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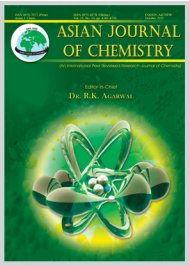

Synthesis and Biological Evaluation of Benzothiazole Incorporated 1-Phenylsulfonylindole-3-acetamide Derivatives

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Indole-3-acetic acid was esterified to give methyl ester (**2**), which was treated with substituted aromatic sulphonyl chloride in alkaline media to give 2-[1-(phenyl sufonyl-1*H*-indole-3-yl]methyl acetate (**3**). Further the compound **3** was converted to acid (**4**). Finally compound **4** was coupled with 6-substituted benzothiazole-2-amines by means of EDC to give acetamide derivatives (**5a-i**). The structures of the newly synthesized compounds have been established by analytical and spectral methods. These compounds have also been screened for analgesic activity.

Key Words: Indole-3-acetic acid, Indole, Analgesic, Benzothiazole.

INTRODUCTION

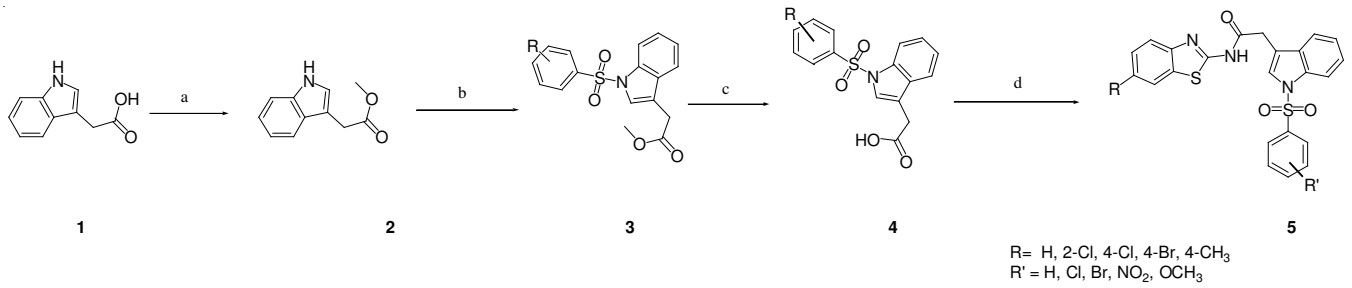
Indole ring system present in various natural and marine alkaloids holds a number of exciting therapeutic potentials[1-7]. While the synthetic origin indole derivatives show good possibilities towards antiinflammatory activity including various other biological activities[8-12]. Various Indole amides also displayed specific cyclooxygenase-2 inhibition activity[13-16]. In view of this, the synthesis of title compounds have been undertaken. For the purpose indole-3-acetic acid (**1**) was esterified and the resulting methyl ester (**2**) was treated with substituted aromatic sulfonyl chloride in alkaline media to give 2-[1-(phenyl sufonyl-1*H*-indole-3-yl]methyl acetate (**3**). Further the compound **3** was converted to acid (**4**). Finally compound **4** was coupled with 6-substituted benzothiazole-2-amines by means of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) to give acetamide derivatives (**5**). Syntheses of all compounds are given under **Scheme-I**.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra (KBr, cm^{-1}) were recorded on Shimadzu 8400S FTIR spectrophotometer. ^1H NMR spectra were recorded on BRUKER 300 MHz NMR spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard (chemical shift in δ ppm). The course of all the reaction and purities of final products were checked by means of TLC. Crystalline samples of sulphonyl derivatives were grown from ethanol.

