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Reaction of 3-Cyano-2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene with Enaminonitriles

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Summary. 2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene with ethyl β-amino-α-cyano-γ-ethoxycarbonylcrotenoate yields the corresponding amide derivative. That compound reacts with benzenediazonium chloride to give the phenyl hydrazone derivative. This type of compounds was cyclized to give pyridazine and pyridine derivatives, respectively. Chemical reactivities of the latter were studied to give fused heterocyclic compounds with antimicrobial activities.

Keywords. Thiophene; Thiazole; Pyridazine; Pyridine.

Introduction

In pharmacological studies of azines and derivatives it has been shown that they possess a variety of activities including antihelmintic [1] and antimicrobial [2–4]. Thiophenes and their fused derivatives have shown diverse pharmacological activities including antibacterial [3], immunomodulatory [4] antiflammatory [5], antidiabatic [6, 7], antiplatele-activating factor [8], and antiviral activities [9, 10]. Therefore, it was thought to be of interest to combine two of the above-mentioned rings together in a molecular framework to give heterocyclic products with high pharmaceutical potentiality.

Results and Discussion

In our earlier publications [11–13] we reported some biologically active 4,5,6,7-tetrahydrobenzo[*b*]thiophene derivatives. In this article, we report the reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**1**) with ethyl

