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Reaction of Ethyl 2-Diazo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate with 3-Iminobutyronitrile: Synthesis of Pyridazines, Thiophenes, and Their Fused Derivatives

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ABSTRACT: *Reaction of ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate* **1** *with 3-iminobutyronitrile* **2** *gave the hydrazone derivative* **3.** *The reactivity of the latter product toward a variety of chemical reagents as well as the biological activity of the newly synthesized products were studied.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:403–412, 2000

INTRODUCTION

During recent years, we have maintained a comprehensive program aimed at investigating the reaction of ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate with active methylene reagents, followed by heterocyclization of the resultant azo derivatives with simple, available reagents. Such a synthetic route has proven to be an easy, facile, and sole approach for the synthesis of hitherto unreported derivatives of polyfunctionally substituted thiophenes, 2,3-dihydrothiazoles, and thiazolidines [1]. The importance of such compounds is due to their diverse pharmacological activities including antibacterial [2], immunomodulatory [3], antiflammatory [4], antidiabatic [5,6], antiplatelet-activating factor [7] and antiviral activities [8,9]. Thus, in continuation of our previous work, we report herein the use of ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate [10] **1** for the synthesis of a variety of azole, azine, or azoloazine derivatives incorporating a tetrahydrobenzo[*b*]thiophene moiety with anticipated biological activity.

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RESULTS AND DISCUSSION

The reaction of ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[*b*]thiophene **1** with a cold solution (0–5 °C) of 2-iminobutyronitrile [11] **2** in ethanolic sodium hydroxide solution gave a single product with molecular formula $C_{15}H_{18}N_4SO_2$. Three possible isomeric structures were proposed for this formula: **3, 4**, and **5**, The possibility of structures **4** and **5** was ruled out on the basis of the ^{1}H NMR spectrum of the reaction product that showed the presence of two singlets (D_2O exchangeable) at δ 8.97 and 9.23 ppm corresponding to two NH groups, together with the absence of any singlet due to a CH group, or any NH_2 group stretching in the IR spectrum of the reaction product, which might be expected to appear if either structure **4** or **5** is to be considered. All other obtained spectral data are in accord with structure **3**

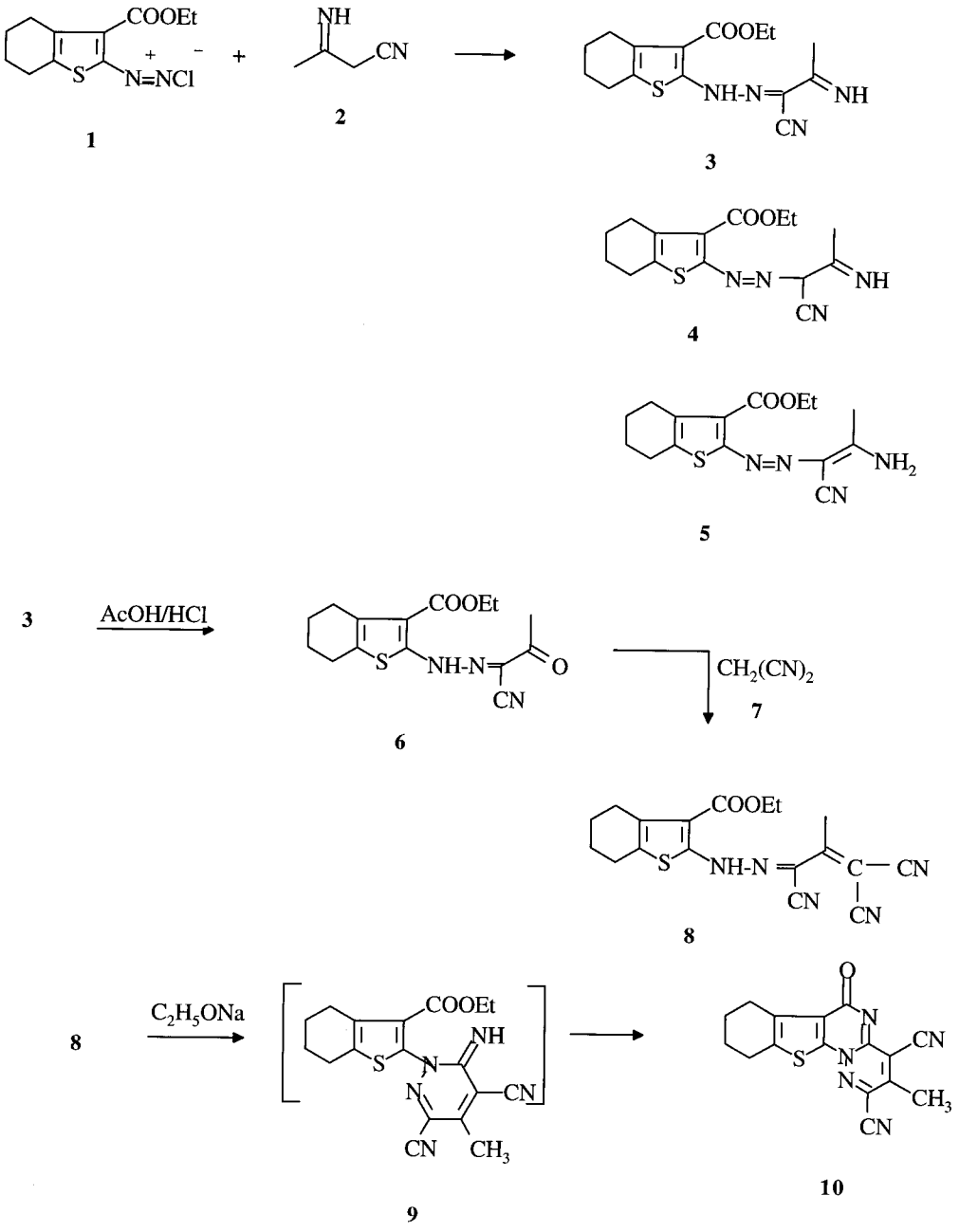
for the reaction product. Further confirmation for structure **3** was obtained through studying its reactivity toward various chemical reagents. Thus, heating of compound **3** in refluxing acetic/hydrochloric acid solution gave the 2-hydrazo-3-oxobutyronitrile **6**. The structure of compound **6** was based on analytical and spectral data. The oxo group in compound **6** showed interesting reactivity toward cyanomethylene reagents. Thus, the reaction of **6** with malononitrile (**7**) in the presence of ammonium acetate gave the corresponding Knoevenagel condensation product **8**. The structure of compound **8** was established on the basis of its IR spectrum, which showed the presence of three CN groups stretching at 2225, 2220, and 2215 cm^{-1}, and ^{13}C NMR data, which showed the presence of δ ppm 28.2 (CH_3), 29.7, 30.2 (cyclohexane C-1, C-4), 23.8, 23.2 (cyclohexane C-2, C-3), 55.7 (CH_2), 84.5 (C=N), 118.4, 119.6, 120.9 (3 CN), 121.0, 122.6 (C=C), 126.8, 132.2, 133.0, 138.2 (thiophene-C), 179.8 (C=O). Compound **8** underwent ready cyclization when heated under reflux in sodium ethoxide solution to give the 4,5,6,7-tetrahydrobenzo[*b*]thieno [2,3:6,5] pyridazino[1,6:*f*]pyrimidine **10**. The latter product is formed through the intermediate formation of the 6-iminopyridazine derivative **9** followed by ethanol elimination (Scheme 1). The structure of compound **10** was confirmed on the basis of analytical and spectral data. Thus, the IR spectrum of the reaction product showed the presence of two CN group stretchings at 2225 and 2220 cm^{-1}. Moreover, the ^1H NMR spectrum revealed, besides the two multiplets characteristic for the two CH_2 groups of the cyclohexane moiety, the presence of only a singlet at δ 2.25 ppm characteristic for a CH_3 group.

