Synthesis of 2,2′-(1,4-Phenylene)bis-3,4-dihydro-2*H*-1,3-thiazin-4-ones and their Facile Recyclization to 2,2′-(1,4-Phenylene)bis(pyrimidin-4-one) and/or 2,2′-(1,4-Phenylene)-bis-(thieno[2,3-*d*]pyrimidin-4(1*H*)-one) Derivatives

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An efficient and direct procedure for the synthesis of 2,2′-(1,4-phenylene)bis-3,4-dihydro-2*H*-1,3-thiazin-4-one derivatives is described. Oxidation of the latter and their base-catalyzed recyclization has been studied. The products were characterized by elemental analyses, and IR, ^{1}H NMR, and ^{13}C NMR spectra.

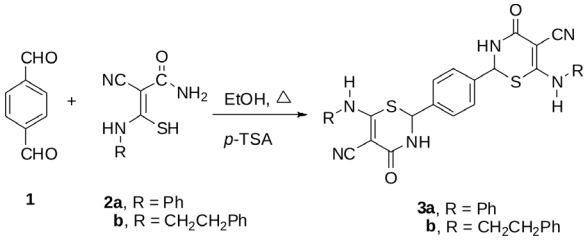
Key words: Terephthalaldehyde, Cyanoacetamide, Phenyl (Phenethyl) Isothiocyanate, Bis-1,3-thiazin-4-one, Bis-pyrimidin-4-one, Bis-thieno[2,3-*d*]pyrimidin-4-one

Introduction

1,3-Thiazines are an important type of heterocycles showing a wide variety of pharmacological properties. Thus, 1,3-thiazine derivatives have recently been reported as cholecystokinin antagonists [1], antimycobacterial agents [2], cannabinoid receptor agonists [3], and inhibitors of NO synthase (NOS) [4], as antibacterial [5], antipyretic [6], anti-inflammatory [6, 7], analgesic [7], antitumor [8], and antioxidant [9] agents, and as calcium channel modulators [10]. Furthermore, the antibiotic activity of cephalosporin is due to the presence of the 1,3-thiazine moiety [11]. A few methods have been reported in the literature for the preparation of 1,3-thiazines [12 – 21], but to the best of our knowledge, there are no reports in the literature for the formation of 2,2′-(1,4-phenylene)bis(3,4-dihydro-2*H*-1,3-thiazin-4-one). Considering the above reports in conjunction with our recent work on the synthesis of bis- [22 – 26] and polyheterocyclic systems [27 – 35], we wish to describe herein an efficient and direct procedure for the synthesis of 2,2′-(1,4-phenylene)bis(3,4-dihydro-2*H*-1,3-thiazin-4-one) derivatives and their base-catalyzed recyclization to bis-pyrimidin-4-one and bis-thieno[2,3-*d*]pyrimidin-4-one derivatives.

Results and Discussion

The bis-1,3-thiazines **3a**, **b** have been synthesized by the cyclocondensation of terephthalaldehyde (**1**) with 2 equivalents of **2a**, **b** in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) in boiling ethanol. High yields of the products **3** also resulted when the reaction was performed in boiling glacial acetic acid (Scheme 1). Compound **2a** was readily prepared by treatment of cyanoacetamide with phenyl isothiocyanate according to a literature procedure [36].



Scheme 1. Synthesis of bis-1,3-thiazines **3**.

The proposed molecular structures of the bis-1,3-thiazines **3a**, **b** are supported by elemental and spectral analyses. For example, compound **3a** exhibits an IR spectrum with strong absorption bands at 3181 (NH), 2206 (CN), and 1645 cm^{-1} (CO). Its ^{1}H NMR spectrum shows a characteristic singlet at δ = 10.18 ppm for the two exocyclic NH protons, a doublet at 8.52 ppm for the two endocyclic NH protons (J = 3 Hz), a multiplet at 7.22 – 7.48 ppm due to the phenyl protons and a doublet at 6.13 ppm for the two thiazine protons (2H, J = 3 Hz). Moreover, the ^{13}C NMR spectrum of **3a** shows signals at δ = 57 (2 × C-2),

