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Synthesis and Biological Evaluation of Substituted 2-Sulfonyl-phenyl-3-phenyl-indoles: A New Series of Selective COX-2 Inhibitors

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Abstract—A new series of substituted 2-sulfonyphenyl-3-phenyl-indole derivatives were synthesized and evaluated for their ability to inhibit COX-2 and COX-1enzymes. Most of the compounds synthesized were found to be highly potent and selective inhibitors of COX-2. This work led to the discovery of 2-aminosulfonylphenyl-3-phenyl-indole **5a** which possesses higher activity and selectivity for COX-2 than Celecoxib both in vitro and in vivo.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain among the most widely prescribed drugs worldwide for the treatment of inflammation that can cause pain and fever among other symptoms. The mechanism of action is through their inhibition of prostaglandin biosynthesis via the enzyme cyclooxygenase-2 (COX-2).[1] COX-2 and COX-1 are two similar but distinct isoforms of cyclooxygenase (COX).[2–5] COX-2 is induced in response to inflammatory stimuli and is responsible for the progression of inflammation, whereas COX-1 is a constitutively expressed isoform and is responsible for the maintenance of physiological homestasis, such as gastrointestinal integrity and renal function. Thus selective inhibition of COX-2 over COX-1 is useful for the treatment of inflammation and inflammation-associated disorders with reduced gastrointestinal toxicities when compared with the traditional NSAIDs.

Current research has focused on developing safer NSAIDs—selective COX-2 inhibitors. Several selective COX-2 inhibitors such as **Celecoxib**,[6] **Rofecoxib**[7,8] and **Valdecoxib**[9] have been marketed as a new generation of NSAIDs. These compounds all have the diarylheterocyclic structural features.[10–32] The other two categories of selective COX-2 inhibitors[33,34] are sulfonanilide inhibitors,[35–37] and modifications of classical NSAIDs,[38–41] The pharmacophore of diarylheterocycles inhibitors is characterized by a central carbocyclic or heterocyclic ring system bearing two vicinal aryl moieties and one benzene ring being substituted with methylsulfonyl or aminosulfonyl group at the para position. The major difference in the compounds of this class is the structure of the central ring. Thus, alteration in the central ring will lead to new COX-2 inhibitors. Indole ring constitutes an important template for drug design such as the classical NSAIDs indomethacin and indoxole.[42] We herein developed a new series of COX-2 inhibitors of diarylheterocycles using indole as the central ring (**I**).

Chemistry

All the compounds (**I**) described here (except compounds **5o** and **5p**) were synthesized by using the general routes outlined in Schemes 1 and 2. The key step of the

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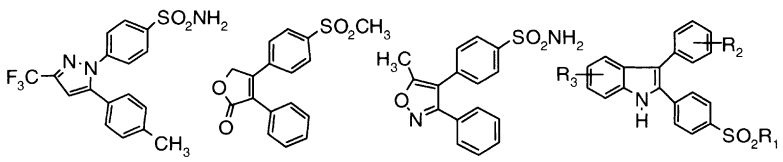


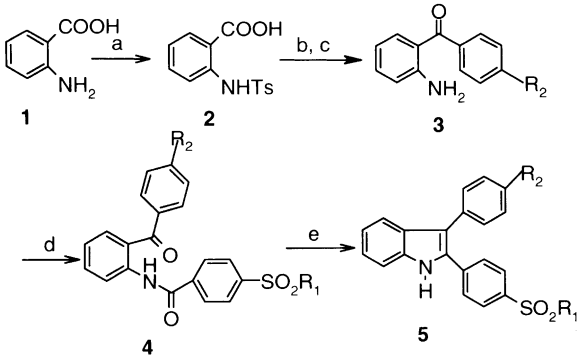
routes is to construct an indole skeleton by McMurry coupling reaction. Aromatic acylamido-substituted benzophenones can be cyclized to indole derivatives upon the treatment with the low-valent titanium reagents.[43–45] In this paper the coupling reagent 'low-valent' Ti was prepared in situ from $TiCl_4$ and Zn in reflux THF. In Scheme 1, *o*-aminobenzoic acid **1** was subjected Friedel–Crafts reaction after being protected by tosylation (**2**), and then hydrolyzed by concentrated H_2SO_4 to give the substituted 2-amino-benzophenone (**3**), which was acylated with 4-methylsulfonyl or 4-aminosulfonyl benzoyl chloride to give rise to **4.** The intermediate **4** was cyclized to provide the final compounds **5** by the McMurry condensation.

An alterative method is outlined in Scheme 2 with a slight difference in the initial steps from Scheme 1.

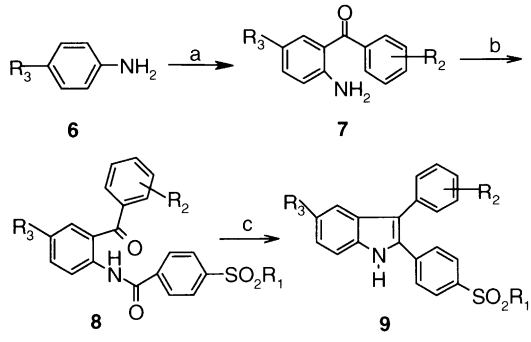
The target compound **5o** containing a hydroxy group cannot be prepared directly from the general synthetic route due to the Friedel–Crafts reaction limitation. The functional group transformation was carried out in the synthesis of **5o** by demethylation of **5i** with BBr_3[46] in CH_2Cl_2 (Scheme 3).

