

One-pot Synthesis of Fused 2-Thiouracils: Pyrimidopyrimidines, Pyridopyrimidines and Imidazolopyrimidines

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Several 6-substitued-1-methyl-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-*d*]pyrimidine-4-ones and ethyl 7-amino-5-aryl-1-methyl-4-oxo-1,2,3,4-tetrahydro-2-thiopyrido[2,3-*d*]pyrimidines-6-carboxylates were synthesized by treatment of 6-amino-1-methyl-2-thiouracil with primary amines and formalin (40 %), and with ethyl 3-aryl-2-cyanoacrylate respectively. 8-Substituted-7-hydroxy-3-methyl-2-thioxanthines were synthesized by the treatment of 6-amino-1-methyl-5-nitroso-2-thiouracil with benzylidene-anilines. Elemental and spectral analyses were performed for the new compounds.

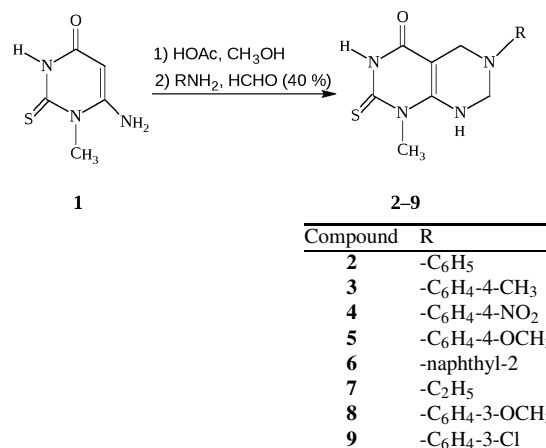
Key words: 6-Amino-1-methyl-2-thiouracil and Nitroso Analogs, 6-Substituted-1-methyl-pyrimido[4,5-*d*]pyrimidines, 1,2,3,4-Tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylates, 8-Aryl-7-hydroxy-3-methyl-2-thiopurines

Introduction

Chemotherapeutically valuable pyrimidopyrimidinedione derivatives have been reported in the patent literature [1]. The synthesis of pyrimidine *via* Mannich bases has been carried out [2]. The Mannich reaction of 3(5)-arylamino-pyrazoles with primary amines has been described [3] as a route to pyrazolo[3,4-*d*]pyrimidines. 6-Amino-1-methyl- or 1-(2-chlorobenzyl)- or 1,3-dimethyl-uracil were the key intermediates for the synthesis of pyrimido[4,5-*d*]pyrimidines *via* a Mannich base [4, 5]. A literature survey revealed no previous reports on 2-thiopyrimido[4,5-*d*]pyrimidines. Due to the importance of thiopurines and thio-pyrimidines as potential biological agents [6 – 10], we now report the synthesis of 2-thiopyrimidopyrimidines, pyrido[2,3-*d*]pyrimidine-6-carboxylates and 7-hydroxy-2-thioxanthines.

Results and Discussion

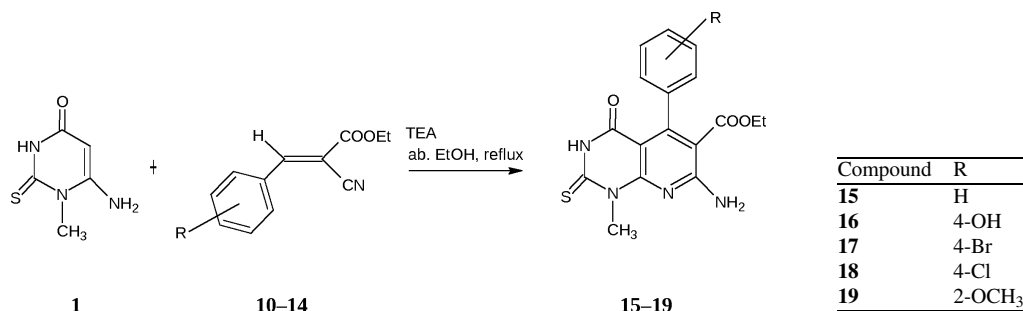
In a one-pot synthesis, 6-amino-1-methyl-2-thiouracil [11] (**1**) in methanol was treated with acetic acid at 40 °C, then a primary aliphatic or aromatic amine in methanol (1 equivalent) and formalin (40 %) (4 equivalents) were added at r. t. This provided the corresponding pyrimido[3,4-*d*]pyrimidines **2–9** (Scheme 1) in excellent yield. The ¹H NMR spectrum (300 MHz,



