (C-8a), 152.4 (C-4), 160.6 (C-2), 165.1 (d, $^1J_{CF}$ 250.2 Hz, C-4′); m/z (100, MH^+) 481; HRMS (ES): MH^+, found 480.9347. $C_{22}H_{12}N_2F^{79}Br_2^+$ requires 480.9351.

4.5.3 Preparation of 6,8-dibromo-2-(4-chlorophenyl)-4-(phenylethynyl)quinazoline 83c (4'-R=Cl)

An experimental procedure employed for the preparation of **83a** was followed using a mixture of **82c** (0.50 g, 1.2 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol), CuI (0.01 g, 0.06 mmol), Cs_2CO_3 (0,60 g, 1.7 mmol) and phenyl acetylene (0.14 g, 1.4 mmol) in THF (30 ml). Work-up and column chromatography afforded **83c** as a yellow solid (0.40 g, 70%), R_f (petroleum ether, toluene 1/1) 0.7, mp. 223−226 °C; IR (neat): ν_{max} 683, 748, 801, 868, 1467, 1524, 1544, 2209 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−750 (5H, m, ArH), 7.77 (2H, d, *J* 6 Hz, ArH), 8.29 (1H, s, ArH), 8.46 (1H, s, ArH), 8.64 (2H, d, *J* 9.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 84.8 (Ph-C≡), 99.4 (C(4)-C≡), 120.7 (C-6), 121.0 (C-1″), 125.5 (C-4a), 125.8 (C-8), 128.3 (C-3″ and C-5″), 128.8 (C-4″), 128.9 (C-1′), 130.3 (C-2′ and C-6′), 130.6 (C-5), 132.7 (C-3′ and C-5′), 135.4 (C-2″ and C-6″), 137.7 (C-4′), 140.4 (C-7), 147.2 (C-8a), 152.4

(C-4), 160.6 (C-2); m/z (100, MH^+) 497; HRMS (ES): MH^+, found 496.8040. $C_{22}H_{12}N_2{}^{35}Cl^{79}Br_2{}^+$ requires 496.8056.

4.5.4 Preparation of 6,8-dibromo-2-(4-methoxyphenyl)-4-(phenylethynyl) quinazoline 83d (4′-R=OCH_3)

An experimental procedure employed for the preparation of **83a** was followed using a mixture of **82d** (0.50 g, 1.2 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol), CuI (0.01 g, 0.06 mmol), Cs_2CO_3 (0,60 g, 1.7 mmol) and phenyl acetylene (0.14 g, 1.4 mmol) in THF (30 ml). Work-up and column chromatography afforded **83d** as a yellow solid (0.42 g, 71%), R_f (petroleum ether, toluene 1/1) 0.3, mp. 194−198 °C; IR (neat): ν_{max} 722, 801, 828, 1255, 1524, 1543, 2210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.89 (3H, s, CH_3), 7.03 (2H, d, *J* 7.2 Hz, ArH), 7.40−7.48 (3H, m, ArH), 7.76 (2H, d, *J* 6.9 Hz, ArH), 8.26 (1H, s, ArH), 8.44 (1H, s, ArH), 8.64 (2H, d, *J* 6.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.4 (OCH_3), 85.0 (Ph-C≡), 98.7 (C(4)-C≡), 114.0 (C-3 and C-5), 120.0 (C-6), 120.8 (C-1″), 125.1 (C-1′), 125.6 (C-4a), 128.3 (C-8), 128.7 (C-3″ and C-5″), 129.9 (C-2′ and C-6′), 130.5 (C-4″), 130.8 (C-5), 132.7 (C-2″ and C-6″), 140.1(C-7), 147.4 (C-8a), 152.2 (C-4), 161.4 (C-4′), 162.4 (C-2); m/z (100, MH^+) 493; HRMS (ES): MH^+, found 492.9541. $C_{23}H_{15}N_2O^{79}Br_2{}^+$ requires 492.9551.

