Synthesis of New Thienotriazolopyrimidine and Thienopyrimidotetrazine Derivatives from Bifunctional Intermediates

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New compounds containing the thienotriazolopyrimidine and thienopyrimidotetrazine skeleton are prepared from the bifunctional intermediates 2,3-diamino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives **13**-**17**. The 2,3-dihydro-3-substituted-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(1*H*)-one derivatives **8**-**12** are also prepared.

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For a long time, our research group has been interested in the synthesis of heterocyclic condensed derivatives, with the aim of evaluating their pharmacological activity, such as analgesic, anti-inflammatory [1-6] and anti-convulsive [7].

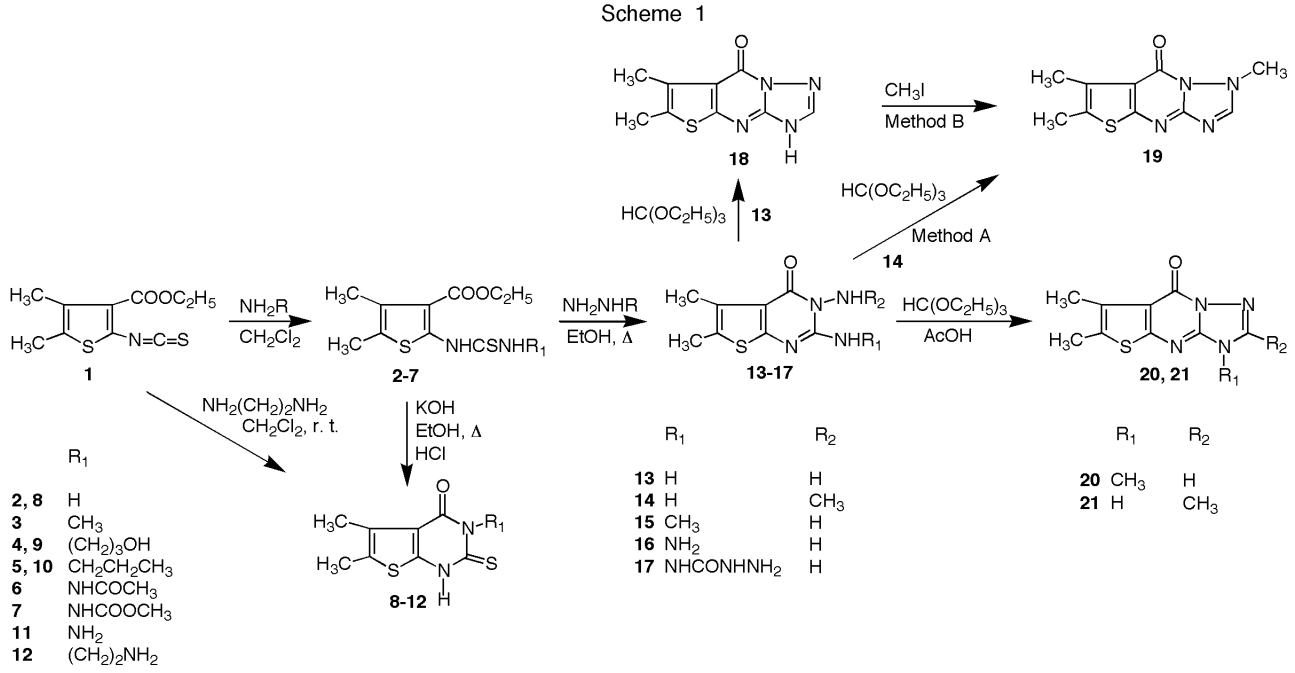
In recent works, we described the preparation of 3-amino-2-thioxothieno[2,3-*d*]pyrimidinone [1,8] and of 3-amino-2-phenylaminothieno[2,3-*d*]pyrimidinone derivatives [7] which are versatile intermediates of bridgehead nitrogen polyheterocycles for the presence of two adjacent reactive functional groups. Through these intermediates, we obtained thiazolothienopyrimidines, thienopyrimidothiadiazoles, thienopyrimidothiadiazines, thienopyrimidotetrazines and thienotriazolopyrimidines [1-9].

In this work, we report the synthesis of new N3-substituted-2-thioxothieno[2,3-*d*]pyrimidinone derivatives (**8**-**12**) and of new 2,3-diamino unsubstituted and substituted thieno[2,3-*d*]pyrimidinone derivatives (**13**-**17**); intermediates **13**-**17** were used for the preparation of remarkably interesting new compounds both from a chemical and pharmacological viewpoint such as the thieno[2,3-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidinone (**18**-**21**), the thieno-[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidinone (**25, 29** and **30**) and the thieno[2',3':4,5]pyrimido[1,2-*b*][1,2,4,5]tetrazin-9-one (**26**-**28**) derivatives. The synthetic procedures used in this paper are reported in Schemes 1 and 2.

