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SYNTHESIS OF 8,9-DIHYDROPYRIMIDO[4,5-*e*][1,4]OXAZEPIN-7(5*H*)-ONES BY THE REACTION OF 1-(4-CHLOROPYRIMIDIN-5-YL)ALKAN-1-OLS WITH *N*-ALKYLGLYCINES

Kazuhiro Kobayashi,^{a*} Takashi Nogi,^a Yuka Tsunomori,^a Hidetaka Hiyoshi,^b and Kazuto Umezu^c

^a Applied Chemistry Field, Chemistry and Biotechnology Course, Department of Engineering, Graduate School of Sustainability Science, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

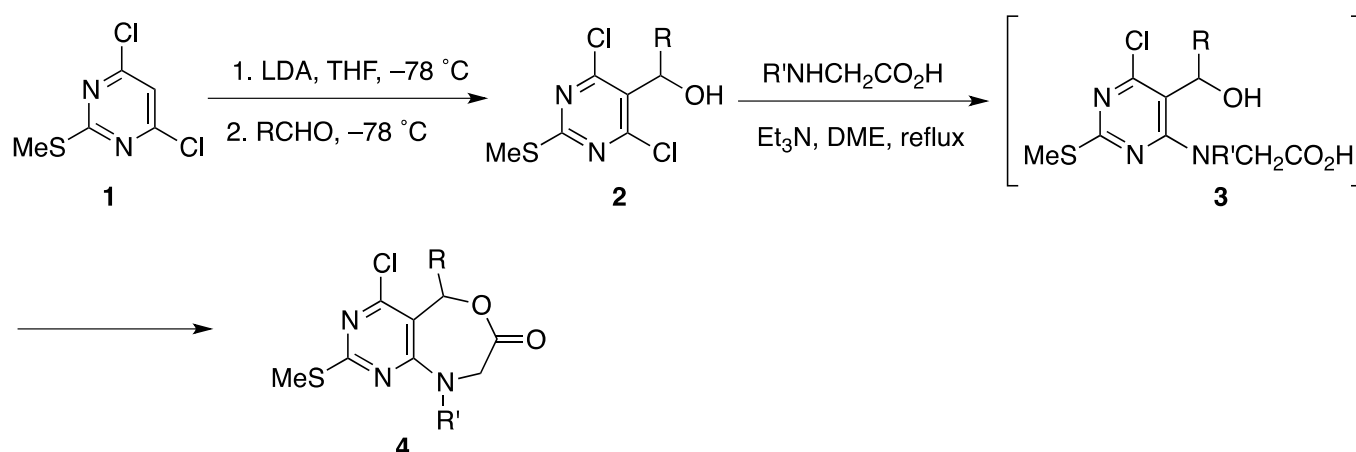
^b A.I. Production Planning Section, Development Promotion Department, Research & Development Division, KUMIAI CHEMICAL INDUSTRY CO., LTD., 4-26 Ikenohata 1-chome, Taito-ku, Tokyo 110-0008, Japan ^c Chemical Development Department, Research & Development Division, KUMIAI CHEMICAL INDUSTRY CO., LTD., 4-26 Ikenohata 1-chome, Taito-ku, Tokyo 110-0008, Japan; E-mail: kazuto.umezu@kumiai-chem.co.jp

Abstract – A facile method for the construction of a new ring system, 8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one, is described. The key feature of the synthetic route includes substitution of one of the two chloro groups of 1-(4,6-dichloropyrimidin-5-yl)alkan-1-ol derivatives, which can easily be derived from the reaction between 5-lithiated compound of 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) and aldehydes, with *N*-alkylglycines in the presence of triethylamine, followed by lactonization of the resulting hydroxy acids catalyzed by *in situ* generated triethylamine hydrochloride.