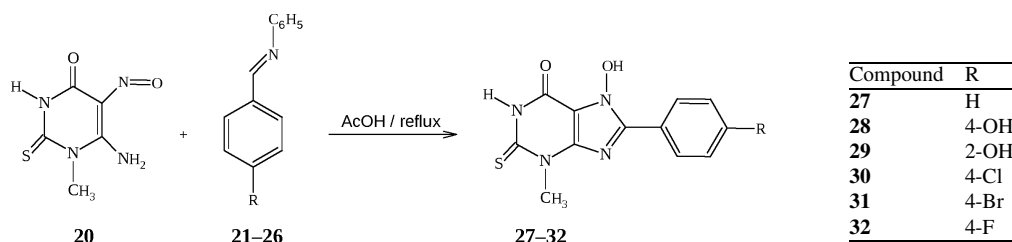
Scheme 1.

[D₆]DMSO) for **4** revealed the absence of proton 5-H of uracil (**1**) at δ = 4.88 and the appearance of a triplet at 7.59 characteristic for N⁸-H and the appearance of a singlet at 4.63 and of a doublet at 5.38 ppm characteristic for the methylene group at C-5 and C-7, respectively. Characteristic IR absorptions were observed at ν = 3356 (NH) and 1643 cm⁻¹ (C=O).

The importance of pyrido[2,3-*d*]pyrimidines as biologically active compounds includes their use as antitumor [12], antibacterial [13 – 15] and anticonvulsive agents [16]. The treatment of **1** with ethyl 3-phenyl-



Scheme 2.



Scheme 3.

2-cyanoacrylates **10–14** in absolute ethanol and in the presence of triethylamine (TEA) (3 mL) by heating under reflux afforded pyrido[2,3-*d*] pyrimidines **15–19** (Scheme 2) in moderate yield. The formation of **15–19** proceeded through a Michael addition which depends on the nucleophilicity of C-5 in uracil towards electrophilic reagents. The ¹H NMR spectrum for **19** showed a triplet at $\delta = 1.12–1.28$ characteristic for a CH₃ group, a quartet at 4.23–4.51 ppm characteristic for a CH₂ group, and a singlet at 6.42 ppm characteristic for a NH₂ group.

7-Hydroxyxanthine and its 8-alkyl or 8-aryl derivatives have been prepared from 6-amino-5-nitrosouracils by the reaction with aliphatic or aromatic aldehydes [17–21]. Due to the various biological activities [18] exhibited by these compounds, we present herein a versatile synthetic procedure for 8-aryl-7-hydroxy-3-methyl-2-thioxanthines [22] **27–32** via a transamination process using aldehyde-anils **21–26**. Thus, refluxing of **21–26** with 6-amino-1-methyl-5-nitroso-2-thiouracil [23] (**20**) in acetic acid took place by the elimination of aniline to give **27–32** (Scheme 3) in 36–55 % yield. The ¹H NMR spectrum of **30** showed a broad singlet at $\delta = 13.14$ characteristic for 7-OH, and a singlet at 12.33 ppm characteristic for N¹-H.

Experimental Section

Melting points were determined with an Electrothermal Mel-Temp II apparatus and are uncorrected. IR spectra were

obtained for the solid state in potassium bromide discs using a Perkin-Elmer model 1430 spectrometer. ¹H and ¹³C NMR spectra were recorded on a Varian Gemini-300 spectrometer at 300 and 75 MHz, respectively, using tetramethylsilane (TMS) as internal standard and [D₆]DMSO as solvent. Mass spectra were recorded on an VG-7035 instrument at 70 or 15 eV. Elemental analyses were determined at the Micro-analytical Center of Cairo University (Giza, Egypt).

General procedure for 6-substitued-1-methyl-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-*d*] pyrimidine-4-ones **2–9**

A mixture of **1** (2.0 mmol) in methanol (20 mL) and acetic acid (2 mL) was heated to 40 °C, and then a primary amine (aromatic or aliphatic) (2.0 mmol) in methanol (5 mL) and formalin (40 %, 4 equivalents) were added dropwise at r.t. with stirring for 1 h. The resulting precipitate was filtered, washed with ethanol and recrystallized from H₂O/DMF (2 : 1) to give **2–9**.