The reaction of compound **8** with elemental sulfur in the presence of a catalytic amount of triethylamine gave the thiophene [12,13] derivative **11**. The latter underwent ready cyclization when heated in dimethylformamide containing triethylamine to give the thieno[4,5-*c*]pyridazine derivative **12**. The structure of compound **12** was established on the basis of analytical and spectral data. Thus the ^1H NMR spectrum of the reaction product showed the presence of a triplet at δ 1.66 ppm corresponding to a CH_3 group, two multiplets at δ 2.23 and 2.47 ppm due to two CH_2 groups of the cyclohexane ring, a singlet at δ 4.89 ppm (D_2O exchangeable) corresponding to an NH_2 group, and a singlet at δ 6.99 ppm due to the thiophene H-5 proton. Moreover, the ^{13}C NMR spectrum showed δ ppm 25.1 (CH_3), 29.6, 30.8 (cyclohexan C-1, C-4), 23.1, 23.7 (cyclohexan C-2, C-3), 55.8 (CH_2), 126.7, 132.2, 133.0, 139.8, 142.1 (pyridazine-C, thiophene-C), 120.3 (CN), 178.4, 179.4 (2 C=O). Compound **12** showed interesting reactivity toward cycloaddition reactions [14]. Thus, **12** reacted with either acrylonitrile (**13a**) or ethyl acrylate (**13b**) to give the phthalazine derivatives **15a** and **15b**, respectively [14]. Formation of the latter products is explained in terms of the intermediate formation of **14a,b** followed by elimination of hydrogen sulfide. Structures **15a** and **15b** were based on analytical and spectral data (Scheme 2).

The reaction of compound **8** with either benzaldehyde (**16a**) or *p*-chlorobenzaldehyde (**16b**) gave the corresponding arylidene derivatives **17a** and **17b** respectively, the analytical and spectral data of which are in agreement with the proposed structures. The reaction of either **17a** or **17b** with either malononitrile (**7**) or ethyl cyanoacetate (**18**) in the presence of triethylamine gave the corresponding benzo[*d*]pyridazine derivatives **20a** and **20b**, respectively. Formation of the latter products was explained in terms of the intermediate formation of **19a** and **19b**, respectively, followed by elimination of hydrogen cyanide. Structures of **20a,b** were based on analytical and spectral data. Further confirmation for the proposed structures was obtained through their synthesis via another reaction route. Thus, the reaction of compound **8** with the cinnamonitrile derivatives **21a** and **21b** gave the same products **20a** and **20b**, respectively (identical m.p. and mixed m.p.) (Scheme 3).

The reaction of **6** with ethyl cyanoacetate (**18**) gave the pyridazine derivative **22**, its structure being based on analytical and spectral data. The latter product reacted with elemental sulfur to give a single product with molecular formula $C_{18}H_{16}N_4S_2O_3$. Two possible isomeric structures were considered, **12** and **23**. The obtained product was found to be identical in all respects (IR, m.p., and mixed m.p.) to the same product **12** obtained before.

The reaction of compound **22** with benzenediazonium chloride gave the phenylhydrazo derivative **24**. The latter underwent ready cyclization when heated under reflux in ethanolic/sodium hydroxide solution to give the pyridazo[4,5-*d*]pyridazine derivative **26** via intermediate formation of **25**. The presence of the 1,3-dicarbonyl moiety in compound **26** showed an interesting reactivity characteristic for such a series of compounds. Thus, reaction of compound **26** with hydrazine hydrate gave the ethyl 2-(1,2,5,6,7,8-hexazacenaphthalene-1-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate derivative **27**. Moreover, with either urea (**28a**) or thiourea (**28b**), compound **25** gave the ethyl 2-(1,2,5,6,7,9-

