SYNTHESIS OF POLYARYL-SUBSTITUTED BISQUINAZOLINONES WITH POTENTIAL PHOTOPHYSICAL PROPERTIES

by

MMAKWENA MODLICIOUS MMONWA

Submitted in accordance with the requirements for the degree of

MASTER OF SCIENCE

in the subject

CHEMISTRY

at the

UNIVERSITY OF SOUTH AFRICA

SUPERVISOR: PROFESSOR M.J. MPHAHLELE

November 2014

Student number: 5304-576-9

I declare that SYNTHESIS OF POLYARYL-SUBSTITUTED BISQUINAZOLINONES 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. M.M. Mmonwa)

This thesis is dedicated to my parents, Mr. Pitsi William and Mrs. Matlou Sarina Mmonwa.

ACKNOWLEDGEMENTS

My sincere gratitude goes to the following:

- My supervisor, Professor M.J. Mphahlele, for his guidance and encouragement throughout this study.
- The University of South Africa and the National Research Foundation (NRF) for financial support.
- Dr Bongumusa Dladla and Ms Christinah Chokwe for proof-reading this dissertation.
- Mr. Albert Semenya, for his guidance, inspiration and support throughout my studies.
- Mr. Noko Matsena for providing me with accommodation throughout this study.
- My aunts Mrs Hendrica Mabitsela and Mrs. Jane Maphelela for their support and always been there when I needed them.
- My parents, brothers, and sisters for their continuous support and for raising my hopes and aspirations.
- Above all, I like to thank almighty God for making it possible for me.

ABSTRACT

3,5-Dibromo-2-aminobenzamide was reacted with 1,3-cyclohexanedione derivatives in the presence of iodine as catalyst in toluene under reflux to afford novel 6,8-dibromo-2-[3-(2´-alkyl-1´,2´,3´,4´-tetrahydro-6´,8´-dibromo-4´-oxoquinazoline-2yl)propyl]quinazolin-4(3*H*)-ones in high yields. Suzuki-Miyaura cross-coupling of the latter with arylboronic acids in the presence of $Pd(PPh_3)_2Cl_2$–Xphos catalyst complex and K_2CO_3 as a base in dioxane-water mixture (3:1, v/v) afforded the corresponding polyaryl-substituted bis-heterocycles in a single step operation. The resultant compounds were characterized using a combination of NMR (^1H and ^{13}C) and IR spectroscopic techniques, as well as mass spectrometry. The electronic absorption and emission properties of these polyaryl-substituted bis-heterocycles comprising 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties linked by a flexible carbon chain were measured in dimethylsulfoxide (DMSO) and acetic acid by means of UV-Vis and fluorescence spectroscopic techniques. The absorption spectra of the resultant polyaryl-substituted bis-heterocycles showed blue-shift in acetic acid and red-shift in DMSO, while their emission spectra are blue-shifted in DMSO and red-shifted in acetic acid. The 4-methoxy groups on aryl-substituents caused red shift on π–π* transition of the aryl-substituents. Moreover, it was also observed that as the propyl linkage becomes more substituted, the absorption and emission intensities decrease.

Keywords: 2,3-dihydroquinazolin-4(1*H*)-ones, Quinazolin-4(3*H*)-ones, 6,8-dibromo-2-[3-(2'-alkyl-1´,2´,3´,4´-tetrahydro-6´,8´-dibromo-4´-oxoquinazoline-2yl)propyl]quinazolin-4(3*H*)-ones, Suzuki-Miyaura cross coupling, polyaryl-substituted bis-heterocycles, photophysical properties

TABLE OF CONTENTS

Declaration i

Dedication ii

Acknowledgements iii

Abstract iv

CHAPTER 1: INTRODUCTION 1–52

1.1 Methods for the synthesis of quinazolin-4-ones 7

1.1.1 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives 7

i) The synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via condensation reactions of anthranilamides with aldehydes or ketones 8

ii) The synthesis of 2,3-dihydroquinazolin-4(*1H*)-ones via a one-pot multicomponent condensation reactions 11

iii) The synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via metal-mediated condensation reactions 12

1.1.2 Methods for the synthesis of quinazolin-4(3*H*)-ones 14

i) Synthesis of quinazolin-4(3*H*)-ones via dehydrogenation of the 2,3-dihydroquinazolin-4(1*H*)-ones 14

ii) Synthesis of quinazolin-4(3*H*)-ones via oxidative condensation reactions 15

iii) Synthesis of quinazolin-4(3*H*)-ones by Aza-Wittig reaction 19

iv) Synthesis of quinazolin-4(3*H*)-ones or quinazolines via transition metal-catalyzed reactions 20

1.2 *N*(3) or *O*-alkylation/arylation/acylation of quinazolin-4(3*H*)-ones 24

1.3 Halogenated quinazolinone or quinazoline derivatives as substrates for metal catalysed cross-coupling reactions to afford polysubstituted derivatives 26

1.3.1 Application of Kumada cross-coupling reactions for the synthesis of polysubstituted quinazolinones and/ or quinazolines 28

1.3.2 Application of Suzuki cross-coupling reactions for the synthesis of polysubstituted quinazolinones and/ or quinazolines 30

1.3.3 Application of Negishi cross-coupling reactions in the synthesis of polysubstituted quinazolinones and/ or quinazolines 34

1.2.4 Application of Sonogashira cross-coupling reactions for the synthesis of polysubstituted quinazolinone and/ or quinazoline derivatives 36

1.3.5 Application of the Heck cross-coupling reactions in the synthesis of polysubstituted quinazolinones and/ or quinazolines 39

1.3.6 Application of the Stille cross-coupling reactions in the synthesis of polysubstituted quinazolinones and/ or quinazolines 42

1.4 Synthesis of bis-heterocyclic compounds 44

1.5 Research hypothesis 50

1.6 Aims and objectives 52

CHAPTER 2: RESULTS AND DISCUSSION 53–82

2.1 Synthesis and transformation of halogenated bis-heterocycles 55

2.1.1 Synthesis of 2-amino-3,5-dibromobenzamide 55

2.1.2 Synthesis of 6, 8-dibromo-2-[3-(2'-alkyl- 6', 8'-dibromo-1', 2', 3', 4'-tetrahydro-4'-oxoquinazoline-2'yl)propyl]quinazolin-4(3*H*)-ones 58

2.1.3 Suzuki-Miyaura cross-coupling reactions of halogenated bis-heterocycles with arylboronic acids 62

2.2 Absorption and emission property studies of halogenated bis-heterocycles and polyaryl-substituted bis-heterocycles 68

2.2.1 Absorption properties of halogenated bis-heterocycles 68

2.2.2 Absorption properties of polyaryl-substituted bis-heterocycles 70

2.2.3 Emission properties of halogenated bis-heterocycles and polyaryl-substituted bis-heterocycles 74

2.2.4 Quantum Chemical Calculations 80

CHAPTER 3: CONCLUSIONS 83–84

CHAPTER 4: EXPERIMENTAL 85–99

4.1 General 85

4.2 Preparation of 2-amino-3, 5-dibromobenzamide 86

4.3 Preparation of 6, 8-dibromo-2-(3-(2'-alkyl- 6', 8'-dibromo-1', 2', 3', 4'-tetrahydro-4'-oxoquinazoline-2'yl)propyl)quinazolin-4(3*H*)-one derivatives 86

4.4 Preparation of 2-(3-(2'-alkyl-1',2',3',4'-tetrahydro-4'-oxo-6',8'-diphenylquinazolin-2'-yl)propyl)-6,8-diphenylquinazolin-4(3*H*)-one derivatives 89

CHAPTER 5: REFERENCES 100–106

APPENDIX

Selected mass spectra 107

CHAPTER 1: INTRODUCTION

Nitrogen-containing heterocyclic compounds comprise the topic of at least half of all organic chemistry research worldwide, because of their important biological and medicinal applications.[1-4] Among the pharmaceutically important nitrogen-based organic heterocycles, the fused pyrimidines, which are found in a variety of natural products,[5] exhibit a wide range of biological properties. These include antibacterial, antifungal, antiviral and antimalarial activities,[6] central nervous system (CNS) depressants and stimulants.[7] Quinazolinones, which form the basis of this investigation, are a class of heterocyclic molecules consisting of a benzo ring fused to pyrimidine ring with one carbonyl group, [i.e. 2,3-dihydroquinazolin-4(1*H*)-one **1**; quinazolin-4(3*H*)-one **2**; 3,4-dihydroquinazolin-2(1*H*)-one **3**] or two carbonyl groups [i.e. quinazoline-2,4(1*H*, 3*H*)-dione **4**] on the pyrimidine framework (Fig. 1).

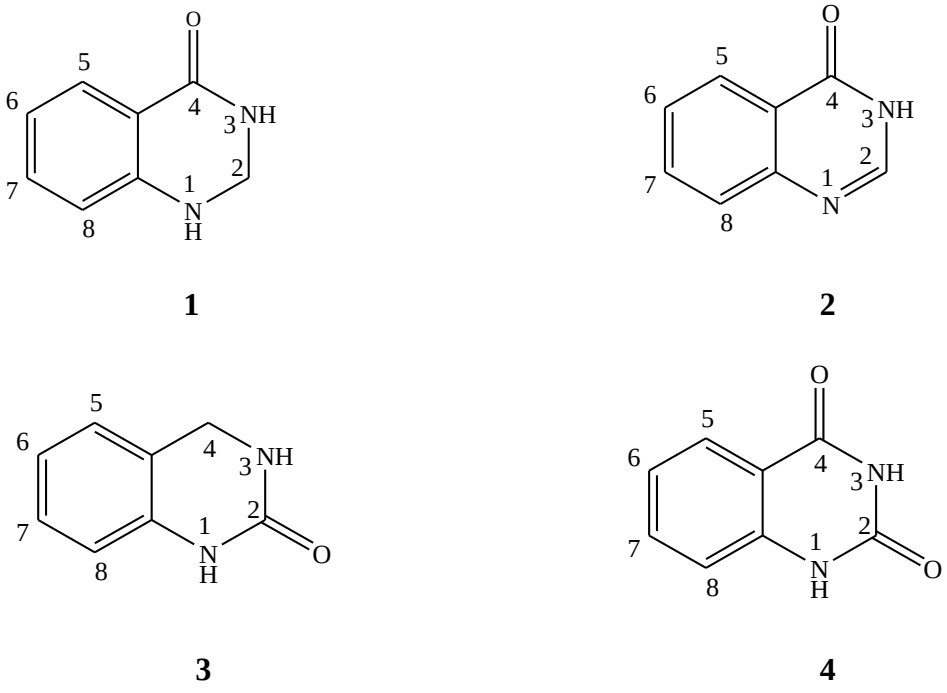


Figure 1: Generalized examples of the quinazolinone framework.

Among the above mentioned quinazolinones, the 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones are the most studied derivatives because of their biological properties and potential application in material chemistry. Quinazolinone alkaloid febrifugine **5a** (Fig. 2), for example, was first isolated from a Chinese plant *Dichroa febrifuga* in 1950 and was found to exhibit antimalarial properties.[8] However, this compound was never used in clinical trials because it was found to cause severe gastrointestinal disorders.[9] This drawback led to a search for analogues of febrifugine with increased potency and reduced side effects.[10] In this regard, a halogenated febrifugine derivative, halofuginone **5b** (Fig. 2), was synthesized and found to exhibit coccidiostat activity.[10] In addition, methaqualone **6**, a quinazolinone derivative synthesized in 1951[11] was found to possess sedative and hypnotic effects.[12] This discovery triggered the research on the isolation, synthesis and biological activity studies of quinazolinone derivatives and their analogues. For example, fenquizone **7** (Fig. 3), a 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one derivative is used for the treatment of oedema and hypertension.[13]

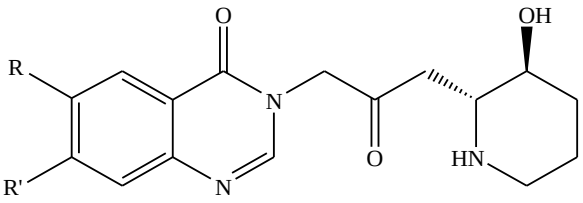
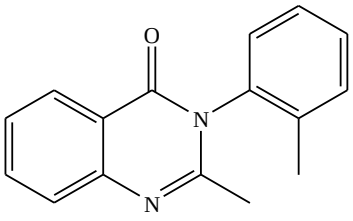


Figure 2: R, R'= H (**5a**)

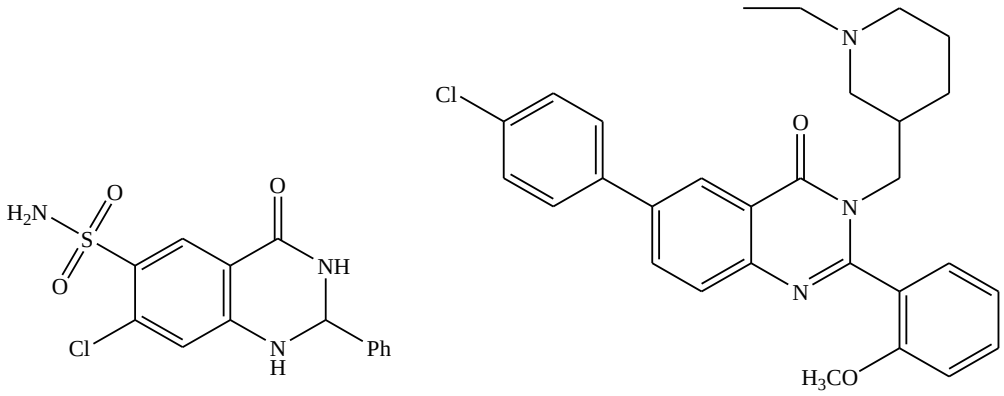
R = Cl, R' = Br (**5b**)



6

The 2,3-dihydroquinazolin-4(1*H*)-one scaffold can enable the introduction of a different degree of unsaturation in the heterocyclic ring through dehydrogenation and subsequent aromatization to afford the corresponding quinazolin-4(3*H*)-ones and quinazoline derivatives, respectively. Quinazolin-4(3*H*)-one-based compounds have been found to exhibit sedative

properties[12] and some derivatives possess growth inhibitory activity against leukaemia cells.[14] The 6-(4-chlorophenyl)-3-[(1-ethylpiperidin-3-yl)methyl]-2-(2-methoxyphenyl)quinazolin-4(3*H*)-one **8** (Fig. 3) previously prepared via Suzuki-Miyaura cross-coupling of the corresponding 6-bromoquinazolin-4(3*H*)-one precursor with 4-chlorophenylboronic acid, on the other hand, was found to be ghrelin receptor antagonist.[15]

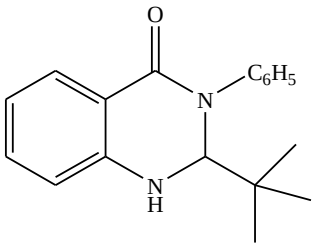


7 **8**

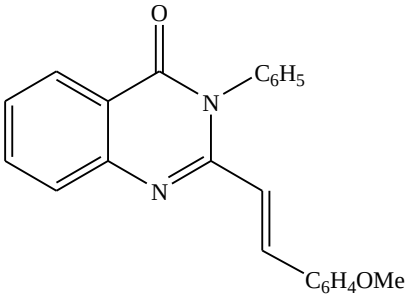
Figure 3: Examples of biologically active quinazolin-4-ones.

The 2,3-dihydroquinazolin-4(1*H*)-ones[16] and quinazolin-4(3*H*)-ones[17] have also been found to exhibit interesting electronic absorption and emission properties and some derivatives have potential application as dyes and/ or components of organic light emitting devices (OLEDs). Attachment of π-electron donating groups such as aryl substituents directly or indirectly through π-conjugated spacers (eg. alkynyl or vinyl groups) to the electron-deficient 2,3-dihydroquinazolin-4(1*H*)-one or quinazolin-4(3*H*)-one skeletons has been found to increase the donor-π-acceptor properties of the resultant carbo-substituted quinazolin-4-one derivatives.[16,17,18,19] For example, 2-*tert*-butyl-2,3-dihydro-3-phenylquinazolin-4(1*H*)-one **9** (Fig. 4) in chloroform was found to absorb in the UV region (λ_{ab} 344 nm) and to emit at visible region (λ_{em} 409 nm).[17] The electronic absorption and emission spectra of 2-(4-methoxystyryl)-3-phenylquinazolin-4(3*H*)-one **10** (Fig. 4) acquired in acetonitrile at 25 °C, on the other hand, also revealed that this compound absorbs in the ultra-violet region

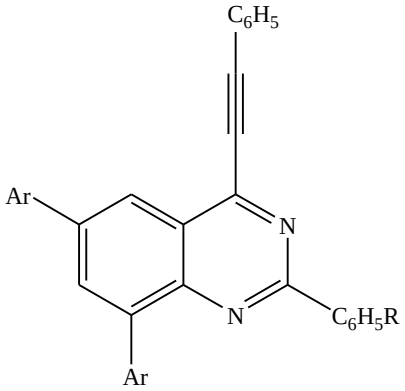
(λ_{ab} 348 nm) and emits in the visible region (λ_{em} 485 nm).[18] Likewise, the absorption spectra of the analogous 2,6,8-triaryl-4-(2-arylethynyl)quinazoline derivatives **11** (Fig. 4) acquired in chloroform or dimethylformamide (DMF) revealed that these compounds absorb in the ultra-violet region λ_{ab} 270–295 nm and emit in the visible region λ_{em} 450−480 nm and 450−500 nm, respectively.[19]



9



10



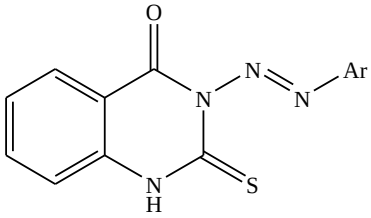
11: R = 4-H, 4-F, 4-Cl, 4-MeO

Ar = C_6H_5, 4-FC_6H_4, 4-$MeOC_6H_4$

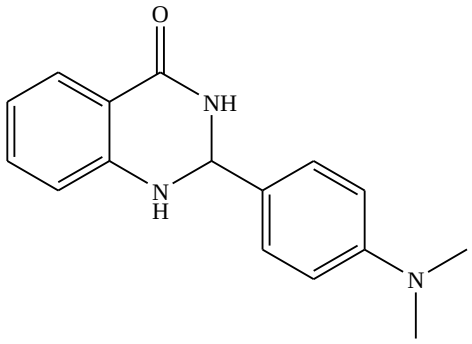
Figure 4: Examples of quinazolin-4-ones and quinazoline derivatives with absorption and emission properties.

Some of the 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one derivatives have been employed as components of dyes or light emitting materials. For example, the disperse dyes such as 3-arylazo-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-ones **12** (Fig. 5) were prepared from coupling of the corresponding 2,3-dihydroquinazolin-4(1*H*)-one diazonium salts with

α-naphthol, β-naphthol, phenol, resorcinol or 8-hydroxyquinoline.[20] These dyes were applied on polyester fabric and then tested for their fastness to washing, perspiration, rubbing and light.[20] The dyes **12** showed remarkable degree of brightness after washing and good perspiration, rubbing and light fastness properties.[20] On the other hand, a three layered greenish-yellow electroluminescent device comprising of 2-[4´-(*N*,*N*-dimethylamino)phenyl]-2,3-dihydroquinazolin-4(1*H*)-one **13** (Fig. 5) as an emissive layer sandwiched between a hole transporting *N*,*N*′-diphenyl-*N*,*N*′-bis(3-methylphenyl)-1,1-biphenyl-4,4'-diamine (TPD) and an electron transporting layer of tris(8-hydroxyquinolinato)aluminium (Alq3) {ITO/TPD/MAPQ/Alq3/Al} has since been developed.[21] In this study, the authors also observed that the addition of hole transporting layer and an electron transporting layer did not only enhance the luminance of the material, but also narrowed the light emission.[21]



12: Ar = 4-hydroxynaphthyl,
2-hydroxynaphthyl,
4-hydroxyphenyl,
8-hydroxyquinolin-5-yl

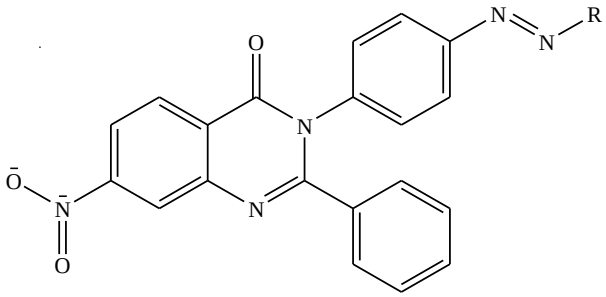


13

Figure 5: Examples of quinazolin-4(1*H*)-one based dyes and light emitting materials.

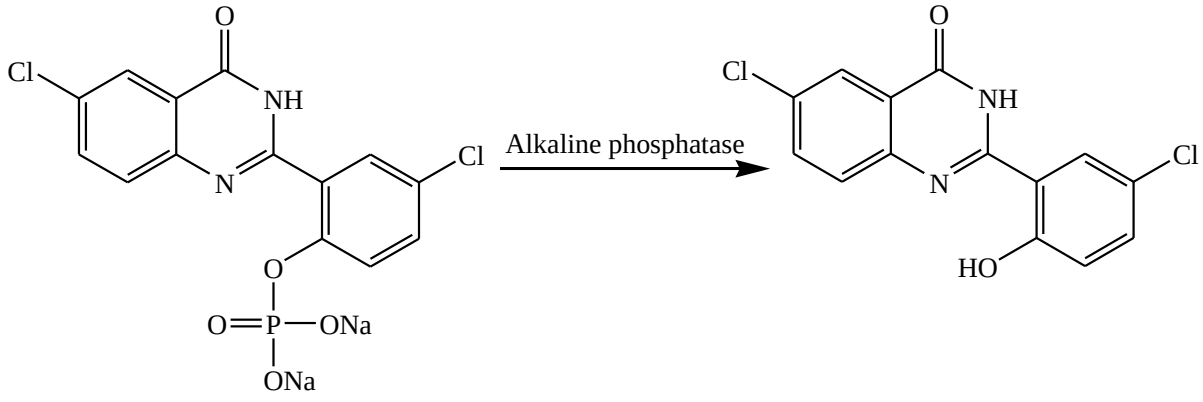
The quinazolin-4(3*H*)-one-based azo dyes and/ or light emitting materials have also been developed. As an example, 3-(4-aminophenyl)-7-nithro-2-phenylquinazolin-4(3*H*)-one-based azo dyes **14** (Fig. 6) prepared from the coupling of the corresponding quinazolin-4(3*H*)-one

diazonium salts with naphthalene based acid components (i.e. H-acid, J-acid, Korch acid, Tobias acid)[22] were reported to exhibit purple, red, orange, and yellow shades when applied on silk, wool or nylon. On the other hand, a weakly blue-fluorescent substrate, sodium 4-chloro-2-(6-chloro-3,4-dihydro-4-oxoquinazolin-2-yl)phenyl phosphate **15** (Fig. 6), which is used as fluoregenic substrate in the field of enzyme-labelled fluorescence (ELF) was found to undergo enzymatic cleavage of the phosphate group to yield an extremely photostable yellow-green fluorescent precipitate, EFL alcohol **16** (Fig. 6), with maximum emission at 530 nm.[23]



R = naphalene based acid component

14



15 **16**

Figure 6: Examples of quinazolin-4(3*H*)-one based dyes and light emitting materials.

Recently, Lu *et al*. prepared novel bis-heterocyclic derivatives consisting of the 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties linked by a propyl

chain.[24] We envisioned that the attachment of various aryl groups on the bis-heterocycles framework could lead to derivatives with interesting absorption and/ or emission properties. In our view, the conjugative effects of the aryl groups could enhance donor-π-acceptor interaction with the π-electron-acceptors quinazolinone moieties. The primary effect of the aryl groups would be to shift the π–π* transition towards the visible region.[25] In order to realize this goal, we conducted a literature search on the known methods for the synthesis of quinazolinones and their bis-quinazolinone derivatives and these are described below.

1.1 Methods for the synthesis of quinazolin-4-ones

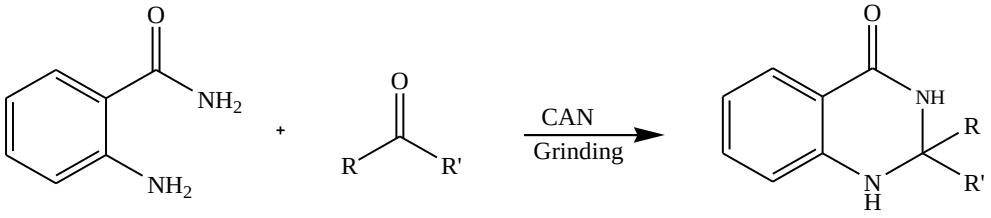
Conventional methods for the synthesis of quinazolin-4-ones commonly involve the condensation of anthranilamide derivatives with carbonyl compounds, such as ketones, aldehydes and dicarbonyl derivatives. A number of these methods will now be discussed in the next section.

1.1.1 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives

Several methods for the synthesis of these compounds have been reported in the literature.[26-35] These include condensation reactions of anthranilamides with aldehydes or ketones,[26-29] multicomponent condensations involving isatoic anhydrides, primary amines or ammonium acetate and ketones or aldehydes,[32,33] and metal-mediated condensation reactions.[34,35] These methods are briefly discussed below.

i) The synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via condensation reactions of anthranilamides with aldehydes or ketones

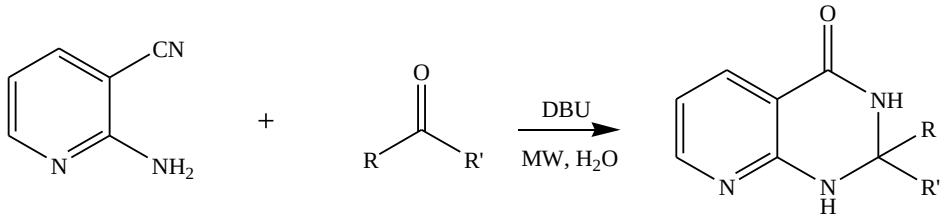
The synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by condensation reactions involves the reaction of anthranilamide derivatives with aldehydes or ketones, with the release of water followed by intramolecular nucleophilic attack of the amide nitrogen on the activated imine group. For example, a mixture of 2-aminobenzamide **17** and the carbonyl derivative (ketone or aldehyde) **18** in the presence of cerium ammonium nitrate (CAN) in water was ground at room temperature. The mixture was then heated at 60 °C to afford the corresponding 2,3-dihydroquinazolin-4(1*H*)-one derivatives **19** (Scheme 1).[26] The grinding step was found to be essential to increase the surface area and to facilitate the reaction to lead to increased yields. Ding *et al.* have also employed the grinding technique for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by condensing 2-aminobenzamides with aldehydes, in the presence citric acid under solvent-free conditions.[27] The authors found that the presence of a nitro group at the *ortho*-, *meta*- or *para*-position of the benzaldehyde derivative had little or no effect on the yields of the desired products. Moreover, the use of an aliphatic aldehyde such as butanal, as a substrate afforded the desired product in relatively high yield (88%). On the other hand, moderate yield (65%) of the desired product was achieved with a long chain decanal as substrate.



17 **18** **19**: R, R´=H, alkyl, aryl

Scheme 1: Condensation of 2-aminobenzamide **17** with aldehydes or ketones **18** by a grinding technique.

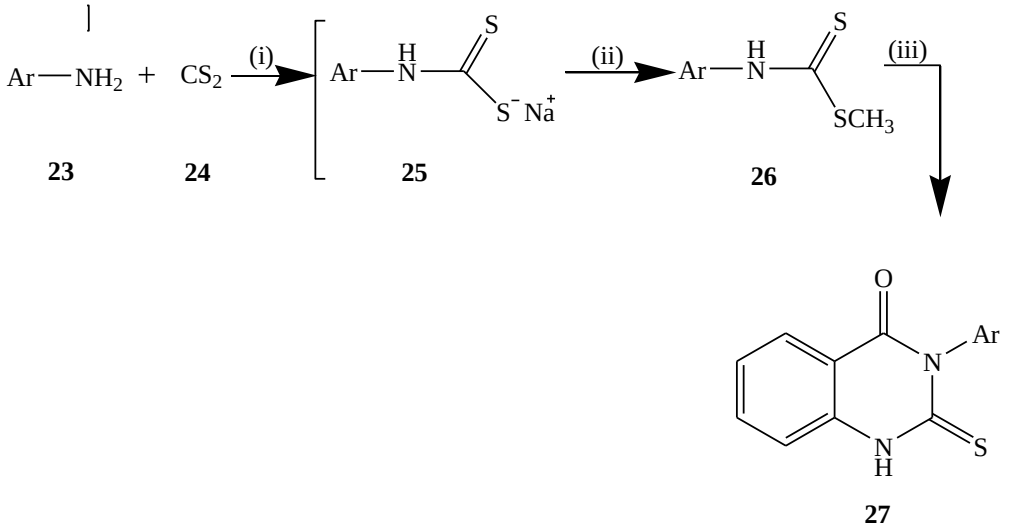
Other condensation methods reported for the synthesis of 2,3-dihydoquinazolin-4(1*H*)-ones, which make use of 2-aminobenzamide and aldehydes or ketones as substrates, employ silica supported polyphosphoric acid[28] and boric acid or sodium dihydrogen phosphate[29] as catalysts under solvent-free conditions. Microwave irradiation has also been employed for the preparation of the analogous 2,3-dihydropyrido[2.3-*d*]pyrimidin-4(1*H*)-ones **22** from condensation of 2-amino-nicotinonitrile **20** with ketones or aldehydes **21**, in the presence of aqueous 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 2).[30]



20 **21** **22**: R, R'= alkyl, aryl

Scheme 2: Microwave assisted cyclocondensation of **20** and **21** to afford **22**.

In another example, aryl amines **23** were reacted with carbon disulphide **24** in alkaline dimethylsulfoxide (DMSO) medium to afford intermediate **25**, which was in turn, methylated with dimethyl sulphate at 0–5 °C to afford methyl arylcarbamodithioates **26** (Scheme 3).[31] Compounds **26** were further reacted with anthranilic acid in the presence of potassium carbonate as a dehydrating agent in ethanol under reflux to afford 3-aryl-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-ones **27**. These conventional conditions produced compounds **27** in 56–72% yields and the reaction involved prolonged reaction time, 20–22 h.[31] Improved yields (71–88%) of compounds **27** were observed within 10–12 min. when methyl arylcarbamodithioates and anthranilic acid were reacted under microwave conditions at 140 W. The resultant 3-aryl-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-ones **27** were screened for biological properties and were found to exhibit anticonvulsant activity.[31]



Compound	Conventional method			Microwave assisted method	
	Ar	% yield	Time (h)	% Yield	Time (min)
27a	C_6H_5	56	20	71	10
27b	4-$NO_2C_6H_4$	67	20	83	11
27c	4-Cl-2-$NO_2C_6H_3$	72	22	88	12
27d	2-Cl-4-$NO_2C_6H_3$	63	22	85	12
27e	3-Cl-4-FC_6H_3	59	21	80	12

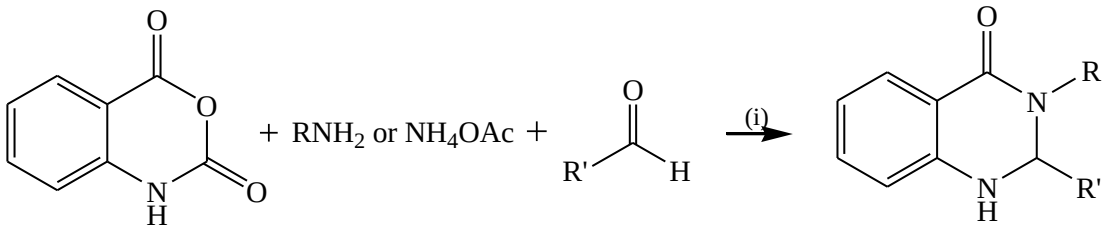
Reagents and conditions: (i) 20 M NaOH (aq), DMSO, 0–5 °C; (ii) DMSO, 0–5 °C; (iii) Anthranilic acid, K_2CO_3, CH_3CH_2OH, reflux (conventional method) or 140 W (microwave assisted method)

Scheme 3: Preparation of compounds **27** by conventional and microwave assisted methods.

Another strategy for the synthesis of novel 2,3-dihydroquinazolin-4(1*H*)-ones involves the condensation of more than two reagents, i.e., isatoic anhydride, primary amines or ammonium acetate and aldehydes or ketones in single-pot operation as described below.

ii) The synthesis of 2,3-dihydroquinazolin-4(*1H*)-ones via a one-pot multicomponent condensation reactions

A one-pot multicomponent approach involves the reaction of more than two reactants, which combine in a sequential manner to yield products that retain the majority of the atoms in the starting materials. For example, the one-pot reaction of the isatoic anhydride **28** with ammonium acetate as a source of ammonia or primary amines **29** afforded anthranilamide derivatives *in situ*, then followed by condensation with aldehydes **30** promoted by silica supported ferric chloride as a catalyst under solvent-free conditions at 80 °C to afford a series of 2,3-dihydroquinazolin-4(1*H*)-ones **31** in 75–91% (Scheme 4).[32] It was envisioned by the authors (Majid *et al*., **2011**) that the loss of CO_2 from the isatoic anhydride is the driving force for the formation of a more reactive intermediate that forms the 2,3-dihydroquinazolin-4(1*H*)-one product. It was found that the condensation of either isatoic anhydride or 2-aminobenzamide with 2-pyridine carbaldehyde does not occur in the presence of silica supported ferric chloride, because pyridine acts as a Lewis base and reacts with the Lewis acid catalyst (iron(III) chloride). On the other hand, the condensation of the isatoic anhydride with ammonium acetate and aldehydes produced the desired products in shorter reaction times than the condensation of 2-aminobenzamides with aldehydes which involves prolonged reaction times. Rostamizadeh *et al.* also condensed isatoic anhydride with ammonium acetate and aldehydes in the presence of iodine as a catalyst under solvent-free conditions to obtain 2,3-dihydroquinazolin-4(1*H*)-ones in excellent yields (94–98%) within 5–25 minutes.[33] Reduced yields were obtained when amines, such as ethylamine, methylamine and aniline, were employed in place of ammonium acetate.



28 **29** **30** **31**: R, R´= H, alkyl, aryl

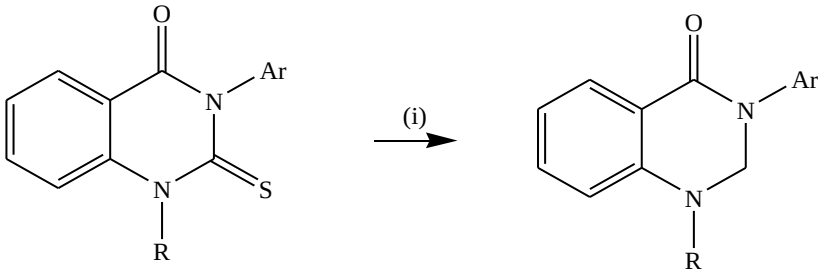
***Reagents and conditions*:** (i) SiO_2-$FeCl_3$, 80 °C.

Scheme 4: Cyclocondensation of isatoic anhydride **28** with ammonia derivatives **29** and aldehydes **30**.

Methods for reductive desulfurization of 2-thioxoquinazolin-4(3)-ones, or reductive cyclization of 2-nitrobenzamides with aldehydes or ketones, which involve the use of transition metals as reducing agents to afford 2,3-dihydroquinazolin-4(1*H*)-ones have also been developed and these are described below.

iii) The synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via metal-mediated condensation reactions

Khurana and Kukreja previously reported the reductive desulfurization of 2-thioxoquinazolin-4(3)-ones **32** using nickel boride in dry methanol at room temperature to afford 2,3-dihydroquinazolin-4(1*H*)-ones **33** (Scheme 5).[34] The desulfurization of 2-thioxoquinazolin-4(1*H*)-ones is thought to proceed through quinazolin-4(3*H*)-one intermediates, which in turn, are reduced to 2,3-dihydroquinazolin-4(1*H*)-ones. The analogous 2-thioxoquinazolin-4(3*H*)-ones were also prepared by condensing 2-aminobenzoic acids with aryl isothiocynates in the presence of nickel boride as a reducing and dethiating agent. The nickel boride used as a catalyst was prepared *in situ* from the reaction of anhydrous nickel chloride and sodium borohydride in dry methanol.[34]



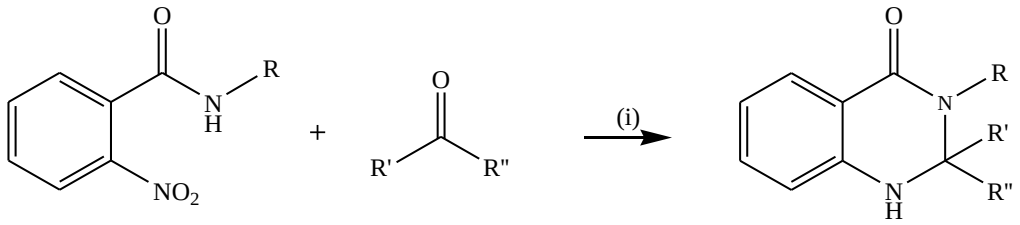
32 **33**: R= H, CH_3;

Ar = C_6H_4, 4-$OMeC_6H_6$, 4-ClC_6H_4

***Reagents and conditions*:** (i) $NiCl_2$, $NaBH_4$, dry CH_3OH, rt.

Scheme 5: Formation of 2,3-dihydroquinazolin-4(1*H*)-ones **33** from 3-aryl-2-thioxoquinazolin-4(3*H*)-ones **32**.

