Polycyclic *N*-Heterocyclic Compounds. Part 80: Synthesis and Evaluation of Effects on *In Vitro* Pentosidine Formation of 5,6-Dihydro[1]benzothieno [3′,2′:2,3]thiepino[4,5-*d*]pyrimidine and Related Compounds

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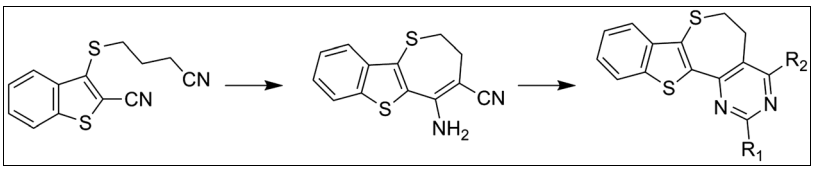
Received February 7, 2012
DOI 10.1002/jhet.1709
Published online 9 December 2013 in Wiley Online Library (wileyonlinelibrary.com).



Reaction of 3-(3-cyanopropylthio)[1]benzothiophene-2-carbonitrile with *tert*-BuONa gave 5-amino-1,2-dihydro[1]benzothieno[3,2-*d*]thieno[2,3-*b*]pyridine and 5-amino-2,3-dihydro[1]benzothieno[3,2-*b*]thiepin-4-carbonitrile. The latter compound served as a convenient scaffold for the synthesis of the new heterocycles, [1]benzothieno[3′,2′:2,3]thiepino[4,5-*d*]pyrimidines. All of our new tetracyclic products were evaluated for *in vitro* inhibitory activity on the formation of pentosidine, which is one of representative advanced glycation end products.

J. Heterocyclic Chem., **51**, 891 (2014).

INTRODUCTION

Formation of carbon–carbon (C–C) bonds is a central issue in synthetic organic chemistry. In this regard, the Truce–Smiles rearrangement is among those useful rearrangement reactions that provide access to complex structures from simple precursors through formation of new C–C bonds [1–5].

We have been investigating the syntheses and biological evaluation of heterocycles containing new ring systems. During the course of this work, we have developed a new synthetic method for aromatic fused furo[2,3-*b*]pyridines (**2**) based on reactions of 2-(3-cyanopropoxy)aryl-1-carbonitriles (**1**) with bases (Scheme 1). This process involves a Truce–Smiles rearrangement followed by intramolecular cyclization [6–9].

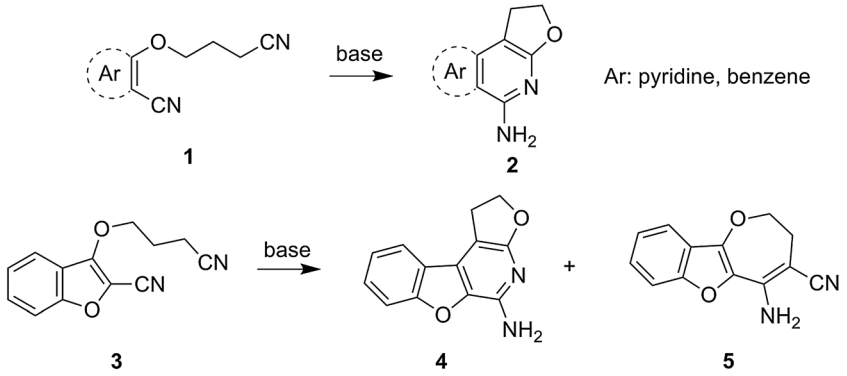
Previously, we had disclosed that the reaction of 3-(3-cyanopropylthio)[1]benzothiophene-2-carbonitrile (**6**) with base gave 5-amino-1,2-dihydro[1]benzothieno[3,2-*d*]thieno[2,3-*b*]pyridine (**7**) in modest yield [8]. Because the key step of Truce–Smiles rearrangement is a nucleophilic attack at an *ipso* position of an aromatic ring, the less reactive electron-rich benzothiophene is a poorer substrate for this rearrangement as already described for 3-(3-cyanopropoxy)[1]benzofuran-2-carbonitriles (**3**) [10]. In those cases, formation of 5-amino-2,3-dihydro[1]benzofuro[3,2-*b*]oxepin-4-carbonitrile (**5**), which is the Thorpe–Ziegler reaction product, also was formed. Therefore, 5-amino-2,3-dihydro[1]benzothieno[3,2-*b*]thiepin-4-carbonitrile (**8**) should also be obtainable from 3-(3-cyanopropylthio)[1]benzothiophene-2-carbonitrile (**6**) by a similar Thorpe–Ziegler reaction. Here, we describe the synthesis of **8** that is formed along with **7**. We also describe the preparation of tetracyclic [1]benzothieno[3′,2′:2,3]thiepino[4,5-*d*]pyrimidines (**9–17**). An *in vitro* screening evaluation of these compounds to measures their effects on anti-pentosidine activity was performed as part of our continuing program to develop agents for hyperglycemia related diseases [11,12].

RESULTS AND DISCUSSION

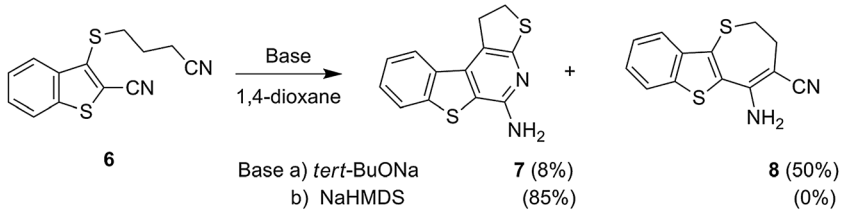
Reaction of **6** and *tert*-BuONa in dry 1,4-dioxane gave **8** in 50%, as we had anticipated, as well as **7** that was formed in 8% (Scheme 2). The characteristic amino and cyano bands in the infrared spectrum of **8** clearly supported the isomer identification. Similar to the case of benzofuran (**3**) [10], in which case the Smiles rearrangement product **4** is the minor product and the Thorpe–Ziegler reaction product **5** is a major product, the Smiles rearrangement product **7** is the minor product and the Thorpe–Ziegler reaction product **8** is the major product in the transformation of benzothiophene (**6**). If the base was changed from *tert*-BuONa to hexamethyldisilazane sodium salt, the reaction gave **7** exclusively in 85% yield. It seems likely that the stronger basicity and/or greater bulkiness of hexamethyldisilazane sodium salt compared with *tert*-BuONa has changed reactivity to give **7**.

In order to access additional potential pharmaceuticals, the functionality present in compound **8** was exploited for the construction of a pyrimidine ring leading to the new heterocyclic ring system [1]benzothieno[3′,2′:2,3]thiepino [4,5-*d*]pyrimidine. Thus, reaction of **8** with the Vilsmeier reagent gave **9a–e** in 72–82% yield (Scheme 3). Structures

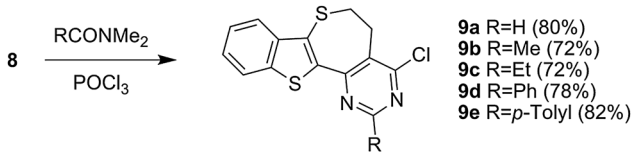
Scheme 1. Substrates (**1** and **3**) and their products (**2**, **4**, and **5**) with base.



Scheme 2. Synthesis of **7** and **8**.



