

Synthesis And Studies On Antimicrobial Activity Of Piperazine Containing 5-Bromo-2-Substituted Piperazines-N-{3-[4-(3-Chlorophenyl)Piperazin-1-Yl]Propyl}Pyrimidin-4-Amines Derivatives

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ABSTRACT: Synthesis of piperazine containing pyrimidine derivatives, which are shown antimicrobial activity such as of 5-bromo-2-substituted piperazines-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amines intermediate, which is characterized and confirmed by elemental analysis, IR and ¹H NMR. 5-bromo-2-substituted piperazines-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amines derivatives prepared by using the two key raw materials like 3-[4-(3-chlorophenyl)piperazin-1-yl]propan-1-amine and 5-bromo-2,4-dichloropyrimidine.

First key raw material 3-[4-(3-chlorophenyl)piperazin-1-yl]propan-1-amine prepared by reaction of m-chloroaniline with bis(2-chloroethyl)amine hydrochloride in presence of water and alkali such as sodium hydroxide, potassium hydroxide, potassium carbonate etc. to form 1-(3-chlorophenyl)piperazine. Then further condensation reaction with 1-bromo-3-chloro propane in toluene and water biphasic media in presence of alkali base such as sodium hydroxide, potassium hydroxide, potassium carbonate etc. to form 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine, which is further simple condensation reaction with (25%) methanolic ammonia yielded 3-[4-(3-chlorophenyl)piperazin-1-yl]propan-1-amine and confirmed by IR, NMR and titrimetric assay analysis.

Second raw material, 5-bromo-2,4-dichloropyrimidine prepared from uracil, which is first brominating using the bromine in aqueous media resulted in white coloured solid material of 5-bromo uracil and confirmed by IR and physical constant. Dry 5-bromo uracil further chlorinated using phosphorous oxychloride at second and fourth position in presence of aniline base reagent as catalyst using toluene as solvent at reflux condition for 12-15 hrs, which is trihalogenated pyrimidine derivative and confirmed by IR, NMR and density.

Further, condensation reaction between 3-[4-(3-chlorophenyl)piperazin-1-yl]propan-1-amine and 5-bromo-2,4-dichloropyrimidine in ethylacetate as a solvent and in presence basic medium using N,N-diisopropylethylamine to get 5-bromo-2-chloro-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine within 8-10 hrs. Finally, synthesis of new series of 5-bromo-2-substituted piperazines-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amines were obtained by condensation of 5-bromo-2-chloro-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine with different types of N-substituted piperazine compounds in presence of N,N-diisopropylethylamine as base in N-methyl pyrrolidinone as a solvent. Substituted N-piperazine derivatives were confirmed and characterized by elemental analysis, IR and ¹H NMR spectroscopy. All the substituted N-piperazine compounds were screened for antimicrobial activity. The newly synthesized compounds show moderate to significant activity.

Key Words: Pyrimidine, Piperazine, Antimicrobial

I. Introduction

Pyrimidines are always an attraction point for researchers because of its efficiency towards various pharmacological usages [1,2]. These compounds are known to possess various biological activities [3-6]. Literature survey shows that various fused pyrimidine derivatives are known to exhibit anti-tubercular [7], antiviral [10], antimicrobial [8,9], anti-inflammatory [11], anti-malarial [12-13], antipsychotic [14] and antitumor [15] activities. Piperazine containing pyrimidine derivatives are also of great interest among medicinal chemists as these compounds have also been reported for a wide spectrum of other biological properties. In the present paper, some novel pyrimidine compounds have been synthesized. The antimicrobial activities of synthesized compounds have been screened against some bacterial (both Gram positive and Gram negative) and fungal strains in DMSO. The results are reported as minimum inhibitory concentrations and minimum bactericidal concentration for all the synthesized compounds.

