J. Chem. Sci. © Indian Academy of Sciences.
DOI 10.1007/s12039-017-1228-z

REGULAR ARTICLE

Synthesis and comparing the antibacterial activities of pyrimidine derivatives

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MS received 29 July 2016; revised 23 September 2016; accepted 29 December 2016

Abstract. A series of 10 derivatives of 5-(5-amino-1,3,4-thiadiazole-2-yl)-3,4-dihydro-6-methyl-4-phenyl-pyrimidin-2(1*H*)-one and 10 derivatives of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenyl pyrimidin-2(1*H*)-one have been synthesized. Among the synthesized derivatives, triazole substituted compounds have shown higher antibacterial inhibition when compared to the thiadiazole derivatives. All the structures of the newly synthesized compounds have been characterized by IR, ^{1}H and ^{13}C NMR, GC-MS and CHN analysis. Most of the compounds have shown promising antibacterial activity when compared with the standard drug ciprofloxacin.

Keywords. 5-amino thiadiazole; 5-amino triazole; hydrazine carbothioamide; *pseudomonas aeruginosa*; *staphylococcus aureus*; *escherichia coli*.

1. Introduction

The pyrimidine and its derivatives have a wide variety of applications in different fields, prominently for biological treatment process,[1–8] such as antitumor, anticancer, anti-inflammatory, anti-hypertensive, antibacterial and antifungal agents, *etc*. The five-membered heterocyclic ring substituted in pyrimidine derivatives have moderate inhibition against the bacterial species.[9] In order to improve the antibacterial activity, we have synthesized twenty pyrimidine derivatives.

The pyrimidine and its derivatives have been synthesized by using various methods. In continuation of this work, novel pyrimidine derivatives were synthesized by using the reported procedure for the first step.[10,11] These pyrimidine derivatives have a large number of reactive sites to produce the substituted derivatives.[12–18]

Herein, the reaction was carried out only in the 5th position of the pyrimidine ring, because the ethanolic group which is present in the position 5 is easily removed by boiling in presence of catalyst and hydrazine carbothioamide.[19,20] The synthesized 10 derivatives of 5-(5-amino-1, 3, 4-thiadiazole-2-yl)-3,4-dihydro-6-methyl-4-phenyl-pyrimidin-2(1*H*)-one and 10 derivatives of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenylpyrimidin-2(1*H*)-one are subjected to *in vitro* study of antibacterial activities by using three different species namely, *Pseudomonas aeruginosa (Gram –ve), Staphylococcus aureus (Gram +ve)* and *Escherichia coli (Gram –ve).* The inhibition values are compared with standard drug, ciprofloxacin. All the synthesized compounds were characterized by using elemental analysis, mass spectra, ^{1}H and ^{13}C NMR spectra.

