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Synthesis and Biological Evaluation of Some Piperazine Derivatives

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ABSTRACT

A series of substituted piperazine derivatives have been synthesized and tested for antibacterial activity. The antibacterial activity was tested against Gram-positive and Gram-negative bacteria strains like *B. subtilis*, *B. pumillis*, *E. coli*, and *P. aeruginosa* . These entire compounds have been characterized by their IR and 1H NMR spectral data. All synthesized compounds showed significant activity against bacterial strains. The biological screening showed that the compounds Vc, Vd and Ve are the most active ones showing an interesting antibacterial activity.

Keywords: Antibacterial activity, Piperazine, Gram negative microorganism, Gram positive microorganism

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INTRODUCTION

Piperazine and their derivatives have their own importance in today's drug discovery. Piperazine moiety certainly deserves the molecule backbone with versatile binding properties representing potent and selective ligands for a range of different biological targets in medicinal chemistry. Thus, piperazine is considered as honored scaffold. A number of substituted piperazines posses significant pharmacological action such as antihistamic[1-2] antimicrobial[3], acetylcholinesterae inhibitors[4], antimalarial[5], dopamine transporter[6-7], D2/D4 antagonist[8], MC4Receptor[9], and HIV-protease inhibitor[10-11]. Under this category, benzhydrilpiperazine (diphenylmethylpiperazine) belongs to the diarylpiperazine family; possesses wide range of pharmacological properties such as anti-lipid-peroxidation activity[12], antiallergic and antioxidant activity[13], antihistamic activity[14], myocardiuminhibiting agent[15] and antimicrobial activitycompounds[16-17]. Hence it was thought interesting to synthesize novel piperazine derivatives containing Thiadiazole group.

MATERIALS AND METHODS:

Chemistry:

The melting points were determined in open capillary tubes in a Hicon melting point apparatus. The elemental analyses (C, H, N) of all compounds were performed on the CHNS Elimentar (Analysen systime, GmbH) Germany Vario EL III. All the Fourier transform infra red (FTIR) spectra were recorded in KBr pellets on a Jasco FT/IR 410 spectrometer. The 1H NMR spectra were taken on a Bruker 400 Ultra shieldTM (400 MHz) NMR spectrometer. Chemical shifts (d) are expressed in parts per million relative to tetramethylsilane (TMS) as an internal standard. The homogeneity of the compounds was checked by thin layer chromatography (TLC) on silica gel G (Merck) coated plates by using toluene:ethylacetate:formic acid (5:4:1) as solvent system. Iodine chamber and UV lamp were used for the visualization of TLC spots.

Experimental work/Synthesis:

Step- 1 Synthesis of 4-Substituted benzaldehyde thiosemicarbazones II a-f

Aromatic aldehyde I (0.2 M) in warm alcohol (300 mL) and thiosemicarbazide (0.2 M) in warm water (300 mL) were mixed slowly with continuous stirring. The product separated immediately on cooling which was filtered with suction, dried and recrystallised in 75% ethanol to yield II.

Step- 2 Synthesis of 2-Amino-5-aryl-1,2,4-thiadiazole III a-f

Thiosemicarbazone II (0.05 M) was suspended in 300 ml warm water, $FeCl_3$ (0.15 M) in 300 ml water was added quantitatively, slowly with constant stirring. The contents were heated at 80-90°C for 45 min. Solution was filtered hot and then citric acid (0.11 M) and sodium citrate (0.05