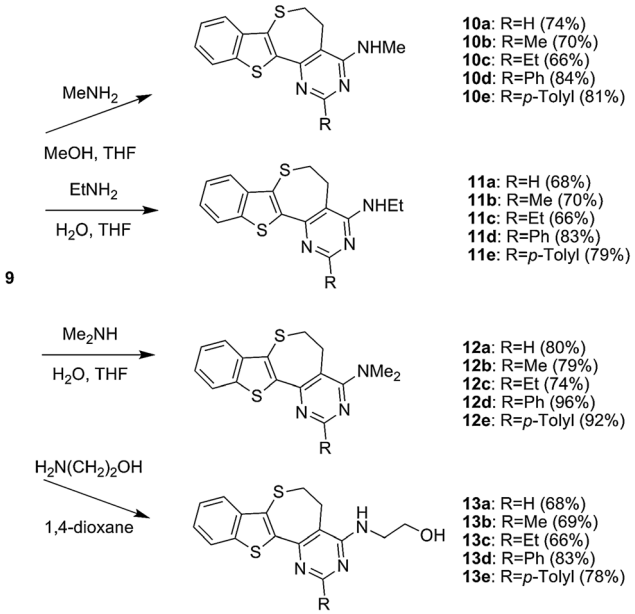
Scheme 3. Preparation of **9**.



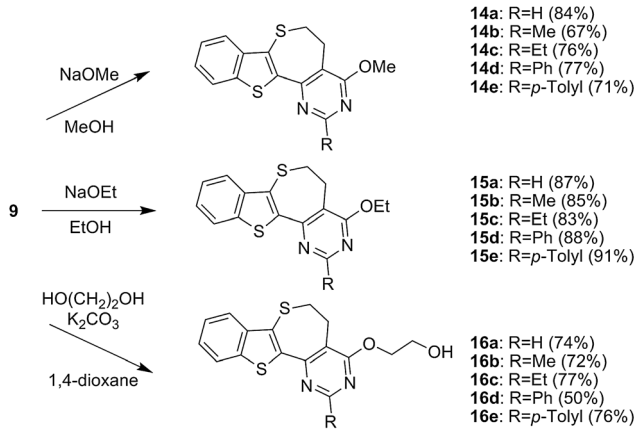
of **9a–e** were determined based on the disappearance of the enamine and nitrile groups and appearance of chlorine atoms in their IR and MS spectra. In addition, the NMR spectra and elemental analyses supported these structures. Next, **9a–e** were treated with several amine nucleophiles such as methylamine to give **10a–e** in 66–84% yield, ethylamine to give **11a–e** in 66–83% yield, dimethylamine to give **12a–e** in 74–96% yield, and 2-aminoethanol to give **13a–e** in 66–83% yield, respectively (Scheme 4). We also used oxygen nucleophiles as reactants. Thus, sodium methoxide gave **14a–e** in 67–84% yield, sodium ethoxide gave **15a–e** in 83–91% yield, and ethylene glycol with potassium carbonate gave **16a–e** in 50–77% yield, respectively (Scheme 5). Finally, the sulfur nucleophile 2-sulfanylethanol was used in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give **17a–e** in 43–86% yield (Scheme 6). All derivatives **10–17** satisfy Lipinski's rule of five, and thus, they are expected to have drug-like properties [13].

With these derivatives (**10–17**) in hand, effects on the formation of pentosidine, which is one of representative

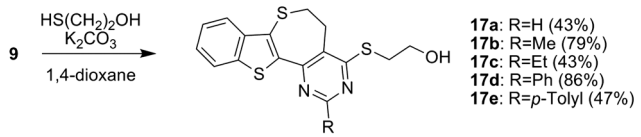
Scheme 4. Preparation of **10–13**.



Scheme 5. Preparation of **14–16**.



Scheme 6. Preparation of **17**.



advanced glycation end products AGEs, were examined using an *in vitro* screening test according to the literature procedure [11]. Aminoguanidine hydrochloride [14,15] was used as a positive control. None showed any significant inhibitory activity (less than 20% inhibition compared with 46.0% for the positive control).

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The fast atom bombardment (FAB)-mass (*m*-nitrobenzyl alcohol was used as the matrix) were obtained on a VG70-SE mass spectrometer. The IR spectra were recorded on a Japan Spectroscopic diffraction grating A-102 spectrophotometer, a FT/IR-200, or a FT/IR-230 spectrophotometer and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Varian VXR-200 instrument with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ) and *J* values in Hz, and the signals are designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet. TLC (Kieselgel $60F_{254}$ (Merck) or silica gel 70FM (Wako)) was used to monitor the completion of reactions.

5-Amino-2,3-dihydro[1]benzothieno[3,2-b]thiepin-4-carbonitrile (8) and 5-amino-1,2-dihydro[1]benzothieno[3,2-d]thieno[2,3-b]pyridine (7). To a preheated solution of **6** (1.00 g, 3.87 mmol) in dry benzene (200 mL) was added *tert*-BuONa (1.86 g, 19.4 mmol), and the mixture was refluxed for 1 h. After evaporation of solvent, ice-water (30 mL) was poured into the residue, and the mixture was extracted with ethyl acetate (3 × 30mL). The organic layer was washed with sat. brine, dried over anhydrous magnesium sulfate, and evaporated. The resulting viscous oil was chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (19:1) was evaporated *in vacuo*, and the residue was recrystallized from ethanol to give **8** (500 mg, 50%) as pale yellow scales. mp 144–145°C; IR (nujol) cm^{-1}: 3450, 3340, 3230 (NH), 2180 (CN); ^1H-NMR (200 MHz, deuterochloroform): δ 2.56 (t, 2H, *J* = 6.0 Hz, H3), 3.60 (t, 2H, *J* = 6.0 Hz, H2), 4.70 (br s, 2H, deuterium oxide exchangeable, NH_2), 7.42–7.52 (m, 2H, H8 and 9), 7.85 (dd, 1H, *J* = 6.3, 1.5 Hz, H10), 8.00 (dd, 1H, *J* = 6.1, 1.7 Hz, H7); FAB-MS *m/z*: 259 (MH^+). *Anal*. Calcd. for $C_{13}H_{10}N_2S_2$: C, 60.44; H, 3.90; N, 10.84. Found: C, 60.35; H, 3.95; N, 10.77.

A further eluate of *n*-hexane-ethyl acetate (9:1) was evaporated *in vacuo* and the residue was recrystallized from benzene to give **7** (80 mg, 8%) as pale yellow needles, mp 207–208°C [8].

5-Amino-1,2-dihydro[1]benzothieno[3,2-d]thieno[2,3-b]pyridine (7). To a solution of **6** (1.00 g, 3.87 mmol) in dry 1,4-dioxane (100 mL) was added hexamethyldisilazane sodium salt [40% in tetrahydrofuran-cumene (3:1)] (8.89 mL, 19.4 mmol) and the reaction was stirred at room temperature for 0.5 h. After evaporation of solvent *in vacuo*, ice-water (200 mL) was poured into the residue. The precipitated solid was collected on a filter and was recrystallized from benzene to give **7** (850 mg, 85%) as pale yellow needles, mp 207–208°C [8].

General procedure for the preparation of 9a–e from 8 with Vilsmeier reagent. To a Vilsmeier reagent prepared from the corresponding *N*,*N*-dimethylamide (3.0 eq. to **8**) and phosphoryl chloride (10 mL) under ice-water cooling for 1 h was added **8** (2.00 g, 7.74 mmol) and the mixture was then stirred at 80°C for 1 h. After removal of phosphoryl chloride *in vacuo*, ice-water (100 mL) was poured into the residue and the solution was neutralized with sodium bicarbonate. The mixture was extracted with ethyl acetate (5 × 50 mL). The combined organic phase was washed with sat. brine, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was purified by recrystallization to give **9a–e**.

4-Chloro-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (9a). Using *N*,*N*-dimethylformamide gave **9a** (80%) as yellow needles from ethanol, mp 134–135°C; ^1H-NMR (200 MHz, deuterochloroform): δ 3.52 (s, 4H, H5 and 6), 7.41 (td, 1H, *J* = 7.3, 1.8 Hz, H9), 7.48 (td, 1H, *J* = 7.3, 1.7 Hz, H10), 7.83–7.90 (m, 2H, H8 and 11), 8.83 (s, 1H, H2); FAB-MS *m/z*: 305 (MH^+), 307 ($MH^+ + 2$). *Anal*. Calcd. for $C_{14}H_9ClN_2S_2$: C, 55.16; H, 2.98; N, 9.19. Found: C, 54.99; H, 3.12; N, 9.05.

