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Derivatives containing the thieno[2,3-*d*]pyrimidin-4-one system, potential selective COX-2 inhibitors, were prepared starting from ethyl ester of 2-isothiocyanato-5-phenyl-3-thiophenecarboxylic acid (**2**); their structural elucidation is also reported.

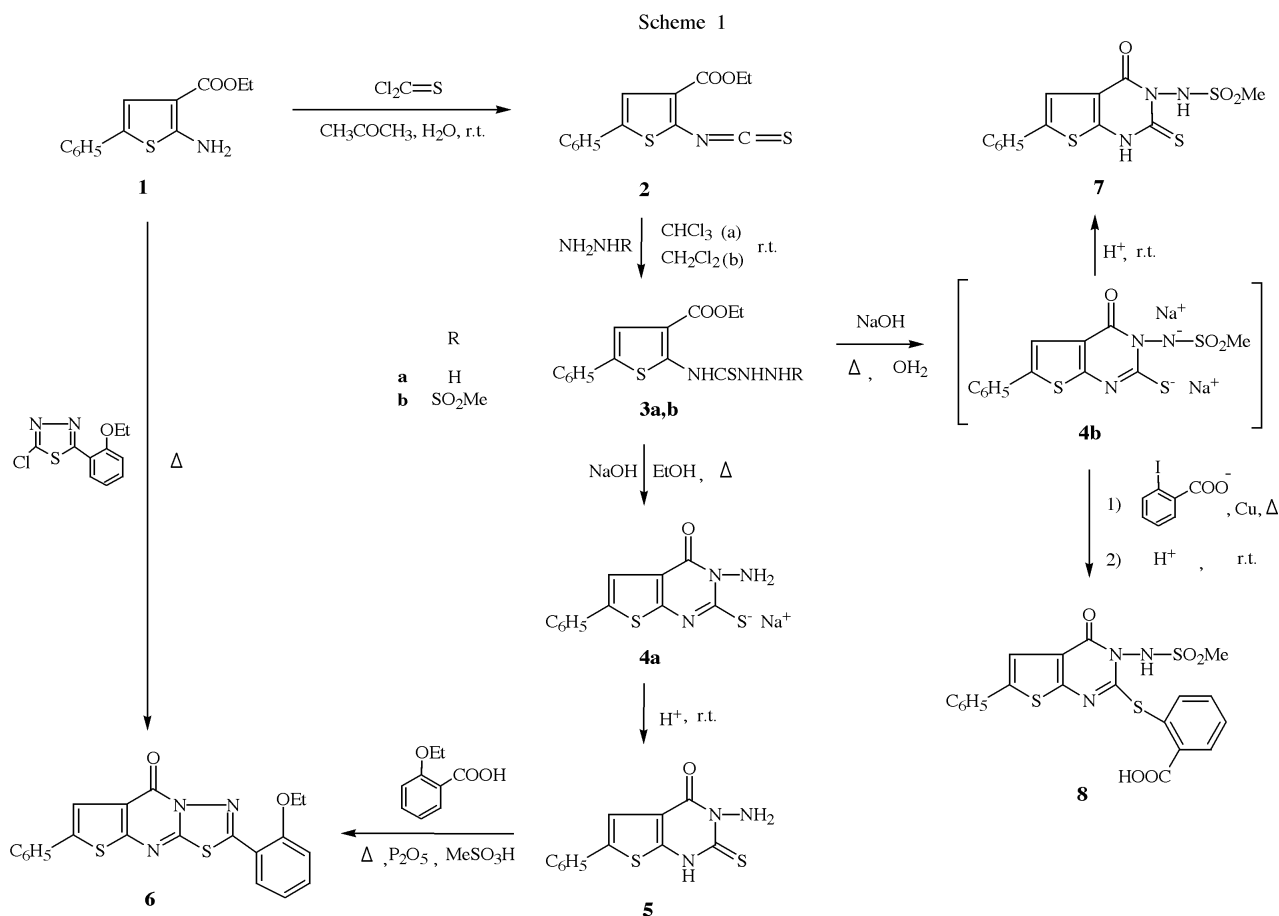
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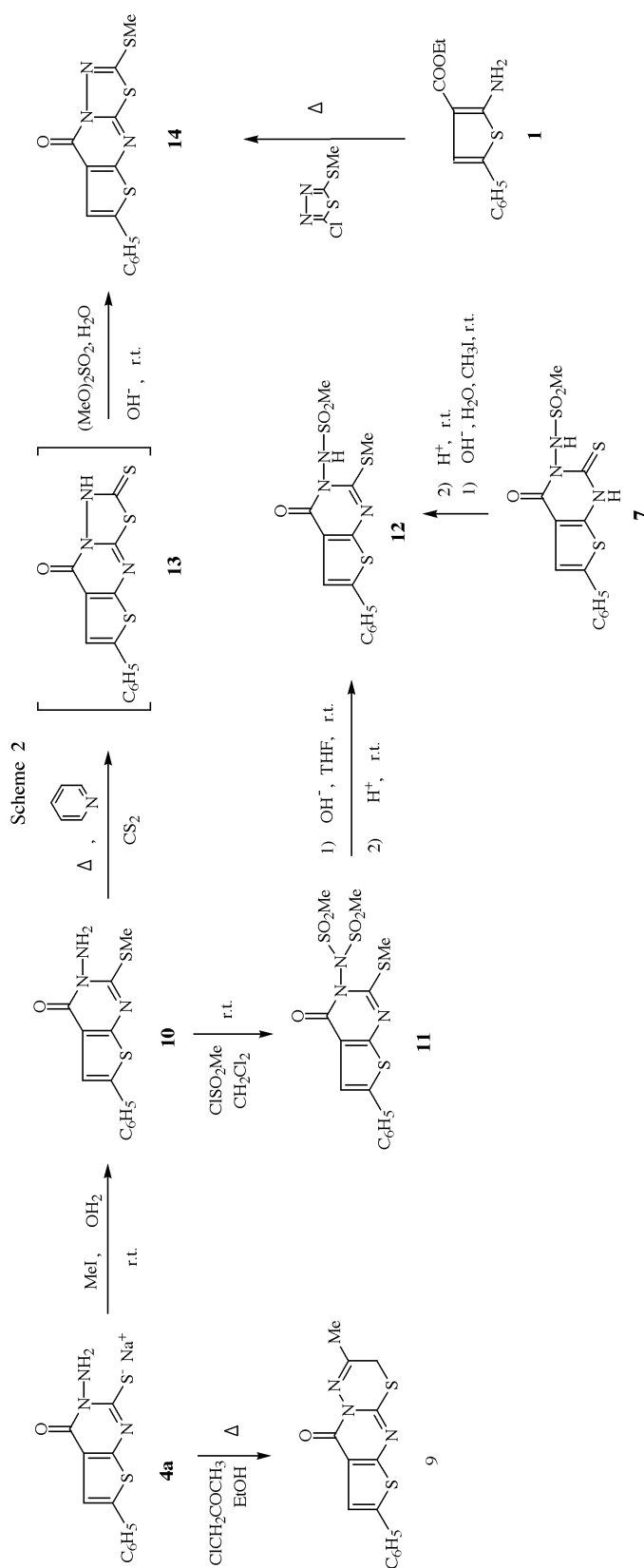
Derivatives containing the thienopyrimidine systems are reported to possess several important pharmacological properties [1]; in particular some derivatives of the 6-phenyl-1,3,4-thiadiazolo[3,2-*a*]thieno[2,3-*d*]pyrimidin-8-one [2] showed interesting anti-inflammatory and analgesic activities without ulcerogenic activity and with low acute toxicity.