General procedure for synthesis of 2-(1*H*-indol-3-yl) methyl acetate (2): The equimolar quantities (5.3 mmol) of indole-3-acetic acid and *p*-toluene sulfonic acid was dissolved in anhydrous methanol (70 mL), the reaction mixture was refluxed for 8 h. The completion of reaction was monitored by TLC (alumina, ethyl acetate). After being cooled to ambient temperature, the methanol solvent was evaporated. Small amount of ethyl acetate was added to the residue and then added saturated aqueous solution of sodium bicarbonate. Additional ethyl acetate was added to extract the maximum product. The organic layer was rinsed with brine, dried over $MgSO_4$, filtered and concentrated to give the methyl ester. Yield 91 %; m.p. 50-52 ºC; R_f -COOH= 0.1, -COOR= 0.9; IR (KBr, ν_{max}, cm^{-1}): 1275 (C-N), 1450 (n, Ar-C=C), 1600 (n Ar-C=C), 1620 (C=C), 1739 (C=O), 3000 (C-H), 3300 (sec. NH); ^1H NMR ($CDCl_3$): 3.5 (2H, CH, methylene), 3.9 (3H, CH, methyl), 6.6 (1H, CH, 2-indole), 7.1-7.5 (4H, Ar-H, indole), 9.6 (1H, NH, indole).

General method of synthesis for 2-[1-(substituted phenylsulfonyl)-1*H*-indol-3-yl]methyl acetate (3): Compound **2** (1 mol) was reacted with 10 % KOH (4 mol) and the solution of substituted benzene sulphonyl chloride (1.5 mol) slowly with constant shaking. It was acidified with dil. HCl and the product was filtered off and re-crystallized from ethanol.



a= MeOH, p-toluenesulfonic acid, reflux 8h; b=10% KOH, aromatic sulphonyl chloride; c= LiOH, THF, d= 2-amino benzothiazoles, $CHCl_3$, pyridine, EDC

Scheme-I: Schematic representation of synthesis of compounds **5a-i**

2-[1-(Phenylsulfonyl)-1*H*-indol-3-yl]methyl acetate (3a): Yield 75 %; m.p. 141-142 ºC; R_f = 0.64; IR (KBr, ν_{max}, cm^{-1}): 1050 (S=O), 1177 (C-N), 1610 (n Ar-C=C), 1640 (C=C), 1750 (C=O), 3000 (C-H); ^{1}H NMR ($CDCl_3$) δ: 3.39 (s, CH_2, methylene), 3.67 (s, 3H, CH_3, methyl), 6.80 (s, 1H, CH, 2-indole), 7.18 (m, 4H, Ar-H, indole), 7.6-8.0 (4H, Ar-H, phenyl).

2-[1-(4-Chlorophenylsulfonyl)-1*H*-indol-3-yl]methyl acetate (3b): Yield 72 %; m.p. 142-144 ºC; IR (KBr, ν_{max}, cm^{-1}): 1075 (R-S=O-R'), 1177 (C-N), 1610 (n Ar-C=C), 1640 (C=C), 1750 (C=O), 3000 (C-H); ^{1}H NMR ($CDCl_3$) δ: 3.39 (s, CH_2, methylene), 3.67 (s, 3H, CH_3, methyl), 6.80 (s, 1H, CH, 2-indole), 7.18 (m, 4H, Ar-H, indole), 7.5-7.7 (4H, Ar-H, phenyl).

2-[1-(4-Bromophenylsulfonyl)-1*H*-indol-3-yl]methyl acetate (3c): Yield 65 %; m.p. 160-162 ºC; IR (KBr, ν_{max}, cm^{-1}): 1055 (R-S=O-R'), 1099 (C-N), 1590 (n Ar-C=C), 1635 (C=C), 1750 (C=O), 3000 (C-H); ^{1}H NMR ($CDCl_3$) δ: 3.6 (s, CH_2, methylene), 3.8 (s, 3H, CH_3, methyl), 6.80 (s, 1H, CH, 2-indole), 7.2 (m, 4H, Ar-H, indole), 7.6-8.0 (4H, Ar-H, phenyl).

2-[1-(2-Chlorophenylsulfonyl)-1*H*-indol-3-yl]methyl acetate (3d): Yield 75 %; m.p. 181-182 ºC; IR (KBr, ν_{max}, cm^{-1}): 1079 (R-S=O-R'), 1181 (C-N), 1630 (n Ar-C=C), 1650 (C=C), 1770 (C=O), 2995 (C-H); ^{1}H NMR ($CDCl_3$) δ: 3.5 (s, CH_2, methylene), 3.8 (s, 3H, CH_3, methyl), 6.6 (s, 1H, CH, 2-indole), 7.6 (m, 4H, Ar-H, indole), 7.6-7.8 (4H, Ar-H, phenyl).