To investigate the effect of the modification of the aminosulfonyl group on the activity, we prepared the acetylsulfonamide compound **5p** by acetylation of **5a** with Ac_2O and DMAP (Scheme 4).

All the target compounds were identified by spectroscopic data and confirmed by elemental analyses.



Scheme 1. Reagent: (a) Na_2CO_3, TsCl, 60–85 °C; (b) (i) PCl_5, 50 °C, (ii) $AlCl_3$, $C_6H_5R_2$, 80–90 °C; (c) H_2SO_4, 120 °C; (d) 4-$R_1SO_2C_6H_4$-COCl, THF, Et_3N, rt; (e) Zn, $TiCl_4$, THF, reflux.

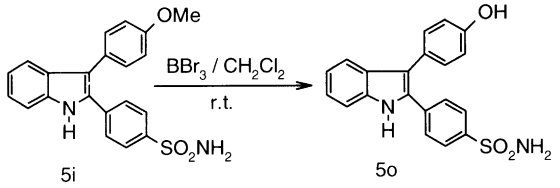


Scheme 2. Reagent: (a) (i) $R_2C_6H_4COCl$, $ZnCl_2$, 205 °C (ii) H_2SO_4, 120 °C; (b) 4-$R_1SO_2C_6H_4COCl$, THF, Et_3N, rt; (c) Zn, $TiCl_4$, THF, reflux.

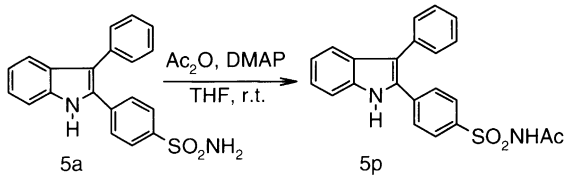
Results and Discussion

We have synthesized three series of the indole analogues (Table 1) with: different substitutents (R_2) at the para-position of the 3-phenyl ring such as hydrogen, halogen, methoxy, methyl and others (**5a–5o**); chloro group at different position of the 3-phenyl ring (**9a–9f**) and various substitutent (R_3) at 5-position of the indole ring (**9g–9n**). All the compounds except for **5o** and **5p** were prepared as both the methyl sulfones and the corresponding sulfonamides.

The compounds synthesized in this work are evaluated for their ability to inhibit COX-2 and COX-1 by cellular assay, using freshly harvested mouse peritoneal macrophages as described in the literature.[47] The details of these assays were described in the Experimental. We were unable to determine the IC_{50} values for COX-1 inhibition by these compounds due to their low inhibitory activities at the concentrations as high as 10 μM. The results showed that all the compounds showed potent inhibition against COX-2 compared to the inhibition for COX-1 ($IC_{50} > 10$ μM) as listed in Table 1.

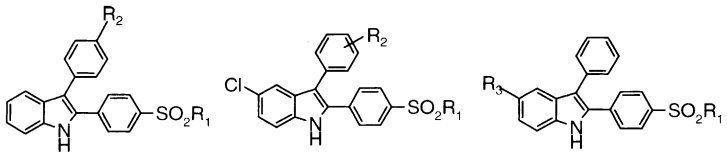


Scheme 3.



Scheme 4.

