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Novel Synthesis of 1,3,4-Thiadiazine Derivatives and Their Cycloaddition Reactions

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4-Phenyl-3-thiosemicarbazide **1** reacted with the α-halocarbonyl compounds **2a, b** to give the thiosemicarbazone derivatives **3a, b**. The latter compounds underwent cyclization to the 1,3,4-thiadiazine derivatives **4a, b** which underwent [2 + 4] cycloaddition reactions to give the 4*H*-thiopyran derivatives **7a, b**. The chemistry of these thiopyrans was studied. Some of the fused derivatives among them compounds **20a**, **20b**, **21a**, **21b** allowed good mycelial growth and sporulation by the two fungi. This indicates that the two fungi can use the N-containing heterocyclic ring as a nitrogen source.

Keywords: Thiadiazine / Thiopyran / Thiosemicarbazide / Toxicity

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Introduction

Heterocycles containing nitrogen or sulfur are common building blocks both incorporated in natural products and pharmaceutical compounds; and the development of simple and effective ways to synthesize heterocycles is a point of major concern in medicinal chemistry [1 – 5]. In this regards, the utilization of the hetero Diels-Alder reaction undoubtedly represents one of the most attractive routes for preparing these heterocycles with maximum atom economy and high selectivity [6 – 9]. Our laboratory has a long-standing interest in the synthesis of heterocyclic compounds beginning with readily available starting materials [10 – 13]. The importance of these groups of compounds is due to their diverse biological and pharmaceutical interest, some of which are known as potent and specific inhibitors of carrier-mediated transport [14], others as antimalarial drugs [15], and yet others possess cytotoxic activity against cells of human bladder cancer cell [16, 17].

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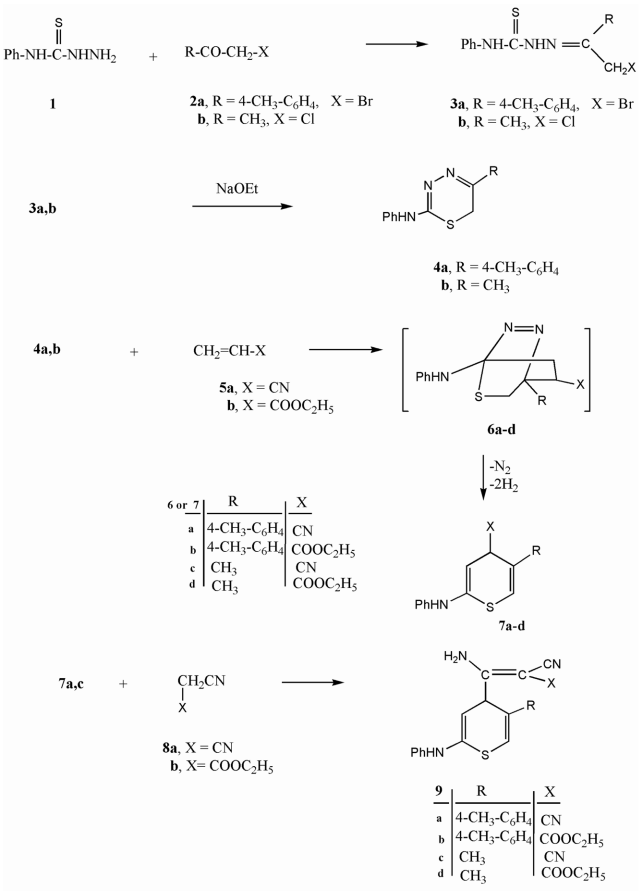
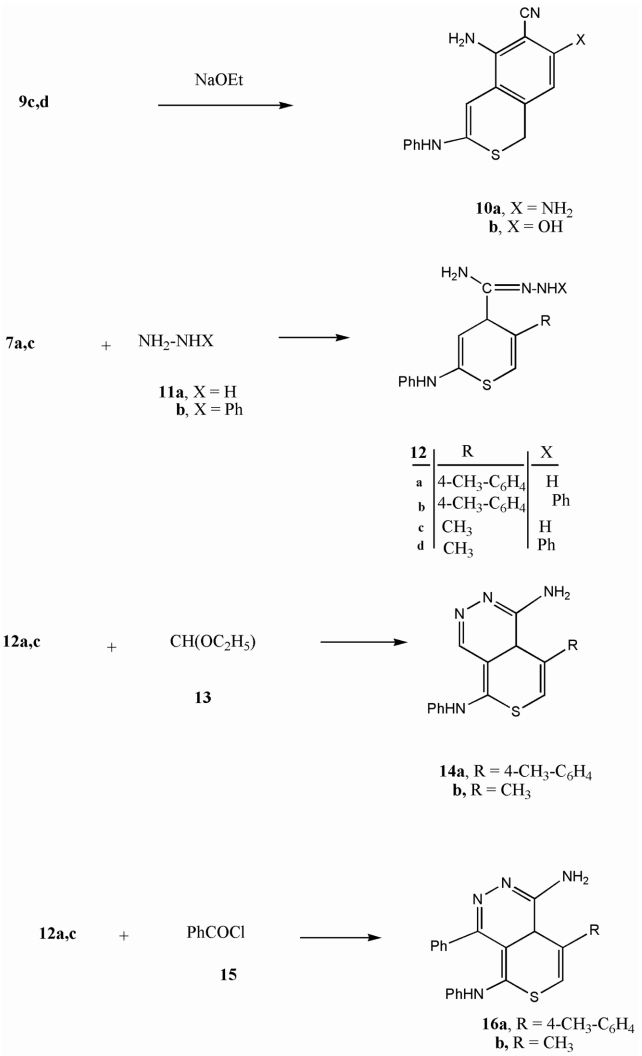
Results and discussion

As a part of our continuing program towards the reactivity and the synthesis of potentially pharmaceutically active heterocycles, we have now investigated the reaction of 4-phenyl-3-thiosemicarbazide [18] with α-haloketons to form acyclic derivatives that undergo cyclization to thiadiazine derivatives. The reaction of thiosemicarbazide **1** with α-halocarbonyl compounds **2a, b** in ethanol at room temperature gave the condensed products **3a, b**. Structures of the latter products are based on analytical and spectral data. The ^{1}H-NMR spectrum of **3a**, for example, showed the presence of a singlet at δ 2.89 corresponding to CH_3, a singlet at δ 5.21 for CH_2, a multiplet at δ 7.32 – 7.45 for aromatic protons, and two singlets (D_2O exchangeable) at δ 8.36, 8.49 for two NH groups. Compounds **3a, b** underwent ready cyclization when heated in sodium ethoxide solution in a boiling water bath to give the 6*H*-1,3,4-thiadiazine derivatives **4a** and **4b**, respectively. The analytical and spectral data are consistent with the proposed structures. Thus, the ^{13}C-NMR of compound **4a** showed δ: 23.9 (CH_3), 28.8 (thiadiazine CH_2), 116.9, 118.7, 129.9, 131.4, 134.5, 140.2, 144.8 (C_6H_5, C_6H_4), 162.9, 164.4 (2 C=N).

