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A FACILE SYNTHESIS OF 1,4-DIHYDRO-2*H*-PYRIMIDO[4,5-*d*][1,3]OXAZIN-2-ONE DERIVATIVES FROM 4,6-DICHLORO-2-(METHYLSULFANYL)PYRIMIDINE

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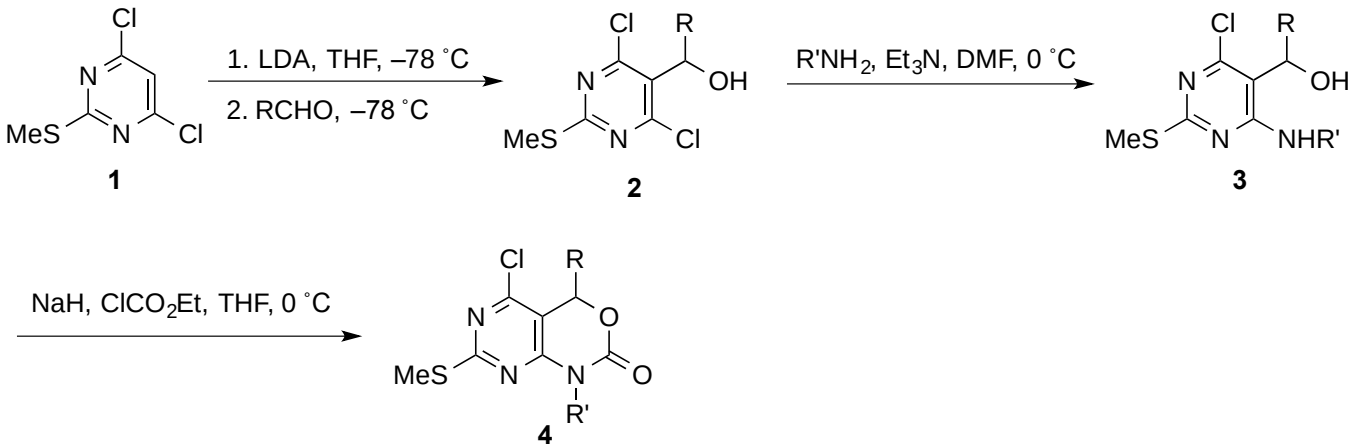
Abstract – A facile three-step sequence has been developed for the preparation of 1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one derivatives from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) under mild conditions. Thus, the starting material is treated with LDA to generate the 5-lithiated compound, which is then allowed to react with (het)aromatic and aliphatic aldehydes to give the corresponding 1-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]alkan-1-ols. The reaction of these compounds with primary amines in the presence of triethylamine gives 1-[4-(alkylamino)-6-chloro-2-(methylsulfanyl)pyrimidin-5-yl]alkan-1-ols, of which subjection to successive treatment with an equimolar amount each of sodium hydride and ethyl chloroformate provides the desired 1,4-disubstituted 7-(methylsulfanyl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-ones.

Compounds with the 1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one structure are known to exhibit a variety of biological activities,[1] such as calcitonin gene-related peptide (CGDR) receptor antagonistic,[1a] mutant isocitrate dehydrogenase 1 (IDH1) inhibitory,[1e] and epidermal growth factor receptor (EGFR) L858R/T790M inhibitory activities.[1g] Previous synthesis of 1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one derivatives involves carbonylation of 1-(4-aminopyrimidin-5-yl)alkanols, derived from 4-aminopyrimidine-5-carboxylic acid derivatives, with di(imidazol-1-yl)methanone.[1] However, this method is of limited general applicability. Recently, 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) (**1**) has been shown to be a versatile starting materials for the preparation of pyrimidine-fused heterocyclic compounds by us.[2] Subsequently, we herein wish to describe the results of our study on exploration of a further utilization of this pyrimidine derivative, which offer a general, mild, and efficient approach to 1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one derivatives (**4**).

