Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(13):262-268
(http://derpharmachemica.com/archive.html)

Synthesis, Antimicrobial activity of piperazin-1-yl (3,4,5-Trimethoxyphenyl)Methanone Derivatives

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ABSTRACT

*Aromatic acid chlorides are coupling with Piperzain-yl(3,4,5-trimethoxyphenyl)methanone in presence of triethylamine base to yield trimethoxyphenyl piperzine derivatives **3a-j**. The structures of all the synthesized compounds have been characterised by elemental analysis and spectral studies. All the compounds have been tested for antifungal activity of and anti bacterial activity. Compounds **3d, 3e** and **3f** showed good antifungal activity and compound **3b, 3c, 3d, 3g** and **3h** showed moderate anti bacterial activity.*

Keywords*:* Piperazine, Trimethoxy, Oxalyl chloride, Antifungal, Antibacterial

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INTRODUCTION

The number of patients suffering from cancer diseases or some life-threatening infections has continued to rise rapidly with years, though great progresses have been made in diagnosis,

prevention, therapy and medicinal chemistry. Especially, the alarming rates of emerging drug resistant strains and cancer cell lines, leading to failure in therapy, continue to serve as impetus for the development of novel and more effective antimicrobial and anticancer agents[1,2]. The piperazine-based research has attracted considerable attention in recent years. Piperazine and substituted piperazine nuclei had constituted an attractive pharmacological scaffold present in various potent marketed drugs. The incorporation of piperazine is an important synthetic strategy in drug discovery due to its easy modifiability, proper alkaline, water solubility, the capacity for the formation of hydrogen bonds and adjustment of molecular physicochemical properties[3-6]. A broad range of biologically active compounds displaying antibacterial[7-9], antifungal[10,11] anticancer[12-14], antiparasitic[15,16], antihistaminic [17] psychotolytic[18] and antidepressive activities[19] have been also found to contain this versatile core. In particular, structurally simple methoxy piperazine, as the efflux pump inhibitor, could exert positive effect on tetracyclines and ciprofloxacin against their resistant bacteria[20,21]. Moreover, benzotriazole based piperazin derivatives and *N*,*N*'-bis(alkyloxymethyl)piperazines had moderate antibacterial and antifungal activities against pathogenic bacterial strains and fungal strains [22,23]. On the other hand, a novel microtubule depolymerizing piperazine derivative,1-(5-chloro-2-methoxybenzoyl)-4-(3-chlorophenyl) piperazine, caused inhibition of proliferation of a wide range of cancer cell lines including a multidrug-resistant cell line, with an average IC50 of 85 nM[24]. These results once again highlighted that piperazine core was an important backbone and prompted us to design some active molecules with piperazine nucleus. Several literatures provided evidence that the introduction of such bulky groups like diphenyl could increase antimicrobial activity by enhancing lipophilicity of the molecule, which may result in more penetration into cells[25]. Thus piperazine derivatives bearing substitution at N1 position also have been introduced to design new antibacterial and antifungal agents, though this moiety has wide application as antihistamine like cetirizine, calcium antagonist (flunarizine) *etc.*

Particularly during the past two decades, a number of different classes of antibacterial[26-33] and antifungal agents[34-39] have been discovered. Although, since the discovery of several synthetic and semi-synthetic antibacterial sulfa drugs, nitrofuranes, penicillins, cephalosporins, tetracyclines, macrolides, and oxazolidinones, and antifungal agents such as fluconazole, ketoconazole and miconazole,

Including amphotericin B, there has been much progress in this field. Despite advances in antibacterial and antifungal therapies, many problems remain to be solved for most antimicrobial drugs available. For example, appearance of multidrug resistant Gram-positive bacteria, in particular, methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococci is causing a serious menace. The use of amphotericin B, known as the gold standard, is limited because of its infusion related reactions and nephrotoxicity[40,41].