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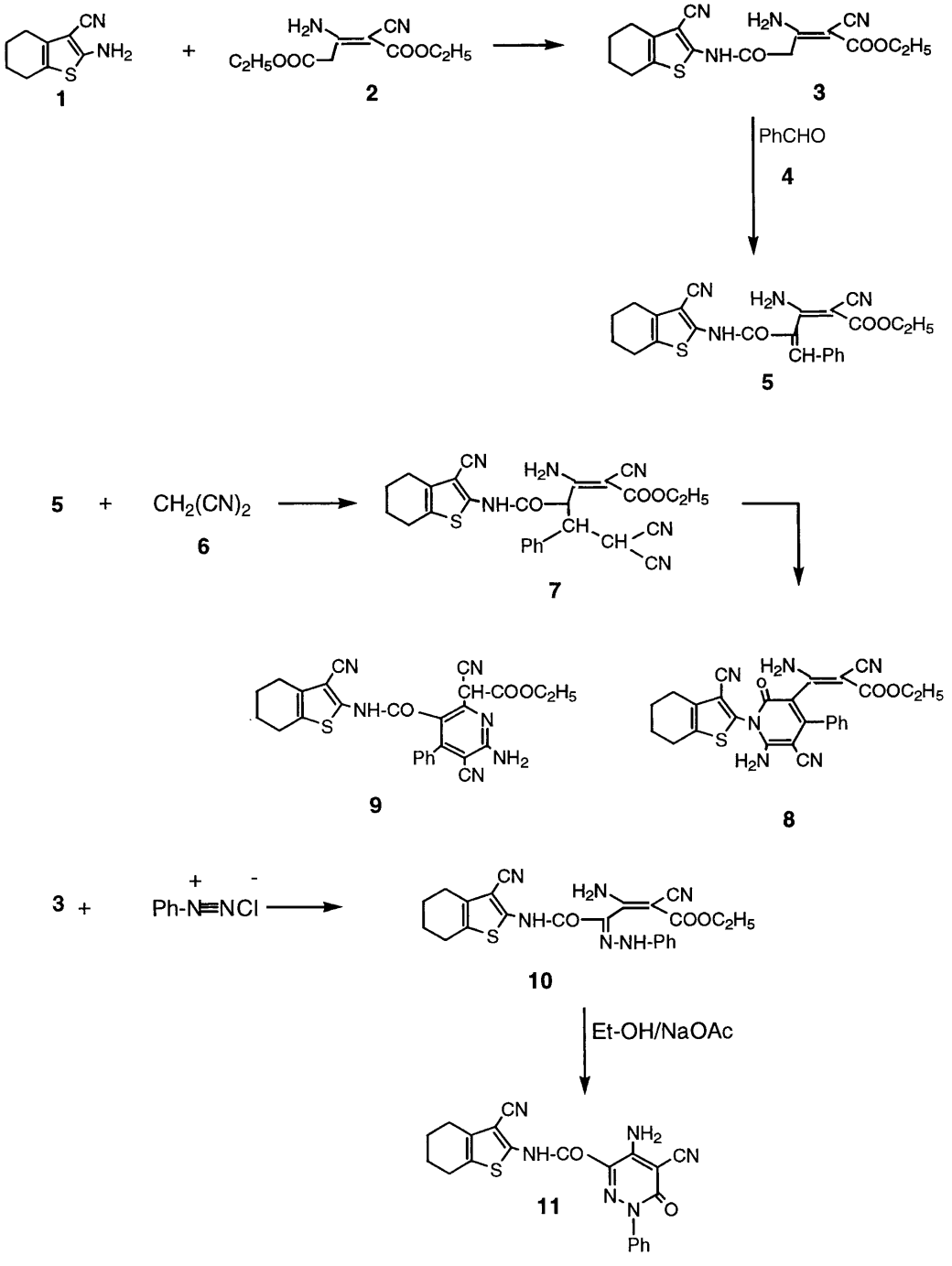
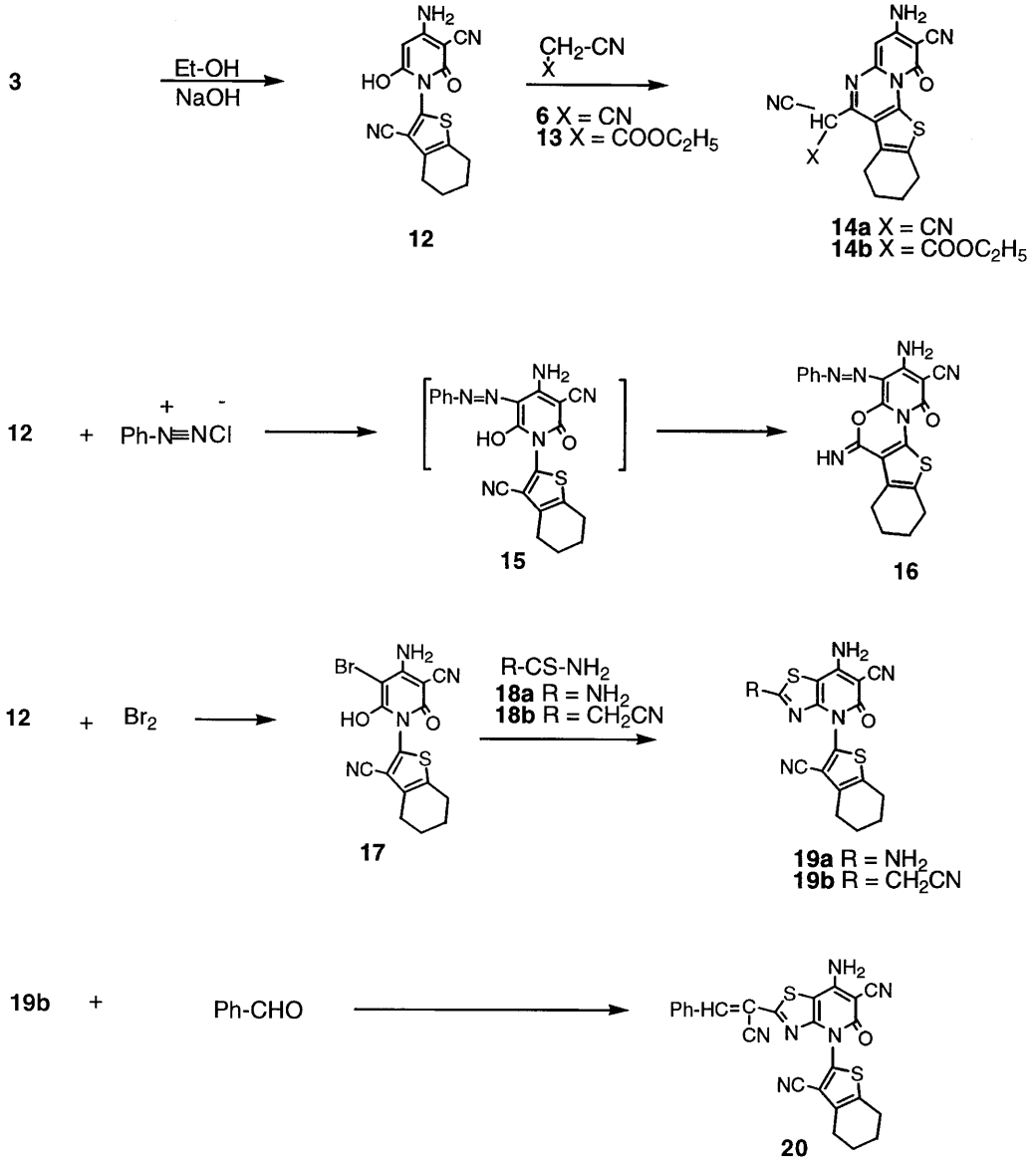
β-amino-α-cyano-γ-ethoxycarbonylcrotenoate (**2**) to form an amide derivative capable for cyclization into azine derivatives incorporating the thiophene ring with anticipated biological activity. Thus, the reaction of **1** with **2** in 1,4-dioxane solution gave the amide derivative **3**. The structure of **3** was established on the basis of



