Heteroatom Chemistry
Volume 12, Number 6, 2001

Reaction of 2-Amino-3-Cyano-4,5,6,7-Tetrahydrobenzo-[*b*]Thiophene with Ethyl Acetoacetate: Novel Syntheses of Pyridines, Pyrazoles, and Their Fused Derivatives

Rafat M. Mohareb and Mona H. Mohamed

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

Received 10 January 2001; accepted 2 April 2001

ABSTRACT: *The reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene* **1** *with ethyl acetoacetate* **2** *gave compound* **3**. *The reactivity of the latter product toward a variety of chemical reagents was studied to give fused thiophene derivatives of potential pharmaceutical interest*. © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:518–527, 2001

INTRODUCTION

Despite fairly intense research on the synthesis and the evaluation of biological properties of compounds containing thiophenes and the thienoazine moiety [1–9], very few perianellated systems with the thienoazine skeleton are known [10–12], and, to our knowledge, a relatively small amount of work has been done on the chemistry of tetrahydrobenzo[*b*]thiophene derivatives. In earlier articles [13–15], our research group described the uses of 4,5,6,7-benzo[*b*]thiophene derivatives in heterocyclic syntheses to give azole and azine derivatives containing the benzothiophene moiety. The importance of these compounds is due to their diverse pharmaceutical activities [16–19].

RESULTS AND DISCUSSION

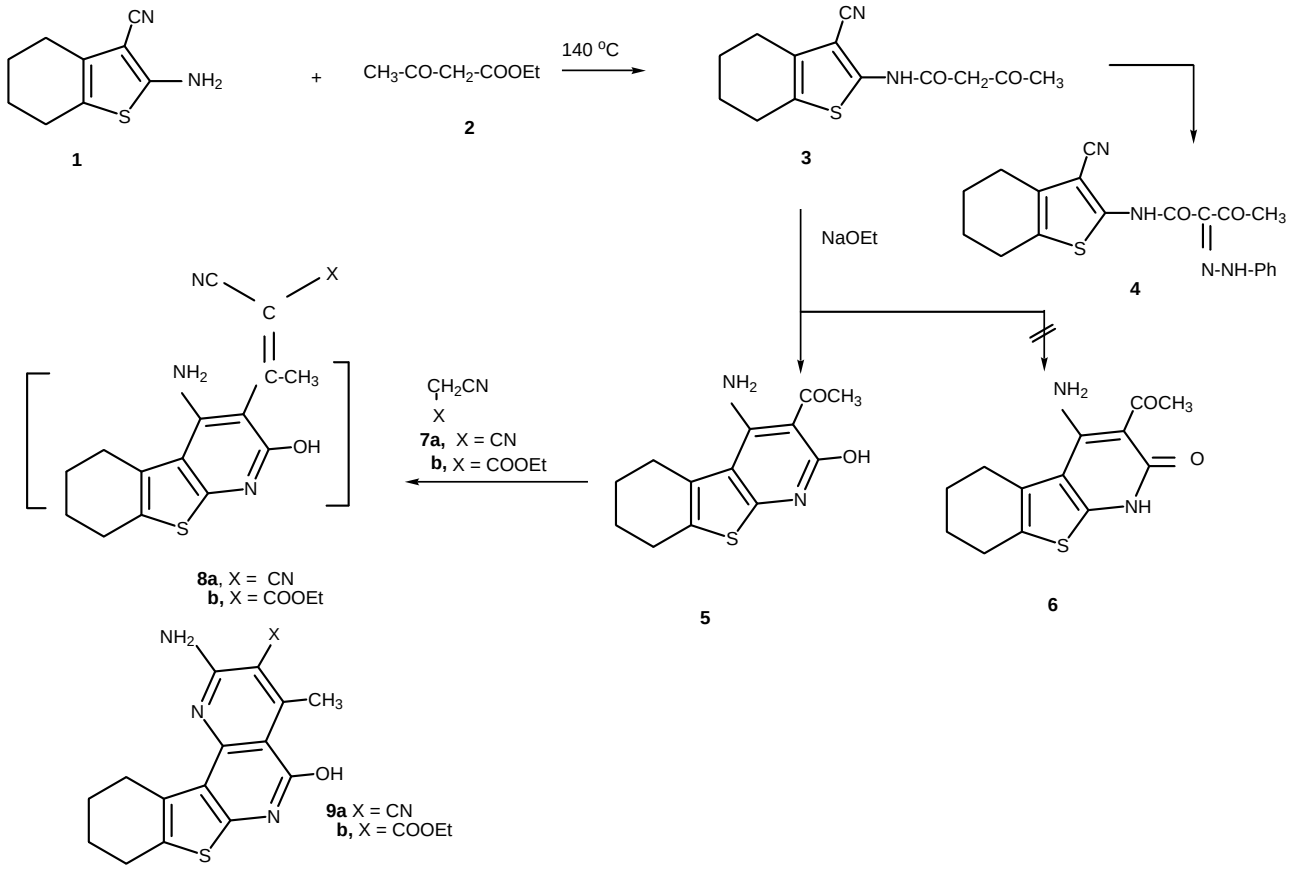
In this article, we report the reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo-[*b*]thiophene **1** with ethyl acetoacetate (**2**) in an oil bath at 140°C to give the acyclic amide derivative **3**. The structure of **3** was elucidated on the basis of analytical and spectral data. Thus, the IR spectrum of the reaction product showed an NH stretching at 3455–3340 cm^{-1}, a CN group stretching at 2223 cm^{-1} and two C=O groups stretching at 1705 and 1687 cm^{-1}. The ^1H NMR spectrum showed, besides the expected multiples corresponding to the four CH_2 groups, a singlet at δ 2.23 for the CH_3 group, a singlet at δ 5.55 for a CH_2 group and a singlet (D_2O exchangeable) at δ 8.81 for an NH group. Further confirmation for structure **3** was obtained through its reactivity toward chemical reagents. Thus, the reaction of **3** with benzenediazonium chloride gave the hydrazone derivative **4**.

Compound **3** underwent ready cyclization when heated in sodium ethoxide solution to give the 3-acetyl-4-amino-2-hydroxytetrahydrobenzo[*b*]thienopyridine derivative **5**, not the tautomeric acetyl-4-amino-2-oxotetrahydrobenzo-[*b*]thienopyridine **6**. The structure of compound **5** was established on the basis of its ^{13}C NMR spectrum which showed the presence of δ 25.9 (CH_3), 23.3, 23.9 (cyclohexene C-2, C-3), 29.3, 30.1 (cyclohexene C-1, C-4), 121.3, 122.4, 123.8, 124.0, 132.2, 133.0, 139.8 (thiephene

