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Synthesis, Characterization and Biological Studies of Thiadiazepine Derivatives of Sultams

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ABSTRACT

The synthesis and characterization of new series of thiadiazepine derivatives of sultams have been presented. The structures were confirmed by elemental analysis, IR spectral, ^{1}*H NMR spectral data. All the compounds were screened for in vitro antimicrobial and anthelmintic activities. The antibacterial activity was tested against Staphylococcus aureus (Gram positive), Bacillus cereus (Gram positive), Escherichia coli (Gram negative) and Pseudomonas aeruginosa (Gram negative). The antifungal activity was tested against Aspergillusniger and Candida albicans. All the compounds showed considerable antimicrobial activity against the microorganism studied. The significant anthelmintic activities of all novel compounds were demonstrated against Pheretima posthuma. Based on the nature of substituent present, the structure-activity correlation of novel compounds was discussed.*

Keywords: Thiadiazepine, Sultam, Antimicrobial, Anthelmintic.

INTRODUCTION

Thiadiazepine derivatives demonstrate a wide range of biological activities and are of versatile utility in drug design. This moiety has been an integral part of a number of established drug molecules like zometapine, etizolam, brotizolam, clozapine and dibenzepine [1]. Diazepine core has also been used as peptidomimetic scaffolds [2], as a scaffold in the design of inhibitors of lymphocyte function associated antigen-1(LFA-1) [3]. Their therapeutical activities include antipro-liferative activity [4], antitumor activity [5], as potent protein inhibitors [2,6-8], CNS activity [9], anthelmintic activity [10], HDM2 antagonists [11], anti-HIV activity[12], etc. Many thiadiazepine derivatives having large-scale physiological and pharmacological significance [13-20] are also known. This prompted us to synthesize new compounds containing diazepine moieties in anticipation of improved biological activity. In view of their medicinal importance, the authors tried to synthesize a new entity to result in com-pounds that demonstrate better therapeutical activities. The present article is an effort in that direction and reports the synthesis, characterization and biological evaluation of some novel thiadiazepine derivatives have been presented.

MATERIALS AND METHODS

All chemicals and reagents were obtained from Merck India Limited. Melting points were determined in open capillary tubes and were uncorrected (in degree Celsius). The infrared spectra of the compounds were recorded in KBr discs on FT-IR (Spectrum ONE) spectrometer manufactured by Perkin-Elmer. The ^{1}H NMR spectra were recorded on a JOEL(300 MHz) spectrometer using TMS as an internal standard(chemical shifts in δ). The Mass spectra were recorded on a mass spectrometer JOEL sx-102 (FAB). The transmittance measurements were made on UV-Visible spectrophotometer, Shimadzu Corporation, Japan. Nutrient broth, nutrientagar and 5 mm diameter antibiotic assay discs were obtained from Hi-Media Laboratories Limited, India. The standard bacterial and fungal strains were procured from National Centre for Cell Science (NCCS), Pune, India.

Synthesis of (E)-methyl 2-(benzylideneamino)acetate[3]: To the suspension of amino acid ester (1.2 equiv., 12 mmol) and MgSO4 (1.25 equiv., 12.5 mmol) in DCM (15 mL) was added Et3N (1.2 equiv., 12 mmol). The mixture was stirred at ambient temperature for 1h. Then the corresponding aldehyde (1 equiv., 10 mmol) was added and the mixture was allowed to stir at ambient temperature overnight. The precipitate was removed by filtration and the filtrate was washed with water (15 mL). The aqueous phase was extracted two times with DCM (10 mL) and the combined organic layer was washed once with brine (15 mL), dried over MgSO4 and concentrated. Organic layer concentrated to get crude compound which on further column purification obtained pure desired compound**[3]**.

