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Efficient synthesis of functionalized 2,4-diaminothiazoles from tetramethylguanidine, isothiocyanates, and α -bromoketones

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The Hantzsch method for thiazole synthesis is modified via the reaction of α -bromocarbonyl compounds with 2-(amidosulfanylenemethyl)-1,1,3,3-tetramethylguanidines (prepared *in situ* from tetramethylguanidine and aroylisothiocyanates), to afford functionalized 2,4-diaminothiazoles in good yields.

Keywords: diaminothiazole; aroylisothiocyanate; α -bromoketones; tetramethylguanidine; MCR

1. Introduction

The thiazole ring system is commonly found in many pharmaceutically important molecules. Numerous natural products containing this heterocycle have been isolated and exhibit significant biological activities (1). Among aromatic heterocycles, thiazoles occupy a prominent position in the drug discovery process (2) and this ring structure is found in several marketed drugs. Amino-thiazoles are known to be ligands of estrogen receptors (3) as well as a novel class of adenosine receptor antagonists (4). Thiazoles are also useful synthetic intermediates and common sub-structures in numerous bioactive compounds. Thus, the thiazole nucleus has been much studied in organic and medicinal chemistry. Several methods (5, 6) for the synthesis of thiazole derivatives have been developed, among which the most widely used method is Hantzsch's synthesis (7–9) (reaction between α -halocarbonyl compounds and thioamides, thioureas, thiocarbamic acids, or dithiocarbamic acids).

2. Results and discussion

As part of our current studies on the development of new routes in thiazole synthesis (10–12), we describe an efficient one-pot method for the synthesis of functionalized 2,4-diaminothiazole derivatives using 1,1,3,3-tetramethylguanidine (**1**) as a nucleophile. The reaction of **1** and isothiocyanates **2** in the presence of α -bromoketones **3** in acetone at room temperature

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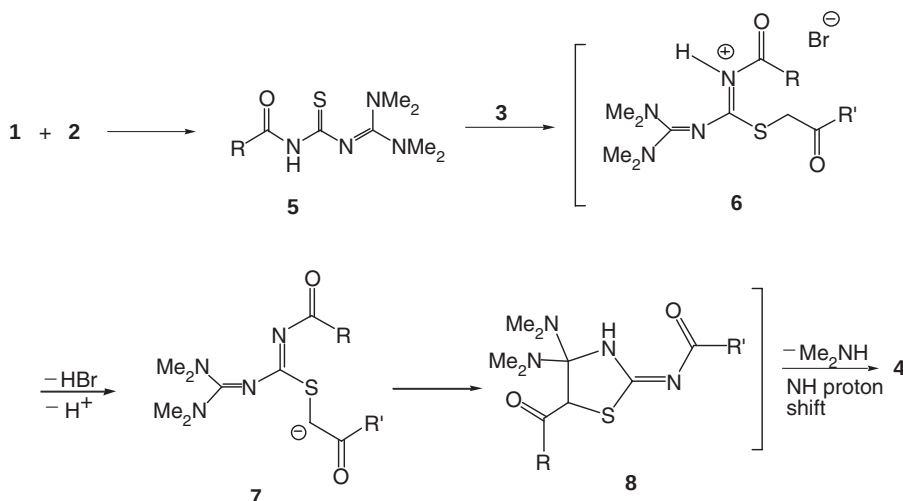
Table 1. Reaction of tetramethylguanidine, isothiocyanates, and α -bromoketones.

	1	2a–h	3a–f	4a–aa	
	Isothiocyanate 2		α -Bromoketone 3		
	R		R'	Product 4	Yield (%)
2a	PhCO	3a	CO ₂ Et	4a	92
2a	PhCO	3b	4-BrC ₆ H ₄	4b	95
2a	PhCO	3c	4-MeOC ₆ H ₄	4c	84
2b	2-ClC ₆ H ₄ CO	3a	CO ₂ Et	4d	67
2b	2-ClC ₆ H ₄ CO	3b	4-BrC ₆ H ₄	4e	73
2b	2-ClC ₆ H ₄ CO	3c	4-MeOC ₆ H ₄	4f	68
2c	4-O ₂ NC ₆ H ₄ CO	3a	CO ₂ Et	4g	58
2d	4-MeC ₆ H ₄ CO	3a	CO ₂ Et	4h	93
2d	4-MeC ₆ H ₄ CO	3b	4-BrC ₆ H ₄	4i	90
2d	4-MeC ₆ H ₄ CO	3c	4-MeOC ₆ H ₄	4j	87
2e	<i>t</i> -BuCO	3a	CO ₂ Et	4k	65
2e	<i>t</i> -BuCO	3b	4-BrC ₆ H ₄	4l	56
2e	<i>t</i> -BuCO	3c	4-MeOC ₆ H ₄	4m	60
2f	Ph	3d	Ph	4n	81
2f	Ph	3c	4-MeOC ₆ H ₄	4o	86
2f	Ph	3e	4-FC ₆ H ₄	4p	81
2f	Ph	3f	4-ClC ₆ H ₄	4q	88
2f	Ph	3b	4-BrC ₆ H ₄	4r	87
2f	Ph	3a	CO ₂ Et	4s	84
2g	4-MeOC ₆ H ₄	3c	4-MeOC ₆ H ₄	4t	75
2g	4-MeOC ₆ H ₄	3b	4-BrC ₆ H ₄	4u	84
2g	4-MeOC ₆ H ₄	3a	CO ₂ Et	4v	84
2h	Et	3d	Ph	4w	84
2h	Et	3c	4-MeOC ₆ H ₄	4x	83
2h	Et	3e	4-FC ₆ H ₄	4y	79
2h	Et	3f	4-ClC ₆ H ₄	4z	97
2h	Et	3b	4-BrC ₆ H ₄	4aa	96

produced functionalized diaminothiazoles **4** in good yields after purification (Table 1). In this procedure, we have modified the Hantzsch method for thiazole synthesis *via* the reaction of 2-(sulfanylenemethyl)-1,1,3,3-tetramethylguanidines (**5**; see Scheme 1) with α -bromocarbonyl compounds. Thus, various thiourea derivatives were prepared from **1** and **2**. Functionalized 2,4-diaminothiazoles **4** were obtained from the reaction of these thioureas with **3**.

