An efficient synthesis, characterization and anti-bacterial activity of pyrimidine bearing 1,3,4-thiadiazole derivatives

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A series of pyrimidine bearing 1,3,4-thiadiazole derivatives have been synthesized and evaluated for antibacterial activity. All the structures of the newly synthesized compounds have been supported by IR, 1H and 13C NMR, GC-MS and CHN analysis. Most of the compounds have shown promising antibacterial activity when compared with the standard drug Ciprofloxacin.

Keywords: Pyrimidine, thiadiazole, hydrazine carbothioamide, antibacterial activity

A literature survey has been revealed the importance of pyrimidine derivatives and antimicrobial agent1, which are found to be associated with variety of biological activities such as insecticidal, antimicrobial, antiviral and so on. Pyrimidine derivatives2-8 are powerful C-C bond forming agents and have wide applications for the preparation of diverse aminalkyl derivatives. It involves the condensation of a compound capable of supplying one or more active hydrogen atom with aldehyde and primary or secondary amine. Mannich bases are physiologically reactive because of the basic function rendering the molecule soluble in aqueous solvent whence it is transformed into ammonium salt. Several medicinally useful Mannich bases have been reviewed by Tromontini and Angiolini9. Besides this, considerable work has been reported on synthesis and pharmacological activities of various Mannich bases for analgesic, antispasmodic, anesthetic and antimalarial as well as intermediates in drug synthesis. Antiviral properties of certain thiourea and urea derivatives have been reported in which the antiviral effect is attributed to the presence of an intact NH-(C=S)-NH and NH-(C=O)-NH grouping10. In this context the synthesis and pharmacological study of Mannich bases of 5-(5-amino-1,3,4-thiadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 3 against Pseudomonas aeruginosa (Gram –ve), Staphylococcus aureus (Gram +ve) and Escherichia coli (Gram –ve). Ciprofloxacin was used as standard drug. For this purpose, heterocyclic precursor DHPMs 1a-j were synthesized by Biginelli reaction of aromatic aldehydes, ethylacetocacetate and thiourea according to the literature procedure. Subsequently, these DHPMs were used to synthesis compounds 2a-j. All the synthesised compounds were characterized by using elemental analysis, mass spectra, 1H and 13C NMR spectral studies.

Results and Discussion

Compounds 3a-j were synthesized as per the Scheme I, where final compound 3 prepared by reacting hydrazine carbothioamide, compound 2 with conc. H2SO4 and NH3. Hydrazine carbothioamide, compound 2 were synthesized by reacting pyrimidine ethyl ester 1 with thiosemicarbazide in acetone followed by condensation reaction23-26. The pyrimidine ethyl ester compound 1 was prepared by reacting 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 (Table I). Formation of compound 2 was confirmed by the presence of N-H stretching peaks at 3365, 3241 and 3116 cm$^{-1}$ and C=O stretching peaks at 1724 cm$^{-1}$ in IR and singlet at $\delta$ 6.50 for NH$_2$ group in $^1$H NMR spectra. Treatment of compound 2 with conc. H$_2$SO$_4$ and NH$_3$ furnished 5-(5-amino-1,3,4-thiadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 3.

The structure of 3 was elucidated on the basis of C-S linkage in the thiadiazole ring, which gave a sharp absorption band at 1225 cm$^{-1}$ in its IR spectrum. $^1$H NMR spectrum showed a singlet at $\delta$ 4.00 due to NH$_2$ functionality confirmation of the structure 3. Physical and analytical data are given in Table II. IR and $^1$H NMR spectral data revealed carbonyl absorption band at 1098 cm$^{-1}$, aliphatic C-H and aromatic C-H stretching at 2976 cm$^{-1}$ and 3027 cm$^{-1}$ for pyrimidine moiety 3. Mass spectrum also supported the proposed structure by displaying molecular ion peak at $m/z$ 287 M$^+$. 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 10 µg/mL concentration. However, the activity was less compared to the standard drugs.

**Experimental Section**

Melting points were determined using open capillary method and are uncorrected. The compounds were

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**Table I — Physical and analytical characterization data of compounds 2a-j**

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<th>Compd</th>
<th>Mol. formula</th>
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<th>Mol. Wt.</th>
<th>Yield(%)</th>
<th>m.p. (°C)</th>
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**Scheme I**

5-(5-Amino-1,3,4-thiadiazole-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 3

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**Table II**

<table>
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<th>Compd</th>
<th>Mol. formula</th>
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<th>$R_1$</th>
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<th>Mol. Wt.</th>
<th>Yield(%)</th>
<th>m.p. (°C)</th>
<th>Calcd (%)</th>
<th>Found</th>
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checked for homogeneity by TLC on silica gel-G. The IR spectra were recorded on FT-IR Thermo Nicolet Avatar 370 spectrophotometer using KBr disc method. The $^1$H and $^{13}$C NMR were recorded on Bruker Avance III 400 MHz – FTNMR 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 compounds gave satisfactory micro analytical results. Pyrimidine I was prepared by reported method.