4.5.5 Preparation of 6,8-dibromo-2-phenyl-4-(pyridin-2-ylethynyl)quinazoline 83e (4′-R=H)

An experimental procedure employed for the preparation of **83a** was followed using a mixture of **82a** (0.50 g, 1.2 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol), CuI (0.01 g, 0.06 mmol), Cs_2CO_3 (0,60 g, 1.7 mmol) and 2-ethynylpyridine (0.14 g, 1.3 mmol) in THF (30 ml). Work-up and column chromatography afforded **83e** as an orange solid (0.36 g, 65%), R_f (toluene) 0.15, mp. 207−209 °C; IR (neat): ν_{max} 688, 733, 775, 1304, 1464, 1527, 1543, 2228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39−7.44 (1H, m, ArH), 7.54−7.55 (4H, m, ArH), 7.78−7.82 (2H, m, ArH), 8.30 (1H, s, ArH), 8.54 (1H, s, ArH), 8.69−8.76 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 83.5 (C″(1)-C≡), 96.4 (C(4)-C≡), 121.1 (C-6), 124.5 (C-4″), 125.5 (C-4a), 125.9 (C-8), 128.2 (C-2′ and C-6′), 128.6 (C-2″), 128.7 (C-4′), 130.0 (C-5), 131.4 (C-3′ and C-5′), 136.5 (C-1′), 136.8 (C-3″), 140.6 (C-7), 141.5 (C-1′), 147.4 (C-5″), 150.6 (C-8a), 151.7 (C-4), 161.5 (C-2); m/z (100, MH^+) 464; HRMS (ES): MH^+, found 463.9398. $C_{21}H_{12}N_3{}^{79}Br_2{}^+$ requires 463.9398.

4.5.6 Preparation of 6,8-dibromo-2-(4-fluorophenyl)-4-(pyridin-2-ylethynyl)quinazoline 83f (4′-R=F)

An experimental procedure employed for the preparation of **83a** was followed using a mixture of **82b** (0.50 g, 1.2 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol), CuI (0.01 g, 0.06 mmol), Cs_2CO_3 (0,60 g, 1.7 mmol) and 2-ethynylpyridine (0.14 g, 1.3 mmol) in THF (30 ml). Work-up and column chromatography afforded **83f** as an orange solid (0.38 g, 67%), R_f (toluene) 0.2, mp. 216−218 °C; IR (neat): ν_{max} 702, 777, 802, 1306, 1409, 1465, 1527, 2219 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ: 7.21 (2H, t, *J* 7.8 Hz, ArH), 7.42−7.44 (1H, m, ArH), 7.81−7.86 (2H, m, ArH), 8.30 (1H, s, ArH), 8.54 (1H, s, ArH), 8.69−8.78 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 83.4 (C″(1)-C≡), 96.6 (C(4)-C≡), 115.6 (d, $^2J_{CF}$ 21.6 Hz), 121.1 (C-6), 124.6 (C-4″), 125.4 (C-4a), 125.7 (C-8), 128.3 (C-2″), 128.6 (C-5), 131.3 (d, $^3J_{CF}$ 8.8 Hz, C-3′ and C-5′), 133.1 (d, $^4J_{CF}$ 3.4 Hz, C-2′ and C-6′), 136.5 (C-3″), 140.7 (C-7), 141.4 (C-1″), 147.4 (C-5″), 150.7 (C-8a), 151.7 (C-4), 160.6 (C-2), 165.1 (d, $^1J_{CF}$ 250.2 Hz, C-4′); m/z (100, MH^+) 482; HRMS (ES): MH^+, found 481.9301. $C_{21}H_{11}N_3F^{79}Br_2^+$ requires 481.9304.

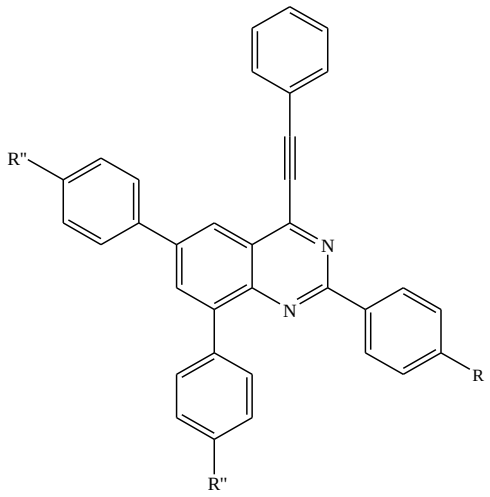
4.5.7 Preparation of 6,8-dibromo-2-(4-methoxyphenyl)-4-(pyridin-2-ylethynyl)quinazoline 83g (4′-R=OCH_3)

