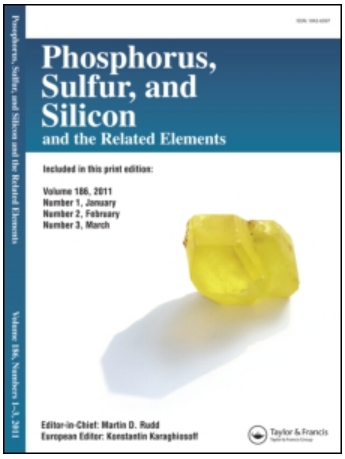

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Synthesis of Some New Benzopyranopyrimidin-2-Thiol Derivatives

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SYNTHESIS OF SOME NEW BENZOPYRANOPYRIMIDIN-2-THIOL DERIVATIVES

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*Reaction of 2-mercapto-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**3**) with phenyl isothiocyanate and methyl acrylate yielded the corresponding 2-(substituted)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-ones (**4**,**5**). Hydrolysis and hydrazinolysis of **5** gave acid derivative **6**, and hydrazone **7**. Treatment of hydrazone **7** with ethyl acetoacetate, diethyl malonate, and phenyl isothiocyanate yielded the corresponding 2-(substituted)thio-4-hydroxy-5H-[1]-benzopyrano- [4,3-*d*]-pyrimidin-5-ones (**8**, **9**, and **11**). Cyclization of **11** with 2N NaOH led to **12**.*

Keywords: Benzopyranopyrimides

As an extension of our previous work,[1–7] this present work describes the synthesis of some new benzopyranopyrimidin-2-thiol derivatives starting from salicylaldehyde. Such compounds are expected to show some pharmacological activities.[8,9]

The 3-ethoxycarbonylcoumarin (**1**) was prepared from salicylaldehyde and diethyl malonate according to a literature method. Condensation[1] of **1** with thiourea in the presence of anhydrous potassium carbonate in methonal under reflux produced the potassium salt of 2-mercapto-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**2**). Dissolving **2** in water and acidifying with 2*N* hydrochloric acid led to the formation of 2-mercapto-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**3**) (Scheme 1).

Treatment of **3** with phenyl isothiocyante and methyl acrylate in pyridine under addition reactions conditions produced 2-(substituted)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-ones (**4**,**5**) (Scheme 1). 2-(Methoxycarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**5**) was hydrolyzed with sodium hydroxide to cleave only the methyl ester and led to the formation of

