Synthesis of tricyclic systems containing a fused thieno[3,4-*d*]pyrimidine nucleus

Farag A. El-Telbany, Maha Abd El Hakeem, Omneya M. Khalil* and Demiana S. Mikhail

Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt

The synthesis and characterisation of novel tricyclic systems containing a fused thieno[3,4-*d*]pyrimidine nucleus starting from a useful synthon, ethyl-4-cyano-3-ethoxymethyleneamino-5-phenylamino-2-thiophenecarboxylate, are reported.

Keywords: imidate, aminothiophene-2-carboxylates, thieno[3,4-*d*]pyrimidine, Dimroth rearrangement, tricyclic heterocycles

Many thieno[3,4-*d*]pyrimidines have been the focus of interest because of their remarkable biological properties in pharmaceuticals. Condensed thieno[3,4-*d*]pyrimidines exhibit interesting biological properties such as anti-cancer,[1,2] anti-viral,[3] anti-allergy,[4] anti-hypertensive,[5] gastric anti-secretory[6] and aldose reductase inhibitory[7] activities. On the other hand, several condensed diazocines[8,9] and diazepines[10,11] have been reported to possess a variety of biological activities. Guided by these findings, we have invetsigated the synthesis and characterisation of some tricyclic systems in which a thieno[3,4-*d*] pyrimidine is fused with either diazocine or diazepine rings.

Our study started with the thiophene derivative **1** which is considered as a root compound and can be used for the preparation of the key intermediate **2**. In this work, compound **1** was obtained according to Gewald's procedure.[12] Ethyl 4-cyano-3-ethoxymethyleneamino-5-phenylamino-2-thiophenecarboxylate **2** was obtained as reported in the literature via condensation of the 3-aminothiophene-2-carboxylic ester (**1**) with triethyl orthoformate as a one carbon donor.

Compounds **3a–f** were successfully prepared through heating of compound **2** with the appropriate primary aromatic amines as shown in Scheme 1. The sequence of reactions involves selective aminolysis of compound **2**, followed by the spontaneous cyclisation to less stable intermediate **A** which further undergoes a Dimroth-type rearrangement[13–15] to yield the thermodynamically stable pyrimidine **3**.

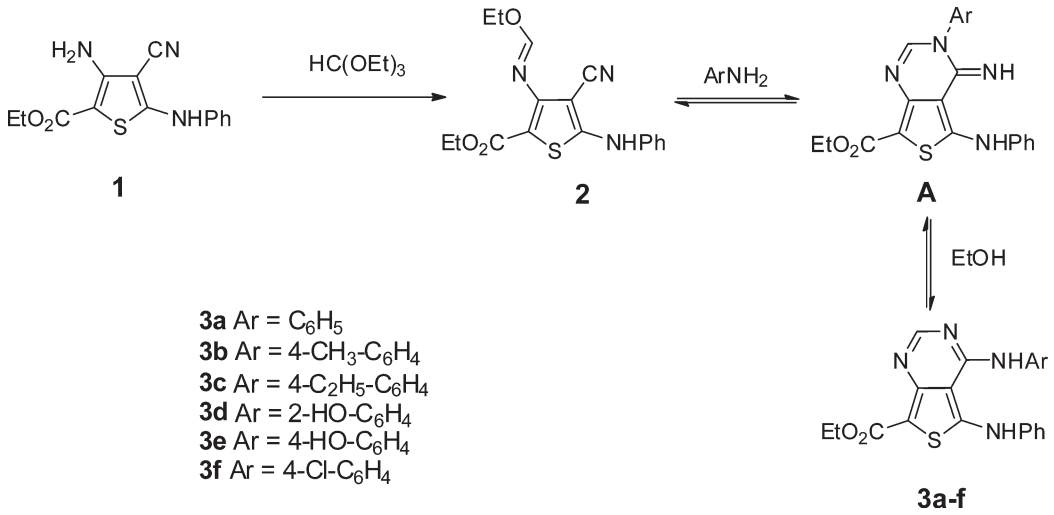
The structures of compounds **3a–f** were substantiated from their elemental analyses, IR, ^{1}H NMR and mass spectroscopy. The IR spectra showed the disappearance of the CN absorption band in **2** and the presence of the ester C=O absorption at 1653 cm^{-1}.

Moreover, the ^{1}H NMR spectra of **3a–f** revealed the presence of the triplet and quartet signals from the ester group in the ranges δ 1.21–1.30 and 4.14–4.24 ppm respectively, indicating that the ester group was not involved in the reaction. They also showed a singlet signal in the region δ 8.09–8.18 ppm for the pyrimidine proton, and two singlets in the ranges δ 6.59–6.76 and 12.20–12.54 ppm corresponding to two NH groups.