The reaction of the isothiocyanate **1** [10] in dichloromethane at room temperature with an ammonium hydroxide solution, with propylamine or methoxycarbonylhydrazine gave the derivatives **2**, **5**, and **7**, respectively.

The 2-thioxo derivatives **8**-**11** were obtained from compounds **2**, **4** [11], **5**, and **7**, respectively, by refluxing in an ethanolic potassium hydroxide solution, followed by acidification of the aqueous suspension of the separated solids. Compounds **8** and **11** are identical with those obtained by other synthetic routes [12,13]. Compound **12** was obtained from the isothiocyanate **1** with ethylenediamine under the same experimental conditions adopted for the synthesis of derivatives **2**, **5**, and **7**. By reaction of compounds **2** and **3** [13] with hydrazine hydrate were prepared the 2,3-diamino derivative **13** and the 2-methylamino derivative **15**, respectively. The 2-amino-3-methylamino derivative **14** was

Scheme 1



prepared from compound **2** with methylhydrazine, derivatives **16** and **17** were obtained from compounds **6** [14] and **7** and hydrazine hydrate.

An interesting synthetic route to obtain unsubstituted triazole moieties is the reaction of the 2,3-diamino derivative **13** with ethyl orthoformate at reflux in presence of *p*-toluenesulfonic acid (*p*-TSA), which gave the unsubstituted triazole derivative **18**, in the same reaction conditions the 1-methyl and the 3-methyl substituted triazoles **19** (method A) and **20** were obtained from the 2-amino-3-methylamino derivative **14** and the 3-amino-2-methylamino derivative **15**, respectively.

The reaction of 2,3-diamino derivative **13** with acetic acid at reflux in presence of methanesulfonic acid and phosphorus pentoxyde gave also the 2-methyl triazolo **21**.

The alkylation of the unsubstitute triazole **18** with methyl iodide in dimethylformamide in presence of sodium hydride gave the 1-methyl isomer **19** (method B); the analytical and spectral data were like those of the compound previously obtained from derivative **14** and ethyl orthoformate.

From the potassium salt of the 3-amino-2-thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-(1*H*)-one **22** [8] with methyl iodide was obtained the 2-methylthio derivative **23**. Derivatives **23** with hydrazine hydrate at reflux gave a compound identical TLC, mp, ir and ^{1}H nmr with the 2-hydrazino derivative **16**, obtained (Scheme 1) from compound **6** and hydrazine monohydrate.

The amino group of the 2-methylthio derivative **23** reacted with 4-bromobenzaldehyde to give the bromophenylmethyleneamino derivative **24**, that with hydrazine hydrate at reflux gave the 2-hydrazino derivative **16**.

Derivative **16** reacted at reflux in acetic acid with ethyl orthoformate to give a mixture of derivatives **25** and **26**; derivative **26**, after cooling, was isolated as a solid, derivative **25** was obtained by removing the solvent under reduced pressure. The yield of derivative **26**, in this reaction, was very low. Pure derivative **26** was isolated by the reaction of 2-hydrazino derivative **16** with dimethylformamide dimethyl acetal at room temperature for 4 hours.

