Synthesis of dihydrobenzo[*b*]pyrimido[4,5-*e*][1,4]thiazepines; derivatives of a novel ring system

Marzieh Akbarzadeh, Mehdi Bakavoli*, Hossein Eshghi, Ali Shiri and Javad Tajabadi

Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, 91775-1436 Mashhad, Iran

Several derivatives of the novel dihydrobenzo[*b*]pyrimido[4,5-*e*][1,4]thiazepine ring system have been synthesised through the initial heterocyclisation of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine with *o*-aminothiophenol followed by treatment with various secondary amines in boiling ethanol.

Keywords: dihydrobenzo[*b*]pyrimido[4,5-*e*][1,4]thiazepine, heterocyclisation, 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine

Nitrogen-containing heterocycles are important targets in synthesis because of their biological properties and their roles as pharmacophores of many biologically active compounds.[1] Among them, 1,4-benzothiazepine exhibit important biological activities in the central nervous system[2-5] which are considered as antipsychotic,[3-5] antihypertensive and antidepressant agents.[6] 1,4-Benzothiazepines have also emerged as privileged structures with cardioprotective effect for the treatment of sudden cardiac death and myocardial infarction.[7-9]

They also act as angiotensin converting enzyme inhibitors, calmodulin antagonists, bradykinin receptor agonists and Ca^{2+} antagonists.[10] Some of the widely used benzo[*b*][1,4]thiazepine drugs are shown in Fig. 1.

Various methods have been reported for the synthesis of benzo[*b*][1,4]thiazepines. Some of the more recent ones involve Cu-catalysed coupling of 2-iodoanilines and 2-mercaptoacetate,[11] reductive ring expansion reactions of cyclic ketoximes using dichloroaluminum hydride,[12] diethylamine promoted α-sulfenylation reaction followed by subsequent acid catalysed condensation reaction[13] and coupling–isomerisation reaction of an electron poor (hetero)aryl halide with a terminal propargyl alcohol followed by cyclocondensation with 2-mercapto anilines.[14]

The literature survey reveals that only a few synthetic procedures have been reported for the synthesis of pyrimidobenzothiazepines. These methods include the condensation of 5-amino-4,6-bis-(arylthio)pyrimidines and carboxylic acids through Bischler–Napieralski-type reactions,[15] Mannich-type cyclisation of 6-[(2-aminophenyl)thio]uracils followed by alkylation at N1 by a one-pot Vorbruggen reaction[16] and rearrangement of an azide compounds.[17]

Due to our interest in the synthesis of various fused heterocyclic derivatives with pyrimidine core,[18-24] we now report a convenient method for the synthesis of 2-substituted-4-methyl-5,11-dihydrobenzo[*b*]pyrimido[4,5-*e*][1,4]thiazepine derivatives (**6a–g**) as members of a new heterocyclic system.

Results and discussion

The precursor, 6-methylpyrimidine-2,4-(1H,3H)-dione (**1**), was prepared by treatment of thiourea and ethylacetoacetate according to the previously published method.[25] The reaction of (**1**) with formaldehyde in aqueous 5% NaOH solution at room temperature gave 5-(hydroxymethyl)-6-methylpyrimidine-2,4(1H,3H)-dione (**2**)[26] which was subsequently converted with a little modification into 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine (**3**) in boiling $POCl_3$ and $N(i\text{-}Pr)_2Et$.[27] The compound (**3**) was treated with *o*-aminothiophenol (**4**) as a binucleophile at –15 ºC in $CHCl_3$. (Scheme 1)

The evidence which confirms both 4-Cl and the chloromethyl group on the pyrimidine core were substituted by sulfur and amino groups of *o*-aminothiophenol, respectively, and formation of compound (**5**) can be deduced from previously published methods. The comparison of the ^1H chemical shifts of methylene group bonded to sulfur or nitrogen in thiazepine moieties with the similar ones in the reported literatures (δ 3.98 ppm for CH_2S [28], δ 4.26 ppm for CH_2N [29]) revealed that the data are in accordance with the ^1H chemical shifts of the CH_2 in compound (**5**) (δ 3.90 ppm) confirming the S_NAr displacement of the 4-Cl function with the thiol group of compound (**4**).