Table 1. In vitro[a] and in vivo[b] inhibitory results



No.	Structure		IC_{50} (nM)[c] COX-2	IC_{50} (μM) COX-1	Carrageenan edema (10 mg/kg, % inhibition)
5a	$R_1 = NH_2$	$R_2 = H$	0.09	>10	53.9
5b	$R_1 = CH_3$	$R_2 = H$	0.60	>10	56.1
5c	$R_1 = NH_2$	$R_2 = 4$-F	5.15	>10	41.2
5d	$R_1 = CH_3$	$R_2 = 4$-F	0.02	>10	18.4
5e	$R_1 = NH_2$	$R_2 = 4$-Cl	33.5	>10	25.6
5f	$R_1 = CH_3$	$R_2 = 4$-Cl	146.0	>10	50.4
5g	$R_1 = NH_2$	$R_2 = 4$-Br	8.36	>10	N.D.[d]
5h	$R_1 = CH_3$	$R_2 = 4$-Br	0.37	>10	16.1
5i	$R_1 = NH_2$	$R_2 = 4$-OCH_3	0.006	>10	38.5
5j	$R_1 = CH_3$	$R_2 = 4$-OCH_3	0.02	>10	27.1
5k	$R_1 = NH_2$	$R_2 = 4$-CH_3	0.07	>10	N.D.
5l	$R_1 = CH_3$	$R_2 = 4$-CH_3	0.09	>10	47.2
5m	$R_1 = NH_2$	$R_2 = 3,4$-$(CH_3)_2$	1.46	>10	N.D.
5n	$R_1 = CH_3$	$R_2 = 3,4$-$(CH_3)_2$	0.17	>10	43.1
5o	$R_1 = NH_2$	$R_2 = 4$-OH	6.44	>10	N.D.
5p	$R_1 = NHAc$	$R_2 = H$	0.18	>10	N.D.
9a	$R_1 = NH_2$	$R_2 = 4$-Cl	0.54	>10	N.D.
9b	$R_1 = CH_3$	$R_2 = 4$-Cl	85.1	>10	N.D.
9c	$R_1 = NH_2$	$R_2 = 3$-Cl	3.13	>10	23.4
9d	$R_1 = CH_3$	$R_2 = 3$-Cl	0.8	>10	N.D.
9e	$R_1 = NH_2$	$R_2 = 2$-Cl	100.0	>10	N.D.
9f	$R_1 = CH_3$	$R_2 = 2$-Cl	10.0	>10	N.D.
9g	$R_1 = NH_2$	$R_3 = 5$-F	2.0	>10	49.4
9h	$R_1 = CH_3$	$R_3 = 5$-F	5.0	>10	60.8
9i	$R_1 = NH_2$	$R_3 = 5$-Cl	0.14	>10	57.8
9j	$R_1 = CH_3$	$R_3 = 5$-Cl	0.36	>10	53.2
9k	$R_1 = NH_2$	$R_3 = 5$-Br	5.0	>10	N.D.
9l	$R_1 = CH_3$	$R_3 = 5$-Br	1.41	>10	N.D.
9m	$R_1 = NH_2$	$R_3 = 5$-CH_3	0.02	>10	22.6
9n	$R_1 = CH_3$	$R_3 = 5$-CH_3	0.28	>10	46.1
Celecoxib			0.52	>10	49.7

[a]Cell level. For details, see Experimental.
[b]% Inhibition produced by tested compounds on rat carrageenan-induced foot pad edema assay. For details, see Experimental.
[c]All IC_{50} determinations including Celecoxib were carried out in triplicate and have less than 10% error.
[d]N.D. = not done.

Nearly half of the compounds (14 out of 30) were found to be more potent and selective than Celecoxib against COX-2, and three compounds (**5b, 9d, 9e**) appeared to be equipotent to Celecoxib. Compound **5i** was the most potent inhibitor in this series with the activity ($IC_{50} = 0.006$ nM) 87-fold higher than Celecoxib ($IC_{50} = 0.52$ nM). Four compounds (**5d, 5j, 5 h, 5k**) ($IC_{50} < 0.02$ nM) were 26 times more active than Celecoxib.

The SAR studies demonstrated that the presence of a methoxy (**5i, 5j**) and methyl group (**5k, 5l**) at the *para*-position of the phenyl ring contributes excellent properties. However substitution with 3-, 4-dimethyl (**5m, 5n**) resulted in the reduction of COX-2 inhibitory activity. Sulfonamides substituted with halogen (**5c, 5e, 5g**) are less potent than the unsubstituted compound **5a,** whereas no correlation existed between halogen substitution (**5d, 5f, 5 h**) and inhibition in the series of methylsulfones.

Acetylation of **5a** gave rise to acetylsulfonamide (**5p**), which did not cause significant variation in the activity ($IC_{50} = 0.09$ nM vs 0.18 nM)

Compounds with alteration in the positions of chloro substitution at the *ortho*-, *meta*- and *para*- positions of the 3-phenyl ring exhibited change in the inhibition against COX-2. Subsitution with chloro at the *ortho*-position (**9e** and **9f**) resulted in low inhibition compared to the *para*-position for sulfonamides (**9a**, $IC_{50} = 0.54$ nM) and *meta*-position for methylsulfones (**9d**, $IC_{50} = 0.8$ nM).

Several 5-substituted indole analogues including F, Cl, Br and CH_3 were prepared. The comparison of the activity among the analogues showed that methyl compounds **9m** and **9n** were more active than the hydrogen compounds **5a** and **5b**, respectively.

Compounds with sufficient potency and selectivity for COX-2 were advanced for assessment of the activity in

Table 2. In vivo pharmacological properties of compounds **5a** and **5b** at 4 h after carrageenan injection

No.	**5a**	**5b**	Celecoxib[a]
ED_{50}, μmol/kg (4 h)	15.0	27.1	29.6

[a]Activity data were from the author's experiments.

the rat carrageenan-induced foot-pad edema model. The results listed in Table 1 showed that six compounds (**5a, 5b, 5f, 9 h, 9i, 9j**) were more potent than Celecoxib and four compounds (**5c, 5l, 9g, 9n**) were comparable to Celecoxib. Some compounds, such as compound **5i,** with higher activity in vitro assay failed to exhibit potency in vivo. This may be due to their low bio-availability.

Compounds **5a** and **5b** with high in vitro and in vivo activities were tested more extensively using the rat paw edema model (Table 2). Compounds **5a** and **5b** possessed an ED_{50} of 15.0 and 27.1 μmol/kg respectively compared to Celecoxib (29.6 μmol/kg) at 4 h.

