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Chapter 1: Introduction

1.1 Importance of heterocyclic compounds in the treatment of cancer

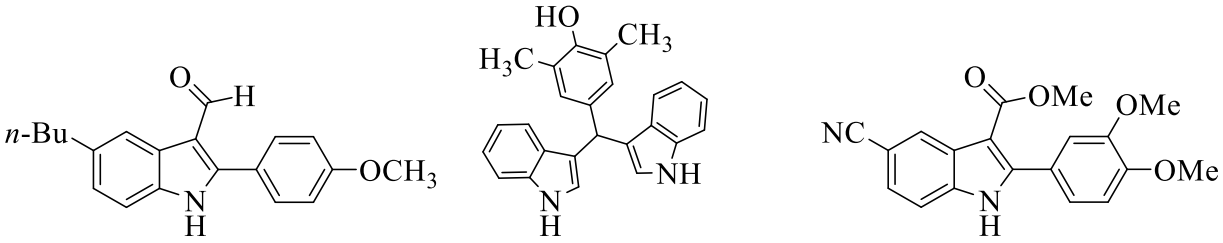
Nitrogen-, oxygen- and sulphur-containing heterocyclic compounds represent the key structural components of many of the anticancer drugs available on the market today. Of the novel molecular anticancer agents approved by the US Food and Drug Administration (FDA) between 2010 and 2015, for example, almost two-thirds contained heterocyclic moieties within their frameworks.[1] The prevalence of heterocyclic moieties in anticancer drug design is partly credited to their occurrence in nature accompanied by their involvement in various cellular processes and interesting mechanisms evolved to interact with them.[1] Despite the wide range of heterocyclic anticancer drugs that are currently available on the market, there are still challenges around multi-drug resistance, poor therapeutic efficacy, adverse side effects and poor bioavailability, which necessitate the continued development of new anticancer agents. Resistance to some of the anticancer drugs currently in the market has resulted in a desperate need to develop new strategies to combat this deadly disease. As such, the use of combinatorial therapies of anticancer drugs has superseded monotherapy drug use. Combinatorial therapy makes up the basis of drug synergy and is defined as the use of two or more drugs simultaneously for cancer treatment. In 2010 the FDA-approved a combination of lapatanib with capecitabine in women with advanced breast cancer resistant to trastuzumab.[2] A combination of cetuximab with irinotecan has also been employed in patients with metastatic colorectal carcinoma.[2] Concurrent inhibition of DNA repair enzymes (eg. PARP1) or checkpoint kinases (eg. CHK1) with chemotherapy has also significantly improved the standard of care in a variety of cancers.[2] The major drawback of the combinatorial approach is that the half-life of inhibitors affects drug efficacy.[3] The other disadvantages attributed to combination chemotherapy include patient noncompliance due to the

increased number of administrations, forgetting to take medication and increased drug dose with consequent side effect and the negative impact on patient's health.[4] The problems associated with combination chemotherapy due to patients' noncompliance led to the invention of molecular hybridization in which two or more of the drugs are linked together on the same molecular framework and available to patients as a single entity.[5] Molecular hybridization involves the fusion of two or more pharmacophoric units of known bioactive molecules to produce a new compound with improved affinity and efficacy compared to the individual parent drugs.[6] The selection of the drugs or pharmacophores is usually based on their observed pharmacological activities to enable the identification of highly active novel chemical entities and it is expected that the hybrid molecules might exhibit different and/or dual modes of action, modified selectivity profile and reduced side effects.[7] The hybridization approach has already been applied in the development of novel antibacterial and anticancer agents to overcome drug resistance. Indoles, benzofurans, quinazolines, chalcones and their derivatives, for example, are among the most valuable compounds proven to induce antiproliferative effect in several cancer cell lines. Our group has for some time focused on the synthesis and structural property studies of quinolinones and their quinoline derivatives,[8] and the analogous quinazolinones[3] and their quinazoline derivatives.[9] The quinolinone derivatives were mainly accessible via acid-mediated cycloisomerization of the corresponding chalcone precursors.[10] We became inspired by the prevalence of the indole and benzofuran scaffolds in naturally occurring and synthetic heterocyclic compounds with anticancer properties. We asked ourselves whether it was possible to merge these scaffolds with the chalcone and quinazoline moieties to construct novel heterocycle-appended chalcone and quinazoline hybrids for further evaluation as potential anticancer agents. To realise our goal, we performed a thorough literature search on the known examples of biologically-relevant indole derivatives and benzofuran analogues and their corresponding molecular hybrids. In the next sections we describe some of the examples of the

indoles and benzofurans as well as the known molecular hybrids of biological importance that are based on these heterocyclic frameworks.

1.2 An overview of indoles and indole-appended molecular hybrids of biological importance

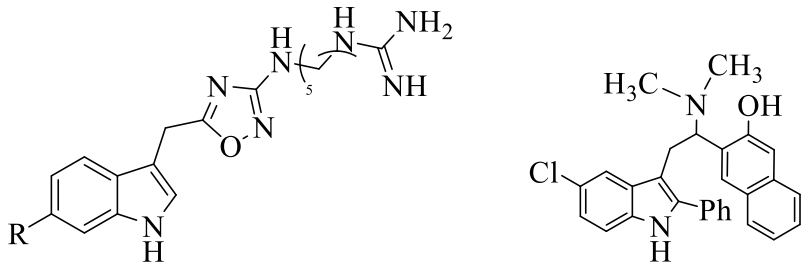
The indole nucleus is an important scaffold in numerous natural and synthetic alkaloids found to exhibit a wide range of biological activities including anticancer, antioxidant and anti-inflammatory properties.[11] The 3-carbaldehyde substituted 2-arylindole derivative **1** shown in Figure 1 has been found to exhibit increased inhibitory activity against tumour growth and tubulin polymerization.[12] Indoles also represent valuable synthons for the preparation of nano- and meso structures with enhanced electronic and photonic properties.[13] The 4-[(3a,7a-dihydro-1*H*-indol-3-yl)(1*H*-indol-3-yl)methyl]-2,6-dimethylphenol dye **2** shown in Figure 1, for example, has been prepared from the reaction of 1*H*-indole with 4-hydroxy-3,5-dimethylbenzaldehyde in methanol and, in turn, used as a probe for the determination of water content in polar aprotic organic solvents such as acetone, acetonitrile, tetrahydrofuran and dioxane.[14] Likewise, the blue electroluminescent device, ITO/NPB/**2**/TPBI/Alq_3/Mg–Ag, comprising of indium tin oxide (ITO) as a substrate, 4,4'-bis[*N*-(1-naphthyl)-*N*-phenylamino]biphenyl(NPB) as a hole, methyl-5-cyano-2-(3,4-dimethoxyphenyl)-1*H*-indole-3-carboxylate **3**, 1,3,5-tris(*N*-phenylbenzimidazol-2-yl)benzene (TPBI) as a hole blocking material, tris(8-hydroxyquinoline)aluminium (Alq_3) as electron transporting material and magnesium-silver (Mg-Ag) as electrode has been developed.[15]



1 **2** **3**

Figure 1: Examples of indoles with biological and photophysical properties.

Phidianidines **4a** and **4b** shown in Figure 2 have been isolated from the shell-less marine opisthobranch mollusk *Phidiana militaris* and found to exhibit antitumour activity against the glioma brain tumour (C6) and cervical cancer (HeLa) cells with the IC_{50} values within nanomolar range.[16] These compounds have also been synthesised by Lin and Snider by coupling the corresponding 2-(1*H*-indol-3-yl)acetyl chloride with (5-azidopentyl)-2-hydroxyguanidine in the presence of triethyl amine in dichloromethane.[17] The analogous 3-[2-(5-chloro-2-phenyl-1*H*-indol-3-yl)-1-(dimethylamino)ethyl]naphthalen-2-ol **5** shown in Figure 2, on the other hand, has been synthesised *via* multicomponent reaction of 2,5-disubstituted indole-3-carboxaldehyde, secondary amine and 2-naphthol and was found to exhibit antifungal activity.[18]

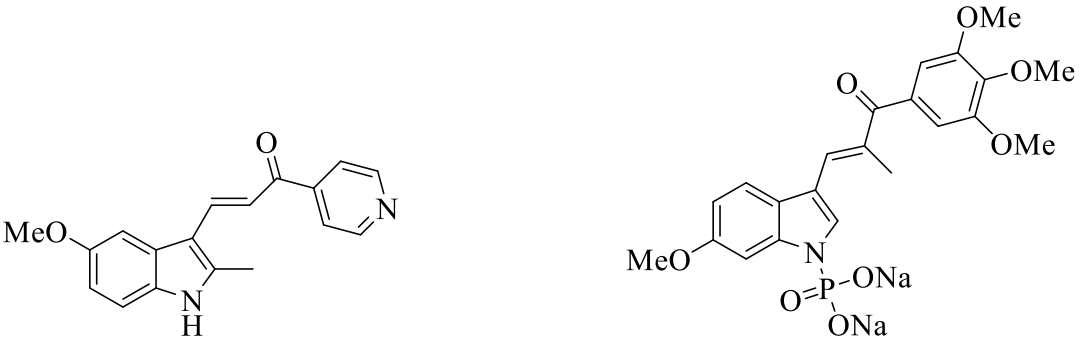


4: R = H **(a),** Br **(b)** **5**

Figure 2: Examples of biologically active indole derivatives **4a**, **b** and **5**.

When an indole moiety is linked to a chalcone framework or another heterocyclic scaffold, the two pharmacophores tend to enhance the overall photophysical (electronic absorption and

emission) properties[19] and/or the biological efficacy of the resultant molecular hybrids.[20] Indole-based chalcones are associated with high-affinity benzodiazepine receptor ligands, interleukin, selective cyclooxygenase-2 (COX-2) and phosphodiesterase (PDE4) inhibition, as well as anticancer and anti-inflammatory properties.[19,20] The 3-substituted 5-methoxy-2-methyl-1-*H*-indol-3-yl)-1-(pyridin-4-yl)chalcone derivative **6** shown in Figure 3, on the other hand, has been found to induce methuosis in glioblastoma and other cancer cells.[21] Likewise, the phosphonate indole-chalcone derivative **7** (see Figure 3) has been found to be a potent tubulin polymerization inhibitor, which binds to the colchicine binding site.[22] Moreover, these compounds inhibited tumour growth in xenograft models in vivo without apparent toxicity.[22]



6 **7**

Figure 3: Examples of medicinally important indole-based chalcones.

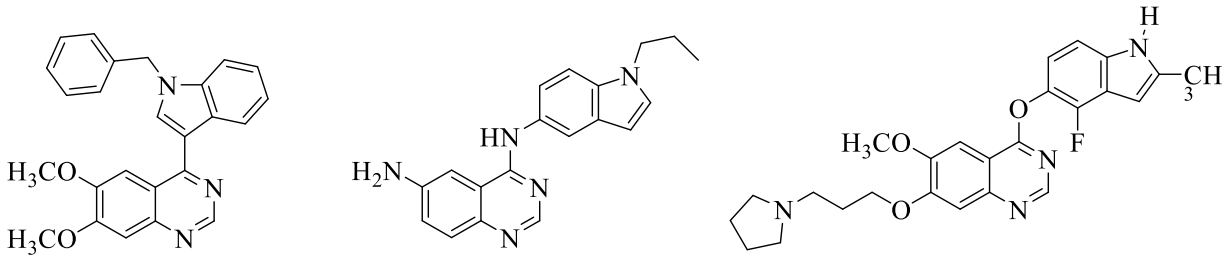
Six-membered benzo-fused nitrogen-containing heterocycles such as quinolines have recently earned great interest in targeted therapies as antimalarial drugs.[23] Among quinoline-based compounds, the 4-aminoquinolines have been found to inhibit the hematin formation by complexing with ferriprotoporphorin IX (FPIX) and thereby prevent its polymerization into hemozoin, which results into the malarial parasite death.[24] Linking an aminoquinoline moiety on the indole framework has been found to enhance the overall biological efficacy of the resultant indole-aminoquinoline hybrids. For example, indole-aminoquinolines **8** have been found to significantly inhibit β-hematin formation and to compromise the mitochondrial function of the

parasite (Figure 4).[25] Song *et al*.[26] have recently reported the synthesis of the indole-based thiochromanone derivatives **9** by an ionic liquid approach. These compounds have been found to be more potent against a wide range of fungi species when compared to the commercially available antifungal drug, fluconazole, which has been used as a reference standard for the assays.

8 **9**

Figure 4: Example of indole-based quinolines **8** and thiaflavanone **9** of medicinal importance

Luth *et al*., recently merged quinazoline and indole nuclei directly to afford the 4-(indole-3-yl)quinazolines **10**.[27] These compounds have been found to exhibit moderate receptor protein tyrosine kinase (ErbB-2) activity with little or no activity against epidermal growth factor receptor (EGFR).[27] The N^4-(1*H*-indol-5-yl)quinazoline-4,6-diamines **11**, on the other hand, have been found to exhibit significant anti-inflammatory properties in a dose-dependent manner in lipopolysaccharide-induced microphages and inhibit TNF-α and IL-6 inflammatory mediators.[28] The analogous indole-ether quinazoline hybrid **12** has been found to inhibit vascular endothelial growth factor (VEGF) inhibitor that selectively inhibits VEGF tyrosine kinase activity associated with VEGFR-1, -2 and -3.[29]



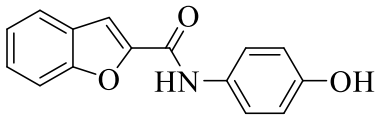
10 **11** **12**

Figure 5: Examples of indole-appended quinazoline hybrids with biological properties

The benzofurans, which are distinguished from indoles by the presence of oxygen in the heterocyclic ring instead of nitrogen are also important heterocycles in the field of medicine and materials.[30] Some of the few examples of benzofurans of biological importance and their hybrids are described in the next section.

1.3 An overview of benzofuran and benzofuran-appended hybrids of biological importance

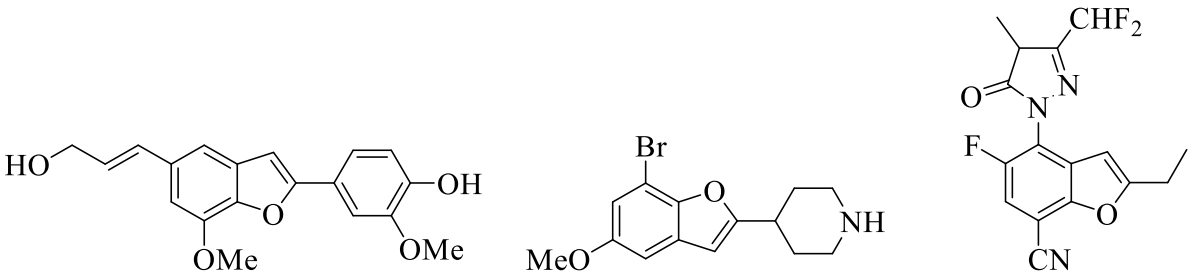
Benzofurans represent another class of oxygen-based heterocycles with a wide range of biological properties and some derivatives serve as cytotoxic,[31] antimicrobial,[32] fungicidal,[33] anti-inflammatory,[34] and anti-oxidant agents.[35] The *N*-(4-hydroxy)phenylamide-substituted benzofuran derivative **13** shown in Figure 6, for example, has been found to exhibit significant cytotoxicity against the colon (HCT15), renal (ACHN), gastric (NUGC-3), breast (MM231), prostate (PC-3) and lung (NCI-H23) cancer cell lines and to inhibit the NF-κB transcriptional activity.[1]



13

Figure 6: Structure of benzofuran derivative **13** with anticancer properties

The naturally occurring ailanthoidol **14** represented in Figure 7 isolated from the Chinese herb (*Zanthoxylum ailanthoide*) has been found to supress lipopolysaccharide-stimulated inflammatory reactions in RAW264.7 cells and endotoxin shock in mice.[36] Papp *et al.*,[37] previously synthesized a 4-(5-methoxy-7-bromobenzofuranyl)-2-piperidine **15** (Figure 7) commonly known as brofaromine and this compound has been found to be a potential anti-depressant after clinical trials. Besides the wide range of bioactivities, benzo[*b*]furan derivatives also act as insecticides and herbicides. The substituted benzo[*b*]furan derivative **16** shown in Figure 7, for example, has been found to be a potential herbicide showing a strong effect against weeds.[38]



14 **15** **16**

Figure 7: Examples of benzofurans with applications.

Conjugates consisting of the benzofuran and chalcone framework linked together tend to exhibit a wide range of biological and pharmacological properties.[39,40] The benzofuran-chalcone hybrids **17** shown in Figure 8, for example, have been found to exhibit significant inhibitory properties against acetylcholine (Ach) in the micro molar levels in vitro, which make them potential

candidates for the treatment of Alzheimer's disease.[39] The benzofuran-chalcone derivative **18**, on the other hand, has shown strong inhibitory effects against the lung (A549), breast (MCF-7) and prostate (PC-3) cell lines with IC_{50} values of 9, 2, and 10 μM, respectively.[40] Molecular analysis indicated that compound **18** induced apoptosis through caspase-dependent pathways in prostate, lung and breast cancer cells.[40]

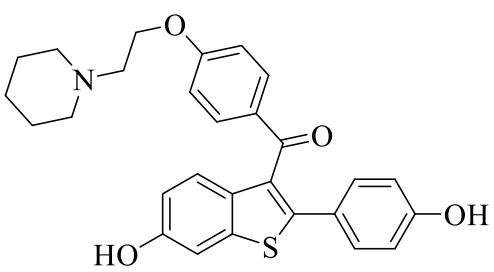
17 **18**

Figure 8: Examples of benzofuran-chalcone hybrids with medicinal applications.

Benzothiophenes comprise another class of five-membered benzo-fused heterocycles characterised by the presence of a sulphur atom in the ring instead of nitrogen or oxygen atom found in the analogous indoles and benzofurans, respectively. This class of compounds and their molecular hybrids are described in the next section.

1.3.1 An overview of benzothiophene-based compounds of biological importance

Several benzothiophene-based compounds have been found to exhibit antifungal,[41] 5-lipoxygenase inhibition and anti-inflammatory properties.[42] Raloxifene **19** shown in Figure 9 is an example of a 3-carbonyl substituted 2-arylbenzo[*b*]thiophene which exhibits selective estrogen receptor modulator activity and has been employed in the treatment of cervical and breast cancers as well as osteoporosis.[43] Sertaconazole nitrate derivative **20**, on the other hand, is an antifungal agent and this compound also exhibits anti-inflammatory activity by activation of the p38–COX-2–PGE2 pathway.[41]



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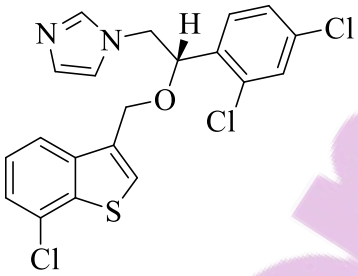
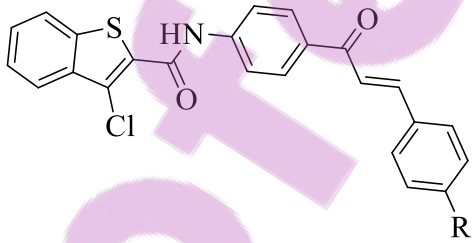


20

Figure 9: Examples of benzothiophene derivatives with medicinal applications.

Molecular hybrids comprising benzothiophene and chalcone moieties linked together also exist in the literature. The benzothiophene-chalcone hybrids **21** shown in Figure 10 below, for example, have been prepared before and found to exhibit significant bioactivity against several fungi species.[44]



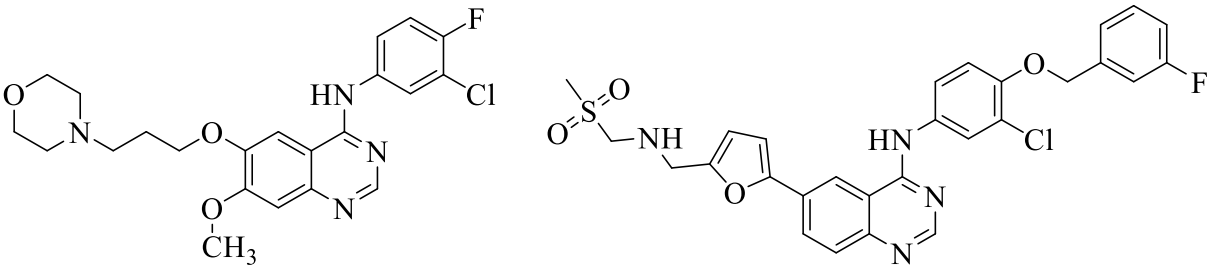
21: R = H (a), OCH_3 (b)

Figure 10: Examples of benzothiophene-chalcone derivatives with medicinal applications.

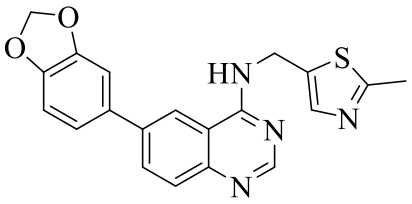
Another class of nitrogen-containing heterocycles of our group's interest are the quinazolines. The biological properties and application of this class of compounds and their molecular hybrids are described in the next section.

1.5 An overview of quinazolines and quinazoline-based hybrids of biological importance

The 4-aminoquinazolines represent an important class of epidermal growth factor receptor tyrosine kinase phosphorylation inhibitors.[45] This tyrosine kinase receptor is over expressed in several human tumours including lung cancer, prostate, breast and ovarian cancers[46] and correlates with a poor prognosis in many cancer patients.[47] Thus, EGFR has become an attractive target for the design and development of compounds that can specifically bind to the receptor and inhibit its tyrosine kinase (TK) activity and its signal transduction pathway in cancer cells. Gefitinib **22** shown in Figure 11 is an example of a 4-anilinoquinazoline derivative that has been found to selectively inhibit EGFR tyrosine kinase and to inhibit tumour pathogenesis, metastasis and angiogenesis, as well as promoting apoptosis.[48] Lapatinib **23**, on the other hand, is an example of a 6-heteroaryl substituted 4-anilinoquinazoline derivative that has been found to exhibit dual inhibitory activity against both EGFR and human epidermal growth factor receptor 2 (HER2) in breast cancer cells and solid tumors.[49] Likewise, 6-arylquinazoline-4-amine **24** has been found to inhibit Cdc2-like kinase 4 (Clk4) and dual specificity tyrosine-phosphorylation-regulated kinase 1A (Dyrk1A), which are protein kinases that are targets for the treatment of diseases caused by abnormal gene splicing.[50]



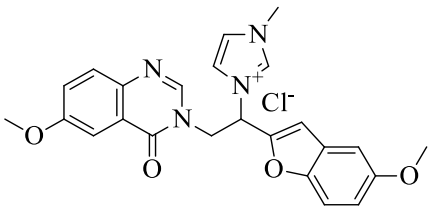
22 **23**



24

Figure 11: The 4-aminoquinazolines **22**–**24** with anticancer properties

The indole-aminoquinazoline **11** and the indole ether-quinazoline, Cediranib **12**, shown in Figure 5 above are examples of indole-appended quinazolines (refer to Figure 5 above) in which the two moieties are linked by an oxygen or a nitrogen. Benzofuranyloxoquinazoline-ethyl-1*H*-imidazolium chloride **25** shown in Figure 12, on the other hand, was found to exhibit significant antifungal activity against *Candida albicans* and also significant cytotoxicity against the breast cancer cell line, MCF7, with an IC_{50} value of 0.57 μM when compared to the chemotherapeutic drug, doxorubicin (IC_{50} = 3.62 μM) used as a reference standard in the assay.[51] Moreover, molecular modelling studies of compound **25** against the enzyme aromatase, which is highly expressed in the MCF-7 cell line have revealed that compound **25** was well accommodated in the hydrophobic cavity and the 5,6-substituted methoxy groups interacted well with the protein residues around the pocket.[51]



25

Figure 12: Example of a benzofuran-appended quinazolinone **25** hybrids of biological importance

We considered previous work from our group on the antiproliferative properties of the 2-arylindoles[52] and 4-aminoquinazolines[53] in combination with the literature analysis on cytotoxic benzofurans[30] and chalcones[54] and decided to design and synthesize molecular hybrids comprising this five-membered heterocyclic scaffold merged with either the chalcone or quinazoline framework, respectively. To achieve this goal, we performed an extensive literature review on the methods developed to-date for the synthesis of the corresponding subunits and how to merge the benzo-fused 5-membered heterocycles with the chalcone or quinazoline scaffold. The methods for the synthesis of the benzo-fused 5-membered heterocycles containing one heteroatom, namely, indoles, benzofurans and their benzothiophene analogues are described in detail in the next sections

1.6 Construction of benzo-fused 5-membered heterocycles containing one heteroatom in the ring

Although there are several examples of benzo-fused five-membered heterocycles described in the literature the focus of this investigation is on the design and synthesis of indoles and benzofurans, which are discussed in detail in the next section. An overview of the methods for the synthesis of benzothiophene analogues will also be presented. The conventional and non-

conventional methods for the synthesis of these structurally related five-membered heterocycles and their derivatives are described in sequence in the following sections.

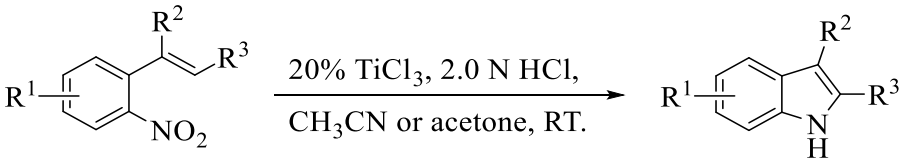
1.6.1 Methods for the synthesis of indole derivatives

Examples of the classical methods for the synthesis of indoles include the Fischer indole synthesis from aryl hydrazones,[55] the Madelung cyclization of *N*-acyl-*o*-toluidines[56] in the presence of strong base. These conventional methods for the synthesis of indole derivatives form part of several review papers.[55,56] Nonconventional methods which involve the use of transition metal as catalysts for C–C or C–N bond formation in the construction of the indole skeleton have also been developed. Since our interest is on the application of transition metals in the construction of the indole framework, we limit the discussion to these nonconventional methods and these are discussed in detail below.

1.6.1.1 Transition metal-mediated methods for the synthesis of indoles

Transition metal-based compounds continue to attract considerable attention in C–C or C–N bond formation and this approach has also been employed for the construction of indole framework. Methods which employ nitrostyrenes as substrates for the construction of indole derivatives in the presence of a reducing agent have been developed. Indoles **27**, for example, have been prepared in 52–87% yield by reductive cyclization of *o*-nitrostyrenes **26** in the presence of a stoichiometric amount of aqueous $TiCl_3$ (8.0 equiv.) dissolved in 2.0 N HCl in acetonitrile and/ or acetone as a solvent at room temperature (Scheme 1).[57] The use of 1-(2'-nitrophenyl)cyclopentene as a substrate under the same reaction conditions required an addition

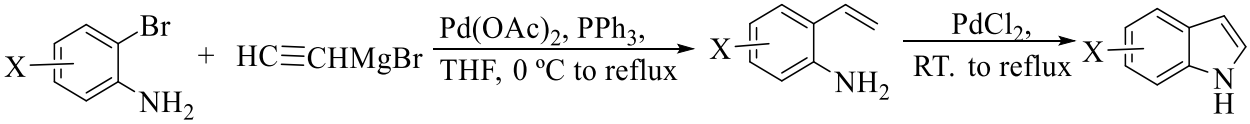
of NH_4OAc buffer solution to afford the corresponding indole. The absence of NH_4OAc led to the corresponding aniline with no traces of indole.



26 **27**

Scheme 1: Reductive cyclization of **26** to afford **27**.

Palladium acetate ($Pd(OAc)_2$) catalysed reaction of 2-bromoanilines **28** with vinylmagnesium bromide **29** in the presence of triphenylphosphine (PPh_3) in THF at 0 ºC to reflux conditions afforded 2-vinyl-phenylamines **30** (Scheme 2).[58] The latter were, in turn, cyclized in the presence of $PdCl_2$ catalyst, stoichiometric amount of *p*-benzoquinone (3.2 equiv.) and LiCl (10.0 equiv.) in THF at room temperature to reflux to afford the corresponding indoles **31**.

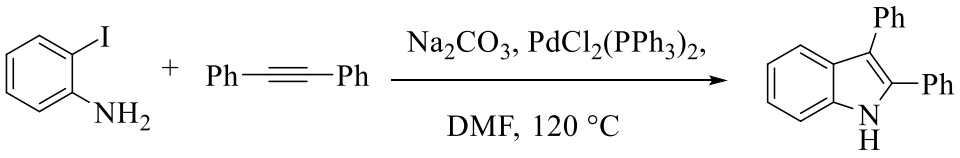


28 **29** **30** **31**

Scheme 2: $PdCl_2$-catalysed heterocyclization of **30** to afford **31**.

Larock developed a method for the synthesis of indoles, which involves the one-pot palladium catalyzed cross-coupling and subsequent heteroannulation of the *o*-haloanilines and internal alkynes to afford the 2,3-disubstituted indole derivatives.[59] The outcome of the reaction depends on the type of palladium(0) catalyst source and the phosphine ligands used. The heteroannulation of 2-iodoaniline **32** with diphenylacetylene **33** in the presence of $Pd(OAc)_2$ as a catalyst, sodium carbonate as a base and lithium chloride (LiCl) as an additive in DMF at 80 °C, for example,

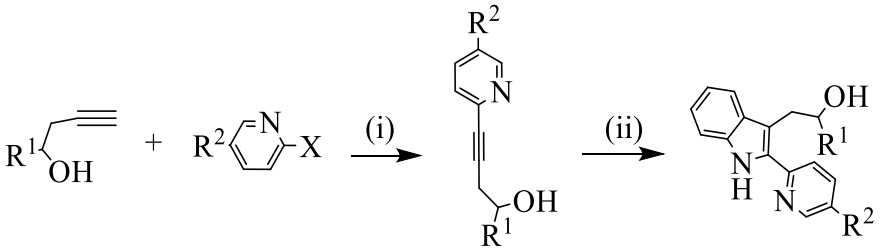
afforded 2,3-diphenylindole **34** in 67% yield (Scheme 3).[59] Poor yields of the product (15-28% yields) were observed when the temperature was increased to 120 °C in the presence or absence of LiCl as an additive. However, the use of phosphine-based palladium catalysts such as palladium dichlorobistriphenylphosphine $PdCl_2(PPh_3)_2$ or palladium dichlorobis(benzonitrile) $PdCl_2(PhCN)_2$ under LiCl-free conditions at 120 °C resulted in increased yields (*ca*.73%) of the product. Improved yields in this case were attributed to the use of phosphine-based palladium catalysts. However, the use of homogenous Pd(0) catalyst sources and the ligands often make it difficult to separate the product from the reaction mixture. Reduced yields were observed when diphenylacetylene was used as a coupling partner in the absence of bulky ligands due to side products resulting from di- or oligomerisation.[60] Modifications of the Larock synthesis that make use of heterogeneous palladium catalysts have since been developed to avoid the problem of isolation of the products from the homogenous catalysts and ligands. Pd/C, for example, was used as a catalyst in the presence of sodium carbonate (Na_2CO_3) as a base in DMF at 120 °C to promote the reaction of 2-iodoaniline **32** with internal alkyne **33**. Under these reaction conditions, 2,3-diphenylindole **34** was isolated in 70% yield (Scheme 3).[61]



32 **33** **34**

Scheme 3: Larock heteroannulation of **32** with **33** to afford **34**.

A combination of Sonogashira cross-coupling and the Larock synthesis has also been employed before in the synthesis of the 2,3-disubstituted indole derivatives. Sonogashira cross coupling of butyne alcohols **35** with pyridine chlorides or bromides **36**, for example, afforded the alkynes **37**, which were in turn, annulated with 2-bromoaniline in the presence of $Pd(OAc)_2$-dppf complex and $KHCO_3$ as a base in DMF at 110 °C to afford the desired indoles **38** (Scheme 4).[62]

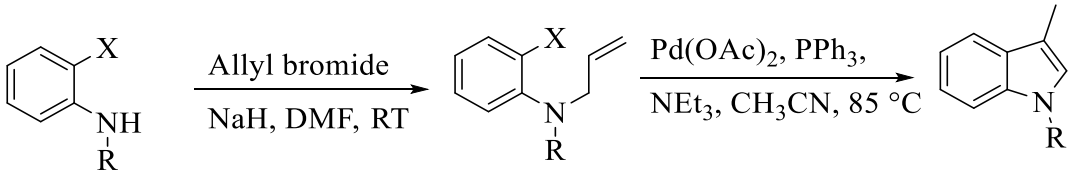


35 **36** **37** **38**

Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, CuI, NEt_3; (ii) 2-bromoaniline, $Pd(OAc)_2$, dppf, $KHCO_3$, DMF, 110 °C

Scheme 4: Sequential Sonogashira and Larock indole synthesis reactions.

Methods that employ intramolecular Heck cross-coupling reactions of *N*-allyl-2-halobenzenamines to construct the indole framework have been developed. For example, the intramolecular Heck cross-coupling reaction of allylated *N*-sulfonyl or *N*-tosyl 2-haloaniline **39** in the presence of $Pd(OAc)_2$ as a catalyst, NEt_3 as a base and PPh_3 as a ligand in anhydrous acetonitrile afforded the 3-methyl-*N*-substituted-1*H*-indoles **41** (Scheme 5).[63] *N*-sulfonyl or *N*-tosyl 2-haloanilines **40** were prepared independently by reacting 2-haloaniline **39** with allyl bromide in the presence of NaH in DMF.

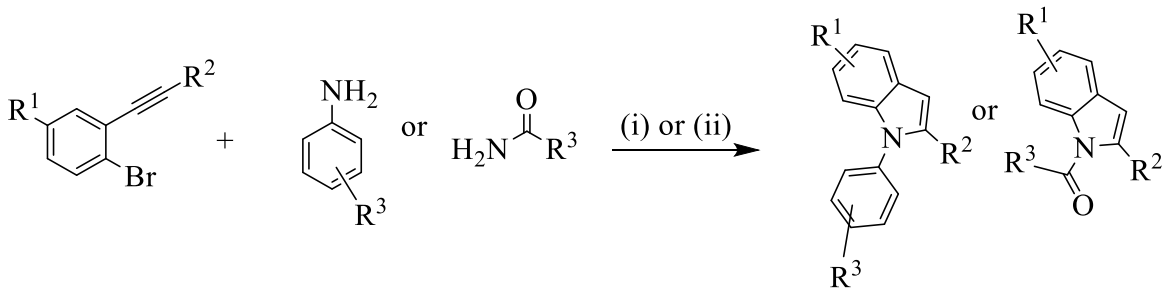


39 **40** **41**

Scheme 5: Synthesis of indoles via intramolecular Heck cross coupling reaction.

Copper-based catalysts have also been employed in the construction of carbon–heteroatom and carbon–carbon bonds and this strategy has also been extended to the construction of indole derivatives. Copper-catalyzed *N*-arylation/hydroamination of *o*-alkynyl bromoarenes **42** with

aniline derivatives **43a** in the presence of ^{t}BuOK or with less nucleophilic amides **43b** in the presence of K_2CO_3 as a base and *N*,*N*'-dimethyl-ethane-1,2-diamine ligand in toluene at 105 °C produced *N*-aryl-indoles **44a** in 60–84% yields or *N*-acylindoles **44b** in 55–71% yields as potential Chek1/KDR kinase inhibitors (Scheme 6).[64]

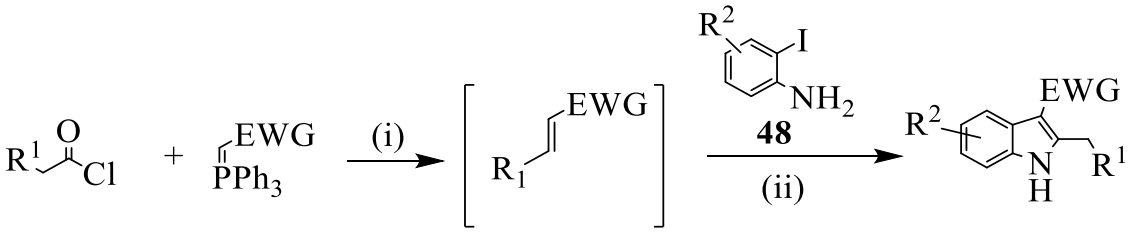


42 **43a** **43b** **44a** **44b**

Reagents and conditions: (i) ^{t}BuOK, toluene, 105 °C. (ii) K_2CO_3, *N*,*N*'-dimethyl-ethane-1,2-diamine, in toluene, 105 °C

Scheme 6: Copper-catalyzed *N*-arylation/hydroamination domino synthesis of indoles.

In another example, a one-pot reaction of acyl chlorides **45** and Wittig reagents **46** in the presence of NEt_3 in dichloromethane at room temperature (RT) afforded allenes **47** (Scheme 7).[65] These allenes were, in turn, reacted with 2-iodoanilines **48** in the presence of CuBr as catalyst and 8-hydroxylquinolone as a ligand, K_2CO_3 as a base in 1,4-dioxane- hexane solvent mixture under reflux to give indoles **49** (EWG = -CO_2Et, R = -CH_3; EWG = -CO_2Et, R = Et). The use of other ligands such as 1,10-phenanthroline, enaminone, and l-proline produced indole **49** in less than 50% yield. A change of a catalyst to other copper(I) and copper(II) salts such $Cu(OAc)_2$, CuI, and Cu_2O led to poor yields.

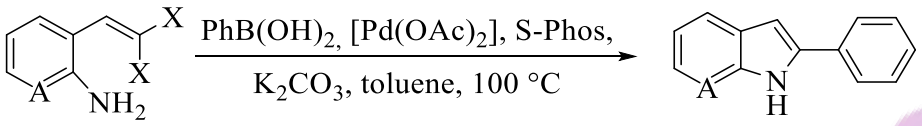


45 **46** **47** **49**

Reagents and conditions: (i) NEt_3, CH_2Cl_2, RT (ii) CuBr, K_2CO_3, 8-hydroxyl quinolone, 1,4-dioxane, reflux.

Scheme 7: Copper-catalysed one-pot tandem reactions toward the synthesis of indoles using 2-iodoaniline, acyl chlorides, and Wittig reagents.

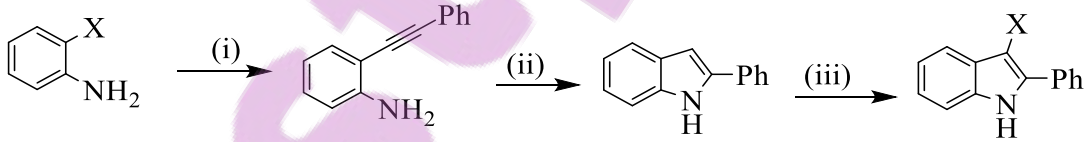
The *gem*-dihalovinylanilines have also been found to undergo transition metal-catalysed reactions to form the indole framework. The $Pd(OAc)_2$ catalysed tandem intramolecular C–N coupling of *gem*-dihalovinylaniline **50a** (X = Br) and intermolecular Suzuki cross-coupling with phenyl boronic acid in the presence of S-Phos as a ligand, K_2CO_3 as a base in toluene at 100 °C afforded 2-phenylindole **51a** (Scheme 8).[66] However, under the same reaction conditions, the use of 3-(2,2-dibromo-vinyl)-pyridin-2-ylamine **50b** (X = Br) as a substrate failed to produce the analogous 7-azaindole **51b**. This was presumably due to the hindering of the Pd-catalyzed C–N coupling cycle of aminopyridines with free a amino group in the presence of monodentate phosphine ligand which forms an aryl palladium bis-amine complex and does not undergo reductive elimination.[66] The introduction of a benzyl substituent on nitrogen of 3-(2,2-dihalo-vinyl)-pyridin-2-ylamine (X = Br or Cl) afforded, under the same reaction conditions used to prepare **50a**, *N*-benzyl 7-azaindole **50b** in 74% (X = Br) and 90% (X = Cl).



50a, **b** **51**: A = C (**a**); A = N (**b**)

Scheme 8: Tandem intramolecular C–N coupling and intermolecular Suzuki-Miyaura cross-coupling of *gem*-dihalovinylanilines with phenyl boronic acid.

Transition metal-based catalysts have also been employed to promote the cyclization of 2-alkynylaniline derivatives to afford indole derivatives. The 2-alkynylaniline derivatives are easily synthesized via Sonogashira cross-coupling of 2-haloanilines with terminal alkynes in the presence of Pd(0)-Cu(I) catalyst mixture. 2-Phenylethynylaniline **53**, for example, was prepared via $PdCl_2(PPh)_3$-CuI catalyzed Sonogashira cross-coupling of 2-haloanilines **52** with phenylacetylene in the presence of NEt_3 as a base in tetrahydrofuran (THF) at room temperature and then subjected to one-pot Sodium tetrachloroaurate(III) dihydrate ($NaAuCl_4{\cdot}2H_2O$) promoted cyclization in ethanol at RT to afford phenylindole **54** (Scheme 9).[67] Further halogenation of **54** with either *N*-bromosuccinimide (NBS) in ethanol at room temperature or molecular iodine in the presence of potassium hydroxide in ethanol at room temperature afforded halogeno-phenylindoles **55a** and **55b**, respectively.

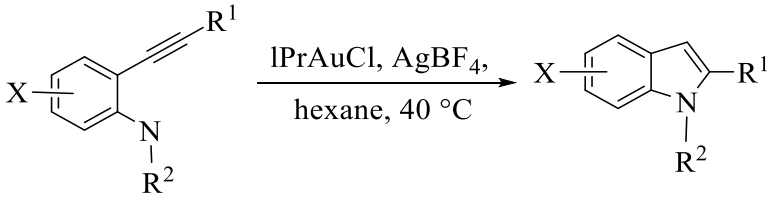


52: X = Cl, Br, I **53** **54** **55**: X = Br (**a**); X = I (**b**)

Reagents and conditions: (i) Phenylacetylene, CuI, NEt_3, $PdCl_2(PPh_3)_2$, THF, RT (ii) EtOH, $NaAuCl_4{\cdot}2H_2O$, RT (iii) NBS, EtOH, RT; or I_2, KOH, EtOH, RT

Scheme 9: Synthesis of halo-indoles through cyclization of 2-alkynylaniline.

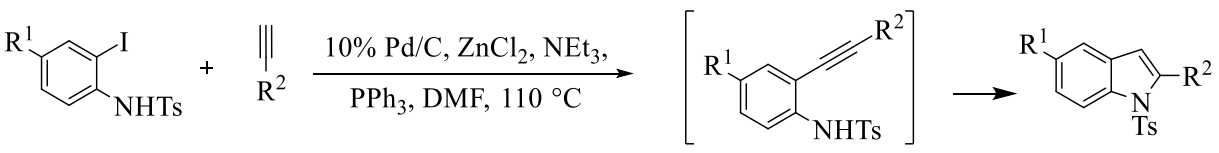
The 2-alkynylanilines **56** were cyclised in the presence of 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (lPrAuCl) as a catalyst, silver tetrafluoroborate ($AgBF_4$) as an additive in hexane at 40 °C to afford indoles **57** (X = H, Br, 5,7-dimethyl-; R = H, CH_3, benzyl; R′ = *n*-hexyl-, Ph) in 81–97% yields (Scheme 10).[68] The starting material was recovered unchanged when 2-(hex-1-yn-1-yl)quinolin-8-aniline or 2-alkynylaniline with trimethylsilyl substituent on acetylene group were employed as substrates.



56 **57**

Scheme 10: lPrAuCl-catalysed cyclization of **56** to afford **57**.

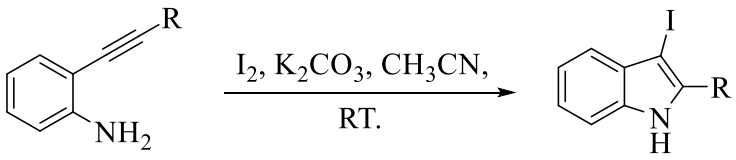
A one-pot Sonogashira cross-coupling of *N*-substituted 2-iodoanilines **58** with phenylacetylenes **59** in the presence of 10% Pd/C-$ZnCl_2$ catalyst complex, NEt_3 as a base and PPh_3 as a ligand in DMF at 110 °C afforded 2-alkynylanilines **60** in *situ*, followed by cyclization of the incipient 2-alkynylanilines to afforded the 2,5-disubstituted indoles **61 (**R_1 = H, CH_3; R_2 = -C_6H_5, 4-$MeOC_6H_4$-) (Scheme 11).[69] The use of anhydrous $ZnCl_2$ led to homocoupling to afford diynes as the predominant products. The authors argued that the released hydroxyl group from moist $ZnCl_2$ facilitates generation of zinc acetylide *in situ* which, in turn, undergoes annulation with *N*-substituted 2-iodoanilines. This observation was further confirmed using NaOH or KOH as bases in the presence of anhydrous $ZnCl_2$, which afforded the desired indoles in appreciable yields.



58 **59** **60** **61**

Scheme 11: Synthesis of 2-substituted indoles through annulation promoted by catalytic $ZnCl_2$.

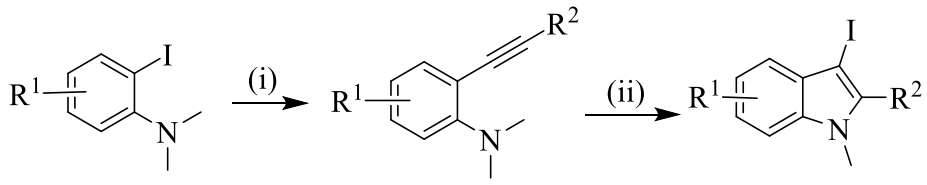
2-Alkynylanilines have also been found to undergo halocyclization in the presence of a base to afford 3-haloindole derivatives.[70-71] Iodine-promoted cyclization of 2-alkynylanilines **62** (R = 2-HO-C_6H_4, 2-$MeOC_6H_4$), for example, afforded 3-substituted indoles **63** in 70–80% (Scheme 12).[71]



62 **63**

Scheme 12: I_2-promoted cyclization of **62** to form **63**.

In another approach the 2-alkynylanilines bearing electron donating groups on nitrogen have been found to undergo halocyclization with ease to afford the 3-haloindole derivatives in high yields.[71,72] For example, 3-iodoindoles **66** (R_1 = H, NO_2, CH_3, OCH_3, CO_2Et; R_2 = Ph, hex-1-ene, $SiMe_3$, *t*-Bu) were prepared *via* iodocyclization of *N*,*N*-diamethyl-*o*-(1-alkynyl)anilines **65** in dichloromethane at room temperature (Scheme 13).[72] 2-(1-Alkynyl)anilines **64** were, in turn, prepared by $PdCl_2(PPh_3)_2$-CuI catalyzed Sonogashira cross-coupling of the corresponding *N*,*N*-diamethyl-*o*-iodoanilines **64** with terminal alkynes in NEt_3 at room temperature. The yields of **66** were found to be dependent on the substituents on the alkynyl group and aniline moiety of **65**. High yields (85–100%) were obtained with **65** bearing phenyl or vinyl groups that were involved in conjugative effect with the triple bond. However, no indole was isolated when **65** was substituted with a bulky trimethylsilyl group on the acetylene moiety. Substituents on the *para* position of the phenyl ring relative to the amino group such as the strong electron withdrawing nitro or ester group or a weak electron donating methyl group were found to enhance iodocyclization and to afford the corresponding 3-iodoindoles in high yields (84–100%) in 30 min. Derivatives substituted with a strong electron donating methoxy group *meta* to the amino group required 2 h to afford the corresponding 3-iodoindoles in 84–100%.



64 **65** **66**

Reagents and conditions: $HC{\equiv}CR_2$, $PdCl_2(PPh_3)_2$, CuI, NEt_3, RT, I_2, K_2CO_3, CH_3CN

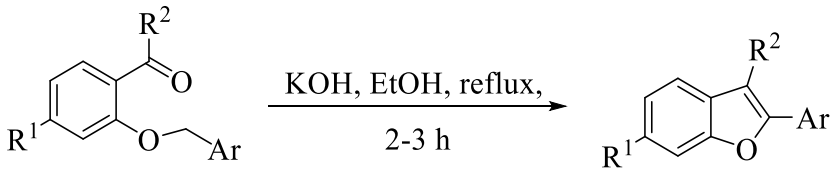
Scheme 13: I_2-promoted cyclization of **65**.

Benzo[*b*]furan is another class of five-membered benzo-fused heterocycles characterised by the presence of an oxygen atom in the ring instead of a nitrogen atom found in the analogous indoles. The development of general and efficient methods for preparation of functionalized benzo[*b*]furan from simple and easily accessible starting materials remains an active research field. A selection of some of the reported synthetic approaches for the construction of the benzo[*b*]furan core will be discussed in the following section.

1.6.2 Methods for the synthesis of benzofuran derivatives

There are several methods available for the synthesis of the 2-arylbenzo[*b*]furans and the most common approaches focus on the annulation of the furan ring on the benzene ring. 2-Alkoxyaryl aldehydes or ketones were reported to undergo base-mediated intramolecular cyclization to afford the corresponding 2-aryl 3-unsubstituted (in the case of aldehydes) or 2-aryl 3-substituted (in the case of ketones) benzo[*b*]furans.[73] Substituted 2-arylbenzo[*b*]furans **68**, for an example, were prepared *via* a ring closure of 2-alkoxyketones **67** in ethanol using KOH as a base under reflux for 3 h (Scheme 14).[73] These type of intramolecular condensation reactions, use strong alkali metal bases (NaOH, KOH, NaOEt, KO^{t}Bu) in dipolar aprotic solvents, and under these

conditions cyclization only works for compounds containing highly electron withdrawing substituents on the aryl ring of the benzyl moiety to stablilize the intermediate benzylic anion.



67 **68**

Scheme 14: Base mediated cyclization of 2-arylalkoxy ketones **67**.

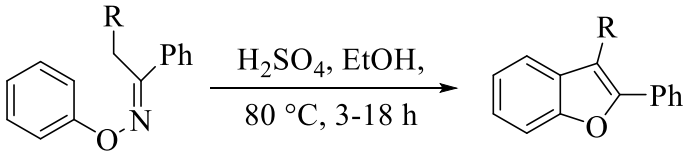
Hellwinkel *et al.*,[74] previously reacted benzyl phenyl ester **69** containing an *ortho*-acetyl group and an electron withdrawing group on the benzylphenyl ring with cesium fluoride aluminium oxide (CsF-Al_2O_3) base system in DMF at 150 °C to afford the 2-(4-nitrophenyl)-substituted benzo[*b*]furans **70** in 57–74% yield (Scheme 15). The presence of a strong electron-withdrawing nitro group activates the methyl group and facilitates deprotonation by a base.

69 **70**

Scheme 15: CsF-Al_2O_3 mediated cyclization of 2-arylalkoxy ketone **69**.

Methods which employ *O*-aryloximes as substrates for the construction of benzo[*b*]furan derivatives in the presence of an acid have also been developed. These methods are analogous to the Fischer indole synthesis and have been extended to the synthesis of benzo[*b*]furan. The sequential [3,3]-sigmatropic rearrangement and condensation between *N*-3 and C-2 of the *O*-aryloxime **71** is easily achieved using oxidants such as hydrochloric,[75] sulphuric acid,[76] formic acid,[77] phosphoric acid,[78] boron trifluoride etherate[79] and phosphorylchloride/DMF[80] mixture to

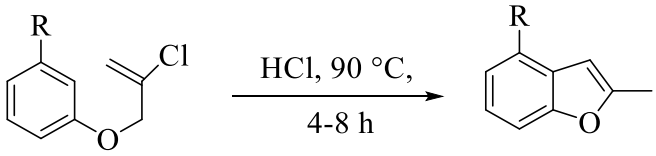
yield the benzo[*b*]furan. The *O*-aryloximes **71**, for example, were reacted with H_2SO_4 in the presence of ethanol at 80 °C to afford the corresponding substituted-benzo[*b*]furan **72** in 81–90% yield (Scheme 16).[76] The reaction was found to be more rapid and to be complete within 2.5–6 h with *O*-aryloximes bearing electron-withdrawing groups and to be relatively slow (18 h to completion) with unsubstituted derivatives.



71 **72**

Scheme 16: Sequential [3,3]-sigmatropic rearrangement and condensation of O-aryloxime **71** to lead to substituted-benzo[*b*]furan **72**.

In the case of allyl arylethers the reaction for benzo[*b*]furan proceeds *via* sequential Claisen rearrangement followed by an acid or metal mediated oxidative cyclization.[81] A series of benzo[*b*]furans **74** were prepared via hydrochloric acid catalysed cyclization of allyl aryl ethers **73** under reflux for 4–8 h in 51–77 % yield (Scheme 17).[81]

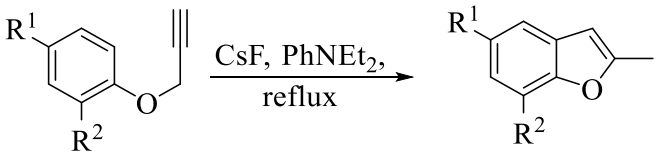


73 **74**

Scheme 17: Acid promoted oxidative cyclization of allylaryl ether **73** to afford benzo[*b*]furan **74**.

The aryl propargyl ethers **75** have previously been reacted with cesium fluoride in diethyl aniline under reflux to afford benzo[*b*]furan derivatives **76** (Scheme 18).[82] The thermal rearrangement of the aryl propargyl ethers **75** containing electron withdrawing groups has been found to afford

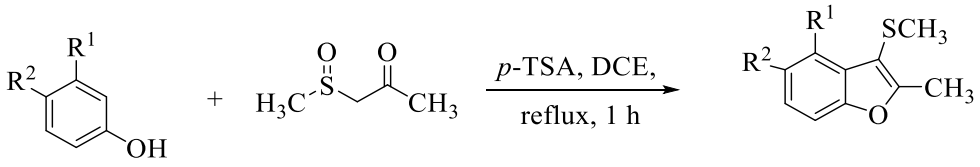
2-methyl benzo[*b*]furan **76**, whilst aryl propargyl ethers containing electron donating groups yielded 2-*H*-benzopyrans or 2-*H*-chromenes.[82]



75 **76**

Scheme 18: Base promoted oxidative cyclization of propargyl ethers **75** to afford benzo[*b*]furans **76**.

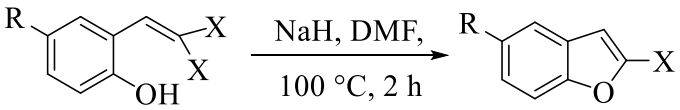
Phenols and *β*-ketosulfoxides have also been employed as substrates in the synthesis of substituted-benzo[*b*]furan derivatives. One-pot reaction of phenols **77** with *β*-ketosulfoxides **78** in the presence of *para*-toluenesulphonic acid (*p*-TSA) in dichloroethane (DCE) under reflux for 1 h afforded benzo[*b*]furans **79** in 65–71% yield (Scheme 19).[83] The reaction takes place *via* the Pummerer-type rearrangement. The transformation proceeds *via* intermolecular nucleophilic attack of the aromatic ring on the 1-acyl-1-thiocarbocation derived from the β-ketosulfoxides **78** in the presence of PTSA and successive dehydrocyclization to afford **79**.[83]



77 **78** **79**

Scheme 19: Synthesis of benzo[*b*]furans **79** from phenols **77** and β-ketosulfoxides **78**.

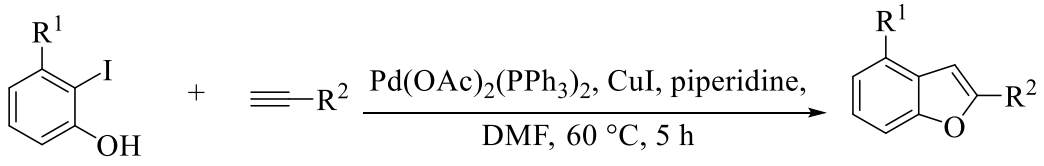
The *gem*-dihalovinylphenols have also been found to undergo base promoted reactions to form benzo[*b*]furans framework. For example, NaH-catalysed intramolecular C–O cyclization of *gem*-dihalovinylphenol **80** (X = Br) in DMF at 60 °C for 2 h afforded 2-bromobenzo[*b*]furans **81** in 99% yield (Scheme 20).[84]



80 **81**

Scheme 20: Base-mediated intramolecular cyclization of *gem*-dihalovinylphenols to afford 2-bromobenzo[*b*]furans.

When considering routes based on metal mediated reactions, the most common approach for the synthesis of benzofurans based on benzenoids involves the intramolecular addition of the phenolic moiety to a C–C triple bond in a 2-alkynylphenol. The most employed strategies to carry out this heterocyclization turn to transition metal catalysis and catalytic systems based on palladium, copper or a combination of both. Palladium catalyzed Sonogashira cross-coupling reaction of 2-iodophenol with terminal acetylenes has been employed for the synthesis of benzo[*b*]furan **84**. 2-Iodophenol **82** and benzyl acetylene **83**, for example, were reacted in the presence of palladium acetate bis(triphenylphosphine)[$Pd(OAc)_2(PPh_3)_2$], copper iodide and piperidine in dimethylformamide (DMF) at 60 °C to afford the substituted-benzo[*b*]furan product in 61–71% yield (Scheme 21).[85]

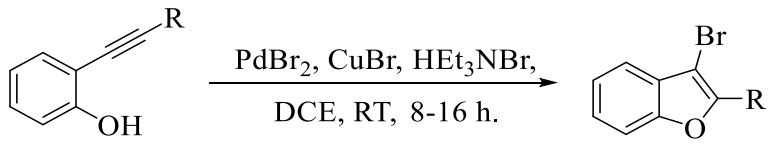


82 **83** **84**

Scheme 21: Sonogashira cross-coupling reaction of iodophenols **82** with terminal acetylenes.

Liang and coworkers, on the other hand, employed palladium bromide as a catalyst to selectively annulate the alkynylphenols.[86] A simple and one-pot synthesis of 2-substituted 3-halobenzo[*b*]furans **86** as major product has been achieved through annulation of 2-

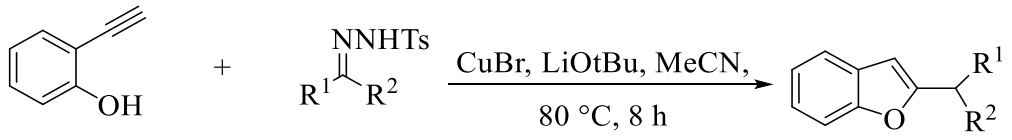
alkynylphenols **85** with $PdBr_2$-CuBr catalyst system and HEt_3NBr as a base in DCE at room temperature for 8–16 h (Scheme 22).[86]



85 **86**

Scheme 22: Palladium-Catalyzed annulations of 2-alkynylphenols to form 2-Substituted 3-halobenzo[*b*]furans.

