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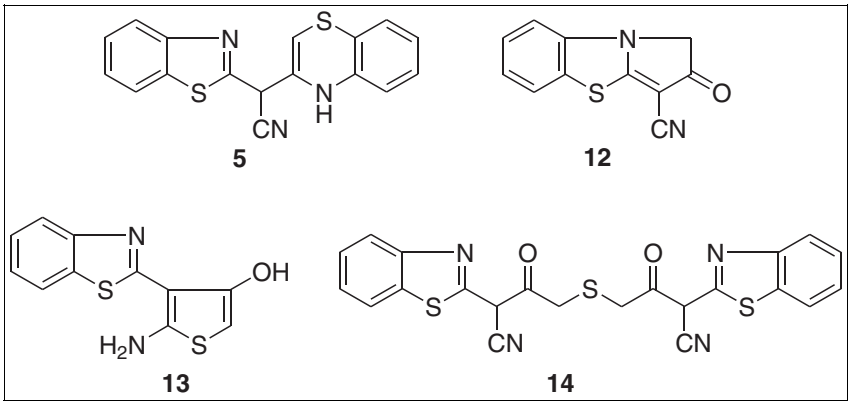

A variety of heterocylic rings incorporating benzothiazole moiety were synthesized by reaction of 1-(2-benzothiazolyl)-1-cyano-3-chloroacetone **1** with salicylaldehyde, *o*-aminothiophenol, 2-aminothiazole, 2-aminobenzothiazole, 2-aminobenzimidazole, alcoholic KOH, and sodium sulfide to give compounds **2**, **5–9**, **12**, and **14**, respectively.

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INTRODUCTION

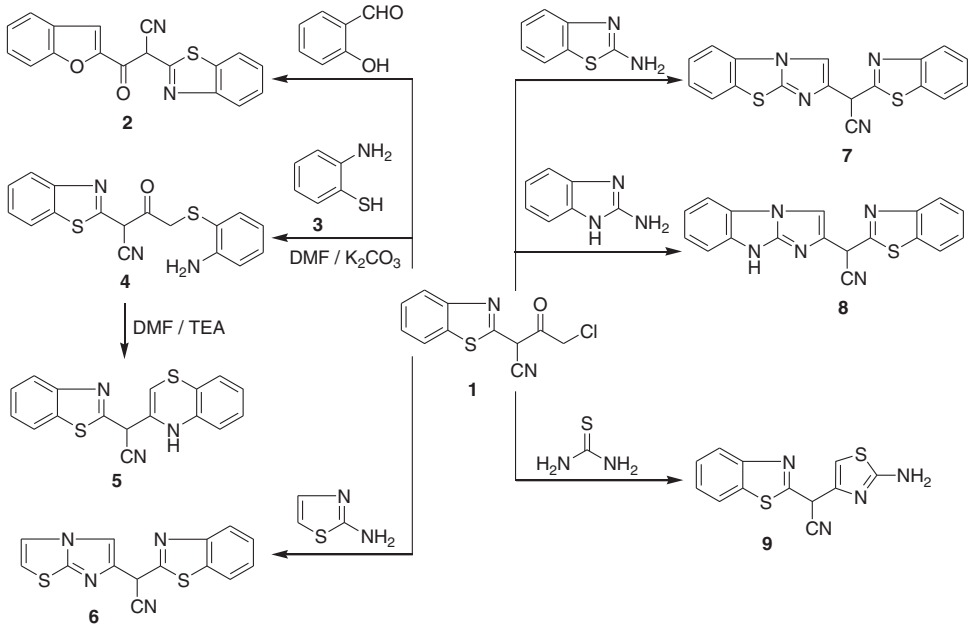
Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds [1]. Chemically, heterocyclic compounds with the benzothiazole moiety are very useful and important organic compounds widely used as dye [2], in laser technologies [3], and fluorescent materials for visualization of biomolecules [4]. Furthermore, these compounds have shown promising activities such as antibacterial, antiviral, and anti-inflammatory activities [5]. They are also valuable synthons. Thus, the synthesis of these heterocyclic compounds is interesting for both organic synthesis and medicinal chemistry.