4-Chloro-2-methyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (9b). Using *N*,*N*-dimethylacetamide gave **9b** (72%) as yellow scales from ethanol, mp 120–121°C; ^1H-NMR (200 MHz, deuterochloroform): δ 2.72 (s, 3H, CH_3), 3.48 (s, 4H, H5 and 6), 7.36–7.51 (m, 2H, H9 and 10), 7.79–7.93 (m, 2H, H8 and 11); FAB-MS *m/z*: 319 (MH^+), 321 ($MH^+ + 2$). *Anal*. Calcd. for $C_{15}H_{11}ClN_2S_2$: C, 56.50; H, 3.48; N, 8.79. Found: C, 56.40; H, 3.63; N, 8.69.

4-Chloro-2-ethyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (9c). Using *N*,*N*-dimethylpropionamide gave **9c** (72%) as yellow needles from ethanol, mp 98–99°C; ^1H-NMR (200 MHz, deuterochloroform): δ 1.42 (t, 3H, *J* = 7.6 Hz, CH_3), 2.97 (q, 2H, *J* = 7.6 Hz, CH_2CH_3), 3.49 (s, 4H, H5 and 6), 7.35–7.51 (m, 2H, H9 and 10), 7.79–7.91 (m, 2H, H8 and 11); FAB-MS *m/z*: 333 (MH^+), 335 ($MH^+ + 2$). *Anal*. Calcd. for $C_{16}H_{13}ClN_2S_2$: C, 57.73; H, 3.94; N, 8.42. Found: C, 57.71; H, 4.03; N, 8.40.

4-Chloro-2-phenyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino [4,5-d]pyrimidine (9d). Using *N*,*N*-dimethylbenzamide gave **9d** (78%) as yellow needles from acetonitrile, mp 170–172°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.44–3.62 (m, 4H, H5 and 6), 7.36–7.57 (m, 5H, H9, 10, and 3′, 4′, 5′), 7.82–7.91 (m, 2H, H9 and 10), 8.45–8.57 (m, 2H, H2′ and 6′); FAB-MS *m/z*: 381 (MH^+), 383 (MH^+ + 2). *Anal*. Calcd. for $C_{20}H_{13}ClN_2S_2$: C, 63.06; H, 3.44; N, 7.35. Found: C, 63.21; H, 3.67; N, 7.38.

4-Chloro-2-p-tolyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino [4,5-d]pyrimidine (9e). Using *N*,*N*-dimethyl-4-methylbenzamide [16] gave **9e** (82%) as yellow needles from ethyl acetate, mp 225–226°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 2.44 (s, 3H, CH_3), 3.44–3.61 (m, 4H, H5 and 6), 7.31 (d, 2H, *J* = 8.3 Hz, H3′ and 5′), 7.36–7.51 (m, 2H, H9 and 10), 7.83–7.91 (m, 2H, H8 and 11), 8.40 (br d, 2H, *J* = 8.3 Hz, H2′ and 6′); FAB-MS *m/z*: 395 (MH^+), 397 (MH^+ + 2). *Anal*. Calcd. for $C_{21}H_{15}ClN_2S_2$: C, 63.86; H, 3.83; N, 7.09. Found: C, 64.11; H, 4.00; N, 7.03.

General procedure for the reaction of 9a–e with methylamine to give 10a–e. To a solution of **9** (100 mg) in THF (10 mL) was added 40% methanolic methylamine (10 mL), and the reaction was stirred at room temperature for the time required for completion of the reaction. After evaporation of the reaction mixture *in vacuo*, ice-water (50 mL) was poured into the residue. The resulting precipitate was collected on a filter and purified by recrystallization to give **10**.

4-Methylamino-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino [4,5-d]pyrimidine (10a). The reaction time was 1 h. Recrystallization of the residue from ethanol gave **10a** (74%) as colorless scales, mp 177–178°C; IR (nujol) cm^{-1}: 3440 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.03 (t, 2H, *J* = 5.7 Hz, H5), 3.11 (d, 3H, *J* = 4.7 Hz, CH_3), 3.49 (t, 2H, *J* = 5.7 Hz, H6), 5.38 (br s, 1H, deuterium oxide exchangeable, NH), 7.38–7.42 (m, 2H, H9 and 10), 7.82–7.87 (m, 2H, H8 and 11), 8.59 (s, 1H, H2); FAB-MS *m/z*: 300 (MH^+). *Anal*. Calcd. for $C_{15}H_{13}N_3S_2$: C, 60.17; H, 4.38; N, 14.03. Found: C, 60.15; H, 4.54; N, 13.98.

2-Methyl-4-methylamino-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (10b). The reaction time was 10 h. Recrystallization of the residue from ethanol gave **10b** (70%) as yellow prisms, mp 234–235°C; IR (nujol) cm^{-1}: 3480 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 2.57 (s, 3H, 2-CH_3), 2.90 (t, 2H, *J* = 5.7 Hz, H5), 3.10 (d, 3H, *J* = 4.8 Hz, NCH_3), 3.46 (t, 2H, *J* = 5.7 Hz, H6), 5.27 (br, 1H, deuterium oxide exchangeable, NH), 7.34–7.41 (m, 2H, H9 and 10), 7.81–7.89 (m, 2H, H8 and 11); FAB-MS *m/z*: 314 (MH^+). *Anal*. Calcd. for $C_{16}H_{15}N_3S_2$: C, 61.31; H, 4.82; N, 13.41. Found: C, 61.41; H, 4.95; N, 13.32.

2-Ethyl-4-methylamino-5,6-dihydro[1]benzothieno[3′,2′2,3] thiepino[4,5-d]pyrimidine (10c). The reaction time was 16 h. Recrystallization of the residue from acetonitrile gave **10c** (66%) as colorless plates, mp 191–192°C; IR (nujol) cm^{-1}: 3470 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.38 (t, 3H, *J* = 7.6 Hz, 2-CH_2CH_3), 2.84 (q, 2H, *J* = 7.6 Hz, 2-CH_2CH_3), 3.00 (t, 2H, *J* = 5.5 Hz, H5), 3.10 (d, 3H, *J* = 4.8Hz NCH_3), 3.43 (t, 2H, *J* = 5.5 Hz, H6), 4.79 (br s, 1H, deuterium oxide exchangeable, NH), 7.36–7.41 (m, 2H, H9 and 10), 7.78–7.91 (m, 2H, H8 and 11); FAB-MS *m/z*: 328 (MH^+). *Anal*. Calcd. for $C_{17}H_{17}N_3S_2$: C, 62.35; H, 5.23; N, 12.83. Found; C,62.35; H, 5.20; N,12.78.

4-Methylamino-2-phenyl-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (10d). The reaction time was 24 h. Recrystallization of the residue from acetonitrile gave **10d** (84%) as yellow plates, mp 181–182°C; IR (nujol) cm^{-1}: 3460 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.10 (t, 2H, *J* = 5.5 Hz, H5), 3.20 (d, 3H, *J* = 4.0 Hz, CH_3), 3.46 (t, 2H, *J* = 5.5 Hz, H6), 5.34 (br s, 1H, deuterium oxide exchangeable, NH), 7.35–7.56 (m, 5H, H9, 10, and 3′, 4′, 5′), 7.81–7.89 (m, 2H, H8 and 11), 8.46–8.58 (m, 2H, H2′ and 6′); FAB-MS *m/z*: 376 (MH^+). *Anal*. Calcd. for $C_{21}H_{17}N_3S_2$: C, 67.17; H, 4.56; N, 11.19. Found: C, 67.23; H, 4.76; N, 11.19.