Conclusions

The series of substituted 2-sulfonylphenyl-3-phenyl-indole described in this paper were proved to be potent and highly selective inhibitors of COX-2. The indole ring was proved to be an effective central ring that derives a new diarylheterocycle class of COX-2 inhibitors. The structure–activity relationship of the series of inhibitors was analyzed and the acetylation of sulfonamide compound still retained the activity against COX-2. This work led to the discovery of compound **5a** possessing higher activity both in vitro and in vivo than Celecoxib as a prominent candidate for further development.

Experimental

Biological methods

1. In vitro test of inhibitory activity for cyclooxygenase-1 and cyclooxygenase-2. Cell culture. Adherent macrophages were harvested from the peritoneal cells of male mice (C57BL-6J, Level 2, from the Experiment Animal Center, Academy of Military Medical Science) after the injection (ip) of brewer thioglycollate medium (5 mL/100 g body weight) for 3 days. Shortly, peritoneal cells obtained from 3–4 mice were mixed and seeded in 48 well cell culture cluster (Costar) at a cell density of 1×10^9 cell/L in RPMI-1640 supplemented with 5% (v/v) newborn calf serum, 100 ku/L penicillin and 100 g/L streptomycin. After settlement for 2–3 h, non-adherent cells were washed by D-Hanks' balanced salt solution. Then macrophages were cultured in RPMI-1640 without serum. Almost all of the adherent cells were macrophages as assessed by Giemsa staining. Cell viability was examined by trypan blue dye exclusion. All incubation procedures were performed with 5% CO_2 in humidified air at 37 °C.

COX-1 assay. Macrophages were incubated with test compound at different concentrations or solvent (Me_2SO) for 1 h and were stimulated with calcimycin 1 μmol L^{-1} for 1 h. The amount of 6-keto-$PGF_{1\alpha}$ (a stable metabolite of PGI_2) in supernatants was measured by RIA according to manufacturer's guide. The inhibitory ratio was calculated as

$$IR = \frac{(Cs - Ct)}{(Cs - Cc)}$$

Cs, *Ct*, *Cc* refer to 6-keto-$PGF_{1\alpha}$ concentration in supernatants of calcimycin, test compound, and control groups, respectively.

COX-2 assay. Macrophages were incubated with test compound at different concentrations or solvent (Me_2SO) for 1 h and were stimulated with LPS 1 mg/L for 9 h. The amount of PGE_2 in supernatants was measured by RIA. The inhibitory ratio was calculated using the same formula as in COX-1 assay section. *Cs*, *Ct*, *Cc* refer to PGE_2 concentration in supernatants of LPS, test compound, and control groups, respectively.

Statistical analysis data were expressed as the mean ± SD of more than three independent experiments. Dose-inhibitory effect curves were fit through 'uphill dose–response curves, variable slope' using Prism, GraphPad version3.00:

$$Y = \frac{1}{1 + 10^{[(\log IC_{50} - X)\times \mathrm{Hillslope}]}}$$

2. In vivo test (rat carrageenan-induced foot pad edema assay). Male Sprgue–Dawley rats (190–220 g) were fasted with free access to water at least 16 h prior to experiments. The rats were dosed orally with a 1 mL suspension of test compound in vehicle (0.5% methyl cellulose and 0.025% Tween-20) or with vehicle alone. One h later a subplantar injection of 0.1 mL of 1% solution of carageenan in 0.9% strile saline was administered to the right hind foot pad. Paw volume was measured with a displacement plethysmometer 4 h after carrageenan injection.

Chemistry

All solvents were dried and freshly distilled. Melting points were determined using Yanaco melting point apparatus and are uncorrected. ^{1}HNMR were recorded on a Bruker AM-300 (300 MHz) spectrometer. Elemental analyses were performed at analytical division of Institute of Material Medica and were within 0.4% of the calculated values.

The general procedure for the preparation of substituted 2-sulfonylphenyl-3-phenyl-indoles (5a–5n) is illustrated below in the synthesis of 2-(4-aminosulfonylphenyl)-3-phenyl-indole (5a). 2-(4-Aminosulfonylphenyl)-3-phenyl-indole (5a)

Step 1: *p*-Toluenesulfonylanthranilic acid (2).[47] Anthranilic acid (1) (13.7 g, 0.1 mol) was added in three

portions to the warmed solution of 26.0 g of sodium carbonate in 150 mL of water, 23.0 g (0.12 mol) of *p*-toluenesulfonyl chloride was added to the solution in 5 portions over a period of 20 min. The reaction mixture was warmed at 60–70 °C for additional 0.5 h, and raised to 85 °C, 1.0 g of Norit was added cautiously and the solution was fitered. The filtrate was cooled and acidified with dilute HCl, the product was collected and washed with dilute hydrochloric acid and then water. Recrystallization from 95% ethanol there was obtained the title compound (20.0 g) as white crystal, yield 68.7%, mp 229–232 °C.