In another example, Shi *et al*. previously synthesized a series of 2,3-dihydroquinazolin-4(1*H*)-one derivatives **46** by coupling 2-nitrobenzamides **44** with aldehydes or ketones **45**, using a low-valent titanium reagent. Compounds **44** were first reduced by low-valent titanium reagent *in situ* to anthranilamides, which in turn reacted with compounds **45**. The low-valent titanium reagent used in this study was prepared *in situ* by the reduction of titanium tetrachloride ($TiCl_4$) with zinc powder in anhydrous tetrahydrofuran (THF) (Scheme 6).[35]



44 **45** **46**: R, R', R"= H, alkyl, aryl

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

Scheme 6: Reactions of 2-nitrobenzamides **44** with ketones or aldehydes **45**.

Of importance is that the 2,3-dihydroquinazolin-4(1*H*)-one framework can allow the introduction of different degrees of unsaturation in the heterocyclic ring via dehydrogenation

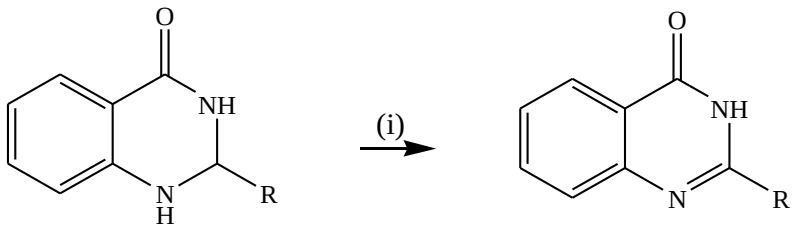
or aromatization to afford the corresponding quinazolin-4(3*H*)-one or quinazoline derivatives. Examples of the methods for the dehydrogenation of 2,3-dihydroquinazolin-4(1*H*)-ones and aromatization of the resultant quinazolin-4(3*H*)-ones are described below.

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

Quinazolin-4(3*H*)-ones can be prepared from their corresponding 2,3-dihydroquinazolin-4(1*H*)-ones by dehydrogenation, using oxidizing agents to introduce unsaturation between the *N*(1)–*C*(2) bond.[36-40] Quinazolin-4(3*H*)-ones can also be prepared directly, and in a single-pot operation from the readily available 2-substituted aniline derivatives and various carbonyl compounds through oxidative condensation reactions,[41-45] Aza-reactions[47] or transition metal-catalyzed reactions.[49-52] Selected examples of these methods are described in detail below.

i) Synthesis of quinazolin-4(3*H*)-ones via dehydrogenation of the 2,3-dihydroquinazolin-4(1*H*)-ones

Oxidizing reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[36] sodium bisulfite ($NaHSO_3$),[37] copper(II) chloride ($CuCl_2$),[38] manganese dioxide (MnO_2)[39] and potassium permanganate ($KMnO_4$)[40] have previously been employed to dehydrogenate 2,3-dihydroquinazolin-4(1*H*)-ones **47** to their corresponding quinazolin-4(3*H*)-one derivatives **48** (Scheme 7).



47 **48**: R= Alkyl, Aryl

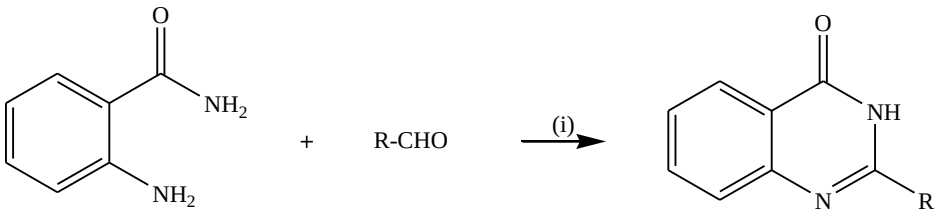
***Reagents and conditions*:** (i) DDQ/EtOH, reflux;[36] $NaHSO_3$/DMA, 150 °C;[37] $CuCl_2$/EtOH, 70 °C;[38] MnO_2/CH_2Cl_2, rt.;[39] or $KMnO_4$/acetone, reflux.[40]

Scheme 7: Dehydrogenation of 2,3-dihydroquinazolin-4(1*H*)-one moieties **47** to afford quinazolin-4(3*H*)-ones **48**

Although effective, these oxidants are often used in stoichiometric amounts or large excess, and most are not easy to decompose and therefore pose an environmental threat. As a consequence, direct methods for the synthesis of these compounds from anthranilamide derivatives have also been developed and these are described in the following sections.

ii) Synthesis of quinazolin-4(3*H*)-ones via oxidative condensation reactions

Oxidative condensation reaction of 2-aminobenzamide **17** with aldehydes **49** in the presence of iron(III) chloride hexahydrate ($FeCl_3.6H_2O$) as an oxidizing agent, previously yielded quinazolin-4(3*H*)-ones **50** (Scheme 8).[41] The 2,3-dihydroquinazolin-4(1*H*)-ones formed *in situ* by the condensation of anthranilamides with the aldehydes undergoes dehydration promoted by $FeCl_3.6H_2O$ to afford quinazolin-4(3*H*)-ones. However, this reaction required stoichiometric amount (2 equiv.) of $FeCl_3.6H_2O$ for completion.

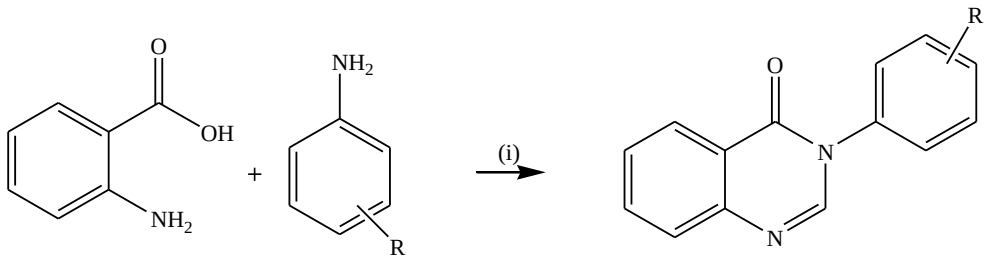


17 **49** **50**: R= H, alkyl, aryl

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

Scheme 8: Oxidative condensation of anthranilamide **17** with aldehydes **49**.

In another example, anthranilic acid **51** was reacted with aniline derivatives **52** (R = H, 2-Cl, 2-CH_3, 3-NO_2, 4-Br, 4-CH_3, 4-OCH_3, 4-NO_2) in the presence of the Vilsmeier reagent (DMF/$POCl_3$) under microwave conditions to afford the 3-arylquinazolin-4(3*H*)-one derivatives **53** (Scheme 9).[42] Of interest was that compounds **53** were found to exhibit antibacterial and antifungal activities.[42]



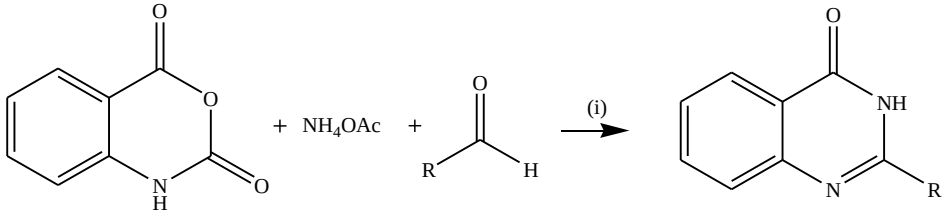
51 **52** **53**: R = H, 4-CH_3, 4-Cl, 2-Cl, 4-OCH_3

Reagents and conditions: (i) $POCl_3$, DMF, microwave, 600 W

Scheme 9: Condensation of anthranilic acid **51** with anilines **52** to afford **53**.

Dimethylsulfoxide (DMSO) has also been used as a solvent and an oxidizing agent in the reaction of isatoic anhydride **28** with ammonium acetate **29** and aldehydes **54,** this time catalyzed by gallium triflate ($Ga(OTf)_3$), to afford quinazolin-4(3*H*)-ones **55** in high yields (Scheme 10).[43] DMSO in this case was found to serve as a mild oxidising agent to oxidise the 2,3-dihydroquinazolin-4(1*H*)-ones generated *in situ*, into the corresponding

quinazolin-4(3*H*)-ones. The use of solvents such as ethanol or nitromethane, on the other hand, afforded the 2,3-dihydroquinazolin-4(1*H*)-ones, exclusively.



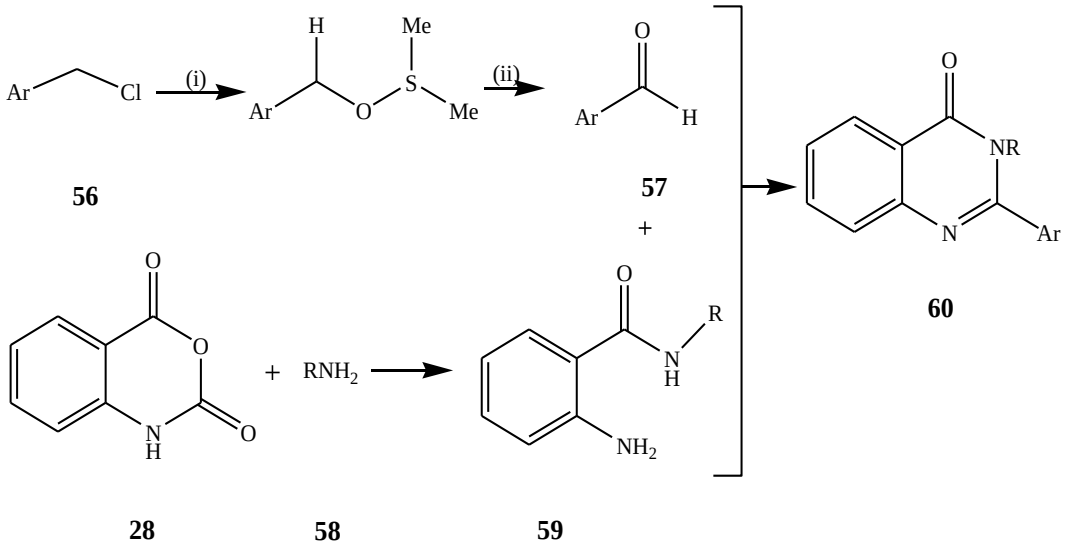
28 **29** **54** **55**

Compound	R	%Yield
55a	C_6H_5	83
55b	4-ClC_6H_4	89
55c	4-BrC_6H_4	86
55d	2,4-$(CH_3O)_2C_6H_3$	89
55e	4-HOC_6H_4	92
55f	4-FC_6H_4	84
55g	4-$NO_2C_6H_4$	82
55h	3-$NO_2C_6H_4$	82
55i	4-$CH_3C_6H_4$	84
55j	4-$CH_3OC_6H_4$	82

Reagents and conditions: (i) $Ga(OTf)_3$, DMSO, 85 °C

Scheme 10: $Ga(OTf)_3$-mediated cyclocondensation of **28** with **29** and **54**.

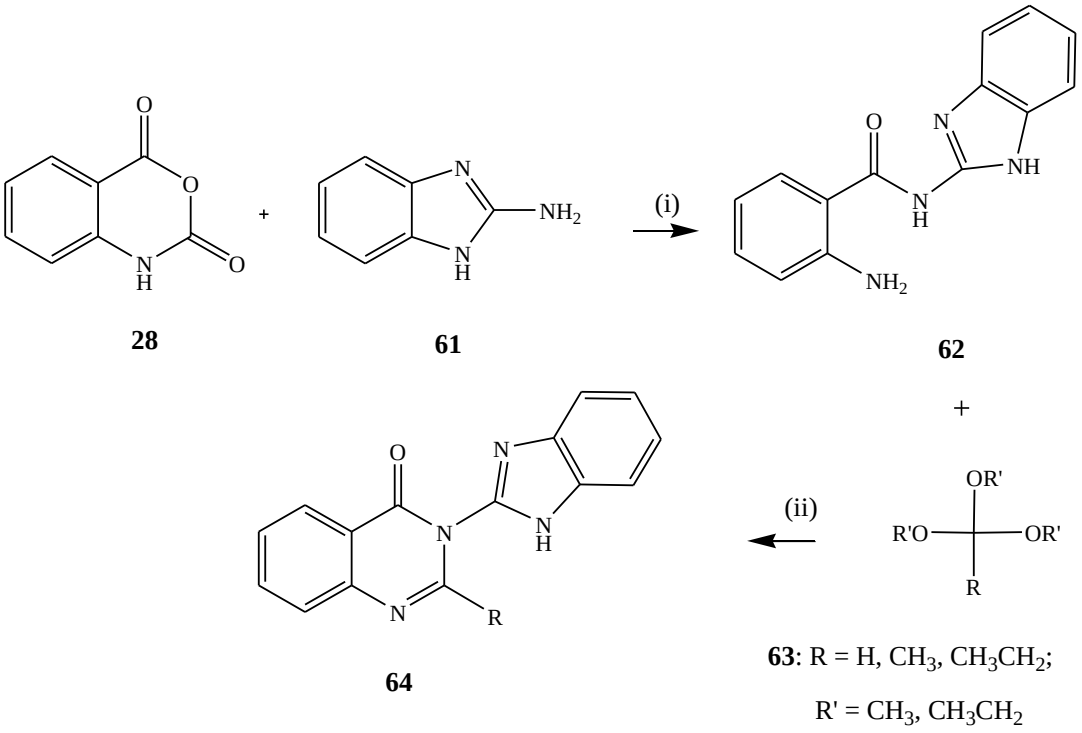
A single-pot oxidative condensation of **28** with benzyl halides **56** and amines **58** in DMSO in the presence of K_2CO_3 previously produced compounds **60** (Scheme 11).[44] In this reaction, benzyl halide was first converted into benzaldehyde **57** under the Kornblum oxidation conditions using a DMSO-K_2CO_3 mixture. The resultant aldehyde then reacted with the 2-aminobenzamide **59** which was generated *in situ* from the reaction of the amine **58** with isatoic anhydride **28**. Furthermore, DMSO was found to oxidise the 2,3-dihydroquinazolin-4(1*H*)-ones generated *in situ* to the corresponding quinazolin-4(3*H*)-one derivatives.



Reagents and conditions: (i) DMSO, (ii) K_2CO_3, 90 °C.

Scheme 11: Oxidative condensation of **28** with **56** and amines **58** in DMSO.

In another example, the reaction of isatoic anhydride **28** with 2-aminobenzimidazole **61** in dimethylacetamide under microwave irradiation (600 W) was found to afford 2-amino-*N*-(1*H*-benzo[*d*]imidazol-2-yl)benzamide **62** (Scheme 12).[45] The latter, which bears three nucleophilic sites was reacted with triethyl- orthoformate **63** in the presence of *para*-toluenesulfonic acid (*p*-TsOH) as catalyst and in dimethylacetamide as solvent under microwave conditions (600 W) to afford compound **64** in 70–95% yield.



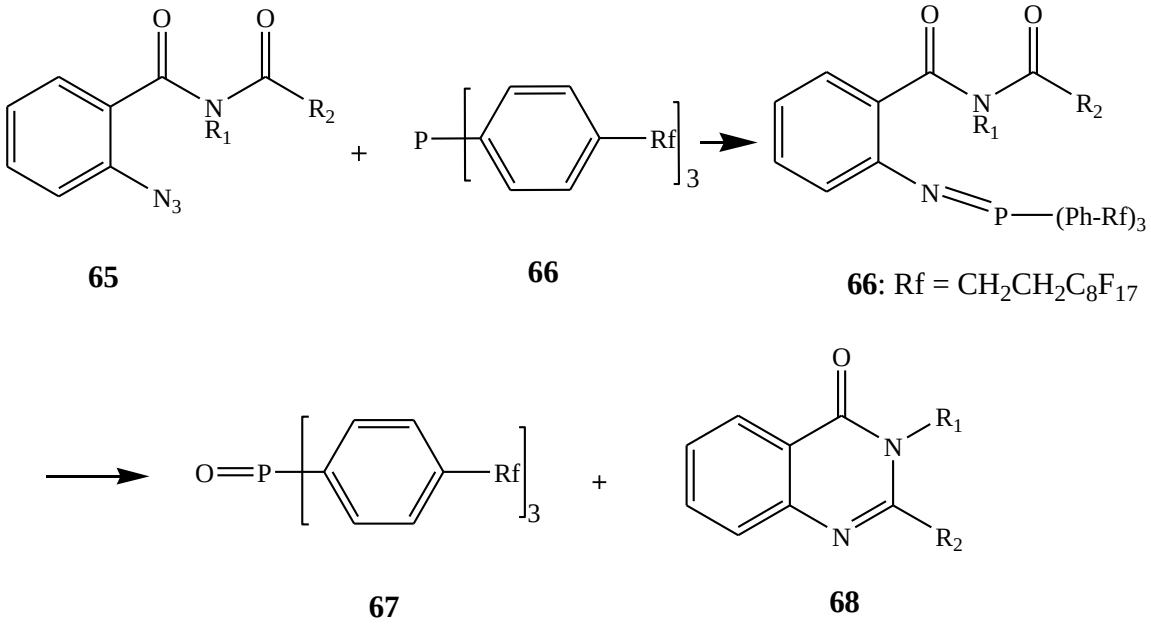
Reagents and conditions: (i) DMAc, MW; (ii) *p*-TsOH, DMAc, microwave (600 W).

Scheme 12: Synthesis of 3-benzimidazolylquinazolin-4(3*H*)-one **64** via microwave-assisted reaction.

iii) Synthesis of quinazolin-4(3*H*)-ones by Aza-Wittig reaction

This widely used method for the synthesis of *N*-heterocycles proceeds by a way of cascade sequence and it is usually carried out under mild conditions.[46] As an example, intramolecular Aza-Wittig reaction of iminophosphoranes **68**,[47] which were obtained from reaction of compounds **65** with perfluoro-tagged phosphine **66** (Rf = $CH_2CH_2C_8F_{17}$), afforded the targeted quinazolinone derivatives **68** (Scheme 13). The perfluoro-tagged phosphine was used because it allows simple work-up procedures such as liquid-liquid extraction between perfluorinated solvents and organic solvents or one can apply a solid-phase extraction

protocols by using fluorous reversed phase silica gels. This reaction occurred in toluene as a solvent and trifluorotoluene as a co-solvent.



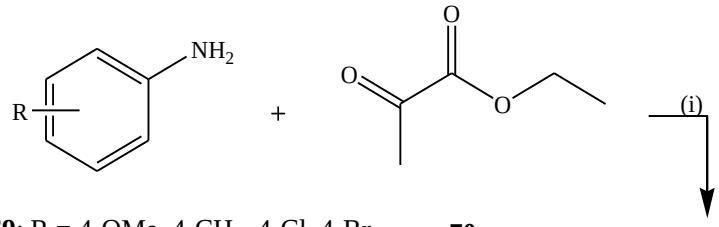
Scheme 13: Synthesis of quinazolin-4(3*H*)-ones **68** via an aza-Wittig reaction

Non-conventional methods which make use of transition metals as reagents or catalysts to prepare quinazolin-4(3*H*)-ones continue to be developed and these examples are described in the following section.

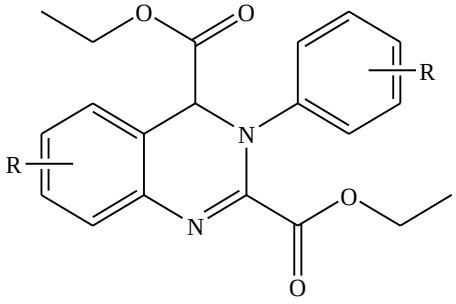
iv) Synthesis of quinazolin-4(3*H*)-ones or quinazolines via transition metal-catalyzed reactions

Imino-Diels-Alder reaction, which involves the reaction of imine derivatives with dienes in the presence of Lewis acid catalyst to form pyridine derivatives has been extended to the synthesis quinazoline derivatives.[48] Chen *et al.*, for example, previously conducted an imino-Diels-Alder reaction of aniline **69** and ethyl glyoxylate **70** in the presence of various Lewis acids [i.e. ferric(III) chloride ($FeCl_3$), aluminum(III) chloride ($AlCl_3$), copper(II) bromide ($CuBr_2$), zinc(II) bromide ($ZnBr_2$)] as catalysts in refluxing toluene to yield the

quinazoline derivative **71** (Scheme 14).[49] The two α-iminoester intermediate obtained from the reaction of **69** and **70** is presumed to form the quinazoline derivative directly. In this study, $CuBr_2$ was identified as the best catalyst that produced products in moderate to high yields (51–76% yields).[49]



69: R = 4-OMe, 4-CH_3, 4-Cl, 4-Br **70**

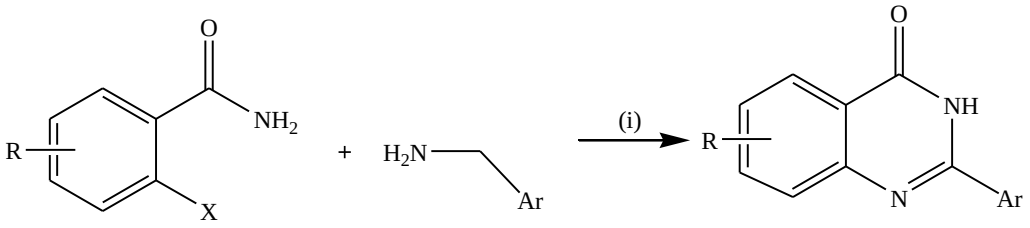


71

Reagents and conditions: (i) $CuBr_2$/toluene, reflux

Scheme 14: Synthesis of **71** by cascade imino-Diels-Alder reaction.

Copper-catalysed Ullmann coupling reaction has showed great progress in recent years. For example, Xu e*t al*. performed the Ullmann coupling reaction of 2-halobenzamides **72** with (aryl)methanamines **73** using $CuBr_2$ as a catalyst in the presence of the K_2CO_3 as a base and air as an oxidant in DMSO to form quinazolin-4(3*H*)-ones **74** (Scheme 15).[50] 2-Halobenzamides (X = Cl, Br, I) bearing electron withdrawing groups were found to be suitable substrates for this reaction. The authors also employed similar reaction conditions to condense 2-aminobenzamides with aryl aldehydes to afford quinzolin-4(3*H*)-one derivatives in high yields.[50]



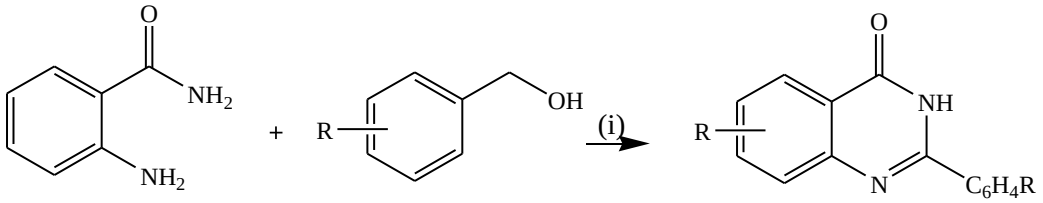
72: X= I, Br, Cl **73** **74**: R = H, 4-NO_2, 4-CH_3, 5-Cl

Reagents and conditions: (i) $CuBr_2$, K_2CO_3, DMSO, air

Scheme 15: Ullmann-type coupling of 2-halobenzamides **72** with (aryl)methanamides **73** under aerobic conditions.

Palladium-catalyzed cross-coupling reaction to form carbon-carbon and/ or carbon-heteroatom bond(s) is a widely used strategy in organic synthesis, and this approach has been extended to the preparation of quinazolinones. For example, palladium-catalyzed reaction of 2-aminobenzamide **17** with benzyl alcohols **75** in water, has been shown to afford the quinazolin-4(3*H*)-ones **76** (Scheme 16).[51] It was reasoned that the palladium catalysts used in this reaction first oxidize the benzyl alcohols to benzaldehydes and then promote the cyclization and oxidation of 2,3-dihydroquinazolin-4(1*H*)-ones generated *in situ*. The reaction did not occur when using DMSO, ethanol, acetic acid, 1,4-dioxane, or toluene as solvents. However, the reaction occurred in aqueous 1,4-dioxane to afford the desired products in high yields (72–90%). Palladium(II) acetate or palladium(II) chloride, in the presence of a water-soluble phosphine ligand such as triphenylphosphine monosulfonate (TPPMS) were found to be the best catalysts for this transformation. Zerovalent palladium catalysts such as tris(dibenzylideneacetone)dipalladium(0) ($Pd(dba)_3$) also afforded the desired products in high yields when the reaction was carried out at 120 °C.[51] The authors suggested that the formation of a $Pd(TPPMS)_n$ complex from $Pd(dba)_3$ and TPPMS occurs at 120° C.[51] It was also observed that benzylic halides, esters, carbonates, or phosphates reacted

much better than benzylic alcohols in the presence of Pd(0). Similarly, Zhou and Fang used pentamethylcyclopentadienyl iridium dichloride dimer $(Cp^*IrCl_2)_2$ to catalyze the reaction of primary alcohols with 2-aminobenzamides to afford quinazolin-4(3*H*)-ones.[52] Lower reactivity towards oxidation to form aldehydes was observed with benzyl alcohols bearing electron-withdrawing groups which then condensed with 2-aminobenzamides to the afford desired quinazolin-4(3*H*)-ones.



17 **75** **76**: R = H, 4-Cl, 4-CH_3

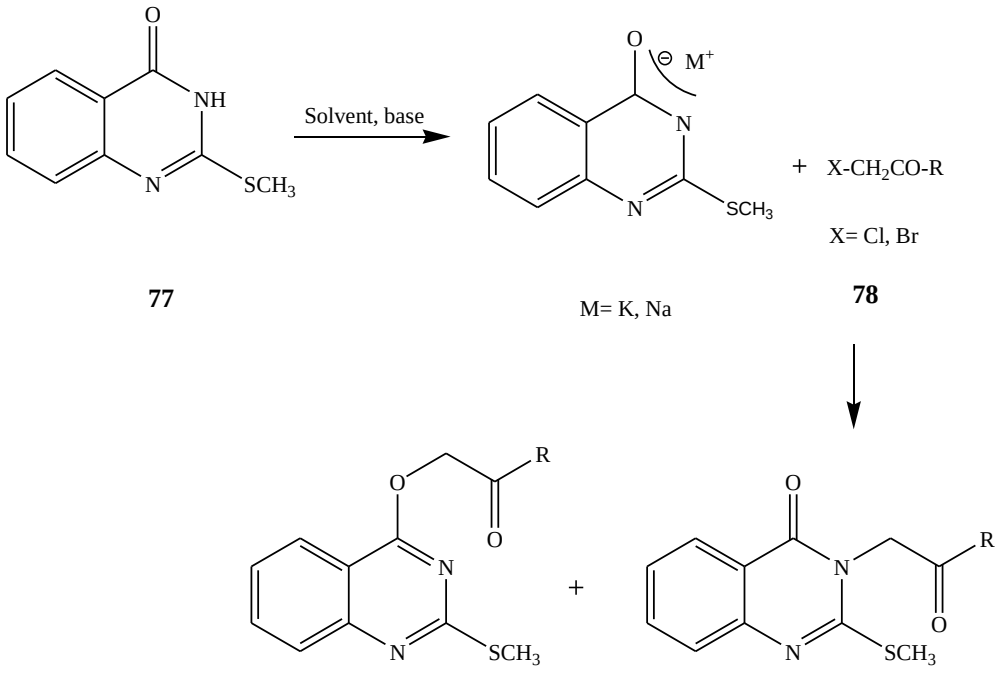
Reagents and conditions: (i) $Pd(OAc)_2$, TPPMS, H_2O, 120° C, sealed tube.

Scheme 16: Synthesis of quinazolin-4(3*H*)-one **15** via a palladium catalysed reaction.

The quinazolin-4(3*H*)-one moiety has also been found to undergo *N*(3) or *O*-alkylation/ arylation/acylation reactions to afford the 4-substituted quinazolines or *N*(3) substituted quinazolin-4(3*H*)-ones.[53-54] These compounds are of interest as they have potential photophysical[18-19] or biological properties.[55-57] 4-Substituted quinazolines were found to be active against fungal diseases[55] and exhibited interesting absorption and emission properties.[19] The *N*(3)-substituted quiazolin-4(3*H*)-ones, on the other hand, were reported to exhibit remarkable absorption and emission properties,[18] and to possess antimalarial,[56] anti-inflammatory and antitumor properties.[57] Selected methods for the preparation of these isomeric compounds are described below.

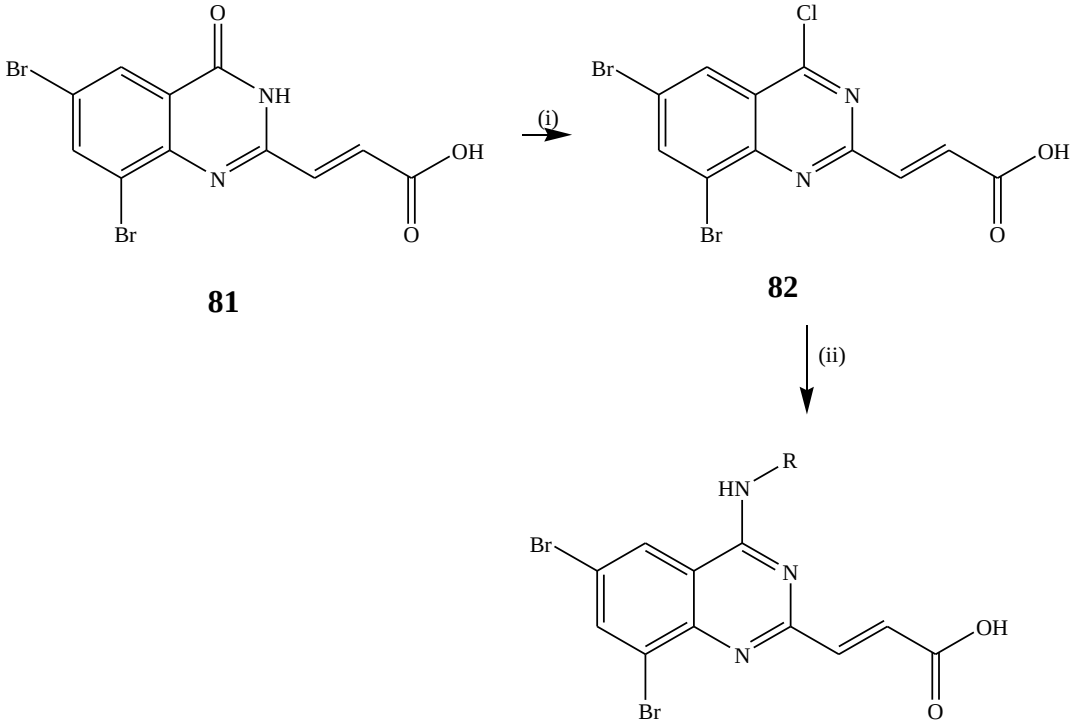
1.2 *N*(3) or *O*-alkylation/arylation/acylation of quinazolin-4(3*H*)-ones

The reaction of 2-methylthioquinazolin-4(3*H*)-one **77** with methyl haloacetate derivatives **78** previously afforded the 4-substituted 2-methylthioquinazolines **79** or *N*(3)-substituted 2-methylthioquinazolin-4(3*H*)-ones **80** exclusively or as a mixture of both products (Scheme 17).[53] The regioselectivity of the reaction was driven by the type of solvent, or base used. When the reaction of **77** with **78** was carried out in acetonitrile, in the presence of sodium methoxide as a base, the mixture of **79** and **80** was obtained in a ratio of 1:6. The use of potassium carbonate in place of sodium methoxide yielded both **79** and **80** in equal amounts.[53] The reaction of bromoacetophenone or ethyl bromoacetate in dimethylformamide (DMF) using potassium carbonate as base afforded **79**, exclusively. In addition, the use of toluene in place of DMF produced **80** without any traces of **79**. Alkylation of 6-haloquinazolin-4(3*H*)-one with ethyl-4-bromobutanoate in dimethylformamide, on the other hand, afforded ethyl 4-[6-halo-4-oxoquinazolin-3(4*H*)-yl]butanoate.[57]



Scheme 17: *N/O*-acylation of **77** with halo acylmethyl derivatives **78**.

In another example, aromatization of quinazolin-4(3*H*)-one **81** with a phosphoryl chloride-phosphorus pentachloride mixture in boiling water afforded the chlorinated quinazoline **82** (Scheme 18).[54] The 4-chloroquinazoline moiety represent suitable framework for further transformation such as nucleophilic substitution with heteroatom-based nucleophiles. Nucleophilic substitution of **82** with primary amines such as 4-methylaniline or aminoalcohols promoted by piperidine in ethanol, for example, afforded the 4-aryl/ alkylaminoquinazoline derivatives **83** (Scheme18).[54]



81 **82**

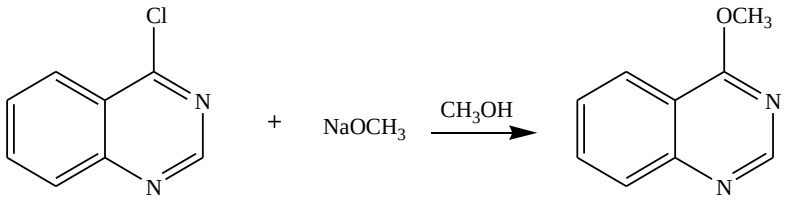
83: R= CH_2CH_2OH, 4-MeC_6H_4

***Reagents and conditions*:** (i) PCl_5, $POCl_3$, 70 °C, (ii) $NH_2CH_2CH_2OH$ or 4-$MeC_6H_4NH_2$, piperidine, EtOH, 70 °C.

Scheme 18: Amination of compound **81** to afford **83**.

The 4-halogenoquinazolines also represent suitable substrates for the indirect preparation of 4-alkoxy-substituted quinazoline derivatives via alkoxylation with alkyl- or aryloxides. This

strategy excludes the formation of the isomeric *N*(3)-substituted derivatives observed from the direct alkylation of the NH-3-oxo derivatives. 4-Chloroquinazoline **84**, for example, was reacted with sodium methoxide **85** in methanol to afford 4-methoxyquinazoline **86** (Scheme 19).[58]



84 **85** **86**

Scheme 19: Alkoxylation of **84** with sodium methoxide to afford **86**.

The increased reactivity of the 4-chloroquinazoline moiety due to α-nitrogen effect has also been found to facilitate metal-catalyzed cross-coupling reactions to form the 4-carbo–substituted quinazoline derivatives with ease. Examples of metal-catalyzed cross-coupling reactions of halogenated quinazolinone and quinazoline derivatives are discussed in detail in the following section.

1.3 Halogenated quinazolinone or quinazoline derivatives as substrates for metal catalysed cross-coupling reactions to afford polysubstituted derivatives

The use of halogenated quinazolinone or quinazoline derivatives in metal-catalyzed cross-coupling reactions allows for the formation of carbon-carbon bond(s) by the displacement of halogen atoms and the reactions employ either nickel- or palladium-based catalysts. Examples of the mostly widely employed cross-coupling reactions include the following: Kumada cross-coupling,[62] Suzuki cross-coupling,[67] Negishi cross-coupling,[73] Sonogashira cross-coupling,[79] Heck cross-coupling[83] and Stille cross-coupling.[87] These reactions require

palladium(0) as catalyst and the Sonogashira cross-coupling reactions also makes use of Cu(I) salts as co-catalyst. These cross-coupling reactions generally involve a catalytic cycle which proceeds in three steps, namely, (i) oxidative addition; (ii) transmetalation and (iii) reductive elimination. The oxidative addition step involves an *in situ* reduction of the 18-electron palladium pre-catalyst to an active Pd(0) species which is classically thought to be the 14-electron $Pd(0)L_2$ catalyst (**A**).[59] This active $Pd(0)L_2$ catalyst then undergoes oxidative addition to a carbon electrophile R^1X (R^1 = aryl, hetaryl or vinyl; X = I, Br, Cl or OTf) to afford a *trans* $R^1Pd(II)L_2X$ complex (**B**).[59-60] The second step involves transmetalation with either copper acetylide (Sonogashira), organostannane (Stille), or organoborane (Suzuki-Miyaura) to form intermediate **C** in which both organic ligands are *trans* oriented. *Trans-cis* isomerization of complex **C** affords complex **D**, which then undergoes a reductive-elimination to afford the cross-coupled product with the regeneration of the Pd(0) catalyst (Fig. 7).