Synthesis of N-benzyl-2-fluorobenzenesulfonamide[6]: To a vigorously stirred solution of amine (8 mmol, 1.2 equiv.) in CH_2Cl_2 (33.0 mL, 0.2 M) in a round bottom flask was added Et_3N (3 equiv.). A solution of α-fluorobenzenesulfonyl Chloride (6.66 mmol, 1.0 equiv.) was added dropwise, and the reaction was stirred for 4-8 hours. Upon disappearance of sulfonyl chloride, 10% HCl (10 mL) was added and the reaction was stirred for 10 min. The organic layer was separated and the aqueous layer extracted with CH2Cl2 (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO4) and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography (3:1, hexane:EtOAc) to afford the desired N-benzyl-2-fluorobenzenesulfonamide**[6].**

Synthesis of methyl 2-benzyl-4-methyl-3-phenyl-2,3,4,5-tetrahydrobenzo [f][1,2,4] thia diazepine-5-carboxylate 1,1-dioxide [7a]: procedure for the synthesis of methyl 2-benzyl-4-methyl-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carboxylate 1,1-dioxide [A] from α-fluorobenzene sulfonamide derivatives: Into a microwave vial (0.5-2.0 mL) was added α-fluorobenzene sulfonamide derivative(0.5 mmol), anhydrous Cs_2CO_3 (1.5 mmol), BnEt3NCl (0.05 mmol),iminium derivative (0.5 mmol) and dry dioxane/DMF (1:1, 1M).The microwave vial was heated at 110 ºC for 20 min, after such time the reaction was purified (directly loading of crude reaction mixture) by flash chromatography (8:2 hexane/EtOAc) to afford the desired sultam**(7a).** Similar procedure was adopted for the synthesis of 7b-7j [29-31]

Synthesis of 2-benzyl-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carbohydrazide 1,1-dioxide [8a]: A solution of (7a) and hydrazine hydrate in ethanol was refluxed for 5 h. The progress of the reaction was monitored by TLC with Acetone: Ethylacetate (7:3) as mobile phase. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystalised from ethanol to afford 2-benzyl-3-phenyl-2,3,4,5-tetrahydrobenzo [f] [1,2,4]thiadiazepine-5-carbohydrazide 1,1-dioxide [8a]. Similar procedure was adopted for the synthesis of 8b-8j [32-34]

Synthesis of (E)-2-benzyl-N'-(2-oxoindolin-3-ylidene)-3-phenyl-2,3,4,5-tetrahydrobenzo [f][1,2,4]thia diazepine-5-carbohydrazide 1,1-dioxide [9a]: Equimolar quantities (0.01 mol) of Isatin and the corresponding acetohydrazide were dissolved in warm ethanol (40 mL) containing DMF (0.5 mL). The reaction mixture was refluxed for 1-4 h and then kept at room temperature overnight. The progress of the

reaction was monitored by TLC with acetone:ethylacetate (7:3) as mobile phase. The resulting solid was filtered and washed with ethanol, dried, recrystallised from ethanol to afford compounds [9a]. Similar procedure was adopted for the synthesis of 9b-9j [35-37]

Procedure for anthelmintic studies: The investigation was performed on adult earthworm, *Pheretima posthuma*, collected from moist soil and washed with double distilled water. The earthworms of 4-6 cm in length were used in present investigations. Six worms i.e.P. *posthuma*, were placed in petri dish containing 50 mL of test solution. Test solution of concentration of 25 mg mL^{-1} was prepared in dimethylformamide. Piperazine citrate (10 mg mL^{-1}) was used as reference standard. Determination of time of paralysis and time of death of the worm were done.

Table: 1 Antimicrobial activity and anthelmintic activity of novel compounds synthesized

Compound	R	Minimum Inhibitory Concentration(MIC) in g/mL							
		Antibacterial activity				Antifungal Activity		Anthelmintic Activity(minute)	
		Staphylococcus Aureus NCCS 2079	Bacillus Cereus NCCS 2106	Escherichia Coli NCCS 2065	Pseudomonas aeruginosa NCCS 2200	Aspergillus Niger NCCS 1196	Candida albicans NCCS 2106	25 mg of ml of comp	
								Paralysis	Death
9i	Furan	3.42	6.46	5.92	7.42	4.08	6.64	28	60
9g	Pyrrole	4.48	10.52	7.18	8.76	5.18	6.68	26	54
9f	Pyridine	9.46	13.9	13.32	14.78	10.14	11.1	21	52
9h	Thiophene	6.76	12.48	8.30	8.32	10.48	9.12	26	50
9a	Phenyl	10.82	21.44	15.86	17.58	15.70	15.0	21	47