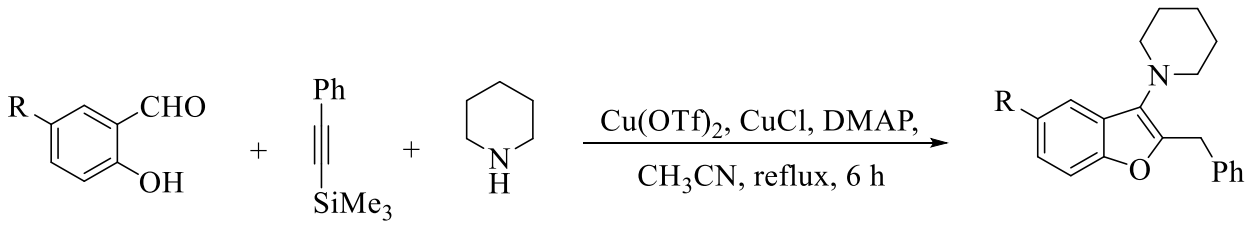
There is an increasing interest in the use of copper metal as a catalyst source in the synthesis of novel heterocycles. Substituted benzo[*b*]furans **89**, for an example, were prepared in 62–89% yield in a single-pot operation *via* copper(I) bromide catalyzed reaction of 2-alkynylphenol **87** and *N*-tosylhydrazones **88** using lithium tert butoxide in dioxane at room temperature for 3 h (Scheme 23).[87]



87 **88** **89**

Scheme 23: Copper-catalyzed heteroannulation of hydrazone **88** with 2-alkynylphenols **87**.

Another copper-catalyzed approach involves the combination of 5 mol % $Cu(OTf)_2$ and CuCl in the presence of 4-dimethylaminopyridine (DMAP) to effectively catalyzed a three-component coupling reaction involving an alkynylsilane **91**, an *o*-hydroxybenzaldehyde derivative **90**, and a secondary amine **92** to afford substituted benzofuran **93** in 61–95% yield (Scheme 24).[88] The reaction proceeded via intramolecular 5-exo-dig cyclization, resulting in direct synthesis of the corresponding benzofuran derivatives in moderate to excellent yields.

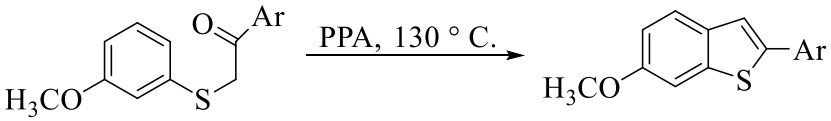


90 **91** **92** **93**

Scheme 24: Copper-catalyzed synthesis of substituted-benzofuran **93**.

1.6.3 Methods for the synthesis of benzothiophene derivatives

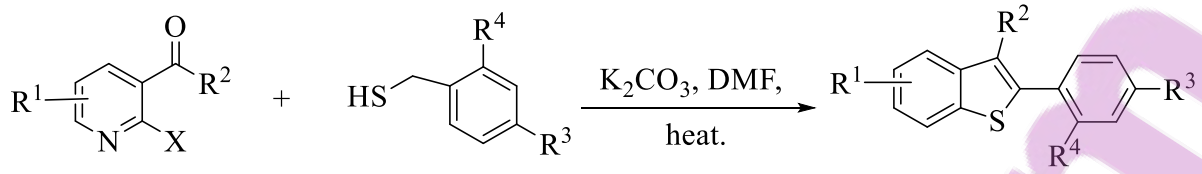
Several approaches for the construction of benzothiophene nucleus have been developed. The most common approach towards synthesis of benzothiophenes makes use of intramolecular condensation reactions. The industrial synthesis of Raloxifene **95**, for example, uses a polyphosphoric acid-catalyzed domino cyclization rearrangement reaction of the ketosulfide **94** to form the 2-arylbenzothiophene **95** (Scheme 25).[89]



94 **95**

Scheme 25: PPA-promoted cyclization of **94** to afford **95**.

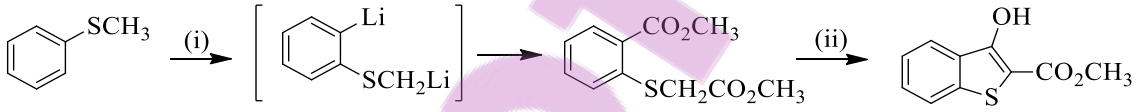
Another approach for the synthesis of benzothiophenes utilizes the Knoevenagel condensation of an *S*-benzyl *ortho*-acylthiophenol generated in situ from the base mediated reaction of ortho-haloketone **96** with benzyl mercaptans **97** in DMF to yield the required 2-arylbenzo[*b*]thiophene derivatives **98** (Scheme 26).[90]



96 **97** **98**

Scheme 26: K_2CO_3-promoted cyclization of **96** to afford **98**.

Cabiddu *et al.*[91] previously used anionic cyclization method for the construction of the benzo[*b*]thiophenes **102** (Scheme 27). A series of benzo[*b*]thiophenes **102**, for example, was synthesized from the treatment of 4-thioanisole **99** with butyllithium using tetramethylethylenediamine (TMEDA) in hexane at 40–58 °C, followed by carboxylation with methylchlorocarbonate in diethyl ether at -80 °C to afford the diester **101** in 71% yield. Ring closure of the resultant diester **101** in the presence of lithium diisopropylamide (LDA) in THF at -80 °C gave the target compound **102** in 75 % yield (Scheme 27).



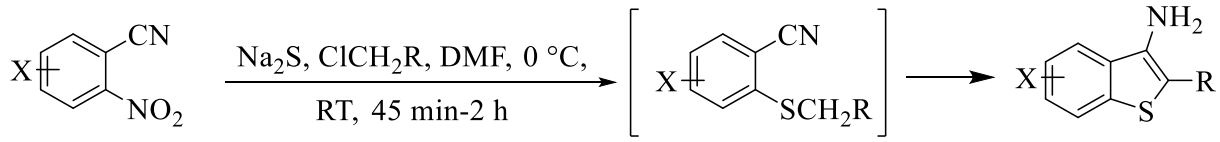
99 **100** **101** **102**

Reagents and conditions: (i) BuLi, TMEDA, hexane, 40–58 °C, 2 h; $ClCO_2CH_3$, Et_2O, at -80 °C, 2 h; (ii) LDA, THF, -80 °C, 2 h

Scheme 27: Synthesis of benzo[*b*]thiophene **102** via anionic cyclization method.

The Gewald reaction is another known method employed for the preparation of benzo[*b*]thiophene derivatives.[92] It is a common protocol employed for the preparation of 2-aminobenzothiophene but can also be modified to synthesize the 3-amino regioisomers. Beck and Yahner, for example, previously applied the modified approach to the synthesis of 3-aminobenzo[*b*]thiophene-2-carboxylate **105** (Scheme 28).[93] This was achieved by the reaction

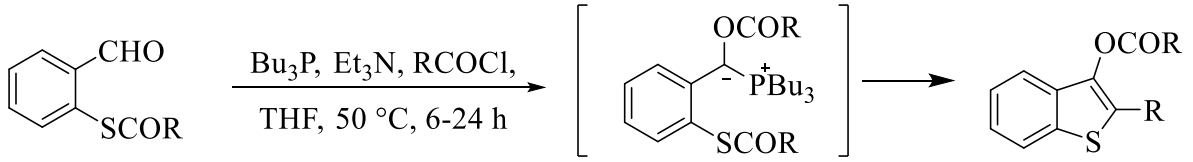
of nitrobenzonitrile **103** with sodium sulphide, followed by alkylation with appropriate chloromethylene derivatives to form intermediate **104** and subsequent ring closure in DMF at 0 °C.



103 **104** **105**

Scheme 28: Synthesis of benzo[*b*]thiophene derivatives **105** by Gewald reaction.

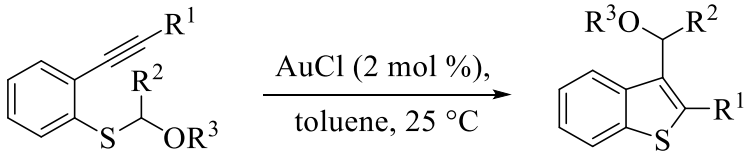
The benzo[*b*]thiophene derivatives **108** have also been synthesized via intramolecular Wittig reaction. Syu *et al*.,[94] for example, previously reacted **106** with carbonyl chlorides in the presence of organophosphorus and a base under reflux to form an ylide **107**, which cyclizes spontaneously to afford compound **108** (Scheme 29).



106 **107** **108**

Scheme 29: Intramolecular Wittig reaction of **106** and acid chlorides to yield **108**.

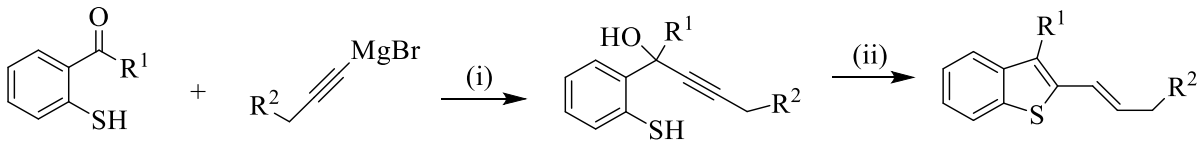
The electrophilic-mediated cyclization and the metal-catalyzed cyclizations of alkynes are the most common among the numerous methods available in the literature for the synthesis of benzo[*b*]thiophenes. Nakamura *et al*.,[95] recently subjected the *S*-substituted *ortho*-alkynylthiophenol **109** to 2 mol% a Gold(I) catalyst in toluene at room temperature to afford the 2,3-disubstituted benzothiophene derivatives **110** (Scheme 30). The reaction proceeds via the formation of the sulfonium intermediate, followed by the 1,3-migration of the substituent on sulphur.



109 **110**

Scheme 30: Nakamura's gold-catalyzed cyclization of alkynyl thiophenols **109**.

The Grignard reaction of the ketothiophenols **111** with alkynes **112** in the presence of THF at 50 °C followed by palladium-mediated cyclization and subsequent dehydration of the intermediate **113** afforded the corresponding benzo[*b*]thiophenes **114** in 52–82% yield (Scheme 31).[96]



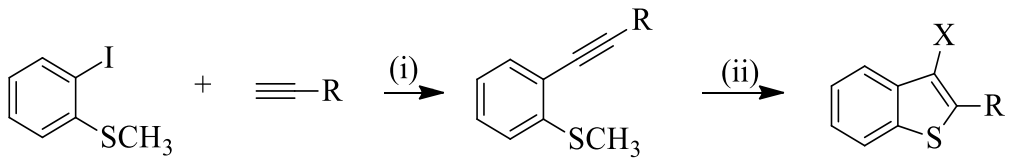
111 **112** **113** **114**

Reagents and conditions: (i) THF, 50 °C, 2h; (ii) PdI_2, KI, CH_3CN, 80-100 °C, 5-15 h

Scheme 31: Synthesis of benzo[*b*]thiophene **114** by Palladium catalysed cyclocondensation reaction.

Larock and Yue developed an alternative method to the transition metal-mediated cyclization of the alkynyl intermediates, which involves the use of an electrophilic halogen species to promote the halocyclization to afford the 2-substituted 3-halobenzo[*b*]thiophenes.[97] Intermediates **117** substituted with an alkynyl group adjacent or *ortho* to the nucleophilic heteroatom undergo halocyclization in the presence of an electrophilic halogen source (eg., NBS, I_2, ICl) to afford the 3-halobenzothiophene derivatives **118** in high 94–100% yields (Scheme 32). Compounds **117** were, in turn, prepared via Sonogashira cross-coupling of **115** with terminal acetylenes **116**.

The halocyclization step works well for bromo- and iodocyclization but is not applicable for the synthesis of the analogous 3-chloro- and 4-fluoro substituted derivatives.

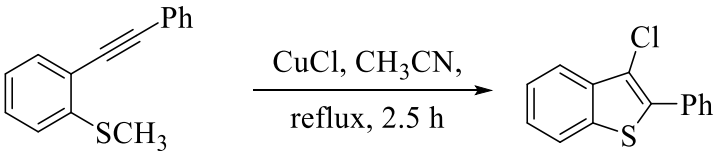


115 **116** **117** **118**

Reagents and conditions: (i) $PdCl_2(PPh_3)_2$ (2 mol%), CuI (1 mol%), NEt_3, 25 °C, 6 h; (ii) E^+ (I_2 or NBS), DCM, 25 °C, 10 min

Scheme 32: Synthesis of benzo[*b*]thiophenes **118** via electrophilic cyclization.

Lu and Wu have since developed an alternative approach for the synthesis of the 3-chlorobenzo[*b*]thiophenes.[98] Thioanisole **119** was subjected to cupric chloride in acetonitrile under reflux for 2.5 h to afford 3-chloro-2-phenylthiophene **120** (Scheme 33). The bromo analogue was prepared under similar reaction conditions using cupric bromide. Attempted fluorocyclization failed to yield 3-fluorobenzo[*b*]thiophene when cupric fluoride was used as a source of electrophilic fluorine.

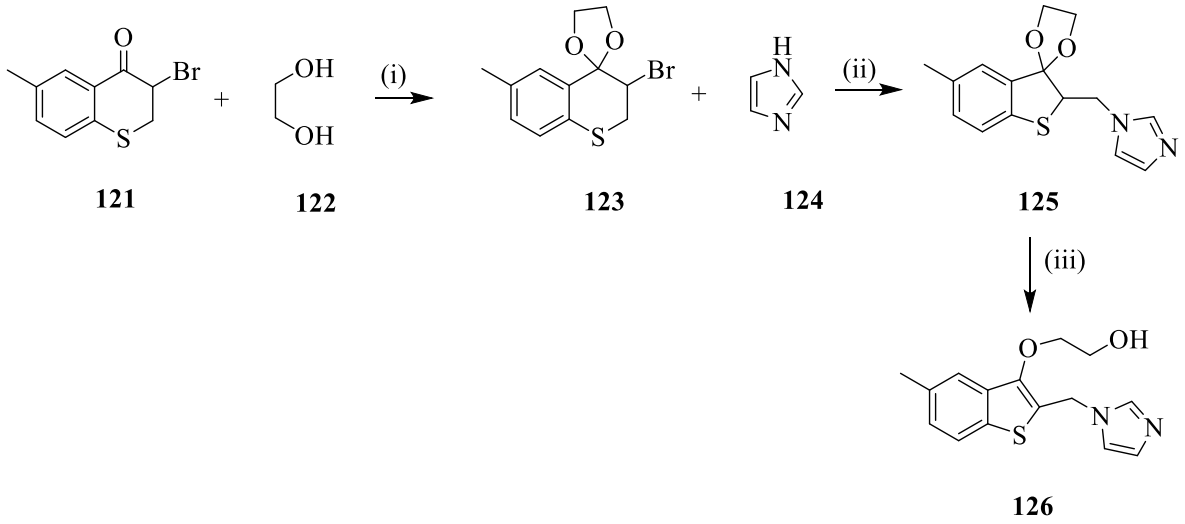


119 **120**

Scheme 33: Synthesis of 3-chlorobenzo[*b*]thiophene **120**.

Apart from cyclization methods, benzo[*b*]thiophene derivatives can also be prepared from rearrangement reactions of six-membered rings. An example is the ring contraction of thiochroman previously developed by Cozzi and Pillan (Scheme 34).[99] Thiochromanone **121** was first converted with ethylene glycol **122** into the corresponding ketal **123**, which rearranged in

the presence of imidazole **124** at high temperature to yield benzo[*b*]thiophane derivative **125**. Cleavage of the ketal moiety in the presence of PTSA afforded a 2,3-disubstituted benzo[*b*]thiophene **126**.



121 **122** **123** **124** **125** **126**

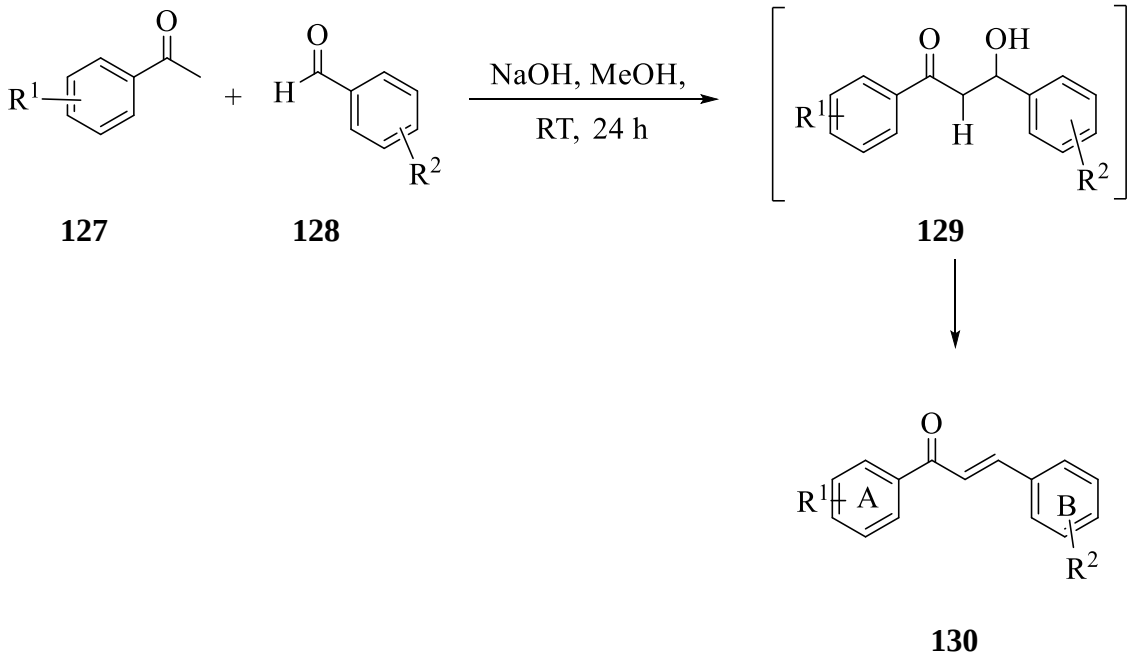
Reagents and conditions: (i) PTSA, benzene, reflux, 24 h; (ii) DMF, 120 °C, 6 h; (iii) 2-butanone, reflux, 3h

Scheme 34: Synthesis of benzo[*b*]thiophene **126** by ring rearrangement.

1.7 Methods for the synthesis of chalcones

Chalcones are characterised by the presence of an α,β-unsaturated enone moiety attached to two aryl rings A and B (Scheme 35) and they belong to the naturally occurring flavonoid family. Several methods for the construction of chalcones have been reported in the literature. Claisen-Schmidt condensation[100,101] of acetophenones and aldehydes under aqueous basic or acidic conditions still stands as the most popular method for the synthesis of chalcones. Non-conventional methods which involve the use of transition metal as catalysts for C–C bond formation in the construction of the chalcone skeleton have also been developed. Examples include the Suzuki using aryl boronic acids[102] and Heck cross-coupling.[103] In the traditional Claisen-Schmidt condensation, acetophenones and benzaldehyde derivatives are reacted in the

presence of a base as a catalyst in an appropriate solvent to afford the chalcone derivative.[100] Different inorganic and organic bases have been employed as catalysts for the Claisen-Schmidt condensation under both homogeneous[54] and heterogeneous[100] conditions. Among the inorganic bases, hydroxides of alkali and alkaline earth metals such as NaOH, KOH, $Ba(OH)_2$, LiOH, *etc.* continue to be employed to facilitate this reaction. Acetophenone **127** and aldehyde **128**, for example, were condensed in the presence of sodium hydroxide (NaOH) in methanol at room temperature to afford the substituted chalcones **130** in more than 80% yield (Scheme 35).[104] The base catalyzed Claisen-Schmidt condensation proceeds via the formation of an enolate ion from the ketone which then attacks the electrophilic aldehyde to form the β-hydroxyketone **129**. The latter undergoes dehydration spontaneously to afford a fully conjugated and more stable *α,β*-unsaturated chalcone as product.

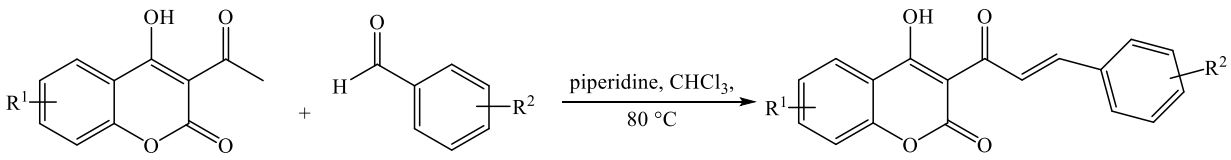


127 **128** **129** **130**

Scheme 35: Synthesis of substituted-chalcone **130** by Claisen-Schmidt condensation.

Solvent free conditions have also been applied for the synthesis of chalcones. Rateb *et al.*[105] developed a grinding method, which utilizes NaOH as a catalyst under solvent free conditions to condense **127** and **128** to yield the substituted chalcones **130** in 80–90 % yield. The grinding

process in this case increases the surface area to facilitate the reaction. The product was isolated by aqueous work-up and recrystallization. Bases such as $LiOH.H_2O$,[54] $Ba(OH)_2.8H_2O$,[54] and Mg-Al-O^{t}Bu hydrotalcite[107] were also utilized for the synthesis of chalcones under homogeneous conditions. Quantitative yields were obtainable when the aromatic rings of the aldehyde and the acetophenone contained no hydroxyl group except in the ortho position.[101] However, in the case of the 2-hydroxyacetophenones there is strong intramolecular hydrogen bonding between the hydroxyl group and the carbonyl oxygen, which masks the polarities in the molecule and make them not available for intermolecular hydrogen bonding. There is an increasing interest in the use of organic bases for the synthesis of chalcones. Chalcone derivatives **133**, for example, were prepared *via* piperidine catalyzed reaction of 3-acetyl substituted-chromen-2-ones **131** with aldehydes **132** in chloroform at 80 °C for 3 h in 71–81% yields (Scheme 36).[108]

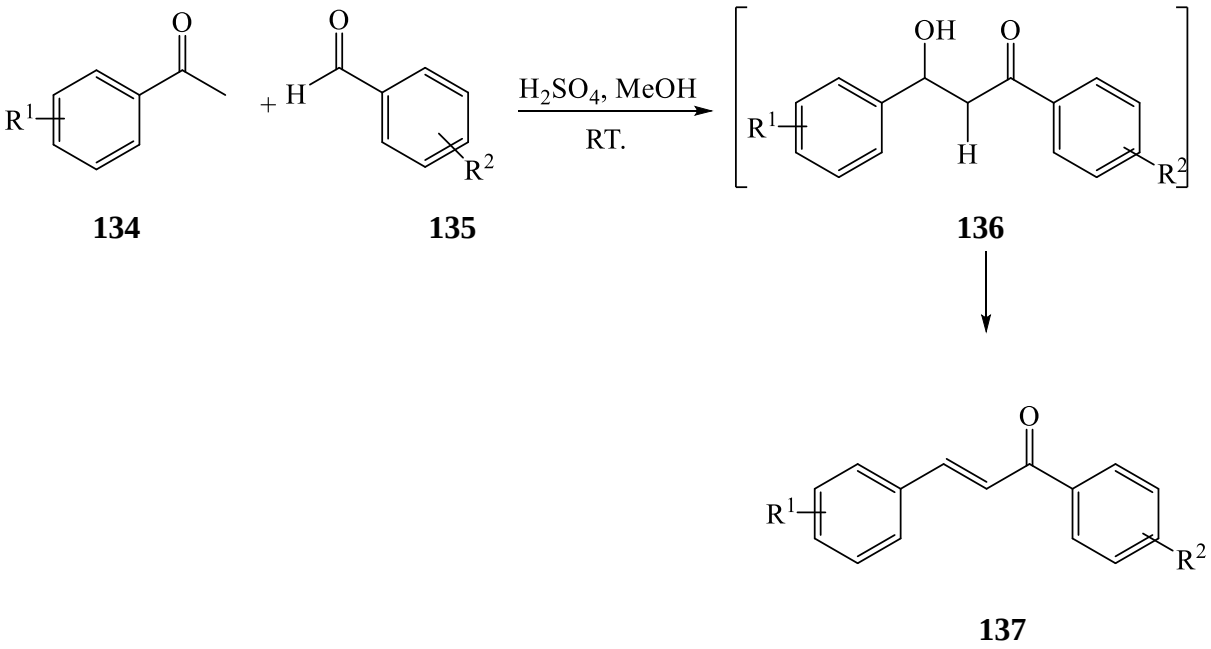


131 **132** **133**

Scheme 36: Piperidine catalyzed synthesis of coumarinyl chalcones **133**.

Claisen-Schmidt condensation of substituted acetophenones with aldehydes has previously been effected using various acids to afford the substituted chalcones. Sulphuric acid, for example, has been widely used as a reagent for the synthesis of heterocyclic compounds including substituted chalcones. Kim *et al.*[109] used H_2SO_4 to catalyze the reaction of acetophenone **134** and aromatic aldehydes **135** in the presence of methanol to afford the corresponding chalcones **137** (Scheme 37). The acid catalysed version of Claisen-Schmidt condensation proceeds through the formation of an enol, which then attacks the protonated aldehyde to yield the addition product **136**. This is followed by elimination of a water molecule to give the product chalcone. When screened against HEK-293 cells, the substituted chalcone derivatives were found to activate and inhibit the

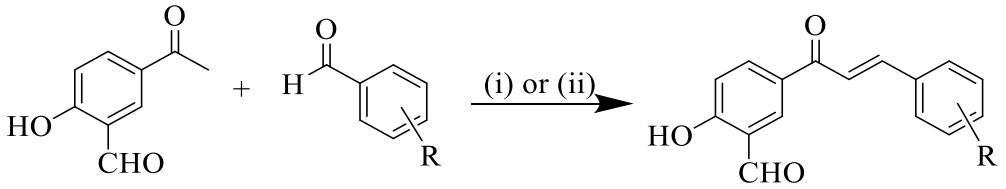
TREK2 channel.[109] The advantage of the Claisen-Schmidt condensation via enol mode over the enolate mode is that, it can be directly applied for the synthesis of hydroxychalcones without prior protection of the hydroxy group.[100]



134 **135** **136** **137**

Scheme 37: Sulphuric acid catalyzed Claisen-Schmidt condensation.

Claisen-Schmidt condensation of acetophenones with aldehydes has also been effected using various Lewis acid catalysts to afford substituted chalcone derivatives.[54] Narender *et al.*,[110] used BF_3-Et_2O as a catalyst to promote the condensation of **138** with aldehyde derivatives **139** in dioxane at room temperature to afford the substituted chalcones **140** (Scheme 38). Wang *et al.*[111] on the other hand, used 10% iodine as catalyst to afford the substituted chalcones **140** in 83–95% under solvent free and grinding conditions.

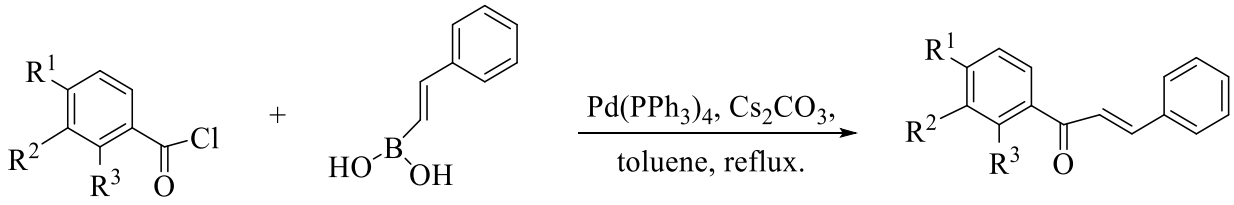


138 **139** **140**

Reagents and conditions: (i) BF_3-Et_2O, dioxane, RT, 24 h; (ii) I_2 (10 mol%), grinding, RT, 30 min.

Scheme 38: Lewis acid mediated synthesis of substituted-chalcones **140**.

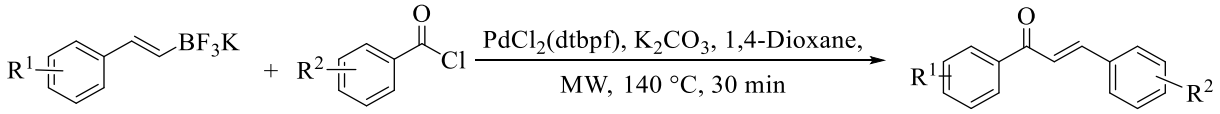
Transition metal-based compounds continue to attract considerable attention in C–C bond formation and this approach has also been employed for the construction of chalcones. Examples of these methods include Suzuki cross coupling of haloarenes with arylboronic acid and Heck cross-coupling of aryl vinyl ketones and aryl halides.[54] Palladium-catalyzed Suzuki cross coupling of haloarenes with arylboronic acid is among the most powerful C–C bond formation reactions available to synthetic organic chemists. Like in many other organic syntheses, palladium catalysed cross coupling reactions find their application in chalcone synthesis. Eddarir *et al*.[112] developed a method for the synthesis of chalcones based on the Suzuki reaction either between cinnamoyl chlorides and phenylboronic acids or between benzoyl chlorides and phenylvinylboronic acids (Scheme 39). Synthesis of chalcones **143** via Suzuki reaction involves the coupling of benzoyl chloride **141** and phenylvinylboronic acid **142** in the presence of cesium carbonate solution as base and anhydrous toluene as solvent.[112] The reaction is not affected by substituents located either on the acyl chloride or on the boronic acid.



141 **142** **143**

Scheme 39: Chalcone synthesis via Suzuki coupling.

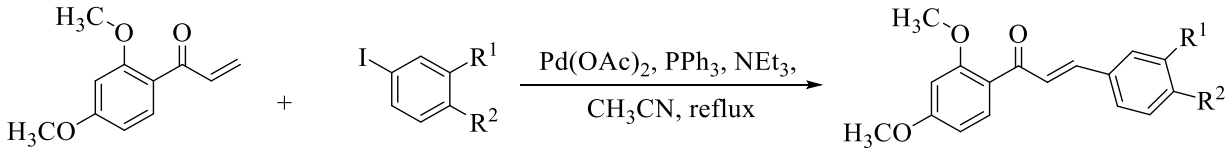
Al-Masum and co-workers developed a method for the direct cross-coupling reaction of benzoyl chlorides **145** and potassium styryltrifluoroborates **144** to the corresponding *α,β*-unsaturated aromatic ketones **146** in the presence of $PdCl_2(d^tbpf)$ catalyst under microwave irradiation. This method was used for the synthesis of chalcones with a variety of substituents (Scheme 40).[113]



144 **145** **146**

Scheme 40: Palladium catalysed Suzuki cross-coupling for the synthesis of chalcones **146**.

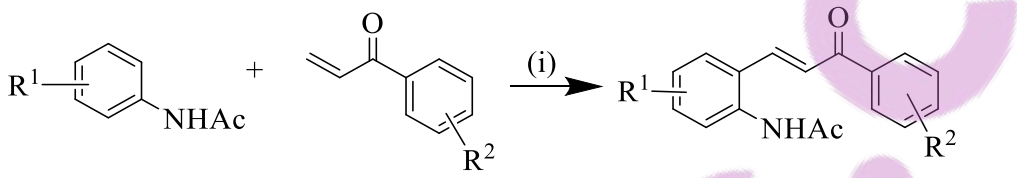
Methods that employ Heck cross-coupling reactions of aryl vinyl ketone and aryl iodides to construct chalcones have also been developed.[103] For an example, the Heck cross-coupling reaction of substituted aryl vinyl ketone **147** and aryl iodide **148** in the presence of $Pd(OAc)_2$ as a catalyst, NEt_3 as a base and PPh_3 as a ligand in anhydrous acetonitrile afforded the substituted chalcone **149** 95-96 % yield (Scheme 41).[114]



147 **148** **149**

Scheme 41: Synthesis of chalcones **149** via intramolecular Heck cross coupling reaction.

Meagawa and co-workers recently described a palladium catalysed direct synthesis of chalcones from anilides with phenyl vinyl ketones by Oxidative Coupling through C−H Bond activation.[115] The reaction of substituted-anilides **150** and phenyl vinyl ketone **151** using palladium trifluoroacetate ($Pd(OCOCF_3)_2$ (20%) and copper acetate ($Cu(OAc)_2$ (20%) in dichloromethane at 50 ℃ for 24 h under oxygen atmosphere afforded 2-aminochalcones **152** in 51–79 % yields (Scheme 42). Selective palladium C−H bond activation occurred at the position ortho to the acetamide group to allow the double bond insertion to afford 2-aminochalcone derivatives.



150 **151** **152**

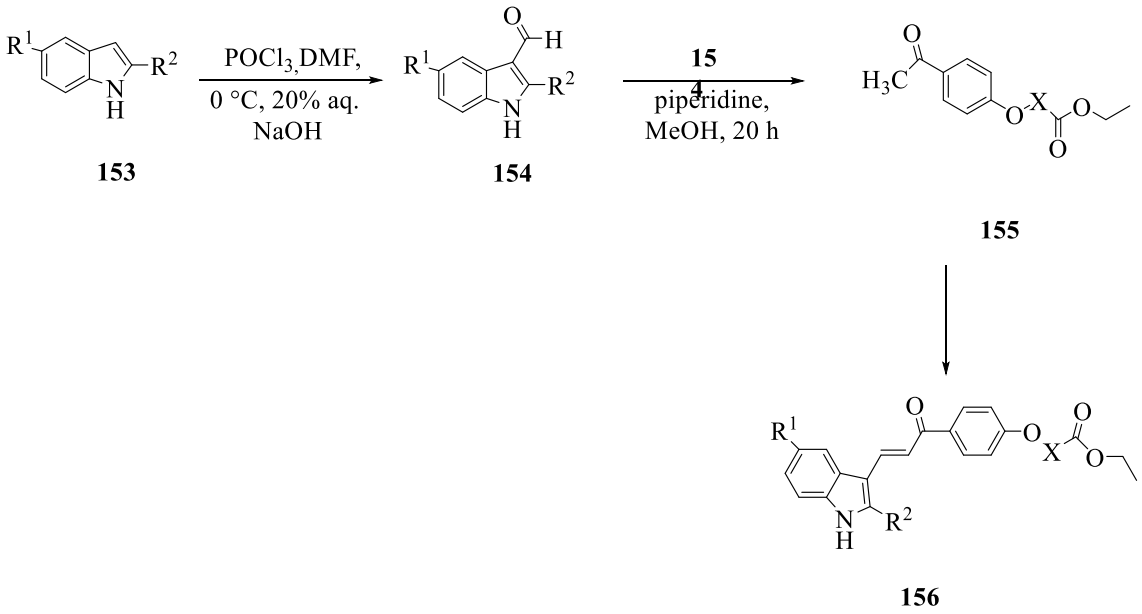
Reagents and conditions: (i) $Pd(OCOCF_3)_2$ (20%), $Cu(OAc)_2$ (20%), CH_2Cl_2, 50 ℃, O_2, 0.5 M, 24 h.

Scheme 42: Synthesis of chalcones **152** via palladium-mediated C-H bond activation.

Chalcones are recognized as a privileged scaffold because they can be synthetically modified to incorporate different molecules or pharmacophores with various biological activities. Indole- and benzofuran-appended chalcone hybrids have gained great interest due to their enhanced biological and photophysical properties. The synthesis of these hybrids or conjugations typically uses the classical condensation or the synthesis methods discussed in the above section to build the chalcone core. In addition to the biological activities for multi-targeting mechanisms, hybrid molecules are also selected for other reasons, such as improving the solubility and oral bioavailability. The methods for the synthesis of the indole- and benzofuran-appended chalcone hybrids is discussed in the next section.

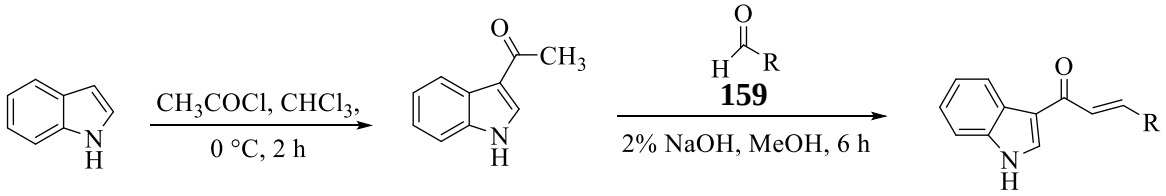
1.8 Methods for the synthesis of indole- and benzofuran-appended chalcones

Sashidhara *et al.*[116] previously synthesized the indole-chalcones **156** by subjecting the commercially available substituted indoles **153** to Vilsmeier-Haack reaction conditions in presence of the $POCl_3$ and DMF at 0 °C to afford the corresponding indole-3-carbaldehydes **154**. The subsequent Claisen-Schmidt condensation of the indole-3-carbaldehydes **154** with the acetophenone **155** in the presence of catalytic amount of piperidine in MeOH or EtOH under reflux conditions yielded the desired indole-chalcone **156** in 75–82%, and the trans isomer was obtained exclusively (Scheme 43). The indole-chalcones **156** were found to exhibit *in vitro* antioxidant and significant *in vivo* antidyslipidemic ativities.[116]



Scheme 43: Synthesis of indole-chalcones **156**.

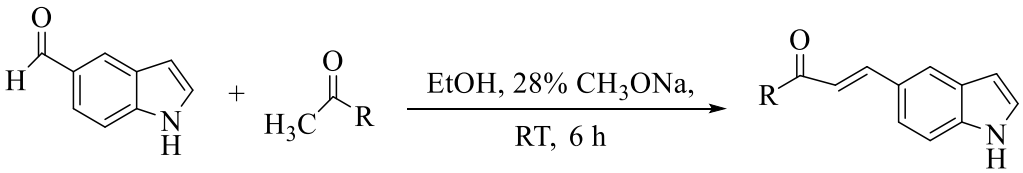
In another example, Jain *et al.*[117] reacted indole **157** with acetylchloride in chloroform at 0 °C to generate the 3-acetylindole **158** followed by condensation with aldehydes **159** in the presence NaOH as a catalyst in methanol to afford the indole-chalcones **160** (Scheme 44). These indole-chalcones **160** were found to show promising antibacterial and antifungal activities.[117]



157 **158** **160**

Scheme 44: Synthesis of indole-chalcones **160**.

Another type of indole-chalcones where *α*,*β*-unsaturated ketone group is at the C-5 have been previously synthesized from indole-5-carbaldehyde.[118] The key step in the synthesis is also the base-catalyzed Claisen condensation reaction. Compounds **163** were obtained from the reaction of substituted acetophenones **162** and 1*H*-indole-5-carbaldehyde **161** in the presence of sodium methoxide catalyst (28%) in ethanol at room temperature in 58–60% yield (Scheme 45). These indole-chalcones were used as *β*-amyloid imaging probes for detecting Alzheimer's disease (AD), targeting A*β*1−42 aggregates with high affinity (Ki = 1.97 nM).[118]

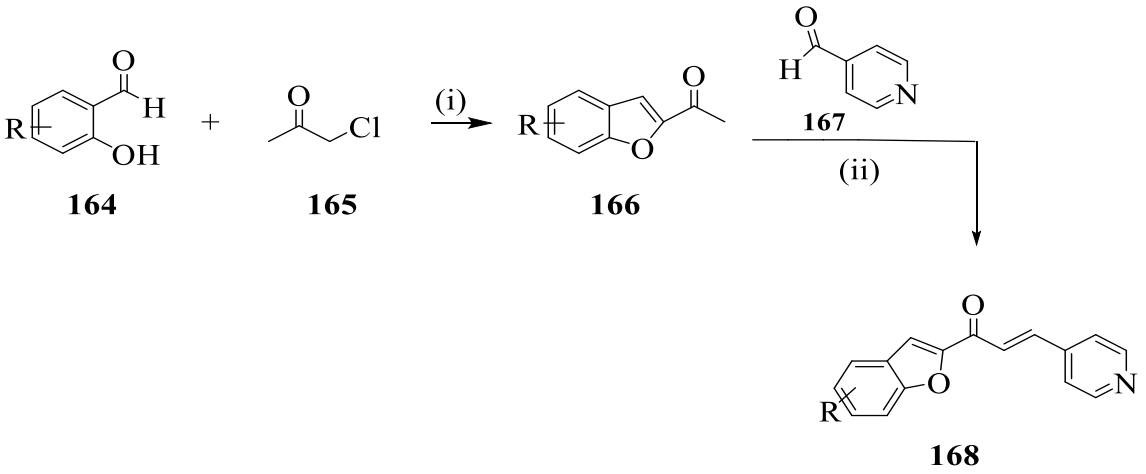


161 **162** **163**

Scheme 45: Synthesis of indole-chalcones **163**.

A series of benzofuran-chalcones **168** have been obtained by the reaction of substituted salicylaldehyde **164** derivatives with chloroacetone **165** using K_2CO_3 as a base to afford the 2-acetylbenzofuran **166** (Scheme 46). Base mediated Claisen-Schmidt reaction of the 2-acetylbenzofuran **166** with different aromatic aldehydes **167** gave substituted benzofuran-chalcone derivatives **168** (Scheme 46).[40] The compounds exhibited the highest activity against tumor cell growth (IC_{50} < 1 μM) and 10−100-fold increases in potency. The mechanism of action

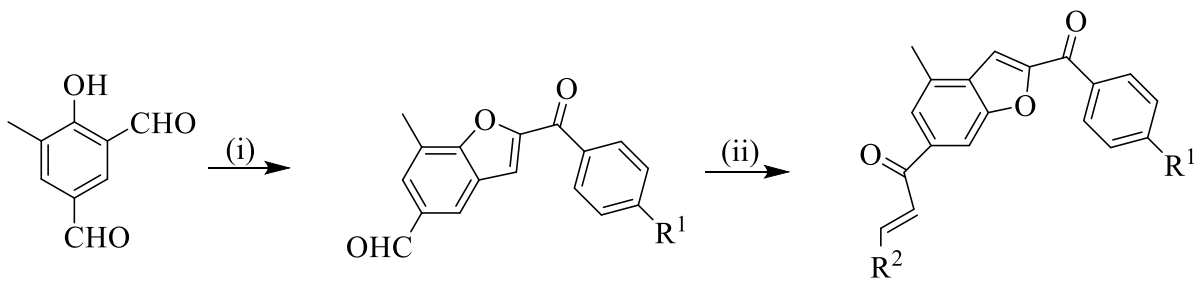
has only been preliminarily studied, and the compounds appear to induce apoptosis mediated by the involvement of the mitochondria and the activation of caspase-3 and 7.[40]



Reagents and conditions: (i) K_2CO_3, dry acetone; (ii) piperidine, *n*-BuOH, MW, 150 °C, 30 min.

Scheme 46: Synthesis of benzofuranchalcones **168**.

Sashidhara and co-workers developed a method for the synthesis of 5-substituted benzofuran-chalcone hybrids **171** starting from the dicarbaldehyde derivative **169**.[39] The Rap-Stoermer condensation of compound **169** with various phenacyl bromides in the presence of potassium carbonate gave the benzofuran carbaldehyde derivatives **170** in quantitative yields. Introduction of the chalcone scaffold was carried out by the reaction of **170** with various acetophenones in methanolic potassium hydroxide at room temperature to yield the final benzofuran-chalcone hybrids **171** (Scheme 45). These compounds **171** were found to decrease acetylcholinesterase (AChE) levels, reduce oxidative stress in the transgenic *Caenorhabditis elegans* worms, lower lipid content, and to provide protection against chemically induced cholinergic neurodegeneration.[39]



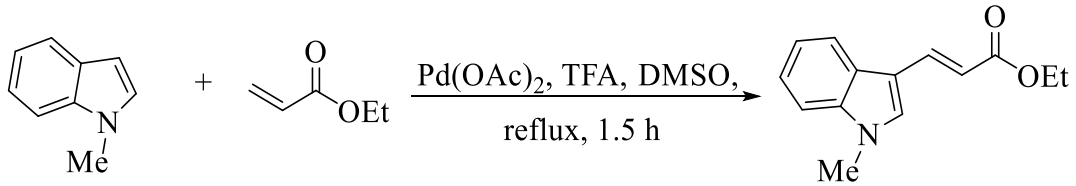
169 **170** **171**

Reagents and conditions: (i) phenacyl bromide derivatives, K_2CO_3, CH_3CN, 110 °C, 3 h;

(ii) R^2COCH_3, KOH (10% in MeOH), 3 h, RT

Scheme 47: Synthesis of benzofuranchalcones **171**.

The use of transition metal-catalyzed C–H bond activation as an efficient method for the synthesis of novel heterocycles has also been applied to the synthesis of indole-chalcones. The analogous indole-chalcone derivative **174**, for example, was prepared in 97% yield *via* palladium(II)-catalyzed intermolecular C-3 alkenylation of indoles **172** with alkenes **173** with TFA in DMSO under reflux in an O_2 atmosphere (Scheme 48).[119]



172 **173** **174**

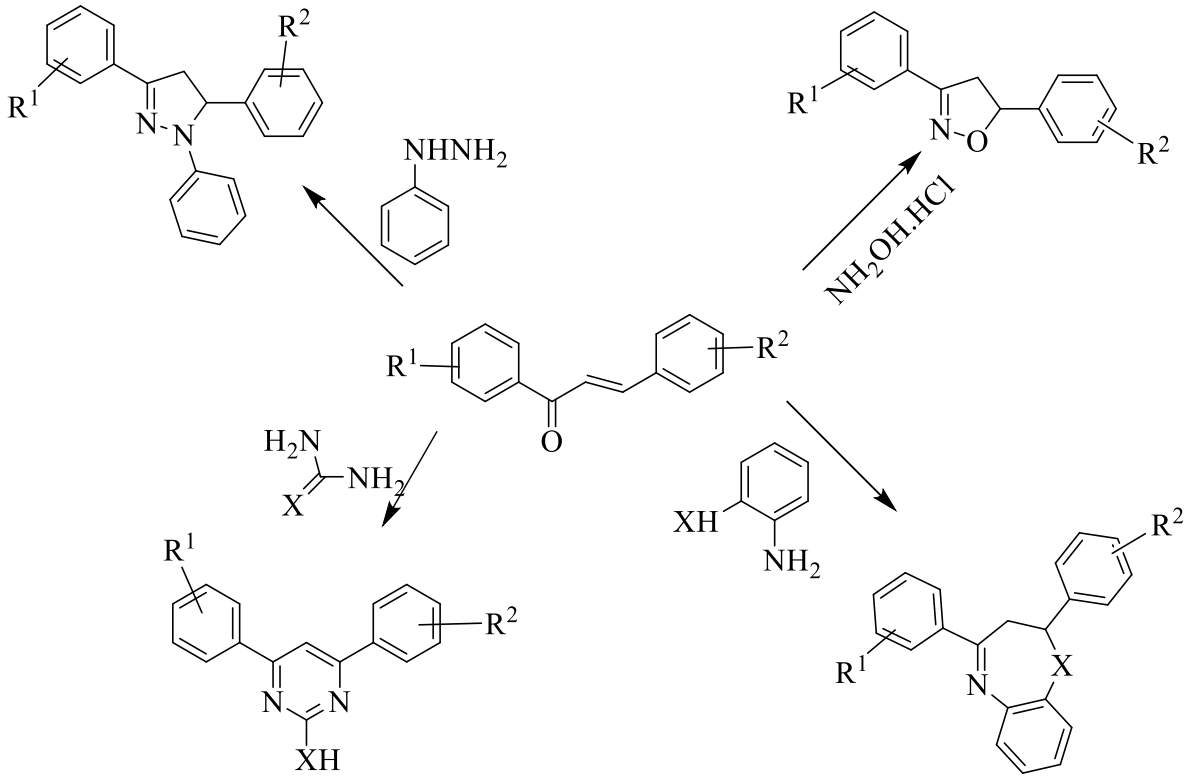
Scheme 48: Synthesis of indole-chalcones *via* the palladium-catalyzed intermolecular direct C-3 alkenylation of indoles.

We could not find in the literature examples of benzofuran- or indole-chalcones in which the α,β-unsaturated moiety is linked directly to the fused benzo ring through the carbonyl carbon to generate linear or angular heterocycle-appended chalcone derivatives. The α,β-unsaturated carbonyl system of chalcones possesses two electrophilic centers, which allows this moiety to

participate in nucleophilic reactions *via* nucleophilic attack to the carbonyl group (1,2-addition) or to the β-carbon (1,4-conjugate addition). The chalcone framework also constitutes a useful scaffold for the reaction with binucleophilic reagents to append 5-, 6- and 7-membered nitrogen-containing heterocycles such as pyrazoles, tetrazoles, imidazoles, isoxazoles and benzothiezapines onto the α,β-unsaturated arm.[120] The methods for the reactions of chalcones with binucleophiles to form 5-, 6- and 7-membered nitrogen-containing heterocycles are described briefly below.

1.9 Chalcone moiety as scaffold for heteroannulation with binucleophiles to afford 5- , 6- and 7-membered heterocyclic derivatives

The reaction of this α,β-unsaturated carbonyl framework with ambident heteroatom-based nucleophiles such as hydroxylamine,[120] hydrazine derivatives,[121-123] 1,2-alkyl/aryldiamines[120] or 1,3-alkyldiamines[124] or aminoalkylthiols,[125-127] on the other hand, result in novel 5-, 6- or 7-membered heterocyclic compounds such as pyrazoles, pyrimidines, isoxazoles, benzothiezapines, *etc.* (Scheme 49).



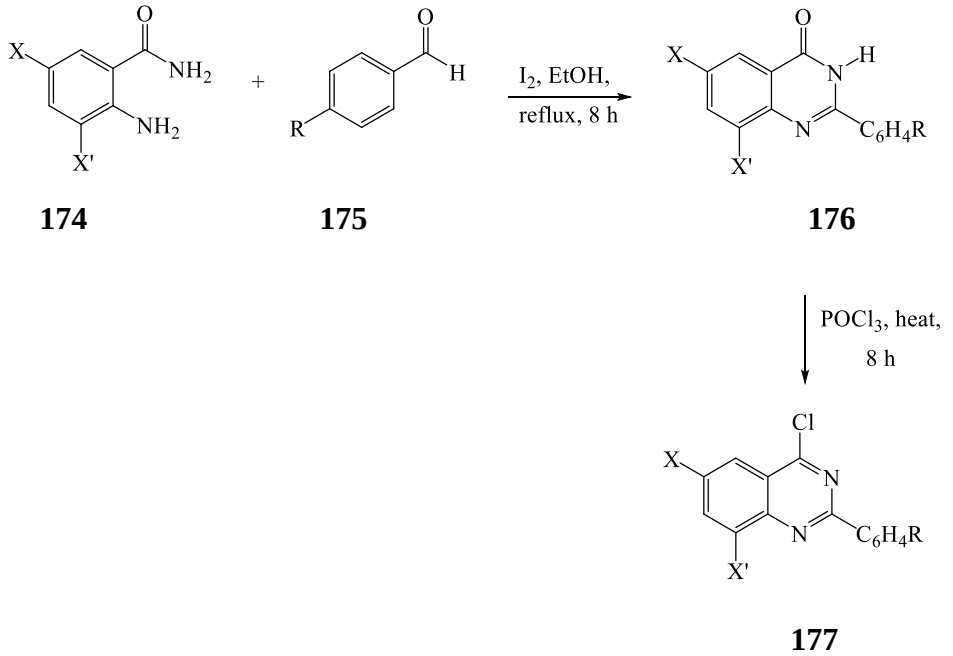
Scheme 49: Examples of reactions of chalcones with binucleophiles.

Another class of molecular hybrids are the indole-appended quinazolines, which may be linked directly through C–C bond or through a heteroatom bridge (O or N). The methods for the construction of the quinazoline skeleton and indole-appended quinazoline hybrids are described in detail below.

1.10 Methods for the synthesis of quinazolines

The quinazoline-based compounds are associated with rich biological activities and excellent pharmacological properties.[128] Quinazolin-4(3*H*)-ones represent versatile building blocks for the design and synthesis of novel polysubstituted quinazolinones[129] and their quinazoline derivatives using the principles of lactam-lactim dynamic equilibrium phenomena.[130] The potentially tautomeric quinazolin-4(3*H*)-one moiety itself is readily accessible via dehydrogenation of the

corresponding 2,3-dihydroquinazolin-4(1*H*)-one precursors using stoichiometric or large excess of oxidants such as $KMnO_4$,[131] $CuCl_2$,[132] DDQ[133] and MnO_2.[134] The 2-substituted quinazolin-4(3*H*)-ones have also been synthesized directly from anthranilamide and aldehydes using reagents such as $NaHSO_3$,[135] DDQ,[133] $CuCl_2$ (3 equiv.),[132] $FeCl_3.6H_2O$[136] or I_2.[137] Quinazolines, on the other hand, are mostly synthesized by the aromatization of the quinazolin-4(3*H*)-one moiety using reagents such as thionyl chloride ($SOCl_2$),[138] phosphoryl chloride ($POCl_3$)[139] or a combination of phosphorus pentachloride (PCl_5) and $POCl_3$[139] to afford the 4-chloroquinazoline derivatives. This strategy has previously been employed in our laboratory to transform the 2-aminobenzamides **174** bearing different halogen atoms as precursors for cyclocondensation with benzaldehyde derivatives **175** followed by dehydrogenation of the incipient quinazolin-4(1*H*)-one intermediates to afford the requisite 2-aryl-6,8-dihalogenoquinazolin-4(3*H*)-ones **176** (Scheme 50).[129] Compounds 2-aryl-6-bromo-8-iodoquinazolin-4(3*H*)-ones **176** were futher subjected to oxidative aromatization with phosphoryl chloride–triethylamine mixture under reflux to afford the corresponding 2-aryl-6-bromo-4-chloro-8-iodoquinazolines **177**.



174 **175** **176**

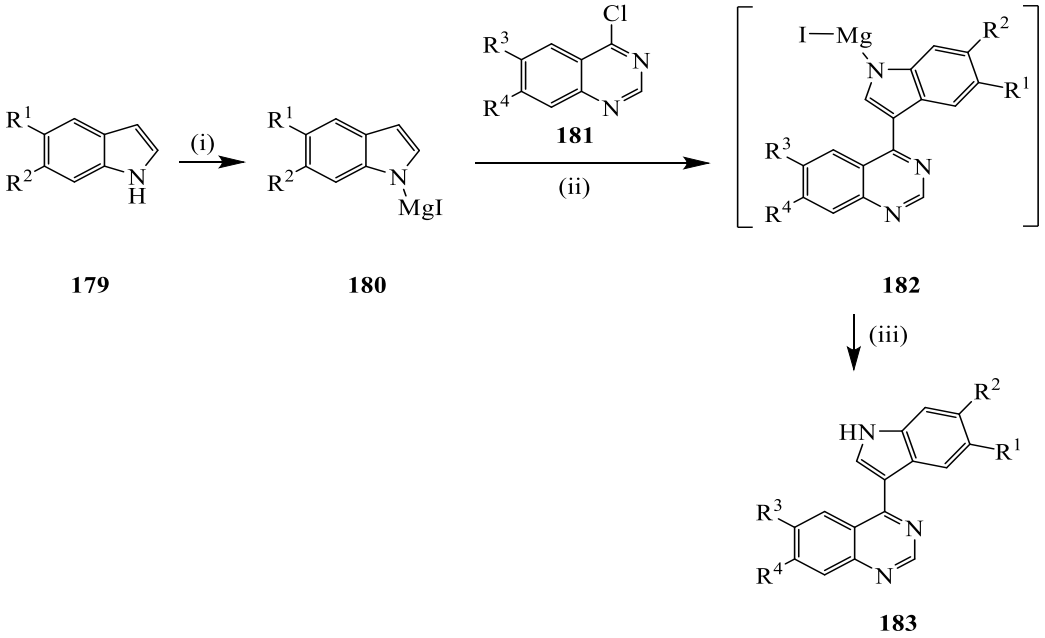
177

Scheme 50: Oxidative aromatization of quinazolin-4(3*H*)-one

The Csp^2–Cl bond of the 4-chloroquinazoline moiety is highly reactive towards substitution with heteroatom-containing nucleophiles, the 4-chloroquinazoline moiety also facilitates metal-catalyzed cross-coupling to afford carbo-substituted quinazoline derivatives. The application of 4-chloroquinazolines in the synthesis of carbo-substituted or heteroatom-substituted quinazolines is described in detail below.

1.11 Methods for the synthesis of C–C and C–heteroatom linked indole-quinazoline hybrids

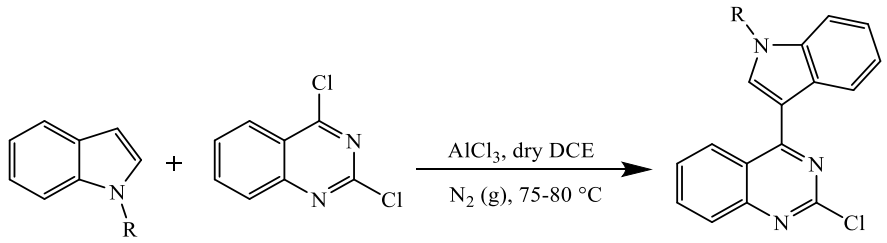
Luth *et al.*[27] reported the synthesis of 4-(indole-3-yl)quinazolines **183** *via* the coupling reaction of indolyl-magnesium compounds **180** with 4-chloroquinazolines **181** in diethyl ether under reflux followed by hydrolysis of the intermediates **182** (Scheme 51). The indole-quinazoline hybrids exhibit EGFR inhibitory activity have also been found to inhibit HER-2 TK-induced at 100 nM.[27]



Reagents and conditions: (i) Mg, I_2, CH_3I, Et_2O, 5 °C; (ii) Et_2O, reflux; (iii) H_2O

Scheme 51: Heteroarylation of indole **180** and quinazoline **181**.

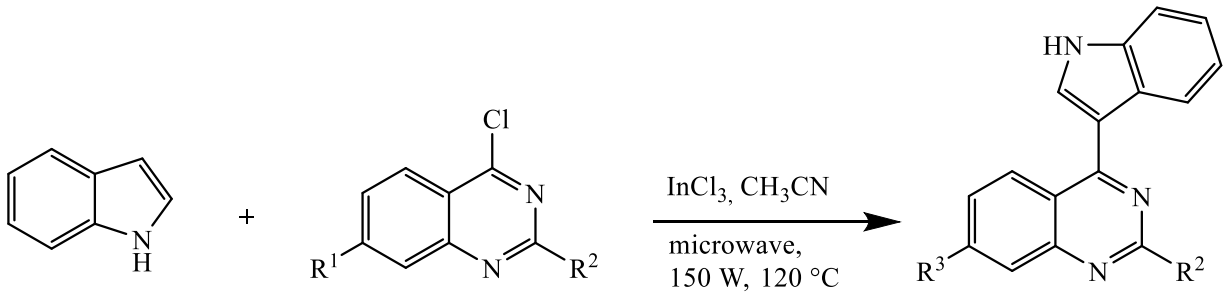
A series of 4-(3-indolyl)quinazolines **186** have been synthesized by the aluminium chloride-catalyzed hybridization of indoles **184** with 2,4-dichloroquinazoline **185** in dry dichloroethane under nitrogen atmosphere at 75–80 °C (Scheme 52).[140] The synthesized compounds were found to exhibit significant anti-leishmanial and/or anti-proliferative activities against a panel of mammalian cancer cell lines such as prostate carcinoma (DU145), breast adenocarcinoma (MCF-7), oral epidermal carcinoma (KB) and cervical carcinoma (C33A).[140]



184 **185** **186**

Scheme 52: Aluminium chloride-mediated cross-coupling of **184** with **185** to afford **186**.