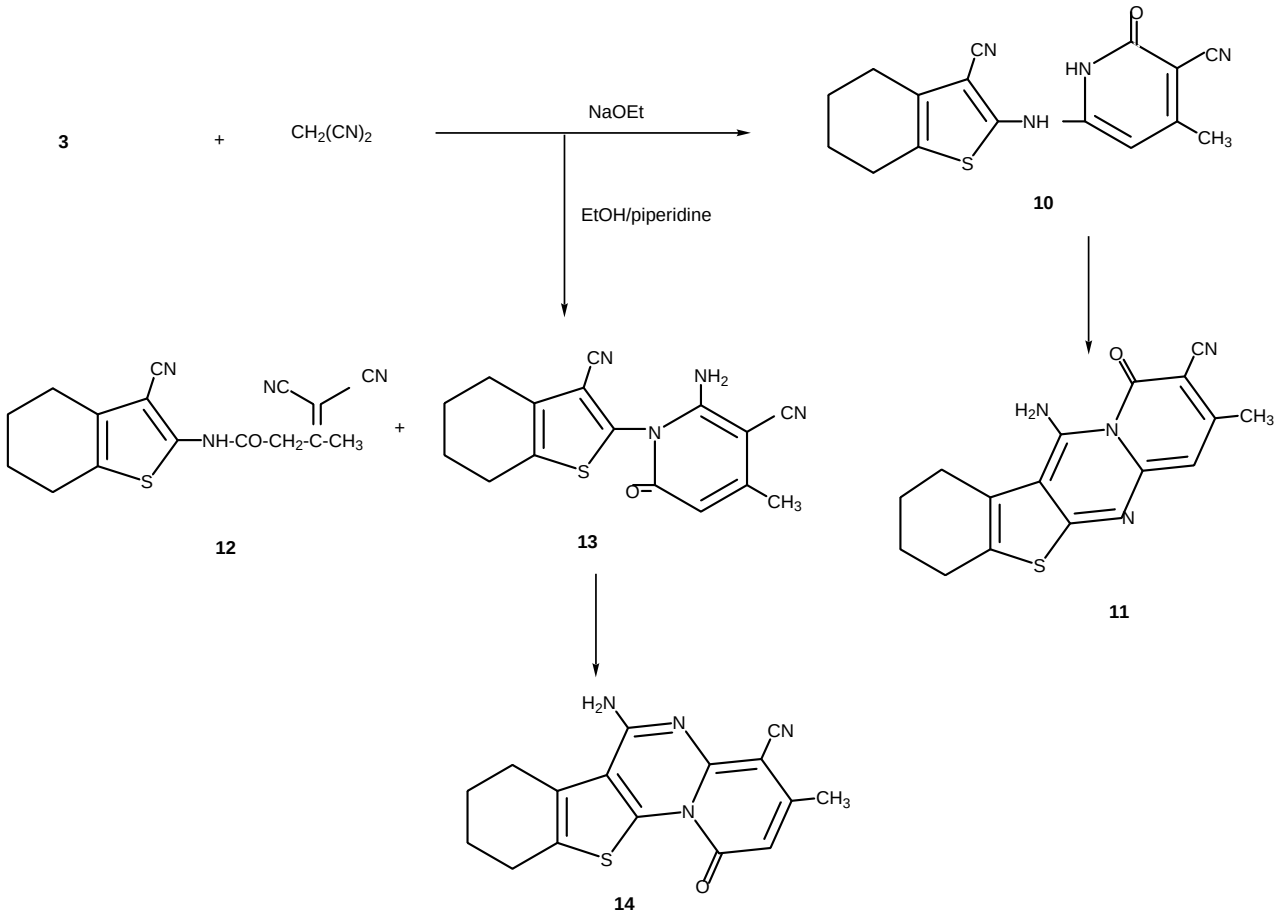
C, pyridine C), 180.3 (C=O). The presence of an acetyl group ortho to the hydroxyl group in the pyridine ring showed interesting reactivity toward active methylene reagents. Thus, with either malononitrile (**7a**) or ethyl cyanoacetate (**7b**) in ammonium acetate and with heating in an oil bath at 130°C, compound **5** gave the tetrahydrobenzo[*b*]thieno[2,3:*b*]pyrido[2,3-*d*]pyridine derivatives **9a** and **9b** respectively. Formation of the latter products took place via the intermediate formation of **8a** and **8b**, respectively. The structures of compounds **9a,b** were based on analytical and spectral data: thus, the ^{13}C NMR spectrum of **9a** showed the presence of δ 24.2 (CH_3), 23.2, 23.5 (cyclohexene C-2, C-3), 29.0, 30.4 (cyclohexene C-1, C-4), 119.6 (CN), 121.1, 122.2, 123.5, 124.2, 132.5, 133.1, 134.6, 139.7, 148.7 (thiophene C, pyridine C) (Scheme 1).

In the past, our research group studied the reaction of acetoacetanilide derivatives with malononitrile under different conditions to give either acyclic products or pyridine derivatives [20]. In continuation of this work, we studied here the reaction of the amide derivative **3** with malononitrile under a variety of conditions. Thus, conducting the reaction in ethanolic sodium, ethoxide solution gave the pyridine derivative **10**. The latter product underwent ready cyclization when heated in ethanolic sodium hydroxide to give the tetrahydrobenzo[*b*]thieno[5,4:4,5]-pyrimidine[2,1:1,2]pyridine derivative **11**. The reaction of compound **3** with malononitrile in ethanolic piperidine solution gave two products. Their separation depended on the far greater solubility of one of them in ethanol over the other. The ethanol soluble product was identified to be the acyclic product **12**, and the ethanol insoluble product was identified to be the 6-oxopyridine derivative **13**, which underwent ready cyclization when heated in sodium ethoxide solution to give the tetrahydrobenzo[*b*]thieno-[5,4:4,5]pyrimidine-[2,1:1,2]pyridine derivative **14** (Scheme 2). Structures of compounds **10–14** were identified on the basis of analytical and spectral data (see Experimental section).

The reaction of compound **3** with benzaldehyde in the presence of a catalytic amount of piperidine



