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Utility of a 2-Aminothiophene-3-carboxamide in the Synthesis of Thienopyridines and Thienopyrimidines

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ABSTRACT: *2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**1**) was prepared according to Gewald procedure. Its reactivity toward a variety of chemical reagents was studied to give thienopyridines and -pyrimidines.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:459–467, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10179

INTRODUCTION

Benzo[*b*]thiophene derivatives have been found to possess good medicinal and biological activities [1–3]. Recently, we were involved in a program using these derivatives in heterocyclic and fused heterocyclic synthesis to afford pyrazole, pyrimidine, and pyridazine derivatives [4–6]. In view of these versatile benefits and in connection with our program, we aimed to extend this route using 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**1**) [7] as a key precursor for the synthesis of some new heterocycles with an expected wide spectrum of potential applications.

RESULTS AND DISCUSSION

Compound **1** was prepared in a one-pot facile high-yield reaction by the alkaline condensation of cyclohexanone, elemental sulfur, and cyanoacetamide in ethanolic triethylamine solution following Gewald synthesis. The reactivity of compound **1** toward a variety of chemical reagents was investigated. It was found that the reaction of compound **1** with triethyl orthoformate, in the presence of acetic anhydride, gave the 4-hydroxybenzo[*b*]thieno[2,3-*d*]pyrimidine derivative **3** and not the keto form **2** (Scheme 1). Structure 3 was established on the basis of analytical and spectral data. Thus, the IR spectrum of the reaction product showed the OH group stretching at 3517–3246 cm^{-1}. Also, its ^{1}H NMR spectrum exhibited a singlet at δ 7.12 ppm for pyrimidine H-2 proton and a broad D_2O-exchangeable singlet at δ 11.59 ppm for the OH group.

Compound **1** reacted with phenyl isothiocyanate in refluxing ethanol containing a catalytic amount of triethylamine, to afford the 2-mercapto-3-phenylbenzo[*b*]thieno[2,3-*d*]pyrimid-4-one derivative **4** via ammonia liberation (Scheme 1). The IR spectrum (KBr) of **4** revealed the SH group stretching at 2558 cm^{-1} and the cyclic C=O group stretching at 1695 cm^{-1}. Moreover, its ^{1}H NMR spectrum exhibited a singlet at δ 3.89 ppm (D_2O-exchangeable) corresponding to SH.

With halides, **1** formed the acyl derivatives **5a,b** (Scheme 1). The IR spectrum of **5a** showed an

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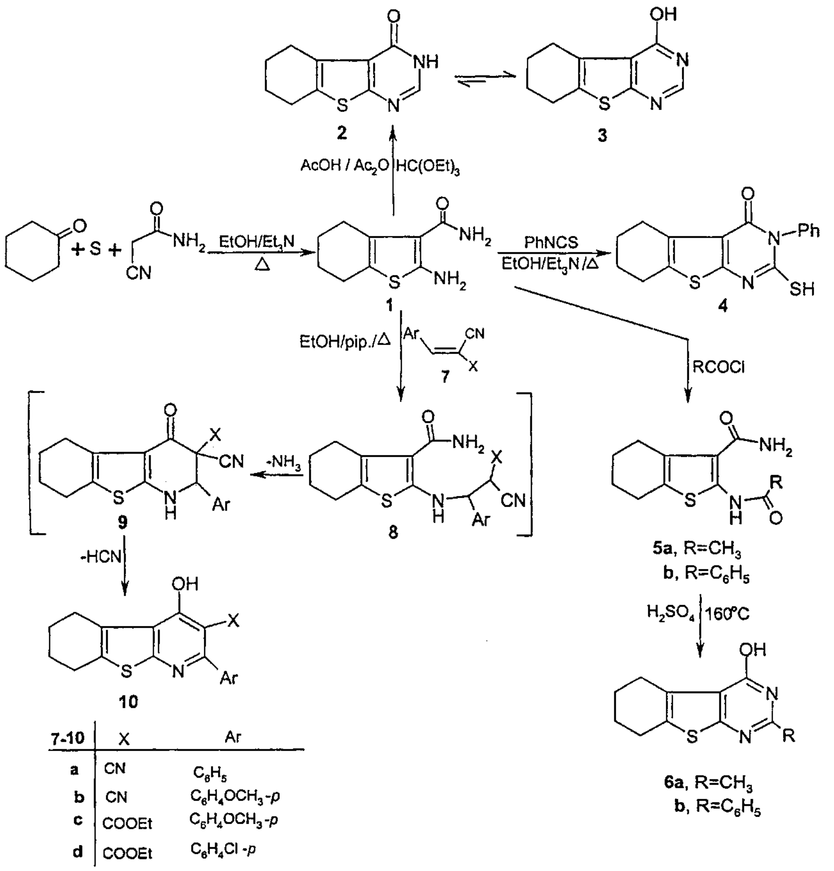


