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Synthesis and Studies on Antimicrobial Activity of Piperazine Containing Pyrimidine Derivatives

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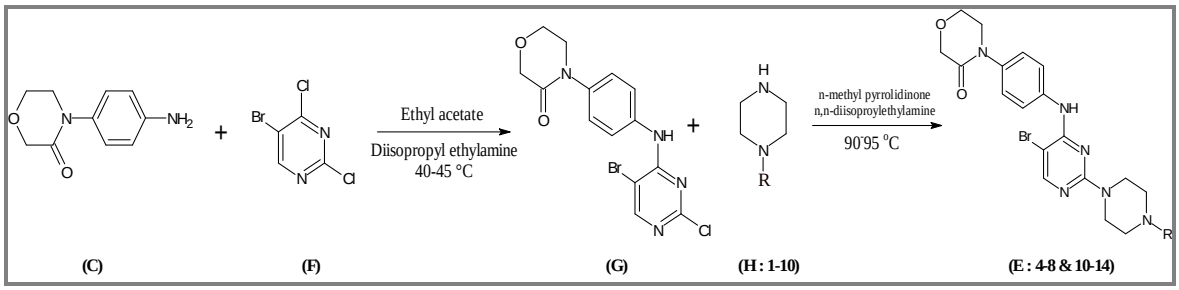
ABSTRACT

A series of novel 4-(4-((5-bromo-2-(4-substitutedpiperazin-1-yl)pyrimidin-4-yl)amino)phenyl) morpholin -3-one, piperazine containing pyrimidine derivatives were synthesized by the reaction of 4-(4-((5-bromo-2-chloropyrimidin-4-yl)amino)phenyl)morpholin-3-one with various piperazine derivatives and there in vitro antimicrobial activities were evaluated. The synthesized compounds were characterized by elemental analyses, FT-IR and ^{1}H NMR spectral studies. 4-(4-((5-bromo-2-(4-substitutedpiperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-one derivatives prepared by using the two key raw materials like 4-(3-Oxo-4-morpholinyl) aniline and 5-bromo-2,4-dichloropyrimidine. The newly synthesis compounds shows moderate to significant activity.

Graphical Abstract



Keywords: Pyrimidine, Piperazine, Antimicrobial, Morpholine.

INTRODUCTION

In recent years, the concept of hybrid molecules, which contain two or more pharmacophore groups coupled together covalently in single molecular structure has been introduced. It has been suggested that such type of hybrid compounds may inhibit two or more conventional targets simultaneously. This multiple objective approach has already resulted in the development of a number of biologically active hybrid molecules [1]. A piperazine ring is a core structure of many marketed drugs including pyrimidine ring in their structures such as imatinib, dasatinib, piribedil, pipemidic acid etc. Piperazine

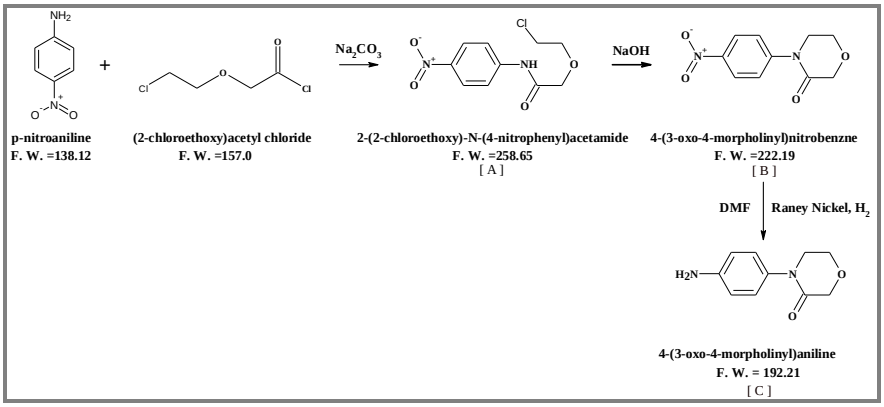
containing pyrimidine derivatives is such a medicinally important heterocyclic nuclei, which consists of an individually six-membered ring containing two nitrogen atoms in their rings. The piperazine nucleus and pyrimidine nucleus has been classified as a privileged structure and is frequently found in biologically active compounds across a number of different therapeutic areas. Halogenated pyrimidines and amino pyrimidines are the most commonly entities attached to the lead molecules. Pyrimidine derivative reported to possess a verity of biological activities [**2, 3**]. Pyrimidine and piperazine derivatives associated with the wide range of biological and pharmacological activities such as antimicrobial [**4, 5**], analgesic [**6, 7**], anticancer [**8-10**], anti-inflammatory [**9, 10**], antimalarial [**11, 12**], anticonvulsant [**13, 14**], antiviral [**15, 16**]. So, it can improve the activity of heterocyclic compounds by coupled the pyrimidine analogs with different heterocyclic moieties like piperazine, quinoline, benzothiazole etc. Bacterial and fungal diseases are the most common all over the world. Though, many antibiotics are currently marketed, they have a tendency of becoming resistant and are prone to severe adverse effects after long term use. Present paper describes the synthesis of 4-{4-[(5-bromo-2-substitutedpiperazines pyrimidin-4yl) amino] phenyl} morpholin-3-one derivatives, characterization and investigation for their antimicrobial activities.