SCHEME 1

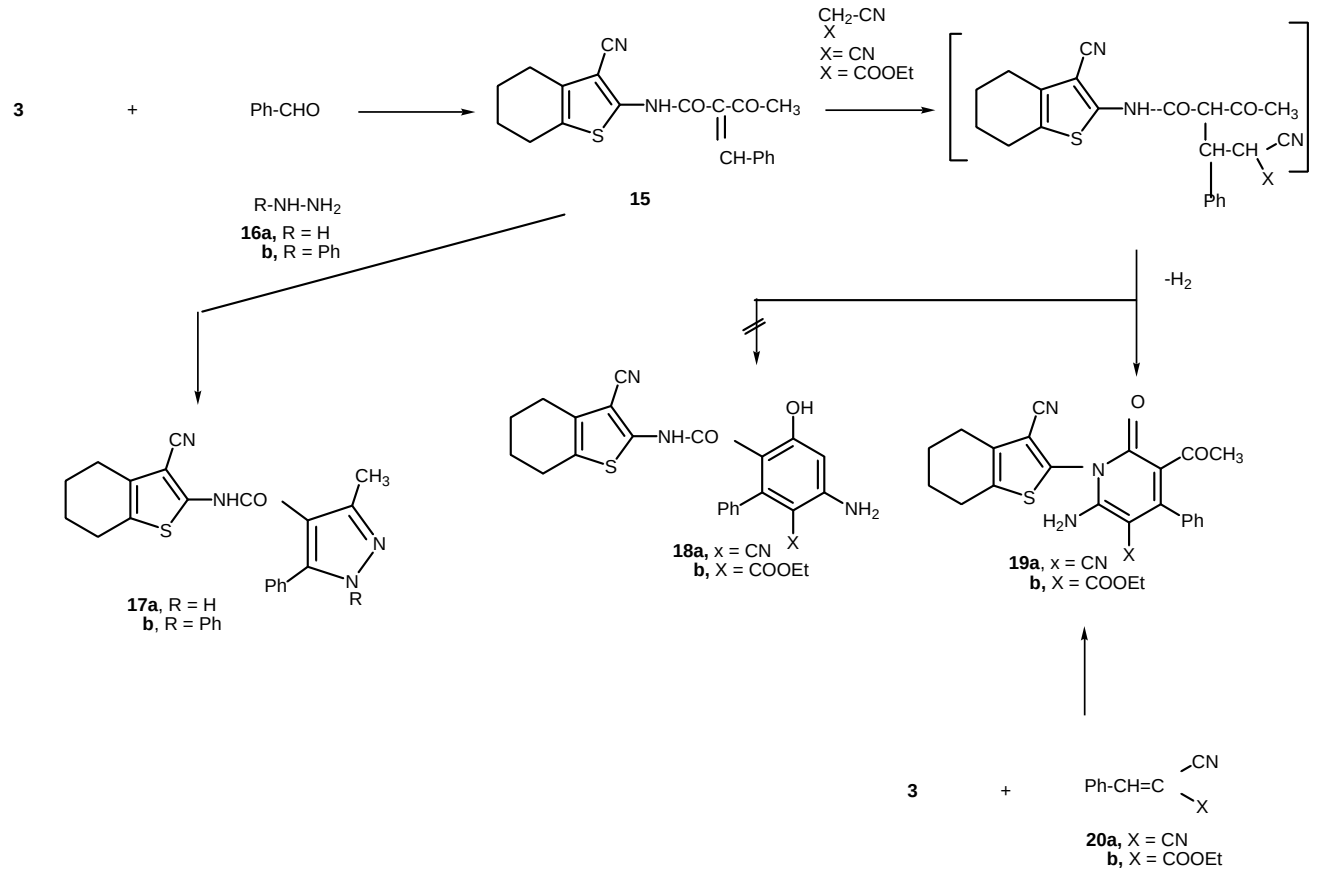


SCHEME 2

gave the benzal derivative **15**. The latter product showed high reactivity toward hydrazines. Thus, with either hydrazine hydrate **16a** or phenylhydrazine **16b**, the pyrazole derivatives **17a** and **17b** were formed, respectively. Moreover, the reaction of **15** with either malononitrile (**7a**) or ethyl cyanoacetate (**7b**) gave, in each case, a single product with molecular formulas $C_{23}H_{18}N_4O_2S$ and $C_{25}H_{23}N_3O_4S$, respectively. Two possible isomeric structures were considered: the benzene derivatives **18a** and **b** or the pyridine derivatives **19a** and **b**. Structures **18a** and **b** were ruled out on the basis of the ^{1}H NMR spectra of the reaction products, which showed the absence of any NH group. Moreover, the presence of singlets at δ 2.78 and 2.68, respectively, corresponding to CH_3 of an acetyl group which confirms structures **19a** and **b**. Further confirmations of structures **19a** and **b** were obtained through their syntheses via another reaction route. Thus, the reaction of **3** with either α-cyanocinnamonitrile (**20a**) or α-ethoxycarbonyl cinnamonitrile (**20b**) gave the same products **19a** and **19b**, respectively (mixed m.p. tests and comparison of IR spectra) (Scheme 3).

The reaction of compound **3** with bromine in the presence of acetic acid at 60°C gave the ω-bromo derivative **21**. Compound **21** showed interesting reactivity toward potassium cyanide and potassium thiocyanate to give the corresponding cyano and thiocyano derivatives **22a** and **22b**, respectively. The reaction of **22a** and **22b** with malononitrile gave the corresponding pyridine derivatives **24a** and **24b**, respectively. Formation of the latter products took place via the intermediate formation of **23a** and **b**, followed by cyclization (Scheme 4).

The reactions of compounds **24a** and **24b** with benzenediazonium chloride in ethanolic sodium hydroxide solution gave the hydrazo derivatives **25a** and **25b**, respectively, not the azo derivatives **26a** and **b**. Confirmations of the structures of the latter products were based on ^{13}C NMR data of the reaction products (see Experimental section). Further confirmations of the structures **25a** and **b** were obtained via the ready cyclization of these products, when



SCHEME 3

heated in ethanolic sodium hydroxide solution, to give the pyrido[4,3-*d*]pyridazine derivatives **26a** and **26b**, respectively (Scheme 5).

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded (KBr) on a Pye Unicam Sp-1000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian EM-390 90 MHz spectrometer in DMSO-d6 as solvent with tetramethylsilane (TMS) as an internal reference. Chemical shifts were expressed as δ. Analytical data were determined at the Microanalytical Data Unit at Cairo University.

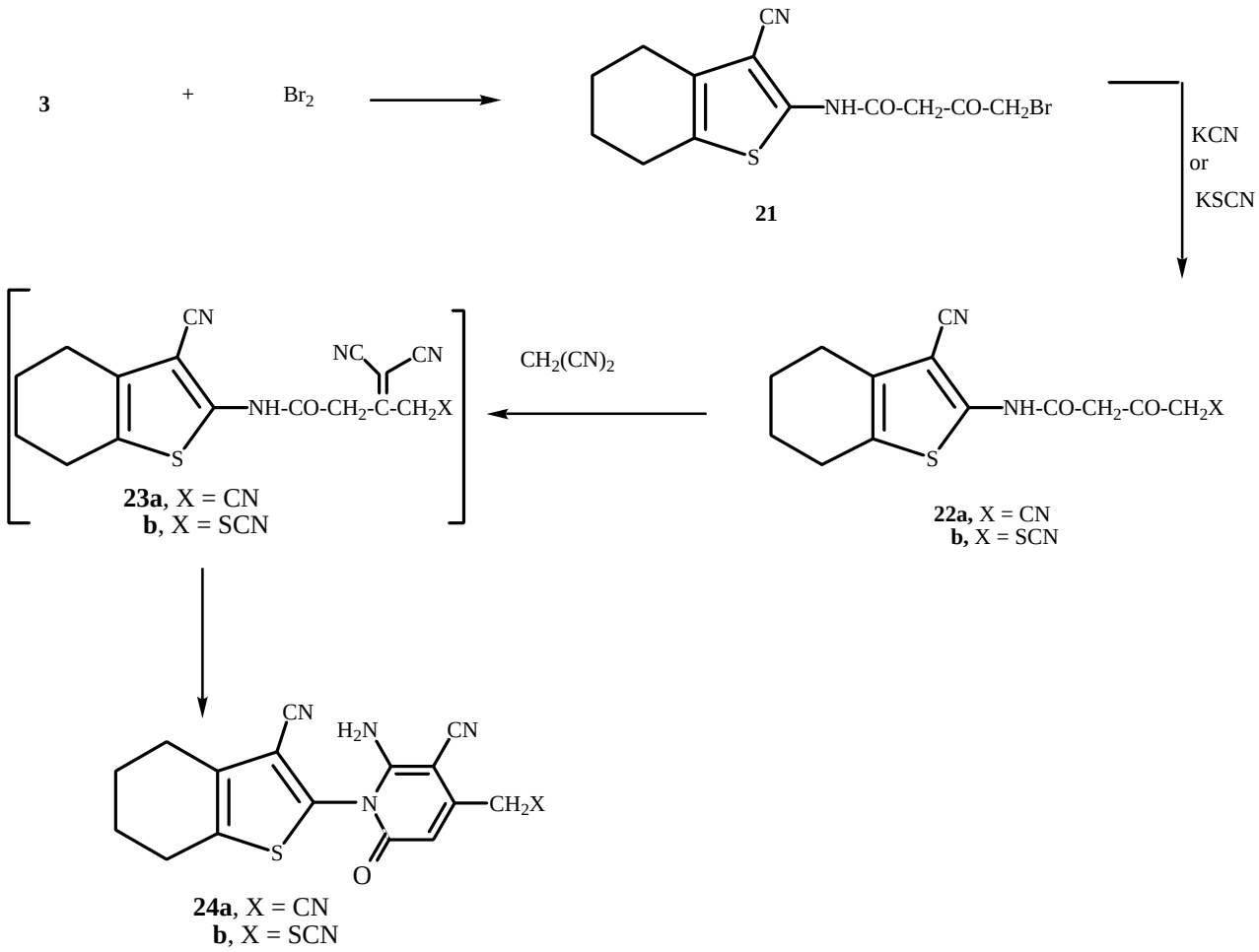
3-Cyano-2-(α-oxobutyramido-N-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene ***3***

