Supporting information

Cooperative Catalysis by Bovine Serum Albumin-Iodine Towards Cascade Oxidative Coupling-C(sp2)-H Sulfenylation of Indoles/Hydroxyaryls with Thiophenols on water

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CDRI communication no:

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1. Experimental Section:

Materials:-

All reagents were obtained from commercial sources (Merck or Acros or Hi-Media). The substrates used for the synthesis of compounds were obtained from Acros or Merck. The albumins (Bovine serum lyophilized powder, ≥96%, product code A2153; LOT No-SLBJ9814V; Pig serum albumin, CAS No. 9048-46-8; and Rabbit serum albumin, CAS No. 9048-46-8) and Lipases (PPL= Porcine pancreatic lipase, lyophilized powder, ≥98%, product code A1830; PPL 100-500U/mg, EC-No-232-619-19, Lot No-SLBC0073V), CAL-B= *Candida antarctica lipase,* CAS No. 900162-1, EC-No-3.1.1.3) used in this work have been purchased from Sigma Aldrich. The solvents used for isolation/purification of compounds were obtained from commercial sources (Merck) and were used without further purification. Iodine, thiols and indoles were purchased from Sigma Aldrich and Alfa-Aesar. Deionized double distilled water was used in all reactions.

Apparatus:

GC-MS analysis was carried out on Shimadzu MS-QP-2010 system equipped with a BP-20 capillary column (SGE international). High performance liquid chromatography (HPLC) was performed on Waters 2998 Photodiode Array Detector (waters 515 HPLC pump). The separation was performed on an ODS-2 hypersil column (250 x 4.6 mm id, 5 µm; Thermo). The mobile phase consisted of 0.05% TFA (Trifluoro acetic acid) in H_2O and methanol/acetonitrile (in 70:30, v/v) with gradient elution (0-5 min, 60-70% B; 5-15 min, 70-100% B; 15-20 min, 100-40% B; 20-25 min, 40% B with a flow rate of 1 ml/min and analysis wavelength was set at 254 and 280 nm. Column chromatography was done on silica gel (60-100 mesh). Thin layer chromatography (TLC) was performed on silica TLC plates and compounds visualized in iodine or under UV lamp (254 nm). The temperature of the reaction mixture was monitored by thermometer. HRMS spectra were recorded as ESI-HRMS on a Q-TOF LC-MS/MS mass spectrometer. Melting points were obtained manually by capillary methods and are uncorrected. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometers. TMS was used as internal reference for NMR.

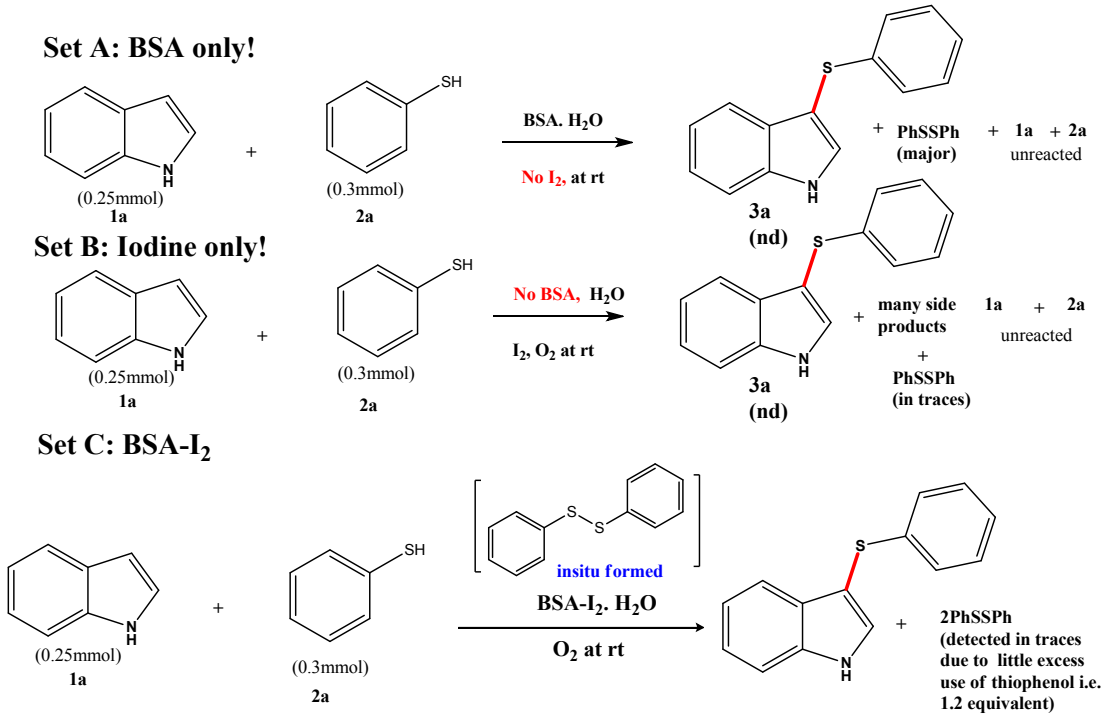
2.Cooperative role of BSA-I_2 for sulfenylation of indole:

Recently, the concept of cooperative catalysis in the field of organic chemistry has emerged as a promising approach to achieve cascade transformations towards formation of complex molecules that cannot be accomplished by individual catalysts. Various catalysts including transition metal-organocatalyst, organocatalyst-metalloenzymes have been used in cooperation manner which are used in a number of organic transformations including formation of C-C bond, however no such cooperative catalyst has been used for C-S bond through sulfenylation of indole with thiophenol due to the problem of

metal poisoning with sulfur atom. Hence, we have developed a metal free condition for C-S bond formation where BSA and Iodine have been used cooperatively for the sulfenylation of indole.

To confirm our hypothesis regarding role of both catalysts (BSA-I_2) operating in cooperative manner, we have done three set of reactions (Scheme 1) which are described as below:

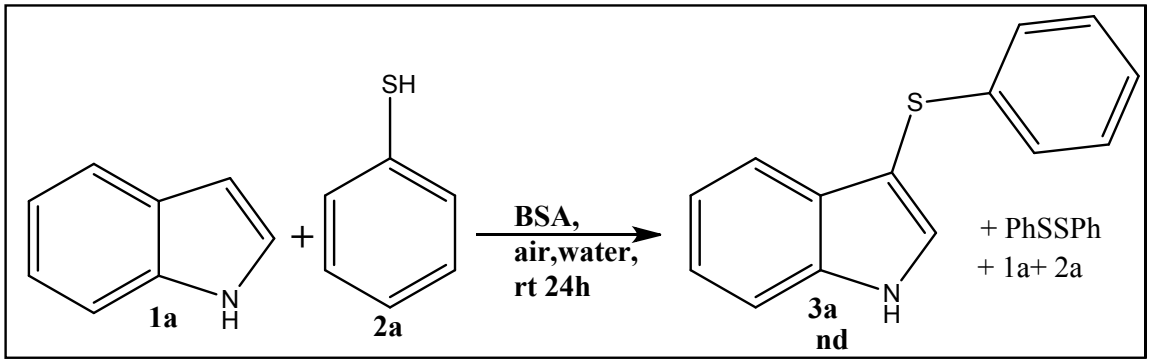
(i) Sulfenylation of indole with thiophenol in presence of BSA (without iodine)- **Set A**
(ii) Sulfenylation of indole with thiophenol in presence of iodine (without BSA)- **Set B**
(iii) Sulfenylation of indole with thiophenol in presence of BSA-iodine- **Set C**



Scheme S1

i) Set A: Sulfenylation of indole in the presence of BSA (without Iodine):

Sulfenylation of indole (**1a**, 0.25 mmol) with thiophenol (**2a**, 0.3 mmol) was conducted in presence of BSA (50 mg) in water (600 µL) at room temperature for 24 h (Scheme 2). TLC analysis of crude product indicates formation of a new spot while indole was found unreacted. After completion of the reaction, saturated solution of sodium thiosulfate (3ml X2) was added to above reaction mixture and extracted with ethyl acetate (3mlX2), organic part dried over Na_2SO_4, filtered and concentrated on rotavap to obtain crude reaction mixture.



Scheme S2: Sulfenylation of indole in the presence of BSA (without Iodine).

The crude reaction mixture was further analyzed by GC-MS where a new product was found to be diphenyldisulfide (as thiophenol itself underwent self-oxidation in the presence of BSA to form diphenyldisulfide; Saima, A.G. Lavekar, R. Kumar, A. K. Sinha, *J. Mol. Catal. B: Enzym.***2015**, *116*, 113-123) along with some amount of unreacted **1a** (10.02%) and **2a** (11.98%) while no peak of desired product (**3a**) was observed as evident from GC-MS (Figure S1).

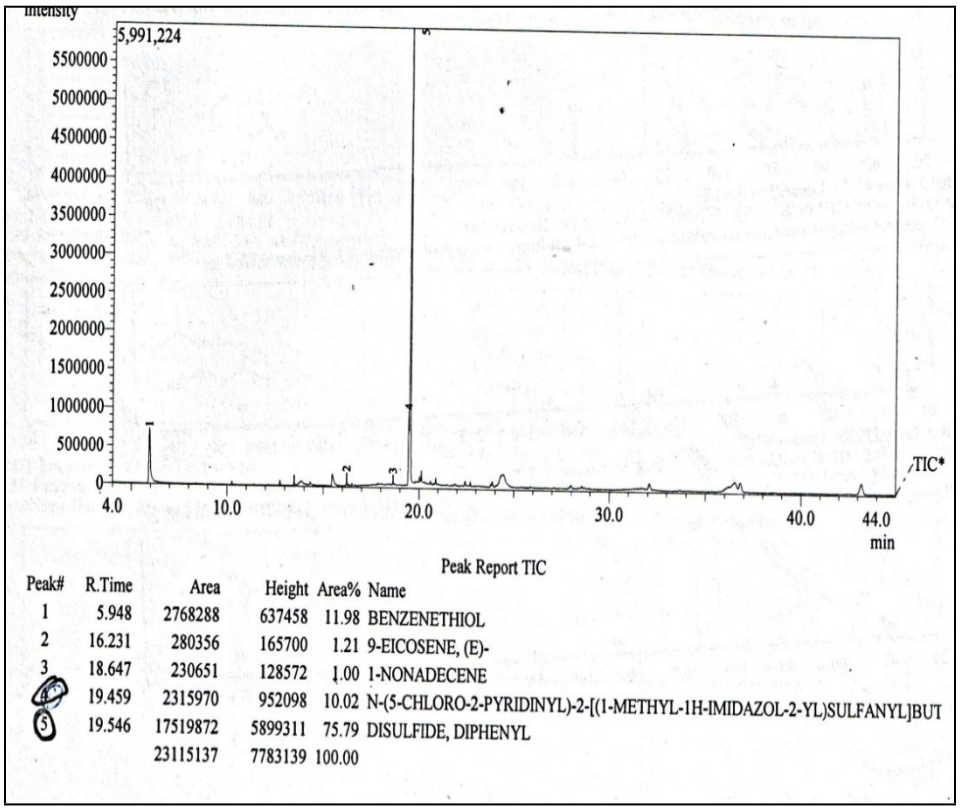


Figure S1: GC-MS of sulfenylation of indole with thiophenol in the presence of BSA.

Library search of peak no.5 of the above GC-MS (Figure S1) confirmed new product (75.79% at RT 19.546, mol wt.=218) as diphenyl disulfide (Figure S2) which is given below:

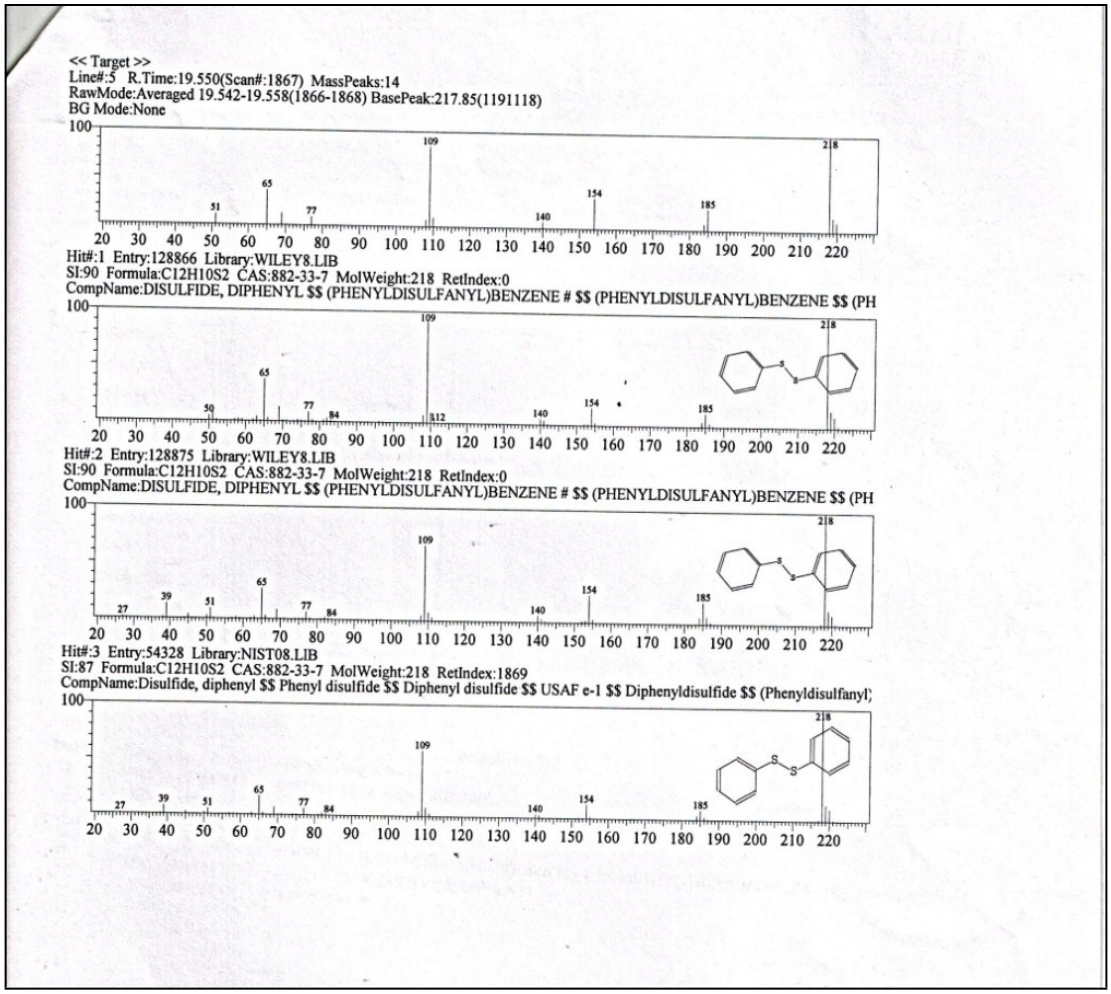
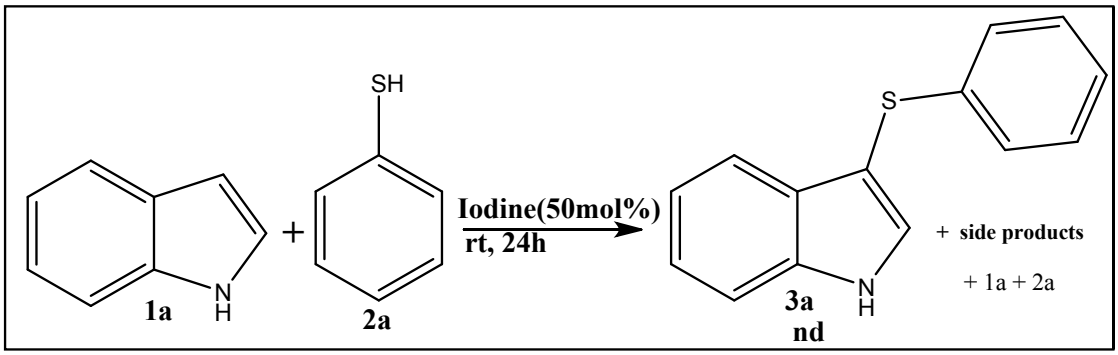


Figure S2: GC-MS Library search of peak no. 5.