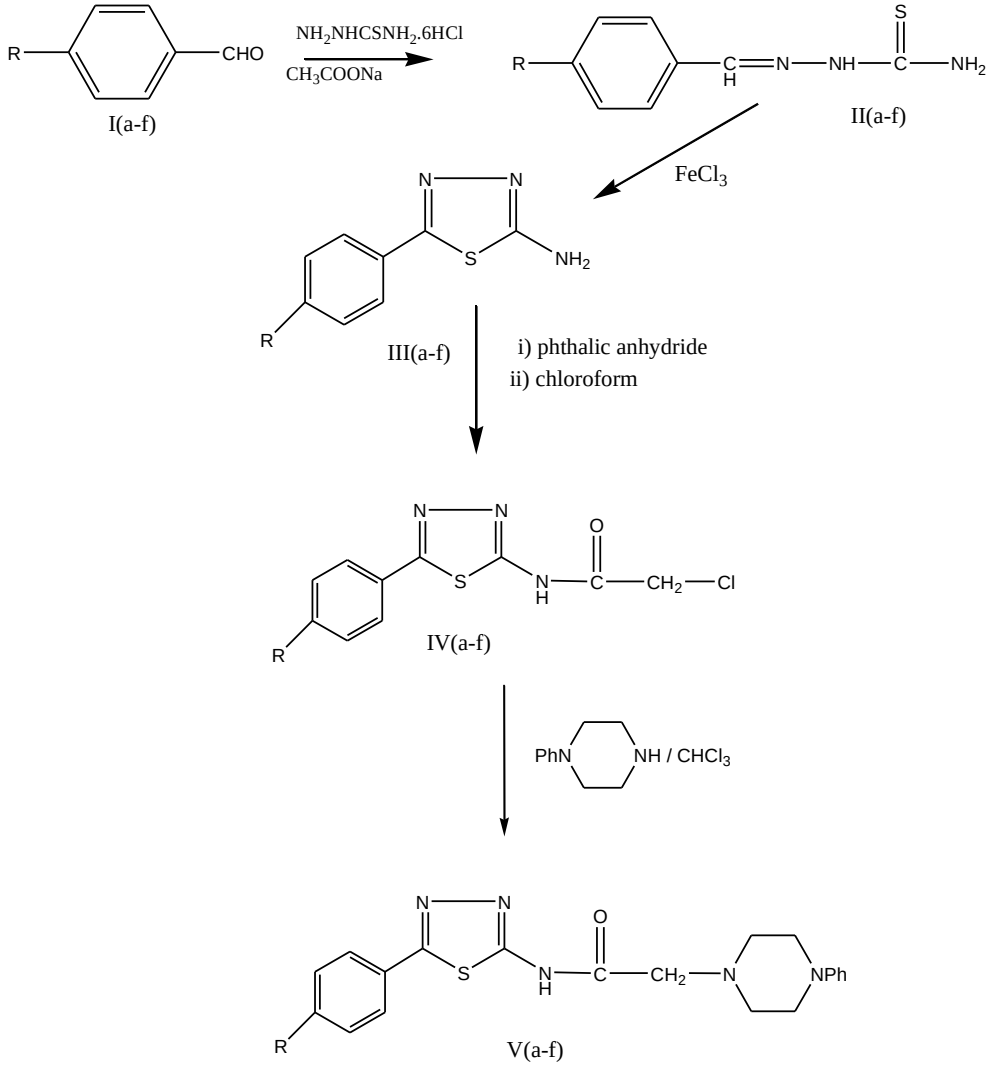
M) were added. The resulting mixture was divided into 4 parts and each part was neutralized separately with ammonia (10%). The required amine separated out, filtered with suction, dried and recrystallised with appropriate solvent.

Step- 3 Synthesis of 1-[5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl]-urea IV a-f

The appropriate 2-Amino-5-aryl-1,2,4-thiadiazole III (0.01mol) add anhy. Potassium carbonate (2.5gm) and 1ml of TEA in dry chloroforms (65ml) was added chloro acetyl chloride (0.006 mole) and the mixture was refluxed for 4-5 hrs. The solvent was then evaporated and the resulting solid was washed with cold water and recrystallized using appropriate solvent.

Step- 4 Synthesis of piperazine derivatives

To a solution of 1-[5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl]-urea, N-phenyl piperazine (0.005 mole) in dry chloroform was added and refluxed for 1-2 hours. The solvent was evaporated and the resulting solid was washed with cold water.



