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A convenient synthesis of some new heterocycles containing dihydro-1H-pyrazolo[3,4-d]pyrimidine scaffold with potential biological activities

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ABSTRACT

A new series of dihydro-1H-pyrazolo[3,4-d]pyrimidine and their derivatives were synthesized by using 4-(4-chlorophenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-amine as a starting material. Twenty new heterocyclic containing a pyrazolo[3,4-d]pyrimidine ring were thus prepared in PEG-400 as a green reaction medium. The biological screening showed that most of these derivatives have good antimicrobial activities.The structures of new compounds were assignedon the basis of chemical and spectroscopic evidences.

Keywords: Dihydro-1H-pyrazolo[3,4-d]pyrimidine, PEG-400, Antimicrobial activity.

INTRODUCTION

The dihydro-1H-pyrazolo[3,4-d]pyrimidine and related heterocycles are found to havebroad relevance in the area of medicine and agriculture. These are biologicallyusefulisomeric purine analogues and havesignificantproperties as antimetabolites in purine biochemical reactions [1-3]. In the course of the program directed towards the synthesis of fused nitrogen heterocyclic compound and as an increasing efforts directed on the way to the development of convenient synthetic approaches for the synthesis of fused pyrazolo[3,4-d]pyrimidine derivatives with an expected broad spectrum of biological activity. Thedihydro-1H-pyrazolo[3,4-d]pyrimidineand their derivatives exhibit diversified pharmacological activities like antipyretic and analgesic[4],tuberculostatic[5], antimicrobial[6], neuroleptic [7], CNS depressant [8], antihypertensive [9] and antileishmanial[10]. Additionally, the pyrazole nucleus has shown to be the fundamental moiety for a number of dyes, drugs and agrochemicals[11-15]. In thepresentpaper, we have synthesized some 4-(4-chlorophenyl)-6-(4-fluorophenyl)-3-methyl-1-phenyl-4,9-dihydro-1H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidine and 5-chloro-2-(((4-(4-chloro-phenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)imino) methyl) phenol derivatives for study their utility as pharmacological agents. Herein, we found that these derivatives of dihydro-1H-pyrazolo[3,4-d]pyrimidinepossess potential antimicrobial activity.

MATERIALS AND METHODS

Melting points were findout in an open capillary tube and are uncorrected. The chemical solvents utilized were distilled prior to practice. End point of the reaction was observed by thin layer chromatography on a precoated sheet of silica gel-G using iodine vaporsfor detection. IR spectra were recorded in Perkin Elmer spectrometer. ^{1}H-NMR spectra were confirmed in dimethyl sulphoxide (DMSO)-d_6 using an Advance spectrometer at a frequency of 400

MHz using tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on an EI-Shimadzu QP2010PLUS GC–MS.

General procedure for the preparation of 4-(3/4-substitutedphenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-amine(4 a-e)

A mixture of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one**1**(1 mmol), aromatic aldehydes **2 a-e** (1 mmol) and guanidine hydrochloride**3** (1 mmol) werestirred at 60-80℃ in PEG-400as green reaction solvent (15 mL) in the presence of catalytic amount of KOHfor 3-4 hours. After the completion of the reaction (monitored byTLC), the reaction mixture was poured in ice cold water, solid separated out. The separated solid was filtered; the crude product was recrystallized from aq. acetic acid to afford the pure intermediate product (**4a-e**).

General procedure for the preparation of 6-(3/4-substitutedphenyl)-4-(4-substitutedphenyl)-3-methyl-1-phenyl-4,9-dihydro-1H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidine (5 a-j)

An equimolar mixture of **4a-e** (1 mmol), and substituted phenacylbromides (1 mmol) were stirred at 60-70˚C in PEG-400 (15 mL)for 2-3 hours. After completion of the reaction (monitored by TLC), the crude mixture was worked up in ice-cold water (100 mL). The product which separated out was filtered andrecrystallized from aq. acetic acid to afford the pureproduct (**5a-j**).