RESULTS AND DISCUSSION

To an amino acid ester suspension in DCM corresponding aldehyde was added and allowed to react overnight to afford methyl 2-(benzylideneamino)acetate [3] . Into a microwave vial (0.5-2.0 mL) was added α-fluorobenzene sulfonamide derivative(0.5 mmol), anhydrous Cs_2CO_3 (1.5 mmol), BnEt3NCl (0.05 mmol),iminium derivative [3] (0.5 mmol) and dry dioxane/DMF (1:1, 1M).The microwave vial was heated at 110 ºC for 20 minutes, after such time the reaction was purified (directly loading of crude reaction mixture) by flash chromatography (8:2 hexane/EtOAc) to afford the desired sultam(7a). A solution of (7a) and hydrazine hydrate in ethanol was refluxed for 5 hours. The progress of the reaction was monitored by TLC with Acetone:Ethylacetate (7:3) as mobile phase. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallised from ethanol to afford 2-benzyl-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carbohydrazide 1,1-dioxide [8a]. Here ester was removed by hydrazine to give hydrazine derivative of sultam, which on further treatment of Isatin afforded the desired compounds whose antimicrobial and anthelmintic properties were presented in the table-1. These results showed that the presented compounds shown good anti microbial and anthelmintic properties varying by the presence of substituent's. The antimicrobial nature appeared that increasing the number of electron donating groups results in significant decrease of antimicrobial activity. Similarly, increasing the number of electron donating substituent groups results in increasing anthelmintic activity.

Characterization of [3a]: Molecular formula: $C_{10}H_{11}NO_2$, yield: 65%; element found% (calculated%): C 67.14(67.24); H 6.20 (6.14); N 7.77 (7.82), IR max in cm−1 (Group): 3050 (Ar-H); 2980 (aliphatic CH2); 1740 (> C=O of Ester), 1610(-C=N); ^{1}H NMR (300 MHz, DMSO-d6) _ ppm: 3.68(s, 3H,O-CH_3), 4.51(s, 2H, N-CH_2), 7.52-7.83(m, Ar-H), 8.65(s,1H, =C-H).

Characterization of [6a]: Molecular formula: $C13H12FNO_2S$, yield: 64%; element found% (calculated%): C 59.04(59.09); H.4.57 (4.54); N 5.25 (5.30),IR max in cm−1(Group):3287(N-H), 1600(C=C), 2960(C-H), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 3.95(s, 2H,CH2-NH-), 7.72 (broad,1H,NH-), 7.22-7.829(m, 8H, Ar-H).

Characterization of [7a]: Molecular formula: $C_{23}H_{22}N_2O_4S$, yield: 61%; element found% (calculated%): C 65.36(64.40); H.5.17 (5.19); N 6.56 (6.61), IR max in cm^{-1}(Group):3286(N-H), 1600(C=C), 2960(C-H), 1740(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 3.95(s, 2H,CH2-NH-), 7.72(broad,1H,NH-), 7.22-7.82(m, 8H, Ar-H).

Characterization of [7b]: Molecular formula: $C_{22}H_{21}N_3O_4S$, yield: 60%; element found% (calculated%): C 64.36(62.40); H.5.04 (5.09); N 9.89 (9.92), IR max in cm^{-1}(Group):3284(N-H), 1610(C=C), 2955(C-H), 1740(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s, H,-NH),3.68(s,3H,O-CH_3-), 4.42(s,2H, Py-CH2),4.74(s,1H,-CH-COO), 5.04(s, 1H, -N-CH-N-), 7.26-7.74(m, Ar-H), 8.55(2H, Py,-CH-N-CH-).

