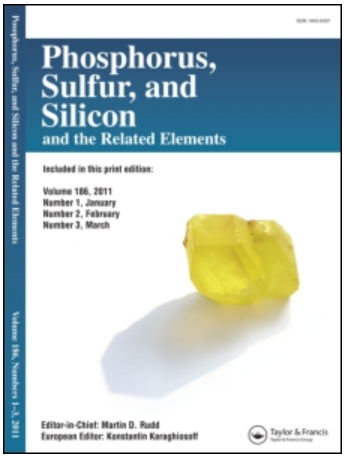

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SYNTHESIS AND TRANSFORMATIONS OF 2-SUBSTITUTED TETRAHYDRO-4*H*-BENZO[4,5]THIENO[2,3-d][1,3]OXAZINES AND 2,3-DISUBSTITUTED HEXAHYDROBENZO[4,5]THIENO[2,3-d]PYRIMIDINES

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*3-(4-Oxo-5,6,7,8-tetrahydro-4*H*-benzo[4,5]thieno[2,3-d][1,3]oxazin-2-yl)propanoic acid and its ethyl ester* ***6a,b*** *have been prepared via succinoylation of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate* ***1****, followed by ester hydrolysis, selective esterification, and acetic anhydride induced cyclization of the thiophenecarboxylic acid derivatives* ***3, 5****. Reaction of* ***1*** *with diethyl malonate gave the malonic acid diamide* ***7****, which on ester hydrolysis followed by acetic anhydride induced water elimination furnished the 2-substituted 4*H*-benzo[4,5]thieno[2,3-d][1,3]oxazine derivative* ***10*** *in high yield. A series of new benzo[4,5]thieno[2,3-d]pyrimidines* ***11–19****, which bear a propanoic acid substituent in the 2-position and an amino, aryl, aminosugar, and arylmethylideneamino-substituents in the 3-position have been prepared via the reaction of* ***6a,b*** *with hydrazine hydrate or aromatic amines followed by treatment with aromatic aldehydes, isatin, or aldoses. The aldimines* ***18a–d*** *underwent unprecedented acid catalyzed tandem cyclization-transannular aldehyde extrusion into octahydro-1*H*-benzo[4′,5′]thieno[2′,3′:4,5]pyrimido[1,2-b]pyridazines* ***21****. Two other unequivocal approaches for* ***21*** *also have been explored, either by treatment of the amino acid derivative* ***11*** *with thionyl chloride or by thermal cyclization of the amino ester derivative* ***12****.*

Keywords: Octahydro-1*H*-benzo[4′,5′]thieno[2′,3′:4,5]pyrimido[1,2-b]pyridazines; synthesis; thieno[2,3-d][1,3]oxazines; thieno[2,3-d]pyrimidines

INTRODUCTION

Several thieno[2,3-d][1,3]oxazines have been reported to exhibit a wide spectrum of biological activity, for example, as antiviral agents,[1–4]

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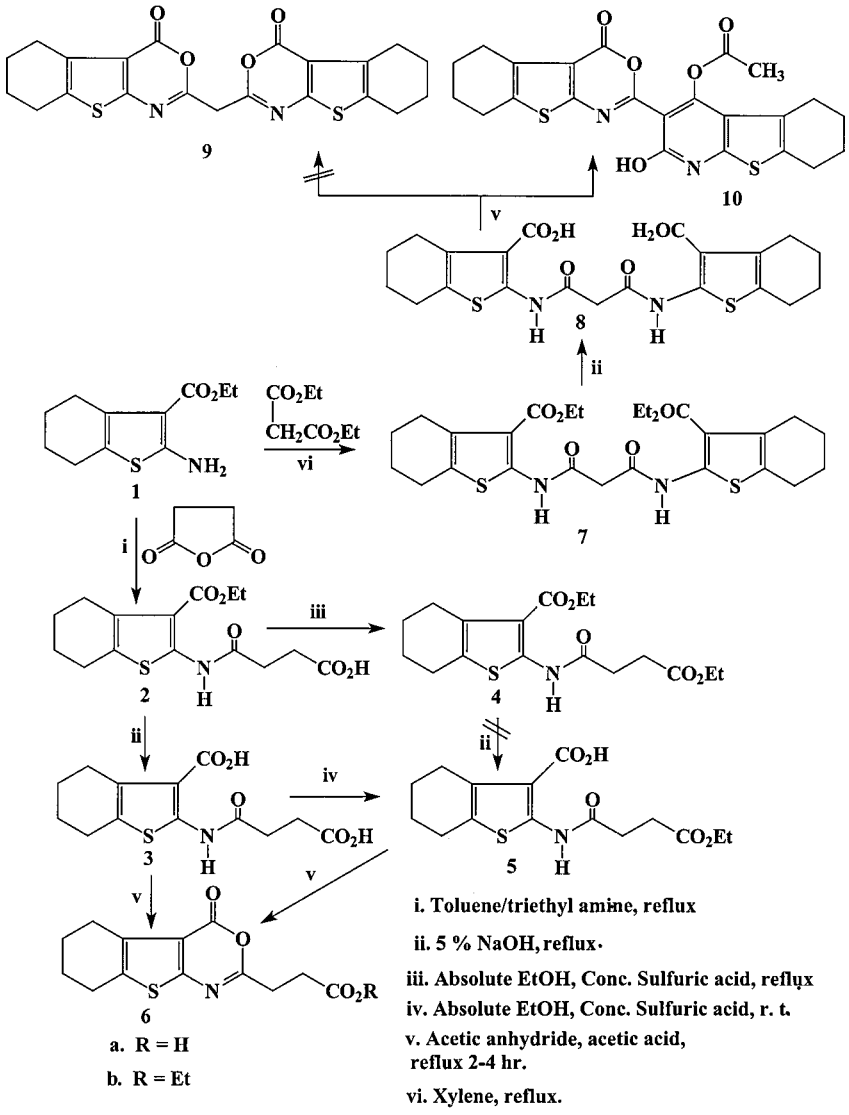
inhibitors of human leukocyte elastase,[5] and as antitumor agents.[6] Annulated 1,3-oxazine-4-ones can be considered as semi-acid anhydrides, which undergo many of the reactions of true acid anhydrides but at a slower rate. This special reactivity allows this class of compounds to be quite useful as serine protease inhibitors.[7] The chemical stability and potency of oxazinones can be tuned by choosing substituents, which influence the reactivity of the carbonyl group by electronic and steric effects. Besides, thieno[2,3-d]pyrimidine derivatives are useful as glutamate receptor antagonists in the treatment of neurodegenerative, psychotropic, induced central and peripheral nervous system disorders;[8,9] as prophylactic or therapeutic agents for the treatment of hormone dependent diseases, for example, a sex hormone dependent cancer.[10]