In spite of the rich chemistry with thiopyran derivatives, it is surprising that there is no report, to the best of our knowledge, of the uses of 1,3,4-thiadiazine deriv-



Scheme 1. Synthesis of Michael adducts **9a – d**.

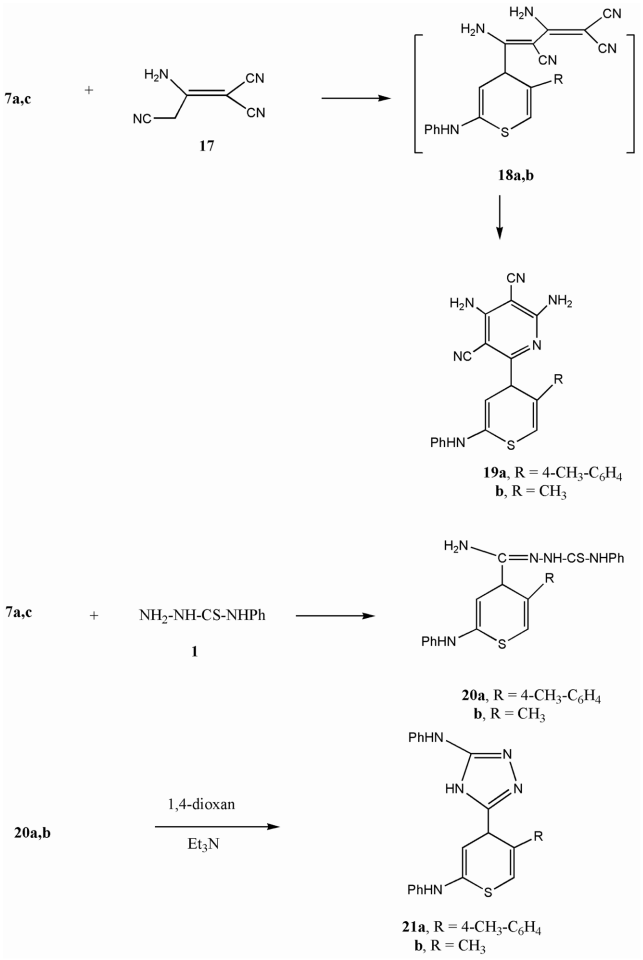


Scheme 2. Synthesis of 5-phenylamino-7*H*-thiopyrano[3,4-d]pyridazine derivatives **16a** and **16b**.

atives that take part in asymmetric hetero Diels-Alder reaction. In this work, we are using 1,3,4-thiadiazine derivatives as precursors for thiopyran derivatives in a one-pot reaction. Thus, compounds **4a, b** underwent [4 + 2] cycloaddition when treated with either acrylonitrile (**5a**) or ethyl acrylate (**5b**) in 1,4-dioxan/acetic acid mixture to give the 4*H*-thiopyran derivatives **7a, b** via the intermediate formation of **6a, b**. The structures of compounds **7a, b** are based on analytical and spectral data. Thus, the ^{13}C-NMR spectrum of **7a** showed δ 29.2, 98.6, 117.3, 140.6 (thiopyran C), 116.8 (CN), 118.3, 119.6, 120.7, 126.5, 129.8, 129.9, 130.4, 136.7 (two phenyl C). Further structure elucidations were obtained through studying the reactivity of **7a, c** towards some chemical reagents. The reaction of **7a** or **7c** with either malononitrile (**8a**) or ethyl cyanoacetate (**8b**) gave the Michael adducts **9a – d**, respectively (Scheme 1). The analytical and spectral data are in agreement with the proposed structures (see Experimental, section 3). Compounds **9c** and **9d** underwent ready cyclization in sodium ethoxide solution to give the benzo[*c*]thiopyran derivatives **10a, b**.

The reaction of **7a** or **7c** with either hydrazine hydrate (**11a**) or phenylhydrazine (**11b**) gave the amidrazone derivatives **12a** and **12b**, respectively. Structures of the latter products were based on analytical and spectral data (see Experimental, section 3). The reaction of either **12a** or **12c** with ethyl orthoformate in concentrated sulfuric acid in a boiling water bath afforded the 7*H*-thiopyrano[3,4-*d*]pyridazine derivatives **14a** and **14b**, respectively. Similarly, the reaction of either **12a** or **12c** with benzoyl chloride (**15**) gave the 5-phenylamino-7*H*-thiopyrano[3,4-d]pyridazine derivatives **16a** and **16b**, respectively (Scheme 2). The analytical and spectral data of compounds **14a, b** and **16a, b** are the basis of their structure elucidations (see Experimental, section 3).

The reaction of **7a** or **7c** with 2-amino-1,1,3-tricyanopropene (**17**) gave the 2-(4*H*-thiopyran-4-yl)-pyridine deriv-



Scheme 3. New procedure for the synthesis of thiopyranyltriazole derivatives.

atives **19a** and **19b**, respectively. The reaction took place through the intermediate formation of **18a, b** followed by Michael addition. On the other hand, the reaction of either **7a** or **7c** with 4-phenyl-3-thiosemicarbazide (**1**) gave the 4-phenyl-3-thiosemicarbazone derivatives **20a** and **20b**, respectively. The latter products readily underwent cyclization when heated under reflux in 1,4-dioxan containing triethylamine to afford the 4*H*-thiopyrano-4-yl-1,3,4-triazole derivatives **21a** and **21b**, respectively. The reaction shows a new procedure for the synthesis of thiopyranyltriazole derivatives (Scheme 3). The structures were confirmed on the basis of ^{1}H- and ^{13}C-NMR analyses (see Experimental, section 3).