Characterization of [7c]: Molecular formula: $C_{21}H_{21}N_3O_4S$, yield: 62%; element found% (calculated%): C 61.22(61.28); H.5.08 (5.12); N 10.14 (10.19), IR max in cm^{-1}(Group):3285(N-H), 1611(C=C), 2958(C-H), 1740(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s, H,-NH),3.68(s,3H,O-CH_3-),4.30(s, 2H, -N-CH2),4.74(s,1H,-CH-COO), 5.0(s,1H, Py-NH), 5.04(s, 1H, -N-CH-N-),5.85(d, 1H,Py-CH), 6.28(d, 1H,Py-CH), 6.42(1H,Py-CH), 7.26-7.74(m, Ar-H).

Characterization of [7d]: Molecular formula: $C_{21}H_{20}N_2O_4S_2$, yield: 61%; element found% (calculated%): C 58.79(58.85); H.4.65 (4.69); N 6.49 (6.53), IR max in cm^{-1}(Group):3280(N-H), 1610(C=C), 2959(C-H), 1740(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s, H,-NH),3.68(s,3H,O-CH_3-),4.42(s, 2H, -N-CH2),4.74(s,1H,-CH-COO), 5.04(s, 1H, -N-CH-N-), 6.74(s, 1H,thiophene-CH), 6.75(s, 1H,thiophene-CH), 7.59(d, 1H,thiophene-CH), 7.26-7.51(m, Ar-H).

Characterization of [7e]: Molecular formula: $C_{21}H_{20}N_2O_5S$, yield: 60%; element found% (calculated%): C 61.10(61.14); H.4.84 (4.88); N 6.73 (6.78), IR max in cm^{-1}(Group):3294(N-H), 1615(C=C), 2958(C-H), 1740(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s, H,-NH),3.68(s,3H,O-CH_3-),4.42(s, 2H, -N-CH2), 4.74(s,1H,-CH-COO), 5.04(s, 1H, -N-CH-N-), 6.13(d, 1H,Furan-CH), 7.10(d, 1H,Furan-CH), 7.11(s,1H, Furan-H), 7.26-7.74(m, Ar-H).

Characterization of [7f]: Molecular formula: $C_{22}H_{21}N_3O_4S$, yield: 62%; element found% (calculated%): C 62.35(62.39); H.4.44 (4.49); N 9.87 (9.91), IR max in cm^{-1}(Group): 3286(N-H), 1605(C=C), 2960(C-H), 1740(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s, H,-NH),3.68(s,3H,O-CH_3-),4.42(s, 2H, -N-CH2), 4.74(s,1H,-CH-COO), 5.04(s, 1H, -N-CH-N-), 7.26-7.43 (m, Ar-H), 7.86(d,1H of Py), 8.45(d,1H of Py), 8.59(s, 1H of Py).

Characterization of [7g]: Molecular formula: $C_{21}H_{21}N_3O_4S$, yield: 63%; element found% (calculated%): C 61.24(61.29); H.5.09 (5.13); N 10.16 (10.20), IR max in cm^{-1}(Group): 3285(N-H), 1609(C=C), 2975(C-H), 1745(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s, H,-NH),3.68(s,3H,O-CH_3-),4.42(s, 2H, -N-CH2), 4.74(s,1H,-CH-COO), 5.0(s, 1H, Py-NH), 5.04(s, 1H, -N-CH-N-), 5.85(d, 1H, Py-H), 6.28(s, 1H,Py-H), 6.42(d,1H, Py-H), 7.26-7.74(m,Ar-H).

Characterization of [7h]: Molecular formula: $C_{21}H_{20}N_2O_4S_2$, yield: 64%; element found% (calculated%): C 58.81(58.85); H.4.65 (4.69); N 6.49 (6.53), IR max in cm^{-1}(Group): 3280(N-H), 1610(C=C), 2978(C-H), 1748(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s, H,-NH),3.68(s,3H,O-CH_3-),4.42(s, 2H, -N-CH2), 4.74(s,1H,-CH-COO), 5.04(s, 1H, -N-CH-N-), 6.74(d,1H, Thiophene-H),6.75(s, 1H, Thiophene-H), 7.23-7.74(m,Ar-H).