SCHEME 1

SPECTRAL ANALYSIS:

N-(5-phenyl-1,3,4-thiadiazol-2-yl)-2-(4-phenylpiperazin-1-yl)acetamide (Va)

IR (cm– 1) (KBr): 3080.3 (aromatic C-H str), 1605.7 & 1503.5 (aromatic C-C str), 735.6 (C-S of 1,3,4-thiadiazole nucleus), 1642.9 (C=N of 1,3,4-thiadiazole nucleus), 1683.2 (C=O str of amide), 3434.2 (N-H str of amide), 1290.5 (aromatic C-N)

1H NMR (DMSO): 6.9–7.5 (10H, ArH), 8.0 (1H, Sec. amide), 2.6-3.5 (5H methylene)

2-(4-phenylpiperazin-1-yl)-N-(5-p-tolyl-1,3,4-thiadiazol-2-yl)acetamide **(Vb)**

IR (cm– 1) (KBr): 3056.4 (aromatic C-H str), 1608.1 & 1504.7 (aromatic C-C str), 746.6 (C-S of 1,3,4-thiadiazole nucleus), 1631.4 (C=N of 1,3,4-thiadiazole nucleus), 1672.4 (C=O str of amide), 3421.4 (N-H str of amide), 1272.7 (aromatic C-N), 2980 (C-Cl)

1H NMR (DMSO): 6.7–7.4 (9H, ArH), 8.0 (1H, Sec. Amide), 2.5-3.6 (5H methylene) 2.35 (1H CH_3)

N-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)-2-(4-phenylpiperazin-1-yl)acetamide **(Vc)**

IR (cm– 1) (KBr): 3065.8 (aromatic C-H str), 1601.5 & 1509.3 (aromatic C-C str), 742.3 (C-S of 1,3,4-thiadiazole nucleus), 1638.2 (C=N of 1,3,4-thiadiazole nucleus), 1660.7 (C=O str of amide), 3429.6 (N-H str of amide), 1279.6 (aromatic C-N), 1390.5 (C-NO_2)

1H NMR (DMSO): 6.9–8.2 (9H, ArH), 8.0 (1H, Sec. amide), 2.4-3.5 (5H methylene)

N-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)-2-(4-phenylpiperazin-1-yl)acetamide **(Vd)**

IR (cm– 1) (KBr): 3098.6 (aromatic C-H str), 1605.8 & 1502.1 (aromatic C-C str), 753.5 (C-S of 1,3,4-thiadiazole nucleus), 1644.2 (C=N of 1,3,4-thiadiazole nucleus), 1676.6 (C=O str of amide), 3433.4 (N-H str of amide), 1293.6 (aromatic C-N), 752.3 (C-Cl)

1H NMR (DMSO): 7.3–7.4 (9H, ArH), 8.0 (1H, Sec. amide), 2.8-3.7 (5H methylene)

N-(5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)-2-(4-phenylpiperazin-1-yl)acetamide **(Ve)**

IR (cm– 1) (KBr): 3078.5 (aromatic C-H str), 1604.6 & 1514.2 (aromatic C-C str), 754.2 (C-S of 1,3,4-thiadiazole nucleus), 1637.5 (C=N of 1,3,4-thiadiazole nucleus), 1684.7 (C=O str of amide), 3438.5 (N-H str of amide), 1280.2 (aromatic C-N), 1254.1 (C-OCH_3) **1H NMR (DMSO):** 6.8–7.3 (9H, ArH), 8.0 (1H, Sec. amide), 2.4-3.4 (5H methylene), 3.73 (1H OCH_3)

N-(5-(4-aminophenyl)-1,3,4-thiadiazol-2-yl)-2-(4-phenylpiperazin-1-yl)acetamide **(Vf)**

