Polycyclic *N*-Heterocyclic Compounds. Part 82: Synthesis and Evaluation of Anti-Platelet Aggregation Activity of 2,4-Disubstituted 5,6-Dihydro[1]benzothiepino[5,4-*d*]pyrimidine and Related Compounds

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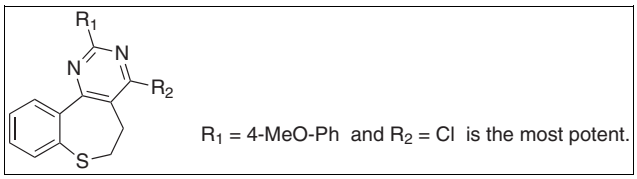

We have synthesized a large number of tricyclic 2-substituted 4-alkylamino-5,6-dihydro[1]benzothiepino [5,4-*d*]pyrimidines as part of our research to develop new effective anti-platelet drugs. A variety of alkyl and aryl groups were used as substituents at the 2-position. Evaluation of the effects of the newly synthesized compounds on collagen-induced platelet aggregation revealed several promising anti-platelet candidates with potencies superior to aspirin.

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INTRODUCTION

We have been involved in research on the synthesis and biological evaluation of a series of polycyclic *N*-heterocyclic compounds. During our investigation of the anti-platelet aggregation activity of these compounds, we discovered that 2-substituted 4-(2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazolines (**1**) [1] and 2-substituted 4-(2-hydroxyethylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines (**2**) [2] had stronger inhibitory activities against collagen-induced aggregation of rabbit platelets *in vitro* than aspirin, the well-known anti-platelet agent (Figure 1) [3]. The most potent **1** (R═Ph) had six times the activity of aspirin, whereas the most potent **2** (R═4-Cl─Ph) had four times the activity of aspirin.

Current anti-platelet drugs are important for the prevention and treatment of acute ischemic syndromes. However, drugs in clinical use often have drawbacks that include side effects and less than ideal efficacy and thus there continues to be much research directed to the development of new drugs in this class [4–13]. In order to develop more active compounds derived from our hit compounds, we decided to explore the structure–activity relationships of 2-substituted 4-(2-hydroxyethylamino)-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidines (**3**), the thia-analogs of **1** and **2**. In this report, we describe in detail the synthesis and evaluation of these compounds.

CHEMISTRY

We synthesized the target molecules by the following method. First, bicyclic enaminonitrile (**5**) was prepared by reaction of 5-oxo-2,3,4,5-tetrahydrobenzo[*b*]thiepin-4-carbonitrile (**4**) [14] with ammonia (Scheme 1). The structure of **5** was supported by the characteristic amino and cyano absorption in the IR spectrum. Next, **5** was allowed to react with Vilsmeier reagents prepared from a series of *N*,*N*-dimethylamides and phosphoryl chloride to give **6a–i**. Structures of **6a–i** were supported by 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 provided confirmation of these structures.

Next, we employed 2-aminoethanol to carry out nucleophilic substitution at the 4-position to give **3**. An advantage of the 2-hydroxyethylamino moiety comes from the expected increase in aqueous solubility of the hydrophobic 5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidines **3a–i** (61–95%, Scheme 2). Because we also expected the 2-hydroxyethylamino substituent to influence bioactivity, to eliminate hydrogen donor ability of amino group, *N*-methyl-2-aminoethanol was also chosen to react with **6a–i** to give **7a–i** (47–84%). Similarly, reaction of dimethylamine with **6a–i** gave **8a–i** (34–95%) thereby eliminating the influence of the hydroxyethyl group of the *N*-methyl-*N*-(2-hydroxyethyl) moiety. Finally, reaction of morpholine with **6a–i** was carried out to give **9a–i** (55–83%),

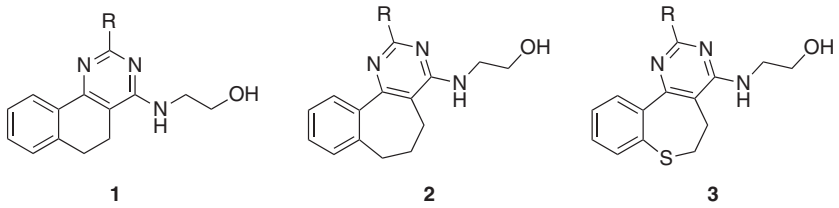
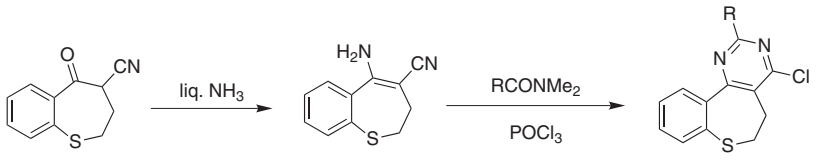


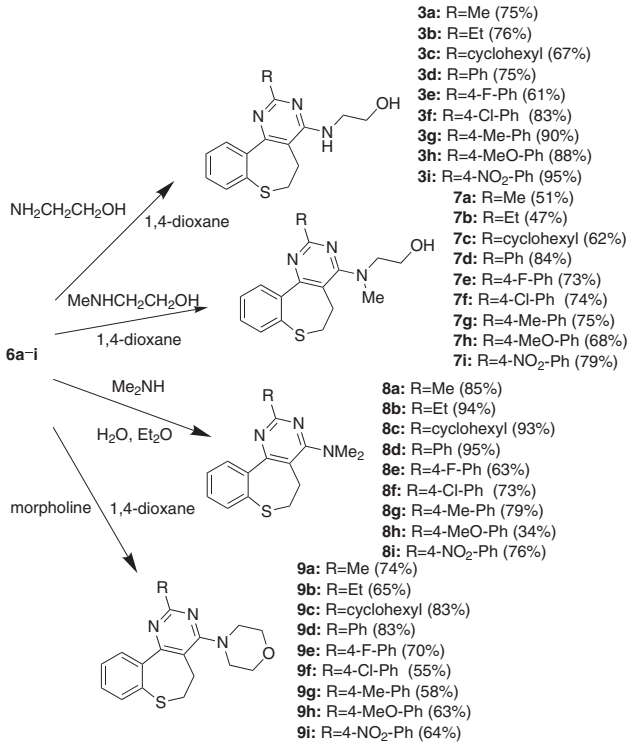
Figure 1. Previous hit compounds (**1** and **2**) as anti-platelet agents and their analogs (**3**) prepared here.

Scheme 1. Preparation of **6**.



6a: R=Me (69%)
6b: R=Et (76%)
6c: R=cyclohexyl (71%)
6d: R=Ph (84%)
6e: R=4-F-Ph (76%)
6f: R=4-Cl-Ph (85%)
6g: R=4-Me-Ph (64%)
6h: R=4-MeO-Ph (71%)
6i: R=4-NO_2-Ph (82%)

Scheme 2. Preparation of **3** and **7–9**.



3a: R=Me (75%)
3b: R=Et (76%)
3c: R=cyclohexyl (67%)
3d: R=Ph (75%)
3e: R=4-F-Ph (61%)
3f: R=4-Cl-Ph (83%)
3g: R=4-Me-Ph (90%)
3h: R=4-MeO-Ph (88%)
3i: R=4-NO_2-Ph (95%)

7a: R=Me (51%)
7b: R=Et (47%)
7c: R=cyclohexyl (62%)
7d: R=Ph (84%)
7e: R=4-F-Ph (73%)
7f: R=4-Cl-Ph (74%)
7g: R=4-Me-Ph (75%)
7h: R=4-MeO-Ph (68%)
7i: R=4-NO_2-Ph (79%)

8a: R=Me (85%)
8b: R=Et (94%)
8c: R=cyclohexyl (93%)
8d: R=Ph (95%)
8e: R=4-F-Ph (63%)
8f: R=4-Cl-Ph (73%)
8g: R=4-Me-Ph (79%)
8h: R=4-MeO-Ph (34%)
8i: R=4-NO_2-Ph (76%)

9a: R=Me (74%)
9b: R=Et (65%)
9c: R=cyclohexyl (83%)
9d: R=Ph (83%)
9e: R=4-F-Ph (70%)
9f: R=4-Cl-Ph (55%)
9g: R=4-Me-Ph (58%)
9h: R=4-MeO-Ph (63%)
9i: R=4-NO_2-Ph (64%)

thus simultaneously eliminating the hydrogen donor ability of the amino and hydroxy groups of the 2-hydroxyethylamino substituent. All derivatives **3** and **6–9** satisfy Lipinski's rule of five, and thus they are expected to have drug-like properties [15].