4-Methylamino-2-p-tolyl-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (10e). The reaction time was 24 h. Recrystallization of the residue from acetonitrile gave **10e** (81%) as colorless needles, mp 208–209°C; IR (nujol) cm^{-1}: 3460 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 2.43 (s, 3H, 2′-CH_3), 3.10 (t, 2H, *J* = 5.0 Hz, H5), 3.20 (d, 3H, *J* = 4.2 Hz, NCH_3), 3.47 (t, 2H, *J* = 5.0 Hz, H6), 5.44 (br, 1H, deuterium oxide exchangeable, NH), 7.28 (d, 2H, *J* = 8.5 Hz, H3′ and 5′), 7.35–7.47 (m, 2H, H9 and 10), 7.80–7.89 (m, 2H, H8 and 11), 8.39 (d, 2H, *J* = 8.5 Hz, H2′ and 6′); FAB-MS *m/z*: 390 (MH^+). *Anal*. Calcd. for $C_{22}H_{19}N_3S_2$: C, 67.83; H, 4.92; N, 10.79. Found: C, 67.80; H, 5.05; N, 10.68.

General procedure for the reaction of 9a–e with ethylamine to give 11a–e. To a solution of **9** (100 mg) in THF (5.0 mL) was added 70% aqueous ethylamine (10 mL), and the mixture was stirred at room temperature for the time required for completion of the reaction. After evaporation of the reaction mixture *in vacuo*, ice-water (50 mL) was poured into the residue. The resulting precipitate was collected on a filter and purified by recrystallization to give **11**.

4-Ethylamino-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino [4,5-d]pyrimidine (11a). The reaction time was 5 h. Recrystallization of the residue from acetonitrile gave **11a** (68%) as colorless needles, mp 173–174°C; IR (nujol) cm^{-1}: 3220 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.31 (t, 3H, *J* = 7.2 Hz, $-CH_2CH_3$), 3.03 (t, 2H, *J* = 5.7 Hz, H5), 3.51 (t, 2H, *J* = 5.7 Hz, H6), 3.69 (dq, 2H, *J* = 7.2, 5.5 Hz, $-CH_2CH_3$), 5.43 (br s, 1H, deuterium oxide exchangeable, NH), 7.36–7.49 (m, 2H, H9 and 10), 7.79–7.94 (m, 2H, H8 and 11), 8.57 (s, 1H, H2); FAB-MS *m/z*: 314 (MH^+). *Anal*. Calcd. for $C_{16}H_{15}N_3S_2$: C, 61.31; H, 4.82; N, 13.41. Found: C, 61.45; H, 4.93; N, 13.30.

4-Ethylamino-2-methyl-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (11b). The reaction time was 18 h. Recrystallization of the residue from ethanol gave **11b** (70%) as yellow prisms, mp 155–156°C; IR (nujol) cm^{-1}: 3440 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.29 (t, 3H, *J* = 7.2 Hz, $-CH_2CH_3$), 2.57 (s, 3H, 2-CH_3), 2.96 (t, 2H, *J* = 6.0 Hz, H5), 3.47 (t, 2H, *J* = 6.0 Hz, H6), 3.60 (dq, 2H, *J* = 7.2, 5.3 Hz, $-CH_2CH_3$), 5.15 (br, 1H, deuterium oxide exchangeable, NH), 7.37–7.43 (m, 2H, H9 and 10), 7.78–7.93 (m, 2H, H8 and 11); FAB-MS *m/z*: 328 (MH^+). *Anal*. Calcd. for $C_{17}H_{17}N_3S_2$: C, 62.35; H, 5.23; N, 12.83. Found: C, 62.29; H, 5.32; N, 12.59.

2-Ethyl-4-ethylamino-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (11c). The reaction time was 20 h. Recrystallization of the residue from methanol gave **11c** (66%) as yellow prisms, mp 106–107°C; IR (nujol) cm^{-1}: 3440 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.25–1.42 (m, 6H, 2 × $-CH_2CH_3$), 2.80–2.96 (m, 4H, H5 and 2-CH_2CH_3), 3.45 (t, 2H, *J* = 6.3 Hz, H6), 3.62 (dq, 2H, *J* = 7.1, 5.5 Hz, NCH_2CH_3), 6.10 (br, 1H, deuterium oxide exchangeable, NH), 7.32–7.45 (m, 2H, H9 and 10), 7.79–7.88 (m, 2H, H8 and 11); FAB-MS *m/z*: 342 (MH^+). *Anal*. Calcd. for $C_{18}H_{19}N_3S_2$: C, 63.31; H, 5.61; N, 12.30. Found; C,63.39; H, 5.73; N,12.10.

4-Ethylamino-2-phenyl-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (11d). The reaction time was 12 h.

Recrystallization of the residue from acetonitrile gave **11d** (83%) as yellow scales, mp 158–159°C; IR (nujol) cm^{-1}: 3440 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.34 (t, 3H, *J* = 7.2 Hz, –CH_2CH_3), 3.09 (t, 2H, *J* = 5.6 Hz, H5), 3.49 (t, 2H, *J* = 5.6 Hz, H6), 3.64–3.82 (m, 2H, –CH_2CH_3), 5.90 (br, 1H, deuterium oxide exchangeable, NH), 7.37–7.43 (m, 2H, H9 and 10), 7.44–7.55 (m, 3H, H3′, 4′, and 5′), 7.81–7.94 (m, 2H, H8 and 11), 8.42–8.55 (m, 2H, H2′ and 6′); FAB-MS *m/z*: 390 (MH^+). *Anal*. Calcd. for $C_{22}H_{19}N_3S_2$: C, 67.83; H, 4.92; N, 10.79. Found: C, 68.13; H, 5.27; N, 10.78.

4-Ethylamino-2-p-tolyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (11e). The reaction time was 30 h. Recrystallization of the residue from acetonitrile gave **11e** (79%) as yellow plates, mp 161–162°C; IR (nujol) cm^{-1}: 3440 (NH); ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.34 (t, 3H, *J* = 7.2 Hz, –CH_2CH_3), 2.43 (s, 3H, 2′-CH_3), 3.09 (t, 2H, *J* = 5.6 Hz, H5), 3.49 (t, 2H, *J* = 5.6 Hz, H6), 3.62–3.80 (m, 2H, –CH_2CH_3), 5.91 (br, 1H, deuterium oxide exchangeable, NH), 7.28 (d, 2H, *J* = 8.0 Hz, H3′ and 5′), 7.37–7.45 (m, 2H, H9 and 10), 7.81–7.92 (m, 2H, H8 and 11), 8.35 (d, 2H, *J* = 8.0 Hz, H2′ and 6′); FAB-MS *m/z*: 404 (MH^+). *Anal*. Calcd. for $C_{23}H_{21}N_3S_2$: C, 68.45; H, 5.24; N, 10.41. Found: C, 68.53; H, 5.46; N, 10.34.

General procedure for the reaction of 9a–e with dimethylamine to give 12a–e. To a solution of **9** (100 mg) in THF (5.0 mL) was added 50% aqueous dimethylamine (10 mL), and the mixture was then stirred at room temperature for the time required for completion of the reaction. After evaporation of the reaction mixture *in vacuo*, ice-water (50 mL) was poured into the residue. The resulting precipitate was collected on a filter and purified by recrystallization to give **12**.

4-Dimethylamino-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (12a). The reaction time was 1 h. Recrystallization of the residue from cyclohexane gave **12a** (80%) as colorless plates, mp 155–156°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.11 (t, 2H, *J* = 5.6 Hz, H5), 3.13 (s, 6H, $N(CH_3)_2$), 3.66 (t, 2H, *J* = 5.6 Hz, H6), 7.38–7.47 (m, 2H, H9 and 10), 7.82–7.98 (m, 2H, H8 and 11), 8.62 (s, 1H, H2); FAB-MS *m/z*: 314 (MH^+). *Anal*. Calcd. for $C_{16}H_{15}N_3S_2$: C, 61.31; H, 4.82; N, 13.41. Found: C, 61.14; H, 4.90; N, 13.22.

