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RESEARCH ARTICLE

Santosh kumar et al, The *Experiment, 2014, Vol. 19(3), 1348-1359*

SYNTHESIS, BIOLOGICAL ACTIVITY AND DOCKING STUDIES OF N,N'-(3S,4S)- BIS(3,4-DISUBSTITUTED PYRROLIDINE)-1-SULFONAMIDE DERIVATIVES AS B-GLUSCOSIDASE INHIBITORS

ABSTRACT

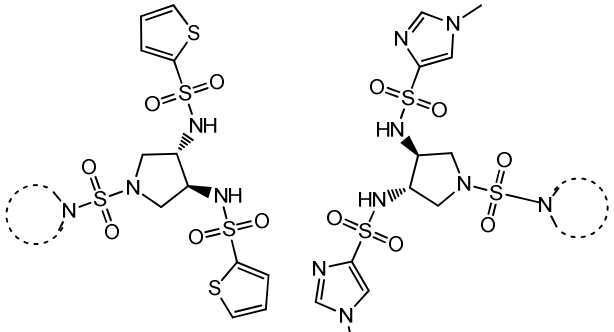
Starting with L-tartaric acid the chiral 3,4-disubstituted pyrrolidine analogue sulfonamide derivatives were prepared. These compounds were examined for anti-bacterial and anti-fungal activity. Further the docking studies were carried out for the model compounds from each series against β-glucosidase and the results found are moderate. The structure–activity relationships are also briefly discussed.

Key Words: L-tartaricacid, pyrrolidine, docking, β-glucosidase

1. INTRODUCTION

Chiral pyrrolidines were found structural subunits in a variety of natural and synthetic bioactive products. [1] Depending on the substitution and functionality, pyrrolidines can be used as effective antibacterials, neuroexcitatory agents, potent venoms, glycosidase inhibitors and fungicides.[2] Numerous bioactive compounds possess pyrrolidine ring are pharmaceutical important. 3,4-substituted pyrrolidines are also more important in asymmetric synthesis. Some of them are successfully transformed into artificial receptor molecules, amino-sugar derivatives as glycosidase inhibitors as well as sugar mimics in nucleoside analogues. Pyrrolidines are identified as suitable substitutes for inhibitor design suited to address the specificity pockets of the respective enzymes in kinases as well as in proteases [3]. Recently, C_2-symmetric pyrrolidines have been discovered as central scaffold for the design and synthesis of aspartic protease inhibitors[4]. Thus these derivatives are either used as structural element to probe structure activity relationship or to enhance the solubility of a respective inhibitor.

Sulfonamides have been used as therapeutic agents for over fifty years. Apart from the commercialized application as antibacterial/antibiotic agents, various sulfonamides are also known to inhibit several enzymes such as carbonic anhydrase [5], cysteine protease [6], HIV protease [7] and cyclooxygenase [8]. Moreover, the widespread potential value of sulfonamides, have led to the discovery of various other therapeutic applications, in cancer chemotherapy [9], diuretics [10], hypoglyceamia [11] and the anti- impotence agent [12].
Hence, in the present investigation we prepared a new series of polysubstituted pyrrolidine derivatives and carried docking studies for the model compounds (12f, 12l).



12a-f

12g-l

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2. Materials and Methods

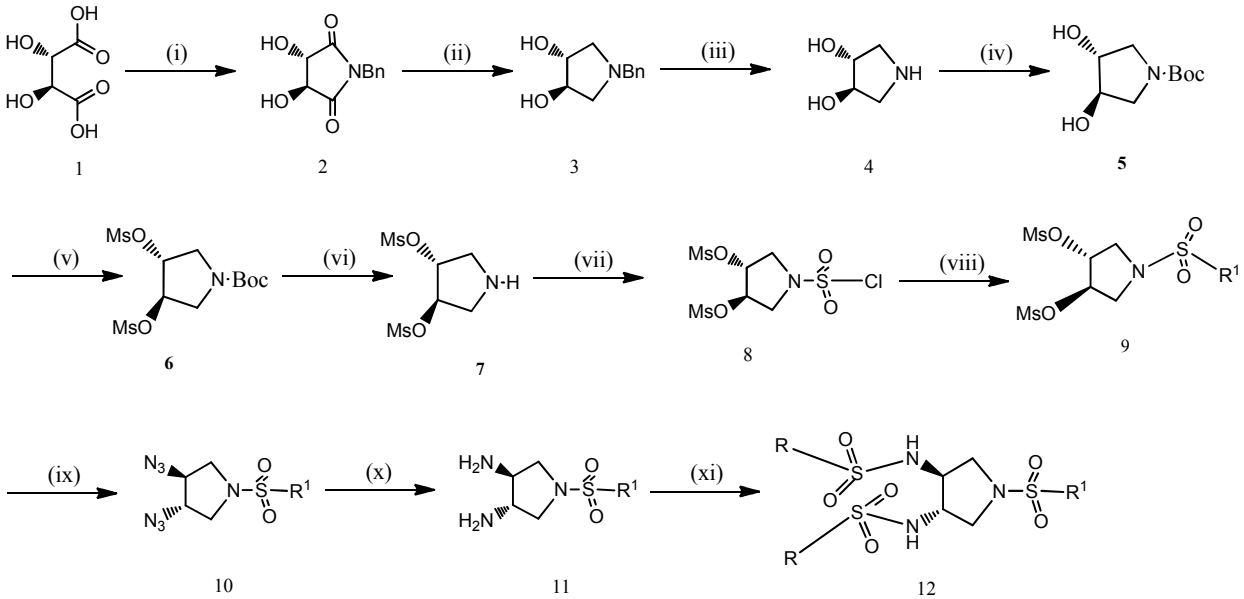
Melting points were determined using X-6 digital display binocular microscope (uncorrected). Infrared spectra were measured on a nicolet nexus 470 FT-IR spectrometer using smear KBr crystal or KBr plate. ^{1}H NMR spectra were recorded on a Bruker Avance (400 MHz) spectrometer. The reaction progress was monitored by TLC with cyclohexane and ethylacetate (9:1) mixture as an elutent. Flash column chromatography was performed using 300 mesh silica gel. The yields were calculated by the last step reaction.