An experimental procedure employed for the preparation of **83a** was followed using a mixture of **82d** (0.50 g, 1.2 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol), CuI (0.01 g, 0.06 mmol), Cs_2CO_3 (0,60 g, 1.7 mmol) and 2-ethynylpyridine (0.14 g, 1.3 mmol) in THF (30 ml). Work-up and column chromatography afforded **83g** as an orange solid (0.32 g, 55%), R_f (toluene) 0.2, mp. 204−206 °C; IR (neat): ν_{max} 723, 801, 868, 1023, 1163, 1258, 1525, 2221 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (3H, s, CH_3), 7.03 (2H, d, *J* 8.7 Hz, ArH), 7.40−743 (1H, m, ArH), 7.79−7.77 (2H, m, ArH), 8.26 (1H, s, ArH), 8.50 (1H, s, ArH), 8.65 (2H, d, *J* 8.7 Hz, ArH), 8.74 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.4 (OCH_3), 83.6 (C″(1)-C≡), 96.1 (C(4)-C≡), 114.0 (C-3′ and C-5′), 120.3 (C-6), 124.5 (C-1′), 125.1 (C-4″), 125.6 (C-4a), 128.2 (C-8), 128.5 (C-2″), 129.5 (C-2′ and C-6′), 130.8 (C-5), 136.4 (C-3″), 140.4 (C-7), 141.5 (C-1″), 147.4 (C-5″), 150.7 (C-8a), 151.4 (C-4), 161.3 (C-4′), 162.4 (C-2); m/z (100, MH^+) 494; HRMS (ES): MH^+, found 493.9517. $C_{22}H_{14}N_3O^{79}Br_2^+$ requires 493.9504.

4.5.8 Preparation of 4-(6,8-dibromo-2-phenylquinazolin-4-yl)but-3-yn-2-ol 83h

An experimental procedure employed for the preparation of **83a** was followed using a mixture of **82a** (0.50 g, 1.2 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol), CuI (0.01 g, 0.06 mmol), Cs_2CO_3 (0,60 g, 1.7 mmol) and 3-butyn-2-ol (0.12 g, 1.7 mmol) in THF (30 ml). Work-up and column chromatography afforded **83h** as a brown solid (0.28 g, 56%), R_f (ethyl acetate, hexane 1/1) 0.7, mp. 162−165 °C; IR (neat): ν_{max} 682, 703, 734, 1304, 1365, 1457, 1529, 2221, 3372 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.68 (3H, d, *J* 6.6 Hz, CH_3), 2.97 (1H, s, OH), 4.90−4.92 (1H, q, *J* 6.6 Hz, CH), 7.48−7.50 (3H, m, ArH), 8.17 (1H, s, ArH), 8.55−859 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6 (CH_3), 58.6 (CHOH), 79.4 (C(4)-C≡), 100.9 ($C(CH_3)$-C≡), 120.8 (C-6), 125.0 (C-4a), 125.7 (C-8), 127.9 (C-2′ and C-6′), 128.6 (C-4′), 128.9 (C-5), 131.4 (C-3′ and C-5′), 136.5 (C-1′), 140.3 (C-7), 147.0 (C-8a), 151.6 (C-4), 161.2 (C-2); m/z (100, MH^+) 433; HRMS (ES): MH^+, found 432.9371. $C_{22}H_{14}N_3O^{79}Br_2^+$ requires 432.9371.