IR (cm– 1) (KBr): 3069.4 (aromatic C-H str), 1607.5 & 1505.1 (aromatic C-C str), 730.2 (C-S of 1,3,4-thiadiazole nucleus), 1623.7 (C=N of 1,3,4-thiadiazole nucleus), 1686.1 (C=O str of amide), 3429.6 (N-H str of amide), 1278.2 (aromatic C-N), 3635.4 (C-NH_2)

1H NMR (DMSO): 6.5–7.2 (9H, ArH), 8.0 (1H, Sec. amide), 2.6-3.7 (5H methylene), 4.0(2H NH_2)

Antibacterial activity:

All the newly synthesized compounds (**Va-f**) were evaluated for *in vitro* antibacterial activity against gram positive and gram negative bacterial strains such as *Bacillus subtilis*, *Bacillus pumilus*, *Escherichia coli* and *Pseudomonas aureginosa* at concentration 100 µg/mL by disc diffusion method[14] by using DMSO as solvent control and nutrient agar was employed as culture media. After 24 h of incubation at 37°C, the zone of inhibition was measured in mm. The activity was compared with known antibiotic ciprofloxacin and the data was represented in the Table 1.

Table 1. Antibacterial activity of compounds Va-f.

Compound	*Inhibition of zone diameter in mm			
	B. subtilis	***B. pumillis***	***E. coli***	***P. aeruginosa***
	100 µg	100 µg	100 µg	100 µg
Va	14	16	17	15
Vb	19	17	14	16
Vc	19	17	18	17
Vd	20	23	19	21
Ve	20	22	19	21
Vf	15	16	13	14
Ciprofloxacin	24	23	25	24
DMSO	_	_	_	_

*Each value is an average of three independent determination ± Standard deviation. Note: **'-'** denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity, 18-20 mm and above good activity.

RESULTS AND DISCUSSION:

The results of antimicrobial evaluation suggest that all the compounds have very good potential to act as antibacterial agents. Compound Vc, Vd, Ve showed very good activities against the entire test microorganism. All synthesized compounds are more active against gram positive microorganism as compared to gram negative one. Compound having substitution in the p-position with Cl and OCH_3 **(Vd & Ve)** are more active**.** Compound Vd and Ve has highest antibacterial activity against all the test microorganisms. The zone inhibition is described in Table .1.

Table. 2. Characterization of compounds

Compound	R	Mol. Formula	Mol. Weight	Melting Point °C	Yield %	C	H	N
1	H	$C_{20}H_{21}N_5OS$	379.48	146	55	63.30	5.58	18.46
2	CH3	$C_{21}H_{23}N_5OS$	393.51	134	61	64.10	5.89	17.80
3	NO2	$C_{20}H_{20}N_6O_3S$	424.48	126	57	56.59	4.75	19.80
4	Cl	$C_{20}H_{20}ClN_5OS$	413.92	128	61	58.03	4.87	16.92
5	OCH3	$C_{21}H_{23}N_5O_2S$	409.5	134	63	61.59	5.66	17.10
6	NH_2	$C_{20}H_{22}N_6OS$	394.49	130	54	52.41	4.40	15.28

CONCLUSION:

All the 06 newly synthesized compounds were screened for antibacterial activity studies at a concentration of 100 µg/mL using DMSO as a control and ciprofloxacin used as standard against gram positive and gram negative bacteria. The data in the Table 1 indicates that among the synthesized compounds **Vd** and **Ve** compounds was found to posses a broad spectrum activity. However, the activities of the tested compounds are much less than those of standard antibacterial agents used.