Docking method

Docking was carried out using GOLD (Genetic Optimization of Ligand Docking) software which is based on genetic algorithm (GA). This method allows as partial flexibility of protein and full flexibility of ligand. The compounds are docked to the active site of the HMG coA reductase. The interaction of these compounds with the active site residues are thoroughly studied using molecular mechanics calculations. The parameters used for GA were population size (100), selection pressure (1.1), number of operations (10,000), number of island (1) and niche size (2). Operator parameters for crossover, mutation and migration were set to 100, 100 and 10 respectively. Default cutoff values of 3.0 A° (dH-X) for hydrogen bonds and 6.0 A° for Van der waals were employed. During docking, the default algorithm speed was selected and the ligand binding site in the alpha glucosidase was defined within a 10 A° radius with the centroid as CE atom of ALA410. The number of poses for each inhibitor was set 100, and early termination was allowed if the top three bound conformations of a ligand were within 1.5A° RMSD. After docking, the individual binding poses of each ligand were observed and their interactions with the protein were studied. The best and most energetically favorable conformation of each ligand was selected.

3. Results and Discussion

Our strategy starts with the synthesis of 3,4-dihydroxy pyrrolidine starting from simple molecule L-tartaric acid[13] which further converted to 3,4-diamine pyrrolidine[14]. Finally these amines were transferred to sulfonamide as shown in the scheme below.



(i) Benzylamine, Xylene (ii) I_2, $NaBH_4$ (iii) $Pd/C/H_2$ (iv) Boc_2O, EtoAc (v) MsCl, Et_3N,DCM (vi) F_3CCOOH, H_2O (vii) SO_2Cl_2, TEA, 4-DMAP, Toluene, 0^{o}C, (viii) R^1H (ix) NaN_3, DMF (x) $Pd/C/H_2$ (xi) RSO_2Cl, Py

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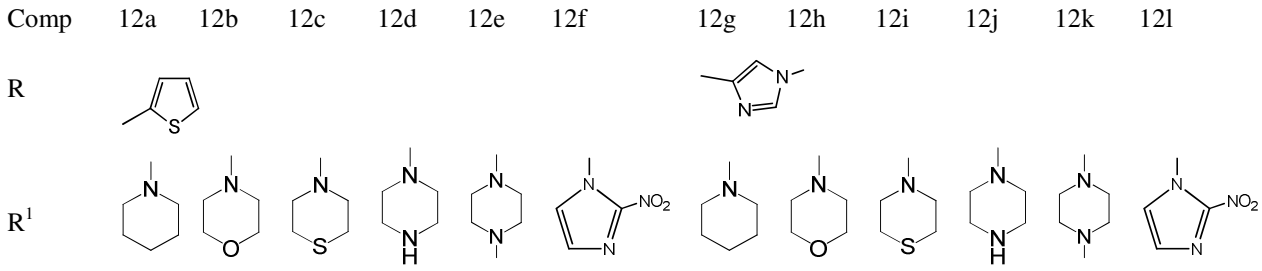

Scheme: 1

3.1 Biological Activities and Preliminary observations

Antibacterial Screening

The antibacterial activity of synthesised compounds 12a-l was studied by the disc diffusion method against Staphylococcus aureus NCCS 2079 and Bacillus cereus NCCS 2106 (gram-positive) and Escherichia coli NCCS2065 and Pseudomonas aeruginosa NCCS2200 (gram-negative) bacteria pathogenic organisms. The synthesised compounds were used at the concentration of 250 µg/ml and 500 µg/ml using DMSO as a solvent. The amoxicillin 10 µg/ml and Streptomycin 10µg/disc were used as a standard. (Himedia Laboratories Ltd, Mumbai). The results were shown in the table 1.

Table 1: Antibacterial activity of compounds 12a-l

S.No	Zone of Inhibition (mm)			
	Staphylococcus aureus	Bacillus cereus	Escherichia coli	Pseudomonas aeruginosa
12a	08	12	13	09
12b	10	11	10	07
12c	06	09	07	11
12d	13	16	14	13
12e	11	14	13	14
12f	14	18	16	15
12g	13	15	14	13
12h	14	16	15	14
12j	12	14	17	12
12k	15	17	14	15
12l	18	22	20	19
Streptomycin	21	27	24	22

* indicate diameter of inhibition in mm.

Antifungal activity

The antifungal activity of synthesised compounds were studied by disc diffusion method against the organisms of Aspergillus niger NCCS1196 and Cadida albicans NCCS34471. Compounds were treated at the concentrations of 100µg/ml, 250µg/ml, 500µg/ml and 1000µg/ml using DMSO as solvent. The standard used was ketaconazole 50µg/ml against both the organisms.

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Table 2: Antifungal activity of compounds 12a-12l

Compound	Zone of Inhibition (mm)			
	Staphylococcus aureus	Bacillus cereus	Escherichia coli	Pseudomonas aeruginosa
12a	08	07	05	06
12b	07	06	06	07
12c	07	06	06	07
12d	10	09	08	10
12e	09	08	07	09
12f	12	11	09	10
12g	11	10	10	09
12h	10	15	09	08
12j	12	14	12	11
12k	11	18	14	15
12l	15	16	17	13
Cefaclor	19	22	19	20

3.2 Docking Studies:

The molecular docking method was performed using the Gold version 3.0.1 program to study the binding affinities of synthesized molecules into the active site of β-glucosidase protein. The structures of the compounds were constructed and optimized using ChemSketch (ACD Labs 11.0) software. The crystal structure of β-glucosidase protein was taken from the Protein Data Bank (PDB_ID:3vkk). Stains were removed from the binding site and the chain A was selected for docking studies. The docking experiments were performed using the binding site of β-glucosidase. Identification of active site was performed by using CASTP server, a new program which automatically locates and measures the protein pockets and cavities.