4.6 Preparation of 2,6,8-triaryl-4-(phenylethynyl)quinazoline derivatives 84a-l



84a-l

4.6.1 Preparation of 2,6,8-triphenyl-4-(phenylethynyl)quinazoline 84a (R=H, R″=H)

A mixture of **83a** (0.30 g, 0.6 mmol), phenylboronic acid (0.20 g; 1.6 mmol), $PdCl_2(PPh_3)_2$ (0.02 g, 0.03 mmol), PCy_3 (0.02 g, 0.06 mmol) and K_2CO_3 (0.23 g, 1.6 mmol) in dioxane-water (3:1 v/v, 20 ml) was purged with nitrogen gas. The mixture was then heated with stirring at 80 °C under nitrogen atmosphere for 2 hours and allowed to cool to room temperature. The reaction mixture was poured into ice-cold water and extracted with chloroform. The organic layer was washed with water and brine, then dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified using a column chromatography on silica gel to afford **84a** as a yellow solid (0.18 g, 71%), R_f (hexane, toluene 1/1) 0.4, mp. 184−186 ˚C; IR (neat): ν_{max} 687, 718, 755, 1534, 1561, 2208 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.43−7.60 (12H, m, ArH), 7.77−7.82 (4H, m, ArH), 7.90 (2H, d, *J* 7.5 Hz, ArH), 8.24 (1H, s, ArH), 8.57−8.59 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 85.9, 97.7, 121.3, 123.3, 124.5, 127.4, 127.8, 127.9, 128.1, 128.5, 128.6, 128.7,

128.9, 129.1, 130.1, 130.6, 131.0, 132.5, 134.2, 137.8, 137.9, 139.9, 140.1, 140.7, 147.9, 153.1, 160.0; m/z (100, MH^+) 459; HRMS (ES): MH^+, found 459.1870. $C_{34}H_{23}N_2^+$ requires 459.1861.

4.6.2 Preparation of 2-(4-fluorophenyl)-6,8-diphenyl-4-(phenylethynyl)quinazoline 84b (R=F, R″=H)

A mixture of **83b** (0.20 g, 0.4 mmol), phenylboronic acid (0.13 g, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), PCy_3 (0.01 g, 0.04 mmol) and K_2CO_3 (0.14 g, 1.0mmol) in dioxane-water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a**. Work-up and column chromatography on silica gel afforded **84b** as a yellow solid (0.12 g, 57%), R_f (hexane, toluene 1/1) 0.54, mp. 250−252 ˚C; IR (neat): ν_{max} 686, 741, 812, 1558, 1574, 2210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.14 (2H, t, *J* 8.7 Hz, ArH), 7.42−7.60 (9H, m, ArH), 7.75−7.81 (4H, m, ArH), 7.87 (2H, d, *J* 8.1 Hz, ArH), 8.22 (1H, s, ArH), 8.53−8.58 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 85.8, 97.9, 115.4 (d, $^2J_{CF}$ 21.6 Hz), 121.3, 123.3, 124.4, 127.4, 127.8, 128.0, 128.2, 128.6, 129.1, 130.1, 130.8 (d, $^3J_{CF}$ 8.8 Hz), 130.9, 132.5, 133.9 (d, $^4J_{CF}$ 3 Hz), 134.3, 137.8, 139.8, 140.1, 140.6, 147.8, 153.1, 159.0, 164.6 (d, $^1J_{CF}$ 255 Hz); m/z(100, MH^+) 477; HRMS (ES): MH^+, found 477.1772. $C_{34}H_{22}FN_2^+$ requires 477.1767.

4.6.3 Preparation of 2-(4-chlorophenyl)-6,8-diphenyl-4-(phenylethynyl)quinazoline 84c (R=Cl, R″=H)

A mixture of **83c** (0.20 g, 0.4 mmol), phenylboronic acid (0.12 g, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), PCy_3 (0.01 g, 0.04 mmol) and K_2CO_3 (0.14 g, 1.0 mmol) in dioxane-

water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a**. Work-up and column chromatography on silica gel afforded **84c** as a yellow solid (0.16 g, 78%), R_f (hexane, toluene 1/1) 0.6, mp. 246−248 ˚C; IR (neat): ν_{max} 686, 739, 752, 1557, 1576, 2211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.42−7.59 (11H, m, ArH) 7.78−7.80 (4H, m, ArH), 7.87 (2H, d, *J* 6.9, ArH), 8.23 (1H, s, ArH), 8.51 (2H, d, *J* 8.7 Hz, ArH), 8.57 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 85.8, 98.0, 121.2, 123.2, 124.5, 127.4, 127.8, 128.0, 128.2, 128.6, 128.7, 129.1, 130.1, 130.9, 132.5, 134.3, 136.3, 136.7, 137.8, 139.7, 140.2, 140.7, 147.8, 153.1, 159.0; m/z (100, MH^+) 493; HRMS (ES): MH^+, found 493.1475. $C_{34}H_{22}ClN_2^+$ requires 493.1472.

