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Synthesis of New Sulfonamide Derivatives of Tryptamine and Their Antimicrobial Activity

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ABSTRACT

A series of new sulfonamide derivatives of tryptamine as N-(2-(1H-indol-3-yl)ethyl)-substituted-sulfonamides ***7(a-j)*** *were synthesized by simple substitution of sulfonyl chlorides containing pharmacologically active functionalities* ***6(a-j)*** *with tryptamine* ***(5)*** *in presence of triethylamine. Structures of all the newly synthesized compounds were characterized by IR,* ^{1}H, ^{13}C *NMR, mass and elemental analysis. Antimicrobial activity of the title compounds was evaluated and minimum inhibitory concentrations (MICs) were also determined. A few of the titled compounds exhibited potential antibacterial and antifungal activities.*

Keywords: Tryptamine, Sulfonamide derivatives, Antimicrobial activity, Minimum inhibitory concentrations (MICs).

INTRODUCTION

Heterocyclic compounds are ubiquitous in pharmaceutical compounds [1]. Nitrogen containing heterocycles either natural or synthetic compounds are showing promising therapeutic activity. Among, indole is an important motif in many drugs and drug intermediates and their derivatives have been showed significant role in various pharmacological activities [2, 3]. Several compounds of this motif derivatives possess potent central nervous systems (CNS), agrochemicals perfumes, anti-inflammatory properties, pharmaceuticals and materials for alkaloids [4-7]. Tryptamine is a biologically active monoamino alkaloid found in plants, fungi, animals and in brains of mammals in trace amounts and is believed to play an important role as a neuromodulator or neurotransmitter [8]. The analogues of tryptamine such as α-methyltryptamine **(1)** is an antidepressant, stimulant, monoamine oxidase inhibitor and powerful psychedelic drug [9,10]. N,N-Dimethyltryptamine **(2)** is a hallucinogenic indole alkaloid that occurs naturally in a variety of plants and preparations used by ancient and modern South American cultures [11,12]. β_3-Adrenergic receptor (β_3-AR) has been shown to mediate for numerous pharmacological and physiological effects such as lipolysis, thermogenesis and relaxation of the urinary bladder. Activation of the β_3-AR is thought to be a possible approach for the treatment of obesity, noninsulin dependent diabetes mellitus (NIDDM) [13] and frequent urination [14]. Several groups have been focused for the development of potent β_3-AR agonists. A few tryptamine based molecules such as AJ-9677 **(3)**, compound **(4)** exhibited agonistic activity with excellent subtype selectivity.

Sulfonamides represent an important class of medicinally important compounds which are extensively used as antitumor [15], hypoglycaemic [16], anti-thyroid [17], anti-cabonic anhydrase [18], anti-inflammatory [19], diuretic [20], COX-inhibitors, the enzyme dihydropteroate synthetase (DHPS)-the key enzyme involved in folate synthesis, anti-impotence drugs [21] and also have been used as azo dyes for achieving improved light stability, water solubility and fixiation to fiber. Sulfonamide-based compounds were extensively used for antibacterial agents and are the second antimicrobial agents. These derivatives still widely used today for the treatment of various bacterial, protozoal and fungal infections [22] and the first effective chemotherapeutic agent used in safe therapeutic dosage ranges [23].

