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Synthesis, Characterization and biological evaluation of chiral pyrrolidine sulphonamide mannich bases from tartaric acid

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ABSTRACT

A series of novel chiral 3,4-disubstituted pyrrolidine sulphonamides containing imidazole mannich bases N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1- (piperidin/morpholino/(4-methyl piperazin)-1-yl methyl)-1H-imidazol-5-yl)methylene)hydrazinyl)-2-oxoethyl)pyrrolidine -3,4-diyl)bis ((thiophene-2)/(1-methyl-1H-imidazole-4-)/(4-nitro benzene)sulphonamide) ***(16a-16i)*** *were synthesized in stereoselective route starting from L-(+) tartaric acid . At the out set, L-(+) tartaric acid was converted into pyrrolidine sulphonamide derivatives N,N'-((3S,4S)-1-(2-hydrazinyl-2-oxoethyl)pyrrolidine-3,4-diyl)bis ((thiophene-2-)/(1-methyl-1H-imidazole-4-)/(4-nitro benzene) sulphonamide)* ***(12a-12c)*** *by following systematic synthetic procedure depicted in the schemes. The intermediates* ***(12a-12c)*** *were condensed with 4-chloro-2-methyl-1-(piperidin/morpholino/(4-methylpiperazin)-1-ylmethyl)-1H-imidazole-5-carbaldehyde* ***(15 a-15c)*** *to afford the title compounds N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-(piperidin /morpholino/(4-methylpiperazin)-1-ylmethyl)-1H-imidazol-5-yl)methylene) hydrazinyl)-2-oxoethyl) pyrrolidine-3,4-diyl)bis((thiophene-2)/(1-methyl-1H-Imidazole-4-)/(4-nitrobenzene) sulphonamide)* ***(16a-i)****. The structure of the newly synthesized compounds were characterized by* ^{1}*HNMR,* C^{13}*NMR, Mass, IR and elemental analysis. The prepared compounds have been screened for their antibacterial and antifungal activities.*

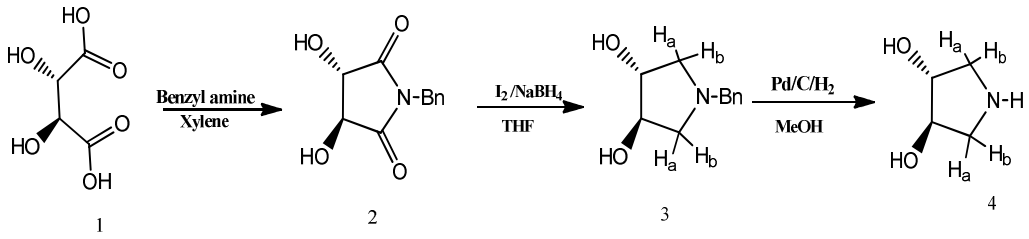
Key words: L-**(+)** tartaric acid, Pyrrolidine Sulphonamides, antibacterial.

INTRODUCTION

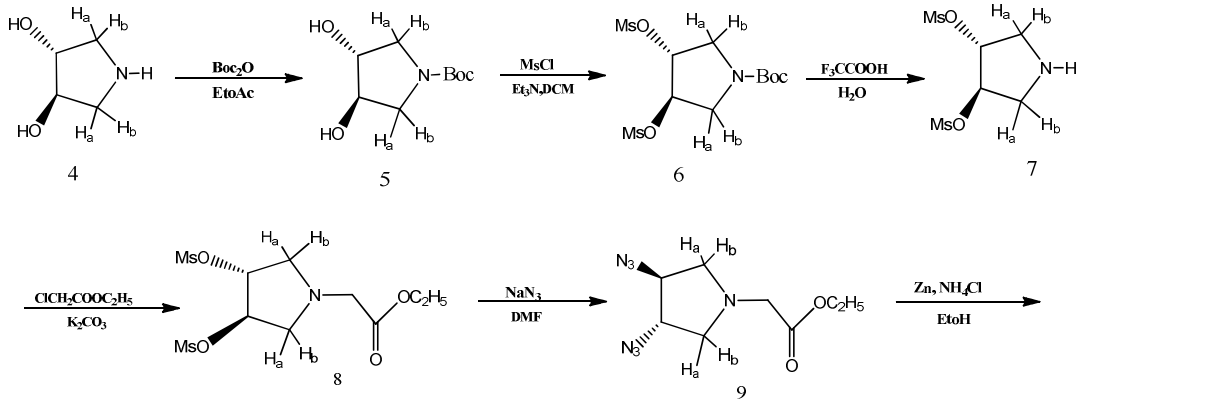
Tartaric acids were used as building blocks in asymmetric synthesis overall catalyst design [1,2]. Literature survey shows the most comprehensive overview of the usage of tartaric acid as well as malic acid in organic synthesis [3]. The pyrrolidines derived from either L-(+) or D-(-) tartaric acid are chiral C_2-symmetry molecules. These derivatives were successfully utilized in several medicinal chemistry projects. The rigid structure was either used as structural element to probe structure-activity relationship or to enhance the solubility of a respective inhibitor. In the field of medicinal chemistry, pyrrolidines were successfully transformed into artificial receptor molecules. In kinases as well as proteases, pyrrolidines were identified as suitable substituents for inhibitor design suited to address the specificity pockets of the respective enzymes [4]. Additionally, 3,4-diamino-pyrrolidine was used as central core element for the design and synthesis of HIV-protease inhibitors, whereas 3,4-dihydroxylated pyrrolidine served as building block for the synthesis of several glycosidase inhibitors [4]. Due to the rigidity of the pyrrolidine ring system, Pyrrolidine-diols were used as D-ring analogues in estradiol mimics [5, 6]. Fluorine-substituted pyrrolidine side chains were utilized during the development of dipeptidyl-peptidase IV (DPP-IV) inhibitors [7, 8]. The pyrrolidine sulphonamides are useful in the treatment of congestive heart failures, stroke, cardiac arrhythmia,

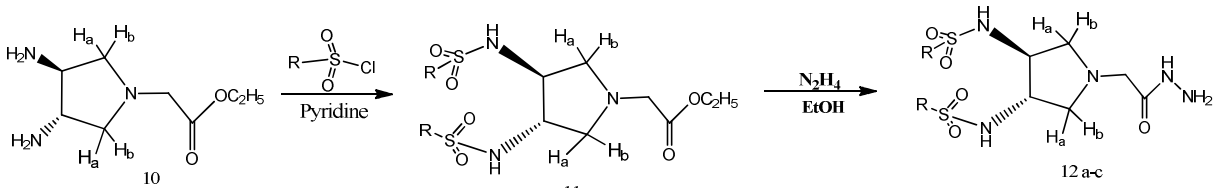
restenosis, hypertension, neurogenic, ischemic heart disease, asthama, inflammation and metabolic vasculopathies, addiction, impulsivity, anxiety, stress, depression, neuromuscular function and diabetes and also as antagonist of urotensin II [9,10].

