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SYNTHESIS OF 7*H*-THIOPYRANO[2,3-*d*]PYRIMIDINES BY HYDROBROMIC ACID-MEDIATED CYCLIZATION OF 1-[4-(1,1-DIMETHYLETHYLSULFANYL)PYRIMIDIN-5-YL]PROP-2-EN-1-OLS

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Abstract – 7-Aryl- or 5,7-diaryl-4-methoxy-2-methylsulfanyl-7*H*-thiopyrano[2,3-*d*]pyrimidines have been prepared in satisfactory overall yields starting from 4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidine by a facile three-step sequence. 4-Chloro-5-lithio-6-methoxy-2-(methylsulfanyl)pyrimidine was generated by the treatment of 4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidine with LDA and was allowed to react with 3-arylprop-2-enals (cinnamaldehyde and its derivatives) or 1,3-diarylprop-2-en-1-ones (chalcone and its derivatives) to give the corresponding 3-aryl- or 1,3-diaryl-1-(4-chloropyrimidin-5-yl)prop-2-en-1-ol derivatives, respectively. Substitution of the 4-chloro group with sodium 1,1-dimethylethylthiolate gave 3-aryl- or 1,3-diaryl-1-[4-(1,1-dimethylethylsulfanyl)pyrimidin-5-yl]prop-2-en-1-ol derivatives, of which treatment with an equivalent of hydrobromic acid provided the desired products.

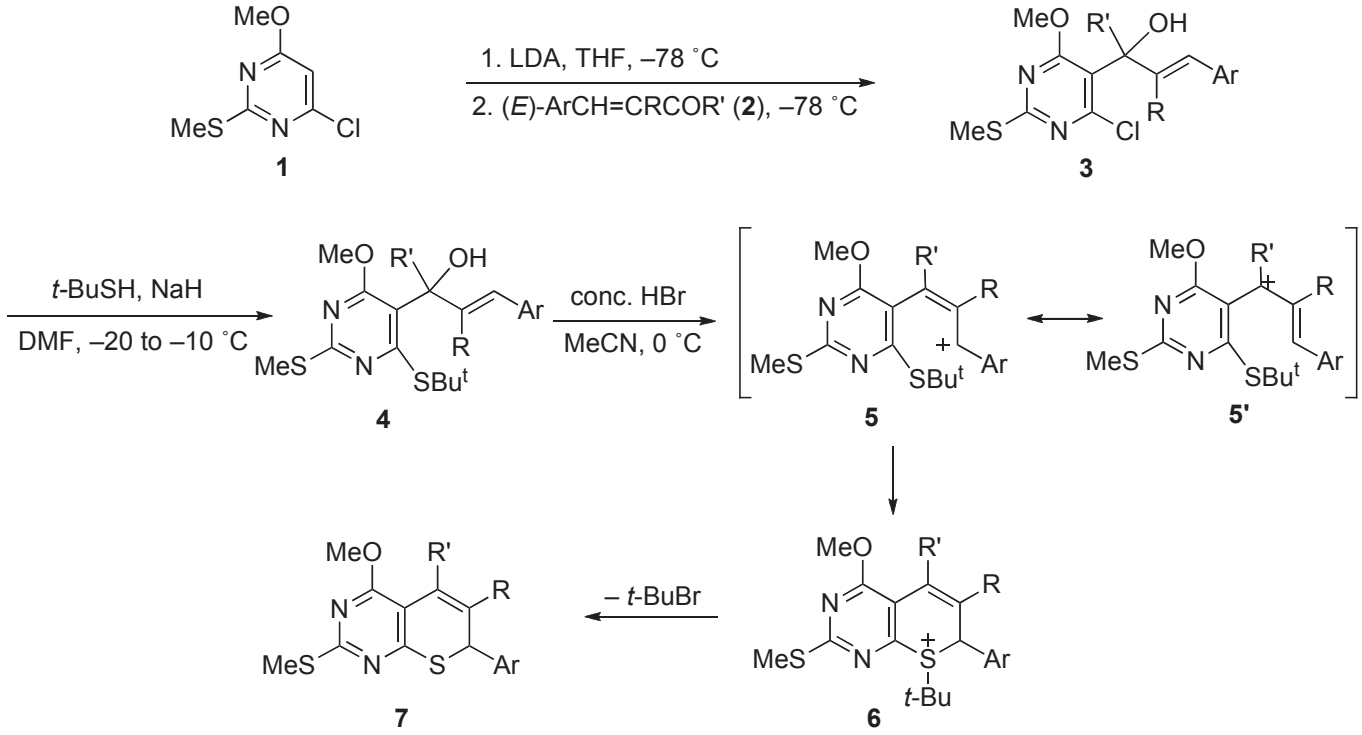
Compounds having the 7*H*-thiopyrano[2,3-*d*]pyrimidine skeleton have received respective attention from a biologically point of view.[1] However, there have been few works on their general preparation to date, while the reaction of 4-chloro-2-(methylsulfanyl)pyrimidine-5-carbonitrile with diethyl 2-sulfanylbutanedioate[2a] and the reaction of 1-(6-methyl-5-phenyl-4-sulfanylpyrimidin-5-yl)ethanone