RESULTS AND DISCUSSION

As a part of a program aimed at the synthesis of novel benzothiazole derivatives [6–11], which could be useful for biological and pharmacological screening, we have investigated the possible utility of 1-(2-benzothiazolyl)-1-cyano-3-chloroacetone **1** [9] for the synthesis of some heterocyclic compounds. It has been found that the reaction of **1** with salicylaldehyde in presence of potassium carbonate afforded 2-(benzo[*d*]thiazol-2-yl)-3-(benzofuran-2-yl)-3-oxopropanenitrile **2** in high yield (Scheme 1). The structure of **2** was established based on both elemental and spectral data. The IR spectrum showed strong absorption bands at 2189 and 1705 cm^{-1} due to CN and C═O, respectively. The ^1H NMR spectrum of **2** revealed singlet signal at δ 5.1 ppm due to CH proton and aromatic protons at δ 7.30–8.26 ppm, whereas its mass spectroscopic measurement showed the molecular ion peak at *m/z* 318 (M^+).

The 1-(2-benzothiazolyl)-1-cyano-3-chloroacetone **1** allowed a fruitful, one-step synthesis of several heterocyclic rings. The reaction of **1** in dimethylformamide (DMF) with *o*-aminothiophenol **3** in presence of potassium carbonate yielded 4-((2-aminophenyl)thio)-2-(benzo[*d*]thiazol-2-yl)-3-oxobutanenitrile **4**, which was cyclized in refluxing DMF containing catalytic amount of triethylamine to yield 2-(4*H*-benzo[*b*][1,4]thiazin-3-yl)-2-(benzo[*d*]thiazol-2-yl)acetonitrile **5** (Scheme 1). The structure of compound **4** is based on its correct elemental analysis and spectroscopic data (IR, ^1H NMR, and MS). The ^1H NMR spectrum of **4** displayed three singlet signals at δ 3.44, 4.11, and 4.54 ppm due to CH_2, CH, and NH_2, respectively, and multiplet at δ 7.42–8.12 ppm due to aromatic protons. The IR spectrum showed strong absorption bands at 3387, 3258, 2197, and 1699 cm^{-1} due to NH_2, CN, and C═O. The mass spectrum of compound **5** showed an intense peak at *m/z* 321 corresponding to its molecular ion peak, whereas its ^1H NMR spectrum displayed three singlet signals at δ 3.65, 4.88, and 5.76 ppm due to NH, CH,

Scheme 1. Reactions of 2-(benzo[*d*]thiazol-2-yl)-4-chloro-3-oxobutanenitrile **1** with different nucleophiles.



and vinylic CH protons, respectively. Compound **1** reacted with 2-aminothiazole, 2-aminobenzothiazole, and 2-amino-benzimidazole in refluxing DMF in the presence of triethylamine as catalyst to afford the 2-(imidazo[2,1-*b*]thiazole-2-yl)-2-(2-benzothiazolyl)acetonitrile **6**, 2-(3a-hydroimidazolo[2,1-*b*]benzothiazole-2-yl)-2-(2-benzo-thiazolyl)acetonitrile **7**, and 2-(imidazo[2,1-*b*]benzo-imid-azole-2-yl)-2-(2-benzo-thiazolyl) acetonitrile **8**, respectively (Scheme 1). The latter structures rely upon analytical and spectral data. In particular, the ^{1}H-NMR spectrum of **6** shows one singlet signal at δ 4.93 ppm due to CH proton and a multiplet at δ 7.32-8.34 ppm due to seven aromatic protons, which is in full agreement with structure **6**. Also, the structure of **6** was confirmed by its mass spectroscopic measurement, which showed the molecular ion peak at *m/z* 296 (M^+) and the base peak at 214 (M^+–CN). The ^{1}H-NMR spectrum of **7** showed one singlet signal at δ 4.43 ppm due to CH proton and a multiplet at δ 7.28–8.08 ppm due to nine aromatic protons, whereas ^{1}H NMR spectrum of **8** showed a broad singlet signal at δ 3.43 ppm due to NH, one singlet signal at δ 4.71 ppm due to CH proton, and a multiplet at δ 7.12–8.16 ppm due to nine aromatic protons.

