Polycyclic *N*-Heterocyclic Compounds 83: Synthesis of 2,4-Disubstituted 5,6-Dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-*d*]pyrimidines and 2,4,5-Trisubstituted 5,6-Dihydro[1]benzofuro[2′,3′:5,6]pyrano[4,3-*d*]pyrimidines from 4-Chloro-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-*d*]pyrimidines

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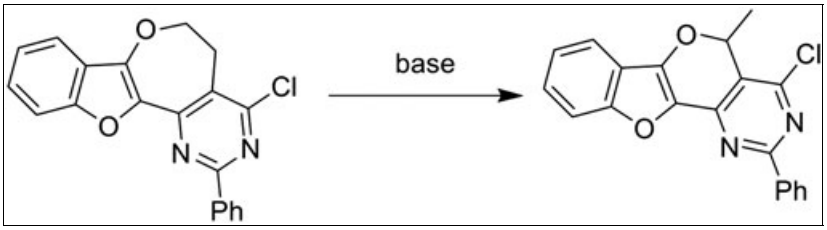

Treatment of 2-substituted 4-chloro-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-*d*]pyrimidines with simple alcohols and thiols as nucleophile afforded 2-substituted 4-alkoxy (or sulfanyl) derivatives. In the case of alkoxide nucleophiles, rearranged reaction products were also obtained. X-ray crystallography was used to support the structure assignment of the rearranged product.

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Previously, we reported preparation and biological evaluation of 4-chloro-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino [4,5-*d*]pyrimidines (**1**) and their 4-amino derivatives (**2**) as part of our research to develop anti-platelet aggregation agents (Figure 1) [1]. Certain of the compounds had potency comparable with aspirin, so we made the decision to study structure-activity relationships in this series. Herein, we describe the further elaboration of **1** to 2,4-disubstituted 5, 6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-*d*]pyrimidines (**3**, **4**, **6**, **8**, and **9**) using several oxygen and sulfur nucleophiles. During these transformations, we isolated rearranged byproducts **5** and **7**.

First, methoxide and ethoxide were used as nucleophiles to replace the reactive 4-chlorine atom of compound **1** to give **3a–e** (24–85%) and **4a–e** (37–43%), respectively (Scheme 1). In the case of **1d** and **1e**, both of which have an aryl group at the 2 position instead of alkyl or H, reaction with sodium ethoxide, also produced the rearranged byproducts **5d** and **5e**. In the ^{1}H NMR spectrum of **5d**, the ethoxy group was clearly indicated by the 3H triplet resonance at 1.48 ppm and 2H double quartet resonance at 4.64 ppm. In addition, a 3H doublet resonance appeared at 1.60 ppm, and 1H quartet resonance appeared at 5.94 ppm, strongly indicating the presence of the 2-methylpyrane moiety, whereas the two 2H triplet resonances at 3.42 and 4.57 ppm that correspond to the oxepine H5 and H6 of **1d** [1] were absent. These data are consistent with the structure of **5d**. Assignment of this structure was further supported by FAB-MS and elemental analysis. The structure of **5e** was similarly supported by spectroscopic and instrumental analysis. Formation of **5d** and **5e** can be rationalized by invoking a [1,2] Wittig type rearrangement, wherein sodium ethoxide functions as a base as well as a nucleophile [2]. Considering that formation of **5** is dependent on the substituent at the 2-position of **1**, the anion stabilizing effect of the 2-aryl group clearly facilitates this rearrangement reaction.

Intrigued by this type of rearrangement reaction with sodium ethoxide, we examined reaction of other alkoxides with **1d**. First, sodium *n*-propoxide was tested, but this reaction afforded only the usual substituted product (**6**) in 20% yield (Scheme 2). In the case of sodium isopropoxide, the reaction gave a complex mixture judged by TLC analysis, and we were unable to isolate any pure product. Finally, reaction with *tert*-butoxide gave the rearranged compound **7**. As expected, *tert*-butoxide did not serve as a nucleophile, and the reactive 4-chlorine was retained in the reaction product. X-ray crystallographic analysis of the 4-chloro-5-methyl derivative (**7**) confirmed that the structures of compounds (**5** and **7**) contained a new ring system (Figure 2) [3]. The proposed reaction mechanism is shown in Scheme 3.

Finally, ethylene glycol and 2-sulfanylethanol were used as nucleophiles in reactions with **1** to give **8a–e** (25–79%) and **9a–e** (55–87%), respectively (Scheme 4). The biological properties of the new products will be examined in due course with the goal of developing new pharmaceutical agents.

EXPERIMENTAL

All melting points were determined on a Yanagimoto (Kyoto, Japan) micro-melting point apparatus, and are uncorrected.