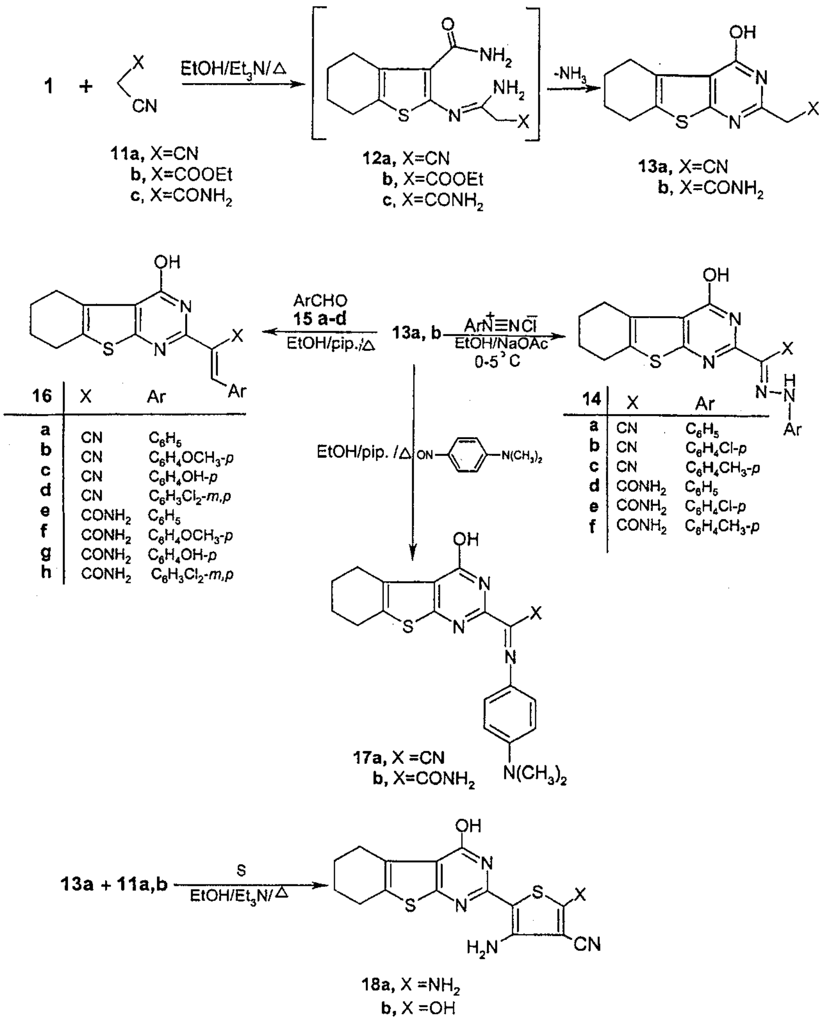
7-10	X	Ar
a	CN	C_6H_5
b	CN	$C_6H_4OCH_3$-*p*
c	COOEt	$C_6H_4OCH_3$-*p*
d	COOEt	C_6H_4Cl-*p*

SCHEME 1

absorption peak at ν 3445–3230 cm^{-1} due to the stretching vibrations of the NH_2 and NH functions as well as two C=O stretching absorption peaks at 1669 and 1660 cm^{-1}. Also, its ^1H NMR spectrum revealed two D_2O-exchangeable singlets at δ 5.95 (2H) and δ 8.63 (1H) ppm corresponding to NH_2 and NH protons, respectively. As expected, compounds **5a,b** underwent cyclization, in concentrated sulfuric acid at 160°C, to give the corresponding 4-hydroxybenzo[*b*]thieno[2,3-*d*]pyrimidine derivatives **6a,b**.

The behavior of **1** toward β-addition was also examined. It reacted with equimolar amounts of α-substituted cinnamonitrile derivatives **7a–d**, in ethanol containing a catalytic amount of piperidine, to yield the corresponding 4-hydroxybenzo-[*b*]thieno[2,3-*b*]pyridine derivatives **10a–d** (Scheme 1). The reaction took place via the intermediacy of **8a–d** and **9a–d** through a Michael-type addition, subsequent intramolecular cyclization via loss of ammonia, followed by elimination of hydrogen cyanide. Similar reactions of cinnamonitrile derivatives have been reported in the literature [8,9]. The structures of **10a–d** were confirmed on the basis of analytical and spectral data. As an example, the IR spectrum of compound **10a** (X = CN; Ar = C_6H_5) showed absorption peaks at ν 3520–3203 and 2220 cm^{-1} corresponding to OH and CN functions, respectively. Also, its ^1H NMR spectrum showed a D_2O-exchangeable singlet at δ 9.92 ppm corresponding to a OH moiety. The reactions open a facile and convenient route to fused pyrimidines and fused pyridines, which are otherwise difficult to access.

As an extension of this synthetic route, the behavior of **1** toward some cyanomethylene reagents **11a–c** was investigated. Thus, compound **1** reacted with equimolar amounts of malononitrile (**11a**), in refluxing ethanol containing a catalytic amount of triethylamine, to yield the corresponding 4-hydroxybenzo[*b*]thieno[2,3-*d*]pyrimidine-2-acetonitrile derivative **13a** (Scheme 2). Formation of **13a** was assumed to proceed through the intermediate formation of **12a**, followed by intramolecular cyclization via ammonia elimination. Both elemental and spectral data of **13a** were consistent with the assigned structure. Thus, its IR spectrum showed the OH group stretching at 3550–3335 cm^{-1} and one CN group stretching at 2220 cm^{-1}. Moreover, its ^1H



SCHEME 2

NMR spectrum (DMSO-d_6) revealed, in addition to the expected agreeable signals, the presence of a singlet signal at δ 4.34 ppm (s, 2H, CH_2) and a D_2O-exchangeable singlet at δ 11.00 ppm (s, 1H, OH). On the other hand, the reaction of **1** with equimolar amounts of ethyl cyanoacetate (**11b**), under the same experimental conditions, surprisingly yielded a product containing a methyleneamide moiety instead of the expected ester moiety. The IR spectrum of this product exhibited absorption bands at 3520–3188 (OH, NH_2) and 1665 cm^{-1} (C=O). Additionally, its ^{1}H NMR spectrum showed the complete absence of both triplet and quartet signals related to the presence of the expected ester group, while the spectrum showed only the presence of a singlet signal at δ 4.29 ppm attributed to the side chain CH_2 group and two types of D_2O-exchangeable protons at δ 5.32 (s, 2H, NH_2) and 10.22 ppm (s, 1H, OH), besides the expected signals for the tetrahydrobenzene moiety. Collecting the above data led to the conclusion that the reaction product could be formulated as the 4-hydroxybenzo[*b*]thieno[2,3-*d*]pyrimidine-2-acetamide structure **13b**. Formation of **13b**, in this reaction, was assumed to proceed via the intermediacy of the initial noneisolable ester **12b**, which underwent cyclization followed by ammonolysis, under the applied reaction conditions, with the ammonia eliminated during the cyclization step affording the final isolable acetamide derivative **13b** via loss of ethanol. A similar observation has been reported previously [10,11]. A conclusive evidence for the structure of **13b** was achieved by its independent synthesis via an alternative route. Thus, compound **1** reacted with equimolar amounts of cyanoacetamide (**11c**) to afford a single product that was found to be identical in all respects (m.p., mixed m.p., and IR data) with **13b**. Compound **13b**, in this case, was believed to be formed through the intermediacy of **12c**, followed by intramolecular cyclization via loss of ammonia molecule.