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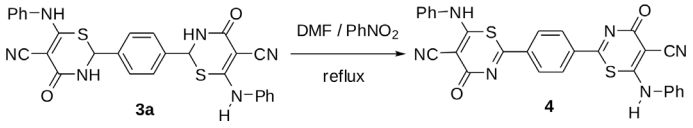
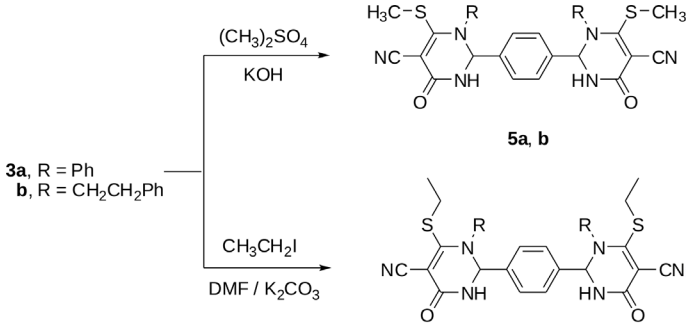
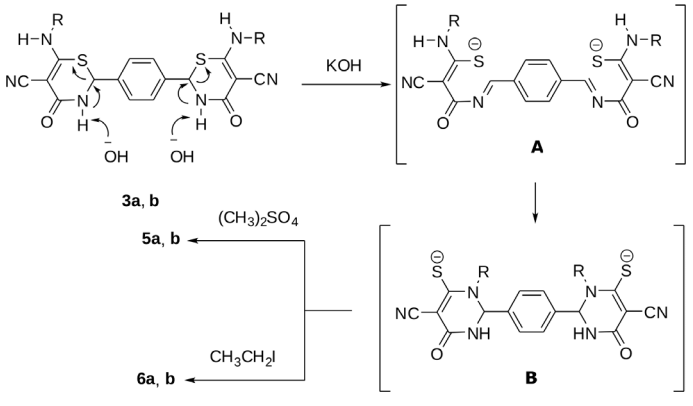


Scheme 2. Oxidation of **3a**.



Scheme 3. Alkylation of **3**.

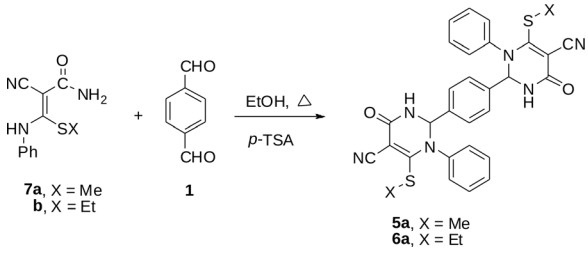


Scheme 4.

77.51 (2 × C-5), 116.18 (CN), 162.07 (2 × C=O), and 164.93 (2 × C-6), in addition to those of the phenyl carbons at δ = 125.48 – 137.79.

Considering the facile oxidation in the presence of nitrobenzene [37], **3a** was converted into **4** in good yield (Scheme 2). The structure **4** was confirmed by elemental analysis and spectral data. The disappearance of 2-H and 3-NH in the ^{1}H NMR spectrum indicated that only these protons were removed from **3a**.

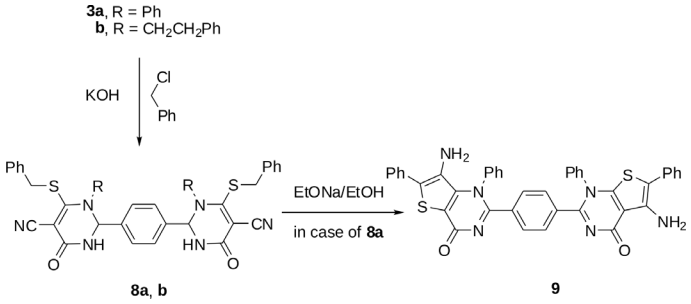
We also studied the alkylation of **3a**, **b** with dimethyl sulfate and/or ethyl iodide under basic conditions. Unexpectedly, the reactions proved to involve the sulfur atom thus affording the *S*-alkylated-bis(pyrimidin-4-one) derivatives **5a**, **b** and/or **6a**, **b**, respectively, in high yields (Scheme 3). The structural assignments of compounds **5** and **6** were confirmed by their spectroscopic data. A distinction between the thiazine and pyrimidine structural types is clearly manifested in the ^{1}H and ^{13}C NMR spectra. For example, the ^{1}HNMR spectrum of