In view of the general interest in the biological activities of thieno[2,3-d][1,3]oxazine and thieno[2,3-d]pyrimidine derivatives and in continuation of our work in this area,[11] we report herein the syntheses of some hitherto unreported thieno[2,3-d][1,3]oxazine-2-propanoic acid and thieno[2,3-d]pyrimidine-2-propanoic acid derivatives for biological evaluation. In this study, we also demonstrate the versatility of ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene carboxylate **1** as a synthetic entry into several thieno[2,3-d][1,3]oxazine and thieno[2,3-d]pyrimidine derivatives.

RESULTS AND DISCUSSION

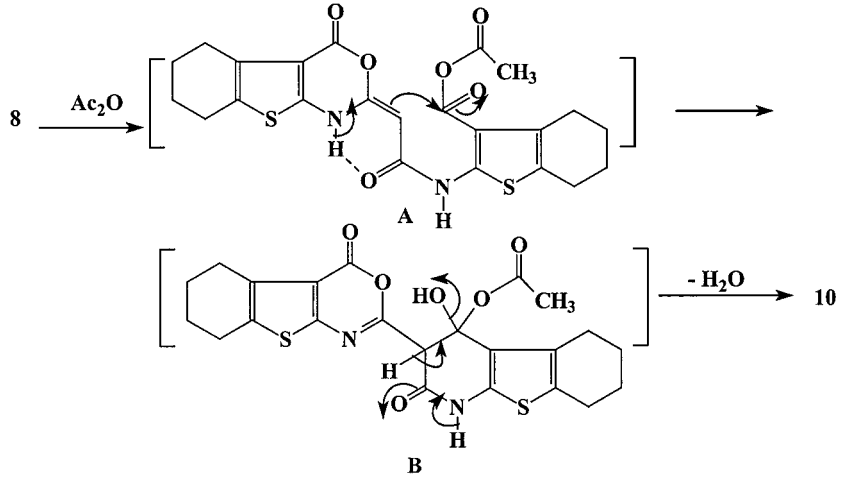
The thieno[2,3-d][1,3]oxazine-2-propanoic acid derivative **6a** was prepared through acetic anhydride induced cyclization of the dicarboxlyic acid derivative **3**, which has been synthesized by respective *N*-succinoylation of the aminothiophene derivative **1**, to give the monoacid derivative **2**, followed by selective ester hydrolysis (5% aqueous-alcoholic sodium hydroxide, Scheme 1). The synthesis of the thieno[2,3-d][1,3]oxazine-2-propanoic acid ester **6b** required the monoacid ester **5**. All attempts to synthesize **5** in reasonable yield, via selective hydrolysis of the diester derivative **4**, gave a mixture of products (TLC). Interestingly, selective acid-catalyzed esterfication of the dicarboxylic acid derivative **3** afforded the monoacid ester **5**. A subsequent acetic anhydride induced cyclodehydration of **5** furnished thieno[2,3-d][1,3]oxazine-2-propanoic acid ester **6b** in good yield.

Successive treatment of the amino thiophene derivative **1** with diethyl malonate in refluxing xylene, followed by ester hydrolysis yielded the amidoester and amidoacid derivatives **7**, **8** respectively. A subsequent acetic anhydride induced cyclodehydration of **8** afforded the thieno[2,3-d][1,3]oxazine derivative **10** rather than the expected



SCHEME 1

bis-oxazine derivative **9** (Scheme 1). A plausible mechanism for the formation of **10** is depicted in Scheme 2. It is believed that **10** is formed through the formation of the enaminic mixed acid anhydride intermediate **A**, which underwent interamolecular enamine acid anhydride cyclization, to give the intermediate **B**, followed by water elimination. This mechanism is consistent with our previously reported work.[11]

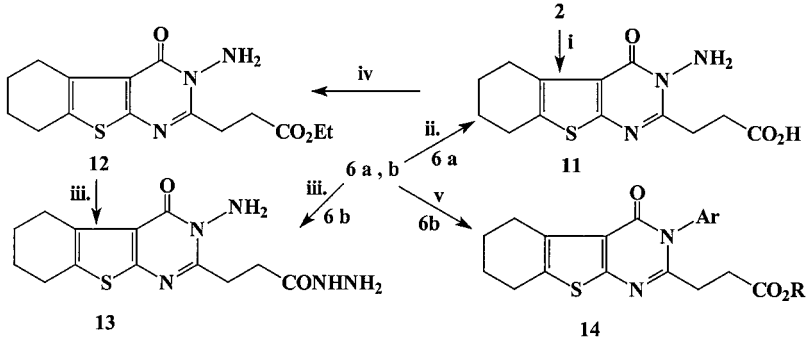


SCHEME 2

The structures of the condensed oxazine heterocycles **6a**,**b** and **10** were established through elemental and spectral analyses. The IR spectra of compounds **6a**,**b** and **10** showed a characteristic strong absorption band at 1750–1780 cm^{-1} attributable to the oxazinone carbonyl group. In particular, the ^{1}H-NMR of **6b** displayed three multiplets at δ 1.8, 2.75, and 2.92 integrated for eight protons and two triplets at δ 2.78 and 3.06 corresponding to two methylene groups.