MATERIALS AND METHODS

The substrates were procured from Spectrochem and their purity confirmed by physical and spectroscopic analyses before use. Open capillary tubes were used for melting points of isolated synthesized compounds. Perkin-Elmer FTIR spectrophotometer was used for IR (KBr) spectra of compounds. The ^{1}H NMR spectra were recorded on spectrometers at 400MHz. The chemical shifts are reported in ppm and were measured in deuterated chloroform and TMS as an internal standard. TLC was used for monitoring the reaction. Reaction being monitored by thin Layer Chromatography using ethylacetate: hexane (1:1). The spots were observed by exposure to iodine vapours or by UV light.

Synthesis of 4-(3-Oxo-4-morpholinyl)nitrobenzene (B): To a cool solution of p-nitroaniline (20 g, 0.14 mol) in 200 mL methylene dichloride, solution of sodium carbonate (sodium carbonate (16.7 g, 0.157 mol) + 34 mL water) was added at 15°C. Start addition of 2-(2-chloroethoxy)acetyl chloride (24.3 g, 0.154 mol) at 15°C in 1-1.5 h. After complete reaction, add 20 mL water and stir for 5-10 min. Separate out layers. Give 10 mL dil. HCl washing and 10 mL water washing to organic layer. Add in one lot tetra butyl ammonium bromide (1 g, 5%) in organic layer. Start addition of sodium hydroxide solution (sodium hydroxide (8.8 g, 0.22 mol) in 35 mL water) in 1 h at 25°C. Maintain the temperature of reaction at 15°C for 2-3 h. Monitor the progress of reaction mass by TLC (Mobile phase: ethyl acetate: hexane: 1:1). After complete reaction, add 200 mL water, stir for 5 min, settle and separate out layer. Take organic layer and distilled out solvent at 45°C. Add 30 mL isopropyl alcohol and chill the reaction mass up to 0°C for 1 h. Filter the reaction mass and wash with 10 mL chilled isopropyl alcohol and dried to give 25 g 4-(3-Oxo-4-morpholinyl) nitrobenzene.