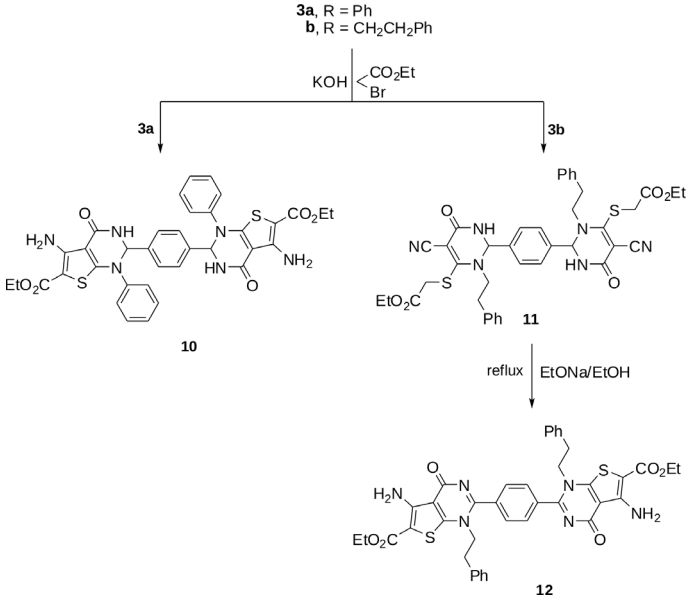
Scheme 5. Synthesis of bis-pyrimidines **5a** and **6a**.

5a showed the absence of exocyclic NH protons, and in its ^{13}C NMR spectrum the resonances of the aminal carbon atoms in compounds **5a** (δ = 73.71) are shifted downfield from those of the thioaminal carbon atoms in compound **3a**.

The transformations shown in Scheme 3 can be accounted for by the following mechanism: A base causes proton abstraction from the nitrogen atom in position 3 and the thiazine ring opening [17]. Then the



Scheme 6. Synthesis of the bis-{thieno[2,3-*d*]-pyrimidin-4(1*H*)-one} **9**.



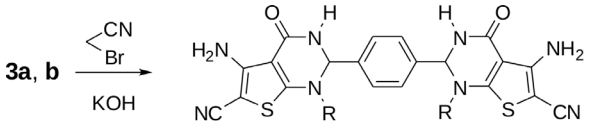
Scheme 7. Synthesis of the bis-{thieno[2,3-*d*]-pyrimidin-4(1*H*)-ones} **10** and **12**.

resulting intermediate **A** cyclizes to the stable thiolate **B**, and alkylation of the latter *in situ* yields products **5** and **6**, respectively (Scheme 4).

Compounds **5** and **6** were prepared independently from 2-cyano-3-(alkylthio)-3-(phenylamino)-acrylamide **7a**, **b** obtained from the reaction of cyanoacetamide with phenyl isothiocyanate in DMF and in the presence of potassium hydroxide, followed by treatment with dimethyl sulfate and/or ethyl iodide. Subsequent reaction of **7a**, **b** with terephthalaldehyde (**1**) in boiling ethanol and in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) afforded **5a** and/or **6a** in excellent yields (Scheme 5). The identity of the products prepared in Scheme 5 with those obtained previously in Scheme 3 was confirmed by comparison of their IR and ^{1}H NMR spectra.

Next, we moved on to develop a facile and convenient route to polyfunctionally substituted thienopyrimidine derivatives using the 1,3-thiazines **3a**, **b** as starting materials. Thus, benzyl chloride, ethyl bromoacetate and bromoacetonitrile were used as alkylating agents for further heterocyclization (Schemes 6 – 8). Benzylation of compounds **3a**, **b** with benzyl chloride in ethanol in the presence of potassium hydroxide gave the *S*-benzylated bis-pyrimidines **8a**, **b** in high yields (Scheme 6). Upon treatment of compound **8a** with sodium ethoxide in ethanol, it underwent intramolecular Thorpe-Ziegler cyclization [38] and partial oxidation to furnish the thienopyrimidine **9** (Scheme 6). Compounds **8a**, **b** and **9** gave satisfactory analytical and spectroscopic data. The IR and ^{1}H NMR spectra of **9** revealed the absence of bands of CN and NH groups and signals attributable to the methylene, methene and NH protons of **8a**, respectively.

Treatment of **3a** with ethyl bromoacetate, in ethanol in the presence of potassium hydroxide, furnished the bis-{thieno[2,3-*d*]pyrimidin-4(1*H*)-one} **10** (Scheme 7).



13a, R = Ph
b, R = CH_2CH_2Ph

Scheme 8. Synthesis of the bis-{thieno[2,3-*d*]pyrimidin-4(1*H*)-one} **13**.

The elemental analysis and the spectral data are in good agreement with the proposed structures. The IR and ^{1}H NMR spectra of **10** revealed the absence of a band of a CN group and of signals attributable to the two exocyclic NH protons of **3a**, respectively.