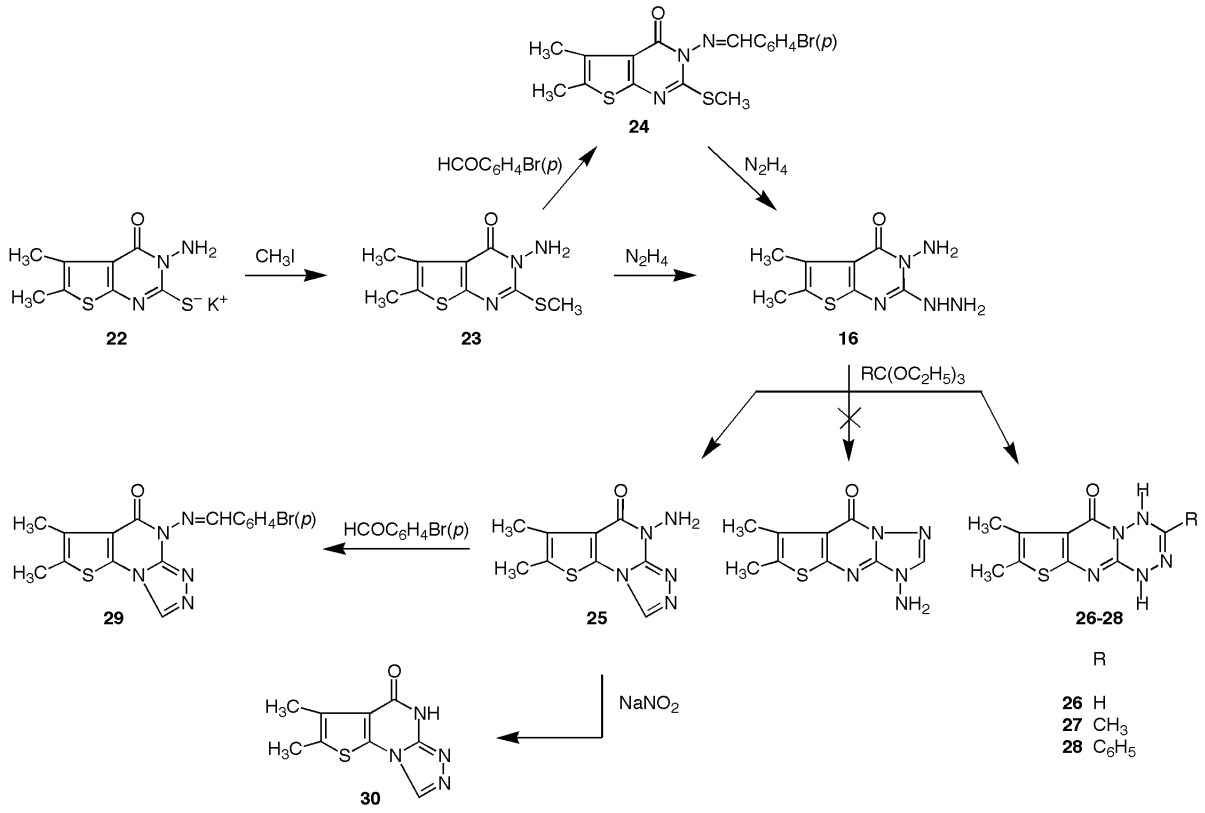
Derivative **16** with ethyl orthoacetate and orthobenzoate gave also compounds **27** and **28**.

Assignment of the structure to thienopyrimido[1,2,4,5]-tetrazine compounds **26-28** was obtained by elemental analysis, ir and ^{1}H nmr. In particular, the ^{1}H nmr spectral data were like that of the tetrahydrobenzothienopyrimido-[1,2,4,5]tetrazine derivative previously prepared [9].

The presence in compound **25** of the 3-amino group was confirmed through the reaction with 4-bromobenzaldehyde, which gave the derivative **29**.

Moreover, for derivative **25** was proposed the angular structure, since its deamination with a solution of sodium

Scheme 2



nitrite in hydrochloric acid gave **30**, which has different TLC, mp, ir, and ^{1}H nmr than that of the triazolo derivative **18** previously prepared and reported in Scheme 1.

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes on a Gallenkamp melting points apparatus. The 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 EA1108 elemental analyzer Fisons-Carlo Erba instrument and were within 0.4% of the theoretical values. The low resolution mass spectra were recorded by direct insertion into the ion source on a VG-2AB2SE mass spectrometer under the following conditions: ionization energy, 70 eV; source temperature 250-300 °C; trap current 60 µA. The ^{1}H nmr spectra were recorded at 200 MHz on a Varian Inova-Unity 200 spectrometer; chemical shifts (δ) are reported in ppm from TMS as internal standard; coupling constants (J) are in Hertz. Signal multiplicities are presented by s (singlet), d (doublet), t (triplet), q (quartet), br s (broad singlet), and m (multiplet). The purity of compounds was checked by tlc 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 2-[[(Amino and Methoxycarbonylhydrazino)thioxomethyl]-amino]-4,5-dimethyl-3-thiophenecarboxylate (**2**) and (**7**).

A solution of isothiocyanate **1** (1.76 g, 7.3 mmol) in dichloromethane (20 ml) was added to a solution of NH_4OH (0.8 ml, 30%) or methoxycarbonylhydrazine (0.66 g, 7.3 mmol) in dichloromethane (10 ml) and the mixture was stirred at room temperature for 0.5-1 hour. The solid was collected, washed with ethanol, dried and recrystallized.

Ethyl 2-(Aminothioxomethyl)amino-4,5-dimethyl-3-thiophenecarboxylate (**2**).