Current efforts in our laboratory focus on the development of convenient methods for the preparation of various pyrimidine-fused heterocycles utilizing 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) (**1**) as a starting material.¹ In studies designed to further explore the utility of this pyrimidine derivative, we have developed a facile two-step sequence leading to the construction of a new heterocyclic ring system, 8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one. We found that the reaction of 5-lithio derivatives of

1^{1a,2} with various aldehydes including aliphatic aldehydes carrying α -hydrogen(s) gives the corresponding 1-(4,6-dichloropyrimidin-5-yl)alkan-1-ol derivatives (**2**), which can be transformed into 8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one derivatives (**4**) on treatment with *N*-alkylglycines in the presence of triethylamine. In this paper, we wish to report the results of our investigation, which provide a facile method for the preparation of this new class of heterocycles. A number of pyrimidooxazepine derivatives were synthesized³ and reported to have a variety of biological activities including epidermal growth factor receptor (EGFR) inhibitory,^{3a} HIV integrase inhibitory,^{3c} and acyl-CoA:diacylglycerol acyltransferase-1 (DGAT-1) inhibitory activities.^{3d} Since this new class of pyrimidooxazepinone derivatives may also be of biological importance, development of a facile synthetic method of them is meaningful.

The synthesis of 5,9-disubstituted 4-chloro-2-(methylsulfanyl)-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-ones (**4**) from DCSMP (**1**) was conducted through formation of [4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]alkan-1-ols (**2**), as illustrated in Scheme 1. (Het)aryl[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]methanols (**2a-f**) were prepared by the reaction of 4,6-dichloro-5-lithio-2-(methylsulfanyl)pyrimidine, which were generated by the treatment of **1** with lithium diisopropylamide (LDA) as reported previously,^{1a,2} with (het)aromatic aldehydes in THF at -78 °C. After aqueous workup, the desired alcohols were obtained in good to excellent yields (Table 1, Entries 1, 3-5, 7, and 8). Aliphatic aldehydes carrying α -hydrogen(s), such as propionaldehyde and isobutyraldehyde, were found to be usable in this reaction to afford the corresponding alcohols (**2g**) and (**2h**), respectively, in good yields (Entries 9 and 10).



Scheme 1

We next examined the formation of the oxepinone ring from **2** and *N*-alkylglycines. It is gratifying to find that when compounds (**2**) were allowed to react with *N*-alkylglycines in the presence of an equimolar amount of triethylamine in 1,2-dimethoxyethane (DME) at reflux temperature, substitution of one of the

two chloro groups with the alkyl(carboxymethyl)amino group and lactonization of the resulting hydroxy acid intermediates (**3**) catalyzed by *in situ* generated triethylamine hydrochloride occurred successively to give the desired products (**4**). The use of *N*-ethylglycine required rather extended reaction times and resulted in the isolation of the desired products (**4a-ii**) and (**4d-ii**) in somewhat decreased yields (Entries 2 and 6). Very slow consumption of the corresponding starting materials (**2a**) and (**2d**) were observed in these cases. It is worth noting that the substrate carrying an acid-sensitive thiophene ring (**2f**) was also usable in the present transformation with *N*-methylglycine. The reaction proceeded relative smoothly to give the corresponding desired product (**4f**) in 83% yield (Entry 8). This yield is comparable to those obtained using 5-[aryl(hydroxy)methyl] substrates (**2a-e**). The reaction of 5-[3,4-dimethoxyphenyl(hydroxy)methyl] substrate (**2e**) with *N*-methylglycine proceeded more smoothly to give the corresponding product (**4e**) in 75% yield (Entry 7). It was found that the reactions of 5-(1-hydroxyalkyl) substrates (**2g**) and (**2h**) with *N*-methylglycine resulted in the relative smooth formation of the corresponding products (**4g**) and (**4h**) (Entries 9 and 10, respectively), though the yield of **4h** was somewhat lower than those of the other products probably due to steric reasons. Unfortunately, however, we have no adequate explanation for relationship between the reaction rates and substituents R.

Table 1. Preparation of 8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-ones (**4**)

Entry	R	2	Yield/% ^a	R'	Time/h	4	Yield/% ^a
1	Ph	2a ^b	87	Me	20	4a-i	81
2				Et	41	4a-ii	75
3	3-MeC ₆ H ₄	2b	81	Me	18	4b	89
4	4-ClC ₆ H ₄	2c	87	Me	24	4c	85
5	4-MeOC ₆ H ₄	2d	97	Me	11	4d-i	78
6				Et	28	4d-ii	73
7	3,4-(MeO) ₂ C ₆ H ₃	2e	98	Me	4	4e	75
8	thiophen-3-yl	2f	90	Me	6	4f	83
9	Et	2g	73	Me	10	4g	75
10	<i>i</i> -Pr	2h	80	Me	12	4h	66

^a Yields of isolated products. ^b Ref. 4.