With these functionalized thieno[2,3-d][1,3]oxazine derivatives **6a**,**b** and **10**, and the succinoylaminothiophene derivative **2** in hand, the possible synthesis of several 2,3-disubstituted and annulated thieno[2,3-d]pyrimidine derivatives was investigated. Thus, treatment of compound **2** with hydrazine hydrate under reflux yielded 3-aminothieno[2,3-d]pyrimidine derivative **11** in high yield. The structure of **11** was based on analytical and spectral data. Furthermore, the structure of **11** was supported by an unequivocal synthesis via hydrazinolysis of thieno[2,3-d][1,3]oxazine **6a**. Treatment of thieno[2,3-d][1,3]oxazine **6b** with hydrazine hydrate furnished the acid hydrazide derivative **13**. The structure of **13** was confirmed by unequivocal synthesis through esterfication of **11** to give the amino ester derivative **12**, followed by hydrazinolysis of **12** in refluxing ethanol.

The reaction of thieno[2,3-d][1,3]oxazine **6b** with aromatic amines (viz. *p*-anisidine and *p*-toluidine) in acetic acid afforded the thieno[2,3-d]pyrimidine derivatives **14a**,**b** (Scheme 3). The structure of **14a**,**b** was assigned on the basis of spectral and analytical data. The IR spectra showed the disappearance of the absorption band which is corresponding to the oxazinone carbonyl group and the ^{1}H-NMR spectrum of **14a**



i. $NH_2.NH_2.H_2O$, 2 hr reflux

ii. $NH_2.NH_2.H_2O$, 1 hr at 40 °C.

iii. $NH_2.NH_2.H_2O$, EtOH, 3 hr reflux.

iv. Absolute EtOH, Conc. H_2SO_4, 2 hr reflux

v. Ar NH_2, AcOH, 3-4 hr reflux.

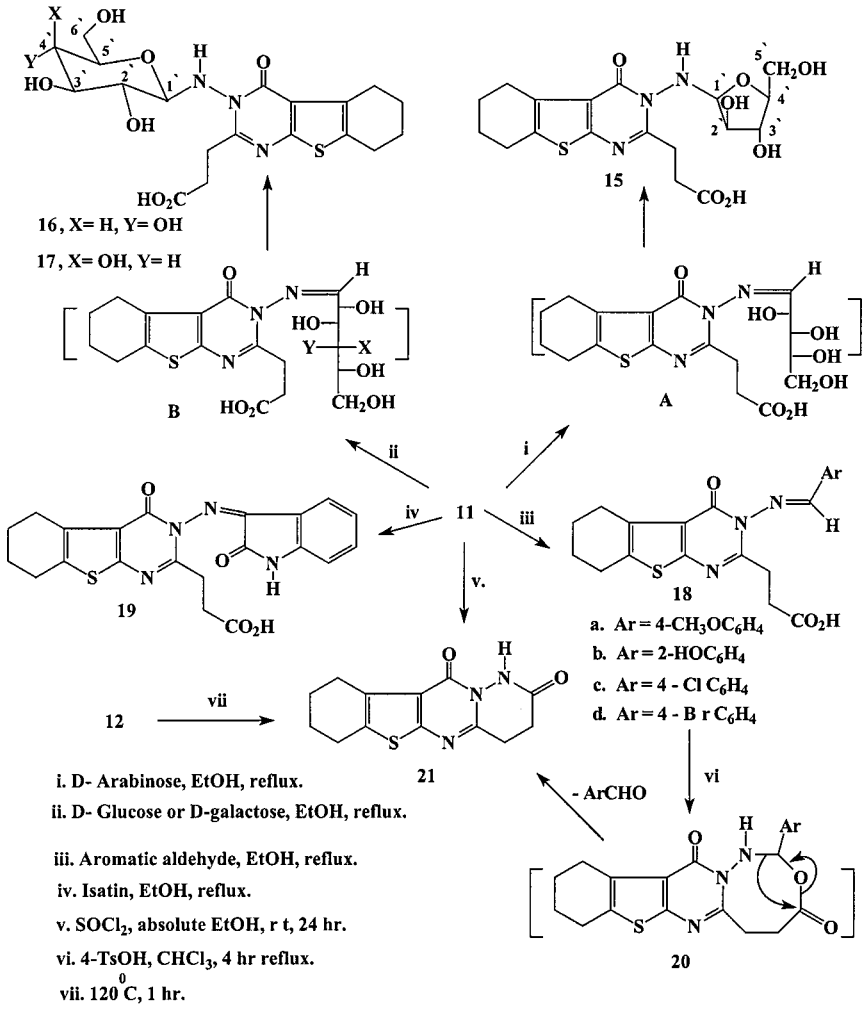
	R	Ar
a.	Et	4- $CH_3C_6H_4$
b.	Et	4- $CH_3OC_6H_4$

SCHEME 3

displayed, in addition to the aliphatic hydrogen resonance, an AB system at δ 7.24 and 7.39 corresponding to *p*-substituted phenyl ring.