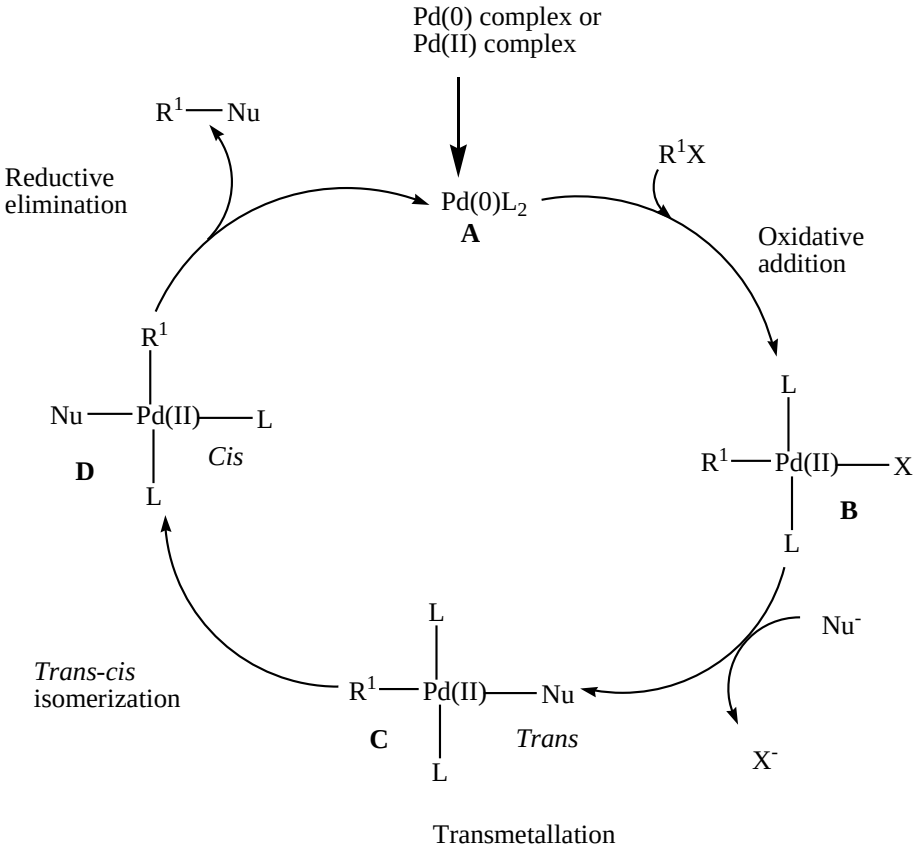
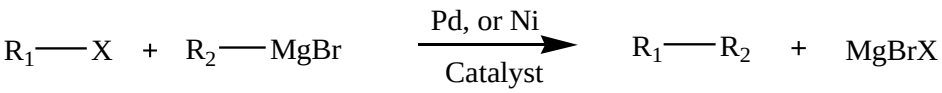


Figure 7: General mechanism for Pd(0)-catalyzed cross-coupling reactions.

The known reactivity of organohalides, Csp^2–I > Br >> Cl, permits the selective coupling of iodides or bromides in the presence of chlorides.[61] However, this trend does not apply for the halogenated 4-chloroquinazolines because the C(4)–Cl bond is highly activated towards oxidative-addition due to α-nitrogen effect. Some of the above-mentioned classical cross-coupling reactions have been employed in the transformation of halogenated quinazolinone and/ or quinazoline derivatives.[19,65,66,69,70,72,76,78,80,81,84-86,89]

1.3.1 Application of Kumada cross-coupling reactions for the synthesis of polysubstituted quinazolinones and/ or quinazolines

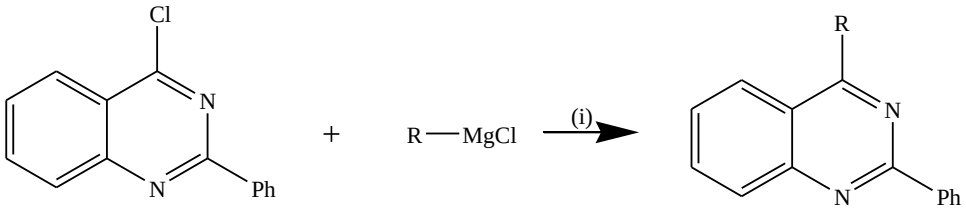
Kumada cross-coupling reactions involve the reaction of organomagnesium compounds with carbon electrophiles such as aryl halide or heteroaryl halides (Scheme 20).[62] The reaction makes use of nickel-based catalysts such as dichloro(1,3-bis(diphenylphosphino)propane)nickel [$NiCl_2$(dppp)], or in some cases a palladium-based catalysts. Diethyl ether is normally used as a solvent[63] and the reaction proceeds readily even at low temperature. The drawback of this reaction is that it uses Grignard reagents which are highly nucleophilic and can affect other functional groups such as aldehydes, ketones, esters, and nitro groups.[64]



Scheme 20: General scheme for Kumada cross-coupling reactions.

Kumada cross-coupling reaction has been employed extensively on 4-halogenated quinazolines. For example, the cross-coupling of 4-chloro-2-phenylquinazoline **87** with alkyl-

or aryl-Grignard reagents **88**, catalysed by manganese chloride in tetrahydrofuran (THF), afforded compounds **89** (Scheme 21).[65]

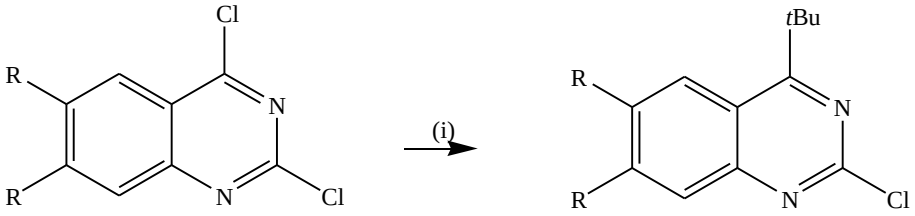


87 **88** **89**: R = Phenyl, *i*-propyl

Reagents and conditions: (i) $MnCl_2$ (5 mol %), THF, 0 °C

Scheme 21: Kumada cross-coupling reaction of **87** with **88** to afford **89**.

On the other hand, 2,4-dichloroquinazolines **90** were subjected to Kumada cross-coupling reactions with *tert*-butylmagnessium chloride (*t*-BuMgCl) in the presence of copper(I) iodide (CuI) and in tetrahydrofuran (THF) at 0 °C to afford the 4-*tert*-butyl-2-chloroquinazolines **91a** and **91b** in 92 and 63% yields, respectively (Scheme 22).[66]



90 **91**: R = H (**a**); R = OMe (**b**)

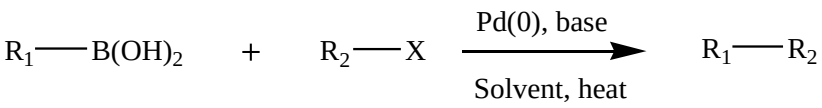
Reagents and conditions: (i) *t*-BuMgCl, CuI, THF, 0 °C.

Scheme 22: Kumada cross-coupling of **90** with *t*-BuMgCl.

In comparison to the use of palladium or nickel salts, copper(I) iodide and manganese chloride offer advantages, such as the mild reaction conditions, the operational simplicity and practicability, as well as the low cost. However, the drawback of the Kumada reaction on quinazolinones is that it uses strongly basic Grignard reagents which are highly nucleophilic and can attack the amide group.

1.3.2 Application of Suzuki cross-coupling reactions for the synthesis of polysubstituted quinazolinones and/ or quinazolines

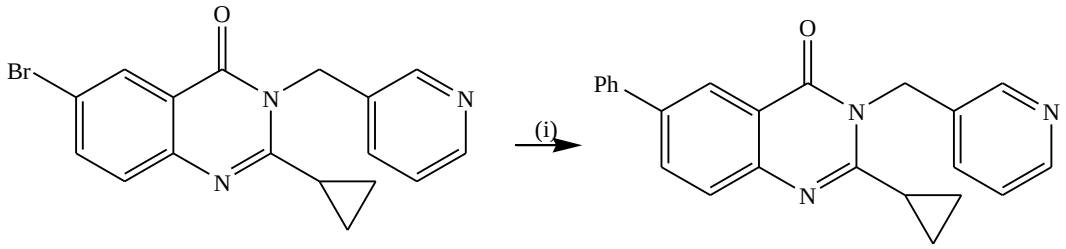
The Suzuki-Miyaura cross-coupling procedure involves reaction of organoboronic acids compounds and carbon electrophiles such as aryl-/vinylhalides or heteroaryl halides (Scheme 24).[67] The availability of organoboron compounds and their high functional group tolerance make the Suzuki cross-coupling reaction particularly attractive for the synthesis of polyaryl or polyvinyl derivatives. The reaction requires the presence of an inorganic base [e.g. sodium hydroxide (NaOH), sodium ethoxide (NaOEt), or potassium hydroxide (KOH)] to activate the weakly nucleophilic boranes in the transmetalation step. This cross-coupling reaction generally requires high temperatures (80–110 °C) and water can also be used as solvent or co-solvent.[68]



Scheme 24: General scheme for palladium-catalysed Suzuki-Miyaura cross-coupling reactions.

Suzuki cross-coupling reaction has been employed extensively on halogenated quinazolinones and quinazolines to afford novel arylated derivatives. For example, the Suzuki-Miyaura cross-coupling of 6-bromo-2-cyclopropyl-3-[(pyridin-3-yl)methyl]quinazolin-4(3*H*)-one **92** with phenylboronic acid has been shown to afford 2-cyclopropyl-6-phenyl-3-[(pyridin-3-yl)methyl]quinazolin-4(3*H*)-one **93** (Scheme 25).[69] In this work, several palladium catalysts were used as Pd(0) sources in the presence of K_2CO_3 as base in tetrahydropyran (THP) as a solvent. Among the tested palladium catalysts, 1,1'-bis(dicyclohexylylphosphino)ferrocene-

palladium(II) dichloride [$PdCl_2$(dcpf)] and 1,1'-bis (di-*tert*-butylphosphino)ferrocene palladium dichloride [$PdCl_2$(dtbpf)] were found to be better catalysts that produced the desired product **93** in 84% and 95% yield, respectively. Of interest, compound **93** was found to have inhibitory activity against α- glucosidase.[69] On the other hand, the 6-aryl-substituted quinazolin-4(3*H*)-ones were found to be ghrelin receptor antagonists.[14]



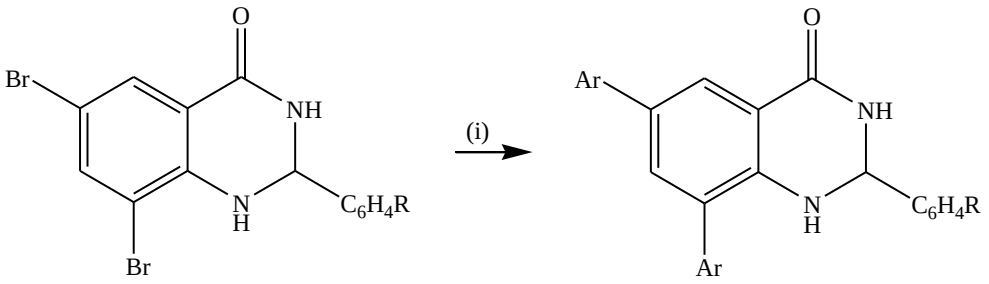
92 **93**

Reagents and conditions: (i) phenylboronic acid, $PdCl_2$(dcpf) (5%) or $PdCl_2$(dtbpf) (10%), K_3PO_4, THP, rt.

Scheme 25: Suzuki-Miyaura cross-coupling reaction of **92** with Ph-$B(OH)_2$.

In another example, the 2-aryl-6,8-dibromo-2,3-dihydroquinazolin-4(1*H*)-ones **94** were found to undergo cross-coupling with excess arylboronic acids in the presence of bis(triphenylphosphine)palladium(II) dichloride [$PdCl_2(PPh_3)_2$] as catalyst, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-phos) as a ligand, potassium carbonate (K_2CO_3) as a base in DMF-water mixture at 120 °C to afford the corresponding 2,6,8-triaryl-2,3-dihydroquinazolin-4(1*H*)-ones **95** (77–91%) without selectivity (Scheme 26).[70] Lack of selectivity was also observed on Suzuki-Miyaura cross-coupling of analogous 4-alkynylated-6,8-dibromo-quinazolines.[19] This non-selectivity is presumed to be due to comparable bond strength of C–Br bonds. Computational studies have confirmed that bond dissociation energies at B3LYP and G3B3 levels of all the positions on the fused benzo

ring of various heterocycles bearing identical halogen atoms have comparable C–X (X = Br, Cl) bond dissociation energies.[71]

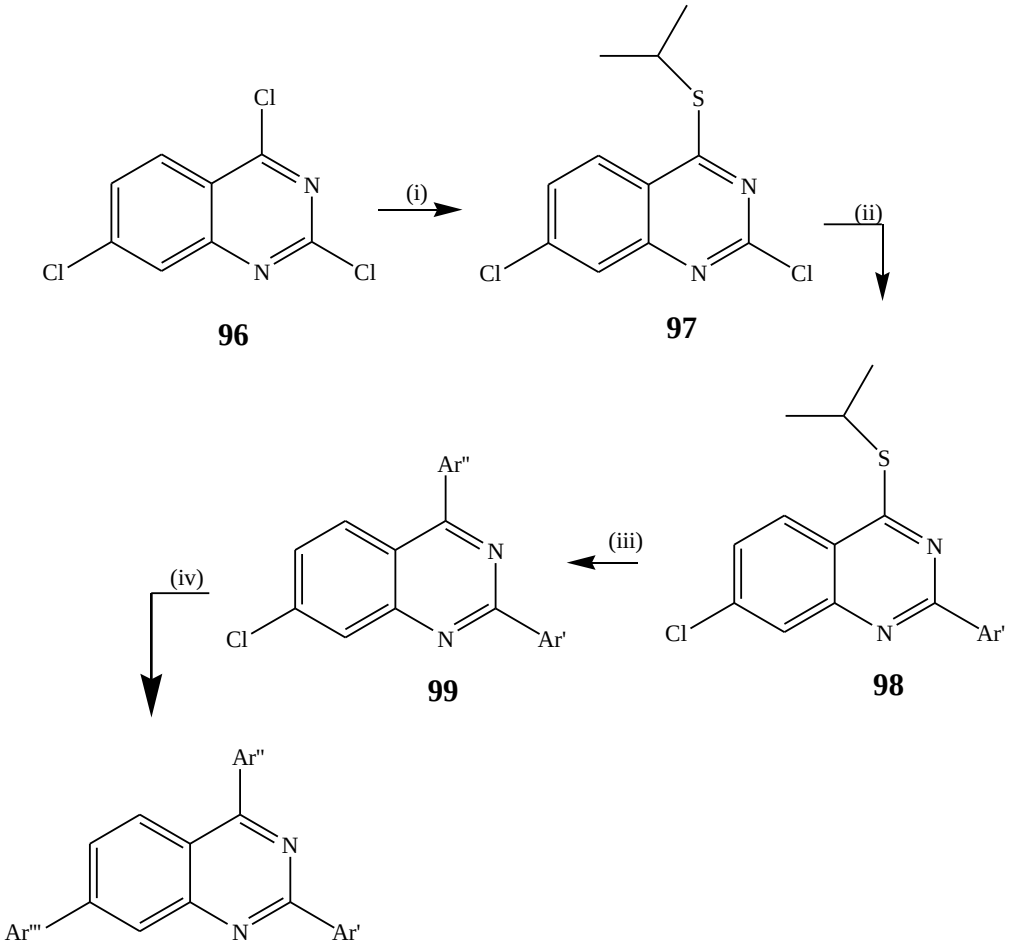


94 **95**: R = 4-H, 4-F, 4-Cl, 4-OMe; Ar = C_6H_5, 4-FC_6H_4

Reagents and conditions: (i) $ArB(OH)_2$ (2.2 equiv.), $PdCl_2(PPh_3)_2$, X-phos, K_2CO_3, DMF-water (4/1, v/v), 120 °C.

Scheme 26: Suzuki-Miyaura cross-coupling of 55 with arylboronic acids.

Wipf and George, on the other hand, set out to achieve the sequential regioselective Pd-catalyzed Suzuki cross-couplings of the 2,4,7-trichloroquinazoline **96** with arylboronic acids. The first coupling took take place at the most electrophilic *C*-4 position in low yield due to competitive hydrolysis at this site.[72] The authors then decided to temporarily deactivate the *C*-4 position as thioether **97** to effect regioselective Suzuki-Miyaura cross-coupling with arylboronic acid derivatives at the *C*-2 position to afford **98,** exclusively (Scheme 27).[72] The *C*-4 position was then transformed via a palladium/copper(I)-mediated desulfitative coupling reaction by using excess copper(I) thiophene-2-carboxylate [Cu(TC)] and arylboronic acids to afford compounds **99**. Finally, the cross-coupling at *C*-7 was effected using arylboronic acids to afford the trisubstituted quinazolines **100**.



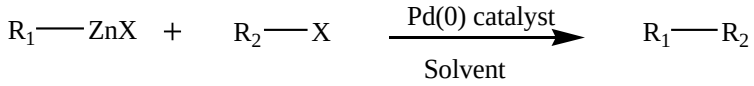
100: Ar', Ar", Ar''' = C_6H_5, 3-$MeOC_6H_4$, 4-EtC_6H_4

Reagents and conditions: (i) propane-2-thiol, NaH, degassed THF, rt. (ii) Ar'$B(OH)_2$, $Pd(OAc)_2$, PPh_3, Na_2CO_3, DME and H_2O (10:1, v /v), 75 °C, N_2. (iii) Ar"$B(OH)_2$, $Pd(PPh_3)_4$, Cu(TC), THF, 50 °C, N_2 atmosphere. (iv) Ar'''$B(OH)_2$, $Pd(OAc)_2$, PPh_3, Na_2CO_3, DME:H_2O (10:1, v/v), reflux.

Scheme 27: Regioselective Suzuki-Miyaura cross-coupling of **50**.

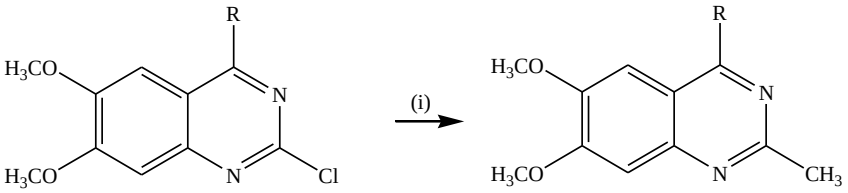
1.3.3 Application of Negishi cross-coupling reactions in the synthesis of polysubstituted quinazolinones and/ or quinazolines

Negishi cross-coupling reactions involve the cross-coupling of organozinc reagents (R–ZnX) with aryl halides or heteroaryl halides in the presence of palladium species as a Pd(0) catalyst source (Scheme 28).[73] The organozinc reagent can either be prepared from the corresponding halide R–X by reductive metalation or via transmetalation of organolithium compounds (R–Li).[74] The reaction frequently makes use of bis(triphenylphosphine)palladium(II) dichloride [$PdCl_2(PPh_3)_2$] or 1,1'-bis(diphenyl-phosphino)ferrocene palladium dichloride [$PdCl_2$(dppf)] as catalysts and either diethyl ether or tetrahydrofuran (THF) as solvent.[75] The advantage of this cross-coupling is that zinc compounds are relatively tolerant to many functional groups and the cross coupling is normally conducted at room temperature or slightly above because higher reaction temperatures can lead to degradation of the zinc compound. This reaction has also been employed for the synthesis of polycarbo-substituted quinazolines.



Scheme 28: General scheme for Negishi cross-coupling reactions.

For example, palladium-catalyzed Negishi cross-coupling between quinazoline **101**, methyllithium (CH_3Li) and zinc(II) chloride ($ZnCl_2$) afforded compound **102** (Scheme 29).[76] It is presumed that the reaction between CH_3Li and $ZnCl_2$ produces CH_3–ZnCl reagent which then undergoes cross-coupling with compounds **101**. Of interest, compounds **102** were found to be phosphodiesterase inhibitors.



101 **102**: R = 3,5-dibenzyloxy-phenyl;

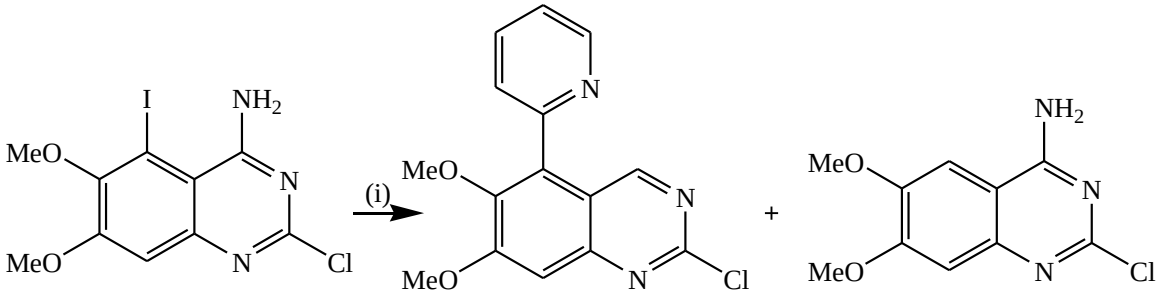
3,5-diisopropyloxy-phenyl;

3,5-dicyclopropylmethyloxy-phenyl

Reagents and conditions: MeLi, $ZnCl_2$, $Pd(PPh_3)_4$, dioxane, 60 min.

Scheme 29: Negishi cross-coupling reaction of **55** with CH_3– ZnCl.

In another example, 2-bromopyridine was reacted with isopropylmagnessium chloride followed by addition of zinc chloride to afford 2-pyridylzinc chloride (2-PyZnCl).[77] The latter was, in turn, subjected to the Negishi cross-coupling reaction with the 2-chloro-5-iodo-6,7-dimethoxyquinazolin-4-amine **103** using palladium acetate-triphenylphosphine [$Pd(OAC)_2$-PPh_3] catalyst complex in THF under reflux to afford the cross-coupled product **104** (Scheme 30).[78] However, due to proximity of the acidic N-H protons, protonation of organozinc intermediate occurred giving rise to reduced product **105**. When compound **103** was treated with 2-iodopyridine in the presence of activated zinc and $Pd(OAc)_2$–PPh_3 mixture in DMF, compound **105** was obtained as a sole product.[78]



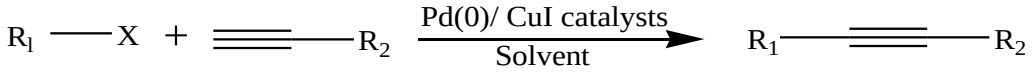
103 **104** **105**

Reagents and conditions: **(**i) 2-PyZnCl, $Pd(OAC)_2$, PPh_3, THF, reflux.

Scheme 30: Negishi cross-coupling reaction of the 2-chloro-5-iodo-6,7-dimethoxyquinazolin-4-amine **57**.

1.2.4 Application of Sonogashira cross-coupling reactions for the synthesis of polysubstituted quinazolinone and/ or quinazoline derivatives

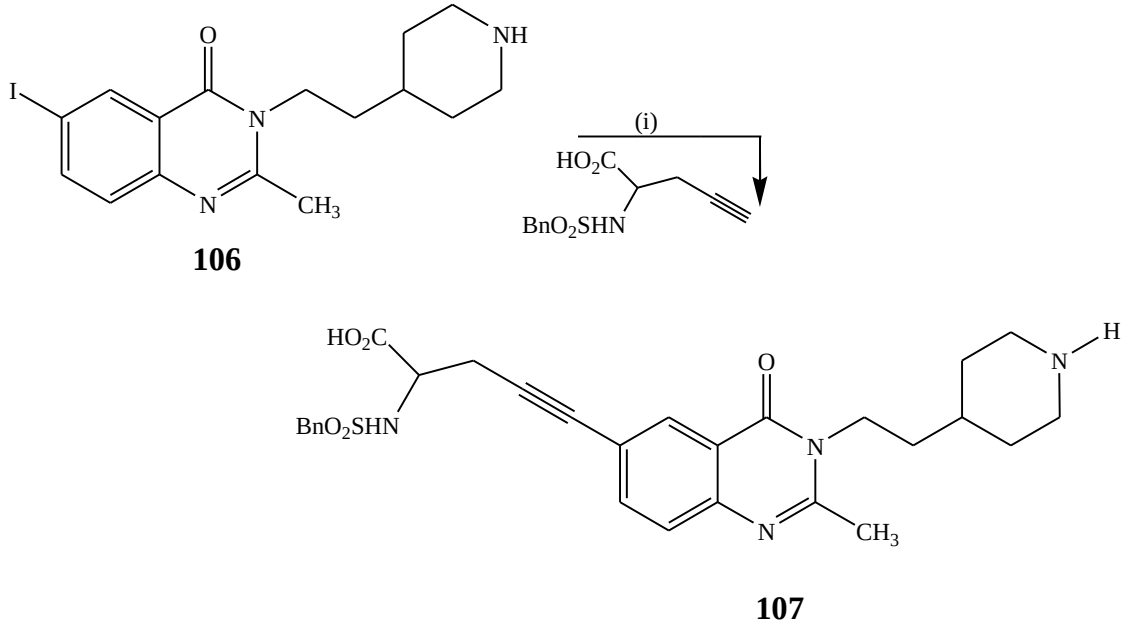
Sonogashira cross-coupling procedure involves the alkynylation of aryl- and heteroaryl halides using terminal alkynes in the presence of Pd(0) sources such as $PdCl_2(PPh_3)_2$, and copper(I) salt as co-catalyst in the presence of an amine base (eg., diethylamine, pyrrolidine, or triethyl amine) or also as a solvent (Scheme 31).[79] The reaction can also occur at room temperature or under relatively mild reflux conditions in the presence of inorganic bases and in various organic solvents.



Scheme 31: General scheme for the Sonogashira cross-coupling reactions.

The Sonogashira cross-coupling reaction has also been employed extensively on halogenated quinazolinones and quinazolines to afford variously substituted alkynylated derivatives. In terms of example, the Sonogashira cross-coupling of compound **106** with

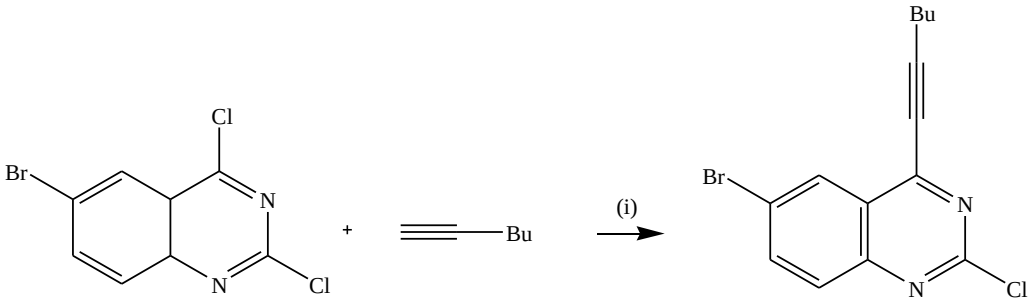
ethyl-2-(1-butanesulfonamido)pent-4-yn-l-oate in the presence of tetrakis(triphenylphosphine) palladium(0) ($Pd(PPh_3)_4$) as a catalyst and copper(I) iodide (Cul) as a co-catalyst afforded **107** with potential application as fibrinogen receptor antagonist (Scheme 32).[80]



Reagents and conditions: (i) $Pd(PPh_3)_4$, Cul, $HNEt_2$, 40° C.

Scheme 32: Sonogashira cross-coupling reaction of **106** with 2-(1-butanesulfonamido)pent-4-ynoic acid.

The Sonogashira cross-coupling reaction between 6-bromo-2,4-dichloroquinazoline **108** and terminal alkynes **109** catalysed by $PdCl_2(PPh_3)_2$ as Pd(0) source and CuI as co-catalyst in triethylamine (NEt_3), also favoured the cross-coupling at the most electrophilic *C*-4 position rather than the less activated *C*(6)–Br bond (Scheme 33).[81]

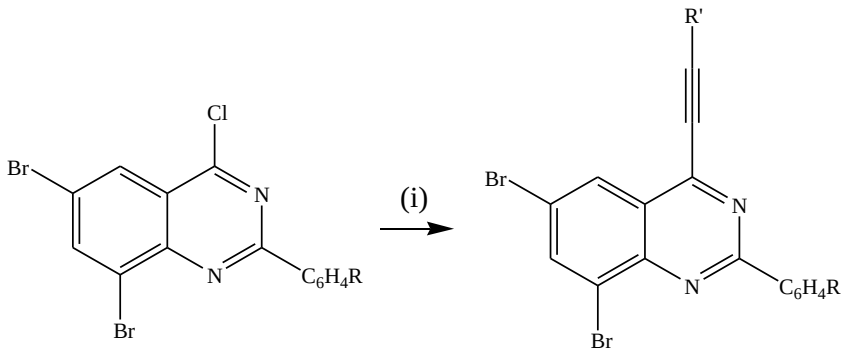


108 **109** **110**

Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, CuI, NEt_3, rt.

Scheme 33: Sonogashira cross-coupling reaction of **108** with **109**.

In another example, the Sonoghashira cross-coupling of the 2-aryl-6,8-dibromo-4-chloroquinazolines **111** with terminal acetylenes such as 3-butyn-2-ol, phenylacetylene and 2-pyridinylacetylene was found to undergo cross-coupling exclusively at 4-chloro atom to afford the 4-alkynyl-6,7-dibromoquinazolines **112** in 53–72% yield (Scheme 34).[19] The observed selectivity was attributed to an α-nitrogen effect, which makes the *C*-4 position highly activated compared to the other positions bearing Cl or Br. 4-Alkynylated quinazoline, 6,7-diethoxy-4-(4-phenylbut-1-ynyl)quinazoline, for example, was reported to be potent epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor.[82]



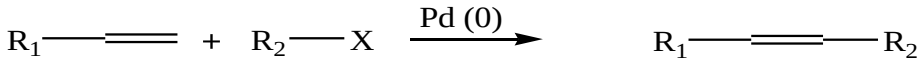
111 **112**: R = 4-H, 4-F, 4-Cl, 4-OMe;
R' = $CH(OH)CH_3$, C_6H_5, 2-pyridyl

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

Scheme 34: Site-selective Sonogashira cross-coupling of **111** with terminal alkynes.

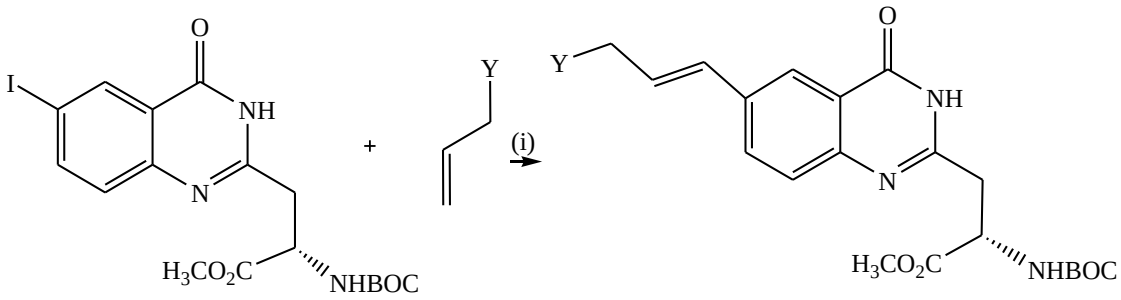
1.3.5 Application of the Heck cross-coupling reactions in the synthesis of polysubstituted quinazolinones and/ or quinazolines

The Heck cross-coupling reaction, which leads to the formation of alkenyl- and arylvinyl derivatives, involves a Pd-catalyzed inter- or intra-molecular cross-coupling reaction between organohalides or triflates with alkenes (Scheme 35).[83] This reaction has been employed for the synthesis of polycarbo-substituted quinazolinones and quinazolines

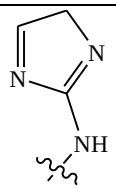
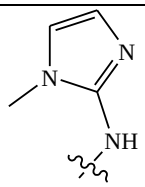
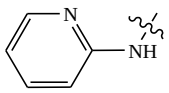
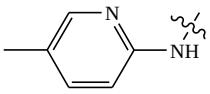
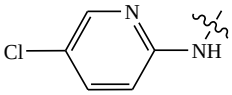


Scheme 35: General scheme for Heck cross-coupling reactions.

In terms of an example of the application of this reaction on halogenated quinazolinones, iodoquinazolin-4(3*H*)-one **113** was cross-coupled with unprotected allyl amidines or guanidines **114** in the presence of palladium (II) acetate–tri-(*o*-tolyl)phosphine catalytic mixture and triethylamine as base in acetonitrile under reflux to afford a series of the 6-vinyl substituted products **115** (Scheme 36).[84] Compounds **115** were not obtained when either benzene or toluene was used in place of acetonitrile and this compound was isolated in low yield when palladium tetrakis(triphenylphosphine) [$Pd(PPh_3)_4$] was used as catalyst. Of interest, compounds **115** were found to be potent vitronectin receptor ($\alpha_v\beta$, integrin) antagonists.[84]



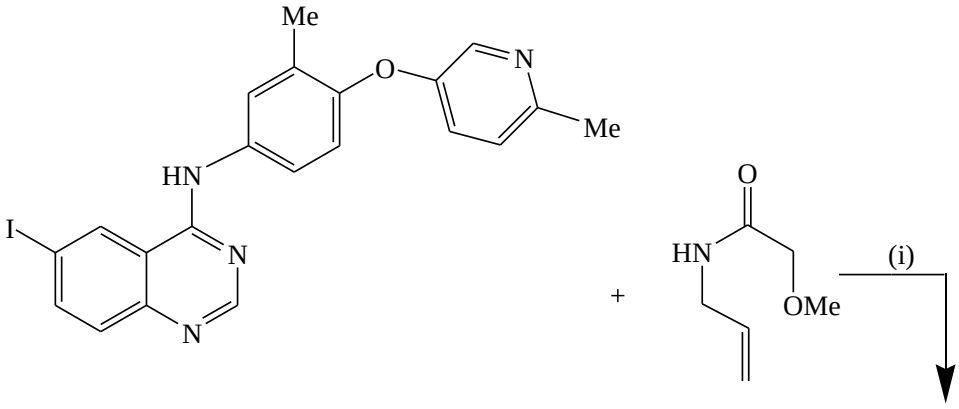
113 **114** **115**

Compound	Y	% Yield
115a		77
115b		79
115c		81
115d		62
115e		54

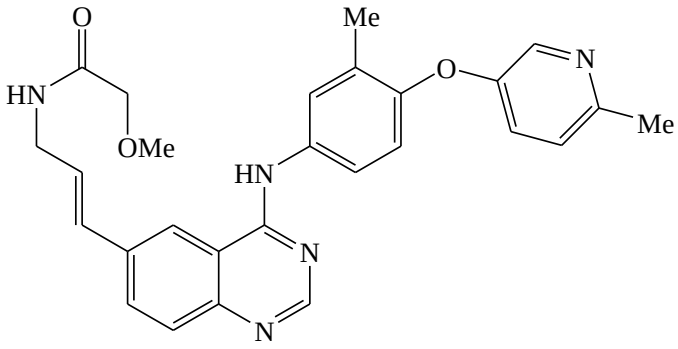
Reagents and conditions: (i) $Pd(OAc)_2$, (*o*-tolyl)$_3$P, NEt_3, CH_3CN, reflux.

Scheme 36: Heck cross-coupling of **113** with allyl amidines or guanidines.

In another example, the Heck cross-coupling reaction of *N*-[4-(6-methylpyridin-3-yloxy)-3-methylphenyl]-6-iodoquinazolin-4-amine **116** and *N*-allyl-2-methoxyacetamide **117**, catalysed by tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) in the presence of triethylamine as a base in 2-propanol as a solvent, afforded *N*-[(*E*)-3-{4-[4-(6-methylpyridin-3-yloxy)-3-methylphenylamino]quinazolin-6-yl}allyl]-2-methoxyacetamide **118** (Scheme 37).[85] Compound **118** is a selective ErbB2 angiogenesis inhibitor and is under investigation for the treatment of breast, ovarian and other types of cancer.[85]



116 **117**

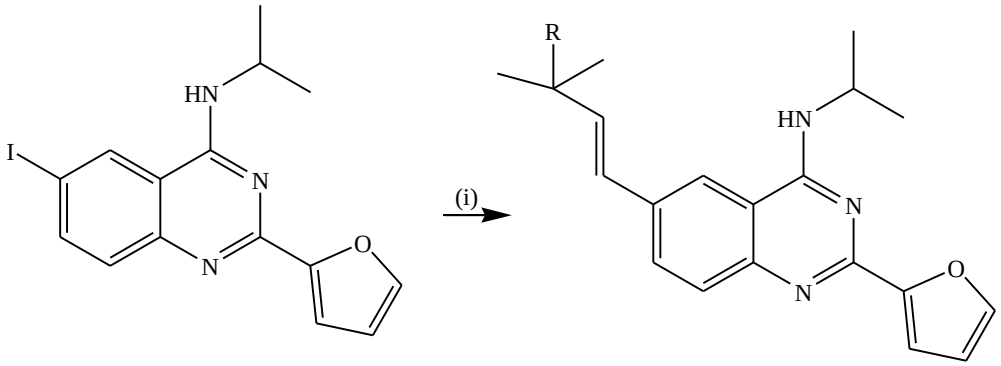


118

Reagents and conditions: (i) $Pd_2(dba)_3$ (5 mol %), 2-propanol: Et_3N (10:1, v/v)

Scheme 37: The Heck cross-coupling reaction of **116** and **117** to afford **118**.