II. EXPERIMENTAL**2.1 Synthesis of Key Raw Material (1-(3-chlorophenyl)-4-(3-aminopropyl)piperazine)****2.1.1 Synthesis of 1-(3-Chlorophenyl)Piperazine(A)**

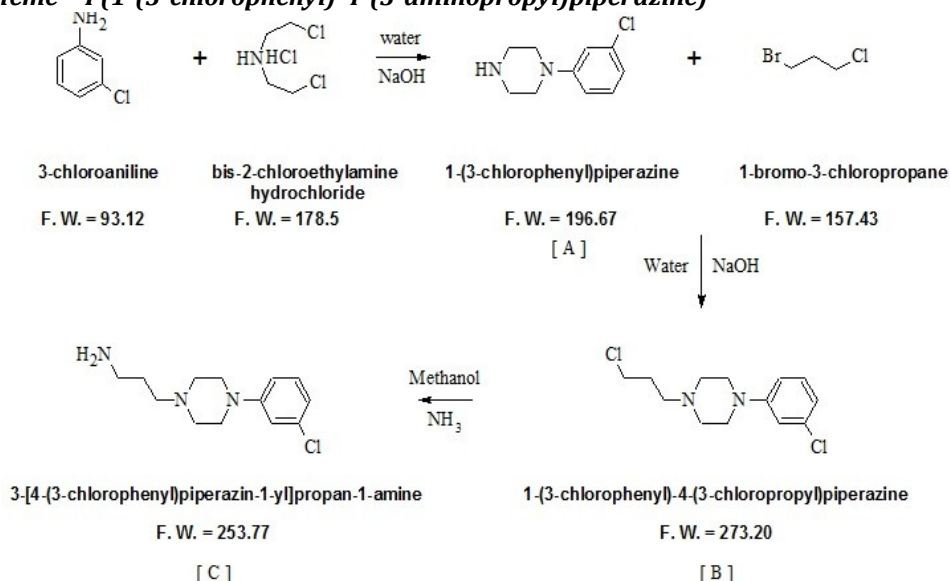
m-chloro aniline(127.5 g, 1.0 moles) and Bis(2-chloroethyl)amine hydrochloride(187.4 g, 1.05 moles) were added to 600 ml water. Mixture was heated up to reflux(i.e 102°C-104°C) for 1-1.5 hrs. Then start dropwise addition of sodium hydroxide 50% sodium hydroxide soln.(120 g sodium hydroxide dissolve in 120 g water) at reflux temperature and pH of reaction mass should be acidic during addition. At the end of reaction, pH of reaction mass brought to 7.0-7.5 by addition of sodium hydroxide soln. The progress of reaction was checked by TLC using ethylacetate : hexane (1:1) as mobile phase and spots were developed using iodine chamber. After completion of reaction, cool the reaction mass up to 25°C-30°C. Slowly add remaining quantity of sodium hydroxide soln. and maintain temperature of reaction mass at 25°C-30°C for 15-20 minutes. Extract the product by 300 ml toluene. Separate out layers, organic layer was dry by sodium sulphate. Toluene was evaporated and finally product was distilled by applying high vacuum. Yield 120 g(A)

2.1.2 Synthesis of 1-(3-Chlorophenyl)-4-(3-Chloropropyl)Piperazine Hydrochloride(B)

1(3-chlorophenyl)piperazine (100 g, 0.51 moles) and 1-bromo-3-chloro propane (159.5 g, 1.02 moles) were added to mixture of 300 ml toluene and 300 ml water at 25°C-30°C. 50% solution of sodium hydroxide (40 g (1.02 moles) was dissolve in 40 ml water) was slowly added to the reaction mixture at 25°C-30°C. Temperature of reaction was raise up to 35°C-40°C. Temperature of reaction mass was maintain for 10-12 hrs at 35°C-40°C. The progress of reaction was checked by TLC using ethylacetate : hexane (1:1) as mobile phase and spots were developed using iodine chamber. After completion of reaction, layers were separated. Organic layer was taken, slowly addition of conc.HCl till dimeric impurity was removed, which was confirmed by TLC. Filter the reaction mass and wash with 50 ml toluene. Take filtrate and start addition of conc.HCl and bring pH of reaction mass up to 1-1.5 at 25°C-30°C. Maintain the temperature of reaction mass for 30-45 minutes at 25°C-30°C. Filter the reaction mass and wash with 50 ml toluene to give 100 g compound(B).

