Synthesis and antimicrobial/antioxidant evaluation of novel pyrimidine-based derivatives with pendant pyrazoles using vinamidinum salts

Roya Maghamifar
Ferdowsi University of Mashhad
Seddigheh Sheikhi-Mohammareh
Ferdowsi University of Mashhad
Ali Shiri (alishiri@um.ac.ir)
Ferdowsi University of Mashhad
Hamid Beyzaei
University of Zabol
Zahra Ebrahimnezhad
University of Zabol

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Abstract

Synthesis of a variety of 5-bromo-4-methyl-2-substituted pyrimidines endowed with pyrazolyl appended in C^4 position is described via treatment of 5-bromo-4-hydrazineyl-6-methyl-2-substituted pyrimidines **(6a–f)** and vinamidinum salt of (*E*)-*N*-(3-(dimethylamino)-2-phenylallylidene)-*N*-methylmethanaminium perchlorate **(5)** in good to excellent yields. The inhibitory and hydrogen-atom donating abilities of the synthesized products were assessed against nine pathogens including six bacterial strains (both Gram-negative and Gram-positive), three fungal strains and DPPH free radicals. Notable antioxidant properties were not observed with the products. The inhibition zone diameters were determined in the range of 10.51–18.44 mm *via* Kirby-Bauer disk diffusion method. 5-Bromo-4-methyl-6-pyrazolylpyrimidine (**7e)** containing 2-(4-methylpiperazin) substituent showed the best antioxidant and antimicrobial effects. It was effective on all the tested microbial strains except *Staphylococcus epidermidis*. All the synthesized pyrazolyl pyrimidines, especially (**7e)** can be used to disinfect the environment and treat infectious diseases.

Introduction

1,5-diazapentadienium salts known as vinamidinium salts are vinylogous of amidinium compounds. They are kind of “push–pull alkene” which their stability spring from ‘push-pull’ or resonance effects between the electron-donating amino group and the electron-withdrawing ammonium group which are located at either end of the alkene chain, and are susceptible of substitution rather than addition reactions. Vinamidinium salts due to an alternation of electron density on different positions within their structures, represent specific reactivities towards both nucleophiles and electrophiles on the electron poor α-carbons and electron rich β-carbon, respectively [1–6]. From the viewpoint of their unique properties, these salts have practically obtained synthetic utility, so that many diversely functionalized vinamidinium salts have hitherto been developed and employed as the potent three-carbon skeletons in organic synthesis [4, 7, 8]. For instance, they are successfully utilized for the synthesis of heterocyclic compounds via the reaction with amidines, hydroxylamines, and hydrazines as bifunctional hetero-nucleophiles [9–14]. These salts are also reported to react with nucleophilic carbons such as enolates or related carbanions. Their reactions with enolates are particularly applied as the ready access pathway to dienaminone derivatives which can be valuable intermediates in natural product synthesis [1, 15–21].

Vinamidinium salts are commonly prepared with counter ions hexafluorophosphate or perchlorate. Despite of their chloride salts, these salts are stable and do not absorb moisture. Both ease of synthesis and their stability, make vinamidinium salts suitable synthons for the synthesis of heterocycles [7, 22–24].

On the other hand, infectious diseases including tuberculosis, lower respiratory infections and diarrheal diseases have always been one of the 10 causes of human death [25]. They have significantly increased the mortality rate in cancer patients [26]. The design of new disinfectant and antimicrobial agents is still one of the scientific research priorities.

On the basis of the ease of access to vinamidinium salts as fascinating precursors and due to our abiding interest in synthesis of potentially bioactive heterocyclic scaffolds [27–35], we have continued to explore the synthetic utility of these salts for the synthesis of novel 5-bromo-4-methyl-6-pyrazolylpyrimidines appended with various secondary amine substituents. To diverse antimicrobial libraries, their antibacterial and antifungal capacities were assessed against nine pathogenic strains. In addition, they evaluated for their possible antioxidant properties on DPPH (2,2-diphenyl-1-picrylhydrazyl) free radicals.