Compound **2** was recrystallized from ethanol/dioxane (1.10 g, 58%), mp 214-215 °C dec.; ir (KBr): ν 3390 and 3200 (NH), 1650 (C=O) cm^{-1}. ^{1}H nmr (dimethylsulfoxide-d_6): δ 1.32 (t, J = 7 Hz, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 4.30 (q, J = 7 Hz, 2H, CH_2), 8.45 (s, 2H, NH_2), 11.40 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_{14}N_2O_2S_2$: C, 46.51; H, 5.43; N, 10.85; S, 24.80. Found: C, 46.12; H, 5.29; N, 10.68; S, 24.66.

Ethyl 2-[[(Methoxycarbonylhydrazino)thioxomethyl]amino]-4,5-dimethyl-3-thiophenecarboxylate (**7**).

Compound **7** was recrystallized from ethanol/dioxane (0.85 g, 35%), mp 224-225 °C dec.; ir (KBr): ν 3210 and 3175 (NH), 1730 and 1700 (C=O) cm^{-1}. ^{1}H nmr (dimethylsulfoxide-d_6): δ 1.31 (t, J = 7 Hz, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.30 (q, J = 7 Hz, 2H, CH_2), 9.78 (s, 1H, NH), 10.28 (s, 1H, NH), 12.32 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{17}N_3O_4S_2$: C, 43.50; H, 5.13; N, 12.69; S, 19.33. Found: C, 43.67; H, 5.16; N, 12.55; S, 19.45.

Ethyl 2-[[(Propylamino)thioxomethyl]amino]-4,5-dimethyl-3-thiophenecarboxylate (**5**).

To a solution of isothiocyanate **1** (1 g, 4.1 mmol) in dichloromethane (15 ml) a solution of propylamine (0.28 ml, 4.7 mmol) in dichloromethane (5 ml) was added and the mixture was stirred at room temperature for 3 hours. The solution obtained was concentrated under reduced pressure and the solid collected with a little amount of ethanol, dried and recrystallized from ethanol to give **5** (0.4 g, 32%), mp 156-158 °C; ir (KBr): ν 3200 (NH), 1650 (C=O) cm^{-1}. ^{1}H nmr (dimethylsulfoxide-d_6): δ 0.89 (t, J = 7 Hz, 3H, CH_3), 1.32 (t, J = 7 Hz, 3H, CH_3), 1.55 (m, 2H, CH_2), 2.17 (s, 6H, $2CH_3$), 4.29 (q, J = 7 Hz, 2H, CH_2), 9.37 (s, 1H, NH), 11.45 (s, 1H, NH). The NCH_2 signal was identified by exchange with D_2O as a singlet at δ 3.34.

Anal. Calcd. for $C_{13}H_{20}N_2O_2S_2$: C, 52.00; H, 6.67; N, 9.33; S, 21.33. Found: C, 52.08; H, 6.40; N, 9.35; S, 21.05.

General Procedure for the Synthesis of 2,3-Dihydro-3-substituted-2-thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(1*H*)-one Derivatives **8**-**11**.

To a solution of KOH (3.21 mmol) in absolute ethanol (13 ml) thiophene ethyl ester derivatives **2**, **4**, **5** and **7** (3.21 mmol), respectively, were added and the mixture was refluxed for 1 hour. The solid was then collected while hot, dried and poured in water (20 ml), the mixture was acidified with concentrated hydrochloric acid and stirred for 1 hour. The solid was collected, washed with water, dried and recrystallized.

Analytical and spectral data of compounds **8** (yield: 0.50 g, 73%) and **11** (yield: 0.60 g, 82%) are identical with those of compounds obtained by other synthetic routes [12,13].

2,3-Dihydro-3-(3-Hydroxypropyl)-2-thioxo-5,6-dimethyl-1*H*-thieno[2,3-*d*]pyrimidin-4-one (**9**).

Compound **9** was obtained after recrystallization from ethanol (0.33 g, 38%), mp 209-210 °C; ir (KBr): ν 3340 and 3080 (OH, NH), 1675 (C=O) cm^{-1}. ^{1}H nmr (dimethylsulfoxide-d_6): δ 1.80 (m, 2H, CH_2), 2.28 (s, 6H, $2CH_3$), 3.46 (t, J = 6.4 Hz, 2H, CH_2), 4.37 (t, J = 7.6 Hz, 2H, CH_2), 13.50 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{14}N_2O_2S_2$: C, 48.89; H, 5.18; N, 10.37; S, 23.70. Found: C, 48.58; H, 5.30; N, 10.03; S, 23.45.

2,3-Dihydro-3-propyl-2-thioxo-5,6-dimethyl-1*H*-thieno[2,3-*d*]pyrimidin-4-one (**10**).