Recent developments in the research of non-steroidal anti-inflammatory drugs (NSAIDs) as selective inhibitors of COX-2 [3,4] have prompted us, on the basis of the above heterocyclic system [2] and structures of leads [3,4], to prepare new derivatives with the characteristic functional groups of selective COX-2 inhibitor drugs.

In this paper we report the synthesis and the structural elucidation of a series of new derivatives containing the 6-phenyl-thieno[2,3-*d*]pyrimidin-4-one heterocyclic system as a stage of research of compounds with effective analgesic and anti-inflammatory activities as selective COX-2 inhibitors.

The key compound was the ethyl ester of 2-isothiocyanato-5-phenyl-3-thiophenecarboxylic acid (**2**) prepared, without the production of pollutants, in acetone at room temperature from the reaction of amino ester **1** and thiophosgene with subsequent dilution in water (Scheme 1). The reaction at room temperature with hydrazine or with mesylhydrazine and treatment of the resulting





thiosemicarbazide derivative **3a** and **3b** with sodium hydroxide in refluxing ethanol or refluxing water afforded the amino-thioxo sodium salt **4a** and **4b**, whose acidification with hydrochloric acid gave the amino-thioxo **5** and methanesulfonamide-thioxo **7** derivatives, respectively.

The structure of the amino-thioxo derivatives **4a** and **5** was confirmed by independent preparation of 2-ethoxyphenyl derivative **6**. The compound obtained from the condensation of amino-ester **1** with 2-chloro-5-(2-ethoxyphenyl)-1,3,4-thiadiazole as reported by Russo *et al.* [2] was identical to that prepared from amino-thioxo derivative **5** and 2-ethoxybenzoic acid under appropriate condition of reaction.

The addition of sodium salt of 2-iodobenzoic acid in the presence of copper powder to an aqueous refluxing solution of methanesulfonamide **4b** in sodium hydroxide gave the disodium salt of the acid derivative **8**. The structure of methanesulfonamide derivatives **7** and **8** is in accordance with analytical and spectral data.

From the sodium salt **4a** of the amino-thioxo derivative, several derivatives were obtained (Scheme 2).

Refluxing in ethanol with chloroacetone gave the 2-methyl thiadiazine derivative **9**; in the ir and ^1H nmr spectra, the absence of a signal attributable to hydrogen bonded to nitrogen and the presence of a signal at δ 3.79 attributable to the methylene protons of C-3 corroborated the formation of the 1,2 unsaturated thiadiazine ring.

The synthetic routes to the methanesulfonamide **12** and tricyclic methylthio derivatives **14** were completed through the amino methyl-thio derivative **10**.

Dimesylation of the amino group and subsequent hydrolysis gave the monomesyl **12**, which in the ir and ^1H nmr spectra showed the characteristic signal attributable to sulfonamidic hydrogen, in contrast with signals attributable to the amino group for compound **10** and with no signals due to hydrogen bonded to nitrogen for the dimesyl **11**, both of which are precursor compounds. The methyl monomesyl derivative **12** was also obtained through the methylation of the amino-thioxo monomesylated derivative **7**, whose structure was thus confirmed.

Refluxing in pyridine with carbon disulfide yielded through the thiadiazole-thioxo derivative **13** and subsequent methylation with dimethyl sulphate the methyl thiadiazole derivative **14**, which was identical to the product obtained according to Russo *et al.* [2] from the condensation of amino ester **1** with 2-chloro-5-methylthio-1,3,4-thiadiazole.

In preliminary tests as COX-2 activity inhibitors in Human Whole Blood (HWB) *ex vivo* [5], derivatives **8** and **12** showed at 10 μM an inhibition of 35 % and 30 %, respectively, in contrast with that of 100 % of indomethacin.

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes on a SMP1 apparatus (Stuart Scientific, Staffordshire). Ir spectra were recorded on a Perkin Elmer 1600 Series FT-IR in potassium bromide disks. Elemental analyses for C, H, N, and S were obtained on an EA 1108 elemental analyzer Fisons-Carlo Erba instrument.

^1H and ^{13}C nmr spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer; chemical shifts (δ) are reported in ppm from tetramethylsilane as internal standard; coupling constants (J) are in Hertz (Hz). The mp's of all crude compounds were within -3°C , if compared with the pure product; therefore, as synthetic intermediates they could be used without further purification. The purity of compounds was checked by thin layer chromatography on Merck silica gel 60 F-254 plates. All commercial chemicals were purchased from Aldrich, Fluka, Merck and Carlo Erba and were used without further purification.