2-(Furan-2-yl)-6-iodo-*N*-isopropylquinazolin-4-amine **119** was subjected to Heck cross-coupling reaction with *tert*-butyl acrylate or 2-methylbut-3-en-2-ol by employing $Pd(OAc)_2$–tri-o-tolylphosphine complex and triethyl amine in acetonitrile at 100 °C to afford the 6-alkynyl-4-(isopropylamino)quinazolin-6-yl)acrylates **120a** and **120b** in 63% and 86% yield, respectively (Scheme 38).[86] Under the same reaction conditions, *N*-(3-fluorophenyl)-6-iodoquinazolin-4-amine was coupled with 2-methylbut-3-en-2-ol to afford the 6-alkynylated derivative in 73% yield.[87]Compunds **120** were further subjected to bio-assays and were found to be selective inhibitors of Aurora A versus Aurora B.[87]



119 **120**: R = -CH_3 (**a**); -OH (**b**)

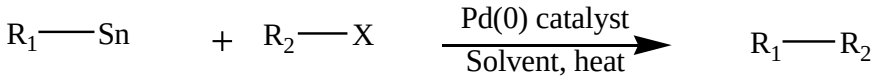
Reagents and conditions: (i) alkene, NEt_3, $Pd(OAc)_2$, $(o\text{-Tol})_3P$, acetonitrile, 100 °C.

Scheme 38: Heck cross-coupling of 6-iodo-4-(isopropylamino)quinazolin-6-yl)acrylates **119** with alkenes.

1.3.6 Application of the Stille cross-coupling reactions in the synthesis of polysubstituted quinazolinones and/ or quinazolines

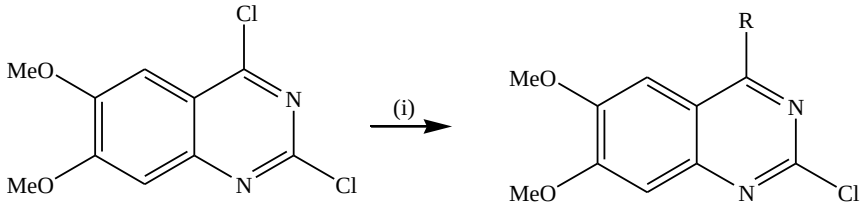
The Stille cross-coupling of organostannanes with aryl halides/triflates[88] depicted in Scheme 39 makes use of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) as catalyst in solvents such as tetrahydrofuran, toluene or dimethylformamide (DMF). The Stille cross-coupling,

however, requires a higher temperature to facilitate the transmetalation step from the weakly nucleophilic stannane to the intermediate arylpalladium halide.[89]



Scheme 39: General scheme for the Stille cross-coupling reactions.

This reaction has thus far only been employed on halogenated quinazoline derivatives. For example, the Stille cross-coupling between compound **121** and the organostannane reagents in the presence of $Pd(PPh_3)_2Cl_2$ as a catalyst in xylene readily afforded compounds **101** in good yields (Scheme 40).[76]



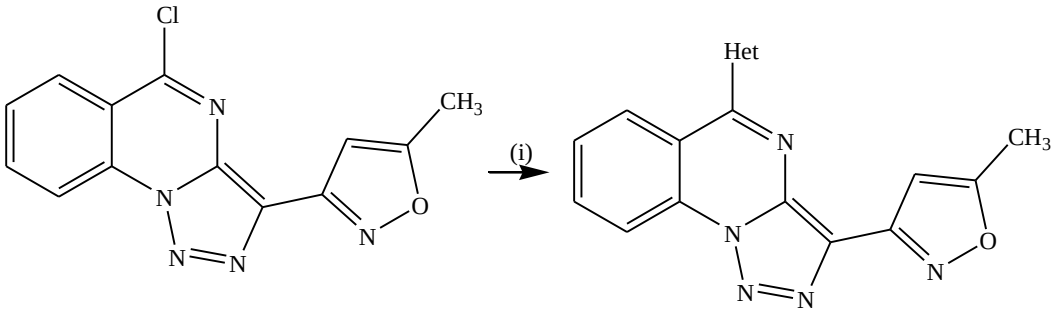
121 **101**: R = 3,5-dibenzyloxyphenyl;
3,5-diisopropyloxyphenyl;
3,5-dicyclopropylmethyloxyphenyl

Reagents and conditions: R–$SnBu_3$, $(PPh_3)_2PdCl_2$, xylene, 110 °C.

Scheme 40: Stille cross-croupling reaction of **121** with R–$SnBu_3$.

The Stille cross-coupling of 5-chlorotriazoloquinazoline **122** with heteroarylstannanes in the presence of $Pd(PPh_3)_4$-CuI catalyst mixture and in DMF at 70 °C, on the other hand, afforded a series of 5-heteroaryl-substituted triazoloquinazolines **123** in 20–78% yields (Scheme 41).[90] In addition, the same reaction conditions were employed for the reaction of the analogous 5-tosyltriazoloquinazoline with heteroarylstannanes to afford the corresponding 5-heteroaryl-substituted derivatives in reasonable yields.[90] The main drawback of the Stille cross-coupling

reaction is the toxicity of the tin compounds used. Moreover, their low polarity makes them poorly soluble in water for disposal.



122 **123**: Het = 2-Thienyl, 2-Furyl, 2-Pyridyl

Reagents and conditions: (i) Het-$SnBu_3$, $Pd(PPh_3)_4$, DMF, 70 °C.

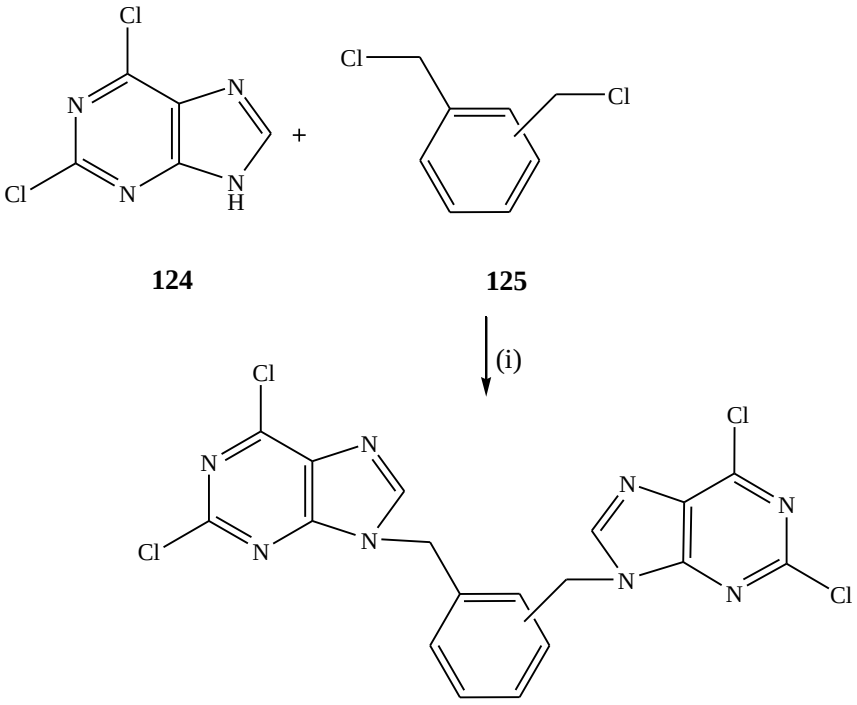
Scheme 41: Stille cross-coupling of 5-chlorotriazoloquinazoline **122** with heterarylstannanes.

In general, the metal-catalyzed cross-coupling reactions serve to increase the degree of conjugation around the heterocyclic framework by attaching substituents with π-conjugative effect (eg. aryl and heteroaryl groups) either directly or through C–C double or triple bond to afford derivatives with interesting biological and/ or photophysical properties.

1.4 Synthesis of bis-heterocyclic compounds

Recently, bis-heterocyclic compounds have attracted attention in synthetic organic chemistry. For example, Kode *et al.* reported that bis-heterocylic compounds possess high sensitivity against many cancer cell lines such as breast cancer cells and leukemia cells.[91] The authors synthesized 9-{[(2,6-dichloro-9*H*-purin-9-yl)methyl]benzyl}-2,6-dichloro-9*H*-purines **126** from the reactions of dichloropurines **124** and dichloroxylenes (*ortho*, *meta*, or *para*) **125**, in the presence of cesium carbonate (Cs_2CO_3) as a catalyst in DMSO (Scheme 42). The biological property studies of compounds **126** showed that 9-{*o*-[(2,6-dichloro-9*H*-purin-9-yl)methyl]benzyl}-2,6-dichloro-9*H*-purine was highly active against non-small lung cancer

NCI-H522 (GI_{50} 3.39 µM) and several breast cancer MCF-7, HS 578T, T-47D (GI_{50} 1.55, 3.09, 2.19 µM) cell lines. 9-{*m*-[(2,6-Dichloro-9*H*-purin-9-yl)methyl]benzyl}-2,6-dichloro-9*H*-purine was found to be active against leukemia CCRF-CEM, K562, MOLT-4, RPMI-8226 (GI50 1.41, 1.95, 1.66 and 0.55 µM), colon cancer COLON 205 (GI_{50} 3.38 µM), and several breast cancer MCF-7, T-47D (GI_{50} 3.63, 3.02 µM, respectively) cell lines. Finally, 9-{*p*-[(2,6-Dichloro-9*H*-purin-9-yl)methyl]benzyl}-2,6-dichloro-9*H*-purine was highly active against non-small lung cancer EKVX, colon cancer HT-29, melanoma SK-MEL-28, renal cancer RXF 393, prostate cancer DU-145 and several breast cancer HS 578T and BT-549 cell lines.



124 **125**

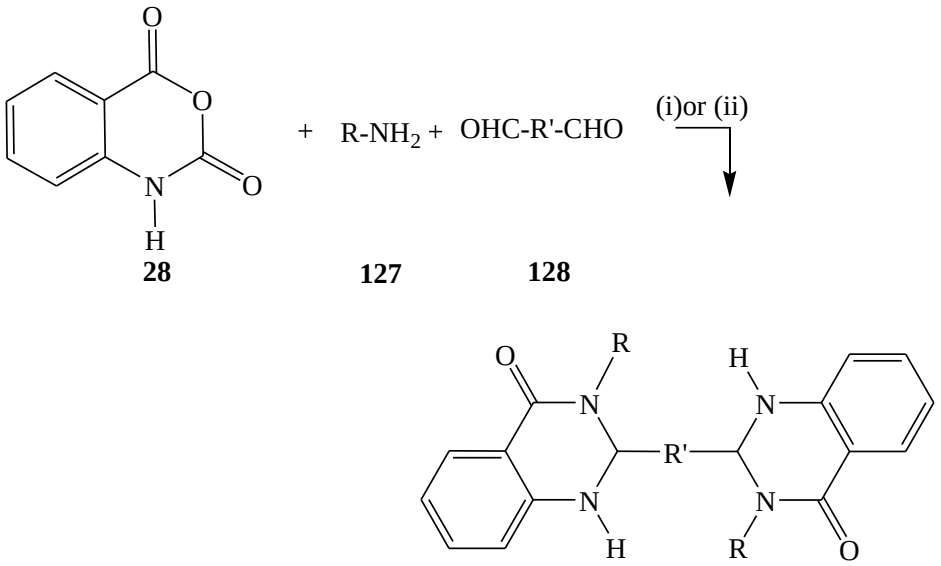
126

Reagents and conditions: (i) Cs_2CO_3, DMSO, rt.

Scheme 42: Alkylation of **124** with **125** to afford compounds **126**

There has been growing interest in the synthesis of novel bis-quinazolinones in which the two quinazolinone moieties are linked together through a carbon chain[24] or aryl group.[92-94] For

example, stoichiometric amounts of isatoic anhydride **28** (2 equiv.), primary amines **127** (2 equiv.) and dialdehydes **128** (1 equiv.) were condensed using *p*-toluenesulfonic acid (*p*-TsOH) as catalyst in ethanol or water under reflux to afford novel bis-2,3-dihydroquinazolin-4(1*H*)-one **129** [Scheme 43 (i)].[92] Molecular iodine was also employed as a catalyst in the reaction of isatoic anhydride **28** (2 equiv.) and primary amines **127** (2 equiv.) with dialdehydes **128** in 1-butyl-3-methylimidazolium bromide ([BMIm]Br) and the bis-2,3-dihydroquinazolin-4(1*H*)-one derivatives **129** were obtained [Scheme 43 (ii)].[93]

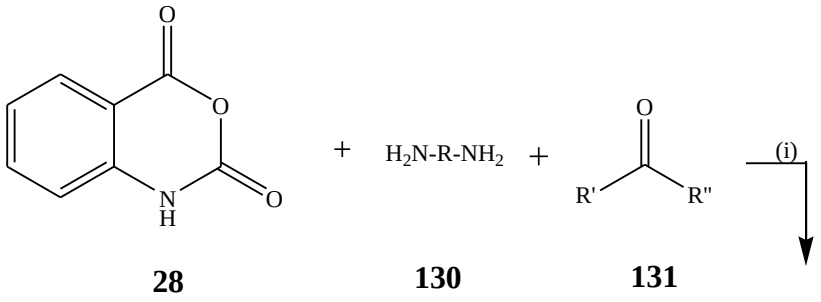


129: R= H, Aryl; R´ = alkyl, aryl

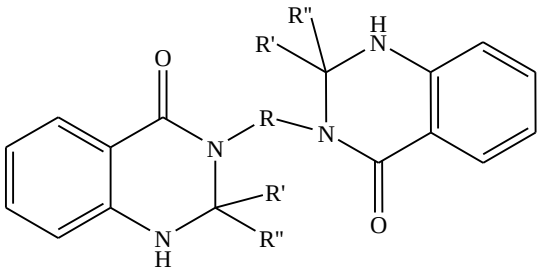
Reagents and conditions: (i) *p*-TsOH, EtOH or H_2O reflux. (ii)) I_2, [BMIm]Br, 50 °C

Scheme 43: Condensation of compound **28** with primary amines **127** and dialdehydes **128**.

Moreover, molecular iodine was again used as a catalyst to condense isatoic anhydride **28** with diamines **130** and in the presence of carbonyl compounds **131** in [BMIm]Br, to afford bis-dihydroquinazolin-4(1*H*)-one derivatives **132** (Scheme 44).[93]



28 **130** **131**

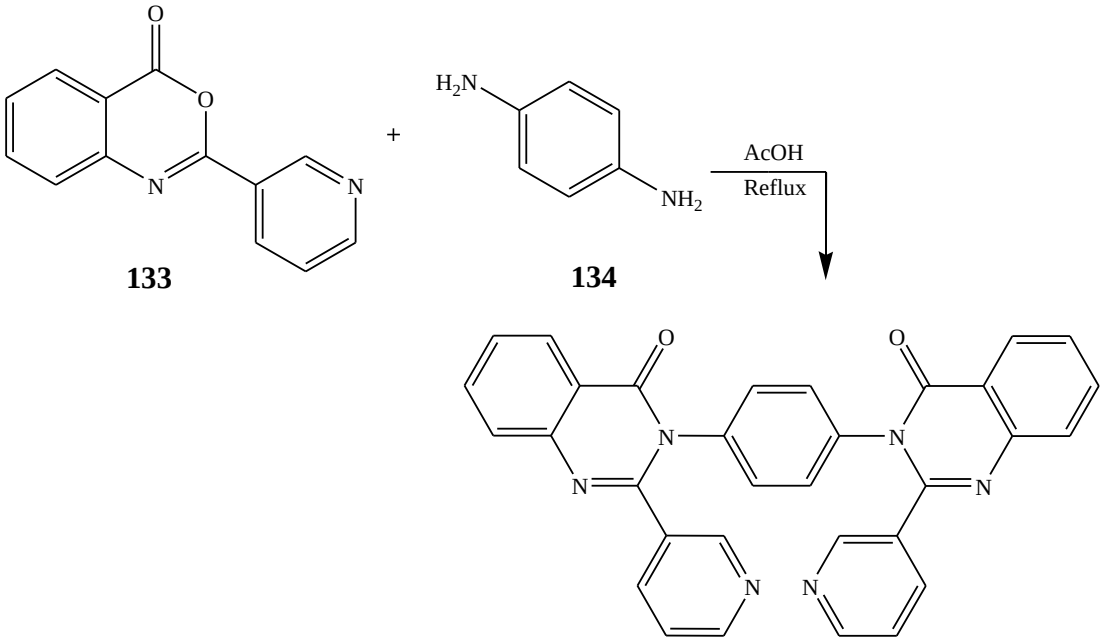


132: R=Aryl, alkyl; R', R''= H, aryl, alkyl

Reagents and conditions: (i) I_2, [BMIm]Br, 50 °C.

Scheme 44: Condensation of **28** with diamines **130** and aldehydes or ketones **131**.

In another example, 2-pyridinyl-3,1-benzoxazinones **133** (2 mol equiv.) was reacted with one mole of 1,4-phenylenediamine **134** in glacial acetic acid and under reflux to afford the bis-quinazolin-4(3*H*)-ones **135** (Scheme 45).[94]

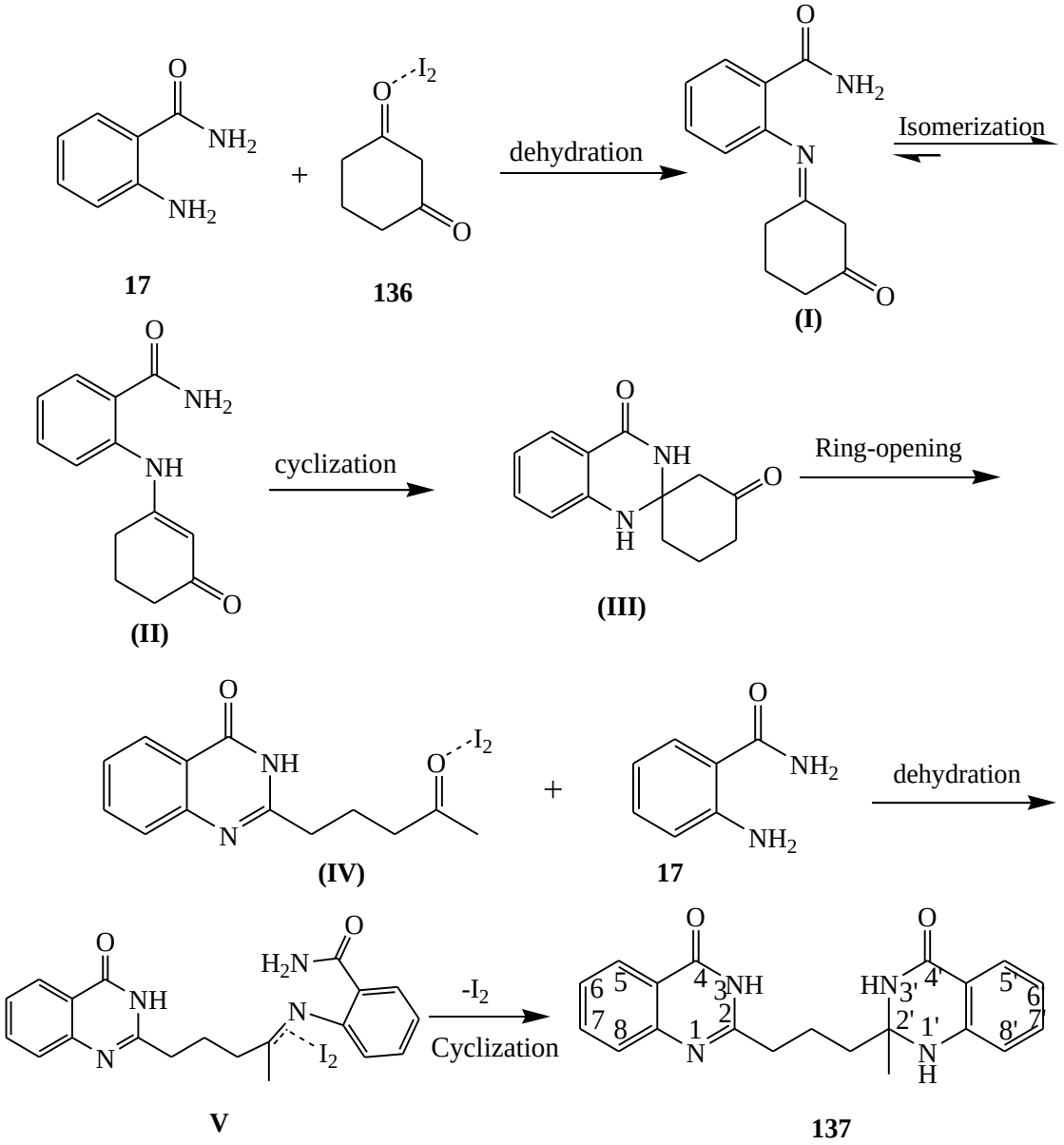


133 **134** **135**

Scheme 45: Condensation of compound **133** with diamine **134** to afford bis-quinazolin-(3*H*)-one **135**.

Lu *et al*., recently reported a convenient method for the synthesis of bis-heterocycles incorporating both the 2,3-dihydroquinazolin-4(1*H*)-ones and the quinazolin-4(3*H*)-ones linked together by an aliphatic carbon.[24] The authors condensed two moles of 2-aminobenzamide **17** with 1,3-cyclohexanedione **136** using iodine in toluene under reflux (Scheme 46). The first step in this reaction involves the condensation of 2-aminobenzamide **17** with 1,3-cyclohexanedione **136**, promoted by molecular iodine to form intermediate (**I**) with the liberation of water. Prototropic shift on (**I**) then occurs to afford intermediate (**II**). Intermediate (**II**) is then converted to (**III**) by intramolecular Michael addition of the amide nitrogen onto the enone carbon. Dehydrogenation between *N*(2)–*C*(3) then occurs, followed by ring opening to form intermediate (**IV**). Likewise, another mole of 2-aminobenzamide **17**

reacts with keto carbon on the open chain of intermediate (**IV**) leading to the formation of **137**.



17 **136** **(I)** **(II)** **(III)** **(IV)** **17** **V** **137**

Scheme 46: Proposed mechanism for condensation of anthranilamide **17** with cyclohexane-1,3-dione **136**.

1.5 Research hypothesis

The 2,3-dihydroquinazolin-4(1*H*)-one[16] and quinazolin-4(3*H*)-one[17] derivatives were found to exhibit interesting electronic absorption and emission properties in solution. For example, the absorption and emission spectra of 2-*tert*-butyl-2,3-dihydro-3-phenylquinazolin-4(1*H*)-one acquired in chloroform revealed that this compound absorbs at λ_{ab} 344 nm and it emits at λ_{em} 409 nm.[16] On the other hand, 2-(4-methoxystyryl)-3-phenylquinazolin-4(3*H*)-one was found to absorb in the ultra-violet region λ_{ab} 348 nm and emit in the visible region at λ_{em} 485 nm in acetonitrile.[18] We envisioned that by linking quinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties together through an aliphatic chain and attaching aryl groups to the fused benzo rings of the resultant bis-heterocyclic compounds could impart some interesting photophysical properties. In our view, by attaching the aryl groups on the two quinazolinone moieties could modify the electronic absorption and emission properties of the resultant polyaryl-substituted bis-heterocycles further. The two frameworks linked together by an inert aliphatic chain could either enhance or quench the absorption and/ or emission properties of the bis-heterocycle. To prove this hypothesis, we decided to investigate the possibility to extend the method of Lu *et al.*[24] to prepare polyaryl-substituted bis-heterocycles comprising the 2,3-dihydroquinazolin-4(1*H*)-one and 2,3-dihydroquinazolin-4(1*H*)-one moieties linked by aliphatic chain. We envisioned that 2-aminobenzamide **17** could be brominated and the resultant bromo derivative **138** could, in turn, be condensed with cyclohexane-1,3-diones **139** to afford the requisite bromo-substituted bis-heterocyclic compounds **140** comprising the halogenated 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties linked together by a carbon chain (Fig. 8). In our view, the presence of bromine atoms on the envisioned bis-heterocycles would enable further transformation via metal-catalysed cross-coupling reactions to afford novel polyaryl

substituted bis-heterocycles **141** with potential photophysical properties. The aryl groups are expected to impart a high degree of conjugation with electron-deficient dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one backbones. This, in turn, would enhance the donor-π-acceptor properties of the resultant polyaryl- or polyalkenyl derivatives.

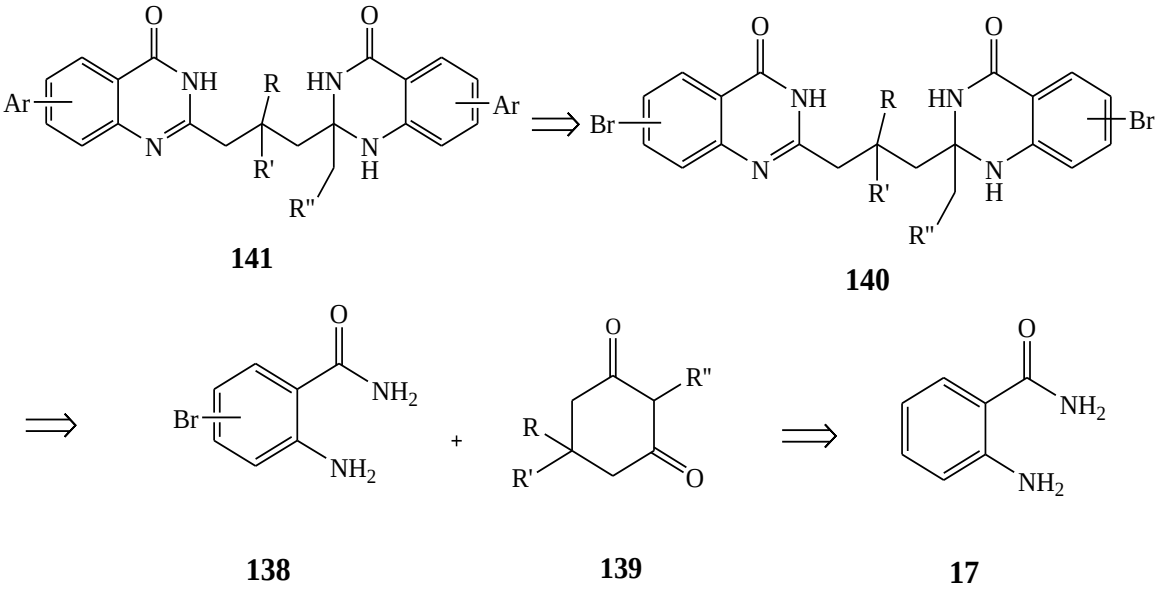


Figure 8: Possible retrosynthetic route to compounds **141**.

With the above hypothesis in mind, we decided to investigate the synthesis of bis-heterocyclic systems comprising of 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties linked together by a carbon chain, based on the condensation of brominated 2-aminobenzamide with cylcohexane-1,3-diones. The main goal was to prepare novel polyaryl substituted bis-heterocycles and to probe them for potential photophysical properties using UV-Vis and emission spectroscopic techniques. We opted for the use of the Suzuki-Miyaura cross-coupling reaction with arylboronic acids to produce novel polyaryl substituted derivatives. In our view, the Kumada cross-coupling which could serve as an alternative for arylation would not be suitable for this transformation because the Grignard reagents would attack the base-sensitive amine and the electrophilic amide groups. The toxicity of organotin

compounds, on the other hand, hampered the use of Stille cross-coupling in this investigation. With these considerations, we decided on the following structured aims and objectives.

1.6 Aims and objectives

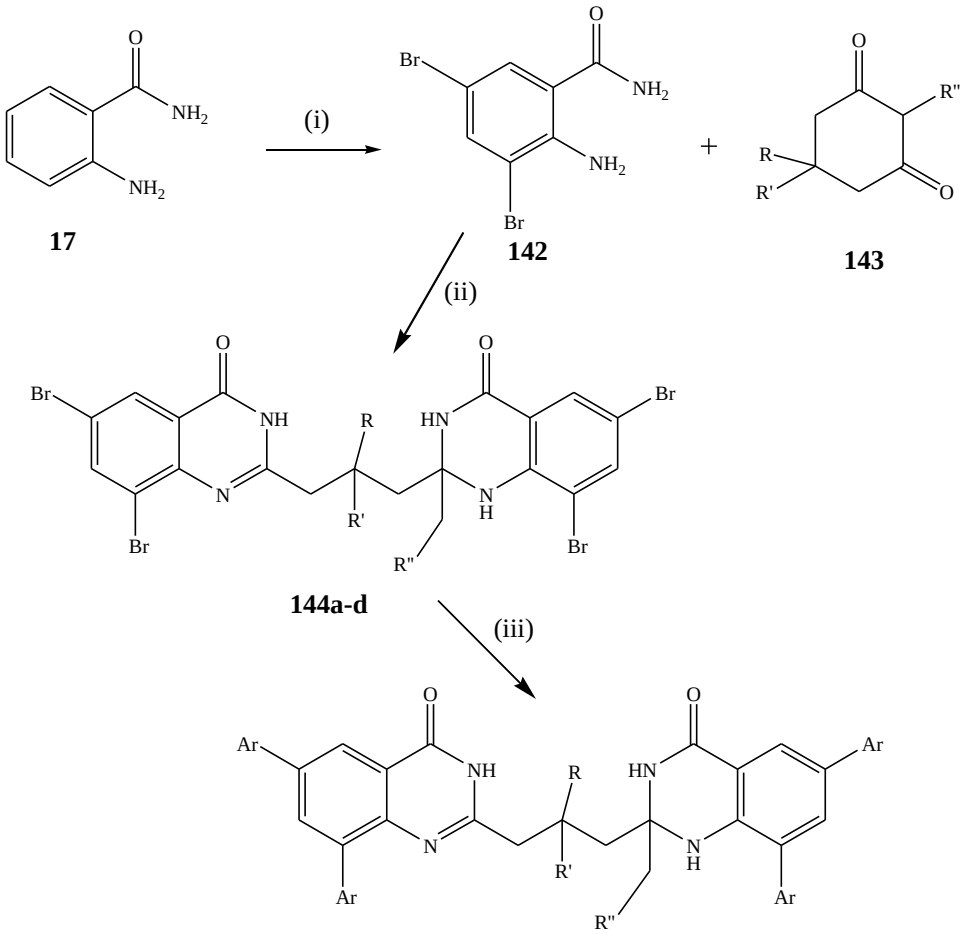
(i) To synthesize polybrominated bis-heterocycles comprising of 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties based on 2-amino-3,5-dibromobenzamide and cylcohexanediones as precursors,

(ii) To subject the resultant halogenated bis-heterocycles to the Suzuki-Miyaura cross-coupling with arylboronic acids,

(iii) To study the photophysical properties (absorption and emission) of the resultant polyaryl substituted bis-heterocycles by the use of electronic absorption and emission spectroscopic techniques.

CHAPTER 2: RESULTS AND DISCUSSION

The reaction of commercially available 2-aminobenzamide **17** with *N*-bromosuccinimide in acetic acid at room temperature afforded 2-amino-3,5-dibromobenzamide **142**. This was followed by condensation with 1,3-cyclohexanedione derivatives **143a–d** in the presence of iodine as catalyst in toluene under reflux to afford novel halogenated bis-heterocycles **144a**–**d**. The latter were, in turn, subjected to Suzuki-Miyaura cross-coupling reactions with substituted arylboronic acids to produce polyaryl-substituted derivatives **145a–l** (Scheme 47). All the compounds were characterised by NMR (^{1}H and ^{13}C) and infrared (IR) spectroscopic techniques and their exact molecular formulae were confirmed by high-resolution mass spectroscopy. To understand the influence of substituents on intramolecular charge transfer (ICT) for the compounds **144a–d** and **145a**–**l**, we determined their absorption and emission properties in dimethylsulfoxide (DMSO) and acetic acid by UV/Vis and fluorescence spectroscopic techniques.



145a-l: R, R', R'' = H, CH_3; Ar = C_6H_5, 4-$MeOC_6H_4$, 4-FC_6H_4

Reagents and conditions: (i) NBS (2 mmol equiv.), AcOH, 3 h, rt. (ii) I_2, toluene, reflux; (iii) $ArB(OH)_2$, K_2CO_3, $PdCl_2(PPh_3)_2$, PCy_3, dioxane-water(3:1, v/v), 100 °C.

Scheme 47: Generalized Scheme for the synthesis of polyaryl-substituted bis-heterocycles described in this investigation

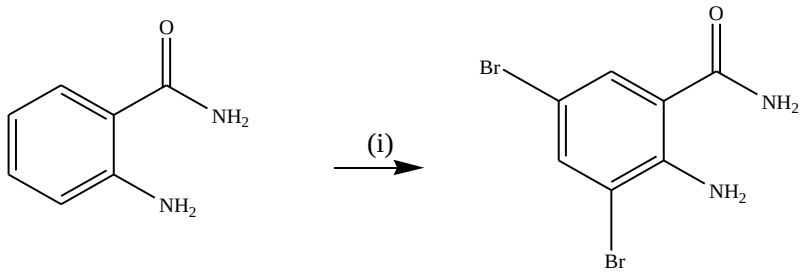
2.1 Synthesis and transformation of halogenated bis-heterocycles

The main aim of this work was to synthesize the novel bis-heterocycles comprising electron deficient 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties as electron-acceptors each linked directly to the aryl groups at the 6- and 8-position to comprise a donor-π-acceptor system. In order to realise our goal we required brominated 2-aminobenzamide as a precursor and that was obtained by the reaction of 2-aminobenzamide with *N*-bromosuccinimide. The results are discussed in detail below.

2.1.1 Synthesis of 2-amino-3,5-dibromobenzamide 142

Aniline derivatives were previously brominated by using molecular bromine in the presence of transition metal-based catalysts such as iron(III) bromide.[95] However, this reaction generates the corrosive and toxic hydrogen bromide. On the other hand, bromine is not selective and was found to form a mixture of mono-, di-, tri-, and even tetra-brominated aniline derivatives.[96] The 2-amino-3,5-dibromobenzamide **142** used in this investigation as a precursor was previously prepared from the commercially available 2-aminobenzamide and *N*-bromosuccinimide (NBS) (2.5 equiv.) in chloroform-carbon tetrachloride mixture (3/2, v/v).[70] However, in this study we found that acetic acid worked well as a solvent at room temperature and produced comparable yield (78%) to that obtained using chloroform-carbon tetrachloride mixture. The reaction of 2-aminobenzamide **17** with NBS in acetic acid at room temperature readily afforded 2-amino-3,5-dibromobenzamide **142** (Scheme 48). The ^{1}H NMR spectrum compared well with the literature spectrum[70] by revealing the presence of proton signals in the aromatic region δ_H 6.5–8.5 ppm with the protons of the amide group showing as a broad singlet at δ_H 6.80 ppm in accordance with the literature precedents.[97] The

amine protons displayed diastereotopic effect and they resonate at δ_H 7.47 ppm and δ_H 8.05 ppm. This non-equivalence of the amine protons is caused by intramolecular H-bonding between the proton at 8.05 ppm and amide oxygen in analogy with literature precedents.[97] The two doublets at δ_H 7.72 ppm and δ_H 7.77 ppm, with coupling constant values of J = 2.4 Hz and J = 2.1 Hz correspond to 4-H and 6-H, respectively.



17 **142** (78%)

Reagents and conditions: (i) NBS (2.0 mmol equiv.), acetic acid, rt, 3 h.

Scheme 48: Bromination of 2-aminobenzamide **17** with NBS.