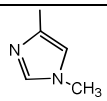
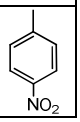
In the following part, the transformation of L-(+) tartaric acid to pyrrolidine sulphonamide containing imidazole mannich bases and their further funsctionalization was described.



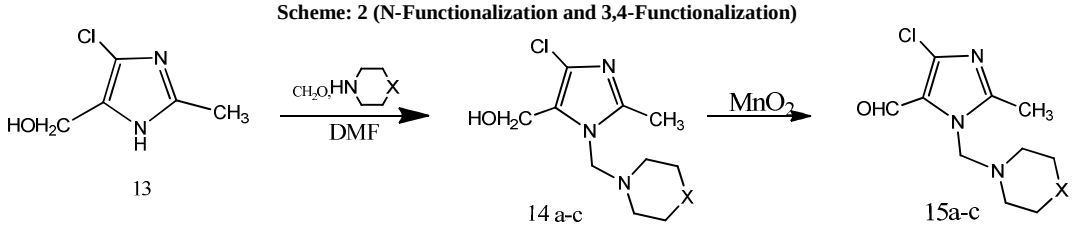
Scheme: 1 (N-Functionalization)





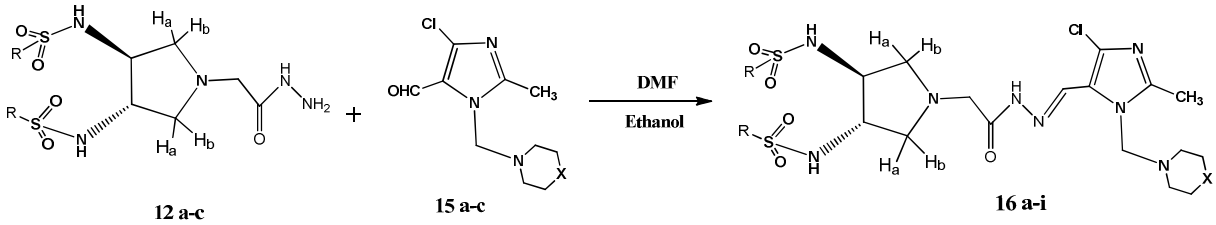
Compound	11a	11b	11c
R =			

Scheme: 2 (N-Functionalization and 3,4-Functionalization)

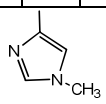
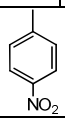


Compound	**14a**	**14b**	**14c**	**15a**	**15b**	**15c**
X	-CH_2-	-O-	-NCH_3	-CH_2-	-O-	-NCH_3

Scheme: 3



12 a-c **15 a-c** **16 a-i**

Compound	16a	16b	16c	16d	16e	16f	16g	16h	16i
X	$-CH_2-$	-O-	$-NCH_3$	$-CH_2-$	-O-	$-NCH_3$	$-CH_2-$	-O-	$-NCH_3$
R									

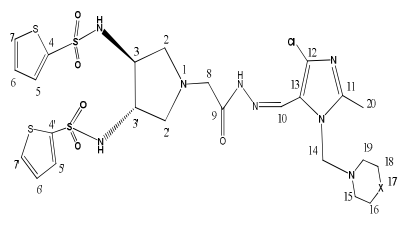
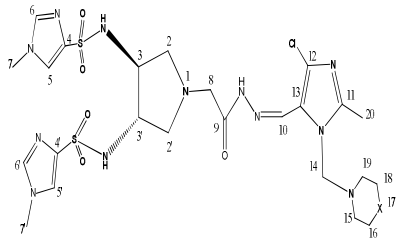
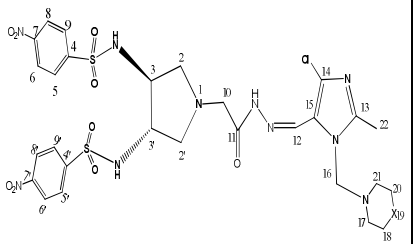
Scheme: 4

MATERIALS AND METHODS

Melting points were determined on open capillaries using a cintex melting point apparatus. Solvents were purified by standard procedures before use. Column chromatography was conducted by using silica gel with different solvent systems as elutes. Purity of the compounds was checked on thin layer chromatography (TLC) plates (Silica gel G) in the solvent system Chloroform: Methanol (9:1, v/v) and Ethyl Acetate: Hexane (3:7, v/v) and benzene: acetone (8:2, v/v), the spots were located under iodine vapors and UV light**.** IR Spectra were recorded in KBr on Perkin-Elmer Spectrum BX series FT-IR spectrometer. 1H-NMR spectrum were recorded on Varian Gemini 300MHz spectrometers using TMS as internal standard (chemical shifts in δ ppm). 13C-NMR Spectra were recorded on a Brucker 75MHz spectrometer. Mass spectra were scanned on a varian MATCH-7 and Jeol JMSD-300 mass spectrometer at 70ev. Elemental analyses were carried out on a carloerba 106 and Perkin-Elmer Analyser. All the chemicals used in the present investigation were purchased from Aldrich chemicals; U.S.A. (4-chloro-2-methyl-1H-imidazol-5-yl)methanol was prepared by a reported method [11].

RESULTS AND DISCUSSION

The pyrrolidine sulphonamides containing imidazole mannich bases[12] were synthesized by following a systematic synthetic organic procedure depicted in given schemes with emphasis on N-functionalization and 3, 4 functionalization on pyrrolidine ring.

16a – 16c	16d – 16f	16g -16i
 X= $-CH_2$ / -O- / $-N-CH_3$	 X= $-CH_2$ / -O- / $-N-CH_3$	 X= $-CH_2$ / -O- / $-N-CH_3$

Synthesis of (3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine-2,5-dione (2) [13]:
Benzylamine (8.0mL,75mmol) was slowly added to a stirred suspension of (2S,3S)-2,3-dihydroxysuccinic acid (11.3g, 75 mmol) in 50% aqueous methanol (15mL). The resulting mixture was heated at 50^{o}C until a clear solution was obtained. The viscous solution was concentrated on rotary evaporator, xylene (75mL) 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 25mL) 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 (25mL) for 5min. The suspension was cooled, crystals were filtered off, washed with ethanol (3 X 5mL) and dried to yield 12.2g (73%) of compound. Combined filters were concentrated to a volume of 25mL. Charcoal (8g) was added and the suspension was refluxed for 5min and then filtered through celite. The filtration cake was washed with hot ethanol (10mL) and combined filtrates were left aside to crystallize. The crystallization of mother liquor was repeated three times to obtain an additional 3.4g (20%) of compound. The total yield was 15.4g (93%) and the melting point is 206-7^{o}C.