Further, cyclisation of **3a–f** with either oxalyl chloride or malonyl chloride in dry benzene afforded the corresponding fused 1,4-diazepine-2,3-diones **4a–f** and the 1,5-diazocine-2,4-diones **5a–f** respectively (Scheme 2).

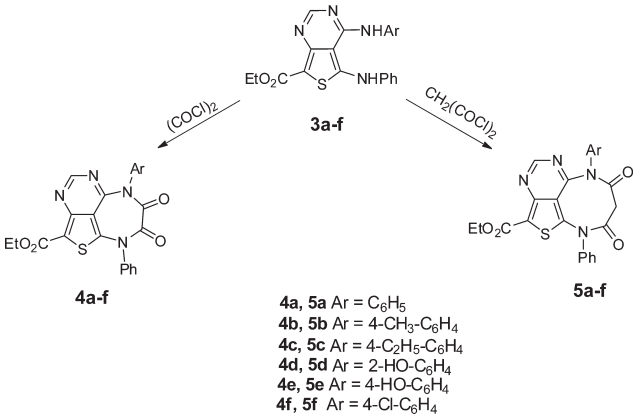
The IR spectra of compounds **4a–f** showed the presence of three C=O absorption bands in the range 1747–1647 cm^{-1} and the absence of an NH stretching band. Furthermore, the ^{1}H NMR spectra of compounds **4a–f** indicated the disappearance of the NH signal from the starting compounds. Meanwhile, the IR spectra of compounds **5a–f** also revealed the presence of three overlapped C=O absorption bands. In addition, the ^{1}H NMR spectra showed a singlet signal corresponding to the methylene protons from the O=C–CH_2–C=O unit that ranged from δ 3.70 to 3.40 ppm. Furthermore, the ^{1}H NMR spectra revealed the absence of the NH signals from compounds **3a–f**.

Ethyl 3-amino-5-phenylamino-4-imino-3,4-dihydrothieno [3,4-*d*]pyrimidine-7-carboxylate (**6**) was prepared as shown in Scheme 3 via condensation of **2** with hydrazine hydrate in ethanol, on a boiling water bath for 10–15 min, through nucleophilic addition of hydrazine to the imidate group, followed by elimination of ethanol and intramolecular cyclisation to give the desired compound **6**. The IR spectrum of the latter showed

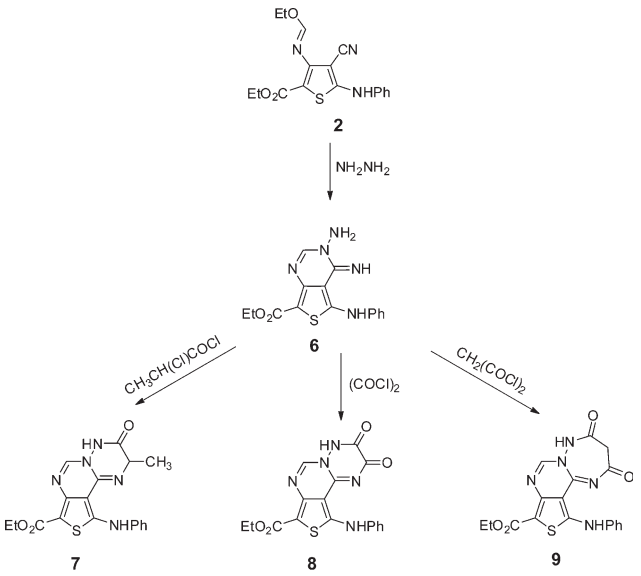


Scheme 1 Synthesis of compounds **3a–f**.

* Correspondent. E-mail: omneyafawzy@yahoo.com



Scheme 2 Synthesis of compounds **4a–f** and **5a–f**.



Scheme 3 Synthesis of compounds **6–9**.

the absence of a CN absorption band and the appearance of a forked band at 3360–3280 cm^{-1} corresponding to the NH_2 group. On the other hand, the ^1H NMR spectrum exhibited a singlet for the =NH proton at δ 5.87 ppm. In addition, it also revealed the presence of singlets for the pyrimidine proton at δ 8.47 and at δ 11.40 corresponding to NH_2 group respectively.