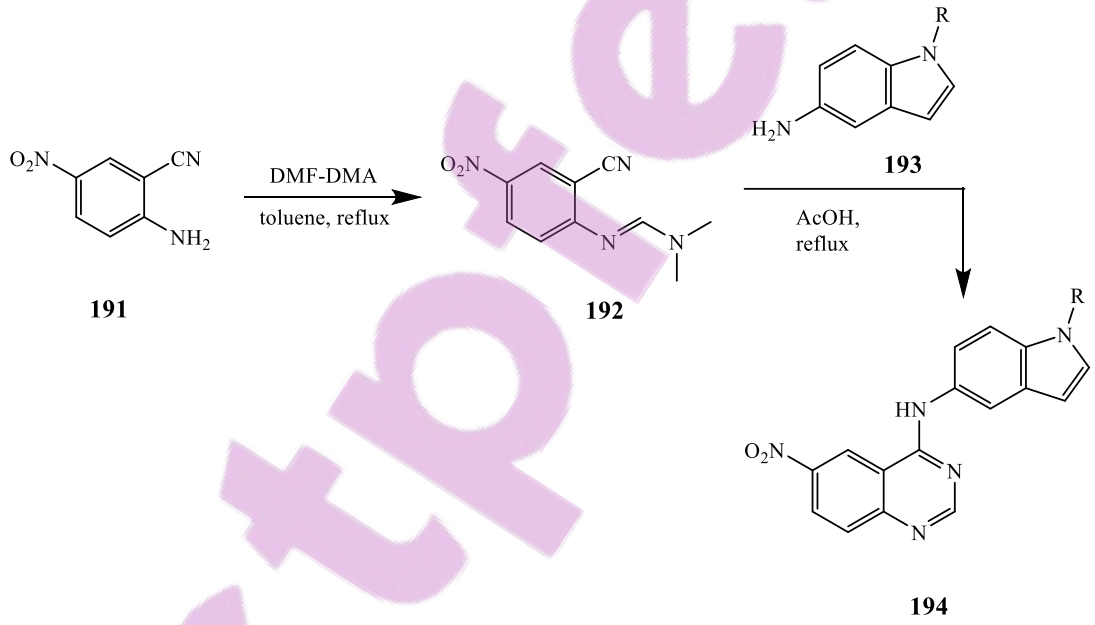
Lewis acids such as Indium(III) chloride ($InCl_3$) have also been utilized for the hybridization of indole **157** with 4-chloroquinazoline **189** in acetonitrile under microwave irradiation at 150 W and 120 °C to afford the substituted 4-(1*H*-Indol-3-yl)-2-phenylquinazoline **190** in 78–89% yield (Scheme 53).[141] Compound **190** was obtained in 82–84% yields when boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$), indium(III) trifluoromethanesulfonate or gallium trichloride were used as catalysts, respectively.



157 **189** **190**

Scheme 53: Hybridization of **157** with **189** to afford **190**.

An alternative route involving condensation and Dimroth rearrangement of the starting anilines with imines obtained from anthranilonitriles with formamide dimethylacetal to afford the 4-aminoquinazolines has also been reported.[28] *N'*-(2-Cyano-4-nitro-phenyl)-*N*,*N*-dimethyl-formamidine **192** was reacted with 5-aminoindoles **193** in acetic acid under reflux to afford (6-nitro-quinazolin-4-yl)-(1*H*-indol-5-yl)-amines **194** (R = -CH_3, propyl, allyl) (Scheme 54). Compound **192** used as precursor was, in turn, prepared via the condensation of 2-amino-5-nitrobenzonitrile **191** with dimethylformamide dimethyl acetal in toluene under reflux (Scheme 54). Compounds **194** were further reduced to their corresponding N^4-(1*H*-indol-5-yl)-quinazoline-4,6-diamine derivatives which were also found exhibit anti-inflammatory properties against lipopolysaccharide-induced TNF-α and IL-6 expression.[28]



Scheme 54: Preparation of **194** from reaction of **192** with **193**.

Despite what looks like a simple molecular framework, there is no literature precedent for the merging benzofuran moiety with the quinazoline scaffold to generate analogues of the indole-aminoquinazoline hybrids shown here or in Figure 5 above.

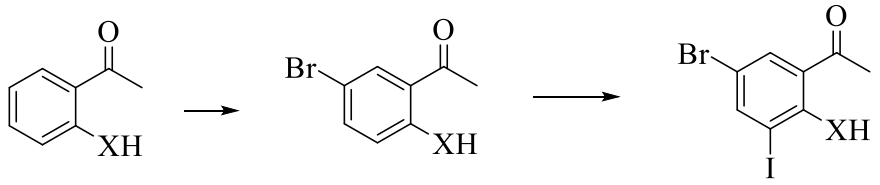
1.12 Main focus of this investigation

Based on the above literature precedents, we asked ourselves whether molecular hybridization strategy could be employed to construct novel indole-chalcones or benzofuran-appended chalcone hybrids and their benzothiazepine-appended derivatives as well as benzofuran- or indole-quinazoline hybrids for evaluation of biological activity as potential anticancer agents.

1.12.1 Aim of the study

The main aim of this investigation was to synthesize novel indole- and benzofuran-appended chalcone hybrids as well as the benzofuran-aminoquinazoline hybrids for further studies of chemical transformation and antiproliferative activity as potential anticancer agents. We envisaged that sequential and/or one-pot successive palladium catalyzed Sonogashira cross-coupling of the 3-halogenated 2-aminochalcones or their 2-hydroxychalcone analogues followed by cycloisomerization of the intermediate 3-alkynylated 2-amino/hydroxychalcone derivatives would afford novel angular indole-chalcones or benzofuran-chalcones, respectively. The presence of the strongly nucleophilic carbon-3 of the indole or benzofuran moiety and the electrophilic α,β-unsaturated carbonyl framework in these compounds would enable further chemical transformation with electrophilic reagents or dinucleophiles, respectively. The mixed 3,5-dihalogenated acetophenone **197**(**a)** and **197**(**b**) derivatives prepared via the sequential halogenation of 2-aminoacetophenone **195**(**a**) and 2-hydroxyacetophenone **195**(**b**) (Scheme 55) were envisaged to represent suitable precursors for the synthesis of the target compounds as shown in Figure 13. The presence of the acetyl group in the 3,5-dihalogenated 2-amino/hydroxyacetophenones would probably facilitate base-mediated Claisen-Schmidt aldol

condensation with benzaldehyde derivatives to afford the 2-amino-5-bromo-3-iodochalcones **198** (X = NH) or 5-bromo-2-hydroxy-3-iodochalcones (X = O) **198**, respectively.



195: X = NH (**a**); O (**b**) **196:** X = NH (**a**); O (**b**) **197:** X = NH (**a**); O (**b**)

Scheme 55: Design and synthesis of mixed 3-,5-dihalogenated acetophenone derivatives.

Palladium catalysed Sonogashira cross-coupling of **198** (X = NH) with terminal acetylenes would yield the 3-arylalkynyl–substituted 2-aminochalcones **200** which upon cyclization would afford the indole-chalcones **201**. The sonogashira cross-coupling of the analogous 5-bromo-2-hydroxy-3-iodochalcones **198** (X=O) with arylacetylenes under the same reaction conditions employed for the synthesis of **200** would afford the benzofuran-chalcones **203**. Further chemical transformation of the indole-chalcones via C-3 acetylation with trifluoroacetic anhydride would afford the 3-trifluoroacetyl–substituted indole-chalcones **204**. The α,β-unsaturated carbonyl moiety of the indole-chalcones **200** and benzofuran-chalcones **203** could be reacted with a binucleophile such as 2-aminothiophenol to yield the benzothiezapine-appended hybrids **205**. Tandem Sonogashira cross-coupling and heteroannulation reaction of 5-bromo-2-hydroxy-3-iodoacetophenone **197** (X = O) with terminal alkynes would afford the 7-acetyl-2-aryl-5-bromobenzofurans **207**. Beckmann rearrangement of the oximes **208** derived from **207** and subsequent hydrolysis of the intermediate **209** derivatives would afford the 7-aminobenzofurans **210** in a single-pot operation. The latter could be condensed with the 4-chloroquinazolines **214** to afford the quinazoline-benzofuran hybrids **215** analogues of the 4-anilinoquinazolines or Cediranib (**12**).

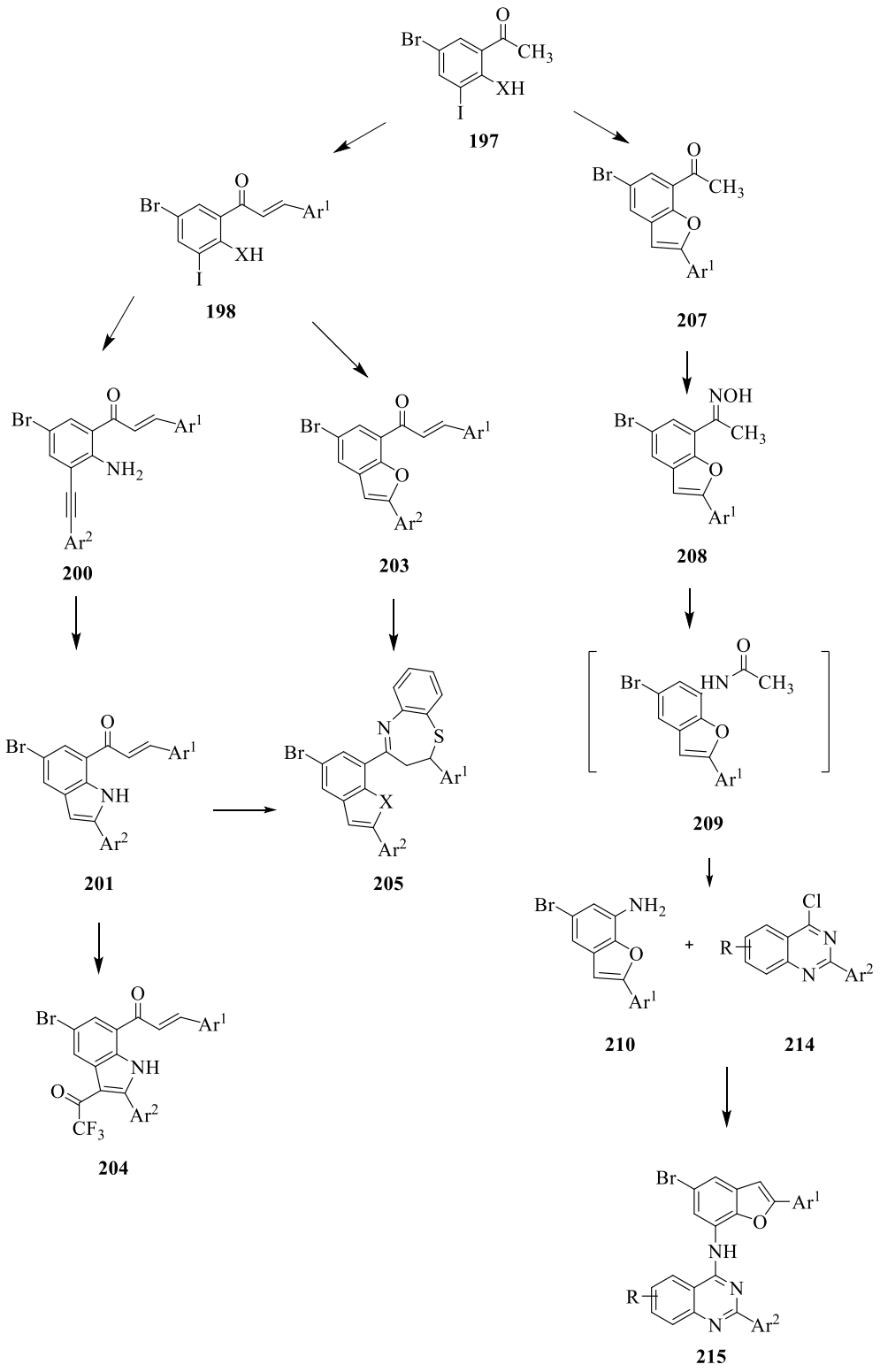


Figure 13: Generalized scheme depicting reaction pathways followed to prepare the compounds described in this investigation.

1.12.2 Specific objectives of the study

Based on thes above assumptions, the aim of this investigation was structured into the following specific objectives according to Figure 13.

(i) To prepare the mixed 3′,5′-dihalogenated 2-amino- and 2-hydroxychalcone derivatives **198** based on 2-amino **197a** and 2-hydroxyacetophenone **197b** as precursors.

(ii) To transform the 3′,5′-dihalogeno–substituted 2-aminochalcones and their 2-hydroxychalcone analogues **198** into the corresponding angular indole-chalcones **201** and benzofuran-chalcones **203**, respectively;

(iii) To effect site-selective C-3 trifluoroacetylation of the indole-chalcones **201**;

(iv) To react the α,β-unsaturated carbonyl framework of the heterocycle-appended chalcones **201** and **203** with a dinucleophile;

(v) To synthesize the 7-amino-2-aryl-5-bromobenzofurans **210** for condensation with the 4-chloroquinazoline **214** to afford benzofuran-aminoquinazoline hybrids **215**;

(vi) To study the structural properties of the prepared compounds using a combination of NMR, IR and mass spectrometric techniques complemented with single crystal X-ray diffraction and/or density functional theory (DFT) methods; and

(vii) To evaluate some of the prepared compounds for anti-proliferative activity *in vitro* complemented with molecular docking studies.

Chapter 2: Results and Discussion

2.1 Preparation of substrates

The synthesis of 2′-amino-5′-bromo-3′-iodoacetophenone and 5′-bromo-2′-hydroxy-5′-iodoacetophenone used as precursors in this investigation and their transformation into the corresponding chalcone derivatives are described in the next sections.

2.1.1 Synthesis of 2′-amino-5′-bromo-3′-iodoacetophenone and 5′-bromo-2′-hydroxy-3′-iodoacetophenone

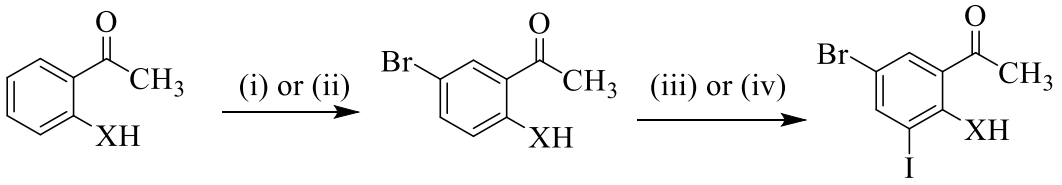
Literature review revealed that 2′-amino-5′-bromoacetophenone and the analogous 5′-bromo-2′-hydroxyacetophenone have been prepared before. Baker *et al*.[142] synthesised 2′-amino-5′-bromoacetophenone in 80% yield from the reaction of 2-aminoacetophenone with pyridinium tribromide in dichloromethane (DCM) at room temperature (RT). The analogous 2-hydroxyacetophenone, on the other hand, was previously brominated with NaBr-oxone in methanol or *N*-bromosuccinimide (NBS) in acetic acid under reflux to afford 2′-hydroxy-5′-bromoacetophenone, exclusively.[143] Under the same reaction conditions, 2-aminoacetophenone furnished a 3,5-dibromo product.[144-145] The 5′-bromo-2′-hydroxyacetophenone has been subjected to further halogenation using pyridinium iodochloride in methanol under reflux to afford 5′-bromo-2′-hydroxy-3′-iodoacetophenone.[146] To our knowledge, the 2′-amino-5′-bromoacetophenone has not been transformed into the mixed dihalogenated derivatives. In this investigation we adapted the method described in literature[142] and subjected 2-aminoacetophenone **195a** (X = NH) to pyridinium tribromide in dichloromethane at room temperature (RT) for 4 h to afford **196a** (Scheme 56). Thin layer chromatography of the crude

product revealed the presence of 2′-amino-5′-bromoacetophenone **196a** (X = NH) as the major product along with traces of the 2′-amino-3′,5′-dibromoacetophenone. The resultant crude product was recrystalized from hexane to afford **196a** in high purity. Treatment of 2-hydroxyacetophenone **195b** (X = O) with *N*-bromosuccinimide (NBS) in acetic acid at RT following a literature procedure,[142] on the other hand, afforded 5′-bromo-2′-hydroxyacetophenone **196b** (X = O).

Although, both the 3- and 5-positions of **195a** or **195b** are doubly activated by the *ortho-para* directing effect of the amino or hydroxyl group and the *meta*-directing effect of the acetyl group, monobromination occurred almost exclusively at the 5-position to generate the 5-bromo–substituted 2-amino- **196a** or 2-hydroxyacetophenone **196b**, respectively. Bromination of 2-aminoacetophenone **195a** by pyridinium tribromide (PTB) is known to release hydrogen bromide, which presumably coordinates with the amino group and reduce its propensity for π-electron delocalization.[147] The steric hindrance at the ortho position relative to NH_3^+ and the meta directing effect of the acetyl group would favour attack at the 5-position by the bulky PTB to form 2′-amino-5′-bromoacetophenone **197a**. The observed site-selective 5-monobromination of the 2-hydroxyacetophenone **196b**, on the other hand, is presumably due to the formation of hydrogen bonds between the phenolic proton and the acetic acid, which would hinder attack at the ortho position by the bulky NBS and thus favour para attack.[148] Compounds **196a** and **196b** were each subjected to *N*-iodosuccinimide in acetic acid at RT or under reflux to afford the previously undescribed 2′-amino-5′-bromo-3′-iodoacetophenone **197a** (X = NH) and the known 5′-bromo-2′-hydroxy-3′-iodoacetophenone **197b** (X = O), respectively (Scheme 56).

The ^{1}H NMR spectra of compounds **196a** and **196a** each revealed the presence of a broad singlet at δ 6.29 ppm and δ 6.97 ppm, respectively, integrating for two protons of the amino group. The

^{1}H-NMR spectrum of **196a** shows the presence of doublet at δ 6.56 ppm (d, *J* = 8.5 Hz) for H-3, doublet of doublets at δ 7.34 ppm (d, *J* = 8.5 Hz and 2.5 Hz) for H-4, and doublet due to long range coupling at δ 7.80 ppm (d, *J* = 2.5 Hz) for H-6. The ^{1}H-NMR spectrum of **197a**, on the other hand, is distinguished from that of **196a** by the presence of two sets of doublets at δ 7.83 ppm and δ 7.88 with coupling constant (*J*) value of 2.0 Hz, which correspond to H-4 and H-6, respectively. The hydroxyl proton of compounds **196b** and **197b** each resonates as a singlet at δ 12.1 ppm and δ 13.1 ppm, respectively. The ^{1}H-NMR spectrum of **196b** shows the presence of additional signals in the aromatic region at δ 6.87 ppm (d, *J* = 8.5 Hz), 7,53 ppm (dd, *J* = 2.5 and 8.5 Hz) and 7.81 ppm (d, *J* = 2.5 Hz) corresponding to H-3, H-4 and H-6, respectively. Incorporation of an iodine atom in compound **197b** was confirmed by the presence of a set of doublets at δ 7.83 ppm and δ 8.04 with coupling constant (*J*) value of 2.1 Hz and these signals were assigned to H-4 and H-6, respectively. The melting point values of compounds **196a** and **196b** were found to be comparable to the literature values (Table 1). Although the observed melting point value for compound **197b** was found to be slightly higher than the reported value, its spectroscopic data was found to be consistent with the assigned structure.



195a, **b** **196a**, **b** **197a**, **b**

Reagents and conditions: (i) PTB, DCM, RT 6 h (ii) NBS, AcOH, reflux 1.5; (iii) NIS, AcOH, RT, 2 h; (iv) NIS, AcOH, reflux, 2 h

Scheme 56: Sequential bromination and iodination of **195a** (X = NH) and **195b** (X = O).

Table 1: Substitution pattern, percentage yields and melting point values of **196**–**197.**

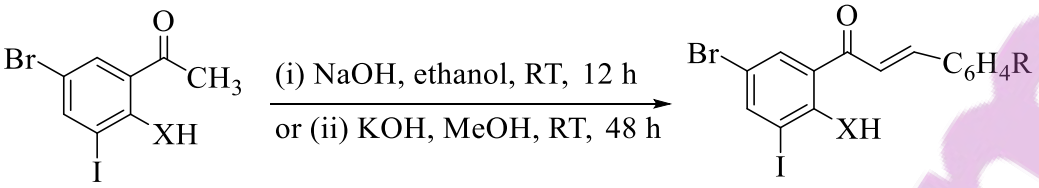
Compound	X	%Yield	m.p. °C (Lit.)
196a	NH	76	81 (83)[142]
196b	O	59	75 (73)[143]
197a	NH	74	97
197b	O	93	112 (105)[146]

Compounds **197a** and **197b** were, in turn, subjected to further transformation via Claisen-Schmidt aldol condensation with benzaldehyde derivatives as described in the next section.

2.1.2 Preparation of the 2-amino- (198a–d) and 2-hydroxy-5-bromo-3-iodochalcones (198e–i)

Numerous methods have been reported in the literature for the synthesis of chalcones and these include the Aldol condensation,[100] Claisen-Schmidt condensation,[101] Wittig reaction,[54] Friedel-Crafts acylation with cinnamoyl chloride,[54] The other methods include the Photo-Fries rearrangement of phenyl cinnamates,[54] Suzuki cross-coupling reaction of benzoyl chloride and arylboronic acid [102] and the Heck cross-coupling reaction of arylhalide and unsaturated ketone.[103] The acid or base mediated Claisen-Schmidt aldol condensation is the most widely used method for the synthesis of chalcones.[101] The method involves relatively cheaper reagents and mild reaction conditions accompanied by aqueous work-up and recrystallization of the products without the need for tedious column chromatographic separation. Consequently, in this investigation, we opted for the Claisen-Schmidt aldol condensation of 2′-amino-5′-bromo-3′-iodoacetophenone **197a** and **197b** with benzaldehyde derivatives. Compound **197a** was reacted with benzaldehyde derivatives in the presence of potassium hydroxide in ethanol at RT for 6 h

(Scheme 57) and we isolated by aqueous work-up and recrystallization the corresponding 2-amino-5-bromo-3-iodochalcones **198a–d** (X = NH) in 81–93% yield (Table 2). 5-Bromo-2-hydroxy-3-iodoacetophenone **197b**, on the other hand, was condensed with benzaldehyde derivatives in the presence of aqueous sodium hydroxide in methanol at RT for 48 h to afford the corresponding 2-hydroxychalcones **198e–i** (X = O) (Scheme 57; Table 2). The prepared chalcones were characterized using a combination of NMR (^{1}H & ^{13}C), IR, and mass spectroscopic techniques. The ^{1}H NMR spectra of the chalcones are easily distinguished from those of the corresponding substrates by the absence of the intense singlet for CH_3 in the aliphatic region and the presence of an increased number of signals in the aromatic region along with a set of doublets for the the vinylic protons with coupling constant values (J_{trans}) in the region J = 15.5–16.0 Hz. These confirm the *E*-geometry of the olefinic moiety in analogy with the literature assignment for the analogous derivatives.[104-105] The ^{1}H NMR spectra of products **198e–i** also revealed the presence of increased number of signals in the aromatic region with a singlet for the phenolic proton resonating around δ 13.00 ppm. This singlet resonates significantly downfield presumably because of hydrogen bonding with the adjacent carbonyl group. Their olefinic nature and *E*-geometry were also confirmed by the presence of the set of doublets around δ 7.48 (α-H) and 7.89 ppm (β-H) with coupling constant values J_{trans} = 15.5–16.0 Hz, respectively. Their IR spectra, on the other hand, reveal the presence of intense absorption bands ν_{max} 1634 cm^{-1} and 3676 cm^{-1}, which correspond to C=O and OH groups, respectively. The mass spectra of compounds **198a–i** showed peaks corresponding to their molecular formula.



197a (X = NH) **198a–d**

197b (X = O) **198e–i**

Scheme 57: Condensation of **197** (X = NH_2 or OH) with benzaldehyde derivatives.

Table 2: Substitution pattern, percentage yields and melting points of **198a–i**

Compound	X	R	% Yield	Mp °C
198a	NH	H	81	103–105
198b	NH	F	84	146–149
198c	NH	Cl	91	142–144
198d	NH	OCH_3	93	139–142
198e	O	H	72	152–154
198f	O	F	80	177–179
198g	O	Cl	80	184–186
198h	O	OCH_3	69	173–175
198i	O	OCF_3	74	106–107

The presence of fluorine atom in a molecule is easily confirmed by the ^{1}H NMR and ^{13}C NMR spectroscopic methods. The presence of a *para*-fluorophenyl group in compound **198f**, was confirmed by the presence of a set of triplets of doubles at δ_H 7.15 with and at δ_H 7.69 with coupling constant values J_{HH} = 8.5 Hz and J_{HF} = 5.3 Hz for H-2',6'; and J_{HH} = 8.5 Hz and J_{HF} = 9.7 Hz for H-3',5'. The ^{13}C NMR spectrum, on the othe hand, shows the presence of sets of doublets with different coupling constant values reflecting the proximity or distance from F. The

carbon-13 signals of the 4-fluorophenyl ring of **198f** resonate as doublets at δ 115.9, 129.3, 134.3 and 162.7 ppm with coupling constant values $^{2}J_{CF}$ 21.4 Hz (C-3′, 5′), $^{3}J_{CF}$ 8.0 Hz (C-2′, 6′), $^{4}J_{CF}$ 3.3 Hz (C-1′) and $^{1}J_{CF}$ 250.2 Hz (C-4′) respectively (Figure 14).

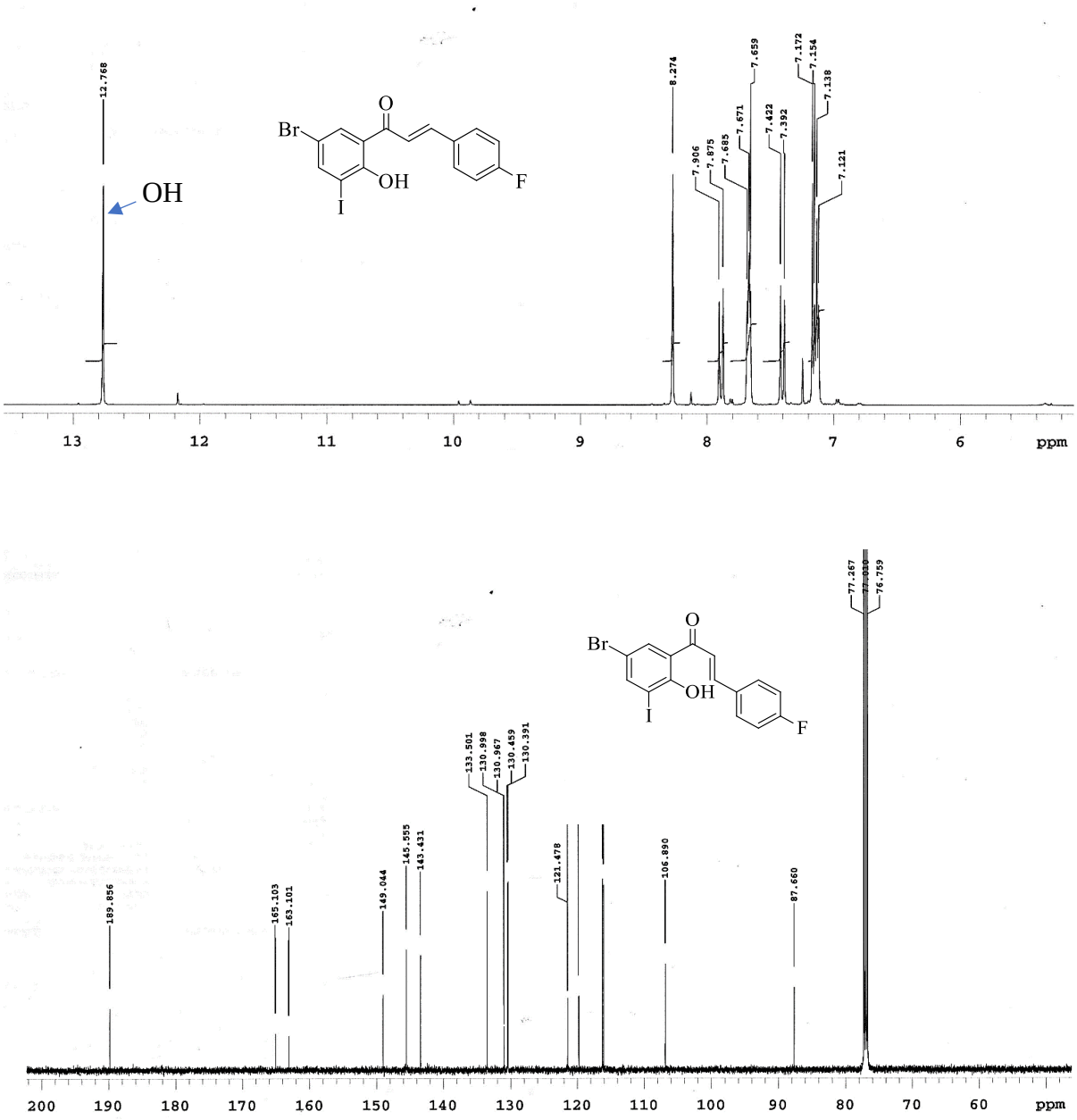


Figure 14: ^{1}H- and ^{13}C-NMR spectra of **198f** in $CDCl_3$ at 500 and 125 MHz, respectively.

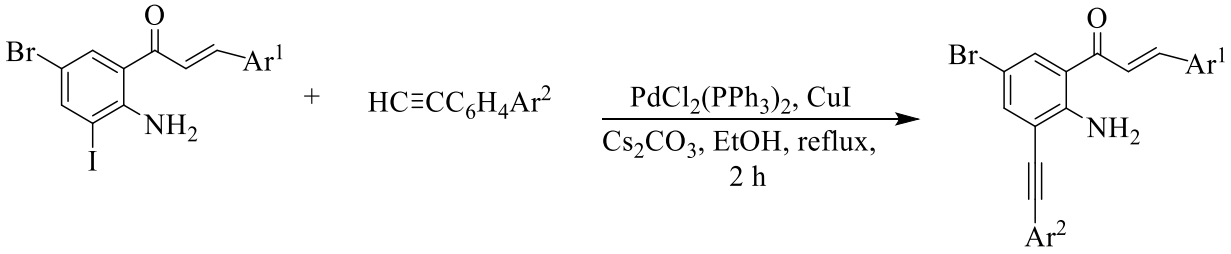
2.2 Design and synthesis of the angular indole- and benzofuran-appended chalcones

The structures of the indole-chalcones and the benzofuran-chalcones described in the literature have the unsaturated carbonyl arm attached to the C-2 or C-3 position of the five-membered ring. Those were generally accessible via the Claisen-Schmidt condensation of the 2- or 3-carbonyl substituted indole or benzofurans with benzaldehyde or acetophenone derivatives.[116-119] The isomeric benzo[*c*]indole/furan–chalcones, on the other hand, have not been prepared before and such angular hybrids do not feature in the recent review by Zhuang *et al.* on chalcones and chalcone hybrids of medicinal importance.[54] This encouraged us to employ the 3,5-dihalogenated 2-amino- **198a**–**d** and the 2-hydroxychalcones **198e**–**i** as scaffolds to append an indole or benzofuran moiety, respectively.

2.2.1 Sonogashira cross-coupling of the 2-amino-5-bromo-3-iodochalcones 198a–d

The *N*-unsubstituted 2-alkynylaniline derivatives undergo heteroannulation with ease,[68,71] however, some derivatives have also been found to fail to react further to afford indole derivatives. In such cases, the amino group of the 2-halogenoanilines is usually activated as the *N*-acetyl,[71] *N*-formyl[69] or *N*-mesyl/tosyl[64] to promote direct one-pot Pd(II) or CuI catalysed Sonogashira cross-coupling and heteroannulation to yield the indole derivatives with either retention or extrusion of the activating group. The halogenated 2-aminochalcones **198a**–**d** were subjected to palladium catalysed Sonogashira cross-coupling with aryl acetylenes **199** (1.2 equiv.) in the presence of $PdCl_2(PPh_3)_2$–CuI catalyst mixture and cesium carbonate as a base in ethanol under reflux for 2 h (Scheme 58). Aqueous work-up and purification by column chromatography on silica gel afforded the corresponding 3-alkynylated 2-amino-5-bromochalcones **200**a–f in 76-82% yield (Table 3) without traces of the indole derivative

detected in the reaction mixture or crude product. The observed selectivity of Csp^2–Csp bond formation through the Csp^2–I bond is a consequence of the relative Csp^2–halogen bond strengths (I < Br < Cl < F), which makes it possible to substitute the iodides in the presence of bromides or chlorides. The ^{1}H NMR spectra of compounds **200** still retained some of the characteristic features observed in the spectra of corresponding substrates, the difference being the presence of the arylalkynyl moiety which was confirmed by the increase in the number of proton signals in the aromatic region (Figure 15) and the presence of the acetylenic carbon signals at δ_C 88.7 and 96.7 ppm in their ^{13}C NMR spectra (Figure 15). Their alkynyl nature was further confirmed by the presence of the IR absorption band around ν_{max} 2201 cm^{-1}, whch correspond to the C≡C stretch.



198a–e **199** **200a–f**

Scheme 58: Sonogashira cross-coupling of **198a–f** with terminal acetylenes **199**.

Table 3: Substitution pattern, percentage yields and melting point values of **200a–f**.

Compound	R^1	R^2	% Yield	Mp °C
200a	4-H	4-H	76	106–108
200b	4-F	4-H	81	121–123
200c	4-Cl	4-H	71	110–113
200d	4-OMe	4-H	62	108–110
200e	4-Cl	4-OCF3	78	120–123
200f	4-OMe	4-OCF3	82	125–127

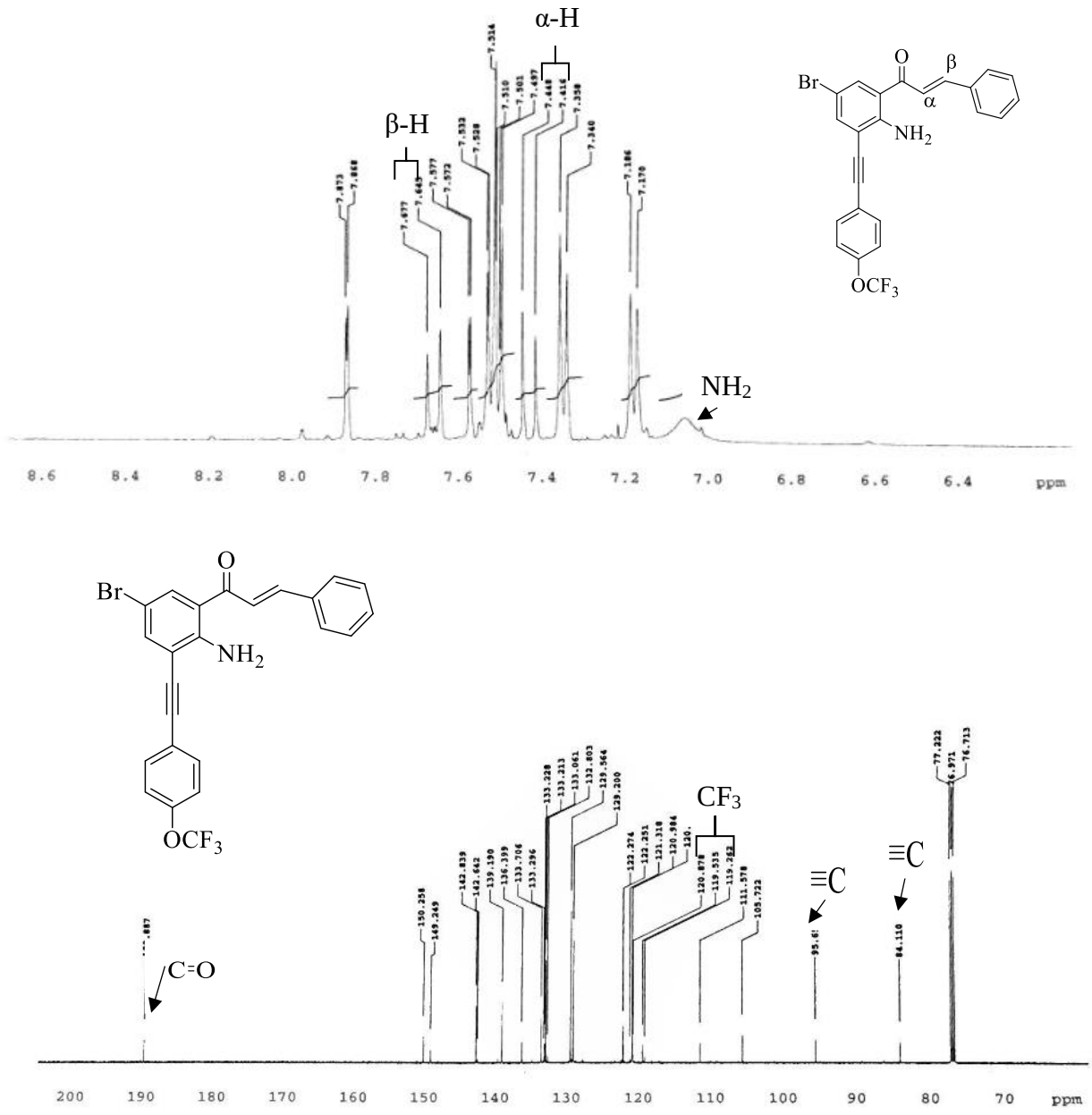
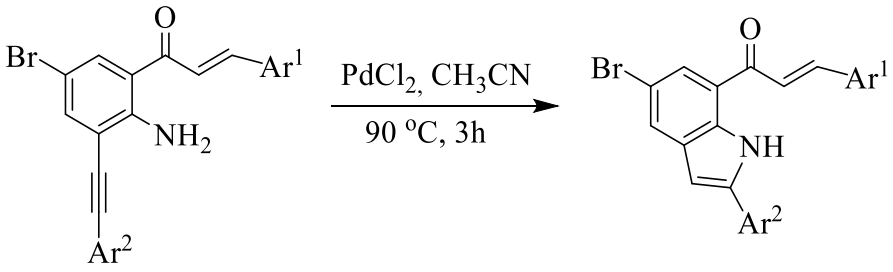


Figure 15: ^{1}H NMR spectrum of compound **200e** in $CDCl_3$ at 500 MHz

Alkynylated anilines in which the alkynyl group is tethered to the nucleophilic heteroatom are known to undergo heteroannulation with ease in the presence of metal or Lewis acid catalyst.[70] This heteroannulation strategy represents a versatile and efficient pathway to polynuclear compounds. The ortho-alkynylated 2-aminochalcones **200a**–**f** were, in turn, subjected to $PdCl_2$–mediated cycloisomerization in acetonitrile at 90 °C for 3 h (Scheme 59). The crude products

were passed through columns of silica gel to remove the catalyst and we isolated the corresponding novel indole-chalcones **201a–f** in 63–81% yield (Table 4). The ^{1}H NMR spectra of compounds **201** show the absence of the signal for NH_2, which is present in the spectra of the corresponding substrates (Figure 16). The spectra further revealed the presence of a singlet around δ 6.83 ppm corresponds to H-3 with the NH signal resonating around δ 11.00 ppm. The other set of doublets around δ 7.99 and 8.00 ppm with coupling constant value J = 1.5 Hz, on the other hand, correspond to the 4-H and 6-H, respectively (Figure 16). Their ^{13}C NMR spectra reveal the absence of the signals in the region δ 84.4-95.2 ppm attributed to the acetylenic carbons and the presence of signals around δ 103.2 and 114.4 ppm, which correspond to C-2 and C-3 as well as the resonance around δ 189.6 ppm for the carbonyl carbon. Moreover, their IR spectra lack the absorption bands corresponding to NH_2 and C≡C groups found in the spectra of the corresponding precursors, but showed the bands corresponding to the NH and C=O around ν_{max} 3411 and 1641 cm^{-1}, respectively.



200a–f **201a–f**

Scheme 59: Palladium chloride-mediated cyclization of **200a–f**.

Table 4: Substitution pattern, percentage yields and melting point values of **201a–f**.

Compound	R^1	R^2	% Yield	Mp °C
201a	4-H	4-H	75	197–199
201b	4-F	4-H	63	187–237
201c	4-Cl	4-H	71	184–186
201d	4-OMe	4-H	53	176–178
201e	4-Cl	4-OCF_3	63	252–254
201f	4-OMe	4-OCF_3	54	197–198

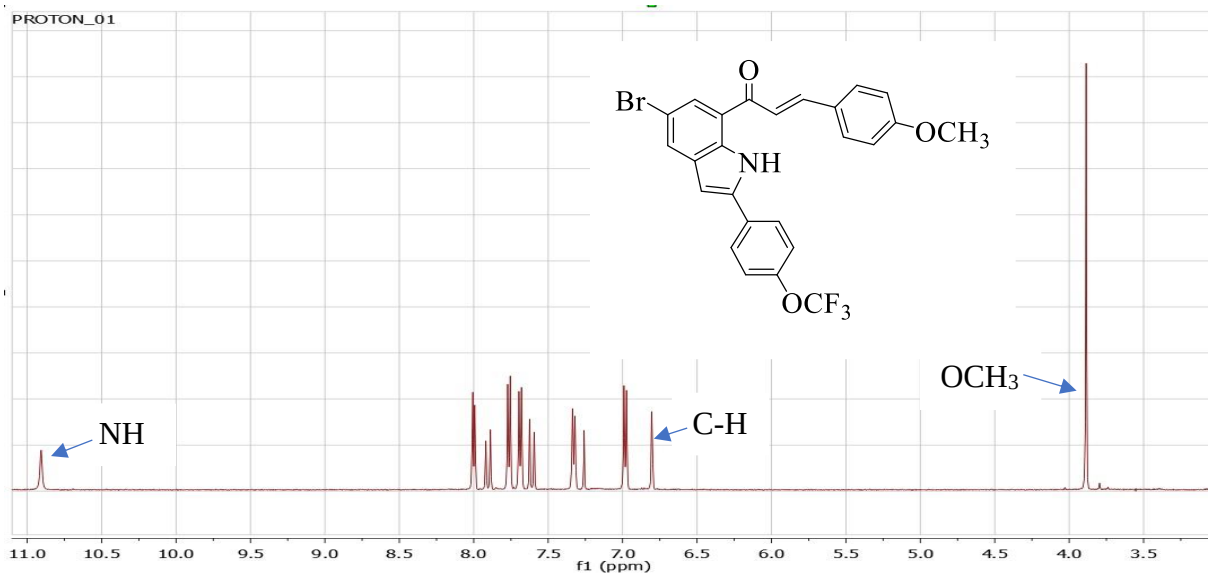


Figure 16: ^{1}H NMR spectrum of compound **201f** in $CDCl_3$ at 500 MHz.

The molecular ion regions of the high-resolution mass spectra (HR-MS) of the compounds **201** revealed the presence of the M+ and M+2, in the ratio of about 1:1, which are typical for molecules containing ^{79}Br and ^{81}Br isotopes (Figure 17).

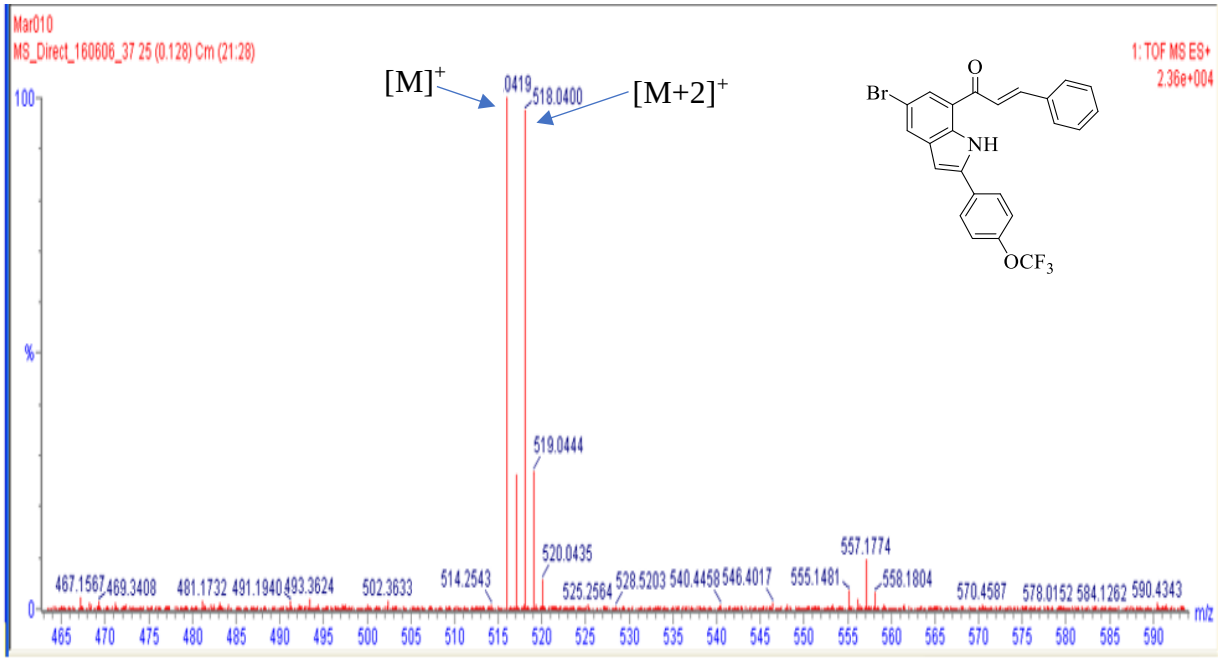


Figure 17: HR-MS of **201e** using positive electrospray ionisation time-of-flight mass spectrometry.

Crystals of quality suitable for X-ray diffraction were obtained for compound **201e** by slow evaporation of acetonitrile. The molecular structure of compounds **201** and the geometry about the C–C double bonds were distinctively confirmed by single crystal X-ray diffraction analysis (Figure 18). In the context of the X-ray analyses for this compound and other examples to follow, crystallographic numbering has been used in the text in place of regular systematic numbering. The crystal structure shows the existence of the α,β-unsaturated framework in *E* configuration with strong intramolecular hydrogen bonding between N-H of the indole ring and the carbonyl oxygen with N–H···O angle and H···O distance of 122° and 2.18 Å, respectively (Figures 18 and 19). Figure 19 shows stacking of the molecules in the unit cell with π-interactions between C11-C12 and C16-C17. The crystallographic data of compound **201e** is summarized in Table 5.

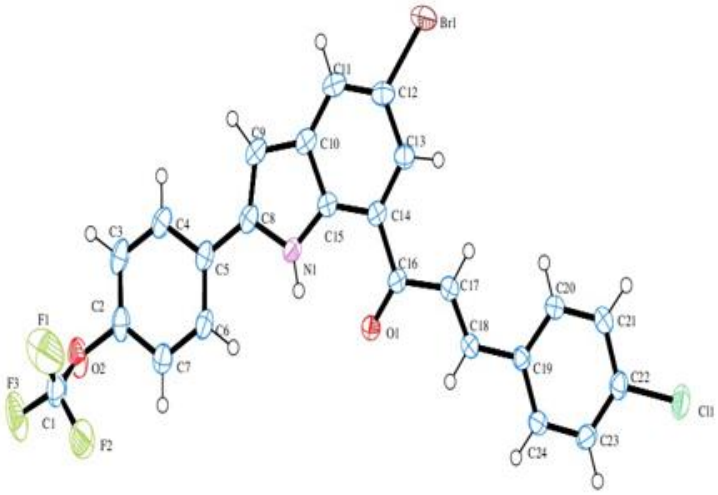


Figure 18: Oak Ridge Thermal Ellipsoid Plot **(**OTERP) diagram (50% probability level) of compound (**201e**). H atoms are shown as small spheres of arbitrary size and for clarity they are not labelled.

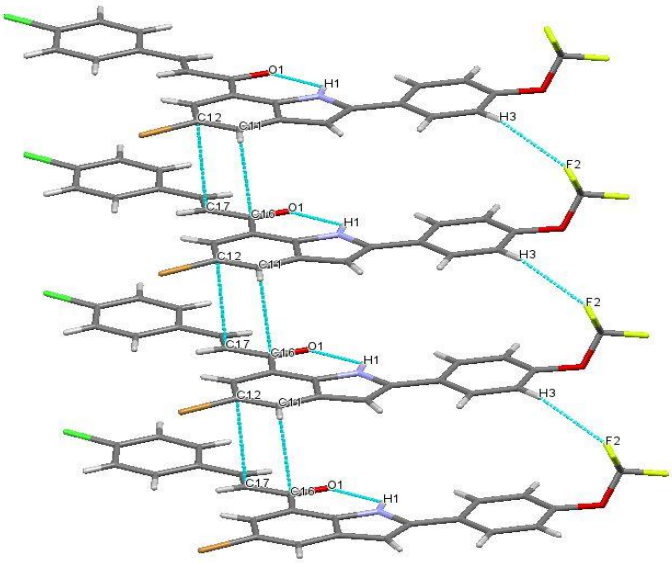


Figure 19: Packing diagram of compound **201e**.

Table 5: Crystallographic data of compound **201e**.

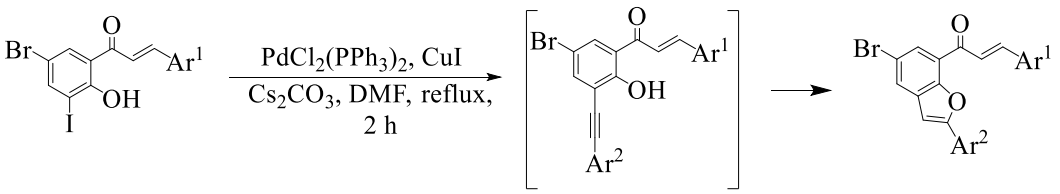
Formula	$C_{24}H_{14}BrClF_3NO_2$
M_r	520.72
Temperature/K	173(2) K
Wavelength/Å	0.71073
Crystal size/mm^3	0.1 x 0.1 x 0.4
Crystal system	Monoclinic
Space group	P2(1)/n
a/Å	17.1066 (17)
b/Å	5.4615 (4)
c/Å	22.279(2)
α/°	90
β/°	101.447(4)
γ/°	90
V/$Å^3$	2040.1(3)
Z	4
ρ (calcd)/Mg m^{-3}	1.695
μ/mm^{-1}	2.196
F(000)	1040
Θ Range for data collection/°	3.26 to 28.00°
Reflections collected	36165
No. of unique data [R(int)]	4921 [0.0527]
No. data with $I \geq 2\sigma(I)$	4921
Final R($I \geq 2\sigma(I)$)	0.0334
Final wR_2 (all data)	0.0835
CCDC deposition number	1490129

The Sonogashira cross-coupling reaction conditions were extended to the analogous 2-hydroxychalcones as described in the next section.

2.2.2 Sonogashira cross-coupling of the (*E*)-2-hydroxy-5-bromo-3-iodochalcones 198e–i

The 2-alkyl/aryl–substituted benzofurans were previously synthesized *via* palladium catalyzed cross coupling-heteroannulation of the 2-bromo/iodophenol derivatives with terminal acetylenes.[84-88] It has however been observed before that $PdCl_2(PPh_3)_2$ was a more efficient catalyst than $Pd(PPh_3)_4$ giving better yields and reproducibility.[86] We subjected the 5-bromo-2-hydroxy-3-iodochalcones **198e–i** to Sonogashira cross-coupling with terminal acetylenes in the presence of $PdCl_2(PPh_3)_2$-CuI catalyst complex in cesium carbonate under reflux and inert atmosphere for 2 h. Column chromatography on silica gel afforded compounds characterized using a combination of spectroscopic techniques as the corresponding benzofuran-chalcones **203a–y** (Scheme 60). The ortho-alkynylated phenol intermediate **202** implicated in the reaction mechanism was not detected by thin layer chromatography or isolated by silica gel column chromatography. This observation is attributed to the increased acidity of the hydroxyl proton when compared to the amino group of **201.** In our view, the cesium carbonate generated phenoxide anion would attack the activated metal coordinated C≡C bond to promote tandem 5-endo-dig cyclization to afford benzofuran-appended chalcones **203a–y**. The ^{1}H-NMR spectra of compounds **203a–y** (Figure 20) revealed the absence of the signal for OH and the presence of an increased number of signals in the aromatic region δ 7.00–7.50 ppm with a singlet around δ 7.07 ppm for H-3. A set of doublets in the region δ 7.74 and 7.80 ppm with coupling constant (*J*) values of about 16.0 Hz are characteristic of the trans geometry for the chalcone framework. The signal of the β-H resonates at a lower field than that of the α-H due to π-electron delocalization towards the carbonyl group. The ^{13}C NMR spectra of compound **203f** for an example, show the presence of doublets due to the C-F interaction of the 4-fluorophenyl ring with the resonances at about δ 116.3, 130.5, 131.3 and 164.2 ppm corresponding to $^1J_{CF}$ 239.0 Hz (C-4′), $^2J_{CF}$ 21.8 Hz (C-3′ & 5′), $^3J_{CF}$ 8.5 Hz (C-2′ & 6′) and $^4J_{CF}$ 2.9 Hz (C-1′), respectively (Figure 20). The

resonance for the C=O appears at about δ 186.4 ppm. The accurately calculated *m/z* values for the molecular ions reveal the presence of the M+ and M+2 peaks in comparable intensities typical of molecules containing ^{79}Br and ^{81}Br isotopes. Their presence confirmed cross-coupling through the most reactive Csp^2–I bond.



198e–i **202a–y** **203a–y**

Scheme 60: Sonogashira cross-coupling of compounds **198e–i** with terminal acetylenes.

Table 6: Substitution pattern, percentage yields and melting point values for **203a–y**.

Compound	Ar^1	Ar^2	%Yield of 203	Mp °C
203a	C_6H_5-	C_6H_5-	66	197–195
203b	4-FC_6H_4-	C_6H_5-	79	220–223
203c	4-ClC_6H_4-	C_6H_5-	78	242–245
203d	4-$MeOC_6H_4$-	C_6H_5-	72	206–208
203e	4-$CF_3OC_6H_4$-	C_6H_5-	67	177–178
203f	C_6H_5-	4-FC_6H_4-	70	224–226
203g	4-FC_6H_4-	4-FC_6H_4-	76	239–242
203h	4-ClC_6H_4-	4-FC_6H_4-	77	231–233
203i	4-$MeOC_6H_4$-	4-FC_6H_4-	73	252–254
203j	4-$CF_3OC_6H_4$-	4-FC_6H_4-	64	203–204
203k	C_6H_5-	3-FC_6H_4-	70	243–245
203l	4-FC_6H_4-	3-FC_6H_4-	77	266–267
203m	4-ClC_6H_4-	3-FC_6H_4-	68	234–235

Table 6 continues

203n	4-$MeOC_6H_4$-	3-FC_6H_4-	73	221–222
203o	4-$CF_3OC_6H_4$-	3-FC_6H_4-	87	186–187
203p	C_6H_5-	3-ClC_6H_4-	75	218–219
203q	4-FC_6H_4-	3-ClC_6H_4	69	232–233
203r	4-ClC_6H_4-	3-ClC_6H_4-	77	257–258
203s	4-$MeOC_6H_4$-	3-ClC_6H_4	71	214–215
203t	4-$CF_3OC_6H_4$-	3-ClC_6H_4-	71	196–197
203u	C_6H_5-	4-$CH_3OC_6H_4$-	72	255–256
203v	4-FC_6H_4-	4-$CH_3OC_6H_4$-	82	241–242
203w	4-ClC_6H_4-	4-$CH_3OC_6H_4$-	79	209–210
203x	4-$MeOC_6H_4$-	4-$CH_3OC_6H_4$-	69	216–217
203y	4-$CF_3OC_6H_4$-	4-$CH_3OC_6H_4$-	67	187–188

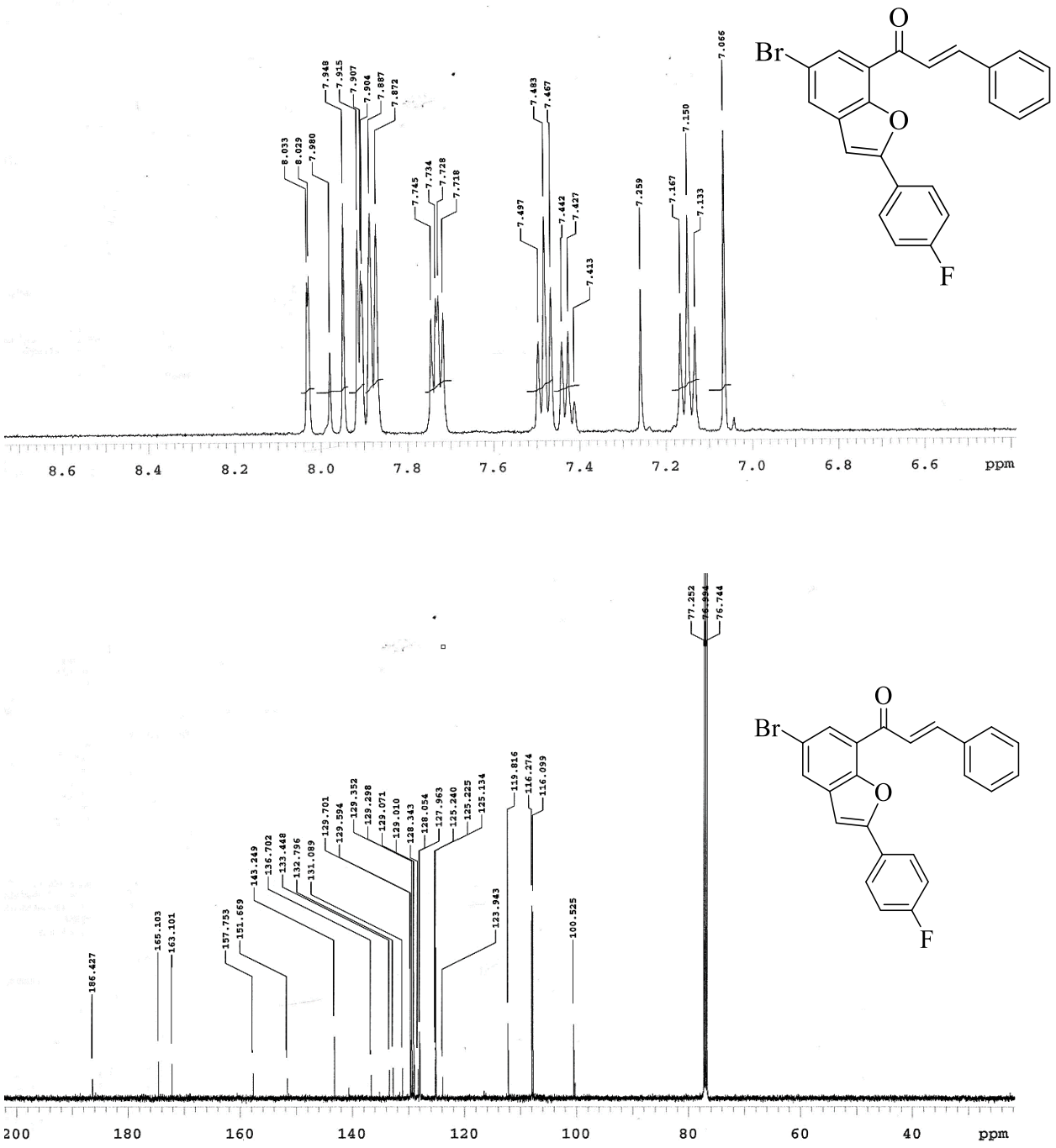


Figure 20: ^{1}H- and ^{13}C-NMR spectra of **203f** in $CDCl_3$ at 500 and 125 MHz, respectively.