Synthesis of (3R,4R)-1-benzylpyrrolidine-3,4-diol (3) [14]**:**
A solution of Iodine (9.5g, 37.5mmol) in tetrahydrofuran(45mL) was added drop wise to vigorously stirred ice-bath cooled suspension of Sodiumborohydride (2.9g, 75mmol) in a solution of 2 (3.4g, 15mmol) in THF (70mL) 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 (Note: Intensive gas evolution occurred when water is added to $NaBH_4$). 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 semi solid. The so obtained semi solid 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) and the melting point is 182-3^{o}C.

(3R,4R)-pyrrolidine-3,4-diol (4) [13]***:***
1-benzylpyrrolidine derivative 3 (14.5g, 75mmol) in 80% aqueous ethanol (90mL) was treated with hydrogen gas (10psi) in the presence of 10% Pd/C (4g) 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 25mL), and dried over P_2O_5 (13Pa). Compound was obtained as yellow oil in 92% yield and the boiling point is 232-3^{o}C. The IR (KBr) spectra of (3R,4R)-pyrrolidine-3,4-diol (4) shows the peaks around 3300, 3240, 1120, 1100 cm^{-1} and these are due to -N-H, -O-H, $^{\upsilon}$C-O/$^{\delta}$ O-H, -C-N respectively. The ^{1}H NMR (300MHz) spectra was recorded in DMSO-d_6 showed the following signals 4.16(s, 2H,-OH), 3.40(m,2H,-C-CH-O-), 3.02(m,2H, two CH_a protons of pyrrolidine), 2.77(m,2H, two CH_b protons of pyrrolidine), 2.12(s,1H, -C-NH-). The CH_a, CH_b protons of pyrrolidine ring show two singnals at two different chemical shifts in ^{1}H NMR, due to their diastereotropic nature.

Synthesis of (3R,4R)-tert-butyl 3,4-dihydroxypyrrolidine-1-carboxylate (5) [15]***:***
t-butyloxycarbonylanhydride (7.5g, 35mmol) was added drop wise to the vigorously stirred mixture of 4 (2.5g, 23.3mmol) and sodiumhydrogen carbonate (17g, 200mmol) in 50% aq.dioxane (200mL). 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. The product 5 was obtained with 85% yield (4.1g) as white solid. The elemental analysis found % C, 53.23; H, 8.48; N, 6.77 and calculated % C, 53.19; H, 8.43; N, 6.89 and the melting point is 174-5^{o}C.
.
Synthesis of (3R,4R)-tert-butyl 3,4-bis((methylsulphonyl)oxy)pyrrolidine-1-carboxylate (6) [16]***:***
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. The organic compound 6 was obtained in 83% yield (1.93g) in the form of yellowish foam. The elemental analysis found % C, 36.73; H, 5.81; N, 3.95 and calculated % C, 36.76; H, 5.89; N, 3.90.

Synthesis of (3R,4R)-pyrrolidine-3,4-diyl dimethanesulphonate (7) [15]***:***
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. The IR (KBr) spectra of (3R,4R)-pyrrolidine-3,4-diyl dimethanesulphonate (7) shows the peaks around 3300, 1375 & 1185, 1150, 1100, 1050, 975, 2923 & 2875 cm^{-1} and these are due to -N-H, asymmetric & symmetric stretching of O=S=O, -C-O, -C-N, C-S, S-O, asymmetric & symmetric stretching of $-CH_3$ respectively. The ^{1}H NMR (300MHz) spectra was

recorded in DMSO-d_6 showed the following signals 3.85(m,2H, -C-CH-O-), 3.16(s,6H, -O-SO_2-CH_3), 3.02 (m,2H, two CH_a protons of pyrrolidine), 2.77 (m,2H, two CH_b protons of pyrrolidine), 2.12(s,1H, -C-NH-). The elemental analysis found % C, 27.63; H, 5.12; N, 5.22; calculated % C, 27.79; H, 5.05; N, 5.40. The yield was 62% with melting point of 190-1^{o}C.

***Synthesis of ethyl 2-((3R,4R)-3,4-bis((methylsulphonyl)oxy)pyrrolidin-1-yl)acetate (8)*:**
A mixture of (3R,4R)-pyrrolidine-3,4-diyldimethanesulphonate(7), anhydrous K_2CO_3, chloroethylacetate and DMF was stirred at room temperature for 8h. The reaction mixture was diluted with ice cold water. The separated solid was identified as 8. This was cooled by filtration, and recrystallization from ethanol. The elemental analysis found % C, 34.73; H, 5.64; N, 4.17 and calculated % C, 34.77; H, 5.54; N, 4.06. Melting Point of the compound is 144-5^{o}C, yield 78%.

Synthesis of ethyl 2-((3S,4S)-3,4-diazidopyrrolidin-1-yl)acetate (9) [16]***:***
A mixture of ethyl 2-((3R,4R)-3,4-bis((methylsulphonyl)oxy)pyrrolidin-1-yl)acetate (8) (4.3g, 1.22mmol) and aqueous Sodium azide (3.43g, 7.35mmol) in DMF (40mL) were heated to 120^{o}C for 18h. Reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into crushed ice and extracted with ethylacetate. The ethylacetate extract was subjected to Flash Chromatographic technique to afford 9 with 68% yield, with melting point of 176-7^{o}C. This reaction involves the nucleophillic substitution of azide ion on C_3, C_4 carbon atoms of (3R,4R) pyrrolidine derivative 8 by S_N2 mechanism and the product ends with inversion in the configuration ((3S,4S) pyrrolidine derivative 9). The elemental analysis found % C, 40.22; H, 5.42; N, 40.89 and calculated %C, 40.16; H, 5.48; N, 40.98.

