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Thiazolo[4,5-*d*]pyrimidines: synthesis and antibacterial evaluation

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Abstract

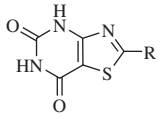
The reaction of 4-amino-5-bromo-2-chloro-6-methylpyrimidine (**1**) with carbon disulfide in the presence of KOH in DMF quantitatively gave 5-chloro-7-methylthiazolo[4,5-*d*] pyrimidine-2 (3*H*)-thione (**2**) which was then alkylated at the sulfur atom with various alkyl halides in the presence of Et_3N in acetonitrile to give alkylthio derivatives **3**. The substitution of the chlorine atom in **3** with morpholine was also investigated. The synthesized compounds were subjected to antibacterial evaluations.

Keywords: antibacterial evaluation; heterocyclization; thiazolo[4,5-*d*]pyrimidine.

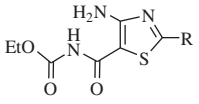
Introduction

In medicinal chemistry, pyrimidine derivatives have been known for their therapeutic applications. The presence of a pyrimidine system in thymine, cytosine, and uracil, which are the essential building blocks of nucleic acids, is one possible reason for the activity (Amir et al., 2007). Similarly, thiazole derivatives possess diverse pharmacological activities. Fused derivatives of pyrimidine and thiazole are also bioactive. For example, thiazolopyrimidine derivatives have been the focus of a great deal of interest owing to their antimicrobial (Vicini et al., 2003; Zitouni et al., 2004), antiviral (Sircar et al., 1986; Nagahara et al., 1990; Kini et al., 1991), and antitumor (El-Subbagh and Alobaid, 1996) activities. They have been used as potent and selective inhibitors of acetyl-CoA carboxylase 2 (Clark et al., 2007) and VEGF receptors I and II (Kiselyov et al., 2006). They have also shown potent and selective human adenosine A_3 receptor (Van Tilburg et al., 2001; Jung et al., 2004; Bhattacharya et al., 2005) and vanilloid receptor I TRPVI antagonism (Xi et al., 2005). Also, some thiazolopyrimidines have been found to possess anti-inflammatory and analgesic activities (Russo et al., 1993; Pawan and Sawhney, 1997; Ashok et al., 2007).

Although thiazole ring construction has been reported numerous times and adequately reviewed in the literature (Metwally et al., 2004), there are few reports on the synthesis of fused thiazolopyrimidines and especially thiazolo [4,5-*d*] pyrimidines. Walek and coworkers (Walek, 1983; Walek et al., 1984) prepared compound (**I**) by heating the thiazole (**II**) at 180°C for 2 h, whereas Wobig (1989) prepared thiazolopyrimidine derivatives (**III**) by cyclization of aminothiazoles (**IV**) with formamide, formic acid, and dimethyl malonate.



(I)



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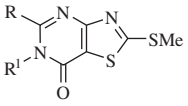

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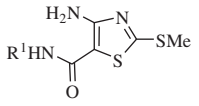


(IV)

Efficient synthesis of various derivatives of thiazolopyrimidine have been reported by the reaction of 4,6-dichloro-5-aminopyrimidine with isothiocyanates (Liu et al., 2005; Lebsack et al., 2009). The reaction of 4-chloro-2,3-dihydrothiazolidine-5-carboxaldehyde with urea in ethanol solution at reflux in the presence of a catalytic amount of Et_3N afforded new polysubstituted thiazolopyrimidine derivatives (El Rady, 2008). Akbari et al. (2008) have synthesized 7-aryl-5-thioxo-4,5,6,7-tetrahydro-3*H*-thiazolo[4,5-*d*]pyrimidin-2-ones by the reaction of 2,4-thiazolidine with thiourea and different aromatic aldehydes.

Taking into account these findings and in continuation of our efforts to develop novel and efficient routes to heterocyclic derivatives of pyrimidine with potential biological activities (Bakavoli et al., 2008, 2009, 2010a, b, 2011a, b), we turned our attention to the synthesis of various new derivatives of thiazolo[4,5-*d*]pyrimidine. It was of interest to investigate antibacterial activity of the new compounds against *Staphylococcus aureus* PTCC 1431, *Bacillus subtilis* PTCC 1365, *Escherichia coli* HB101 BA 7601C, and *Pseudomonas aeruginosa* PTCC 1074 bacteria.