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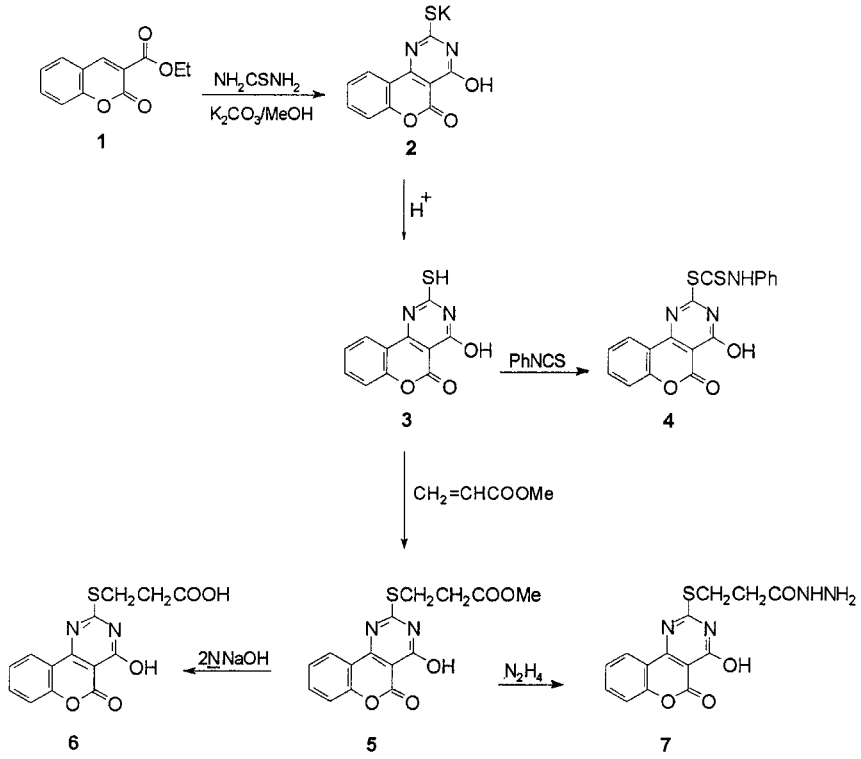
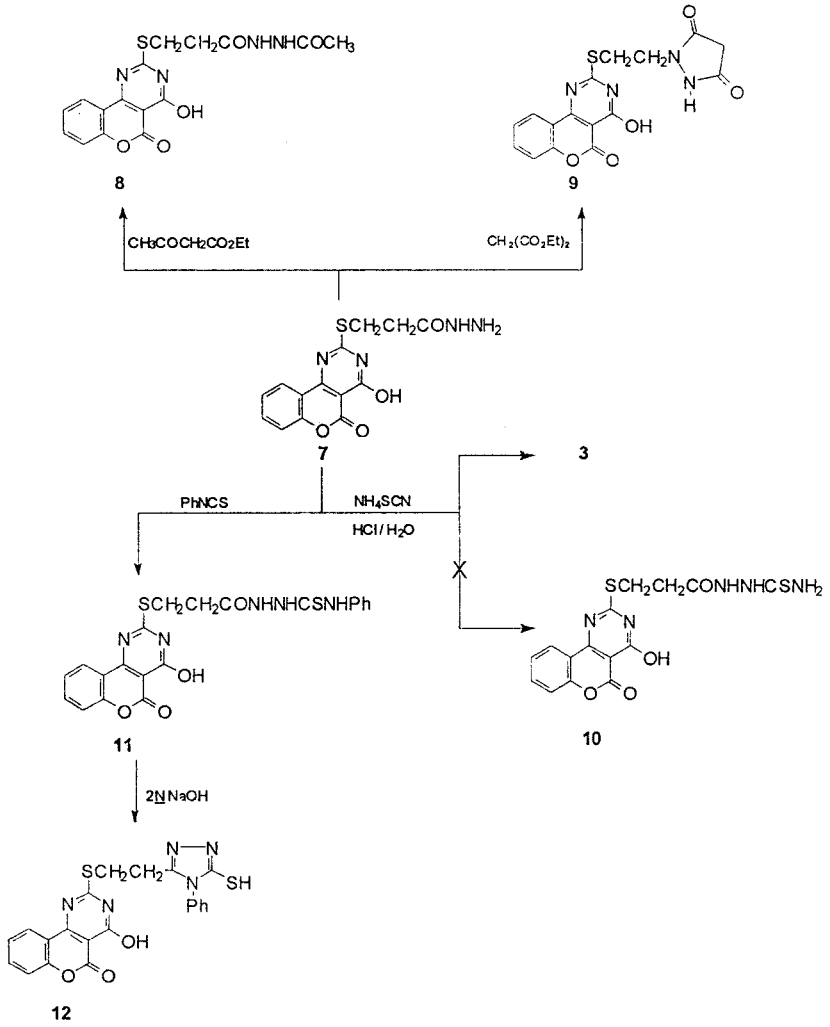


SCHEME 1

2-(hydroxycarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**6**) (Scheme 1). On the other hand, the condensation of **5** with hydrazine hydrate under reflux yielded the corresponding 2-(hydrazinylcarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**7**) (Scheme 1).

The reaction of 2-(hydrazinylcarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**7**) with dicarbonyl compounds (such as ethyl acetoacetate and diethyl malonate) in presence of triethyl amine in dimethyl formamide under reflux produced 2-(hydrazinylcarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**8**) and 1-[(4-hydroxy-5-oxo-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-2-thio)propionyl]-pyrazolidin-3,5-dione (**9**) (Scheme 2).

Reaction of **7** with ammonium thiocyanate in presence of concentrated hydrochloric acid in water under reflux 4 h was expected to give 2-(thiosemicarbazide-1′-ylcarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**10**), but only 2-mercapto-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**3**) was yielded.