Human β-glucosidase protein was chosen as the target protein to screen the synthesised compounds for antidiabetic activity, because β-glucosidase and related proteins are key regulators of apoptosis or programmed cell death implicated in human disease including diabetis.

Gold Score fitness function:

Gold Score performs a force field based scoring function and is made up of four components:
1. Protein-ligand hydrogen bond energy (external H-bond); 2. Protein-ligand van der Waals energy (external vdw); 3. Ligand internal van der Waals energy (internal vdw); 4. Ligand intramolecular hydrogen bond energy (internal- H- bond). The external vdw score is multiplied by a factor of 1.375 when the total fitness score is computed. This is an empirical correction to encourage protein-ligand hydrophobic contact. The fitness function has been optimized for the prediction of ligand binding positions.

Gold Score = S (hb_ext) + S (vdw_ext) + S (hb_int) + S (vdw_int)

Where S (hb_ext) is the protein-ligand hydrogen bond score, S (vdw_ext) is the protein-ligand van der Waals score, S (hb_int) is the score from intermolecular hydrogen bond in the ligand and S (vdw_int) is the score from intramolecular strain in the ligand.
The GOLD Score fitness and bonding interactions of the model compounds from 4, 6 and 7 series was shown in the table below.

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Table 3: Hydrogen bonding interactions of compounds 4f, 6f and 7f moieties with β-glucosidase protein

Compound	Number of hydrogen bonds	Atoms		Bond length (A^O)	Fitness
		Protein	Compound		
12e	6	Glu 152 (H)	O7	1.787	47.6790
		Arg 98 (H)	O24	2.557	
		Arg 98	O23	2.240	
		Gly 101	O23	2.202	
		Glu 152	O15	1.959	
		Val 148	N	1.650	
12j	6	Tyr 18	O	2.607	55.9517
		Tyr 21	O	2.084	
		Arg 98	O	2.711	
		Arg 98	O	1.665	
		Glu 152	O	2.493	
		Glu 152	N	2.481	
		Glu 152	O	1.793	
		Glu 152	O	2.674	

4. CONCLUSIONS

In conclusion, a series of novel pyrrolidine sulfonamide derivatives were synthesized. The anti bacterial and anti fungal activities have been carried out. Among tested compounds, the derivatives possessing imidazole nucleus found to be more active, some of the compounds are moderately active and some of them are slightly active.

The docking studies reveal, among the model compounds tested the pyrrolidine-1-sulfonamide derivatives possessing imidazole nucleus (12l) is more potent inhibitor against β-glucosidase than that of the derivatives possessing thiophene nucleus (12f). The results were presented in the table-1 and docking conformations of 12f and 12l was shown in the fig-1 and fig-2 represents the active site of β-glucosidase protein. SAR studies indicated that the introduction of imidazole sulfonyl group at the 3 and 4 positions pyrrolidine ring favored the inhibitory activity against ß-glucosidase. The docking was consistent with the above SAR results.

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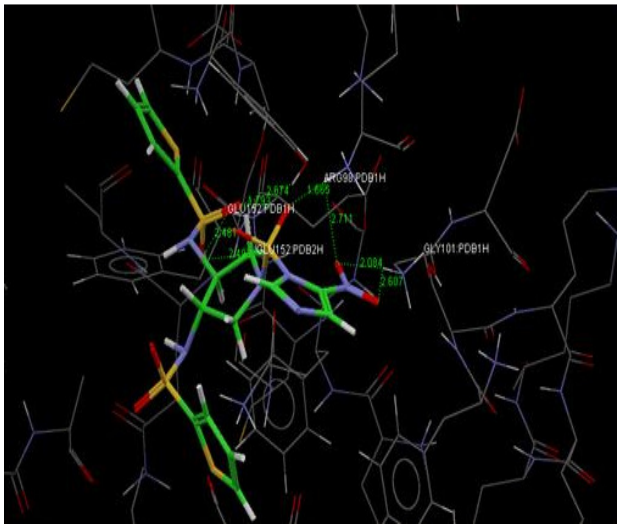

Figure 1

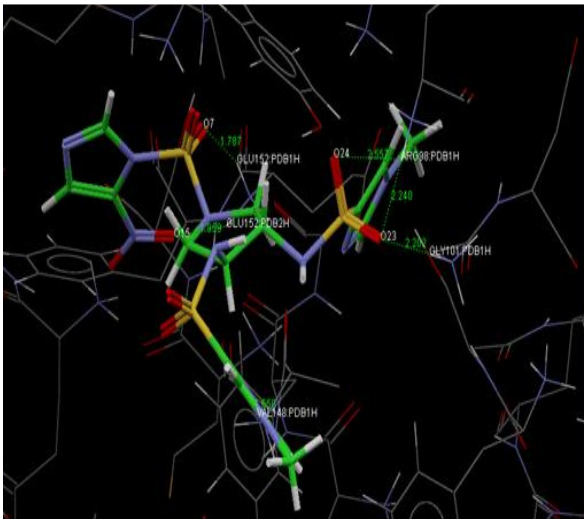

Figure 2

5. Experimental

(3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine-2,5-dione (2):

Benzylamine (1.6mL,15mmol) was slowly added to a stirred suspension of (2S,3S)-2,3-dihydroxysuccinic acid (2.25g, 15mmol) in 50% aqueous methanol (8mL). The resulting mixture was heated at 50^{o}C until a clear solution was obtained. The viscous solution was concentrated on rotary evaporator, xylene (25mL) was added, and the reaction mixture was refluxed in Dean-stark apparatus in oil bath at 190^{o}C for 8h. During that period additional xylene (2 X 15mL) was added. The resulting solution was cooled and concentrated in vacuo. The obtained solid material was co-evaporated with ethanol (2 X10mL) to remove traces of xylene and refluxed in ethanol (15mL) for 5min. The suspension was cooled and crystals were filtered off, washed with ethanol (3 X 5mL) and dried. Filters were combined and concentrated to a volume of 10 mL. Charcoal (3g) was added and the suspension was refluxed for 5min and then filtered through celite. The filtration cake was washed with hot ethanol (5mL) and combined filtrates were left aside to crystallize. The crystallization of mother liquor was repeated three times to obtain an additional of the compound.