with diethyl (*Z*)-but-2-enedioate[2b] have been reported to give the corresponding 7*H*-thiopyrano[2,3-*d*]pyrimidines. Accordingly, we became interested in developing a general method for the preparation of 7*H*-thiopyrano[2,3-*d*]pyrimidine derivatives. In this report, we wish to demonstrate that 7-aryl- or 5,7-diaryl-4-methoxy-2-methylsulfanyl-7*H*-thiopyrano[2,3-*d*]pyrimidines (**7**) can be readily prepared utilizing hydrobromic acid-mediated cyclization of 3-aryl- or 1,3-diaryl-1-[4-(1,1-dimethylethylsulfanyl)pyrimidin-5-yl]prop-2-en-1-ol derivatives (**4**), derived from 4-chloro-6-methoxy-2-methylsulfanylpyrimidine (**1**) and 3-arylprop-2-enals (**2a–e**) (cinnamaldehyde and its derivatives) or 1,3-diarylprop-2-en-1-ones (**2f–j**) (chalcone and its derivatives), respectively.

Our three-step sequence for the preparation **7** from **1** was conducted as illustrated in Scheme 1. We first synthesized 3-aryl-1-(4-chloropyrimidin-5-yl)prop-2-en-1-ol derivatives (**3a-e**) by reacting 4-chloro-5-lithio-6-methoxy-2-(methylsulfanyl)pyrimidine, generated by treating **1** with LDA under the conditions reported previously,[3] with **2a–e**. The yields of these products were fair to good as summarized Table 1 (Entries 1-5). The Michael adduct was not obtained in each case. Substitution of each of the 6-chloro group of **3a-e** with 1,1-dimethylsulfanyl group could be performed with 1,1-dimethylethanethiol in the presence of sodium hydride as a base to afford the corresponding 3-aryl-1-[4-(1,1-dimethylethylsulfanyl)pyrimidin-5-yl]prop-2-en-1-ol derivatives (**4a-e**) in good yields. The final ring closure of these precursors forming the thiopyrano ring proved to be efficiently achieved on treatment with an equivalent of concentrated hydrobromic acid. The reaction proceeded smoothly and was complete within 20 min or less at 0 ˚C to give the desired 7-aryl-4-methoxy-2-methylsulfanyl-7*H*-thiopyrano[2,3-*d*]pyrimidines (**7a-e**) in good to excellent yields, as listed in Table 1 as well. The use of an equivalent of the acid was essential for complete conversion. When the reaction was carried out using a catalytic amount of the acid, a considerable amount of **4** was recovered in each reaction. The use of hydriodic acid or hydrochloric acid in place of hydrobromic both gave disappointing results; a complex mixture of products was produced in each case. It should be noted that the 2-methylsulfanyl group on the pyrimidine ring is necessary for successful cyclization of **4** to **7**. For example, 1-[4-(1,1-dimethylethylsulfanyl)pyrimidin-5-yl]-3-phenylprop-2-en-1-ol could be similarly prepared from 4-chloro-6-methoxypyrimidine. However, an attempt of its cyclization to the corresponding 7*H*-thiopyrano[2,3-*d*]pyrimidine under the same conditions as described above resulted in the formation of an intractable mixture of products.

Next, we examined the usability of chalcone and its derivatives (**2f–j**) in the present reaction sequence. Fair yields of 1,3-diaryl-1-(4-chloropyrimidin-5-yl)prop-2-en-1-ol derivatives (**3f-j**) were obtained by the reaction of 4-chloro-5-lithio-6-methoxy-2-(methylsulfanyl)pyrimidine with **2f–j**. Again, the Michael adduct was not obtained in each case. Transformation of **3f-j** into the corresponding 1,1-dimethylsulfanyl derivatives (**4f-j**) was similarly achieved with sodium 1,1-dimethylethylthiolate in good yields. The

conversion to desired 5,7-diaryl-4-methoxy-2-methylsulfanyl-7*H*-thiopyrano[2,3-*d*]pyrimidines (**7f-j**) was carried out by treatment of **4f-j** with concentrated hydrobromic acid under the same conditions as described for the preparation of **7a-e**. The yields of these products listed in Table 1, Entries 6–10 are generally somewhat lower than those of **7a-e**. This may be ascribed to the steric encumbrance between 4-methoxy and 5-aryl substituents of the products (**7f-j**).