Bioassay

Materials and methods: test organisms

The fungi selected for this study were *Fusarium oxysporum* f.sp. *Lycoperici* (SACC) and *Helminthosporium oryea* (*Cochliobolus miyabeanus*). The former organism, an important plant pathogen causing tomato wilt in Egypt, was isolated from infected tomato plants. The latter organism was isolated from infected rice plants.

The newly synthesized products were dissolved in aqueous ethanol to give a logarithmic series of concentrations from 2 to 256 mg/L upon tenfold dilution with the growth medium and spore suspension of the test fungi. The toxicity of compounds was determined by sporeling growth bioassay described by Spendley and Ride [19] which is based on the technique of Skipp and Bailey [20], a suspension of fungal spores was prepared in water and pipetted into the wells of multi-well slides, followed with 25 μL of the culture medium. The inoculated slides were then incubated at 25°C until short germ tubes appeared; approximately 50 μm in length was calculated (at 0 h). 5 μL volumes of the prepared compound test solutions were added to the inoculated wells, one control well on each slide being treated with solvent only. The slides were then returned to the incubator until germ tubes 400 ± 50 μm in length were visible in the control wells. Further growth was arrested by the addition of lactophenol aniline blue to each of the wells. Based on these assays, the percent inhibition of germ-tube growth (with respect to the controls) was plotted against the logarithm of concentration of each compound. From this, the concentrations producing 50% inhibition (ED_{50}) and 100% inhibition (MLD) were directly obtained. When the ED_{50} or MLD values exceeded the maximum concentrations of the compound used, extrapolation was performed when the last point was within 5% of the ED_{50} or MLD line, otherwise the result was expressed as >256 mg/L.

Growth

Since some compounds are lethal at relatively high doses and others at lower doses, comparison of the effect of compound on the growth, sporulation, and nucleic acid synthesis of the test fungi was undertaken at a concentration of 64 mg/L.

A series of conical flasks (250 mL capacity) containing 50 mL Czapek-Dox liquid medium were used for each fungus. Each of three flasks was supplemented with 64 mg/L of each compound. The flasks were inoculated with a 5 mm-diameter agar disc cut from the margin of actively growing colonies. The flasks were incubated at 28°C for seven days after which the produced mycelial felts were collected, washed several times with distilled water and oven-dried at 80°C to constant mass.

Sporulation

Plates of Czapek-Dox agar supplemented with 64 mg/L of each compound were inoculated with a 5 mm-diameter agar disc of the used fungus. The plates were then incu-

bated for seven days at 28°C. A 1 cm^2 section was cut from the margin of the colony and transferred to a vial containing 10 mL sterile distilled water. The suspension was spontaneously shaken for 5 min and the concentration of spores per mL was counted in a hemocytometer. Three plates were used for each treatment.

Nucleic acids

The nucleic acids (RNA and DNA) of each fungus were estimated in the mycelia harvested from liquid Czapek-Dox medium amended with 64 mg/L of each thiophene derivative after seven days of incubation at 28°C. The method used for quantitative determination of RNA is that of Ashwell [21]. It depends on a colorimetric analysis of ribose, using the oreintol reaction. The quantitative estimation of DNA depends on measuring the color developed after treating the extracted DNA with diphenylamine reagent.

Most of the tested compounds showed significant toxicity which is dependent on their chemical structure. The toxicity pattern of the compounds toward the two fungi is similar although the levels of compounds that were required to produce ED_{50} and MLD for *Helminthosporium oryzae* were higher than those required for *Fusarium oxyporum* f. sp. *Lycopersici*.

The effect of all tested compounds on growth, sporulation was tested at a concentration of 64 mg/L. Compounds **20a, 20b, 21a, 21b** allowed good mycelial growth, sporulation by the two fungi. This indicates that the two fungi can use the N-containing heterocyclic ring as a nitrogen source.

The toxicity of the newly synthesized products were measured by Professor S. A. Ouf, his kind help is greatly appreciated.

Experimental

All melting points were determined in open capillaries and are uncorrected. IR spectra were measured using KBr discs on a Pye Unicam SP-1000 spectrophotometer (Pye Unicam Ltd. Cambridge, England). ^{1}H-NMR and ^{13}C-NMR spectra was measured on a Varian EM390-200 MHz instrument (Varian Inc., Palo Alto, CA, USA) in CD_3SOCD_3 as solvent using TMS as internal standard, and chemical shifts are expressed as d ppm.

1-ω-Bromo(4-methyl-acetophenone)-4-phenyl-3-thiosemicarbazone 3a; and 1-a-chloroacetone-4-phenyl-3-thiosemicarbazone 3b

General procedure: To a solution of compound **1** (1.67 g, 0.01 mol) in absolute ethanol (40 mL) either **2a** (2.0 g, 0.01 mol) or **2b** (0.92 g, 0.01 mol) was added. The reaction mixture was stirred at room temperature over night. The solid product, formed upon pouring onto ice/water, was collected by filtration.

*Compound **3a***

White crystals from ethanol, yield 68% (2.46g), m. p. 148°C; Analysis for $C_{16}H_{16}BrN_3S$ (362.29). Anal. Calcd.: C, 53.04; H, 4.45; N, 11.60; S, 8.85. Found: C, 53.43; H, 4.21; N, 11.94; S, 8.58. IR (υ/cm^{-1}): 3478-3321 (2 NH), 3058 (CH aromatic), 1663 (C=N), 1638 (C=C), 1204 – 1194 (CS); ^{1}H-NMR (δ ppm): 2.89 (s, 3H, CH_3), 5.21 (s, 2H, CH_2), 7.32 – 7.45 (m, 9H, C_6H_5, C_6H_4), 8.36, 8.49 (2s, 2H, 2NH).

*Compound **3b***

Colorless crystals from ethanol, yield 73% (1.76 g), m. p. 180°C. Analysis for $C_{10}H_{12}ClN_3S$ (241.74). Anal. Calcd.: C, 49.68; H, 5.00; N, 17.38; S, 13.26. Found: C, 49.91; H, 4.68; N, 17.05; S, 12.94. IR (υ/cm^{-1}): 3466-3319 (2 NH), 3050 (CH aromatic), 1660 (C=N), 1639 (C=C), 1208-1196 (CS); ^{1}H-NMR (δ ppm): 3.04 (s, 3H, CH_3), 5.09 (s, 2H, CH_2), 7.33-7.39 (m, 5H, C_6H_5), 8.32, 8.47 (2s, 2H, 2NH).