On the other hand, 2-(2-aminothiazol-4-yl)-2-(benzo[*d*] thiazol-2-yl)acetonitrile **9** was obtained by Hantzsch thiazole synthesis via condensation of **1** with thiourea (Scheme 1). The structure of **9** was proved by its elemental and spectral analyses.

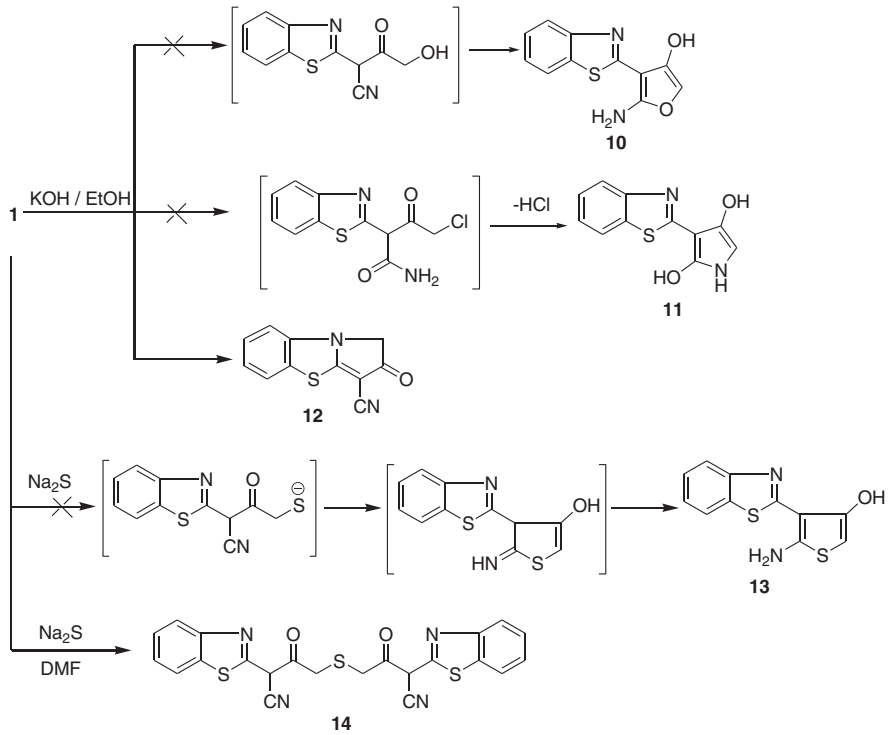
Moreover, it was found that treatment of **1** with potassium hydroxide in ethanol afforded 2-oxo-1,2-dihydro-benzo[*d*]pyrrolo[2,1-*b*]thiazole-3-carbonitrile **12** instead of the expected products 5-amino-4-(benzo[*d*]thiazol-2-yl)-furan-3-ol **10** or 3-(benzo[*d*]thiazol-2-yl)-1*H*-pyrrole-2,4-diol **11** as shown in Scheme 2. Structure **12** was suggested for the reaction product on the basis of elemental analysis and spectral data. The IR spectrum of **12** showed absorption bands at 2220 (CN) and 1668 cm^{-1} (C═O). The ^{1}H NMR spectrum of **12** revealed a singlet signal at δ 4.71 ppm assigned to CH_2 protons and a multiplet at δ 7.3–8.3 ppm assigned to four aromatic protons.