Scheme 1

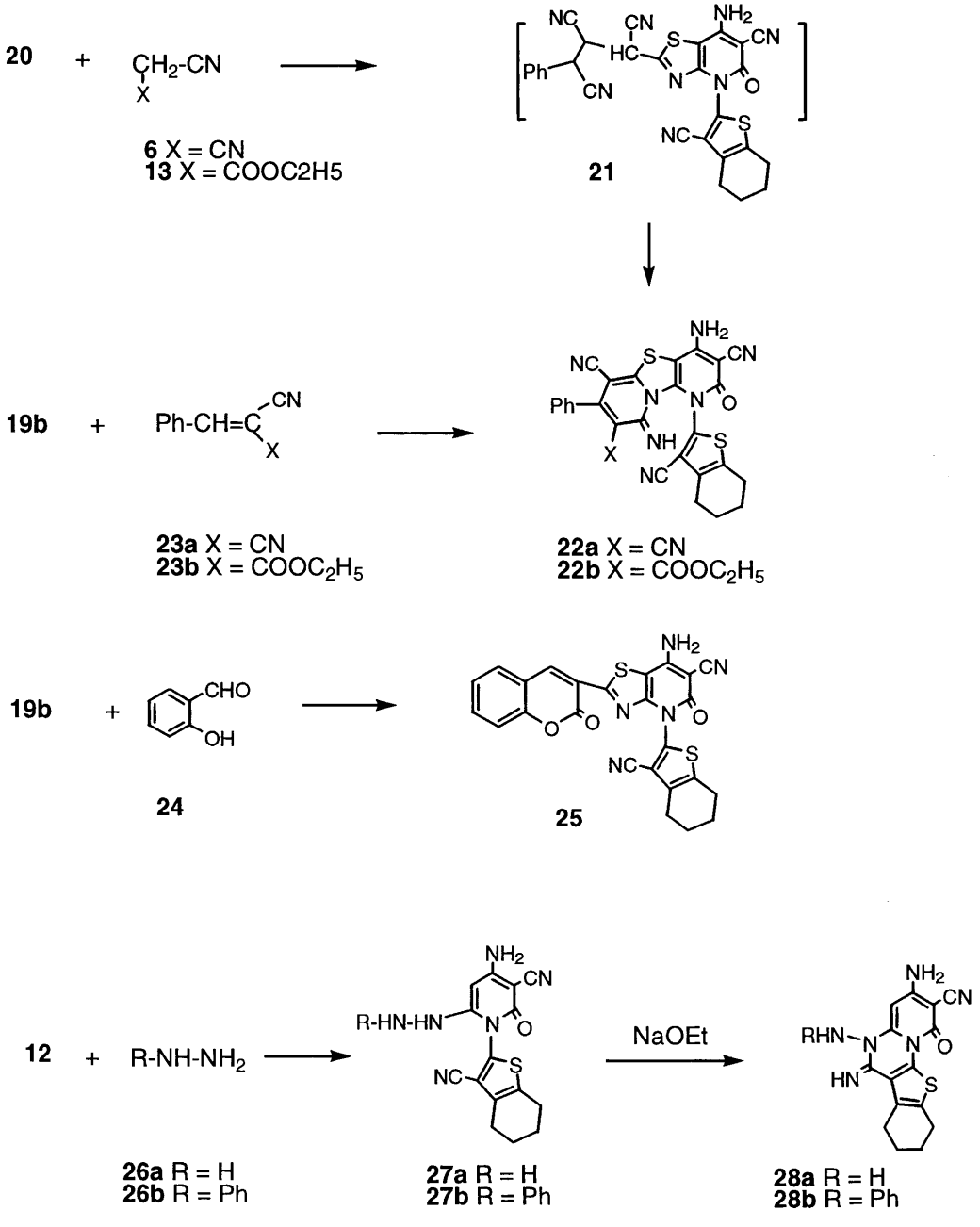
analytical and spectral data. The ^{1}H NMR spectrum of the reaction product showed a triplet at $\delta = 1.16$ ppm corresponding to a CH_3 group, two multiplets at 2.22, 2.67 ppm for four CH_2 groups, a quartet at 4.24 ppm for the ester CH_2 group, a singlet at 4.52 ppm (D_2O exchangeable) for NH_2, a singlet at 5.67 ppm for CH_2 group, a singlet at 8.86 ppm for the NH group. The ^{13}C NMR spectrum showed resonances at $\delta = 26.8$ (CH_3), 33.6, 34.2, 34.5 (4 CH_2), 55.9, 66.13 (2 CH_2), 108.9, 110.1 (C=C), 119.2, 120.2 (2 CN), 126.5, 125.4, 135.1, 140.0 (thiophene-C), and finally 179.5, 180.2 (2 C=O) ppm.

The reaction of **3** with benzaldehyde (**4**) in ethanol/piperidine solution gave the benzal derivative **5**. The reaction of **5** with malononitrile (**6**) gave a single product



Scheme 2

with the molecular formula $C_{27}H_{22}N_6SO_3$. Two possible isomeric structures **8** and **9** were assigned for this formula. Both of these structures were assumed on the basis of the intermediate formation of **7**. Structure **9** was established for the reaction product on the basis of the ^{1}H NMR spectrum which showed, beside the expected peaks, a singlet at 5.45 ppm corresponding to one NH_2 group, a singlet at 6.21 ppm corresponding to CH group, and a singlet at 8.91 ppm for the NH group.