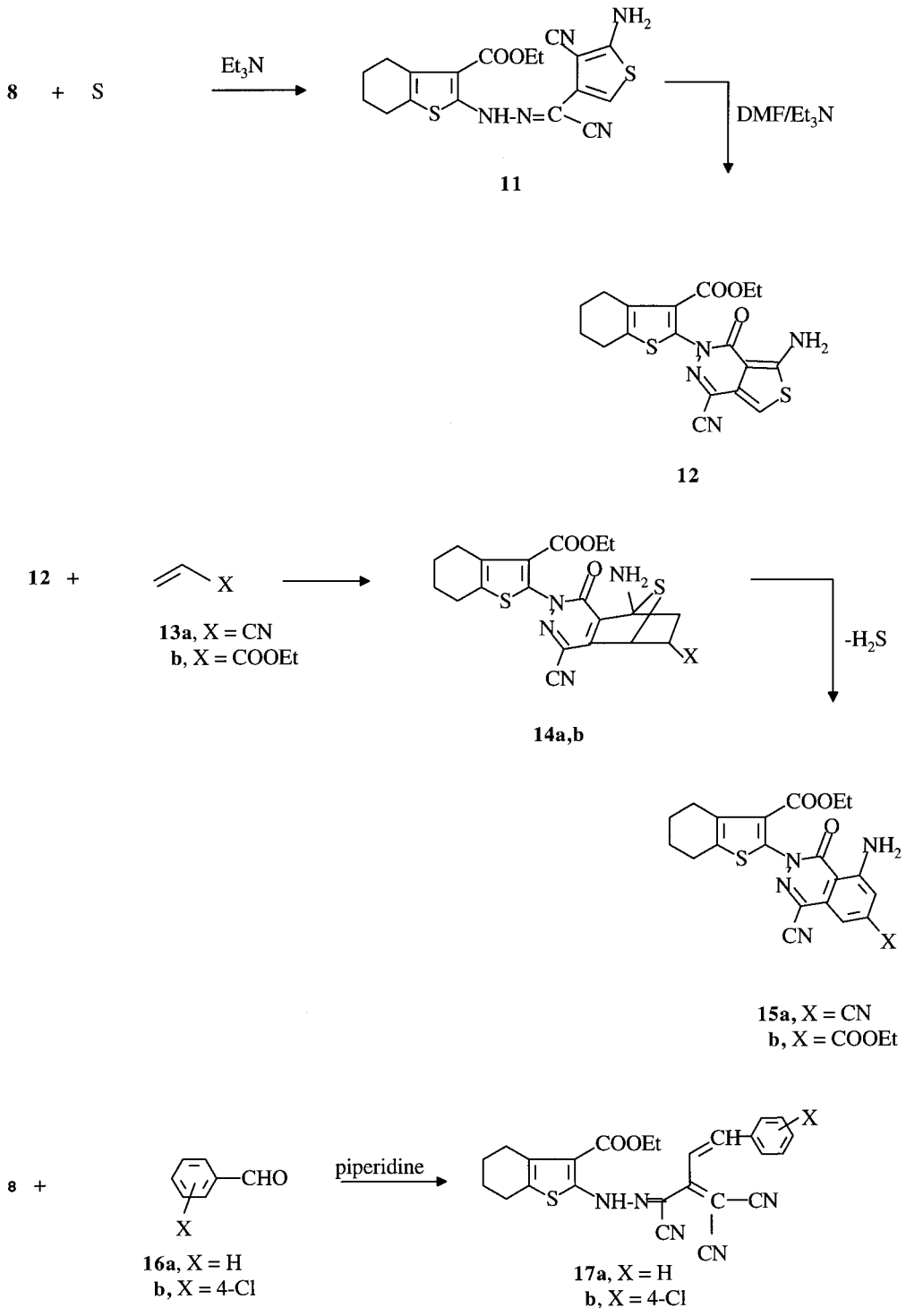


SCHEME 1

hexazaphenantherene-1-yl)-4,5,6,7-tetrahydrobenzo [*b*]-thiophene-3-carboxylate derivatives **29a** and **29b**, respectively (Scheme 4).

ANTIMICROBIAL ACTIVITY

The diverse biological activities of azole and azine derivatives prompted us to test and study the biological activities of some of the newly synthesized products. Their bactericidal and antifungal activities [15,16] were studied. A disc of blotting paper was impregnated with a known volume and appropriate concentration of a compound to be tested, which was then placed on a sensitivity testing agar plate that was inoculated with the test organism. The compound diffused from the disc into the medium. The culture was examined for areas of no growth around the disc (zones of inhibition) after overnight incubation. Growth of bacterial strains sensitive to a compound is inhibited at certain distances from the