BIOLOGY

The products prepared as described earlier were screened for inhibitory activity against rabbit platelet aggregation by a turbidimetric method using an aggregometer as described by Born and Cross [16]. Platelet aggregation was induced by the addition of collagen (final concentration 14.3 μg/mL). A 10% solution of dimethylsulfoxide (DMSO, final concentration 0.71%) or 60% *N*,*N*-dimethylformamide (DMF, final concentration 4.3%, in the case of poor aqueous solubility) was used as a cosolvent to dissolve drugs. The results are shown in Table 1. Comparison of the inhibition potency of test compounds with that of aspirin revealed that none of **8** and **9** showed any significant improvement in potency over aspirin (data not shown). However, certain of the substituted tricyclic compounds **3**, **6**, and **7** showed bioactivity superior to aspirin. A detailed comparison of the inhibitory activity (IC_{50}) of the compounds that showed significant difference ($P < 0.01$) from the activity of aspirin at the same concentration was determined. Among them, **6h** with the 2-(4-methoxyphenyl)-4-Cl substituent, is the most potent, having three times more activity than aspirin. It is, however, less potent than either **1** (R═Ph) or **2** (R═4-Cl—Ph), which were the most potent of the **1** and **2** series, respectively. It seems that the substitution of the 2-phenyl group of **6** had substantial effects

Table 1

Effects of **3**, **6**, and **7** on rabbit platelet aggregation *in vitro* induced by collagen.

Compound	% inhibition[a]	IC_{50} (μM)[b]	Compound	% inhibition[a]	IC_{50} (μM)[b]
3a[c]	7.9 ± 3.6	–	**3f**[d]	10.3 ± 2.2	–
3b[c]	7.3 ± 1.6	–	**3g**[c]	35.3 ± 3.2*	35.1 (28.4–46.0)
3c[c]	45.6 ± 5.0*	18.4 (10.5–30.4)	**3h**[d]	14.0 ± 1.7	–
3d[d]	13.5 ± 1.9	–	**3i**[d]	18.9 ± 3.2	–
3e[c]	10.8 ± 3.6	–			
6a[d]	2.1 ± 0.7	–	**6f**[d]	40.7 ± 0.5*	2.8 (1.4–5.0)
6b[d]	22.7 ± 1.4	–	**6g**[d]	21.6 ± 4.6	–
6c[d]	10.1 ± 0.2	–	**6h**[d]	46.5 ± 10.4*	2.1 (0.8–4.3)
6d[d]	10.1 ± 8.6	–	**6i**[d]	34.8 ± 0.8	–
6e[d]	9.5 ± 1.0	–			
7a[c]	2.7 ± 1.8	–	**7f**[d]	21.9 ± 3.2	–
7b[c]	29.1 ± 2.2*	55.4 (39.7–93.3)	**7g**[d]	20.0 ± 2.6	–
7c[d]	22.1 ± 2.9	–	**7h**[d]	13.2 ± 2.2	–
7d[d]	9.5 ± 3.3	–	**7i**[d]	17.6 ± 10.8	–
7e[d]	14.0 ± 4.8	–			
Aspirin[c]	15.7 ± 1.0	48.0 (44.1–53.3)	Aspirin[d]	26.1 ± 1.7	6.5 (5.3–8.8)

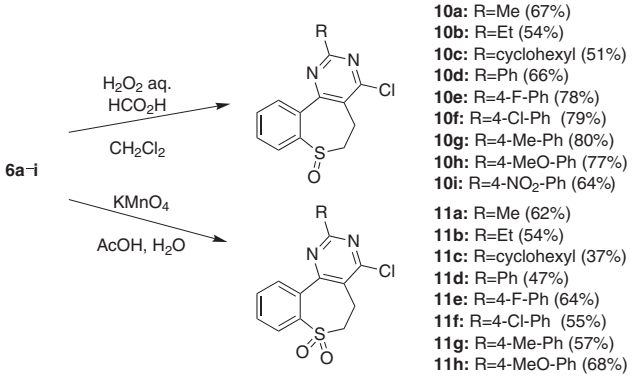
[a]Data represent % inhibition of the vehicle control group (Mean ± SE of three experiments at least) at a final concentration of 25 μM (in the case of 10% DMSO) or 2.5 μM (in the case of 60% DMF).
*Means significantly different from aspirin at $P < 0.01$.
[b]Experiments were repeated at least three times each at final concentration of 5.0, 25, 50 μM (**3** and **7** in the case of 10% DMSO), 25, 50, 100 μM (aspirin in the case of 10% DMSO), 1.0, 2.5, 5.0 μM (**3**, **6**, and **7** in the case of 60% DMF), or 2.5, 5.0, 10 μM (aspirin in the case of 60% DMF). Figures in parentheses represent 95% confidence limits of IC_{50}.
[c]10% DMSO was used as a cosolvent.
[d]60% DMF was used as a cosolvent.

on activity (**6d–6i**). When the 4-substituent was either the 2-hydroxyethylamino moiety (**3**) or *N*-methyl-*N*-(2-hydroxyethylamino) moiety (**7**), the favored 2-substitution is not 4-methoxyphenyl but rather cyclohexyl (**3c**), 4-tolyl (**3g**), or ethyl (**7b**), although potencies of these compounds were less than that of **6h**.

We were also interested in the effect of the oxidation state of the S atom on activity. Among the tested compounds, **6h** was the most potent. Therefore, sulfoxides **10** and sulfones **11** were prepared from sulfides **6** by the usual procedures (Scheme 3). Thus, performic acid oxidation of **6a–i** gave **10a–i** (51–80%). Structures of **10** were verified based on the appearance of the sulfoxide groups in their IR spectra. In addition, the NMR and MS spectra and elemental analyses supported these structures. Potassium permanganate oxidation of **6a–i** gave **11a–i** (37–68%). Structures of **11** were supported by the appearance of the sulfone groups in their IR spectra. None of the compounds in series **10** and **11** showed any significant improvement in potency over aspirin (data not shown). More detailed examination will be needed to clarify this structure–activity relationship.

On the basis of the promising results reported herein, we are currently exploring development of additional derivatives with anti-platelet aggregation activity.

Scheme 3. Preparation of **10** and **11**.



10a: R=Me (67%)
10b: R=Et (54%)
10c: R=cyclohexyl (51%)
10d: R=Ph (66%)
10e: R=4-F-Ph (78%)
10f: R=4-Cl-Ph (79%)
10g: R=4-Me-Ph (80%)
10h: R=4-MeO-Ph (77%)
10i: R=4-NO_2-Ph (64%)

11a: R=Me (62%)
11b: R=Et (54%)
11c: R=cyclohexyl (37%)
11d: R=Ph (47%)
11e: R=4-F-Ph (64%)
11f: R=4-Cl-Ph (55%)
11g: R=4-Me-Ph (57%)
11h: R=4-MeO-Ph (68%)
11i: R=4-NO_2-Ph (56%)

EXPERIMENTAL

All melting points were determined on a Yanagimoto (Kyoto, Japan) micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto (Kyoto, Japan) MT-5 CHN Corder elemental analyzer. The electron impact (EI)-mass and fast atom bombardment (FAB)-mass (*m*-nitrobenzyl alcohol was used as the matrix) were obtained on a VG (UK) 70-SE mass spectrometer. The IR spectra were recorded on a Japan Spectroscopic (Hachioji, Japan) diffraction grating A-102 spectrophotometer, and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Varian (Palo Alto, CA) VXR-200 instrument or a

Hitachi (Tokyo, Japan) R-1500 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; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet. Reactions were monitored by thin layer chromatography to determine the appropriate time for termination.

5-Amino-2,3-dihydro-1-benzothiepin-4-carbonitrile (5). Compound **4** (10.0 g, 49.2 mmol) and liquid ammonia (30 mL) were heated at 150 °C in a pressure reactor vessel equipped with a manometer under 46 kg/cm^2 for 40 h. After ice cooling, the vessel was opened carefully in a fume food and ammonia was removed. The residue was recrystallized from ethanol to give **5** (8.60 g, 86%) as colorless plates; mp 148–150 °C; IR (potassium bromide) cm^{-1}: 2180 (CN), 3440, 3340, 3240 (NH); ^{1}H NMR (deuterochloroform): δ 2.24 (t, 2H, *J* = 6.5 Hz, H3), 3.38 (t, 2H, *J* = 6.5 Hz, H2), 4.68 (br, 2H, deuterium oxide exchangeable, NH_2), 7.20–7.75 (m, 4H, H6, 7, 8, and 9); EIMS *m/z*: 202 (M^+). *Anal*. Calcd. for $C_{11}H_{10}N_2S$: C, 65.31; H, 4.98; N, 13.84. Found: C, 65.30; H, 5.01; N, 13.80.

2-Substituted 4-chloro-5,6-dihydro[1]benzothiepino[5,4-d] pyrimidine (6a–i). General procedure. To a Vilsmeier reagent prepared from phosphoryl chloride (74.3 mmol) and the corresponding *N*,*N*-dimethylamide [17–20] (24.8 mmol) by stirring for 1 h under ice-water cooling was added compound **5** (1.00 g, 4.95 mmol), and the reaction was then refluxed for 0.5 h. After evaporation of excess phosphoryl chloride in vacuo, ice water (40 mL) was poured into the residue. The mixture was neutralized with sodium hydrogen carbonate and was extracted with chloroform (30 mL × 3). The organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue was recrystallized from the appropriate solvent to give **6a–i**.