Compound **10** was obtained after recrystallization from ethanol (0.22 g, 27%), mp 224-225 °C; ir (KBr): ν 3130 (NH), 1690 (C=O) cm^{-1}. ^{1}H nmr (dimethylsulfoxide-d_6): δ 0.89 (t, J = 7.4 Hz, 3H, CH_3), 1.65 (m, 2H, CH_2), 2.27 (s, 6H, $2CH_3$), 4.27 (t, J = 7.4 Hz, 2H, CH_2), 13.51 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{14}N_2OS_2$: C, 51.97; H, 5.51; N, 11.02; S, 25.20. Found: C, 51.82; H, 5.68; N, 10.89; S, 25.29.

2,3-Dihydro-3-(2-Aminoethyl)-2-thioxo-5,6-dimethyl-1*H*-thieno[2,3-*d*]pyrimidin-4-one (**12**).

To a solution of ethylenediamine (0.56 g, 9.3 mmol) in dichloromethane (10 ml) a solution of isothiocyanate **1** (2 g, 8.3 mmol) in dichloromethane (30 ml) was added and the solution was stirred at room temperature for 3 hours. The suspension was concentrated under reduced pressure, the solid was collected, washed with diethyl ether, dried and recrystallized from dimethylformamide to give derivative **12** (1 g, 47%), mp 245 °C; ir (KBr): ν 3130 (NH), 1640 (C=O) cm^{-1}. ^{1}H nmr (dimethylsulfoxide-d_6): δ 2.22 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.16 (t, J = 6 Hz, 2H, CH_2), 4.72 (t, J = 6 Hz, 2H, CH_2), 7.78 (s, 2H, NH_2).

Anal. Calcd. for $C_{10}H_{13}N_3OS_2$: C, 47.06; H, 5.10; N, 16.47; S, 25.10. Found: C, 46.89; H, 5.31; N, 16.31; S, 24.83.

General Procedure for the Synthesis of 2,3-Substituted-5,6-dimethyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-one Derivatives **13**, **15**, **16** and **17**.

A mixture of thiophene ethyl ester derivitives **2**, **3**, **6**, and **7** (1.78 mmol), respectively, and hydrazine hydrate (4 ml) was kept at reflux for 12 hours in ethanol (5 ml). After cooling, the solid was collected, washed with ethanol, dried and recrystallized.

2,3-Diamino-5,6-dimethyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one (**13**).

Compound **13** was obtained after recrystallization from dioxane/dimethylformamide (0.1 g, 27%), mp 279-280 °C dec.; ir (KBr): ν 3260 and 3180 (NH), 1660 (C=O) cm^{-1}. ^1H nmr (dimethylsulfoxide-d_6): δ 2.22 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.70 (br s, 2H, NH_2), 8.14 (s, 2H, NH_2).

Anal. Calcd. for $C_8H_{10}N_4OS$: C, 45.71; H, 4.76; N, 26.67; S, 15.24. Found: C, 46.08; H, 5.01; N, 26.43; S, 15.03.

3-Amino-5,6-dimethyl-2-methylamino-3*H*-thieno[2,3-*d*]pyrimidin-4-one (**15**).

Compound **15** was obtained after recrystallization form ethanol (0.1 g, 25%), mp 255-257 °C; ir (KBr): ν 3300 (NH), 1665 (C=O) cm^{-1}. ^1H nmr (dimethylsulfoxide-d_6): δ 2.24 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 4.37 (s, 2H, NH_2), 8.33 (s, 1H, NH).

Anal. Calcd. for $C_9H_{12}N_4OS$: C, 48.21; H, 5.36; N, 25.00; S, 14.28. Found: C, 48.04; H, 5.37; N, 24.89; S, 14.51.

3-Amino-2-hydrazino-5,6-dimethyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one (**16**).

Compound **16** was obtained after recrystallization from ethanol/dioxane (0.1 g, 25%), mp 266-268 °C; ir (KBr): ν 3330 and 3080 (NH), 1680 (C=O) cm^{-1}. ^1H nmr (dimethylsulfoxide-d_6): δ 2.37 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 5.83 (br s, 4H, NH_2), 8.32 (s, 1H, NH).

Anal. Calcd. for $C_8H_{11}N_5OS$: C, 42.67; H, 4.89; N, 31.11; S, 14.22. Found: C, 42.92; H, 4.96; N, 31.15; S, 14.03.

3-Amino-2-isocarbonohydrazido-5,6-dimethyl-3*H*-thieno[2,3-*d*]-pyrimidin-4-one (**17**).