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REFERENCES:

1. Gyoten M, Nagaya H, Fukuda S, Ashida Y, Kawano Y. Synthesis of Eosinophil Infiltration Inhibitors with Antihistaminic Activity. Chem Pharm Bull Tokyo, 2003;51(2):122-133.
2. Magid A G, John A, Moyer Susan T N, Michael W, Usha P. New Antihistamines: Substituted Piperazine and Piperidine Derivatives as Novel H1-Antagonists J Med Chem, 1995; 38:4026- 4032
3. Chaudhary P, Kumar R, Verma AK, Singh D.Synthesis and antimicrobial activity of *N*-alkyl and *N*-aryl piperazine derivatives Bioorg Med Chem 2006; 14:1819-1826
4. Hachiro S, Hiroo O,Yasuo A, Youichi I, Yoshiharu Y. Synthesis and Antimicrobial Activity of Amino Acids Conjugated Diphenyl methylpiperazine Derivatives. Japanese J Pharmacol. 2002; 89(1):7-20.
5. Rebecca DP, Patricia M, Combinatorial Chemistry & High Throughput Screenings, 1, 4-Bis(3-Aminopropyl)Piperazine Libraries: From the Discovery of Classical Chloroquine-Like Antimalarials to the Identification of New Targets.2005;8;39-48.
6. Makoto K, Tomoko M, Koji Y, Masaki M, Nobuo K, Nobuyuki K, Kenichi K, Masato I, Yuji K, Katsuji O ,Takayuki N. Novel diphenylalkyl piperazine derivatives with high affinities for the dopamine transporter. Bioorg & Med Chem 2003; 11:3953-3963.
7. Makoto K, Tomoko M, Koji Y, Masaki M, Nobuo K, Nobuyuki K, Kenichi K, Masato I, Yuji K, Katsuji O, Takayuki N. Efficient asymmetric syntheses, determination of absolute configurations and biological activities of 1-[4,4-bis(4-fluorophenyl)butyl]-4-[2-

hydroxy-3-(phenylamino)propyl]piperazine as a novel potent dopamine uptake inhibitor in the central nervous system. Bioorg & Med Chem 2004;12:3069-3078.

8. He Zhao, Xiaoshu He, Andrew T, Diane H, Andrzej K, Robbin B, Renee P, Jan WF. Indoline and piperazine containing derivatives as a novel class of mixed D_2/D_4 receptor antagonists. Part 2: Asymmetric synthesis and biological evaluation. Bioorg & Med Chem Lett., 2002; 12:3111-3115.
9. Brian D, Jessica P, Teresa P, Lee C, Brian M, Robin S, Julia H, Tracy B, Mary C, John S and Val G. Aryl piperazine melanocortin MC4 receptor agonists. Bioorg & Med Chem Lett., 2003; 13:3793-3796.
10. Rossen K, Steven AW, Sager J, Reamer RA, Askin D, Volante RP, Reider PJ. Asymmetric hydrogenation of tetrahydro pyrazines: Synthesis of (S)-piperazine-2-tert-butylcarboxamide, an intermediate in the preparation of the HIV protease inhibitor indinavir. Tetrahedron Lett 1995; 36:6419-6422.
11. David A, Kan KE, Kai R, Robert MP, Kenneth M W, Volante RP, Paul JR. Highly diastereo selective reaction of a chiral, non-racemic amide enolate with (S)-glycidyl tosylate. Synthesis of the orally active HIV-1 protease inhibitor L-735,524, Tetrahedron Lett., 1994; 35(5):673-676.
12. Kawasaki N, Miyataka H, Nishiki M, Matsumato H, Inagaki N, Nagai H, Satoh T. Synthesis of Trimethyl hydroquinone Derivatives as Anti-allergic Agents with Anti-oxidative Actions, Chem Pharma Bull 1999;47(2):177-181.
13. Sugiyama N, Akahoshi S, Kuwahara M, Kajii. Synthesis and Topical Anti-inflammatory and Anti-allergic Activities of Antioxidant o-Aminophenol Derivatives. J Med Chem 1994; 37:1977-1982
14. Cruickshank R, Duguid JP, Marmion BP, Swam HA. The Practice of MedicalMicrobiology, 12th ed., Churchill Livingstone, London, 1975: 544-557.