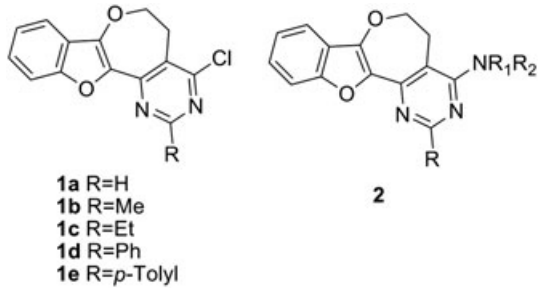


Figure 1. Substrate (**1**) and product (**2**).

Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The FAB-mass (*m*-nitrobenzyl alcohol was used as the matrix) and ESI–MS were obtained on a VG (UK) 70-SE mass spectrometer or a Micromass (Manchester, UK) AutoSpec-OA-Tof. The IR spectra were recorded on a Japan Spectroscopic (Hachioji, Japan) diffraction grating A-102 or FT/IR-200 spectrophotometer, and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Varian (Palo Alto, CA) VXR-200 instrument with tetramethylsilane as an internal standard. Chemical shifts are given in parts per million (δ) and *J* values in Hertz, and the signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; dq, double quartet; sex, sextet; br, broad; and m, multiplet. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso, Osaka, Japan). TLC was carried out on Kieselgel 60 F254 (Merck, Darmstadt, Germany) or silica gel 70FM (Wako, Osaka, Japan).

The structure on X-ray analysis was solved by direct methods with MITHRIL [4] and DIRDIF [5] and refined by the full-matrix least squares method by using TEXSAN [6]. H atoms were found by different synthesis and refined isotopically. The displacement ellipsoids were drawn with the aid of ORTEP II [7]. Most of the calculations were performed on a VAX 3100 computer using TEXSAN at the X-ray Laboratory of Okayama University.

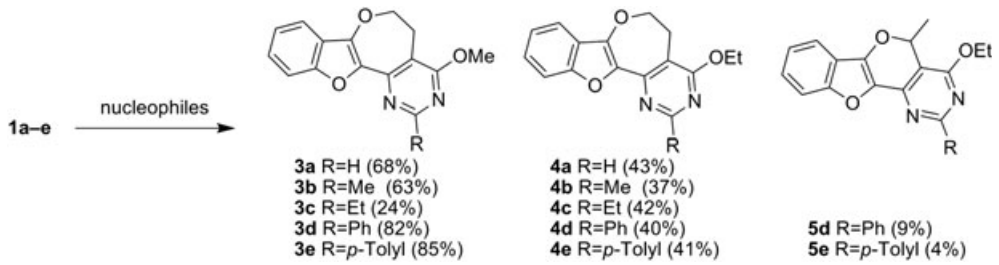
General procedure for synthesis of 2-substituted 4-methoxy-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidines (3a–e). In the case of **1a** and **1c**, a solution of compound (200 mg) in methanol (5.0 mL) was heated at 60°C with potassium carbonate (2 equiv) for an appropriate time. After removal of inorganic salt by filtration, the filtrate was evaporated in vacuo. Ice-water (50 mL) was poured into the residue; the resulting precipitate was collected on a filter and recrystallized from acetonitrile. In the case of **1b**, **1d**, and **1e**, a solution of compound (200 mg) was refluxed with sodium methoxide [freshly prepared from Na metal (2 equiv) and anhydrous methanol (10 mL)] for an appropriate time. After removal of solvent in vacuo, ice-water (50 mL) was poured into the residue and the resulting precipitate was recrystallized from acetonitrile.

4-Methoxy-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (3a). The reaction was stirred at 60°C for 1.5 h to produce, after workup, **3a** (68%) as colorless needles, mp 209–210°C. ^1H NMR (200 MHz, deuterochloroform): δ 3.25 (2H, br t, *J* = 4.5 Hz, H5), 4.04 (3H, s, CH_3), 4.49 (2H, br t, *J* = 4.5 Hz, H6), 7.23–7.68 (4H, m, H8, 9, 10, and 11), 8.78 (1H, s, H2); FAB-MS: *m/z* 269 (MH^+). *Anal.* Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.03; H, 4.63; N, 10.45.