Thus, based on these observations in the literature, the present study was initiated with aim of identifying the structural requirements of trimethoxyphenyl substituted piperazines in terms of antifungal and antibacterial activity.

MATERIALS AND METHODS

^{1}H NMR spectra were measured on Bruker AV 400MHZ using DMSO as solvent. Chemical shifts are expressed in δ ppm. All the reactions were followed and checked by TLC (silica coated on alumina) using ethyl acetate-pet ether (1:1) and further purification was done by column chromatography using 60-120 mesh silica gel. LC-MS analysis was performed on Agilent LC-1200 series coupled with 6140 single quad mass spectrometer with ESI +ve and –ve mode, MS range 100-2000. Elemental analyses were recorded using Perkin Elmer CHNS analyzer.

6.1. *Tert*-butyl 4-(3, 4, 5-trimethoxybenzoyl) piperazine-1-carboxylate (1)

3, 4, 5-trimethoxybenzoic acid (10 g, 0.0475 mol, 1.0 eq) was dissolved in dry tetrahydrofuran (150 mL).The solution was stirred for 10 min at ambient temperature. To this added 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (21.67g, 0.057 mol, 1.2 eq), followed by *N*, *N*-diisopropylethylamine (12.27 g, 0.095 mol, 2.0 eq). The reaction mixture was stirred for 20 min at ambient temperature, then it was cooled to 0 °C, and added commercially available boc-piperazine (8.84 g, 0.0475 mol, 1.0 eq). The stirring was continued for 3-4 h at ambient temperature. The completion of the reaction was monitored by TLC. The reaction mass was diluted with ethyl acetate (250 mL) and washed with 10% sodium bicarbonate solution (50 mL) and 1.5 N HCl solution (50 mL) followed by water (50 mL) and brine (50 mL) and dried with anhydrous sodium sulphate (10.0 g) and evaporate under reduced pressure. The crude reaction mass was purified by column chromatography using silica gel with 30% ethyl acetate in hexane (3:7) to get 8 g of tert-butyl 4-(3,4,5-trimethoxybenzoyl)piperazine-1-carboxylate **(1).**

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 382.5**;** ^{1}H NMR: (400 MHz, DMSO-d_6): δ 6.68 (s, 2H), 3.78 (s, 6H), 3.68 (s, 3H), 3.7-3.34 (m, 8H), 1.40 (s, 9H); Elemental analysis: Calculated (%) for $C_{19}H_{28}N_2O_6$:C 59.98, H 7.42, N 7.36; Found: C 59.95, H 7.45, N 7.35.

6.2. Piperazin-1-yl (3, 4, 5-trimethoxyphenyl) methanone (2)

Compound **1** (7 g, 0.01841 mol, 1.0 eq) was dissolved in dry dichloromethane (70 mL). The reaction mixture was cooled to 0 ^{0}C and added slowly trifluoroacetic acid (6.3 g, 0.05523 mol, 3.0 eq). The reaction mixture was stirred for 2-3 hr at ambient temperature. The completion of the reaction was confirmed by TLC. The reaction mixture was evaporated under reduced pressure and the crude reaction mass was dissolved in dichloromethane (100 mL). The organic layer was washed with water (50 mL), 10% sodium bicarbonate (50 mL) followed by brine (50 mL) and dried with anhydrous sodium sulphate (10 g). The organic layer was evaporated under reduced pressure. The obtained crude reaction mass was purified by column chromatography using silica gel with 3% methanol in dichloromethane (3:97) to get 5 g of purified Piperazin-1-yl(3,4,5-trimethoxyphenyl)methanone (**2**).

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 282.1**;** ^{1}H NMR: (400 MHz, DMSO-d_6): δ 6.66 (s, 2H), 3.79 (s, 6H), 3.68 (s, 3H), 3.41(bs,4H) 2.74 (bs, 4H); Elemental analysis: Calculated for $C_{14}H_{20}N_2O_4$: C 59.99, H 7.19, N 9.99; Found: C 59.95, H 7.21, N 9.96.

