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SYNTHESIS AND ANTIMICROBEAL ACTIVITY OF SULFONYL AND CARBOXAMIDE DERIVATIVES OF CYCLOPROPYL PIPERAZINE

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ABSTRACT

A series of molecule containing di substituted piperzines are designed and synthesized. The structure of synthesized compounds were elucidated and confirmed by ^{1}H NMR, LCMS and purity was checked through HPLC. Total 18 analogs were synthesized containing urea amide and sulfonamide linkage. The synthesized compounds are evaluated for their anti-bacterial activity against gram-positive and gram negative bacteria. The some of the sulfonyl and carbamaide derivatives showed excellent zone of inhibition against tested bacteria.

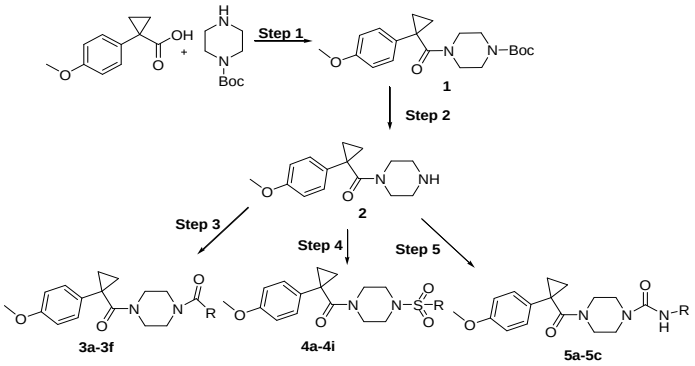
KEYWORDS Piperazine, carboxamide, sulfonylamide, E.coli, S.aureus.

INTRODUCTION

Developing conceptually newer synthetic strategies and their applications in the stereo-selective synthesis of biologically active natural products constitutes major research activity in the discipline of organic chemistry research. In this context, we have developed different reaction strategies and successfully applied to carbohydrate substrate. As an interest in synthesis and biological study, we planned to design the methodologies in the synthesis of biologically active sulfonyl derivatives of piperazine **1** and urea derivatives of piperazine **2**. Piperazine is an interesting heterocyclic moiety as a constituent of several biologically active molecules. The polar nitrogen atoms in piperazine confer bioactivity to molecules and enhance favorable interaction with micromolecules.[1,2] Di substituted piperazine exhibits wide range of biological properties, a number of piperazine derivatives have been synthesized and evaluated for their cytotoxic activity.[3,4] Additional clinical drug development studies of piperazine compounds in small animal models by US National Cancer Institute (NCI)

demonstrate that these targets had the ability to suppress experimental tumours. Some piperazines have been found to anti-tuberculosis activity.[5] The study of [1-(4-chlorophenyl) cyclopropyl] (piperazine-yl) methanone derivatives refers that these compounds possess anticancer and anti-tuberculosis activities.[6,7] Piperazine derivatives play a significant role in metabolism and are considered relatively non-toxic bio-active substances. It is known that piperazine derivatives differing by the type and numbers of substitution patterns show Anti tuberculosis, Antibacterial and Anticancer activity. Thus based on these observations in the literature the present study is initiated with aim of identifying the structural requirements of piperazine. Synthesis of new sulfonyl and amide derivatives of piperazine and compare their antibacterial and antibiotic properties with others heterocyclic compounds. The main objective of present proposal is the synthesis of sulfonyl and amide derivatives of piperzine using easily available substrate. The designed methodologies are having high merit of success as far as better yield and economy is concerned. Thus, the present study will give an easy access to target molecules and the developed reactions would find widespread applications in the synthesis of biologically active products.

The synthesized compounds are depicted in **scheme 1**



Reagent and conditions: (Step1) EDC HCl, DIPEA, DCM, rt 16 h.(**Step 2)** 4N Dioxane-HCl, rt 2 h**. (Step 3)** Substituted amines, DIPEA, DCM rt 2 h. **(Step 4)** Substituted sulfonyl chlorides, DIPEA, DCM rt 2 h. **(Step 5)** Substituted isocyanides, DIPEA, DCM rt 2 h.

RESULT AND DISCUSSION

The synthetic methods adopted for the synthesis of compounds **3a-3f**, **4a-4i** and **5a-5c** are given in scheme **1**. We have optimized the reaction conditions for all the 5 steps and final optimized conditions are given in the experimental section. For amide coupling we have used different coupling reagents, different bases, different solvents and different temperature. We have tabulated the results in **table 1**.