Scheme 1

Table 1. Preparation of 7*H*-Thiopyrano[2,3-*d*]pyrimidines (**7**)

Entry	**2**	**3**	Yield[a]	**4**	Yield[a]	**7**	Yield[a]
1	**2a** (Ar = Ph, R = H, R' = H)	**3a**	71	**4a**	90	**7a**	74
2	**2b** (Ar = Ph, R = Me, R' = H)	**3b**	73	**4b**	85	**7b**	89
3	**2c** (Ar = 4-MeC_6H_4, R = H, R' = H)	**3c**	73	**4c**	87	**7c**	99
4	**2d** (Ar = 4-ClC_6H_4, R = H, R' = H)	**3d**	78	**4d**	84	**7d**	99
5	**2e** (Ar = 4-$MeOC_6H_4$, R = H, R' = H)	**3e**	94	**4e**	88	**7e**	75
6	**2f** (Ar = Ph, R = H, R' = Ph)	**3f**	72	**4f**	89	**7f**	61
7	**2g** [Ar = Ph, R = H, R' = 3,4-$(MeO)_2C_6H_3$]	**3g**	62	**4g**	82	**7g**	64
8	**2h** [Ar = Ph, R = H, R' = 3,4-$(OCH_2O)C_6H_3$]	**3h**	68	**4h**	92	**7h**	71
9	**2i** [Ar = 4-$MeOC_6H_4$, R = H, R' = 4-ClC_6H_4]	**3i**	75	**4i**	78	**7i**	79
10	**2j** [Ar = 4-ClC_6H_4, R = H, R' = 4-$MeOC_6H_4$]	**3j**	60	**4j**	97	**7j**	73

[a] Yields/% of isolated products.

The need for an equivalent of hydrobromic acid may be explained as follows (Scheme 1). Treatment of **4** with concentrated hydrobromic acid generates the allylic carbenium ion intermediate (**5**), which is trapped

with the sulfur lone pair electrons to form the sulfonium ion intermediate (**6**). The subsequent removal of *t*-butyl bromide, *via* formation of *t*-butyl cation, from this intermediate gives **7**.

In summary, we have presented a convenient synthesis of a new class of 7*H*-thiopyrano[2,3-*d*]-pyrimidines. This method may find some value in the synthesis of this type of fused heterocycles because of the ready availability of the starting materials and the ease of operations.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400FT NMR spectrometer operating at 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz or a JEOL LA400FT NMR spectrometer operating at 100 MHz. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidine (**1**) was prepared from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) according to the reported procedure.[3] Chalcone derivatives **2g**,[4] **h**,[4] **i**,[5] and **j**[5] were prepared according to the appropriate reported procedures. Butyllithium was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Pyrimydinylalkenols (3). (*E*)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-phenylprop-2-en-1-ol (3a). To a stirred solution of LDA (2.0 mmol) in THF (3 mL), generated by the standard method from *n*-BuLi and *i*-Pr_2NH, at –78 °C was added dropwise a solution of **1** (0.38 g, 2.0 mmol) in THF (3 mL). After 1.5 h, (*E*)-3-phenylprop-2-enal (0.26 g, 2.0 mmol) was added and stirring was continued for additional 30 min at the same temperature before saturated aqueous NH_4Cl and water (5 mL each) were added. The mixture was warmed to rt and extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to give **3a** (0.46 g, 71%); a pale-yellow oil; R_f 0.14 (AcOEt–hexane 1:10); IR (neat) 3403, 1562, 1523, 1360, 1036 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.56 (s, 3H), 3.18 (d, *J* = 10.7 Hz, 1H), 4.09 (s, 3H), 5.70 (dd, *J* = 10.7, 5.9 Hz, 1H), 6.42 (dd, *J* = 15.6, 5.9 Hz, 1H), 6.60 (d, *J* = 15.6 Hz, 1H), 7.26 (t, *J* = 6.8 Hz, 1H), 7.32 (dd, *J* = 7.8, 6.8 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 2H). Anal. Calcd for $C_{15}H_{15}ClN_2O_2S$: C, 55.81; H, 4.68; N, 8.68.

Found: C, 55.73; H, 4.54; N, 8.53.

(*E*)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-methyl-3-phenylprop-2-en-1-ol (3b): a colorless oil; R_f 0.06 (THF–hexane 1:15); IR (neat) 3429, 1563, 1522, 1369, 1038 cm^{-1}; ^1H NMR (500 MHz) δ 1.83 (s, 3H), 2.57 (s, 3H), 3.21 (d, *J* = 10.9 Hz, 1H), 4.05 (s, 3H), 5.58 (d, *J* = 10.9 Hz, 1H), 6.53 (s, 1H), 7.21–7.24 (m, 3H), 7.33 (dd, *J* = 8.0, 7.4 Hz, 2H). Anal. Calcd for $C_{16}H_{17}ClN_2O_2S$: C, 57.05; H, 5.09; N, 8.32. Found: C, 56.77; H, 5.24; N, 8.04.

(*E*)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-methylphenyl)prop-2-en-1-ol (3c): a pale-yellow oil; R_f 0.16 (AcOEt–hexane 1:5); IR (neat) 3413, 1564, 1523, 1369, 2036 cm^{-1}; ^1H NMR (500 MHz) δ 2.33 (s, 3H), 2.56 (s, 3H), 3.13 (d, *J* = 10.9 Hz, 1H), 4.08 (s, 3H), 5.68 (dd, *J* = 10.9, 6.3 Hz, 1H), 6.37 (dd, *J* = 16.0, 6.3 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H). Anal. Calcd for $C_{16}H_{17}ClN_2O_2S$: C, 57.05; H, 5.09; N, 8.32. Found: C, 57.06; H, 5.15; N, 8.28.