2-Methyl-4-dimethylamino-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (12b). The reaction time was 1 h. Recrystallization of the residue from acetonitrile gave **12b** (79%) as colorless plates, mp 120–121°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 2.59 (s, 3H, 2-CH_3), 3.07 (t, 2H, *J* = 5.7 Hz, H5), 3.10 (s, 6H, $N(CH_3)_2$), 3.63 (t, 2H, *J* = 5.7 Hz, H6), 7.37–7.46 (m, 2H, H9 and 10), 7.81–7.97 (m, 2H, H8 and 11); FAB-MS *m/z*: 328 (MH^+). *Anal*. Calcd. for $C_{17}H_{17}N_3S_2$: C, 62.35; H, 5.23; N, 12.83. Found: C, 62.18; H, 5.22; N, 12.74.

2-Ethyl-4-dimethylamino-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (12c). The reaction time was 1 h. Recrystallization of the residue from acetonitrile gave **12c** (74%) as colorless prisms, mp 125–126°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.37 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.85 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 3.08 (t, 2H, *J* = 5.8 Hz, H5), 3.10 (s, 6H, $N(CH_3)_2$), 3.62 (t, 2H, *J* = 5.8 Hz, H6), 7.36–7.45 (m, 2H, H9 and 10), 7.81–7.95 (m, 2H, H8 and 11); FAB-MS *m/z*: 342 (MH^+). *Anal*. Calcd. for $C_{18}H_{19}N_3S_2$: C, 63.31; H, 5.61; N, 12.30. Found: C, 63.41; H, 5.56; N, 12.32.

4-Dimethylamino-2-phenyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (12d). The reaction time was 24 h. Recrystallization of the residue from acetonitrile gave **12d** (96%) as colorless prisms, mp 183–184°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.17 (s, 6H, $N(CH_3)_2$), 3.21 (t, 2H, *J* = 5.7 Hz, H5), 3.62 (t, 2H, *J* = 5.7 Hz, H6), 7.36–7.54 (m, 5H, H9, 10, and 3′, 4′, 5′), 7.82–7.96 (m, 2H, H8 and 11), 8.49–8.58 (m, 2H, H2′ and 6′); FAB-MS *m/z*: 390 (MH^+). *Anal*. Calcd. for $C_{22}H_{19}N_3S_2$: C, 67.83; H, 4.92; N, 10.79. Found: C, 68.04; H, 5.00; N, 10.78.

4-Dimethylamino-2-p-tolyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (12e). The reaction time was 24 h. Recrystallization of the residue from acetonitrile gave **12e** (92%) as colorless prisms, mp 200–201°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 2.43 (s, 3H, 2′-CH_3), 3.16 (s, 6H, $N(CH_3)_2$), 3.20 (t, 2H, *J* = 6.0 Hz, H5), 3.61 (t, 2H, *J* = 6.0 Hz, H6), 7.28 (d, 2H, *J* = 8.0 Hz, H3′ and 5′), 7.37–7.47 (m, 2H, H9 and 10), 7.83–7.95 (m, 2H, H8 and 11), 8.42 (d, 2H, *J* = 8.0 Hz, H2′ and 6′); FAB-MS *m/z*: 404 (MH^+). *Anal*. Calcd. for $C_{23}H_{21}N_3S_2$: C, 68.45; H, 5.24; N, 10.41. Found: C, 68.39; H, 5.33; N, 10.29.

General procedure for the reaction of 9a–e with 2-aminoethanol to give 13a–e. To a solution of **9** (100 mg) in dry 1,4-dioxane (5.0 mL) was added 2-aminoethanol (10 eq. to **9**), and the mixture was then refluxed for the time required for completion of the reaction. After evaporation of the reaction mixture *in vacuo*, ice-water (50 mL) was poured into the residue. The resulting precipitate was collected on a filter and purified by recrystallization to give **13**.

4-(2-Hydroxyethylamino)-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (13a). The reaction time was 10 h. Recrystallization of the residue from acetonitrile gave **13a** (68%) as colorless scales, mp 172–173°C; IR (nujol) cm^{-1}: 3400, 3170 (NH, OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 3.06 (t, 2H, *J* = 5.3 Hz, H5), 3.45–3.63 (m, 6H, NCH_2CH_2O and H6), 4.76, 7.32 (each t, each 1H, *J* = 5.3, 5.0 Hz, deuterium oxide exchangeable, NH and OH), 7.40–7.53 (m, 2H, H9 and 10), 7.76–7.87, 7.97–8.05 (each m, each 1H, H8 and 11), 8.39 (s, 1H, H2); FAB-MS *m/z*: 330 (MH^+). *Anal*. Calcd. for $C_{16}H_{15}N_3OS_2$: C, 58.33; H, 4.59; N, 12.76. Found: C, 58.33; H, 4.76; N, 12.57.

4-(2-Hydroxyethylamino)-2-methyl-5,6-dihydro[1]benzothieno[3′,2′;2,3]thiepino[4,5-d]pyrimidine (13b). The reaction time was 22 h. Recrystallization of the residue from acetonitrile gave **13b** (69%) as colorless needles, mp 179–180°C; IR (nujol) cm^{-1}: 3450, 3400, 3150 (NH, OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.38 (s, 3H, 2-CH_3), 3.02 (t, 2H, *J* = 5.3 Hz, H5), 3.43–3.62 (m, 6H, NCH_2CH_2O and H6), 4.76, 7.15 (each t, each 1H, *J* = 5.3, 5.1 Hz, each deuterium oxide exchangeable, NH and OH), 7.40–7.52 (m, 2H, H9 and 10), 7.78–7.83, 7.95–8.00 (each m, each 1H, H8 and 11); FAB-MS *m/z*: 344 (MH^+). *Anal*. Calcd. for $C_{17}H_{17}N_3OS_2 \cdot 1/4\ H_2O$: C, 58.68; H, 5.07; N, 12.08. Found: C, 59.03; H, 5.02; N, 12.04.

2-Ethyl-4-(2-hydroxyethylamino)-5,6-dihydro[1]benzothieno[3′,2′2,3]thiepino[4,5-d]pyrimidine (13c). The reaction time was 26 h. Recrystallization of the residue from acetonitrile gave **13c** (66%) as colorless scales, mp 163–164°C; IR (nujol) cm^{-1}: 3450, 3400, 3160 (NH, OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.26 (t, 3H, *J* = 7.5 Hz, 2-CH_2CH_3), 2.65 (q, 2H, *J* = 7.5 Hz, 2-CH_2CH_3), 3.04 (t, 2H, *J* = 5.5 Hz, H5), 3.43–3.63 (m, 6H, NCH_2CH_2O and H6), 4.76, 7.16 (each t, each 1H, *J* = 5.4, 5.2 Hz, deuterium oxide exchangeable, NH and OH), 7.40–7.50 (m, 2H, H9 and 10), 7.76–7.84, 7.94–8.03 (each m, each 1H, H8 and 11); FAB-MS *m/z*: 358 (MH^+). *Anal*. Calcd. for $C_{18}H_{19}N_3OS_2$: C, 60.47; H, 5.36; N, 11.75. Found: 60.12; H, 5.34; N, 11.64.

4-(2-Hydroxyethylamino)-2-phenyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (13d). The reaction time

was 33 h. Recrystallization of the residue from acetonitrile gave **13d** (83%) as colorless prisms, mp 153–154°C; IR (nujol) cm^{-1}: 3370, 3180 (NH, OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 3.17 (br t, 2H, J = 5.0 Hz, H5), 3.52 (br t, 2H, J = 5.0 Hz, H6), 3.63–3.70 (m, 4H, NCH_2CH_2O), 4.81 (t, 1H, J = 5.5 Hz, deuterium oxide exchangeable, NH or OH), 7.34 (br s, 1H, deuterium oxide exchangeable, NH or OH), 7.43–7.56 (m, 5H, H9, 10, and 3′, 4′, 5′), 7.79–7.84, 8.01–8.06 (each m, each 1H, H8 and 11), 8.35–8.46 (m, 2H, H2′ and 6′); FAB-MS *m/z*: 406 (MH^+). *Anal*. Calcd. for $C_{22}H_{19}N_3OS_2$: C, 65.16; H, 4.72; N, 10.36. Found: C, 64.89; H, 4.86; N, 10.30.