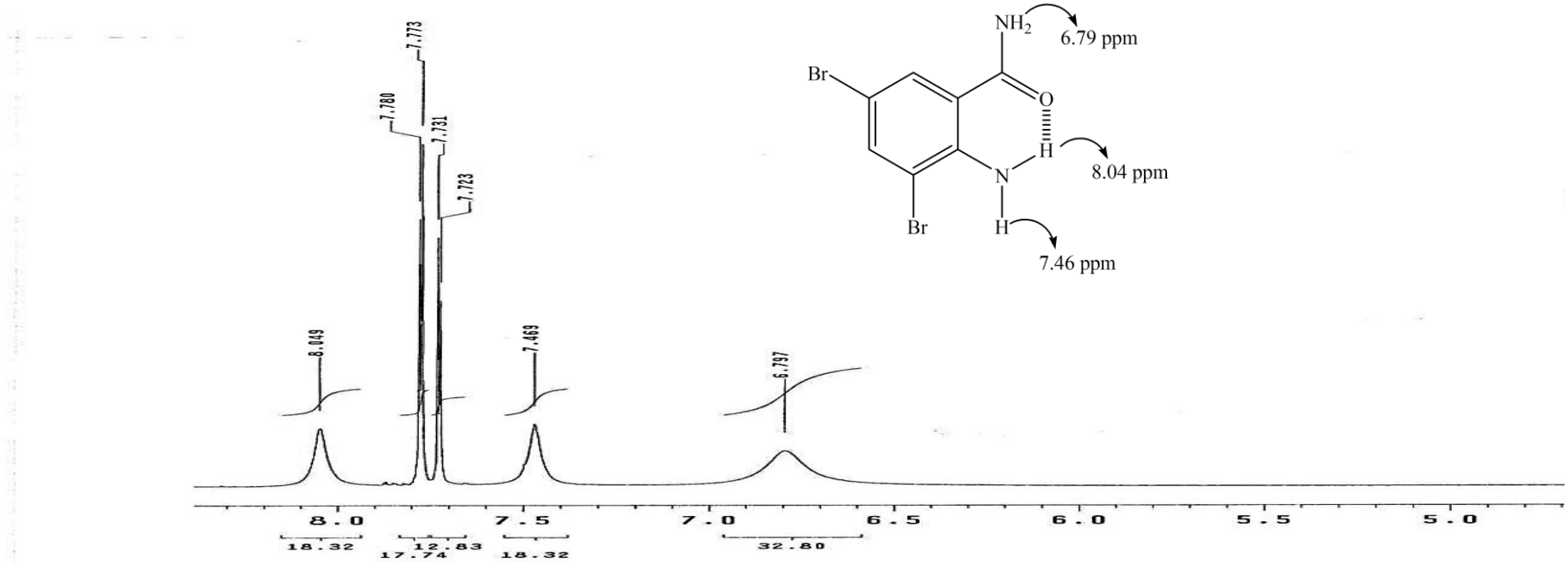


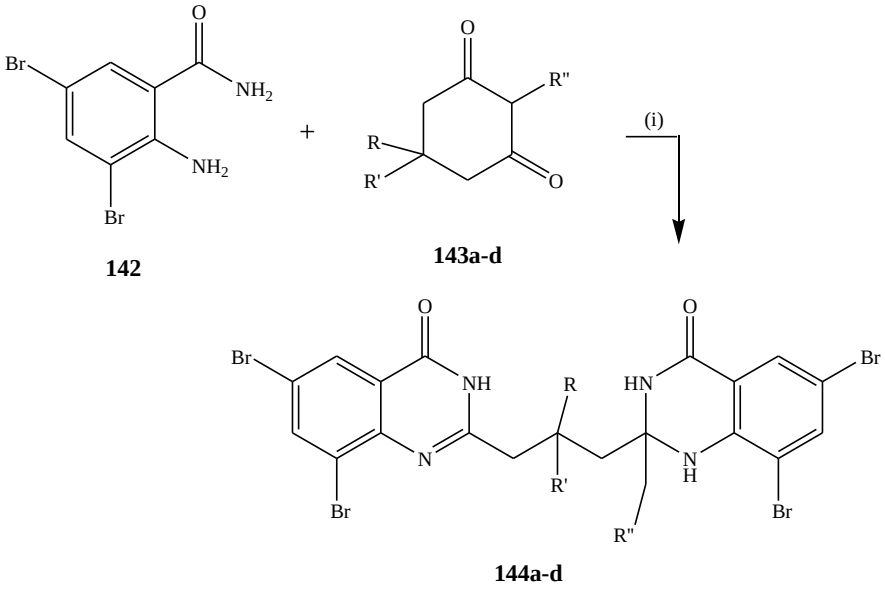
Figure 9: ^{1}H NMR spectrum of 2-amino-3, 5-dibromobenzamide **142** in DMSO-d_6 at 300 MHz.

With 2-amino-3,5-dibromobenzamide **142** in hand, we decided to investigate its reactivity with cyclohexane-1,3-dione derivatives with the aim to prepare halogenated bis-heterocycles.

2.1.2 Synthesis of 6, 8-dibromo-2-[3-(2'-alkyl- 6', 8'-dibromo-1', 2', 3', 4'-tetrahydro-4'-oxoquinazoline-2'yl)propyl]quinazolin-4(3*H*)-ones (144a–d)

In this investigation, we opted for the method previously described by Lu *et al*., which involves the condensation of 2-aminobenzamide with cyclohexane-1,3-dione **143** in the presence of iodine as a catalyst in toluene under reflux.[24] The initial use of 2.0 mol equiv. of **142** with 1.0 equiv. of **143a** catalysed by iodine in toluene under reflux afforded the targeted bis-heterocycle **144a** in low yield (40%). This prompted us to use a slight excess amount of **142** (2.2 mmol) with 1.0 equivalent of derivatives **143a** and to our delight, within 5 hours (tlc monitored), we isolated compound **144a** in high yield (85%) by just filtration and recrystallization from ethanol (Scheme 49). These reaction conditions were extended to substrates **143b–d** to study the effects of substituent(s) on 2nd and 5th position of cyclohexane-1,3-dione on the yields and reaction times. Relatively high yield (83%) was observed when 5-methylcyclohexane-1,3-dione **143b** was used as substrate, however, it involved prolonged reaction time (12 h) than cyclohexane-1,3-dione **143a**. The use of 2-methyl-substituted and 5,5-dimethylcyclohexane-1,3-dione as substrates afforded after 24 h the corresponding products in 60 and 63% yield, respectively. Prolonged reaction time and reduced yields are presumably due to steric hindrance caused by the methyl groups. The resultant halogenated bis-heterocycles **144a**–**d** were characterized using a combination of NMR (^{1}H and ^{13}C), and IR as well as mass spectroscopic techniques. The ^{1}H NMR spectra of compounds **144a**–**d** revealed the presence of groups of multiplets in the aliphatic region corresponding to the substituted propyl chain. The methylene protons of compound **144c** are diastereotopic with

large germinal coupling constants ^{2}J *ca.* 13.5 Hz and 15.3 Hz. This observed diastereotopicity of methylene protons is probably due to their position relative to the two non-equivalent methyl groups on the position 2 of the propyl linkage. Only four singlets were observed in the aromatic region corresponding to the protons of the fused benzo rings. The other three singlets at δ_H *ca.* 6.0 ppm, 8.0 ppm, and 12.0 ppm correspond to 1'–NH, 3'–NH, and 3–NH, respectively. The formation of halogenated bis-heterocycles **144a–d** was further confirmed by the presence of ^{13}C signals in the aliphatic region corresponding to propyl carbons, as well as increased number of ^{13}C signals in the aromatic region of the ^{13}C NMR spectra.



142 **143a-d**

144a-d

144	R	R´	R´´	Time (h)	% Yield	Melting point (°C)
144a	H	H	H	5	85	286–290
144b	CH_3	H	H	12	83	312–314
144c	CH_3	CH_3	H	24	63	315–318
144d	H	H	CH_3	24	60	307–310

Reagents and conditions: **142** (2.2mmol), **143** (1mmol), (i) I_2 (15% of **142**), toluene reflux

Scheme 49: Condensation of compound **142** with **143a–d**.

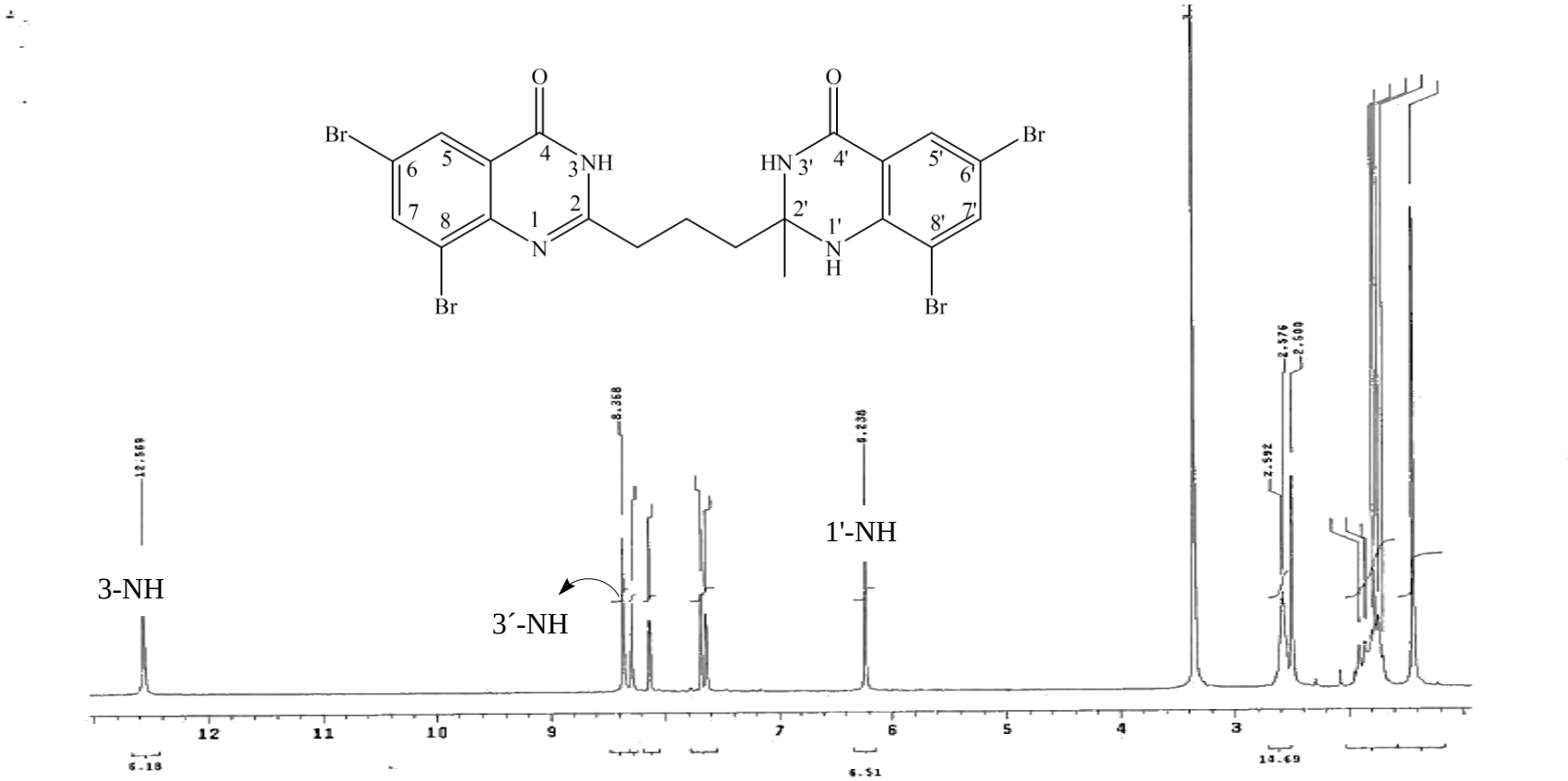


Figure 10: ^{1}H NMR spectrum of 6,8-dibromo-2-[3-(6',8'-dibromo-1',2',3',4'-tetrahydro-2'-methyl-4'-oxoquinazolin-2'-yl)propyl]quinazolin-4(3*H*)-one **144a** in DMSO-d_6 at 300 MHz.

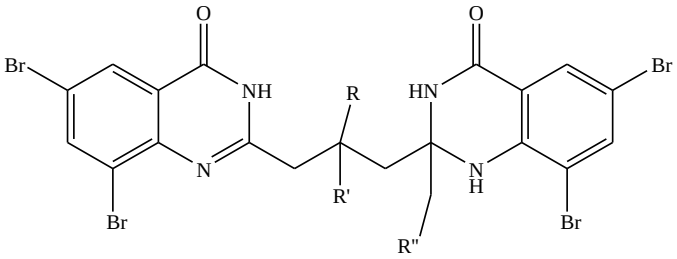
The presence of bromine atoms in compounds **144a**–**d** makes them suitable candidates for further studies of chemical transformation via metal-catalysed cross-coupling reactions to afford the novel polycarbo-subtituted derivatives. For example, the 6,8-dibromo bis-heterocycles **144a**–**d** could be subjected to Kumada cross-coupling with organomagnesium compounds,[62] Suzuki cross-coupling with organoboronic acids,[67] Negishi cross-coupling with organozinc reagents,[73] Sonogashira cross-coupling with terminal alkynes,[79] Heck cross-coupling with alkenes[83] or Stille cross-coupling with organostannane compounds[87] to afford polycarbo-substituted bis-heterocycles. Our aim is to prepare the bis-heterocycles comprising the electron deficient 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties as electron-acceptors attached to the aryl groups as π-electron donors to comprise donor-π-acceptor systems. The aryl groups attached to an electron-deficient heterocyclic framework have been found to shift the π–π* transition towards the visible region.[25] Consequently, we decided to study the photophysical properties (electronic absorption and emission) of compounds **144a–d** and **145a–l** in solution using UV-Vis and emission spectroscopic techniques. In order to realise our goal and to attach the aryl groups to the bis-heterocyclic compounds, we decided to employ the Suzuki-Miyaura cross coupling reaction of halogenated bis-heterocycles **144a**–**d** with arylboronic acids as coupling partners. The choice over alternatives such as Stille- and Kumada cross-coupling reactions was influenced by the ready availability of organoboronic acids compounds and their ability to tolerate a wide range of functional groups as well as easy work-up.[70] The Stille cross-coupling, for example, makes use of the toxic organotin compounds, which are less polar and therefore poorly soluble in some organic solvents. On the other hand, the Kumada cross-coupling reaction uses the highly basic and nucleophilic Grignard reagents, which could attack the amide groups or deprotonate them thus complicating the outcome of the reaction.

2.1.3 Suzuki-Miyaura cross-coupling reactions of halogenated bis-heterocycles 144a–d with arylboronic acids

The Suzuki-Miyaura cross-coupling of analogous 6,8-dibromoquinazolin-4(1*H*)-ones with arylboronic acids in the presence of bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$) as catalyst and potassium carbonate as a base in aqueous *N*,*N*-dimethylformamide was conducted before.[70] However, a complex mixture of products was obtained, and that prompted the authors to use an alkylphosphine ligand which is known to coordinate with palladium and increase its electron density, and consequently accelerate the oxidative addition and reductive elimination steps in the catalytic cycle.[70] With the literature precedents in mind and as a preliminary study, we reacted 6,8-dibromo bis-heterocycle **144a** (1.0 equiv.) with phenylboronic acid (4.0 equiv.) in the presence of $PdCl_2(PPh_3)_2$ as a catalyst, tricyclohexylphosphine (PCy_3) as a ligand and potassium carbonate (K_2CO_3) as a base in dioxane-water at 100 °C. However, the reaction led to the formation of complex mixture of products which could not be separated by column chromatography due to similar R_f values. The previous literature results for the Suzuki-Miyaura cross-coupling reactions of the analogous 4-alkynyl-2-aryl-6,8-dibromo-quinazolines[19] bearing two bromine atoms on the fused benzo ring revealed that these cross-couplings occur without selectivity presumably due to comparable C–Br bond strength. Computational studies on bond dissociation energies at B3LYP and G3B3 levels revealed that all of the positions on the fused benzo ring of various heterocycles bearing identical halogen atoms have comparable carbon-halogen (X = Br, Cl) bond dissociation energies.[71] As a result, the cross-coupling reactions involving dihalogenated heterocycles bearing identical halogen atoms are usually conducted using an excess of the coupling partner to drive the reaction to completion.[97] In analogy with these literature precedents, we decided to subject the 6,8-dibromo bis-heterocycles **144a** to Suzuki-Miyaura

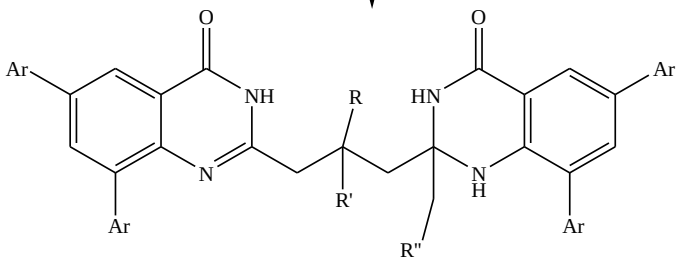
cross-coupling with an excess of phenylboronic acid (4.5 equiv.) in the presence of $PdCl_2(PPh_3)_2$-PCy_3 catalyst complex and potassium carbonate as a base in aqueous dioxane at 100 °C. We again isolated a complex mixture of products. We then employed 5.0 equivalent of phenylboronic acid with bis-heterocycle **144a** (1.0 equiv.) and after the completion of the reaction (tlc monitoring) we isolated polyaryl-substituted derivative **145a** in high yield (80%) by recrystallization with mixture of ethyl acetate and *n*-hexane. These reaction conditions were extended to substrates **144b–d** with phenylboronic, 4-methoxyphenylboronic and 4-fluorophenylboronic acids (5.0 equiv.) as coupling partners to afford the polyaryl-substituted derivatives **145a–l** in high yields (60–81%) and high purity without a need for column chromatography. Compounds **145a**–**l** were characterised by NMR spectroscopy (^{1}H and ^{13}C), IR, and mass spectroscopy techniques. The resultant polyaryl-substituted derivatives **145a–l** were distinguished from the corresponding precursors by the presence of an increased number of protons in the aromatic region δ_H (6.5–8.5 ppm). The NMR spectra of the methoxyphenyl-substituted derivatives **145c, 145f, 84i** and **145l** revealed the presence of four singlets in the region δ_H 3.5–3.8 ppm (OCH_3) and four carbon peaks in the region δ_C 54–56 ppm (OCH_3) thus confirming complete substitution of the four bromine atoms. The replacement of bromo atoms by 4-fluoroaryl groups, on the other hand, was confirmed by the presence of ^{13}C NMR signals at δ_C 161.0–163.0 ppm (4 x $^1J_{CF}$ *ca*. 24.0 Hz), δ_C 115.0–116.5 ppm (4 x $^2J_{CF}$ *ca*. 21.0 Hz), δ_H 128.0–133.0 ppm (4 x $^3J_{CF}$ *ca*. 8.0 Hz) and δ_C 134.5–137.0 ppm (4 x $^4J_{CF}$ *ca*. 3.0 Hz). Furthermore, the absence of the bromine isotopes (^{79}Br and ^{81}Br) in the molecular ion peaks in the mass spectra of these compounds confirmed complete replacement of the bromo atoms by the aryl groups (see selected mass spectra under appendix). The absence of carbon-bromine bands in the region 515–690 cm^{-1} of their IR spectra, on the other hand, further confirmed complete substitution of the halogen atoms by the aryl groups. It was difficult to assign the 1-H and C-13 chemical shifts to their corresponding nuclei due to

increased number of proton and carbon signals in the NMR spectra of the resultant polyaryl-substituted derivatives **145a–l**.



144a-d

(i)



145a-l

Compound	R	R´	R´´	Ar	Time (h)	%Yield	Melting point (°C)
145a	H	H	H	C_6H_5	4	80	203–206
145b	H	H	H	4-FC_6H_4	4	81	241–243
145c	H	H	H	4-$MeOC_6H_4$	4	74	181–184
145d	CH_3	H	H	C_6H_5	4	75	211–215
145e	CH_3	H	H	4-FC_6H_4	4	70	265–268
145f	CH_3	H	H	4-$MeOC_6H_4$	4	73	194–196
145g	CH_3	CH_3	H	C_6H_5	4	76	289–292
145h	CH_3	CH_3	H	4-FC_6H_4	4	77	303–305
145i	CH_3	CH_3	H	4-$MeOC_6H_4$	4	81	228–230
145j	H	H	CH_3	C_6H_5	4	63	223–226
145k	H	H	CH_3	4-FC_6H_4	4	63	252–254
145l	H	H	CH_3	4-$MeOC_6H_4$	4	60	192–195

Reagents and conditions: (i) $ArB(OH)_2$ (5.0 mmol equiv.), K_2CO_3 (4.5 mmol equiv.), $PdCl_2(PPh_3)_2$, (10% of **144**), PCy_3 (20% of **144**), and dioxane-water (3:1, v/v), 100 °C.

Scheme 50: Suzuki-Miyaura cross-coupling of **144a**–**d** with arylboronic acids.

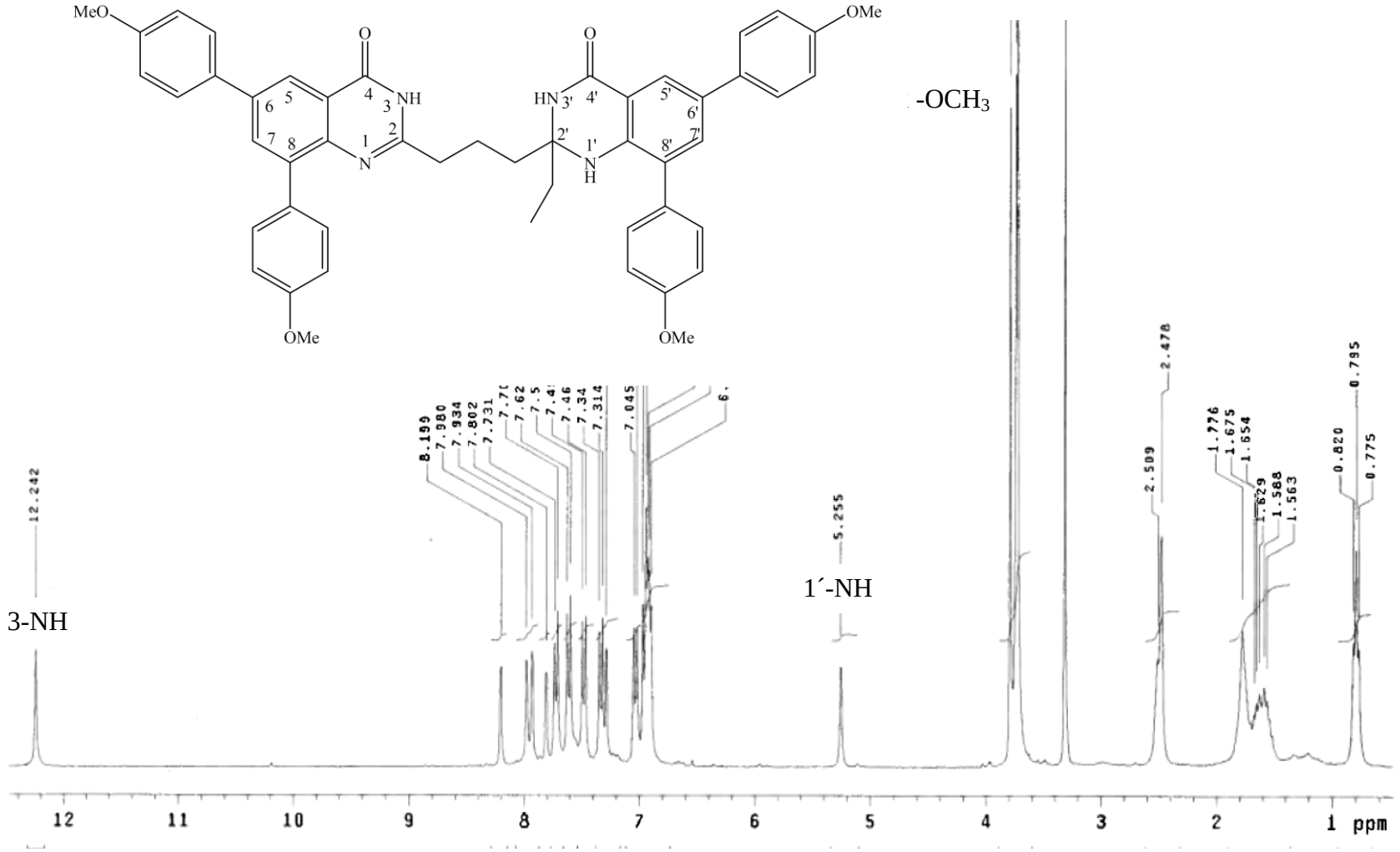


Figure 11: ^{1}H NMR spectrum of 2-{3-[2-ethyl-1,2,3,4-tetrahydro-6,8-bis(4-methoxyphenyl)-4-oxoquinazolin-2-yl]propyl}-6,8-bis(4-methoxyphenyl)quinazolin-4(3*H*)-one **145l** in DMSO-d_6 at 300 MHz.

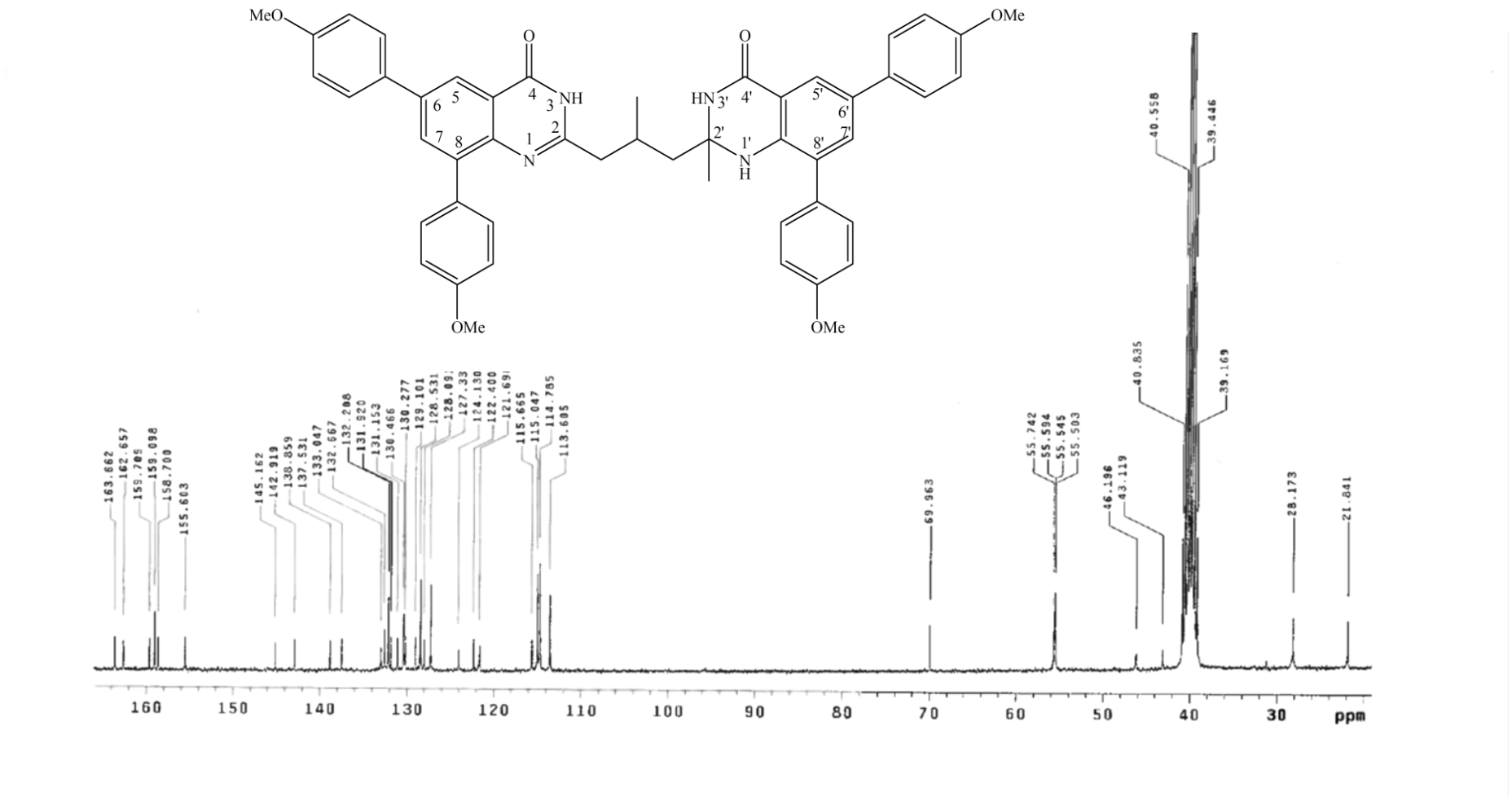


Figure 12: ^{13}C NMR spectrum of 2-{3-[1',2',3',4'-tetrahydro-6',8'-bis(4-methoxyphenyl)-2'-methyl-4'-oxoquinazolin-2-yl]-2'-methylpropyl}-6,8-bis(4-methoxyphenyl)quinazolin-4(3*H*)-one **145f** in DMSO-d_6 at 75 MHz.

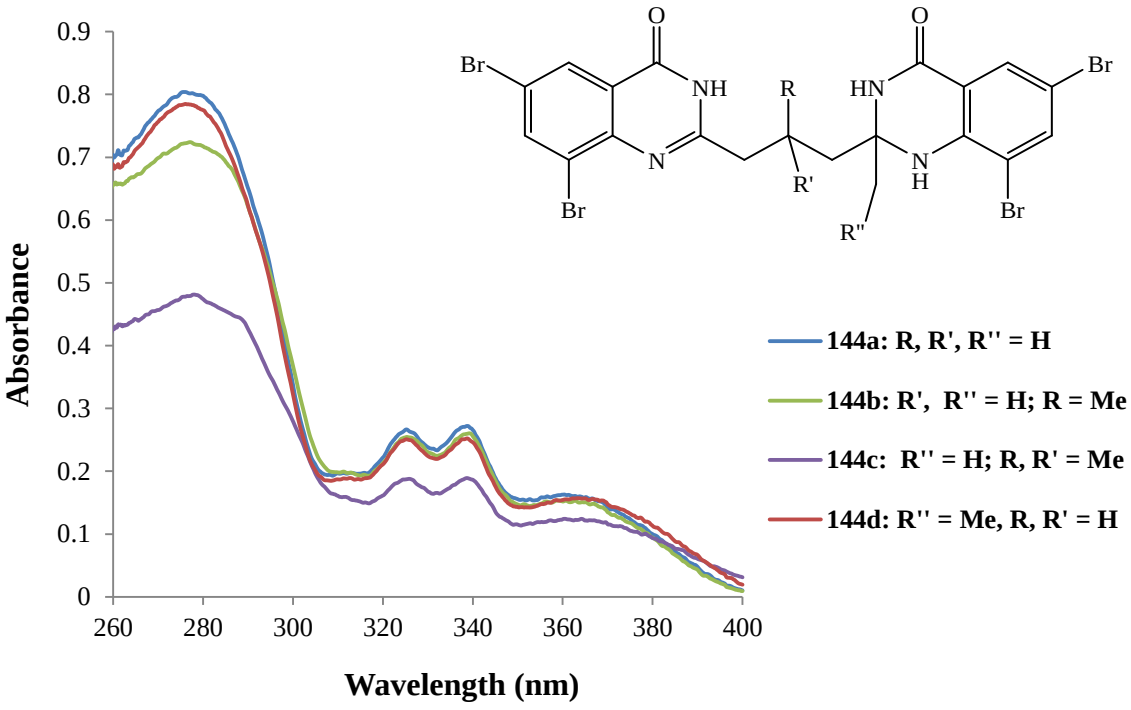
The prepared polyaryl-substituted bis-heterocycles **145a–l** contain electron-deficient 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties as electron-acceptors, each linked directly to the 4-substituted aryl ring to comprise a donor-π-acceptor system. It was envisioned that the presence of 4-substituted aryl-substituents would enhance the electronic absorption and emission properties of the resultant polyaryl-substituted bis-heterocycles towards visible region in analogy with literature precedents.[25] To prove this hypothesis and in order to understand the influence of substituents on intramolecular charge transfer (ICT), we measured the absorption and emission spectra of compounds **144a–d** and **145a–l** in solution using UV/Vis and emission spectroscopic techniques.

2.2 Absorption and emission property studies of halogenated bis-heterocycles (144a–d) and polyaryl-substituted bis-heterocycles (145a–l)

2.2.1 Absorption properties of halogenated bis-heterocycles (144a–d)

We first measured the absorption properties of bis-heterocycles **144a–d** in DMSO at room temperature (concentration 5 x 10^{-5} M). DMSO was chosen as the solvent for this purpose because of poor solubility of these compounds in other solvents. The absorption property results of the bis-heterocycles **144a–d** are listed in Table 1. The bis-heterocycles **144a–d** show similar absorption patterns and their spectra are characterised by four absorption bands, one intense band in the region λ_{max} 275–278 nm, two shorter bands at λ_{max} *ca.* 325 and 339 nm and the fourth broad band at 360 nm (Fig. 13). According to literature reports, the intense absorption bands in the region λ_{max} 275–278 nm are due to n–π* transition of the carbonyl fragments and the π–π* transition caused by intramolecular charge transfer from phenyl ring and N═C–N fragments to carbonyl fragment.[98] A significant red shift observed on the shorter

absorption bands for compounds **144a**–**d** at λ_{max} *ca.* 325, 339 and 360 nm are probably due to the influence of the four bromine atoms on the electronic transitions within the phenyl rings. The substitution of the hydrogen atom(s) with methyl group(s) on position 2 of the propyl linkage and on methyl group on position 2 of the 2,3-dihydroquinazolin-4(1*H*)-one decrease the molar extinction coefficient in the order: **144a** > **144d** > **144b** > **144c** at shorter wavelengths (λ_{max} 275–278 nm). However, at higher wavelengths (λ_{max} *ca.* 325, 339 and 360 nm), the substitution of the hydrogen atom(s) with methyl group(s) on position 2 of the open chain and on methyl group of **144b** and **144c** have slight or no effect on the molar extinction coefficients.



Figures 13: UV-Vis spectra of **144a-d** in DMSO at rt. (conc. = 5 x10^{-5} mol/L)

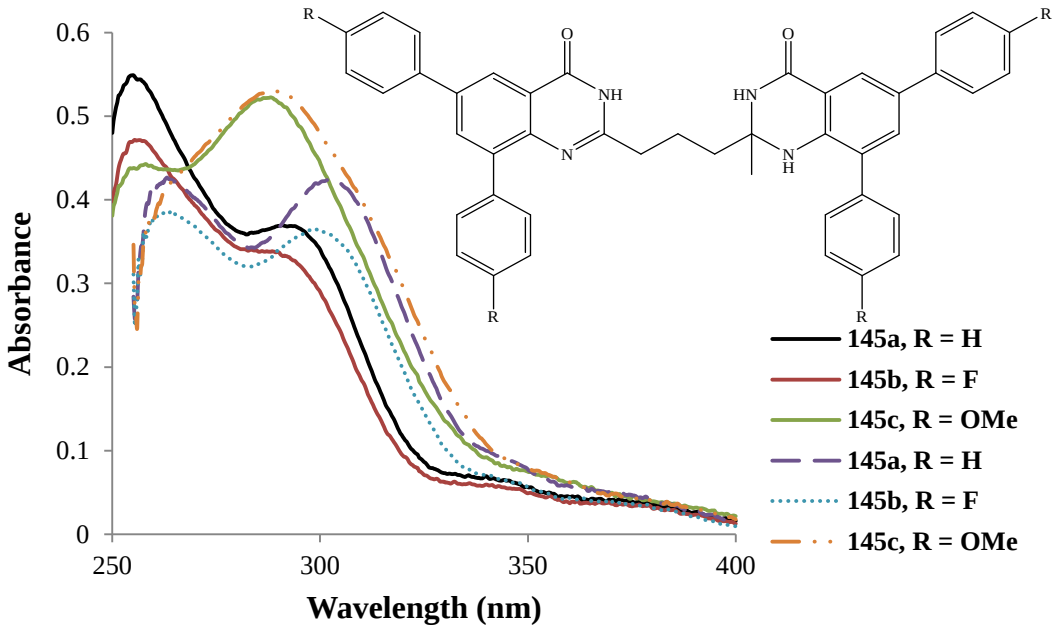
Table 1: The absorption data for compounds **144a**–**d**.