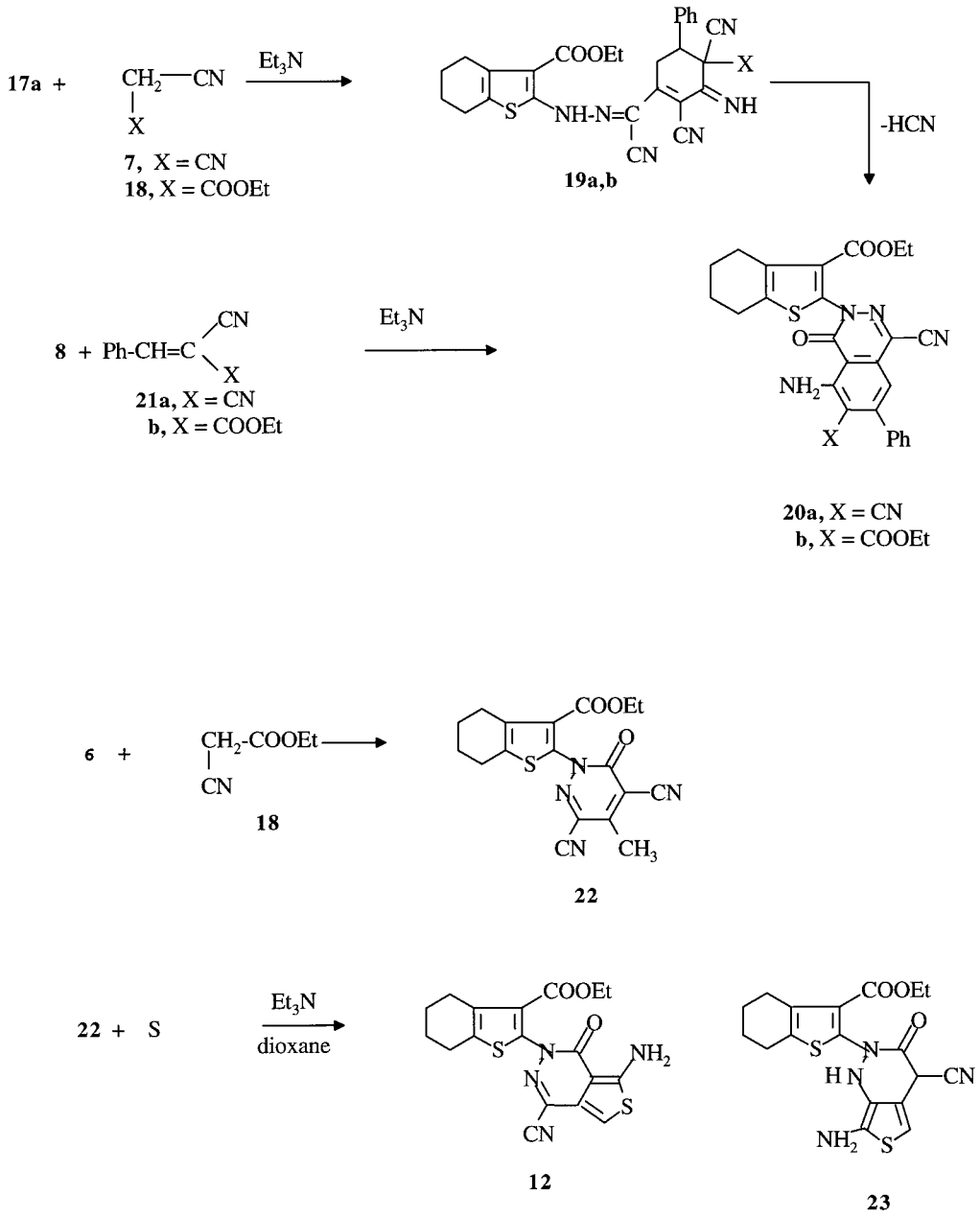


SCHEME 2

center of the disc whereas resistant strains grow up to the edge of the disc.

EXPERIMENTAL

All melting points are not corrected. IR spectra were recorded for KBr discs on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian EM390-200 MHZ instrument in CD_3SOCD_3 as solvent using TMS as internal standard, and chemical shifts are expressed as δ ppm. Analytical data were obtained from the Microanalytical Data Unit at Cairo University, Giza, Egypt.

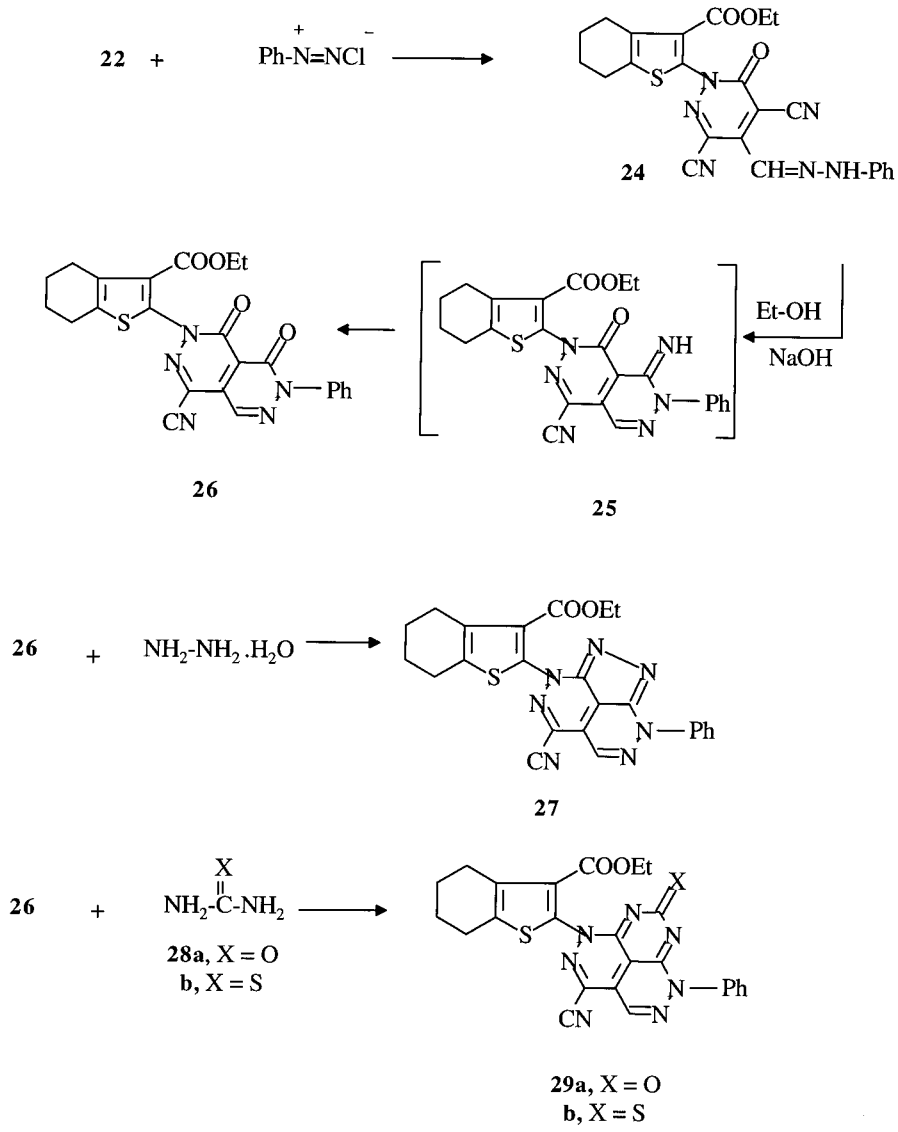


SCHEME 3

Ethyl 2-hydrazono(3-iminobutyronitrile-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**3**)

To a cold solution of **2** (0.82 g, 0.01 mol) in ethanol (50 mL) containing sodium acetate (10.0 g), a cold solution of the diazonium salt **1** (0.01 mol) which was prepared by adding sodium nitrite solution (0.7 g, 0.1 mol) to a cold solution of the amine precursor of **1** (3.81 g, 0.01 mol) in acetic acid (20 mL), hydrochloric acid (5 mL) was added dropwise with stirring with continuous stirring for 1 hour at 0–5 °C. The formed solid product was collected by filtration.