Results And Discussion

Chemistry

The synthetic pathways to assemble the desired 5-bromo-4-methyl-6-(4-phenyl-1H-pyrazol-1-yl)- 2-substituted-pyrimidine **(7a-f)** are outlined in **Schemes 1** & **2**. Initially, the required starting materials namely 5-bromo-2-chloro-4-hydrazineyl-6-methylpyrimidine **(4)** and (E)-N-(3-(dimethylamino)-2-phenylallylidene)-N-methylmethanaminium perchlorate (**5)** were prepared in good overall yields according to the published methods [9, 36], as depicted in **Scheme 1**.

Subsequently, the reaction of compound (**4)** with excess quantities of various secondary amines in boiling EtOH underwent S_NAr substitution of Cl-2 on pyrimidine core to give new derivatives of 5-bromo-4-hydrazineyl-6-methyl-2-substituted pyrimidine **(6a–f)** in good yields. In continuation, the reaction of each of compounds **(6a-f)** as a nucleophile with **(5)** as an electrophile gave **(7a-f)** through a simple two-step inter- and intramolecular reactions in the presence of diisopropylethylamine (DIPEA) in CH_3CN, as depicted in **Scheme 2**.

The structural elucidation of all the synthesized compounds **(7a–f)** was accomplished using their physical, chemical and spectral data. As an example, the ^1H NMR spectrum of compound **(7a)** exhibited a multiple signal around δ_H 2.02 ppm and a triplet signal at δ_H 3.62 ppm due to methylene groups of pyrrolidine substituent and a singlet signal at δ_H 2.64 ppm corresponding to the methyl group. Aromatic protons of phenyl moiety were identified by a triplet signal at δ_H 7.31 ppm (J= 7.3 Hz), a triplet signal at δ_H 7.43 ppm (J= 7.6 Hz) and a doublet signal at δ_H 7.60 ppm (J= 7.0 Hz). Tow singlet signals at δ_H 8.11 ppm and 8.50 ppm was assigned to the hydrogens of the pyrazole moiety, as well. ^{13}C NMR spectrum of **(7a)** showed fourteen distinguished signals for the corresponding carbons ranged from δ_C 25.5-1702.3 ppm. The IR spectrum showed absorption bands at v 1612 and 1570 cm^{-1} corresponding to C=N and C=C groups, respectively. Additionally, the observation of the molecular ion peak at m/z 384 in the mass spectrum together with the complimentary results of the elemental analysis of **(7a)** substantiated the substitution of phenyl pyrazolyl on the C^4 position of pyrimidine core endowed with 2-pyrrolidinyl pendant.

Biological Evaluation

DPPH, ceftriaxone and ketoconazole were prepared from Sigma-Aldrich company. Staphylococcus epidermidis (PTCC 1435, ATCC 14990), Bacillus cereus (PTCC 1665, ATCC 14579) and Streptococcus

pyogenes (PTCC 1447, ATCC 12204) as Gram-positive bacterial strains, Pseudomonas aeruginosa (PTCC 1310, ATCC 10145), Escherichia coli (PTCC 1399, ATCC 25922) and Klebsiella pneumoniae (PTCC 1290, NCTC 5056) as Gram-negative bacterial strains and Candida albicans (PTCC 5027, ATCC 10231), Fusarium oxysporum (PTCC 5115, CBS 620.87) and Aspergillus fumigatus (PTCC 5009) as fungal strains were purchased from the Persian Type Culture Collection (PTCC), Karaj, Iran. The inhibition zone diameter (IZD) and the half maximal inhibitory concentration (IC_{50}) values were determined via Kirby-Bauer disk diffusion susceptibility test and DPPH free radical scavenging assay, respectively [37, 38]. In antimicrobial experiments, the synthesized products and drugs were respectively dissolved in DMSO and distilled water to give initial concentrations of 10 and 0.02 $mg.ml^{-1}$. The results of biological tests were expressed as the average of three independent experiments.