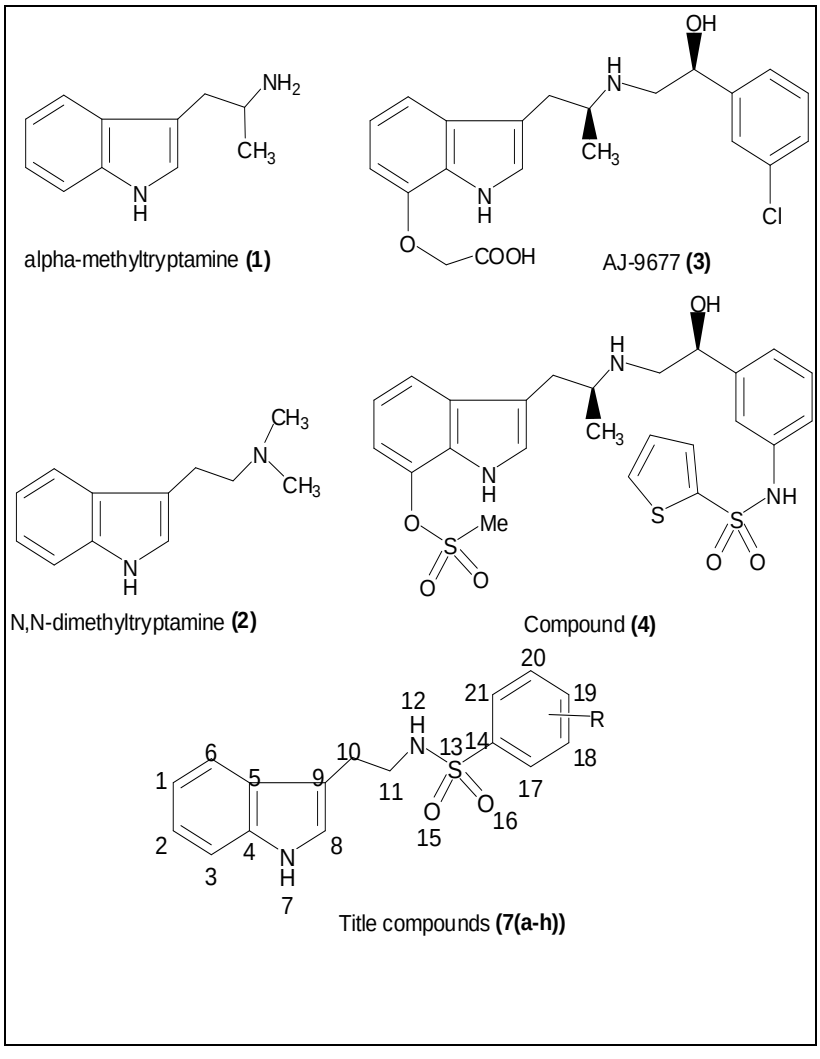


Figure. 1 Biologically active selected tryptamine derivatives

The biological potency, chemical applications and as pharmaceutical ingredients, sulfonamides and tryptamine derivatives find lot of importance in literature, here in we reported the synthesis of new class of sulfonamide derivatives N-(2-(1*H*-indol-3-yl)ethyl)-substituted-sulfonamides **7(a-j)** from tryptamine **(5)** by the reaction of sulfonylchlorides containing pharmacologically active functionalities **6(a-j)** in presence of triethylamine (TEA). All the structures of the synthesized compounds were confirmed by spectral studies. Antibacterial and antifungal activities of the titled compounds were evaluated.

MATERIALS AND METHODS

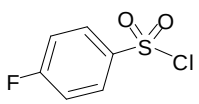
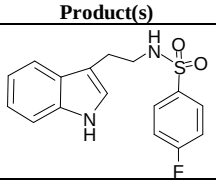
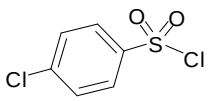
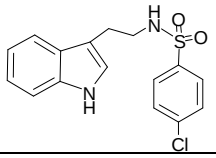
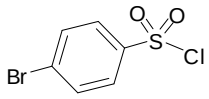
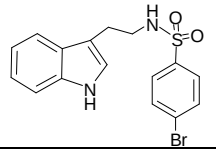
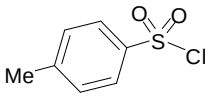
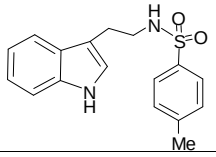
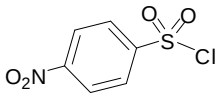
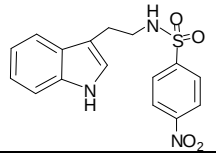
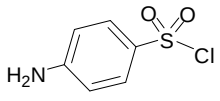
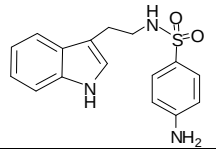
2.1 General Chemistry

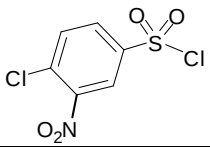
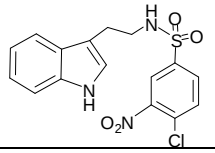
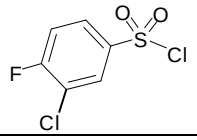
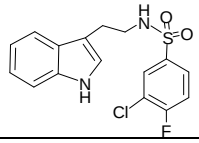
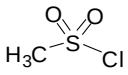
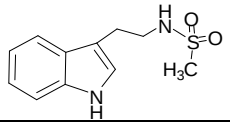
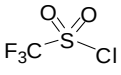
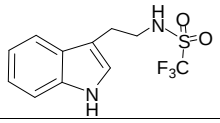
All chemicals were purchased from Merck, Aldrich and S. D. Fine. Chem. (India) and used without further purification. Melting points were determined in open capillaries on Guna digital melting point apparatus and are uncorrected. IR spectra were recorded on JASCO FT-IR 5300 using KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-500 spectrometer operating at 500 MHz for ^{1}H, 125 MHz for ^{13}C-NMR. Mass spectra were recorded on LCMS 2010A, SHIMADZU (positive mode). Perkin-Elmer 240C (Flash EA-1112 series) was used for C, H, N elemental analysis. Results are presented as, chemical shift δ in ppm, multiplicity, J values in Hertz (Hz). Multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), m (multiplet).