General procedure for the preparation of 5-chloro-2-(((4-(4-chlorophenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)imino)methyl)phenol (6 a-j)

An equimolar mixture of **4 a-e** (1 mmol), and substituted aromatic aldehydes (1 mmol) add to it 2-3 drops of acetic acid andthe mixture were stirred at 70˚Cin PEG-400 (15 mL)for 2 hours. After completion of the reaction (monitored by TLC), the crude mixture was worked up in ice-cold water (100 mL). The product which separated out was filtered andrecrystallized from aq. acetic acid to afford the pureproduct (**6a-j**).

Spectroscopic data of selected compounds:

4-(4-chlorophenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-amine(**4a**);IR (KBr, vmax cm^{-1}) 3357, 3321, 1607, 1573, 754: ^{1}HNMR (DMSO d^6, 400 Hz) δ 12.07 (s, 1H, NH),7.72-7.21 (m, 13H, 11Ar-H and 2H of NH_2), 4.94 (s, 1H, CH), 2.31(s, 3H,CH_3) ; ESMS for Molecular Formula$C_{18}H_{16}ClN_5$; 336.7

4-(4-fluorophenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-amine (**4b**); IR (KBr, vmax cm^{-1}) 3365, 3315, 1612, 1580, 754: ^{1}HNMR (DMSO d^6, 400 Hz) δ 12.15 (s, 1H, NH), 7.83-7.39 (m, 13H, 11Ar-H and 2Hof NH_2), 4.80 (s, 1H, C-H), 2.41(s, 3H,CH_3); ESMS for Molecular Formula$C_{18}H_{16}FN_5$; 321.36

3-methyl-4-(4-nitrophenyl)-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-amine (**4d**); IR (KBr, vmax cm^{-1}) 3373, 3300, 1612, 1580, 754;^{1}HNMR (DMSO d^6, 400 Hz) δ 12.00 (s, 1H, NH), 7.88-7.23 (m, 13H, 11Ar-H and2H of NH_2), 4.77 (s, 1H, C-H), 2.20(s, 3H,CH_3); ESMS for Molecular Formula$C_{18}H_{16}N_6O_2$; 348.36

4,6-bis(4-chlorophenyl)-3-methyl-1-phenyl-4,9-dihydro-1H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidine (**5a**);IR (KBr, vmax cm^{-1}) 3321, 2942, 1613, 1574, 751: ^{1}HNMR (DMSO d^6, 400 Hz) δ 11.70 (s, 1H, NH), 8.31-6.31 (m, 15 H,Ar-H and pyrazole), 4.83 (s, 1H, CH), 2.10 (s, 3H, CH_3); ESMS for Molecular Formula for; $C_{26}H_{19}Cl_2N_5$; 472.37

6-(4-chlorophenyl)-3-methyl-4-(4-nitrophenyl)-1-phenyl-4,9-dihydro-1H-imidazo[1,2-a] pyrazolo[3,4-d]pyrimidine(**5d**);IR (KBr, vmax cm^{-1}) 3309, 2958, 1609, 1588, 758: ^{1}HNMR (DMSO d^6, 400 Hz) 12.19 (s, 1H, NH), δ 7.98-7.12 (m, 15 H, Ar-H and pyrazole), 4.30 (s, 1H, NH), 1.75 (s, 3H, CH_3); ESMS for Molecular Formula for; $C_{26}H_{19}ClN_6O_2$; 482.92

4-(4-fluorophenyl)-3-methyl-6-(4-nitrophenyl)-1-phenyl-4,9-dihydro-1H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidine (**5g**); IR (KBr, vmax cm^{-1}) 3314, 2939, 1610, 1591, 750: ^{1}HNMR (DMSO d^6, 400 Hz) δ 11.89 (s, 1H, NH), 8.12-7.29 (m, 15 H,Ar-H and pyrazole), 4.20 (s, 1H, NH), 1.60 (s, 3H, CH_3); ESMS for Molecular Formula for; $C_{26}H_{19}FN_6O_2$; 466.16