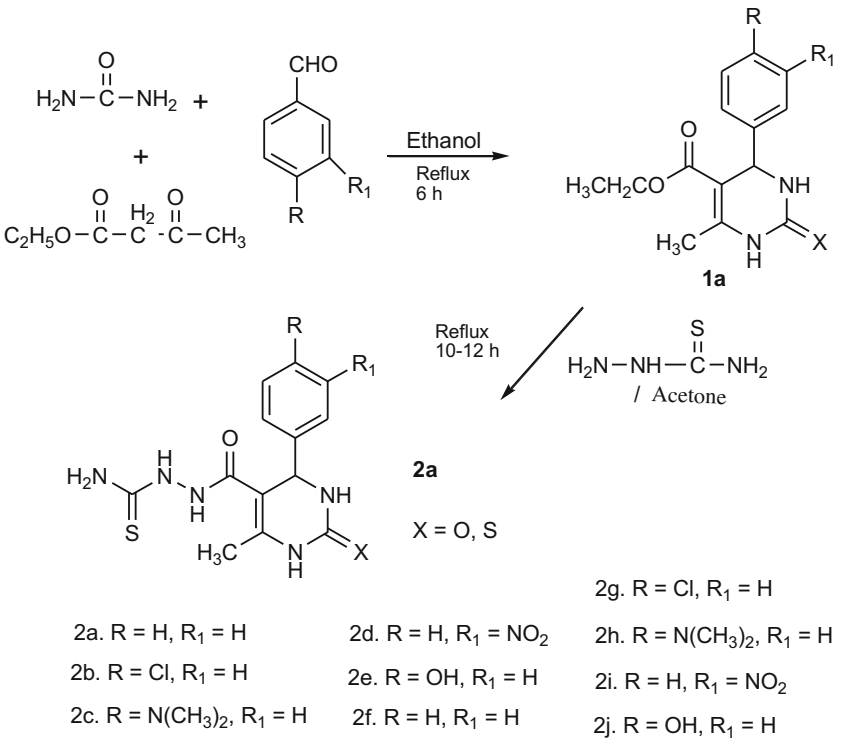
2. Experimental

Melting points were determined using open capillary method and are uncorrected. The compounds are checked for homogeneity by TLC on silica gel-G using pet ether and ethyl acetate as eluent in 3:5 ratio. The IR spectra were recorded on FT-IR THERMO NICOLET AVATAR 370 spectrometer using KBr disc. The ^{1}H and ^{13}C NMR were recorded on Bruker Avance-III 400 MHz - NMR spectrometer using DMSO-d_6. Elemental analyses were recorded on elemental vario EL III instrument. The mass spectra were recorded on Joel GC-mate spectrometer. All the compounds gave satisfactory micro analytical results.

2.1 *General Procedure*

The synthesize 5-(hydrazine carbothioamide)-3,4-dihydro-6-methyl-4-phenyl pyrimidin-2(1H)-one (Scheme 1)

*For correspondence



Scheme 1. Synthesis of 5-(hydrazine carbothioamide)-3,4-dihydro-6-methyl-4-phenyl pyrimidin-2 (1***H***)-one **2(a–j)**.

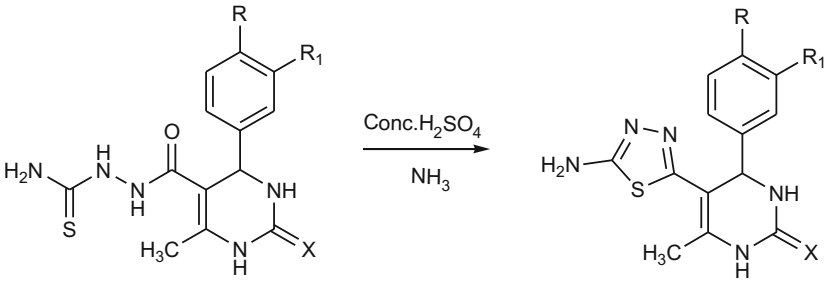
2(a–j), an equimolar mixture of compound **1a** (2.61 g, 0.01 mol) and thiosemicarbazide (0.91 g, 0.01 mol) in acetone was refluxed for 10–12 h and allowed to cool. The yellow crude solid was purified by recrystallization from alcohol. M.p.: 139–141°C. [Yield: 2.4 g, 82%] Analysis: Calculated (%) for $C_{13}H_{15}O_2N_5S$: C, 51.17; H, 4.94; N, 22.50; S, 10.47. Found (%): C, 51.10; H, 4.85; N, 22.24; S, 10.94. GCMS: m/z 305 [M^+]. FT-IR (KBr, cm^{-1}): 3365, 3241, 3116 (NH), 3079 (Ar–H), 2978 (CH), 1724 (C=O), 1385 (C–N), 1219 (C=S), 1089 (N–N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.251 (s, 3H), 5.152 (d, J = 3.2 Hz, 1H), 6.501 (s, 2H), 7.213–7.336 (m, 5H), 7.702 (d, J = 2.8 Hz, 1H), 8.175 (d, J = 6.4 Hz, 2H,), 9.149 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 17.72, 59.17, 99.33, 126.21, 127.23, 128.34, 148.25, 151.71, 152.16, 165.33, 178.40.