SCHEME 2

Subsequent, condensation of **7** with phenyl isothiocyanate under reflux yielded the corresponding 2-(4′-phenyl-3′-thiosemicarbazide-1′-ylcarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**11**) (Scheme 2).

2-(4′-phenyl-3′-thiol-1′,2′,4′-triazol-5′-ylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**12**) (Scheme 2) was obtained by treatment of **11** with aqueous sodium hydroxide.

EXPERIMENTAL

NMR spectra were recorded on a General Electric QE 300 instrument and chemical shifts were given with respect to TMS. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer and a Biorad FTS7 (KBr). Mass spectra were obtained on a VG Autospec (EI and FAB+) and a Hewlett Packard MS-Engine Thermospray. Microanalyses were conducted using an elemental analyzer 1106. Melting points were determined on a Reichert Hot stage and uncorrected.

2-Mercapto-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (3)

2-Mercapto-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (**3**) was prepared according to literature procedures.[1,2] The crude product was crystallized from dimethyl formamide, yield 87%, m.p.: 360°C. ν_{max}(KBr): 3430–2253 (br.OH), 3173 (NH), 1747 (C=O), 1632 (C=N), 1109, 1056 (C—O) cm^{-1}. δ_H (DMSO-d_6): 7.31–7.38 (dd, 2 H, Ar—H), 7.73–7.78 (dt, 2 H, Ar—H), 8.83 (s, 1 H, OH), 8.88 (s, 1 H, SH) ppm. δ_c (DMSO-d_6): 176.75 (C—SH), 154.86 (C—OH), 156.40 (C=O), 153–83 (C—O), 151.72 (C—N), 117.04 (=C= of pyrane ring), 98.08 (=C= of aromatic ring), 110.75 (CH), 125.30 (CH), 124.26 (CH), 135.40 (CH) ppm. MS: m/z = 248 [(M^++2), 11.70], 247 [(M^++1), 77.10], 246 [(M^+, 100]. Anal. $C_{11}H_6N_2O_3S$ for Calcd: C, 53.66; H, 2.44; N, 11.38; S, 13.00. Found: C, 53.52; H, 2.36; N, 11.35; S, 13.03.

2-(Substituted)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-ones (4 and 5)

A mixture of **3** (0.01 mol) and phenyl isothiocyanate or methyl acrylate (0.01 mol) in pyridine (50 mL) was heated under reflux for 8 h. The reaction mixture was cooled and acidified with 4*N* hydrochloric acid. The solid obtained was filtered off, washed with water, dried, and purified by recrystallization (ethanol) to give **4** and **5**.

Compound **4** as brown crystals, yield 73%, m.p.: 152°C. ν_{max}(KBr): 3411–2450 (br.OH), 3241 (NH), 1742 (C=O), 1626 (C=N), 1135 (C=S), 1112, 1082 (C—O) cm^{-1}. δ_H (DMSO-d_6): 7.31–7.39 (dd, 2 H, Ar—H), 7.72–7.78 (dt, 2 H, Ar—H), 8.83 (s, 1 H, OH), 11.03 (s, 1 H, NH) ppm. δ_C (DMSO-d_6): 194.21 (C=S), 179.35 (C—S), 154.83 (C—OH), 156.42 (C=O) 153.81 (C—O), 151.71 (C—N), 138.42 (C—NH), 117.10 (C= of pyrane ring), 98.12 (=C= of aromatic ring), 110.73 (CH), 125.31 (CH), 124.25 (CH), 135.39 (CH), 128.63 (2 × CH), 125.13 (2 × CH), 124.51 (CH) ppm. MS: m/z = 382 [(M^++1), 9.70], 381[M^+, 11.21], 359 (15.23), 304 (46.51),

244 (18.72), 194 (21.23), 179.30 (12.32), 144 (26.32), 115 (79.20), 101 (100). Anal. $C_{18}H_{11}N_3O_3S_2$ for Calcd: C, 56.69; H, 2.88; N, 11.02; S, 16.79. Found: C, 56.52; H, 2.59; N, 11.01; S, 16.63.