(*E*)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-chlorophenyl)prop-2-en-1-ol (3d): a pale-yellow oil; R_f 0.17 (AcOEt–hexane 1:5); IR (neat) 3406, 1563, 1523, 1369, 1036 cm^{-1}; ^1H NMR (500 MHz) δ 2.56 (s, 3H), 3.16 (d, *J* = 10.9 Hz, 1H), 4.08 (s, 3H), 5.68 (ddd, 10.9, 6.3, 1.7 Hz, 1H), 6.39 (dd, *J* = 16.0, 6.3 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 7.28 (d, *J* = 9.1 Hz, 2H), 7.29 (d, *J* = 9.1 Hz, 2H). Anal. Calcd for $C_{15}H_{14}Cl_2N_2O_2S$: C, 50.43; H, 3.95; N, 7.84. Found: C, 50.24; H, 3.95; N, 7.74.

(*E*)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-methoxyphenyl)prop-2-en-1-ol (3e): a pale-yellow oil; R_f 0.29 (AcOEt–hexane 1:2); IR (neat) 3419, 1607, 1563, 1523, 1370, 1035 cm^{-1}; ^1H NMR (500 MHz) δ 2.56 (s, 3H), 3.11 (d, *J* = 10.3 Hz, 1H), 3.80 (s, 3H), 4.08 (s, 3H), 5.67 (ddd, *J* = 10.3, 6.3, 1.1 Hz, 1H), 6.29 (dd, *J* = 16.0, 6.3 Hz, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H). Anal. Calcd for $C_{16}H_{17}ClN_2O_3S$: C, 54.46; H, 4.86; N, 7.94. Found: C, 54.42; H, 4.90; N, 7.76.

(*E*)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-1,3-diphenylprop-2-en-1-ol (3f): a white solid; mp 47–49 °C (hexane); IR (KBr) 3531, 1550, 1508, 1337, 1033 cm^{-1}; ^1H NMR (400 MHz) δ 2.56 (s, 3H), 3.95 (s, 3H), 4.71 (s, 1H), 6.55 (d, *J* = 15.6 Hz, 1H), 6.81 (d, *J* = 15.6 Hz, 1H), 7.22–7.42 (m, 10H). Anal. Calcd for $C_{21}H_{19}ClN_2O_2S$: C, 63.23; H, 4.80; N, 7.02. Found: C, 63.12; H, 5.03; N, 6.74.

(*E*)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-(3,4-dimethoxyphenyl)-1-phenylprop-2-en-1-ol (3g): a yellow oil; R_f 0.17 (AcOEt–hexane 1:4); IR (neat) 3502, 1548, 1510, 1365, 1029 cm^{-1}; ^1H NMR (500 MHz) δ 2.56 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.74 (s, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.946 (s, 1H), 6.952 (d, *J* = 8.6 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.38 (d, *J* = 7.4 Hz, 2H). Anal. Calcd for $C_{23}H_{23}ClN_2O_4S$: C, 60.19; H, 5.05; N, 6.10. Found: C, 60.08; H, 5.28; N, 6.04.

(*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-1-[2-chloro-6-methoxy-4-(methylsulfanyl)pyrimidin-5-yl]-1-phenyl-

prop-2-en-1-ol (3h): a yellow solid; mp 169–171 ˚C (hexane–CH_2Cl_2); IR (KBr) 3537, 1550, 1504, 1336, 1036 cm^{-1}; ^1H NMR (500 MHz) δ 2.56 (s, 3H), 3.94 (s, 3H), 4.68 (s, 1H), 5.95 (s, 2H), 6.43 (d, *J* = 15.5 Hz, 1H), 6.63 (d, *J* = 15.5 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.96 (d, *J* = 1.7 Hz, 1H), 7.27–7.36 (m, 5H). Anal. Calcd for $C_{22}H_{19}ClN_2O_4S$: C, 59.66; H, 4.32; N, 6.32. Found: C, 59.69; H, 4.30; N, 6.14.

(*E*)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-1-(4-chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-ol (3i): a pale-yellow solid; mp 43–45 ˚C (hexane); IR (KBr) 3527, 1551, 1511, 1337, 1034 cm^{-1}; ^1H NMR (400 MHz) δ 2.56 (s, 3H), 3.81 (s, 3H), 3.96 (s, 3H), 4.73 (s, 1H), 6.44 (d, *J* = 15.6 Hz, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.30 (s, 4H), 7.34 (d, *J* = 8.8 Hz, 2H). Anal. Calcd for $C_{22}H_{20}Cl_2N_2O_3S$: C, 57.02; H, 4.35; N, 6.05. Found: C, 56.82; H, 4.51; N, 6.07.

(*E*)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-chlorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-ol (3j): a pale-yellow oil; R_f 0.19 (AcOEt–hexane 1:5); IR (neat) 3528, 1607, 1549, 1509, 1337, 1034 cm^{-1}; ^1H NMR (500 MHz) δ 2.56 (s, 3H), 3.81 (s, 3H), 3.96 (s, 3H), 4.70 (s, 1H), 6.46 (d, *J* = 15.5 Hz, 1H), 6.77 (d, *J* = 15.5 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H). Anal. Calcd for $C_{22}H_{20}Cl_2N_2O_3S$: C, 57.02; H, 4.35; N, 6.05. Found: C, 57.23; H, 4.42; N, 6.05.