Further proof of the structures **13a,b** was obtained by studying their behavior toward various chemical reagents. Their reactivity was attributed to the electron-withdrawing cyano or amide group attached to the methylene moiety. Thus, compounds **13a** and **13b** could be easily coupled with aryldiazonium chloride in ethanolic sodium acetate solutions at 0–5°C, to afford the arylhydrazone derivatives **14a–f** (Scheme 2). Their structures were confirmed on the basis of their correct elemental analyses as well as compatible spectral data. Thus, the IR spectra (KBr) of **14a–c** showed the presence of CN function in the 2221–2216 cm^{-1} region. The arylhydrazone derivative **14a**, as an example, revealed in its ^1H NMR spectrum two D_2O-exchangeable singlets at δ 8.29 (1H) and δ 11.54 (1H) ppm corresponding to NH and OH groups, respectively. On the other hand, the IR spectra of **14d–f** showed the presence of C=O function in the 1666–1662 cm^{-1} region. The arylhydrazone derivative **14d** revealed in its ^1H NMR spectrum three D_2O-exchangeable singlets at δ 5.51 (2H), δ 8.92 (1H), and δ 9.88 (1H) ppm corresponding to NH_2, NH, and OH protons, respectively.

As expected, the methylene moiety in **13a,b** proved to be highly reactive toward aldehydes. Thus, the condensation of **13a,b** with benzaldehyde (**15a**), 4-methoxybenzaldehyde (**15b**), 4-hydroxybenzaldehyde (**15c**), or 3,4-dichlorobenzaldehyde (**15d**), in boiling ethanol containing a catalytic amount of piperidine, yielded the corresponding arylidene derivatives **16a–h** in reasonable yields (Scheme 2). As an example, the structure **16d** was established on the basis of IR spectrum, which revealed a broad peak at ν 3520–3315 cm^{-1} characteristic for OH function and a peak at ν 2215 cm^{-1} characteristic of CN function. Also, its ^1H NMR spectrum exhibited a singlet at δ 6.68 (1H) ppm, a multiplet at δ 7.22–7.41 (3H) ppm, and a D_2O-exchangeable singlet at δ 11.31 (1H) ppm corresponding to CH ylidene, C_6H_3, and OH moieties, respectively.

The condensation of **13a,b** with *N,N*-dimethyl-4-nitrosoaniline gave the imino derivatives **17a,b** (Scheme 2). Compound **17b**, as an example, exhibited in its ^1H NMR spectrum two singlets at δ 2.79 and 2.88 ppm for the two CH_3 groups and a multiplet at δ 7.12–7.34 ppm attributed to C_6H_4 moiety.

The reactivity of 2-acetonitrile derivative **13a** toward the formation of thiophenes via Gewald reaction [6,12,13] was studied. Thus, when compound **13a** was allowed to react with equimolar amounts of each of malononitrile (**11a**) and elemental sulfur, upon boiling under reflux in ethanol–triethylamine solution, it yielded the corresponding 3-cyano-2,4-diaminothiophen-5-yl derivative **18a** (Scheme 2). A proposed mechanism for the formation of **18a** involved initial addition of the active methylene in **11a** to the cyano moiety in **13a**, followed by intramolecular cyclization to give the stable product **18a**. Its IR spectrum revealed absorption bands at 3525–3205 cm^{-1} due to one OH and two NH_2 functions, and at 2217 cm^{-1} due to CN function. Moreover, its ^1H NMR spectrum showed three singlets (D_2O-exchangeable) at δ 6.31 (2H), δ 7.51 (2H), and δ 11.25 (1H) ppm corresponding to two NH_2 and one OH protons, respectively. Analogously, the reaction of **13a** with ethyl cyanoacetate (**11b**) and elemental sulfur, under the same experimental conditions, yielded the 4-amino-3-cyano-2-hydroxythiophen-5-yl derivative **18b** via ethanol elimination. Its IR spectrum showed an absorption peak at 3545–3216 cm^{-1} due to the stretching vibrations of the two OH and one NH_2 functions as well as one CN stretching absorption peak at 2220 cm^{-1}. Also, its ^1H NMR spectrum (DMSO-d_6) revealed three D_2O-exchangeable protons at δ 5.95 (s, 2H, NH_2), 9.52 (s, 1H, OH), and 11.61 ppm (s, 1H, OH).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam Sp-1000 spectrophotometer. ^1H NMR spectra were obtained on a Varian EM-390 90 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts δ are expressed in ppm. Compound **1** was prepared as reported previously [7].

*4-Hydroxy-5,6,7,8-tetrahydrobenzo[b]-thieno[2,3-d]pyrimidine (**3**)*

Equimolar amounts (0.01 mol) of **1** and triethyl orthoformate, in acetic acid (20 ml) containing acetic anhydride (10 ml), were heated under reflux for 5 h. The reaction mixture was allowed to stand overnight at room temperature. The formed solid product was collected by filtration.

3: Pale yellow crystals (from AcOH–H_2O), yield 68% (1.40 g), m.p. 82–84°C. IR (ν/cm^{-1}) = 3517–3246 (OH), 2925, 2853 (CH_2), 1630 (C=N). ^1H NMR δ = 1.63–2.04 (m, 4H, 2H-6, 2H-7), 2.27–2.83 (m, 4H, 2H-5, 2H-8), 7.12 (s, 1H, pyrimidine H-2), 11.59 (s, br, 1H, OH, D_2O-exchangeable). $C_{10}H_{10}N_2OS$ (206.25): Calcd: C, 58.23; H, 4.88; N, 13.58; S, 15.54; Found: C, 58.0; H, 4.7; N, 13.5; S, 15.3.

*2-Mercapto-3-phenyl-5,6,7,8-tetrahydrobenzo-[b]thieno[2,3-d]pyrimid-4(3H)-one (**4**)*

A mixture of **1** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in ethanol (30 ml) containing a catalytic amount of Et_3N (0.5 ml) was heated, under reflux, for 6 h. The reaction mixture was then poured onto ice/water and neutralized with dilute HCl. The solid product, so formed, was collected by filtration.