From GC-MS (Figure S1 and S2) analysis, it was evident that no desired product **3a** was formed during the sulfenylation reaction between **1a** and **2a** in the presence of BSA.

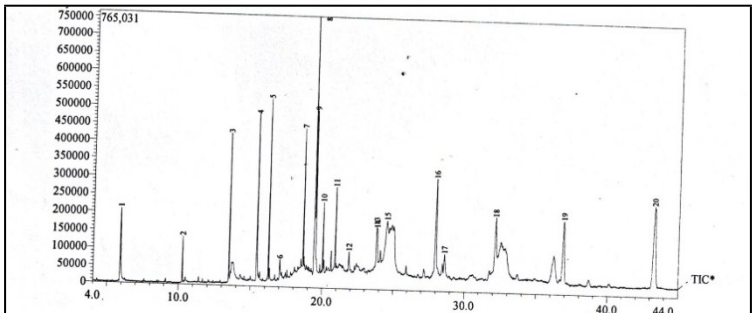
ii) Set B: Sulfenylation of indole in the presence of iodine (without BSA) :

Sulfenylation of indole (**1a**, 0.25 mmol) with thiophenol (**2a**, 0.3 mmol) was conducted in presence of iodine (50 mol%) in water (600 µL) at room temp. for 24 h (Scheme S3). After completion of the reaction, saturated solution of sodium thiosulfate (3mlX2) was added to above reaction mixture and extracted with ethyl acetate (3mlX2), organic part dried over Na_2SO_4, filtered and concentrated on rotavap to obtain crude reaction mixture.



Scheme S3: Sulfenylation of indole in the presence of iodine (without BSA)

GC-MS analysis of crude reaction mixture indicates no formation of product **3a** while many side products were observed along with some amount of unreacted indole (**1a,** 12.19%), thiophenol (**2a,** 5.13%) and intermediate disulfide (7.47%) as evident from Figure S3.



Peak Report TIC

Peak#	R.Time	Area	Height	Area%	Name
1	5.923	827957	202842	5.13	BENZENETHIOL
2	10.269	226137	130206	1.40	1-DODECENE
3	13.503	725749	412646	4.50	1-TETRADECANOL
4	15.417	1253198	468758	7.77	`PHENOL, 2,4-BIS(1,1-DIMETHYLETHYL)-
5	16.239	891074	508605	5.53	1-HEXADECENE
6	17.040	188176	53695	1.17	Barbituric acid 3ME P707
7	18.656	709626	388217	4.40	1-NONADECENE
8	19.427	1965219	722508	12.19	N-(5-CHLORO-2-PYRIDINYL)-2-[(1-METHYL-1H-IMIDAZOL-2-YL)SULFANYL]BUT
9	19.502	1204103	454389	7.47	DISULFIDE, DIPHENYL
10	20.035	375080	196492	2.33	BENZENE, (1-METHYLDODECYL)-
11	20.902	457004	224006	2.83	n-Tetracosanol-1
12	21.879	172651	52752	1.07	3,7,11,15-Tetramethyl-hexadecanol, trimethylsilyl ether
13	23.807	345923	105269	2.15	Nonadecyl pentafluoropropionate
14	23.850	282685	96820	1.75	HEXADECANAMIDE
15	24.546	300398	38220	1.86	TRICOSANE
16	27.979	1353213	253431	8.39	9-OCTADECENAMIDE
17	28.606	303753	52879	1.88	Tridecanol, 2-ethyl-2-methyl-
18	32.157	727064	123163	4.51	Heptadecane, 2,3-dimethyl-
19	36.915	1381334	167594	8.57	DOCOSANE
20	43.284	2434102	215193	15.10	DOCOSANE
		16124446	4867685	100.00	

Figure S3: GC-MS of sulfenylation of indole with thiophenol in the presence of Iodine.

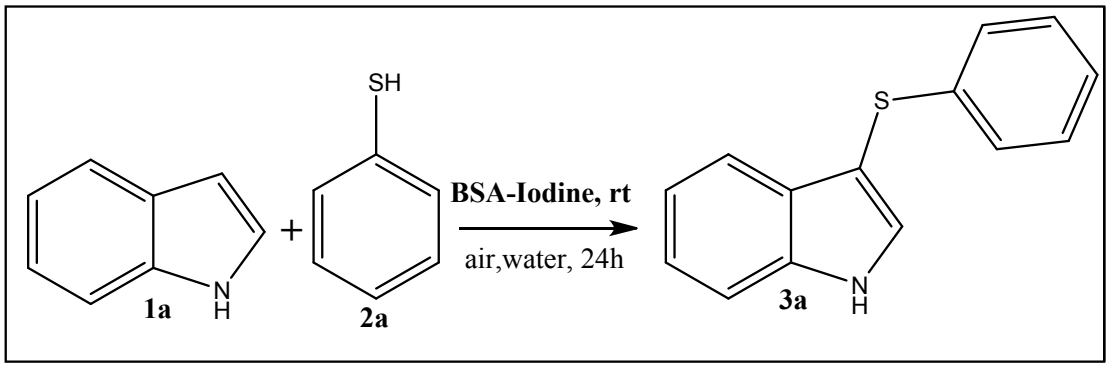
After analysis of GC-MS (Fig S1,S2 and S3), it was found that individually BSA or Iodine did not allow sulfenylation reaction, hence, no product (**3a**) was observed.

iii) Set C: Sulfenylation of indole in the presence of both BSA-Iodine:

Sulfenylation of indole (**1a**, 0.25 mmol) with thiophenol (**2a**, 0.3 mmol) was conducted in presence of BSA (50 mg) and iodine (50 mol%) in water (600 µL) at room temp. for 24 h (Scheme S4). After completion of the reaction, saturated solution of sodium thiosulfate (3mlX2) was added to above reaction mixture and

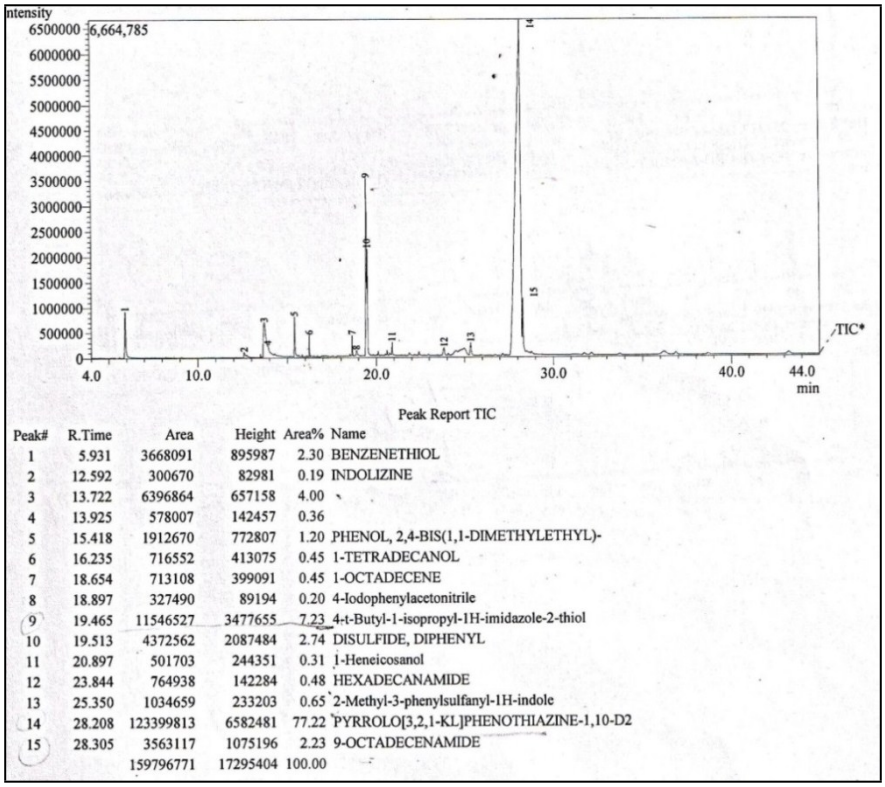
extracted with ethyl acetate (3mlX2), organic part dried over Na_2SO_4, filtered and concentrated on rotavap to obtain crude reaction mixture.

TLC analysis of crude product indicates formation of a prominent new spot .



Scheme S4: Sulfenylation of indole in the presence of both BSA-Iodine.

The above crude reaction mixture was further analyzed by GC-MS (Figure S4) where a new peak was found in 77.22% yield along with some amount of unreacted **2a** (2.30%) and intermediate disulfide (2.74%).



Peak#	R.Time	Area	Height	Area%	Name
1	5.931	3668091	895987	2.30	BENZENETHIOL
2	12.592	300670	82981	0.19	INDOLIZINE
3	13.722	6396864	657158	4.00	
4	13.925	578007	142457	0.36	
5	15.418	1912670	772807	1.20	PHENOL, 2,4-BIS(1,1-DIMETHYLETHYL)-
6	16.235	716552	413075	0.45	1-TETRADECANOL
7	18.654	713108	399091	0.45	1-OCTADECENE
8	18.897	327490	89194	0.20	4-Iodophenylacetonitrile
9	19.465	11546527	3477655	7.23	4-t-Butyl-1-isopropyl-1H-imidazole-2-thiol
10	19.513	4372562	2087484	2.74	DISULFIDE, DIPHENYL
11	20.897	501703	244351	0.31	1-Heneicosanol
12	23.844	764938	142284	0.48	HEXADECANAMIDE
13	25.350	1034659	233203	0.65	2-Methyl-3-phenylsulfanyl-1H-indole
14	28.208	123399813	6582481	77.22	PYRROLO[3,2,1-KL]PHENOTHIAZINE-1,10-D2
15	28.305	3563117	1075196	2.23	9-OCTADECENAMIDE
		159796771	17295404	100.00	

Figure S4: Sulfenylation of indole with 2a in presence of both BSA-I_2.

Library search of peak no.14 of above GC-MS (Figure S4), confirmed new peak as sulfenylated indole **3a** (Figure S5, mol. Wt. = 225) which is given below:

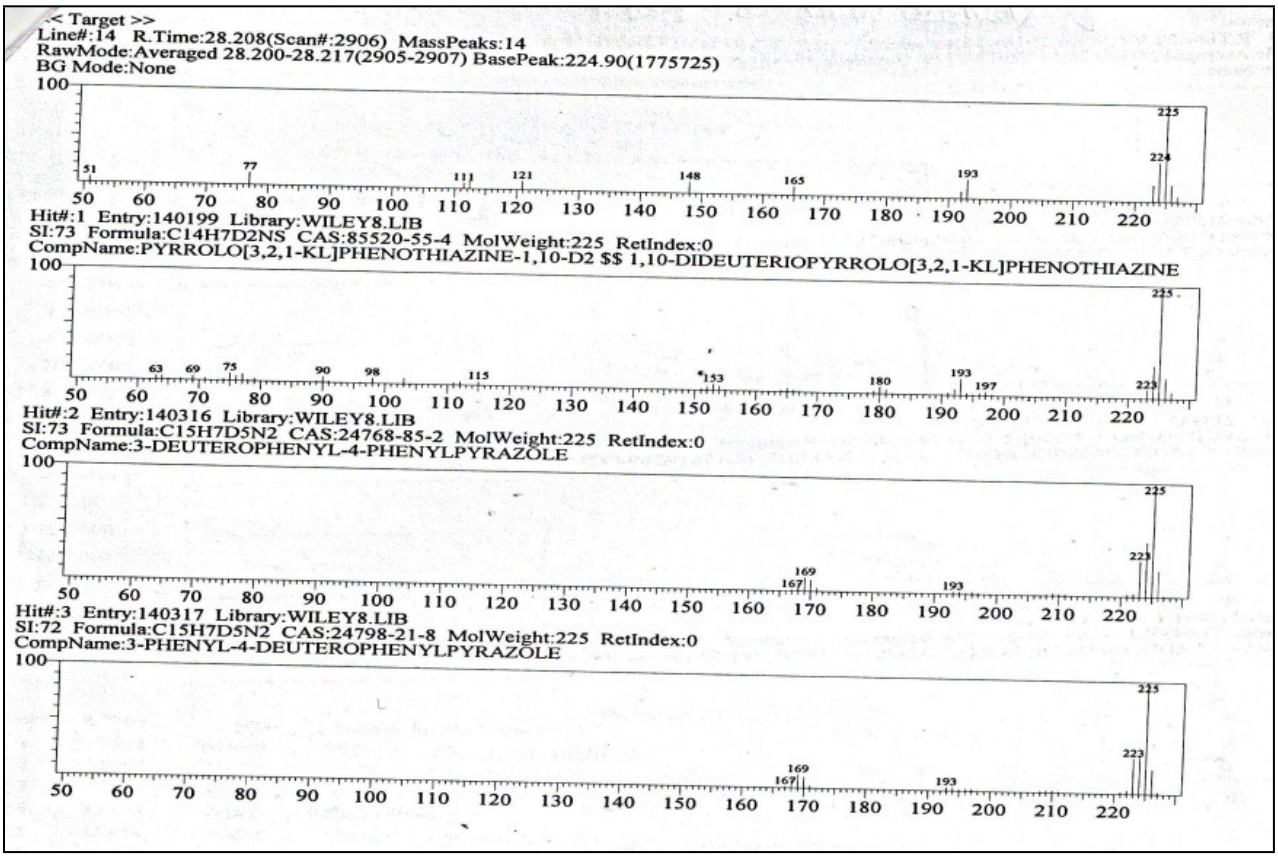


Figure S5: Library search of the line no.14.