Ethyl Ester of 2-Isothiocyanato-5-phenyl-3-thiophenecarboxylic Acid (**2**).

A solution of amino-ester **1** [6] (5.0 g, 21.6 mmoles) in acetone (30 ml) was added slowly drop-wise at room temperature to a stirred solution of thiophosgene (1.6 ml, 97%, $d=1.508$, 20.35 mmoles) in acetone (15 ml). After 20 minutes of stirring at room temperature water was added (200 ml): the solid separated was collected, washed first with 5% sodium hydroxide and then with water, dried and crystallized from *n*-hexane to give the isothiocyanate **2** as yellow micro-needles; yield 50%; mp $94-95^\circ$. The isothiocyanate **2** was identical to the sample obtained according to previous paper [7,8]. The unreported spectra data are now reported; ir: 2145 and 2100 ($\text{N}=\text{C}=\text{S}$), 1695 ($\text{C}=\text{O}$) cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 1.26 (t, $J=7.0$ Hz, 3H, CH_3), 4.23 (q, $J=7.0$ Hz, 2H, CH_2), 7.22-7.68 (m, 6H, Ar-H and thiophene-H); ^{13}C nmr (dimethylsulfoxide- d_6): δ 14.47, 59.10, 121.02, 122.20, 123.97, 125.28, 126.23, 128.95, 129.23, 133.69, 163.38, 164.28.

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{NO}_2\text{S}_2$: C, 58.13; H, 3.80; N, 4.84; S, 22.14. Found: C, 58.50; H, 3.85; N, 4.80; S, 22.40

Ethyl Ester of 2-((Hydrazinothioxomethyl)amino)-5-phenyl-3-thiophene-carboxylic Acid (**3a**).

To a stirred solution of hydrazine hydrate (0.35 ml, 7.0 mmoles) in chloroform (15 ml) isothiocyanate **2** (1.7 g, 6.2 mmoles) in chloroform (15 ml) was added drop-wise at room temperature. After the addition was complete, the mixture was stirred at room temperature for 2 hours. The resulting solid was collected, washed with chloroform, dried and crystallized from ethanol to give **3a** as yellow crystals; yield 55%; mp $224-26^\circ$ dec. The analytical and spectral data of **3a** were identical to those of a sample obtained according to previous paper [9]; ir: 3345, 3245 and 3185 (NH or NH_2), 1685 ($\text{C}=\text{O}$) cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 1.33 (t, $J=7.2$ Hz, 3H, CH_3), 4.32 (q, $J=7.2$ Hz, 2H, CH_2), 6.5 (br s, 3H, NH and NH_2), 7.27-7.63 (m, 6H, Ar-H and thiophene-H), 9.92 (s, 1H, NH); ^{13}C nmr (dimethylsulfoxide- d_6): δ 14.28, 60.48, 113.42, 119.25, 124.99, 127.29, 129.15, 131.10, 133.39, 150.11, 164.16, 176.71.

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2\text{S}_2$: C, 52.33; H, 4.67; N, 13.08; S, 19.93. Found: C, 52.50; H, 4.75; N, 12.95; S, 19.60.

Ethyl Ester of 2-((2-(Methylsulfonyl)hydrazino)carbonothioyl)amino)-5-phenylthiophene-3-carboxylic Acid (**3b**).