Compound **5** as colorless crystals, yield 71% m.p.: 212 °C. ν_{max}(KBr): 3412–2651 (br.OH), 1760 (C=O) of ester), 1730 (C=O), 1630 (C=N), 1160, 1105, 1010 (C—O) cm^{-1}. δ_H (DMSO-d_6): 2.61 (t, 2 H, CH_2CO), 3.31 (t, 2 H, SCH_2), 3.93 (s, 3 H, OCH_3), 7.32–7.38 (dd, 2 H, Ar—H), 7.727.79 (dt, 2 H, Ar—H), 8.83 (s, 1 H, OH) ppm. δ_C (DMSO-d_6): 159.39 (C—S), 154.82 (C—OH), 156.42 (C=O), 153.82 (C—O), 151.70 (C—N), 117.14 (=C= of pyrane ring), 98.12 (=C= of aromatic ring), 110.75 (CH), 125.31 (CH), 124.25 (CH), 135.42 (CH), 52.89 (OCH_3), 168.62 (COOMe), 35.81 (CH_2CO), 31.21 (SCH_2) ppm. MS: m/z = 334 [(M^++2), 2.54], 333 [(M^++1), 8.00], 332 [M^+, 26.68], 301 (10.87), 274 (12.11), 273 (50.74), 272 (100), 247 (12.32), 246 (11.63), 230 (27.77), 213 (11.30), 188 (13.30), 145 (8.11). Anal. $C_{15}H_{12}N_2O_5S$ for Calcd: C, 54.22; H, 3.61; N, 8.43; S, 9.63. Found: C, 54.02; H, 3.43; N, 8.27; S, 9.49.

2-(Hydroxycarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-ones (6)

A mixture of **5** (0.01 mol) and 20 mL of 2*N* sodium hydroxide was heated under reflux for 2 h. The reaction mixture was cooled and acidified with 2 *N* hydrochloric acid. The resulting solid was recrystallized (acetic acid) to give **6** as pale yellow crystals, yield 63%, m.p.: 325°C. ν_{max}(KBr): 3452–2346 (br.OH), 1739–1703 (C=O), 1622 (C=N), 1107, 1041, 1009(C—O) cm^{-1}. δ_H (DMSO-d_6): 2.52 (t, 2H, CH_2CO), 3.17 (t, 2 H, SCH_2), 7.31–7.39 (dd, 2 H, Ar—H), 7.71–7.78 (dt, 2 H, Ar—H), 8.84 (s, 1 H, OH), 10.72 (br. s, 1 H, OH) ppm. δ_C (DMSO-d_6): 159.37 (C—S), 154.79 (C—OH), 156.43 (C=O), 153.80 (C—O), 151.72 (C—N), 117.09 (=C= of pyrane ring), 98.14 (=C= of aromatic ring), 110.73 (CH), 125.32 (CH), 124.23 (CH), 135.46 (CH), 30.33 (SCH_2), 36.92 (CH_2CO), 173.36 (COOH) ppm. MS: m/z = 320 [(M^++2), 1.87], 319 [(M^++1), 6.69], 318 [M^+, 24.57], 293 (1.15) 292 (4.72), 285 (2.66), 274 (25.62), 273 (60.16), 272 (100), 247 (13.18), 246 (44.71), 245 (2.71), 231 (5.08), 230 (37.67), 220 (17.55), 213 (15.10), 188 (27.94), 186 (15.72), 145 (11.04), 119 (13.22), 102 (7.50). Anal. $C_{14}H_{10}N_2O_5S$ for Calcd: C, 52.83; H, 3.14; N, 8.80; S, 10.06. Found: C, 52.67; H, 3.00; N, 8.59; S, 9.97.