Scheme 3

The reaction of **3** with benzenediazonium chloride in alcoholic sodium acetate solution at 0°C gave the phenylhydrazono derivative **10**. The latter underwent readily cyclization when heated in ethanolic sodium hydroxide solution to give the pyridazine derivative **11**. Similar pyridazine formations have been reported in Refs. [14, 15]. Cyclization of **3** in EtOH/NaOH gave the pyridine derivative **12**. The reaction of the latter product with either **16** or **13** gave **14a** and **14b**, respectively.

The reaction of **12** with benzenediazonium chloride gave the 4-phenylazotetrahydrobenzo[*b*]thieno[5,4:4,5]-1,3-oxazino[2,3:6,1]-pyridine derivative **16**. Formation of the latter product was based on the intermediate formation of **15** followed by cyclization. Analytical and spectral data are consistent with the assigned structure (see Exp.). The reaction of **12** with bromine in hot acetic acid solution gave the 5-bromopyridine derivative **17**. The α-oxohalo moiety present in **17** showed an interesting reactivity towards thioamides to form pyridothiazole derivatives of potential biological activities. Thus, **17** reacted with either thiourea (**18a**) or cyanothioacetamide (**18b**) to give the thiazolo[4,5-b]pyridine derivatives **19a** and **19b**. Structures of the latter products were based on analytical and spectral data (see Exp.). The Reaction of **19b** with **4** gave the benzal derivative **20**, the latter reacted with either **6** or **13** to give the pyrido[6,1:2,3]thiazolo[4,5:2,3]pyridine derivatives **22a** and **22b**. Formation of **22a** and **22b** took place through the intermediate formation of **21a** and **21b**. The analytical and spectral date are consistent with the assigned structures (see Exp.). The latter products were obtained through another reaction route. Thus, the reaction of **19b** with either α-cyanocinnamonitrile (**23a**) or ethyl α-cyanocinnamate (**23b**) gave the same products **22a** and **22b**.

Table 1. *In vitro* bactericidal activity of some of the newly synthesized compounds

Compound No.	*Bacillus cereus* (Gram positive)	*Staph. aureus* (Gram positive)	*E. coli* (Gram negative)	*K. pneumonia* (Gram negative)
5	+++	++	+++	+
9	++	+++	++	+++
10	++	++	+++	+++
11	+	+++	+	++
16	+++	++	+++	+++
17	+++	+++	+	+
19a	+	+	++	+
19b	++	+++	+++	++
20	+++	++	++	++
22a	+++	+	++	+++
22b	++	+++	+++	++
25	+++	+	+	+
27a	+	++	+++	+++
27b	++	+	+++	++
28a	+++	+	++	++
28b	++	++	+	+++

Slight inhibition +, moderate inhibition ++, strong inhibition +++; rating percent control: no inhibition 0, slight inhibition 10, 20, 30, moderate inhibition 40, 50, 60, strong inhibition 70, 80, 90, complete inhibition 100

On the other hand the reaction of **19b** with salicyladehyde (**24**) gave the 6-coumarin-3-yl-thiazolo[4,5:b]pyridine derivative **25**.

The reaction of **12** with either hydrazine hydrate (**26a**) or phenyl hydrazine (**26b**) gave the 6-hydrazinopyridine derivatives **27a** and **27b**. The latter products underwent cyclization in sodium ethoxide solution to give the pyrido[6,1-b]pyrimidine derivatives **28a** and **28b**. Structures of the latter products were based on analytical and spectral data. Thus, the IR spectrum of **28a** showed only one CN group stretching at $\nu = 2220\,cm^{-1}$ and its ^{13}C NMR spectrum showed resonances at 33.8, 34.2, 34.5 (4 CH_2), 118.9, 119.2 (2 CN), 122.6, 124.6, 138.2, 140.0 (pyridine, pyrimidine and thiophene-C), 177.3 (C=O), and 179.9 (C=N) ppm.

Bactericidal activity

The diverse biological activities of thiophenes and their fused derivatives prompted us to test and study the biological activities of some of the newly synthesized products. Their bactericidal activities were measured applying the literature procedure [16, 17]. The results are compiled in Table 1.

Experimental

All melting points are uncorrected. IR spectra were recorded for KBr discs on a Pye Unicam SP-1000 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were measured on a Varian EM-390-200 MHz in CD_3SOCD_3 as solvent and using *TMS* as internal standard.

2-Acetylamino-α-(Ethyl α-cyano-β-aminoacrylate)-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene (**3**, $C_{17}H_{18}N_4SO_3$)

To a solution 1.78 g of the 4,5,6,7-tetrahydrobenzo[*b*]thiophene derivative **1** (0.01 mol) in 30 cm^3 *DMF*, 2.26 g **2** (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h and then poured into ice/water mixture containing few drops of HCl. Yield 80%; m.p. 130–133°C (ethanol); IR: $\bar{\nu} = 3465 - 3435$ (NH_2, NH), 2988, 2895 (CH_3, CH_2), 2225, 2220 (2 CN), 1720, 1695 (2 C=O), 1633 (C=C) cm^{-1}; ^1H NMR $\delta = 1.16$ (t, $J = 7$ Hz, CH_3), 2.22, 2.67 (2m, 4 CH_2), 4.24 (q, $J = 7$ Hz, CH_2), 4.52 (s, NH_2), 5.67 (s, CH_2), 8.86 (s, NH) ppm. ^{13}C NMR (*DMSO-d_6*) $\delta = 26.8$ (CH_3), 33.6, 34.2, 34.5 (4 CH_2), 55.9, 66.13 (2 CH_2), 108.9, 110.1 (C=C), 119.2, 120.2 (2 CN), 126.5, 125.4, 135.1, 140.0 (thiophene-C), 179.5, 180.2 (2 C=O) ppm.