The structures of compounds **4a–4aa** were deduced from their IR, ¹H NMR, and ¹³C NMR. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The ¹H NMR spectrum of **4a** in CDCl₃ showed two singlets for methyl (δ = 3.16) and NH (δ = 9.90) protons, along with characteristic signals for the ethyl and phenyl groups. The carbonyl group resonances in the ¹³C NMR spectra of **4a** appear at 165.4, 170.5, and 185.0 ppm. The mass spectrum of **4a** displayed the molecular ion peak at *m/z* = 347. The ¹H NMR and ¹³C NMR spectra of **4b–4aa** were similar to those for **4a** except for the side chains, which exhibited characteristic resonances in the appropriate regions of the spectrum.

Mechanistically, the reaction starts with the formation of 2-(sulfanylenemethyl)-1,1,3,3-tetramethylguanidines (**5**) from tetramethylguanidine (**1**) and isothiocyanates (**2**). Subsequent nucleophilic alkylation of thiourea derivative **5** with α -bromoketones (**3**) yields intermediate **6**. This intermediate undergoes HBr elimination and subsequent enolization to generate **7**, which



Scheme 1. Proposed mechanism for the formation of compounds 4.

is transformed to the heterocyclic intermediate **8** by intramolecular cyclization reaction. Subsequent NH proton shift and loss of dimethylamine afford functionalized 2,4-diaminothiazoles **4** (Scheme1).

3. Conclusions

In conclusion, we have described a convenient route for the synthesis of functionalized 2,4-diaminothiazoles from tetramethylguanidine and isothiocyanates in the presence of α -bromoketones. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The procedure described here also provides an efficient one-pot methodology for the preparation of functionalized 2,4-diaminothiazoles.

4. Experimental

4.1. General

All purchased solvents and chemicals were of analytical grade and used without further purification. Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. The ^1H and ^{13}C spectra were obtained with a BRUKER DRX-300 AVANCE instrument using CDCl_3 as the applied solvent and TMS as the internal standard at 300 and 75 MHz, respectively. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer.

4.2. General procedure for the preparation of compounds 4

To a stirred solution of the isothiocyanate (**2**, 2 mmol) in acetone (10 ml) was added, at r.t., 0.23 g (2 mmol) of tetramethylguanidine (**1**). The mixture was stirred at r.t. for 30 min. Then, the

α -bromoketone **3** (2 mmol) was added to the reaction mixture and stirred at r.t. After completion of the reaction (8–12 h; TLC (AcOEt/hexane 2:1)), the solvent was evaporated, and the residue was purified by column chromatography (silica gel (230–240 mesh; Merck), hexane/AcOEt 4:1).

4.2.1. Ethyl 2-benzoylamino-4-dimethylamino-thiazol-5-yl-oxo-acetate (**4a**)

Orange powder, m.p. 177–178°C; yield: 0.64 g (92%). IR (KBr): 3437, 1724, 1676, 1616, 1542, 1307, 1226, 1098 cm⁻¹. ¹H NMR: δ = 1.38 (3 H, t, ³J 7.1, Me), 3.16 (6 H, s, Me₂N), 4.38 (2 H, q, ³J 7.1, CH₂O), 7.52 (2 H, t, ³J 7.4, CH), 7.64 (1 H, t, ³J 7.4, CH), 8.01 (2 H, d, ³J 7.4, 2 CH), 9.90 (1 H, s, NH). ¹³C NMR: δ = 14.5 (Me), 43.0 (Me₂N), 62.9 (CH₂O), 99.5 (C), 128.0 (2 CH), 129.5 (2 CH), 131.7 (CH), 133.8 (C), 164.1 (C), 165.2 (C), 165.4 (C=O), 170.5 (C=O), 185.0 (C=O). EI-MS: m/z (%) = 347 (M⁺, 6), 332 (38), 302 (66), 242 (21), 105 (100), 77 (39), 45 (22). Anal. Calcd for C₁₆H₁₇N₃O₄S (347.39): C, 55.32; H, 4.93; N, 12.10%; found: C, 55.7; H, 5.0; N, 11.9%.

4.2.2. N-(5-(4-Bromobenzoyl)-4-dimethylamino-thiazol-2-yl)benzamide (**4b**)

Yellow powder, m.p. 233–235°C; yield: 0.81 g (95%). IR (KBr): 3450, 1674, 1589, 1534, 1387, 1251, 1211, 1170 cm⁻¹. ¹H NMR: δ = 3.15 (6 H, s, Me₂N), 7.56 (2 H, t, ³J 7.3, 2 CH), 7.60 (2 H, d, ³J 8.4, 2 CH), 7.65 (1 H, t, ³J 7.3, CH), 7.73 (2 H, d, ³J 8.4, 2 CH), 7.95 (2 H, d, ³J 7.3, 2 CH), 9.90 (1 H, br s, NH). ¹³C NMR: δ = 42.7 (Me₂N), 100.1 (C), 126.7 (C), 127.9 (2 CH), 128.6 (CH), 129.5 (2 CH), 130.5 (2 CH), 131.5 (C), 132.0 (2 CH), 133.8 (C), 133.9 (C), 140.5 (C), 160.9 (C), 165.1 (C=O), 184.2 (C=O). EI-MS: m/z (%) = 431 (M⁺ + 1, 8), 429 (M⁺, 13), 416 (33), 414 (30), 185 (11), 183 (11), 105 (100), 77 (43). Anal. Calcd for C₁₉H₁₆BrN₃O₂S (430.32): C, 53.03; H, 3.75; N, 9.76%; found: C, 52.8; H, 3.8; N, 9.8%.

