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# The synthesis of 2- and 3-substituted indoles

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# The Synthesis of 2- and 3-Substituted Indoles

**Tlabo Caiphus Leboho**

*A dissertation submitted to the Faculty of Science,*

*University of the Witwatersrand,*

*Johannesburg,*

*in fulfilment of the requirement for the*

*degree of Master of Science*.

January 2008

# Declaration

I declare that the work presented in this dissertation was carried out exclusively by myself under the supervision of Professors C. B. de Koning and J. P. Michael. It is being submitted for the degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

Tlabo Caiphus Leboho

January 2008

# Abstract

One of the main groups of organic compounds containing nitrogen in both cyclic systems and straight chains is the alkaloids. Indole is perhaps the single most common heterocycle in all of chemistry and it is embodied in a myriad of natural products, pharmaceutical agents and a growing list of polymers. This dissertation presents method for the synthesis of substituted indoles bearing aryl substituents onto the 2- and 3- position as well as 2,3-fused indoles. The route for the synthesis of the aryl substituted indoles starts from the indole nucleus which was protected using the phenylsulfonyl group because it was found that the group is easy to remove and does not require harsh conditions. After successful protection of the indole nucleus NH as *N*-phenylsulfonyl, bromine was introduced at the 3-position of the indole nucleus while iodine was introduced at the 2-position of the indole nucleus. The bromination of the indole nucleus was not easily achieved because the reaction of molecular bromine with indole resulted in the formation of 2,3-dibromoindole while activated 5-methoxyindole gave an insoluble 2,3,4-tribromoindole. However, this problem was solved by refluxing indole with molecular bromine in the presence of sodium methoxide while activated 5-methoxyindole was refluxed with *N*-bromosuccinimide in the presence of catalytic benzoyl peroxide. 2-Iodoindoles were synthesized using directed *ortho* metallation, where isopropyl magnesium chloride was used in the presence of catalytic amount of diisopropylamine. Using standard aqueous Suzuki-Miyaura cross-coupling in the presence of sodium carbonate as a base, 2-aryl, 3-aryl as well as 2,3-diaryl substituted indoles were synthesized in good to excellent yields. The synthesis of 2,3-fused indoles was achieved in poor yields starting from 1-(phenylsulfonyl)indole which was alkylated using allyl bromide at the 2-position and formylated at the 3-position of the indole nucleus to the cyclization of the alcohols using mercury acetate.

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# List of Abbreviations

| | |
|---|---|
| AcOH | acetic acid |
| Ar | aromatic |
| $Bi(OTf)_3$ | bismuth(III) triflate |
| $Boc_2O$ | di-*tert*-butyl dicarbonate (Boc anhydride) |
| BuLi | *n*-butyllithium |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| DNA | deoxyribonucleic acid |
| DOM | directed *ortho* metallation |
| $E^+$ | electrophile |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| $GI_{50}$ | growth inhibition |
| h | hour |
| h*v* | light |
| $IC_{50}$ | inhibition concentration |
| $KO^tBu$ | potassium *tert*-butoxide |
| $LD_{50}$ | lethal dose |
| LDA | lithium diisopropylamine |
| M | molar |
| Me | methyl |
| MeOH | methanol |

| | |
|---|---|
| $Me_3SnCl$ | trimethyltin chloride |
| min | minutes |
| NaOMe | sodium methoxide |
| NMR | nuclear magnetic resonance |
| OMe | methoxy |
| OTf | trifluoromethanesulfonate (triflate) |
| Ph | phenyl |
| $PhSO_2Cl$ | phenylsulfonyl chloride |
| psi | pounds per square inch |
| rt | room temperature |
| TBAB | tetrabutylammonium bromide |
| TBAF | tetrabutylammonium fluoride |
| THF | tetrahydrofuran |
| TsCl | *p*-toluenesulfonyl chloride (tosyl chloride) |

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# Chapter 1: Introduction

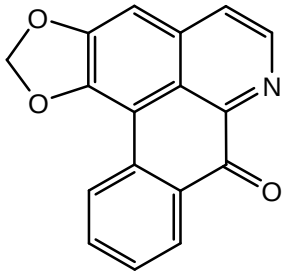
## 1.1 Alkaloids

One of the main groups of organic compounds containing nitrogen in both cyclic systems and straight chains is the alkaloids. Alkaloids are nitrogenous bases which occur naturally in plants and other living organisms. They nearly always contain their nitrogen as part of a heterocyclic system with few exceptions and are often complex in structure; however there is no very sharp distinction between alkaloids and many other naturally occurring nitrogenous compounds. In addition, the alkaloids usually show specific pharmacological activity[1]. As in the case of other classes of natural products, no uniform system of nomenclature has so far been devised for alkaloids. The name of the alkaloid in most cases is derived from the plant or organism name, usually the systematic name.

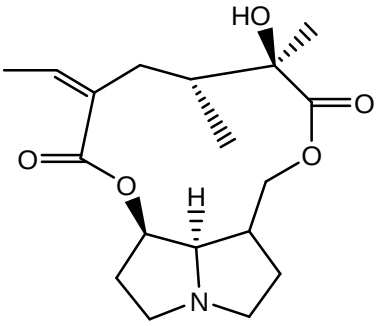
Alkaloids, with few exceptions, are weak bases that usually occur in plants as salts of the inorganic or organic acids. The crude alkaloid salt is often separated from the powdered plant material by extraction with water, dilute acid or alcohol. Some material may be neutralized with alkali and the organic bases extracted with organic solvent. The crude mixture is often purified by fractional distillation of sparingly soluble salts such as hydrohalide, sulfate, oxalate, perchlorate, nitrate and others[2]. In “working up” the plant material for the isolation of alkaloids, various extraction and concentration steps have to be carried out during which solvents, acids, and bases are brought into contact with the crude plant material[3].

It is believed that plants, animals and microorganisms produce alkaloids for specific purposes. Many alkaloids show biological activity. For example, some alkaloids show antifungal activity such as aporphine alkaloid, liriodenine (**1**), which displays a broad activity spectrum against fungi such as the yeast *Candila albicans, Trichophyton mentagrophytes,* and has high activity against phytopathogenic fungi, this provides a plausible reason for the synthesis of the compound

in terms of the plant's survival strategy. (–)-Senecionine (**2**) (**Figure 1**), a pyrrolizidine alkaloid can be regarded as a feeding deterrent where it is taken in by herbivores from plants and safely stored in the body as *N*-oxides which are nontoxic and rapidly transformed into toxic form when required[4].



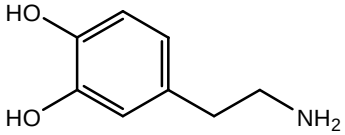

**1** Liriodenine



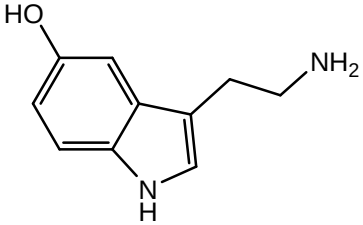

**2** (–)-Senecionine

**Figure 1**

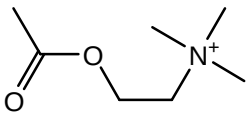
Some alkaloids have remarkable structural similarities to neurotransmitters in the central nervous system of humans. Examples include dopamine (**3**), serotonin (**4**) and acetylcholine (**5**) (**Figure 2**). The amazing effect of these alkaloids on humans has led to the development of powerful medications and "spiritual" drugs[5].




**3** dopamine




**4** serotonin

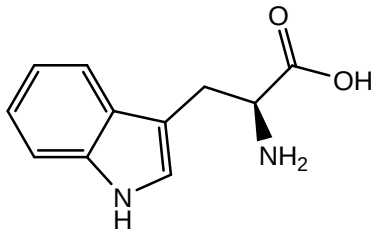



**5** acetylcholine

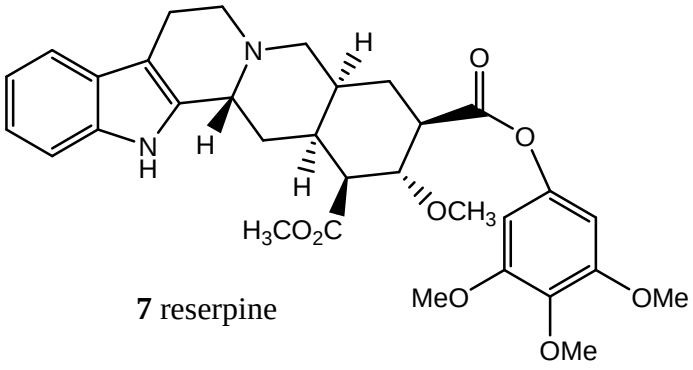
**Figure 2**

Alkaloids also form the basis of many drugs which are useful in treating diseases and pain, while other drugs such as cocaine, heroin and morphine can be harmful if abused but are believed to be helpful medicines[6]. Among the alkaloids in **Figure 2**, only (**4**) is an indole derivative. There are over 1200 naturally occurring indole alkaloids and many of them have biological applications[7].

Some of the known naturally occurring indoles include, as mentioned above, serotonin (**4**) a monoamine neurotransmitter synthesized in serotonergic neurons in the central nervous system and enterochromaffin cells in the gastrointestinal tract[8], tryptophan (**6**) which is an essential amino acid[7], and reserpine (**7**), a more complicated derivative which is used for the treatment of high blood pressure, as well as being a tranquilliser[9] (**Figure 3**).




**6** tryptophan




**7** reserpine

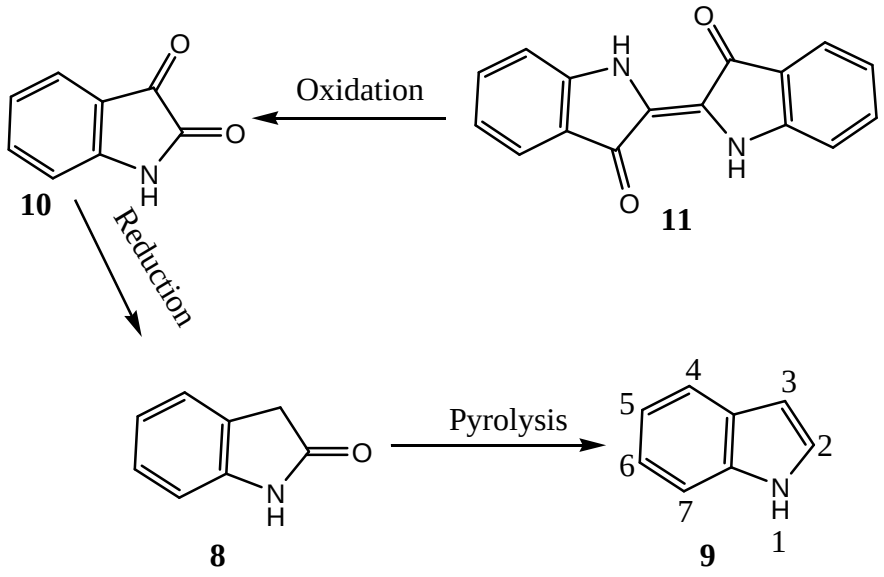
**Figure 3**

Many reviews have been written on indole and its derivatives[10, 11]. Indole is perhaps the single most common heterocyclic system in all of chemistry. It is embodied in a myriad of natural products, pharmaceutical agents and a growing list of polymers. In addition to the hundreds of well-known indole plant alkaloids, the indole ring is present in an array of other structures. The central importance of the indole derivatives in living organisms has inspired chemists to design and synthesize indole-containing compounds[12, 13, 14]. The following sections cover some of these aspects.

## 1.2 Indole: Discovery, Synthesis and Reactivity

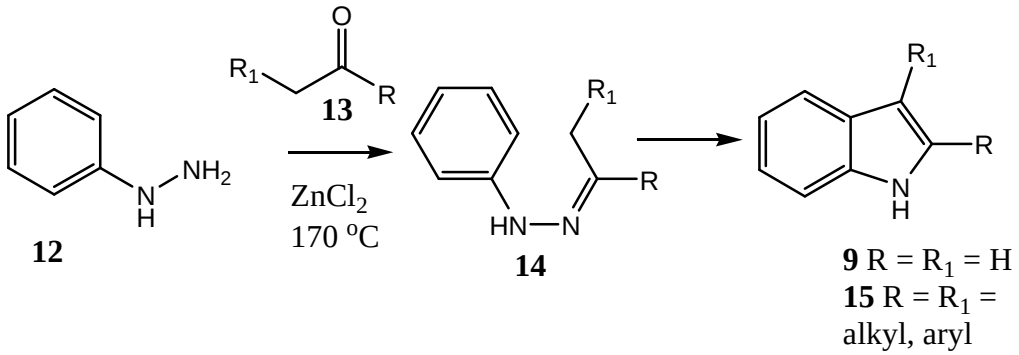
Indole is a benzopyrrole in which the benzene and pyrrole rings are fused through the 2-and 3-positions of the pyrrole nucleus. The indole ring is also found in many natural products such as the indole alkaloids, fungal metabolites and marine natural products[15]. The first preparation of indole dates from 1866 but the Fisher indole synthesis, which remains one of the most versatile methods for preparing indoles, was first reported in 1883[16].

The principal commercial source of indole is extraction from coal tar, although the feasibility of industrial synthesis from starting materials such as aniline, ethylene glycol and others has also been demonstrated[16]. Indole (**9**) itself was first obtained by Adolf Baeyer by pyrolysis of oxindole (**8**) with zinc dust in 1886. Oxindole (**8**) was obtained from the reduction of isatin (**10**) which was obtained from oxidizing the natural insoluble dark blue dye called indigo (**11**) (**Scheme 1**)[17].



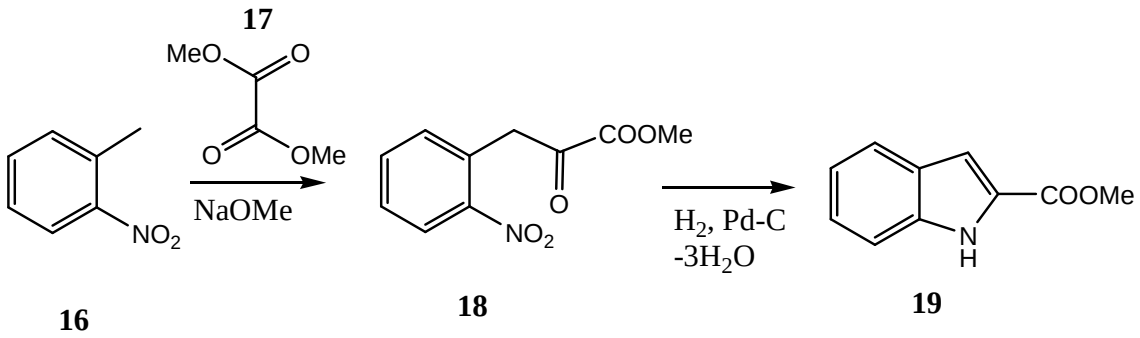

**Scheme 1**

Although the main source of indole is extraction from coal tar, many researchers have reported synthetic methods for the preparation of various substituted indoles from readily available starting materials owing to their importance in natural products synthesis and pharmaceutical chemistry. One of the most widely used methods as mentioned previously is the Fischer indole synthesis. This method involves heating phenylhydrazine (**12**) with aldehyde or ketone (**13**) in acetic acid, forming phenylhydrazone (**14**) which subsequently rearranges with the loss of ammonia to give indole or 2- and 3-substituted indoles (**9** and **15**) as outlined in **Scheme 2**.



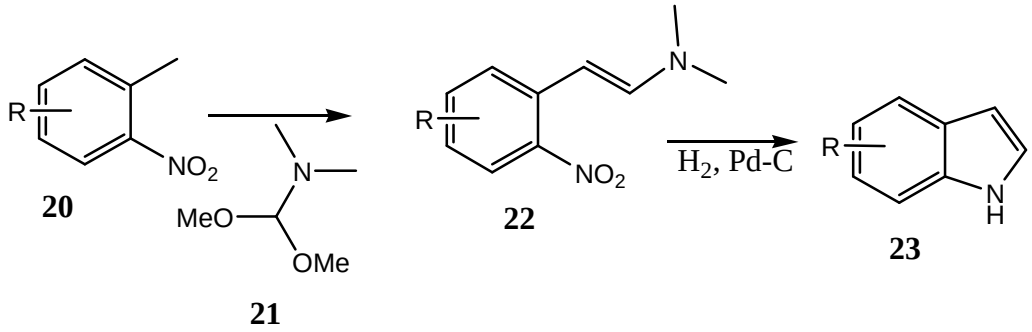

**Scheme 2**

Other methods include the Grandberg synthesis, Reissert synthesis, Leimgruber-Batcho synthesis, Madelung synthesis and Bischler synthesis to name a few. Both the Reissert and Leimgruber-Batcho syntheses depend on the acidity of methyl group *ortho* to an aromatic nitro group while Madelung synthesis proceeds via a Wittig-type reaction[18]. The Reissert synthesis is suitable for the preparation of 2-substituted indoles. For example, when 1-methyl-2-nitrobenzene (**16**) is treated with dimethyl oxalate (**17**) in the presence of sodium methoxide as a base it gave methyl 3-(2-nitrophenyl)-2-oxopropanoate (**18**), which upon catalytic hydrogenation ($H_2$, Pd-C) reduced the nitro group to an amino group followed by a spontaneous cyclodehydration to give indole-2-carboxylic acid methyl ester (**19**) (**Scheme 3**)[19].




**Scheme 3**

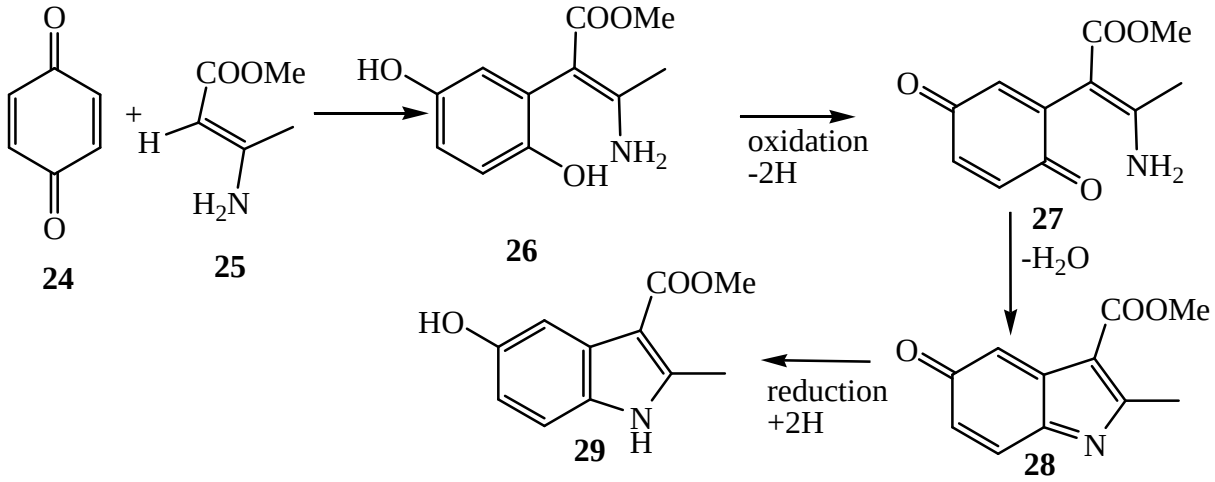
On the other hand, the Leimgruber-Batcho synthesis is particularly suitable for the synthesis of indoles with substituents on the benzene ring but is unsubstituted on the pyrrole moiety. In this method, substituted 1-methyl-2-nitrobenzene (**20**) is treated with *N*,*N*-dimethylformamide dimethyl acetal (**21**) to give substituted 1-dimethylamino-2-(*o*-nitrophenyl)ethene (**22**), which on reductive cyclization yielded substituted indole (**23**) (**Scheme 4**). Madelung synthesis (not illustrated) is essentially confined to the preparation of 2-alkylindoles due to the vigorous reaction conditions, while Bischler synthesis (not illustrated) is particularly suitable for 2-and 3-disubstituted indoles[19].




**Scheme 4**

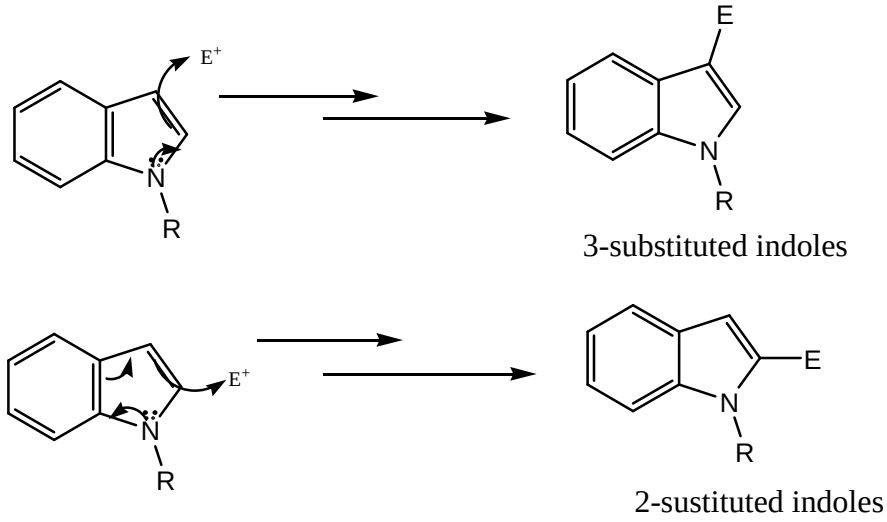
Up until now the methods discussed in the synthesis of indole have nitrogen atom bonded directly to an arene. Only a few indole syntheses make use of building blocks in which the nitrogen atom is not directly bonded an arene. The Nenitzescu synthesis is an example of this

type. In this synthesis, 1,4-quinone (**24**) is condensed with (*E*)-methyl 3-aminobut-2-enoate (**25**) by a Michael addition to give (*E*)-methyl 3-amino-2-(2,5-dihydroxyphenyl)but-2-enoate (**26**). When (**26**) was subjected to oxidation, it gave (*E*)-methyl 3-amino-2-(3,6-dioxocyclohexa-1,4-dienyl)but-2-enoate (**27**) which was followed by a cyclodehydration to give methyl 2-methyl-5-oxo-5*H*-indole-3-carboxylate (**28**) and the reduction of (**28**) furnished 2,3-disubstituted indole, methyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (**29**) (**Scheme 5**)[19]. This method provides a rapid means of preparing functionalized 5-hydroxyindoles from simple, readily accessible starting materials[10,] and the hydroxyl group can also be introduced onto the indole nucleus[20].




**Scheme 5**

Indole undergoes electrophilic substitution mainly on position 3 of the nucleus when the hydrogen on the indole nitrogen atom is substituted or when a strong magnesium base is used. This is because indole nitrogen is the most reactive towards reactions with electrophiles followed by position 3 of the indole nucleus. When both positions 1 and 3 of the indole nucleus are occupied by substituents other than hydrogen, position 2 is the most reactive one and when position 2 is occupied the electrophile occupies a position on the benzene ring[21].




**Reactivity of indole**

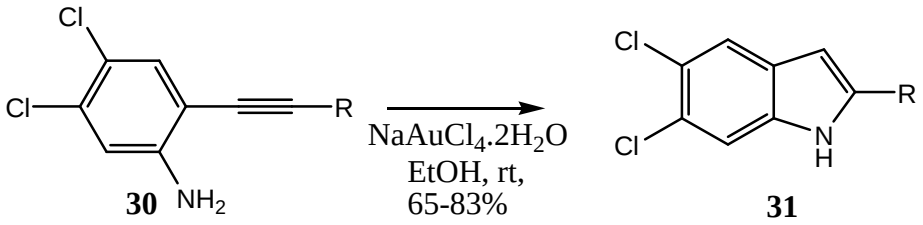
## 1.3 2-Substituted Indoles: Synthesis and Biological Importance

### 1.3.1 Synthesis

The synthesis of indoles is currently the object of wide investigations owing to their central role as useful building blocks in the synthesis of alkaloids and in the design of therapeutic agents and this would include the topic of this section, 2-substituted indoles. Some general methods for preparing 2-substituted indoles were discussed in the preceding section, but several more specific methods are described below.

As the 2-alkynylphenylamine derivatives (**30**) are easily available by established synthetic procedures, the syntheses of 2-substituted indoles with these compounds as starting materials are some of the most useful procedures. Both base-promoted and electrophilic cyclization reactions of (**30**) to furnish 2-substituted indoles have been developed. For example, when (**30**) was treated with gold salts such as sodium chloroaurate ($NaAuCl_4$) as a catalyst, it yielded 2-substituted indoles (**31**) in reasonable yields. This procedure is compatible with a variety of functional

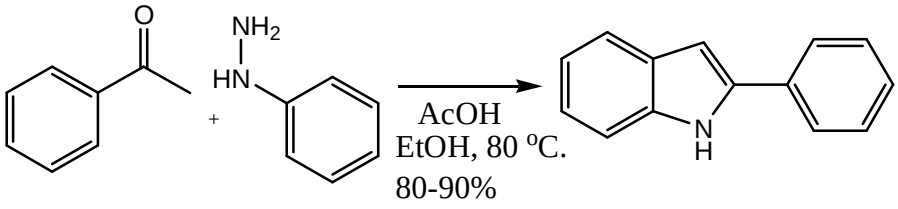
groups on the benzene ring of (**30**) as illustrated in **Scheme 6**, where the R group can be hydrogen, alkyl, aryl or a variety of substituted aryls[22].




**30** **31**

**Scheme 6**

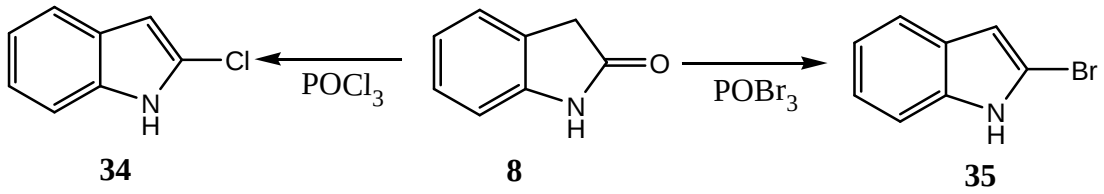
2-Substituted indoles can also be synthesized by the previously discussed methods for indole synthesis. Fischer indole synthesis methodology can be generally employed. For example, treating acetophenone (**32**) with phenylhydrazine (**12**) in the presence of acetic acid in ethanol at 80 °C as illustrated in **Scheme 7** gave 2-phenylindole (**33**) in good yield[23].




**32** **12** **33**

**Scheme 7**

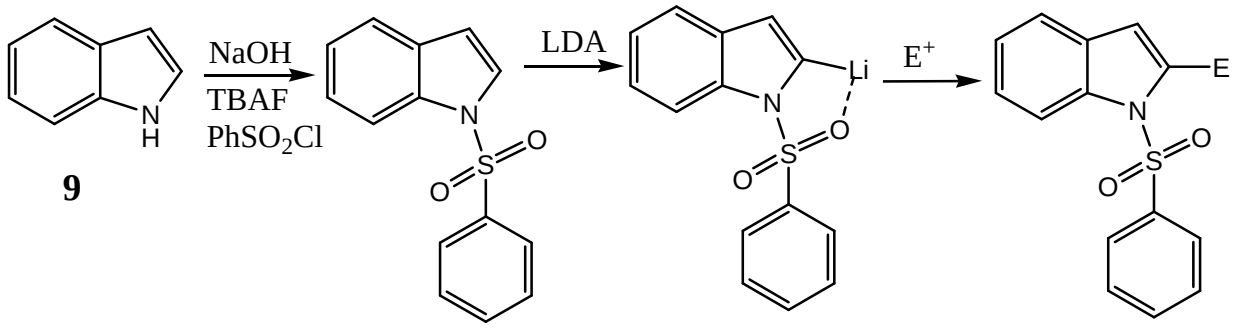
Indole can also be halogenated at the 2-position but this has proved to be a difficult reaction if 3-position is not substituted. Powers reported the synthesis of 2-haloindoles (**34** and **35**) with phosphorus oxyhalides through a Vilsmeyer salt. This was performed using oxindole (**8**) as a source of the indole moiety but these compounds have limited stability as they cannot be stored for long without decomposing[24, 90].




**34** **8** **35**

**Scheme 8**

There is other methodology for introducing substituents at the 2-position of indole. This methodology employs the *ortho*-metallation of *N*-protected indoles. The most commonly used *N*-protecting groups are phenylsufonyl ($PhSO_2$), *p*-toluenesulfonyl (4-$MeC_6H_4SO_2$ or Ts) and *tert*-butoxycarbonyl (Boc). The *N*-protecting groups like these are required to effect metal stabilization at the 2-postion of the indole nucleus by lone pair donating properties of the "protecting" group to allow for what is called directed *ortho* metallation (DOM). For instance, when 1-phenylsulfonylindole (**36**) is treated with a strong base like lithium diisopropylamide (LDA) at low temperatures, it gives a regioselective 2-lithiation product (**37**) which can be quenched with various electrophiles including halogen sources to afford 2-substituted indoles (**38**)[25] (**Scheme 9**).



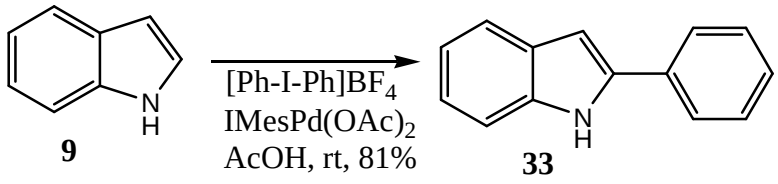

**9** **36** **37** **38**

**Scheme 9**

When the electrophile is a halogen as in (**35**), this can also allow C-C bond formation through the now well-developed catalytic cross-coupling reactions. Most frequently, palladium cross-coupling reactions are used for the formation of C-C bonds. One of the most commonly used methods is the Suzuki-Miyaura cross-coupling reaction which employs palladium(0) under basic conditions, usually with aryl or heteroaryl boronic acids or esters to effect C-C bond formation[26].

Apart from the regioselective lithiation of *N*-protected indoles at the 2-position with strong bases such as LDA, the hydrogen at the 2-position of (**36**) can also be replaced by magnesium metal. Kondo *et al*. devised a methodology of replacing the hydrogen at the 2-position of (**36**) with magnesium using magnesium amide bases. When hydrogen is replaced by magnesium in (**36**), it acts much like lithiated (**37**) but this reaction can be achieved at room temperature while lithiation is achieved at lower temperatures due to the instability of lithiating reagents[27]. This methodology was modified by using Grignard reagents in the presence of a catalytic amount of amines instead of using magnesium amide bases and this showed improved yields[28].

The direct C-arylation of free (NH) indole holds a significant synthetic potential as it eliminates the need for introducing the protecting groups and reactive functionalities prior to C-C formation, thereby enabling direct access to valuable heteroaromatic compounds[29]. 2-Arylindoles in particular are important structures that serve as key components of variety of biologically active molecules. Many traditional approaches to these compounds have involved cross-coupling between 2-functionalized indole and functionalized arene derivative, a strategy that often requires more than one step. Recently, methodology has been developed to affect C-2 arylation of indoles without protecting the NH group or the requirement of the introduction of a halogen or boronic acid. For instance, treating (**9**) with phenyliodonium tetrafluoroborate ($Ph_2I^+BF_4^-$) in the presence of 1,3-bis(2,4,6-trimethylphenyl)imidazo-2-ylidene palladium acetate ($IMesPd(OAc)_2$) as a catalyst afforded (**33**) in good yield at room temperature and this methodology is compatible with a diverse selection of electron-donating and electron-withdrawing substituents on indoles without competing *N*-arylation or other undesirable side reactions[30].



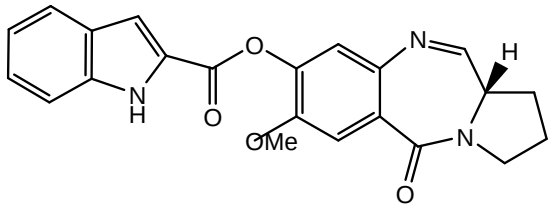

**9** **33**

**Scheme 10**

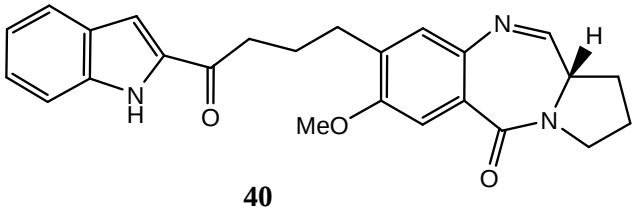
### 1.3.2 Biological importance

2-Substituted indoles can have complex structures and interesting biological activities, but not all compounds having the indole skeleton have biological importance. For example, compound (**39**) and compound (**40**) both possessing a substituents at the 2-position of the indole nucleus were both tested for *in vitro* cytotoxic effects as well as *in vivo* cytotoxic effects. They were used on human melanoma cell line A2058 using an MTS cell proliferation assay. Compound (**39**) showed a mean $GI_{50}$ value of 0.38 µM while compound (**40**) showed a mean $GI_{50}$ value of 0.182 µM, indicating that these compounds have the potential for use as highly potent broad-spectrum anticancer compounds to inhibit the growth of a variety cancer cell lines[31].

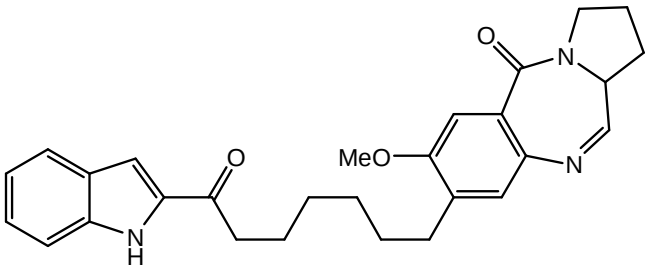
When compounds (**39**) and (**40**) were tested for *in vivo* cytotoxic effects, they both showed intraperitoneal (ip) plus subcutaneous (sc) scores of larger than 20. If ip plus sc scores are larger than 20, the compounds are considered to be active and have potential as an antitumour or anticancer drug candidates. The *in vivo* test results showed that compounds (**39**) and (**40**) had total scores of 22 and 30 respectively. Another example is compound (**41**)**,** again a 2-substituted indole, and this was tested for the inhibition of the cleavage activity of restriction endonuclease *BamHI*. The experimental results showed that compound (**41**) inhibits *BamHI* digestion and this is because it can bind to the DNA more efficiently[31].



**39**



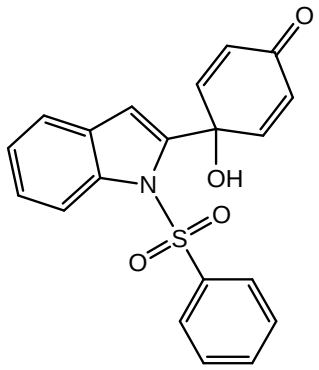
**40**



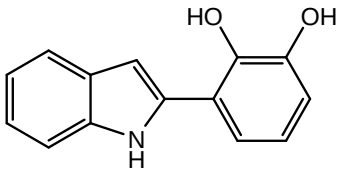
**41**

**Figure 4**

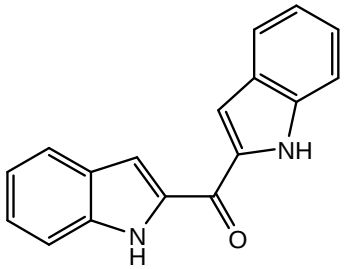
In another example, evaluation of the growth-inhibitory properties of the novel quinol (**42**) shown in **Figure 5** was undertaken in two human colon cancer cell lines (HCT 116 and HT 29). The valuation results show that 4-(1-phenylsulfonyl-1*H*-6-fluoroindol-2-yl)-4-hydroxycyclohexa-2,5-dienone (**42**) was the most potent against the cell lines with the mean $GI_{50}$ value of 16 nM and mean $LC_{50}$ value of 2.2 μM[32]. Finally in this section, compound (**43**) was examined for *in vitro* inhibitory effects towards the lipid peroxidation induced by free radicals in a rat brain homogenate and their scavenging activity towards DPPH (1,1-diphenyl-2-picrylhydrazyl) radicals and it showed antioxidative activity[33] while bis(1*H*-2-indolyl)methanone (**44**) caused a strong inhibition of PDGF receptor activity with $IC_{50}$ value of 1 μM[34].




**42**




**43**




**44**

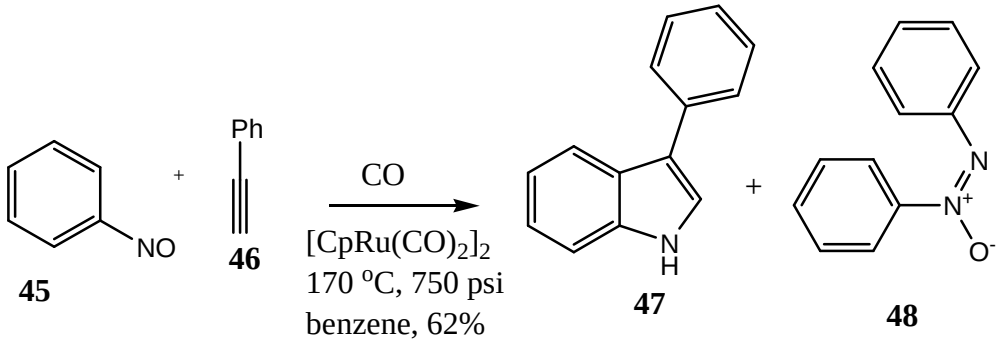
**Figure 5**

## 1.4 3-Substituted Indoles: Synthesis and Their Biological Importance

### 1.4.1 Synthesis

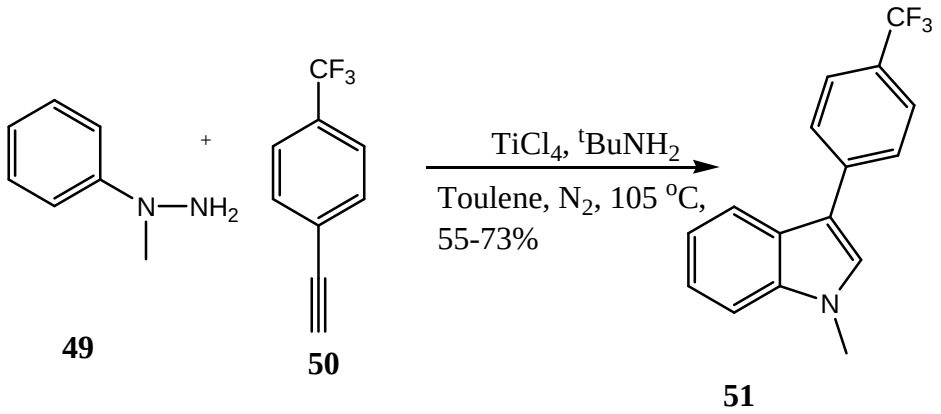
As stated earlier in this dissertation, indole undergoes electrophilic substitution mainly on position 3 when the indole nitrogen is protected. The widespread natural occurrence and importance of indoles has stimulated the continuing development of new methods for their preparation. There are attractive reactions but only few directly produce indoles by annulation of commercially available *N*-aromatic precursors, as in the Fischer-indole synthesis. However, despite recently developed methodologies, the classical Fischer indole synthesis remains one of the most important approaches to 3-substituted indoles. In the traditional Fischer indole synthesis, the required hydrazone is generated via the condensation of the corresponding carbonyl compound with a hydrazine derivative.

The desire for broad substrate scope, more accessible starting materials, improved regioselectivity, milder reaction conditions, and functional group tolerance has also spawned several transition metal-promoted route to indoles, most of which are intramolecular reactions that require a substituted *N*-aromatic precursor. When ntirosobenzene (**45**) and phenylacetylene (**46**) were heated together in the presence of $[CpRu(CO)_2]_2$ as a catalyst with carbon monoxide in benzene, at 170 $^oC$ and 750 psi, it produced regioselectively the 3-substituted indole, 3-phenylindole (**47**), in good yields and some small traces of aniline and azoxybenzene (**48**) but no trace of 2-phenylindole was detected[35].




**Scheme 11**

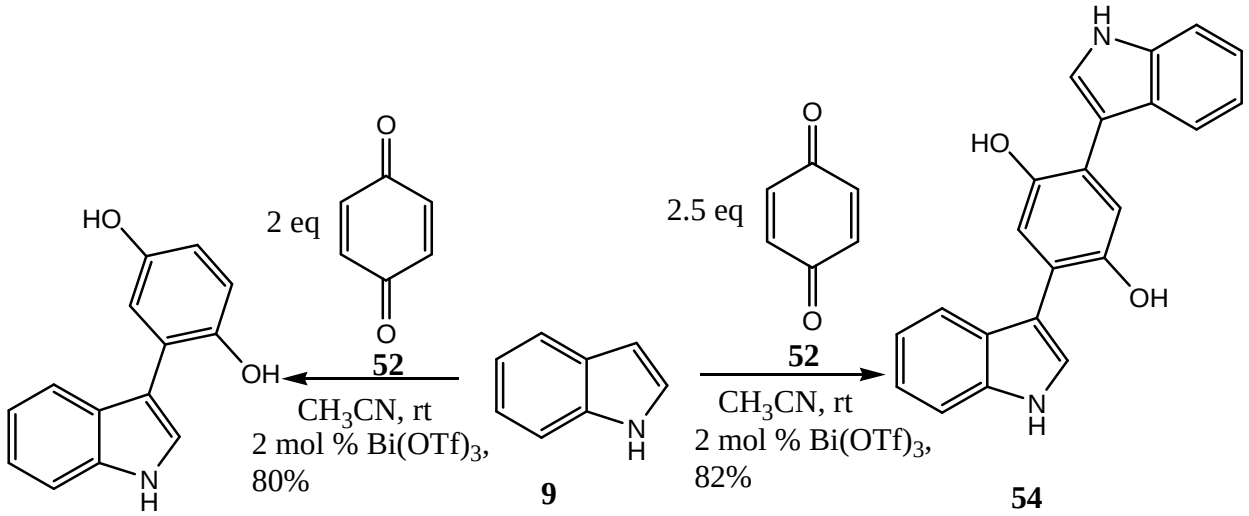
Recently, Odom and co-workers reported an elegant atom-economical methodology of indole synthesis based on intermolecular titanium amide-catalyzed hydroamination reaction of alkynes with hydrazine derivatives followed by a cyclization employing Zinc chloride ($ZnCl_2$). This methodology uses Fischer indole synthesis strategy, with the formation of a hydrazone intermediate. The method employs the inexpensive Lewis-acid titanium tetrachloride ($TiCl_4$) as a precatalyst and amine like *tert*-butylamine ($^tBuNH_2$) to transform hydrazines and unsymmetrical alkynes into indoles. For example, 1,1-disubstituted hydrazine (**49**) is treated with unsymmetrical alkyne (**50**) in the presence of $TiCl_4$ and $^tBuNH_2$ to afford 1,3-diubstituted indole (**51**) as depicted in **Scheme 12**[36].




**49** **50** **51**

**Scheme 12**

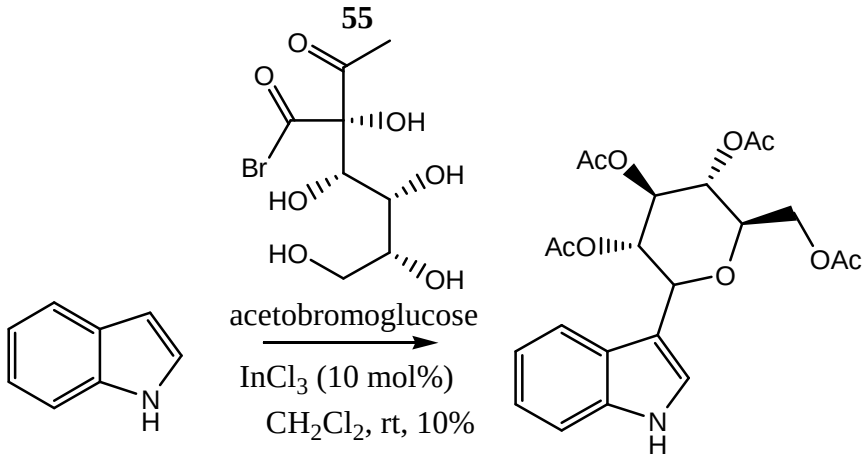
Recently, methodology which employs the inexpensive bismuth(III) trifluoromethanesulfonate (triflate) ($Bi(OTf)_3$ which can be easily prepared on multi-gram scale in the laboratory from bismuth(III) oxide and triflic acid has been used to synthesize 3-substituted indoles. It was found that treating indole (**9**) with quinone (**52**) in the presence of $Bi(OTf)_3$ as a catalyst in acetonitrile at room temperature gave exclusively 3-indolyhydroquinones (**53** and **54**) (**Scheme 13**).This method is clean and free from chlorinated side products that are usually observed under protic acid conditions and is applicable to both electron-rich and electron-deficient indoles[37].




**53** **9** **54**

**Scheme 13**

*C*-Glycosides, wherein a carbon atom replaces the glycosidic oxygen have attracted considerable attention in carbohydrate and biological chemistry owing to their stability towards enzymatic and acidic hydrolysis. Indole *C*-glycosides are model compounds for the synthesis of nucleosides of 9-deazapurines and are believed to exist in biological systems. Indole *C*-glycosides are usually synthesized in the presence of Lewis acids such as zinc chloride ($ZnCl_2$), mixture of boron trifluoride and diethyl ether ($BF_3$-$Et_2O$) or trimethylsilyl trifluoromethanesulfonate (TMSOTf) but these usually give unsatisfactory results with low stereoselectivity. Recently, the use of $InCl_3$ to perform such reactions has been evaluated due to its water stability. When indole (**9**) is treated with acetobromoglucose (**55**) in the presence of indium trichloride ($InCl_3$) as a catalyst in dichloromethane at room temperature, afforded exclusively 3-substituted-C-glycoside indole (**56**) in poor yields and high stereoselectivity as outlined in **Scheme 14**[38].

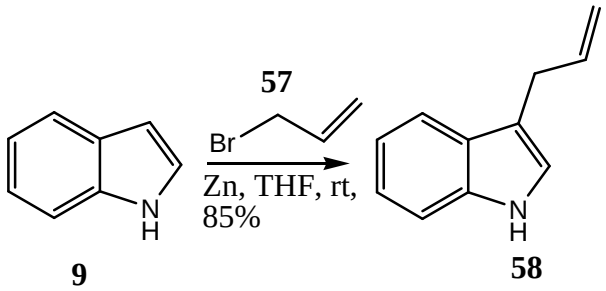



**Scheme 14**

*C*-Alkylation of indoles is one of the most common methods used to introduce substituents onto the 3-position but this methodology usually gives mixtures of products. The methodology employs metals like zinc and magnesium. Recently organometallic reactions have found a wide application in organic synthesis including *C*-alkylation of indoles and pyrroles. Organozinc

reagents are especially owing to their compatibility with other functional groups, stability, reactivity and selectivity; and they also exhibit low nucleophilicity, thus permitting chemoselective transformations of groups with similar reactivity.

Here preparation of 3-allylindole (**58**) through the zinc-mediated Barbier-type reaction is illustrated. Indole (**9**) was treated with allyl bromide (**57**) in the presence of zinc in tetrahydrofuran (THF) at room temperature to give 3-allylindole (**58**) in good yield and high regioselectivity. The methodology can also be used with crotyl, prenyl bromides and substituted indoles[39].

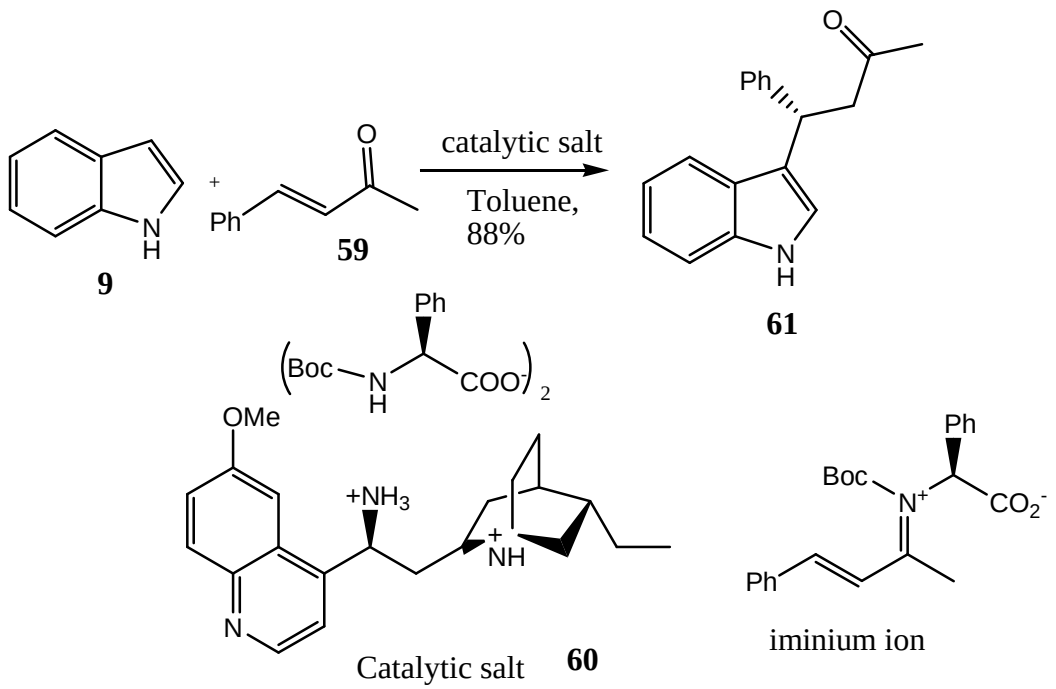



**9** **58**

**Scheme 15**

The development of effective asymmetric entries to indole architecture constitutes an important research field. Some catalytic enantioselective additions of indoles to unsaturated carbonyl compounds, in particular Friedel-Crafts (F-C) alkylations, have been of particular recent interest. A number of highly selective metal-catalyzed F-C reactions of bidentate chelating carbonyls have been developed. Here efficient asymmetric organocatalytic addition of indoles to simple enones is demonstrated, a general and trivial protocol that allows rapid access to a broad range of highly enantioenriched 3 -indolyl derivatives. The method uses iminium ion activation strategy with enone substrates, based on catalytic use of an amine salt in which both the cation and the anion are chiral. Indole (**9**) was reacted with (*E*)-4-phenylbut-3-en-2-one (**59**) in the presence of

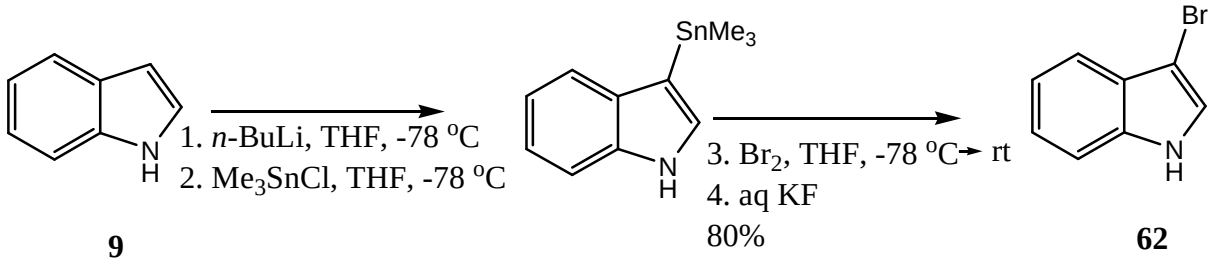
chiral amine catalyst salt (**60**) to give 4-(1*H*-indol-3-yl)-4-phenylbutan-2-one (**61**) in good yield and with >90% ee. This method shows a significant tolerance towards steric and electronic demands of the β -olefin substituents[40] (**Scheme 16**).




**Scheme 16**

Electrophilic aromatic bromination is one of the older reactions known to organic chemists. Aryl halides are important synthetic intermediates for a variety of transformations that range from formation of functionalized aromatic compounds to aryl organometallic reagents that are used in other reactions. Despite the many halogenation methods available, regioselective reaction of activated aromatic compounds such as 5-methoxyindole still remains a problem. Although bromination of indole gives mostly 3-bromoindole, sometimes it gives mixture of products where bromination can take place on the electron-rich benzene ring. However, there are a handful of selective bromination procedures. For example, the procedure outlined below proved to be selective with high yields. Treatment of indole (**9**) with *n*-butyllithium and trimethyltin chloride followed by the addition of bromine at –78 °C gave 3-bromoindole (**62**) with no sign of

other brominated indole product and this method worked well with activated 5-methoxyindole[41] (**Scheme 17**).

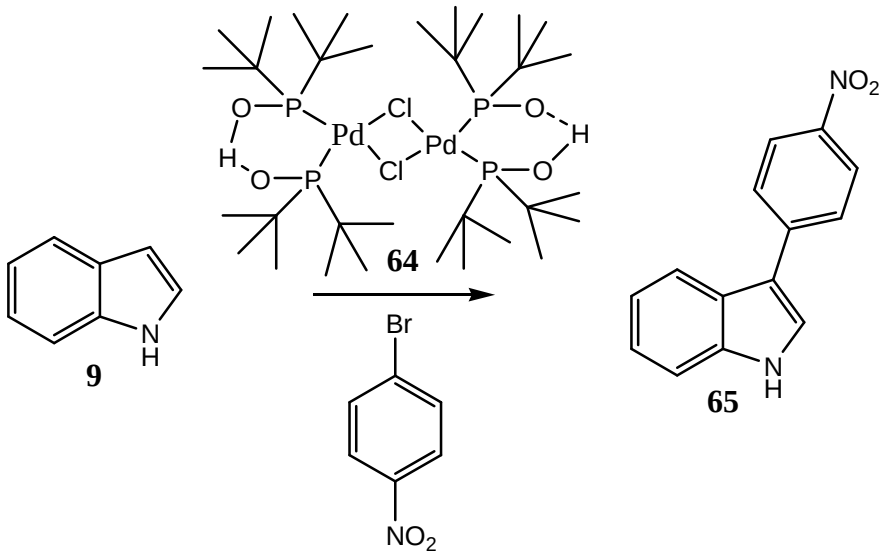



**9** **62**

**Scheme 17**

The 3-arylindole structure represented is some of the biologically active indole containing compounds. Among the arylated indole compounds, 3-phenylindole is an antimicrobial compound active towards many fungi and Gram-positive bacteria[42].