On the other hand, the condensation of **3b** with ethyl bromoacetate under the previous conditions gave the bis *S*-substituted thiopyrimidine **11**. The cyclization and partial oxidation of **11** to the bis-thienopyrimidine **12** proceeds upon treatment with sodium ethoxide in ethanol (Scheme 7). The structures of **11** and **12** were established on the basis of their correct elemental analyses as well as compatible spectral data. The IR and ^{1}H NMR spectra of **12** revealed the absence of CN and NH groups and of signals attributable to the SCH_2, CH and NH protons of **11**, respectively.

Finally, as described in Scheme 8, the thienopyrimidine derivatives **13a** and **13b** were prepared in aq. KOH by cycloalkylation of **3a**, **b** with bromoacetonitrile. Based on the spectroscopic data, the structure of compound **13** is undoubtedly confirmed.

Experimental Section

General procedures

Melting points were measured with a Gallenkamp apparatus and are uncorrected. The reactions and purity were monitored by thin layer chromatography (TLC) on aluminum plates coated with silica gel with fluorescence indicator (Merck, 60 F_{254}) using $CHCl_3$/CH_3OH (10 : 1) as eluent. The infrared spectra were recorded on a Jasco FT/IR-450 Plus infrared spectrophotometer. The NMR spectra were obtained on a JHA-LAA 400 WB-FT spectrometer (300 MHz for ^{1}H NMR, 75 MHZ for ^{13}C NMR) with deuterated chloroform ($CDCl_3$) or dimethylsulfoxide ([D_6]DMSO) as solvent. Chemical shifts are quoted in δ and are referenced to the solvent signal. Elemental analyses were measured with a Vario EL III CHNOS Elemental Analyzer, Germany, in the Microanalytical Center of Cairo University.

Compounds **2a** [36] and **7a** [39] were synthesized using the published procedures.

*2-Cyano-3-mercapto-3-phenethylamino-acrylamide (**2b**)*

This compound was prepared in 88 % isolated yield by treatment of cyanoacetamide with phenethyl isothiocyanate using the procedure described for the synthesis of **2a** [36]; pale-yellow crystals, m. p. 148 – 150 °C. – IR (film): ν = 3423, 3340, 2185, 1635, 1527 cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.85 (t, 2H, CH_2, J = 7.5 Hz), 3.72 (t, 2H, CH_2, J = 7.5 Hz), 6.97 (s, 2H, NH_2), 7.21 – 7.36 (m, 5H, ArH), 8.78 (s, 1H, SH), 10.45 (brs, 1H, NH).

*2,2′-(1,4-Phenylene)-bis(5-cyano-6-arylamino-3,4-dihydro-2H-1,3-thiazin-4-ones) **3a, b***

Method A: A mixture of terephthalaldehyde (**1**) (1.34 g, 0.01 mol), **2a**, **b** (0.02 mol), and *p*-toluenesulfonic acid (0.076 g, 0.01 mol) in ethanol (20 mL) was refluxed, a pale-yellow precipitate was formed after 30 min, and stirring was continued for 2 h. The precipitate was filtered off, washed with ethanol, dried, and recrystallized from DMF/EtOH.

Method B: A mixture of terephthalaldehyde (**1**) (1.34 g, 0.01 mol) and **2a**, **b** (0.02 mol), in glacial acetic acid (20 mL) was boiled, and a pale-yellow precipitate was formed after 30 min. Stirring was continued for 2 h, the precipitate was filtered off, washed with ethanol, dried, and recrystallized from DMF/EtOH.

*2,2′-(1,4-Phenylene)-bis(5-cyano-6-phenylamino-3,4-dihydro-2H-1,3-thiazin-4-one) (**3a**)*

Yellow powder, yield: method A: 84 %; method B: 81 %, m. p. 286 – 288 °C. – IR (film): ν = 3181, 3064, 2206, 1645, 1548 cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 6.13 (d, 2H, 2CH, J = 3 Hz), 7.22 – 7.48 (m, 14H, ArH), 8.52 (d, 2H, 2NH, J = 3 Hz), 10.18 (s, 2H, 2NH). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 57.49 (C-2, C-2′), 77.51 (C-5, C-5′), 116.18 (2CN), 125.48, 126.82, 127.46, 127.71, 128.91, 129.63, 137.49, 137.56, 137.79 (C-Ar), 162.07 (C=O), 164.93 (C-6, C-6′). – Anal. for $C_{28}H_{20}N_6O_2S_2$: calcd. C 62.67, H 3.76, N 15.66, S 11.95; found C 62.59, H 3.87, N 15.57, S 11.84.