4.2.3. N-(4-Dimethylamino-5-(4-methoxy-benzoyl)thiazol-2-yl)benzamide (**4c**)

Yellow powder, m.p. 217–218°C; yield: 0.64 g (84%). IR (KBr): 3445, 1679, 1591, 1520, 1367, 1221, 1157 cm⁻¹. ¹H NMR: δ = 3.11 (6 H, s, Me₂N), 3.89 (3 H, s, MeO), 6.95 (2 H, d, ³J 8.7, 2 CH), 7.53 (2 H, d, ³J 7.8, 2 CH), 7.63 (1 H, t, ³J 7.8, CH), 7.86 (2 H, d, ³J 8.7, 2 CH), 7.94 (2 H, t, ³J 7.8, 2 CH), 9.10 (1 H, br s, NH). ¹³C NMR: δ = 42.6 (Me₂N), 55.9 (MeO), 100.4 (C), 114.0 (2 CH), 127.9 (2 CH), 128.4 (CH), 129.5 (2 CH), 131.6 (2 CH), 131.7 (C), 133.7 (C), 134.4 (C), 160.3 (C), 160.9 (C), 162.8 (C), 165.0 (C=O), 184.9 (C=O). EI-MS: m/z (%) = 381 (M⁺, 12), 366 (41), 276 (35), 246 (12), 135 (22), 105 (100), 77 (37). Anal. Calcd for C₂₀H₁₉N₃O₃S (381.45): C, 62.97; H, 5.02; N, 11.02%; found: C, 63.2; H, 5.1; N, 11.1%.

4.2.4. Ethyl (2-(2-chloro-benzoylamino)-4-dimethylamino-thiazol-5-yl)oxoacetate (**4d**)

Orange powder, m.p. 153–155°C; yield: 0.51 g (67%). IR (KBr): 3439, 1723, 1624, 1545, 1394, 1307, 1232, 1116 cm⁻¹. ¹H NMR: δ = 1.43 (3 H, t, ³J 7.1, Me), 3.18 (6 H, s, Me₂N), 4.40 (2 H, q, ³J 7.1, CH₂O), 7.41–7.92 (4 H, m, 4 CH), 9.85 (1 H, s, NH). ¹³C NMR: δ = 14.5 (Me), 43.0 (Me₂N), 63.0 (CH₂O), 99.4 (C), 128.0 (CH), 131.2 (CH), 131.5 (C), 131.7 (C), 131.9 (CH), 133.7 (CH), 164.0 (C), 164.2 (C), 164.3 (C=O), 170.5 (C=O), 184.7 (C=O). EI-MS: m/z (%) = 381 (M⁺, 13), 366 (45), 336 (65), 242 (14), 139 (100), 111 (18), 45 (21). Anal. Calcd for C₁₆H₁₆ClN₃O₄S (381.83): C, 50.33; H, 4.22; N, 11.01%; found: C, 50.1; H, 4.3; N, 11.1%.

4.2.5. *N*-(5-(4-Bromo-benzoyl)-4-dimethylamino-thiazol-2-yl)-2-chlorobenzamide (**4e**)

Yellow powder, m.p. 206–207°C; yield: 0.67 g (73%). IR (KBr): 3385, 1688, 1610, 1539, 1386, 1263, 1129 cm⁻¹. ¹H NMR: δ = 3.17 (6 H, s, Me₂N), 7.41–7.91 (4 H, m, 4 CH), 7.61 (2 H, d, ³*J* 8.4, 2 CH), 7.74 (2 H, d, ³*J* 8.4, 2 CH), 9.78 (1 H, br s, NH). ¹³C NMR: δ = 42.3 (Me₂N), 100.5 (C), 126.5 (C), 127.7 (CH), 128.0 (C), 128.7 (CH), 130.4 (2 CH), 130.4 (C), 131.5 (CH), 132.0 (2 CH), 132.8 (CH), 132.9 (C), 133.5 (C), 140.7 (C), 162.5 (C), 164.1 (C), 166.4 (C=O), 184.2 (C=O). EI-MS: *m/z* (%) = 465 (M⁺ + 1, 6), 463 (M⁺, 12), 450 (45), 448 (34), 185 (21), 183 (21), 139 (100), 43 (9). Anal. Calcd for C₁₉H₁₅BrClN₃O₂S (464.76): C, 49.04; H, 3.25; N, 9.04%; found: C, 49.4; H, 3.3; N, 9.1%.

4.2.6. *N*-[4-Dimethylamino-5-(4-methoxybenzoyl)thiazol-2-yl]-2-chlorobenzamide (**4f**)

Yellow powder, m.p. 203–205°C; yield: 0.56 g (68%). IR (KBr): 3410, 1679, 1608, 1541, 1391, 1255, 1117 cm⁻¹. ¹H NMR: δ = 3.13 (6 H, s, Me₂N), 3.89 (3 H, s, MeO), 6.96 (2 H, d, ³*J* 8.7, 2 CH), 7.41–7.86 (4 H, m, 4 CH), 7.87 (2 H, d, ³*J* 8.7, 2 CH), 9.79 (1 H, br s, NH). ¹³C NMR: δ = 42.5 (Me₂N), 55.8 (MeO), 100.5 (C), 113.9 (2 CH), 127.9 (CH), 131.2 (2 CH), 131.5 (CH), 132.0 (CH), 132.6 (C), 132.9 (C), 133.4 (CH), 133.5 (CH), 134.4 (C), 159.6 (C), 161.8 (C), 162.8 (C), 164.1 (C=O), 184.9 (C=O). EI-MS: *m/z* (%) = 417 (M⁺ + 1, 8), 415 (M⁺, 20), 400 (48), 304 (33), 276 (24), 139 (100), 135 (19). Anal. Calcd for C₂₀H₁₈ClN₃O₃S (415.89): C, 57.76; H, 4.36; N, 10.10%; found: C, 58.0; H, 4.4; N, 10.2%.

4.2.7. Ethyl (4-dimethylamino-2-(4-nitro-benzoylamino)-thiazol-5-yl)oxoacetate (**4g**)

Viscous oil; yield: 0.45 g (58%). IR (KBr): 3460, 1729, 1682, 1621, 1562, 1317, 1216, 1078 cm⁻¹. ¹H NMR: δ = 1.40 (3 H, t, ³*J* 7.2, Me), 3.19 (6 H, s, Me₂N), 4.40 (2 H, q, ³*J* 7.2, CH₂O), 8.23 (2 H, d, ³*J* 8.7, 2 CH), 8.41 (2 H, d, ³*J* 8.7, 2 CH), 10.21 (1 H, br s, NH). ¹³C NMR: δ = 14.5 (Me), 43.1 (Me₂N), 63.1 (CH₂O), 100.1 (C), 124.6 (2 CH), 129.4 (2 CH), 132.1 (C), 137.0 (C), 151.1 (C), 163.5 (C), 164.0 (C=O), 170.6 (C=O), 184.2 (C=O). EI-MS: *m/z* (%) = 392 (M⁺, 11), 377 (39), 347 (59), 242 (24), 150 (100), 122 (16), 45 (23). Anal. Calcd for C₁₆H₁₆N₄O₆S (392.39): C, 48.97; H, 4.11; N, 14.28%; found: C, 49.3; H, 4.2; N, 14.4%.