4: Buff crystals (from 1,4–dioxane), yield 71% (2.23 g), m.p. 73°C. IR (ν/cm^{-1}) = 3035 (CH aromatic), 2926, 2852 (CH_2), 2558 (SH), 1695 (C=O), 1628 (C=N). ^{1}H NMR $\delta = 1.61$–2.05 (m, 4H, 2H-6, 2H-7), 2.22–2.61 (m, 4H, 2H-5, 2H-8), 3.89 (s, 1H, SH, D_2O-exchangeable), 7.09–7.29 (m, 5H, C_6H_5). $C_{16}H_{14}N_2OS_2$ (314.41): Calcd: C, 61.12; H, 4.48; N, 8.90; S, 20.39; Found: C, 61.0; H, 4.5; N, 8.7; S, 20.0.

*2-Acetamido-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxamide (**5a**)*

A mixture of **1** (0.01 mol) and acetyl chloride (0.01 mol) in glacial acetic acid (15 ml) was heated, under reflux, for 5 h. The reaction mixture was cooled at room temperature and poured onto ice, whereby the resulting solid product was collected by filtration.

5a: Pale yellow crystals (from AcOH–H_2O), yield 69% (1.64 g), m.p. 180°C. IR (ν/cm^{-1}) = 3445–3230 (NH_2, NH), 2959–2865 (CH_3, CH_2), 1669, 1660, (2C=O). ^{1}H NMR $\delta = 1.55$–1.79 (m, 4H, 2CH_2), 2.03–2.39 (m, 4H, 2CH_2), 2.59 (s, 3H, CH_3CO), 5.95 (s, 2H, NH_2, D_2O-exchangeable), 8.63 (s, 1H, NH, D_2O-exchangeable). $C_{11}H_{14}N_2O_2S$ (238.29): Calcd: C, 55.44; H, 5.91; N, 11.75; S, 13.45; Found: C, 55.4; H, 5.7; N, 11.5; S, 13.4.

*2-Benzamido-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxamide (**5b**)*

To a cold solution (0–5°C) of **1** (0.01 mol) in pyridine (15 ml), benzoyl chloride (0.01 mol) was added dropwise with continuous stirring for 1 h. The reaction mixture was heated, under reflux, for 3 h and then evaporated in vacuo. The remaining product was triturated with ethanol and the formed solid product was isolated by filtration.

5b: Pale brown crystals (from EtOH), yield 58% (1.74 g), m.p. 238°C. IR (ν/cm^{-1}) = 3450–3240 (NH_2, NH), 3033 (CH aromatic), 2923, 2855 (CH_2), 1675, 1660 (2C=O). ^{1}H NMR $\delta = 1.58$–2.05 (m, 4H, 2CH_2), 2.22–2.51 (m, 4H, 2CH_2), 6.13 (s, 2H, NH_2, D_2O-exchangeable), 7.21–7.39 (m, 5H, C_6H_5), 9.14 (s, 1H, NH, D_2O-exchangeable). $C_{16}H_{16}N_2O_2S$ (300.36): Calcd: C, 63.98; H, 5.36; N, 9.32; S, 10.67; Found: C, 63.7; H, 5.2; N, 9.3; S, 10.7.

*4-Hydroxy-2-methyl-5,6,7,8-tetrahydrobenzo[b]-thieno[2,3-d]pyrimidine (**6a**) and 4-Hydroxy-2-phenyl-5,6,7,8-tetrahydrobenzo[b]thieno-[2,3-d]pyrimidine (**6b**)*

General Procedure. A suspension of dry solid of each of **5a** or **5b** (0.02 mol) in concentrated sulfuric acid (10 ml) was heated in an oil bath (160°C) for 6 h and then left to cool. The reaction mixture was poured over water and neutralized with sodium hydroxide (10%), and then left aside overnight at room temperature. The formed solid product, in each case, was collected by filtration and crystallized from the proper solvent.

6a: Yellow crystals (from EtOH), yield 61% (2.68 g), m.p. 220°C. IR (ν/cm^{-1}) = 3552–3335 (OH), 2960–2862 (CH_3, CH_2), 1625 (C=N). ^{1}H NMR $\delta = 1.61$–2.02 (m, 4H, 2CH_2), 2.25–2.77 (m, 7H, 2CH_2, CH_3), 9.68 (s, 1H, OH, D_2O-exchangeable). $C_{11}H_{12}N_2OS$ (220.28): Calcd: C, 59.97; H, 5.48; N, 12.71; S,14.55; Found: C, 60.0; H, 5.3; N, 12.7; S, 14.4.

6b: Yellow crystals (from 1,4–dioxane), yield 58% (3.27 g), m.p. 199°C. IR (ν/cm^{-1}) = 3560–3350 (OH), 3030 (CH aromatic), 2927, 2855 (CH_2), 1625 (C=N). ^{1}H NMR $\delta = 1.61$–2.08 (m, 4H, 2CH_2), 2.24–2.68 (m, 4H, 2CH_2), 7.12–7.33 (m, 5H, C_6H_5), 10.20 (s, 1H, OH, D_2O-exchangeable). $C_{16}H_{14}N_2OS$ (282.35): Calcd: C, 68.06; H, 4.99; N, 9.92; S, 11.35; Found: C, 67.9; H, 4.7; N, 9.9; S, 11.2.

*4-Hydroxy-2-phenyl-5,6,7,8-tetrahydrobenzo[b]-thieno[2,3-b]pyridine-3-carbonitrile (**10a**), 4-Hydroxy-2-(4-methoxyphenyl)-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-b]pyridine-3-carbonitrile (**10b**), Ethyl 4-hydroxy-2-(4-methoxyphenyl)-5,6,7,8-tetrahydrobenzo[b]-thieno[2,3-b]pyridine-3-carboxylate (**10c**), and Ethyl 2-(4-chlorophenyl)-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-b]-pyridine-3-carboxylate (**10d**)*

General Procedure. To a suspension of **1** (0.01 mol), in ethanol (30 ml) containing a catalytic amount of piperidine (0.5 ml), the appropriate α-substituted cinnamonitrile derivative **7a–d** (0.01 mol) was added. The reaction mixture was refluxed for 6 h and then evaporated in vacuo. The reaction mixture was triturated with cold water and neutralized with HCl. The resulting solid product, in each case, was collected by filtration and crystallized from the proper solvent.

