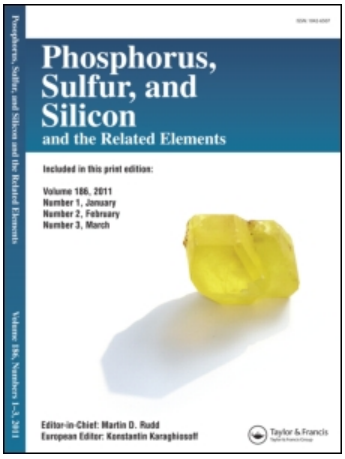

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Utility of 2-Aminothiophene-3-carboxamide in the Synthesis of Biologically Active, Fused Heterocyclic Derivatives

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*2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**1**) reacted with 3-iminobutyronitrile (**2**) to give the imino product **3**. The latter product was used in synthesis of a series of annulated products which have pharmaceutical interest. The in vitro antimicrobial activity of some newly synthesized compounds against bacteria was studied.*

Keywords Antimicrobial; benzo[*b*]thiophene; pyridazine; pyridine; triazine

INTRODUCTION

Over recent years there has been an increasing interest in the chemistry of thiophenes because of their biological significance. Many of them have been widely investigated for therapeutic uses especially as antifungal,[1,2] antibacterial,[3] antinflammatory,[4] anticonvulsant,[5] antiasthmatic,[6] and analgesic[7] agents. They also were known to show anti-HIV,[8] antiproliferative,[9] germicidal,[10] and D2 dopaminergic[11] activities. Moreover, they were reported to act as selective type 4 phosphodiesterase inhibitors,[12] of the response to oxytocin,[13] and high-affinity retinoic acid receptor antagonists.[14] As a continuation of our systematic investigations dealing with application of 2-aminothiophenes in

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the synthesis of polyfunctionally substituted heterocycles,[15–17] we decided to synthesize a series of novel annulated heterocyclic derivatives with a potential spectrum of bio-responses. The antimicrobial activities of the new synthesized compounds against gram-positive and gram-negative bacteria were studied.

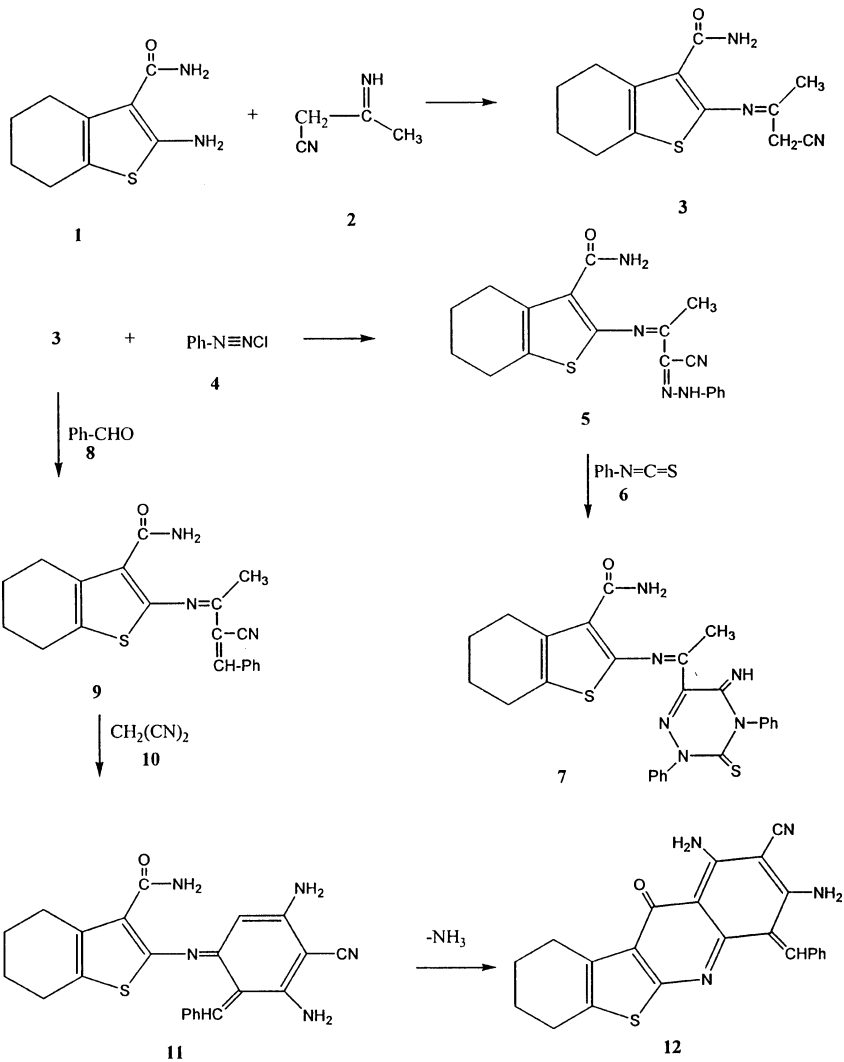
RESULTS AND DISCUSSION

Chemistry

2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**1**)[18] reacted with 3-iminobutyronitrile via heating in an oil bath to give the imino product **3**. The structure of **3** was based on analytical and spectral data. The ^{1}H NMR spectrum of the product showed, besides the expected signal for the cyclohexenyl moiety, a singlet at δ 2.89 for a CH_3 group, a singlet at δ 5.40 for an NH_2 group and a singlet at δ 5.21 for a CH_2 group. Moreover, the ^{13}C NMR (ppm) data showed signals at 26.73 (CH_3), δ 36.8, 44.2, 46.8 (4 CH_2), 60.7 (CH_2), 117.2, 118.8, 119.4, 119.9 (thiophene C), 120.3 (CN), 160.7 (C=N), and 180.4 (C=O).