Characterization of [7i]: Molecular formula: $C_{21}H_{20}N_2O_5S$, yield: 65%; element found% (calculated%): C 61.10(61.14); H.4.83 (4.88); N 6.73 (6.78), IR max in cm^{-1}(Group): 3295(N-H), 1615(C=C), 2980(C-H), 1748(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s, H,-NH),3.68(s,3H,O-CH_3-),4.42(s, 2H, -N-CH2), 4.74(s,1H,-CH-COO), 5.04(s, 1H, -N-CH-N-), 6.13(d,1H, Furan-H),7.10(d, 1H, Furan-H),7.11(s, Furan-H), 7.23-7.74(m,Ar-H).

Characterization of [8a]: Molecular formula: $C_{22}H_{22}N_4O_3S$, yield: 64%; element found% (calculated%): C 62.49(62.53); H.5.20 (5.24); N 13.21 (13.25), IR max in cm^{-1}(Group): 1600(C=C), 2960(C-H), 3180(N-H), 3300(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H,N-CH-N), 7.23-7.74(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH).

Characterization of [8b]: Molecular formula: $C_{21}H_{21}N_5O_3S$, yield: 63%; element found% (calculated%): C 59.50(59.55); H.4.94 (4.98); N 16.50 (16.53), IR max in cm^{-1}(Group): 1605(C=C), 2965(C-H), 3190(N-H), 3300(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H,N-CH-N), 7.23-7.74(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH).8.55(d, 2H, Py-H).

Characterization of [8c]: Molecular formula: $C_{20}H_{21}N_5O_3S$, yield: 63%; element found% (calculated%): C 58.34(58.39); H.5.10 (5.13); N 16.97 (17.01), IR max in cm^{-1}(Group): 1604(C=C), 2960(C-H), 3190(N-H), 3300(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2), 4.30(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.0(s, 1H, Py-NH),5.04(s,1H,N-CH-N), 5.85(d,1H, Py-H), 6.28(s, 1H, Py-H), 6.42(d, 1H, Py-H), 7.26-7.74(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH).

Characterization of [8d]: Molecular formula: $C_{20}H_{20}N_4O_3S_2$, yield: 64%; element found% (calculated%): C 56.01(56.05); H.4.64 (4.69); N 13.01 (13.06), IR max in cm^{-1}(Group): 1600(C=C), 2958(C-H), 3188(N-H), 3300(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 6.74(d,1H,Thiophene-H), 6.75(s,1H,Thiophene-H), 7.59(d, 1H, Thiophene-H), 7.33-7.74(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH).

Characterization of [8e]: Molecular formula: $C_{20}H_{20}N_4O_4S$, yield: 65%; element found% (calculated%): C 58.19(58.24); H.4.84 (4.89); N 13.53 (13.58), IR max in cm^{-1}(Group): 1600(C=C), 2960(C-H), 3188(N-H), 3300(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 6.13(d,1H,Furan-H), 7.11(s,1H,Furan-H), 7.10(d, 1H, Furan-H), 7.33-7.74(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH).

Characterization of [8f]: Molecular formula: $C_{21}H_{21}N_5O_3S$, yield: 60%; element found% (calculated%): C 59.52(59.56); H.4.94 (4.99); N 16.49 (16.53), IR max in cm^{-1}(Group): 1600(C=C), 2930(C-H), 3188(N-H), 3300(N-H), 1650(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 7.26-7.74(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH), 8.55(d, 1H,Py-H).

Characterization of [8g]: Molecular formula: $C_{20}H_{21}N_5O_3S$, yield: 64%; element found% (calculated%): C 58.34(58.38); H.5.10 (5.14); N 16.96 (17.01), IR max in cm^{-1}(Group): 1600(C=C), 2930(C-H), 3188(N-H), 3300(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH),5.0(s,1H, Py-NH), 5.04(s,1H, N-CH-N), 5.85(d,1H, Py-H), 6.28(s, 1H, Py-H), 6.42(d,1H, Py-H), 7.23-7.51(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH).

Characterization of [8h]: Molecular formula: $C_{20}H_{20}N_4O_3S_2$, yield: 65%; element found% (calculated%): C 56.01(56.05); H.4.64 (4.69); N 13.01 (13.06), IR max in cm^{-1}(Group): 1600(C=C), 2932(C-H), 3186(N-H), 3295(N-H), 1630(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2),

4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 6.74(s, 1H, Thiophene-H), 6.75(s,1H, Thiophene-H), 7.59(d,1H, Thiophene-H), 7.23-7.74(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH).