2-Benzalacetylamino-α-(Ethyl α-cyano-β-aminoacrylate)-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene (**5**, $C_{24}H_{22}N_4SO_3$) *and*
4-Amino-3-cyano-6-benzalcyano-methyleno-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene-2-yl)-2-oxo-thiazolo[4,5-b]pyridine (**20**, $C_{25}H_{16}N_6S_2O$)

To a solution of either 3.58 g **3** (0.01 mol) or 3.92 g **19b** (0.01 mol) in 50 cm^3 1,4-dioxane containing 0.5 cm^3 piperidine, 1.08 g benzaldehyde (0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h and then poured into ice/water containing a few drops of HCl. The formed solid product was collected by filtration.

5: Yield 66%; m.p. 165–168°C (ethanol); IR: $\bar{\nu} = 3466 - 3420$ (NH_2), 2986, 2888 (CH_3, CH_2), 2222, 2220 (2 CN), 1710, 1690 (2 C=O), 1637 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*) $\delta = 1.15$

(t, $J = 6$ Hz, CH_3), 2.26, 2.66 (2m, 4 CH_2), 4.23 (q, $J = 6$ Hz, CH_2), 4.55 (s, NH_2), 7.01 (s, CH=C), 7.32–7.38 (m, C_6H_5), 8.86 (s, NH) ppm.

20: Yield 62%; m.p. 190–193°C (ethanol); IR: $\bar{\nu} = 3462 - 3339$ (2 NH_2), 2895 (CH_2), 2225, 2220, 2218 (3 CN), 1701 (C=O), 1651 (C=N), 1637 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 2.26$, 2.69 (2m, 4 CH_2), 5.21 (s, NH_2), 6.78 (s, CH=C), 7.32–7.40 (m, C_6H_5) ppm.

3-Cyano-2-aminocarbonyl-(2-amino-3-cyano-4-phenyl-6-ethyl cyanoacetato-α-yl-pyridin-5-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene (**9**, $C_{27}H_{22}N_6SO_3$)

Equimolecular amounts of 4.47 g **5** (0.01 mol) and 0.66 g **6** (0.01 mol) in 40 cm^3 1,4-dioxane containing 1.0 cm^3 triethylamine was heated under reflux for 6 h. After cooling the reaction mixture, the solution was evaporated in vacuum. The remaining product was triturated in ethanol and the formed solid product was collected by filtration. Yield 70%; m.p. 220–222°C (1,4-dioxane); IR: $\bar{\nu} = 3470 - 3410$ (NH, NH_2), 2980, 2750 (CH_3, CH_2), 2225, 2215, 2210 (3 CN), 1720, 1693 (2 C=O), 1634 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 1.16$ (t, $J = 7$ Hz, CH_3), 2.25, 2.66 (2m, 4 CH_2), 4.25 (q, $J = 7$ Hz, CH_2), 5.45 (s, NH_2), 6.21 (s, CH), 7.30–7.41 (m, C_6H_5), 8.91 (s, NH) ppm.

3-Cyano-2-amino(α-phenylhydrazono-α-(ethyl α-cyano-β-aminoacrylato)-acetyl-4,5,6,7-tetrahydrobenzo[b]thiophene (**10**, $C_{23}H_{22}N_6SO_3$) *and 3-Amino-2-cyano-4-phenylazo-6-imino-4,5,6,7-tetrahydrobenzo[b]thieno-[5,4:4,5]-1,3-oxazino[3,2:1,2]pyridine* (**16**, $C_{21}H_{16}N_6SO_2$)

To a cold solution (0°C) of either 3.58 g **3** (0.01 mol) or 3.12 g **12** (0.01 mol) in 50 cm^{-1} ethanol containing 10.0 g sodium acetate benzenediazonium chloride (0.01 mol) was added with continuous stirring. The reaction mixture was stirred at room temperature for 2 h and the formed solid product, in each case, was collected by filtration.

10: Yield 84%; m.p. 231–233°C (acetic acid); IR: $\bar{\nu} = 3455 - 3370$ (NH_2, 2 NH), 2982, 2776 (CH_3, CH_2), 2225, 2212 (2 CN), 1710, 1680 (2 C=O), 1660 (C=N), 1640 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 1.15$ (t, $J = 5$ Hz, CH_3), 2.24, 2.68 (2m, 4 CH_2), 4.22 (q, $J = 5$ Hz, CH_2), 5.23 (s, NH_2), 7.32–7.39 (m, C_6H_5), 8.72, 9.47 (2s, 2NH) ppm.