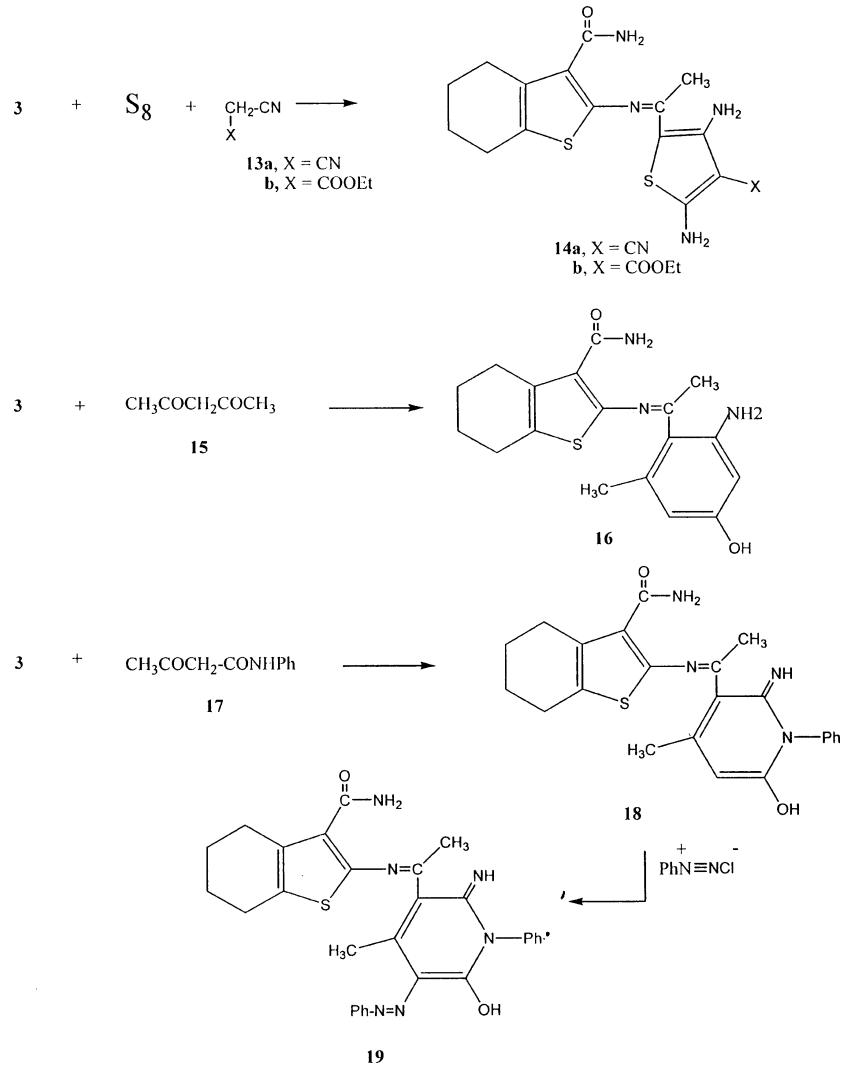
Compound **3** is the key starting material used for the synthesis of a variety of heterocyclic and fused compounds with pharmaceutical importance. Thus, the reaction of **3** with benzenediazonium chloride **4** at 0–5°C, gave the phenyl hydrazone derivative **5**. The latter product reacted with phenyl isothiocyanate **6** to give the 1,2,4-triazine derivative **7**. The structure of the latter product was based on the analytical and spectral data. Thus the ^{1}H NMR spectrum showed, besides the expected cyclohexene protons, a singlet at δ 2.91 for CH_3 group, a singlet at δ 5.42 (D_2O exchangeable) characteristic for the NH_2 group, a mutiplet at δ 7.26–7.35 for the two phenyl protons, and a singlet at δ 8.65 (D_2O exchangeable) characteristic for NH group.

The reaction of compound **3** with benzaldehyde in a boiling 1,4-dioxane solution containing a catalytic amount of piperidine gave the benzal derivative **9**. The reaction of the latter product with malononitrile **10** gave a single product with molecular formula $C_{23}H_{20}N_5O$. The cyclohexadiene structure **11** was assigned for the reaction product. Confirmation for this structure was based on analytical and spectral data. Thus, the ^{13}C NMR (ppm) spectrum of **11** showed signals at 36.4, 44.3, 46.6 (4 CH_2), 117.0, 118.5, 118.7, 119.0, 119.7, 120.0, 120.2, 139.3, 140.0 (thiophene, benzene, cyclohexadiene), 120.6, 120.8 (2 CN), 160.4 (C=N), and 180.2 (C=O). Compound **11** underwent cyclization when heated in sodium ethoxide solution to give the 4,5,6,7-tetrahydrobenzo[*b*]thieno[4,5:2,3]cyclohexadieno[*e*]pyridine derivative **12**, via ammonia elimination.