Step 2: 2-amino-benzophenone (3a).[47] A mixture of 14.6 g (0.050 mol) of *p*-toluenesulfonylanthranilic acid (**2**) and 11.9 g (0.057 mol) of phosphorus pentachloride in 150 mL of dry benzene was heated to about 50 °C for 0.5 h. Cooled to 20–25 °C, 29.0 g (0.218 mol) of anhydrous aluminum chloride was added in portions. When addition was complete, the mixture was heated at 80–90 °C for 4 h and then cooled, poured onto a mixture of ice and 60 mL of 1 N hydrochloride acid. The benzene was removed by vacuo distillation, the crude product was collected by filtration and washed with sodium carbonate and water. The filter cake is dissolved in 160 mL of concd sulfuric acid and heated to 120 °C for 15 min. The reaction mixture was cooled and poured onto a mixture of ice and 1 g of norit, and the solution is filtered. The filtrate was neutralized with 12 N ammonium hydroxide. The solid was filtered off, washed with water, dried and recrystallized from 95% ethanol to give the title compound (6.63 g) as yellow crystal, yield 65.0%, mp 105–106 °C.

Step 3: 2-*N*-(4-aminosulfonylbenzoyl)-amide-benzophenone (4a). To a solution of 2.0 g (0.010 mol) of 2-aminobenzophenone (**3a**), 1.6 mL (0.011 mol) of triethylamine in 20 mL of dry THF under nitrogen was added a solution of 2.0 g (0.010 mol) of 4-aminosulfonylbenzoyl chloride in 10 mL of dry THF. The reaction mixture was stirred at room temperature for 2 h, and filtered. The filtrate was concentrated and the residue was purified by column chromatograph on silica gel (eluent: petroleum ether–ethyl acetate, 1:1) to give the title compound as white needle crystal, yield 59.5%, mp 216–218 °C; anal. calcd for: $C_{20}H_{16}N_2O_4S$: C 63.15, H 4.24, N 7.36; found: C 63.37, H 4.36, N 7.44.

Step 4: 2-(4-aminosulfonylphenyl)-3-phenyl-indole (5a). 2-N-(4 - aminosulfonylbenzoyl) - amide - benzophenone (**4a**) (1.04 g, 3 mmol), 0.87 g (12 mmol) of 90% Zn was suspended in 20 mL dry THF. To the mixture 0.7 mL (6.2 mmol) of $TiCl_4$ was added dropwise and heated to reflux for 1.5 h. The solvent was removed in vacuo and the residue was purified by column chromatography using petroleum ether–ethyl acetate (3:1) as elutant. The title compound (0.45 g) was obtained as white crystal, yield 43.9%, mp 231–232 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.03 (s, 2H, SO_2NH_2), 7.03–7.49 (m, 9H, Ar–H), 7.65–7.89(dd, 4H, Ar–H), 10.8 (s, 1H, N-H); anal. calcd for: $C_{20}H_{16}N_2O_2S$: C 68.94, H 4.63, N 8.04; found: C 68.99, H 4.61, N 8.18.

The following compounds (**5b–5n**) were prepared according to the general procedure described above.

2-(4-Methylsulfonylphenyl)-3-phenyl-indole (5b). The title compound was obtained as white crystal, yield 56.2%, mp 221–222 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.23 (s, 3H, SO_2CH_3), 7.03–7.49 (m, 9H, Ar–H), 7.55–8.15 (dd, 4H, Ar–H), 11.67 (s, 1H, N–H). Anal. calcd for: $C_{21}H_{17}NO_2S$: C 72.60, H 4.93, N 4.03; Found: C 72.39, H 5.14, N 3.83.

2-(4-Aminosulfonylphenyl)-3-(4-fluorophenyl)-indole (5c). The title compound was obtained as white crystal, yield 54.3%, mp 228–230 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.33 (s, 2H, SO_2NH_2), 7.04–7.80 (m, 12H, Ar–H), 11.71 (s, 1H, N–H); anal. calcd for: $C_{20}H_{15}N_2FO_2S$: C 65.56, H 4.13, N 7.65; found: C 65.46, H 4.23, N 7.35.

2-(4-Methylsulfonylphenyl)-3-(4-fluorophenyl)-indole (5d). The title compound was obtained as white crystal, yield 75.3%, mp 224–226 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.24 (s, 3H, SO_2CH_3), 7.04–7.91 (m, 12H, Ar–H), 11.77 (s, 1H, N-H); anal. calcd for: $C_{21}H_{16}NFO_2S$: C 69.02, H 4.41, N 3.83; found: C 69.19, H 4.56, N 4.00.

2-(4-Aminosulfonylphenyl)-3-(4-chlorophenyl)-indole (5e). The title compound was obtained as white crystal, yield 73.9%, mp 298–300 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.29 (s, 2H, SO_2NH_2), 7.05–7.50 (m, 8H, Ar–H), 7.53–7.81 (dd, 4H, Ar–H), 11.75 (s, 1H, N–H); anal. calcd for: $C_{20}H_{15}ClN_2O_2S$: C 62.74, H 3.95, N 7.35; found: C 62.68, H 3.77, N 7.44.

2-(4-Methylsulfonylphenyl)-3-(4-chlorophenyl)-indole (5f). The title compound was obtained as white crystal, yield 65.5%, mp 198.5–200.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H, SO_2CH_3), 7.16–7.85 (m, 12H, Ar–H), 8.65 (s, 1H, N–H); anal. calcd for: $C_{21}H_{16}ClNO_2S$: C 66.05, H 4.22, N 3.67; found: C 66.03, H 4.48, N 3.64.