Table 1: optimization of amide formation (step 1)

Coupling Reagent	Base	Solvent	Time	Yield
HATU (1.1 eq.)	TEA (1,2 eq.)	DMF	8h	25%
	DIPEA (1.2 eq.)			35%
PyBOP (1.1 eq.)	TEA (1,2 eq.)	THF	8h	27%
	DIPEA (1.2 eq.)			40%
EDC HCl(2 eq.)	DIPEA (3 eq.)	DCM	2 h	74%
EDCI (1.5 eq.)	DIPEA (2.5 eq.)	DMF	12h	30%
HOBt (1.5 eq.)				
EDCI (1.5 eq.)	TEA (4 eq.)	DMF	12h	46%
HOBt (1.5 eq.)	DIPEA (4 eq.)			55%
T3P (1.2 eq.)	TEA (2.5 eq.)	DCM	8h	40%
	DIPEA (2.5eq)			30%

Acid (1 eq.) and Amine (1 eq.).

From above table it is confirmed that when we use EDC HCl in 2 eq. along with DIPEA as base and DCM as solvent for 2h there is formation of 74% of product. The work is easy and purification is much easy simple filter column is to be performed for obtaining desired intermediate **2** in good yield compare to other methods used for amide formation reaction. Reaction time is also less compare to other amide formation conditions. Only EDCI, HOBt and DIPEA in DMF after 12h gives 55% yield for obtaining compound 2. But work up of DMF reaction is tedious and DMF interfere in the purifications and pure compounds also if we are not doing work up properly. Those problems will not arise in our condition. For step 2 we have deprotected BOC by using 4N HCl in dioxane for 2h. This reaction is at room temperature and work up of this reaction is also easy. The reaction mixture concentrated to obtain crude semisolid material which was washed with 25 ml of hexane and 25 ml of pentane to obtain (1-(4-methoxyphenyl) cyclopropyl) (piperazine-1yl)methanone **(2)** as key intermediate for all the final compound synthesis. For step 3 we have coupled different amines to obtain final compounds **3a-3f**.We have used substitiuted amines (1mmol),THF, DIPEA (3 mmol), phenyl chloroformate (1.2 mmol) we synthesized mixed anhydride and later added (1-(4-methoxyphenyl) cyclopropyl) (piperazine-1yl) methanone (1.1 mmol) by dissolving in THF and DIPEA. All these steps carried at 0 ^{0}C later we heated reaction at 80 ^{0}C for 6h by using this simple step we have obtained reasonable good yields of all the final compounds **3a-3f**. For step 4 we have coupled different sulfonyl chlorides in DCM and DIPEA used as base this reaction completes in 2h. in most of derivatives **4a-4i**. For step 5 we have used different isocyanides reacted in DCM and DIPEA used as base this reaction also

completes in 2h in most of derivatives **5a-5c**. All the detailed experimental procedures are given in experimental section.

All the synthesized compounds **3a-3f**, **4a-4i** and **5a-5c** were screened for *in vitro* antimicrobial activity against two bacteria; *Staphylococcus aureus (NCIM-2901), Escherichia coli (NCIM-2256),* and two fungal strains; *Candida albicans* (NCIM-3471) and *Aspergillus Niger* (NCIM-1196). Minimum inhibitory concentration (MIC, µg/mL) of antibacterial activity was determined using broth dilution methodas per CLSI guidelines. Ciprofloxacin and Ampicillin as control drugs. While the antifungal study was carried by the standard agar dilution method, Fluconazole and Miconazole used as control drugs. Dimethyl sulfoxide was used as solvent control.