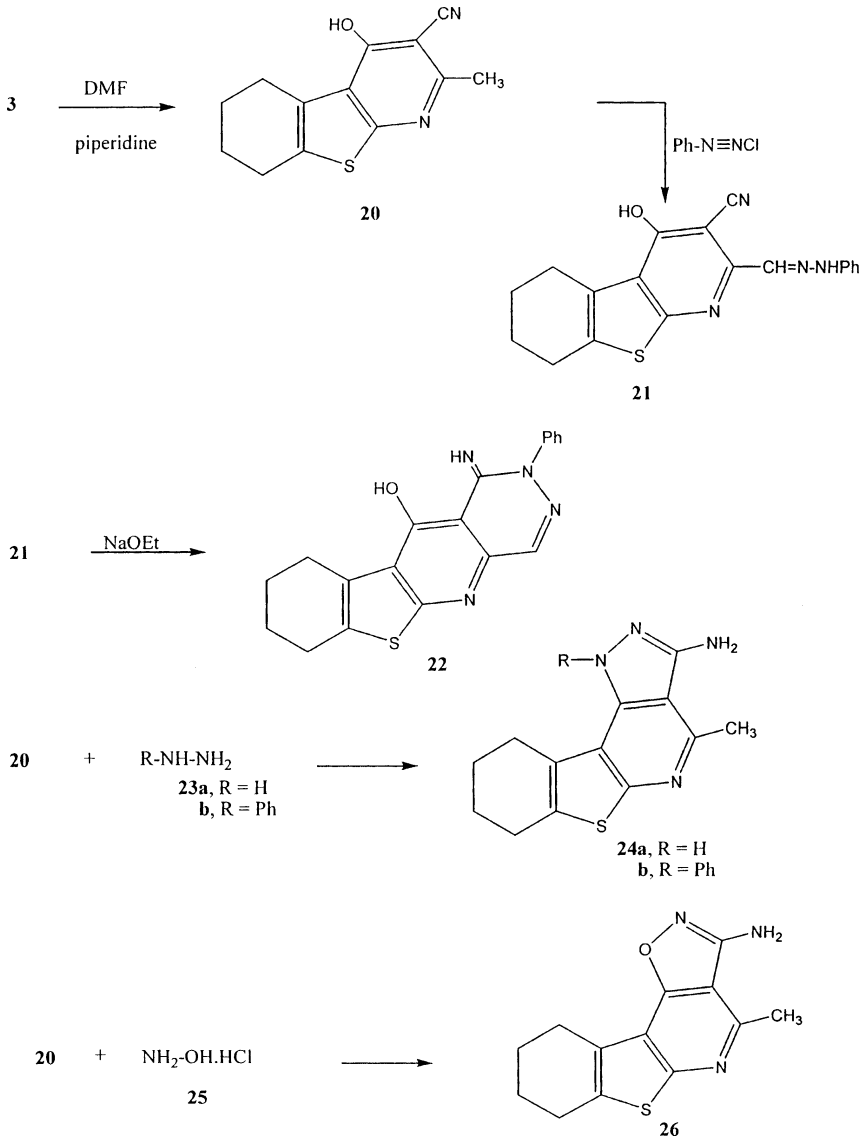
SCHEME 1

The behavior of **3** toward thiophene formation via Gewald's thiophene synthesis[18] was also examined. Thus, **3** reacted with sulfur and the cyanomethylene reagents, namely malononitrile (**13a**) and ethyl cyanoacetate (**13b**), to give the thiophene derivatives **14a** and **14b** respectively. Both elemental and spectral data of the latter products were consistent with the assigned structure.



SCHEME 2

As an extension of this synthetic route, the behavior of **3** toward some 1,3-dicarbonyl compounds was investigated. Thus, **3** reacted with acetylacetone (**15**) to give the benzene derivative **16**; its structure being based on analytical and spectral data. Thus, the ^{1}H NMR spectrum of **16** showed, besides the expected signals, a singlet at δ 3.24 characteristic for a CH_3 group, a singlet at δ 5.38 for an NH_2 group, two singlets at δ 7.32, 7.38 for benzene H-2, H-4, and a broad singlet



SCHEME 3

(D_2O exchangeable) for an OH group. In a similar way, the reaction of **3** with acetoacetanilide **17** afforded the 2-iminopyridine derivative **18**. The C-3 position in **18** showed interesting reactivity towards coupling with diazonium salts. Thus, compound **18** reacted with benzene diazonium chloride to give the phenylazo derivative **19**. Both elemental and

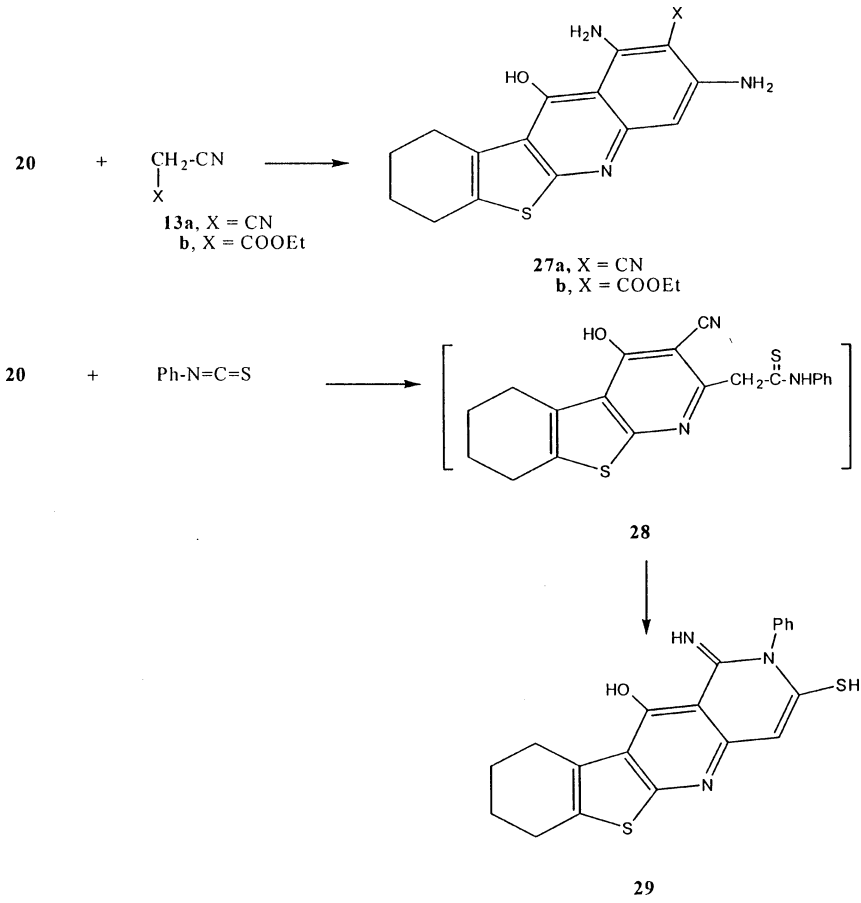
spectral data of **18** and **19** were consistent with the assigned structures (cf. experimental data).