3: Reddish brown crystals, yield 79% (2.51 g), m.p. 165–168 °C (acetic acid). IR (υ/cm^{-1}) = 3465–3435 (2 NH), 2980, 2865 (CH_3, CH_2), 2220 (CN), 1695 (C=O). ^{1}H NMR: δ/ppm: 1.65 (t, 3H, CH_3), 2.21 (m, 4H, 2 CH_2), 2.31 (m, 4H, 2CH_2), 4.28 (q, 2H, CH_2), 8.97, 9.23 (2s, 2H, 2NH). $C_{15}H_{18}N_4SO_2$. Calcd: C, 56.54; H, 5.65; N, 17.59; S, 10.05 (318.34). Found: C, 56.32; H, 5.43; N, 17.62; S, 9.86



SCHEME 4

Ethyl 2-hydrazono(3-oxobutyronitrile-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**6**)

A solution of compound **3** (3.18 g, 0.01 mol) in acetic acid (40 mL) containing hydrochloric acid (5 mL) was heated under reflux for 4 hours and then poured into an ice water mixture containing sodium hydroxide (to pH 6). The formed solid product was collected by filtration.

6: Reddish brown crystals, yield 79% (2.51 g), m.p. 115°C (acetic acid). IR (υ/cm^{-1}): 3470–3430 (NH), 2988, 2875 (CH_3, CH_2), 2220 (CN), 1690, 1682 (2 C=O). ^{1}H NMR: δ/ppm 1.60 (t, 3H, CH_3), 2.23 (m, 4H, 2 CH_2), 2.30 (m, 4H, 2CH_2), 4.25 (q, 2H, CH_2), 8.92 (s, 1H, NH). $C_{15}H_{17}N_3SO_3$ Calcd: C, 56.72; H, 5.35; N, 13.23; S, 10.08 (317.34). Found: C, 56.44; H, 5.27; N, 13.06; S, 10.09.

Ethyl 2-hydrazono(3-dicyanocarbonylideno-butyronitril-2-ylideno)-4,5,6,7-tetra-hydrobenzo-[b]thiophene-3-carboxylate (**8**) *and 3,4 Ethyl 2-(3,5-dicyano-4-methyl-6-oxopyridazin-1-yl)-4,5,6,7-tetra-hydrobenzo-[b]thiophene-3-carboxylate* (**22**)

To the dry solid **6** (3.17 g, 0.01 mol), either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) and ammonium acetate (0.63 g, 0.01 mol) were added. The reaction mixture was heated in an oil bath at 140°C for 1 hour and left to cool. The solidified product was triturated with ethanol

TABLE 1 In Vitro Bactericidal and Fungicidal Activity of Some of the Newly Synthesized Compounds[a]

Compound No.	*Bacillus cerceus* (*Gram positive*)	*Staph. aureus* (*Gram positive*)	*E. Coli* (*Gram negative*)	*K. Pneumonia* (*Gram negative*)
3	+ +	+ + +	+ + +	+
8	+ +	+ + +	+ +	+
10	+ + +	+ +	+ +	+
11	+ +	+ + +	+ +	+ + +
12	+ +	+ +	+	+
15a	+	+ + +	+ +	+ + +
17a	+	+ +	+ +	+ + +
20b	+ +	+	+ +	+ +
22	+ + +	+ +	+	+
24	+	+ + +	+ + +	+ + +
26	+ +	+ +	+	+
29a	+ +	+ +	+	+
29b	+ + +	+ +	+ +	+ +

[a]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.

and collected by filtration. **8:** Yellow crystals, yield 77% (2.82 g); m.p. 140°C (ethanol). IR (υ/cm^{-1}): 3468–3444 (NH), 2990, 2865 (CH_3, CH_2), 2225, 2220–2215 (3 CN), 1690 cm^{-1} (C=O). ^{1}H NMR: δ/ppm 1.60 (t, 3H, CH_3), 2.23 (m, 4H, 2 CH_2), 2.38 (m, 4H, 2CH_2), 4.25 (q, 2H, CH_2), 8.96 (s, 1H, NH). ^{13}C NMR: δ/ppm 28.2 (CH_3), 29.7, 30.2 (cyclohexan C-1, C-4), 23.8, 23.2 (cyclohexan C-2, C-3), 55.7 (CH_2), 84.5 (C=N), 118.4, 119.6, 120.9 (3 CN), 121.0, 122.6 (C=C), 126.8, 132.2, 133.0, 138.2 (thiophene-C), 179.8 (C=O). $C_{18}H_{17}N_5SO_2$ Calcd: C, 58.75; H, 4.62; N, 19.04; S, 8.70 (367.62). Found: C, 58.66; H, 4.78; N, 18.94; S, 8.51.

22: White crystals, yield 69% (2.55 g); m.p. 95°C (1,4-dioxane). IR: (υ/cm^{-1}) 2979, 2870 (CH_3, CH_2), 2225, 2220 (2 CN), 1696, 1683 (2 C=O), 1655 (C=N), 1636 (C=C). ^{1}H NMR: (δ ppm): 1.64 (t, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.24 (m, 4H, 2 CH_2), 2.32 (m, 4H, 2CH_2), 4.22 (q, 2H, CH_2). $C_{18}H_{16}N_4SO_3$ (368.41).

8-Oxo-3,5-dicyano-4-methyltetrahydrobenzo[b] thieno[2,3:6,5]pyrimidino-[6,1:f] pyridazine (**10**)

A suspension of **8** (3.7 g, 0.01 mol) in sodium ethoxide, which was prepared by adding sodium metal (0.23 g, 0.01 mol) to 40 mL absolute ethanol, was heated in a boiling water bath for 3 hours and poured into ice water containing hydrochloric acid (pH 6). The formed solid product was collected by filtration.