3-Arylated indoles have been prepared by ring closure synthesis or by introducing protecting groups on heterocyclic nitrogen atom and introducing functionalities prior to C-C formation. For example, *N*-protected 3-bromoindoles allow C-C bond formation through the developed catalytic cross-coupling reactions. One of the most commonly used methods is the Suzuki-Miyaura cross-coupling reaction[26]. C-3 Arylation of indoles containing an unprotected heterocyclic nitrogen atom is also possible with a highly specific palladium catalyst as illustrated here. When indole (**9**) was treated with 1-bromo-4-nitrobenzene (**63**) in the presence of the exotic catalyst (**64**) abbreviated a POPd, it gave 3-(4-nitrobenzene)indole (**65**) in good yield and selectivity. Palladium-phosphinous acid complex abbreviated (POPd) (**64**) has been found to be a superior catalyst in this type of cross-coupling reactions due to its air-stability[42] (**Scheme 18**).

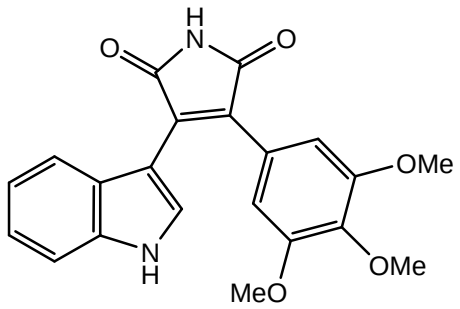



Dioxane, 48%

**Scheme 18**

### 1.4.2 Biological Importance

Many indoles substituted at C-3 have also been found to be biologically active. Most of the active 3-C substituted indoles were found to be anticancer agents and kinase inhibitors. Many have been synthesized but some are also found in Nature. For example, compound (**66**) was found to have strong potency against vessel growth *in vivo* chick embryo assay with 82% inhibition of vessel area after 24 hours incubation by application of 10 µg per pellet and it was also found to be active against the kinase involved in the angiogenic process resulting in *in vivo* activity[43]. Angiogenesis, the formation of new capillaries from preexisting blood vessels, is essential in several physiological situations, including embryo development, female reproductive cycle, and wound healing during which angiogenesis is under strict control. The angiogenic process is regulated by a variety of endogenous molecules including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factors (TGF) and cytokines interleukin IL-2 and Il-8[45].



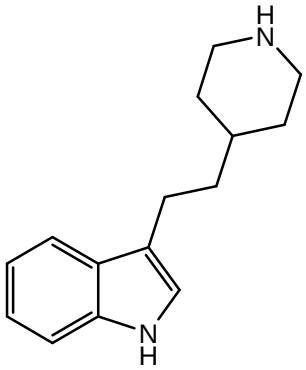

**66**

**Figure 6**

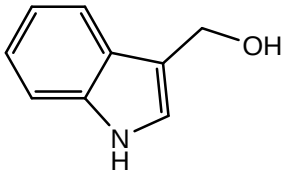
Uptake into the presynaptic neuron is the principal mechanism for the rapid inactivation of released biogenic amines in the neural synapse. The tricyclic antidepressant agents inhibit to a varying extent the uptake of noradrenaline (NA) and 5-hydroxytryptamine (5-HT). Clomipramine was the most selective inhibitor of 5-HT uptake *in vitro*, but the selectivity was greatly reduced *in vivo* due to the biotransformation into chlordesipramine, an NA uptake inhibitor. In more detailed *in vivo* studies, indalpine (**67**) was shown to be the most potent and the most selective inhibitor of 5-HT and it was found to be the most active 5-hydroxytryptophan (5-HTP) potentiator[44].

It was found that indole-3-carbinol (**68**) inhibits the proliferation and tube formation, an *in vitro* maker of angiogenesis of phorbol myristate acetate (PMA) activated EA hy926 endothelial cells, a potential angiogenesis stimulator and such suppression is associated with decrease in secretion of VEGF and matrix metalloproteinase (MMP-2 and MMP-9)[45]. Indole-3-carbinol (**68**) is a naturally occurring anticancer agent and has entered clinical trials for cancer prevention. It (**68**) is a dietary component found in exclusively in cruciferous vegetables and it is known to suppress proliferation and induce apoptosis of various cancer cells, including breast, ovarian, lung, cervical, colon, prostate and liver.

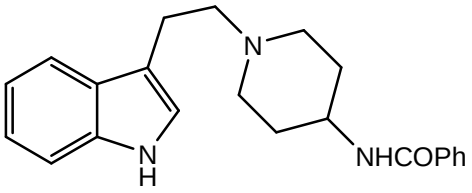
Compound (**68**) was able to selectively inhibit activation of Akt in the tumor-derived MDA-MB-468 breast and PC-3 prostate cancer cell lines, but not in nontumorigenic human HBL100 breast and CRL2221 prostate epithelial cells[46]. Adrenaline or noradrenaline are prominent in the cardiovascular system, acting through α- and β-adrenergic receptors, which exist as a number of subtypes. The interaction of effects from these receptors is quite complex. Many common drugs are simple carbocyclic analogues of adrenaline but few of the important compounds are heterocyclic. One of them is indoramin (**69**) which is used for the treatment of hypertension and benign prostatic hypertrophy[47].




**67**




**68**




**69**

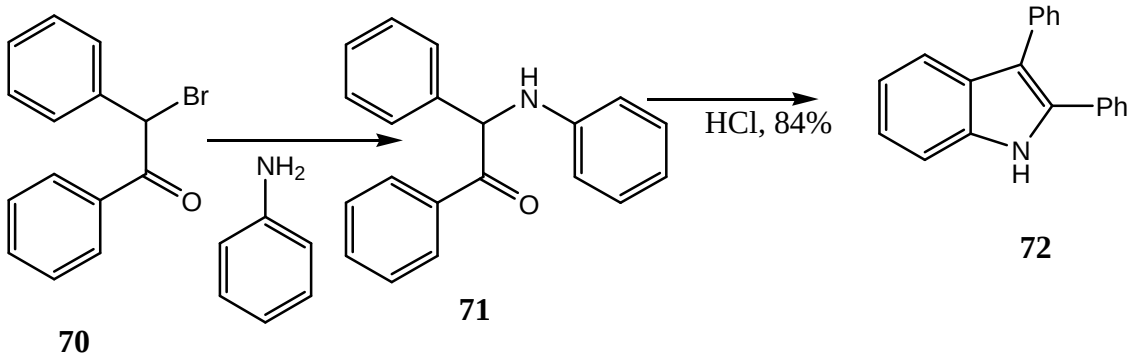
**Figure**

## 1.5 2- and 3-Disubstituted Indoles: Synthesis and Biological Importance

### 1.5.1 Synthesis

2-and 3-Disubstituted indoles can be synthesized from either 3-substituted indoles by introducing substituents onto the 2-position, from 2-substituted indole by introducing substituents onto the 3-position or by cyclization reactions using starting materials that already bear the substituents that will occupy 2-and 3-positions of the indole nucleus. They can be formed from α-halogenated or

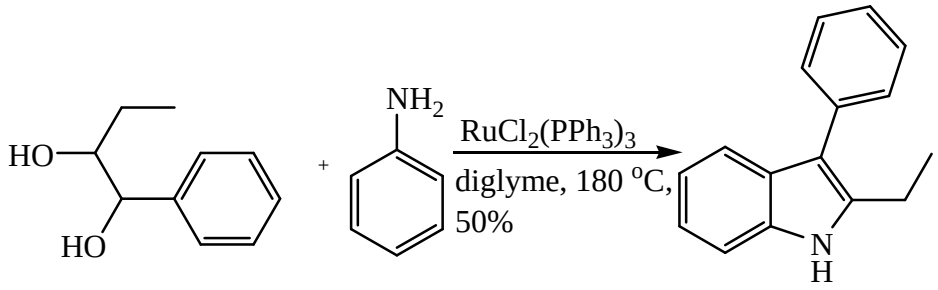
α-hydroxy ketones with arylamines in the presence of halogen acid. For example, treating 2-bromo-1,2-diphenylethanone (**70**) with aniline gave 1,2-diphenyl-3-(phenylamino)propan-1-one (**71**). Heating (**71**) with aniline in the presence of hydrochloric acid for several hours under a nitrogen atmosphere gave 2,3-diphenylindole (**72**) in excellent yield[48].




**70** **71** **72**

**Scheme 19**

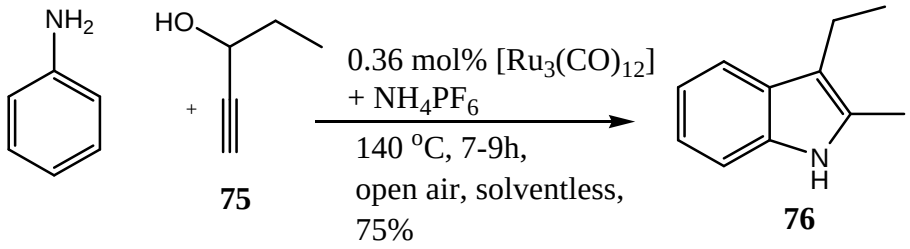
The simplest way of building the indole skeleton with substituents at the 2-and 3-postions would be through intermolecular reaction between aminoarene and $C_2$ fragments. The problem is that these types of reaction are usually carried out over a heterogeneous catalyst under very severe reaction conditions and at high temperatures. The ruthenium-catalyzed reactions between aminoarenes and glycols have paved a way for homogeneous transition metal catalysis at reduced reaction temperatures. It has been shown that aniline reacted smoothly with 1-phenylbutane-1,2-diol (**73**) in the presence of catalytic amount of ruthenium complex with the spontaneous hydrogen evolution to give 2-ethyl-3-phenylindole (**74**) in good yield[49].




**73** **74**

**Scheme 20**

Bischler indole synthesis is one the classical indole synthesis methods and it involves the reaction of aniline with α-haloketones. Its use has been limited by the low accessibility of α-haloketones. A Bischler-type indole synthesis that would avoid the use of haloketones, thereby making it a halogen-free reaction, has been used for the preparation of 2,3-disubstituted indoles. The reaction is based on the intermolecular addition of anilines to terminal alkynes and is efficiently catalyzed by a commercially available ruthenium carbonyl/additive mixture. As described in the literature, aniline was reacted with pent-1-yn-3-ol (**75**) in the presence of ruthenium carbonyl as a catalyst and ammonium hexafluorophosphate ($NH_4PF_6$) as an additive to give 3-ethyl-2-methylindole (**76**) in good yield[50].

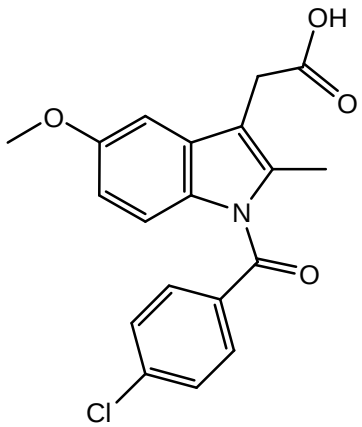



**75** **76**

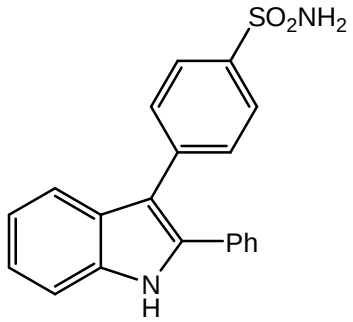
**Scheme 21**

### 1.5.2 Biological Importance

Indoles substituted at both the 2-and 3-positions are also of biological importance. The biological activities depend on the type of groups in these positions and the substituents can be aromatic, straight chains and non-aromatic rings. Indomethacin (**77**), a 5-methoxy indole ring which contains an acetic acid moiety at position 3 and a methyl substituent at position 2 has shown biological activities. Position 1 is occupied by 4-chlorobenzoyl group which also contributes to the observed properties. Indomethacin is a potent non-steroidal anti-inflammatory agent used primarily in the treatment of rheumatoid arthritis and has potential for use in uveitis, a common disease responsible for blindness. Indomethacin may also be used in the management of cystoid macular edema (CME), a disease characterized by a build-up of serous fluid in the extracellular space in the retina caused by a disruption of the blood-retinal barrier[51]. Nonsteroidal anti-inflammatory drugs (NSAIDs) remain among the most widely prescribed drugs worldwide for the treatment of inflammation including pain-releasing, antipyretic and rheumatoid arthritis. The mechanism of action is through their inhibition of prostaglandin biosynthesis via the enzyme cyclooxygenase-2 (COX-2). An example of a synthetic NSAID is 2-phenyl-3-phenylsulfonamide-1*H* indole (**78**), which was found to be more potent and selective against COX-2 than COX-1[52].




**77**

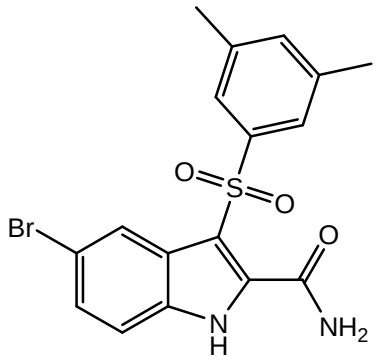



**78**

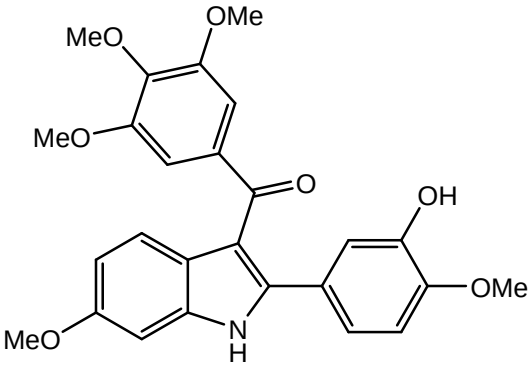
**Figure 8**

Current drugs effective against the HIV-1 reverse transcriptase (RT) are classified according to their structure as nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs, respectively). NRTIs interfere with the enzyme activity following metabolic activation to the triphosphate forms and incorporation into the growing DNA strand, which causes chain termination. On the other hand, NNRTIs do not require preliminary phosphorylation and are less toxic than NRTIs because they do not affect the activity of cellular polymerases and they give rise to the rapid emergence of drug-resistance strains which are cross-resistance of other inhibitors within the class.

5-Bromo-3-(3,5-dimethylphenylsulfonyl)indole-2-carboxamide (**79**) was tested against HIV-1 in acutely infected MT-4 cells. It showed to be very potent and selective anti-HIV-1 activity not only on wild type strains, but also against mutants carrying NNRTI-resistance mutations[53]. Compounds that interfere with the microtubule-tubulin equilibria in cells are useful in the treatment of human disease. [2-(3-Hydroxy-4-methoxyphenyl)-6-methoxy-indol-3-yl](3,4,5-trimethoxyphenyl)methanone (**80**) was showed good activity as tubulin polymerase inhibitors and was further evaluated for inhibitory effect on the binding of [$^3$H]colchicine to tubulin and cytotoxicity against MCF-7 human breast carcinoma cells. However, (**80**) was found to be less potent than combretastatin A-4 (CA-4) as an inhibitor of [$^3$H]colchicine binding to tubulin and as cytotoxins against MCF-7 human breast carcinoma cells and its cytotoxicity was less compared to CA-4[54].




**79**



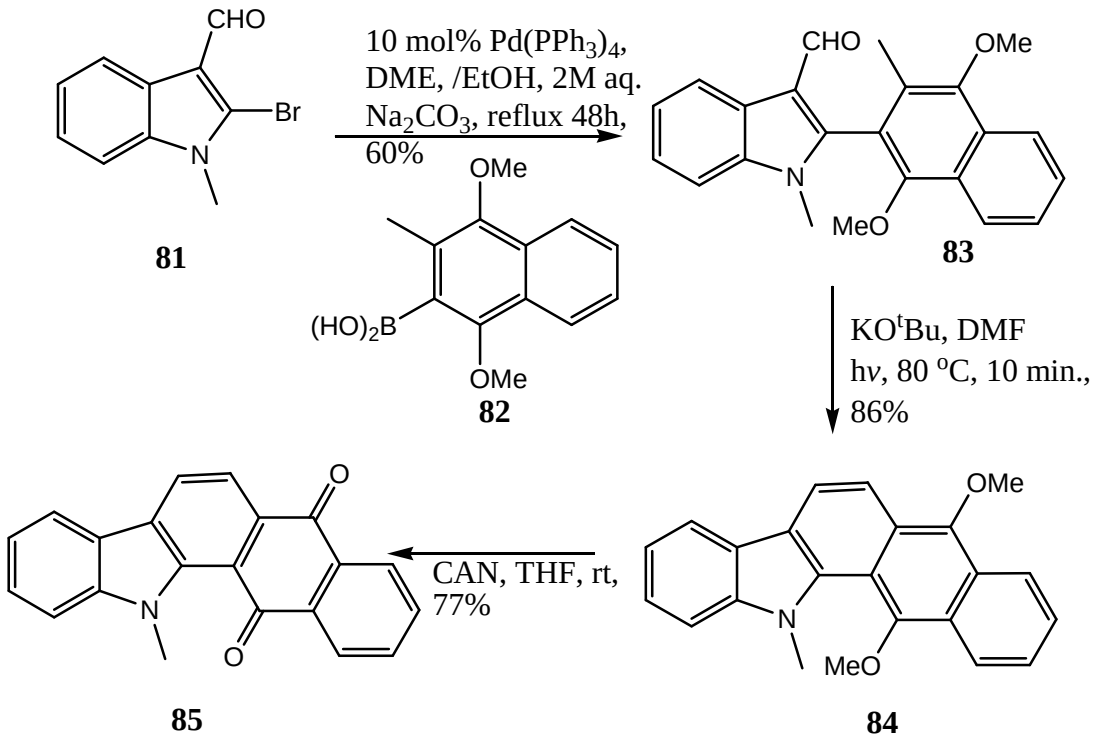

**80**

**Figure 9**

## 1.6 Fused indoles: Synthesis and Biological Importance of Carbazoles

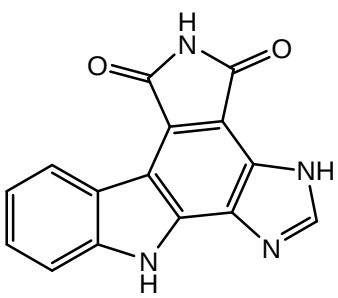
### 1.6.1 Synthesis

Carbazoles (benzo[*b*]indole) are natural products of medicinal and biochemical importance[55]. They display a range of biological activities that make them attractive compounds to synthetic and medicinal chemists. Many methods exist for their preparation in our laboratories. Synthetic methodology has been developed for the synthesis of indolocarbazoles employing a light-and base-assisted cyclization reaction. Starting from *N*-methyl-2-bromoindole-3-carbaldehyde (**81**) and treating it with 1,4-dimethoxy-3-methylnaphthalen-2-ylboronic acid (**82**) under aqueous Suzuki-Miyaura cross-coupling reaction conditions afforded the desired compound (**83**) in good yield. Compound (**83**) was then exposed to potassium *tert*-butoxide and light in 1,2-dimethylformamide (DMF) at 80 °C to give the naphtho-fused carbazole (**84**) in fair yield and (**84**) was further oxidized with ceric(IV) ammonium nitrate (CAN) to afford (**85**) (**Scheme 22**)[56].

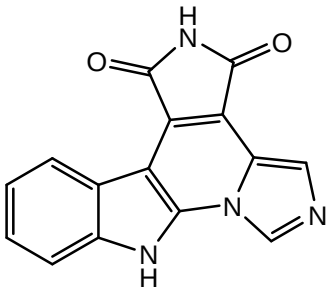



**Scheme 22**

Many natural occurring compounds such as granulatimide (**86**) and isogranulatimide (**87**) isolated from the ascidian *Didemnum granulatum* (**Figure 10**) contain a maleimide unit attached to the carbazole. Their biological activity is linked to their capacity to interfere with the G2 checkpoint in cell growth, which represents a promising target for the development of new chemotherapeutic anticancer agents.



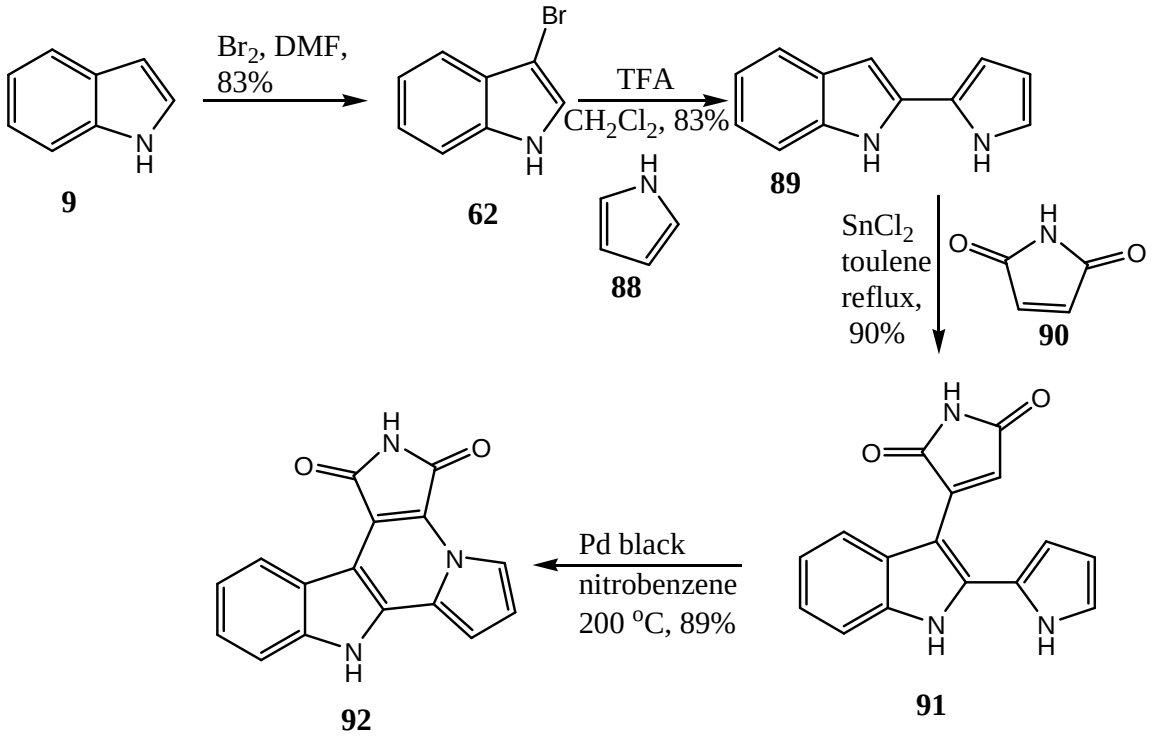
**86**



**87**

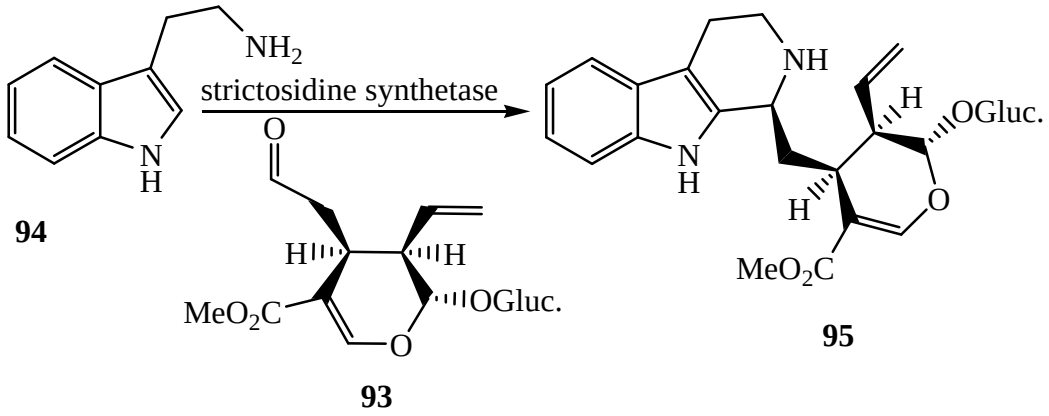
**Figure10**

Other related compounds have also been assembled. For example, there is a new family of isogranulatimide analogues in which the imidazole moiety is replaced by a pyrrole heterocycle. In the synthesis of these examples, indole (**9**) was selectively brominated to give 3-bromoindole (**62**) which was then reacted with pyrrole (**88**) at room temperature in the presence of trifluoroacetic acid in dichloromethane which led to 2-(pyrrol-2-yl)indole (**89**). Reaction of (**89**) with pyrrole-2,5-dione (**90**) in the presence of stannous chloride gave the Michael adduct (**91**) in good yield. When (**91**) was treated with palladium black in nitrobenzene as a solvent at 200 °C followed by elimination of the solvent by filtration over silica afforded the isogranulatimide analogue (**92**) in good yield[57].




**Scheme 23**

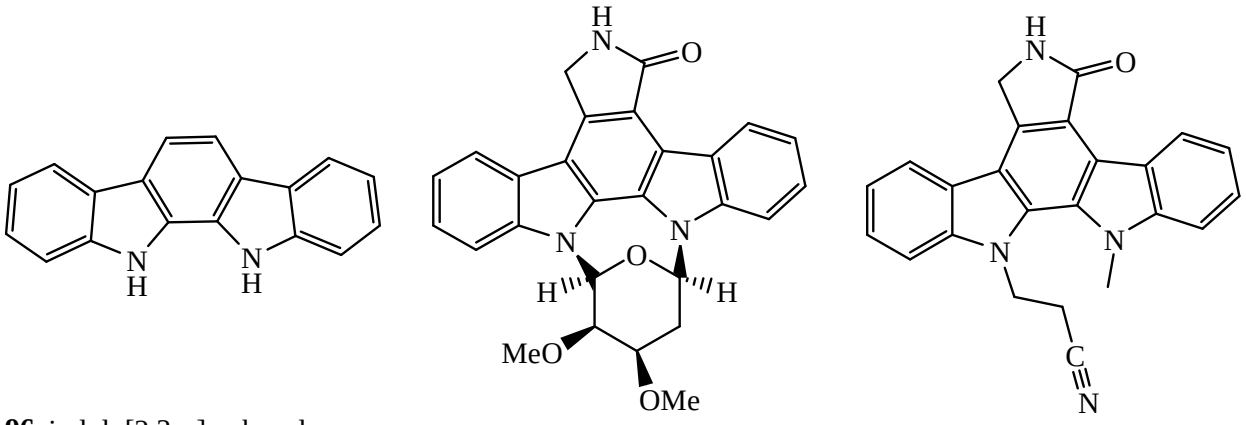
A very large number of indole alkaloids belong to a class in which an unrearranged secologanin unit (**93**) can be recognized in combination with either tryptamine (**94**) or tryptophan (**6**). For example, tryptamine (**94**) was condensed with secologanin (**93**), catalyzed by the enzyme strictosidine synthetase which controls C-ring closure mechanism, resulting in the formation of strictosidine (**95**) (**Scheme 24**)[58].




**Scheme 24**

### 1.6.2 Biological Importance

The indolo[2,3-*a*]carbazole (**96**) framework contains an embedded indole unit and is found in many natural products which have a broad range of potent biological activities, such as antifungal, antimicrobial, antitumor, and antihypertensive activity. These carbazoles can be potent inhibitors of protein kinase C[59]. For example, staurosporine **(97)** and Gö 6976 (**98**) both contain the indolo[2,3-*a*]carbazole nucleus. Staurosporine **(97)** has interesting biological activities including cytotoxic, antimicrobial, inhibition of protein kinase C, and platelet aggregation inhibition. Staurosporine (**83**) was also found to be one of the best ATP competitive kinase inhibitors with $IC_{50}$ values in the nanomolar range for the serine kinases, protein kinase C, CDK2, CDK4, and CDK6[60]. Gö 6976 (**98**), a non-glycosidic indolo[2,3-*a*]carbazole, exhibits selective inhibition of protein kinase C and also acts as an antagonist of human immunodeficiency virus 1 (HIV-1) (**Figure 11**)[59].



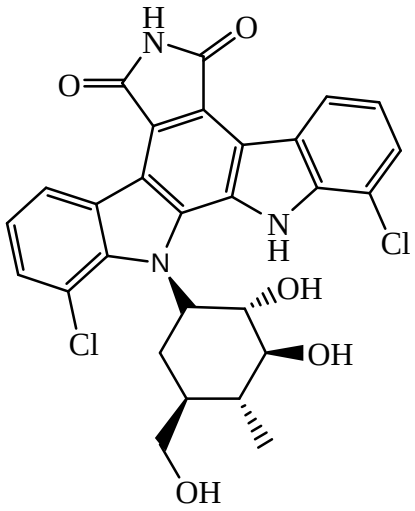

**96** indolo[2,3-*a*]carbazole

**97** staurosporine

**98** Gö 6976

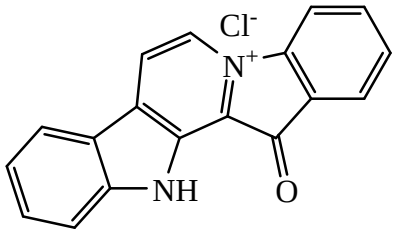
**Figure 11**

Rebeccamycin (**99**) is an antitumor secondary metabolite isolated from cultures of *Saccharothrix aerocolonigenes*. Rebeccamycin (**99**) was found to have significant activity against P388 leukemia, L1210 leukemia and B-16 melanoma implanted in mice and inhibited the growth of human lung adenocarcinoma cells. It was found that (**99**) produces single-strand breaks in DNA and in a modified form, it is currently being considered for clinical evaluations as a potential treatment for cancer in humans[61]. On the other hand, fascaplysin (**100**), a red pigment isolated from the Fijian sponge *Fascaplysinopsis* Bergquist sp. was reported to inhibit the growth of several microbes including *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, *Saccharomyces cerevisiae* and was also found to suppress proliferation of mouse leukemia cells L-1210 while its analogue, cryptolepine (**101**) has been demonstrated to efficiently intercalate into DNA and to act as a potent topoisomerase II inhibitor[62].



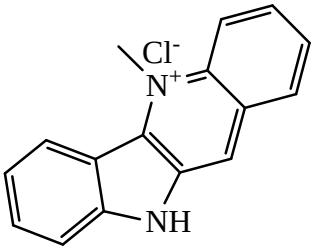

Rebeccamycin

**99**




Fascaplysin

**100**



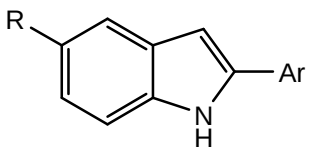

Cryptolepine

**101**

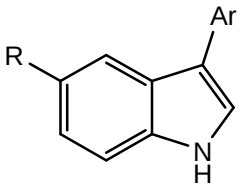
**Figure 12**

## 1.7 Aims of the Project

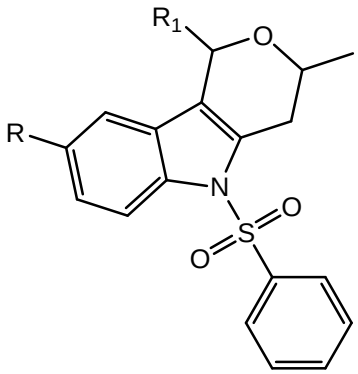
In this MSc project we wished to develop methodology to synthesize 2- and 3-substituted indoles, specifically with aryl substituents at those positions. The first part of the MSc project was to synthesize 2-arylsubstituted indoles using, as a key step, Suzuki reactions and conditions. Alternative methodology to the Suzuki-Miyaura coupling for introducing aryl substituents at C-2 was developed. For the second part of the project we focused on synthesizing 3-aryl substituted indoles with general formula 3-arylindole. In order to place aryl substituents in the 3-position, the method we wished to use was the Suzuki-Miyaura coupling reaction, which requires an aromatic halide as one component and an aromatic boronic acid as the other. Once these 2-arylindoles and 3-arylindoles were synthesized, they would be subjected to a range of biological screens. After we finished synthesizing 2- and 3-arylindoles, we turned our attention to fused indoles. We wished to explore the methodology to synthesize indolo fused pyrans and this was achieved by using mercury acetate as a key reagent for ring closure.




2-arylindoles




3-arylindoles




indolo fused pyrans

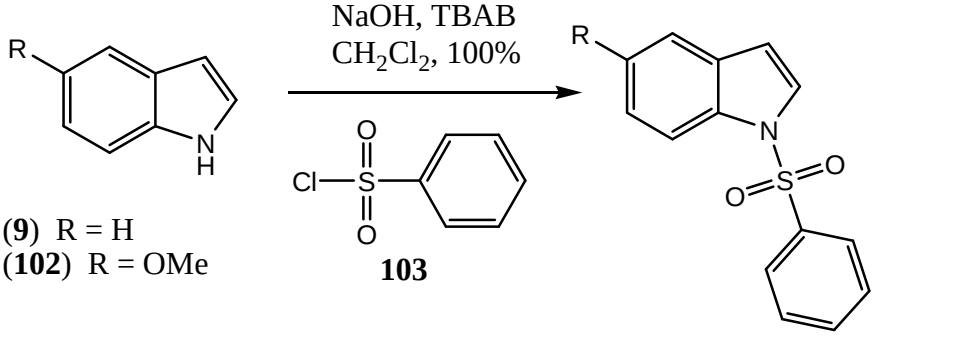
**Figure 13**

# Chapter 2: Results and Discussion

## 2.1 Protection and halogenations of the indole nucleus

In this section we will outline the synthesis of halogenated 2- and 3-substituted indole precursors. We required these precursors for the introduction of aryl substituents at both of these positions using a variety of different procedures that will be discussed later. However, initially we needed to protect the indole nitrogen such that it can also act as a directed *ortho* metallation (DOM) group, but this group needed to be readily removed once the required 2- and 3-arylindoles were synthesized.

### 2.1.1 Synthesis of 1-(phenylsulfonyl)-1*H*-indole (23) and 5-methoxy-1-(phenylsulfonyl)-1*H*-indole (104)




(**9**) R = H
(**102**) R = OMe

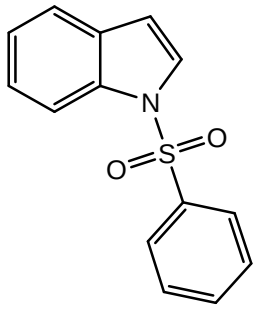
**103**

(**36**) R = H
(**104**) R = OMe

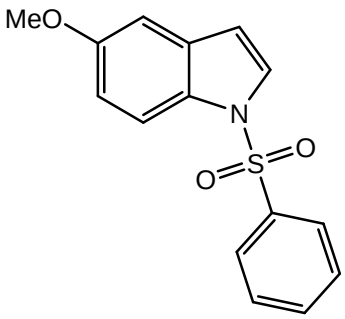
**Scheme 25**

Gribble *et al*. have described procedures for introducing the phenylsulfonyl group at low temperatures. The method employs air and water sensitive chemicals namely, *n*-butyllithium at –

78 °C [63]. Some of recently developed methodologies involve sodium hydroxide as base which is not sensitive to either air or water and the reaction takes place at 0 °C to room temperature as compared to –78 °C. In this project, commercially available indole (**9**) or 5-methoxyindole (**102**) was treated with sodium hydroxide and phenylsulfonyl chloride (**103**) in the presence of a catalytic amount of tetrabutylammonium bromide to afford 1-(phenylsulfonyl)indole (**36**) and 5-methoxy-1-(phenylsufonyl)indole (**104**) in excellent yields of 100%[60]. Compound (**36**) was obtained as a cream white solid, with the melting point 75-78 °C and the literature reported (**36**) isolated as colourless needles with melting point 76.5-77 °C [64]. The $^{1}$H NMR spectra of both compounds showed the disappearance of the NH signal. The $^{1}$H NMR spectrum of (**36**) was also characterized by the appearance of a doublet ($J$ = 7.50) at 7.87 ppm integrating for two hydrogens which belonged to two equivalent hydrogens on the phenylsulfonyl group and other three hydrogens are embedded in the multiplet. This was also evident from the increased number of hydrogens in the aromatic region due to the introduction of the phenylsulfonyl group. The $^{13}$C NMR spectrum of (**36**) showed two peaks at 129.66 and 127.14 ppm each accounting for two equivalent carbons bearing a hydrogen of the phenyl ring of (**36**).




**36**




**104**

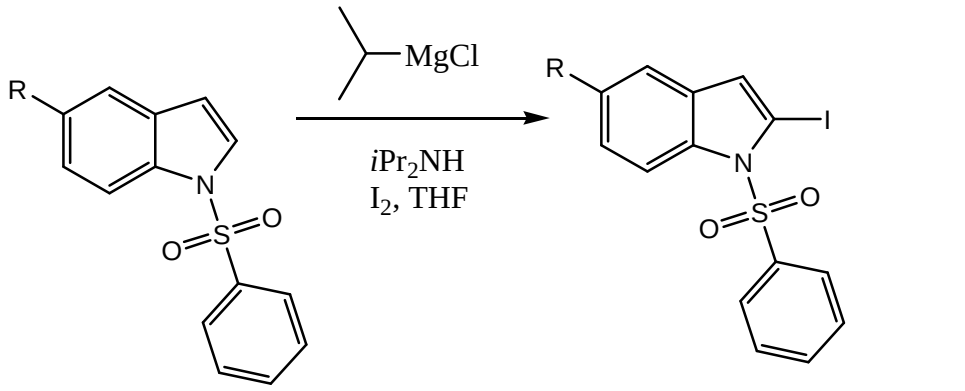
**Figure 14**

Compound (**104**) was isolated as white solid with melting point 96-99 °C. The literature reported that (**104**) was isolated as colourless crystals[34, 63] with melting point 97-98 °C[34].On the other hand, the $^{1}$H NMR of compound (**104**) also showed two doublets at 7.83 ($J$ = 7.51) and 7.40 ($J$ =

7.89) ppm each integrating for two hydrogens which belonged to the four hydrogens on the phenylsulfonyl group. The $^{13}C$ NMR spectrum showed two distinct peaks at 129.61 and 127.06 ppm belonging to the four carbons on the phenylsulfonyl group.

### 2.1.2 Synthesis of 2-iodo-1-(phenylsulfonyl)-1*H*-indole (105) and 2-iodo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (106)

As a next step we needed to use methodology to introduce halogens at the 2-position of the indole nucleus for the proposed Suzuki coupling reaction.




(**36)** R = H
(**104**) R = OMe

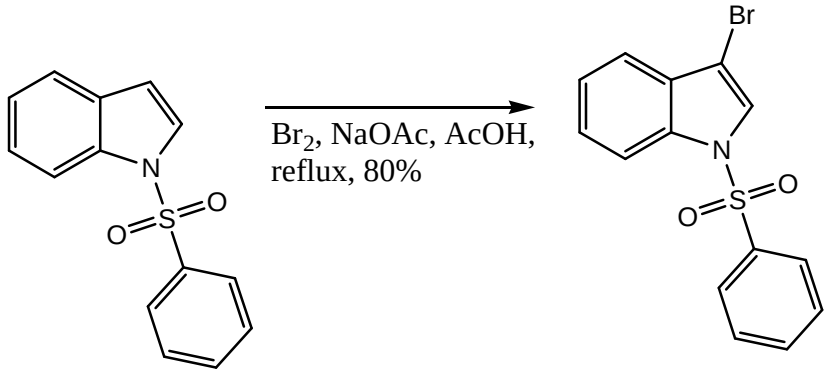
(**105)** R = H (79%)
(**106**) R = OMe (85%)

**Scheme 26**

Encouraged by the good yields obtained for compounds (**36**) and (**104**), we decided to attempt the next step, i.e. iodination at the 2-position of the indole nucleus. The iodination of these compounds proved not to be straight forward. The first method attempted was using lithium diisopropylamine as a base at –78 °C as described in the literature[65] but this method failed. We attempted numerous methods without success until we tried a method developed in our

laboratories. The method was mainly used on pyrroles to introduce substituents onto the 2-position[28], and is an extension of a procedure by Kondo *et al*. for introducing substituents at the 2–position of indole using magnesium amide bases[27]. Both compounds (**36**) and (**104**) were dissolved in THF and treated with isopropylmagnesium chloride and a catalytic amount of diisopropylamine, after which the reaction was left to stir at room temperature for 16 hours. After this time, the reaction mixture was treated with iodine and left to stir for 1 hour before being quenched by the aqueous solution of ammonium chloride as a part of the work up. Products (**105**) and (**106**) were obtained in yields of 79% and 85% respectively. Compound (**105**) was isolated as a cream white solid with melting point 95-98 °C. The literature reported the isolation of (**105**) as colourless solid[27] and tan crystalline solid[65] with melting point 96-98 °C[66]. The $^{1}$H NMR spectrum of (**105**) showed a distinctive singlet at 6.99 ppm integrating for one hydrogen. This signal belongs to the 3-position, showing that the 2-position is occupied by a substituent. The $^{13}$C NMR spectrum showed a distinctive quaternary carbon at 121.85 ppm that did not appear in the $^{13}$C NMR spectrum of (**36**). Compound (**106**) was isolated as a cream white solid with the melting point 127-130 °C. The $^{1}$H NMR spectrum of (**106**) also showed the similar distinctive singlet at 6.89 ppm integrating for one hydrogen for the 3-position of indole nucleus (**106**).

### 2.1.3 Synthesis of 3-bromo-1-(phenylsulfonyl)-1*H*-indole (107)

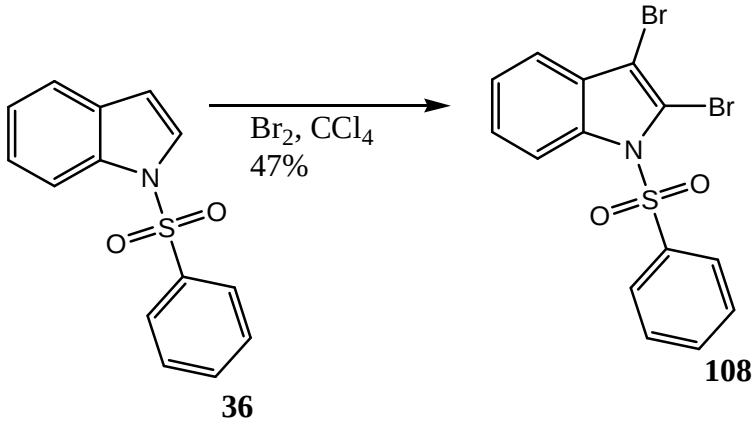



**36** **107**

**Scheme 27**

The next step for this project was to introduce a halogen at the 3-position of the indole nucleus. There are many different methods for preparing (**107**) described in the literature. One of the methodologies involves using reagents such as *n*-butyllithium and trimethyltin chloride followed by addition of bromine in order to convert (**9**) to 3-bromoindole (**62**)[41] (**Scheme 17**). Compound (**62**) was then treated with phenysulfonyl chloride in the presence of potassium hydroxide to afford (**107**) but the problem with this method was the instability of compound (**62**) [68]. Compound (**36**) can also be brominated using molecular bromine at room temperature using the correct number of equivalents of bromine[67]. In our case, a mixture of (**36**) and sodium acetate in acetic acid was treated with bromine. The overall mixture was the refluxed for 18 hours over which time it turned from brown to light yellow. After being allowed to cool to room temperature, the reaction mixture was filtered to remove sodium acetate and the acetic acid removed under reduced pressure. This was followed by water work up to give (**107**) as a white solid with a melting point of 120-124 °C, literature reported (**107**) as a white solid with a melting point 122-124 °C[68]. The $^1$H NMR spectrum of (**107**) showed a distinctive singlet at 7.62 ppm integrating for one hydrogen belonging to the hydrogen at the 2-position of (**10**7) and disappearance of a doublet at about 6.50 ppm due to the hydrogen at the 3-position when compared to the $^1$H NMR spectrum of (**36**).

### 2.1.4 Synthesis of 2,3-dibromo-1-(phenylsulfonyl)-1*H*-indole (108)

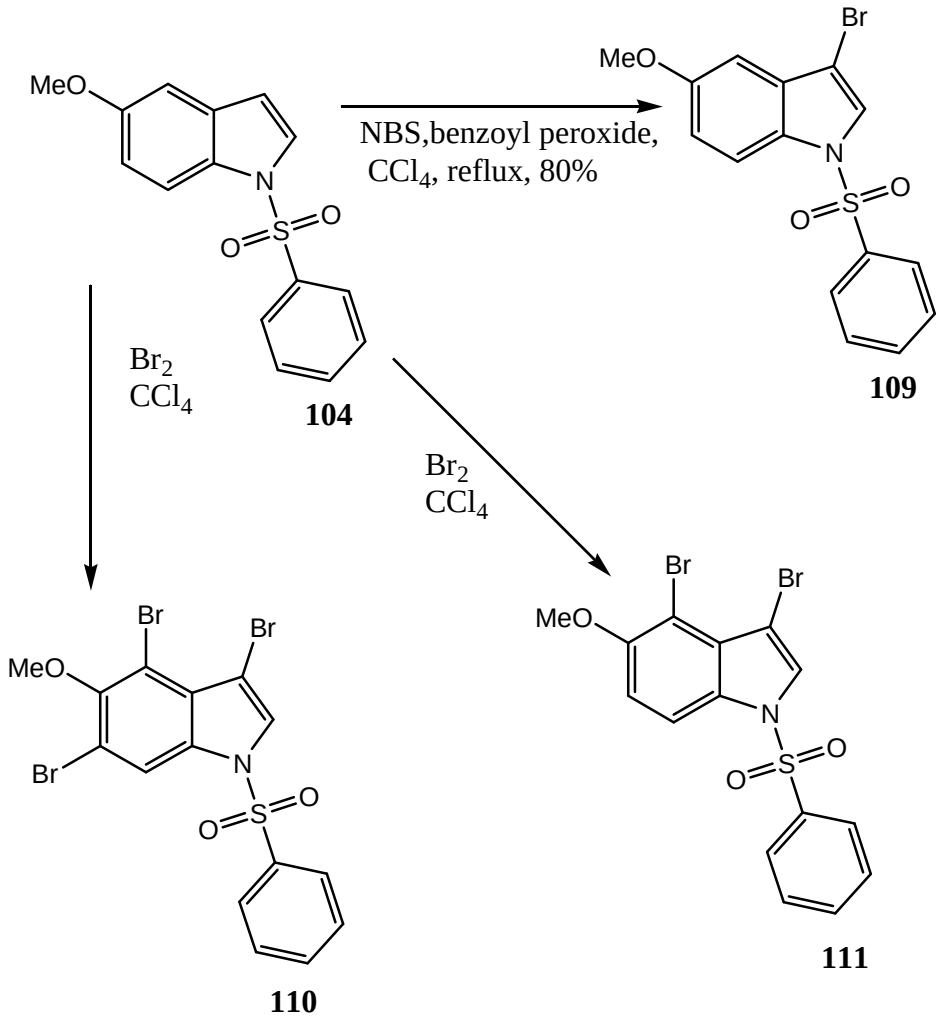



**36** **108**

**Scheme 28**

We also wished to assemble indoles containing aryl substituents at the 2- and 3-positions. If we wished to use Suzuki coupling methodology we required a substituted indole such as (**108**) with halogens in both the 2- and 3-position. There are also many different routes for the synthesis of (**108**). One can first synthesize (**107**) and subsequent bromination of (**107**) will yield (**108**)[69]. In our laboratories, (**36**) was dissolved in carbon tetrachloride and treated with 1.1 eq of bromine at room temperature and the reaction left to stir overnight. After this time, the reaction mixture was poured into a saturated solution of aqueous sodium hydrogen carbonate and washed successively with water, aqueous solution of sodium metabisulfate and brine to remove excess bromine. This resulted in a cream white solid in 47% yield with melting point 140-145 °C while the literature reported (**108**) was isolated as white crystals with melting point 141-143 °C[70]. When the $^{1}H$ NMR spectrum of (**108**) was examined, there was no indication of the doublet at about 6.50 ppm for one hydrogen due to presence of both 2-and 3-position hydrogens. Neither was there the singlet at about 6.99 ppm that result when 2-position is occupied nor the singlet at about 7.62 ppm indicating that the 3-position is occupied was observed. Examination of $^{13}C$ NMR spectrum revealed two distinctive quaternary carbons at 120.52 and 107.13 ppm showing that positions 2- and 3- are occupied by substituents other than hydrogen. The chemical shifts indicated that most likely a halogen occupied both of these positions.

### 2.1.5 Synthesis of 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (109)




**Scheme 29**

Once the synthesis of indole (**108**) was complete we turned our attention to the same set of reactions starting from 5-methoxyindole (**104**) also protected as the *N*-phenylsulfonyl derivative. However, the bromination of (**104**) proved not to be straightforward as compared to bromination of a (**36**). When (**104**) was brominated under the same conditions as for (**36**) ($Br_2$, $CCl_4$), the less soluble tribromide (**110**) was identified instead of the monobromo product (**109**). This was confirmed by mass spectroscopy with the $M^+$ at 523.85 for $^{79}Br$ isotope and 525.81 for $^{81}Br$ isotope. It has been shown that bromination of (**104**) with molecular bromine as shown in

**Scheme 29** does not afford (**109**) as required but usually affords (**111**) although not detected in this case and for one to obtain (**109**) under these conditions, one must be very careful in conducting this reaction[56]. Bromination of the benzene ring of the indole is occurring due to the activation of the benzene ring by the methoxy group.

To resolve this problem, indole (**104**) was dissolved in dry carbon tetrachloride and mixed with *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide at room temperature. The reaction mixture was then refluxed overnight after which excess succinimide was filtered off. Trace amounts succinimide were removed by washing with 5% solution of aqueous sodium hydroxide and water. This resulted in a cream white solid (**109**) being obtained with the melting point 129-132 °C while the literature reported a white solid 131-133 °C[56]. When $^{1}$H NMR spectrum of (**109**) was examined, a singlet integrating for one hydrogen at 7.58 ppm was observed. This singlet belonged to the proton at the 2-position and this showed that 3-position of the indole nucleus was occupied. Examination of $^{13}$C NMR spectrum of (**109**) showed the presence of a quaternary carbon at 98.69 ppm belonging to the carbon at the 3-postion.

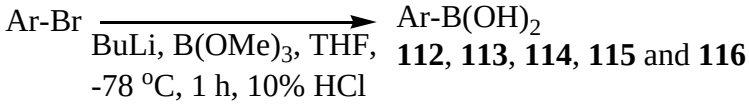
## 2.2 Synthesis of 2-arylindoles and 3-arylindoles

As the desired halogenated substrates (**105**)-(**109**) had now been synthesized, this section will deal with the synthesis of 2-arylindoles and 3-arylindoles from these precursors. The key step used in this section is the aqueous Suzuki-Miyaura cross-coupling of haloindoles and arylboronic acids, mediated by palladium catalyst.

### 2.2.1 Synthesis of boronic acids

The other precursors required for the coupling reactions, the boronic acids, were prepared from the requisite halogenated aryl compounds using traditional methodology, i.e treatment with *n*-

butyllithium, followed by trimethyl borate and then converting the boronic ester into the required boronic acid by treating each intermediate with 10% aqueous hydrochloric acid. The boronic acids obtained in this way are difficult to purify and hence they were used in the subsequent reactions as crude materials. The boronic acids synthesized and used in this project were phenylboronic acid (**112**), *o*-tolylboronic acid (**113**), 1-naphthylboronic acid (**114**), *p*-methoxyphenylboronic acid (**115**) and 3,4,5-trimethoxyphenylboronic acid (**116**) (**Scheme 30**). Although some of these are also commercially available. **Table 1** below lists the approximate yields of the crude boronic acids.

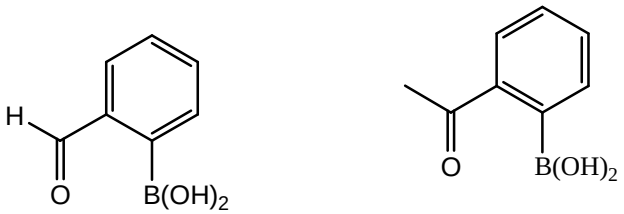



**Scheme 30**

**Table 1**: % Yields of boronic acids

| Ar | Boronic acid | % yield |
|---|---|---|
| Phenyl | **112** | 88 |
| *o*-Tolyl | **113** | 92 |
| 1-Naphthyl | **114** | 70 |
| *p*-Methoxyphenyl | **115** | 81 |
| 3,4,5-Trimethoxyphenyl | **116** | 80 |

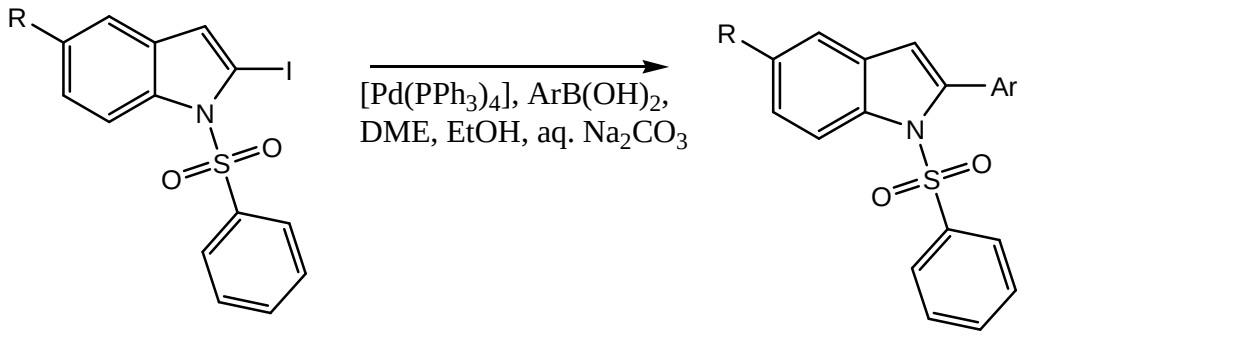
The other boronic acids used in this project were 2-formylphenylboronic acid (**117**) and 2-acetylphenyboronic acid (**118**), which are commercially available (**Figure 15**) and were bought for this project.