Compound **3** underwent ready cyclization when heated in sodium ethoxide solution using a boiling water bath to give the 4,5,6,7-tetrahydrobenzo[*b*]thieno[5,4:2,3]pyridine derivative **20**, via ammonia elimination. Compound **20**, with its methyl group in ortho position to the electronegative cyano group, showed interesting reactivity towards electrophilic reagents. Thus it is coupled with benzene diazonium chloride to give the phenylhydrazone derivative **21**. The latter product underwent ready cyclization when heated in a boiling sodium ethoxide solution to give the pyridazine derivative **22**. Moreover, the *o*-hydroxy nitrile moiety present in compound **20** showed interesting reactivity toward nucleophilic reagents. Thus, with either hydrazine hydrate (**23a**) or phenyl hydrazine (**23b**) it gave the 4,5,6,7-tetrahydrobenzo[*b*]-thieno[5,4:2,3]pyrido[5,4:4,5]pyrazole derivatives **24a** and **24b**, respectively. In a similar manner, the reaction of **20** with hydroxylamine hydrochloride (**25**) gave the 4,5,6,7-tetrahydrobenzo[*b*]thieno[5,4:2,3]-pyrido[5,4:4,5]isoxazole derivative **26**. Structures of **24a**,**b** and **26** were established on the basis of elemental and spectral data (cf. experimental section).

The reactivity of compound **20** toward cyanomethylene reagents was studied in the aim to form annulated products with potential pharmaceutical interest. Thus, compound **20** reacts with either malononitrile (**13a**) or ethyl cyanoacetate (**13b**) in refluxing 1,4-dioxane containing a catalytic amount of triethylamine to afford the annulated products **27a** and **27b**, respectively. Moreover, the reaction of **20** with phenyl isothiocyanate gave the 4,5,6,7-tetrahydrobenzo[*b*]thieno-[5,4:2,3]pyrido[5,6:3,4]pyridine derivative **29**. Structures of **27a**,**b** and **29** were based on analytical and spectral data, which are consistent with the assigned structures (Scheme 4).

ANTIMICROBIAL ACTIVITY

The diverse biological activities of thiophene and fused derivatives prompted us to test and study the biological activities of some of the newly synthesized products. Many antimicrobial agents have been introduced into therapy; however the field still needs extensive efforts for the development of new antimicrobial agents to overcome the highly resistant strains of microorganisms. The bactericidal activity of the newly synthesized products against two groups of microorganisms, including two strains of gram-positive bacteria and two strains of gram-negative bacteria, was investigated in vitro by the hole plate and filter paper disc



SCHEME 4

methods[19,20] (Table I). A disc of blotting paper was impregnated with a known volume and appropriate concentration of a compound to be tested. This paper 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 center of the disc whereas resistant stains grow up to the edge of the disc. In conclusion, the data of the susceptibility tests for the compounds clearly showed significant and potent antibacterial activity (bactericidal) against all gram-positive and gram-negative tested bacteria. Further studies should be done to elucidate the

TABLE I In Vitro Bactericidal Activity of Some of the Newly Synthesized Compounds[a]

Compound no.	*Bacillus cereus* (Gram-positive)	*Staph. Aureus* (Gram-positive)	*E. Coli* (Gram-negative)	*K. Pneumonia* (Gram-negative)
3	++	+++	++	++
5	+++	++	+++	+++
7	++	+++	++	++
6b	++	+++	+++	++
9	+	+	++	+++
11	++	+++	+	+
14a	+	+++	+++	+++
14b	+++	+	++	+++
16	+++	++	++	++
18	+	+	+++	++
19	+++	+++	+	+++
20	++	+	+++	+
21	+++	++	++	−
22	+	++	+++	+
24a	+++	++	+	++
26	++	+++	++	++
27a	++	−	++	+
27b	++	+	+++	+
29	+++	++	+	+++

[a]no inhibition (−); 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%.

mechanism of action of the tested novel compounds and to determine whether their activity is lethal or merely inhibitory to the microorganisms. In addition, the bioactivity of the promising compounds and their structure–activity relationships will be studied.

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian EM-390 90 MHz spectrophotometer in DMSO-d_6 as the solvent and TMS as internal reference. Chemical shifts are expressed in δ or ppm. Antibacterial results were recorded by Professor S. A. Aouf, Botany Department, Faculty of Science, Cairo University, Giza, Egypt

2-Imino(butyronitrilo-β-ylidino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (3)

To a dry mixture of **1** (1.96 g, 0.01 mol) and β-iminobutyronitrile (**2**) (0.82 g, 0.01 mol) was added ammonium acetate (1.44 g, 0.02 mol).

The reaction mixture was heated in an oil bath (120°C) for 8 h and then left to cool. The solid product, obtained upon triturating the fused product with ethanol followed by pouring onto ice water, was collected by filtration.

Orange crystals of **3** from 1,4-dioxane, yield 2.08 g (80%), m.p. 282–5°C. $C_{13}H_{15}N_3SO$ (261.35). Calcd: C, 59.74; H, 5.78; N, 16.07; S, 12.26. Found: C, 59.61; H, 5.56; N, 16.22; S, 12.44. IR (υ/cm^{-1}): 3465, 3387 (NH_2), 2987, 2886 (CH_3, CH_2), 2220 (CN), 1687 (C=O), 1665 (C=N), 1643 (C=C); ^{1}H NMR (δ): 2.23–2.26 (m, 4H, $2CH_2$), 2.35–2.38 (m, 4H, $2CH_2$), 2.89 (s, 3H, CH_3), 5.21 (s, 2H, CH_2), 5.40 (s, 2H, NH_2, D_2O exchangeable). ^{13}C NMR (ppm): 26.73 (CH_3), 36.8, 44.2, 46.8 (4 CH_2), 60.7 (CH_2), 117.2, 118.8, 119.4, 119.9 (thiophene C), 120.3 (CN), 160.7 (C=N), 180.4 (C=O).