Results and discussion

Chemistry

5-Bromo-2,4-dichloro-6-methylpyrimidine, which was prepared as reported by us previously (Bakavoli et al., 2006), was treated with ammonia in ethanol at room temperature to give 4-amino-5-bromo-2-chloro-6-methyl-pyrimidine **(1)**. The heterocyclization of compound **1** with carbon disulfide in the presence of KOH at room temperature quantitatively afforded 5-chloro-7-methyl-2,3-dihydropyrimido[4,5-*d*][1,3]thiazol-2-thione **(2)**. The ^{1}H NMR spectrum of this compound shows a singlet at δ 2.52 ppm and a broad singlet at δ 3.85 for the methyl and NH groups of the compound **2**, respectively. In the mass spectra of this compound, molecular ion peak is observed at *m/z* 217, which corresponds to the desired molecular formula. To prepare new derivatives of thiazolo [4,5-*d*] pyrimidine, compound **2** was treated with various alkyl halides bearing different functional groups in the presence of Et_3N in boiling acetonitrile. The desired new derivatives of thiazolo[4,5-*d*]pyrimidine **3a–f** were obtained in good to excellent yields (Scheme 1).

The structures of the synthesized compounds **3** were determined by the spectral and microanalytical data. For example, the ^{1}H NMR spectrum of compound **3a** does not exhibit a signal for an NH moiety that is present at δ 3.85 in the spectrum of the precursor **2**. Product **3a** shows two sharp singlets at δ 2.55 and δ 2.88 for two methyl groups. The IR spectrum of **3a** does not show the stretching vibration band at 3280 cm^{-1} for the NH group that is found in the IR spectrum to the NH group of the precursor **2**. Instead, a new C=N stretching vibration band at 1640 cm^{-1} is observed. The molecular ion peaks in the mass spectrum of compound **3a** are observed at *m/z* 231 and 233, which is consistent with the presence of one chlorine atom in the molecule. These results, together with the results of microanalysis fully support the molecular formula of $C_7H_6ClN_3S_2$ for **3a**.

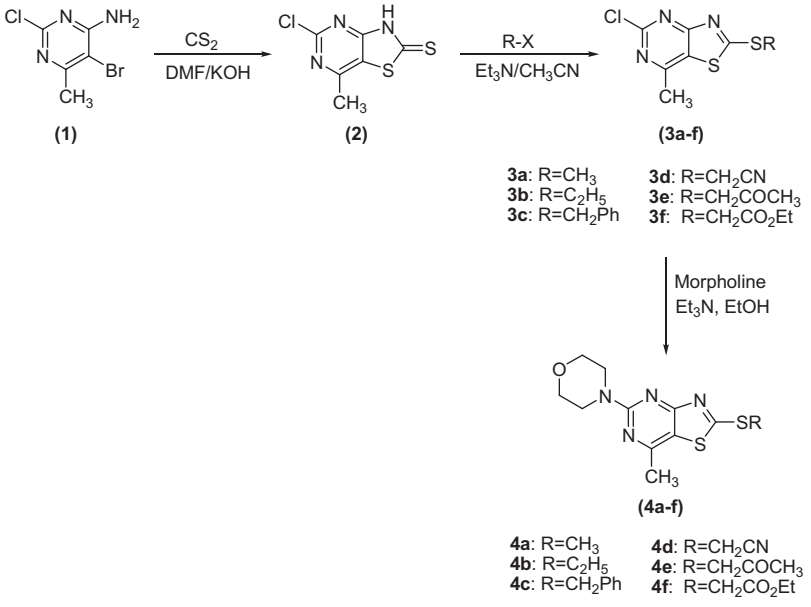
A nucleophilic substitution of the chlorine atom at the 5-position of the pyrimidine ring of the synthesized compounds **3a–f** with morpholine yielded the corresponding morpholine-substituted derivatives **4a–f** in good yields. The ^{1}H NMR spectra of all new compounds **4a–f** exhibit the characteristic signals of the morpholine unit, which along with other data unambiguously confirm the desired structures of compounds **4a–f**.