The structure of these compounds and the *E*-geometry around the olefinic framework were distinctly confirmed by single crystal X-ray diffraction (XRD) analysis of compound **203a** (Figure 21). Compound **203a** crystallizes in the $P2_12_12_1$ space group with each asymmetric unit containing one molecule of **203a**. In the asymmetric unit, there is intramolecular hydrogen

bonding between the oxygen acceptor (O1) and the α- hydrogen bond donor [d(C(16)-H(16)···O(1) = 2.24 Å] forming an $S_1^1(6)$ ring (Figures 22). The molecule packs into a one-dimensional ribbon via bifurcated hydrogen bonding from the oxygen acceptor (O2) and the C–H···O hydrogen bond donors (H2 and H4). The crystallographic data of compound **203a** is summarized in Table7.

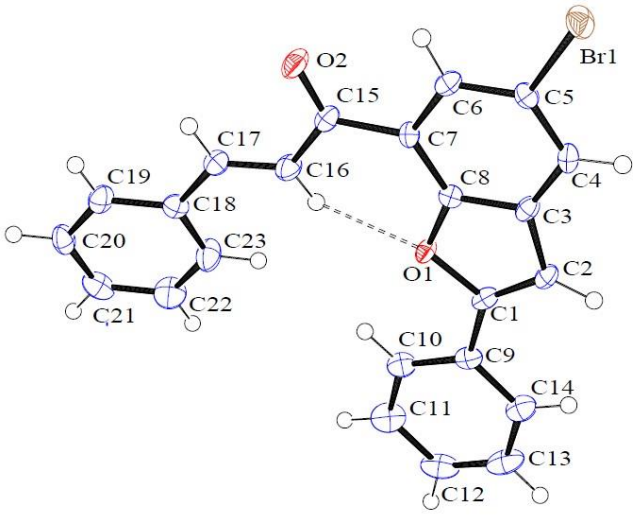


Figure 21: Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagram of **203a**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii

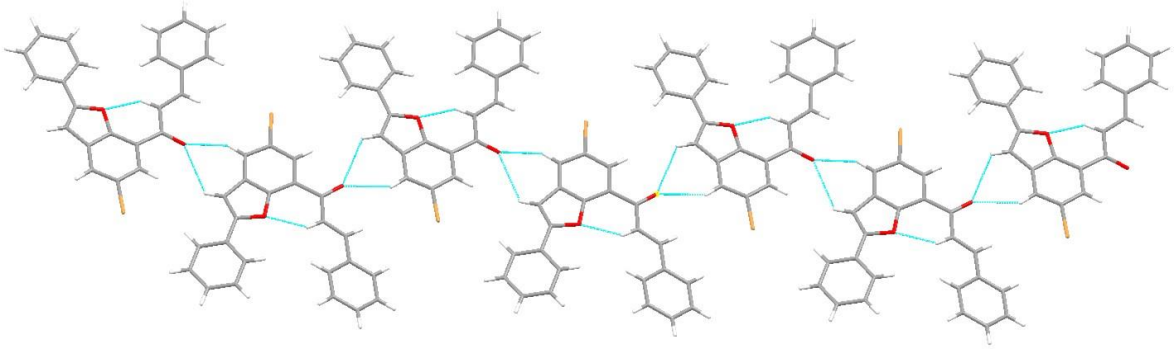


Figure 22: Packing diagram of **203a** showing the 1D ribbon

Table 7: Crystallographic data for compound **203a**.

Formula	$C_{23}H_{15}BrO_2$
M_r	403.26
Temperature/K	173(2)
Wavelength/Å	0.71073
Crystal size/mm^3	0.3 x 0.1x 0.040
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	4.7121(7)
b/Å	15.719(2)
c/Å	23.152(3)
α/°	90
β/°	90
γ/°	90
V/Å^3	1714.9(4)
Z	4
ρ (calcd)/Mg m^{-3}	1.562
μ/mm^{-1}	2.412
F(000)	816
Θ Range for data collection/°	2.940 to 25.496
Reflections collected	19664
No. of unique data [R(int)]	3190 [0.0721]
No. data with $I \geq 2\sigma(I)$	2641
Final R($I \geq 2\sigma(I)$)	0.0299
Final wR_2 (all data)	0.0697
CCDC deposition number	1561911

2.3 Transformation of the indole-chalcones and benzofuran-chalcone hybrids

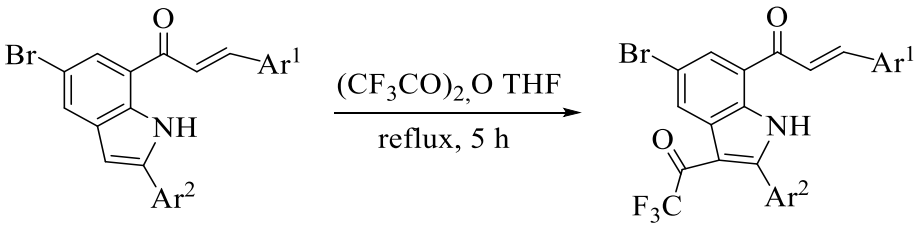
The 3-acetyl moiety on the indole framework is an important hydrogen-bond acceptor for interaction with biological receptors.[149] As a result, acylation of the C-3 position of the indole moiety has become one of the most important reactions in indole chemistry because of the

reactivity and biological activities of the resultant 3-acylated indoles. The electron-withdrawing effect of -CF_3, on the other hand, has been found to increase the lipophilicity, metabolic stability and activity profile compared to that of the methyl analogues.[150] Trifluoroacetylation of indole moiety is a well-established procedure,[151] this method has not been applied to the indole-chalcone derivatives. Indole-chalcones **201** have ambident nucleophilic and electrophilic characters. The nucleophilic character is distributed at the C-3 position and at the N-1 position of the indole nucleus. The electrophilic character of the α,β-unsaturated carbonyl arm is distributed at the carbonyl and β-carbons. We took advantage of the ambident nucleophilic character of the indole moiety and decided to incorporate a trifluoroacetyl group on indole-chalcones as described in the next section.

2.3.1 Trifluoroacetic acid-promoted C-3 trifluoroacetylation of the indolechalcones

Friedel-Crafts fluoroacetylation of indoles was previously achieved with fluorinated acetic acids (3 equiv.) in dichloroethane at 100 °C in the absence of catalyst or additive to afford novel fluoromethyl indol-3-yl ketones.[152] Based on this literature precedents, we decided to incorporate a trifluoroacetyl group at the C-3 position of the indole moiety of compounds **201a–f**. Compounds **201a**–**f** were subjected to trifluoroacetic anhydride (1.2 equiv.) in THF under reflux and we isolated after 5 h by aqueous work-up and recrystallization the corresponding 3-trifluoroacetylindole-chalcones **204a**–**f**, exclusively (Scheme 61). The ^{1}H NMR spectra of compounds **204** show the absence of the signal for H-3 (Figure 23). Their ^{19}F NMR spectra reveal the presence of a signal around δ -72 ppm corresponging to the three fluorine atoms. The ^{13}C NMR spectra on the other hand, revealed the presence of two set of quartets in the regions δ 120–121 ppm and δ 176–177 ppm with coupling constant values $^{1}J_{CF}$ = 288.0 Hz and $^{2}J_{CF}$ = 37.0

Hz. The set of quartets corresponds to the trifluoromethyl (CF_3) group and the adjacent carbonyl carbon, respectively.



201a–f **204a–f**

Scheme 61: TFAA-promoted C-3 acetylation of compounds **204a**–**f**.

Table 8: Substitution pattern, percentage yields and melting point values for **204a**–**f**.

Compound	Ar_1	Ar_2	% Yield	Mp °C
204a	C_6H_5-	C_6H_5-	88	195–197
204b	4-FC_6H_4-	C_6H_5-	76	164–166
204c	4-ClC_6H_4-	C_6H_5-	91	180–183
204d	4-$MeOC_6H_4$-	C_6H_5-	62	173–175
204e	4-ClC_6H_4-	4-$CF_3OC_6H_4$-	90	266–269
204f	4-$MeOC_6H_4$-	4-$CF_3OC_6H_4$-	88	200–203

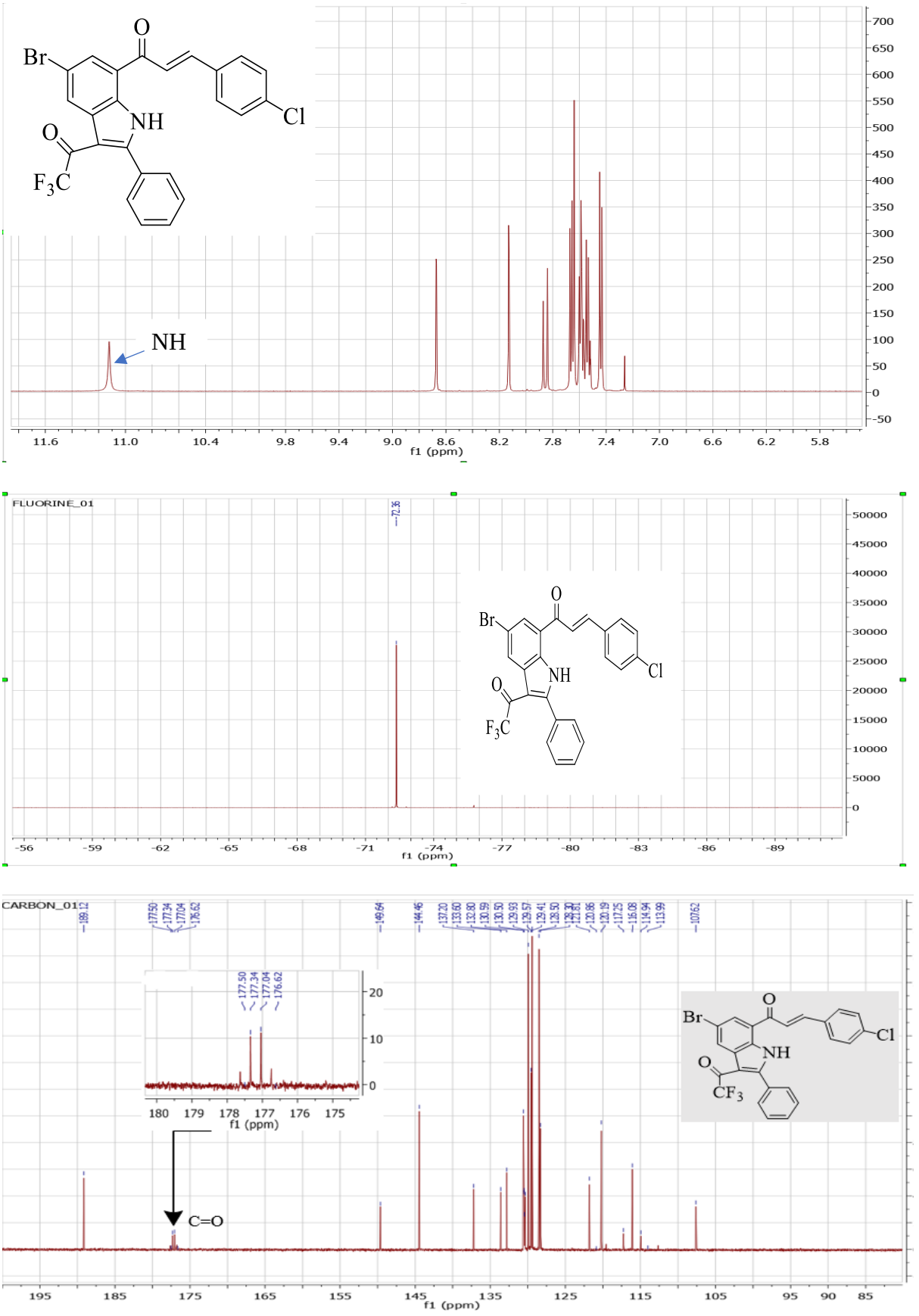


Figure 23: ^{1}H-, ^{19}F- and ^{13}C-NMR spectra of **204d** in $CDCl_3$ at 500 and 125 MHz, respectively.

Incorporation of the trifluoroacetyl group onto the indole-chalcone framework and the existence of the α,β-unsaturated moiety in *E* configuration were also confirmed by the X-ray crystal structure of compound **204e** obtained by recrystallization from toluene. The crystal studied of this compound shown in Figure 24 (CCDC 1490104) was found to exist in the asymmetric unit as an inversion twin. Inversion twins are usually observed for compounds with a chiral centre.[153] Twinning in the case of compound **204e** is presumably due to the presence of the prochiral group (-C(O)CF_3) as this phenonomemnon was not observed in the single X-ray cryustal structure of the corresponding chalcone precursor (refer to Figure 18 above). As shown in Figure 25, the crystal structure of **204e** packs as a 1-dimensional (1D) chain ribbon stabilized by the bromine hydrogen bonded network without any π-stacking interactions. The crystallographic data of compound **204e** is summarized in Table 9. The synthesis of novel 3-(2′,2′,2′-trifloroacetyl)indole-chalcones based on initial annulation of the indole ring onto the 1,3-diaryl-2-propen-1-one (chalcone) scaffolds have since been published.[154]

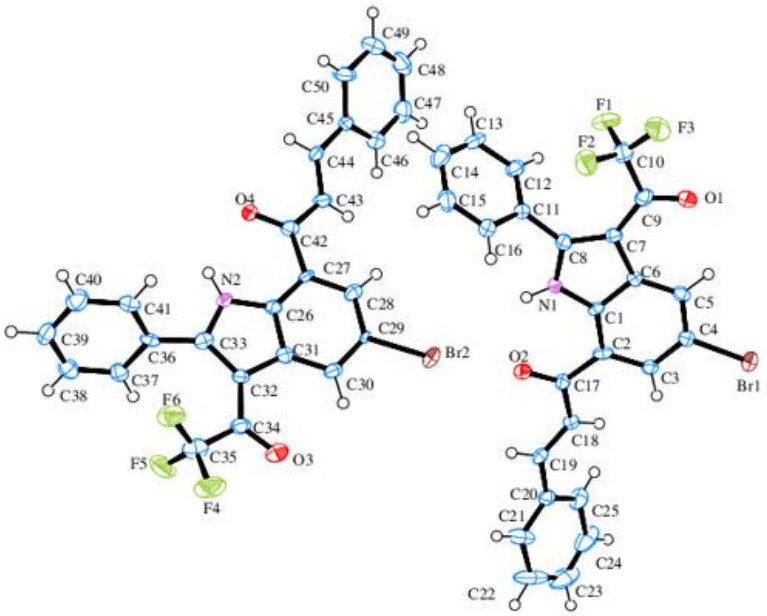


Figure 24: OTERP diagram (50% probability level) of compound **204e**

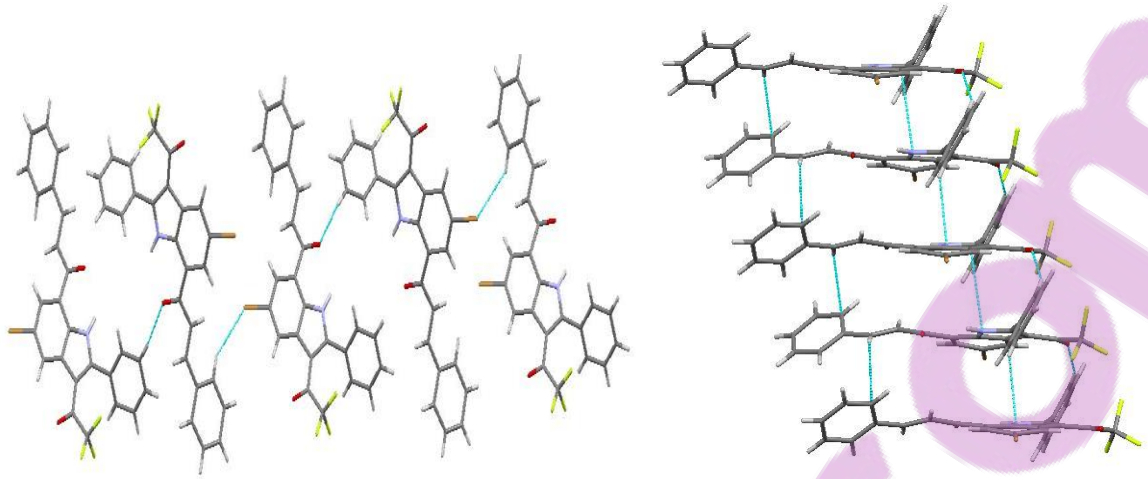


Figure 25: Packing diagram of compound **204e**

Table 9: Crystallographic data of compound **204e**.

Formula	$C_{25}H_{15}BrF_3NO_2$
M_r	498.29
Temperature/K	173(2)
Wavelength/Å	0.71073
Crystal size/mm^3	0.8 x 0.1 x 0.03
Crystal system	Monoclinic
Space group	P 21/c
a/Å	18.034(3)
b/Å	7.8136(15)
c/Å	30.308(6)
α/°	90
β/°	105.298(4)
γ/°	90
V/Å^3	4119.3(13)
Z	8
ρ (calcd)/Mg m^{-3}	1.607
μ/mm^{-1}	2.046
F(000)	2000
Θ Range for data collection/°	2.956 to 25.498
Reflections collected	31860
No. of unique data [R(int)]	7788 [0.1440]

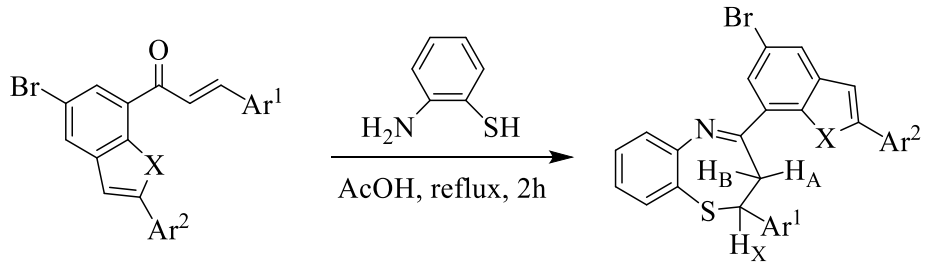
Table 9 continues	
No. data with $I \geq 2\sigma(I)$	2236
Final R($I \geq 2\sigma(I)$)	0.0832
Final wR_2 (all data)	0.2140
CCDC deposition number	1490104

Compounds **201** and **203** contain the ambident electrophilic α,β-unsaturated carbonyl moiety (carbonyl carbon *vs* β-carbon), which has previously been shown to facilitate 1,2-addition and/ or conjugate addition with nucleophilic reagents. The reactions of chalcone moiety with binucleophilic reagents, for example, afford novel heterocyclic compounds with various biological properties. The reaction of chalcones with 2-aminothiophenol, for example, has previously been found to afford benzothiazepines with anticonvulsant activities.[126] Inspired by the biological properties of the 1,5-benzothiazepines, we decided to append the 1,5-benzothiazepine moiety onto the chalcone arm of the benzofuran-chalcones and indole-chalcones as described in the next section.

2.3.2 Synthesis of benzofuran-appended benzothiezepines

The non-conventional methods for the synthesis of benzothiazepines make use of transition metal-mediated coupling-isomerization sequence of an electron poor aryl/heteroaryl halide and a propargyl alcohol derivative followed by a cyclocondensation with 2-amino-, 2-hydroxy-, or 2-mercaptoanilines.[126-127] Michael addition and further cyclocondensation reaction of chalcones with 2-aminothiophenol was previously accomplished in refluxing ethanol in the presence of glacial acetic acid as a catalyst to afford benzothiazepines.[126] We adapted this literature method and subjected the Indole–chalcones **201a**–**c** and indole-chalcones **203a**–**d** to 2-aminothiophenol as a binucleophilic reagent in acidic medium to afford the corresponding 2,3-dihydrobenzo[*b*][1,4]thiazepine–appended indoles **205a**–**c** or -benzofurans **205d**–**g**, respectively

(Scheme 62). The structures of the synthesized compounds were characterized based on a combination of ^{1}HNMR, ^{13}C-NMR, IR and high-resolution mass spectral data. The aliphatic region of the ^{1}H NMR spectra of these compounds represents an ABX system with the two diastereotopic protons of the methylene (CH_2) group and the methine (CH) proton of the dihydrobenzothiazepine ring resonating as three set of doublets of doublet (dd) around δ 3.18, 3.82 and 5.57 ppm with coupling constant (*J*) values of 12.5, 13.0 and 4.5 Hz



201a–**c** (X=NH) **205a**–**c**

203a–**d** (X=O) **205d**–**g**

Scheme 62: Synthesis of benzothiezapines **205a**–**c** and **205d**–**g**.

Table 10: Substitution pattern and percentage yields of compounds **205a**–**g**

Compound	X	Ar^1	Ar^2	%Yield
205a	NH	C_6H_5-	4-FC_6H_4-	92
205b	NH	4-FC_6H_4-	4-FC_6H_4-	90
205c	NH	3-FC_6H_4-	4-FC_6H_4-	90
205d	O	C_6H_5-	C_6H_5-	86
205e	O	4-FC_6H_4-	C_6H_5-	79
205f	O	3-ClC_6H_4-	C_6H_5-	82
205g	O	4-$MeOC_6H_4$-	4-$OCH_3C_6H_4$-	78

We performed through-space correlation 2D selective nuclear overhauser effect spectroscopy (NOESY) experiment to be able to assign the set of peaks to specific aliphatic protons (Figure

26). The residual signal (B) can be well explained by strong geminal coupling between H_A and H_B ($J_{gem/AM}$ = 13.0 Hz) and exhibit strong dipole interaction. Signal (A) corresponds to the real NOESY resulting from *cis* (gauche) orientated H_A and H_B and H_X ($J_{trans/BX}$ = 12.5 Hz). The smallest coupling constant value $J_{guache/AX}$ = 4.5 Hz is due to the trans oriented H_A and H_X. The signals for the non-equivalent methylene protons (H_A and H_B) resonate at different frequencies and the signal for H_A is more downfield presumably due to hydrogen bond interaction with O or NH. In ^{13}C-NMR spectra compounds **205** showed a signal at about δ 37.4, 43.2 and 161.8 ppm due to C-3, C-2 and C-4 carbons of the benzothiazepine ring. The IR spectra showed absorption bands around 1606, 665 and 862 cm^{-1} corresponding to C=N, C–S and C–Br bond stretches, respectively.

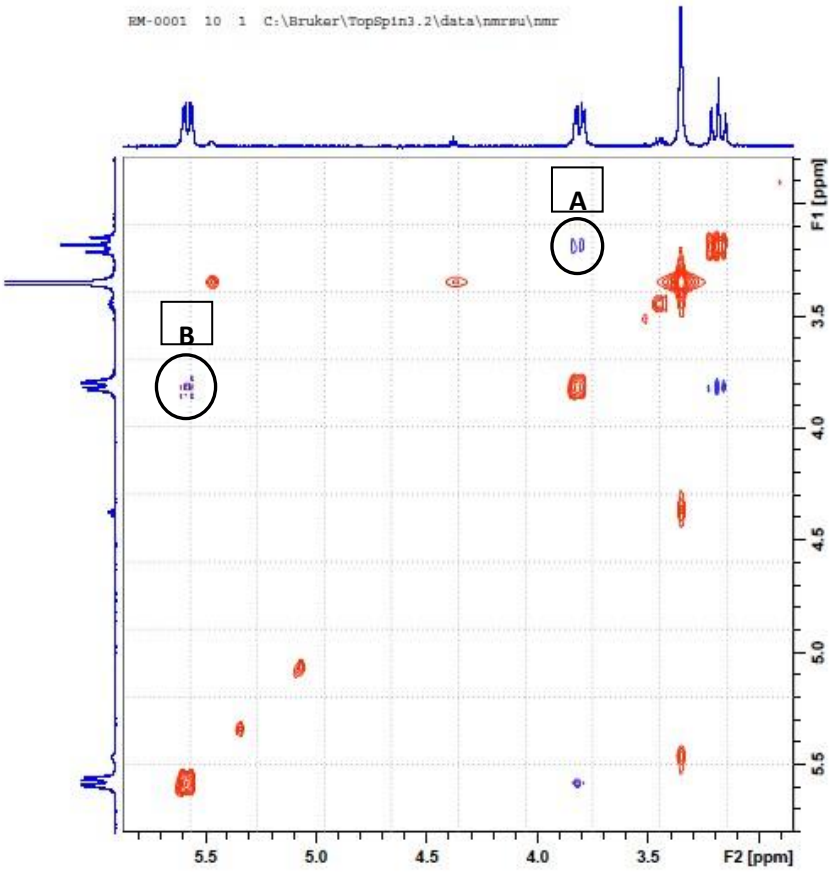


Figure 26: NOESY spectrum of the aliphatic region of compound **205a**

The optimized structure of **205f** is shown in Figure 27 below was obtained by the density functional theory (DFT) method using hybrid functional Becke's three parameter nonlocal exchange functional with the Lee-Yang-Parr correlation function (B3LYP) using the 6-311G basis set. Some of the optimized parameters, namely, the bond lengths, bond angles and torsion angles are given in Table 11. Density functional theory at the B3YLYP level revealed that the 7-membered ring is non-planar with hydrogen bonding interaction between oxygen and H_A (Figure 27). This interaction may account for the observed significant downfield shift of the resonance corresponding to this proton in the ^{1}H NMR spectra of these compounds (refer to Figure 26 above). The dihedral angles of the three protons of the AMX system are 179.0° and 62.6°, which represent a staggered conformation as confirmed by the ^{1}H NMR spectral data.

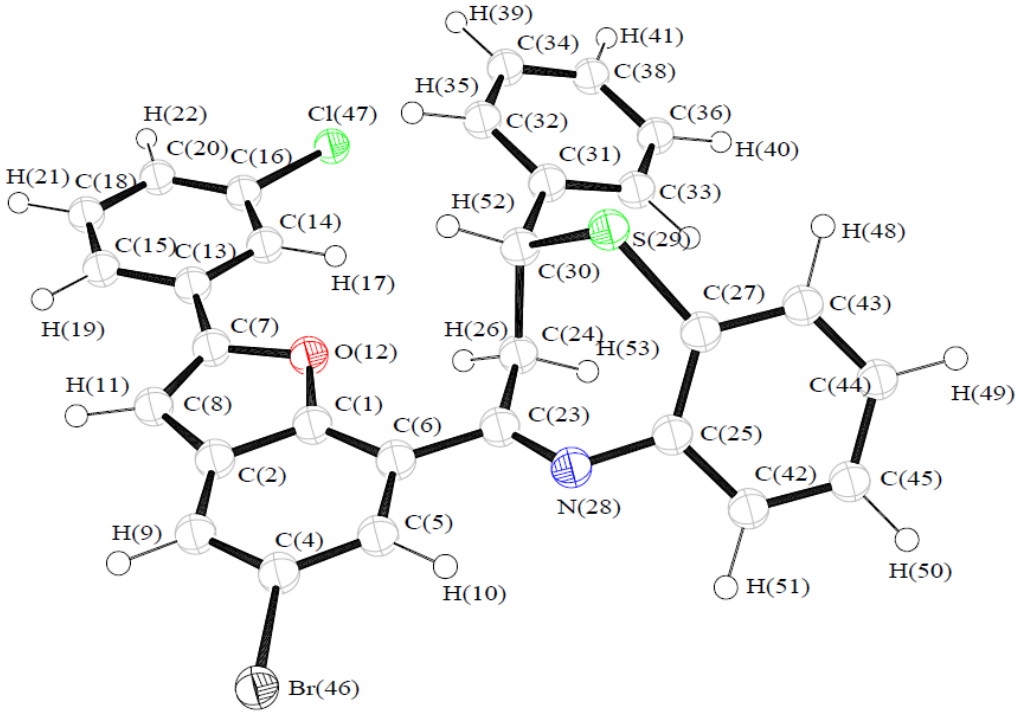
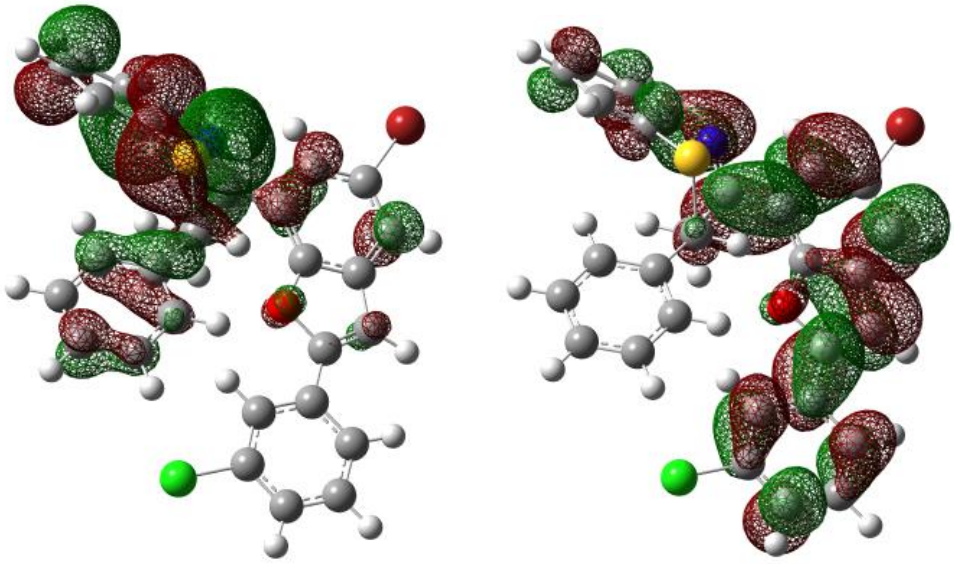


Figure 27: Optimized structure of **205f** from DFT calculations.

Table 11: Selected theoretical bond lengths (Å) and angles (°) of **205f**.

Geometric parameters	
Bond lengths (Å)	
C(1)-C(6)	1.398
C(1)-O(12)	1.401
C(27)-S(29)	1.841
C(7)-O(12)	1.423
C(23)-N(28)	1.292
C(25)-N(28)	1.407
C(27)-S(29)	1.841
C(30)-S(29)	1.934
C(30)-C(24)	1.545
C(34)-C(38)	1.394
Bond angles (°)	
C(6)-C(1)-O(12)	128.5
O(12)-C(7)-C(13)	117.2
N(28)-C(25)-C(27)	118.1
C(31)-C(30)-S(29)	112.0
C(27)-C(30)-S(29)	109.4
Torsion angles (°)	
O(12)-C(1)-C(6)-C(5)	179.7
N(28)-C(23)-N(6)-C(1)	178.5
S(29)-C(27)-C(25)-C(23)	25.1

The HOMO and LUMO surfaces of compound **205f** were also computed at the B3LYP/6-311G level and these are represented in Figure 28. DFT calculations revealed that the HOMO is mainly localized on the benzothiazepine moeity and partially on the benzofuran ring. The LUMO, on the other hand, is spread throughout the molecule, except for the phenyl ring attached to the benzothiazepine framework. The value of the energy separation between HOMO and LUMO is -0.138 eV. This small energy gap indicates that this compound could be excited using minimal energy.



HOMO (-0.2166 eV) LUMO (-0.0781 eV)

Figure 28. Frontier molecular orbitals of **205f** using the B3LYP/6-311++G(d,p) basis set.

Most of the EGFR-tyrosine kinase inhibitors available in the literature have the 4-anilinoquinazoline framework the difference is on the substituents and the side chains. Therefore, the replacement of the aniline structure with a benzofuran nucleus could enhance biological activity of the resulting heterocycle-appended quinazoline. Although molecular hybridization has been employed before in the synthesis of an indole-ether quinazoline hybrid, Cediranib/Recentin™ (1**2**) shown in Figure 5,[29] to our knowledge, no attempts have been made

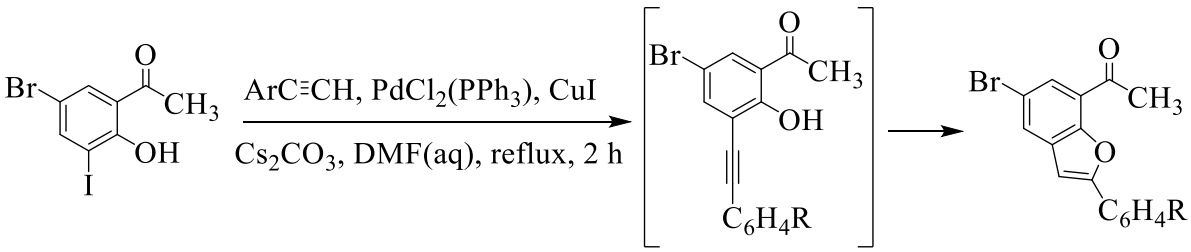
towards the synthesis of the analogous quinazoline-benzofuran hybrids linked either through C–C or C–heteroatom bond.

2.4 Design and synthesis of the benzofuran-aminoquinazoline hybrids

In the next section we decided to synthesize the benzofuran-aminoquinazoline hybrids by condensing the 7-aminobenzofurans with the 4-chloroquinazolines to provide a more general method to obtain analogues of Cediranib **12**.

2.4.1 Synthesis of the 5-bromo-2-arylbenzofuran-7-amines

In order to prepare the 7-amino-2-aryl-5-bromobenzofurans to serve as substrates for the amination of the 4-chloroquinazolines, the previously prepared 5-bromo-2-hydroxy-3-iodoacetophenone **197b** were subjected to tandem palladium catalysed Sonogashira cross-coupling with terminal acetylenes and subsequent *endo-dig* Csp–O cyclization to afforded the corresponding 1-(5-bromo-2-arylbenzofuran-7-yl)ethanones **207a**–**e** in 73–77% yield (Scheme 63). The ^{1}H- and ^{13}C NMR spectra of compounds **207** revealed the presence of an increased number of signals in the aromatic region δ_H 6.9–7.9 ppm and δ_C 100–160 ppm, respectively, due to the incorporated aryl ring. The *endo-dig* Csp–O cyclization to form the benzofuran ring was confirmed by the absence of the signal for OH which was present in the spectra of the previous substrates, and there is an observed singlet in the region 7.07 ppm belonging to H-3 of the benzofuran ring.



197b **206 a–e** **207a–e**

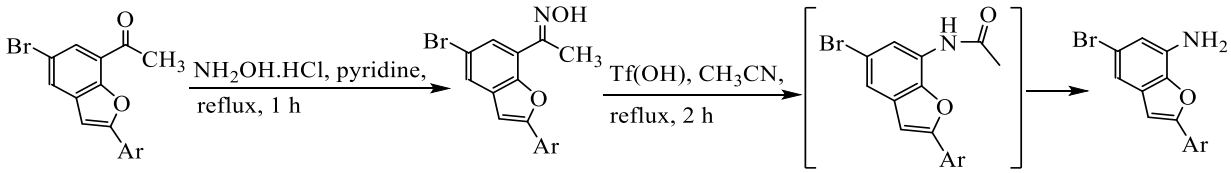
Scheme 63: Tandem Pd-catalysed Sonogashira cross-coupling and heteroannulation to afford **207a–e**.

Table 12: Substitution pattern, percentage yields and melting points of compounds **207a–e**.

Compound	Ar	%Yield	Mp °C
207a	C_6H_5-	73	130–133
207b	3-FC_6H_4-	76	161–164
207c	4-FC_6H_4-	76	178–180
207d	3-ClC_6H_4-	74	139–141
207e	4-$CF_3OC_6H_4$-	77	170–173

The 1-(5-bromo-2-arylbenzofuran-7-yl)ethanones **207** were then subjected to a nucleophilic substitution reaction with hydroxylamine hydrochloride in the presence of pyridine under reflux for 1 h followed by aqueous work-up and recrystallization to afforded the corresponding oximes **208a–e** (Scheme 64). Compounds **208** were characterized using a combination of NMR (^{1}H and ^{13}C NMR) and IR spectroscopic techniques as well as mass spectrometry. Their oxime nature, on the other hand, was confirmed by the additional singlet around δ_H 11.6 ppm and carbon signal significantly upfield around $\delta_{C=N}$ 154 ppm in their ^{1}H-NMR and ^{13}C-NMR spectra, respectively. The presence of the OH group was further confirmed by the presence of a broad band around ν_{OH} 3300 cm^{-1} in their IR spectra. The Beckmann rearrangement of these oximes **208** with 20% mol equivalent of trifluoromethanesulfonic acid (triflic acid, TfOH) in acetonitrile under reflux

for 4 h afforded the 7-aminobenzofuran derivatives **210a**–**e** exclusively (Scheme 64). The latter are the results of the initial Beckmann rearrangement via aryl carbon migration followed by an *in situ* acid-mediated hydrolysis of the intermediate benzofuranacetamide derivatives **209**. Compounds **210a**–**e** were easily distinguished from the corresponding precursors by the absence of signals corresponding to the oxime group in their ^{1}H- and ^{13}C-NMR spectra. The ^{1}H NMR spectra of compounds **210** reveal the presence of a broad singlet at about δ 5.82 ppm corresponding to the amino group. The presence of the NH_2 groups was also confirmed by the corresponding IR absorption bands at about ν_{max} 3385 cm^{-1}.



207a–**e** **208a**–**e** **207a**–**e** **210a**–**e**

Scheme 64: One-pot Beckmann rearrangement and hydrolysis of oximes **208a**–**e** into amines **210a**–**e**.

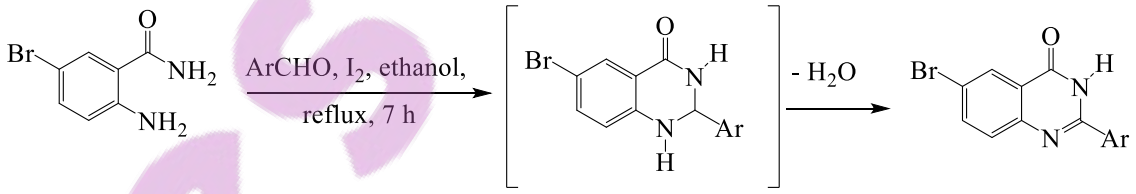
Table 13: Substitution pattern and percentage yields of compounds **208** and **210**.

Compound	Ar	%Yield of 208	%Yield of 210
a	C_6H_5-	93	62
b	3-FC_6H_4-	86	78
c	4-FC_6H_4-	72	71
d	3-ClC_6H_4-	81	65
e	4-$CF_3OC_6H_4$-	78	85

The 4-chloroquinazolines were then synthesized to serve as coupling partners with the 7-aminobenzofurans **210**. This was achieved *via* cyclocondensation of substituted 2-aminobenzamides with benzaldehyde derivatives as highlighted in the next section.

2.4.2 Synthesis of the 4-chloroquinazolines

Quinazolin-4(3*H*)-ones are readily accessible via cyclocondensation-dehydration of anthranilimide with carbonyl compounds (aldehydes and ketones) using reagents such as $NaHSO_3$,[135] DDQ,[132] $CuCl_2$ (3 equiv.),[133] $FeCl_3.6H_2O$[136] or I_2.[137] We exploited the combined electrophilic and oxidative properties of iodine in ethanol under reflux to effect the cyclocondensation of the previously prepared 2-amino-5-bromobenzamide **211** with benzaldehyde derivatives and subsequent dehydrogenation of the intermediate quinazolin-4(1*H*)-one **212a, b** to afford the 2-aryl-6-halogenoquinazolin-4(3*H*)-ones **213a** and **213b** in single-pot operation without the need for column chromatographic separation (Scheme 65). The solid residue was washed with water and then recrystallized from ethanol to afford pure product **213a, b**. Compounds **213** were characterized using a combination of ^{1}H NMR, IR, and mass spectroscopic techniques. Their N-4(3*H*)-oxo nature of compounds was confirmed by the presence of the N-3 proton signal that is significantly downfield at about δ 12.35 ppm. Their amide nature was also confirmed by the presence of IR bands in the region ν_{max} 1660−1680 cm^{-1} and ν_{max} 1550−1595 cm^{-1} corresponding to C=O and C-N, respectively. The accurate calculated *m/z* values in each case are consistent with the observed molecular weight of the assigned structure.



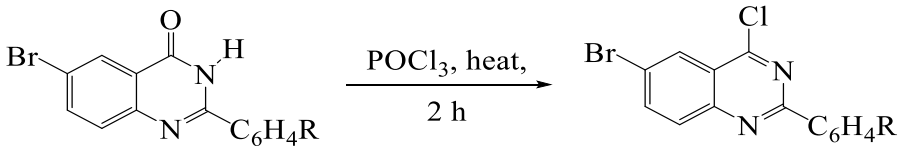
211 **212a, b** **213a, b**

Scheme 65: Iodine-promoted cyclocondensation-dehydrogenation to yield quinazolin-4(3*H*)-ones **213**

Table 14: Substitution pattern, percentage yields and melting points of compounds **213a**–**b**.

Compounds	Ar	% Yield	Mp. (°C)
213a	4-FC_6H_4-	91	278–280 °C
213b	4-ClC_6H_4	93	342–344 °C

The quinazolin-4(3*H*)-one scaffold has been employed extensively for the synthesis of the 4-heteroatom and 4-carbo substituted quinazoline derivatives via initial aromatization with phosphoryl chloride or thionyl chloride and subsequent nucleophilic displacement of chlorine with nucleophilic reagents or cross-coupling reactions.[138] In this investigation, we subjected 2-aryl-6-dibromoquinolin-4(3*H*)-ones **213a, b** to phosphoryl chloride under reflux for 2 h to yield the corresponding substituted 4-chloroquinazolines **214a, b** (Scheme 66). The 4-chloroquinazoline nature of compounds **214a, b** was confirmed by the absence of an N-H signal in their ^{1}H NMR spectra. Moreover, the IR spectra of products **214** are characterized by the absence of the C=O stretch found in the spectra of the corresponding substrates and the molecular ion region of the mass spectra of these substituted derivatives reveal the presence of the M+ and M+2 peaks in the ratio 3:1 typical for molecules containing the ^{35}Cl and ^{37}Cl isotopes.



213a, b **214a, b**

Scheme 66: $POCl_3$–promoted aromatization of **213a**, **b**.

Table 15: Substitution pattern, percentage yields and melting points of compounds **214a**–**b**.

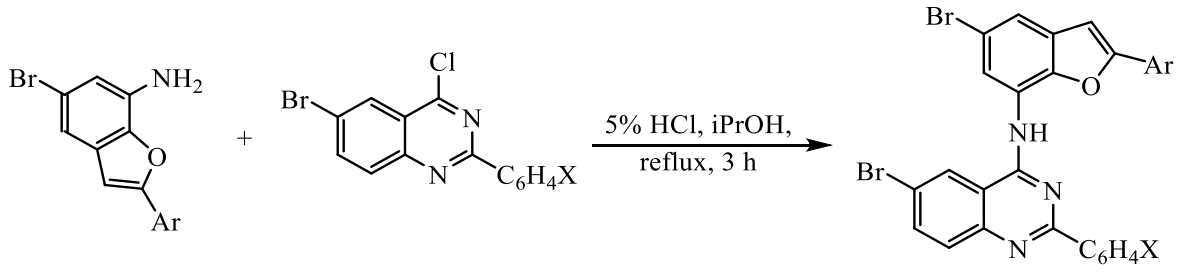
Compounds	Ar	% Yield	Mp. (°C)
214a	4-FC_6H_4-	85	208−210 °C
214b	4-ClC_6H_4-	91	244–246 °C

The C(4)–Cl position of the 4-chloroquinazoline is highly activated than other positions due to the α-nitrogen effect, which makes this position more electrophilic than any other position on the quinazoline scaffold.[129] This encouraged us to merge compounds **214** with the 7-amino-2-aryl-5-bromobenzofurans **210a**–**e** as described in the next section.

2.4.3 Reactions of the 5-bromo-2-arylbenzofuran-7-amines and the 4-chloroquinazolines

We subjected the electrophilic 4-chloroquinazoline derivatives **214a** and **214b** to the amino-dechlorination with the nucleophilic 7-aminobenzofurans **210a**–**e** in the presence of 5% HCl in isopropanol (iPrOH) under reflux (Scheme 67). We isolated after 4 h by aqueous work-up and recrystallization, compounds characterized using a combination of NMR and IR spectroscopic techniques as well as mass spectrometry as the quinazoline-benzofuran hybrids **215a**–**j**. The ^{1}H NMR spectra of compounds **215** revealed the presence of an increased number of signals in the aromatic region due to incorporated aryl rings as well as a singlet around 11.4 ppm which correspond to the nitrogen bridge (4-amino group). The calculated m/z values for the molecular hybrids **215a**–**h**, on the other hand, were found to be consistent with the molecular ions of the assigned structures. The structure of these compounds was distinctly confirmed by single crystal X-ray diffraction (XRD) analysis of compound **215i** (Figure 29; CCDC 1815109). The crystal structure reveals the presence of intramolecular hydrogen bonding between the amine proton and

endocyclic oxygen atom. The crystallographic data of compound **215i** is presented in Table 17 below.



210a–**e** **X** = F (**214a**); Cl (**214b**) **215a**–**j**

Scheme 67: Amination of 4-chloroquinazolines **214a**, **b** with the 7-aminobenzofurans **210a**–**e**

Table 16: Substitution pattern and percentage yields of compounds **215a**–**j**.

Compound	Ar	X	%Yield of 215
215a	C_6H_5-	F	75
215b	3-FC_6H_4-	F	82
215c	4-FC_6H_4-	F	87
215d	3-ClC_6H_4-	F	78
215e	4-$CF_3OC_6H_4$-	F	82
215f	C_6H_5-	Cl	83
215g	3-FC_6H_4-	Cl	81
215h	4-FC_6H_4-	Cl	78
215i	3-ClC_6H_4-	Cl	67
215j	4-$CF_3OC_6H_4$-	Cl	82

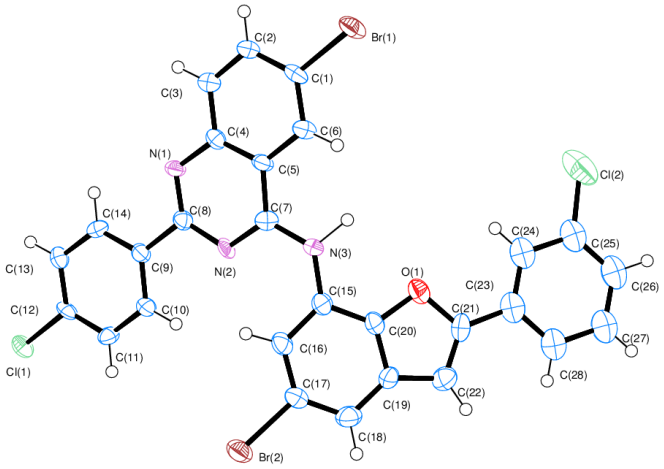


Figure 29: Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagram of **215i**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Table 17: Crystallographic data of compound **215i** (CCDC deposition number: 1815109).

Formula	$C_{28}H_{15}Br_2Cl_2N_3O$
M_r	640.15
Temperature/K	173(2)
Wavelength/Å	0.71073
Crystal size/mm^3	0.2 x 0.1 x 0.1
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	3.7696(18)
b/Å	52.52(2)
c/Å	12.732(6)
α/°	90
β/°	90.044(6)
γ/°	90
V/Å^3	2521(2)
Z	4
ρ (calcd)/Mg m^{-3}	1.687
μ/mm^{-1}	3.456

Table 17 *continues*	
F(000)	1264
Θ Range for data collection/°	3.103 to 25.493
Reflections collected	8866
No. of unique data [R(int)]	4187 [0.0909]
No. data with $I \geq 2\sigma(I)$	2354
Final R($I \geq 2\sigma(I)$)	0.1150
Final wR_2 (all data)	0.3234
CCDC deposition number	1815109

The molecular framework of compounds **215a**–**j** resembles that of the biologically important 4-anilinoquinazolines such as the EGFR-TK inhibitor, Gefitinib. This encouraged us to evaluate these quinazoline-appended benzofuran hybrids for potential *in vitro* anti-proliferative properties as described in the next section.

2.5 Biological activity of the benzofuran-chalcones and benzofuran-aminoquinazolines

The benzofuran-appended chalcone hybrids **203a**–**y** and the benzofuran-aminoquinazoline hybrids **215a**–**j** were evaluated for potential antiproliferative properties *in vitro*. Their modes of cancer cell death were evaluated experimemntally complemented with molecular docking studies as described in the next sections.

2.5.1 Evaluation of the benzofuran-chalcone hybrids for antiproliferative properties

All the synthesized benzofuran-chalcone hybrids **203a**–**y** were evaluated for their anti-proliferative activity against human breast cancer cell line (MCF-7) using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) method.[155] Actinomycin D,

which is a known antibiotic drug with antibacterial and antitumour activities was used as a positive control in this investigation.[156] The results were expressed as median growth inhibitory concentration (IC_{50}) values, which represent the compound concentration required to produce a 50% inhibition of cell growth after 48 h of incubation and are summarized in Table 18. It is observed that all the synthesized compounds showed significant anti-proliferative activity with IC_{50} values ranging from 3.55×10^{-4} to 69.0 μM while the positive control, actinomycin D demonstrated the IC_{50} at 36.7 μM. Compounds **203b**, **203d** and **203e** substituted with a phenyl ring on the benzofuran moiety and electron withdrawing groups such as a 4-fluorophenyl, 4-methoxyphenyl or 4-trifluoromethoxyphenyl group on the chalcone functionality exhibited more significant cytotoxicity against the MCF-7 cells than the reference standard (IC_{50} = 37.82 μM) with the IC_{50} values of 0.55, 22.78 and 0.59 μM, respectively. However, cytotoxicity decreased within the series **203f**–**j** substituted with a 2-(4-fluorophenyl) group on the benzofuran ring. A combination of 4-fluorophenyl ring on the benzofuran moiety and a 4-methoxyphenyl or 4-trifluoromethoxyphenyl group on the chalcone framework in compounds **203i** and **203j** resulted in increased cytotoxicity against the MCF-7 cell line for these compounds with the IC_{50} values of 3.55 ×10-4 μM and 16.00 μM, respectively. Similarly, compound **203l** substituted with a 2-(3-fluorophenyl) ring on the benzofuran moiety and a 4-fluorophenyl group on the chalcone arm displayed low activity. Moreover, compounds **203k**, **203m**, and **203o** replaced with a phenyl, 4-chlorophenyl and 4-trifluoromethoxyphenyl group on the chalcone fragment were found to exhibit increased cytotoxicity when compared to actinomycin D with IC_{50} values of 23.01, 14.75 and 7.87 μM, respectively. The derivative **203n** substituted with 4-methoxyphenyl on the benzofuran moiety exhibited cytotoxic activity comparable to actinomycin D. The 3-chlorophenyl group substitution at the 2-position of the benzofuran framework in compounds **203p**, **203q**, **203s** and **203t** and a phenyl, 4-fluorophenyl, 4-methoxyphenyl and 4-

trifluoromethoxy group on the chalcone fragment, on the other hand, resulted in significant cytotoxicity with IC_{50} values of 12.63, 23.82, 2.69 and 26.62 µM, respectively.

Table 18: Cytotoxic effects of **203a**–**y** against MCF-7 cell line. The results are presented as IC_{50} (µM) ± standard deviation (SD) from three individual experiments.

Compounds	IC_{50} (µM) ± SD
203a	47.96 ± 2.10
203b	0.55 ± 0.24
203c	>100
203d	22.78 ± 0.86
203e	0.59 ± 0.21
203g	48.59 ± 2.10
203h	54.16 ± 0.40
203i	3.55×10^{-4} ± 0.07
203j	16.00 ± 0.62
203k	23.01 ± 0.38
203l	>100
203m	14.75 ± 0.33
203n	39.25 ± 0.42
203o	7.87 ± 0.25
203p	12.63 ± 0.23
203q	23.82 ± 0.29
203r	66.75 ± 0.84
203s	2.69 ± 0.23
203t	26.62 ± 0.27

Table 18 *continues*

203u	48.96 ± 0.30
203v	28.43 ± 0.46
203w	30.62 ± 0.35
203x	69.09 ± 0.76
203y	43.17 ± 0.28
Actinomycin D	37.82 ± 1.30

Many anticancer compounds exert their growth inhibitory effect either by arresting the cell or by inducing apoptosis or a combined effect of both cycle arrest and apoptosis.[154] Moreover, regulation of the cell cycle and apoptosis are effective approaches in the development of cancer therapeutics.

2.5.2 Mode of cancer cell death (apoptosis vs necrosis)

Syam and coworkers previously synthesized a (*E*)-3-(3-chlorophenyl)-1-phenylprop-2-en-1-one derivative which was found to exhibit significant antiproliferative activity against breast cancer cell line (MCF-7) and to induce apoptosis through the intrinsic and extrinsic pathways.[157] Based on this literature, we performed dual Annexin V-Cy3 and SYTOX staining to assess the apoptosis status of MCF-7 cells after 48 h of treatment with the most cytotoxic compounds, **203b** and **203i** through flow cytometry (Figure 30). Annexin V-Cy3 can detect the externalisation of phosphatidylserine of the cell membrane, which is one of the mode of actions of apoptosis, whereas SYTOX checks the integrity of the cell membrane.[158] Analysis proved that the tested compounds significantly induced programmed cell death in MCF-7 cells in comparison with the control (untreated cells) and the reference standard (Actinomycin D). The highest pro-apoptotic

potential was observed after 48 h of incubation with the compounds **203b** and **203i** in breast cancer cells, where we observed 23.3% and 32.2% viable cells; and 73.5% and 64.8% apoptotic cells, respectively (Table 19)

Figure 30: Annexin V staining of MCF-7 cells treated with **203b**, **203i** and actinomycin D at 1 µM concentration for 48 h, respectively.

203b **203i** **Actinomycin D**

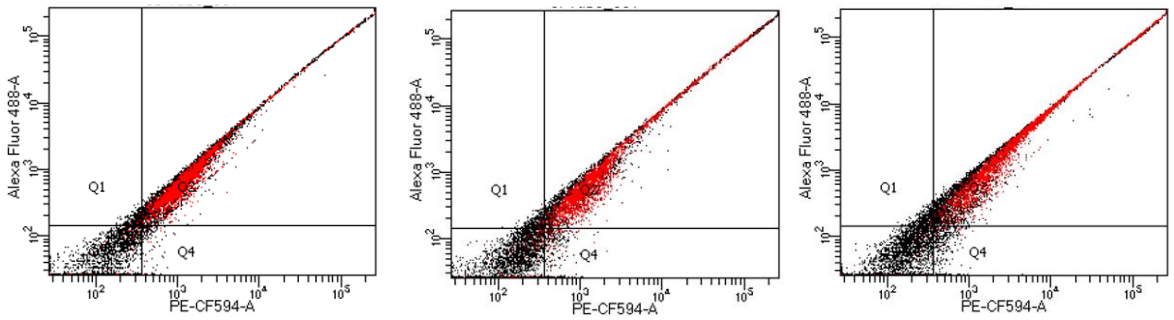


Table 19: Quantitive apoptosis assay of MCF-7 using Annexin V SYTOX staining

Compound	%Viable cells (Q3)	%Early apoptosis (Q4)	%Late apoptosis (Q2)	%Necrosis (Q1)
203b	23.3	1.5	72	3.2
203i	32.2	3.1	61.7	3.1
Actinomycin D	30.7	3.4	61.4	4.5

Caspases (cysteinyl-directed aspartate-specific proteases) are cysteine proteases that play a central role in propagating the process of programmed cell death (apoptosis) in response to proapoptotic signals.[159] While some caspases primarily act to initiate intracellular event cascade, other caspases that are called effector caspases act further downstream and direct cellular breakdown through cleavage of structural proteins (Caspase-3, and Caspase-7). [160]Activation of Caspase-3/7 is thus a mode of actin of apoptosis. We performed a caspase activation assay to

further understand the role of compounds **203b** and **203i** plays in promoting cancerous cell death in MCF-7 cells. It was observed that MCF-7 cells treated with compounds **203b** and **203i** experienced a moderate caspase-3 activity when compared with actinomycin D. The results from caspase-3 activation (Figure 31) indicate that compound **203b**, which induced increased apoptosis according to the Annexin staining, does not induce significant caspase activation when compared to **203i** and actinomycin D. Since the breast cancer cell line MCF-7 lacks a functional caspase-3 gene product,[161] apoptosis induction in these cells by these compounds may be through other molecular pathways that do not involve caspase activation.

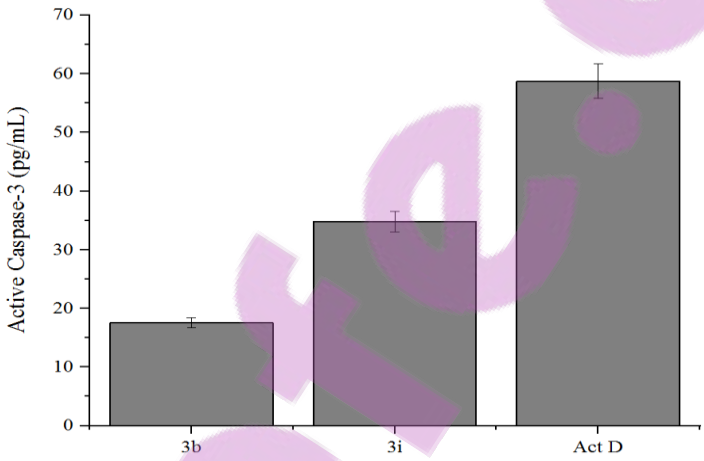


Figure 31. Effects of compounds **203b**, **203i**, and actinomycin D (Act. D) at 1 μM on human Caspase-3 (Asp175) activity in MCF-7 cells, respectively.

Inhibition of tubulin polymerization activity is regarded as the other approach for innovative therapeutic strategies in cancer treatment and the chalcone derivatives are known to produce their anticancer activity through inhibition of tubulin polymerization by binding to colchicine-binding site.[162] Compounds that bind to the colchicine binding site are defined as inhibitors of tubulin assembly and considered as microtubule destabilizing agents. Replacement of the A-ring of the chalcone framework with different aryl and heteroaryl moieties has previously been found to result in derivatives with potent anti-tubulin activity. The anologous *(E)*-3-(6-chloro-2*H*-chromen-3-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one, for example, was found to bind

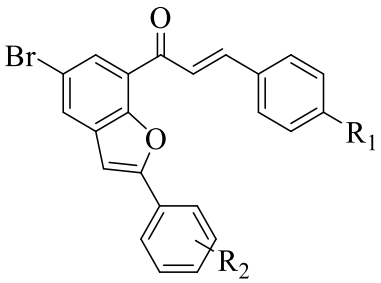
directly to tubulin and disturb microtubule stability and the function of the spindle apparatus, which causes cancer cells to undergo apoptosis.[163] Based on this literature precedence, we then decided to investigate the effect on tubulin polymerization of the benzofuran-chalcones **203**.