2-[1-(4-Methylphenylsulfonyl)-1*H*-indol-3-yl]methyl acetate (3e): Yield 72%; m.p. 168-170 ºC; IR (KBr, ν_{max}, cm^{-1}): 1070 (R-S=O-R'), 1170 (C-N), 1600 (n Ar-C=C), 1642 (C=C), 1755 (C=O), 3010 (C-H); ^{1}H NMR ($CDCl_3$) δ: 3.45 (s, CH_2, methylene), 3.55 (s, 3H, CH_3, methyl), 6.88 (s, 1H, CH, 2-indole), 7.5 (m, 4H, Ar-H, indole), 7.5-7.6 (4H, Ar-H, phenyl).

General method of synthesis of 2-[1-(4-substituted phenylsulfonyl)-1*H*-indol-3-yl]acetic acid (4a-e): A solution of lithium hydroxide monohydrate (3 mol) in water (1 mL/mmol of ester) was added to a stirred solution of the ester (**3a-e**) in methanol (1 mL/mmol) and THF (1 mL/mmol). The suspension was stirred for 8-10 h and then concentrated in vacuum. The residue was diluted with water and acidified with 6 N HCl, then extracted three times with diethyl ether. The organic extracts were combined and rinsed twice with water and brine. The product was dried over $MgSO_4$ to get the crude acid. Yield: 80 %; m.p. 164-166 ºC; R_f = 0.21; IR (KBr, ν_{max}, cm^{-1}): 1150 (C-N), 1490 (n, Ar C=C), 1600 (n Ar-C=C), 1610 (C=C, indole), 1695 (n, C=O), 3050 (b, C-H), 3990 (b, O-H); ^{1}H NMR ($CDCl_3$) δ: 3.3 (2H, CH_2, methylene), 6.89 (1H, CH, indole), 7.18 (4H, Ar-H, indole), 7.3 (4H, phenyl), 10.9 (1H, O-H).

General method of synthesis of 2-[1-(phenylsulfonyl)-1*H*-indol-3-yl]N-(6-substituted benzothiazol-2-yl) acetamide 5(a-i): A solution of the 6-substituted 2-amino benzothiazole (1 mol) and compound **4** (1.5 mol) was stirred in chloroform (100 mL) was added to pyridine (100 mL) containing 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 1.5 mol) at 0 ºC and the mixture was stirred at ambient temperature for 8-18 h. The solvents were evaporated and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 times). The organic layers were combined and rinsed with brine (2 times), dried over $MgSO_4$, filtered and concentrated to give the amide.

2-[1-(Phenylsulfonyl)-1*H*-indol-3-yl]N-(benzothiazol-2-yl) acetamide (5a): Yield = 90 %; m.p. 179-181 ºC; R_f = 0.45; IR (KBr, ν_{max}, cm^{-1}): 1050 (S=O),1100 (C-N), 1450 (n, Ar-C=C), 1600 (n Ar-C=C), 1620 (C=C, indole), 1640 (C=N), 1710 (n, C=O), 3300 (b, sec. N-H); ^{1}H NMR ($CDCl_3$) δ: 3.3 (2H, CH_2, methylene), 6.6 (1H, CH, indole), 7.2 (4H, Ar-H, indole), 7.3-7.5 (4H, Ar-H, phenyl), 7.5-8.3 (4H, Ar-H, benzothiazole), 7.9 (1H, NH, acetamide).

2-[1-(4-Chlorophenylsulfonyl)-1*H*-indol-3-yl]N-(benzothiazol-2-yl) acetamide (5b): Yield = 85 %; m.p. 155-157 ºC; IR (KBr, ν_{max}, cm^{-1}): 1045 (S=O),1090 (C-N), 1410 (n, Ar-C=C), 1610 (n Ar-C=C), 1640 (C=C, indole), 1650 (C=N), 1675 (n, C=O), 3250 (b, sec. N-H); ^{1}H NMR ($CDCl_3$) δ: 3.19 (2H, CH_2, methylene), 6.5 (1H, CH, indole), 7.1 (4H, Ar-H, indole), 7.2-7.25 (3H, Ar-H, phenyl), 7.15-8.8 (4H, Ar-H, benzothiazole), 8.0 (1H, NH, acetamide).