2.1.3 Synthesis of 1-(3-Chlorophenyl)-4-(3-Aminopropyl)Piperazine(C)

Slowly add 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine hydrochloride (100 g, 0.32 moles) to stirrer soln. of 25% methanolic ammonia.(544 g, 8 moles) at 25°C-30°C in 1 hr. Slowly raise temperature of reaction mass up to 35°C-40°C in 1.5 to 2.0 hrs duration. Maintain the temperature of reaction mass at 35°C-40°C for 10-12 hrs. The progress of reaction was checked by TLC using ethylacetate : hexane (1:1) as mobile phase and spots were developed using iodine chamber. After complete reaction, excess ammonia and methanol were evaporated under vacuum to give thick semi solid residue was diluted with 200ml toluene and filtered. Filtrate was taken and distilled out toluene and traces of methanol to give crude compound containing dimer impurity, which was distilled at 150°C-170°C at high vacuum to get 65 g pure compound(C).

Reaction scheme - I (1-(3-chlorophenyl)-4-(3-aminopropyl)piperazine)

2.2 Synthesis Of Key Raw Material (5-Bromo-2,4-Dichloro Pyrimidine)

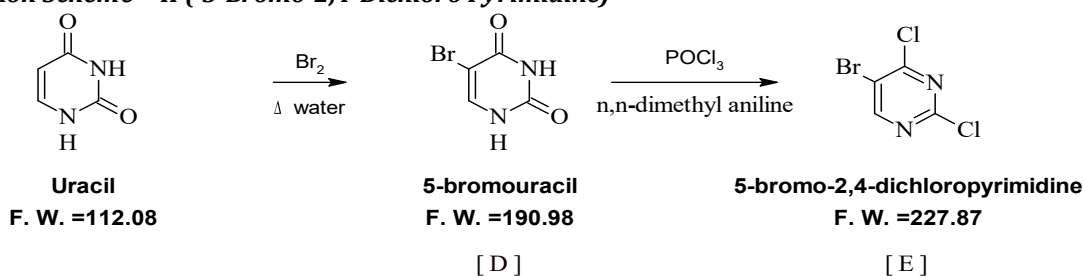
2.2.1 Synthesis Of 5- Bromo Uracil (D)

Uracil (112 gm , 1.0 moles) was added to 500 ml water at 25°C-30°C. slowly addition of bromine (175.8 gm , 1.1 moles) at 25-30°C in 1 hour. Maintain the temperature of reaction mass at 25°C-30°C for 10-15 minutes. Slowly raise temperature of reaction mass 90°C -95°C and maintain at this temperature for 4-5 hours. Cool the reaction mass up to 25°C-30°C and maintain for 30 minutes and filtered to give 156 gm dry compound (D).

2.2.2 Synthesis Of 5-Bromo-2,4-Dichloro Pyrimidine (E) [16]

5-bromo uracil (150 gm , 0.785 moles) , n,n-dimethyl aniline (95 gm , 0.785 moles) were added to Toluene (300 ml). Slowly addition of phosphorous oxichloride (601 gm , 3.9 moles) in 1 hour duration. Raise temperature of reaction up to reflux (i.e. 105°C-110°C) and maintain at this temperature for 10-12 hours. White coloured solution turn into light brown coloured clear solution. The progress of reaction was checked by TLC using ethylacetate : Hexane [1 : 1] as mobile phase. After complete reaction, cool the reaction mass up to 25°C-30°C. and 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 gm compound [E].

Reaction Scheme - II (5-Bromo-2,4-Dichloro Pyrimidine)

