CHAPTER-2

Potassium persulfate-glucose mediated synthesis of (3)-S-arylthioindoles from indole and thiophenols in water

2.1 Introduction

Indole structure motifs are commonly found in various natural products, bioactive molecules, drugs, agrochemicals, and materials [1]. Iprindole, indomethacin and tenidap are a few examples of clinically used indole-based medicines in the market [1b,1d-f,i] (**Figure 2.1**). Hence, developing efficient synthetic approaches to construct functionalized indoles received significant attention in organic synthesis and medicinal chemistry [2]. Among the different derivatives of indoles, synthesis of (3)-*S*-arylthioindoles (i.e. 3-sulfenylindoles) received considerable interest in medicinal chemistry due to their broad spectrum of biological activities, including anti-cancer, anti-HIV, antiallergic, antiviral and antibacterial activities) [3] (**Figure 2.1**). Synthesis of 3-(*S*)-arylthioindoles has been achieved through direct C-H functionalization of indole with various sulfenylating agents, such as aryl thiols, sulfonium salts, sulfenyl halides, sulfinates, sulfonyl hydrazides and disulfides [4]. Among these approaches, direct coupling of aryl thiols to indole is considered to be a more straightforward and economical route when compared with other methods. Because water or hydrogen is only the by-product generated in these reactions. In this regard, coupling of aryl thiols with indoles has been achieved using different reagents, including iodine-DMSO, HBr-DMSO, KIO_3, graphene oxide, selectfluor, vanadium oxyacetylacetonate, $B(C_6F_5)_3$ and KI/SeO_2 [4n-t]. Nevertheless, most of these existing methods suffer from the use of high reaction temperatures, hazardous solvents, expensive thiol surrogates, longer reaction times, etc. Hence, there is still room for developing a green and practical method for synthesizing 3-(*S*)-arylthioindoles under mild conditions.

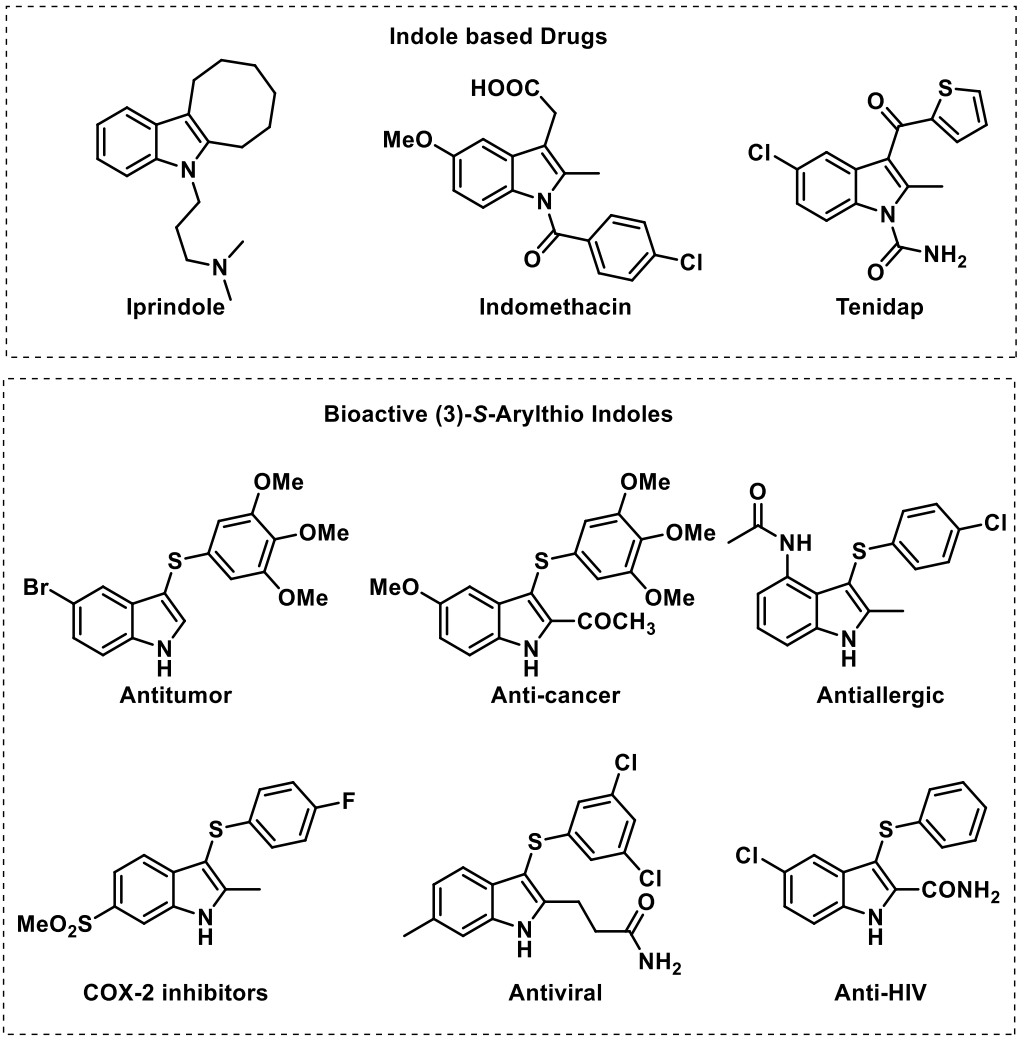
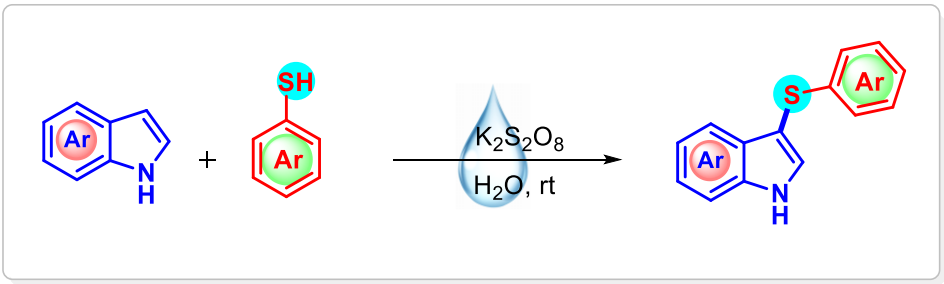


Figure 2.1 Some indole-based drugs and bioactive 3-(S)-arylthioindoles.

Water is often called as universal solvent due to its non-toxic nature, availability, capability to dissolve many biomolecules, etc. In this context, "organic reactions in water" emerged as an important topic in synthetic organic chemistry [5]. For instance, cycloaddition reactions, cross-coupling reactions, redox reactions, asymmetric reactions, etc., have been successfully demonstrated in water with high selectivity and yield [6]. On the other hand,

potassium persulfate ($K_2S_2O_8$) is a cheap and commercially available oxidant and it was frequently used in C-H functionalization reactions in organic synthesis[7]. Our research group is focused on the development of new synthetic routes for organic synthesis [8]. In this context, we have also demonstrated the application of potassium persulfate in the preparation of *N*-nitroso amines from secondary amines and nitromethane under mild reaction conditions [8a]. In continuation of our previous works in this field, here we explored the potassium persulfate mediated 3-arylsulfenylation of indoles in water under transition metal-free conditions at room temperature (**Scheme 2.1**).



Scheme 2.1. Synthesis of (3)-*S*-arylthioindoles.