2-(Hydrazinylcarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (7)

A solution of **5** (0.01 mol) and hydrazine hydrate (0.01 mol) ethanol (70 mL) was heated under reflux for 4 h. The solid obtained after cooling

was filtered off, washed with ethanol, dried and recrystallized (dimethyl formamide) to give **7** as yellow crystals, yield 68%, m.p.: 335°C. ν_{max} (KBr): 3351, 3182 (NH_2), 3276 (NH), 1721 (C=O), 1629 (C=N), 1076, 1018 (C–O) cm^{-1}. δ_H (DMSO-d_6): 2.51 (t, 2 H, CH_2CO), 3.13 (t, 2 H, SCH_2), 5.10 (br. s, 2 H, NH_2), 7.31–7.38 (dd, 2 H, Ar–H), 7.72–7.78 (dt, 2 H, Ar–H), 8.84 (s, 1 H, OH), 10.30 (br. s, 1 H, CONH) ppm. δ_C (DMSO-d_6): 159.36 (C–S), 154.76 (C–OH), 156.42 (C=O), 153.82 (C–O), 151.71 (C–N), 117.08 (=C= of pyrane ring), 98.13 (=C= of aromatic ring), 110.72, 125.33, 124.22, 135.42 (CH of aromatic ring), 30.21 (SCH_2), 35.89 (CH_2CO), 170.52 (CONH) ppm. MS: m/z = 334 [(M^++2), 2.47], 333 [(M^++1), 8.28], 332 [M^+, 28.71], 301 (12.35), 300 (3.28), 274 (11.00), 273 (49.86), 272 (92.33), 269 (20.98), 268 (100), 267 (17.04), 247 (14.09), 245 (10.25), 230 (28.87), 213 (11.14), 188 (13.55), 145 (8.41), 104 (16.01). Anal. $C_{14}H_{12}N_4O_4S$ for Calcd: C, 50.60; H, 3.61; N, 16.87; S, 9.64. Found: C, 50.48; H, 3.53; N, 16.72; S, 9.46.

2-[(Substituted)carbonylethyl]thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-ones (8 and 9)

A mixture of **7** (0.01 mol), dicarbonyl compounds (such as ethyl acetoacetate and diethyl malonate) (0.01 mol) and triethyl amine (1 mL) in dimethyl formamide (70 mL) was heated under reflux for 4 h. The reaction mixture was cooled and poured into water. The product formed was collected by filtration, washed with water, dried, and purified by recrystallization (acetic acid) to give **8** and **9**.

Compound **8** as yellow crystals, yield 67%, m.p.: 300°C. ν_{max}(KBr): 3417–2575 (br.OH), 3276 (NH), 1738 (C=O of pyrane), 1689 (CO of amide) 1627 (C=N), 1105, 1096 (C–O) cm^{-1}. δ_H (DMSO-d_6): 2.11 (s, 3 H, CH_3CO), 2.53 (t, 2 H, CH_2CO), 3.12 (t, 2 H, SCH_2), 7.32–7.38 (dd, 2 H, Ar–H), 7.71–7.78 (dt, 2 H, Ar–H), 8.83 (s, 1 H, OH), 10.02–10.12 (br. s, 2H, NH) ppm. MS: m/z = 376 [(M^++2), 18.47], 374[M^+, 27.35], 338 (4.04), 337 (6.10), 336 (6.45), 312 (2.82), 311 (18.08), 310 (100), 282 (9.42), 254 (5.00), 253 (1.53), 252 (3.95), 214 (10.50), 213 (26.29), 172 (1.15), 171 (4.17), 146 (2.18), 145 (5.85), 144 (2.86), 119 (4.38), 102 (5.83). Anal. $C_{16}H_{14}N_4O_5S$ for Calcd: C, 51.33; H, 3.74; N, 17.97; S, 8.55. Found: C, 51.13; H, 3.55; N, 14.61; S, 8.29.

Compound **9** as pale yellow crystals, yield 62%, m.p.: 310°C. ν_{max} (KBr): 3453–2650 (br.OH), 3240 (NH), 1735, 1720, 1689 (C=O), 1629 (C–N), 1192, 1030 (C–O) cm^{-1}. δ_H (DMSO-d_6): 2.51 (t, 2 H, CH_2CO), 3.19 (t, 2 H, SCH_2), 3.23 (s, 2 H, $COCH_2CO$), 7.31–7.37 (dd, 2 H, Ar–H), 7.71–7.78 (dt, 2 H, Ar–H), 8.82 (s, 1 H, OH), 10.02 (s, 1 H, NH) ppm. MS: m/z = 402 [(M^++2), 2.53)], 401 [(M^++1), 6.01], 400 [M^+, 13.05], 353 (1.01), 341 (4.92), 340 (18.27), 326 (1.26), 295 (7.66), 294 (8.31), 282

(4.44), 281 (4.54), 269 (14.72), 268 (100), 267 (59.25), 254 (12.01), 253 (9.27), 213 (22.61), 198 (20.17), 144 (4.13), 143 (5.24), 114 (13.97), 104 (14.38), 103 (10.66), 102 (8.24). Anal. $C_{17}H_{12}N_4O_6S$ for Calcd: C, 51.00; H, 3.00; N, 14; S, 8.00. Found: C, 50.98; H, 2.87; N, 13.88; S, 8.07.

