Synthesis of some derivatives of pyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine; a novel heterocyclic system

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Several new derivatives of pyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine have been synthesised through the reaction of 5-hydrazinyl-1*H*-tetrazole with 5-bromo-2,4-dichloro-6-methylpyrimidine in $CHCl_3$ solution at ambient conditions. Further treatment of the synthesised compound with secondary amines gave the corresponding substituted heterocycles which were subsequently cyclised into pyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazines as derivatives of a novel heterocyclic system on treatment with $NaNH_2$ in CH_3CN.

Keywords: pyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine, heterocyclisation, 5-hydrazinyl-1*H*-tetrazole

Tetrazoles are a class of heterocycles that have received attention due to their wide range of applications. They have been used as explosives and rocket and gun propellants in construction and mining, in emergency escape devices and in automobile air bags.[1-3] This nitrogen-rich ring system is also used in pharmaceuticals.[4-6] In addition, they are important as synthons and precursors of carbenes in flash vacuum pyrolysis[7] and have a wide range of practical applications in organic syntheses.[8] The other main application of tetrazole derivatives is as gas-generating compositions.[9] Various tetrazole-based compounds have also shown good coordination properties and are able to form stable complexes with several metal ions.[10-12]

Furthermore, tetrazole derivatives have been used in organic synthesis as derivatising agents for the chemical modification of alcohols.[13] They are also significant precursors for the synthesis of various nitrogen-containing heterocycles and in many useful transformations.[14]

On the other hand, there are reviews dealing with the synthesis of condensed 1,2,4-triazines.[15–17] This heterocyclic moiety plays a vital role in many biological activities including antiviral,[18] antihypertensive,[19] blood-platelet aggregation inhibitory,[20] analgesic,[21] and antibacterial properties[22, 23] as well as some new anti-HIV and anticancer agents.[24]

Encouraged by the research activities in the field of tetrazole and triazine moieties and in pursuit of our continuing interest in developing new protocols for the synthesis of new heterocyclic ring systems,[25] we envisioned the synthesis of new derivatives of pyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine **6a–d** as a novel heterocyclic ring system.

Results and discussion

The starting material, 1-phenyl-5-methylsulfanyltetrazole **1** was easily obtained from the treatment of phenyl isothiocyanate with NaN_3 in the presence of pyridine in water at room temperature and subsequent methylation with methyl iodide.[26] The reaction of compound **1** with hydrazine hydrate gave, quantitatively, the desired hydrazine derivative **2** which has been synthesised previously with modifications, but not completely characterised.[27-29] On the other hand, 5-bromo-2,4-dichloro-6-methylpyrimidine **3** was prepared through the reaction of thiourea and ethyl acetoacetate in a four-stage method.[30] The treatment of compound **2** with the latter in a mixture of NaOH in DMF at 0 ºC afforded 5-bromo-2-chloro-4-methyl-6-[2-(1-phenyl-1*H*-tetrazol-5-yl)hydrazinyl]pyrimidine **4** (Scheme 1).

The ^{1}H NMR spectrum of compound **3** showed a singlet signal at 2.5 ppm indicating the presence of the CH_3 group of the pyrimidine ring, a multiplet in the range δ 6.61–7.53 corresponded to the phenyl moiety and the removal of the broad singlet signal at 6.70 ppm from the NH_2 group of the precursor **2** was replaced by the appearance of two NH signals at δ 8.46 and 8.60. In the IR spectrum, the disappearance of stretching vibration bands for the NH_2 group at ν_{max} 3346 and 3238 cm^{-1} also confirmed the occurrence of the hydrazine substitution step. Compound **4** was further treated with various secondary amines in refluxing EtOH, and gave the corresponding substituted derivatives **5a–d** in quantitative yields.

In an attempt to prepare new derivatives of the pyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine ring system, compounds **5a–d** were treated with $NaNH_2$ in refluxing acetonitrile. After 8 h it was observed that the only products obtained were **6a–d**, derivatives of a novel heterocyclic system.

Beside the correct elemental analyses, the spectral data of compounds **6a–d** are in agreement with the assigned structures. For instance, the IR spectrum of compound **5a** displayed two stretching vibration bands for the NH group at ν_{max} 3283 and 3117 cm^{-1}. The ^{1}H NMR spectrum showed the signals for the pyrrolidine moiety at 1.83 and 3.03 ppm, a singlet at 2.48 ppm due to the methyl protons, a multiplet in the region 7.09–7.63 ppm due to the phenyl group and two signals at 6.67 ppm and 8.07 ppm corresponding to the NH groups. The mass spectrum of **5a** showed a molecular ion peak at *m/z* 416 (M^+) consistent with a molecular formula of $C_{16}H_{18}BrN_9$.