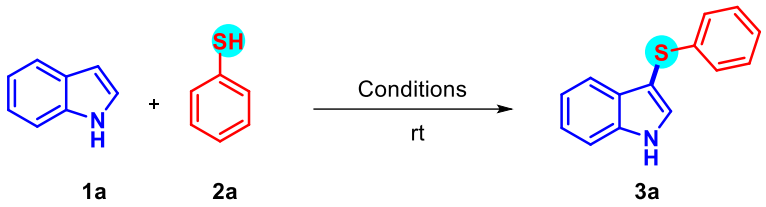
2.2. Results and Discussion

At the outset, the reaction condition was optimized using indole (**1a**) and thiophenol (**2a**) as the model substrates (**Table 2.1**). The reaction was performed in different solvents, including DCM, acetonitrile, DMSO, THF, methanol, glycerol and water at room

temperature for 24 hrs in the presence of 2.5 equiv. of $K_2S_2O_8$. Interestingly, the reaction in water provided the desired product **3a** in 65% yield, while low yields were obtained in

other solvents (**Table 2.1, entries 1-7**). The reaction in the acetonitrile-water mixture gave product **3a** in 45% yield (**Table 2.1, entry 8**). Considering the recent reports on glucose-mediated potassium persulfate activation [7k,l], the coupling reaction was investigated in the presence of various monosaccharides and disaccharides including glucose, galactose, mannose and maltose. To our delight, the reaction with glucose proceeded efficiently, providing product **3a** with an 85% yield within 12 hrs (**Table 2.1, entry 9**). It is important to note that no homocoupling product of indole was observed in the absence of thiols. The reactions in the presence of other saccharides also delivered product **3a** in comparable yields to that of glucose (**Table 2.1, entries 10-12**). Further, we investigated the efficiency of sodium and ammonium persulfates in 3-arylsulfenylation of indoles. These reagents also gave **3a** in good yield, i.e. 79% and 82% yields, respectively (**Table 2.1, entries 13-14**). It is also worth noting that the reaction with diphenyl disulfide (instead of thiophenol) gave a low yield of the desired product (**Table 2.1, entry 15**). Furthermore, we investigated the reaction with other oxidants including diacetoxy iodobenzene and DDQ. However, these reactions provided the desired product 3a in low yields (**Table 2.1, entries 16 and 17**) in comparison to potassium persulfate.

Table 2.1 Optimization of the reaction conditions[a,b]



1a 2a 3a

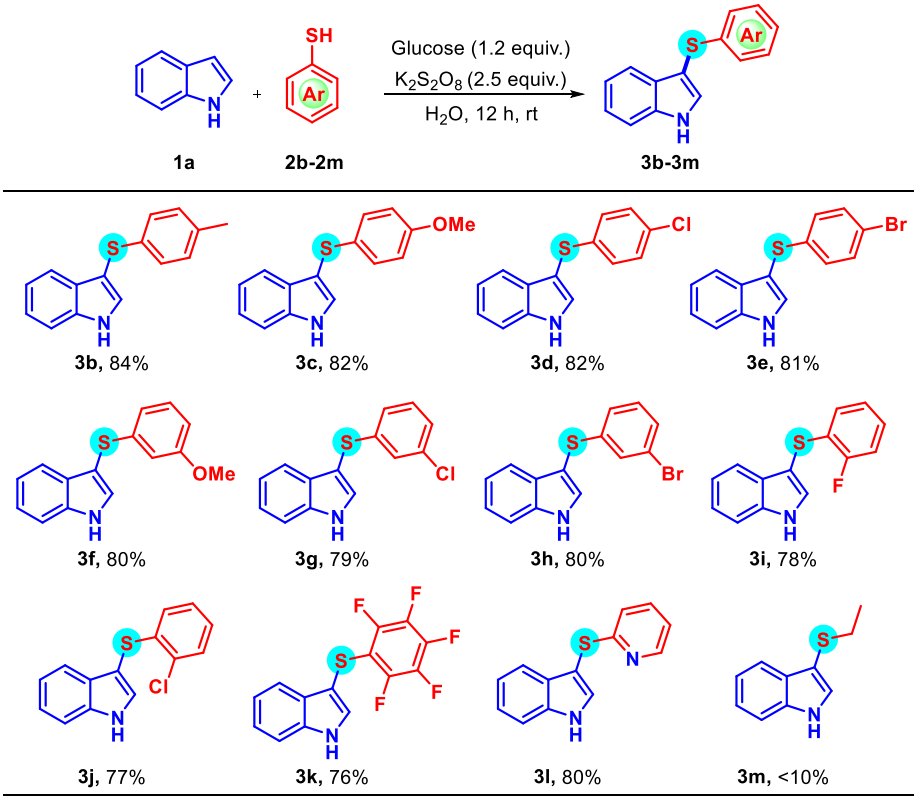
Entry	Oxidant	Solvent	Additives	Time (h)	Yield (%)[b]
1	$K_2S_2O_8$	DCM	-	24	<5
2	$K_2S_2O_8$	THF	-	24	19
3	$K_2S_2O_8$	DMSO	-	24	42
4	$K_2S_2O_8$	CH_3CN	-	24	28
5	$K_2S_2O_8$	CH_3OH	-	24	15
6	$K_2S_2O_8$	Glycerol	-	24	31
7	$K_2S_2O_8$	H_2O	-	24	65
8	$K_2S_2O_8$	CH_3CN-H_2O (1:1)	-	24	45
9	**$K_2S_2O_8$**	**H_2O**	**Glucose**	**12**	**85**
10	$K_2S_2O_8$	H_2O	Galactose	12	74
11	$K_2S_2O_8$	H_2O	Mannose	12	76
12	$K_2S_2O_8$	H_2O	Maltose	12	71
13	$Na_2S_2O_8$	H_2O	Glucose	12	79
14	$(NH_4)_2S_2O_8$	H_2O	Glucose	12	82
15[c]	$K_2S_2O_8$	H_2O	Glucose	12	36
16	$PhI(OAc)_2$	H_2O	-	24	58
17	DDQ	H_2O	-	24	51

[a]**Reaction conditions:** Indole **1a** (70 mg, 0.6 mmol), thiophenol (72 mg, 0.66 mmol), sugar (0.72 mmol) and persulfate (1.5 mmol) were stirred in a solvent (4 mL) for 12 h at room temperature. [b]Isolated yields. [c]The reaction was carried out with diphenyl disulfide instead of thiophenol.

After establishing the optimized conditions, we investigated the scope of thiols in the coupling reaction (**Table 2.2**). Initially, the coupling of electron-donating groups such as methyl and methoxy functionalized thiophenols (*para*-substitution) with indole **1a** was performed under optimized conditions. These reactions provided the desired products **3b-3c** in 82–84% yields. On the other hand, halogens such as chloro and bromo functionalized thiophenols also gave the desired products **3d** and **3e** in 81–82% yields. Further, we

investigated cross-coupling reactions with *meta* and *ortho*-substituted thiophenols under optimized conditions. To our delight, these reactions provided the desired products **3f-3k** in 76–80% yields. Moreover, heteroaryl thiol underwent a coupling reaction with indole, giving the desired product **3l** in 80% yield. However, aliphatic thiol provided the desired product **3m** in negligible yield.

Table 2.2 Scope of thiophenols[a,b]

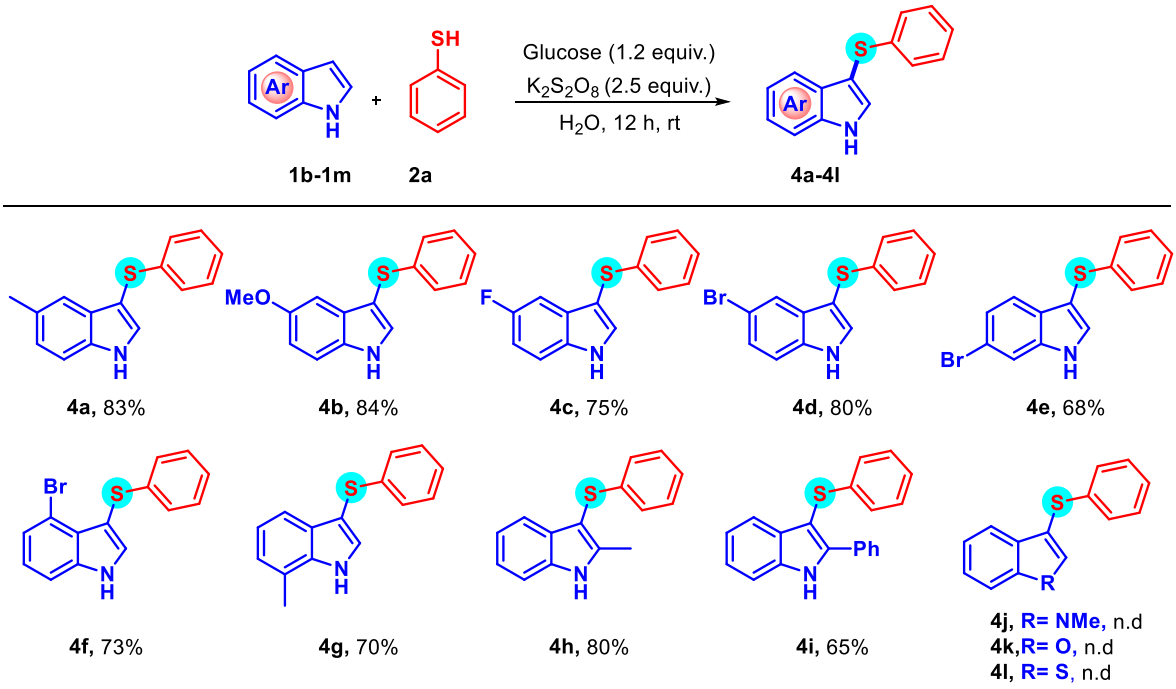


[a]**Reaction condition:** Indole **1a** (70 mg, 0.6 mmol), thiophenol (0.66 mmol), glucose (139 mg, 0.72 mmol) and $K_2S_2O_8$ (404 mg, 1.5 mmol) were stirred in water (4 mL) for 12 h at room temperature. [b]Isolated yields.