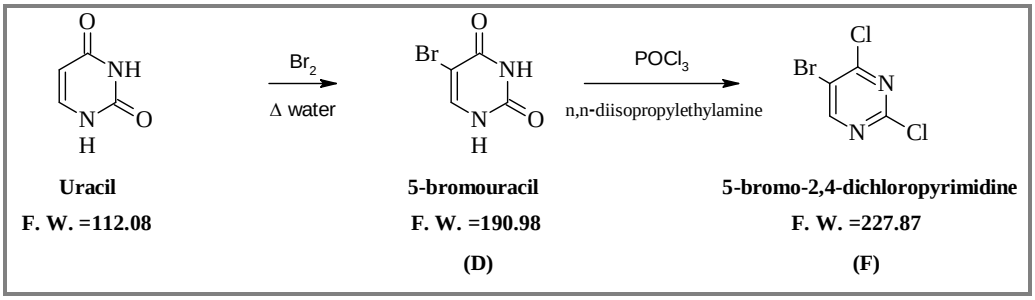
Synthesis of 4-(3-Oxo-4-morpholinyl) aniline (C): Prepare solution of 4-(3-Oxo-4-morpholinyl) nitro benzene (12 g, 0.054 mol) in dimethylformamide (50 mL). Add Raney nickel (1.2 g, 10%) and flush with dimethylformamide (10 mL). Solution is heated to 40-45°C. Slowly start purging of hydrogen gas by maintaining temperature 40-45°C. Monitor reaction by TLC. (Mobile phase: ethyl acetate: hexane: 1:1) After complete reaction, cool the reaction mass up to 25-30°C. Filter the reaction mass and wash with dimethylformamide(10 mL). Take filtrate, add water (100 mL) and chill the reaction mass up to 5-10°C. Maintain the temperature of reaction mass at 5-10°C for 1 h. Resulting precipitate was filtered, washed with cold water and dried to give 4-(3-Oxo-4-morpholinyl)aniline (8 g, 77%) as a light brown solid.



Scheme 1. Synthesis of 4-(3-Oxo-4-morpholinyl) aniline.

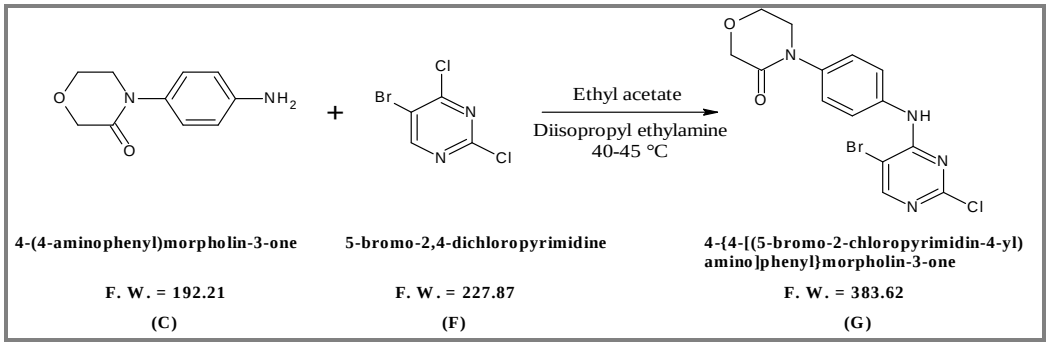
Synthesis of 5- Bromo Uracil(D): Uracil (112 g, 1.0 mol) was added to 500 mL water at 25°C-30°C. Start slowly addition of bromine (175.8 g, 1.1 mol) at 25-30°C in 1 h. Maintain the temperature of reaction mass at 25°C-30°C for 10-15 min. Slowly raise temperature of reaction mass 90°C-95°C and maintain at this temperature for 4-5 h. Cool the reaction mass up to 25°C-30°C and maintain for 30 min and resulting precipitate was filtered, washed with cold water and dried to give (156 g, 68%) as a off white coloured solid(D).

Synthesis of 5-Bromo-2,4-Dichloro Pyrimidine(F): 5-bromo uracil(D) (150 g, 0.785 mol), N,N-isopropyl ethylamine (202.9 g, 1.57 mol) were added to toluene (300 mL). Start slowly addition of phosphorous oxychloride (601 g, 3.9 mol) in 1 h duration. Raise temperatue of reaction up to reflux (i.e. 105°C-110°C) and maintain at this temperature for 10-12 h. During maintaining, white coloured solution turn into light brown coloured clear solution. The progress of reaction was checked by TLC (Mobile phase: ethyl acetate: hexane: 1:1). After complete reaction, cool the reaction mass up to 25°C-30°C. Quench the reaction mass in 2.0 kg crushed ice. Stir the reaction mass for 20-30 minutes. Separate out layers. Take organic layer and distilled out toluene and finally apply high vacuum and distilled out 5-bromo-2,4-dichloro pyrimidine at 115°C-130°C to get 140 g compound(F).