2-[1-(4-Bromophenylsulfonyl)-1*H*-indol-3-yl]N-(benzothiazol-2-yl) acetamide (5c): Yield = 79%; m.p. 185-187 ºC; IR (KBr, ν_{max}, cm^{-1}): 1045 (S=O),1088 (C-N), 1425 (n, Ar-C=C), 1600 (n Ar-C=C), 1620 (C=C, indole), 1650 (C=N), 1675 (n, C=O), 3275 (b, sec. N-H); ^{1}H NMR ($CDCl_3$) δ: 3.19 (2H, CH_2, methylene), 6.4 (1H, CH, indole), 7.0 (4H, Ar-H, indole), 7.1-7.25 (3H, Ar-H, phenyl), 7.5-8.8 (4H, Ar-H, benzothiazole), 8.0 (1H, NH, acetamide).

2-[1-(4-Methylphenylsulfonyl)-1*H*-indol-3-yl]N-(benzothiazol-2-yl) acetamide (5d): Yield = 79%; m.p. 201-203 ºC; IR (KBr, ν_{max}, cm^{-1}): 1045 (S=O),1088 (C-N), 1425

(n, Ar-C=C), 1600 (n Ar-C=C), 1620 (C=C, indole), 1650 (C=N), 1675 (n, C=O), 3275 (b, sec. N-H); ^{1}H NMR ($CDCl_3$) δ: 2.4 (3H, CH, methyl), 3.19 (2H, CH_2, methylene), 6.4 (1H, CH, indole), 7.0 (4H, Ar-H, indole), 7.1-7.25 (3H, Ar-H, phenyl), 7.5-8.8 (4H, Ar-H, benzothiazole), 8.0 (1H, NH, acetamide).

2-[1-(4-Methoxyphenylsulfonyl)-1*H*-indol-3-yl]N-(benzothiazol-2-yl) acetamide (5e): Yield = 65 %; m.p. 154-157 ºC; IR (KBr, ν_{max}, cm^{-1}): 1045 (S=O),1090 (C-N), 1410 (n, Ar-C=C), 1600 (n Ar-C=C), 1620 (C=C, indole), 1640 (C=N), 1675 (n, C=O), 3300 (b, sec. N-H); ^{1}H NMR ($CDCl_3$) δ: 3.3 (2H, CH2, methylene), 6.6 (1H, C-H, indole), 7.2 (4H, Ar-H, indole), 7.0-7.6 (3H, Ar-H, phenyl), 7.9-8.3 (4H, Ar-H, benzothiazole), 9.9 (1H, NH, acetamide).

2-[1-(Phenylsulfonyl)-1*H*-indol-3-yl]N-(6-chlorobenzothiazol-2-yl) acetamide (5f): Yield = 89 %; m.p. 220-222 ºC; IR (KBr, ν_{max}, cm^{-1}): 1050 (S=O),1090 (C-N), 1400 (n, Ar-C=C), 1600 (n Ar-C=C), 1645 (C=C, indole), 1665 (C=N), 1700 (n, C=O), 3275 (b, sec. N-H); ^{1}H NMR ($CDCl_3$) δ: 3.29 (2H, CH_2, methylene), 6.2 (1H, C-H, indole), 6.9 (4H, Ar-H, indole), 7.0-7.6 (4H, Ar-H, phenyl), 7.2-8.0 (3H, Ar-H, benzothiazole), 9.6 (1H, NH, acetamide).

2-[1-(Phenylsulfonyl)-1*H*-indol-3-yl]N-(6-bromobenzothiazol-2-yl) acetamide (5g): Yield = 68 %; m.p. 170-172 ºC; IR (KBr, ν_{max}, cm^{-1}): 1050 (S=O),1100 (C-N), 1400 (n, Ar-C=C), 1620 (n Ar-C=C), 1640 (C=C, indole), 1660 (C=N), 1720 (n, C=O), 3300 (b, sec. N-H); ^{1}H NMR ($CDCl_3$) δ: 3.2 (2H, CH_2, methylene), 6.5 (1H, C-H, indole), 6.19 (4H, Ar-H, indole), 7.2-7.6 (4H, Ar-H, phenyl), 7.5-8.5 (3H, Ar-H, benzothiazole), 10.1 (1H, NH, acetamide).