3-methyl-4,6-bis(4-nitrophenyl)-1-phenyl-4,9-dihydro-1H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidine(**5i**);IR (KBr, vmax cm^{-1}) 3320, 2947, 1605, 1584; ^{1}HNMR (DMSO d^6, 400 Hz) δ 12.05 (s, 1H, NH), 8.12-7.29 (m, 15 H,Ar-H and pyrazole), 4.20 (s, 1H, NH), 1.60 (s, 3H, CH_3); ESMS for Molecular Formula for; $C_{26}H_{19}N_7O_4$; 493.47

2-(((4-(4-chlorophenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-imino)methyl)phenol (**6a**); IR (KBr, vmax cm^{-1}) 3473, 3415, 2923, 1610, 1494; ^{1}HNMR (DMSO d^6, 400 Hz) δ 13.88 (s, 1H, NH),12.52 (s, 1H, OH), 7.71-7.16 (m, 14 H, 1H of imine andAr-H), 4.96 (s, 1H, NH), 2.31 (s, 3H, CH_3); ESMS for Molecular Formula for; $C_{25}H_{20}ClN_5O$; 442

2-(((4-(4-fluorophenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)imino)methyl)phenol (**6b**);IR (KBr, vmax cm^{-1}) 3470, 3402, 2930, 1618, 1500; ^{1}HNMR (DMSO d^6, 400 Hz) δ 13.72 (s, 1H, NH), 12.65 (s, 1H, OH), 7.81-7.20 (m, 14 H, 1H of imine, andAr-H), 4.86 (s, 1H, NH), 2.28 (s, 3H, CH_3); ESMS for Molecular Formula for; $C_{25}H_{20}FN_5O$; 425.46

2-(((3-methyl-4-(4-nitrophenyl)-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)imino)methyl)phenol(**6d**); IR (KBr, vmax cm^{-1}) 3473, 3415, 2924, 1617, 1520; ^{1}HNMR (DMSO d^6, 400 Hz) δ 13.88 (s, 1H, NH), 12.52 (s, 1H, OH), 7.71-7.16 (m, 14 H, 1H of imine andAr-H), 4.96 (s, 1H, NH), 2.31 (s, 3H, CH_3); ESMS for Molecular Formula for; $C_{25}H_{20}ClN_6O_3$; 452.46

4-chloro-2-(((4-(4-chlorophenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)imino)methyl)phenol (**6f**);IR (KBr, vmax cm^{-1}) 3463, 3400, 2910, 1600, 1509; ^{1}HNMR (DMSO d^6, 400 Hz) δ 13.50 (s, 1H, NH), 12.45 (s, 1H, OH), 7.75-7.25 (m, 14 H, 1H of imine andAr-H), 4.85 (s, 1H, NH), 2.20 (s, 3H, CH_3); ESMS for Molecular Formula for; $C_{25}H_{19}Cl_2N_5O$; 476.36

Biology

The antimicrobial activity of the synthesized compounds (**5a-j**) and (**6a-j**) were determined bythe agar diffusion method [16],the compounds were evaluated for antibacterial activity against*Escherichia coli*(MTCC 443), *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96). The antibiotic Ampicillin (25µg/mL) was used asastandardfor antibacterial activity.