General procedure: To dry solid **1** (1.78 g, 0.01 mol), ethyl acetoacetate (1.52 g, 0.01 mol) was added. The reaction mixture was heated in an oil bath at 140°C for 2 hours, then left to cool. Ethanol (50 mL, 95%) was added to the reaction mixture, the whole mixture was heated, and the formed solid product was collected by filtration.

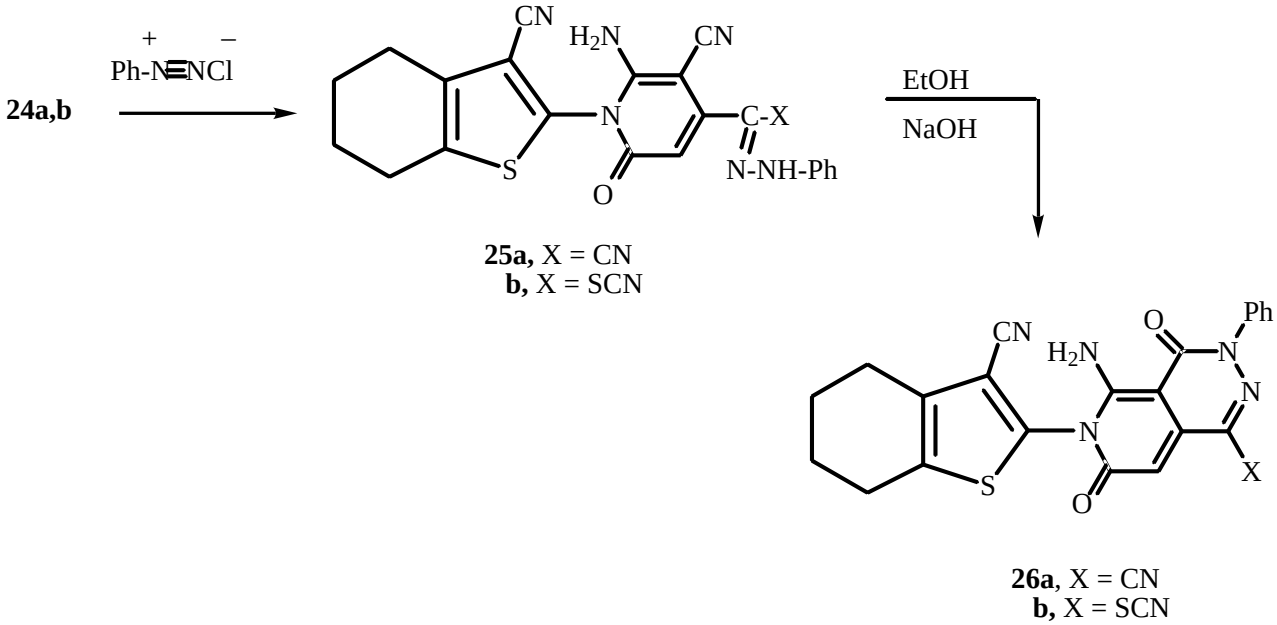
Compound **3:** Yellow crystals (from ethanol), yield 80% (2.09 g), m.p. 165°C. IR (υ^-/cm^{-1}) = 3455–3340 (NH), 2990, 2885 (CH_3, CH_2), 2223 (CN), 1705, 1687 (2 C=O), 1638 (C=C). ^{1}H NMR δ = 2.23 (s, 3H, CH_3), 2.22, 2.64 (2m, 8H, $4CH_2$), 5.55 (s, 2H, CH_2), 8.81 (s, 1H , NH). $C_{13}H_{14}N_2O_2S$ (262.32): Calcd: C, 59.52; H, 5.38; N, 10.68; S, 12.22%. Found: C, 59.27; H, 5.59, N, 9.87; S, 12.38%.

3-Cyano-2-(β-oxo-α-phenylhydrazobutyramido-N-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene ***4***

To a cold solution (0–5°C) of **3** (2.62 g, 0.01 mol) in ethanol (40 mL), a cold solution of benzenediazonium chloride (0.01 mol) (prepared by adding cold sodium nitrite solution [0.7 g, 0.01 mol] to a cold suspension [0–5°C] of aniline [0.92 g, 0.01 mol] in concentrated hydrochloric acid [8 mL] with stirring) was added with continuous stirring. The whole reaction mixture was left at room temperature for



SCHEME 4



SCHEME 5

4 hours, and the formed solid product was collected by filtration.

Compound **4:** Red crystals (from ethanol), yield 80% (2.92 g), m.p. 95°C. IR (υ^-/cm^{-1}) = 3466–3320 (NH), 2980, 2970 (CH_3, CH_2), 2220 (CN), 1705, 1685 (2 C=O), 1640 (C=C). ^{1}H NMR $\delta = 2.24$ (s, 3H, CH_3), 2.25, 2.76 (2m, 8H, $4CH_2$), 7.30–7.44 (m, 5H, C_6H_5), 8.90, 9.87 (2s, 2H , 2NH). $C_{19}H_{18}N_4O_2S$ (366.44): Calcd: C, 62.22; H, 4.91; N, 15.28; S, 8.73%. Found: C, 62.46; H, 4.87, N, 14.95; S, 8.77%.

4-Amino-3-acetyl-2-hydroxy-4,5,6,7-tetrahydrobenzo[b]thieno[5,4:2,3]pyridine ***5***

A solution of compound **3** (2.62 g, 0.01 mol) in sodium ethoxide (0.01 mol) (prepared by dissolving sodium metal [0.23 g, 0.01 mol] in absolute ethanol [40 mL]) was heated in a boiling water bath for 8 hours and then left to cool. The solid product formed upon pouring the mixture into ice/water containing hydrochloric acid (to pH 6) was collected by filtration.

Compound **5:** Pale yellow crystals (from acetic acid), yield 77% (2.02 g), m.p. 220–222°C. IR (υ^-/cm^{-1}) = 3580–3314 (OH, NH_2), 2985, 2880 (CH_3, CH_2), 1680 (C=O), 1660 (C=N), 1642 (C=C). ^{1}H NMR $\delta = 2.26$, 2.69 (2m, 8H, $4CH_2$), 2.41 (s, 3H, CH_3), 4.94 (s, 2H, NH_2), 9.86 (s, 1H, OH). ^{13}C NMR $\delta = 25.9$ (CH_3), 23.3, 23.9 (cyclohexene C-2, C-3), 29.3, 30.1 (cyclohexene C-1, C-4), 121.3, 122.4, 123.8, 124.0, 132.2, 133.0, 139.8 (thiephene C, pyridine C), 180.3 (C=O). $C_{13}H_{14}N_2O_2S$ (262.32): Calcd: C, 59.52; H, 5.38; N, 10.68; S, 12.22%. Found: C, 59.69; H, 5.30, N, 10.99; S, 11.87%.