4-Chloro-2-methyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (6a). The product was recrystallized from acetonitrile to give **6a** (69%) as colorless needles, mp 126–127 °C; ^{1}H NMR (deuterochloroform): δ 2.77 (s, 3H, CH_3), 2.93 (t, 2H, *J* = 6.0 Hz, H5), 3.44 (t, 2H, *J* = 6.0 Hz, H6), 7.40–7.85 (m, 4H, H8, 9, 10, and 11); EIMS *m/z*: 262 (M^+), 264 ($M^+ + 2$). *Anal*. Calcd. for $C_{13}H_{11}ClN_2S$: C, 59.42; H, 4.22; N, 10.66. Found: C, 59.37; H, 4.32; N, 10.58.

4-Chloro-2-ethyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (6b). The product was recrystallized from acetonitrile to give **6b** (76%) as colorless plates, mp 86–89 °C; ^{1}H NMR (deuterochloroform): δ 1.41 (t, 3H, *J* = 7.5 Hz, CH_3), 2.96 (t, 2H, *J* = 6.5 Hz, H5), 3.02 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 3.45 (t, 2H, *J* = 6.5 Hz, H6), 7.44, 7.52 (each ddd, each 1H, each *J* = 8.0, 7.0, 1.0 Hz, H9 and 10), 7.64 (br d, 1H, *J* = 8.0 Hz, H8), 7.77 (dd, 1H, *J* = 8.0, 1.0 Hz, H11); EIMS *m/z*: 276 (M^+), 278 ($M^+ + 2$). *Anal*. Calcd. for $C_{14}H_{13}ClN_2S$: C, 60.75; H, 4.73; N, 10.12. Found: C, 60.97; H, 4.90; N, 9.94.

4-Chloro-2-cyclohexyl-5,6-dihydro[1]benzothiepino[5,4-d] pyrimidine (6c). The product was recrystallized from ethanol to give **6c** (71%) as colorless prisms, mp 128–129 °C; ^{1}H NMR (deuterochloroform): δ 1.23–2.16 (m, 10H, cyclohexyl-H), 2.93 (t, 2H, *J* = 5.8 Hz, H5), 2.65–3.03 (m, 1H, H1′), 3.45 (t, 2H, *J* = 5.8 Hz, H6), 7.37–7.82 (m, 4H, H8, 9, 10, and 11); EIMS *m/z*: 330 (M^+), 332 ($M^+ + 2$). *Anal*. Calcd. for $C_{18}H_{19}ClN_2S$: C, 65.34; H, 5.79; N, 8.47. Found: C, 65.44; H, 5.78; N, 8.46.

4-Chloro-2-phenyl-5,6-dihydro[1]benzothiepino[5,4-d] pyrimidine (6d). The product was recrystallized from ethyl acetate-acetonitrile to give **6d** (84%) as colorless needles, mp 161–163 °C; ^{1}H NMR (deuterochloroform): δ 3.01 (t, 2H, *J* = 6.0 Hz, H5), 3.50 (t, 2H, *J* = 6.0 Hz, H6), 7.32–7.72 (m, 6H, H8, 9, 10 and 3′, 4′, 5′), 7.85–7.99 (m, 1H, H11), 8.44–8.60 (m, 2H, H2′ and 6′); EIMS *m/z*: 324 (M^+), 326 ($M^+ + 2$). *Anal*. Calcd. for $C_{18}H_{13}ClN_2S$: C, 66.56; H, 4.03; N, 8.62. Found: C, 66.62; H, 4.23; N; 8.58.

4-Chloro-2-(4-fluorophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (6e). The product was recrystallized from ethyl acetate to give **6e** (76%) as colorless prisms, mp 191–192 °C; ^{1}H NMR (deuterochloroform): δ 3.00 (t, 2H, *J* = 6.4 Hz, H5), 3.49 (t, 2H, *J* = 6.4 Hz, H6), 7.00–7.97 (m, 6H, H8, 9, 10, 11 and 3′, 5′), 8.41–8.64 (m, 2H, H2′ and 6′); EIMS *m/z*: 342 (M^+), 344 ($M^+ + 2$). *Anal*. Calcd. for $C_{18}H_{12}ClFN_2S$: C, 63.06; H, 3.53; N, 8.17. Found: C, 63.15; H, 3.74; N, 8.22.

4-Chloro-2-(4-chlorophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (6f). The product was recrystallized from benzene-ethyl acetate to give **6f** (85%) as colorless prisms, mp 196–197 °C; ^{1}H NMR (deuterochloroform): δ 2.99 (br t, 2H, *J* = 5.8 Hz, H5), 3.50 (t, 2H, *J* = 5.8 Hz, H6), 7.43 (br d, 2H, *J* = 8.8 Hz, H3′ and 5′), 7.55–7.97 (m, 4H, H8, 9, 10, and 11), 8.46 (br d, 2H, *J* = 8.8 Hz, H2′ and 6′); EIMS *m/z*: 358 (M^+), 360 ($M^+ + 2$), 362 ($M^+ + 4$). *Anal*. Calcd. for $C_{18}H_{12}Cl_2N_2S$: C, 60.18; H, 3.37; N, 7.80. Found: C, 60.24; H, 3.54; N, 7.74.

4-Chloro-2-(4-methylphenyl)-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (6g). The product was recrystallized from acetonitrile to give **6g** (64%) as colorless needles, mp 190–191 °C; ^{1}H NMR (deuterochloroform): δ 2.41 (s, 3H, CH_3), 2.99 (t, 2H, *J* = 5.8 Hz, H5), 3.49 (t, 2H, *J* = 5.8Hz, H6), 7.28 (d, 2H, *J* = 8.2 Hz, H3′ and 5′), 7.39–7.94 (m, 4H, H8, 9, 10, and 11), 8.41 (d, 2H, *J* = 8.2 Hz, H2′ and 6′); EIMS *m/z*: 338 (M^+), 340 ($M^+ + 2$). *Anal*. Calcd. for $C_{19}H_{15}ClN_2S$: C, 67.35; H, 4.46; N, 8.27. Found: C, 67.26; H, 4.56; N, 8.21.

4-Chloro-2-(4-methoxyphenyl)-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (6h). The product was recrystallized from ethyl acetate-acetonitrile to give **6h** (71%) as colorless needles, mp 188–190 °C; ^{1}H NMR (deuterochloroform): δ 2.98 (t, 2H, *J* = 6.0 Hz, H5), 3.48 (t, 2H, *J* = 6.0 Hz, H6), 3.88 (s, 3H, OCH_3), 6.98 (d, 2H, *J* = 9.0 Hz, 3′ and 5′), 7.43–7.93 (m, 4H, H8, 9, 10, and 11), 8.47 (d, 2H, *J* = 9.0 Hz, H2′ and 6′); EIMS *m/z*: 354 (M^+), 356 ($M^+ + 2$). *Anal*. Calcd. for $C_{19}H_{15}ClN_2OS$: C, 64.31; H, 4.26; N, 7.89. Found: C, 64.20; H, 4.39; N, 7.96.

4-Chloro-2-(4-nitrophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (6i). The product was recrystallized from ethyl acetate-acetonitrile to give **6i** (82%) as colorless needles, mp 221–222 °C; ^{1}H NMR (deuterochloroform): δ 3.05 (t, 2H, *J* = 6.0 Hz, H5), 3.53 (t, 2H, *J* = 6.0 Hz, H6), 7.47–7.99 (m, 4H, H8, 9, 10, and 11), 8.31 (d, 2H, *J* = 8.8 Hz, H3′ and 5′), 8.71 (d, 2H, *J* = 8.8 Hz, H2′ and 6′); EIMS *m/z*: 369 (M^+), 371 ($M^+ + 2$). *Anal*. Calcd. for $C_{18}H_{12}ClN_3O_2S$: C, 58.46; H, 3.27; N, 11.36. Found: C, 58.44; H, 3.47; N, 11.29.

2-Substituted 4-(2-hydroxyethylamino)-5,6-dihydro[1] benzothiepino[5,4-d]pyrimidine (3a–i). General procedure. A mixture of **6a–i** (400 mg) and 2-aminoethanol (10 eq. of **6a–i**) in dry 1,4-dioxane (8.0 mL) was refluxed for the appropriate time. After removal of solvent in vacuo, ice water (40 mL) was poured into the residue. The resulting crystalline precipitate was collected by filtration and then recrystallized from a suitable solvent to give **3a–i**.

4-(2-Hydroxyethylamino)-2-methyl-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (3a). The reaction was refluxed for 34 h, and the product was recrystallized from acetonitrile to give **3a** (75%) as colorless prisms, mp 198–199 °C; IR (potassium bromide) cm^{-1}: 3370, 3200, 3130 (NH, OH); ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 2.59 (t, 2H, *J* = 6.0 Hz, H5), 3.31–3.69 (m, 6H, H6

and NCH_2CH_2O), 4.75 and 7.09 (each br, each 1H, each deuterium oxide exchangeable, NH and OH), 7.33–7.75 (m, 4H, H8, 9, 10, and 11); EIMS *m/z*: 287 (M^+). *Anal*. Calcd. for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62. Found: C, 62.47; H, 6.00; N, 14.62.