2.2 *General procedure for synthesis of 5-(5-amino-1, 3, 4-thiadiazole-2-yl)-3, 4-dihydro-6-methyl-4-phenyl-pyrimidin-2(1H)-one (Scheme 2),* ***3(a–j)***

Hydrazine carbothioamide **2a** (3.05 g, 0.01 mol) was dissolved in 5 mL conc. H_2SO_4. This solution was stirred at RT and left overnight. It was then poured in crushed ice. The resulting suspension was kept in ammoniacal water for 2 h, filtered and purified by recrystallization from alcohol as white crystals. M.p.: 174–176°C. [Yield: 2.7 g; 81%]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.258 (s, 3H), 4.004 (s, 2H), 5.159 (d, J = 3.2 Hz, 1H), 7.227–7.347 (m, 5H), 7.701 (d, J = 2 Hz, 1H), 9.151 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 17.03, 59.15, 99.30,126.20, 127.20, 128.34, 144.82, 148.27, 152.10, 165.32. FT-IR (KBr, cm^{-1}): 3354, 3227, 3110 (NH), 3027 (Ar–H), 2976 (CH), 1689 (C=O), 1460 (C=N), 1225 (C–S), 1378 (C–N), 1098 (N–N). GCMS: m/z 287 [M^+]. Analysis: Calculated (%) for $C_{13}H_{13}ON_5S$: C, 54.38; H, 4.56; N, 24.39; S, 11.13. Found (%): C, 54.35; H, 4.56; N, 24.64; S, 11.68.

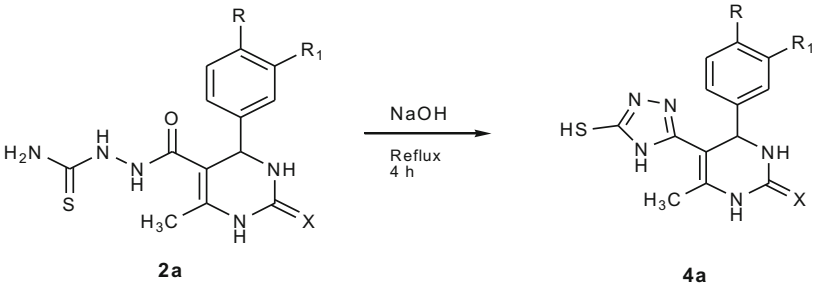
2.3 *General procedure for Synthesis of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenyl pyrimidin-2(1H)-one (Scheme 3)* ***4(a–j)***

The carbothioamide **2a** (3.05 g, 0.01 mol) was added into (8 g in 100 mL) 8% NaOH; it was refluxed for 4 h. The reaction mixture was cooled to room temperature and acidified with dilute acetic acid, then filtered and washed well with water and purified by recrystallization from alcohol as shiny crystals. M.p.:119–121°C, [Yield: 2.42 g; 80%]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.304 (s, 3H), 3.217 (s, 1H), 5.507 (d, J = 3.6 Hz, 1H), 6.975 (s, 1H), 7.268–7.338 (m, 5H), 7.766 (d, J = 2.4 Hz, 1H), 9.217 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 17.74, 59.14, 99.24, 126.22, 127.21, 128.33, 144.84, 148.29, 152.15, 155.11, 165.32. FT-IR (KBr, cm^{-1}): 3423 (NH), 3027 (Ar–H), 2968 (CH), 2235 (SH),



3a. R = H, R_1 = H
3b. R = Cl, R_1 = H
3c. R = $N(CH_3)_2$, R_1 = H
3d. R = H, R_1 = NO_3
3e. R = OH, R_1 = H
3f. R = H, R_1 = H
3g. R = Cl, R_1 = H
3h. R = $N(CH_3)_2$, R_1 = H
3i. R = H, R_1 = NO_3
3j. R = OH, R_1 = H

Scheme 2. Synthesis of 5-(5-amino-1, 3, 4-thiadiazole-2-yl)-3, 4-dihydro-6-methyl-4-phenyl pyrimidin-2(1***H***)-one 3(**a–j**).



4a. R = H, R_1 = H
4b. R = Cl, R_1 = H
4c. R = $N(CH_3)_2$, R_1 = H
4d. R = H, R_1 = NO_3
4e. R = OH, R_1 = H
4f. R = H, R_1 = H
4g. R = Cl, R_1 = H
4h. R = $N(CH_3)_2$, R_1 = H
4i. R = H, R_1 = NO_3
4j. R = OH, R_1 = H

Scheme 3. Synthesis of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenyl pyrimidin-2(1***H***)-one **4**(**a**–**j**).