4.2.8. Ethyl (4-dimethylamino-2-(4-methyl-benzoylamino)-thiazol-5-yl)oxoacetate (**4h**)

Orange powder, m.p. 168–169°C; yield: 0.67 g (93%). IR (KBr): 3426, 1689, 1604, 1556, 1377, 1273, 1120 cm⁻¹. ¹H NMR: δ = 1.42 (3 H, t, ³*J* 7.1, Me), 2.46 (3 H, s, Me), 3.18 (6 H, s, Me₂N), 4.39 (2 H, q, ³*J* 7.1, CH₂O), 7.34 (2 H, d, ³*J* 8.2, 2 CH), 7.88 (2 H, d, ³*J* 8.2, 2 CH), 9.72 (1 H, br s, NH). ¹³C NMR: δ = 14.5 (Me), 22.1 (Me), 43.0 (NMe₂), 62.9 (CH₂O), 99.9 (C), 128.0 (2 CH), 128.8 (C), 130.2 (2 CH), 144.8 (C), 164.1 (C), 165.1 (C), 165.2 (C=O), 170.5 (C=O), 185.1 (C=O). EI-MS: *m/z* (%) = 361 (M⁺, 17), 346 (40), 316 (73), 242 (18), 119 (100), 91 (31), 45 (19). Anal. Calcd for C₁₇H₁₉N₃O₄S (361.42): C, 56.50; H, 5.30; N, 11.63%; found: C, 56.3; H, 5.4; N, 11.7%.

4.2.9. *N*-(5-(4-Bromobenzoyl)-4-(dimethylamino)thiazol-2-yl)-4-methylbenzamide (**4i**)

Yellow powder, m.p. 185–187°C; yield: 0.80 g (90%). IR (KBr): 3443, 1678, 1598, 1543, 1390, 1246, 1136 cm⁻¹. ¹H NMR: δ = 2.45 (3 H, s, Me), 3.16 (6 H, s, Me₂N), 7.34 (2 H, d, ³*J* 8.1, 2 CH), 7.59 (2 H, d, ³*J* 8.4, 2 CH), 7.73 (2 H, d, ³*J* 8.4, 2 CH), 7.84 (2 H, d, ³*J* 8.1, 2 CH), 9.62 (1 H, br s, NH). ¹³C NMR: δ = 22.1 (Me), 42.7 (NMe₂), 100.1 (C), 126.6 (C), 127.9 (2 CH), 128.7

(C), 130.2 (2 CH), 130.5 (2 CH), 132.0 (2 CH), 140.6 (C), 144.8 (C), 161.1 (C), 161.1 (C), 165.1 (C=O), 184.2 (C=O). EI-MS: m/z (%) = 445 (M^+ + 1, 8), 443 (M^+ , 18), 430 (31), 428 (32), 185 (13), 183 (13), 119 (100), 91 (45). Anal. Calcd for $C_{20}H_{18}BrN_3O_2S$ (444.34): C, 54.06; H, 4.08; N, 9.46%; found: C, 54.3; H, 4.2; N, 9.5%.

4.2.10. *N*-(4-(Dimethylamino)-5-(4-methoxybenzoyl)thiazol-2-yl)-4-methylbenzamide (**4j**)

Yellow powder, m.p. 211–212°C; Yield: 0.68 g (87%). IR (KBr): 3434, 1681, 1595, 1539, 1389, 1258, 1150 cm^{-1} . 1H NMR: δ = 2.44 (3 H, s, Me), 3.11 (6 H, s, Me_2N), 3.89 (3 H, s, MeO), 6.94 (2 H, d, 3J 8.2, 2 CH), 7.32 (2 H, d, 3J 8.2, 2 CH), 7.84 (2H, d, 3J 7.1, 2 CH), 7.87 (2 H, d, 3J 7.1, 2 CH), 9.68 (1 H, br s, NH). ^{13}C NMR: δ = 22.0 (Me), 42.5 (Me_2N), 55.8 (MeO), 100.3 (C), 114.0 (2 CH), 127.9 (2 CH), 128.9 (C), 130.2 (2 CH), 131.1 (2 CH), 134.4 (C), 144.6 (C), 160.4 (C), 161.7 (C), 162.8 (C), 164.9 (C=O), 184.9 (C=O). EI-MS: m/z (%) = 395 (M^+ , 15), 380 (38), 276 (25), 260 (18), 135 (27), 119 (100), 91 (57). Anal. Calcd for $C_{21}H_{21}N_3O_3S$ (395.47): C, 63.78; H, 5.35; N, 10.63%; found: C, 64.1; H, 5.4; N, 10.8%.

4.2.11. Ethyl 2-(4-(dimethylamino)-2-pivalamidothiazol-5-yl)-2-oxoacetate (**4k**)

Viscous oil, yield: 0.42 g (65%). IR (KBr): 3430, 1724, 1680, 1610, 1543, 1407, 1310, 1231, 1105 cm^{-1} . 1H NMR: δ = 1.36 (9 H, s, Me_3C), 1.41 (3 H, t, 3J 7.1, Me), 3.18 (6 H, s, Me_2N), 4.37 (2 H, q, 3J 7.1, CH_2O), 8.97 (1 H, br s, NH). ^{13}C NMR: δ = 14.5 (Me), 27.5 (Me_3C), 39.9 (Me_3C), 43.1 (Me_2N), 62.9 (CH_2O), 100.0 (C), 164.0 (C), 164.9 (C), 170.5 (C=O), 177.1 (C=O), 185.0 (C=O). EI-MS, m/z (%): 381 (M^+ , 13), 366 (45), 336 (65), 242 (14), 139 (100), 111 (18), 45 (21). EI-MS: m/z (%) = 327 (M^+ , 17), 312 (35), 282 (36), 239 (100), 57 (66). Anal. Calcd for $C_{14}H_{21}N_3O_4S$ (327.40): C, 51.36; H, 6.47; N, 12.83%; found: C, 51.6; H, 6.6; N, 12.9%.