(3R,4R)-1-benzylpyrrolidine-3,4-diol (3):

A solution of Iodine (2.03g, 8mmol) in tetrahydrofuran(10mL) was added drop wise to vigorously stirred ice-bath cooled suspension of Sodiumborohydride (0.62g, 16mmol) in a solution of 2 (0.68g, 3mmol) in THF (14mL) under argon atmosphere. The reaction mixture was stirred at room temperature overnight, then cooled to 0^{o}C, and the excess of $NaBH_4$ was decomposed with ice water. The reaction mixture was diluted with water and extracted with ethylacetate. The ethylacetate layer was washed with sodiumthiosulphate, water and finally with brine solution. The organic layer was dried over anhydrous sodiumsulphate. The organic layer on concentration forms semisolid. The so obtained semisolid was scratched with 5% ethylacetate/hexane and filtered, the filtrate on concentration afford an yellow crystals of compound (3R,4R)-1-benzylpyrrolidine-3,4-diol (3) was obtained.

(3R,4R)-pyrrolidine-3,4-diol (4):

1-benzylpyrrolidine derivative 3 (2.9g, 15mmol) in 80% aqueous ethanol (18mL) was treated with hydrogen gas (10psi) in the presence of 10% Pd/C (3g) at room temperature for 2 days. The catalyst was filtered off, the filtrate was concentrate in vacuum, the residue was co-evaporated with ethanol (2 X 8mL), and dried over P_2O_5 (13Pa).

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(3R,4R)-tert-butyl 3,4-dihydroxypyrrolidine-1-carboxylate (5):

t-butyloxycarbonylanhydride (1.5g, 7mmol) was added drop wise to the vigorously stirred mixture of 4 (0.5g, 4.7mmol) and sodiumhydrogen carbonate (3.4g, 40mmol) in 50% aq.dioxane (40mL). The reaction mixture was stirred at room temperature for 2h. The suspension was filtered and the filtrate was concentrate in vacuo. Pure compound was obtained by chromatography on silicagel by using ethanol and chloroform as an elutent.

(3R,4R)-tert-butyl 3,4-bis((methylsulphonyl)oxy)pyrrolidine-1-carboxylate (6):

Mesyl chloride was added dropwise to the reaction mixture of 5 (4mmol) and 4-Dimethylaminopyridine (DMAP) (2.4g, 20mmol) in dichloromethane (DCM) (30mL) at 0^{o}C, and quenched with water (3mL). The solution was washed with a saturated solution of sodium hydrogen carbonate, and the organic layer was dried over sodium sulphate. Solvents were evaporated and pure compound was obtained by chromatography on silicagel using a linear gradient of toluene in petroleum ether followed by a linear gradient of ethyl acetate in toluene.

(3R,4R)-pyrrolidine-3,4-diyl dimethanesulphonate (7):

The compound (3R,4R)-tert-butyl 3,4-bis((methylsulphonyl)oxy)pyrrolidine-1-carboxylate (6) was dissolved in 1:1 trifluoroaceticacid : water mixture and stirred at room temperature for two hours. The reaction was monitored by TLC. The solution is concentrated in vacuum and purified by flash chromatography.

(3R,4R)-1-(chlorosulfonyl)pyrrolidine-3,4-diyl dimethanesulfonate (8a):

To a stirred solution of (3R,4R)-pyrrolidine-3,4-diyl dimethanesulfonate (2.4 g, 10.0 mmol) in dry toluene (25mL) were added drop wise TEA (2.3 g, 21.0 mmol) and DMAP (0.12g) followed by addition of sulfuryl dichloride (2.7g, 20.0 mmol) in dry toluene (15mL) at –10 °C and the mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with dichloromethane (15mL) and washed with saturated. aqueous NH4Cl solution (20 mL) and water (35mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 15% ethyl acetate in hexanes) to give 8a**.**

(3R,4R)-1-(piperidin-1-ylsulfonyl)pyrrolidine-3,4-diyl dimethanesulfonate (9a):

A mixture of Piperidine (1.2g, 25mmol) and (3R,4R)-1-(chlorosulfonyl)pyrrolidine-3,4-diyl dimethanesulfonate (1.78g, 5mmol) and 10mL of pyridine was refluxed for 2h. The reaction mixture was poured into 15mLcold water and stirred to crystallize the product. The solid was filtered off and recrystallised from ethanol.

Compounds **9b-f** were prepared from piperidine, morpholine, thiomorpholine, piperizine, N-methylpiperizine, 2-nitroimidazole respectively by using a procedure similar to that described for the synthesis of 9a.

$C_{11}H_{22}N_2O_8S_3$; M.P. 172-173^{o}C; about 70%; IR (KBr, cm^{-1}): 2923 & 2875, 1292, 1315 & 1181, 1100 cm^{-1} corresponding to -CH_3, C-O, O=S=O, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm) 5.04 (s, 2H –O-CH-), 3.94 (m,2H, -CH_b- protons of pyrrolidine), 3.71(m,2H, -CH_a- protons of pyrrolidine), 3.29 & 3.05(t, 4H, piperidine -N-CH_2-), 2.96(s,6H, two –CH_3), 1.58 (m, 4H, piperidine –N-C-CH_2-), 1.43(m, 4H, piperidine -CH_2- para to N); The elemental analysis found% C, 32.45; H, 5.49; N, 6.92 and calculated % C, 32.50; H, 5.46; N, 6.89.