Further, we studied the scope of substituted indoles in the coupling reactions (**Table 2.3**). Initially, the reactivity of indoles with electron-donating and withdrawing groups at the 5-

carbon was investigated. To our delight, these substrates participated in the coupling reactions with thiophenol and gave the desired products **4a-4d** in 75–84% yields. On the other hand, indoles with 6-C, 4-C and 7-C substitutions also underwent coupling reactions and gave the products **4e-4g** in 68–73% yields. More importantly, indoles bearing substitutions on 2-C also provided the desired products **4h-4i** in 65-80% yields. However, no reaction was observed with *N*-methyl indole, benzofuran, benzothiophene and carbazole substrates (**4j-4l**). On the other hand, 3-arylsulfenylation of pyrrole and imidazole with thiophenol delivered the desired products in a trace amount along with unidentified products.

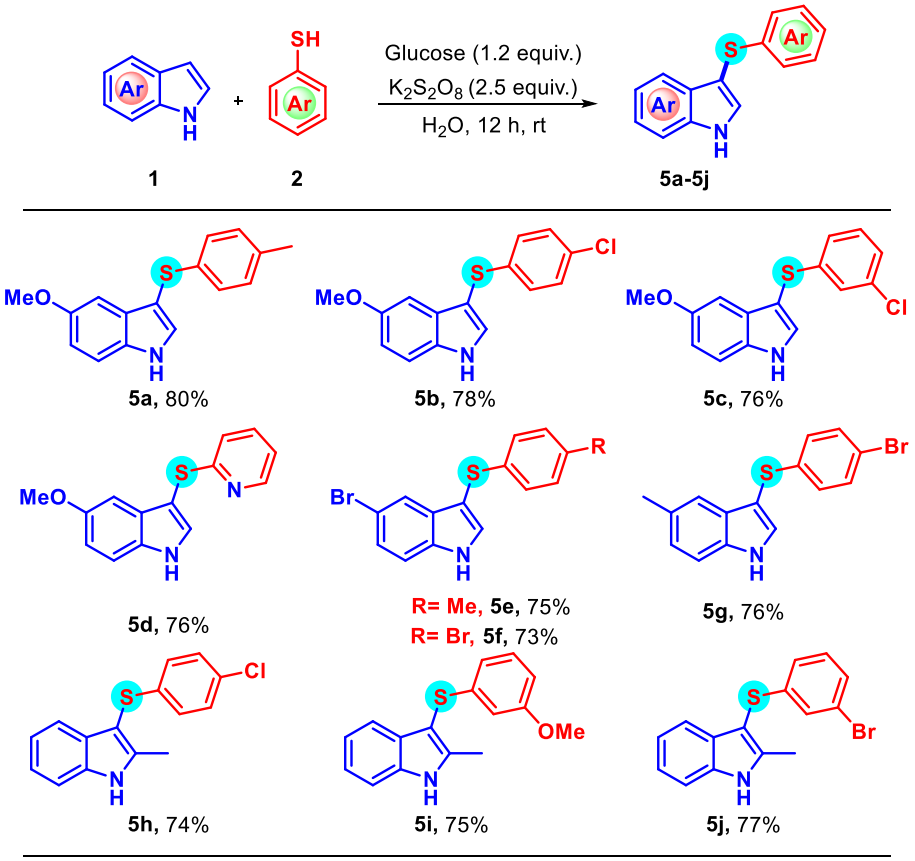
Table 2.3. Scope of indoles [a,b]



[a]**Reaction condition:** substituted indole **1b-1m** (0.6 mmol), thiophenol (72 mg, 0.66 mmol), glucose (0.72 mmol) and $K_2S_2O_8$ (1.5 mmol) were stirred in water (4 mL) for 12 h at room temperature. [b]Isolated yields.

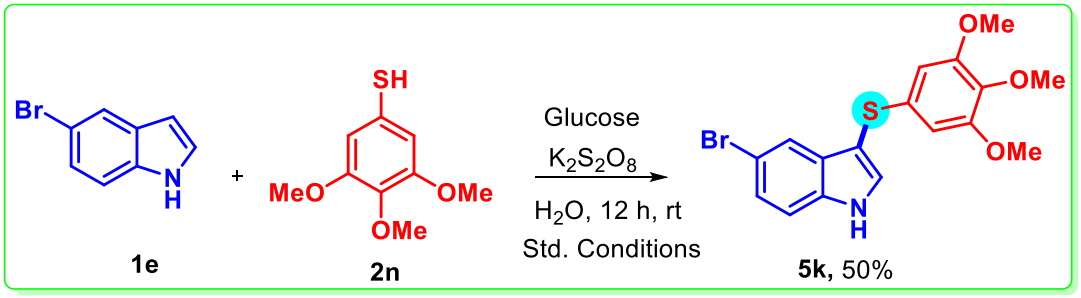
Further, we explored the coupling reactions between substituted thiols and functionalized indoles under optimized conditions (**Table 2.4**). For instance, indoles bearing electron-donating and withdrawing groups at different positions underwent sulfenylation with *o*-, *m*- and *p*-functionalized thiols at C-3 place and gave the corresponding (3)-*S*-arylthioindoles **5a-5j** in 73-80% yields.

Table 2.4. Scope of indoles and thiophenols[a,b]

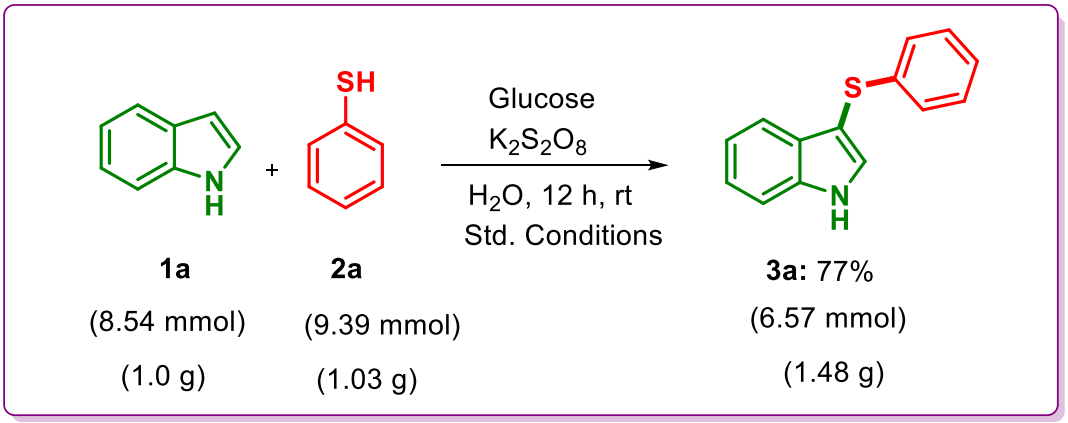


[a]**Reaction condition:** Substituted indole (0.6 mmol), substituted thiophenol (0.66 mmol), glucose (0.72 mmol) and $K_2S_2O_8$ (1.5 mmol) were stirred in water (4 mL) for 12 h in room temperature. [b]Isolated yields.