On the other hand, the reaction of **1** with sodium sulfide in refluxing DMF afforded 4,4′-thiobis(2-(benzo[*d*]thiazol-2-yl)-3-oxobutanenitrile **14** instead of the expected product 5-amino-4-(benzo[*d*]thiazol-2-yl)thiophen-3-ol **13** (Scheme 2). The structure of **14** was established by IR spectrum that showed absorption bands at 2228 cm^{-1} due to CN group, in addition to 1698 cm^{-1} attributable to C═O group. The ^{1}H NMR spectrum of compound **14** showed singlet signal at δ 4.7 [(4H) due to two methylene group protons] and singlet signal at δ 5.0 (2H) due to two methyne group protons in addition to a multiplet at δ 7.34–8.10 for eight aromatic protons, which is in agreement with the proposed structure **14**. The mass spectrum showed the molecular ion peak at *m/z* 462 (M^+).

EXPERIMENTAL

Melting points were recorded on Gallenkamp electric melting point apparatus (Electronic Melting Point Apparatus, Great Britain, London) and are uncorrected. Infrared spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer (Thermo-electron Co. Egelsbach, Germany) using a KBr wafer technique. The ^{1}H NMR spectra were determined on Varian Gemini 200 MHz (Varian Co., Fort Collins, USA). DMSO-d_6 was used as solvent, TMS was used as internal standard and chemical shifts were measured in δ ppm. Mass spectra were determined on a GC-MS.QP-100 EX Shimadzu (Japan). Elemental analyses were recorded on Perkin-Elmer 2400 Elemental analyzer at the Micro-analytical Center at Cairo University, Cairo, Egypt.

Scheme 2. Synthesis of benzo[*d*]pyrrolo[2,1-*b*]thiazole-3-carbonitrile **12** and bis(2-(benzo[*d*]thiazol-2-yl)-3-oxobutanenitrile **14**.



2-(Benzo[d]thiazol-2-yl)-3-(benzofuran-2-yl)-3-oxopropanenitrile 2. A mixture of **1** (2.5 g, 0.01 mol) and salicylaldehyde (1.07 mL, 0.01 mol) was refluxed in DMF for 9 h. The reaction mixture was left to cool at room temperature and then poured onto ice cold water (100 mL). The solid product was collected by filtration and crystallized from ethanol–DMF mixture to give **2**. Dark brown crystals; yield (82%); mp > 300°C; IR (KBr): ν_{max}, cm^{-1}: 2189 (CN), 1705 (C═O); ^{1}H NMR (DMSO-d_6): δ 5.1 (s, 1H, CH), 7.30–8.26 (m, 9H, Ar–H); ^{13}C NMR (DMSO-d_6): δ 44 (CH–CN), 104 (CH–furan), 116 (CN), 110–170 (14 peaks due to C–Ar), 189 (C═O); MS: *m/z* 318 (M^+). *Anal*. Calcd. for $C_{18}H_{10}N_2O_2S$: C, 67.91; H, 3.17; N, 8.80; S, 10.07%. Found: C, 67.83; H, 3.21; N, 8.75; S, 10.10%.

4-((2-Aminophenyl)thio)-2-(benzo[d]thiazol-2-yl)-3-oxobutanenitrile 4. A mixture of **1** (2.5 g, 0.01 mol) and 2-aminothiophenol (1.06 mL, 0.01 mol) was stirred in DMF at room temperature for 3 h in presence of a catalytic amount of potassium carbonate. The reaction mixture then was poured onto ice cold water (100 mL) and neutralized with dilute hydrochloric acid. The solid product was collected by filtration and recrystallized from ethanol–DMF to give **4**. White crystals; yield (67%); mp 159°C; IR (KBr): ν_{max}, cm^{-1}: 3387, 3258 (NH_2), 2197 (CN), 1699 (C═O); ^{1}H NMR (DMSO-d_6): δ 3.44 (s, 2H, CH_2), 4.11 (s, 1H, CH), 4.54 (s, 2H, NH_2), 7.42–8.12 (m, 8H, aromatic protons); ^{13}C NMR (DMSO-d_6): δ 41 (CH_2), 47 (CH–CN), 116 (CN), 110–170 (13 peaks due to C–Ar), 202(C═O); MS: *m/z* 339 (M^+). *Anal*. Calcd. for $C_{17}H_{13}N_3OS_2$: C, 60.15; H, 3.86; N, 12.38; S, 18.89%. Found: C, 60.24; H, 3.92; N, 12.44; S, 18.92%.