The IR spectrum of compound **6b** displayed a stretching vibration band for the NH group at ν_{max} 3333 cm^{-1}. The ^{1}H NMR spectrum showed the signals of the morpholine moiety at 2.50 and 3.39 ppm, a singlet signal at 2.36 ppm due to the methyl protons, a multiplet in the range 6.98–7.66 ppm due to the phenyl group and a signal at 9.32 ppm corresponding to the NH group. The mass spectrum of **6b** showed a molecular ion peak at *m/z* 351 (M^+) related to the molecular formula of $C_{16}H_{17}N_9O$.

Conclusion

In summary, we have demonstrated a novel and efficient synthetic protocol for the preparation of the pyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine systems **6a–d**. The desired ring formation could be carried out through the treatment of 5-hydrazinyl-1-phenyl-1*H*-tetrazole **2** and 5-bromo-2,4-dichloro-6-methylpyrimidine **3** in NaOH/DMF which was subsequently treated with secondary amines in boiling EtOH. The reaction of the hydrazinyltetrazoles **5a–d** with $NaNH_2$ in CH_3CN eventually gave the desired novel derivatives of the pyrimido[5,4-**e**]tetrazolo[5,1-*c*][1,2,4]triazine system **6a–d**. These new compounds like all other biologically active heterocyclic compounds may be good candidates for

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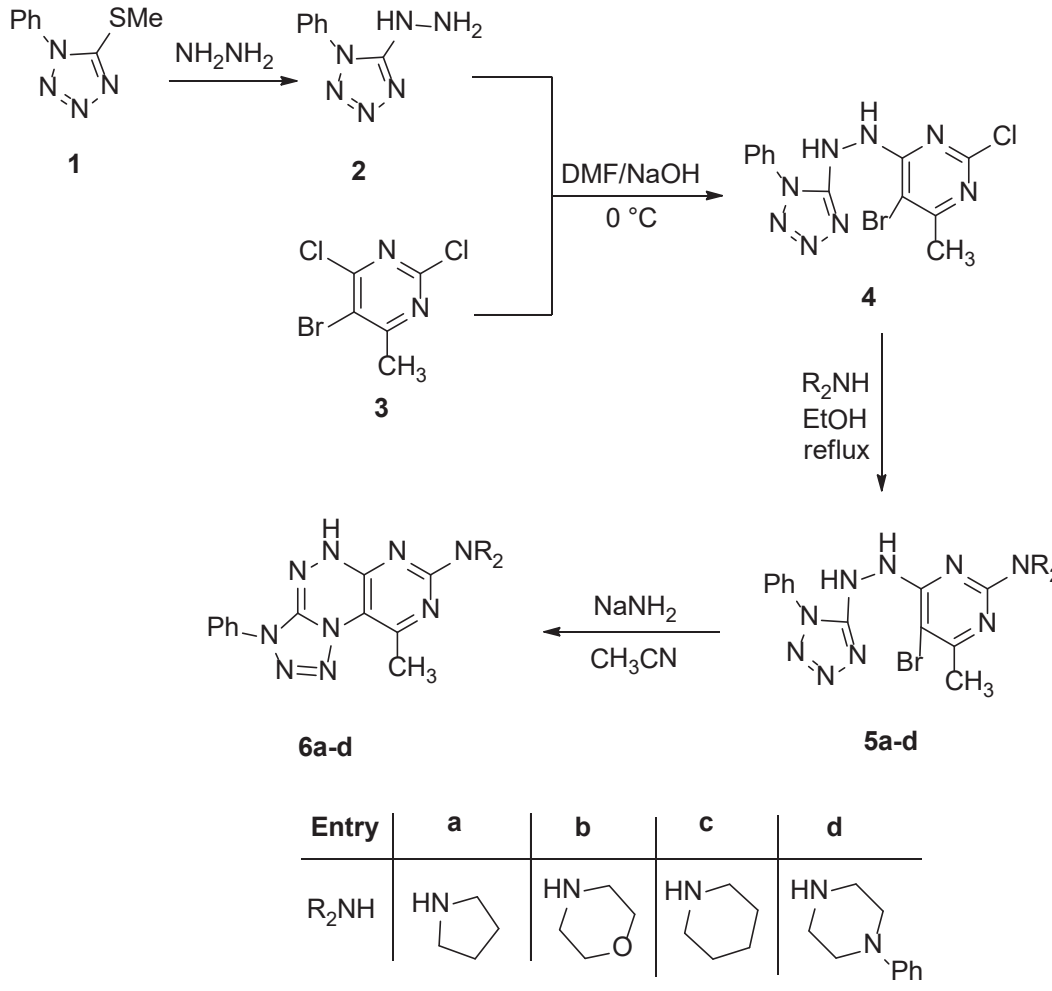

