# DESIGN, SYNTHESIS AND STRUCTURE OF 2,4-DICARBO SUBSTITUTED QUINAZOLINE 3-OXIDES

by

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JULY 2021

## DECLARATION

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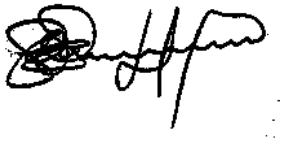

28/07/2021

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## DEDICATION

**This thesis is dedicated to my parents Engr. Eugene U. Onwu and Janet C. Onwu.**

**ACKNOWLEDGEMENTS**

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## ABSTRACT

2-Amino-5-bromoacetophenone was prepared by treating 2-aminoacetophenone with pyridinium tribromide in dichloromethane. The 2-amino-5-iodoacetophenone was synthesized by the reaction of 2-aminoacetophenone with *N*-iodosuccinimide in acetic acid. Acetylation and benzoylation of the 2-aminoacetophenone and its 5-halogeno derivatives with 1.2 equiv. of acetic anhydride and aryl chloride derivatives in pyridine under reflux afforded the *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halo-phenyl)amide derivatives, respectively. Nucleophilic substitution reaction of the latter with hydroxylamine hydrochloride in pyridine under reflux afforded the corresponding *N*-[2-(1-hydroxyiminoethyl)phenyl]amide and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives. The *N*-[2-(1-hydroxyiminoethyl)phenyl]amide and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives were, in turn, subjected to intramolecular cyclization with triflouroacetic acid under reflux to afford the 2,4-dicarbo substituted quinazoline 3-oxides. The 6-iodo substituted quinazoline 3-oxides were subjected to palladium catalysed Suzuki-Miyaura cross-coupling reaction with 4-fluorophenylboronic acid to afford 2,4,6-tricarbo substituted quinazoline 3-oxides. The prepared compounds were characterized using a combination of NMR ($^{1}$H and $^{13}$C), IR and mass spectrometric techniques. The geometry of the 2,4-dicarbo substituted quinazoline 3-oxides were confirmed through X-ray diffraction analysis of compound **92b**.



**Keywords**: 2-Amino-5-halogenoacetophenones, amides, oximes, 2,4-dicarbo substituted quinazoline 3-oxides, Suzuki-Miyaura cross-coupling reaction, 2,4,6-tricarbo substituted quinazoline 3-oxides; X-ray diffraction analysis

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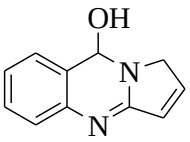
# CHAPTER 1 INTRODUCTION

## 1.1 Structure and application of quinazolines

Quinazoline derivatives are heterocyclic compounds bearing benzene ring attached to a pyrimidine ring.[1] These class of compounds were found to exhibit numerous biological properties such as anti-histamine,[2] antileishmanial activity,[3] hypersensitivity activity,[4] anti-tuberculosis,[5] and anti-cancer[6-8] activities. As a result of their planar configuration, some examples of quinazoline analogues exhibit photophysical properties,[9] and are also part of organic electroluminescent diodes.[9] Peganol **1** shown in Figure 1 was extracted from *Nitraria komarovii*, and was found to exhibit substantial metabolic activity on lysine.[10] Vasicine **2** was isolated from the leaves of *Adhatoda vasica nees* and found to exhibit substantial bronchodilation response.[11] Prazosin **3** is used as a high blood pressure drug and also as a precursor for the preparation of Terazosin, Doxazosin and Trimazosin.[12] Gefitinib **4**, is used in anti-lung cancer drug.[13] Vandetanib **5** is used as an anti-breast cancer drug.[14]

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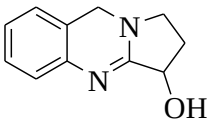


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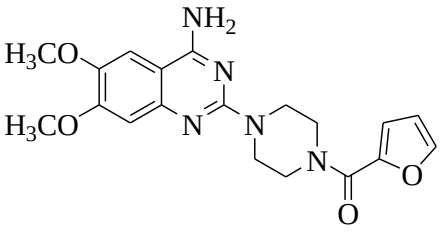


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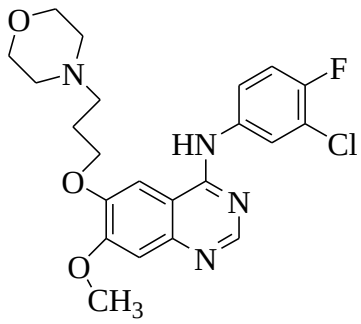

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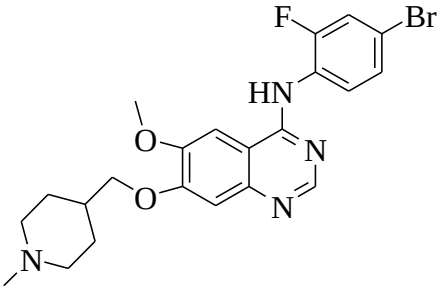
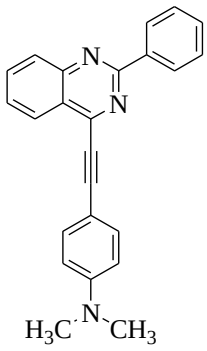


**5**

**Figure 1**: Examples of medicinally important quinazolines.

Quinazoline derivatives have been utilized in the development of compounds with potent photophysical properties as shown in Figure 2. The 4-(4-dimethylaminophenylethynyl)-2-phenylquinazoline **6**, for instance, was found to exhibit high fluorescence quantum yields as well as strong emission in nonpolar solvents such as trifluoroacetic acid.[15] The 4,7-bis(6-methoxynaphthalen-2-yl)quinazoline **7**, in contrast, exhibited white photoluminescence both in aqueous and in the solid state.[16] 2-(3,5-Bis(trifluoromethyl) phenyl)-quinazoline **8** exhibited outstanding photoluminescence quantum yield (QY), strong emissions in nanoparticles, powders, crystals and films.[17] This compound also exhibited mechanochromic properties originating from crystal grinding.[17]



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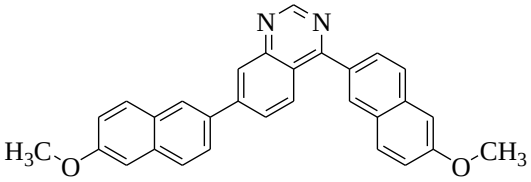

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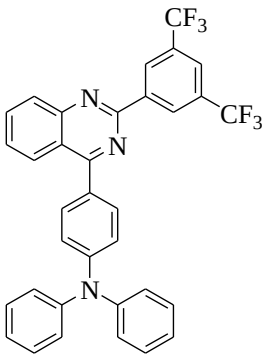


**8**

**Figure 2**: Examples of quinazolines with luminescent properties.

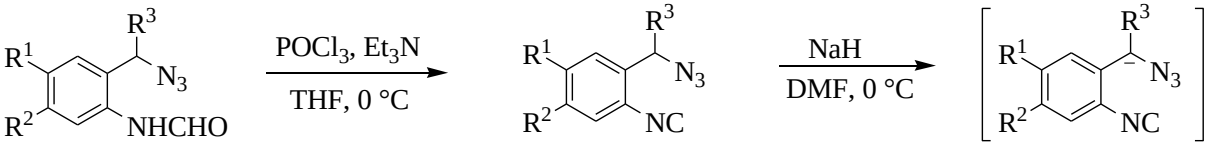
The varied uses of quinazolines resulted to widespread investigation for the advancement of methods for their synthesis. Some examples of these methods are demonstrated in the subsequent sections.

## 1.2 Methods for the synthesis of quinazolines

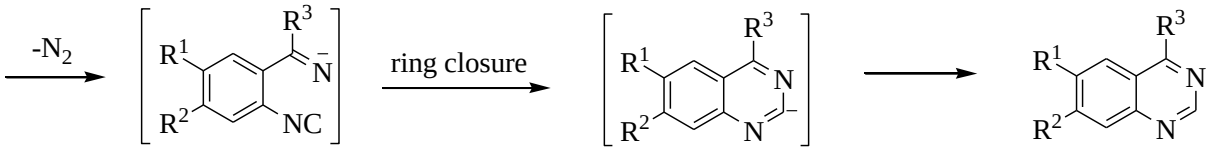
The two most common approaches for the synthesis of quinazoline scaffold consist of intramolecular cyclization of *N*-substituted anthranilamides or aromatization of dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones.

### 1.2.1 Direct synthesis of quinazolines from anthranilamide derivatives

The direct synthesis of quinazolines have been achieved through cycloaddition of formamidine with anilines and subsequent cylization of the intermediate under reflux.[18] The sodium hydroxide facilitated synthesis of quinazoline was achieved through the reaction of arylbenzamidines with formic acid at 90 °C.[19] 2-(Azidoethyl)phenylisocyanides **10** were prepared in 69–86% yield by abstracting protons from azido formamides **9** in a mixture of phosphoryl chloride ($POCl_3$), triethylamine and tetrahydrofuran (THF) at 0 °C (Scheme 1).[20] Compounds **10** were deprotonated with NaH in DMF at 0 °C to afford benzyl anion intermediate **11**, which upon removal of $N_2$ cyclized to quinazolines **14** in 34–96% yield.



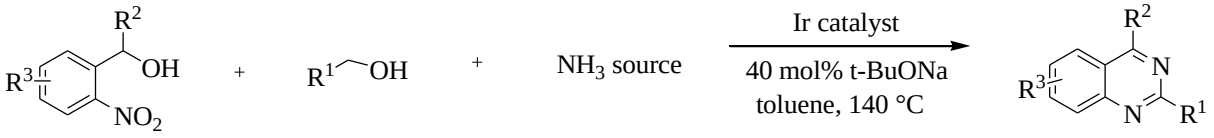

**9** **10** **11**




**12** **13** **14**

**Scheme 1**: Cyclization of alkylideneamines **12** to quinazolines **14**

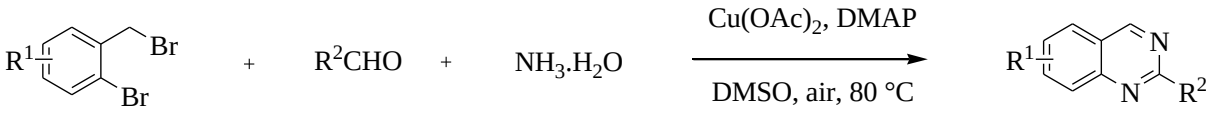
The 2-nitrobenzylalcohols have also been used to construct quinazoline scaffold. The nitrophenylalcohols **15** were reacted with excess benzylalcohols **16** and ammonium salts **17** (nitrogen source) in the presence of naphthyridine-based iridium catalyst and a base in toluene under reflux to afford the tricarbo substituted quinazolines **18** in 61–82% yield (Scheme 2).[21] The drawbacks of this method is difficult proton exchanges between ammonia and alcohols, difficult control of functional group selectivity and catalyst deactivation by the lone pair of electrons on the nitrogen of excess ammonia.[21]




**15** **16** **17** **18**

**Scheme 2**: Naphthyridine-based Iridium catalysis of nitrophenylalcohols **15**

Quinazolines **22** were obtained in 27–75% yield via copper-acetate catalyzed cycloaddition reaction of 2-bromobenzyl bromides **19** with a mixture of aldehydes **20**, aqueous ammonia **21** and 4-dimethylaminopyridine (DMAP) in dimethyl sulfoxide (DMSO) at 80 °C (Scheme 3).[22]




**19** **20** **21** **22**

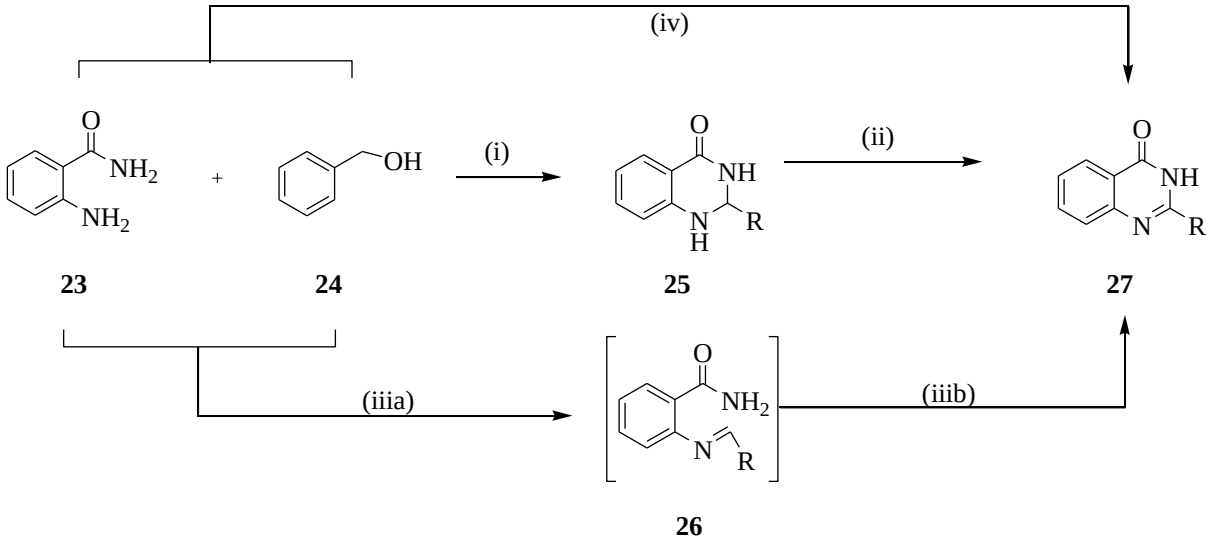
**Scheme 3**: $Cu(OAc)_2$ catalyzed cycloaddition of 2-bromobenzyl bromides **19**

Methods for the synthesis of quinazolinones have been reviewed extensively in the literature [23,24] and some of the examples are discussed in detail below.

### 1.2.2 Methods for the synthesis of quinazolin-4-ones

Dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-one derivatives are bicyclic compounds containing benzene ring fused to pyrimidine ring with one carbonyl group.[23] Quinazolin-4(3*H*)-ones are potentially tautomeric derivatives of the dihydroquinazolin-4(1*H*)-ones due to the presence of N1–C2 bonds on the pyrimidine ring.[23] Quinazolin-4(3*H*)-ones are derived from cyclocondensation of anthranilamide or isatoic acid derivatives in the presence of catalysts. The most common methods for the synthesis of quinazolin-4-ones (dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-one derivatives) involve the cyclocondensation of anthranilamide or isatoic acid derivatives with carbonyl compounds.[23,24] Dihydroquinazolin-4(1*H*)-one derivatives **25** were prepared from reductive cyclization of anthranilamide **23** or isatoic acid derivatives with carbonyl compounds **24** in the presence of catalysts such as copper(II) chloride ($CuCl_2$), ammonium chloride ($NH_4Cl$), scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$, zinc(II) perfluorooctanoate ($Zn(PFO)_2$), copper(II) iodide (CuI), titanium tetrachloride ($TiCl_4$), tetrabutylammonium bromide (TBAB), iron(III)chloride ($FeCl_3$) and palladium chloride ($PdCl_2$) as represented by pathway (i) Scheme 4.[23] A multi-component approach which involves the cyclocondensation of isatoic acids, carbonyl compounds and ammonia derivatives in the presence of a catalyst to afford 2,3-dihydroquinazolin-4(1*H*)-ones has also been reported.[23] Catalysts such as zinc(II) perfluorooctanoate [$Zn(PFO)_2$], gallium(III) triflate ($Ga(OTf)_3$) and molecular iodine ($I_2$) have been used for this transformation.[23,24] Quinazolin-4(3*H*)-ones **27** can also be synthesized through the dehydrogenation of the dihydroquinazolin-4(1*H*)-ones **25** in the presence of oxidizing reagents such as copper(II) chloride ($CuCl_2$),

manganese dioxide ($MnO_2$), and potassium permanganate ($KMnO_4$) (pathway (ii) Scheme 4).[23,24] Anthranilamide **23** was condensed with a mixture of ethanol and aldehyde **24** at 70 °C for 3 h to afford a schiff base as an intermediate product **26**. The later was converted to quinazolin-4(3*H*)-ones **27** through intramolecular nucleophilic attack by the amide nitrogen in the presence of copper(II) chloride under the same conditions (pathway (iiia) and (iiib) Scheme 4).[25] Methods involving transition metal catalyzed cyclocondensation of 2-halogenobenzamides with benzyl alcohols or benzylamines to afford quinazolin-4-ones have been reported.[26–29] The reaction of anthranilamide **23** with benzyl alcohol **24** in the presence of sodium(diphenylphosphino)benz-ene-3-sulfonate (TPPMS) as a ligand and palladium(II)acetate $Pd(OAc)_2$ as the catalyst in water at 120 °C for 16 h to afford 2-phenylquinazolin-4(3*H*)-ones **27** (pathway (iv) Scheme 4).[30] The reaction proceeds through the palladium catalyzed oxidation of the benzyl alcohol to an aldehyde followed by intramolecular nucleophilic addition reaction between the aldehyde and the amino group of the benzamide.[30]

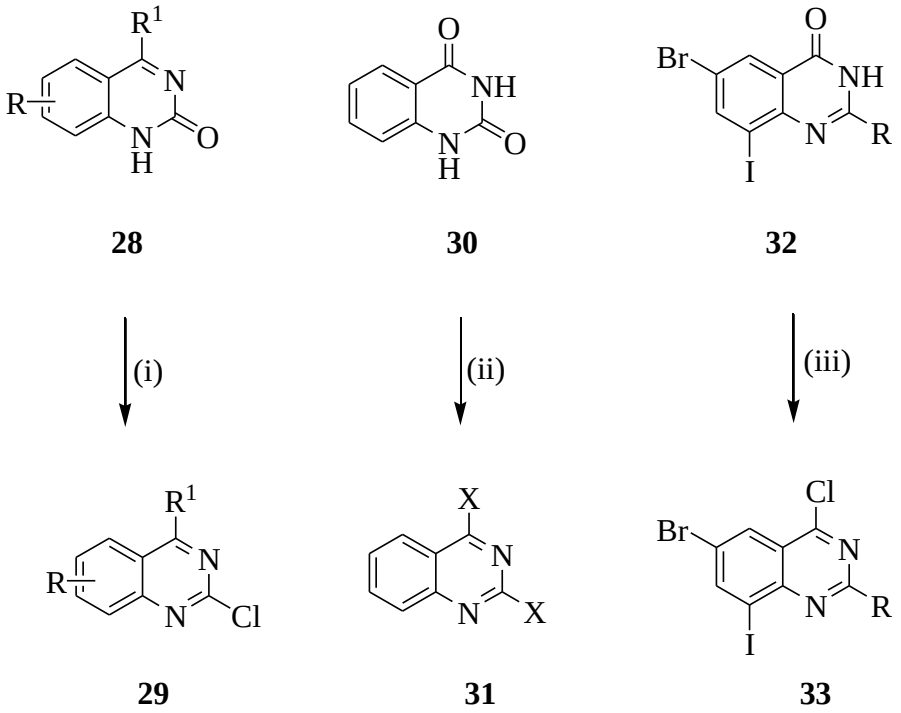



**Scheme 4**: Generalized scheme for the synthesis of quinazolin-4-ones

Quinazolin-4(3*H*)-one framework has been employed for the preparation of 4-halogenoquinazolines through aromatization of quinazolin-4(3*H*)-one derivatives. Some representative examples of these methods will be discussed in the succeeding section.

### 1.2.3 Synthesis of 2-, 4- and 2,4-halogenated quinazolines

Halogenated quinazolines represent important frameworks for transformation into the 2-, 4- and 2,4-heteroatom/carbo substituted quinazolines through nucleophilic substitution reactions and/or metal-catalyzed cross coupling reactions.[31,32] The 2/4-quinazolinone and quinazoline-2,4-diones continue to be transformed into the corresponding 2-, 4- and 2,4-halogenated quinazoline derivatives using reagents such as thionyl chloride ($SOCl_2$),[33] phosphoryl chloride ($POCl_3$),[34,35] or a combination of phosphorus pentachloride ($PCl_5$) and $POCl_3$,[36] tetrabutylammonium bromide (TBABr) or tetrabutylammonium iodide (TBAI)[32] and phosphoryl tribromide $POBr_3$.[37] The quinazolin-2(1*H*)-ones **28**, for example, were converted into the 2-chloroquinazolines **29** in the presence of phosphoryl chloride at 100 °C (as shown in pathway (i) Scheme 5).[31] The 2,4-dihalogenated quinazolines **31** substituted with identical halogens at C–2 and C–4 positions of the pyrimidine ring, on the other hand were prepared by treating quinazoline-2,4(1*H*,3*H*)-dione **30** with either phosphoryl chloride or phosphoryltribromide in *N*,*N*-dimethylaniline under reflux for 14 h or 4 h (pathway (ii) Scheme 5).[35,37] The mono- and dihalogenated quinazolines substituted with identical or different halogen atom on the fused benzene ring have also been transformed into the corresponding 4-chloroquinazoline derivatives.[37,38] The 2-aryl-6-bromo-8-iodoquinazolin-4(3*H*)-ones **32**, for example were subjected to phosphoryl chloride in triethylamine under reflux for 6 h to afford the 2-aryl-6-bromo-4-chloro-8-iodoquinazolines **33** in 77–91% yield (pathway (iii) Scheme 5).[39]

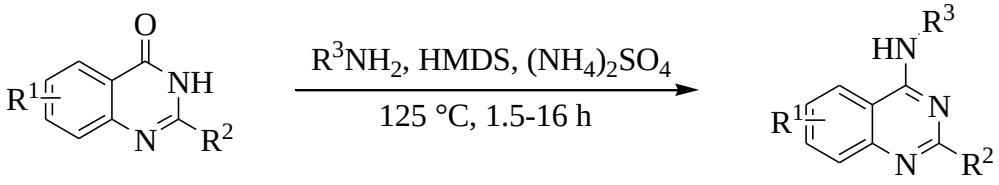



**Scheme 5**: Generalized scheme for the synthesis of halogenated quinazolines

4-Halogenoquinazolines represent suitable intermediates for the indirect synthesis of 4-heteroatom substituted quinazoline derivatives. This is due to the increased reactivity of the C(4)–Cl bond due to α-nitrogen effect. α-Nitrogen effect makes the C(4)–Cl position more electrophilic than the other halogenated positions on the heterocyclic scaffolds.[40] Examples of nitrogen based nucleophiles previously employed for the substitution of the 2- or 4-halogen atom on the quinazoline scaffold include piperidine,[31] sodium azide[41] and ammonia derivatives.[43] Alkoxy substituted quinazoline derivatives have also been prepared before.[42] Some of the examples of the methods for the preparation of heteroatom-substituted quinazolines will be discussed in depth in the subsequent section.

### 1.2.4 Synthesis of quinazolines from 4-quinazolinones

4-Substtituted quinazolines have also been prepared from the 4-quinazolinones with the use of less hazardous reagents such as hexamethyldisilazane (HMDS)[43] and diphenylphosphorylazide (DPPA).[44] Quinazolin-4(3*H*)-ones **34** was treated with excess primary amines in the presence of HMDS as catalyst under reflux for 1.5–16 h to afford 4-aminoquinazolines **35** in 83–97% yield (Scheme 6).[43]

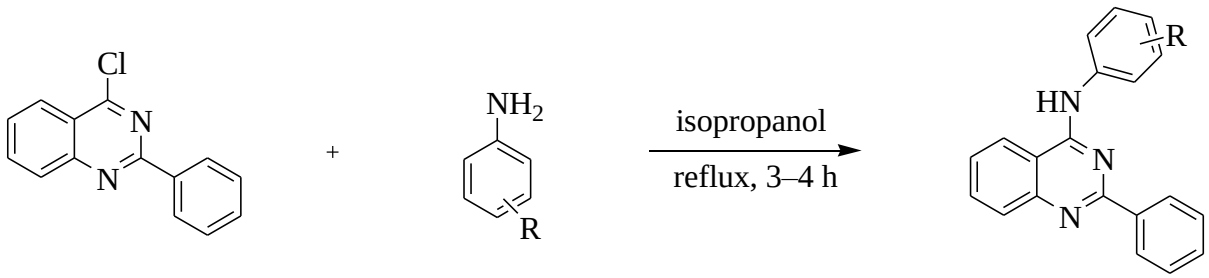



**34** **35**

**Scheme 6**: HMDS mediated synthesis of 4-aminoquinazolines **35**

### 1.2.5 Nucleophilic substitution on the 2/4-halogenoquinazolines

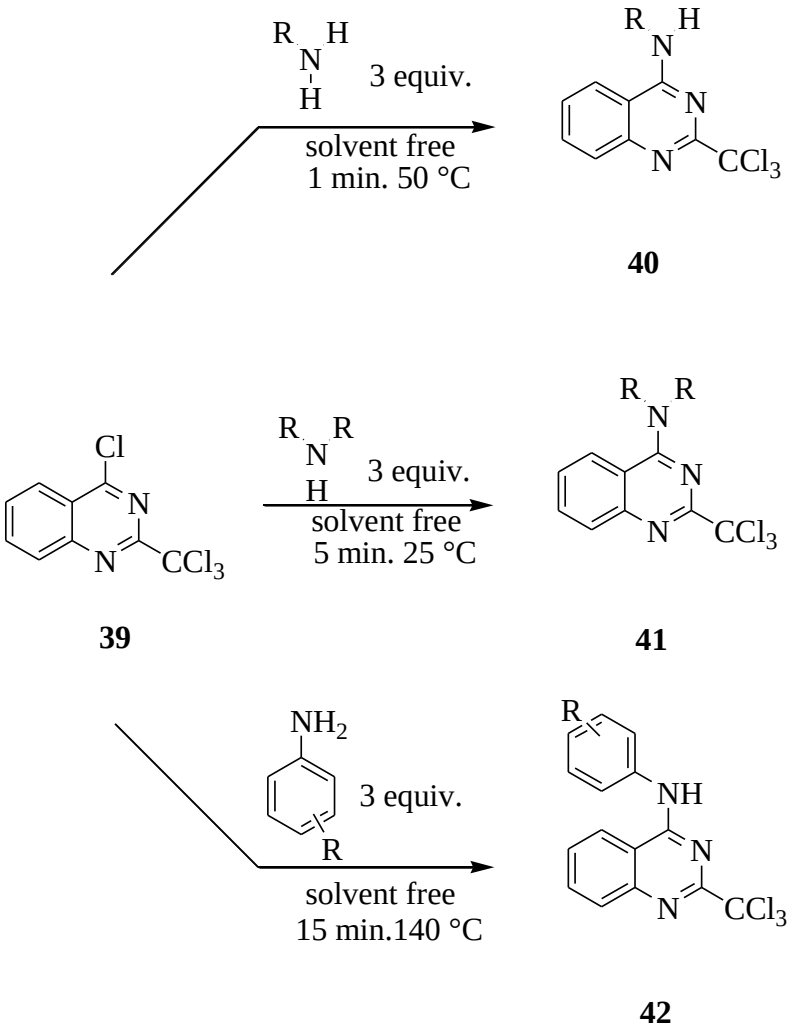
The 4-anilinoquinazolines can be prepared from nucleophilic substitution of 4-chloroquinazolines with aniline derivatives.[45,46] 2-Phenyl-4-chloroquinazoline **36** was treated with anilines **37** in boiling isopropanol for 3–4 h to afford 4-anilinoquinazolines **38** in 55–80% yield (Scheme 7).[45]




**36** **37** **38**

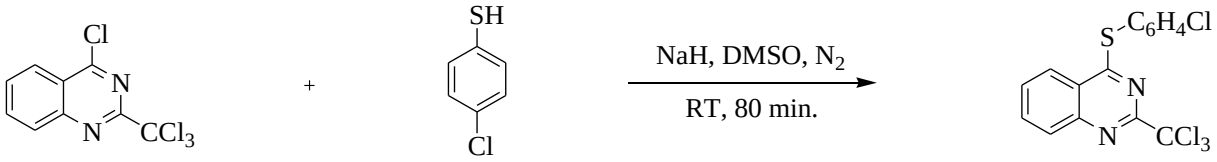
**Scheme 7**: Synthesis of 4-anilinoquinazolines **38**

Verhaeghe *et al* used 4-chloro-2-trichloromethylquinazoline **39** as precursor for the preparation of secondary alkylaminoquinazolines **40**, tertiary aminoquinazolines **41** and 4-anilinoquinazolines **42** respectively.[46] Compound **39** was treated with excess primary alkylamine under solvent free condition for 1 minute at 50 °C to afford secondary alkylaminoquinazolines **40** in 73–79% yield (Scheme 8).[46] Tertiary aminoquinazolines **41** were prepared in 89–99% yield following similar conditions.[46] The synthesis of 4-anilino-2-trichloromethylquinazolines **42** was achieved with anilines in 9–98% yield for 15 minutes (longer reaction time) at 140 °C due to steric effect originating from the amino group of the aniline analogues such as 2,6-dichloro-bisubstituted-aniline (Scheme 8).[46] Analogues of compound **42** were found to exhibit anti-plasmodial activity.[46]




**Scheme 8**: Dechloroamination of 4-chloro-2-trichloromethylquinazoline **39**

Sulfur based nucleophiles have also been employed for further transformation of 4-halogenoquinazolines into 4-thio substituted quinazolines.[47] 4-Chloroquinazolines **39** was reacted with a mixture of 4-chlorothiophenol **43** and dimethylsulfoxide in the presence of sodium hydride under nitrogen atmosphere at room temperature for 80 minutes to afford 4-thiophenoxy-2-trichloromethyquinazoline **44** in 68% yield (Scheme 9).[47]




**39** **43** **44**

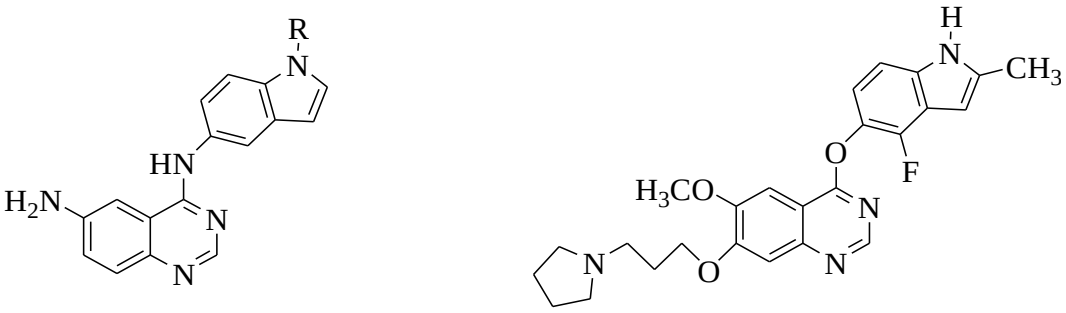
**Scheme 9**: Sodium hydride catalyzed condensation of 4-chloroquinazolines **39**

Molecular hybrids based on 4-chloroquinazoline as scaffold to append other heterocyclic scaffolds have also been reported in the literature. These methods will be described fully in the following sections.