To a stirred solution of methanesulphonyl hydrazide [10] (0.8 g, 98%, 8.15 mmoles) in dichloromethane (25 ml) isothiocyanate **2** (2.10 g, 7.62 mmoles) in dichloromethane (50 ml) was added drop-wise at room temperature. After the addition was complete, the mixture was stirred at room temperature for 2 hours. The resulting solid was collected, washed with dichloromethane, dried and crystallized from ethanol/water to give **3b** as a yellow amorphous solid; yield 70%; mp $232-34^\circ$ dec.; ir: 3295 and 3300 (NH), 1665 ($\text{C}=\text{O}$), 1315 and 1150 ($\text{SO}_2\text{-N}$) cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 1.33 (t, $J=7.0$ Hz, 3H, CH_3), 3.13 (s, 3H, SO_2CH_3), 4.36 (q, $J=7.0$ Hz, 2H, CH_2), 7.25-7.65 (m, 6H, Ar-H and thiophene-H), 10.10, 10.91 and 12.40 (s, 1H, NH); ^{13}C nmr (dimethylsulfoxide- d_6): δ 14.23, 38.73, 60.85, 114.86, 119.37, 125.16, 127.59, 129.18, 132.04, 133.05, 148.64, 164.23, 177.30.

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4\text{S}_3$: C, 45.11; H, 4.26; N, 10.52; S, 24.06. Found: C, 44.85; H, 4.10; N, 10.20; S, 23.75.

3-Amino-2,3-dihydro-6-phenyl-2-thioxo-thieno[2,3-*d*]pyrimidin-4(1*H*)-one (**5**) from its Sodium Salt (**4a**).

A mixture of hydrazino-thioxo derivative **3a** (3.2 g, 9.9 mmoles) in a solution of sodium hydroxide (0.42 g, 10.5 mmoles) in ethanol (120 ml); was refluxed under stirring for 1 hour; the resulting solid was collected while hot, washed with warm dioxane and dried to give **4a** as pale yellow powder; yield 80%; mp $311-14^\circ$ dec.; ir: 3205 and 3120 (NH_2), 1640 ($\text{C}=\text{O}$) cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 6.42 (s, 2H, NH_2), 7.24-7.65 (m, 6H, Ar-H and thiophene-H); ^{13}C nmr (dimethylsulfoxide- d_6): δ 117.20, 117.30, 124.86, 127.05, 128.98, 131.98, 134.07, 154.23, 162.05, 169.72.

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{N}_3\text{NaOS}_2$: C, 48.48; H, 2.69; N, 14.14; S, 21.54. Found: C, 48.20; H, 2.50; N, 14.20; S, 21.60.

To a suspension of sodium salt **4a** (1.0 g, 3.36 mmoles) in water (50 ml) concentrated hydrochloric acid was added drop-wise under stirring to obtain pH 3-4; the mixture was stirred at room temperature for 1 hour; the resulting solid was collected, treated with 5% sodium hydrogencarbonate, washed with water, dried and crystallized from dimethylsulfoxide/water to give **5** as a white powder; yield 50%; mp $278-281^\circ$ dec. The analytical and spectral data of compound **5** are identical to those of a sample obtained according to previous paper [9]; ir: 3285 and 3155 (NH_2 or NH), 1655 ($\text{C}=\text{O}$) cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 4.47 (br s, 2H, NH_2), 7.19-7.72 (m, 6H, Ar-H and thiophene-H), 13.94 (br s, 1H, NH); ^{13}C nmr (dimethylsulfoxide- d_6): δ 117.46, 117.97, 125.47, 128.44, 129.27, 132.17, 136.41, 148.00, 152.54, 167.15.

Anal. Calcd. for $\text{C}_{12}\text{H}_9\text{N}_3\text{OS}_2$: C, 52.35; H, 3.27; N, 15.27; S, 23.27. Found: C, 52.20; H, 3.15; N, 15.30; S, 23.40.

2-(2-Ethoxyphenyl)-6-phenyl-8*H*-[1,3,4]thiadiazolo[3,2-*a*]thieno[2,3-*d*]pyrimidin-8-one (**6**).