The introduction of sugar moieties to the thieno[2,3-d]pyrimidine derivatives is expected to affect their pharmacological activity, since the sugar would render the molecules more hydrophilic and, accordingly, ensure better pervasion into biological systems.[12] Thus, reaction of 3-aminotheino[2,3-d]pyrimidine **11** with the aldoses, D-arabinose, D-glucose and D-galactose gave the respective saccharide hydrzone intermediates **A** and **B**, which underwent self-acid catalyzed cyclization to give the nucleotides **15**, **16**, and **17** in good yields (Scheme 4). The given structures of **15**, **16**, and **17** were established unequivocally by ^1H and ^{13}C-NMR. One of the diagnostic features of the ^{13}C-NMR spectra of the reaction products is the lack of any absorption peaks corresponding to azomethine carbon in the intermediates **A** and **B**. Instead peaks at δ 91.17–91.45 were observed, being assigned to the 1′-carbon atoms of the glycosyl amines **15–17**.[13] The antiperiplanar coupling constant (8 Hz) of the proton 1′-H and 2′-H in **16** shows that a β-glucoside is involved.[14] The presence of compound **15** in the arabinofuranose form was depicted on the basis of comparing its ^{13}C-data with those reported in the literature for similar structures.[13,15]

The treatment of 3-aminothieno[2,3-d]pyrimidine **11** with aromatic aldehydes (4-methoxy, 2-hydroxy, 4-chloro and 4-bromobenzaldehyde) and isatin in refluxing ethanol afforded the aldimines **18a–d** and **19**,



SCHEME 4

respectively, in good yields. The aldimines **18a–d** underwent unprecedented consecutive acid catalyzed cyclization and transannular aldehyde extrusion, in refluxing chloroform containing a catalytic amount of 4-toluenesulphonic acid, to furnish the tetracyclic structure **21** through the formation of the oxadiazocine intermediate **20** (Scheme 4). The structure of **21** was assigned on the basis of spectral and analytical data. The ^{1}H-NMR of **21** showed three multiplets at δ 1.78, 2.72, and 2.87 integrated for eight protons and two triplets, two protons each, at δ 2.63 and 3.11. Two other unequivocal approaches for **21** have been

investigated, either by treatment of the amino acid **11** with thionyl chloride and absolute ethanol in a stoppered flask at room temperature or by heating the aminoester **12** at 120°C.

In summary, we have described a multi step procedure to synthesize thieno[2,3-d][1,3]oxazine subsystems of **6a**,**b**. Several synthetically useful transformations of substrates **6a**,**b** are also given in Schemes 3 and 4. Specific attention was given to the aldimines **18a–d**, which underwent unprecedented acid-catalyzed tandem cyclization-transannular aldehyde extrusion to afford the tetracyclic compound **21** (Scheme 4). It is important to note that no chromatography was involved and analytically pure products were obtained by crystallization in all cases studied.

Experimental

Melting points (Pyrex capillary) are not corrected. IR spectra were recorded on MATTSON 5000 FT-IR Spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian-Gemini 300 MHz instrument at 300 and 75 MHz, respectively. The NMR spectra were taken in $CDCl_3$ or DMSO-d_6 as solvents, with TMS as an internal standard. Mass spectra were recorded on GC-MS GP-1000 EX. Shimadzu machine. Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Mansoura University.

4-{[3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl]amino}-4-oxobutanoic Acid (2)

A mixture of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **1** (50 mmol, 11.25 g) and succinic anhydride (50 mmol, 5.0 g) in toluene (150 mL), containing a catalytic amount of triethylamine, was refluxed for 3 h. After cooling, the formed precipitate was filtered and recrystallized from ethanol. Yield (95%); m.p. 155–158°C; IR (KBr) 3383, 2937, 2852, 1685, 1660, 1543, 1437, 1410, 1330, 1285, 1252, 1212, 1169, 1137, 926 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.49 (t, 3H, $J = 7$ Hz), 1.88 (m, 4H), 2.73 (m, 4H), 2.89 (m, 4H), 3.60 (br s, 1H), 4.45 (q, 2H, $J = 7$ Hz), 11.2 (s, 1H); ^{13}C-NMR (DMSO-d_6): δ 14.08, 22.29, 22.48, 23.67, 25.80, 28.70, 30.75, 60.30, 111.06, 125.82, 130.32, 146.03, 164.96, 169.08, 173.46. *Anal*. Calcd. for $C_{15}H_{19}NO_5S$ (325.379): C, 55.37; H, 5.89. Found: C, 55.19; H, 6.02.

2-[3-(Carboxypropanoyl)amino]-4,5,6,7-tetrahydrobenzo-[b]thiophene-3-carboxylic Acid (3)

To a suspension of the monoacid-ester **2** (50 mmol, 16.25 g) in ethanol (100 mL) was added a 10% sodium hydroxide solution (100 mL). The reaction mixture was refluxed for 3 h, cooled (0°C), and acidified with dilute hydrochloric acid (pH = 4). The formed precipitate was

filtered, washed with excess water, and recrystallized from ethanol. Yield (69%); m.p. 204–206°C; IR (KBr) 3383, 3026, 2937, 2852, 1685, 1650, 1543, 1437, 1410, 1330, 1285, 1252, 1212, 1169, 1137, 926 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.77 (m, 4H), 2.64 (m, 4H), 2.76 (m, 4H), 3.46 (br s, 1H, NH), 11.28 (s, 1H), 12.63 (br s, 1H); ^{13}C-NMR (DMSO-d_6): δ 22.28, 22.54, 23.66, 25.83, 28.61, 30.73, 111.64, 125.31, 130.78, 148.06, 166.89, 168.77, 173.42. *Anal*. Calcd. for $C_{13}H_{15}NO_5S$ (297.325): C, 52.52; H, 5.09. Found: C, 52.84; H, 5.27.

Ethyl 2-[(4-Ethoxy-4-oxobutanoyl)amino]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (4)

A suspension of compound **2** (5 mmol, 1.63 g) in absolute ethanol (50 mL) containing a few drops of conc. sulfuric acid was refluxed for 1 h. The reaction mixture was cooled and poured onto ice (80 g). The formed colorless precipitate was filtered, washed with water, and recrystallized from ethyl acetate/pet. ether (60–80°C) (1:3). Yield (71%); m.p. 95–97°C; IR (KBr) 3291, 2983, 2937, 2859, 1736, 1687, 1669, 1562, 1535, 1440, 1329, 1277, 1231, 1163, 1033 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.57 (t, 3H, $J = 7$ Hz), 1.70 (t, 3H, $J = 7$ Hz), 2.09 (m, 4H), 2.95 (m, 2H), 3.05 (m, 4H), 3.17 (t, 2H, $J = 7$ Hz), 4.45 (q, 2H, $J = 7$ Hz), 4.65 (q, 2H, $J = 7$ Hz), 11.42 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 14.02 (2C), 22.29, 22.47, 23.67, 25.81, 28.57, 30.58, 60.05, 60.29, 111.05, 125.80, 130.27, 146.07, 165.0, 168.73, 171.92; *Anal*. Calcd. for $C_{17}H_{23}NO_5S$ (353.433): C, 57.77; H, 6.56. Found: C, 57.36; H, 6.43.