16: Yield 72%; m.p. 177–179°C (1,4-dioxane); IR: $\bar{\nu} = 3465 - 3350$ (NH_2, NH), 2223 (CN), 1702 (C=O), 1668 (C=N), 1645 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 2.24$, 2.68 (2m, 4 CH_2), 5.52 (s, NH_2), 7.31–7.42 (m, C_6H_5), 8.37 (s, NH) ppm.

3-Cyano-2-aminocarbonyl-(4-amino-5-cyano-1-phenyl-6-oxopyridazino)-4,5,6,7-tetrahydrobenzo[b]thiophene (**11**, $C_{21}H_{16}N_6SO_2$) *and 3-Cyano-2-(4-amino-3-cyano-5-hydroxy-6-oxopyridine-1-yl)-4,5,6,7-tetrahydrobenzo[b]-thiophene* (**12**, $C_{15}H_{12}N_4SO_2$)

A solution of either 4.62 g **10** (0.01 mol) or 3.58 g **3** (0.01 mol) in 60 cm^3 ethanol containing 0.5 g solid NaOH was heated under reflux for 1 h, then poured into ice/H_2O containing a few drops HCl (till $pH = 6$). The solid product was collected by filtration.

11: Yield 88%; m.p. 234–237°C (acetic acid); IR: $\bar{\nu} = 3489 - 3410$ (NH_2, NH), 2980, 2773 (CH_3, CH_2), 2222, 2217 (2 CN), 1705, 1686 (2 C=O), 1655 (C=N), 1638 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 2.27$, 2.70 (2m, 4 CH_2), 5.78 (s, NH_2), 7.32–7.38 (m, C_6H_5), 8.21 (s, NH) ppm.

12: Yield 77%; m.p. 156°C (acetic acid); IR: $\bar{\nu} = 3580 - 3340$ (OH, NH_2), 2987, 2879 (CH_3, CH_2), 2227, 2213 (2 CN), 1698 (C=O), 1644 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 2.25$, 2.68 (2m, 4 CH_2), 5.44 (s, NH_2), 7.06 (s, pyridine CH), 9.82 (s, OH); ^{13}C NMR (*DMSO-d_6*): $\delta = 33.5$, 34.6, 34.2 (4 CH_2), 119.0, 120.6 (2 CN), 124.5, 125.1, 134.8, 138.9, 140.0, 143.2 (thiophene-C, pyridine-C), 179.6 (C=O) ppm.

3-Amino-2-cyano-6-dicyanomethino-1-oxo-4,5,6,7-tetrahydrobenzo-[b]thieno[5,4:4,5]pyrimidino[3,2:1,2]pyridine (**14a**, $C_{18}H_{12}N_6SO$) *and 3-Amino-2-cyano-1-oxo-6-ethyl cyanoacetato-4,5,6,7-tetrahydrobenzo-[b]thieno[5,4:4,5]-pyrimidino[3,2:1,2]pyridine* (**14b**, $C_{20}H_{17}N_5SO_3$)

Equimolecular amounts of 3.12 g **12** (0.01 mol) and either 0.66 g **6** (0.01 mol) or 1.13 g **13** (0.01 mol) in 40 cm^3 1,4-dioxane containing triethylamine (1.00 ml) was heated under reflux for 4 h. The solution was evaporated under vacuum and the remaining product was triturated with ethanol and the formed solid product, was collected by filtration.

14a: Yield 68%; m.p. $>300°C$ (acetic acid); IR: $\bar{\nu} = 3488 - 3370$ (NH_2), 2984, 2888 (CH_3, CH_2), 2225, 2217, 2212 (3 CN), 1703 (C=O), 1655 (C=N), 1640 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 2.29$, 2.66 (2m, 4 CH_2), 5.61 (s, NH_2), 6.12 (s, CH), 7.02 (s, pyridine CH) ppm; ^{13}C NMR (*DMSO-d_6*): $\delta = 33.8$, 33.9, 34.2, 36.6 (4 CH_2), 66.3 (CH), 119.8, 120.9, 121.2 (3 CN), 122.4, 124.5, 125.1, 134.1, 136.9, 141.2, 143.9, 144.8 (thiophene-C, pyrimidine-C, pyridine-C), 178.3 (C=O) ppm.

14b: Yield 70%; m.p. 280–284°C (acetic acid); IR: $\bar{\nu} = 3477 - 3315$ (NH_2), 2979, 2884 (CH_3, CH_2), 2227, 2213 (2 CN), 1702, 1688 (2 C=O), 1653 (C=N), 1633 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 1.15$ (t, $J = 6$ Hz, CH_3), 2.28, 2.69 (2m, 4 CH_2), 4.27 (q, $J = 6$ Hz, CH_2), 5.62 (s, NH_2), 7.02 (s, pyridine CH) ppm.