4-(2-Hydroxyethylamino)-2-p-tolyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (13e). The reaction time was 20 h. Recrystallization of the residue from acetonitrile gave **13e** (78%) as yellow needles, mp 216–217°C; IR (nujol) cm^{-1}: 3370, 3180 (NH, OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.39 (s, 3H, 2′-CH_3), 3.15 (t, 2H, J = 5.3 Hz, H5), 3.50 (t, 2H, J = 5.3 Hz, H6), 3.58–3.73 (m, 4H, NCH_2CH_2O), 4.80 (t, 1H, J = 5.5 Hz, deuterium oxide exchangeable, NH or OH), 7.32 (d, 2H, J = 8.0 Hz, H3′ and 5′), 7.41–7.53 (m, 2H, H9 and 10), 7.79–7.83, 8.01–8.05 (each m, each 1H, H8 and 11), 8.30 (d, 2H, J = 8.0 Hz, H2′ and 6′); FAB-MS *m/z*: 420 (MH^+). *Anal*. Calcd. for $C_{23}H_{21}N_3OS_2 \cdot 1/3\ H_2O$: C, 64.91; H, 5.13; N, 9.87. Found: C, 65.15; H, 5.06; N, 9.76.

General procedure for the reaction of 9a–e with sodium methoxide to give 14a–e. To a methanolic solution (5.0 mL) of sodium methoxide (2 eq. to **9**) was added **9** (100 mg) and the solution was then refluxed for the time required for completion of the reaction. After removal of solvent *in vacuo*, ice-water (50 mL) was poured into the residue. The resulting precipitate was collected on a filter and purified by recrystallization to give **14**.

4-Methoxy-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (14a). The reaction time was 3 h. Recrystallization of the residue from acetonitrile gave **14a** (84%) as yellow needles, mp 171–172°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.30–3.52 (m, 4H, H5 and 6), 4.09 (s, 3H, OCH_3), 7.36–7.54 (m, 2H, H9 and 10), 7.82–7.94 (m, 2H, H8 and 11), 8.75 (s, 1H, H2); FAB-MS *m/z*: 301 (MH^+). *Anal*. Calcd. for $C_{15}H_{12}N_2OS_2$: C, 59.97; H, 4.03; N, 9.33. Found: C, 59.68; H, 4.31; N, 9.37.

4-Methoxy-2-methyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (14b). The reaction time was 1.5 h. Recrystallization of the residue from acetonitrile gave **14b** (67%) as colorless scales, mp 192–193°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 2.69 (s, 3H, 2-CH_3), 3.27 (br t, 2H, J = 5.0 Hz, H5), 3.44 (br t, 2H, J = 5.0 Hz, H6), 4.04 (s, 3H, OCH_3), 7.35–7.48 (m, 2H, H9 and 10), 7.80–7.91 (m, 2H, H8 and 11); FAB-MS *m/z*: 315 (MH^+). *Anal*. Calcd. for $C_{16}H_{14}N_2OS_2 \cdot 1/4\ H_2O$: C, 60.26; H, 4.58; N, 8.78. Found: C, 60.52; H, 4.79; N, 9.01.

2-Ethyl-4-methoxy-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (14c). The reaction time was 1 h. Recrystallization of the residue from acetonitrile gave **14c** (76%) as yellow needles, mp 139–140°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.41 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.03 (q, 2H, J = 7.5 Hz, CH_2CH_3), 3.23–3.32 (m, 2H, H5), 3.40–3.49 (m, 2H, H6), 4.07 (s, 3H, OCH_3), 7.39–7.43 (m, 2H, H9 and 10), 7.82–7.91 (m, 2H, H8 and 11); FAB-MS *m/z*: 329 (MH^+). *Anal*. Calcd. for $C_{17}H_{16}N_2OS_2$: C, 62.16; H, 4.91; N, 8.53. Found: C, 62.15; H, 5.26; N, 8.48.

4-Methoxy-2-phenyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (14d). The reaction time was 7 h. Recrystallization of the residue from acetonitrile gave **14d** (77%) as yellow needles, mp 200–201°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.43 (br s, 4H, H5 and 6), 4.15 (s, 3H, OCH_3), 7.38–7.59 (m, 5H, H9, 10, and 3′, 4′, 5′), 7.81–7.90 (m, 2H, H8 and 11), 8.44–8.61 (m, 2H, H2′ and 6′); FAB-MS m/z 377 (MH^+). *Anal*. Calcd. for $C_{21}H_{16}N_2OS_2 \cdot 1/4\ H_2O$: C, 66.20; H, 4.37; N, 7.35. Found: C, 66.58; H, 4.38; N, 7.34.

4-Methoxy-2-p-tolyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (14e). The reaction time was 93 h. Recrystallization of the residue from acetonitrile gave **14e** (71%) as colorless prisms, mp 198–199°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 2.44 (s, 3H, 2′-CH_3), 3.42 (s, 4H, H5 and 6), 4.14 (s, 3H, OCH_3), 7.30 (d, 2H, J = 8.2 Hz, H3′ and 5′), 7.38–7.45 (m, 2H, H9 and 10), 7.82–7.90 (m, 2H, H8 and 11), 8.43 (d, 2H, J = 8.2 Hz, H2′ and 6′); FAB-MS *m/z*: 391 (MH^+). *Anal*. Calcd. for $C_{22}H_{18}N_2OS_2$: C, 67.66; H, 4.65; N, 7.17. Found: C, 67.47; H, 4.93; N, 7.15.

General procedure for the reaction of 9a–e with sodium ethoxide to give 15a–e. To an ethanolic solution (5.0 mL) of sodium ethoxide (2 eq. to **9**) was added **9** (100 mg), and the solution was then refluxed for the time required of completion of the reaction. After evaporation of solvent *in vacuo*, ice-water (50 mL) was poured into the residue. The resulting precipitate was collected on a filter and purified by recrystallization to give **15**.

4-Ethoxy-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (15a). The reaction time was 2 h. Recrystallization of the residue from ethanol gave **15a** (87%) as colorless prisms, mp 167–168°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.46 (t, 3H, J = 7.0 Hz, CH_2CH_3), 3.33–3.49 (m, 4H, H5 and 6), 4.52 (q, 2H, J = 7.0 Hz, OCH_2), 7.40–7.48 (m, 2H, H9 and 10), 7.82–7.92 (m, 2H, H8 and 11), 8.71 (s, 1H, H2); FAB-MS *m/z*: 315 (MH^+). *Anal*. Calcd. for $C_{16}H_{14}N_2OS_2$: C, 61.12; H, 4.49; N, 8.91. Found: C, 60.95; H, 4.49; N, 8.93.

4-Ethoxy-2-methyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (15b). The reaction time was 2 h. Recrystallization of the residue from ethanol gave **15b** (85%) as colorless needles, mp 160–162°C; ^{1}H-NMR (200 MHz, deuterochloform): δ 1.43 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.66 (s, 3H, 2-CH_3), 3.27–3.32 (m, 2H, H5), 3.41–3.46 (m, 2H, H6), 4.48 (q, 2H, J = 7.0 Hz, OCH_2), 7.38–7.43 (m, 2H, H9 and 10), 7.82–7.89 (m, 2H, H8 and 11); FAB-MS *m/z*: 329 (MH^+). *Anal*. Calcd. for $C_{17}H_{16}N_2OS_2 \cdot 1/3\ H_2O$: C, 61.05; H, 5.02; N, 8.38. Found: C, 61.39; H, 4.89: N, 8.39.