2.2 General Procedure for synthesis of N-(2-(1*H*-indol-3-yl)ethyl)-substituted-sulfonamides 7(a-j)

Tryptamine **(5)** (0.0012 mol, 1.2 eq) was dissolved in 10 mL of THF containing triethylamine (0.0015 mol, 1.5 eq) and 4-nitrophenylsulfonyl chloride **(6e)** (0.001 mol, 1 eq) was added. Reaction mixture was stirred for 3 h at 55-60 ^{o}C. TLC indicated the formation of product and completion of the reaction by disappearance of the sulfonyl chloride **6e**. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude content was washed with aqueous ammonium hydrogen chloride (3 × 20 mL) to remove unreacted amine followed by re-crystallization from methanol to afforded pure N-(2-(1*H*-indol-3-yl)ethyl)-4-nitrobenzenesulfonamide **(7e)**. This successive procedure was employed to synthesize remaining titled compounds.

Table-1: Physical characteristics of sulfonamide derivatives 7(a-j) of tryptamine

Compd	Sulfonyl chlorides	Product(s)	Time (h)	Yields (%)	M. P °C
7a			3.5	82	133-134
7b			3.5	80	127-129
7c			4.0	77	123-125
7d			4.0	76	110-113
7e			3.0	89	107-109
7f			3.75	75	140-142

7g			3.5	88	113-115
7h			4.0	80	108-111
7i			4.0	75	101-103
7j			3.0	79	113-115

N-(2-(1H-Indol-3-yl)ethyl)-4-fluorobenzenesulfonamide (7a):
Brown solid; IR (KBr, cm^{-1}): 3401 (indole –N-H, str), 3263 (-N-H, str), 2982 (=C-H, str), 2882 (-C-H, str), 1316 (-SO_2, asym str), 1154 (-SO_2, sym str), 1170 (Ar-F, str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.95 (t, J = 6.4 Hz, 2H, -CH_2-CH_2-NH), 3.28-3.30 (m, 2H, -CH_2-NH), 6.98 (s, 1H, Ar-H), 7.07 (t, J = 7.6 Hz, 1H, -SO_2-NH), 7.26 (s, 1H, Ar-H), 7.19-7.26 (m, 3H, Ar-H), 7.69-7.73 (m, 2H, Ar-H), 8.18 (s, br, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 29.7 (C_{10}), 43.1 (C_{11}), 114.3 (C_3), 111.4 (C_9), 116.1 ($C_{18,\ 20}$), 116.3 (C_6), 118.4 (C_1), 119.6 (C_2), 122.3 (C_8), 122.7 (C_5), 126.8 ($C_{17,\ 21}$), 135.7 (C_4), 136.4 (C_{14}), 166.2 ($C_{19,}$ C-F); LC-MS (m/z): 319 ($M+H^+$). Anal. Calcd. for $C_{16}H_{15}FN_2O_2S$: C, 60.36; H, 4.75; N, 8.80; Found: C, 60.21; H, 4.82; N, 8.67.

N-(2-(1H-Indol-3-yl)ethyl)-4-chlorobenzenesulfonamide (7b):
Brown solid; IR (KBr, cm^{-1}): 3401 (indole –N-H, str), 3258 (-N-H, str), 2983 (=C-H, str), 2876 (-C-H, str), 1342 (-SO_2, asym str), 1156 (-SO_2, sym str), 742 (-C-Cl, str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.94 (t, J = 6.3 Hz, 2H, -CH_2-CH_2-NH), 3.26 (m, 2H, -CH_2-NH), 6.96 (s, 1H, Ar-H), 7.03-7.08 (m, 3H, Ar-H), 7.19 (t, J = 7.5 Hz, 1H, -SO_2-NH), 7.26 (s, 1H, Ar-H), 7.34-7.40 (m, 2H, Ar-H), 7.62 (d, J = 7.6 Hz, 2H, Ar-H), 8.07 (s, br, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 29.3 (C_{10}), 40.2 (C_{11}), 106.3 (C_3), 111.4 (C_9), 112.5 (C_6), 115.1 (C_1), 115.9 (C_2), 118.3 (C_8), 119.1 (C_5), 121.8 ($C_{17,\ 21}$), 123.8 ($C_{18,\ 20}$), 132.8 (C_4), 136.2 ($C_{19,}$ C-Cl), 138.5 (C_{14}); LC-MS (m/z): 335 ($M+H^+$), 337 ($M+2+H^+$).