*2,2′-(1,4-Phenylene)-bis(5-cyano-6-phenethylamino-3,4-dihydro-2H-1,3-thiazin-4-one) (**3b**)*

Pale-yellow powder, yield: method A: 82 %; method B: 79 %, m. p. 242 – 244 °C. – IR (film): ν = 3227, 3150, 3020, 2203, 1638, 1565 cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.78 – 2.87 (t, 4H, $2CH_2N$, J = 6 Hz), 3.41 – 3.51 (t, 4H, $2CH_2Ph$, J= 6 Hz), 6.07 (d, 2H, 2CH, J = 2.4 Hz), 7.14 – 7.30 (m, 14H, ArH), 7.49 (d, 2H, 2NH, J = 2.4 Hz), 8.33 (t, 2H, 2 NH, J = 6 Hz). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 35.59 (2 CH_2Ph), 46.59 (2 CH_2N), 57.38 (C-2, C-2′), 73.72 (C-5, C-5′), 116.94 (CN), 126.37, 127.37, 127.68, 128.21, 128.36, 128.56, 128.70, 129.56, 136.27, 137.71, 137.80,

138.03, 143.95 (C-Ar), 165.31 (2CO), 166.60 (C-6, C-6′). – Anal. for $C_{32}H_{28}N_6O_2S_2$: calcd. C 64.84, H 4.76, N 14.18, S 10.82; found C 64.72, H 4.65, N 14.06, S 10.75.

*2,2′-(1,4-Phenylene)bis(5-cyano-6-phenylamino-4H-1,3-thiazin-4-one) (**4**)*

A solution of compound **3a** (2 mmol) was refluxed in DMF/$PhNO_2$ (1 : 5) for 2 h, and the solvent was evaporated under vacuum. The product **4** was crystallized by using chloroform/petroleum ether. Pale-grey powder, yield: 73 %, m. p. 210 – 212 °C. – IR (film): ν = 3175, 3070, 2202, 1650 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 7.27 – 7.99 (m, 14H, ArH), 10.49 (s, 2H, 2NH). – Anal. for $C_{28}H_{16}N_6O_2S_2$: calcd. C 63.14, H 3.03, N 15.78, S 12.04; found C 63.04, H 3.16, N 15.69, S 11.96.

*Synthesis of **5a**, **b***

To a stirred 0.75 N aqueous KOH solution (20 mL), compound **3a b** (10 mmol) and dimethyl sulfate (40 mmol) were added successively. The resulting precipitate was filtered off, washed with water, dried and recrystallized from DMF/EtOH.

*2,2′-(1,4-Phenylene)bis(5-cyano-6-methylthio-1-phenyl-1,2,3,4-tetrahydropyrimidin-4-one) (**5a**)*

Yellow crystals, yield: 80 %, m. p. 296 – 298 °C. – IR (film): ν = 3175, 3060, 2206, 1650, 1545 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.12 (s, 6H $2CH_3$), 6.14 (d, 2H, 2CH, J = 2.4 Hz), 7.39 – 7.60 (m, 14H, ArH), 8.94 (d, 2H, 2 NH, D_2O-exchangeable, J = 2.4 Hz). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 15.29 (2 SCH_3), 73.71 (C-2, C-2′), 90.0 (C-5, C-5′), 115.72 (2CN), 125.40, 125.44, 126.41, 126.69, 126.84, 127.46, 127.59, 129.70, 129.81, 139.33, 142.93 (C-Ar), 160.40 (2CO), 165.02 (C-6, C-6′). – Anal. for $C_{30}H_{24}N_6O_2S_2$: calcd. C 63.81, H 4.28, N 14.88, S 11.36; found C 63.72, H 4.37, N 14.75, S 11.24.

*2,2′-(1,4-Phenylene)bis(5-cyano-6-methylthio-1-phenethyl-1,2,3,4-tetrahydropyrimidin-4-one) (**5b**)*

Pale-yellow crystals, yield: 82 %, m. p. 210 – 214 °C. – IR (film): ν = 3383, 3057, 3028, 2926, 2203, 1649, 1525 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.29 (s, 6H, $2CH_3$), 2.9 (t, 4H, $2CH_2N$, J = 5.4 Hz), 3.35 (t, 4H, $2CH_2$-Ph, J = 5.4 Hz), 6.10 (d, 2H, 2CH, J = 4.8 Hz), 7.21 – 7.35 (m, 14H, ArH), 8.65 (d 2H, 2 NH D_2O-exchangeable, J = 4.8 Hz). – Anal. for $C_{34}H_{32}N_6O_2S_2$: calcd. C 65.78, H 5.20, N 13.54, S 10.33; found C 65.69, H 5.31, N 13.46, S 10.24.