10a: Buff crystals (from 1,4–dioxane-H_2O), yield 70% (2.14 g), m.p. 97°C. IR (ν/cm^{-1}) = 3520–3203 (OH), 3031 (CH aromatic), 2928, 2853 (CH_2), 2220 (CN), 1630 (C=N). ^{1}H NMR $\delta = 1.65$–2.01 (m, 4H, $2CH_2$), 2.25–2.71 (m, 4H, $2CH_2$), 7.52–7.81 (m, 5H, C_6H_5), 9.92 (s, 1H, OH, D_2O-exchangeable). $C_{18}H_{14}N_2OS$ (306.37): Calcd: C, 70.56; H, 4.60; N, 9.14; S, 10.46; Found: C, 70.2; H, 4.5; N, 9.0; S, 10.4.

10b: Brown crystals (from 1,4–dioxane-H_2O), yield 74% (2.49 g), m.p. 77°C. IR (ν/cm^{-1}) = 3525–3203 (OH), 3025 (CH aromatic), 2960–2857 (CH_3, CH_2), 2216 (CN), 1627 (C=N). $C_{19}H_{16}N_2O_2S$ (336.39): Calcd: C, 67.83; H, 4.78; N, 8.32; S, 9.53; Found: C, 67.5; H, 4.9; N, 8.1; S, 9.4.

10c: Yellowish brown crystals (from EtOH-H_2O), yield 69% (2.64 g), m.p. 62°C. IR (ν/cm^{-1}) = 3550–3340 (OH), 3026 (CH aromatic), 2962–2871 (CH_3, CH_2), 1716 (C=O), 1630 (C=N). ^{1}H NMR $\delta = 1.31$ (t, 3H, CH_3), 1.59–2.12 (m, 4H, $2CH_2$), 2.23–2.59 (m, 4H, $2CH_2$), 3.72 (s, 3H, OCH_3), 4.15 (q, 2H, CH_2), 7.01–7.17 (m, 4H, C_6H_4), 10.72 (s, 1H, OH, D_2O-exchangeable). $C_{21}H_{21}NO_4S$ (383.44): Calcd: C, 65.78; H, 5.51; N, 3.65; S, 8.36; Found: C, 65.8; H, 5.2; N, 3.5; S, 8.1.

10d: Pale brown crystals (from EtOH), yield 65% (2.52 g), m.p. 68°C. IR (ν/cm^{-1}) = 3540–3331 (OH), 3028 (CH aromatic), 2966–2855 (CH_3, CH_2), 1720 (C=O), 1625 (C=N). ^{1}H NMR $\delta = 1.39$ (t, 3H, CH_3), 1.61–2.04 (m, 4H, $2CH_2$), 2.21–2.60 (m, 4H, $2CH_2$), 4.23 (q, 2H, CH_2), 7.11–7.31 (m, 4H, C_6H_4), 10.12 (s, 1H, OH, D_2O-exchangeable). $C_{20}H_{18}ClNO_3S$ (387.87): Calcd: C, 61.93; H, 4.67; N, 3.61; S, 8.26; Found: C, 61.9; H, 4.5; N, 3.3; S, 8.0.

*4-Hydroxy-5,6,7,8-tetrahydrobenzo[b]-thieno[2,3-d]pyrimidine-2-acetonitrile (***13a***)*

Equimolar amounts (0.01 mol) of **1** and malononitrile (**11a**), in ethanol (30 ml) containing a catalytic amount of Et_3N (0.5 ml), were heated under reflux for 6 h. The reaction mixture was then cooled, poured onto cold water, neutralized with HCl, whereby the solid product, so formed, was collected by filtration.

13a: Yellowish brown crystals (from DMF–H_2O), yield 58% (1.42 g), m.p. 139°C. IR (ν/cm^{-1}) = 3550–3335 (OH), 2927, 2852 (CH_2), 2220 (CN), 1630 (C=N). ^{1}H NMR $\delta = 1.61$–2.00 (m, 4H, $2CH_2$), 2.25–2.71 (m, 4H, $2CH_2$), 4.34 (s, 2H, CH_2), 11.00 (s, 1H, OH, D_2O-exchangeable). $C_{12}H_{11}N_3OS$ (245.29): Calcd: C, 58.75; H, 4.51; N, 17.12; S, 13.07; Found: C, 58.6; H, 4.4; N, 17.1; S, 12.9.

*4-Hydroxy-5,6,7,8-tetrahydrobenzo[b]-thieno[2,3-d]pyrimidine-2-acetamide (***13b***)*

Method A. A mixture of equimolar amounts (0.01 mol) of **1** and ethyl cyanoacetate (**11b**) was heated, under reflux, in ethanol (30 ml) containing a catalytic amount of Et_3N for 8 h. The reaction mixture was then cooled, poured onto cold water, neutralized with dilute HCl, whereby the resulting solid product was collected by filtration.

Method B. The same experimental procedure described before for the synthesis of **13b** was followed up except for using cyanoacetamide (**11c**) (0.01 mol) instead of ethyl cyanoacetate. The product was found to be identical in all respects (m.p., mixed m.p., and IR spectrum) with authentic sample prepared according to method A.

13b: Buff crystals (from DMF–H_2O), yield 61% (1.60 g), m.p. 129°C. IR (ν/cm^{-1}) = 3520–3188 (OH, NH_2), 2927, 2852 (CH_2), 1665 (C=O), 1630 (C=N). ^{1}H NMR $\delta = 1.63$–2.03 (m, 4H, $2CH_2$), 2.20–2.61 (m, 4H, $2CH_2$), 4.29 (s, 2H, CH_2), 5.32 (s, br, 2H, NH_2, D_2O-exchangeable), 10.22 (s, 1H, OH, D_2O-exchangeable). $C_{12}H_{13}N_3O_2S$ (263.30): Calcd: C, 54.73; H, 4.97; N, 15.95; S, 12.17; Found: C, 54.7; H, 4.9; N, 16.0; S, 11.9.