2-Imino(α-phenylhydrazonobutyronitrilo-β-ylidino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (5), 2-Iminoacetylideno(2-imino-6-hydroxy-4-methyl-5-phenylazo-1-phenylpyridin-3-yl)-4,5,6,7-tetrahydro-benzo-[b]thiophene-3-carboxamide (19), 3-Cyano-4-hydroxy-2-phenyl-hydrazomethino-4,5,6,7-tetrahydrobenzo-[b]thieno[5,4:2,3]pyridine (21)

General procedure. To a cold solution (0–5°C) of either **3** (2.61 g, 0.01 mol), **18** (3.90 g, 0.01 mol), or **20** (2.44 g, 0.01 mol) in ethanol (50 ml) containing sodium hydroxide (10 ml, 40%), was added with continuous stirring benzenediazonium chloride (0.01 mol) [prepared by adding a cold solution of sodium nitrite (0.7 g, 0.01 mol) to a cold solution (0–5°C) of aniline (0.93 g, 0.01 mol) in concentrated hydrochloric (3 ml)]. The reaction mixture, in each case, was left at room temperature for 3 h after which was formed a solid product which was collected by filtration.

*Compound **5**.* Orange crystals from acetic acid, yield 4.37 g (72%), m.p. 166–70°C. $C_{19}H_{19}N_5SO$ (365.46). Calcd: C, 62.44; H, 5.24; N, 19.16; S, 8.77. Found: C, 62.60; H, 5.46; N, 19.28; S, 8.54. IR (υ/cm^{-1}): 3455–3330 (NH_2, NH), 3055 (CH aromatic), 2984, 2883 (CH_3, CH_2), 2222 (CN), 1681 (C=O), 1659 (C=N), 1638 (C=C); ^{1}H NMR (δ): 2.22–2.24 (m, 4H, $2CH_2$), 2.32–2.36 (m, 4H, $2CH_2$), 2.92 (s, 3H, CH_3), 5.19 (s, 2H, CH_2), 5.42 (s, 2H, NH_2, D_2O exchangeable), 7.30–7.36 (m, 5H, C_6H_5), 8.87 (s, 1H, NH).

*Compound **19**.* Red crystals from acetic acid, yield 3.36 g (66%), m.p. 222–25°C. $C_{29}H_{28}N_6SO_2$ (524.65). Calcd: C, 66.39; H, 5.37; N, 16.01; S, 6.11. Found: C, 66.61; H, 5.49; N, 16.32; S, 6.34. IR (υ/cm^{-1}): 3434–3320 (NH_2, NH, OH), 3050 (CH aromatic), 2982, 2890 (CH_3, CH_2), 1685 (C=O), 1660 (C=N), 1634 (C=C); ^{1}H NMR (δ): 2.20–2.25 (m, 4H, $2CH_2$),

2.34–2.38 (m, 4H, $2CH_2$), 2.91, 3.24 (2s, 6H, $2CH_3$), 5.40 (s, 2H, NH_2, D_2O exchangeable), 7.31–7.37 (m, 10H, $2C_6H_5$), 8.90 (s, 1H, NH), 9.85 (s, br, 1H, OH).

Compound ***21.*** Reddish brown crystals from 1,4-dioxane, yield 2.02 g (58%), m.p. >300°C. $C_{19}H_{16}N_4SO$ (348.43). Calcd: C, 65.49; H, 4.63; N, 16.07; S, 9.20. Found: C, 65.14; H, 4.60; N, 16.37; S, 9.51. IR (υ/cm^{-1}): 3487–3305 (OH, NH), 3045 (CH aromatic), 2980, 2885 (CH_3, CH_2), 1665 (C=N), 1639 (C=C); ^{1}H NMR (δ): 2.22–2.26 (m, 4H, $2CH_2$), 2.32–2.37 (m, 4H, $2CH_2$), 7.28–7.34 (m, 6H, C_6H_5, pyridazine H-3), 9.21 (s, 1H, NH), 10.37 (s, br, 1H, OH).

*2-Iminoacetylideno(6-imino-1,3-diphenyl-2-thioxo-1,3,4-triazine-5-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (7)*

To a solution of compound **5** (3.64 g, 0.01 mol) in 1,4-dioxane (50 ml) containing triethylamine (0.5 ml) was added phenylisothiocyanate (**6**) (1.3 g, 0.01 mol). The reaction mixture was heated under reflux for 3 h and then poured onto ice/water containing a few drops of hydrochloric acid. The solid product was collected by filtration.

Yellow crystals of **7** from ethanol, yield 3.45 g (69%), m.p. 154–6°C. $C_{26}H_{24}N_6S_2O$ (500.65). Calcd: C, 62.37; H, 4.83; N, 16.78; S, 12.81. Found: C, 62.53; H, 4.62; N, 16.67; S, 12.56. IR (υ/cm^{-1}): 3474, 3325 (NH, NH_2), 2985, 2882 (CH_3, CH_2), 2222 (CN), 1677 (C=O), 1660 (C=N), 1636 (C=C), 1210, 1190 (C=S); ^{1}H NMR (δ): 2.22–2.26 (m, 4H, $2CH_2$), 2.34–2.35 (m, 4H, $2CH_2$), 2.91 (s, 3H, CH_3), 5.42 (s, 2H, NH_2, D_2O exchangeable), 7.26–7.35 (m, 10H, $2C_6H_5$), 8.65 (s, br, 1H, NH).

*2-Imino(α-benzalbutyronitrilo-β-ylidino)-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxamide (9)*

Equimolecular amounts of compound **3** (1.96 g, 0.01 mol) and benzaldehyde (1.08, 0.01 mol) in dimethylformamide (30 ml) containing piperidine (0.5 ml) was heated under reflux for 5 h and then was evaporated in vacuum. The remaining product was triturated with diethyl ether, and the solid product was collected by filtration.

Yellow crystals of **9** from ethanol, yield 2.44 g (70%), m.p. 246–8°C. $C_{20}H_{19}N_3SO$ (349.46). Calcd: C, 68.74; H, 5.48; N, 12.02; S, 9.17. Found: C, 68.50; H, 5.22; N, 12.37; S, 8.96. IR (υ/cm^{-1}): 3490–3330 (NH_2), 3040 (CH aromatic), 2988, 2891 (CH_3, CH_2), 2225 (CN), 1665 (C=N), 1639 (C=C); ^{1}H NMR (δ): 2.22–2.28 (m, 4H, $2CH_2$), 2.30–2.37 (m, 4H, $2CH_2$), 5.23 (s, 2H, NH_2), 6.87 (s, 1H, CH=C), 7.29–7.36 (m, 5H, C_6H_5).