2.5.3 Inhibition of tubulin polymerisation of compound 203 complemented with molecular docking

To determine the effect of compounds **203** on tubulin polymerization, a fluorescence-enhanced tubulin polymerization assay kit was used. The benzofuran-chalcone hybrids **203a**–**y** were evaluated for their ability to inhibit tubulin polymerization using actinomycin D and colchicine as reference standards in a cell-free in vitro assay. The IC_{50} values for these compounds were also determined and these are listed in Table 20. Although moderately cytotoxic against the MCF-7 cells, the parent compound **203a** was found to inhibit tubulin polymerization more so than the other derivatives bearing substituents at the 4-position of the phenyl ring on the benzofuran framework. Compounds **203f**, **203i** and **203j** were found to exhibit increased inhibitory effect against tubulin polymerization and the observed trend in IC_{50} values: **203f** (23.3 μM) < **203j** (8.85×10^{-3} μM) < **203i** (5.51×10^{-5} μM) compares well with their antiproliferative effect against the MCF-7 cell line. A combination of a 2-(3-fluorophenyl) group on the chalcone arm and a 2-(4-trifluoromethoxyphenyl) group on the benzofuran scaffold in compound **203o** resulted in increased inhibitory effect against tubulin polymerization ($IC_{50} = 1.76 \times 10^{-3}$ μM) than the analogous compounds within the series **203k**–**o**. Moderate activity was observed for compound **203n** substituted with a 4-methoxyphenyl group on the benzufuran framework. A combination of a 2-(3-chlorophenyl) group on the chalcone moiety and a phenyl ring (**203p**) or 4-methoxyphenyl group (**203s**) on the benzofuran framework resulted in significant inhibitory effect against tubulin polymerization compared to the other derivatives within the series **203p**–

t. A combination of the 2-(4-fluorophenyl) group on the benzofuran framework and a 2-(4-methoxyphenyl) substituent on the chalcone arm in compound **203v** resulted in significant inhibitory effect (IC_{50} = 1.62 × 10^{-2} µM) against tubulin polymerization compared to the other derivatives within the series **203u**–**y**. The benzofuran-chalcone hybrids described in this investigation significantly interfere with tubulin polymerization by lowering the rate of assembly (Table 20), which suggests that the molecular target of these chalcone derivatives might be tubulin. However, the strong anti-tubulin polymerization activity among other series does not necessarily correspond well with the poor or lack of cytotoxicity for the other derivatives. Nonlinearity between antiproliferative activity and the effect on tubulin polymerization has been observed for some inhibitors before where highly cytotoxic compounds were not necessarily potent inhibitors of tubulin polymerization and vice versa.[162-163] In addition to induction of apoptosis and/or tubulin inhibition, chalcones have also been found to exhibit anticancer activity through other mechanisms of action.[164]

Table 20. IC_{50} values of 203a-y against tubulin using colchicine as a positive control



203a–**y**

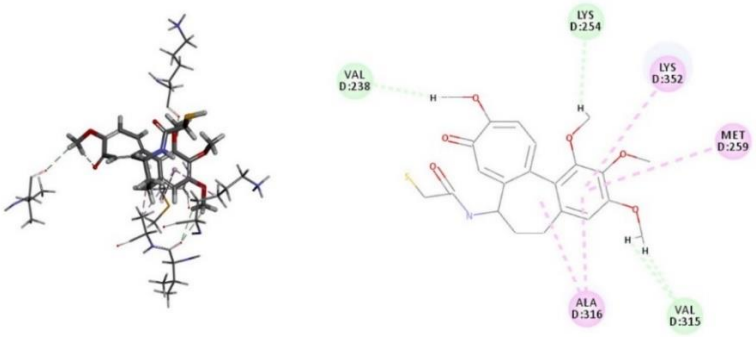
Compounds	R^1	R^2	IC_{50} (µM)
203a	H	H	15.6 ± 0.06
203b	F	H	26.5± 0.17
203c	Cl	H	26.6± 0.27

Table 20 *continues*

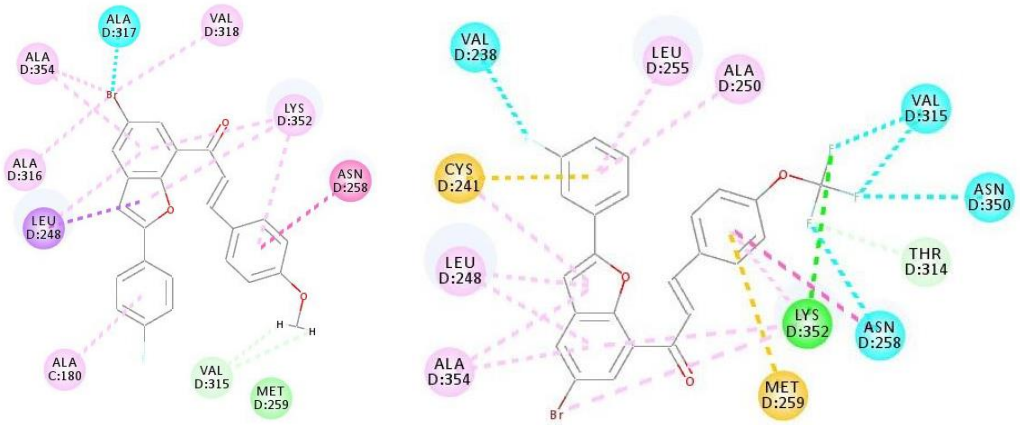
203d	CH_3O-	H	34.5± 0.22
203e	CF_3O-	H	25.4 ± 0.24
203f	H	4-F	23.3± 0.11
203g	F	4-F	13.2 ± 0.17
203h	Cl	4-F	1.33 ± 0.38
203i	CH_3O-	4-F	5.51×10^{-5} ± 0.39
203j	CF_3O-	4-F	8.85×10^{-3} ± 0.42
203k	H	3-F	77.0 ± 0.21
203l	F	3-F	3.98 ± 0.07
203m	Cl	3-F	10.2 ± 0.19
203n	CH_3O-	3-F	0.80± 0.37
203o	CF_3O-	3-F	1.76×10^{-3} ± 0.11
203p	H	3-Cl	9.37×10^{-2} ± 0.21
203q	F	3-Cl	51.3×10^{-2} ± 0.22
203r	Cl	3-Cl	345.0± 0.16
203s	CH_3O-	3-Cl	0.71 ± 0.30
203t	CF_3O-	3-Cl	2.83± 0.07
203u	H	4-OCH_3	18.3 ± 0.16
203v	F	4-OCH_3	1.62×10^{-3} ± 0.12
203w	Cl	4-OCH_3	48.4 ± 0.11
203x	CH_3O-	4-OCH_3	67.4 ± 0.14
203y	CF_3O-	4-OCH_3	7.80 ± 0.07
Colchicine			9.88×10^{-2} ± 0.17

To help us understand the anticancer activity of compounds **203a**–**y** and guide further structure activity relationship (SAR) studies, we selected compounds **203i** and **203o** and docked them into tubulin. Compounds **203i** and **203o**, which exhibited increased inhibitory effects against tubulin polymerization and colchicine, were docked into tubulin (PDB ID: 1SAO) and their docked poses are represented in Figure 32 below. The docking poses of colchicine (Figure 32) and the benzofuran-chalcones **203i** (Figure 32) and **203o** (Figure 32) revealed that the hybrids occupy the hydrophobic pocket of the colchicine-binding site at the interface between the α and β-chains. Increased hydrophobic (alkyl, pi-alkyl, pi-sigma, amide-pi) interactions exist between the most active compound **203i** with the side chains of tubulin residues Ala180, Ala316, Ala354, Val318, Lys352, and Leu248 (Figure 32). The hydrogen atoms of the methoxy group are involved in carbon hydrogen bonding with Val315 (Hb distances = 2.71 and 2.54 Å) and van der Waals interaction with Met259. The bromine atom, on the other hand, is involved in halogen bond interaction with the protein residue Ala317. The docking pose of **203o** (Figure 32) also revealed the presence of several hydrophobic interactions between the benzofuran moiety and the 4-trifluoromethoxyphenyl group of the chalcone arm with the protein residues Ala250, Ala354, Leu255, and Lys352. There are also pi-sulfur bond interactions between the 3-fluorophenyl and 4-trifluoromethoxyphenyl groups with Cys241 and Met259, respectively. The trifluoromethoxy group is involved in a hydrogen bond interaction with Lys352 (Hb distance = 2.73 Å) and Thr314 (Hb distance = 2.73 Å). The fluorine atom of the 3-fluorophenyl ring interacts with Val238 via halogen bonding while the fluorine atoms of the trifluoromethoxy group are involved in halogen bond interaction with Asn350, Asn358, Val238, and Val315. The modeling studies against tubulin suggest that the hydrophobic interactions and hydrogen and/or halogen bonding with the protein residues helps to stabilize the binding of these compounds in the colchicine-binding domain of α,β-tubulin interface. This probably accounts for the observed significant tubulin

polymerization inhibitory effect and the increased cytotoxicity of these compounds against the MCF-7 cell line.



Colchicine



203i **203o**

Figure 32. (a) 2D interaction diagrams for the binding of tubulin (PDB code: 1SAO) with colchicine, **203i** and **203o**. Residues are annotated with their three-letter amino acid code.

The chalcone-based compounds were found to exhibit anticancer activity via several mechanisms of action, including tyrosine kinase inhibition,[164] we decided to evaluate the most cytotoxic compounds from against the MCF-7 cell line for their potential to inhibit EGFR-TK phosphorylation.

2.5.4 Inhibition of EGFR-TK phosphorylation of 203 complemented with molecular docking

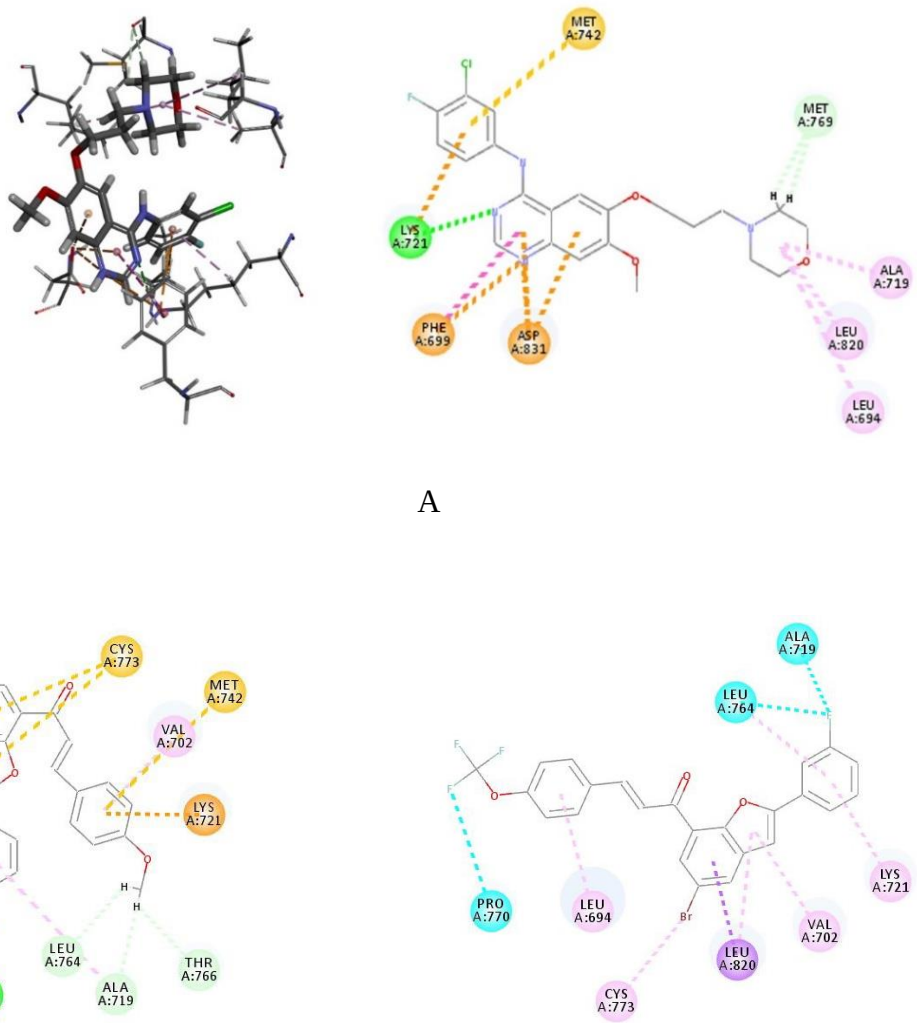
The most cytotoxic benzofuran-appended hybrids namely, **203b**, **203j**, **203o**, **203p** and **203v**, and evaluated them for their potential to inhibit EGFR-tyrosine kinase phosphorylation against actinomycin D and gefitinib. The treatment of NIH3T3 (SAA) and B104-1-1 (neuroblast-transformed NIH3T3) cells with actinomycin D has previously been found to block Shc/Grb2 interaction for the treatment of specific tumors caused by EGFR.[165] Gefitinib, on the other hand, is a selective inhibitor of the EGFR-TK and it inhibits tumour pathogenesis, metastasis, and angiogenesis, and also promotes apoptosis.[48] The test compounds and the two reference standards were evaluated for inhibitory effects against EGFR-tyrosine kinase phosphorylation and the corresponding IC_{50} values are represented in Table 21. The results of this assay revealed that the title compounds also exhibit significant inhibitory effect against EGFR-TK phosphorylation when compared to gefitinib. Compound **203b** exhibited an increased cytotoxicity and apoptotic effect but poor anti-tubulin activity was also found to exhibit significant inhibitory activity against EGFR with an IC_{50} value of 0.17 μM. The most cytotoxic compound **203i** against the MCF-7 cells seems to exhibit inhibitory effects against tubulin polymerization and EGFR-TK phosphorylation. Moderate inhibitory effects against the EGFR were also observed for compounds **203o**, **203p**, and **203v** with IC_{50} values of 0.12, 0.17 and 0.15 μM, respectively.

Table 21: IC_{50} values (in μM) of EGFR-TK by **203b, 203i**, **203o**, **203p**, and **203v** against actinomycin D and gefitinib.

Compound	IC_{50} (μM)
203b	0.17 ± 0.03
203i	0.09 ± 0.03
203o	0.12 ± 0.04
203p	0.17 ± 0.06
203v	0.15 ± 0.02
Actinomycin D	0.04 ± 0.03
Gefitinib	0.03 ± 0.02

An *in silico* docking of the most potent compounds **203i** and **203o** in the active site of the EGFR complexed with the reversible ATP competitive drug Gefitinib (PDB ID: 1M17) predicted that the compounds might exhibit a binding conformation similar to that of Gefitinib (Figure 33). The important protein residues in the hydrophobic pocket of the ATP-competitive site that interacts with **203i** are Leu694, Leu820, Arg817, and Val702 (Figure 33). The benzofuran moiety is also involved in pi-sulfur interaction with Cyst773 and pi-sulfur interaction also exists between the methoxyphenyl group on the chalcone arm with Met743. The Lys721 residue establishes a cation-interaction with the 4-methoxyphenyl ring of **203i**. There is also a pi-anion interaction between the benzofuran core of **203i** and carboxylic side chain of Asp831 located on the phosphate-binding region along the sugar pocket. Carbon-hydrogen bond interactions, which are the most common kinase-inhibitor interactions exist between Leu764 (Hb distance = 2.66 Å), Ala719 (Hb distance = 2.52 Å) and Thr766 (Hb distance = 2.43 Å) with the methoxy group of **203i**. The fluorine atom on the 2-phenyl ring of the benzofuran scaffold is involved in hydrogen bonding with the NH backbone of Met769 (Met769-NH···F distance = 2.18 Å), which is known

to hydrogen bond to N-1 of the adenine ring of ATP and help to fix it in the binding pocket. This interaction, in our view, would account for the increased inhibitory effect of this compound against the EGFR and therefore its increased cytotoxicity against the EGFR-positive MCF-7 cell line. The docking pose of compound **203o** (Figure 33) reveals the presence of hydrophobic (alkyl, pi-alkyl and pi-sigma) interactions with the protein residues Leu764, Leu694, Cys773, Lys721, Val702, and Leu820. Val702, Leu820, and Ala719 are located near the gatekeeper residue, Thr766, and its location is envisaged to control the access of an inhibitor to the hydrophobic pocket of the ATP-competitive site.[166] The Lys721 in the ATP-binding site of EGFR is considered to be one of the key residues to decide the biological activity of the EGFR. The fluorine atom on the 4-fluorophenyl group is involved in halogen bonding with Ala719 and Leu764 and additional halogen bonding exists between the trifluoromethoxy group and the protein residue Pro770. Halogen-bonds are known to confer the specificity of inhibitors against protein kinases.[167] Moreover, fluorine-containing groups have been found to enhance the efficacy of the molecule by promoting electrostatic interactions with targets, improving cellular membrane permeability due to its lipophilicity, and increasing strength toward oxidative metabolism of the drug.[168] Compounds **203i** and **203o** exhibit increased interactions with the protein residues in the binding pocket of EGFR and a better binding affinity in line with their strong EGFR binding activity in addition to its significant cytotoxicity against the MCF-7 cells. The results of the synthesis and biological activity studies of the benzofuran-chalcone hybrids prepared in this investigation have since been published.[169]



A

203i **203o**

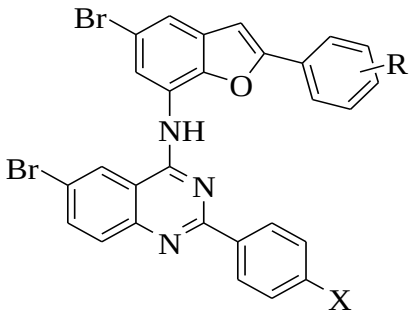
Figure 33. 2D interaction diagrams for the binding of EGFR (PDB code 1M17) with gefitinib (A), **203i** and **203o**. Residues are annotated with their three-letter amino acid code.

2.5.6 Evaluation of the benzofuran-quinazoline hybrids for antiproliferative properties

The in vitro anti-proliferative activity of the benzofuran-quinazolines **215a-j** was examined against four EGFR-expressing cancer cell lines; the A549 (lung cancer), Caco-2 (colon carcinoma), HeLa (cervical cancer) and C3A (Hepatocellular carcinoma) cell lines using the 3-(4,5dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay.[155]

Gefitinib was used as a reference drug. The results were expressed as median growth inhibitory concentration (IC_{50}) values, which represent the compound concentration required to produce a 50% inhibition of cell growth after 72 h of incubation, compared to untreated controls and standard (Gefitinib) (Table 22). Investigations of the anti-proliferative activity against A549 indicated that compound **215j** (IC_{50} 47.4 ± 0.07 µM) was found to be the most potent derivative, being significantly more active than Gefitinib (IC_{50} 51.3 ± 0.17). Also, compound **215f** possessed slightly higher anti-proliferative activities than the reference drug (IC_{50} 48.0 ± 0.10 and 51.3 ± 0.17 µM, respectively). Compounds **215b** and **215c** were almost equipotent to Gefitinib (IC_{50} 54.3 ± 0.19 and 52.6 ±0.20 µM, respectively). The evaluation of the anti-proliferative activity in Caco-2 cell line, on the other hand, revealed that compound **215j** (IC_{50} 18.4 ± 0.07 µM) was the most potent counterpart when compared to gefitinib (IC_{50} 27.9 ± 1.05 µM). The presence of a 4-trifluoromethoxyphenyl group on the benzofuran framework in compound **215j** led to significant cytotoxicity against the A549 (IC_{50} = 47.4 µM) and HeLa (IC_{50} = 28.1 µM) and more so against the Caco-2 cell line (IC_{50} = 18.4 µM) with no activity against the C3A cells when compared with Gefitinib. The incorporation of 3-Cl substituent to the benzofuran moiety in **215d** enhanced the anti-proliferative activity against C3A (IC_{50} = 9.0 µM) and the HeLa (IC_{50} = 22.1 µM) cell lines, especially when accompanied with 4-flourophenyl moiety on the quinazoline core at 2-position and resulted in reduced cytotoxicity against the A549 and Caco-2 cell lines. Also, incorporation of electron withdrawing groups at 4-position is not favorable for the anti-proliferative activity, except for the 4-Cl substituent which is well tolerated with a 4-chlorophenyl group on the quinazoline framework seems to be more desirable for cytotoxicity than with a 2-(4-fluorophenyl) ring, which resulted in diminished cytotoxicity for **215e**.

Table 22: Cytotoxic effects of **215a**–**j** and Gefitinib against A549, Caco-2, C3A and HeLa cell lines



215a–**e** (X = F) & **215f**–**j** (X = Cl)

		Cancer cells IC_{50} (µM)			
Compound	**R**	**A549**	**Caco-2**	**C3A**	**HeLa**
215a	H	64.7 ± 0.11	96.3 ± 0.10	81.0 ± 0.03	17.6 ± 0.39
215b	3-F	54.3 ± 0.19	83.9 ± 0.07	90.1 ± 0.02	47.0 ± 0.38
215c	4-F	52.6 ±0.20	98.8 ± 0.02	> 100	11.4 ± 0.56
215d	3-Cl	65.1 ± 0.12	47.7 ± 0.01	9.0 ± 0.01	22.1 ± 1.10
215e	4-OCF_3	97.6 ± 0.07	65.2 ± 0.10	> 100	23.4 ± 0.49
215f	H	48.0 ± 0.10	75.0 ± 0.02	73.9 ± 0.02	15.4 ± 0.45
215g	3-F	78.5 ± 0.15	94.4 ± 0.02	79.1 ± 0.01	53.5 ± 4.46
215h	4-F	74.1 ± 0.21	49.1 ± 0.01	> 100	28.6 ± 1.12
215i	3-Cl	86.6 ± 0.16	33.5 ± 0.10	68.2 ± 0.02	75.1 ± 5.25
215j	4-OCF_3	47.4 ± 0.07	18.4 ± 0.07	> 100	28.1 ± 0.79
Gefitinib		51.3 ± 0.17	27.9 ± 1.05	5.0 ± 0.04	98.8 ± 0.56

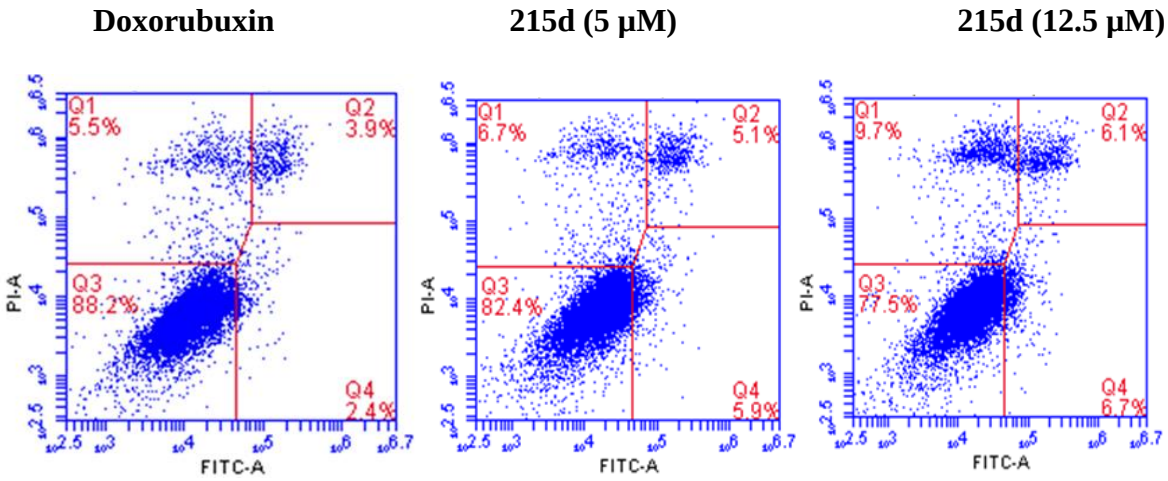
The 4-anilinoquinazolines[48-50] and benzofuran derivatives[30] are known to be cytotoxic to cancer cells by inducing apoptosis. In this study, to confirm that compounds **215d** and **215j** which

showed the strongest cytotoxic effect, induced apoptosis, the Annexin-V FITC test was performed as an indicator of early apoptosis.

2.5.7 Mode of cancer cell death (apoptosis vs necrosis)

To elucidate the molecular mechanism of the cytotoxic effects of **215d** and **215j**, we investigated whether these compounds induced the morphological changes characteristic of apoptotic cell death in the C3A and Caco-2 cell lines against doxorubicin hydrochloride as a reference standard, respectively. The population of apoptotic cells was determined by means of Annexin-V and propium iodide (PI) double staining by flow cytometry, which is a useful tool for evaluation of molecular and morphological events that take place during cell death and cell proliferation. It was determined that compounds **215d** and **215j** showed an apoptotic effect from 5 µM onwards and as the dose increased, so did the apoptotic effect figure (34). The highest pro-apoptotic potential was observed after 24 h of incubation with compounds **215d** in hepatocellular carcinoma cells, where we observed 82.4% viable cells and 17.7% apoptotic cells. In the case of compound **215j** in colon cancer cells most of the apoptotic effect was at the stage of early apoptosis (19.8%–21.1%) and the cell death rate (11%–23.9%) was determined to be increased with the increasing concentration.

(a) Compound **215d** asgainst C3A cell line



(b) Compound **215j** against Caco-2 cell line

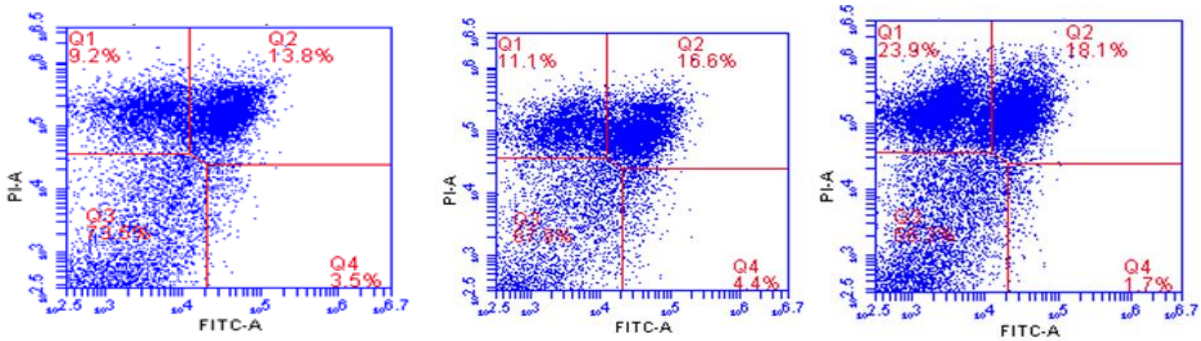


Figure 34: Effects of compounds **215d** and **215j** on the induction of apoptosis in C3A (a) and Caco-2 cells (b) as determined by Annexin V/PI staining. Data represent the percentage of apoptotic cells for the control and compounds **215d** and **215j** at 5 and 12.5 µM after 24 h.

Apoptosis may start through intrinsic or extrinsic pathways. To better identify the initial pathway of apoptosis, the caspase activation assay for apoptosis regulators was applied. The presence of cleaved caspase-3 was investigated to determine by which route cellular apoptosis had occurred. Consequently, we evaluated compounds **215d** and **215j** for potential to induce caspase-3 activation in C3A and Caco-2 cells using Gefitinib as a reference standard (Figure 35). The

results of this study indicate that these compounds induce apoptosis through activation of caspase-3 that subsequently leads to cell membrane alterations.

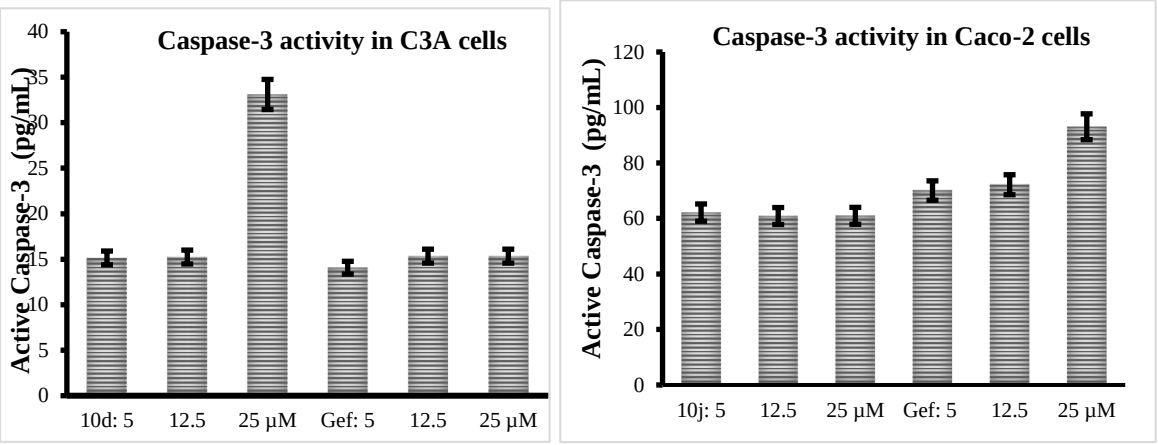


Figure 35: Effects of compounds **215d** and **215j** on Human Caspase-3 (Asp175) activity in C3A and Caco-2 cells against Gefinitib (Gef), respectively.

The hepatocellular carcinoma and the colorectal adenocarcinoma cell lines have been found to express high levels of EGFR and sensitivity to Gefitinib.[170,171] Inhibition of EGFR-TK activity is regarded as the most promising approach for innovative therapeutic strategies in cancer treatment.[172]

2.5.8 Inhibition of EGFR-TK phosphorylation complemented with molecular docking

The benzofuran-based 4-aminoquinazolines **215a-j** were tested for their inhibitory potency against human EGFR against Gefitinib as the reference standard (Table 23). Compound **215j** was found to exhibit significant cytotoxicity against the A549, Caco-2 and Hela cells showed moderate EGFR inhibitory activity (IC_{50} = 61.46 nM) compared to the reference standard. The most cytotoxic compound **215d** against the C3A cell line and compound **215e** were found to inhibit the EGFR IC_{50} = 29.26 nM and 31.1 nM more so than the reference drug. Based on the

observed results, we can conclude that the EGFR-TK inhibitory activity of the benzofuran-aminoquinazolines **215** is correlated to their antiproliferative activities.

Table 23: Percentage inhibition and IC_{50} values (in nM) of EGFR-TK by **215a-j** against Gefitinib

Compound	IC_{50} (nM)
215a	111.3 ± 0.42
215b	122.5 ± 0.50
215c	52.2 ± 0.18
215d	29.3 ± 0.02
215e	31.1 ± 0.12
215f	40.4 ± 0.16
215g	132.9 ± 0.55
215h	125.7 ± 0.52
215i	90.2 ± 0.34
215j	61.5 ± 0.01
Gefitinib	33.1 ± 0.02

Molecular docking studies in were also performed performed using AutoDock to validate whether compounds **215** have comparable binding mode to that of gefitinib for EGFR. A crystal structure of EGFR that previously co-crystalized with Erlotinib (an inhibitor of EGFR) was obtained from the protein data bank (PDB ID: 1M17). The control (Gefitinib) docked on Erlotinib binding site produced root mean square deviation (RMSD) of 1.6 Å with the crystal structure (Figure 36). Binding free energy calculation showed that Gefitinib is more favourable

for the inhibition towards EGFR compared with Erlotinib. The binding conformation of Gefitinib might explain the better binding affinity compared with Erlotinib. The morpholine region of Gefitinib was positioned as anti-parallel with Phe699 side chain, but no such orientation was observed in Erlotinib. In addition, the 3-chloro-4-fluorophenyl moiety of Gefitinib also docked deeper into the EGFR binding pocket compared with Erlotinib. Compound **215i** has the highest binding affinity among the 2-arylbenzofuran-appended 4-aminoquinazoline hybrids **215a**–**j** with the binding free energy of -11.54 kcal/mol.

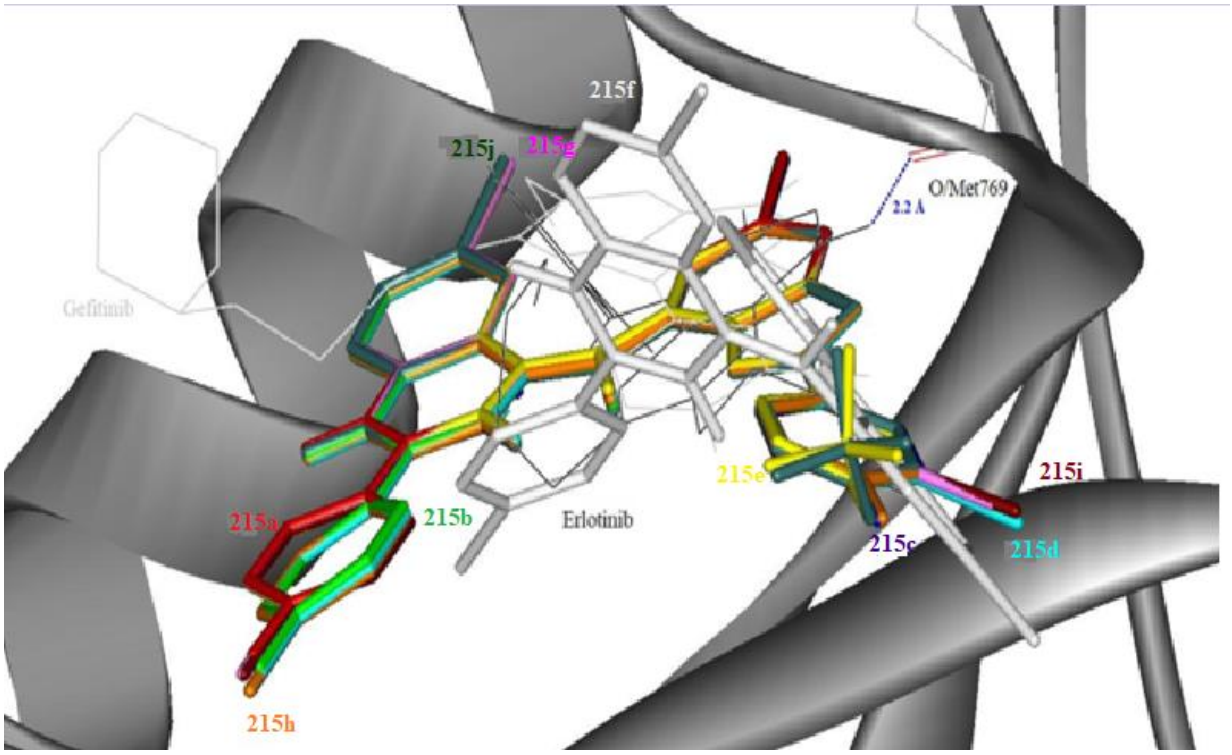


Figure 36: Docked conformation of Erlotinib (as docking control), Gefitinib and 4-aminoquinazoline–appended 2-arylbenzofurans (compound **215**; stick representation) in the binding pocket of epidermal growth factor receptor (EGFR) kinase domain (surface and ribbon representation). Blue dotted lines are the direct hydrogen bonding formed between docked ligands and EGFR. The results for the synthesis and biological evaluation of the 4-aminoquinazoline–appended 2-arylbenzofurans have since been published.[173]

Chapter 3: Conclusions

In summary, the 2-amino-3-halogenochalcone and 2-hydroxy-3-halogenochalcone moieties represent suitable scaffolds for sequential alkynylation and heteroannulation for the construction of the five-membered heterocyclic ring onto the 1,3-diaryl-2-propen-1-one framework to afford novel indole-and benzofuran-chalcones, respectively. The indole-chalcones were found to undergo site-selective acetylation with triflouroacetic anhydride (TFAA) in the absence of a catalyst or additive to afford the corresponding 3-trifluoroacetylindole-chalcones without traces of the isomeric *N*-1 acetylated derivatives. The ambident electrophilic C=C–C=O framework of the indole- and benzofuran-chalcones, in turn, facilitated one-pot nucleophilic attack on the carbonyl group (1,2-addition) and subsequent conjugate addition at the β-carbon (1,4- or Michael addition) with 2-aminothiophenol to afford indole- and benzofuran-benzothiezapine hybrids. A simple method for linking the 2-arylbenzofuran and quinazoline scaffolds through an amino bridge to comprise analogues of the medicinally important 4-anilinoquinazolines or Cediranib (**12**) has also been developed.

Most of benzofuran-chalcone hybrids exhibited moderate to significant antigrowth effects in vitro against the MCF-7 cell line when compared to the reference standard actinomycin D. The presence of a 2-phenyl substituent on the benzofuran moiety and a 4-fluorophenyl group in compound **203b** or a combination of a 2-phenyl group on the benzofuran moiety and a 4-(trifluoromethoxy)phenyl group on the chalcone arm of **203e** increased cytotoxicity against the MCF-7 cell line. The presence of a 4-methoxyphenyl group on the chalcone and 4-fluorophenyl group (**203i**) or 3-chlorophenyl group (**203s**) on the benzofuran framework of the benzofuran-chalcone hybrids The most cytotoxic benzofuran-chalcone hybrids **203b** and **203i**, have been evaluated for apoptosis by Annexin V-Cy3 SYTOX staining and caspase-3 activation The

experimental and molecular docking results suggest that the title compounds have potential to inhibit tubulin polymerization and epidermal growth factor receptor tyrosine kinase (EGFR-TK) phosphorylation. The modeled structures of representative compounds displayed hydrophobic interactions as well as hydrogen and/or halogen bonding with the protein residues in the colchicine binding site of tubulin or ATP binding pocket of the EGFR. These interactions presumably account for the observed increased binding affinity of these compounds against the two receptors and their significant antigrowth effect against the MCF-7 cell line.

The benzofuran-aminoquinazoline hybrids **215a**–**j** were found to exhibit moderate to significant cytotoxicity against the HeLa cells with the exception of **215b**, **215g** and **215i** substituted with a fluorine or chlorine atom on the 3-position of the phenyl substituent on the benzofuran arm. Although most of these compounds are less active against the Caco-2 and C3A cell lines, a combination of a 2-(3-chlorophenyl) group on the benzofuran moiety and a 2-(4-fluorophenyl) group on the quinazoline framework of **215d** resulted in significant cytotoxicity against the C3A cell line (IC_{50} = 9.0 µM) when compared to Gefitinib (IC_{50} = 5.01 µM). Likewise, compound **215j** substituted with a 4-chlorophenyl group at the 2-position of the quinazoline moiety and 4-trifluoromethoxyphenyl group at the 2-position of the benzofuran framework was found to exhibit increased cytotoxicity against the Caco-2 cells (IC_{50} = 18.4 µM) more so than Gefitinib (IC_{50} = 27.9 µM). Compounds **215d** and **215j**, which were selected for further evaluation of the mode of cell death were able to trigger apoptosis in C3A and Caco-2 cells, respectively. This demonstrates that the benzofuran-aminoquinazoline hybrids exhibit cytotoxicity and pro-apoptotic properties. Compounds **215d** and **215j** not only demonstrated strong antiproliferation activities against some of the tested cancer cell lines, but also showed significant inhibitory activity towards EGFR (IC_{50} = 29.3 nM and 61.5 nM, respectively) compared to the medicinally important EGFR inhibitor, Gefitinib (IC_{50} = 33.1 nM). Molecular docking of compounds **215**

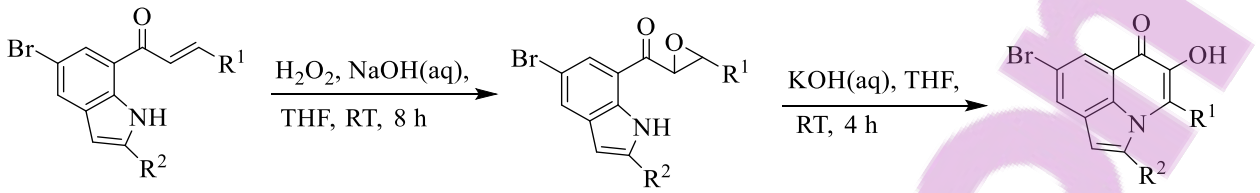
into EGFR-TK active site suggests that they bind to the region of EGFR like Gefitinib does. The benzofuran-aminoquinazoline and their derivatives may also target other protein kinases. Therefore, future studies will be extended to other types of protein kinases to explore their mechanism of action and selectivity.

The Csp^2–Br bond of the compounds prepared in this investigation could be transformed via other transition metal catalysed cross-coupling reactions to afford polycarbosubstitued derivatives. The reactions may include Kumada cross-coupling with organomagnesium compounds[174], Suzuki cross-coupling with organoboronic acids[175], Negishi cross-coupling with organozinc reagents[176], Heck cross-coupling with alkenes[177], Sonogashira cross-coupling with terminal alkynes[129], Stille cross-coupling with organostannane compounds[174] or Buchwald-Hartwig reaction which represents an important example for the carbon-heteroatom bond formation between aryl/heteroarylhalides with amines[178] to afford poly-substituted derivatives.

Future research extending from this study will include the following:

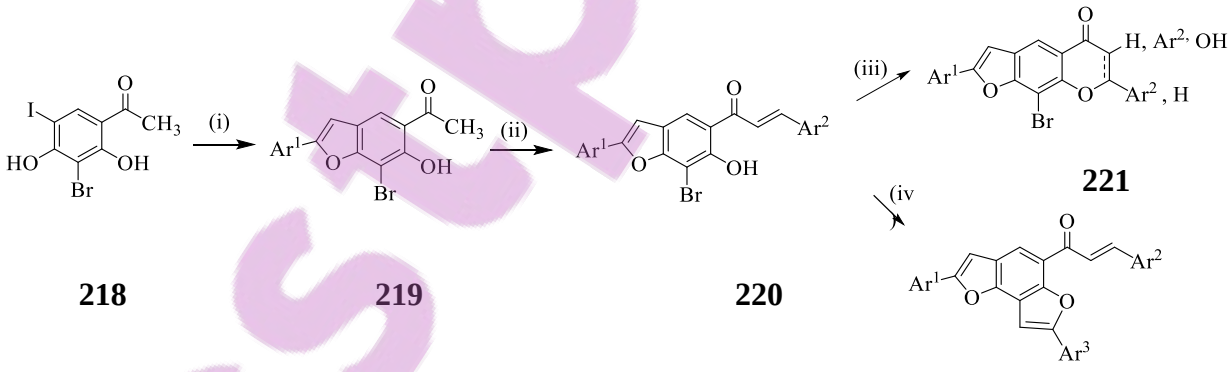
i. Synthesis of polysubstituted pyrroloquinolinones **217** via initial epoxidation of the indole-appended chalcones **201** followed by base-mediated cyclization of the incipient epoxide derivatives **216**. The pyrroloquinoline-based compounds, for example, are antimitotic agents[179] capable of disruption of tubulin polymerization[180,181] Microtubule targeting agents are effective anti-cancer drugs and have also been instrumental as biological probes to identify the nature of tubulin and the role of tubulin dynamics in mitosis[182-183] Some pyrroloquinolinones have also been found to induce cell cycle arrest[184,185] and act as dual topoisomerase I and II inhibitors.[186] Compounds **217** would then be evaluated for their capability to serve as dual inhibitors of

tubulin polymerization and DNA topoisomerase I/II activity complemented with molecular docking.



201 **216** **217**

ii. To effect the site-selective tandem Sonogashira cross-coupling and cyclization of 3-bromo-2,4-dihydroxy-5-iodobenzophenone **218** with terminal acetylenes followed by Claisen-Schmidt aldol condensation of the intermediate 5-acetyl-2-aryl-7-bromo-6-hydroxybenzofurans **219** with benzaldehyde derivatives to afford the corresponding linear benzofuran-chalcone hybrids **220**. Further cclization of the ortho-hydroxy chalcone moiety would afford furoflavanones, furoflavones, furoisoflavones or furofavanols with potential biological activity. Moreover, tandem Sonogashira cross-coupling and cyclization of **220** with terminal acetyls would afford diarylbenzodifuranyl-chalcone hybrids **222** with potential biological or photophysical properties.

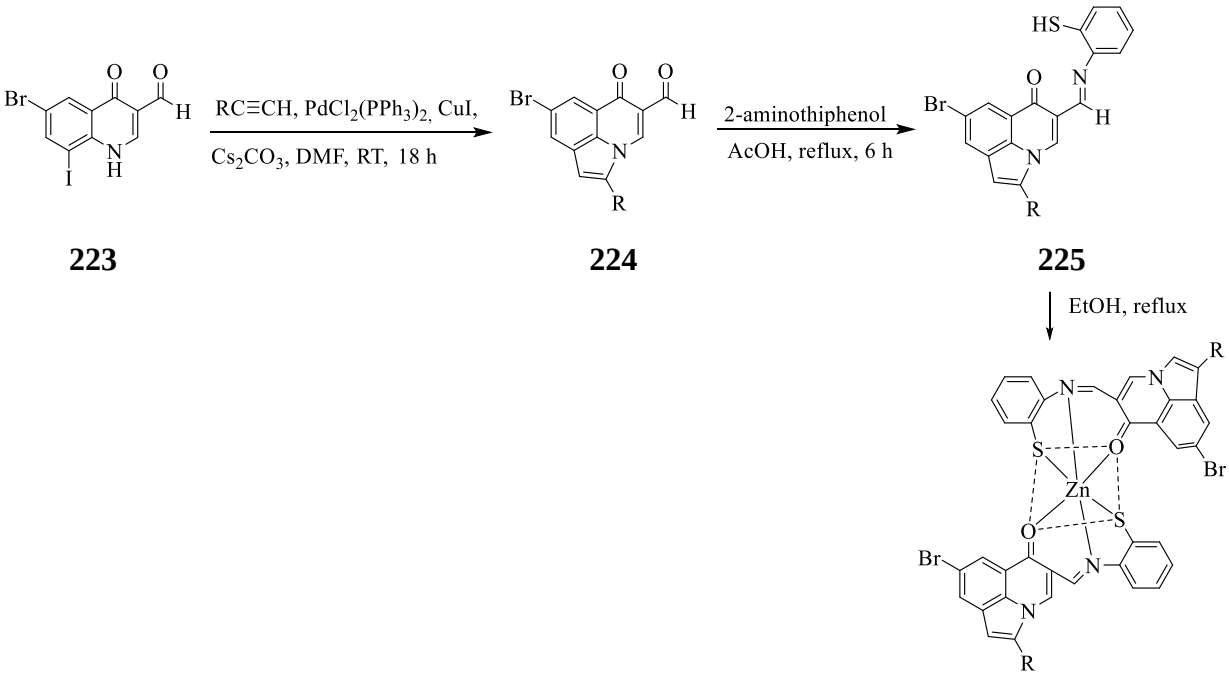


218 **219** **220** **221**

222

iii. Transformation of 2-amino-5-bromo-3-iodoacetophenone **197a** via Vilsmeier-Haack reaction with $POCl_3$-DMF mixture followed by acid-mediated hydrolysis of the intermediate 6-bromo-4-chloro-8-iodoquinoline-3-carbaldehyde to afford 6-bromo-8-iodo-4-oxo-1,4-dihydroquinoline-3-carbaldehyde. One-pot palladium catalysed tandem Sonogashira cross-

coupling and cycloisomerization of **223** with terminal acetylenes, for example, would afford the corresponding 2-aryl-8-bromo-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carbaldehydes. Compound **224** has several reactive centres, anmely the electrophilic unsaturated dicarbonyl framework, Csp^2–Br and Csp^2–H bonds for further transformation with nucleophilic reagents and transition metal mediated C–C and/or C–N bond formation. The Schiff bases **225** of **224**, on the other hand, could be complexed with Zn(II) metal, for example, to afford complexes **226** with potential biological and photophysical properties.



223 **224** **225**

226

Chapter 4: Experimental

4.0 General

Commercially available solvents and reagents were used as supplied or purified by conventional methods before use. Melting points were recorded on a Thermocouple digital melting point apparatus (Mettler Toledo LLC, Columbus, OH, USA) and are uncorrected. IR spectra (Bruker Optics, Billerica, MA, USA) were recorded as powders using a Bruker VERTEX 70 FT-IR Spectrometer (Bruker Optics, Billerica, MA, USA) with a diamond ATR (attenuated total reflectance) accessory by using the thin-film method. For column chromatography, Merck kieselgel 60 (0.063–0.200 mm) (Merck KGaA, Frankfurt, Germany) was used as stationary phase. NMR spectra were obtained as $CDCl_3$ or DMSO-d_6 solutions using Varian 300 MHz (Varian Inc., Palo Alto, CA, USA) or Agilent 500 MHz NMR (Agilent Technologies, Oxford, UK) spectrometers and the chemical shifts are quoted relative to the TMS peak. High-resolution mass spectra were recorded using 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 spectroscopy:

ppm = parts per million

J = coupling constant in Hz

δ = chemical shift values in ppm

s = singlet, br s = broad singlet

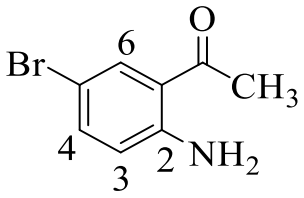
d = doublet, dd = doublet of doublets

t = triplet, q = quartet,

m = multiplet; qt = quintet

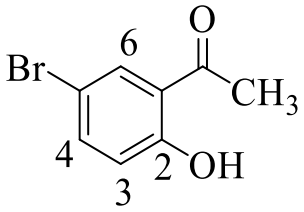
4.1 Halogenation of 2-aminoacetophenone (195a) and 2-hydroxyacetophenone (195b)

4.1.1 Synthesis of 2-amino-5-bromo-3-iodoacetophenone (196a)



A stirred solution of 2-aminoacetophenone **195a** (5.00 g, 36.99 mmol) in CH_2Cl_2 (500 mL) at 0 °C was treated slowly with pyridinium tribromide (11.83 g, 36.9 mmol). The reaction mixture was allowed to warm up to room temperature (RT) and then stirred at this temperature for 3 h. The resultant precipitate was filtered and recrystalized from hexane to afford **196a** as a yellow solid (6.02 g, 76%), mp. 79–81 °C (lit.[142] 82–83 °C); ν_{max} (ATR) 3453, 3316, 1653, 1609, 1563, 1540, 1464, 1360, 1287, 1217, 1160, 956, 888, 822, 738, 671, 623, 517 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 2.65 (3H, s, CH_3), 6.29 (2H, br s, NH_2), 6.56 (1H, d, *J* = 8.5 Hz, H-3), 7.34 (1H, dd, *J* = 2.5 and 8.5 Hz, H-4), 7.80 (1H, d, *J* = 2.5 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) 27.7, 106.5, 118.9, 119.2, 134.0, 136.9, 149.0, 199.6.

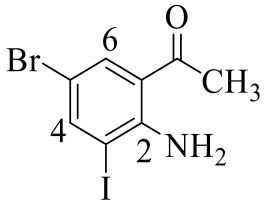
4.1.2 Synthesis of 5-bromo-2-hydroxyacetophenone (196b)



A stirred solution of 2-hydroxyacetophenone **195b** (5.26 g, 38.7 mmol) in acetic acid (400 mL) was treated with *N*-bromosuccinimide (18.02 g, 38.7 mmol) at RT. The mixture was stirred under

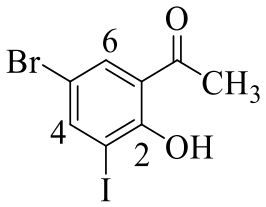
reflux for 1.5 h and then quenched with an ice-cold water. The resulting precipitate was filtered and recrystallized to afford 5-bromo-2-hydroxyacetophenone **196b** (4.92 g, 59%); mp. 74–75 °C (lit.[143] 82–83 °C) (hexane); ν_{max} (ATR) 491, 516, 624, 735, 879, 1081, 1195, 1285, 1346, 1473, 1559, 1640, 3280 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.63 (3H, s, CH_3), 6.87 (1H, d, *J* = 8.5 Hz, H-3), 7.53 (1H, dd, *J* = 2.4 and 8.5 Hz, H-4), 7.81 (1H, d, *J* = 2.4 Hz, H-6), 12.14 (1H, s, OH); ^{13}C NMR ($CDCl_3$) 26.6, 87.6, 106.7, 118.9, 134.7, 145.7, 148.5, 203.02.

4.1.3 Synthesis of 2-amino-5-bromo-3-iodocetophenone (197a)



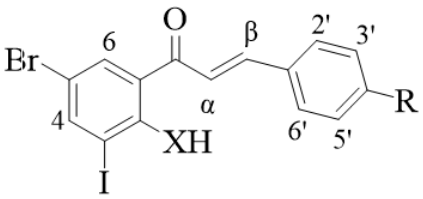
A stirred solution of **196a** (5.00 g, 23.36 mmol) in acetic acid (400 mL) was treated with *N*-iodosuccinimide (5.78 g, 25.69 mmol) at RT. The mixture was stirred at RT for 2 h and then quenched with an ice-cold water. The resulting precipitate was filtered and recrystallized from ethanol to afford **197a** (5.88 g, 74%); mp 95–97 °C (EtOH); ν_{max} (ATR) 3453, 3383, 1637, 1590, 1558, 1510, 1425, 1353, 1226, 949, 862, 741, 675, 625, 535, 443 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 2.58 (3H, s, CH_3), 6.97 (2H, br s, NH_2), 7.83 (1H, d, *J* = 2.0 Hz, H-4), 7.88 (1H, d, *J* = 2.0 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) 27.7, 87.6, 106.7, 118.9, 134.7, 145.7, 148.5, 199.0; HRMS (ES): MH^+, found 339.8838. $C_8H_8NO^{79}BrI^+$ requires: 339.8834.

4.1.4 Synthesis of 5-bromo-2-hydroxy-3-iodoacetophenone (197b)



A mixture of 5-bromo-2-hydroxyacetophenone **196b** (3.23 g, 15.0 mmol) and *N*-iodosuccinimide (5.78 g, 18,0 mmol) in acetic acid (400 mL) was treated as for **197a** above. Work-up and recrystallization afforded **197b** as a brown solid (4.78 g, 93%), mp. 111–112 °C (Lit.[146] 104–105 °C); ν_{max} (ATR) 441, 539, 670, 779, 862, 968, 1077, 1190, 1233, 1362, 1420, 1581, 1650, 3259 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.65 (3H, s, CH_3), 7.83 (1H, d, *J* = 2.1 Hz, H-4), 8.04 (1H, d, *J* = 2.1 Hz, H-6), 13.07 (1H, s, OH); ^{13}C NMR ($CDCl_3$) 26.4, 87.6, 111.1, 120.2, 133.1, 147.1, 160.2, 203.2; HRMS (ES): MH^+, found. $C_8H_7O_2{}^{79}BrI^+$ requires: 341.8575.

4.2 Synthesis of the (*E*)-2-amino-5-bromo-3-iodochalcones 198a–d



198a–d

(*E*)-1-(2-Amino-5-bromo-3-iodophenyl)-3-phenylprop-2-en-1-one (198a); X = NH, R = H

A mixture of 2-amino-5-bromo-3-iodocetophenone **197a** (3.00 g, 8.84 mmol), benzaldehyde (0.98 g, 8.84 mmol) and potasium hydroxide (4 pellets, *ca* 0.8 g) in ethanol (30 mL) was stirred for 6 hours at room temperature. The mixture was quenched with ice cold water (120 mL) and the precipitate was filtered to afford **198a** as a yellow solid (3.20 g, 86%), mp. 103–105 °C

(EtOH); ν_{max} (ATR) 453, 581, 676, 889, 976, 1070, 1173, 1281, 1335, 1581, 1642, 3278, 3432 cm^{-1}; δ_H (500 MHz, $CDCl_3$) ; δ_C (125 MHz, $CDCl_3$) 7.01 (2H, br s, NH_2), 7.41–7.44 (3H, m, ArH), 7.50 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.64 (1H, d, *J* = 2.0 Hz, 4-H), 7.65 (2H, d, *J* = 6.5 Hz, ArH), 7.76 (1H, d, J_{trans} = 15.5 Hz, β-H), 7.91 (1H, d, *J* 2.0 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 99.0, 105.6, 111.3, 119.7, 122.0, 128.4, 130.6, 133.7, 134.8, 139.3, 144.4, 150.3, 190.3; HRMS (ES): MH^+, found. 427.9144. $C_{15}H_{12}NO^{79}BrI^+$ requires: 427.9147.

(*E*)-1-(2-Amino-5-bromo-3-iodophenyl)-3-(4′-fluorophenyl)prop-2-en-1-one (198b); X = NH, R = F

A mixture of 2-amino-5-bromo-3-iodocetophenone **197a** (3.00 g, 8.84 mmol), 4-fluorobenzaldehyde (1.09 g, 8.84 mmol) and potasium hydroxide (4 pellets, *ca* 0.8 g) in ethanol (30 mL) was treated as described for **198a.** Work-up afforded **198b** as a yellow solid (3.50 g, 89%), mp. 146–149 °C (EtOH); ν_{max} (ATR) 454, 542, 674. 825, 975, 1155, 1190, 1504, 1550, 1643, 3302, 3447 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.00 (2H, br s, NH_2), 7.12 (2H, *J* = 8.7 Hz, 3′,5′-H), 7.41 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.64 (2H, t, *J* = 8.7 Hz, 2′,6′-H), 7.73 (1H, d, J_{trans} = 15.5 Hz, β-H), 7.92 (1H, d, *J* = 2.1 Hz, 4-H), 7.94 (1H, d, *J* 2.1 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 87.7, 106.9, 116.1 (d, $^2J_{CF}$ = 21.8 Hz), 119.8, 121.4, 130.4 (d, $^3J_{CF}$ = 8.5 Hz), 130.9 (d, $^4J_{CF}$ = 3.3 Hz), 133.5, 143.4, 145.6, 149.0, 164.1 (d, $^1J_{CF}$ = 250.2 Hz), 189.9; HRMS (ES): MH^+, found 445.9050. $C_{15}H_{11}NO^{79}BrIF^+$ requires: 445.9053.

(*E*)-1-(2-Amino-5-bromo-3-iodophenyl)-3-(4′-chlorophenyl)prop-2-en-1-one (198c); X = NH, R = Cl)

A mixture of 2-amino-5-bromo-3-iodocetophenone **197a** (3.00 g, 8.84 mmol), 4-chlorobenzaldehyde (1.24 g, 8.84 mmol) and potasium hydroxide (4 pellets, *ca* 0.8 g) in ethanol (30 mL) was treated as described for **198a.** Work-up afforded **198c**. as a yellow solid (3.71 g, 93%), mp. 142–144°C (EtOH); ν_{max} (ATR) 460, 675, 821, 1013, 1091, 1189, 1488, 1506, 154, 1584, 1641, 3314, 3456 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.00 (2H, br s, NH_2), 7.12 (2H, *J* = 8.7 Hz, 3′,5′-H), 7.41 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.64 (2H, t, *J* = 8.7 Hz, 2′,6′-H), 7.73 (1H, d, J_{trans} = 15.5 Hz, β-H), 7.92 (1H, d, *J* = 2.1 Hz, 4-H), 7.94 (1H, d, *J* 2.1 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 87.7, 106.9, 119.7, 122.2, 129.3, 129.7, 135.5, 136.5, 143.2, 143.2, 145.6, 149.1, 189.7; HRMS (ES): MH^+, found 461.8745. $C_{15}H_{11}NO^{79}Br^{35}ClI^+$ requires: 461.8757.