2-(4-Aminosulfonylphenyl)-3-(4-bromophenyl)-indole (5g). The title compound was obtained as white crystal, yield 51.7%, mp 277–279 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (s, 2H, SO_2NH_2), 7.04–7.80 (m, 12H, Ar–H), 11.70 (s, 1H, N–H); anal. calcd for: $C_{20}H_{15}BrNO_2S$: C 56.21, H 3.54, N 6.56; found: C 56.46, H 3.70, N 6.72.

2-(4-Methylsulfonylphenyl)-3-(4-bromophenyl)-indole (5h). The title compound was obtained as white crystal, yield 75.2%, mp 225–226 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.09 (s, 3H, SO_2CH_3), 7.16–7.84 (m, 12H, Ar–H), 8.69 (s, 1H, N-H); anal. calcd for: $C_{21}H_{16}BrNO_2S$: C 59.16, H 3.78, N 3.29; found: C 59.04, H 3.85, N 3.20.

2-(4-Aminosulfonylphenyl)-3-(4-methoxyphenyl)-indole (5i). The title compound was obtained as white crystal, yield 73.9%, mp 280–282 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.28 (s, 2H, SO_2NH_2), 3.79 (s, 3H, OCH_3), 6.97–7.78 (m, 12H, Ar–H), 11.59 (s, 1H, N–H); anal. calcd for: $C_{21}H_{18}N_2O_3S$: C 66.65, H 4.79, N 7.40; found: C 66.35, H 5.02, N 6.86.

2-(4-Methylsulfonylphenyl)-3-(4-methoxyphenyl)-indole (5j). The title compound was obtained as white crystal, yield 74.7%, mp 218.5–220.5 °C; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 3.08 (s, 3H, SO_2CH_3), 3.87 (s, 3H, OCH_3), 6.95–7.86 (m, 12H, Ar–H), 8.41 (s, 1H, N–H); anal. calcd for: $C_{22}H_{19}NO_3S$: C 69.98, H 5.07, N 3.71; found: C 69.90, H 5.12, N 3.99.

2-(4-Aminosulfonylphenyl)-3-(4-methylphenyl)-indole (5k). The title compound was obtained as white crystal, yield 55.3%, mp 293–295 °C; ^{1}H NMR (300 MHz, DMSO) δ 2.34 (s, 3H, CH_3), 3.43 (s, 2H, SO_2NH_2), 7.01–7.77 (m, 12H, Ar–H), 11.59 (s, 1H, N–H); anal. calcd for: $C_{21}H_{18}N_2O_2S$: C 69.60, H 5.01, N 7.73; found: C 69.45, H 5.25, N 7.53.

2-(4-Methylsulfonylphenyl)-3-(4-methylphenyl)-indole (5l). The title compound was obtained as white crystal, yield 77.4%, mp 197–198 °C; ^{1}H NMR (300 MHz, DMSO) δ 2.35(s, 3H, CH_3), 3.21 (s, 3H, SO_2CH_3), 7.01–7.88 (m, 12H, Ar–H), 11.64 (s, 1H, N–H); anal. calcd for: $C_{22}H_{19}NO_2S$: C 73.10, H 5.02, N 3.88; found: C 72.82, H 5.42, N 3.97.

2-(4-Aminosulfonylphenyl)-3-(3,4-dimethylphenyl)-indole (5m). The title compound was obtained as white crystal, yield 49.6%, mp 251–253 °C; ^{1}H NMR (300 MHz, DMSO) δ 2.24 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.43 (s, 2H, SO_2NH_2), 7.00–7.78 (m, 11H, Ar–H), 11.64 (s, 1H, N-H); anal. calcd for: $C_{22}H_{20}N_2O_2S$: C 70.19, H 5.35, N 7.44; found: C 70.13, H 5.42, N 7.33.

2-(4-Methylsulfonylphenyl)-3-(3,4-dimethylphenyl)-indole (5n). The title compound was obtained as white crystal, yield 67.0%, mp 206–207 °C; ^{1}H NMR (300 MHz, DMSO) δ 2.23 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.21 (s, 3H, SO_2CH_3), 6.99–7.88 (m, 11H, Ar–H), 11.62 (s, 1H, N–H); anal. calcd for: $C_{23}H_{21}NO_2S$: C 73.57, H 5.64, N 3.73; found: C 73.32, H 5.65, N 3.58.

2-(4-Aminosulfonylphenyl)-3-(4-hydroxyphenyl)-indole (5o). 2-(4-Aminosulfonylphenyl)-3-(4-methoxyphenyl)-indole (5i) (300 mg, 0.79 mmol) was suspended in 20 mL of CH_2Cl_2 cooled in an ice-salt bath and the cold solution of 0.41 mL (4.4 mmol) of BBr_3 in 5 mL of CH_2Cl_2 was added in dropwise. When addition was complete, the ice-salt bath was removed and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed and the residue was purified by column chromtography eluting with 3:1 petroleum: ethyl acetate to give 180 mg of title compound as light yellow crystal, yield 62.31%, mp 241–243 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.26 (s, 2H, SO_2NH_2), 6.80–7.77 (m, 11H, Ar–H), 9.43 (s, 1H, OH), 11.56 (s, 1H, N–H); anal. calcd for: $C_{20}H_{16}N_2O_3S$: C 56.92, H 4.43, N 7.69; Found: C 56.81, H 4.34, N 7.47.