*Synthesis of **6a**, **b***

Ethyl iodide (40 mmol) was added to a mixture of **3a**, **b** (10 mmol) and anhydrous potassium carbonate (4 mmol) in DMF (5 mL). The reaction mixture was stirred for 18 – 20 h at r. t. and then poured into cold water. After stirring for 15 min, the precipitated product was collected by filtration, washed with water, dried and crystallized from ethanol.

*2,2′-(1,4-Phenylene)-bis(5-cyano-6-ethylthio-1-phenyl-1,2,3,4-tetrahydro-pyrimidin-4-one) (**6a**)*

Pale-yellow crystals, yield: 76 %, m. p. 290 – 292 °C. – IR (film): ν = 3263, 3058, 2969, 2211, 1663, 1513 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 0.92 (t, 6H, $2CH_3$, J = 3 Hz), 2.74 (q, 4H, $2CH_2$, J = 3 Hz), 6.08 (d, 2H, 2CH, J = 4.8 Hz), 7.34 – 7.54 (m, 14H, ArH), 8.84 (d, 2H, 2 NH, J = 4.8 Hz). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 14.08 ($2CH_3$), 26.79 ($2CH_2$), 73.57 (2CH), 90.70 (C-5, C-5′), 115.68 (2CN), 125.82, 125.96, 126.01, 126.54, 127.58, 129.58, 129.71, 139.09, 143.04 (C-Ar), 160.50 (2C=O), 163.49 (C-6, C-6′). – Anal. for $C_{32}H_{28}N_6O_2S_2$: calcd. C 64.84, H 4.76, N 14.18, S 10.82; found C 64.75, H 4.82, N 14.11, S 10.71.

*2,2′-(1,4-Phenylene)bis(5-cyano-6-ethylthio-1-phenethyl-1,2,3,4-tetrahydropyrimidin-4-one) (**6b**)*

Pale-yellow crystals, yield: 76 %, m. p. 278 – 279 °C. – IR (film): ν = 3163, 3045, 2203, 1665, 1515 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.01 (t, 6H, $2CH_3$, J = 7.2 Hz), 2.80 (t, 4H, $2CH_2N$, J = 7.2 Hz), 2.93 (t, 4H, $2CH_2Ph$, J = 7.2 Hz), 4.41 (q, 4H, $2CH_2$, J = 7.2 Hz), 6.13 (d, 2H, 2CH, J = 1.5 Hz), 7.23 – 7.35 (m, 14H, ArH), 8.60 (d, 2H, 2 NH, J = 1.5 Hz). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 14.55 ($2CH_3$), 28.47 ($2CH_2$), 35.44 (2 CH_2Ph), 53.79 (2 CH_2N), 68.30 (C-2, C-2′), 86.31 (C-5, C-5′), 120.60 (CN), 125.69, 126.51, 128.31, 128.93, 137.57, 139.43 (C-Ar), 161.60 (2C=O), 162.89 (C-6, C-6′). – Anal. for $C_{36}H_{36}N_6O_2S_2$: calcd. C 66.64, H 5.59, N 12.95, S 9.88; found C 66.52, H 5.48, N 12.86, S 9.77.

*2-Cyano-3-ethylthio-3-phenylamino-acrylamide (**7b**)*

This compound was prepared in 90 % isolated yield by treatment of cyanoacetamide with phenyl isothiocyanate and ethyl iodide using the procedure described for the synthesis of **7a** [39]; pale-yellow crystals, m. p. 128 – 130 °C. – IR (film): ν = 3382, 3201, 2195, 1652, 1555 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.20 (t, 3H, CH_3, J = 7.5 Hz), 2.63 (q, 2H, CH_2, J = 7.5 Hz), 7.25 – 7.42 (m, 7H, ArH + NH_2), 12.44 (s 1H, NH).

*Alternative synthesis of **5a** and **6a***

A mixture of terephthalaldehyde (**1**) (1.34 g, 0.01 mol), **7a**, **b** (0.02 mol), and *p*-toluenesulfonic acid (0.076 g, 0.01 mol) in ethanol (20 mL) was refluxed. A yellow precipitate was formed after 30 min, and stirring was continued for 2 h. The precipitate was filtered off, washed with ethanol, dried, and recrystallized from the appropriate solvents.