2-[(4-Ethoxy-4-oxobutanoyl)amino]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic Acid (5)

A suspension of 2-[3-(carboxypropanoyl)amino]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid **3** (5 mmol, 1.49 g) in absolute ethanol (50 mL) containing a few drops of conc. sulfuric acid was left overnight, then poured onto ice (80 g). The formed colorless precipitate was filtered, washed with water, and recrystallized from ethyl acetate. Yield (63%); m.p. 165–166°C; IR (KBr) 3279, 3134, 2942, 1737, 1701, 1641, 1543, 1531, 1454, 1238, 1210, 1026, 905, 702 cm^{-1}; *Anal.* Calcd. for $C_{15}H_{19}NO_5S$ (325.379): C, 55.37; H, 5.89. Found: C, 55.58; H, 5.63.

3-(4-Oxo-5,6,7,8-tetrahydro-4 H*-benzo[4,5]thieno[2,3-d]-[1,3]oxazin-2-yl)propanoic Acid (6a)*

The dicarboxylic acid **3** (25 mmol, 7.43 g) was refluxed for 4 h in a mixture of acetic anhydride and acetic acid (3:1, 75 mL). The solvent was distilled off under reduced pressure and the residue was recrystallized from chloroform/ether (1:1). Yield (81%); m.p. 214–216°C; IR (KBr) 3030, 2940, 2860, 1765, 1676, 1490, 1442, 1354, 1273, 1239, 1163,

717, 660 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.00 (m, 4H), 2.80 (m, 4H), 2.85 (m, 4H), 12.60 (s, 1H, CO_2H); MS (m/z, %): 279.16 (M^+, 38), 261.15 (60), 235.18 (50), 221.16 (80), 193.13 (58), 179.14 (100) 151.03 (80), 135.02 (84), 125.04 (86), 108 (50), 91.13 (48), 69.04 (58), 55.04 (70); *Anal*. Calcd. for $C_{13}H_{13}NO_4S$ (279.31): C, 55.90; H, 4.69. Found: C, 55.63; H, 5.02.

Ethyl 3-(4-Oxo-5,6,7,8-tetrahydro-4 H*-benzo[4,5]thieno-[2,3-d][1,3]oxazin-2-yl)propanoate (6b)*

The monoacid ester **5** (25 mmol, 8.13 g) was refluxed for 2 h in a mixture of acetic anhydride, and acetic acid (3:1, 75 mL). The solvent was distilled off under reduced pressure and the residue was recrystallized from ethyl acetate/pet. ether (60–80°C) (2:3). Yield (74%); m.p. 115–117°C; IR (KBr) 2929, 1780, 1730, 1601, 1421, 1314, 1310, 1209, 1166, 1165, 1021, 1019, 909, 645 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H, $J = 7$ Hz), 1.86 (m, 4H), 2.75 (m, 2H), 2.78 (t, 2H, $J = 7$ Hz), 2.92 (m, 2H), 3.06 (t, 2H, $J = 7$ Hz), 4.16 (q, 2H). *Anal*. Calcd. for $C_{15}H_{17}NO_4S$ (307.364): C, 58.62; H, 5.58. Found: C, 58.86; H, 5.73.

Ethyl-2-[(3-{[3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo-[b]thiophen-2-yl]-amino}-3-oxopropanoyl)amino]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (7)

A mixture of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**1**) (50 mmol, 11.25 g) and diethyl malonate (50 mmol, 8 g) in xylene (100 mL) was refluxed for 5 h. After cooling, the formed precipitate was filtered and recrystallized from ethanol. Yield (90%); m.p. 210–212°C; IR (KBr) 3219, 3163, 2937, 2859, 1705, 1669, 1561, 1522, 1443, 1404, 1330, 1277, 1229, 1173, 1136, 1024, 779 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.31 (dt, 6H, 2 × CH_3), 1.72 (m, 8H), 2.61 (m, 4H), 2.71 (m, 4H), 3.97 (s, 2H), 4.30 (dq, 4H, 2 × CH_2), 11.38 (s, 2H, 2 × NH); *Anal*. Calcd. for $C_{25}H_{30}N_2O_6S_2$ (518.643): C, 57.90; H, 5.83. Found: C, 57.58; H, 6.00.

2-({3-[(3-Carboxy-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino]-3-oxopropanoyl}-amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic Acid (8)

To a suspension of the dicarboxylic acid ester **7** (50 mmol, 25.9 g) in ethanol (100 mL) was added a 10% sodium hydroxide solution (100 mL). The reaction mixture was refluxed for 2 h, cooled (0°C) and acidified with dilute hydrochloric acid (pH = 4). The formed precipitate was filtered, washed with excess water and recrystallized from ethanol. Yield (59%); m.p. 197–199°C; IR (KBr) 3472, 3320, 3215, 3131, 3075, 3040, 3020, 2932, 2850, 1707, 1644, 1537, 1445, 1365, 1328, 1277, 1226, 787, 710 cm^{-1}. *Anal*. Calcd. for $C_{21}H_{22}N_2O_6S_2$ (462.535): C, 54.53; H, 4.79. Found: C, 54.92; H, 4.52.