**General procedure for the synthesis of 5-(hydrazine carbothioamide)-3, 4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one, 2a-j**

An equimolar mixture of compound 1 (0.01 mol) and thiosemicarbazide (0.01 mol) in acetone was refluxed for 10-12 hr and allowed to cool and the yellow crude solid was purified by recrystallization from alcohol. m.p.140°C. Yield 85%. $^1$H NMR (DMSO-$d_6$): δ 2.251 (s, 3H, CH$_3$), 5.146 ($J = 3.6$ Hz, d, 1H, CH)$_2$, 6.530 (s, 2H, NH$_2$), 7.249 ($J = 8.4$ Hz, dd, 2H, Ar-H), 7.388 ($J = 8.8$ Hz, dd, 2H, Ar-H), 7.733 ($J = 1.2$ Hz, d, 1H, NH), 8.096 ($J = 2$ Hz, d, 2H, NH$_x$2), 9.204 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 17.75, 59.22, 98.87, 128.15, 128.34, 131.74, 143.74, 148.64, 151.92, 161.18, 178.43; FT-IR(KBr): 3365, 3240, 3118 (NH), 3053 (Ar-H), 2978(CH), 1724(C=O), 1340(C-N), 1220 (C=S), 1090 cm$^{-1}$ (N-N); GCMS: $m/z$ 339 M$^+$.

**Synthesis of 5-(hydrazine carbothioamide)-4-(4-(dimethylamino)phenyl)-3, 4-dihydro-6-methylpyrimidin-2(1H)-one, 2c**: $^1$H NMR (DMSO-$d_6$): δ 2.226 (s, 3H, CH$_3$), 2.846 (s, 6H, N(CH$_3$)$_2$), 5.5036 (J = 3.2 Hz, d, 1H, CH), 6.130 (s, 2H, NH$_2$), 6.650 ($J = 8.8$ Hz, d, 2H, Ar-H).7.036 ($J = 8.8$ Hz, d, 2H, Ar-H), 7.534 ($J = 2$ Hz, d, 2H, NH$_x$2), 9.036 ($J = 1.2$ Hz, d, 1H, NH), 9.866 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 17.67, 53.29, 59.06, 99.93, 112.20, 126.85, 132.61, 149.73, 151.27, 165.46, 178.43; FT-IR(KBr): 3365, 3241, 3116 (NH), 3053 (Ar-H), 2978(CH), 1724(C=O), 1340(C-N), 1220 (C=S), 1089 cm$^{-1}$ (N-N); GCMS: $m/z$ 349 M$^+$. 

**Synthesis of 5-(hydrazine carbothioamide)-4-(3-nitrophenyl)-3, 4-dihydro-6-methylpyrimidin-2(1H)-one, 2d**: $^1$H NMR (DMSO-$d_6$): δ 2.276 (s, 3H, CH$_3$), 5.309 ($J = 4$ Hz, d, 1H, CH), 6.970 (s, 2H, NH$_2$), 7.656-7.760 (m, 4H, Ar-H), 7.826 ($J = 3.7$ Hz, d, 2H, NH$_x$2), 9.345 ($J = 2.4$ Hz, d, 1H, NH), 9.872 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 17.81, 58.61, 98.35,
129.61, 130.19, 132.95, 142.33, 145.28, 164.96, 178.43, 183.89;
FT-IR (KBr): 3379, 3273, 3175 (NH), 3088 (Ar-H), 2982 (CH), 1727 (C=O), 1315 (C-N), 1233 (C=S), 1117 cm⁻¹ (N-N); GCMS: m/z 366 M⁺.

Synthesis of 5-(hydrazine carbothioamide)-4-(3-nitrophenyl)-3, 4-dihydro-6-methylpyrimidin-2(1H)-thione, 2i: ¹H NMR (DMSO-d₆): δ 2.22 (s, 3H, CH₃), 5.063 (J = 3.6 Hz, d, 1H, CH), 6.120 (s, 2H, NH₂), 6.699-6.720 (m, 2H, Ar-H), 6.999-7.070 (q, 2H, Ar-H), 7.500 (s, 1H, Ar-H), 7.965 (J = 3.5 Hz, d, 2H, NHx2), 9.528 (J = 1.6 Hz, d, 1H, NH), 9.883 (s, 1H, NH); ¹³C NMR (DMSO-d₆): δ 17.50, 59.47, 101.12, 115.17, 127.61, 134.08, 143.42, 151.68, 156.18, 178.38, 183.83; FT-IR (KBr): 3429 (OH), 3245, 3179, 3079 (NH), 3036 (Ar-H), 2988 (CH), 1715 (C=O), 1314 (C-N), 1259 (C=S), 1082 cm⁻¹ (N-N); GCMS: m/z 337 M⁺.