Formation of the tricyclic thienopyrimidine derivatives **7**, **8** and **9** was accomplished via cyclisation of **6** with 2-chloropropionyl chloride, oxalyl chloride and malonyl chloride in dry benzene. Structures of the cyclised compounds were substantiated by spectral data. The IR spectrum of compound **7** indicated the presence of two overlapped C=O bands ranging from 1680 to 1668 cm^{-1} and its ^1H NMR spectrum revealed the absence of a =NH proton signal at δ 5.87. It also exhibited the appearance of a doublet signal corresponding to methyl protons at δ 1.57, and a quartet at δ 5.02 for the methine proton. In addition, the IR spectrum of **8** showed the presence of three C=O absorption bands in the range 1720–1647 cm^{-1}. The ^1H NMR spectrum indicated the absence of a signal for the =NH proton at δ 5.87, and the presence of only two NH proton signals at δ 10.47, 12.44 ppm (exchangeable with D_2O). The IR spectrum of **9** indicated the presence of three overlapped C=O absorption band at 1668–1647 cm^{-1}, while its ^1H NMR spectrum showed the absence of =NH proton signal at δ 5.87 ppm in addition to the appearance of a singlet corresponding to the O=C–CH_2–C=O unit at 3.70 ppm.

Experimental

Melting points were obtained on a Griffin apparatus and the values given are uncorrected. IR spectra were recorded on a Shimadzu 435 spectrophotometer, using KBr discs. ^1H NMR spectra were recorded on a Varian Mercury-300BB (300 MHz) or a Varian GEMINI-200 (200 MHz) spectrometer using TMS as internal standard. Mass spectra were recorded on a JEOL JMS-AX 500 Spectrometer. Elemental analyses for C, H and N were performed at the Microanalytical Center, Cairo University. The progress of reactions was monitored by TLC using precoated aluminium sheets (silica gel MERCK 60 F 254) and visualised by a UV lamp. Compound **1** was prepared adopting Gewald conditions.[12] All the chemicals were purchased from the Sigma-Aldrich Company.

Synthesis of compounds **3a–f**; *general procedure*

A mixture of **2** (3.43 g, 0.01 mol) and the appropriate amine (0.01 mol) in absolute ethanol (20 mL) was heated under reflux for 1 h. The reaction mixture was cooled and the separated solid was filtered, dried and recrystallised from ethanol. Using this method the following compounds were prepared.

*Ethyl 5-phenylamino-4-(phenylamino)thieno[3,4-*d*]pyrimidine-7-carboxylate* (**3a**): Red solid, yield: 66.6%, m.p. 192–194 °C; IR (KBr) ν/cm^{-1} 3294 (2 NH), 2978–2893 (CH aliphatic), 1654 (C=O); ^1H NMR (200 MHz, DMSO-d_6) δ 1.23 (t, 3H, CH_3, J = 6.80 Hz), 4.14 (q, 2H, CH_2, J = 6.80 Hz), 6.74 (s, 1H, NH, D_2O exchangeable), 7.18–7.72 (m, 10H, ArH), 8.12 (s, 1H, pyrimidine), 12.40 (s, 1H, NH, D_2O exchangeable); MS (*m/z*) (relative abundance %) (26.24), 392.10 $(M+2)^{+\cdot}$ (7.93), 391.10 $(M+1)^+$, 390.10 $(M)^{+\cdot}$ (100). Anal. Calcd for $C_{21}H_{18}N_4O_2S$ (390.44): C, 64.59; H, 4.64; N, 14.35. Found: C, 64.70; H, 4.52; N, 14.51%.

*Ethyl5-phenylamino-4-(4-methylphenylamino)thieno[3,4-*d*]pyrimidine-7-carboxylate* (**3b**): Red solid, yield: 64.3%, m.p. 198–200 °C; IR (KBr) ν/cm^{-1} 3444, 3282 (2 NH), 2800–2924 (CH aliphatic), 1651 (C=O); ^1H NMR (200 MHz, DMSO-d_6) δ 1.30 (t, 3H, CH_3, J = 7.00 Hz), 2.36 (s, 3H, CH_3), 4.24 (q, 2H, CH_2, J = 7.00 Hz), 6.76 (s, 1H, NH, D_2O exchangeable), 7.25–7.67 (m, 9H, ArH), 8.18 (s, 1H, pyrimidine), 12.39 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 14.60, 20.45, 38.68, 38.95, 39.23, 39.51, 39.79, 40.06, 40.34, 59.14, 101.07, 120.72, 121.55, 123.49, 129.22, 129.36, 133.86, 134.98, 150.12, 154.62, 159.34; MS (*m/z*) (relative abundance %): 402 $(M-2)^+$ (100). Anal. Calcd for $C_{22}H_{20}N_4O_2S$ (404.47): C, 65.32; H, 4.98; N, 13.85. Found: C, 65.40; H, 5.20; N, 13.7.1%.