2-Hydroxy-3-(4-oxo-5,6,7,8-tetrahydro-4 H*-benzo[4,5]-thieno[2,3-d][1,3]oxazin-2-yl)-5,6,7,8-tetrahydrobenzo-[4,5]thieno[2,3-b]pyridin-4-yl Acetate (10)*

The dicarboxylic acid **8** (25 mmol, 11.55 g) was refluxed for 3 h in a mixture of acetic anhydride and acetic acid (3:1, 75 mL). The solvent was distilled off under reduced pressure and the residue was recrystallized from ether. Yield (81%); m.p. 216–218°C; IR (KBr): 2937, 2860, 2830, 1750, 1735, 1600, 1553, 1478, 1420, 1373, 1334, 1283, 1227, 1160, 1095, 1016, 895, 767 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.72 (m, 8H), 2.22 (s, 3H), 2.59 (m, 4H), 2.71 (m, 4H), 11.18 (s, 1H). *Anal*. Calcd. for $C_{23}H_{20}N_2O_5S_2$ (468.542): C, 58.96; H, 4.30. Found: C, 58.63; H, 4.01.

3-(3-Amino-4-oxo-3,4,5,6,7,8-hexahydro-4 H*-benzo[4,5]-thieno[2,3-d]pyrimidin-2-yl)propanoic Acid (11)*

Method A. A mixture of the monoacid-ester **2** (50 mmol, 16.25 g) and hydrazine hydrate (25 mL) was heated under reflux for 2 h. After cooling, the formed precipitate was filtered and washed with ether and recrystallized from chloroform/ethanol (1:1) to afford **11** in 87% yield.

Method B. A mixture of thieno[2,3-d][1,3]-oxazine-2-propanoic acid **6a** (10 mmol, 2.79 g) and hydrazine hydrate (4 mL) was heated at 40°C for 1 h. The reaction mixture was poured onto ice water. The formed precipitate was filtered, washed with water, and recrystallized from chloroform/ethanol (1:1). Yield (72%); m.p. 214–215°C; IR: 3309, 3215, 3173, 2932, 2852, 1671, 1644, 1538, 1489, 1436, 1391, 1342, 1287, 1184, 1003 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.75 (m, 4H) 2.46 (m, 2H), 2.68 (m, 2H), 2.84 (m, 2H), 3.12 (t, 2H, $J = 7.5$ Hz), 4.10 (br s, 2H, NH_2), 9.00 (s, 1H, CO_2H); ^{13}C-NMR (DMSO-d_6): δ 21.75, 22.46, 24.48, 25.14, 28.96, 29.47, 119.2, 130.28, 131.86, 156.43, 156.93, 160.21, 170.66; *Anal*. Calcd. for $C_{13}H_{15}N_3O_3S$ (293.341): C, 53.23; H, 5.15. Found: C, 52.86; H, 5.41.

Ethyl-3-(3-amino-4-oxo-3,4,5,6,7,8-hexahydro-4 H*-benzo[4,5]thieno[2,3-d]pyrimidin-2-yl)propanoate (12)*

A suspension of compound **11** (5 mmol, 1.47 g) in absolute ethanol (25 mL) containing a few drops of conc. sulfuric was refluxed for 2 h. The reaction mixture was cooled and poured onto ice (80 g). The formed colorless precipitate was filtered, washed with water, and recrystallized from ethyl acetate/pet. ether (60–80°C) (1:2). Yield (74%); m.p. 125°C; IR (KBr) 3304, 3247, 3212, 2977, 2934, 2860, 1731, 1669, 1562, 1463, 1416, 1352, 1280, 1182, 1161 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ: 1.26 (t, 3H, $J = 7$ Hz), 1.85 (m, 4H), 2.75 (m, 2H), 2.85 (t, 2H, $J = 7$ Hz), 2.98 (m, 2H), 3.30 (t, 2H, $J = 7$ Hz), 4.14 (q, 2H, $J = 7$ Hz), 5.00 (br s, 2H, NH_2);

^{13}C-NMR ($CDCl_3$): δ 14.21, 22.19, 22.89, 25.14, 25.34, 28.46, 30.65, 60.63, 119.98, 130.95, 133.23, 155.17, 158.0, 161.2, 172.79; *Anal*. Calcd. for $C_{15}H_{19}N_3O_3S$ (321.395): C, 56.06; H, 5.96. Found: C, 56.28; H, 6.07.

3-(3-Amino-4-oxo-3,4,5,6,7,8-hexahydrobenzo-[4,5]thieno[2,3-d]pyrimidin-2yl)propanehydrazide (13)

Method A. A mixture of **6b** (10 mmol, 3.07 g) and hydrazine hydrate (2 mL, 80%) in absolute ethanol (25 mL) was refluxed for 3 h. The solvent and excess hydrazine hydrate was distilled off and the residue was recrystallized from ethanol to furnish **13** in 68% yield.

Method B. A mixture of the thieno[2,3-d]pyrimidine derivative **12** (10 mmol, 3.21 g) and hydrazine hydrate (2 mL, 80%) in absolute ethanol (25 mL) was refluxed for 3 h. The solvent and excess hydrazine hydrate was distilled off and the residue was recrystallized from ethanol. Yield (85%); m.p. 225–226°C; IR (KBr) 3303, 3200, 3160, 2933, 2852, 1662, 1652, 1600, 1536, 1488, 1486, 1441, 1341, 1207, 1183, 1101, 1029, 1003 cm^{-1}; *Anal*. Calcd. for $C_{13}H_{17}N_5O_2S$ (307.372): C, 50.80; H, 5.58. Found: C, 50.97; H, 5.27.

Reaction of Thieno[1,3]oxazine Derivative (6b) with Aromatic Amines

A mixture of compound **6b** (5 mmol, 1.54 g) and the respective aromatic amine (*p*-toluidine or *p*-anisidine) (5 mmol) was refluxed in glacial acetic acid (10 mL) for 3–4 h. The solvent was distilled off and the residue was poured onto ice-water. The formed precipitate was filtered and recrystallized from ethanol to afford **14a**,**b**.