10: Pale yellow crystals, yield 65% (2.1 g); m.p. 130°C (from DMF). IR: υ/cm^{-1} 2865 (CH_3), 2225, 2220 (2 CN), 1706 (C=O). ^{1}H NMR: δ/ppm 2.19 (s, 3H, CH_3), 2.24 (m, 4H, 2 CH_2), 2.35 (m, 4H, 2CH_2). $C_{16}H_{11}N_5SO$ Calcd: C, 59.74; H, 3.42; N, 21.78; S, 9.96 (321.35). Found: C, 59.56; H, 3.21; N, 21.95; S, 9.64.

Ethyl 2-hydrazono(2-amino-3-cyano-4-acetonitrilo-ylideno)-4,5,6,7-tetra-hydro-benzo[b]thiophene-3-carboxylate (**11**)

To a solution of **8** (3.7 g, .01 mol) in 1,4-dioxane (30 mL) containing triethylamine (0.5 mL) elemental sulfur (0.32 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 hours and left to cool. The formed solid product, upon pouring into ice water, was collected by filtration.

11: Orange crystals, yield 55% (2.1 g); m.p. 177°C (from ethanol). IR: υ/cm^{-1} 3475–3420 (NH_2, NH), 2987, 2855 (CH_3, CH_2), 2223 (CN), 1703, 1695 (2 C=O). ^{1}H NMR: δ/ppm 1.62 (t, 3H, CH_3), 2.20 (m, 4H, 2 CH_2), 2.34 (m, 4H, 2CH_2), 4.22 (q, 2H, CH_2), 5.55 (s, 2H, NH_2) 6.89 (s, 1H, thiophene H-5), 8.84 (s, 1H, NH). $C_{18}H_{17}N_5S_2O_2$ Calcd: C, 54.13; H, 4.24; N, 17.54; S, 16.22 (399.44). Found: C, 54.56; H, 3.88; N, 17.83; S, 16.09.

Ethyl 2-(7-Amino-3-cyano-8-oxothieno[3,4-d]pyridazino-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxylate (**12**)

To a solution of either compound **11** (3.9 g, 0.01 mol) or **22** (3.6 g, 0.01 mol) in dimethylformamide (30 mL) containing triethylamine (0.5 mL) elemental sulfur (g, 0.01 mol) was added. The reaction mixture in each case was heated under reflux for 12 hours and then evaporated in a vacuum. The remaining product was triturated with diethyl ether, and the formed solid product was collected by filtration.

12: White crystals, yield 50% (2.0 g); m.p. 222–225°C (from 1,4-dioxane). IR: υ/cm^{-1} 3460, 3355 (NH_2), 2992, 2843 (CH_3, CH_2), 2220 (CN), 1700, 1690 (2 C=O), 1655 (C=N), 1644 (C=C). ^{1}H NMR: δ/ppm 1.66 (t, 3H, CH_3), 2.23 (m, 4H, 2 CH_2), 2.38 (m, 4H, 2CH_2), 4.26 (q, 2H, CH_2), 5.38 (s, 2H, NH_2) 6.99 (s, 1H, thiophene H-5). ^{13}C NMR: δ/ppm 25.1 (CH_3), 29.6, 30.8 (cyclohexan C-1, C-4), 23.1, 23.7 (cyclohexan C-2, C-3), 55.8 (CH_2), 126.7, 132.2, 133.0, 139.8, 142.1 (pyridazine-C, thiophene-C), 120.3 (CN), 178.4, 179.4 (2 C=O). $C_{18}H_{16}N_4S_2O_3$ Calcd: C, 53.93; H, 3.99; N, 13.98; S, 15.98 (400.47). Found: C, 53.74; H, 4.08; N, 14.18; S, 16.07.

Ethyl 2-(7-Amino-3,5-dicyano-8-oxobenzo[d]pyridazino)-4,5,6,7-tetrahydrobenzo-[b]thiophene-3-carboxylate (**15a**) *and Ethyl 2-(7-Amino-3-cyano-5-ethoxycarbonyl-8-oxobenzo[d]-pyridazino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate* (**15b**)

General Procedure. Equimolecular amounts of **12** (4.0 g, 0.01 mol) and either acrylonitrile (**13a**) (0.53 g, 0.01 mol) or ethyl acrylate (**13b**) (1.0 g, 0.01 mol) in dioxane (40 mL) containing triethylamine (0.5 mL) were heated under reflux for 6 hours until all hydrogen sulfide was liberated. The remaining product, obtained upon evaporating the solution under vacuum, was triturated with ethanol, and the formed solid product was collected by filtration.

15a: White crystals, yield 58% (2.6 g); m.p. 188–191°C (from 1,4-dioxane). IR: υ/cm^{-1} 3475, 3362 (NH_2), 2977, 2880 (CH_3, CH_2), 2225, 2222 (2 CN), 1705, 1686 (2 C=O), 1645 (C=N), 1638 (C=C). ^{1}H NMR: δ/ppm 1.64 (t, 3H, CH_3), 2.21 (m, 4H, 2 CH_2), 2.30 (m, 4H, 2CH_2), 4.22 (q, 2H, CH_2), 5.20 (s, 2H, NH_2), 7.32–7.41 (m, 2H, C_6H_2). ^{13}C NMR: δ/ppm 24.0 (CH_3), 29.4, 30.5 (cyclohexan C-1, C-4), 23.0, 23.4 (cyclohexan C-2, C-3), 55.6 (CH_2), 120.1, 124.7, 130.4, 133.8, 137.9, 140.6, 146.2 (pyridazine-C, thiophene-C, benzene-C), 119.6, 120.8 (2 CN), 178.8, 180.3 (2 C=O). $C_{21}H_{17}N_5SO_3$ Calcd: C, 60.08; H, 4.05; N, 16.68; S, 7.63 (419.45). Found: C, 60.21; H, 3.87; N, 16.47; S, 7.53.