*Ethyl 5-phenylamino-4-(4-ethylphenylamino)thieno[3,4-*d*]pyrimidine-7-carboxylate* (**3c**): Red solid, yield: 62.2%, m.p. 212–214 °C; IR (KBr) ν/cm^{-1} 3253 (2 NH), 2872–2962 (CH aliphatic), 1653 (C=O); ^1H NMR (200 MHz, DMSO-d_6) δ 1.21 (t, 3H, CH_3, J = 7.00 Hz), 1.25 (t, 3H, CH_3, J = 7.20 Hz), 2.61 (q, 2H, CH_2, J = 7.00 Hz), 4.20 (q, 2H, CH_2, J = 7.20 Hz), 7.28–7.32 (m, 9H, ArH), 8.13 (s, 1H, pyrimidine), 12.40 (s, 1H, NH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 419 $(M+1)^+$ (7.54), 418 $(M)^{+\cdot}$(26.7). Anal. Calcd for $C_{23}H_{22}N_4O_2S$ (418.50): C, 66.00; H 5.29; N, 13.38. Found: C, 66.00; H, 5.20; N, 13.35%.

*Ethyl5-phenylamino-4-(2-hydroxyphenylamino)thieno[3,4-*d*]pyrimidine-7-carboxylate* (**3d**): Red solid, yield: 61.5%, m.p. 208–210 °C; IR (KBr) ν/cm^{-1} 3305 (OH), 3182 (2 NH), 2978–3000 (CH aliphatic), 1635 (C=O); ^1H NMR (200 MHz, DMSO-d_6) δ 1.21 (t, 3H, CH_3, J = 6.90 Hz), 4.15 (q, 2H, CH_2, J = 6.90 Hz), 6.59 (s, 1H, NH, D_2O exchangeable), 6.90–7.37 (m, 9H, ArH), 8.13 (s, 1H, pyrimidine), 10.37 (s, 1H, OH, D_2O exch.), 12.54 (s, 1H, NH, D_2O exchangeable); MS (*m/z*) (relative abundance %) 408.10 $(M+2)^+$ (8.40), 407.10 $(M+1)^+$ (24.80), 406.10 $(M)^{+\cdot}$ (100). Anal. Calcd for $C_{21}H_{18}N_4O_3S$ (406.44): C, 62.05; H, 4.46; N, 13.78. Found: C, 62.16; H, 4.69; N, 13.67%.

*Ethyl5-phenylamino-4-(4-hydroxyphenylamino)thieno[3,4-*d*]pyrimidine-7-carboxylate* (**3e**): Red solid, yield: 64%, m.p. 205–207 °C; IR (KBr) ν/cm^{-1} 3400–3294 (2 NH,OH), 2850–2950 (CH aliphatic), 1651 (C=O); ^1H NMR (200 MHz, DMSO-d_6) δ 1.24 (t, 3H, CH_3, J = 7.00 Hz), 4.22 (q, 2H, CH_2, J = 7.00 Hz), 6.78–7.51 (m, 9H, ArH), 8.09 (s, 1H, pyrimidine), 9.52 (s, 1H, OH, D_2O exchangeable), 12.20 (s, 1H, NH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 407 $(M+1)^+$ (6.51), 406 $(M)^+$, (30.32). Anal. Calcd for $C_{21}H_{18}N_4O_3S$ (406.44): C, 62.05; H, 4.46; N, 13.78. Found: C, 62.00; H, 4.30; N, 13.53%.

*Ethyl5-phenylamino-4-(4-chlorophenylamino)thieno[3,4-*d*]pyrimidine-7-carboxylate* (**3f**): Red solid, yield: 61.3%, m.p. 202–204 °C; IR

(KBr) ν/cm^{-1} 3437, 3282 (2 NH), 2800–2950 (CH aliphatic), 1651 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.27 (t, 3H, CH_3, J = 7.20 Hz), 4.19 (q, 2H, CH_2, J = 7.20 Hz), 6.76 (s, 1H, NH, D_2O exchangeable), 7.14–7.76 (m, 9H, ArH), 8.15 (s, 1H, pyrimidine), 12.45 (s, 1H, NH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 425 $(M+1)^+$ (0.72). Anal. Calcd for $C_{21}H_{17}ClN_4O_2S$ (424.89): C, 59.35; H, 4.03; N, 13.18. Found: C, 59.30; H, 3.90; N, 12.90%.

Synthesis of compounds (**4a–f**); *general procedure*

A mixture of **3a–f** (0.01 mol) and oxalyl chloride (1.9 g, 0.015 mol) in dry benzene (20 mL) was heated under reflux for 10 h. The reaction mixture was cooled and the separated solid was filtered, dried and recrystallised from acetonitrile. Using this method the following compounds were prepared.