5-Amino-4-cyano-2-hydroxy-3-methyl-4,5,6,7-tetrahydrobenzo[b]thieno[5,4:2,3]pyridino[4,5:2,3]pyridine ***9a*** *and 5-Amino-4-ethoxycarbonyl-2-hydroxy-3-methyl-4,5,6,7-tetrahydrobenzo[b]thieno[5,4:2,3]pyridino[4,5:2,3]pyridine* ***9b***

To dry solid compound **5** (2.62 g, 0.01 mol), ammonium acetate (0.77 g, 0.01 mol) was added followed by addition of either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol). The reaction mixture, in each case, was heated in an oil bath at 130°C for 0.5 hours and then left to cool. The solid product formed after triturating with ethanol was collected by filtration.

Compound **9a:** Yellow crystals (from 1,4-dioxane), yield 82% (2.64 g), m.p. 188–190°C. IR (υ^-/cm^{-1}) = 3570–3385 (OH, NH_2), 2980, 2877 (CH_3, CH_2), 2225 (CN), 1660 (C=N), 1638 (C=C). ^{1}H NMR $\delta = 2.38$ (s, 3H, CH_3), 2.28, 2.71 (2m, 8H, $4CH_2$), 4.89 (s, 2H, NH_2), 10.56 (s, 1H, OH). ^{13}CNMR $\delta = 24.2$ (CH_3), 23.2, 23.5 (cyclohexene C-2, C-3), 29.0, 30.4 (cyclohexene C-1, C-4), 119.6 (CN), 121.1, 122.2, 123.5, 124.2, 132.5, 133.1, 134.6, 139.7, 148.7 (thiophene C, pyridine C). $C_{16}H_{14}N_4OS$ (310.97): Calcd: C, 61.74; H, 4.50; N, 18.01; S, 10.29%. Found: C, 61.53; H, 4.30, N, 17.99; S, 9.87%.

Compound **9b:** Orange crystals (from ethanol), yield 72% (2.77 g), m.p. 166–169°C. IR (υ^-/cm^{-1}) = 3555–3345 (OH, NH_2), 2988, 2865 (CH_3, CH_2), 1695 (C=O), 1658 (C=N), 1644 (C=C). ^{1}H NMR $\delta = 1.16$ (t, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.25, 2.73 (2m, 8H, $4CH_2$), 4.22 (q, 2H, CH_2), 4.77 (s, 2H, NH_2), 10.31 (S, 1H, OH). $C_{18}H_{19}N_3O_3S$ (357.41): Calcd: C, 60.43; H, 5.31; N, 11.75; S, 8.95%. Found: C, 60.19; H, 5.44, N, 11.61; S, 8.49%.

2-Amino-N(3-cyano-4-methyl-6-oxopyridine-6-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene ***10***

General procedure: To a suspension of **3** (2.62 g, 0.01 mol) in sodium ethoxide solution (prepared by dissolving sodium metal [0.46 g, 0.02 mol] in absolute ethanol [60 mL]), malononitrile was added. The reaction mixture was heated in a boiling water bath for 5 hours and then poured into ice/water containing hydrochloric acid (to pH 6). The formed solid product was collected by filtration.

Compound **10:** Buff crystals (from ethanol), yield 81% (2.51 g), m.p. 271–274°C. IR (υ^-/cm^{-1}) = 3460–3345 (2 NH), 3035 (pyridine CH), 2979, 2880 (CH_3, CH_2), 2225, 2220 (2 CN), 1693 (C=O), 1665 (C=N), 1638 (C=C). ^{1}H NMR $\delta = 2.39$ (s, 3H, CH_3), 2.29, 2.68 (2m, 8H, $4CH_2$), 4.99 (s, 2H, NH_2), 7.43 (s, 1H, pyridine H-3). $C_{16}H_{14}N_4OS$ (310.37): Calcd: C, 61.92; H, 4.55; N, 18.05; S, 10.33%. Found: C, 61.72; H, 4.11, N, 17.68; S, 10.09%.

6-Amino-4-cyano-3-methyl-5-oxo-4,5,6,7-tetrahydrobenzo[b]thieno[5,4:4,5]pyrimidino[2,1:1,2]pyridine ***11***

A suspension of **10** (3.10 g, 0.01 mol) in sodium ethoxide solution (prepared by dissolving sodium metal [0.46 g, 0.02 mol] in absolute ethanol [60 mL]) was heated in a boiling water bath for 7 hours. The solid product, so formed upon pouring the mixture into ice/water containing hydrochloric acid (to pH 6) was collected by filtration.

Compound **11:** Pale yellow (from DMF), yield 70% (2.17 g), m.p. 189–191°C. IR (υ^-/cm^{-1}) = 3480, 3700 (NH_2), 3050 (pyridine CH), 2988, 2892 (CH_3, CH_2), 2223 (CN), 1688 (C=O), 1660 (C=N), 1645 (C=C). ^{1}H NMR $\delta = 2.41$ (s, 3H, CH_3), 2.27, 2.71 (2m, 8H, $4CH_2$), 5.32 (s, 2H, NH_2), 7.31 (s, 1H, pyridine

H-3). ^{13}C NMR δ = 34.1 (CH_3), 23.1, 23.9 (cyclohexene C-2, C-3), 29.5, 31.2 (cyclohexene C-1, C-4), 120.7 (CN), 122.1, 122.0, 123.9, 124.7, 132.2, 134.9, 135.6, 139.7, 148.7 (thiophene C, pyridine C, pyrimidine C), 178.7 (C=O). $C_{16}H_{14}N_4OS$ (310.37): Calcd: C, 61.92; H, 4.55; N, 18.05; S, 10.33%. Found: C, 61.66; H, 4.42, N, 18.27; S, 10.27.

*2-Aminocarbonyl[α-cyano-β-methyl-crotononitril-γ-yl]-4,5,6,7-tetrahydrobenzo[b] thiophene **12** and 3-Cyano-2-[2-amino-3-cyano-4-methyl-6-oxopyridine-1-yl]-4,5,6,7-tetrahydrobenzo[b]thiophene **13***

General procedure: To a solution of **3** (2.62 g, 0.01 mol) in absolute ethanol (70 mL) containing piperidine (1.0 mL), malononitrile (0.66 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 1 hour, and the formed solid product that precipitated from the hot solution was filtered off as compound **13**. The filtrate was dropped into ice/water containing a few drops of hydrochloric acid, and the formed solid product was filtered off as compound **12**.

Compound **12:** Orange crystals (from ethanol), yield 53% (1.64 g), m.p. 188–190°C. IR (υ^-/cm^{-1}) = 3440–3320 (NH), 2981, 2895 (CH_3, CH_2), 2225, 2220, 2217 (3 CN)1686 (C=O), 1644 (C=C). ^{1}H NMR δ = 2.24 (s, 3H, CH_3), 2.27, 2.72 (2m, 8H, 4CH_2), 5.46 (s, 2H, CH_2), 8.87 (s, 1H, NH). $C_{16}H_{14}N_4OS$ (310.37): Calcd: C, 61.92; H, 4.55; N, 18.05; S, 10.33%. Found: C, 61.59; H, 4.61, N, 18.31; S, 10.46%.