Compound **17** was obtained after recrystallization from ethanol/dioxane (0.09 g, 18%), mp >280 °C dec.; ir (KBr): ν 3260 and 3180 (NH), 1645 (C=O) cm^{-1}. ^1H nmr (dimethylsulfoxide-d_6): δ 2.25 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 5.02 (s, 2H, NH_2), 7.27 (s, 3H, NH).

Anal. Calcd. for $C_9H_{13}N_7O_2S$: C, 38.16; H, 4.59; N, 34.63; S, 11.31. Found: C, 38.03; H, 4.75; N, 34.24; S, 11.42.

2-Amino-5,6-dimethyl-3-methylaminothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**14**).

The ethyl 2-[(aminothioxomethyl)amino]-4,5-dimethyl-3-thiophenecarboxylate (**2**) (0.46 g, 1.78 mmol) was refluxed with methylhydrazine (3.2 ml) in ethanol (10 ml) for 12 hours. After cooling, the solution was extracted with chloroform, the organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The solid was collected with water, dried and recrystallized from 1-propanol to give compound **14** (0.1 g, 25%), mp 237-240 °C; ir (KBr): ν 3340, 3240 and 3100 (NH), 1650 (C=O) cm^{-1}. ^1H nmr (dimethylsulfoxide-d_6): δ 2.22 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 5.17 (br s, 2H, NH_2), 8.16 (s, 1H, NH).

Anal. Calcd. for $C_9H_{12}N_4OS$: C, 48.21; H, 5.36; N, 25.00; S, 14.28. Found: C, 47.95; H, 5.29; N, 24.75; S, 14.63.

General Procedure for the Synthesis of 6,7-Dimethylthieno[2,3-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidin-8(3*H*)-one (**18**) and of its 1- and 3-Methyl Derivatives **19** (method A) and **20**.

A mixture of diamino derivatives **13-15** (2.32 mmol), respectively, and *p*-toluensulfonic acid (3.48 mmol) was refluxed for 6 hours in ethyl orthoformate (10 ml). After cooling, the solid was collected, washed with ethanol, dried and recrystallized.

6,7-Dimethylthieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-8(3*H*)-one (**18**).

Compound **18** was obtained after recrystallization from ethanol/dioxane (0.12 g, 23%), mp 298-299 °C; ir (KBr): ν 3130 (NH), 1695 (C=O) cm^{-1}. ^1H nmr (dimethylsulfoxide-d_6): δ 2.29 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 9.06 (s, 1H, ArH), 14.04 (s, 1H, NH).

Anal. Calcd. for $C_9H_8N_4OS$: C, 49.09; H, 3.64; N, 25.45; S, 14.54. Found: C, 49.32; H, 3.90; N, 25.07; S, 14.53.

1,6,7-Trimethylthieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-8(3*H*)-one (**19**).

Method A.

Compound **19** was obtained after recrystallization from ethanol (0.14 g, 26%), mp 250-252 °C; ir (KBr): ν 1690 (C=O) cm^{-1}; ms: m/z 234 (100%) $[M^+]$; ^1H nmr (dimethylsulfoxide-d_6): δ 2.30 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 9.13 (s, 1H, ArH).

Anal. Calcd. for $C_{10}H_{10}N_4OS$: C, 51.28; H, 4.27; N, 23.93; S, 13.67. Found: C, 50.91; H, 4.55; N, 23.57; S, 14.02.

Method B.

To a solution of triazolo **18** (0.35 g, 1.59 mmol) in dimethylformamide (9.5 ml) sodium hydride (0.038 g, 1.58 mmol) was added, the mixture was stirred at room temperature for 30 minutes, then methyl iodide (0.11 ml) was added and the mixture was refluxed for 5 hours. After cooling, the solid was collected, dried and recrystallized from ethanol to give derivative **19** (0.09 g, 24%). Physical and chemical data were like those of the compound **19** prepared with the previous procedure.

3,6,7-Trimethylthieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-8(3*H*)-one (**20**).

Compound **20** was obtained after recrystallization from ethanol (0.11 g, 20%), mp 259-261 °C; ir (KBr): ν 1660 (C=O) cm^{-1}; ms: m/z 234 (100%) $[M^+]$; ^1H nmr (dimethylsulfoxide-d_6): δ 2.30 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 9.12 (s, 1H, ArH).

Anal. Calcd. for $C_{10}H_{10}N_4OS$: C, 51.28; H, 4.27; N, 23.93; S, 13.67. Found: C, 51.18; H, 4.40; N, 23.59; S, 13.71.

2,6,7-Trimethylthieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-8(3*H*)-one (**21**).