Ethyl-3-[3-(4-methylphenyl)-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl)-propanoate (14a)

Yield (84%); m.p. 125–127°C; IR (KBr) 2924, 2851, 1732, 1682, 1636, 1600, 1549, 1512, 1283, 1220, 1165, 1017 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.19 (t, 3H, $J = 7$ Hz), 1.77 (m, 4H), 2.29 (s, 3H), 2.65–2.83 (m, 6H), 4.05 (q, 2H, $J = 7$ Hz), 7.24 (d, 2H, $J = 8$ Hz), 7.39 (d, 2H, $J = 8$ Hz). *Anal*. Calcd. for $C_{22}H_{24}N_2O_3S$ (396.505): C, 66.64; H, 6.10. Found: C, 66.93; H, 5.75.

Ethyl-3-[3-(4-methoxyphenyl)-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl)-propanoate (14b)

Yield (81%); m.p. 138–140°C; IR (KBr) 3070, 2927, 2837, 1729, 1655, 1604, 1514, 1243, 1175, 1029, 830, 770 cm^{-1}; *Anal*. Calcd.

for $C_{22}H_{24}N_2O_4S$ (412.504): C, 64.06; H, 5.86. Found: C, 64.47; H, 5.63.

Reaction of 3-(3-Amino-4-oxo-3,4,5,6,7,8-tetrahydro-4H-benzo[4,5]thieno[2,3-d]pyrimidin-2-yl)propanoic Acid (11) with Aldopentoses and Aldohexoses

To a solution of 3-(3-amino-4-oxo-3,4,5,6,7,8-tetrahydro-4*H*-benzo[4,5]thieno[2,3-d]pyrimidin-2-yl)propanoic acid **11** (10 mmol, 2.93 g) in ethanol (50 mL) was added the appropriate aldose (10 mmol). The reaction mixture was heated under reflux on a water bath for 2–3 h. The formed precipitate was filtered off and recrystallized from aqueous/ethanol to afford **15–17**.

3-(3-{[β-D-Arabinofuranosyl]amino}-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl)-propanoic Acid (15)

Yield (76%); m.p. 205–207°C; IR (KBr) 3491, 3433, 3398, 3367, 2928, 2856, 1655, 1543, 1090, 1082 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.58 (m, 4H), 2.43 (m, 2H), 2.65 (m, 2H), 2.94 (m, 2H), 3.34 (m, 5H), 4.28 (m, 1H), 4.58 (m, 1H), 4.77 (br s, 1H), 5.43 (br, 3H), 9.32 (s, 1H); ^{13}C-NMR (DMSO-d_6): δ 21.71, 22.42, 24.45, 25.09, 28.38, 29.35, 66.09, 67.73, 68.34, 72.41, 91.45, 119.18, 130.22, 131.82, 156.33, 156.95, 160.16, 170.48; *Anal*. Calcd. for $C_{18}H_{23}N_3O_7S$ (425.456): C, 50.82; H, 5.45. Found: C, 50.61; H, 5.73.

3-(3-{[β-D-Glucopyranosyl]amino}-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl)-propanoic Acid (16)

Yield (71%); m.p. 132–133°C; IR (KBr) 3482, 2938, 2848, 1658, 1620, 1546, 1431, 1347, 1290 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.70 (m, 4H), 2.62 (m, 2H), 2.77 (m, 2H), 2.97 (m, 2H), 3.08 (m, 4H), 3.39 (m, 2H), 3.62 (m, 2H), 4.35 (m, 1H), 4.57 (m, 2H), 5.55 (m, 1H) 5.66 (d, 1H, $J = 8$ Hz), 9.44 (s, 1H); ^{13}C-NMR (DMSO-d_6): δ 21.92, 22.64, 24.68, 25.30, 29.17, 29.61, 61.54, 70.38, 70.57, 76.79, 78.09, 91.17, 119.26, 130.44, 132.18, 156.43, 157.21, 160.37, 171.25; *Anal*. Calcd. for $C_{19}H_{25}N_3O_8S$ (455.479): C, 50.10; H, 5.53. Found: C, 50.48; H, 5.86.

3-(3-{[β-D-Galactopyranosyl]amino}-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl)-propanoic Acid (17)

Yield (88%); m.p. 255–257°C; IR (KBr) 3429, 3316, 3057, 2938, 1677, 1647, 1552, 1440, 1153, 1097, 1065, 1041 cm^{-1}; *Anal*. Calcd.

for $C_{19}H_{25}N_3O_8S$ (455.479): C, 50.10; H, 5.53. Found: C, 50.41; H, 5.26.

3-{3-[1-(Arylmethylidene)amino]-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl}-propanoic Acid (18a–d)

A mixture of 2-aminothieno[2,3-d]pyrimidine-2-propanoic acid **11** (5 mmol, 1.47 g) and the appropriate aromatic aldehyde (5 mmol) was taken in ethanol (25 mL). The reaction mixture was refluxed for 2–3 h. The formed precipitate was filtered and recrystallized from chloroform/ethanol (1:1) to furnish the aldimines **18a–d**.

3-{3-[1-(4-Methoxyphenylmethylidene)amino]-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl}propanoic Acid (18a)

Yield (85%); m.p. 260–261°C; IR (KBr) 3441, 2935, 2879, 2831, 1709, 1673, 1626, 1601, 1570, 1489, 1464, 1431, 1373, 1354, 1318, 1300, 1279, 1251, 1213, 1163, 1109, 1023, 936, 831, 768 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.80 (m, 4H), 2.65 (t, 2H, $J = 7$ Hz), 2.88 (m, 2H), 3.13 (t, 2H, $J = 7$ Hz), 3.82 (s, 3H), 7.04 (d, 2H, $J = 8$ Hz), 7.79 (d, 2H, $J = 8$ Hz), 8.60 (s, 1H), 11.10 (s, 1H); MS (m/z, %): 276 (M^+-135, 100), 260 (10), 248 (25), 231 (50), 218 (12), 204 (5), 191 (5), 55 (25); *Anal*. Calcd. for $C_{21}H_{21}N_3O_4S$ (411.476): C, 61.30; H, 5.14. Found: C, 61.48; H, 5.36.