### 1.2.6 Synthesis of C–C and C–heteroatom linked indole/benzofuran-quinazoline hybrids

Several molecular hybrids formed by linking quinazoline and another heterocyclic scaffold directly or through a heteroatom bridge/linkage have been prepared and found to exhibit interesting biological activities. 4-(1-Benzyl-1*H*-indol-3-yl)-6,7-dimethoxyquinazoline, for example, was found to exhibit good receptor tyrosine-protein kinase (ErbB-2) activity with little or no activity against the epidermal growth factor receptor.[48] 4-(Indole-3-yl)quinazoline derivatives were found to inhibit epidermal growth factor receptor tyrosine kinase (EGFR-TK) better than the reference standard tyrphostin with high cytotoxic properties against numerous cancer cell lines[49] $N^4$-(1*H*-indol-5-yl)quinazoline-4,6-diamines **45** (Figure 3) were found to

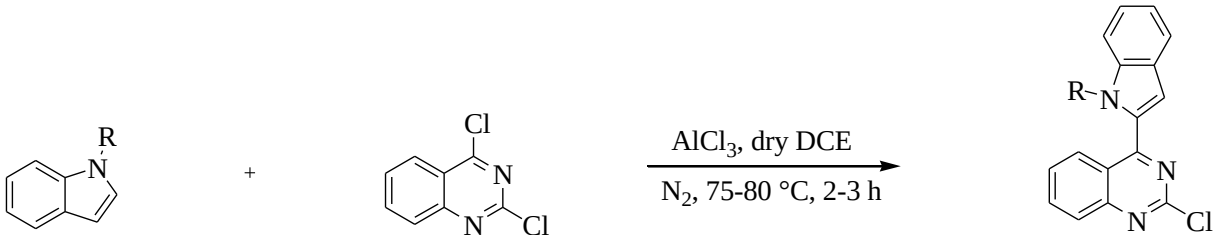
exhibit anti-inflammatory properties.[50] Cediranib or Recentin **46** (Figure 3) was used as anticancer drug.[51,52]




**45** **46**

**Figure 3**: Heterocycle appended quinazoline hybrids of biological importance

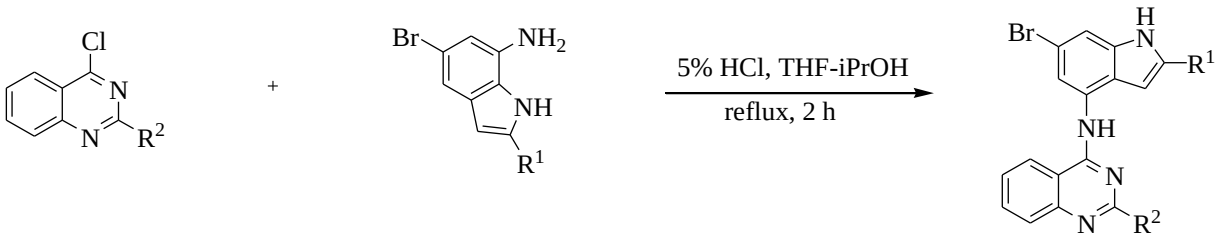
The synthesis of indole/benzofuran-quinazoline hybrids has been achieved through coupling of indolyl-magnesium compounds with 4-chloroquinazolines in diethyl ether under reflux and subsequent hydrolysis of the intermediates,[48] indium(III) chloride ($InCl_3$) catalyzed cross coupling of indole and 4-chloroquinazoline in acetonitrile under microwave irradiation to obtain indole-quinazoline hybrids[50] as well as cyclocondensation and Dimroth rearrangement of formamidine derivative and 5-substituted indoles in boiling acetic acid to afford indole-quinazoline hybrids.[53] 4-(3-Indolyl)quinazolines **49** were prepared in 83–85% yield from the reaction of indoles **47** with 2,4-dichloroquinazoline **48** in the presence of aluminium chloride as catalyst in hot dichloroethane (DCE) as solvent under inert atmosphere for 2–3 h (Scheme 10).[54] Compounds **49** exhibited anti-leishmanial and/or anti-proliferative activities against several cancer cell lines. [54]




**47** **48** **49**

**Scheme 10**: Synthesis of 4-(3-indolyl)quinazolines **49**

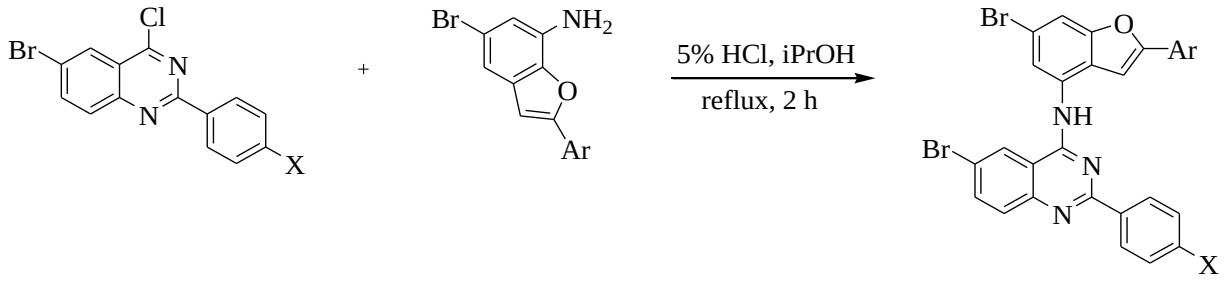
The acid-catalyzed nucleophilic substitution of the 4-chloroquinazoline derivatives **50** was achieved with 7-aminoindoles **51** in a mixture of tetrahydrofuran-isopropanol (THF–iPrOH) under reflux for 2 h to afford indole-4-aminoquinazoline analogues **52** in 67–83% yield (Scheme 11).[55] Compounds **52** were found to exhibit high cytotoxicity against numerous cancer cell lines and inhibitory activity towards EGFR-TK comparable to the reference standard gefitinib.




**50** **51** **52**

**Scheme 11**: Preparation of indole-4-aminoquinazoline analogues **52**

4-Chloroquinazoline derivatives **53** were condensed with benzofuran amines **54** using HCl as catalyst and isopropanol as solvent under reflux for 2 h to afford benzofuran-4-aminoquinazolines **55** in 67–87% yield (Scheme 12).[56] Compounds **55** were found to exhibit moderate to high cytotoxicity activity against A549 and HeLa cancer cell lines *in vitro* and inhibitory activity towards EGFR-TK similar to the reference standard gefitinib.




**53** **54** **55**

**Scheme 12**: Synthesis of benzofuran-4-aminoquinazolines **55**

The 2-, 4- and 2,4-dichloroquinazolines substituted with chlorine, bromine and/or iodine on the fused benzene ring were utilized in transition metal catalyzed cross-coupling reactions to produce polycarbo substituted quinazolines. These strategies will be described in detail in the following section.

### 1.3.1 Transition metal catalyzed cross-coupling of the halogenated quinazoline derivatives

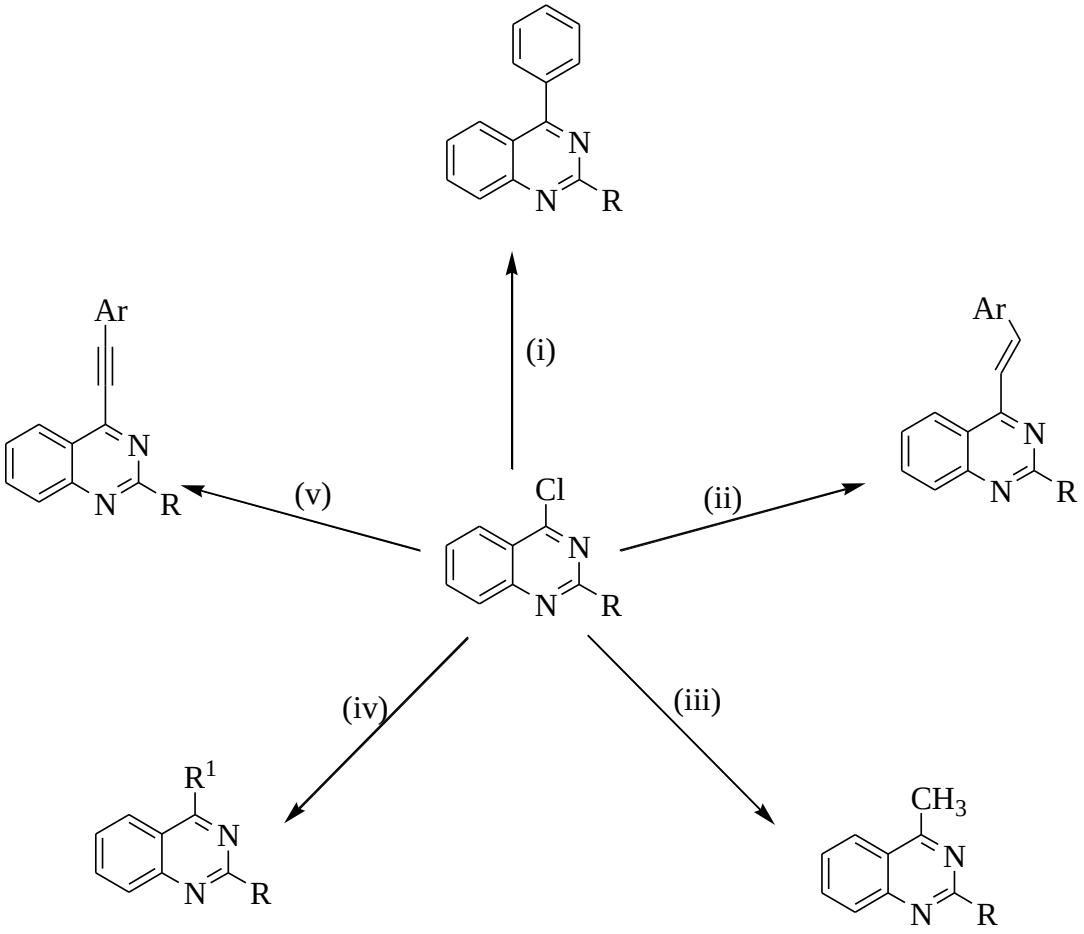
The transition metal-catalyzed cross-coupling reactions on halogenated quinazolines encourages the construction of carbon-carbon ($Csp^2$–$Csp^2$ or $Csp^2$–Csp) bond(s) using transition metals such as palladium- or nickel-based salts, copper(I) iodide and manganese chloride have been utilized broadly as catalysts in cross-coupling reactions such as the Kumada cross-coupling,[57,58] Suzuki cross-coupling,[57,59] Negishi cross-coupling,[57,60] Stille cross-coupling.[57,61] Sonogashira cross-coupling.[57,62] Sonogashira cross-coupling reaction which also uses Cu(I) salts as co-catalyst. The sequence of reactivity of the C$sp^2$–halogen bond of halogenated quinazolines is C$sp^2$–Cl < C$sp^2$–Br < C$sp^2$–I.[63] This comes out from the difference in C$sp^2$–halide bond strength which encourages selective coupling with bromides or iodides in the presence of chlorides.[63] Nevertheless, the C(4)–Cl bond of the 4-chloroquinazolines is initially substituted in the existence of C$sp^2$–Br due to α-nitrogen effect. Examples involving transformation of halogenated quinazolines into carbo

substituted derivatives using the above-mentioned transition metal catalyzed cross-coupling reactions form part of several review papers.[57–62] Some representative examples are discussed in this study and are generalized in Scheme 13 below.

Kumada cross-coupling reaction includes the reaction of organomagnesium reagents with aryl or heteroaryl halides.[57] The reaction is advanced by nickel-based catalysts such as dichloro(1,3-bis(diphenylphosphino)propane)nickel [$NiCl_2$(dppp)] or palladium Ni,[64] Fe,[65] Mn[66] and Co-based.[67] The reaction readily occurs at low temperature and diethyl ether is mostly used as a solvent of choice.[64] Kumada cross-coupling reaction has been employed for the fusion of carbo-substituted quinazolines. For example, 4-chloro-2-phenylquinazoline was exposed to Kumada cross-coupling reaction with phenylmagnesium chloride in the presence of manganese chloride as catalyst in THF for 1.5 h to afford 2,4-diphenylquinazoline in 71% yield (pathway (i) in Scheme 13).[57] The shortcoming of this reaction is the use of exceedingly nucleophilic organomagnesium reagents which react with other useful groups such as aldehydes, ketones, esters, and nitro groups.[68] The Suzuki-Miyaura cross-coupling reaction is the reaction of organoboronic acids and aryl-/vinylhalides or heteroaryl halides within presence of palladium catalysts to form C$sp^2$–C$sp^2$ bonds.[57] Inorganic bases such as sodium hydroxide (NaOH), caesium carbonate ($Cs_2CO_3$), or potassium hydroxide (KOH)] to stimulate the weakly nucleophilic boranes in the transmetalation step.[59] The Suzuki-Miyaura cross-coupling reaction has been widely used in the synthesis of polycarbo substituted quinazolines from halogenated antecedents. 4-Chloro-2-trichloromethylquinazoline, for example, was previously reacted with arylboronic acids in the presence of palladium acetate and $Cs_2CO_3$ in DMF for 2 h to afford 4-aryl-2-trichloromethylquinazolines in 50–65% yield (pathway (ii) in Scheme 13).[32,57] This method has several advantages over the Kumada reaction such as substantial functional group compatibility, little toxicity of reagents and intermediates, readily accessible boron compounds,

high temperature stability and good tolerance toward air and aqueous solvents.[57,69] Negishi cross-coupling reaction involves the reaction of organozinc reagents (R–ZnX) with aryl halides or heteroaryl halides in the presence of palladium catalysts.[57,60] The organozinc reagent can also be produced from the equivalent halide R–X by reductive metalation or via transmetalation of organolithium compounds (R–Li).[70] Bis(triphenylphosphine)palladium(II)dichloride [$PdCl_2(PPh_3)_2$] or 1,1'bis(diphenyl-phosphino)ferrocene palladium dichloride [$PdCl_2$(dppf)] are mostly used as catalyst in either diethyl ether or tetrahydrofuran as solvent.[71] This reaction has also been employed for the preparation of polycarbo-substituted quinazolines. The palladium-catalyzed Negishi cross-coupling reaction of 4-halogenoquinazoline with methyllithium ($CH_3Li$) and zinc(II) chloride ($ZnCl_2$) in dioxane for 1 h afforded carbo substituted quinazoline (pathway (iii) in Scheme 13).[57] The advantages of Negishi cross-coupling reaction include moderate tolerance to various functional groups and the reaction can be carried out at room temperature or under warm conditions because zinc compounds are unstable at higher temperatures.[57] The Stille cross-coupling reaction involves the cross coupling of organostannanes with organic halides or triflates in the presence of palladium catalysts.[57,61] This method has also been used to prepare carbo-substituted quinazolines. 2,4-Dichloro-6,7-dimethoxyquinazoline was subjected to a mixture of organostannane reagents, $Pd(PPh_3)_2Cl_2$ as a catalyst and xylene as solvent at 110 °C to afford 4-alkylated analogues (pathway (iv) in Scheme 13).[72] The observed selectivity was because C–4 is more electrophilic than C–2 due to α-nitrogen effect. The drawbacks of this method include catalysts poisoning by tin compounds used and little solubility in water for easy work up.[57,61] The Sonogashira cross-coupling reaction is the construction of a C$sp^2$–C$sp$ bond *via* the reaction of organic halides with terminal alkynes using palladium catalysts, copper iodide as a co-catalyst, a base and a solvent under inert atmosphere.[57,62] This reaction has also been employed for the construction of carbo-substituted quinazolines. 2,4-Dichloroquinazoline, for

example was subjected with phenylacetylene under Sonogashira conditions to afford 2-chloro-4-phenyl-substituted quinazoline (pathway (v) in Scheme 13).[73]



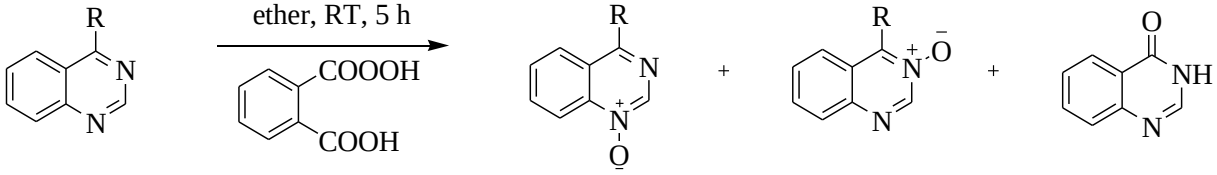

**Scheme 13**: Generalized scheme for metal catalyzed cross-coupling reactions

The nitrogen atom of the quinazoline scaffolds are susceptible to oxidation to form quinazoline 1- or 3-oxides. The methods of preparation of quinazoline oxides will be examined in detail in subsequent section.

### 1.3.2 Oxidation of quinazoline ring

#### 1.3.2.1 Synthesis of quinazoline 1-oxides

A mixture 4-alkylsubstituted quinazoline 1-oxide **58a**–**b**, 4-alkylsubstituted quinazoline 3-oxide **59a**–**b** and quinazolin-4-one **60** were prepared in one pot procedure through direct oxidation of 4-alkylsubstituted quinazoline **56a**–**b** with 1.2–1.3 (equiv.) of monoperphthalic acid **57** in ether at room temperature for 5 h (Scheme 14).[74] The use of 1.2–1.3 (equiv.) of monoperphthalic acid **57** in the reaction resulted in the formation of mixture of products.[74]




R = $CH_3$ (a), $CH_2CH_3$ (b)

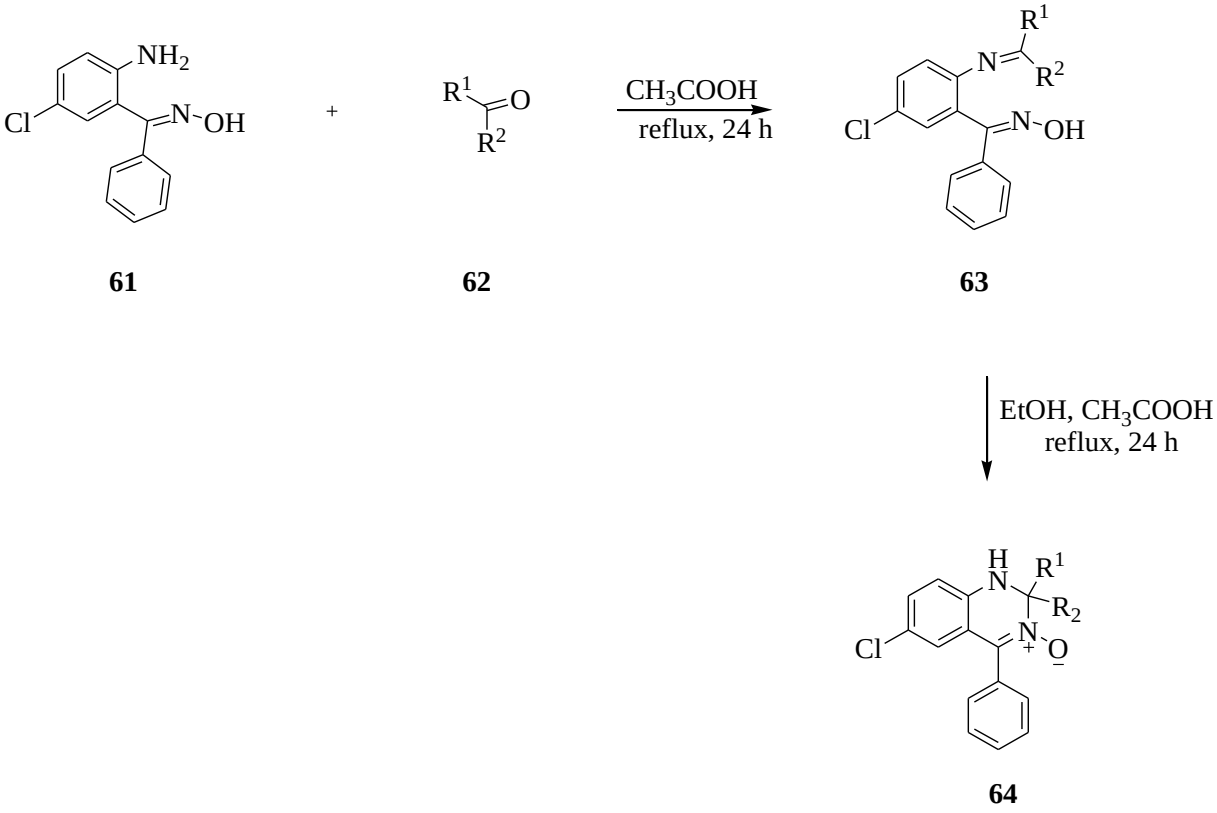
**56a–b** **57** **58a–b** **59a–b** **60**

**Scheme 14**: Oxidation of 4-alkylsubstituted quinazoline **56a**–**b**

#### 1.3.2.2 Synthesis of quinazoline 3-oxides

The most common strategies for the preparation of the quinazoline 3-oxides are based upon coordinate oxidation of quinazoline ring,[74,75] cycloaddition of acylaminoacetophenone derivatives with hydroxylamine hydrochloride,[76] intramolecular cyclization of 2-amino aldoximes with isothiocyanate under reflux[77] and *p*-toluenesulfonic acid facilitated cyclization of 2-aminoacetophenone oxime derivatives with benzaldehydes at room temperature.[78] Rh(III)/Zn(II) catalysts have been used to react ketoximes with dioxazolone to afford quinazoline 3-oxides.[79] Silver-promoted transformation of *o*-acylaryl isocyanides with hydroxylamine

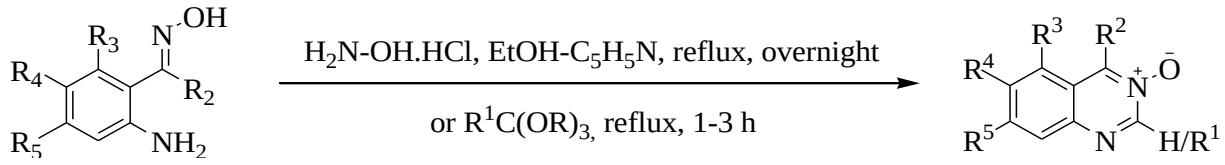
hydrochloride also afforded quinazoline 3-oxides.[80] 2-Aminoacetophenone oxime analogue **61** were reacted with boiling butanedione monooxime **62** to afford ketoximes **63** (Scheme 15).[81] Compounds **63** were cyclized in ethanol-acetic acid mixture under reflux for 24 h to afford quinazoline 3-oxides **64** in 60–75% yield.[81] Compounds **64** were found to exhibit antitumor activity.




**61** **62** **63** **64**

**Scheme 15**: Synthesis of quinazoline 3-oxides **64**

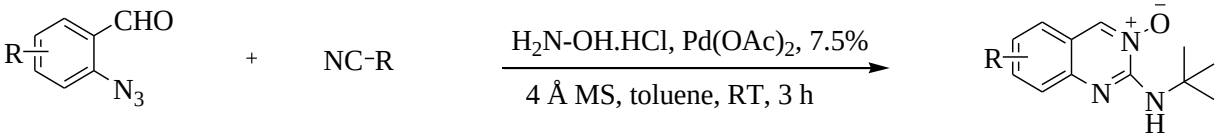
Multisubstituted quinazoline 3-oxides **66** were constructed in 12–95% yield by the reaction of 2-aminoacetophenone oximes **65** with hydroxylamine hydrochloride in boiling EtOH–$C_5H_5N$ mixture overnight (Scheme 16).[82] Compounds **66** can also be prepared from the treatment of compounds **65** with triethylorthopropionate or triethylorthoacetate under reflux for 1–3 h.[82] Analogues of compound **66** were used as cardiotonic and bronchodilating agents.




**65** **66**

**Scheme 16**: Synthesis of multisubstituted quinazoline 3-oxides **66**

The synthesis of quinazoline 3-oxides has also been achieved via a multi-component reaction of 2-azido benzaldehydes **67** with isocyanides **68** and hydroxylamine hydrochloride in $Pd(OAc)_2$-toluene mixture at room temperature for 3 h to afford quinazoline 3-oxides **69** in 71–92% yield (Scheme 17).[83]




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

**Scheme 17**: Multi-component strategy for the synthesis of quinazoline 3-oxides **69**

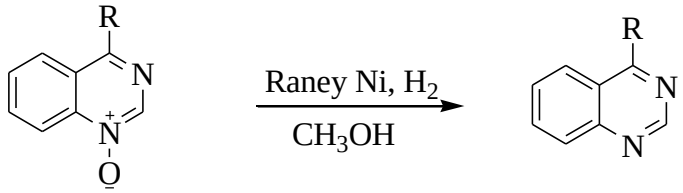
Quinazolines *N*-oxides have been transformed into quinazolines. Moreover, quinazoline oxides can be transformed into other heterocyclic compounds of biological importance. These methods will be discussed in detail in the following sections.