Moreover, computational evaluations can be used for the elucidation of ambiguity in the structure of the seven membered heterocycle (**5**). First, compound (**5**) and its regioisomer which

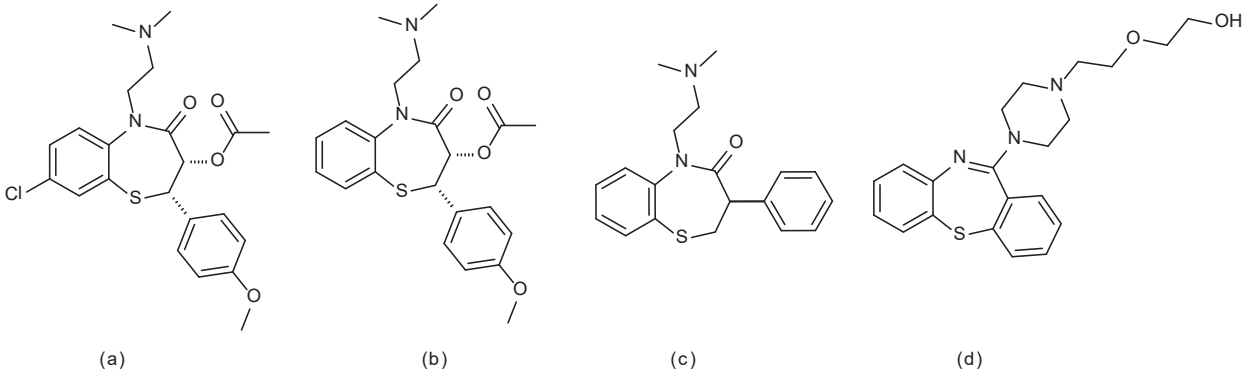
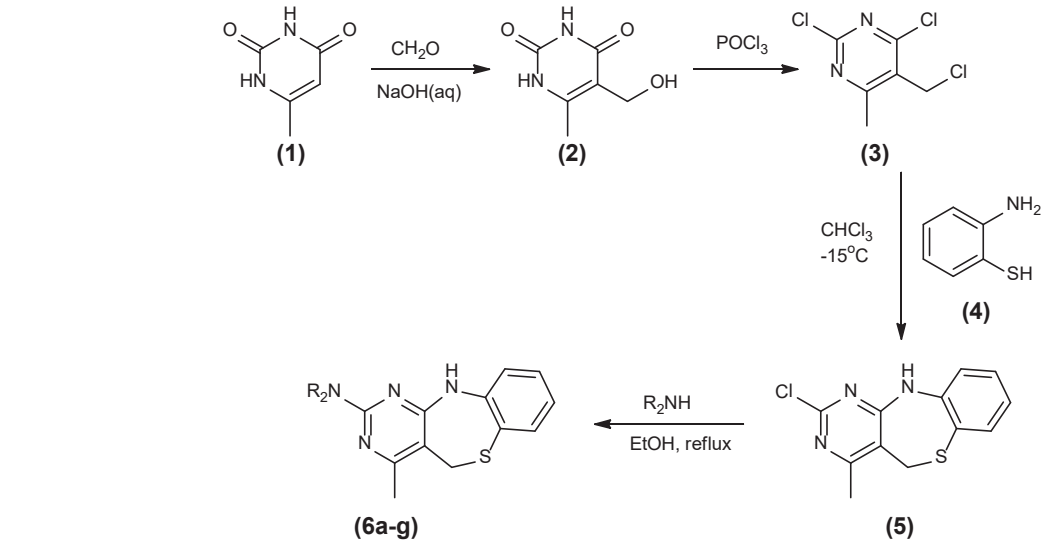
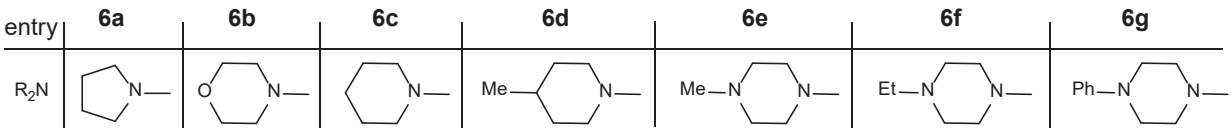