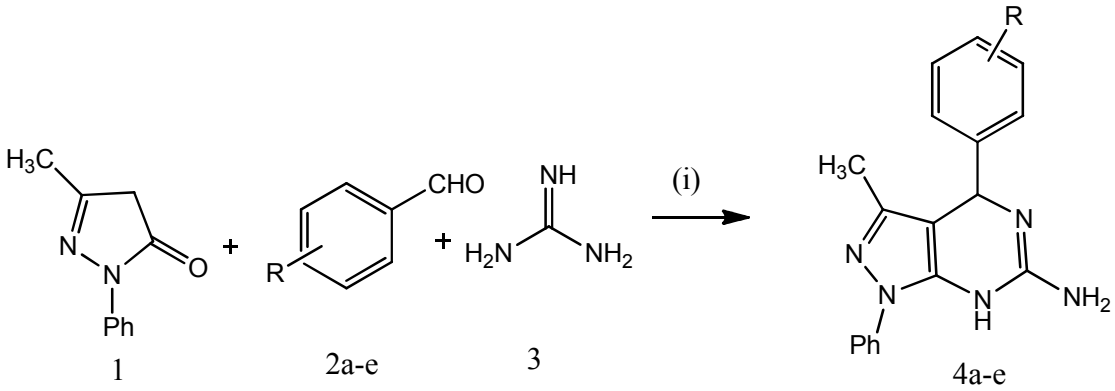
The culture strains of the bacteria were maintained on nutrientagar slants at 37 ± 0.5 ^oC for 24 h. The antibacterial activity was evaluated using nutrient agar plates seeded with 0.1 ml of the respective bacterial culture strain suspension prepared in sterile saline (0.85 %) at 10^5 CFU/mL dilutions. The stock solutions were made by diluting compounds in DMSO to final concentrations ranging from 25 to 100 µg/mL. The wells, of 6 mm diameter, were filled with 0.1 ml of the compound solution separately for each bacterial strain. All the plates were incubated at 37 ± 0.5 ^oC for 24 h. Zones of inhibition of compounds in mm and MIC were noted.Theresults of antibacterial activity were given in **Table-3**.

RESULTS AND DISCUSSION

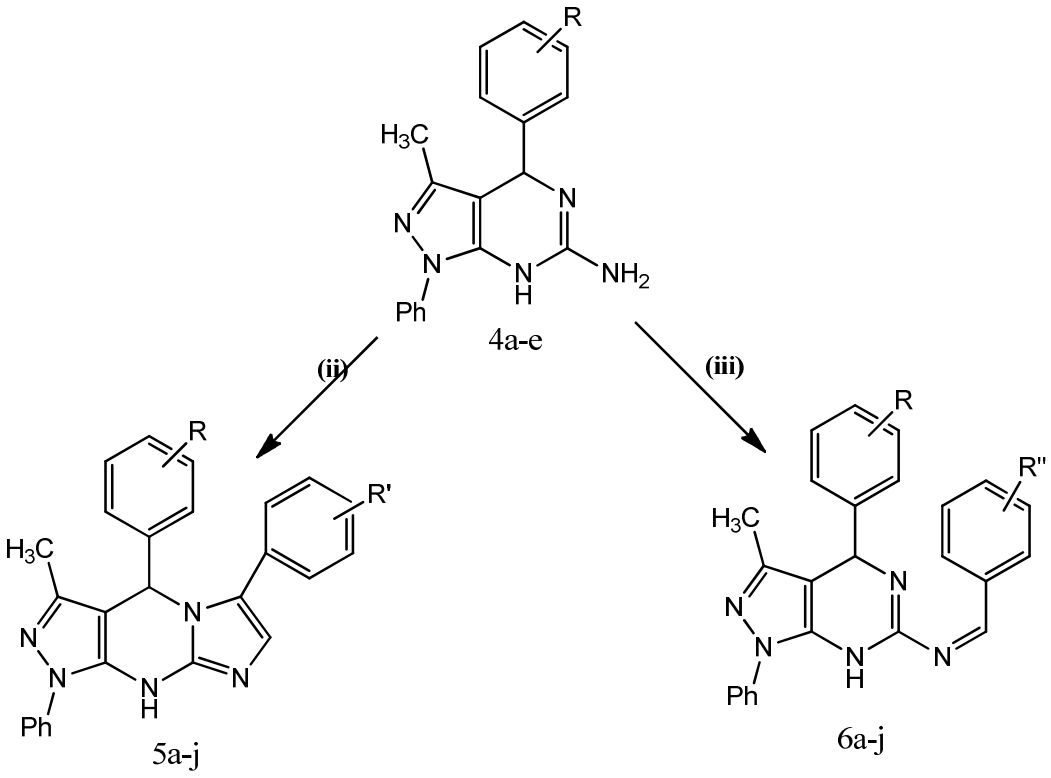
Encouraged by the varied biological activities of these heterocycles and as a part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds [17-23].Herein, we report a green, effective, and clean procedure for one-pot synthesis of4-(3/4-substitutedphenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-amine (**4a-e)**by the reaction between pyrazolone ketone, aromatic aldehydes and guanidine hydrochloride in presence of catalytic amount of KOH and polyethy- lene glycol (PEG-400) as green reaction solvent. In further reaction, the bifunctional compound was used for the preparation of derivatives of dihydro-1H-pyrazolo[3,4-d]pyrimidine.The reaction with substituted phenacyl bromide afforded the product6-(3/4-substitutedphenyl)-4-(4-substitutedphenyl)-3-methyl-1-phenyl-4,9-dihydro-1H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidine (**5a-j**) and treatments with aromatic aldehydes in PEG-400 obtained product 5-chloro-2-(((4-(4-chlorophenyl)-3-methyl-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)imino)methyl)phenol (**6a-j**). The reaction time, yield and melting point of these derivatives (**5a-j**) and (**6a-j**) have been presented in **Table-1** and **Table-2** respectively. The reactions ensued rapidly and completed within 2-3 hrs.

