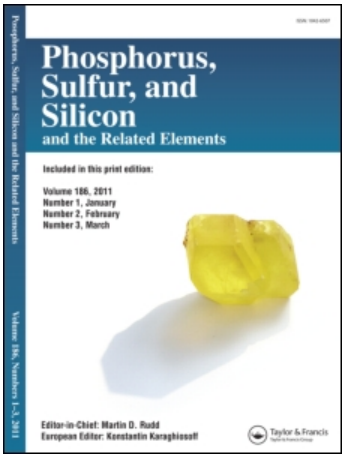

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A Facile and Simple Synthesis of Some New Pyridobenzothiazepine and Pyrimidobenzothiazepine Derivatives

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A Facile and Simple Synthesis of Some New Pyridobenzothiazepine and Pyrimidobenzothiazepine Derivatives

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2-Amino-3-cyano-4-(2-thienyl)[1,5]benzothiazepine ***5*** *has been synthesized and reacted with some active methylene and nucleophile reagents to yield new pyrido[6,5-b][1,5]benzothiazepine and pyrimido[6,5-b][1,5]benzothiazepine derivatives.*

Keywords 1,5-Benzothiazepine; pyridobenzothiazepine; pyrimidobenzothiazepine

Benzothiazepine derivatives are supposed to posses interesting biological properties and are used as chemotherapeutic agents. A number of biological and pharmaceutical activities have been associated with it, such as it displayed noticeable antiderpresent activity in several classical screening testes,[1] screening for in vitro anti-HIV-1 activity,[2] antihypertensive activity,[3] antiasthemic activity,[4] analgesic activity,[5] cardiovascular activity,[6] evaluated in vitro as arginine vaso-pressin antagonists,[7] angio-tensine converting enzyme inhibition,[8,9] platelate aggregation inhibitor, Ca antagonist, and spasmolytic activities.[10–13] They are also useful as anticonvulsant,[14] histamine H_2 and gastrin receptor antagonists.[15] Recently, 1,5-benzothiazepine derivatives have been used as a potential anticancer drug.[16–18] The importance of pyridobenzothiazepine derivatives was found to be a potential central nervous system agent.[19] On all these bases, the 1,5-benzothiazepines are useful compounds in drug research that stimulated the invention of various synthetic procedures for their preparation and chemical transformation. The 2-aminothiophenol has been widely applied as a precursor in the synthesis of benzothiazepine derivatives.[20–32] Kambe and Saito previously either used 2-aminothiophenol to react with two moles of benzylidenemalononitrile or used one mole of malononitrile with one mole of benzylidenemalononitrile in ethanol containing triethylamine

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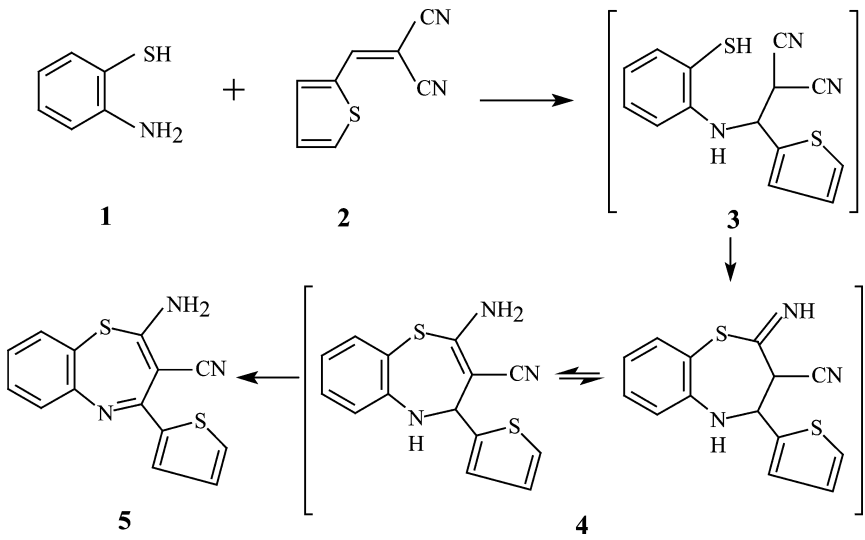
to yield 2-amino-6-(2-amino-phenylthio)-4-aryl-3,5-dicyano-pyridine.[33] However, in a mixture of acetic acid and ethanol they obtained 2-benzylidene-cyanomethyl-1,3-benzothiazole.[34] In continuation of our interest to prepare a seven-membered ring,[35–39] we report herein the reaction of 2-aminothiophenol with one mole of thienylidenemalononitrile in ethanolic piperidine solution to afford 1,5-benzothiazepine derivative, which represents an excellent precursor to prepare new derivatives of tricyclic systems, which might have useful biological and therapeutic activities.

RESULTS AND DISCUSSION

Thus, an equimolar reaction of 2-aminothiophenol **1** with thienylidenemalononitrile **2** in refluxing ethanol containing a catalytic amount of piperidine for 30 min resulted in the formation of 2-amino-3-cyano-4-(2-thienyl)[1,5]benzothiazepine **5** in good yield (Scheme 1). The formation of **5** may proceeded via an addition of an amino function of **1** to the activated double bond of **2** to give the intermediate **3**, which cyclized by a nucleophilic addition of a thiol function into one of the cyano group, to afford the intermediate **4**. The intermediate **4** tautomerized to 2-amino-4,5-dihydro-benzothiazepine and released hydrogen under an aerobic oxidation to give the starting material **5**.