2-(*N*-Acetamide-sulfonylphenyl)-3-phenyl-indole (5p). To a solution of 1.5 g (4.3 mmol) of 2-(4-aminosulfonylphenyl)-3-phenyl-indole (5a), 5 mg of DMAP and 0.5 g (5.2 mmol) of triethylamine in 20 mL dry THF was added dropwise 0.5 g (5.2 mmol) of acetic anhydride. The reaction mixture was stirred at room temperature for 5 h and then the solvent was removed in vacuo. The residue was crystallized from dichloromethane to afford 1.0 g of the title compound as needle yellow crystal, yield 59.30%, mp 221–222 °C; ^{1}H NMR (300 MHz, DMSO) δ 1.92(s, 3H, CH_3), 7.05–7.86 (m, 13H, Ar–H), 11.69 (s, 1H, N–H), 12.04 (s, 1H, N–H); anal. calcd for: $C_{22}H_{18}N_2O_3S$: C 67.67, H 4.65, N 7.17; Found: C 67.79, H 4.68, N 7.08.

The general procedure for the preparation of substituted 2-sulfonylphenyl-3-phenyl-indole (9a–9n) is illustrated below in the synthesis of 2-(4-aminosulfonylphenyl)-3-(4-chlorophenyl)-5-chloro-indole (9a). 2-(4-aminosulfonylphenyl)-3-(4-chlorophenyl)-5-chloro-indole (9a)

Step 1: 2-amino-5-chloro-4′-chloro-benzophenone (7a). A mixture of 21.0 g (0.135 mol) of *p*-chlorobenzoic acid (6) and 20 mL of thionyl chloride was heated under reflux to give a clear solution. Removal of the excess of thionyl chloride under reduced pressure obtained white solid and immediately used for the next reaction. To the benzoyl chloride heated to 120 °C was added in portions with stirring 6.3 g (0.05 mol) of 4-chloroaniline. The mixture was heated to 180 °C and 8.5 g (0.063 mol) of $ZnCl_2$ was added. The temperature was gradually increased to about 205 °C and kept there for 2 h. After cooling to 120 °C, 60 mL of 3 N HCl was added and the mixture stirred and heated to reflux. The hot acid layer was decanted and this procedure repeated two or three times. The water-insoluble residue was dissolved in 80 mL of 70% sulfuric acid and reflux for 8 h and then, after cooling poured into a large amount of ice water. The reaction mixture was neutralized with aqueous ammonia hydroxy and extracted with ethyl acetate, dried over Na_2SO_4. The solvent was removed and the residue was crystallized from 95% ethanol to give the title compound as golden yellow crystal 5.1 g, yield 38.5%, mp 106–107 °C; HRMS *m*/*e* calcd, 265.006119; found, 265.008696.

Step 2: 2-N-(4-aminosulfonylbenzoyl)-amide-5-chloro-4′-chloro-benzophenone (8a). The procedure is in the same manner as described in the preparation of **4a**. The title compound was obtained as needle yellow crystal, yield 76.2%, mp 234–236 °C; HRMS *m*/*e* calcd, 448.005134; found, 448.005693.

Step 3: 2-(4-aminosulfonylphenyl)-3-(4-chlorophenyl)-5-chloro-indole (9a). The procedure is in the same manner as described in the preparation of **5a**. The title compound was obtained as white crystal, yield 71.8%, mp 245–247 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.32 (s, 2H, SO_2NH_2), 7.20–7.83 (m, 11H, Ar–H), 12.00 (s, 1H, N–H); anal. calcd for: $C_{20}H_{14}N_2O_2SCl_2$: C 57.56, H 3.38, N 6.71; found: C 57.65, H 3.34, N 6.56.

The following compounds (9b–9o) were prepared according to the general procedure described above.

2-(4-Methylsulfonylphenyl)-3-(4-chlorophenyl)-5-chloro-indole (9b). The title compound was obtained as white crystal, yield 76.9%, mp 281–283 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.26 (s, 3H, SO_2CH_3), 7.22–7.95 (m, 11H, Ar–H), 12.06 (s, 1H, N-H); anal. calcd for: $C_{21}H_{15}NO_2SCl_2$: C 60.58, H 3.63, N 3.36; found: C 60.72, H 3.79, N 3.30.

2-(4-Aminosulfonylphenyl)-3-(3-chlorophenyl)-5-chloro-indole (9c). The title compound was obtained as white crystal, yield 68.2%, mp 249–251 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.27 (s, 2H, SO_2NH_2), 7.21–7.84 (m, 11H, Ar–H), 12.00 (s, 1H, N–H); anal. calcd for: $C_{20}H_{14}NO_2SCl$: C 57.56, H 3.38, N 6.71; found: C 57.53, H 3.44, N 6.43

2-(4-Methylsulfonylphenyl)-3-(3-chlorophenyl)-5-chloro-indole (9d). The title compound was obtained as white crystal, yield 56.0%, mp 254–257 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.26 (s, 3H, SO_2CH_3), 7.22–7.96 (m, 11H, Ar–H), 12.10 (s, 1H, N–H); anal. calcd for: $C_{21}H_{15}NO_2SCl_2$: C 60.58, H 3.63, N 3.36; found: C 60.56, H 3.75, N 3.34.