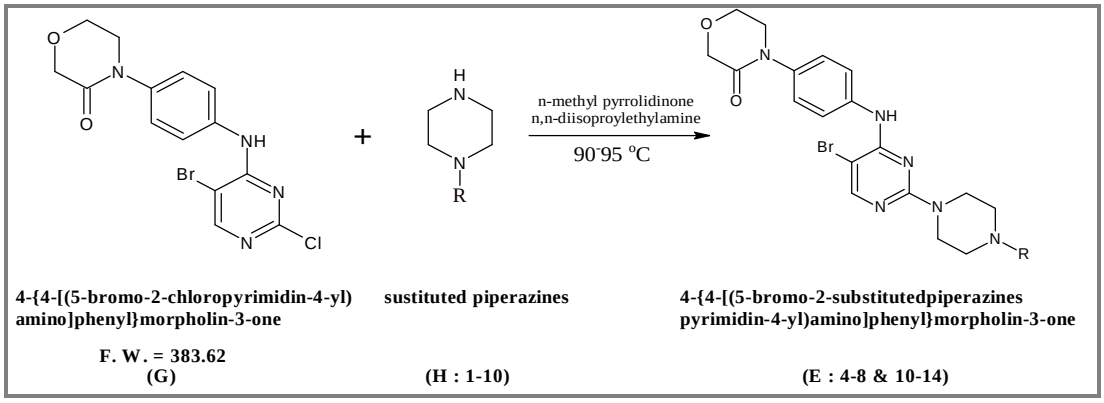
Scheme 2. Synthesis of 5-Bromo-2,4-Dichloro Pyrimidine.

Synthesis of 4-{4-[(5-bromo-2-chloropyrimidin-4-yl) amino] phenyl} morpholin-3-one(G): 4-(3-Oxo-4-morpholinyl) aniline(C) (38 g, 0.2 mol), N, N-diisopropylethylamine (28 g, 0.216 mol) were added to ethylacetate (114 mL. 3 time) at 25°C-30°C. Start slowly addition of 5-bromo-2,4-dichloro pyrimidine(F) (45 g, 0.2 mol) in 1 h. Slowly raise temperature of reaction mass up to 40°C-45°C and maintain at this temperature for 4-5 h. Monitor the progress of reaction mass by TLC (Mobile phase : ethyl acetate : hexane : 1:1). After complete reaction, cool the reaction mass up to 25°C-30°C, slowly add 150 mL water at 25°C-30°C. Stir for 10-15 min. Separate out layers. Organic layer was dry by sodium sulphate and solvents were evaporated to give 64 g compound (G). Crude compound was recrystallized in diisopropylether to give purified (60 g, 79%) compound (G).



Scheme 3. Synthesis of (4-{4-[(5-bromo-2-chloropyrimidin-4-yl)amino]phenyl}morpholin-3-one (G).

Synthesis of 4-{4-[(5-bromo-2-substitutedpiperazinespyrimidin-4-yl)amino]phenyl}morpholin-3-one(E: 4-8 and 10-14): 4-{4-[(5-bromo-2-chloropyrimidin-4-yl)amino]phenyl}morpholin-3-one(G) (4.2 g, 0.011 mol), N,N-diisopropylethylamine(2.2 g, 0.017 mol) were added to n-methyl-2-pyrrolidinone (21 mL, 5 time) at 25°C-30°C. Start slowly addition of substituted piperazine derivative(compounds (H: 1-10)(0.017 mol) in 1 h. Slowly raise temperature of reaction mass up to 90°C-95°C and maintain at this temperature for 4-5 h. Monitor the progress of reaction mass by TLC (Mobile phase : ethyl acetate : hexane : 1:1). After complete reaction, cool the reaction mass up to 25°C-30°C. Slowly add 150 mL water at 25°C-30°C. Stir for 10-15 min. Filter the reaction mass and wash with water to give compound (E: 4-8 and 10-14). Crude compound was recrystallized in isopropyl alcohol to give purified compound (E: 4-8 and 10-14).



Scheme 4. Synthesis of (4-{4-[(5-bromo-2-substitutedpiperazines pyrimidin-4yl)amino]phenyl} morpholin-3-one (E: 4-8 and10-14).