Antibacterial evaluation

The tested microorganisms were Gram-positive and Gram-negative bacteria. The sensitivity of the selected microorganisms, *S. aureus* PTCC 1431, *B. subtilis* PTCC 1365, *E. coli* HB101 BA 7601C, and *P. aeruginosa* PTCC 1074, to all synthesized compounds **3a–f** and **4a–f** was determined *in vitro*. The compounds were dissolved in DMSO and the tests were carried out using a disk diffusion method (Reeves and White, 1983). Streptomycin was used as a reference bactericidal antibiotic (Table 1). The evaluations were obtained in triplicate and the results with differences greater than 5% were discarded, and the measurements repeated. It can be concluded from the data in Table 1 that all compounds **3a–f** and **4a–f** are highly active against *B. subtilis* and *P. aeruginosa*. A slightly lower activity is observed against *S. aureus*. Compounds **3c**, **3d**, and **4b** are highly active against *E. coli*, which is a Gram-negative bacteria.

Conclusion

In summary, a new series of thiazolo[4,5-*d*]pyrimidine derivatives were synthesized and their antibacterial activities evaluated. Many compounds proved to be more active against *B. subtilis* and *P. aeruginosa* than streptomycin, the reference



Scheme 1 Synthesis of thiazolo[4,5-*d*]pyrimidines.

Table 1 Antibacterial data for compounds **3a–f** and **4a–f**.

Compound	Gram-negative bacteria		Gram-positive bacteria	
	Escherichia coli HB101 BA 7601C	*Pseudomonas aeruginosa* PTCC 1074	*Staphylococcus aureus* PTCC 1431	*Bacillus subtilis* PTCC 1365
3a	15[a](-)[b,c]	14(++)	12(-)	15(++)
3b	17(+)	15(++)	12(-)	15(++)
3c	18(++)	15.5(++)	14(-)	14(++)
3d	18(++)	13(++)	14(-)	14(++)
3e	17(+)	14(++)	14(-)	13(++)
3f	17(+)	15(++)	13(-)	14(++)
4a	15(-)	15.3(++)	12(-)	14(++)
4b	20(++)	15(++)	13(-)	14.5(++)
4c	13(-)	15.5(++)	12(-)	15(++)
4d	14(-)	16(++)	15(+)	14(++)
4e	15(-)	13(++)	13(-)	13.5(++)
4f	17(+)	9(-)	14.5(-)	14.3(++)
Streptomycin (standard)	17	10	15	10

[a] Zones of inhibition in millimeters.

[b] (++) highly sensitive; (+) moderately sensitive; (-) slightly sensitive.

[c] The maximum inhibition zone for each compound has been shown. Discs of each concentration were placed in triplicate in Muller-Hinton agar medium seeded with fresh bacteria separately and the average was reported.

antibiotic. Hence, it is concluded that there is a promising scope for further development in this field.

Experimental

Melting points were recorded on an electrothermal type 9100 melting point apparatus and are not corrected. The IR spectra were obtained in KBr pellets on a Thermo Nicolet Avatar 370-FTIR spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer in $CDCl_3$ solution with TMS as an internal reference. The electron impact mass spectra were obtained on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA 1112 instrument.

5-Chloro-7-methylthiazolo[4,5-*d*]pyrimidine-2(3*H*)-thione (2)

To a magnetically stirred solution of 4-amino-5-bromo-2-chloro-6-methyl-pyrimidine **(1)** (1 mmol, 0.22 g) and carbon disulfide (0.1 ml) in dry DMF (5 ml), powdered KOH (1 mmol, 0.056 g) was added, and the mixture stirred for 2 h at room temperature. Then, the mixture was heated at 70–80°C for 0.5 h. After cooling, water (10 ml) was added and the solution was neutralized with acetic acid. The resulting precipitate was filtered off and crystallized from ethanol: yield 80%; mp 197°C (decomp.); ^{1}H NMR: δ 2.52 (s, 3H, CH_3-pyrimidine), 3.85 (s, 1H, NH, D_2O exchangeable); IR: ν 3010, 1233 (C=S) cm^{-1}; MS: *m/z* 217 (M^+ for ^{35}Cl), 219 (M^+ for ^{37}Cl). Analysis calculated for $C_6H_5ClN_3S_2$: C, 33.00; H, 1.85; N, 19.30; S, 29.45. Found: C, 29.91; H, 2.71; N, 16.95; S, 21.54.