Entry	a	b	c	d
R_2NH	HN	HN, O	HN	HN, N, Ph

Scheme 1

investigating their pharmaceutical properties in biological systems. These studies are in progress in our laboratory and will be published in due course.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on Avatar 370 FTIR Thermo Nicolet spectrophotometer and only noteworthy absorptions are listed. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 microanalyser.

*5-Hydrazinyl-1-phenyl-1*H*-tetrazole* (**2**): Excess hydrazine hydrate (2 mL) was added to a stirred solution of 5-(methylthio)-1-phenyl-1*H*-tetrazole (**1**) (0.19 g, 1 mmol) in pyridine (2 mL) and the solution was refluxed for 1 day. After the completion of the reaction, the solvent was removed under reduced pressure and the resulting solid was washed with water (2 × 20 mL) and recrystallised from EtOAc to obtain the pure product as a white solid; yield 57%; m.p. 215–217 ºC, ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 6.70 (2H, s, NH_2), 6.95–6.98 (3H_{arom}, m, phenyl), 7.32–7.36 (2H_{arom}, m, phenyl), 9.2 (1H. s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 128.4, 128.7, 128.8, 129.3, 156.4; IR (KBr) ν_{max}/cm^{-1} 3346, 3238, 3113, 3031, 1643; MS (*m/z*) 176 (M). Anal. calcd for $C_7H_8N_6$: C, 47.72; H, 4.58; N, 47.70; found: C, 47.65; H, 4.50; N, 47.61%.

*5-Bromo-2-chloro-4-methyl-6-[2-(1-phenyl-1*H*-tetrazol-5-yl) hydrazinyl]pyrimidine* (**4**): 5-Hydrazinyl-1-phenyl-1*H*-tetrazole **2** (1 mmol, 0.18 g) was added slowly to a stirred mixture of 5-bromo-2,4-dichloro-6-methylpyrimidine **3** (0.24 g, 1 mmol) and powdered NaOH (1 g) in DMF (5 mL) at temperature of 0–5 ºC. After the completion of the reaction, which was monitored by TLC using EtOAc: *n*-hexane (3:7) as eluent, water (10 mL) was added and the resulting solid was separated and washed with water (2 × 10 mL) and dried *in vacuo*. Further purification was performed by washing the precipitate with petroleum ether.Yield 90%; m.p. 250–252 ˚C, ^{1}H NMR (DMSO-d_6) δ_H 2.50 (3H, s, CH_3), 6.61–7.53 (5H_{arom}, m, phenyl), 8.46 (1H, s, NH), 8.60 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c 23.8, 115.2, 117.4, 117.5, 121.7, 128.8, 129.1, 144.7, 162.3, 167.4; IR (KBr) ν_{max}/cm^{-1} 3361, 2941, 2916, 1624; MS (*m/z*) 381 (M), 383 (M+2), 345 (M-Cl, 35), 330 (M-Cl,-CH_3, 15). Anal. calcd for $C_{12}H_{10}BrClN_8$: C, 37.77; H, 2.64; N, 29.36; found: C, 37.69; H, 2.58; N, 29.28%.

Preparation of 2-amino-5-bromo-4-methyl-6-[2-(1-phenyl-1H-tetrazol-5-yl)hydrazinyl]pyrimidines **5a–d***; general procedure*

The appropriate secondary amine (1.5 mmol) was added to a stirred solution of compound **4** (0.38 g, 1 mmol,) and Et_3N (0.2 mL, 1.5 mmol,) in EtOH (5 mL), and the solution was heated under reflux for 12 h. After the completion of the reaction, the mixture was cooled and the solvent was removed under reduced pressure. The resulting solid was washed with water (2 × 10 mL) and recrystallised from EtOH.