2-Ethyl-4-(2-hydroxyethylamino)-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (3b). The reaction was refluxed for 32 h, and the product was recrystallized from acetonitrile to give **3b** (76%) as colorless needles, mp 143–145 °C; IR (potassium bromide) cm^{-1}: 3300, 3130 (NH, OH); ^1H NMR (deuterochloroform): δ 1.35 (t, 3H, $J = 7.6$ Hz, CH_3), 2.58 (t, 2H, $J = 6.4$ Hz, H5), 2.84 (q, $J = 7.6$ Hz, 2H, CH_2CH_3), 3.48 (t, 2H, $J = 6.4$ Hz, H6), 3.58–3.97 (m, 5H, changed to 4H with addition of deuterium oxide, NCH_2CH_2O and NH or OH), 5.36 (br, 1H, deuterium oxide exchangeable, NH or OH), 7.34–7.84 (m, 4H, H8, 9, 10, and 11); FAB MS *m/z*: 302 (MH^+). *Anal*. Calcd. for $C_{16}H_{19}N_3OS$: C, 63.76; H, 6.35; N, 13.94. Found: C, 63.57; H, 6.29; N, 13.86.

2-Cyclohexyl-4-(2-hydroxyethylamino)-5,6-dihydro[1] benzothiepino[5,4-d]pyrimidine (3c). The reaction was refluxed for 45 h, and the product was recrystallized from acetonitrile to give **3c** (67%) as colorless prisms, mp 168–170 °C; IR (potassium bromide) cm^{-1}: 3430 (sh.), 3300, 3130 (NH, OH); ^1H NMR (deuterochloroform): δ 1.27–2.17 (m, 10H, cyclohexyl-H), 2.59 (t, 2H, $J = 6.4$ Hz, H5), 2.56–3.00 (m, 1H, H1′), 3.40 (t, 2H, $J = 6.4$ Hz, H6), 3.68–3.91 (m, 5H, changed to 4H with addition of deuterium oxide, NCH_2CH_2O and NH or OH), 5.33 (br, 1H, deuterium oxide exchangeable, NH or OH), 7.36–7.85 (m, 4H, H8, 9, 10, and 11); EIMS *m/z*: 355 (M^+). *Anal*. Calcd. for $C_{20}H_{25}N_3OS$: C, 67.57; H, 7.09; N, 11.82. Found: C, 67.41; H, 6.99; N, 11.77.

4-(2-Hydroxyethylamino)-2-phenyl-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (3d). The reaction was refluxed for 30 h, and the product was recrystallized from acetonitrile to give **3d** (75%) as colorless needles, mp 207–208 °C; IR (potassium bromide) cm^{-1}: 3350, 3240 (sh.), 3140 (NH, OH); ^1H NMR (deuterochloroform): δ 2.69 (t, 2H, $J = 6.5$ Hz, H5), 3.46 (t, 2H, $J = 6.5$ Hz, H6), 3.67 (br, 1H, deuterium oxide exchangeable, NH or OH), 3.82–3.97 (m, 4H, NCH_2CH_2O), 5.34 (br, 1H, deuterium oxide exchangeable, NH or OH), 7.35–7.65 (m, 6H, H8, 9, 10 and 3′, 4′, 5′), 7.92 (dd, 1H, $J = 7.5$, 1.4 Hz, H11), 8.41–8.46 (m, 2H, H2′ and 6′); FAB MS *m/z*: 350 (MH^+). *Anal*. Calcd. for $C_{20}H_{19}N_3OS$: C, 68.74; H, 5.48; N, 12.02. Found: C, 68.75; H, 5.57; N, 12.07.

2-(4-Fluorophenyl)-4-(2-hydroxyethylamino)-5,6-dihydro[1] benzothiepino[5,4-d]pyrimidine (3e). The reaction was refluxed for 24 h, and the product was recrystallized from ethyl acetate to give **3e** (61%) as colorless needles, mp 186–189 °C; IR (potassium bromide) cm^{-1}: 3450, 3340, 3140 (NH, OH); ^1H NMR (deuterochloroform): δ 2.68 (t, 2H, $J = 6.3$ Hz, H5), 3.45 (br t, 3H, $J = 6.3$ Hz, changed to 2H (br t, $J = 6.3$ Hz) with addition of deuterium oxide, H6, NH or OH), 3.81–3.94 (m, 4H, NCH_2CH_2O), 5.34 (br, 1H, deuterium oxide exchangeable, NH or OH), 7.06–7.16 (m, 2H, H3′ and 5′), 7.39 (ddd, 1H, $J = 7.5$, 7.4, 1.7 Hz, H9), 7.54 (ddd, 1H, $J = 7.6$, 7.5, 1.4 Hz, H10), 7.63 (dd, 1H, $J = 7.4$, 1.4 Hz, H8), 7.89 (dd, 1H, $J = 7.6$, 1.7 Hz, H11), 8.41–8.48 (m, 2H, H2′ and 6′); EIMS *m/z*: 367 (M^+). *Anal*. Calcd. for $C_{20}H_{18}FN_3OS$: C, 65.38; H, 4.94; N, 11.44. Found: C, 65.41; H, 5.06; N, 11.42.

2-(4-Chlorophenyl)-4-(2-hydroxyethylamino)-5,6-dihydro[1] benzothiepino[5,4-d]pyrimidine (3f). The reaction was refluxed for 24 h, and the product was recrystallized from benzene to give **3f** (83%) as colorless needles, mp 162–165 °C; IR (potassium bromide) cm^{-1}: 3300, 3250 (NH, OH); ^1H NMR (deuterochloroform): δ 2.63 (t, 2H, $J = 6.5$ Hz, H5), 3.42 (t, 2H, $J = 6.5$ Hz, H6), 3.86 (br s, 5H, changed to 4H (br s) with addition of deuterium oxide, NCH_2CH_2O and NH or OH), 5.38 (br, 1H, deuterium oxide exchangeable, NH or OH), 7.32–7.70 (m, 5H, H8, 9, 10 and 3′, 5′), 7.81–7.97 (m, 1H, H11), 8.27–8.45 (m, 2H, H2′ and 6′); FAB MS *m/z*: 384 (MH^+), 386 ($MH^+ + 2$). *Anal*. Calcd. for $C_{20}H_{18}ClN_3OS$: C, 62.57; H, 4.73; N, 10.95. Found: C, 62.78; H, 4.87; N, 10.99.

4-(Hydroxyethylamino)-2-(4-methylphenyl)-5,6-dihydro[1] benzothiepino[5,4-d]pyrimidine (3g). The reaction was refluxed for 46 h, and the product was recrystallized from benzene to give **3g** (90%) as colorless needles, mp 172–174 °C; IR (potassium bromide) cm^{-1}: 3310, 3250 (NH, OH); ^1H NMR (deuterochloroform): δ 2.37 (s, 3H, CH_3), 2.58 (t, 2H, $J = 6.5$ Hz, H5), 3.37 (t, 2H, $J = 6.5$ Hz, H6), 3.81 (br s, 5H, changed to 4H (br s) with addition of deuterium oxide, NCH_2CH_2O and NH or OH), 5.36 (br, 1H, deuterium oxide exchangeable, NH or OH), 7.23 (d, 2H, $J = 8.2$ Hz, H3′ and 5′), 7.35–7.65 (m, 3H, 8, 9, and 10), 7.83–7.98 (m, 1H, H11), 8.30 (d, 2H, $J = 8.2$ Hz, H2′ and 6′);. FAB MS *m/z*: 364 (MH^+). *Anal*. Calcd. for $C_{21}H_{21}N_3OS$: C, 69.39; H, 5.82; N, 11.56. Found: C, 69.66; H, 6.00; N, 11.28.

4-(2-Hydroxyethylamino)-2-(4-methoxyphenyl)-5,6-dihydro[1] benzothiepino[5,4-d]pyrimidine (3h). The reaction was refluxed for 48 h, and the product was recrystallized from benzene to give **3h** (88%) as colorless plates, mp 103–107 °C; IR (potassium bromide) cm^{-1}: 3440, 3330 (NH, OH); ^1H NMR (deuterochloroform): δ 2.61 (t, 2H, $J = 6.4$ Hz, H5), 3.40 (t, 2H, $J = 6.4$ Hz, H6), 3.82 (br s, 8H, changed to 7H (br s) with addition of deuterium oxide, OCH_3, NCH_2CH_2O, and NH or OH), 5.33 (br, 1H, deuterium oxide exchangeable, NH or OH), 6.94 (d, 2H, $J = 9.4$ Hz, H3′ and 5′), 7.35–7.65 (m, 3H, H8, 9, and 10), 7.82–7.92 (m, 1H, H11), 8.38 (d, 2H, $J = 9.4$ Hz, H2′ and 6′); FAB MS *m/z*: 380 (MH^+). *Anal*. Calcd. for $C_{21}H_{21}N_3O_2S$: C, 66.47; H, 5.58; N, 11.07. Found: C, 66.40; H, 5.65; N, 11.26.