### 1.3.3 Transformation of quinazoline *N*-oxides

The procedures for the deoxygenation and/or expansion of quinazolines *N*-oxides to quinazolines or benzodiazepines include catalytic reduction of quinazolines *N*-oxides using Raney Ni catalyst,[74] acetoxylation[79] and ring expansion to benzodiazepines.[84,85]

### 1.3.3.1 Deoxygenation of quinazoline *N*-oxides

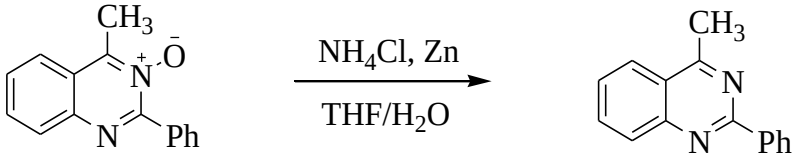
Deoxygenation of quinazoline 1-oxide was achieved through catalytic hydrogenation of 4-substituted quinazolines 1-oxides **70** in the presence of Raney Ni catalyst under $H_2$ stream in MeOH to afford 4-substituted quinazoline **71** in 33–43% yield (Scheme 18).[74]




**70** **71**

**Scheme 18**: Catalytic hydrogenation of 4-substituted quinazolines 1-oxides **70**

4-Methyl-2-phenylquinazoline 3-oxide **72** was also deoxygenated by Zn in the presence of aqueous $NH_4Cl$ in THF to afford 4-methyl-2-phenylquinazoline **73** in 71% yield (Scheme 19).[79]



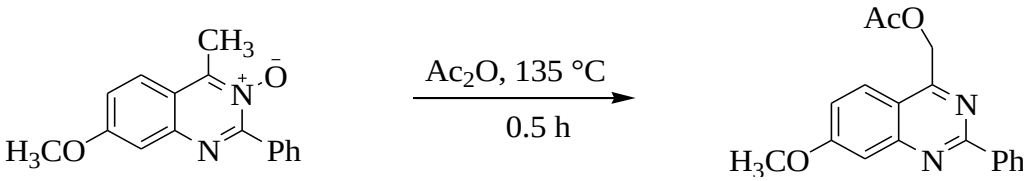

**72** **73**

**Scheme 19**: Zn-catalyzed deoxygenation of 4-methyl-2-phenylquinazoline 3-oxide **72**

### 1.3.3.2 Alkylation of quinazoline *N*-oxides

The highly acidic proton of methyl group has been found to promote the acetoxylation of methyl substituted quinazoline-3-oxide derivative to ester derivatives.[79] 4-Methyl-7-methoxy-2-phenyl substituted quinazoline 3-oxide **74**, for example, was subjected to acetoxylation

reaction with acetic anhydride under reflux for 0.5 h to afford ester **75** in 82% yield (Scheme 20).[79]

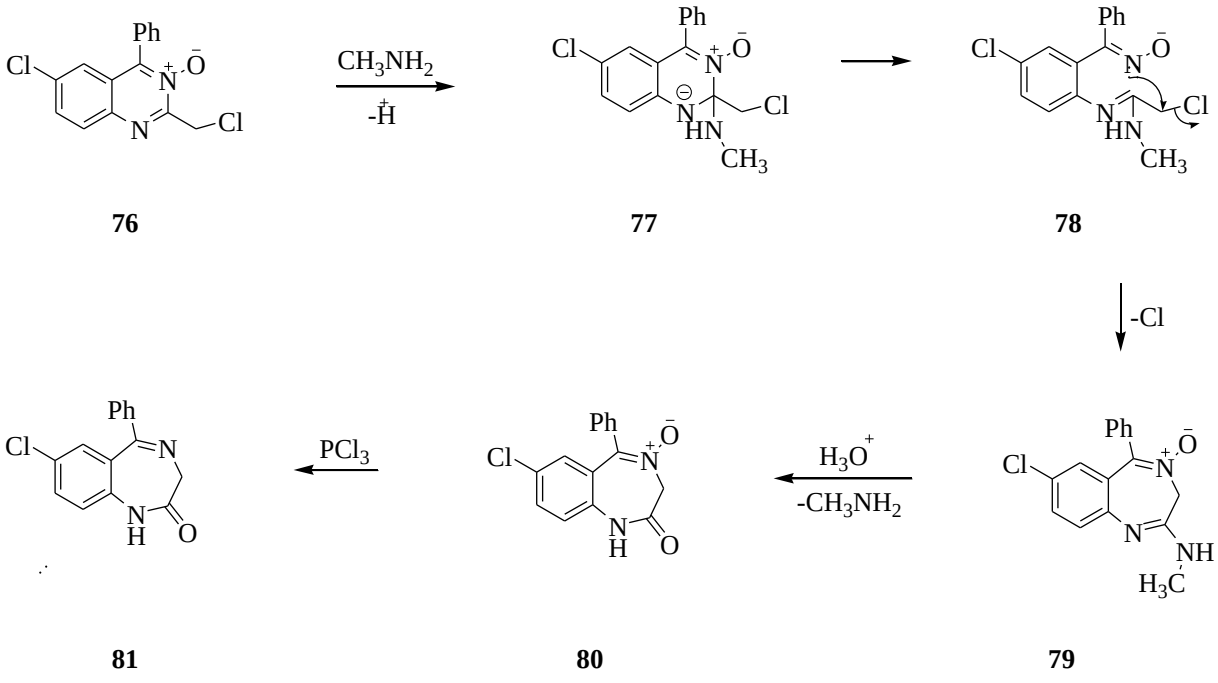



**74** **75**

**Scheme 20**: Alkoxylation of 4-methyl-7-methoxy-2-phenyl substituted quinazoline 3-oxide **74**

### 1.3.3.3 Ring expansion of quinazoline 3-oxides

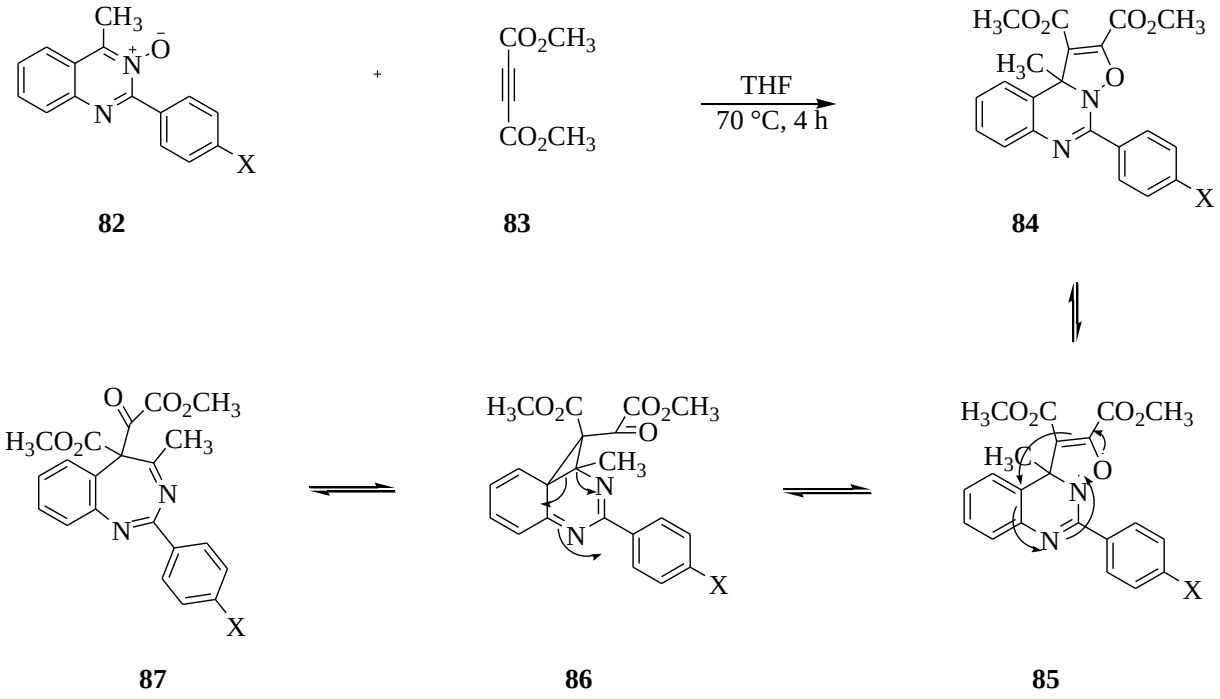
The benzodiazepine derivatives have been prepared from deoxygenation and ring expansion of quinazoline 3-oxide.[84,85] 2-Chloromethyl quinazoline 3-oxide **76** was subjected to ring expansion and rearrangement to afford chlorodiazepoxide **79** via intermediates **77** and **78** (Scheme 21).[84,85] Acid hydrolysis of the later afforded benzodiazepin-2-one-4-oxide **80** which was subsequently deoxygenated with $PCl_3$ to afford 1,4-benzodiazepine (diazepam) **81**.[84,85]




**76** **77** **78** **79** **80** **81**

**Scheme 21**: Ring expansion of 2-chloromethyl quinazoline 3-oxide **76**

In another example, 2,4-disubstituted quinazoline-3-oxide **82** was subjected to 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) **83** in THF at 70 °C for 4 h to afford methyl 5-(2-methoxy-2-oxoacetyl)-4-methyl-2-phenylsubstituted-5*H*-benzo[*d*][1,3]diazepine-5-carboxylate **87** in 67–74% yield via intermediates **84**, **85** and **86** respectively (Scheme 22).[85]




**82** **83** **84**

**87** **86** **85**

**Scheme 22**: DMAD **83** assisted ring expansion of 2,4-disubstituted quinazoline-3-oxide **82**

### 1.4. Research hypothesis

The methods of synthesizing quinazoline 3-oxides have attracted interest in organic synthesis due to their biological properties as antitumor,[81] cardiotonic and bronchodilating agents.[82] However, the shortfalls of these methods include poor yield, hazardous reaction conditions and expensive reagents.[80] We envisaged that 2,4-dicarbo substituted quinazoline 3-oxides could be afforded upon aqueous workup from ring closure of oximes with trifluoroacetic acid (TFA) under reflux. The advantages of using TFA include low boiling point and high soulubility in water as

well as promoting rearrangement reactions such as the Beckmann rearrangement of keto-oximes into amides or lactams.[86,87] The halogenated quinazoline 3-oxides can further be subjected to metal catalyzed (Suzuki) cross-coupling reaction to afford 2,4,6-tricarbo substituted quinazoline 3-oxides analogues. The following aims and objectives were drafted based on these assumptions.

### 1.5 Aims and objectives of study

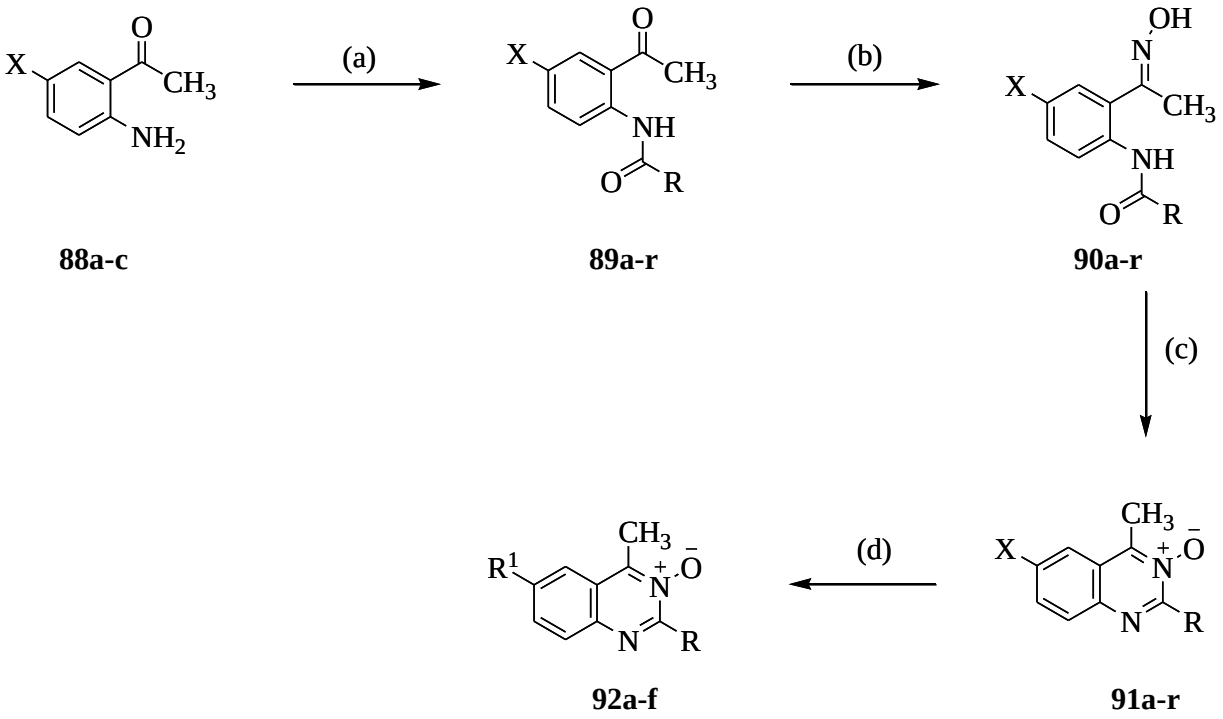
The aims and objectives of this research are:

- to synthesize *N*-[2-(1-hydroxyiminoethyl)phenyl]amide derivatives and *N*-(5-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives from the *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halophenyl)amide precursors.
- to subject the *N*-[2-(1-hydroxyiminoethyl)phenyl]amide derivatives and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives to intramolecular cyclization to afford 2,4-dicarbo substituted quinazoline 3-oxides.
- to further subject 6-iodo quinazoline 3-oxides to metal catalyzed (Suzuki) cross-coupling reaction to afford the 2,4,6-tricarbo substituted quinazoline 3-oxides.

# CHAPTER 2 RESULTS AND DISCUSSION

## 2.0 Generalized reaction pathway

The reaction pathways executed in this investigation are represented in Figure 4 below. The 5-halogeno-2-aminoacetophenone derivatives **88b**–**c** (X = Br (b), and I (c)) used as substrates in this investigation were prepared via halogenation of the commercially available 2-aminoacetophenone **88a** (Sigma-Aldrich (PTY) LTD, Kempton Park, Gauteng, South Africa). The 2-aminoacetophenones **88a**–**c** were subjected to acetylation and benzoylation reaction with acetic anhydride and benzoyl chloride derivatives to afford *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halophenyl)amide derivatives **89a**–**r**. The *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halophenyl)amide derivatives **89a**–**r** were treated with hydroxylamine hydrochloride in pyridine under reflux to afford the *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives **90a**–**r**. Ring closure of the *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives **90a**–**r** with trifluoroacetic acid under reflux afforded the 2,4-dicarbo substituted quinazoline 3-oxides **91a**–**r**. Suzuki-Miyaura cross-coupling reaction of the 6-iodo substituted quinazoline 3-oxides **91m**–**r** with 4-fluorophenylboronic acid as a coupling partner afforded the 2,4,6-tricarbo substituted quinazoline 3-oxides **92a–f**.




**88a-c** **89a-r** **90a-r** **91a-r** **92a-f**

(a) Acetylation/benzoylation; (b) oxime preparation; (c) ring closure; (d) Suzuki-Miyaura cross-coupling

**Figure 4:** Generalized scheme describing the reaction pathways undertaken to prepare the compounds depicted in this research.

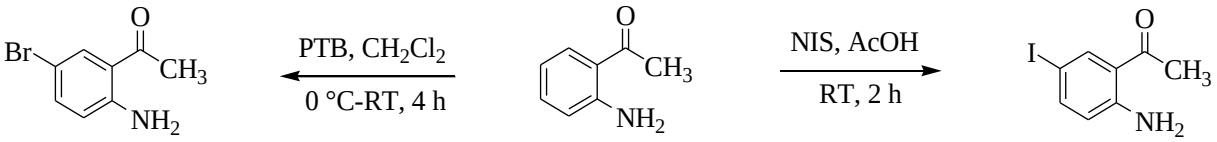
### 2.1 Preparation of substrates

The synthesis of 5-substituted-2-aminoacetophenone derivatives **88b–c** (X = Br (b) and I (c)) used as precursors in this study and their transformation into *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halophenyl)amide derivatives are described in the next sections.

### 2.1.1 Synthesis of 2-amino-5-bromoacetophenone 88b and 2-amino-5-iodoacetophenone 88c

Numerous methods have been reported for the preparation of 2-amino-5-bromoacetophenone and 2-amino-5-iodoacetophenone. Baker *et al*.[88] prepared 2-amino-5-bromoacetophenone in 80% yield by subjecting 2-aminoacetophenone to pyridinium tribromide (1 equiv.) in dichloromethane (DCM) at 0 °C to room temperature. In another example, 2-amino-5-bromoacetophenone was prepared by reacting 2-aminoacetophenone with *N*-bromosuccinimide (1 equiv.) in acetonitrile at 0 °C to room temperature for 3 h.[89] 2-Amino-5-bromoacetophenone and 2-amino-3,5-bromoacetophenone were prepared from the reaction of 2-aminoacetophenone with excess pyridine hydrobromide perbromide (ca. 40% activated bromine) at 0 °C to room temperature.[90] We opted for a less hazardous and easy to control literature procedure by Baker *et al*.[88] and subjected 2-aminoacetophenone **88a** (X = H) to pyridinium tribromide in dichloromethane at 0 °C to room temperature for 2 h to afford **88b** (X = Br) in 82% yield (Scheme 23). 2-Amino-5-iodoacetophenone was previously prepared by reacting 2-aminoacetophenone with *N*-iodosuccinimide in acetic acid at room temperature for 2 h.[91] Aqueous potassium dichloroiodate was added slowly to a solution of 2-aminoacetophenone in water and the reaction mixture was stirred at room temperature overnight to afford 2-amino-5-iodoacetophenone in 86% yield.[92] We opted for the method with lesser reaction time[91] and subjected 2-aminoacetophenone to *N*-iodosuccinimide in acetic acid at room temperature for 2 h to afford 2-amino-5-iodoacetophenone **88c** in 92% yield (Scheme 23). Both the 3- and 5-position of **88a** are jointly activated by the *ortho-para* directing and *meta*-directing effect of the amino and the acetyl group, respectively. However, steric hindrance at the *ortho* position to $NH_2$ would direct electrophilic attack by the bulky pyridinium tribromide or *N*-iodosuccinimide to the 5-position to form **88b** or **88c**, respectively. The $^1H$

NMR spectrum of **88b** used as representative model in Figure 5a revealed the presence of a broad singlet at δ 6.44 ppm which correspond to the proton of the amino group. The spectrum also shows the presence of doublet of doublet at δ 7.47 ppm for H-4 (dd, *J* = 2.4 and 8.7 Hz), doublet at δ 6.70 ppm for H-3 (d, *J* = 8.7 Hz), and doublet due to long range coupling at δ 7.93 ppm for H-6 (d, *J* = 2.4 Hz) (Figures 5a). The $^{13}$C NMR spectrum of **88b** differs from that of **88c** by the presence of C–Br peak at δ 106.6 ppm (Figure 5b) while C–I peak was revealed at δ 75.4 ppm.

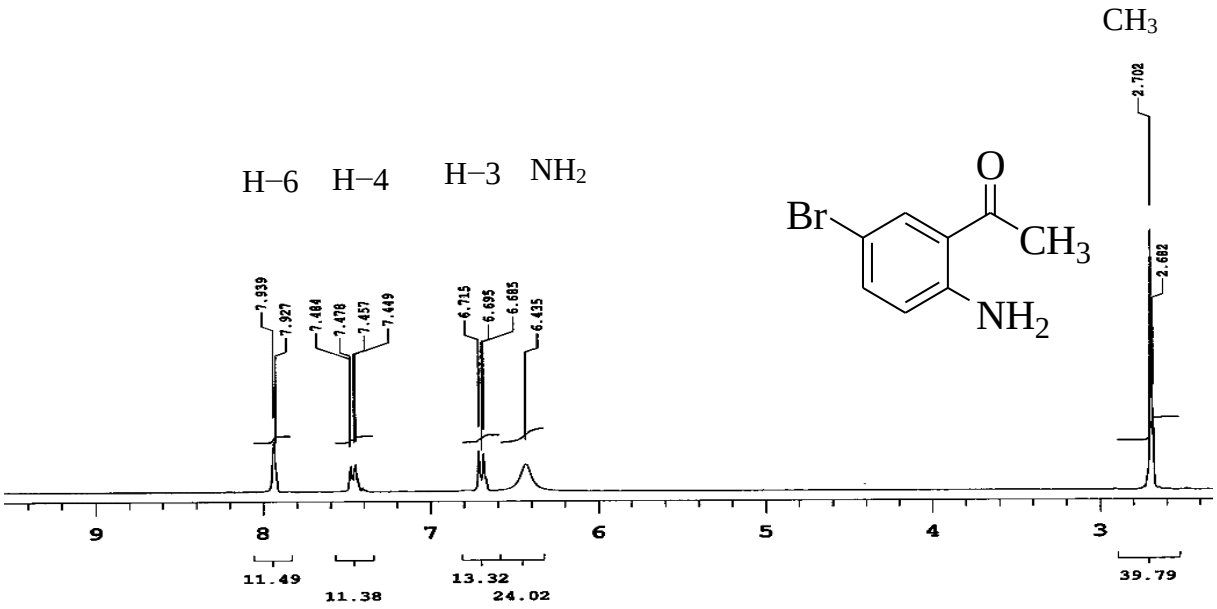



**88b** **88a** **88c**

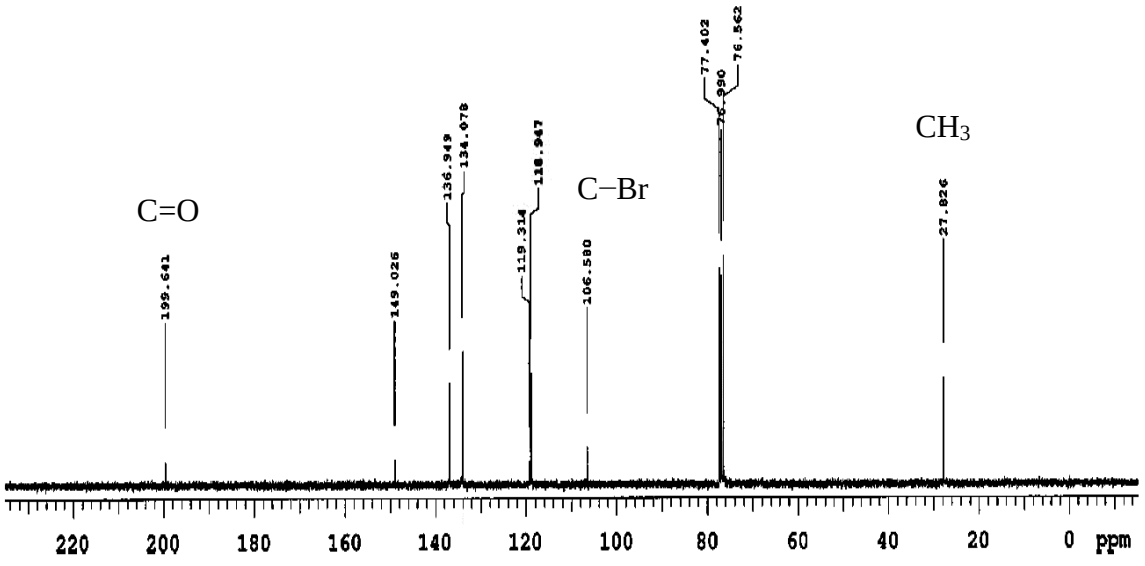
**Scheme 23**: Regioselective C–5 halogenation of 2-aminoacetophenone **88a**

**Table 1:** Substitution pattern, percentage yields and melting point values of **88b**–**c**

| **88** | **X** | **%Yield** | **mp. °C (Lit.)** |
|---|---|---|---|
| **b** | Br | 82% | 83−84 (Lit.[88] 82−83) |
| **c** | I | 92% | 97−98 (Lit.[91] 98.5−99) |




(**a**)



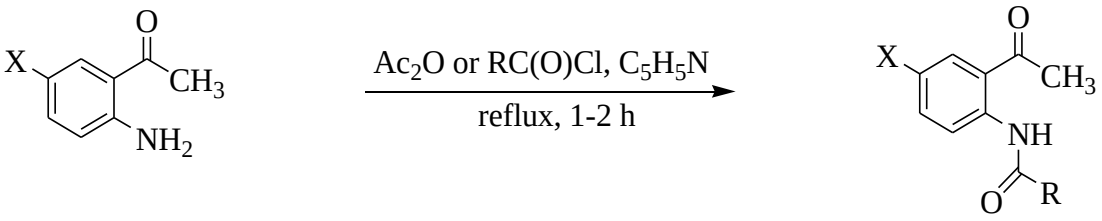

(**b**)

**Figure 5**: $^{1}$H- and $^{13}$C NMR spectra of 2-amino-5-bromoacetophenone **88b** in $CDCl_3$ at 300 MHz (a) and 75 MHz (b), respectively.

The prepared compounds **88b**−**c** could serve as substrates for the transformation of 5-substituted 2-aminoacetophenone derivatives **88a**−**c** into *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halophenyl)amide derivatives **89a**−**r** are described in the next section.

### 2.1.2 Acetylation/benzoylation of 2-aminoacetophenone derivatives 88a−c

Several methods have been reported in the literature for the acetylation or benzoylation of 2-aminoacetophenone derivatives.[93−95] In one method, 2-aminoacetophenone was condensed with aryl chlorides in dichloromethane (DCM) at room temperature for 24 h in the presence of triethylamine as a base to capture HCl to afford the corresponding amides.[93] 2-Aminoacetophenone has also been reacted with aryl chlorides in the presence of pyridine as a catalyst in anhydrous DCM at room temperature for 16 h to afford the amides.[94] Verma *et al*, prepared the amides by treating 2-aminoacetophenone derivatives with a solution of acetic anhydride or aryl chlorides in DCM in the presence of triethylamine at 0 °C for 4−5 h.[95] We envisioned that 2-amino group would activate the enolizable acetyl group of 2-aminoacetophenone derivatives **88a–c** towards acetylation or benzoylation reaction in the presence of acetic anhydride or aryl chlorides in pyridine to afford the corresponding amides **89a**−**r**. We modified the method used by Luo *et al*[93] by adding acetic anhydride or aryl chloride derivatives dropwise to a mixture of 2-aminoacetophenone **88a**−**c** in pyridine (10 mL). The reaction mixtures were heated under reflux for 1−2 h to afford *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halophenyl)amide derivatives **89a**−**r** in 68−95% yield (Scheme 24). The prepared *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halophenyl)amide derivatives **89a**−**r** were characterized using NMR ($^{1}$H and $^{13}$C), IR and mass spectrometric techniques. The $^{1}$H NMR spectrum of **89a** used as a representative model is shown in Figure 6a, revealed the presence of a set of singlets at δ 2.38 ppm and δ 11.84 ppm integrating for three (3) protons and one (1) proton which correspond to the methyl group and N-H proton, respectively. The peaks at δ 169.7 ppm (amide) and δ 203.0 ppm (acetyl) in the $^{13}$C NMR spectrum correspond to the two carbonyl carbons (Figure 6b). Their presence was also confirmed by the infrared bands at $\nu_{max}$ 1650 cm$^{-1}$ (amide) and 1686 (acetyl) cm$^{-1}$ (Figure 7), respectively.



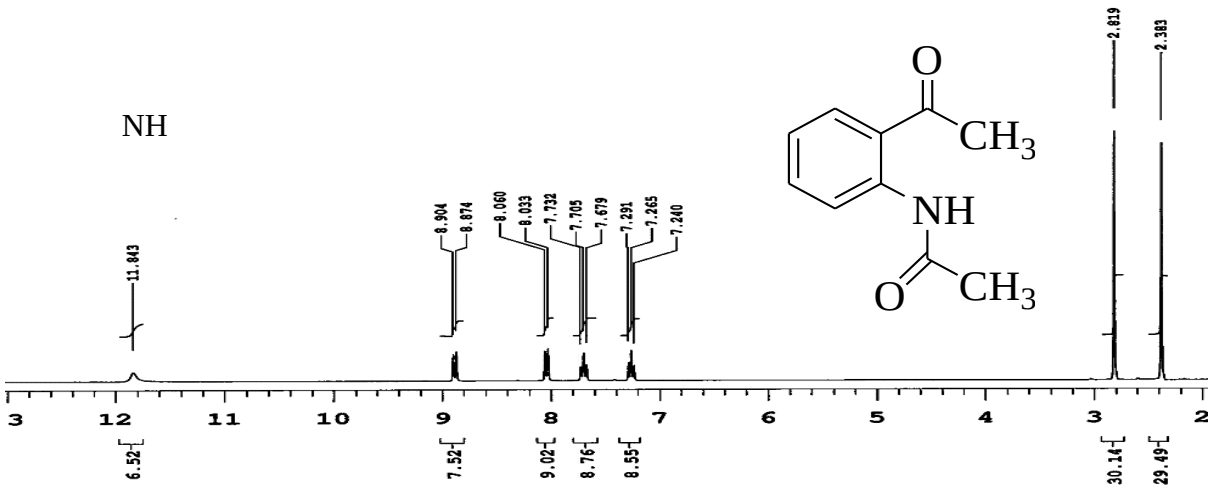

**88** X = H (**a**), Br (**b**), I (**c**) **89a**–r

**Scheme 24**: Acetylation and benzoylation of 2-aminoacetophenone derivatives **88a**–**c**

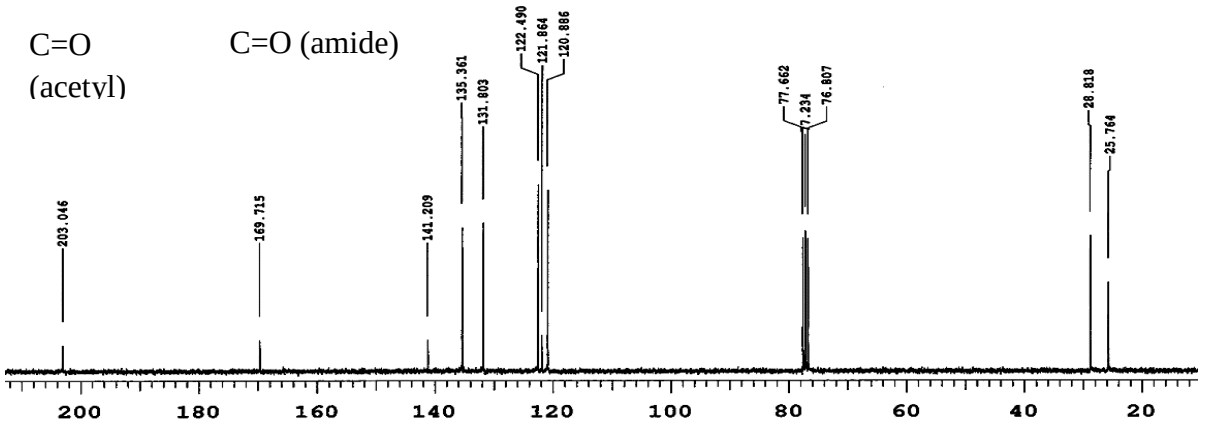
**Table 2**: Substitution pattern, percentage yields and melting point values of **89a**–**r**

| 89 | X | R | % Yield | mp. (°C) |
|---|---|---|---|---|
| **a** | H | -$CH_3$ | 68 | 64−66 (Lit.[95] 62−64) |
| **b** | H | -$CH(CH_3)_2$ | 90 | liquid (Lit.[95]) |
| **c** | H | -$C_6H_5$ | 90 | 101−103 (Lit.[95] 98−100) |
| **d** | H | - $C_6H_4F$ | 78 | 92−94 (Lit.[95] 90−92) |
| **e** | H | - $C_6H_4Cl$ | 93 | 111−113 (Lit.[96] 113−115) |
| **f** | H | -$C_6H_4OMe$ | 95 | 120−122 (Lit.[95] 119−120) |
| **g** | Br | -$CH_3$ | 79 | 160−162 (Lit.[96] 158−160) |
| **h** | Br | -$CH(CH_3)_2$ | 87 | 107−109 |
| **i** | Br | -$C_6H_5$ | 84 | 105−107 (Lit.[96] 105−106) |
| **j** | Br | - $C_6H_4F$ | 95 | 182−184 |
| **k** | Br | - $C_6H_4Cl$ | 85 | 158−160 |
| **l** | Br | -$C_6H_4OMe$ | 87 | 167−169 |
| **m** | I | -$CH_3$ | 86 | 171−173 |
| **n** | I | -$CH(CH_3)_2$ | 84 | 92−94 |
| **o** | I | -$C_6H_5$ | 75 | 101−103 |
| **p** | I | - $C_6H_4F$ | 83 | 145−147 |

| | | | | |
|---|---|---|---|---|
| **q** | I | - $C_6H_4Cl$ | 90 | 155−157 |
| **r** | I | -$C_6H_4OMe$ | 93 | 156−158 |




(**a**)




(**b**)

**Figure 6**: $^{1}H$- and $^{13}C$ NMR Spectra of *N*-(2-acetyl-phenyl)-acetamide **89a** in $CDCl_3$ at 300 MHz (**a**) and 75 MHz (**b**) respectively.