1 **2** **3** **4** **5**

SCHEME 1

The structure of compound **5** was established based on analytical and spectral analysis. The IR spectrum of compound **5** confirmed the presence of intense absorption bands at ν 2217–2220 and 3370 cm^{-1} due to cyano and amino groups, respectively. The MS of **5** showed m/z at 283 (M^+, 20), 285 (M + 2, 24), 264 (M-NH_3, $-H_2$, 20), 256 (M—HCN, 5), 227 (M—CH_2=C=S, + 2H, 27), 250 (M—H_2S, + H, 20), 203 (M-thienyl, 28), 171 (M—HCN, − thienyl, −2H, 43%). The ^{1}H NMR of **5** showed a singlet signal at δ9.8 and a multiplet at δ 7.0–8.1 ppm due to the amino and aromatic protons, respectively. The ^{13}C NMR of **5** revealed absorption signals at 15.1 (CN), 118.3–128 (C-aryl), 135.3 (C-3), 140.1 (C-4), and 142.2 (C-2). The reactivity of thienobenzothiazepine **5** was investigated toward many laboratory-available reagents.

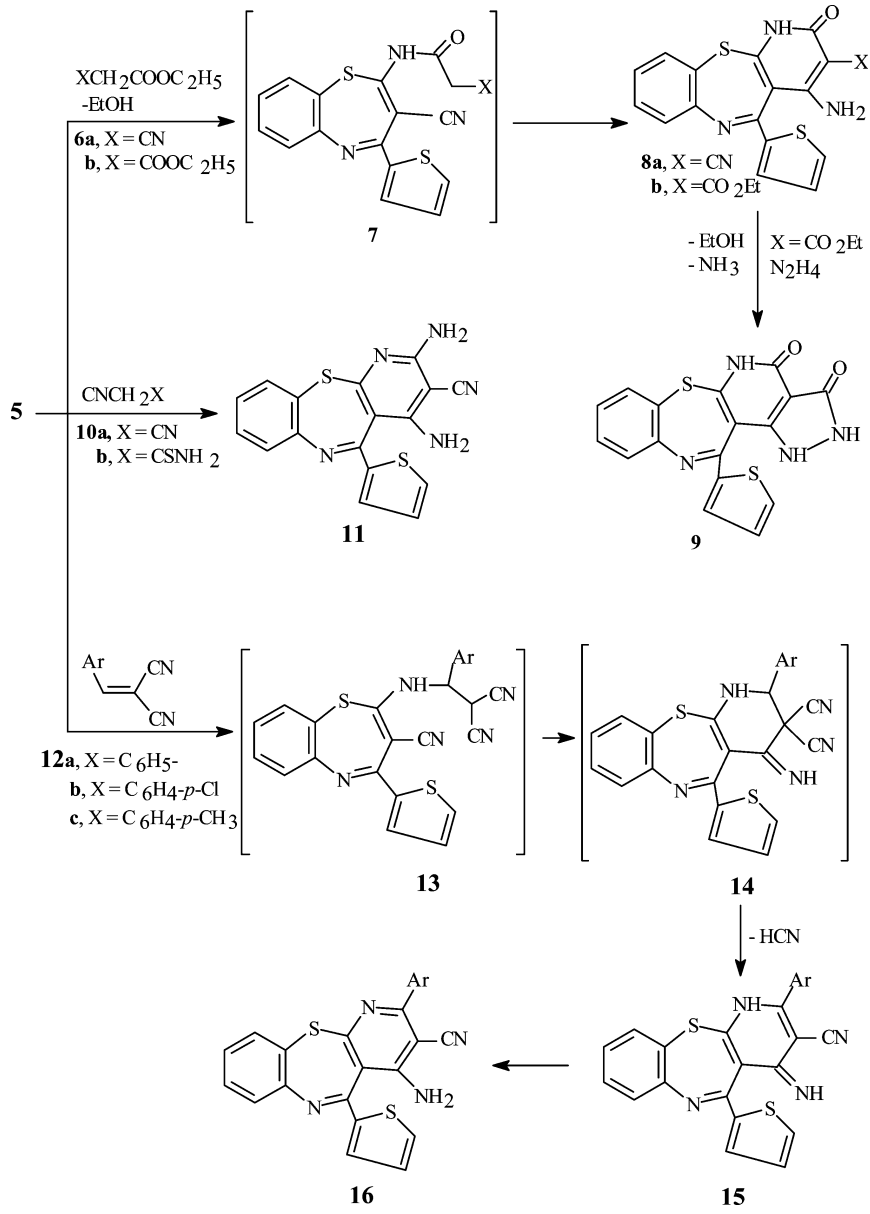
Compound **5** reacted with ethyl cyanoacetate **6a** and diethyl malonate **6b** in acetic acid and afforded pyridobenzothiazepine derivatives **8a**,**b**. It seemed that the elimination of ethanol from the acetate group gave the intermediate **7**, which subsequently cyclized via the addition of active methylene hydrogens to the cyano function yielding 4-amino-5-[2-thienyl]pyrido[6,5-*b*][1,5]benzothiazepine-1,2-dihydro-2-one derivatives **8a,b**. However, the MS of **8a** showed m/z at 351 (M + 1, 7), 350 (M^+, 19), 316 (M—H_2S, 100), 289 (M—H_2S, —HCN, 5), 261(289-CO, 2), 214 (8), and 171 (5%). Its IR spectrum revealed absorption bands at ν3390 (NH_2), 3193 (NH), 2225 (CN), and 1695 cm^{-1} (CO). The ^{1}H NMR showed signals at δ 7.1–8.0 for aromatic protons and two singlets at 9.3 and 10.3 for NH_2 and NH protons, respectively. However, the IR spectrum of **8b** showed the characteristic absorption bands at ν3388, 3200, and 1699 cm^{-1} due to NH_2, NH, and CO groups, respectively. The MS of **8b** showed m/z at 397 (M^+, 20), 369 (M—C_2H_4, 30), 341 (369-CO, 15), 325 (M—$CO_2C_2H_5$, 20), 308 (325-NH_3, 25), and 225 (308-thienyl, 35%). The ^{1}H NMR spectrum of **8b** showed characteristic absorption signals of ethoxy protons of ester groups at δ1.3 and 4.2 and showed two singlet signals at δ10.2 and 9.4 ppm due to NH and NH_2; the aromatic protons showed as a multiplet at δ 7.1–8.0 ppm. To confirm this structure, compound **8b** (X = $CO_2C_2H_5$) has been boiled at reflux with hydrazine hydrate in ethanolic piperidine solution to afford the pyrazolo[3,4: 4′,3′]pyrido[6,5-*b*]benzothiazepine derivatives **9**. The MS of **9** showed m/z at 366 (M^+, 23%). However, the ^{1}H NMR of **9** revealed the absence of characteristic absorption signals of ethoxy protons of an ester group. Similarly, the azepine compound **5** reacted with malononitrile **10a** and cyanothioacetamide **10b** in acetic acid at a reflux temperature to give in each case the same the product **11**. In the case of malononitrile **10a**, 2 successive steps of a nucleophilic addition to the cyano functions yielded **11**, whereas in case of **10b**, a condensation between the thione group of the amide and the amine of **5** released hydrogen