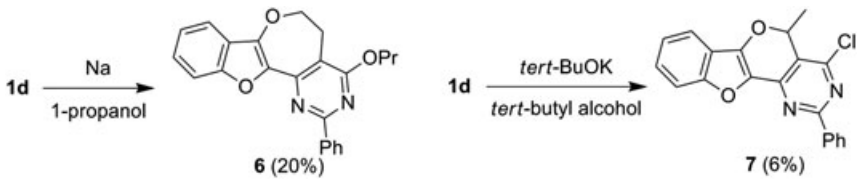
4-Methoxy-2-methyl-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (3b). The reaction was refluxed for 1h to produce **3b** (63%) as colorless needles, mp 204–205°C. ^1H NMR (200 MHz, deuterochloroform): δ 2.72 (3H, s, 2-CH_3), 3.20 (2H, br t, *J* = 4.3 Hz, H5), 4.01 (3H, s, OCH_3), 4.46 (2H, br t, *J* = 4.3 Hz, H6) 7.21–7.66 (4H, m, H8, 9, 10, and 11); ESI–MS: *m/z* 283 (MH^+). *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.10; H, 5.02; N, 9.87.

2-Ethyl-4-methoxy-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (3c). The reaction was stirred at 60°C for 2 h to produce **3c** (24%) as colorless needles, mp 104–105°C. ^1H NMR (200 MHz, deuterochloroform): δ 1.41 (3H, t, *J* = 7.6 Hz, CH_2CH_3), 2.99 (2H, q, *J* = 7.6 Hz, CH_2CH_3), 3.21 (2H, br t, *J* = 4.3 Hz, H5), 4.02 (3H, s, OCH_3), 4.46 (2H, br t, *J* = 4.3 Hz, H6), 7.21–7.68 (4H, m, H8, 9, 10, and 11); FAB-MS: *m/z* 297 (MH^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.54; H, 5.49; N, 9.57.

Scheme 1. Preparation of **3**, **4**, and rearranged product **5**.



Scheme 2. Synthesis of **6** and **7**.



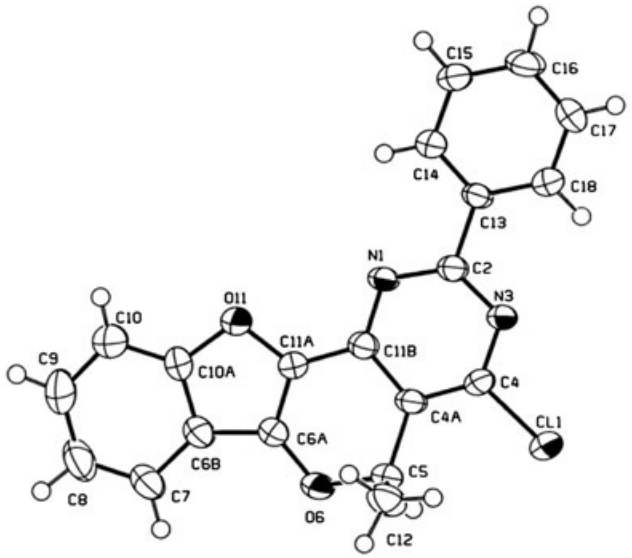


Figure 2. ORTEP representation of **7**.

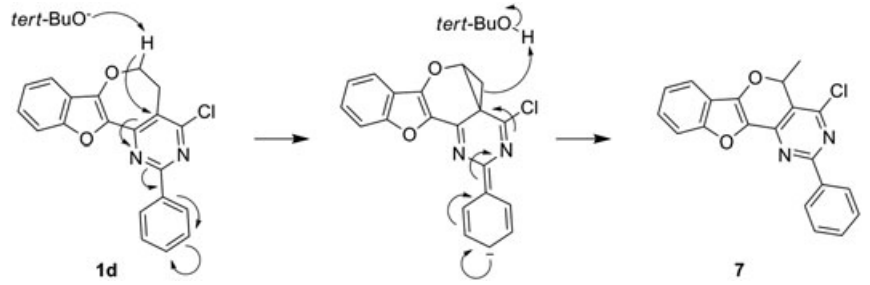
4-Methoxy-2-phenyl-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (3d). The reaction was refluxed for 115 h to produce **3d** (82%) as colorless plates, mp 222–224°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 3.28 (2H, br t, J = 4.2 Hz, H5), 4.14 (3H, s, OCH_3), 4.50 (2H, br t, J = 4.2 Hz, H6), 7.22–7.68 (7H, m, H8, 9, 10, 11, and 3′, 4′, 5′), 8.54–8.63 (2H, m, H2′ and 6′); FAB-MS: m/z 345 (MH^+). *Anal*. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.54; H, 4.81; N, 8.10.