4-(2-Hydroxyethylamino)-2-(4-nitrophenyl)-5,6-dihydro[1] benzothiepino[5,4-d]pyrimidine (3i). The reaction was refluxed for 6 h, and the product was recrystallized from benzene to give **3i** (95%) as yellow needles, mp 211–213 °C; IR (potassium bromide) cm^{-1}: 3400 (br, NH and OH); ^1H NMR (deuterochloroform): δ 2.72 (t, 2H, $J = 6.0$ Hz, H5), 3.48 (t, 2H, $J = 6.0$ Hz, H6), 3.85–3.98 (m, 5H, changed to 4H (m) with addition of deuterium oxide, NCH_2CH_2O, and NH or OH), 5.43 (br, 1H, deuterium oxide exchangeable, NH or OH), 7.42 (ddd, 1H, $J = 7.5$, 7.0, 1.5 Hz, H9), 7.56 (ddd, 1H, $J = 7.5$, 7.0, 1.4 Hz, H10), 7.65 (dd, 1H, $J = 7.5$, 1.4 Hz, H8), 7.98 (dd, 1H, $J = 7.5$, 1.5 Hz, H11), 8.29 (d, 2H, $J = 9.0$ Hz, H3′ and 5′), 8.63 (d, 2H, $J = 9.0$ Hz, H2′ and 6′); FAB MS *m/z*: 395 (MH^+). *Anal*. Calcd. for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.97; H, 4.68; N, 13.92.

2-Substituted 4-(N-methyl-2-hydroxyethylamino)-5,6-dihydro [1]benzothiepino[5,4-d]pyrimidine (7a–i). General procedure. A mixture of compound **6a–i** (400 mg) and 2-methylaminoethanol (10 eq. of **6a–i**) in 1,4-dioxane (8.0 mL) was refluxed for the appropriate time. After removal of solvent in vacuo, ice water (40 mL) was poured into the residue. In the case of **7a–c**, the mixture was extracted with benzene (30 mL × 3). The combined organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated in vacuo. The residue was purified by recrystallization or column chromatography. In the case of **7d–i**, the precipitate that formed was collected by filtration and recrystallized from the appropriate solvent to give **7d–i**.

2-Methyl-4-(N-methyl-2-hydroxyethylamino)-5,6-dihydro[1] benzothiepino[5,4-d]pyrimidine (7a). The reaction was refluxed for 12 h, and the product was recrystallized from *n*-hexane to give

7a (51%) as colorless plates, mp 129–130 °C; IR (potassium bromide) cm^{-1}: 3150 (OH); ^1H NMR (deuterochloroform): δ 2.60 (s, 3H, 2-CH_3), 2.75 (t, 2H, *J* = 6.0 Hz, H5), 3.25 (s, 3H, NCH_3), 3.49 (t, 2H, *J* = 6.0 Hz, H6), 3.66–3.97 (m, 4H, NCH_2CH_2O), 7.37–7.73 (m, 4H, H8, 9, 10, and 11); FAB MS *m/z*: 302 (MH^+), High resolution FAB MS *m/z*: Calcd. for $C_{16}H_{20}N_3OS$: 302.1327. Found: 302.1334 (MH^+). *Anal*. Calcd. for $C_{16}H_{19}N_3OS{\cdot}4/5H_2O$: C, 60.85; H, 6.57; N, 13.31. Found: C, 60.45; H, 6.12; N, 13.11.

2-Ethyl-4-(N-methyl-2-hydroxyethylamino)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (7b). The reaction was refluxed for 11 h, and the product was recrystallized from acetonitrile to give **7b** (47%) as colorless plates, mp 143–145 °C; IR (potassium bromide) cm^{-1}: 3210 (OH); ^1H NMR (deuterochloroform): δ 1.36 (t, 3H, *J* = 7.6 Hz, CH_2CH_3), 2.75 (t, 2H, *J* = 6.4 Hz, H5), 2.86 (q, 2H, *J* = 7.6 Hz, CH_2CH_3), 3.25 (s, 3H, NCH_3), 3.50 (t, 2H, *J* = 6.4 Hz, H6), 3.72–3.96 (m, 4H, NCH_2CH_2O), 6.04 (br, 1H, deuterium oxide exchangeable, OH), 7.36–7.88 (m, 4H, H8, 9, 10, and 11); FAB MS *m/z*: 316 (MH^+). *Anal*. Calcd. for $C_{17}H_{21}N_3OS$: C, 64.73; H, 6.71; N, 13.32. Found: C, 64.68; H, 6.64; N, 13.29.

2-Cyclohexyl-4-(N-methyl-2-hydroxyethylamino)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (7c). The reaction was refluxed for 12 h, and the crude product was chromatographed on silica gel. The eluate of benzene-ethyl acetate (1:4) was evaporated in vacuo to give **7c** (62%) as a viscous oil. IR ($CHCl_3$) cm^{-1}: 3200 (OH); ^1H NMR (deuterochloroform): δ 1.22–2.17 (m, 10H, cyclohexyl-H), 2.75 (t, 2H, *J* = 6.0 Hz, H5), 2.78–3.00 (m, 1H, H1′), 3.26 (s, 3H, CH_3), 3.51 (d, 2H, *J* = 6.0 Hz, H6), 3.55–4.02 (m, 4H, NCH_2CH_2O), 7.31–7.86 (m, 4H, H8, 9, 10, and 11); FAB MS *m/z*: 370 (MH^+). *Anal*. Calcd. for $C_{21}H_{27}N_3OS{\cdot}1/2H_2O$: C, 66.63; H, 7.46; N, 11.10. Found: C, 66.83; H, 7.17; N, 10.99.

4-(N-Methyl-2-hydroxyethylamino)-2-phenyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (7d). The reaction was refluxed for 8 h, and the product was recrystallized from benzene-cyclohexane to give **7d** (84%) as colorless needles, mp 122–124 °C; IR (potassium bromide) cm^{-1}: 3350 (OH); ^1H NMR (deuterochloroform): δ 2.82 (t, 2H, *J* = 6.5 Hz, H5), 3.30 (s, 3H, CH_3), 3.53 (t, 2H, *J* = 6.5 Hz, H6), 3.77–4.10 (m, 4H, NCH_2CH_2O), 4.84 (br, 1H, deuterium oxide exchangeable, OH), 7.40–7.75 (m, 6H, H8, 9, 10 and 3′, 4′, 5′), 7.91–8.04 (m, 1H, H11), 8.34–8.50 (m, 2H, H2′ and 6′); FAB MS *m/z*: 364 (MH^+). *Anal*. Calcd. for $C_{21}H_{21}N_3OS$: C, 69.39; H, 5.82; N, 11.56. Found: C, 69.18; H, 5.75; N, 11.40.

2-(4-Fluorophenyl)-4-(N-methyl-2-hydroxyethylamino)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (7e). The reaction was refluxed for 13 h, and the product was recrystallized from benzene-cyclohexane to give **7e** (73%) as colorless needles, mp 161–163 °C; IR (potassium bromide) cm^{-1}: 3200 (OH); ^1H NMR (deuterochloroform): δ 2.82 (t, 2H, *J* = 5.8 Hz, H5), 3.30 (s, 3H, CH_3), 3.53 (t, 2H, *J* = 5.8 Hz, H6), 3.84–4.05 (m, 4H, NCH_2CH_2O), 4.69 (br, 1H, deuterium oxide exchangeable, OH), 6.97–7.65 (m, 5H, H8, 9, 10 and 3′, 5′), 7.86–7.97 (m, 1H, H11), 8.30–8.55 (m, 2H, H2′ and 6′); FAB MS *m/z*: 382 (MH^+). *Anal*. Calcd. for $C_{21}H_{20}FN_3OS$: C, 66.12; H, 5.28; N, 11.02. Found: C, 66.28; H, 5.38, N, 10.77.

2-(4-Chlorophenyl)-4-(N-methyl-2-hydroxyethylamino)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (7f). The reaction was refluxed for 6 h, and the product was recrystallized from benzene to give **7f** (74%) as colorless needles, mp 155–157 °C; IR (potassium bromide) cm^{-1}: 3290 (OH); ^1H NMR (deuterochloroform): δ 2.82 (t, 2H, *J* = 6.0 Hz, H5), 3.31 (s, 3H, CH_3), 3.54 (t, 2H, *J* = 6.0 Hz, H6), 3.76–4.13 (m, 4H, NCH_2CH_2O), 4.54 (br, 1H, deuterium oxide exchangeable, OH), 7.41–7.71 (m, 3H, H8, 9, and 10), 7.42 (d, 2H, *J* = 8.8 Hz, H3′ and 5′), 7.86–8.01 (m, 1H, H11), 8.36 (d, 2H, *J* = 8.8 Hz, H2′ and 6′); FAB MS *m/z*: 398 (MH^+), 400 ($MH^+ + 2$). *Anal*. Calcd. for $C_{21}H_{20}ClN_3OS$: C, 63.39; H, 5.07; N, 10.56. Found: C, 63.56; H, 5.20; N, 10.58.