A mixture of diamino derivative **13** (0.37 g, 1.76 mmol), phosphorus pentoxide (0.25 g, 1.76 mmol), acetic acid (0.13 ml), and of methanesulfonic acid (0.5 ml) was kept at reflux for 9 hours at 100 °C. After cooling, the solution was poured into cold water, neutralized with a NaOH 10% solution and the solid was collected, washed with water, dried and recrystallized from ethanol/dioxane to give compound **21** (0.20 g, 49%), mp 290-292 °C dec.; ir (KBr): ν 1695 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.26 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 13.59 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_{10}N_4OS$: C, 51.28; H, 4.27; N, 23.93; S, 13.67. Found: C, 51.09; H, 4.50; N, 23.72; S, 13.60.

3-Amino-5,6-dimethyl-2-methylthiothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**23**).

To a suspension of the monopotassium salt **22** (1.6 g, 6.04 mmol) in water (100 ml), methyl iodide (1.2 ml) was added and the mixture was stirred at room temperature for 2 hours. The suspension was filtered and the solid thus obtained was washed with water, dried and recrystallized from ethanol/dioxane to give derivative **23** (1 g, 69%); mp 192-194 °C; ir (KBr): ν 3310 and 3210 (NH), 1645 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.38 (s, 3H, SCH_3), 5.69 (s, 2H, NH_2).

Anal. Calcd. for $C_9H_{11}N_3OS_2$: C, 44.81; H, 4.56; N, 17.42; S, 26.50. Found: C, 44.52; H, 4.76; N, 17.09; S, 26.17.

3-[[(4-Bromophenyl)methylene]amino]-5,6-dimethyl-2-methylthiothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**24**).

A mixture of the 3-amino-2-methylthio derivative **23** (0.7 g, 2.9 mmol) and of 4-bromobenzaldehyde (1 g, 5.4 mmol) was refluxed for 4 hours in acetic acid (20 ml). After cooling, the solid was collected washed with ethanol, dried and recrystallized from ethanol/dioxane to give derivative **24** (0.25 g, 21%), mp 232-234 °C; ir (KBr): ν 1675 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.36 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.48 (s, 3H, SCH_3), 7.78-7.91 (s, 4H, ArH), 9.19 (s, 1H, ArH).

Anal. Calcd. for $C_{16}H_{14}BrN_3OS_2$: C, 47.06; H, 3.43; N, 10.29; S, 15.69. Found: C, 46.71; H, 3.66; N, 9.95; S, 15.38.

3-Amino-2-hydrazino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (**16**).

This compound was also obtained with the following two procedures: a mixture of the 2-methylthio derivative **23** (3 g, 12.45 mmol) and of hydrazine monohydrate (25 ml) was refluxed for 6 hours in 2-propanol (50 ml). After cooling, the solid was collected, washed with ethanol, dried and recrystallized from ethanol/dioxane to give derivative **16** (1.1 g, 39%).

A mixture of 4-bromophenylmethyleneamino derivative **24** (0.44 g, 1.08 mmol) and of hydrazine monohydrate (3 ml) was refluxed for 6 hours in 2-propanol (8 ml). After cooling, the solid was collected, washed with ethanol, dried and recrystallized from ethanol/dioxane to give derivative **16** (0.15 g, 62%).

9-Amino-6,7-dimethyl-thieno[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-8(9*H*)-one (**25**) and 1,4-Dihydro-7,8-dimethyl-9*H*-thieno-[2',3':4,5]pyrimido[1,2-*b*][1,2,4,5]tetrazin-9-one (**26**).

A mixture of 2-hydrazino derivative **16** (0.82 g, 3.64 mmol) and ethyl orthoformate (0.66 ml) was refluxed for 30 minutes in acetic acid (16 ml). After cooling, the solid was collected, dried and recrystallized from ethanol to give derivative **26** in poor yield (0.015 g). Then, the solvent was evaporated under reduced pressure and the solid collected, washed with ethanol, dried and recrystallized from ethanol to give derivative **25** (0.34 g, 40%).

Compound **25** had mp 247-249 °C dec.; ir (KBr): ν 3315 and 3215 (NH), 1670 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.40 (s, 6H, $2CH_3$), 5.68 (s, 2H, NH_2), 9.21 (s, 1H, ArH).

Anal. Calcd. for $C_9H_9N_5OS$: C, 45.95; H, 3.82; N, 29.78; S, 13.62. Found: C, 45.88; H, 4.15; N, 29.45; S, 13.50.