Compound **13:** Orange crystals (from ethanol), yield 40% (1.24 g), m.p. >300°C. IR (υ^-/cm^{-1}) = 3470, 3340 (NH_2), 2977, 2892 (CH_3, CH_2), 2225, 2218 (2 CN)1682 (C=O), 1639 (C=C). ^{1}H NMR δ = 2.48 (s, 3H, CH_3), 2.23, 2.70 (2m, 8H, 4CH_2), 4.95 (s, 2H, NH_2), 7.09 (s, 1H, pyridine H-3). $C_{16}H_{14}N_4OS$ (310.37): Calcd: C, 61.92; H, 4.55; N, 18.05; S, 10.33%. Found: C, 61.78 H, 4.31, N, 18.28; S, 10.57%.

*6-Amino-4-cyano-3-methyl-1-oxo–4,5,6,7-tetrahydrobenzo[b]thieno[5,4:4,5] pyrimidino[3,2:1,2]pyridine **14***

A suspension of **13** (3.10 g, 0.01 mol) in sodium ethoxide solution (prepared by dissolving sodium metal [0.23 g, 0.01 mol] in absolute ethanol [60 mL]) was heated in a boiling water bath for 8 hours and left to cool. The solid product formed upon pouring the mixture into ice/water containing hydrochloric acid (to pH 6) was collected by filtration.

Compound **14:** Pale yellow crystals (from DMF), yield 78% (2.42 g), m.p. 173–175°C. IR (υ^-/cm^{-1}) = 3462, 3380 (NH_2), 2965, 2872 (CH_3, CH_2), 2220 (CN), 1678 (C=O), 1642 (C=C). ^{1}H NMR δ = 2.39 (s, 3H, CH_3), 2.26, 2.63 (2m, 8H, 4CH_2), 4.72 (s, 2H, NH_2), 7.09 (s, 1H, pyridine H-3). $C_{16}H_{14}N_4OS$ (310.37): Calcd: C, 61.92; H, 4.55; N, 18.05; S, 10.33%. Found: C, 62.31 H, 4.79, N, 17.72; S, 10.08%.

*3-Cyano-2-(β-benzal-α-oxobutyramido-N-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene **15***

To a solution of **3** (2.62 g, 0.01 mol) in 1,4-dioxane (50 mL) containing piperidine (0.5 mL), benzaldehyde (1.10 mL, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 hours and then evaporated in a vacuum, and the remaining semisolid product was triturated with ethanol. The solid product was collected by filtration.

Compound **15:** Colorless crystals (from ethanol), yield 82% (2.87 g), m.p. 122–124°C. IR (υ^-/cm^{-1}) = 3455–3340 (NH), 3060 (CH aromatic), 2979, 2868 (CH_3, CH_2), 2222 (CN), 1696, 1682 (2 C=O), 1638 (C=C). ^{1}H NMR δ = 2.44 (s, 3H, CH_3), 2.29, 2.74 (2m, 8H, 4CH_2), 7.06 (s, 1H, C=CH), 7.28–7.35 (m, 5H, C_6H_5), 8.76 (s, 1H NH). $C_{20}H_{18}N_2O_2S$ (350.54): Calcd: C, 68.52; H, 5.17; N, 8.02; S, 9.15%. Found: C, 68.33; H, 4.85, N, 7.95; S, 8.86%.

*2-Aminocarbonyl(3-methyl-5-phenylpyrazole-4-yl)-3-cyano-4,5,6,7-tetrahydrobenzo[b] thiophene **17a** and 2-Aminocarbonyl (3-methyl-1,5-diphenylpyrazole-4-yl)-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene **17b***

General procedure: To a solution of **15** (3.50 g, 0.01 mol) in ethanol (70 mL) either hydrazine hydrate (0.5 mL, 0.01 mol) or phenylhydrazine (1.1 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 5.5 hours, then poured into ice/water containing a few drops of hydrochloric acid. The solid product formed was collected by filtration.

Compound **17a:** Yellow crystals (from acetic acid), yield 70% (2.53 g), m.p. 158–160°C. IR (υ^-/cm^{-1}) = 3440–3387 (2 NH), 2980, 2872 (CH_3, CH_2), 2225 (CN), 1680 (C=O), 1645 (C=C). ^{1}H NMR δ = 2.35 (s, 3H, CH_3), 2.26, 2.69 (2m, 8H, 4CH_2), 7.30–7.42 (m, 5H, C_6H_5), 8.88, 9.31 (2s, 2H, 2NH). $C_{20}H_{18}N_4OS$ (362.68): Calcd: C, 66.23; H, 5.00; N, 15.51; S, 8.84%. Found: C, 66.09; H, 4.69, N, 15.82; S, 9.32%.

Compound **17b:** Orange crystals (from acetic acid), yield 66% (2.39 g), m.p. 186–188°C. IR (υ^-/cm^{-1}) = 3442–3325 (NH), 2980, 2878 (CH_3, CH_2), 2220 (CN), 1688 (C=O), 1640 (C=C). ^{1}H NMR δ = 2.42 (s, 3H, CH_3), 2.28, 2.71 (2m, 8H, 4CH_2),

7.26–7.39 (m, 10H, $2C_6H_5$), 8.43 (s, 1H NH). $C_{26}H_{22}N_4OS$ (438.78): Calcd: C, 71.17; H, 5.05; N, 12.82; S, 7.31%. Found: C, 69.93; H, 4.79, N, 13.17; S, 7.08%.

3-Cyano-2-aminocarbonyl(2-amino-5-acetyl-3-cyano-4-phenyl-6-oxopyridine-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene ***19a*** *and 3-Cyano-2-(2-amino-5-acetyl-3-cyano-4-phenyl-6-oxopyridine-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene* ***19b***

Method (A): To a solution of **15** (3.5 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (1.0 mL), either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 hours, evaporated in a vacuum, and the remaining product was triturated with ethanol. The formed solid product, in each case, was collected by filtration.

Method (B): Equimolar amounts of compound **3** (2.62 g, 0.01 mol) and either α-cyanocinnamonitrile (1.45 g, 0.01 mol) or α-ethoxycarbonylcinnamonitrile (2.10 g, 0.01 mol) were mixed with 1, 4-dioxane (60 mL) containing triethylamine (1 mL). The reaction mixture was heated under reflux for 2 hours and then poured into ice/water containing a few drops of hydrochloric acid. The formed solid product, in each case, was collected by filtration.

Compound **19a:** White (from ethanol), yield 75% (3.10 g), m.p. 233–236°C. IR (υ^-/cm^{-1}) = 3455, 3385 (NH_2), 3055 (CH aromatic), 2988, 2866 (CH_3, CH_2), 2223, 2220 (2 CN), 1693, 1683 (2 C=O), 1641 (C=C). ^{1}H NMR δ = 2.78 (s, 3H, CH_3), 2.23, 2.74 (2m, 8H, $4CH_2$), 5.21 (s, 2H, NH_2), 7.33–7.40 (m, 5H, C_6H_5). $C_{23}H_{18}N_4O_2S$ (414.71): Calcd: C, 66.55; H, 4.34; N, 13.50; S, 7.71%. Found: C, 66.44; H, 4.39, N, 13.59; S, 7.50%.