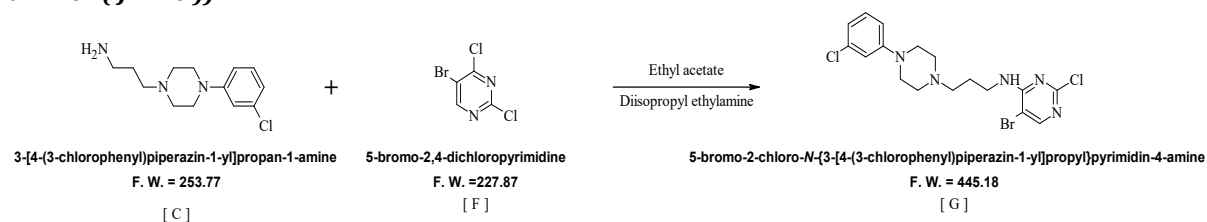


2.3 Reaction scheme I

2.3.1 Synthesis of 5-bromo-2-chloro-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine (G)

Compound [C] (50 gm , 0.2 mol) , N,N-diisopropyl ethyl amine (28 gm , 0.216 moles) were added to ethylacetate (150 ml . 3 time) at 25°C-30°C. Slowly addition of 5-bromo-2,4-dichloro pyrimidine (compound (E)) (45 gm , 0.2 moles) in 1 hour. Slowly raise temperature of reaction mass up to 40°C -45°C and maintain at this temperature for 4-5 hours. Monitor the progress of reaction mass by TLC using ethylacetate : Hexane [1 : 1] as mobile phase .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 minutes. Separate out layers. organic layer was dry by sodium sulphate and solvents were evaporated to give 75 gm compound [G]. Crude compound was recrystallized .in diisopropyl ether to give purified 65 gm compound [G]

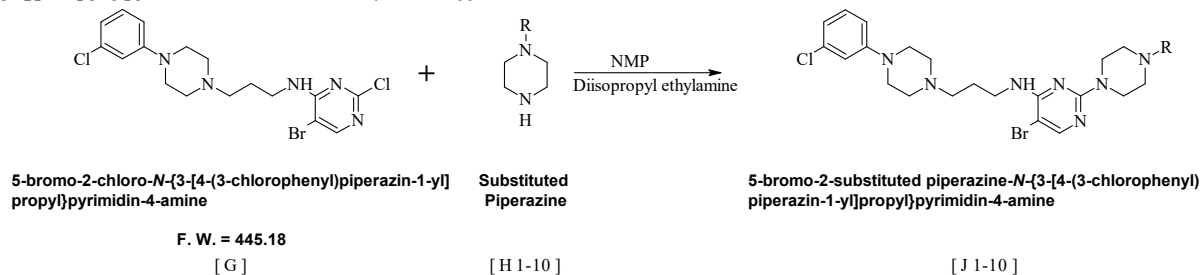
Reaction Scheme - III (5-bromo-2-chloro -N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine (J 1-10))



2.3.2 Synthesis of 5-bromo-2-substituted piperazine -N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine (J 1-10)

Compound (G) (5 gm , 0.011 mol) , N,N-diisopropyl ethyl amine (2.2 gm , 0.017 moles) were added to n-methyl-2-pyrrolidinone (25 ml . 5 time) at 25°C-30°C. Slowly addition of substituted piperazine derivative (compounds (H 1-10)) (0.017 moles) in 1 hour. Slowly raise temperature of reaction mass up to 90°C -95°C and maintain at this temperature for 4-5 hours. Monitor the progress of reaction mass by TLC using ethylacetate : Hexane [1 : 1] as mobile phase. 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 minutes. Filter the reaction mass and wash with water to give compound (J 1-10). Crude compound was recrystallized .in Isopropyl alcohol to give purified compound (J 1-10).

Reaction Scheme - III (5-bromo-2-substituted piperazine -N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine (J 1-10))



III. RESULT AND DISCUSSION

3.1.1 Elemental Analysis (Experimental and physical data of compounds (J 1-10) prepare by reaction between 5-bromo-2-chloro -N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine and substituted piperazine (H 1-10)

Sr. No	-R	M.F. and M.W.	Yield %	M.P. °C
J1	-C ₆ H ₅	C ₂₇ H ₃₃ BrClN ₇ 570.95	84	178
J2	-CH ₃	C ₂₂ H ₃₁ BrClN ₇ 508.88	78	147
J3	-C ₆ H ₄ (3-OCH ₃)	C ₂₈ H ₃₅ BrClN ₇ O 600.98	75	175
J4	-C ₆ H ₄ (3-Cl)	C ₂₇ H ₃₂ BrCl ₂ N ₇ 605.40	74	180
J5	-C ₆ H ₃ (1-CH ₃ , 3-C ₆ H ₅)	C ₂₈ H ₃₅ BrClN ₇ 584.98	60	189
J6	-C ₆ H ₄ (2-OCH ₃)	C ₂₈ H ₃₅ BrClN ₇ O 600.98	70	170
J7	-C ₆ H ₄ (2-Cl, 3-Cl)	C ₂₇ H ₃₁ BrCl ₃ N ₇ 639.84	80	175
J8	-COOCH ₂ CH ₃	C ₂₄ H ₃₃ BrClN ₇ O ₂ 566.92	75	110
J9	-C ₄ H ₉ (N-Butyl)	C ₂₅ H ₃₇ BrClN ₇ 550.96	78	127
J10	-C ₄ H ₇ (Cyclobutyl)	C ₂₅ H ₃₅ BrClN ₇ 548.94	72	140

3.1.2 EXPERIMENTAL

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 ¹H NMR spectra were recorded on spectrometers at 400MHz. 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.