**117** **118**

**Figure 15**

### 2.2.2 Suzuki-Miyaura cross-coupling of iodoindoles (105) and (106) followed by deprotection




R = H (**105**)
R = OMe (**106**)

R = H (**119**, **121**, **123**, **125** and **127**)
R = OMe (**120**, **122**, **124** and **126**)

**Scheme 31**

The next step in this synthesis was to perform the Suzuki-Miyaura cross-coupling of either indole (**105**) or methoxyindole (**106**) with the boronic acids (**112**)-(**116**). The two iodoindoles

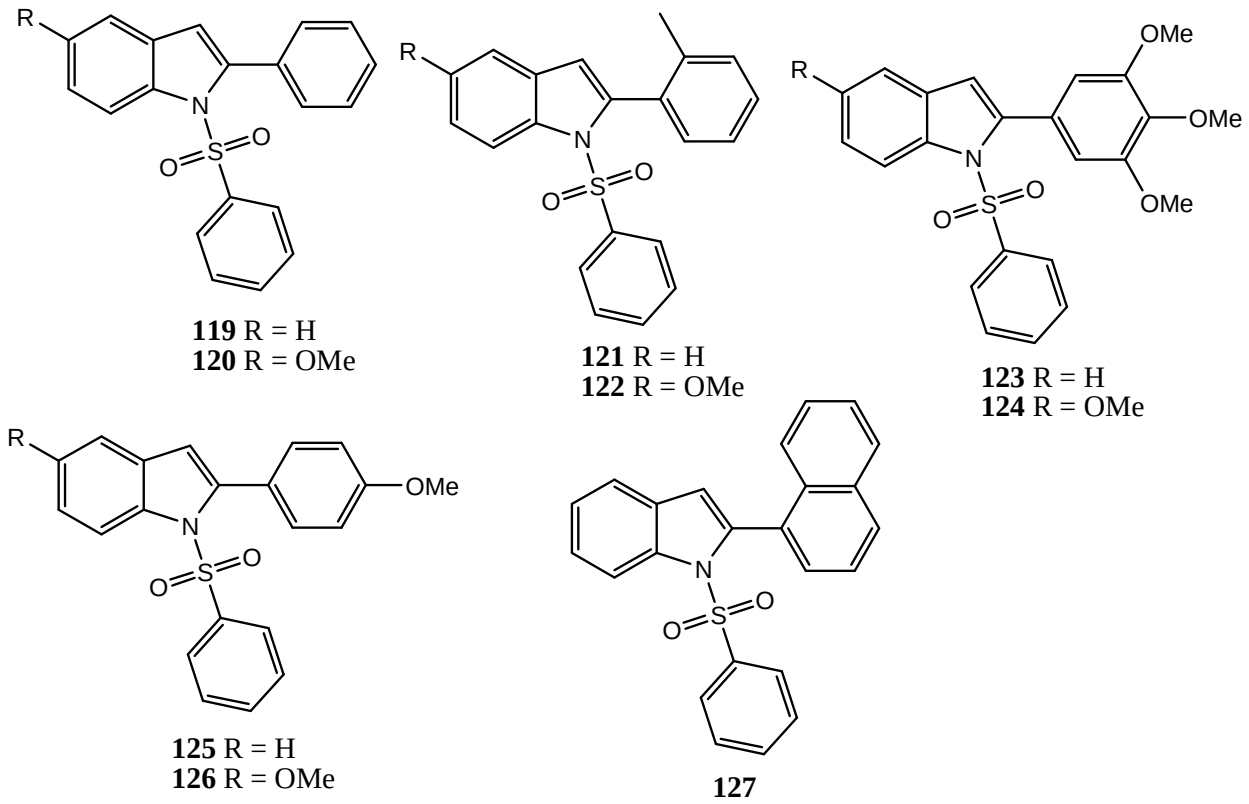
(**105**) and (**106**) were exposed to the boronic acids (**112**)-(**116**) in the presence of catalytic amounts of [$Pd(PPh_3)_4$] and aqueous sodium carbonate and dimethoxyethane/ethanol under reflux to afford the desired cross-coupling products (**119**), (**121**), (**123**), (**125**) and (**127**) for R = H while for R = OMe, the products obtained were (**120**), (**122**), (1**24**) and (**126**) in fair to excellent yields (**Table 2**).

**Table 2**: The % yields of cross-coupling of iodoindoles (**105**) and (**106**) with the boronic acids (**112**)-(**116**)

| R = | Ar | Boronic acid | Product | % yield | $\delta_{3\text{-}H}$ ppm | Melting point °C |
|---|---|---|---|---|---|---|
| H | Phenyl | **112** | **119** | 82 | 6.52 | 100-104 lit. 104-105[64] |
| OMe | Phenyl | **112** | **120** | 60 | 6.48 | Oil |
| H | *o*-Tolyl | **113** | **121** | 44 | 6.46 | Oil |
| OMe | *o*-Tolyl | **113** | **122** | 78 | 6.32 | Oil |
| H | 3,4,5-Trimethoxyphenyl | **114** | **123** | 56 | 6.40 | Oil |
| OMe | 3,4,5-Trimethoxyphenyl | **114** | **124** | 77 | 6.48 | Oil |
| H | *p*-Methoxyphenyl | **115** | **125** | 60 | 6.53 | 209-212 |
| OMe | *p*-Methoxyphenyl | **115** | **126** | 61 | 6.33 | Oil |
| H | 1-Naphthyl | **116** | **127** | 60 | 6.52 | Oil |

The formation of all products was confirmed by $^1H$ and $^{13}C$ NMR spectroscopy. The $^1H$ NMR spectra of (**119**)-(**127**) showed distinct singlet at ~6.00-6.55 ppm (**Table 2**) integrating for one

hydrogen, suggesting that the 2-position of each compound is occupied by a substituent other than hydrogen. The $^{1}$H NMR spectra of (**121**) and (**122**) showed further two singlets at 2.19 and 2.13 ppm respectively each accounting for three hydrogens, thereby suggesting the presence of methyl groups. The $^{1}$H NMR spectra of (**123**) and (**124**) were further characterized by two singlets. Compound (**123**) showed a singlet at 3.85 ppm accounting for nine hydrogens while compound (**124**) showed two singlets at 3.94 ppm accounting for three hydrogens and 3.87 ppm accounting for six hydrogens, hence indicating the presence of methoxy substituents in the compounds. The examination of $^{1}$H NMR spectra of (**125**) and (**126**) also revealed some useful information. Their spectra showed one singlets each at 3.80 and 3.79 ppm respectively each integrating for three hydrogens, suggesting the presence of methoxy substituents in the compounds. The examination of $^{1}$H NMR spectrum of (**127**) showed an increase in number of hydrogens in the aromatic region suggesting the presence of an aromatic system, and in our case, the presence of naphthalene moiety.




**119** R = H
**120** R = OMe

**121** R = H
**122** R = OMe

**123** R = H
**124** R = OMe

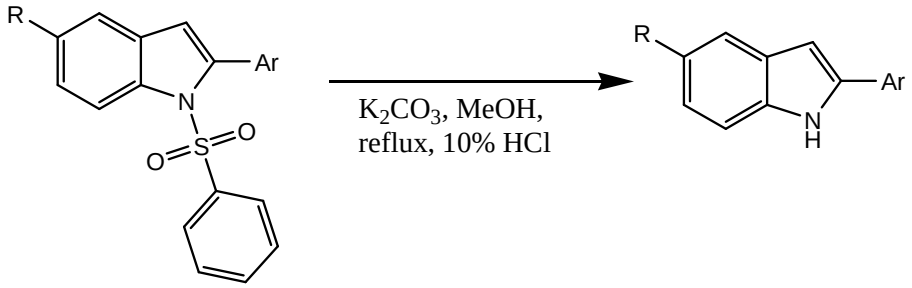
**125** R = H
**126** R = OMe

**127**

**Figure 16**

The $^{13}C$ NMR spectra of these compounds further confirmed the results obtained. The $^{13}C$ NMR spectra of (**119**) and (**120**) showed two quaternary carbons at 115.79 and 131.72 ppm respectively, indicating that the 2-position of the two compounds is occupied and further showed two carbon signals at 114.19 and 103.22 ppm respectively suggesting that the 3-position of the two compounds is bonded to a hydrogen atom. On the other hand, the $^{13}C$ NMR spectra of (**121**) and (**122**) showed one carbon signal each at 20.89 and 20.87 ppm respectively, suggesting the presence of methyl substituents of these compounds. The $^{13}C$ NMR spectra of (**123**) and (**124**) showed two carbon signals each, 62.38 and 57.63 ppm for (**123**), 60.39 and 55.58 ppm for (**124**), all indicating the presence of methoxy groups in these compounds while the $^{13}C$ NMR spectra of (**125**) and (**126**) showed one carbon signals each at 55.75 and 55.26 ppm respectively indicating the presence of methoxy groups of these compounds and overall the $^{13}C$ NMR spectra of all compounds showed an increase in the number of aromatic carbons compared to those observed for starting materials (**105**) and (**106**).

The next step was the removal of the phenylsulfonyl protecting group of the compounds (**119**)-(**127**) discussed above. This was done by treating the solution of the compounds (**119**)-(**127**) in methanol with potassium carbonate under reflux followed by treatment with 10% hydrochloric acid solution and subjection to column chromatography to afford the unprotected compounds (**128**)-(**136**) (**Scheme 32**). The envisaged unprotected compounds (**128**)-(**136**) were produced in good to excellent yields (**Table 3**), and their structures were confirmed by spectroscopy.



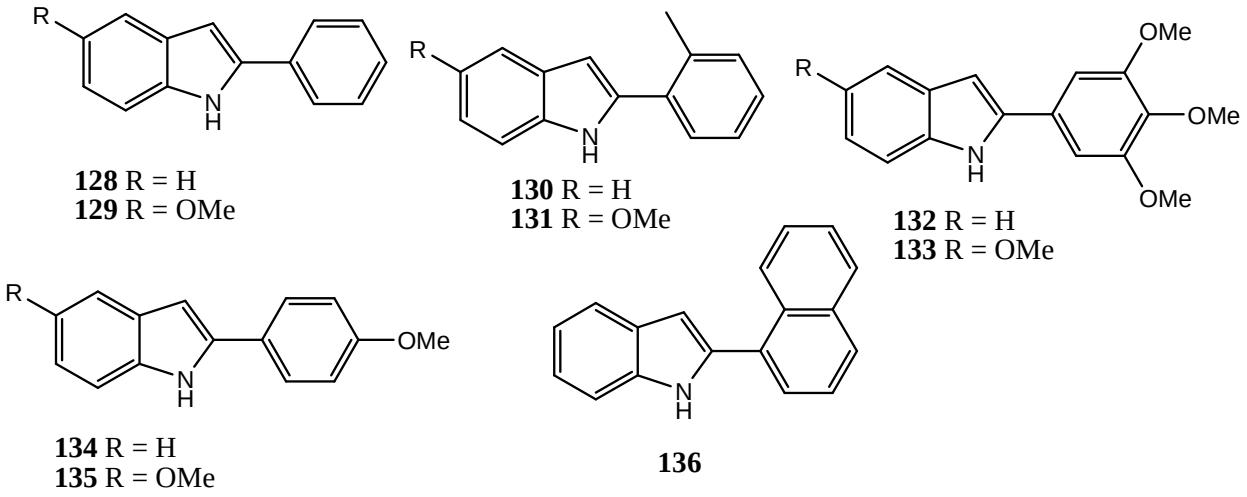

R = H (**119**, **121**, **123**, **125** and **127**)
R = OMe (**120**, **122**, **124** and **126**)

R = H (**128**, **130**, **132**, **134** and **136**)
R = OMe (**129**, **131**, **133** and **135**)

**Scheme 32**

**Table 3**: The % yields of unprotected indoles (**139**)-(**147**)

| R = | Ar | Product | % yield | $\delta_{NH}$ ppm | Melting point °C |
|---|---|---|---|---|---|
| H | Phenyl | 128 | 78 | 8.36 | 182-186 lit. 182-184[79] |
| OMe | Phenyl | **129** | 61 | 8.21 | 162-165 |
| H | *o*-Tolyl | **130** | 82 | 8.04 | 81-85, lit. 92-93[80] |
| OMe | *o*-Tolyl | **131** | 67 | 8.03 | Oil |
| H | 3,4,5-Trimethoxyphenyl | **132** | 51 | 8.42 | 206-209, lit. 205-206.5[81] |
| OMe | 3,4,5-Trimethoxyphenyl | **133** | 86 | 8.38 | 152-155 |
| H | *p*-Methoxyphenyl | **134** | 52 | 11.40 | 228-230, lit. 227-231[82] |
| OMe | *p*-Methoxyphenyl | **135** | 51 | 10.22 | 116-120 |
| H | 1-Naphthyl | **136** | 52 | 8.19 | 96-100, lit. 99-102[83] |




**128** R = H
**129** R = OMe

**130** R = H
**131** R = OMe

**132** R = H
**133** R = OMe

**134** R = H
**135** R = OMe

**136**

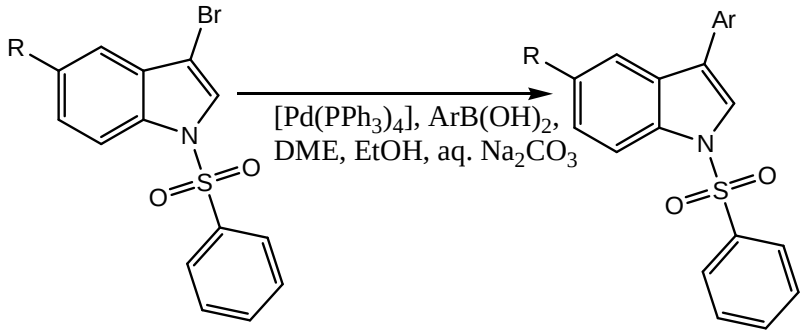
**Figure 17**

The $^{1}$H NMR spectra of all compounds (**128**)-(**136**) showed a decrease in number of protons in the aromatic region, suggesting that the phenylsulfonyl group was no longer present. The spectra further confirmed the results by showing the appearance of a new peak integrating for one hydrogen between 8.00 and 11.50 ppm (**Table 3**), suggesting the presence of NH groups of the indole. The examination of $^{13}$C NMR spectra of compounds (**128**)-(**136**) showed a decrease in number of carbon signals in the aromatic region, also suggesting that the phenylsulfonyl group was no longer present. A further confirmation of these results was also made through infrared spectroscopy. The infrared spectroscopy of compounds (**128**)-(**136**) showed medium to strong broad peak at a range of 3300-3450 wavenumbers, suggesting the presence of NH group in these compounds.

### 2.2.3 Suzuki-Miyaura cross-coupling of bromoindoles (107) and (109) followed by deprotection

After the successful synthesis of 2-arylindoles, the next step was to synthesize 3-arylindoles. This was achieved because compounds (**107**) and (**108**) were successfully synthesized and

characterized as discussed previously. To achieve the synthesis of 3-aryindoles, the two compounds (**107**) and (**109**) were exposed to the boronic acids (**112**)-(**116**) and the other two boronic acids (**117**) and (**118**) as shown in **Figure 15** in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ and aqueous sodium carbonate and dimethoxyethane/ethanol under reflux to afford the desired cross-coupling products (**150**)-(**161**). The products obtained for R = H were (**137**), (**139**), (**141**), (**143**), (**145**) and (**147**) while the ones obtained for R = OMe were (**138**), (**140**), (**142**), (**144**), (**146**) and (**148**) and they were obtained in good to excellent yields (**Table 4**). The structures are shown in **Figure 18**.




R = H (**107**)
R = OMe (**109**)

R = H (**137**, **139**, **141**, **143, 145,** and **147**)
R = OMe (**138**, **140**, **142, 144, 146** and **148**)

**Scheme 33**

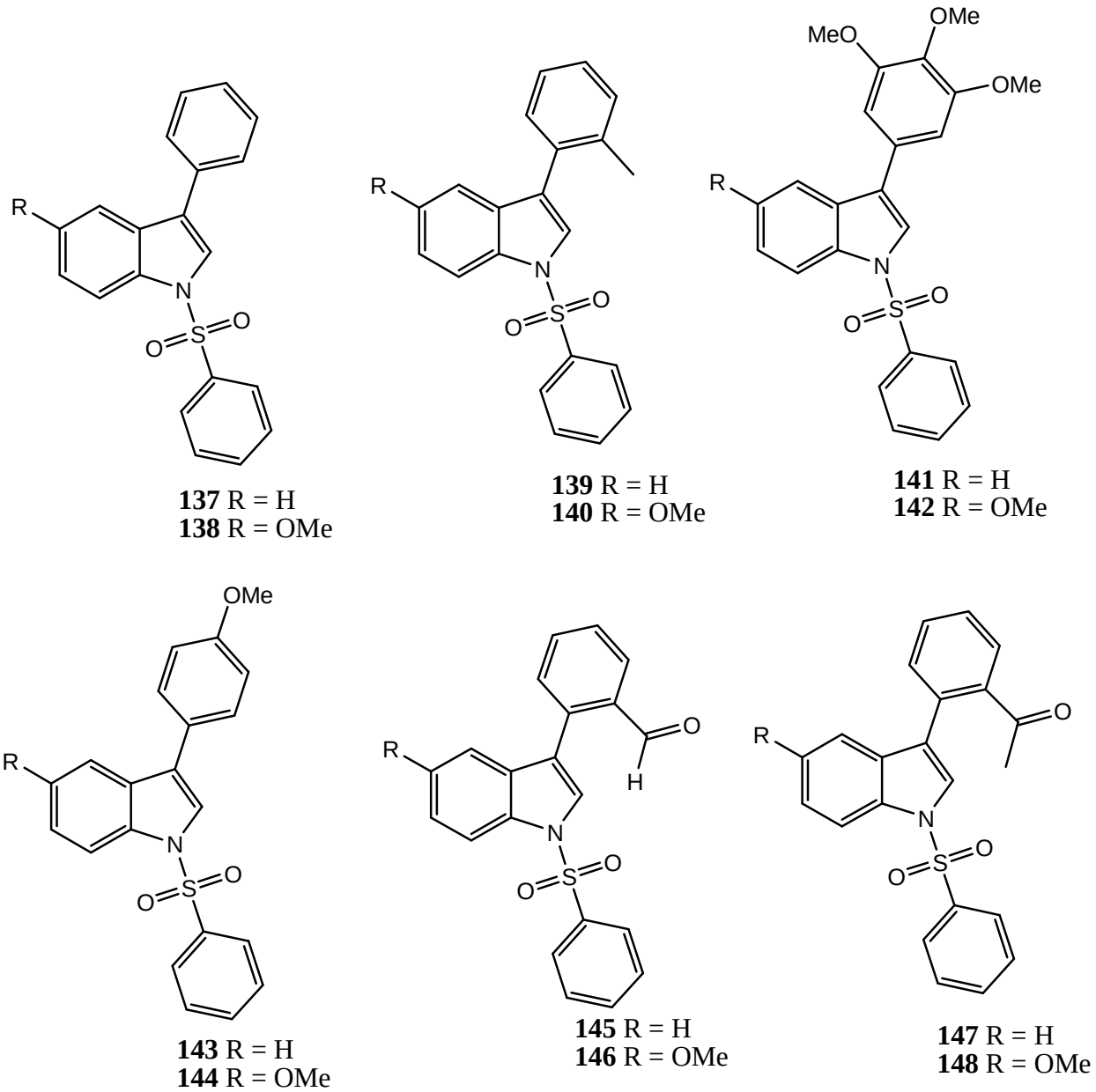
**Table 4**: The % yields of cross-coupling of (**107**) and (**109**) with boronic acids (**112**)-(**118**)

| R = | Ar | Boronic acid | Product | % yield | $\delta_{2\text{-H}}$ ppm | Melting point °C |
|---|---|---|---|---|---|---|
| H | Phenyl | **112** | **137** | 81 | 7.70 | 139-142, lit. 141-143[64] |
| OMe | Phenyl | **112** | **138** | 85 | 7.65 | Oil |

| | | | | | | |
|---|---|---|---|---|---|---|
| H | *o*-Tolyl | **113** | **139** | 64 | 7.87 | Oil, lit. Oil[56] |
| OMe | *o*-Tolyl | **113** | **140** | 86 | 7.41 | 111-114, lit. 127-128[56] |
| H | 3,4,5-Trimethoxyphenyl | **114** | **141** | 65 | 7.67 | Oil |
| OMe | 3,4,5-Trimethoxyphenyl | **114** | **142** | 72 | 7.47 | 132-136 |
| H | *p*-Methoxyphenyl | **115** | **143** | 79 | 7.63 | 132-137, lit Oil[84] |
| OMe | *p*-Methoxyphenyl | **115** | **144** | 72 | 7.58 | Oil |
| H | 2-Formylphenyl | **117** | **145** | 72 | 7.68 | Oil |
| OMe | 2-Formylphenyl | **117** | **146** | 94 | 7.59 | 129-132 |
| H | 2-Acetylphenyl | **118** | **147** | 92 | 7.46 | Oil |
| OMe | 2-Acetylphenyl | **118** | **148** | 82 | 7.42 | 105-109 |

Compounds (**137**)-(**148**) were characterized and the identity confirmed by spectroscopic techniques. Examination of the $^{1}$H NMR spectra of compounds (**137**)-(**148**) showed a distinctive singlet for the hydrogens at C-2 between 7.00 and 7.80 ppm, suggesting that the 3-position in the compounds was a substituent other than hydrogen. The spectra further showed an increase in number of hydrogens in the aromatic region, suggesting the presence of extra aromatic signals in comparison with the starting materials (**107**) and (**109**). The $^{1}$NMR spectrum of (**137**) showed a singlet at 7.69 ppm and a distinct doublet at 7.60 ppm due to the presence of phenyl ring at the 3-position of (**137**) while that of (**138**) showed a singlet at 7.65 ppm and a distinct doublet at 7.57 ppm also due to the presence of the phenyl at the 3-position of (**138**). The $^{1}$H NMR spectra of (**139**) and (**140**) showed one distinct singlet each at 2.21 ppm for (**139**) and 2.19 ppm for (**140**), each accounting for three hydrogens, suggesting the presence of a methyl substituent in the compounds (**139**) and (**140**). Further examination of the $^{1}$H NMR spectra of (**141**) and (**142**)

revealed a singlet at 6.80 ppm for (**141**) integrating for two hydrogens and a singlet at 3.91 ppm accounting for nine hydrogens indicating the presence of three methoxy substituents of (**141**) while that of (**142**) revealed a singlet at 6.77 ppm accounting for two hydrogens and further showed an additional two singlets at 3.91 ppm, accounting for six hydrogens and 3.90ppm accounting for three hydrogens, both indicating the presence of the extra three methoxy substituents of (**142**).




**137** R = H
**138** R = OMe

**139** R = H
**140** R = OMe

**141** R = H
**142** R = OMe

**143** R = H
**144** R = OMe

**145** R = H
**146** R = OMe

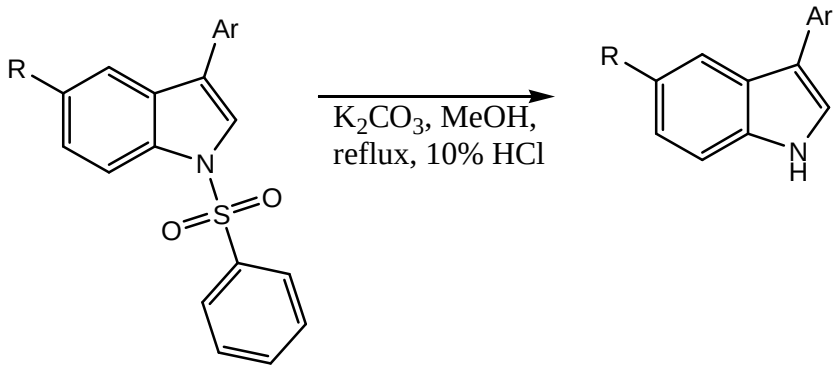
**147** R = H
**148** R = OMe

**Figure 18**

The $^{1}$H NMR spectra of (**143**) and (**144**) showed two singlets each, accounting for one hydrogen at 7.63 ppm for (**143**) and 7.58 ppm for (**144**) suggesting that the 3-position of the compounds was occupied and they further showed two singlets at 3.85 ppm for (1**43**) and 3.86 ppm for (**144**) each integrating for three hydrogens, suggesting the presence of methoxy substituents in the compounds. The $^{1}$H NMR spectra of (**145**) and (**146**) showed two singlets at 9.90 and 9.87 ppm respectively, each accounting for one hydrogen, suggesting the presence of aldehydes of the compounds and the $^{1}$H NMR spectra of (**147**) and (**148**) revealed two singlets at 1.90 and 1.87 ppm respectively, each integrating for three hydrogens, indicating the presence of the acetyl group in the compounds.

The examination of the $^{13}$C NMR spectra of compounds (**137**)-(**148**) showed an increase in the number of carbon signals in the aromatic region in comparison with those of the starting materials (**107**) and (**109**). The $^{13}$C NMR spectra of (**139**) and (**140**) showed two distinct carbon signals at 20.80 and 20.78 ppm respectively, supporting the $^{1}$H NMR, suggesting the presence of methyl groups on (**139**) and (**140**). Two carbon signals at 59.26 and 54.53 ppm suggesting the presence of methoxy groups were observed on the $^{13}$C NMR spectrum of (**141**) and the examination of the $^{13}$C NMR spectrum of (**142**) also revealed two distinct carbon signals at 60.41 and 55.73 ppm, indicating the presence of methoxy groups on (**142**). Further examination of the $^{13}$C NMR spectra of (**143**) and (**144**) showed two carbon signals at 55.41 and 55.79 ppm suggesting the presence of methoxy groups on (**143**) and (**144**) while the $^{13}$C NMR spectra of (**145**), (**146**), (**147**) and (**148**) showed distinct carbon signals at 192.00, 192.11, 203.89 and 204.21 ppm respectively, which are characteristic of a carbonyl groups. The $^{13}$C NMR spectra of (**147**) and (**148**) also showed two distinct carbon signals at 30.14 and 30.11 ppm which is indicative of the presence of methyl groups on (**147**) and (**148**). The results of the formation of (**145**), (**146**), (**147**) and (**148**) were further supported by the information from infrared spectroscopy. The infrared spectra of (**145**), (**146**), (**147**) and (**148**) showed strong absorption peaks at 1693, 1681, 1685 and 1690 wavenumbers respectively, confirming the presence of carbonyl groups of the products.

After the successful synthesis of compounds (**137**)-(**148**), the next step was to remove the phenylsulfonyl protecting group of these compounds. This would be achieved as before by treating the solutions of compounds (**137**)-(**148**) in methanol with potassium carbonate under reflux followed by treatment with 10% hydrochloric acid and subjection to column chromatography afforded unprotected indoles (**149**)-(**160**) (**Scheme 34**). The envisaged unprotected indoles (**149**)-(**160**) were produced in good to excellent yields (**Table 5**) and their structures were confirmed by spectroscopic techniques.




R = H (**137**, **139**, **141**, **143, 145,** and **147**)
R = OMe (**138**, **140**, **142, 144, 146** and **148**)

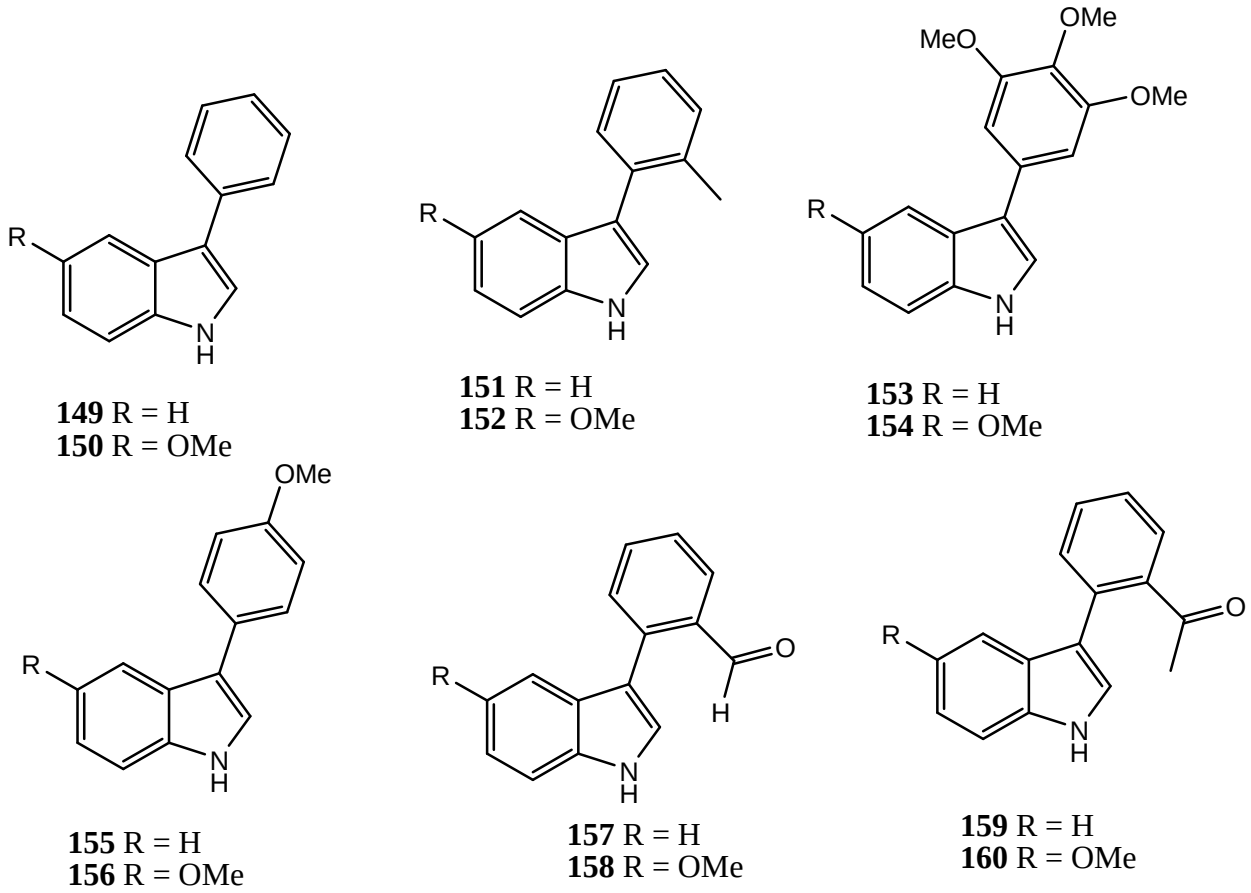
R = H (**149**, **151**, **153**, **155**, **157** and **159**)
R = OMe (**150**, **152**, **154**, **156**, **158** and **160**)

**Scheme 34**

**Table 5**: The % yields of unprotected indoles (**149**)-(**160**)

| R = | Ar | Product | % yield | $\delta_H$ ppm | Melting point °C |
|---|---|---|---|---|---|
| H | Phenyl | **149** | 81 | 8.17 | 86-89, lit. 89[85] |
| OMe | Phenyl | **150** | 85 | 8.01 | Oil, lit. 66-67[86] |
| H | *o*-Tolyl | **151** | 64 | 8.17 | Oil, li. Oil[56] |

| | | | | | |
|---|---|---|---|---|---|
| OMe | *o*-Tolyl | **152** | 86 | 8.11 | Oil, lit. Oil[56] |
| H | 3,4,5-Trimethoxyphenyl | **153** | 65 | 8.35 | Oil |
| OMe | 3,4,5-Trimethoxyphenyl | **154** | 72 | 8.46 | Oil |
| H | *p*-Methoxyphenyl | **155** | 79 | 8.13 | 130-134, lit. 131-133[87] |
| OMe | *p*-Methoxyphenyl | **156** | 72 | 8.10 | Oil, lit. 151.2-152[88] |
| H | 2-Formylphenyl | **157** | 72 | 8.61 | Oil |
| OMe | 2-Formylphenyl | **158** | 95 | 8.51 | Oil |
| H | 2-Acetylphenyl | **159** | 92 | 8.61 | Oil |
| OMe | 2-Acetylphenyl | **160** | 82 | 8.56 | 116-120 |




**149** R = H
**150** R = OMe

**151** R = H
**152** R = OMe

**153** R = H
**154** R = OMe

**155** R = H
**156** R = OMe

**157** R = H
**158** R = OMe

**159** R = H
**160** R = OMe

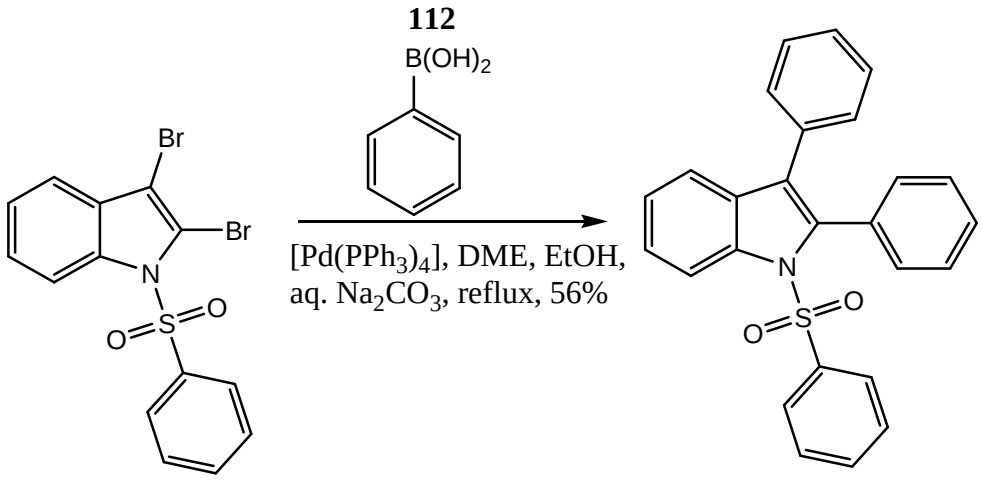
**Figure 19**

The formation of compounds (**149**)-(**160**) was confirmed by the $^{1}$H NMR spectra in which the singlet between 8.00 and 8.65 ppm (**Table 5**) accounting for one hydrogen indicating the presence of the indole NH group. The results were further confirmed by $^{1}$H NMR spectra of the compounds when they showed a decrease in number of hydrogens in the aromatic region suggesting the removal of the phenylsulfonyl protecting group. When the $^{13}$C NMR spectra of (**149**)-(**160**) were examined, a decrease in the number of carbon signals in the aromatic region was noted further suggesting the removal of the phenylsulfonyl protecting group. The infrared spectra of these compounds further supported the results by showing medium to strong

absorption in the range of 3200-3480 wavenumbers suggesting the presence of NH group in these compounds.

### 2.2.4 Suzuki-Miyaura cross-coupling of dibromindole (108) followed by deprotection

The next step was to attempt the synthesis of 2,3-disubstituted indoles by using the 2,3-dibromoindole (**108**) as the starting material with the hope of producing 2,3-diaryl substituted indoles.

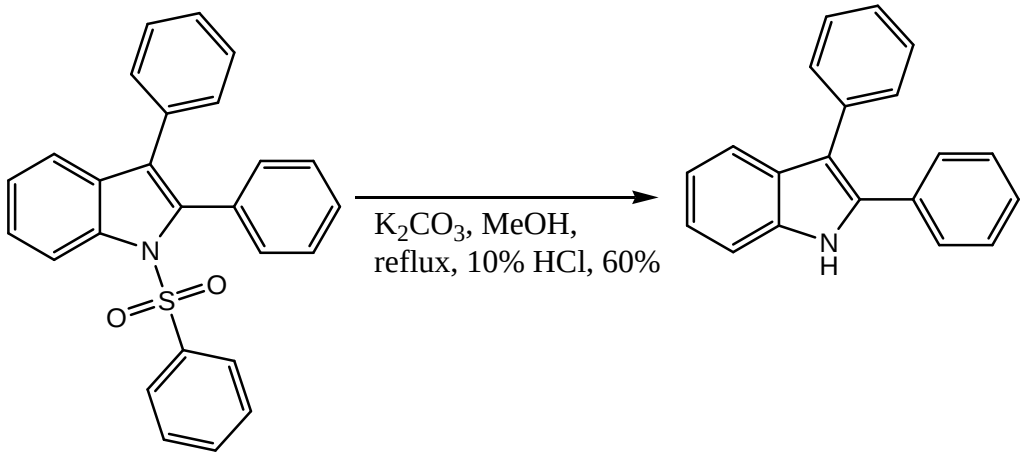



**108** **161**

**Scheme 35**

Compound (**108**) was successfully synthesized and characterized as described in section **2.1.4** of this project. After the synthesis of (**108**), the next step required was to perform the Suzuki-Miyaura cross-coupling reaction with the boronic acids (**112**)-(**116**) (**Table 1**), however only phenylboronic acid (**112**) shown in **Scheme 35** was successfully utilized in the cross-coupling reaction. Presumably the other boronic acids were not successful as a result of steric factors, Heck trapping or electron withdrawing groups for (**114**) and (**115**) in placing two substituted aryl substituents in adjacent positions on the indole nucleus. Compound (**108**) was treated with boronic acid (**112**) in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ and aqueous sodium

carbonate and dimethoxyethane/ethanol under reflux to afford the desired cross-coupling product (**161**) in 56% yield (**Scheme 35**) as a cream white solid with melting point 173-175 °C with literature melting point of 174-176 °C[69]. The formation of (**161**) was confirmed by spectroscopy. The $^{1}$H NMR spectrum showed that the number of hydrogens in the aromatic region has increased, suggesting the presence of extra aromatic systems in comparison with the starting material (**108**). This was further supported by the $^{13}$C NMR spectrum which also showed that the number of carbon signals in the aromatic region has increased.




**161** **162**

**Scheme 36**

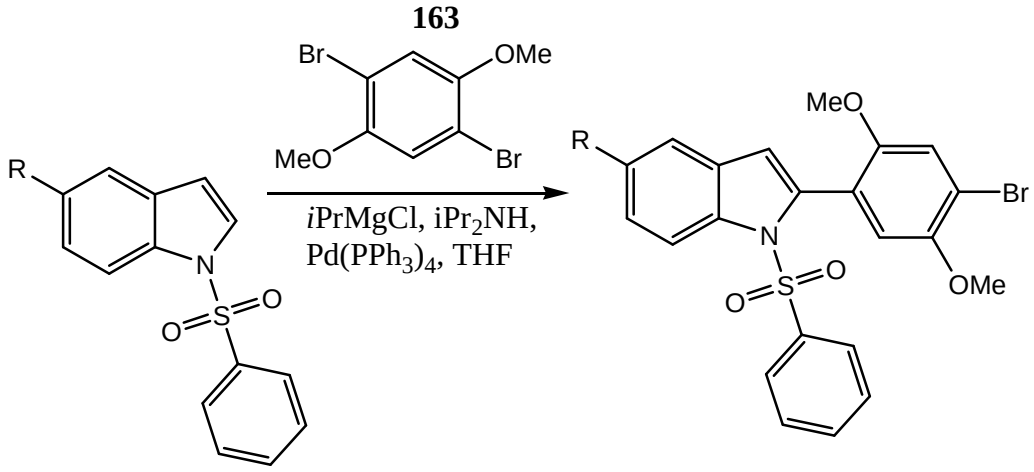
The next step was to remove the protecting group of (**161**). This was be achieved by treating the solution of compound (**161**) in methanol with potassium carbonate under reflux followed by treatment with 10% hydrochloric acid and subsequent column chromatography to afford (**162**) in 60% yield as a yellow solid with melting point 224-227 °C (**Scheme 36**). The formation of (**162**) was verified by spectroscopic techniques. The examination of the $^{1}$H NMR spectrum of (**162**) showed a decrease in number of hydrogens in the aromatic region which is indicative of the removal of the phenylsulfonyl protecting group and a singlet at 8.21 ppm integrating for one hydrogen, indicating the presence of the indole NH group. This was further supported by the $^{13}$C NMR spectrum which showed that the number of carbon signals in the aromatic region has

decreased in comparison with that of the starting material (**161**). The infrared spectrum of (**162**) showed a medium-intensity absorption peak at 3461 wavenumbers, indicating the presence of the indole NH group of (**162**).

## 2.3 Synthesis of 2-arylindoles via one-pot synthesis

The next step in the preparation of 2-arylsubstituted indoles was to attempt their construction without first preparing the 2-halogenated indoles. This would remove the need to form halogenated precursors. Fewer steps would then be needed in the synthesis and the use of reagents used for the introduction of a halogen would no longer be necessary. This can be important as often these reagents are toxic and especially from an industrial point of view their elimination is highly desirable.

### 2.3.1 Synthesis of 2-(4-bromo-2,5-dimethoxyphenyl)-1-(phenylsulfonyl)-1*H*-indole (164) and 2-(4-bromo-2,5-dimethoxyphenyl)-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (165) followed by deprotection



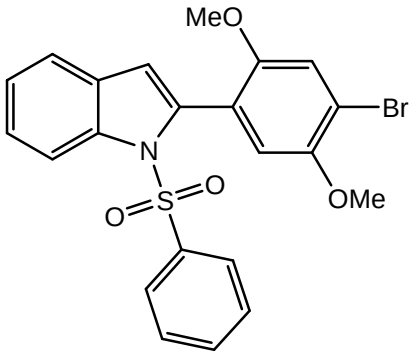

R = H (**36**)
R = OMe (**104**)

R = H (**164**) 21%
R = OMe (**165**) 35%

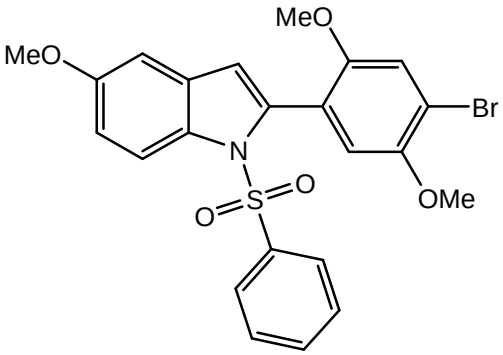
**Scheme 37**

As shown in **Scheme 37**, 2-substituted indoles were successfully synthesized via organomagnesium intermediate, made by treating the indole with magnesium amide base. Either previously prepared (**36**) or (**104**) was treated with isopropylmagnesium chloride and a catalytic amount of diisopropylamine in tetrahydrofuran at room temperature. The reaction mixture was stirred for 16 hours before being treated with 1,4-dibromo-2,5-dimethoxybenzene (**163**) in the presence of palladium(0) catalyst ($Pd(PPh_3)_4$) and the reaction mixture was left to stir for another 48 hours. After this time, the reaction mixture was quenched by the addition of saturated solution of aqueous ammonium chloride and then worked up. Following the work up, the excess solvent was removed, resulting in a black oil that was subjected to column chromatography and recrystallized from the mixture of dichloromethane and diethyl ether which gave white solids for both (**164**) and (**165**) in low yields with melting points of 181-183 °C and 159-162 °C respectively.

The $^{1}H$ NMR spectrum of (**164**) was characterized by two singlets at 7.13 and 6.77 ppm each integrating for one hydrogen belonging to hydrogens on the newly introduced benzene ring of (**164**). The spectrum also showed a singlet at 6.58 ppm integrating for one hydrogen, which belongs to the 3-position of the indole nucleus (**164**). The identity of the product was further proved by the presence of two singlets at 3.82 and 3.68 ppm, each accounting for three hydrogens, indicating the presence of methoxy group of (**164**). The $^{13}C$ NMR spectrum of (**164**) also proved the results by showing two distinctive carbons signals at 57.36 and 56.54 ppm indicating the presence of methoxy groups supported by their respective quaternary carbons at 153.08 and 149.63 ppm.




**164**

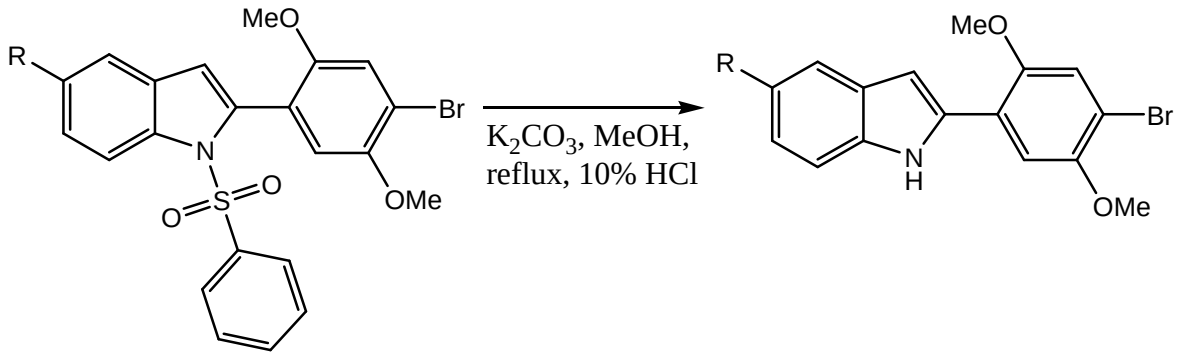



**165**

**Figure 20**

The formation of (**165**) was confirmed by the $^{1}$H NMR spectrum where two singlets each integrating for one hydrogen at 7.13 and 6.78 ppm were observed. The presence of a singlet at 6.52 ppm accounting for one hydrogen belongs to the hydrogen on the 3-position of indole (**165**). One singlet at 3.82 ppm accounting for six hydrogens and another singlet at 3.69 ppm accounting for three hydrogens indicating the presence of three methoxy groups on (**165**). The $^{13}$C NMR spectrum further confirmed the results by showing three carbon signals at 57.36, 56.56 and 56.05 ppm supported by their respective quaternary carbons at 157.24, 152.97 and 149.62 ppm indicating the presence of the three methoxy groups on (**165**).

After the synthesis of (**164**) and (**165**) (**Scheme 37**), we then attempted to remove the phenylsufonyl protecting group. This was done by treating the solutions of the compounds (**164**) and (**165**) in methanol with potassium carbonate under reflux followed by treatment with 10% hydrochloric acid solution and subjection to column chromatography to afford the unprotected compounds (**166**) and (**167**) (**Scheme 38**). The envisaged unprotected compounds were produced in moderate yields.




R = H **(164**) 21%
R = OMe (**165**) 35%

R = H **(166**) 52%
R = OMe (**167**) 40%

**Scheme 38**

The formation of (**166**) and (**167**) was also confirmed by spectroscopy. The $^{1}$H NMR spectra of (**166**) and (**167**) showed a decrease in the number of hydrogens in the aromatic region, suggesting that the phenylsulfonyl group was removed. The spectra further supported the formation of (**166**) and (**167**) by showing one singlet for each at ~9.00 ppm. The peak positions were 9.63 ppm for (**166**) and 9.54 ppm for (**167**), indicating the presence of NH groups of the indole. The $^{13}$C NMR spectra of (**166**) and (**167**) further agreed with the results from $^{1}$H NMR spectra by showing that the number of carbons in the aromatic region has decreased, suggesting that the phenylsulfonyl group was no longer present. The infrared spectroscopy of (**166**) showed a medium-sized signal at 3450 wavenumbers and that of (**167**) showed a signal at 3397 wavenumbers, both suggesting the presence of the NH group.

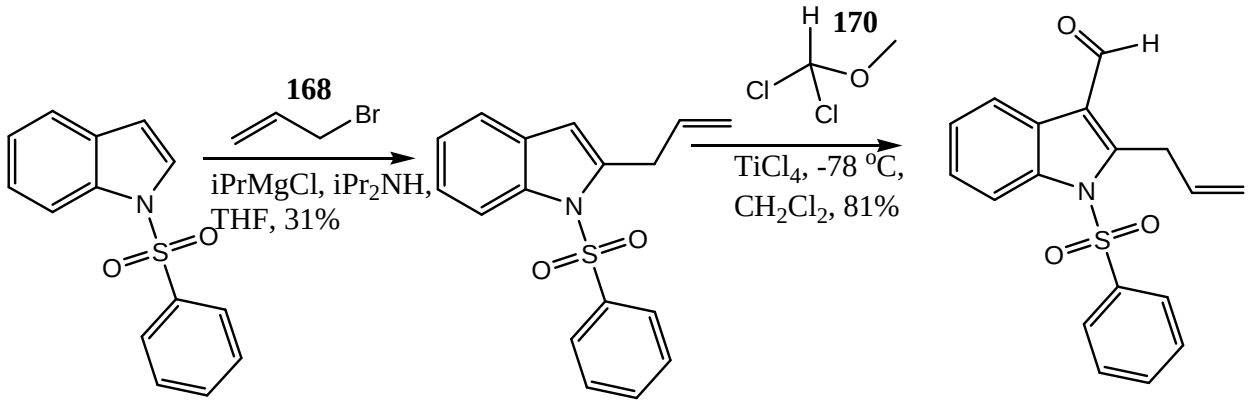
## 2.4 Synthesis of indolopyrans

Substituted pyrans are ubiquitous structural elements in natural products, and some have important biological activity[71]. Their derivatives are often important intermediates in the synthesis of many natural products[72]. Apart from their biological activity, pyrans such as diaryl-

benzopyrans and naphthopyrans display highly desirable photochromic properties[73]. We wished to construct the pyran ring onto the 2- and 3-position of the indole nucleus using the methodology developed in our laboratories. This would represent a novel pyran fused to an indole nucleus.

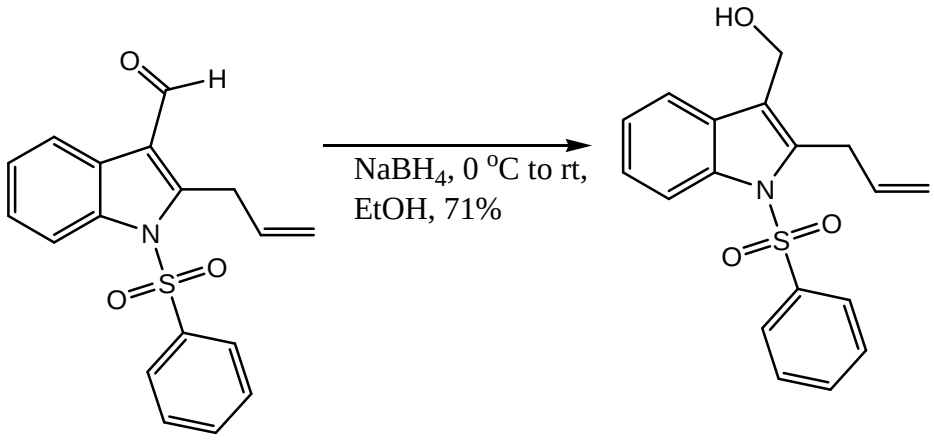
### 2.4.1 Synthesis of 2-allyl-1-(phenylsulfonyl)-1*H*-indole (169) and 2-Allyl-1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde (171)

In order to construct the desired indolopyrans, substituents needed to be introduced at both the 2- and 3- position. Metallation at the 2-position of indole, for example using lithiation as a synthetic route to 2-substituted indoles, has been studied extensively. Owing to the low temperatures required for lithiating reagents and their instability including that of their intermediates, methods have been developed that use reagents that are more stable. Recently metallation of indoles using magnesium amide bases and their extension has been reported[27, 28]. In our laboratories, when (**36**) was treated with *iso*propylmagnesium chloride and allyl bromide (**168**) in the presence of catalytic amount of diisopropylamine, followed by quenching with saturated solution of aqueous ammonium chloride it gave a brown oil (**Scheme 39**). The oil was then subjected to column chromatography and the resultant solid recrystallized from a mixture of dichloromethane and diethyl ether to give (**169**) as a white solid in poor yield of 31% with melting point 88-91 °C. The formation of (**169**) was confirmed by the $^{1}$H NMR spectrum which showed a distinct singlet at 6.40 ppm accounting for one hydrogen which belongs to the 3-position of (**169**). This was further confirmed by a multiplet at 6.08-5.96 ppm accounting for one hydrogen, another multiplet at 5.22-5.16 ppm accounting for two hydrogens and a triplet at 3.78-3.76 ppm integrating for two hydrogens, indicating the presence of an allyl group. The $^{13}$C NMR spectrum further confirmed the results by showing two distinct carbon signals in the aromatic region at 134.06 and 118.22 ppm and one at 33.78 ppm which also indicate the presence of allyl group of (**169**).


168
Br
iPrMgCl, iPr2NH,
THF, 31%
H 170
Cl
O
Cl
TiCl4, -78 °C,
CH2Cl2, 81%
O
H
N
S
O
O
O

### 2.4.2 Synthesis of (2-allyl-1-(phenylsulfonyl)-1*H*-indol-3-yl) methanol (172)

After the successful synthesis of (**171**), the next step was to reduce the aldehyde to alcohol. Due to the reactivity of aldehydes, sodium borohydride is usually employed in this regard. The reduction with sodium borohydride should be carried out at lower temperatures due the heat released during the reaction and requires that sodium borohydride be added in portions[76]. Compound (**171**) was treated with sodium borohydride at 0 °C in ethanol and the reaction mixture was stirred for 6h. After this time, the solvent was removed under reduced pressure and the resulting white solid shaken up with 5% aqueous solution of sodium hydroxide and extracted with dichloromethane to give (**172**) as a yellow oil in 71% yield.




**171** **172**

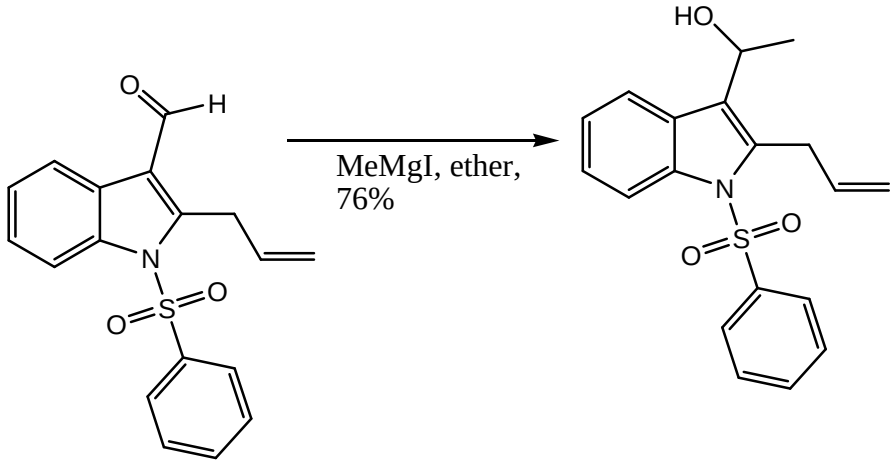
**Scheme 40**

The literature reported that (**172**) was isolated as solid with melting point 82-83 °C[76]. The $^{1}$H NMR spectrum of (**172**) showed that the aldehyde peak had disappeared and the appearance of new broad singlet at 1.96 ppm suggesting the presence of the OH group on the desired product. This was further confirmed by the presence of another new singlet at 4.62 ppm, suggesting the presence of the methylene of the desired product. An investigation of the $^{13}$C NMR spectrum

showed that the carbonyl peak had disappeared, and there was a new carbon signal at 53.82 ppm again indicating the presence of the methylene substituent bearing oxygen. The infrared spectrum showed a broad absorption at 3406 wavenumbers which clearly suggests the presence of OH group on the desired product (**172**).

### 2.4.3 Synthesis of 1-(2-allyl-1-(phenylsulfonyl)-1*H*-indol-3-yl) ethanol (173)

After the successful synthesis of (**172**), we wanted to attempt the synthesis of similar alcohols. When (**172**) was synthesized, $NaBH_4$ was used as a source of hydrogen for the reduction of the aldehyde. We attempted the synthesis of alcohol (**173**) using a Grignard reagent to added to the aldehyde (**171**) and in this case, methylmagnesium iodide in THF was used.