(*E*)-1-(2-Amino-5-bromo-3-iodophenyl)-3-(4′-methoxyphenyl)prop-2-en-1-one (198d); X = NH, R = OCH_3

A mixture of 2-amino-5-bromo-3-iodocetophenone **197a** (3.00 g, 8.84 mmol), 4-methoxybenzaldehyde (1.20 g, 8.84 mmol) and potasium hydroxide (4 pellets, *ca* 0.8 g) in ethanol (30 mL) was treated as described for **198a.** Work-up afforded **198d** as a yellow solid (3.64 g, 91%), mp. 139–142 °C (EtOH); ν_{max} (ATR) 537, 673, 824, 985, 1166, 1259, 1506, 1548, 1634, 3276, 3448 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.92 (2H, br s, NH_2), 6.94 (2H, *J* = 8.0 Hz, 3′,5′-H), 7.36 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.60 (2H, t, *J* = 8.0 Hz, 2′,6′-H), 7.74 (1H, d, J_{trans} = 15.5 Hz, β-H), 7.90 (1H, d, *J* = 1.5 Hz, 4-H), 7.94 (1H, d, *J* 1.5 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 55.4, 87.6, 106.9, 114.4, 119.4, 120.2, 127.5, 130.3, 135.4, 144.7, 145.2, 148.9, 161.7, 190.1; HRMS (ES): MH^+, Found 457.9251. $C_{16}H_{14}NO_2{}^{79}BrI^+$ requires: 457.9253.

(*E*)-1-(5-Bromo-2-hydroxy-3-iodophenyl)-3-phenylprop-2-en-1-one (197e); X = O, R = H

A mixture of **197b** (2.90 g, 8.33 mmol), benzaldehyde (1.05 g, 9.99 mmol) and KOH (2.74 g, 48.9 mmol) in methanol (100 mL) was treated as described for **198a** to afford **198e** as an orange solid (2.57 g, 72%), mp. 152–154 °C (EtOH); ν_{max} (ATR) 581, 676, 889, 976, 1070, 1173, 1281, 1335, 1581, 1642, 3278 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.47 (1H, t, *J* = 7.0, Ar), 7.50 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.68 (2H, d, *J* = 8.0 Hz, Ar), 7.65 (2H, d, *J* = 7.5 Hz, Ar), 8.00 (1H, d, J_{trans} = 15.5 Hz, β-H), 8.01 (1H, d, *J* 2.0 Hz, H-4), 8.07 (1H, d, *J* 2.0 Hz, H-6), 13.5 (1H, br s, OH); δ_C (125 MHz, $CDCl_3$) 110.9, 114.5, 115,9, 120.8, 126.9, 130.1, 130.9, 131.2, 131.9, 142.6, 147.5, 160.3, 190.7; HRMS (ES): found 428.8997. $C_{15}H_{11}O_2{}^{79}BrI^+$ requires 428.8987. *Anal* calcd for $C_{15}H_{10}O_2BrI$: C, 41.99; H, 2.35. Found: C, 41.96; H, 2.32.

(*E*)-1-(5-Bromo-2-hydroxy-3-iodophenyl)-3-(4′-fluorophenyl)prop-2-en-1-one (198f); X = O, R = F

A mixture of **197b** (3.78 g, 11.08 mmol), 4-flourobenzaldehyde (1.86 g, 13.30 mmol) and KOH (3.44 g, 61.3 mmol) in methanol (100 mL) was treated as described for **198a** to afford **198f** as an orange solid (4.11 g, 80%), mp. 177–179 °C (EtOH); ν_{max} (ATR) 542, 674, 825, 975, 1155, 1190, 1504, 1550, 1643, 3202 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.15 (2H, t, *J* = 8.5 Hz) 7.46 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.69 (2H, t, *J* = 8.0 Hz), 7.95 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.00 (1H, d, *J* 1.5 Hz. H-4), 8.07 (1H, d, *J* 2.5 Hz, H-6), 13.7 (1H, br s, OH); δ_C (125 MHz, $CDCl_3$) 87.7, 106.9, 116.1 (d, $^2J_{CF}$ = 21.8 Hz), 119.8, 121.4, 130.4 (d, $^3J_{CF}$ = 8.5 Hz), 130.9 (d, $^4J_{CF}$ = 3.3 Hz), 133.5, 143.4, 145.6, 149.0, 164.1 (d, $^1J_{CF}$ = 250.2 Hz), 189.3; HRMS (ES): found 446.8815. $C_{15}H_{10}O_2F^{79}BrI^+$ requires 446.9053. *Anal* calcd for $C_{15}H_9O_2FBrI$: C, 40.30; H, 2.03. Found: C, 40.19; H, 1.98.

(*E*)-1-(5-Bromo-2-hydroxy-3-iodophenyl)-3-(4-chlorophenyl)prop-2-en-1-one (198g); X = O, R = Cl

A mixture of **197b** (3.78 g, 11.08 mmol), 4-chlorobenzaldehyde (1.86 g, 13.30 mmol) and KOH (3.44 g, 61.3 mmol) in methanol (100 mL) was treated as described for **198a** to afford **198g** as an orange solid (4.11 g, 80%), mp. 184–186 °C (EtOH); ν_{max} (ATR) 675, 821, 1013, 1091, 1189, 1488, 1506, 154, 1584, 1641, 3249 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.58 (1H, br s, OH) 7.03 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.39 (2H, d, *J* = 8.5 Hz, H-2',6'), 7.55 (2H, d, *J* = 8.5 Hz, H-3',5'), 7.67 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.84 (1H, d, *J* 2.5 Hz. H-4), 8.05 (1H, d, *J* 2.5 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 87.7, 111.1, 120.2, 125.7, 129.3, 129.5, 133.1, 133.2, 136.5, 142.1, 147.4, 160.2, 188.3 (C=O); HRMS (ES): found 462.8519. $C_{15}H_{10}O_2{}^{35}Cl^{79}BrI^+$ requires 462.8499. *Anal* calcd for $C_{15}H_9O_2ClBrI$: C, 38.87; H, 1.96. Found: C, 38.77; H, 2.04.

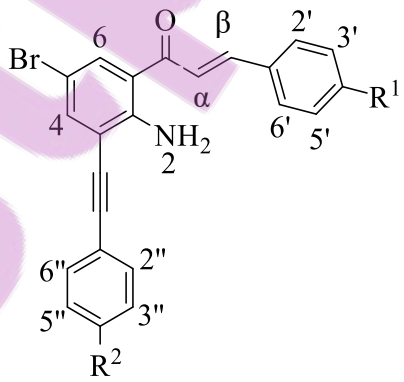
(*E*)-1-(5-Bromo-2-hydroxy-3-iodophenyl)-3-(4′-methoxyphenyl)prop-2-en-1-one (198h); X = O, R = OCH_3

A mixture of **197b** (4.08 g, 11.96 mmol), 4-methoxybenzaldehyde (1.95 g, 14.35 mmol) and KOH (3.34 g, 59.80 mmol) in methanol (100 mL) was treated as described for **198a** to afford **198h** as an orange solid (3.83 g, 69%), mp. 173–175 °C (EtOH); ν_{max} (ATR) 537, 673, 824, 985, 1166, 1259, 1506, 1548, 1634, 3276 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3) 6.96 (2H, d, *J* = 8.5 Hz, H-3',5'), 7.42 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.65 (2H, d, *J* = 8.5 Hz, H-2',6'), 7.96 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.01 (1H, d, *J* 2.0 Hz, H-4), 8.05 (1H, d, *J* 2.0 Hz, H-6), 13.5 (1H, br s, OH); δ_C (125 MHz, $CDCl_3$) 55.6, 114.3, 115.9, 126.8, 129.9, 130.0, 130.9, 131.0, 131.9, 140.9, 147.5, 162.5, 164.6, 190.7; HRMS (ES): MH^+, found 458.9095. $C_{16}H_{13}O_3{}^{79}BrI^+$ requires 458.9093. *Anal* calcd for $C_{16}H_{12}O_3BrI$: C, 41.86; H, 2.63. Found: C, 41.93; H, 2.75.

(*E*)-1-(5-Bromo-2-hydroxy-3-iodophenyl)-3-(4′-(trifluoromethoxy)phenyl)prop-2-en-1-one (185i); X = O, R = OCF_3

A mixture of **197b** (2.98 g, 8.79 mmol), 4-trifluoromethoxybenzaldehyde (2.15 g, 10.54 mmol) and KOH (2.46 g, 43.95 mmol) in methanol (100 mL) was treated as described for **198a** to afford **198i** as an orange solid (3.33 g, 74%), mp. 106–107 ºC; ν_{max} (ATR) 542, 691, 869, 1033, 1140, 1259, 1343, 1447, 1573, 1642, 3283 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.33 (1H, d, *J* = 8.0 Hz, H-3'), 7.50 (2H, d, *J* = 8.5 Hz, H-2',6'), 7.54 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.61 (1H, d, *J* = 8.0 Hz, H-5'), 7.94 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.01 (1H, d, *J* 2.0 Hz, H-4), 8.10 (1H, d, *J* 2.0 Hz, H-6), 13.6 (1H, br s, OH); δ_C (125 MHz, $CDCl_3$) 112, 120.2 (t, J_{CF} = 256.0 Hz), 123.8, 127.2, 129.9, 130.6, 132.0, 133.1, 136.1, 145.5, 147.3, 147.5, 161.4, 191.9; HRMS (ES): MH^+, found 510.8633 $C_{16}H_9O_3{}^{79}BrIF_3{}^+$ requires 510.8654. *Anal* calcd for $C_{16}H_{12}O_3BrI$: C, 41.86; H, 2.63. Found: C, 41.93; H, 2.75.

4.3 Sonogashira cross-coupling of compounds 198a–f



198a–f

(*E*)-1-(2-Amino-5-bromo-3-(phenylethynyl)phenyl)-3-phenylprop-2-en-1-one (200a); R^1 = H, R^2 = H

A mixture of **198a** (2.00 g, 4.67 mmol), phenylacetylene (0.57 g, 5.60 mmol), $PdCl_2(PPh_3)_2$ (0.16 g, 0.23 mmol), Cs_2CO_3 (1.82 g, 5.60 mmol) and CuI (0.09 g, 0.46 mmol) in ethanol (40 mL) 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 5 min. and a balloon filled with argon gas was connected to the top of the condenser. The mixture was stirred at 70 °C for 4 h, cooled to r.t. and then quenched with an ice-cold water. The mixture 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 **200a** as a solid (1.44 g, 76%); R_f (toluene) 0.37, mp. 106–108 °C; ν_{max} (ATR) 535, 728, 850, 922, 1019, 1113, 1202, 1308, 1440, 1587, 1644, 3300, 3331, 3470 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.12 (2H, br s, NH_2), 7.38–7.40 (3H, m. PhH), 7.42–7.45 (3H, m, PhH), 7.42 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.54–7.56 (2H, m, PhH), 7.65 (1H, *J* = 2.5 Hz, 6-H), 7.66–7.68 (2H, m, Ph), 7.80 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.95 (1H, d, *J* 2.5 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 97.2, 105.7, 112.1, 119.7, 122.1, 122.4, 128.4, 128.5, 128.8, 129.0, 130.5, 131.6, 133.5, 134.9, 139.0, 144.0, 144.3, 150.3, 190.4; HRMS (ES): MH^+, found 402.0490. $C_{23}H_{17}NO^{79}Br^+$ requires: 402.0494.

(*E*)-1-(2-Amino-5-bromo-3-(phenylethynyl)phenyl)-3-(4′-fluorophenyl)prop-2-en-1-one (200b); R^1 = F, R^2 = H

A mixture of **198b** (2.00 g, 4.50 mmol), phenylacetylene (0.52 g, 5.40 mmol), $PdCl_2(PPh_3)_2$ (0.16 g, 0.23 mmol), Cs_2CO_3 (1.80 g, 5.40 mmol) and CuI (0.08 g, 0.45 mmol) in ethanol-water (40

mL) was treated as described for **200a**; work up and column chromatography on silica gel afforded **200b** as a solid (1.52 g, 81%); R_f (toluene) 0.35, mp. 121–123 °C; ν_{max} (ATR) 536, 638, 753, 850, 948, 1028, 1131, 1250, 1302, 1441, 1508, 1585, 1643, 3294, 3340, 3469 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.11 (2H, t, J = 8.7 Hz, 3′,5′-H), 7.12 (2H, br s, NH_2), 7.36–7.38 (3H, m, PhH), 7.43 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.51–7.54 (2H, m, PhH), 7.62 (1H, d, J = 2.5 Hz, 4-H), 7.64 (2H, t, J = 8.7 Hz, 2′,6′-H), 7.72 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.91 (1H, d, J = 2.4 Hz, 6-H); δ_C (75 MHz, $CDCl_3$) 83.3, 97.2, 105.7, 112.1, 116.0 (d, $^2J_{CF}$ = 21.8 Hz), 119.5, 121.6, 121.7, 122.3, 128.4, 128.9, 130.4 (d, $^3J_{CF}$ = 8.6 Hz), 131.0 (d, $^4J_{CF}$ = 3.4 Hz), 131.6, 133.4, 143.0, 150.3, 164.0 (d, $^1J_{CF}$ = 250.5 Hz), 190.1; δ_F (470 MHz, $CDCl_3$) -109.0; HRMS (ES): MH^+, found 420.0394. $C_{23}H_{16}NO^{79}BrF^+$ requires: 420.0399.

(*E*)-1-(2-Amino-5-bromo-3-(phenylethynyl)phenyl)-3-(4′-chlorophenyl)prop-2-en-1-one (200c); R^1 = 4, R^2 = H

A mixture of **198c** (2.00 g, 4.35 mmol), phenylacetylene (0.53 g, 5.21 mmol), $PdCl_2(PPh_3)_2$ (0.15 g, 0.22 mmol), Cs_2CO_3 (1.69 g, 5.21 mmol) and CuI (0.08 g, 0.44 mmol) in ethanol (40 mL) was treated as described for **200a**; work up and column chromatography on silica gel afforded **200c** as a solid (1.32, 71%); R_f (toluene) 0.37, mp. 110–113 °C; ν_{max} (ATR) 484, 688, 751, 817, 98, 1011, 1089, 1196, 1483, 1532, 1585, 1644, 3330, 3462 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.12 (2H, br s, NH_2), 7.40 (1H, t, J = 8.0 Hz, 4"-H), 7.44 (2H, t, J = 8.0 Hz, 3",5"-H), 7.49 (2H, d, J = 8.5 Hz, 3',5'-H), 7.65 (2H, d, J = 8.5 Hz), 7.68 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.72 (2H, d, J = 8.0, 2",6"-H), 7.87 (1H, J_{trans} = 16.0 Hz, β-H), 7.97 (1H, d, J = 1.5 Hz, 4-H), 8.00 (1H, d, J = 1.5 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 87.5, 97.3, 106.7, 122.0, 128.3, 128.7, 129.1, 129.4, 129.5, 131.4, 133.0, 133.2, 133.2, 136.3, 138.9, 142.6, 145.6, 148.9, 189.5; HRMS (ES): MH^+, found 436.0106. $C_{23}H_{16}NO^{35}Cl^{79}Br^+$ requires: 436.0104.

(*E*)-1-(2-Amino-5-bromo-3-(phenylethynyl)phenyl)-3-(4′-methoxyphenyl)prop-2-en-1-one (200d); R^1 = OCH_3, R^2 = H

A mixture of **198d** (2.00 g, 4.36 mmol), phenylacetylene (0.53 g, 5.20 mmol), $PdCl_2(PPh_3)_2$ (0.15 g, 0.22 mmol), Cs_2CO_3 (1.70 g, 5.23 mmol) and CuI (0.08 g, 0.436 mmol) in ethanol (40 mL) was treated as described for **200a**; work up and column chromatography on silica gel afforded **200d** as a solid (1.17 g, 62%); R_f (toluene) 0.32, mp. 108–110 °C; ν_{max} (ATR) 497, 535, 687, 752, 822, 984, 1027, 1171, 1197, 1582, 1584, 1643, 2852, 3342, 3469 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.93 (2H, *J* = 8.7 Hz, 3′,5′-H), 7.08 (2H, br s, NH_2), 7.36–7.40 (3H, m, PhH), 7.42 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.51–7.53 (2H, m, PhH), 7.60 (2H, d, *J* = 8.7 Hz, 2′,6′-H), 7.62 (1H, d, *J* = 2.1 Hz, 4-H), 7.73 (1H, d, J_{trans} = 15.5 Hz, β-H), 7.92 (1H, d, *J* = 2.1 Hz, 4-H), 7.93 (1H, d, *J* 2.1 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 55.4, 83.5, 97.1, 105.7, 112.0, 114.4, 119.6, 119.9, 122.4, 127.6, 128.5, 128.8, 130.2, 131.6, 133.4, 138.8, 144.2, 161.6, 190.4; HRMS (ES): MH^+, found 432.0602. $C_{24}H_{19}NO_2{}^{79}Br^+$ requires: 432.0599.

(*E*)-3-(2-Amino-5-bromo-3-((4′′-(trifluoromethoxy)phenyl)ethynyl)phenyl)-3-(4′-chlorophenyl)prop-2-en-1-one (200e); R^1 = Cl, R^2 = OCF_3

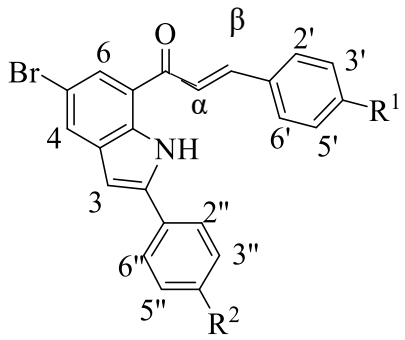
A mixture of **198c** (2.00 g, 4.35 mmol), trifluoromethoxyphenylacetylene (0.97 g, 5.21 mmol), $PdCl_2(PPh_3)_2$ (0.15 g, 0.22 mmol), Cs_2CO_3 (1.69 g, 5.21 mmol) and CuI (0.08 g, 0.44 mmol) in ethanol (40 mL) was treated as described for **200a**; work up and column chromatography on silica gel afforded **200e** as a solid (1.76 g, 78%); R_f (toluene) 0.44, mp. 120–123 °C; ν_{max} (ATR) 486, 654, 778, 843, 1090, 1156, 1291, 1344, 1566, 1646, 3346, 3463 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.10 (2H, br s, NH_2), 7.15 (2H, d, *J* = 8.0 Hz, 3",5"-H), 7.40 (2H, d, *J* = 8.0 Hz, 3',5'-H), 7.49 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.56 (2H, d, *J* 8.5 Hz, 2",6"-H), 7.58 (2H, d, *J* 8.5 Hz, 2',6'-H),

7.63 (1H, d, *J* 2.0 Hz, 4-H), 7.72 (1H, d, J_{trans} = 15.5 Hz, β-H), 7.93 (1H, d, *J* 2.0 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 84.1, 95.6, 105.7, 111.6, 119.5, 120.9, 121.0, 122.2, 122.3 129.2, 129.6, 133.1, 133.2, 133.7, 136.4, 139.2, 142.8, 149.2, 150.2, 189.9; δ_F (470 MHz, $CDCl_3$) -57.8; HRMS (ES): MH^+, found 519.9913. $C_{24}H_{15}NO_2{}^{35}Cl^{79}BrF_3{}^+$ requires: 519.9927.

(*E*)-3-(2-Amino-5-bromo-3-((4′′-(trifluoromethoxy)phenyl)ethynyl)phenyl)-1-(4′-methoxyphenyl)prop-2-en-1-one (200f); R^1 = OCH_3, R^2 = OCF_3

A mixture of **198d** (2.00 g, 4.36 mmol), trifluoromethoxyphenylacetylene (0.97 g, 5.20 mmol), $PdCl_2(PPh_3)_2$ (0.15 g, 0.22 mmol), Cs_2CO_3 (1.70 g, 5.23 mmol) and CuI (0.08 g, 0.44 mmol) in ethanol (40 mL) was treated as described for **200a**; work up and column chromatography on silica gel afforded **200f** as a solid (1.83 g, 82%); R_f (toluene) 0.44, mp. 125–127 °C (EtOH); ν_{max} (ATR) 556, 791, 886, 1034, 1170, 1202, 1249, 1350, 1422, 1507, 1644, 3331, 3470 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.78 (2H, s, NH_2), 6.98 (2H, d, *J* = 8.5 Hz, 3",5"-H), 7.33 (2H, d, *J* = 7.5 Hz, 3',5'-H), 7.59 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.67 (2H, d, *J* 7.0 Hz, 2",6"-H), 7.75 (2H, d, *J* 2.5 Hz, 4-H), 7.72 (1H, d, J_{trans} = 15.5 Hz, β-H), 7.95 (2H, d, *J* 2.0 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 55.2, 84.4, 95.5, 105.8, 111.5, 114.4, 119.5, 120.0, 121.0, 121.2, 127.5, 127.9, 130.3, 133.1, 133.4, 133.8, 138.9, 144.3, 150.2, 161.7, 190.3; δ_F (470 MHz, $CDCl_3$) -57.8; HRMS (ES): MH^+, found 516.0419. $C_{25}H_{18}NO_3{}^{79}BrF_3{}^+$ requires: 516.0419.

4.4 $PdCl_2$-mediated cyclization of compounds 200a–f.



200a–f

(*E*)-1-(5-Bromo-2-phenyl-1*H*-indol-7-yl)-3-phenylprop-2-en-1-one (201a); R^1 = H, R^2 = H

A mixture of **200a** (1.20 g, 2.99 mmol) and $PdCl_2$ (0.11 g, 0.60 mmol) in acetonitrile (20 mL) was heated at 90 °C for 3 h. The solvent was evaporated under reduced pressure and the residue was quenched with saturated sodium thiosulfate. The resultant precipitate was washed thoroughly with cold water and then recrystallized to afford **201a** as a solid (0.90 g, 75%), mp. 197–199 °C (EtOH); ν_{max} (ATR) 568, 685, 707, 758, 841, 889, 1128, 1448, 1576, 1649, 3419 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.82 (1H, d, *J* = 2.5 Hz, 3-H), 7.17 (1H, d, *J* = 7.0 Hz, ArH), 7.26 (1H, t, *J* = 8.0 Hz, ArH), 7.39 (1H, t, *J* = 7.5 Hz, ArH), 7.46–7.50 (4H, m, ArH), 7.71–7.76 (4H, m, ArH), 7.92 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.99 (2H, d, *J* 2.0 Hz, 4-H and 6-H), 10.90 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 98.7, 112.0, 120.5, 121.4, 125.5, 126.3, 126.5, 128.7, 129.0, 129.1, 129.2, 130.8, 131.3, 132.5, 134.8, 135.3, 140.8, 144.7, 189.8; HRMS (ES): MH^+, found 402.0483. $C_{23}H_{17}NO^{79}Br^+$ requires: 402.0494.

(*E*)-1-(5-Bromo-2-phenyl-1*H*-indol-7-yl)-3-(4′-fluorophenyl)prop-2-en-1-one (201b); R^1 = F; R^2 = H

A mixture of **200b** (1.36 g, 3.10 mmol) and $PdCl_2$ (0.109 g, 0.62 mmol) in acetonitrile (20 mL) was treated as for **201a** to afford **201b** as a solid (0.83 g, 63%), mp. 237–239 °C (EtOH); ν_{max} (ATR) 575, 886, 754, 821, 973, 1128, 1229, 1505, 1572, 1597, 1645, 3426 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.83 (1H, d, *J* = 2.5 Hz, 3-H), 7.17 (2H, t, *J* = 8.5 Hz, ArH), 7.40 (1H, t, *J* = 7.5 Hz, ArH), 7.50 (2H, t, *J* = 7.5 Hz, ArH), 7.69 (1H, d, J_{trans} = 15.0 Hz, α-H), 7.71–7.77 (4H, m, ArH), 7.89 (1H, d, J_{trans} = 15.5 Hz, β-H), 8.00 (2H, d, *J* 2.0 Hz, 4-H and 6-H), 10.90 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 98.7, 112.0, 116.2 (d, $^2J_{CF}$ = 21.8 Hz), 120.3, 121.3, 125.5, 126.3, 128.5, 129.1, 129.2, 130.6 (d, $^3J_{CF}$ = 8.5 Hz), 131.0 (d, $^4J_{CF}$ = 2.8 Hz), 131.3, 132.5, 135.3, 140.8, 143.3, 163.4 (d, $^1J_{CF}$ = 246.7 Hz), 189.5; δ_F (470 MHz, $CDCl_3$) -106.2; HRMS (ES): MH^+, found 420.0399. $C_{23}H_{16}NO^{79}BrF^+$ requires: 420.0394.

(*E*)-1-(5-Bromo-2-phenyl-1*H*-indol-7-yl)-3-(4′-chlorophenyl)prop-2-en-1-one (201c); R^1 = Cl, R^2 = H

A mixture of **200c** (1.10 g, 2.52 mmol) and $PdCl_2$ (0.09 g, 0.51 mmol) in acetonitrile (20 mL) was was treated as for **201a** to to afford **201c** as a solid (0.79 g, 71%), mp. 184–186 °C (EtOH); ν_{max} (ATR) 577, 685, 753, 815, 890, 1011, 1087, 1130, 1301, 1449, 1487, 1601, 1647, 3429 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.82 (1H, s, *J* = 2.0 Hz, 3-H), 7.40 (1H, t, *J* = 8.0 Hz, 4''-H), 7.44 (2H, t, *J* = 8.0 Hz, 3'',5''-H), 7.49 (2H, d, *J* = 8.5 Hz, 3',5'-H), 7.65 (2H, d, *J* = 8.5 Hz), 7.68 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.72 (2H, d, *J* = 8.0, 2'',6''-H), 7.87 (1H, J_{trans} = 15.5 Hz, β-H), 7.97 (1H, d, *J* = 1.5 Hz, 4-H), 8.00 (1H, d, *J* = 1.5 Hz, 6-H), 10.88 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 98.7, 112.0, 121.0, 121.3, 125.6, 126.3, 128.6, 129.1, 129.2, 129.3, 129.8, 131.3, 132.5, 133.3, 135.3,

136.7, 140.9, 143.1, 189.5; HRMS (ES): MH^+, found 436.0092. $C_{23}H_{16}NO^{35}Cl^{79}Br^+$ requires: 436.0104.

(*E*)-1-(5-Bromo-2-phenyl-1*H*-indol-7-yl)-3-(4′-methoxyphenyl)prop-2-en-1-one (201d); R^1 = OCH_3, R^2 = H

A mixture of **200d** (1.00 g, 2.32 mmol) and $PdCl_2$ (0.08 g, 0.46 mmol) in acetonitrile (20 mL) was treated as for **201a** to to afford **201d** as a solid (0.53 g, 53%), mp. 176–179 °C (EtOH); ν_{max} (ATR) 578, 688, 822, 972, 1034, 1128, 1176, 1292, 1448, 1569, 1641, 3411 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.90 (3H, s, OCH_3), 6.83 (1H, s, *J* = 2.0 Hz, 3-H), 7.00 (2H, d, *J* = 9.0 Hz, 2',6'-H), 7.39 (2H, t, *J* = 8.0 Hz, 4''-H), 7.49 (2H, t, *J* = 8.0 Hz, 3'',5''-H), 7.63 (1H, d, J_{trans} = 15.0 Hz, α-H), 7.70 (2H, d, *J* = 9.0 Hz, 3',5'-H), 7.76 (1H, dd, *J* = 1.0 and 8.0 Hz, 2'',6''-H), 7.91 (1H, J_{trans} = 15.0 Hz, β-H), 7.99 (1H, d, *J* = 1.5 Hz, 4-H), 8.00 (1H, d, *J* = 1.5 Hz, 6-H), 10.93 (1H, br s, NH), NH); δ_C (125 MHz, $CDCl_3$) 55.5, 89.6, 112.0, 114.5, 118.2, 121.7, 125.5, 126.1, 127.5, 128.5, 128.8, 129.1, 130.5, 131.4, 132.4, 135.3, 140.7, 144.5, 161.9, 189.7; HRMS (ES): MH^+, found 431.0511$C_{24}H_{18}NO_2{}^{79}Br$ requires 431.0521.

(*E*)-3-(5-Bromo-2-(4′′-(trifluoromethoxy)phenyl)-1*H*-indol-7-yl)-1-(4′-chlorophenyl)-prop-2-en-1-one (201e); R^1 = Cl, R^2 = OCF_3

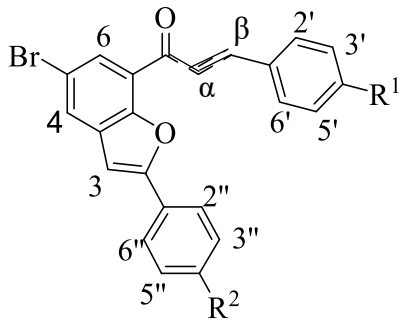
A mixture of **200e** (1.30 g, 2.51 mmol) and $PdCl_2$ (0.09 g, 0.50 mmol) in acetonitrile (20 mL) was treated as for **201a** to **201e** as a solid (0.83 g, 63%) mp. 252–254 °C °C (EtOH); ν_{max} (ATR) 572, 685, 762, 846, 967, 1086, 1157, 1256, 1350, 1456, 1566, 1648, 3426 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.81 (1H, d, *J* = 2.5 Hz, 3-H), 7.15 (1H, t, *J* = 8.0 Hz, 3'',5''-H), 7.38 (1H, t, *J* = 8.0 Hz, 3',5'-H), 7.48 (2H, d, *J* = 8.0 Hz, 2'',6''-H), 7.65 (1H, d, J_{trans} = 15.0 Hz, α-H), 7.71 (2H, d, *J* 8.5

Hz,), 7.74 (2H, d, *J* 8.0 Hz, 2',6'-H), 7.87 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.97 (1H, d, *J* 2.0 Hz, 4-H), 7.99 (1H, d, *J* 2.0 Hz, 6-H), 10.88 (1H, br s, NH); δ_C (125 MHz, $CDCl_3$) 99.2, 112.2, 114.5, 117.9, 121.4, 121.5, 121.7, 126.4, 126.8, 127.4, 128.9, 130.1, 130.5, 132.2, 135.4, 139.1, 144.6, 149.1, 161.9, 189.6; δ_F (470 MHz, $CDCl_3$) -58.2; HRMS (ES): MH^+ found 519.9944. $C_{24}H_{15}NO_2F_3{}^{35}Cl^{79}Br^+$ requires: 519.9927.

(*E*)-3-(5-Bromo-2-(4′′-(trifluoromethoxy)phenyl)-1*H*-indol-7-yl)-1-(4′-methoxyphenyl)-prop-2-en-1-one (201f); R^1 = OCH_3, R^2 = OCF_3

A mixture of **200f** (0.90 g, 1.75 mmol) and $PdCl_2$ (0.06 g, 0.35 mmol) in acetonitrile (20 mL) was treated as for **201a** to **201f** as a solid (0.49 g, 54%), mp. 197–198 °C (EtOH); ν_{max} (ATR) 573, 692, 760, 889, 919, 1032, 1158, 1276, 1351, 1460, 1509, 1644, 3421 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3) 6.80 (1H, d, *J* = 2.5 Hz, 3-H), 6.98 (2H, d, *J* = 8.5 Hz, 3',5'-H), 7.32 (2H, d, *J* = 8.0 Hz, 3'',5''-H), 7.61 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.68 (2H, d, *J* = 8.0 Hz, 2'',6''-H), 7.76 (2H, d, *J* 8.5 Hz, 2',6'-H), 7.87 (1H, d, J_{trans} = 15.5 Hz, β-H), 7.97 (1H, d, *J* 2.0 Hz, 4-H), 7.99 (1H, d, *J* 2.0 Hz, 6-H), 10.90 (1H, s, NH); δ_C (75 MHz, $CDCl_3$); δ_C (125 MHz, $CDCl_3$) 55.4, 99.2, 112.2, 114.4, 117.9, 121.4, 121.5, 121.7, 126.4, 126.8, 127.4, 128.9, 130.1, 130.5, 132.2, 135.4, 139.1, 144.6, 149.0, 161.9, 189.6; δ_F (470 MHz, $CDCl_3$) -57.8; HRMS (ES): MH^+, found 516.0408. $C_{25}H_{18}NO_3F_3{}^{79}Br^+$ requires: 516.0422.

4.5 Synthesis of benzofuran-chalcone hydrids 203a–y.



203a–y

(*E*)-1-(5-Bromo-2-phenylbenzofuran-7-yl)-3-phenylprop-2-en-1-one (203a); R^1 = 4-H, R^2 = H

To a three-necked round-bottom flask equipped with a stirrer bar, condenser and rubber septa compound **198d** (1.02 g, 2.38 mmol), phenylacetylene (0.29 g, 2.85 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.12 mmol), Cs_2CO_3 (0.93 g, 2.85 mmol) and CuI (0.05 g, 0.24 mmol) and aqueous DMF (20 mL) were added in sequence. The mixture was purged with nitrogen gas for 20 min. and a balloon filled with nitrogen gas was connected to the top of the condenser and the mixture was heated at 80 °C for 2 h. The mixture was quenched with an ice-cold water and the product was extracted with chloroform. The combined organic solutions were washed with brine and dried over anhydrous $MgSO_4$. The salt was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by recrystallization from acetone to afford **203a** as a solid (0.63 g, 66%); mp. 197–195 °C; ν_{max} (ATR) 567, 680, 758, 853, 972, 1097, 1176, 1283, 1365, 1491, 1574, 1596, 1656 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.06 (1H, s, =CH), 7.15 (1H, t, *J* = 7.5 Hz), 7.42 (2H, d, *J* =7.0 Hz), 7.54–7.49 (3H, m, Ar), 7.56 (2H, d, *J* = 8.0 Hz, Ar), 7.65 (1H, *J* = 2.5 Hz, H-4), 7.68 (2H, d, *J* = 8.0 Hz, Ar), 7.74 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.80 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.95 (1H, d, *J* 2.5 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 88.6, 88.9, 100.9, 118.5, 122.0,

123.1, 125.1, 128.3, 128.4, 128.6, 128.8, 129.0, 129.3, 129.4, 131.1, 131.6, 152.8, 157.8, 195.2; HRMS (ES): found 403.0325. $C_{23}H_{16}O_2{}^{79}Br$ requires 403.0334. *Anal* calcd for $C_{23}H_{15}O_2Br$: C, 68.50; H, 3.75. Found: C, 68.38; H, 3.73.

(*E*)-1-(5-Bromo-2-phenylbenzofuran-7-yl)-3-(4′-fluorophenyl)prop-2-en-1-one (203b); R^1 = 4-F, R^2 = H

A mixture of **198b** (0.98 g, 2.20 mmol), phenylacetylene (0.269 g, 2.64 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.11 mmol), Cs_2CO_3 (0.86 g, 2.64 mmol) and CuI (0.04 g, 0.22 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203b** as a solid (0.73 g, 79%); mp. 220–223 °C; ν_{max} (ATR) 579, 690, 798, 835, 997, 1098, 1155, 1278, 1363, 1433, 1502, 1585, 1673 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.07 (1H, s, =CH), 7.15 (2H, t, *J* = 8.5 Hz, Ar), 7.43 (2H, d, *J* = 8.5 Hz, Ar), 7.48 (2H, t, *J* = 8.0 Hz, Ar), 7.73 (1H, t, *J* = 8.0 Hz, Ar), 7.88 (2H, d, *J* = 7.5 Hz, Ar), 7.91 (1H, d *J* = 1.5 Hz, H-4), 7.93 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.95 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.03 (1H, d, *J* = 2.4 Hz, H-6); δ_C (75 MHz, $CDCl_3$) 100.5, 116.3 (d, $^2J_{CF}$ = 21.8 Hz), 116.5, 124.1, 124.6, 125.1, 127.8, 128.1, 129.1, 129.3, 129.5, 130.5 (d, $^3J_{CF}$ = 8.5 Hz), 131.2 (d, $^4J_{CF}$ = 2.9 Hz), 132.8, 143.5, 151.6, 157.7, 164.2 (d, $^1J_{CF}$ = 239.0 Hz), 186.5; HRMS (ES): found 421.0254. $C_{23}H_{15}O_2F^{79}Br^+$ requires 421.0239. *Anal* calcd for $C_{23}H_{14}O_2FBr$: C, 65.58; H, 3.35. Found: C, 65.42; H, 3.41.

***(E)*-1-(5-Bromo-2-phenylbenzofuran-7-yl)-3-(4′-chlorophenyl)prop-2-en-1-one (203c); R^1 = 4-Cl, R^2 = H**

A mixture of **198c** (1.07 g, 2.32 mmol), phenylacetylene (0.28 g, 2.78 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.12 mmol), Cs_2CO_3 (0.90 g, 0.78 mmol) and CuI (0.04 g, 0.23 mmol) in aqueous DMF (20

mL) was treated as for the preparation of **203a** to afford **203c** as a solid (0.79, 78%); mp. 242–245 °C; ν_{max} (ATR) 524, 685, 751, 814, 974, 1090, 1217, 1317, 1365, 1489, 1588, 1592, 1659 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.06 (1H, s, =CH), 7.42 (2H, d, *J* = 8.5 Hz, Ar), 7.49 (1H, t, *J* = 8.5 Hz, Ar), 7.67 (2H, d, *J* = 8.7 Hz, Ar), 7.84 (2H, d, *J* = 8.0 Hz, Ar), 7.86 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.88 (1H, d, *J* = 1.5 Hz, H-4), 7.91 (1H, d, *J* = 2.5 Hz, 6-H), 8.02 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.04 (2H, d, *J* = 7.0 Hz, Ar); δ_C (125 MHz, $CDCl_3$) 116.5, 125.1, 125.2, 125.3, 127.9, 128.1, 128.3, 129.0, 129.3, 129.6, 129.7, 131.1, 132.8, 133.4, 136.7, 143.2, 151.6, 157.7, 186.4; HRMS (ES): found 436.9937. $C_{23}H_{15}O_2ClBr^+$ requires 436.9944. *Anal* calcd for $C_{23}H_{14}O_2ClBr$: C, 63.11; H, 3.22. Found: C, 63.08; H, 3.17.

(*E*)-1-(5-Bromo-2-phenylbenzofuran-7-yl)-3-(4′-methoxyphenyl)prop-2-en-1-one (203d); R^1 = 4-OCH_3, R^2 = H

A mixture of **198d** (0.96 g, 2.10 mmol), phenylacetylene (0.26 g, 2.52 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 0.11 mmol), Cs_2CO_3 (0.82 g, 2.52 mmol) and CuI (0.04 g, 0.21 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203d** as a solid (0.65 g, 72%); mp. 206–208 °C; ν_{max} (ATR) 531, 672, 766, 870, 991, 1023, 1170, 1256, 1365, 1422, 1509, 1558, 1654 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.98 (2H, d, *J* = 8.5 Hz, Ar), 7.14 (1H, s, =CH), 7.19 (1H, t, *J* = 8.0 Hz, Ar), 7.44 (2H, d, *J* = 8.7 Hz, Ar), 7.81 (2H, d, *J* = 8.0 Hz, Ar), 7.83 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.88 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.92 (2H, d, *J* = 8.5 Hz, Ar), 8.00 (1H, d, *J* = 2.5 Hz, 4-H), 8.02 (1H, d, *J* = 2.5 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 55.4, 83.5, 97.1, 105.7, 112.0, 114.4, 119.6, 119.9, 122.4, 127.6, 128.5, 128.8, 129.4, 130.2, 131.6, 133.4, 138.8, 144.2, 161.6, 186.7; HRMS MH^+, found 433.0364. $C_{24}H_{18}O_3{}^{79}Br^+$ requires 433.0361. *Anal* calcd for $C_{24}H_{17}O_3Br$: C, 66.53; H, 3.95. Found: C, 66.59; H, 3.93.

(*E*)-1-(5-Bromo-2-phenylbenzofuran-7-yl)-3-(4′-(trifluoromethoxy)phenyl)prop-2-en-1-one (203e); R^1 = 4-OCF_3, R^2 = H

A mixture of **198e** (0.52 g, 1.02 mmol), phenylacetylene (0.12 g, 1.22 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.05 mmol), Cs_2CO_3 (0.37 g, 1.22 mmol) and CuI (0.02 g, 0.12 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203e** as a solid (0.33 g, 67%); 177–178 °C; ν_{max} (ATR) 568, 685, 790, 866, 969, 1036, 1147, 1253, 1409, 1492, 1600, 1658 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.07 (1H, s, =CH), 7.31 (1H, d, *J* = 8.0 Hz, Ar), 7.43 (1H, t, *J* =8.0 Hz, Ar), 7.47 (2H, d, *J* = 8.0 Hz, Ar), 7.49 (2H, *J* = 7.5 Hz, Ar), 7.62 (2H, d, *J* = 8.7 Hz, Ar), 7.88 (1H, d, *J* = 8.7 Hz, Ar), 7.91 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.92 (1H, d, *J* 2.0 Hz, H-4), 8.06 (1H, d, *J* 2.0 Hz, H-6), 8.09 (1H, d, J_{trans} = 16.0 Hz, β-H); δ_C (125 MHz, $CDCl_3$) 100.5, 116.6, 119.9 (t, J_{CF} = 256.0 Hz), 122.8, 123.6, 125.1, 126.2, 129.6, 128.1, 129.0, 129.2, 129.6, 130.5, 132.9, 137.1, 142.8, 149.7, 151.8, 157.9, 186.1; HRMS (ES): found 487.0157. $C_{24}H_{15}O_3{}^{79}BrF_3$ requires 487.0157. *Anal* calcd for $C_{24}H_{14}O_3BrF_3$: C, 59.16; H, 2.90. Found: C, 59.13; H, 3.01.

(*E*)-1-(5-Bromo-2-(4′′-fluorophenyl)benzofuran-7-yl)-3-phenylprop-2-en-1-one (203f); R^1 = 4-H, R^2 = F

A mixture of **198a** (0.96 g, 2.35 mmol), 4-flourophenylacetylene (0.32 g, 2.70 mmol), $PdCl_2(PPh_3)_2$ (0.11 g, 0.16 mmol), Cs_2CO_3 (0.88 g, 2.70 mmol) and CuI (0.04 g, 0.24 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203f** as a solid (0.69 g, 70%); mp. 224–226 °C; ν_{max} (ATR) 575, 682, 751, 826, 976, 1099, 1172, 1217, 1366, 1432, 1508, 1587, 1656 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.97 (1H, s, =CH), 7.18 (1H, t, *J* = 8.5 Hz, Ar), 7.44–7.46 (4H, m, Ar), 7.51 (2H, t, *J* = 8.0 Hz, Ar), 7.72 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.74 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.84 (2H, t, *J* = 8.5 Hz, Ar), 7.86 (1H, d, *J* = 2.0 Hz, H-4), 7.87 (1H, d, *J* = 2.0 Hz, H-

6); δ_C (125 MHz, $CDCl_3$) 100.5, 116.2 (d, $^2J_{CF}$ = 21.9 Hz), 116.5, 124.0, 124.5, 125.1, 127.9, 128.1, 129.0, 129.3, 129.5, 130.4 (d, $^3J_{CF}$ = 8.5 Hz), 131.2, 132.4 (d, $^4J_{CF}$ = 3.8 Hz), 143.5, 151.5, 157.8, 161.2 (d, $^1J_{CF}$ = 245.0 Hz), 186.5; HRMS (ES): found: 421.0161. $C_{23}H_{15}FO_2{}^{79}Br^+$ requires 421.0141. *Anal* calcd for $C_{23}H_{14}FO_2Br$: C, 65.58; H, 3.35. Found: C, 68.49; H, 3.33.

(*E*)-1-(5-Bromo-2-(4′′-fluorophenyl)benzofuran-7-yl)-3-(4′-fluorophenyl)prop-2-en-1-one (203g); R^1 = F, R^2 = F

A mixture of **198b** (1.18 g, 2.65 mmol), 4-flourophenylacetylene (0.38 g, 3.18 mmol), $PdCl_2(PPh_3)_2$ (0.09 g, 0.13 mmol), Cs_2CO_3 (1.03 g, 3.18 mmol) and CuI (0.05 g, 0.27 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203g** as a solid (0.88 g, 76%); mp. 239–242 °C; ν_{max} (ATR) 575, 645, 755, 860, 977, 1096, 1157, 1285, 1365, 1414, 1598, 1658, 1678 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.99 (1H, s, =CH), 7.17 (2H, t, *J* = 8.5 Hz, Ar), 7.46 (2H, t, *J* = 8.5 Hz, Ar), 7.73 (2H, t, *J* = 8.7 Hz, Ar), 7.86 (2H, t, *J* = 8.5 Hz, Ar), 7.89 (1H, d, *J* = 2.0 Hz, H-4), 7.94 (1H, d, J_{trans} = 16.0 Hz, α-H), 8.00 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.02 (1H, d, *J* = 2.5 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 100.5, 115.1 (d, $^2J_{CF}$ = 21.9 Hz), 116.2 (d, $^2J_{CF}$ = 21.9 Hz), 124.1, 124.6, 125.1, 127.9, 128.1, 129.0, 129.6 (d, $^4J_{CF}$ = 3.8 Hz), 130.4 (d, $^3J_{CF}$ = 8.5 Hz), 132.0 (d, $^3J_{CF}$ = 8.5 Hz), 132.7 (d, $^4J_{CF}$ = 3.8 Hz), 143.4, 151.6, 157.3, 162.1 (d, $^1J_{CF}$ = 248.0 Hz), 162.9 (d, $^1J_{CF}$ = 267.3 Hz), 186.5; HRMS (ES): found 439.0132. $C_{23}H_{14}O_2F_2{}^{79}Br^+$ requires 439.0145. *Anal* calcd for $C_{23}H_{13}O_2F_2Br$: C, 62.89; H, 2.98. Found: C, 62.87; H, 2.93.

(*E*)-1-(5-Bromo-2-(4′′-fluorophenyl)benzofuran-7-yl)-3-(4′-chlorophenyl)prop-2-en-1-one (203h); R^1 = 4-Cl, R^2 = F

A mixture of **198c** (0.92 g, 2.00 mmol), 4-flourophenylacetylene (0.29 g, 2.40 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 0.10 mmol), Cs_2CO_3 (0.78 g, 2.40 mmol) and CuI (0.04 g, 0.20 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203h** as a solid (0.69 g, 77%); mp. 231–233 °C; ν_{max} (ATR) 579, 666, 741, 891, 987, 1097, 1145, 1248, 1337, 1447, 1502, 1598, 1674 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.06 (1H, s, =CH), 7.15 (2H, t, *J* = 8.0 Hz, Ar), 7.46 (2H, d, *J* = 8.0 Hz, Ar), 7.72 (2H, t, *J* = 8.5 Hz, Ar), 7.87 (2H, d, *J* = 7.5 Hz, Ar), 7.91 (1H, d, *J* = 2.0 Hz, H-4), 7.93 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.98 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.03 (1H, d, *J* = 2.0 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 100.5, 116.3 (d, $^2J_{CF}$ = 21.9 Hz), 120.2, 124.1, 124.3, 124.4, 125.6, 129.3, 129.5, 130.4 (d, $^3J_{CF}$ = 8.7 Hz), 131.2, 132.4 (d, $^4J_{CF}$ = 3.8 Hz), 142,1, 143.6, 147.3, 151.5, 156.8, 161.3 (d, $^1J_{CF}$ = 245.0 Hz), 188.4; HRMS (ES): found 454.9873. $C_{23}H_{14}O_2F^{35}Cl^{79}Br^+$ requires 454.9850. *Anal* calcd for $C_{23}H_{13}O_2FClBr$: C, 60.62; H, 2.88. Found: C, 60.68; H, 2.85.

(*E*)-1-(5-Bromo-2-(4′′-fluorophenyl)benzofuran-7-yl)-3-(4′-methoxyphenyl)prop-2-en-1-one (203i); R^1 = 4-OCH_3, R^2 = F

A mixture of **198d** (1.05 g, 2.30 mmol), 4-flourophenylacetylene (0.33 g, 2.76 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.12 mmol), Cs_2CO_3 (0.89 g, 2.76 mmol) and CuI (0.04 g, 0.23 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203i** as a solid (0.65 g, 72%); mp. 252–254 °C; ν_{max} (ATR) 526, 654, 791, 878, 976, 1099, 1159, 1287, 1364, 1455, 1572, 1589, 1655 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.98 (2H, d, *J* = 8.5 Hz, Ar), 7.14 (1H, s, =CH), 7.19 (1H, t, *J* = 8.0 Hz, Ar), 7.44 (2H, d, *J* = 8.7 Hz, Ar), 7.81 (1H, d, *J* = 8.0 Hz, Ar),

7.83 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.88 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.92 (2H, d, *J* = 8.5 Hz, Ar), 8.00 (1H, d, *J* = 2.5 Hz, H-4), 8.02 (1H, d, *J* = 2.5 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 55.5, 100.2, 114.6, 116.3 (d, $^2J_{CF}$ = 21.9 Hz), 124.1, 124.3, 124.4, 125.8, 127.0, 127.6, 128.8, 130.4 (d, $^3J_{CF}$ = 8.7 Hz), 131.2, 132.4 (d, $^4J_{CF}$ = 3.8 Hz), 143.6, 144.9, 151.5, 156.8, 161.6 (d, $^1J_{CF}$ = 245.0 Hz), 186.8; HRMS (ES): found 451.0327. $C_{24}H_{17}O_3{}^{79}Br^+$ requires 451.0345. *Anal* calcd for $C_{24}H_{16}O_3Br$: C, 63.87; H, 3.57. Found: C, 68.83; H, 3.62.

(*E*)-1-(5-Bromo-2-(4′′-fluorophenyl)benzofuran-7-yl)-3-(4′(trifluoromethoxy)phenyl)-prop-2-en-1-one (203j); R^1 = 4-OCF_3, R^2 = F

A mixture of **198e** (0.76 g, 1.49 mmol), 4-flourophenylacetylene (2.14 g, 1.78 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), Cs_2CO_3 (0.58 g, 1.78 mmol) and CuI (0.03 g, 0.15 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203j** as a solid (0.48 g, 64%); mp. 203–204 °C; ν_{max} (ATR) 580, 695, 789, 892, 978, 1094, 1169, 1262, 1345, 1577, 1601, 1660 cm^{-1}; 7.01 (1H, s, =CH), 7.17 (1H, t, *J* = 8.5 Hz, Ar), 7.31 (2H, d, *J* = 7.5 Hz, Ar), 7.49 (1H, t, *J* = 8.0 Hz, Ar) 7.60 (2H, d, *J* = 7.5 Hz, Ar), 7.96 (2H, t, *J* = 8.5 Hz, Ar), 7.90 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.92 (1H, d, *J* = 2.0 Hz, H-4), 8.00 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.05 (1H, d, *J* = 2.0 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 100.3, 116.3 (d, $^2J_{CF}$ = 21.9 Hz), 116.7, 119.8 (t, J_{CF} = 256.0 Hz), 123.7, 124.3, 125.5, 126.1, 127.0 (d, $^3J_{CF}$ = 8.7 Hz), 127.5, 128.1 (d, $^4J_{CF}$ = 3.8 Hz), 130.5, 132.8, 136.9, 142.9, 149.8, 151.6, 156.9, 163.4 (d, $^1J_{CF}$ = 245.0 Hz), 186.1; HRMS (ES): found 504.0044. $C_{24}H_{14}O_3{}^{79}BrF_4{}^+$ requires 504.0066. *Anal* calcd for $C_{24}H_{13}O_3BrF_4$: C, 57.05; H, 2.59. Found: C, 57.08; H, 2.64.

(*E*)-1-(5-Bromo-2-(3′′-fluorophenyl)benzofuran-7-yl)-3-phenylprop-2-en-1-one (203k); R^1 = 4-H, R^2 = 3-F

A mixture of **198a** (1.05 g, 2.50 mmol), 3-flourophenylacetylene (0.36 g, 3.00 mmol), $PdCl_2(PPh_3)_2$ (0.09 g, 0.13 mmol), Cs_2CO_3 (0.98 g, 3.00 mmol) and CuI (0.05 g, 0.25 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203k** as a solid (0.73 g, 70%); mp. 243–245°C; ν_{max} (ATR) 503, 664, 765, 854, 939, 1039, 1159, 1220, 1325, 1448, 1588, 1655 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.08 (1H, s, =CH), 7.11 (1H, t, *J* = 8.0 Hz, Ar), 7.43 (1H, t, *J* = 8.0 Hz, Ar), 7.46 (1H, d, *J* = 8.0 Hz, Ar), 7.47 (1H, d, *J* = 8.0 Hz, Ar), 7.59 (1H, dt, *J* = 8.0 and 2.0 Hz, Ar), 7.65 (1H, d, *J* = 8.0 Hz, Ar), 7.73-7.75 (3H, m, Ar), 7.91 (1H, d, *J* = 2.0 Hz, H-4), 7.93 (1H, d, J_{trans} = 16.0 Hz, α-H), 8.02 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.06 (1H, d, *J* = 2.0 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 101.5, 112.2 (d, $^3J_{CF}$ = 23.7 Hz), 116.3 (d, $^2J_{CF}$ = 21.9 Hz), 116.7, 120.8, 120.9, 124.2, 124.6, 128.1, 128.6, 129.1, 130.7, 130.8 (d, $^6J_{CF}$ = 1.8 Hz), 131.4 (d, $^4J_{CF}$ = 8.6 Hz), 132.5, 134.8, 145.1, 151.6, 156.3 (d, $^5J_{CF}$ = 2.8 Hz), 163.1 (d, $^1J_{CF}$ = 245.0 Hz), 186.4; HRMS (ES): found: 421.0243. $C_{23}H_{15}FO_2{}^{79}Br^+$ requires 421.0239. *Anal* calcd for $C_{23}H_{14}FO_2Br$: C, 65.52; H, 3.35. Found: C, 65.80; H, 3.41.

(*E*)-1-(5-Bromo-2-(3′′-fluorophenyl)benzofuran-7-yl)-3-(4′-fluorophenyl)prop-2-en-1-one (203l); R^1 = F, R^2 = 3-F

A mixture of **198b** (0.89 g, 2.00 mmol), 3-flourophenylacetylene (0.29 g, 2.40 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 0.10 mmol), Cs_2CO_3 (0.78 g, 2.40 mmol) and CuI (0.04 g, 0.20 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203l** as a solid (0.67 g, 77%); mp. 266–267 °C; ν_{max} (ATR) 572, 680, 779, 891, 976, 1171, 1281, 1346, 1488, 1597, 1660 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.08 (1H, s, =CH), 7.12 (1H, t, *J* = 8.5 Hz, Ar), 7.42 (1H, d, *J* = 8.0 Hz,

Ar), 7.45 (2H, d, *J* = 7.5 Hz, Ar), 7.59 (1H, dt, *J* = 8.5 and 2.0 Hz, Ar), 7.64 (1H, d, *J* = 8.0 Hz, Ar), 7.73 (2H, t, *J* = 8.5 Hz, Ar), 7.90 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.92 (1H, d, *J* = 2.5 Hz, H-4), 7.95 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.05 (1H, d, *J* = 2.5 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 100.5, 112.0 (d, $^2J_{CF}$ = 23.9 Hz), 116.3 (d, $^2J_{CF}$ = 21.9 Hz), 116.9 (d, $^2J_{CF}$ = 21.9 Hz), 120.8 (d, $^2J_{CF}$ = 2.9 Hz), 124.1, 124.3, 124.4, 128.1, 128.5, 130.4 (d, $^4J_{CF}$ = 8.6 Hz), 130.7 (d, $^3J_{CF}$ = 8.5 Hz), 131.2 (d, $^3J_{CF}$ = 2.9 Hz), 131.4 (d, $^4J_{CF}$ = 8.5 Hz), 132.4, 143.7, 151.6, 156.3 (d, $^2J_{CF}$ = 2.7 Hz), 163.1 (d, $^1J_{CF}$ = 245.6 Hz), 164.3 (d, $^1J_{CF}$ = 251.2 Hz), 186.3; HRMS (ES): found 438.0028. $C_{23}H_{14}O_2F_2{}^{79}Br^+$ requires 439.0067. *Anal* calcd for $C_{23}H_{13}O_2F_2Br$: C, 62.89; H, 2.98. Found: C, 62.91; H, 3.01.

(*E*)-1-(5-Bromo-2-(3′′-fluorophenyl)benzofuran-7-yl)-3-(4′-chlorophenyl)prop-2-en-1-one (203m); R^1 = Cl, R^2 = 3-F

A mixture of **198c** (0.87 g, 1.89 mmol), 3-flourophenylacetylene (0.27 g, 2.26 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 0.09 mmol), Cs_2CO_3 (0.73 g, 2.26 mmol) and CuI (0.04 g, 0.19 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203m** as a solid (0.58 g, 68%); mp. 234–235°C; ν_{max} (ATR) 515, 662, 728, 880, 1036, 1169, 1219, 1315, 1448, 1571, 1655 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.09 (1H, s, =CH), 7.14 (1H, t, *J* = 8.0 Hz, Ar), 7.45 (2H, d, *J* = 8.5 Hz, Ar), 7.58 (1H, d, *J* = 8.5 Hz, Ar), 7.63-7.68 (4H, d, *J* = 7.5 Hz, Ar), 7.89 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.92 (1H, d, *J* = 2.0 Hz, H-4), 7.99 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.05 (1H, d, *J* = 2.0 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 101.5, 112.9 (d, $^3J_{CF}$ = 23.7 Hz), 116.4 (d, $^2J_{CF}$ = 21.9 Hz), 116.7, 120.8 (d, $^2J_{CF}$ = 2.87 Hz), 124.0, 124.9, 128.2, 128.6, 129.4, 129.7, 130.8 (d, $^6J_{CF}$ = 8.5 Hz), 131.4 (d, $^4J_{CF}$ = 8.6 Hz), 132.5, 133.3, 136.8, 143.5, 151.6, 156.3 163.1 (d, $^1J_{CF}$ = 245.0 Hz), 186.2; HRMS (ES): found 454.9931 $C_{23}H_{14}O_2F^{35}Cl^{79}Br^+$ requires 454.9771. *Anal* calcd for $C_{23}H_{13}O_2FClBr$: C, 60.62; H, 2.88. Found: C, 60.59; H, 2.90.

(*E*)-1-(5-Bromo-2-(3′′-fluorophenyl)benzofuran-7-yl)-3-(4′-methoxyphenyl)prop-2-en-1-one (203n); R^1 = OCF_3, R^2 = 3-F

A mixture of **198d** (1.10 g, 2.40 mmol), 3-flourophenylacetylene (0.35 g, 2.88 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.12 mmol), Cs_2CO_3 (0.94 g, 2.88 mmol) and CuI (0.05 g, 0.24 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203n** as a solid (0.79 g, 73%); mp. 221–222 °C; ν_{max} (ATR) 562, 683, 778, 893, 973, 1076, 1194, 1257, 1348, 1487, 1591, 1655 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.98 (2H, d, *J* = 8.5 Hz, Ar), 7.08 (1H, s, =CH), 7.11 (1H, t, *J* = 8.5 Hz, Ar), 7.45 (1H, d, *J* = 7.5 Hz, Ar), 7.69 (1H, d, *J* = 8.5 Hz, Ar), 7.65 (1H, d, *J* = 8.0 Hz, Ar), 7.69 (2H, d, *J* = 8.5 Hz, Ar), 7.87 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.89 (1H, d, *J* = 1.5 Hz, H-4), 7.92 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.04 (1H, d, *J* = 2.5 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 55.4, 112,2 (d, $^3J_{CF}$ = 23.7 Hz), 114.6, 116.3 (d, $^2J_{CF}$ = 20.9 Hz), 116.7, 121.0 (d, $^4J_{CF}$ = 2.8 Hz), 122.4, 123.7, 124.5, 127.5, 127.7, 128.5, 129.9, 130.4, (d, $^3J_{CF}$ = 7.5 Hz),130.7, 131.4 (d, $^3J_{CF}$ = 7.6 Hz), 132.4, 145.0, 151.6, 156.2 (d, $^4J_{CF}$ = 2.9 Hz),163.1 (d, $^1J_{CF}$ = 263.6 Hz), 186.4; HRMS (ES): found 451.0327. $C_{24}H_{17}O_3{}^{79}Br^+$ requires 451.0345. *Anal* calcd for $C_{24}H_{16}O_3Br$: C, 63.87; H, 3.57. Found: C, 63.92; H, 3.64.