In conclusion, we have demonstrated that a new pyrimidooxazepinone ring system can be constructed utilizing a two-step sequence starting from commercially available 4,6-dichloro-2-(methylsulfonyl)pyrimidine (DCSMP) in satisfactory overall yields. Since the present method is attractive with respect to the experimental easiness as well as the ready availability of the starting materials, it may be of value in heterocyclic synthesis. Further functionalization at the 2- and 4-positions of the products may offer the possibility to access compounds of potential biological importance. Investigations toward the synthesis of other pyrimidine-fused heterocycles, which are hard to prepare by previous methods, utilizing this pyrimidine derivative are currently underway in our laboratory.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded as KBr disks with a Perkin–Elmer Spectrum 65 FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 (unless otherwise stated) using TMS as an internal reference with a Bruker Biospin AVANCE II 600 spectrometer operating at 600 MHz and 150 MHz, respectively, or 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 PF₂₅₄. 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. *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-[4,6-Dichloro-(2-methylsulfanyl)pyrimidin-5-yl]alkan-1-ols (2). **[4,6-Dichloro-(2-methylsulfanyl)pyrimidin-5-yl](phenyl)methanol (2a).** 5-Lithio-4,6-dichloro-2-(methylsulfanyl)pyrimidine (1.9 g, 10 mmol) in THF (35 mL) was generated by the treatment of 4,6-dichloro-2-(methylsulfanyl)pyrimidine (1.9 g, 10 mmol) with LDA (12 mmol) at $-78\text{ }^\circ\text{C}$ according to the procedure reported previously.^{1a} Then, PhCHO (1.3 g, 12 mmol) was added dropwise under stirring and it was continued for 5 min at the same temperature. After addition of saturated aqueous NH_4Cl (50 mL), the mixture was warmed to rt and extracted with AcOEt (3×30 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized from hexane/ CH_2Cl_2 to give **2a** (2.6 g, 87%); a pale-yellow solid; mp $84\text{--}86\text{ }^\circ\text{C}$ (lit.,⁴ mp $83.9\text{--}84.6\text{ }^\circ\text{C}$). The ^1H NMR data for this product were identical those reported previously.²

[4,6-Dichloro-(2-methylsulfanyl)pyrimidin-5-yl](3-methylphenyl)methanol (2b): a pale-yellow solid; mp $108\text{--}110\text{ }^\circ\text{C}$ (hexane/ CHCl_3); IR 3371, 1606, 1546, 1485 cm^{-1} ; ^1H NMR (500 MHz) δ 2.35 (s, 3H), 2.59 (s, 3H), 2.99 (d, $J = 9.7$ Hz, 1H), 6.45 (d, $J = 9.7$ Hz, 1H), 7.08–7.13 (m, 3H), 7.25 (t, $J = 7.4$ Hz, 1H); ^{13}C NMR (125 MHz) δ 14.42, 21.52, 70.76, 122.31, 125.89, 126.85, 128.46, 128.61, 138.35, 139.75, 161.01, 172.35. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{Cl}_2\text{N}_2\text{OS}$: C, 49.54; H, 3.84; N, 8.89. Found: C, 49.53; H, 3.84; N, 8.94.

(4-Chlorophenyl)[4,6-dichloro-(2-methylsulfanyl)pyrimidin-5-yl]methanol (2c): a white solid; mp $155\text{--}157\text{ }^\circ\text{C}$ (hexane/ CH_2Cl_2); IR 3388, 1542, 1484 cm^{-1} ; ^1H NMR (500 MHz) δ 2.59 (s, 3H), 2.96 (d, $J = 9.2$ Hz, 1H), 6.45 (d, $J = 9.2$ Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz) δ 14.42, 70.17, 126.34, 126.72, 128.70, 133.71, 138.38, 160.95, 172.78. Anal. Calcd for $\text{C}_{12}\text{H}_9\text{Cl}_3\text{N}_2\text{OS}$: C, 42.94; H, 2.70; N, 8.35. Found: C, 42.78; H, 2.82; N, 8.17.