Typical Procedure for the Preparation of [(1,1-Dimethylethylsulfanyl)pyrimidinyl]alkenols (4). (*E*)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-phenylprop-2-en-1-ol (4a). To a stirred suspension of NaH (60 % in mineral oil; 37 mg, 0.93 mmol) in DMF (1 mL) at –20 ˚C was added 2-methylpropan-2-thiol (84 mg, 0.93 mmol). After evolution of H_2 had ceased, a solution of **3a** (0.30 g, 0.93 mmol) in DMF (3 mL) was added slowly. The temperature was warmed to –10 ˚C and stirring was continued for 30 min before saturated aqueous NH_4Cl and water (5 mL each) were added. The mixture was warmed to rt and extracted with AcOEt (3 × 10 mL). The combined extracts were washed with water twice and brine once (10 mL each), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt–hexane 1:3) to give **4a** (0.32 g, 90%); a white solid; mp 82–84 ˚C (hexane–Et_2O); IR (KBr) 3553, 1548, 1518, 1360, 1036 cm^{-1}; ^1H NMR (400 MHz) δ 1.63 (s, 9H), 2.56 (s, 3H), 3.49 (d, *J* = 10.7 Hz, 1H), 4.01 (s, 3H), 5.61 (dd, *J* = 10.7, 5.9 Hz, 1H), 6.39 (dd, *J* = 16.6, 5.9 Hz, 1H), 6.56 (d, *J* = 16.6 Hz, 1H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.37 (d, *J* = 7.3 Hz, 2H). Anal. Calcd for $C_{19}H_{24}N_2O_2S_2$: C, 60.61; H, 6.42; N, 7.44. Found: C, 60.50; H, 6.72; N, 7.32.

(*E*)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-methyl-3-phenylprop-2-en-1-ol (4b): a colorless oil; R_f 0.34 (THF–hexane 1:7); IR (neat) 3449, 1545, 1519, 1361, 1041 cm^{-1}; ^1H NMR (500 MHz) δ 1.62 (s, 9H), 1.82 (s, 3H), 2.57 (s, 3H), 3.53 (d, *J* = 11.5 Hz, 1H), 3.98 (s, 3H), 5.51 (d, *J* = 11.5 Hz, 1H), 6.48 (s, 1H), 7.20 (t, *J* = 7. 4 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.32

(dd, *J* = 8.0, 7.4 Hz, 2H). Anal. Calcd for $C_{20}H_{26}N_2O_2S_2$: C, 61.50; H, 6.71; N, 7.17. Found: C, 61.30; H, 6.72; N, 7.08.

(*E*)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-methylphenyl)prop-2-en-1-ol (4c): a colorless oil; R_f 0.26 (AcOEt–hexane 1:5); IR (neat) 3430, 1547, 1519, 1361, 1039 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.63 (s, 9H), 2.32 (s, 3H), 2.56 (s, 3H), 3.44 (d, *J* = 10.9 Hz, 1H), 4.00 (s, 3H), 5.60 (dd, *J* = 10.9, 6.3 Hz, 1H), 6.34 (dd, *J* = 16.0, 6.3 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 2H). Anal. Calcd for $C_{20}H_{26}N_2O_2S_2$: C, 61.50; H, 6.71; N, 7.17. Found: C, 61.43; H, 7.00; N, 7.12.

(*E*)-3-(4-Chlorophenyl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-prop-2-en-1-ol (4d): a colorless oil; R_f 0.26 (AcOEt–hexane 1:5); IR (neat) 3436, 1547, 1520, 1361, 1039 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.63 (s, 9H), 2.56 (s, 3H), 3.48 (d, *J* = 10.7 Hz, 1H), 4.01 (s, 3H), 5.60 (dd, *J* = 10.7, 5.9 Hz, 1H), 6.36 (dd, *J* = 15.6, 5.9 Hz, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H). Anal. Calcd for $C_{19}H_{23}ClN_2O_2S_2$: C, 55.53; H, 5.64; N, 6.82. Found: C, 55.41; H, 5.68; N, 6.75.

(*E*)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-methoxyphenyl)prop-2-en-1-ol (4e): a colorless oil; R_f 0.36 (AcOEt–hexane 1:3); IR (neat) 3455, 1607, 1547, 1513, 1362, 1038 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.63 (s, 9H), 2.56 (s, 3H), 3.42 (d, *J* = 10.3 Hz, 1H), 3.80 (s, 3H), 4.00 (s, 3H), 5.59 (dd, *J* = 10.3, 6.3 Hz, 1H), 6.27 (dd, *J* = 15.5, 6.3 Hz, 1H), 6.49 (d, *J* = 15.5 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H). Anal. Calcd for $C_{20}H_{26}N_2O_3S_2$: C, 59.08; H, 6.45; N, 6.89. Found: C, 59.04; H, 6.54; N, 6.84.