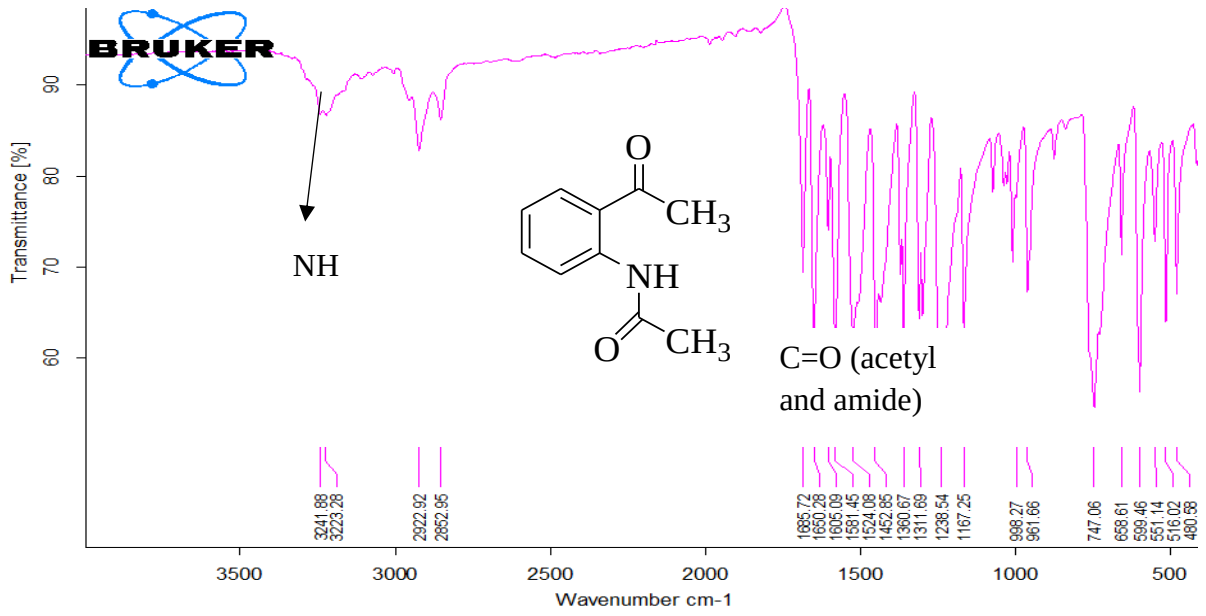


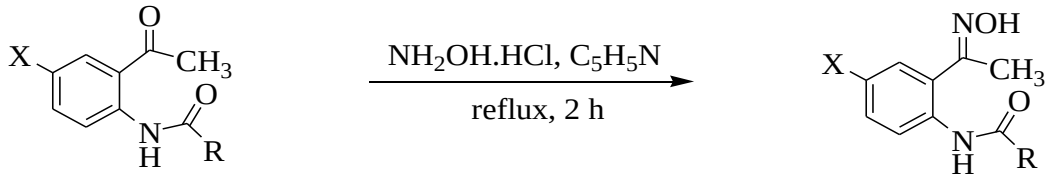

**Figure 7**: IR Spectrum of *N*-(2-acetyl-phenyl)-acetamide **89a**.

The presence of the carbonyl in compounds **89a**–**r** facilitates further transformation of the amides to *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives. Compounds **89a**–**r** were subjected to nucleophilic substitution reaction with hydroxylamine hydrochloride to afford *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives **90a–r** as described below.

## 2.2 Preparation of *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives 90a–r

The most widely used methods for the synthesis of ketoximes include nucleophilic substitution reaction of ketone with hydroxylamine hydrochloride in boiling pyridine[97] and/or boiling mixture of ethanol and pyridine.[97,98] Aldoximes can be prepared from the reaction of aldehydes with hydroxylamine hydrochloride $KF/Al_2O_3$ in microwave oven.[97] We treated compound

**89a**–**r** with hydroxylamine hydrochloride in pyridine under reflux to afford *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives **90a**–**r** in 70–95% yield (Scheme 25). We opted for the use of pyridine as solvent and base because the oximes were obtained as the major product in a shorter time whereas the boiling mixture of ethanol and pyridine as catalyst afforded a mixture of products which were difficult to isolate on column chromatography. Compounds **90a**–**r** were characterized using NMR ($^{1}$H- and $^{13}$C NMR), IR spectroscopic techniques and mass spectrometry. The $^{1}$H NMR spectra of compounds **90a**–**r** represented by spectrum of compound **90a** in Figure 8a revealed the presence of singlet signal at $\delta_H$ 8.67 ppm which correspond to -OH group. The $^{13}$C NMR spectrum of compound **90a** (Figure 8b) revealed the C=N signal more up-field at $\delta_C$ 157.9 ppm than that of the corresponding precursor's C=O signal at $\delta_C$ 203.0 ppm which confirmed complete conversion of **89a** to **90a**. The IR spectrum further confirms the presence of $\nu_{OH}$ and $\nu_{C=N}$ at 3172 cm$^{-1}$ and 1631 cm$^{-1}$ respectively as shown in Figure 9.



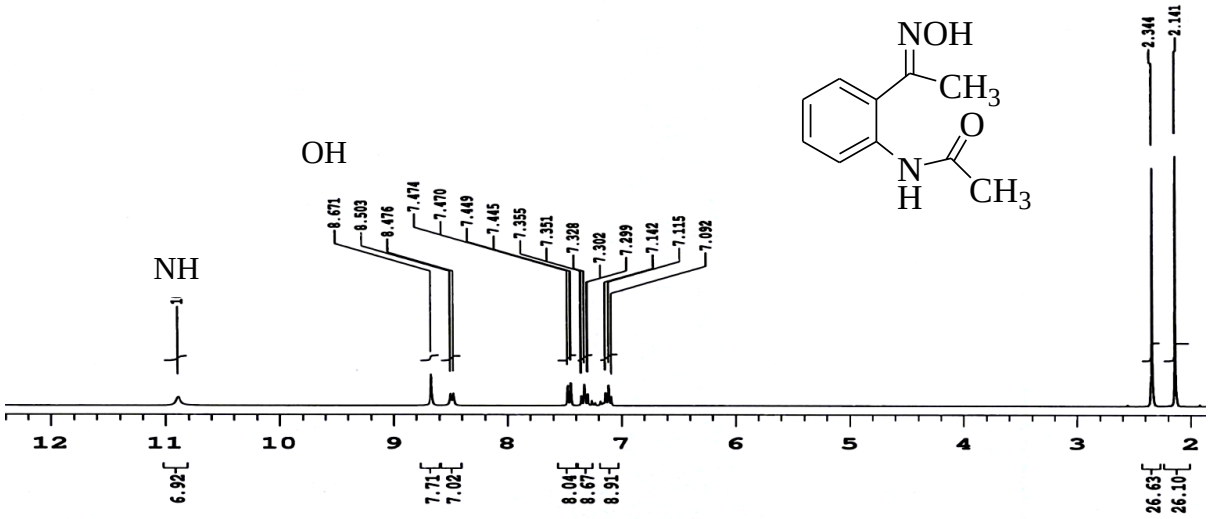

**89a**–r **90a**–r

**Scheme 25**: Preparation of **90a**–**r**.

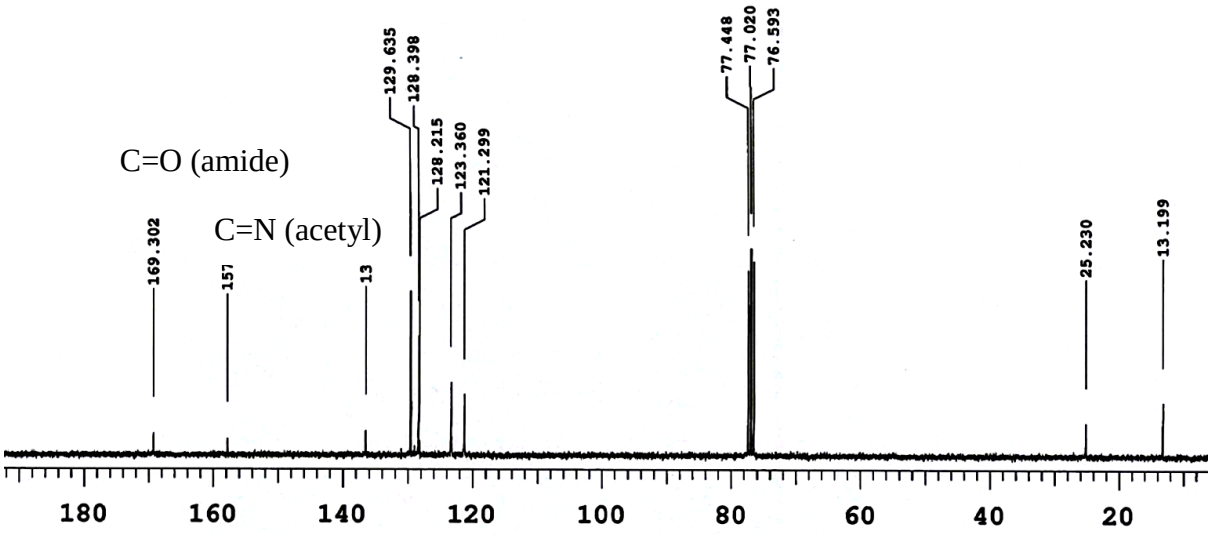
**Table 3**: Substitution pattern, percentage yields and melting point values of **90a**–**r**

| 90 | X | R | % Yield | mp. (°C) |
|---|---|---|---|---|
| **a** | H | -$CH_3$ | 78 | 75–77 |
| **b** | H | -$CH(CH_3)_2$ | 75 | 118–119 |
| **c** | H | -$C_6H_5$ | 70 | 182–185 (Lit.[79] 183) |
| **d** | H | - $C_6H_4F$ | 84 | 192–194 |

| | | | | |
|---|---|---|---|---|
| **e** | H | - $C_6H_4Cl$ | 76 | 152–154 |
| **f** | H | -$C_6H_4OMe$ | 73 | 147–149 |
| **g** | Br | -$CH_3$ | 73 | 158–160 |
| **h** | Br | -$CH(CH_3)_2$ | 77 | 173–175 |
| **i** | Br | -$C_6H_5$ | 84 | 186–188 |
| **j** | Br | - $C_6H_4F$ | 95 | 205–207 |
| **k** | Br | - $C_6H_4Cl$ | 75 | 194–196 |
| **l** | Br | -$C_6H_4OMe$ | 74 | 184–186 |
| **m** | I | -$CH_3$ | 73 | 203–205 |
| **n** | I | -$CH(CH_3)_2$ | 79 | 166–168 |
| **o** | I | -$C_6H_5$ | 76 | 161–163 |
| **p** | I | - $C_6H_4F$ | 82 | 199–202 |
| **q** | I | - $C_6H_4Cl$ | 85 | 182–184 |
| **r** | I | -$C_6H_4OMe$ | 81 | 170–172 |




(**a**)




(**b**)

**Figure 8**: $^{1}H$- and $^{13}C$ NMR Spectrum of *N*-[2-(1-hydroxyiminoethyl)phenyl]acetamide **90a** in $CDCl_3$ at 300 MHz (**a**) and 75 MHz (**b**) respectively.

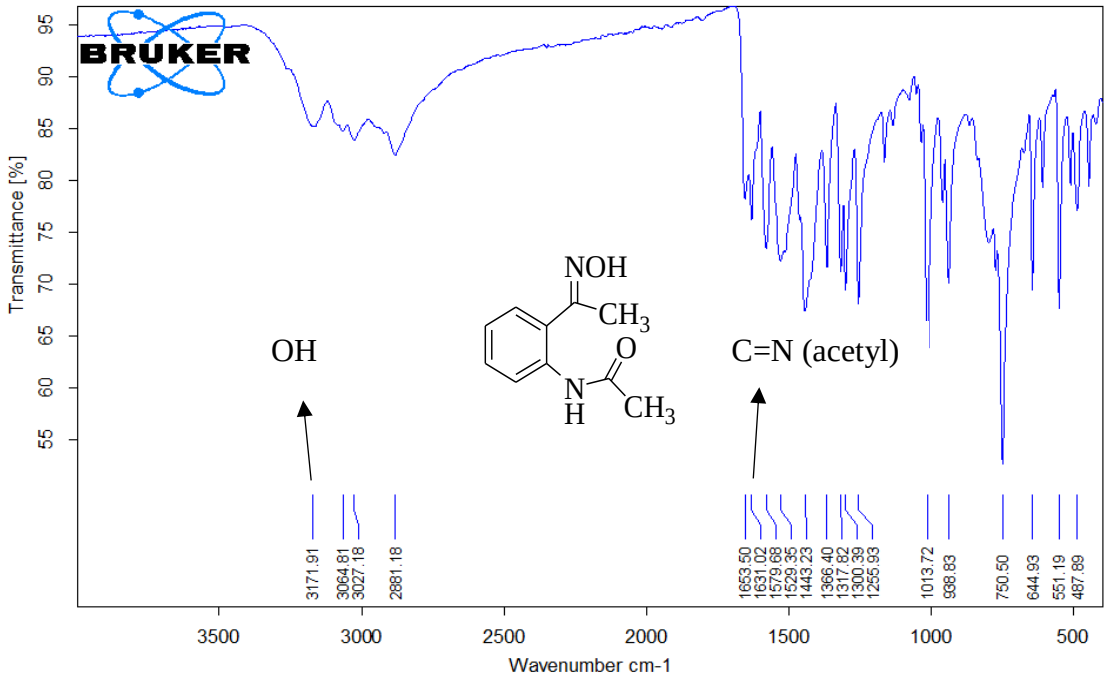


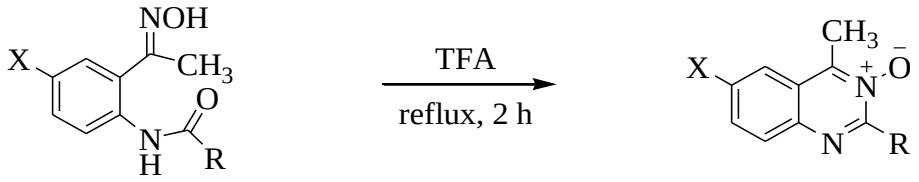

**Figure 9**: IR Spectrum of *N*-[2-(1-hydroxyiminoethyl)phenyl]acetamide **90a**.

With the transformation of compound **89a–r** into *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives **90a–r** achieved, attention was paid on transforming *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives **90a–r** into 2,4-dicarbo substituted quinazoline 3-oxides **91a–r**. This will be discussed in detail in the following section

### 2.3 Cyclocondensation-dehydration of 90a–r to form 2,4-dicarbo substituted quinazoline 3-oxides 91a–r

It has been reported that the presence of amide carbonyl group, a lewis acid such as hydroxamic acid[84] and/or metal catalysts of Zn, Rh (III) promoted the cyclization of the oximes to quinazoline 3-oxides.[79,84] In this study, the *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives **90a**–**r** were subjected to acid promoted intramolecular cyclization with low boiling and water miscible triflouroacetic acid under reflux for 2 h to isolate upon aqueous workup and column chromatography 2,4-dicarbo substituted quinazoline 3-oxides **91a**–**r i**n 72–89% yield (Scheme 26). The presence of the amide carbonyl group in the *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide derivatives **90a**–**r** promoted nucleophilic addition of compounds **90a**–**r** with triflouroacetic acid to afford 2,4-dicarbo substituted quinazoline 3-oxides **91a**–**r**. Compounds **91a**–**r** were characterized using a combination of ($^{1}$H- and $^{13}$C NMR), IR spectroscopic techniques completed with mass spectrometry. The $^{1}$H NMR spectra of compounds **91a**–**r** represented by spectrum of compound **91a** in Figure 10a revealed the absence of -OH and -NH group singlets respectively. The $^{13}$C NMR spectrum of compound **91a** (Figure 10b) revealed the second C=N signal more up-field at $\delta_C$ 150.3 ppm than that of the corresponding precursor's C=O signal at $\delta_C$ 169.3 ppm which confirmed the complete

conversion of **90a** to **91a**. Their IR spectra (Figure 11) further confirmed the presence of two $_{\nu C=N}$ bands at 1645 and 1684 $cm^{-1}$ respectively. The molecular structure of compound **91b** was confirmed with X-ray diffraction data (Figure 12). In the context of the X-ray analyses, we used crystallographic numbering in place of nomenclature numbering. The compound was crystallized in the orthorhombic space group F d d 2 with unit cell dimensions (a = 18.7529(12) Å, b = 49.438(3) Å, c = 4.5081(3) Å; α= β = γ = 90°) (see Table 5). Compound **91b** reveals the quinazoline-3-oxide moiety with substituents at C–7 and C–8 positions. The quinazoline 3-oxide scaffold was found to exhibit planar conformation with torsion angle O(1)-N(2)-C(8) of 118.30°. The data obtained from the crystal structure of **91b** is shown in Table 5 below.




**90a**–r **91a**–r

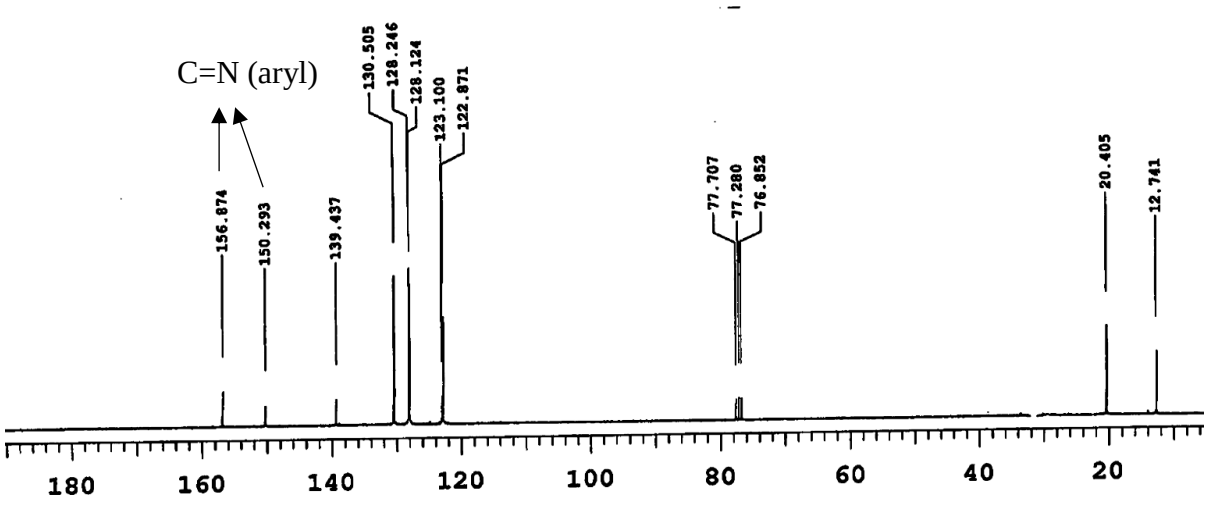
**Scheme 26**: Intramolecular cyclization of oximes **90a**–r

**Table 4**: Substitution pattern, percentage yields and melting point values of **91a**–**r**

| 91 | X | R | % Yield | mp. (°C) |
|---|---|---|---|---|
| **a** | H | -$CH_3$ | 79 | 102–104 (Lit.[84]101–102) |
| **b** | H | -$CH(CH_3)_2$ | 81 | 118–120 (Lit.[84] 117–118) |
| **c** | H | -$C_6H_5$ | 87 | 140–142 (Lit.[84] 140–141) |
| **d** | H | - $C_6H_4F$ | 84 | 170–172 (Lit.[85] 169–170) |
| **e** | H | - $C_6H_4Cl$ | 86 | 184–186 (Lit.[85] 183–184) |
| **f** | H | -$C_6H_4OMe$ | 72 | 156–158 (Lit.[85]158–159) |
| **g** | Br | -$CH_3$ | 78 | 106–108 (Lit.[84]102–104) |
| **h** | Br | -$CH(CH_3)_2$ | 85 | 162–164 |

| | | | | |
|---|---|---|---|---|
| **i** | Br | -$C_6H_5$ | 81 | 158–160 (Lit.[85]160–161) |
| **j** | Br | - $C_6H_4F$ | 77 | 182–184 |
| **k** | Br | - $C_6H_4Cl$ | 83 | 172–174 (Lit.[85] 170–171) |
| **l** | Br | -$C_6H_4OMe$ | 75 | 167–169 |
| **m** | I | -$CH_3$ | 75 | 113–115 (Lit.[84] 112–113) |
| **n** | I | -$CH(CH_3)_2$ | 83 | 159–162 |
| **o** | I | -$C_6H_5$ | 79 | 200–202 |
| **p** | I | - $C_6H_4F$ | 79 | 200–203 |
| **q** | I | - $C_6H_4Cl$ | 89 | 204–206 |
| **r** | I | -$C_6H_4OMe$ | 79 | 149–153 |


(**a**)




(**b**)

**Figure 10**: $^{1}$H- and $^{13}$C NMR Spectra of 2,4-dimethyl quinazoline 3-oxide **91a** in $CDCl_3$ at 300 MHz (**a**) and 75 MHz (**a**) respectively.

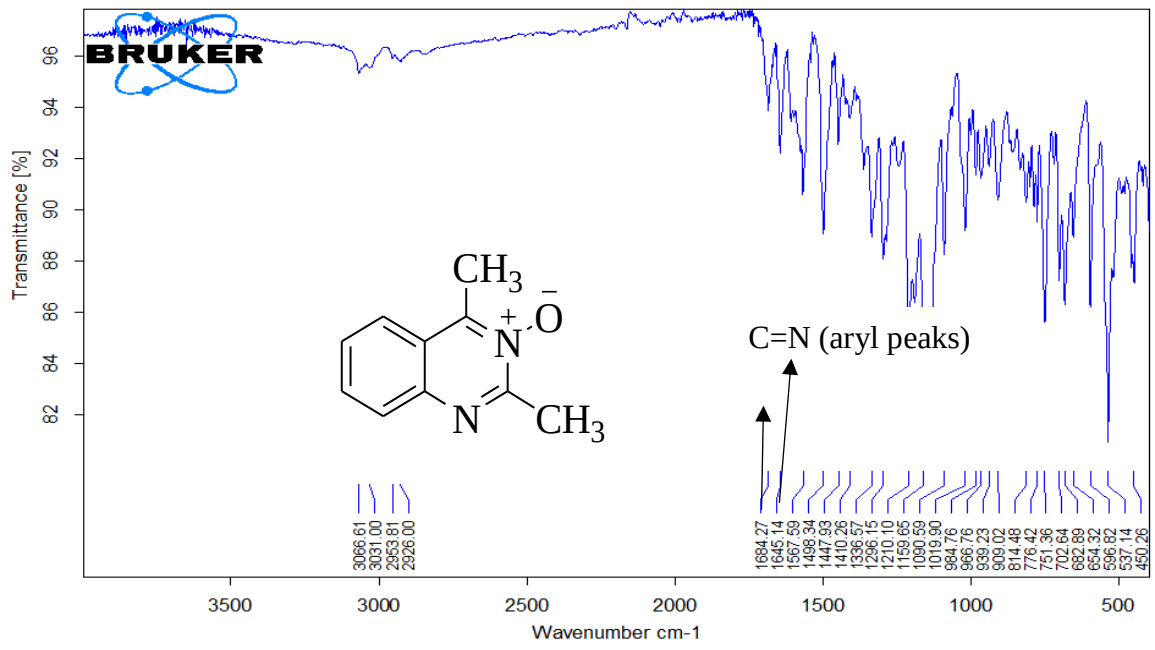



**Figure 11**: IR Spectrum of 2,4-dimethyl quinazoline 3-oxide **91a**.

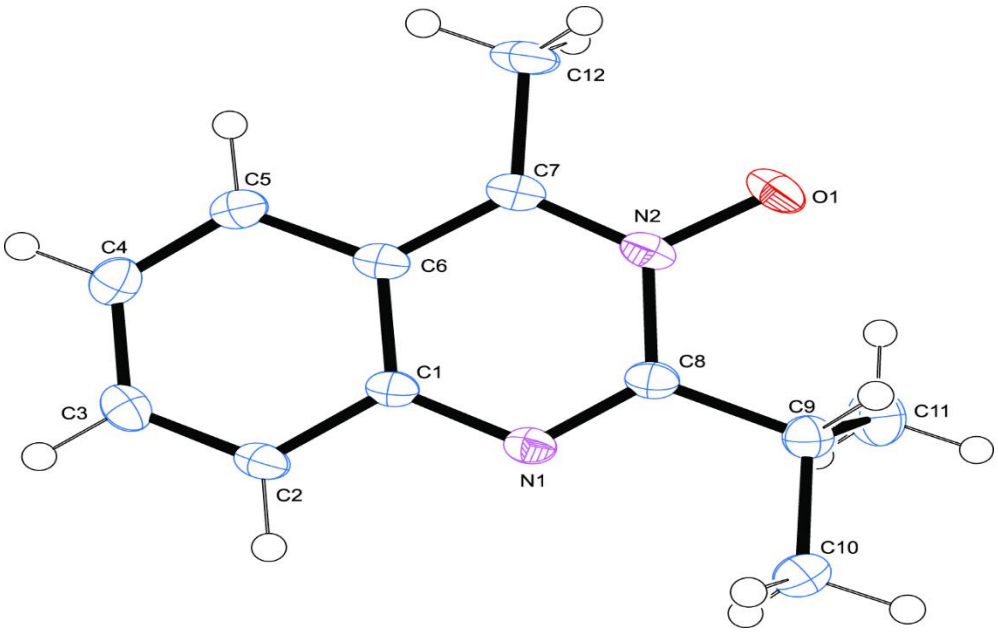



**Figure 12**: Crystal structure of 2-isopropyl-4-methyl quinazoline 3-oxide **91b**.

**Table 5**: Crystal data and structure refinement for 2-isopropyl-4-methyl quinazoline 3-oxide **91b**

| | |
|---|---|
| Empirical formula | $C_{12}H_{14}N_2O$ |
| Formula weight | 202.25 |
| Temperature | 170(2) K |
| Wavelength | 0.56086 Å |
| Crystal system | Orthorhombic |
| Space group | F d d 2 |
| Unit cell dimensions | a = 18.7529(12) Å, α = 90° |
| | b = 49.438(3) Å, β = 90° |
| | c = 4.5081(3) Å, γ = 90° |
| Z | 16 |
| Density (calculated) | 1.286 $Mg/m^3$ |

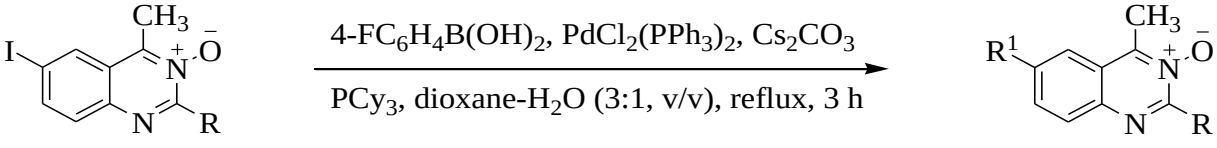
| | |
|---|---|
| Absorption coefficient | 0.053 $mm^{-1}$ |
| F(000) | 1728 |
| Theta range for data collection | 2.597 to 21.977°. |
| Reflections collected | 41876 |
| Independent reflections | 2579 [R(int) = 0.0499] |
| Completeness to theta = 19.665° | 99.2 % |
| Data / restraints / parameters | 2579 / 1 / 139 |
| Final R indices [I>2sigma(I)] | R1 = 0.0406, wR2 = 0.1085 |
| R indices (all data) | R1 = 0.0411, wR2 = 0.1089 |

The presence of an iodine atom on the 2,4-quinazoline 3-oxides can make them suitable substrates for further transformation using metal mediated reactions. The C$sp^2$–I bond of 6-iodo-substituted quinazoline 3-oxides **91m–r** plays a vital role in metal catalyzed (Suzuki) cross-coupling reaction because of C$sp^2$–halogen bond strength as shown in the trend: C$sp^2$–I<C$sp^2$–Cl<C$sp^2$–Br.[40] This will promote preferential substitution of iodine in the presence of bromine and chlorine. This will be discussed in detail in the following sections.