Synthesis of ethyl 2-((3S,4S)-3,4-diaminopyrrolidin-1-yl)acetate (10) [19,20]***:***
To the solution of ethyl 2-((3R,4R)-3,4-diazidopyrrolidin-1-yl)acetate (9)(7.17g, 30mmol) and ammonium chloride (4g,70mmol) in ethyl alcohol (80 mL) and water (27 mL), zinc powder (2.4g, 40mmol) was added, the mixture was stirred vigorously at room temperature or at refluxing. The progress of the reaction was monitored by TLC. After completion of the reaction ethyl acetate (100 mL) and aqueous ammonia (10 mL) was added. The mixture was filtered, and the filtrate was washed with brine, dried over anhydrous sodium sulphate. After removal of solvent under reduced pressure, the residue was purified by a flash chromatography or recrystallization to give the corresponding amine ethyl 2-((3S,4S)-3,4-diaminopyrrolidin-1-yl)acetate (10) with yield 745% with melting point of 154-5^{o}C. The IR (KBr) spectra of ethyl 2-((3R,4R)-3,4-diaminopyrrolidin-1-yl)acetate (10) shows the peaks around 3450, 3315, 2923,2875, 1737, 1317, 1280, 1100 cm^{-1} and these are due to asymmetric and symmetric stretching of -NH_2, asymmetric and symmetric stretching of -CH_3, -C=O, -C-O-, exo -C-N, cyclic C-N respectively. The ^{1}H NMR (300MHz) spectra of (10) was recorded in DMSO-d_6 showed the following signals 5.11 (s,4H, -C-NH-), 4.13 (q,2H, -O-CH_2-), 3.32 (s,2H, -COO-CH_2-), 2.95 (m,2H, -CH-N-), 2.60 (m,2H, two CH_a protons of pyrrolidine), 2.35 (m,2H, two CH_b protons of pyrrolidine), 1.29 (t,3H, -CH_3). The elemental analysis found % C, 50.52; H, 7.75 ; N, 7.25 and calculated % C, 50.78 ; H, 7.99 ; N, 7.40.

Synthesis of ethyl 2-((3S,4S)-3,4-bis(thiophene-2-sulphonamido)pyrrolidin-1-yl)acetate (11) [17]***:***
A mixture of 10 (6g, 125mmol) and thiophen-2-sulphonyl chloride (46g, 25mmol) and 15mL of pyridine was refluxed for 3h. The reaction mixture was poured into 50mL of cold water and stirred to crystallize the product. The solid was filtered off and recrystallised from ethanol. The total yield of the compound ethyl 2-((3S,4S)-3,4-bis(thiophene-2-sulphonamido)pyrrolidin-1-yl)acetate (11) was 82%, with melting point of 184-5^{o}C. Similar procedure was extended for the synthesis of other compounds(11b & c) of the series and their physical characterization data is given in Table 1.

Synthesis of N,N'-((3S,4S)-1-(2-hydrazinyl-2-oxoethyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulphonamide) (12a-c) [17]***:***
A solution of ethyl 2-((3S,4S)-3,4-bis(thiophene-2-sulphonamido)pyrrolidin-1-yl)acetate (11) and hydrazine hydrate in ethanol was refluxed for 5 hours. The reaction mixture was cooled and poured into ice cooled water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford (12). Similar procedure was extended for the synthesis of other compounds(12b & c) of the series and their physical characterization data is given in Table 1. IR (KBr): 3410 & 3310, 3520, 3210, 1670, 1117, 1100, 1320 & 1185, 1388 cm^{-1} due to asymmetric & symmetric stretching of -NH_2, N-H, N-H, C=O, C-N, asymmetric & symmetric stretching of O=S=O, C-S respectively. NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 7.65-7.22 (m, 6H,

thiophen), 7.47 (s, 2H, SO_2-NH-), 4.22 (s,2H, hydrazide -NH_2), 3.25 (s,2H, -N-CH_2-CO), 3.50 (m,2H, -SO_2-N-CH-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.29 (m,2H, -CH_b- protons of pyrrolidine).

N,N'-((3S,4S)-1-(2-hydrazinyl-2-oxoethyl)pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulphonamide) (12b):
IR (KBr): 3412 & 3313, 3522, 3213, 1672, 1119, 1103, 1322 & 1187, 1520, 2915 & 2875cm^{-1} due to asymmetric & symmetric stretching of -NH_2, N-H, N-H, C=O, C-N, asymmetric & symmetric stretching of O=S=O, C-N (Imidazole), -CH_3 respectively. NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 7.90(2H, -N-CH-N- of two imidazole rings), 7.47 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.22 (s,2H, hydrazide -NH_2), 3.65 (s, 6H, N- CH_3 of two two imidazole rings) 3.50 (m,2H, -SO_2-N-CH-),3.25 (s,2H, -N-CH_2-CO-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.29 (m,2H, -CH_b- protons of pyrrolidine).

N,N'-((3S,4S)-1-(2-hydrazinyl-2-oxoethyl)pyrrolidine-3,4-diyl)bis(4-nitrobenzenesulphonamid e) (12c):
IR (KBr): 3413 & 3317, 3527, 3217, 1678, 1120, 1107, 1325 & 1190, 1542, & 1330 cm^{-1} due to asymmetric & symmetric stretching of -NH_2, N-H, N-H, C=O, C-N, asymmetric & symmetric stretching of O=S=O, -NO_2 respectively. NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.12-8.39 (m,8H, aromatic protons), 7.47 (s, 2H, SO_2-NH-), 4.22 (s,2H, hydrazide -NH_2), 3.25 (s,2H, -N-CH_2-CO-), 3.50 (m,2H, -SO_2-N-CH-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.29 (m,2H, -CH_b- protons of pyrrolidine).

Table 1: physical characterization data of synthesized compounds 11a-11c and 12a-12c

Compound	R	M.P. /^{0}C	YIELD	Molecular Formula	Found % (Calculated %)		
					C	H	N
11a		182-3	70	$C_{16}H_{21}N_3O_6S_4$	40.15 (40.07	4.49 (4.41)	8.79 (8.76)
11b		164-5	75	$C_{16}H_{25}N_7O_6S_2$	40.49 (40.41)	5.35 (5.30	20.59 (20.62)
11c		158-9	70	$C_{20}H_{23}N_5O_{10}S_2$	43.18 (43.08)	4.22 (4.16)	21.52 (12.56)
12a		206-7	70	$C_{14}H_{19}N_5O_5S_4$	36.39 (36.12)	4.09 (4.11)	15.12 (15.04)
12b		195-6	75	$C_{14}H_{23}N_9O_5S_2$	36.52 (36.43)	4.98 (5.02)	27.27 (27.31)
12c		177-8	70	$C_{18}H_{21}N_7O_9S_2$	39.63 (39.78)	3.82 (3.89)	18.12 (18.04)

***Synthesis of (4-chloro-2-methyl-1-(piperidin-1-ylmethyl)-1H-imidazol-5-yl)methanol (14a)[16]*:**
The second key intermediate 14 was synthesized by stirring a mixture of (4-chloro-2-methyl-1H-imidazol-5-yl)methanol (13) (14.65g, 100mmol), piperidine (12.75g, 100mmol) and water (20mL) until a clear solution was obtained. To this solution, HCHO (1.5g, 50mmol) and DMF were added in ice-cold condition and stirred for 2hours in ice-bath and left overnight at room temperature. The obtained white solid was isolated and crystallized from ethanol to give compound (4-chloro-2-methyl-1-(piperidin-1-ylmethyl)-1H-imidazol-5-yl)methanol (14a). The reaction procedure leading to 14a was then extended to the synthesis of 14a&c. The physical characterization data was shown in the table 2.