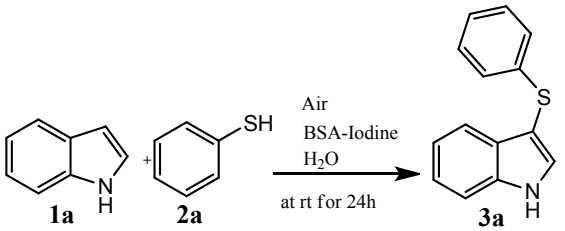
The above crude reaction mixture (77.22% yield by GC-MS) upon column purification provided a solid compound which upon ^{1}HNMR analysis confirmed as sulfenylated indole (**3a**).

From the above experiments (Set A, Set B, Set C), it was clear that presence of both BSA-I_2 (Set C, Scheme S4) was necessary for the sulfenylation, where both BSA-I_2 act cooperatively for the product formation (**3a**) via in situ generation of disulfide as an intermediate.

3. **Optimization study:**

Further to increase the yield of **3a**, sulfenylation of indole was conducted by varying amount of thiolphenol upto 1.3 equiv., where crude product was analyzed by HPLC. Recently our group have disclosed HPLC method (R. Kumar, Richa, N.H. Andhare, A. Shard, A. K. Sinha, *Chem. Eur. J.***2013**, *19*, 14798 – 14803) for establishing the mechanistic path for Aldol-Suzuki/Heck reaction. Hence, the progress of sulfenylation reaction towards formation of **3a** was analyzed by HPLC.

Table S1. Screening of amount of thiophenol required during sulfenylation of indole[a]



S.No.	Amount of 2a (equiv)	Yield(%)[b]
1	1.2	78
2	1.3	77
3	1.1	63
4	1.0	57

[a] Reaction condition: 1a (0.25 mmol), BSA=50 mg; I_2= 50mol%; H_2O=600µL; at rt for 24h [b] HPLC yield.

Above results indicated that 1.2 equivalent thiophenol was found sufficient for the sulfenylation of indole to obtain maximum yield of **3a** (78% on HPLC basis).

Now, another optimization parameters like temp. (r.t to 60°C), solvents (water, DMSO, DMF etc), amount of iodine (50% to 30%), different biocatalyst (BSA, PPL, CAL B etc) and PTC (TBAB or TBAI) were screened for improving the yield of **3a** (see Table 1 of manuscript for detail). In addition, scope of different indoles and thiols were studied where 41 compounds were successfully synthesized using our cooperative catalysis BSA-I_2 catalyzed protocol (see Table 2, 3 and 4 of manuscript for detail).

Further from above GC-MS/HPLC results it was clear that insitu generated disulfide may involve during sulfenylation of indole (1a) with thiophenol (2a). To prove our assumption, HPLC/ESI-MS techniques were employed.

4. Mechanistic study:

Mechanistic study for in-situ generation/cleavage of S-S bond and formation of C-S bond during sulfenylation of indole with thiophenol (2a):

i) In-situ generation/cleavage of disulfide in sulfenylation reaction monitored by HPLC:

HPLC is an important analytical tools which gives fast analysis of compound even if they are present in traces amount.

Initially, HPLC method was developed to obtain the chromatogram of each reactants, intermediate and product like i) thiophenol (**2a**), ii) indole (**1a**) iii) disulfide and (iv) the product (**3a**) as shown in Figure (S6-S9) below:

Standard used in mechanistic study:

i) HPLC of reactant indole (1a)

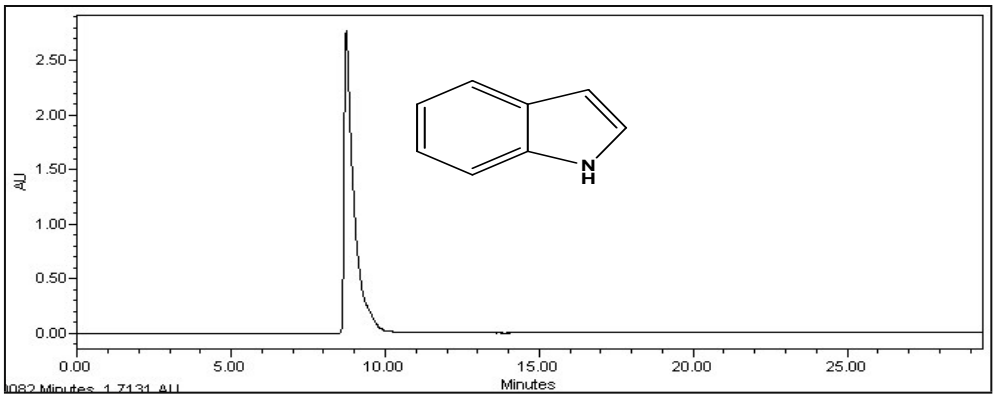


Figure S6: HPLC of indole (1a)

ii) HPLC of reactant thiophenol (2a)

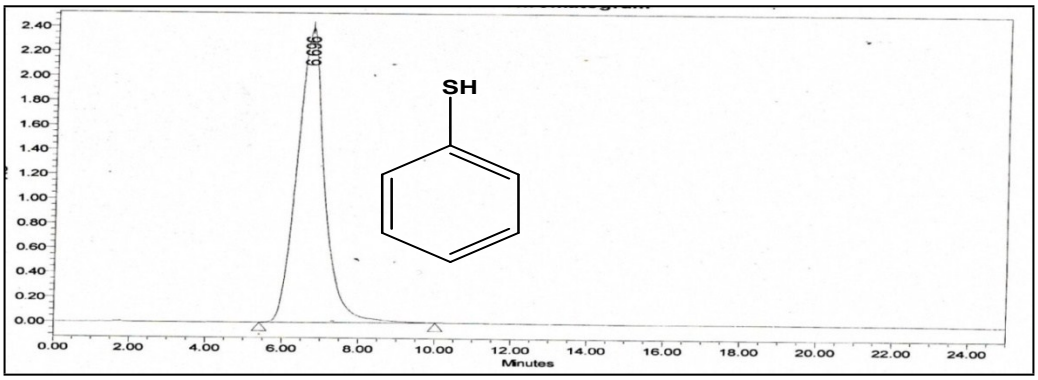


Figure S7: HPLC of thiophenol (2a).

iii) HPLC of intermediate disulfide

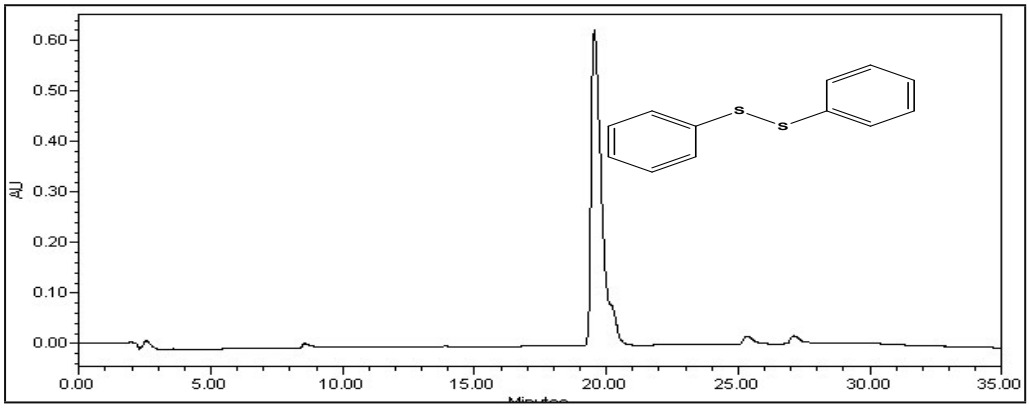


Figure S8: HPLC of intermediate disulfide.

iv) HPLC of product, sulfenylated indole (3a)

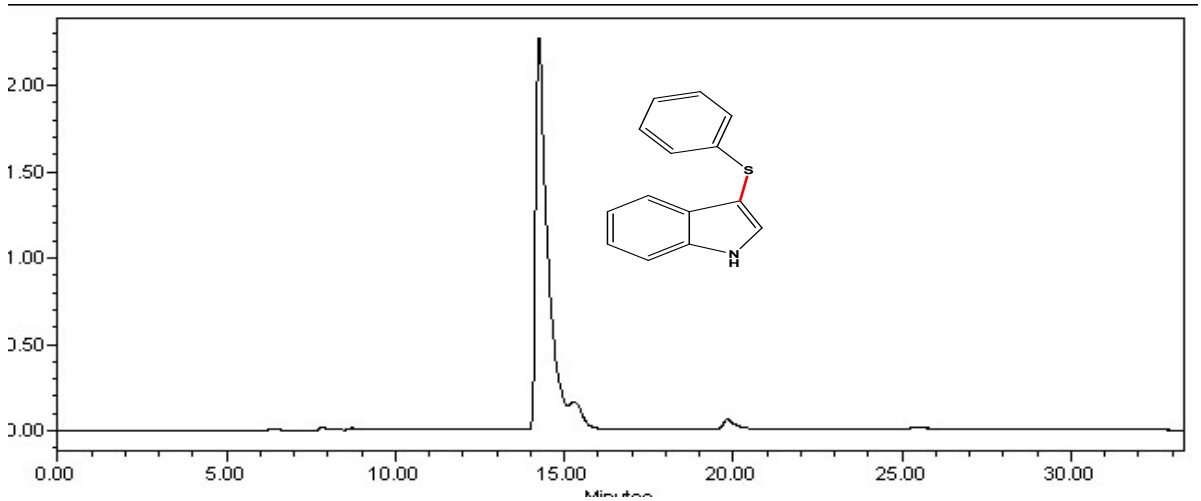
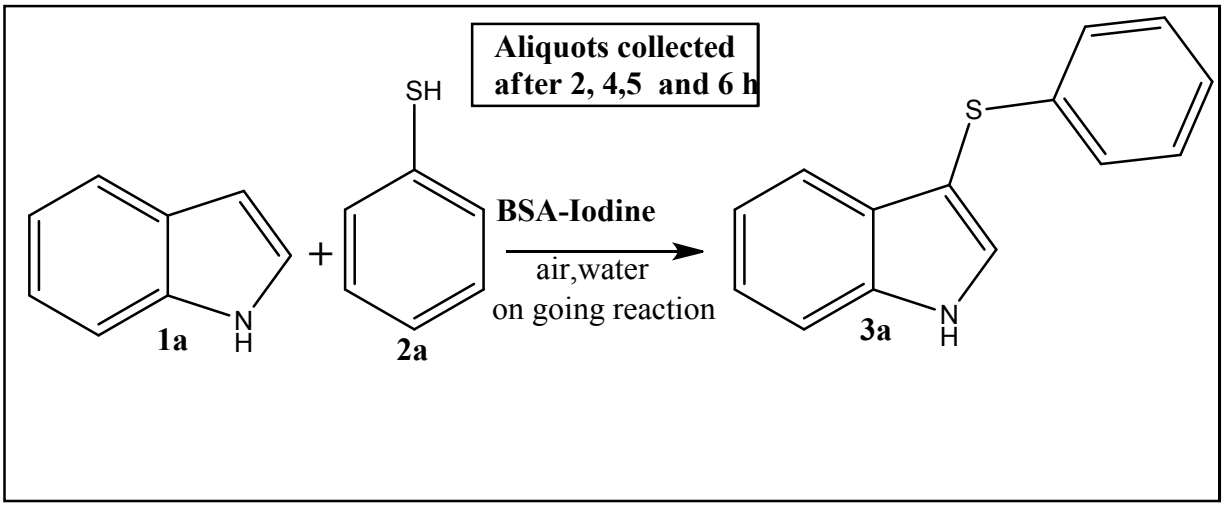


Figure S9: HPLC of product (3a).

After having HPLC chromatogram of reactants (**1a and 2a**), intermediate (disulfide) and product (**3a**) in hand (Figure S6-S9), HPLC analysis of ongoing reaction mixture was conducted and aliquots were collected after 2, 4, 5 and 6 h (Figure S10-S13) as shown below:



Progress of the reaction monitored by HPLC at different time intervals of 2, 4, 5 and 6 h

(A) HPLC analysis of aliquots after 2 h

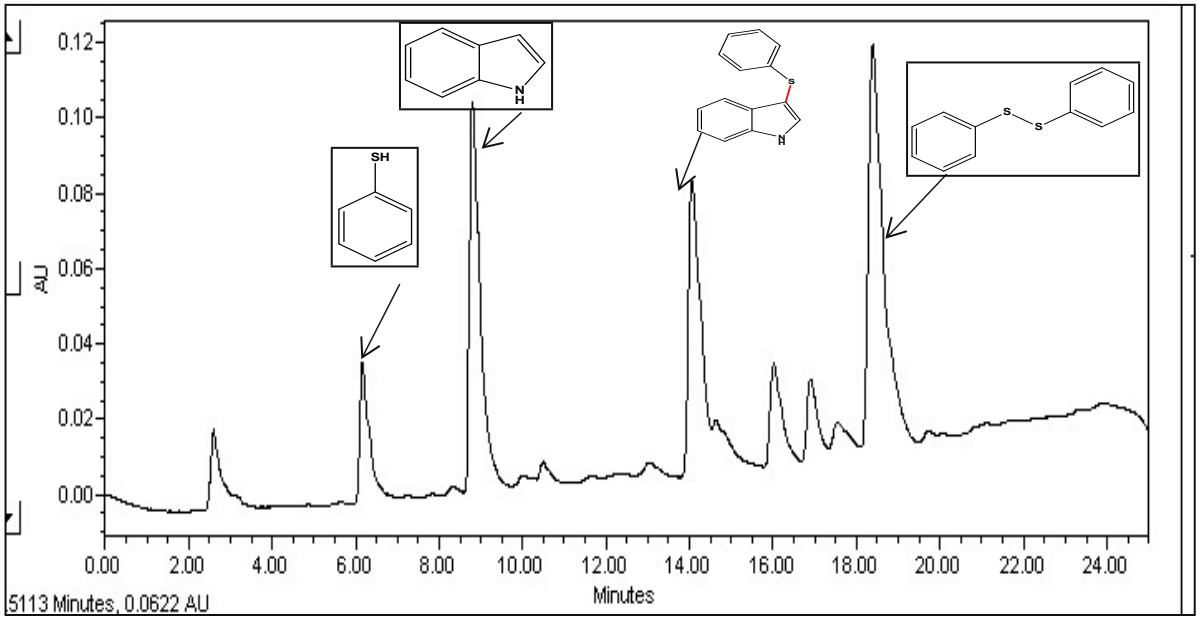


Figure S10: HPLC analysis of aliquot after 2h.