Compound	λ_{max} (nm) DMSO	Molar extinction coefficient (ε) × 10^4 Mol^{-1} cm^{-1}
144a	275.8, 325.3, 338.8, 360.4	1.6, 0.5, 0.5, 0.3
144b	276.1, 325.3, 338.8, 362.2	1.5, 0.5, 0.5, 0.3
144c	277.0, 325.3, 339.1, 359.5	1.4, 0.5, 0.5, 0.3
144d	277.9, 325.9, 338.8, 360.4	1.6, 0.4, 0.4, 0.2

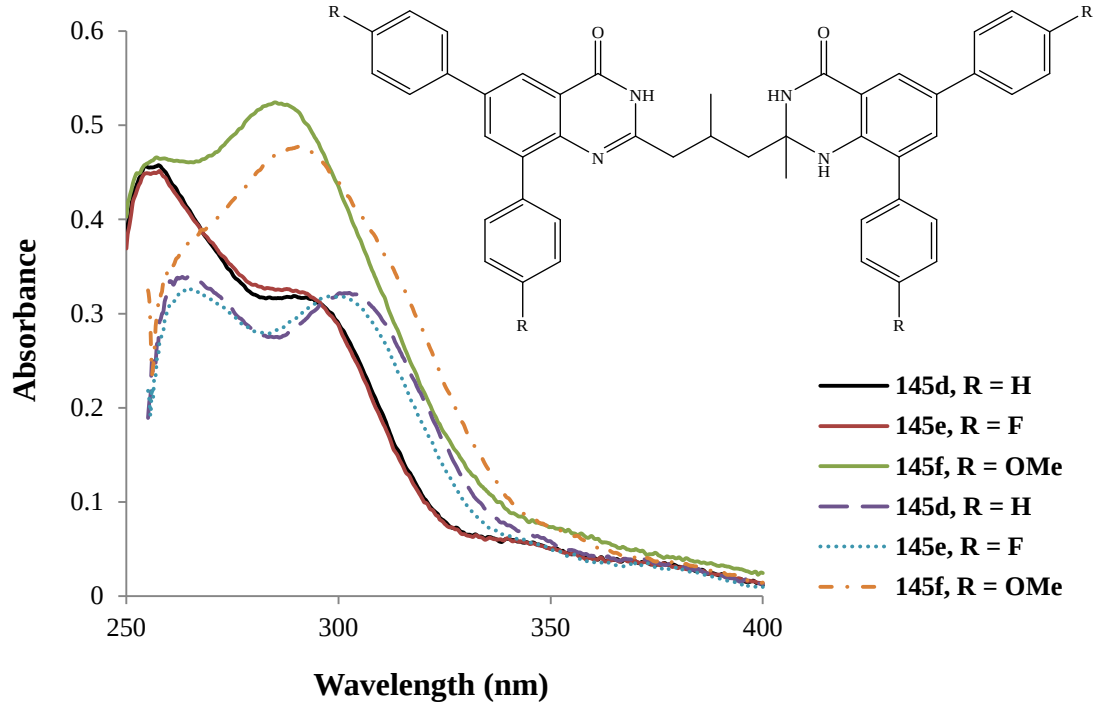
2.2.2 Absorption properties of polyaryl-substituted bis-heterocycles (145a–l)

Absorption spectra of polyaryl-substituted bis-heterocycles **145a**–**l** were acquired in DMSO (dashed lines) and acetic acid (solid lines) and their absorption results are listed in Table 2. These solvents were chosen due to poor solubility of these compounds in other solvents. Polyaryl-substituted bis-heterocycles **145** with phenyl- or 4-fluorophenyl groups on the fused benzo rings display similar absorption patterns in DMSO (dashed lines) and are characterised by intense absorption bands at λ_{max} *ca.* 262 and 302 nm with comparable molar extinction coefficients (Fig. 14–17). The absorption spectra of bis-heterocycles **145c, 145f, 145i,** and **145l** bearing strong electron donating 4-methoxyphenyl groups on the fused benzo rings in DMSO, on the other hand, are characterized by broad intense bands at λ_{max} *ca.* 291 nm. Compounds **145a**–**l** showed blue shifts in acetic acid (solid lines) with phenyl- or 4-fluorophenyl-substituted derivatives displaying similar absorption patterns and their absorption spectra are characterized by two absorption maxima, one intense band in the regions λ_{max} 255–260 nm and one less intense band in the region λ_{max} 283–295 nm (Fig. 14–17). The less intense wavelength bands are presumed to be caused by hydrogen-bonding between the hydroxyl group of acetic acid and carbonyl groups of 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties. The 4-methoxyphenyl-

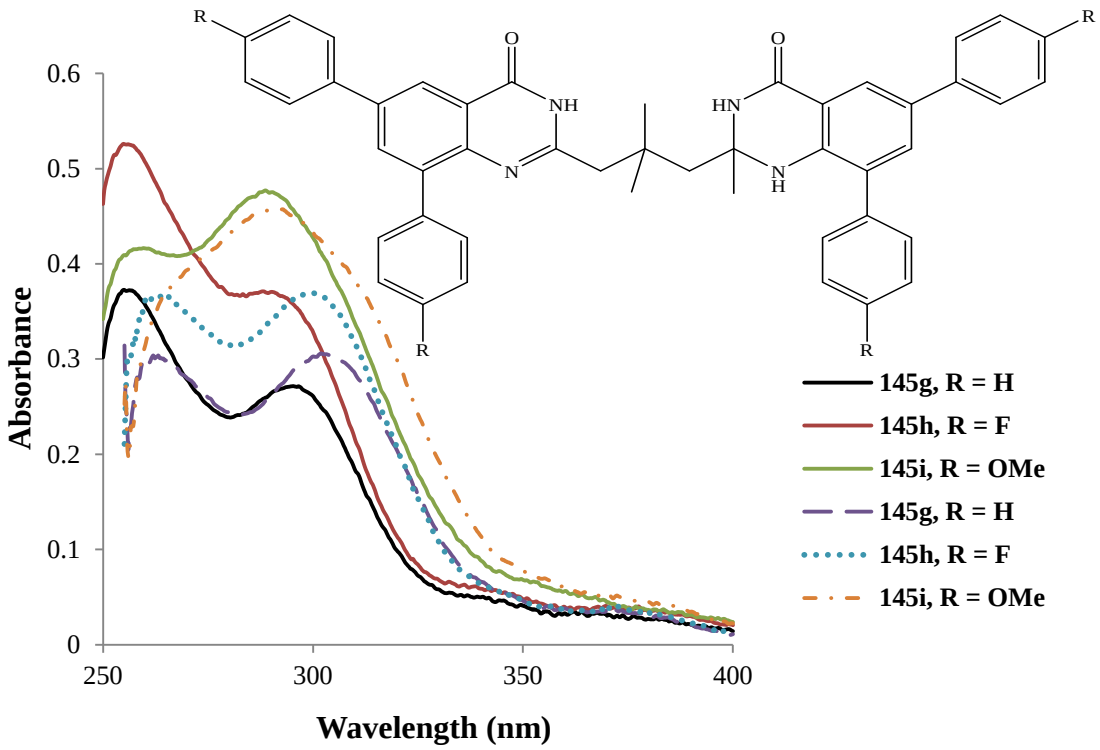
substituted derivatives **145c, 145f, 145i,** and **145l** in acetic acid are characterized by weak absorption bands at lower wavelength maxima and broad intense bands at higher wavelength maxima. The absorption bands at λ_{ab} *ca.* 302 nm in DMSO (dashed lines) and at λ_{ab} 283–295 nm in acetic acid (solid lines) are due to n–π* transition of the carbonyl fragments and to the π–π* transition caused by intramolecular charge transfer from phenyl ring and N═C–N fragment to carbonyl fragment in analogy with the literature assignments.[98] The observed broad absorption bands of the 6,8-bis(4-methoxyphenyl)-substituted bis-heterocycles **145c, 145f, 145i,** and **145l** in DMSO are presumably due to the overlap of the two absorption bands from π–π* transition from aryl substituents and from those of n–π* transition of the carbonyl fragments and the π–π* transition caused by intramolecular charge transfer from phenyl ring and N═C–N fragments to carbonyl fragment. The strong electron donating methoxyphenyl groups are presumed to cause bathochromic effect (red shift) of the π–π* transition from aryl substituents resulting in the overlap of the two bands. The observed weak wavelength bands at λ_{max} *ca.* 260 nm of 4-methoxyphenyl-substituted derivatives **145c, 145f, 145i,** and **145l** in acetic acid, on the other hand, are probably due to H-bonding from hydroxyl group of acetic acid with methoxy groups and therefore slightly causing the blue-shift of bands of π–π* transition from aryl substituents. The presence of electron-withdrawing fluoroaryl substituents was found to have little effect on shifting of the wavelength maxima. It was also observed that as the carbon chain joining the 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties becomes bulky, the molar extinction coefficients are reduced.



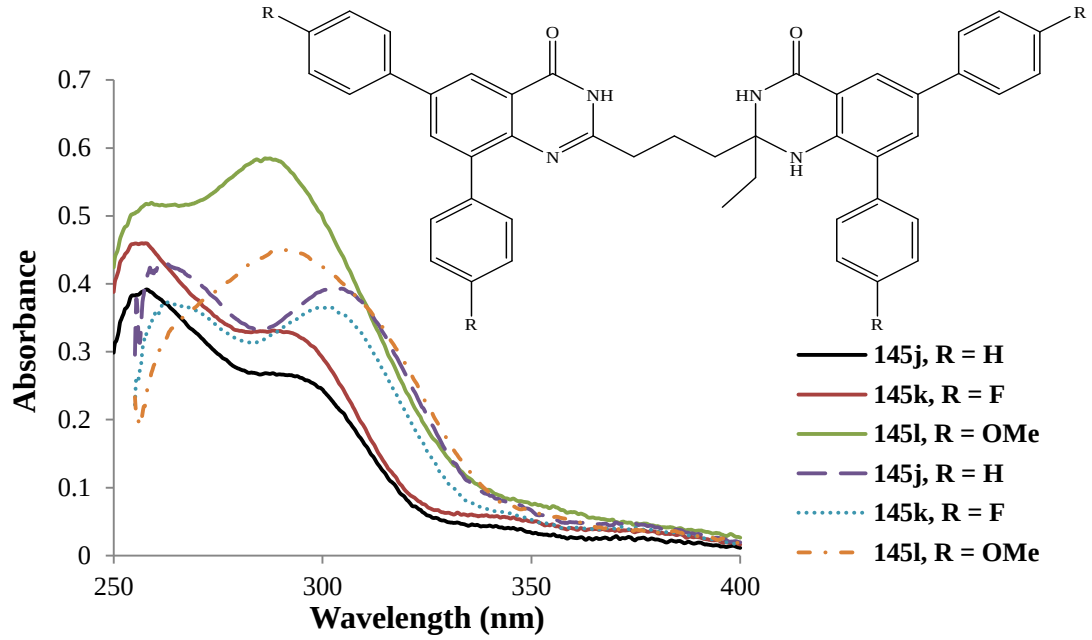
Figures 14: UV-Vis spectra of **145a-c** in DMSO (dashed lines) and CH_3CO_2H (solid lines) at rt. (conc. = 1 x 10^{-5} mol/L)



Figures 15: UV-Vis spectra of **145d-f** in DMSO (dashed lines) and CH_3CO_2H (solid lines) at rt. (conc. = 1 x 10^{-5} mol/L)



Figures 16: UV-Vis spectra of **145g-i** in DMSO (dashed lines) and CH_3CO_2H (solid lines) at rt. (conc. = 1 x 10^{-5} mol/L)



Figures 17: UV-Vis spectra of **145j-l** in DMSO (dashed lines) and CH_3CO_2H (solid lines) at rt. (conc. = 1 x 10^{-5} mol/L)

The observed electron absorption properties of compounds **144a–d** and **145a–l** prompted us to investigate their emission properties and the results are described below.

2.2.3 Emission properties of halogenated bis-heterocycles (144a-d) and polyaryl-substituted bis-heterocycles (145a–l)

The emission spectra of the halogenated bis-heterocycles **114a-d** acquired in DMSO (concentration = 1 x 10^{-5} M) revealed the presence of bands of negligible intensity. This effect is presumably due to the presence of heavy bromine atoms.[99] The analogous 8-benzyloxy-5,7-dibromoquinoline was reported to be non-fluorescent because its S_1 state is a π–σ* excited state, where the LUMO is a σ*-orbital localized at the C–Br bonds.[100] The photoluminescence spectra of the polyaryl-substituted bis-heterocycles **145a–l** were also acquired at room temperature in DMSO (dashed lines) and CH_3CO_2H (solid lines) at concentrations of 1 x 10^{-4} M and excitation wavelength λ_{ex} 370 nm (Figures 18–21). The emission spectra of compounds **145a–l** displayed similar emission profiles and their spectra are characterized by single emission bands in the region λ_{em} 430–450 nm in DMSO (dashed lines) and in the region λ_{em} 475–505 nm in CH_3CO_2H (solid lines). These bands are due to π–π* transition attributed to the conjugated quinazolinone scaffold. The emission spectra of compounds **145c, 145f, 145i and 145l** bearing the strong electron-donating 6,8-bis(4-methoxyphenyl)-substituted groups are slightly red shifted in both DMSO and CH_3CO_2H as compared to those bearing phenyl- (**145a, 145d, 145g, 145j**) or 4-fluorophenyl groups (**145b, 145e, 145h, 145k**). The observed slight red shift is presumably due to activating methoxy groups which donate electrons to the aryl groups. Compounds **145a–l** exhibit bathochromic shift and low intensity emission bands in CH_3CO_2H than in DMSO (Fig. 18–21). The observed red shift and the reduction in intensity of the emission bands are presumably the consequence of strong hydrogen-bonding between acetic acid and carbonyl groups of quinazolinone moieties, which

would reduce the electron density around carbonyl oxygens. This effect, in turn, would increase the Stokes shift and reduce the quantum yields values. As the carbon chain joining the 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties becomes bulky, the intensity of the emission bands decreases in DMSO (dashed lines), while in acetic acid (solid lines), the bulkiness of the carbon chain had no significant effect on the intensity of emission bands. Compounds **145g–i** with 2,2-dimethyl-substituted propyl groups were found to have reduced quantum yields as compared to compounds **145a–f** and **145j–l** which had comparable quantum yields with respect to the substituent on the aryl substituents.

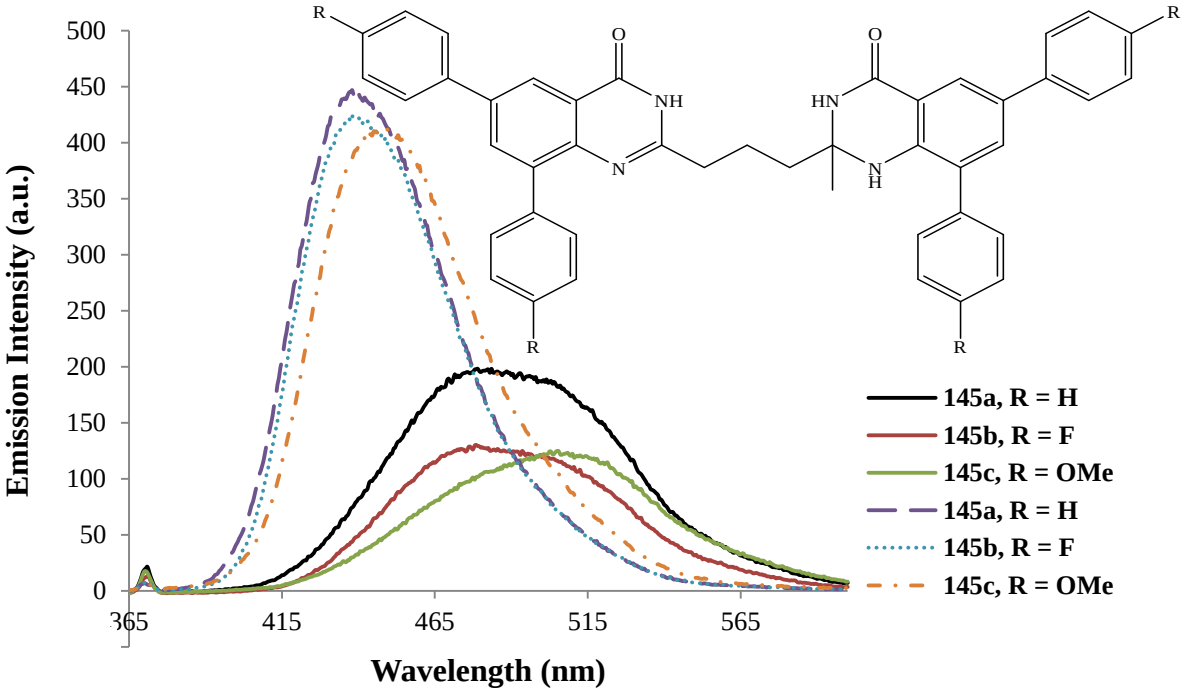


Figure 18: Emission spectra of **145a-c** in DMSO (dashed lines) and CH_3CO_2H (solid lines) at rt. (conc. = 1 x 10^{-4} mol/L)

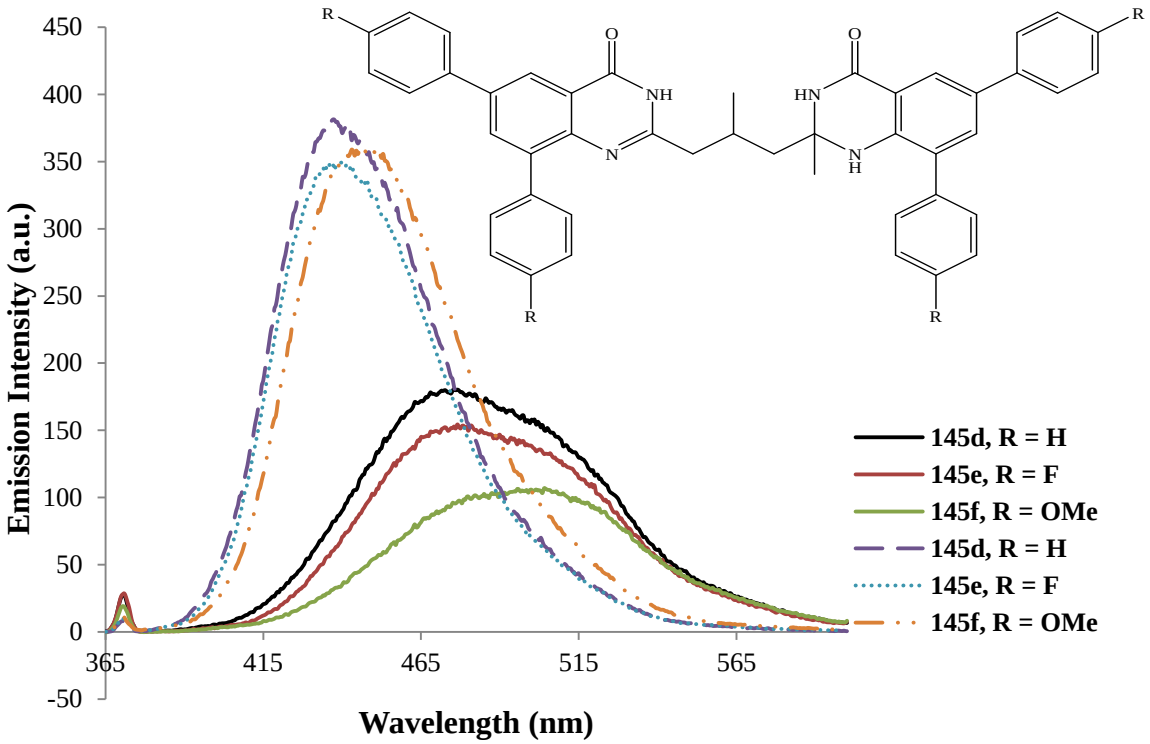


Figure 19: Emission spectra of **145d-f** in DMSO (dashed lines) and CH_3CO_2H (solid lines) at rt. (conc. = 1 x 10^{-4} mol/L)

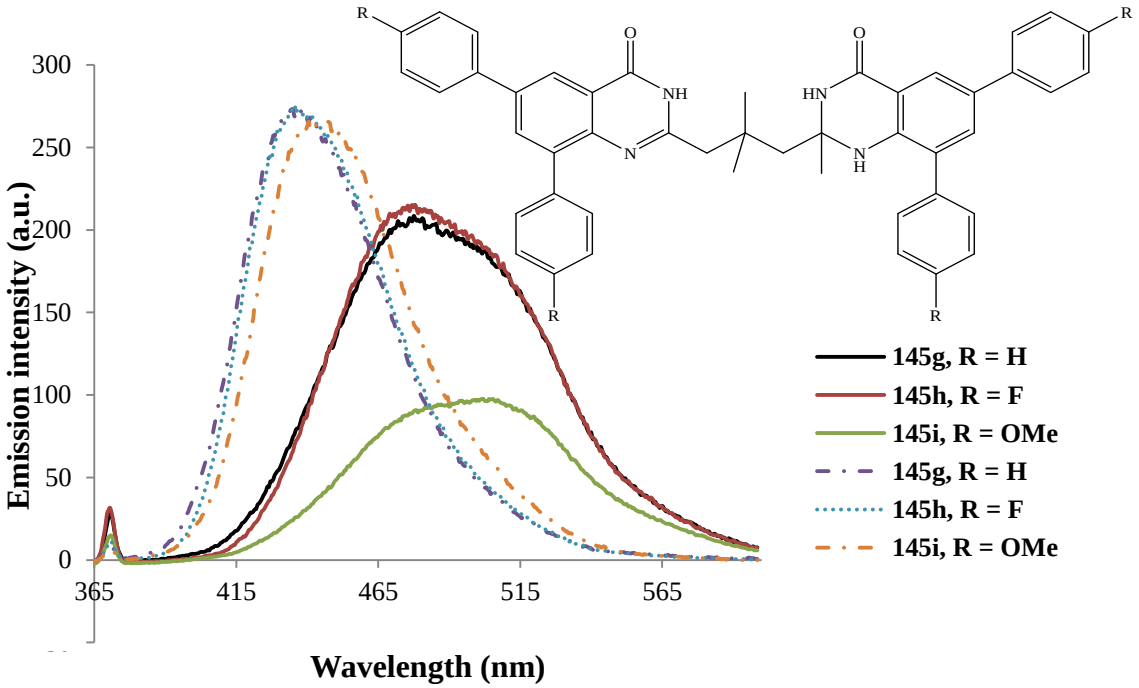


Figure 20: Emission spectra of **145g-i** in DMSO (dashed lines) and CH_3CO_2H (solid lines) at rt. (conc. = 1 x 10^{-4} mol/L)

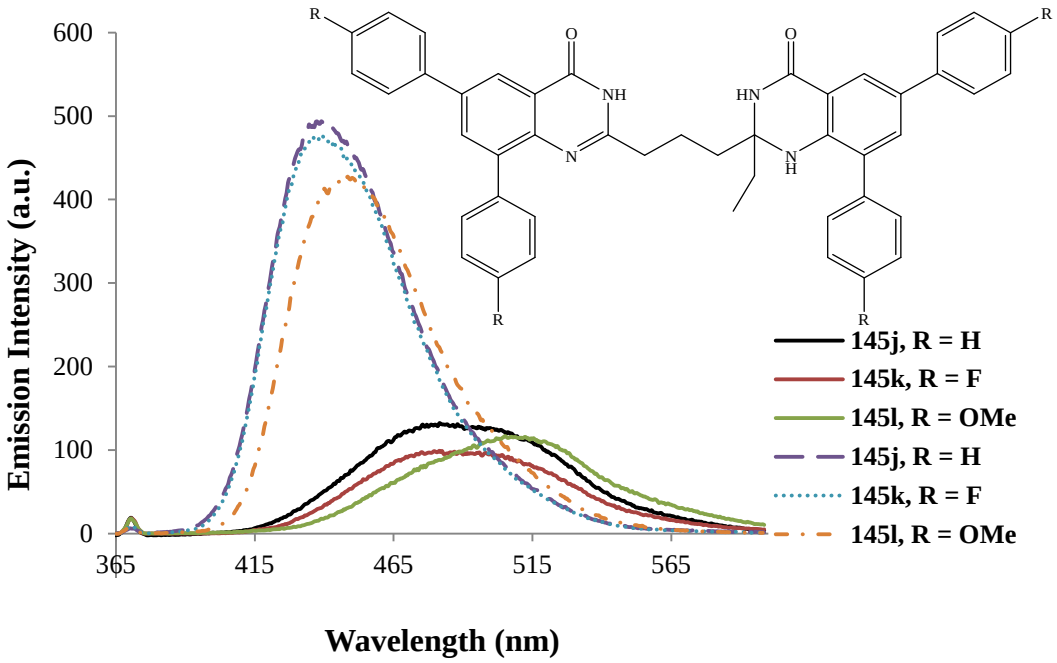


Figure 21: Emission spectra of **145j-l** in DMSO (dashed lines) and CH_3CO_2H (solid lines) at rt. (conc. = 1 $x10^{-4}$ mol/L)

Table 2: The absorption and emission data for compounds **145a–l**.

145	**λ_{max} (nm) DMSO**	**(ε) x 10^4 $M^{-1}cm^{-1}$ DMSO**	**λ_{max} (nm) CH_3CO_2H**	**(ε) x 10^4 $M^{-1}cm^{-1}$ CH_3CO_2H**	**λ_{em} (nm) DMSO**	**λ_{em} (nm) CH_3CO_2H**	**[a]Quantum yields (Φ) x 10^{-3} DMSO**	**[a]Quantum yields (Φ) x 10^{-3} CH_3CO_2H**	**Stokes shift DMSO**	**Stokes shift CH_3CO_2H**
145a	263.2	4.2	255.1	5.5	438.0	479.0	7.5	2.6	174.8	223.9
	302.5	4.2	292.3	3.7	438.0	479.0	7.5	3.8	135.5	186.7
145b	263.2	3.9	255.4	4.7	439.0	478.5	7.8	2.0	175.8	223.1
	300.1	3.6	283.6	3.4	439.0	478.5	8.3	2.7	138.9	194.9
145c	291.4	5.3	258.1	4.4	448.0	505.5	5.5	2.0	156.6	247.4
			288.1	5.2		505.5		1.7		217.4
145d	263.2	3.4	257.5	4.6	437.5	475.5	8.0	2.8	174.3	218.0
	302.5	3.2	292.3	3.2	437.5	475.5	8.4	4.1	135.0	183.2
145e	263.5	3.3	257.8	4.5	437.0	476.5	7.7	2.4	173.5	218.7
	300.4	3.2	288.4	3.3	437.0	476.5	7.8	3.3	136.6	188.1

145f	290.5	4.8	257.2	4.7	443.0	504.0	5.4	1.6	152.5	246.8
			285.1	5.2		504.0		1.5		218.9
145g	262.0	3.0	254.8	3.7	434.5	477.5	6.4	4.0	172.5	222.7
	304.0	3.0	295.3	2.7	434.5	477.5	6.4	5.5	130.5	182.2
145h	262.6	3.7	254.8	5.2	436.0	477.0	5.3	2.9	173.4	222.2
	300.1	3.7	288.1	3.7	436.0	477.0	5.3	4.2	135.9	188.9
145i	293.3	4.6	259.6	4.2	447.5	502.0	4.2	1.7	154.2	242.4
			288.7	4.8		502.0		1.5		213.3
145j	262.0	4.3	257.8	3.9	439.0	481.5	8.2	2.4	177.0	223.7
	303.4	3.9	293.8	2.6	439.0	481.5	9.0	3.6	135.6	187.7
145k	261.7	3.6	257.5	4.6	439.0	484.5	9.1	1.5	177.3	227.0
	302.2	3.6	291.4	3.3	439.0	484.5	9.3	2.1	136.8	193.1
145l	291.4	4.5	259.0	5.2	447.5	505.0	6.8	1.6	156.1	246.0
			286.3	5.8		505.0		1.4		218.7

[(a)]Obtained by calculation, based on the quinine sulfate in 1.0 N H_2SO_4 as the standard ($\Phi q = 0.55$).[101]

2.2.4 Quantum Chemical Calculations

We carried out a theoretical approach to establish the structural features and molecular orbitals of the bis-heterocycles **145a–l**, by means of density functional theory at the LC-BLYP/6-31+G(d,p)[102] level as implemented in Gaussian 09 suite.[103] The reasonable structures for the electronic structure computations were obtained from geometries optimized at the LC-BLYP/6- 31G(d,p) level in DMSO. The bulk solvent effects were included via the Polarisable Continuum Model (PCM), using the integral equation formalism variant (IEFPCM)[104] in DMSO. The computed spectral profiles of compounds **145c**, **145f** and **145k** in DMSO were chosen and their absorption spectra were reproduced at LC-BLYP level with three absorption peaks at λ_{ab} *ca*. 235, 260 and 300 nm (Figure 22). Compounds **145c**, **145f** and **145k** were chosen in order to reveal the effect of substituent on the *para* position of the 6- and 8-aryl groups and/ or the effect of substituent on propyl group on the electronic spectra. The experimental and computed wavelength maxima were found to be comparable to within an average error of ± 3 nm (Table 3). About 60% of the transfer band at λ *ca*. 300 nm can be attributed to an electronic transition from HOMO to LUMO+2 and approximately 20% is attributed to an electronic transition from HOMO-4 to LUMO+2. The electronic transitions from HOMO-1 to LUMO+1 (50%) and the other from HOMO-1 to LUMO (33%) give rise to absorption band at λ_{ab} *ca*. 260 nm. The computed ground- and excited-state dipole moments were inspected using LC-BLYP functional and they confirmed that the first singlet excited state is rather of more polar character than the ground state (Table 3). The dipole moments of the excited state are slightly larger than those of the ground state by one debye. Similar results were obtained for these compounds presumably due to the highly symmetric molecular structure.

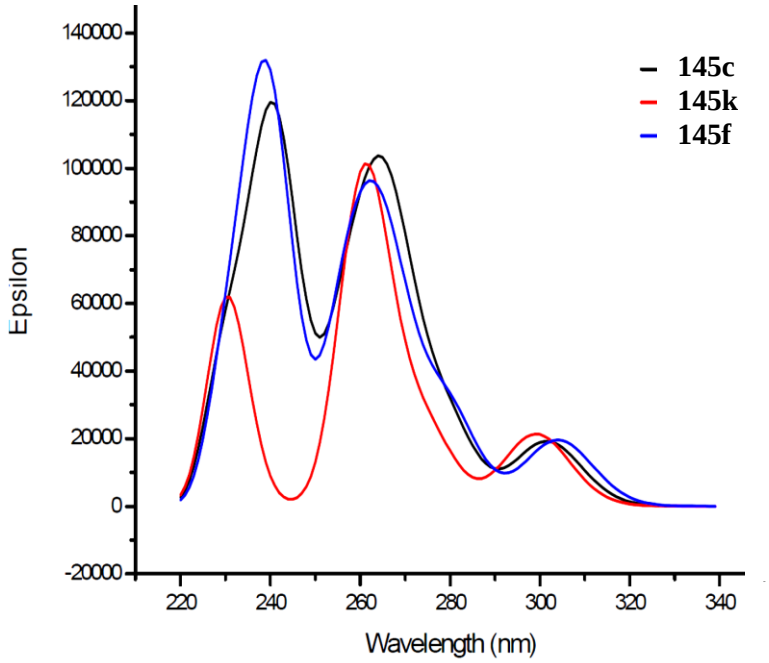


Figure 22. Computed absorption spectra of **145c**, **145f** and **145k**.

Table 3: The computed dipole moments and absorption spectra of compounds **415a–l**.

Compound	**$D_{ground\ (Debye)}$**	**$D_{excited\ (Debye)}$**	**$\lambda_{max\ (nm)}$**
145a	7.66	8.24	260, 299
145b	7.45	8.37	261, 300
145c	5.96	5.44	266, 301
145d	5.71	6.62	262, 301
145e	9.84	9.92	261, 300
145f	8.99	9.02	260, 304
145g	5.62	6.07	262, 299
145h	6.45	6.47	262, 298
145i	5.81	5.94	260, 297
145j	7.70	8.09	261, 299
145k	8.19	8.33	262, 299
145l	6.35	7.41	266, 301

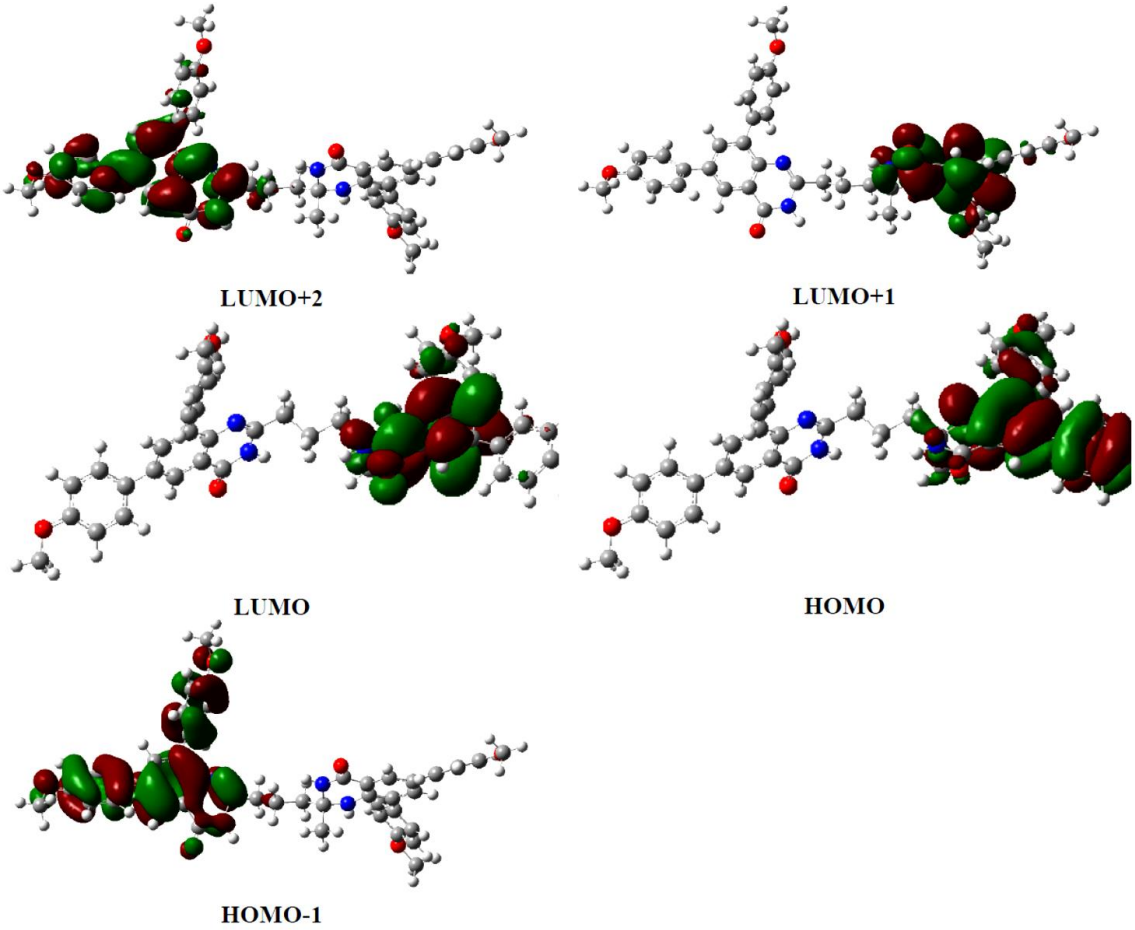


Figure 23: Orbital topology for **145c** as representative compound.

CHAPTER 3: CONCLUSIONS

Bromination of 2-aminobenzamide with 2.0 equiv. of *N*-bromosuccinimide afforded 2-amino-3,5-dibromobenzamide. The dibromination of 2-aminobenzamide is favoured by the combined *ortho-para* directing amino group and *meta* directing effect of the amide group. Iodine-promoted cyclisation of 2-amino-3,5-dibromobenzamide with 1,3-cyclohexanedione derivatives and subsequent *in situ* dehydrogenation of one the quinazolinone moieties to afford novel 6,8-dibromo-2-(3-(2´-alkyl-1´,2´,3´,4´-tetrahydro-6´,8´-dibromo-4´-oxoquinazoline-2yl)propyl)quinazolin-4(3*H*)-ones. Suzuki-Miyaura cross-coupling of the latter with phenylboronic acid, 4-fluorophenylboronic acid and 4-methoxyphenylboronic acid afforded the corresponding 2-(3-(2'-alkyl-1',2',3',4'-tetrahydro-4'-oxo-6',8'-diphenylquinazolin-2'-yl)propyl)-6,8-diphenylquinazolin-4(3*H*)-one derivatives without selectivity due to comparable C–Br bonds bond strengths. Our results demonstrate the importance of the 6,8-dibromo-2-(3-(2´-alkyl-1´,2´,3´,4´-tetrahydro-6´,8´-dibromo-4´-oxoquinazoline-2yl)propyl)quinazolin-4(3*H*)-ones as precursors for the synthesis of polycarbo-substituted bis-heterocycles with potential photophysical properties. From the preliminary electronic absorption and emission spectral property studies, it can be concluded that the resultant polyaryl-substituted bis-heterocycles **145a–l** have low fluorescent quantum yields and therefore do not represent potential fluorophores. The results of this investigation have since been published as a full paper.[105]

Future research extending from this investigation in order to enhance the photophysical and/ or biological activities of the resultant bis-heterocycles is expected to include the following:

- Application of other metal-catalysed cross-coupling reactions such as Sonoghashira, or Heck cross-coupling of the 6,8-dibromo-2-(3-(2´-alkyl-1´,2´,3´,4´-tetrahydro-6´,8´-

dibromo-4´-oxoquinazoline-2yl)propyl)quinazolin-4(3*H*)-ones to afford corresponding polyalkynyl or polyvinyl bis-heterocycles

- *N*(3)-alkylation, acylation, or arylation of the bis-heterocycles to afford the corresponding *N*(3) alkylated, acylated, or arylated bis-heterocycles .
- Complete aromatisation of quinazolin-4(3*H*)-one by introducing chlorine atom on the *C*–4 position and subsequent amination with primary amines or metal-catalyzed cross-coupling to form bis-heterocyclic compounds consisting of both 4-substituted quinazoline and 2,3-dihydroquinazolin-4(1*H*)-one moieties.
- Screening the resultant compounds for potential photophysical properties and/ or biological properties.