sulfide followed by a nucleophilic addition of the active methylene to the cyano function affording the same final product **11** (Scheme 2). The MS of **11** showed m/z *at* 350 (M + 1, 20%). The IR spectrum of **11** revealed absorption bands at ν 3390–3380 (NH_2) and 2225 (CN) cm^{-1}. Also, the reaction of **5** with arylidenemalononitrile **12a-c** afforded pyridobenzothiazepine derivatives **16a-c**. Compounds **16a-c** were formed by an addition of an amino group in **5** to the double bond in **12** to form the intermediate **13**, which cyclized via a nucleophilic addition of sp3 hydrogen of arylidene to a cyano function of benzothiazepine to form dihydropyridine intermediate **14**. The latter released hydrogen cyanide to give **15**, which finally tautomerized to form the final product **16**. Compounds **16a-c** were established by elemental and spectral data (Scheme 2).

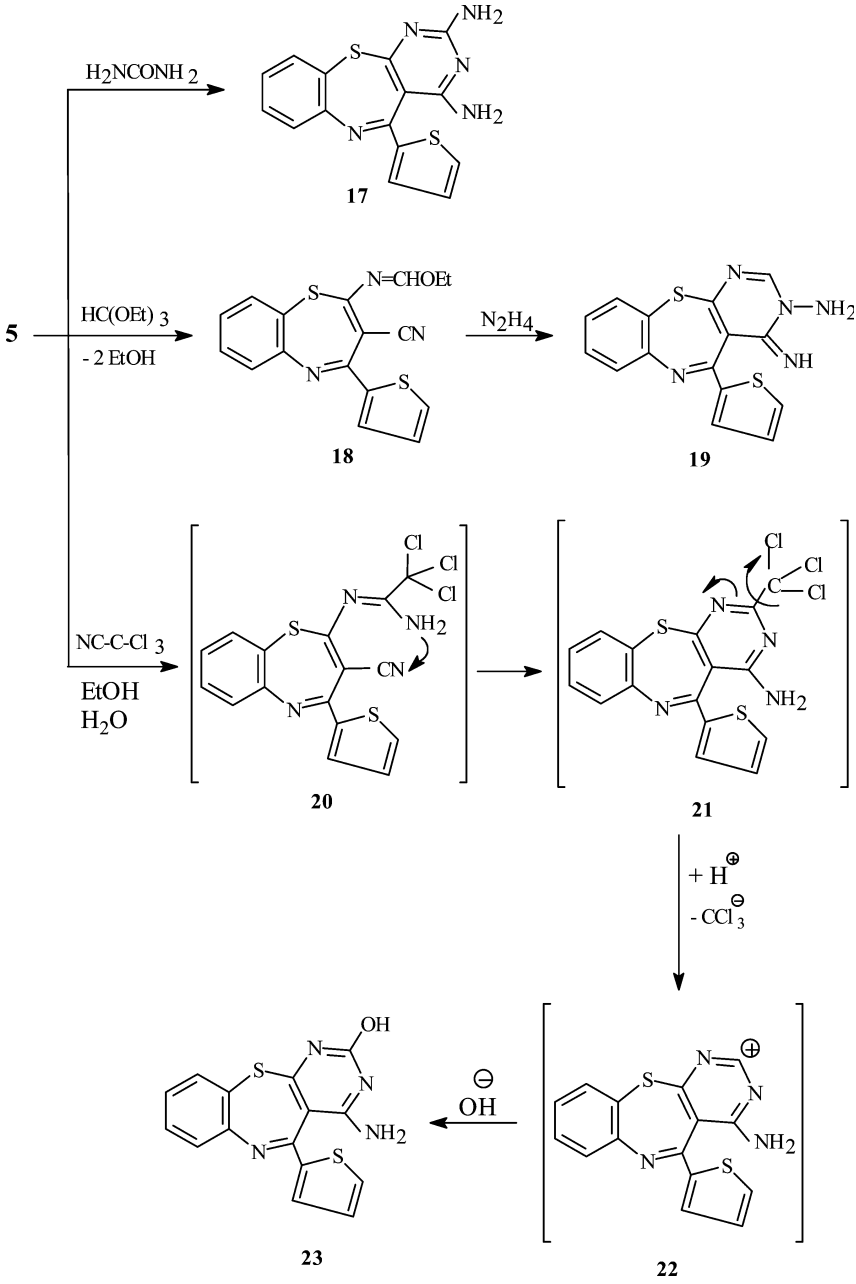
However, compound **5** represents a good synthon for pyrimidines synthesis, which found considerable interest in field of medicine and biology.[40–46] Compound **5** reacted easily with urea in acetic acid to afford 2,4-diaminopyrimidobenzothiazepine **17** via an addition-cyclocondensation reaction. The MS of **17** showed m/z at 325 (M, 45), 326 (M + 1, 9), 327 (M + 2, 3), 280 (M—NH_3, $-C_2H_4$, 6), 251 (27), 223 (15), 176 (18), and 161 (46%). The IR spectrum of **17** showed an absorption for amino functions only.