General procedure for the synthesis of thiazolo[4,5-*d*]pyrimidines 3a–f

To a solution of 5-chloro-7-methyl-2,3-dihydropyrimido[4,5-*d*][1,3]thiazol-2-thione **(1)** (1 mmol, 0.21 g) and Et_3N (1 mmol, 0.1 g) in CH_3CN (15 ml), the appropriate alkyl halide (1.1 mmol) was added, and the solution was heated under reflux for 2–3 h. The progress of the reaction was monitored by TLC using *n*-hexane/EtOAc (6:4). Then, the solvent was removed on a rotary evaporator and the resulting solid was crystallized from methanol.

5-Chloro-7-methyl-2-(methylthio)thiazolo[4,5-*d*]pyrimidine (3a) Yield 60%; mp 137–144°C; ^{1}H NMR: δ 2.55 (s, 3H, CH_3-pyrimidine), 2.88 (s, 3H, -SCH_3); IR: ν 3010, 1650 cm^{-1}; MS: *m/z* 231 (M^+), 233 (M^++2). Analysis calculated for $C_7H_6ClN_3S_2$: C, 36.28; H, 2.61; N, 18.13; S, 27.67. Found: C, 36.01; H, 2.57; N, 18.02; S, 27.44.

5-Chloro-2-(ethylthio)-7-methylthiazolo[4,5-*d*]pyrimidine (3b) Yield 65%; mp 107°C; ^{1}H NMR: δ 1.53 (t, 3H, CH_3), 2.70 (s, 3H, CH_3-pyrimidine), 3.43 (q, 2H, -SCH_2); IR: ν 3015, 1630 cm^{-1}; MS: *m/z* 245 (M^+), 247 (M^++2). Analysis calculated for $C_8H_8ClN_3S_2$: C, 39.10; H, 3.28; N, 17.10; S, 26.10. Found: C, 38.88; H, 3.20; N, 16.90; S, 25.78.

2-(Benzylthio)-5-chloro-7-methylthiazolo[4,5-*d*]pyrimidine (3c) Yield 70%; mp 98–100°C; ^{1}H NMR: δ 2.70 (s, 3H, CH_3), 4.71 (s, 2H, CH_2), 7.31–7.62 (m, 5H, phenyl); IR: ν 3000, 1660 cm^{-1}; MS: *m/z* 307 (M^+), 309 (M^++2). Analysis calculated for $C_{13}H_{10}ClN_3S_2$: C, 50.72; H, 3.27; N, 13.65; S, 20.83. Found: C, 50.66; H, 3.16; N, 13.57; S, 20.69.

2-(5-Chloro-7-methylthiazolo[4,5-*d*]pyrimidin-2-ylthio) acetonitrile (3d) Yield 63%; mp 104–110°C; ^{1}H NMR: δ 2.78 (s, 3H, CH_3), 4.32 (s, 2H, CH_2); IR: ν 2990, 2215, 1640 cm^{-1}; MS: *m/z* 256 (M^+), 258 (M^++2). Analysis calculated for $C_8H_5ClN_4S_2$: C, 37.43; H, 1.96; N, 21.82; S, 24.98. Found: C, 37.22; H, 1.88; N, 21.90; S, 24.89.

1-(5-Chloro-7-methylthiazolo[4,5-*d*]pyrimidin-2-ylthio)propan-2-one (3e) Yield 73%; mp 114°C; ^{1}H NMR: δ 2.41 (s, 3H, CH_3), 2.82 (s, 3H, CH_3-pyrimidine), 4.41 (s, 2H, -SCH_2); IR: ν 3010, 1710, 1660 cm^{-1}; MS: *m/z* 273 (M^+), 275 (M^++2). Analysis calculated for $C_9H_8ClN_3OS_2$: C, 39.49; H, 2.95; N, 15.35; S, 23.43. Found: C, 39.51; H, 2.92; N, 15.18; S, 23.35.

Ethyl-2-(5-chloro-7-methylthiazolo[4,5-*d*]pyrimidin-2-ylthio) acetate (3f) Yield 58%; mp 109°C; ^{1}H NMR: δ 1.38 (t, 3H, CH_3), 2.73 (s, 3H, CH_3-pyrimidine), 4.31 (q, 2H, -SCH_2); IR: ν 3010, 1680, 1630 cm^{-1}; MS: *m/z* 303 (M^+), 305 (M^++2). Analysis calculated for $C_{10}H_{10}ClN_3O_2S_2$: C, 39.54; H, 3.32; N, 13.83; S, 21.11. Found: C, 39.45; H, 3.29; N, 13.78; S, 20.79.