Our three-step synthesis of 1,4-disubstituted 7-(methylsulfanyl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-ones (**4**) from DCSMP (**1**) was conducted according to the sequence illustrated in Scheme 1. Compound (**1**) was converted into 1-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]alkan-1-ols (**2**) by the treatment with LDA in THF at –78 ˚C, followed by reaction of the resulting 5-lithio derivative with various aldehydes, as reported in the previous paper.[2f] Displacement of one of the two chloro substituents of **2** with primary amines in the presence of triethylamine in DMF at 0 ˚C proceeded smoothly and cleanly to give the corresponding 1-[4-(alkylamino)-6-chloro-2-(methylsulfanyl)pyrimidin-5-yl]alkan-1-ols (**3**) in excellent yields as listed in Table 1.



Scheme 1

Initially, after treatment of compounds (**3**) with two molar equivalents of sodium hydride in DMF or THF at 0 ˚C, the resulting reaction mixtures were treated with an equimolar amount of ethyl chloroformate at the same temperature. The reactions resulted in the immediate formation of rather complicated mixtures of products, from which only about 30% yields of the desired products (**4**) were isolated. Reactions of **3**

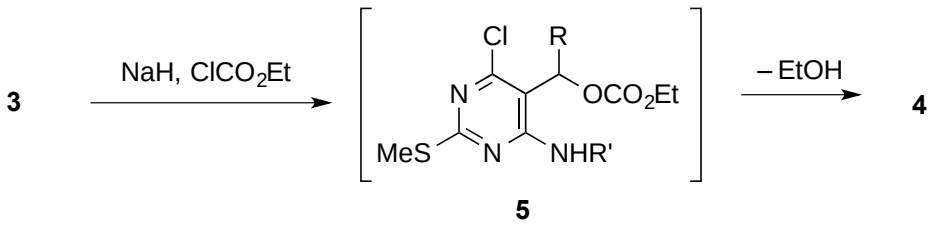
with an equimolar amount each of sodium hydride and ethyl chloroformate in THF at 0 ˚C were then examined and we were pleased to find that the oxazinone ring formation proceeded smoothly and relative cleanly under these conditions to afford, after usual aqueous workup and subsequent purification by column chromatography on silica gel, the desired products (**4**). The results are also summarized in Table 1, which shows that the products were obtained in moderate to fair yields.

Table 1. Preparation of 3,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-ones (**4**)

Entry	**2**	R' in $R'NH_2$	**3**	Yield/%[a]	**4**	Yield/%[a]
1	**2a** (R = Ph)	Me	**3a**	93	**4a**	75
2	**2a**	Et	**3b**	88	**4b**	71
3	**2a**	Bn	**3c**	94	**4c**	70
4	**2b** (R = 4-ClC_6H_4)	Me	**3d**	87	**4d**	76
5	**2b**	*n*-Bu	**3e**	90	**4e**	72
6	**2c** (R = 4-$MeOC_6H_4$)	Me	**3f**	70	**4f**	73
7	**2c**	$Ph(CH_2)_2$	**3g**	88	**4g**	68
8	**2d** (R = thiophen-3-yl)	Me	**3h**	89	**4h**	67
9	**2e** (R = Et)	Me	**3i**	88	**4i**	76
10	**2f** (R = *i*-Pr)	Me	**3j**	95	**4j**	59

[a] Yields of isolated products.

It is presumed that the deprotonation of the hydroxy hydrogen of **3** with sodium hydride generates the corresponding sodium alkoxides. These are then ethoxycarbonylated with ethyl chloroformate to give the intermediate ethyl carbonates (**5**), which cyclize to the desired cyclic urethanes (**4**). The reactions using phenyl chloroformate or dimethyl carbonate in place of ethyl chloroformate under similar conditions were attempted. However, these gave somewhat decreased yields of the desired products. As can be seen from Entries 1-7, the sizes of the R' substituents slightly affected the reactivity of **3**. The yields of the products decreased, according as the substituents were bulkier. A similar steric effect was observed with regard to the R substituents; the yield of the product (**4j**) from (**3j**) (R = *i*-Pr, Entry 10) was rather lower than those of **4a**, **4d**, **4f**, **4h**, and **4i**.