1-Methyl-6-phenyl-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-*d*]pyrimidin-4-one (**2**)

Yield 0.48 g (87 %). – M. p. > 300 °C. – IR (KBr): $\nu = 3360$ (NH), 3340 (NH), 3072 (CH ar.), 1680 (C=S), 1633 (C=O), 1604 (C=C) cm⁻¹. – ¹H NMR: $\delta = 4.0$ (s, 3H, NMe), 4.52 (s, 5-H₂, CH₂), 5.08–5.10 (d, 7-H₂, CH₂), 7.54–7.98 (m, 5H-ar.), 8.17 (t, 1H, 8-H), 13.19 (bs, 1H, 3-H). – ¹³C NMR: $\delta = 28.79$ (NCH₃), 43.15 (CH₂), 45.61 (CH₂), 125.29, 128.53, 130.77, 133.72, 134.51, 154.53, 162.32, 166.13. – MS (70 eV): m/z (%) = 274 (37) [M]⁺, 174 (51), 146 (100), 132 (39), 104 (33), 91 (21), 77 (41), 60 (36). – Anal. for C₁₃H₁₄N₄OS: calcd. C 56.92, H 5.14, N 20.42; found C 56.88, H 5.06, N 20.31.

1-Methyl-6-(4-tolyl)-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-d]pyrimidin-4-one (3)

Yield 0.41 g (74 %). – M. p. 212–14 °C. – IR (KBr): ν = 3226 (NH), 3107 (CH ar.), 1642 (C=O), 1609 (C=C) cm^{-1} . – ^1H NMR: δ = 2.33 (s, 3H, Me), 3.89 (s, 3H, NMe), 4.41 (s, 5-H₂, CH₂), 4.99 (d, 7-H₂, CH₂), 7.28–7.66 (dd, 4H-ar.), 8.0 (t, 1H, 8-H), 12.89 (s, 1H, 3-H). – ^{13}C NMR: δ = 20.82 (CH₃), 28.67 (NCH₃), 41.73 (CH₂), 45.03 (CH₂), 118.34, 125.19, 129.23, 132.68, 134.09, 154.32, 162.21, 165.61. – MS (70 eV): m/z (%) = 288 (64) [M]⁺, 273 (42), 244 (73), 201 (69), 154 (61), 106 (28), 91 (100), 60 (36). – Anal. for C₁₄H₁₆N₄OS: calcd. C 58.32, H 5.59, N 19.43; found C 58.02, H 5.47, N 20.10.

1-Methyl-6-(4-nitrophenyl)-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-d]pyrimidin-4-one (4)

Yield 0.50 g (82 %). – M. p. > 300 °C. – IR (KBr): ν = 3356 (NH), 3096 (CH ar.), 1680 (C=S), 1643 (C=O), 1501, 1265, 1085 cm^{-1} . – ^1H NMR: δ = 3.78 (s, 3H, Me), 4.63 (s, 5-H₂, CH₂), 5.38 (d, 7-H₂, CH₂), 6.91–6.94 (d, 2H, J = 7.5 Hz, 2H-ar.), 7.80–7.84 (d, 2H, J = 7.5 Hz, 2H-ar.), 7.59 (t, 1H, NH), 12.23 (s, 1H, NH). – ^{13}C NMR: δ = 28.82 (NCH₃), 43.19 (CH₂), 45.76 (CH₂), 125.84, 128.92, 131.25, 133.87, 134.62, 154.55, 162.63, 168.03. – MS (70 eV): m/z (%) = 319 (8) [M]⁺, 272 (4), 150 (100). – Anal. for C₁₃H₁₃N₅O₃S: calcd. C 48.90, H 4.10, N 21.93; found C 49.01, H 4.07, N 21.80.

1-Methyl-6-(4-methoxyphenyl)-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-d]pyrimidin-4-one (5)

Yield 0.46 g (79 %). – M. p. 220–22 °C. – IR (KBr): ν = 3330 (NH), 3040 (CH ar.), 2906 (CH aliph.), 1640 (C=O), 1602 (C=C), 1507 cm^{-1} . – ^1H NMR: δ = 3.76 (s, 3H, Me), 4.09 (s, 3H, OMe), 4.53 (s, 5-H₂, CH₂), 5.08–5.10 (d, 7-H₂, CH₂), 6.69–7.73 (dd, 4H-ar.), 7.79 (t, 1H, 8-H), 13.0 (bs, 1H, 3-H). – MS (70 eV): m/z (%) = 304 (66) [M]⁺, 289 (15), 216 (23), 183 (12), 146 (31), 104 (33), 92 (100), 88 (39), 73 (18). – Anal. for C₁₄H₁₆N₄O₂S: calcd. C 55.25, H 5.30, N 18.41; found C 55.37, H 5.19, N 18.70.