The newly synthesized compounds were established on the basis of spectroscopic methods. The compounds **5a-**were confirmed by IR spectra showed the absence of unsaturated >C=O stretch at (1680) cm^{-1}, presence of –N-H stretch at (3415) $cm^{-1}$and C=N stretch at (1614)cm^{-1} indicating the formation of product on the basis of IR and also proton NMR spectra, NH peak appear at singlet δ 11.70ppm, singlet of –C-H proton of imidazo appear at δ 8.31 ppm,singlet of –C-H proton of pyrimidine at δ 4.83 ppm and singlet of 3H at δ 2.10 ppm, while other aromatic protons were observed at expected regions. On the other hand IR spectra of the compounds **6a** showed the

characteristics band of –OH in the range of (3473), and C=N stretch at (1610) cm^{-1}. In proton NMR spectra, singlet at δ 13.88 ppm due to presence of -NH, a singlet at δ12.52 ppm due to presence of –OH, singlet of –C-H proton of pyrimidine at δ 4.96 ppm,singlet of 3H at δ 2.10 ppmandother aromatic protons were observed as desired regions. The mass spectra of the all dihydro-1H-pyrazolo[3,4-d]pyrimidine derivatives were showed molecular ion peak corresponding to their molecular formula.



Scheme-1: i) PEG-400, KOH, stirring 60-70℃, 3-4 Hrs



Scheme-2: ii) PEG-400, $PhCOCH_2Br$, stirring, 60-70˚C, 2-3 Hrs
iii) PEG-400, Ar-CHO, stirring, 60-70˚C, 2-3, Hrs

Table 1:Physical data of compounds (5a-j)

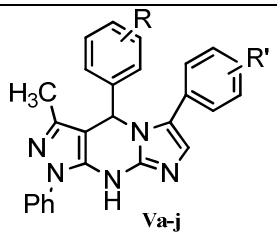
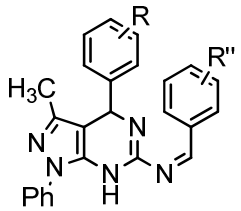
Sr. No.	Entry	Ar/Het	Yields in %	MP in ˚C
		 **Va-j**		
1	**5a**	R= 4-Cl, R'= 4-Cl	87	170-180
2	**5b**	R= 4-F, R'= 4-Cl	90	160-150
3	**5c**	R= 3-NO_2, R'= 4-Cl	89	165-175
4	**5d**	R= 4-NO_2, R'= 4-Cl	85	175-185
5	**5e**	R= 4-Br, R'= 4-Cl	88	160-150
6	**5f**	R= 4-Cl, R'= 4-NO_2	91	170-180
7	**5g**	R= 4-F, R'= 4-NO_2	90	170-180
8	**5h**	R= 3- NO_2, R'= 4-NO_2	89	165-175
9	**5i**	R= 4- NO_2, R'= 4-NO_2	82	155-165
10	**5j**	R= 4- Br, R'= 4-NO_2	86	160-150