6.3. General procedure for 3a-j

Preparation of Acid chlorides

Aromatic or hetrocycli acid (1.0 eq) was dissolved in dry Dichloromethane (10 mL), and cool to 0 ^{0}C. To this added oxalyl chloride, followed by 2 drops of DMF. The reaction mass was stirred for 1 hr at cooled condition. Then the solution was slowly added to pre cooled solution containing compound **2**.

Compound **2** (0.5 g, 0.00218 mol 1.0 eq) was dissolved in dry Dichloromethane (10 mL). The solution was stirred for 10 min at 0^{o}C. To this added triethylamine (3.0 eq). The reaction mixture was stirred for 1 hr at cooled solution and completion of reaction was monitored by TLC. The reaction mass was diluted with dichloromethane (75 mL), the organic layer was washed with water (25mL) followed by 10% sodium bicarbonate solution (25 mL), brine (25 mL) and dried with anhydrous sodium sulphate. The organic layer was evaporated under reduced pressure and the crude reaction mass was purified by column chromatography.

6.3.1. (4-(2-amino-5-chlorobenzoyl)piperazin-1-yl)(3,4,5-trimethoxyphenyl)methanone (3a)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 434.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13-7.10 (dd, *J* =7.6 Hz,3.2Hz, 1H), 7.02-7.01 (d, *J* = 3.2 Hz, 1H), 6.72 (s, 1H), 6.69 (s, 2H), 5.36 (s, 2H) 3.79 (s, 6H), 3.68 (s, 3H), 3.55-3.44 (m, 8H); Elemental analysis: Calculated (%) for $C_{21}H_{24}ClN_3O_5$:C 58.13, H 5.58, N 6.98; Found: C 58.12, H 5.57, N 6.99.

6.3.2. (3-chlorobenzo[b]thiophen-2-yl)(4-(3,4,5-trimethoxybenzoyl)piperazin-1-yl)methanone (3b)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 477.4; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13-8.11 (d, *J*=6.8 Hz, 1H), 7.88-7.85 (dd, *J* =7.2 Hz, 3.2 Hz 1H), 7.62-7.55 (m, 2H), 6.72 (s, 2H), 3.79 (s, 6H) 3.67 (s, 3H), 3.56-3.46 (m, 8H); Elemental analysis: Calculated (%) for $C_{23}H_{23}ClN_2O_5S$: C 58.16, H 4.88, N 5.90, S 6.75; Found: C 58.17, H 4.87, N 5.89, S 6.73.

6.3.3. (4-(2-Amino-4,5-dichlorobenzoyl)piperazin-1-yl)(3,4,5-trimethoxyphenyl)methanone (3c)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 470.1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43-7.42 (d, *J*=2.4 Hz, 1H), 7.09-7.08 (d, *J* =2.4 Hz, 1H), 6.68 (s, 2H), 5.47 (s, 2H), 3.79 (s, 6H) 3.67 (s, 3H), 3.56-3.46 (m, 8H); Elemental analysis: Calculated (%) for $C_{21}H_{23}Cl_2N_3O_5$: C 53.86, H 4.95, N 8.97; Found: C 53.87, H 4.96, N 8.96.

6.3.4. (4-(2-Amino-5-hydroxybenzoyl)piperazin-1-yl)(3,4,5-trimethoxyphenyl)methanone (3d)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 416.1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (s, 1H), 6.69 (s, 2H), 6.58-6.57 (m, 2H), 6.44 (s, 1H), 4.55 (s, 2H), 3.79 (s, 6H) 3.67 (s, 3H), 3.56-3.46 (m, 8H); Elemental analysis: Calculated (%) for $C_{21}H_{25}N_3O_6$: C 60.71, H 6.07, N 10.11; Found: C 60.70, H 6.08, N 10.10.