### 2.4 Suzuki-Miyaura cross-coupling of 6-iodo substituted quinazoline 3-oxides 91m–r

Metal catalyzed cross-coupling reactions such as Kumada and Stille can also be used to append aryl group at C–6 of 6-iodo substituted quinazoline 3-oxides **91m–r**. However, Suzuki cross-coupling was preferred over the Kumada cross-coupling because Grignard reagent reacts with other functional groups such as carbonyls, esters, and nitro groups.[68] The Stille cross-coupling, on the other hand, makes use of tin compounds which are toxic and insoluble in water resulting to difficult work up.[99] The arylboronic acids are readily available and are less toxic in nature.[100]

The substitution of C$sp^2$–I bond of 6-iodo substituted quinazoline 3-oxides **91m–r** with 4-fluorophenyl group derived from 4-fluorophenylboronic acids was envisioned to increase the physicochemical properties such as solubility, CNS penetration, metabolic stability and selective reactivities of the corresponding compounds more than other phenylboronic acid derivatives.[101,102] The Suzuki coupling of 6-iodo substituted quinazoline 3-oxides **91m–r** in the presence of $PdCl_2(PPh_3)_2$ as a source of an active Pd(0) species, tricyclohexylphosphine ($PCy_3$) as a ligand, and $Cs_2CO_3$ as a base in dioxane-water (3:1, v/v), 4-fluorophenylboronic acids as coupling partners under reflux for 3 h afforded 2,4,6-tricarbo substituted quinazoline 3-oxides **92a–f** in 75–81% yield (Scheme 27). The transformation of **91m–r** into **92a–f** was confirmed using a combination of NMR ($^1$H and $^{13}$C), IR and mass spectrometric techniques. The $^1$H NMR spectrum (Figure 13a) revealed the presence of a triplet integrating for two protons at 7.97 (2H, t, $J$ = 8.5 Hz, H-2',6') and two doublets of doublets at 7.20 (2H, dd, $J$ = 5.0 Hz and 8.0 Hz, H-3',5') respectively in the aromatic region due to the incorporation of the (-4$FC_6H_4$) group . The $^{13}$C NMR spectrum (Figure 13b) reveals the presence of C–F peaks at 116.1 (d, $^2J_{CF}$ = 21.8 Hz), 129.2 (d, $^3J_{CF}$ = 7.5 Hz), 135.9 (d, $^4J_{CF}$ = 3.9 Hz) and 163.0 (d, $^1J_{CF}$ = 246.6 Hz) respectively. The IR spectrum (Figure 14) reveals the presence of strong C–F bands at $\nu_{max}$ 1224 (-4$FC_6H_4$) $cm^{-1}$ and 1499 (-4$FC_6H_4$) $cm^{-1}$ respectively. The HRMS analysis of compound **92a** (Figure 15a) was found to be 269.1095 which is closest to the calculated mass of 269.1090 $[M+H]^+$.

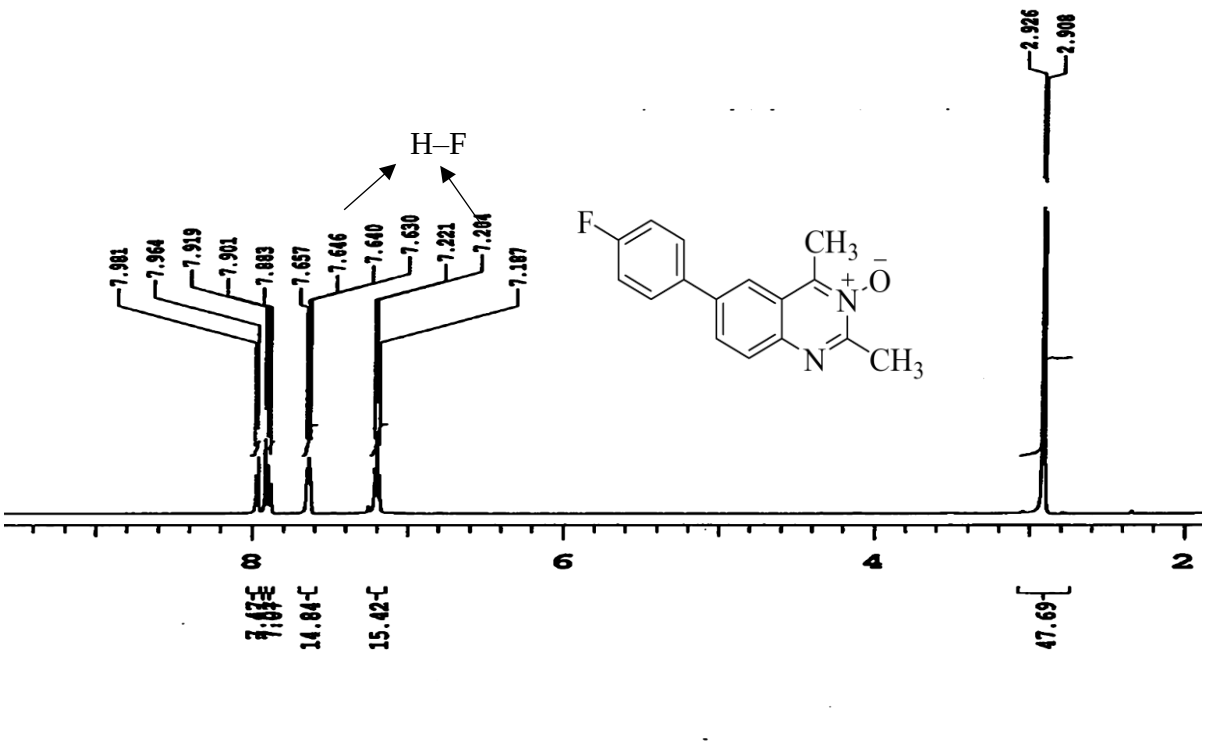



**91m–r** **92a–f**

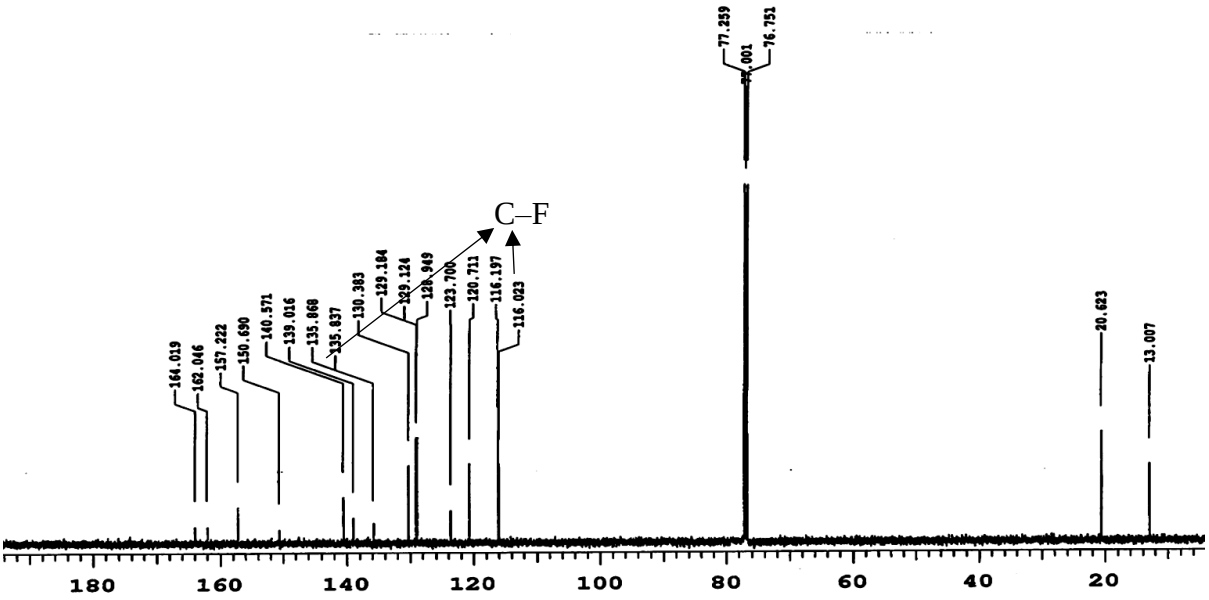
**Scheme 27**: Suzuki-Miyaura cross-coupling of 6-iodo substituted quinazoline 3-oxides **91m–r**

**Table 6**: Substitution pattern, percentage yields and melting point values of **92a–f**

| 92 | $R^1$ | R | % Yield | mp. (°C) |
|---|---|---|---|---|
| **a** | 4-$FC_6H_4$- | -$CH_3$ | 81 | 197–198 |
| **b** | 4-$FC_6H_4$- | -$CH(CH_3)_2$ | 74 | 134–136 |
| **c** | 4-$FC_6H_4$- | -$C_6H_5$ | 79 | 158–160 |
| **d** | 4-$FC_6H_4$- | - $C_6H_4F$ | 77 | 202–205 |
| **e** | 4-$FC_6H_4$- | - $C_6H_4Cl$ | 75 | 238–240 |
| **f** | 4-$FC_6H_4$- | -$C_6H_4OMe$ | 76 | 225–209 |




(**a**)




(**b**)

**Figure 13**: $^{1}$H- and $^{13}$C-NMR spectra of 2,4-dimethyl-6-(4-fluoro phenyl) quinazoline 3-oxide **92a** in $CDCl_3$ at 500 MHz (**a**) and 125 MHz (**b**), respectively.

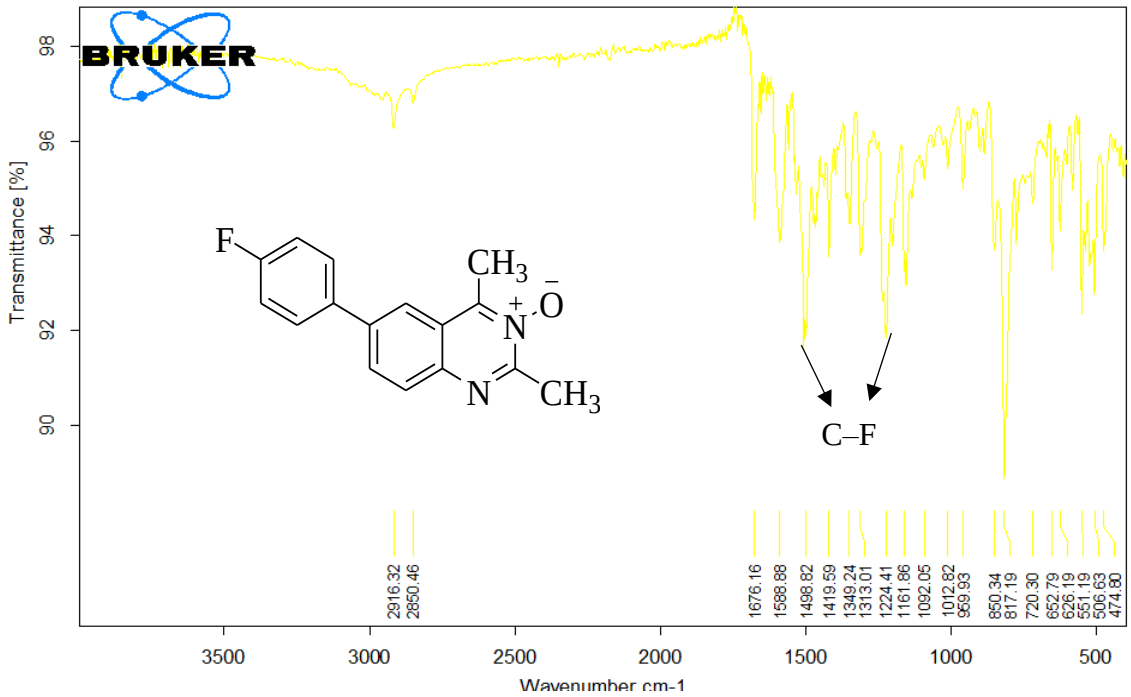
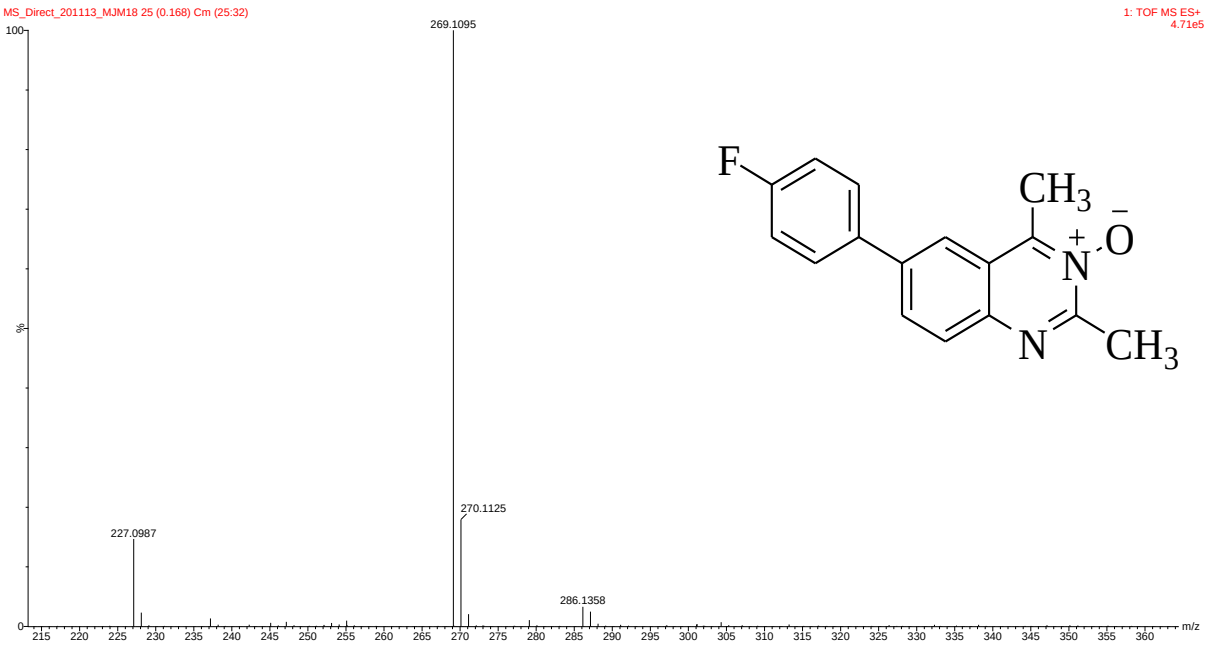



**Figure 14**: IR spectrum of 2,4-dimethyl-6-(4-fluoro-phenyl) quinazoline 3-oxide **92a**.




(**a**)

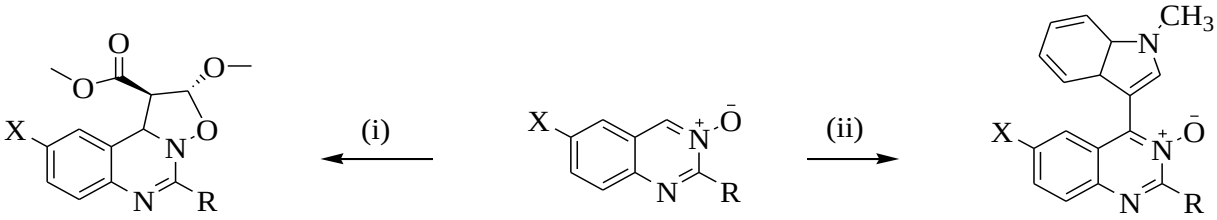
**Figure 15**: HRMS spectrum of 2,4-dimethyl-6-(4-fluoro phenyl) quinazoline 3-oxide **92a**.

## CHAPTER 3 CONCLUSIONS

Simple and efficient methods for the construction of the 2,4-dicarbo substituted quinazoline 3-oxide derivatives have been developed and characterized in this investigation. It was found that the proximity of the 2-amino group to the enolizable acetyl group of 2-aminoacetophenone derivatives **88a–c** promoted acetylation or benzoylation reaction in the presence of acetic anhydride or aryl chlorides in pyridine to afford *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halophenyl)amide derivatives **89a–r**. The presence of the acetyl moiety in *N*-(2-acetylphenyl)amides and *N*-(2-acetyl-4-halophenyl)amide derivatives **89a–r** facilitated nucleophilic substitution reaction with hydroxylamine hydrochloride in pyridine to afford *N*-[2-(1-hydroxyiminoethyl)phenyl]amides and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl) amide derivatives **90a–r**. The amide carbonyl group promoted the acid-mediated intramolecular cyclization of **90a–r** into 2,4-dicarbo substituted quinazoline 3-oxides **91a–r**. The iodine atom at C–6 of the fused benzo ring of 6-iodo substituted quinazoline 3-oxides **91m–r** facilitated palladium catalyzed Suzuki-Miyaura cross-coupling reaction with 4-fluorophenylboronic acid to afford the corresponding 2,4,6-tricarbo substituted quinazoline 3-oxide derivatives **92a–f**.

The C–I bond of the prepared of 6-iodo substituted quinazoline 3-oxides **91m–r** derivatives in this investigation could be transformed via Sonogashira cross-coupling reaction with terminal acetylenes to afford the corresponding 2,4,6-tricarbo substituted quinazoline 3-oxide derivatives. 2,4-Dicarbo substituted quinazoline 3-oxides derivatives **91a–r** could be expanded to benzo-1,3-diazepine derivatives using dimethyl acetylenedicarboxylate (DMAD) in THF.[85] Quinazoline 3-oxide analogues **93** could be transformed into isoxazolo[2,3-*c*] quinazoline derivatives **94** by treatment with methyl 3-methoxyacrylate in 1,4-dioxane (Scheme 28).

Quinazoline 3-oxides derivatives **93** could be subjected to copper-catalyzed dehydrogenative cross-coupling with indoles to afford indole-quinazoline 3-oxide molecular hybrids **95** (Scheme 28). These compounds **94** and **95** could be evaluated against multiple targets linked to chronic inflammation as well as their photophysical properties.




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

**Scheme 28**: Plausible route for further transformation of quinazoline 3-oxides derivatives **93**

# CHAPTER 4 EXPERIMENTAL

## 4.0 Materials and Instrumentation

Melting points were recorded on a Stuart melting point apparatus (SMP3) and are uncorrected. IR spectra were recorded by using the thin-film method on a Bruker VERTEX 70 FT-IR Spectrometer with a diamond ATR (attenuated total reflectance) accessory. For column chromatography, Merck kieselgel 60 (0.063–0.200 mm) (Merck KGaA, Frankfurt, Germany) was used as stationary phase. NMR spectra were obtained using $CDCl_3$ and DMSO-$d_6$ solutions and Agilent 300 and 500 MHz NMR (Agilent Technologies, Oxford, UK) spectrometers and the chemical shifts are quoted relative to the TMS peak. Low- and high-resolution mass spectra were recorded at an ionization potential of 70 eV using Waters Synapt G2 Quadrupole Time-of-flight mass spectrometer (Waters Corp., Milford, MA, USA) at the University of Stellenbosch Mass Spectrometry Unit.

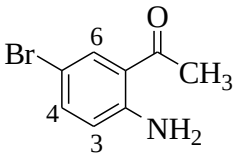
The following abbreviations are used throughout for NMR spectral data:

- δ = chemical shift values in ppm (parts per million),
- *J* = coupling constant in Hz,
- s = singlet,
- d = doublet,
- dd = doublet of doublets,
- dt = doublet of triplets,
- t = triplet,
- q = quartet,
- m = multiplet

- br s = broad singlet
- qt = quintet

### 4.1 Halogenation of 2-aminoacetophenone

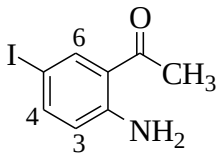
#### 4.1.1 Synthesis of 2-amino-5-bromoacetophenone 88b




**88b**

A stirred solution of 2-aminoacetophenone **88a** (1.00 g, 7.40 mmol) in dichloromethane (50 mL) at 0 °C was treated slowly with pyridinium tribromide (2.37 g, 7.40 mmol). The reaction mixture was warmed up to room temperature and then stirred for 2 h at this temperature. Cold water (30 mL) was added to the reaction mixture and the organic phase was separated. The aqueous phase was extracted into chloroform (3 x 30 mL) and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated under reduced pressure to afford **88b** as an off-white solid (1.19 g, 75%), mp 83−84 °C (Lit.[88] 82−83 °C); $\nu_{max}$ (ATR) 517, 623, 671, 738, 821, 888, 956, 1159, 1160, 1216, 1287, 1360, 1464, 1540, 1603, 1654 (C=O), 3453 ($NH_2$) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.70 (3H, s, -$CH_3$), 6.44 (1H, br s, $NH_2$), 6.70 (1H, d, *J* = 8.7 Hz, H-3), 7.47 (1H, dd, *J* = 2.4 Hz and *J* = 8.7 Hz, H-4), 7.93 (1H, d, *J* = 2.4 Hz, H-6); $^{13}$C NMR (75 MHz, $CDCl_3$) 27.9, 106.5, 118.9, 119.3, 134.0, 136.9, 149.0, 199.6 (C=O).

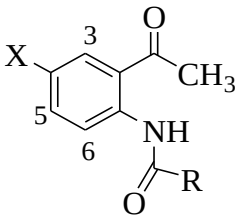
### 4.1.2 Synthesis of 2-amino-5-iodoacetophenone 88c



**88c**

A stirred solution of 2-aminoacetophenone **88a** (1.00 g, 7.40 mmol) in acetic acid (30 mL) was treated slowly with *N*-iodosuccinimide (1.67 g, 7.40 mmol) and the reaction mixture was stirred at room temperature for 2 h. At completion, the reaction mixture was poured into ice-cold saturated aqueous solution of sodium thiosulphate. The resultant precipitate was filtered, washed with ice cold water and recrystallized from hexane to afford **88c** as a yellowish brown solid (1.77 g, 92%), mp 97−98 °C (Lit.[91] 98.5−99 °C) $\nu_{max}$ (ATR) 517, 623, 671, 738, 821, 887, 956, 1292, 1310, 1419, 1460, 1530, 1572, 1602, 1627 (C=O), 3310, 3424 ($NH_2$) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 2.73 (3H, s, -$CH_3$), 5.73 (1H, br s, $NH_2$), 6.64 (1H, d, *J* = 8.7 Hz, H-3), 7.65 (1H, d, *J* = 8.7 Hz, H-4), 8.14 (1H, s, H-6); $^{13}C$ NMR (75 MHz, $CDCl_3$) 28.1, 75.4, 119.6, 120.5, 140.5, 142.6, 149.7, 199.8 (C=O).

### 4.2 Synthesis of *N*-(2-acetylphenyl)amide and *N*-(2-acetyl-4-halophenyl)amide derivatives 89a–r



**89a–r**

### 4.2.1 Synthesis of *N*-(2-acetylphenyl)acetamide 89a (X = H, R = $CH_3$)

Acetic anhydride (0.91 g, 8.88 mmol) was added dropwise to a solution of 2-aminoacetophenone **88a** (1.00 g, 7.40 mmol) in pyridine (10 mL) and the reaction mixture was heated under reflux for 1−2 h. The reaction mixture was poured into ice-cold water and the resultant precipitate was filtered, washed with hexane to afford **89a** as a white solid (0.89 g, 68%), mp 64−66 °C (Lit.[95] 62−64 °C); $\nu_{max}$ (ATR) 747, 820, 962, 1239, 1312, 1361, 1524, 1581, 1650 (C=O acetyl), 1686 (C=O amide), 2923 (CH alkyl), 3242 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.38 (3H, s, -$CH_3$), 2.82 (3H, s, -$CH_3$), 7.27 (1H, t, *J* = 7.5 Hz, H-4), 7.71 (1H, t, *J* = 7.5 Hz, H-5), 8.05 (1H, d, *J* = 8.1 Hz, H-6), 8.89 (1H, d, *J* = 9.0 Hz, H-3), 11.84 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 25.8, 28.8, 120.9, 121.9, 122.5, 131.8, 135.4, 141.2, 169.7 (C=O amide), 203.0 (C=O acetyl).

### 4.2.2 Synthesis of *N*-(2-acetylphenyl)isopropylamide 89b (X = H, R = -$CH(CH_3)_2$)

A stirred mixture of isobutyryl chloride (0.95 g, 8.88 mmol) and 2-aminoacetophenone **88a** (1.00 g, 7.40 mmol) in pyridine was reacted as described for **89a** to afford **89b** as a brown liquid (1.37 g, 90%), (Lit.[95]); $\nu_{max}$ (ATR) 755, 959, 1158, 1245, 1308, 1360, 1449, 1519, 1651 (C=O acetyl), 1688 (C=O amide), 2875, 2932, 2972, (CH alkyl), 3224 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 1.24 (3H, d, *J* = 7.2 Hz, -$CH_3$), 1.34 (3H, d, *J* = 6.9 Hz, -$CH_3$), 2.58−2.68 (1H, m, -CH), 2.70 (3H, s, -$CH_3$), 7.14 (1H, t, *J* = 7.5 Hz, H-4), 7.58 (1H, t, *J* = 8.4 Hz, H-5), 7.94 (1H, d, *J* = 8.4 Hz, H-6), 8.82 (1H, d, *J* = 8.1 Hz, H-3), 11.84 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 18.8, 19.5, 28.6, 37.6, 120.8, 121.8, 122.3, 131.8, 135.2, 141.2, 176.9 (C=O amide), 203.0 (C=O acetyl).

### 4.2.3 Synthesis of *N*-(2-acetylphenyl)benzamide 89c (X = H, R = -$C_6H_5$)

A stirred mixture of benzoyl chloride (1.25 g, 8.88 mmol) and 2-aminoacetophenone **88a** (1.00 g, 7.40 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89c** as a white solid (1.59 g, 90%), mp 101−103 °C (Lit.[95] 98−100 °C); $\nu_{max}$ (ATR) 763, 894, 962, 1028, 1245, 1359, 1447, 1534, 1585, 1644 (C=O acetyl), 1673 (C=O amide), 3058 (CH alkyl), 3209 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.91 (3H, s, -$CH_3$), 7.35 (1H, t, *J* = 7.5 Hz, H-4), 7.70−7.77 (3H, m, 3', 4' and 5'), 7.82 (1H, t, *J* = 7.5 Hz, H-5), 8.15 (1H, d, *J* = 8.4 Hz, H-6), 8.28 (2H, d, *J* = 6.6 Hz, 2' and 6'), 9.19 (1H, d, *J* = 9.0 Hz, H-3), 12.90 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 28.4, 120.6, 121.8, 122.3, 127.3, 128.6, 131.6, 131.8, 134.6, 135.2, 141.2, 165.9 (C=O amide), 203.1 (C=O acetyl).