(*E*)-1-(5-Bromo-2-(3′′-fluorophenyl)benzofuran-7-yl)-3-(4′-(trifluoromethoxy)phenyl)-prop-2-en-1-one (203o); R^1 = OCF_3, R^2 = 3-F

A mixture of **198e** (1.03 g, 2.01 mmol), 3-flourophenylacetylene (2.90 g, 2.42 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 0.10 mmol), Cs_2CO_3 (0.79 g, 2.42 mmol) and CuI (0.04 g, 0.20 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203o** as a solid (0.88 g, 87%); mp. 186–187 °C; ν_{max} (ATR) 575, 696, 779, 892, 978, 1075, 1160, 1256, 1346, 1487, 1573, 1656 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.09 (1H, s, =CH), 7.14 (1H, t, *J* = 8.0 Hz, Ar), 7.31 (1H, d, *J* = 8.7

Hz, Ar), 7.43 (1H, d, *J* = 8.5 Hz, Ar), 7.45 (1H, d, *J* = 8.5 Hz, Ar), 7.50 (1H, t, *J* = 8.0 Hz, Ar), 7.55 (1H, dt, *J* = 8.5 and 2.5 Hz, Ar), 7.59 (1H, d, *J* = 8.0 Hz, Ar), 7.65 (1H, t, *J* = 8.5 Hz, Ar), 7.91 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.93 (1H, d, *J* = 2.5 Hz, H-4) 8.04 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.08 (1H, d, *J* = 1.5 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 100.5, 112.0 (d, $^2J_{CF}$ = 23.9 Hz), 116.5 (d, $^2J_{CF}$ = 21.9 Hz), 116.8, 120.2 (q, J_{CF} = 256.0 Hz), 122.9, 123.7, 125.9, 127.2, 128.4, 128.7, 130.5, 130.6 (d, $^4J_{CF}$ = 7.5 Hz), 131.2 (d, $^3J_{CF}$ = 8.5 Hz), 132.5, 136.9, 143.1, 149.8 (d, $^2J_{CF}$ = 1.9 Hz), 151.7, 156.4 (d, $^2J_{CF}$ = 3.8 Hz), 163.1 (d, $^1J_{CF}$ = 245.6 Hz), 198.9; HRMS (ES): found 505.0085. $C_{24}H_{14}O_3{}^{79}BrF_4{}^+$ requires 505.0062. *Anal* calcd for $C_{24}H_{13}O_3BrF_4$: C, 57.05; H, 2.59. Found: C, 57.12; H, 2.61.

(*E*)-1-(5-Bromo-2-(3′′-chlorophenyl)benzofuran-7-yl)-3-phenylprop-2-en-1-one (203p); R^1 = H, R^2 = 3-Cl

A mixture of **198a** (0.99 g, 2.32 mmol), 3-chlorophenylacetylene (0.38 g, 2.78 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.12 mmol), Cs_2CO_3 (0.90 g, 2.78 mmol) and CuI (0.04 g, 0.23 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203p** as a solid (0.75 g, 75%); mp. 218–219 °C; ν_{max} (ATR) 575, 663, 780, 893, 944, 1012, 1194, 1279, 1345, 1488, 1585, 1602, 1657 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.09 (1H, s, =CH), 7.40 (2H, d, *J* = 8.0 Hz, Ar), 7.47 (2H, d, *J* = 8.0 Hz, Ar), 7.73-7.77 (5H, m, Ar), 7.90 (1H, d, *J* = 2.5 Hz, H-4), 7.92 (1H, d, *J* = 1.5 Hz, H-6), 7.96 (1H, d, J_{trans} = 16.0 Hz, α-H), 8.06 (1H, d, J_{trans} = 16.0 Hz, β-H); δ_C (125 MHz, $CDCl_3$) 101.3, 116.4, 123.2, 124.0, 124.5, 125.1, 128.1, 128.6, 128.7, 129.2, 129.4, 130.4, 130.9, 131.0, 132.4, 134.8, 135.2, 145.1, 151.7, 156.0, 186.2; HRMS (ES): found 436.9942. $C_{23}H_{15}O_2Cl^{79}Br$ requires 436.9942. *Anal* calcd for $C_{23}H_{14}O_2ClBr$: C, 63.11; H, 3.22. Found: C, 63.08; H, 3.16.

(*E*)-1-(5-Bromo-2-(3′′-chlorophenyl)benzofuran-7-yl)-3-(4′-fluorophenyl)prop-2-en-1-one (203q); R^1 = F, R^2 = 3-Cl

A mixture of **198b** (0.96g, 2.16 mmol), 3-chlorophenylacetylene (0.35 g, 2.59 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.11 mmol), Cs_2CO_3 (0.84 g, 2.59 mmol) and CuI (0.04 g, 0.22 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203q** as a solid (0.67 g, 69%); mp. 232–233 °C; ν_{max} (ATR) 570, 630, 781, 891, 973, 1078, 1102, 1221, 1376, 1494, 1584, 1596, 1655 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.09 (1H, s, =CH), 7.17 (2H, t, *J* = 8.5 Hz, Ar), 7.41 (2H, t, *J* = 8.5 Hz, Ar), 7.21-7.76 (3H, m, Ar), 7.91 (1H, d, *J* = 8.0 Hz, Ar), 7.92 (1H, d *J* = 2.0 Hz, H-4), 7.95 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.98 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.08 (1H, d, *J* = 2.0 Hz, H-6); δ_C (75 MHz, $CDCl_3$) 100.2, 116.3 (d, $^2J_{CF}$ = 21.8 Hz), 116.5, 124.1, 124.3, 124.4, 125.6, 125.7, 127.1, 127.8, 128.0, 129.8, 130.4 (d, $^3J_{CF}$ = 8.5 Hz), 131.1 (d, $^4J_{CF}$ = 2.8 Hz), 132.7, 136.9, 143.6, 151.6, 156.8, 164.4 (d, $^1J_{CF}$ = 239.0 Hz), 186.6; HRMS (ES): found 454.9851. $C_{23}H_{14}O_2F^{79}BrCl^+$ requires 454.9850. *Anal* calcd for $C_{23}H_{13}O_2FBrCl$: C, 60.62; H, 2.88. Found: C, 60.64; H, 2.90.

(*E*)-1-(5-Bromo-2-(3′′-chlorophenyl)benzofuran-7-yl)-3-(4′-chlorophenyl)prop-2-en-1-one (203r); R^1 = Cl, R^2 = 3-Cl

A mixture of **198c** (1.00 g, 2.17 mmol), 3-chlorophenylacetylene (0.35 g, 2.60 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.11 mmol), Cs_2CO_3 (0.85 g, 2.60 mmol) and CuI (0.04 g, 0.22 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203r** as a solid (0.79, 77%); mp. 257–258 °C; ν_{max} (ATR) 574, 639, 776, 859, 980, 1077, 1192, 1238, 1346, 1476, 1507, 1562, 1656 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.08 (1H, s, =CH), 7.41 (2H, d, *J* = 7.5 Hz, Ar), 7.46-7.48 (3H, m, Ar), 7.73-7.77 (2H, m, Ar), 7.91 (1H, d, *J* = 2.0 Hz, H-4), 7.94 (1H, d, *J* =

8.0 Hz, Ar), 7.96 (1H, d, J_{trans} = 16.0 Hz, α-H), 8.06 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.08 (1H, d, *J* = 7.0 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 101.6, 116.8, 123.2, 124.0, 124.5, 125.1, 128.1, 128.6, 128.7, 129.1, 129.4, 130.3, 130.9, 131.0, 132.4, 134.8, 135.2, 145.1, 151.7, 156.0, 186.2; HRMS (ES): found 470.9995. $C_{23}H_{14}O_2Cl_2Br^+$ requires 470.9476. *Anal* calcd for $C_{23}H_{13}O_2Cl_2Br$: C, 58.51; H, 2.78. Found: C, 58.60; H, 2.82.

(*E*)-1-(5-Bromo-2-(3′′-chlorophenyl)benzofuran-7-yl)-3-(4′-methoxyphenyl)prop-2-en-1-one (203s); R^1 = OCH_3, R^2 = 3-Cl

A mixture of **198d** (0.89 g, 1.95 mmol), 3-chlorophenylacetylene (0.32 g, 2.34 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 0.10 mmol), Cs_2CO_3 (0.76 g, 2.34 mmol) and CuI (0.04 g, 0.20 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203s** as a solid (0.65 g, 71%); mp. 214–215 °C; ν_{max} (ATR) 551, 695, 772, 893, 1076, 1169, 1255, 1346, 1474, 1508, 1585, 1654 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.99 (2H, d, J = 8.5 Hz, Ar), 7.09 (1H, s, =CH), 7.40 (2H, t, *J* = 8.0 Hz, Ar), 7.71 (2H, d, *J* = 9.0 Hz, Ar), 7.74 (2H, d, *J* = 7.5 Hz, Ar), 7.90 (1H, d, *J* = 2.5 Hz, 4-H), 8.00 (1H, d, J_{trans} = 16.0 Hz, α-H), 8.04 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.06 (1H, d, *J* = 2.5 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 55.4, 101.5, 113.5, 114.6, 116.7, 122.3, 124.4, 125.1, 127.8, 128.6, 129.3, 130.3, 130.4, 131.1, 132.2, 132.4, 135.1, 145.0, 151.7, 156.0, 162.0, 186.2; HRMS MH^+, found 467.0046. $C_{24}H_{17}O_3{}^{79}BrCl^+$ requires 467.0050. Anal calcd for $C_{24}H_{16}O_3BrCl$: C, 61.63; H, 3.45. Found: C, 61.58; H, 3.48.

(*E*)-1-(5-Bromo-2-(3′′-chlorophenyl)benzofuran-7-yl)-3-(4′-(trifluoromethoxy)phenyl)-prop-2-en-1-one (203t); R^1 = OCF_3, R^2 = 3-Cl

A mixture of **198e** (1.02 g, 2.00 mmol), 3-chlorophenylacetylene (0.33 g, 2.40 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 0.10 mmol), Cs_2CO_3 (0.78 g, 2.40 mmol) and CuI (0.04 g, 0.20 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203t** as a solid (0.73 g, 71%); mp. 196–197 °C; ν_{max} (ATR) 575, 695, 776, 893, 997, 1076, 1172, 1260, 1344, 1490, 1561, 1599, 1656 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.03 (1H, s, =CH), 7.31 (1H, d, *J* = 7.5 Hz, Ar), 7.40 (2H, d, *J* =7.0 Hz, Ar), 7.51 (1H, t, *J* = 8.0 Hz, Ar), 7.56 (1H, d, *J* = 8.0 Hz, Ar), 7.68 (1H, d, *J* =7.5 Hz, Ar). 7.75 (1H, dt, *J* = 2.0 and 8.0 Hz, Ar), 7.78 (1H, d, *J* =8.0 Hz, Ar), 7.90 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.93 (1H, d, *J* 2.0 Hz, H-4), 8.05 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.09 (1H, d, *J* 2.0 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 101.3, 116.4, 119.5 (t, J_{CF} = 256.0 Hz), 123.2, 124.0, 124.5, 125.1, 128.1, 128.6, 128.7, 129.2, 129.4, 130.4, 130.9, 131.0, 132.4, 134.8, 135.2, 145.1, 151.7, 156.0, 186.2; HRMS (ES): found 520.9930. $C_{24}H_{14}O_3{}^{79}BrF_3Cl$ requires 520.9923. *Anal* calcd for $C_{24}H_{13}O_3BrF_3Cl$: C, 55.25; H, 2.51. Found: C, 55.30; H, 2.54.

(*E*)-1-(5-Bromo-2-(4′′-methoxyphenyl)benzofuran-7-yl)-3-phenylprop-2-en-1-one (203u); R^1 = H, R^2 = 4-OCH_3

A mixture of **198a** (0.93 g, 2.18 mmol), 4-methoxyphenylacetylene (0.34 g, 2.61 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.11 mmol), Cs_2CO_3 (0.84 g, 2.61 mmol) and CuI (0.04 g, 0.22 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203u** as a solid (0.68 g, 72%); mp. 255–256 °C; ν_{max} (ATR) 571, 680, 765, 889, 979, 1098, 1156, 1254, 1347, 1435, 1580, 1596, 1657 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 6.92 (1H, s, =CH), 6.98 (2H, d, *J* = 9.0 Hz, Ar), 7.45-7.46 (3H, m, Ar), 7.74 (2H, d, *J* = 8.0 Hz, Ar), 7.81 (2H, d, *J* = 9.0 Hz,

Ar), 7.85 (1H, *J* = 1.5 Hz, H-4), 7.92 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.98 (1H, d, *J* 2.5 Hz, H-6), 8.02 (1H, d, J_{trans} = 16.0 Hz, β-H); δ_C (125 MHz, $CDCl_3$) 55.4, 98.8, 114.4, 116.4, 122.1, 123.9, 124.9, 126.7, 127.4, 128.6, 129.1, 130.7, 133.1 (2C), 134.9, 144.7, 151.5, 157.9, 160.5, 186.8; HRMS (ES): found 433.0439. $C_{24}H_{18}O_3{}^{79}Br$ requires 433.0439 *Anal* calcd for $C_{24}H_{17}O_3Br$: C, 66.53; H, 3.95. Found: C, 66.54; H, 3.95.

(*E*)-1-(5-Bromo-2-(4′′-methoxyphenyl)benzofuran-7-yl)-3-(4′-fluorophenyl)prop-2-en-1-one (203v); R^1 = F, R^2 = 4-OCH_3

A mixture of **198b** (0.94 g, 2.11 mmol), 4-methoxyphenylacetylene (0.33 g, 2.53 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.11 mmol), Cs_2CO_3 (0.82 g, 2.53 mmol) and CuI (0.04 g, 0.21 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203v** as a solid (0.78 g, 82%); mp. 241–242 °C; ν_{max} (ATR) 575, 695, 776, 893, 997, 1076, 1172, 1260, 1344, 1490, 1561, 1599, 1656 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.91 (1H, s, =CH), 6.98 (2H, d, *J* = 9.0 Hz, Ar), 7.14 (2H, t, *J* = 8.5 Hz, Ar), 7.72 (2H, t, *J* = 8.5 Hz, Ar), 7.79 (2H, d, *J* = 9.0 Hz, Ar), 7.85 (1H, d *J* = 1.5 Hz, H-4), 7.90 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.93 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.98 (1H, d, *J* = 2.4 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 55.5, 100.2, 114.6, 116.3 (d, $^2J_{CF}$ = 21.9 Hz), 124.1, 124.3, 124.4, 125.8, 127.0, 127.6, 128.8, 130.4 (d, $^3J_{CF}$ = 8.7 Hz), 131.2, 132.4 (d, $^4J_{CF}$ = 3.8 Hz), 143.6, 144.9, 151.5, 156.8, 161.6 (d, $^1J_{CF}$ = 245.0 Hz), 186.8; HRMS (ES): found 451.0333. $C_{24}H_{17}O_3F^{79}Br^+$ requires 451.0345. *Anal* calcd for $C_{24}H_{16}O_3FBr$: C, 63.87; H, 3.57. Found: C, 63.89; H, 3.62.

(*E*)-1-(5-Bromo-2-(4′′-methoxyphenyl)benzofuran-7-yl)-3-(4′-chlorophenyl)prop-2-en-1-one (203w); R^1 = Cl, R^2 = 4-OCH_3

A mixture of **198c** (1.04 g, 2.26 mmol), 4-methoxyphenylacetylene (0.36 g, 2.71 mmol), $PdCl_2(PPh_3)_2$ (0.08 g, 0.11 mmol), Cs_2CO_3 (0.88 g, 2.71 mmol) and CuI (0.04 g, 0.23 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203w** as a solid (0.83, 79%); mp. 209–210 °C; ν_{max} (ATR) 550, 646, 784, 982, 1098, 1173, 1254, 1346, 1436, 1579, 1657 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.98 (2H, d, *J* = 9.0 Hz, Ar), 7.08 (1H, s, =CH), 7.40 (2H, d, *J* = 8.0 Hz, Ar), 7.72 (2H, d, *J* = 9.0 Hz, Ar), 7.75 (2H, d, *J* = 8.5 Hz, Ar), 7.90 (1H, d, *J* = 2.5 Hz, 4-H), 7.92 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.97 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.08 (1H, d, *J* = 2.5 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 55.4, 101.6, 114.6, 116.7, 122.3, 123.2, 124.4, 125.1, 127.6, 129.4, 130.3, 130.4, 131.0, 132.3, 135.1, 145.0, 151.7, 155.9, 162.0, 186.2; HRMS (ES): found 466.381. $C_{24}H_{17}O_3ClBr^+$ requires 466.0377. *Anal* calcd for $C_{24}H_{16}O_3ClBr$: C, 61.63; H, 3.45. Found: C, 61.65; H, 3.47.

(*E*)-1-(5-Bromo-2-(4′′-methoxyphenyl)benzofuran-7-yl)-3-(4′-methoxyphenyl)prop-2-en-1-one (203x); R^1 = OCH_3, R^2 = 4-OCH_3

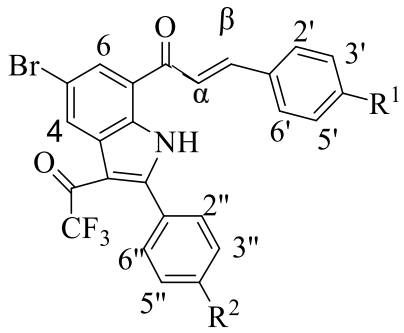
A mixture of **198d** (0.95 g, 2.00 mmol), 4-methoxyphenylacetylene (0.32 g, 2.40 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 0.10 mmol), Cs_2CO_3 (0.78 g, 2.40 mmol) and CuI (0.04 g, 0.20 mmol) in aqueous DMF was treated as for the preparation of **203a** to afford **203x** as a solid (0.64 g, 69%); mp. 216–217 °C; ν_{max} (ATR) 550, 699, 783, 980, 1093, 1213, 1346, 1506, 1585, 1657 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.87 (6H, s, 2xOCH_3), 6.91 (1H, s, =CH), 6.97 (2H, d, *J* = 9.0 Hz, Ar), 6.98 (2H, d, *J* = 9.0 Hz, Ar), 7.68 (2H, d, *J* = 8.0 Hz, Ar), 7.81 (2H, d, *J* = 8.5 Hz, Ar), 7.83 (1H, d, *J* = 8.0 Hz, Ar), 7.84 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.87 (1H, d, J_{trans} = 16.0 Hz, β-H), 7.89 (1H,

d, *J* = 2.5 Hz, 4-H), 7.97 (1H, d, *J* = 2.5 Hz, 6-H); δ_C (125 MHz, $CDCl_3$) 55.4, 55.5, 98.8, 114.4, 114.5,116.3, 122.2, 122.6, 124.3, 126.7, 127.1, 127.3, 130.4, 133.0, 144.6, 151.5, 157.8, 160,7, 161.9, 186.8; HRMS MH^+, found 463.0532. $C_{25}H_{20}O_4{}^{79}Br^+$ requires 463.0545. *Anal* calcd for $C_{25}H_{19}O_4Br$: C, 64.81; H, 4.13. Found: C, 64.78; H, 4.20.

(*E*)-1-(5-Bromo-2-(4′′-methoxyphenyl)benzofuran-7-yl)-3-(4′-(trifluoromethoxy) phenyl) prop-2-en-1-one (203y); R^1 = OCF_3, R^2 = 4-OCH_3

A mixture of **198e** (0.87 g, 1.70 mmol), 4-methoxyphenylacetylene (0.27 g, 2.04 mmol), $PdCl_2(PPh_3)_2$ (0.06 g, 0.01 mmol), Cs_2CO_3 (0.66 g, 2.04 mmol) and CuI (0.03 g, 0.17 mmol) in aqueous DMF (20 mL) was treated as for the preparation of **203a** to afford **203y** as a solid (0.59 g, 67%); mp. 187–188 °C; ν_{max} (ATR) 549, 694, 797, 866, 999, 1023, 1171, 1248, 1349, 1481, 1569, 1598, 1655 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 6.93 (1H, s, =CH), 7.00 (2H, d, *J* = 8.5 Hz), 7.31 (1H, d, *J* =8.0 Hz), 7.49 (1H, t, *J* = 8.0 Hz, Ar), 7.61 (1H, d, *J* = 8.0 Hz, Ar), 7.65 (1H, d, *J* = 8.0 Hz, Ar), 7.81 (2H, d, *J* = 8.5 Hz, Ar), 7.87 (1H, *J* = 2.0 Hz, H-4), 7.91 (1H, d, J_{trans} = 16.0 Hz, α-H), 8.03 (1H, d, *J* 2.0 Hz, H-6), 8.11 (1H, d, J_{trans} = 16.0 Hz, β-H); δ_C (125 MHz, $CDCl_3$) 55.4, 98.9, 114.5, 116.5, 119.5 (t, J_{CF} = 256.0 Hz), 119.8, 121.9, 122.8, 123.4, 126.3, 126.6, 127.5, 127.7, 127.8, 130.5, 133.2, 139.4, 142.7, 158.0, 160.8, 186.2; HRMS (ES): found 517.0262. $C_{25}H_{17}O_4{}^{79}BrF_3$ requires 517.0262. *Anal* calcd for $C_{25}H_{16}O_4BrF_3$: C, 58.05; H, 3.12. Found: C, 58.06; H, 3.13.

4.6 C-3 Trifluoroacetylation of compounds 201a–f with TFAA in THF



201a–f

(*E*)-1-(5-Bromo-2-phenyl-3-(trifluoroacetyl)-1*H*-indol-7-yl)-3-phenylprop-2-en-1-one (204a); R^1 = H, R^2 = H

A mixture of **201a** (1.00 g, 2.48 mmol) and TFAA (0.78 g, 3.72 mmol) in THF (20 mL) was heated at 60 °C for 5 h. The mixture was allowed to cool to RT and then quenched with an ice-cold water. The resultant precipitate was filtered, washed thoroughly with cold water and then recrystallized to afford **204a** as a solid (1.09 g, 88%), mp. 195–197 °C (EtOH); ν_{max} (ATR) 527, 678, 775, 846, 971, 1099, 1193, 1285, 1339, 1478, 1599, 1647, 1666, 3388 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.47–7.61 (10H, m, ArH), 7.70 (1H, d, J_{trans} = 16.0 Hz, α-H), 7.92 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.16 (1H, d, *J* 2.0 Hz, 4-H), 8.68 (1H, d, *J* 2.0 Hz, 6-H), 11.15 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 107.5, 112.5, 115.9 (q, $^1J_{CF}$ 286.4 Hz, CF_3), 119.6, 121.8, 128.2, 128.4, 128.6, 128.7, 129.0, 129.4, 130.2, 130.4, 130.5, 131.1, 133.5, 134.2, 145.9, 149.5, 176.9 (q, $^2J_{CF}$ 37.0 Hz, CF_3**C**=O), 189.3 (C=O); δ_F (470 MHz, $CDCl_3$) -77.1; HRMS (ES): MH^+, found: 498.0315. $C_{25}H_{16}NO_2F_3{}^{79}Br^+$ requires: 498.0317.

(*E*)-1-(5-Bromo-2-phenyl-3-(trifluoroacetyl)-1*H*-indol-7-yl)-3-(4′-fluorophenyl) prop-2-en-1-one (204b); R^1 = F, R^2 = H

A mixture of **201b** (0.42 g, 0.99 mmol) and TFAA (0.31 g, 1.49 mmol) in THF (10 mL) was treated as for the preparation of **204a** to afford **204b** as a solid (0.39 g, 76%), mp. 164–166 °C (EtOH); ν_{max} (ATR) 584, 665, 759, 831, 980, 1092, 1198, 1225, 1351, 1478, 1598, 1646, 1665, 3391 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.15 (2H, t, *J* = 8.5 Hz, 3',5'-H), 7.52–7.59 (5H, m, PhH), 7.61 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.72 (2H, t, *J* 8.0 Hz, 2',6'-H), 7.87 (1H, d, J_{trans} = 16.0 Hz, β-H), 8.14 (1H, d, *J* 1.8 Hz, 4-H), 8.67 (1H, d, *J* 1.8 Hz, 6-H), 11.14 (1H, s, NH); δ_C (125 MHz, DMSO-d_6) 107.6, 115.6 (q, $^1J_{CF}$ 288.2 Hz, CF_3), 116.2 (d, $^2J_{CF}$ = 21.8 Hz), 120.3, 121.3, 125.5, 126.3, 128.5, 129.1, 129.2, 130.6 (d, $^3J_{CF}$ = 8.5 Hz), 131.0 (d, $^4J_{CF}$ = 2.8 Hz), 131.3, 132.5, 135.3, 140.8, 143.3, 157.4 163.4 (d, $^1J_{CF}$ = 246.7 Hz), 177.1 (q, $^2J_{CF}$ 37.0 Hz, CF_3**C**=O), 189.2 (C=O); δ_F (470 MHz, $CDCl_3$) -75.1, -72.3; HRMS (ES): MH^+, found 516.0228. $C_{25}H_{15}NO_2F_4{}^{79}Br^+$ requires: 516.0222.

(*E*)-1-(5-Bromo-2-phenyl-3-(trifluoroacetyl)-1*H*-indol-7-yl)-3-(4′-chlorophenyl)prop-2-en-1-one (204c); R^1 = Cl, R^2 = H

A mixture of **201c** (0.37 g, 0.84 mmol) and TFAA (0.27 g, 1.28 mmol) in THF (10 mL) was treated as for the preparation of **204a** to afford **204c** as a solid (0.41 g, 91%), mp. 180–183 °C; ν_{max} (ATR) 573, 693, 799, 889, 971, 1083, 1159, 1299, 1351, 1495, 1571, 1644, 1696, 3421 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.43 (2H, d, *J* = 8.5 Hz), 7.52–7.63 (7H, m, PhH), 7.66 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.87 (1H, d, J_{trans} = 15.5 Hz, β-H), 8.15 (1H, d, *J* 2.0 Hz, 4-H), 8.67 (1H, d, *J* 2.0 Hz, 6-H), 11.12 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 107.6, 116.1 (q, $^1J_{CF}$ 288.2 Hz, CF_3), 120.2, 121.8, 128.3, 128.5, 129.4, 129.5, 129.9, 130.3, 130.4, 130.5, 130.5, 130.6, 132.8, 133.6, 137.2,

144.4, 149.7, 177.1 (q, $^{2}J_{CF}$ 37.0 Hz, CF_3**C**=O) 189.1 (C=O); δ_F (470 MHz, $CDCl_3$) -72.4; HRMS (ES): MH^+, found 531.9919. $C_{25}H_{15}NO_2F_3{}^{35}Cl^{79}Br^+$ requires: 531.9927.

(*E*)-1-(5-Bromo-2-phenyl-3-(trifluoroacetyl)-1*H*-indol-7-yl)-3-(methoxyphenyl)prop -2-en-1-one (204d); R^1 = OCH_3, R^2 = H

A mixture of **201d** (0.21 g, 0.49 mmol) and TFAA (0.15 g, 0.73 mmol) in THF (10 mL) was treated as for the preparation of **204a** to afford **204d** as a solid (0.16 g, 62%), mp. 173–175 °C (EtOH); ν_{max} (ATR) 561, 665, 761, 846, 935, 1040, 1130, 1257, 1350, 1426, 1545, 1603, 1648, 3426 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.89 (3H, s, OCH_3), 6.98 (2H, d, *J* = 8.5 Hz), 7.51–7.60 (6H, m, ArH), 7.69 (2H, d, *J* 8.5 Hz, ArH), 7.90 (1H, d, J_{trans} = 15.0 Hz, β-H), 8.14 (1H, d, *J* 2.0 Hz, 4-H), 8.65 (1H, d, *J* 2.0 Hz, 6-H), 11.20 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 55.5, 107, 116.1 (q, $^{1}J_{CF}$ 288.2 Hz, CF_3) 119.3, 120.1, 120.7, 122.2, 127.1, 128.2, 128.5, 129.6, 130.1, 130.3, 130.5, 130.8, 133.7, 145.9, 149.6, 151.1, 162.3, 177.3 (q, $^{2}J_{CF}$ 37.0 Hz, CF_3**C**=O) 189.3 (C=O); δ_F (470 MHz, $CDCl_3$) -72.3; HRMS (ES): MH^+, found 528.0425. $C_{26}H_{18}NO_3F_3{}^{79}Br^+$ requires: 528.0422.

(*E*)-3-(5-Bromo-3-(trifluoroacetyl)-2-(4′′-(trifluoromethoxy)phenyl)-1*H*-indol-7-yl)-3-(4′-chlorophenyl)prop-2-en-1-one (204e); R^1 = Cl, R^2 = OCF_3

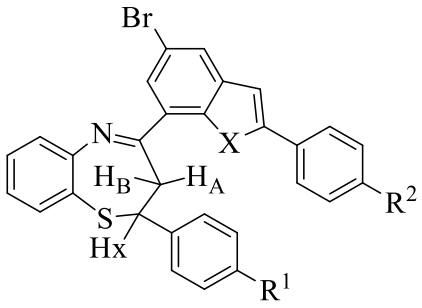
A mixture of **201e** (0.27 g, 0.52 mmol) and TFAA (0.16 g, 0.78 mmol) in THF (10 mL) was treated as for the preparation of **204a** to afford **204e** as a solid (0.29 g, 90%), mp. 266–269 °C (EtOH); ν_{max} (ATR) 578, 695, 796, 853, 978, 1090, 1195, 1278, 1339, 1195, 1278, 1339, 1489, 1586, 1652, 1681 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.38 (2H, d, *J* = 7.5 Hz), 7.4 (2H, d, *J* = 7.0 Hz), 7.64-7.67 (4H, s, ArH), 7.66 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.87 (1H, d, J_{trans} = 15.5 Hz, β-H), 8.15 (1H, d, *J* 2.0 Hz, 4-H), 8.65 (1H, d, *J* 2.0 Hz), 11.18 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 107,

116.3 (q, $^{1}J_{CF}$ 288.2 Hz, CF_3) 119.3, 120.1, 120.7, 121.9, 128.6, 128.9, 129.4, 129.9, 130.0, 130.5, 130.9, 131.4, 132.7, 133.6, 137.3, 144.8, 148.1, 150.8, 176.8 (q, $^{2}J_{CF}$ 37.0 Hz, CF_3**C**=O) 189.3 (C=O); δ_F (470 MHz, $CDCl_3$) -75.9, -72.6, -57.7; HRMS (ES): MH^+ found 614.0261. $C_{26}H_{14}NO_3F_6{}^{35}Cl^{79}Br^+$ requires: 614. 9651.

(*E*)-3-(5-Bromo-3-(trifluoroacetyl)-2-(4′′-(trifluoromethoxy)phenyl)-1*H*-indol-7-yl)-3-(4′-methoxyphenyl)prop-2-en-1-one (204f); $R^1 = OCH_3$, $R^2 = OCF_3$

A mixture of **201f** (0.42 g, 0.82 mmol) and TFAA (0.26 g, 1.22 mmol) in THF (10 mL) was treated as for the preparation of **204a** to afford **204f** as a solid (0.44 g, 88%), mp. 200–203 °C (EtOH); ν_{max} (ATR) 564, 694, 745, 859, 972, 1096, 1199, 1261, 1342, 1484, 1596, 1641, 1674 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.89 (3H, s, OCH_3), 6.98 (2H, d, *J* = 8.5 Hz, 2',6'-H), 7.38 (2H, d, *J* = 8.0 Hz, 2",6"-H), 7.58 (1H, d, J_{trans} = 15.5 Hz, α-H), 7.65 (2H, d, *J* 8.5 Hz, 3',5'-H), 7.69 (2H, d, *J* 8.0 Hz, 3",5"-H), 7.90 (1H, d, J_{trans} = 15.0 Hz, β-H), 8.16 (1H, d, *J* 2.0 Hz, 4-H), 8.63 (1H, d, *J* 2.0 Hz, 6-H), 11.25 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 55.5, 88.9, 107, 116.3 (q, $^{1}J_{CF}$ 288.2 Hz, -CF_3) 119.3, 120.7, 121.4, 122.3, 127.0, 128.4, 129.0, 129.8, 130.1, 131.4, 133.7, 146.1, 147.9, 150.7, 162.3 176.8 (q, $^{2}J_{CF}$ 37.0 Hz, CF_3**C**=O) 189.3 (C=O); δ_F (470 MHz, $CDCl_3$) -57.7, -72.7; HRMS (ES): MH^+, found 612.0262. $C_{27}H_{17}NO_4F_6{}^{79}Br^+$ requires: 612.0245.

4.7 Typical procedure for the synthesis of benzothiazepine derivatives 205a–g.



205a–g

4-(5-Bromo-2-phenyl-1*H*-indol-7-yl)-2-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepine (205a); X = NH, R^1 = H, R^2 = H

A stirred mixture of **201a (**0.41 g, 1.02 mmol) and 2-aminothiophenol (0.15g ,1.26 mmol) in glacial acetic acid (10 mL) was heated at 120 °C for 2 h and then allowed to cool to RT. The mixture was quenched with an ice-cold water and the resulting precipitate was filtered and recrystallized from ethanol to afford **205** as a green solid. (0.38 g, 92%), mp.225–227 ℃ (EtOH); ν_{max} (ATR) 568.1, 685.4, 707.4, 758.0, 841.2, 889.1, 1128.6, 1448.3, 16.06, 3418.8 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.05 (1H, dd, *J* = 13.0 and 12.5 Hz, H_A), 3.45 (1H, dd, *J* = 12.5 and 4.5 Hz, H_M),6.85 (1H, d, *J* = 2.5 Hz, 3-H), 7.17 (1H, t, *J* = 7.0 Hz, Ar), 7.26 (2H, d, *J* = 8.0 Hz, Ar), 7.39 (2H, d, *J* = 7.5 Hz, ArH), 7.46–7.50 (9H, m, ArH),7.93 (1H, d, *J* = 2.0 Hz, H-4), 7.99 (1H, d, *J* 2.0 Hz, 6-H), 11.60 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 38.5, 53.9, 111.3, 111.8, 120.3, 122.6, 122.9, 123.6, 125.3, 125.5, 125.9, 127.1, 127.7, 128.8, 129.8, 130.4, 130.9, 134.9, 140.8, 144.7, 151.5, 153.1,155.1, 155.2, 160.3 HRMS (ES): MH^+, found . 510.0588 $C_{29}H_{21}N_2S^{79}Br^+$ requires 510.0609.

4-(5-Bromo-2-phenyl-1*H*-indol-7-yl)-2-(4-fluorophenyl)-2,3-dihydrobenzo[b][1,4]-thiazepine (205b); X= NH, R^1 = H, R^2 = F

A mixture of **201b (**0.45 g, 1.07 mmol) and 2-aminothiophenol (0.16 g, 1.28 mmol) in acetic acid (10 mL) was treated as described for **201a** to afford **205b** as a green solid (0.40 g, 90%), mp.228–230 ℃ (EtOH); ν_{max} (ATR) 575.2, 885.9, 754.4, 821.1, 972.6, 1128.0, 1229.6, 1505.4, 1572.0, 16.03, 3426.4 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.02 (1H, dd, *J* = 13.0 and 12.5 Hz, H_A), 3.76 (1H, dd, *J* = 12.5 and 4.5 Hz, H_M), 5.54 (1H, dd, *J* = 12.5 and 4.5 Hz, H_X), 7.21 (2H, t, *J* = 8.5 Hz, Ar) 7.31 (1H, t, *J* = 8.5 Hz, Ar), 7.34–7.38 (6H, m, Ar), 7.50 (1H, s, =CH), 7.56 (1H, d, *J* = 8.5 Hz, Ar), 7.80 (2H, t, *J* = 8.5 Hz, Ar), 8.05 (1H, dd, *J* = 1.5, 12.0 Hz, Ar), 8.24 (1H, d, *J* = 2.0 Hz, H-4), 8.30 (1H, d, *J* = 2.0 Hz, H-6), 10.90 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 39.8, 59.5,102.0, 112.2,116.2 (d, $^2J_{CF}$ = 21.8 Hz), 120.3, 121.3,122.5, 125.5, 125.8, 125.9, 126.3, 128.5, 129.1, 129.2, 129.6,129.9, 130.6 (d, $^3J_{CF}$ = 8.5 Hz), 131.0 (d, $^4J_{CF}$ = 2.8 Hz), 131.3, 132.5, 135.3, 140.8, 143.3, 163.4 (d, $^1J_{CF}$ = 246.7 Hz); HRMS (ES): MH^+, found .528.0494 $C_{29}H_{20}N_2S^{79}BrF^+$ requires 528.0515.

4-(5-Bromo-2-phenyl-1*H*-indol-7-yl)-2-(4-chlorophenyl)-2,3 -dihydrobenzo[*b*][1,4]-thiazepine (205c); X = NH, R^1 = H, R^2 = 4-Cl

A mixture of **201c** (0.35 g, 0.84 mmol) and 2-aminothiophenol (0.12 g, 0.96 mmol) in acetic acid (10 mL) was treated as described for **201a** to afford **205c** as a green solid (0.32 g, 90%), mp. 245–247 ℃ (EtOH); ν_{max} (ATR) cm^{-1}; 577.2, 684.6, 753.1, 815.3, 890.2, 1010.8, 1087.2, 1130.3, 1301.5, 1449.2, 1487.6, 1600.8, 1647.3, 3429.0 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.17 (1H, dd, *J* = 13.0 and 12.5 Hz, H_A), 3.32 (1H, dd, *J* = 12.5 and 4.5 Hz, H_M), 5.54 (1H, dd, *J* = 12.5 and 4.5 Hz, H_X), 6.82 (1H, s, *J* = 2.0 Hz, 3-H), 7.40 (2H, t, *J* = 8.0 Hz, Ar), 7.43-7.547 (8H, m, Ar), 7.69

(2H, d, *J* = 8.5 Hz, Ar), 8.00 (1H, d, *J* = 1.5 Hz, 4-H), 8.02 (1H, d, *J* = 1.5 Hz, 6-H), 11.60 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 37.4, 59.9,111.6, 111.7, 115.0, 122.5, 122.6, 123.6, 125.2, 126.3, 128.6, 129.1, 129.2, 129.3, 129.8, 131.3, 132.5, 133.3, 135.3, 136.7, 140.9, 143.1, 153.0, 154.3, 159.9; HRMS (ES): MH^+, found .544.0199 $C_9H_{20}N_2S^{79}BrCl^+$ requires 544.0219.

4-(5-Bromo-2-phenylbenzofuran)-2-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepine (205d); X = O, R^1 = H, R^2 = H

A mixture of **203a (**0.20 g, 0.50 mmol) and 2-aminothiophenol (0.07 g, 0.60 mmol) in acetic acid (4 mL) was treated as described for **201a** to afford **205d** as a green solid (0.22 g, 86 %), mp. 189–191 °C (EtOH); ν_{max} (ATR) 567, 680, 758, 853, 972, 1097, 1176, 1283, 1365, 1491, 1574, 1596, 1605 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.18 (1H, t, *J* =12.5 Hz, H_A), 3.82 (1H, dd, *J* = 12.5 and 4.5 Hz, H_M), 5.57 (1H, dd, *J* = 12.5 and 4.5 Hz, H_X), 7.23 (1H, t, *J* = 7.5 Hz, Ar) 7.32 (1H, t, *J* = 8.5 Hz, Ar), 7.34–7.38 (8H, m, Ar), 7.40 (1H, d, *J* = 7.0 Hz, Ar), 7.54 (1H, s, =CH), 7.56 (1H, d, *J* = 8.5 Hz, Ar), 7.75 (2H, d, *J* = 7.5 Hz, Ar), 8.08 (1H, dd, *J* = 2.0 Hz, H-4), 8.25 (1H, d, *J* = 2.0 Hz, H-6); δ_C (125 MHz, DMSO-d_6) 39.5, 59.5, 102.1, 113.9, 117.7, 122.4, 123.8, 124.2, 125.2, 125.7, 126.0, 127.4, 127.9, 129.0, 129.5, 130.0, 130.2, 131.0, 133.2, 134.9, 135.5, 142.4, 151.5, 155.8, 165.2; HRMS (ES): MH^+, found .511.0449 $C_{29}H_{20}NOS^{79}Br^+$ requires 511.0429.

4-(5-Bromo-2-phenylbenzofuran)-2-(4-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (205e); X = O, R^1 = H, R^2 = F

A mixture of **203b (**0.39 g, 0.93 mmol) and 2-aminothiophenol (0.14 g, 1.11 mmol) in acetic acid (10 mL) was treated as described for **201a** to afford **205e** as a green solid (0.31 g, 79%), mp.179–181 (EtOH); ν_{max} (ATR) 550, 699, 764,783, 980, 1093, 1135, 1213, 1346, 1506,

1585cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.04 (1H, t, J =12.5 Hz, H_A), 3.31 (1H, dd, J = 12.5 and 4.5 Hz, H_M), 5.07 (1H, dd, J = 12.5 and 4.5 Hz, H_X), 7.21 (2H, t, J = 8.0 Hz, Ar), 7.25-7.36 (4H, m, Ar), 7.5 (1H, s, =CH), 7.54 (2H, d, J = 8.5 Hz, Ar), 7.67 (2H, t, J = 8.0 Hz, Ar), 7.80 (2H, t, J = 9.0 Hz, Ar) 8.05 (1H, dd, J = 9.0 and 1.5 Hz, Ar) 8.23 (1H, d, J = 2.0 Hz, H-4), 8.30 (1H, d, J = 2.0 Hz, H-6); δ_C (125 MHz, DMSO-d_6) 39.1, 59.7, 101.9, 116.1 (d, $^2J_{CF}$ = 21.8 Hz) , 123.3, 123.7, 125.6, 125.7, 126.2, 126.5, 126.7, 128.2, 129.2, 129.3, 130.0, 130.4 (d, $^3J_{CF}$ = 8.5 Hz) 130.9 (d, $^4J_{CF}$ = 3.3 Hz) 133.4, 135.3, 144.3, 151.6, 151.9,157.5, 162.1 (d, $^1J_{CF}$ = 250.2 Hz), 165.6; HRMS (ES): MH$^+$, found .529.0334 $C_{29}H_{20}NOS^{79}FBr^+$ requires 529.0355.

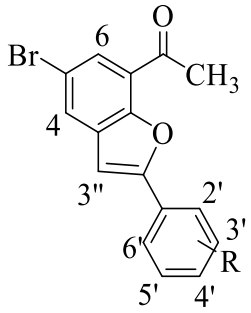
4-(5-Bromo-2-phenylbenzofuran)-2-(4-chlorophenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (205f); X = O, R^1 = H, R^2 = 4-Cl

A mixture of **203c (**0.50 g, 1.14 mmol) and 2-aminothiophenol (0.17 g, 1.37 mmol) in acetic acid (10 mL) was treated as described for **201a** to afford **205f** as a green solid (0.41 g, 82%), mp. 181–183 °C (EtOH); ν_{max} (ATR) 549, 694, 797, 866, 999, 1023, 1171, 1248, 1349, 1481, 1569, 1598, 1603 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.04 (1H, t, J =12.5 Hz, H_A), 3.31 (1H, dd, J = 12.5 and 4.5 Hz, H_M), 5.07 (1H, dd, J = 12.5 and 4.5 Hz, H_X), 7.25–7.27 (5H, m, Ar), 7.28-7.31 (5H, m, Ar), 7.47 (1H, s, =CH), 7.64 (2H, d, J = 8.0 Hz, Ar), 7.79 (1H, d, J = 7.5 Hz, Ar), 7.99 (2H, d, J = 2.0 Hz, Ar); δ_C (125 MHz, DMSO-d_6) 39.5, 59.4, 102.1, 117.2, 122.9, 123.3, 123.8, 124.9, 125.4, 126.3, 127.4, 127.6, 129.0, 129.4, 130.2, 131.0, 132.2, 133.5, 135.1, 135.2, 142.4, 151.5, 151.9, 155.8, 165.2; HRMS (ES): MH$^+$, found 543.0059 $C_{29}H_{20}NOS^{79}BrCl^+$ requires 543.0039.

4-(5-Bromo-2-(3-chlorophenyl)benzofuran-7-yl)-2-phenyl-2,3-dihydrobenzo[*b*][1,4]-thiazepine (205g); X = O, R_1 = H, R_2 = OCH_3

A mixture of **203d (**0.50 g, 1.15 mmol) and 2-aminothiophenol (0.17 g, 1.38 mmol) in acetic acid (10 mL) was treated as described for **201a** to afford **205g** as a solid (0.39 g, 78%), mp.197–199 °C (EtOH); ν_{max} (ATR) 550, 646, 784, 982, 1098, 1173, 1254, 1346, 1436, 1579 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.05 (1H, t, *J* = 13.0 Hz),3.31 (1H, dd, *J* = 13.0 and 5.0 Hz), 3.83 (3H, s, OCH_3), 5.25 (1H, dd, *J* = 13.0Hz and 5.0 Hz), 6.88 (2H, d, *J* = 8.0 Hz, Ar), 7.22 (2H, d, *J* = 7.5 Hz, Ar), 7.29 (2H, d, *J* = 7.5 Hz, Ar), 7.53 (2H, d, *J* = 7.5 Hz, Ar), 7.57 (2H, d, *J* = 8.0 Hz, Ar), 7.62 (2H, d, *J* = 8.0 Hz, Ar), 7.72 (1H, d, *J* = 8.0 Hz, Ar), 8.03 (1H, s, =CH),8.33 (1H, d, *J* = 1.5 Hz, H-4);8.39 (1H, d, *J* = 1.5 Hz, H-6); δ_C (125 MHz, DMSO-d_6) 39.8, 55.1, 59.5, 95.4, 110.8, 113.8, 113.9,122.5, 124.8, 125.3, 125.8, 127.2, 129.6, 129.9, 130.0, 130.4, 131.2, 133.4, 134.9,136.0, 144.4, 151.2, 154.0, 154.3, 158.7, 159.8; HRMS (ES): MH^+, found 541.0534 $C_{30}H_{23}O_2S^{79}Br^+$ requires 541.0555.

4.8 Synthesis of benzofuran derivatives 207a–e.



207a–e

1-(5-Bromo-2-phenylbenzofuran-7-yl)ethanone (207a); R = 4-H

A mixture of **197b** (1.02 g, 2.99 mmol), phenylacetylene (0.366 g, 3.59 mmol), $PdCl_2(PPh_3)_2$ (0.10 g, 0.15 mmol), Cs_2CO_3 (1.16 g, 3.59 mmol) and CuI (0.06 g, 0.29 mmol) in 10:1 dioxane-water (20 mL). The mixture was purged with nitrogen gas for 20 min. and a balloon filled with nitrogen gas was connected to the top of the condenser and was heated at 80 °C for 2 h and then quenched with an ice-cold water. The product was extracted with chloroform and the combined organic layers were washed with brine and dried over $MgSO_4$. 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 using 30% toluene-hexane mixture as an eluent to afford **207a** as a solid (0.69 g, 73%), R_f = 0.33, mp. 130–133 °C; ν_{max} (ATR) 684, 790, 884, 989, 1095, 1179, 1279, 1360, 1490, 1567, 1586, 1677, 3064 cm^{-1}; δ_H ($CDCl_3$) 2.95 (3H, s, CH_3), 7.03 (1H, s, H-3), 7.42 (2H, d, *J* = 7.0 Hz, Ar), 7.48 (1H, t, *J* = 7.5 Hz, Ar) 7.85 (2H, d, *J* = 8.0 Hz, Ar), 7.98 (1H, d, *J* = 1.5 Hz, H-4), 7.99 (1H, d, *J* = 1.5 Hz, H-6); δ_C ($CDCl_3$) 31.0, 100.5, 116.4, 122.9, 125.2, 127.5, 128.1, 128.6, 129.0, 129.5, 132.8, 152.1, 157.8, 194.6; HRMS (ES): found 316.9743. $C_{16}H_{12}O_2{}^{79}Br^+$ requires 316.9726. *Anal* calcd for $C_{16}H_{11}O_2Br$: C, 60.98; H, 3.58. Found: C, 60.96; H, 3.44.

1-(5-Bromo-2-(3′-fluorophenyl)benzofuran-7-yl)ethanone (207b); R = 3-F

A mixture of **197b** (0.99 g, 2.90 mmol), 3-fluorophenylacetylene (0.418 g, 3.48 mmol), $PdCl_2(PPh_3)_2$ (0.10 g, 0.14 mmol), Cs_2CO_3 (1.13 g, 3.48 mmol) and CuI (0.06 g, 0.29 mmol) in 10:1 dioxane-water (20 mL) was treated as for the preparation of **207b** to afford **207b** as a solid (0.73 g, 76%), R_f = 0.32, mp. 161–164 °C; ν_{max} (ATR) 667, 781, 878, 987, 1081, 1163, 1280, 1365, 1488, 1556, 1686; δ_H ($CDCl_3$) 2.94 (3H, s, CH_3), 7.06 (1H, s, H-3), 7.12 (1H, t, *J* = 8.5

Hz, Ar), 7.40 (2H, dd, *J* = 8.5 and 2.0 Hz, Ar), 7.64 (1H, d, *J* = 8.5 Hz, Ar), 7.89 (1H, d, *J* 2.0 Hz, H-4), 8.00 (1H, d, *J* 2.0 Hz, H-6); δ_C ($CDCl_3$) 30.9, 101.6, 112.1 (d, $^2J_{CF}$ =23.6 Hz) 116.4 (d, $^2J_{CF}$ = 21.9 Hz), 116.5, 120.9 (d, $^4J_{CF}$ = 2.8 Hz), 123.1, 127.5, 128.1, 128.4, 130.7 (d, $^3J_{CF}$ = 7.5 Hz), 132.5, 152.1, 156.4 (d, $^4J_{CF}$ = 2.9 Hz), 163.1 (d, $^1J_{CF}$ = 249.4 Hz) 194.4; HRMS (ES): found 332.9828. $C_{16}H_{11}O_2F^{79}Br^+$ requires 332.9826. *Anal* calcd for $C_{16}H_{10}O_2FBr$: C, 57.68; H, 3.03. Found: C, 57.50; H, 2.99.

1-(5-Bromo-2-(4′-fluorophenyl)benzofuran-7-yl)ethanone (207c); R = 4-F

A mixture of **197b** (0.99 g, 2.90 mmol), 4-fluorophenylacetylene (0.418 g, 3.48 mmol), $PdCl_2(PPh_3)_2$ (0.10 g, 0.14 mmol), Cs_2CO_3 (1.13 g, 3.48 mmol) and CuI (0.06 g, 0.29 mmol) in 10:1 dioxane-water (20 mL) was treated as for the preparation of **207b** to afford **207c** as a solid (0.82 g, 76%), R_f = 0.31, mp. 178–180 °C; ν_{max} (ATR) 668, 784, 898, 987, 1029, 1166, 1280, 1365, 1488, 1555, 1682 cm^{-1}; δ_H ($CDCl_3$) 2.93 (3H, s, -CH_3), 6.98 (1H, s, H-3), 7.18 (2H, t, *J* = 8.5 Hz, H-2',6'), 7.83 (2H, t, *J* = 8.7 Hz, H-3',5') 7.86 (1H, d, *J* 1.8 Hz, H-4), 7.97 (1H, d, *J* 1.8 Hz, H-6); δ_C ($CDCl_3$) 30.9, 100.1, 116,3 (d, $^2J_{CF}$ = 22.8 Hz), 125.6, 127.1, 127.6, 128.1, 128.5 (d, $^3J_{CF}$ = 12.2 Hz), 132.2 (d, $^4J_{CF}$ = 10.3 Hz), 132.8, 151.9, 156.9, 163.4 (d, $^1J_{CF}$ = 249.4 Hz) 194.5; HRMS (ES): found 332.9848. $C_{16}H_{11}O_2F^{79}Br^+$ requires 333.9828. *Anal* calcd for $C_{16}H_{10}O_2ClBr$: C, 57.68; H, 3.03. Found: C, 57.63; H, 3.01.

1-(5-Bromo-2-(3-chlorophenyl)benzofuran-7-yl)ethanone (207d); R = 3-Cl

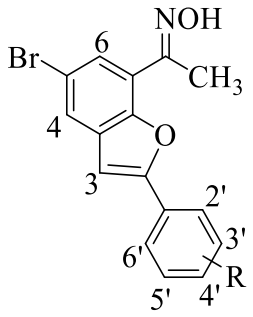
A mixture of **197b** (1.00 g, 2.93 mmol), 3-chlorophenylacetylene (0.479 g, 3.52 mmol), $PdCl_2(PPh_3)_2$ (0.10 g, 0.15 mmol), Cs_2CO_3 (1.14 g, 3.52 mmol) and CuI (0.05 g, 0.29 mmol) in 10:1 dioxane-water (20 mL) was treated as for the preparation of **207b** to afford **207d** as a solid

(0.76 g, 74%), R_f = 0.28, mp. 139–141 °C; ν_{max} (ATR) 682, 788, 882, 1078, 1144, 1275, 1359, 1474, 1561, 1587, 1675, 3081 cm^{-1}; δ_H ($CDCl_3$) 2.94 (3H, s, CH_3), 7.07 (1H, s, H-3), 7.41 (2H, dd, *J* = 1.5 and 8.0 Hz, Ar), 7.78 (1H, d, *J* = 8.0 Hz, Ar), 7.83 (1H, d, *J* = 2.0 Hz, H-4), 7.90 (1H, d, *J* = 1.5 Hz, Ar), 7.97 (1H, d, *J* = 2.0 Hz, H-6); δ_C ($CDCl_3$) 30.9, 101.6, 116.6, 123.1, 123.2, 125.2, 128.1, 128.4, 129.4, 130.4, 130.9, 132.5, 135.1, 152.1, 156.3, 194.4; HRMS (ES): found 348.9634. $C_{16}H_{11}O_2{}^{35}Cl^{79}Br^+$ requires 348.9631. *Anal* calcd for $C_{16}H_{10}O_{43}ClBr$: C, 54.97; H, 2.88. Found: C, 54.64; H, 2.95.

1-(5-Bromo-2-(4′-(trifluoromethoxy)phenyl)benzofuran-7-yl)ethanone (207e); R = 4-OCF_3

A mixture of **197** (1.04 g, 3.04 mmol), phenylacetylene (0.679 g, 3.65 mmol), $PdCl_2(PPh_3)_2$ (0.11 g, 0.15 mmol), Cs_2CO_3 (1.18 g, 3.65 mmol) and CuI (0.06 g, 0.30 mmol) in 10:1 dioxane-water (20 mL) was treated as for the preparation of **207b** to afford **207d** as a solid (0.93 g, 77%), R_f = 0.35, mp. 170–173 °C; ν_{max} (ATR) 666, 746, 854, 987, 1033, 1199, 1267, 1363, 1405, 1502, 1614, 1676, 3082 cm^{-1}; δ_H ($CDCl_3$) 2.92 (3H, s, CH_3), 7.03 (1H, s, H-3), 7.34 (2H, d, *J* = 8.1 Hz, Ar), 7.85 (2H, d, *J* = 9.3 Hz, Ar), 7.98 (2H, d, *J* = 1.8 Hz, Ar); δ_C ($CDCl_3$) 30.8, 101.1, 116.6, 121.5, 123.0, 126.7, 127.7, 127.9, 128.0, 128.3, 130.2 (t, *J* = 25.6 Hz) 132.6, 152.1, 156.4, 194.4; HRMS (ES): 398.9663. found $C_{17}H_{11}O_3F_3{}^{79}Br^+$ requires 398.9745. *Anal* calcd for $C_{17}H_{10}O_3F_3Br$: C, 51.15; H, 2.53. Found: C, 51.32; H, 2.67.

4.9 Synthesis of oxime derivatives 208a–e.



208a–e

1-(5-Bromo-2-phenylbenzofuran-7-yl)ethanone oxime (208a); R = 4-H

A mixture of **207a** (0.78 g, 2.49 mmol) and $NH_2OH.HCl$ (0.25 g, 3.74 mmol) in pyridine (20 mL) was heated at 120 °C for 1 h. The mixture was quenched with an ice-cold water and the product was filtered. The resultant precipitate was washed thoroughly with cold hexane and then recrystallized from ethanol to afford **208a** as a solid (0.76 g, 93%), mp. 177–179 °C; ν_{max} (ATR) 748, 777, 874, 1029, 1230, 1366, 1429, 1445, 1562, 1601, 3107, 3200 cm^{-1}; δ_H (DMSO-d_6) 2.42 (3H, s, CH_3), 7.41 (2H, d, *J* = 7.0 Hz, Ar), 7.47 (1H, s, H-3), 7.53 (1H, t, *J* = 8.5 Hz, Ar), 7.58 (2H, d, *J* = 8.5 Hz, Ar), 7.61 (1H, d, *J* = 1.5 Hz, H-4), 7.84 (1H, d, *J* = 1.5 Hz, H-6), 11.5 (1H, s, OH); δ_C (DMSO-d_6) 14.0, 102.2, 117.8, 122.9, 124.7, 125.3, 126.4, 129.2, 129.8, 130.8, 131.8, 151.0, 151.6, 156.9; HRMS (ES): found 330.0031. $C_{16}H_{13}O_2N^{79}Br^+$ requires 330.0051. *Anal* calcd for $C_{16}H_{12}O_2NBr$: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.33; H, 3.71; N, 4.00.

1-(5-Bromo-2-(3′-fluorophenyl)benzofuran-7-yl)ethanone oxime (208b); R = 3-F

A mixture of **207b** (0.64 g, 1.92 mmol) and $NH_2OH.HCl$ (0.19 g, 2.87 mmol) in pyridine (20 mL) was heated at 120 °C for 1 h and was treated as for the preparation of **208b** to afford **208b**

as a solid (0.57 g, 86%), mp. 199–201 °C; ν_{max} (ATR) 748, 906, 1029, 1154, 1262, 1316, 1453, 1555, 1603, 3108, 3187 cm^{-1}; δ_H (DMSO-d_6); 2.38 (3H, s, CH_3), 7.48 (1H, s, H-3), 7.49 (1H, d, *J* = 8.0 Hz, H-6'), 7.54 (1H, t, *J* 7.5 Hz, H-4'), 7.59 (1H, d, *J* = 7.5 Hz, H-2'), 7.86 (1H, t, *J* = 7.0 Hz, H-5'), 7.88 (1H, d, *J* = 2.0 Hz, H-4), 7.94 (1H, d, *J* = 2.0 Hz, H-6), 11.6 (1H, s, OH); δ_C (DMSO-d_6) 14.0, 103.3, 112.1 (d, $^2J_{CF}$ =23.6 Hz) 116.1 (d, $^2J_{CF}$ = 21.9 Hz), 119.5, 120.9 (d, $^4J_{CF}$ = 2.8 Hz), 123.9, 127.7, 129.6, 130.8, 131.5 (d, $^3J_{CF}$ = 7.5 Hz), 132.2, 134.4, 150.7 (d, $^4J_{CF}$ = 2.9 Hz), 156.5, 163.1 (d, $^1J_{CF}$ = 249.4 Hz); HRMS (ES): found 348.0028 $C_{16}H_{12}NO_2F^{79}Br^+$ requires 348.0035. *Anal* calcd for $C_{16}H_{11}NO_2FBr$: C, 55.20; H, 3.18; N, 4.02. Found: C, 55.43; H, 3.33; N, 3.99.