15b: White crystals, yield 70% (3.4 g); m.p. 212–214°C (from acetic acid). IR: υ/cm^{-1} 3475, 3362 (NH_2), 2977, 2880 (CH_3, CH_2), 2222 (CN), 1705, 1686 (2 C=O), 1645 (C=N), 1638 (C=C). ^{1}H NMR: δ/ppm 1.64, 1.66 (2t, 6H, 2 CH_3), 2.21 (m, 4H, 2 CH_2), 2.30 (m, 4H, 2CH_2), 4.22, 4.26 (2q, 4H, 2 CH_2), 5.20 (s, 2H, NH_2), 7.32–7.41 (m, 2H, C_6H_2). $C_{23}H_{22}N_4SO_5$ (466.51).

Ethyl 2-hydrazono(3-dicyanocarbonylideno-4-benzalbutyronitril-2-ylideno)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**17a**) *and 3.11 Ethyl 2-hydrazono(3-dicyanocarbonylideno-4-p-chlorobenzalbutyronitril-2-ylideno)-4,5,6,7-tetra-hydrobenzo-[b]thiophene-3-carboxylate* (**17b**)

General Procedure. To a solution of **8** (g, 0.01 mol) in dimethylformamide (40 mL) containing piperidine 0.5 mL of either benzaldehyde (1.1 g, 0.01 mol) or *p*-chlorobenzaldehyde (1.4 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 4 hours and evaporated in a vacuum. The remaining product, in each case, was collected by filtration.

17a: Yellow crystals, yield 79% (3.5 g); m.p. 220–202°C (from ethanol). IR: υ/cm^{-1} 3466–3343 (NH), 2982, 2889 (CH_3, CH_2), 2225, 2220–2215 (3 CN), 1700 (C=O), 1642 (C=N), 1630 (C=C). ^{1}H NMR: δ/ppm 1.61 (t, 3H, CH_3), 2.25 (m, 4H, 2 CH_2), 2.36 (m, 4H, 2CH_2), 4.25 (q, 2H, CH_2), 7.30–7.44 (m, 5H, C_6H_5). $C_{25}H_{21}N_5SO_2$ Calcd: C, 65.85; H, 4.61; N, 15.36; S, 7.02 (455.53). Found: C, 65.64; H, 4.48; N, 15.49; S, 6.86.

17b: Orange crystals, yield 72% (3.5 g); m.p. 155–158°C (from ethanol). IR: υ/cm^{-1} 3458–3336 (NH), 2980, 2895 (CH_3, CH_2), 2225, 2220–2215 (3 CN), 1695 (C=O), 1640 (C=N), 1637 (C=C). ^{1}H NMR: δ/ppm 1.64 (t, 3H, CH_3), 2.25 (m, 4H, 2 CH_2), 2.33 (m, 4H, 2CH_2), 4.25 (q, 2H, CH_2), 7.28–7.39 (m, 4H, C_6H_4). $C_{25}H_{20}N_5SO_2Cl$ Calcd: C, 61.23; H, 4.08; N, 14.28; S, 6.53 (489.98). Found: C, 61.07; H, 3.86; N, 14.04; S, 6.43.

Ethyl 2-(7-amino3,6-dicyano-5-phenyl-8-oxobenzo[d]pyridazino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**20a**) *and 3.13 Ethyl 2-(7-amino-3-cyano-6-ethoxycarbonyl-5-phenyl-8-oxobenzo[d]pyridazino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate* (**20b**)

General Procedure. (Method A) Equimolecular amounts of **17a** (4.55 g, 0.01 mol) and either malononitrile (**7**) (0.66 g, 0.01 mol) or ethyl cyanoacetate (**18**) (1.13 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.5 mL) was heated under reflux for 8 hours. The solid product, so formed upon pouring into ice water containing a few drops of hydrochloric acid, was collected by filtration.

(*Method B*) To a solution of compound **8** (3.67 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (0.5 mL), either of the cinnamonitrile derivatives **21a** (1.56 g, 0.01 mol) or **21b** (2.03 g, 0.01 mol)

was added. The reaction mixture, in each case, was heated under reflux for 5 hours and poured into ice water containing a few drops of hydrochloric acid. The solid product formed was collected by filtration.

20a: Orange crystals, yield 66% (3.3 g); m.p. 190–193°C (from acetic acid). IR υ/cm^{-1} 3470–3385 (NH_2), 2989, 2873 (CH_3, CH_2), 2222, 2217 (2 CN), 1697, 1683 (2 C=O), 1648 (C=N), 1631 (C=C). ^{1}H NMR: δ/ppm 1.61 (t, 3H, CH_3), 2.22 (m, 4H, 2 CH_2), 2.32 (m, 4H, 2CH_2), 4.22 (q, 2H, CH_2), 7.32–7.41 (m, 6H, C_6H_5, benzene CH). $C_{27}H_{21}N_5SO_3$ Calcd: C, 65.38; H, 4.24; N, 14.13; S, 6.46 (495.55). Found: C, 65.04; H, 4.18; N, 14.09; S, 6.66.

20b: Orange crystals, yield 54% (2.9 g); m.p. >300°C (from acetic acid). IR: υ/cm^{-1} 3470–3385 (NH_2), 2989, 2873 (CH_3, CH_2), 2220 (CN), 1697, 1683 (2 C=O), 1648 (C=N), 1631 (C=C). ^{1}H NMR: δ/ppm 1.61, 1.65 (2t, 6H, 2 CH_3), 2.22 (m, 4H, 2 CH_2), 2.32 (m, 4H, 2CH_2), 4.22, 4.26 (2q, 4H, 2 CH_2), 7.32–7.41 (m, 6H, C_6H_5, benzene CH). $C_{29}H_{26}N_4SO_5$ Calcd: C, 64.13; H, 4.79; N, 10.32; S, 5.89 (542.61). Found: C, 64.09; H, 4.67; N, 10.39; S, 5.88.