**171** **173**

**Scheme 41**

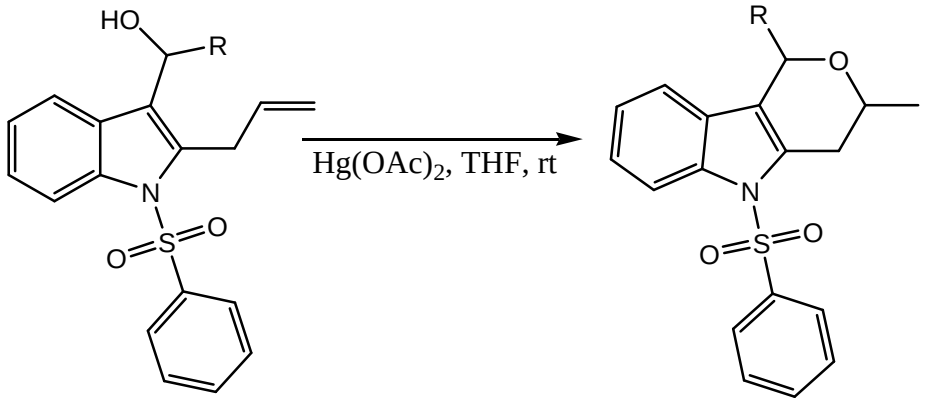
Methylmagnesium iodide was prepared *in situ* from dry magnesium turnings and methyl iodide in ether. The resulting solution was then treated with the solution of (**171**) in ether. The reaction

mixture was left to stir overnight before being quenched with saturated aqueous ammonium chloride solution followed by work up to give alcohol (**173**) as a yellow oil in 76% yield.

The $^{1}$H NMR spectrum of (**173**) showed that the aldehyde peak that was at 10.31 ppm for (**171**) had disappeared. The $^{1}$H NMR also showed a multiplet at 5.04-4.92 ppm accounting for one hydrogen, a doublet at 1.56-1.54 ppm suggesting the presence of a methyl substituent on (**173**) and a broad singlet at 1.91 ppm accounting for one hydrogen suggesting the presence of OH group on (**173**). This was further confirmed by infrared spectrum which showed a broad peak at 3567 wavenumbers suggesting the presence of OH group. An examination of the $^{13}$C NMR spectrum showed two distinctive carbon signals, one at 64.56 ppm which suggests the presence of methylene related substituent and another at 30.44 ppm which suggests the presence of a methyl substituent.

### 2.4.4 Synthesis of 3-methyl-5-(phenylsulfonyl)-1,3,4,5-tetrahydropyrano[4,3-*b*]indole (174) and 1,3-dimethyl-5-(phenylsulfonyl)-1,3,4,5-tetrahydropyrano[4,3-*b*]indole (175)

After the successful synthesis of alcohols (**172**) and (**173**), the next step was to perform the ring closure reaction to afford a novel compound, a pyran-fused indole. The two alcohols were treated with mercury acetate in tetrahydrofuran at room temperature. The reaction mixture was left to stir for 38 hours after which it was quenched with mixture of aqueous sodium hydroxide and sodium borohydride whilst stirring and the reaction mixture was stirred for further 1h before the addition of aqueous solution of sodium carbonate (**Scheme 42**). The reaction mixture was allowed to stand and worked up according to literature procedures[77]. This gave (**174**) as clear solid with melting point 145-148 °C and (**175**) as a clear oil.




R = H (**172**)
R = Me (**173**)

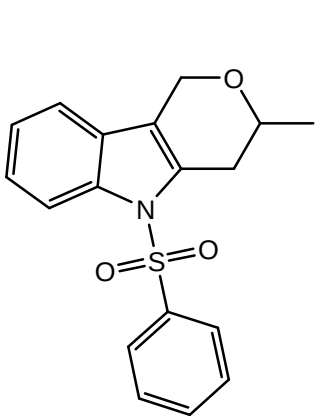
R = H (**174**) 31%
R = Me (**175**) 25%

**Scheme 42**

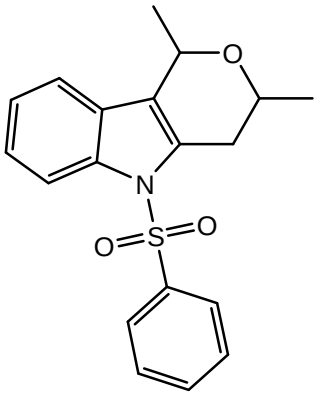
The formation of (**174**) was confirmed by $^{1}$H NMR spectroscopy which showed that the broad singlet has disappeared. It also showed a multiplet at 5.19-5.04 ppm integrating for two hydrogens, a multiplet at 4.17-4.10 ppm accounting for one hydrogen, a multiplet at 3.56-3.50 accounting for one hydrogen, another multiplet at 3.16-3.07 ppm accounting for one hydrogen and finally a doublet at 1.78-1.74 ppm accounting for three hydrogens. The identity of the product was further confirmed by $^{13}$C NMR spectrum which showed the alkene carbons that previously were in the aromatic region had disappeared. It also showed two carbon signals at 69.81 and 62.15 ppm which suggests the presence of carbons that are bonded to oxygen, another two carbon signals at 31.78 and 20.38 ppm which probably suggests the presence of methyl and methylene groups on (**174**).

The $^{1}$H NMR of (**175**) also showed the disappearance of the broad singlet peak. It also showed multiplets at 5.10-5.04 ppm, 4.14-4.08 ppm, 3.26-3.16 and 2.85-2.69 ppm, each accounting for one hydrogen and finally two doublets at 1.56-1.54 and 1.40-1.38 ppm which clearly suggest the presence of two methyl substituents on the desired product (**175**). The $^{1}$H NMR also suggested the presence of the two isomers, with one isomer more than the other but this has to be correctly determined. Further confirmation of the results was obtained from the $^{13}$C NMR spectrum of

(**175**) which showed that alkene carbons that were observed in the aromatic region disappeared. It also showed two carbon signals at 67.55 and 64.04 ppm which suggests the presence of carbons that are bonded to oxygen, one carbon signal at 32.54 ppm which suggests the presence of a methylene substituent and two carbon signals at 21.19 and 19.98 ppm which suggest the presence of two methyl substituents on (**175**). The two compounds (**174**) and (**175**) were obtained in low yields. I was later found that the compounds stick to the silica during the filtration of mercury and purification stage. One should take care and make sure more solvent is used to get the product especially during the filtration process.




**174**



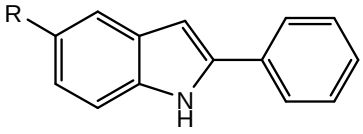

**175**

**Figure 21**

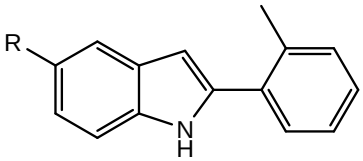
In summary, we managed to synthesis 2-allylindoles using isopropylmagnesium chloride and isopropylamine. The synthesis of 2-allyindole was followed by the formylation to afford 2-allyl-3-formylindoles which were later reduced to afford the respective alcohols was a success. In addition to the alcohols, we managed to cyclize the alcohols to construct indolo-fused pyrans, a novel class of compounds.

# Chapter 3: Conclusion and Future Work

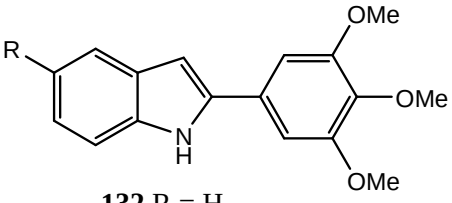
During the course of this MSc we managed to synthesis 2-arylindoles (**128**)-(**136**) in fair to excellent yields. The 2-arylindoles (**128**)-(**136**) were synthesized in three steps starting from 2-iodo-1-(phenylsulfonyl)-1*H*-indole (**105)** or 2-iodo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**106**) while (**166**) and (**167**) were synthesized in two steps starting from (**36**) and (**104**) respectively in a one-pot synthesis to the removal of the phenylsulfonyl protecting group. The future work on this will include improving the yields of the protected compounds (**120**), (**121**), (**123**), (**125**)-(**127**) and unprotected compounds (**129**), (**131**), (**132**), and (**134**)-(**136**). We will be submitting the compounds (**128**)-(**136**) for testing against cancer cells and malarial cell lines.



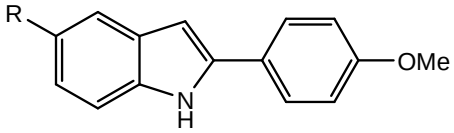

**128** R = H
**129** R = OMe



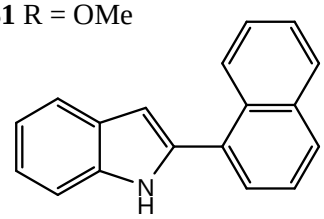

**130** R = H
**131** R = OMe




**132** R = H
**133** R = OMe




**134** R = H
**135** R = OMe

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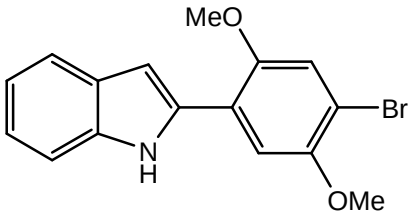
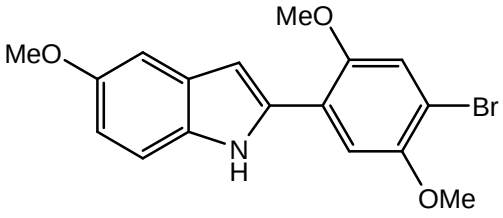
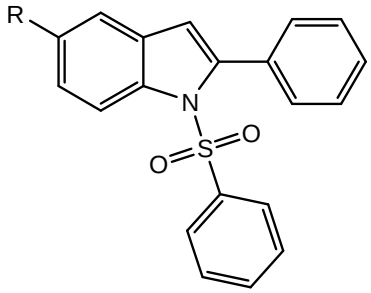


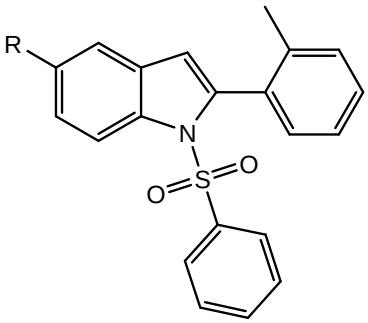

**166**



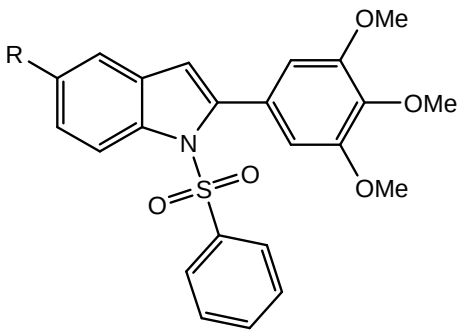

**167**



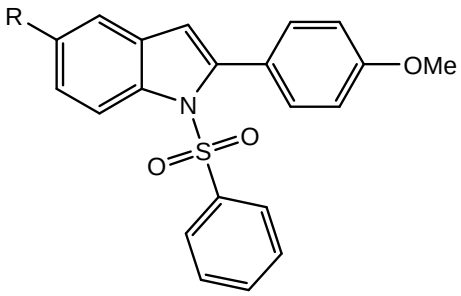

**119** R = H
**120** R = OMe



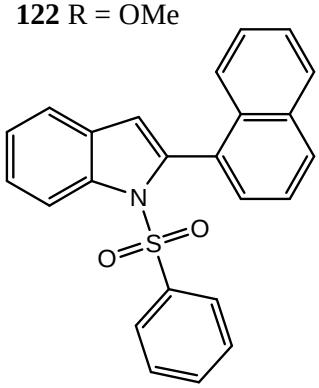

**121** R = H
**122** R = OMe




**123** R = H
**124** R = OMe

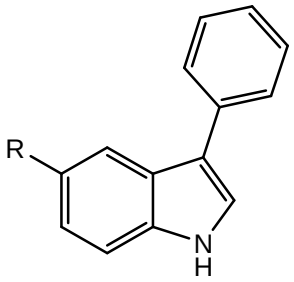



**125** R = H
**126** R = OMe

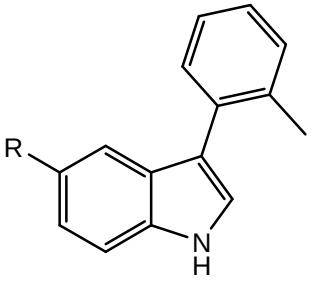



**127**

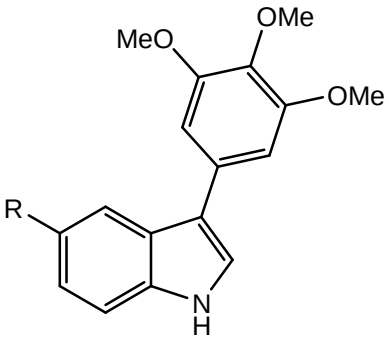
Also, we managed to synthesize the 3-arylindoles (**149**)-(**160**) in fair to excellent yields. The 3-arylindoles (**149**)-(**160**) were synthesized in three steps starting from 3-bromo-1-(phenylsulfonyl)-1*H*-indole (**107**) and 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**109**). The future work in this section will involve submitting the compounds (**149**)-(**160**) for testing against cancer and malarial cell lines. Infact, (**149**) has been tested and showed promising results against bacterial and fungal cell lines. Also in the future work of this section will be to improve the yields in the reactions leading to the desired products (**139**), (**141**), (**151**) and (**153**).



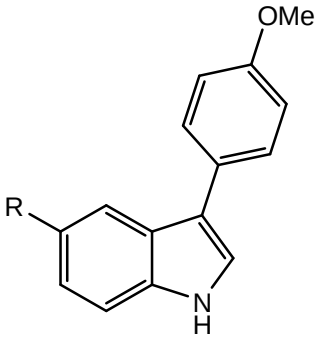

**149** R = H
**150** R = OMe



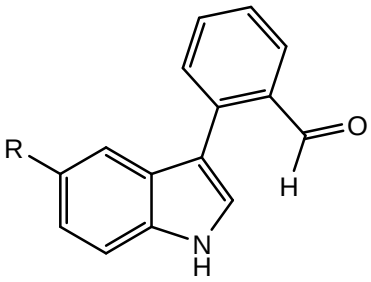

**151** R = H
**152** R = OMe



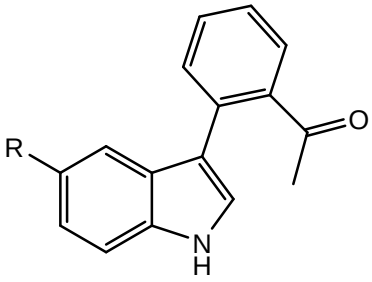

**153** R = H
**154** R = OMe




**155** R = H
**156** R = OMe

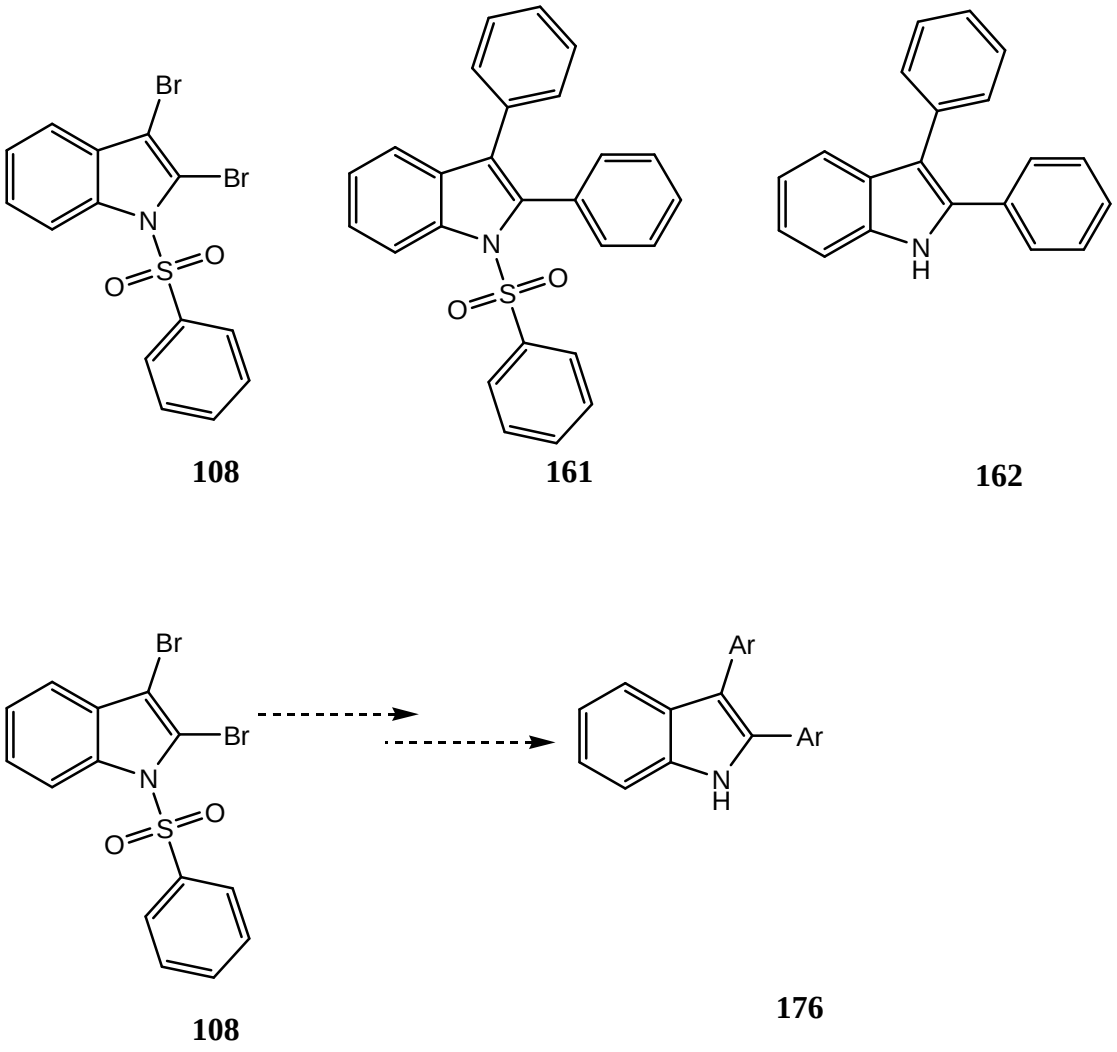



**157** R = H
**158** R = OMe




**159** R = H
**160** R = OMe

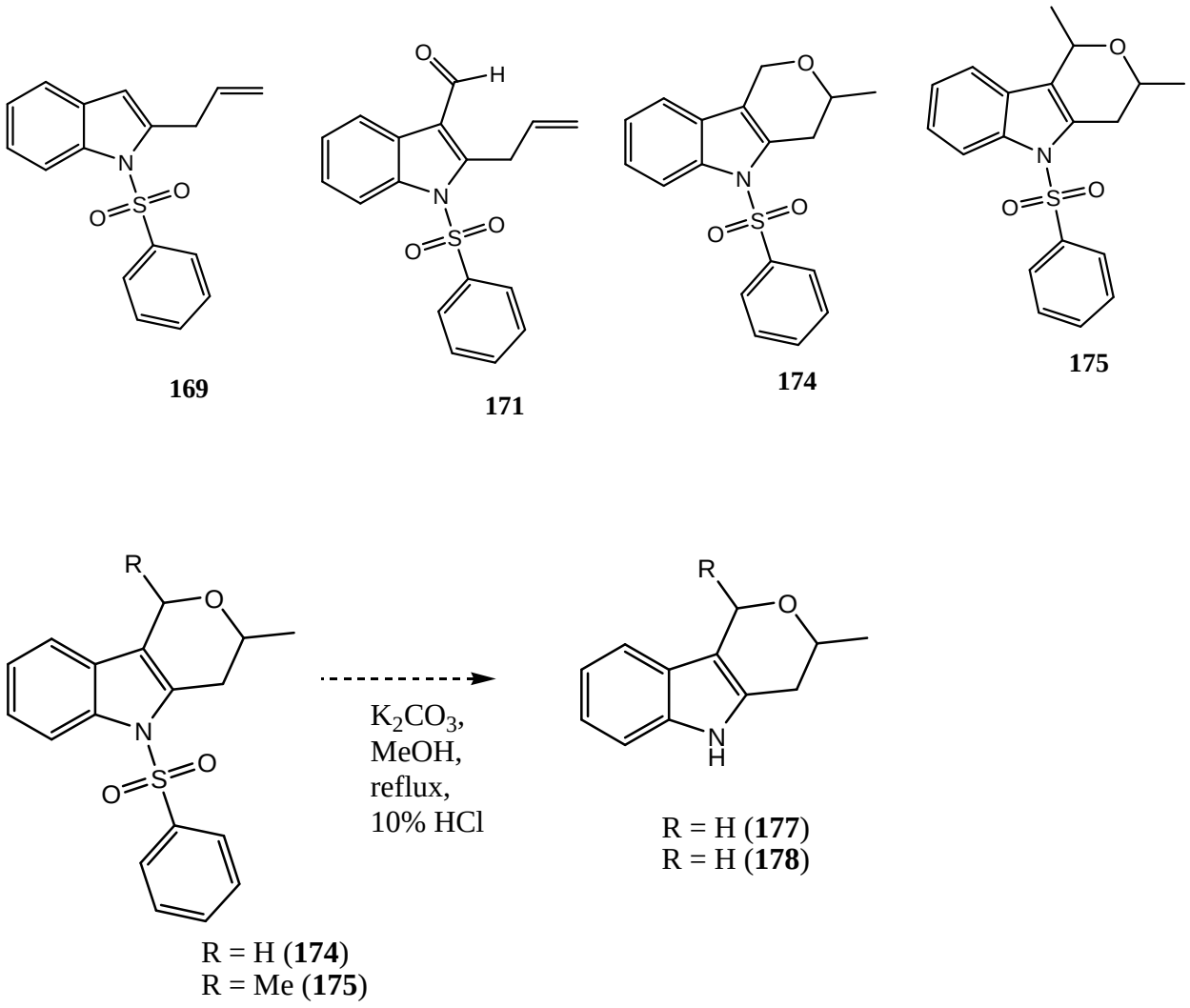
We also successfully synthesized 2,3-dibromo-1-(phenylsulfonyl)-1*H*-indole (**108**) by treating (**36**) with bromine in carbon tetrachloride in acceptable yield of 47%. After synthesizing (**108**), we managed to synthesise 2,3-diphenyl-1-(phenylsulfonyl)-1*H*-indole (**161**) in a fair yield of 56% which was successfully deprotected using potassium carbonate in methanol to give 2,3-diphenyl-1*H*-indole (**162**) in a fair yield of 60%. The future work in this section will include submitting (**162**) for testing against cancer and malarial cell lines and as well improving the yields of (**108**), (**161**) and (**162**). Other future work will involve reacting (**108**) with other boronic acids such as (**114**), (**115**) and others to give a range of 2,3-diarylindoles (**176**) (**Scheme 43**) because boronic acid such as (**113**), (**117)** and (**118**) have been generated. However, there was no success in synthesizing these 2,3-diarylindoles with these boronic acids. Instead, 3-arylindoles were obtained and we attributed this to steric effects.



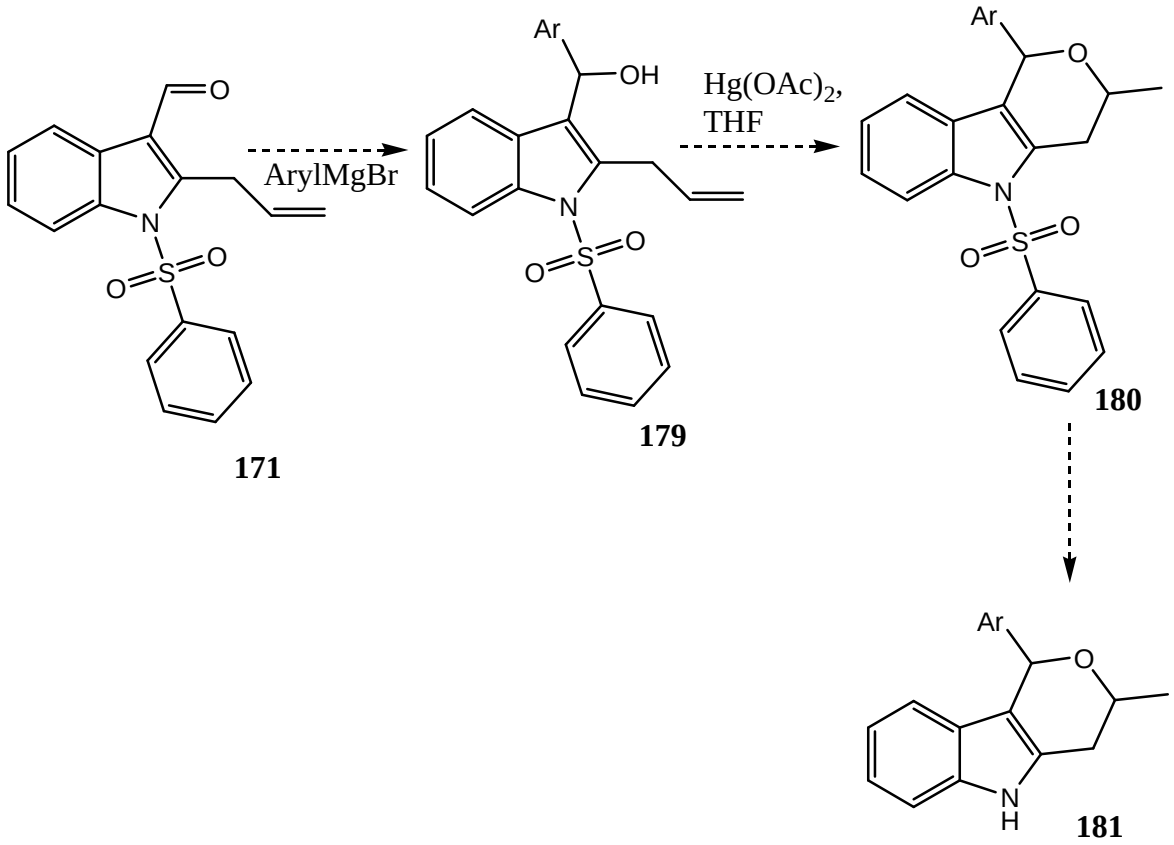

**Scheme 43**

Using methodology developed in our laboratories, we also managed to synthesize compounds (**174**) and (**175**) in four steps starting from the allylation of (**36**), formylation of (**169**) to cyclization of (**172**) and (**173**) using mercury acetate in tetrahydrofuran at room temperature. Compounds (**174**) and (**175**) were synthesized successfully in poor yields of 31% and 25% respectively. The future work in this section will include improving the yield of (**169**) which was obtained at the highest yield of 31% and the yields of (**174**) and (**175**) will also need to be improved. Further future work will involve taking (**174**) and (**175**) and treating them with potassium carbonate in methanol in an attempt to remove the phenylsulfonyl protecting group to

give unprotected compounds (**177**) and (**178**) (**Scheme 44**). If compounds (**176**) and (**177**) can be successfully obtained, they will be submitted for biological testing. Other future work will include treating (**171**) with different arylmagnesium halides followed by cyclization reaction using mercury acetate to give cyclized compound (**180**) which can be deprotected to give compound (**181**) (**Scheme 45**).




**Scheme 44**




**Scheme 45**

# Chapter 4: Experimental Procedures

## 4.0 General Experimental Procedures

### 4.0.1 Purification of Solvents and Reagents

All solvents used for reactions and preparative chromatography were distilled prior to use. Where necessary, they were also dried by standard methods as recommended by Perrin *et al*[78]. Tetrahydrofuran was distilled from the sodium benzophenone ketyl radical, dichloromethane, triethylamine from calcium hydride and toluene from sodium. Where necessary, solvents were stored over activated molecular sieves (4 Å) under nitrogen atmosphere. Unless otherwise noted, other reagents were obtained from commercial sources and used without further purification.

### 4.0.2 Chromatographic Separations

Thin layer chromatography (TLC) was carried out on aluminum-backed Macherey-Nagel Alugram Sil G/$UV_{254}$ plates pre-coated 0.25 mm silica gel 60. Detection was done by under ultra violet light at 254 nm. Preparative column chromatography was carried out on dry-packed columns using Macherey-Nagel Kieselgel 60 silica gel 60 (particle size 0.063-0.200 mm) as the adsorbent. Mixtures of EtOAc and hexane were used as the mobile phase.

### 4.0.3 Spectroscopic and Physical Data

All melting points were obtained on a Reichert hot-stage microscope and are uncorrected.

The $^{1}$H NMR (nuclear magnetic resonance) spectra were recorded on a Bruker AVANCE 300 (300.13 MHz) or a Bruker AVANCE 400 (400.13 MHz) spectrophotometer. Spectra were

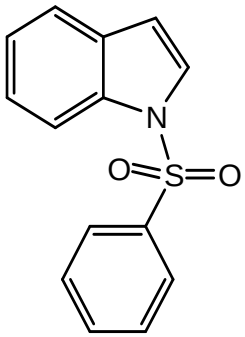
recorded in deuterated chloroform ($CDCl_3$) or deuterated acetone (acetone-$d_6$) and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), the internal standard; coupling constants are given in Hertz (Hz). Splitting patterns are designated as "s", "d", "t", "q", and "m"; and these symbols indicate "singlet", "doublet", "triplet", "quartet" and "multiplet" respectively. The $^{13}C$ NMR ($^{1}H$ decoupled) spectra were recorded on a Bruker AVANCE 300 (75.47 MHz) or Bruker DRX 400 (100.63 MHz) spectrometer. Spectra were recorded in deuterated chloroform ($CDCl_3$) or deuterated acetone (acetone-$d_6$) and chemical shifts are reported in parts per million (ppm) relative to the central signal of deuterated chloroform, taken as δ 77.00

IR (infrared) spectra were recorded on a Bruker IFS-25 Fourier Transform spectrometer or on a Bruker Vector-22 Fourier Transform spectrometer. Liquid samples were recorded as thin films between sodium chloride plates while solid samples were recorded as solutions in dichloromethane in sodium chloride cells. The signals were reported on the wavenumber scale ($\nu$/$cm^{-1}$). Signals were designated as "s", "m", "w" and "b"; these symbols indicate "strong", "medium", "weak" and "broad" respectively.

Mass spectra were recorded on Thermo Fisher LXQ, Thermo Fisher DFS or VG 70 SEQ mass spectrometer.

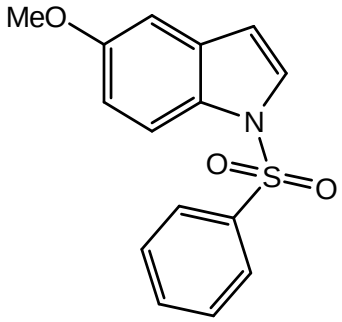
## 4.1 Protection of the indole nucleus

### 4.1.1 1-(Phenylsulfonyl)-1*H*-indole (36)



To an ice-cold mixture of aqueous NaOH (4.10 g, 102 mmol, 3 eq) and tetra-*n*-butylammonium bromide (0.29 g, 0.89 mmol, 0.026 eq) in dichloromethane (20.0 ml) under $N_2$, was added solid indole (**9**) (4.00 g, 34 mmol) in one portion followed by slow addition of phenylsulfonyl chloride (5.3 ml, 43 mmol, 1.25 eq).The light pink mixture was stirred at rt under $N_2$ for 18 h over which time it turned milky white. Water was added and the reaction mixture was then extracted with $CH_2Cl_2$ (3 × 20 ml). The organic extracts were combined, dried over $MgSO_4$, filtered with the celite plug and the solvent removed on a rotary evaporator. The resulting brown oil was dried further on a high vacuum line. When it was left to stand, it became a cream white solid (**36**) (8.74g, 100%) Melting point: 75-78 °C, lit. value 76.5-77 °C[64]; $\nu_{max}$ (Solid)/cm$^{-1}$ 3065 (w, CH), 1481 (m), 1448 (m), 1362 (m), 1264 (m), 1177 (s), 1092 (m), 726 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.99 (1H, d, *J* = 8.20, ArH), 7.87 (2H, d, *J* = 7.50, 2 × ArH), 7.56 (1H, d, *J* = 3.70, ArH), 7.53-7.19 (6H, m, 6 × ArH), 6.65 (1H, d, *J* = 3.7, ArH); $\delta_C$ (75 MHz; $CDCl_3$) 138.70 (C), 135.30 (C), 134.20 (CH), 131.20 (C), 129.70 (2 × CH), 127.10 (2 × CH), 126.70 (CH), 125.10 (CH), 123.80 (CH), 121.80 (CH), 113.90 (CH), 109.70 (CH); *m/z* 257 ($M^+$, 100%), 141 (19%), 116 (85%), 89 (21%), 77 (43%) (Found: $M^+$, 257.0521. $C_{14}H_{11}SO_2N$ requires 257.0511).

### 4.1.2 1-(Phenylsulfonyl)-5-methoxy-1*H*-indole (104)

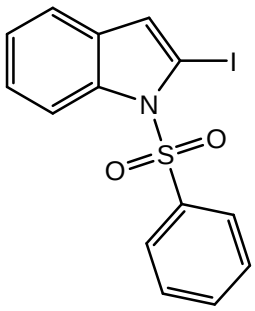


To an ice-cold mixture of sodium hydroxide (0.57 g, 14.30 mmol, 3 eq) and tetra-*n*-butylammonium bromide (0.04 g, 0.12 mmol, 0.026 eq) in dichloromethane (20.0 ml) under $N_2$, was added solid 5-methoxyindole (**102**) (0.70 g, 4.77 mmol) in one

portion followed by slow addition of phenylsulfonyl chloride (0.77 ml, 6.00 mmol, 1.25 eq).The light pink mixture was stirred at rt under $N_2$ for 18 h over which time it turned milky white. Water was added and the reaction mixture was then extracted with $CH_2Cl_2$ (3 × 20 ml). The organic extracts were combined, dried over magnesium sulphate, filtered with the celite plug and the solvent removed on a rotary evaporator. The resulting light brown oil was dried further on a high vacuum line. When it was left to stand, it became a cream white solid (**104**) 1.37 g, (100%). Melting point: 96-99 °C, lit. value 97-98 °C[34]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3002 (w, C-H), 1613 (m), 15384 (m), 1471 (s), 1372 (s), 1226 (m, C-O), 1150 (m), 1092 (m), 940 (w), 844 (w), and 755 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.90-7.82 (3H, m, 3 × ArH), 7.52-7.37 (4H, m, 4 × ArH), 6.96-6.91 (2H, m, 2 × ArH), 6.58 (1H, d, *J* = 3.60, ArH), 3.79 (3H, s, $CH_3O$); $\delta_C$ (300 MHz; $CDCl_3$) 156.50 (C), 138.20 (C), 133.70 (CH), 129.60 (C), 129.40 (C), 129.20 (2 × CH), 126.90 (CH), 126.70 (2 × CH), 114.40 (CH), 113.80 (CH), 109.40 (CH), 103.70 (CH), 55.60 ($CH_3O$); *m*/z 287 ($M^+$, 61%), 218 (3%), 147 (11%), 146 (100%), 125 (8%), 103 (10%), 77 (16%), 51 (9%), 49 (3%).

## 4.2 Iodination of indoles (36) and (104)

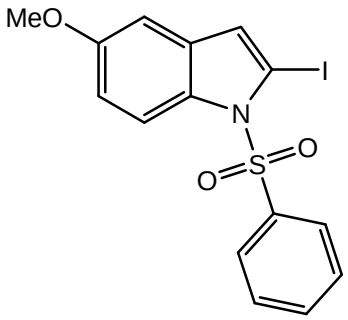
### 4.2.1 2-Iodo-1-(phenylsulfonyl)-1*H*-indole (105)




To 1-(phenylsulfonyl)-1*H* indole (**36**) (1.00 g, 3.89 mmol) in a dry flask was added *iso*propyl magnesium chloride solution in THF (~0.8 M in excess) and *iso*propyl amine (1.0 ml). The reaction mixture was maintained at rt under $N_2$ atmosphere for 16 h. Iodine (2.50 g, 9.73 mmol, 2.5 eq) was added and the mixture was stirred at rt for 1 h. The reaction mixture was quenched by the addition of saturated aqueous solution of ammonium chloride. The mixture was extracted with $CH_2CH_2$ (3 × 30 ml), the organic layers combined and dried over $MgSO_4$, then filtered though celite plug and excess solvent removed on a rotary evaporator. This resulted in a brown oil that was subjected to column chromatography to give cream white solid (**105**) 1.18 g, (79%). Melting point: 96-99 °C,

lit. value 96-98 °C[66]; $\nu_{max}$ (Solid)/cm$^{-1}$ 2924 (w, CH), 1449(w), 1430 (s), 1372 (s), 1215 (s), 1182 (s), 1123 (s), 1090 (s), 1013 (s), 812 (s), 761 (m), 725 (s), 684 (s), 646 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.27 (1H, d, *J* = 8.32 ArH), 7.90-7.87 (2H, m, 2 × ArH), 7.56-7.51 (1H, m, ArH), 7.44-7.38 (3H, m, 2 × ArH), 7.29-7.20 (2H, m, 2 × ArH), 6.99 (1H, s, ArH); $\delta_C$ (75MHz; $CDCl_3$) 141.80 (C), 137.22 (C), 136.94 (C), 132.74 (CH), 130.43 (C), 127.84 (CH), 125.85 (CH), 123.65 (CH), 123.36 (CH), 122.52 (CH), 118.44 (CH), 114.14 (CH); *m/z* 383 ($M^+$, 5%), 263 (31%), 219 (100%), 150 (5%), 131 (55%), 69 (95%), (Found: 382.9471. $C_{21}H_{17}NSO_3I$ requires 382.9477).

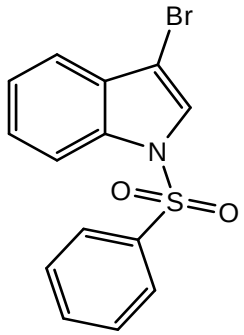
### 4.2.2 2-Iodo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (106)




To 5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**104**) (0.50 g, 1.74 mmol) in a dry flask was added *iso*propyl magnesium chloride solution in THF (~0.8M in excess) and *iso*propyl amine (1.0 ml). The reaction mixture was maintained at rt under $N_2$ atmosphere for 16 h. Iodine (0.88 g, 3.48 mmol, 2.5 eq) was added and the mixture was stirred at rt for 1 h. The reaction mixture was quenched by the addition of saturated aqueous solution of ammonium chloride. The mixture was extracted with $CH_2CH_2$ (3 × 30 ml), organic layers combined and dried over $MgSO_4$, then filtered though celite plug and excess solvent removed on a rotary evaporator. The resulting brown oil was subjected to column chromatography to give cream white solid (**106**) 0.61 g, (85%). Melting point: 127-130 °C; $\nu_{max}$ (Solid)/cm$^{-1}$ 2936 (w, CH), 1611 (m), 1446 (s), 1374 (s), 1226 (m), 1179 (s), 1146 (s), 1082 (s), 1023 (m), 840 (m), 800 (s), 756 (m), 724 (s), 687 (s), 621 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.18 (1H, d, *J* = 9.14, ArH), 7.87 (2H, d, *J* = 7.49, 2 × ArH), 7.58-7.53 (1H, m, ArH), 7.46-7.41 (2H, m, 2 × ArH), 6.93 (1H, s, ArH), 6.89 (1H, d, *J* = 2.59, ArH), 6.85 (1H, d, *J* = 2.47, ArH), 3.83 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 156.94 (C), 138.47 (C), 134.56 (CH), 133.66 (C), 133.05 (C), 129.49 (2 × CH), 127.48 (2 × CH), 124.81 (CH), 116.79 (CH), 114.20 (CH), 102.39 (CH), 76.39 (C), 56.02 ($CH_3O$); *m/z* 412 ($M^+$, 88%), 397 (100%), 330 (18%), 272 (12%), 257 (20%), 191 (3%), 117 (3%), (Found: 412.1070. $C_{15}H_{12}INO_3$ requires 412.9583).

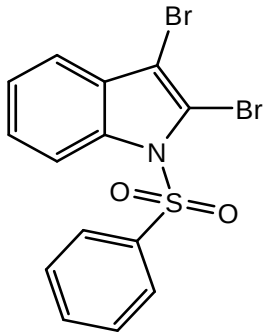
## 4.3 Bromination of indoles (36) and (104)

### 4.3.1 3-Bromo-1-(phenylsulfonyl)-1*H*-indole (107)



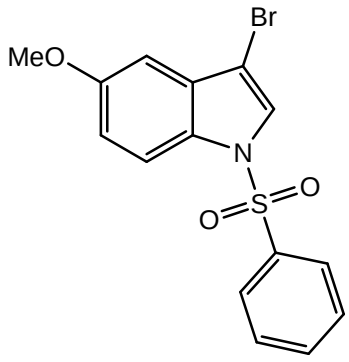

To a mixture of 1-phenylsulfonylindole (**36**) (1.00 g, 3.9 mmol) and sodium acetate (0.32 g, 3.9 mmol, 1eq) in acetic acid (20.0 ml) at 0 °C, bromine (0.50 ml, and 3.9 mmol, 1 eq) was added dropwise. The reaction mixture was then allowed to warm up to rt before being refluxed under $N_2$ for 14 h over which time it turned from brown to light yellow. After being allowed to cool to rt, the mixture was filtered and the acetic acid from the reaction mixture was removed on the rotary evaporator. The resultant oil was partitioned between water (20 ml) and $CH_2Cl_2$ and extracted with $CH_2Cl_2$ (3 × 20 ml). The organic extracts were combined, dried over $MgSO_4$, then filtered with celite plug and excess solvent removed on rotary evaporator. The resulting oil was purified by column chromatography using 10% EtOAc/Hexane as an eluent and this gave the product in 80% yield as a white solid (**107**). Melting point: 120-124 °C, lit. value 122-124 °C[68]; $\nu_{max}$ (Solid)/ $cm^{-1}$ 3139 (w, CH), 1446 (m), 1376 (m), 1176 (s), 1091 (m), 1032 (w), 932 (w), 728 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.00 (1H, d, *J* = 8.21, ArH), 7.88 (2H, d, *J* = 7.62, 2 × ArH), 7.62 (1H, s, ArH), 7.57-7.21 (6H, m, 6 × ArH); ) $\delta_C$ (75 MHz; $CDCl_3$) 138.21 (C), 134.72 (C), 134.5 (CH), 130.23 (C), 129.80 (2 × CH), 127.30 (2 × CH), 126.34 (CH), 125.25 (CH), 124.40 (CH), 120.56 (CH), 113.93 (CH), 99.80 (C); *m/z* 336 ($^{79}$Br-$M^+$, 63%), 334 (57%), 257 (11%), 196 (98%), 194 (10%), 193 (100%), 141 (18%), 116 (14%), 115 (27%), 88 (12%), 77 (53%), 51 (17%) (Found: $^{79}$Br-$M^+$, 336.9650. $C_{14}H_{10}SO_2N^{79}Br$ requires 334.9616).

### 4.3.2 2,3-Dibromo-1-(phenylsulfonyl)-1*H*-indole (108)




1-(Phenylsulfonyl)-1*H*-indole (**36**) (3.00 g, 11.7 mmol) was dissolved in dry DMF (10.0 ml) and bromine (1.6 ml, 12.9 mmol, 1.1 eq) was added dropwise at rt. The red solution was then stirred at rt for 18 h. The resulting reaction mixture was poured into a saturated solution of aqueous $NaHCO_3$ (20 ml). The layers were separated, and extracted with $CH_2Cl_2$ (3 × 20 ml), washed successively with aqueous $Na_2S_2O_3$ (20.0 ml) and then finally washed with brine (20.0 ml). The organic extracts were dried over $MgSO_4$, filtered with the celite plug and solvent removed on a rotary evaporator. This gave a crude brown solid which was purified by column chromatography using 10% EtOAc/Hexane as an eluent. After the chromatography, the product was recrystallized from ethyl acetate and gave 47% yield of the product as a cream white solid (**108**). Melting point: 141-144 °C, lit. value 141-143 °C[70]; $\nu_{max}$ (Solid)/cm$^{-1}$ 3071 (w, CH), 1443 (m), 1383 (s),1194 (s), 1092 (m), 1038 (m), 909 (s), 739 (s), 570 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.30 (1H, d, $J$ = 8.31 ArH), 7.88 (2H, d, $J$ = 7.52, 2 × ArH), 7.62-7.31 (6H, m, 6 × ArH); $\delta_C$ (75 MHz; $CDCl_3$) 138.21 (C), 137.0 (C), 134.82 (CH), 129.43 (2 × CH), 127.74 (2 × CH), 127.55 (C), 127.26 (CH), 125.17 (CH), 120.08 (CH), 115.79 (CH), 111.60 (C), 107.11 (C); m/z 416 ( $^{81}$Br-M$^+$, 30%), 415 ($^{79}$Br-M$^+$, 10%), 414 (58%), 412 (27%), 336 (17%), 275 (49%), 273 (100%), 271 (47%), 195 (24%), 193 (27%), 141 (41%), 114 (40%), 77 (58%), 51 (18%) (Found: $^{79}$Br-M$^+$, 415.8816. $C_{14}H_9SO_2NBr_2$ requires 412.8721 $^{79}$Br).

### 4.3.3 3-Bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (109)



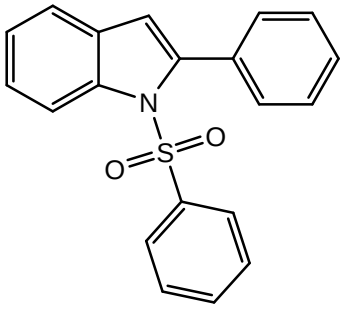

A mixture of *N*-bromosuccinimide (0.060 g, 0.35 mmol, 1.01 eq), 5-methoxy-1 (phenylsulfonyl)-1*H*-indole (**104**) (0.10 g, 0.35 mmol) and benzoyl peroxide (0.01g) in dry $CCl_4$ (5 ml), was gently refluxed for 18 h. The reaction mixture was allowed to cool to rt, cooled in ice bath before the succinimide was

separated by filtration. The last traces of succinimide were removed by shaking the filtrate in a separating funnel with an ice cooled aqueous sodium hydroxide (5%) solution followed by shaking with water. The organic layer was dried over $MgSO_4$ before being evaporated on a rotary evaporator to afford a white solid (**109**) 0.11 g (85%). Melting point: 129-132 °C, lit. value 131-133 °C[56]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3146 (m, CH), 1612 (m), 1474 (s), 1445 (s), 1361 (s), 1313 (m), 1275 (s), 1211 (s), 1159 (s), 1136 (s), 1089 (s), 1034 (s), 963 (s), 835 (m), 819 (m), 800 (m), 765 (s), 749 (s), 722 (s), 683 (s), 650 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.90-7.85 (3H, m, 3 × ArH), 7.58-7.53 (2H, m, 2 × ArH), 7.47-7.42 (2H, m, 2 × ArH), 6.98 (1H, d, *J* = 9.03, ArH), 6.89 (1H, d, *J* = 1.79, ArH), 3.84 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 155.92 (C), 136.60 (C), 132.93 (CH), 129.65 (C), 128.24 (2 × CH), 126.70 (C), 125.65 (2 × CH), 124.22 (CH), 114.33 (CH), 113.56 (CH), 100.69 (CH), 98.69 (C), 54.59 ($CH_3O$);

## 4.4 Typical procedure for the synthesis of 2-aryl-1-(phenylsulfonyl)-1*H*-indole and 2-aryl-5-methoxy-1-(phenylsulfonyl)-1*H*-indole

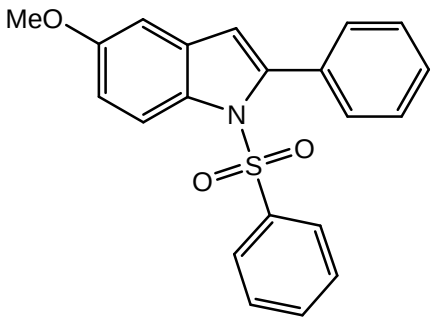
To $Pd(PPh_3)_4$ (10 mol%) under $N_2$ was added a deoxygenated mixture of 2-iodo-1-(phenylsulfonyl)-1*H*-indole or 2-iodo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole in DME (5 ml) and arylboronic acid in ethanol (3 ml). The reaction mixture was stirred for about 10 min followed by the addition of a deoxygenated 2 M solution of $Na_2CO_3$ in water. The resulting reaction mixture was stirred for further 10 min at rt before being heated to reflux for 8 h. The reaction mixture was allowed to cool to room temperature, quenched with water (10.0 ml) and the organic extracts extracted with $CH_2Cl_2$ (3 × 30 ml). The organic fractions were combined, dried over $MgSO_4$, filtered through a celite plug and then the excess solvent was removed using a rotary evaporator. The resulting black oils were purified by column chromatography using 10% EtOAc/Hexane as an eluent.

**(a) 2-Phenyl-1-(phenylsulfonyl)-1*H*-indole (119)**



$Pd(PPh_3)_4$ (0.35 g, 10%), 2-iodo-1-(phenylsulfonyl)-1*H*-indole (**105**) (1.00 g, 3.04 mmol) phenyl boronic acid (0.56 g, 4.56 mmol, 1.5 eq), $Na_2CO_3$ (2.73 g, 25.8 mmol, 8.5 eq) in water (12.9 ml). This gave white solid (**119**) (0.89 g, 82%). Melting point: 100-104 °C, lit value 104-105 °C[64]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3055 (w, CH), 1585 (w), 1479 (m), 1434 (s), 1372 (s), 1248 (m), 1171 (s), 1115 (m), 1089 (s), 1049 (s), 1026 (s), 976 (s), 837 (m), 754 (s), 732 (s), 682 (s), 635 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.31 (1H, d, *J* = 8.28, ArH), 7.48-7.35 (9H, m, 9 × ArH), 7.27-7.18 (4H, m, 4 × ArH), 6.52 (1H, s, ArH); $\delta_C$ (75MHz; $CDCl_3$) 142.54 (C), 138.73 (C), 137.94 (C), 133.99 (CH), 132.73 (C), 130.79 (CH), 129.15 (CH), 129.02 (CH), 127.99 (CH), 127.17 (CH), 125.32 (CH), 124.88 (CH), 121.22 (CH), 117.07 (CH), 115.79 (C), 114.19 (CH); *m/z* 333 ($M^+$, 80%), 277 (35%), 219 (96%), 192 (100%), 164 (53%), 131 (37%), 69 (80%), (Found: 333.0826. $C_{21}H_{17}NSO_3$ requires 333.0824).

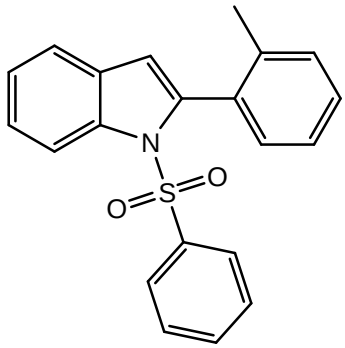
**(b) 5-Methoxy-2-phenyl-1-(phenylsulfonyl)-1*H*-indole (120)**



$Pd(PPh_3)_4$ (0.11 g, 10%), 2-iodo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**106**) (0.40 g, 0.97 mmol), phenylboronic acid (0.18 g, 1.46 mmol, 1.5 eq), $Na_2CO_3$ (0.87 g, 8.23 mmol, 8.5 eq) in water (4.1 ml). This gave a brown oil (**120**), 0.21 g (60%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3061 (w, CH), 1609 (m), 1468 (s), 1446 (s), 1386 (s), 1207 (m), 1175 (s), 1145 (s), 1089 (m), 1028 (m), 909 (m), 849 (m), 809 (s), 759 (m), 725 (s), 685 (s), 635 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.19 (1H, d, *J* = 9.08, ArH), 7.51-7.45 (2H, m, 2 × ArH), 7.43-7.39 (4H, m, 4 × ArH), 7.36-7.33 (2H, m, 2 × ArH), 7.26-7.21 (2H, m, 2 × ArH), 6.96 (1H, dd, *J* = 2.57 and 2.50, ArH), 6.87 (1H, d, *J* = 2.53, ArH), 6.48 (1H, s, ArH), 3.18 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 157.14 (C), 143.06 (C), 137.22 (C),

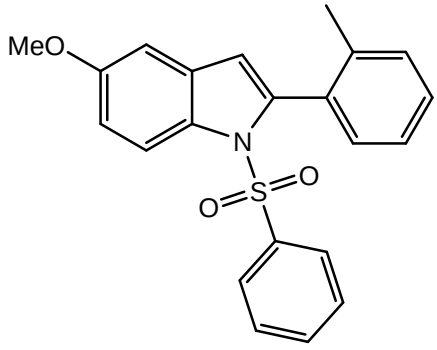
133.43 (CH), 132.82 (C), 132.29 (C), 131.72 (C), 130.20 (2 × CH), 128.68 (CH), 128.49 (2 × CH), 127.53 (2 × CH), 126.74 (2 × CH), 117.70 (CH), 113.96 (CH), 113.50 (CH), 103.22 (CH), 55.57 ($CH_3O$); *m/z* 364 ($M^+$, 48%), 279 (6%), 223 (100%), 208 (2%), 149 (2%), (Found: 363.1920. $C_{21}H_{17}NO_3S$ requires 363.0929).

**(c) 1-(Phenylsulfonyl)-2-*o*-tolyl-1*H*-indole (121)**



$Pd(PPh_3)_4$ (0.24 g, 10%), 2-iodo-1-(phenylsulfonyl)-1*H*-indole (**105**) (0.50 g, 1.31 mmol), *o*-tolyl boronic acid (0.41 g, 3.10 mmol, 1.5 eq), $Na_2CO_3$ (1.84 g, 17.30 mmol, 8.5 eq) in water (8.7 ml). This gave a brown oil (**121**), 0.20 g (44%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3063 (w, CH), 1585 (w), 1485 (s), 1369 (s), 1247 (m), 1220 (m), 1174 (s), 1121 (s), 1090 (s), 1064 (s), 995 (m), 822 (m), 747 (s), 724 (s), 684 (s), 641 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.37 (1H, d, *J* = 8.33, ArH), 7.50-7.42 (4H, m, 4 × ArH), 7.39-7.33 (2H, m, 2 × ArH), 7.30-7.24 (3H, m, 3 × ArH), 7.21-7.16 (1H, m, ArH), 7.11-7.03 (2H, m, 2 × ArH), 6.46 (1H, s, ArH), 2.19 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 140.67 (C), 139.79 (C), 138.97 (C), 137.81 (C), 134.09 (CH), 132.35 (C), 131.42 (CH), 130.52 (C), 130.10 (CH), 129.61 (CH), 129.22 (2 × CH), 127.30 (2 × CH), 125.15 (CH), 124.40 (CH), 121.21 (CH), 116.14 (CH), 115.35 (C), 112.90 (CH), 20.89 ($CH_3$); *m/z* 348 ($M^+$, 100%), 297 (3%), 222 (3%), 207 (80%), 141 (2%), (Found: 347.246. $C_{21}H_{17}NO_2S$ requires 347.098).