Fig. 1 Examples of some clinically used benzothiazepine derivatives: (a) clentiazem (calcium channel blocker); (b) diltiazem (calcium channel blocker); (c) thiazesim (antidepressant); (d) quetiapine (antipsychotic agent).

* Correspondent. E-mail: mbakavoli@um.ac.ir; mbakavoli@yahoo.com





Scheme 1

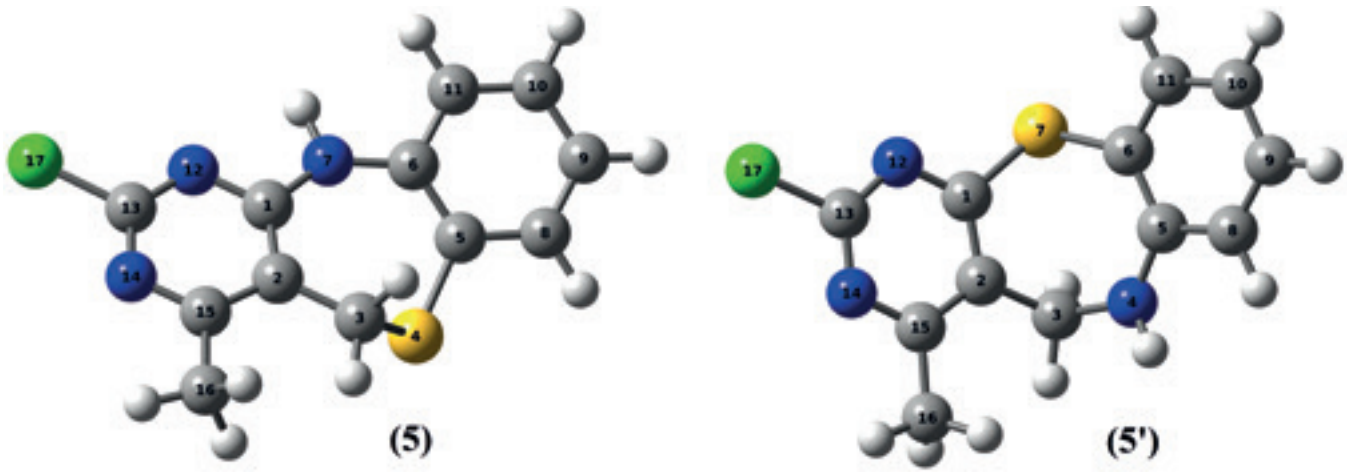


Fig. 2 The optimised structures of (**5**) and (**5'**).

we named it (**5′**) were optimised at mPW1PW91/6-31G(d) level of theory in the gas phase (Fig. 2).

The stationary points were characterised by frequency calculations. The comparison of Gibbs energy difference in the gas phase indicated that isomer (**5**) was more thermodynamically stable than isomer (**5'**) (15.9 kcal mol^{-1}).

As we recently applied GIAO/^{13}C NMR calculations for elucidation of organic compound structures,[30, 31] therefore, the GIAO ^{13}C chemical shifts for (**5**) and (**5′**) were computed by Sarotti and Pellegrinet method [32] at the mPW1PW91/6-31G(d)// mPW1PW91/6-31G(d) level of theory. The experimental and unscaled GIAO ^{13}C chemical shifts of compounds (**5**) and (**5′**) using multistandard approach (MSTD) have been represented in Table 1. As shown in Table 1, the differences between calculated and experimental chemical shifts demonstrated that the formation of compound (**5**) is preferred. The ^{1}H NMR spectrum of compound (**5**) shows two singlet signals at δ 2.56 and 3.90 ppm, attributed to CH_3 and CH_2S hydrogens, respectively. The doublet and a triplet signals between 7.07–7.13 ppm and 7.29–7.49 ppm assignable to the hydrogens of aryl group as well as a broad singlet signal at δ 8.22 ppm due to NH moiety confirm the structure (**5**). The IR spectrum of (**5**) displays the stretching vibration bands at 3468 cm^{-1} due to NH group.