HPLC analysis of the ongoing reaction after 2h (Figure S10) and by comparing the RT (retention time) of all peaks with HPLC chromatograms of standards of reactants/intermediate/product (Figure S6-S9), we observed that thiophenol (**2a**) start converting into disulfide while a new peak of sulfenylated indole (3a) appeared.

B) HPLC analysis after 4 h

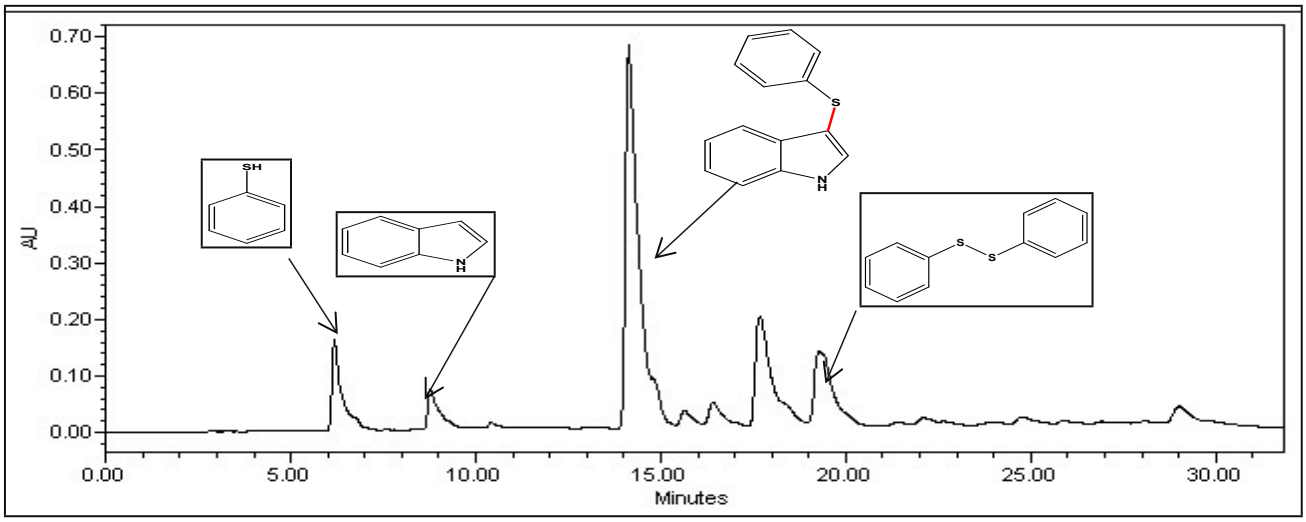


Figure S11: HPLC analysis after 4 h

From the HPLC after 4h (Figure S11) it was clear that concentration of thiophenol (**2a**), indole (**1a**) and intermediate disulfide further started decreasing while concentration of product (**3a**) increased.

C) HPLC analysis after 5 h

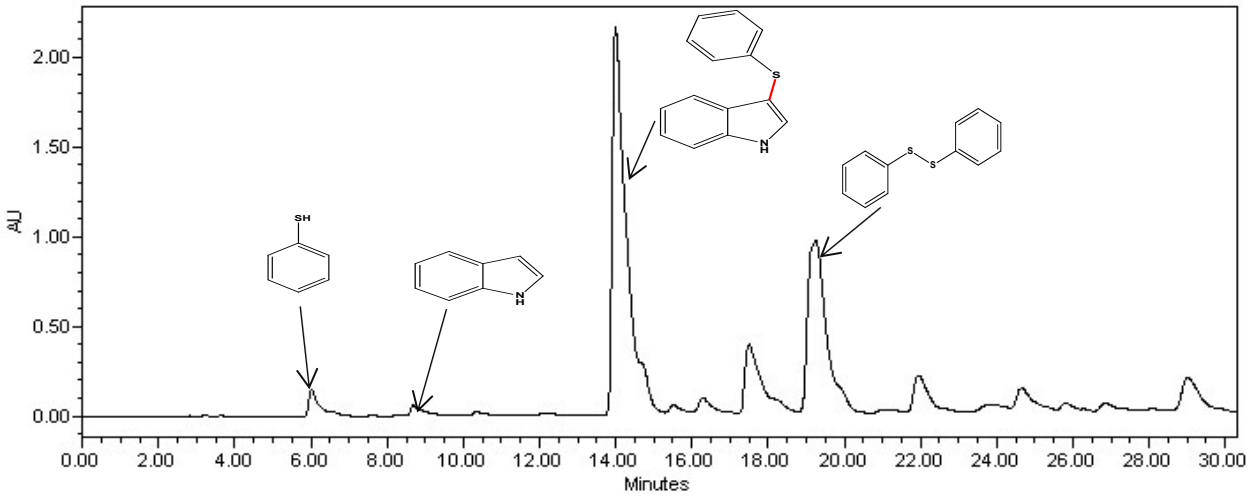


Figure S12: HPLC analysis after 5 h

HPLC of aliquots after 5hr (Figure S12), indicated that indole (**1a**), thiophenol (**2a**) along with intermediate disulfide almost disappeared with the domination of desired product peak (**3a**).

D) HPLC analysis after 6 h

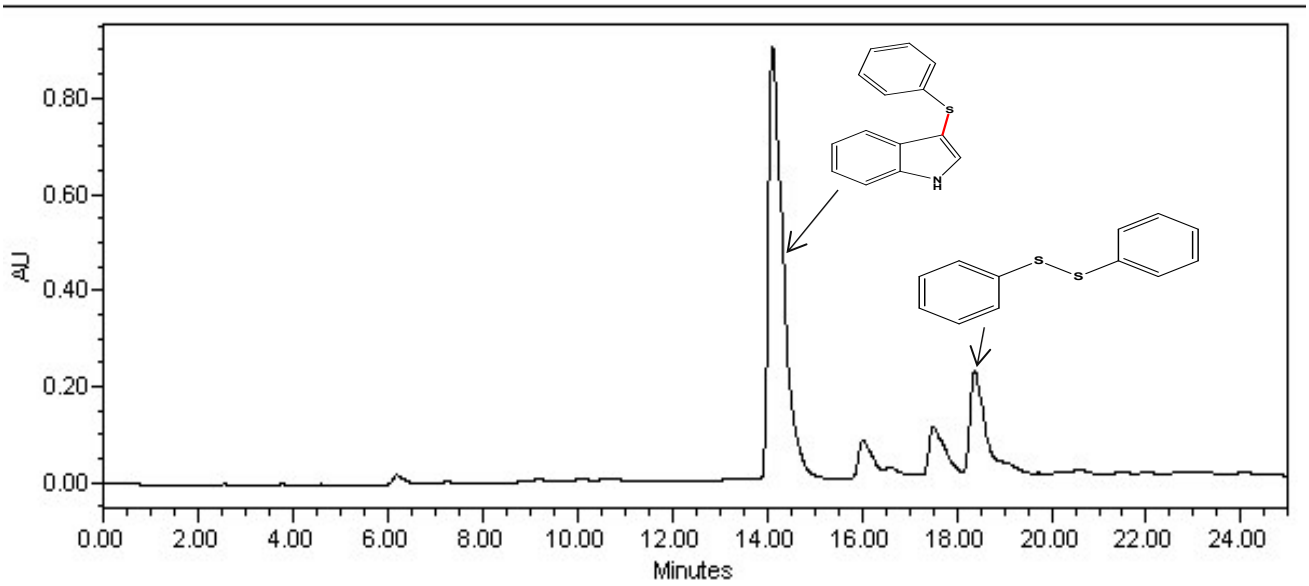


Figure S13: HPLC analysis after 6 h

HPLC analysis after 6h, showed a prominent peak of sulfenylated product (**3a**) with some amount disulfide as little excess of thiophenol (1.2 equiv.) was used during above sulfenylation reaction.

Thus HPLC chromatograms analysis clearly revealed that sulfenylation of indole (1a) with 2a underwent via insitu generation/cleavage of disulfide bond (S-S) followed by formation of desired C-S bond. In-situ generation/cleavage of disulfide bond (S-S) during sulfenylation reaction was further proved by ESI-MS.

ii) In-situ generation/cleavage of disulfide in reaction monitored by ESI/MS:

Aliquots collected after different time intervals (2, 4 and 6h) was analyzed by ESI-MS which show peaks of disulfide and ionic intermediates as evident from Figure S14- S16.

A) ESI-MS spectrum after 2h:

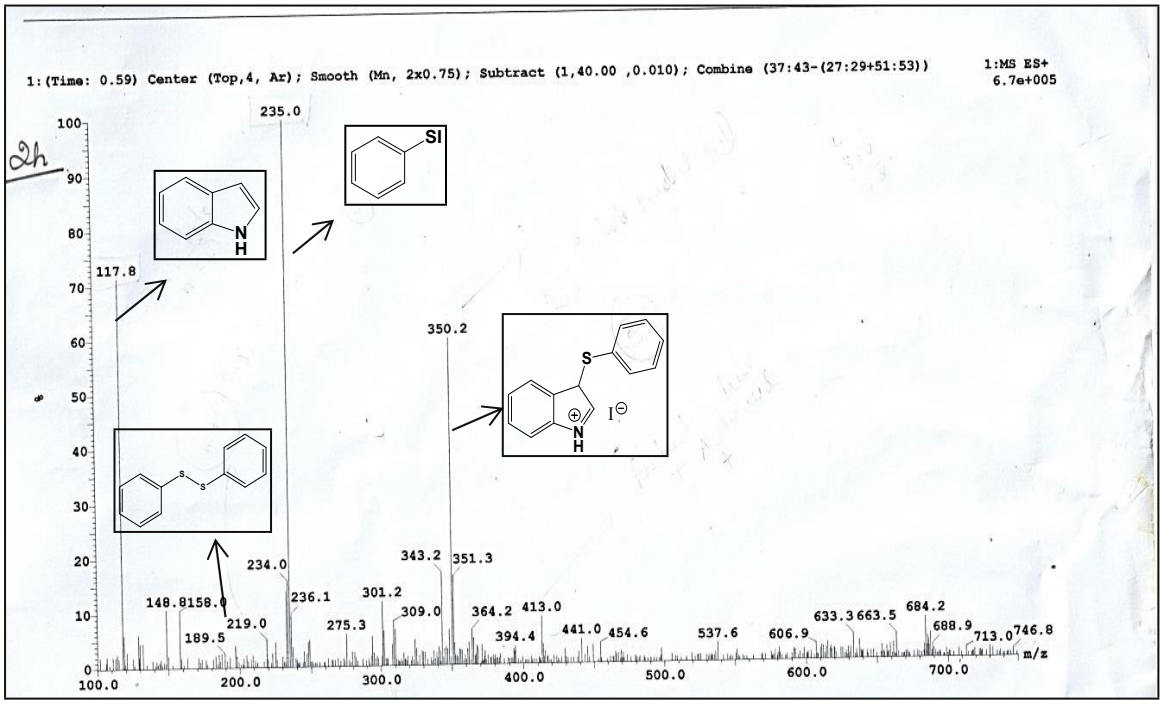


Figure S14: ESI-MS spectrum after 2h

During ESI-MS analysis (Figure S14) of sulfenylation reaction, after 2h, it was found that a peak of indole, phenylsulfenyl iodide (PhSI), intermediate ionic species of sulfenylated indole iodide and disulfide were appeared without formation of product (3a)

B) ESI-MS spectrum after 4h

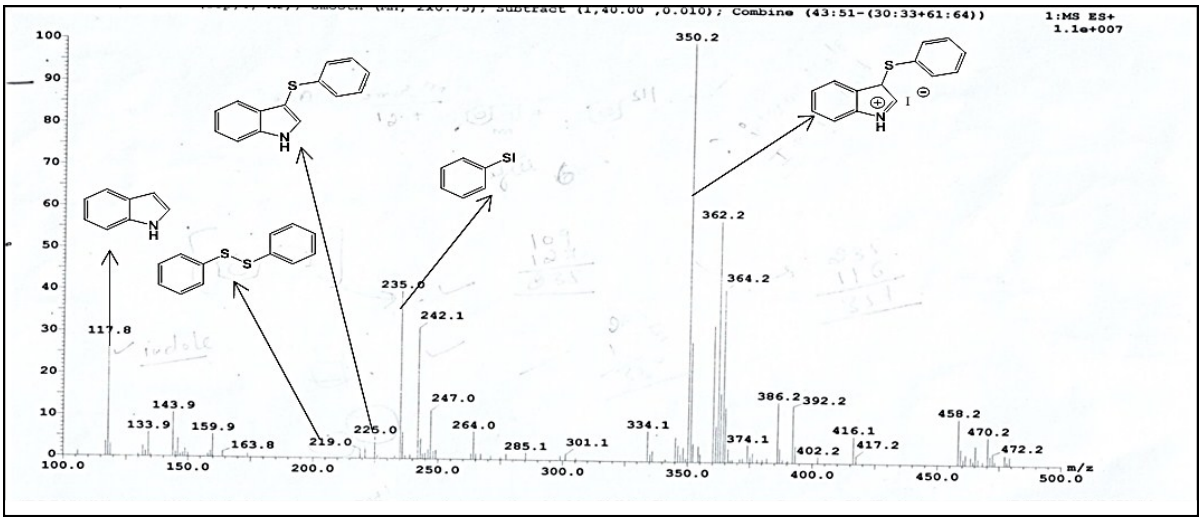


Figure S15: ESI-MS spectrum after 4h

After 4h (Figure S15) it was observed that peak of product (3a) started appearing while concentration of ionic species of sulfenylated indole iodide further increased.

i) ESI-MS spectrum after 6h:

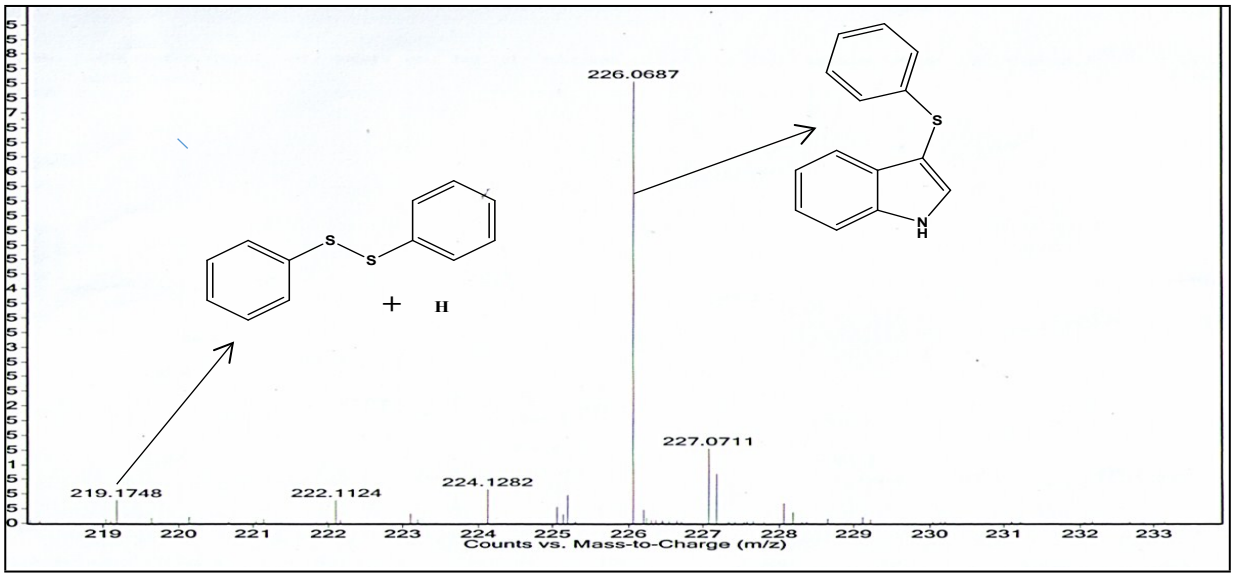
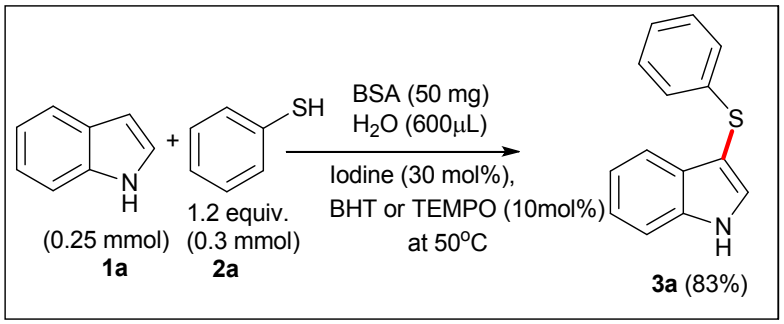


Figure S16:ESI-MS spectrum after 6h

From the ESI-MS spectra (Figure S16) it was revealed that sulfenylation reaction got completed with formation of desired peak of product (3a, mol. Wt 225+H, sulfenylated indole) via in-situ generation/cleavage of disulfide bond (Figure S13-S16).

To prove the involvement of ionic or radical mechanism in sulfenylation reaction of indole with thiophenol:

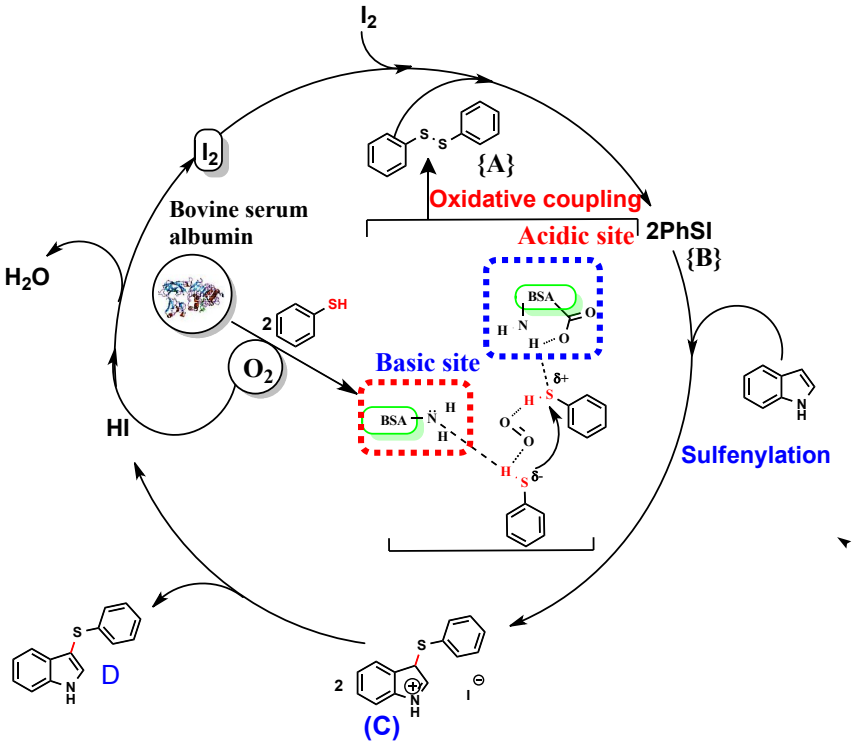
HPLC analysis show that BSA-I_2 catalytic system underwent sulfenylation reaction via insitu generation/cleavage of disulfide. Moreover in literature, sulfenylation reaction occurred either through ionic or radical mechanism. Hence, we conducted the BSA-I_2 catalysed sulfenylation of indole with thiophenol in the presence of radical scavenger like TEMPO or BHT (10 mol%) (Scheme S5) wherein product (**3a**) was still formed in good yield which ruled out the possibility of radical pathway in our biochemocatalytic protocol for sulfenylation reaction.



Scheme S5

Plausible mechanism for cascade sulphenylation reaction:

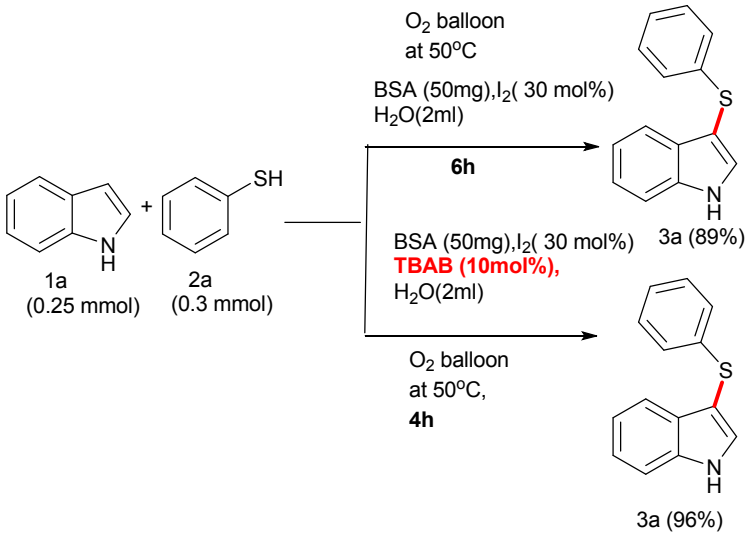
A plausible mechanism was proposed for sulfenylation of indole in our BSA-I_2 biochemoctalytic protocol as shown in Scheme S6. Initially, BSA catalyzed oxidative coupling of thiophenol in water pooled by molecular oxygen forming in-situ disulfide (“A”) which combined with iodine to afford an electrophilic species PhSI marked as “B” (Scheme S6). Subsequent insertion of indole with "B" resulted ionic intermediate “C” then HI was extruded out from “C” to generate the sulfenyl product “D”, further eliminated HI was oxidized by molecular oxygen to regenerate I_2 which again enter in the catalytic cycle.



Scheme 6. Proposed mechanism for sulfenylation of indole via insitu generation of disulfide.

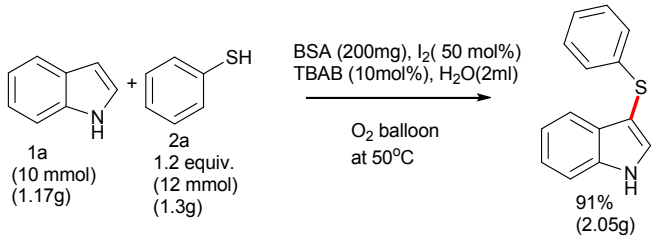
5. Role of Phase transfer catalyst in sulfenylation reaction of indole:

Role of phase transfer catalyst (PTC) was found very important which not only increases the yield of **3a** from 89% to 96% (HPLC basis) but also reduces the reaction time from 6h to 4h.



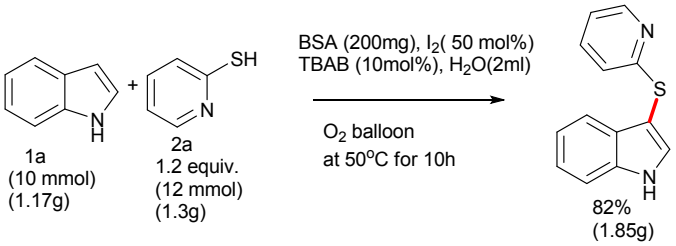
6. Gram scale reaction of BSA-I_2 Cooperative catalytic system for sulfenylation reaction:

To prove the practical utility of this cooperative biochemocatalytic system (BSA-I_2), the reaction was carried out on a gram scale (Scheme S7) where 10mmol (1.17g) of indole (**1a**) reacts with thiophenol (**2a**) (1.2 equiv., 12 mmol) in the presence of iodine(50 mol%), TBAB (10mol%) and BSA (200 mg) in H_2O (2 ml) at 50°C for 4 h which provided sulfenylated indole (3a) in 91% yield (isolated).



Scheme S7: Gram scale reaction

Gram scale reaction of biologically important COX-inhibitor compound **5a** (3-(pyridin-2-ylthio)-1H-indole) (Scheme S8) was conducted in our cooperative catalytic system (BSA-I_2). 10mmol (1.17g) of indole (**1a**) reacts with 2 mercapto pyridine (**4a**) (1.2 equiv, 12 mmol) in the presence of iodine (50 mol%), TBAB (10 mol%) and BSA (200 mg) in H_2O (2 ml) at 50°C for 10 h which provided the sulfenylated indole (5a) with 82% isolated yield (see Figure 2 of manuscript).



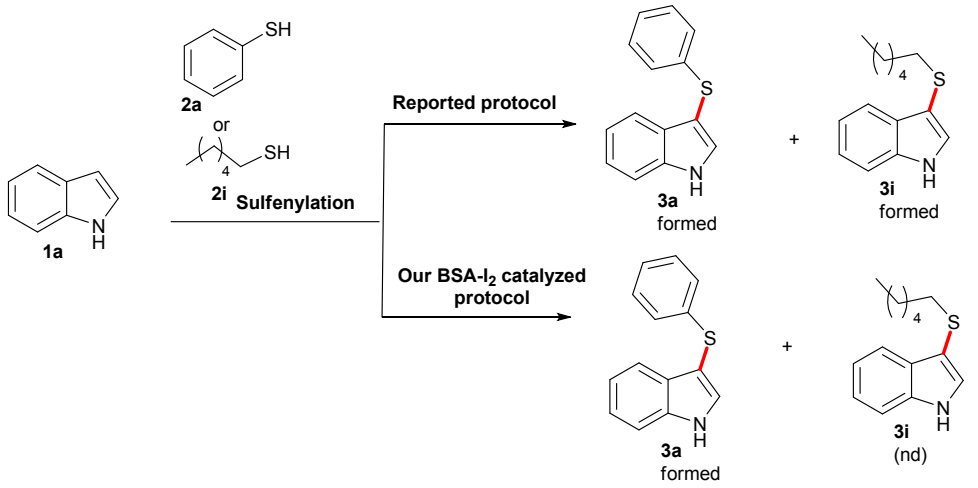
Scheme S8

7. Chemo and Regioselectivity study:

Chemo and regioselectivity play an important role in total synthesis of many biologically important compounds.

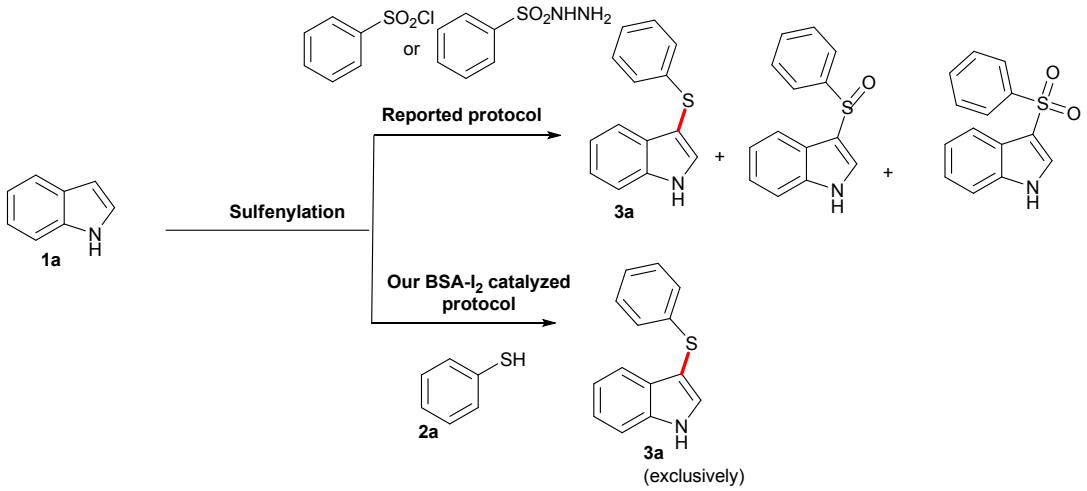
Chemoselectivity:

A) Our developed biochemocatalytic protocol show chemoselectivity for aromatic thiols over aliphatic thiols as illustrated in Scheme S9.



Scheme S9 Chemoselectivity experiment for aromatic verses aliphatic sulfenylation reaction.