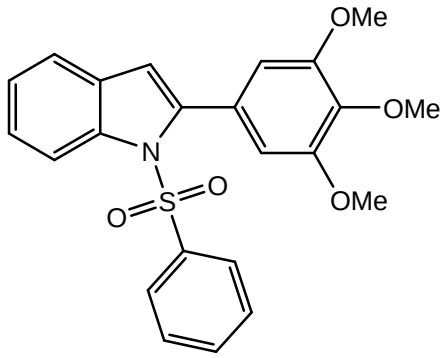
**(d) 5-Methoxy-1-(phenylsulfonyl)-2-*o*-tolyl-1*H*-indole (122)**



$Pd(PPh_3)_4$ (0.10 g, 0.078 mmol, 10%), 2-iodo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**106**) (0.33 g, 0.78 mmol), *o*-tolylboronic acid (0.16 g, 1.18 mmol, 1.5e q), $Na_2CO_3$ (0.71 g, 6.66 mmol, 8.5 eq) in water (3.3 ml). This gave a

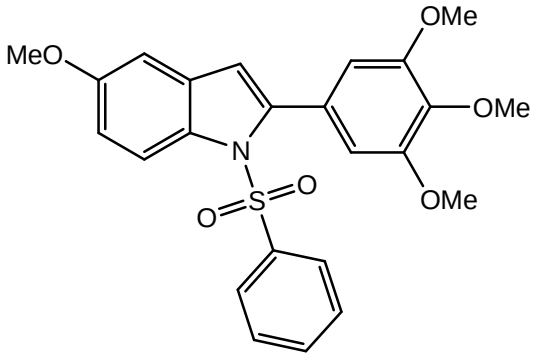
yellow oil (**122**), 0.23 g (78%); $\nu_{max}$ (Liquid)/cm$^{-1}$ 2930 (w, CH), 1611 (m), 1464 (s), 1446 (s), 1367 (s), 1201 (s), 1175 (s), 1144 (s), 1089 (m), 1038 (s), 995 (m), 854 (m), 807 (m), 753 (s), 722 (s), 684 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.14 (1H, d, *J* = 8.97, ArH), 7.36 (3H, d, *J* = 7.71, 3 × ArH), 7.28-7.17 (5H, m, 5 × ArH), 7.11 (1H, t, *J* = 14.82, ArH), 6.98 (1H, d, *J* = 7.50, ArH), 6.92-6.87 (2H, m, 2 × ArH), 6.32 (1H, s, ArH), 3.76 (3H, s, $CH_3O$), 2.13 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 157.24 (C), 141.55 (C), 139.67 (C), 138.78 (C), 133.95 (CH), 132.39 (C), 132.34 (C), 131.57 (C), 131.27 (CH), 130.08 (CH), 129.53 (CH), 129.12 (2 × CH), 127.23 (2 × CH), 125.11 (CH), 117.13 (CH), 113.87 (CH), 113.12 (CH), 103.57 (CH), 56.05 ($CH_3O$), 20.87 ($CH_3$).

**(e) 1-(Phenylsulfonyl)-2-(3,4,5-trimethoxyphenyl)-1*H*-indole (123)**



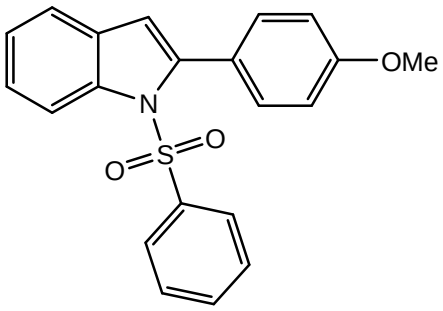

$Pd(PPh_3)_4$ (0.24 g, 10%), 2-iodo-1-(phenylsulfonyl)-1*H*-indole (**105**) (0.50 g, 1.31 mmol), 3,4,5-trimethoxy-phenyl boronic acid (0.66 g, 3.10 mmol, 1.5 eq), $Na_2CO_3$ (1.84 g, 17.30 mmol, 8.5 eq) in water (8.7 ml). This gave a cream white oil (**123**), 0.20 g (56%); $\nu_{max}$ (Liquid)/cm$^{-1}$ 3066 (w, CH), 1584 (m), 1481 (m), 1447 (s), 1359 (s), 1263 (s), 1203 (s), 1175 (s), 1113 (s), 1091 (s), 1022 (m), 991 (s), 878 (s), 764 (s), 754 (s), 741 (s), 724 (s), 709 (s), 983 (s), 654 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.80 (1H, d, *J* = 8.24, ArH), 7.87 (1H, d, *J* = 7.58, ArH), 7.56 (1H, d, *J* = 3.64, ArH), 7.53-7.47 (2H, m, 2 × ArH). 7.42-7.37 (2H, m, 2 × ArH), 7.33-7.28 (1H, m, ArH), 7.24-7.19 (1H, m, ArH), 6.65 (1H, d, *J* = 3.61, ArH), 6.57 (1H, d, *J* = 8.40, ArH), 3.85 (9H, s, 3 × $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 155.10 (C), 139.83 (C), 136.41 (C), 135.35 (CH), 132.31 (C), 130.80 (2 × CH), 128.28 (2 × CH), 127.86 (CH), 126.20 (CH), 125.20 (2 × C), 124.93 (CH), 122.97 (CH), 115.07 (CH), 110.79 (CH), 106.84 (CH), 62.38 ($CH_3O$), 57.63 (2 × $CH_3O$).

**(f) 5-Methoxy-1-(phenylsulfonyl)-2-(3,4,5-trimethoxyphenyl)-1*H*-indole (124)**




$Pd(PPh_3)_4$ (0.10 g, 0.078 mmol, 10%), 2-iodo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**106**) (0.33 g, 0.78 mmol), 3,4,5-trimethoxyphenylboronic acid (0.20 g, 1.00 mmol, 1.5 eq), $Na_2CO_3$ (0.71 g, 6.66 mmol, 8.5 eq) in water (3.3 ml). This gave a brown oil (**124**), 0.20 g (77%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 2936 (w, CH), 1608 (w), 1581 (m), 1501 (w), 1470 (m), 1447 (m), 1411 (m), 1367 (m), 1336 (m), 1232 (m), 1173 (m), 1144 (m), 1121 (m), 1087 (m), 1029 (m), 998 (m), 909 (m), 840 (m), 803 (m), 754 (m), 721 (m), 685 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.21 (1H, d, *J* = 9.08, ArH), 7.44 (1H, t, *J* = 14.49, ArH), 7.36 (2H, d, *J* = 7.91, 2 × ArH), 7.28-7.23 (2H, m, 2 × ArH), 6.97 (1H, d, *J* = 9.11, ArH), 6.89 (1H, s, ArH), 6.66 (2H, s, 2 × ArH), 6.48 (1H, s, ArH), 3.94 (3H, s, $CH_3O$), 3.87 (6H, s, 2 × $CH_3O$), 3.83 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 156.48 (C), 151.65 (2 × C), 142.21 (C), 137.93 (C), 136.73 (C), 132.84 (CH), 132.26 (C), 130.85 (C), 127.82 (2 × CH), 126.71 (C), 126.16 (2 × CH), 117.12 (CH), 112.85 (2 × CH), 107.21 (2 × CH), 102.49 (CH), 60.39 ($CH_3O$), 55.58 (2 × $CH_3O$), 54.93 ($CH_3O$).

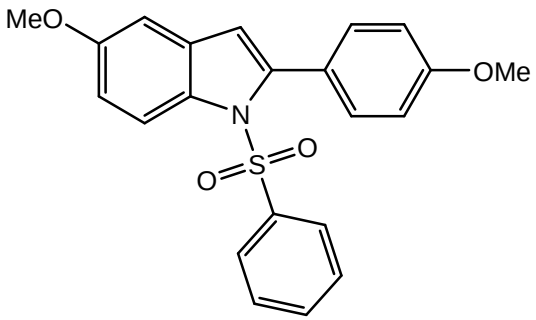
**(g) 2-(4-Methoxyphenyl)-1-(phenylsulfonyl)-1*H*-indole (125)**




$Pd(PPh_3)_4$ (0.24 g, 10%), 2-iodo-1-(phenylsulfonyl)-1*H*-indole (**105**) (0.79 g, 2.06 mmol), 4–methoxy-phenyl boronic acid (0.47 g, 3.09 mmol, 1.5 eq), $Na_2CO_3$ (1.86 g, 17.51 mmol, 8.5 eq) in water (8.9 ml). This gave a cream white solid (**125**), 0.40 g (60%). Melting point 209-212 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 3066 (w, CH), 1614 (m), 1566 (m), 1503 (s), 1442 (s), 1353 (s), 1300 (m), 1249 (s), 1224 (m), 1172 (s), 1151 (m), 1121 (m), 1069 (m), 1027 (m), 998 (m), 833 (s), 809 (s), 772 (m), 732 (s), 698 (m), 660 (s); $\delta_H$ (300

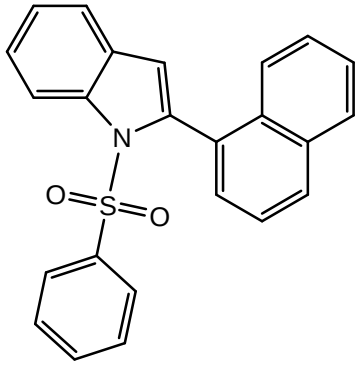
MHz; $CDCl_3$; $Me_4Si$) 8.25 (1H, d, *J* = 8.27, ArH), 7.90 (1H, d, *J* = 7.42, ArH), 7.56 (1H, d, *J* = 7.51, ArH), 7.38-7.26 (4H, m, 4 × ArH), 7.11-7.01 (4H, m, 4 × ArH), 6.67 (2H, d, *J* = 8.53, 2 × ArH), 6.53 (1H, s, ArH), 3.80 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 160.30 (C), 142.95 (C), 142.71 (CH), 140.39 (C), 139.76 (C), 133.91 (CH), 132.46 (2 × CH), 131.89 (CH), 129.22 (C), 127.94 (CH), 124.74 (CH), 123.82 (CH), 121.09 (CH), 116.96 (CH), 113.33 (2 × CH), 111.49 (CH), 92.39 (C), 55.75 ($CH_3O$); *m/z* 364 ($M^+$, 82%), 347 (28%), 328 (4%), 267 (2%), 127 (2%), (Found: 362.2600. $C_{21}H_{17}NO_3S$ requires 363.0929).

**(h) 5-Methoxy-2-(4-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-indole (126)**




$Pd(PPh_3)_4$ (0.10 g, 0.078 mmol, 10%), 2-iodo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**106**) (0.33 g, 0.78 mmol), 4-methoxy-phenylboronic acid (0.18 g, 1.18 mmol, 1.5 eq), $Na_2CO_3$ (0.71 g, 6.66 mmol, 8.5 eq) in water (3.3 ml). This gave a yellow oil (**126**), 0.19 g (61%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 2933 (w, CH), 1609 (m), 1505 (m), 1467 (s), 1446 (m), 1366 (m), 1248 (m), 12074 (m), 1172 (m), 1144 (m), 1088 (m), 1061 (m), 990 (m), 946 (m), 832 (m), 805 (m), 789 (m), 753 (m), 724 (m), 684 (m), 629 (m), 611 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.11 (1H, d, *J* = 9.04, ArH), 7.32 (3H, d, *J* = 8.58, 3 × ArH), 7.26 (2H, d, *J* = 8.00, 2 × ArH), 7.18-7.13 (2H, m, 2 × ArH), 6.88-6.84 (3H, m, 3 × ArH), 6.78 (1H, d, *J* = 2.31, ArH), 6.69 (2H, s, × ArH), 6.33 (1H, s, ArH), 3.79 (3H, s, $CH_3O$), 3.73 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 159.75 (C), 156.79 (C), 142.67 (C)136.95 (C), 133.08 (CH), 132.40 (C), 131.53 (C), 131.22 (2 × CH), 128.16 (2 × CH), 126.42 (2 × CH), 124.31 (C), 117.41 (CH), 115.71 (CH), 114.51 (CH), 112.87 (CH), 112.72 (2 × CH), 102.80 (CH), 55.26 ($CH_3O$), 55.00 ($CH_3O$).

**(i) 2-(Naphthalen-1-yl)-1-(phenylsulfonyl)-1*H*-indole (127)**



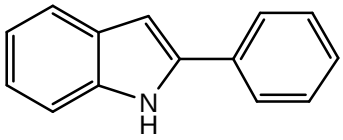
$Pd(PPh_3)_4$ (0.24 g, 10%), 2-iodo-1-(phenylsulfonyl)-1*H*-indole (**105**) (0.50 g, 1.31 mmol), naphthalen-1-ylboronic acid (0.34 g, 1.97 mmol, 1.5 eq), $Na_2CO_3$ (1.84 g, 17.30 mmol, 8.5 eq) in water (8.7 ml). This gave a brown oil (**127**), 0.30 g (60%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3061 (w, CH), 1575 (w), 1480 (m), 1423 (s), 1349 (s), 1263 (m), 1184 (s), 1119 (m), 1081 (s), 1043 (s), 1021 (s), 979 (s), 833 (m), 756 (s), 739 (s), 687 (s), 639 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.00 (1H, d, *J* = 8.26, ArH), 7.93 (1H, d, *J* = 8.06, ArH), 7.85 (2H, d, *J* = 7.75, 2 × ArH), 7.63 (1H, d, *J* = 8.46, ArH), 7.55 (1H, d, *J* = 3.64, ArH), 7.51-7.12 (10H, m, 10 × ArH), 6.65-6.62 (1H, m, ArH); $\delta_C$ (75MHz; $CDCl_3$) 140.22 (C), 139.64 (C), 139.01 (C), 136.25 (C), 135.18 (CH), 134.92 (CH), 134.46 (C), 132.14 (C), 130.98 (CH), 130.74 (CH), 130.62 (2 × CH), 130.02 (CH), 129.45 (CH), 128.21 (CH), 128.09 (2 × CH), 127.69 (CH), 127.45 (CH), 127.25 (CH), 126.29 (CH), 126.03 (CH), 125.84 (CH), 125.46 (CH), 124.77 (CH), 122.27 (CH), 117.17 (CH), 115.28 (C), 114.91 (CH), 110.64 (CH); *m/z* 382 ($M^-$, 60%), 257 (20%), 242 (100%), 213 (10%), 141 (10%), 116 (21%), 88 (8%), 77 (25%) (Found: 383.9120. $C_{24}H_{17}NSO_2$ requires 383.4623).

## 4.5 Typical procedure for removing of phenylsulfonyl protecting group on 2-aryl-1-(phenylsulfonyl)-1*H*-indoles and 2-aryl-5-methoxy-1-(phenylsulfonyl)-1*H*-indoles

The substrate was dissolved in methanol (20 ml) at rt under $N_2$ atmosphere, $K_2CO_3$ was added to the solution and the reaction mixture was heated to reflux under $N_2$ for 18 h. The reaction mixture was then allowed to cool to rt and filtered through a celite plug and then the filtrate concentrated under reduced pressure. Water was added to the crude material and slowly acidified to pH 2-4 with aqueous 10% HCl. The aqueous portion was saturated with solid NaCl and the organic material extracted with $CH_2Cl_2$ (3 × 30 ml). The combined organic extracts were washed

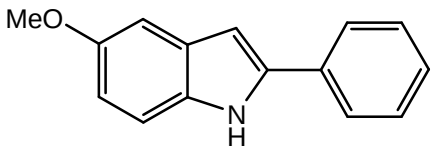
two times with water (20 ml), brine (20 ml), dried over $MgSO_4$ and concentrated under reduced pressure. This resulted in brown oils that were subjected to column chromatography using 10% EtOAc/Hexane as an eluent.

**(a) 2-Phenyl-1-*H*-indole (128)**



2-Phenyl-1-phenylsulfonylindole (**119**) (0.79 g, 2.37 mmol), $K_2CO_3$ (62.30 g, 450 mmol, 190 eq). Column chromatography gave a cream white solid (**128**) 0.36 g (78%). Melting point 182-186 °C, lit. value 182-184 °C[79]; $\nu_{max}$ (Solid)/cm$^{-1}$ 3441 (s, NH), 3050 (w, CH), 1601 (w), 1542 (m), 1480 (s), 1446 (s), 1403 (m), 1352 9s), 1298 (s), 1230 (m), 1184 (s), 1075 (m), 907 (s), 797 (m), 763 (s), 738 (s), 687 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.36 (1H, s, NH), 7.70 (3H, d, *J* = 7.31, 3 × ArH), 7.51-7.35 (4H, m, 4 × ArH), 7.28-7.16 (2H, m, 2 × ArH), 6.88 (1H, s, ArH); $\delta_C$ (75MHz; $CDCl_3$) 138.33 (C), 137.27 (C), 132.81 (C), 129.71 (C), 129.45 (2 × CH), 128.14 (CH), 125.56 (2 × CH), 122.79 (CH), 120.71 (CH), 111.36 (CH), 100.43 (CH); *m/z* 194 ($M^+$, 100%), 167 (4%), 116 (4%), (Found: 193.2140. $C_{14}H_{10}N$ requires 193.0892).

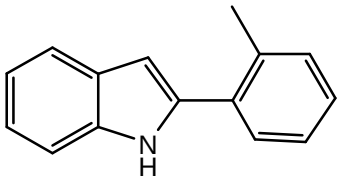
**(b) 5-Methoxy-2-phenyl-1*H*-indole (129)**



5-Methoxy-2-phenyl-1-(phenylsulfonyl)-1*H*-indole (**120**) (0.15 g, 0.41 mmol), $K_2CO_3$ (10.83 g, 79 mmol, 190 eq). Column chromatography gave a cream white solid (**129**) 0.055 g (61%). Melting point 162-165 °C; $\nu_{max}$ (Solid)/cm$^{-1}$ 3427 (m, NH), 2999 (w, CH), 1621 (m), 1476 (s), 1448 (s), 1301 (m), 1215 (s), 1150 (s), 1116 (m), 1026 (s), 945 (w), 840 (s), 801 (s), 763 (s), 736 (s), 692 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.21 (1H, s, NH), 7.64 (2H, d, *J* = 8.31, 2 × ArH), 7.45-7.40 (2H, m, 2 × ArH), 7.33-7.25 (2H, m, 2 × ArH), 7.09 (1H, s, ArH), 6.85 (1H, dd, *J* = 2.37 and 2.34, ArH), 6.76 (1H, s, ArH),

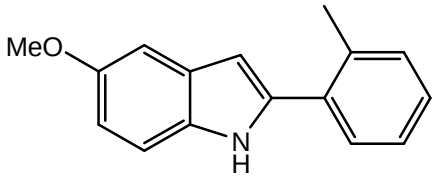
3.86 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 154.93 (C), 139.01 ($C^1$), 132.85 ($C^1$), 132.43 (C), 130.15 (C), 129.40 (2 × CH), 128.03 (CH), 125.45 (2 × CH), 113.04 (CH), 112.01 (CH), 102.71 (CH), 100.26 (CH), 56.26 ($CH_3O$); *m/z* 224 ($M^+$, 100%), 209 (6%), 143 (2%), (Found: 223.2430. $C_{15}H_{13}NO$ requires 223.0997).

**(c) 2-*o*-Tolyl-1*H*-indole (130)**



1-(phenylsulfonyl)-2-*o*-tolyl-1H-indole (**121**) (0.19 g, 0.55 mmol), $K_2CO_3$ (14.37 g, 104 mmol, 190 eq). Column chromatography gave a cream white solid (**130**) 0.09 g (82%). Melting point 81-85 °C, lit. value 92-93 °C[80]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3396 (s, NH), 3050 (w, CH), 1485 (m), 1452 (s), 1400 (m), 1345 (s), 1301 (s), 1230 (m), 1118 (m), 797 (s), 742 (s), 719 (s), 677 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.04 (1H, s, NH), 7.63 (1H, d, *J* = 7.65, ArH), 7.44-7.41 (1H, m, ArH), 7.35 (1H, d, *J* = 7.87, ArH), 7.27-7.24 (3H, m, 3 × ArH), 7.19-7.10 (2H, m, 2 × ArH), 6.59 (1H, s, ArH), 2.47 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 137.89 (C), 136.61 (C), 136.55 (C), 133.09 (C), 131.51 (CH), 129.44 (CH), 129.31 (C), 128.41 (CH), 126.53 (CH), 122.50 (CH), 120.98 (CH), 120.50 (CH), 111.23 (CH), 103.42 (CH), 21.55 ($CH_3$); *m/z* 208 ($M^+$, 100%), 193 (4%), 130 (2%), (Found: 207.2320. $C_{15}H_{13}N$ requires 207.1048).

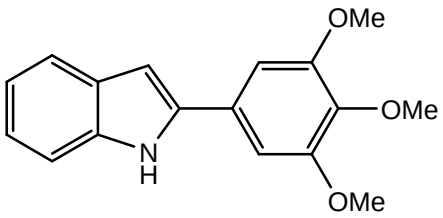
**(d) 5-methoxy-2-*o*-tolyl-1*H*-indole (131)**



5-Methoxy-2-*o*-tolyl-1-(phenylsulfonyl)-1*H*-indole (**122**) (0.19 g, 0.50 mmol), $K_2CO_3$ (13.21 g, 96 mmol, 190 eq). Column chromatography gave a yellow oil (**131**) 0.080 g (67%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3408 (m, NH), 2918 (m, CH), 1621 (w), 1585 (w), 1479 (s), 1436 (s), 1275 (w), 1215 (s), 1150 (m), 1117 (m), 1032 (m), 844 (m), 798 (m), 752 (s), 722 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.03 (1H, s, NH), 7.46 (1H, t, *J* =

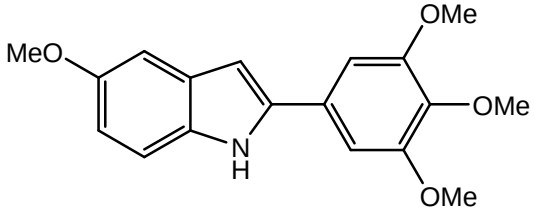
8.31, ArH), 7.28-7.25 (4H, m, 4 × ArH), 7.11 (1H, s, ArH), 6.87 (1H, dd, *J* = 10.56, ArH), 6.55 (1H, s, ArH), 3.87 (3H, s, $CH_3O$), 2.50 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 154.43 (C), 138.24 (C), 136.07 (C), 132.71 (C), 131.32 (C), 131.08 (CH). 129.30 (C), 128.90 (CH), 127.93 (CH), 126.10 (CH), 112.36 (CH), 111.48 (CH), 102.86 (CH), 102.25 (CH), 55.94 ($CH_3O$), 21.13 ($CH_3$).

**(e) 2-(3,4,5-Trimethoxyphenyl)-1*H*-indole (132)**




1-(phenylsulfonyl)-2-(3,4,5-trimethoxyphenyl)-1*H*-indole (**123**) (0.15 g, 0.35 mmol), $K_2CO_3$ (9.18 g, 67 mmol, 190 eq). Column chromatography gave a white solid (**132**) 0.05 g (51%). Melting point 206-209 °C, lit. value 205-206.5 °C[81]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3321 (m, NH), 3000 (w, CH), 1593 (s), 1501 (m), 1445 (m), 1427 (m), 1364 (m), 1286 (m), 1234 (s), 1126 (s), 996 (s), 836 (m), 784 (s), 728 (s), 693 (m), 633 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.42 (1H, s, NH), 7.62 (1H, d, *J* = 7.68, ArH), 7.40 (1H, d, *J* = 7.95, ArH), 7.25-7.10 (2H, m, 2 × ArH), 6.86 (2H, s, 2 × ArH), 6.75 (1H, s, ArH), 3.93 (6H, s, 2 × $CH_3O$), 3.90 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 154.13 ( 2 × C), 138.54 (C), 137.22 (C), 129.65 (C), 128.82 (C), 122.71 (CH), 120.95 (CH), 120.71 (CH), 111.30 (CH), 103.20 (2 × CH), 100.31 (CH), 93.33 (C), 61.43 ($CH_3O$), 56.66 (2 × $CH_3O$); *m/z* 284 ($M^+$, 100%), 253 (4%), 155 (2%), 118 (2%), (Found: 283.2900. $C_{17}H_{17}NO_3$ requires 283.1208).

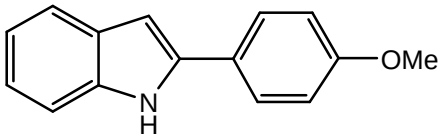
**(f) 5-Methoxy-2-(3,4,5-trimethoxyphenyl)-1H-indole (133)**




5-Methoxy-1-(phenylsulfonyl)-2-(3,4,5-trimethoxyphenyl)-1*H*-indole (**124**) (0.22 g, 0.49 mmol), $K_2CO_3$ (12.70 g, 92 mmol, 190 eq). Column chromatography gave a white solid (**133**)

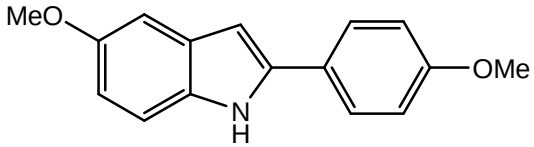
0.12 g (86%). Melting point 152-155 °C; $\nu_{max}$ (Solid)/cm$^{-1}$ 3366 (m, NH), 2917 (m, CH), 1610 (w), 1583 (s), 1461 (s), 1354 (m), 1297 (s), 1227 (m), 1124 (s), 1001 (s), 804 (s), 765 (s), 727 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.38 (1H, s, NH), 7.30-7.26 (1H, m, ArH), 7.08 (1H, s, ArH), 6.85 (2H, s, 2 × ArH), 7.72-6.66 (2H, m, 2 × ArH), 3.93 (6H, s, 2 × $CH_3O$), 3.90 (3H, s, $CH_3O$), 3.86 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 154.88 (C), 154.09 (2 × C), 153.78 (C), 139.29 (C), 132.40 (C), 130.11 (C), 128.87 (C), 112.86 (CH), 112.04 (CH), 103.03 (2 × CH), 102.59 (CH), 100.12 (H), 66.43 ($CH_3O$), 56.63 (2 × $CH_3O$), 56.25 ($CH_3O$).

**(g) 2-(4-Methoxyphenyl)-1*H*-indole (134)**




2-(4-Methoxyphenyl)-1-(phenylsulfonyl)-1H-indole (**125**) (0.40 g, 1.10 mmol), $K_2CO_3$ (28.40 g, 209 mmol, 190 eq). Column chromatography gave a cream white solid (**134**) 0.13 g (52%). Melting point 228-230 °C, lit. value 227-231 °C[82]; $\nu_{max}$ (Solid)/cm$^{-1}$ 3428 (m, NH), 2837 (w, CH), 1543 (m), 1431 (s), 1350 (m), 1287 (m), 1242 (m), 1114 (m), 1026 (s), 933 (w), 834 (s), 782 (s), 738 (s), 659 (m); $\delta_H$ (300 MHz; DMSO; $Me_4Si$) 11.40 (1H, s, NH), 7.79 (2H, d, *J* = 8.65, 2 × ArH), 7.49 (1H, d, *J* = 7.71, ArH), 7.37 (1H, d, *J* = 7.96, ArH), 7.08-6.95 (4H, m, 4 × ArH), 6.76 (1H, s, ArH), 3.81 (3H, s, $CH_3O$); $\delta_C$ (75MHz; DMSO) 160.96 (C), 139.93 (C), 139.09 (C), 130.99 (C), 128.53 (2 × CH), 127.08 (C), 123.19 (CH), 121.81 (CH), 121.38 (CH), 116.52 (2 × CH), 113.22 (CH), 99.50 (CH), 57.38 ($CH_3O$); *m/z* 224 ($M^+$, 100%), 209 (4%), 141 (2%), (Found: 223.2450. $C_{15}H_{13}NO$ requires 223.0997).

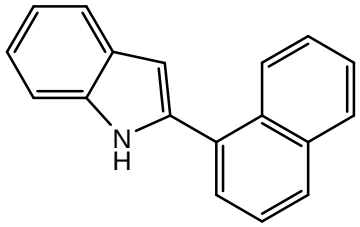
**(h) 5-Methoxy-2-(4-methoxyphenyl)-1*H*-indole (135)**




5-Methoxy-2-(4methoxyphenyl)-1-(phenylsulfonyl)-1*H*-indole (**126**) (0.16 g, 0.41 mmol), $K_2CO_3$ (10.67 g, 77 mmol, 190 eq). Column chromatography gave a white solid (**135**)

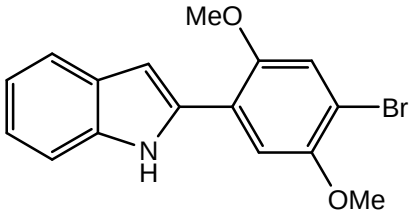
0.051 g (51%). Melting point 116-120 °C; $\nu_{max}$ (Solid)/cm$^{-1}$ 3444 (w, NH), 2931 (w, CH), 1609 (m), 1504 (m), 1467 (s), 1352 (m), 1249 (m), 1210 (m), 1171 (s), 1143 (m), 1089 (m), 1067 (s), 946 (w), 829 (m), 800 (m), 790 (s), 764 (m), 678 (s), 624 (s); $\delta_H$ (300 MHz; acetone-$d_6$; $Me_4Si$) 10.22 (1H, s, NH), 7.64-7.61 (2H, m, 2 × ArH), 7.13 (1H, d, J = 8.71, ArH), 6.91-6.89 (2H, m, 2 × ArH), 6.89 (1H, s, ArH), 6.60 (1H, d, *J* = 2.46, ArH), 6.58 (1H, d, *J* = 2.41, ArH), 6.55 (1H, s, ArH), 3.71 (3H, s, $CH_3O$), 3.66 (3H, s, $CH_3O$); $\delta_C$ (75 MHz; acetone-$d_6$) 160.26 (C), 155.29 (C), 139.60 (C), 133.40 (C), 130.92 (C), 127.18 (2 × CH), 126.47 (C), 115.20 (2 × CH), 112.45 (CH), 112.36 (CH), 102.55 (CH), 98.67 (CH), 55.82 ($CH_3O$), 55.66 ($CH_3O$);

**(i) 2-(Naphthalen-1-yl)-1*H*-indole (136)**



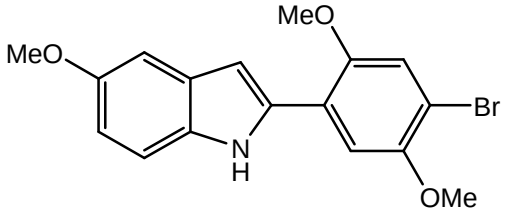
2-(naphthalen-1-yl)-1-(phenylsulfonyl)-1*H*-indole (**127**) (0.30 g, 0.78 mmol), $K_2CO_3$ (20.57 g, 147 mmol, 190 eq). Column chromatography gave a cream white solid (**136**) 0.10 g (52%). Melting point 96-100 °C, lit. value 99-102 °C[83]; $\nu_{max}$ (Solid)/cm$^{-1}$ 3344 (m, NH), 3048 (w, CH), 1595 (w), 1508 (w), 1453 (m), 1394 (m), 1344 (m), 1299 (m), 1107 (w), 783 (s), 773 (s), 737 (s), 693 (s), 656 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.30-8.27 (1H, m, ArH), 8.19 (1H, s, NH), 7.90-7.84 (2H, m, 2 × ArH), 7.69 (1H, d, *J* = 7.60, ArH), 7.57 (1H, d, *J* = 6.23, ArH), 7.58-7.45 (3H, m, 3 × ArH), 7.37 (1H, d, *J* = 7.85, ArH), 7.24-7.14 (2H, m, 2 × ArH), 6.77 (1H, s, ArH); $\delta_C$ (75MHz; $CDCl_3$) 137.67 (C), 137.34 ($C^1$), 134.89 (C), 132.51 (C), 132.07 ($C^1$), 129.84 (C), 129.53 (CH), 129.43 (CH), 128.15 (CH), 127.63 (CH), 127.12 (CH), 126.66 (CH), 126.29 (CH), 123.15 (CH), 121.58 (CH), 1231.14 (CH), 111.84 (CH), 104.66 (CH); *m/z* 244 ($M^+$, 100%), 217 92%), 155 (2%), 105 (2%), (Found: 243.2380. $C_{18}H_{13}N$ requires 243.1048).

**(j) 2-(4-Bromo-2,5-dimethoxyphenyl)-1*H*-indole (166)**




2-(4-Bromo-2,5-dimethoxyphenyl)-1-phenylsulfonylindole (**164**) (0.38 g, 0.806 mmol), $K_2CO_3$ (20.73 g, 150 mmol, 190 eq). Column chromatography gave a cream white solid (**166**) 0.14 g (52%). Melting point 158-161 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 3450 (m, NH), 2938 (w, CH), 1531 (m), 1482 (s), 1415 (m), 1325 (m), 1211 (s), 1178 (m), 1028 (m), 930 (w), 853 (w), 785 (s), 753 (s), 672 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 9.63 (1H, s, NH), 7.63 (1H, d, *J* = 7.79, ArH), 7.41 (1H, d, *J* = 8.03, ArH), 7.32 (1H, s, ArH), 7.24-7.17 (2H, m, 2 × ArH), 7.14-7.08 (1H, m, ArH), 6.88 (1H, s, ArH), 3.94 (3H, s, $CH_3O$), (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 151.12 (C), 150.51 (C), 136.65 ($C^1$), 135.51 (C), 128.27 (C), 122.68 (CH), 120.96 (CH), 120.75 (C), 120.45 (CH), 118.04 (CH), 111.81 (C), 111.46 CH), 111.12 (CH), 100.56 (CH) 57.31 ($CH_3O$), 57.19 ($CH_3O$); *m/z* 331 ($M^+$, 78%), 316 (22%), 264 (26%), 219 (100%), 131 (44%), 69 (90%), (Found: 331.0234. $C_{21}H_{17}NSO_3$ requires 331.0208).

**(k) 2-(4-Bromo-2,5-dimethoxyphenyl)-5-methoxy-1*H*-indole (167)**




2-(4-Bromo-2,5-dimethoxyphenyl)-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**165**) (0.070 g, 0.14 mmol), $K_2CO_3$ (3.67 g, 27 mmol, 190 eq). Column chromatography gave a yellow solid (**167**) 0.020 g (40%). Melting point 166-170 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 3397 (m, NH), 2919 (m, CH), 1623 (w), 1531 (w), 1497 (m), 1464 (m), 1438 (m), 1413 (m), 1275 (m), 1204 (s), 1181 (w), 1149 (m), 1023 (s), 948 (w), 843 (m), 825 (m), 750 (s), 618 (w); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 9.54 (1H, s, NH), 7.33-7.26 (2H, m, 2 × ArH), 7.21 (1H, s, ArH), 7.08 (1H, s, ArH), 6.88-6.82 (2H, m, 2 × ArH), 3.97 (3H, s, $CH_3O$), 3.94 (3H, s, $CH_3O$), 3.86 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 154.41 (C), 150.77 (C), 150.10 (C), 135.69 (C), 131.57 (C),

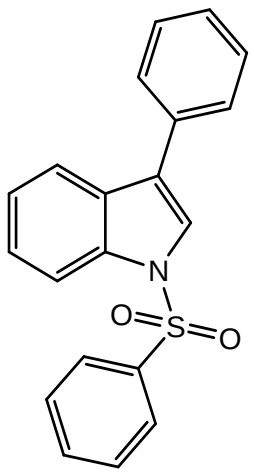
128.32 (C), 120.66 (C), 117.67 (CH), 112.82 (CH), 111.80 (CH), 111.41 (CH), 110.63 (C), 101.73 (CH), 99.89 (CH), 56.95 ($CH_3O$), 56.81 ($CH_3O$), 55.85 ($CH_3O$);

## 4.6 General procedure for the synthesis of 3-aryl-1-(phenylsulfonyl)indole and 3-aryl-5-methoxy-1-(phenylsulfonyl)indole

To $Pd(PPh_3)_4$ (10 mol%) under $N_2$ was added a deoxygenated mixture of 3-bromo-1-(phenylsulfonyl)-1*H*-indole or 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole in DME (5 ml) and arylboronic acid in ethanol (3 ml). The reaction mixture was stirred for about 10 min followed by the addition of deoxygenated solution of $Na_2CO_3$ in water. The resulting reaction mixture was stirred for further 10 mins at rt before being heated to reflux for 8 h.

The reaction mixture was allowed to cool to rt, quenched with water (10.0 ml) and the organic extracts extracted with $CH_2CH_2$ (3 × 30 ml). The organic fractions were combined, dried over $MgSO_4$, filtered through a celite plug and then the excess solvent was removed on a rotary evaporator. The resulting black oil was purified by column chromatography using 10% EtOAc/Hexane as an eluent.

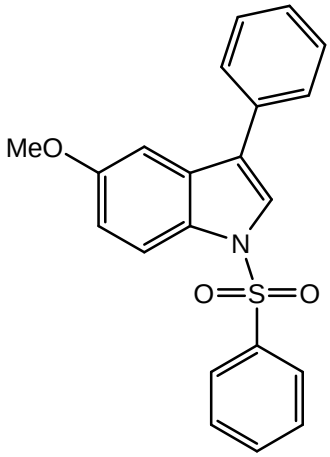
**(a) 3-Phenyl-1-(phenylsulfonyl)-1*H*-indole (137)**




$Pd(PPh_3)_4$ (0.16 g, 10%), 3-bromo-1-(phenylsulfonyl)-1*H*-indole (**107**) (0.45 g, 1.34 mmol), phenylboronic acid (0.25 g, 2.01 mmol, 1.5 eq), $Na_2CO_3$ (1.21 g, 11.4 mmol, 8.5 eq). This gave a yellow oil (**137**) that solidified on standing in 89% yield. Melting point: 139-142 °C, lit. value 141-143 °C[64]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3067 (m, CH), 1607 (w), 1447 (s), 1373 (s), 177 (s), 1132 (s), 1015 (m), 909 (s), 733 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.07 (1H, d, *J* = 8.21, ArH), 7.92 (2H, d, *J* = 7.52, 2 ×

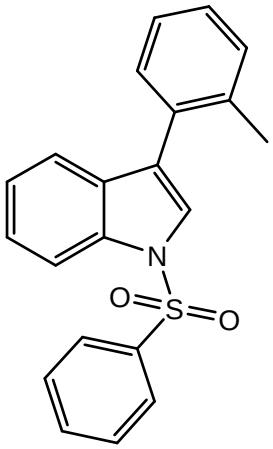
ArH), 7.77 (1H, d, *J* = 7.83, ArH) 7.70 (1H, s, ArH), 7.61-7.24 (10H, m, 10 × ArH); $\delta_C$ (75 MHz; $CDCl_3$) 138.61 (C), 135.92 (C), 134.30 (CH), 133.43 (C),129.74 (2 × CH), 129.62 (C), 129.48 (2 × CH), 128.39 (2 × CH), 128.06 (CH), 127.27 (2 × CH), 125.40 (CH), 124.55 (C), 124.11 (CH), 123.38 (CH), 120.94 (CH), 114.30 (CH); *m*/z 333 ($M^+$, 42%), 193 (18%), 192 (100%), 165 (13%) and 77 (7%) (Found: 333.0830. $C_{20}H_{15}SO_2N$ requires 333.0824).

**(b) 5-Methoxy-3-phenyl-1-(phenylsulfonyl)-1*H*-indole (138)**



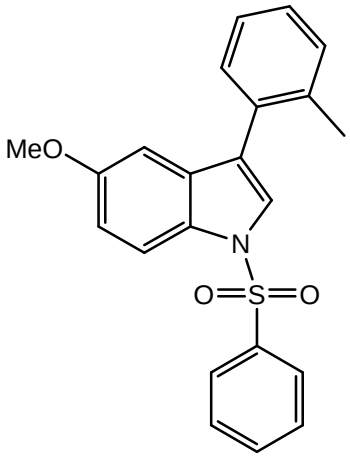

$Pd(PPh_3)_4$ (0.10 g, 0.055 mmol, 10%), 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**109**) (0.20 g, 0.55 mmol), phenylboronic acid (0.10 g, 0.82 mmol, 1.5 eq), $Na_2CO_3$ (0.49 g, 4.70 mmol, 8.5 eq) in water (2.3 ml). This gave a yellow oil (**138**), 0.17 g (86%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3004 (w, CH), 1607 (m), 1470 (s), 1448 (s), 1364 (s), 1262 (s), 1211 (s), 1171 (s), 1143 (s), 1129 (s), 1086 (s), 1029 (s), 997 (w), 958 (m), 850 (m), 836 (m), 801 (s), 750 (s), 723 (s), 682 (s), 650 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.96 (1H, d, *J* = 8.64, ArH), 7.89 (2H, d, *J* = 7.69, 2 × ArH), 7.65 (1H, s, ArH), 7.57 (2H, d, *J* = 7.68, 2 × ArH), 7.51-7.37 (6H, m, 6 × ArH), 7.19 (1H, s, ArH), 6.98 (1H, d, *J* = 9.13, ArH), 3.80 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 156.23 (C), 137.49 (C), 133.26 (CH), 132.46 (C), 129.77 (C), 128.72 (2 × CH), 128.41 (2 × CH), 127.24 (2 × CH), 127.03 (CH), 126.35 (C), 126.19 (2 × CH), 123.72 (C), 123.20 (CH), 114.18 (CH), 113.37 (CH), 102.39 (CH), 55.17 ($CH_3O$).

**(c) 3-*ortho*-Tolyl-1-(phenylsulfonyl)-1*H*-indole (139)**



$Pd(PPh_3)_4$ (0.17g, 10%), 3-bromo-1-(phenylsulfonyl)-1*H*-indole (**107**) (0.50 g, 1.49 mmol), *o*-tolylboronic acid (0.30 g, 2.23 mmol, 1.5 eq), $Na_2CO_3$ (1.34 g, 12.7 mmol, 8.5 eq) in water (6.3 ml). This gave a brown oil (**139**) that did not solidify on standing (0.35g, 68%) literature reported (**139**) as a light orange oil[56]; $\nu_{max}$ (Liquid)/$cm^{-1}$ 3069 (w, CH), 1600 (m), 1448 (m), 1376 (m), 1186 (m), 1014 (w), 909 (s), and 731 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.07 (1H, d, *J* = 8.21, ArH), 7.98-7.87 (2H, m, 2 × ArH), 7.52-7.22 (11H, m, 11 × ArH), 2.21 (3H, s, $CH_3$); $\delta_C$ (75 MHz; $CDCl_3$) 138.60 (C), 137.91 (C), 137.33 (C), 135.42 (C), 134.23 (CH), 130.94 (CH), 129.96 (C), 129.78 (2 × CH), 128.45 (CH), 127.20 (2 × CH), 126.25 (CH), 125.36 (CH), 124.57 (CH), 123.90 (CH), 121.23 (CH), 114.29 (CH), 120.50 (CH), 100.38 (C), 20.85 ($CH_3$); *m*/z 347 ($M^+$, 9%), 336 (37%), 334 (36%), 258 (16%), 257 (100%), 206 (13%), 195 (52%), 193 (55%), 141 (31%), 117 (13%), 116 (88%), 89 (29%), 88 (10%), 77 (84%), 63 (11%), 51 (28%) (Found: 347.0979. $C_{21}H_{17}SO_2N$ requires 347.0980).

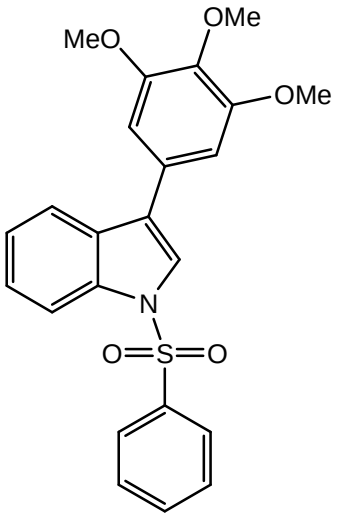
**(d) 5-Methoxy-1-(phenylsulfonyl)-3-*o*-tolyl-1*H*-indole (140)**



$Pd(PPh_3)_4$ (0.10 g, 0.055 mmol, 10%), 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**109**) (0.20 g, 0.55 mmol), *o*-tolylboronic acid (0.11 g, 0.82 mmol, 1.5 eq), $Na_2CO_3$ (0.49 g, 4.70 mmol, 8.5 eq) in water (2.3 ml). This gave a cream white solid (**140**), 0.20 g (95%). Melting point 111-114 °C, lit. value 127-128 °C[56]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3198 (w, CH), 1606 (m), 1470 (s), 1445 (s), 1362 (s), 1257 (s), 1213 (m), 1172 (s), 1134 (s), 1085 (s), 1030 (s), 985 (m), 855 (s), 804 (m), 755 (s), 720 (s), 682 (s), 652 (s), 630 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.96 (1H, d, *J* = 9.02, ArH), 7.87 (2H, d, *J* = 8.47, 2 × ArH), 7.56-7.41 (4H, m, 4 × ArH), 7.32-7.24 (4H,

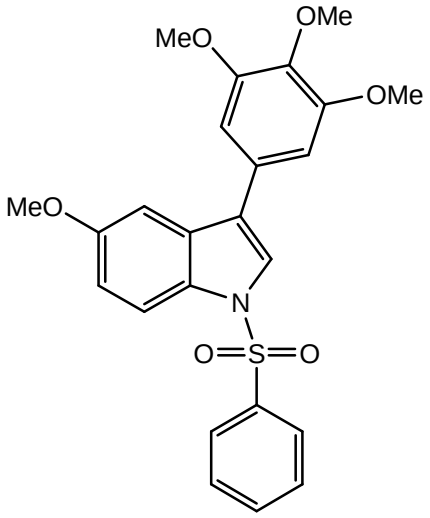
m, 4 × ArH), 6.96 (1H, dd, *J* = 2.12 and 2.16, ArH), 6.73 (1H, d, *J* = 2.04, ArH), 3.73 (3H, s, $CH_3O$), 2.19 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 157.17 (C), 138.44 (C), 137.28 (C), 134.18 (CH), 132.31 (C), 132.22 (C), 130.95 (CH), 130.78 (CH), 130.07 (C), 129.63 (2 × CH), 128.04 (CH), 127.13 (2 × CH), 126.28 (CH), 125.30 (CH), 124.38 (C), 115.20 (CH), 114.48 (CH), 103.29 (CH), 56.10 ($CH_3O$), 20.78 ($CH_3$).

**(e) 1-(Phenylsulfonyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-indole (141)**



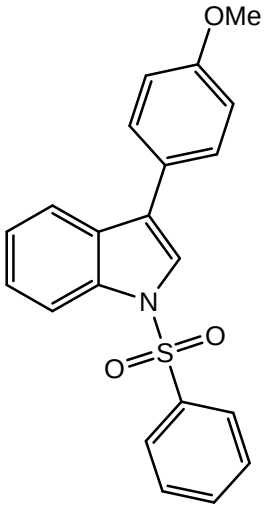

$Pd(PPh_3)_4$ (0.10 g, 0.060 mmol, 10%), 3-bromo-1-(phenylsulfonyl)-1*H*-indole (**107**) (0.20 g, 0.60 mmol), 3,4,5-trimethoxyphenylboronic acid (0.10 g, 0.89 mmol, 1.5 eq), $Na_2CO_3$ (0.53 g, 5.06 mmol, 8.5 eq) in water (2.5 ml). This gave a yellow oil (**141**), 0.19 g (83%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 2935 (w, CH), 1587 (m), 1502 (m), 1446 (m), 1415 (m), 1359 (s), 1268 (m), 1238 (s), 1173 (s), 1123 (s), 1090 (s), 999 (m), 969 (m), 908 (m), 837 (m), 724 (s), 684 (s), 657 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.07 (1H, d, *J* = 8.16, ArH), 7.93 (2H, d, *J* = 7.62, 2 × ArH), 7.77 (1H, d, *J* = 7.75, ArH), 7.67 (1H, s, ArH), 7.38-7.31 (2H, m, 2 × ArH), 7.11-7.06 (3H, m, 3 × ArH), 6.80 (2H, s, × x ArH), 3.91 (9H, s, 3 × $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 151.91 (3 × C), 136.33 (C), 133.71 (C), 132.77 (CH), 132.23 (CH), 128.97 (C), 128.26 (CH), 127.63 (2 × CH), 125.94 (CH), 125.11 (2 × CH), 124.86 (C), 123.36 (CH), 122.45 (C), 121.99 (CH), 120.98 (CH), 118.66 (CH), 112.15 (CH), 103.31 (2 × CH), 59.26 ($CH_3O$), 54.53 (2 × $CH_3O$); *m/z* 424 ($M^+$, 10%), 371 (4%), 295 (2%), 273 (26%), 231 (51%), 213 (89%), 173 (100%), 133 (10%), 119 (2%) (Found: 423.3420. $C_{23}H_{21}NO_5S$ requires 423.1140).

**(f) 5-Methoxy-1-(phenylsulfonyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-indole (142)**




$Pd(PPh_3)_4$ (0.10 g, 0.055 mmol, 10%), 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**109**) (0.20 g, 0.55 mmol), 3,4,5-trimethoxyphenylboronic acid (0.17 g, 0.82 mmol, 1.5 eq), $Na_2CO_3$ (0.49 g, 4.70 mmol, 8.5 eq) in water (2.3 ml). This gave a cream white solid (**142**), 0.15 g (60%). Melting point 132-136 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 2934 (w, CH), 1576 (m), 1503 (m), 1445 (m), 1364 (m0, 1276 (m), 1240 (m), 1221 (m), 1170 (s), 1122 (s), 1031 (m), 997 (m), 976 (m), 903 (m), 833 (m), 815 (m), 751 (s), 725 (m), 691 (m), 643 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.96 (1H, d, *J* = 905, ArH), 7.90 (2H, d, *J* = 7.62, 2 × ArH), 7.64 (1H, s, ArH), 7.57-7.52 (1H, m, ArH), 7.47-7.42 (2H, m, 2 × ArH), 7.20 (1H, d, *J* = 2.12, ArH), 6.99 (1H, dd, *J* = 2.14 and 2.22, ArH), 6.77 (2H, s, 2 × ArH), 3.94 (3H, s, $CH_3O$), 3.91 (6H, s, 2 × $CH_3O$), 3.90 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 156.20 (C), 153.10 (C), 152.82 (2 × C), 137.47 (C), 137.09 (C), 137.02 (C), 133.31 (CH), 129.75 (C), 129.55 (C), 128.76 (2 × CH), 128.02 (C), 126.22 (2 × CH), 123.68 (C), 122.97 (CH), 114.23 (CH), 113.33 (CH), 104.39 ( 2 × CH), 104.03 (2 × CH), 102.41 (CH), 60.41 ($CH_3O$), 55.73 (2 × $CH_3O$), 55.69 ($CH_3O$).

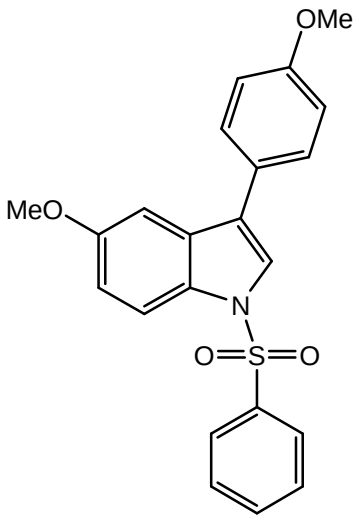
**(g) 3-(4-Methoxyphenyl)-1-(phenylsulfonyl)-1*H*-indole (143)**




$Pd(PPh_3)_4$ (0.34 g, 10%), 3-bromo-1-(phenylsulfonyl)-1*H*-indole (**107**) (1.00 g, 2.98 mmol), 4-methoxyphenylboronic acid (0.68 g, 5.84 mmol, 1.5 eq), $Na_2CO_3$ (2.68 g, 33.10 mmol, 8.5 eq) in water (2.5 ml). This gave a white solid (**143**) (0.89 g, 82%). Melting point: 132-137 °C, literature reported (**143**) as an oil[84]; $\nu_{max}$ (Solid)/$cm^{-1}$ 2964 (w, CH), 1610 (m), 1501 (m), 1446 (m), 1361 (m), 1242 (m), 1131 (s), 1018 (m), 998 (m), 832 (m), 774 (s), 684(m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$)

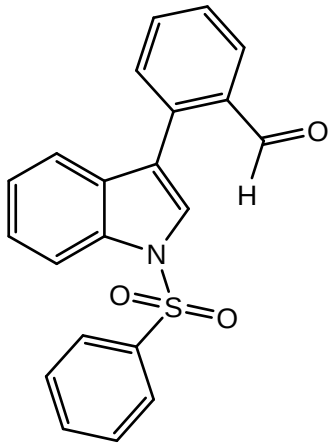
8.06 (1H, d, *J* = 8.20, ArH), 7.91 (2H, d, *J* = 7.58, 2 × ArH), 7.74 (1H, d, *J* = 7.65, ArH), 7.63 (1H, s, ArH), 7.53-7.51 (3H, m, 3 × ArH), 7.30-7.25 (2H, m, 2 × ArH), 7.14 (1H, d, *J* = 8.72, ArH)7.03-6.98 (2H, m, 2 × ArH), 6.82-6.76 (1H, m, ArH), 3.85 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 159.67 (C), 138.19 (C), 133.87 (CH), 133.41 (CH), 130.92 (CH). 129.59 (C), 129.33 (2 × CH), 129.08 (2 × CH), 126.84 (2 × CH), 125.38 (C), 125.05 (CH), 123.61 (CH), 120.49 (CH), 119.93 (C), 116.33 (C), 114.41 (2 × CH), 55.41 ($CH_3O$); *m/z* 363 ($M^+$, 16%), 263 (24%), 219 (100%), 131 (35%), 100 (15%), 69 (35%), (Found: 363.0931. $C_{21}H_{17}NSO_3$ requires 363.0929).

**(h) 5-Methoxy-3-(4-methoxyphenyl)-1-(phenylsulfonyl)-1H-indole (144)**



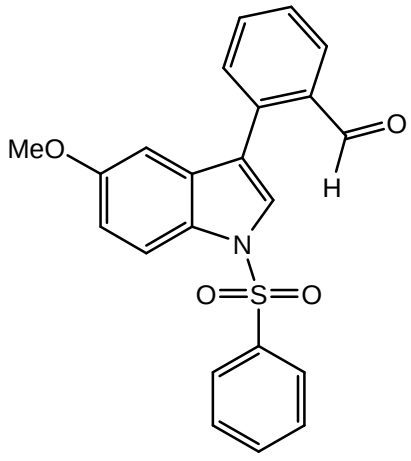

$Pd(PPh_3)_4$ (0.10 g, 0.055 mmol, 10%), 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**109**) (0.20 g, 0.55 mmol), 4-methoxyphenylboronic acid (0.12 g, 0.82 mmol, 1.5 eq), $Na_2CO_3$ (0.49 g, 4.70 mmol, 8.5 eq) in water (2.3 ml). This gave a yellow oil (**144**), 0.18 g (83%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 2933 (w, CH), 1610 (m), 1589 (m), 1571 (m), 1507 (s), 1469 (s), 1445 (s), 1366 (s), 1303 (s), 1244 (s), 1211 (s), 1172 (s), 1129 (s), 1103 (s), 1087 (s), 1031 (s), 958 (m), 835 (s), 788 (s), 769 (s), 751 (s), 722 (s), 684 (s), 665 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.95 (1H, d, *J* = 9.02, ArH), 7.88 (2H, d, *J* = 8.23, 2 × ArH), 7.58-7.40 (5H, m, 5 × ArH), 7.15 (1H, s, ArH), 7.02-6.95 (3H, m, 2 × ArH), 6.77 (1H, s, ArH), 3.86 (3H, s, $CH_3O$), 3.81 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 159.60 (C), 157.14 (C), 138.49 (C), 134.17 (CH), 131.01 (C), 130.61 (C), 129.66 (2 × CH), 129.37 (2 × CH), 127.16 (2 × CH), 125.79 (C), 124.44 (C), 123.54 (CH), 116.42 (C), 115.15 (CH), 114.83 (2 × CH), 114.22 (CH), 103.36 (CH), 56.15 ($CH_3O$), 55.79 ($CH_3O$).