2-Phenylamino-5-(4-methylphenyl)-6H-1,3,4-thiadiazine 4a; and 2-Phenyl-amino-5-methyl-6H-1,3,4-thiadiazine 4b

General procedure: A suspension of either **3a** (3.62 g, 0.01 mol) or **3b** (2.41 g, 0.01 mol) in sodium ethoxide solution (0.02 mol) [obtained by dissolving sodium metal (0.46 g, 0.01 mol) in absolute ethanol (40 mL)] was heated in a boiling water bath for 8 h, then left to cool. The solid product, formed in each case, obtained upon pouring onto ice/water containing a few drops of hydrochloric acid (till pH 7) was collected by filtration.

*Compound **4a***

Yellow crystals from 1,4-dioxan, yield 5% (1.54 g), m. p. 223 – 226°C. Analysis for $C_{16}H_{15}N_3S$ (281.38). Anal. Calcd.: C, 68.30; H, 5.37; N, 14.93; S, 11.40. Found: C, C, 68.52; H, 5.77; N, 15.41; S, 11.82. IR (υ/cm^{-1}): 3466 – 3328 (NH), 3056 (CH aromatic), 1636 (C=C); ^{1}H-NMR (δ ppm): 2.72 (s, 3H, CH_3), 3.44 (s, 2H, thiadiazine CH_2), 7.30 – 7.43 (m, 9H, C_6H_5, C_6H_4); ^{13}C-NMR δ: 23.9 (CH_3), 28.8 (thiadiazine CH_2), 116.9, 118.7, 129.9, 131.4, 134.5, 140.2, 144.8 (C_6H_5, C_6H_4), 162.9, 164.4 (2 C=N).

*Compound **4b***

Pale yellow crystals from 1,4-dioxan, yield 60% (1.23 g), m. p. >300°C. Analysis for $C_{10}H_{11}N_3S$ (205.28). Anal. Calcd.: C, 58.51; H, 5.40; N, 20.47; S, 15.62. Found: C, 58.22; H, 5.27; N, 20.56; S, 15.98. IR (υ/cm^{-1}): 3456-3312 (NH), 3058 (CH aromatic), 1641 (C=C); ^{1}H-NMR (δ ppm): 2.89 (s, 3H, CH_3), 3.46 (s, 2H, thiadiazine CH_2), 7.33-7.38 (m, 5H, C_6H_5).

4-Cyano-2-phenylamino-5-(4-methylphenyl)-4H-thiopyran 7a; Ethyl 2-phenylamino-5-(methylphenyl)-4H-thiopyran-4-carboxylate 7b; 4-Cyano-2-phenylamino-5-methyl-4H-thiopyran 7c; and Ethyl 2-phenylamino-5-methyl-4H-thiopyran-4-carboxylate 7d

General procedure: To a solution of either **4a** (2.81 g, 0.01 mol) or **4b** (2.05 g, 0.01 mol) in 1,4-dioxan (50 mL) containing glacial acetic acid (10 mL) either acrylonitrile (0.53 g, 0.01 mol) or ethyl acrylate (1.00 g, 0.01 mol) was added. The reaction mixture in each case was heated under reflux for 8 h, then left to cool. The

solid product formed after evaporating around 60% of the solvent and cooling was collected by filtration.

*Compound **7a***

Yellow crystals from acetic acid, yield 70% (2.13 g), m. p. 187 – 191°C. Analysis for $C_{19}H_{16}N_2S$ (304.41). Anal. Calcd.: C, 74.97; H, 5.30; N, 9.20; S, 10.53. Found: C, 75.33; H, 5.20; N, 8.95; S, 10.44. IR (υ/cm^{-1}): 3462 – 3318 (NH), 3062 (CH aromatic), 2225 (CN), 1640 (C=C); ^{1}H-NMR (δ ppm): 2.82 (s, 3H, CH_3), 4.38 (m, 1H, thiopyran H-4), 6.23 – 6.70 (m, 2H, thiopyran H-3, H-6), 7.30 – 7.48 (m, 9H, C_6H_5, C_6H_4)), 8.36 (s, 1H, NH); ^{13}C NMR δ: 29.2, 98.6, 117.3, 140.6 (thiopyran C), 116.8 (CN), 118.3, 119.6, 120.7, 126.5, 129.8, 129.9, 130.4, 136.7 (two phenyl C).

*Compound **7b***

Yellow crystals from acetic acid, yield 72% (2.57 g), m. p. 180 – 184°C, Analysis for $C_{21}H_{21}NO_2S$ (351.46). Anal. Calcd.: C, 71.76; H, 6.02; N, 3.99; S, 9.12. Found: C, 72.05; H, 5.83; N, 4.21; S, 8.89. IR (υ/cm^{-1}): 3464 – 3337 (NH), 3056 (CH aromatic), 1687 (CO), 1638 (C=C); ^{1}H-NMR (δ ppm): 1.14 (t, 3H, J = 6.77 Hz, CH_3), 2.79 (s, 3H, CH_3), 4.23 (q, 2H, J = 6.77 Hz, CH_2), 4.41 (m, 1H, thiopyran H-4), 6.32-6.67 (m, 2H, thiopyran H-3, H-6), 6.82-7.38 (m, 9H, C_6H_5, C_6H_4), 8.30 (s, 1H, NH).

*Compound **7c***

Yellow crystals from acetic acid, yield 68% (1.96 g), m. p. 266-269°C. Analysis for $C_{13}H_{12}N_2S$ (228.31). Anal. Calcd.: C, 68.39; H, 5.30; N, 12.27; S, 14.04. Found: C, 68.66; H, 5.02; N, 12.52; S, 13.78. IR (υ/cm^{-1}): 3470 – 3323 (NH), 3060 (CH aromatic), 2220 (CN), 1641 (C=C); ^{1}H-NMR (δ ppm): 2.78 (s, 3H, CH_3), 4.29 (s, 1H, thiopyran H-4), 6.30-6.77 (m, 2H, thiopyran H-3, H-6), 7.33-7.38 (m, 5H, C_6H_5), 8.26 (s, 1H, NH).