N-(2-(1H-Indol-3-yl)ethyl)-4-bromobenzenesulfonamide (7c):
White solid; IR (KBr, cm^{-1}): 3436 (indole –N-H, str), 3243 (-N-H, str), 2981 (=C-H, str), 2872 (-C-H, str), 1328 (-SO_2, asym str), 1159 (-SO_2, sym str), 604 (-C-Br, str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.95 (t, J = 6.0 Hz, 2H, -CH_2-CH_2-NH), 3.37-3.41 (m, 2H, -CH_2-NH), 6.98 (s, 1H, Ar-H), 7.01-7.05 (m, 2H, Ar-H), 7.19 (t, J = 6.0 Hz, 1H, -SO_2-NH), 7.26 (s, 1H, Ar-H), 7.30-7.35 (m, 3H, Ar-H), 7.34-7.40 (m, 2H, Ar-H), 7.62 (dd, J = 6.4 Hz, 2 Hz, 2H, Ar-H), 8.03 (s, br, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 29.1 (C_{10}), 39.5 (C_{11}), 109.6 (C_3), 110.2 (C_9), 110.8 (C_6), 113.6 (C_1), 117.1 (C_2), 119.9 (C_8), 123.3 (C_5), 123.8 (C_{19}, -C-Br), 124.9 ($C_{17,\ 21}$), 126.4 ($C_{18,\ 20}$), 132.1 (C_4), 140.3 (C_{14}); LC-MS (m/z): 380 ($M+H^+$), 382 ($M+2+H^+$).

N-(2-(1H-Indol-3-yl)ethyl)-4-methylbenzenesulfonamide (7d):
Pale brown solid; IR (KBr, cm^{-1}): 3328 (indole –N-H, str), 3170 (-N-H, str), 3012 (=C-H, str), 2987 (-C-H, asym str), 2884 (-C-H, sym str), 1337 (-SO_2, asym str), 1162 (-SO_2, sym str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.65 (s, 3H, -CH_3), 2.89 (t, J = 6.8 Hz, 2H, -CH_2-CH_2-NH), 3.42 (m, 2H, -CH_2-NH), 7.18-7.20 (m, 2H, Ar-H), 7.37 (dd, J = 8.0 Hz, 2H, Ar-H), 7.48-7.51 (m, 2H, Ar-H), 7.63 (s, 1H, Ar-H), 7.70 (m, 2H, Ar-H), 7.81 (t, J = 7.6 Hz, 1H, -SO_2-NH), 8.06 (s, br, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 28.4 (C_{19}-CH_3), 31.3 (C_{10}), 48.8 (C_{11}), 110.4 ($C_{3,\ 9}$), 114.7 ($C_{6,\ 1}$), 116.3 (C_2), 119.7 (C_8), 120.9 (C_5), 123.8 ($C_{18,\ 20}$), 133.5 (C_4), 136.2 ($C_{17,\ 21}$), 138.9 ($C_{14,\ 19}$).

N-(2-(1H-Indol-3-yl)ethyl)-4-nitrobenzenesulfonamide (7e):
Yellow amorphous solid; IR (KBr, cm^{-1}): 3366 (indole –N-H, str), 3179 (-N-H, str), 3048 (=C-H, str), 2925 (-C-H, asym str), 2854 (-C-H, sym str), 1521 (-N=O, str), 1340 ($-SO_2$, asym str), 1148 ($-SO_2$, sym str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.02 (t, J = 6.4 Hz, 2H, -CH_2-CH_2-NH), 3.57 (m, 2H, -CH_2-NH), 7.03 (s, 1H, Ar-H), 7.15 (t, J = 7.2 Hz, 1H, -SO_2-NH), 7.20-7.26 (m, 4H, Ar-H), 7.37 (d, J = 8.0 Hz, 2H, Ar-H), 7.62 (d, J = 8 Hz, 2H, Ar-H), 8.15 (s, br, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 32.5 (C_{10}), 55.9 (C_{11}), 107.1 ($C_{3,\ 9}$), 108.9 (C_6), 112.1 (C_2), 118.4 (C_1), 114.5 (C_8), 120.9 ($C_{18,\ 20}$), 125.3 (C_5), 145.6 ($C_{17,\ 21}$), 146.9 (C_4), 149.6 (C_{14}), 152.2 ($C_{19,}$ C-F); LC-MS (m/z): 346 ($M+H^+$). Anal. Calcd. for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17. Found: C, 55.48; H, 4.31; N, 12.32.