4-Methoxy-2-(4-methylphenyl)-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (3e). The reaction was refluxed for 120 h to produce **3e** (85%) as colorless needles, mp 220–223°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 2.44 (3H, s, 4′-CH_3), 3.27 (2H, br t, J = 4.2 Hz, H5), 4.14 (3H, s, OCH_3), 4.50 (2H, br t, J = 4.2 Hz, H6), 7.22–7.69 (6H, m, H8, 9, 10, 11, and 3′, 5′), 8.47 (2H, d, J = 8.2 Hz, H2′ and 6′); ESI–MS: m/z 359 (MH^+). *Anal*. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 74.08; H, 5.30; N, 7.90.

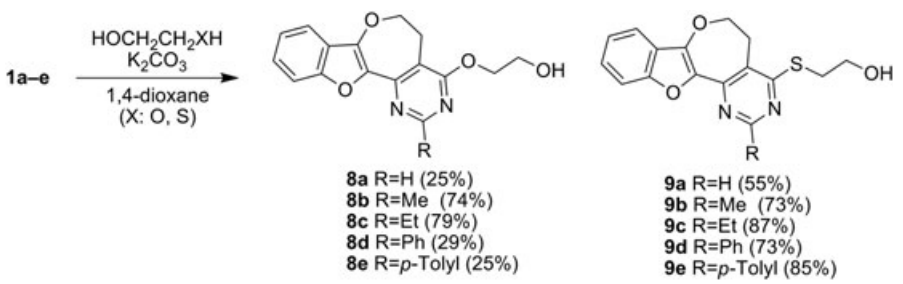
General procedure for synthesis of 2-substituted 4-ethoxy-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidines (4a–e) and rearranged compounds (5d and 5e). In the case of **1a** and **1c**, a solution of compound (200 mg) in dry ethanol (5.0 mL) was heated at 60°C (**1a**) or refluxed (**1c**) with potassium carbonate (2 equiv) for an appropriate time. After removal of inorganic salts by filtration, the filtrate was evaporated in vacuo. Ice-water (50 mL) was poured into the residue, and the resulting precipitate was collected on a filter and purified by recrystallization or chromatography on silica gel followed by recrystallization to give **4a** and **4c**. In the case of **1b**, **1d**, and **1e**, a solution of compound (200 mg) was refluxed with sodium ethoxide (freshly prepared from Na metal (2 equiv) and anhydrous ethanol (10 mL)) for an appropriate time. After removal of solvent in vacuo, ice-water (50 mL) was poured into the residue, and the resulting precipitate was purified by chromatography on silica gel followed by recrystallization from a suitable solvent to give **4b**, **4d**, **5d**, **4e**, and **5e**, as described in the succeeding text.

4-Ethoxy-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (4a). The reaction was stirred at 60°C for 23 h, and the product was recrystallized from acetonitrile to give **4a** (43%) as colorless plates, mp 176–178°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 1.44 (3H, t, J = 7.2 Hz, CH_3), 3.25 (2H, br t, J = 4.5 Hz, H5), 4.47 (2H, q, J = 7.2 Hz, CH_2CH_3), 4.49 (2H, br t, J = 4.5 Hz, H6), 7.23–7.68 (4H, m, H8, 9, 10, and 11), 8.75 (1H, s, H2); FAB-MS: m/z 283 (MH^+). *Anal*. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.15; H, 5.12; N, 10.10.

Scheme 3. The proposed mechanism for formation of **7**.



Scheme 4. Preparation of **8** and **9**.



4-Ethoxy-2-methyl-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino [4,5-d]pyrimidine (4b). The reaction was refluxed for 2 h, and the product was recrystallized from acetonitrile to give **4b** (37%) as colorless needles, mp 181–183°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 1.42 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.70 (3H, s, 2-CH_3), 3.21 (2H, br t, J = 4.2 Hz, H5), 4.46 (2H, q, J = 7.1 Hz, CH_2CH_3), 4.47 (2H, br t, J = 4.2 Hz, H6), 7.22–7.68 (4H, m, H8, 9, 10, and 11); ESI–MS: m/z 297 (MH^+). *Anal*. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.77; H, 5.50; N, 9.45.

4-Ethoxy-2-ethyl-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino [4,5-d]pyrimidine (4c). The reaction was refluxed for 120 h, and the residue was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (24:1) was evaporated in vacuo, and the residue was recrystallized from acetonitrile to give **4c** (42%) as colorless needles, mp 171–174°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 1.39, 1.43 (each 3H, each t, J = 7.1, 7.2 Hz, 2 × CH_3), 2.97 (2H, q, J = 7.1 Hz, 2-CH_2CH_3), 3.21 (2H, br t, J = 4.3 Hz, H5), 4.47 (2H, br t, J = 4.3 Hz, H6), 4.49 (2H, q, J = 7.2 Hz, OCH_2CH_3), 7.21–7.67 (4H, m, H8, 9, 10, and 11); FAB-MS: m/z 311 (MH^+). *Anal*. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.68; H, 5.79; N, 8.89.