2-Imino(5-benzal-4-cyano-3,5-diamino-1-ylideno)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (11)

To a solution of compound **9** (3.49 g, 0.01 mol) in 1,4-dioxane (40 ml) containing triethylamine (0.5 ml) was added malononitrile (**10**) (0.66 g, 0.01 mol). The reaction mixture was heated under reflux for 3 h and then was evaporated in vacuum. The remaining product was triturated with diethyl ether, and the solid product was collected by filtration.

Yellow crystals of **11** from DMF, yield 2.48 g (60%), m.p. 144–6°C. $C_{23}H_{21}N_5SO$ (415.52). Calcd: C, 66.48; H, 5.09; N, 16.85; S, 7.71. Found: C, 66.63; H, 4.92; N, 16.53; S, 7.50. UV ($CHCl_3$) ($\lambda_{max/nm}$, log ε): 216, 4.47; 229, 5.53; 284, 4.30. IR (υ/cm^{-1}): 3446–3312 ($3NH_2$), 3060 (CH aromatic), 2980, 2875 (CH_3, CH_2), 2220 (CN), 1655 (C=N), 1630 (C=C); ^{1}H NMR (δ): 2.22–2.26 (m, 4H, $2CH_2$), 2.32–2.37 (m, 4H, $2CH_2$), 4.45, 4.48, 5.31 (3s, 6H, $3NH_2$), 6.89 (s, 1H, CH=C), 7.28–7.34 (m, 6H, C_6H_5, benzene H-2); ^{13}C NMR (ppm): 36.4, 44.3, 46.6 (4 CH_2), 117.0, 118.5, 118.7, 119.0, 119.7, 120.0, 120.2, 139.3, 140.0 (thiophene, benzene, cyclohexadiene), 120.6, 120.8 (2 CN), 160.4 (C=N), 180.2 (C=O).

2-Imino[acetyl-α-(4-cyano-3,5-diaminothiopheno-2-yl)]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (14a) and 2-Imino[acetyl-α-(ethyl-3,5-diaminothiopheno-2-yl-4-carboxylato)]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (14b)

General procedure. To a solution of **3** (2.61 g, 0.01 mol) in absolute ethanol (40 ml) containing triethylamine (0.5 ml) was added either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol). To each reaction mixture was added elemental sulfur (0.23 g, 0.01 mol) and the whole reaction mixture was heated under reflux for 1 h and then left to cool. The solid product formed in each case was collected by filtration.

*Compound **14a**.* Orange crystals from acetic acid, yield 2.70 g (60%), m.p. 232–5°C. $C_{16}H_{17}N_5S_2O$ (359.48). Calcd: C, 53.46; H, 4.76; N, 19.48; S, 17.84. Found: C, 53.39; H, 4.56; N, 19.32; S, 17.52. IR (υ/cm^{-1}): 3541–3323 ($3NH_2$), 2987, 2870 (CH_3, CH_2), 2218 (CN), 1688 (C=O), 1662 (C=N), 1637 (C=C); ^{1}H NMR (δ): 2.24–2.28 (m, 4H, $2CH_2$), 2.31–2.38 (m, 4H, $2CH_2$), 2.88 (s, 3H, CH_3), 4,46, 4.47, 5.30 (3s, 6H, $3NH_2$).

*Compound **14b**.* Pale brown crystals from acetic acid, yield 2.88 g (71%), m.p. 176–9°C. $C_{18}H_{22}N_4S_2O_3$ (406.53) Calcd: C, 53.18; H, 5.45; N, 13.78; S, 15.77. Found: C, 53.37; H, 5.76; N, 13.47; S, 15.48. IR (υ/cm^{-1}): 3532–3347 ($3NH_2$), 2982, 2889 (CH_3, CH_2), 1660 (C=N), 1643 (C=C);

^{1}H NMR (δ): 1.35 (t, 3H, CH_3), 2.23–2.26 (m, 4H, $2CH_2$), 2.32–2.36 (m, 4H, $2CH_2$), 2.92 (s, 3H, CH_3), 4.22 (q, 2H, CH_2), 4,44, 4.49, 5.34 (3s, 6H, $3NH_2$).

*2-Imino[acetyl-α-(3-amino-5′-methylphenol-4-yl)]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (16) and 2-Imino[acetyl-α-(6-hydroxy -2-Imino-4-methyl-1-phenylpyridino-3-yl]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (18)*

General procedure. To a solution of compound **3** (2.61 g, 0.01 mol) in 1,4-dioxane (40 ml) containing triethylamine (0.5 ml), was added either acetylacetone (**15**) (1.0 g, 0.01 mol) or acetoacetanilide (**17**) (1.78 g, 0.01 mol). The whole reaction mixture in each case was heated under reflux for 45 min and then left to cool. A solid product formed upon pouring onto ice/water containing few drops of hydrochloric acid and was collected by filtration.

*Compound **16**.* Yellow crystals from 1,4-dioxane, yield 2.05 g (66%), m.p. 222–5°C. $C_{18}H_{21}N_3SO_2$ (343.45). Calcd: C, 62.94; H, 6.16; N, 12.23; S, 9.33. Found: C, 62.67; H, 5.96; N, 12.40; S, 9.58.IR (υ/cm^{-1}): 3577–3321 (OH, $2NH_2$), 2980, 2873 (CH_3, CH_2), 1684 (C=O), 1662 (C=N), 1639 (C=C); ^{1}H NMR (δ): 2.22–2.25 (m, 4H, $2CH_2$), 2.34–2.38 (m, 4H, $2CH_2$), 2.90, 3.24 (2s, 6H, $2CH_3$), 4.56, 5.38 (2s, 4H, $2NH_2$), 7.32, 7.38 (2s, 2H, C_6H_2), 8.97 (s, br, 1H, OH).