Table 1. Experimental and physical data of compounds (E 4-8 and 10-14) prepare by reaction between 4-{4-[(5-bromo-2-substitutedpiperazines pyrimidin-4yl)amino]phenyl}morpholin-3-one and substituted piperazine (H : 1-10)

Compound No	-R	Molecular Formula	Molecular Weight	Yield %	M.P. °C
E4	-CO(cyclopropyl)	$C_{22}H_{25}BrN_6O_3$	501.37	75	180
E5	$-C_6H_5$	$C_{24}H_{25}BrN_6O_2$	509.39	84	207
E6	$-C_4H_7$(cyclobutyl)	$C_{22}H_{27}BrN_6O_2$	487.39	72	196
E7	$-C_6H_4$(3-OCH_3)	$C_{25}H_{27}BrN_6O_3$	539.42	75	165
E8	$-C_4H_9$ (n-butyl)	$C_{22}H_{29}BrN_6O_2$	489.40	78	140
E10	- C_6H_4(2-Cl, 3-Cl)	$C_{24}H_{23}BrCl_2N_6O_2$	578.28	80	190
E11	$-C_6H_4$ (4-OCH_3)	$C_{25}H_{27}BrN_6O_3$	539.42	70	195
E12	$-C_6H_4$(3-Cl)	$C_{24}H_{24}BrClN_6O_2$	543.84	74	210
E13	1-CH_3, 3-C_6H_5	$C_{25}H_{27}BrN_6O_2$	523.42	60	170
E14	-CH_3	$C_{19}H_{23}BrN_6O_2$	447.32	78	197

RESULTS AND DISCUSSION

Spectral and Elemental Analysis

4-(3-Oxo-4-morpholinyl) aniline(C): Brown coloured solid, Yield 77 %. IR (KBr/ cm^{-1}) 2914-2937 ($-NH_2$), 1640 (-C=O), 3314 (-CH) ; 1H NMR (400MHz, DMSO-d6/ppm) 3.52-3.55 (m, 4H, $-CH_2$), 4.31 (s, 2H, $-CH_2$), 6.27 (s, 2H, $-NH_2$), 6.51-6.68 (m, 4H, Ar-H), Elemental analysis calculated data for $C_{10}H_{12}N_2O_2$; C : 62.49 ; N : 14.57. Found: C: 61.5; N: 14.10.

5-bromo-2,4-dichloro pyrimidine(F): Clear liquid, Yield: 61% IR (liquid film) 685 (C-Br), 837 (C-Cl). 1H NMR (400MHz, $CDCl_3$) 8.7(s, 1H, -CH), Elemental analysis calculated data for $C_4HBrCl_2N_2$; C :21.08; N, 12.29. Found: C, 21.22; N, 12.20.

4-{4-[(5-bromo-2-chloropyrimidin-4-yl) amino] phenyl} morpholin-3-one(G): White solid, Yield: 74 % IR (KBr/cm^{-1}) 3302 (-NH), 679 (C-Br). 1H NMR (400MHz, $CDCl_3$) 3.52-3.55 (m, 4H, $-CH_2$), 4.0 (s, 1H, -NH), 4.31 (s, 2H, -CH), 6.51-6.68 (m, H, -ArH), 8.01(s, 1H, -CH). Elemental analysis calculated data for $C_{14}H_{12}BrClN_4O_2$; C: 43.83, N: 15.73. Found: C: 43.70; N: 15.60.

4-(4-((5-bromo-2-(4-(cyclopropane carbonyl) piperazin-1-yl) pyrimidin-4-yl) amino) phenyl) orpholin-3-one(E-4): White solid, Yield : 75 % IR (KBr, cm^{-1}) 3300 (-NH), 691 (C-Br), 1670 (-C=O). 1H NMR (400MHz, $CDCl_3$) 0.64-0.90 (m, 4H, $-CH_2$), 1.15 (m, 1H, -CH), 3.31-3.57 (m, 12H, $-CH_2$), 4.0 (s, H, -NH), 4.31(s, 2H, $-CH_2$), 6.51-6.70 (m, H, -ArH), 8.1 (s, 1H, -CH). Elemental analysis calculated data for $C_{21}H_{25}BrN_6O_4$; C: 52.70; N: 16.76 Found: C: 52.06; N: 16.52.