[4,6-Dichloro-(2-methylsulfanyl)pyrimidin-5-yl](4-methoxyphenyl)methanol (2d): a pale-yellow solid; mp 191–193 °C (hexane/THF); IR 3404, 1541, 1484 cm^{-1} ; ^1H NMR (600 MHz, DMSO- d_6) δ 2.55 (s, 3H), 3.74 (s, 3H), 6.286 (d, $J = 8.6$ Hz, 1H), 6.294 (d, $J = 8.6$ Hz, 1H), 6.89 (d, $J = 8.8$ Hz, 2H), 7.25 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (150 MHz, DMSO- d_6) δ 13.86, 54.99, 68.20, 113.40, 126.54, 128.41, 132.68, 158.18, 160.73, 170.63. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_2\text{S}$: C, 47.14; H, 3.65; N, 8.45. Found: C, 46.99; H, 3.70; N, 8.19.

[4,6-Dichloro-(2-methylsulfanyl)pyrimidin-5-yl](3,4-dimethoxyphenyl)methanol (2e): a white solid; mp 142–144 °C (hexane/ CH_2Cl_2); IR 3523, 1543, 1486 cm^{-1} ; ^1H NMR (500 MHz) δ 2.59 (s, 3H), 3.11 (br s, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 6.42 (br s, 1H), 6.68 (dd, $J = 8.0, 1.1$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 7.00 (d, $J = 1.1$ Hz, 1H); ^{13}C NMR (125 MHz) δ 14.43, 55.85, 55.91, 70.57, 108.79, 110.71, 117.45, 126.59, 132.18, 148.57, 149.08, 160.90, 172.30. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_3\text{S}$: C, 46.55; H, 3.91; N, 7.76. Found: C, 46.61; H, 4.05; N, 7.64.

[4,6-Dichloro-(2-methylsulfanyl)pyrimidin-5-yl](thiophen-3-yl)methanol (2f): a white solid; mp 121–123 °C (hexane/ CH_2Cl_2); IR 3402, 1551, 1483 cm^{-1} ; ^1H NMR (500 MHz) δ 2.58 (s, 3H), 3.12 (d, $J = 9.7$ Hz, 1H), 6.44 (d, $J = 9.7$ Hz, 1H), 6.97 (dd, $J = 5.2, 1.1$ Hz, 1H), 7.16 (dd, $J = 2.9, 1.1$ Hz, 1H), 7.33 (dd, $J = 5.2, 2.9$ Hz, 1H); ^{13}C NMR (125 MHz) δ 14.42, 68.68, 121.51, 125.48, 126.35, 126.69, 141.19, 160.63, 172.44. Anal. Calcd for $\text{C}_{10}\text{H}_8\text{Cl}_2\text{N}_2\text{OS}_2$: C, 39.10; H, 2.62; N, 9.12. Found: C, 39.06; H, 2.82; N, 8.85.

1-[4,6-Dichloro-(2-methylsulfanyl)pyrimidin-5-yl]propan-1-ol (2g): a pale-yellow solid; mp 149–151 °C (hexane/ CH_2Cl_2); IR 3401, 1543, 1484 cm^{-1} ; ^1H NMR (500 MHz) δ 1.01 (t, $J = 7.4$ Hz, 3H), 1.90–1.98 (m, 1H), 2.03–2.12 (m, 1H), 2.52 (d, $J = 9.2$ Hz, 1H), 2.57 (s, 3H), 5.14–5.21 (m, 1H); ^{13}C NMR (125 MHz) δ 10.46, 14.36, 28.35, 71.69, 126.62, 160.26, 171.64. Anal. Calcd for $\text{C}_8\text{H}_{10}\text{Cl}_2\text{N}_2\text{OS}$: C, 37.96; H, 3.98; N, 11.07. Found: C, 37.90; H, 4.01; N, 10.84.