Synthesis of 4-chloro-2-methyl-1-(piperidin-1-ylmethyl)-1H-imidazole-5-carbaldehyde (15a) [11]***:***
A suspension of (4-chloro-2-methyl-1-(piperidin-1-ylmethyl)-1H-imidazol-5-yl)methanol (14a) (17.3g, 71mmol) and activated MnO_2 (31g, 350mmol) in acetonitrile (100mL) was heated at reflux for 24h. The hot mixture was filtered and washed with warm acetonitrile. The solvent was removed under reduced pressure. The residue was crystallised from CH_2Cl_2 to give the compound 4-chloro-2-methyl-1-(piperidin-1-ylmethyl)-1H-imidazole-5-carbaldehyde (15a)at the yield of as 70% as white crystals with a Melting Point 146-147^{o}C. Similar procedure was

extended for the synthesis of other compounds (15b & c) of the series and their characterization data is given in Table 2 .IR (KBr): 1725, 745, 1550, 1344, 1325, and 745cm^{-1} corresponding to the bonds C=O, C-N in imidazole, exo C-N, C-N of piperidine, and C-Cl respectively. ^{1}H-NMR (300MHz) in DMSO-d_6: 9.75 (s,1H, -HC=O), 4.80 (s,2H, -N-CH_2-N-), 2.51 (s,3H, -CH_3 attached to imidazole ring,2.45(t,4H, -CH_2 -N-CH_2- of piperidine), 1.52-1.60 (m,6H, –CH_2- of piperidine ring).

4-chloro-2-methyl-1-(morpholin-1-yl)-1-ylmethyl-1H-imidazole-5-carbaldehyde (15b):
IR (KBr): 1728, 745, 1553, 1346, 1310, and 745cm^{-1} corresponding to the bonds C=O, C-N in imidazole, exo C-N, C-O and C-Cl respectively. ^{1}H-NMR (300MHz) in DMSO-d_6: 9.75 (s,1H, -HC=O), 4.80 (s,2H, -N-CH_2-N-), 3.65 (t,4H, –O-CH_2- of morpholine), 2.59 (t,4H, -N-CH_2- of morpholine), 2.51 (s,3H, -CH_3 attached to imidazole ring).

4-chloro-2-methyl-1-(4-methylpiperazin-1-yl)-1-ylmethyl-1H-imidazole-5-carbaldehyde (15c):
IR (KBr): 1729, 745, 1556, 1349, 2915 & 2875, 749cm^{-1} corresponding to the bonds C=O, C-N in imidazole, exo C-N, -CH_3 and C-Cl respectively. ^{1}H-NMR (300MHz) in DMSO-d_6: 9.75 (s,1H, -HC=O), 4.80 (s,2H, -N-CH_2-N-), 2.51 (s,3H, -CH_3 attached to imidazole ring), 2.35 (m,8H, -N-CH_2- of piperizine), 2.26 (s,3H, -N-CH_3 of N-methyl piperizine).

Table 2: physical characterization data of synthesized compounds 14a-14c and 15a-15c

Compound	X	M.P. /°C	YIELD	Molecular Formula	Found % (Calculated %)		
					C	H	N
14a	-CH_2-	145-6	65	$C_{11}H_{18}ClN_3O$	54.28 (54.21)	7.42 (7.44)	17.27 (17.24)
14b	-O-	164-5	60	$C_{10}H_{16}ClN_3O$	48.87 (48.88)	6.54 (6.56)	17.12 (17.10)
14c	-NCH_3	138-9	70	$C_{11}H_{19}ClN_4O$	51.08 (51.06)	7.32 (7.40)	21.63 (21.65)
15a	-CH_2-	172-3	65	$C_{11}H1_6ClN_3O$	54.59 (54.66)	6.75 (6.67)	17.45 (17.38)
15b	-O-	183-4	75	$C_{10}H1_4ClN_3O_2$	49.07 (49.29)	5.84 (5.79)	17.32 (17.24)
15c	-NCH_3	164-5	70	$C_{11}H_{17}ClN_4O$	51.38 (51.46)	6.72 (6.67)	21.63 (21.82)

Synthesis of N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-(piperidin-1-ylmethyl)-1H-imidazol-5-yl)methylene) hydrazinyl)-2-oxoethyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulphonamide) (16a) **:**
Equimolar quantities of N,N'-((3S,4S)-1-(2-hydrazinyl-2-oxoethyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulphon -amide) (12) (4.65g, 10mmol) and 4-chloro-2-methyl-1-(piperidin-1-ylmethyl)-1H-imidazole-5-carbaldehyde (15a) (2.42g, 10mmol) were dissolved in warm ethanol (40mL) containing DMF (0.5mL). The reaction mixture was refluxed for 3-4hours and then kept at room temperature overnight. The resulting solid was filtered and washed with ethanol, dried and recrystallized from ethanol to afford compound N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-(piperidin-1-ylmethyl)-1H-imidazol-5-yl)methylene)hydrazinyl)-2-oxoethyl)pyrrolidine-3,4-diyl) bis(thiophene-2-sulphonamide) (16a). Similar procedure was extended for the synthesis of other compounds(16b-i) of the series and their characterization data is given in Table 3.