*Compound **18**.* Yellowish brown crystals from 1,4-dioxane, yield 3.06 g (73%), m.p. 180–3°C. $C_{23}H_{24}N_4SO_2$ (420.54). Calcd: C, 65.69; H, 5.75; N, 13.32; S, 7.62. Found: C, 65.75; H, 6.03; N, 13.59; S, 7.40. IR (υ/cm^{-1}): 3567–3342 (OH, NH, NH_2), 2986, 2893 (CH_3, CH_2), 1688 (C=O), 1667 (C=N), 1641 (C=C); ^{1}H NMR (δ ppm): 2.21–2.25 (m, 4H, CH_2), 2.32–2.36 (m, 4H, $2CH_2$), 2.87, 3.09 (2s, 6H, $2CH_3$), 7.28–7.34 (m, 6H, C_6H_5, benzene H-5), 9.24 (s, br, 1H, OH).

*3-Cyano-4-hydroxy-2-methyl-4,5,6,7-tetrahydrobenzo-[*b*]thieno[5,4:2,3]pyridine (20)*

A solution of compound **3** (0.01 mol) in dimethylformamide containing piperidine (0.5 ml) was heated under reflux for 8 h and then poured onto ice/water. The formed solid product was collected by filtration.

Pale yellow crystals of **20** from methanol, yield 1.36 g (56%), m.p. >300°C. $C_{13}H_{12}N_2SO$ (244.32). Calcd: C, 63.91; H, 4.95; N, 11.46; S, 13.12. Found: C, 63.72; H, 4.66; N, 11.74; S, 13.48. IR (υ/cm^{-1}): 3543–3387 (OH), 2990, 2872 (CH_3, CH_2), 2220 (CN), 1658 (C=N), 1636 (C=C). ^{1}H NMR (δ): 2.22–2.27 (m, 4H,CH_2), 2.30–2.35 (m, 4H, $2CH_2$), 3.09 (s, 3H, CH_3), 9.11 (s, br, 1H, OH).

1-Benzal-3-cyano-2,4-diamino-4,5,6,7-tetrahydrobenzo-[b]thieno[5,4:2′,3′]pyridine[e]1,3-cyclohexadiene (12) and 4-Imino-5-hydroxy-3-phenyl-4,5,6,7-tetrahydrobenzo[b]-thieno[5,4:2,3]pyridine[6,5:4,5]pyridazine (22)

General procedure. A solution of either compound **11** (4.41 g, 0.01 mol) or **21** (3.48 g, 0.01 mol) in sodium ethoxide solution (0.02 mol) [prepared by dissolving sodium metal (0.46 g, 0.02 mol) in absolute ethanol (50 ml)] was heated in a boiling water bath for 8 h and then was poured onto ice/water containing hydrochloric acid (to pH 6). The formed solid product was collected by filtration.

Compound ***12****.* Yellow crystals from DMF, yield 2.62 g (66%), m.p. >300°C. $C_{23}H_{18}N_4SO$ (398.49). Calcd: C, 69.32; H, 4.55; N, 14.05; S, 8.04. Found: C, 69.62; H, 4.86; N, 14.38; S, 7.88. UV ($CHCl_3$) (λ max/nm, log ε): 220, 4.24; 227, 4.26; 277, 4.13; 284, 4.15. IR (υ/cm^{-1}): 3466–3332 ($2NH_2$), 3055 (CH aromatic), 2875 (CH_2), 2222 (CN), 1683 (C=O), 1652 (C=N), 1638 (C=C); ^{1}H NMR (δ): 2.22–2.25 (m, 4H, $2CH_2$), 2.32–2.36 (m, 4H, $2CH_2$), 4,47, 4.49 (2s, 4H, $2NH_2$), 6.88 (s, 1H, CH=C), 7.29–7.32 (m, 5H, C_6H_5).

Compound ***22****.* Orange crystals from acetone, yield 2.15 g (62%), m.p. >284–7°C. $C_{19}H_{16}N_4SO$ (348.43). Calcd: C, 65.49; H, 4.62; N, 16.07; S, 9.20. Found: C, 65.77; H, 4.90; N, 16.40; S, 9.54. IR (υ/cm^{-1}): 3552–3314 (OH, NH), 2982, 2878 (CH_3, CH_2), 1693–1680 (3 C=O), 1663 (C=N), 1633 (C=C); ^{1}H NMR (δ): 2.20–2.25 (m, 4H, CH_2), 2.32–2.35 (m, 4H, $2CH_2$), 7.28–7.32 (m, 5H, C_6H_5, pyridazine H-3), 9.26 (s, br, 1H, OH).

3-Amino-5[H]-2-methyl-4,5,6,7-tetrahydrobenzo[b]thieno-[5,4:2,3]pyrido[5,4:4,5]pyrazole (24a) and 3-Amino-5-phenyl-2-methyl-4,5,6,7-tetrahydrobenzo[b]thieno-[5,4:2,3]pyrido[5,4:4,5]pyrazole (24b)

General procedure. To a solution of compound **20** (2.44 g, 0.01 mol) in 1,4-dioxane (40 ml) was added either hydrazine hydrate (0.5 g, 0.01 mol) or phenyl hydrazine (1.08 g, 0.01 mol). The reaction mixture was heated under reflux for 2 h and then poured onto water containing few drops of hydrochloric acid. The solid product was collected by filtration.

Compound ***24a****.* Brown crystals from 1,4-dioxane, yield 1.80 g (70%), m.p. 222–5°C. $C_{13}H_{14}N_4S$ (258.35). Calcd: C, 60.43; H, 5.46; N, 21.68; S, 12.41. Found: C, 60.64; H, 5.80; N, 21.41; S, 12.59. IR (υ/cm^{-1}): 3446–3315 (NH, NH_2), 2986, 2881 (CH_3, CH_2), 1687, 1682 (2 C=O), 1652 (C=N), 1640 (C=C); ^{1}H NMR (δ): 2.23–2.26 (m, 4H,CH_2), 2.32–2.36 (m, 4H, $2CH_2$), 3.13 (s, 3H, CH_3), 4.67 (s, 2H, NH_2), 8.08 (s, br, 1H, NH).