*5-Bromo-4-methyl-6-[2-(1-phenyl-1*H*-tetrazol-5-yl)hydrazinyl]-2-(pyrrolidin-1-yl)pyrimidine* (**5a**): White powder; yield 75%; m.p. 200–202 ˚C; ^{1}H NMR (DMSO-d_6) δ_H 1.83 (4H, t, J = 6.2 Hz, CH_2-pyrrolidine), 2.48 (3H, s, -CH_3), 3.03 (2H, t, J = 6.2 Hz, CH_2N-pyrrolidine), 3.45 (2H, s, CH_2N-pyrrolidine), 7.09–7.63 (5H_{arom}, m, phenyl), 6.67 (1H, s, NH), 8.07 (1H, s, NH); ^{13}C NMR (DMSO-d_6): δ_c 23.5, 25.1, 54.1, 96.3, 128.1, 128.2, 129.0, 155.6, 158.2, 165.2, 169.1; IR (KBr) ν_{max}/cm^{-1} 3283, 3117, 2964, 2917, 2867, 1622,750; MS (*m/z*)

415 (M), 417 (M+2). Anal. calcd for $C_{16}H_{18}BrN_9$: C, 46.16; H, 4.36; N, 30.28; found: C, 46.02; H, 4.30; N, 30.21%

*4-(5-Bromo-4-methyl-6-[2-(1-phenyl-1*H*-tetrazol-5-yl)hydrazinyl]-2-(morpholin-4-yl)pyrimidine* (**5b**): White powder; yield 71%; m.p. 180–181 °C; ^{1}H NMR (DMSO-d_6) δ_H 2.43 (3H, s, CH_3), 3.65 (4H, t, J = 6.1 Hz, CH_2N-morpholine), 3.74 (4H, t, J = 6.1 Hz, CH_2O-morpholine), 6.71 (1H, s, NH), 7.45–7.62 (5H, m, phenyl), 8.12 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_c 23.1, 48.9, 66.7, 96.1, 128.1, 128.4, 129.2, 156.0, 158.3, 165.2, 169.3; IR (KBr) ν_{max}/cm^{-1} 3333, 2959, 2850, 1666, 751; MS (*m/z*) 431 (M), 433 (M+2). Anal. calcd for $C_{16}H_{18}BrN_9O$: C, 44.46; H, 4.20%; N, 29.16; found: C, 44.39; H, 4.16; N, 29.10%.

*5-Bromo-4-methyl-6-[2-(1-phenyl-1*H*-tetrazol-5-yl)hydrazinyl]-2-(piperidin-1-yl)pyrimidine* (**5c**): Brown powder; yield 65%; m.p. 195–197 °C; ^{1}H NMR (DMSO-d_6) δ_H 1.45 (4H, t, J = 6.3 Hz, $CH_2C\underline{H}_2CH_2$N), 1.59 (2H, m, CH_2), 2.40 (3H, s, CH_3-pyrimidine), 3.71 (4H, t, J = 6.3 Hz, CH_2N-piperidine), 6.73 (1H, s, NH), 7.45–7.62 (5H, m, Ar), 8.05 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_c 23.2, 24.3, 25.2, 58.1, 96.3, 128.2, 128.4, 129.3, 156.0, 158.8, 165.5, 169.2; IR (KBr) ν_{max}/cm^{-1} 3020, 2990, 1592, 1555, 1015; MS (*m/z*) 429 (M), 431 (M+2). Anal. calcd for $C_{17}H_{20}BrN_9$: C, 47.45; H, 4.68; N, 29.30; found: C, 47.40; H, 4.61; N, 29.25%.

*5-Bromo-4-methyl-6-[2-(1-phenyl-1*H*-tetrazol-5-yl)hydrazinyl]-2-(4-phenylpiperazin-1-yl)pyrimidine* (**5d**): Brown powder; yield 78%; m.p. 205–206 °C; ^{1}H NMR (DMSO-d_6) δ_H 2.43 (3H, s, CH_3), 3.23 (4H, t, J = 6.3 Hz, CH_2N), 3.51 (4H, t, J = 6.3 Hz, CH_2N), 6.73–7.59 (10H$_{arom}$, m, phenyl); ^{13}C NMR (DMSO-d_6) δ_c 23.2, 49.5, 49.6, 96.3, 114.1, 121.7, 128.6, 128.4, 128.3, 129.6, 129.5, 149.1, 156.0, 158.3, 165.2, 169.1; IR (KBr) ν_{max}/cm^{-1} 3457; 3353, 2962, 2922, 1620, 749; MS (*m/z*) 506 (M), 508 (M+2), 429 (M-Ph), 345 (M-piperazine), 266 (M-Br), 251 (M-CH_3), 174 (M-Ph). Anal. calcd for $C_{22}H_{23}BrN_{10}$: C, 52.08; H, 4.57; N, 27.61; found: C, 51.98; H, 4.50; N, 27.53%.