2-[1-(Phenylsulfonyl)-1H-indol-3-yl]N-(6-nitrobenzothiazol-2-yl) acetamide (5h): Yield = 72 %; m.p. 191-192 ºC; IR (KBr, ν_{max}, cm^{-1}): 1050 (S=O),1100 (C-N), 1350 (n, Ar-C=C), 1525 (NO_2), 1620 (n Ar-C=C), 1640 (C=C, indole), 1680 (C=N), 1700 (n, C=O), 3300 (b, sec. N-H); ^{1}H NMR ($CDCl_3$) δ: 3.39 (2H, CH_2, methylene), 6.5 (1H, C-H, indole), 7.3 (4H, Ar-H, indole), 7.5-7.9 (4H, Ar-H, phenyl), 8.15-9.0 (3H, Ar-H, benzothiazole), 9.1 (1H, NH, acetamide).

2-[1-(Phenylsulfonyl)-1H-indol-3-yl]N-(6-methoxybenzothiazol-2-yl) acetamide (5f): Yield = 75%; m.p. 130-132 ºC; IR (KBr, ν_{max}, cm^{-1}): 1050 (S=O),1100 (C-N), 1450 (n, Ar-C=C), 1610 (n Ar-C=C), 1645 (C=C, indole), 1650 (C=N), 1690 (n, C=O), 3300 (b, sec. N-H); ^{1}H NMR ($CDCl_3$) δ: 3.4 (2H, CH_2, methylene), 3.81(s, 3H, $-CH_3$), 6.6 (1H, C-H, indole), 6.9 (4H, Ar-H, indole), 7.0-7.6 (3H, Ar-H, phenyl), 7.18-8.1 (4H, Ar-H, benzothiazole), 8.5 (1H, NH, acetamide).

Analgesic and antiinflammatory activity: Analgesic activity was performed using albino rats, body wt. 75-150 g of both sexes. The compounds were dissolved in PEG 200 and administered through i.p. six animals per group were used with reference drug (aspirin) and with the synthesized compounds. Analgesic studies were done using tail flick response as described by Pandeya *et al.*[17]. The tail was subjected to radiant heat and the time to withdrawal (or flick) was recorded before and after 0.5 h of the drug administration. The cut-off value was one minute. All the test compounds were administered in a dose of 5 mg/kg.

RESULTS AND DISCUSSION

Result of analgesic activity is given in Table-1. All the synthesized compounds showed significant analgesic activity with a latent period in range 8.00 ± 0.30 - 18.00 ± 1.10 s. Compound **5d** was found to be most active with a latent period of 18.00 ± 1.10 s. However, none of the synthesized compounds was found to be more active than that of standard (aspirin). Finally, it is conceivable that further derivatization of such compounds will be of interest with the hope to get more potent, selective and analgesic agents.

TABLE-1
ANALGESIC ACTIVITY DATA OF COMPOUNDS **5a-5i**

Compound No.	Analgesic activity[a]	
	Control	Treated
5a	3.00 ± 0.50	14.80 ± 0.60
5b	4.60 ± 0.80	10.16 ± 0.50
5c	5.29 ± 0.45	15.30 ± 1.45
5d	5.00 ± 0.50	18.00 ± 1.10
5e	1.00 ± 1.00	9.16 ± 0.50
5f	3.00 ± 0.50	8.00 ± 0.30
5g	1.00 ± 0.60	10.00 ± 0.56
5h	2.00 ± 0.70	12.00 ± 0.40
5i	15.16 ± 0.70	10.50 ± 0.50
Acetylsalicylic acid[#]	7.00 ± 0.41	22.30 ± 1.10

Determined at dose of mg/kg between [a]Latent period of tail flick response(s), [#]Standard drug

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