4-Ethoxy-2-phenyl-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino [4,5-d]pyrimidine (4d) and 4-ethoxy-5-methyl-2-phenyl[1] benzofuro[2′,3′:5,6]pyrano[4,3-d]pyrimidine (5d). The reaction was refluxed for 5 h, and the residue was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (99:1) was evaporated in vacuo, and the residue was recrystallized from *n*-hexane to give **5d** (9%) as colorless needles. A further eluate of *n*-hexane/ethyl acetate (49:1) was evaporated in vacuo, and the residue was recrystallized from acetone to give **4d** (40%) as colorless needles. **4d**: mp 195–196°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 1.49 (3H, t, J = 7.1 Hz, CH_3), 3.28 (2H, br t, J = 4.2 Hz, H5), 4.51 (2H, br t, J = 4.2 Hz, H6), 4.62 (2H, q, J = 7.1 Hz, CH_2CH_3), 7.22–7.69 (7H, m, H8, 9, 10, 11, and 3′, 4′, 5′), 8.51–8.62 (2H, m, H2′ and 6′); FAB-MS: m/z 359 (MH^+). *Anal*. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.73; H, 5.21; N, 7.73. **5d**: mp 130°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 1.48 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.60 (3H, d, J = 6.6 Hz, 5-CH_3), 4.64 (2H, dq, J = 7.1, 2.0 Hz, 4-CH_2CH_3), 5.94 (1H, q, J = 6.6 Hz, H5), 7.23–7.68 (7H, m, H7, 8, 9, 10, and 3′, 4′, 5′), 8.47–8.58 (2H, m, H2′ and 6′); FAB-MS: m/z 359 (MH^+). *Anal*. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.59; H, 5.22; N, 7.83.

4-Ethoxy-2-(4-methylphenyl)-5,6-dihydro[1]benzofuro[3′,2′:2,3] oxepino[4,5-d]pyrimidine (4e) and 4-ethoxy-5-methyl-2-(4-methylphenyl)[1]benzofuro[2′,3′:5,6]pyrano[4,3-d]pyrimidine (5e). The reaction was refluxed for 40 h, and the residue was chromatographed on silica gel. The eluate of *n*-hexane/benzene (2:1) was evaporated in vacuo, and the residue was recrystallized from *n*-hexane to give **5e** (4%) as colorless needles. A further eluate of *n*-hexane/benzene (1:2) was evaporated in vacuo, and the residue was recrystallized from acetonitrile to give **4e** (41%) as colorless needles. **4e**: mp 229–231°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 1.49 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.44 (3H, s, 2′-CH_3), 3.27 (2H, br t, J = 4.2 Hz, H5), 4.50 (2H, br t, J = 4.2 Hz, H6), 4.61 (2H, q, J = 7.1 Hz, 4-CH_2CH_3), 7.23–7.69 (6H, m, H8, 9, 10, 11, and 3′, 5′), 8.45 (2H, d, J = 8.9 Hz, H2′ and 6′); ESI–MS: m/z 373 (MH^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.58; H, 5.64; N, 7.60. **5e**: mp 145–147°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 1.47 (3H, t, J = 7.1 Hz, 4-CH_2CH_3), 1.60 (3H, d, J = 6.6 Hz, 5-$CHCH_3$), 2.43 (3H, s, 2′-CH_3), 4.62 (2H, dq, J = 7.1, 2.0 Hz, 4-CH_2CH_3), 5.92 (1H, q, J = 6.6 Hz, H5), 7.23–7.68 (6H, m, H7, 8, 9, 10, and 3′, 5′), 8.41 (2H, d, J = 8.1 Hz, H2′ and 6′); FAB-MS: m/z 373 (MH^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.20; H, 5.58; N, 7.52.

2-Phenyl-4-propoxy-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino [4,5-d]pyrimidine (6). A solution of **1d** (100 mg, 0.287 mmol) was stirred at 80°C with sodium propoxide (freshly prepared from Na metal (2 equiv) and anhydrous 1-propanol (5.0 mL)) for 4 h. After removal of solvent in vacuo, ice-water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (38:1) was evaporated in vacuo, and the residue was recrystallized from cyclohexane to give **6** (21 mg, 20%) as colorless needles, mp 170–171°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 1.09 (3H, t, J = 7.4 Hz, CH_3), 1.90 (2H, sex, J = 7.4 Hz, CH_2CH_3), 3.29 (2H, br t, J = 4.3 Hz, H5), 4.52 (2H, br t, J = 4.3 Hz, H6), 4.52 (2H, br t, J = 7.4 Hz, $CH_2CH_2CH_3$), 7.22–7.68 (7H, m, H8, 9, 10, 11, and 3′, 4′, 5′), 8.52–8.63 (2H, m, H2′ and 6′); FAB-MS: m/z 373 (MH^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.96; H, 5.55; N, 7.55.