2-(4H-Benzo[b][1,4]thiazin-3-yl)-2-(benzo[d]thiazol-2-yl)acetonitrile 5. Compound **4** (3.39 g, 0.01 mol) in DMF containing a catalytic amount of triethylamine was refluxed for 6 h then left to cool at room temperature and poured onto ice cold water (100 mL). The solid product was collected by filtration and recrystallized from ethanol–DMF mixture to give **5**. Brown crystals; yield (59%); mp 255°C; IR (KBr): ν_{max}, cm^{-1}: 3144 (NH), 2188(CN); ^{1}H NMR (DMSO-d_6): δ 3.65 (s, 1H, NH), 4.88 (s, 1H, CH), 5.76 (s, 1H, CH), 7.30–8.20 (m, 8H, aromatic protons); ^{13}C NMR (DMSO-d_6): δ 41 (CH–CN), 103 (CH-1,4-thiazine), 116 (CN), 110–170 (14 peaks due to C–Ar); MS: *m/z* 321 (M^+). *Anal*. Calcd. for $C_{17}H_{11}N_3S_2$: C, 63.53; H, 3.45; N, 13.07; S, 19.95%. Found: C, 63.58; H, 3.51; N, 13.17; S, 19.92%.

General procedure for the preparation of compounds 6–8. A mixture of **1** (2.5 g, 0.01 mol) and 0.01 mol of 2-aminothiazole or 2-aminobenzthiazole or 2-aminobenzimidiazole was refluxed in DMF for 6–10 h (TLC controlled) then left to cool at room temperature and poured onto ice cold water (100 mL). The solid product was collected by filtration and recrystallized from DMF to give compounds **6–8**.

2-(Imidazo[2,1-b]thiazole-2-yl)-2-(2-benzothiazolyl)acetonitrile 6. Brown crystals; yield (68%); mp 260°C; IR (KBr): ν_{max}, cm^{-1}: 2201(CN); ^{1}H NMR (DMSO-d_6): δ 4.93 (s, 1H, CH), 7.32–8.34 (m,7H, aromatic protons); ^{13}C NMR (DMSO-d_6): δ 39 (CH–CN), 118 (CN), 110–170 (12 peaks due to C–Ar); MS: *m/z* 296 (M^+). *Anal*. Calcd. for $C_{14}H_8N_4S_2$: C, 56.74; H, 2.72; N, 18.90; S, 21.64%. Found: C, 56.71; H, 2.69; N, 18.88; S, 21.59%.

2-(3a-Hydroimidazolo[2,1-b]benzothiazole-2-yl)-2-(2-benzothiazolyl)acetonitrile 7. Brown crystals; yield (59%); mp 297°C; IR (KBr): ν_{max}, cm^{-1}: 2199(CN); ^{1}H NMR (DMSO-d_6): δ 4.43 (s, 1H, CH), 7.28–8.08 (m, 9H, aromatic protons); ^{13}C NMR (DMSO-d_6): δ 39 (CH–CN), 119 (CN), 110–170 (14 peaks due to C–Ar); MS: *m/z* 346 (M^+). *Anal*. Calcd. for $C_{18}H_{10}N_4S_2$: C, 62.41; H, 2.91; N, 16.17; S, 18.51%. Found: C, 62.38; H, 2.87; N, 16.12; S, 18.55%.

2-(Imidazo[2,1-b]benzoimidazole-2-yl)-2-(2-benzothiazolyl) acetonitrile 8. Brown crystals; yield (64%); mp 240°C; IR

(KBr): ν_{max}, cm^{-1}: 3199 (NH), 2199 (CN); ^1H NMR (DMSO-d_6): δ 3.43 (s, 1H, NH), 4.71 (s, 1H, CH), 7.12–8.16 (m, 9H, aromatic protons); ^{13}C NMR (DMSO-d_6): δ 39 (CH–CN), 119 (CN), 110–170 (16 peaks due to C–Ar); MS: *m/z* 329 (M^+). *Anal*. Calcd. for $C_{18}H_{11}N_5S$: C, 65.64; H, 3.37; N, 21.26; S, 9.74%. Found: C, 65.62; H, 3.29; N, 21.31; S, 9.77%.