Antibacterial and antifungal potentials of pyrazolylpyrimidines **(7a-f)** were investigated on pathogenic strains and compared with those of ceftriaxone and ketoconazole (Table 1).

Table 1. IZD values of the synthesized pyrazolylpyrimidines and drugs (in mm)

Microorganisms	Compounds						Drugs	
	(7a)	(7b)	(7c)	(7d)	(7e)	(7f)	Ceftriaxone	Ketoconazole
E. coli	ND[a]	ND	14.05	13.31	18.44	13.22	31.49	-
P. aeruginosa	ND	10.69	11.12	10.51	15.28	12.06	16.21	-
K. pneumoniae	16.30	14.54	14.21	13.02	14.06	14.28	25.13	-
B. cereus	13.13	ND	13.55	11.43	17.52	ND	ND	-
S. pyogenes	10.52	10.56	12.07	14.15	14.71	15.11	25.88	-
S. epidermidis	ND	ND	ND	ND	ND	ND	18.54	-
C. albicans	14.02	14.05	13.83	11.14	17.07	12.46	-	8.13
A. fumigatus	16.30	14.77	14.67	14.05	17.11	14.44	-	14.63
F. oxysporum	ND	ND	ND	ND	11.38	ND	-	ND

[a] ND: Not detected.

All the synthesized pyrazolylpyrimidines **(7a-f)** were effective in inhibiting the growth of K. pneumoniae, S. pyogenes, C. albicans and A. fumigatus strains. No inhibitory activity was observed with them against S. epidermidis. 5-Bromo-4-methyl-2-(4-methylpiperazin-1-yl)-6-(4-phenyl-1H-pyrazol-1-yl)pyrimidine **(7e)** displayed the best antimicrobial activities and it was the only effective pyrazolylpyrimidine on F. oxysporum. Pyrazolylpyrimidine **(7e)** containing 2-(4-methylpiperazin) substituent had better and wider antimicrobial effects than analogue **(7f)** containing 2-(4-phenylpiperazin) substituent.

Antibacterial, antifungal, antimalarial and antituberculosis activities of some N-thiomide analogues of ethyl 5-methyl-1-(6-(piperazin-1-yl)pyrimidin-4-yl)-1H-pyrazole-4-carboxylate were studied against a variety of microorganisms [39]. The minimum inhibitory concentrations (MICs) were in the range of 25-1000 μg.ml^{-1}. Some of them showed better antibacterial effects than ciprofloxacin, ampicillin and chloramphenicol antibiotics.

No significant scavenging activities were observed with the synthesized products against DPPH free radicals. IC_{50} values were in the range of 107.49-929.16 μg.ml^{-1}. Resembling to the antimicrobial activities, pyrazolylpyrimidine **(7e)** showed the best antioxidant effects, too.

Conclusion

In this study, a novel series of 5-bromo-4-methyl-6-pyrazolylpyrimidines **(7a-f)** which are 2-substituted with pyrrolidine, morpholine, piperidine, 4-methyl piperidine, *N*-methyl piperazine and *N*-phenyl piperazine were synthesized in good to excellent yields via an inter- and intramolecular cyclization reaction of 5-bromo-4-hydrazineyl-6-methyl-2-substituted pyrimidine **(6a–f)** and (*E*)-*N*-(3-(dimethylamino)-2-phenylallylidene)-*N*-methylmethanaminium perchlorate **(5)** in refluxing CH_3CN. Their antimicrobial and antioxidant efficiencies were investigated on bacterial and fungal strains as well as DPPH free radicals. They could inhibit the growth of a variety of pathogenic microorganisms. Compound **(7e)** was recognized as a new wide-spectrum antimicrobial agent. It is predicted that *N*-alkylation and thioamidation of piperazine substituent will intensify its antimicrobial effects.