General procedure for synthesis of 5-(5-amino-1, 3, 4-thiadiazole-2-yl)-3, 4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)thione, 3a-j

Hydrazine carbothioamide 2 (0.01mol) was dissolved in 5 mL conc. H₂SO₄. This solution was stirred at RT and left overnight. It was then poured in crushed ice. The resulting suspension was kept in ammonical water for 2 hr, filtered and purified by recrystallization from alcohol as white crystals. m.p 175°C. Yield 92%. ¹H NMR (DMSO-d₆): δ 2.258 (s, 3H, CH₃), 4.004 (s, 2H, NH₂), 5.159 (J = 3.2 Hz, d, 1H, CH), 7.227-7.347 (m, 5H, Ar-H), 7.701 (J = 2 Hz, d, 1H, NH), 9.151 (s, 1H, NH); ¹³C NMR (DMSO-d₆): δ 17.03, 59.15, 99.30, 101.12, 117.83, 128.27, 128.52, 142.33, 145.28, 164.96, 178.43, 183.89; FT-IR (KBr): 3379, 3273, 3175 (NH), 3158 (Ar-H), 2996 (CH), 1731 (C=O), 1335 (C-N), 1281 (C=S), 1041 cm⁻¹ (N-N); GCMS: m/z 355 M⁺.

Synthesis of 5-(hydrazine carbothioamide)-4-(4-(dimethylamino)phenyl)-3, 4-dihydro-6-methylpyrimidin-2(1H)-thione, 2h: ¹H NMR (DMSO-d₆): δ 2.277 (s, 3H, CH₃), 2.855 (s, 6H, N(CH₃)₂), 5.048 (J = 4 Hz, d, 1H, CH), 6.305 (s, 2H, NH₂), 6.663 (J = 8.8 Hz, d, 2H, Ar-H), 7.016 (J = 8.8 Hz, d, 2H, Ar-H), 9.509 (J = 1.6 Hz, d, 2H, NHx2), 9.887 (s, 1H, NH), 10.197 (J = 0.8 Hz, d, 1H, NH); ¹³C NMR (DMSO-d₆): δ 17.48, 53.53, 59.43, 101.27, 112.16, 127.08, 131.19, 149.93, 151.56, 165.25, 178.47, 183.93; FT-IR (KBr): 3377, 3356, 3168 (NH), 3105 (Ar-H), 2981 (CH), 1669 (C=O), 1366 (C-N), 1285 (C=S), 1117 cm⁻¹ (N-N); GCMS: m/z 364 M⁺.

Synthesis of 5-(hydrazine carbothioamide)-4-(3-hydroxyphenyl)-3, 4-dihydro-6-methylpyrimidin-2(1H)-thione, 2j: ¹H NMR (DMSO-d₆): δ 2.227 (s, 3H, CH₃), 5.063 (J = 3.6 Hz, d, 1H, CH), 6.120 (s, 2H, NH₂), 6.699-6.720 (t, 2H, Ar-H), 6.999-7.070 (q, 2H, Ar-H), 7.500 (s, 1H, Ar-H), 7.965 (J = 3.5 Hz, d, 2H, NHx2), 9.528 (J = 1.6 Hz, d, 1H, NH), 9.883 (s, 1H, NH); ¹³C NMR (DMSO-d₆): δ 17.50, 59.47, 101.12, 115.17, 127.61, 134.08, 143.42, 151.68, 156.18, 178.38, 183.83; FT-IR (KBr): 3429 (OH), 3245, 3179, 3079 (NH), 3036 (Ar-H), 2988 (CH), 1715 (C=O), 1314 (C-N), 1259 (C=S), 1082 cm⁻¹ (N-N); GCMS: m/z 337 M⁺.
Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(4-dimethylamino)phenyl)-3, 4-dihydro-6-methylpyrimidin-2(1H)-one, 3c: 1H NMR (DMSO-d6): δ 2.856 (s, 6H, N(CH3)2), 3.996 (s, 2H, NH2), 5.048 (J = 3.2 Hz, d, 1H, CH), 6.660 (J = 8.8 Hz, d, 2H, Ar-H), 7.048 (J = 8.4 Hz, d, 2H, Ar-H), 7.556 (J = 2.4 Hz, d, 1H, NH), 9.053 (s, 1H, NH); 13C NMR (DMSO-d6): δ 17.68, 53.30, 59.04, 99.94, 112.19, 126.85, 132.62, 147.46, 149.74, 152.27, 165.46; FT-IR (KBr): 3357, 3242, 3110 (NH), 3018 (Ar-H), 2977 (CH), 1721 (C=N), 1526 (C=N), 1221 (C-S), 1093 cm⁻¹ (N-N); GCMS: m/z 334 M⁺.

Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(3-nitrophenyl)-3, 4-dihydro-6-methylpyrimidin-2(1H)-one, 3d: 1H NMR (DMSO-d6): δ 2.066 (s, 3H, CH3), 3.805 (s, 2H, NH2), 5.098 (J = 3.2 Hz, d, 1H, CH), 7.036-7.802 (m, 4H, Ar-H), 8.482 (J = 3.2 Hz, d, 1H, NH), 9.126 (s, 1H, NH); 13C NMR (DMSO-d6): δ 17.81, 59.35, 98.35, 122.29, 123.87, 132.94, 143.46, 149.96, 147.73, 145.38, 149.36, 165.03, 178.39; FT-IR (KBr): 3429, 3396, 3245(NH), 3153 (Ar-H), 2980 (CH), 1705 (C=N), 1526 (C=N), 1348 (C-N), 1294 (C-S), 1094 cm⁻¹ (N-N); GCMS: m/z 332 M⁺.

Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(4-hydroxyphenyl)-3, 4-dihydro-6-methylpyrimidin-2(1H)-one, 3e: 1H NMR (DMSO-d6): δ 2.127 (s, 3H, CH3), 3.991 (s, 2H, NH2), 5.051 (J = 3.2 Hz, d, 1H, CH), 6.887-7.115 (m, 4H, Ar-H), 7.563 (J = 1.6 Hz, d, 1H, NH), 9.074 (s, 1H, NH), 10.296 (br, 1H, OH); 13C NMR (DMSO-d6): δ 17.69, 59.08, 99.79, 110.97, 127.76, 129.67, 135.22, 147.65, 150.32, 156.51, 165.40; FT-IR (KBr): 3607 (OH), 3429, 3396, 3245(NH), 3030 (Ar-H), 2980 (CH), 1705 (C=N), 1526 (C=N), 1348 (C-N), 1294 (C-S), 1094 cm⁻¹ (N-N); GCMS: m/z 303 M⁺.

Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-3, 4-dihydro-6-methyl-4-phenyl pyrimidin-2(1H)-thione, 3f: 1H NMR (DMSO-d6): δ 2.301 (s,3H,CH3), 4.030 (s, 2H, NH2), 5.189 (J = 4 Hz, d, 1H, CH), 7.222-7.372 (m, 4H, Ar-H), 9.634 (J = 1.6 Hz, d, 1H, NH), 9.074 (s, 1H, NH); 13C NMR (DMSO-d6): δ 17.12, 59.57, 100.75, 126.35, 127.65, 128.51, 144.43, 144.95, 165.12, 174.23; FT-IR (KBr): 3328, 3174, 3106 (NH), 3033 (Ar-H), 2979 (CH), 1574 (C=N), 1384 (C-N), 1282 (C=S), 1195 (C-S), 1001 cm⁻¹ (N-N); GCMS: m/z 303 M⁺.

Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(4-chlorophenyl)-3, 4-dihydro-6-methyl pyrimidin-2(1H)-thione, 3g: 1H NMR (DMSO-d6): δ 2.301 (s, 3H, CH3), 4.027 (s, 2H, NH2), 5.179 (J = 3.6 Hz, d, 1H, CH), 7.227-7.254 (J = 10.8 Hz, dd, 2H, Ar-H), 7.419-7.440 (J = 8.4 Hz, dd, 2H, Ar-H), 9.653 (J = 2 Hz, d, 1H, NH), 10.369 (s, 1H, NH); 13C NMR (DMSO-d6): δ 17.14, 59.62, 100.30, 128.28, 128.54, 132.24, 142.34, 145.32, 164.97, 174.24; FT-IR (KBr): 3327, 3174, 3104 (NH), 3030 (Ar-H), 2982 (CH), 1573 (C=N), 1380 (C-N), 1281 (C-S), 1196 (C-S), 1092 (N-N), 1014 cm⁻¹ (Cl-C); GCMS: m/z 337 M⁺.

Antibacterial studies
The newly synthesized pyrimidine derivatives were screened for their antibacterial activity in vitro against
the species of *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 hr at 37°C. Ciprofloxacin was used as a reference standard and the results are shown in Table III. Most of the tested compounds showed antibacterial activity comparable with that of the standard drug ciprofloxacin.

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good inhibition at 10 µg/mL concentration. Especially, the compounds 3e and 3j showed very good activity in comparison to the others. However, the activity was less compared to the standard drug.

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### References