3-{3-[1-(2-Hydroxyphenylmethylidene)amino]-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl}propanoic Acid (18b)

Yield (74%); m.p. 240–241°C; IR (KBr) 3454, 3253, 3045, 2935, 2861, 1702, 1641, 1618, 1549, 1483, 1433, 1407, 1381, 1355, 1273, 1194, 1174, 1157, 748 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.76 (m, 4H), 2.74 (m, 4H), 2.86 (m, 2H), 3.28 (m, 2H), 6.93 (m, 3H), 7.41 (m, 1H), 8.37 (s, 1H), 8.97 (s, 1H), 11.12 (s, 1H); *Anal.* Calcd. for $C_{20}H_{19}N_3O_4S$ (397.449): C, 60.44; H, 4.82. Found: C, 60.84; H, 5.05.

3-{3-[1-(4-Chlorophenylmethylidene)amino]-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl}propanoic Acid (18c)

Yield (82%); m.p. 207–209°C; IR (KBr) 3390, 2932, 1712, 1671, 1629, 1591, 1569, 1545, 1486, 1422, 1373, 1354, 1283, 1175, 1152, 1089, 1013, 822, 510 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.86 (m, 4H), 2.77 (m, 4H), 3.00 (m, 2H), 3.24 (m, 2H), 7.43 (d, 2H, $J = 7.5$ Hz), 7.78 (d, 2H, $J = 7.5$ Hz), 8.61 (s, 1H), 9.72 (s, 1H); *Anal*. Calcd. for $C_{20}H_{18}ClN_3O_3S$ (415.895): C, 57.76; H, 4.36. Found: C, 57.38; H, 4.71.

3-{3-[1-(4-Bromophenylmethylidene)amino]-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl}propanoic Acid (18d)

Yield (70%); m.p. 225–226°C; IR (KBr) 3285, 3194, 3132, 3109, 2982, 2932, 2843, 1708, 1661, 1607, 1541, 1483, 1443, 1392, 1345, 1285, 1261, 1211, 1172, 1137, 1065, 1006, 933, 809, 773 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.56 (m, 4H), 2.62 (m, 4H), 3.05 (m, 4H), 7.71 (d, 2H, $J = 7.5$ Hz) 7.83 (d, 2H, $J = 7.5$ Hz), 8.70 (s, 1H), 11.08 (s, 1H). *Anal*. Calcd. for $C_{20}H_{18}BrN_3O_3S$ (460.346): C, 52.18; H, 3.94. Found: C, 52.42; H, 4.25.

3-{4-Oxo-3-[(2-oxo-2,3-dihydro-1 H*-3-indolylidene)amino]-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidin-2-yl}propanoic Acid (19)*

A mixture of 2-aminothieno[2,3-d]pyrimidine-2-propionic acid **11** (5 mmol, 1.47 g) and isatin (5 mmol, 0.74 g) in ethanol (25 mL) was refluxed for 5 h. The formed precipitate was filtered and recrystallized from DMF/ethanol (1:5). Yield (51%); m.p. 251–252°C; IR (KBr) 3184, 3124, 2934, 1721, 1690, 1654, 1603, 1541, 1479, 1441, 1345, 1177, 1159, 1120, 1000 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.77 (m, 4H), 2.69 (m, 2H), 2.87 (m, 2H), 3.18 (m, 2H), 3.28 (m, 2H), 6.88 (d, 1H, $J = 8$ Hz), 7.01 (t, 1H, $J = 8$ Hz), 7.36 (t, 1H, $J = 8$ Hz), 8.05 (d, 1H, $J = 8$ Hz), 10.67 (s, 1H), 11.0 (s, 1H). *Anal*. Calcd. for $C_{21}H_{18}N_4O_4S$ (422.459): C, 59.71; H, 4.29. Found: C, 59.47; H, 4.52.

2,3,4,7,8,9,10,11-Octahydro-1 H*-benzo[4′,5′]thieno[2′,3′:4,5]pyrimido[1,2-b]pyridazin-2,11-dione (21)*

Method A. A solution of the aldimines **18a–d** (5 mmol) in chloroform (30 mL), containing a catalytic amount of 4-toluenesulphonic acid, was refluxed for 3–4 h. After cooling the formed precipitate was filtered and recrystallized from ethanol. Yield (65–77%).

Method B. To a solution of the amino acid **11** (5 mmol, 1.47 g) in ethanol (25 mL) was added thionyl chloride (20 mmol, 2.38 g). The reaction mixture was kept in a stoppered flask at room temperature for 24 h, the solvent was distilled off and the residue was recrystallized from ethanol in 92% yield.

Method C. Compound **12** (5 mmol, 1.47 g) was heated at 120°C in an oil bath for 1 h to give a molten sticky mass, which was triturated with ethanol and cooled to room temperature. The separated solid was filtered and recrystallized from ethanol. Yield (74%); m.p. 294°C; IR (KBr) 3161, 2935, 2864, 2830, 1707, 1673, 1568, 1486, 1466, 1430, 1374, 1353, 1317, 1279, 1212, 1175, 1155 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.78 (m, 4H), 2.63 (t, 2H, $J = 7$ Hz), 2.72 (m, 2H), 2.87 (m, 2H), 3.11 (t, 2H,

$J = 7$ Hz), 11.08 (s, 1H, NH); *Anal*. Calcd. for $C_{13}H_{13}N_3O_2S$ (275.326): C, 56.71; H, 4.76. Found: C, 56.95; H, 4.53.

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