6.3.5. (4-(2-Chloronicotinoyl)piperazin-1-yl)(3,4,5-trimethoxyphenyl)methanone (3e)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 420.1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49-8.48 (m, 1H), 7.95-7.90 (m, 1H), 7.56-7.51 (m, 1H), 6.71 (s, 2H), 3.79 (s, 6H) 3.67 (s, 3H), 3.56-3.46 (m, 8H); Elemental analysis: Calculated (%) for $C_{20}H_{22}ClN_3O_5$: C 57.21, H 5.28, N 10.01; Found: C 57.20, H 5.27, N 10.03.

6.3.6. (4-(3-Fluoro-2-nitrobenzoyl)piperazin-1-yl)(3,4,5-trimethoxyphenyl)methanone (3f)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 448.1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82-7.75 (m, 1H), 7.70-7.67 (m, 1H), 7.54-7.51 (m, 1H), 6.72 (s, 2H), 3.79 (s, 6H) 3.67 (s, 3H), 3.56-3.46 (m, 8H); Elemental analysis: Calculated (%) for $C_{21}H_{22}FN_3O_7$: C 56.37, H 4.96, N 9.39; Found: C, 56.36, H 4.97, N 9.37.

6.3.7. 2-(1H-indol-3-yl)-1-(4-(3,4,5-trimethoxybenzoyl)piperazin-1-yl)ethanone (3g)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 438.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H) 7.57-7.55 (d, *J*=7.2 Hz, 1H), 7.34-7.32 (d, *J*=7.2 Hz, 1H), 7.22 (s, 1H), 7.08-7.04 (m, 1H) 6.98-6.94 (m, 1H), 6.67 (s, 2H) 3.79 (s, 6H) 3.67 (s, 3H), 3.56-3.46 (m, 8H), 3.35 (s, 2H); Elemental analysis: Calculated (%) for $C_{24}H_{27}N_3O_5$: C 65.89, H 6.22, N 9.60; Found: C 65.90, H 6.23, N 9.61.

6.3.8. (4-(1-(4-Chlorophenyl)cyclopropanecarbonyl)piperazin-1-yl) (3,4,5-trimethoxyphenyl)methanone (3h)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 459.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38-7.35(d, *J*=8.7 Hz, 2H) 7.20-7.17 (d, *J*=8.7 Hz, 2H), 6.65 (s, 2H), 3.79 (s, 6H) 3.67 (s, 3H), 3.56-3.46 (m, 8H) 1.32-1.17 (m, 4H); Elemental analysis: Calculated (%) for $C_{24}H_{27}ClN_2O_5$: C 62.81, H 5.93, N 6.10; Found: C 62.80, H 5.92, N 6.11.

6.3.9. (2-Tert-butylpyrimidin-4-yl)(4-(3,4,5-trimethoxybenzoyl)piperazin-1-yl)methanone (3i)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 443.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.93-8.92 (d, *J*=5.2 Hz, 1H) 7.95 (s, 1H), 7.49-7.48 (d, *J*=5.2 Hz, 1H), 6.73 (s, 2H), 3.79 (s, 6H) 3.67 (s, 3H), 3.56-3.46 (m, 8H) 1.35 (s, 9H); Elemental analysis: Calculated (%) for $C_{23}H_{30}N_4O_5$: C 62.43, H 6.83, N 12.66; Found: C 62.44, H 6.84 N 12.63.

6.3.10. (4-(4-Chlorobenzoyl)piperazin-1-yl)(3,4,5-trimethoxyphenyl)methanone (3j)
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 419.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54-7.51 (d, *J*=8.4 Hz, 2H) 7.46-7.43 (d, *J*=8.4 Hz, 2H), 6.70 (s, 2H), 3.79 (s, 6H) 3.67 (s, 3H), 3.56-3.46 (m, 8H); Elemental analysis: Calculated (%) for $C_{21}H_{23}ClN_2O_5$: C 60.22, H 5.53, N 6.69; Found: C 60.23, H 5.54, N 6.70.