4.2.12. *N*-(5-(4-Bromobenzoyl)-4-(dimethylamino)thiazol-2-yl)pivalamide (**4l**)

Viscous oil, yield: 0.46 g (56%). IR (KBr): 3420, 1687, 1602, 1538, 1390, 1297, 1134 cm^{-1} . 1H NMR: δ = 1.34 (9 H, s, Me_3C), 3.17 (6 H, s, Me_2N), 7.57 (2 H, d, 3J 8.3, 2 CH), 7.69 (2 H, d, 3J 8.3, 2 CH), 9.22 (1 H, br s, NH). ^{13}C NMR: δ = 27.4 (CMe_3), 39.7 (Me_3C), 42.6 (Me_2N), 100.2 (C), 126.3 (C), 130.4 (2 CH), 131.9 (2 CH), 140.8 (C), 160.9 (C), 162.5 (C), 177.2 (C=O), 184.1 (C=O). EI-MS: m/z (%) = 411 (M^+ + 2, 13), 409 (M^+ , 12), 396 (31), 394 (31), 239 (100), 185 (21), 183 (21), 57 (54). Anal. Calcd for $C_{17}H_{20}BrN_3O_2S$ (410.33): C, 49.76; H, 4.91; N, 10.24%; found: C, 50.1; H, 5.0; N, 10.1%.

4.2.13. *N*-(4-(Dimethylamino)-5-(4-methoxybenzoyl)thiazol-2-yl)pivalamide (**4m**)

Yellow powder, m.p. 88–89°C; yield: 0.43 g (60%). IR (KBr): 3427, 1686, 1604, 1542, 1383, 1252, 1137 cm^{-1} . 1H NMR: δ = 1.34 (9 H, s, Me_3C), 3.15 (6 H, s, Me_2N), 3.88 (3 H, s, MeO), 6.93 (2 H, d, 3J 8.7, 2 CH), 7.83 (2 H, d, 3J 8.7, 2 CH), 9.15 (1 H, br s, NH). ^{13}C NMR: δ = 27.4 (Me_3C), 39.7 (Me_3C), 42.5 (Me_2N), 55.8 (MeO), 100.3 (C), 113.9 (2 CH), 131.0 (2 CH), 134.5 (C), 160.4 (C), 161.8 (C), 162.7 (C), 177.1 (C=O), 184.8 (C=O). EI-MS: m/z (%) = 361 (M^+ , 10), 346 (40), 276 (25), 239 (100), 135 (32), 57 (62). Anal. Calcd for $C_{18}H_{23}N_3O_3S$ (361.46): C, 59.81; H, 6.41; N, 11.63%; found: C, 60.2; H, 6.3; N, 11.7%.

4.2.14. (4-(Dimethylamino)-2-(phenylamino)thiazol-5-yl)(phenyl)methanone (**4n**)

Yellow powder, m.p. 136–138°C; yield: 0.52 g (81%). IR (KBr): 3412, 1516, 1394 cm⁻¹. ¹H NMR: δ = 3.00 (6 H, s, Me₂N), 7.03 (1 H, t, ³J 7.4 Hz, CH), 7.33 (2 H, t, ³J 8.4 Hz, CH), 7.43 (2 H, t, ³J 6.3 Hz, CH), 7.49 (1 H, t, ³J 6.8 Hz, CH), 7.58 (2 H, d, ³J 7.7 Hz, CH), 7.61 (2 H, d, ³J 8.4 Hz, CH), 10.67 (1 H, s, NH). ¹³C NMR: δ = 41.9 (Me₂N), 94.9 (C), 118.4 (CH), 122.8 (CH), 127.5 (CH), 128.1 (CH), 129.0 (CH), 130.6 (CH), 139.7 (C), 142.3 (C), 163.2 (C), 164.8 (C), 181.9 (C=O). EI-MS: m/z (%) = 323 (M⁺, 5), 308 (40), 246 (25), 218 (59), 105 (100), 77 (42). Anal. Calcd for C₁₈H₁₇N₃OS (323.41): C, 66.85; H, 5.30; N, 12.99%; found: C, 66.2; H, 5.3; N, 12.8%.

4.2.15. (4-(Dimethylamino)-2-(phenylamino)thiazol-5-yl)(4-methoxyphenyl)methanone (**4o**)

Yellow powder, m.p. 149–152°C; yield: 0.60 g (86%). IR (KBr): 3250, 1592, 1518, 1398 cm⁻¹. ¹H NMR: δ = 2.99 (6 H, s, Me₂N), 3.79 (3 H, s, MeO), 6.97 (2 H, d, ³J 8.7 Hz, CH), 7.02 (1 H, t, ³J 7.4 Hz, CH), 7.32 (2 H, t, ³J 8.4 Hz, CH), 7.58 (2 H, d, ³J 7.8 Hz, CH), 7.62 (2 H, d, ³J 8.7 Hz, CH), 10.64 (1 H, s, NH). ¹³C NMR: δ = 41.8 (Me₂N), 55.2 (MeO), 94.5 (C), 113.3 (CH), 118.4 (CH), 122.7 (CH), 129.0 (CH), 129.6 (CH), 134.5 (C), 139.8 (C), 161.2 (C), 162.7 (C), 164.4 (C), 181.4 (C=O). EI-MS: m/z (%) = 353 (M⁺, 3), 338 (40), 276 (25), 218 (100), 135 (32), 77 (48). Anal. Calcd for C₁₉H₁₉N₃O₂S (353.44): C, 64.57; H, 5.42; N, 11.89%; found: C, 64.8; H, 5.3; N, 11.8%.