(*E*)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-1,3-diphenylprop-2-en-1-ol (4f): a colorless oil; R_f 0.33 (THF–hexane 1:7); IR (neat) 3528, 1534, 1505, 1328, 1038 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.53 (s, 9H), 2.56 (s, 3H), 3.80 (s, 3H), 4.95 (s, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.81 (d, *J* = 15.6 Hz, 1H), 7.20–7.36 (m, 8H), 7.41 (d, *J* = 7.3 Hz, 2H). Anal. Calcd for $C_{25}H_{28}N_2O_2S_2$: C, 66.34; H, 6.24; N, 6.19. Found: C, 66.27; H, 6.20; N, 6.16.

(*E*)-3-(3,4-Dimethoxyphenyl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-1-phenylprop-2-en-1-ol (4g): a pale-yellow oil; R_f 0.29 (AcOEt–hexane 1:3); IR (neat) 3517, 1601, 1535, 1506, 1329, 1036 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.53 (s, 9H), 2.56 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.96 (s, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.97 (s, 1H), 7.25 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.37 (d, *J* = 7.4, 1.7 Hz, 2H). Anal. Calcd for $C_{27}H_{32}N_2O_4S_2$: C, 63.25; H, 6.29; N, 5.46. Found: C, 63.28; H, 6.56; N, 5.16.

(*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)-pyrimidin-5-yl]-1-phenylprop-2-en-1-ol (4h): a yellow oil; R_f 0.18 (AcOEt–hexane 1:7); IR (neat) 3527,

1536, 1504, 1353, 1039 cm^{-1}; ^1H NMR (500 MHz,) δ 1.54 (s, 9H), 2.56 (s, 3H), 3.79 (s, 3H), 4.91 (s, 1H), 5.94 (s, 2H), 6.41 (d, *J* = 15.5 Hz, 1H), 6.62 (d, *J* = 15.5 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.97 (s, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.34 (d, *J* = 7.4 Hz, 2H). Anal. Calcd for $C_{26}H_{28}N_2O_4S_2$: C, 62.88; H, 5.68; N, 5.64. Found: C, 62.82; H, 5.72; N, 5.53.

(*E*)-1-(4-Chlorophenyl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-3-(4-methoxyphenyl)-2-(methylsulfanyl)pyrimidin-5-yl]-1-phenylprop-2-en-1-ol (4i): a white solid; mp 126–128 ˚C (hexane); IR (KBr) 3525, 1607, 1536, 1505, 1357, 1037 cm^{-1}; ^1H NMR (500 MHz) δ 1.53 (s, 9H), 2.55 (s, 3H), 3.81 (s, 3H), 3.96 (s, 3H), 4.96 (s, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H). Anal. Calcd for $C_{26}H_{29}ClN_2O_3S_2$: C, 60.39; H, 5.65; N, 5.42. Found: C, 60.30; H, 5.68; N, 5.34.

(*E*)-3-(4-Chlorophenyl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-1-(4-methoxyphenyl)-2-(methylsulfanyl)pyrimidin-5-yl]-1-phenylprop-2-en-1-ol (4j): a white solid; mp 45–47 ˚C (hexane); IR (KBr) 3532, 1607, 1534, 1505, 1357, 1037 cm^{-1}; ^1H NMR (500 MHz) δ 1.53 (s, 9H), 2.55 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.95 (s, 1H), 6.44 (d, *J* = 15.5 Hz, 1H), 6.77 (d, *J* = 15.5 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H). Anal. Calcd for $C_{26}H_{29}ClN_2O_3S_2$: C, 60.39; H, 5.65; N, 5.42. Found: C, 60.09; H, 5.67; N, 5.46.

Typical Procedure for the Preparation of 7*H*-Thiopyrano[2,3-*d*]pyrimidines (7). 4-Methoxy-2-methylsulfanyl-7-phenyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7a). To a stirred solution of **4a** (0.11 g, 0.29 mmol) in MeCN (3 mL) at 0 ˚C was added dropwise concd. HBr (50 mg, 0.29 mmol). After the consumption of **4a** had been confirmed by TLC (SiO_2) analyses (*ca*. 20 min), saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to give **7a** (65 mg, 74%); a pale-yellow oil; R_f 0.65 (AcOEt–hexane 1:5); IR (neat) 1632, 1550, 1515, 1361, 1052 cm^{-1}; ^1H NMR (500 MHz) δ 2.52 (s, 3H), 4.01 (s, 3H), 5.05 (d, *J* = 4.9 Hz, 1H), 5.83 (dd, *J* = 9.8, 4.9 Hz, 1H), 6.78 (d, *J* = 9.8 Hz, 1H), 7.28–7.34 (m, 5H); ^{13}C NMR (125 MHz) δ 14.15, 44.81, 54.10, 107.15, 120.28, 122.00, 127.64, 128.04, 128.87, 141.43, 163.21, 164.16, 169.66. HR MS. Calcd for $C_{15}H_{15}N_2OS_2$ (M+H): 303.0627. Found: *m/z* 303.0619. Anal. Calcd for $C_{15}H_{14}N_2OS_2$: C, 59.57; H, 4.67; N, 9.26. Found: C, 59.36; H, 4.72; N, 9.26.