A mixture of amino-thioxo derivative **5** (0.38 g, 1.38 mmoles), phosphorus pentoxide (0.3 g), methanesulfonic acid (0.6 ml) and 2-ethoxybenzoic acid (2.0 g, 98%, 11.8 mmoles) was heated at 100° for 2 hours. After cooling to room temperature, the reaction mixture was treated with ice/water and 5% sodium hydroxide was added to obtain pH 9-10. The resulting solid was collected, washed with water, dried and crystallized from dioxane/water to give **6** as a pale yellow powder; yield: 40%; mp $258-61^\circ$. The analytical and spectral data of 2-ethoxyphenyl derivative **6** were identical to those of a sample obtained according to Russo *et al.* [2] (see Scheme 1); ir: 1705 ($\text{C}=\text{O}$) cm^{-1} ; ^1H nmr (trifluoroacetic

acid-d): δ 1.73 (t, $J=7.0$ Hz, 3H, CH₃), 4.40 (q, $J=7.0$, 2H, CH₂), 7.68-7.09 (m, 10H, Ar-H and thiophene-H).

Anal. Calcd. for C₂₁H₁₅N₃O₂S₂: C, 62.22; H, 3.70; N, 10.37; S, 15.80. Found: C, 62.50; H, 3.55; N, 10.40; S, 15.95.

N-(4-Oxo-6-phenyl-2-thioxo-1,4-dihydrothieno[2,3-*d*]pyrimidin-3(2*H*)-yl)methanesulfonamide (**7**).

A solution of mesylthiosemicarbazide derivative **3b** (1.0 g, 2.5 mmoles) and sodium hydroxide (0.22 g, 5.5 mmoles) in water (30 ml) was refluxed under stirring for 3 hours; the solution, containing the disodium salt **4b**, was filtered, quenched and acidified with concentrated hydrochloric acid to pH 3-4: the resulting solid was collected, washed with water, dried and crystallized from acetonitrile/water to give the monomesyl amino derivative **7** as grey amorphous powder; yield 45%; mp 280-84° dec.; ir: 3215 (NH), 1675 (C=O), 1350 and 1165 (SO₂-N) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 3.28 (s, 3H, CH₃), 7.30-7.71 (m, 6H, Ar-H and thiophene-H), 10.43 (s, 1H, NH), 14.00 (br s, 1H, NH); ¹³C nmr (dimethylsulfoxide-*d*₆): δ 44.48, 117.98, 118.42, 125.47, 128.53, 129.26, 132.00, 136.93, 149.54, 155.23, 174.98.

Anal. Calcd. for C₁₃H₁₁N₃O₃S₃: C, 44.19; H, 3.11; N, 11.89; S, 27.19. Found: C, 44.51; H, 3.13; N, 11.52; S, 26.80.

2-({3-[(Methylsulfonyl)amino]-4-oxo-6-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl}thio)benzoic Acid (**8**).

A mixture of methylsulfonylhydrazino derivative **3b** (2.0 g, 5.0 mmoles) and sodium hydroxide (0.4 g, 10 mmoles) in water (100 ml) was refluxed under stirring for 2 hours; the mixture was filtered while hot and to the resulting solution 2-iodobenzoic acid (1.27 g, 98%, 5.0 mmoles), dissolved in a small amount of 5% sodium hydroxide, and 65 mg of powdery copper were added. The mixture was then refluxed under stirring for 7 hours. After cooling to room temperature, the mixture was filtered and the resulting solution was quenched and acidified with concentrated hydrochloric acid to pH 3-4. The resulting solid was collected, washed with water, dried and purified by chromatography on silica gel column (eluent: ethyl acetate/methanol 1/3) to give **8** as a whitish powder; yield 50%; mp 239-41° dec.; ir: 3302 (NH), 1700 (C=O), 1345 and 1155 (SO₂-N) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 3.38 (s, 3H, CH₃), 7.32-7.95 (m, 10H, Ar-H and thiophene-H), 11.45 (br s, 1H, NH), 13.15 (br s, 1H, COOH); ¹³C nmr (dimethylsulfoxide-*d*₆): δ 43.44, 118.22, 125.21, 125.34, 125.76, 126.43, 127.21, 128.10, 128.31, 129.18, 129.79, 131.99, 132.26, 132.83, 134.45, 135.69, 168.41, 170.32.

Anal. Calcd. for C₂₀H₁₅N₃O₅S₃: C, 50.73; H, 3.17; N, 8.88; S, 20.29. Found: C, 50.40; H, 3.22; N, 8.70; S, 19.90.