Experimental

Melting points were recorded on an electrothermal type 9200 melting point apparatus. The IR spectra were obtained on Avatar 370 FT-IR Thermo Nicolet and only noteworthy absorptions are listed. The ^{1}H NMR (300 MHz) and the ^{13}C NMR (75 MHz) spectra were recorded on a Bruker

Avance-III 300 NMR Fourier transformer spectrometer. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 microanalyzer.

Synthesis of 5-bromo-4-hydrazineyl-6-methyl-2-substituted pyrimidine (6a-f); general procedure

A mixture of 5-bromo-2-chloro-4-hydrazineyl-6-methylpyrimidine (**4)** (1 mmol, 0.24 g) and the appropriate secondary amin (3 mmol) in EtOH (5 mL) was refluxed for 12 h. After reaction completion, which was monitored by TLC using $CHCl_3$:MeOH (30:1), The solvent was evaporated and the crude product was purified by chromatography to give 5-bromo-4-hydrazineyl-6-methyl-2-substituted pyrimidine (**6a-f)**.

5-Bromo-4-hydrazineyl-6-methyl-2-(pyrrolidin-1-yl) pyrimidine (6a)

White solid; yield 60%; m.p.:120– 122°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94- 2.04 (m, 4H, 2 CH_2), 2.47 (s, 3H, CH_3–pyrimidine), 3.60- 3.64 (m, 4H, 2 NCH_2), 6.68 (s, 2H, NH_2), 8.23 (s, 1H, NH) ppm; ^{13}C NMR (75

MHz, $CDCl_3$): δ = 24.4, 25.5, 47.2, 89.7, 158.0, 159.5, 165.4 ppm; IR (KBr): ῡ = 3295, 3125, 2986, 2870, 1625, 1557, 1510, 1457, 1341, 1222, 1014 cm^{-1}; MS: *m/z*= 272. Anal. calcd for C_9HBrN_5 (%): C, 39.72; H, 5.19; N, 25.73; Found: C, 39.69; H, 5.18; N, 25.71%.

4-(5-Bromo-4-hydrazineyl-6-methylpyrimidin-2-yl) morpholine (6b)

White solid; yield 57%; m.p.:128– 130 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H, CH_3), 3.67 (s, 8H, 4 CH_2), 6.45 (s, 2H, NH_2), 7.99 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.1, 44.3, 44.4, 66.8, 66.9, 90.5, 159.4, 159.9, 162.9 ppm; IR (KBr): ῡ = 3329, 3244, 2959, 2892, 2850, 1555, 1475, 1449, 1352, 1303, 1275, 1248, 1111 cm^{-1}; MS: *m/z* = 288. Anal. calcd for $C_9H_{14}BrN_5O$ (%): C, 37.51; H, 4.90; N, 24.31; Found: C, 37.49; H, 4.89; N, 24.28%.

5-Bromo-4-hydrazineyl-6-methyl-2-(piperidin-1-yl) pyrimidine (6c)

White solid, yield 56%; m.p.: 118- 120°C; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60- 1.77 (m, 6H, 3 CH_2), 2.58 (s, 3H, CH_3), 3.89- 4.06 (m, 4H, 2 NCH_2), 6.66 (s, 2H, NH2), 8.22 (s, 1H, NH) ppm; IR (KBr): ῡ = 3398, 3305, 3186, 2933, 2854, 1613, 1556, 1442, 1397, 1287, 1252, 1022 cm^{-1}; MS: *m/z* = 286. Anal. calcd for $C_{10}H_{16}$-BrN_5 (%): C, 41.97; H, 5.64; N, 24.47; Found: C, 41.96; H, 5.63; N, 24.45%.