4-(N-Methyl-2-hydroxyethylamino)-2-(4-methylphenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (7g). The reaction was refluxed for 9 h, and the product was recrystallized from cyclohexane to give **7g** (75%) as colorless needles, mp 143–144 °C; IR (potassium bromide) cm^{-1}: 3380 (OH); ^1H NMR (deuterochloroform): δ 2.39 (s, 3H, tolyl-CH_3), 2.81 (t, 2H, *J* = 6.4 Hz, H5), 3.29 (s, 3H, NCH_3), 3.53 (t, 2H, *J* = 6.4 Hz, H6), 3.84–4.04 (m, 4H, NCH_2CH_2O), 4.95 (br, 1H, deuterium oxide exchangeable, OH), 7.26 (d, 2H, *J* = 8.2 Hz, H3′ and 5′), 7.40–7.70 (m, 3H, H8, 9, and 10), 7.87–7.98 (m, 1H, H11), 8.30 (d, 2H, *J* = 8.2 Hz, H2′ and 6′); FAB MS *m/z*: 378 (MH^+). *Anal*. Calcd. for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13. Found: C, 69.94; H, 6.12; N, 11.14.

2-(4-Methoxyphenyl)-4-(N-methyl-2-hydroxyethylamino)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (7h). The reaction was refluxed for 10 h, and the product was recrystallized from benzene-cyclohexane to give **7h** (68%) as colorless needles, mp 152–154 °C; IR (potassium bromide) cm^{-1}: 3200 (OH); ^1H NMR (deuterochloroform): δ 2.81 (t, 2H, *J* = 6.0 Hz, H5), 3.29 (s, 3H, NCH_3), 3.53 (t, 2H, *J* = 6.0 Hz, H6), 3.76–4.09 (m, 4H, NCH_2CH_2O), 3.86 (s, 3H, OCH_3), 5.06 (br, 1H, deuterium oxide exchangeable, OH), 6.98 (d, 2H, *J* = 8.8 Hz, H3′ and 5′), 7.36–7.75 (m, 3H, H8, 9, and 10), 7.82–7.97 (m, 1H, H11), 8.38 (d, 2H, *J* = 8.8 Hz, H2′ and 6′); FAB MS *m/z*: 394 (MH^+). *Anal*. Calcd. for $C_{22}H_{23}N_3O_2S$: C, 67.15; H, 5.89; N, 10.68. Found: C, 67.06; H, 5.91; N, 10.53.

4-(N-Methyl-2-hydroxyethylamino)-2-(4-nitrophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (7i). The reaction was refluxed for 2 h, and the product was recrystallized from benzene-cyclohexane to give **7i** (79%) as yellow needles, mp 148–150 °C; IR (potassium bromide) cm^{-1}: 3400 (OH); ^1H NMR (deuterochloroform): δ 2.86 (t, 2H, *J* = 6.0 Hz, H5), 3.34 (s, 3H, NCH_3), 3.56 (t, 2H, *J* = 6.0 Hz, H6), 3.76–4.16 (m, 5H, changed to 4H with addition of deuterium oxide, OH and NCH_2CH_2O), 7.39–7.78 (m, 3H, H8, 9, and 10), 7.88–8.01 (m, 1H, H11), 8.26 (d, 2H, *J* = 9.0 Hz, H3′ and 5′), 8.60 (d, 2H, *J* = 9.0 Hz, H2′ and 6′); FAB MS *m/z*: 409 (MH^+). *Anal*. Calcd. for $C_{21}H_{20}N_4O_3S$: C, 61.75; H, 4.94; N, 13.72. Found: C, 61.45; H, 4.96; N, 13.60.

2-Substituted 4-dimethylamino-5,6-dihydro[1]benzothieno[5,4-d]pyrimidine (8a–i). General procedure. A mixture of compound **6a–i** (100 mg), 50% aqueous dimethylamine (2.0 mL) and diethyl ether (2.0 mL) was stirred at room temperature for the appropriate time. The reaction mixture was evaporated in vacuo, and ice water (30 mL) was poured into the residue. The mixture was extracted with chloroform (30 mL × 3). The combined organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue was recrystallized from a suitable solvent or purified by silica gel column chromatography.

2-Methyl-4-dimethylamino-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (8a). The reaction was stirred for 1 h, and the product was recrystallized from acetonitrile to give **8a** (85%) as colorless needles, mp 94–97 °C; ^1H NMR (deuterochloroform): δ 2.60 (s, 3H, 2-CH_3), 2.73 (t, 2H, *J* = 8.0 Hz, H5), 3.13 (s, 6H, $N(CH_3)_2$), 3.50 (t, 2H, *J* = 8.0 Hz, H6), 7.35–7.51 (m, 4H, H8,

9, 10, and 11); EIMS *m/z*: 271 (M^+). *Anal*. Calcd. for $C_{15}H_{17}N_3S$: C, 66.39; H, 6.31; N, 15.48. Found: C, 66.61; H, 6.38; N, 15.46.

2-Ethyl-4-dimethylamino-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (8b). The reaction was stirred for 2 h, and the product was chromatographed on silica gel. The eluate of benzene-ethyl acetate (9:1) was evaporated in vacuo to give **8b** (94%) as a colorless viscous oil. ^{1}H NMR (deuterochloroform): δ 1.37 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.66–2.80 (q, 2H, J = 7.0 Hz, CH_2CH_3), 2.83 (t, 2H, J = 5.8 Hz, H5), 3.14 (s, 6H, $N(CH_3)_2$), 3.49 (t, 2H, J = 5.8 Hz, H6), 7.40–7.73 (m, 4H, H8, 9, 10, and 11); EIMS *m/z*: 285 (M^+). *Anal*. Calcd. for $C_{16}H_{19}N_3S$: C, 67.33; H, 6.71; N, 14.72. Found: C, 67.58; H, 6.69; N, 14.63.

2-Cyclohexyl-4-dimethylamino-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (8c). The reaction was stirred for 6 h, and the product was chromatographed on silica gel. The eluate of benzene was evaporated in vacuo to give **8c** (93%) as a colorless viscous oil. ^{1}H NMR (deuterochloroform): δ 1.26–2.29 (m, 10H, cyclohexyl-H), 2.73 (t, 2H, J = 6.4 Hz, H5), 2.58–2.90 (m, 1H, H1′), 3.14 (s, 6H, $N(CH_3)_2$), 3.50 (t, 2H, J = 6.4 Hz, H6), 7.32–7.90 (m, 4H, H8, 9, 10, and 11); EIMS *m/z*: 339 (M^+). *Anal*. Calcd. for $C_{20}H_{25}N_3S$: C, 70.76; H, 7.42; N, 12.38. Found: C, 70.88; H, 7.38; N, 12.41.

4-Dimethylamino-2-phenyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (8d). The reaction was stirred for 3 h, and the product was recrystallized from cyclohexane to give **8d** (95%) as colorless needles, mp 133–136 °C; ^{1}H NMR (deuterochloroform): δ 2.79 (t, 2H, J = 6.0 Hz, H5), 3.22 (s, 6H, $N(CH_3)_2$), 3.53 (t, 2H, J = 6.0 Hz, H6), 7.18–7.74 (m, 6H, H8, 9, 10 and 3′, 4′, 5′), 7.89–8.04 (m, 1H, H11), 8.45–8.60 (m, 2H, H2′ and 6′); EIMS *m/z*: 333 (M^+). *Anal*. Calcd. for $C_{20}H_{19}N_3S$: C, 72.04; H, 5.74; N, 12.60. Found: C, 72.15; H, 5.84; N, 12.72.

2-(4-Fluorophenyl)-4-dimethylamino-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (8e). The reaction was stirred for 2 h, and the product was recrystallized from cyclohexane to give **8e** (63%) as colorless plates, mp 137–139 °C; ^{1}H NMR (deuterochloroform): δ 2.79 (t, 2H, J = 7.0 Hz, H5), 3.22 (s, 6H, $N(CH_3)_2$), 3.53 (t, 2H, J = 7.0 Hz, H6), 6.96–7.74 (m, 5H, H8, 9, 10 and 3′, 5′), 7.85–8.02 (m, 1H, H11), 8.40–8.64 (m, 2H, H2′ and 6′); EIMS *m/z*: 351 (M^+). *Anal*. Calcd. for $C_{20}H_{18}FN_3S$: C, 68.35; H, 5.16; N, 11.96. Found: C, 68.55; H, 5.44; N, 11.96.