Table 2: Physical data of compounds (6a-j)

Sr. No.	Entry	Ar/Het	Yields in %	MP in ˚C
		 **VIa-j**		
1	**6a**	R= 4-Cl, R"= 2-OH	88	180-190
2	**6b**	R= 4-F, R"= 2-OH	91	165-175
3	**6c**	R= 3-NO_2, R"= 2-OH	89	155-165
4	**6d**	R= 4-NO_2, R"= 2-OH	87	175-185
5	**6e**	R= 4-Br, R"= 2-OH	90	175-185
6	**6f**	R= 4-Cl, R"= 2-OH,4-Cl	85	160-170
7	**6g**	R= 4-F, R"= 2-OH,4-Cl	84	170-180
8	**6h**	R= 3- NO_2, R"= 2-OH,4-Cl	89	165-175
9	**6i**	R= 4- NO_2, R"= 2-OH,4-Cl	90	160-170
10	**6j**	R= 4- Br, R"= 2-OH,4-Cl	87	180-190

Biology

Antibacterial activityof compounds (5a-j) and (6a-j):

The recently synthesized dihydro-1H-pyrazolo[3,4-d]pyrimidinederivatives **(5a-j)**and **(6a-j)** exhibited a varying pattern of antimicrobial activity, outcomes shown in **Table 3**. A cursory look at the results of *in vitro* antibacterial activity reveals that most of the synthesized compounds **(5a-j)** and **(6a-j)** exhibited equipotent activity in compared with standard drug. The compounds **5a, 5c**,**5d,5e, 5i**and **5j**shown good zone of inhibition against *E.coli*, *B.subtilis*, and *S.aureus*. The compounds **5b**, **5f**, and **5h**shown moderate zone of against *E.coli*andcompound Vg is inactive against*Escherichia coli*and *S.aureus*.on the other hand the compounds **5a-j** shown good zone of inhibition against *E.coli*, *B.subtilis*, and *S.aureus.*Here ampicillin is employed as reference drug for antibacterial activity.

Table 3: Antibacterial Activity of synthesized compounds (5a-j) and (6a-j)

Product	*Escherichia coli (MTCC443)*	*Bacillus subtilis (MTCC441)*	*Staphylococcus aureus (MTCC96)*
5a	22(25)	19(25)	20(25)
5b	12(25)	20(25)	22(25)
5c	17(25)	21(25)	17(25)
5d	19(25)	22(25)	20(25)
5e	25(50)	23(25)	19(50)
5f	15(50)	19(50)	23(50)
5g	-	24(50)	-
5h	12(25)	21(25)	22(25)
5i	22(25)	25(50)	21(25)
5j	20(25)	23(50)	23(50)
6a	19(25)	18(25)	19(25)
6b	23(50)	22(25)	20(25)
6c	19(25)	25(50)	18(25)
6d	17(50)	17(25)	18(25)
6e	17(50)	18(25)	19(50)
6f	24(50)	23(25)	20(25)
6g	23(50)	21(25)	19(25)
6h	19(25)	20(25)	25(50)
6i	18(25)	19(50)	18(25)
6j	23(50)	21(50)	20(25)
Ampicillin	27(25)	18(25)	24(25)

Zones of inhibition measured in mm; MIC values (µg/ml) are given in parentheses

CONCLUSION

In summary, we synthesized some new derivatives of dihydro-1H-pyrazolo[3,4-d]pyrimidine. The dihydro-1H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidine derivatives (**5a-j**) and dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)imino)methyl)phenol derivatives (**6a-j**) showed significant antibacterial activity. The compounds **5a, 5c, 5d, 5e, 5i** and **5j**andamong **6a-j**thecompounds 6a, 6d, 6e and 6i were exhibited moderateantibacterial activity against *E.coli*, *B.subtilis*, and *S.aureus*and all others were exhibited good antibacterial activity against *E.coli*, *B.subtilis*, and *S.aureus*.Hence, it is assumed that there is sufficient scope for further study in the developing these as a superior lead molecules.

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