*Ethyl6-phenyl-7,8-dioxo-9-phenyl-6,7,8,9-tetrahydro-1-thia-3,5,6,9-tetraazabenz[*cd*]azulene-2-carboxylate* (**4a**): Yellow solid, yield: 58.5%, m.p. 276–278 °C; IR (KBr) ν/cm^{-1} 2978–2890 (CH aliphatic), 1743, 1712, 1651 (3 C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.26 (t, 3H, CH_3, J = 7.20 Hz), 4.25 (q, 2H, CH_2, J = 7.20 Hz), 7.47–7.68 (m, 10H, ArH), 8.45 (s, 1H, pyrimidine); MS (*m/z*) (relative abundance %): 445.10 $(M+1)^+$ (6.47), 444.20 $(M)^+$, (8.56). Anal. Calcd for $C_{23}H_{16}N_4O_4S$ (444.45): C, 62.15; H, 3.62; N, 12.60. Found: C, 62.08; H, 3.92; N, 12.28%.

*Ethyl 6-(4-methylphenyl)-7,8-dioxo-9-phenyl-6,7,8,9-tetrahydro-1-thia-3,5,6,9-tetraazabenz[*cd*]azulene-2-carboxylate* (**4b**): Yellow solid, yield: 52.4%, m.p. 270–272 °C; IR (KBr) ν/cm^{-1} 2941–2978 (CH aliphatic), 1739, 1712, 1647 (3 C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.23 (t, 3H, CH_3, J = 7.00 Hz), 2.34 (s, 3H, CH_3), 4.27 (q, 2H, CH_2, J = 7.00 Hz), 7.38–7.70 (m, 9H, ArH), 8.45 (s, 1H, pyrimidine); MS (*m/z*) (relative abundance %): 459 $(M+1)^+$ (82.99). Anal. Calcd for $C_{24}H_{18}N_4O_4S$ (458.47): C, 62.86; H, 3.95; N, 12.22. Found: C, 62.90; H, 3.80; N, 12.0%.

*Ethyl 6-(4-ethylphenyl)-7,8-dioxo-9-phenyl-6,7,8,9-tetrahydro-1-thia-3,5,6,9-tetraazabenz[*cd*]azulene-2-carboxylate* (**4c**): Yellow solid, yield: 50.8%, m.p. 286–288 °C; IR (KBr) ν/cm^{-1} 2870–2960 (CH aliphatic), 1743, 1714, 1647 (3 C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.24 (t, 3H, CH_3, J = 7.20 Hz), 1.28 (t, 3H, CH_3, J = 7.40 Hz), 2.68 (q, 2H, CH_2, J = 7.20 Hz), 4.23 (q, 2H, CH_2, J = 7.40 Hz), 7.38–7.68 (m, 9H, ArH), 8.43 (s, 1H, pyrimidine); ^{13}C NMR (DMSO-d_6): δ 14.32, 15.38, 27.87, 38.69, 38.97, 39.25, 39.53, 39.81, 40.09, 40.37, 60.30, 104.64, 120.73, 120.79, 126.78, 128.46, 128.51, 130.28, 130.47, 131.89, 137.02, 144.65, 147.28, 149.69, 153.16, 156.57, 160.78, 161.02; MS (*m/z*) (relative abundance %): 444 $(M-CO)^+$ (9.50). Anal. Calcd for $C_{25}H_{20}N_4O_4S$ (472.50): C, 63.54; H, 4.26; N, 11.85. Found: C, 63.60; H, 4.11; N, 11.62%.

*Ethyl 6-(2-hydroxyphenyl)-7,8-dioxo-9-phenyl-6,7,8,9-tetrahydro-1-thia-3,5,6,9-tetraazabenz[*cd*]azulene-2-carboxylate* (**4d**): Yellow solid, yield: 45.6%, m.p. 190–192 °C; IR (KBr) ν /cm^{-1} 3350–3500 (OH), 2843–2981 (CH aliphatic), 1735, 1701, 1647 (3 C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.26 (t, 3H, CH_3, J = 7.2 Hz), 4.25 (q, 2H, CH_2, J = 7.2 Hz), 6.94–7.69 (m, 9H, ArH), 8.48 (s, 1H, pyrimidine), 9.8 (s, 1H, OH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 460.79 $(M+1)^+$ (100); Anal. Calcd for $C_{23}H_{16}N_4O_5S$ (460.45): C, 59.99; H, 3.5; N, 12.16. Found: C, 59.94; H, 3.5; N, 11.97%.