1-[4,6-Dichloro-(2-methylsulfanyl)pyrimidin-5-yl]-2-methylpropan-1-ol (2h): a white solid; mp 93–95 °C (hexane/ CH_2Cl_2); IR 3435, 1543, 1486 cm^{-1} ; ^1H NMR (500 MHz) δ 0.80 (d, $J = 6.9$ Hz, 3H), 1.20 (d, $J = 6.3$ Hz, 3H), 2.41–2.49 (m, 2H), 2.57 (s, 3H), 4.84 (t, $J = 9.7$ Hz, 1H); ^{13}C NMR (125 MHz) δ 14.36, 18.96, 19.80, 32.98, 76.14, 126.51, 160.65, 171.65. Anal. Calcd for $\text{C}_9\text{H}_{12}\text{Cl}_2\text{N}_2\text{OS}$: C, 40.46; H, 4.53; N, 10.49. Found: C, 40.64; H, 4.58; N, 10.33.

Typical Procedure for the Preparation of Pyrimidooxazepinones (4). 4-Chloro-9-methyl-2-(methylsulfanyl)-5-phenyl-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one (4a-i). A solution of **2a** (0.30 g, 1.0 mmol), MeNHCO_2H (88 mg, 1.0 mmol), and Et_3N (0.10 g, 1.0 mmol) in DME (5 mL) was heated at reflux temperature until complete consumption of **2a** had been confirmed by TLC analyses on SiO_2 (AcOEt/hexane 1:5). After cooling, the precipitate was filtered off under reduced pressure and

AcOEt and H₂O (30 mL each) were added to the filtrate. The layers were separated and the organic layer was washed with brine (15 mL), dried (Na₂SO₄), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH₂Cl₂ to give **4a-i** (0.27 g, 81%); a white solid; mp 175–177 °C; IR 1749, 1541 cm⁻¹; ¹H NMR (500 MHz) δ 2.54 (s, 3H), 3.30 (s, 3H), 3.60 (d, *J* = 15.5 Hz, 1H), 4.17 (d, *J* = 15.5 Hz, 1H), 6.87 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.45 (dd, *J* = 8.0, 7.4 Hz, 2H); ¹³C NMR (125 MHz) δ 14.20, 39.92, 55.11, 76.75, 104.97, 126.50, 128.99, 129.49, 139.27, 159.94, 160.65, 167.44, 171.52. HR-MS (ESI). Calcd for C₁₅H₁₅ClN₃O₂S (M+H): 336.0573. Found: *m/z* 336.0558. Anal. Calcd for C₁₅H₁₄ClN₃O₂S: C, 53.62; H, 4.20; N, 12.51. Found: C, 53.62; H, 4.22; N, 12.47.

4-Chloro-9-ethyl-2-(methylsulfanyl)-5-phenyl-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one (4a-ii): a pale-yellow solid; mp 152–154 °C (hexane/CH₂Cl₂); IR 1760, 1547 cm⁻¹; ¹H NMR (500 MHz) δ 1.17 (t, *J* = 7.4 Hz, 3H), 2.53 (s, 3H), 3.61 (d, *J* = 14.9 Hz, 1H), 3.70–3.77 (m, 1H), 3.80–3.87 (m, 1H), 4.10 (d, *J* = 14.9 Hz, 1H), 6.86 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.39 (tt, *J* = 6.9, 1.1 Hz, 1H), 7.44 (dd, *J* = 8.0, 6.9 Hz, 2H); ¹³C NMR (125 MHz) δ 12.45, 14.15, 47.20, 53.09, 77.26, 104.86, 126.54, 128.97, 129.50, 139.40, 160.16, 160.19, 167.89, 171.51. HR-MS (ESI). Calcd for C₁₆H₁₇ClN₃O₂S (M+H): 350.0730. Found: *m/z* 350.0724. Anal. Calcd for C₁₆H₁₆ClN₃O₂S: C, 54.93; H, 4.61; N, 12.01. Found: C, 54.65; H, 4.36; N, 11.77.

4-Chloro-5-(3-methylphenyl)-9-methyl-2-(methylsulfanyl)-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one (4b): a pale-yellow solid; mp 126–128 °C (hexane/CH₂Cl₂); IR 1751, 1553 cm⁻¹; ¹H NMR (500 MHz) δ 2.37 (s, 3H), 2.55 (s, 3H), 3.33 (s, 3H), 3.59 (d, *J* = 14.9 Hz, 1H), 4.21 (d, *J* = 14.9 Hz, 1H), 6.83 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.31 (dd, *J* = 8.0, 7.4 Hz, 1H); ¹³C NMR (125 MHz) δ 14.18, 21.50, 39.92, 55.15, 77.26, 105.18, 123.61, 127.08, 129.34, 129.79, 139.30, 139.52, 159.95, 160.69, 167.53, 171.48. HR-MS (ESI). Calcd for C₁₆H₁₇ClN₃O₂S (M+H): 350.0730. Found: *m/z* 350.0724. Anal. Calcd for C₁₆H₁₆ClN₃O₂S: C, 54.93; H, 4.61; N, 12.01. Found: C, 54.88; H, 4.61; N, 12.06.