Table 2: Antimicrobial screenings data

Compound		MIC values[a] (µg/ml)		
	E.coli	***S.aureus***	***C.Albicans***	***A.Nigar***
3a	22	15	50	25
3b	24	24	25	12.5
3c	20	20	75	50
3d	22	22	100	100
3e	24	24	25	12.5
3f	24	18	75	25
4a	22	20	100	50
4b	24	24	25	12.5
4c	22	18	100	25
4d	23	22	75	50
4e	19	17	50	50
4f	17	15	50	25
4g	19	18	75	12.5
4h	18	22	100	100
4i	22	21	50	50
5a	230	17	50	12.5
5b	25	19	75	12.5
5c	24	22	50	25
Levofloxacin	**29**	**28**	-	-
Fluconazole	-	-	**25**	**25**
Miconazole	-	-	**12.5**	**12.5**

The synthesized compounds of present novel series shows variety of antibacterial and antifungal activity, ranging from broad spectrum molecule active against the majority of bacterial and fungal strains tested to the narrow spectrum compounds, active only against only one strains. Amongst these, the compounds **3a**, **3b, 3c**, **4a**, **4b, 4c, 4e**, **4f,** and **5b-5c** showed highest antibacterial and antifungal activity and they are specific towards the gram

positive bacterial, *S. aureus* and *E. coli*. The compound **3a, 3b, 3e** and **3f** is specific active (MIC of 20, 18, 21 and 14 µg/mL) respectively against *E. coli* and compound **3c** and **3d** (MIC of 15 and 16 µg/mL) are fungal specific molecule specifically active towards the *A. niger*, while the compound (**4fm** and **4g**) (MIC of 12.5-25 µg/mL against all tested strains. Interestingly the compound **4g** (MIC of 12.5 µg/mL) against *A. Nigar*, and its same value compared to standard drugs of miconazole. The compound **3f** (MIC of 14 µg/mL) have more activity than Ciprofloxacin. Although compounds (**5b-5c**) have somewhat better activity both the standard drugs, more important is that, they are broad spectrum in nature and shows the activity against majority of bacterial and fungal strains, against bacteria *S. aureus* and *E. coli*, and fungus *A. niger* and *C. albicans*. Remaining compounds of the series have high MIC values and therefore they are inactive as antimicrobial agents.

Detailed procedure and experimental Data

Step-1: Synthesis of tert-butyl 4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxylate

To a stirred solution of 1-(4- methoxy phenyl) cyclopropane carboxylic acid. (3.0g, 15.60mmol) in dry DCM (20 ml) was added EDC.HCl (5.96g, 31.21 mmol) followed by addition of N-boc piperazine (2.9g, 15.60 mmol). The reaction mixture was cooled to 0^0C for 10min. Then add diisopropylethylamine (3 eq.) at 0^0C. The reaction stirred at room temperature for 2h. After 2 hours the reaction mixture was -diluted with DCM (20 mL) and washed with water (2 X 10mL). The combined organic layer was dried over sodium sulfate and concentrated to obtain 3.5g crude material. The crude product was purified by column chromatography silica (100-200 mesh) using 30-40% ethyl acetate in hexane as an eluent to obtain tert-butyl 4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxylate 4.2g as white solid (74.73% yield). ^{1}H NMR: (400 MHZ, DMSO): δ: 7.09 (dd, *J*=8.8 Hz, 2H); 6.86 (dd, *J*=8.8 Hz, 2H); 3.72 (s, 3H); 3.4 (m, 4H); 3.28-3.06 (m, 4H); 1.38 (s, 9H); 1.23 (bs, 2H); 1.82 (bs, 2H); LCMS: (M+1) 305; rt-2.65; 99.85%; HPLC: 99.84%; rt-9.294%.

Step-2: Synthesis of (1-(4-methoxyphenyl) cyclopropyl) (piperazine-1yl) methanone

To a stirred solution of tert-butyl 4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxylate (4.0 g, 11. 09 mmol) in 1, 4 dioxane (5 mL)was added 4N HCl in dioxane (30 mL)at 0^0C. The reaction stirred at room temperature for 2h. The reaction mixture concentrated to obtain crude semisolid material which was washed with 25 ml of hexane and

25 ml of pentane to obtain (1-(4-methoxyphenyl) cyclopropyl) (piperazine-1yl) methanone 2.5g as white solid. (86.80% yield). ^{1}H NMR: (400 MHZ, DMSO): δ: 7.11 (dd, *J*=8.8 Hz, 2H); 6.88 (dd, *J*=8.8 Hz, 2H); 3.72 (s, 3H); 3.4 (m, 4H); 3.63 (m, 4H);2.92(m, 4H); 1.96 (bs, 1H); 1.28 (bs, 2H); 1.09 (m, 2H); LCMS: (M+1) 261; rt-1.93; 99.78%; HPLC: 99.82%; rt-5.273.