IR (KBr): 3522(–N-H amide), 3210(-N-H sulphonamide), 1725(C=O), 1615(C=N), 1550(C-N imidazole), 1320 & 1185(asymmetric & symmetrical stretching of O=S=O), 1117(exo C-N), 1100(cyclic C-N), 748(C-Cl) cm^{-1}. ^{1}H-NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.03 (s,1H, -N=CH-), 7.65-7.22 (m, 6H, thiophene), 7.47 (s, 2H, SO_2-NH-), 4.80 (s,2H, -N-CH_2-N-), 4.22 (s,2H, hydrazide -NH_2), 3.25 (s,2H, -N-CH_2-CO), 3.50 (m,2H, -SO_2-N-CH-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.51 (s,3H, -CH_3 attached to imidazole ring,2.45(t,4H, -CH_2 -N-CH_2- of piperidine), 2.29 (m,2H, -CH_b- protons of pyrrolidine), 1.52-1.60 (m,6H, –CH_2- of piperidine ring). ^{13}C NMR (75MHz): 62.6(C_2, C_2'), 64.0(C_3, C_3'), 137.1(C_4, C_4'), 136.8(C_5, C_5'), 128.3(C_6, C_6'), 129.6(C_7,C_7'), 58.1(C_8), 162.0(C_9), 123.3(C_{10}), 142.8(C_{11}), 138.0(C_{12}), 127.4(C_{13}), 67.1(C_{14}), 53.6(C_{15},C_{19}), 24.5(C_{16}, C_{18}), 23.4(C_{17}), 15.5(C_{20}).

N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-morpholin-1-ylmethyl)-1H-imidazol-5-yl) methylene) hydrazinyl)-2-oxoethyl) pyrrolidine-3,4-diyl)bis(thiophene-2-sulphonamide) (16b):
IR (KBr): 3523(–N-H amide), 3215(-N-H sulphonamide), 1729(C=O), 1617(C=N), 1559(C-N imidazole), 1326 & 1185(asymmetric & symmetrical stretching of O=S=O), 1120(exo C-N), 1116(cyclic C-N), 741(C-Cl) cm^{-1}. ^{1}H-NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.03 (s,1H, -N=CH-), 7.65-7.22 (m, 6H, thiophen), 7.47 (s, 2H, SO_2-NH-), 4.80 (s,2H, -N-CH_2-N-), 4.22 (s,2H, hydrazide -NH_2), 3.65 (t,4H, –O-CH_2- of morpholine), 3.25

(s,2H, -N-CH_2-CO), 3.50 (m,2H, -SO_2-N-CH-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.59 (t,4H, -N-CH_2- of morpholine), 2.51 (s,3H, -CH_3 attached to imidazole ring), 2.29 (m,2H, -CH_b- protons of pyrrolidine). ^{13}C NMR (75MHz): 62.6(C_2, C_2'), 64.0(C_3, C_3'), 137.1(C_4, C_4'), 136.8(C_5, C_5'), 128.3(C_6, C_6'), 129.6(C_7,C_7'), 58.1(C_8), 162.0(C_9), 123.3(C_{10}), 142.8(C_{11}), 138.0(C_{12}), 127.4(C_{13}), 67.1(C_{14}), 52.6 (C_{15},C_{19}), 66.8 (C_{16}, C_{18}), -(C_{17}), 15.5(C_{20}).

N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-4-methylpiperazin-1-ylmethyl)-1H-imidazol-5-yl) methylene) hydrazinyl)-2-oxoethyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulphonamide) (16c):
IR (KBr): 3521(–N-H amide), 3217(-N-H sulphonamide), 1717(C=O), 1619(C=N), 1557(C-N imidazole), 1323 & 1187(asymmetric & symmetrical stretching of O=S=O), 1125(exo C-N), 1122(cyclic C-N), 750(C-Cl) cm^{-1}. ^{1}H-NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.03 (s,1H, -N=CH-), 7.65-7.22 (m, 6H, thiophen), 7.47 (s, 2H, SO_2-NH-), 4.80 (s,2H, -N-CH_2-N-), 4.22 (s,2H, hydrazide -NH_2), 3.25 (s,2H, -N-CH_2-CO), 3.50 (m,2H, -SO_2-N-CH-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.51 (s,3H, -CH_3 attached to imidazole ring), 2.35 (m,8H, -N-CH_2- of piperizine), 2.29 (m,2H, -CH_b- protons of pyrrolidine), 2.26 (s,3H, -N-CH_3 of N-methyl piperizine). ^{13}C NMR (75MHz): 62.6(C_2, C_2'), 64.0(C_3, C_3'), 137.1(C_4, C_4'), 136.8(C_5, C_5'), 128.3(C_6, C_6'), 129.6(C_7,C_7'), 58.1(C_8), 162.0(C_9), 123.3(C_{10}), 142.8(C_{11}), 138.0(C_{12}), 127.4(C_{13}), 67.1(C_{14}), 52.8(C_{15},C_{19}), 54.2 (C_{16}, C_{18}), 45.9 (C_{17}), 15.5(C_{20}).

N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-piperidin-1-ylmethyl)-1H-imidazol-5-yl)methylene)hydrazinyl)-2-oxo ethyl) pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulphonamide) (16d):
IR (KBr): 3523(–N-H amide), 3230(-N-H sulphonamide), 1729(C=O), 1617(C=N), 1560(C-N imidazole), 1341& 1189(asymmetric & symmetrical stretching of O=S=O), 1130(exo C-N), 1129(cyclic C-N), 739(C-Cl) cm^{-1}. ^{1}H-NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.03 (s,1H, -N=CH-), 7.90(2H, -N-CH-N- of two imidazole rings), 7.47 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.80 (s,2H, -N-CH_2-N-), 4.22 (s,2H, hydrazide -NH_2), 3.25 (s,2H, -N-CH_2-CO), 3.65 (s, 6H, N- CH_3 of two imidazole rings) 3.50 (m,2H, -SO_2-N-CH-), 2.51 (s,3H, -CH_3 attached to imidazole ring), 2.45(t,4H, -CH_2 -N-CH_2- of piperidine), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.29 (m,2H, -CH_b- protons of pyrrolidine), 1.52-1.60 (m,6H, –CH_2- of piperidine ring). ^{13}C NMR (75MHz): 62.0 (C_2, C_2'), 64.0(C_3, C_3'), 145.0 (C_4, C_4'), 134.6 (C_5, C_5'), 144.4 (C_6, C_6'), 35.4 (C_7,C_7'), 58.1(C_8), 162.0(C_9), 123.3(C_{10}), 142.8(C_{11}), 138.0(C_{12}), 127.4(C_{13}), 67.1(C_{14}), 53.6 (C_{15}, C_{19}), 24.5 (C_{16}, C_{18}), 23.4 (C_{17}), 15.5(C_{20}).