4-Chloro-5-methyl-2-phenyl-5,6-dihydro[1]benzofuro[2′,3′:5,6] pyrano[4,3-d]pyrimidine (7). To a solution of **1d** (200 mg, 0.573 mmol) in dry *tert*-butyl alcohol (10 mL) was added potassium *tert*-butoxide (110 mg, 1.00 mmol), and the reaction was refluxed for 1.5 h. After evaporation of solvent in vacuo, ice-water (100 mL) was added to the residue. The precipitated solid was collected on a filter and recrystallized from acetonitrile to give **7** (11 mg, 6%) as colorless plates, mp 188–191°C. ^{1}H NMR (200 MHz, deuterochloroform): δ 1.70 (3H, d, J = 7.0 Hz, CH_3), 6.01 (1H, q, J = 7.0 Hz, H5), 7.31–7.68 (7H, H7, 8, 9, 10, and 3′, 4′, 5′), 8.46–8.57 (2H, m, H2′ and 6′); ESI–MS: m/z 349 (MH^+), 351 ($MH^+ + 2$). *Anal*. Calcd for $C_{20}H_{13}ClN_2O_2$: C, 68.87; H, 3.76; N, 8.03. Found: C, 68.95; H, 3.98; N, 7.98.

Crystal structure analysis of 7 [3]. Crystals for X-ray analysis were grown from an acetonitrile solution by slow evaporation. This analytical sample was dried around 100°C under vacuum and subjected to X-ray crystallographic analysis. Crystal data $C_{20}H_{13}N_2O_2Cl$; M = 348.79; monoclinic, space group $P2_1/n$, a = 7.811(4), b = 10.803 (2), c = 19.276(4) Å, β = 94.82(3)°, V = 1621(2) Å^3; Z = 4; Dc = 1.429 g cm^{-3}. A crystal of size 0.280 × 0.150 × 0.440 mm was examined by the ω-2θ scan technique using graphite-monochromated MoK α radiation (λ = 0.71073 Å). Cell dimensions were obtained from 25 reflections (21.0 < 2θ < 22.0°). A total of 3210 unique data points were obtained, and 1752 of these having $I > 3.00\ \sigma\ (I)$ were used in the refinement; R = 0.064, Rw = 0.056, S = 3.83.

General procedure for synthesis of 2-substituted 4-(2-hydroxyethoxy)-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d] pyrimidine (8a–e). To a solution of **1a–e** (200 mg) in dry 1,4-dioxane (2.0 mL) was added ethylene glycol (2.0 mL) and potassium carbonate (2 equiv), and the reaction was stirred at 80°C for an appropriate time. After removal of solvent in vacuo, ice-water (50 mL) was poured into the residue. The precipitated solid was collected on a filter. The product was purified by recrystallization and/or chromatography on silica gel, as described in the succeeding text.

4-(2-Hydroxyethoxy)-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino [4,5-d]pyrimidine (8a). The reaction was stirred at 80°C for 4 h, and the product was recrystallized from acetonitrile to give **8a** (25%) as colorless needles, mp 210–212°C. IR (potassium bromide): 3310 (OH) cm^{-1}; ^{1}H NMR (200 MHz, deuterochloroform): δ 2.01 (1H, br,

deuterium oxide exchangeable, OH), 3.28 (2H, br t, $J = 4.2$ Hz, H5), 3.96–4.05 (2H, m, CH_2OH), 4.50 (2H, br t, $J = 4.2$ Hz, H6), 4.55–4.65 (2H, m, OCH_2), 7.22–7.68 (4H, m, H8, 9, 10, and 11), 8.74 (1H, s, H2); FAB-MS: *m/z* 299 (MH^+). *Anal*. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.13; H, 4.86; N. 9.58.

4-(2-Hydroxyethoxy)-2-methyl-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (8b). The reaction was stirred at 80°C for 1.5 h, and the product was recrystallized from chloroform to give **8b** (74%) as colorless needles, mp 247–248°C. IR (potassium bromide): 3320 (OH) cm^{-1}; ^{1}H NMR (200 MHz, deuterochloroform): δ 2.71 (3H, s, CH_3), 3.23 (2H, br t, $J = 4.3$ Hz, H5), 3.61 (1H, br t, $J = 4.7$ Hz, deuterium oxide exchangeable, OH), 3.99 (2H, m, CH_2OH), 4.48 (2H, br t, $J = 4.3$ Hz, H6), 4.56–4.62 (2H, m, OCH_2), 7.21–7.68 (4H, m, H8, 9, 10, and 11); ESI–MS: *m/z* 313 (MH^+). *Anal*. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.59; H, 5.34; N, 8.95.