N-(2-(1H-Indol-3-yl)ethyl)-4-aminobenzenesulfonamide (7f):
Pale yellow solid; IR (KBr, cm^{-1}): 3413 (-N-H, str), 3348 (indole –N-H, str), 3268 (-N-H, str), 2927 (=C-H, str), 2893 (-C-H, str), 1345 ($-SO_2$, asym str), 1131 ($-SO_2$, sym str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.91 (t, J = 6.4 Hz, 2H, -CH_2-CH_2-NH), 3.41-3.42 (m, 2H, -CH_2-NH), 4.98 (s, 2H, Ar-NH_2), 7.12 (d, J = 7.2 Hz, 2H, Ar-H), 7.22-7.23 (m, 2H, Ar-H), 7.29 (s, 1H, Ar-H), 7.41 (d, J = 7.2 Hz, 2H, Ar-H), 7.63-7.64 (m, 2H, Ar-H), 7.75 (t, J = 7.2 Hz, 1H, -SO_2-NH), 8.68 (s, br, 1H, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 29.2 (C_{10}), 42.8 (C_{11}), 110.3 (C_3), 111.6 (C_9), 115.2 ($C_{18,\ 20}$), 116.3 (C_6), 116.9 (C_1), 119.4 (C_2), 123.1 (C_8), 123.7 (C_5), 128.4 (C_{17}), 128.8 (C_{21}), 136.2 (C_{14}), 137.1 (C_4), 154.6 (C_{19}).

N-(2-(1H-Indol-3-yl)ethyl)-4-chloro-3-nitrobenzenesulfonamide (7g):
Yellow solid; IR (KBr, cm^{-1}): 3381 (indole –N-H, str), 3267 (-N-H, str), 2973 (=C-H, str), 2890 (-C-H, str), 1537 (-N=O, str),1343 ($-SO_2$, asym str), 1148 ($-SO_2$, sym str), 961 (Ar-Cl, str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.07 (t, J = 6.4 Hz, 2H, -CH_2-CH_2-NH), 3.37-3.39 (m, 2H, -CH_2-NH), 7.08-7.10 (m, 2H, Ar-H), 7.28-7.29 (m, 1H, Ar-H), 7.33 (s, 1H, Ar-H), 7.41 (d, J = 6.8 Hz, 1H, Ar-H), 7.54-7.55 (m, 1H, Ar-H), 7.68 (s, 1H, Ar-H), 7.83 (t, J = 7.2 Hz, 1H, -SO_2-NH), 7.88 (d, J = 6.82 Hz, 1H, Ar-H), 8.51 (s, br, 1H, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 28.9 (C_{10}), 45.1 (C_{11}), 111.5 (C_3), 112.5 (C_9), 114.8 ($C_{6,\ 18}$), 115.7 (C_1), 116.2 (C_2), 122.9 (C_8), 124.3 (C_5), 124.9 (C_{17}), 125.1 (C_{21}), 131.2 (C_{19}), 134.5 (C_4), 134.8 (C_{14}), 148.4 (C_{20}).

N-(2-(1H-Indol-3-yl)ethyl)-3-chloro-4-fluorobenzenesulfonamide (7h):
Brown powdered solid; IR (KBr, cm^{-1}): 3374 (indole –N-H, str), 3263 (-N-H, str), 2985 (=C-H, str), 2889 (-C-H, str), 1352 ($-SO_2$, asym str), 1143 ($-SO_2$, sym str), 1136 (Ar-F, str), 954 (Ar-Cl, str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.87 (t, J = 6.4 Hz, 2H, -CH_2-CH_2-NH), 3.41-3.42 (m, 2H, -CH_2-NH), 7.13-7.14 (m, 2H, Ar-H), 7.24-7.25 (m, 1H, Ar-H), 7.34 (d, J = 6.8 Hz, 1H, Ar-H), 7.38 (s, 1H, Ar-H), 7.57-7.58 (m, 1H, Ar-H), 7.61 (s, 1H, Ar-H), 7.64 (t, J = 7.2 Hz, 1H, -SO_2-NH), 7.69 (d, J = 6.82 Hz, 1H, Ar-H), 8.23 (s, br, 1H, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 28.2 (C_{10}), 40.8 (C_{11}), 111.2 (C_3), 111.9 (C_9), 115.4 ($C_{6,\ 18}$), 115.9 (C_1), 116.8 (C_2), 120.3 (C_{20}), 121.2 (C_8), 121.8 (C_5), 124.1 (C_{17}), 125.3 (C_{21}), 135.8 (C_4), 136.1 (C_{14}), 161.2 ($C_{19,}$ C-F); LC-MS (m/z): 353 ($M+H^+$), 355 ($M+2+H^+$).