Using the developed methodology, we attempted the synthesis of anti-tumor agent **5k** [3a] (**Scheme 2.2**). The compound 5-bromo indole was reacted with 3,4,5-trimethoxythiophenol in the presence of potassium persulfate under optimized conditions. To our delight, this reaction provided the compound **5k** in 50% yield. Further, we attempted a gram scale reaction with model substrates and obtained the desired product **3a** in 77% yield (**Scheme 2.3**).



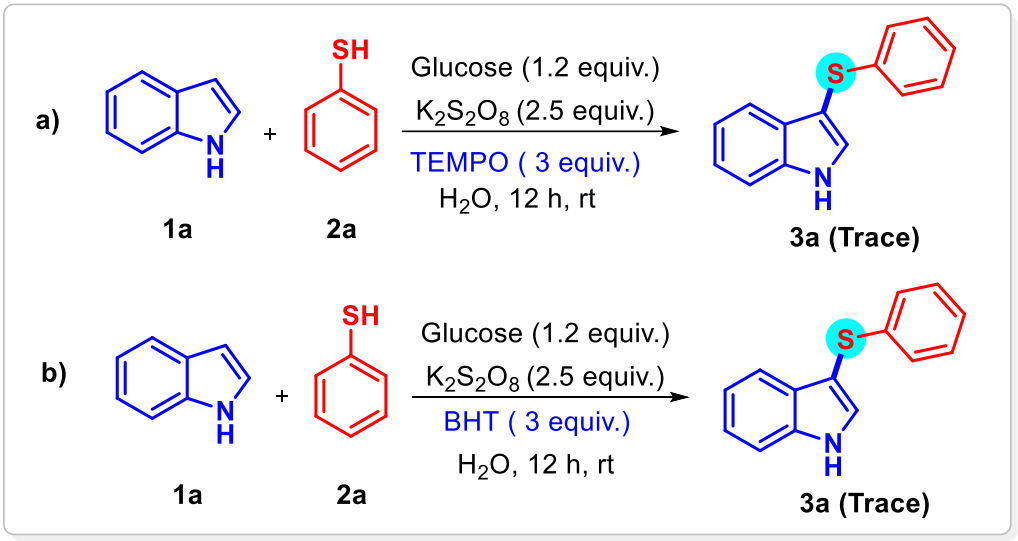
Scheme 2.2. Synthesis of anti-tumour compound **5K**.



Scheme 2.3. Gram-scale reaction for compound **3a.**

2.3 Control Experiments

Control experiments were performed in the presence of radical scavengers such as TEMPO and BHT to understand the reaction mechanism (**Scheme 2.4, a and b**). These reactions provided compound **3a** in negligible yields, indicating the radical pathway of the reaction mechanism.



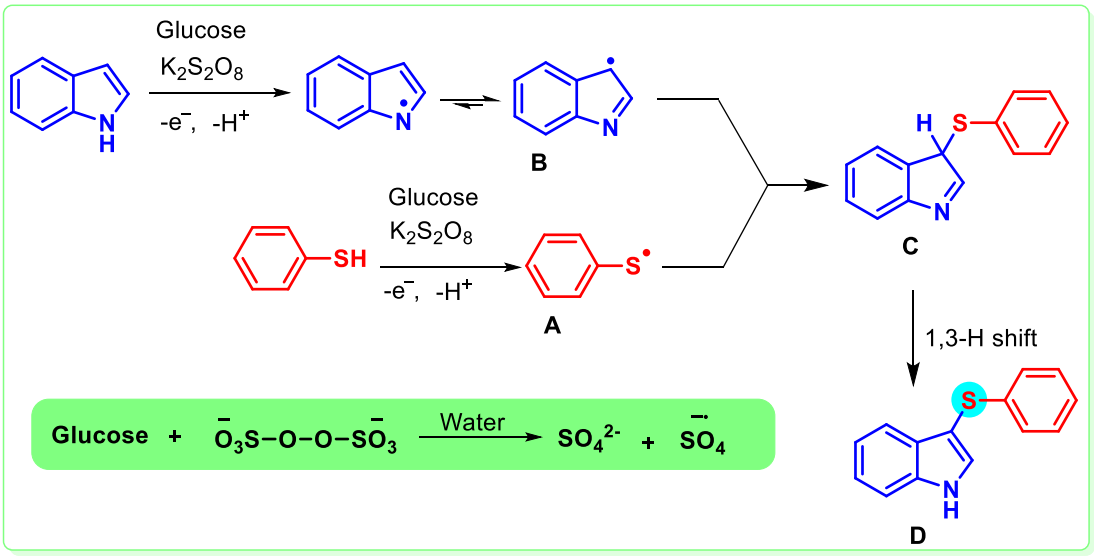
Scheme 2.4. Control experiments

2.4 Plausible Reaction Mechanism

The proposed mechanism of the reaction is shown in (**Scheme 2.5**). Initially, glucose facilitates the generation of thiol and indole radicals **A** and **B**, respectively, in the presence of potassium persulfate in water [7i, k, l]. Subsequently, these radicals undergo a coupling reaction and generate the intermediate **C,** which is converted into the desired product **D** via 1,3-hydrogen shift. Control experiments were performed in the presence of radical

scavengers such as TEMPO and BHT to understand the reaction mechanism (**Scheme 2.4, a and b**). These reactions provided compound **3a** in negligible yields, indicating the radical pathway of the reaction mechanism.

Glucose is responsible to generate the key oxidant, the sulfate radical anion ($SO_4^{\bullet-}$, a strong one electron oxidant (2.5–3.1 V)) and sulfate anion (SO_4^{2-}), involving the heterolytic cleavage of the peroxy linkage by the transfer of one electron from glucose to $S_2O_8^{2-}$ at room temperature.



Scheme 2.5. Plausible reaction mechanism

2.5. Conclusions

Synthesis of 3-(*S*)-arylthioindoles from indole and thiophenol was achieved in good to excellent yields in water. The reaction was promoted by $K_2S_2O_8$ in the presence of glucose at room temperature. Broad substrate scope, functional group tolerance, and metal-free conditions are important advantages of the developed methodology.