*4-Hydroxy-α-(phenylhydrazono)-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-2-acetonitrile (***14a***), α-(4-Chlorophenylhydrazono)-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]-thieno[2,3-d]pyrimidine-2-acetonitrile (***14b***), and 4-Hydroxy-α-(4-methylphenylhydrazono)-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]-pyrimidine-2-acetonitrile (***14c***)*

General Procedure. A solution of compound **13a** (0.005 mol) in ethanol (30 ml) containing sodium acetate (1.0 g) was cooled to 0–5°C with stirring. The reaction mixture was then treated gradually with a cold solution of the appropriate aryldiazonium chloride salt [prepared from the corresponding arylamine (0.005 mol) and the appropriate quantities of concentrated HCl and $NaNO_2$]. After the addition of the diazonium salts was completed, the reaction mixture was stirred at room temperature for an additional 30 min. The precipitated product, in each case, separated upon dilution with cold water (30 ml), was filtered off, washed with water several times, dried, and crystallized from the appropriate solvent.

14a: Orange crystals (from 1,4–dioxane–H_2O), yield 80% (1.40 g), m.p. 120°C. IR (ν/cm^{-1}) = 3508–3212 (OH, NH), 3033 (CH aromatic), 2935, 2858 (CH_2), 2221 (CN), 1640 (C=N). ^{1}H NMR $\delta = 1.58$–2.00 (m, 4H, $2CH_2$), 2.25–2.83 (m, 4H, $2CH_2$), 7.13–7.29 (m, 5H, C_6H_5), 8.29 (s, 1H, NH, D_2O-exchangeable), 11.54 (s, 1H, OH, D_2O-exchangeable). $C_{18}H_{15}N_5OS$ (349.40): Calcd: C, 61.87; H, 4.32; N, 20.04; S, 9.17; Found: C, 61.9; H, 4.3; N, 19.9; S, 9.0.

14b: Reddish brown crystals (from 1,4–dioxane–H_2O), yield 75% (1.44 g), m.p. 107°C. IR (ν/cm^{-1}) = 3510–3194 (OH, NH), 3031 (CH aromatic), 2935, 2860 (CH_2), 2216 (CN), 1635 (C=N). ^{1}H NMR $\delta = 1.61$–2.00 (m, 4H, $2CH_2$), 2.23–2.72 (m, 4H, $2CH_2$), 7.12–7.30 (m, 4H, C_6H_4), 8.41 (s, 1H, NH, D_2O-exchangeable), 10.81 (s, 1H, OH, D_2O-exchangeable). $C_{18}H_{14}ClN_5OS$ (383.84): Calcd: C, 56.32; H, 3.67; N, 18.24; S, 8.35; Found: C, 56.3; H, 3.5; N, 18.0; S, 8.3.

14c: Yellow crystals (from 1,4–dioxane), yield 67% (1.22 g), m.p. 160°C. IR (ν/cm^{-1}) = 3520–3199 (OH, NH), 3033 (CH aromatic), 2970–2862 (CH_3, CH_2), 2220 (CN), 1632 (C=N). $C_{19}H_{17}N_5OS$ (363.42): Calcd: C, 62.79; H, 4.71; N, 19.26; S, 8.82; Found: C, 62.5; H, 4.7; N, 19.1; S, 8.8.

*4-Hydroxy-α-(phenylhydrazono)-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-2-acetamide (**14d**), α-(4-Chlorophenylhydrazono)-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno-[2,3-d]pyrimidine-2-acetamide (**14e**), and 4-Hydroxy-α-(4-methylphenylhydrazono)-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]-pyrimidine-2-acetamide (**14f**)*

General Procedure. The same experimental procedure as described before for the synthesis of **14a–c** was carried out except that 2-acetamide derivative **13b** (0.005 mol) was used in place of **13a**.

14d: Red crystals (from 1,4–dioxane–H_2O), yield 66% (1.21 g), m.p. 214°C. IR (ν/cm^{-1}) = 3530–3193 (OH, NH_2, NH), 3033 (CH aromatic), 2933, 2858 (CH_2), 1666 (C=O), 1635 (C=N). ^{1}H NMR $\delta = 1.52$–2.00 (m, 4H, $2CH_2$), 2.19–2.40 (m, 4H, $2CH_2$), 5.51 (s, br, 2H, NH_2, D_2O-exchangeable), 7.14–7.28 (m, 5H, C_6H_5), 8.92 (s, 1H, NH, D_2O-exchangeable), 9.88 (s, 1H, OH, D_2O-exchangeable). $C_{18}H_{17}N_5O_2S$ (367.41): Calcd: C, 58.84; H, 4.65; N, 19.06; S, 8.72; Found: C, 58.7; H, 4.4; N, 18.8; S, 8.7.

14e: Orange crystals (from EtOH), yield 62% (1.24 g), m.p. 102°C. IR (ν/cm^{-1}) = 3552–3207 (OH, NH_2, NH), 3035 (CH aromatic), 2933, 2858 (CH_2), 1662 (C=O), 1635 (C=N). $C_{18}H_{16}ClN_5O_2S$ (401.85): Calcd: C, 53.80; H, 4.00; N, 17.42; S, 7.97; Found: C, 53.8; H, 3.9; N, 17.1; S, 8.0.

14f: Reddish brown crystals (from 1,4–dioxane–H_2O), yield 59% (1.12 g), m.p. 150°C. IR (ν/cm^{-1}) = 3560–3210 (OH, NH_2, NH), 3033 (CH aromatic), 2975–2860 (CH_3, CH_2), 1664 (C=O), 1633 (C=N). ^{1}H NMR $\delta = 1.57$–1.91 (m, 4H, $2CH_2$), 2.00–2.31 (m, 4H, $2CH_2$), 2.59 (s, 3H, CH_3), 4.93 (s, br, 2H, NH_2, D_2O-exchangeable), 7.12–7.29 (m, 4H, C_6H_4), 8.61 (s, 1H, NH, D_2O-exchangeable), 10.41 (s, 1H, OH, D_2O-exchangeable). $C_{19}H_{19}N_5O_2S$ (381.43): Calcd: C, 59.82; H, 5.01; N, 18.35; S, 8.40; Found: C, 59.8; H, 4.8; N, 18.3; S, 8.2.