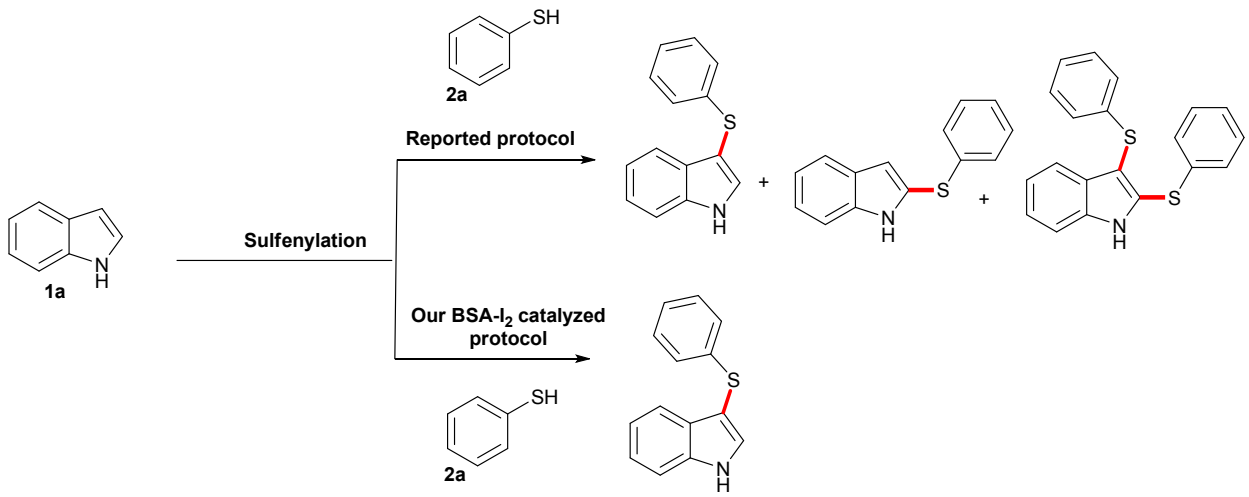
B) Many sufenylating reagents such as sulfonyl hydrazide, sulfonyl chloride, thiophenol, disulphide etc provides desired product 3a, however, possibility of over oxidation of sulfenylated indole provide many undesired product as mentioned in scheme S10 depending upon the reaction conditions.



Scheme S10

Regioselectivity:

In literature there is possibility of both C-3 or C-2 sulfenylation of indole besides bissulfenylated indole , however, our biochemocatalytic protocol provides exclusively C-3 sulfenylated indole (3a) as illustrated in Scheme S11

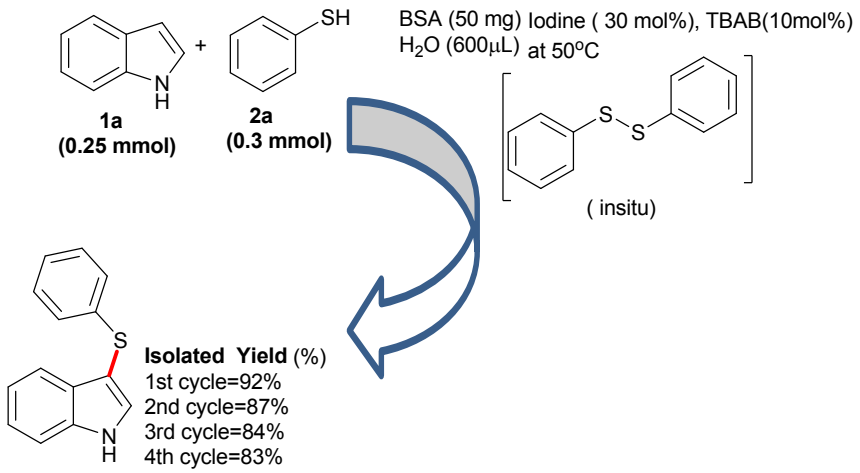


Scheme S11: Regioselective sulfenylation reaction

8. Recyclability of BSA-I_2 cooperative catalytic system for sulfenylation reaction:

After exploring the substrate scope (Table 2, 3 and 4 in manuscript), we next probed the recyclability of BSA-I_2 catalytic system for sulfenylation of indole (**1a**) (Scheme S12) where the recovered BSA show recyclability upto four cycles, wherein addition of I_2 (30 mol%) was required in each cycle and the desired product (3a) was obtained in varying yield from 92-83% (on HPLC basis). After fourth cycle the yield of **3a** falls drastically due to coagulation of BSA as illustrated in Scheme S12.

In this experiment, **1a** (0.25 mmol), **2a** (0.3 mmol) BSA (50 mg), I_2 (30 mol%) and TBAB (10mol%) was taken in water (0.6 µL) and were stirred at 50ºC under O_2 balloon for 4h. The aqueous solution containing BSA was extracted using ethyl acetate. The organic layer was vacuum evaporated to obtain **3a**, whereas the aqueous solution containing BSA was used repeatedly for carrying out the next batch of reaction for sulfenylation of indole (Note: aqueous solution containing BSA was concentrated under vacuum to remove the last traces of organic solvent if any before going for next catalytic cycle).



Scheme S12: Recyclability of biochemocatalytic BSA-I_2 catalytic system for sulfenylation of indole

9. General procedure for sulfenylation of indole with thiols (Table 2, 3a-3i, 5a-5h, 6a-6i) and Table 3 (7a-7f in manuscript):

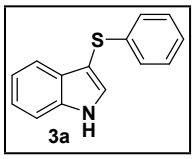
A mixture of indole (0.25mmol), thiol (0.3mmol), BSA (50mg), iodine (30 mol%) and TBAB (10 mol%) in deionized water (600 µL) under oxygen balloon was stirred at 50°C till completion of reaction (monitored by TLC). After completion of the reaction, saturated solution of sodium thiosulfate (3 mlX2)) was added to reaction mixture and extracted with ethyl acetate (3 mlX2), organic part dried over Na_2SO_4, filtered and concentrated on rotavap. The crude product was then chromatographed over silica gel (60-120 mesh size) using hexane/ethyl acetate (varying ratio from 95:5 to 50:50) as an eluent. The obtained products **3a-3i**, **5a-5h** and **6a-6i** (Table 2 of manuscript) and products **7a-7f** (Table 3 in main manuscript) were characterized and confirmed by ^{1}H NMR and ^{13}C NMR data and was further compared with those reported in the literature.

General procedure for sulfenylation of hydroxyaryls (2-naphthol or 4-hydroxy coumarin with thiols (Table 4 (10a-10d, 11a-11h in manuscript)):

A mixture of hydroxyaryls (2-naphthol (**8**) or 4-hydroxy coumarins (**9**) thiols (0.3 mmol), BSA (50 mg), iodine (30 mol%) and TBAB (10 mol%) in deionized water (600 µL) under oxygen balloon was stirred at 50oC till completion of reaction (monitored by TLC). After completion of the reaction, saturated solution of sodium thiosulfate (3 mlX2) was added to reaction mixture and extracted with ethyl acetate (3 mlX2), organic part dried over Na_2SO_4, filtered and concentrated on rotavap. The crude product was then

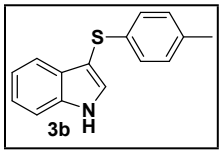
chromatographed over silica gel (60-120 mesh size) using hexane/ethyl acetate (varying ratio from 95:5 to 50:50) as an eluent. The obtained products **3a-3i**, **5a-5h** and **6a-6i** (Table 2 of manuscript) and products 7a-7d (Table 3 in main manuscript) were characterized and confirmed by ^{1}H NMR and ^{13}C NMR data and was further compared with those reported in the literature.

10.^{1}H and ^{13}C NMR and HRMS values of synthesized compounds (Table 2, 3 and 4 in manuscript):



3-(phenylthio)-1H-indole (3a)[1]

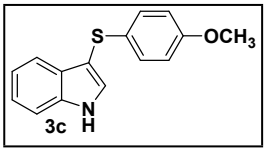
92%; colorless solid; mp 150-152^{0}C (Lit. [1]-150-152^{0}C); R_f = 0.476 (Hexane: EtOAc, 90:10, v/v); ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.48 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.51-7.45 (m, 2H), 7.32-7.28 (m, 1H), 7.22 – 7.07 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 139.2, 136.5, 130.7, 129.1, 128.7, 125.8, 124.8, 123.0, 120.9, 119.6, 111.6, 102.7.; $(M+H)^{+}$ ESI-HRMS calculated for $C_{14}H_{11}NS$+H-226.0690Found -226.0687.



3-(p-tolylthio)-1H-indole (3b)[1]

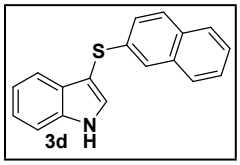
90%; white solid; mp130-132^{0}C (Lit. [1]-124-126^{0}C); R_f = 0.458 (Hexane: EtOAc, 90:10, v/v); ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.40 (s, 1H), 7.64- (d, J = 8.0 Hz, 1H), 7.50-7.44 (m 2H), 7.29 – 7.28 (m, 1H), 7.21-7.19 (m, 1H), 7.08 –7.00 (m, 4H), 2.28 (s, 3H).;^{13}C NMR (100MHz, $CDCl_3$)δ = 136.4, 135.4, 134.6, 130.4, 129.5, 129.1, 126.2 122.9, 120.8, 119.7, 111.5, 103.5, 20.8.; $(M+H)^{+}$ESI-HRMS calculated for $C_{15}H_{13}NS$+H-240.0847 Found -240.0813.

3-((4-methoxyphenyl)thio)-1H-indole (3c) [1]

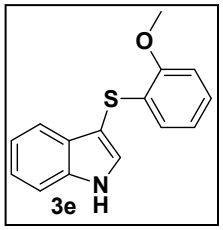


92%; pale yellow solid; mp 111-113^{0}C (Lit. [1]-111-112^{0}C); R_f = 0.650 (Hexane: EtOAc, 80:20, v/v); ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.36 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.42 – 7.19 (m, 6H), 6.87-6.78 (m, 2H), 3.77 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 157.8, 136.5, 133.5, 130.2, 129.6, 129.3, 129.0, 128.6, 122.9, 120.8, 119.6, 114.6, 111.6, 104.3, 55.4.; $(M+H)^{+}$ESI-HRMS calculated for $C_{15}H_{13}NOS$+H-256.0796 Found -256.0783.

3-(naphthalen-2-ylthio)-1H-indole (3d)[2]



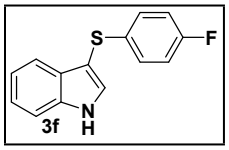
80%; white solid; mp 142-144^{0}C (Lit. [2] -141-143^{0}C); R_f = 0.485 (Hexane: EtOAc, 70:30, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ = 11.75 (s, 1H), 7.84 – 7.76 (m, 3H), 7.65 (d, J = 4Hz, 1H), 7.53-7.45 (m, 2H), 7.43 – 7.38 (m, 3H), 7.23 – 7.18 (m, 2H), 7.07-7.04 (m, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ = 137.3, 133.7, 133.0, 131.3, 129.1, 128.8, 128.0, 125.7, 124.8, 123.3, 122.6, 120.6, 118.7, 112.8, 99.6.; $(M+H)^{+}$ESI-HRMS calculated for $C_{18}H_{13}NS$+H-276.0847 Found – 276.0829.



3-((2-methoxyphenyl)thio)-1H-indole (3e)[3]

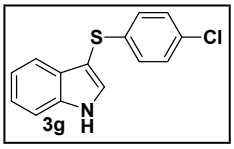
83%; yellow solid; mp 138-139°C (Lit. [3]-138-140^{0}C); R_f = 0.590 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 8.50 (s, 1H) 7.65 (d, J = 8.0, Hz, 1H), 7.51 – 7.47 (m, 2H), 7.30 –7.19 (m, 2H), 7.09-7.05 (m, 1H), 6.89 – 6.70 (m, 1H), 6.69-6.66 (m, 2H), 4.0 (s, 3H);^{13}C NMR (100MHz, $CDCl_3$) δ = 155.1, 136.6, 131.1,

129.3, 127.9, 125.9, 125.3, 123.0, 121.1, 120.8, 119.7, 111.5, 101.4, 55.8; $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{13}NOS$- 255.0718 Found – 255.1861.



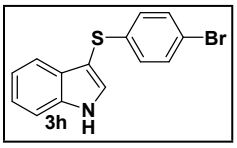
3-((4-fluorophenyl)thio)-1H-indole (3f)[2]

82%; white solid; mp 134-136^{0}C (Lit. [2]-132-134^{0}C); R_f = 0.536 (Hexane: EtOAc, 70:30, v/v); ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.43 (s, 1H),7.63 (d, J = 8.0 Hz, 1H), 7.51-7.45 (m, 2H), 7.32 – 7.29 (m, 1H), 7.22 – 7.19 (m, 1H), 7.15-7.11 (m, 2H), 6.92–6.88 (m, 2H);^{13}C NMR (100MHz, $CDCl_3$) δ = 159.7, 136.5, 134.0, 130.4, 128.8, 127.9, 123.1, 120.9, 119.5, 115.8, 115.6, 111.6, 103.4; $(M+H)^+$ESI-HRMS calculated for $C_{14}H_{10}NSF$+H-244.0596Found – 244.0586.



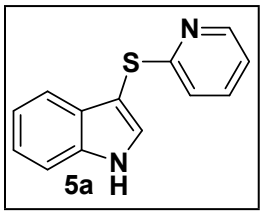
3-((4-chlorophenyl)thio)-1H-indole (3g)[1]

89%; white solid; mp 134-135^{0}C (Lit. [1]-129-131^{0}C); R_f = 0.517(Hexane: EtOAc, 85:15, v/v);^{1}H NMR (400MHz, $CDCl_3$,) δ = 8.49 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.51 (d, J=4.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.33-7.28 (m, 1H), 7.22-7.13 (m, 3H), 7.06-7.04 (m, 2H);^{13}C NMR (100MHz, $CDCl_3$)δ = 137.8, 136.5, 130.7, 130.5, 128.7, 127.1, 123.2, 121.0, 119.5, 111.6, 102.5; $(M+H)^+$ESI-HRMS calculated for $C_{14}H_{10}NSCl$+H-260.0300 Found – 260.0304.



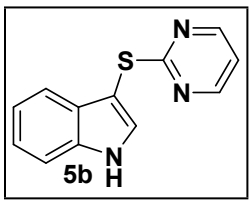
3-((4-bromophenyl)thio)-1H-indole (3h) [1]

86%; white solid; mp 145-147^{0}C (Lit. [1]-141-143^{0}C); R_f = 0.591 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 8.48 (s, 1H), 7.60 (d, J = 8.0Hz, 1H), 7.52 – 7.47 (m, 4H), 7.32-7.28 (m, 3H), 7.22-7.18 (m, 1H),7.00 – 6.97 (m, 2H);^{13}C NMR (100MHz, $CDCl_3$) δ = 138.5, 136.5, 131.6, 130.7, 128.8, 127.4, 123.2, 121.0, 119.5, 118.3, 111.6, 102.3.; $(M+H)^+$ESI-HRMS calculated for $C_{14}H_{10}NSBr$+H-303.9795Found -303.9799.