4.2.16. (4-(Dimethylamino)-2-(phenylamino)thiazol-5-yl)(4-fluorophenyl)methanone (**4p**)

Yellow powder, m.p. 208–211°C; yield: 0.56 g (81%). IR (KBr): 3278, 1596, 1525, 1394 cm⁻¹. ¹H NMR: δ = 3.11 (6 H, s, Me₂N), 7.07 (2 H, t, ³J 8.4 Hz, CH), 7.12 (1 H, t, ³J 7.2 Hz, CH), 7.34 (2 H, d, ³J 8.2 Hz, CH), 7.40 (2 H, d, ³J 7.8 Hz, CH), 7.54–7.94 (2 H, m, CH), 8.03 (1 H, s, NH). ¹³C NMR: δ = 42.4 (Me₂N), 96.4 (C), 115.2 (d, ²J_{CF} 21.3 Hz, CH), 119.5 (CH), 124.3 (CH), 129.5 (CH), 130.4 (d, ³J 8.5, CH), 132.8 (d, ³J_{CF} 9.9 Hz, CH), 138.5 (d, ⁴J_{CF} 2.5 Hz, C), 138.8 (C), 163.3 (C), 165.3 (C), 165.4 (d, ¹J_{CF} 287 Hz, CF), 182.2 (C=O). EI-MS: m/z (%) = 341 (M⁺, 5), 326 (67), 264 (51), 218 (100), 123 (100), 77 (38). Anal. Calcd for C₁₈H₁₆FN₃OS (341.40): C, 63.32; H, 4.72; N, 12.31%; found: C, 63.2; H, 4.8; N, 12.4%.

4.2.17. (4-Chlorophenyl)(4-(dimethylamino)-2-(phenylamino)thiazol-5-yl)methanone (**4q**)

Yellow powder, m.p. 214–217°C; yield: 0.63 g (88%). IR (KBr): 3271, 1593, 1520, 1392 cm⁻¹. ¹H NMR: δ = 3.02 (6 H, s, Me₂N), 7.05 (1 H, t, ³J 7.4 Hz, CH), 7.34 (2 H, t, ³J 7.6 Hz, CH), 7.51 (2 H, d, ³J 8.4 Hz, CH), 7.57 (2 H, d, ³J 8.1 Hz, CH), 7.64 (2 H, d, ³J 8.4 Hz, CH), 10.75 (1 H, s, NH). ¹³C NMR: δ = 41.9 (Me₂N), 94.7 (C), 118.5 (CH), 122.9 (CH), 128.2 (CH), 128.9 (CH), 129.4 (CH), 135.2 (C), 139.7 (C), 140.9 (C), 163.5 (C), 164.9 (C), 180.4 (C=O). EI-MS: m/z (%) = 359 (M⁺, 7), 357 (30), 344 (32), 342 (35), 239 (100), 282 (32), 218 (100), 77 (37). Anal. Calcd for C₁₈H₁₆ClN₃OS (357.86): C, 60.41; H, 4.51; N, 11.74%; found: C, 60.2; H, 4.6; N, 11.8%.

4.2.18. (4-Bromophenyl)(4-(dimethylamino)-2-(phenylamino)thiazol-5-yl)methanone (**4r**)

Yellow powder, m.p. 211–214°C; yield: 0.70 g (87%). IR (KBr): 3270, 1587, 1520, 1396 cm⁻¹. ¹H NMR: δ = 3.01 (6 H, s, Me₂N), 7.04 (1 H, t, ³J 7.3 Hz, CH), 7.34 (2 H, t, ³J 7.8 Hz, CH), 7.56 (2 H, d, ³J 8.5 Hz, CH), 7.57 (2 H, d, ³J 8.2 Hz, CH), 7.65 (2 H, d, ³J 8.2 Hz, CH), 10.67

(1 H, s, NH); ^{13}C NMR: δ = 41.9 (Me₂N), 94.6 (C), 118.5 (CH), 123.0 (CH), 124.1 (C), 129.1 (CH), 129.6 (CH), 131.2 (CH), 139.6 (C), 141.2 (C), 163.5 (C), 164.9 (C), 180.5 (C=O). EI-MS: m/z (%) = 403 (M⁺, 6), 401 (7), 388 (22), 386 (25), 326 (43), 324 (45), 218 (100), 185 (37), 77 (32). Anal. Calcd for C₁₈H₁₆BrN₃OS (402.31): C, 53.74; H, 4.01; N, 10.44%; found: C, 53.5; H, 4.2; N, 10.3%.

4.2.19. Ethyl 2-(4-(dimethylamino)-2-(phenylamino)thiazol-5-yl)-2-oxoacetate (**4s**)

Yellow powder, m.p. 196–197°C; yield: 0.64 g (84%). IR (KBr): 3440, 1667, 1594, 1362, 1290, 1221, 1157 cm⁻¹. ^1H NMR: δ = 1.35 (3 H, t, 3J 7.1, Me), 3.24 (6 H, s, Me₂N), 4.33 (2 H, q, 3J 7.1, CH₂O), 7.16–7.46 (5 H, m, 5 CH), 7.99 (1 H, br s, NH). ^{13}C NMR: δ = 14.5 (Me), 43.1 (Me₂N), 62.7 (CH₂O), 101.8 (C), 120.5 (2 CH), 121.9 (C), 125.2 (CH), 129.3 (C), 129.9 (2 CH), 138.8 (C), 165.1 (C=O), 183.3 (C=O). EI-MS: m/z (%) = 319 (M⁺, 7), 279 (40), 251 (33), 223 (18), 92 (100), 91 (56), 45 (12). Anal. Calcd for C₁₅H₁₇N₃O₃S (319.38): C, 56.41; H, 5.37; N, 13.16%; found: C, 56.2; H, 5.3; N, 13.3%.

4.2.20. (4-(Dimethylamino)-2-(4-methoxyphenylamino)thiazol-5-yl)(4-methoxyphenyl) methanone (**4t**)

Yellow powder, m.p. 207–208°C; yield: 0.57 g (75%). IR (KBr): 3410, 1670, 1581, 1320, 1245, 1132 cm⁻¹. ^1H NMR: δ = 3.12 (6 H, s, Me₂N), 3.77 (3 H, s, MeO), 3.85 (3 H, s, MeO), 6.87 (2 H, d, 3J 8.3, 2 CH), 7.28 (2 H, d, 3J 8.5, 2 CH), 7.49 (2 H, d, 3J 8.3, 2 CH), 7.76 (2 H, d, 3J 8.5, 2 CH), 8.05 (1 H, br s, NH). ^{13}C NMR: δ = 42.5 (Me₂N), 55.7 (MeO), 56.2 (MeO), 92.7 (C), 114.4 (2 CH), 115.5 (2 CH), 124.6 (C), 128.2 (C), 129.7 (C), 130.6 (2 CH), 132.6 (2 CH), 160.0 (C), 166.1 (C), 174.8 (C), 192.7 (C=O). EI-MS: m/z (%) = 383 (M⁺, 15), 260 (40), 247 (25), 136 (100), 123 (52), 45 (23). Anal. Calcd for C₂₀H₂₁N₃O₃S (383.46): C, 62.64; H, 5.52; N, 10.96%; found: C, 62.3; H, 5.4; N, 11.0%.