4-Ethoxy-2-ethyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (15c). The reaction time was 1 h. Recrystallization of the residue from ethanol gave **15c** (83%) as colorless needles, mp 113–114°C; ^{1}H-NMR (200 MHz, deuterochloform): δ 1.39 (t, 3H, J = 7.5 Hz, 2-CH_2CH_3), 1.44 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.96 (q, 2H, J = 7.5 Hz, 2-CH_2CH_3), 3.25–3.35 (m, 2H, H5), 3.39–3.48 (m, 2H, H6), 4.51 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 7.34–7.47 (m, 2H, H9 and 10), 7.81–7.91 (m, 2H, H8 and 11); FAB-MS *m/z*: 343 (MH^+). *Anal*. Calcd. for $C_{18}H_{18}N_2OS_2$: C, 63.13; H, 5.30; N, 8.18. Found: C, 62.88; H, 5.38; N, 8.00.

4-Ethoxy-2-phenyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-d]pyrimidine (15d). The reaction time was 1 h. Recrystallization of the residue from acetonitrile gave **15d** (88%) as colorless needles, mp 145–146°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.50 (t, 3H, J = 7.0 Hz, CH_2CH_3), 3.43 (br s, 4H, H5 and 6), 4.63 (q, 2H, J = 7.0 Hz, OCH_2), 7.31–7.64 (m, 5H, H9, 10, and 3′, 4′, 5′), 7.82–7.92 (m, 2H, H8 and 11), 8.49–8.58 (m, 2H, H2′ and 6′); FAB-MS *m/z*: 391. *Anal*. Calcd. for $C_{22}H_{18}N_2OS_2$: C, 67.66; H, 4.65; N, 7.17. Found: C, 67.33; H, 4.81; N, 7.09.

4-Ethoxy-2-p-tolyl-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (15e). The reaction time was 4.5 h. Recrystallization of the residue from acetonitrile gave **15e** (91%) as colorless needles, mp 167–168°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.49 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.44 (s, 3H, 4′-CH_3), 3.42 (s, 4H, H5 and 6), 4.62 (q, 2H, J = 7.0 Hz, OCH_2), 7.30 (br d, 2H, J = 8.0 Hz, H3′ and 5′), 7.37–7.45 (m, 2H, H9 and 10), 7.82–7.91 (m, 2H, H8 and 11), 8.42 (br d, 2H, J = 8.0 Hz, H2′ and 6′); FAB-MS *m/z*: 405 (MH^+). *Anal*. Calcd. for $C_{23}H_{20}N_2OS_2$: C, 68.29; H, 4.98; N, 6.92. Found: C, 67.91; H, 4.93; N, 6.84.

General procedure for the reaction of 9a–e with ethylene glycol to give 16a–e. To a solution of **9** (100 mg) in dry 1,4-dioxane (5.0 mL) were added ethylene glycol (2.0 mL), and potassium carbonate (2 eq. to **9**) and the mixture was then stirred at 80°C for the time required for completion of the reaction. After evaporation of the reaction mixture *in vacuo*, ice-water (20 mL) was poured into the residue. The resulting precipitate was collected on a filter and purified by column chromatography and/or recrystallization to give **16**.

4-(2-Hydroxyethoxy)-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (16a). The reaction time was 2 h. The precipitated solid was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (4:1) was evaporated and the residue was recrystallized from benzene to give **16a** (74%) as colorless needles, mp 123–124°C. IR (nujol) cm^{-1}: 3401, 3315 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 3.42 (br s, 4H, H5 and 6), 3.99–4.04 (m, 2H, OCH_2CH_2OH), 4.59–4.63 (m, 2H, OCH_2CH_2OH), 7.37–7.48 (m, 2H, H9 and 10), 7.80–7.91 (m, 2H, H8 and 11), 8.65 (s, 1H, H2); FAB-MS *m/z*: 331 (MH^+). *Anal*. Calcd. for $C_{16}H_{14}N_2O_2S_2$: C, 58.16; H, 4.27; N, 8.48. Found: C, 57.92; H, 4.51; N, 8.52.

4-(2-Hydroxyethoxy)-2-methyl-5,6-dihydro[1]benzothieno [3′,2′:2,3]thiepino[4,5-d]pyrimidine (16b). The reaction time was 5 h. The precipitated solid was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (4:1) was evaporated, and the residue was recrystallized from cyclohexane to give **16b** (72%) as colorless needles, mp 135–136°C; IR (nujol) cm^{-1}: 3384 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.67 (s, 3H, 2-CH_3), 3.30–3.35 (m, 2H, H5), 3.41–3.46 (m, 2H, H6), 3.98–4.02 (m, 2H, OCH_2CH_2OH), 4.59–4.64 (m, 2H, OCH_2CH_2OH), 7.39–7.44 (m, 2H, H9 and 10), 7.82–7.89 (m, 2H, H8 and 11); FAB-MS *m/z*: 345 (MH^+). *Anal*. Calcd. for $C_{17}H_{16}N_2O_2S_2 \cdot 1/4\ H_2O$: C, 58.51; H, 4.77; N, 8.03. Found: C, 58.81; H, 4.90; N, 7.99.

2-Ethyl-4-(2-hydroxyethoxy)-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (16c). The reaction time was 3 h. Recrystallization of the precipitated solid from cyclohexane gave **16c** (77%) as colorless needles, mp 120–121°C; IR (nujol) cm^{-1}: 3172 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.39 (t, 3H, J = 7.5 Hz, 2-CH_2CH_3), 2.95 (q, 2H, J = 7.5 Hz, 2-CH_2CH_3), 3.32–3.45 (m, 4H, H5 and 6), 3.98–4.02 (m, 2H, OCH_2CH_2OH), 4.61–4.65 (m, 2H, OCH_2CH_2OH), 7.36–7.48 (m, 2H, H9 and 10), 7.79–7.90 (m, 2H, H8 and 11); FAB-MS *m/z*: 359 (MH^+). *Anal*. Calcd. for $C_{18}H_{18}N_2O_2S_2 \cdot 1/3\ H_2O$: C, 59.31; H, 5.16; N, 7.69. Found: 59.64; H, 5.20; N, 7.74.

4-(2-Hydroxyethoxy)-2-phenyl-5,6-dihydro[1]benzothieno [3′,2′:2,3]thiepino[4,5-d]pyrimidine (16d). The reaction time was 18 h. The precipitated solid was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (9:1) was evaporated, and the solid was recrystallized from acetonitrile to give **16d** (50%) as yellow needles, mp 93–95°C; IR (nujol) cm^{-1}: 3291 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 3.38–3.52 (m, 4H, H5 and 6), 4.04–4.12 (m, 2H, OCH_2CH_2OH), 4.70–4.78 (m, 2H, OCH_2CH_2OH), 7.39–7.45 (m, 2H, H9 and 10), 7.48–7.52 (m, 3H, H3′, 4′, and 5′), 7.82–7.88 (m, 2H, H8 and 11), 8.46–8.51 (m, 2H, H2′ and 6′); FAB-MS *m/z*: 407 (MH^+). *Anal*. Calcd. for $C_{22}H_{18}N_2O_2S_2$: C, 65.00; H, 4.46; N, 6.89. Found: C, 64.65; H, 4.67; N, 6.64.

4-(2-Hydroxyethoxy)-2-p-tolyl-5,6-dihydro[1]benzothieno [3′,2′:2,3]thiepino[4,5-d]pyrimidine (16e). The reaction time was 36 h. Recrystallization of the precipitated solid from acetonitrile gave **16e** (76%) as yellow needles, mp 188–189°C; IR (nujol) cm^{-1}: 3366 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.44 (s, 3H, 2′-CH_3), 3.38–3.52 (m, 4H, H5 and 6), 4.03–4.11 (m, 2H, OCH_2CH_2OH), 4.70–4.78 (m, 2H, OCH_2CH_2OH), 7.30 (br d, 2H, J = 8.0 Hz, H3′ and 5′), 7.38–7.46 (m, 2H, H9 and 10), 7.81–7.89 (m, 2H, H8 and 11), 8.37 (d, 2H, J = 8.0 Hz, H2′ and 6′); FAB-MS *m/z*: 421 (MH^+). *Anal*. Calcd. for $C_{23}H_{20}N_2O_2S_2$: C, 65.69; H, 4.79; N, 6.66. Found: C, 65.29; H, 4.73; N, 6.58.