CHAPTER 4: EXPERIMENTAL

4.1 General

Solvents and commercially available reagents were used as were supplied or purified by conventional methods before use. All methods used were standard to synthetic chemistry and all compounds were synthesised in glass flasks, then subjected to the appropriate purification technique, such as, chromatography on silica supports, and recrystallization. Thin layer chromatography was carried out on silica gel plates, Merck silica gel 60 F254, as stationary phase. All air and moisture sensitive reactions were carried out in heat dried glassware under inert gas (argon or nitrogen) atmosphere. All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded as powders using a Bruker VERTEX 70 FT-IR Spectrometer with a diamond ATR (attenuated total reflectance) accessory by using the thin-film method. The UV-vis spectra were recorded on a Cecil CE 9500 (9000 Series) UV-Vis spectrometer while emission spectra were taken using a Perkin Elmer LS 55 fluorescence spectrometer. The quantum efficiencies of fluorescence (Φx) were obtained with the following equation:

$$\Phi x = \Phi st*(Fx/Fst)*(Ast/Ax)*(nx^2/nst^2)$$

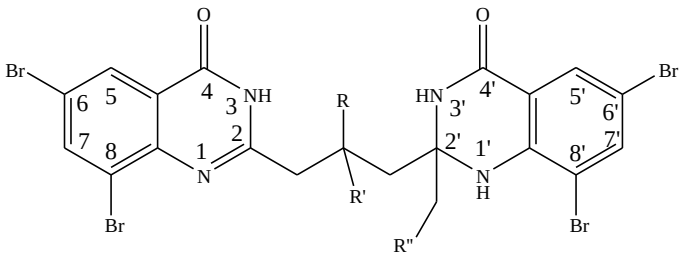
F denotes the area under the fluorescence band (*F* = a*I*fl(λ), where *I*fl(λ) is the fluorescence intensity at each emission wavelength), A denotes the absorbance at the excitation wavelength, and *n* is the refractive index of the solvent.[20] ^{1}H NMR spectra were obtained on a varian mercury 300 MHz NMR spectrometer using DMSO-d_6 as solvents. The chemical shifts (δ) are recorded as parts per million (ppm) and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). Coupling constant *J* values are in hertz (Hz). Low- and high-resolution mass spectra were recorded at the University of

Stellenbosch Mass Spectrometry Unit using Synapt G2 Quadrupole Time-of-flight mass spectrometer.

4.2 Preparation of 2-amino-3, 5-dibromobenzamide 142

A stirred solution of 2-aminobenzamide **17** (5.00 g, 36.75 mmol) in acetic acid was treated with *N*-bromosuccinimide (14.39 g, 80.84 mmol). The mixture was stirred at room temperature for 3 hours. The reaction was quenched by addition of cold water and the precipitate obtained was filtered and washed with warm ethanol to afford **82** (8.41 g, 78%); m.p. 211–215 °C (Lit. 216–217 ºC);[70] ^{1}H NMR (DMSO-d_6, 300 MHz): δ_H 6.79 (2H, s, NH_2), 7.46 (1H, s, NH_2), 7.73 (1H, d, *J* 2.4 Hz, ArH), 7.78 (1H, d, *J* 2.1 Hz, ArH), 8.050 (1H, s, NH_2)

4.3 Preparation of 6, 8-dibromo-2-(3-(2'-alkyl- 6', 8'-dibromo-1', 2', 3', 4'-tetrahydro-4'-oxoquinazoline-2'yl)propyl)quinazolin-4(3*H*)-one derivatives (144a–d)



144a–d

4.3.1 Preparation of 6,8-dibromo-2-(3-(6',8'-dibromo-1',2',3',4'-tetrahydro-2'-methyl-4'-oxoquinazolin-2'-yl)propyl)quinazolin-4(3*H*)-one (144a)

A mixture of 2-amino-3,5-dibromobenzamide **142** (1.10 g, 3.74 mmol), 1,3-cyclohexanedione **143a** (0.19 g, 1.70 mmol), and iodine (0.13 g, 0.51 mmol) in refluxing toluene was stirred for 5 hours. The progress of the reaction was monitored by TLC (ethyl acetate/n-hexane). After the completion of the reaction, toluene was evaporated under reduced pressure and the solid obtained was purified by recrystallization from ethanol to afford **144a** as solid (0.96 g, 85%); m.p. 286–290 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ_H 1.44 (3H, s, CH_3), 1.70–1.91 (4H, m, 4H, 2 x CH_2), 2.41 (2H, d, J 4.8 Hz, CH_2), 6.24 (1H, s, NH), 7.65 (1H, s, ArH), 7.69 (1H, s, ArH), 8.14 (1H, s, ArH), 8.29 (1H, s, ArH), 8.37 (1H, s, NH), 12.57 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ_C 21.76, 28.27, 34.84, 70.23 (2 x C), 107.59, 108.66, 117.19, 118.47, 123.48, 123.91 128.13, 129.57, 138.17, 139.86, 143.83, 145.95, 159.36, 160.80, 161.22; ν_{max} (neat)/cm^{-1} 3379, 3196, 3056, 1669, 1600, 1464, 1386, 1253, 1075, 897, 808, 760, 697, 619; m/z (100, MH^+) 656; HRMS (ES): MH^+, found: 664.8046. $C_{20}H_{17}Br_4N_4O_2^+$ requires: 664.8044.

4.3.2 Preparation of 6,8-dibromo-2-(3-(1',2',3',4'-tetrahydro-6',8'-dibromo-2'-methyl-4'-oxoquinazoline-2'-yl)2-methylpropyl)quinazoline-4(3*H*)-one (144b)

2-Amino-3,5-dibromobenzamide **142** (1.10 g; 3.74 mmol) was reacted with 5-methyl-1,3-cyclohexanedione **143b** (0.215 g; 1.70 mmol), and iodine (0.13 g; 0.51 mmol) in refluxing toluene for 12 hours. Solvent evaporation and recrystallization from ethanol afforded **144b** as a solid (0.96 g, 83%); m.p. 312–314 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ_H 1.03 (3H, d, J 7.8 Hz, CH_3), 1.45 (H, s, 3 x CH_3), 1.54–1.62 (1H, q, CH), 2.39–2.50 (4H, m, 2 x CH_2), 6.23

(1H, s, NH), 7.29 (1H, s, ArH), 7.59 (1H, s, ArH), 8.12 (1H, s, ArH), 8.25 (1H, s, ArH), 8.34 (1H, s, NH), 12.52 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ_C 22.66, 28.04, 28.39, 43.16, 46.04, 70.19, 107.55, 108.40, 117.19, 118.47, 123.45, 123.78, 128.03, 129.65, 137.62, 139.90, 143.17, 145.73, 158.37, 160.78, 161.22; ν_{max} (neat)/cm^{-1} 3389, 3177, 1673, 1614, 1597, 1560, 1488, 1445, 1364, 1344, 1225, 1133, 1017, 939, 875, 737, 681, 626; m/z (100, MH^+) 679; HRMS (ES): MH^+, found: 678.8203. $C_{21}H_{19}Br_4N_4O_2^+$ requires: 678.8201.

4.3.3 Preparation of 6,8-dibromo-2-(3-(1',2',3',4'-tetrahydro-6',8'-dibromo-2'-methyl-4'-oxoquinazoline-2'-yl)2,2-dimethylpropyl)quinazoline-4(3*H*)-one (144c)

2-Amino-3, 5-dibromobenzamide **142** (1.10 g, 3.74 mmol) was reacted with 5,5-dimethyl-1,3-cyclohexanedione **143c** (0.24 g, 1.70 mmol), and iodine (0.13 g, 0.51 mmol) in refluxing toluene for 24 hours. After the work-up and recrystallization from ethanol, **144c** was afforded as solid (0.74 g, 63%); m.p. 315–318 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz): δ_H 1.04 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.79 (1H, d, *J* 15.3 Hz, CH_2), 2.28 (1H d, *J* 15.3 Hz, , CH_2), 2.65 (1H, d, *J* 13.8 Hz, CH_2), 3.04 (1H, d, *J* 13.5 Hz, CH_2), 6.68 (1H, s, NH), 7.63 (1H, s, ArH), 7.71 (1H, s, ArH), 8.18 (1H, s, ArH), 8.34 (1H, s, ArH), 8.45 (1H, s, NH), 12.64 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ_C 29.07, 30.07, 32.08, 35.08, 44.73, 46.53, 71.02, 107.26, 108.57, 116.39, 118.76, 123.09, 123.91, 128.23, 129.53, 138.23, 140.07, 143.33, 145.49, 158.34, 160.61, 160.91; ν_{max} (neat)/cm^{-1} 3397, 3167, 3053, 1685, 1655, 1606, 1491, 1464, 1440, 1318, 1250, 1214, 1028, 894, 794, 758, 696, 642, 612; m/z (100, MH^+) 693; HRMS (ES): MH^+, found: 692.8359. $C_{22}H_{21}Br_4N_4O_2^+$ requires: 692.8357.

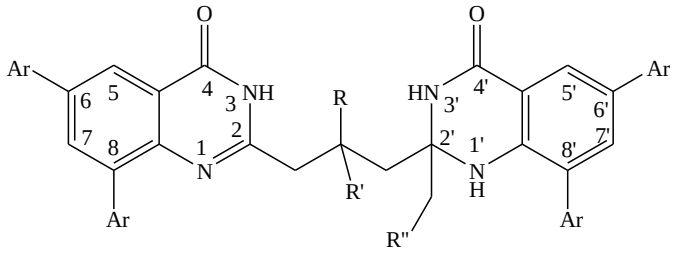
4.3.4 Preparation of 6,8-dibromo-2-(3-(1',2',3',4'-tetrahydro-6',8'-dibromo-2'-ethyl-4'-oxoquinazoline-2'-yl)propyl)quinazoline-4(3*H*)-one (144d)

A mixture of 2-amino-3,5-dibromobenzamide **142** (1.10 g, 3.74 mmol), 2-methyl-1,3-cyclohexanedione **143d** (0.22 g, 1.70 mmol), and iodine (0.13 g, 0.51 mmol) in refluxing toluene was stirred at 110º C for 24 hours. After the work-up and recrystallization from ethanol, **144d** was afforded as a solid (0.69 g, 60%); m.p. 307–310 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz): δ_H 0.83 (3H, t, *J* 6 Hz, CH_3), 1.57–1.92 (6H, m, 3 x CH_2), 2.59–2.60 (2H, m, CH_2), 6.05 (1H, s, NH), 7.63 (1H, s, ArH), 7.67 (1H, s, ArH), 8.130 (1H, s, ArH), 8.22 (1H, s, NH), 8.28 (1H, s, ArH), 12.56 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ_C 8.31, 21.43, 33.43, 34.89, 73.11 (2 x C), 106.97, 108.10, 116.54, 118.47, 123.47, 123.94, 128.14, 129.42, 138.15, 139.87, 144.25, 145.97, 159.41, 160.82, 161.39; ν_{max} (neat)/cm^{-1} 3389.38, 3178, 1673, 1614, 1489, 1445, 1363, 1344, 1259, 1225, 1133, 1017, 939, 870, 780, 737, 681, 626; m/z (100, MH^+) 679; HRMS (ES): MH^+, found: 678.8203. $C_{21}H_{19}Br_4N_4O_2^+$ requires: 678.8201.

4.4 Preparation of 2-(3-(2'-alkyl-1',2',3',4'-tetrahydro-4'-oxo-6',8'-diphenylquinazolin-2'-yl)propyl)-6,8-diphenylquinazolin-4(3*H*)-one derivatives (145a–l)

A stirred mixture of **144** (1.0 mmol), arylboronic acid (5.0 equiv.), K_2CO_3 (4.0 equiv.), $PdCl_2(PPh_3)_2$ (10% of **144**), PCy_3 (20% of **144**) in dioxane-water (3:1, v/v) was placed in a two-necked flask with a stirrer bar, rubber septum, and a condenser. The mixture was flushed with N_2 gas for five minutes and a balloon filled with N_2 gas was connected on top of the condenser. The mixture was heated under stirring for four hours. The progress of the reaction was monitored by tlc (methanol:ethyl acetate). After the completion of the reaction, the mixture was cooled to room temperature and then quenched with ice-cold water. The mixture

was filtered and the solid obtained was dried and recrystallized from 20% ethyl acetate/hexane to afford **145a**–**l**.



145a–l

The following products were prepared in this fashion:

4.4.1 Preparation of 2-(3-(1',2',3',4'-tetrahydro-2'-methyl-4'-oxo-6',8'-diphenylquinazolin-2'-yl)propyl)-6,8-diphenylquinazolin-4(3*H*)-one (145a)

A mixture of **144a** (0.50 g, 0.75 mmol), phenylboronic acid (0.50 g, 3.77 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mol), PCy_3 (0.04 g; 0.15 mmol) and K_2CO_3 (0.42 g; 3.01 mmol) in dioxane-water (40 mL) afforded **145a** as a solid (0.39 g, 80%); mp. 203–206 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.37 (s, 3H), 1.69–1.84 (m, 4H), 2.55 (s, 2H), 5.62 (s, 1H), 7.25–7.52 (m, 15H), 7.61 (d, *J* 7.8 Hz, 2H), 7.68 (d, *J* 7.5 Hz, 2H), 7.80 (d, *J* 7.5 Hz, 2H), 7.95 (s, 1H), 8.02 (s, 1H), 8.18 (s, 1H), 8.33 (s, 1H), 12.33 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 27.0, 33.2 (2 × C), 39.9, 74.9, 120.5, 127.5, 128.0, 130.1, 131.2, 132.0, 132.2, 132.4, 132.7, 133.0, 133.1, 133.4, 134.1, 134.3, 134.4 (2 × C), 134.5, 134.6, 136.1, 138.3, 138.8, 142.8, 143.2, 143.8, 144.3, 144.5, 145.1, 148.5, 150.8, 162.1, 167.6, 168.3; ν_{max} (neat) cm^{-1} 3389, 3178, 1673, 1614, 1560, 1488, 1445, 1364, 1344, 1259, 1225, 1133, 1017, 939, 875, 737, 681; m/z (100, MH^+) 653; HRMS (ES): MH^+, found: 653.2914. $C_{44}H_{37}N_4O_2^+$ requires: 653.2917.

4.4.2 Preparation of 2-(3-(6',8'-bis(4-fluorophenyl)-1',2',3',4'-tetrahydro-2'-methyl-4'-oxoquinazolin-2'-yl)propyl)-6,8-bis(4-fluorophenyl)quinazolin-4(3*H*)-one (145b)

A mixture of **144a** (0.50 g, 0.75 mmol), 4-fluorophenylboronic acid (0.53 g, 3.77 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), PCy_3 (0.04 g; 0.15 mmol) and K_2CO_3 (0.42 g; 3.01 mmol) in dioxane-water (40 mL) afforded **145b** as a solid (0.44 g, 81%); mp. 241–243 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.36 (s, 3H), 1.64–1.80 (m, 4H), 2.50–2.54 (m, 2H), 5.70 (s, 1H), 7.17–7.35 (m, 7H), 7.40 (d, *J* 3.0 Hz, 1H), 7.47 (dd, *J* 6.0 and 6.9 Hz, 2H), 7.62 (dd, *J* 8.4 and 4.8 Hz, 2H), 7.74 (dd, *J* 8.4 and 4.8 Hz, 2H), 7.84–7.89 (m, 4H), 8.02 (s, 1H), 8.16 (s, 1H), 8.29–8.30 (d, *J* = 3.0 Hz, 1H), 12.34 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.9, 28.3 (2 × C), 34.8, 69.9, 114.9 (d, $^2J_{CF}$ 21.0 Hz), 115.4, 116.1 (d, $^2J_{CF}$ 21.4 Hz), 116.3 (d, $^2J_{CF}$ 21.1 Hz), 116.4 (d, $^2J_{CF}$ 21.3 Hz), 122.4, 123.0, 125.1, 127.1, 128.0, 128.1 (d, $^3J_{CF}$ 8.3 Hz), 129.5 (d, $^3J_{CF}$ 7.9 Hz), 131.5 (d, $^3J_{CF}$ 8.3 Hz), 133.0 (d, $^3J_{CF}$ 7.9 Hz), 133.3, 133.7, 134.5 (d, $^4J_{CF}$ 3.2 Hz), 135.0 (d, $^4J_{CF}$ 3.2 Hz), 135.9 (d, $^4J_{CF}$ 3.2 Hz), 136.6 (d, $^4J_{CF}$ 2.9 Hz), 136.8, 138.1, 143.6, 145.6, 157.2, 160.5, 161.7 (d, $^1J_{CF}$ 241.1 Hz), 162.2 (d, $^1J_{CF}$ 242.2 Hz, 2 × C), 162.7 (d, $^1J_{CF}$ 243.6 Hz), 162.5, 163.3; ν_{max} (neat) cm^{-1} 3409, 3180, 3043, 1685, 1653, 1623, 1608, 1508, 1480, 1465, 1225, 1158, 905, 824, 557; m/z (100, MH^+) 725; HRMS (ES): MH^+, found: 725.2546. $C_{44}H_{33}F_4N_4O_2^+$ requires: 725.2540.

4.4.3 Preparation of 2-(3-(1',2',3',4'-tetrahydro-6',8'-bis(4-methoxyphenyl)-2'-methyl-4'-oxoquinazolin-2'-yl)propyl)-6,8-bis(4-methoxyphenyl)quinazolin-4(3*H*)-one (145c)

A mixture of **144a** (0.50 g, 0.75 mmol), 4-methoxyphenylboronic acid (0.57 g, 3.77 mmol), $PdCl_2(PPh_3)_2$ (0.054 g, 0.07 mmol), PCy_3 (0.04 g; 0.15 mmol) and K_2CO_3

(0.42 g; 3.01 mmol) in dioxane-water (40 mL) afforded **145c** as a solid (0.43 g, 74%); mp. 181–184 ºC; ^{1}H NMR (300 MHz, DMSO-*d*6): δ_H 1.32 (s, 3H), 1.62–1.78 (m, 4H), 2.46 (s, 2H), 5.47 (s, 1H), 3.72 (s, 2H), 3.73 (s, 3H), 3.78 (s, 3H), 6.90 (d, *J* 3.0 Hz, 2H), 6.90–6.96 (m, 6H), 7.03 (d, *J* 9.3 Hz, 2H), 7.34 (d, *J* 7.5 Hz, 2H), 7.48 (d, *J* 7.8 Hz, 2H), 7.61 (d, *J* 7.8 Hz, 2H), 7.71 (d, *J* 9.0 Hz, 2H), 7.80 (s, 1H), 7.92 (s, 1H), 8.10 (s, 1H), 8.20 (s, 1H), 12.24 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 28.2 (2 × C), 34.8, 55.4, 55.5, 55.6, 55.7, 66.9, 69.8, 113.6, 114.8, 114.9, 115.0, 115.4, 121.7, 122.5, 124.2, 126.7, 127.3, 127.7, 127.8, 128.3 128.5, 129.0, 130.4, 130.5, 131.2, 131.9, 132.2, 132.7, 133.0, 137.5, 138.8, 143.2, 145.2, 156.5, 158.7, 159.1, 159.7, 162.7, 163.5; ν_{max} (neat) cm^{-1} 3376, 3195, 2933, 1668, 1607, 1513, 1462, 1379, 1287, 1254, 1177, 1028, 1109, 9345, 824, 792; m/z (100, MH^+) 773; HRMS (ES): MH^+, found: 773.3356. $C_{48}H_{45}N_4O_6^+$ requires: 773.3339.

4.4.4 Preparation of 2-(3-(1',2',3',4'-tetrahydro-2'-methyl-4'-oxo-6',8'-diphenylquinazolin-2'-yl)2-methylpropyl)-6,8-diphenylquinazolin-4(3*H*)-one (145d)

A mixture of **144b** (0.50 g, 0.74 mmol), phenylboronic acid (0.45 g, 3.69 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), PCy_3 (0.04 g, 0.15 mmol) and K_2CO_3 (0.41 g, 2.95 mmol) in dioxane-water (40 mL) afforded **145d** as a solid (0.37 g, 75%); mp. 211–215 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.00 (d, *J* 4.5 Hz, 3H), 1.35 (s, 3H), 1.69–1.82 (m, 2H), 2.32–2.55 (m, 3H), 5.62 (s, 1H), 7.26–7.53 (m, 15H), 7.61 (d, *J* 7.8 Hz, 2H), 7.68 (d, *J* 6.0 Hz, 2H), 7.79 (d, *J* 6.3, 2H), 7.96 (s, 1H), 8.01 (s, 1H), 8.16 (s, 1H), 8.32 (s, 1H), 12.26 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.8, 28.4 (2 × C), 43.2, 46.1, 70.1, 115.7, 122.5, 123.0, 125.1, 126.2, 127.0, 127.4 (2 × C), 127.6, 128.0, 128.1, 128.3, 128.4, 129.3, 129.4 (2 × C), 129.6, 131.0, 133.2, 133.8, 137.8, 138.2, 138.9, 139.4, 139.5, 140.1, 143.4, 145.8, 156.2, 162.6,

163.5 ; ν_{max} (neat) cm^{-1} 3397, 3167, 1685, 1655, 1606, 1491, 1464, 1388, 1318, 1250, 1195, 1028, 894, 758, 696; m/z (100, MH^+) 668; HRMS (ES): MH^+, found: 667.3065. $C_{45}H_{39}N_4O_2^+$ requires: 667.3073.

4.4.5 Preparation of 2-(3-(6',8'-bis(4-fluorophenyl)-1',2',3',4'-tetrahydro-2'-methyl-4'-oxoquinazolin-2'-yl)-2-methylpropyl)-6,8-bis(4-fluorophenyl)quinazolin-4(3*H*)-one (145e)

A mixture of **144b** (0.50 g, 0.74 mmol), 4-fluorophenylboronic acid (0.52 g, 3.69 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), PCy_3 (0.04 g, 0.15 mmol) and K_2CO_3 (0.41 g, 2.95 mmol) in dioxane-water (40 mL) afforded **145e** as a solid (0.38 g, 70%); mp. 265–268 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.99 (d, *J* 6.3 Hz, 3H), 1.33 (s, 3H), 1.63–1.84 (m, 2H), 2.34–2.43 (m, 3H), 5.76 (s, 1H), 7.11–7.24 (m, 5H), 7.29–7.38 (m, 3H), 7.44 (dd, *J* 6.3 and 8.4 Hz, 2H), 7.62 (dd, *J* 6.3 and 8.4 Hz, 2H), 7.73 (dd, *J* 6.0 and 9.3 Hz, 3H), 7.84 (dd, *J* 6.0 and 8.5 Hz, 2H), 7.89 (d, *J* 3.0 Hz, 1H) 8.15 (s, 1H), 8.23 (s, 1H), (s, 1H), 12.27 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 22.1, 28.4 (2 × C), 46.6, 70.1, 114.8 (d, $^2J_{CF}$ 21.1 Hz), 115.8, 116.1 (d, $^2J_{CF}$ 21.4 Hz), 116.2 (d, $^2J_{CF}$ 21.0 Hz), 116.3 (d, $^2J_{CF}$ 21.1 Hz), 122.3, 123.3, 125.1, 127.4, 128.1 (2 × C), 128.2 (d, $^3J_{CF}$ 7.7 Hz), 129.2 (d, $^3J_{CF}$ 8.3 Hz), 131.5 (d, $^3J_{CF}$ 7.9 Hz), 132.1, 132.9 (d, $^3J_{CF}$ 7.9 Hz), 133.1, 134.4 (d, $^4J_{CF}$ 2.9 Hz), 134.8, 135.8 (d, $^4J_{CF}$ 2.9 Hz), 136.6 (d, $^4J_{CF}$ 3.1 Hz), 136.7 (d, $^4J_{CF}$ 3.1 Hz), 137.1, 143.6 (2 × C), 147.2, 161.8 (d, $^1J_{CF}$ 239.6 Hz), 161.9 (d, $^1J_{CF}$ 242.2 Hz), 162.1 (d, $^1J_{CF}$ 241.0 Hz), 162.4 (d, $^1J_{CF}$ 242.8 Hz), 163.4 (2 × C); ν_{max} (neat) cm^{-1} 3409, 3178, 3042, 1692, 1655, 1608, 1507, 1467, 1227, 1158, 1096, 1012, 907, 821, 558; m/z (100, MH^+) 739; HRMS (ES): MH^+, found: 739.2703. $C_{45}H_{35}F_4N_4O_2^+$ requires: 739.2696.

4.4.6 Preparation of 2-(3-(1',2',3',4'-tetrahydro-6',8'-bis(4-methoxyphenyl)-2'-methyl-4'-oxoquinazolin-2-yl)-2'-methylpropyl)-6,8-bis(4-methoxyphenyl)quinazolin-4(3*H*)-one (145f)

A mixture of **144b** (0.50 g, 0.74 mmol), 4-methoxyphenylboronic acid (0.56 g, 3.69 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), PCy_3 (0.04 g, 0.15 mmol) and K_2CO_3 (0.41 g, 2.95 mmol) in dioxane-water (40 mL) afforded **145f** as a solid (0.42 g, 73%); mp. 194–196 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.97 (d, *J* 6.3 Hz, 3H), 1.35 (s, 3H), 1.67–1.81 (m, 2H), 2.35–2.41 (m, 3H), 3.71 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 5.50 (s, 1H), 6.94 (t, *J* 7.5 Hz, 3 × 2H), 7.05 (d, *J* 9.0 Hz, 2H), 7.32–7.34 (m, 3H), 7.51 (d, *J* 7.5, 2H), 7.63 (d, *J* 7.5 Hz, 2H), 7.73 (d, *J* 7.8 Hz, 2H), 7.85 (s, 1H), 7.94 (s, 1H), 8.13 (s, 1H), 8.22 (s, 1H), 12.18 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.8, 28.2 (2 × C), 43.1, 46.2, 55.4, 55.5, 55.6, 55.7, 70.0, 113.6, 114.8 (2 × C), 115.0, 115.7, 121.7, 122.4, 124.1, 127.3, 128.1, 128.5, 129.1, 130.3, 130.5, 131.1, 131.9, 132.2 (2 × C), 132,7, 133.0, 137.5, 138.9, 142.9, 145.2, 155.6, 158.7, 159.0 (2 × C), 159.7, 162.6, 163.7; ν_{max} (neat) cm^{-1} 33946, 3158.7, 2834, 1677, 1607, 1512, 1463, 1285, 1244, 1178, 1030, 828; m/z (100, MH^+) 787; HRMS (ES): MH^+, found: 787.3502. $C_{49}H_{47}N_4O_6^+$ requires: 787.3496.

4.4.7 Preparation of 2-(3-(1',2',3',4'-tetrahydro-2'-methyl-4'-oxo-6',8'-diphenylquinazolin-2'-yl)2,2-dimethylpropyl)-6,8-diphenylquinazolin-4(3*H*)-one (145g)

A mixture of **144c** (0.50 g, 0.72 mmol), phenylboronic acid (0.44 g, 3.62 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), PCy_3 (0.04 g, 0.15 mmol) and K_2CO_3 (0.40 g, 2.89 mmol) in dioxane-water (40 mL) afforded **145g** as a solid (0.37 g, 76%); mp. 289–292 ºC; ^{1}H NMR

(300 MHz, DMSO-d_6): δ_H 0.89 (s, 3H), 1.02 (s, 3H), 1.11 (s, 3H) 1.55 (d, *J* 15.0 Hz, 1H), 2.10 (d, *J* 13.8 Hz, 1H), 2.64 (d, *J* 15.3 Hz, 1H), 2.97 (d, *J* 13.5 Hz, 1H), 5.26 (s, 1H), 7.08 (t, *J* 7.8 Hz, 2H) 7.22–7.45 (m, 13H), 7.52 (t, *J* 7.5 Hz, 2H), 7.61 (d, *J* 7.8 Hz, 2H), 7.84 (d, *J* 7.8 Hz, 2H), 7.93 (d, *J* 6.0 Hz, 2H), 7.99 (s, 1H), 8.36 (s, 1H) 12.27 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 29.7, 29.9, 31.0, 35.0, 45.2, 46.6, 56.6, 70.6, 115.1, 122.4, 123.1, 125.1, 126.2, 127.0, 127.2, 127.4, 127.7, 127.8, 127.9, 128.1, 128.4, 129.0, 129.1, 129.4, 129.7, 130.6, 133.2, 134.1, 137.8, 139.3, 139.4, 139.8, 140.1, 142.9, 145.4, 156.1, 162.4, 162.8; ν_{max} (neat) cm^{-1} 3410, 3194, 3055, 1688, 1627, 1601, 1518, 1495, 1465, 1385, 1260, 1213, 1029, 894, 788, 762, 698; m/z (100, MH^+) 682; HRMS (ES): MH^+, found: 681.3232. $C_{46}H_{41}N_4O_2^+$ requires: 681.3230.

4.4.8 Preparation of 2-(3-(6',8'-bis(4-fluorophenyl)-1',2',3',4'-tetrahydro-2'-methyl-4'-oxoquinazolin-2'-yl)-2,2-dimethylpropyl)-6,8-bis(4-fluorophenyl)quinazolin-4(3*H*)-one (145h)

A mixture of **144c** (0.50 g, 0.72 mmol), 4-fluorophenylboronic acid (0.51 g, 3.62 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), PCy_3 (0.04 g, 0.15 mmol) and K_2CO_3 (0.40 g, 2.89 mmol) in dioxane-water (40 mL) afforded **145h** as a solid (0.42 g, 77%); mp. 303–305 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.01 (s, 3H), 1.05 (s, 3H), 1.07 (s, 3H) 1.59 (d, *J* 15.3 Hz, 1H), 2.06 (d, *J* 15.3 Hz, 1H), 2.67 (d, *J* 13.8 Hz, 1H), 2.85 (d, *J* 15.3 Hz, 1H), 5.39 (s, 1H), 7.05 (t, *J* 9.0 Hz, 2H), 7.17 (t, *J* 9.0 Hz, 2H), 7.20 (t, *J* 9.0 Hz, 2H), 7.30–7.39 (m, 5H), 7.50 (t, *J* 6.3 Hz, 2H), 7.62 (t, *J* 6.3 Hz, 2H), 7.85–7.88 (m, 3H), 7.93 (s, 1H), 8.02 (br s, 1H), 8.32 (s, 1H), 12.27 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 29.7, 30.0, 30.9, 35.0, 45.4, 47.0, 70.5, 115.0, 115.2 (d, $^2J_{CF}$ 20.5 Hz), 116.0 (d, $^2J_{CF}$ 21.1 Hz), 116.1 (d, $^2J_{CF}$ 21.4 Hz), 116.4 (d, $^2J_{CF}$ 21.4 Hz), 122.3, 123.1, 125.0, 127.1, 128.0, 128.1 (d, $^3J_{CF}$ 8.0 Hz), 129.5 (d, $^3J_{CF}$ 8.0 Hz),

131.2 (d, $^{3}J_{CF}$ 8.3 Hz), 132.7 (d, $^{3}J_{CF}$ 8.0 Hz), 133.2, 134.0, 134.1 (d, $^{4}J_{CF}$ 3.2 Hz), 135.4 (d, $^{4}J_{CF}$ 3.2 Hz), 135.9 (d, $^{4}J_{CF}$ 2.9 Hz), 136.5 (d, $^{4}J_{CF}$ 2.9 Hz), 136.9, 138.5, 143.0, 145.3, 156.4, 161.8 (d, $^{1}J_{CF}$ 241.7 Hz), 162.0 (d, $^{1}J_{CF}$ 243.0 Hz), 162.1 (d, $^{1}J_{CF}$ 242.4 Hz), 162.6 (d, $^{1}J_{CF}$ 243.5 Hz), 162.3, 162.6; ν_{max} (neat) cm^{-1} 3387, 3181, 3048, 1688, 1653, 1608, 1507, 1466, 1381, 1222, 1158, 1015, 825, 804, 791, 636, 565, 517; m/z (100, MH^{+}) 753; HRMS (ES): MH^{+}, found: 753.2855. $C_{46}H_{37}F_{4}N_{4}O_{2}^{+}$ requires 753.2853.

4.4.9 Preparation of 2-(3-(1',2',3',4'-tetrahydro-6',8'-bis(4-methoxyphenyl)-2'-methyl-4'-oxoquinazolin-2'-yl)-2,2-dimethylpropyl)-6,8-bis(4-methoxyphenyl)quinazolin-4(3*H*)-one (145i)

A mixture of **144c** (0.50 g, 0.72 mmol), 4-methoxyphenylboronic acid (0.55 g, 3.62 mmol), $PdCl_{2}(PPh_{3})_{2}$ (0.05 g, 0.07 mmol), PCy_{3} (0.04 g, 0.15 mmol) and $K_{2}CO_{3}$ (0.40 g, 2.89 mmol) in dioxane-water (40 mL) afforded **145i** as a solid (0.47 g, 81%); mp. 228–230 ºC; ^{1}H NMR (300 MHz, DMSO-d_{6}): δ_{H} 0.93 (s, 3H), 1.03 (s, 3H), 1.08 (s, 3H) 1.57 (d, *J* 15.3 Hz, 1H), 2.06 (d, *J* 13.8 Hz, 1H), 2.67 (d, *J* 13.8 Hz, 1H), 2.94 (d, *J* 13.8 Hz, 1H), 3.56 (s, 3H), 3.69 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 5.27 (s, 1H), 6.79 (d, *J* 9.0 Hz, 2H) 6.88 (d, *J* 9.3 Hz, 2H), 6.96 (d, *J* 9.3 Hz, 2H), 7.07 (d, *J* 9.3 Hz, 2H), 7.31 (d, *J* 7.8 Hz, 2 x 2H), 7.52 (d, *J* 9.0 Hz, 2H), 7.75 (d, *J* 9.0 Hz, 2 × 2H), 7.85 (d, *J* 3.3 Hz, 2H), 7.95 (s, 1H), 12.22 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_{6}): δ_{C} 29.8, 30.0, 30.7, 35.1, 45.2, 46.7, 55.4, 55.5, 55.6, 55.7, 70.5, 113.9, 114.5, 114.8, 115.0, 121.8, 122.2, 124.1, 126.7, 127.3, 127.7, 127.9, 128.3, 128.5, 128.9, 129.4, 130.1, 130.3, 131.6, 131.8, 132.7, 133.5, 137.5, 139.4, 142.6, 145.0, 155.6, 158.7, 159.0, 159.7, 162.5, 163.0; ν_{max} (neat) cm^{-1} 3177, 3037, 2834, 1677, 1607, 1511, 1463, 1386, 1244, 1178, 1034, 899, 827; m/z (100, MH^{+}) 801; HRMS (ES): MH^{+}, found: 801.3665. $C_{50}H_{49}N_{4}O_{6}^{+}$ requires: 801.3652.

4.4.10 Preparation of 2-(3-(2'-ethyl-1',2',3',4'-tetrahydro-4'-oxo-6',8'-diphenylquinazolin-2'-yl)propyl)-6,8-diphenylquinazolin-4(3*H*)-one (145j)

A mixture of **144d** (0.500 g, 0.738 mmol), phenylboronic acid (0.45 g, 3.69 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), PCy_3 (0.041 g, 0.15 mmol) and K_2CO_3 (0.41 g, 2.95 mmol) in dioxane-water (40 mL) afforded **145j** as a solid (0.31 g, 63%); mp. 223–226 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.84 (t, *J* 7.5 Hz, 3H), 1.57–1.81 (m, 6H), 2.50–2.54 (m, 2H), 5.40 (s, 1H), 7.27–7.53 (m, 15H), 7.60 (d, *J* 7.8 Hz, 2H), 7.68 (d, *J* 7.8 Hz, 2H), 7.81 (d, *J* 7.5 Hz, 2H), 7.94 (d, *J* 3.0 Hz, 1H), 8.03 (m, 2H) 8.33 (s, 1H), 12.33 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 7.9, 21.1, 30.6, 33.1, 34.5, 72.1, 114.2, 121.9, 122.4, 124.5, 125.6, 126.4, 126.8, 126.9, 127.1, 127.5 (2 × C), 127.8, 128.0, 128.7, 128.8, 129.0, 129.1, 130.5, 132.7, 133.2, 137.3, 137.7, 138.3, 138.7, 138.9, 139.6, 143.3, 145.2, 157.1, 162.5, 163.3; ν_{max} (neat) cm^{-}1 3384, 3177, 1665, 1600, 1486, 1462, 1438, 1248, 896, 808, 758, 695; m/z (100, MH^+) 668; HRMS (ES): MH^+, found: 667.3094. $C_{45}H_{39}N_4O_2^+$ requires: 667.3073.

4.4.11 Preparation of 2-(3-(2'-ethyl-6',8'-bis(4-fluorophenyl)-1',2',3',4'-tetrahydro-4'-oxoquinazolin-2'-yl)propyl)-6,8-bis(4-fluorophenyl)quinazolin-4(3*H*)-one (145k)

A mixture of **144d** (0.50 g, 0.74 mmol), 4-fluorophenylboronic acid (0.52 g, 3.69 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), PCy_3 (0.04 g, 0.15 mmol) and K_2CO_3 (0.41 g, 2.95 mmol) in dioxane-water (40 mL) afforded **145k** as a solid (0.34 g, 63%); mp. 252–254 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.81 (t, *J* 7.5 Hz, 3H), 1.52–1.77 (m, 6H), 2.48–2.52 (m, 2H), 5.47 (s, 1H), 7.13–7.33 (m, 9H), 7.44 (dd, *J* 6.0 and 6.9 Hz, 2H), 7.59 (dd, *J* 6.3 and 8.4 Hz, 2H),

7.71 (dd, *J* 6.3 and 8.4 Hz, 2H), 7.81–7.86 (m, 3H), 8.00 (s, 2H), 8.27 (s, 1H), 12.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 8.4, 21.5, 33.7 (2 × C), 34.8, 72.7, 114.5, 114.9 (d, $^2J_{CF}$ 21.1 Hz), 116.1 (d, $^2J_{CF}$ 21.1 Hz), 116.4 (d, $^2J_{CF}$ 21.4 Hz), 116.5, 122.5, 123.0, 125.0, 126.5, 127.4, 128.0 (d, $^3J_{CF}$ 7.9 Hz), 129.5 (d, $^3J_{CF}$ 8.3 Hz), 131.5 (d, $^3J_{CF}$ 8.3 Hz), 133.0 (d, $^3J_{CF}$ 8.0 Hz), 133.3, 133.7, 134.5 (d, $^4J_{CF}$ 3.1 Hz), 134.9 (d, $^4J_{CF}$ 3.2 Hz), 135.9 (d, $^4J_{CF}$ 3.1 Hz), 136.6 (d, $^4J_{CF}$ 3.2 Hz), 136.8, 138.1, 144.1, 145.6, 157.2, 161.7 (d, $^1J_{CF}$ 241.9 Hz), 162.1 (d, $^1J_{CF}$ 242.5 Hz, 2 × C), 162.5, 163.3, 162.6 (d, $^1J_{CF}$ 243.6 Hz); ν_{max} (neat) cm^{-1} 3430, 3186, 1690, 1656, 1652, 1608, 1509, 1482, 1464, 1227, 1158, 1098, 1014, 900, 825, 565; m/z (100, MH^+) 740; HRMS (ES): MH^+, found: 739.2709. $C_{45}H_{35}F_4N_4O_2^+$ requires: 739.2696.