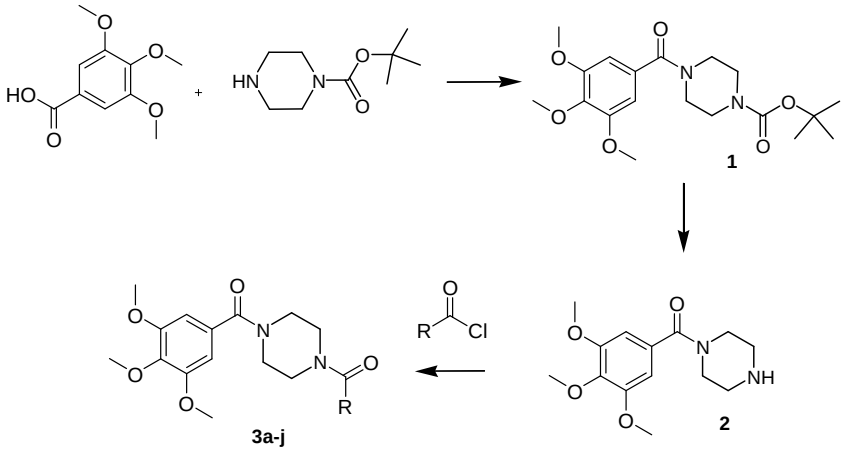
RESULTS AND DISCUSSION

2.1. Chemistry

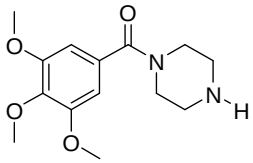
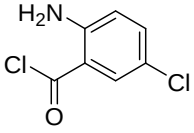
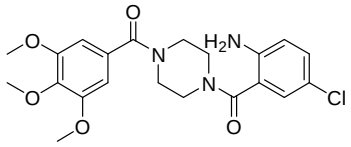
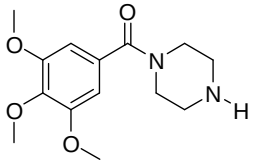
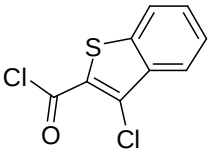
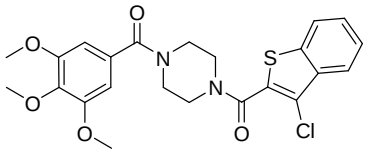
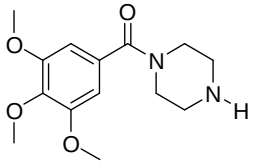
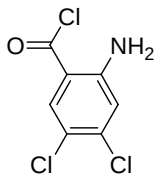
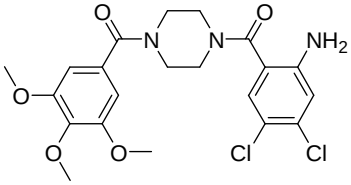
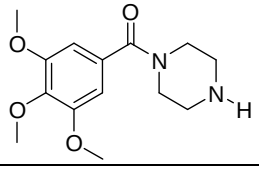
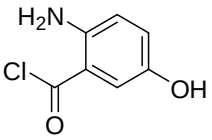
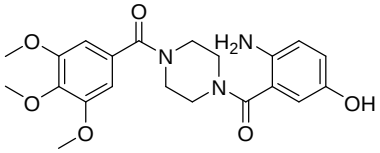
According to our aim, we planned to synthesize compounds **3a-j** using aromatic or heterocyclic acyl chlorides with compound **2**.