2.6. Experimental Procedures

2.6.1. Starting Materials used for Sulfenylation of Indoles

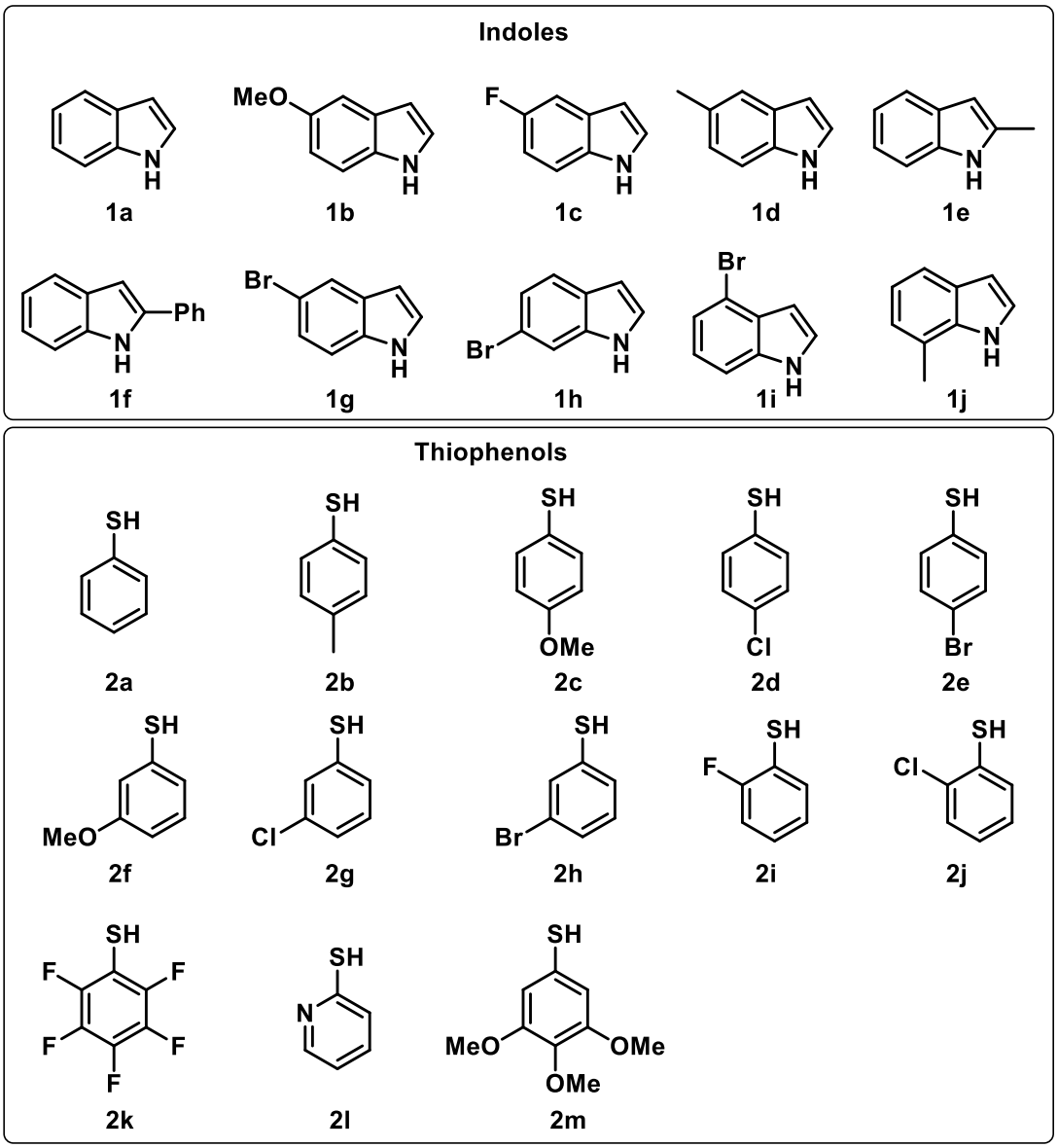
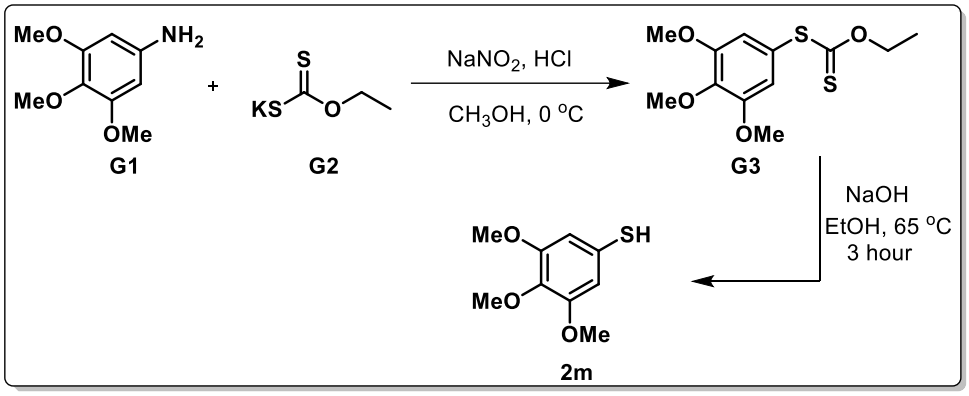


Figure 2.2 Starting material used for sulfenylation

2.6.2. Synthesis of 3,4,5-trimethoxybenzenethiol [19] (2m)



Scheme 2.6 Synthesis of 3,4,5-trimethoxybenzenthiol

3,4,5 trimethoxyaniline (1 g, 5.5 mmol) was added into the mixture of methanol (2.5 mL) and concentrated HCl (2.5 mL) of 500 mL dry round bottom flask. And the solution was cooled at 0 ^{o}C. then, a solution of $NaNO_2$ (489 mg, 7 mmol) with water (2.5 mL) was added slowly into above mixture. The reaction mixture was stirred continuously until became a clear solution at below 5 ^{o}C. Further, the reaction mixture was added slowly into a solution of potassium xanthogenate (1.7 g, 10.4 mmol) with water (10 mL) at 65 ^{o}C and continuously stirred at 65 ^{o}C for 30 minutes. After coming reaction mixture to room temperature and extracted with ethyl acetate (3 × 50 mL). and the organic layer was washed from the brine solution and dried with Na_2SO_4. Then concentrated with rota evaporator. The concentrated organic layer was purified by column chromatography on silica gel (100-200 mesh) using ethyl acetate: hexane (1:15) to give **G3** (802 mg) in 51% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.73 (s, 2H), 4.62 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 6H), 1.34

(t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 213.1, 153.3, 139.6, 124.4, 112.2, 70.2, 60.8, 56.2, 13.6.

A solution of sodium hydroxide (3 M, 16 mL) was added slowly into a solution of **G3** (802 mg, 2.7 mmol) with ethanol (16 mL) at 65 ^{o}C. continuously stirred for 3 h at 65 ^{o}C. after coming to room temperature. The reaction mixture was acidified with 10% aqueous solution of HCl and extracted with ethyl acetate (3 × 80 mL), further organic layer was washed with brine solution and dried over Na_2SO_4. The concentrated organic layer was purified by fresh column chromatography on silica gel (100-200 mesh) using ethyl acetate: Hexane (1:8). Thiol **(2m)** was obtained in 90% yield (437 mg) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 2H), 3.81 (s, 3H), 3.80 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.4, 138.0, 131.9, 106.5, 60.8, 56.1.

2.6.3. General Procedure for the Preparation of 3-Arylthioindoles

A dry 25 mL round bottom flask was charged with indole (0.6 mmol, 1.0 equiv.), arylthiol (0.65 mmol, 1.1 equiv.), $K_2S_2O_8$ (1.2 mmol, 2.0 equiv.) and glucose (0.6 mmol, 1.0 equiv.) in water (4 ml). The obtained solution was stirred continuously at room temperature for 12 h. after completion of the reaction mixture, diluted with water (15 mL), and then extracted with ethyl acetate (3x30 mL). combine the organic layer dried over Na_2SO_4. The concentrated organic layer was purified by column chromatography on silica gel (100-200 mesh) using ethyl acetate: hexane.

2.7. Analytical Data

2.7.1. 3-(phenylthio)-1H-indole [20] (3a):

Colourless Solid (m.p. 151-152 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.34. Yield 85% (114 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.78 (brs, 1H), 8.36 (d, J = 4.6 Hz, 1H), 7.80 (d, J = 2.5 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.49-7.45 (m, 2H), 7.41 (d, J = 7.9 Hz, 1H), 7.20 (t, J = 7.06 Hz, 1H), 7.09 (t, J = 7.05Hz, 1H), 7.04-7.02 (m, 1H), 6.61 (d, J = 8.1 Hz, 1H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 162.2, 149.0, 136.9, 136.8, 132.7, 128.5, 122.2, 120.2, 119.4, 118.9, 118.1, 112.4, 98.0.

2.7.2. 3-(p-tolylthio)-1H-indole [20] (3b):

Colourless Solid (m.p. 123-124 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.43. Yield 84% (120 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.74 (d, J = 2.6 Hz, 1H), 7.50-7.48 (m, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.07-7.04 (m, 1H), 7.01-6.94 (m, 4H), 2.18 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 136.6, 135.4, 134.0, 132.1, 129.4, 128.6, 125.7, 122.0, 119.9, 118.3, 112.3, 99.9, 20.3.

2.7.3. 3-((4-methoxyphenyl)thio)-1H-indole [20] (3c):

Colourless Solid (m.p. 115-116 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.36. Yield 82% (125 mg).^{1}H NMR (500 MHz, DMSO-d_6) δ 11.60 (brs, 1H), 7.73 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.07-7.04 (m, 3H), 6.80 (d, J = 8.8 Hz, 2H), 3.66 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 157.4, 136.6, 131.7, 129.2, 128.5, 128.1, 121.9, 119.9, 118.3, 114.5, 112.2, 101.2, 55.0.

2.7.4. 3-((4-chlorophenyl)thio)-1H-indole [20] (3d):

Colourless Solid (m.p. 129-130 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.37. Yield 82% (127 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.75 (brs, 1H), 7.79 (d, J = 2.6 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.25-7.23 (m, 2H), 7.21-7.18 (m, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H).**^{13}C NMR** (125 MHz, DMSO-d_6) δ 138.3, 136.7, 132.5, 129.2, 128.7, 128.3, 126.8, 122.1, 120.2, 118.1, 112.3, 98.6.