3.1.3 SPECTRAL ANALYSIS

1-(3-chlorophenyl)-4-(3-aminopropyl)piperazine)(C)

Thicky clear liquid, Yield 79 %. IR (KBr, cm⁻¹) 2914,2937 (-NH₂), 3314 (-CH). ¹H NMR (400MHz, DMSO-d₆ / ppm) 1.3-1.4(m, 2H, -CH₂), 2.62-2.68(t, 2H, -CH₂), 3.06-3.19(m, 2H, -CH₂), 6.5-7.5(m, 8H, Ar-H), Elemental analysis calculated data for C₁₃H₂₀ClN₃; C: 61.53; N: 16.56. Found: C: 61.5; N:16.10.

5-bromo-2,4-dichloro pyrimidine(E)

Clear liquid, Yield : 61% IR (liquid film), 685 (C -Br), 837 (C-Cl). ¹H NMR (400MHz, CDCl₃) 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.

5-bromo-2-chloro-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine(G)

White solid, Yield : 74 % IR (KBr, cm^{-1}) 3150 (-NH), 683 (C-Br). 1H NMR (400MHz, $CDCl_3$) 1.72-1.79 (m, 2H, -CH₂), 4.55(s, 1H, -NH), 8.66(s, 1H, -NH), 6.76-7.30 (m, H, -ArH). Elemental analysis calculated data for $C_{17}H_{20}BrCl_2N_5$; C :45.88; N : 15.73 Found ; C :45.70 ; N :15.60.

5-bromo-2-(4-phenylpiperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine(J1)

Yield : 84 % IR (KBr, cm^{-1}) 3275 (-NH), 683 (C-Br). 1H NMR (400MHz, $CDCl_3$) 1.76-1.87(m, 2H, -CH₂), 2.40-3.79(m, 16H, -CH₂), 2.56-2.59(t, 2H, -CH₂), 3.88-3.91(t, 2H, -CH₂), 6.77-7.30(m, H, -ArH), 7.9(s, 1H, -NH). Elemental analysis calculated data for $C_{27}H_{33}BrClN_2$; C :56.80 ; N : 17.17 Found ; C : 56.70; N :17.20.

5-bromo-2-(4-methylpiperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine(J2)

White coloured solid, Yield : 78 % IR (KBr, cm^{-1}) 3252 (-NH), 624 (C-Br), 842(C-Cl). 1HNMR (400MHz, $CDCl_3$) 1.73-1.85 (m, 2H, -CH₂), 2.40-3.50(m, 16H, -CH₂), 2.56-2.59(t, 2H, -CH₂), 3.50-3.70(t, 2H, -CH₂), 6.32-7.50(m, H, -ArH), 7.82(s, 1H, -NH), 2.40(s, 1H, -CH₃). Elemental analysis calculated data for $C_{22}H_{31}BrClN_7$; C :52.01; N :19.79 Found ; C :51.92 ; N :19.27.

5-bromo-2-(4-(3-methoxyphenyl)piperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine(J3)

White coloured solid, Yield : 75 % IR (KBr, cm^{-1}) 3224 (-NH), 683(C-Br), 873(C-Cl). 1H NMR (400MHz, $CDCl_3$) 1.76-1.87(m, 2H, -CH₂), 2.55-3.59(m, 16H, -CH₂), 2.55-2.60(t, 2H, -CH₂), 3.55-3.59(t, 2H, -CH₂), 6.40-7.26(m, H, -ArH), 7.9(s, 1H, -NH), 3.79(s, 1H, -CH₃). Elemental analysis calculated data for $C_{28}H_{35}BrClN_7O$; C :56.12 ; N : 16.18 Found ; C : 55.96 ; N : 16.31.