Compound **26** had mp 264-266 °C dec.; ir (KBr): ν 3210 (NH), 1680 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.26 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 7.02 (d, J = 3 Hz, 1H, ArH), 9.61 (d, J = 3 Hz, 1H, NH exchanges with D_2O), 9.79 (s, 1H, NH exchanges with D_2O).

Anal. Calcd. for $C_9H_9N_5OS$: C, 45.95; H, 3.82; N, 29.78; S, 13.62. Found: C, 46.24; H, 4.08; N, 29.61; S, 13.61.

1,4-Dihydro-7,8-dimethyl-9*H*-thieno[2',3':4,5]pyrimido[1,2-*b*]-[1,2,4,5]tetrazin-9-one (**26**).

A mixture of 2-hydrazino derivative **16** (0.2 g, 0.88 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.11 ml) was stirred at room temperature for 4 hours in acetic acid (4 ml). The solid was collected, dried and recrystallized from ethanol to give derivative **26** (0.050 g, 25%).

1,4-Dihydro-3,7,8-trimethyl-9*H*-thieno[2',3':4,5]pyrimido[1,2-*b*][1,2,4,5]tetrazin-9-one (**27**).

A mixture of 2-hydrazino derivative **16** (0.4 g, 1.78 mmol) and ethyl orthoacetate (0.39 ml) was refluxed for 1 hour in acetic acid (10 ml). After cooling, to the solution was added water and the solid which separated was collected, washed with water, dried and recrystallized from ethanol to give derivative **27** (0.15 g, 34%), mp 283-285 °C dec.; ir (KBr): ν 3260, 3190 and 3120 (NH), 1665 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 1.93 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 9.44 (s, 1H, NH), 9.68 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_{11}N_5OS$: C, 48.19; H, 4.41; N, 28.11; S, 12.85. Found: C, 48.41; H, 4.56; N, 27.88; S, 12.73.

1,4-Dihydro-7,8-dimethyl-3-phenyl-9*H*-thieno[2',3':4,5]-pyrimido[1,2-*b*][1,2,4,5]tetrazin-9-one (**28**).

A mixture of 2-hydrazino derivative **16** (0.4 g, 1.78 mmol) and ethyl orthobenzoate (0.48 ml) was refluxed for 1 hour in acetic acid (12 ml). After cooling, to the solution was added water and the solid which separated was collected, washed with water, dried and recrystallized from ethanol to give derivative **28** (0.20 g, 36%), mp 206-208 °C; ir (KBr): ν 3260 and 3180 (NH), 1675 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.28 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.47-7.79 (m, 5H, ArH), 9.36 (s, 1H, NH), 10.31 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{13}N_5OS$: C, 57.87; H, 4.18; N, 22.50; S, 10.28. Found: C, 58.17; H, 4.56; N, 22.15; S, 10.38.

6,7-Dimethyl-3-[[(4-bromophenyl)methylene]amino]-thieno-[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-8(9*H*)-one (**29**).

A mixture of the triazolo derivative **25** (0.2 g, 0.8 mmol) and of 4-bromobenzaldehyde (0.35 g, 1.8 mmol) was refluxed for 4 hours in acetic acid (4 ml). After cooling, the solid was collected, washed with ethanol, dried and recrystallized from ethanol/dioxane to give derivative **29** (0.1 g, 29%), mp 260-261 °C dec.; ir (KBr): ν 1690 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.33 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.74-7.87 (m, 5H, ArH), 9.37 (s, 1H, ArH), 9.56 (s, 1H, ArH).

Anal. Calcd. for $C_{16}H_{12}BrN_5OS$: C, 47.76; H, 2.98; N, 17.41; S, 7.96. Found: C, 47.77; H, 3.06; N, 17.16; S, 7.51.

6,7-Dimethylthieno[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-8(1*H*)-one (**30**).

To a suspension of derivative **25** (0.13 g, 0.55 mmol) in 6 *N* hydrochloric acid (2.6 ml) a sodium nitrite solution (0.15 g, 2.17 mmol in 4.8 ml of water) was added dropwise with stirring at 0 °C. The mixture was stirred at room temperature for 45 minutes,

the solid was collected, washed with water and ethanol, dried and recrystallized from ethanol to give derivative **30** (0.04 g, 33%), mp 285-287 °C dec.; ir (KBr): ν 3090 (NH), 1680 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.38 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 9.13 (s, 1H, ArH), 12.69 (s, 1H, NH).

Anal. Calcd. for $C_9H_8N_4OS•1/2H_2O$: C, 47.16; H, 3.93; N, 24.45; S, 13.97. Found: C, 47.00; H, 4.14; N, 24.06; S, 13.92.

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