1-(5-Bromo-2-(4′-fluorophenyl)benzofuran-7-yl)ethanone oxime (208c); R = 4-F

A mixture of **207c** (0.73 g, 2.19 mmol) and $NH_2OH.HCl$ (0.22 g, 3.29 mmol) in pyridine (20 mL) was heated at 120 °C for 1 h and was treated as for the preparation of **208b** to afford **208c** as a solid (0.61 g, 81%), mp. 216–218 °C; ν_{max} (ATR) 690, 769, 852, 944, 1029, 1188, 1276, 1339, 1411, 1503, 1574, 1604 3108, 3187 cm^{-1}; δ_H (DMSO-d_6) 2.39 (3H, s, CH_3), 7.36 (2H, t, *J* = 8.7 Hz, H-2',6'), 7.43 (1H, s, H-3), 7.56 (1H, d, *J* = 2.0 Hz, H-4), 7.86 (2H, d, *J* = 2.0 Hz, H-6), 7.97 (2H, t, *J* = 8.7 Hz, H-3',5'), 11.6 (1H, s, OH); δ_C (DMSO-d_6) (125 MHz, $CDCl_3$) 14.0, 101.7, 115.9, 116,7 (d, $^2J_{CF}$ = 21.9 Hz), 123.9, 124.0, 125.2, 126.1, 126.2, 127.7 (d, $^3J_{CF}$ = 8.5 Hz), 132.5, 150.7 (d, $^4J_{CF}$ = 4.7 Hz), 156.3, 163.1 (d, $^1J_{CF}$ = 245.6 Hz), HRMS (ES): found: 348.9934. $C_{16}H_{12}NO_2F^{79}Br^+$ requires 348.9937. *Anal* calcd for $C_{16}H_{11}NO_2FBr$: C, 55.20; H, 3.18; N, 4.02. Found: C, 55.41; H, 3.31; N, 4.00.

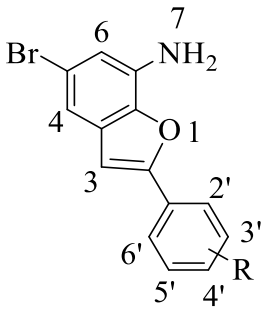
1-(5-Bromo-2-(3′-chlorophenyl)benzofuran-7-yl)ethanone oxime (208d); R = 3-Cl

A mixture of **207d** (0.50 g, 1.43 mmol) and $NH_2OH.HCl$ (0.19 g, 2.87 mmol) in pyridine (20 mL) was heated at 120 °C for 1 h and was treated as for the preparation of **208b** to afford **208d** as a solid (0.39 g, 81%), mp. 192–195 °C; ν_{max} (ATR) 748, 849, 916, 1006, 1090, 1162, 1278, 1314, 1337, 1429, 1448, 1561, 1604, 3106, 3211 cm^{-1}; δ_H (DMSO-d_6) 2.29 (3H, s, CH_3), 7.47 (1H, s, H-3), 7.58 (1H, dd, *J* = 2.0 and 8.5 Hz, H-6'), 7.58 (1H, t, *J* = 8.5 Hz, H-5'), 7.67 (1H, d, *J* = 2.0 Hz, H-4), 7.85 (1H, d, *J* = 2.0 Hz, H-6), 7.67 (1H, d, *J* = 8.0 Hz, H-4'), 7.98 (1H, d, *J* = 2.0 Hz, H-2), 11.0 (1H, s, OH); δ_C (DMSO-d_6) 14.0, 103.3, 116.1, 123.9, 124.1, 124.3, 124.9, 125.7, 129.6, 131.5, 131.6, 132.2, 134.4, 150.7, 150.8, 155.5; HRMS (ES): found: 364.9722. $C_{16}H_{12}NO_2{}^{35}Cl^{79}Br^+$ requires 364.9641. *Anal* calcd for $C_{16}H_{11}NO_2ClBr$: C, 52.70; H, 3.04; N, 3.84. Found: C, 52.65; H, 3.14; N, 3.88.

1-(5-Bromo-2-(4′-(trifluoromethoxy)phenyl)benzofuran-7-yl)ethanone oxime (207e); R = OCF_3

A mixture of **207e** (0.51 g, 1.88 mmol) and $NH_2OH.HCl$ (0.21 g, 2.82 mmol) in pyridine (20 mL) was heated at 120 °C for 1 h and was treated as for the preparation of **208b** to afford **208e** as a solid (0.61 g, 78%), mp. 167–169 °C; ν_{max} (ATR) 681, 777, 908, 1029, 1161, 1279, 1337, 1449, 1460, 1510, 1583, 3074, 3208 cm^{-1}; δ_H (DMSO-d_6) 2.51 (3H, s, CH_3), 6.99 (1H, s, H-3), 7.30 (2H, d, *J* = 8.5 Hz, H-3',5'), 7.61 (1H, d, *J* = 1.5 Hz, H-4), 7.72 (1H, d, *J* = 1.5 Hz, H-6), 7.88 (2H, d, *J* = 8.0 Hz, H-2',6'), 8.34 (1H, s, OH); δ_C (DMSO-d_6) 13.6, 101.3, 116.3, 121.3, 121.3, 122.7, 124.3, 126.1, 126.8, 130.1 (t, J_{CF} = 25.6 Hz), 133.2, 149.6, 150.9, 153.1, 156.1; HRMS (ES): found 414.9932. $C_{17}H_{12}NO_3F_3{}^{79}Br^+$ requires 414.9854. *Anal* calcd for $C_{17}H_{11}NO_3F_3Br$: C, 49.30; H, 2.68; N, 3.38. Found: C, 49.19; H, 2.59; N, 3.42.

4.10 One-pot Beckmann rearrangement and hydrolysis of the oxime derivatives 208a–e.



208a–e

5-Bromo-2-(phenyl)benzofuran-7-amine (210a); R = 4-H

A mixture of **208a** (0.78 g, 2.00 mmol) and triflic acid (0.12 g, 0.80 mmol) in acetonitrile (20 mL) was heated at 120 °C for 1 h. The mixture was cooled to room temperature and quenched with ice-cold water. The resultant precipitate was washed thoroughly with cold hexane and then recrystallized from ethanol to afford **210a** as a solid (0.35 g, 62%), mp. 177–179 °C; ν_{max} (ATR) 736, 915, 1156, 1214, 1309, 1433, 1502, 1572, 1583, 1611, 3351, 3464 cm^{-1}; δ_H (DMSO-d_6) 5.70 (2H, s, NH_2), 7.21 (1H, s, H-3), 7.28 (2H, d, *J* = 8.5 Hz, Ar), 7.41 (2H, d, *J* = 8.0 Hz, Ar), 7.50 (1H, t, *J* = 8.5 Hz, Ar), 7.65 (1H, d, *J* = 1.5 Hz, H-6), 7.84 (1H, d, *J* = 7.5 Hz, Ar); δ_C (DMSO-d_6) 103.3, 111.1, 125.2, 128.7, 129.3, 129.4, 130.1, 133.6, 134.2, 136.2, 145.9, 156.1; HRMS (ES): found 287.9946. $C_{14}H_{11}NO^{79}Br^+$ requires 287.9925. *Anal* calcd for $C_{14}H_{10}NOBr$: C, 58.36; H, 3.50; N, 4.85. Found: C, 58.68; H, 3.20; N, 4.77.

5-Bromo-2-(3′-fluorophenyl)benzofuran-7-amine (210b); R = 3-F

A mixture of **208b** (0.51 g, 1.47 mmol) and triflic acid (0.09 g, 0.58 mmol) in acetonitrile (15 mL) was heated at 120 °C for 4 h and was treated as for the preparation of **210a** to afford **210b** as a solid (0.34 g, 78 %), mp. 124–126 °C; ν_{max} (ATR) 721, 765, 834, 1100, 1261, 1309, 1433,

1572, 1583, 1611, 3375, 3482 cm^{-1}; δ_H (DMSO-d_6) 5.81 (2H, br s, NH_2), 6.68 (1H, d, *J* = 1.5 Hz, H-6), 6.95 (1H, d, *J* = 1.5 Hz, H-4), 7.22 (1H, t, *J* 8.0 Hz, H-4'), 7.35 (1H, s, H-3), 7.52 (1H, dd, *J* 1.5 and 7.5 Hz, H-5'), 7.79 (1H, d, *J* = 8.0 Hz, H-6'), 7.82 (1H, s, H-2'); δ_C (DMSO-d_6) 103.5, 110.5, 111,7 (d, $^3J_{CF}$ = 8.5 Hz), 111.9, 115.9 (d, $^2J_{CF}$ = 20.9 Hz), 116.7, 121.3 (d, $^4J_{CF}$ = 2.9 Hz), 130.8, 131.5 (d, $^3J_{CF}$ = 8.5 Hz), 132.4 (d, $^3J_{CF}$ = 8.6 Hz), 135.7, 142.1, 154.3 (d, $^4J_{CF}$ = 2.8 Hz),163.1 (d, $^1J_{CF}$ = 240.6 Hz); HRMS (ES): found: 305.9852. $C_{14}H_{10}NOF^{79}Br^+$ requires 305.9831. *Anal* calcd for $C_{14}H_9NOFBr$: C, 54.93; H, 2.96; N, 4.58. Found: C, 54.87; H, 3.09; N, 4.72.

5-Bromo-2-(4′-fluorophenyl)benzofuran-7-amine (210c); R = 4-F

A mixture of **208c** (0.63 g, 1.82 mmol) and triflic (0.11 g, 0.73 mmol) in acetonitrile (15 mL) was heated at 120 °C for 4 h and was treated as for the preparation of **210a** to afford **210c** as a solid (0.39 g, 71%), mp. 121–123 °C; ν_{max} (ATR) 688, 765, 915, 1100, 1214, 1309, 1433, 1502, 1583, 1612, 3370, 3473 cm^{-1}; δ_H (DMSO-d_6) 5.75 (2H, brs, NH_2), 6.66 (1H, d, *J* = 2.0 Hz, H-6), 6.93 (1H, d, *J* = 2.0 Hz, H-4), 7.23 (1H, s, H-3), 7.34 (2H, t, *J* 8.7 Hz, H-3',5'), 7.99 (2H, t, *J* = 8.5 Hz, H-2',6'); δ_C (DMSO-d_6) 102.1, 110.5, 111.4, 116,4 (d, $^2J_{CF}$ = 21.8 Hz), 116.6, 126.8 (d, $^4J_{CF}$ = 2.9 Hz) 127.4 (d, $^3J_{CF}$ = 8.5 Hz), 131.1, 135.6, 142.1, 154.8, 162.7 (d, $^1J_{CF}$ = 244.7 Hz); HRMS (ES): found 305.9715. $C_{14}H_{10}NOF^{79}Br^+$ requires 305.9776. *Anal* calcd for $C_{14}H_9NOFBr$: C, 54.93; H, 2.96; N, 4.58. Found: C, 54.88; H, 3.07; N, 4.70.

5-Bromo-2-(3′-chlorophenyl)benzofuran-7-amine (210d); R = 3-Cl

A mixture of **208d** (0.55 g, 1.51 mmol) and triflic acid (0.10 g, 0.60 mmol) in acetonitrile (15 mL) was heated at 120 °C for 4 h and was treated as for the preparation of **210a** to afford **210d**

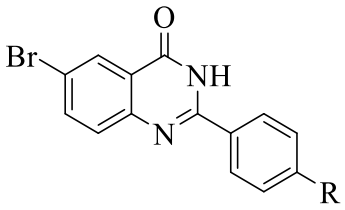
as a solid (0.31 g, 65%), mp. 106–108 °C; ν_{max} (ATR) 737, 854, 879, 1126, 1270, 1429, 1593, 1615, 3372, 3482 cm^{-1}; δ_H (DMSO-d_6) 5.82 (2H, br s, NH_2), 6.68 (1H, d, *J* = 2.0 Hz, H-6), 6.94 (1H, d, *J* = 2.0 Hz, H-4) 7.37 (1H, s, H-3), 7.43 (1H, d, *J* = 8.0, H-4'), 7.51 (1H, t, *J* = 7.5 Hz, H-5'), 7.90 (1H, d, *J* = 7.5 Hz, H-6'), 8.05 (1H, d, *J* = 8.0 Hz, H-2'); δ_C (DMSO-d_6) 103.6, 110.6, 111.7, 116.7, 123.7, 124.7, 128.9, 130.8, 131.3, 132.2, 134.4, 135.7, 142.2, 154.0; HRMS (ES): found 321.9556. $C_{14}H_{10}NO^{35}Cl^{79}Br^+$ requires 321.9536. *Anal* calcd for $C_{14}H_9NOClBr$: C, 52.13; H, 2.81; N, 4.34. Found: C, 52.31; H, 2.66; N, 4.28.

5-Bromo-2-(4′-(trifluoromethoxy)phenyl)benzofuran-7-amine (210e); R = 4-OCF_3

A mixture of **208e** (0.62 g, 1.49 mmol) and triflic acid (0.11 g, 0.60 mmol) in acetonitrile (15 mL) was heated at 120 °C for 4 h and was treated as for the preparation of **210a** to afford **210e** as a solid (0.47 g, 85 %), mp. 118–119 °C; ν_{max} (ATR) 685, 737, 823, 947, 1044, 1214, 1468, 1568, 1614, 3382, 3484 cm^{-1}; δ_H (DMSO-d_6) 5.78 (2H, br s, NH_2), 6.95 (1H, d, *J* = 2.0 Hz, H-4), 6.68 (1H, d, *J* = 2.0 Hz, H-6), 7.32 (1H, s, H-3), 7.49 (2H, d, *J* = 8.5 Hz, H-3',5'), 8.05 (2H, d, *J* = 8.0 Hz, H-2',6'); δ_C (DMSO-d_6) 101.3, 116.3, 121.3, 122.7, 124.3, 126.1, 126.8, 130.1 (t, J_{CF} = 25.6 Hz), 133.2, 149.6, 150.9, 153.1, 156.1; HRMS (ES): found 371.9748. $C_{15}H_{10}NO_2F_3{}^{79}Br^+$ requires 371.9769. *Anal* calcd for $C_{15}H_9NO_2F_3Br$: C, 48.41; H, 2.44; N, 3.76. Found: C, 48.14; H, 2.65; N, 3.89.

4.11 Synthesis of the 2-aryl-6-bromo-4-chloroquinazolines 214a and 214b from the 2-ary-6-bromoquinazolin-4(3*H*)-ones 213a and 213b.

(a) Typical procedure for the synthesis of 213a and 213b



214a and 214b

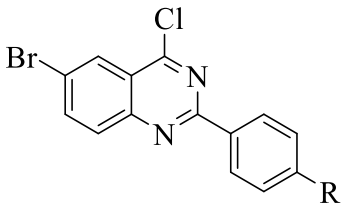
6-Bromo-2-(4′-fluorophenyl)quinazolin-4(3*H*)-one (213a); R = F

A stirred mixture of 2-amino-5-bromobenzamide **211** (1.00 g, 4.65 mmol), 4-flourobenzaldehyde **212** (0.86 g, 6.97 mmol) and iodine (2.36 g, 9.30 mmol) in ethanol (30 mL) in a round-bottomed flask equipped with a stirrer bar and a condenser was refluxed for 8 h and then allowed to cool to room temperature. An ice-cold saturated aqueous solution of sodium thiosulphate was added to the mixture and the resultant precipitate was filtered and washed with cold water. The product was recrystallized from acetonitrile to afford **213a** as an off white solid (0.95 g, 91%), mp. 278–280; ν_{max} (ATR) 493, 563, 622, 824, 924, 1237, 1271, 1316, 1387, 1462, 1603, 1688, 2809, 3445 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.20 (2H, t, *J* 8.5 Hz, Ar), 7.42 (2H, t, *J* 8.5 Hz, Ar), 7.93 (1H, dd, *J* = 2.5 and 8.5 Hz, Ar), 8.12 (1H, d, *J* = 8.5 Hz), 8.16 (1H, d, *J* = 2.0 Hz,), 12.40 (br s, 1H);. δ_C (125 MHz, DMSO-d_6) 64.8, 108.5, 109.3, 115.7 (d, $^2J_{CF}$ Hz), 118.3, 128.6 (d, $^3J_{CF}$ 21.7 Hz), 129.8, 138.4, 138.8 (d, $^4J_{CF}$ 3.0 Hz), 143.8, 161.5, 162.4 (d, $^1J_{CF}$ 242.4 Hz); HRMS (ES): MH^+, found 317.9794. $C_{14}H_9BrFN_2O^+$ requires 317.9804.

6-Bromo-2-(4′-chlorophenyl)quinazolin-4(3*H*)-one (213b); R = Cl

A mixture of 2-amino-5-bromobenzamide (1.00 g, 4.65 mmol), 4-chlorobenzaldehyde (0.97 g, 6.97 mmol) and iodine (2.36 g, 9.30 mmol) in ethanol (30 mL) and was treated as described for **213a** to afforded **213b** as a white solid (1.45 g, 93%), mp. 342–344 °C; ν_{max} (ATR) 538, 559, 649, 728, 831, 940, 1091, 1276, 1413, 1460, 1556, 1601, 1672, 3442 cm $^{-1}$; δ_H (500 MHz, DMSO-d_6) 7.60 (2H, d, *J* = 8.5 Hz, Ar), 7.66 (1H, d, *J* = 8.5 Hz, Ar), 7.95 (1H, dd, *J* = 2.5 and 8.5 Hz, Ar), 8.16 (2H, d, *J* = 8.5 Hz, Ar), 8.19 (1H, d, *J* = 2.0 Hz, Ar), 12.76 (1H, brs, NH); δ_C (125 MHz, DMSO-d_6) 104.7, 112.5, 112.9, 119.9, 128.4, 129.2, 129.9, 130.2, 138.0, 139.1, 155.3, 159.3; HRMS (ES): MH^+, found 334.9578. $C_{14}H_9Br^{35}ClN_2O^+$ requires 334.9587.

(b) Typical procedure for the synthesis of 2-aryl-6-bromo-4-chloroquinazoline (214a); R = F.



6-Bromo-4-chloro-3-(4′-flourophenyl)quinazoline (214a); R = F.

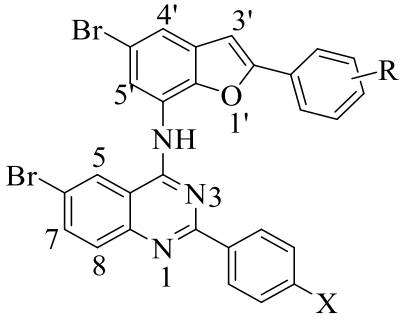
A mixture of **213a** (0.50 g, 1.06 mmol) and $POCl_3$ (10 mL) was heated at 120° C for 3 h. The reaction mixture was then allowed to cool to room temperature and then quenched slowly with a mixture of ice and ammonia and the product was extracted with chloroform. The combined organic layers were washed with an aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was recrystallized from ethanol to afford **214a** as a white solid (0.46 g, 85%), mp. 208–210; ν_{max} (ATR) 499, 539, 850, 1021, 1169, 1271, 1352, 1389, 1468, 1474, 1560, 1630, 2932 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.20 (2H, t, *J*

8.5 Hz, Ar), 7.42 (2H, t, *J* 8.5 Hz, Ar)8.06 (1H, dd, *J* = 2.5 and 8.5 Hz, Ar), 8.16 (1H, d, *J* = 2.0 Hz, Ar), 8.44 (1H, d, *J* = 2.0 Hz, Ar);

6-Bromo-4-chloro-3-(4′-chlorophenyl)quinazoline (214b); R = Cl

A stirred mixture of **213b** (0.50 g,1.49 mmol) and phosphoryl chloride (10 mL) was treated as for the preparation of **214a** to afford **214b** as a yellow solid (0.48 g, 91%), mp. 244–246 °C; ν_{max} (ATR) 505, 531, 732, 829, 991, 1090, 1294, 1318, 1402, 1415, 1469, 1493,1539, 1556, 1592, 1633 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.48 (2H, d, *J* = 8.5 Hz,), 7.93 (1H, d, *J* = 8.0 Hz,), 7.99 (1H, dd, *J* = 2.5 and 8.5 Hz,), 8.40 (d, *J* = 2.0 Hz, 1H), 8.51 (d, *J* = 8.5 Hz, 2H); δ_C (125 MHz, DMSO-d_6) 104.8, 112.5, 112.9, 128.5, 129.2, 129.9, 130.2, 138.0, 139.2, 149.1, 152.0 159.3; HRMS (ES): MH^+ found 334.9571. $C_{14}H_9{}^{79}Br^{35}Cl_2{}^+$ requires 334.9587.

4.12 Amination of 214a and 214b with the 7-aminobenzofurans 210a–e to afford 215a–j.



215a–j

6-Bromo-*N*-(5-bromo-2-phenylbenzofuran-7-yl)-2-(4-fluorophenyl)quinazolin-4-amine (215a); R = 4-H, X=F

A mixture of **210a** (0.18 g, 0.63 mmol), **214a** (0.21 g, 0.63 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) was stirred under reflux for 2 h. After completion of the reaction (tlc monitoring) the mixture was cooled to room temperature and quenched with an ice-cold water. The resultant precipitate was washed thoroughly with hot acetonitrile and then recrystallized from DMSO to afford **215a** as a solid (0.28 g, 75%) mp. > 300 °C; ν_{max} (ATR) 688, 782, 873, 911, 1047, 1161, 1221, 1373, 1515, 1603, 1631, 3082, 3169 cm^{-1}; δ_H (DMSO-*d*$_6$) 7.29 (2H, t, *J* = 8.5 Hz, Ar), 7.34 (2H, d, *J* = 8.5 Hz, Ar), 7.47 (1H, s, =C-H), 7.78–7.79 (5H, m, Ar), 7.85 (1H, d, *J* = 8.5 Hz, Ar), 8.04 (1H, d, *J* = 8.0 Hz, Ar), 8.11 (2H, d, *J* = 8.5 Hz, Ar), 8.91 (1H, d, *J* = 1.5 Hz, Ar), 10.89 (1H, s, NH); δ_C (DMSO-*d*$_6$) 103.3, 115.8 ,116.2 (d, $^2J_{CF}$ = 21.8 Hz), 119.5, 121.1, 122.9, 125.4, 126.9, 128.4, 128.8, 129.4, 129.8, 130.2, 131.0 (d, $^4J_{CF}$ = 2.8 Hz) 131.2 (d, $^3J_{CF}$ = 9.5 Hz), 133.0, 135.7, 137.9, 147.9, 150.7, 152.5, 157.4, 158.3, 162.7 (d, $^1J_{CF}$ = 272.1 Hz); HRMS (ES): found 589.9715. $C_{28}H_{16}N_3OFBr_2^+$ requires 588.9624. *Anal* calcd for $C_{28}H_{15}N_3OFBr$: C, 57.07; H, 2.74; N, 7.13. Found: C, 57.11; H, 2.97; N, 7.12.

6-Bromo-*N*-(5-bromo-2-(3-fluorophenyl)benzofuran-7-yl)-2-(4- fluorophenyl)quinazolin-4-amine (215b); R = 3-F, X=F

A mixture of **210b** (0.20 g, 0.65 mmol), **214a** (0.23 g, 0.65 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) and was treated as for the preparation of **215a** to afford **215b** as a solid (0.32 g, 82%) mp. > 300 °C; ν_{max} (ATR) 683, 775, 874, 937, 1089, 1086, 1239, 1365, 1454, 1594, 1632, 3070, 3171 cm^{-1}; δ_H (DMSO-*d*$_6$) 7.16 (2H, t, *J* = 9.0 Hz, Ar), 7.39 (2H, d, *J* = 8.5 Hz, Ar), 7.60 (2H, d, *J* = 8.5 Hz, Ar), 7.61 (1H, s, =C-H), 7.81 (1H, dd, *J* = 1.5 and 9.0 Hz, Ar),

7.99 (1H, d, J = 8.5 Hz, Ar), 8.12 (1H, d, J = 8.5 Hz, Ar), 8.16 (2H, t, J = 8.5 Hz, Ar), 8.22 (1H, t, J = 8.5 Hz, Ar), 9.03 (1H, d, J = 1.5 Hz, Ar), 11.02 (1H, s, NH); δ_C (DMSO-d_6) 103.5, 112.0 (d, $^2J_{CF}$ = 23.8 Hz), 115.3 (d, $^3J_{CF}$ = 8.5 Hz), 115.6, 116.1, (d, $^2J_{CF}$ = 21.9 Hz), 116.5, (d, $^2J_{CF}$ = 20.9 Hz), 119.8, 121.7, 123.0, 126.8, 128.4, 130.0, 130.2, 131.5 (d, $^3J_{CF}$ = 9.5 Hz), 130.6 (d, $^2J_{CF}$ = 8.5 Hz), 131.7, 132.3, 136.5, 137.9, 147.2, 148.0, 152.5, 155.5, 158.0 (d, $^4J_{CF}$ = 2.9 Hz), 162.7 (d, $^1J_{CF}$ = 224.7 Hz) 164.7 (d, $^1J_{CF}$ = 231.3 Hz); HRMS (ES): found 607.9629. $C_{28}H_{16}N_3OF_2{}^{79}Br_2{}^+$ requires 607.9628. *Anal* calcd for $C_{28}H_{15}N_3OF_2Br$: C, 55.38; H, 2.49; N, 6.97. Found: C, 55.62; H, 2.57; N, 6.85.

6-Bromo-*N*-(5-bromo-2-(4-fluorophenyl)benzofuran-7-yl)-2-(4- fluorophenyl)quinazolin-4-amine (215c); R = 4-F; X=F

A mixture of **210c** (0.20 g, 0.65 mmol), **214a** (0.22 g, 0.65 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) and was treated as for the preparation of **215a** to afford **215c** as a solid (0.19 g, 87%) mp. 287–289 °C; ν_{max} (ATR) 737, 846, 943, 1088, 1156, 1289, 1365, 1454, 1572, 1607, 1627, 3064, 3170 cm^{-1}; δ_H (DMSO-d_6) 7.15 (2H, t, J = 8.5 Hz, Ar), 7.22 (1H, t, J = 8.5 Hz, Ar), 7.38 (1H, t, J = 8.5 Hz, Ar), 7.48 (1H, s, =C-H) 7.66 (1H, d, J = 8.5 Hz, Ar), 7.77–7.82 (2H, m, Ar), 7.94–7.97 (2H, m, Ar), 8.08 (1H, d, J = 7.5 Hz, Ar), 8.16 (1H, t, J = 8.5 Hz, Ar), 8.20–8.23 (1H, m, Ar), 8.99 (1H, d, J = 1.5 Hz, Ar), 10.89 (1H, s, NH); δ_C (DMSO-d_6) 102.1, 115.8, 116.2 (d, $^2J_{CF}$ = 21.8 Hz), 116.5 (d, $^2J_{CF}$ = 21.8 Hz) , 119.5, 121.3, 122.9, 123.5, 124.3, 126.0 (d, $^4J_{CF}$ = 3.9 Hz), 126.6, 127.7 (d, $^3J_{CF}$ = 8.5 Hz), 128.5, 129.4 (d, $^4J_{CF}$ = 2.8 Hz), 130.2, 130.8 (d, $^3J_{CF}$ = 8.5 Hz), 130.9, 132.6, 137.5, 147.9, 157.8, 161.6, 164.5 (d, $^1J_{CF}$ = 248.8 Hz), 164.5 (d, $^1J_{CF}$ = 267.3 Hz); HRMS (ES): found 605.9629. $C_{28}H_{16}N_3OF_2Br_2{}^+$ requires 605.9628. *Anal* calcd for $C_{28}H_{15}N_3OF_2Br$: C, 55.38; H, 2.49; N, 6.97. Found: C, 55.59; H, 2.61; N, 7.01.

6-Bromo-*N*-(5-bromo-2-(3-chlorophenyl)benzofuran-7-yl)-2-(4-fluorophenyl)quinazolin-4-amine (215d); R = 3-Cl; X=F

A mixture of **210d** (0.11 g, 0.30 mmol), **214a** (0.12 g, 0.30 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) and was treated as for the preparation of **215a** to afford **215d** as a solid (0.14 g, 78%) mp. > 300 °C; ν_{max} (ATR) 738, 856, 938, 1030, 1129, 1254, 1347, 1458, 1596, 1634, 3109, 3169 cm^{-1}; δ_H (DMSO-d_6) 7.09 (2H, t, *J* = 8.0 Hz, Ar), 7.38 (2H, d, *J* = 8.5 Hz, Ar), 7.58 (1H, s, =C-H), 7.85 (1H, d, *J* = 8.5 Hz, Ar), 7.96 (1H, dd, *J* = 2.5 and 8.5 Hz, Ar), 8.05 (1H, dd, *J* = 1.5 and 8.5 Hz, Ar), 8.07 (2H, d, *J* = 8.5 Hz, Ar), 8.15 (2H, t, *J* = 8.5 Hz, Ar), 8.20 (1H, d, *J* = 1.5 Hz, Ar), 8.90 (1H, d, *J* = 1.0 Hz, Ar), 10.45 (1H, s, NH); δ_C (DMSO-d_6) 103.6, 115.3, 115.5, 116.1 (d, $^2J_{CF}$ = 21.9 Hz), 119.0, 121.9, 123.6, 124.9, 126.3, 127.3, 128.4, 128.7, 129.2, 129.4, 130.3 (d, $^3J_{CF}$ = 8.7 Hz), 132.3, 134.6, 137.0, 137.8, 147.3, 149.0 (d, $^4J_{CF}$ = 3.8 Hz) 149.9, 155.4, 157.5, 158.8, 164.1 (d, $^1J_{CF}$ = 246.5 Hz); HRMS (ES): found 621.9328. $C_{28}H_{16}N_3OF^{35}Cl^{79}Br_2^+$ requires 621.9327. *Anal* calcd for $C_{28}H_{15}N_3OFClBr$: C, 53.92; H, 2.42; N, 6.74. Found: C, 53.97; H, 2.35; N, 6.848.

6-Bromo-*N*-(5-bromo-2-(4-(trifluoromethoxy)phenyl)benzofuran-7-yl)-2-(4-fluorophenyl) quinazolin-4-amine (215e); R = 4-OCF_3, X=F

A mixture of **210e** (0.19 g, 0.56 mmol), **214a** (0.20 g, 0.56 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) and was treated as for the preparation of **215a** to afford **215e** as a solid (0.36 g, 82%) mp. > 300 °C; ν_{max} (ATR) 736, 856, 938, 1060, 1128, 1259, 1347, 1455, 1599, 1634, 3111, 3169 cm^{-1}, δ_H (DMSO-d_6) 7.09 (2H, t, *J* = 8.0 Hz, Ar), 7.38 (2H, d, *J* = 8.5 Hz, Ar), 7.56 (1H, s, =C-H), 7.82–785 (4H, m, Ar), 8.04 (1H, d, *J* = 8.5 Hz, Ar), 8.15 (2H, t, *J* = 8.5 Hz, Ar), 8.20 (1H, d, *J* = 1.5 Hz, Ar), 8.90 (1H, d, *J* = 1.0 Hz, Ar), 10.45 (1H, s, NH); δ_C (DMSO-

d_6) 103.6, 115.3, 115.5, 116.1 (d, $^2J_{CF}$ = 21.9 Hz), 119.0, 121.9, 123.6, 124.9, 126.3, 127.3, 128.4, 128.7, 130.3 (d, $^3J_{CF}$ = 8.7 Hz), 130.9 (t, J_{CF} = 25.6 Hz) 132.3, 134.6, 137.0, 137.8, 147.3, 149.0 (d, $^4J_{CF}$ = 3.8 Hz) 149.9, 155.4, 157.5, 158.8, 164.1 (d, $^1J_{CF}$ = 246.5 Hz); HRMS (ES): found 672.9227. $C_{29}H_{16}N_3O_2F_4{}^{79}Br_2{}^+$ requires 672.9447. *Anal* calcd for $C_{29}H_{15}N_3OF_4Br$: C, 51.74; H, 2.25; N, 6.24. Found: C, 51.68; H, 2.11; N, 6.35.

6-Bromo-*N*-(5-bromo-2-phenylbenzofuran-7-yl)-2-(4-chlorophenyl)quinazolin-4-amine (215f); R = 4-H, X=Cl

A mixture of **210a** (0.21 g, 0.62 mmol), **214b** (0.24 g, 0.62 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) and was treated as for the preparation of **215a** to afford **215f** as a solid (0.32 g, 83%) mp. > 300 °C; ν_{max} (ATR) 683, 775, 874, 937, 1089, 1086, 1239, 1365, 1454, 1594, 1632, 3070, 3171 cm^{-1}; δ_H (DMSO-d_6) 7.31–7.37 (3H, m, Ar), 7.61 (1H, d, *J* = 8.5 Hz, Ar), 7.65 (1H, d, *J* = 7.0 Hz, Ar), 7.68 (1H, s, =C-H), 7.75 (1H, d, *J* = 7.5 Hz, Ar), 7.89 (1H, d, *J* = 8.7 Hz, Ar), 7.96 (1H, dd, *J* = 2.5 and 8.5 Hz, Ar), 8.07 (1H, d, *J* = 8.7 Hz, Ar), 8.17 (1H, d, *J* = 8.5 Hz, Ar), 8.21 (1H, d, *J* = 2.5 Hz, Ar), 8.26 (1H, d, *J* = 8.5 Hz, Ar), 8.42 (1H, d, *J* = 1.5 Hz, Ar), 8.97 (1H, d, *J* = 8.5 Hz, Ar), 10.71 (1H, s, NH); δ_C (DMSO-d_6) 103.3, 115.6, 119.6, 120.9, 126.4, 127.0, 128.5, 128.7, 129.1, 129.4, 129.9, 130.2, 130.8, 131.7, 132.9, 135.8, 136.9, 137.2, 137.9, 147.9, 150.7, 152.5, 157.2, 157.8, 158.8 161.6; HRMS (ES): found 605.9349. $C_{28}H_{17}N_3O^{35}Cl^{79}Br_2{}^+$ requires 605.9328. *Anal* calcd for $C_{28}H_{16}N_3OClBr$: C, 55.52; H, 2.66; N, 6.94. Found: C, 55.65; H, 2.78; N, 7.04.

6-Bromo-*N*-(5-bromo-2-(3-fluorophenyl)benzofuran-7-yl)-2-(4-chlorophenyl)quinazolin-4-amine (215g); R = 3-F, X=Cl

A mixture of **210b** (0.20 g, 0.65 mmol), **214b** (0.23 g, 0.65 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) and was treated as for the preparation of **215a** to afford **215g** as a solid (0.26 g, 81%) mp. > 300 °C; ν_{max} (ATR) 687, 777, 850, 1108, 1217, 1366, 1464, 1519, 1520, 1627, 3102, 3170 cm^{-1}; δ_H (DMSO-d_6) 7.15 (1H, t, J = 8.0 Hz, Ar), 7.37 (2H, d, J = 8.0 Hz, Ar), 7.42 (1H, s, =C-H), 7.66 (1H, d, J = 8.5 Hz, Ar), 7.57–7.60 (2H, m, Ar), 7.65 (1H, d, J = 8.5 Hz, Ar), 7.83 (1H, d, J = 8.5 Hz, Ar), 7.97 (1H, dd, J = 1.5 and 9.0 Hz, Ar), 8.10 (2H, d, J = 8.5 Hz, Ar), 8.15 (1H, d, J = 8.5 Hz, Ar), 9.03 (1H, d, J = 1.5 Hz, Ar), 11.00 (1H, s, NH); δ_C (DMSO-d_6) 103.5, 112.0 (d, $^2J_{CF}$ = 23.8 Hz), 115.4, 116.4 (d, $^2J_{CF}$ = 20.9 Hz), 119.6, (d, $^4J_{CF}$ = 2.8 Hz), 121.4, 123.0, 123.8, 124.5, 126.6, 128.5, 129.1, 130.0, 130.2 (d, $^3J_{CF}$ = 8.5 Hz), 130.5 (d, $^4J_{CF}$ = 2.9 Hz), 131.7 (d, $^3J_{CF}$ = 8.6 Hz), 132.3, 136.5, 137.0, 137.9, 147.1, 149.0, 152.5, 155.5, 158.8, 162.7 (d, $^1J_{CF}$ = 241.7 Hz); HRMS (ES): found 621.9329. $C_{28}H_{16}N_3OF^{35}Cl^{79}Br_2^+$ requires 621.9333. *Anal* calcd for $C_{28}H_{15}N_3OFClBr$: C, 53.92; H, 2.42; N, 6.74. Found: C, 53.99; H, 2.35; N, 6.87.

6-Bromo-*N*-(5-bromo-2-(4-fluorophenyl)benzofuran-7-yl)-2-(4 -chlorophenyl)quinazolin-4-amine (215h); R = 4-F, X=Cl

A mixture of **210c** (0.12 g, 0.39 mmol), **214b** (0.14 g, 0.39 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) and was treated as for the preparation of **215a** to afford **215h** as a solid (0.15 g, 78%) mp. > 300 °C; ν_{max} (ATR) 736, 874, 1061, 1168, 1288, 1398, 1475, 1572, 1629, 3101, 3170 cm^{-1}; δ_H (DMSO-d_6) 7.29 (2H, t, J = 8.5 Hz, Ar), 7.34 (2H, d, J = 8.5 Hz, Ar), 7.47 (1H, s, =C-H), 7.78–7.79 (4H, m, Ar), 7.85 (1H, d, J = 8.5 Hz, Ar), 8.04 (1H, d, J = 8.0 Hz, Ar),

8.11 (2H, d, *J* = 8.5 Hz, Ar), 8.91 (1H, d, *J* = 1.5 Hz, Ar), 10.89 (1H, s, NH); δ_C (DMSO-d_6) 102.0, 115.4, 116.5 (d, $^2J_{CF}$ = 21.8 Hz), 119.5, 120.8, 122.9, 123.3, 124.8, 126.1, 126.3, 127.6, 127.7 (d, $^3J_{CF}$ = 8.5 Hz), 128.8, 129.8, 130.8, 132.5, 135.8, 137.0 (d, $^4J_{CF}$ = 2.9 Hz), 147.1, 149.9, 155.9, 157.5, 158.7, 162.9 (d, $^1J_{CF}$ = 245.6 Hz); HRMS (ES): found 621.9333. $C_{28}H_{15}N_3OF^{35}Cl^{79}Br_2^+$ requires 621.9333. *Anal* calcd for $C_{28}H_{14}N_3OFClBr$: C, 53.92; H, 2.42; N, 6.74. Found: C, 53.88; H, 2.58; N, 6.91.

6-Bromo-*N*-(5-bromo-2-(3-chlorophenyl)benzofuran-7-yl)-2-(4-chlorophenyl)quinazolin-4-amine (215i); R = 3-Cl, X=Cl

A mixture of **210d** (0.24 g, 0.68 mmol), **214b** (0.22 g, 0.68 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) and was treated as for the preparation of **215a** to afford **215i** as a solid (0.29 g, 67%) mp. 282–285 °C; ν_{max} (ATR) 683, 736, 829, 940, 1012, 1159, 1372, 1501, 1530, 1516, 3048, 3170 cm^{-1}; δ_H (DMSO-d_6) 7.35 (1H, d, *J* = 8.5 Hz, Ar), 7.38 (1H, d, *J* = 7.0 Hz, Ar), 7.60 (2H, d, *J* = 8.5 Hz, 2H), 7.67 (2H, d, *J* = 8.5 Hz, Ar), 7.81 (1H, s, C-H), 7.85 (1H, d, *J* = 8.5 Hz), 7.96 (1H, dd, *J* = 2.5 and 8.5 Hz, Ar), 8.05 (1H, dd, *J* = 1.5 and 8.5 Hz, Ar), 8.13 (1H, d, *J* = 8.0 Hz, Ar), 8.17 (1H, d, *J* = 8.5 Hz, Ar), 8.20 (1H, d, *J* = 2.5 Hz, Ar), 8.93 (1H, d, *J* = 1.5 Hz, Ar), 10.51 (1H, s, NH); δ_C (DMSO-d_6) 103.6, 115.6, 119.5, 121.0, 123.0, 124.8, 126.4, 128.4, 129.2, 129.4, 129.8, 130.2, 130.5, 131.3, 131.4, 131.7, 132.2, 134.2, 135.9, 136.9, 137.9, 147.0, 152.4, 155.2, 157.5, 158.6; HRMS: found 637.9041. $C_{28}H_{16}N_3O^{35}Cl_2^{79}Br_2^+$ requires 637.9037. *Anal* calcd for $C_{28}H_{15}N_3OCl_2Br$: C, 52.53; H, 2.36; N, 6.56. Found: C, 52.68; H, 2.50; N, 6.45.

6-Bromo-*N*-(5-bromo-2-(4-(trifluoromethoxy)phenyl)benzofuran-7-yl)-2-(4-chlorophenyl) quinazoline-4-amine (215j); R = 4-OCF_3, X=Cl

A mixture of **210e** (0.19 g, 0.56 mmol), **214b** (0.20 g, 0.56 mmol) and HCl (0.001 g, 0.03 mmol) in isopropanol (10 mL) and was treated as for the preparation of **215a** to afford **215j** as a solid (0.17 g, 82%) mp. > 300 °C; ν_{max} (ATR) 682, 781, 858, 938, 1091, 1199, 1259, 1372, 1455, 1553, 1615, 3082, 3170 cm^{-1}; δ_H (DMSO-d_6) 7.33 (1H, d, *J* = 8.0 Hz, Ar), 7.36 (1H, d, *J* = 8.0 Hz, Ar), 7.59 (1H, s, =C-H), 7.61 (1H, d, *J* = 8.5 Hz, Ar), 7.67 (1H, d, *J* = 8.0 Hz, Ar), 7.81 (1H, d, *J* = 9.0 Hz, Ar), 7.85 (2H, d, *J* = 8.5 Hz, Ar), 7.96 (1H, d, *J* = 9.0 Hz, Ar), 8.04 (1H, d, *J* = 9.0 Hz, Ar), 8.11 (1H, d, *J* = 8.5 Hz, Ar), 8.17 (1H, d, *J* = 8.5 Hz, Ar), 8.20 (1H, d, *J* = 1.5 Hz, Ar), 8.91 (1H, d, *J* = 1.5 Hz, Ar), 10.48 (1H, s, NH); δ_C (DMSO-d_6) 103.6, 115.3, 119.6, 121.9, 123.0, 124.8, 126.3, 127.2, 128.4, 128.7, 129.2, 129.8, 130.7, 131.7, 132.3, 135.8, 136.9 (t, J_{CF} = 25.6 Hz), 137.9, 147.2, 149.0, 149.8, 152.4, 155.4, 157.5, 158.6; HRMS (ES): found 687.9236. $C_{29}H_{16}N_3O_2F_3{}^{35}Cl^{79}Br_2{}^+$ requires 687.9250. *Anal* calcd for $C_{28}H_{15}N_3O_2F_3ClBr$: C, 50.50; H, 2.19; N, 6.09. Found: C, 50.29; H, 2.32; N, 6.02.

4.13 Crystal Structure Solution and Refinement

The intensity data for the eight co-crystals were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo-K_α radiation (50 kV, 30 mA) at 173K. The collection method involved ω-scans having a width of 0.5°. Data reduction was carried out using *SAINT+* version 6.02.6 software and SADABS was used to make empirical absorption corrections.[174] The crystal structures were solved through direct methods using *SHELXS-97*.[187] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXL-97*.[187] C-bound H atoms were first

located in the difference electron density map, then positioned geometrically and allowed to ride on their respective parent atoms, with thermal displacement parameters 1.2 times that of the parent C atom. Where possible, the coordinates and isotropic displacement parameters of the N-bound and O-bound H atoms involved in hydrogen bonding interactions were allowed to refine freely, except for crystals **215i** due to poor refinement stability. The diffraction data and refinement statistics of co-crystal **215i** were poor even after numerous attempts at recrystallization. Diagrams and publication material were generated using *WinGX*,[188] *ORTEP-3*,[189] *PLATON*[190] and *DIAMOND.*[191]

4.14 Computational methods

The density functional theory (DFT) computations were carried out using the B3LYP exchange correlation functional,[192] together with the 6-311++G(d,p) [16,17] basis set for all atoms. All computations were performed using the Gaussian 09 software suite.[193] The geometrical optimizations were performed in the gas phase without solvent corrections because it was reported that gas phase calculations frequently correspond quite well with crystal structures [194].

4.15 In Vitro Cytotoxicity Assay

4.15.1 Cell culturing and evaluation of cytotoxicity of the benzofuran-chalcones 203a–y

The human breast (MCF-7) cancer cell line was maintained in culture flasks containing Dulbecco's Modified Eagles Medium (DMEM). The media was supplemented with 1% antibiotics (100 µg/mL penicillin, 100 µg/mL streptomycin and 250 µg/L fungizone) and 10% heat-inactivated fetal bovine serum. The cells were grown at 37 °C in a humidified incubator set

at 5% CO_2. The cells were sub-cultured every two-to-three days after the cells had formed a confluent monolayer. Cytotoxicity was measured by the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) method using the Cell Proliferation Kit I (Sigma-Aldrich, Missouri, USA) according to the method developed by Mosmann et al.[155] The cells were seeded (100 µL) in a 96-well microtiter plates at a concentration of 1x105 cells/mL and incubated for 24 h at 37 °C and 5% CO_2 to allow the cells to attach to the bottom of the wells. The compounds were assessed at 0–100 µM. The control wells included vehicle treated cells exposed to 2% DMSO and the positive control, actinomycin D, with concentrations ranging between 5, 10, 25, and 50, and 100 µM. The microtitre plates were incubated for 48 h. After the 48 h incubation period the MTT reagent (10 µL) was added to a final concentration of 0.5 mg/mL and the plate was further incubated for another 4 h. After 4 h, 100 µL of the solubilisation solution was added to each well and the plate was allowed to stand overnight. Subsequently, the absorbance of the color complex was read at 550 nm with a reference wavelength set at 650 nm using a BIO-TEK Power-Wave XS multi-well plate reader (BioTech Instruments, Midrand, South Africa). The IC_{50} values of the compounds were calculated using OriginPro software (OriginLab Corporation, Northampton, MA, USA).

4.15.2 Determination of apoptotic cell death by annexin V-Cy3 SYTOX staining assay

The percentage population of apoptotic cells were determined using Annexin V–Cy3 SYTOX apoptosis detection kit (Abcam, Milton, Cambridge, UK) according to the manufacturer's instructions. The MCF-7 cells were seeded into six well plates in concentration of 1.5 × 106 cells per well and treated with compound **203b** or **203i** at a concentration of 1 µM against actinomycin D (1 µM) as a reference standard, respectively. The cells were incubated for 48 h and then stained

with Annexin V–Cy3 SYTOX green dye. The cells were analyzed using BD Biosciences FACSAria III flow cytometer (BD Biosciences, San Jose, CA, USA).

4.15.3 Caspase-3 activation of compound 203b and 203i

Caspase-3 activity was detected by means of Caspase-3 Colorimetric Assay Kit (Abcam, Cambridge, MA, USA). The cells were cultured in 24 well plates and treated for 24 h with **203b** or **203i** at a concentration of 1 µM against actinomycin D (1 µM) as a reference standard, respectively. The cells were then washed with PBS buffer and lysed on ice. The experiments were carried out according to the manufacturer's instructions. Optical density was measured at absorbance of 450 nm using the BioTek microplate reader. The concentration of active Caspase-3 (Asp 175) were measured in duplicates and interpolated from the active caspase-3 (Asp 175) standard curve and corrected for sample dilution.

4.15.4 Tubulin polymerization assay of compounds 203a–y

Tubulin polymerization assays were carried out using the tubulin polymerization assay kit (Cytoskeleton, Inc., Denver, Co, USA) following the instruction by the manufacturer. 50 µL of 1.3 mg/mL tubulin (>99% pure) proteins in G-PEM buffer (80 mmol/L PIPES, pH 6.9, 2 mmol/L $MgCl_2$, 0.5 mmol/L EGTA, 1 mmol/L GTP, and 15% glycerol) were placed in a quartz cuvette in the presence of the test agent. Polymerization was measured at 37 °C at every three seconds for 1 h using an Applied Photophysics Chirascan spectroflourimeter (Applied Photophysics Ltd., Surrey, UK), excitation at 360 nm, and emission at 450 nm.

4.15.5 EGFR-TK phosphorylation inhibition assays of compounds 203e, 203i, 203o, 203p, and 203v

The inhibitory activities of compounds **203e**, **203i**, **203o**, **203p**, and **203v** against actinomycin D and gefitinib towards EGFR-TK were tested using enzyme-linked immunosorbent assay (ELISA) technique with purified Epidermal Growth Factor Receptor (Sigma-Aldrich, Bradford, UK). The procedure was carried out according to the manufacturer's protocol. Ninety-six-well plates were pre-coated with 100 µL of a 4:1 poly(Glu,Tyr) solution (5 mg/mL) at 37 ºC overnight. The enzyme reaction was conducted in freshly prepared kinase reaction buffer (25 mmol/L HEPES, pH 7.4, 5 mmol/L $MgCl_2$, 2 mmol/L $MnCl_2$, 100 µmol/L Na_3VO_4 and 1 mmol/L dithiothreitol). Ten microlitres of the test samples at five different concentrations (0.02–0.4 µM) and 20 µL of dilute solution of purified recombinant EGFR tyrosine kinase proteins were added to each reaction well. The kinase reaction was initiated by the addition of 50 µL of a solution of adenosine-50-triphosphate, disodium salt (5 mmol/L). DMSO and EGFR (without any test sample) were also included in this experiment as negative and positive controls, respectively. The plates were then incubated at 37 ºC for 1 h and washed three times with phosphate-buffered saline (PBS). Phosphorylated proteins were probed with monoclonal anti-phosphotyrosine antibody produced in mouse (Sigma-Aldrich, St. Louis, MO, USA). After another 1 h incubation at 37 ºC, the plates were again washed three times with PBS, followed by the addition 100 µL of freshly prepared peroxidase substrate solution. After incubation in the dark for extra 10 min, the reaction was terminated by adding 100 µL of 2 M H_2SO_4 solution. The plates were analysed using the Thermo Varioskan Flash Spectral Scanning Multimode Reader (Thermo Fisher Scientific, Waltham, MA, USA) at 492 nm. The assay was performed in triplicate. The EGFR-TK inhibition percentage was determined as follows:

$$\%\,\text{Inhibition} = \frac{(OD_{samples} - OD_{positive})}{(OD_{negative} - OD_{positive})} \text{ x } 100$$

OD: Optical Density

The half-maximal inhibitory concentration value (IC_{50}) were calculated using OriginPro software (OriginLab Corporation, Northampton, MA, USA).

4.16 Cell culturing and evaluation of cytotoxicity for compounds 215a–j against panel of cancer cell lines

The cytotoxic activities of the compounds were screened against the C3A/HepG2 human liver cells, human colorectal tumor (Caco-2) cells, the human lung carcinoma (A549) and the cervical cancer (HeLa) cells. The lethal concentration was determined using the 3-(4,5-dimethylthiazol)-2,5-diphenyl tetrazolium bromide (MTT) assay previously developed by Mosmann.[155] The cells were maintained in Dubelsco minimal essential medium (DMEM, Highveld Biological, South Africa) supplemented with 10% foetal calf serum (Adcock-Ingram, Midrand, South Africa) and sodium pyruvate for C3A liver cells. Cell suspensions were prepared from confluent monolayer cultures and plated at a density of 0.1×10^6 cells into each well of 96-well microtitre plates. For cell attachment, plates were incubated for 24 h at 37 ºC in a 5% CO_2 incubator prior to the exposure. The compounds were dissolved in DMSO (5 mg/mL) and appropriate dilutions were prepared, added to the wells and incubated for 48 h. Doxorubicin hydrochloride (Pfizer Laboratories, Sandton, South Africa) was used as a positive control while DMSO was the negative control. After incubation for 48 h, the wells were rinsed with 150 µL of phosphate buffered saline PBS (Sigma-Aldrich, GmBH, Schnelldorf, Germany) and 200 µL of fresh medium was dispensed into the wells. MTT was dissolved in PBS (30 µL) then added to each well and the contents were incubated for 4 h at 37 ºC. The medium was removed and MTT

formazan crystals were dissolved in 50 µL DMSO. The amount of MTT reduction was measured immediately by detecting the absorbance using a BioTek microplate reader (BioTek Synergy, Analytical and Diagnostic Products, Johannesburg, South Africa) at a wavelength of 570 nm. Each dilution of the test sample was assayed in quadruplicate and the experiments were repeated three times. The percentage of cell viability was calculated using the formula below:

$$\%\text{Cell viability} = \frac{\text{Mean Absorbance of sample} \times 100}{\text{Mean Absorbance of control}}$$

The LC_{50} values (lethal concentration at which 50% of the cells are killed) were calculated as the concentration of the test sample that resulted in 50% reduction of absorbance compared to untreated cells. The intensity of the MTT formazan produced by living metabolically active cells is directly proportional to the number of live cells present.

4.16.1 Annexin V-FITC staining assay on 215d and 215j against C3A and Caco-2, respectively

Apoptotic cells were quantified using flow cytometry. The C3A or Caco-2 cells were cultured in 24 well plates and each was then treated with compound **215d** or **215j** at concentrations 5, 12.5 and 25 µM against doxorubicin hydrochloride (0.20 µM) as a reference standard, respectively. After the cells were incubated for 24 h, both treated and untreated cells were harvested, washed two times with ice PBS and then adjusted at a density of 1 x 10^6 cells/sample. Cells were harvested and transferred into plastic flow tubes (BD Biosciences, South Africa). The cells were, in turn, stained with Annexin-V-FUOS staining kit (Roche, Mannheim, Germany) according to the manufacturer's instructions. The cells were analysed using Becton, Dickinson and Company FACS Accuri flow cytometer.

4.16.2 Caspase-3 analysis on 215d and 215j against C3A and Caco-2, respectively

Caspase-3 activity was detected by means of Caspace-3 Colorimetric Assay Kit (Abcam, Cambridge, MA, USA). The cells were cultured in 24 well plates and treated for 24 h. The cells were then washed with PBS buffer and lysed on ice. The experiments were carried out according to the manufacturer's instructions. Optical density was measured at absorbance of 450 nm using the BioTek microplate reader. The concentration of active Caspase-3 (Asp 175) were measured in duplicates and interpolated from the active caspase-3 (Asp 175) standard curve and corrected for sample dilution.

4.16.3 Inhibition for EGFR-TK

The inhibitory activities of compound **215a**–**j** and Gefitinib towards EGFR-TK were tested using enzyme-linked immunosorbent assay (ELISA) technique with purified epidermal growth factor receptor (Sigma-Aldrich, Bradford, UK). The procedure was carried out according to the manufacturer's protocol. Ninety-six-well plates were pre-coated with 100 µL of a 4:1 poly(Glu,Tyr) solution (5 mg/mL) at 37 ºC overnight. The enzyme reaction was conducted in freshly prepared kinase reaction buffer (25 mmol/L HEPES, pH 7.4, 5 mmol/L $MgCl_2$, 2 mmol/L $MnCl_2$, 100 µmol/L Na_3VO_4 and 1 mmol/L dithiothreitol). Ten microlitres of the test samples at five different concentrations (0.02–0.4 µM) and 20 µL of dilute solution of purified recombinant EGFR tyrosine kinase proteins were added to each reaction well. The kinase reaction was initiated by the addition of 50 µL of a solution of adenosine-50-triphosphate, disodium salt (5 mmol/L). DMSO and EGFR (without any test sample) were also included in this experiment as negative and positive controls, respectively. The plates were then incubated at 37 ºC for 1 h and washed three times with phosphate-buffered saline (PBS). Phosphorylated proteins were probed

with monoclonal anti-phosphotyrosine antibody produced in mouse (Sigma-Aldrich, St. Louis, MO, USA). After another 1 h incubation at 37 ºC, the plates were again washed three times with PBS, followed by the addition 100 µL of freshly prepared peroxidase substrate solution. After incubation in the dark for extra 10 min, the reaction was terminated by adding 100 µL of 2 M H_2SO_4 solution. The plates were analysed using the Thermo Varioskan Flash Spectral Scanning Multimode Reader (Thermo Fisher Scientific, Waltham, MA, USA) at 492 nm. The assay was performed in triplicate. The EGFR-TK inhibition percentage was determined as follows:

$$\%\,\text{Inhibition} = \frac{(OD_{samples} - OD_{positive})}{(OD_{negative} - OD_{positive})} \text{ x } 100$$

OD: Optical Density

The half-maximal inhibitory concentration value (IC_{50}) was obtained from the curves of percentage inhibition.

4.17 Molecular Docking against Tubulin and EGFR

Molecular docking of compounds **203i** and **203o** to the 3D structure of a tubulin heterodimer (PDB ID: 1SAO)[196] and EGFR (PDB ID: 1M17)[197] as carried out using the CDOCKER protocol[198] in Discovery Studio 2017 (Biovia, San Diego, CA, USA). Prior to performing the docking, compounds were drawn using Discovery Studio and prepared using the 'Prepare Ligand' protocol. The protein structures were downloaded from the Protein Data Bank, prepared using the 'Prepare Protein' protocol in Discovery Studio, which included removing any existing ligands bound, leaving the water molecules unaltered in the model. The binding sites were defined from receptor cavities and docking was performed using default settings and the best conformation of the ligand were selected and evaluated.

The structure of epidermal growth factor receptor (EGFR) kinase domain was obtained from RCSB PDB (id: 1M17)[199] where all heteroatoms and water molecules were first removed. Polar hydrogen atoms, Kollman-Amber united atom partial charges and solvation parameters were then added by utilizing AutoDockTools.[200] The coordinates for erlotinib (control) docking were retrieved from the ligand co-crystallised with EGRF (PDB id: 1M17) while the coordinates for compounds **215a**–**j** were generated using ChemDraw Professional 15.0 (PerkinElmer Informatics, Waltham, MA, USA). Minimization of compounds **215** was then performed with Chem3D module in ChemOffice Professional 15.0 (PerkinElmer Informatics). Ligands were in united atom format where only polar hydrogen atoms remained. Gasteiger charges and torsional angles of all ligands were assigned by AutoDockTools. Hydrated docking was performed with standard protocol from AutoDock4.2 where random water atoms were added around the ligand. A total of 200 runs were performed by AutoDock4.2.6[200] with semi-empirical free energy scoring function, Lamarckian genetic algorithm of 1,000,000 energy evaluations each run and the maximum number of 27,000 generations. The number of individuals in population was set as 350 and the rate of crossover was 0.8. All docked conformations were clustered with root mean square of 2.0 Å.

Chapter 5: References

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