(3R,4R)-1-(morpholinosulfonyl)pyrrolidine-3,4-diyl dimethanesulfonate (9b):

$C_{10}H_{20}N_2O_9S_3$; M.P. 191-2^{o}C; about 75%; IR (KBr, cm^{-1}): 2924 & 2873, 1284, 1317 & 1179, 1113 cm^{-1} corresponding to -CH_3, C-O, O=S=O, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 5.05 (s, 2H –O-CH-), 3.95 (m,2H, -CH_b- protons of pyrrolidine), 3.72(m,2H, -CH_a- protons of pyrrolidine), 3.69(t, 4H, mortpholine –O-CH_2), 3.11(t, 4H, mortpholine –N-CH_2), 2.96(s,6H, two –CH_3); The elemental analysis found% C, 29.42; H, 4.98; N, 6.88 and calculated % C, 29.40; H, 4.94; N, 6.86.

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(3R,4R)-1-(thiomorpholinosulfonyl)pyrrolidine-3,4-diyl dimethanesulfonate (9c)

$C_{10}H_{20}N_2O_8S_4$; M.P. 162-3°C; about 75%; IR (KBr, cm^{-1}): 2922 & 2876, 1285, 1318 & 1177, 1122 cm^{-1} corresponding to -CH_3, C-O, O=S=O, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 5.04 (s, 2H –O-CH-), 3.94 (m,2H, -CH_b- protons of pyrrolidine), 3.71(m,2H, -CH_a- protons of pyrrolidine), 3.36 & 3.14(t, 4H, thiomortpholine –N-CH_2), 2.96(s,6H, two –CH_3), 2.93(t, 4H, thiomortpholine –S-CH_2); The elemental analysis found% C, 28.21; H, 4.79; N, 6.63 and calculated % C, 28.29; H, 4.75; N, 6.60.

(3R,4R)-1-(piperazin-1-ylsulfonyl)pyrrolidine-3,4-diyl dimethanesulfonate (9d)

$C_{10}H_{21}N_3O_8S_3$; M.P. 181-2°C; about 75%; IR (KBr, cm^{-1}): 2925 & 2874, 1288, 1319 & 1182, 1111 cm^{-1} corresponding to -CH_3, C-O, O=S=O, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 5.03 (s, 2H –O-CH-), 3.99 (m,2H, -CH_b- protons of pyrrolidine), 3.73(m,2H, -CH_a- protons of pyrrolidine), 2.96(s,6H, two –CH_3), 2.94 & 2.72 (m, 8H, piperizine -H), 1.13(s, 1H, piperizine –N-H); The elemental analysis found% C, 29.42; H, 5.22; N, 10.35 and calculated % C, 29.48; H, 5.19; N, 10.31.

(3R,4R)-1-((4-methylpiperazin-1-yl)sulfonyl)pyrrolidine-3,4-diyl dimethanesulfonate (9e)

$C_{11}H_{23}N_3O_8S_3$; M.P. 157-8°C; about 75%; IR (KBr, cm^{-1}): 2929 & 2879, 1286, 1320 & 1183, 1114 cm^{-1} corresponding to -CH_3, C-O, O=S=O, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 4.93 (s, 2H –O-CH-), 4.09(m,2H, -CH_b- protons of pyrrolidine), 3.81(m,2H, -CH_a- protons of pyrrolidine), 3.33(m, 4H, piperizine -H), 2.96(s,6H, two –CH_3), 2.67(m, 4H, piperizine -H), 2.27(s, 3H, piperizine –N-CH_3); The elemental analysis found% C, 31.33; H, 5.53; N, 9.99 and calculated % C, 31.34; H, 5.50; N, 9.97.

(3R,4R)-1-((2-nitro-1H-imidazol-1-yl)sulfonyl)pyrrolidine-3,4-diyl dimethanesulfonate (9f)

$C_9H_{14}N_4O_{10}S_3$; M.P. 196-7°C; about 70%; IR (KBr, cm^{-1}): 2929 & 2879, 1289, 1324 & 1189, 1119 cm^{-1} corresponding to -CH_3, C-O, O=S=O, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.53 & 7.69 (d, 2H, imidazole-H), 4.84 (s, 2H –O-CH-), 4.24(m,2H, -CH_a- protons of pyrrolidine), 3.42 (m,2H, -CH_b- protons of pyrrolidine), 2.96(s,6H, two –CH_3); The elemental analysis found% C, 24.86; H, 3.29; N, 12.95 and calculated % C, 24.88; H, 3.25; N, 12.90.

1-(((3S,4S)-3,4-diazidopyrrolidin-1-yl)sulfonyl)piperidine (10a):

A mixture of **9a** (0.122mol) and aqueous sodium azide (0.735mol) in DMF (400mL) were heated to 120°C for 18h. Reaction was monitored by TLC by using 15% ethylacetate in cylohexane. After completion of the reaction, the reaction mixture was poured into crushed ice and extracted with ethylacetate. The pure organic compound 10 was obtained by subjecting the ethylacetate extract by chromatography on silicagel using a linear gradient of toluene in petroleum ether.

Compounds 10b-f were prepared from 9b, 9c, 9d, 9e and 9f respectively by using a procedure similar to that described for the synthesis of 10a.

(3S,4S)-1-(piperidin-1-ylsulfonyl)pyrrolidine-3,4-diamine (11a):

A mixture of 10a (2.5g), 10% Pd/C (0.5g) and methanol (15mL) in pressure reactor were hydrogenated for 10h. After completion of reaction, catalyst filtered through celite and wash with methanol. The filtrate concentrated under reduced pressure to get 1-(Piperidine-1-sulfonyl)-pyrrolidine-3,4-diamine.

Compounds 11b-f were prepared from 10b, 10c, 10d, 10e and 10f respectively by using a procedure similar to that described for the synthesis of 11a.