3-(pyridin-2-ylthio)-1H-indole (5a)[4]

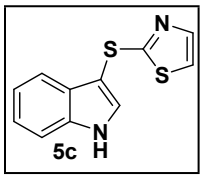
85%; colorless solid; mp 135-136^{0}C (Lit. [4]-136-137^{0}C); R_f = 0.555 (Hexane: EtOAc, 70:30, v/v); ^{1}H NMR (400MHz, $CDCl_3$) δ = 9.57 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.46-7.42 (m, 2H), 7.39-7.35. (m, 1H), 7.30 – 7.26 (m, 1H), 7.22-7.18 (m, 1H), 6.99 – 6.95 (m, 1H), 6.84 (d, J = 8.0 Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$) δ 162.9, 148.9, 136.8, 131.6, 128.8, 122.9, 120.8, 120.1, 119.4, 119.2, 112.0, 100.2; $(M+H)^+$ESI-HRMS calculated for $C_{13}H_{10}N_2S$+H-227.0643 Found - 227.0638.



3-(pyrimidin-2-ylthio)-1H-indole (5b)[5]

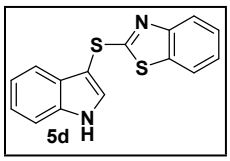
80%; white solid; mp 270-272^{0}C (Lit. [5]-275^{0}C); R_f= 0.724 (Hexane: EtOAc, 70:30, v/v); ^{1}H NMR (400MHz,DMSO-d_6)δ = 11.55 (s, 1H), 8.46-8.45 (m 2H), 7.64 (d, J = 4.0 Hz, 1H), 7.48 (d, J = 8.0 Hz 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.20-7.12 (m, 2H), 7.08 – 7.04 (m, 1H);^{13}C NMR (100MHz, DMSO-d_6) δ = 172.4, 158.2, 136.9, 132.6,

129.4, 122.5, 120.6, 118.8, 118.0, 112.7, 98.2; $(M+H)^+$ESI-HRMS calculated for $C_{12}H_9N_3S$+H-228.0595Found - 228.0586.



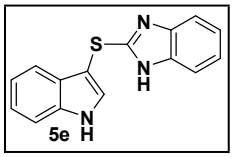
2-((1H-indol-3-yl)thio)thiazole (5c).

82%; viscous oil; R_f= 0.563 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ = 11.90 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 4.0 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.41 (d, J = 4.0 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.16 – 7.12 (m, 1H);^{13}C NMR (100MHz, DMSO-d_6) δ = 170.5, 143.6, 137.1, 133.7, 128.2, 122.9, 121.0, 120.5, 118.4, 113.0, 98.7; $(M+H)^+$ESI-HRMS calculated for $C_{11}H_8N_2S_2$+H-233.0207 Found – 233.0206.



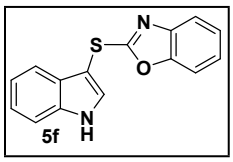
2-((1H-indol-3-yl)thio)benzo[d]thiazole(5d).

83%; reddish brown solid; mp 142-144^{0}C; R_f= 0.475 (Hexane: EtOAc, 70:30, v/v); ^{1}H NMR (400MHz, $CDCl_3$) δ= 8.88 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.81-7.75 (m, 1H), 7.68-7.67 (m, 1H), 7.58 – 7.47 (m, 2H), 7.40 – 7.32 (m, 2H), 7.26-7.21 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 167.9, 154.4, 136.4, 136.1, 131.9, 128.3, 126.6, 125.9, 123.8, 122.6, 121.5, 120.7, 119.3, 111.9, 100.7; $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{10}N_2S_2$+H-283.0363 Found – 283.0362.



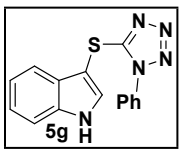
2-((1H-indol-3-yl)thio)-1H-benzo[d]imidazole (5e).

75%; brown solid; mp195-198^{0}C ; R_f= 0.750 (Hexane: EtOAc, 60:40, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ= 11.81 (s, 1H), 7.87 (d, J = 4.0 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.47-7.45 (m, 2H), 7.36 – 7.06 (m, 5H); ^{13}C NMR (100MHz, DMSO-d_6) δ 151.5, 137.1, 133.5, 132.5, 129.2, 122.7, 121.9, 120.7, 118.5, 114.4, 112.8, 95.9; $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{11}N_3S$+H-266.0752 Found – 266.0745.



2-((1H-indol-3-yl)thio)benzo[d]oxazole(5f).

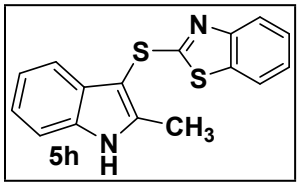
82%; brown solid; mp 118-120^{0}C, R_f= 0.800 (Hexane: EtOAc, 60:40, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 9.01 (s, 1H), 7.71 (d, J = 4.0 Hz, 1H), 7.57 – 7.54 (m, 2H), 7.42 – 7.38 (m, 2H), 7.25 – 7.21 (m, 4H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 176.7, 150.8, 149.1, 147.0, 139.9, 129.9, 126.0, 125.9, 125.5, 120.3, 113.2, 111.1, 110.3; $(M+H)^+$; ESI-HRMS calculated for $C_{15}H_{10}N_2OS$+H-267.0592 Found – 267.0585.



3-((1-phenyl-1H-tetrazol-5-yl)thio)-1H-indole(5g).

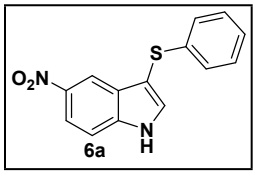
68%; white solid; mp182-184^{0}C, R_f = 0.572 (Hexane: EtOAc, 70:30, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 9.81 (s, 1H), 7.76 –7.74 (m, 2H), 7.69-7.63(m, 3H), 7.52 (d, J= 8.0 Hz 1H), 7.21 (d, J = 4.0 Hz, 1H), 7.18 – 7.10 (m, 3H);^{13}C NMR (100MHz, $CDCl_3$) δ =

155.7, 136.5, 133.8, 132.4, 130.3, 129.8, 128.0, 124.2, 123.1, 121.1, 118.3, 112.2, 93.9; $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{11}N_5S$+H-294.0813 Found – 294.0804.



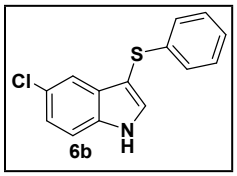
2-((2-methyl-1H-indol-3-yl)thio)benzo[d]thiazole (5h)[6]

72%; creamish solid; mp164-165^{0}C (Lit. [6]- 165-168^{0}C); R_f= 0.667 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, MeOD, DMSO-d_6) δ = 8.14 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0, 1H), 7.81 (d, J = 8.0, 1H), 7.79-7.75 (m, 1H), 7.63-7.59 (m, 1H), 7.57-7.53 (m, 1H), 7.50-7.46 (m, 1H), 2.92 (s, 3H);.^{13}C NMR (100MHz, MeOD, DMSO-d_6) δ = 174.7, 154.6, 143.6, 136.1, 135.3, 129.3, 126.2, 124.0, 122.2, 121.3, 121.1, 120.8, 117.6, 111.5, 95.6, 11.1; $(M+H)^+$ESI-HRMS calculated for $C_{16}H_{12}N_2S_2$+H-297.0520 Found – 297.0526.



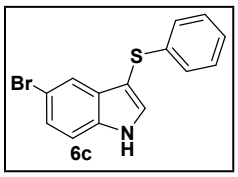
5-nitro-3-(phenylthio)-1H-indole (6a)[2]

80%; yellow solid; mp157-160^{0}C (Lit.[2]-156-158^{0}C); R_f= 0.700 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 8.53 (s 1H), 8.13-8.10 (m, 1H), 7.66-7.50 (m, 3H), 7.37-7.08 (m, 5H).;^{13}C NMR (100MHz, $CDCl_3$) δ 142.4, 139.8, 138.2, 134.3, 128.8, 126.1, 125.3, 118.2, 116.6, 112.0, 105.3; $(M+H)^+$ESI-HRMS calculated for $C_{14}H_{10}N_2O_2S$+H-271.0541 Found -271.0534.



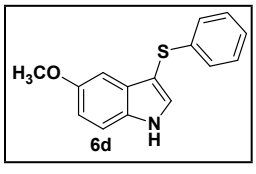
5-chloro-3-(phenylthio)-1H-indole (6b)[7]

82%; white solid; mp 111-112^{0}C (Lit. [7]-112.5-113.5^{0}C); R_f = 0.542 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 8.49 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 4.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.21 (t, J = 4.0 Hz, 1H), 7.18-7.13 (m, 2H), 7.06-7.04 (m, 2H).;^{13}C NMR (100MHz, $CDCl_3$) δ = 137.8, 136.5 130.7, 130.5, 128.7, 127.1, 123.2, 121.0, 119.5, 111.6, 102.5; $(M+H)^+$ESI-HRMS calculated for $C_{14}H_{10}NSCl$+H-260.0300 Found – 260.0288.



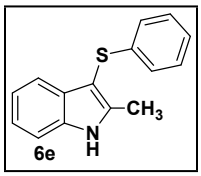
5-bromo-3-(phenylthio)-1H-indole (6c)[1]

86%; white solid; mp 119-121^{0}C (Lit. [1]-120-121^{0}C); R_f = 0.852 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ= 8.47 (s, 1H), 7.79-7.18 (m, 1H), 7.50 (d, J = 4 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.23 – 7.18 (m, 2H), 7.12-7.10 (m, 3H);^{13}C NMR (100MHz, $CDCl_3$) δ 138.7, 135.1, 131.9, 131.0, 128.8, 126.1, 125.9, 125.0, 122.2, 114.5, 113.1, 102.7; $(M+H)^+$ESI-HRMS calculated for $C_{14}H_{10}NSBr$+H-303.9795 Found – 303.9781.



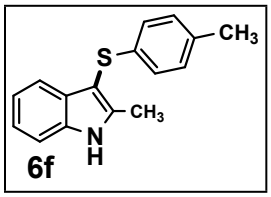
5-methoxy-3-(phenylthio)-1H-indole (6d) [1]

85%; white solid; mp78-79^{0}C (Lit. [1]-77-78^{0}C); R_f= 0.382 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 8.37 (s, 1H), 7.46 (d, J = 4.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.22 – 7.19 (m, 2H), 7.15-7.07 (m, 4H), 6.97-6.94 (m, 1H),3.82 (s 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 155.1, 139.3, 131.3, 130.0, 128.7, 125.7, 124.7, 113.6, 112.4, 102.2, 100.8, 55.8. $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{13}NOS$+H-256.0796 Found -256.0709.



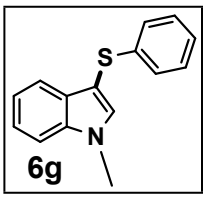
2-methyl-3-(phenylthio)-1H-indole (6e) [1]

90%; white solid; mp 109-110^{0}C (Lit. [1]-109-111^{0}C); R_f= 0.571 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ= 8.19 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.28 – 7.18 (m, 4H), 7.13 – 7.11 (m, 3H), 2.53 (s, 3H);^{13}C NMR (100MHz, $CDCl_3$) δ 141.1, 139.3, 135.4, 130.3, 128.7, 125.5, 124.5, 122.2, 120.7, 119.0, 110.6, 99.4, 12.1; $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{13}NS$+H-240.0847 Found – 240.0837.



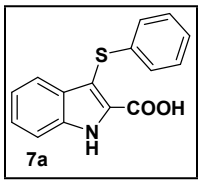
2-methyl-3-(p-tolylthio)-1H-indole (6f)[1]

81%; yellow solid; mp 96-98^{0}C (Lit. [1]-97-99^{0}C); R_f = 0.774 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 8.23 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.25-7.20 (m, 1H), 7.18 – 7.14 (m, 1H), 7.0 (s, 4H), 2.54 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 140.9, 135.7, 135.4, 134.3, 130.3, 129.5, 125.8, 122.1, 120.6, 119.0, 110.6, 99.9, 20.8, 12.1; $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{15}NS$+H-254.1003Found – 254.1002.



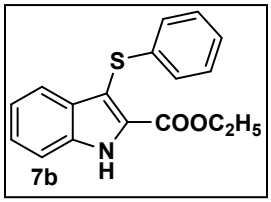
1-methyl-3-(phenylthio)-1H-indole (6g) [1]

58%; white solid; mp 86-87^{0}C (Lit. [1]-86-87^{0}C); R_f = 0.208 (Hexane: EtOAc, 95:05, v/v); ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.63 (d, J = 4.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.36-7.31 (m, 2H), 7.21-7.18 (m, 4H), 7.16-7.12 (m, 2H), 7.07 (t, J =8Hz,1H), 3.88 (s, 3H);^{13}C NMR (100MHz, $CDCl_3$) δ = 139.6, 137.5, 135.0, 129.8, 128.6, 124.6, 122.5, 120.5, 119.7, 109.7, 100.5, 29.7; $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{13}NS$+H—240.0802 Found-240.0835.



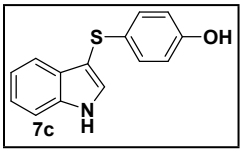
3-(phenylthio)-1H-indole-2-carboxylic acid (7a)[3]

78%; brown solid; mp160-161^{0}C (Lit. [3]-160-161^{0}C); R_f = 0.238 (Hexane: EtOAc, 80:20, v/v); ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.98 (s, 1H), 11.74 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.45-7.40 (m, 2H), 7.38-7.30 (m, 2H), 7.29 – 7.05 (m, 3H);^{13}C NMR (100MHz, DMSO-d_6) δ = 163.2, 137.7, 130.6, 129.9, 129.3, 128.8, 127.6, 127.3, 126.7, 125.5, 124.7, 122.3, 120.4, 112.9, 107.7; $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{11}NO_2S$+NH_4^+-286.0538 Found- 286.0538.



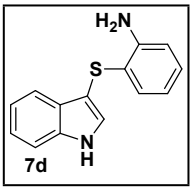
ethyl 3-(phenylthio)-1H-indole-2-carboxylate (7b)[3]

75%; creamish solid; mp129-130^{0}C (Lit. [3]-130-132^{0}C); R_f = 0.793 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ = 12.38 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.22-7.20 (m, 2H), 7.12-7.07 (m, 4H), 4.3 (q, J = 7.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H);^{13}C NMR (100MHz, DMSO-d_6) δ = 160.8, 138.2, 136.7, 129.7, 129.6, 129.3, 126.9, 125.8 125.7, 121.6, 120.7, 113.6, 107.8, 61.2, 14.5; (M+H)$^+$ESI-HRMS calculated for $C_{17}H_{15}NO_2S$+H-298.0901Found – 298.0869.