2.7.5. 3-((4-bromophenyl)thio)-1H-indole [20] (3e):

Colourless Solid (m.p. 140-141 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.35. Yield 81% (147 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.76 (brs, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.39-7.35 (m, 3H), 7.19 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 8.5 Hz, 2H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 138.9, 136.7, 132.6, 131.5, 128.3, 127.1, 122.2, 120.2, 118.1, 117.4, 112.4, 98.5.

2.7.6. 3-((3-methoxyphenyl)thio)-1H-indole [21] (3f):

Colourless Solid (m.p. 85-86 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.32. Yield 80% (122 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.60 (brs, 1H), 7.73 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.07-7.04 (m, 3H), 6.80 (d, J = 8.8 Hz, 2H), 3.66 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 157.4, 136.6, 131.7, 129.2, 128.5, 128.1, 121.9, 119.9, 118.3, 114.5, 112.2, 101.2, 55.0.

2.7.7. 3-((3-chlorophenyl)thio)-1H-indole [21] (3g):

Colourless Solid (m.p. 78-79 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.36. Yield 79% (122 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.80 (brs, 1H), 7.82 (d, *J* = 2.3 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.23-7.19 (m, 2H), 7.12-7.07 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 1.5 Hz, 1H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 142.1, 136.7, 133.6, 132.8, 130.4, 128.3, 124.6, 124.2, 123.7, 122.2, 120.3, 118.1, 112.4, 98.0.

2.7.8. 3-((3-bromophenyl)thio)-1H-indole [22] (3h):

Colourless Solid (m.p. 99-100 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.37. Yield 80% (145 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.80 (brs, 1H), 7.82 (d, *J* = 2.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.25-7.19 (m, 2H), 7.15-7.07 (m, 3H), 7.03 (d, *J* = 7.9 Hz, 1H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 142.3, 136.7, 132.8, 130.7, 128.3, 127.5, 127.0, 124.1, 122.2, 122.2, 120.3, 118.1, 112.4, 98.1

2.7.9. 3-((2-fluorophenyl)thio)-1H-indole [23] (3i):

Colourless Solid (m.p. 134-135 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.32. Yield 78% (113 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.79 (brs, 1H), 7.82 (d, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.21-7.17 (m, 2H), 7.13-7.07 (m, 2H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.65 (t, *J* = 7.9 Hz, 1H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 158.1(d, *J* = 724 Hz), 136.9, 133.1, 128.6, 127.3 (d, *J* = 2.5 Hz), 126.5 (d, *J* = 7.5 Hz), 126.2 (d, *J* = 16.2 Hz), 124.8 (d, *J* = 2.5 Hz), 122.2, 120.3, 118.1, 115.1 (d, *J* = 20 Hz), 112.5, 96.6

2.7.10. 3-((2-chlorophenyl)thio)-1H-indole [21] (3j):

Colourless Solid (m.p. 140-141 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.36. Yield 77% (119 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.84 (brs, 1H), 7.82 (d, *J* = 2.1 Hz, 1H), 7.54 (d, *J* = 5.9 Hz, 1H), 7.41-7.37 (m, 2H), 7.21 (d, *J* = 6.6 Hz, 1H), 7.09-7.03 (m, 3H), 6.56 (s, 1H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 138.3, 136.8, 133.1, 129.2, 128.8, 128.4, 127.3, 125.9, 125.7, 122.3, 120.3, 118.1, 112.5, 97.3.

2.7.11. 3-((perfluorophenyl)thio)-1H-indole [24] (3k):

Colourless Solid (m.p. 151-152 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.1. Yield 76% (143 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.80 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.14-7.09 (m, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 146.5 (d, *J* = 248.75 Hz), 140.8 (d, *J* = 251.25 Hz), 137 (d, *J* = 246.25 Hz), 136.0, 132.8, 128.3, 122.1, 120.3, 117.7, 112.2, 110.7, 98.5.

2.7.12. 3-(pyridin-2-ylthio)-1H-indole [22] (3l):

Yellow Solid (m.p. 138-139 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.1. Yield 80% (108 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.78 (brs, 1H), 8.36 (d, *J* = 4.6 Hz, 1H), 7.80 (d, *J* = 2.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.49-7.45 (m, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.03 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 162.2, 149.0, 136.9, 136.8, 132.7, 128.5, 122.2, 120.2, 119.4, 118.9, 118.1, 112.4, 98.0.

2.7.13. 5-methyl-3-(phenylthio)-1H-indole [23] (4a):

Colourless Solid (m.p. 134-135 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.37. Yield 83% (119 mg).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.26 (brs, 1H), 7.45 (d, *J* = 0.7 Hz, 1H), 7.42 (d,

J = 2.6 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.21-7.18 (m, 2H), 7.15-7.06 (m, 4H), 2.44 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.4, 134.7, 130.8, 130.3, 129.3, 128.6, 125.6, 124.6, 124.6, 119.1, 111.2, 101.9, 21.3.

2.7.14. 5-methoxy-3-(phenylthio)-1H-indole [20] (4b):

Colourless Solid (m.p. 78-79 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.3. Yield 84% (128 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.57 (brs, 1H), 7.70 (d, *J* = 2.7 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 2H), 7.07-7.02 (m, 3H), 6.84-6.80 (m, 2H), 3.68 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 154.2, 139.3, 132.8, 131.6, 129.4, 128.7, 125.1, 124.6, 113.1, 112.2, 99.7, 98.7, 55.2.

2.7.15. 5-fluoro-3-(phenylthio)-1H-indole [23] (4c):

Colourless Solid (m.p. 163-164 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.3. Yield 75% (109 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 (brs, 1H), 7.51 (d, *J* = 2.6 Hz, 1H), 7.35 (dd, *J* = 8.8, 4.2 Hz, 1H), 7.28 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.20-7.17 (m, 2H), 7.12-7.02 (m, 3H), 7.02 (td, *J* = 9.0, 2.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.5, 157.7, 138.7, 132.8, 132.2, 130.0, 129.9, 128.7, 125.9, 124.9, 112.4, 112.3, 111.7, 111.5, 104.7, 104.5, 103.1.

2.7.16. 5-bromo-3-(phenylthio)-1H-indole [20] (4d):

Colourless Solid (m.p. 123-124 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.37. Yield 80% (146 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.91 (brs, 1H), 7.85 (d, *J* = 2.6 Hz, 1H), 7.49-7.46 (m, 2H), 7.30 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* =

7.7 Hz, 2H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 138.58, 135.4, 134.1, 130.5, 128.9, 125.3, 125.0, 124.7, 120.2, 114.5, 112.8, 99.1.

2.7.17. 6-bromo-3-(phenylthio)-1H-indole [23] (4e):

Colourless Solid (m.p. 161-162 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.33. Yield 68% (124 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.40 (brs, 1H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.47-7.45 (m, 2H), 7.26 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.19-7.15 (m, 2H), 7.09-7.07 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.6, 137.2, 131.0, 128.7, 128.0, 125.9, 125.0, 124.3, 121.0, 116.6, 114.5, 103.6.

2.7.18 4-bromo-3-(phenylthio)-1H-indole [20] (4f):

Colourless Solid (m.p. 135-136 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.30. Yield 73% (133 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.03 (brs, 1H), 7.85 (d, *J* = 2.6 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 2H), 7.10-7.03 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 141.2, 138.1, 135.3, 128.6, 125.5, 125.0, 124.6, 124.4, 123.2, 112.8, 112.1, 99.8.

2.7.19. 7-methyl-3-(phenylthio)-1H-indole [25] (4g):

Brown oil, R_f (10 % ethyl acetate in hexane): 0.4. Yield 70% (100 mg).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.32 (brs, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.20-7.07 (m, 7H), 2.54 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.2, 136.0, 130.3, 128.6, 125.8, 124.7, 123.5, 121.0, 120.7, 117.3, 103.1, 16.3.

2.7.20. 2-methyl-3-(phenylthio)-1H-indole [20] (4h):

Colourless Solid (m.p. 114-115 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.52. Yield 80% (115 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.65 (brs, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.06-7.00 (m, 2H), 6.96 (d, J = 7.5 Hz, 2H), 2.45 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 142.1, 139.1, 135.6, 129.6, 128.8, 125.0, 124.5, 121.3, 119.8, 117.5, 111.3, 96.2, 11.6.