*α-(Benzylidene)-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-2-acetonitrile (**16a**), 4-Hydroxy-α-(4-methoxybenzylidene)-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-2-acetonitrile (**16b**), 4-Hydroxy-α-(4-hydroxybenzylidene)-5,6,7,8-tetrahydrobenzo-[b]thieno [2,3-d]pyrimidine-2-acetonitrile (**16c**), and α-(3,4-Dichlorobenzylidene)-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]-pyrimidine-2-acetonitrile (**16d**)*

General Procedure. A mixture of equimolar amounts (0.005 mol) of **13a** and the appropriate aromatic aldehyde **15a–d**, in ethanol (30 ml) containing a catalytic amount of piperidine (0.5 ml), was heated under reflux for 5 h. The solution was then poured over iced water and neutralized with dilute HCl to precipitate the solid product. The formed product, in each case, was isolated by suction filtration and crystallized from the appropriate solvent.

16a: Buff crystals (from DMF–H_2O), yield 74% (1.23 g), m.p. 92°C. IR (ν/cm^{-1}) = 3565–3351 (OH), 3030 (CH aromatic), 2931, 2854 (CH_2), 2221 (CN), 1630 (C=N). ^{1}H NMR $\delta = 1.58$–2.06 (m, 4H, $2CH_2$), 2.26–2.51 (m, 4H, $2CH_2$), 6.59 (s, 1H, CH ylidene), 7.17–7.32 (m, 5H, C_6H_5), 11.17 (s, 1H, OH, D_2O-exchangeable). $C_{19}H_{15}N_3OS$ (333.39): Calcd: C, 68.45; H, 4.53; N, 12.60; S, 9.61; Found: C, 68.5; H, 4.2; N, 12.5; S, 9.5.

16b: Brown crystals (from DMF–H_2O), yield 72% (1.31 g), m.p. 247°C. IR (ν/cm^{-1}) = 3552–3340 (OH), 3031 (CH aromatic), 2962–2858 (CH_3, CH_2), 2220 (CN), 1631 (C=N). ^{1}H NMR $\delta = 1.63$–2.03 (m, 4H, $2CH_2$), 2.27–2.81 (m, 4H, $2CH_2$), 3.82 (s, 3H, OCH_3), 6.76 (s, 1H, CH ylidene), 7.03–7.22 (m, 4H, C_6H_4), 10.83 (s, 1H, OH, D_2O-exchangeable). $C_{20}H_{17}N_3O_2S$ (363.42): Calcd: C, 66.10; H, 4.71; N, 11.56; S, 8.82; Found: C, 66.0; H, 4.4; N, 11.5; S, 8.8.

16c: Pale brown crystals (from EtOH), yield 60% (1.05 g), m.p. 165°C. IR (ν/cm^{-1}) = 3580–3365 (2OH), 3033 (CH aromatic), 2933, 2856 (CH_2), 2225 (CN), 1629 (C=N). $C_{19}H_{15}N_3O_2S$ (349.39): Calcd: C, 65.31; H, 4.32; N, 12.02; S, 9.17; Found: C, 65.1; H, 4.3; N, 11.9; S, 9.0.

16d: Yellow crystals (from DMF), yield 63% (1.27 g), m.p. 155°C. IR (ν/cm^{-1}) = 3520–3315 (OH), 3034 (CH aromatic), 2933, 2856 (CH_2), 2215 (CN), 1630 (C=N). ^{1}H NMR $\delta = 1.63$–2.10 (m, 4H, $2CH_2$), 2.19–2.43 (m, 4H, $2CH_2$), 6.68 (s, 1H, CH ylidene), 7.22–7.41 (m, 3H, C_6H_3), 11.31 (s, 1H, OH, D_2O-exchangeable). $C_{19}H_{13}Cl_2N_3OS$ (402.29): Calcd: C, 56.72; H, 3.25; N, 10.44; S, 7.97; Found: C, 56.7; H, 3.2; N, 10.2; S, 7.8.

*α-(Benzylidene)-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-2-acetamide (**16e**), 4-Hydroxy-α-(4-methoxybenzylidene)-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]-pyrimidine-2-acetamide (**16f**), 4-Hydroxy-α-(4-hydroxybenzylidene)-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-2-acetamide (**16g**), and α-(3,4-Dichlorobenzylidene)-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno-[2,3-d]pyrimidine-2-acetamide (**16h**)*

General Procedure. Equimolar amounts (0.005 mol) of **13b** and the appropriate aromatic aldehyde **15a–d**, in ethanol (30 ml) containing a catalytic amount of piperidine (0.5 ml), were heated under reflux for 4 h. The reaction mixture was evaporated in vacuo and triturated with cold water, whereby the resulting solid product, in each case, was collected by filtration and crystallized from the proper solvent.

16e: Buff crystals (from 1,4–dioxane), yield 73% (1.28 g), m.p. 229°C. IR (ν/cm^{-1}) = 3520–3197 (OH, NH_2), 3028 (CH aromatic), 2927, 2852 (CH_2), 1666 (C=O), 1635 (C=N). ^1H NMR $\delta = 1.60–1.82$ (m, 4H, $2CH_2$), 2.01–2.43 (m, 4H, $2CH_2$), 5.13 (s, br, 2H, NH_2, D_2O-exchangeable), 6.64 (s, 1H, CH ylidene), 7.16–7.32 (m, 5H, C_6H_5), 10.55 (s, 1H, OH, D_2O-exchangeable). $C_{19}H_{17}N_3O_2S$ (351.41): Calcd: C, 64.94; H, 4.87; N, 11.95; S, 9.12; Found: C, 65.0; H, 4.6; N, 11.9; S, 8.9.

16f: Pale yellow crystals (from DMF–H_2O), yield 79% (1.50 g), m.p. 188°C. IR (ν/cm^{-1}) = 3530–3204 (OH, NH_2), 3033 (CH aromatic), 2962–2859 (CH_3, CH_2), 1664 (C=O), 1635 (C=N). $C_{20}H_{19}N_3O_3S$ (381.43): Calcd: C, 62.97; H, 5.01; N, 11.01; S, 8.40; Found: C, 62.9; H, 4.8; N, 10.9; S, 8.1.