4.6.4 Preparation of 2-(4-methoxyphenyl)-6,8-diphenyl-4-(phenylethynyl)quinazoline 84d (R=OCH_3, R″=H)

A mixture of **83d** (0.20 g, 0.4 mmol), phenylboronic acid (0.13 g, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), PCy_3 (0.01 g, 0.04 mmol) and K_2CO_3 (0.14 g, 1.0 mmol) in dioxane-water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a.** Work-up and column chromatography on silica gel afforded **83d** as a yellow solid (0.14 g, 68%), R_f (hexane, toluene 1/2) 0.17, mp. 220−223 ˚C; IR (neat): ν_{max} 685, 699, 752, 1161, 1247, 1533, 2205 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.88 (3H, s, ArH), 7.01 (2H, d, *J* 7.5 Hz, ArH), 7.43−7.59 (9H, m, ArH), 7.78−7.81 (4H, m, ArH), 7.89 (2H, d, *J* 7.5 Hz, ArH), 8.22 (1H, s, ArH), 8.51−8.54 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3, 86.0, 97.5, 113.8, 121.4, 123.3, 124.2, 127.4, 127.7, 127.9, 128.0, 128.4, 128.6, 129.1, 130.0, 130.3, 130.5, 130.9, 132.5, 134.1, 138.0, 139.5, 140.0, 140.4, 148.0, 153.0, 159.8, 161.8; m/z (100, MH^+) 489; HRMS (ES): MH^+, found 489.1976. $C_{35}H_{25}ON_2^+$ requires 489.1967.

4.6.5 Preparation of 6,8-bis(4-fluorophenyl)-2-phenyl-4-(phenylethynyl)quinazoline 84e (R=H, R″=F)

A mixture of **83a** (0.20 g, 0.43 mmol), 4-fluorophenylboronic acid (0.15 g, 1.07 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), PCy_3(0.01 g, 0.04 mmol) and K_2CO_3 (0.15 g, 1.1 mmol) in dioxane-water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a.** Work-up and column chromatography on silica gel afforded **83e** as a yellow solid (0.14 g, 66%), R_f (hexane, toluene 1/1) 0.48, mp. 228−230 ˚C; IR (neat): ν_{max} 691, 708, 825, 1232, 1509, 2205 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.44−7.49 (6H, m, ArH), 7.72−7.79 (4H, m, ArH), 7.85 (2H, ddd, *J* 3.3, 6.45, 9.15 Hz, ArH), 8.12 (1H, d, *J* 2.1 Hz, ArH), 8.49 (1H, d, 2.1 Hz, ArH), 8.55 (2H, dd, *J* 2.1, 7.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 85.8, 97.9, 114.9 (d $^2J_{CF}$ 21.3 Hz), 116.1 (d, $^2J_{CF}$ 21.3 Hz) 121.3, 123.2, 124.5, 128.5 (d,$^3J_{CF}$ 8.3 Hz), 128.7, 129.1 (d,$^3J_{CF}$ 8.2 Hz), 130.1, 130.7, 132.5, 132.6, 133.7 (d, $^4J_{CF}$ 3.4 Hz), 133.8, 135.9 (d, $^4J_{CF}$ 3.1 Hz), 137.6, 139.8, 147.7, 153.1, 160.1, 162.7 (d, $^1J_{CF}$ 245.9 Hz), 162.9 (d, $^1J_{CF}$ 246.9 Hz); m/z (100, MH^+) 495; HRMS (ES): MH^+, found 495.1685. $C_{34}H_{21}F_2N_2^+$ requires 495.1673.

4.6.6 Preparation of 2,6,8-tris(4-fluorophenyl)-4-(phenylethynyl)quinazoline 84f (R=F, R″=F)

A mixture of **83b** (0.20 g, 0.4 mmol), 4-fluorophenylboronic acid (0.15 g, 1.1 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), PCy_3 (0.01 g, 0.04 mmol) and K_2CO_3 (0.15 g, 1.1 mmol) in dioxane-water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a.** Work-up and column chromatography on silica gel afforded **84f** as a yellow solid (0.16 g, 76%), R_f (hexane, toluene 1/1) 0.58, mp. 255−257 ˚C; IR (neat): ν_{max} 685, 750, 824, 1232, 1536, 2207

cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.12−7.29 (6H, m, ArH), 7.47−7.49 (3H, m, ArH), 7.72−7.85 (6H, m, ArH), 8.12 (1H, d, *J* 2.1 Hz, ArH), 8.49 (1H, d, 2.1 Hz, ArH), 8.54 (2H, dd, *J* 3, 8.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 85.7, 98.1, 114.9 (d, $^{2}J_{CF}$ 21.3 Hz), 115.5 (d, $^{2}J_{CF}$ 21.6 Hz), 116.1 (d, $^{2}J_{CF}$ 21.6 Hz) 121.2, 123.2, 124.3, 128.5, 128.7, 129.1(d, $^{3}J_{CF}$ 8.2 Hz), 130.2, 130.7 (d, $^{3}J_{CF}$ 8.7 Hz), 132.4 (d, $^{3}J_{CF}$ 8.1 Hz), 132.5, 132.6, 133.6 (d, $^{4}J_{CF}$ 3.1 Hz), 133.8 (d, $^{4}J_{CF}$ 2.8 Hz), 133.9, 135.8 (d, $^{4}J_{CF}$ 3.1 Hz), 139.0, 139.7, 147.7, 153.1, 159.2 , 162.7 (d, $^{1}J_{CF}$ 245.9 Hz), 162.9 (d, $^{1}J_{CF}$ 246.9 Hz), 164.6 (d, $^{1}J_{CF}$ 247.5 Hz); m/z (100, MH^+) 513; HRMS (ES): MH^+, found 513.1585. $C_{34}H_{20}F_3N_2^+$ requires 513.1579.

4.6.7 Preparation of 6,8-bis(4-fluorophenyl)-2-(4-chlorophenyl)-4-(phenylethynyl) quinazoline 84g (R=Cl, R″=F)

A mixture of **83c** (0.20 g, 0.4 mmol), 4-fluorophenylboronic acid (0.14 g, 1.1 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), PCy_3 (0.01 g, 0.04 mmol) and K_2CO_3 (0.14 g, 1.1 mmol) in dioxane-water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a**. Work-up and column chromatography on silica gel afforded **84g** as a yellow solid (0.16 g, 75%), R_f (hexane, toluene 1/1) 0.72, mp. 243−245 ˚C; IR (neat): ν_{max} 683, 747, 809, 1231, 1508, 2205 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (4H, dd, *J* 6.9, 15.3, ArH) 7.44−7.49 (6H, m, ArH), 7.43−7.51 (5H, m, ArH), 7.72−7.84 (6H, m, ArH), 8.12 (1H, d, *J* 2.4 Hz, ArH), 8.46−8.49 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 85.7, 98.2, 114.9 (d $^{2}J_{CF}$ 21.3 Hz), 116.1 (d, $^{2}J_{CF}$ 21.3 Hz) 121.1, 123.1, 124.4, 128.7, 128.8, 129.1 (d, $^{3}J_{CF}$ 8.2 Hz), 129.9, 130.2, 132.4 (d, $^{3}J_{CF}$ 8.3 Hz), 132.5, 133.6 (d,$^{4}J_{CF}$ 3.3 Hz), 133.8, 135.8 (d,$^{4}J_{CF}$ 3.3 Hz), 136.1, 136.9, 139.1, 139.7, 147.6, 153.1, 159.0, 162.7 (d, $^{1}J_{CF}$ 246.2 Hz), 163.0 (d, $^{1}J_{CF}$ 247.0 Hz); m/z (100, MH^+) 529; HRMS (ES): MH^+, found 529.1282. $C_{34}H_{20}ClF_2N_2^+$requires 529.1283.