2-Methyl-7-phenyl-3*H*,9*H*-thieno[2',3':4,5]pyrimido[2,1-*b*][1,3,4]thiadiazin-9-one (**9**).

A mixture of sodium salt **4a** (0.39 g, 1.33 mmoles), chloroacetone (0.15 ml, 95%, $d=1.162$) in ethanol (20 ml) was refluxed for 2.5 hours. After cooling to room temperature, the resulting solid was collected, washed firstly with ethanol and then with water, dried and crystallized from ethanol/dioxane to give **9** as yellow microcrystals; yield 60%; mp 252-254° dec.; ir: 1680 (C=O) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 2.36 (s, 3H, CH₃), 3.79 (s, 2H, CH₂), 7.32-7.83 (m, 6H, Ar-H and thiophene-H); ¹³C nmr (dimethylsulfoxide-*d*₆): δ 23.44, 24.80, 118.02, 123.32, 125.64, 128.59, 129.25, 132.60, 139.14, 151.23, 153.98, 159.65, 160.31.

Anal. Calcd. for C₁₅H₁₁N₃O₂S₂: C, 57.50; H, 3.51; N, 13.41; S, 20.44. Found: C, 57.20; H, 3.50; N, 13.15; S, 20.35.

3-Amino-2-(methylthio)-6-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (**10**).

A mixture of sodium salt **4** (0.68 g, 2.3 mmoles), and methyl iodide (0.45 ml, 99 %, $d=2.27$) in water (40 ml) was stirred at room temperature for 1.5 hours. The resulting solid was collected, washed with water, dried and crystallized from dioxane/water to give **10** as pale yellow microcrystals; yield 60 %; mp 217-20°; ir: 3290 and 3175 (NH₂), 1680 (C=O) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 2.42 (s, 3H, SCH₃), 5.81 (s, 2H, NH₂), 7.30-7.76 (m, 6H, Ar-H and thiophene-H); ¹³C nmr (dimethylsulfoxide-*d*₆): δ 14.39, 117.15, 120.93, 125.54, 128.35, 129.20, 132.79, 138.06, 157.06, 161.83, 162.34.

Anal. Calcd. for C₁₃H₁₁N₃OS₂: C, 53.97; H, 3.80; N, 14.53; S, 22.14. Found: C, 53.70; H, 3.65; N, 14.20; S, 21.95.

N-(Methylsulfonyl)-*N*-[2-(methylthio)-4-oxo-6-phenylthieno[2,3-*d*]pyrimidin-3(4*H*)-yl]methanesulfonamide (**11**).

To a stirred solution of methyl derivative **10** (0.25 g, 0.865 mmoles) and triethylamine (1 ml) in dichloromethane (30 ml) a solution of methanesulfonyl chloride (0.22 ml, 2.85 mmoles, 99.5 %, $d=1.480$) in dichloromethane (10 ml) was added slowly drop-wise; the mixture was stirred at room temperature for 3 hours; the organic phase was washed with water, dried on sodium sulphate and concentrated under vacuum to give a solid that was collected, washed with diethyl ether, dried to give derivative **11** as an orange powder, resulted pure on thin layer chromatography; yield 68 %; mp > 185° dec.; ir: 1715 (C=O), 1370 and 1165 (SO₂-N) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 2.60 (s, 3H, SCH₃), 3.79 (s, 6H, 2xSO₂CH₃), 7.43-7.83 (m, 6H, Ar-H and thiophene-H); ¹³C nmr (dimethylsulfoxide-*d*₆): δ 14.36, 45.94, 117.14, 120.92, 125.53, 128.33, 129.19, 132.77, 138.03, 157.04, 161.80, 162.33.

Anal. Calcd. for C₁₅H₁₅N₃O₅S₄: C, 40.44; H, 3.37; N, 9.43; S, 28.76. Found: C, 40.10; H, 3.15; N, 9.60; S, 28.50.