2-(2-Aminothiazol-4-yl)-2-(benzo[d]thiazol-2-yl)acetonitrile 9. A mixture of **1** (2.5 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) was refluxed in DMF containing catalytic amount of triethylamine for 8–10 h (TLC-controlled). The reaction mixture was left to cool at room temperature and poured onto ice cold water (100 mL). The solid product was collected by filtration and recrystallized from ethanol–DMF to give **9**. Dark yellow; yield (58%); mp > 300°C; IR (KBr): ν_{max}, cm^{-1}: 3252, 3398 (NH_2), and 2212 (CN); ^1H NMR (DMSO-d_6): δ 4.98 (s, 1H, CH), 6.90–8.20 (m, 7H, aromatic protons + NH_2); ^{13}C NMR (DMSO-d_6): δ 38 (CH–CN), 106 (CH thiazole), 119 (CN), 110–170 (9 peaks due to C-Ar); MS: *m/z* 272 (M^+). *Anal*. Calcd. for $C_{12}H_8N_4S_2$: C, 52.92; H, 2.96; N, 20.57; S, 23.55%. Found: C, 52.95; H, 3.02; N, 20.61; S, 23.53%.

2-Oxo-1,2-dihydrobenzo[d]pyrrolo[2,1-b]thiazole-3-carbonitrile 12. An appropriate mixture of **1** (2.5 g, 0.01 mol) and 3 mL of 15% of alcoholic solution potassium hydroxide was refluxed in ethanol for 4 h. The reaction mixture was left to cool at room temperature and poured onto ice-water (100 mL) to yield precipitates, which were filtered off, dried, and recrystallized from DMF–ethanol mixture to give compound **12**. Pale brown crystals; yield (91%); mp 285°C; IR (KBr): ν_{max}, cm^{-1}: 1668 (C═O), 2220 (CN); ^1H NMR (DMSO-d_6): δ 4.71 (s, 2H, CH_2), 7.3–8.3 (m, 4H, aromatic protons); ^{13}C NMR (DMSO-d_6): δ 69 (CH_2), 104 (C-3), 113 (CN), 110–150 (6 peaks due to C–Ar), 178 (C3a), 196 (C═O); MS: *m/z* 214 (M^+). *Anal*. Calcd. for $C_{11}H_6N_2OS$: C, 61.67; H, 2.82; N, 13.08; S, 14.97%. Found: C, 61.65; H, 2.79; N, 13.10; S, 14.98%.

***4,4′-Thiobis(2-(benzo[d]*thiazol-2-yl)-3-oxobutanenitrile 14**. A mixture of **1** (2.5 g, 0.01 mol) and sodium sulfide (0.78 g, 0.01 mol) was refluxed in DMF for 8 h. The separated solid was filtered off, dried, and recrystallized from DMF to afford **14**. Brown crystals; yield (68%); mp 258°C; IR (KBr): ν_{max}, cm^{-1}: 1698 (C═O), 2228 (CN); ^1H NMR (DMSO-d_6): δ 4.7 (s, 4H, two CH_2), 5.0 (s, 2H, two CH), 7.34–8.10 (m, 8H, aromatic protons); ^{13}C NMR (DMSO-d_6): δ 34 (two CH_2), 48 (two CHCN), 117 (two CN), 110–170 (7 peaks due to 14 C–Ar), 178 (C3a), 207 (two C═O); MS: *m/z* 462 (M^+). *Anal*. Calcd. for $C_{22}H_{14}N_4O_2S_3$: C, 57.12; H, 3.05; N, 12.11; S, 20.80%. Found: C, 57.09; H, 3.09; N, 12.14; S, 20.82%.

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