4-(4-((5-bromo-2-(4-phenylpiperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-one(E-5): White solid, Yield: 84 % IR (KBr, cm^{-1}) 3300 (-NH), 674 (C-Br), 1666 (-C=O). 1H NMR (400MHz, $CDCl_3$) 3.28-3.29 (m, 4H, $-CH_2$), 3.52-3.57 (m, 8H, $-CH_2$), 4.01 (s, H, -NH), 4.31 (s, 2H, $-CH_2$), 6.51-7.27 (m, H, -ArH), 8.05 (s, 1H, -CH). Elemental analysis calculated data for $C_{24}H_{25}BrN_6O_2$; C: 56.59; N: 15.69. Found: C: 55.70; N:15.20.

4-(4-((5-bromo-2-(4-cyclobutylpiperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-one (E-6): White solid, Yield: 72 % IR (KBr, cm^{-1}) 3305 (-NH), 676 (C-Br), 1645 (-C=O). 1H NMR (400MHz, $CDCl_3$) 1.90-2.15 (m, 6H, $-CH_2$), 2.48 (m, 4H, -CH2), 3.09-3.15 (m, 5H, -CH,-CH2), 3.52-3.55 (m, 4H, $-CH_2$), 4.0 (s, H, -NH), 4.31(m, 2H, $-CH_2$), 6.51-6.68 (m, H, -ArH), 8.1 (s, 1H, -CH). Elemental analysis calculated data for $C_{22}H_{27}BrN_6O_2$; C: 54.21; N: 17.24. Found: C: 54.07; N: 17.50

4-(4-((5-bromo-2-(4-(3-methoxyphenyl) piperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-ne (E-7): White solid, Yield : 75 % IR (KBr, cm^{-1}) 3322 (-NH), 667 (C-Br), 1665 (-C=O). 1H NMR (400MHz, $CDCl_3$) 3.09-3.12 (m, 4H, $-CH_2$), 3.70 (s, 3H, $-OCH_3$), 3.74-4.09 (m, 8H, $-CH_2$), 4.36 (s, 2H, $-CH_2$), 6.31-7.16 (m, H, -ArH), 8.1 (s, 1H, -CH). Elemental analysis calculated data for $C_{25}H_{27}BrN_6O_3$; C: 55.66; N: 15.58. Found: C: 55.62; N: 15.15.

4-(4-((5-bromo-2-(4-butylpiperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-one(E-8): White solid, Yield: 78 % IR (KBr, cm^{-1}) 3309 (-NH), 671 (C-Br), 1656(-C=O). 1H NMR (400MHz, $CDCl_3$) 0.913-0.95 (t, 3H, $-CH_3$), 1.2-1.54 (m, 4H, $-CH_2$), 2.34-2.38 (t, 2H, $-CH_2$), 2.46-2.48 (m, 4H, $-CH_2$), 3.75-4.05 (m, 8H, $-CH_2$), 4.35 (s, 1H, -NH), 7.02 (s, 2H, $-CH_2$), 7.26-7.67 (m, H, -ArH), 8.07 (s, 1H, -CH). Elemental analysis calculated data for $C_{22}H_{29}BrN_6O_2$; C: 53.99; N: 17.17. Found: C: 53.70; N: 17.20.

4-(4-((5-bromo-2-(4-(2,3-dichlorophenyl) piperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholine -3-one(E-10): White solid, Yield : 80 % IR (KBr, cm^{-1}) 3305 (-NH), 625 (C-Br), 1657 (-C=O). 1H NMR (400MHz, $CDCl_3$) 3.27 (m, 4H, $-CH_2$), 3.55-3.58 (m, 8H, $-CH_2$), 4.35(s, 2H, $-CH_2$),

6.51-7.13 (m, H, -ArH), 8.1 (s, 1H, -CH). Elemental analysis calculated data for $C_{24}H_{23}BrCl_2N_6O_2$; C: 49.85; N: 14.53. Found: C: 50.06; N: 14.15.