4.6.8 Preparation of 6,8-bis(4-fluorophenyl)-2-(4-methoxyphenyl)-4-(phenylethynyl) quinazoline 84h (R=OCH_3, R″=F)

A mixture of **83d** (0.20 g, 0.4 mmol), 4-fluorophenylboronic acid (0.14 g, 1.1 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), PCy_3(0.01 g, 0.04 mmol) and K_2CO_3 (0.14 g, 1.1 mmol) in dioxane-water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a**. Work-up and column chromatography on silica gel afforded **84h** as a yellow solid (0.14 g, 65%), R_f (hexane, toluene 1/2) 0.5, mp. 211−213 ˚C; IR (neat): ν_{max} 683, 750, 809, 1157, 1507, 2205 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (3H, s, ArH), 6.99 (3H, d, *J* 7.8, ArH), 7.24−7.21 (4H, m, ArH), 7.47 (3H, s, ArH), 7.83−7.73 (5H, m, ArH), 8.06 (1H, s, ArH), 8.48 (3H, t, *J* 7.8 Hz, ArH); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 55.3, 85.9, 97.6, 113.8, 114.9 (d $^2J_{CF}$ 21.3 Hz), 116.1 (d, $^2J_{CF}$ 21.3 Hz) 121.3, 123.1, 124.1, 128.5, 128.7, 129.0 (d, $^3J_{CF}$ 8.2 Hz), 130.1, 130.3, 131.7, 132.5, 132.6 (d, $^3J_{CF}$ 8.5 Hz),, 133.7, 133.8 (d, $^4J_{CF}$ 3.1 Hz), 135.9 (d, $^4J_{CF}$ 3.1 Hz), 138.4, 139.4, 147.8, 152.9, 159.9, 161.8 162.7 (d, $^1J_{CF}$ 245.5 Hz), 162.9 (d, $^1J_{CF}$ 246.7 Hz); m/z (100, MH^+) 525; HRMS (ES): MH^+, found 525.1785. $C_{35}H_{23}OF_2N_2^+$ requires 525.1778.

4.6.9 Preparation of 6,8-bis(4-methoxyphenyl)-2-phenyl-4-(phenylethynyl)quinazoline 84i (R=H, R″=OCH_3)

A mixture of **83a** (0.30 g, 0.6 mmol), 4-methoxyphenylboronic acid (0.20 g, 1.6 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), PCy_3 (0.01 g, 0.04 mmol) and K_2CO_3 (0.23 g, 1.6 mmol) in dioxane-water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a**. Work-up and column chromatography on silica gel afforded **84i** as a yellow solid (0.23 g, 69%), R_f (hexane, toluene 1/2) 0.28, mp. 209−212 ˚C; IR (neat): ν_{max} 691, 758, 831, 1243, 1510, 2209

cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.89 (3H, s, CH_3), 3.93 (3H, s, CH_3), 7.07 (4H, dd, *J* 8.4, 12.6 Hz, ArH), 7.17 (2H, d, *J* 2.1 Hz, ArH), 7.44−7.47 (6H, m, ArH), 7.72−7.80 (4H, m, ArH), 7.86 (2H, d, *J* 8.7 Hz, ArH), 8.47 (1H, d, *J* 2.1 Hz, ArH), 8.56−8.60 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3, 86.0, 97.5, 113.4, 114.5, 121.4, 121.7, 124.5,128.4, 128.5, 129.9, 130.3, 130.4, 132.1, 132.4, 133.4, 137.8, 139.5, 133.9, 140.0, 147.5, 152.7, 159.3, 159.4, 159.7; m/z (100, MH^+) 519; HRMS (ES): MH^+, found 519.2071. $C_{36}H_{27}O_2N_2^+$ requires 519.2073.

4.6.10 Preparation of 2-(4-fluorophenyl)-6,8-bis(4-methoxyphenyl)-4-(phenylethynyl) quinazoline 84j (R=F, R″=OCH_3)

A mixture of **83b** (0.40 g, 0.8 mmol), 4-methoxyphenylboronic acid (0.26 g, 2.1 mmol), $PdCl_2(PPh_3)_2$ (0.03 g, 0.04 mmol), PCy_3(0.02 g, 0.08 mmol) and K_2CO_3 (0.30 g, 2.1 mmol) and dioxane-water (3:1 v/v, 30 ml) was treated as described for the synthesis of **84a**. Work-up and column chromatography on silica gel afforded **84j** as a yellow solid (0.29 g, 62%), R_f (hexane, toluene 1/2) 0.33, mp. 236−239 ˚C; IR (neat): ν_{max} 760, 808, 831, 1248, 1508, 2208 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.89 (3H, s, CH_3), 3.93 (3H, s, CH_3), 7.04−7.17 (6H, m, ArH), 7.44−7.47 (3H, m, ArH), 7.70−7.83 (6H, m, ArH), 8.16 (1H, s, ArH), 8.45 (1H, s, ArH), 8.56 (2H, t, *J* 5.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3, 55.4, 85.9, 97.7, 113.4, 114.5, 115.4 (d, $^{2}J_{CF}$ 21.3 Hz), 121.3, 121.9, 124.5, 128.5, 128.6, 130.0, 130.3,130.6 (d,$^{3}J_{CF}$ 8.4 Hz), 132.0, 132.2, 132.5,133.6, 134 (d, $^{4}J_{CF}$ 3.0 Hz), 139.7, 140.1, 147.6, 152.8, 158.6, 159.8, 164.5 (d, $^{1}J_{CF}$ 247.5 Hz); m/z(100, MH^+) 537; HRMS (ES): MH^+, found 537.1986. $C_{36}H_{26}O_2FN_2^+$ requires 537.1978.