*Synthesis of **8a, b***

To a stirred 75 N aqueous KOH solution (20 mL), **3a**, **b** (10 mmol) and benzyl chloride (40 mmol) were added successively. The resulting precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

*2,2′-(1,4-Phenylene)bis(6-benzylthio-5-cyano-1-phenyl-1,2,3,4-tetrahydropyrimidin-4-one) (**8a**)*

Colorless crystals, yield: 81%, m. p. 280 – 282 °C. – IR (film): ν = 3284, 2979, 2210, 1671, 1535 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.91 (d, 2H, CH^AH^B, J = 13 Hz), 4.08 (d, 2H, CH^AH^B, J = 13 Hz), 6.09 (d, 2H, 2CH, J = 6.6 Hz), 7.03 – 7.53 (m, 24H, ArH), 8.93 (d 2H, NH, J = 6.6 Hz). – Anal. for $C_{42}H_{32}N_6O_2S_2$: calcd. C 70.37, H 4.50, N 11.72, S 8.95; found C 70.24, H 4.41, N 11.65, S 8.88.

*2,2′-(1,4-Phenylene)bis(6benzylthio-5-cyano-1-phenethyl-1,2,3,4-tetrahydropyrimidin-4-one) (**8b**)*

Pale-yellow crystals, yield: 80 %, m. p. 260 – 263 °C. – IR (film): ν = 3361, 3127, 2210, 1678, 1526 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.87 (t, 4H, $2CH_2$, J = 6 Hz), 3.75 (t, 4H, $2CH_2$, J = 6 Hz), 4.14 (d, 2H, CH^AH^B, J = 13 Hz), 4.35 (d, 2H, CH^AH^B, J = 13 Hz), 6.06 (d, 2H, 2CH, J = 4.8 Hz), 7.17–7.32 (m, 14H, ArH), 8.63 (d, 2H, 2NH, J = 4.8 Hz). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 35.17 (2 SCH_2Ph), 37.87 (2 CH_2Ph), 53.68 (2 CH_2-*N*), 68.78 (2CH), 85.68 (C-5, C-5′), 117.27 (CN), 125.80, 126.50, 127.81, 128.33, 128.69, 128.81, 136.31, 137.45, 139.09 (C-Ar), 161.47 (2 C=O), 162.46 (C-6, C-6′). – Anal. for $C_{46}H_{40}N_6O_2S_2$: calcd. C 71.48, H 5.22, N 10.87, S 8.30; found C 71.37, H 5.28, N 10.76, S 8.22.

*2,2′-(1,4-Phenylene)bis(5-amino-1,6-diphenylthieno[2,3-d]pyrimidin-4(1H)-one) (**9**)*

A mixture of compound **8a** (1 mmol) and sodium ethoxide (0.046 g Na/15 mL ethanol) was heated under reflux for 2 h, and then allowed to cool. The solid product was collected by filtration and washed with water. Brown powder, yield: 81 %, m. p. 200 – 202 °C. – IR (film): ν = 3745, 3352, 3028, 2921, 1637, 1591 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 6.96 (s, 4H $2NH_2$), 7.27 – 7.51 (m, 24H, ArH). – Anal. for $C_{42}H_{28}N_6O_2S_2$: calcd. C 70.77, H 3.96, N 11.79, S 9.00; found C 70.69, H 3.88, N 11.71, S 8.89.

*Synthesis of compounds **10** and **11***

To a stirred 0.75 N aqueous KOH solution (20 mL), **3a b** (10 mmol) and ethyl bromoacetate (40 mmol) were added successively. The resulting precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

*2,2′-(1,4-Phenylene)bis(5-amino-6ethoxycarbonyl-1-phenyl-2,3-dihydro-thieno[2,3-d]pyrimidin-4(1H)-one) (**10**)*

Pale-yellow powder, yield: 82 %, m. p. 274 – 276 °C. – IR (film): ν = 3389, 3059, 1661, 1512, 1428, 1378 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.16 (t, 6H, $2CH_3$, J = 7.2 Hz), 4.10 (q, 4H, $2CH_2$, J = 7.2 Hz), 6.15 (d, 2H, 2CH, J = 1.2 Hz), 6.50 (s, 4H, $2NH_2$), 7.41 – 7.59 (m, 14H, ArH), 8.98 (d, 2H, 2NH, J = 1.2 Hz). – Anal. for $C_{36}H_{32}N_6O_6S_2$: calcd. C 61.00, H 4.55, N 11.86, S 9.05; found C 60.88, H 4.66, N 11.75, S 8.96.