Also, the reaction of **5** with triethyl orthoformate yielded the ethoxymethylidenamino derivatives **18**. The IR spectrum of **18** showed the absence of amino absorption, and its MS showed m/z at 338 (M-1, 100) and 339 (M + 1, 45) with less intense peaks recorded at 289 (M—C_2H_5OH, —H, 11), 251 (14), and 170 (16%). Further a reaction of **18** with hydrazine hydrate afforded the corresponding pyrimidobenzothiazepine **19** via the elimination of ethanol followed by a nucleophilic addition to the cyano function. The IR spectrum of **19** revealed the absence of an absorption band at ν 2215–2220 cm^{-1} of a cyano function indicating the cycloaddition step, whereas showed intense absorption bands at ν 3390–3150 cm^{-1} due to NH_2 and NH groups. The MS of **19** showed m/z at 325 (M^+, 23).

However, the 2-hydroxypyrimidobenzothiazepine derivative **23** was formed by a reflux of trichloroacetonitrile with compound **5** in ethanol solution plausibly via a formation of the intermediate **20** through an addition of an amino function of **5** to the nitrile function of trichloroacetonitrile. A similar reaction using trichloroacetonitrile in dry toluene was reported, and the corresponding intermediate was boiled either with water or ethanol to obtain the hydroxy or ethoxy derivatives.[47] However, in the present case (ethanol 95%), the intermediate **20** cyclized via a nucleophilic addition of an amine function to the cyano group forming the pyrimidine ring. Because of the strong inductive



SCHEME 2



SCHEME 3

effect of trichlorine atoms and due to the electronic drift of the two nitrogen atoms of pyrimidine, the trichloro moiety carrying a negative charge acts as a leaving group forming chloroform. The *C*-2 of pyrimidine became a relative positive, which accepted easily the hydroxide ion from water yielding the final product **23** (Scheme 3). The IR spectrum of **23** indicated the presence of NH_2 and OH at ν 3395–3410 cm^{-I}. The MS of **23** showed m/z at 326 (M^+, 12), (327 (M + 1, 11), 328 (M + 2, 16), 243 (M-thienyl, 3), 226 (243-NH_3, 2), and 107 (100%). The ^1H NMR spectrum of **23** revealed two singlet signals at δ9.3 and 8.9 ppm due to the NH_2 and OH groups, respectively; the aromatic protons showed as a multiplet at δ 7.1–8.0 ppm.

The previously discussed reactions described a simple, one-pot synthetic procedure to prepare new derivatives of benzothiazepine compounds, which might have important biological and pharmaceutical applications.

EXPERIMENTAL

Melting points are uncorrected. Ethanol (95%) and glacial acetic acid were used as solvents. The IR spectra (potassium bromide, ν in cm^{-1}) were recorded on a Pye-Unicam SP-1100 spectrophotometer. ^1H NMR and ^{13}C NMR spectra (deuterodimethyl-sulfoxide, δ in ppm) were run on a Varian EM-390 spectrometer using Tetramethylsilane as internal standard. Mass spectra were recorded on a Varian MAT 311 A spectrometer, and the elemental analysis were determined at the Microanalytical Center, Cairo University, Egypt.