2.7.21. 2-phenyl-3-(phenylthio)-1H-indole [25] (4i):

Yellow oil, R_f (10 % ethyl acetate in hexane): 0.3. Yield 65% (117 mg).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.77 (d, J = 7.4 Hz, 2H), 7.66 (d, J = 7.9 Hz, 1H), 7.47-7.38 (m, 4H), 7.29 (t, J = 7.5 Hz, 1H), 7.21-7.16 (m, 3H), 7.12 (d, J = 7.1 Hz, 2H), 7.07 (t, J = 7.2 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.0, 139.2, 135.8, 131.3, 131.1, 128.7, 128.7, 128.6, 128.1, 125.5, 124.5, 123.3, 121.1, 119.9, 111.1, 99.4.

2.7.22. 5-methoxy-3-(p-tolylthio)-1H-indole [22] (5a):

Light yellow solid, (m.p. 55-56 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.33. Yield 80% (128 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.52 (brs, 1H), 7.67 (d, J = 2.5 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 7.9 Hz, 2H), 6.94 (d, J = 8.1 Hz, 2H), 6.84-6.81 (m, 2H), 3.68 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 154.2, 135.6, 134.0, 132.6, 131.5, 129.4, 125.5, 124.4, 113.0, 112.1, 99.7, 99.3, 55.2, 20.3

2.7.23. 3-((4-chlorophenyl)thio)-5-methoxy-1H-indole [21] (5b):

Colourless Solid (m.p. 95-96 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.31. Yield 78% (135 mg).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.42 (brs, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.14-7.12 (m, 2H), 7.03-7.01 (m, 3H), 6.93 (dd, J = 8.8, 2.4 Hz, 1H), 3.80 (s,

3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.2, 137.9, 131.3, 130.4, 129.6, 128.7, 126.8, 113.6, 112.5, 101.7, 100.6, 55.7.

2.7.24. 3-((3-chlorophenyl)thio)-5-methoxy-1H-indole (5c):

Colourless Solid (m.p. 85-86 ^oC), R_f (10 % ethyl acetate in hexane): 0.32. Yield 76% (131 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.66 (brs, 1H), 7.75 (d, *J* = 2.7 Hz, 1H), 7.42 (d, *J* = 9.4 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 7.13-7.10 (m, 1H), 7.00-6.98 (m, 1H), 6.96 (t, *J* = 1.8 Hz, 1H), 6.86-6.84 (m, 2H), 3.69 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 154.4, 142.2, 133.6, 133.3, 131.6, 130.4, 129.2, 124.6, 124.0, 123.6, 113.3, 112.4, 99.4, 97.4, 55.2. HRMS (ESI): m/z $[M + H]^+$ calculated for : $C_{15}H_{13}ClNOS$: 290.0406; found: 290.0425.

2.7.25. 5-methoxy-3-(pyridin-2-ylthio)-1H-indole [26] (5d):

Greyish powder (m.p. 151-152 ^oC), R_f (20 % ethyl acetate in hexane): 0.2. Yield 76% (116 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.65 (brs, 1H), 8.36 (dd, *J* = 4.8, 1.0 Hz, 1H), 7.73 (d, *J* = 2.7 Hz, 1H), 7.51-7.47 (m, 1H), 7.43-7.41 (m, 1H), 7.04-7.02 (m, 1H), 6.85-6.83 (m, 2H), 6.62 (d, *J* = 8.1 Hz, 1H), 3.68 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 162.3, 154.4, 149.0, 136.9, 133.1, 131.6, 129.2, 119.4, 118.8, 113.2, 112.4, 99.5, 97.5, 55.2.

2.7.26. 5-bromo-3-(p-tolylthio)-1H-indole [22] (5e):

Colourless Solid (m.p. 124-125 ^oC), R_f (10 % ethyl acetate in hexane): 0.42. Yield 75% (143 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.90 (brs, 1H), 7.84 (d, *J* = 2.6 Hz, 1H), 7.49-7.46 (m, 2H), 7.30 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 135.4, 134.9, 134.8, 133.9, 130.4, 126.9, 126.4, 124.7, 120.2, 114.5, 112.8, 99.4, 15.0.

2.7.27. 5-bromo-3-((4-bromophenyl)thio)-1H-indole [27] (5f):

Colourless Solid (m.p. 157-158 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.34. Yield 73% (168 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.96 (brs, 1H), 7.87 (d, *J* = 2.7 Hz, 1H), 7.49-7.47 (m, 2H), 7.42-7.39 (m, 2H), 7.31 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.96-6.93 (m, 2H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 138.4, 135.5, 134.3, 131.7, 130.3, 127.2, 124.9, 120.1, 117.7, 114.6, 113.0, 98.4.

2.7.28. 3-((4-bromophenyl)thio)-5-methyl-1H-indole (5g):

Colourless oil, R_f (10 % ethyl acetate in hexane): 0.5. Yield 76% (145 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.31 (brs, 1H), 7.43 (d, *J* = 2.6 Hz, 1H), 7.39 (d, *J* = 0.6 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.30-7.27 (m, 2H), 7.12 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.99-6.96 (m, 2H), 2.44 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.7, 134.7, 131.6, 130.8, 130.5, 129.0, 127.2, 124.8, 118.9, 118.1, 111.3, 101.3, 21.4. HRMS (ESI): m/z $[M + H]^+$ calculated for : $C_{15}H_{13}BrNS$: 317.9952; found: 317.9978.

2.7.29. 3-((4-chlorophenyl)thio)-2-methyl-1H-indole [27] (5h):

yellow oil, R_f (10 % ethyl acetate in hexane): 0.45. Yield 74% (122 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.70 (brs, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.23-7.21 (m, 2H), 7.13-7.10 (m, 1H), 7.03-7.00 (m, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 2.45 (s, 3H).**^{13}C NMR** (125 MHz, DMSO- d_6) δ 142.2, 138.3, 135.6, 129.4, 129.1, 128.7, 126.5, 121.4, 119.9, 117.4, 111.3, 95.8, 11.6.

2.7.30. 5-methoxy-3-(p-tolylthio)-1H-indole [28] (5i):

Brown solid (m.p. 75-76 ^{o}C), R_f (10 % ethyl acetate in hexane): 0.38. Yield 75% (121 mg).**^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.64 (brs, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J*

= 7.8 Hz, 1H), 7.13-7.08 (m, 2H), 7.04-7.00 (m, 1H), 6.62 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.51-6.48 (m, 1H), 3.62 (s, 3H), 2.45 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 159.6, 142.1, 140.6, 135.6, 129.7, 129.6, 121.3, 119.8, 117.6, 117.2, 111.2, 110.7, 109.8, 96.1, 54.8, 11.6.

2.7.31. 3-((3-bromophenyl)thio)-2-methyl-1H-indole [3a] (5j):

Brown oil, R_f (10 % ethyl acetate in hexane): 0.47. Yield 77% (147 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.72 (brs, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.24-7.22 (m, 1H), 7.15-7.11 (m, 2H), 7.06-7.02 (m, 2H), 6.98-6.95 (m, 1H), 2.45 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 142.4, 142.2, 135.6, 130.7, 129.3, 127.3, 126.7, 123.8, 122.2, 121.5, 120.0, 117.4, 111.4, 95.1, 11.5.

2.7.32. 5-bromo-3-((3,4,5-trimethoxyphenyl)thio)-1H-indole [3a] (5k):

White solid (m.p 152-153 ^{o}C) R_f (20 % ethyl acetate in hexane): 0.2. Yield 50% (118 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.80 (brs, 1H), 7.78 (d, *J* = 1.6 Hz, 1H), 7.48 (d, *J* = 2.6 Hz, 1H), 7.34-7.28 (m, 2H), 6.37 (s, 2H), 3.79 (s, 3H), 3.68 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.46, 136.00, 135.09, 133.60, 131.75, 130.88, 126.08, 122.19, 114.40, 113.13, 103.75, 103.11, 60.87, 56.07.