*2,2′-(1,4-Phenylene)bis(5-cyano-4-oxo-1-phenethyl-1,2,3,4-tetrahydropyrimidin-6-yl-sulfanylacetic acid ethyl ester) (**11**)*

Yellowish-white powder, yield: 80 % m. p. 240 – 242 °C. – IR (film): ν = 3286, 3060, 2210, 1727, 1670, 1630, 1535 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.08 (t, 6H, $2CH_3$, J = 4.8 Hz), 2.99 (t, 4H, $2CH_2$Ph, J = 6.3 Hz), 3.82 (t, 4H, $2CH_2$N, J = 6.3 Hz), 3.98 (s, 4H, $2CH_2$S), 4.28 (q, 4H, $2CH_2$O, J = 6.6 Hz), 6.15 (d, 2H, 2CH, J = 6 Hz), 7.28 – 7.33 (m, 14H, ArH), 8.72 (d, 2H, 2 NH, J = 6 Hz). – Anal. for $C_{40}H_{40}N_6O_6S_2$: calcd. C 62.81, H 5.27, N 10.99, S 8.38; found C 62.70, H 5.35, N 10.91, S 8.29

*2,2′-(1,4-Phenylene)bis(5-amino-6-ethoxycarbonyl-1-phenethyl-thieno[2,3-d]-pyrimidin-4(1H)-one) (**12**)*

A mixture of compound **11** (0.764 g, 1 mmol) with sodium ethoxide (0.046 g Na/15 mL ethanol) was heated under reflux for 2 h, and then allowed to cool. The solid product was collected by filtration and washed with water. Brown powder, yield: 74 %, m. p. 240 – 242 °C. – IR (film): ν = 3745, 3352, 3028, 2921, 1637, 1591 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.23 (t, 6H, $2CH_3$, J = 6 Hz), 2.92 (t, 4H, $2CH_2$Ph, J = 6 Hz), 3.82 (t, 4H, $2CH_2$N, J = 6 Hz), 4.04 (q, 4H, $2CH_2$O, J = 6.6 Hz), 6.96 (s, 4H, $2NH_2$), 7.27 – 7.31 (m, 14H, ArH). – Anal. for $C_{40}H_{36}N_6O_6S_2$: calcd. C 6314, H 4.77, N 11.05, S 8.43; found C 6305, H 4.88, N 10.98, S 8.33.

*2,2′-(1,4-Phenylene)bis(5-amino-1-aryl-6-cyano-2,3-dihydro-thieno[2,3-d]-pyrimidin-4(1H)-ones) **13a, b***

To a stirred 0.75 N aqueous KOH solution (20 mL), **3a b** (10 mmol) and bromoacetonitrile (40 mmol) were added successively. The resulting precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

*2,2′-(1,4-Phenylene)bis(5-amino-6-cyano-1-phenyl-2,3-dihydro-thieno[2,3-d]pyrimidin-4(1H)-one) (**13a**)*

Yellowish-white powder, yield: 84 %, m. p. 276 – 278 °C. – IR (film): ν = 3426, 3325, 3200, 3065, 3028, 2177,

1659 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 6.29 (d, 2H, 2CH, J = 4.8 Hz), 6.77 (s, 4H, $2NH_2$), 7.24 – 7.41 (m, 14H, ArH), 8.55 (d, 2H, 2NH, J = 4.8 Hz). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 73.77 (C-2, C-2′), 101.28 (C-6, C-6′), 115.74 (2CN), 124.19, 126.89, 127.36, 129.70, 139.35 (C-Ar), 141.35 (C-5a, C-5a′), 155.18 (C-4a, C-4a′), 159.74 (*S*C*N*), 160.76 (2C=O). – Anal. for $C_{32}H_{22}N_8O_2S_2$: calcd. C 62.53, H 3.61, N 18.23, S 10.43; found C 62.46, H 3.66, N 18.15, S 10.36.

*2,2′-(1,4-Phenylene)bis(5-amino-6-cyano-1-phenethyl-2,3-dihydro-thieno[2,3-d]pyrimidin-4(1H)-one) (**13b**)*

Pale-grey powder, yield: 82 %, m. p. 262 – 264 °C. – IR (film): ν = 3224, 3155, 3065, 3030, 2165, 1660, 1610, 1518 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.80 (t, 4H, $2CH_2Ph$, J = 6.9 Hz), 3.39 (t, 4H, $2CH_2N$, J = 6.9 Hz), 5.86 (d, 2H, 2CH, J = 2.4 Hz), 6.80 (s, 4H, $2NH_2$), 7.15 – 7.40 (m, 14H, ArH), 8.34 (d, 2H, 2NH, J = 2.4 Hz). – Anal. for $C_{36}H_{30}N_8O_2S_2$: calcd. C 64.46, H 4.51, N 16.70, S 9.56; found C 64.38, H 4.62, N 16.59, S 9.48.

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