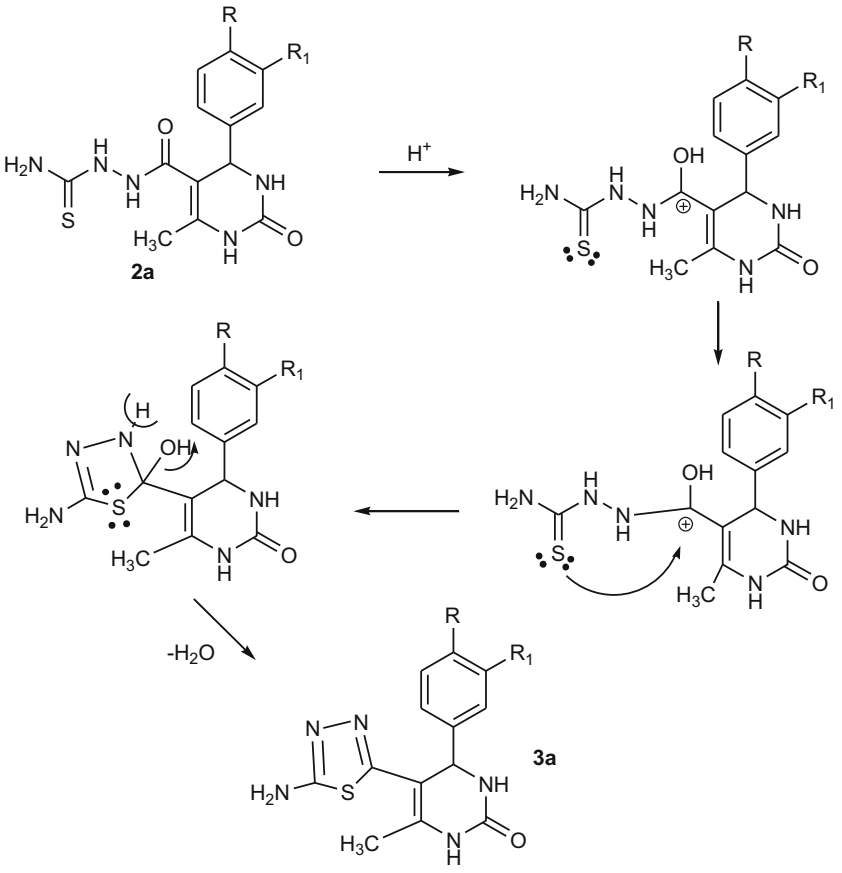
1654 (C=O), 1590 (C=N), 1373 (C–N), 1057 (N–N). GCMS: m/z 287 [M^+]. Analysis: Calculated (%) for $C_{13}H_{13}ON_5S$: C, 54.38; H, 4.56; N, 24.39; S, 11.13. Found (%): C, 54.41; H, 4.22; N, 24.35; S, 11.53.

3. Results and Discussion

Compounds **3(a–j)** and **4(a–j)** were synthesized as per the Schemes 1, 2 and 3. The final compound **3a** was prepared by the reaction of hydrazine carbothioamide **2a**, conc.H_2SO_4 and NH_3, whereas **4a** was prepared by refluxing hydrazine carbothioamide **2a** with NaOH. Hydrazine carbothioamide **2a** was synthesized by reaction of pyrimidine ethyl ester **1** with thiosemicarbazide in acetone, followed by condensation reaction.

The pyrimidine ethyl ester **1a** was prepared by the reaction of benzaldehyde, ethylacetoacetate and urea or thiourea in the presence of mineral acid, followed by Biginelli reaction. The structures of the synthesized compounds were confirmed by IR, ^{1}H and ^{13}C NMR, GC-MS and CHN analysis. Formation of **2a** was confirmed by the presence of N–H stretching peaks at 3365, 3241 cm^{-1} and 3116 cm^{-1} and C=O stretching peaks at 1724 cm^{-1} in IR and singlet at δ 6.50 for NH_2 group in ^{1}H NMR spectrum.

Treatment of compound **2a** with conc. H_2SO_4 and NH_3, furnished 5-(5-amino-1,3,4-thiadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenyl pyrimidin-2(1***H***)-one **(3a)**. The structure of **3a** was elucidated on the basis of C-S linkage in the thiadiazole ring, which causes a sharp absorption band at 1225 cm^{-1} in its IR spectrum. ^{1}H NMR spectrum shows a singlet at δ 4.00 due to NH_2 functional group of the compound **3a**. The mechanism for compounds **3(a–j)** is shown in Scheme 4.