2.8 Spectra of Few Synthesized Compounds

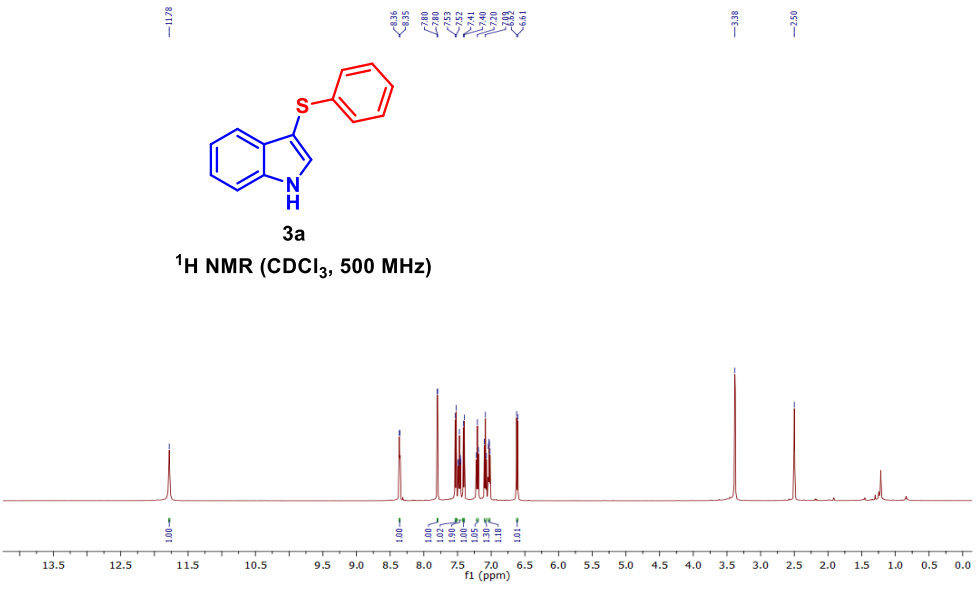


Figure2.3 ^{1}H NMR Spectra for 3a in DMSO-d$_6$

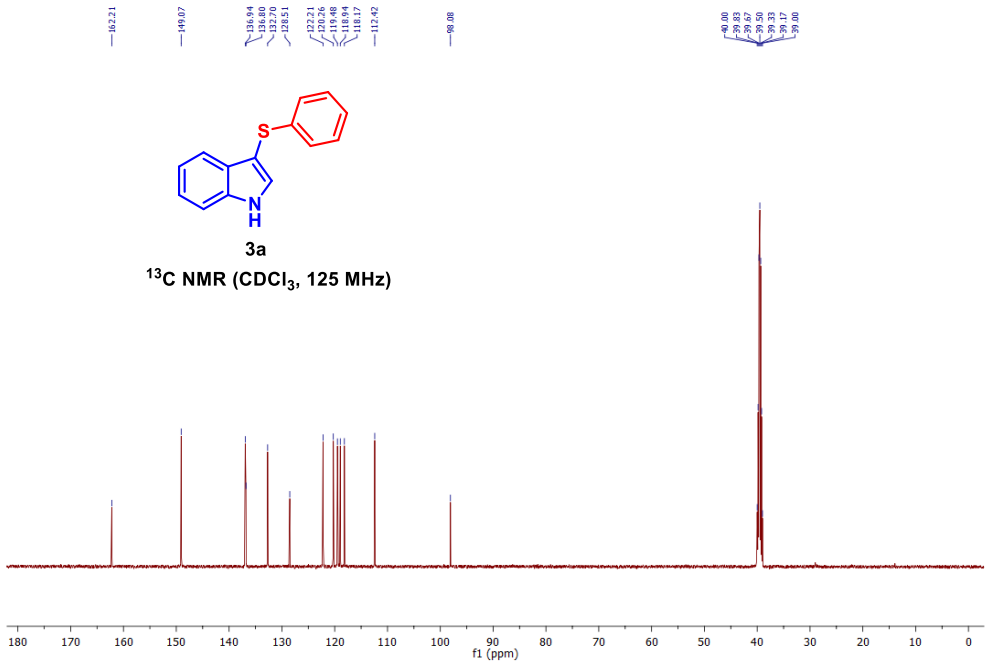


Figure 2.4 ^{13}C NMR Spectra for 3a in DMSO-d$_6$

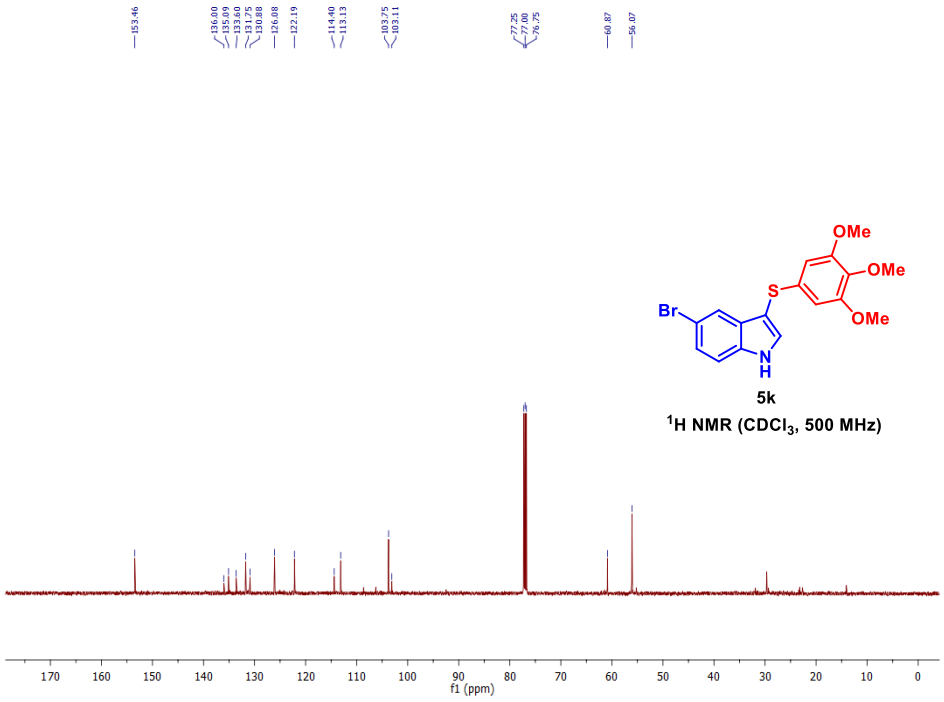


Figure 2.5 ^{1}H NMR Spectra for 5k in CDCl$_3$

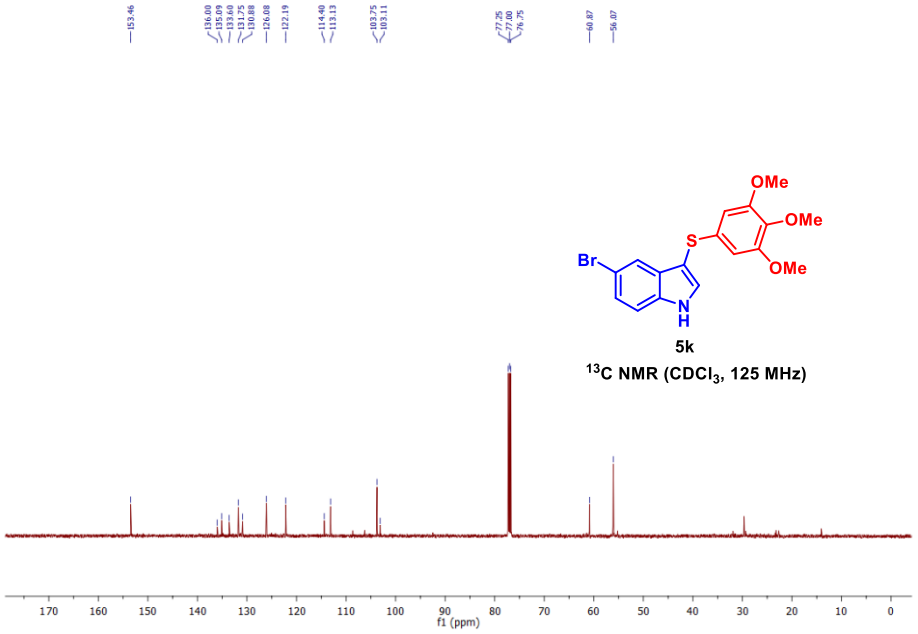


Figure 2.6 ^{13}C NMR of the product 5k in CDCl$_3$

2.9 References

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