The Preparation of 2-amino-3-cyano-4-(2-thienyl)[1,5]benzothiazepine (5)

Equimolar amounts (1 mmoles) of 2-aminothiophenol **1** (1.2 g) and **2** (1.6 g) were refluxed in 30 mL ethanol for 30 min in the presence of 0.1 mL of piperidine. The formed crystals during reflux were filtered, washed well with 2 mL of methyl alcohol, and recrystallized from a mixture of EtOH/DMF (3:1). Yield: 75%. m.p.: 230°C , IR: ν3370 (NH_2), 2217–2220 cm^{-1} (CN); ^1H NMR: δ 7.0–8.1 (*m*, 7H, Ar-*H*), 9.8 (*s*, 2H, NH_2);^{13}C NMR: 15.1 (CN), 118.3–130 (C-aryl and thiophene), 135.3 (C-3), 140.1 (C-4), 142.2 (C-2). MS (70 eV) m/z (%): 283 (M^+, 20), 285 (M+2, 24), 264 (M—NH_3, —H_2, 20), 256 (M—HCN, 5), 227 (M − CH_2 = C═S, + 2H, 27), 250 (M − H_2S, + H, 20), 203 (M-thienyl, 28), 171 (M—HCN, − thienyl, −2H, 43%). Anal. Calcd. for $C_{14}H_9N_3S_2$ (283.37): C, 59.34; H, 3.20; N, 14.83. Found: C, 59.63; H, 3.50; N, 14.55.

The Preparation of Compounds 8a,b: General Procedure

A solution of **5** (0.28 g, 1 mmoles), and ethyl cyanoacetate **6a** (0.15 g, 1 mmoles) in 20 mL of acetic acid was warmed to reflux for 2 h. The solid formed during reflux was collected by filtration, washed well with 3 mL of methanol, and crystallized from acetic acid to give **8a**. Analogously, **5** (0.28 g, 1 mmoles) was reacted with diethyl malonate **6b** (1 mmoles) to give **8b**.

4-Amino-3-cyano-5-(2-thienyl)-pyrido[6,5-*b*][1,5] benzothiazepine-1,2-dihydro-2-one (8a)

Yield: 70% m.p.: 290°C, IR: ν3390 (NH_2), 3193 (NH), 2225 (CN) 1695 cm^{-1} (CO); ^1H NMR: δ 7.1–8.0 (*m*, 7H, Ar-H), 9.3 (*s*, 2H, NH_2), 10.3 (*s*, H, NH); MS (70 eV) *m*/*z* (%): 351 (M+1, 7), 350 (M^+, 19), 316 (M—H_2S, 100), 289 (M—H_2S, —HCN, 5), 261(289-CO, 2), 214 (8), 171 (5%). Anal. calcd. for $C_{17}H_{10}N_4S_2O$ (350.41): C, 58.27; H, 2.88; N, 15.99. Found: C, 58.56; H, 3.12; N, 16.23.

Ethyl 4-Amino-2-oxo-5-(2-thienyl)-1*H*-pyrido[6,5-*b*][1,5] benzothiazepine-3-carboxylate (8b)

Yield: 60% m.p.: 280°C, IR: ν3388 (NH_2), 3200 (NH), 1699 cm^{-1} (CO); ^1H NMR: δ1.3 (*t*, 3H, CH_3), 4.2 (*q*, 2H,CH_2), 7.1–8.0 (*m*, 7H, Ar—H), 9.4 (*s*, 2H, NH_2), 10.2 (*s*, 1H, NH); MS (70 eV) *m*/*z* (%): 397 (M^+, 20), 369 (M—C_2H_4, 30), 341 (369-CO, 15), 325 (M—$CO_2C_2H_5$, 20), 308 (325-NH_3, 25), 225 (308-thienyl, 35%). Anal. calcd. for $C_{19}H_{15}N_3S_2O_3$ (397.47): C, 57.42; H, 3.80; N, 10.57. Found: 57.76; H, 3.99; N, 10.88.

The Synthesis of 2,3-dioxo-1H,4H,5H-6-(2-theinyl)-pyrazolo-[3,4:4′,3`]pyrido[6,5-b][1,5]benzothiazepine (9)

A solution of **8** (0.39 g, 1 mmoles), hydrazine hydrate (0.3 mL, excess), and 0.3 mL of piperidine in 20 mL of ethanol was warmed to reflux for 7 h. The reaction mixture was concentrated under vacuum, and the solid formed after an addition of acidified cold water (1 mL Hcl, 20 mL H_2O) was collected by filtration, washed well with 100 mL of cold water, and crystallized from diluted ethanol to give **9**. Yield: 50%. m.p.: 170°C, IR: ν3190 (NH), 1695 cm^{-1} (CO); ^1H NMR: δ 7.0–8.1 (*m*, 8H, Ar-H+NH), 10.7 (*s*, 2H, 2NH); MS (70 eV) *m*/*z* (%): 366 (M^+, 23). Anal. calcd. for $C_{17}H_{10}N_4O_2S_2$ (366.41): C, 55.73; H, 2.75; N, 15.29. Found: C, 55.53; H, 2.57; N, 15.46.