4-Amino-3-bromo-5-cyano-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]-thiophene-2-yl)-2,6-dioxopyridine (**17**, $C_{15}H_{11}N_4SO_2Br$)

A solution of 3.12 g **12** (0.01 mol) in 40 cm^3 glacial acetic acid was warmed to 60°C then 1.6 g bromine (0.01 mol) in 10 cm^3 acetic acid was added dropwise with continuous stirring. The reaction mixture was stirred for 1.5 h then poured into ice/H_2O and the formed solid product was collected by filtration. Yield 64%; m.p. 188–190°C (acetic acid); IR: $\bar{\nu} = 3577 - 3315$ (OH, NH_2), 2890 (CH_2), 2225, 2217 (2 CN), 1705 (C=O), 1633 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 2.25$, 2.68 (2m, 4 CH_2), 5.34 (s, NH_2), 9.79 (s, OH) ppm.

4,6-Diamino-3-cyano-2-oxo-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]-thiophene-2-yl)-thiazolo[4,5-b]pyridine (**19a**, $C_{16}H_{12}N_6S_2O$) *and 4-Amino-3-cyano-6-cyanomethyleno-2-oxo-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene-2-yl) thiazolo[4,5-b]pyridine* (**19b**, $C_{18}H_{12}N_6S_2O$)

To a solution of 3.91 g **17** (0.01 mol) in 50 cm^3 ethanol either 0.76 g **18a** (0.01 mol) or 1.00 g **18b** (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h then left to cool. The solid product, so formed in each case, was collected by filtration.

19a: Yield 75%; m.p. 177–180°C (ethanol); IR: $\bar{\nu} = 3483 - 3331$ (2 NH_2), 2887 (CH_2), 2223, 2213 (2 CN), 1699 (C=O), 1639 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 2.27$, 2.71 (2m, 4 CH_2), 4.99, 5.33 (2s, $2NH_2$) ppm.

19b: Yield 71%; m.p. 245–246°C (acetic acid); IR: $\bar{\nu} = 3477 - 3320$ (NH_2), 2880 (CH_2), 2227, 2223, 2219 (3 CN), 1702 (C=O), 1667 (C=N), 1640 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 2.26$, 2.69 (2m, 4 CH_2), 4.21 (s, CH_2), 5.21 (s, NH_2) ppm.

4-Amino-3,6,8-tricyano-7-phenyl-9-imino-2-oxo-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-pyrido[2,1:2,3]thiozolo[4,5:2,3]pyridine (**22a**, $C_{28}H_{16}N_8S_2O$) *and 4-Amino-3,6-dicyano-8-ethoxycarbonyl-7-phenyl-9-imino-2-oxo-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-pyrido[2,1:2,3]-thiazolo[4,5:2,3]pyridine* (**22b**, $C_{30}H_{21}N_7S_2O_3$)

Method (A): To a suspension of 3.9 g **19b** (0.01 mol) in sodium ethoxide solution (0.01 mol) either 0.66 g **6** (0.01 mol) or 1.13 g **13** (0.01 mol) was added. The reaction mixture, in each case, was heated

in a boiling H_2O bath for 4 h then poured into ice/H_2O containing HCl (till *pH* 6) and left with continuous stirring for 2 h. The formed solid product was collected by filtration.

Method (B): Equimolecular amounts of 3.9 g **19b** (0.01 mol) and either 1.4 g **23a** (0.01 mol) or 2.03 g **23b** (0.01 mol) in 50 cm^3 *DMF* containing 1.0 cm^3 trimethyl amine was heated under reflux for 2 h. The reaction mixture was left to cool, then poured into H_2O and the formed solid product was collected by filtration.

22a: Yield 75%; m.p. 266–270°C (1,4-dioxane); IR: $\bar{\nu} = 3495 - 3306$ (NH_2, NH), 2229, 2220 − 2215 (4 CN), 1700 (C=O), 1677 (C=N), 1638 (C=C) cm^{-1}; ^{1}H NMR (*DMSO-d_6*): $\delta = 2.28$, 2.71 (2m, 4 CH_2), 5.23 (s, NH_2), 7.25–7.34 (m, C_6H_5), 8.78 (s, NH) ppm.

22b: Yield 66%; m.p. 132°C (1,4-dioxane); IR: $\bar{\nu} = 3488 - 3328$ (NH_2, NH), 2227, 2223, 2219 (3 CN), 1700, 1694 (2 C=O), 1673 (C=N), 1643 (C=C) cm^{-1}; ^{1}H NMR (*DMSO-d_6*): $\delta = 1.16$ (t, $J = 5$ Hz, CH_3), 2.25, 2.66 (2m, 4 CH_2), 4.25 (q, $J = 5$ Hz, CH_2), 5.44 (s, NH_2), 7.30–7.35 (m, C_6H_5), 8.90 (s, NH) ppm.