16g: Pale yellow crystals (from 1,4–dioxane), yield 66% (1.21 g), m.p. 203°C. IR (ν/cm^{-1}) = 3560–3224 (2OH, NH_2), 3022 (CH aromatic), 2933, 2857 (CH_2), 1668 (C=O), 1630 (C=N). ^1H NMR $\delta =$ 1.61–1.83 (m, 4H, $2CH_2$), 2.00–2.33 (m, 4H, $2CH_2$), 4.82 (s, br, 2H, NH_2, D_2O-exchangeable), 6.79 (s, 1H, CH ylidene), 7.37–7.45 (m, 4H, C_6H_4), 9.79 (s, 1H, OH, D_2O-exchangeable), 12.00 (s, 1H, OH, D_2O-exchangeable). $C_{19}H_{17}N_3O_3S$ (367.41): Calcd: C, 62.11; H, 4.65; N, 11.43; S, 8.72; Found: C, 61.9; H, 4.6; N, 11.4; S, 8.4.

16h: Yellow crystals (from DMF–H_2O), yield 82% (1.72 g), m.p. 174°C. IR (ν/cm^{-1}) = 3540–3209 (OH, NH_2), 3035 (CH aromatic), 2933, 2857 (CH_2), 1665 (C=O), 1630 (C=N). ^1H NMR $\delta = 1.60–2.04$ (m, 4H, $2CH_2$), 2.23–2.82 (m, 4H, $2CH_2$), 4.99 (s, br, 2H, NH_2, D_2O-exchangeable), 6.72 (s, 1H, CH, ylidene), 7.15–7.33 (m, 3H, C_6H_3), 9.97 (s, 1H, OH, D_2O-exchangeable). $C_{19}H_{15}Cl_2N_3O_2S$ (420.30): Calcd: C, 54.29; H, 3.59; N, 9.99; S, 7.62; Found: C, 54.0; H, 3.5; N, 9.8; S, 7.5.

*α-[4-(N,N-Dimethylamino)phenylimino]-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]-pyrimidine-2-acetonitrile (**17a**) and α-[4-(N,N-Dimethylamino)phenylimino]-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-2-acetamide (**17b**)*

General Procedure. To a mixture of each of **13a** or **13b** (0.005 mol) and *N*,*N*-dimethyl-4-nitrosoaniline (0.005 mol), in ethanol (30 ml), a catalytic amount of piperidine (0.5 ml) was added. The reaction mixture was heated, under reflux, for 5 h and then left aside to cool and poured onto ice/water containing few drops of HCl. The solid product so formed, in each case, was collected by filtration.

17a: Brown crystals (from DMF), yield 77% (1.45 g), m.p. 208°C. IR (ν/cm^{-1}) = 3530–3293 (OH), 3030 (CH aromatic), 2966–2856 (CH_3, CH_2), 2221 (CN), 1630 (C=N). ^1H NMR $\delta = 1.57–2.04$ (m, 4H, $2CH_2$), 2.26–2.51 (m, 4H, $2CH_2$), 2.77, 2.85 (2s, 6H, $2NCH_3$), 7.15–7.35 (m, 4H, C_6H_4), 11.35 (s, 1H, OH, D_2O-exchangeable). $C_{20}H_{19}N_5OS$ (377.45): Calcd: C, 63.64; H, 5.06; N, 18.55; S, 8.49; Found: C, 63.6; H, 4.9; N, 18.5; S, 8.3.

17b: Brown crystals (from DMF), yield 58% (1.15 g), m.p. 170°C. IR (ν/cm^{-1}) = 3528–3224 (OH, NH_2), 3030 (CH aromatic), 2968–2857 (CH_3, CH_2), 1665 (C=O), 1630 (C=N). ^1H NMR $\delta = 1.61–1.83$ (m, 4H, $2CH_2$), 2.00–2.33 (m, 4H, $2CH_2$), 2.79, 2.88 (2s, 6H, $2NCH_3$), 5.12 (s, br, 2H, NH_2, D_2O-exchangeable), 7.12–7.34 (m, 4H, C_6H_4), 10.45 (s, 1H, OH, D_2O-exchangeable). $C_{20}H_{21}N_5O_2S$ (395.46): Calcd: C, 60.74; H, 5.34; N, 17.70; S, 8.10; Found: C, 60.7; H, 5.0; N, 17.8; S, 8.0.

*2-(3-Cyano-2,4-diaminothiophen-5-yl)-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno-[2,3-d]pyrimidine (**18a**) and 2-(4-Amino-3-cyano-2-hydroxythiophen-5-yl)-4-hydroxy-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]-pyrimidine (**18b**)*

General Procedure. Equimolar amounts (0.005 mol) of **13a**, elemental sulfur, and malononitrile (**11a**) or ethyl cyanoacetate (**11b**), in ethanol (30 ml) containing a catalytic amount of

Et_3N, were heated under reflux for 5 h and, after being allowed to cool, poured onto iced water. The solutions were then neutralized with dilute HCl and the formed products were collected by suction filtration and crystallized from the proper solvents.

18a: Brown crystals (from 1,4–dioxane), yield 79% (1.35 g), m.p. 195°C. IR (ν/cm^{-1}) = 3525–3205 (OH, $2NH_2$), 2931, 2854 (CH_2), 2217 (CN), 1635 (C=N). ^{1}H NMR $\delta = 1.60$–2.05 (m, 4H, $2CH_2$), 2.24–2.83 (m, 4H, $2CH_2$), 6.31 (s, 2H, NH_2, D_2O-exchangeable), 7.51 (s, 2H, NH_2, D_2O-exchangeable); 11.25 (s, 1H, OH, D_2O-exchangeable). $C_{15}H_{13}N_5OS_2$ (343.41): Calcd: C, 52.46; H, 3.81; N, 20.39; S, 18.67; Found: C, 52.5; H, 3.5; N, 20.4; S, 18.6.

18b: Grey crystals (from EtOH), yield 75% (1.29 g), m.p. 225°C. IR (ν/cm^{-1}) = 3545–3216 (2OH, NH_2), 2933, 2854 (CH_2), 2220 (CN), 1630 (C=N). ^{1}H NMR $\delta = 1.63$–2.04 (m, 4H, $2CH_2$), 2.27–2.83 (m, 4H, $2CH_2$), 5.95 (s, 2H, NH_2, D_2O-exchangeable), 9.52 (s, 1H, OH, D_2O-exchangeable), 11.61 (s, 1H, OH, D_2O-exchangeable). $C_{15}H_{12}N_4O_2S_2$ (344.40): Calcd: C, 52.31; H, 3.50; N, 16.26; S, 18.62; Found: C, 52.3; H, 3.4; N, 16.0; S, 18.5.

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