Ethyl 2-(3,5-dicyano-4-phenylhydrazomethino-6-oxopyridazin-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**24**)

To a cold (0–5°C) solution of **22** (3.68 g, 0.01 mol) in ethanol (50 mL) containing sodium hydroxide (10 mL, 10%) a solution of benzenediazonium chloride (0.01 mol)—which was prepared by adding sodium nitrite (0.7 g, 0.01 mol) solution to a cold (0–5°C) solution of aniline (0.93 g, 0.01 mol) containing the appropriate amount of hydrochloric acid and with stirring—was added with continuous stirring. The formed solid product was collected by filtration.

24: Orange crystals, yield 72% (3.4 g); m.p. 113–115°C (from acetic acid). IR: 3455–3332 (NH), 2995, 2880 (CH_3, CH_2), 2225, 2220 (2 CN), 1698, 1690 (2 C=O), 1655 (C=N), 1640 (C=C). ^{1}H NMR: δ/ppm 1.63 (t, 3H, CH_3), 2.26 (m, 4H, 2 CH_2), 2.37 (m, 4H, 2CH_2), 4.27 (q, 2H, CH_2), 6.55 (s, 1H, CH=N), 7.29–7.37 (m, 5H, C_6H_5). $C_{24}H_{20}N_6SO_3$ Calcd: C, 60.94; H, 4.23; N, 17.77; S, 6.77 (472.52). Found: C, 60.68; H, 4.09; N, 17.89; S, 7.00.

Ethyl 2-(3-cyano-7,8-dioxo-6-phenylpyridazo[4,5-d]pyridazine-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**26**)

A solution of **24** (g, 0.01 mol) in ethanol (50 mL) containing sodium hydroxide (0.5 g) was heated under reflux for 5 hours and poured into ice water containing a few drops of hydrochloric acid. The solid product formed was collected by filtration.

26: Pale yellow crystals, yield 64% (3.0 g); m.p. 192–195°C (from 1,4-dioxane). IR υ/cm^{-1} 2983, 2872 (CH_3, CH_2), 2223 (CN), 1703, 1690–1683 (3 C=O), 1660 (C=N), 1634 (C=C). ^{1}H NMR: δ/ppm 1.61 (t, 3H, CH_3), 2.22 (m, 4H, 2 CH_2), 2.31 (m, 4H, 2CH_2), 4.24 (q, 2H, CH_2), 7.29–7.37 (m, 6H, C_6H_5, pyridazine CH). $C_{24}H_{19}N_5SO_4$ Calcd: C, 60.82; H, 4.01; N, 14.78; S, 6.76 (473.50). Found: C, 60.77; H, 4.08; N, 14.65; S, 6.53.

Ethyl 2-(3-cyano-7-phenylhexazaace-naphthalene-1-yl)-4,5,6,7-tetrahydro-benzo[b]-thiophene-3-carboxylate (**27**)

To a solution of **26** (4.89 g, 0.01 mol) in 1,4-dioxane (30 mL), hydrazine hydrate (g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 hours and poured into ice water containing a few drops of hydrochloric acid.

27: Pale yellow crystals, yield 66% (3.1 g); m.p. 283–285°C (from ethanol). IR: υ/cm^{-1} 2980, 2883 (CH_3, CH_2), 2226 (CN), 1694 (C=O), 1655 (C=N), 1630 (C=C). ^{1}H NMR: δ/ppm 1.62 (t, 3H, CH_3), 2.20 (m, 4H, 2 CH_2), 2.32 (m, 4H, 2CH_2), 4.20 (q, 2H, CH_2), 7.26–7.31 (m, 6H, C_6H_5, pyridazine H). $C_{24}H_{19}N_7SO_2$ Calcd: C, 61.34; H, 4.05; N, 20.87; S, 6.81 (469.50). Found: C, 61.26; H, 3.86; N, 20.67; S, 7.02.

Ethyl 1-(3-cyano-7-phenyl-10-oxophenan-threne)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxylate (**29a**) *and Ethyl 1-(3-cyano-7-phenyl-10-thioxophenanthrene)-4,5,6,7-tetra-hydrobenzo[b]-thiophene-3-carboxylate* (**29b**)

To a suspension of **26** (4.89 g, 0.01 mol) in sodium ethoxide solution—prepared by dissolving sodium metal (0.23 g, 0.01 mol) in absolute ethanol (40 mL)—either urea (0.7 g, 0.01 mol) or thiourea (0.84 g, 0.01 mol) was added. The reaction mixture was heated in a boiling water bath for 5 hours and poured into an ice water mixture containing hydrochloric acid (to pH 6). The formed solid product, in each case, was collected by filtration.

29a: Pale yellow crystals, yield 55% (2.7 g); m.p. 120–123°C (from 1,4-dioxane). IR: υ/cm^{-1} 2984, 2876 (CH_3, CH_2), (CN), 1692, 1683 (2 C=O), 1650 (C=N), 1636 (C=C). ^{1}H NMR: δ/ppm 1.64 (t, 3H, CH_3), 2.25 (m, 4H, 2 CH_2), 2.34 (m, 4H, 2CH_2), 4.25 (q, 2H, CH_2), 7.24–7.30 (m, 6H, C_6H_5, pyridazine H). $C_{25}H_{19}N_7SO_3$ Calcd: C, 60.30; H, 3.82; N, 19.69; S, 6.43. (497.53). Found: C, 60.22; H, 3.93; N, 19.47; S, 6.62.

29b: Pale yellow crystals, yield 70% (3.6 g); m.p. 177–80°C (from 1,4-dioxane). IR: υ/cm^{-1} 2980, 2883 (CH_3, CH_2), 2226 (CN), 1694 (C=O), 1655 (C=N),

1630 (C = C). ^{1}H NMR: δ/ppm 1.62 (t, 3H, CH_3), 2.20 (m, 4H, 2 CH_2), 2.32 (m, 4H, 2CH_2), 4.20 (q, 2H, CH_2), 7.26–7.31 (m, 5H, C_6H_5). $C_{25}H_{19}N_7S_2O_2$ Calcd: C, 58.41; H, 3.69; N, 19.08; S, 12.46 (513.59). Found: C, 58.33; H, 3.85; N, 18.79; S, 12.32.

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