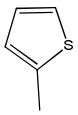
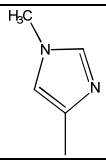
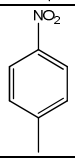
N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-morpholin-1-ylmethyl)-1H-imidazol-5-yl)methyl ene) hydrazinyl)-2-oxo ethyl)pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulphonamide) (16e):
IR (KBr): 3519(–N-H amide), 3235(-N-H sulphnamide), 1728(C=O), 1616(C=N), 1545(C-N imidazole), 1345& 1192(asymmetric & symmetrical stretching of O=S=O), 1127(exo C-N), 1126(cyclic C-N), 757(C-Cl) cm^{-1}. ^{1}H-NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.03 (s,1H, -N=CH-), 7.90(2H, -N-CH-N- of two imidazole rings), 7.47 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.80 (s,2H, -N-CH_2-N-), 4.22 (s,2H, hydrazide -NH_2), 3.25 (s,2H, -N-CH_2-CO), 3.69 (t,4H, –O-CH_2- of morpholine), 3.65 (s, 6H, N- CH_3 of two imidazole rings) 3.50 (m,2H, -SO_2-N-CH-), 2.59 (t,4H, -N-CH_2- of morpholine), 2.51 (s,3H, -CH_3 attached to imidazole ring), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.29 (m,2H, -CH_b- protons of pyrrolidine). ^{13}C NMR (75MHz): 62.0 (C_2, C_2'), 64.0(C_3, C_3'), 145.0 (C_4, C_4'), 134.6 (C_5, C_5'), 144.4 (C_6, C_6'), 35.4 (C_7,C_7'), 58.1(C_8), 162.0(C_9), 123.3(C_{10}), 142.8(C_{11}), 138.0(C_{12}), 127.4(C_{13}), 67.1(C_{14}), 52.6 (C_{15},C_{19}), 66.8 (C_{16}, C_{18}), 15.5(C_{20}).

N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-4-methylpiperazin-1-ylmethyl)-1H-imidazol-5-yl) methylene) hydra - zinyl)-2-oxoethyl)pyrrolidine-3,4-diyl)bis(1-methyl-1H-imidazole-4-sulphonamide) (16f):
IR (KBr): 3523(–N-H amide), 3230(-N-H sulphonamide), 1726(C=O), 1615(C=N), 1539(C-N imidazole), 1347& 1186(asymmetric & symmetrical stretching of O=S=O), 1125(exo C-N), 1123(cyclic C-N), 733(C-Cl) cm^{-1}. ^{1}H-NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.03 (s,1H, -N=CH-), 7.90(2H, -N-CH-N- of two imidazole rings), 7.47 (s, 2H, SO_2-NH-), 6.93 (s, 2H, N-CH- of two imidazole rings), 4.80 (s,2H, -N-CH_2-N-), 4.22 (s,2H, hydrazide -NH_2), 3.25 (s,2H, -N-CH_2-CO), 3.65 (s, 6H, N- CH_3 of two imidazole rings) 3.50 (m,2H, -SO_2-N-CH-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.51 (s,3H, -CH_3 attached to imidazole ring), 2.35 (m,8H, -N-CH_2- of piperizine), 2.29 (m,2H, -CH_b- protons of pyrrolidine), 2.26 (s,3H, -N-CH_3 of N-methyl piperizine). ^{13}C NMR (75MHz): 62.0 (C_2, C_2'), 64.0(C_3, C_3'), 145.0 (C_4, C_4'), 134.6 (C_5, C_5'), 144.4 (C_6, C_6'), 35.4 (C_7,C_7'), 58.1(C_8), 162.0(C_9), 123.3(C_{10}), 142.8(C_{11}), 138.0(C_{12}), 127.4(C_{13}), 67.1(C_{14}), 52.8(C_{15},C_{19}), 54.2 (C_{16}, C_{18}), 15.5(C_{20}).

N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-piperidin-1-yl methyl)-1H-imidazol-5-yl) methylene) hydrazinyl)-2-oxoethyl)pyrrolidine-3,4-diyl)bis(4-nitrobenzenesulphonamide)(16g):
IR (KBr): 3524 (–N-H amide), 3250 (-N-H sulphonamide), 1728(C=O), 1619(C=N), 1545(C-N imidazole), 1351 & 1192 (asymmetric & symmetrical stretching of O=S=O), 1128 (exo C-N), 1124 (cyclic C-N), 756 (C-Cl) cm^{-1}. ^{1}H-NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.12-8.39 (m,8H aromatic protons), 8.03 (s,1H, -N=CH-), 7.47 (s, 2H, SO_2-NH-), 4.80 (s,2H, -N-CH_2-N-), 4.22 (s,2H, hydrazide -NH_2), 3.50 (m,2H, -SO_2-N-CH-), 3.25 (s,2H, -N-CH_2-CO-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.51 (s,3H, -CH_3 attached to imidazole ring), 2.45(t,4H, -CH_2 -N-CH_2- piperidine), 2.29 (m,2H, -CH_b- protons of pyrrolidine), 1.52-1.60 (m,6H, –CH_2- of piperidine ring). ^{13}C NMR (75MHz): 62.6 (C_2, C_2'), 63.6 (C_3, C_3'), 153.2 (C_4, C_4'), 130.0 (C_5, C_5'), 123.0 (C_6, C_6'), 150.1 (C_7,C_7'), 123.0 (C_8, C_8'), 130.0 (C_9, C_9'), 58.1 (C_{10}), 162.0 (C_{11}), 123.3(C_{12}), 142.8 (C_{13}), 138.0 (C_{14}), 127.4 (C_{15},) 67.1 (C_{16}), 53.6(C_{17},C_{21}), 24.5(C_{18},C_{20}), 23.4(C_{19}), 15.5(C_{22}).

N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-morpholin-1-ylmethyl)-1H-imidazol-5-yl) methylene)hydrazinyl)-2-oxoethyl)pyrrolidine-3,4-diyl)bis(4-nitrobenzenesulphonamide)(16h):
IR (KBr): 3520 (–N-H amide), 3255 (-N-H sulphonamide), 1723 (C=O), 1620 (C=N), 1547 (C-N imidazole), 1356 & 1189 (asymmetric & symmetrical stretching of O=S=O), 1123 (exo C-N), 1111 (cyclic C-N), 747 (C-Cl) cm^{-1}. ^{1}H-NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.12-8.39 (m,8H aromatic protons), 8.03 (s,1H, -N=CH-), 7.47 (s, 2H, SO_2-NH-), 4.80 (s,2H, -N-CH_2-N-), 4.22 (s,2H, hydrazide -NH_2), 3.65 (t,4H, –O-CH_2- of morpholine), 3.50 (m,2H, -SO_2-N-CH-), 3.25 (s,2H, -N-CH_2-CO-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.59 (t,4H, -N-CH_2- of morpholine), 2.51 (s,3H, -CH_3 attached to imidazole ring), 2.29 (m,2H, -CH_b- protons of pyrrolidine). ^{13}C NMR (75MHz): 62.6 (C_2, C_2'), 63.6 (C_3, C_3'), 153.2 (C_4, C_4'), 130.0 (C_5, C_5'), 123.0 (C_6, C_6'), 150.1 (C_7,C_7'), 123.0 (C_8, C_8'), 130.0 (C_9,C_9'), 58.1 (C_{10}), 162.0 (C_{11}), 123.3(C_{12}), 142.8 (C_{13}), 138.0 (C_{14}), 127.4 (C_{15},) 67.1 (C_{16}), 52.6(C_{17},C_{21}), 66.8(C_{18},C_{20}), -(C_{19}), 15.5(C_{22}).