5-bromo-2-(4-(3-chlorophenyl)piperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine(J4)

Light yellow coloured solid, Yield : 74 % IR (KBr, cm^{-1}) 3238 (-NH), 634 (C-Br), 882(C-Cl). 1H NMR (400MHz, $CDCl_3$) 1.72-1.79(m, 2H, -CH₂), 2.38-3.40(m, 16H, -CH₂), 2.56-2.59(t, 2H, -CH₂), 3.47-3.74 (t, 2H, -CH₂), 6.47-7.56(m, H, -ArH), 7.82(s, 1H, -NH). Elemental analysis calculated data for $C_{27}H_{32}BrCl_2N_7$; C :53.20 ; N : 16.45 Found ; C : 53.57; N :16.20.

5-bromo-2-(4-methyl-3-phenylpiperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine(J5)

Light yellow coloured solid, Yield : 84 % IR (KBr, cm^{-1}) 3240 (-NH), 693 (C-Br). 1H NMR (400MHz, $CDCl_3$) 1.80-1.86(m, 2H, -CH₂), 2.54-3.59(m, 16H, -CH₂), 2.56-2.59(t, 2H, -CH₂), 3.88-3.91(t, 2H, -CH₂), 2.35(s, 1H, -CH₃), 6.77-7.30(m, H, -ArH), 7.9(s, 1H, -NH). Elemental analysis calculated data for $C_{28}H_{35}BrClN_7$; C :57.11 ; N :16.64 Found ; C : 57.49 ; N : 16.76.

5-bromo-2-(4-(2-methoxyphenyl)piperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine(J6)

Off white coloured solid, Yield : 70 % IR (KBr, cm^{-1}) 3242 (-NH), 651 (C-Br), 812(C-Cl). 1H NMR (400MHz, $CDCl_3$) 1.76-1.87(m, 2H, -CH₂), 2.55-3.59(m, 16H, -CH₂), 2.55-2.60(t, 2H, -CH₂), 3.55-3.59(t, 2H, -CH₂), 6.40-7.26(m, H, -ArH), 7.9(s, 1H, -NH), 3.84(s, 1H, -CH₃). Elemental analysis calculated data for $C_{28}H_{35}BrClN_7O$; C :55.66 ; N : 16.58 Found ; C :55.96 ; N :16.31.

5-bromo-2-(4-(2,3-dichlorophenyl)piperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine(J7)

Yellow coloured solid, Yield : 80 % IR (KBr, cm^{-1}) 3264 (-NH), 634 (C-Br), 844(C-Cl). 1H NMR (400MHz, $CDCl_3$) 1.71-1.80(m, 2H, -CH₂), 2.36-3.39(m, 16H, -CH₂), 2.55-2.60(t, 2H, -CH₂), 3.45-3.73(t, 2H, -CH₂), 6.47-7.56(m, H, -ArH), 7.81(s, 1H, -NH). Elemental analysis calculated data for $C_{27}H_{31}BrCl_3N_7$; C :50.62; N :15.43 Found: C : 50.68 ; N :15.32.

5-bromo-2-(4-carbethoxypiperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine (J8)

White coloured solid, Yield : 72 % IR (KBr, cm^{-1}) 3233 (-NH), 675 (C-Br), 852(C-Cl). 1H NMR (400MHz, $CDCl_3$) 1.23-1.27(t, 3H, -CH₃), 1.72-1.81(m, 2H, -CH₂), 2.36-3.39(m, 16H, -CH₂), 2.55-2.60(t, 2H, -CH₂), 3.45-3.73(t, 2H, -CH₂), 4.1-4.16(q, 2H, -CH₂), 6.47-7.56(m, H, -ArH), 7.81(s, 1H, -NH). Elemental analysis calculated data for $C_{24}H_{33}BrClN_7O_2$; C :50.91 ; N :17.63 Found: C :50.85 ; N :17.29

5-bromo-2-(4-carbethoxypiperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine (J9)