1-Methyl-6-(2-naphthyl)-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-d]pyrimidin-4-one (6)

Yield 0.44 g (71 %). – M. p. > 300 °C. – IR (KBr): ν = 3333 (NH), 3171 (NH), 3063 (CH arom), 2939 (CH aliph.), 1651 (C=S), 1635 (C=O), 1620 (C=C), 1589, 1489 cm^{-1} . – ^1H NMR: δ = 3.73 (s, 3H, NMe), 4.14 (s, 5-H₂, CH₂), 4.63–4.65 (d, 7-H₂, CH₂), 6.59–7.61 (m, 7 H-ar.), 8.24 (t, 1H, 8-H), 11.98 (s, 1H, 3-H). – MS (70 eV): m/z (%) = 324 (48) [M]⁺, 309 (42), 236 (9), 198 (11), 140 (15), 127 (100), 88 (39), 73 (22). – Anal. for C₁₇H₁₆N₄OS: calcd. C 62.95, H 4.97, N 17.27; found C 62.83, H 5.04, N 17.35.

1-Methyl-6-ethyl-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-d]pyrimidin-4-one (7)

Yield 0.29 g (68 %). – M. p. 210–12 °C. – IR (KBr): ν = 3240 (NH), 2963 (CH aliph.), 1632 cm^{-1} (C=O), 1616 (C=C), 1538, 1262 cm^{-1} . – ^1H NMR: δ = 1.12–1.37 (t, 3H, Me), 2.62–2.98 (q, 2H, CH₂), 3.42 (s, 3H, NMe), 4.07 (s, 5-H₂, CH₂), 4.47–4.49 (d, 7-H₂, CH₂), 8.25 (t, 1H, 8-H), 12.57 (bs, 1H, 3-H). – ^{13}C NMR: δ = 14.89 (CH₃), 16.51 (CH₂), 28.79 (NCH₃), 41.00 (CH₂), 43.72 (CH₂), 125.29, 128.53, 154.53, 160.03. – MS (70 eV): m/z (%) = 226 (17) [M]⁺, 198 (40), 153 (71), 138 (29), 127 (100), 73 (22). – Anal. for C₉H₁₄N₄OS: calcd. C 47.78, H 6.23, N 24.76; found C 47.71, H 6.16, N 25.30.

1-Methyl-6-(3-methoxyphenyl)-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-d]pyrimidin-4-one (8)

Yield 0.39 g (68 %). – M. p. 250–252 °C. – IR (KBr): ν = 3348 (NH), 3178 (CH ar.), 2939 (CH aliph.), 1651 (C=O), 1620 (C=C) cm^{-1} . – ^1H NMR: δ = 3.57 (s, 3H, NMe), 3.98 (s, 3H, OMe), 4.42 (s, 5-H₂, CH₂), 4.87–4.89 (s, 7-H₂, CH₂), 6.88–7.76 (m, 4H-ar.), 8.05 (t, 1H, 8-H), 13.0 (bs, NH). – ^{13}C NMR: δ = 28.22 (NCH₃), 43.11 (CH₂), 45.40 (CH₂), 54.87 (OCH₃), 115.41, 119.64, 125.27, 128.47, 130.53, 133.23, 134.12, 154.19, 162.03, 165.80. – Anal. for C₁₄H₁₆N₄O₂S: calcd. C 55.25, H 5.30, N 18.41; found C 55.12, H 5.18, N 18.07.