4.4.12 Preparation of 2-(3-(2'-ethyl-'1',2',3',4'-tetrahydro-6',8'-bis(4-methoxyphenyl)-4'-oxoquinazolin-2'-yl)propyl)-6,8-bis(4-methoxyphenyl)quinazolin-4(3*H*)-one (145l)

A mixture of **144d** (0.50 g, 0.74 mmol), 4-methoxyphenylboronic acid (0.56 g, 3.69 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), PCy_3 (0.04 g, 0.15 mmol) and K_2CO_3 (0.41 g, 2.95 mmol) in dioxane-water (40 mL) afforded **145l** as a solid (0.35 g, 60%); mp. 192–195 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.82 (t, *J* 7.8 Hz, 3H), 1.54–1.80 (m, 6H), 2.50–2.54 (m, 2H), 3.75 (s, 6H), 3.77 (s, 3H), 3.81 (s, 3H), 5.26 (s, 1H), 6.92–6.99 (m, 5H,), 7. 06 (d, *J* 9.3 Hz, 2H), 7.31 (d, *J* 3.3 Hz, 2H), 7.35 (d, *J* 9.3 Hz, 2H), 7.50 (d, *J* 9.3 Hz, 2H), 7.63 (d, *J* 9.0 Hz, 2H), 7.74 (d, *J* 9.0 Hz, 2H), 7.83 (s, 1H), 7.97 (d, *J* 9.3 Hz, 2H), 8.23 (s, 1H), 12.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 8.5, 21.7, 33.5, 34.9, 55.5, 55.6, 55.7, 55.8, 66.9, 72.6, 113.6, 114.6, 114.8, 114.9, 115.0, 121.7, 122.5, 124.1, 126.7, 127.2, 127.7, 128.3, 128.4, 128.5, 129.4, 130.4, 130.5, 131.2, 131.9, 132.2, 132.8, 133.0, 137.5, 138.8, 143.6, 145.2, 156.5, 158.6, 159.1, 159.1, 162.7, 163.6; ν_{max} (neat) cm^{-1} 3387, 3175, 1668, 1607, 1513, 1484, 1464,

1286, 1246, 1180, 1028, 829; m/z (100, MH^+) 787; HRMS (ES): MH^+, found: 787.3500. $C_{49}H_{47}N_4O_6^+$ requires: 787.3496.

CHAPTER 5: REFERENCES

1. J.H. Chan, J.S. Hong, L.F. Kuyper, M.L. Jones, D.P. Baccanari, R.L. Tansik, C.M. Boytos, S.K. Rudolph, A.D. Brown, *J. Heterocycl. Chem*., **1997**, *34*, 145–151.
2. H.C. Kolb, M.G. Finn, K.B. Sharpless, *Angew. Chem. Int. Edit. Engl*., **2001**, *40*, 2004–2021.
3. G.M. Chinigo, M. Paige, S. Grindrod, E. Hamel, S. Dakshanamurthy, M. Chruszcz, W. Minor, M.L. Brown, *J. Med. Chem*., **2008**, *51*, 4620–4631.
4. A. Chawla, C. Batra, *Int. Res. J. Pharm*., **2013**, *4*, 49–58.
5. E.C. Taylor, M. Patel, *J. Heterocycl. Chem*., **1991**, *28*, 1857–1861.
6. N.J. Leverton, D.J. Armstrong, D.A. Claremon, D.C. Remy, J.J. Baldwin, R.J. Lynch, G. Zhang, R.J. Gould, *Bioorg. Med. Chem. Lett*., **1998**, *8*, 483–486.
7. S. Sinha, M. Srivastava, *Prog. Drug Res*., **1994**, *43*, 143–238.
8. J.B. Koepfli, J.F. Mead, J.A. Brockman, Jr., *J. Am. Chem. Soc*., **1947**, *69*, 1837.
9. J.B. Koepfli, J.F. Mead, J.A. Brockman, Jr., *J. Am. Chem. Soc*., **1949**, *71*, 1048–1054.
10. M. Pines, A. Nagler, *Gen. Pharmac*., **1998**, *30*, 445–450.
11. I.K. Kacker, S.H. Zaheer, *J. Indian Chem. Soc*., **1951**, *28*, 344–346.
12. A.H. Amin, D.R. Mehta, S.S. Samarth, *Prog. Drug Res*., **1970**, *14*, 218–268.
13. P. Yvore, N. Foure, J. Aycardi, G. Bennejean, *Rec. Med*., **1974**, *150*, 495–503.
14. J.B. Jiang, D.P. Hesson, B.A. Dusak, D.L. Dexter, G.J. Kang, E. Hamel, *J. Med. Chem*., **1990**, *33*, 1721–1728.
15. J. Rudolph, W.P. Esler, S. O'Connor, P.G.D. Coish, P.L. Wickens, M. Brands, D.E. Bierer, B.T. Bloomquist, G. Bondar, L. Chen, C.Y. Chuang, T.H. Claus, Z. Fathi, W. Fu, U.R. Khire, J.A. Kristie, X.G. Liu, D.B. Lowe, A.C. McClure, M. Michels, A.A. Ortiz, P.D. Ramsden, R.W. Schoenleber, T.E. Shelekhin, A. Vakalopoulos, W. Tang, L.

Wang, L. Yi, S.J. Gardell, J.N. Livingston, L.J. Sweet, W.H. Bullock, *J. Med. Chem*., **2007**, *50*, 5202–5216.

16. F.A. Cabrera-Rivera, J. Escalante, H. Morales-Rojas, D.F. Zigler, R.D. Schmidt, L.E. Jarocha, M.D.E. Forbes, *J. Photochem. Photobiol. A*, **2014**, *294*, 31–37.
17. T.V. Trashakhova, E.V. Nosova, M.S. Valova, P.A. Slepukhin, G.N. Lipunova, V.N. Charushin, *Russ. J. Org. Chem*., **2011**, *47*, 753−761.
18. E.V. Nosova, T.V. Stupina, G.N. Lipunova, M.S. Valova, P.A. Slepukhin, V.N. Charushin, *Int. J. Org. Chem*., **2012**, *2*, 56–53.
19. M.J. Mphahlele, H.K. Paumo, A.M. El-Nahas, M.M. El-Hendawy, *Molecules*, 2014, *19*, 795–818.
20. M.F. Abdel-Megeed, M.M. Azaam, G.A. El-Hiti, *Monatsh. Chem*., **2007**, *138*, 153–156.
21. S. Wang, H. Lui, G. Yu, P. Lu, D. Zhu, *J. Mater. Chem*., **2001**, *11*, 2971–2973.
22. N.M. Parekh, S.R. Lokhandwala, *Arch. Appl. Sci.* Res., **2012**, *4*, 2391–2395.
23. V.B. Paragas, A. Yu-Zhong, R.P. Haugland, V.L. Singer, *J. Histochem. Cytochem*., **1997**, *45*, 345–357.
24. L. Lu, M.-M. Zhang, H. Jiang, X.-S. Wanga, *Tetrahedron Lett*., **2013**, *54*, 757–760.
25. A.N.J. Diaz, *Photochem. Photobiol. A*, **1990**, *53*, 141–167.
26. M. Wang, J.J. Gao, Z.G. Song, L. Wang, *Chem. Heterocycl. Compd*., **2011**, *47*, 851–854.
27. Q.-S. Ding, J.-L. Zhang, J.-X. Chen, M.-C. Liu, J.-C. Ding, H.-Y. Wu, *J. Heterocycl. Chem*., **2012**, *49*, 375–380.
28. H.R. Shaterian, A.R. Oveisi, *Chin. J. Chem*., **2009**, *27*, 2418–2422.
29. Z.K. Jaberi, L. Zarei, *S. Afr. J. Chem*., **2012**, *65*, 36–38.
30. L. Yang, D. Shi, S. Chen, H. Chai, D. Huang, Q. Zhang, J. Li, *Green Chem.* **2012**, *14*, 945–951.

31. B.M. Sahoo, S.C. Dinda, B.V.V.R. Kumar, J.R. Panda, *Int. J. Pharm. Sci. Nanotech*., **2013**, *6*, 2046–2052.

32. G. Majid, A. Kobra, M.-P. Hamed, H.R. Shaterian, *Chin. J. Chem.*, **2011**, *29*, 1617–1623.

33. S. Rostamizadeh, A. M. Amani, R. Aryan, H. R. Ghaieni, N. Shadjou, *Synth. Commun*., **2008**, *38*, 3567–3576.

34. J. M. Khurana, G. Kukreja, *J. Heterocycl. Chem*., **2003**, *40*, 677–679.

35. D. Shi, L. Rong, J. Wang, Q. Zhuang, X. Wang, H. Hu, *Tetrahedron Lett*., **2003**, *44*, 3199–3201.

36. J.J. Naleway, C.M.J. Fox, D.R. Robinhold, E. Terpetsching, N.A. Olson, R.P. Hauland, *Tetrahedron Lett*., **1994**, *35*, 8569–8572.

37. S.E. Lopez, M.E. Rosales, N. Urdaneta. M.V. Godoy, J.E. Charris, *J. Chem. Res.*, **2000**, *6*, 258–259.

38. R.J. Abdel-Jalil, W. Voelter, M. Saeed, *Tetrahedron Lett*., **2004**, *45*, 3475–3476.

39. C. Balakumar, P. Lamba, D.P. Kishore, B. L. Narayana, K.V. Rao, K. Rajwinder, A.R. Rao, B. Shireesha, B. Narsaiah, *Euro. J. Med. Chem*., **2010**, *45*, 4904–4913.

40. T. Hisano, M. Ichikawa, A. Nakagawa, M. Tsuji, *Chem. Pharm. Bull*., **1975**, *23*, 1910–1916.

41. G.-W. Wang, C.-B. Miao, H. Kang, *Bull. Chem. Soc. Jpn*. **2006**, *9*, 1426–1430.

42. M.G.R. Priya, Y. Zulykama, K. Girija, S. Murugesh, T.T. Perumal, *Indian J. Chem*, **2011**, *50B*, 98–102.

43. J.X. Chen, D. Wu, F. He, M.C. Liu, H. Wu, J.C. Ding, W.K. Su, *Tetrahedron Lett*. **2008**, *49*, 3814–3818.

44. M. Adib, E. Sheikhi, H.R. Bijanzadeh, *Synlett.* **2012**, *23*, 85–88.

45. H. Hazarkhani, B. Karimi, *Tetrahedron*, **2003**, *59*, 4757–4760.

46. P. Molina, M.J. Vilaplana, *Synthesis*, **1994**, *1994*, 1197–1218.

47. S. Barthelemy, S. Schneider, W. Bannwarth, *Tetrahedron Lett*. **2002**, *43*, 807–810.

48. S. Reymond, J. Cossy, *Chem. Rev*., **2008**, *108*, 5359–5406.

49. X. Chen, H. Wei, L. Yin, X. Li, *Chin. Chem. Lett*., **2010**, *21*, 782–786.

50. W. Xu, Y. Jin, H. Liu, Y. Jiang, H. Fu, *Org. Lett*., **2011**, *6*, 1274–1277.

51. H. Hikawa, Y. Ino, H. Suzuki, Y. Yokonyama, *J. Org. Chem*., **2012**, *77*, 7046–7051.

52. J. Zhou, J. Fang, *J. Org. Chem*., **2011**, *76*, 7730–7736.

53. M.M. Burbulience, R. Mazeikaite, P. Vailavicius, *J. Heterocycl. Chem.*, **2008**, *45*, 607–610.

54. Y.A.-M. El-Badry, *Acta Chim. Slov*., **2010**, *57*, 836–841.

55. C. Lamberth, *Heterocycles*, **2006**, *68*, 561–603.

56. Y. Takaya, H. Tasaka, T. Chiba, K. Uwai, M.-A. Tanitsu, H.-S. Kim, Y. Wataya, M. Miura, M. Takeshita, Y. Oshima, *J. Med. Chem.*, **1999**, *42*, 3163–3166.

57. Q. Chao, L. Deng, H. Shih, L.M. Leoni, D. Genini, D.A. Carson, H.B. Cottan, *J. Med. Chem*., **1999**, *42*, 3860–3973.

58. J.R. Keneford, J.S. Morley, J.C.E. Simpson, P.H. Wright, *J. Chem. Soc*., **1950**, 1104–1111.

59. A.O. Adeloye, M. J. Mphahlele, *J. Chem. Res*., **2014**, *38*, 254–259.

60. R. Chinchilla, C. Na´jera, *Chem. Rev*., **2007**, *107*, 874–922.

61. V.V. Grushin, H. Alper, *Chem. Rev*., **1994**, *94*, 1047–1062.

62. K. Tamao, K. Sumitami, M. Kumada, *J. Am. Chem. Soc*. **1972**, *94*, 4374–4376.

63. M. Kumada, K. Tamao, K. Sumitami, *Org. Synth.*, **1988**, *6*, 407–411.

64. G. Ren, X. Cui, Y. Wu, *Eur. J. Org. Chem*., **2010**, *12*, 2372–2378.

65. M. Rueping, W. Leawsuwan, *Synlett*., **2007**, *2*, 247–250.

66. L. Hintermann, L. Xiao, A. Labonne, *Angew. Chem. Int. Ed*., **2008**, *47*, 8246–8250.

67. N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett*., **1979**, *20*, 3437–3440.

68. K. Smith, *Organometal. Synth*., **2002**, 512–514.

69. R. Garlapati, N. Pottabathini, V. Gurram, K.S. Kasani, R. Gundla, C. Thulluri, P.K. Machiraju, A.B. Chaudhary, U. Addepally, R. Dayam, V. R. Chunduri, B. Patroa, *Org. Biomol. Chem*., **2013**, *11*, 4778–4791.

70. M.J. Mphahlele, M.M. Maluleka, T.A. Khoza, *Bull. Chem. Soc. Ethiop*., **2014**, *28*, 81–90.

71. Y. Garcia, F. Schoenebeck, C.Y. Legault, C.A. Merlic, K.N. Houk, *J. Am. Chem. Soc*., **2009**, *131*, 6632–6639.

72. P. Wipf, K.M. George, *Synlett*., **2010**, *4*, 644–648.

73. E. Negishi, A.O. King, N. Okukado, *J. Org. Chem*., **1977**, *42*, 1821–1823.

74. P. Knochel, R.D. Singer, *Chem. Rev*., **1993**, *93*, 2117–2188.

75. E. Nakamura, *Organometal. Synth*., **2002**, 656–657.

76. B. Charpiot, J. Brun, I. Donze, R. Naef, M. Stefani, T. Muetler, *Bioorg. Med. Chem. Lett*., **1998**, *8*, 2891–2896.

77. A. Krasovsky, P.A. Knochel, *Angew. Chem. Int. Ed*., **2004**, *43*, 3333–3336.

78. L.T. Boulton, M.E. Fox, P.B. Hodgson, I.C. Lennon, *Tetrahedron Lett*., **2005**, *46*, 983–986.

79. K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett*., **1975**, *16*, 4467–4470.

80. N.J. Liverton, D.J. Armstrong, D.A. Claremon, D.C. Remy, J.J. Baldwin, R.J. Lynch, G. Zhang, R.J. Gould, *Bioorg. Med. Chem. Lett*., **1998**, *8*, 483–186.

81. I. Mangalagiu, T. Benneche, K. Undheim, *Acta Chem. Scand*., **1996**, *50*, 914–917.

82. Y. Kitano, T. Suzuki, E. Kawahara, T. Yamazaki, *Bioorg. Med. Chem. Lett*., **2007**, *17*, 5863−5867.

83. R.F. Heck, J.P. Nolley, *J. Org. Chem*., *37*, **1972**, 2320–2322.

84. E.C. Lawson, W.A. Kinney, D.K. Luci, S.C. Yabut, D.Wisnoski, B.E. Maryanoff, *Tetrahedron Lett*., **2002**, *43*, 1951–1953.

85. D.H. B. Ripin, D.E. Bourassa, T. Brandt, M.J. Castaldi, H.N. Frost, J. Hawkins, P.J. Johnson, S.S. Massett, K. Neumann, J. Phillips, J.W. Raggon, P.R. Rose, J.L. Rutherford, B. Sitter, A.M. Stewart, M.G. Vetelino, L. Wei, *Org. Proc. Res. Dev*., **2005**, 9, 440–450.

86. T. Sardon, T. Cottin, J. Xu, A. Giannis, I. Vernos, *Chem. Bio. Chem*., **2009**, *10*, 464–478.

87. D. Milstein, J.K. Stille, *J. Am. Chem. Soc*., **1979**, *101*, 4992–4998.

88. V. Farina, V. Krishnamurthy, W.J. Scott, *Org. React.*, **1997**, *50*, 1–652.

89. P. Jones, M. Chambers, *Tetrahedron*, **2002**, *58*, 9973–9981.

90. N. Kode, L. Chen, D. Murthy, D. Adewumi, S. Phadtare, *Europ. J. Med. Chem*., **2007**, *42*, 327–333.

91. M. Baghbanzadeh, P. Salehi, M. Dabiri, G. Kozehgary, *Synthesis*, **2006**, *2*, 344–348.

92. Y. Liu, L. Lu, Y.-J. Zhou, *Res. Chem. Intermed*., **2014**, *40*, 2823–2835.

93. Y.A. Ammar, Y.A. Mohamed, A.M. El-Sharief, M.S.A. El-Gaby, S.Y. Abbas, *Chem. Sci. J*., **2011**, 1–10.

94. R.H. Mitchell, Y-H. Lai, R.V. Williams, *J. Org. Chem*., **1979**, *44*, 4733–4735.

95. S.R.K. Pingali, M. Madhav, B.S. Jursic, *Tetrahedron Lett*., **2010**, 1383–1385.

96. W. E. Stewart, T. H. Siddall, *Chem. Rev*., **1970**, *70*, 517–551.

97. L.-X. Wang, B.-Q. Hu, J.-F. Xiang, J. Cui, X. Hao, T.-L. Liang, Y.-L. Tang, *Tetrahedron*, **2014**, *70*, 8588–8591

98. A.G. Eshibetov, E.L. Kristallovich, N.D. Abdullaev, T.S. Tulyagnov, K.M. Shakhidoyatov, *Spectrochimica Acta. Part A*, **2006**, *65*, 299–307.

99. C.D. Geddes, *Meas. Sci. Technol*., **2001**, *12*, 53–88.

100. S. Kappaun, T. Sović, F. Stelzer, A. Pogantsch, E. Zojer, C. Slugovc, *Org. Biomol. Chem.*, **2006**, *4*, 1503–1511

101. A.T.C. Tsin, H.A. Pedrozo-Fernandez, J.M. Gallas, J.P. Chambers, *Life Sciences*, **1988**, *43*, 1379–1384.

102. H. Iikura, T. Tsuneda, Y. Yanai, K. Hirao, *J. Chem. Phys.*, **2001**, *115*, 3540–3544.

103. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani,.; V. Barone, B. Mennucci , G.A. Petersson, *et al*. *Gaussian 09*, Revision B.01; Gaussian, Inc.: Wallingford, CT, USA, **2010**.

104. M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Comp. Chem.* **2003**, *24*, 669–681.

105. M.M. Mmonwa, M.J. Mphahlele, M.M. El-Hendawy, A.M. El-Nahas, N. Koga, *Molecules*, **2014**, *19*, 9712–9735.

APPENDIX

Mass spectra of **144a**, **145a**, **145f** and **145h**

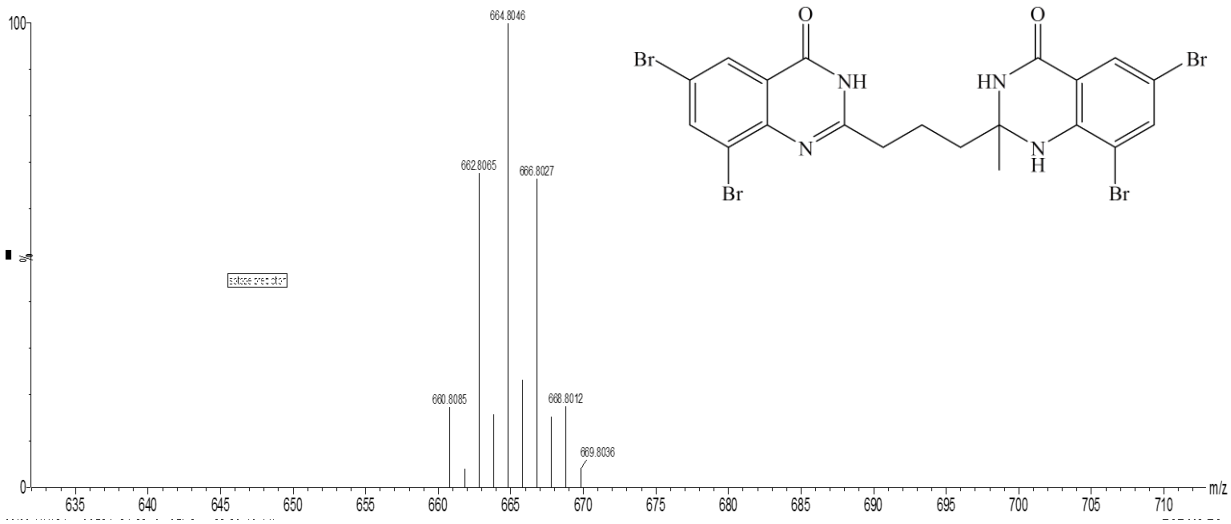


Figure 24: Mass spectrum of 6,8-dibromo-2-(3-(6,8-dibromo-1,2,3,4-tetrahydro-2-methyl-4-oxoquinazolin-2-yl)propyl)quinazolin-4(3*H*)-one (**144a**)

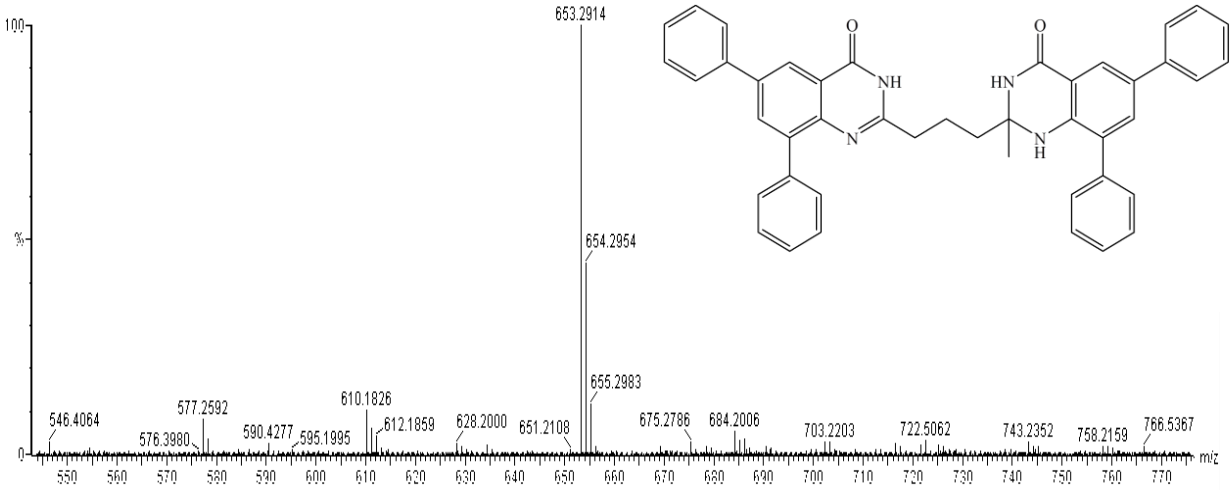


Figure 25: Mass spectrum of 2-(3-(1,2,3,4-tetrahydro-2-methyl-4-oxo-6,8-diphenylquinazolin-2-yl)propyl)-6,8-diphenylquinazolin-4(3*H*)-one (**145a**)

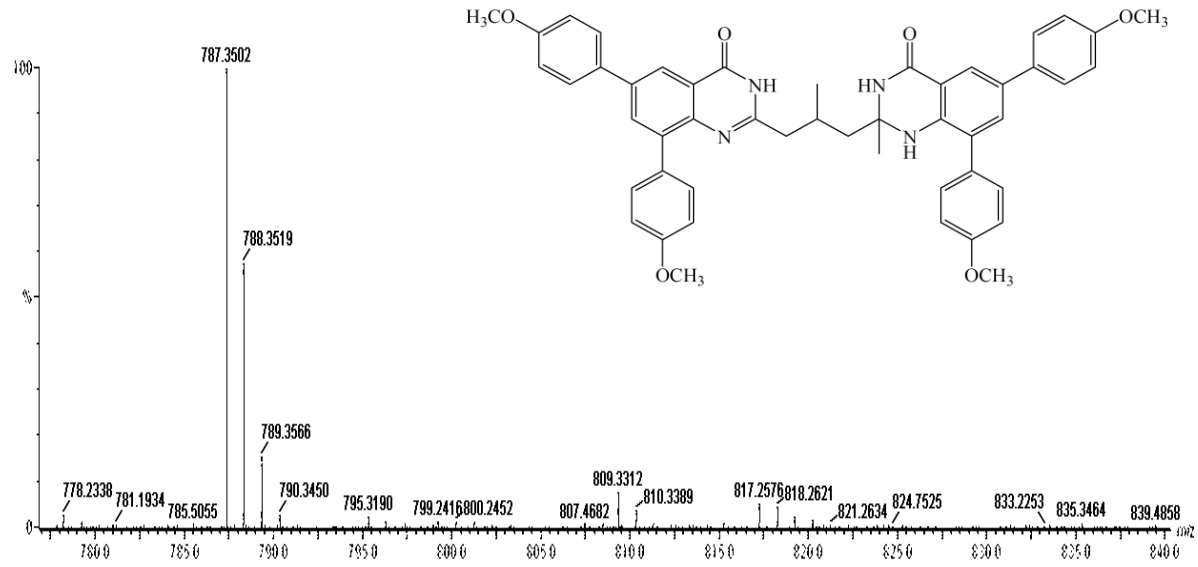


Figure 26: Mass spectrum of 2-(3-(1,2,3,4-tetrahydro-6,8-bis(4-methoxyphenyl)-2-methyl-4-oxoquinazolin-2-yl)-2-methylpropyl)-6,8-bis(4-methoxyphenyl)quinazolin-4(3*H*)-one (**145f**)

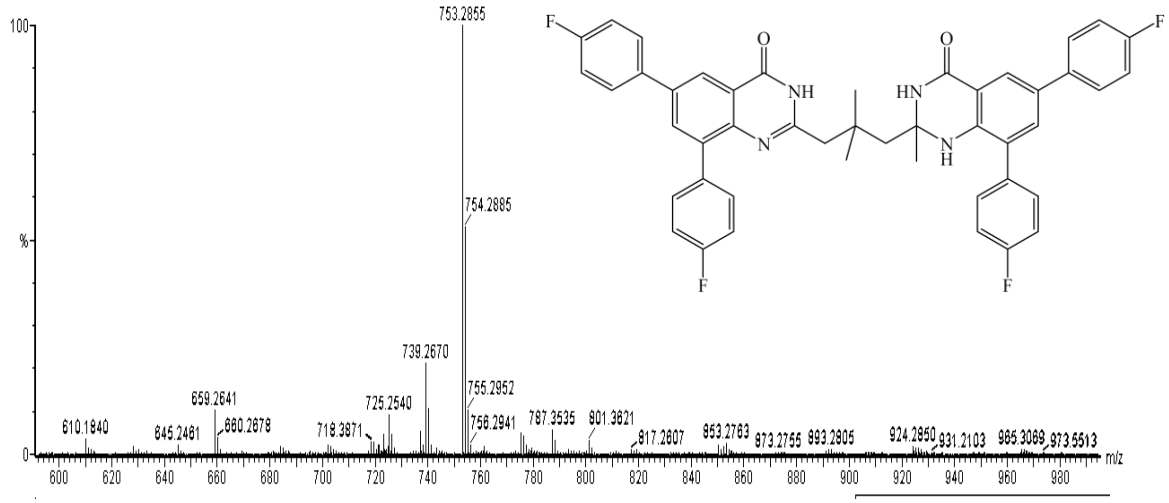


Figure 27: Mass spectrum of 2-(3-(6,8-bis(4-fluorophenyl)-1,2,3,4-tetrahydro-2-methyl-4-oxoquinazolin-2-yl)-2,2-dimethylpropyl)-6,8-bis(4-fluorophenyl)quinazolin-4(3*H*)-one (**145h**)

SYNTHESIS OF POLYARYL-SUBSTITUTED BISQUINAZOLINONES WITH POTENTIAL PHOTOPHYSICAL PROPERTIES

by

MMAKWENA MODLICIOUS MMONWA

Submitted in accordance with the requirements for the degree of

MASTER OF SCIENCE

in the subject

CHEMISTRY

at the

UNIVERSITY OF SOUTH AFRICA

SUPERVISOR: PROFESSOR M.J. MPHAHLELE

November 2014

Student number: 5304-576-9

I declare that SYNTHESIS OF POLYARYL-SUBSTITUTED BISQUINAZOLINONES 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. M.M. Mmonwa)

This thesis is dedicated to my parents, Mr. Pitsi William and Mrs. Matlou Sarina Mmonwa.

ACKNOWLEDGEMENTS

My sincere gratitude goes to the following:

- My supervisor, Professor M.J. Mphahlele, for his guidance and encouragement throughout this study.
- The University of South Africa and the National Research Foundation (NRF) for financial support.
- Dr Bongumusa Dladla and Ms Christinah Chokwe for proof-reading this dissertation.
- Mr. Albert Semenya, for his guidance, inspiration and support throughout my studies.
- Mr. Noko Matsena for providing me with accommodation throughout this study.
- My aunts Mrs Hendrica Mabitsela and Mrs. Jane Maphelela for their support and always been there when I needed them.
- My parents, brothers, and sisters for their continuous support and for raising my hopes and aspirations.
- Above all, I like to thank almighty God for making it possible for me.

ABSTRACT

3,5-Dibromo-2-aminobenzamide was reacted with 1,3-cyclohexanedione derivatives in the presence of iodine as catalyst in toluene under reflux to afford novel 6,8-dibromo-2-[3-(2´-alkyl-1´,2´,3´,4´-tetrahydro-6´,8´-dibromo-4´-oxoquinazoline-2yl)propyl]quinazolin-4(3*H*)-ones in high yields. Suzuki-Miyaura cross-coupling of the latter with arylboronic acids in the presence of $Pd(PPh_3)_2Cl_2$–Xphos catalyst complex and K_2CO_3 as a base in dioxane-water mixture (3:1, v/v) afforded the corresponding polyaryl-substituted bis-heterocycles in a single step operation. The resultant compounds were characterized using a combination of NMR (^1H and ^{13}C) and IR spectroscopic techniques, as well as mass spectrometry. The electronic absorption and emission properties of these polyaryl-substituted bis-heterocycles comprising 2,3-dihydroquinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one moieties linked by a flexible carbon chain were measured in dimethylsulfoxide (DMSO) and acetic acid by means of UV-Vis and fluorescence spectroscopic techniques. The absorption spectra of the resultant polyaryl-substituted bis-heterocycles showed blue-shift in acetic acid and red-shift in DMSO, while their emission spectra are blue-shifted in DMSO and red-shifted in acetic acid. The 4-methoxy groups on aryl-substituents caused red shift on π–π* transition of the aryl-substituents. Moreover, it was also observed that as the propyl linkage becomes more substituted, the absorption and emission intensities decrease.

Keywords: 2,3-dihydroquinazolin-4(1*H*)-ones, Quinazolin-4(3*H*)-ones, 6,8-dibromo-2-[3-(2'-alkyl-1´,2´,3´,4´-tetrahydro-6´,8´-dibromo-4´-oxoquinazoline-2yl)propyl]quinazolin-4(3*H*)-ones, Suzuki-Miyaura cross coupling, polyaryl-substituted bis-heterocycles, photophysical properties

TABLE OF CONTENTS

Declaration i

Dedication ii

Acknowledgements iii

Abstract iv

CHAPTER 1: INTRODUCTION 1–52

1.1 Methods for the synthesis of quinazolin-4-ones 7

1.1.1 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives 7

i) The synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via condensation reactions of anthranilamides with aldehydes or ketones 8

ii) The synthesis of 2,3-dihydroquinazolin-4(*1H*)-ones via a one-pot multicomponent condensation reactions 11

iii) The synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via metal-mediated condensation reactions 12

1.1.2 Methods for the synthesis of quinazolin-4(3*H*)-ones 14

i) Synthesis of quinazolin-4(3*H*)-ones via dehydrogenation of the 2,3-dihydroquinazolin-4(1*H*)-ones 14

ii) Synthesis of quinazolin-4(3*H*)-ones via oxidative condensation reactions 15

iii) Synthesis of quinazolin-4(3*H*)-ones by Aza-Wittig reaction 19

iv) Synthesis of quinazolin-4(3*H*)-ones or quinazolines via transition metal-catalyzed reactions 20

1.2 *N*(3) or *O*-alkylation/arylation/acylation of quinazolin-4(3*H*)-ones 24

1.3 Halogenated quinazolinone or quinazoline derivatives as substrates for metal catalysed cross-coupling reactions to afford polysubstituted derivatives 26

1.3.1 Application of Kumada cross-coupling reactions for the synthesis of polysubstituted quinazolinones and/ or quinazolines 28

1.3.2 Application of Suzuki cross-coupling reactions for the synthesis of polysubstituted quinazolinones and/ or quinazolines 30

1.3.3 Application of Negishi cross-coupling reactions in the synthesis of polysubstituted quinazolinones and/ or quinazolines 34

1.2.4 Application of Sonogashira cross-coupling reactions for the synthesis of polysubstituted quinazolinone and/ or quinazoline derivatives 36

1.3.5 Application of the Heck cross-coupling reactions in the synthesis of polysubstituted quinazolinones and/ or quinazolines 39

1.3.6 Application of the Stille cross-coupling reactions in the synthesis of polysubstituted quinazolinones and/ or quinazolines 42

1.4 Synthesis of bis-heterocyclic compounds 44

1.5 Research hypothesis 50

1.6 Aims and objectives 52

CHAPTER 2: RESULTS AND DISCUSSION 53–82

2.1 Synthesis and transformation of halogenated bis-heterocycles 55

2.1.1 Synthesis of 2-amino-3,5-dibromobenzamide 55

2.1.2 Synthesis of 6, 8-dibromo-2-[3-(2'-alkyl- 6', 8'-dibromo-1', 2', 3', 4'-tetrahydro-4'-oxoquinazoline-2'yl)propyl]quinazolin-4(3*H*)-ones 58

2.1.3 Suzuki-Miyaura cross-coupling reactions of halogenated bis-heterocycles with arylboronic acids 62

2.2 Absorption and emission property studies of halogenated bis-heterocycles and polyaryl-substituted bis-heterocycles 68

2.2.1 Absorption properties of halogenated bis-heterocycles 68

2.2.2 Absorption properties of polyaryl-substituted bis-heterocycles 70

2.2.3 Emission properties of halogenated bis-heterocycles and polyaryl-substituted bis-heterocycles 74

2.2.4 Quantum Chemical Calculations 80

CHAPTER 3: CONCLUSIONS 83–84

CHAPTER 4: EXPERIMENTAL 85–99

4.1 General 85

4.2 Preparation of 2-amino-3, 5-dibromobenzamide 86

4.3 Preparation of 6, 8-dibromo-2-(3-(2'-alkyl- 6', 8'-dibromo-1', 2', 3', 4'-tetrahydro-4'-oxoquinazoline-2'yl)propyl)quinazolin-4(3*H*)-one derivatives 86

4.4 Preparation of 2-(3-(2'-alkyl-1',2',3',4'-tetrahydro-4'-oxo-6',8'-diphenylquinazolin-2'-yl)propyl)-6,8-diphenylquinazolin-4(3*H*)-one derivatives 89

CHAPTER 5: REFERENCES 100–106

APPENDIX

Selected mass spectra 107