4.2.21. (4-Bromophenyl)(4-(dimethylamino)-2-(4-methoxyphenylamino)thiazol-5-yl) methanone (**4u**)

Yellow powder, m.p. 200–202°C; yield: 0.64 g (84%). IR (KBr): 3512, 1710, 1601, 1520, 1343, 1250, 1105 cm⁻¹. ^1H NMR: δ = 3.15 (6 H, s, Me₂N), 3.82 (3 H, s, MeO), 6.91 (2 H, d, 3J 9.0, 2 CH), 7.19 (2 H, d, 3J 9.0, 2 CH), 7.53 (2 H, d, 3J 8.8, 2 CH), 7.62 (2 H, d, 3J 8.8, 2 CH), 7.7 (1 H, br s, NH). ^{13}C NMR: δ = 42.7 (Me₂N), 55.8 (MeO), 96.7 (C), 114.8 (2 CH), 123.8 (2 CH), 127.1 (C), 130.1 (2 CH), 131.7 (2 CH), 137.3 (C), 141.7 (C), 159.5 (C), 165.5 (C), 170.5 (C), 192.8 (C=O). EI-MS: m/z (%) = 433 (M⁺ + 1, 6), 432 (M⁺, 7), 387 (29), 309 (34), 185 (21), 186 (100), 123 (50), 43 (21). Anal. Calcd for C₁₉H₁₈BrN₃O₂S (432.33): C, 52.78; H, 4.20; N, 9.72%; found: C, 52.5; H, 4.3; N, 9.8%.

4.2.22. Ethyl 2-(4-(dimethylamino)-2-(4-methoxyphenylamino)thiazol-5-yl)-2-oxoacetate (**4v**)

Yellow powder, m.p. 220–222°C; yield: 0.64 g (84%). IR (KBr): 3342, 1675, 1531, 1505, 1317, 1261, 1137 cm⁻¹. ^1H NMR: δ = 1.35 (3 H, t, 3J 7.1, Me), 3.23 (6 H, s, Me₂N), 3.84 (3 H, s, MeO), 4.31 (2 H, q, 3J 7.1, CH₂O), 6.94 (2 H, d, 3J 9.0, 2 CH), 7.33 (2 H, d, 3J 9.0, 2 CH), 7.85 (1 H, br s, NH). ^{13}C NMR: δ = 14.5 (Me), 43.1 (Me₂N), 55.9 (MeO), 62.8 (CH₂O), 98.9 (C), 115.3 (2 CH), 124.1 (2 CH), 131.8 (C), 155.6 (C), 161.4 (C), 163.7 (C), 170.4 (C=O), 182.3 (C=O). EI-MS: m/z (%) = 349 (M⁺, 8), 248 (40), 226 (73), 198 (18), 123 (100), 101 (31), 73

(31), 45 (34). Anal. Calcd for $C_{16}H_{19}N_3O_4S$ (349.40): C, 55.00; H, 5.48; N, 12.03%; found: C, 55.3; H, 5.4; N, 11.9%.

4.2.23. (4-(Dimethylamino)-2-(ethylamino)thiazol-5-yl)(phenyl)methanone (**4w**)

Yellow powder, m.p. 170–175°C; yield: 0.46 g (84%). IR (KBr): 3206, 1520, 1393 cm^{-1} . 1H NMR: δ = 1.10 (3 H, t, 3J 7.2 Hz, Me), 2.94 (6 H, s, Me_2N), 3.17 (2 H, s, CH_2), 7.39 (2 H, t, 3J 7.3 Hz, CH), 7.43 (1 H, t, 3J 7.0 Hz, CH), 7.55 (2 H, d, 3J 7.0 Hz, CH), 8.50 (1 H, s, NH). ^{13}C NMR: δ = 14.1 (Me), 33.9 (CH_2), 41.8 (Me_2N), 94.3 (C), 127.4 (CH), 128.0 (CH), 130.2 (CH), 142.8 (C), 164.6 (C), 169.3 (C), 181.1 (C=O). EI-MS: m/z (%) = 275 (M^+ , 5), 230 (36), 198 (25), 170 (49), 105 (100), 77 (22), 45 (30). Anal. Calcd for $C_{14}H_{17}N_3OS$ (275.37): C 61.06, H 6.22, N 15.26%; found: C, 61.3; H, 6.3; N, 15.4%.

4.2.24. (4-(Dimethylamino)-2-(ethylamino)thiazol-5-yl)(4-methoxyphenyl)methanone (**4x**)

Yellow powder, m.p. 175–180°C; yield: 0.50 g (83%). IR (KBr): 3206, 1551, 1540, 1406 cm^{-1} . 1H NMR: δ = 1.11 (3 H, t, 3J 7.2 Hz, Me), 2.92 (6 H, s, Me_2N), 3.17 (2 H, s, CH_2), 6.93 (2 H, d, 3J 8.6 Hz, CH), 7.55 (2 H, d, 3J 8.6 Hz, CH), 8.4 (1 H, s, NH). ^{13}C NMR: δ = 14.1 (Me), 34.2 (CH_2), 41.7 (Me_2N), 55.2 (MeO), 93.9 (C), 113.2 (CH), 129.4 (CH), 135.1 (C), 160.9 (C), 164.1 (C), 169.0 (C), 180.6 (C=O). EI-MS: m/z (%) = 305 (M^+ + 1, 5), 360 (42), 197 (39), 269 (24), 135 (100), 108 (19), 45 (23). Anal. Calcd for $C_{15}H_{19}N_3O_2S$ (305.40): C, 58.99; H, 6.27; N, 13.76%; found: C, 59.2; H, 6.3; N, 13.8%.