Scheme 2

In conclusion, a new three-step sequence starting from commercially available 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) (**1**) has been shown to provide an efficient approach to 1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one derivatives (**4**). Notable advantages of the present synthesis include the simplicity of the procedure, the mild reaction conditions, and the ready availability of the starting materials. We are currently investigating the use of this pyrimidine derivative to prepare other important pyrimidine-fused heterocycles.

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 Spectrum 65 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer (ESI, positive) or a JEOL JMS-T100GCV (EI, TOF; 70eV) spectrometer. Elemental analyses were performed with an Elementar Vario EL II instrument. 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. 1-[4,6-Dichloro-2-(methylsulfanyl)pyrimidin-5-yl]alkan-1-ols (**2**) were prepared according to the reported method.[2f] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of 1-(Pyrimidin-5-yl)alkanols (3). [4-Chloro-6-(methylamino)-2-(methylsulfanyl)pyrimidin-5-yl]phenylmethanol (3a). To a stirred solution of **2a** (0.22 g, 0.73 mmol) in DMF (2 mL) containing Et_3N (74 mg) at 0 ˚C was added $MeNH_2$ (40% in H_2O; 0.73 mmol) dropwise. After 30 min, H_2O (30 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with H_2O (3 × 15 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized from CH_2Cl_2 to give **3a** (0.20 g, 93%); a white solid; mp 180–182 ˚C; IR (KBr) 3393, 3181, 1568 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 2.89 (d, *J* = 4.6 Hz, 3H), 3.75 (br s, 1H), 6.38 (s, 1H), 6.54 (q, *J* = 4.6 Hz, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 28.1, 70.6, 110.0, 125.5, 127.8, 128.5, 139.5, 153.7, 161.2, 170.5. Anal. Calcd for $C_{13}H_{14}ClN_3OS$: C, 52.79; H, 4.77; N, 14.21. Found: C, 52.68; H, 4.82; N, 14.03.

[4-Chloro-6-(ethylamino)-2-(methylsulfanyl)pyrimidin-5-yl]phenylmethanol (3b): a pale-yellow solid; mp 169–171 ˚C (hexane/THF); IR (KBr) 3391, 3315, 1570 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.98 (t, *J* = 7.4 Hz, 3H), 2.44 (s, 3H), 3.29–3.36 (m, 2H), 6.14 (d, *J* = 3.8 Hz, 1H), 6.79 (d, *J* = 3.8 Hz, 1H), 7.13 (t, *J* = 6.4 Hz, 1H), 7.25 (t, *J* = 6.9 Hz, 1H), 7.32 (dd, *J* = 7.6, 6.9 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR

(DMSO-d_6) δ 13.4, 14.2, 35.4, 69.2, 110.9, 125.3, 127.3, 128.2, 141.2, 154.5, 160.2, 168.8. Anal. Calcd for $C_{14}H_{16}ClN_3OS$: C, 54.28; H, 5.21; N, 13.56. Found: C, 54.21; H, 5.32; N, 13.60.

{4-Chloro-2-(methylsulfanyl)-6-[(phenylmethyl)amino]pyrimidin-5-yl}phenylmethanol (3c): a white solid; mp 189–191 ˚C ($CHCl_3$); IR (KBr) 3350, 3204, 1571 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.52 (br s, 1H), 4.46 (dd, J = 15.5, 5.2 Hz, 1H), 4.68 (dd, J = 15.5, 6.3 Hz, 1H), 6.43 (s, 1H), 6.79 (dd, J = 6.3, 5.2 Hz, 1H), 6.93–6.94 (m, 2H), 7.18–7.20 (m, 3H), 7.29–7.35 (m, 3H), 7.39 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 44.8, 70.4, 110.3, 125.5, 127.0, 127.1, 127.8, 128.4, 128.5, 138.2, 139.6, 156.0, 160.0, 170.6. HR-MS (EI). Calcd for $C_{19}H_{18}ClN_3OS$ (M): 371.0859. Found: *m/z* 371.0853.