White coloured solid, Yield : 78 % IR (KBr, cm^{-1}) 3212 (-NH), 674 (C-Br), 811(C-Cl). 1H NMR (400MHz, $CDCl_3$) 0.83-0.87(t, 3H, -CH₃), 1.26-1.35(m, 2H, -CH₂), 1.40-1.47(m, 2H, -CH₂), 2.62-2.66(t, 2H, -CH₂) 1.72-1.81(m, 2H, -CH₂), 2.35-3.40(m, 16H, -CH₂), 2.55-2.60(t, 2H, -CH₂), 3.45-3.73(t, 2H, -CH₂), 6.47-7.56

(m, H, -ArH),7.83(s, 1H, -NH). Elemental analysis calculated data for C₂₅H₃₇BrClN₇; C :54.59 ; N : 17.17 Found ;C : 54.50 ; N :17.80.

5-bromo-2-(4-carbethoxypiperazinyl)-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}pyrimidin-4-amine (J10)

Off white coloured solid, Yield : 78 % IR (KBr, cm⁻¹) 3215 (-NH), 638 (C-Br),865(C-Cl).¹H NMR(400MHz, CDCl₃)1.12-1.36(t, 4H, -CH₂), 1.63-1.86(m, 2H, -CH₂), 1.72-1.81(m, 2H, -CH₂), 2.33-3.38(m, 16H, -CH₂),2.53-2.62(t, 2H, -CH₂), 3.43-3.72(t, 2H, -CH₂),6.47-7.56(m, H, -ArH),7.81(s, 1H, -NH).]. Elemental analysis calculated data for C₂₅H₃₅BrClN₇; C :54.40 ; N : 17.45 Found ;C :54.70 ; N :17.8.

IV. BIOLOGICAL EVALUATION

Antibacterial activity was carried out by broth dilution method [17-18].The compounds J1 - J10 were screened for antibacterial activity against Staphylococcus aureus and Bacillus subtilis (Gram positive bacteria), Escherichia coli and pseudomonas aeruginosa (Gram negative bacteria).. The same compounds were tested against Candida albicans (fungi.) The standard drug used in the present study was ciprofloxacin for antibacterial activity .Ciprofloxacin which showed MIC at 20, 05 , 10, 10 against Staphylococcus aureus , Bacillus subtilis, Escherichia coli and pseudomonas aeruginosa respectively for antibacterial activity. Fluconazole drus for antifungal activity.

Table 2: Antibacterial and antifungal activity of tested compounds (J1 - J10)

Compounds	MINIMUM INHIBITION CONCENTRATION FOR BACTERIA (µg/ ml)				
	Gram Positive		Gram Negative		
	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Candida albicans</i>
J1	250	250	250	250	500
J2	250	20	20	100	250
J3	100	250	250	100	1000
J4	250	250	250	250	500
J5	250	250	100	250	500
J6	100	100	250	100	500
J7	250	250	250	200	250
J8	100	200	100	200	1000
J9	500	250	100	250	1000
J10	50	20	20	100	500
Ciprofloxacin	20	05	10	10	-
Fluconazole	-	-	-	-	10

V. CONCLUSION

In conclusion, a new class of piperazine encompassing pyrimidine derivatives were successfully synthesized. All the newly synthesized compounds were characterized spectroscopically and using analytical techniques such as ¹H-NMR, IR and elemental analysis, and evaluated as antibacterial agents and antifungal agent. The newly synthesized hetero cyclic compounds exhibite mordarate antibactrial activity aganist Staphylococcus aureus , Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa , and significant antifungal activity against Candida albicans.. Anti-bacterial activity studies reveal that compounds J2 and J10 have shown the highest activity among all newly synthesized compounds as compared to standard drug .It can be concluded that these class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress

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VI. References

1. Goudgoan NM, Basha NJ, Patil SB. Synthesis and antimicrobial evaluation of iodopyrimidine analogs. *Indian J Pharm Sci.* 71:672-677 (2009)
2. Nargund LVG, Badiger V, Yamal V. Synthesis and antimicrobial and anti-inflammatory activities of substituted 2-mercapto-3-(N-aryl)pyrimido[5,4-c]cinnolin-4-(3H)-ones. *J. Pharm. Sci.* 81:365-366 (1992).
3. Barakat A., et al. "Synthesis and structure investigation of novel pyrimidine-2, 4, 6-trione derivatives of highly potential biological activity as anti-diabetic agent". *Russian Journal of Bioorganic Chemistry* 41 ;192-200 (2015)
4. McCarthy O, Musso-Buendia A, Kaiser M, Brun R, Ruiz-Perez LM, Johansson NG, Pacanowska DG, Gilbert IH. Design, Synthesis and evaluation of novel uracil acetamide derivatives as potential inhibitors of *Plasmodium falciparum* dUTP nucleotidohydrolase. *Eur. J. Med. Chem.* 44:678-688 ; (2009)
5. Amin KM, Awadalla FM, Eissa AAM, Abou-Seri SM, Hassan GS. Design, synthesis and vasorelaxant evaluation of novel coumarin-pyrimidine hybrids. *Bioorg. and Med. Chem.* 19 ; 6087-6097 ; (2011)
6. Rahaman SA, Pasad YR, Kumar P, Kumar B. Synthesis and anti-histaminic activity of some novel pyrimidines. *Saudi Pharmaceutical Journal.* 17 : 255-258 ; (2009)
7. R B Patel, P S Desai, K R Desai, K H Chikhalia, *J. Ind. Chem.* 45 (B), 773. ; (2006)
8. Abdel Reheim MAM, SM Baker. "Synthesis, characterization and in vitro antimicrobial activity of novel fused pyrazolo [3,4-c] pyridazine, pyrazolo[3,4-d] pyrimidine, thieno [3,2-c] pyrazole and pyrazolo [3',4':4,5] thieno [2,3-d] pyrimidine derivatives". *Chemistry Central Journal* 11(1) ; 112-125 ; (2017).
9. Khalifa NM., et al. "A convenient synthesis of some new fused pyridine and pyrimidine derivatives of antimicrobial profiles". *Research on Chemical Intermediates* 41(4) ; 2295-2305. (2015)
10. Huckova D, Holy A, Masojdkova M, Andrei G, Snoeck R, De Clercq E, Balzarini J, Synthesis and antiviral activity of 2,4-diamino-5-cyano-6-[2-(phosphonomethoxy) ethoxy] pyrimidine and related compounds, *Bioorg. Med. Chem.* 12(12) ; 3197-3202 ; (2004)
11. Isobe Y, Tobe M, Inoue Y, Isobe M, Tsuchiya M, Hayashi H. Structure and activity relationships of novel uracil derivatives as topical anti-inflammatory agents. *Bioorg. Med. Chem.* 11:4933-4940 ; (2003)
12. J. N. Domínguez, C. Le'ón, J. Rodrigues, N. G. De Domínguez, J. Gut, and P. J. Rosenthal, "Synthesis and evaluation of new antimalarial phenylurenyl chalcone derivatives," *Journal of Medicinal Chemistry*, vol. 48, no. 10, pp. 3654-3658 (2005)
13. A. Valla, B. Valla, D. Cartier et al., "New syntheses and potential antimalarial activities of new retinoid-like chalcones," *European Journal of Medicinal Chemistry*, vol. 41, no. 1, pp. 142-146 (2006)
14. Barcelo M, Ravina E, Masaguer CF, Dominguez E, Areias FM, Brea J Synthesis and binding affinity of new pyrazole and isoxazole derivatives as potential atypical antipsychotics. *Bioorgan Med Chem Lett* 17:4873-4877. (2007)
15. E. Wagner, K. Al-Kadasi, M. Zimecki, and W. Sawka-Dobrowolska, "Synthesis and pharmacological screening of derivatives of isoxazolo[4,5-d]pyrimidine," *European Journal of Medicinal Chemistry*, vol. 43, no. 11, pp. 2498-2504, (2008)
16. S. Gopalakrishnan, E. Vadivel, P. Pon Sathiesh Kumar and M. S. Praba. "Synthesis, molecular docking and ADME prediction of some pyridine and pyrimidine derivatives as anti-colorectal cancer drugs". *J. Chem. Pharm. Res.*, 2(5): 60-66 (2010)
17. Irith Wiegand, Kai Hilpert & Robert EW Hancock. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances. *Nat. Protoc.* 3:163-175 ; (2008)
18. Robert C. Medical Microbiology, ELBS, Livingstone, Briton 11th edition, 895, (1970)