General procedure for Synthesis of N-(substituted)-4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxamide derivatives (3a-3f)

To a stirred solution of Substituted amines (1mmol) in dry THF. The reaction mixture was cooled to 0^{0}C then added DIPEA (3 mmol), followed by addition of phenyl chloroformate (1.2 mmol) stirred reaction mixture for 30 min. Then add (1-(4-methoxyphenyl) cyclopropyl) (piperazine-1yl) methanone (1.1 mmol) by dissolving in THF with DIPEA at 0^{0}C. The reaction stirred at 80^{0}C for 6h. Progress of reaction monitored by TLC. Cooled reaction mixture to room temperature and diluted with ethyl acetate (20 mL) and washed with water (2 X 10ml). The combined organic layer was dried over sodium sulfate and concentrated to obtain 0.4g crude material. The crude product was purified by column chromatography silica (100-200 mesh) using 60-80 % ethyl acetate in hexane as an eluent to obtain product as a off white solid.

3a. Synthesis of N-(4-hydroxy-2-methyl phenyl)- 4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxamide

^{1}H NMR: (400 MHZ, DMSO): δ: 9.09 (s, 1H); 7.834 (s, 1H); 7.123-7.102 (dd, *J*=8.4 Hz, 2H); 6.898-6.877(dd, *J*=8.4 Hz, 2H); 6.501-6.479 (dd, *J*=8.8 Hz, 2H);3.797 (s, 3H); 3.444 (m, 4H); 3.150(m, 4H); 2.012 (s, 3H); 1.26 (bs, 2H); 1.102 (bs, 2H); LCMS: (M+1) 410;rt-2.04;96.60%; HPLC: 98.94%; rt-6.87.

3b. Synthesis of N-(4-methoxy-2-methyl phenyl)- 4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxamide

^{1}H NMR: (400 MHZ, DMSO): δ: 7.920 (s,1H); 7.128-7.107 (dd, *J*=8.4 Hz, 2H); 7.003-6.981(dd, *J*=8.4 Hz, 1H); 6.900-6.880 (dd, *J*=8 Hz, 2H); 6.740(bs, 1H); 6.863-6.661 (dd, *J*=8.8Hz, 1H); 3.720-3.700 (s, 6H); 3.452 (m, 4H); 3.164(m, 4H); 2.080 (s, 3H); 1.265 (m, 2H); 1.105 (m, 2H). LCMS: (m+1)-424; rt-2.33; 99.61%; (Yield: 76.68%). HPLC: 99.75%; rt-7.82.

3c.Synthesi of N-(4-isopropoxy-2-methyl phenyl)- 4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxamide

^{1}H NMR: (400 MHZ, DMSO): δ: 7.899 (s,1H); 7.127-7.105 (dd, *J*=8.4 Hz, 2H); 6.976-6.955 (dd, *J*=8.4 Hz, 1H); 6.899-6.879 (dd, *J*=8 Hz, 2H); 6.714(bs, 1H); 6.660-6.638 (dd, *J*=8.8Hz, 1H); 4.55-4.492 (m, 1H); 3.28 (s, 3H); 3.451(m, 4H); 3.160(m, 4H); 2.063 (s, 3H); 1.263 (bs, 2H); 1.235-1.220 (bs, 6H). 1.105 (bs, 2H); LCMS: (m+1)-452; rt-2.54; 98.83%; (Yield: 69.36%). HPLC: 99.70%; rt-8.59.

3d. Synthesis of N-(2-methyl-4-trifluoromethoxy) phenyl) - 4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxamide

^{1}H NMR: (400 MHZ, DMSO): δ: 8.126 (s, 1H); 7.272-7.251 (dd, *J*=8.4 Hz, 2H); 7.178 (bs, 1H); 7.111-7.091 (dd, *J*=8 Hz, 2H); 6.900-6.879 (dd, *J*=8.4 Hz, 2H); 3.727 (s, 3H); 3.47 (m, 4H); 3.187 (m, 4H); 2.151 (s, 3H); 1.267 (m, 2H); 1.106 (m, 2H); LCMS:(m+1)-478; rt-2.67; 97.52%; (Yield: 56.64%). HPLC: 99.41%; rt-9.078.