General procedure for the reaction of 9a–e with 2-sulfanylethanol to give 17a–e. To a solution of **9** (100 mg) in dry 1,4-dioxane (5.0 mL) were added 2-sulfanylethanol (2 eq. to **9**) and 1,8-diazabicyclo potassium carbonate (2 eq. to **9**), and the mixture was then refluxed for the time required for completion of the reaction. After evaporation of the reaction mixture *in vacuo*, ice-water (20 mL) was poured into the residue. The resulting precipitate was collected on a filter and purified by column chromatography and/or recrystallization to give **17**.

4-(2-Hydroxyethylsulfanyl)-5,6-dihydro[1]benzothieno[3′,2′:2,3] thiepino[4,5-d]pyrimidine (17a). The reaction time was 33 h. The precipitated solid was collected on a filter and was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (4:1) was evaporated *in vacuo* and was recrystallized from acetonitrile to give **17a** (43%) as yellow needles, mp 105–106°C; IR (nujol) cm^{-1}: 3176 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 3.31–3.45 (m, 4H, H5 and SCH_2CH_2OH), 3.51–3.58 (m, 2H, H6), 3.66 (t, 2H, J = 6.7 Hz, SCH_2CH_2OH), 5.10 (br, 1H, deuterium oxide exchangeable, OH), 7.42–7.58 (m, 2H, H9 and 10), 7.78–7.85 (m, 1H, H11), 7.98–8.50 (m, 1H, H8), 8.85 (s, 1H, H2); FAB-MS *m/z*: 347 (MH^+). *Anal*. Calcd. for $C_{16}H_{14}N_2OS_3 \cdot 1/3\ H_2O$: C, 54.52; H, 4.19; N, 7.95. Found: C, 54.52; H, 4.22; N, 7.76.

4-(2-Hydroxyethylsulfanyl)-2-methyl-5,6-dihydro[1]benzothieno [3′,2′:2,3]thiepino[4,5-d]pyrimidine (17b). The reaction time was 25 h. Recrystallization of the precipitated solid from acetonitrile gave **17b** (79%) as yellow needles, mp 125–126°C; IR (nujol) cm^{-1}: 3188 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.59 (s, 3H, 2-CH_3), 3.26–3.37 (m, 4H, H5 and SCH_2CH_2OH), 3.48–3.53 (m, 2H, H6), 3.67 (t, 2H, J = 6.5 Hz, SCH_2CH_2OH), 5.10 (br, 1H, deuterium oxide exchangeable, OH), 7.41–7.57 (m, 2H, H9 and 10), 7.79 (br dd, 1H, J = 6.7, 2.0 Hz, H11), 8.00 (br dd, 1H, J = 6.4, 1.8 Hz, H8); FAB-MS *m/z*: 361 (MH^+). *Anal*. Calcd. for $C_{17}H_{16}N_2OS_3 \cdot 1/3\ H_2O$: C, 55.71; H, 4.58; N, 7.64. Found: C, 55.97; H, 4.59; N, 7.67.

2-Ethyl-4-(2-hydroxyethylsulfanyl)-5,6-dihydro[1]benzothieno [3′,2′:2,3]thiepino[4,5-d]pyrimidine (17c). The reaction time was 26 h. Recrystallization of the precipitated solid from acetonitrile gave **17c** (43%) as colorless needles, mp 114–115°C; IR (nujol) cm^{-1}: 3364, 3290 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.33 (t, 3H, J = 7.6 Hz, 2-CH_2CH_3), 2.86 (q, 2H, J = 7.6 Hz, 2-CH_2CH_3), 3.27–3.38 (m, 4H, H5 and SCH_2CH_2OH), 3.48–3.53 (m, 2H, H6), 3.68 (t, 2H, J = 6.4 Hz, SCH_2CH_2OH), 5.00 (br, 1H, deuterium oxide exchangeable, OH), 7.46 (td, 1H, J = 7.1, 1.5 Hz, H9), 7.52 (td, 1H, J = 7.1, 1.6 Hz, H10), 7.79 (br dd, 1H, J = 7.1, 2.1 Hz, H11), 8.01 (br dd, 1H, J = 7.1, 1.8 Hz, H8); FAB-MS *m/z*:

375 (MH^+). *Anal*. Calcd. for $C_{18}H_{18}N_2OS_3$: C, 57.72; H, 4.84; N, 7.48. Found: 57.93; H, 4.94; N, 7.50.

4-(2-Hydroxyethylsulfanyl)-2-phenyl-5,6-dihydro[1]benzothieno [3′,2′:2,3]thiepino[4,5-d]pyrimidine (17d). The reaction time was 24 h. Recrystallization of the precipitated solid from acetonitrile gave **17d** (86%) as yellow needles, mp 175–176°C; IR (nujol) cm^{-1}: 3367, 3173 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 3.37–3.61 (m, 6H, H5, 6, and SCH_2CH_2OH), 3.76 (br t, 2H, J = 6.0 Hz, SCH_2CH_2OH), 5.10 (br s, 1H, deuterium oxide exchangeable, OH), 7.45–7.68 (m, 5H, H9, 10, and 3′, 4′, 5′), 7.81 (br dd, 1H, J = 6.5, 1.7 Hz, H11), 8.06 (br dd, 1H, J = 7.5, 1.7 Hz, H8), 8.45–8.50 (m, 2H, H2′ and 6′); FAB-MS *m/z*: 423 (MH^+). *Anal*. Calcd. for $C_{22}H_{18}N_2OS_3$: C, 62.53; H, 4.29; N, 6.63. Found: C, 62.15; H, 4.58; N, 6.61.

4-(2-Hydroxyethylsulfanyl)-2-p-tolyl-5,6-dihydro[1]benzothieno [3′,2′:2,3]thiepino[4,5-d]pyrimidine (17e). The reaction time was 24 h. The precipitated solid was chromatographed on silica gel. The eluate of *n*-hexane/ethyl acetate (4:1) was evaporated, and the residue was recrystallized from acetonitrile to give **17e** (47%) as yellow needles, mp 188–189°C; IR (nujol) cm^{-1}: 3368, 3185 (OH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.42 (s, 3H, 2′-CH_3), 3.32–3.56 (m, 6H, H5, 6, and SCH_2CH_2OH), 3.75 (t, 2H, J = 6.0 Hz, SCH_2CH_2OH), 7.39 (d, 2H, J = 8.2 Hz, H3′ and 5′), 7.42–7.58 (m, 2H, H9 and 10), 7.80 (br dd, 1H, J = 6.6, 1.7 Hz, H11), 8.06 (br dd, 1H, J = 6.8, 1.7 Hz, H8), 8.36 (d, 2H, J = 8.2 Hz, H2′ and 6′); FAB-MS *m/z*: 437 (MH^+). *Anal*. Calcd. for $C_{23}H_{20}N_2OS_3$: C, 63.27; H, 4.62; N, 6.42. Found: C, 63.02; H, 4.91; N, 6.35.

Determination of pentosidine formation *in vitro*. The effects were assayed according to the literature procedure [11]. Aminoguanidine hydrochloride was used as a reference compound.

Acknowledgments. The authors are grateful to the SC-NMR Laboratory of Okayama University for 200 MHz ^{1}H-NMR experiments. They also thank Dr. K. L. Kirk (NIDDK, NIH) for helpful comments on the manuscript.

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