$C_9H_{20}N_4O_2S$; M.P. 154-5°C; about 77%; IR (KBr, cm^{-1}): 3450 & 3315, 1292, 1311 & 1181 and 1117cm^{-1} corresponding to -NH_2, C-O, O=S=O and C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 3.78(m,2H, -CH_a- protons of pyrrolidine), 3.32 (m,2H, -CH_b- protons of pyrrolidine), 3.29 (t, 4H, piperidine -N-CH_2-), 2.96(s, 2H –N-CH-), 2.15(s,4H, two –NH_2), 1.58-1.43(m, 6H, piperidine ring); The elemental analysis found% C, 43.51; H, 8.15; N, 22.57 and calculated % C, 43.53; H, 8.12; N, 22.56.

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(3S,4S)-1-(morpholinosulfonyl)pyrrolidine-3,4-diamine (11b)

$C_8H_{18}N_4O_3S$; M.P. 176-7°C; about 75%; IR (KBr, cm^{-1}): 3452 & 3315, 1294, 1313 & 1184 and 1116cm^{-1} corresponding to -NH_2, C-O, O=S=O and C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 3.78(m,2H, -CH_a- protons of pyrrolidine), 3.69(t, 4H, mortpholine –O-CH_2), 3.32 (m,2H, -CH_b- protons of pyrrolidine), 3.11(t, 4H, mortpholine –N-CH_2),2.96(s, 2H –N-CH-), 2.15(s,4H, two –NH_2); The elemental analysis found% C, 38.35; H, 7.29; N, 22.33 and calculated % C, 38.39; H, 7.25; N, 22.38.

(3S,4S)-1-(thiomorpholinosulfonyl)pyrrolidine-3,4-diamine (11c)

$C_8H_{18}N_4O_2S_2$; M.P. 142-3°C; about 70%; IR (KBr, cm^{-1}): 3455 & 3315, 1295, 1316 & 1185 and 1110cm^{-1} corresponding to -NH_2, C-O, O=S=O and C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 3.78(m,2H, -CH_a- protons of pyrrolidine), 3.36 (t, 4H, thiomortpholine –N-CH_2), 3.32 (m,2H, -CH_b- protons of pyrrolidine), 2.96(s, 2H –N-CH-), 3.04(t, 4H, thiomortpholine –S-CH_2), 2.15(s,4H, two –NH_2); The elemental analysis found% C, 36.03; H, 6.89; N, 21.07 and calculated % C, 36.07; H, 6.81; N, 21.03.

(3S,4S)-1-(piperazin-1-ylsulfonyl)pyrrolidine-3,4-diamine (11d)

$C_8H_{19}N_5O_2S$; M.P. 165-6°C; about 70%; IR (KBr, cm^{-1}): 3458 & 3315, 1298, 1318 & 1187 and 1111cm^{-1} corresponding to -NH_2, C-O, O=S=O and C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 3.78(m,2H, -CH_a- protons of pyrrolidine), 3.32 (m,2H, -CH_b- protons of pyrrolidine), 2.96(s, 2H –N-CH-), 2.94 - 2.72 (m, 8H, piperizine -H), 2.15(s,4H, two –NH_2), 1.13(s, 1H, piperizine –N-H); The elemental analysis found% C, 38.52; H, 7.71; N, 28.05 and calculated % C, 38.54; H, 7.68; N, 28.09.

(3S,4S)-1-((4-methylpiperazin-1-yl)sulfonyl)pyrrolidine-3,4-diamine (11e)

$C_9H_{21}N_5O_2S$; M.P. 137-8°C; about 75%; IR (KBr, cm^{-1}): 3454 & 3315, 1296, 1315 & 1188 and 1119cm^{-1} corresponding to -NH_2, C-O, O=S=O and C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 3.92(m,2H, -CH_a- protons of pyrrolidine), 3.39 (m,2H, -CH_b- protons of pyrrolidine), 3.33 (m, 8H, piperizine -H), 2.99(s, 2H –N-CH-), 2.27(s, 3H, piperizine –N-CH_3), 2.15(s,4H, two –NH_2); The elemental analysis found% C, 41.03; H, 8.05; N, 26.51 and calculated % C, 38.54; H, 7.68; N, 28.09.

(3S,4S)-3,4-diamino-N-(2-methyl-1H-imidazol-1-yl)pyrrolidine-1-sulfonamide (11f)

$C_7H_{12}N_6O_4S$; M.P. 186-7°C; about 75%; IR (KBr, cm^{-1}): 3459 & 3315, 1299, 1321 & 1192 and 1124cm^{-1} corresponding to -NH_2, C-O, O=S=O and C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.53 & 7.69 (d, 2H, imidazole-H), 3.78(m,2H, -CH_a- protons of pyrrolidine), 3.32 (m,2H, -CH_b- protons of pyrrolidine), 2.96(s, 2H –N-CH-), 2.15(s,4H, two –NH_2); The elemental analysis found% C, 30.41; H, 4.42; N, 30.38 and calculated % C, 30.43; H, 4.38; N, 30.42.

N,N'-((3S,4S)-1-(piperidin-1-ylsulfonyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulfonamide) (12a):

A mixture of 11a (0.66g, 12.5mmol) and thiophen-2-sulphonyl chloride (4.6g, 2.5mmol) and 15mL of pyridine was refluxed for 1h. The reaction mixture was poured into 15mL of cold water and stirred to crystallize the product. The solid was filtered off and recrystallised from ethanol.

Similar procedure was adopted for the synthesis of compounds 12b-l by using corresponding heterocyclic compounds.
Compounds 12b-f were prepared from 11b, 11c, 11d, 11e and 11f respectively by using a procedure similar to that described for the synthesis of 12a.

$C_{17}H_{24}N_4O_6S_5$; M.P. 184-5°C; about 70%; IR (KBr, cm^{-1}): 3210, 1114, 1100, 1320 & 1185, 1385cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-S, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.48-7.07 (m, 6H, thiophen), 7.49 (s, 2H, SO_2-NH-), 4.53(m,2H, -CH_a- protons of pyrrolidine), 3.63 (m,2H, -CH_b- protons of pyrrolidine), 3.59 (m,2H, -SO_2-N-CH-), 3.29 & 3.05(t, 4H, piperidine -N-CH_2-), 1.58-1.43 (m, 6H, piperidine ring); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 137.1, 128.7, 131.6, 136.3 (thiophene), 48.6, 25.2, 23.2 (piperidine); The elemental analysis found% C, 37.73; H, 4.51; N, 10.35 and calculated % C,

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37.76; H, 4.47; N, 10.36.