4-Chloro-5-(4-chlorophenyl)-9-methyl-2-(methylsulfanyl)-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one (4c): a white solid; mp 194–196 °C (hexane/CH₂Cl₂); IR 1763, 1559 cm⁻¹; ¹H NMR (500 MHz) δ 2.54 (s, 3H), 3.31 (s, 3H), 3.63 (d, *J* = 15.5 Hz, 1H), 4.13 (d, *J* = 15.5 Hz, 1H), 6.80 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz) δ 14.20, 39.89, 55.09, 76.37, 104.55, 128.01, 129.72, 135.24, 137.79, 159.98, 160.62, 167.02, 171.83. HR-MS (ESI). Calcd for C₁₅H₁₄Cl₂N₃O₂S (M+H): 370.0184. Found: *m/z* 370.0180. Anal. Calcd for C₁₅H₁₃Cl₂N₃O₂S: C, 48.66; H, 3.54; N, 11.35. Found: C, 48.48; H, 3.47; N, 11.10.

4-Chloro-5-(4-methoxyphenyl)-9-methyl-2-(methylsulfanyl)-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one (4d-i): a yellow solid; mp 190–192 °C (hexane/CH₂Cl₂); IR 1755, 1559 cm⁻¹; ¹H NMR (500 MHz) δ 2.55 (s, 3H), 3.30 (s, 3H), 3.61 (d, *J* = 14.9 Hz, 1H), 3.82 (s, 3H), 4.23 (d, *J* = 14.9 Hz, 1H), 6.80

(s, 1H), 6.94 (d, $J = 8.6$ Hz, 2H), 7.19 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (500 MHz) δ 14.18, 39.92, 55.25, 55.37, 76.85, 105.22, 114.73, 128.08, 131.22, 159.76, 159.97, 160.72, 167.62, 171.40. HR-MS (ESI). Calcd for $\text{C}_{16}\text{H}_{17}\text{ClN}_3\text{O}_3\text{S}$ (M+H): 366.0679. Found: m/z 366.0674.

4-Chloro-9-ethyl-5-(4-methoxyphenyl)-2-(methylsulfanyl)-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one (4d-ii): a pale-yellow solid; mp 149–151 °C (hexane/ CH_2Cl_2); IR 1761, 1551 cm^{-1} ; ^1H NMR (500 MHz) δ 1.18 (t, $J = 6.9$ Hz, 3H), 2.53 (s, 3H), 3.61 (d, $J = 14.9$ Hz, 1H), 3.73–3.87 (m containing s at 3.83, 5H), 4.17 (d, $J = 14.9$ Hz, 1H), 6.79 (s, 1H), 6.95 (d, $J = 8.6$ Hz, 2H), 7.20 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (125 MHz) δ 12.46, 14.15, 47.20, 53.17, 55.37, 76.89, 105.02, 114.73, 127.30, 128.07, 131.29, 159.93, 159.95, 160.19, 168.09. HR-MS (ESI). Calcd for $\text{C}_{17}\text{H}_{19}\text{ClN}_3\text{O}_3\text{S}$ (M+H): 380.0835. Found: m/z 380.0831. Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{ClN}_3\text{O}_3\text{S}$: C, 53.75; H, 4.78; N, 11.06. Found: C, 53.71; H, 4.75; N, 10.93.