*Compound **7d***

Orange crystals from 1,4-dioxan, yield 60% (1.65 g), m. p. 144°C. Analysis for $C_{15}H_{17}NO_2S$ (275.37). Anal. Calcd.: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.07;H, 5.97; N, 5.17;S, 11.62. IR (υ/cm^{-1}): 3458 – 3322 (NH), 3054 (CH aromatic), 1689 (CO), 1636 (C=C); ^{1}H-NMR (δ ppm): 1.15 (t, 3H, J = 7.03 Hz, CH_3), 2.79 (s, 3H, CH_3), 4.24 (q, 2H, J = 7.03 Hz, CH_2), 4.43 (m, 1H, thiopyran H-4), 6.34-6.64 (m, 2H, thiopyran H-3, H-6), 6.88-7.37 (m, 5H, C_6H_5), 8.29 (s, 1H, NH).

4-(β-Amino-a-cyanoacrylonitrilo)-2-phenylamino-5-(4-methylphenyl)-4H-thiopyran 9a, 4-(Ethyl-amino-a-cyanoacrylate)-2-phenylamino-5-(4-methylphenyl)-4H-thiopyran 9b, 4-(ß-Amino-a-cyanoacrylonitrilo)-2-phenyl-amino-5-methyl-4H-thiopyran 9c; and 4-(Ethyl-ß-Amino-a-cyanoacrylate)-2-phenylamino-5-methyl-4H-thiopyran 9d

General procedure: A solution of either **7a** (3.04 g, 0.01 mol) or **7c** (2.28 g, 0.01 mol) in 1,4-dioxan (50 mL) containing triethylamine (0.50 mL) either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then evaporated *in vacuo*. In each case, the remaining product was triturated with ethanol and the formed solid product was collected by filtration.

*Compound **9a***

Pale brown crystals from 1,4-dioxan, yield 80% (2.96 g), m. p. 180 – 184°C. Analysis for $C_{22}H_{18}N_4S$ (370.47). Anal. Calcd.: C, 71.32; H, 4.90; N, 15.12; S, 8.66. Found: C, 71.64; H, 5.32; N, 15.06; S, 8.41. IR (υ/cm^{-1}): 3440 – 3312 (NH_2, NH), 3050 (CH aromatic), 2222, 2220 (2 CN), 1638 (C=C); ^{1}H-NMR (δ ppm): 2.83 (s, 3H, CH_3), 4.22 (s, 2H, NH_2), 4.46 (m, 1H, thiopyran H-4), 6.36 – 6.65 (m, 2H, thiopyran H-3, H-6), 7.22-7.37 (m, 9H, C_6H_5, C_6H_4), 8.32 (s, 1H, NH).

*Compound **9b***

Yellowish orange crystals from 1,4-dioxan, yield 68% (2.84 g), m. p. 211 – 214°C. Analysis for $C_{24}H_{23}N_3O_2S$ (417.52). Anal. Calcd.: C, 69.04; H, 5.55; N, 10.06; S, 7.68. Found: C, 68.73; H, 5.28; N, 9.84; S, 7.29. IR (υ/cm^{-1}): 3454 – 3322 (NH_2, NH), 3052 (CH aromatic), 1641 (C=C); ^{1}H-NMR (δ ppm): 1.13 (t, 3H, J = 7.04 Hz, CH_3), 2.96 (s, 3H, CH_3), 4.20 (s, 2H, NH_2), 4.26 (q, 2H, J = 7.04 Hz, CH_2), 4.50 (m, 1H, thiopyran H-4), 6.33 – 6.67 (m, 2H, thiopyran H-3, H-6), 7.20 – 7.42 (m, 9H, C_6H_5, C_6H_4), 8.38 (s, 1H, NH).

*Compound **9c***

Yellow crystals from acetic acid, yield 73% (2.14 g), m. p. 177°C. Analysis for $C_{16}H_{14}N_4S$ (294.37). Anal. Calcd.: C, 65.28; H, 4.79; N, 19.03; S, 10.89. Found: C, 64.98; H, 4.66; N, 18.87; S, 11.26. IR (υ/cm^{-1}): 3466 – 3320 (NH_2, NH), 3055 (CH aromatic), 2225 (CN), 1638 (C=C); ^{1}H-NMR (δ ppm): 2.99 (s, 3H, CH_3), 4.36 (s, 2H, NH_2), 4.55 (m, 1H, thiopyran H-4), 6.31 – 6.64 (m, 2H, thiopyran H-3, H-6), 7.31 – 7.38 (m, 5H, C_6H_5), 8.36 (s, 1H, NH).

*Compound **9d***

Yellow crystals from ethanol, yield 76% (2.59 g), m. p. 222 – 225°C. Analysis for $C_{18}H_{19}N_3O_2S$ (341.43). Anal. Calcd.: C, 63.32; H, 5.61; N, 12.31; S, 9.39. Found: C, 63.11; H, 5.78; N, 12.09; S, 9.56. IR (υ/cm^{-1}): 3457 – 3318 (NH_2, NH), 3058 (CH aromatic), 1633 (C=C); ^{1}H-NMR (δ ppm): 1.14 (t, 3H, J = 6.77 Hz, CH_3), 4.23 (q, 2H, J = 6.77 Hz, CH_2), 2.87 (s, 3H, CH_3), 4.40 (s, 2H, NH_2), 4.58 (m, 1H, thiopyran H-4), 6.33 – 6.62 (m, 2H, thiopyran H-3, H-6), 7.33 – 7.39 (m, 5H, C_6H_5), 8.34 (s, 1H, NH).

5-Cyano-4,6-Diamino-2-phenylamino-8H-benzo[d]thiopyran 10a and Ethyl-4-amino-2-phenylamino-8H-benzo[d]thiopyran-6-carboxylate 10b

A suspension of either **9c** (2.94 g, 0.01 mol) or **9d** (3.41 g, 0.01 mol) in sodium ethoxide (0.02 mol) [obtained by dissolving sodium metal (0.46 g, 0.02 mol) in absolute ethanol (40 mL)] was heated in a boiling water bath for 5 h. The solid product formed upon pouring onto ice/water containing few drops of hydrochloric acid (till pH 6) was collected by filtration.