Compound **19b:** Pale yellow (from acetic acid), yield 59% (2.72 g), m.p. 192–194°C. IR (υ^-/cm^{-1}) = 3475, 3363 (NH_2), 3060 (CH aromatic), 2983, 2869 (CH_3, CH_2), 2220 (CN), 1690–1680 (3 C=O), 1648 (C=C). ^{1}H NMR δ = 1.36 (t, 3H, CH_3), 2.68 (s, 3H, CH_3), 2.26, 2.70 (2m, 8H, $4CH_2$), 4.22 (q, 2H, CH_2), 5.45 (s, 2H, NH_2), 7.31–7.38 (m, 5H, C_6H_5). $C_{25}H_{23}N_3O_4S$ (461.51): Calcd: C, 64.90; H, 4.98; N, 9.11; S, 6.93%. Found: C, 64.85; H, 4.89, N, 9.37; S, 6.69%.

3-Cyano-2-(ω-bromo-α-oxobutyramido-N-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene ***21***

To a hot solution (60°C) of **3** (2.62 g, 0.01 mol) in acetic acid (40 mL), bromine (0.5 mL, 0.01 mol) in acetic acid (10 mL) was added dropwise with stirring for 10 minutes. The reaction mixture was allowed to attain room temperature and was poured into ice/water, and the formed solid product was collected by filtration.

Compound **21:** Orange crystals (from acetic acid), yield 88% (3.0 g), m.p. 171–173°C. IR (υ^-/cm^{-1}) = 3445–3315 (NH), 2885 CH_2), 2225 (CN), 1700, 1680 (2 C=O), 1643 (C=C). ^{1}H NMR δ = 2.25, 2.69 (2m, 8H, $4CH_2$), 4.29, 5.58 (2s, 4H, $2CH_2$), 8.66 (s, 1H , NH). $C_{13}H_{13}N_2O_2SBr$ (341.42): Calcd: C, 45.73; H, 3.83; N, 8.24; S, 9.39; Br, 23.43%. Found: C, 45.49; H, 3.67, N, 8.05; S, 9.02; Br, 23.01%.

2-Aminocarbonyl-(β-oxobutyronitrilo-γ-yl)-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene ***22a*** *and 2-Aminocarbonyl-(β-oxobutyrothionitrilo-γ-yl)-3-cyano-4,5,6,7-tetrahydrobenzo[b] thiophene* ***22b***

General procedure: To a hot solution (50°C) of **21** (3.41 g, 0.01 mol) in ethanol (40 mL), a solution (in 5 mL water) of either potassium cyanide (0.76 g, 0.01 mol) or potassium thiocyanide (0.98 g, 0.01 mol) was added dropwise. The reaction mixture, in each case, was left at room temperature for 4 hours with stirring. The solid product, formed in each case, upon pouring into ice/water containing hydrochloric acid (to pH 6) was collected by filtration.

Compound **22a:** Yellow crystals (from ethanol), yield 72% (2.06 g), m.p. 122°C. IR (υ^-/cm^{-1}) = 3465–3342 (NH), 2877 (CH_2), 2225, 2218 (2 CN), 1690, 1675 (2C=O), 1634 (C=C). ^{1}H NMR δ = 2.20, 2.71 (2m, 8H, $4CH_2$), 4.77, 5.05 (2s, 4H, $2CH_2$), 8.41 (s, 1H, NH). $C_{14}H_{13}N_3O_2S$ (287.33): Calcd: C, 58.52; H, 4.56; N, 14.62; S, 11.16%. Found: C, 58.31; H, 4.72, N, 14.43; S, 11.07%.

Compound **22b:** Orange crystals (from acetic acid), yield 66% (2.10 g), m.p. 196–199°C. IR (υ^-/cm^{-1}) = 3433–3320 (NH), 2890 (CH_2), 2220, 2213 (2 CN), 1693, 1680 (2C=O), 1644 (C=C). ^{1}H NMR δ = 2.22, 2.69 (2m, 8H, $4CH_2$), 4.70, 4.89 (2s, 4H, $2CH_2$), 8.38 (s, 1H, NH). $C_{14}H_{13}N_3O_2S_2$ (319.39): Calcd: C, 52.64; H, 4.10; N, 13.15; S, 20.07%. Found: C, 52.39; H, 3.88, N, 13.39; S, 19.89%.

3-Cyano-2-(2-amino-3-cyano-4-cacetonitrilo-6-oxopyridine-1-yl)-4,5,6,7-tetrahydrobenzo[b] thiophene ***24a*** *and 3-Cyano-2-(2-amino-3-cyano-4-thioacetonitrilo-6-oxopyridine-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophenene* ***24b***

General procedure: To a solution of either **22a** (2.87 g, 0.01 mol) or **22b** (3.19 g, 0.01 mol) in dimethylformamide (30 mL) containing piperidine (1.0 mL), malononitrile (0.66 g, 0.01 mol) was added. The

reaction mixture, in each case, was heated under reflux for 5 hours and then poured into ice/water. The formed solid product, in each case, was collected by filtration.

Compound **24a:** Yellow crystals (from 1,4-dioxane), yield 61% (2.04 g), m.p. 156–159°C. IR (υ^-/cm^{-1}) = 3455, 3387 (NH_2), 3045 (CH pyridine), 2877 (CH_2), 2225–2218 (3 CN), 1683 (C=O), 1646 (C=C). ^{1}H NMR δ = 2.22, 2.68 (2m, 8H, 4CH_2), 4.22 (s, 2H, NH_2), 5.12 (s, 2H, CH_2), 7.29 (s, 1H, pyridine H-5). $C_{17}H_{13}N_5OS$ (335.33): Calcd: C, 60.87; H, 3.91; N, 20.88; S, 9.56%. Found: C, 60.67; H, 4.11, N, 21.28; S, 9.64%.

Compound **24b:** Yellow crystals (from acetic acid), yield 70% (2.57 g), m.p. 210–212°C. IR (υ^-/cm^{-1}) = 3465, 3375 (NH_2), 3060 (CH pyridine), 2890 (CH_2), 2225–2215 (3 CN), 1679 (C=O), 1639 (C=C). ^{1}H NMR δ = 2.26, 2.74 (2m, 8H, 4CH_2), 4.29 (s, 2H, NH_2), 5.08 (s, 2H, CH_2), 7.27 (s, 1H, pyridine H-5). $C_{17}H_{13}N_5OS_2$ (367.47): Calcd: C, 55.56; H, 3.56; N, 19.06; S, 17.45%. Found: C, 55.43; H, 3.60, N, 19.35; S, 17.84%.

3-Cyano-2-(2-amino-3-cyano-4-phenylhydrazoacetonitrilo-6-oxopyridine-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene ***25a*** *and 3-Cyano-2-(2-amino-3-cyano-4-phenylhydrazoacetothionitrilo-6-oxopyridine-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene* ***25b***

General procedure: To a cold solution (0°C) of either **24a** (2.78 g, 0.01 mol) or **24b** (3.67 g, 0.01 mol) in ethanol (50 mL) containing sodium hydroxide (1.0 g in water, 5 mL), benzenediazonium chloride (prepared by adding sodium nitrite solution [0.7 g, 0.01 mol in water 5 mL] to a cold suspension [0°C] of aniline [0.93 g, 0.01 mol] in hydrochloric acid) was added with continued stirring. The solid product formed upon stirring for 3 hours was collected by filtration.