### 4.2.4 Synthesis of *N*-(2-acetylphenyl)-4-fluorobenzamide 89d (X = H, R = -$C_6H_4F$)

A stirred mixture of 4-flourobenzoyl chloride (1.41 g, 8.88 mmol) and 2-aminoacetophenone **88a** (1.00 g, 7.40 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89d** as a dark brown solid (1.48 g, 78%), mp 92−94 °C (Lit.[95] 90−92 °C); $\nu_{max}$ (ATR) 749, 847, 959, 1163, 1230, 1317, 1357, 1447, 1504, 1588, 1650 (C=O acetyl), 1671 (C=O amide), 3077 (CH alkyl), 3168 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.86 (3H, s, -$CH_3$), 7.32 (2H, t, *J* = 8.1 Hz, 3' and 5'), 7.32 (1H, t, *J* = 8.1 Hz, H-4), 7.76 (1H, t, *J* = 7.5 Hz, H-5), 8.10 (1H, d, *J* = 8.1 Hz, H-6), 8.22 (2H, dd, *J* = 8.1 Hz and *J* = 2.4 Hz, 2' and 6'), 9.09 (1H, d, *J* = 8.7 Hz, H-3), 12.84 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 28.8, 116.0 (d, $^2J$ = 22.8 Hz), 120.9, 122.1, 122.8, 130.1(d, $^3J$ = 9.1 Hz), 131.2 (d, $^4J$ = 2.25 Hz), 132.0, 135.6, 141.5, 165.1 (C=O amide), 165.3, (d, $^1J$ = 251.9 Hz), 203.6 (C=O acetyl).

### 4.2.5 Synthesis of *N*-(2-acetylphenyl)-4-chlorobenzamide 89e (X = H, R = -$C_6H_4Cl$)

A stirred mixture of 4-chlorobenzoyl chloride (1.55 g, 8.88 mmol) and 2-aminoacetophenone **88a** (1.00 g, 7.40 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89e** as a white solid. (1.88 g, 93%), mp 111−113 °C (Lit.[96] 113−115 °C); $\nu_{max}$ (ATR) 743, 850, 955, 1011, 1090, 1244, 1255, 1448, 1533, 1586, 1647 (C=O acetyl), 1668 (C=O amide), 2995 (CH alkyl), 3225 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.88 (3H, s, -$CH_3$), 7.34 (1H, t, *J* = 7.5 Hz, H-4), 7.65 (2H, d, *J* = 8.4 Hz, 3' and 5'), 7.79 (1H, t, *J* = 7.5 Hz, H-5), 8.12 (1H, d, *J* = 8.1 Hz, H-6), 8.17 (2H, d, *J* = 8.1 Hz, 2' and 6') 9.11 (1H, d, *J* = 8.7 Hz, H-3), 12.88 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 28.8, 120.9, 122.1, 122.9, 129.1, 129.2, 132.0, 133.4, 135.6, 138.5, 141.4, 165.1 (C=O amide), 203.6 (C=O acetyl).

### 4.2.6 Synthesis of *N*-(2-acetylphenyl)-4-methoxybenzamide 89f (X = H, R = -$C_6H_4OMe$)

A stirred mixture of 4-methoxybenzoyl chloride (1.55 g, 8.88 mmol) and 2-aminoacetophenone **88a** (1.00 g, 7.40 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89f** as a yellowish brown solid. (1.89 g, 95%), mp 120−122 °C (Lit.[95] 119−120 °C); $\nu_{max}$ (ATR) 759, 847, 1021, 1186, 1248, 1357, 1453, 1508, 1585, 1643 (C=O acetyl), 1667 (C=O amide), 2839 (CH aryl), 3071 (CH alkyl), 3222 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.92 (3H, s, -$CH_3$), 4.09 (3H, s, -$OCH_3$), 7.23 (2H, d, *J* = 8.7 Hz, 3' and 5'), 7.34 (1H, t, *J* = 7.2 Hz, H-4), 7.81 (1H, t, *J* = 7.5 Hz, H-5), 8.15 (1H, d, *J* = 7.8 Hz, H-6), 8.27 (2H, d, *J* = 8.1 Hz, 2' and 6'), 9.19 (1H, d, *J* = 8.4 Hz, H-3), 12.85 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 28.7, 55.6, 114.2, 114.3, 120.8, 122.3, 127.3, 129.6, 132.0, 133.0, 135.5, 141.9, 162.8 (C=O amide), 203.4 (C=O acetyl).

### 4.2.7 Synthesis of *N*-(2-acetyl-4-bromophenyl)acetamide 89g (X = Br, R = -$CH_3$)

A stirred mixture of acetic anhydride (0.57 g, 5.60 mmol) and 2-amino-5-bromoacetophenone **88b** (1.00 g, 4.67 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89g** as an off-white solid (0.94 g, 79%), mp 160−162 °C (Lit.[96] 158−160 °C); $\nu_{max}$ (ATR) 769, 827, 909, 964, 1068, 1099, 1225, 1287, 1308, 1359, 1395, 1497, 1598, 1653 (C=O acetyl), 1685 (C=O amide), 2999 (CH alkyl), 3214 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.41 (3H, s, -$CH_3$), 2.85 (3H, s, -$CH_3$), 7.82 (1H, d, *J* = 9.6 Hz, H-6), 8.17 (1H, s, H-3), 8.87 (1H, d, *J* = 8.7 Hz, H-5), 11.76 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 25.4, 28.4, 114.3, 122.3, 122.9, 133.8, 137.6, 139.8, 169.3 (C=O amide), 201.5 (C=O acetyl).

### 4.2.8 Synthesis of *N*-(2-acetyl-4-bromophenyl)isopropylamide 89h (X = Br, R = -$CH(CH_3)_2$)

A stirred mixture of isobutyryl chloride (0.49 g, 4.67 mmol) and 2-amino-5 bromoacetophenone **88b** (1.00 g, 4.67 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89h** as an off-white solid (1.15 g, 87%), mp 107−109 °C; $\nu_{max}$ (ATR) 732, 804, 938, 959, 1094, 1153, 1220, 1358, 1387, 1503, 1572, 1656 (C=O acetyl), 1684 (C=O amide), 2877, 2902, 2936, 2972 (CH alkyl), 3244 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 1.42 (6H, d, *J* = 6.9 Hz, -$CH_3$), 2.80 (3H, s, -$CH_3$), 2.62 (1H, m, -CH), 7.77 (1H, d, *J* = 8.7 Hz, H-6), 8.12 (1H, s, H-3), 8.87 (1H, d, *J* = 9.3 Hz, H-5), 11.80 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 19.6 (2 x -$CH_3$), 28.8, 37.7, 114.5, 122.7, 123.3, 134.2, 137.9, 140.4, 176.8 (C=O amide), 201.9 (C=O acetyl); HRMS (ES): $MH^+$ found 284.0288 $C_{12}H_{14}BrNO_2^+$ requires 284.0286.

### 4.2.9 Synthesis of *N*-(2-acetyl-4-bromophenyl)benzamide 89i (X = Br, R = -$C_6H_5$)

A stirred mixture of benzoyl chloride (0.79 g, 5.60 mmol) and 2-amino-5-bromoacetophenone **88b** (1.00 g, 4.67 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89i** as a brown solid. (1.25 g, 84%), mp 105−107 °C (Lit.[96] 105−106 °C); $\nu_{max}$ (ATR) 703, 800, 833, 962.1, 1223, 1305, 1357, 1397, 1493, 15178, 1576, 1648 (C=O acetyl), 1673 (C=O amide), 3057 (CH alkyl), 3220 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.85 (3H, s, -$CH_3$), 7.64–7.71 (3H, m, 3', 4' and 5'), 7.85 (1H, d, *J* = 8.7 Hz, H-6), 8.19 (3H, s, 2H-2' and 6' and 1H-3), 9.07 (1H, d, *J* = 9.0 Hz, H-5), 12.72 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 28.3, 114.5, 122.3, 123.1, 127.2, 128.6, 131.9, 134.0, 134.2, 137.7, 140.1, 165.8 (C=O amide), 201.9 (C=O acetyl).

### 4.2.10 Synthesis of *N*-(2-acetyl-4-bromophenyl)-4-fluorobenzamide 89j (X = Br, R = $C_6H_4F$)

A stirred mixture of 4-flourobenzoyl chloride (0.89 g, 5.60 mmol) and 2-amino-5-bromoacetophenone **88b** (1.00 g, 4.67 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89j** as a brown solid (1.49 g, 95%), mp 182−184 °C; $\nu_{max}$ (ATR) 744, 840, 957, 1020, 1090, 1221, 1366, 1357, 1396, 1504, 1576, 1602, 1646 (C=O acetyl), 1681 (C=O amide), 2971 (CH alkyl), 3223 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.91 (3H, s, -$CH_3$), 7.39 (2H, t, *J* = 8.1 Hz, 3' and 5'), 7.90 (1H, d, *J* = 9.0 Hz, H-6), 8.23 (2H, d, *J* = 7.5 Hz, 2' and 6'), 8.24 (1H, s, H-3), 9.08 (1H, d, *J* = 9.3 Hz, H-5), 12.76 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 28.8, 115.0, 116.1 (d, $^2J$ = 21.8 Hz), 122.7, 123.5, 130.1 (d, $^3J$ = 9.2 Hz), 130.8 (d, $^4J$ = 2.33 Hz), 134.4, 138.2, 140.5, 165.1 (C=O amide), 165.4 (d, $^1J$ = 251.9 Hz), 202.5 (C=O acetyl); HRMS (ES): $MH^+$, found 336.0039 $C_{15}H_{11}BrFNO_2^+$ requires 336.0035.

### 4.2.11 Synthesis of *N*-(2-acetyl-4-bromophenyl)-4-chlorobenzamide 89k (X = Br, R = -$C_6H_4Cl$)

A stirred mixture of 4-chlorobenzoyl chloride (0.98 g, 5.60 mmol) and 2-amino-5-bromoacetophenone **88b** (1.00 g, 4.67 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89k** as a yellow solid (1.68 g, 85%), mp 158−160 °C; $\nu_{max}$ (ATR) 743, 840, 958, 1012, 1092, 1222, 1306, 1358, 1394, 1488, 1575, 1599, 1651 (C=O acetyl), 1680 (C=O amide), 2971 (CH alkyl), 3216 (NH) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 1.98 (3H, s, -$CH_3$), 6.76 (2H, d, *J* = 6.9 Hz, 3' and 5'), 6.97 (1H, d, *J* = 8.7 Hz, H-6), 7.24 (2H, d, *J* = 7.8 Hz, 2' and 6'), 7.31 (1H, s, H-3 ), 8.14 (1H, d, *J* = 8.1 Hz, H-5), 11.85 (1H, br s, NH); $^{13}C$ NMR (75 MHz, $CDCl_3$) 28.7, 115.1, 122.6, 123.4, 129.0, 129.3, 132.9, 134.4, 138.2, 138.7, 140.3, 165.0 (C=O amide), 202.4 (C=O acetyl); HRMS (ES): $MH^+$, found 351.9745 $C_{15}H_{11}BrClNO_2^+$ requires 351.9740.

### 4.2.12 Synthesis of *N*-(2-acetyl-4-bromophenyl)-4-methoxybenzamide 89l (X = Br, R = -$C_6H_4$OMe)

A stirred mixture of 4-methoxybenzoyl chloride (0.96 g, 5.60 mmol) and 2-amino-5-bromoacetophenone **88b** (1.00 g, 4.60 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89l** as a brown solid (1.41 g, 87%), mp 167−169 °C; $\nu_{max}$ (ATR) 741, 839, 957, 1021, 1181, 1221, 1357, 1504, 1575, 1602, 1654 (C=O acetyl), 1670 (C=O amide), 2840 (CH aryl), 3060 (CH alkyl), 3224 (NH) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 2.56 (3H, s, -$CH_3$), 3.43 (3H, s, -$OCH_3$), 6.56 (2H, d, *J* = 8.7 Hz, 3' and 5'), 7.23 (1H, d, *J* = 8.7 Hz, H-6), 7.56 (2H, d, *J* = 8.7 Hz, 2' and 6'), 7.58 (1H, s, H-3), 8.46 (1H, d, *J* = 8.7 Hz, H-5), 12.05 (1H, br s, NH); $^{13}C$ NMR (75 MHz, $CDCl_3$) 28.8, 55.6, 114.2, 114.5, 122.6, 123.3, 126.8, 129.6, 134.3, 138.0,

140.8, 162.9, 165.7 (C=O amide), 202.3 (C=O acetyl); HRMS (ES): $MH^+$, found 348.0240 $C_{16}H_{14}BrNO_3^+$ requires 348.0235.

### 4.2.13 Synthesis of *N*-(2-acetyl-4-iodophenyl)acetamide 89m (X = I, R = -$CH_3$)

A stirred mixture of acetic anhydride (0.47 g, 4.59 mmol) and 2-amino-5-iodoacetophenone **88c** (1.00 g, 3.83 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89m** as a brown solid (0.99g, 86%), mp 171−173 °C; $\nu_{max}$ (ATR), 763, 836, 961, 1217, 1287, 1355, 1506, 1599, 1651 (C=O acetyl), 1681 (C=O amide), 3115 (CH alkyl), 3190 (NH), $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 1.98 (3H, s, -$CH_3$), 2.40 (3H, s, -$CH_3$), 7.56 (1H, d, *J* = 8.7 Hz, H-6), 7.91 (1H, s, H-3), 8.30 (1H, d, *J* = 8.7 Hz, H-5), 11.33 (1H, br s, NH); $^{13}C$ NMR (75 MHz, $CDCl_3$) 25.8, 28.8, 84.8, 122.9, 123.7, 140.1, 140.7, 143.7, 169.7 (C=O amide), 201.8 (C=O acetyl); HRMS (ES): $MH^+$, found 303.9839 $C_{10}H_{10}INO_2^+$ requires 303.9835.

### 4.2.14 Synthesis of *N*-(2-acetyl-4-iodophenyl)isopropylamide 89n (X = I, R = $CH(CH_3)_2$)

A stirred mixture of isobutyryl chloride (0.40 g, 3.83 mmol) and 2-amino-5-iodoacetophenone **88c** (1.00 g, 3.83 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89n** as a dark grey solid (1.28 g, 84%), mp 92−94 °C; $\nu_{max}$ (ATR) 837, 957, 1090, 1154, 1219, 1300, 1358, 1383, 1501, 1566, 1655 (C=O acetyl), 1686 (C=O amide), 2876, 2899, 2935, 2971 (CH alkyl), 3262 (NH) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 1.45 (6H, d, *J* = 7.2 Hz, -$CH_3$), 2.82 (3H, s, -$CH_3$), 2.62−2.74 (1H, m, -CH), 7.97 (1H, d, *J* = 8.7 Hz, H-6), 8.33 (1H, s, H-3), 8.76 (1H, d, *J* = 8.7 Hz, H-5), 11.84 (1H, br s, NH); $^{13}C$ NMR (75 MHz, $CDCl_3$) 19.6 (2 x -$CH_3$), 28.8, 37.8, 84.6, 123.0, 123.8, 140.2, 141.1, 143.7, 176.8 (C=O amide), 201.8 (C=O acetyl), HRMS (ES): $MH^+$, found 332.0152 $C_{12}H_{14}INO_2^+$ requires 332.0148.

### 4.2.15 Synthesis of *N*-(2-acetyl-4-iodophenyl)benzamide 89o (X = I, R = -$C_6H_5$)

A stirred mixture of benzoyl chloride (0.65 g, 4.60 mmol) and 2-amino-5-iodoacetophenone **88c** (1.00 g, 3.83 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89o** as a brown solid (1.05 g, 75%), mp 101−103 °C; $\nu_{max}$ (ATR) 741, 832, 960, 1024, 1222, 1301, 1491, 1572, 1650 (C=O acetyl), 1674 (C=O amide), 2963 (CH alkyl), 3240 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.88 (3H, s, -$CH_3$), 7.72−7.86 (3H, m 3', 4' and 5'), 8.06 (1H, d, *J* = 8.7 Hz, H-6), 8.23 (2H, d, *J* = 7.2 Hz, 2' and 6'), 8.40 (1H, s, H-3), 8.97 (1H, d, *J* = 9.0 Hz, H-5), 12.76 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 28.8, 85.0, 123.0, 127.6, 128.6, 129.0, 132.4, 134.6, 140.4, 141.1, 143.9, 166.2 (C=O amide), 202.2 (C=O acetyl); HRMS (ES): $MH^+$, found 365.9992 $C_{15}H_{12}INO_2^+$ requires 365.9991.

### 4.2.16 Synthesis of *N*-(2-acetyl-4-iodophenyl)-4-fluorobenzamide 89p (X = I, R = -$C_6H_4F$)

A stirred mixture of 4-flourobenzoyl chloride (0.73 g, 4.60 mmol) and 2-amino-5-iodoacetophenone **88c** (1.00 g, 3.83 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89p** as a brown solid (1.22 g, 83%), mp 145−148 °C; $\nu_{max}$ (ATR) 742, 843, 880, 939, 1064, 1165, 1229, 1319, 1379, 1500, 1564, 1602, 1625 (C=O acetyl), 1659 (C=O amide), 2975 (CH alkyl), 3237 (NH) $cm^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) 2.48 (3H, s, -$CH_3$), 7.42 (3H, t, *J* = 9.0 Hz, 3' and 5', H-6 ), 7.97−8.01 (3H, m, 2' and 6', H-5 ), 8.29 (1H, d, *J* = 8.5 Hz, H-3), 12.05 (1H, br s, NH); $^{13}$C NMR (125 MHz, DMSO-$d_6$) 29.3, 87.5, 116.5 (d, $^2J$ = 22.8 Hz), 123.3, 126.9, 130.4 (d, $^3J$ = 9.5 Hz), 131.1 (d, $^4J$ = 2.9 Hz), 139.2, 140.0, 143.0, 164.5 (C=O amide), 164.9 (d, $^1J$ = 249.4 Hz), 202.8 (C=O acetyl); HRMS (ES): $MH^+$, found 383.9902 $C_{15}H_{11}FINO_2^+$ requires 383.9897.

### 4.2.17 Synthesis of *N*-(2-acetyl-4-iodophenyl)-4-chlorobenzamide 89q (X = I, R = -$C_6H_4Cl$)

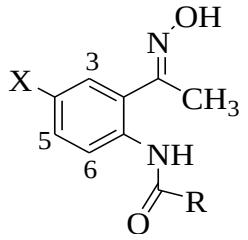
A stirred mixture of 4-chlorobenzoyl chloride (0.81 g, 4.60 mmol) and 2-amino-5-iodoacetophenone **88c** (1.00 g, 3.83 mmol) in pyridine (10 mL) was reacted as described for **88a** to afford **89q** as a brown solid. (1.38 g, 90%), mp 155−157 °C; $\nu_{max}$ (ATR) 740, 840, 896, 956, 1091, 1183, 1297, 1360, 1385, 1421, 1486, 1565, 1595, 1651 (C=O acetyl), 1675 (C=O amide), 3048 (CH alkyl), 3204 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.81 (3H, s, -$CH_3$), 7.60 (2H, d, *J* = 7.5 Hz, 3' and 5'), 7.99 (1H, d, *J* = 9.0 Hz, H-6), 8.09 (2H, d, *J* = 8.1 Hz, 2' and 6'), 8.33 (1H, s, H-3), 8.85 (1H, d, *J* = 9.0 Hz, H-5), 12.71 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 28.7, 85.2, 122.9, 123.9, 129.0, 129.3, 132.9, 138.7, 140.4, 140.9, 144.0, 165.0 (C=O amide), 202.3 (C=O acetyl); HRMS (ES): $MH^+$, found 399.9605 $C_{15}H_{11}ClINO_2^+$ requires 399.9601.

### 4.2.18 Synthesis of *N*-(2-acetyl-4-iodophenyl)-4-methoxybenzamide 89r (X = I, R = -$C_6H_4OMe$)

A stirred mixture of 4-methoxybenzoyl chloride (0.78 g, 4.60 mmol) and 2-amino-5-iodoacetophenone **88c** (1.00 g, 3.83 mmol) in pyridine (10 mL) was reacted as described for **89a** to afford **89r** as a brown solid. (1.41 g, 93%), mp 156−158 °C; $\nu_{max}$ (ATR) 758, 833, 1022, 1176, 1255, 1468, 1508, 1569, 1591, 1608, 1650 (C=O acetyl), 1740 (C=O amide), 2838 (CH aryl), 2937 (CH alkyl), 3204 (NH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.85 (3H, s, -$CH_3$), 4.04 (3H, s, -$OCH_3$), 7.16 (2H, d, *J* = 8.7 Hz, 3' and 5'), 8.01 (1H, d, *J* = 8.7 Hz, H-6), 8.17 (2H, d, *J* = 8.7 Hz, 2' and 6'), 8.36 (1H, s, H-3), 8.93 (1H, d, *J* = 9.6 Hz, H-5), 12.67 (1H, br s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) 28.8, 55.6, 84.6, 114.2, 122.9, 123.8, 126.9, 129.6, 140.4, 141.4,

143.9, 163.0, 165.7 (C=O amide), 202.2 (C=O acetyl); HRMS (ES): $MH^+$, found 396.0112 $C_{16}H_{14}INO_3^+$ requires 396.0097.

### 4.3 Synthesis of *N*-[2-(1-hydroxyiminoethyl)phenyl]amide and *N*-(4-halo-2-(1-(hydroxyimino)ethyl)phenyl)amide 90a–r




**90a–r**

#### 4.3.1 Synthesis of *N*-[2-(1-hydroxyiminoethyl)phenyl]acetamide 90a (X = H, R = -$CH_3$)

*N*-(2-Acetyl phenyl) acetamide **89a** (1.00 g, 5.64 mmol) was added to a solution of ammonium hydroxyl chloride (0.47 g, 6.77 mmol) in pyridine (10 mL) and the reaction mixture was stirred under reflux for 2 h. The reaction mixture was poured into ice cold water and the resultant precipitate was filtered, washed with cold water and recrystallized from ethanol to afford **90a** as an off-white solid (1.36 g, 78%), mp 75–77 °C $\nu_{max}$ (ATR) 751, 1014, 1256, 1300, 1366, 1443, 1529, 1580, 1631 (C=O), 1654 (C=N), 2881 (CH alkyl), 3065 (NH), 3172 (OH) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 2.14 (3H, s, -$CH_3$), 2.34 (3H, s, -$CH_3$), 7.12 (1H, t, *J* = 6.9 Hz, H-4), 7.33 (1H, t, *J* = 6.6 Hz, H-5), 7.46 (1H, d, *J* = 7.5 Hz, H-6), 8.49 (1H, d, *J* = 8.1 Hz, H-3), 8.67 (1H, s, NH), 10.89 (1H, s, OH); $^{13}C$ NMR (75 MHz, $CDCl_3$) 13.2, 25.2, 121.3, 123.4, 128.2, 128.4, 129.6, 136.5, 157.9 (C=N), 169.3 (C=O); HRMS (ES): $MH^+$, found 191.0817. $C_{10}H_{12}N_2O_2^+$ requires: 191.0821.

### 4.3.2 Synthesis of *N*-(2-(1-(hydroxyimino)ethyl)phenyl)isopropylamide 90b (X = H, R = $CH(CH_3)_2$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89b** (1.00g, 4.87 mmol) and ammonium hydroxyl chloride (0.41 g, 5.85 mmol) in pyridine (10 mL) to afford **90b** as a light brown solid (0.81 g, 75%), mp. 118–119 °C; $\nu_{max}$ (ATR) 751, 937, 1010, 1244, 1366, 1450, 1529, 1578, 1633 (C=O), 1659 (C=N), 2927 (CH alkyl), 2980 (NH), 3376 (OH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 1.46 (6H, d, *J* = 6.0 Hz, -CH(**$CH_3$**)$_2$), 2.59 (3H, s, -$CH_3$), 2.73–2.77 (1H, m, -**CH**($CH_3$)$_2$), 7.35 (1H, t, *J* = 6.9 Hz, H-4), 7.55 (1H, t, *J* = 6.9 Hz, H-5), 7.69 (1H, d, *J* = 7.8 Hz, H-6), 8.30 (1H, s, NH), 8.78 (1H, d, *J* = 8.4 Hz, H-3), 11.01 (1H, s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$) 13.4, 19.7 (2 x -$CH_3$), 37.5, 121.4, 123.2, 123.5, 128.5, 129.8, 136.8, 158.0 (C=N), 176.4 (C=O); HRMS (ES): $MH^+$, found 221.1295 $C_{12}H_{16}N_2O_2^+$ requires 221.1290.

### 4.3.3 Synthesis of *N*-(2-(1-(hydroxyimino)ethyl)phenyl)benzamide 90c (X = H, R = -$C_6H_5$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89c** (1.00 g, 4.18 mmol) and ammonium hydroxyl chloride (0.35 g, 5.02 mmol) in pyridine (10 mL) to afford **90c** as a white solid (1.19 g, 70%), mp. 182–185 °C (Lit.[79] 183 °C); $\nu_{max}$ (ATR) 679, 754, 859, 1003, 1223, 1427, 1533, 1579, 1619 (C=O), 1649 (C=N), 2890 (CH alkyl), 2981 (NH), 3362 (OH) $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) 2.27 (3H, s, $CH_3$), 7.20 (1H, t, *J* = 6.9 Hz, H-4), 7.40 (1H, t, *J* = 7.5 Hz, H-5), 7.54−7.63 (4H, m, H-3', 4', 5' and H-3), 7.95 (2H, d, *J* = 7.5 Hz, H-2',6'), 8.51(1H, d, *J* = 8.1 Hz, H-6), 11.73 (1H, s, NH), 11.80 (1H, s, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) 13.6, 121.7, 124.1, 125.5, 129.3, 129.4, 129.5, 132.4, 134.8, 136.9, 156.4 (C=N), 165.1 (C=O).

### 4.3.4 Synthesis of 4-fluoro-*N*-(2-(1-(hydroxyimino)ethyl)phenyl)benzamide 90d (X = H, R = -$C_6H_4F$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89d** (1.00 g, 3.89 mmol) and ammonium hydroxyl chloride (0.32 g, 4.66 mmol) in pyridine (10 mL) to afford **90d** as a brown solid (1.32 g, 84%), mp. 192–194 °C; $\nu_{max}$ (ATR) 754, 847, 1003, 1235, 1426, 1580, 1621 (C=O), 1656 (C=N), 2834 (CH alkyl), 2981 (NH), 3363 (OH) $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) 2.26 (3H, s, -$CH_3$), 7.20 (1H, t, *J* = 7.5 Hz, H-4), 7.32–7.42 (3H, m, H-4 and H-2',6'), 7.60 (1H, d, *J* = 8.1 Hz, H-6), 8.00 (2H, dd, *J* = 5.4 Hz and 8.7 Hz, H-3',5'), 8.46 (1H, d, *J* = 8.1 Hz, H-3), 11.68 (1H, s, NH), 11.77 (1H, s, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) 13.6, 116.3 (d, $^2J_{CF}$ = 21.8 Hz), 121.8, 124.2, 125.6, 129.3, 129.5, 130.5 (d, $^3J_{CF}$ = 9.2 Hz), 131.3 (d, $^4J_{CF}$ = 2.3 Hz), 136.9, 156.4 (C=N), 164.1 (C=O), 164.7 (d, $^1J_{CF}$ = 248.5 Hz); HRMS (ES): $MH^+$, found 273.1046. $C_{15}H_{13}FN_2O_2^+$ requires: 273.1039.

### 4.3.5 Synthesis of 4-chloro-*N*-(2-(1-(hydroxyimino)ethyl)phenyl)benzamide 90e (X = H, R = -$C_6H_4Cl$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89e** (1.00 g, 3.65 mmol) and ammonium hydroxyl chloride (0.30 g, 4.38 mmol) in pyridine (10 mL) to afford **90e** as an off-white solid (1.31 g, 76%), mp. 152–154 °C; $\nu_{max}$ (ATR) 517, 679, 753, 859, 1003, 1324, 1505, 1529, 1582, 1619, 1619 (C=O), 1650 (C=N), 2890 (CH alkyl), 2981 (NH), 3362 (OH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.48 (3H, s, -$CH_3$), 7.25 (1H, t, *J* = 7.8 Hz, H-4), 7.47 (3H, d, *J* = 8.1 Hz, H-4 and H-2',6'), 7.61 (1H, d, *J* = 8.4 Hz, H-6), 7.91 (2H, d, *J* = 8.1 Hz, H-3',5'), 8.23 (1H, s, NH), 8.76 (1H, d, *J* = 8.1 Hz, H-3), 11.73 (H, s, OH); $^{13}$C NMR (75 MHz,

$CDCl_3$) 13.2, 121.4, 123.5, 128.6, 128.8, 129.0, 129.9, 133.8, 136.7, 137.9, 158.5 (C=N), 165.1 (C=O); HRMS (ES): $MH^+$, found 289.0753. $C_{15}H_{13}ClN_2O_2^+$ requires: 289.0744.