4-Methoxy-6-methyl-2-methylsulfanyl-7-phenyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7b): a pale-yellow solid; mp 105–108 ˚C (hexane–Et_2O); IR (KBr) 1545, 1527, 1368, 1054 cm^{-1}; ^1H NMR (500 MHz) δ 1.92 (s, 3H), 2.50 (s, 3H), 4.01 (s, 3H), 4.60 (s, 1H), 6.62 (s, 1H), 7.23–7.29 (m, 5H); ^{13}C NMR (125 MHz) δ 14.10, 23.30, 48.55, 54.03, 107.76, 116.45, 127.11, 127.95, 128.86, 130.86, 141.32, 161.95, 162.79, 168.55. HR MS. Calcd for $C_{16}H_{17}N_2OS_2$ (M+H): 317.0783. Found: *m/z* 317.0755. Anal. Calcd for $C_{16}H_{16}N_2OS_2$: C, 60.73; H, 5.10; N, 8.85. Found: C, 61.03; H, 5.12; N, 8.59.

4-Methoxy-7-(4-methylphenyl)-2-methylsulfanyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7c): a yellow oil; R_f 0.40 (AcOEt–hexane 1:7); IR (neat) 1550, 1515, 1360, 1052 cm^{-1}; ^1H NMR (500 MHz) δ 2.32 (s, 3H), 2.51 (s, 3H), 4.00 (s, 3H), 5.03 (d, *J* = 5.2 Hz, 1H), 5.81 (dd, *J* = 10.3, 5.2 Hz, 1H), 6.73 (dd, *J* = 10.3, 1.7 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz) δ 14.13, 21.09, 44.62, 54.06, 107.18, 120.12, 122.26, 127.55, 129.54, 137.88, 138.49, 163.21, 164.31, 169.58. HR MS. Calcd for $C_{16}H_{17}N_2OS_2$ (M+H): 317.0783. Found: *m/z* 317.0765. Anal. Calcd for $C_{16}H_{16}N_2OS_2$: C, 60.73; H, 5.10; N, 8.85. Found: C, 60.62; H, 5.12; N, 8.87.

7-(4-Chlorophenyl)-4-methoxy-2-methylsulfanyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7d): a pale-yellow solid; mp 96–98 °C (hexane); IR (KBr) 1550, 1515, 1361, 1052 cm^{-1}; ^1H NMR (500 MHz) δ 2.51 (s, 3H), 4.01 (s, 3H), 4.99 (d, *J* = 5.9 Hz, 1H), 5.80 (dd, *J* = 8.8, 5.9 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (125 MHz) δ 14.15, 44.01, 54.14, 107.06, 120.66, 121.35, 128.96, 129.00, 133.87, 139.97, 163.25, 163.76, 169.92. HR MS. Calcd for $C_{15}H_{14}ClN_2OS_2$ (M+H): 337.0237. Found: *m/z* 337.0236. Anal. Calcd for $C_{15}H_{13}ClN_2OS_2$: C, 53.48; H, 3.89; N, 8.32. Found: C, 53.47; H, 3.98; N, 8.58.

4-Methoxy-7-(4-methoxyphenyl)-2-methylsulfanyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7e): a pale-yellow oil; R_f 0.44 (AcOEt–hexane 1:5); IR (neat) 1609, 1550, 1511, 1361, 1051 cm^{-1}; ^1H NMR (500 MHz) δ 2.51 (s, 3H), 3.78 (s, 3H), 4.00 (s, 3H), 5.02 (dd, *J* = 5.2, 1.1 Hz, 1H), 5.80 (dd, *J* = 10.3, 5.2 Hz, 1H), 6.73 (dd, *J* = 10.3, 1.1 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz) δ 14.12, 44.35, 54.05, 55.29, 107.17, 114.22, 120.10, 122.38, 128.84, 133.59, 159.37, 163.23, 164.30, 169.60. HR MS. Calcd for $C_{16}H_{17}N_2O_2S_2$ (M+H): 333.0732. Found: *m/z* 333.0717. Anal. Calcd for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; H, 4.85; N, 8.43. Found: C, 57.74; H, 5.06; N, 8.22.

4-Methoxy-2-methylsulfanyl-5,7-diphenyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7f): a white solid; mp 179–181 °C (hexane–Et_2O); IR (KBr) 1604, 1538, 1503, 1358, 1048 cm^{-1}; ^1H NMR (400 MHz) δ 2.55 (s, 3H), 3.63 (s, 3H), 5.03 (d, *J* = 5.4 Hz, 1H), 6.02 (d, *J* = 5.4 Hz, 1H), 7.18 (dd, *J* = 7.3, 1.9 Hz, 2H), 7.29–7.36 (m, 6H), 7.43 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz) δ 14.14, 44.54, 58.59, 109.78, 124.76, 126.81, 127.34, 127.83, 128.07, 128.14, 128.84, 137.68, 139.04, 140.29, 163.96, 168.62, 169.60. HR MS. Calcd for $C_{21}H_{19}N_2OS_2$ (M+H): 379.0940. Found: *m/z* 379.0939. Anal. Calcd for $C_{21}H_{18}N_2OS_2$: C, 66.64; H, 4.79; N, 7.40. Found: C, 66.79; H, 4.90; N, 7.10.