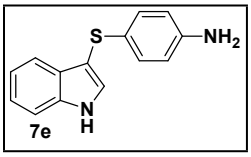
4-((1H-indol-3-yl)thio)phenol (7c)[8]

76%; white solid; mp166-169^{0}C (Lit. [8]-169-172^{0}C); R_f = 0.511 (Hexane: EtOAc, 70:30, v/v); ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.52 (s, 1H), 9.33 (s, 1H), 7.68 (d, J = 4.0 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.17 – 7.13 (m, 1H), 7.07-6.99 (m, 3H), 6.65 – 6.62 (m, 2H).; ^{13}C NMR (100MHz, DMSO-d_6) δ = 156.1, 137.0, 131.9, 129.3, 129.1, 127.3, 122.3, 120.3, 118.8, 116.3, 112.6, 102.5.; (M+H)$^+$ESI-HRMS calculated for $C_{14}H_{11}NOS$+H-242.0639 Found – 242.0638.



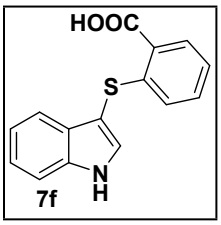
2-((1H-indol-3-yl)thio)aniline (7d)[1]

85%; white solid; mp 93-95^{0}C (Lit. [1]-93-94^{0}C); R_f = 0.666 (Hexane: EtOAc, 70:30, v/v); ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.32 (s, 1H), 7.70 (d, J = 4.0 Hz, 1H), 7.37 – 7.36 (m, 2H), 7.26 – 7.04 (m, 3H), 6.72 – 6.65 (m, 3H), 4.29 (bs, 2H);^{13}C NMR (100MHz, $CDCl_3$) δ = 145.6, 136.3, 131.9, 129.0, 128.7, 128.0, 122.8, 120.7, 120.6, 119.4, 118.9, 115.4, 111.5, 104.2; (M+H)$^+$ESI-HRMS calculated for $C_{14}H_{12}N_2S$+H -241.0799 Found – 241.0810.



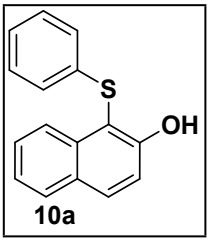
4-((1H-indol-3-yl)thio)aniline (7e).

82%; off white solid; mp 132-135^{0}C; R_f = 0.708 (Hexane: EtOAc, 70:30, v/v); ^{1}HNMR (400MHz, $CDCl_3$) δ = 8.34 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.43 – 7.09 (m, 6H), 6.55 (d, J = 8.0 Hz, 2H), 3.04 (bs, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 144.5, 136.4, 129.6, 129.3, 129.0, 126.6, 122.8, 121.8, 120.6, 119.7, 115.8, 111.4, 105.4; (M+H)$^+$ESI-HRMS calculated for $C_{14}H_{12}N_2S$+H -241.0799 Found – 241.0800.



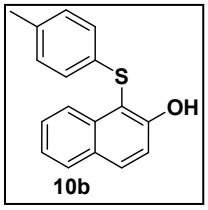
2-((1H-indol-3-yl)thio)benzoic acid (7f)[8]

75%; yellow solid; mp250-254^{0}C (Lit[8]-254-255^{0}C); R_f = 0.314 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ = 13.12 (br, 1H), 11.71 (s, 1H), 7.92 (d, J = 8.0Hz, 1H), 7.73 – 7.72 (m, 1H), 7.52 (d, J = 8.0Hz, 1H), 7.32 (d, J = 8.0Hz, 1H), 7.24-7.18 (m, 2H), 7.13 – 7.04 (m, 2H), 6 68 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ = 167.9, 144.2, 137.4, 133.1, 132.5, 131.4, 129.1, 127.1, 126.0, 124.2, 122.6, 120.6, 118.7, 112.8, 100.4; (M+H)$^+$ESI-HRMS calculated for $C_{15}H_{11}NO_2S$+H- 270.0588 Found – 270.0585.



1-(phenylthio)naphthalen-2-ol (10a)[9]

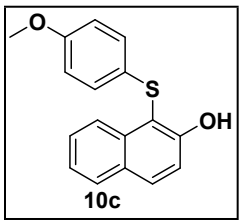
75%; white solid; mp 57-58 ^{0}C (Lit. [9]- 58-59 ^{0}C);; R_f = 0.446 (Hexane: EtOAc, 85:15, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 8.24 (d, J = 12 Hz, 1H), 79.2 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.40-7.35 (m, 2H), 7.29 (br, 1H), 7.19-7.12 (m, 2H), 7.06-7.04 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 157.0, 135.4, 132.8, 129.1, 128.5, 127.9, 126.3, 125.8, 124.7, 123.8, 116.9, 108.0; $(M-H)^+$ESI-HRMS calculated for $C_{16}H_{12}$SH-251.0531Found – 251.0518.



10b

1-(p-tolylthio)naphthalen-2-ol (10b) [9]

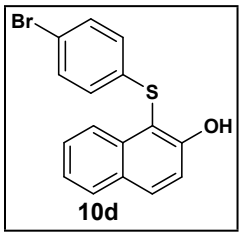
72% as a white solid; mp71-74^{0}C (Lit.[9] -72.5-73.5^{0}C); R_f = 0.533 (Hexane: EtOAc, 85:15, v/v);^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0, Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.56-7.52 (m, 1H), 7.42-7.38 (m, 2H), 7.16–7.01 (m, 4H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.9, 135.9, 135.5, 132.6, 131.8, 129.9, 129.5, 128.5, 127.9, 126.7, 124.7, 123.8, 116.8, 108.7, 20.9; $(M-H)^+$ESI-HRMS calculated for $C_{17}H_{14}$S+H- 265.0687 Found – 265.0670.



10c

1-((4-methoxyphenyl)thio)naphthalen-2-ol (10c) [9]

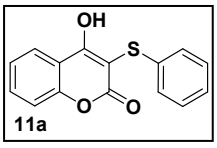
69%; yellow solid; mp 68-69^{0}C (Lit·[9]-68-70^{0}C); R_f = 0.314 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 8.30 (d, J = 8.0, 1H), 7.90 (d, J = 8.0, Hz, 1H), 7.82 (d, J = 8.0, Hz, 1H), 7.55-7.51 (m, 1H), 7.41–7.32 (m, 2H), 7.07 (d, J = 8.0Hz, 2H), 6.77-6.75 (d, J = 8.0Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 158.4, 156.7, 135.3, 132.5, 129.5, 128.7, 128.5, 127.8, 125.9, 124.7, 123.7, 116.8, 114.9, 109.7, 55.3; $(M+H)^+$ESI-HRMS calculated for $C_{17}H_{14}O_2$S+H- 283.0748 Found – 283.0710.



10d

1-((4-bromophenyl)thio)naphthalen-2-ol) (10d) [9]

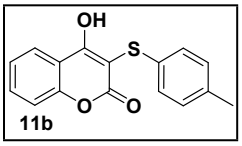
68%; yellow solid; mp104-105^{0}C (Lit.[9]-103-105^{0}C); R_f = 0.700 (Hexane: EtOAc, 80:20, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 8.17 (s, J = 8.0 Hz 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.55-7.51 (m, 1H), 7.41 – 7.37 (m, 2H), 7.35-7.30 (m, 2H), 7.11 (s, 1H), 6.91 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 157.0, 134.6, 133.1, 132.2, 129.5, 128.6, 128.1, 127.9, 124.4, 124.0, 119.6, 116.9, 107.6; $(M+H)^+$ESI-HRMS calculated for $C_{16}H_{11}$BrOS+H-330.9796 Found –.330.9844



11a

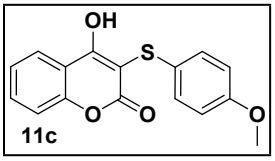
4-hydroxy-3-(phenylthio)-2H-chromen-2-one (11a)[10]

80%; white solid; mp198-199^{0}C (Lit. [10]- 200-202^{0}C); R_f = 0.700 (Hexane: EtOAc, 10:90, v/v);^{1}H NMR (400MHz, MeOD + DMSO-d_6) δ = 7.91-7.88 (m, 1H), 7.59 – 7.55 (m, 1H), 7.30 – 7.25 (m, 2H), 7.19-7.13 (m, 4H), 7.08-7.04 (m, 1H); ^{13}C NMR (100MHz, MeOD + DMSO-d_6) δ = 173.6, 166.6, 158.1, 140.7, 138.4, 133.9, 131.6, 130.7, 129.4, 129.0, 121.3, 120.7, 99.8. $(M+H)^+$ESI-HRMS calculated for $C_{15}H_{10}O_3$S-271.0429 Found – 271.0429.



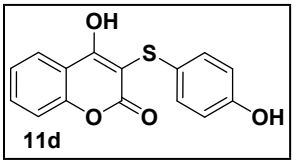
4-hydroxy-3-(p-tolylthio)-2H-chromen-2-one (11b)[10]

74%; white solid; mp 160–161^{0}C (Lit. [10]- 160–161^{0}C); R_f = 0.633 (Hexane: EtOAc, 10:90, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 7.94 – 7.91 (m, 1H), 7.64 – 7.59 (m, 1H), 7.37 – 7.31 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.10-7.05 (m, 2H), 2.27 (s, 3H).^{13}C NMR (100MHz, $CDCl_3$) δ 167.1, 161.5, 153.5, 137.3, 133.7, 130.0, 128.8, 124.4, 124.2, 116.8, 114.3, 97.5, 20.9; (M+H)$^+$ESI-HRMS calculated for $C_{16}H_{12}O_3S$-285.0585 Found – 285.0572.



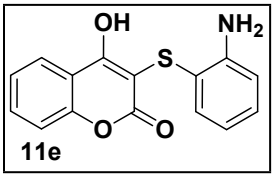
4-hydroxy-3-((4-methoxyphenyl)thio)-2H-chromen-2-one (11c)

70%; white solid; mp 123-125^{0}C; R_f = 0.750 (Hexane: EtOAc, 10:90, v/v);^{1}H NMR (400MHz, $CDCl_3$) δ = 7.94-7.91 (m, 1H), 7.65 – 7.61 (m, 1H), 7.44 – 7.35 (m, 4H), 6.85 – 6.83 (m, 2H), 3.78 (s, 3H);^{13}C NMR (100MHz, $CDCl_3$) δ = 166.1, 160.9, 159.7, 153.5, 133.7, 132.2, 124.4, 124.2, 123.3, 116.9, 115.0, 113.9, 99.1, 55.3; (M+H)$^+$ESI-HRMS calculated for $C_{16}H_{12}O_4S$-301.0534 Found – 301.0384.



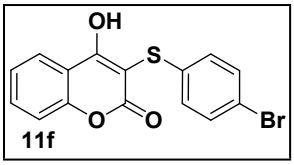
3-((4-bromophenyl)thio)-4-hydroxy-2H-chromen-2-one(11d)

63%; yellow solid; mp 156-158^{0}C; R_f =0.391 (Hexane: EtOAc, 10:90, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ 9.86 (s, 1H), 9.63 (s, 1H), 7.28 (d, J = 8.0Hz, 2H), 7.14 (d, J = 8.0Hz, 2H), 6.78 – 6.73 (m, 4H);^{13}C NMR (100MHz DMSO-d_6) δ 171.5, 162.8, 153.2, 133.1, 124.8, 124.1, 118.0, 116.5, 96.9; (M+H)$^+$; ESI-HRMS calculated for $C_{15}H_{10}O_4S$-H-287.0379 Found 287.0568.



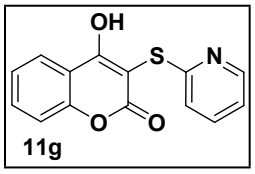
3-((2-aminophenyl)thio)-4-hydroxy-2H-chromen-2-one (11e)

60%; yellow solid; mp 224-226 ^{0}C; R_f = 0.426 (Hexane: EtOAc, 10:90, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ 7.89-7.80 (m, 2H), 7.50-7.46 (m, 1H), 7.39-7.30 (m, 3H), 7.26-7.12 (m, 2H), 3.17 (s, 2H);^{13}C NMR (100MHz, DMSO-d_6) δ 170.7, 159.3, 140.3, 135.9, 128.6, 128.5, 125.4, 124.5, 124.4, 119.3, 118.0, 114.3, 86.6; (M+H)$^+$ESI-HRMS calculated for $C_{15}H_{11}NO_3S$+H-286.0539 Found -286.0531.



4-hydroxy-3-((4-hydroxyphenyl)thio)-2H-chromen-2-one (11f)[10]

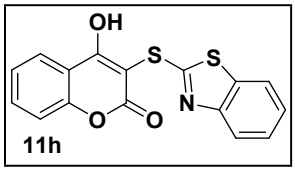
72%; white solid; mp196-197^{0}C (Lit.[10]-197–198 ^{0}C); R_f = 0.600 (Hexane: EtOAc, 10:90, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.83-7.80 (m, 1H), 7.46-7.42 (m, 1H), 7.31 – 7.29 (m, 2H), 7.16 – 7.12 (m, 2H), 6.93 – 6.91 (m, 2H); ^{13}C NMR(100MHz, DMSO-d_6) δ = 169.2, 161.3, 153.5, 136.3, 134.1, 132.2, 128.7, 124.9, 124.6, 118.6, 116.9, 116.4, 94.1; (M+H)$^+$ESI-HRMS calculated for $C_{15}H_9O_3SBr$-348.9535 Found – 348.9528.



11g

4-hydroxy-3-(pyridin-2-ylthio)-2H-chromen-2-one (11g)

60%; yellow solid; mp 172-174^{0}C; R_f = 0.635(Hexane: EtOAc, 10:90, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ = 8.39 (m, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.79 – 7.75 (m, 1H), 7.69 – 7.65 (m, 1H), 7.39 – 7.29 (m, 3H), 7.24 – 7.21 (m, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ = 171.5, 162.4, 159.8, 153.8, 147.3, 139.6, 133.4, 125.1, 124.1, 121.7, 120.7, 118.7, 116.8, 88.1; $(M+H)^+$ESI-HRMS calculated for $C_{14}H_9NO_3S$-272.0381 Found -272.0377.



11h

3-(benzo[d]thiazol-2-ylthio)-4-hydroxy-2H-chromen-2-one (11h)

65%; yellow solid; mp 192-194^{0}C; R_f = 0.652 (Hexane: EtOAc, 10:90, v/v);^{1}H NMR (400MHz, DMSO-d_6) δ = 7.89 – 7.86 (m, 1H), 7.79-7.75 (m, 1H), 7.73-7.68 (m, 1H), 7.53-7.48 (m, 1H), 7.37 – 7.33 (m, 1H), 7.22 – 7.16 (m, 3H).;^{13}C NMR (100MHz, DMSO-d_6) δ = 178.0, 174.9, 163.9, 155.4, 154.3, 135.4, 131.9, 125.9, 125.9, 123.4, 122.7, 121.5, 120.7, 116.4, 85.4; $(M+H)^+$ESI-HRMS calculated for $C_{16}H_9NO_3S_2$+H- 328.0102 Found – 328.0089.

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