Characterization of [8i]: Molecular formula: $C_{20}H_{20}N_4O_4S$, yield: 62%; element found% (calculated%): C 58.19(58.23); H.4.84 (4.89); N 13.53 (13.57), IR max in cm^{-1}(Group): 1610(C=C), 2950(C-H), 3190(N-H), 3295(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 6.13(d, 1H, Furan-H), 7.11(s,1H, Furan-H), 7.10(d,1H, Furan-H), 7.23-7.74(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH).

Characterization of [9a]: Molecular formula: $C_{30}H_{25}N_5O_4S$, yield: 60%; element found% (calculated%): C 65.27(65.31); H.4.54 (4.57); N 12.64 (12.69), IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2950(C-H), 3340(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 7.0(s, O=C-NH-N), 7.23-7.74 (m, 16H, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H), 8.0(s, 1H, Isatin -CO-NH-).

Characterization of [9b]: Molecular formula: $C_{29}H_{24}N_6O_4S$, yield: 62%; element found% (calculated%): C 62.97(63.02); H.4.34 (4.37); N 15.16 (15.20), IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2950(C-H), 3340(N-H),3300(H-C=N), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 7.0(s, O=C-NH-N), 7.23-7.74 (m, 16H, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H), 8.0(s, 1H, Isatin -CO-NH-), 8.55(d, 1H, Py-CH).

Characterization of [9c]: Molecular formula: $C_{28}H_{24}N_6O_4S$, yield: 64%; element found% (calculated%): C 62.17(62.21); H.4.42 (4.46); N 15.49 (15.54), IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2950(C-H), 3340(N-H),3400(H-C-N), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 4.30(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.0(s, Pyrrole NH), 5.04(s,1H, N-CH-N),5.85(d,1H, Pyrrole-H), 6.28(s, 1H, Pyrrole-H), 6.42(d, 1H, Pyrrole-H), 7.0(s, O=C-NH-N), 7.23-7.74 (m, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H), 8.0(s, 1H, Isatin -NH-).

Characterization of [9d]: Molecular formula: $C_{28}H_{23}N_5O_4S_2$, yield: 63%; element found% (calculated%): C 60.00(60.30); H.4.10 (4.15); N 12.51 (12.55), IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2950(C-H), 3340(N-H),3100(H-C-S), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 6.74(d,1H, Thiophene-H), 6.75(s, 1H, Thiophene-H), 7.0(s, O=C-NH-N), 7.59(d, 1H, Thiophene-H), 7.26-7.74 (m, 11H, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H), 8.0(s, 1H, Isatin -NH-).

Characterization of [9e]: Molecular formula: $C_{28}H_{23}N_5O_5S$, yield: 61%; element found% (calculated%): C 62.04(62.10); H.4.23 (4.27); N 12.89 (12.92), IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2980(C-H), 3340(N-H), 3130(H-C-O), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 6.13 (d,1H, Furan-H), 7.0(s, O=C-NH-N), 7.10(d,1H,Furan-H), 7.11(s, 1H, Furan-H), 7.26-7.51 (m, 10H, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H), 8.0(s, 1H, Isatin -NH-).

Characterization of [9f]: Molecular formula: $C_{29}H_{24}N_6O_4S$, yield: 60%; element found% (calculated%): C 62.97(63.02); H.4.34 (4.37); N 15.16 (15.20), IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2980(C-H), 3340(N-H), 3300(H-C=N), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 7.0(s, O=C-NH-N), 7.26-7.51 (m, 11H, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H),7.86(d, 1H, Pyridine-H), 8.0(s, 1H, Isatin -NH-), 8.45(d,1H, Pyridine-H), 8.59(s, 1H, Pyridine-H).