Compound **5** on treatment with excess amount of various secondary amines in boiling ethanol underwent the chlorine substitution to give derivatives of the new heterocyclic ring system, dihydrobenzo[*b*]pyrimido[4,5-*e*][1,4]thiazepines (**6a–g**) in good to excellent yields. All the physical, chemical and spectral data were in agreement with the newly proposed structures. The ^{1}H NMR spectrum of product (**6a**), as an example, showed a triplet signal at 1.97 and 3.57 ppm due to the methylene protons of pyrrolidine ring, a singlet signal at 2.37 ppm indicating the presence of methyl group on the pyrimidine ring and a singlet signal at δ 3.89 ppm attributed to CH_2S hydrogens. The signals of the aryl hydrogens and D_2O exchangeable broad peak of NH moiety were also appeared around 6.9–7.41 and 7.28 ppm,

Table 1 Experimental and unscaled GIAO ^{13}C chemical shift values (δ), in ppm, for structures (**5**) and (**5′**) (atom numbering is according to Fig. 2)

No. of carbon	δ	Δδ[a]	Exp.	No. of carbon	δ	Δδ[a]	Exp.	No. of carbon	δ	Δδ[a]	Exp.
5(C_{16})	22.36	1.13	21.23	**5**(C_9)	121.84	−2.02	123.86	**5**(C_6)	140.01	−0.42	140.43
5′(C_{16})	22.25	1.02		**5′**(C_{10})	118.08	−5.78		**5′**(C_5)	142.74	2.31	
5(C_3)	35.21	2.45	32.76	**5**(C_{10})	128.41	0.43	127.98	**5**(C_1)	156.33	0.67	155.66
5′(C_3)	42.42	9.66		**5′**(C_9)	129.25	1.27		**5′**(C_{15})	164.25	8.59	
5(C_2)	114.64	0.01	114.63	**5**(C_5)	130.47	1.42	129.05	**5**(C_{15})	164.51	4.44	160.07
5′(C_6)	113.88	−0.75		**5′**(C_2)	133.71	4.66		**5′**(C_{13})	166.26	6.19	
5(C_{11})	120.53	−1.63	122.16	**5**(C_8)	134.13	0.82	133.31	**5**(C_{13})	165.15	1.42	163.73
5′(C_8)	115.86	−6.3		**5′**(C_{11})	135.4	2.09		**5′**(C_1)	174.82	11.09	

[a]Δδ, the difference between the calculated and experimental (Exp.) ^{13}C chemical shifts.

respectively. The IR spectrum of compound (**6a**) revealed the existence of the stretching vibration band of CH_2 around 2800–2900 cm^{-1} in the product confirming the occurrence of substitution.

Conclusion

In conclusion, we have developed a novel and efficient synthetic method for the preparation of 5,11-dihydrobenzo[*b*] pyrimido[4,5-*e*][1,4]thiazepine derivatives (**6a–g**). The initial treatment of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine (**3**) with *o*-aminothiophenol in $CHCl_3$ leads to simultaneous substitution and heterocyclisation. The reaction of the synthesised compound (**5**) with various *sec*-amines led to the substitution of the 2-Cl atom to give the derivatives of a new ring system (**6a–g**). Further investigation towards construction of other novel heterocyclic ring systems is underway in our laboratory.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on Avatar 370 FT-IR Thermo Nicolet and only noteworthy absorptions were listed. The ^1H NMR (300 MHz) and the ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance DRX-400 Fourier transformer spectrometer. Chemical shifts were reported in ppm downfield from TMS as internal standard. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyser.