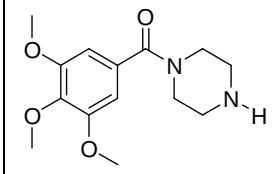
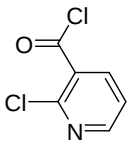
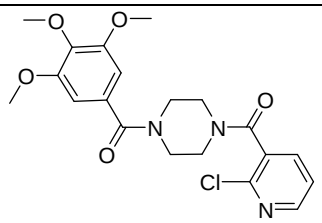
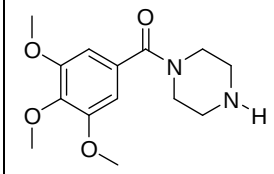
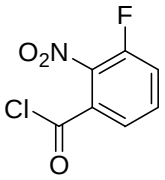
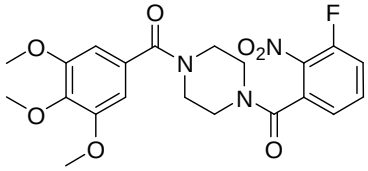
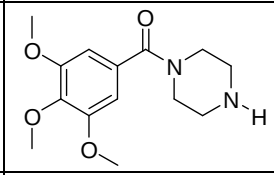
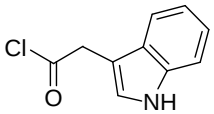
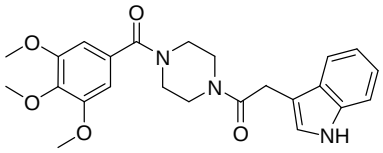
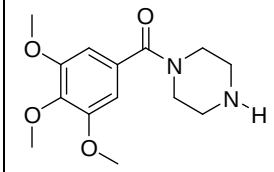
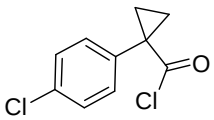
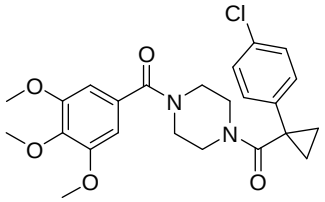
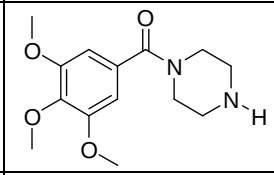
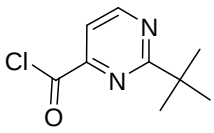
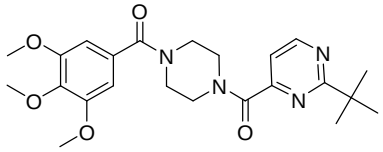
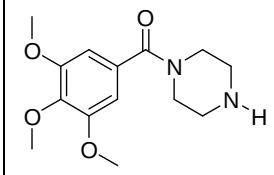
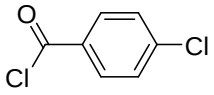
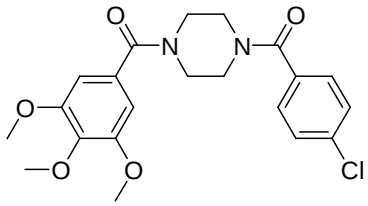
Aromatic or heterocyclic acids (1.0 eq) was dissolved in dry Dichloromethane (10 mL), and cool to 0 ^{0}C. To this added oxalyl chloride, followed by 2 drops of DMF. The reaction mass was stirred for 1 hr at cooled condition. Then the solution was slowly added to pre cooled solution containing compound **2**. Compound **2** (0.5 g, 0.00218 mol 1.0 eq) was dissolved in dry Dichloromethane (10 mL). The solution was stirred for 10 min at 0^{o}C. To this added triethylamine (3.0 eq). The reaction mixture was stirred for 1 hr at cooled solution and completion of reaction was monitored by TLC. The reaction mass was diluted with dichloromethane (75 mL), the organic layer was washed with water (25mL) followed by 10% sodium bicarbonate solution (25 mL), brine (25 mL) and dried with anhydrous sodium sulphate. The organic layer was evaporated under reduced pressure and the crude reaction mass was purified by column chromatography.

All the synthesized compounds have been purified by column chromatography. The structures have been confirmed by elemental analysis and spectroscopic techniques like, ^{1}H-NMR, LC-MS. All the compounds have been tested for *in vitro* antifungal and antibacterial activity.