2-Mercapto-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (3)

A mixture of **7** (0.01 mol), ammonium thiocyanate (0.02 mol), and concentrated hydrochloric acid (10 mL) in water (70 mL) was heated under reflux for 4 h. The solid obtained after cooling was filtered off, washed with water, dried, and recrystallized (dimethyl formamide) to give **3** as orange crystals, yield 53%, m.p.: 360°C.

2-(4′-Phenyl-3′-thiosemicarbazide-1′-ylcarbonylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (11)

A mixture of **7** (0.01 mol) and phenyl is thiocyanate (0.01 mol) in acetic acid (70 mL) was heated under reflux for 4 h, then cooled and poured into water. The solid obtained was filtered off, washed with water, dried, and purified by recrystallization (ethanol) to give **11** as yellow crystals, yield 62%, m.p.: 209°C. ν_{max} (KBr): 3461–2576 (br.OH), 3242 (NH), 1732 (C=O), 1689 (C=O), 1630 (C=N), 1130, 1020 (C—O) cm^{-1}. δ_H (DMSO-d_6): 2.52 (t, 2 H, CH_2CO), 3.11 (t, 2 H, SCH_2), 7.29–7.81 (m, 9 H, Ar—H), 8.84 (s, 1 H, OH), 9.60–9.63 (br. s, 2 H, NHCSNH), 10.31 (br. s, 1 H, CONH). MS: m/z = 467[M^+, 0.28], 332 (27.30), 301 (11.33), 274 (11.03), 273 (49.66), 272 (92.21), 268 (100), 267 (14.00), 247 (14.09), 246 (10.35), 230 (28.77), 213 (11.10), 212 (5.50), 188 (13.52), 150 (24.70), 146 (1.73), 145 (8.31), 144 (1.01), 136 (11.92), 135 (2.97), 133 (11.02), 109 (6.27), 93 (14.63), 77 (29.09). Anal. $C_{21}H_{17}N_5O_4S_2$ for Calcd: C, 53.96; H, 3.64; N, 14.99; S, 13.70. Found: C, 53.73; H, 3.48, N, 14.63; S, 13.55.

2-(4′-Phenyl-3′-thiol-1′,2′,4′-triazol-5′-ylethyl)thio-4-hydroxy-5H-[1]-benzopyrano-[4,3-*d*]-pyrimidin-5-one (12)

A solution of **11** (0.01 mol) in 2*N* sodium hydroxide (30 mL) was heated under reflux for 2 h. The reaction mixture was cooled and acidified with 2*N* hydrochloric acid. The solid obtained was filtered off, washed with water, dried, and purified by recrystallization (dimethyl formamide) to give **12** as pale yellow crystals, yield 65%, m.p.: 348°C. ν_{max} (KBr): 3459–2532 (br.OH), 1736 (C=O), 1631 (C=N), 11.30, 1021 (C—O) cm^{-1}, δ_H (DMSO-d_6): 4 (t, 2 H, CH_2C=N), 3.18 (t, 2 H, SCH_2), 7.28–7.82 (m,

9 H, Ar—H), 8.83 (s, 1 H, OH), 9.01 (s, 1 H, SH) ppm. MS: m/z = 450 [(M^++1), 12.35], 449 [M^+, 33.25], 246 (100), 203 (86), 145 (23.21), 77 (28.21). Anal. $C_{21}H_{15}N_5O_3S_2$ for Cacld: C, 56.12; H, 3.34; N, 15.59; S, 14.25. Found: C, 56.01, H, 3.23; N, 15.29; S, 14.04.

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