*Compound **10a***

Pale yellow crystals from DMF, yield 76% (2.23 g), m. p. >300°C. Analysis for $C_{16}H_{14}N_4S$ (294.37), Anal. Calcd.: C, 65.28; H, 4.79; N, 19.03; S, 10.89. Found: C, 65.44; H, 5.14; N, 18.82; S, 10.68. IR (υ/cm^{-1}): 3462 – 3332 (2 NH_2), 3056 (CH aromatic), 2222 (CN), 1633 (C=C); ^{1}H-NMR (δ ppm): 4.22, 4.83 (2s, 4H, 2NH_2), 4.37 (m, 2H, thiopyran CH_2), 5.99, 6.88 (2s, 2H, thiopyran H-3, benzene CH), 7.28–7.38 (m, 5H, C_6H_5), 8.66 (s, 1H, NH); ^{13}C-NMR: 44.8 (thiopyran CH_2), 80.4 (thiopyran C-3) 116.2 (CN), 118.9, 119.2, 120.5, 129.3, 134.1, 135.7, 142.6, 143.8, 144.6, 148.8 (aromatic C).

*Compound **10b***

Orange crystals from 1,4-dioxan, yield 70% (2.06 g), m. p. 245 – 247°C. Analysis for $C_{16}H_{13}N_3OS$ (295.36). Anal. Calcd.: C, 65.06; H, 4.44; N, 14.23; S, 10.86. Found: C, 64.69; H, 4.28; N, 13.86; S, 11.19. IR (υ/cm^{-1}): 3520 – 3330 (NH_2, OH), 3057 (CH aromatic), 2220 (CN), 1640 (C=C); ^{1}H-NMR (δ ppm): 4.23 (s, 2H, NH_2), 4.57 (m, 2H, thiopyran CH_2), 5.99, 6.39 (2s, 2H, thiopyran H-3, benzene CH), 7.25-7.40 (m, 5H, C_6H_5), 8.78 (s, 1H, NH), 10.88 (s, 1H, OH).

4-Amidrazono-2-phenylamino-5-(4-methylphenyl)-4H-thiopyran 12a; 4-Phenyl-amidrazono-2-phenylamino-5-(4-methylphenyl)-4H-thiopyran 12b; 4-Amidrazono-2-phenylamino-5-methyl-4H-thiopyran 12c; and 4-Phenylamidrazono-2-phenylamino-5-methyl-4H-thiopyran 12d

General procedure: To a solution of either **7a** (3.04 g, 0.01 mol) or **7c** (2.28 g, 0.01 mol) in dimethylformamide (30 mL) either hydrazine hydrate (0.50 mL, 0.01 mol) or phenylhydrazine (1.08 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h then poured onto ice/water containing few drops of hydrochloric acid. The precipitated solid product was collected by filtration.

*Compound **12a***

Pale yellow crystals from 1,4-dioxan, yield 80% (2.68 g), m. p. 244 – 247°C. Analysis for $C_{19}H_{20}N_4S$ (336.45). Anal. Calcd.: C, 67.83; H, 5.99; N, 16.65; S, 9.53. Found: C, 67.77; H, 6.11; N, 16.35; S, 9.53. IR (υ/cm^{-1}): 3455 – 3329 (2 NH_2, NH), 3054 (CH aromatic), 2986 (CH_3), 1670 (C=N), 1636 (C=C); ^{1}H-NMR (δ ppm): 2.74 (s, 3H, CH_3), 2.90 (d, 1H, J = 2.84 Hz, thiopyran H-4), 4.20, 5.31 (2s, 4H, $2NH_2$), 6.01 (d, 1H, J = 2.84 Hz, thiopyran H-3), 7.28 – 7.38 (m, 10H, C_6H_5, C_6H_4, thiopyran H-6), 8.32 (s, 1H, NH).

*Compound **12b***

Reddish brown crystals from 1,4-dioxan, yield 69% (2.84 g), m. p. 180 – 182°C. Analysis for $C_{25}H_{24}N_4S$ (412.55). Anal. Calcd.: C, 72.78; H, 5.86; N, 13.58; S, 7.77. Found: C, 72.69; H, 6.11; N, 13.47; S, 8.09. IR (υ/cm^{-1}): 3473 – 3321 (NH_2, 2NH), 3060 (CH aromatic), 2877 (CH_3), 1667 (C=N), 1643 (C=C); ^{1}H-NMR (δ ppm): 2.79 (s, 3H, CH_3), 2.89 (d, 1H, J = 2.77 Hz, thiopyran H-4), 4.21 (s, 2H, NH_2), 6.12 (d, 1H, J = 2.77 Hz, thiopyran H-3), 7.22-7.48 (m, 10H, C_6H_5, C_6H_4, thiopyran H-6), 8.30, 8.51 (2s, 2H, 2NH).

*Compound **12c***

Yellow crystals from acetic, yield 70% (1.82 g), m. p. 160°C. Analysis for $C_{13}H_{16}N_4S$ (260.36). Anal. Calcd.: C, 59.97; H, 6.19; N, 21.52; S, 12.32. Found: C, 60.33; H, 6.08; N, 21.36; S, 12.22. IR (υ/cm^{-1}): 3467 – 3318 (2 NH_2, NH), 3051 (CH aromatic), 1663 (C=N), 1639 (C=C); ^{1}H-NMR (δ ppm): 2.76 (s, 3H, CH_3), 2.86 (d, 1H, thiopyran H-4), 4.23, 5.35 (2s, 4H, $2NH_2$), 6.17 (d, 1H, thiopyran H-3), 7.24 – 7.37 (m, 6H, C_6H_5, thiopyran H-6), 8.30 (s, 1H, NH).

*Compound **12d***

Orange crystals from DMF, yield 56% (2.22 g), m. p. 140°C. Analysis for $C_{19}H_{20}N_4S$ (336.45). Anal. Calcd.: C, 67.83; H, 5.99; N, 16.65; S, 9.53. Found: C, 67.67; H, 6.21; N, 16.89; S, 9.45. IR (υ/cm^{-1}): 3462 – 3324 (NH_2, 2 NH), 3055 (CH aromatic), 2880 (CH_3), 1668 (C=N), 1633 (C=C); ^{1}H-NMR (δ ppm): 2.69 (s, 3H, CH_3), 2.82 (d, 1H, J = 3.01 Hz, pyran H-4), 4.25 (s, 2H, NH_2), 6.09 (d, 1H, J = 3.01 Hz, thiopyran H-3), 7.21 – 7.42 (m, 11H, $2C_6H_5$, thiopyran H-6), 8.33, 8.41 (2s, 2H, 2NH).