2-(4-Chlorophenyl)-4-dimethylamino-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (8f). The reaction was stirred for 2 h, and the product was recrystallized from acetonitrile to give **8f** (73%) as colorless plates, mp 143–145 °C; ^{1}H NMR (deuterochloroform): δ 2.80 (t, 2H, J = 5.8 Hz, H5), 3.22 (s, 6H, $N(CH_3)_2$), 3.53 (t, 2H, J = 5.8 Hz, H6), 7.40 (d, 2H, J = 8.2 Hz, H3′ and 5′), 7.47–7.65 (m, 3H, H8, 9, and 10), 7.85–7.97 (m, 1H, H11), 8.47 (d, 2H, J = 8.2 Hz, H2′ and 6′); EIMS *m/z*: 367 (M^+), 369 ($M^+ + 2$). *Anal*. Calcd. for $C_{20}H_{18}ClN_3S$: C, 65.29; H, 4.93; N, 11.42. Found: C, 65.49; H, 5.12; N, 11.37.

4-Dimethylamino-2-(4-methylphenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (8g). The reaction was stirred for 5 h, and the product was recrystallized from ethyl acetate to give **8g** (79%) as colorless prisms, mp 159–161 °C; ^{1}H NMR (deuterochloroform): δ 2.40 (s, 3H, CH_3), 2.79 (t, 2H, J = 5.8 Hz, H5), 3.21 (s, 6H, $N(CH_3)_2$), 3.52 (t, 2H, J = 5.8 Hz, H6), 7.25 (d, 2H, J = 8.0 Hz, H3′ and 5′), 7.44–7.69 (m, 3H, H8, 9, and 10), 7.87–8.03 (m, 1H, H11), 8.39 (d, 2H, J = 8.0 Hz, H2′ and 6′); EIMS *m/z*: 347 (M^+). *Anal*. Calcd. for $C_{21}H_{21}N_3S$: C, 72.59; H, 6.09; N, 12.09. Found: C, 72.73; H, 6.10; N, 12.11.

4-Dimethylamino-2-(4-methoxyphenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (8h). The reaction was stirred for 6 h, and the product was recrystallized from *n*-hexane to give **8h** (34%) as colorless plates, mp 138–140 °C; ^{1}H NMR (deuterochloroform): δ 2.78 (t, 2H, J = 7.0 Hz, H5), 3.21 (s, 6H, $N(CH_3)_2$), 3.53 (t, 2H, J = 7.0 Hz, H6), 3.87 (s, 3H, OCH_3), 6.96 (d, 2H, J = 9.0 Hz, H3′ and 5′), 7.39–7.68 (m, 3H, H8, 9, and 10), 7.88–8.02 (m, 1H, H11), 8.48 (d, 2H, J = 9.0 Hz, H2′ and 6′); EIMS *m/z*: 363 (M^+). *Anal*. Calcd. for $C_{21}H_{21}N_3OS$: C, 69.39; H, 5.82; N, 11.56. Found: C, 69.58; H, 5.85; N, 11.64.

4-Dimethylamino-2-(4-nitrophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (8i). The reaction was stirred for 1 h, and the product was recrystallized from ethyl acetate to give **8i** (76%) as yellow needles, mp 213–215 °C; ^{1}H NMR (deuterochloroform): δ 2.83 (t, 2H, J = 6.0 Hz, H5), 3.26 (s, 6H, $N(CH_3)_2$), 3.56 (t, 2H, J = 6.0 Hz, H6), 7.42–7.77 (m, 3H, H8, 9, and 10), 7.87–8.02 (m, 1H, H11), 8.27 (d, 2H, J = 8.8 Hz, H3′ and 5′), 8.69 (d, 2H, J = 8.8 Hz, H2′ and 6′); FAB MS *m/z*: 379 (MH^+). *Anal*. Calcd. for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N, 14.80. Found: C, 63.46; H, 4.75; N, 14.62.

2-Substituted 4-morpholino-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (9a–i). General procedure. To a mixture of **6a–i** (100 mg) in dry 1,4-dioxane (2.0 mL) was added morpholine (10 eq. of **6a–i**), and the reaction mixture was refluxed for the appropriate time. Ice water (30 mL) was poured into the reaction mixture, and the resulting solid (except for **9c**) was collected on a filter. The precipitate was recrystallized from a suitable solvent to give **9a–i**.

2-Methyl-4-morpholino-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (9a). The reaction mixture was refluxed for 24 h, and the product was recrystallized from cyclohexane to give **9a** (74%) as colorless prisms, mp 180–182 °C; ^{1}H NMR (deuterochloroform): δ 2.65 (s, 3H, CH_3), 2.74 (t, 2H, J = 6.4 Hz, H5), 3.35–3.54 (m, 6H, H6 and 3′, 5′), 3.78–3.93 (m, 4H, H2′ and 6′), 7.32–7.83 (m, 4H, H8, 9, 10, and 11); EIMS *m/z*: 313 (M^+). *Anal*. Calcd. for $C_{17}H_{19}N_3OS$: C, 65.15; H, 6.11; N, 13.41. Found: C, 64.92; H, 6.01; N, 13.16.

2-Ethyl-4-morpholino-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (9b). The reaction was refluxed for 24 h, and the product was recrystallized from methanol to give **9b** (65%) as colorless plates, mp 152–154 °C; ^{1}H NMR (deuterochloroform): δ 1.37 (t, 3H, J = 7.6 Hz, CH_3), 2.63–3.10 (m, 4H, H5 and CH_2CH_3), 3.35–3.55 (m, 6H, H6 and 3′, 5′), 3.79–3.94 (m, 4H, H2′ and 6′), 7.32–7.85 (m, 4H, H8, 9, 10, and 11); EIMS *m/z*: 327 (M^+). *Anal*. Calcd. for $C_{18}H_{21}N_3OS$: C, 66.02; H, 6.46; N, 12.83. Found: C, 65.74; H, 6.37; N, 12.78.

2-Cyclohexyl-4-morpholino-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (9c). The reaction was refluxed for 24 h. In this case, the resulting oily residue was chromatographed on silica gel. The eluate of benzene-ethyl acetate (19:1) was evaporated in vacuo to give **9c** (83%) as a colorless viscous oil, ^{1}H NMR (deuterochloroform): δ 1.26–2.17 (m, 10H, cyclohexyl-H), 2.73 (t, 2H, J = 6.4 Hz, H5), 2.65–3.05 (m, 1H, H1′), 3.36–3.56 (m, 6H, H6 and morpholino-3′, 5′), 3.78–3.94 (m, 4H, morpholino-2′ and 6′), 7.36–7.82 (m, 4H, H8, 9, 10, and 11); EIMS *m/z*: 381 (M^+). *Anal*. Calcd. for $C_{22}H_{27}N_3OS \cdot 1/4H_2O$: C, 68.45; H, 7.18; N, 10.88. Found: C, 68.74; H, 7.17; N, 10.72.

4-Morpholino-2-phenyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (9d). The reaction was refluxed for 24 h, and the product was recrystallized from ethanol to give **9d** (83%) as colorless needles, mp 191–192 °C; ^{1}H NMR (deuterochloroform): δ 2.82 (t, 2H, J = 6.4 Hz, H5), 3.40–3.65 (m, 6H, H6 and

morpholino-3′, 5′), 3.84–3.98 (m, 4H, morpholino-2′ and 6′), 7.39–7.69 (m, 6H, H8, 9, 10 and phenyl-3′, 4′, 5′), 7.85–8.00 (m, 1H, H11), 8.44–8.59 (m, 2H, phenyl-2′ and 6′); EIMS *m/z*: 375 (M^+). *Anal*. Calcd. for $C_{22}H_{21}N_3OS$: C, 70.37; H, 5.64; N, 11.19. Found: C, 70.27; H, 5.75; N, 10.94.

2-(4-Fluorophenyl)-4-morpholino-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (9e). The reaction was refluxed for 24 h, and the product was recrystallized from ethanol-ethyl acetate to give **9e** (70%) as colorless prisms, mp 234–235 °C; ^{1}H NMR (deuterochloroform): δ 2.81 (t, 2H, *J* = 6.4 Hz, H5), 3.40–3.63 (m, 6H, H6 and morpholino-3′, 5′), 3.84–3.98 (m, 4H, morpholino-2′ and 6′), 6.97–7.76 (m, 5H, H8, 9, 10 and fluorophenyl-3′, 5′), 7.83–7.97 (m, 1H, H11), 8.39–8.63 (m, 2H, fluorophenyl-2′ and 6′); EIMS *m/z*: 393 (M^+). *Anal*. Calcd. for $C_{22}H_{20}FN_3OS$: C, 67.15; H, 5.12; N, 10.68. Found: C, 67.16; H, 5.24; N, 10.60.