*2-Chloro-4-methyl-5,11-dihydrobenzo[*b*]pyrimido[4,5-*e*][1,4] thiazepine* (**5**): A solution of *o*-aminothiophenol (**4**) (1 mmol, 0.12 g) in $CHCl_3$(1 mL) was added dropwise to a cooled (–15°C) stirred solution of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine (**3**) (1 mmol, 0.21 g) and Et_3N (2 mmol, 0.2 g) in $CHCl_3$ (5 mL). The resulting mixture was allowed to warm to room temperature for 5 h, then water (10 mL) was added and the mixture was extracted with $CHCl_3$ (3× 10 mL). The combined organic solvents were dried over anhydrous sodium sulfate and concentrated. The resulting solid was purified using silica gel column chromatography $CHCl_3$: methanol (30:1) as eluent. Yield 74%; white powder; m.p. 200–203 °C, IR (KBr disc) 3468, 3068, 3002, 2917, 2847, 1608, 1544, 1524, 1478, 1446, 1332, 1310, 1222, 1159 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 7.7–7.13 (m, 2H, ArH), 7.32 (td, *J* = 6.9 Hz, *J* = 1.1 Hz, 1H, ArH), 7.48 (dd, *J* = 6.9 Hz, *J* = 1.1 Hz, 1H, ArH), 8.22 (s, 1H, NH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 32.8, 114.6, 122.2, 123.9, 127.9, 129.1, 133.3, 140.4, 155.7, 160.1, 163.7, MS (*m/z*) 263.8 (M^+), 228 (M - Cl), 187 (M – C_6H_4). Anal. calcd for $C_{12}H_{10}ClN_3S$: C, 54.65; H, 3.82; N, 15.93; S, 12.16; found: C, 54.56; H, 3.74; N, 15.87; S, 12.00%.

*Synthesis of 2-substituted-4-methyl-5,11-dihydrobenzo[*b*] pyrimido-[4,5-e][1,4]thiazepine (***6a–g***); general procedure*

The appropriate secondary amine (5 mmol), was added to a stirred solution of 2-chloro-4-methyl-5,11-dihydrobenzo[*b*]pyrimido[4,5-*e*] [1,4]thiazepine (**5**) (1 mmol, 0.26 g) in EtOH (10 mL) and the solution was refluxed. After the completion of the reaction which was monitored by TLC using chloroform: methanol (30:1), the solvent was concentrated and the resulting white precipitate was filtered, washed with water (2 × 20 mL) and dried.

*4-Methyl-2-(pyrrolidin-1-yl)-5,11-dihydrobenzo[*b*]pyrimido[4,5-*e*] [1,4]thiazepine* (**6a**): Yield 74%; white powder; m.p. 178–180 °C, IR (KBr disc) 3384, 3056, 2951, 2859, 1597, 1548, 1472, 1400, 1336, 1275, 1175, 1127 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (t, *J* = 6.9 Hz, 4H, CH_2), 2.37 (s, 3H, CH_3), 3.57 (t, *J* = 6.9 Hz, 4H, CH_2–N), 3.89 (s, 2H, CH_2), 6.92 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H, ArH), 6.97 (dd, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H, ArH), 7.21 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H, ArH), 7.28 (s, 1H, NH), 7.39 (d, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H, ArH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 25.5, 32.9, 54.4, 105.8, 120.9, 121.9, 127.0, 128.3, 133.2, 142.2, 159.1, 159.5, 163.5, MS (*m/z*) 298 (M^+), 228 (M - C_4H_8N). Anal. calcd for $C_{16}H_{18}N_4S$: C, 64.40; H, 6.08; N, 18.78, 10.74; found: C, 64.34; H, 5.98; N, 18.71; S, 10.63%.