4-Amino-3-cyano-6-(coumarin-3-yl)-2-oxo-1-(3-cyano-4,5,6,7-tetrahydro-benzo[b]thiophene-2-yl)-thiazolo[4,5-b]pyridine (**25**, $C_{25}H_{15}N_5S_2O_3$)

To a solution of 3.94 g **19b** (0.01 mol) in 40 cm^3 1,4-dioxane containing 1.0 cm^3 piperidine, 1.18 g **24** (0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then evaporated in vacuum. The remaining product was triturated with ethanol and the formed solid product was collected by filtration. Yield 70%; m.p. 208–211°C (1,4-dioxane); IR: $\bar{\nu} = 3488 - 3328$ (NH_2), 2225, 2220 (2 CN), 1705, 1688 (2 C=O), 1660 (C=N), 1640 (C=C) cm^{-1}; ^{1}H NMR (*DMSO-d_6*): $\delta = 2.23$, 2.70 (2m, 4 CH_2), 5.22 (s, NH_2), 6.99 (s, coumarin H-4), 7.29–7.39 (m, C_6H_5) ppm.

4-Amino-3-cyano-6-hydrazino-2-oxo-1-(3-cyano-4,5,6,7-tetrahydrobenzo-[b]thiophene-2-yl)-pyridine (**27a**, $C_{15}H_{14}N_6SO$) *and 4-Amino-3-cyano-6-phenylhydrazino-2-oxo-1-(3-cyano-4,5,6,7-tetrahydrobenzo-[b]thiophene-2-yl)-pyridine* (**27b**, $C_{21}H_{18}N_6SO$)

To a solution of 3.94 g **12** (0.01 mol) in 30 cm^3 1,4-dioxane either 0.5 g **26a** (0.01 mol) or 1.18 g **26b** (0.01 mol) was added. The reaction mixture was heated under reflux for 4 h then poured into ice/water containing few drops of hydrochloric acid. The formed solid product, in each case, was collected by filtration.

27a: Yield 70%; m.p. 196–199°C (*DMF*); IR: $\bar{\nu} = 3493 - 3300$ (2 NH_2, NH), 2227, 2221 (2 CN), 1699 (C=O), 1633 (C=C) cm^{-1}; ^{1}H NMR (*DMSO-d_6*): $\delta = 2.23$, 2.68 (2m, 4 CH_2), 4.87, 5.31 (2s, 2 NH_2), 7.08 (s, pyridine H-5), 8.72 (s, br, NH) ppm.

27b: Yield 55%; m.p. 210–214°C (*DMF*); IR: $\bar{\nu} = 3460 - 3300$ (NH_2, 2 NH), 2225, 2220 (2 CN), 1692 (C=O), 1637 (C=C) cm^{-1}; ^{1}H NMR (*DMSO-d_6*): $\delta = 2.24$, 2.67 (2m, 4 CH_2), 5.22 (s, NH_2), 6.91 (s, NH), 7.07 (s, pyridine H-5), 7.33–7.39 (m, C_6H_5), 8.62 (s, br, NH) ppm.

2-Cyano-3,5-Diamino-6-imino-2-oxo-4,5,6,7-tetrahydrobenzo[b]thieno[5,4:4,5]pyrimidino[2,1:1,2]pyridine (**28a**, $C_{15}H_{14}N_6SO$) *and 3-Amino-2-cyano-5-phenylamino-6-imino-2-oxo-4,5,6,7-tetrahydrobenzo-[b]thieno[5,4:4,5]pyrimidino[2,1:1,2]pyridine* (**28b**, $C_{15}H_{14}N_6SO$)

A suspension of either 3.26 g **27a** (0.01 mol) or 4.01 g **27b** (0.01 mol) in sodium ethoxide solution (obtained by dissolving, 0.46 g Na (0.02 mol) in 40.0 cm^3 absolute ethanol) was heated in a boiling water bath for 4 h and then left to cool. The solid product formed upon pouring into ice/H_2O was collected by filtration.

28a: Yield 70%; m.p. 155–157°C (*DMF*); IR: $\bar{\nu} = 3486 - 3279$ (2 NH_2, NH), 2225 (CN), 1703 (C=O), 1668 (C=N), 1638 (C=C) cm^{-1}; ^{1}H NMR (*DMSO-d_6*): $\delta = 2.25$, 2.70 (2m, 4 CH_2), 4.77, 5.30

(2s, 2 NH_2), 7.08 (s, pyridine H-5), 9.33 (s, br, NH) ppm; ^{13}C NMR (*DMSO-d_6*): $\delta = 33.8$, 34.2, 34.5 (4 CH_2), 118.9, 119.2 (CN), 122.6, 124.6, 138.2, 140.0 (pyridine, pyrimidine and thiophene-C), 177.3 (C=O), 179.9 (C=N) ppm.

28b: Yield 50%; m.p. 167–169°C (*DMF*); IR: $\bar{\nu} = 3465 - 3309$ (NH_2, 2 NH), 2222 (CN), 1690 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 2.24$, 2.67 (2m, 4 CH_2), 5.22 (s, NH_2), 6.91 (s, NH), 7.07 (s, pyridine H-5), 7.33–7.39 (m, C_6H_5), 8.62, 903 (2s, br, 2 NH) ppm.

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