Scheme 4. Mechanism of 5-(5-amino-1, 3, 4-thiadiazole-2-yl)-3, 4-dihydro-6-methyl-4-phenyl pyrimidin-2(1 ***H***)-one **3(a–j)**.

The IR and ^{1}H NMR spectral data reveal that the carbonyl absorption band at 1689 cm^{-1} of NH–CO–NH group, N–N stretching band at 1098 cm^{-1}, aliphatic C–H and aromatic C–H stretching at 2976 cm^{-1} and 3027 cm^{-1}, in the pyrimidine compound **3a**. Mass spectrum also supports the proposed structure by the presence of molecular ion peak at m/z 287 M$^+$.

The structure of (**4a)** was elucidated on the basis of C–N linkage in the triazole ring, which causes an absorption band at 1373 cm^{-1} in its IR spectrum. ^{1}H NMR spectrum shows a singlet at δ 3.21 due to SH functional group of compound **4a**. The IR and ^{1}H NMR spectral data reveal that the carbonyl absorption band at 1654 cm^{-1} of NH–CO–NH group, N–N stretching band at 1053 cm^{-1}, aliphatic C–H and aromatic C–H stretching at 2968 cm^{-1} and 3027 cm^{-1}, in the group of pyrimidine compound **(4a)**. Molecular ion peak at m/z 287 M$^+$ in the mass spectrum also supports the proposed structure. The mechanism of compounds **4(a–j)** is shown in Scheme 5.

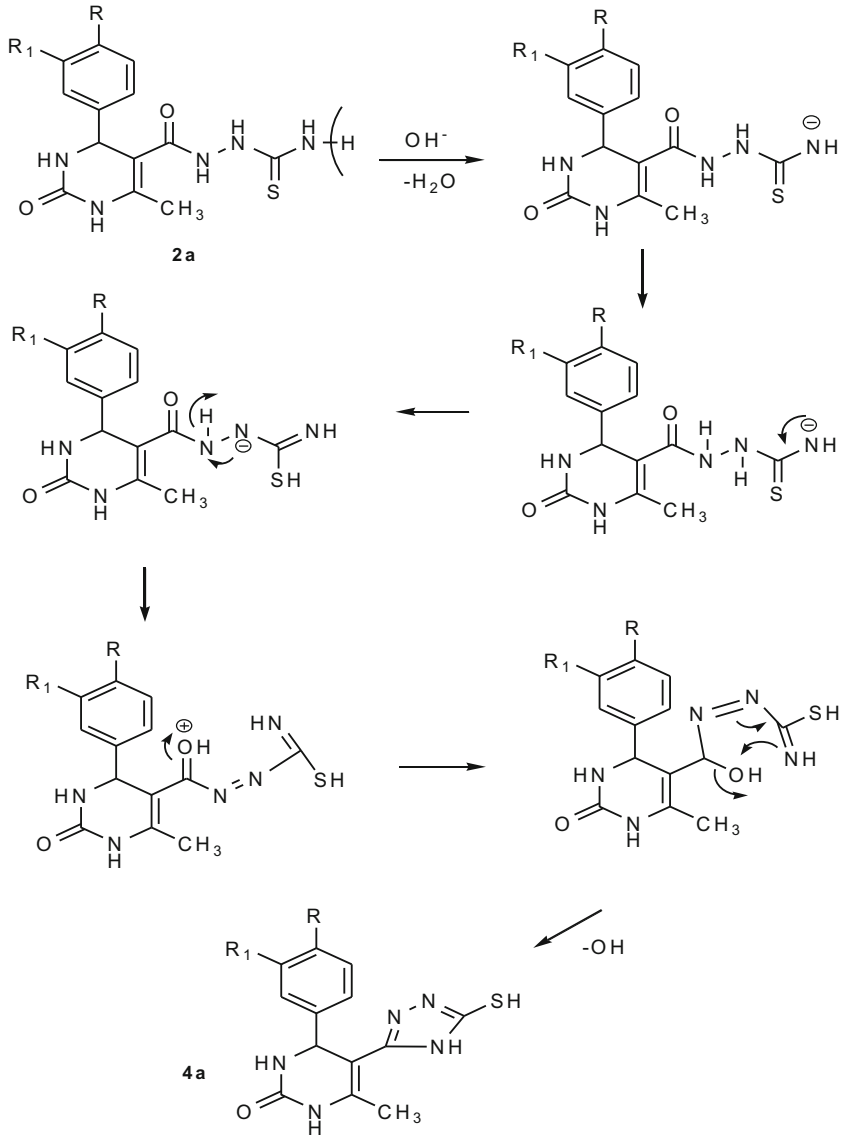
All these compounds were screened for antibacterial activity by *pseudomonas aeruginosa (Gram –ve), staphylococcus aureus (Gram +ve)* and *escherichia coli (Gram –ve).* Ciprofloxacin was used as standard drug. Most of the synthesized compounds showed moderate to good inhibition at a concentration of 10 μg/mL.