**(i) 3-(2-Formylphenyl)-1-(phenylsulfonyl)-1*H*-indole (145)**



$Pd(PPh_3)_4$ (10%, 0.34 g), starting material (**107**) (1.00 g, 2.98 mmol), 2-formylphenylboronic acid (0.67g, 4.46 mmol, 1.5 eq), $Na_2CO_3$ (2.68 g, 25.3 mmol, 8.5 eq) in water (12.6 ml). This gave a brown oil (**145**) that did not solidify on standing in 67% yield; $\nu_{max}$ (Liquid)/$cm^{-1}$ 3065 (w, CH), 1693 (s, C=O), 1599 (m), 1447 (s), 1374 (s), 1184 (s), 1131 (s), 1014 (m), 911 (m), 784 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 9.90 (1H, s, CHO), 8.08 (2H, t, *J* = 8.10, 2 × ArH), 7.95 (2H, d, *J* = 7.80, 2 × ArH) and 7.68-7.26 (10H, m, 10 × ArH); $\delta_C$ (75 MHz; $CDCl_3$) 192.00 (CHO), 141.61 (C), 138.43 (C), 136.35 (C), 135.39 (C), 134.61 (CH), 134.43 (CH), 131.80 (CH), 129.97 (2 × CH), 129.22 (C),128.93 (CH), 128.46 (CH), 127.35 (2 × CH), 126.00 (CH), 125.92 (CH), 124.68 (CH), 120.55 (CH), 120.39 (C), 114.34 (CH); *m*/z 361 ($M^+$, 4%), 220 (11%), 210 (11%), 182 (15%), 181 (100%), 165 (10%), 153 (13%), 152 (24%), 151 (7%), 83 (11%), 77 (7%), 76 (9%) (Found: 361.0789. $C_{21}H_{15}SO_3N$ requires 361.0773).

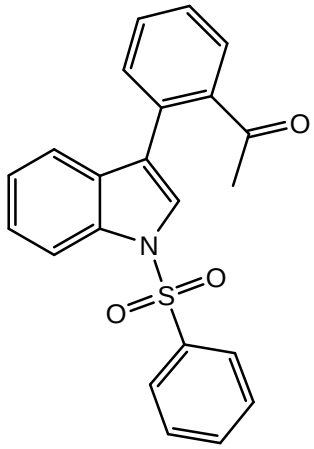
**(j) 2-(5-Methoxy-1-(phenylsulfonyl)-1H-indol-3-yl)benzaldehyde (146)**



$Pd(PPh_3)_4$ (0.10 g, 0.085 mmol, 10%), 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**109**) (0.31 g, 0.85 mmol), 2-formylphenylboronic acid (0.20 g, 1.27 mmol, 1.5 eq), $Na_2CO_3$ (0.76 g, 7.22 mmol, 8.5 eq) in water (3.6 ml). This gave a white solid (**146**), 0.25 g (76%); Melting point 129-132 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 2920 (w, CH), 1681 (s, C=O), 1601 (m), 1468 (m), 1446 (m), 1364 (s), 1256 (m), 1214 (m), 1173 (s), 1134 (s), 1086 (m), 1029 (m), 996 (m), 960 (m), 838 (w), 810 (m), 750 (s), 723 (s), 683 (s), 628 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 9.87 (1H, s, CHO), 8.07 (1H, d, *J* = 7.75, ArH), 7.98 (1H, d, *J* = 9.06,

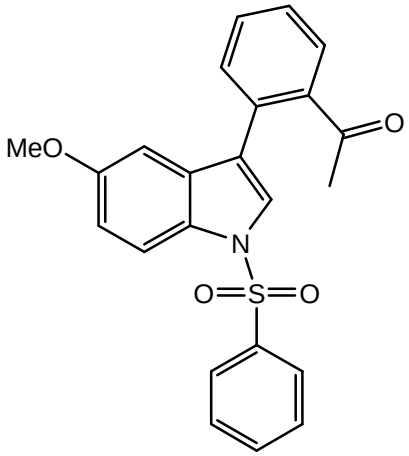
ArH), 7.92 (2H, d, *J* = 7.77, 2 × ArH), 7.69 (1H, t, *J* = 14.83, ArH), 7.59-7.46 (6H, m, 6 × ArH), 7.26 (1H, s, ArH), 7.01 (1H, d, *J* = 9.05, ArH), 6.76 (1H, s, ArH), 3.73 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 192.11 (C=O), 157.61 (C), 138.26 (C), 136.41 (C), 134.87 (C), 134.55 (CH), 134.52 (CH), 132.24 (C), 131.64 (CH), 129.83 (2 × CH), 128.89 (CH), 128.37 (CH), 127.18 (2 × CH), 126.57 (CH), 120.40 (C), 115.25 (CH), 102.44 (CH), 56.10 ($CH_3O$).

**(k) 1-(2-(1-(Phenylsulfonyl)-1*H*-indol-3-yl) acetophenone (147)**




$Pd(PPh_3)_4$ (0.14 g, 10%), 3-bromo-1-(phenylsulfonyl)-1*H*-indole (**107**) (0.40 g, 1.19 mmol), 2-acetylphenylboronic acid (0.29 g, 1.79 mmol, 1.5 eq), $Na_2CO_3$ (1.61 g, 15.2 mmol, 8.5 eq) in water (7.6 ml). This gave a brown oil (**147**), 0.38 g (84%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3063 (w, CH), 1685 (s, C=O), 1446 (s), 1370 (s), 1273 (m), 1242 (m), 1175 (s), 1127 (s), 1089 (s), 1012 (s), 931 (m), 745 (s), 724 (s), 684 (s), 636 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.09 (1H, d, *J* = 8.11, ArH), 7.92 (2H, d, *J* = 7.49, 2 × ArH), 7.61 (1H, d, *J* = 7.30, ArH), 7.55 (1H, s, ArH), 7.52 (2H, d, *J* = 7.34, 2 × ArH), 7.46-7.35 (6H, m, 6 × ArH), 7.27-7.22 (1H, m, ArH), 1.90 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 203.89 (C=O), 141.77 (C), 138.61 (C), 135.52 (C), 134.42 (CH), 131.40 (CH), 131.37 (CH), 130.76 (C), 130.53 (C), 129.78 (2 × CH), 128.56 (CH), 127.18 (2 × CH), 125.83 (CH), 124.91 (CH), 124.40 (CH), 123.45 (C), 120.57 (CH), 114.37 (CH), 30.14 ($CH_3$); *m/z* 376 ($M^+$, 80%), 358 (2%), 248 (3%), 235 (32%), 218 (2%), 163 (1%), 135 (4%), (Found: 375.1530. $C_{22}H_{17}NO_3S$ requires 375.0929).

**(l) 1-(2-(5-Methoxy-1-(phenylsulfonyl)-1*H*-indol-3-yl) acetophenone (148)**



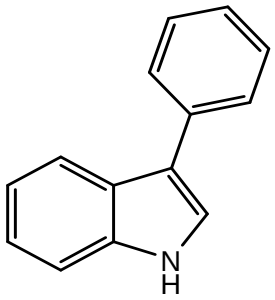

$Pd(PPh_3)_4$ (0.10 g, 0.055 mmol, 10%), 3-bromo-5methoxy-1-(phenylsulfonyl)-1*H*-indole (**109**) (0.20 g, 0.55 mmol), 2-acetylphenylboronic acid (0.14 g, 0.82 mmol, 1.5 eq), $Na_2CO_3$ (0.49 g, 4.70 mmol, 8.5 eq) in water (2.3 ml). This gave a cream white solid (**148**), 0.17 g (77%). Melting point 105-109 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 2895 (w, CH), 1690 (s, C=O), 1610 (w), 1478 (s), 1447 (m), 1363 (s), 1271 (m), 1246 (s), 1212 (s), 1174 (s), 1134 (s), 1089 (s), 1030 (m), 961 (s), 851 (m), 834 (m), 757 (m), 724 (s), 687 (m), 632 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.98 (1H, d, *J* = 9.05, ArH), 7.89 (2H, d, *J* = 7.73, 2 × ArH), 7.62-7.42 (8H, m, 8 × ArH), 6.99 (1H, dd, *J* = 1.95 and 1.96, ArH), 6.77 (1H, s, ArH), 3.74 (3H, s, $CH_3O$), 1.87 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 204.21 (C=O), 157.44 (C), 141.77 (C), 138.50 (C), 134.35 (CH), 131.51 (CH), 131.21 (CH), 130.78 (C), 130.09 (C), 129.73 (2 × CH), 128.60 (CH), 128.57 (CH), 127.11 (2 × CH), 125.50 (CH), 123.71 (C), 115.39 (CH), 115.21 (C), 102.50 (CH), 56.05 ($CH_3O$), 30.11 ($CH_3$).

## 4.7 Typical procedure for removing of phenylsulfonyl protecting group on 3-aryl-1-(phenylsulfonyl)-1*H*-indoles and 3-aryl-5-methoxy-1-(phenylsulfonyl)-1*H*-indoles

The substrate was dissolved in methanol (20 ml) at rt under $N_2$ atmosphere, $K_2CO_3$ was added to the solution and the reaction mixture was heated to reflux under $N_2$ for 18 h. The reaction mixture was then allowed to cool down to rt and filtered through a celite plug and then the filtrate concentrated under reduced pressure. Water was added to the crude material and slowly acidified to pH 2-4 with aqueous 10% HCl. The aqueous portion was saturated with solid NaCl and the organic material extracted with $CH_2Cl_2$ (3 × 30 ml). The combined organic extracts were washed two times with water (20 ml), brine (20 ml), dried over $MgSO_4$ and concentrated under

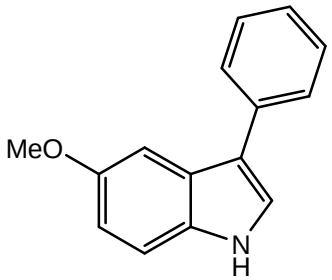
reduced pressure. This resulted in brown oils that were subjected to column chromatography using 10% EtOAc/Hexane as an eluent.

**(a) 3-Phenyl-1*H* indole (149)**



3-Phenyl-1-phenylsulfonylindole (**137**) (0.36 g, 1.08 mmol), $K_2CO_3$ (28.35 g, 205.4 mmol, 190 eq). Column chromatography gave a yellow oil that solidified on standing to yellow solid (**149**) in 81% yield. Melting point: 86-89 °C, li. value 89 °C[85]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3412 (s, NH), 3055 (m, CH), 1602 (m), 1545 (m), 1457 (m), 1416 (m), 1337 (m), 1264 (s), 1100 (m), 1014 (w), 960 (w), 823 (w), 741 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.17 (1H, s, NH), 7.94 (1H, d, *J* = 7.70, ArH), 7.66 (2H, d, *J* = 7.10, 2 × ArH), 7.46-7.18 (7H, m, 7 × ArH); $\delta_C$ (75 MHz; $CDCl_3$) 137.15 (C), 136.00 (C), 129.23 (2 × CH), 127.98 (2 × CH), 126.43 (CH), 126.27 (C), 122.86 (CH), 122.34 (CH), 120.7 (CH), 120.20 (CH), 118.71 (C), 111.90 (CH); *m*/*z* 193 ($M^+$, 100%), 192 (9%), 191 (4%), 165 (21%), 164 (4%), 163 (4%), 96 (6%), 95 (6%), 90 (3%) (Found: 193.0897. $C_{14}H_{10}N$ requires 193.0892).

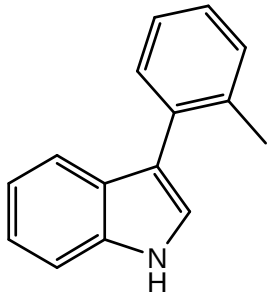
**(b) 5-Methoxy-3-phenyl-1*H*-indole (150)**



5-Methoxy-3-phenyl-1-(phenylsulfonyl)-1*H*-indole (**138**) (0.17 g, 0.47 mmol), $K_2CO_3$ (12.30 g, 89 mmol, 190 eq). Column chromatography gave a brown oil (**150**) 0.085 g (85%), literature reported (**150**) as a solid with melting point 66-67 °C[86]; $\nu_{max}$ (Liquid)/$cm^{-1}$ 3409 (s, NH), 2935 (w, CH), 1620 (m), 1601 (m), 1581 (m), 1542 (s), 1477 (m), 1437 (m), 1310 (m0, 1293 (m), 1268 (s), 1238 (s), 1207 (m), 1175 (m), 1154 (m), 1109 (s), 1071 (m), 1026 (m), 966 (m), 913 (m), 834 (s), 797 (s), 762 (s), 697 (s), 679 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.01 (1H, s, NH), 7.56 (2H, d, *J* = 7.83, 2 × ArH), 7.39-7.34 (2H, m, 2 × ArH), 7.31 (1H, s, ArH), 7.23-7.16 (3H,

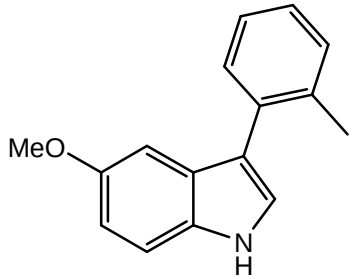
m, 3 × ArH), 6.83 (1H, d, *J* = 8.46, ArH), 3.77 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 154.14 (C), 135.18 (C), 130.21 (C), 128.51 (C), 128.31 (2 × CH), 126.83 (2 × CH), 126.46 (C), 125.38 (CH), 122.15 (CH), 112.12 (CH), 111.64 (CH), 55.46 ($CH_3O$).

**(c) 3-*ortho*-Tolyl-1*H*-indole (151)**



3-*ortho*-olyl-1-phenylsulfonylindole (**139**) (0.21 g, 0.61 mmol), $K_2CO_3$ (15.87 g, 115.0 mmol, 190 eq). Column chromatography a gave brown oil (**151**) that did not solidify on standing in 64% yield, literature reported (**151**) as an oil[56]; $\nu_{max}$ (Liquid)/$cm^{-1}$ 3476 (s, NH), 3061 (w, CH), 1620 (w), 1551 (w), 1456 (m), 1344 (w), 1253 (w), 1094 (m), 909 (s), 731 (s), 650 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.17 (1H, s, NH), 7.52 (1H, d, *J* = 7.91, ArH), 7.43-7.39 (2H, m, 2 × ArH), 7.32-7.23 (4H, m, 4 × ArH), 7.14-7.10 (2H, m, 2 × ArH), 2.31 (3H, s, $CH_3$); $\delta_C$ (75 MHz; $CDCl_3$) 137.30 (C), 136.35 (C), 134.93 (C), 131.39 (CH), 130.85 (CH), 127.67 (C), 127.26 (CH), 126.12 (CH), 123.24 (CH), 122.68 (CH), 120.60 (CH), 120.41 (CH), 117.97 (C), 111.63 (CH), 21.16 ($CH_3$); *m*/*z* 207 ($M^+$, 100%), 206 (73%), 205 (7%), 204 (16%), 180 (7%), 179 (10%), 178 (15%), 103 (7%), 102 (8%), 89 (6%) (Found: 207.1051. $C_{15}H_{13}N$ requires 207.1048).

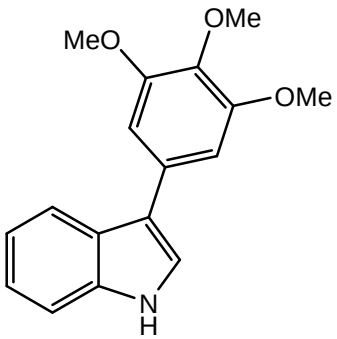
**(d) 5-Methoxy-3-o-tolyl-1*H*-indole (152)**



5-Methoxy-1-(phenylsulfonyl)-3-*o*-tolyl-1*H*-indole (**140**) (0.25 g, 0.74 mmol), $K_2CO_3$ (19.5 g, 140 mmol, 190 eq). Column chromatography gave a yellow oil (**152**) 0.16 g (86%), literature reported (**151**) as an oil[56]; $\nu_{max}$ (Liquid)/$cm^{-1}$ 3411 (m, NH), 1622 (m), 1580 (m), 1478 (s), 1437 (s), 1261 (s), 1208 (s), 1175 (s), 1122 (m), 1093 (s), 1026 (s), 916 (m), 790 (s), 763 (s), 745 (s), 724 (m), 668 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.11 (1H, s, NH), 7.43-7.40 (1H, m, ArH),

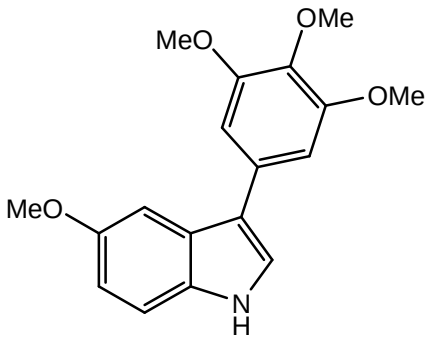
7.35-7.22 (3H, m, 3 × ArH), 7.12 (1H, d, *J* = 1.95, ArH), 6.94 (1H, s, ArH), 6.89 (1H, dd, *J* = 1.81 and 1.92, ArH), 3.78 (3H, s, $CH_3O$), 2.32 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 154.63 (C), 137.13 (C), 134.80 (C), 131.20 (C), 130.99 (CH), 130.60 (CH), 127.71 (C), 126.96 (CH), 125.90 (CH), 123.81 (CH), 117.50 (C), 112.83 (CH), 112.18 (CH), 101.75 (CH), 56.12 ($CH_3O$), 20.93 ($CH_3$).

**(e) 3-(3,4,5-Trimethoxyphenyl)-1*H*-indole (153)**




1-(Phenylsulfonyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-indole (**141**) (0.19 g, 0.45 mmol), $K_2CO_3$ (11.80 g, 85 mmol, 190 eq). Column chromatography gave a brown oil (**153**) 0.085 g (65%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3350 (m, NH), 2931 (m), CH), 1583 (s), 1498 (m), 1456 (s), 1408 (m), 1361 (m), 1334 (m), 1120 (s), 999 (s), 836 (m), 739 (s), 659 (m), 623 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.35 (1H, s, NH), 7.92 (1H, d, *J* = 7.74, ArH), 7.44 (1H, d, *J* = 7.96, ArH), 7.35 (1H, d, *J* = 2.34, ArH), 7.24-7.21 (2H, m, 2 × ArH), 6.88 (2H, s, 2 × ArH), 3.93 (6H, s, 2 × $CH_3O$), 3.91 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 152.06 (2 × C), 151.94 (C), 135.17 (C), 129.87 (C), 124.28 (C), 121.05 (CH), 120.19 (CH), 118.90 (CH), 118.17 (CH), 117.01 (C), 110.06 (CH), 103.27 (2 × CH), 54.85 ($CH_3O$), 54.74 (2 × $CH_3O$);

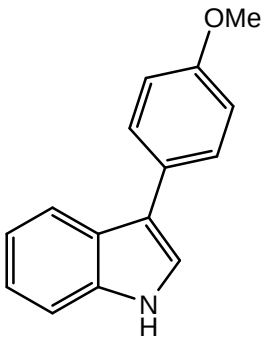
**(f) 5-Methoxy-3-(3,4,5-trimethoxyphenyl)-1*H*-indole (154)**




5-Methoxy-1-(phenylsulfonyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-indole (**142**) (0.11 g, 0.24 mmol), $K_2CO_3$ (6.40 g, 46 mmol, 190 eq). Column chromatography gave a brown oil (**154**) 0.055 g (72%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3348 (m, NH), 2937 (w, CH), 1586 (s), 1481 (s), 1334 (m), 1212 (m), 1172 (s), 1118 (s), 994 (s),

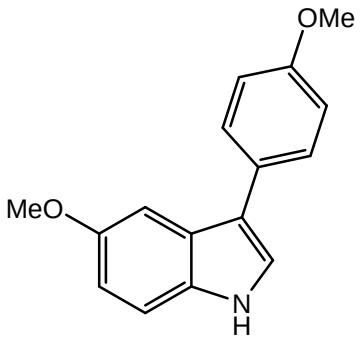
798 (m), 725 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.46 (1H, s, NH), 7.37-7.32 (3H, m, 3 × ArH), 6.93 (1H, d, *J* = 8.82, ArH), 6.85 (2H, s, 2 × ArH), 6.10 (2H, s, 2 × ArH), 3.87 (3H, s, $CH_3O$), 3.78 (3H, s, $CH_3O$), 3.77 (6H, s, 2 × $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 154.20 (C), 153.33 (C), 153.13 (2 × C), 131.47 (C), 131.27 (C), 125.74 (C), 122.26 (CH), 117.66 (C), 112.19 (CH), 111.96 (CH), 101.14 (CH), 92.52 (2 × CH), 60.68 ($CH_3O$), 55.81 (2 × $CH_3O$), 55.60 ($CH_3O$).

**(g) 3-(4-Methoxyphenyl)-1*H*-indole (155)**




3-(4-Methoxyphenyl)-1-(phenylsulfonyl)-1*H*-indole (**143**) (0.83 g, 2.39 mmol), $K_2CO_3$ (62.40 g, 452 mmol, 190 eq). Column chromatography gave a cream white solid (**155**) (0.53 g, 79%). Melting point: 130-134 ˚C, lit. value 131-133 °C[87]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3427 (s, NH), 2955 (w, CH), 1611 (m), 1542 (m), 1440 (m), 1322 (m), 1241 (s), 1181 (m), 1030 (s), 957 (w), 809 (m), 794 (m), 648 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.13 (1H, NH), 7.89 (1H, d, *J* = 7.77, ArH), 7.58 (2H, d, *J* = 8.68, 2 × ArH), 7.38 (1H, d, *J* = 7.90, ArH), 7.25-7.17 (3H, m, 3 × ArH), 6.99 (2H, d, *J* = 8.67, 2 × ArH), 3.85 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 158.49 (C), 136.98 (C), 131.30 (C), 129.01 (2 × CH), 128.52 (C), 122.69 (CH), 121.56 (CH), 120.53 (CH), 120.12 (CH), 114.66 (2 × CH), 113.25 (C), 111.75 (CH), 55.76 ($CH_3$); *m/z* 223 ($M^+$, 32%), 219 (100%), 208 (21%), 131 (41%), 100 (16%), 69 (80%), (Found: 223.0995. $C_{21}H_{17}NO$ requires 223.0997).

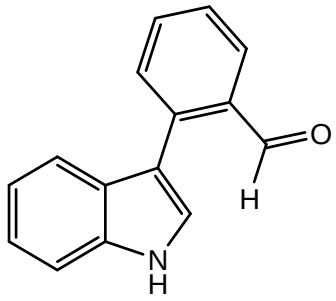
**(h) 5-Methoxy-3-(4-methoxyphenyl)-1H-indole (156)**




5-Methoxy-3-(4-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-indole (**144**) (0.15 g, 0.38 mmol), $K_2CO_3$ (10.00 g, 73 mmol, 190 eq). Column chromatography gave a yellow oil (**156**) 0.070 g (72%), literature reported (**156**) as a solid with melting point 151.2-152 °C[88]; $\nu_{max}$ (Liquids)/$cm^{-1}$ 3405 (m), NH), 2916 (w),

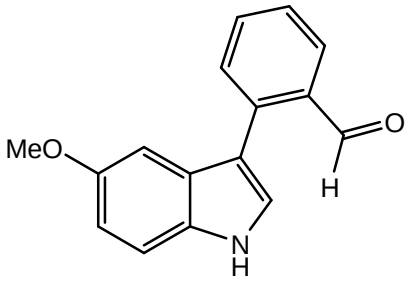
CH), 1612 (m), 1547 (m), 1503 (s), 1479 (s), 1438 (m), 1296 (m), 1276 (s), 1240 (s), 1207 (s), 1173 (s), 1104 (s), 1027 (s), 968 (m), 916 (m), 833 (m), 790 (s), 750 (m), 638 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.10 (1H, s, NH), 7.56 (2H, d, *J* = 8.49, 2 × ArH), 7.33-7.25 (3H, m, 3 × ArH), 7.01 (2H, d, *J* = 8.50, 2 × ArH), 6.91 (1H, dd, *J* = 2.03 and 2.08, ArH), 3.86 (6H, s, 2 × $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 158.43 (C), 154.99 (C), 132.12 (C), 128.93 (2 × CH), 126.68 (C), 122.45 (CH), 118.21 (C), 116.43 (C), 115.22 (C), 114.71 (2 × CH), 112.99 (CH), 112.46 (CH), 101.86 (CH), 56.40 ($CH_3O$), 55.79 ($CH_3O$)

**(i) 3-(2-Formylphenyl)-1*H*-indole (157)**



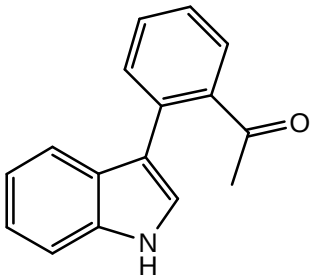

3-(2-formylphenyl)-1-phenylsulfonylindole (**145**) (0.36 g, 0.99 mmol), $K_2CO_3$ (25.96 g, 188.1 mmol, 190 eq), Column chromatography gave a brown oil (**157**) that did not solidify on standing in 72% yield; $\nu_{max}$ (Liquid)/$cm^{-1}$ 3461 (m, NH), 3055 (m, CH), 1687 (m, C=O), 1600 (w), 1545 (w), 1420 (m), 1265 (s), 1196 (w), 1099 (w), 896 (m), 735 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 10.10 (1H, s, CHO), 8.61 (1H, s, NH), 8.06 (1H, d, *J* = 1.10, ArH), 7.67-7.60 (3H, m, 3 × ArH), 7.47 (2H, d, *J* = 8.08, 2 × ArH), 7.26-7.19 (3H, m, 3 × ArH); $\delta_C$ (75 MHz; $CDCl_3$) 193.63 (CHO), 139.30 (C), 136.52 (C), 134.82 (C), 131.84 (CH), 128.09 (CH), 127.78 (C), 127.47 (CH), 125.43 (CH), 123.44 (CH), 121.35 (CH), 119.73 (CH), 111.96 (CH); *m*/*z* 221 ($M^+$, 98%), 193 (100%), 165 (58%), 86 (24%), 84 (38%), 71 (15%), 57 (27%), 43 (25%) (Found: 221.2001. $C_{15}H_{11}NO$ requires 221.0841).

**(j) 2-(5-Methoxy-1H-indol-3-yl)benzaldehyde (158)**



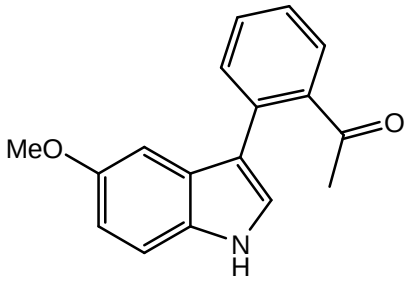

2-(5-Methoxy-1-(phenylsulfonyl)-1H-indol-3-yl)benzaldehyde (**146**) (0.50 g, 1.28 mmol), $K_2CO_3$ (33.50 g, 240 mmol, 190 eq). Column chromatography gave a brown oil (**158**) 0.30 g (94%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3359 (m, NH), 2830 (w, CH), 1680 (s, C=O), 1622 (m), 1597 (m), 1537 (m), 1448 (s), 1438 (s), 1389 (s), 1290 (s), 1258 (s), 1176 (m), 1117 (m), 1027 (s), 969 (s), 917 (s), 830 (m), 799 (s), 766 (s), 729 (s), 690 (s), 638 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 10.01 (1H, s, CHO), 8.51 (1H, s, NH), 8.06 (1H, d, *J* = 7.79, ArH), 7.70-7.62 (2H, m, 2 × ArH), 7.56-7.46 (2H, m, 2 × ArH), 7.35 (1H, d, *J* = 8.91, ArH), 7.21 (1H, s, ArH), 7.02 (1H, s, ArH), 6.94 (1H, d, *J* = 8.87, ArH), 3.80 (H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 194.29 (CHO), 156.15 (C), 140.05 (C), 135.26 (C), 134.91 (CH), 134.22 (C), 132.23 (CH), 130.30 (C), 128.67 (CH), 127.93 (CH), 126.60 (CH), 114.46 (CH), 113.34 (CH), 101.55 (CH), 56.85 ($CH_3O$).

**(k) 1-(2-(1*H*-indol-3-yl) acetophenone (159)**



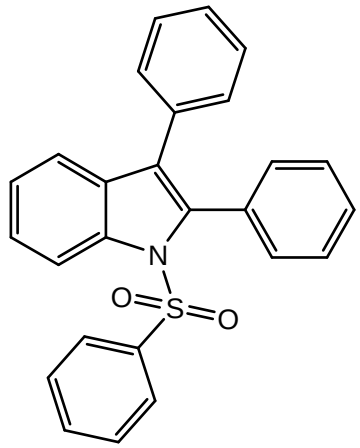

1-(2-(1-(Phenylsulfonyl)-1*H*-indol-3-yl) acetophenone (1**47**) (0.21 g, 0.56 mmol), $K_2CO_3$ (14.68 g, 106 mmol, 190 eq). Column chromatography gave a brown oil (**159**) 0.13 g (92%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3329 (b, NH), 3057 (w, CH), 1670 (s, C=O), 1596 (m), 1544 (m), 1456 (m), 1352 (m), 1277 (m), 1224 (m), 1098 (m), 1009 (m), 739 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.61 (1H, s, NH), 7.66-7.50 (4H, m, 4 × ArH), 7.42-7.36 (2H, m, 2 × ArH), 7.27-7.14 (2H, m, 2 × ArH), 7.09 (1H, d, *J* = 2.44, ArH), 2.02 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 206.60 (C=O), 142.03 (C), 136.68 (C), 133.44 (C), 131.28 (CH), 131.12 (CH), 128.07 (CH), 127.09 (CH), 126.83 (C), 124.27 (CH), 123.19 (CH), 120.98 (CH), 119.80 (CH), 116.72 (C), 111.94 (CH), 30.45 ($CH_3$); *m/z* 236 ($M^+$, 100%), 218 (18%), 194 (3%), 143 (3%), (Found: 235.2560. $C_{16}H_{13}NO$ require 235.0997).

**(l) 1-(2-(5-Methoxy-1*H*-indol-3-yl) acetophenone (160)**




1-(2-(5-Methoxy-1-(phenylsulfonyl)-1*H*-indol-3-yl) acetophenone (**148**) (0.17 g, 0.42 mmol), $K_2CO_3$ (11.01 g, 80 mmol, 190 eq). Column chromatography gave a cream white solid (**160**) 0.090 g (82%). Melting point 116-120 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 3268 (m, NH), 2987 (w, CH), 1666 (s, C=O), 1592 (m), 1537 (m), 1486 (m), 1353 (m), 1281 (s), 1214 (s), 1135 (m), 1031 (m), 920 (m), 842 (m), 805 (s), 764 (s), 701 (s), 645 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.56 (1H, s, NH), 7.59-7.51 (3H, m, 3 × ArH), 7.42-7.37 (1H, m, ArH), 7.31-7.25 (1H, m, ArH), 7.10 (1H, d, *J* = 2.36, ArH), 7.05 (1H, d, *J* = 1.72, ArH), 6.91 (1H, dd, *J* = 2.14 and 2.11, ArH), 3.80 (3H, s, $CH_3O$), 2.03 (3H, s, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 204.82 (C=O), 153.38 (C), 140.05 (C), 131.70 (C), 129.79 (C), 129.33 (CH), 129.20 (CH), 126.26 (CH), 125.34 (C), 125.17 (CH), 122.87 (CH), 114.70 (C), 111.77 (CH), 110.81 (CH), 99.21 (CH), 55.33 ($CH_3O$), 28.49 ($CH_3$).

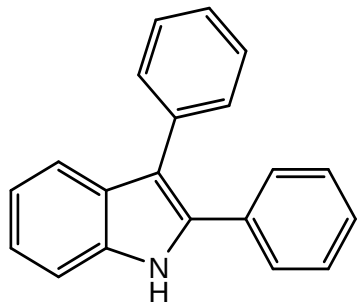
## 4.8 Synthesis of 2,3-Diphenyl-1-(phenylsulfonyl)-1*H*-indole (161)




To $Pd(PPh_3)_4$ (10%, 0.17 g) was added a deoxygenated mixture of the 2,3-dibromo-1-(phenylsulfonyl)-1*H*-indole (**108**) (0.50 g, 1.49 mmol) in DME (5 ml) and phenylylboronic acid (**123**) (0.27 g, 2.23 mmol, 1.5 eq) in ethanol (3 ml). The reaction mixture was stirred at rt for about 10 min followed by the addition of deoxygenated solution $Na_2CO_3$ (1.34 g, 12.7 mmol, 8.5 eq) in water (6.3 ml). The resulting reaction mixture was stirred for further 10 min at rt before being heated to reflux for 8 h. The reaction mixture was allowed to cool to rt, quenched with water (10 ml) and the organic extracts extracted with $CH_2Cl_2$ (3 × 30 ml). The organic fractions were combined, dried over $MgSO_4$,

filtered through a celite plug and the excess solvent was removed on a rotary evaporator. The resulting black oil was purified by column chromatography using 10% EtOAc/Hexane as an eluent. This gave a light red solid (**161**) which was recrystallized from $CH_2Cl_2$ to give a cream white solid in 56% yield. Melting point: 173-175 °C, lit. value 174-176 °C[69]; $\nu_{max}$ (Solid)/cm$^{-1}$ 3065 (m, CH), 1604 (w), 1447 (s), 1379 (s), 1184 (s), 1128 (m), 1087 (s), 910 (s), 733 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.41 (1H, d, *J* = 8.42, ArH), 7.50-7.43 (5H, m,5 × ArH), 7.321-7.20 (11H, m, 11 × ArH ), 7.09-7.06 (2H, m, 2 × ArH); $\delta_C$ (75 MHz; $CDCl_3$) 138.20 (C), 137.45 (C), 136.88 (C), 133.56 (CH), 132.60 (C), 132.19 (2 × CH), 130.87 (C), 130.44 (C), 129.83 (2 × CH), 128.77 (2 × CH), 128.61 (CH), 128.50 (2 × CH), 127.34 (2 × CH), 127.01 (CH), 126.95 (2 × CH), 125.31 (CH), 124.93 (C), 124.38 (CH), 120.16 (CH), 116.33 (CH); *m/z* 409 ($M^+$, 42%), 334 (7%), 269 (29%), 268 (100%), 267 (58%), 266 (13%), 219 (21%), 213 (10%), 193 (12%), 190 (7%), 165 (21%), 163 (10%), 77 (19%), 51 (7%) (Found: 409.1195. $C_{26}H_{19}SO_2N$ requires 409.1137).

## 4.9 Synthesis of 2,3-Diphenyl-1*H* indole (162)



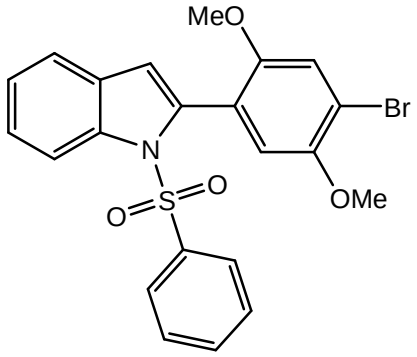

2,3-Diphenyl-1-(phenylsulfonyl)-1*H*-indole (**161**) (0.28 g, 0.69 mmol) was dissolved in methanol (20 ml) at rt under $N_2$ atmosphere, $K_2CO_3$ (17.80 g, 131.1 mmol, 190 eq) was added to the solution and the reaction mixture was heated to reflux under $N_2$ for 18 h. The reaction mixture was then allowed to cool to rt and filtered through a celite plug and then the filtrate concentrated under reduced pressure. Water was added to the crude material and slowly acidified to pH 2-4 with aqueous 10% HCl. The aqueous portion was saturated with solid NaCl and the organic material extracted with $CH_2Cl_2$ (3 × 30 ml). The combined organic extracts were washed two times with water (20.0 ml), brine (20.0 ml), dried over $MgSO_4$ and concentrated under reduced pressure. This resulted in brown oils that were subjected to column chromatography using 10% EtOAc/Hexane as an eluent. Column chromatography gave a yellow oil (**162**) that solidified on standing in 60% yield. Melting point: 224-227˚C; $\nu_{max}$ (Solid)/cm$^{-1}$ 3461 (m, NH), 3062 (w, CH), 1603 (w), 1454 (m), 1330 (w), 1250

(w), 1184 (w), 1093 (w), 909 (s), 732 (s), 650 (m); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.21 (1H, s, NH), 7.68 (1H, d, *J* = 7.90 ArH), 7.45-7.37 (6H, m, 6 × ArH), 7.34-7.12 (7H, m, 7 × ArH); $\delta_C$ (75 MHz; $CDCl_3$) 136.3 ($C^1$), 135.5 ($C^1$), 134.5 (C), 133.1 (C), 132.5 (C), 130.6 (2 × CH), 130.3 (C), 129.1 (2 × CH), 128.9 (2 × CH), 128.6 (2 × CH), 128.1 (CH), 126.7 (CH), 123.1 (CH), 120.9 (CH), 120.1 (CH), 111.3 (CH); *m*/z 269 ($M^+$, 100%), 268 (17%), 267 (22%), 266 (5%), 254 (4%), 241 (3%), 193 (18%), 165 (13%), 163 (3%), 134 (7%), 133 (10%), 132 (5%), 127 (6%), 42 (4%) (Found: 269.1217. $C_{20}H_{15}N$ requires 269.1205).

## 4.10 Synthesis of a novel class compounds

### 4.10.1 Synthesis of 2-arylindoles via one-pot synthesis

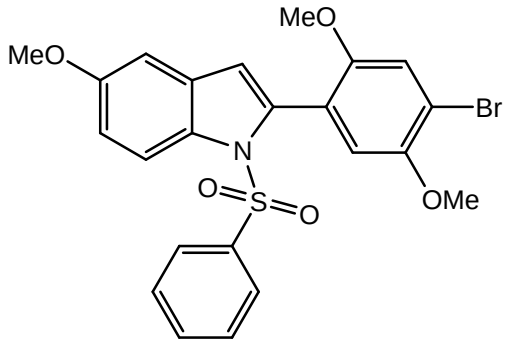
#### 4.10.1.1 2-(4-Bromo-2,5-dimethoxyphenyl)-1-(phenylsulfonyl)-1-*H*-indole (164)




To 1-(phenylsulfonyl)-1*H*-indole (**36**) (1.00 g, 3.89 mmol) in a dry flask was added isopropylmagnesium chloride solution in THF (~0.8 M in excess) and diisopropylamine (1 ml). The reaction mixture was maintained at rt under $N_2$ atmosphere for 16 h. The reaction mixture was treated with 1,4-dibromo-2,5-dimethoxybenzene (2.30 g, 7.78 mmol, 2 eq) and $Pd(PPh_3)_4$ (0.23 g, 0.20 mmol, 0.050 eq). After stirring at rt for 48 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of $NH_4Cl$. The mixture was extracted with $CH_2Cl_2$ (3 × 30 ml), the organic layers combined and dried over $MgSO_4$, filtered though celite plug and excess solvent removed on a rotary evaporator. This resultant black oil was subjected to column chromatography. The resultant light black oil was recrystallized from the mixture of $CH_2Cl_2$ and hexane to give white solid (**164**) (0.38 g, 21%). Melting point: 181-183 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 2838 (w, CH), 1585 (w), 1489 (s), 1439 (m), 1431 (m), 1367 (s), 1279 (m), 1213 (s), 1177 (s), 1118 (m), 1090 (m), 1068 (s), 1034 (s), 999 (s), 850 (s), 810 (s), 752 (s), 730 (s), 686 (s), 639 (s);$\delta_H$ (300 MHz; $CDCl_3$;

$Me_4Si$) 8.25 (1H, d, *J* = 8.33, ArH), 7.51-7.44 (4H, m, 4 × ArH), 7.37-7.23 (4H, m, 4 × ArH), 7.12 (1H, s, ArH), 6.78 (1H, s, ArH), 6.58 (1H, s, ArH), 3.82 (3H, s, $CH_3O$), 3.68 (3H, s, $CH_3O$); $\delta_C$ (75MHz; $CDCl_3$) 153.08 (C), 149.63 (C), 139.05 (C), 137.99 (C), 137.04 (C), 133.85 (CH), 130.14 (C), 129.06 (2 × CH), 127.13 (2 × CH), 125.25 (CH), 124.32 (CH), 121.25 (CH), 116.72 (CH), 116.46 (CH), 113.13 (CH), 113.54 (CH), 57.36 ($CH_3O$), 55.53 ($CH_3O$); *m/z* 470 ($M^+$, 46%, $^{79}Br$), 472 ($M^+$, 44%, $^{81}Br$), 392 (12%), 373 (100%), 332 (14%), 317 (6%), 219 (4%), 113 (4%), (Found: 470.3100. $C_{22}H_{18}NSO_4Br$ requires 471.0140).

#### 4.10.1.2 2-(4-Bromo-2,5-dimethoxyphenyl)-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (165)

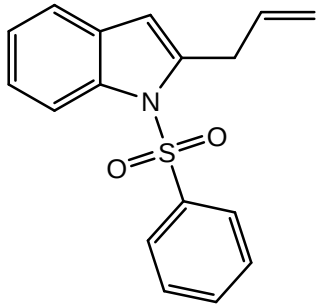



To 1-(phenylsulfonyl)-5-methoxy-1*H*-indole (**102**) (0.97 g, 3.89 mmol) in a dry flask was added isopropylmagnesium chloride solution in THF (~0.8 M in excess) and diisopropylamine (1 ml). The reaction mixture was maintained at rt under $N_2$ atmosphere for 16 h. The reaction mixture was treated with 1,4-dibromo-2,5-dimethoxybenzene (1.93 g, 6.76 mmol, 2 eq) and $Pd(PPh_3)_4$ (0.20 g, 0.17 mmol, 0.050 eq). After stirring at rt for 48 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of $NH_4Cl$. The mixture was extracted with $CH_2Cl_2$ (3 × 30 ml), the organic layers combined and dried over $MgSO_4$, filtered though celite plug and excess solvent removed on a rotary evaporator. This resulted in a black oil that was subjected to column chromatography. The resultant light black oil was recrystallized from the mixture of $CH_2Cl_2$ and hexane to give white solid (**165**) (0.60 g, 35%). Melting point: 159-162 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 2941 (w, CH), 1611 (m), 1494 (m), 1382 (m), 1207 (s), 1171 (s), 1027 (m), 1028 (m), 950 (w), 857 (m), 814 (s), 752 (s), 722 (m), 685 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.14 (1H, d, *J* = 8.92, ArH), 7.45 (3H, d, *J* = 8.13, 3 × ArH), 7.31-7.26 (2H, m, 2 × ArH), 7.13 (1H, s, ArH), 6.97-6.92 (2H, m, 2 × ArH), 6.77 (1H, s, ArH), 6.52 (1H, s, ArH); $\delta_C$ (75MHz; $CDCl_3$) 157.24 (C), 152.97 (C), 149.62 (C), 138.76 (C), 137.87 (C), 133.80 (CH), 132.64 (C), 131.55 (C), 128.99 (2 × CH), 127.10 (2 × CH), 121.49 (C), 117.20

(CH), 116.75 (CH), 116.50 (CH), 114.08 (CH), 113.93 (CH), 113.29 (CH), 103.65 (CH), 57.36 ($CH_3O$), 56.56 ($CH_3O$), 56.05 ($CH_3O$);

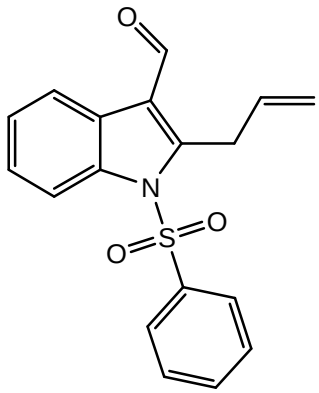
### 4.10.2 Synthesis of indolo-fused pyrans

#### 4.10.2.1 2-Allyl-1-(phenylsulfonyl)-1*H*-indole (169)



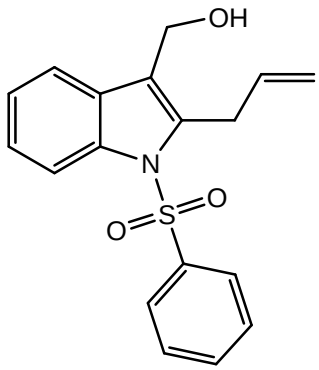
To 1-(phenylsulfonyl)-1*H*-indole (**36**) (3.00 g, 12 mmol) in a dry flask was added isopropylmagnesium chloride solution in THF (~0.8 M in excess) and diisopropylamine (1 ml). The reaction mixture was maintained at rt under $N_2$ atmosphere for 16 h. Allyl bromide (4.23 g, 35 mmol, 3.1 ml, 2.9 eq) was added and the mixture was stirred at rt for an hour. The reaction mixture was quenched by the addition of a saturated aqueous solution of $NH_4Cl$. The mixture was extracted with $CH_2Cl_2$ (3 × 30 ml), the organic layers combined and dried over $MgSO_4$, filtered though celite plug and excess solvent removed on a rotary evaporator. This resulted in brown oil that was subjected to column chromatography. The resultant light brown oil was recrystallized from the mixture of $CH_2Cl_2$ and hexane to give white solid (**169**) (1.1 g, 31%). Melting point: 88-91 °C, literature reported (**169**) as an oil[89]; $\nu_{max}$ (Solid)/$cm^{-1}$ 3083 (w, CH), 1591 (w), 1448 (s), 1366 (s), 1270 (m), 1219 (m), 1170 (m), 1141 (s), 1092 (s), 1045 (s), 998 (s), 918 (m), 759 (s), 739 (s), 721 (s), 684 (s), 651 (s), 623 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.16 (1H, d, *J* = 7.87, ArH), 7.76 (2H, d, *J* = 7.63, 2 × ArH), 7.54-7.38 (4H, m, 4 × ArH), 7.29-7.18 (2H, m, 2 × ArH), 6.40 (1H, s, ArH), 7.01-5.96 (1H, m, CH=C), 5.22-5.16 (2H, m, $C=CH_2$), 3.78-3.76 (2H, m, $CH_2$-C=C); $\delta_C$ (75MHz; $CDCl_3$) 140.53 (C), 139.56 (C), 137.66 (C), 134.49 (CH), 134.06 (CH), 130.04 (C), 129.63 (CH), 126.69 (CH), 124.49 (CH), 123.99 (CH), 120.69 (CH), 118.22 ($CH_2$), 115.11 (CH), 109.99 (CH), 33.80 ($CH_2$); *m/z* 298 ($M^+$, 100%), 223 (6%), 157 (42%), 141 (4%), (Found: 297.0260. $C_{17}H_{15}NO_2S$ requires 297.0824).

#### 4.10.2.2 2-Allyl-1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde (171)



2-Allyl-1-(phenylsulfonyl)-indole (**169**) (0.7 g, 2.3mmol) in $CH_2CH_2$ (6 ml) was added to a solution of $TiCl_4$ (0.51 ml, 4.7 mmol, 2 eq) and $Cl_2CHOCH_3$ (0.47 ml, 4.7 mmol, 2 eq) in $CH_2Cl_2$ (6 ml) at -78 °C, and the resulting reaction mixture was stirred at –78 °C for 3 h. The reaction mixture was allowed to warm to rt and diluted with water. The reaction mixture was made basic with 10% aqueous $Na_2CO_3$ and then extracted with $CH_2Cl_2$ (3 × 30 ml). The organic extracts were combined, dried over $MgSO_4$, filtered through celite plug and the excess solvent removed on a rotary evaporator to result in a brown oil residue. This oily residue was subjected to column chromatography using 10% EtOAc/Hexane as an eluent to give a brown oil (**171**) (0.61 g, 81%), literature reported (**171**) isolated as solid with melting point 157-158.5 °C[75]. $\nu_{max}$ (Liquid)/cm$^{-1}$ 3063 (w, CH), 1666 (s, C=O), 1553 (m), 1448 (s), 1372 (s), 1265 (w), 1172 (s), 1119 (m), 1087 (s), 1026 (m), 995 (s), 915 (s), 749 (s), 726 (s), 683 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 10.31 (1H, s, CHO), 8.32-8.29 (1H, m, ArH), 8.21-8.18 (1H, m, ArH), 7.88 (2H, d, *J* = 8.14, 2 × ArH) 7.64-7.59 (1H, m, ArH), 7.52-7.46 (2H, m, 2 × ArH), 7.41-7.38 (2H, m, 2 × ArH), 6.15-6.02 (1H, m, HC=C), 5.17-5.06 (2H, m, C=$CH_2$), 4.26-4.24 (2H, m, $CH_2$-C=C); $\delta_C$ (75MHz; $CDCl_3$) 186.18 (CHO), 149.31 (C), 138.96 (C), 136.41 (C), 134.90 (CH), 134.68 (CH), 129.94 (CH), 127.10 (CH), 126.53 (C), 126.17 (CH), 126.60 (CH), 121.91 (CH), 119.99 (C), 118.12 ($CH_2$), 114.83 (CH), 29.89 ($CH_2$); *m/z* 325 ($M^+$, 7%), 264 (23%), 219 (100%), 184 (11%), 156 (7%), 131 (40%), 100 (15%), 69 (50%), (Found: 325.0771. $C_{21}H_{17}NSO_3$ requires 325.0773).

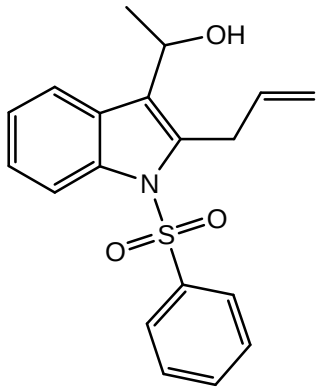
#### 4.10.2.3 (2-Allyl-1-(phenylsulfonyl)-1*H*-indol-3-yl) methanol (172)



2-Allyl-1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde (**171**) (0.50 g, 1.54 mmol) was dissolved in ethanol. $NaBH_4$ (0.12 g, 3.08 mmol, 2 eq) was added during which time the temperature was not

allowed to rise above 20 °C. Stirring was then continued for 6 h at rt, before the solvent was removed in *vacuo*. The residual white solid in round bottom flask was shaken up with 80 ml of aqueous 15% NaOH and the alkaline solution was extracted with $CH_2Cl_2$ (3 × 30 ml). The combined organic extracts were dried over $MgSO_4$, filtered with celite plug and the excess solvent removed on a rotary evaporator to give a yellow oil. The oil was subjected to column chromatography using 50% EtOAc/Hex as an eluent to get yellow oil (**172**) 0.36g (71%), literature reported (**172**) isolated as solid with melting point 82-83 °C[76]; $\nu_{max}$ (Liquid)/$cm^{-1}$ 3406 (b, OH), 2923 (w, CH), 1606 (w), 1448 (s), 1362 (s), 1217 (w), 1170 (s), 1089 (s), 993 (s), 778 (s), 745 (s), 723 (s), 684 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.47 (1H, d, *J* = 8.10, ArH), 8.04 ( 2H, d, *J* = 8.04, 2 × ArH), 7.89 (1H, d, *J* = 7.54, ArH), 7.80-7.76 (1H, m, ArH), 7.69-7.63 (2H, m, 2 × ArH), 7.60-7.52 (2H, m, 2 × ArH), 7.38-6.25 (1H, m, C-CH=C), 5.33-5.26 (2H, m, C-C=$CH_2$), 5.01 (2H, s, $CH_2O$), 4.17 (2H, d, *J* = 5.67, $CH_2$-C=C), 1.96 (1H, s, OH); $\delta_C$ (75MHz; $CDCl_3$) 139.45 (C), 136.93 (C), 136.90 (C), 136.06 (=CH-), 134.15 (CH), 129.61 (2 × CH), 126.81 (2 × CH), 125.10 (CH), 124.16 (CH), 121.10 (C), 119.37 (CH), 116.70 (=$CH_2$), 115.34 (CH), 55.74 ($CH_2O$), 30.38 (-$CH_2$-); *m/z* 326 ($M^+$, 24%), 310 (100%), 284 (5%), 185 (3%), 141 (3%), 109 (2%), (Found: 326.1990. $C_{17}H_{18}NO_3S$ requires 327.0929).

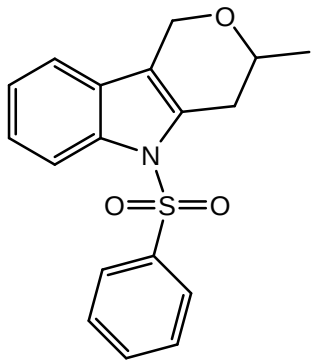
#### 4.10.2.4 1-(2-Allyl-1-(phenylsulfonyl)-1*H*-indol-3-yl)ethanol (173)




Magnesium turnings (0.030 g, 1.23 mmol, 4.0 eq) were placed in a two necked round bottom flask and dried in an oven. The flask fitted with a dropping funnel and cooled under $N_2$. Dry ether was then placed into the round bottom flask and $CH_3I$ was added to the suspension. The mixture immediately started going cloudy with slight rise in temperature. Once all the magnesium has reacted, the dropping funnel was charged with the solution of 2-allyl-1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde (**171**) (0.10 g, 0.308 mmol) in ether, and this was added dropwise to the cloudy Grignard solution. The resulting yellow solution was left to stir for 18 h under $N_2$ over which time the solution turned milky orange. Water was added to the reaction mixture to quench the excess Grignard reagent and this

formed a white slurry of $Mg(OH)_2$. The slurry was made soluble by adding an aqueous solution of $NH_4Cl$ and the mixture was transferred to the separating funnel and extracted with $CH_2Cl_2$ (3 × 30 ml). The organic fractions were combined, dried over $MgSO_4$, filtered through a celite plug and the excess solvent removed on a rotary evaporator. The resulting yellow oil was purified by column chromatography using 30% EtOAc/Hexane as an eluent to give yellow oil (**173**), 0.080 g (76%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 3567 (b, OH), 2977 (w, CH), 1603 (w), 1448 (s), 1364 (s), 1223 (w), 1171 (s), 1150 (m), 1089 (m), 1022 (m), 960 (w), 913 (m), 730(s), 685 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.19 (1H, d, *J* = 7.91, ArH), 7.81 (1H, d, *J* = 7.13, ArH), 7.73 (2H, d, *J* = 8.85, 2 × ArH), 7.51-7.46 (1H, m, ArH), 7.40-7.35 (2H, m, 2 × ArH), 7.29-7.22 (2H, m, 2 × ArH), 6.03-5.93 (1H, m, $CH_2C\underline{H}CH_2$), 5.18-5.12 (1H, m, $C\underline{H}(OH)CH_3$), 5.04-4.92 (2H, m, $CH_2CHC\underline{H_2}$), 3.93 (1H, dd, *J* = 5.55 and 5.54, $C\underline{H_2}CHCH_2$), 3.77 (1H, dd, *J* = 5.99 and 5.97, $C\underline{H_2}CHCH_2$), 1.91 (1H, s, OH), 1.55 (3H, d, *J* = 6.57, $CH(OH)C\underline{H_3}$); $\delta_C$ (75MHz; $CDCl_3$) 1139. 48 (C), 137.29 (C), 135.85 (CH), 134.16 (C), 134.06 (CH), 129.56 (2 × CH), 128.42 (C), 127.11 (C), 126.80 (2 × CH), 125.14 (C), 124.80 (CH), 123.82 (CH), 122.02 (CH), 116.55 (CH), 115.17 (CH), 64.56 ($\underline{C}H(OH)CH_3$), 30.44 ($\underline{C}H_2CHCH_2$), 23.57 ($CH(OH)\underline{C}H_3$); *m/z* 340 ($M^-$, 10%), 324 (100%), 284 (2%), 198 (4%), 183 (30%), 168 (6%), 109 (2%), (Found: 341.2530. $C_{19}H_{19}NO_3S$ requires 341.1086).