N,N'-((3S,4S)-1-(morpholinosulfonyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulfonamide)(12b):
$C_{16}H_{22}N_4O_7S_5$; M.P. 201-2°C; about 70%; IR (KBr, cm^{-1}): 3213, 1115, 1103, 1326 & 1186, 1382cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-S, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.48-7.07 (m, 6H, thiophen), 7.49 (s, 2H, SO_2-NH-), 4.53(m,2H, -CH_a- protons of pyrrolidine), 3.69(t, 4H, mortpholine –O-CH_2), 3.63 (m,2H, -CH_b- protons of pyrrolidine), 3.59 (m,2H, -SO_2-N-CH-),3.11(t, 4H, mortpholine –N-CH_2); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 137.1, 128.7, 131.6, 136.3 (thiophene), 47.7, 65.9 (morpholine); The elemental analysis found% C, 35.39; H, 4.05; N, 10.36 and calculated % C, 35.41; H, 4.09; N, 10.32.

N,N'-((3S,4S)-1-(thiomorpholinosulfonyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulfonamide) (12c):
$C_{16}H_{22}N_4O_6S_6$; M.P. 167-8°C; about 65%; IR (KBr, cm^{-1}): 3211, 1115, 1107, 1325 & 1192, 1384cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-S, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.48-7.07 (m, 6H, thiophen), 7.49 (s, 2H, SO_2-NH-), 4.53(m,2H, -CH_a- protons of pyrrolidine), 3.63 (m,2H, -CH_b- protons of pyrrolidine), 3.59 (m,2H, -SO_2-N-CH-),3.36 (t, 4H, thiomortpholine –N-CH_2),2.93(t, 4H, thiomortpholine –S-CH_2); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 137.1, 128.7, 131.6, 136.3 (thiophene), 47.9, 27.7 (thiomorpholine); The elemental analysis found% C, 34.33; H, 3.96; N, 10.07 and calculated % C34.39; H, 3.97; N, 10.03.

N,N'-((3S,4S)-1-(piperazin-1-ylsulfonyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulfonamide) (12d):
$C_{16}H_{23}N_5O_6S_5$; M.P. 190-1°C; about 65%; IR (KBr, cm^{-1}): 3212, 1117, 1102, 1324 & 1184, 1386cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-S, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.48-7.07 (m, 6H, thiophen), 7.49 (s, 2H, SO_2-NH-), 4.53(m,2H, -CH_a- protons of pyrrolidine), 3.63 (m,2H, -CH_b- protons of pyrrolidine), 3.59 (m,2H, -SO_2-N-CH-), 2.94 - 2.72 (m, 8H, piperizine -H), 1.13(s, 1H, piperizine –N-H); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 137.1, 128.7, 131.6, 136.3 (thiophene), 47.9, 43.2 (pyperizine); The elemental analysis found% C, 35.42; H, 4.25; N, 12.88 and calculated % C 35.47; H, 4.28; N, 12.93.

N,N'-((3S,4S)-1-((4-methylpiperazin-1-yl)sulfonyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulfonamide) (12e):
$C_{17}H_{25}N_5O_6S_5$; M.P. 162-3°C; about 70%; IR (KBr, cm^{-1}): 3211, 1118, 1103, 1327 & 1187, 1387cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-S, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.48-7.07 (m, 6H, thiophen), 7.49 (s, 2H, SO_2-NH-), 4.53(m,2H, -CH_a- protons of pyrrolidine), 3.63 (m,2H, -CH_b- protons of pyrrolidine), 3.59 (m,2H, -SO_2-N-CH-),3.33 (m, 4H, piperizine -H), 2.67 (m, 4H, piperizine -H), 2.27(s, 3H, piperizine –N-CH_3); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 137.1, 128.7, 131.6, 136.3 (thiophene), 47.4, 52.1, 45.0 (N-methylpiperizine); The elemental analysis found% C, 36.71; H, 4.49; N, 12.58 and calculated % C 36.74; H, 4.53; N, 12.60.

N,N'-((3S,4S)-1-((5-nitro-1H-imidazol-1-yl)sulfonyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulfonamide) (12f):
$C_{15}H_{16}N_6O_8S_5$; M.P. 211-2°C; about 65%; IR (KBr, cm^{-1}): 3217, 1121, 1109, 1329 & 1190, 1389cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-S, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.69 & 7.53 (d, 2H, imidazole-H), 7.48-7.07 (m, 6H, thiophen), 7.49 (s, 2H, SO_2-NH-), 4.53(m,2H, -CH_a- protons of pyrrolidine), 3.63 (m,2H, -CH_b- protons of pyrrolidine), 3.59 (m,2H, -SO_2-N-CH-); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 137.1, 128.7, 131.6, 136.3 (thiophene), 132.5, 135.7, 141.1 (nitroimidazole); The elemental analysis found% C, 31.62; H, 2.81; N, 14.75 and calculated % C 31.68; H, 2.84; N, 14.78.

N,N'-((3S,4S)-1-(piperidin-1-ylsulfonyl)pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulfonamide) (12g):
$C_{17}H_{28}N_8O_6S_3$; M.P. 191-2°C; about 70%; IR (KBr, cm^{-1}): 3213, 1117, 1105, 1323 & 1184, 1522cm^{-1} corresponding to -N-H, C-N(exo),

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C-N(cyclic), SO_2, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.90(2H, -N-CH-N- of two imidazole rings), 7.49 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.02(m,2H, -CH_a- protons of pyrrolidine), 3.65 (s, 6H, N- CH_3 of two two imidazole rings), 3.53 (m,2H, -CH_b- protons of pyrrolidine), 3.31 (m,2H, -SO_2-N-CH-), 3.29 & 3.05(t, 4H, piperidine -N-CH_2-), 1.58-1.43 (m, 6H, piperidine ring); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 145.5, 139.5, 134.6, 34.0 (imidazole), 48.6, 25.2, 23.2 (piperidine); The elemental analysis found% C, 38.09; H, 2.24; N, 20.83 and calculated % C 38.05; H, 5.26; N, 20.88.