N-(2-(1H-Indol-3-yl)ethyl)-methanesulfonamide (7i):
White solid; IR (KBr, cm^{-1}): 3303 (indole –N-H, str), 3214 (-N-H, str), 3020 (=C-H, str), 2974 (-C-H, asym str), 2837 (-C-H, sym str), 1343 ($-SO_2$, asym str), 1151 ($-SO_2$, sym str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.8 (t, J = 6.4 Hz, 2H, -CH_2-CH_2-NH), 3.14 (m, 2H, -CH_2-NH), 3.38 (s, 3H, -CH_3), 6.74 (m, 1H, -SO_2-NH), 7.16-7.17 (m, 1H, Ar-H), 7.24-7.25 (m, 3H, Ar-H), 7.42 (s, 1H, Ar-H), 8.10 (s, br, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 34.2 (C_{10}), 46.3 (-CH_3), 54.7 (C_{11}), 107.2 (C_9), 111.5 (C_3), 115.8 (C_6), 116.2 (C_1), 119.1 (C_2), 123.3 (C_8), 123.8 (C_5), 137.4 (C_4).

N-(2-(1H-Indol-3-yl)ethyl)-triflyromethanesulfonamide (7j):
Light brown amorphous solid; IR (KBr, cm^{-1}): 3289 (indole –N-H, str), 3145 (-N-H, str), 3012 (=C-H, str), 2967 (-C-H, asym str), 2846 (-C-H, sym str), 1361 ($-SO_2$, asym str), 1234 (C-F, str), 1157 ($-SO_2$, sym str); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.87 (t, J = 6.4 Hz, 2H, -CH_2-CH_2-NH), 3.27 (m, 2H, -CH_2-NH), 6.83 (m, 1H, -SO_2-NH), 7.22-7.23 (m, 2H, Ar-H), 7.45-7.46 (m, 2H, Ar-H), 7.49 (s, 1H, Ar-H), 8.32 (s, br, -NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 34.1 (C_{10}), 51.3 (C_{11}), 109.6 (C_9), 110.4 (C_3), 117.3 (C_6), 117.8 (C_1), 119.6 (C_2), 120.1 (C_8), 123.4 (C_5), 134.1 (C_4), 152.3 (CF_3); LC-MS (m/z): 293 ($M+H^+$).

2.3 BIO ASSAY

2.3.1 Antibacterial activity

All the newly synthesized sulfonamides of tryptamine **7(a-j)** were screened against two Gram positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis* and one gram negative bacteria such as *Escherichia coli* pathogens by the agar well diffusion method [24-26]. Bacterial cultures of 24 hour old inocula containing approximately 1-2 x

10^{-7} CFU/mL were spread on the surface of the nutrient agar with the help of sterile cotton swab. Nutrient agar medium was prepared by suspending nutrient agar 20 g in one liter of distilled water (P^H 7.0), autoclaved and cooled to 45 ^oC. The wells having 6 mm were created in the media with the help of sterile metallic borer with centre at least 24 mm apart. Different concentrations such as 100, 200 µg/mL of the tested compounds were prepared in DMF solvent. These recommended concentrations of the tested compounds samples were introduced in culture wells and other well was supplemented for controller DMF and antibiotic standard drug Ciprofloxacin. Experimental plates were incubated for 24 h and antibacterial activity was assayed by measuring zones of inhibition in diameter around the well. The zone of inhibition of the tested solution was compared with standard. The bacterial assays were performed in triplicate and results are presented in **Table.2**. Minimum inhibitory concentrations (MICs) were determined by broth dilution technique [27]. Different concentrations like 2.5, 5, 7.5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80 µg/mL of test solutions were evaluated. Specifically 0.1 mL of standardized inoculum (1-2 x 10^7 CFU/mL) was added to test tubes and incubated for 24 h at 37 ^oC and two controls were maintained for each test sample. The growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC) and the MICs of the test solutions are represented in **Table 2**.

Table-2: Antibacterial zone of inhibition and minimum inhibition concentrations (MICs) of the sulfonamide derivatives 7(a-j).