Compound ***24b.*** Orange crystals from 1,4-dioxane, yield 2.20 g (66%), m.p. 145–7°C. $C_{19}H_{18}N_4S$ (334.44). Calcd: C, 68.23; H, 5.42; N, 16.75; S, 9.58. Found: C, 67.97; H, 5.56; N, 16.48; S, 9.81. IR (υ/cm^{-1}): 3439, 3356 (NH_2), 2984, 2880 (CH_3, CH_2), 1655 (C=N), 1637 (C=C). ^{1}H NMR (δ): 2.22–2.26 (m, 4H, CH_2), 2.32–2.38 (m, 4H, $2CH_2$), 3.17 (s, 3H, CH_3), 4.88 (s, 2H NH_2), 7.32–7.38 (m, 5H, C_6H_5).

*3-Amino-5[*H*]-2-methyl-4,5,6,7-tetrahydrobenzo[*b*]thieno-[5,4:2,3]pyrido[5,4:4,5]isoxazole (26)*

Equimolecular amounts of compounds **20** (2.44 g, 0.01 mol) and hydroxylamine hydrochloride (0.69 g, 0.01 mol) in absolute ethanol (50 ml) containing sodium acetate (1.0 g) was heated under reflux for 7 h and then poured onto water. The solid product formed upon stirring at room temperature overnight was collected by filtration.

Yellow crystals of **26** from diethyl ether, yield 1.55 g (60%), m.p. 170–3°C. Found: C, 60.57; H, 4.92; N, 15.94; S, 12.68. $C_{13}H_{13}N_3SO$ (259.33). Calcd: C, 60.21; H, 5.05; N, 16.20; S, 12.36. IR (υ/cm^{-1}): 3444, 3349 (NH_2), 2990, 2876 (CH_3, CH_2), 1650 (C=N), 1640 (C=C). ^{1}H NMR (δ): 2.20–2.24 (m, 4H,CH_2), 2.31–2.36 (m, 4H, $2CH_2$), 3.20 (s, 3H, CH_3), 4.49 (s, 2H, NH_2).

*3-Cyano-2,4-diamino-5-hydroxy-4,5,6,7-tetrahydrobenzo-[*b*]thieno[5,4:2,3]pyrido[*e*]benzene (27a) and 2,4-Diamino-3-ethoxycarbonyl-5-hydroxy-4,5,6,7-tetrahydrobenzo[*b*]thieno[5,4:2,3]pyrido[*e*]benzene (27b)*

General procedure. To a solution of compound **20** (2.44 g, 0.01 mol) in 1,4-dioxane (40 ml) containing triethylamine (0.5 ml) was added 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 under reflux for 2 h and then evaporated in vacuum. The remaining product was triturated with ethanol, and the formed solid product was collected by filtration.

Compound ***27a.*** Orange crystals from 1,4-dioxane, yield 2.23 g (72%), m.p. 256–7°C. $C_{16}H_{14}N_4SO$ (310.38). Calcd: C, 61.91; H, 4.54; N, 18.05; S, 10.33. Found: C, 62.07; H, 4.76; N, 18.36; S, 10.60. IR (υ/cm^{-1}): 3562–3315 (OH, $2NH_2$), 2880 (CH_2), 2225 (CN), 1660 (C=N), 1633 (C=C); ^{1}H NMR (δ): 2.20–2.25 (m, 4H,CH_2), 2.32–2.35 (m, 4H, $2CH_2$), 4.88, 5.34 (2s, 4H, $2NH_2$), 7.44 (s, 1H, benzene CH), 9.11 (s, br, 1H, OH).

Compound ***27b.*** Pale brown crystals from 1,4-dioxane, yield 2.14 g (60%), m.p. 190–3°C. $C_{18}H_{19}N_3SO_3$ (357.43). Calcd: C, 60.48; H, 5.35; N, 11.75; S, 8.97. Found: C, 60.72; H, 5.63; N, 11.66; S, 9.17. IR

(υ/cm^{-1}): 3555–3323 (OH, $2NH_2$), 2887 (CH_2), 1689 (C=O), 1656 (C=N), 1640 (C=C); ^{1}H NMR (δ): 1.37 (t, 3H, CH_3), 2.22–2.26 (m, 4H,CH_2), 2.33–2.38 (m, 4H, $2CH_2$), 4.23 (q, 2H, CH_2), 4.92, 5.30 (2s, 4H, $2NH_2$), 9.08 (s, br, 1H, OH).

*5-Hydroxy-4-imino-3-phenyl-2-thiolo-4,5,6,7-tetrahydrobenzo[*b*]thieno[5,4:2,3]pyrido-[5,6:3,4]pyridine (29)*

To a solution of compound **20** (2.44 g, 0.01 mol) in 1,4-dioxane (40 ml) containing triethylamine (1.0 ml) was added phenyl isothiocyanate (1.30 g, 0.01 mol). The reaction mixture was heated under reflux for 2 h and then was poured onto ice/water. The solid product formed was collected by filtration.

Orange crystals of **29** from acetic acid, yield 2.05 g (55%), m.p. 130–2°C. Found: C, 61.99; H, 4.46; N, 11.34; S, 16.68. $C_{20}H_{17}N_3S_2O$ (379.51). Calcd: C, 63.29; H, 4.51; N, 11.07; S, 16.89. IR (υ/cm^{-1}): 3547–3323 (OH, NH), 3056 (CH aromatic), 2876 (CH_2), 2240 (SH), 1668 (exocyclic C=N), 1642 (C=C); ^{1}H NMR (δ ppm): 2.21–2.24 (m, 4H,CH_2), 2.32–2.34 (m, 4H, $2CH_2$), 4.66 (s, br, 1H, SH), 7.25–7.33 (m, 5H, C_6H_5), 8.79 (s, 1H, NH), 9.11 (s, br, 1H, OH).

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