General procedure for the substitution of chlorine atom in 5-position with morpholine (4a–f)

To a solution of compounds **(3a–f)** (1 mmol) and morpholine (1.1 mmol, 0.088 g) in ethanol (10 ml), Et_3N (1.1 mmol, 0.1 g) was added and the solution was heated for approximately 8 h. The solvent of the reaction was reduced to half of the initial volume. The resulting solid was filtered off and recrystallized in ethanol.

7-Methyl-2-(methylthio)-5-morpholinothiazolo[4,5-*d*]pyrimidine (4a) Yield 64%; mp 204–205°C; ^{1}H NMR: δ 2.52 (s, 3H, CH_3), 2.83 (s, 3H, CH_3-pyrimidine), 3.71–3.92 (m, 8H, morpholine); IR: ν 3020, 1610 cm^{-1}; MS: *m/z* 282 (M^+). Analysis calculated for $C_{11}H_{14}N_4OS_2$: C, 46.79; H, 5.00; N, 19.84; S, 22.71. Found: C, 46.70; H, 4.97; N, 19.78; S, 22.64.

2-(Ethylthio)-7-methyl-5-morpholinothiazolo[4,5-*d*]pyrimidine (4b) Yield 50%; mp 129–131°C; ^{1}H NMR: δ 1.47 (t, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.43 (q, 2H, -SCH_2), 3.71–4.05 (m, 8H, morpholine); IR: ν 3030, 1650 cm^{-1}; MS: *m/z* 296 (M^+). Analysis calculated for $C_{12}H_{16}N_4OS_2$: C, 48.62; H, 5.44; N, 18.90; S, 21.64. Found: C, 48.52; H, 5.41; N, 18.86; S, 21.53.

2-(Benzylthio)-7-methyl-5-morpholinothiazolo[4,5-*d*]pyrimidine (4c) Yield 55%; mp 143–145°C; ^{1}H NMR: δ 2.51 (s, 3H, CH_3), 3.72–4.03 (m, 8H, morpholine), 4.71 (s, 2H, -SCH_2), 7.31–7.52 (m, 5H, phenyl); IR: ν 3050, 1630 cm^{-1}; MS: *m/z* 358 (M+). Analysis calculated for $C_{17}H_{18}N_4OS_2$: C, 56.96; H, 5.06; N, 15.63; S, 17.89. Found: C, 56.89; H, 5.01; N, 15.56; S, 17.80.

2-(7-Methyl-5-morpholinothiazolo[4,5-*d*]pyrimidin-2-ylthio) acetonitrile (4d) Yield 48%; mp 185–189°C; ^{1}H NMR: δ 2.48 (s, 3H, CH_3), 3.72–3.91 (m, 8H, morpholine), 4.33 (s, 2H, -SCH_2); IR: ν 3030, 2215, 1650 cm^{-1}; MS: *m/z* 307 (M^+). Analysis calculated for $C_{12}H_{13}N_5OS_2$: C, 46.89; H, 4.26; N, 22.78; S, 20.86. Found: C, 46.75; H, 4.22; N, 22.77; S, 20.79.

1-(7-Methyl-5-morpholinothiazolo[4,5-*d*]pyrimidin-2-ylthio) propan-2-one (4e) Yield 43%; mp 185–189°C; ^{1}H NMR: δ 2.48 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.72–3.93 (m, 8H, morpholine), 4.46 (s, 2H, -SCH_2); IR: ν 3010, 1720, 1640 cm^{-1}; MS: *m/z* 324 (M^+). Analysis calculated for $C_{13}H_{16}N_4O_2S_2$: C, 48.13; H, 4.97; N, 17.27; S, 19.77. Found: C, 48.12; H, 4.95; N, 17.25; S, 19.75.

Ethyl2-(7-methyl-5-morpholinothiazolo[4,5-*d*]pyrimidin-2-ylthio)acetate (4f) Yield 43%; mp 173–180°C; ^{1}H NMR: δ 1.32 (s, 3H, CH_3), 2.61 (s, 2H, -SCH_2), 3.82 (m, 8H, morpholine), 4.27 (s, 2H, -OCH_2). IR: ν 3030, 1690, 1630 cm^{-1}. MS: *m/z* 354 (M^+). Analysis calculated for $C_{14}H_{18}N_4O_3S_2$: C, 47.44; H, 5.12; N, 15.81; S, 18.09. Found: C, 47.39; H, 5.04; N, 15.69; S, 17.89.

Acknowledgments

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