2-(4-Aminosulfonylphenyl)-3-(2-chlorophenyl)-5-chloro-indole (9e). The title compound was obtained as white crystal, yield 47.6%, mp 268–240 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.28 (s, 2H, SO_2NH_2), 7.10–7.77 (m, 11H, Ar–H), 12.01 (s, 1H, N–H); anal. calcd for: $C_{20}H_{14}N_2O_2SCl$: C 57.56, H 3.38, N 6.71; found: C 57.30, H 3.48, N 6.15.

2-(4-Methylsulfonylphenyl)-3-(2-chlorophenyl)-5-chloro-indole (9f). The title compound was obtained as white crystal, yield 70.2%, mp 300–301.5 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.23 (s, 3H, SO_2CH_3), 7.10–7.91 (m, 11H, Ar–H), 12.13 (s, 1H, N–H); anal. calcd for: $C_{21}H_{15}NO_2SCl_2$: C 60.58, H 3.63, N 3.36; Found: C 60.59, H 3.62, N 3.40.

2-(4-Aminosulfonylphenyl)-3-phenyl-5-fluoro-indole (9g). The title compound was obtained as white crystal, yield 59.3%, mp 302–304 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.35 (s, 2H, SO_2NH_2), 7.01–7.79 (m, 12H, Ar–H), 11.82 (s, 1H, N–H); anal. calcd for: $C_{20}H_{15}N_2FO_2S$: C 65.56, H 4.13, N 7.65; found: C 65.46, H 4.16, N 7.43.

2-(4-Methylsulfonylphenyl)-3-phenyl-5-fluoro-indole (9h). The title compound was obtained as white crystal, yield 79.8%, mp 243–245 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.24 (s, 3H, SO_2CH_3), 7.02–7.91 (m, 12H, Ar–H), 11.89 (s, 1H, N–H); anal. calcd for: $C_{21}H_{16}NFO_2S$: C 69.02, H 3.83, N 4.41; found: C 69.18, H 4.34, N 3.65.

2-(4-Aminosulfonylphenyl)-3-phenyl-5-chloro-indole (9i). The title compound was obtained as white crystal, yield 27.5%, mp 297–299 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.32 (s, 2H, SO_2NH_2), 7.18–7.79 (m, 12H, Ar–H), 11.94 (s, 1H, N–H); anal. calcd for: $C_{20}H_{15}ClN_2O_2S$: C 62.74, H 3.95, N 7.32; found: C 62.59, H 4.08, N 7.30.

2-(4-Methylsulfonylphenyl)-3-phenyl-5-chloro-indole (9j). The title compound was obtained as white crystal, yield 84.3%, mp 281–283 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.24 (s, 3H, SO_2CH_3), 7.20–7.91 (m, 12H, Ar–H), 12.00 (s, 1H, N–H); anal. calcd for: $C_{21}H_{16}ClNO_2S$: C 66.05, H 4.22, N 3.67; found: C 66.11, H 4.04, N 3.91.

2-(4-Aminosulfonylphenyl)-3-phenyl-5-bromo-indole (9k). The title compound was obtained as white crystal, yield 55.3%, mp 310–312 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.31 (s, 2H, SO_2NH_2), 7.29–7.78 (m, 12H, Ar–H), 11.94 (s, 1H, N–H); anal. calcd for: $C_{20}H_{15}N_2O_2SBr$: C 56.23, H 3.54, N 6.56; found: C 56.45, H 3.76, N 6.60.

2-(4-Methylsulfonylphenyl)-3-phenyl-5-bromo-indole (9l). The title compound was obtained as white crystal, yield 69.1%, mp 262–264 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.23 (s, 3H, SO_2CH_3), 7.30–7.90 (m, 12H, Ar–H), 12.01 (s, 1H, N–H); anal. calcd for: $C_{21}H_{16}NO_2SBr$: C 59.17, H 3.78, N 3.29; found: C 59.11, H 3.71, N 3.44.

2-(4-Aminosulfonylphenyl)-3-phenyl-5-methyl-indole (9m). The title compound was obtained as white crystal, yield 76.2%, mp 242–244 °C; ^{1}H NMR (300 MHz, DMSO) δ 2.36 (s, 3H, CH_3), 3.32 (s, 2H, SO_2NH_2), 7.01–7.77 (m, 12H, Ar–H), 11.57 (s, 1H, N–H); anal. calcd for: $C_{21}H_{18}N_2O_2S$: C 69.59, H 5.01, N 7.73; found: C 69.78, H 4.95, N 7.71.

2-(4-Methylsulfonylphenyl)-3-phenyl-5-methyl-indole (9n). The title compound was obtained as white crystal, yield 71.8%, mp 245–247 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.21 (s, 3H, SO_2CH_3), 7.20–7.83 (m, 11H, Ar–H), 12.00 (s, 1H, N–H); anal. calcd for: $C_{20}H_{14}N_2O_2SCl_2$: C 57.56, H 3.38, N 6.71; found: C 57.65, H 3.34, N 6.56.

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