N-[2-(Methylthio)-4-oxo-6-phenylthieno[2,3-*d*]pyrimidin-3(4*H*)-yl]methanesulfonamide (**12**).

A mixture of dimesyl derivative **11** (0.1 g, 0.22 mmoles) in a solution of potassium hydroxide (1 *M*) in water (10 ml) and tetrahydrofuran (90 ml) was stirred for 1 hour; the resulting solution was acidified with concentrated hydrochloric acid to pH 4-5, and then extracted with ethyl acetate; the extracts were concentrated under vacuum to give a residue that was collected and dissolved in 10% sodium hydroxide; the resulting solution was filtered and acidified with concentrated hydrochloric acid to pH 4-5, and the solid that separated was collected, washed with water and dried to give the monosulfonyl derivative **12** as an amorphous powder, resulted pure on thin layer chromatography; yield 42 %; mp 248-51° dec.; ir: 3190 (NH), 1700 (C=O), 1345 and 1160 (SO₂-N) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 2.48 (s, 3H, SCH₃), 3.34 (s, 3H, SO₂CH₃), 7.40-7.80 (m, 6H, Ar-H and thiophene-H), 11.27 (s, 3H, NH, deuterium oxide exchangeable); ¹³C nmr (dimethylsulfoxide-*d*₆): δ 14.99, 45.96, 117.69, 121.04, 125.84, 129.22, 129.32, 132.20, 140.50, 155.36, 161.48, 161.90.

Anal. Calcd. for C₁₄H₁₃N₃O₃S₃: C, 45.77; H, 3.54; N, 11.44; S, 26.15. Found: C, 45.80; H, 3.85; N, 11.10; S, 25.75.

From Monomesyl Derivative **7**.

To a solution of thioxo-monomesyl derivative **7** (0.13 g, 0.37 mmoles), dissolved in a solution of potassium hydroxide (42 mg, 0.73 mmoles) in water (20 ml), methyl iodide (0.3 ml, 99 %, 99 %)

d=2.27) was added and the mixture was stirred at room temperature for 1.5 hour; the mixture was filtered and the filtrate was acidified with concentrated hydrochloric acid to pH 4-5, and the solid that separated was collected, washed with water and dried to give **12** as an amorphous powder, resulted pure at thin layer chromatography; yield 50 %. This compound was identical to that obtained from hydrolysis of dimesyl derivative **11**.

2-(Methylthio)-6-phenyl-8H-[1,3,4]thiadiazolo[3,2-a]thieno[2,3-d]pyrimidin-8-one (**14**).

A mixture of amino thiomethyl derivative **10** (0.2 g, 0.7 mmoles) and carbon disulfide (0.7 ml, 99.9 %, d=1.266) in pyridine (2 ml), was refluxed under stirring for 12 hours. The reaction mixture was cooled to room temperature, and the yellow solid that separated was collected by filtration under vacuum, washed with diethylether and dried to give the crude 6-phenyl-2-thioxo-1,2-dihydro-8H-[1,3,4]thiadiazolo[3,2-a]thieno[2,3-d]pyrimidin-8-one (**13**) as a yellow powder (0.2 g). A mixture of the crude derivative **13** (0.20 g) suspended in water (30 ml) with sodium hydroxide (25 mg) and dimethyl sulphate (0.5 ml, 99% d=1.33) was stirred at room temperature for 4 hours. The resulting solid was collected, washed with water, dried and crystallized from dimethylformamide to give **14** as yellow microcrystals; yield: 47 %; mp 260-63°; the analytical and spectral data of thiomethyl derivative **14** were identical to those of a sample obtained according to Russo *et al* [2], (see Scheme 2); ir: 1690 (C=O) cm⁻¹; ¹H

nmr (trifluoroacetic acid-d): δ 2.83 (s, 3H, SCH₃), 7.40-7.67 (m, 6H, Ar-H and thiophene-H).

Anal. Calcd. for C₁₄H₉N₃OS₃: C, 50.75; H, 2.72; N, 12.68; 29.00. Found: C, 50.50; H, 2.75; N, 12.50; S, 28.80.

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