4-(4-((5-bromo-2-(4-(4-methoxyphenyl) piperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-one (E-11): White solid, Yield: 70 % IR (KBr, cm^{-1}) 3301 (-NH), 679 (C-Br), 1667 (-C=O). 1H NMR (400MHz, $CDCl_3$) 3.09-3.11 (m, 4H, $-CH_2$), 3.708 (s, 3H, $-OCH_3$), 3.77-4.06 (m, 8H, $-CH_2$), 4.36 (s, 2H, $-CH_2$), 6.84-7.67 (m, H, -ArH), 8.1 (s, 1H, -CH). Elemental analysis calculated data for $C_{25}H_{27}BrN_6O_3$; C : 55.66 ; N : 15.58. Found: C: 55.70; N: 15.20.

4-(4-((5-bromo-2-(4-(3-chlorophenyl)piperazin-1-yl)pyrimidin-4-yl)amino)phenyl)morpholin-3-one (E-12): White solid, Yield : 74 % IR (KBr, cm^{-1}) 3315 (-NH), 679 (C-Br), 1664 (-C=O). 1H NMR (400MHz, $CDCl_3$) 3.28 (m, 4H, $-CH_2$), 3.52-3.58 (m, 8H, -CH2), 4.35 (s, 2H, $-CH_2$), 6.51-7.21 (m, H, -ArH), 8.1 (s, 1H, -CH). Elemental analysis calculated data for $C_{24}H_{24}BrClN_6O_2$; C: 53.00; N: 15.45. Found: C: 53.06; N: 15.15.

4-(4-((5-bromo-2-(4-methyl-2-phenylpiperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-one (E-13): White solid, Yield: 60 % IR (KBr, cm^{-1}) 3328 (-NH), 658 (C-Br), 1654 (-C=O). 1H NMR (400MHz, $CDCl_3$) 2.26 (s, 3H, $-CH_3$), 2.75-3.0 (m, 6H, $-CH_2$), 3.52-3.55 (m, 4H, $-CH_2$), 4.41 (m, H, -CH), 4.35 (s, 2H, $-CH_2$), 6.51-7.3 (m, H, -ArH), 8.1 (s, 1H, -CH). Elemental analysis calculated data for $C_{25}H_{27}BrN_6O_2$; C: 57.37; N: 16.06. Found: C: 57.20; N: 16.35.

4-(4-((5-bromo-2-(4-methylpiperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-one(E-14): White solid, Yield: 78 % IR (KBr, cm^{-1}) 3301 (-NH), 672 (C-Br), 1667 (-C=O). 1H NMR (400MHz, $CDCl_3$) 2.26 (s, 3H, $-CH_3$), 2.36 (m, 4H, $-CH_2$), 3.15-3.56 (m, 8H, $-CH_2$), 4.0 (s, H, -NH), 4.31 (s, 2H, $-CH_2$), 6.51-6.68 (m, H, -ArH), 8.07 (s, 1H, -CH). Elemental analysis calculated data for $C_{19}H_{23}BrN_6O_2$; C: 51.01; N: 18.79. Found: C: 51.70; N: 18.20.

In this the novel 4-(4-((5-bromo-2-(4-substitutedpiperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-one derivatives were synthesized by the method summarized in scheme 4. The reactions of 4-{4-[(5-bromo-2-chloropyrimidin-4-yl) amino] phenyl} morpholin-3-one with different substituted piperazines were carried out in the presence of N, N-diisopropylethylamine as a base and N-methyl pyrrolidinone as solvent. Synthesized compounds were characterized by UV-Visible, FT-IR and ^1H NMR spectral studies. Compounds were purified by recrystallization method using isopropyl alcohol.

The IR spectrum of the compound was run using single beam FT-IR. The absorptions around 3000 cm^{-1} in compound E-2 confirm the aromatic C-H stretching. The absorptions around 3301 cm^{-1}, 1667 cm^{-1} and 672 cm^{-1} confirm –NH, -C=O and –C-Br groups in IR spectra respectively of synthesized compound.