1-Methyl-6-(3-chlorophenyl)-2,5,7,8-tetrahydro-2-thiopyrimido[4,5-d]pyrimidin-4-one (9)

Yield 0.43 g (73 %). – M. p. 180–182 °C. – IR (KBr): ν = 3260 (NH), 3081 (CH ar.), 2963 (CH aliph), 1639 (C=O), 1612 (C=C) cm^{-1} . – ^1H NMR: δ = 3.46 (s, 3H, NMe), 4.41 (s, 5-H₂, CH₂), 5.02 (s, 7-H₂, CH₂), 6.86–7.23 (m, 4H-ar.), 8.01–8.06 (t, 1H, 8-H), 12.92 (s, 1H, 3-H). – ^{13}C NMR: δ = 28.60 (NCH₃), 43.05 (CH₂), 45.11 (CH₂), 125.18, 128.43, 129.71, 133.50, 134.51, 154.53, 162.32, 166.13. – MS (70 eV): m/z (%) = 310 (2) [M+2]⁺, 309 (3) [M+1]⁺, 308 (7) [M]⁺, 292 (66), 234 (24), 204 (14), 138 (33), 102 (18), 75 (20), 68 (100), 53 (33). – Anal. for C₁₃H₁₃ClN₄OS: calcd. C 50.56, H 4.24, N 18.14; found C 50.71, H 4.11, N 18.22.

General procedure for ethyl 5-aryl-7-amino-1-methyl-4-oxo-2-thio-1,2,3,4-tetra-hydropyrido[2,3-d]pyrimidine-6-carboxylates 15–19

A mixture of equimolar amounts of **1** (2.0 mmol) and the appropriate ethyl 3-aryl-2-cyanoacrylate **10–14** (2 mmol) in absolute ethanol (10 mL) in the presence of TEA (3 mL) was refluxed for 4 h. After cooling, the solid precipitate was collected by filtration, washed with ethanol and recrystallized from EtOH-DMF (3 : 1), to afford the desired compounds **15–19** in 60–85 % yield.

Ethyl 7-amino-1-methyl-4-oxo-5-phenyl-1,2,3,4-tetrahydro-2-thiopyrido[2,3-d]pyrimidine-6-carboxylate (15)

Yield 0.57 g (84 %). – M. p. 254–256 °C. – ^1H NMR: δ = 1.17–1.32 (t, 3H, Me), 3.89 (s, 3H, NCH₃), 4.46–4.61 (q, 2H, CH₂), 6.42 (s, 2H, NH₂), 6.86–6.88 (m, 3H-ar.), 7.68–7.70 (m, 2H-ar.), 13.05 (s, 1H, 3-H). – ^{13}C NMR: δ = 13.89 (CH₃), 29.01 (NCH₃), 37.12 (CH₂), 91.15, 126.78, 126.93, 128.44, 128.63, 128.95, 139.21, 141.01, 156.42, 161.72, 163.53, 168.82. – MS (70 eV): m/z (%) = 356 (24) [M]⁺, 328 (61), 284 (18), 268 (100), 211 (41), 183 (7), 131 (29), 115 (25), 77 (48), 44 (12). – Anal. for C₁₇H₁₆N₄O₃S: calcd. C 57.29, H 4.52, N 15.72; found C 57.08, H 4.49, N 15.80.

Ethyl 7-amino-1-methyl-4-oxo-5-(4-hydroxyphenyl)-1,2,3,4-tetrahydro-2-thiopyrido[2,3-d]pyrimidine-6-carboxylate (16)

Yield 0.65 g (91 %). – M. p. 249–251 °C. – ^1H NMR: δ = 1.11–1.23 (t, 3H, Me), 3.78 (s, 3H, NMe), 4.39–4.47 (q, 2H, CH₂), 6.33 (s, 2H, NH₂), 6.79–6.81 (d, J = 9.0 Hz, 2H-ar.), 7.38–7.40 (d, J = 9.0 Hz, 2H-ar.), 11.80 (s, 1H, OH), 12.97 (s, 1H, 3-H). – ^{13}C NMR: δ = 13.88 (CH₃), 29.11 (NCH₃), 37.18 (CH₂), 91.22, 126.89, 127.01, 128.14, 128.52, 128.79, 139.03, 140.76, 156.23, 161.45, 163.53, 168.75. – Anal. for C₁₇H₁₆N₄O₄S: calcd. C 54.83, H 4.33, N 15.04; found C 54.95, H 4.23, N 14.97.

Ethyl 7-amino-1-methyl-4-oxo-5-(4-bromophenyl)-1,2,3,4-tetrahydro-2-thiopyrido[2,3-d]pyrimidine-6-carboxylate (17)

Yield 0.76 g (92 %). – M. p. 266 °C. – ^1H NMR: δ = 1.14–1.26 (t, 3H, Me), 3.81 (s, 3H, NMe), 4.43–4.49 (q, 2H, CH₂), 6.34 (s, 2H, NH₂), 6.81–6.83 (d, J = 8.8 Hz, 2H-ar.), 7.42–7.44 (d, J = 8.8 Hz, 2H-ar.), 12.96 (s, 1H, 3-H). – ^{13}C NMR: δ = 13.74 (CH₃), 29.08 (NCH₃), 37.07 (CH₂), 91.12, 126.87, 126.01, 128.14, 128.49, 128.72, 139.01, 140.69, 156.13, 161.32, 163.49, 168.73. – Anal. for C₁₇H₁₅BrN₄O₃S: calcd. C 46.90, H 3.47, N 12.86; found C 46.67, H 3.44, N 12.79.