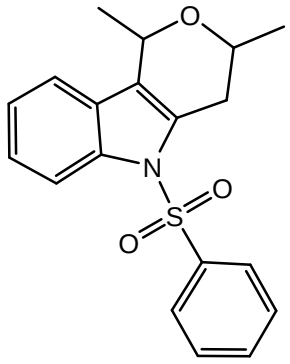
### 4.10.2.5 3-Methyl-5-(phenylsulfonyl)-1,3,4,5-tetrahydropyrano[4,3-b]indole (174)




$Hg(OAc)_2$ (2.34 g, 0.73 mmol, 1.5 eq) was added to (2-allyl-1-(phenylsulfonyl)-1H-indol-3-yl) methanol (**172**) (0.16 g, 0.49 mmol) dissolved in dry THF (15 ml). The resulting yellow mixture was stirred under $N_2$ for 20 h at rt. A further portion of $Hg(OAc)_2$ (0.23 g, 0.73 mmol, 1.5 eq) was added and the mixture was stirred at rt for further 18 h. A mixture of $NaBH_4$ (0.042 g, 1.22 mmol, 2.5 eq) in aqueous NaOH (5 ml, 2.5 M) was added whilst stirring. After stirring for further 1 h, a saturated solution aqueous $Na_2CO_3$ (5 ml) was added and the mixture was stirred for further 20 minutes. The reaction mixture was allowed to stand for 30 minutes and the THF removed under reduced pressure. Saturated aqueous brine solution (20 ml) and $CH_2Cl_2$

(20.0 ml) were added and the mixture was extracted with $CH_2Cl_2$ (3 × 30 ml). The organic fractions were combined, dried over $MgSO_4$, filtered with the celite plug and silica to remove traces of Hg and the excess solvent was removed on a rotary evaporator. This gave clear oil that solidified on standing and it was dissolved in $CH_2Cl_2$ and subjected to column chromatography using 20% EtOAc/Hexane as an eluent to give a clear solid (**174**) 0.05 g (31%), melting point 145-148 °C; $\nu_{max}$ (Solid)/$cm^{-1}$ 3061 (w, CH), 1620 (m), 1449 (m), 1404 (s), 1363 (s), 1304 (m), 1220 (s), 1201 (m), 1170 (s), 1119 (m), 1083 (s), 1049 (m), 1022 (m), 979 (m), 931 (s), 852 (s), 794 (m), 759 (s), 725 (s), 687 (s), 664 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.46 (1H, d, *J* = 8.18, ArH), 8.09 (1H, d, *J* = 8.61, 2 x ArH), 7.85-7.80 (1H, m, ArH), 7.74-7.69 (2H, m, 2 × ArH), 7.63-7.52 (3H, m, 3 × ArH), 5.19-5.03 (2H, m, $CH_2O$), 4.17-4.10 (1H, m, CH), 3.56-3.55 (1H, m, CH), 3.16-3.07 (1H, m, CH), 1.75 (3H, d, *J* = 6.20, $CH_3$); $\delta_C$ (75MHz; $CDCl_3$) 137.80 (C), 135.18 (C), 132.69 (CH), 131.68 (C), 128.28 (2 × CH), 126.36 (C), 125.32 (2 × CH), 123.33 (CH), 122.56 (CH), 116.99 (CH), 116.02 (C), 113.47 (CH), 69.81 (CH), 62.25 ($CH_2O$), 31.78 ($CH_2$), 20.38 ($CH_3$); *m/z* 328 ($M^+$, 37%), 284 (100%), 220 (3%), 187 (13%), 143 (7%), 109 (2%), (Found: 327.1570. $C_{17}H_{18}NO_3S$ requires 327.0929).

### 4.10.2.6 1,3-Dimethyl-5-(phenylsulfonyl)-1,3,4,5-tetrahydropyrano[4,3-*b*]indole (175)




$Hg(OAc)_2$ (0.12 g, 0.37 mmol, 1.5 eq) was added to 1-(2-allyl-1-(phenylsulfonyl)-1*H*-indol-3-yl)ethanol (**173**) (0.080 g, 0.25 mmol) dissolved in dry THF (15 ml). The resulting yellow mixture was stirred under $N_2$ for 20 h at rt. A further portion of $Hg(OAc)_2$ (0.080 g, 0.25 mmol, 1 eq) was added and the mixture was stirred at rt for further 18 h. A mixture of $NaBH_4$ (0.023 g, 0.61 mmol, 2.5 eq) in aqueous NaOH (5 ml, 2.5 M) was added whilst stirring. After stirring for further 1 h, a saturated solution aqueous $Na_2CO_3$ (5 ml) was added and the mixture was stirred for further 20 minutes. The reaction mixture was allowed to stand for 30 minutes before the THF removed under reduced pressure. An aqueous saturated brine solution (20 ml) and $CH_2Cl_2$ (20.0 ml) were added and the reaction mixture was extracted with $CH_2Cl_2$ (3 × 30 ml). The organic fractions were combined, dried over $MgSO_4$, filtered with the celite plug and silica

to remove traces of Hg and the excess was solvent removed on a rotary evaporator. This gave clear oil that solidified on standing and it was dissolved in $CH_2Cl_2$ and subjected to column chromatography using 20% EtOAc/Hexane as an eluent to give clear oil (**175**) 0.02 g (25%); $\nu_{max}$ (Liquid)/$cm^{-1}$ 2920 (w, CH), 1615 (w), 1448 (s), 1369 (s), 1203 (m), 1171 (s), 1150 (s), 1090 (s), 1028 (s), 975 (m), 885 (m), 777 (s), 744 (s), 723 (s), 684 (s); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 8.16 (1H, d, *J* = 8.12, ArH), 7.78 (2H, d, *J* = 7.39, 2 × ArH), 7.55-7.750 (1H, m, ArH), 7.44-7.37 (2H, m, 2 × ArH), 7.31-7.22 (2H, m, 2 × ArH), 5.10-5.04 (1H, m, C<u>H</u>(O)$CH_3$), 4.14-4.08 (1H, m, $CH_2$C<u>H</u>(O)$CH_3$), 3.26-3.16 (1H, m, C<u>$H_2$</u>CH(O)$CH_3$), 2.85-2.69 (1H, m, C<u>$H_2$</u>CH(O)$CH_3$), 1.60-1.54 (3H, m, CH(O)C<u>$H_3$</u>), 1.45-1.38 (3H, m, $CH_2$CH(O)C<u>$H_3$</u>); $\delta_C$ (75MHz; $CDCl_3$) 138.86 (C), 136.31 (C), 133.69 (CH), 132.28 (C), 129.29 (2 × CH), 127.49 (C), 126.35 (2 ×CH), 124.18 (CH), 124.04 (C), 123.49 (CH), 120.97 (C), 119.18 (C), 118.43 (CH), 114.54 (CH), 67.55 (<u>C</u>H(O)$CH_3$), 64.04 ($CH_2$<u>C</u>H(O)$CH_3$), 32.54 (<u>C</u>$H_2$CH(O)$CH_3$), 21.19 (CH(O)<u>C</u>$H_3$), 19.98 ($CH_2$CH(O)<u>C</u>$H_3$); *m/z* 342 ($M^+$, 66%), 298 (100%), 201(8%), 157 (10%), 130 (2%), (Found: 341.1290. $C_{19}H_{19}NO_3S$ requires 341.1086).

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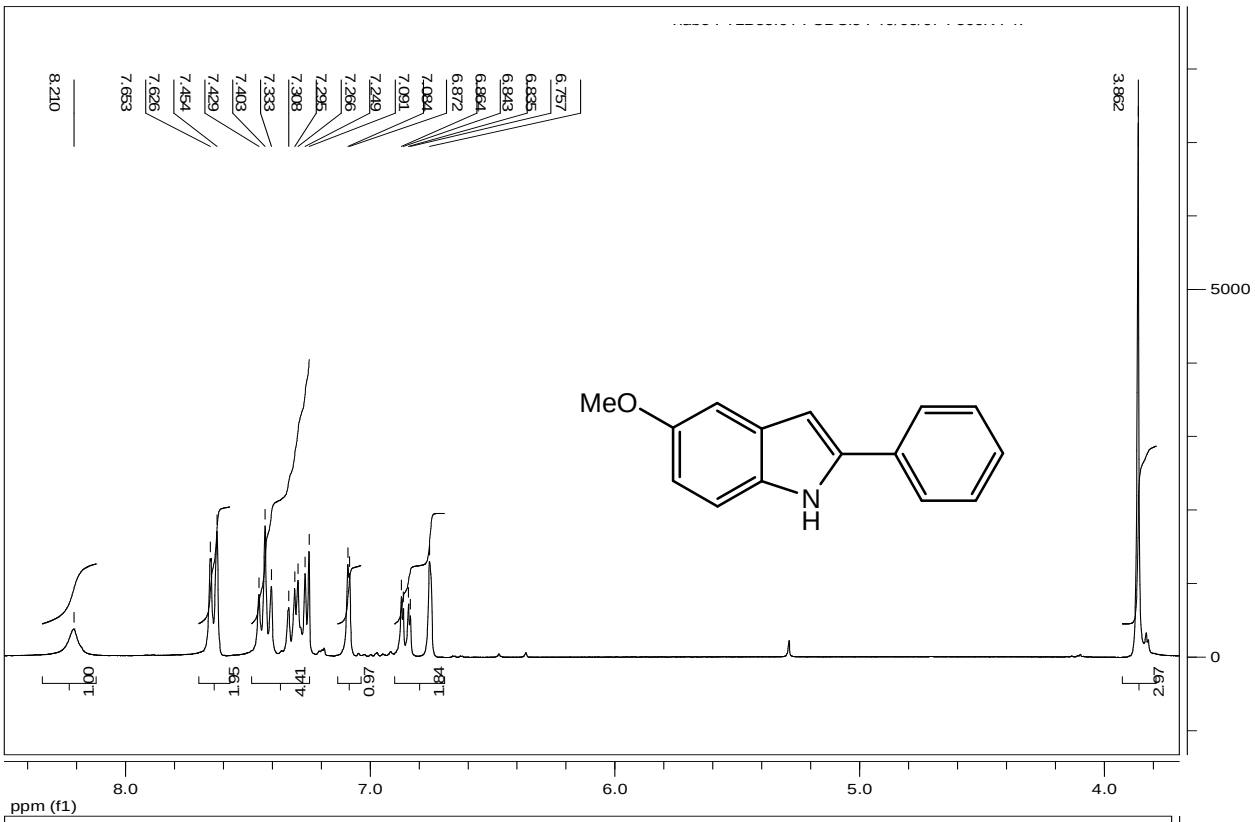
# Appendix

**Appendix 1: Selected $^{1}$H and $^{13}$C NMR spectra**


| Compound | Page |
|---|---|
| 5-Methoxy-2-phenyl-1*H*-indole (**129**) | 130 |
| 2-*o*-Tolyl-1*H*-indole (**130**) | 131 |
| 5-Methoxy-2-*o*-tolyl-1*H*-indole (**131**) | 132 |
| 2-(4-Methoxyphenyl)-1*H*-indole (**134**) | 133 |
| 5-Methoxy-3-o-tolyl-1*H*-indole (**152**) | 134 |
| 3-(4-Methoxyphenyl)-1*H*-indole (**155**) | 135 |
| 1-(2-(1*H*-indol-3-yl) acetophenone (**159**) | 136 |
| 1-(2-(5-Methoxy-1*H*-indol-3-yl) acetophenone (**160**) | 137 |
| 2-(4-Bromo-2,5-dimethoxyphenyl)-1-(phenylsulfonyl)-1-*H*-indole (**164**) | 138 |
| 2-(4-Bromo-2,5-dimethoxyphenyl)-5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**165**) | 139 |
| 2-(4-Bromo-2,5-dimethoxyphenyl)-1*H*-indole (**166**) | 140 |
| 2-(4-Bromo-2,5-dimethoxyphenyl)-5-methoxy-1*H*-indole (**167**) | 141 |
| 2-Allyl-1-(phenylsulfonyl)-1*H*-indole (**169**) | 142 |
| 3-Methyl-5-(phenylsulfonyl)-1,3,4,5-tetrahydropyrano[4,3-b]indole (**174**) | 143 |
| 1,3-Dimethyl-5-(phenylsulfonyl)-1,3,4,5-tetrahydropyrano[4,3-*b*]indole (**175**) | 144 |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7.249
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7.084
6.872
6.864
6.843
6.835
6.757
3.862
MeO
N
H
1.00
1.95
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1.84
2.92
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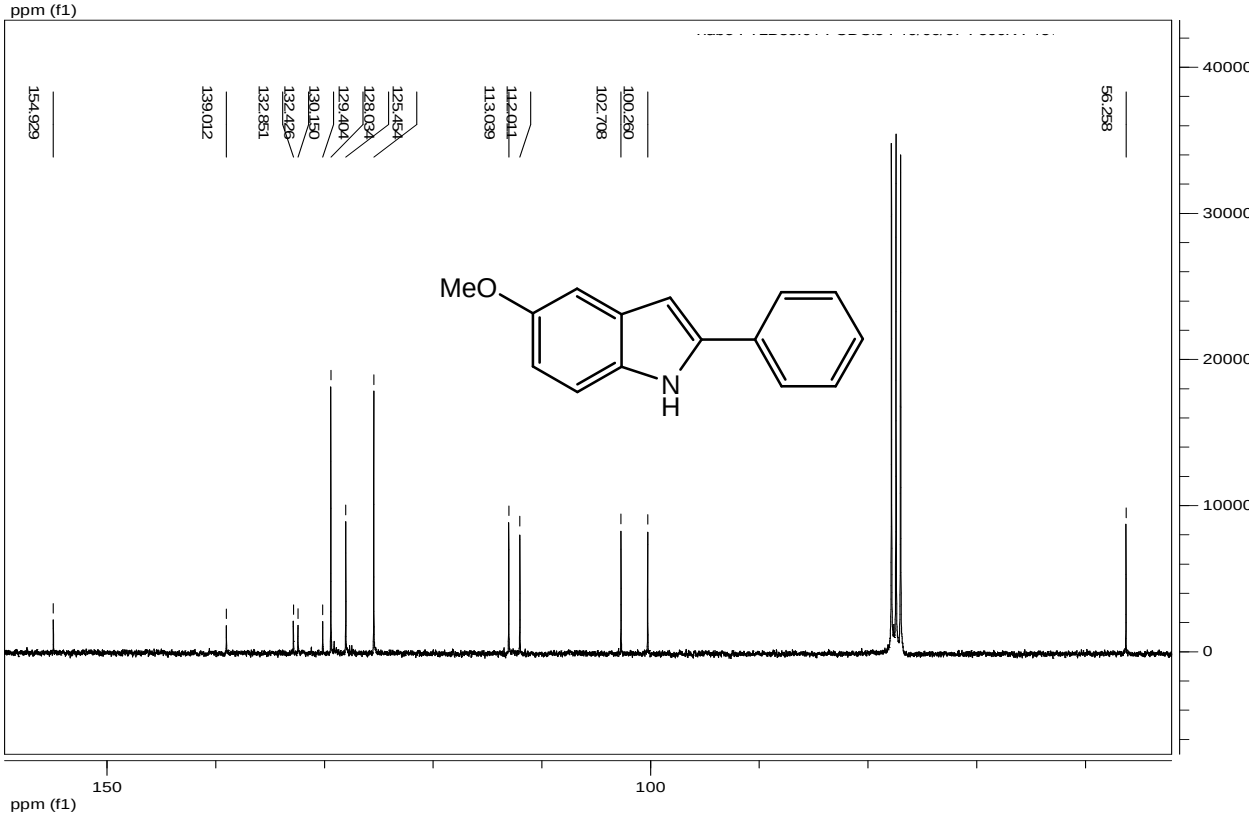
8.0
7.0
6.0
5.0
4.0
ppm (f1)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132.851
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130.150
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113.039
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MeO
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H
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30000
20000
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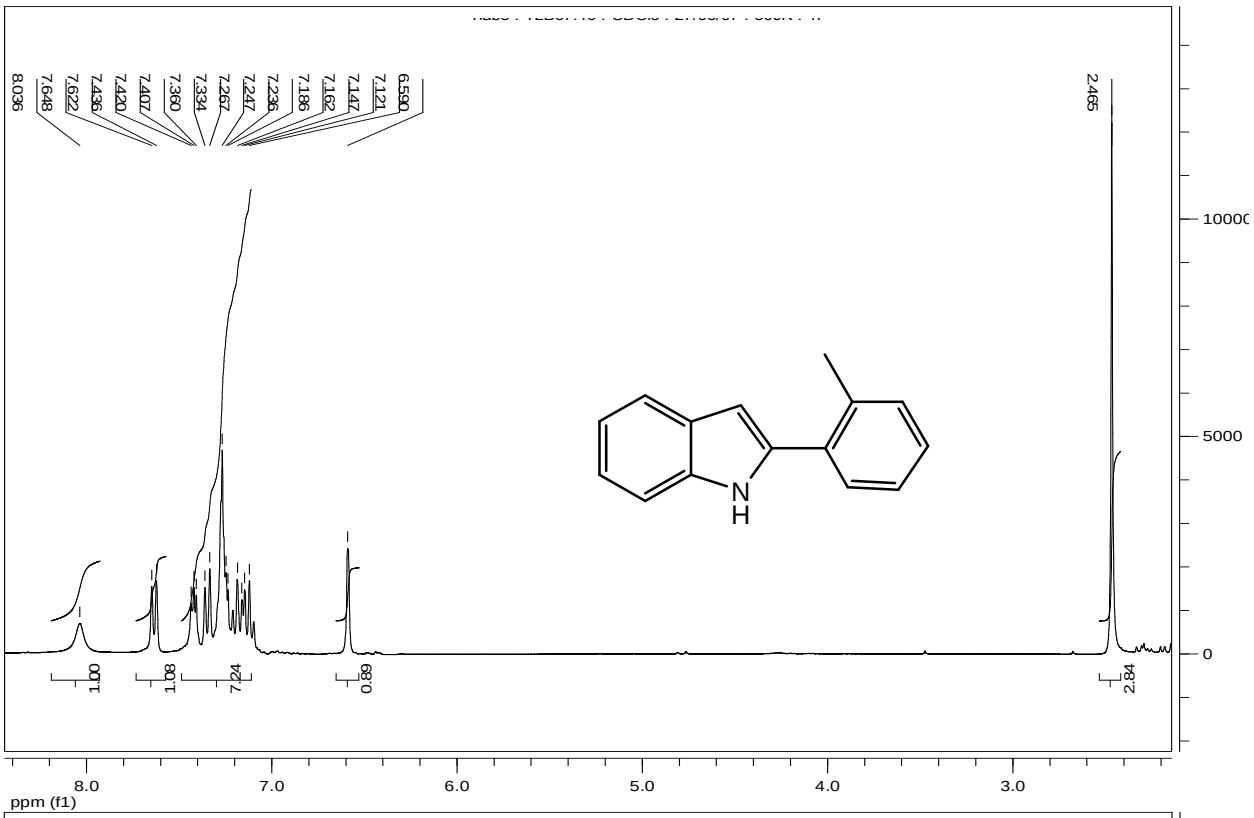
0
150
100
ppm (f1)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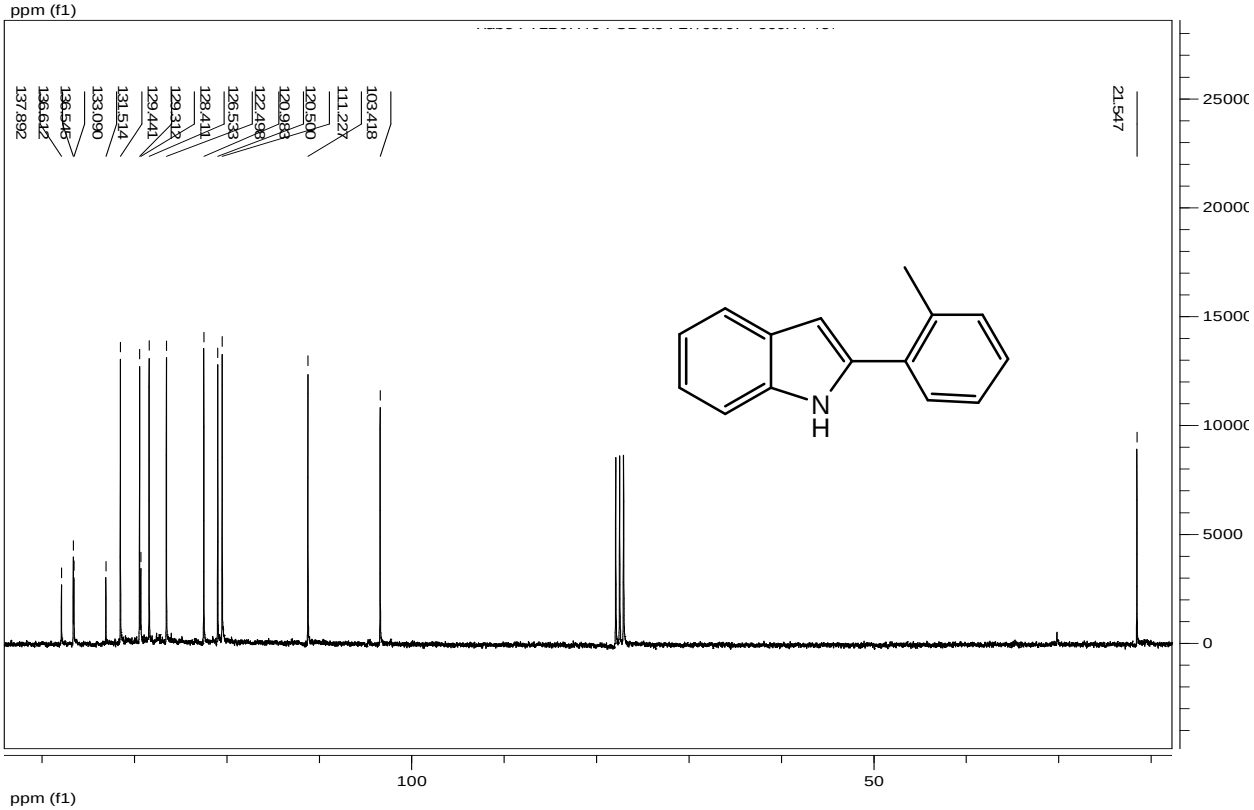
7.162
7.147
7.121
6.590
2.465
1.00
1.08
7.24
0.88
2.84
8.0
7.0
6.0
5.0
4.0
3.0
ppm (f1)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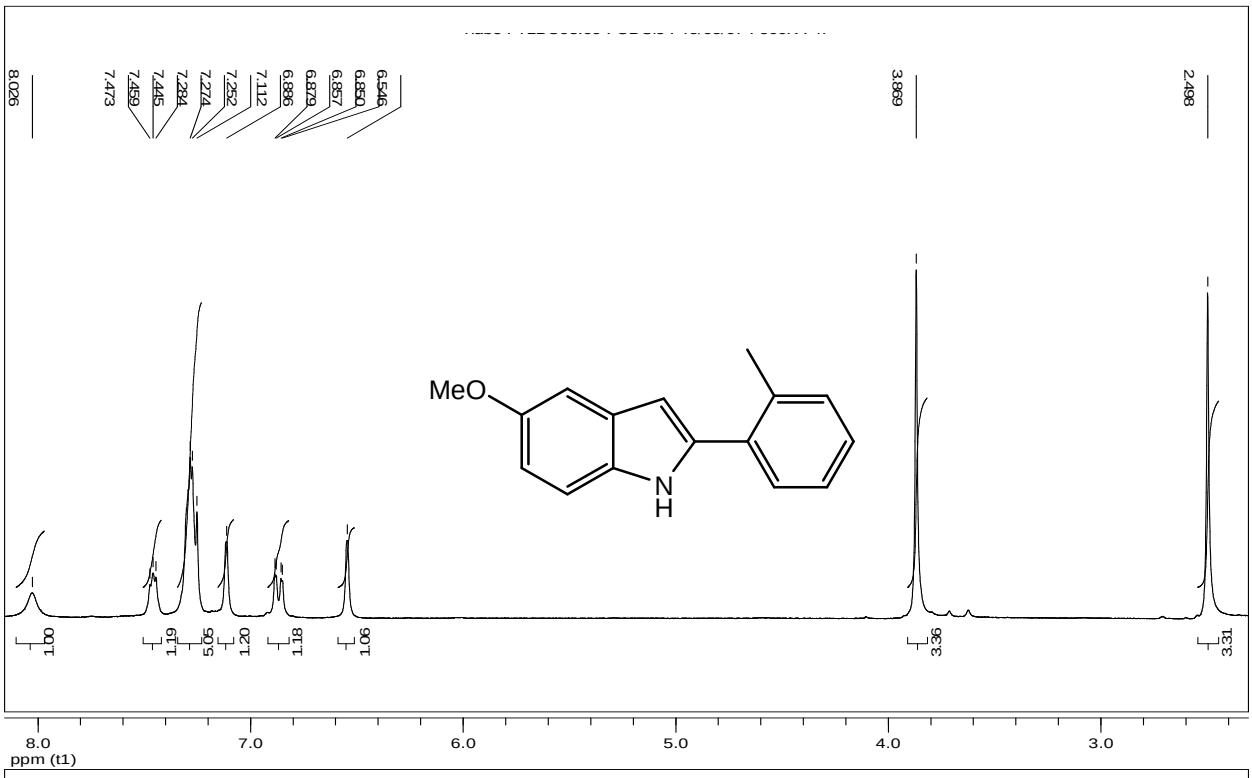
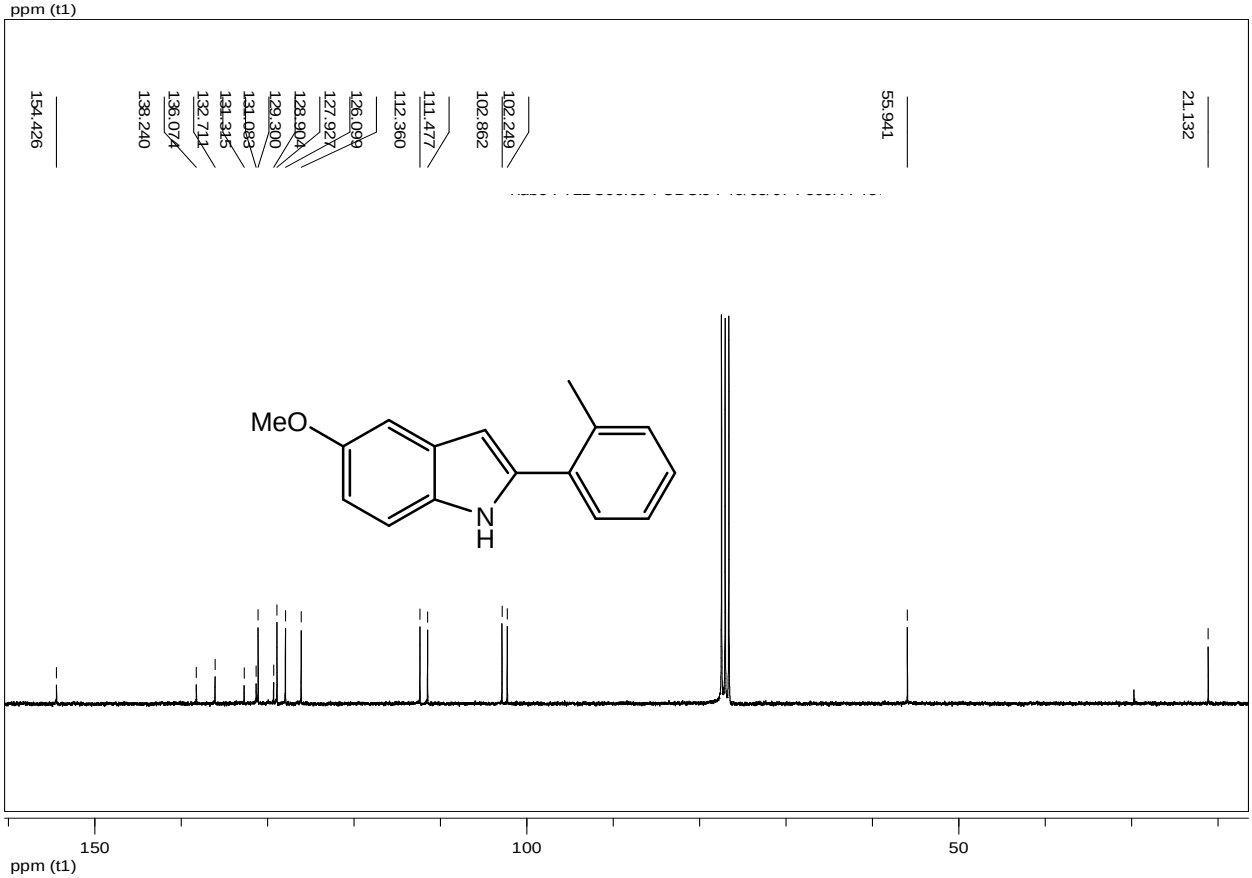
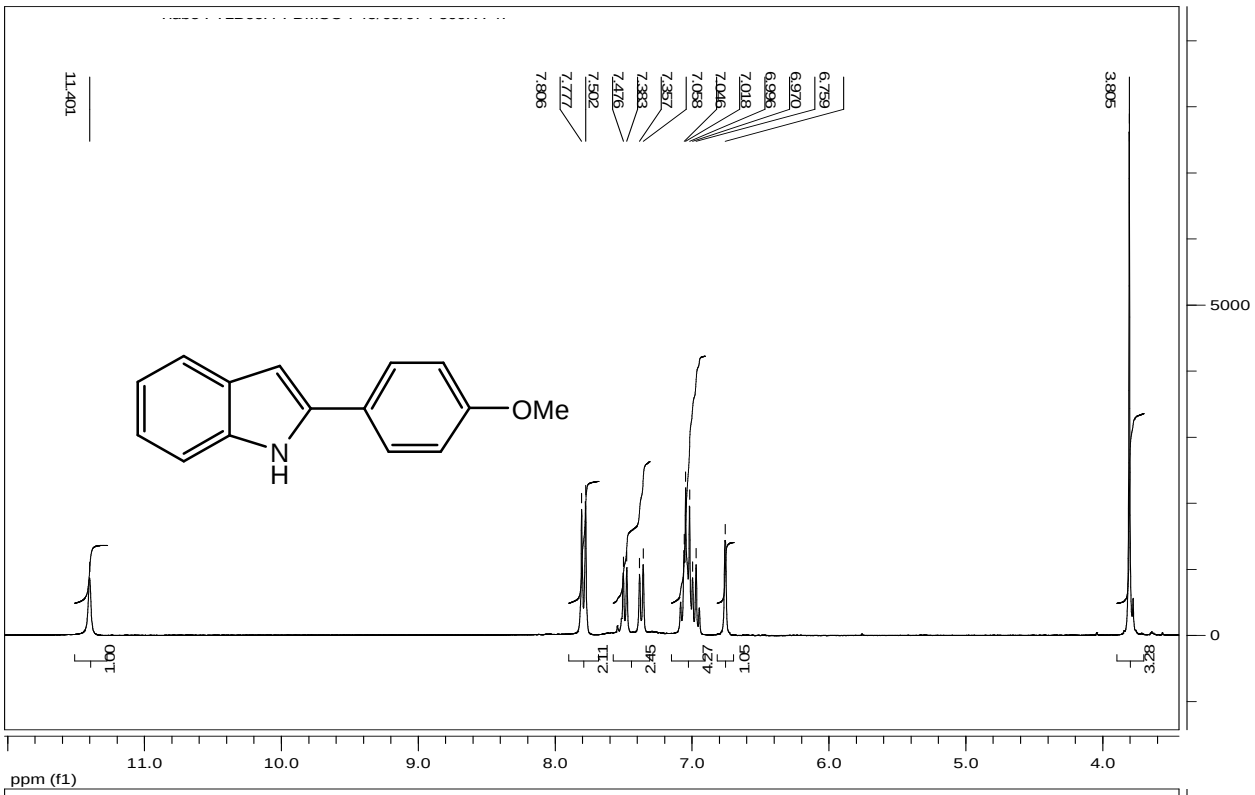
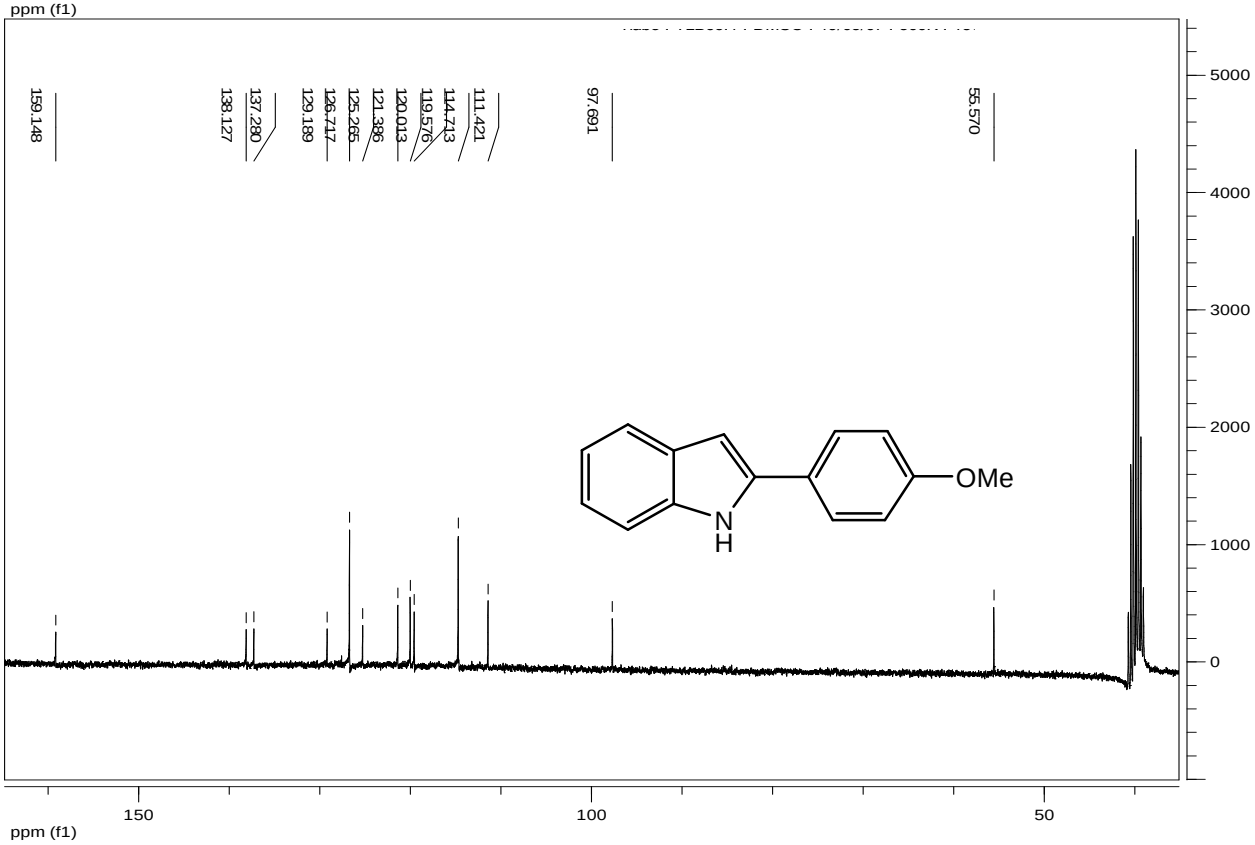
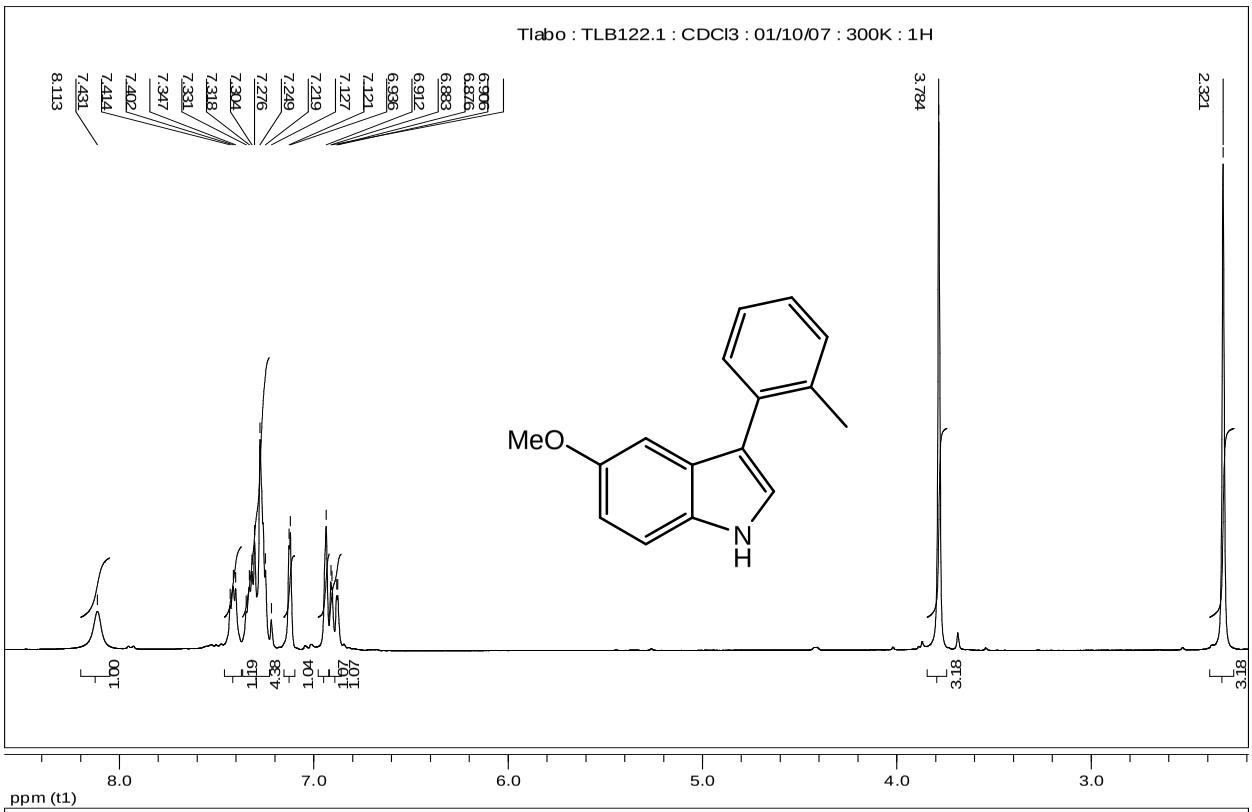
103.418
21.547
100
50
ppm (f1)

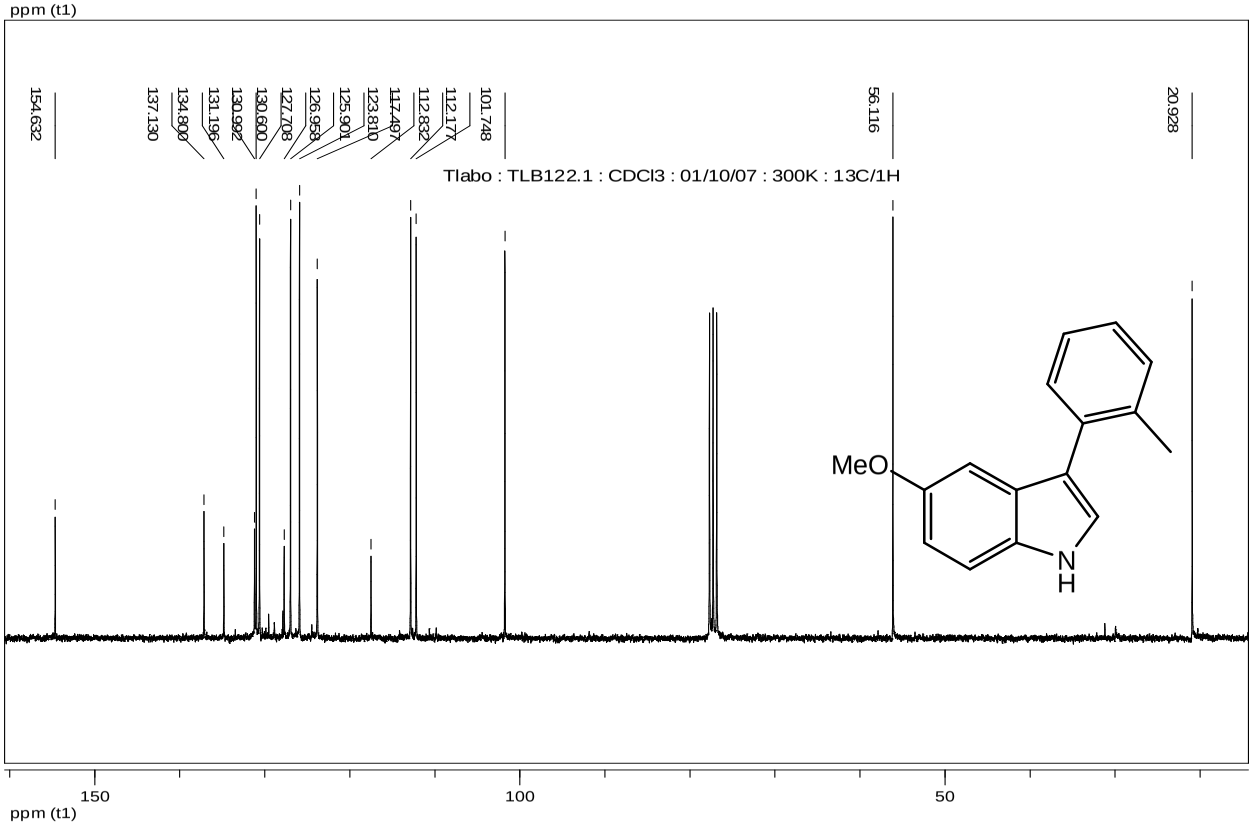

8.026
7.473
7.459
7.445
7.284
7.274
7.252
7.112
6.886
6.879
6.857
6.850
6.546
3.869
2.498
MeO
N
H
1.00
1.91
5.05
1.20
1.18
1.06
3.36
3.11
8.0
7.0
6.0
5.0
4.0
3.0
ppm (t1)

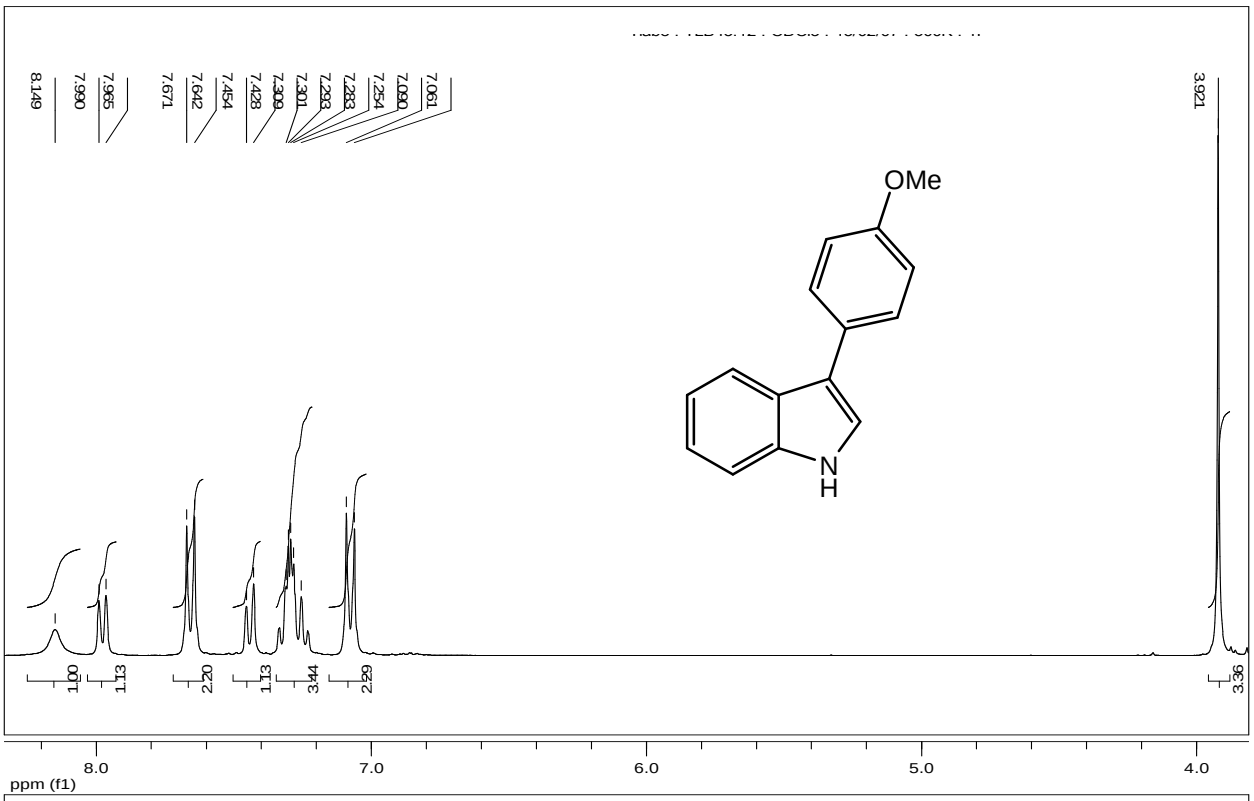

154.426
138.240
136.074
132.711
131.315
131.083
129.300
128.904
127.927
126.099
112.360
111.477
102.862
102.249
55.941
21.132
MeO
N
H
150
100
50
ppm (t1)

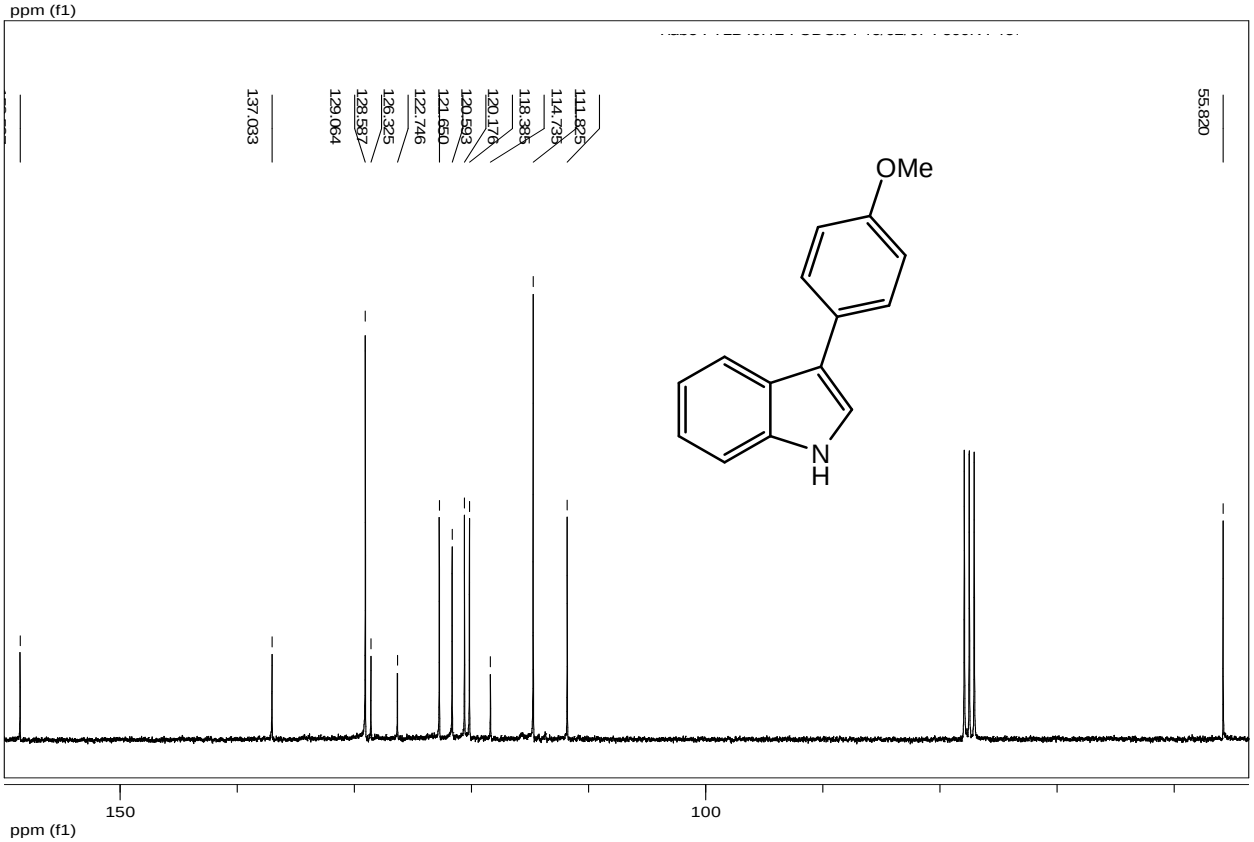

11.401
7.806
7.777
7.502
7.476
7.383
7.357
7.058
7.046
7.018
6.996
6.970
6.759
3.805
OMe
N
H
1.00
2.11
2.45
4.27
1.05
3.28
5000
0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
ppm (f1)

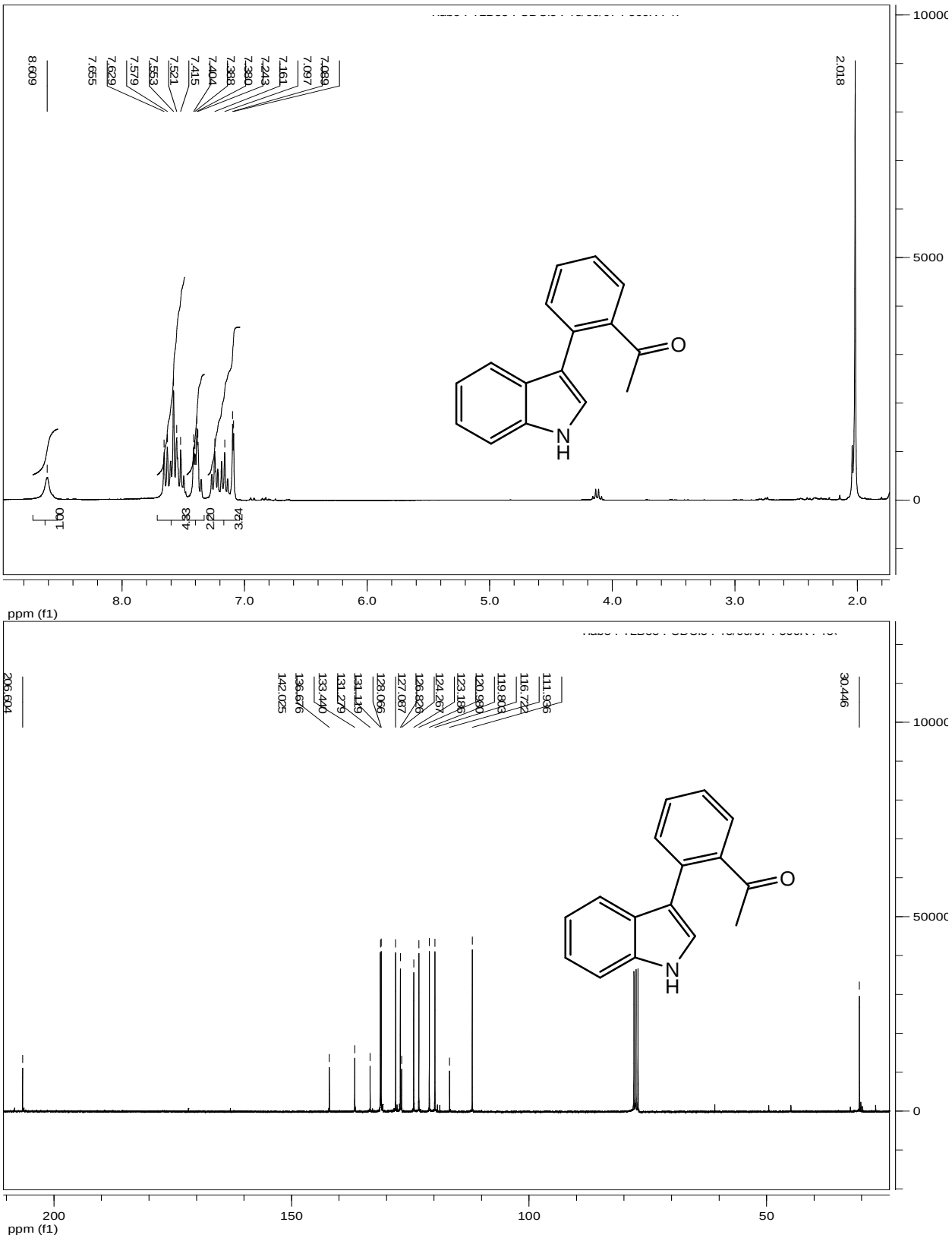

159.148
138.127
137.280
129.189
126.717
125.265
121.386
120.013
119.578
114.713
111.421
97.691
55.570
OMe
N
H
5000
4000
3000
2000
1000
0
150
100
50
ppm (f1)