Scheme 1: Synthesis of Methoxy phenyl piperazine derivatives 3a-j

Compound No.	Compound 2	R	Trimethoxy Piperazine derivative	% Yield
3a				78
3b				77
3c				81
3d				82

3e				81
3f				80
3g				78
3h				80
3i				80
3j				80

3. Microbiology

Preparation of discs:

The test drug stock solution was prepared by dissolving 10mg of drug in DMSO with sonication. Partially dissolved drug was separated by centrifugation. Required amount of stock solution was loaded on to the sterile discs to prepare 500 and 250µg/ml. The discs were allowed to drying under aseptic conditions.

Microorganisms:

The microbial cultures *Escherichia coli* and *A.niger* were procured from National Centre for Industrial Microorganisms (NCIM), Pune, India.

Preparation and Standardization of Stock cultures:

Cultures on receipt were sub cultured in NA (Nutrient Agar) and SDA (Sabouraud dextrose Agar) plates and further stored in slants as stock cultures. For the experiments, stock culture was prepared by inoculating each culture from slants to flask in sterile NB and SDB and incubated at 37^0C for 24hr and at room temperature for 48hrs. The stock culture was adjusted to 0.3 OD (Bacteria) 0.11 OD (Fungi) at 650nm by using spectrophotometer.

Experiment

Sterile NA (Nutrient Agar) and SDA (Sabouraud dextrose Agar) plates were prepared and 0.1 ml of the inoculum from standardized culture of test organism was spread uniformly with L shaped rods. The prepared discs of the test substance, standard antibiotic and solvent control were placed on to the plates carefully. The plates were placed at 4^0C for 1 h to allow the diffusion of test solution into the medium and plates were incubated at a temperature

optimal for the test organism and for a period of time sufficient for the growth of at least 10 to15 generations (usually 24 hours at 37^0C) for bacteria and (usually 48hrs at room temperature) for fungi. The zone of inhibition of microbial growth around the disc was measured in mm.

Given samples shows inhibitory activity against bacteria and fungal strain. The results are tabulated in Table.1 and Table.2.

Table 1: Disc diffusion susceptibility of Test drugs (Bacteria)

Comp number	Disc diffusion susceptibility in mm	
	E.coli	
	500µg/disc	250µg/ disc
3a	26.1	15.2
3b	28.2	16.5
3c	28.6	19.3
3d	29.2	20.1
3e	25.6	19.2
3f	26.8	21.0
3g	28.1	18.4
3h	29.2	21.3
3i	24.6	19.5
3j	25.1	21.0
Standard (Ciprofloxacin) 30µl	37.3	

Table 2: Disc diffusion susceptibility of Test drugs (Fungi)

Comp Name.	Disc diffusion susceptibility in mm	
	A.niger	
	500µg/disc	250µg/ disc
3a	13.5	11.2
3b	12.3	12.1
3c	11.3	10.8
3d	15.8	11.4
3e	16.2	12.2
3f	16.6	13.1
3g	13.8	11.2
3h	11.8	11.8
3i	12.9	10.6
3j	13.7	10.8
Standard (Ketoconazole) 30µl	18.3	

CONCLUSION

The research work is focused on the efficient synthesis of trimethoxybenzene piperazine derivatives **(3a-j).** In addition, some of the tested compounds have exhibited significant antifungal and antibacterial activity. The publication of these facts would be of significant use for the scientific community. Some trimethoxybenzene piperazine derivatives have been tested for antifungal and antibacterial activity. The Compounds **3d, 3e** and **3f** showed good antifungal activity and compound **3b, 3c, 3d, 3g** and **3h** showed moderate anti bacterial activity. The compounds **3a**, **3b, 3c, 3g**, **3h, 3i, and 3j** have shown moderate antifungal activity and **3a**, **3e**, **3f, 3i** and **3j** have shown mild antibacterial activity.

Acknowledgement
We are thankful to the Principal, Sahyadri Science College, Shimoga, for providing laboratory facilities.

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