1-Amino-5-phenylamino-8-(4-methylphenyl)-7H-thiopyrano[d]pyridazine 14a; 1-Amino-5-phenylamino-4-methyl-7H-thiopyrano[d]pyridazine 14b

General procedure: To a solution of either **12a** (3.36 g, 0.01 mol) or **12c** (2.60 g, 0.01 mol) in concentrated sulfuric acid (10 mL), ethyl orthoformate (0.58 g, 0.01 mol) was added. The reaction mixture was heated in a boiling water bath for 40 min then left to cool. The whole mixture was poured onto ice/water and the formed solid product was collected by filtration.

*Compound **14a***

Buff crystals from DMF, yield 75% (2.61 g), m. p. 166°C. Analysis for $C_{20}H_{18}N_4S$ (346.45). Anal. Calcd.: C, 69.34; H, 5.24; N, 16.17; S, 9.26. Found: C, 69.22; H, 5.54; N, 16.08; S, 8.93. IR (υ/cm^{-1}): 3448 – 3312 (NH_2, NH), 3056 (CH aromatic), 1662 (C=N), 1632 (C=C); ^{1}H-NMR (δ ppm): 2.81 (s, 3H, CH_3), 2.88 (d, 1H, J = 2.76 Hz, thiopyran H-4), 4.34 (s, 2H, NH_2), 7.21 – 7.42 (m, 11H, C_6H_5, C_6H_4, pyridazine H-3, thiopyran H-6), 8.22 (s, 1H, NH).

*Compound **14b***

Pale brown crystals from DMF, yield 56% (1.51 g), m. p. 222 – 225°C. Analysis for $C_{14}H_{14}N_4S$ (270.35). Anal. Calcd.: C, 62.20; H, 5.22; N, 20.72; S, 11.86. Found: C, 62.56; H, 5.43; N, 20.92; S, 11.67. IR (υ/cm^{-1}): 3466 – 3329 (NH_2, NH), 3055 (CH aromatic), 2879 (CH_3), 1656 (C=N), 1640 (C=C); ^{1}H-NMR (δ ppm): 2.84 (s, 3H, CH_3), 2.83 (d, 1H, J = 2.81 Hz, thiopyran H-4), 4.09 (s, 2H, NH_2), 7.20–7.34 (m, 7H, C_6H_5, pyridazine H-3, thiopyran H-6), 8.30, (s, 1H, NH).

1-Amino-4-phenyl-5-phenylamino-8-(4-methylphenyl)-7H-thiopyrano-[d]pyridazine 16a; and 1-Amino-4-phenyl-5-phenylamino-4-methyl-7H-thiopyrano[d]pyridazine 16b

General procedure: To a solution of either **12a** (3.36 g, 0.01 mol) or **12c** (2.60 g, 0.01 mol) in pyridine (50 mL) in an ice bath (0 – 5°C), benzoyl chloride (1.45 g, 0.01 mol) was added drop-wise with continuous stirring for 20 min. The whole reaction mixture was heated under reflux for 1 h then poured onto ice/water containing few drops of hydrochloric acid.

*Compound **16a***

Buff crystals from 1,4-dioxan, yield 80% (3.37 g), m. p. 222 – 226°C. Analysis for $C_{26}H_{22}N_4S$ (422.54). Anal. Calcd.: C, 73.90; H, 5.25; N, 13.26; S, 7.59. Found: C, 74.26; H, 5.01; N, 13.31; S, 7.82. IR (υ/cm^{-1}): 3472 – 3334 (NH_2, NH), 3050 (CH aromatic), 1658 (C=N), 1639 (C=C); ^{1}H-NMR (δ ppm): 2.88 (s, 3H, CH_3), 2.91 (d, 1H, J = 2.79 Hz, thiopyran H-4), 4.32 (s, 2H, NH_2), 7.20 – 7.40 (m, 15H, $2C_6H_5$, C_6H_4, thiopyran H-6), 8.28 (s, 1H, NH).

*Compound **16b***

Brown crystals from 1,4-dioxan, yield 66% (2.28 g), m. p. 190 – 193°C. Analysis for $C_{20}H_{18}N_4S$ (346.45). Anal. Calcd.: C, 69.34; H, 5.24; N, 16.17; S, 9.26. Found: C, 69.22; H, 5.09; N, 16.35; S, 9.52. IR (υ/cm^{-1}): 3456 – 3333 (NH_2, NH), 3058 (CH aromatic), 1660 (C=N), 1637 (C=C); ^{1}H-NMR (δ ppm): 2.88 (s, 3H, CH_3), 2.80 (d, 1H, J

= 2.80 Hz, thiopyran H-4), 4.13 (s, 2H, $2NH_2$), 7.25 – 7.44 (m, 11H, $2C_6H_5$, thiopyran H-6), 8.37 (s, 1H, NH).

2,4-Diamino-3,5-dicyano-6-(2-phenylamino-5-(4-methylphenyl)-4H-thiopyran-4-yl)-pyridine 19a; and 2,4-Diamino-3,5-dicyano-6-(2-phenylamino-5-methyl-4H-thiopyran-4-yl)-pyridine 19b

General procedure: To a solution of either **7a** (3.04 g, 0.01 mol) or **7c** (2.28 g, 0.01 mol) in dimethylformamide (30 mL) containing triethylamine (0.50 mL), compound **17** was added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water. In each case, the formed solid product was collected by filtration.

*Compound **19a***

Pale yellow crystals from 1,4-dioxan, yield 70% (3.05 g), m. p. 130°C. Analysis for $C_{25}H_{20}N_6S$ (436.53). Anal. Calcd.: C, 68.78; H, 4.62; N, 19.25; S, 7.35. Found: C, 68.66; H, 4.93; N, 18.90; S, 7.48. IR (υ/cm^{-1}): 3460 – 3329 (2 NH_2, NH), 3053 (CH aromatic), 2225, 2220 (2 CN), 1658 (C=N), 1634 (C=C); ^{1}H-NMR (δ ppm): 2.86 (s, 3H, CH_3), 2.89 (d, 1H, J = 2.78 Hz, thiopyran H-4), 4.30, 4.87 (2s, 4H, 2 NH_2), 5.42 (d, 1H, J = 2.78 Hz, thiopyran H-3), 7.25-7.38 (m, 10H, C_6H_5, C_6H_4, thiopyran H-6), 8.09 (s, 1H, NH).