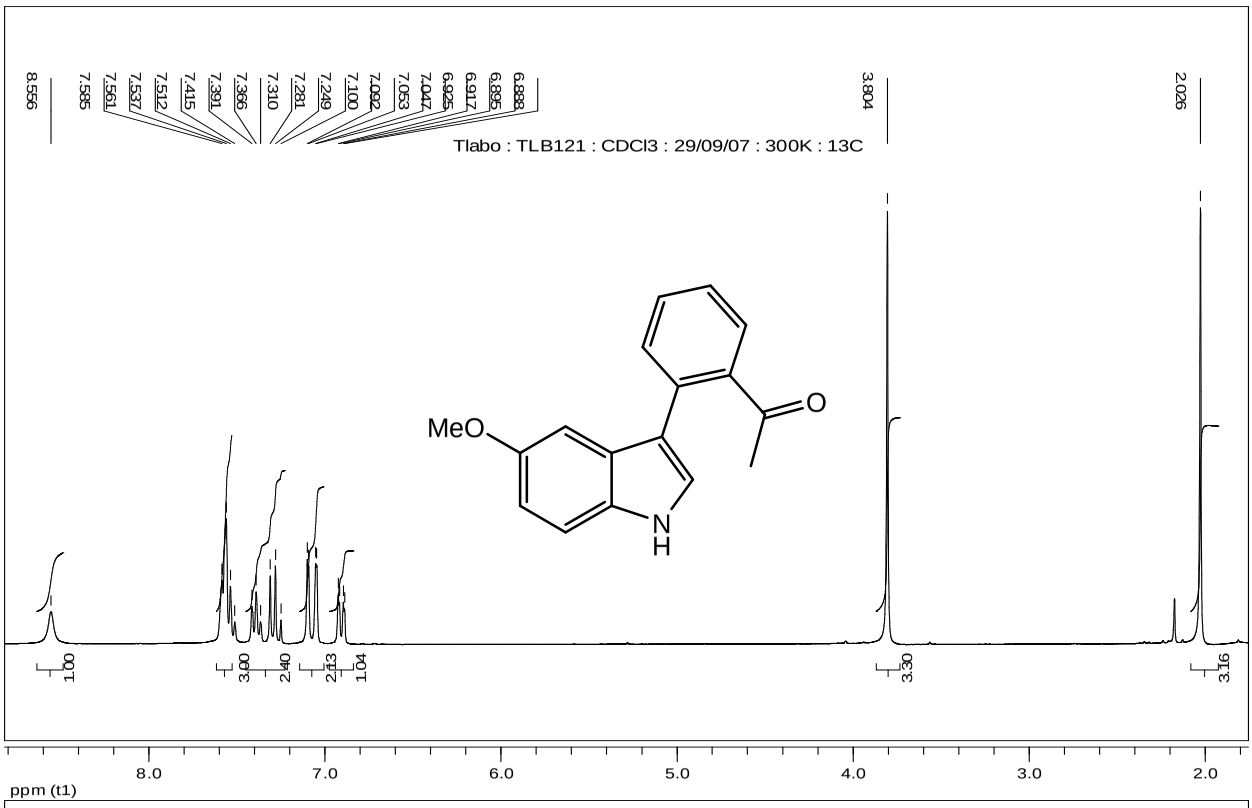

Tlabo : TLB122.1 : CDCl3 : 01/10/07 : 300K : 1H
8.113
7.431
7.414
7.402
7.347
7.331
7.318
7.304
7.276
7.249
7.219
7.127
7.121
6.936
6.912
6.883
6.876
6.905
3.784
2.321
MeO
N
H
1.00
1.19
4.38
1.04
1.97
1.01
3.18
3.18
8.0
7.0
6.0
5.0
4.0
3.0
ppm (t1)

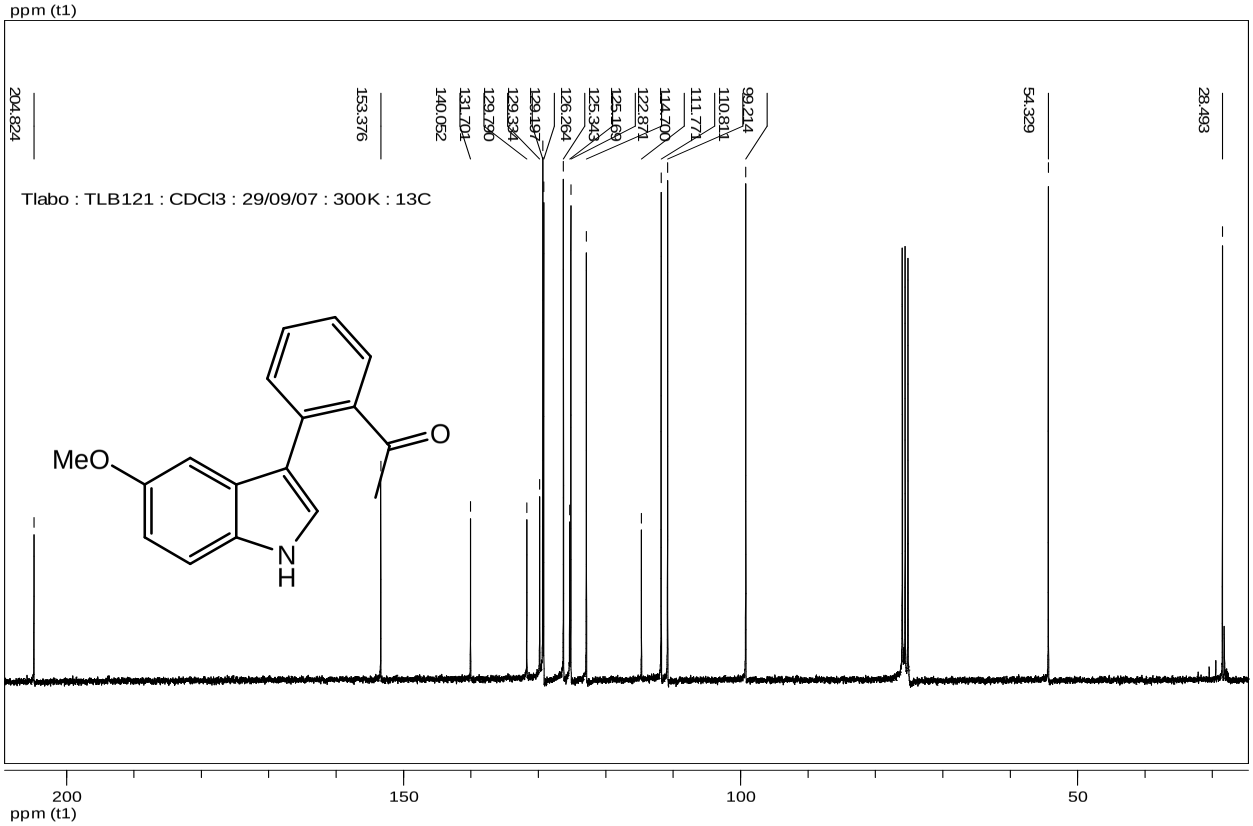

154.632
137.130
134.800
131.196
130.982
130.600
127.708
126.958
125.904
123.810
117.497
112.832
112.177
101.748
56.116
20.928
Tlabo : TLB122.1 : CDCl3 : 01/10/07 : 300K : 13C/1H
MeO
N
H
150
100
50
ppm (t1)

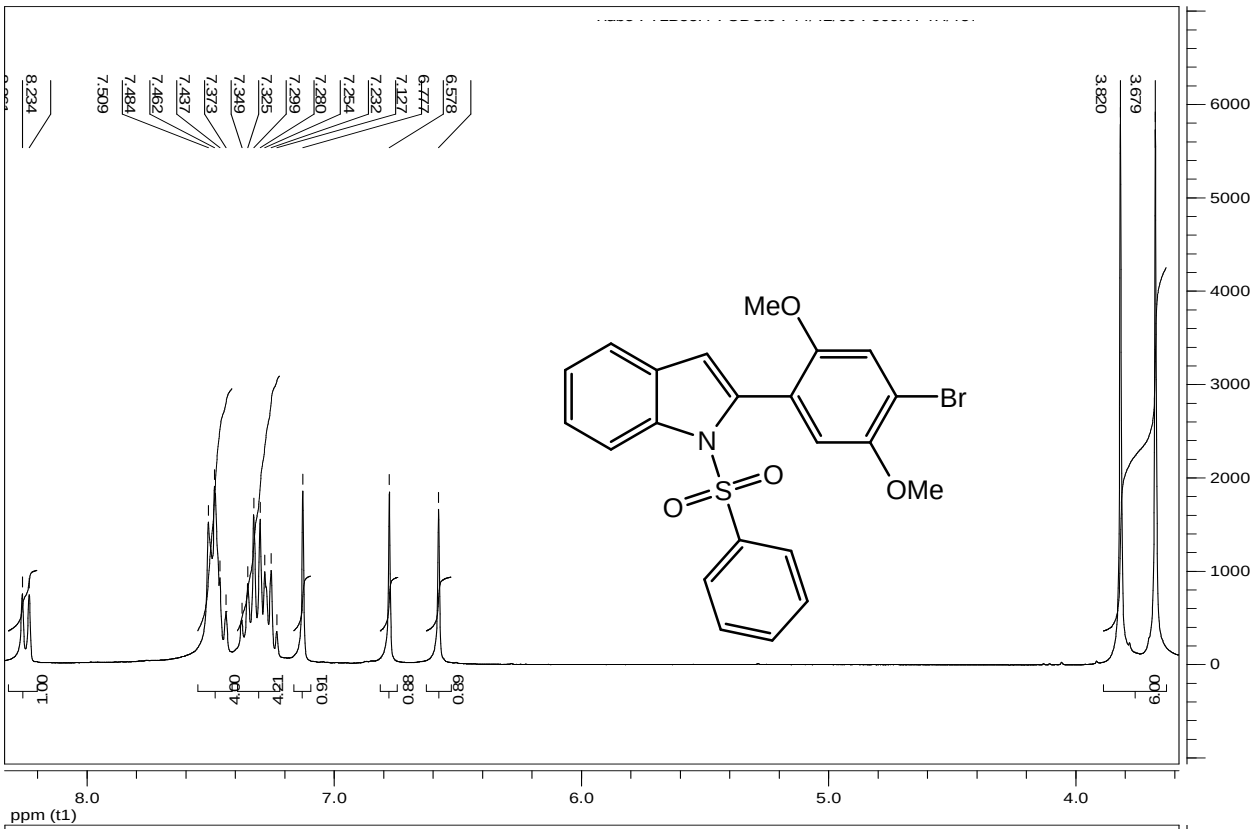

8.149
7.990
7.965
7.671
7.642
7.454
7.428
7.309
7.301
7.293
7.283
7.254
7.090
7.061
3.921
OMe
N
H
1.00
1.13
2.20
1.13
3.44
2.69
3.36
8.0
7.0
6.0
5.0
4.0
ppm (f1)

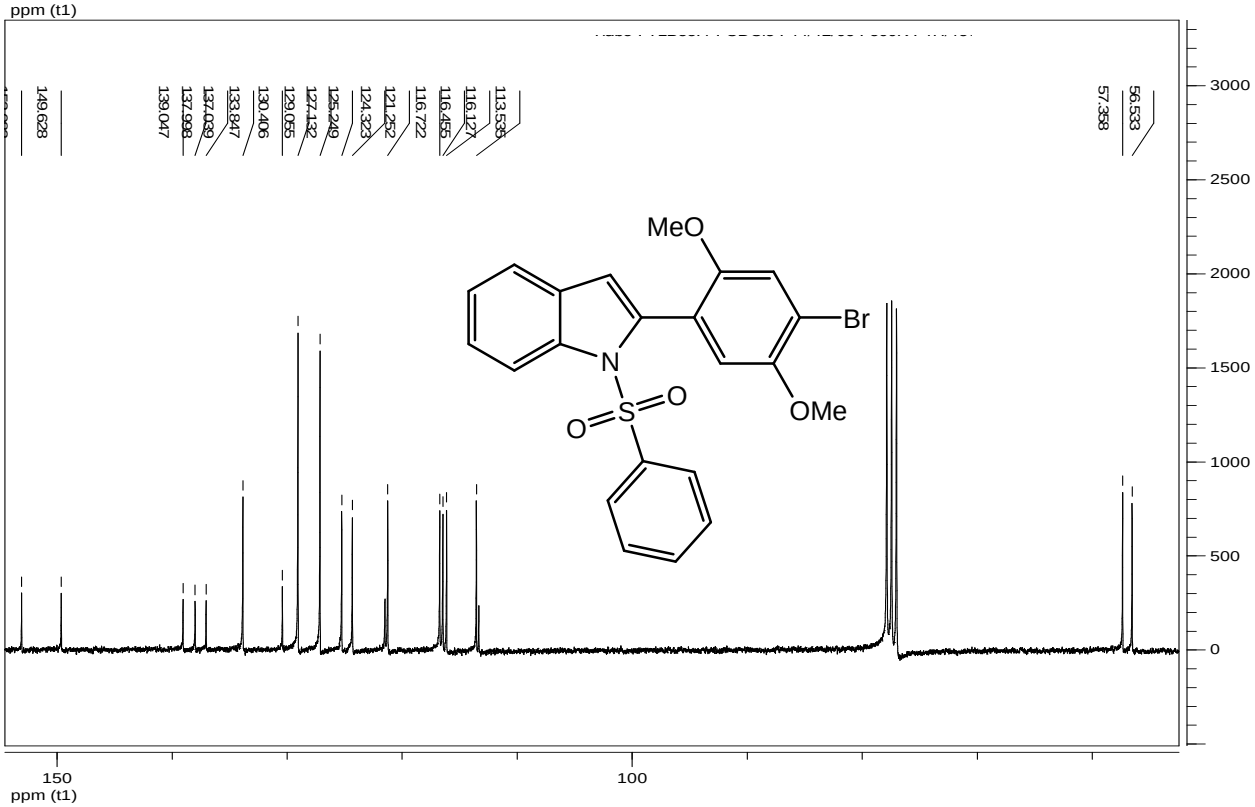

137.033
129.064
128.587
126.325
122.746
121.650
120.593
120.176
118.385
114.735
111.825
55.820
OMe
N
H
150
100
ppm (f1)

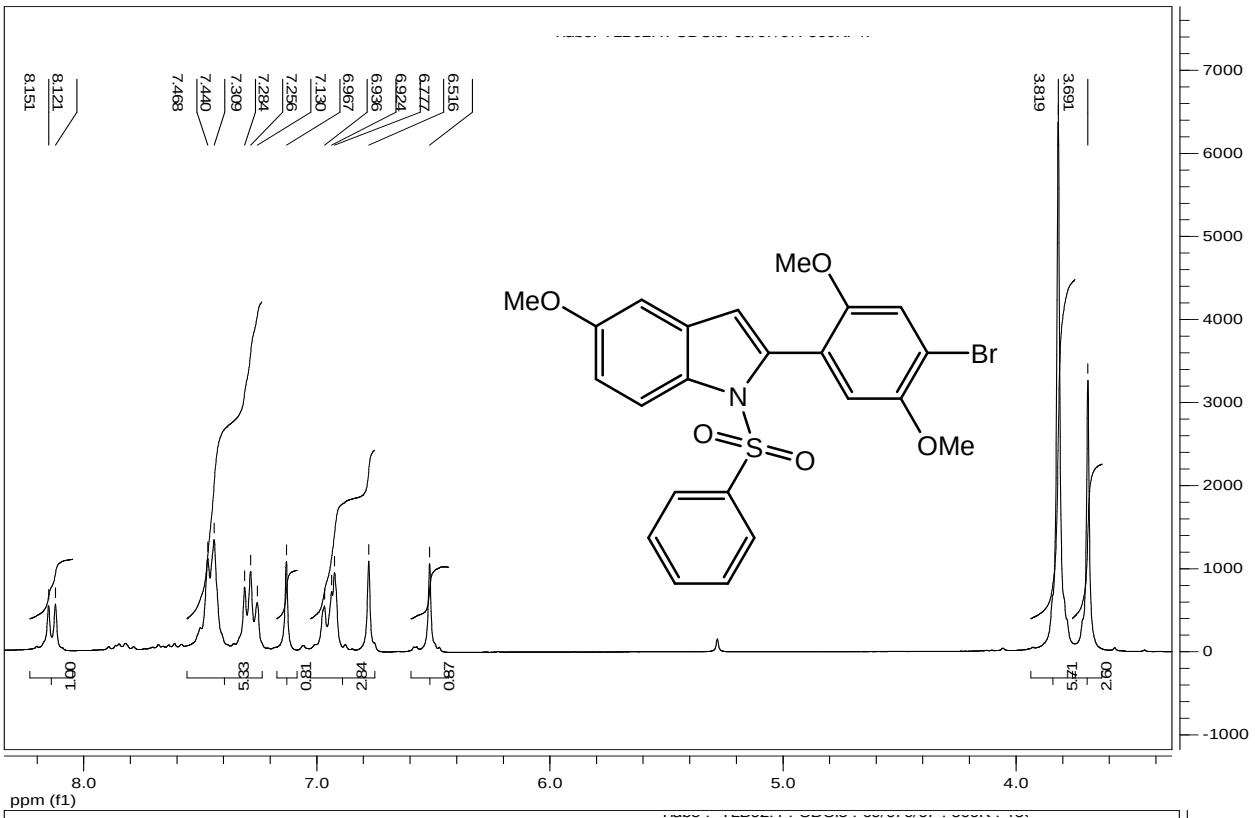

8.609
7.655
7.629
7.579
7.553
7.521
7.415
7.404
7.388
7.380
7.243
7.161
7.097
7.089
2.018
1.00
4.33
2.20
3.24
O
N
H
ppm (f1)
206.604
142.025
136.676
133.440
131.279
131.116
128.066
127.087
126.926
124.267
123.186
120.930
119.803
116.722
111.936
30.446
ppm (f1)

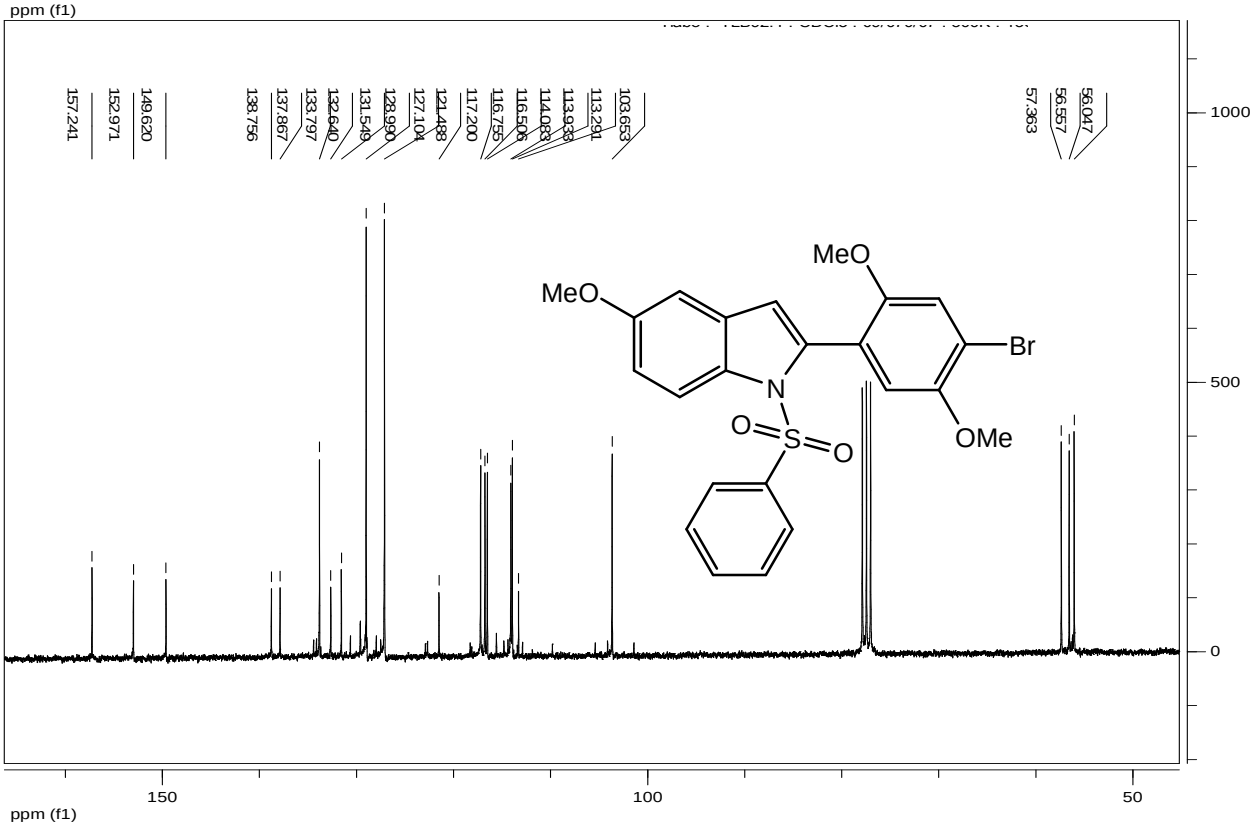

8.556
7.585
7.561
7.537
7.512
7.415
7.391
7.366
7.310
7.281
7.249
7.100
7.092
7.053
7.047
6.925
6.917
6.895
6.888
3.804
2.026
Tlabo : TLB121 : CDCl3 : 29/09/07 : 300K : 13C
MeO
O
N
H
1.00
3.00
2.40
2.13
1.04
3.30
3.19
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)

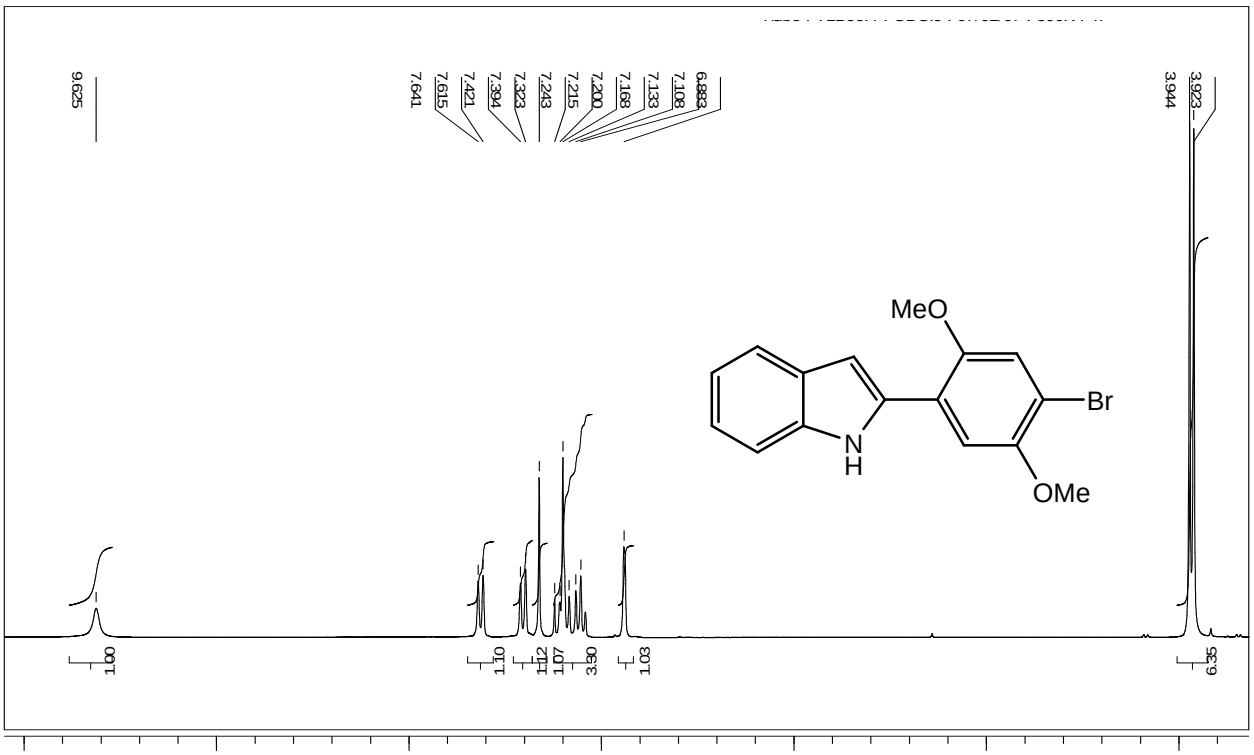

204.824
153.376
140.052
131.701
129.790
129.334
129.197
126.264
125.343
125.168
122.871
114.700
111.771
110.811
98.214
54.329
28.493
Tlabo : TLB121 : CDCl3 : 29/09/07 : 300K : 13C
MeO
O
N
H
200
150
100
50
ppm (t1)

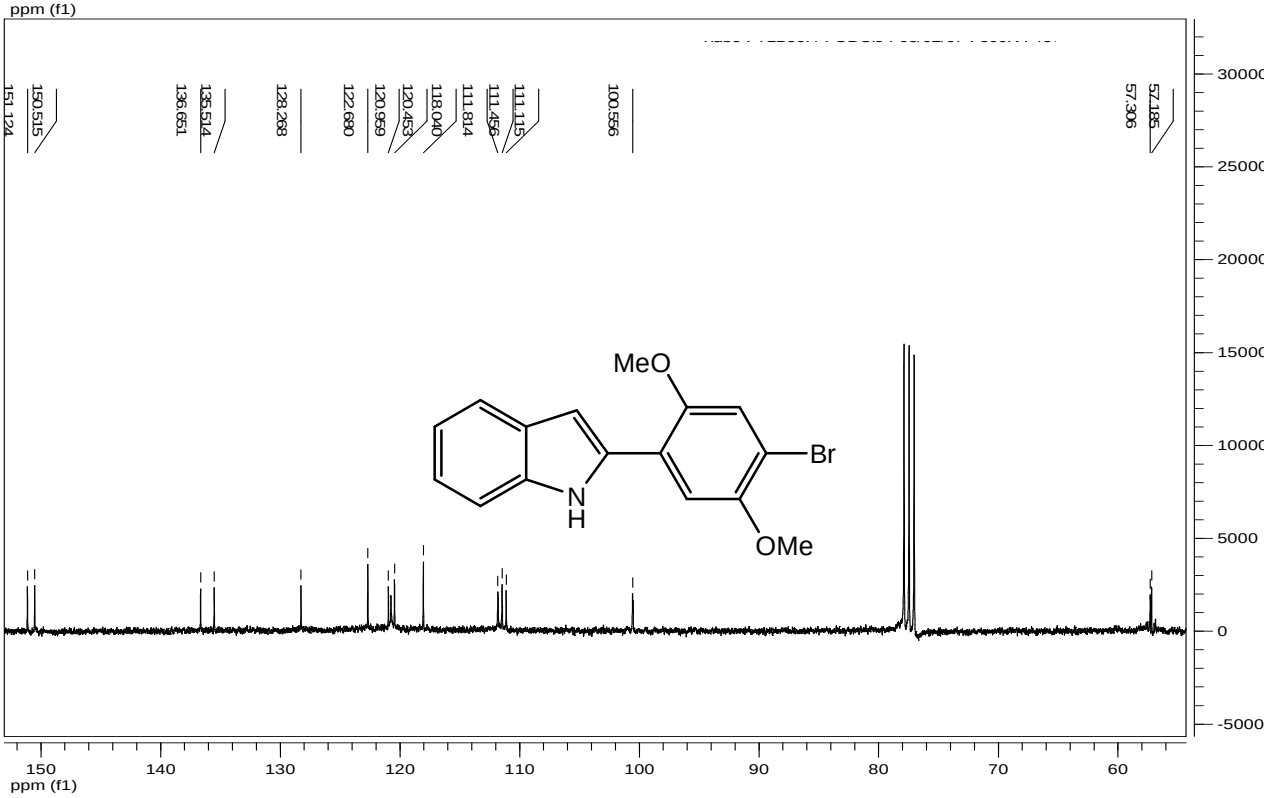

8.234
7.509
7.484
7.462
7.437
7.373
7.349
7.325
7.299
7.280
7.254
7.232
7.127
6.777
6.578
3.820
3.679
MeO
Br
N
O
S
O
O
OMe
1.00
4.00
2.14
1.60
8.80
6.80
9.09
8.0
7.0
6.0
5.0
4.0
ppm (t1)
6000
5000
4000
3000
2000
1000
0

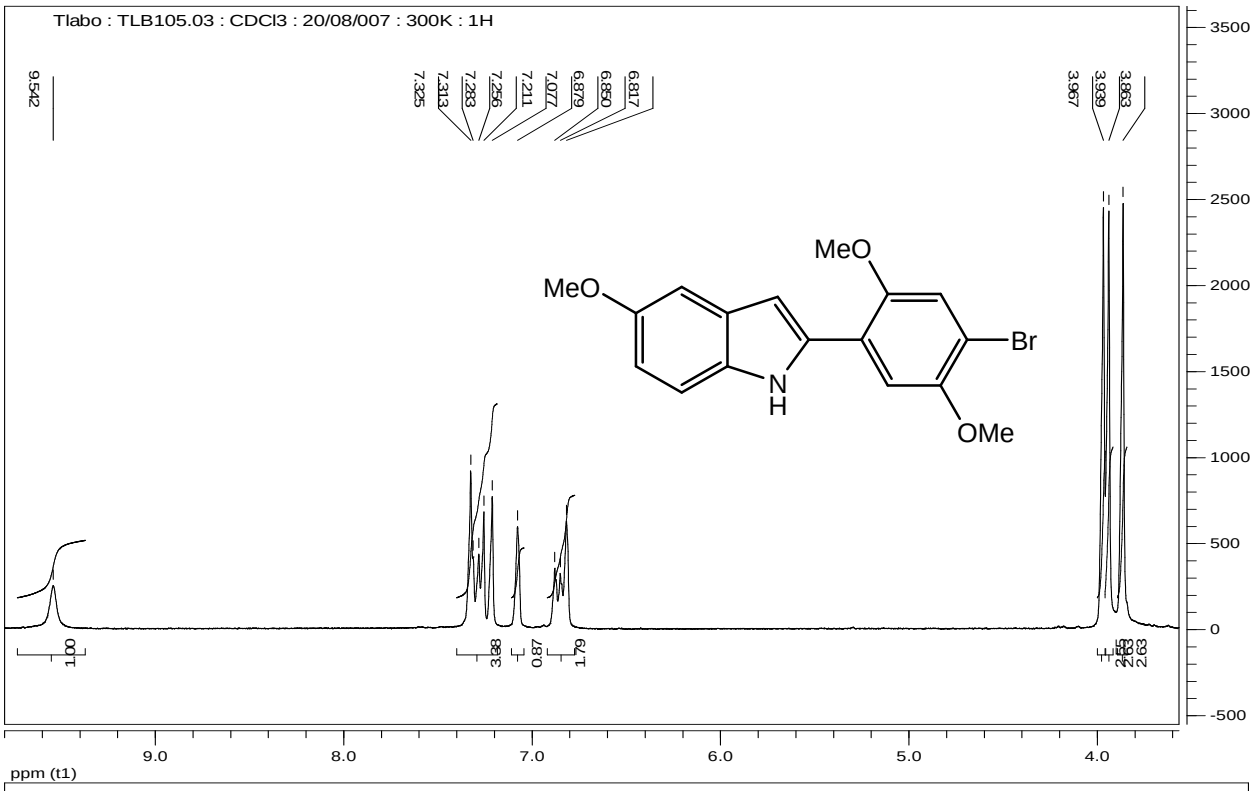

149.628
139.047
137.988
137.039
133.847
130.406
129.055
127.132
125.249
124.323
121.252
116.722
116.455
116.127
113.535
57.358
56.533
MeO
Br
N
O
S
O
O
OMe
150
100
ppm (t1)
3000
2500
2000
1500
1000
500
0

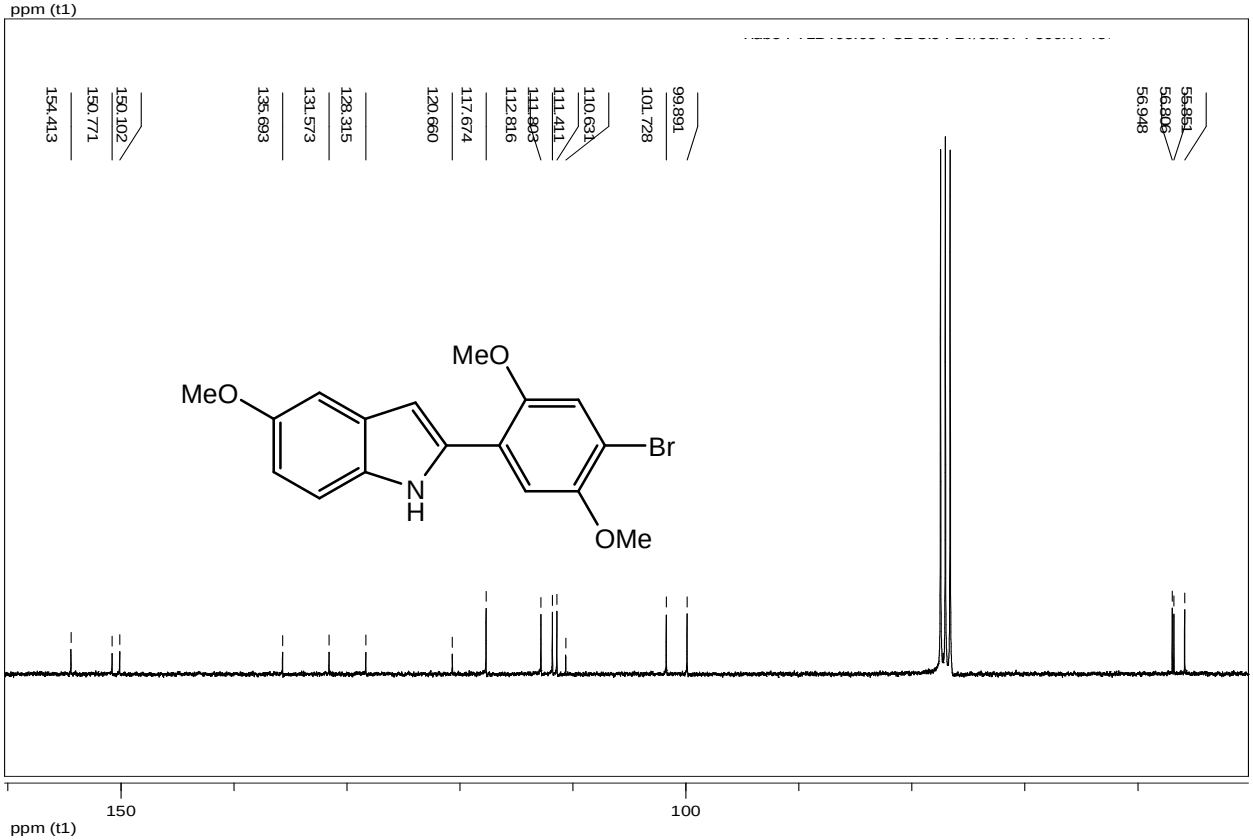

8.151
8.121
7.468
7.440
7.309
7.284
7.256
7.130
6.967
6.936
6.924
6.777
6.516
3.819
3.691
MeO
MeO
Br
OMe
N
O
S
O
1.00
5.33
1.80
2.84
4.80
5.71
2.60
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.0
7.0
6.0
5.0
4.0
ppm (f1)

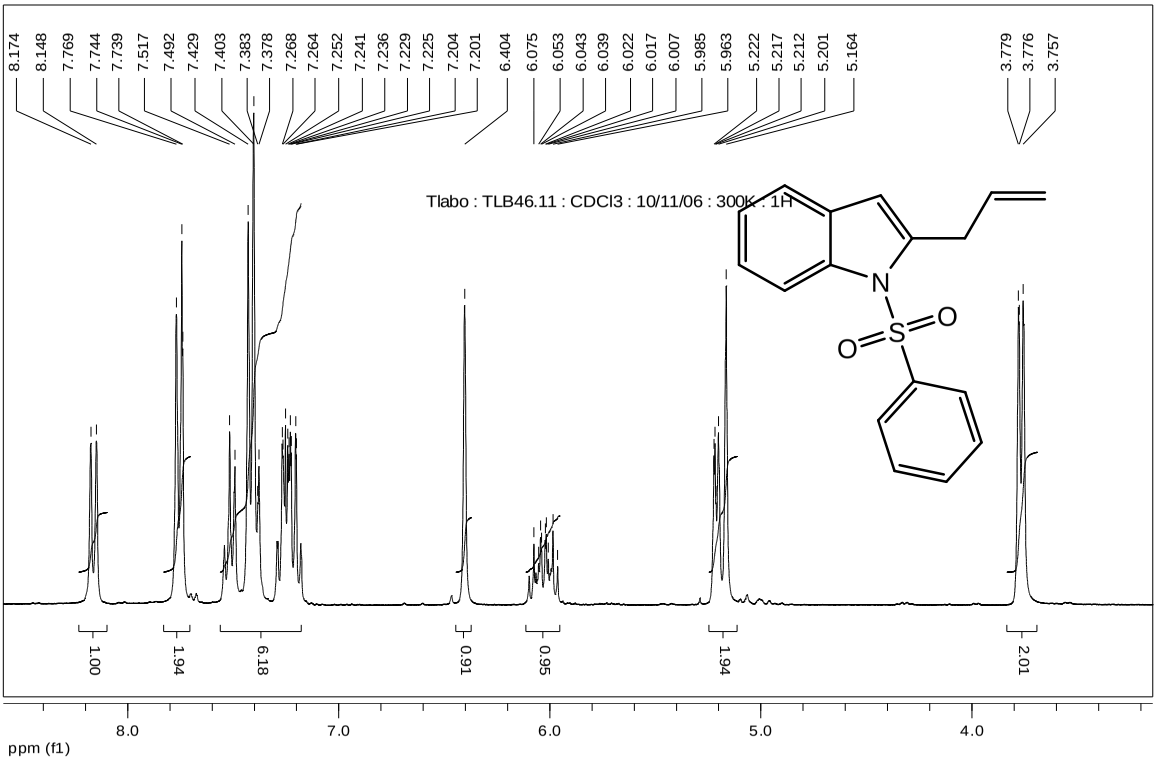

157.241
152.971
149.620
138.756
137.867
133.797
132.640
131.549
128.990
127.104
121.488
117.200
116.755
116.506
114.083
113.938
113.291
103.653
57.363
56.557
56.047
MeO
MeO
Br
OMe
N
O
S
O
1000
500
0
150
100
50
ppm (f1)

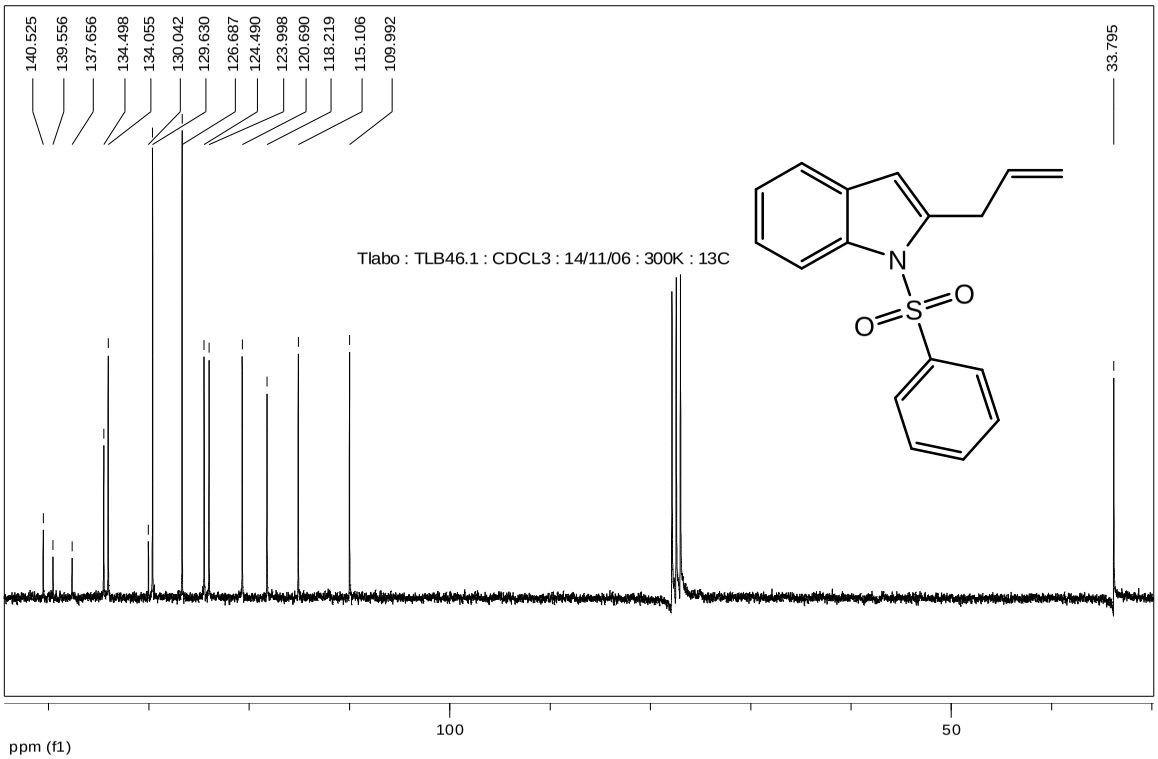

9.625
7.641
7.615
7.421
7.394
7.323
7.243
7.215
7.200
7.168
7.133
7.108
6.883
3.944
3.923
MeO
Br
N
H
OMe
1.00
1.10
2.11
2.11
1.07
3.30
1.03
9.35
10.0
9.0
8.0
7.0
6.0
5.0
4.0
ppm (f1)

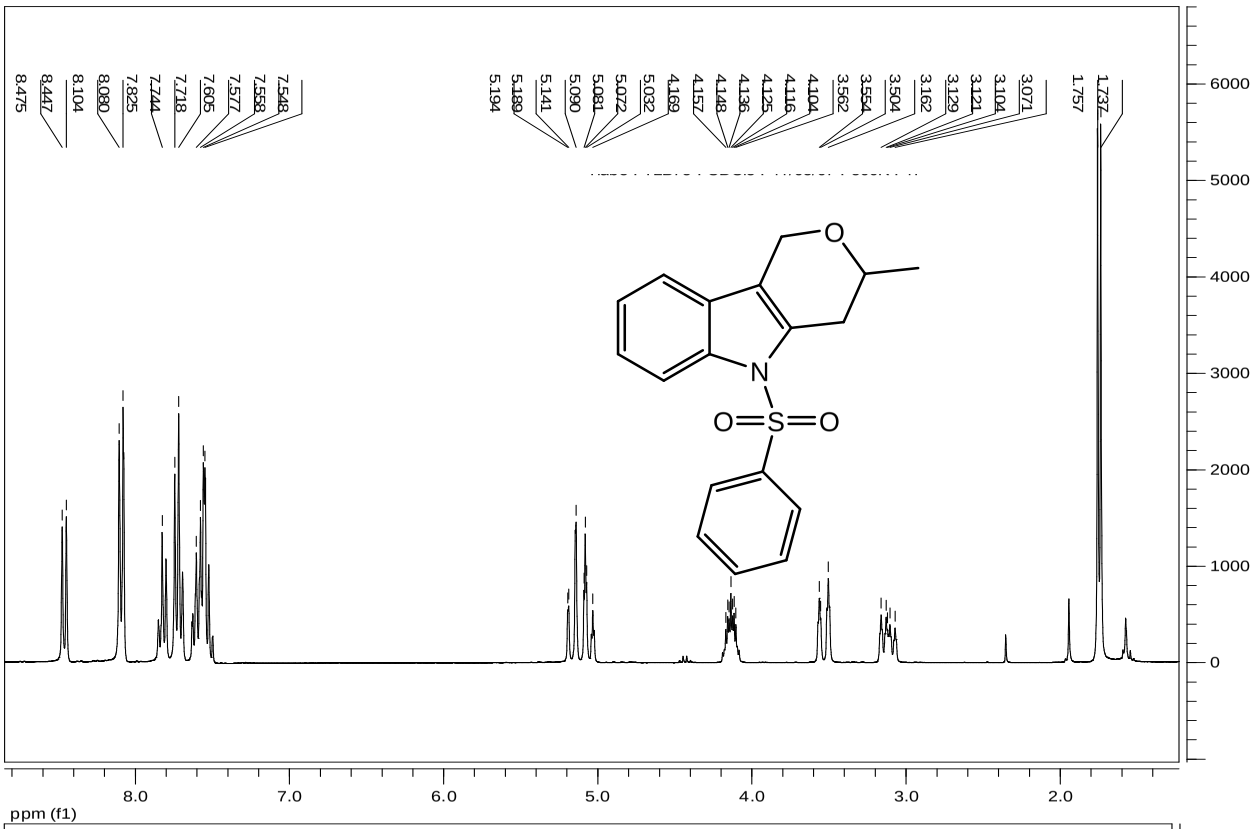

151.124
150.515
136.651
135.514
128.268
122.680
120.959
120.453
118.040
111.814
111.456
111.115
100.556
57.306
57.185
MeO
Br
N
H
OMe
30000
25000
20000
15000
10000
5000
0
-5000
150
140
130
120
110
100
90
80
70
60
ppm (f1)

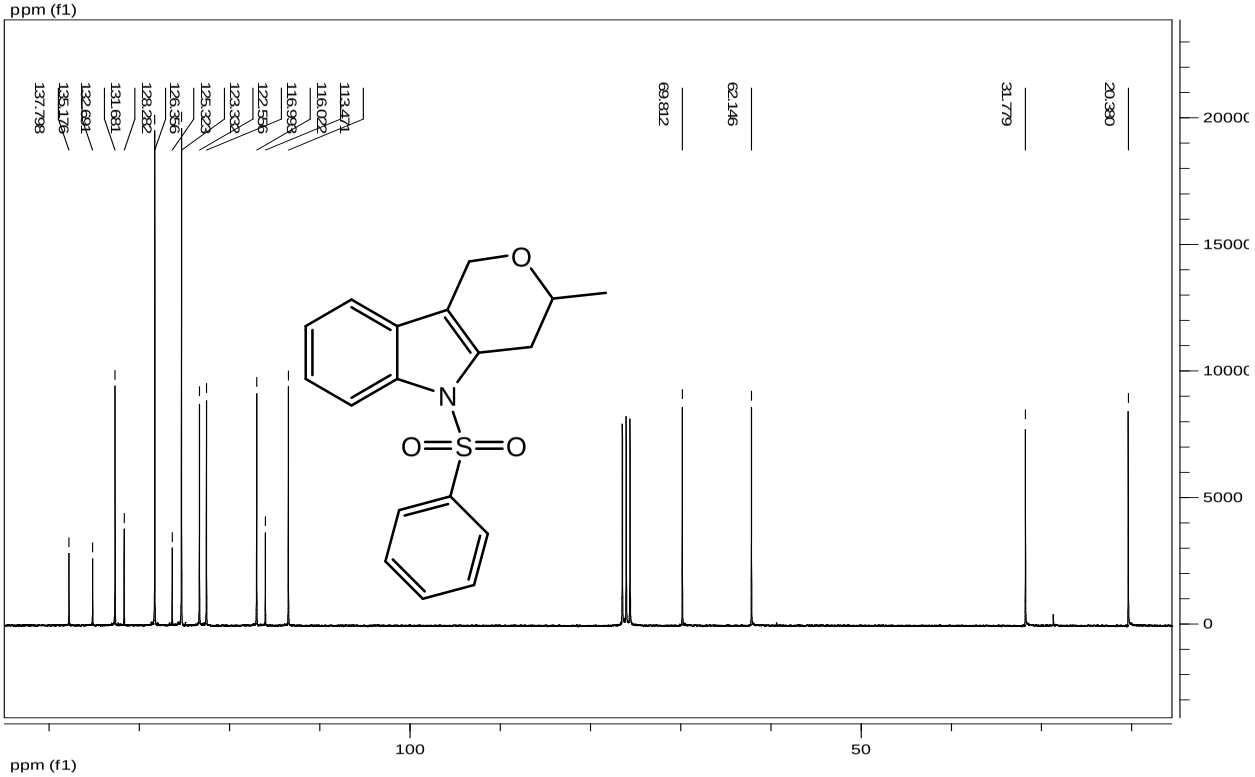

Tlabo : TLB105.03 : CDCl3 : 20/08/007 : 300K : 1H
9.542
7.325
7.313
7.283
7.256
7.211
7.077
6.879
6.850
6.817
3.967
3.939
3.863
MeO
MeO
Br
N
H
OMe
1.00
3.38
0.87
1.79
2.55
2.63
2.63
3500
3000
2500
2000
1500
1000
500
0
-500
9.0
8.0
7.0
6.0
5.0
4.0
ppm (t1)

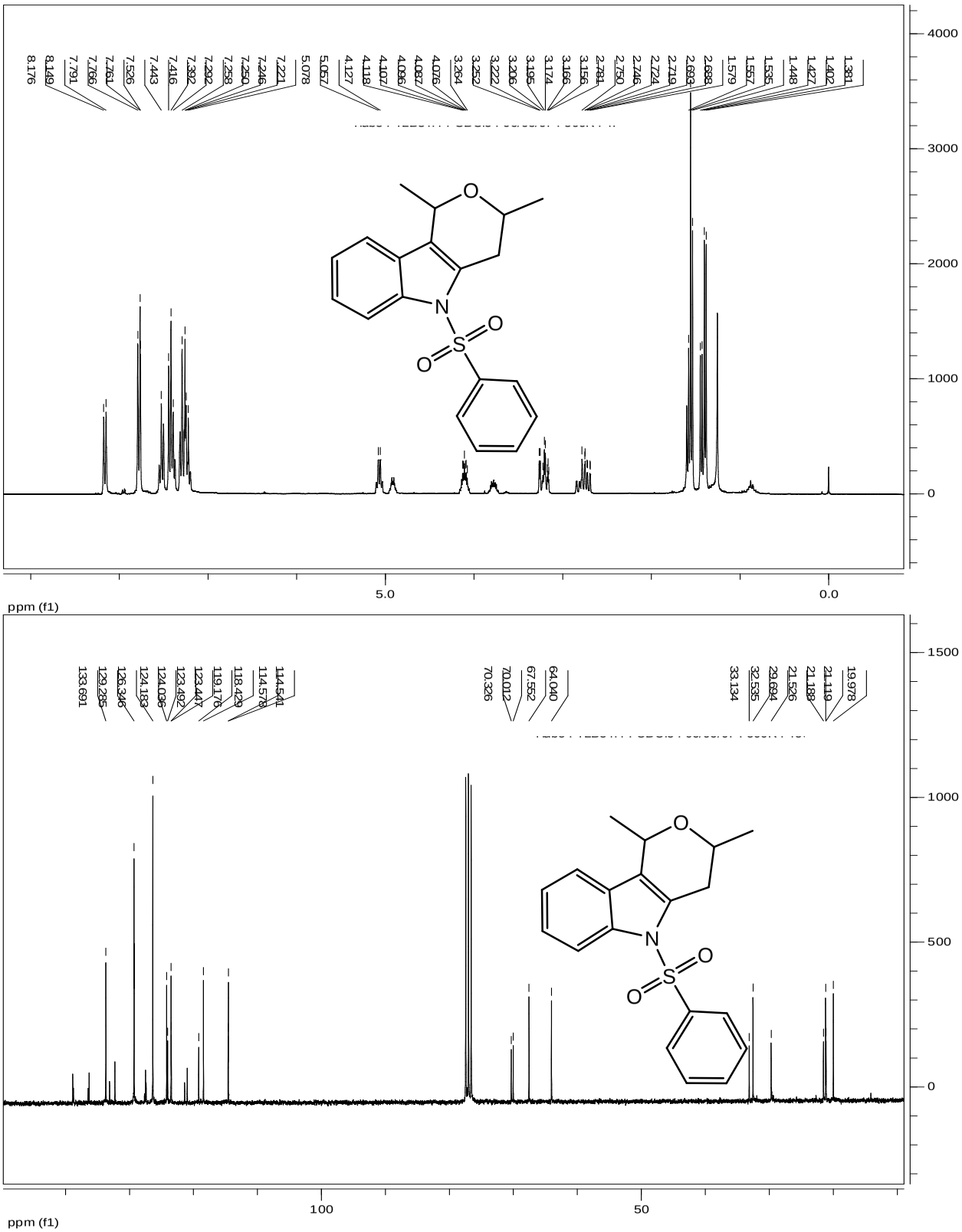

154.413
150.771
150.102
135.693
131.573
128.315
120.660
117.674
112.816
111.803
111.411
110.631
101.728
99.891
56.948
56.806
55.851
MeO
MeO
Br
N
H
OMe
150
100
ppm (t1)


8.174
8.148
7.769
7.744
7.739
7.517
7.492
7.429
7.403
7.383
7.378
7.268
7.264
7.252
7.241
7.236
7.229
7.225
7.204
7.201
6.404
6.075
6.053
6.043
6.039
6.022
6.017
6.007
5.985
5.963
5.222
5.217
5.212
5.201
5.164
3.779
3.776
3.757
Tlabo : TLB46.11 : CDCl3 : 10/11/06 : 300K : 1H
N
S
O
O
1.00
1.94
6.18
0.91
0.95
1.94
2.01
8.0
7.0
6.0
5.0
4.0
ppm (f1)


140.525
139.556
137.656
134.498
134.055
130.042
129.630
126.687
124.490
123.998
120.690
118.219
115.106
109.992
33.795
Tlabo : TLB46.1 : CDCL3 : 14/11/06 : 300K : 13C
N
S
O
O
100
50
ppm (f1)


8.475
8.447
8.104
8.080
7.825
7.744
7.718
7.605
7.577
7.558
7.548
5.194
5.189
5.141
5.090
5.081
5.072
5.032
4.169
4.157
4.148
4.136
4.125
4.116
4.104
3.562
3.554
3.504
3.162
3.129
3.121
3.104
3.071
1.757
1.737
O
N
O=S=O
6000
5000
4000
3000
2000
1000
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (f1)


137.798
135.176
132.691
131.681
128.262
126.356
125.323
123.332
122.556
116.903
116.022
113.471
69.812
62.146
31.779
20.390
O
N
O=S=O
20000
15000
10000
5000
0
100
50
ppm (f1)


8.176
8.149
7.791
7.766
7.761
7.526
7.443
7.416
7.392
7.292
7.258
7.250
7.246
7.221
5.078
5.057
4.127
4.118
4.107
4.096
4.087
4.076
3.264
3.252
3.222
3.206
3.195
3.174
3.166
3.156
2.781
2.750
2.746
2.724
2.719
2.693
2.688
1.579
1.557
1.535
1.448
1.427
1.402
1.381
O
N
S
O
O
4000
3000
2000
1000
0
5.0
0.0
ppm (f1)
133.691
129.285
126.346
124.183
124.036
123.492
123.447
119.176
118.429
114.578
114.541
70.326
70.012
67.552
64.040
33.134
32.535
29.694
21.526
21.188
21.119
19.978
O
N
S
O
O
1500
1000
500
0
100
50
ppm (f1)