Ethyl 7-amino-1-methyl-4-oxo-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-thiopyrido[2,3-d]pyrimidine-6-carboxylate (18)

Yield 0.71 g (95 %). – M. p. 256 °C. – ^1H NMR: δ = 1.13–1.28 (t, 3H, Me), 3.82 (s, 3H, NMe), 4.41–4.49 (q, 2H, CH₂), 6.37 (s, 2H, NH₂), 6.83–6.85 (d, J = 8.3 Hz, 2H-ar.), 7.45–7.47 (d, J = 8.3 Hz, 2H-ar.), 12.98 (s, 1H, 3-H). – MS (70 eV): m/z (%) = 392 (17) [M+2]⁺, 391 (32) [M+1]⁺, 390 (15) [M]⁺, 362 (22), 317 (67), 274 (59), 244 (73), 186 (18), 171 (9), 131 (24), 112 (100), 77 (73). – Anal. for C₁₇H₁₅ClN₄O₃S: calcd. C 52.24, H 3.86, N 14.33; found C 52.05, H 3.81, N 14.29.

Ethyl 7-amino-1-methyl-4-oxo-5-(4-methoxyphenyl)-1,2,3,4-tetrahydro-2-thiopyrido[2,3-d]pyrimidine-6-carboxylate (19)

Yield 0.57 g (78 %). – M. p. 238 °C. – ^1H NMR: δ = 1.12–1.28 (t, 3H, Me), 3.83 (s, 3H, NMe), 4.32 (s, 3H, OMe), 4.43–4.61 (q, 2H, CH₂), 6.42 (s, 2H, NH₂), 7.35–7.42 (d, J = 8.8 Hz, 2H-ar.), 7.69–7.71 (d, J = 8.3 Hz, 2H-ar.), 12.86 (s, 1H, 3-H). – ^{13}C NMR: δ = 13.73 (CH₃), 29.06 (NCH₃), 37.16 (CH₂), 54.36 (OCH₃), 91.18, 126.84, 127.01, 128.12, 128.47, 128.75, 140.13, 141.56, 156.21, 161.46, 163.47, 169.31. – MS (70 eV): m/z (%) = 386 (15) [M]⁺, 315 (22), 257 (9), 231 (100), 186 (37), 172 (79), 131 (24), 115 (13), 77 (12). – Anal. for C₁₈H₁₈N₄O₄S: calcd. C 55.95, H 4.69, N 14.50; found C 55.81, H 4.72, N 14.39.

General procedure for 8-substituted 3-methyl-7-hydroxy-2-thioxanthines (27–32)

Imines **21–26** (2.0 mmol) were added to a solution of compound **20** (2.0 mmol) in glacial acetic acid (10 mL) with stirring. The reaction mixture was heated under reflux, whereupon the color started to fade. Heating was continued for 6 h. After cooling, the formed precipitate was filtered, washed with ethanol and recrystallized from DMF. Compounds **27–32** had melting points > 300 °C.

7-Hydroxy-3-methyl-8-phenyl-2-thioxanthine (27)

Yield 0.48 g (93 %). – ^1H NMR: δ = 3.85 (s, 3H, NMe), 7.51–7.53 (m, 3H-ar.), 8.13–16 (m, 2H-ar.), 12.45 (s, 1H, 3-H), 14.10 (s, 1H, OH). – ^{13}C NMR: δ = 29.06 (NCH₃), 107.42, 113.29, 120.89, 127.23, 137.67, 149.81, 150.74, 154.31, 165.23. – MS (70 eV): m/z (%) = 274 (32) [M]⁺, 260 (51), 234 (29), 201 (14), 138 (35), 102 (21), 77 (100). – Anal. for C₁₂H₁₀N₄O₂S: calcd. C 52.55, H 3.67, N 20.43; found C 52.41, H 3.63, N 19.98.