Characterization of [9g]: Molecular formula: $C_{28}H_{24}N_6O_4S$, yield: 63%; element found% (calculated%): C 62.16(62.20); H.4.41 (4.46); N 15.50 (15.54), IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2980(C-

H), 3340(N-H), 3400(H-C-N), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.0(s, 1H, Pyrrole-NH), 5.04(s,1H, N-CH-N), 5.85(d, 1H, Pyrrole-H), 6.28(s, 1H,Pyrrole-H), 6.42(d, 1H, Pyrrole-H), 7.0(s, O=C-NH-N), 7.26-7.51 (m, 10H, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H), 8.0(s, 1H, Isatin -NH-).

Characterization of [9h]: Molecular formula: $C_{28}H_{23}N_5O_4S_2$, yield: 61%; element found% (calculated%): C 60.26(60.30); H.4.11 (4.15); N 12.51 (12.55), IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2980(C-H), 3340(N-H), 3100(H-C-S), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 6.74(d, 1H, Thiophene-H),6.75(s, 1H, Thiophene-H), 7.0(s, O=C-NH-N), 7.26-7.51 (m, 11H, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H), 8.0(s, 1H, Isatin -NH-).

Characterization of [9i]: Molecular formula: $C_{28}H_{23}N_5O_5S$, yield: 60%; element found% (calculated%): C 62.04(62.09); H.4.23 (4.27); N 12.87 (12.92), IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2980(C-H), 3340(N-H), 3130(H-C-O), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^6)_ ppm: 2.0(s,1H, N-H), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 6.13(d, 1H, Furan-H), 7.0(s, O=C-NH-N), 7.10(d,1H, Furan-H), 7.11(s, 1H, Furan-H), 7.26-7.51 (m, 10H, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H), 8.0(s, 1H, Isatin -NH-).

APPLICATIONS

Antimicrobial activity: All synthesized compounds were screened for antibacterial activity against *Staphylococus aureus* NCCS 2079, *Bacil-lus cereus* NCCS 2106, *Escherichia coli* NCCS 2065 and *Pseudomonas aeruginosa* NCCS 2200 and antifungal activityagainst *Aspergillus niger* NCCS 1196 and *Candida albicans*NCCS 2106. The activity of novel compounds was expressed in terms of minimum inhibitory concentration (MIC). Broth dilution method [21] was used to determine the minimum inhibitory concentration of an antimicrobial agent. It can be seen from table 1 that introduction of electron donating groups has significantly decreased antimicrobial activity. Similar results were reported in the literature [22-25].

Anthelmintic activity: Anthelmintic activity studies were performed on *P. posthuma*. The selection of *P. posthuma* for the anthelmintic studies is owing to its anatomical and physiological resemblance with the intestinal round worm parasites of human beings [26-28]. Time for paralysis was noted when no movement of any sort could be observed except when the worms were shaken vigorously. Time for death of worms was recorded after ascertaining that worms neither moved when shaken vigorously nor when dipped in warm water (50◦C) followed with fading away of their body colors. It can be seen from the Table 1 that greater the electron donating nature of the substituent groups, the greater will be the anthelmintic activity. The conclusion matches with that reported in the literature [22].

CONCLUSIONS

A series of new class of substituted thiadiazepine derivatives has been reported. The compounds were characterized by elemental analysis data, IR,1H NMR spectral data. The novel heterocycles were evaluated for antimicrobial activity and anthelmintic activity by comparison to reference compounds. The compounds demonstrated moderate antimicrobial activity against selected fungal and bacterial stains and considerable amount of anthelmintic activity against *P. posthuma*. Fromthese results, it appeared that increasing the number of electron donating groups results in significant decrease of antimicrobial activity. Similarly, increasing the number of electron donating substituent groups results in increasing anthelmintic activity.