3e. Synthesis of N-(5-cyanopyridine-2-yl)-4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxamide

^{1}H NMR: (400 MHZ, DMSO): δ: 9.877 (s, 1H); 8.677 (s, 1H); 8.105-8.083 (dd, *J*=8.8 Hz, 1H); 7.862-7.840 (dd, *J*=8.8 Hz, 1H); 7.118-7.096 (dd, *J*=8.8 Hz, 2H); 6.892-6.871 (dd, *J*=8.4 Hz, 2H); 3.723 (s, 3H); 3.456(m, 4H); 3.242(m, 4H); 1.257-1.236 (bs, 2H); 1.101-1.087 (bs, 2H); LCMS: (m+1)-406; rt-2.25; 95.42%;(Yield: 80.64%). HPLC: 89.44%; rt-8.99

3f. Synthesis of N-(isoquinoline-5-yl)-4-(-1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxamide

^{1}H NMR: (400 MHZ, DMSO): δ: 9.614 (bs, 1H); 8.214-8.191 (d, *J*=9.2 Hz, 1H); 7.917-7.893 (d, *J*=9.6 Hz, 1H); 7.851-7.831 (d, *J*=8 Hz, 1H);7.744-7.723 (d, *J*=8.4 Hz, 1H); 7.662-7.644 (dd, *J*=7.2 Hz, 1H); 7.435-7.416 (d, *J*=7.6 Hz, 1H); 7.128-7.107 (dd, *J*=8.4 Hz, 2H); 6.901-6.880 (d, *J*=8.4 Hz, 1H); 3.726 (s, 3H); 3.475(m, 8H); 2.12(m, 2H); 1.850 (m, 2H); LCMS: (m+1)-431; rt-2.51; 99.06%; (Yield: 66.66%). HPLC: 93.65%; rt-8.96.

General procedure for sulfonyl chloride derivatives (4a-4i)

To a stirred solution of (1-(4-methoxyphenyl) cyclopropyl) (piperazine-1yl) methanone (1mmol) in dry DCM was added DIPEA (3 mmol) at 0^0C followed by addition of sulfonyl chloride (1.2 mmol). Stirred reaction mixture at room temperature for 2h. Progress of reaction monitored by TLC. Reaction mixture was diluted with DCM (10 mL) and washed with water (2 X 10 ml). Combined organic layer was dried over sodium sulfate and concentrated to obtain quantitative crude material. The crude product was purified by column

chromatography silica 100-200 mesh using 60-80% ethyl acetate in hexane as an eluent to obtain product as off white solid.

4a. Synthesis of 4 – ((1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-yl) sulfonyl) benzonitrile

^{1}H NMR: (400 MHZ, DMSO): δ: 8.116-8.096 (dd, *J*=8.0 Hz, 2H); 7.840-7.818 (dd, *J*=8.8 Hz, 2H); 6.998-6.977 (dd, *J*=8.4 Hz, 2H); 6.755-6734 (dd, *J*=8.4 Hz, 2H); 3.723 (s, 3H); 3.506(m, 4H); 2.870-2.617 (m, 4H); 1.234(m, 2H); 1.024 (m, 2H); LCMS: (m+1)-426; rt-2.44; 99.46%; (Yield: 61.34%).

HPLC: 99.88%; rt-10.13.

4b. Synthesis of 1-(4-methoxyphenyl) cyclopropyl (4- ((4-methoxyphenyl) sulfonyl) piperazine-1-yl)) methanone

^{1}H NMR: (400 MHZ, DMSO): δ:7.584-7.563 (dd, *J*=8.4 Hz, 2H); 7.141-7.119 (dd, *J*=8.8 Hz, 2H); 6.990-6.969 (dd, *J*=8.4 Hz, 2H); 6.752-6.731 (dd, *J*=8.4 Hz, 2H); 3.874 (s, 3H); 3.717(m,3H); 3.501 (bs, 3H); 3.313 (bs, 2H); 2.737-2.671 (bs, 3H); 1.158 (m,2H); 1.026(m,2H). LCMS: (m+1)-431; rt-2.55; 99.90%; (Yield: 60.60%). HPLC: 99.88%; rt-10.29.

4c. Synthesis of 1-(4-methoxyphenyl) cyclopropyl (4- (morpholinosulfonyl) piperazine-1-yl)) methanone

^{1}H NMR: (400 MHZ, DMSO): δ: 7.111-7.090 (dd, *J*=8.4 Hz, 2H); 6.893-6.872 (dd, *J*=8.4Hz, 2H); 3.725 (s, 3H); 3.628-3.496 (m, 8H); 3.153-2.936 (m, 8H); 1.279-1.236 (m, 2H); 1.097-1.071 (m, 2H). LCMS: (m+1)-410; rt-2.27; 99.91%; (Yield: 63.69%). HPLC: 99.54%; rt-9.13.