Compound **25a:** Reddish brown crystals (from ethanol), yield 77% (3.38 g), m.p. 167–169°C. IR (υ^-/cm^{-1}) = 3499–3332 (NH_2, NH)), 3058 (CH aromatic), 2896 (CH_2), 2227–2212 (3 CN), 1684 (C=O), 1659 (C=N), 1644 (C=C). ^{1}H NMR δ = 2.28, 2.71 (2m, 8H, 4CH_2), 4.43 (s, 2H, NH_2), 7.29 (s, 1H, pyridine H-5), 7.35–7.42 (m, 5H, C_6H_5), 8.77 (s, 1H, NH). $C_{23}H_{17}N_7OS$ (439.46): Calcd: C, 62.86; H, 3.89; N, 22.31; S, 7.30%. Found: C, 62.58; H, 3.99, N, 21,99; S, 7.24%.

Compound **25b:** Reddish brown crystals (from ethanol), yield 81% (3.81 g), m.p. 222–224°C. IR (υ^-/cm^{-1}) = 3471–3338 (NH_2, NH)), 3063(CH aromatic), 2890 (CH_2), 2226–2210 (3 CN), 1688 (C=O), 1665 (C=N), 1639 (C=C). ^{1}H NMR δ = 2.26, 2.70 (2m, 8H, 4CH_2), 4.59 (s, 2H, NH_2), 7.25 (s, 1H, pyridine H-5), 7.34–7.41 (m, 5H, C_6H_5), 8.59 (s, 1H, NH). $C_{23}H_{17}N_7OS_2$ (471.52): Calcd: C, 58.58; H, 3.63; N, 20.79; S, 13.60%. Found: C, 58.21; H, 3.19, N, 20.45; S, 13.38%.

3-Cyano-2-(7-amino-3-cyano-5,8-dioxopyrido[4,3-d]pyridazino-6-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene ***26a*** *and 3-Cyano-2-(7-amino-3-thiocyano-5,8-dioxopyrido[4,3-d]pyridazino-6-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene* ***26b***

A solution of either **25a** (4.39 g, 0.01 mol) or **25b** (4.71 g, 0.01 mol) in ethanol (70 mL) containing sodium hydroxide pellets (0.4 g, 0.01 mol) was heated under relfux for about 3 hours until all ammonia gas evolution ceased. The reaction mixture was left to cool, then poured into an ice/water mixture and hydrochloric acid was added dropwise (to pH 6). The formed solid product, in each case, was collected by filtration.

Compound **26a:** Buff crystals (from 1,4-dioxane), yield 70% (3.10 g), m.p. >300°C. IR (υ^-/cm^{-1}) = 3480, 3339 (NH_2)), 3060 (CH aromatic), 2899 (CH_2), 2222, 2219 (2 CN), 1690, 1680 (2 C=O), 1640 (C=C). ^{1}H NMR δ = 2.22, 2.74 (2m, 8H, 4CH_2), 4.48 (s, 2H, NH_2), 7.22 (s, 1H, pyridine H-5), 7.30–7.38 (m, 5H, C_6H_5). ^{13}CNMR δ 23.0, 23.8 (cyclohexene C-2, C-3), 29.2, 30.6 (cyclohexene C-1, C-4), 119.9, 120.2 (2 CN), 119.2, 120.3, 121.3, 122.7, 123.9, 124.6, 130.9, 132.7, 133.8, 134.9, 135.7, 139.7, 144.6, 148.7 (thiophene C, aromatic C), 178.9, 180.2 (2 C=O). $C_{23}H_{16}N_6O_2S$ (440.52): Calcd: C, 62.72; H, 3.65; N, 19.08; S, 7.28%. Found: C, 62.94; H, 3.74, N, 18.87; S, 7.00%.

Compound **26b:** Pale brown crystals (from acetic acid), yield 68% (3.21 g), m.p. >300°C. IR (υ^-/cm^{-1}) = 3483, 3365 (NH_2)), 3055 (CH aromatic), 2886 (CH_2), 2220, 2213 (2 CN), 1693, 1676 (2 C=O), 1635 (C=C). ^{1}H NMR δ = 2.20, 2.70 (2m, 8H, 4CH_2), 4.51 (s, 2H, NH_2), 7.20 (s, 1H, pyridine H-5), 7.35–7.42 (m. 5H. C_6H_5). ^{13}CNMR δ 23.3, 23.1 (cyclohexene C-2, C-3), 29.0, 31.0 (cyclohexene C-1, C-4), 119.5, 120.4 (2 CN), 119.9, 120.4, 121.0, 122.9, 123.9, 124.3, 130.2, 132.9, 133.2, 134.6, 135.6, 136.3, 142.3, 147.7 (thiophene C, aromatic C), 179.3, 180.0 (2 C=O) $C_{23}H_{16}N_6O_2S_2$ (472.51): Calcd: C, 58.46; H, 3.41; N, 17.79; S, 13.57%. Found: C, 58.28; H, 3.55, N, 18.01; S, 13.49%.

REFERENCES

[1] Taylor, E. C.; Patel, H. H.; Sabitha, G.; Chandari, R. Heterocycles 1996, 43, 349.
[2] Geies, A. N. J Chem Res 1998 (S), 290; (M) 1248.

[3] Robba, M.; Laduree, D.; Fossey, C.; Renault, J.; Jaurdan, F. J. Pharm Belefg 1995, 50, 121.
[4] Hozien, Z. A.; Atta, F. M.; Hassan, K. M.; Abdel-Wahab, A. A.; Ahmed, S. A. Synth Commun 1996, 26, 3733.
[5] Rosowsky, A.; Papoulis, A. T.; Quaner, S. F. J Med Chem 1997, 40, 3694.
[6] El-Dean, A. M. K. Monatsh Chem 1998, 129, 523.
[7] Clark, J.; Hitiris G. J Chem Soc Perkin Trans 1, 1984, 2005.
[8] Meeson, M. L.; Parsons, M. E.; Theobald, J. C. J Med Chem 1995, 38, 2763.
[9] Shishoo, C. J.; Devani, M. B.; Bhadt, V. G.; Jain, K. S.; Rathod, I. S.; Goyal, R. K.; Gandhi, T. P.; Patel, R. B.; Nail, G. R. Arzneim-Forsch 1990, 40, 567.
[10] Russel, R. K.; Rampulla, R. A. U. S. Patent 1990/4939/37; Chem Abstr 1990, 113, 212008.
[11] Grinev, A. N.; Kaplina, N. V. Khim Geterotsikl Soedin 1985, 925.
[12] Russel, R. K.; Rampulla, R. A.; Nievelt, C. E.; Klaubert, D. H. J. Heterocyclic Chem 1990, 27, 1761.
[13] Mohareb, R. M.; Manhi, F. M. Heteroat Chem 2000, 11, 403.
[14] Mohareb, R. M.; El-Omran, F. A.; Ho, J. Heteroat Chem 2001, 12, 168.
[15] Zodi, H. F.; Wardakhan, W. W.; Doss, S. H.; Mohareb, R. M. J Chem Res (S), 1996, 440; (M), 1996, 2526.
[16] Wardakhan, W. W. Phosphorus Sulfur Silicon 2000, 162, 275.
[17] Magni, A.; Signorelli, G.; Bochiola, G.; Arzeneim-Forsch J Drug Res 1994, 44, 1420.
[18] El-Feky, S. A.; Avdel-Samii, Z. K. Pharmazie 1995, 50, 341.
[19] Nanteuil, G. D.; Herve, Y.; Duhault, J.; Espinal, J.; Boulanger, M.; Ravel, D. Arzeneim-Forsch J Drug Res 1995, 45, 1175.
[20] Habashi, A.; Ibrahim, N. S.; Mohareb, R. M.; Fahmy, S. M., Liebigs Ann Chem 1986, 1632.