5-Bromo-4-hydrazineyl-6-methyl-2-(4-methylpiperidin-1-yl) pyrimidine (6d)

White solid; yield 80%; m.p.: 142- 144 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.4 Hz, 3H, CH_3– piperidine), 0.99- 1.12 (m, 2H, CH_2), 1.47- 1.54 (m, 1H, CH), 1.57- 1.63 (m, 2H, CH_2), 2.26 (s, 3H, CH_3– pyrimidine), 2.71 (td, *J* = 12.7, 2.8 Hz, 2H, NCH_2), 4.63 (d, *J* = 8.2 Hz, 2H, NCH_2), 6.31 (s, 2H, NH2) ppm; 13C NMR (75 MHz, $CDCl_3$): δ = 21.9, 22.0, 24.2, 31.3, 34.1, 44.2, 90.0, 159.4, 159.9, 162.9 ppm; IR (KBr): ῡ = 3317, 3277, 2948, 2917, 2842, 1562, 1455, 1309, 1273, 1247, 1122, 1082 cm^{-1}; MS: *m/z* = 300. Anal. calcd for $C_{11}H_{18}BrN_5$ (%): C, 44.01; H, 6.04; N, 23.33; Found: C, 44.00; H, 6.02; N, 23.31%.

5-Bromo-4-hydrazineyl-6-methyl-2-(4-methylpiperazin-1-yl) pyrimidine (6e)

White solid; yield 65%; m.p.: 104- 106 °C; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.29 (s, 3H, CH_3–pyrimidine), 2.47- 2.57 (m, 4H, 2 NCH_2), 2.76 (s, 3H, CH_3–piperazine), 3.94- 4.01 (m, 4H, 2 NCH_2), 6.39 (s, 2H, NH2) ppm; IR (KBr): ῡ = 3313, 3276, 2923, 2843, 2799, 1570, 1548, 1478, 1442, 1301, 1273, 1249, 1002 cm^{-1}; MS: *m/z* = 304. Anal. calcd for $C_{10}H_{17}BrN_6$ (%): C, 39.88; H, 5.69; N, 27.90; Found: C, 39.86; H, 5.68; N, 27.88 %.

5-Bromo-4-hydrazineyl-6-methyl-2-(4-phenylpiperazin-1-yl) pyrimidine (6f)

White solid; yield 70%; m.p.: 102- 104°C; ^1H NMR (300MHz, $CDCl_3$): δ = 2.50 (s, 3H, CH_3), 3.18- 3.36 (m, 4H, 2 NCH_2), 3.97- 4.27 (m, 4H, 2 NCH_2), 6.58 (s, 2H, NH2), ῡῡ7.20- 7.50 (m, 5H, aromatic) ppm; IR (KBr): ῡ = 3380, 2950, 2925, 2843, 2814, 1646, 1598, 1570, 1552, 1493, 1444, 1375, 1280, 1230, 1155 cm^{-1}; MS: *m/z* = 363. Anal. calcd for $C_{15}H_{19}BrN_6$ (%): C, 49.60; H, 5.27; N, 23.14; Found: C, 49.58; H, 5.26; N, 23.11%.

General procedure for the synthesis of 5-bromo-4-methyl-2-substituted-6-(4-phenyl-1*H*-pyrazol-1-yl) pyrimidine (7a-f);

Vinamidinium salt (**5)** (1.0 mmol) was dissolved in CH_3CN (5 ml) and the mixture was added dropwise to the stirred solution of 5-bromo-4-hydrazineyl-6-methyl-2-substituted pyrimidine **(6a-f)** (1.0 mmol) and *N*, *N*-Diisopropylethylamine (2mmol, 0.28 mL) in CH_3CN (5mL). The solution was heated to reflux for 8-12 h. TLC was used to monitor the progress of the reactions. After the completion of reaction, the solvent was evaporated and the crude product was purified by chromatography to give 5-bromo-4-methyl-2-substituted-6-(4-phenyl-1*H*-pyrazol-1-yl) pyrimidines **(7a-f)**, quantitively.