*Compound **19b***

Yellow crystals from 1,4-dioxan, yield 76% (2.73 g), m. p. 240 – 245°C. Analysis for $C_{19}H_{16}N_6S$ (360.44). Anal. Calcd.: C, 63.31; H, 4.47; N, 23.32; S, 8.90. Found: C, 63.20; H, 4.89; N, 23.64; S, 9.11. IR (υ/cm^{-1}): 3450 – 3322 (2 NH_2, NH), 3053 (CH aromatic), 2891 (CH_3), 2227, 2221 (2 CN), 1664 (C=N), 1632 (C=C); ^{1}H-NMR (δ ppm): 2.91 (s, 3H, CH_3), 2.83 (d, 1H, J = 2.80 Hz, thiopyran H-4), 4.16, 4.78 (2s, 4H, $2NH_2$), 5.44 (d, 1H, J = 2.80 Hz, thiopyran H-3), 7.23 – 7.38 (m, 6H, C_6H_5, thiopyran H-6), 8.37 (s, 1H, NH).

2-Phenylamino-4-(formamido-4-phenyl-3-thiosemicarbazono)-5-(4-methylphenyl)-4H-thiopyran 20a; and 2-Phenylamino-4-(formamido-4-phenyl-3-thiosemicarbazono)-5-methyl-4H-thiopyran 20b

General procedure: To a solution of either **7a** (3.04 g, 0.01 mol) or **7c** (2.28 g, 0.01 mol) in 1,4-dioxan (30 mL) containing triethylamine (0.50 mL), 4-phenyl-3-thiosemicarbazide (1.67 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h then evaporated under vacuum. The remaining product was triturated with diethyl ether and the formed solid product was collected by filtration.

*Compound **20a***

Yellowish white crystals from acetic acid, yield 80% (3.76 g), m. p. 166°C. Analysis for $C_{26}H_{25}N_5S_2$ (471.64). Anal. Calcd.: C, 66.21; H, 5.34; N, 14.85; S, 13.60. Found: C, 66.44; H, 5.82; N, 15.16; S, 13.95. IR (υ/cm^{-1}): 3456 – 3332 (NH_2, 3 NH), 3060 (CH aromatic), 1662 (C=N), 1638 (C=C); ^{1}H-NMR (δ ppm): 2.79 (s, 3H, CH_3), 2.92 (d, 1H, J = 2.66 Hz, thiopyran H-4), 4.33 (s, 1H, NH), 5.31 (d, 1H, J = 2.66 Hz, thiopyran H-3), 5.41 (s, 2H, NH_2), 7.28 – 8.01 (m, 15H, $2C_6H_5$, C_6H_4, thiopyran H-6), 8.28, 8.34 (2s, 2H, 2NH).

*Compound **20b***

Yellow crystals from acetic acid, yield 82% (3.24 g), m. p. 120°C. Analysis for $C_{20}H_{21}N_5S_2$ (396.54). Anal. Calcd.: C, 60.73; H, 5.35; N, 17.71; S, 16.21. Found: C, 60.47; H, 5.82; N, 18.09; S, 16.34. IR (υ/cm^{-1}): 3474 – 3338 (NH_2, 3NH), 3057 (CH aromatic), 2888 (CH_3), 1657 (C=N), 1641 (C=C); ^{1}H-NMR (δ ppm): 2.65 (s, 3H, CH_3), 2.90 (d, 1H, J = 2.57 Hz, thiopyran H-4), 4.30 (s, 1H, NH), 5.36 (d, 1H, J = 2.57 Hz, thiopyran H-3), 5.45 (s, 2H, NH_2), 7.25 – 7.37 (m, 11H, $2C_6H_5$, thiopyran H-6), 8.26, 8.37 (2s, 2H, 2NH).

4-Phenylamino-3-(2-phenylamino-5-(4-methylphenyl)-4H-thiopyran-4-yl)-1,2,4-triazole 21a; and 4-Phenylamino-3-(2-phenylamino-5-methyl-4H-thiopyran-4-yl)-1,2,4-triazole 21b

General procedure: A solution of either **20a** (4.71 g, 0.01 mol) or **20b** (3.96 g, 0.01 mol) in 1,4-dioxan (40 mL) containing triethylamine (1.0 mL) was heated under reflux for 5 h then poured onto ice water. The formed solid product was collected by filtration.

*Compound **21a***

Pale yellow crystals from acetic acid, yield 77% (2.59 g), m. p. >300°C. Analysis for $C_{26}H_{23}N_5S$ (437.56). Anal. Calcd.: C, 71.37; H, 5.30; N, 16.01; S, 7.33. Found: C, 71.66; H, 5.47; N, 15.98; S, 7.05. IR (υ/cm^{-1}): 3477 – 3341 (3 NH), 3063 (CH aromatic), 1660 (C=N), 1640 (C=C); ^{1}H-NMR (δ ppm): 2.83 (s, 3H, CH_3), 2.90 (d, 1H, J = 2.39 Hz, thiopyran H-4), 4.36 (s, 1H, NH), 5.30 (d, 1H, J = 2.39 Hz, thiopyran H-3), 7.29 – 7.57 (m, 15H, $2C_6H_5$, C_6H_4, thiopyran H-6), 8.28, 8.34 (2s, 2H, 2NH); ^{13}C-NMR: 26.7 (CH_3), 44.6 (thiopyran C-4), 92.7 (thiopyran C-3), 117.0, 118.9, 119.2, 122.7, 126.5, 127.8, 129.0, 133.3, 134.7, 136.2, 143.8, 144.9 (2 C_6H_5, C_6H_4, thiozole C-3, C-5, thiopyran C-2, C-6), 159.9, 164.7 (2 C=N).

*Compound **21b***

Yellow crystals from acetic acid, yield 50% (1.80 g), m. p. 188 – 193°C. Analysis for $C_{20}H_{19}N_5S$ (361.46). Anal. Calcd.: C, 66.46; H, 5.30; N, 19.37; S, 8.87. Found: C, 66.45, H, 5.21; N, 19.32; S, 8.45. IR (υ/cm^{-1}): 3456 – 3323 (3 NH), 3055 (CH aromatic), 2980 (CH_3), 1655 (C=N), 1643 (C=C); ^{1}HNMR ((δ ppm): 2.74 (s, 3H, CH_3), 2.93 (d, 1H, thiopyran H-4), 4.33 (s, 1H, NH), 5.32 (d, 1H, thiopyran H-3), 7.27 – 7.45 (m, 11H, $2C_6H_5$, thiopyran H-6), 8.29, 8.33 (2s, 2H, 2NH).

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