4d. Synthesis of 1-(4-methoxyphenyl) cyclopropyl- (4- ((2,6-dichlorophenyl) sulfonyl) piperazine-1-yl)) methanone

^{1}H NMR: (400 MHZ, DMSO): δ:7.673-7.652 (dd, *J*=8.4 Hz, 2H); 7.590-7.566 (dd, *J*=9.6Hz, 1H); 7.077-7.055 (dd, *J*=8.8 Hz, 2H); 6.840-6.819 (dd, *J*=8.4 Hz, 2H); 3.717 (s, 3H); 3.492 (m, 4H); 3.288-3.310 (m, 4H); 1.240 (bs, 2H) ; 1.059 (bs, 2H). LCMS: (m+1)-469; rt-2.77; 99.95%; (Yield: 67.03%). HPLC: 99.97%; rt-9.90.

4e. Synthesis of 1-(4-methoxyphenyl) cyclopropyl- (4- ((trifluorophenyl) sulfonyl) piperazine-1-yl)) methanone

^{1}H NMR: (400 MHZ, DMSO): δ:8.020-7.890 (d, *J*=16 Hz, 2H); 7.909-7.887 (d, *J*=8Hz, 2H); 7.062-7.040 (dd, *J*=8.8 Hz, 2H); 6.818-6.797 (dd, *J*=8.4 Hz, 2H); 3.712 (s, 3H); 3.53 (m, 4H); 3.064-2.939 (m, 4H); 1.231- (m, 2H); 1.055 (m, 2H). LCMS: (m+1)-469; rt-2.71; 99.80%; (Yield: 66.66%). HPLC: 99.36%; rt-10.92.

4f. Synthesis of 1-(4-methoxyphenyl) cyclopropyl- (4-bezeneylsulfonyl) piperazine-1-yl)) methanone

^{1}H NMR: (400 MHZ, DMSO): δ:8.287-8.267 (d, *J*=8 Hz, 2H); 8.084 (s,1H); 7.923-7.904 (d, *J*=7.6 Hz, 1H); 7.816-7.777 (dd, *J*=15.6 Hz, 1H); 6.964-6.943 (d, *J*= 8.4 Hz, 2H); 6.703-6.682 (d, *J*=8.4 Hz, 2H); 3.907 (s, 3H); 3.718 (s, 3H); 3.501-3.317 (m, 4H); 2.836-2.537 (m, 4H); 1.162-1.097 (bs, 2H); 1.012-0.998 (bs, 2H). LCMS: (m+1)-459; rt-3.007; 99.06%; (Yield: 79.54%). HPLC: 93.27%; rt-6.98

4g. Synthesis of 1-(4-methoxyphenyl) cyclopropyl- (4- octanesulfonyl) piperazine-1-yl)) methanone

^{1}H NMR: (400 MHZ, DMSO): δ:7.107-7.085 (d, *J*=8.8 Hz, 2H); 6.884-6.863 (d, *J*=8.8 Hz, 2H); 3.720 (s, 3H); 3.496-3.335 (m, 4H); 3.036-2.955 (m, 6H); 1.611-1.55 (m,2H); 1.334-1.239 (m, 13H); 1.099-1.078 (m, 2H);1.871-0.855 (m, 2H) ; 0.871-0.838 (m,3H); LCMS: (m+1)-437; rt-3.67; 99.56%; (Yield: 71.85%). HPLC: 97.14%; rt-8.26.

4h. Synthesis of 1-(4-methoxyphenyl) cyclopropyl- (4-ethanesulfonyl) piperazine-1-yl)) methanone

^{1}H NMR: (400 MHZ, DMSO): δ:7.106-7.084 (d, *J*=8.8 Hz, 2H); 6.888-6.866 (d, *J*=8.8 Hz, 2H); 3.721 (s, 3H); 3.496-3.352 (m, 4H); 3.101-2.988 (m, 6H); 1.276-1.233 (m, 2H); 1.178-1.168 (m, 3H); 1.141-1.072 (m,2H). LCMS: (m+1)-353; rt-2.60; 99.49%; (Yield: 74.07%). HPLC: 97.01%; rt-5.99.