Compd	*S. aureus*		MICs	*B. subtilis*		MICs	*E. coli*		MICs
	100	200		100	200		100	200	
7a	7.9	17.5	40	9.07	18.0	25	9.0	17.6	30
7b	7.1	16.3	40	6.9	13.9	50	6.4	14.7	50
7c	5.06	12.7	80	5.0	11.8	70	8.3	15.7	40
7d	7.2	13.3	60	7.8	14.1	50	6.6	12.8	60
7e	10.8	18.4	25	10.0	17.8	30	10.5	18.0	25
7f	5.6	11.1	80	8.0	15.6	25	6.8	14.9	60
7g	8.07	17.1	40	9.8	18.05	25	10.1	18.7	25
7h	6.1	13.5	60	9.5	18.1	30	6.8	14.4	60
7i	6.3	14.1	50	7.1	14.9	50	9.5	17.1	30
7j	11.0	18.1	25	9.02	18.3	25	8.6	16.5	40
Std (Ciprofloxacin)		21	04		23	07		23	05

2.3.2 Antifungal activity:

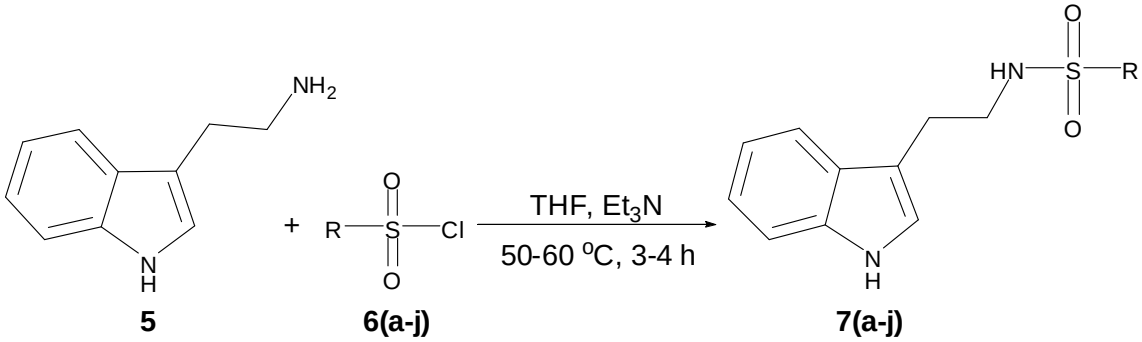
The antifungal activity was evaluated for sulfonamide derivatives **7(a-j)** of tryptamine against *Candida albicans* and *Aspergillus niger* fungal strains using agar disc-diffusion method [27a]. The fungal strains were maintained at 37 ^oC on potato dextrose agar (PDA) medium (Hi-Media). A loopful of culture from the slant was inoculated into the potato dextrose broth and incubated at 37˚C for 48-72 h. All the compounds were dissolved in dimethylformamide (DMF, Merck). Sterile discs of Whatmann No.1 filter paper of about 6 mm diameter were impregnated on the surface of the media. Different concentrations (100, 200 µg/mL) of various test compounds were prepared and applied on the discs and incubated for 48-72 h at 37 ˚C. The zone of inhibition around the disc was calculated edge to edge zone of the confluent growth which corresponds to the sharpest edge of the zone and was measured in millimeters. All tests were repeated for three times and average data taken as final result. Blank test showed that the DMF solvent used in the preparations of the test solutions did not affect the test organisms. Griseofluvin was used as a standard drug and the inhibition zones of the test compounds were compared with controls **(Table 3).** Minimum Inhibitory Concentration (MIC) was determined by micro-broth-dilution method [27 (a)]. The minimum concentration, at which there was no visually detectable fungal growth, was taken as MIC. To examine MICs of the test solutions, various concentrations 2.5, 5, 7.5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80 µg/mL of the test solutions were evaluated. Specifically 0.1 mL of standardized inoculum (1-2 x 10^7 CFU/mL) was added to each test tube. The tubes were incubated aerobically at 37 ^oC for 48-72 h. Control was maintained for each test sample. The lowest concentration (highest dilution) of test compound that produced no visible signs of fungal growth (no turbidity) when compared with the control tubes were regarded as MIC **(Table 3)**.

Table-3: Antifungal zone of inhibition and minimum inhibition concentrations (MICs) of the sulfonamide derivatives 7(a-j).

Compd	*A. niger*		MICs	*C. albicans*		MICs
	100	200		100	200	
7a	8.2	17.40	40	8.9	16.8	30
7b	5.8	13.05	70	6.3	14.6	60
7c	3.8	10.03	80	4.9	11.4	<100
7d	7.8	16.5	40	8.0	16.1	40
7e	10.03	18.0	25	12.1	19.8	25
7f	6.6	11.03	50	6.2	13.5	60
7g	9.9	17.1	40	10.5	18.7	40
7h	10.0	18.6	25	12.0	19.04	25
7i	3.0	8.9	<100	5.5	11.4	<100
7j	11.1	18.0	25	10.6	16.7	30
Std (Greseofulvin)		21	05		23	05