4.6.11 Preparation of 2-(4-chlorophenyl)-6,8-bis(4-methoxyphenyl)-4-(phenylethynyl) quinazoline 84k (R=Cl, R″=OCH_3)

A mixture of **83c** (0.30 g, 0.6 mmol), 4-methoxyphenylboronic acid (0.20 g, 1.6 mmol), $PdCl_2(PPh_3)_2$ (0.02 g, 0.03 mmol), PCy_3 (0.02 g, 0.06 mmol) and K_2CO_3 (0.23 g, 1.6 mmol) in dioxane-water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a**. Work-up and column chromatography on silica gel afforded **84k** as a yellow solid (0.27 g, 76%), R_f (hexane, toluene 1/2) 0.38, mp. 233−235 °C; IR (neat): ν_{max} 746, 807, 830, 1248, 1511, 2210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.88 (3H, s, CH_3), 3.92 (3H, s, CH_3), 7.42−7.59 (11H, m, ArH), 7.78−7.80 (4H, m, ArH), 7.87 (2H, d, *J* 6.9, ArH), 8.23 (1H, s, ArH), 8.51 (2H, d, *J* 8.7 Hz, ArH), 8.57 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3, 55.4, 85.9, 97.8, 113.4, 114.6, 115.4, 121.3, 121.8, 124.6, 128.5, 128.6, 128.7, 129.9 130.1, 130.2, 130.6, 132.0, 132.2, 132.5, 133.6, 136.4, 136.6, 138.2, 140.1, 147.6, 152.8, 158.6, 159.4, 159.8; m/z (100, MH^+) 553; HRMS (ES): MH^+, found 553.1689. $C_{36}H_{26}O_2ClN_2^+$ requires 553.1683.

4.6.12 Preparation of 2,6,8-tris(4-methoxyphenyl)-4-(phenylethynyl)quinazoline 84l (R=OCH_3, R″=OCH_3)

A mixture of **83d** (0.20 g, 0.4 mmol), 4-methoxyphenylboronic acid (0.15 g, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), PCy_3 (0.01 g, 0.04 mmol) and K_2CO_3 (0.14 g, 1.0 mmol) in dioxane-water (3:1 v/v, 20 ml) was treated as described for the synthesis of **84a**. Work-up and column chromatography on silica gel afforded **84l** as a yellow solid (0.13 g; 60%), R_f (hexane, toluene 1/2) 0.2, mp 237−239 °C; IR (neat): ν_{max} 685, 753, 808, 8.32, 1243, 1491, 2207 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.87 (3H, s, CH_3), 3.88 (3H, s, CH_3), 3.93 (3H, s,

CH_3), 6.98−7.12 (6H, m, ArH) 7.47 (3H, s, ArH), 7.78−7.80 (4H, m, ArH), 7.81−7.86 (6H, m, ArH), 8.16 (1H, s, ArH), 8.46 (1H, s, ArH), 8.55 (2H, d, *J* 9.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3, 55.3, 55.4, 86.1, 97.2, 113.3, 113.7, 114.5, 121.4, 121.8, 124.3, 128.4, 128.5, 129.9, 130.2 130.4, 130.6, 132.1, 132.3, 132.4, 133.4, 139.0, 139.8, 147.6, 152.6, 159.3, 159.4, 159.7, 161.6; m/z (100, MH^+) 549; HRMS (ES): MH^+, found 549.2192. $C_{37}H_{29}O_3N_2^+$ requires 549.2178.

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