[4-Chloro-6-(methylamino)-2-(methylsulfanyl)pyrimidin-5-yl](4-chlorophenyl)methanol (3d): a white solid; mp 179–181 ˚C (hexane/CH_2Cl_2); IR (KBr) 3409, 3218, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H), 2.90 (d, J = 4.6 Hz, 3H), 3.98 (br s, 1H), 6.34 (s, 1H), 6.50 (q, J = 4.6 Hz, 1H), 7.31 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1, 28.1, 70.0, 109.6, 127.0, 128.6, 133.6, 138.0, 155.6, 161.1, 170.7. Anal. Calcd for $C_{13}H_{13}Cl_2N_3OS$: C, 47.28; H, 3.97; N, 12.72. Found: C, 47.23; H, 3.99; N, 12.76.

[4-(Butylamino)-6-chloro-2-(methylsulfanyl)pyrimidin-5-yl](4-chlorophenyl)methanol (3e): a white solid; mp 152–154 ˚C (hexane/CH_2Cl_2); IR (KBr) 3380, 3193, 1575 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.75 (t, J = 7.6 Hz, 3H), 1.03 (sext, J = 7.6 Hz, 2H), 1.33 (quint, J = 7.6 Hz, 2H), 2.40 (s, 3H), 3.23–3.28 (m, 1H), 3.33–3.37 (m, 1H), 6.12 (d, J = 3.8 Hz, 1H), 6.91 (d, J = 3.8 Hz, 1H), 6.97 (t, J = 5.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 13.4, 13.5, 19.2, 30.6, 39.9, 68.5, 110.6, 127.2, 128.2, 131.9, 140.2, 154.6, 160.2, 169.1. Anal. Calcd for $C_{16}H_{19}Cl_2N_3OS$: C, 51.62; H, 5.14; N, 11.29. Found: C, 51.51; H, 5.17; N, 11.40.

[4-Chloro-6-(methylamino)-2-(methylsulfanyl)pyrimidin-5-yl](4-methoxyphenyl)methanol (3f): a white solid; mp 191–193 ˚C (hexane/THF); IR (KBr) 3420, 1575 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.42 (s, 3H), 2.82 (d, J = 4.6 Hz, 3H), 3.71 (s, 3H), 6.07 (d, J = 3.8 Hz, 1H), 6.68 (d, J = 3.8 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.20 (q, J = 4.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 13.4, 27.9, 55.1, 69.0, 111.3, 113.7, 126.7, 133.2, 154.2, 158.5, 160.8, 168.7. HR-MS (EI). Calcd for $C_{14}H_{16}ClN_3O_2S$ (M): 325.0652. Found: *m/z* 325.0643.

{4-Chloro-2-(methylsulfanyl)-6-[(2-phenylethyl)amino]pyrimidin-5-yl}(4-methoxyphenyl)methanol (3g): a white solid; mp 135–137 ˚C (hexane/CH_2Cl_2); IR (KBr) 3361, 3234, 1571 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H), 2.78 (t, J = 7.4 Hz, 2H), 3.58–3.72 (m, 2H), 3.79 (s, 3H), 6.28 (s, 1H), 6.63 (t, J = 5.2 Hz, 1H), 6.81 (d, J = 9.2 Hz, 2H), 7.06 (dd, J = 6.9, 1.7 Hz, 2H), 7.18–7.26 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 14.1, 35.3, 42.4, 55.3, 70.6, 109.8, 113.8, 126.4, 126.9, 128.5, 128.7, 131.5, 138.8, 155.8, 159.1, 160.5, 170.3. Anal. Calcd for $C_{21}H_{22}ClN_3O_2S$: C, 60.64; H, 5.33; N, 10.10. Found: C, 60.62; H, 5.36; N, 9.94.