*4-(4-Methyl-5,11-dihydrobenzo[*b*]pyrimido[4,5-*e*][1,4]thiazepin-2-yl)morpholine* (**6b**): Yield 68%; white powder; m.p. 189–191 °C, IR (KBr disc) 3329, 3060, 2983, 2944, 2889, 2844, 1598, 1573, 1557, 1476, 1405, 1357, 1301, 1262, 1190, 1102, 1071 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 3.75–3.88 (m, 10H, CH_2, CH_2–O, CH_2–N), 6.94–6.95 (m, 2H, ArH), 7.21 (t, *J* = 7.5 Hz, 1H, ArH), 7.31 (s, 1H, NH), 7.88 (d, *J* = 7.5 Hz, 1H, ArH), 8.05 (s, 1H, NH) , ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 32.9, 43.4, 66.9, 105.9, 121.0, 121.9, 127.1, 128.3, 133.2, 142.2, 159.0, 159.5, 163.6, MS (*m/z*) 314 (M^+), 257 (M – C_3H_7O). Anal. calcd for $C_{16}H_{18}N_4OS$: C, 61.12; H, 5.77; N, 17.82; S, 10.20; found: C, 61.05; H, 5.71; N, 17.74; S, 10.12%.

*4-Methyl-2-(piperidin-1-yl)-5,11-dihydrobenzo[*b*]pyrimido[4,5-*e*] [1,4]thiazepine* (**6c**): Yield 82%; white powder; m.p. 150–153°C, IR (KBr disc) 3260, 3072, 3015, 2925, 2859, 1605, 1576, 1549, 1525, 1474, 1400, 1361, 1259, 1192, 1135 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 1.60–1.67 (m, 6H, CH_2), 2.35 (s, 3H, CH_3), 3.15 (t, *J* = 7.5 Hz, 4H, CH_2–N), 3.76 (t, *J* = 5.3 Hz, 4H, CH_2–N), 3.88 (s, 2H, CH_2), 6.90–6.97 (m, 2H, ArH), 7.24 (td, *J* = 7.9 Hz, *J* = 1.5 Hz, 1H, ArH), 7.26 (s, 1H, NH), 7.4 (dd, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H, ArH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 24.9, 25.8, 32.9, 44.7, 104.8, 120.9, 121.6, 126.9, 128.2, 133.1, 142.4, 158.9, 159.6, 163.5, MS (*m/z*) 312 (M^+), 228 (M – $C_5H_{10}N$). Anal. calcd for $C_{17}H_{20}N_4S$: C, 65.35; H, 6.45; N, 17.93; S, 10.26; found: C, 65.27; H, 6.39; N, 17.88; S, 10.19%.

*4-Methyl-2-(4-methylpiperidin-1-yl)-5,11-dihydrobenzo[*b*] pyrimido[4,5-*e*][1,4]thiazepine* (**6d**): Yield 62%; white powder; m.p. 130–132 °C, IR (KBr disc) 3267, 3064, 3011, 2962, 2949, 2916, 2850, 1602, 1575, 1523, 1473, 1452, 1366, 1358, 1303, 1255, 1191, 1131 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, *J* = 4.5, 3H, CH_3), 1.10–1.19 (m, 1H, CH), 1.59–1.69 (m, 2H, CH), 2.33 (s, 1H, CH_3), 2.78 (m, 2H, CH–N), 3.84 (s, 2H, CH_2), 4.69 (m, 2H, CH–N), 6.88–6.93 (m, 3H, ArH), 7.18 (t, *J* = 5.7 Hz, 1H, ArH), 7.26 (s, 1H, NH), 7.37 (d, *J* = 5.7 Hz, 1H, ArH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 22.5, 31.4, 32.9, 34.1, 44.1, 104.9, 120.9, 121.7, 126.9, 128.2, 133.1, 142.4, 158.9, 159.6, 163.5, MS (*m/z*) 326 (M^+), 271 (M – $C_4H_{10}N$). Anal. calcd for $C_{18}H_{22}N_4S$: C, 66.22; H, 6.79; N, 17.16; S, 9.82; found: C, 66.17; H, 6.71; N, 17.12; S, 9.74%.