*Ethyl 6-(4-hydroxyphenyl)-7,8-dioxo-9-phenyl-6,7,8,9-tetrahydro-1-thia-3,5,6,9-tetraazabenz[*cd*]azulene-2-carboxylate* (**4e**): Yellow solid, yield: 50%, m.p. 220–222 °C; IR (KBr) ν/cm^{-1} 3271–3184 (OH), 2883–2980 (CH aliphatic), 1741, 1699, 1649 (3 C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.22 (t, 3H, CH_3, J = 7.20 Hz), 4.23 (q, 2H, CH_2, J = 7.20 Hz), 6.92–7.70 (m, 9H, ArH), 8.48 (s, 1H, pyrimidine), 10.40 (s, 1H, OH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 461.89 $(M+2)^+$ (21.94), 460.89 $(M+1)^+$ (100), 459.89 $(M)^{+\cdot}$ (27.96). Anal. Calcd for $C_{23}H_{16}N_4O_5S$ (460.45): C, 59.99; H, 3.5; N, 12.16. Found: C, 59.93; H, 3.5; N, 11.96%.

*Ethyl 6-(4-chlorophenyl)-7,8-dioxo-9-phenyl-6,7,8,9-tetrahydro-1-thia-3,5,6,9-tetraazabenz[*cd*]azulene-2-carboxylate* (**4f**): Yellow solid, yield: 50.2%, m.p. 273–275 °C; IR (KBr) ν/cm^{-1} 2929–2983 (CH aliphatic), 1747, 1708, 1649 (3 C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.28 (t, 3H, CH_3, J = 7.00 Hz), 4.27 (q, 2H, CH_2, J = 7.00 Hz), 7.45–7.71 (m, 9H, ArH), 8.47 (s, 1H, pyrimidine). Anal. Calcd for $C_{23}H_{15}ClN_4O_5S$ (478.89): C, 57.68; H, 3.15; N, 11.69. Found: C, 57.50; H, 3.00; N, 11.51%.

Synthesis of compounds **5a–f**; *general procedure*

A mixture of **3a–f** (0.01 mol) and malonyl dichloride (2.11 g, 0.015 mol) in dry benzene (20 mL) was heated under reflux for 15 h. The reaction mixture was cooled, and the separated solid was filtered, dried and recrystallised from acetonitrile. Using this method the following compounds were prepared.

*Ethyl 6-phenyl-7,9-dioxo-10-phenyl-7,8,9,10-tetrahydro-6*H*-1-thia-3,5,6,10-tetraazacycloocta[*cd*]indene-2-carboxylate* (**5a**): Brick red solid, yield: 56.7%, m.p. 223–225 °C; IR (KBr) ν/cm^{-1} 2978–2931 (CH aliphatic), 1681 (3 overlapped C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.24 (m, 3H, CH_3), 3.41 (s, 2H, CH_2), 4.18 (m, 2H, CH_2), 7.32–7.67 (m, 10H, ArH), 8.14 (s, 1H, pyrimidine); MS (*m/z*) (relative abundance %): 458.40 $(M)^{+\cdot}$, (1.18). Anal. Calcd for $C_{24}H_{18}N_4O_4S$ (458.47): C, 62.86; H, 3.95; N, 12.22. Found: C, 62.76, H, 3.74; N, 12.00%.

*Ethyl 6-(4-methylphenyl)-7,9-dioxo-10-phenyl-7,8,9,10-tetrahydro-6*H*-1-thia-3,5,6,10-tetraazacycloocta[*cd*]indene-2-carboxylate* (**5b**): Brick red solid, yield: 63.5%, m.p. 239–241 °C; IR (KBr) ν/cm^{-1} 2978–2870 (CH aliphatic), 1750, 1681 [3 overlapped C=O)]; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.26 (m, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 4.22 (m, 2H, CH_2), 7.26–7.53 (m, 9H, ArH), 8.45 (s, 1H, pyrimidine). MS (*m/z*) (relative abundance %): 473 $(M+1)^{+\cdot}$, (1.54). Anal. Calcd for $C_{25}H_{20}N_4O_4S$ (472.50): C 63.54; H, 4.26; N, 11.85. Found: C, 63.39; H, 3.74; N, 11.51%.

*Ethyl 6-(4-ethylphenyl)-7,9-dioxo-10-phenyl-7,8,9,10-tetrahydro-6*H*-1-thia-3,5,6,10-tetraazacycloocta[*cd*]indene-2-carboxylate* (**5c**): Brick red solid, yield: 63.7%, m.p. 247–249 °C; IR (KBr) ν/cm^{-1} 2960–2927 (CH aliphatic), 1740, 1683, 1670 (3 overlapped C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.18 (br. t, 3H, CH_3), 1.23 (br. t, 3H, CH_3), 2.73 (br. q, 2H, CH_2), 3.70 (s, 2H, CH_2), 4.14 (br. q, 2H, CH_2), 6.90–7.60 (m, 9H, ArH), 8.00 (s, 1H, pyrimidine). MS (*m/z*) (relative abundance %): 485.20 $(M-1)^+$, (18.84). Anal. Calcd $C_{26}H_{22}N_4O_4S$ (486.53): C 64.18; H, 4.55; N, 11.51. Found: C, 64.00; H, 4.39, N, 11.62%.