[4-Chloro-6-(methylamino)-2-(methylsulfanyl)pyrimidin-5-yl](thiophen-3-yl)methanol (3h): a white solid; mp 168–170 ˚C (hexane/CH_2Cl_2); IR (KBr) 3339, 3120, 1560 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.42 (s, 3H), 2.85 (d, J = 5.4 Hz, 3H), 6.14 (d, J = 3.8 Hz, 1H), 6.69 (d, J = 3.8 Hz, 1H), 7.01 (dd, J = 5.4, 1.5 Hz, 1H), 7.26 (q, J = 5.4 Hz, 1H), 7.41 (dd, J = 3.1, 1.5 Hz, 1H), 7.46 (dd, J = 5.4, 3.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 13.4, 27.9, 67.1, 110.7, 121.7, 125.8, 126.5, 142.4, 153.8, 160.6, 168.7. HR-MS (EI). Calcd for $C_{11}H_{12}ClN_3OS_2$ (M): 301.0110. Found: *m/z* 301.0095.

1-[4-Chloro-6-(methylamino)-2-(methylsulfanyl)pyrimidin-5-yl]propan-1-ol (3i): a white solid; mp 171–173 ˚C (hexane/CH_2Cl_2); IR (KBr) 3357, 3267, 1568 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.86 (t, J = 7.6 Hz, 3H), 1.54–1.63 (m, 1H), 1.68–1.77 (m, 1H), 2.42 (s, 3H), 2.88 (d, J = 4.6 Hz, 3H), 4.87 (t, J = 8.4 Hz, 1H), 6.04 (br s, 1H), 7.39 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 10.4, 13.4, 27.1, 27.8, 70.0, 111.1, 153.7, 161.0, 168.2. Anal. Calcd for $C_9H_{14}ClN_3OS$: C, 43.63; H, 5.70; N, 16.96. Found: C, 43.62; H, 5.68; N, 16.63.

1-[4-Chloro-6-(methylamino)-2-(methylsulfanyl)pyrimidin-5-yl]-2-methylpropan-1-ol (3j): a white solid; mp 202–204 ˚C (CH_2Cl_2); IR (KBr) 3326, 3209, 1562 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.73 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H), 2.00–2.04 (m, 1H), 2.42 (s, 3H), 2.87 (d, J = 4.6 Hz, 3H), 4.60 (dd, J = 8.0, 3.4 Hz, 1H), 6.03 (d, J = 3.4 Hz, 1H), 7.29 (q, J = 4.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 13.4, 19.1, 19.2, 27.9, 31.7, 73.9, 110.7, 154.5, 161.2, 168.2. Anal. Calcd for $C_{10}H_{16}ClN_3OS$: C, 45.88; H, 6.16; N, 16.05. Found: C, 45.74; H, 6.05; N, 15.85.

Typical Procedure for the Preparation of 1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-ones (4). 5-Chloro-1-methyl-7-(methylsulfanyl)-4-phenyl-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (4a). To a stirred suspension of NaH (60% in mineral oil; 25 mg, 0.63 mmol) in THF (3 mL) at 0 ˚C was added a solution of **3a** (0.19 g, 0.63 mmol) in THF (2 mL) dropwise. After evolution of H_2 gas had ceased, $ClCO_2Et$ (68 mg, 0.63 mmol) was added, and stirring was continued for 10 min at the same temperature. Saturated aqueous NH_4Cl (15 mL) was added and 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 (AcOEt/hexane 1:6) to give **4a** (0.15 g, 75%); a white solid; mp 102–104 ˚C (hexane/CH_2Cl_2); IR (KBr) 1740, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.45 (s, 3H), 6.46 (s, 1H), 7.27 (dd, J = 6.9, 1.7 Hz, 2H), 7.38–7.39 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.4, 30.1, 75.9, 106.9, 126.6, 129.2, 129.8, 135.9, 150.4, 156.1, 156.3, 173.5. HR-MS (EI). Calcd for $C_{14}H_{12}ClN_3O_2S$ (M): 321.0339. Found: *m/z* 321.0330. Anal. Calcd for $C_{14}H_{12}ClN_3O_2S$: C, 52.26; H, 3.76; N, 13.06. Found: C, 52.28; H, 3.90; N, 12.92.