7-(3,4-Dimethoxyphenyl)-4-methoxy-2-methylsulfanyl-5-phenyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7g): a pale-yellow solid; mp 135–137 °C (hexane–Et_2O); IR (KBr) 1603, 1538, 1503, 1357, 1046 cm^{-1}; ^1H NMR (500 MHz) δ 2.56 (s, 3H), 3.64 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 5.00 (d, *J* = 5.7 Hz, 1H), 6.82 (d, *J* = 9.2 Hz, 1H), 6.95–6.96 (m, 2H), 7.18–7.20 (m, 2H), 7.30–7.31 (m, 4H); ^{13}C NMR (125 MHz) δ 14.15, 44.61, 53.60, 55.84, 109.79, 110.92, 111.03, 120.44, 125.04, 126.80 (2C), 127.37, 127.86, 131.08, 137.60, 140.26, 148.87, 149.02, 163.96, 168.78, 169.61. HR MS. Calcd for $C_{23}H_{23}N_2O_3S_2$ (M+H):

439.1151. Found: *m/z* 439.1145. Anal. Calcd for $C_{23}H_{22}N_2O_3S_2$: C, 62.99; H, 5.06; N, 6.39. Found: C, 62.75; H, 5.30; N, 6.36.

7-(Benzo[*d*][1,3]dioxol-5-yl)-4-methoxy-2-methylsulfanyl-5-phenyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7h): a white solid; mp 154–156 ˚C (hexane–CH_2Cl_2); IR (KBr) 1607, 1539, 1502, 1358, 1041 cm^{-1}; ^1H NMR (400 MHz) δ 2.55 (s, 3H), 3.63 (s, 3H), 4.95 (d, *J* = 5.9 Hz, 1H), 5.95 (s, 2H), 5.98 (d, *J* = 5.9 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.87 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.92 (s, 1H), 7.15–7.20 (m, 3H), 7.30 (dd, *J* = 7.8, 2.9 Hz, 2H); ^{13}C NMR (125 MHz) δ 14.14, 44.44, 53.58, 101.25, 108.36, 108.44, 109.65, 121.54, 124.80, 126.80, 127.35, 127.83, 132.80, 137.64, 140.29, 147.49, 147.92, 163.96, 168.47, 169.63. HR MS. Calcd for $C_{22}H_{19}N_2O_3S_2$ (M+H): 423.0838. Found: *m/z* 423.0825. Anal. Calcd for $C_{22}H_{18}N_2O_3S_2$: C, 62.54; H, 4.29; N, 6.63. Found: C, 62.46; H, 4.32; N, 6.40.

5-(4-Chlorophenyl)-4-methoxy-7-(4-methoxyphenyl)-2-methylsulfanyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7i): a white solid; mp 126–128 ˚C (hexane); IR (KBr) 1614, 1540, 1503, 1361, 1051 cm^{-1}; ^1H NMR (500 MHz) δ 2.55 (s, 3H), 3.66 (s, 3H), 3.80 (s, 3H), 4.98 (d, *J* = 5.2 Hz, 1H), 5.98 (d, *J* = 5.2 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz) δ 14.14, 43.98, 53.66, 55.30, 109.35, 114.23, 125.54, 127.97, 128.16, 129.19, 130.70, 133.05, 136.43, 138.88, 159.47, 163.80, 168.77, 169.83. HR MS. Calcd for $C_{22}H_{20}ClN_2O_2S_2$ (M+H): 443.0655. Found: *m/z* 443.0646. Anal. Calcd for $C_{22}H_{19}ClN_2O_2S_2$: C, 59.65; H, 4.32; N, 6.32. Found: C, 59.94; H, 4.47; N, 6.25.

7-(4-Chlorophenyl)-4-methoxy-5-(4-methoxyphenyl)-2-methylsulfanyl-7*H*-thiopyrano[2,3-*d*]pyrimidine (7j): a white solid; mp 48–50 ˚C (hexane); IR (KBr) 1607, 1539, 1510, 1359, 1046 cm^{-1}; ^1H NMR (500 MHz) δ 2.55 (s, 3H), 3.67 (s, 3H), 3.83 (s, 3H), 4.95 (d, *J* = 6.3 Hz, 1H), 5.93 (d, *J* = 6.3 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz) δ 14.12, 43.65, 53.74, 55.27, 109.72, 113.23, 122.82, 128.96, 129.38, 130.37, 132.58, 133.93, 137.53, 137.70, 159.11, 164.05, 168.11, 169.66. HR MS. Calcd for $C_{22}H_{20}ClN_2O_2S_2$ (M+H): 443.0655. Found: *m/z* 443.0647. Anal. Calcd for $C_{22}H_{19}ClN_2O_2S_2$: C, 59.65; H, 4.32; N, 6.32. Found: C, 59.60; H, 4.29; N, 6.17.

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