Preparation of pyrimido[5,4-e]tetrazolo[5,1-c][1,2,4]triazines **6a–d***; general procedure*

A mixture of compounds **5a–d** (1 mmol) and $NaNH_2$ (0.12 g, 3 mmol) in dry CH_3CN (5 mL) was heated for 8 h under reflux. After completion of the reaction, the solvent was removed under reduced pressure and the mixture was neutralised with acetic acid. The precipitate was filtered off, washed with water and recrystallised from EtOH.

*9-Methyl-3-phenyl-7-(pyrrolidin-1-yl)-3,5-dihydropyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine* (**6a**): Brown powder; yield 76%; m.p. 225–226 °C; ^{1}H NMR (DMSO-d_6) δ_H 1.92 (4H, t, J = 7.1 Hz, CH_2), 2.33 (3H, s, CH_3), 3.32 (4H, t, J = 7.1 Hz, CH_2N), 6.76–7.20 (5H$_{arom}$, m, phenyl), 8.07 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_c 17.5, 25.3, 54.1, 117.4, 119.0, 122.8, 129.1, 144.2, 150.3, 155.1, 156.6; IR (KBr) ν_{max}/cm^{-1} 3422, 3143, 2966, 2923, 2854, 1626; MS (*m/z*) 335 (M), 258 (M-Ph), 243 (M-CH_3), 173 (M-pyrrolidine). Anal. calcd for $C_{16}H_{17}N_9$: C, 57.30; H, 5.11; N, 37.59; found: C, 57.24; H, 5.05; N, 37.49%.

*9-Methyl-3-phenyl-7-(morpholin-4-yl)-3,5-dihydropyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine* (**6b**): Brown powder; yield 65%; m.p. 180–181 °C; ^{1}H NMR (DMSO-d_6) δ_H 2.36 (3H, s, CH_3), 2.50 (4H, t, J = 6.4 Hz, CH_2N), 3.39 (4H, t, J = 6.4 Hz, CH_2O), 6.98–7.66 (5H$_{arom}$, m, phenyl), 9.32 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_c 17.4, 48.8, 66.4, 117.4, 119.1, 122.3, 129.5, 144.9, 150.5, 155.6, 156.8; IR (KBr) ν_{max}/cm^{-1} 3333, 2959, 2850, 1666; MS (*m/z*) 351 (M), 274 (M-Ph), 259 (M-CH_3), 173 (M-morpholine). Anal. calcd for $C_{16}H_{17}N_9O$: C, 54.69; H, 4.88; N, 35.88; found: C, 54.60; H, 4.82; N, 35.79%.

*9-Methyl-3-phenyl-7-(piperidin-1-yl)-3,5-dihydropyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine* (**6c**): Brown powder; yield 65%; m.p. 195–197 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (6H, m, $CH_2CH_2CH_2$), 2.26 (3H, s, CH_3), 3.35 (4H, t, J = 6.8 Hz,2 × CH_2N), 6.88–7.68 (5H$_{arom}$, m, Ar), 8.24 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_c 17.5, 24.2, 25.1, 54.3, 117.3, 119.0, 122.4, 129.6, 144.8, 150.4, 155.5, 156.7; IR (KBr) ν_{max}/cm^{-1} 3020, 2990, 1592, 1555, 1015; MS (*m/z*) 349 (M), 265 (M-piperidine), 250 (M-CH_3). Anal. calcd for $C_{17}H_{19}N_9$: C, 58.44; H, 5.48; N, 36.08; found: C, 58.36; H, 5.40; N, 35.98%.

*9-Methyl-3-phenyl-7-(4-phenylpiperazin-1-yl)-3,5-dihydropyrimido[5,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine* (**6d**): Brown powder; yield 78%; m.p. 205–207 °C; ^{1}H NMR (DMSO-d_6) δ_H 2.40 (3H, s, CH_3), 2.85–2.92 (8H, m, CH_2), 6.89–7.40 (10H, m, phenyl), 9.50 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_c 17.5, 49.5, 49.6, 117.5, 114.6, 119.3, 121.7, 122.3, 129.6, 129.7, 143.3, 146.4, 149.5, 150.4, 156.2, 154.3; IR (KBr) ν_{max}/cm^{-1} 3457, 3353, 2962, 2922, 2851, 1620, 749; MS (*m/z*) 426 (M), 349 (M-Ph), 265 (M-piperazine). Anal. calcd for $C_{22}H_{22}N_{10}$: C, 61.96; H, 5.20; N, 32.84; found: C, 61.89; H, 5.15; N, 32.77%.

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