5-Bromo-4-methyl-6-(4-phenyl-1*H*-pyrazol-1-yl)-2-(pyrrolidin-1-yl)pyrimidine (7a)

White solid; yield 75%; m.p.: 130-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.02 (p, *J* = 3.3 Hz, 4H, 2 CH_2), 2.65 (s, 3H, CH_3), 3.62 (m, 4H, 2 N CH_2); 7.31 (t, *J* = 7.3, 1H, aromatic), 7.43 (t, *J* = 7.6 Hz, 2H, aromatic), 7.60 (d, *J* = 7.0 Hz, 2H, aromatic), 8.11 (s, 1H, Pyrazole), 8.50 (s, 1H, Pyrazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 26.2, 46.9, 95.1, 124.2, 125.9, 126.7, 127.0, 128.9, 131.7, 139.7, 154.2, 157.9, 170.3 ppm; IR (KBr): ῡ = 3137, 3043, 2965, 2866, 1570, 1529, 1455, 1417, 1342, 1242, 1210 cm^{-1}; MS: *m/z*= 384. Anal. calcd for $C_{18}H_{18}BrN_5$ (%): C, 56.26; H, 4.72; N, 18.22; Found: C, 56.25; H, 4.70; N, 18.21%.

4-(5-Bromo-4-methyl-6-(4-phenyl-1*H*-pyrazol-1-yl) pyrimidin-2-yl) morpholine (7b)

White solid; yield 81%; m.p.:149-151 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (s, 3H, CH_3), 3.83- 3.86 (m, 4H, 2 NCH_2), 3.91- 3.94 (m, 4H, 2 OCH_2), 7.30- 7.35 (m, 1H, aromatic),7.44 (t, *J* = 7.5 Hz, 2H, aromatic),7.63 (d, *J* =7.0 Hz, 2H, aromatic), 8.06 (s, 1H, Pyrazole), 8.74 (s, 1H, Pyrazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 44.3, 66.9, 96.6, 123.3, 125.0, 125.8, 127.2, 128.9, 131.6, 140.6, 157.6, 161.3, 170.4 ppm; IR (KBr): ῡ = 3088, 2994, 2969, 2855, 1600, 1561, 1428, 1361, 1263, 1240, 1175 cm^{-1}; MS: *m/z* = 400. Anal. calcd for $C_{18}H_{18}BrN_5O$ (%): C, 54.01; H, 19.96; N, 17.50; Found: C, 53.98; H, 19.95; N, 17.48%.

5-Bromo-4-methyl-6-(4-phenyl-1*H*-pyrazol-1-yl)-2-(piperidin-1-yl)pyrimidine (7c)

White solid; yield 75%; m.p.: 108-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69 (dt, *J* = 9.0, 4.7 Hz, 6H, 3 CH_2), 2.69 (s, 3H, CH_3), 3.87 (t, *J* = 5.3 Hz, 4H, 2 NCH_2), 7.33 (m, 1H, aromatic), 7.45 (t, *J* = 7.6 Hz, 2H, aromatic), 7.62 (d, *J* = 7.0 Hz, 2H, aromatic), 8.12 (s, 1H, Pyrazole), 8.47 (s, 1H, Pyrazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 25.7, 25.8, 45.3, 94.8, 124.5, 126.0, 126.7, 127.7, 128.9, 131.6, 140.0, 169.9 ppm; IR (KBr): ῡ = 2998, 2930, 2851, 1573, 1520, 1428, 1402, 1392, 1291, 1257 cm^{-1}; MS: *m/z* = 398. Anal. calcd for $C_{19}H_{20}BrN_5$ (%): C, 57.29; H, 5.06; N, 17.58; Found: C, 57.26; H, 5.05; N, 17.56%.