*Ethyl 6-(2-hydroxyphenyl)-7,9-dioxo-10-phenyl-7,8,9,10-tetrahydro-6*H*-1-thia-3,5,6,10-tetraazacycloocta[*cd*]indene-2-carboxylate* (**5d**): Brick red solid, yield: 63.2%, m.p. 250–252 °C; IR (KBr) ν/cm^{-1} 3421–3244 (OH), 2981–2935 (CH aliphatic); 1740, 1685 (3 overlapped C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.23 (br. t, 3H, CH_3), 3.40 (s, 2H, CH_2), 4.18 (br. q, 2H, CH_2), 6.94–7.37 (m, 9H, ArH), 8.44 (s, 1H, pyrimidine), 10.40 (s, 1H, OH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 475.36 $(M+1)^{+\cdot}$, (7.80), 474.16 $(M)^+$ (14.60). Anal. Calcd $C_{24}H_{18}N_4O_4S$ (474.47): C, 60.74; H, 3.82; N, 11.80. Found: C, 60.54; H, 3.85, N, 11.76%.

*Ethyl 6-(4-hydroxyphenyl)-7,9-dioxo-10-phenyl-7,8,9,10-tetrahydro-6*H*-1-thia-3,5,6,10-tetraazacycloocta[*cd*]indene-2-carboxylate* (**5e**): Brick red solid, yield: 56.9%, m.p. 250–252 °C; IR (KBr) ν/cm^{-1} 3350–3255 (OH), 2954–2848 (CH aliphatic); 1741, 1683 (3 overlapped C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.29 (br. t, 3H, CH_3), 3.44 (s, 2H, CH_2), 4.22 (br. q, 2H, CH_2), 6.90–7.80 (m, 9H, ArH), 8.19 (s, 1H, pyrimidine), 12.43 (s, 1H, OH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 474.80 $(M)^+$ (100). Anal. Calcd $C_{24}H_{18}N_4O_5S$ (474.47): C, 60.74; H, 3.82; N, 11.80. Found: C, 60.70; H, 3087, N, 11.86%.

*Ethyl 6-(4-chlorophenyl)-7,9-dioxo-10-phenyl-7,8,9,10-tetrahydro-6*H*-1-thia-3,5,6,10-tetraazacycloocta[*cd*]indene-2-carboxylate* (**5f**): Brick red solid, yield: 65.0%, m.p. 220–222 °C; IR (KBr) ν/cm^{-1} 2873–2978 (CH aliphatic), 1740, 1701, 1685 (3 overlapped C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.23 (m, 3H, CH_3), 3.43 (s, 2H, CH_2), 4.23 (m, 2H, CH_2), 7.21–7.54 (m, 9H, ArH), 8.20 (s, 1H, pyrimidine); MS (*m/z*) (relative abundance %): 492.06 $(M)^+$ (100). Anal. Calcd for $C_{24}H_{17}ClN_4O_4S$ (492.92): C 58.47; H, 3.47; N, 11.36. Found: C, 58.25; H, 3.70, N, 10.96%.

*Ethyl 3-amino-5-phenylamino-4-imino-3,4-dihydrothieno[3,4-*d*]pyrimidine-7-carboxylate* (**6**): A solution of **2** (3.43 g, 0.01 mol) in absolute ethanol (20 mL) was heated on a water bath for 10–15 min until the solid dissolved. Hydrazine hydrate (80%) (11 mL, 0.22 mol) was added and heating was continued for 10 minutes more. The reaction mixture was cooled, and the separated solid was filtered, dried and recrystallised from ethanol to give the title compound as a yellowish brown solid, yield: 82.0%; m.p. 210–212 °C; IR (KBr) ν/cm^{-1} 3400, 3360–3280 (2 NH, NH_2), 2950–3000 (CH aliphatic), 1653 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, 3H, CH_3, J = 6.80 Hz), 4.22 (q, 2H, CH_2, J = 7.00 Hz), 5.87 (s, 1H, =NH, D_2O exchangeable), 7.15–7.47 (m, 5H, ArH), 8.47 (s, 1H, pyrimidine), 11.40 (br s, 2H, NH_2, D_2O exchangeable), 13.40 (s, 1H, NH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 331 $(M+2)^+$ (4.52), 330 $(M+1)^+$ (12.55), 329 $(M)^+$ (47.30). Anal. Calcd for $C_{15}H_{15}N_5O_2S$ (329.37): C, 54.69; H, 4.59; N, 21.26. Found: C, 54.80; H, 4.70; N, 21.03%.