2-Ethyl-4-(2-hydroxyethoxy)-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (8c). The reaction was stirred at 80°C for 7 h, and the product was recrystallized from acetonitrile to give **8c** (79%) as colorless needles, mp 226–227°C. IR (potassium bromide): 3330 (OH) cm^{-1}; ^{1}H NMR (200 MHz, deuterochloroform): δ 1.40 (3H, t, $J = 7.7$ Hz, CH_3), 2.99 (2H, q, $J = 7.7$ Hz, C$H_2$$CH_3$), 3.23 (2H, br t, $J = 4.2$ Hz, H5), 3.63 (1H, br, deuterium oxide exchangeable, OH), 4.00 (2H, br, CH_2OH), 4.48 (2H, br t, $J = 4.2$ Hz, H6), 4.55–4.66 (2H, m, OCH_2), 7.21–7.67 (4H, m, H8, 9, 10, and 11); FAB-MS: *m/z* 327 (MH^+). *Anal*. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C,66.06; H, 5.51; N, 8.45.

4-(2-Hydroxyethoxy)-2-phenyl-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (8d). The reaction was stirred at 80°C for 4 h, and the precipitated solid was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (3:2) was evaporated in vacuo, and the residue was recrystallized from ethyl acetate to give **8d** (29%) as colorless plates, mp 222–223°C. IR (potassium bromide): 3500 (OH) cm^{-1}; ^{1}H NMR (200 MHz, deuterochloroform): δ 2.80 (1H, br, deuterium oxide exchangeable, OH), 3.31 (2H, br t, $J = 4.2$ Hz, H5), 4.04–4.13 (2H, m, CH_2OH), 4.53 (2H, br t, $J = 4.2$ Hz, H6), 4.69–4.78 (2H, m, OCH_2), 7.22–7.71 (7H, H8, 9, 10, 11, and 3′, 4′, 5′), 8.45–8.60 (2H, m, H2′ and 6′); FAB-MS: *m/z* 375 (MH^+). *Anal*. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.81; H, 5.03; N, 7.49.

***4-(2-Hydroxyethoxy)-2-(4-methylphenyl)-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]*pyrimidine (8e).** The reaction was stirred at 80°C for 6 h, and the precipitated solid was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (3:2) was evaporated in vacuo, and the residue was recrystallized from acetonitrile to give **8e** (25%) as colorless needles, mp 249–251°C. IR (potassium bromide): 3420 (OH) cm^{-1}; ^{1}H NMR (200 MHz, deuterochloroform): δ 2.44 (3H, s, CH_3), 2.92 (1H, br, deuterium oxide exchangeable, OH), 3.30 (2H, br t, $J = 4.2$ Hz, H5), 4.02–4.13 (2H, m, CH_2OH), 4.52 (2H, br t, $J = 4.2$ Hz, H6), 4.68–4.77 (2H, m, OCH_2), 7.23–7.71 (6H, m, H8, 9, 10, 11, and 3′, 5′), 8.40 (2H, d, $J = 8.3$ Hz, H2′ and 6′); FAB-MS: *m/z* 389 (MH^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.23; H, 5.33; N, 7.21.

General procedure for synthesis of 2-substituted 4-(2-hydroxyethylsulfanyl)-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (9a–e). To a solution of **1** (**1a**, 100 mg, **1b–e**, 200 mg) in dry 1,4-dioxane (2.0 mL) was added 2-sulfanylethanol (2 equiv) and potassium carbonate (2 equiv), and the reaction was stirred at the temperature and time described in the succeeding text for the specific examples. After evaporation of solvent in vacuo, ice-water (50 mL) was added to the residue. The precipitated solid was collected on a filter then recrystallized from acetonitrile.

4-(2-Hydroxyethylsulfanyl)-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (9a). The reaction was stirred at 80°C for 11 h to produce, after workup, **9a** (55%) as colorless needles, mp 227–229°C. IR (potassium bromide): 3450 (OH) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.19 (2H, br t, $J = 4.3$ Hz, H5), 3.28–3.38 (2H, m, SCH_2), 3.64 (2H, q, $J = 5.8$ Hz, CH_2OH), 4.55 (2H, br t, $J = 4.3$ Hz, H6), 5.05 (1H, t, $J = 5.8$ Hz, deuterium oxide exchangeable, OH), 7.23–7.78 (4H, m, H8, 9, 10, and 11), 8.85 (1H, s, H2); FAB-MS: *m/z* 315 (MH^+). *Anal*. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.19; H, 4.63; N, 9.04.