3.1 *Antibacterial studies*

The newly synthesized pyrimidine derivatives were screened for their antibacterial activity *in vitro* against *pseudomonas aeruginosa*, *staphylococcus aureus* and *escherichia coli*, using agar well disk diffusion method. The test compounds were dissolved in DMSO to get a solution of 10 μg/mL concentration. The inhibition zones were measured in millimeters at the end of an incubation period of 18 h at 37°C. Ciprofloxacin was used as a standard drug and the results are shown in Tables 1 and 2. The investigation of antibacterial screening data reveals that, all the tested compounds show moderate to good inhibition at 10 μg/mL concentration.

3.2 *Comparison of anti bacterial activity*

Comparison of antibacterial activity for all the synthesised compounds are shown in Figures S1–S3 (in Supplementray Information). Based on the comparative



Scheme 5. Mechanism of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenyl pyrimidin-2(1***H***)-one **4(a–j)**.

Table 1. Antibacterial activity of compounds **3(a–j)**.

Compound	*Pseudomonas aeruginosa* (mm)	*Staphylococcus aureus* (mm)	*Escherichia coli* (mm)
Control (DMSO)	0	0	0
3a	6	7	7
3b	5	7	8
3c	5	8	9
3d	5	5	8
3e	14	16	18
3f	5	5	6
3g	7	10	7
3h	5	5	6
3i	5	8	10
3j	10	11	14

Table 2. Antibacterial activity of compounds **4(a–j)**.

Compound	*Pseudomonas aeruginosa* (mm)	*Staphylococcus aureus* (mm)	*Escherichia coli* (mm)
Control (DMSO)	0	0	0
4a	7	8	8
4b	9	12	11
4c	5	7	7
4d	5	7	5
4e	20	14	10
4f	7	12	12
4g	23	8	14
4h	8	6	15
4i	10	10	12
4j	8	10	9

studies, 5-(5-amino-1,3,4-thiadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1***H***)-one, **3(a–j)** compounds have less inhibition than the 3,4-dihydro-5-(5-mercapto-4H-l,2,4-triazol-3-yl)-6-methyl-4-phenylpyrimidin-2(1***H***)-one **4(a–j)** compounds at 10 μg/mL concentration. A few compounds showed very good inhibition, which are closer to the standard drug.

4. Conclusions

The investigation of antibacterial screening data for synthesized compounds reveal that, the **4(a–j)** triazole substituted compounds have higher inhibition than the **3(a–j)** thiadiazole substituted compounds, because the triazole ring which is substituted in the pyrimidine, enhances the inhibition of the compound, against the three species of *pseudomonas aeruginosa*, *staphylococcus aureus and escherichia coli*.

Supplementary Information (SI)

All additional information pertaining to characterization of the compounds using FT-IR spectra (Figures S1 to S10 and S31 to S40), ^{1}H NMR spectra (Figures S11 to S20 and S41 to S50), ^{13}C NMR spectra (Figures S21 to S30 and S51 to S60), antibacterial screening data (Tables S1, S2) and antibacterial activities comparative diagram (Figure S1, S2 and S3) are given in the supporting information available at www.ias.ac.in/chemsci.

Acknowledgements

The authors are thankful to the Principal and Research Department of Chemistry, Islamiah College, Vaniyambadi, Vellore district, Tamil Nadu, India for constant encouragement and providing necessary facilities.

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