5-Chloro-1-ethyl-7-(methylsulfanyl)-4-phenyl-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (4b): a white solid; mp 113–115 ˚C (hexane/CH_2Cl_2); IR (KBr) 1734, 1546 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26

(t, J = 6.9 Hz, 3H), 2.59 (s, 3H), 4.06–4.14 (m, 2H), 6.42 (s, 1H), 7.38 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 12.7, 14.4, 38.7, 76.0, 106.9, 126.7, 129.2, 129.8, 136.0, 149.8, 155.9, 156.2, 173.4. HR-MS (EI). Calcd for $C_{15}H_{14}ClN_3O_2S$ (M): 335.0495. Found: *m/z* 335.0491. Anal. Calcd for $C_{15}H_{14}ClN_3O_2S$: C, 53.65; H, 4.20; N, 12.51. Found: C, 53.47; H, 4.31; N, 12.55.

5-Chloro-7-(methylsulfanyl)-4-phenyl-1-(phenylmethyl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (4c): a white solid; mp 136–138 ˚C (hexane/CH_2Cl_2); IR (KBr) 1742, 1542 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.25 (d, J = 14.9 Hz, 1H), 5.31 (d, J = 14.9 Hz, 1H), 6.44 (s, 1H), 7.17–7.47 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.4, 46.0, 76.1, 107.4, 126.8, 127.7, 128.0, 128.4, 129.1, 129.7, 135.8, 136.0, 150.3, 155.8, 156.2, 173.3. HR-MS (ESI). Calcd for $C_{20}H_{17}ClN_3O_2S$ (M+H): 398.0730. Found: *m/z* 398.0719. Anal. Calcd for $C_{20}H_{16}ClN_3O_2S$: C, 60.38; H, 4.05; N, 10.56. Found: C, 60.15; H, 4.11; N, 10.58.

5-Chloro-4-(4-chlorophenyl)-1-methyl-7-(methylsulfanyl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (4d): a pale-yellow solid; mp 157–159 ˚C (AcOEt); IR (KBr) 1736, 1544 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.44 (s, 3H), 6.43 (s, 1H), 7.21 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 30.2, 75.2, 106.3, 127.3, 128.0, 129.1, 129.4, 134.4, 156.1, 156.2, 173.8. HR-MS (ESI). Calcd for $C_{14}H_{12}Cl_2N_3O_2S$ (M+H): 356.0027. Found: *m/z* 356.0014. Anal. Calcd for $C_{14}H_{11}Cl_2N_3O_2S$: C, 47.20; H, 3.11; N, 11.80. Found: C, 47.30; H, 3.46; N, 11.66.

1-Butyl-5-chloro-4-(4-chlorophenyl)-7-(methylsulfanyl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (4e): a white solid; mp 89–91 ˚C (hexane/CH_2Cl_2); IR (KBr) 1734, 1578 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H), 1.23–1.28 (m, 2H), 1.57–1.63 (m, 2H), 2.58 (s, 3H), 3.97–4.02 (m, 1H), 4.07–4.13 (m, 1H), 6.40 (s, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.4, 19.8, 29.4, 43.1, 75.1, 106.5, 128.0, 129.4, 134.5, 135.8, 149.8, 156.0, 156.2, 173.7. HR-MS (ESI). Calcd for $C_{17}H_{18}Cl_2N_3O_2S$ (M+H): 398.0497. Found: *m/z* 398.0492. Anal. Calcd for $C_{17}H_{17}Cl_2N_3O_2S$: C, 51.26; H, 4.30; N, 10.55. Found: C, 51.34; H, 4.36; N, 10.59.

5-Chloro-4-(4-methoxyphenyl)-1-methyl-7-(methylsulfanyl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]-oxazin-2-one (4f): a white solid; mp 128–130 ˚C (hexane/CH_2Cl_2); IR (KBr) 1738, 1578 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.45 (s, 3H), 3.80 (s, 3H), 6.40 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 30.1, 55.3, 75.9, 107.0, 114.5, 127.9, 128.3, 150.5, 156.1, 156.3, 160.6, 173.3. HR-MS (ESI). Calcd for $C_{15}H_{15}ClN_3O_3S$ (M+H): 352.0522. Found: *m/z* 352.0526. Anal. Calcd for $C_{15}H_{14}ClN_3O_3S$: C, 51.21; H, 4.01; N, 11.94. Found: C, 51.21; H, 4.02; N, 11.93.