### 4.3.6 Synthesis of *N*-(2-(1-(hydroxyimino)ethyl)phenyl)-4-methoxybenzamide 90f (X = H, R = -OMeC$_6$H$_4$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89f** (1.00 g, 3.71 mmol) and ammonium hydroxyl chloride (0.31 g, 4.46 mmol) in pyridine (10 mL) to afford **90f** as a light brown solid (0.77 g, 73 %), mp. 149–151 °C; $\nu_{max}$ (ATR) 732, 825, 949, 1030, 1161, 1256, 1291, 1382, 1446, 1487, 1542, 1559, 1625 (C=O), 1644 (C=N), 2989 (CH alkyl), 2971 (NH) 3360 (OH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.47 (3H, s, -$CH_3$), 3.84 (3H, s, -$OCH_3$), 6.97 (2H, d, *J* = 6.9 Hz, H-2',6'), 7.22 (1H, t, *J* = 7.5 Hz, H-4), 7.46 (1H, t, *J* = 7.8 Hz, H-5), 7.60 (1H, d, *J* = 7.5 Hz, H-6), 7.96 (2H, d, *J* = 6.9 Hz, H-3',5'), 8.68 (1H, s, NH), 8.79 (1H, d, *J* = 8.1 Hz, H-3), 11.69 (1H, s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$) 13.4, 55.4, 114.0, 121.5, 123.3, 123.6, 127.7, 128.6, 129.4, 129.9, 137.2, 158.5 (C=N), 162.4, 165.9 (C=O); HRMS (ES): $MH^+$, found 285.1141 $C_{16}H_{16}N_2O_3^+$ requires 285.1239

### 4.3.7 Synthesis of *N*-(4-bromo-2-(1-(hydroxyimino)ethyl)phenyl)acetamide 90g (X = Br, R = -CH$_3$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89g** (1.00 g, 3.90 mmol) and ammonium hydroxyl chloride (0.33 g, 4.69 mmol) in pyridine (10 mL) to afford **90g** as an off-white solid (1.25 g, 73%), mp. 158–160 °C; $\nu_{max}$ (ATR) 659, 790, 814, 876, 963, 1018, 1071, 1253, 1323, 1366, 1389, 1533, 1572, 1629 (C=O), 1664 (C=N), 2890 (CH alkyl), 2981 (NH), 3361 (OH) $cm^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) 2.05 (3H, s, -$CH_3$), 2.15 (3H, s, -

$CH_3$), 7.49 (1H, dd, *J* = 2.0 Hz and 8.5 Hz, H-5), 7.58 (1H, d, *J* = 2.0 Hz, H-3), 8.05 (1H, d, *J* = 8.5 Hz, H-6), 10.67 (1H, s, NH), 11.73 (1H, s, OH); $^{13}$C NMR (125 MHz, DMSO-$d_6$) 13.7, 24.8, 115.8, 124.4, 128.6, 131.5, 131.8, 136.2, 154.6 (C=N), 168.8 (C=O); HRMS (ES): $MH^+$, found 271.0084 $C_{10}H_{11}BrN_2O_2^+$ requires 271.0082.

### 4.3.8 Synthesis of *N*-(4-bromo-2-(1-(hydroxyimino)ethyl)phenyl)isopropylamide 90h (X = Br, R = $CH(CH_3)_2$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89h** (1.00 g, 3.52 mmol) and ammonium hydroxyl chloride (0.29 g, 4.22 mmol) in pyridine (10 mL) to afford **90h** as an off-white solid (0.81 g, 77%), mp. 173–175 °C; $\nu_{max}$ (ATR) 749, 818, 847, 942, 1025, 1073, 1243, 1393, 1506, 1525, 1573, 1625 (C=O), 1662 (C=N), 2889 (CH alkyl), 2981 (NH), 3365 (OH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 1.27 (6H, d, *J* = 6.9 Hz, -CH(**$CH_3$**)$_2$), 2.40 (1H, s, -$CH_3$), 2.54–2.58 (1H, m, -**CH**($CH_3$)$_2$), 7.49 (1H, d, *J* = 9.0 Hz, H-6), 7.63 (1H, s, H-3), 8.52 (1H, s, NH), 8.59 (1H, d, *J* = 9.0 Hz, H-5), 10.89 (1H, s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$) 13.3, 19.7 (2 x -$CH_3$), 37.6, 115.8, 123.1, 125.3, 131.3, 132.5, 136.0, 157.2 (C=N), 176.4 (C=O); HRMS (ES): $MH^+$, found 299.0397 $C_{12}H_{15}BrN_2O_2^+$ requires 299.0395.

### 4.3.9 Synthesis of *N*-(4-bromo-2-(1-(hydroxyimino)ethyl)phenyl)benzamide 90i (X = Br, R = -$C_6H_5$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89i** (1.00 g, 3.14 mmol) and ammonium hydroxyl chloride (0.26 g, 3.77 mmol) in pyridine (10 mL) to afford **90i** as a brown solid (0.82 g, 84%), mp. 186–188°C; $\nu_{max}$ (ATR) 699, 747, 1013, 1252, 1325, 1371, 1447, 1574, 1625 (C=O), 1653 (C=N), 2889 (CH alkyl), 2981 (NH), 3376 (OH) $cm^{-1}$; $^1$H NMR

(300 MHz, $CDCl_3$) 2.36 (3H, s, -$CH_3$), 7.42–7.50 (4H, m, , H-3',4',5' and H-6), 7.62 (1H, s, H-3), 7.88 (1H, d, *J* = 7.5 Hz, H-5), 8.65 (2H, d, *J* = 9.0 Hz, H-2',6'), 8.23 (1H, s, NH), 11.57 (1H, s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$) 13.2, 115.9, 122.9, 125.2, 127.3, 128.8, 131.2, 131.9, 132.6, 135.3, 136.0, 157.5 (C=N), 166.1 (C=O); HRMS (ES): $MH^+$, found 333.0241 $C_{15}H_{13}BrN_2O_2^+$ requires 333.0239.

### 4.3.10 Synthesis of *N*-(4-bromo-2-(1-(hydroxyimino)ethyl)phenyl)-4-fluorobenzamide 90j (X = Br, R = -$C_6H_4F$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89j** (1.00 g, 2.97 mmol) was added to a solution of ammonium hydroxyl chloride (0.25 g, 3.57 mmol) in pyridine (10 mL) to afford **90j** as a brown solid (0.99 g, 95%), mp. 205–207 °C; $\nu_{max}$ (ATR) 671, 811, 1086, 1318, 1493, 1575, 1625 (C=O), 1657 (C=N), 2889 (CH alkyl), 2981 (NH), 3377 (OH) $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) 2.25 (3H, s, -$CH_3$), 7.35 (2H, dt, *J* = 8.1 Hz and *J* = 9.0 Hz, H-2',6'), 7.58 (1H, d, *J* = 9.0 Hz, H-6), 7.72 (1H, s, H-3), 7.98 (2H, dt, *J* = 5.4 and *J* = 7.5 Hz , H-3',5'), 8.39 (1H, d, *J* = 8.7 Hz, H-5), 11.71 (1H, s, NH) 11.85 (1H, s, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) 13.5, 116.2, 116.4 (d, $^2J_{CF}$ = 21.8 Hz), 123.8, 127.9, 130.6 (d, $^3J_{CF}$ = 9.2 Hz), 131.0 (d, $^4J_{CF}$ = 3.5 Hz), 131.6, 132.1, 136.2, 155.5 (C=N), 164.2 (C=O), 164.7 (d, $^1J_{CF}$ = 248.5 Hz); HRMS (ES): $MH^+$, found 351.0144. $C_{15}H_{12}BrFN_2O_2^+$ requires: 351.0141.

### 4.3.11 Synthesis of *N*-(4-bromo-2-(1-(hydroxyimino)ethyl)phenyl)-4-chlorobenzamide 90k (X = Br, R = -$C_6H_4Cl$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89k** (1.00 g, 2.84 mmol) and ammonium hydroxyl chloride (0.24 g, 3.40 mmol) in pyridine (10 mL)

to afford **90k** as a pale-yellow solid (1.28 g, 75%), mp. 194–196 °C; $\nu_{max}$ (ATR) 818, 843, 1023, 1096, 1247, 1305, 1318, 1492, 1522, 1616 (C=O), 1656 (C=N), 2889 (CH alkyl), 2981 (NH), 3360 (OH) $cm^{-1}$; $^{1}H$ NMR (500 MHz, DMSO-$d_6$) $^{1}H$ NMR (500 MHz, DMSO-$d_6$) 2.24 (3H, s, -$CH_3$), 7.59 (3H, d, *J* = 8.0 Hz, H-3', 5' and 6), 7.73 (1H, s, H-3), 7.92 (1H, d, *J* = 8.5 Hz, H-2',6'), 8.37 (1H, d, *J* = 9.0 Hz, H-5), 11.72 (1H, s, NH), 11.81 (1H, s, OH); $^{13}C$ NMR (125 MHz, DMSO-$d_6$) 13.5, 116.3, 123.9, 128.1, 129.5, 129.7, 131.6, 132.1, 133.4, 136.1, 137.3, 155.5 (C=N), 164.2 (C=O); HRMS (ES): $MH^+$, found 366.9763. $C_{15}H_{12}BrClN_2O_2^+$ requires: 366.9761.

### 4.3.12 Synthesis of *N*-(4-bromo-2-(1-(hydroxyimino)ethyl)phenyl)-4-methoxybenzamide 90l (X = Br, R = -OMe$C_6H_4$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89l** (1.00 g, 2.87 mmol) and ammonium hydroxyl chloride (0.24 g, 3.45 mmol) in pyridine (10 mL) to afford **90l** as a brown solid (0.77 g, 74%), mp. 184–186 °C; $\nu_{max}$ (ATR) 746, 847, 946, 1015, 1069, 1250, 1308, 1385, 1506, 1574, 1619 (C=O), 1642 (C=N), 2889 (CH alkyl), 2981 (NH), 3370 (OH) $cm^{-1}$; $^{1}H$ NMR (500 MHz, DMSO-$d_6$) 2.25 (3H, s, -$CH_3$), 3.84 (3H, s, -$OCH_3$), 7.06 (2H, d, *J* = 8.5 Hz, H-3',5'), 7.56 (1H, dd, *J* = 2.0 Hz and *J* = 9.0 Hz, H-5), 7.72 (1H, d, *J* = 2.0 Hz, H-3), 7.89 (2H, d, *J* = 9.0 Hz, H-2',6'), 8.45 (1H, d, *J* = 8.5 Hz, H-6), 11.66 (1H, s, NH), 11.86 (1H, s, OH); $^{13}C$ NMR (125 MHz, DMSO-$d_6$) 13.5, 55.9, 114.6, 115.7, 123.5, 126.7, 127.4, 129.8, 131.6, 132.1, 136.5, 155.7 (C=N), 162.6, 164.7 (C=O); HRMS (ES): $MH^+$, found 362.0269 $C_{16}H_{15}BrN_2O_3^+$ requires 362.0266.

### 4.3.13 Synthesis of *N*-(4-iodo-2-(1-(hydroxyimino)ethyl)phenyl)acetamide 90m (X = I, R = -$CH_3$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89m** (1.00 g, 3.30 mmol) and ammonium hydroxyl chloride (0.28 g, 3.96 mmol) in pyridine (10 mL) to afford **90m** as a brown solid (0.77 g, 73%), mp. 203–205 °C; $\nu_{max}$ (ATR) 746, 814, 845, 942, 963, 1018, 1068, 1252, 1383, 1503, 1526, 1573, 1636 (C=O), 1653 (C=N), 2890 (CH alkyl), 2981 (NH), 3362 (OH) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 2.15 (3H, s, -$CH_3$), 2.32 (3H, s, -$CH_3$), 7.62 (1H, d, *J* = 8.7 Hz, H-6), 7.73 (2H, s, H-3 and NH), 8.30 (1H, d, *J* = 8.7 Hz, H-5), 10.61 (1H, s, OH); $^{13}C$ NMR (75 MHz, $CDCl_3$) 13.3, 25.4, 86.1, 123.1, 125.1, 136.4, 137.0, 138.5, 157.2 (C=O), 168.8 (C=O); HRMS (ES): $MH^+$, found 318.9949 $C_{10}H_{11}IN_2O_2^+$ requires 318.9944.

### 4.3.14 Synthesis of *N*-(4-iodo-2-(1-(hydroxyimino)ethyl)phenyl)isopropylamide 90n (X = I, R = $CH(CH_3)_2$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89n** (1.00 g, 3.01 mmol) and ammonium hydroxyl chloride (0.25 g, 3.62 mmol) in pyridine (10 mL) to afford **90n** as a brown solid (0.82 g, 79%), mp. 166–168 °C; $\nu_{max}$ (ATR) 747, 815, 844, 943, 1016, 1068, 1251, 1311, 1381, 1461, 1504, 1568, 1622 (C=O), 1660 (C=N), 2889 (CH alkyl), 2980 (NH), 3361 (OH) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 1.39 (6H, d, *J* = 6.9 Hz, -CH(**$CH_3$**)$_2$), 2.50 (3H, s, -$CH_3$), 2.62–2.69 (1H, m, -**CH**($CH_3$)$_2$), 7.78 (1H, d, *J* = 8.4 Hz, H-6), 7.91 (1H, s, H-3), 8.40 (1H, s, NH), 8.52 (1H, d, *J* = 8.4 Hz, H-5), 10.92 (1H, s, OH); $^{13}C$ NMR (75 MHz, $CDCl_3$) 12.7, 19.0 (2 x -$CH_3$), 36.9, 85.5, 122.6, 124.9, 136.1, 136.4, 137.8, 156.4 (C=N), 175.7 (C=O); HRMS (ES): $MH^+$, found 347.0262 $C_{12}H_{15}IN_2O_2^+$ requires 347.0257.

### 4.3.15 Synthesis of *N*-(4-iodo-2-(1-(hydroxyimino)ethyl)phenyl)benzamide 90o (X = I, R = -$C_6H_5$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89o** (1.00 g, 2.74 mmol) and ammonium hydroxyl chloride (0.23 g, 3.29 mmol) in pyridine (10 mL) to afford **90o** as a dark brown solid (0.79 g, 76%), mp. 161–163 °C; $\nu_{max}$ (ATR) 746, 844, 943, 1018, 1068, 1251, 1311, 1380, 1504, 1572, 1620 (C=O), 1643 (C=N), 2889 (CH alkyl), 2981 (NH), 3364 (OH) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.35 (3H, s, -$CH_3$), 7.42–7.53 (3H, m, 3', 4' and 5'), 7.66 (1H, d, *J* = 8.7 Hz, H-6), 7.79 (1H, s, H-3), 7.87 (2H, d, *J* = 6.9 Hz, H-2',6'), 8.21 (1H, s, NH), 8.51 (1H, d, *J* = 8.7 Hz, H-5), 11.57 (1H, s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$) 13.2, 86.3, 123.1, 125.5, 127.3, 128.8, 131.9, 135.3, 136.7, 137.1, 138.6, 157.4 (C=N), 166.1 (C=O); HRMS (ES): $MH^+$, found 381.0105 $C_{15}H_{13}IN_2O_2^+$ requires 381.0100.

### 4.3.16 Synthesis of *N*-(4-iodo-2-(1-(hydroxyimino)ethyl)phenyl)-4-fluorobenzamide 90p (X = I, R = -$C_6H_4F$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89p** (1.00 g, 2.61 mmol) and ammonium hydroxyl chloride (0.22 g, 3.13 mmol) in pyridine (10 mL) to afford **90p** as a brown solid (0.85 g, 82%), mp. 192–194°C; $\nu_{max}$ (ATR) 746, 814, 845, 942, 963, 1018, 1068, 1252, 1383, 1503, 1526, 1573, 1620 (C=O), 1657 (C=N), 2890 (CH alkyl), 2981 (NH), 3367 (OH) $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) 1.72 (3H, s, $CH_3$), 6.84 (2H, t, *J* = 9.0 Hz, H-2',6'), 7.22 (1H, d, *J* = 8.7 Hz, H-6), 7.35 (1H, s, H-3), 7.47 (2H, dt, *J* = 4.5 Hz and *J* = 7.2 Hz, H-3',5'), 7.73 (1H, d, *J* = 8.7 Hz, H-5), 11.17 (1H, s, NH), 11.31 (1H, s, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) 13.6, 88.3, 116.4 (d, $^2J_{CF}$ = 21.8 Hz), 124.0, 128.1, 130.6 (d, $^3J_{CF}$ = 9.2 Hz), 131.1 (d,

$^{4}J_{CF}$ = 2.3 Hz), 132.6, 136.6, 137.3, 138.0, 155.4 (C=N), 164.1 (C=O), 164.7 (d, $^{1}J_{CF}$ = 248.5 Hz); HRMS (ES): $MH^+$, found 399.0011 $C_{15}H_{12}FIN_2O_2^+$ requires 399.0006.

### 4.3.17 Synthesis of *N*-(2-(1-(hydroxyimino)ethyl)-4-iodophenyl)-4-chlorobenzamide 90q (X = I, R = -$C_6H_4Cl$)

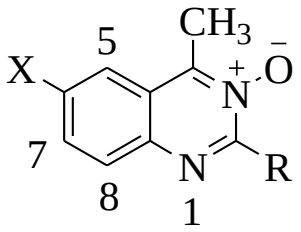
The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **89q** (1.00 g, 2.50 mmol) and ammonium hydroxyl chloride (0.21 g, 3.00 mmol) in pyridine (10 mL) to afford **90q** as a brown solid (0.88 g, 85 %), mp. 182–184 °C; $\nu_{max}$ (ATR) 747, 816, 843, 943, 1018, 1067, 1251, 1311, 1381, 1505, 1568, 1618, 1626 (C=O), 1659 (C=N), 2889 (CH alkyl), 2981 (NH), 3359 (OH) $cm^{-1}$; $^{1}$H NMR (500 MHz, DMSO-$d_6$) 2.22 (3H, s, -$CH_3$), 7.58 (2H, d, *J* = 8.0 Hz, H-2',6'), 7.72 (1H, d, *J* = 8.0 Hz, H-6), 7.85 (1H, s, H-3), 7.91 (2H, d, *J* = 8.0 Hz, H-2',6'), 8.22 (1H, d, *J* = 8.5 Hz, H-5), 11.71 (1H, s, NH), 11.79 (1H, s, OH); $^{13}$C NMR (125 MHz, DMSO-$d_6$) 13.5, 88.4, 124.0, 128.1, 129.5, 129.7, 133.4, 136.6, 137.2, 137.3, 138.0, 155.4 (C=N), 164.2 (C=O); HRMS (ES): $MH^+$, found 414.9715 $C_{15}H_{12}ClIN_2O_2^+$ requires 414.9710.

### 4.3.18 Synthesis of *N*-(4-iodo-2-(1-(hydroxyimino)ethyl)phenyl)-4-methoxybenzamide 90r (X = I, R = -$OMeC_6H_4$)

The experimental procedure used for the synthesis of **90a** was adopted using a mixture of **90r** (1.00 g, 2.53 mmol) and ammonium hydroxyl chloride (0.21 g, 3.4 mmol) in pyridine (10 mL) to afford **90r** as a brown solid (0.84 g, 81%), mp. 170–172 °C; $\nu_{max}$ (ATR) 746, 843, 943, 1018, 1068, 1251, 1310, 1381, 1454, 1504, 1568, 1623 (C=O), 1649 (C=N), 2889 (CH alkyl), 2981 (NH), 3362 (OH) $cm^{-1}$; $^{1}$H NMR (300 MHz, DMSO-$d_6$) 2.24 (3H, s, -$CH_3$), 3.84 (3H, s, -$OCH_3$), 7.06 (2H, d, *J* = 8.1 Hz, H-3',5'), 7.71 (1H, d, *J* = 8.7 Hz, H-6), 7.85 (1H, s, H-3), 7.90 (2H, d, *J* =

8.7 Hz, H-2',6'), 8.31 (1H, d, *J* = 8.7 Hz, H-5), 11.65 (1H, s, NH), 11.85 (1H, s, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) 13.5, 55.9, 87.6, 114.6, 123.7, 126.7, 127.5, 129.8, 137.0, 137.3, 138.0, 155.5 (C=O), 162.6, 164.7 (C=O); HRMS (ES): $MH^+$, found 411.0211 $C_{16}H_{15}IN_2O_3^+$ requires 411.0206.

## 4.4 Typical procedure for the synthesis of 2,4-dicarbosubstituted quinazoline 3-oxides 91a–r




**91a–r**

### 4.4.1 Synthesis of 2,4-dimethylquinazoline 3-oxide 91a (X = H, R = -CH$_3$)

A stirred solution of the *N*-(2-(1-(hydroxyimino)ethyl)phenyl)acetamide **90a** (1.00g, 5.20 mmol) in triflouroacetic acid (10 mL/mmol of **90a**) was heated at 80 °C for 2 h. The mixture was cooled to room temperature, quenched with ice cold water and the product was extracted with chloroform (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the salt was filtered off. The solvent was evaporated under reduced pressure on a rotary evaporator and the residue was purified by column chromatography on silica gel using 3:2 toluene-ethyl acetate as eluent to afford **91a** as a pale-yellow solid (0.71 g, 79%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.04, mp. 102–104 °C (Lit.[84] 101–102 °C); $\nu_{max}$ (ATR) 1020, 1091, 1645 (C=N), 3031 (CH alkyl), 3067 (CH aryl) cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) 2.64 (3H, s, 2-$CH_3$), 2.67 (3H, s, 4-$CH_3$), 7.38 (1H, t, *J* = 7.8 Hz, H-6), 7.48 (1H, t, *J* = 7.5 Hz, H-7), 7.60 (1H, d, *J* = 8.1 Hz, H-5), 7.65 (1H, d, *J* =

8.4 Hz, H-8); $^{13}$C NMR (75 MHz, $CDCl_3$) 12.7, 20.4, 122.8, 123.1, 128.1, 128.2, 130.5, 139.4, 150.3, 156.9.

### 4.4.2 Synthesis of 2-isopropyl-4-methylquinazoline 3-oxide 91b (X = H, R = $CH(CH_3)_2$)

The method of preparing **91a** was followed using a mixture of **90b** (1.00 g, 4.54 mmol) in triflouroacetic acid (10 mL/mmol of **90b**) to afford **91b** as a white solid (0.73 g, 81%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.12, mp. 118–120 °C (Lit.[84] 117–118 °C); $\nu_{max}$ (ATR) 1019, 1067, 1649 (C=N), 2922 (CH alkyl), 2972 (CH aryl) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 1.40 (6H, d, *J* = 6.5 Hz, -CH(**CH$_3$**)$_2$), 2.86 (3H, s, 4-$CH_3$), 4.08–4.14 (1H, m, -**CH**($CH_3$)$_2$), 7.58 (1H, t, *J* = 8.0 Hz, H-6), 7.66 (1H, t, *J* = 8.5 Hz, H-7), 7.82 (1H, d, *J* = 8.0 Hz, H-5), 7.93 (1H, d, *J* = 8.5 Hz, H-8); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.0, 19.9 (2 x -$CH_3$), 29.6, 123.0, 123.1, 128.3, 128.8, 130.5, 139.8, 150.6, 163.6.

### 4.4.3 Synthesis of 4-methyl-2-phenylquinazoline 3-oxide 91c (X = H, R = -$C_6H_5$)

The method of preparing **91a** was followed using a mixture of **90c** (1.00 g, 3.93 mmol) in triflouroacetic acid (10 mL/mmol of **90c**) to afford **91c** as a brown solid (0.81 g, 87%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.10, mp. 140–142 °C (Lit.[84] 140–141 °C); $\nu_{max}$ (ATR) 1026, 1147, 1672 (C=N), 2958 (CH alkyl), 2982 (CH aryl) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.78 (3H, s, 4-$CH_3$), 7.47–7.55 (3H, m, H-3', 4', 5'), 7.64 (1H, t, *J* = 7.5 Hz, H-6), 7.71 (1H, t, *J* = 7.5 Hz, H-7), 7.87 (1H, d, *J* = 8.0 Hz, H-5), 8.02 (1H, d, 8.5 Hz, H-8), 8.30 (2H, d, *J* = 5.5 Hz, H-2',6'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 123.1, 123.6, 127.9, 129.1, 129.2, 130.3, 130.9, 132.7, 140.3, 152.2, 154.7.

### 4.4.4 Synthesis of 2-(4-fluorophenyl)-4-methylquinazoline 3-oxide 91d (X = H, R = -$C_6H_4F$)

The method of preparing **91a** was followed using a mixture of **90d** (1.00 g, 3.67 mmol) in triflouroacetic acid (10 mL/mmol of **90d**) to afford **91d** as an off-white solid (0.78 g, 84%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.16, mp. 170–172 °C (Lit.[85] 169–170 °C); $\nu_{max}$ (ATR) 1018, 1148, 1671 (C=N), 2891 (CH alkyl), 2981 (CH aryl) $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.91 (3H, s, 4-$CH_3$), 7.18 (2H, t, *J* = 9.0 Hz, H-3',5'), 7.64 (1H, t, *J* = 8.5 Hz, H-6), 7.73 (1H, t, *J* = 8.0 Hz, H-7), 7.87 (1H, d, *J* = 8.0 Hz, H-5), 8.00 (1H, d, *J* = 8.0 Hz, H-8), 8.31 (2H, dd, *J* = 6.0 Hz and *J* = 8.5 Hz, H-2',6'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 114.9 (d, $^2J_{CF}$ = 21.9 Hz), 123.1, 123.5, 128.7 (d, $^4J_{CF}$ = 3.9 Hz), 129.1, 129.2, 131.0, 132.8 (d, $^3J_{CF}$ = 8.6 Hz), 140.2, 152.4, 153.5, 164.2 (d, $^1J_{CF}$ = 250.3 Hz).

### 4.4.5 Synthesis of 2-(4-chlorophenyl)-4-methylquinazoline 3-oxide 91e (X = H, R = -$C_6H_4Cl$)

The method of preparing **91a** was followed using a mixture of **90e** (1.00 g, 3.46 mmol) in triflouroacetic acid (10 mL/mmol of **90e**) to afford **91e** as a pale-yellow solid (0.81 g, 86%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.26, mp. 184–186 °C (Lit.[85] 183–184 °C); $\nu_{max}$ (ATR) 1026, 1130, 1649 (C=N), 2962 (CH alkyl), 2981 (CH aryl) $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.92 (3H, s, 4-$CH_3$), 7.48 (2H, d, *J* = 8.5 Hz, H-2',6'), 7.66 (1H, t, *J* = 7.5 Hz, H-6), 7.74 (1H, t, 7.5 Hz, H-7), 7.89 (1H, d, *J* = 8.5 Hz, H-5), 8.35 (1H, d, *J* = 8.5 Hz, H-8), 8.35 (2H, d, *J* = 8.0 Hz, H-3',5'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 123.2, 123.6, 128.1, 129.2, 129.3, 131.0, 131.1, 131.9, 136.9, 140.3, 152.5, 153.5.

### 4.4.6 Synthesis of 2-(4-methoxyphenyl)-4-methylquinazoline 3-oxide 91f (X = H, R = -OMeC$_6$H$_4$)

The method of preparing **91a** was followed using a mixture of **90f** (1.00 g, 3.52 mmol) in triflouroacetic acid (10 mL/mmol of **90f**) to afford **91f** as a brown solid (0.67 g, 72%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.21, mp. 156–158 °C (Lit.[85] 158–159 °C); $\nu_{max}$ (ATR) 1017, 1088, 1646 (C=N), 2890 (CH alkyl), 2982 (CH aryl) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.91 (3H, s, 4-$CH_3$), 3.88 (3H, s, -$OCH_3$), 7.01 (2H, d, *J* = 8.0 Hz, H-2',6'), 7.61 (1H, t, *J* = 7.5 Hz, H-6), 7.70 (1H, t, *J* = 7.5 Hz, H-7), 7.85 (1H, d, *J* = 8.5 Hz, H-5), 7.98 (1H, d, *J* = 8.5 Hz, H-8), 8.43 (2H, d, *J* = 8.5 Hz, H-3',5'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 55.4, 113.3, 123.1, 123.3, 124.9, 128.6, 129.0, 130.8, 132.4, 140.4, 152.2, 154.1, 161.7.

### 4.4.7 Synthesis of 6-bromo-2,4-dimethylquinazoline 3-oxide 91g (X = Br, R = -CH$_3$)

The method of preparing **91a** was followed using a mixture of **90g** (1.00 g, 3.69 mmol) in triflouroacetic acid (10 mL/mmol of **90g**) to afford **91g** as a yellow solid (0.72 g, 78%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.08, mp. 106–108 °C (Lit.[84] 102–104 °C); $\nu_{max}$ (ATR), 1017, 1065, 1667 (C=N), 2953 (CH alkyl), 2995 (CH aryl) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.82 (3H, s, 2-$CH_3$), 2.85 (3H, s, 4-$CH_3$), 7.75 (1H, s, H-5), 7.77 (1H, d, *J* = 9.0 Hz, H-8), 7.97 (1H, d, *J* = 8.5 Hz, H-7); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.0, 20.6, 122.6, 124.7, 125.3, 130.1, 134.0, 138.2, 149.5, 157.7.