RESULTS AND DISCUSSION

Synthesis of new sulfonamide derivatives **7(a-j)** was carried out in straightforward manner of simple substitution of substituted arylsulfonyl chlorides with tryptamine and schematic representation was underlined in **Scheme. 1**. Primarly, tryptamine **(5)** was substituted with electron withdrawing group containing sulfonyl chloride such as 4-nitrophenylsulfonyl chloride **(6e)** in presence of triethyl amine (TEA) by stirring at 55-60 ^{o}C for about 3 h, resulted N-(2-(1*H*-indol-3-yl)ethyl)-4-nitrobenzenesulfonamide **(7e)** with 89% of yield. The progress of the reaction was indicated by TLC. The pure product of the synthesized compound was obtained by washing the crude reaction mixture with aqueous ammonium hydrogen chloride (3 × 20 mL) to remove unreacted amine compound followed by re-crystallization from methanol. All the titled compounds were synthesized by using same procedure and results are represented in **Table 1**. It was observed from the results that electron withdrawing group having sulfonyl chlorides **6e**, **6g** gave more yields as compared with electron donating groups, the reason is electron withdrawing group enhances the electrophilicity at sulfonyl sulfur to make feasible nucleophilic substitution by tryptamine.



5 **6(a-j)** **7(a-j)**

R		R	
4-Fluorophenyl	**7a**	4-Aminophenyl	**7f**
4-Chlorophenyl	**7b**	4-Chloro-3-nitrophenyl	**7g**
4-Bromophenyl	**7c**	3-Chloro-4-flluorophenyl	**7h**
4-Methylphenyl	**7d**	Methyl	**7i**
4-Nitrophenyl	**7e**	Trifluoromethyl	**7j**

Scheme. 1 Synthesis of new sulfonamide derivatives of tryptamne

Structures of the titled compounds were established by IR, ^{1}H, ^{13}C NMR, mass and elemental spectral analysis data. IR spectrums of sulfonamide derivatives **7(a-j)** showed bands at 3175-3450 cm^{-1} for –N-H, 1310-1350 cm^{-1} for –

SO_2 (asymmetric), 1114-1195 cm^{-1} (symmetric), 1500-1580 cm^{-1} for $–NO_2$ in **7e** and **7g** and 680-1150 for C-X stretchings. ^{1}H-NMR spectrums of the sulfonamide derivatives were exhibited chemical shifts at δ 8.0-8.3 for –NH (indole), δ 7.0-7.2 for –NH in sulfonamides, δ 6.5-7.9 for aromatic protons, δ 2.5-3.0 for aliphatic $–CH_2$- and δ 3.1-3.4 for $–CH_2$ which is directly attached with sulfonamide nitrogen. ^{13}C-NMR spectra showed chemical shifts at 150-160 ppm for C-F, 135-150 ppm for C-N, 102-140 ppm for simple aromatic carbons and 27-48 ppm for aliphatic carbons. Molecular ion peaks in mass spectra and elemental analytical data of the titled compounds have provided further evidence for confirmation of the synthesized compounds.

The antibacterial and antifungal activities of the titled compounds were investigated against bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* using agar well diffusion method and fungi such as *Candida albicans* and *Aspergillus niger* using agar disc-diffusion method respectively. Ciprofloxacin was used as standard for antibacterial study and Griseofluvin was used as standard for antifungal study. In addition, the lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC), minimum inhibitory concentrations of the tested samples were determined (**Table. 2** and **Table. 3**). Results revealed that all the compounds showed potent to moderate zone of inhibition by killing the bacterial and fungal strains. Some of the compounds which are bearing fluorine and nitro group exhibited potent activity. Compounds **7a**,**7e**, **7g** and **7j** showed potent zone inhibition activity against all tested bacterial strains and compound **7h** exhibited good activity against *B. subtilis*. Compounds such as **7a**, **7e**, **7g** and **7j** exhibited potent antifungal activity against tested fungal strains and **7d** and **7h** showed good zone of inhibition against *C. albicans* fungal strains.

CONCLUSION

In summary, we successfully designated and synthesized a new class of sulfonamide derivatives of tryptamine such as N-(2-(1*H*-indol-3-yl)ethyl)-substituted-sulfonamides by simple substitution reaction at sulfonyl sulfur with easy work-up procedure. *In vitro* antimicrobial activity of the synthesized compounds was screened against selected bacterial and fungal strains at two different concentrations (100, 200 µg/mL) and minimum inhibitory concentrations (MICs) of tested samples were also determined. Fluorinated and nitrogenated sulfonamide derivatives exhibited potent antimicrobial activity.

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