N,N'-((3S,4S)-1-(morpholinosulfonyl)pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulfonamide) (12h):
$C_{16}H_{26}N_8O_7S_3$; M.P. 152-3°C; about 65%; IR (KBr, cm^{-1}): 3215, 1118, 1107, 1326 & 1183, 1525cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.90(2H, -N-CH-N- of two imidazole rings), 7.49 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.02(m,2H, -CH_a- protons of pyrrolidine), 3.69(t, 4H, mortpholine –O-CH_2), 3.65 (s, 6H, N- CH_3 of two two imidazole rings), 3.53 (m,2H, -CH_b- protons of pyrrolidine), 3.29 (m,2H, -SO_2-N-CH-), 3.11(t, 4H, mortpholine –N-CH_2); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 145.5, 139.5, 134.6, 34.0 (imidazole), 47.7, 65.9 (morpholine);T he elemental analysis found% C, 38.62; H, 4.83; N, 20.76 and calculated % C 38.68; H, 4.83; N, 20.80.

N,N'-((3S,4S)-1-(thiomorpholinosulfonyl)pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulfonamide) (12i):
$C_{16}H_{26}N_8O_6S_4$; M.P. 175-6°C; about 65%; IR (KBr, cm^{-1}): 3214, 1118, 1108, 1325 & 1186, 1523cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.90(2H, -N-CH-N- of two imidazole rings), 7.49 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.02(m,2H, -CH_a- protons of pyrrolidine), 3.65 (s, 6H, N- CH_3 of two two imidazole rings), 3.53 (m,2H, -CH_b- protons of pyrrolidine), 3.36 (t, 4H, thiomortpholine –N-CH_2), 3.29 (m,2H, -SO_2-N-CH-), 2.93(t, 4H, thiomortpholine –S-CH_2); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 145.5, 139.5, 134.6, 34.0 (imidazole), 47.9, 27.7 (thiomorpholine);The elemental analysis found% C, 38.63; H, 4.69; N, 20.17 and calculated % C 38.64; H, 4.72; N, 20.20.

N,N'-((3S,4S)-1-(piperazin-1-ylsulfonyl)pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulfonamide) (12j):
$C_{16}H_{27}N_9O_6S_3$; M.P. 153-4°C; about 70%; IR (KBr, cm^{-1}): 3216, 1122, 1106, 1323 & 1183, 1527cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): .90(2H, -N-CH-N- of two imidazole rings), 7.49 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.02(m,2H, -CH_a- protons of pyrrolidine), 3.65 (s, 6H, N- CH_3 of two two imidazole rings) , 3.53 (m,2H, -CH_b- protons of pyrrolidine), 3.29 (m,2H, -SO_2-N-CH-), 2.94 - 2.72 (m, 8H, piperizine -H), 1.13(s, 1H, piperizine –N-H); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 145.5, 139.5, 134.6, 34.0 (imidazole), 47.9, 43.2 (pyperizine); The elemental analysis found% C, 35.77; H, 5.01; N, 23.41 and calculated % C 35.74; H, 5.06; N, 23.45.

N,N'-((3S,4S)-1-((4-methylpiperazin-1-yl)sulfonyl)pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulfonamide) (12k):
$C_{17}H_{29}N_9O_6S_3$; M.P. 183-4°C; about 70%; IR (KBr, cm^{-1}): 3217, 1124, 1107, 1324 & 1184, 1525cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.90(2H, -N-CH-N- of two imidazole rings), 7.49 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.02(m,2H, -CH_a- protons of pyrrolidine), 3.65 (s, 6H, N- CH_3 of two two imidazole rings) , 3.53 (m,2H, -CH_b- protons of pyrrolidine), 3.33 (m, 4H, piperizine -H), 3.29 (m,2H, -SO_2-N-CH-), 2.67 (m, 4H, piperizine -H), 2.27(s, 3H, piperizine –N-CH_3); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 137.1, 128.7, 131.6, 136.3 (imidazole), 47.4, 52.1, 45.0 (N-methylpiperizine); The elemental analysis found% C, 37.08; H, 5.26; N, 22.79 and calculated % C 37.01; H, 5.30; N, 22.85.

N,N'-((3S,4S)-1-((5-nitro-1H-imidazol-1-yl)sulfonyl)pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulfonamide) (12l)
$C_{15}H_{20}N_{10}O_8S_3$; M.P. 173-4°C; about 65%; IR (KBr, cm^{-1}): 3220, 1127, 1111, 1329 & 1192, 1529cm^{-1} corresponding to -N-H, C-N(exo), C-N(cyclic), SO_2, C-N respectively; ^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): 7.90(2H, -N-CH-N- of two imidazole rings), 7.53 & 7.69 (d, 2H, imidazole-H), 7.49 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.02(m,2H, -CH_a- protons of pyrrolidine), 3.65

(s, 6H, N- CH_3 of two two imidazole rings), 3.53 (m,2H, -CH_b- protons of pyrrolidine), 3.29 (m,2H, -SO_2-N-CH-); ^{13}C NMR (DMSO-d_6, 75MHz, δ ppm): 50.4, 63.2(pyrrolidine), 145.5, 139.5, 134.6, 34.0 (imidazole), 132.5, 135.7, 141.1 (nitroimidazole); The elemental analysis found% C, 31.88; H, 3.56; N, 24.77 and calculated % C 31.91; H, 3.57; N, 24.81.

5. ACKNOWLEDGEMENTS

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