The Synthesis of 2,4-Diamino-3-cyano-5-(2-thienyl)-pyrido[6,5-*b*][1,5]benzothiazepine (11)

A solution of **5** (0.56 g, 2 mmoles), malononitrile **10a** (0.13 g, 2 mmoles) in 20 mL of acetic acid was refluxed for 2 h. The solid formed during reflux was collected by filtration, washed well with 3 mL of methanol, and crystallized from acetic acid to give **11**. Analogously, **5** (0.56 g, 2 mmoles) was reacted with cyanothioacetamide **10b** (0.2 g, 2 mmoles) to give the same compound **11**. Yield: 67%. m.p.: 293°C, IR: ν 3390–3380 (NH_2) 2225 cm^{-1} (CN); ^1H NMR: δ 7.0–8.0 (*m*, 7H, Ar-H), 9.9 (*s*, 4H, $2NH_2$); MS (70 eV) *m*/*z* (%): 350 (M + 1, 20), 248 (M-thienyl, $-NH_3$, $-H$, 62%). Anal. calcd. for $C_{17}H_{11}N_5S_2$ (349.43): C, 58.43; H, 3.17; N, 20.04. Found: C, 58.80; H, 3.38; N, 20.33.

The Preparation of Compounds 16a–c and 17: General Procedure

A solution of **5** (0.28 g, 1 mmoles), and benzylidenemalononitrile **12a** (0.15 g, 1 mmoles) in 20 mL of acetic acid was warmed to reflux for 2 h. The solid formed during reflux was collected by filtration, washed well with 5 mL of methanol, and crystallized from acetic acid to give **16a**. Analogously, **5** (0.28 g, 1 mmoles) was reacted with **12b**,**c** to give **16b**,**c**. Similarly, compound **5** (0.28 g, 1 mmoles) reacted with urea (0.06 g, 1 mmoles) under the same reaction conditions to give **17**.

4-Amino-3-cyano-2-phenyl-5-(2-thienyl)-1*H*-pyrido[6,5-*b*][1,5] benzothiaepine (16a)

Yield: 65% m.p.: 265°C, IR: ν3395 (NH_2) 2220 cm^{-1} (CN); ^1H NMR: δ 6.9–8.0 (*m*, 12H, Ar-H), 10.1 (*s*, 2H, NH_2); MS (70 eV) *m*/*z* (%): 411 (M+1, 25). Anal. calcd. for $C_{23}H_{14}N_4S_2$ (410.51): C, 67.30; H, 3.44; N, 13.65. Found: C, 67.47; H, 3.96; N, 13.90.

4-Amino-3-cyano-2-(4-chlorophenyl)-5-(2-thienyl)-1*H*-pyrido [6,5-*b*][1,5]benzothiazepine (16b)

Yield: 66% m.p.: 267°C, IR: ν3399 (NH_2), 2222 cm^{-1} (CN); ^1H NMR: δ6.9–8.1 (*m*, 11H, Ar-H), 10.0 (*s*, 2H, NH_2); MS (70 eV) *m*/*z* (%): 444 (M^+, 20). Anal. calcd. for $C_{23}H_{13}ClN_4S_2$ (444.96): C, 62.08; H, 2.94; N, 12.59. Found: C, 62.22; H, 3.12; N, 12.87.

4-Amino-3-cyano-2-(4-methylphenyl)-5-(2-thienyl)-1*H*-pyrido [6,5-*b*][1,5]benzothiazepine (16c)

Yield: 60%. m.p.: 267°C, IR: ν3390 (NH_2), 2221 cm^{-1} (CN); ^1H NMR: δ 2.1 (s, 3H, CH_3), 6.9–8.0 (*m*, 11H, Ar-H), 10.3 (*s*, 2H, NH_2); MS (70 eV) *m*/*z* (%): 424 (M^+, 20). Anal. calcd. for $C_{24}H_{16}N_4S_2$ (424.54): C, 67.90; H, 3.80; N, 13.20. Found: C, 67.99; H, 4.22; N, 13.49.

2,4-Di-amino-5-(2-thienyl)-pyrimido[6,5-*b*][1,5] benzothiazepine (17)

Yield: 65%. m.p.: 290°C, IR: ν3395-3400 cm^{-1} (NH_2); ^1H NMR: δ 7.2–8.0 (*m*, 7H, Ar-H), 10.1(*s*, 4H, $2NH_2$); MS (70 eV) *m*/*z* (%): 325 (M^+, 45), 326 (M+1, 9), 327 (M+2, 3), 280 (M—NH_3, -C_2H_4, 6), 251 (27), 223 (15), 176 (18), 161 (46). Anal. calcd. for $C_{15}H_{11}N_5S_2$ (325.41): C, 55.37; H, 3.41; N, 21.52. Found: 55.60; H, 3.76; N, 21.81.

2-Ethoxymethylideneamino-3-cyano-4-(2-thienyl)[1,5] benzothiazepine (18)

Equimolar amounts of **5** (2.8 g, 10 mmoles) and triethylorthformate (1.5 g, 10 mmoles) were refluxed in 30 mL ethanol for 4 h in the presence of 0.2 mL of piperidine. The reaction mixture was concentrated under vacuum; the residue was triturated with acidified cold water (1 mL Hcl, 20 mL H_2O); and the solid was collected by filtration, washed well with 100 mL of cold water, and crystallized from diluted ethanol to give **18**. Yield: 61%. m.p.: 290°C, IR: ν2220 cm^{-1} (CN); ^1H NMR: δ1.3 (*s*, 3H, CH_3), 7.0–8.1 (*m*, 7H, Ar-H); MS (70 eV) *m*/*z* (%): 338 (M-1, 100), 339 (M^+1, 45), 289 (M—C_2H_5OH, —H, 11), 251 (14), 170 (16%). Anal. calcd. for $C_{17}H_{13}N_3S_2O$ (339.43): C, 60.16; H, 3.86; N, 12.38. Found: C, 60.35; H, 3.99; N, 12.57.