5-Chloro-4-(4-methoxyphenyl)-7-(methylsulfanyl)-1-(2-phenylethyl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (4g): a pale-yellow solid; mp 130–132 ˚C (hexane/CH_2Cl_2); IR (KBr) 1740, 1611, 1576 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 2.95–3.00 (m, 2H), 3.80 (s, 3H), 4.22–4.28 (m, 1H),

4.35–4.40 (m, 1H), 6.37 (s, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.19–7.22 (m, 3H), 7.26 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 33.7, 44.3, 55.3, 76.0, 107.0, 114.5, 126.6, 127.9, 128.3, 128.5, 128.8, 137.8, 149.9, 155.9, 156.2, 160.6, 173.2. HR-MS (ESI). Calcd for $C_{22}H_{21}ClN_3O_3S$ (M+H): 442.0992. Found: *m/z* 442.0984. Anal. Calcd for $C_{22}H_{20}ClN_3O_3S$: C, 59.79; H, 4.56; N, 9.51. Found: C, 59.81; H, 4.50; N, 9.39.

5-Chloro-1-methyl-7-(methylsulfanyl)-4-(thiophen-3-yl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (4h): a white solid; mp 119–121 ˚C (hexane/CH_2Cl_2); IR (KBr) 1733, 1582 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.45 (s, 3H), 6.50 (s, 1H), 7.07 (d, *J* = 5.2 Hz, 1H), 7.17 (br s, 1H), 7.36 (dd, *J* = 5.2, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 30.1, 72.2, 107.3, 124.0, 125.5, 127.8, 137.1, 150.5, 155.6, 156.2, 173.5. HR-MS (ESI). Calcd for $C_{12}H_{11}ClN_3O_2S_2$ (M+H): 327.9981. Found: *m/z* 327.9979. Anal. Calcd for $C_{12}H_{10}ClN_3O_2S_2$: C, 43.97; H, 3.08; N, 12.82. Found: C, 44.10; H, 3.22; N, 12.78.

5-Chloro-4-ethyl-1-methyl-7-(methylsulfanyl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (4i): a pale-yellow solid; mp 118–120 ˚C (hexane/CH_2Cl_2); IR (KBr) 1729, 1548 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J* = 7.4 Hz, 3H), 1.89 (quint, *J* = 7.4 Hz, 2H), 2.57 (s, 3H), 3.46 (s, 3H), 5.38 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.0, 14.3, 28.2, 30.0, 76.6, 107.7, 150.7, 155.0, 156.0, 172.8. HR-MS (EI). Calcd for $C_{10}H_{12}ClN_3O_2S$ (M): 273.0339. Found: *m/z* 273.0352. Anal. Calcd for $C_{10}H_{12}ClN_3O_2S$: C, 43.88; H, 4.42; N, 15.35. Found: C, 43.85; H, 4.43; N, 15.06.

5-Chloro-1-methyl-4-(1-methylethyl)-7-(methylsulfanyl)-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (4j): a white solid; mp 95–97 ˚C (hexane/CH_2Cl_2); IR (KBr) 1747, 1543 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 2.13–2.19 (m, 1H), 2.57 (s, 3H), 3.45 (s, 3H), 5.24 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 16.2, 18.6, 29.9, 34.0, 80.1, 106.8, 150.9, 155.7, 156.3, 172.8. HR-MS (EI). Calcd for $C_{11}H_{14}ClN_3O_2S$ (M): 287.0495. Found: *m/z* 287.0486. Anal. Calcd for $C_{11}H_{14}ClN_3O_2S$: C, 45.91; H, 4.90; N, 14.60. Found: C, 45.89; H, 5.02; N, 14.48.

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