The proposed structures with respect to the number of protons agreed and their chemical shifts with the ^1H spectral data. The proton spectral data of the intermediate, 4-(4-((5-bromo-2-(4-(4-methoxyphenyl) piperazin-1-yl) pyrimidin-4-yl) amino) phenyl) morpholin-3-one (**E-11**) shows at singlet peak at 3.7 ppm, confirm the protons of $–OCH_3$ group. The most characteristic singlet peak observed at 8.1 ppm confirms the single proton of pyrimidine ring in all compounds. Another singlet peak at 4.359 ppm, confirm the protons of –CH2 group in morpholine ring of all synthesized compounds.

The synthesized compounds were screened for their in vitro antibacterial and antifungal activities. The prepared compounds were tested against the standard strains *Staphylococcus aureus* and *Bacillus subtillis* (Gram positive bacteria), *Escherichia coli* and *pseudomonas aeruginosa* (Gram negative bacteria). The same compounds were tested against *Candida albicans* and *Aspergillus niger* (fungi.) Microbiological results showed that from the synthesized compounds, **E-5** possesses excellent activity

against gram positive and gram- negative bacteria and compound **E-4** possesses excellent activity against gram positive bacteria compared with standard drugs. The compounds **E-8** have sensible activity against *E. coli* and against *B. subtillis*. Compound **E-10** has sensible activity against S. aureus. The remaining compounds displayed average to poor activities against all four bacterial species. The antifungal screening of the synthesized compounds **E-4**, **E-5** and **E-10** had shown extremely promising against *C. albicans*. The rest of the compounds of the series exhibited average to poor activity.

APPLICATION

Antibacterial activity was carried out by broth dilution method [17]. The compounds **E4, E5, E6, E7, E8, E10, E12** and **E-14** were screened for antibacterial activity against *Staphylococcus aureus* and *Bacillus subtillis* (Gram positive bacteria), *Escherichia coli* and *Pseudomonas aeruginosa* (Gram negative bacteria). The same compounds were tested against Candida albicans and *Aspergillus niger* (fungi). The standard drugs used in the present study were Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin for antibacterial activity and Nystatin and Griseofulvin for antifungal activity.

Table 2. Antibacterial activity of tested compounds (E4, E5, E6, E7, E8, E10, E12 and E-14)

Compound No	Minimal bactericidal concentration ug mL^{-1}				Minimal fungicidal concentration ug/ml	
	Gram negative bacteria		Gram positive bacteria			
	E. coli MTCC 443	*P.aeruginosa* MTCC 1688	*S.aureus* MTCC 96	*B.subtillis* MTCC 441	*C.albicans* MTCC 227	*A.niger* MTCC 282
E 4	500	500	100	**62.5**	250	>1000
E 5	**62.5**	100	**62.5**	125	250	>1000
E 6	100	125	125	200	1000	500
E 7	250	200	250	500	1000	>1000
E 8	100	250	250	100	500	500
E 10	200	200	100	250	200	1000
E 12	125	200	500	500	1000	1000
E 14	200	200	500	500	500	500
Gentamycin	0.05	1	1	0.25	--	--
Ampicillin	100	--	250	250	--	--
Chloramphenicol	50	50	50	50	--	--
Ciprofloxacin	25	25	50	50	--	--
Norfloxacin	10	10	100	10	--	--
Nystatin	--	--	--	--	100	100
Greseofulvin	--	--	--	--	500	100

The characters in bold show the antimicrobial activity of the synthesized compounds like **E-5** possesses excellent activity against gram positive and gram negative bacteria and compound **E-4** possesses excellent activity against gram positive bacteria compared with standard drugs. The compounds **E-8** have sensible activity against *E. coli* and against *B.subtillis*. Compound **E-10** has sensible activity against S.aureus. The remaining compounds displayed average to poor activities against all four bacterial species. The antifungal screening of the synthesized Compounds **E-4**, **E-5** and **E-10** show extremely promising against *C. albicans*. The rest of the compounds of the series exhibited average to poor activity.

CONCLUSION

In conclusion, a new class of piperazine encompassing pyrimidine derivatives were synthesized in good yield, characterized by different spectral studies and evaluated as antibacterial agents and antifungal agent. The compound **E-5** was the most potent with good efficacy against E. coli and S. aureus and **E-4** against B. subtillis. It can be concluded that these classes of compounds certainly holds great promise towards good active leads in medicinal chemistry.

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