Ethyl 10-phenylamino-2-methyl-3-oxo-3,4-dihydro-2H-thieno[3',4':4,5] pyrimido[1,6-b][1,2,4]triazine-8-carboxylate (**7**): A mixture of **6** (0.329 g, 0.001 mol), and 2-chloropropionoyl chloride (0.127 g, 0.001 mol) in dry benzene (10 mL) and few drops of dry pyridine was heated under reflux for 12 h. The reaction mixture was cooled, water was added and the separated solid was filtered, dried and recrystallised from ethanol to give a brown solid, yield: 52.2%; m.p. 250–252 °C; IR (KBr) ν/cm^{-1} 3307, 3246 (2 NH), 2929–2980 (CH aliphatic), 1680, 1668 (2 overlapped C=O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, 3H, CH_3, J = 7.20 Hz), 1.57 (d, 3H, CH_3, J = 6.90 Hz), 4.26 (q, 2H, CH_2, J = 6.90 Hz), 5.02 (q, 1H, CH, J = 6.60 Hz), 7.12–7.74 (m, 5H, ArH), 8.45 (s, 1H, pyrimidine), 11.31 (s, 1H, NH, D_2O exchangeable), 11.93 (s, 1H, NH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 381 (M-2)$^+$ (0.07). Anal. Calcd for $C_{18}H_{17}N_5O_3S$ (383.42): C, 56.38; H, 4.47; N, 18.26. Found: C, 56.32; H, 4.46; N, 18.59%.

Ethyl 10-phenylamino-2,3-dioxo-3,4-dihydro-2H-thieno[3',4':4,5] pyrimido[1,6-b][1,2,4]triazine-8-carboxylate (**8**): A mixture of **6** (0.329 g, 0.001 mol) and oxalyl chloride (0.19 g, 0.0015 mol) in dry benzene (15 mL) was heated under reflux for 14 h. The reaction mixture was cooled, and the separated solid was filtered, dried and recrystallised from acetonitrile to give an orange solid, yield: 52.2%; m.p. 260–262 °C; IR (KBr) ν/cm^{-1} 3184 (2 NH), 2981–2927 (CH aliphatic), 1720, 1685, 1647 (3 overlapped C=O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (t, 3H, CH_3 J = 6.90 Hz), 4.27 (q, 2H, CH_2 J = 6.90 Hz), 7.03–7.73 (m, 5H, ArH), 8.45 (s, 1H, pyrimidine), 10.47 (s, 1H, NH, D_2O exchangeable), 12.44 (s, 1H, NH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 384 (M+1)$^+$ (0.22), Anal. Calcd for $C_{17}H_{13}N_5O_4S$ (383.37): C, 53.25 H, 3.41; N, 18.26. Found: C, 53.64; H, 3.32; N, 18.00%.

Ethyl 11-phenylamino-2,4-dioxo-2,3,4,5-tetrahydrothieno[3',4':4,5] pyrimido[1,6-b][1,2,4]triazepine-9-carboxylate (**9**): A mixture of **6** (0.329 g, 0.001 mol) and malonyl dichloride (2.11 g, 0.015 mol) in dry benzene (15 mL) was heated under reflux for 15 h. The reaction mixture was cooled, and the separated solid was filtered, dried and recrystallised from acetonitrile to give a yellowish-brown solid, yield: 75.5%; m.p. 225–227 °C; IR (KBr) ν/cm^{-1} 3232, 3188 (2 NH), 2926–2850 (CH aliphatic), 1668, 1647 (3 overlapped C=O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22 (br. t, 3H, CH_3), 3.70 (s, 2H, CH_2), 4.12 (br. q, 2H, CH_2), 7.12–7.46 (m, 5H, ArH), 8.44 (s, 1H, pyrimidine), 10.40 (s, 1H, NH, D_2O exchangeable), 11.60 (s, 1H, NH, D_2O exchangeable); MS (*m/z*) (relative abundance %): 396 (M-1)$^+$ (0.31). Anal. Calcd for $C_{18}H_{15}N_5O_4S$ (397.40): C, 54.39; H 3.80; N, 17.62. Found: C, 54.75; H, 3.76; N, 17.65%.

Received 9 March 2012; accepted 7 June 2012
Paper 1201203 doi: 10.3184/174751912X13400242909892
Published online: 8 August 2012

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