4-Chloro-5-(3,4-dimethoxyphenyl)-9-methyl-2-(methylsulfanyl)-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one (4e): a pale-yellow solid; mp 179–181 °C (hexane/ CH_2Cl_2); IR 1754, 1552 cm^{-1} ; ^1H NMR (500 MHz) δ 2.52 (s, 3H), 3.28 (s, 3H), 3.58 (d, $J = 15.5$ Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.26 (d, $J = 15.5$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 6.76 (s, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 6.85 (s, 1H); ^{13}C NMR (125 MHz) δ 14.16, 39.92, 55.10, 55.91, 56.05, 76.74, 105.03, 108.99, 110.99, 119.43, 131.58, 149.44, 149.83, 159.82, 160.64, 167.71, 171.42. HR-MS (ESI). Calcd for $\text{C}_{17}\text{H}_{19}\text{ClN}_3\text{O}_4\text{S}$ (M+H): 396.0785. Found: m/z 396.0781.

4-Chloro-9-methyl-2-(methylsulfanyl)-5-(thiophen-3-yl)-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one (4f): a yellow solid; mp 156–158 °C (hexane/ CH_2Cl_2); IR 1753, 1549 cm^{-1} ; ^1H NMR (500 MHz) δ 2.51 (s, 3H), 3.28 (s, 3H), 3.63 (d, $J = 15.5$ Hz, 1H), 4.26 (d, $J = 15.5$ Hz, 1H), 6.75 (s, 1H), 7.05 (d, $J = 4.0$ Hz, 2H), 7.42 (t, $J = 4.0$ Hz, 1H); ^{13}C NMR (125 MHz) δ 14.16, 39.93, 55.02, 74.19, 106.00, 123.91, 125.61, 128.48, 141.24, 159.33, 160.57, 167.34, 171.49. HR-MS (ESI). Calcd for $\text{C}_{13}\text{H}_{13}\text{ClN}_3\text{O}_2\text{S}_2$ (M+H): 342.0137. Found: m/z 342.0132. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{ClN}_3\text{O}_2\text{S}_2$: C, 45.68; H, 3.54; N, 12.29. Found: C, 45.52; H, 3.68; N, 11.90.

4-Chloro-5-ethyl-9-methyl-2-(methylsulfanyl)-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-7(5*H*)-one (4g): a white solid; mp 101–103 °C (hexane/ CH_2Cl_2); IR 1742, 1551 cm^{-1} ; ^1H NMR (500 MHz) δ 1.16 (t, $J = 7.4$ Hz, 3H), 2.01–2.09 (m, 1H), 2.16–2.25 (m, 1H), 2.51 (s, 3H), 3.31 (s, 3H), 4.01 (d, $J = 16.0$ Hz, 1H), 4.65 (d, $J = 16.0$ Hz, 1H), 5.53 (dd, $J = 10.2, 4.6$ Hz, 1H); ^{13}C NMR (125 MHz) δ 10.82, 14.13, 31.43, 39.93, 56.05, 78.26, 107.99, 158.55, 160.65, 166.90, 170.51. HR-MS (EI). Calcd for $\text{C}_{11}\text{H}_{14}\text{ClN}_3\text{O}_2\text{S}$ (M): 287.0495. Found: m/z 287.0506. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{ClN}_3\text{O}_2\text{S}$: C, 45.91; H, 4.90; N, 14.60. Found: C, 45.88; H, 4.88; N, 14.33.

4-Chloro-9-methyl-5-(1-methylethyl)-2-(methylsulfanyl)-8,9-dihydropyrimido[4,5-*e*][1,4]oxazepin-

7(5H)-one (4h): a white solid; mp 121–123 °C (hexane/CH₂Cl₂); IR 1748, 1548 cm⁻¹; ¹H NMR (500 MHz) δ 0.92 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 2.36–2.43 (m, 1H), 2.51 (s, 3H), 3.27 (s, 3H), 4.13 (d, *J* = 16.6 Hz, 1H), 4.62 (d, *J* = 16.6 Hz, 1H), 5.37 (d, *J* = 10.9 Hz, 1H); ¹³C NMR (125 MHz) δ 14.12, 19.26, 19.35, 34.35, 40.05, 56.98, 81.17, 106.97, 159.56, 160.36, 166.17, 170.97. HR-MS (EI). Calcd for C₁₂H₁₆ClN₃O₂S (M): 301.0652. Found: *m/z* 301.0651. Anal. Calcd for C₁₂H₁₆ClN₃O₂S: C, 47.76; H, 5.34; N, 13.92. Found: C, 47.77; H, 5.34; N, 13.69.

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