Table 3: physical characterization data of synthesized compounds 16a-16i

Compound	R=	X=	M.P. /°C	Yield	Molecular Formula	Found % (Calculated %)		
						C	H	N
16a		**-CH_2**	187-8	55	$C_{25}H_{33}ClN_8O_5S_4$	43.12 (43.56)	4.56 (4.83)	16.23 (16.26)
16b		**-O-**	174-5	64	$C_{24}H_{31}ClN_8O_6S_4$	41.25 (41.70)	4.23 (4.52)	16.13 (16.21)
16c		**-N-CH_3**	158-9	50	$C_{25}H_{34}ClN_9O_5S_4$	42.52 (42.63)	4.84 (4.87)	17.87 (17.90)
16d		**-CH_2**	190-1	65	$C_{25}H_{37}ClN_{12}O_5S_2$	43.69 (43.82)	5.34 (5.44)	24.63 (24.53)
16e		**-O-**	168-9	55	$C_{24}H_{35}ClN_{12}O_6S_2$	41.88 (41.95)	5.36 (5.13)	24.58 (24.46)
16f		**-N-CH_3**	158-9	60	$C_{25}H_{38}ClN_{13}O_5S_2$	42.65 (42.88)	5.36 (5.47)	26.09 (26.00)
16g		**-CH_2-**	204-5	55	$C_{29}H_{35}ClN_{10}O_9S_2$	45.23 (45.40)	4.52 (4.60)	18.32 (18.26)
16h		**-O-**	232-3	60	$C_{28}H_{33}ClN_{10}O_{10}S_2$	43.69 (43.72)	4.58 (4.32)	18.39 (18.21)
16i		**-N-CH_3**	196-7	65	$C_{29}H_{36}ClN_{11}O_9S_2$	44.43 (44.53)	4.53 (4.64)	19.59 (19.70)

N,N'-((3S,4S)-1-(2-(2-((4-chloro-2-methyl-1-4-methylpiperazin-1-ylmethyl)-1H-imidazol -5-yl) methylene) hydra -zinyl)-2-oxoethyl)pyrrolidine-3,4-diyl)bis(4-nitrobenzenesulphonamide) (16i):
IR (KBr): 3528(–N-H amide), 3253 (-N-H sulphonamide), 1721 (C=O), 1617 (C=N), 1542 (C-N imidazole), 1353 & 1197 (asymmetric & symmetrical stretching of O=S=O), 1128 (exo C-N), 1123(cyclic C-N), 749 (C-Cl) cm^{-1}. ^{1}H-NMR (300MHz) in DMSO-d_6: 8.92(s,1H, -CO-NH-), 8.12-8.39 (m,8H, aromatic protons), 8.03 (s,1H, -N=CH-), 7.47 (s, 2H, SO_2-NH-), 4.80 (s,2H, -N-CH_2-N-), 4.22 (s,2H, hydrazide -NH_2), 3.50 (m,2H, -SO_2-N-CH-), 3.25 (s,2H, -N-CH_2-CO-), 2.88(m,2H, -CH_a- protons of pyrrolidine), 2.51 (s,3H, -CH_3 attached to imidazole ring), 2.35 (m,8H, -N-CH_2- of piperizine 2.29 (m,2H, -CH_b- protons of pyrrolidine), 2.26 (s,3H, -N-CH_3 of N-methyl piperizine). ^{13}C NMR (300MHz): 62.6(C_2, C_2'), 63.6 (C_3,C_3'), 153.2 (C_4,C_4'), 130.0 (C_5,C_5'), 123.0 (C_6,C_6'), 150.1 (C_7,C_7'), 123.0 (C_8, C_8'), 130.0 (C_9, C_9'), 58.1 (C_{10}), 162.0 (C_{11}), 123.3(C_{12}), 142.8 (C_{13}), 138.0 (C_{14}), 127.4 (C_{15},) 67.1 (C_{16}), 52.8(C_{17},C_{21}), 54.2(C_{18},C_{20}), 45.9(C_{19}), 15.5(C_{22}).

Biological Activities

Antibacterial Screening and preliminary observations[21,22]

The antibacterial activity of the series 16a-16i been carried out against *Staphylococcus aureus, Escherichia coli*. To determine the antibacterial activity of these agents, the Agar cup plate method was used, with Streptomycin as the reference antibiotic. The prepared compounds were examined against gram-positive and gram-negative bacteria. The test results, presented in table 4, suggest that compounds 16b, 16e and 16h are highly active against gram-positive and gram-negative bacteria showing the broad spectra of antibacterial activity. The rest of the compounds were found to be moderately active, slightly active or inactive against the tested microorganisms.

Table 4 : Antibacterial activity of compounds 16a-16i

Compound	Zone of inhibition	
	Staphylococcus aureus	*Escherichia coli*
16a	10	09
16b	14	13
16c	11	09
16d	09	08
16e	15	14
16f	10	09
16g	08	07
16h	13	12
16i	11	09
Streptomycin	20	22

** indicate diameter of inhibition in mm.*

Antifungal activity

The antifungal activity of 6a-h were tested against two different fungi such as *Asperigillus flavus* and *Candida albicans* by disc diffusion method[18] with Clotrimazole as standard (250µg/ml). The test results presented in the table 5**,** suggest that 16b, 16e and 16h exhibit high activity against the fungi species tested, the rest of the compounds were found to be either moderately active or slightly active against the fungi species tested.

Table 5 : Antifungal activity of compounds 16a-16i

Compound	Zone of inhibition	
	Asperigillus flavus	*Candida albicans*
16a	10	09
16b	15	16
16c	11	08
16d	14	11
16e	18	14
16f	12	09
16g	11	08
16h	14	15
16i	11	09
Clotrimazole	25-30	25-30

** indicate diameter of inhibition in mm.*

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