3-Amino-4-imino-5-(2-thienyl)-pyrimido[6,5-b][1,5] benzothiazepine (19)

A solution of **18** (0.28 g, 1 mmoles), hydrazine hydrate (0.3 mL, excess), and 0.3 mL of piperidine in 20 mL of ethanol was warmed to reflux for 5 h. The reaction mixture was concentrated under vacuum, and the solid formed after an addition of acidified cold water (1 mL Hcl, 20 mL H_2O) was collected by filtration, washed well with 100 mL of cold water, and crystallized from ethanol to give **19**. Yield: 60%. m.p.: 290°C, IR: ν 3390–3150 cm^{-1} (NH_2, NH); ^1H NMR: δ 7.0–8.1 (*m*, 8H, Ar-*H*), 9.7 (*s*, 1H, NH), 10.1(*s*, 2H, NH_2); MS (70 eV) *m*/*z* (%): 325 (M^+, 23). Anal.

calcd. for $C_{15}H_{11}N_5S_2$ (325.41): C, 55.37; H, 3.41; N, 21.52. Found: C, 55.69; H, 3.77; N, 21.80.

4-Amino-2-hydroxy-5-(2-thienyl)-pyrimido[6,5-*b*][1,5] benzothiazepine (23)

Equimolar amounts of trichloroacetonitrile (0.15 g, 1 mmoles) and **5** (0.28 g, 1 mmoles) were refluxed in 30 mL ethanol (95%) for 3 h in the presence of 0.2 mL of piperidine. The solid product isolated during reflux was filtered, washed well with 2 mL of methyl alcohol, and recrystallized with a mixture of EtOH/DMF (3:1). Yield: 60%. m.p.: 290°C, IR: ν 3395–3410 cm^{-1} (OH, NH_2); ^1H NMR: δ 7.0–8.1 (*m*, 7H, Ar-H), 8.9 (*s*, 1H, OH), 9.3 (*s*, 2H, NH_2); MS (70 eV) m/z (%): 326 (M^+, 12), (327 (M+1, 11), 328 (M+2, 16), 243 (M-thienyl, 3), 226 (243-NH_3, 2), 107 (100%). Anal. calcd. for $C_{15}H_{10}N_4S_2O$ (326.39): C, 55.20; H, 3.09; N, 17.17. Found: C, 55.56; H, 3.39; N, 17.39.

REFERENCES

[1] S. Vega, A. J. Diaz, M. A. Exposito, C. C. Sanchez Mateo, and V. Darias, *Arch. Pharm. Med. Chem*., **329,** 352 (1996).

[2] G. Grandolini, L. Perioli, and V. Ambrogi, *Eur. J. Med. Chem*., **34,** 701 (1999).

[3] H. A. Salim, R. Abdul, S. Mohamed, and G. M. Dahab, *J. Appl. Toxicol.*, **13,** 85 (1993), *Chem. Abstr*., **118,** 204993 (1993).

[4] H. Ben, S. Ruben, S. Melissa, and M. Kenneth, *Life Sci*., **51,** (1992); *Chem. Abstr*., **118,** 52185 (1993).

[5] H. F. Miranda, T. Pelissier, and F. Sierralta, *Gen. Pharmacol*., **24,** 201 (1993); *Chem. Abstr*., **118,** 22558 (1993).

[6] Y. Hiroki, F. Koichi, S. Yasuo, K. Takuro, K. Hiroyuki, and N. Hiroshi, *Eur. Pat. Appl*. EP 353, 032 (ClCO7D281/10), 31 Jan (1990), JP Appl. 88/185, 097, 25 Jul (1988); *Chem. Abstr*., **114,** 122434 (1991).

[7] J. U. Maud, H. C. Robert, T. D. Keith, G. Joseph, L. Richard, E. Eric, V. M. William, J. R. Philip, and Z. Xiaoyan. *Bioorg. Med. Chem. Lett*., **13,** 4031 (2003).

[8] Y. Inda, K. Itoh, K. Kamiya, H. Sugihara, and K. Nishikawa, *Japan J. Pharmacol*., **47,** 135 (1988).

[9] K. Itoh, M. Kori, Y. Inda, K. Nishikawa, Y. Kawamatsu, and H. Sugihara, *Chem. Pharm. Bull*., **34,** 1128, 2078, 3747 (1986).

[10] A. Lochead, J. C. Muller, C. Hoornaert, and C. Denys, *Eur. Pat. Appl*. EP 320, 362 (ClA61K31/55) 14 Jun (1989). FR Appl. 87/17. 044, 08 Dec (1987); *Chem. Abstr.*, **112,** 172330 (1990).

[11] M.J. Kendall and J. V. Okopski, *J. Clin. Hosptial Pharm*., **11,** 159 (1986).

[12] S. Murata, H. Kikrawn, H. Yabana, and T. Nagao, *Arzneim. Forsch*. (Drug Res.), **38,** 521 (1988).

[13] H. Narita, M. Gaino, T. Suzuki, H. Kurosawa, H. Inoue, and T. Nagao, *Chem. Pharm. Bull*., **38,** 407 (1990).

[14] C. Candelaria, V. D. Sanchez-Mateo, E. O. Auxiliadora, and M. L. Albertos, *II Farmaco*, **58,** 1–10 (2003).