*4-Methyl-2-(4-methylpiperazin-1-yl)-5,11-dihydrobenzo[*b*] pyrimido[4,5-*e*][1,4]thiazepine* (**6e**): Yield 89%; white powder; m.p.

160–163 °C, IR (KBr disc) 3397, 2956, 2925, 2869, 2833, 2787, 2760, 2733, 1598, 1548, 1527, 14775, 1445, 1401, 1356, 1323, 1298, 1260, 1196, 1143, 1048 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H, CH_3–N), 2.40 (s, 3H, CH_3), 2.54 (t, *J* = 5 Hz, 4H, CH_2–N), 3.85–3.87 (m, 6H, CH_2, CH_2–N), 6.91–9.96 (m, 2H, ArH), 7.21 (td, *J* = 5.7 Hz, *J* = 1.5 Hz, 1H, ArH), 7.3 (s, 1H, NH), 7.39 (d, *J* = 5.7 Hz, 1H, ArH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 32.9, 43.5, 46.1, 54.9, 105.7, 120.9, 121.9, 126.7, 128.3, 133.1, 142.2, 158.9, 159.5, 163.6), MS (*m/z*) 327 (M^+), 228 (M – $C_5H_{11}N_2$). Anal. calcd for $C_{17}H_{21}N_5S$: C, 62.36; H, 6.46; N, 21.39; S, 9.79; found: C, 62.31; H, 6.37; N, 21.32; S, 9.71%.

*2-(4-Ethylpiperazin-1-yl)-4-methyl-5,11-dihydrobenzo[*b*]pyrimido[4,5-*e*][1,4]thiazepine* (**6f**): Yield 74%; white powder; m.p. 157–159 °C, IR (KBr disc) 3272, 3060, 2970, 2925, 2864, 2794, 2761, 1675, 1603, 1574, 1547, 1521, 1472, 1401, 1354, 1354, 1294, 1254, 1123 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.5 Hz, 3H, CH_3), 2.36 (s, 1H, CH_3), 2.46–2.54 (m, 6H, CH_2, CH_2–N), 3.84 (t, *J* = 7.5 Hz, 4H, CH_2–N), 3.88 (s, 2H, CH_2), 6.91–6.97 (m, 2H, ArH), 7.22 (td, *J* = 8.5 Hz, *J* = 1.5 Hz, 1H, ArH), 7.23 (s, 1H, NH), 7.40 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H, ArH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 22.4, 32.9, 43.3, 48.7, 52.9, 105.8, 120.7, 122.0, 126.8, 128.2 133.2, 142.3, 158.9, 159.5, 163.6, MS (*m/z*) 341 (M^+), 270 (M – C_4H_9N). Anal. calcd for $C_{18}H_{23}N_5S$: C, 63.31; H, 6.79; N, 20.51; S, 9.39; found: C, 63.25; H, 6.71; N, 20.43; S, 9.22%.

*4-Methyl-2-(4-phenylpiperazin-1-yl)-5,11-dihydrobenzo[*b*]pyrimido[4,5-*e*][1,4]thiazepine* (**6g**): Yield 87%; white powder; m.p. 130–132 °C, IR (KBr disc) 3387, 3064, 2966, 2900, 2810, 2676, 1596, 1575, 1552, 1524, 1476, 1405, 1368, 1266, 1229, 1188, 1041, 1000 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 3.22 (t, 4H, *J* = 5 Hz, CH_2), 3.85 (s, 2H, CH_2), 3.93 (t, *J* = 5 Hz, 4H, CH_2–N), 6.86–7.39 (m, 10H, ArH, NH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 32.9, 43.8, 49.5, 105.8, 116.5, 120, 120.9, 121.9, 127.1, 128.3, 129.2, 133.2, 142.2, 151.5, 159.0, 159.5, 163.6, MS (*m/z*) 389 (M^+), 252 (M – C_7H_7NS). Anal. calcd for $C_{22}H_{23}N_5S$: C, 67.84; H, 5.95; N, 17.98; S, 8.23; found: C, 67.78; H, 5.88; N, 17.93; S, 8.18%.

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