4-(2-Hydroxyethylsulfanyl)-2-methyl-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (9b). The reaction was refluxed for 6 h to produce **9b** (73%) as colorless needles, mp 187–189°C. IR (potassium bromide): 3200 (OH) cm^{-1}; ^{1}H NMR (200 MHz, deuterochloroform): δ 2.76 (3H, s, CH_3), 3.23 (2H, br t, $J = 4.2$ Hz, H5), 3.44 (2H, br t, $J = 5.2$ Hz, SCH_2), 4.41 (2H, br t, $J = 5.2$ Hz, CH_2OH), 4.50 (3H, br t, $J = 4.2$ Hz, and br, changed to 2H with addition of deuterium oxide, H6 and OH), 7.23–7.69 (4H, m, H8, 9, 10, and 11); ESI–MS: *m/z* 329 (MH^+). *Anal*. Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found: C, 61.90; H, 4.97; N, 8.92.

2-Ethyl-4-(2-hydroxyethylsulfanyl)-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (9c). The reaction was refluxed for 4.5 h to produce **9c** (87%) as colorless needles, mp 165–166°C. IR (potassium bromide): 3350 (OH) cm^{-1}; ^{1}H NMR (200 MHz, deuterochloroform): δ 1.42 (3H, t, $J = 7.6$ Hz, CH_3), 3.03 (2H, q, $J = 7.6$ Hz, C$H_2$$CH_3$), 3.23 (2H, br d, $J = 4.2$ Hz, H5), 3.46 (2H, br t, $J = 5.3$ Hz, SCH_2), 3.96–4.06 (2H, m, CH_2OH), 4.15 (1H, br, deuterium oxide exchangeable, OH), 4.50 (2H, br t, $J = 4.2$ Hz, H6), 7.22–7.69 (4H, m, H8, 9, 10, and 11); FAB-MS: *m/z* 343 (MH^+). *Anal*. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 63.25; H, 5.37; N, 8.09.

4-(2-Hydroxyethylsulfanyl)-2-phenyl-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (9d). The reaction was refluxed for 22 h to produce **9d** (73%) as colorless needles, mp 188–190°C. IR (potassium bromide): 3240 (OH) cm^{-1}; ^{1}H NMR: (200 MHz, deuterochloroform): δ 3.08 (1H, br t, $J = 5.0$ Hz, deuterium oxide exchangeable, OH), 3.28 (2H, br t, $J = 4.2$ Hz, H5), 3.61 (2H, t, $J = 5.0$ Hz, SCH_2), 4.06 (2H, br q, $J = 5.0$ Hz, CH_2OH), 4.53 (2H, br t, $J = 4.2$ Hz, H6), 7.23–7.71 (7H, m, H8, 9, 10, 11, and 3′, 4′, 5′), 8.46–8.58 (2H, m, H2′ and 6′); ESI–MS: *m/z* 391 (MH^+). *Anal*. Calcd for $C_{22}H_{18}N_2O_3S$: C, 67.67; H, 4.65; N, 7.17. Found: C, 67.65; H, 4.83; N, 7.21.

4-(2-Hydroxyethylsulfanyl)-2-(4-methylphenyl)-5,6-dihydro[1]benzofuro[3′,2′:2,3]oxepino[4,5-d]pyrimidine (9e). The reaction was refluxed for 3.5 h to produce **9e** (85%) as colorless prisms, mp 227–228°C. IR (potassium bromide): 3430 (OH) cm^{-1}; ^{1}H NMR (200 MHz, deuterochloroform): δ 2.44 (3H, s, CH_3), 3.18 (1H, br t, $J = 5.3$ Hz, deuterium oxide exchangeable, OH), 3.27 (2H, br t, $J = 4.2$ Hz, H5), 3.60 (2H, t, $J = 5.3$ Hz, SCH_2), 4.05 (2H, br q, $J = 5.3$ Hz, CH_2OH), 4.54 (2H, br t, $J = 4.2$ Hz, H6), 7.23–7.71 (6H, m, H8, 9, 10, 11, and 3′, 5′), 8.41 (2H, d, $J = 8.4$ Hz, H2′ and 6′); ESI–MS: *m/z* 405 (MH^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_3S$: C, 68.30; H, 4.98; N, 6.93. Found: C, 68.50; H, 5.13; N, 7.04.

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