### 4.4.8 Synthesis of 6-bromo-2-isopropyl-4-methylquinazoline 3-oxide 91h (X = Br, R = $CH(CH_3)_2$)

The method of preparing **91a** was followed using a mixture of **90h** (1.00 g, 3.34 mmol) in triflouroacetic acid (10 mL/mmol of **90h**) to afford **91h** as a pale-yellow solid (0.80 g, 85%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.15, mp. 162–164 °C; $\nu_{max}$ (ATR) 1018, 1066, 1668 (C=N), 2953 (CH alkyl), 2983 (CH aryl) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 1.39 (6H, d, *J* = 7.0 Hz, -CH(**$CH_3$**)$_2$), 2.81 (3H, s, 4-$CH_3$), 4.04–4.09 (1H, m, -C**H**$(CH_3)_2$), 7.73 (1H, dd, *J* = 2.0 Hz and 8.5 Hz, H-7), 7.80 (1H, d, *J* = 8.5 Hz, H-8), 7.96 (1H, d, *J* = 2.0 Hz, H-5); $^{13}C$ NMR (125 MHz, $CDCl_3$) 13.1, 19.8 (2 x -$CH_3$), 29.6, 122.4, 124.4, 125.2, 130.4, 133.7, 138.1, 149.4, 164.1; HRMS (ES): $MH^+$, calc for $C_{12}H_{14}BrN_2O^+$: 281.0290; found: 281.0287.

### 4.4.9 Synthesis of 6-bromo-4-methyl-2-phenylquinazoline 3-oxide 91i (X = Br, R = -$C_6H_5$)

The method of preparing **91a** was followed using a mixture of **90i** (1.00 g, 3.00 mmol) in triflouroacetic acid (10 mL/mmol of **90i**) to afford **91i** as a brown solid (0.76 g, 81%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.13, mp.158–160 °C (Lit.[85] 160–161 °C); $\nu_{max}$ (ATR) 1027, 1065, 1669 (C=N), 2954 (CH alkyl), 2983 (CH aryl) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 2.87 (3H, s, 4-$CH_3$), 7.49–7.53 (3H, m, H-3', 4', 5'), 7.77 (1H, dd, *J* = 2.0 Hz and 8.5 Hz, H-7), 7.88 (1H, d, *J* = 9.0 Hz, H-8), 8.02 (1H, d, *J* = 2.0 Hz, H-5), 8.27 (2H, d, *J* = 7.3 Hz, H-2',6'); $^{13}C$ NMR (125 MHz, $CDCl_3$) 13.3, 123.3, 124.8, 125.3, 128.0, 130.3, 130.8, 131.0, 132.4, 134.1, 138.7, 151.1, 155.0.

### 4.4.10 Synthesis of 6-bromo-2-(4-fluorophenyl)-4-methylquinazoline 3-oxide 91j (X = Br, R = -$C_6H_4F$)

The method of preparing **91a** was followed using a mixture of **90j** (1.00 g, 2.85 mmol) in triflouroacetic acid (10 mL/mmol of **90j**) to afford **91j** as a brown solid (0.73 g, 77%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.22, mp.182–184 °C; $\nu_{max}$ (ATR) 1019, 1059, 1670 (C=N), 2925 (CH alkyl), 2982 (CH aryl) $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.86 (3H, s, 4-$CH_3$), 7.18 (2H, t, *J* = 9.0 Hz, H-2',6'), 7.77 (1H, dd, *J* = 2.0 Hz and 8.5 Hz, H-7), 7.86 (1H, d, *J* = 9.0 Hz, H-8), 8.01 (1H, d, *J* = 1.0 Hz, H-5), 8.41 (2H, dd, *J* = 5.5 Hz and 9.0 Hz, H-3',5'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 115.0 (d, $^2J_{CF}$ = 21.8 Hz), 123.3, 124.7, 125.3, 128.5 (d, $^4J_{CF}$ = 3.8 Hz), 130.7, 132.9 (d, $^3J_{CF}$ = 8.5 Hz), 134.2, 138.6, 151.3, 153.8, 164.4 (d, $^1J_{CF}$ = 251.3 Hz); HRMS (ES): $MH^+$, calc for $C_{15}H_{11}BrFN_2O^+$: 333.0039; found: 333.0037.

### 4.4.11 Synthesis of 6-bromo-2-(4-chlorophenyl)-4-methylquinazoline 3-oxide 91k (X = Br, R = -$C_6H_4Cl$)

The method of preparing **91a** was followed using a mixture of **90k** (1.00 g, 2.72 mmol) in triflouroacetic acid (10 mL/mmol of **90k**) to afford **91k** as a brown solid (0.78 g, 83%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.30, mp. 172–174 °C (Lit.[85] 170–171 °C); $\nu_{max}$ (ATR) 1021, 1059, 1671 C=N), 2956 (CH alkyl), 2982 (CH aryl) $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.87 (3H, s, 4-$CH_3$), 7.48 (2H, d, *J* = 8.5 Hz, H-2',6'), 7.79 (1H, dd, *J* = 1.5 Hz and 9.0 Hz, H-7), 7.87 (1H, d, *J* = 8.5 Hz, H-8), 8.02 (1H, d, *J* = 1.5 Hz, H-5), 8.34 (2H, d, *J* = 1.5 Hz, H-3',5'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 123.5, 124.8, 125.3, 128.2, 130.6, 130.8, 131.8, 134.3, 137.3, 138.6, 151.4, 153.8.

### 4.4.12 Synthesis of 6-bromo-2-(4-methoxyphenyl)-4-methylquinazoline 3-oxide 91l (X = Br, R = -OMeC$_6$H$_4$)

The method of preparing **91a** was followed using a mixture of **90l** (1.00 g, 2.75 mmol) in triflouroacetic acid (10 mL/mmol of **90l**) to afford **91l** as a brown solid (0.71 g, 75%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.40, mp. 167–169 °C; $\nu_{max}$ (ATR) 1018, 1087, 1647 (C=N), 2957(CH alkyl), 2982 (CH aryl) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.84 (3H, s, 4-$CH_3$), 3.88 (3H, s, -$OCH_3$), 7.00 (2H, d, *J* = 9.0 Hz, H-2',6'), 7.73 (1H, dd, *J* = 2.0 Hz and 8.5 Hz, H-7), 7.83 (1H, d, *J* = 9.0 Hz, H-8), 7.97 (1H, d, *J* = 1.5 Hz, H-8), 8.43 (2H, d, *J* = 9.5 Hz, H-3',5'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 55.4, 113.3, 122.7, 124.4. 124.5, 125.2, 130.6, 132.4, 134.0, 138.7, 151.1, 154.4, 161.9; HRMS (ES): $MH^+$, calc for $C_{16}H_{13}BrN_2O_2^+$: 345.0290; found 345.0287.

### 4.4.13 Synthesis of 6-iodo-2,4-dimethylquinazoline 3-oxide 91m (X = I, R = -CH$_3$)

The method of preparing **91a** was followed using a mixture of **90m** (1.00 g, 3.14 mmol) in triflouroacetic acid (10 mL/mmol of **90m**) to afford **91m** as a brown solid (0.71 g, 75%), $R_f$ (toluene-ethylacetate, 3:2 v/v) 0.12, mp. 113–115 °C (Lit.[84] 112–113 °C); $\nu_{max}$ (ATR) 1017, 1088, 1663 (C=N), 2957 (CH alkyl), 2982 (CH aryl) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.79 (3H, s, 2-$CH_3$), 2.82 (3H, s, 4-$CH_3$), 7.58 (1H, d, *J* = 7.5 Hz, H-7), 7.89 (1H, d, *J* = 7.5 Hz, H-8), 8.16 (1H, s, H-5); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.0, 20.6, 94.2, 125.0, 129.9, 131.8, 138.5, 139.4, 149.3, 157.9.

### 4.4.14 Synthesis of 6-iodo-2-isopropyl-4-methylquinazoline 3-oxide 91n (X = I, R = $CH(CH_3)_2$)

The method of preparing **91a** was followed using a mixture of **90n** (1.00 g, 2.89 mmol) in triflouroacetic acid (10 mL/mmol of **90n**) to afford **91n** as a brown solid (0.79 g, 83%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.19, mp. 159–162 °C; $\nu_{max}$ (ATR) 1056, 1086, 1665 (C=N), 2925 (CH alkyl), 3078 (CH aryl) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 1.28 (6H, d, *J* = 7.2 Hz, -CH(**$CH_3$**)$_2$), 2.71 (3H, s, 4-$CH_3$), 3.83–3.93 (1H, m, -**CH**$(CH_3)_2$), 7.64 (1H, d, *J* = 8.7 Hz, H-8), 7.98 (1H, dd, *J* = 1.2 Hz and 8.7 Hz, H-7), 8.43 (1H, d, *J* = 1.2 Hz, H-5); $^{13}C$ NMR (125 MHz, $CDCl_3$) 13.4, 20.1, 29.6, 95.7, 125.1, 130.1, 132.4, 137.8, 139.3, 149.8, 163.7; HRMS (ES): $MH^+$, calc for $C_{12}H_{14}IN_2O^+$: 329.0151; found 329.0156.

### 4.4.15 Synthesis of 6-iodo-4-methyl-2-phenylquinazoline 3-oxide 91o (X = I, R = -$C_6H_5$)

The method of preparing **91a** was followed using a mixture of **90o** (1.00 g, 2.63 mmol) in triflouroacetic acid (10 mL/mmol of **90o**) to afford **91o** as a brown solid (0.75 g, 79%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.18, mp. 200–202 °C; $\nu_{max}$ (ATR) 1028, 1057, 1667 (C=N), 2999 (CH alkyl), 3076 (CH aryl) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 2.86 (3H, s, 4-$CH_3$), 7.49–7.53 (3H, m, H-3', 4', 5'), 7.72 (1H, d, *J* = 8.5 Hz, H-8), 7.94 (1H, d, *J* = 9.25 Hz, H-7), 8.24 (1H, s, H-5), 8.29 (1H, d, *J* = 8.0 Hz, H-2', 6',); $^{13}C$ NMR (125 MHz, $CDCl_3$) 13.3, 95.0, 125.2, 127.9, 130.3, 130.6, 131.0, 131.8, 132.3, 139.0, 139.5, 150.9, 155.2; HRMS (ES): $MH^+$, calc for $C_{15}H_{11}IN_2O^+$: 362.9994; found 362.9996.

### 4.4.16 Synthesis of 2-(4-fluorophenyl)-6-iodo-4-methylquinazoline 3-oxide 91p (X = I, R = -$C_6H_4F$)

The method of preparing **91a** was followed using a mixture of **90p** (1.00 g, 2.51 mmol) in triflouroacetic acid (10 mL/mmol of **90p**) to afford **91p** as a brown solid (0.75 g, 79%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.23, mp. 200–203 °C; $\nu_{max}$ (ATR) 1019, 1054, 1669 (C=N), 2952 (CH alkyl), 3058 (CH aryl) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 2.87 (3H, s, 4-$CH_3$), 7.19 (2H, t, *J* = 9.0 Hz, H-2',6'), 7.72 (1H, d, *J* = 9.0 Hz, H-7), 7.95 (1H, d, *J* = 8.5 Hz, H-8), 8.42 (2H, dd, *J* = 5.5 Hz and 8.5 Hz, H3',5'); $^{13}C$ NMR (125 MHz, $CDCl_3$) 13.3, 95.1, 115.0 (d, $^2J_{CF}$ = 21.8 Hz), 125.1, 128.3 (d, $^4J_{CF}$ = 2.9 Hz), 130.6, 131.9, 132.9 (d, $^3J_{CF}$ = 8.5 Hz), 139.0, 139.7, 151.1, 154.0, 164.4 (d, $^1J_{CF}$ = 251.3 Hz); HRMS (ES): $MH^+$, calc for $C_{15}H_{10}FIN_2O^+$: 380.9822; found 380.9855.

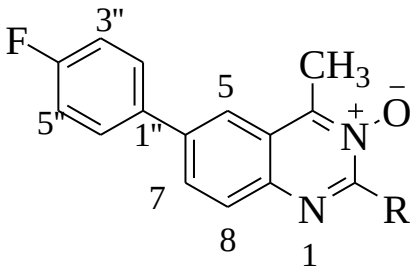
### 4.4.17 Synthesis of 2-(4-chlorophenyl)-6-iodo-4-methylquinazoline 3-oxide 91q (X = I, R = -$C_6H_4Cl$)

The method of preparing **91a** was followed using a mixture of **90q** (1.00 g, 2.42 mmol) in triflouroacetic acid (10 mL/mmol of **90q**) to afford **91q** as a brown solid (0.85 g, 89%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.34, mp. 202–204 °C; $\nu_{max}$ (ATR) 1019, 1054, 1668 (C=N), 2952 (CH alkyl), 3058 (CH aryl) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 2.86 (3H, s, 4-$CH_3$), 7.48 (2H, d, *J* = 8.5 Hz, H-2',6'), 7.71 (1H, d, *J* = 9.0 Hz, H-8), 7.96 (1H, dd, *J* = 2.0 Hz and 8.5 Hz, H-8), 8.24 (1H, d, *J* = 1.5 Hz, H-5), 8.35 (2H, d, *J* = 9.0 Hz, H-3',5'); $^{13}C$ NMR (125 MHz, $CDCl_3$) 13.3, 95.2, 125.2, 128.2, 130.6, 130.6, 131.9, 131.9, 137.3, 138.9, 139.7, 151.1, 153.9; HRMS (ES): $MH^+$, calc for $C_{15}H_{10}ClIN_2O^+$: 396.9605; found 396.9608.

### 4.4.18 Synthesis of 6-iodo-2-(4-methoxyphenyl)-4-methylquinazoline 3-oxide 91r (X = I, R = -OMeC$_6$H$_4$)

The method of preparing **91a** was followed using a mixture of **90r** (1.00 g, 2.44 mmol) in triflouroacetic acid (10 mL/mmol of **90r**) to afford **91r** as a brown solid (0.76 g, 79%), $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.44, mp. 149–153 °C; $\nu_{max}$ (ATR) 1026, 1058, 1668 (C=N), 2997 (CH alkyl), 3063 (CH aryl) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.84 (3H, s, 4-$CH_3$), 3.88 (3H, s, -$OCH_3$), 6.99 (2H, d, *J* = 9.5 Hz, H-2',6'), 7.67 (1H, d, *J* = 8.5 Hz, H-7), 7.90 (1H, d, *J* = 8.5 Hz, H-8), 8.19 (1H, s, H-5), 8.4 (2H, d, *J* = 9.0 Hz, H-3',5'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 55.4, 94.4, 113.3, 124.5, 124.8, 131.8, 132.4, 139.1, 139.4, 151.6, 154.4, 161.9; HRMS (ES): $MH^+$, calc for $C_{16}H_{13}IN_2O_2^+$: 393.0100; found 393.0104.

## 4.5. Typical procedure for the Suzuki-Miyaura cross-coupling of 91m–r to afford 92a–f




**92a–f**

### 4.5.1 Synthesis of 6-(4-fluorophenyl)-2,4-dimethylquinazoline 3-oxide 92a (R = -$CH_3$)

A stirred mixture of **91m** (0.30 g, 0.99 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.05 mmol), $PCy_3$ (0.03 g, 0.099 mmol), $Cs_2CO_3$ (0.39 g, 1.49 mmol) in 3:1 dioxane-water (v/v, 20 mL/mmol of **91m**) was placed in a two-necked round bottom flask equipped with a stirrer bar, rubber septum and a condenser. The mixture was flushed with argon gas for 0.5 hour. and then a balloon filled with

argon gas was connected to the top of the condenser. 4-Fluorophenylboronic acid (0.18 g, 1.18 mmol), was added to the reaction mixture and the mixture was stirred at 80 °C for 2.5 hours, cooled to room temperature and then quenched with ice-cold water. The product was extracted with chloroform (3 x 30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. The salt was filtered off and the solvent was evaporated under reduced pressure on a rotary evaporator. The residue was purified by column chromatography on silica gel to afford **92a** as a brown solid (0.22 g, 81%), mp. 197–198 °C; $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.58, $\nu_{max}$ (ATR) 1224, 1499, 1589, 1676 (C=N), 2850 (CH alkyl), 2916 (CH aryl) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 2.91 (3H, s, 2-$CH_3$), 2.93 (3H, s, 4-$CH_3$), 7.97 (2H, t, *J* = 8.5 Hz, H-2',6'), 7.20 (2H, dd, *J* = 5.0 Hz and 8.0 Hz, H-3',5'), 7.89 (1H, d, *J* = 9.0 Hz, H-7), 7.92 (1H, s, H-5), 8.40 (1H, d, *J* = 8.5 Hz, H-8); $^{13}C$ NMR (125 MHz, $CDCl_3$) 13.0, 20.6, 116.1 (d, $^2J_{CF}$ = 21.8 Hz), 120.7, 123.7, 128.9, 129.2 (d, $^3J_{CF}$ = 7.5 Hz), 130.4, 135.9 (d, $^4J_{CF}$ = 3.9 Hz), 139.0, 140.6, 150.7, 157.2, 163.0 (d, $^1J_{CF}$ = 246.6 Hz); HRMS (ES): $MH^+$, calc for $C_{16}H_{14}N_2OF^+$: 269.1090; found 269.1095.

### 4.5.2 Synthesis of 6-(4-fluorophenyl)-2-isopropyl-4-methylquinazoline 3-oxide 92b (R = $CH(CH_3)_2$)

The experimental procedure employed for the preparation of **92a** was followed using a mixture of **91n** (0.30 g, 0.91 mmol), $PdCl_2(PPh_3)_2$ (0.03 g, 0.05 mmol), $PCy_3$ (0.03 g, 0.091 mmol), $Cs_2CO_3$ (0.44 g, 1.37 mmol) and 4-fluorophenylboronic acid (0.15 g, 1.09 mmol) to afford **92b** as a pale-brown solid (0.20 g, 74%), mp. 134–136°C; $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.57, $\nu_{max}$ (ATR) 1414, 1502, 1595, 1680 (C=N), 2852 (CH alkyl), 2929 (CH aryl) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 1.43 (6H, d, *J* = 7.0 Hz, -CH(**$CH_3$**)$_2$), 2.93 (3H, s, 4-$CH_3$), 4.13–4.17 (1H, m, -**CH**($CH_3$)$_2$), 7.20 (2H, t, *J* = 8.5 Hz, H-2',6'), 7.64 (1H, dd, *J* = 4.5 Hz and 7.0 Hz, H-7), 7.88 (1H, d, *J* = 8.8 Hz, H-7), 7.91 (1H, s, H-5), 8.01 (1H, d, *J* = 9.0 Hz, H-8); $^{13}C$ NMR (125 MHz, $CDCl_3$) 13.2, 13.3, 20,

29.7, 116.1 (d, $^{2}J_{CF}$ = 20.9 Hz), 120.7, 123.3 (d, $^{4}J_{CF}$ = 2.8 Hz), 129.1 (d, $^{3}J_{CF}$ = 8.5 Hz), 129.3, 130.2, 130.3, 135.9, 139.1, 140.5, 163.6, 163.0 (d, $^{1}J_{CF}$ = 247.5 Hz); HRMS (ES): $MH^{+}$, calc for $C_{18}H_{18}N_{2}OF^{+}$: 297.1403; found 297.1406.

### 4.5.3 Synthesis of 6-(4-fluorophenyl)-4-methyl-2-phenylquinazoline 3-oxide 92c (R = -$C_6H_5$)

The experimental procedure employed for the preparation of **92a** was followed using a mixture of **91o** (0.30 g, 0.83 mmol), $PdCl_2(PPh_3)_2$ (0.03 g, 0.04 mmol), $PCy_3$ (0.02 g, 0.083 mmol), $Cs_2CO_3$ (0.32 g, 1.00 mmol) and 4-fluorophenylboronic acid (0.14 g, 1.00 mmol) to afford **92c** as a yellow solid (0.22 g, 79%), mp. 158–160 °C; $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.63; $\nu_{max}$ (ATR) 1490, 1554, 1651 (C=N), 2926 (CH alkyl), 2970 (CH aryl) $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$) 2.97 (3H, s, 4-$CH_3$), 7.72 (2H, t, *J* = 8.5 Hz, H-2",6"), 7.52–7.53 (3H, m, H-3', 4', 5'), 7.67 (2H, dd, *J* = 5.5 Hz and 8.5 Hz, H-2',6'), 7.94 (1H, d, *J* = 8.25 Hz, H-7), 7.85 (1H, s, H-5), 8.08 (1H, d, *J* = 8.5 Hz, H-8), 8.32 (2H, dd, *J* = 2.5 Hz and 7.5 Hz, H-3",5"); $^{13}C$ NMR (125 MHz, $CDCl_3$) 13.3, 114.1, 116.2 (d, $^{2}J_{CF}$ = 20.9 Hz), 120.6, 123.9 (d, $^{4}J_{CF}$ = 2.8 Hz), 127.9, 129.2 (d, $^{3}J_{CF}$ = 8.5 Hz), 129.8, 130.3, 130.5, 130.8, 132.6, 135.8, 139.5, 141.1, 152.2, 154.6, 163.1 (d, $^{1}J_{CF}$ = 247.5 Hz); HRMS (ES): $MH^{+}$, calc for $C_{21}H_{16}N_{2}OF^{+}$: 331.1247; found 331.1251.

### 4.5.4 Synthesis of 2,6-bis-(4-fluorophenyl)-4-methylquinazoline 3-oxide 92d (R = -$C_6H_4F$)

The experimental procedure employed for the preparation of **92a** was followed using a mixture of **91p** (0.30 g, 0.79 mmol), $PdCl_2(PPh_3)_2$ (0.03 g, 0.04 mmol), $PCy_3$ (0.02 g, 0.079 mmol), $Cs_2CO_3$ (0.31 g, 0.95 mmol) and 4-fluorophenylboronic acid (0.13 g, 0.95 mmol) to afford **92d** as a yellow solid (0.22 g, 77%), mp. 202–205 °C; $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.67; $\nu_{max}$ (ATR) 1490, 1530, 1599, 1658 (C=N), 2923 (CH alkyl), 2970 (CH aryl) $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$) 2.97

(3H, s, 4-$CH_3$), 7.19–7.27 (4H, m, H-2',6' and H-2",6"), 7.68 (2H, dd, *J* = 4.5 Hz and 8.0 Hz, H-3',5'), 7.93 (2H, dd, *J* = 1.5 Hz and 8.5 Hz, H-7), 7.96 (1H, d, *J* = 1.5 Hz, H-5), 8.08 (1H, d, *J* = 9.0 Hz, H-8), (2H, dd, *J* = 4.5 Hz and 8.0 Hz, H-3",5"); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.4, 115.0 (d, $^2J_{CF}$' = 20.9 Hz), 116.2 (d, $^2J_{CF}$" = 21.8 Hz), 120.7, 123.8, 128.6 (d, $^4J_{CF}$' = 2.8 Hz), 129.2 (d, $^3J_{CF}$' = 8.5 Hz), 129.7, 130.6, 132.9 (d, $^3J_{CF}$" = 8.6 Hz), 135.8 (d, $^4J_{CF}$" = 3.8 Hz), 139.5, 141.2, 152.4, 153.4, 163.1 (d, $^1J_{CF}$' = 247.5 Hz), 164.3 (d, $^1J_{CF}$" = 250.3 Hz); HRMS (ES): $MH^+$, calc for $C_{21}H_{15}N_2OF_2^+$: 349.1152; found 349.1161.

### 4.5.5 Synthesis of 2-(4-chlorophenyl)-6-(4-fluorophenyl)-4-methylquinazoline 3-oxide 92e (R = -$C_6H_4Cl$)

The experimental procedure employed for the preparation of **92a** was followed using a mixture of **91q** (0.30 g, 0.76 mmol), $PdCl_2(PPh_3)_2$ (0.03 g, 0.04 mmol), $PCy_3$ (0.02 g, 0.076 mmol), $Cs_2CO_3$ (0.31 g, 0.91 mmol) and 4-fluorophenylboronic acid (0.13 g, 0.91mmol) to afford **92e** as a yellow solid (0.21 g, 75%), mp. 238–240 °C; $R_f$ (toluene-ethyl acetate, 3:2 v/v 0.69; $\nu_{max}$ (ATR) 1491, 1515, 1594, 1673 (C=N), 2927 (CH alkyl), 2973 (CH aryl) $cm^{-1}$; $^1$H NMR ($CDCl_3$ 500 MHz) 2.97 (3H, s, 4-$CH_3$), 7.23 (2H, t, *J* = 8.5 Hz, H-2",6"), 7.50 (2H, d, *J* = 8.0 Hz, H-2',6'), 7.68 (2H, dd, *J* = 5.5 Hz and 9.0 Hz, H-3",5"), 7.93 (1H, s, H-5), 7.95 (1H, dt, *J* = 1.5 Hz and *J* = 9.0 Hz, H-7), 8.08 (1H, d, *J* = 9.0 Hz, H-8), 8.38 (2H, d, *J* = 8.5 Hz, H-3',5'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 116.2 (d, $^2J_{CF}$ = 21.8 Hz), 120.7, 123.9, 128.2, 129.2 (d, $^3J_{CF}$ = 8.6 Hz), 129.8, 130.7, 131.0, 131.9, 135.9 (d, $^4J_{CF}$ = 2.88 Hz), 137.0, 139.5, 141.3, 152.5, 153.4, 163.1 (d, $^1J_{CF}$ = 247.5 Hz); HRMS (ES): $MH^+$, calc for $C_{21}H_{15}N_2ClOF^+$: 365.0857; found 365.0855.

### 4.5.6 Synthesis of 6-(4-fluorophenyl)-2-(4-methoxyphenyl)-4-methylquinazoline 3-oxide 92f (R = -OMeC$_6$H$_4$)

The experimental procedure employed for the preparation of **92a** was followed using a mixture of **91r** (0.30 g, 0.76 mmol), $PdCl_2(PPh_3)_2$ (0.03 g, 0.04 mmol), $PCy_3$ (0.02 g, 0.076 mmol), $Cs_2CO_3$ (0.31 g, 0.91 mmol) and 4-fluorophenylboronic acid (0.13 g, 0.91mmol) to afford **92f** as a brown solid ( 0.20 g, 76%), mp. 225–209 °C; $R_f$ (toluene-ethyl acetate, 3:2 v/v) 0.48; $\nu_{max}$ (ATR) 1496, 1507, 1601, 1664 (C=N), 2838 (CH alkyl), 2937 (CH aryl) $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 2.95 (3H, s, 4-$CH_3$), 3.89 (3H, s, -$OCH_3$), 7.01 (2H, d, *J* = 8.5 Hz, H-2',6'), 7.21 (2H, t, *J* = 8.0 Hz, H-2",6"), 7.66 (2H, dd, *J* = 6.0 Hz and 7.5 Hz, H-3",5"), 7.90 (1H, d, *J* = 9.0 Hz, H-7), 7.92 (1H, s, H-5), 8.04 (2H, d, *J* = 8.5 Hz, H-8), 8.45 (2H, d, *J* = 8.5 Hz, H-3',5'); $^{13}$C NMR (125 MHz, $CDCl_3$) 13.3, 55.4, 113.3, 116.1 (d, $^2J_{CF}$ = 21.9 Hz), 120.6, 123.5, 124.9, 129.1 (d, $^3J_{CF}$ = 8.6 Hz) 129.5, 130.4, 135.9 (d, $^4J_{CF}$ = 2.9 Hz), 139.6, 140.6, 152.2, 154.0, 161.7, 163.0 (d, $^1J_{CF}$ = 246.6 Hz); HRMS (ES): $MH^+$, calc for $C_{22}H_{18}N_2O_2F^+$: 361.1352; found 361.1353.

### 4.6 XRD data collection and refinement

Intensity data was determined on a Bruker Venture D8 Photon CMOS diffractometer with graphite-monochromated AgK$\alpha_1$ ($\lambda$ = 0.56086 Å) radiation at 173 K using an Oxford Cryostream 600 cooler. Data reduction was carried out using the program SAINT+, version 6.02[103] and empirical absorption corrections were made using SADABS.[103] Space group assignments was made using *XPREP*.[103] The structure was solved in the *WinGX*[104] Suite of programs, using intrinsic phasing through *SHELXT*[105] and refined using full-matrix least-squares/difference Fourier techniques on $F^2$ using *SHELXL-2017*.[106] All C bound hydrogen atoms were placed at idealized positions and refined as riding atoms with isotropic parameters 1.2 times those of their parent atoms. O- and N-bound

hydrogen atoms were in the difference Fourier map and their coordinates and isotropic displacement parameters refined freely. Diagrams and publication material were generated using ORTEP-3,[104] and PLATON.[107]

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