5-Bromo-4-methyl-2-(4-methylpiperidin-1-yl)-6-(4-phenyl-1*H*-pyrazol-1-yl)pyrimidine (7d)

White solid; yield 78%; m.p.: 82- 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.4 Hz, 3H, CH_3-piperidine), 1.23 (m, 2H, CH_2), 1.63– 1.79 (m, 3H, CH_2 and CH), 2.63 (s, 3H, CH_3–pyrimidine), 2.91 (td, *J* =

12.7, 2.8 Hz, 2H, N CH_2), 4.78 (dt, *J* = 13.4, 2.7 Hz, 2H, N CH_2), 7.31 (t, *J* = 7.4 Hz, 1H, aromatic), 7.44 (t, *J* = 7.4 Hz, 2H, aromatic), 7.61 (d, *J* = 7.0 Hz, 2H, aromatic), 8.11(s, 1H, Pyrazole), 8.46 (s, 1H, Pyrazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 26.2, 31.1, 34.0, 44.4, 95.0, 124.0, 126.0, 126.7, 127.1, 128.9, 131.7, 139.7, 154.3, 159.0, 170.4 ppm; IR (KBr): ῡ = 2949, 2917, 2842, 1571, 1521, 1430, 1253 cm-1; MS: *m/z* = 411. Anal. calcd for $C_{20}H_{22}BrN_5$ (%): C, 58.26; H, 5.38; N, 16.98; Found: C, 58.24; H, 5.35; N, 16.97%.

5-Bromo-4-methyl-2-(4-methylpiperazin-1-yl)-6-(4-phenyl-1*H*-pyrazol-1-yl) pyrimidine(7e)

White solid; yield 75%; m.p.: 105- 107 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3–piperazine), 2.49-2.53 (m, 4H, 2 NCH_2), 2.64 (s, 3H, CH_3-pyrimidine), 3.90 (t, *J* = 5.2 Hz, 4H, 2 NCH_2), 7.31 (m, 1H, aromatic), 7.43 (t, *J* = 7.5 Hz, 2H, aromatic), 7.60 (d, *J* = 7.0 Hz, 2H, aromatic), 8.11 (s, 1H, Pyrazole), 8.45 (s, 1H, Pyrazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 43.8, 46.2, 54.8, 95.9, 124.4, 126,126.1, 126.7, 128.9, 131.64, 139.9, 154.4, 159.0, 170.6 ppm; IR (KBr): ῡ = 2937, 2847, 2789, 2736, 1578, 1528, 1431, 1369, 1287 cm^{-1}; MS: *m/z* = 413.

Anal. calcd for $C_{19}H_{21}BrN_6$ (%): C, 55.21; H, 5.12; N, 20.33; Found: 55.20; H, 5.10; N, 20.31%.

5-Bromo-4-methyl-2-(4-phenylpiperazin-1-yl)-6-(4-phenyl-1*H*-pyrazol-1-yl) pyrimidine(7f)

White solid; yield 84%; m.p.: 142-144 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.57 (s, 3H, CH_3), 3.30 (br s, 4H, 2 NCH_2), 4.13 (br s, 4H, 2 NCH_2), 7.20- 7.52 (m, 10H, aromatic), 8.02 (s, 1H, Pyrazole), 8.36 (s, 1H, Pyrazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 43.8, 46.2, 54.8, 95.9, 124.4, 126,126.1, 126.7, 128.9, 131.64, 139.9, 154.4, 159.0, 170.6 ppm; IR (KBr): ῡ = 3101, 3011, 2978, 2847, 2814, 2757, 1597, 1566, 1530, 1489, 1426, 1373, 1230, 1152 cm^{-1}; MS: *m/z* = 476. Anal. calcd for $C_{24}H_{23}BrN_6$ (%): C, 60.64; H, 4.88; N, 17.68; Found: C, 60.62; H, 4.87; N, 17.65%.

Declarations

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Scheme

Scheme 1 and 2 are available in the Supplementary Files section.

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