4i. Synthesis of 1-(4-methoxyphenyl) cyclopropyl- (4-propyl sulfonyl) piperazine-1-yl)) methanone

^{1}H NMR: (400 MHZ, DMSO): δ:7.093-7.071 (d, *J*=8.8 Hz, 2H); 6.874-6.852 (d, *J*=8.8 Hz, 2H); 3.709 (s, 3H); 3.344-3.007 (m, 4H); 2.976-2.938 (m, 4H); 1.668-1.575 (m, 2H); 1.250-1.220 (m, 2H); 1.124-1.058 (m, 3H); 0.989-0.922 (m, 3H). LCMS:(m+1)-367; rt-2.77; 98.74%; (Yield: 78.01%). HPLC: 98.70%; rt-6.49

General procedure for isocyanate derivatives (5a-5c)

To a stirred solution (1-(4-methoxyphenyl) cyclopropyl) (piperazine-1yl) methanone (1mmol) in dry DCM was added DIPEA (2 mmol) at 0^0C followed by addition of substituted isocyanate (1.2 mmol). Then reaction stirred at room temperature for 2h. The progress of reaction monitored by TLC. After 2 hours the reaction mixture was diluted with DCM (10mL) and washed with water (2 X 10 ml). The combined organic layer was dried over Sodium sulfate and concentrated to obtain quantitative crude material. The crude product was purified by column chromatography silica 100-200 mesh using 50-80% ethyl acetate in hexane as an eluent to obtain product as off white solids.

5a. Synthesis of 4 - (1-(4-methoxyphenyl) cyclopropane-1-carbonyl) N-(2-(trifluoromethyl) phenyl)-4-piperazine-1-carboxamide

^{1}H NMR: (400 MHZ, DMSO): δ:8.241 (bs,1H); 7.676-7.596 (dd, *J*=8 Hz, 2H); 7.405-7.388 (d, *J*=6.8 Hz, 2H); 7.130-7.110 (d, *J*=8 Hz, 2H); 6.901-6.881 (d, *J*=8 Hz, 2H); 3.729 (s, 3H); 3.462 (m, 5H); 3.173 (m, 3H); 1.286 (bs, 2H); 1.105 (bs, 2H); LCMS: (m+1)-448; rt-2.57; 85.63%; (Yield: 78.26%). HPLC: 99.49%; rt-8.61.

5b. Synthesis of N- (cyclohexylmethyl)-4-(1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxamide

^{1}H NMR: (400 MHZ, DMSO): δ 7.101-7.080 (dd, *J*=8.8 Hz, 2H); 6.883-6.862 (d, *J*=8.4 Hz, 2H); 6.424 (t, 1H);3.719 (s, 3H); 3.373-2.816(m, 9H); 1.620-1.599 (m, 6H); 1.345 (m, 1H);1.235-1.085 (m, 7H); 0.801-0.776 (m, 2H); LCMS: (m+1)-400; rt-2.63; 98.08%; (Yield: 73.92%). HPLC: 98.92%; rt-8.87.

5c. Synthesis of N- benzoyl)-4-(1-(4-methoxyphenyl) cyclopropane-1-carbonyl) piperazine-1-carboxamide

^{1}H NMR: (400 MHZ, DMSO): δ 10.209 (bs;1H)7.843-7.823 (d, *J*=8 Hz, 2H); 7.601-7.584 (dd, *J*=6.8 Hz, 1H); 7.498-7.481 (dd, *J*=6.8 Hz, 2H); 7.115-7.094 (dd, *J*=8.4 Hz, 2H); 6.890-6.868 (d, *J*=8.8 Hz, 2H);3.722 (s, 3H); 3.484 (m, 6H); 3.369-3.204 (m, 2H); 1.267 (bs, 2H); 1.087 (bs, 2H); LCMS: (m+1) -408; rt-2.20; 99.97%; (Yield: 85.47%). HPLC: 99.69%; rt-8.87.

CONCLUSION

We have developed simple and convenient method for the synthesis of di substituted piperazines, we have optimized all the reaction steps , no costly reagent is involved, no tedious work up and purification is required, all the compounds obtained in good yields. We

have synthesized 18 derivatives comprising different amide, sulfonamide and urea derivatives and most of the compounds are showing good antibacterial activity as compared to standards.

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