[15] Y. Kawanishi, S. Ishihara, T. Tsushima, K. S. Hagishta, M. Ishikawa, and Y. Ishihara, *Bioorg. Med. Chem.*, **5,** 1411 (1997).
[16] N. K. Ahmed, *Can. Pat. Appl*. CA 2, 030, 159 (ClA61K31/55) 23 May (1991); US Appl. 441, 083, 22 Nov. (1989).
[17] N. K. Ahmed, *Eur. Pat. Appl*. EP430, 036 (ClA61K31/55), 05 Jun (1991); *US Appl*. 440, 121, 22 Nov (1989); *Chem. Abstr.*, **116,** 717 (1992).
[18] X. Fang Che, Y. Nakajima, T. Sumizawa, R. Ikeda, X. Q. Ren, C. Lei Zheng, M. Mukai, T. Furukawa, M. Haraguchi, H. Gao, Y. Sugimoto, and S. Akiyama, *Cancer Lett*., **187,** 111 (2002).
[19] J. F. Iegeois, F. A Rogister, J. Bruhwyler, J. Damas, T. P. Nguven, M. O. Inarejos, E. M. Chleide, M. G. Mercier, and J. E. Delarge, *J. Med. Chem.*, **37,** 519 (1994).
[20] T. Ganesh, and G. L. Krupadanam, *Indian J. Chem. Sect. B*., **37,** 34 (1998).
[21] B. Torsten, S. Dieter, W. Horst, *J. Heterocyclic. Chem*., **34,** 453 (1997).
[22] U. C. Pant, U. Mani, P. Seema, D. Anshu, G. K. Patnaik, and A. K. Goel, *Phosphorous, Sulfur Silicon*., **126,** 193 (1997).
[23] W. Ried and E. König, *Liebigs Ann. Chem*., **755,** 24 (1972).
[24] A. Manferd and J. Peter, *Synthesis*, **10,** 937 (1987).
[25] A. Levai, R. Bognar, and J. Kagtar, *Acta Chim. Acad. Sci. Hung*., **103,** 27 (1980).
[26] K. Sucheta, A. Prashant, and N. R. Rao, *Indian J. Chem. Sect. B*., **34,** 893 (1995).
[27] A. Lèvai, *Sci. Pharm*., **64,** 523 (1996).
[28] A. Lèvai, *Heterocyclic Commun*., **3,** 211 (1997).
[29] K. A. Sharma, G. Singh, A. K. Yadav, and K. Prakash, *Molecules*, **2,** 129 (1997).
[30] U. C. Pant, B. A. Gaur, and M. Chug, *Indian J. Chem*., **26b,** 947 (1987).
[31] V. Ambrogi, and G. Grandolini, *Synthesis*, 724 (1987).
[32] K. Blitzke, D. Sicker, and H. Wilde, *J. Heterocyclic Chem*., **34,** 453 (1997).
[33] S. Kambe, and K. Saito, *Synthesis*, 531 (1981).
[34] S. Kambe, K. Saito, and Y. Nakano, *Synthesis*, 210 (1982).
[35] A. E. El Rady, *J. Heterocyclic Chem*., **39,** 1109 (2002).
[36] A. E. El-Rady, *J. Chin. Chem. Soc.*, **51,** 859 (2004).
[37] M. F. Latif, A. E. El Rady, A. M. Khalil, and A. M. El Maghraby, *J. Heterocyclic Chem*., **39,** 299 (2002).
[38] A. E. El Rady, A. M. Kahlil, and M. F. Latif, *Heteroatom Chemistry*, **15,** 407 (2004).
[39] M. F. Latif, and A. E. El Rady, *Phosphorus, Sulfur, and Silicon*, **179**, 215 (2004).
[40] T. C. Maria, C. Cenzo, L. Valentina, and O. Valentina, *Bioorg. Med. Chem*., **14,** 366 (2006).
[41] P. L. Michael, M. B. Thomas, D. L. Miles, and F. B. Michael, *J. Exper. Marine Biology and Ecology.*, **328,** 10 (2006).
[42] W. Rudolf, B. Birgit, B. Christian, B. Thomas, E. Jörg. F. Roland, H. Rene J. Philipp, R. Laszlo, Z. Hans-Günter, and S. Achim, *Bioorg. Med. Chem. Lett.*, **16,** 108 (2006).
[43] J. Monika, M. Tracey, Y. K. Dennis, and K. Rakesh, *Bioorg. Med. Chem*., **13,** 6663 (2005).
[44] A. Anu, G. Neena, M. S. C. Prem, and G. Suman, *Bioorg. Med. Chem*., **13,** 6678 (2005).
[45] A. Anu, S. Kumkum, S. K. Puri, S. Sinha, and M. S. C. Prem, *Bioorg. Med. Chem. Lett*., **15,** 5218 (2005).
[46] V. Katia, G. Stefania, M. Stefania, V. Fabrizio, C. Elena, B. Annalisa, K. Karl- Norbert, G. B. Pier, A. T. Mojgan, M. L. Stephen, L. Edward, and A. B. Pier, *Biochem. Pharm*., **70,** 1601 (2005).
[47] F. M. Razek, N. S. Ibrahim, Z. Kandell, and M.H. El nagdi, *Synthesis*, 970 (1984).