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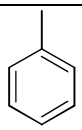
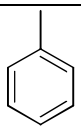
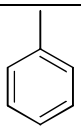
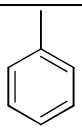
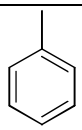
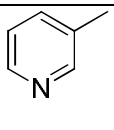
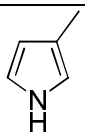
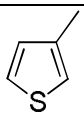
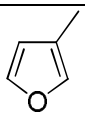
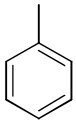
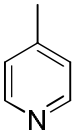
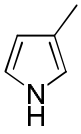
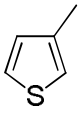
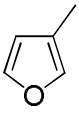
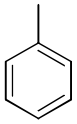
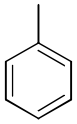
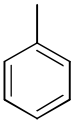
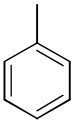
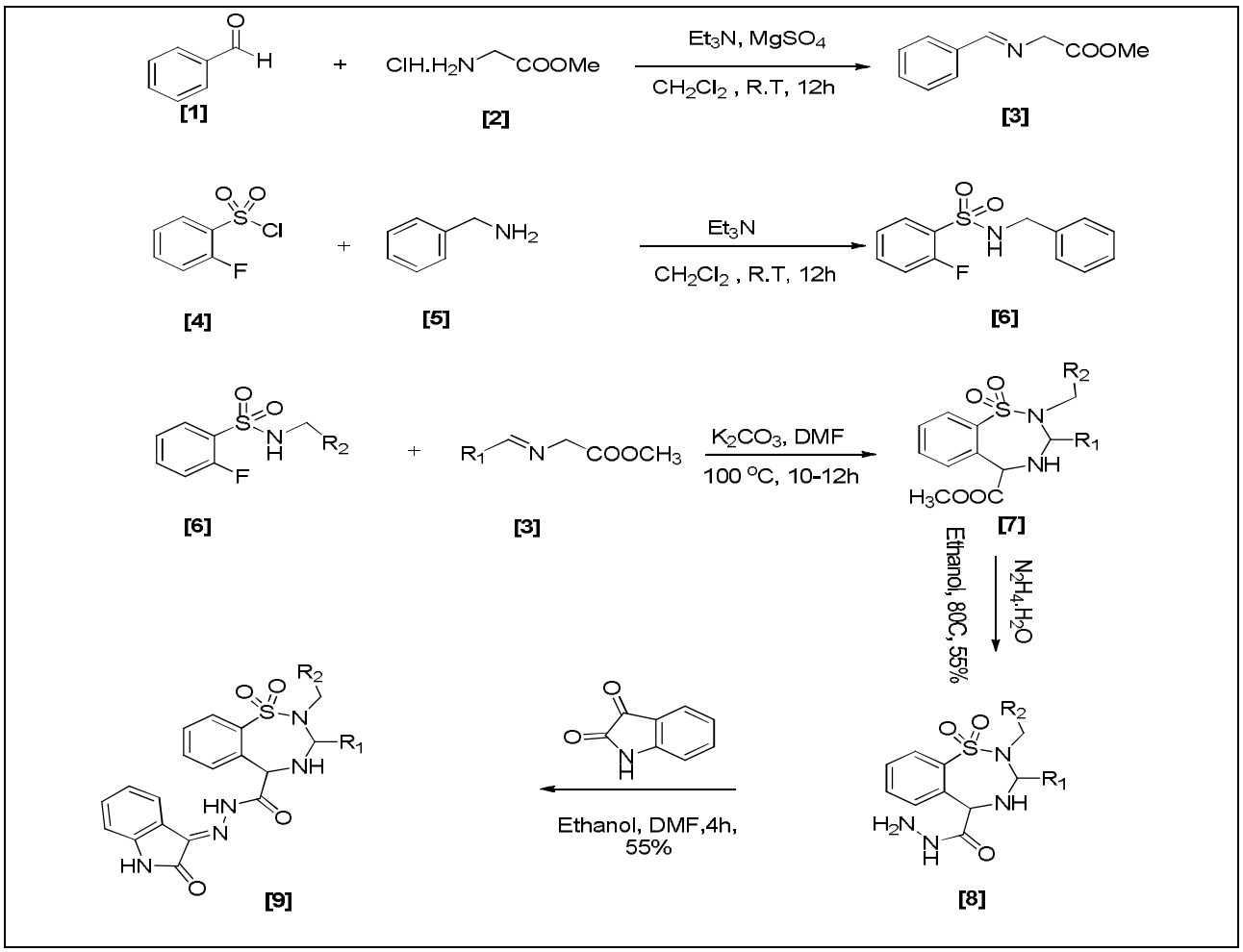
R_1									
R_2									



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