4.2.25. (4-(Dimethylamino)-2-(ethylamino)thiazol-5-yl)(4-fluorophenyl)methanone (**4y**)

Yellow powder, m.p. 223–227°C; yield: 0.46 g (79%). IR (KBr): 3205, 1581, 1514, 1398 cm^{-1} . 1H NMR: δ = 1.24 (3 H, t, 3J 7.2 Hz, Me), 3.08 (6 H, s, Me_2N), 3.23 (2 H, dq, 3J 7.2 and 6.0 Hz, CH_2), 7.06 (2 H, t, 3J 8.5 Hz, CH), 7.73 (2 H, t, 3J 5.6 Hz, CH), 8.01 (1 H, br t, 3J 6.0, NH). ^{13}C NMR: δ = 14.4 (Me), 40.0 (CH_2), 42.2 (Me_2N), 96.1 (C), 115.0 (d, $^2J_{CF}$ 21.3 Hz, CH), 130.2 (d, $^3J_{CF}$ 8.6 Hz, CH), 138.9 (C), 164.2 (d, $^1J_{CF}$ 289 Hz, CF), 165.1 (C), 170.8 (C), 181.5 (C=O). EI-MS: m/z (%) = 293 (M^+ , 5), 248 (37), 216 (48), 190 (45), 123 (100), 77 (38), 45 (27). Anal. Calcd for $C_{14}H_{16}FN_3OS$ (293.36): C, 57.32; H, 5.50; N, 14.32%; found: C, 57.1; H, 5.4; N, 14.4%.

4.2.26. (4-Chlorophenyl)(4-(dimethylamino)-2-(ethylamino)thiazol-5-yl)methanone (**4z**)

Yellow powder, m.p. 206–209°C; yield: 0.60 g (97%). IR (KBr): 3202, 1551, 1518, 1406 cm^{-1} . 1H NMR: δ = 1.12 (3 H, t, 3J 7.2 Hz, Me), 2.94 (6 H, s, Me_2N), 3.18 (2 H, s, CH_2), 7.47 (2 H, d, 3J 8.3 Hz, CH), 7.57 (2 H, d, 3J 8.3 Hz, CH), 8.54 (1 H, s, NH). ^{13}C NMR: δ = 14.0 (Me), 34.0 (CH_2), 41.8 (Me_2N), 94.1 (C), 128.1 (CH), 129.3 (CH), 134.8 (C), 141.5 (C), 164.8 (C), 169.4 (C), 179.5 (C=O). EI-MS: m/z (%) = 309 (M^+ , 7), 264 (19), 173 (42), 136 (100), 77 (17), 45 (32). Anal. Calcd for $C_{14}H_{16}ClN_3OS$ (309.81): C, 54.27; H, 4.21; N, 13.56%; found: C, 54.0; H, 4.3; N, 13.7%.

4.2.27. (4-Bromophenyl)(4-(dimethylamino)-2-(ethylamino)thiazol-5-yl)methanone (**4aa**)

Yellow powder, m.p. 214–216°C; yield: 0.68 g (96%). IR (KBr): 3203, 1551, 1517, 1407 cm^{-1} . 1H NMR: δ = 1.11 (3 H, t, 3J 7.2 Hz, Me), 2.94 (6 H, s, Me_2N), 3.18 (2 H, s, CH_2), 7.50 (2 H, d,

3J 8.3 Hz, CH), 7.60 (2 H, d, 3J 8.3 Hz, CH), 8.51 (1 H, s, NH). ^{13}C NMR: δ = 14.1 (Me), 34.3 (CH_2), 41.9 (Me_2N), 94.1 (C), 123.6 (C), 129.4 (CH), 131.1 (CH), 141.8 (C), 164.7 (C), 169.4 (C), 179.6 (C=O). EI-MS: m/z (%) = 356 ($\text{M}^+ + 2$, 8), 354 (M^+ , 7), 311 (31), 309 (31), 185 (100), 183 (91), 45 (24). Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{BrN}_3\text{OS}$ (354.27): C, 47.46; H, 4.55; N, 11.86%; found: C, 47.71; H, 4.62; N, 11.9%.

References

- (1) Jin, Z. *Nat. Prod. Rep.* **2003**, 20, 584–605.
- (2) Sperry, J.B.; Wright, D.L. *Curr. Opin. Drug. Discov. Dev.* **2005**, 8, 723–740.
- (3) Fink, B.A.; Mortensen, D.S.; Stauffer, S.R.; Aron, Z.D.; Katzenellenbogen, J.A. *Chem. Biol.* **1999**, 6, 205–219.
- (4) Van Muijlwijk-Koezen, J.E.; Timmerman, H.; Vollinga, R.C.; Von Drabbe-Kunzel, J.F.; De Groote, M.; Visser, S.; Ijzerman, A.P. *J. Med. Chem.* **2001**, 44, 749–762.
- (5) Millan, D.S.; Prager, R.H.; Brand, C.; Hart, P.H. *Tetrahedron* **2000**, 56, 811–816.
- (6) Wang, W.L.; Yao, D.Y.; Gu, M.; Fan, M.Z.; Li, J.W.; Xing, Y.C.; Nan, F.J. *Bioorg. Med. Chem. Lett.* **2005**, 15, 5284–5287.
- (7) Hantzsch, A.; Weber, J.H. *Dtsch. Chem. Ges.* **1887**, 20, 3118–3130.
- (8) Aguilar, E.; Meyers, A.I. *Tetrahedron Lett.* **1994**, 35, 2473–2476.
- (9) Varma, R.S. *Pure Appl. Chem.* **2001**, 73, 193–198.
- (10) Yavari, I.; Seyfi, S.; Hossaini, Z.; Sabbaghan, M.; Shirgahi-Talari, F. *Monatsh. Chem.* **2008**, 139, 1479–1482.
- (11) Yavari, I.; Hossaini, Z.; Seyfi, S.; Shirgahi-Talari, F. *Helv. Chim. Acta* **2008**, 91, 1177–1180.
- (12) Yavari, I.; Sanaeishoar, T.; Ghazvini, M.; Iravani, N. *J. Sulfur Chem.* **2010**, 31, 169–176.