7-Hydroxy-3-methyl-8-(4-hydroxyphenyl)-2-thioxanthine (28)

Yield 0.51 g (88 %). – ^1H NMR: δ = 3.83 (s, 3H, NMe), 6.86–6.93 (d, 2H-ar.), 7.98–8.00 (d, 2H-ar.), 10.17 (s, 1H, OH), 12.44 (s, NH), 13.80 (s, OH-7). – MS (70 eV): m/z (%) = 290 (33) [M]⁺, 274 (68), 257 (41), 217 (9), 138 (12), 94 (100), 68 (8). – Anal. for C₁₂H₁₀N₄O₃S: calcd. C 49.65, H 3.47, N 19.30; found C 49.48, H 3.42, N 19.19.

7-Hydroxy-3-methyl-8-(2-hydroxyphenyl)-2-thioxanthine (29)

Yield 0.52 g (90 %). – ^1H NMR: δ = 3.82 (s, 3H, NMe), 6.93–7.01 (m, 2H-ar.), 7.33–7.38 (m, 1H-ar.), 8.03–8.05 (d, 1H-ar.), 12.50 (s, 1H, 3-H), 14.15 (bs, 1H, OH). – ^{13}C NMR: δ = 29.03 (NCH₃), 107.61, 113.22, 121.09,

126.95, 127.29, 128.15, 137.67, 149.81, 150.74, 154.31, 165.23. – Anal. for $C_{12}H_{10}N_4O_3S$: calcd. C 49.65, H 3.47, N 19.30; found C 49.35, H 3.39, N 19.08.

7-Hydroxy-3-methyl-8-(4-chlorophenyl)-2-thioxanthine (30)

Yield 0.48 g (79 %). – 1H NMR: δ = 3.78 (s, 3H, NMe), 7.13–7.26 (dd, 2H-ar.), 7.63–7.65 (d, 2H-ar.), 12.33 (s, 1H, 3-H), 13.14 (s, 1H, OH). – ^{13}C NMR: δ = 28.89 (NCH₃), 112.40, 118.51, 124.17, 129.23, 141.52, 149.22, 151.63, 154.90, 166.97. – MS (70 eV): m/z (%) = 310 (3) [M+2]⁺, 309 (8) [M + 1]⁺, 308 (12) [M]⁺, 292 (66), 234 (24), 204 (14), 138 (33), 102 (18), 68 (100). – Anal. for $C_{12}H_9ClN_4O_2S$: calcd. C 46.68, H 2.93, N 18.14; found C 46.57, H 3.01, N 18.18.

7-Hydroxy-3-methyl-8-(4-bromophenyl)-2-thioxanthine (31)

Yield 0.58 g (83 %). – 1H NMR: δ = 3.78 (s, 3H, NMe), 7.77–7.79 (d, 2H-ar.), 8.07–8.10 (d, 2H-ar.), 12.77

(s, 1H, 3-H), 13.13 (s, 1H, OH). – ^{13}C NMR: δ = 29.24 (NCH₃), 106.83, 117.70, 125.32, 128.15, 139.15, 150.49, 150.74, 155.28, 167.14. – MS (70 eV): m/z (%) = 355 (7) [M+2]⁺, 354 (5) [M+1]⁺, 353 (9) [M]⁺, 338 (89), 278 (23), 182 (24), 102 (23), 68 (100). – Anal. for $C_{12}H_9BrN_4O_2S$: calcd. C 40.80, H 2.56, N 15.86; found C 40.46, H 2.44, N 16.02.

7-Hydroxy-3-methyl-8-(4-fluorophenyl)-2-thioxanthine (32)

Yield 0.45 g (77 %). – 1H NMR: δ = 3.78 (s, 3H, NMe), 7.0–7.04 (t, 1H-ar.), 7.12–7.15 (t, 1H-ar.), 7.37–7.44 (t, 1H-ar.), 8.18–8.20 (m, 1H-ar.), 12.32 (s, 1H, 3-H), 14.16 (s, 1H, OH). – MS (70 eV): m/z (%) = 294 (14) [M+2]⁺, 293 (20) [M + 1]⁺, 292 (100) [M]⁺, 261 (24), 234 (4), 183 (18), 157 (41), 129 (13), 57 (64). – Anal. for $C_{12}H_9FN_4O_2S$: calcd. C 49.32, H 3.10, N 19.17; found C 49.09, H 3.15, N 18.80.

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