2-(4-Chlorophenyl)-4-morpholino-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (9f). The reaction was refluxed for 9 h, and the product was recrystallized from ethyl acetate to give **9f** (55%) as colorless prisms, mp 226–228 °C; ^{1}H NMR (deuterochloroform): δ 2.82 (t, 2H, *J* = 6.4 Hz, H5), 3.41–3.64 (m, 6H, H6 and morpholino-3′, 5′), 3.84–3.94 (m, 4H, morpholino-2′ and 6′), 7.34–7.76 (m, 5H, H8, 9, 10 and chlorophenyl-3′, 5′), 7.83–7.99 (m, 1H, H11), 8.46 (d, 2H, *J* = 8.1 Hz, chlorophenyl-2′ and 6′); EIMS *m/z*: 409 (M^+), 411 ($M^+ + 2$). *Anal*. Calcd. for $C_{22}H_{20}ClN_3OS$: C, 64.46; H, 4.92; N, 10.25. Found: C, 64.37; H, 5.08; N, 10.12.

2-(4-Methylphenyl)-4-morpholino-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (9g). The reaction was refluxed for 47 h, and the product was recrystallized from ethanol to give **9g** (58%) as colorless needles, mp 176–178 °C; ^{1}H NMR (deuterochloroform): δ 2.41 (s, 3H, CH_3), 2.81 (t, 2H, *J* = 6.4 Hz, H5), 3.39–3.63 (m, 6H, H6 and morpholino-3′, 5′), 3.83–3.97 (m, 4H, morpholino-2′ and 6′), 7.26 (d, 2H, *J* = 8.2 Hz, tolyl-3′ and 5′), 7.39–7.65 (m, 3H, H8, 9, and 10), 7.84–7.99 (m, 1H, H11), 8.40 (d, 2H, *J* = 8.2 Hz, tolyl-2′ and 6′); EIMS *m/z*: 389 (M^+). *Anal*. Calcd. for $C_{23}H_{23}N_3OS$: C, 70.92; H, 5.95; N, 10.79. Found: C, 71.14; H, 5.97; N, 10.80.

2-(4-Methoxyphenyl)-4-morpholino-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (9h). The reaction was refluxed for 24 h, and the product was recrystallized from ethanol to give **9h** (63%) as colorless needles, mp 167–168 °C; ^{1}H NMR (deuterochloroform): δ 2.80 (t, 2H, *J* = 6.4 Hz, H5), 3.38–3.63 (m, 6H, H6 and morpholino-3′, 5′), 3.84–3.97 (m, 7H, OCH_3 and morpholino-2′, 6′), 6.97 (d, 2H, *J* = 8.8 Hz, methoxyphenyl-3′ and 5′), 7.45–7.82 (m, 4H, H8, 9, 10, and 11), 8.46 (d, 2H, *J* = 8.8 Hz, methoxyphenyl-2′ and 6′); EIMS *m/z*: 405 (M^+). *Anal*. Calcd. for $C_{23}H_{23}N_3O_2S$: C, 68.12; H, 5.72; N, 10.36. Found: C, 67.96; H, 5.89; N, 10.30.

4-Morpholino-2-(4-nitrophenyl)-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine (9i). The reaction was refluxed for 5 h, and the product was recrystallized from benzene to give **9i** (64%) as yellow needles, mp 274–276 °C; ^{1}H NMR (deuterochloroform): δ 2.85 (t, 2H, *J* = 6.4 Hz, H5), 3.42–3.68 (m, 6H, H6 and morpholino-3′, 5′), 3.86–4.01 (m, 4H, morpholino-2′ and 6′), 7.49–7.85 (m, 4H, H8, 9, 10, and 11), 8.28 (d, 2H, *J* = 9.3 Hz, nitrophenyl-3′ and 5′), 8.68 (d, 2H, *J* = 9.3 Hz, nitrophenyl-2′ and 6′); EIMS *m/z*: 420 (M^+). *Anal*. Calcd. for $C_{22}H_{20}N_4O_3S$: C, 62.84; H, 4.79; N, 13.32. Found: C, 62.57; H, 4.90; N, 13.13.

2-Substituted 4-chloro-5,6-dihydro[1]benzothiepino[5,4-d] pyrimidine 7-oxide (10a–i). General procedure. To a solution of compound **6a–i** (100 mg) in dichloromethane (2.0 mL) were added 31% aqueous hydrogen peroxide (1.2 eq. of **6a–i**) and formic acid (4.0 eq. of **6a–i**), and the reaction was then stirred at room temperature for the appropriate time. Water (40 mL) was added and the mixture was extracted with dichloromethane (30 mL × 3). The combined organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel. The eluate of benzene-ethyl acetate (1:1) was evaporated in vacuo. The residue was recrystallized from a suitable solvent to give **10a–i**.

4-Chloro-2-methyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7-oxide (10a). The reaction was stirred for 8 h, and the product was recrystallized from benzene-cyclohexane to give **10a** (67%) as colorless plates, mp 210–211 °C; IR (potassium bromide) cm^{-1}: 1030 (SO); ^{1}H NMR (deuterochloroform): δ 2.77 (s, 3H, CH_3), 2.72–3.37 (m, 3H, H5 and one of H6), 4.03–4.54 (m, 1H, one of H6), 7.73–8.12 (m, 4H, H8, 9, 10, and 11); FAB MS *m/z*: 279 (MH^+), 281 ($MH^+ + 2$). *Anal*. Calcd. for $C_{13}H_{11}ClN_2OS$: C, 56.01; H, 3.98; N, 10.05. Found: C, 55.94; H, 4.04; N, 10.00.

4-Chloro-2-ethyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7-oxide (10b). The reaction was stirred for 5 h, and the product was recrystallized from cyclohexane to give **10b** (54%) as colorless prisms, mp 136–137 °C; IR (potassium bromide) cm^{-1}: 1030 (SO); ^{1}H NMR (deuterochloroform): δ 1.43 (t, 3H, *J* = 7.6 Hz, CH_3), 2.70–2.77 (m, 1H, one of H5), 3.03 (q, 2H, *J* = 7.6 Hz, CH_2CH_3), 3.18–3.22 (m, 1H, one of H5), 3.29–3.33 (m, 1H, one of H6), 4.25–4.31 (m, 1H, one of H6), 7.71 (dd, 1H, *J* = 7.6, 7.6 Hz, H10), 7.80 (dd, 1H, *J* = 7.6, 7.5 Hz, H9), 7.86 (d, 1H, *J* = 7.5 Hz, H8), 8.03 (d, 1H, *J* = 7.6 Hz, H11); FAB MS *m/z*: 293 (MH^+), 295 ($MH^+ + 2$). *Anal*. Calcd. for $C_{14}H_{13}ClN_2OS$: C, 57.43; H, 4.48; N, 9.57. Found: C, 57.53; H, 4.50; N, 9.61.

4-Chloro-2-cyclohexyl-5,6-dihydro[1]benzothiepino[5,4-d] pyrimidine 7-oxide (10c). The reaction was stirred for 5 h, and the product was recrystallized from *n*-hexane to give **10c** (51%) as colorless needles, mp 160–161 °C; IR (potassium bromide) cm^{-1}: 1035 (SO); ^{1}H NMR (deuterochloroform): δ 1.20–2.39 (m, 10H, cyclohexyl-H), 2.70–3.60 (m, 4H, H5, one of H6, and H1′), 4.08–4.44 (m, 1H, one of H6), 7.69–8.12 (m, 4H, H8, 9, 10, and 11); FAB MS *m/z*: 347 (MH^+), 349 ($MH^+ + 2$); High resolution FAB MS *m/z*: Calcd. for $C_{18}H_{20}ClN_2OS$: 347.0985. Found: 347.0936 (MH^+). *Anal*. Calcd. for $C_{18}H_{19}ClN_2OS \cdot 1/6n$-hexane: C, 63.18; H, 5.94; N, 7.76. Found: C, 63.53; H, 5.99; N, 8.16.

4-Chloro-2-phenyl-5,6-dihydro[1]benzothiepino[5,4-d] pyrimidine 7-oxide (10d). The reaction was stirred for 7 h, and the product was recrystallized from benzene-cyclohexane to give **10d** (66%) as colorless needles, mp 201–203 °C; IR (potassium bromide) cm^{-1}: 1035 (SO); ^{1}H NMR (deuterochloroform): δ 2.59–3.54 (m, 3H, H5 and one of H6), 4.08–4.53 (m, 1H, one of H6), 7.45–7.56 (m, 3H, H3′, 4′, and 5′), 7.70–8.15 (m, 4H, H8, 9, 10, and 11), 8.36–8.59 (m, 2H, H2′ and 6′); FAB MS *m/z*: 341 (MH^+), 343 ($MH^+ + 2$). *Anal*. Calcd. for $C_{18}H_{13}ClN_2OS$: C, 63.43; H, 3.84; N, 8.22. Found: C, 63.18; H, 3.90; N; 8.06.

4-Chloro-2-(4-fluorophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7-oxide (10e). The reaction was stirred for 8 h, and the product was recrystallized from benzene-cyclohexane to give **10e** (78%) as colorless needles, mp 217–218 °C; IR (potassium bromide) cm^{-1}: 1035 (SO); ^{1}H NMR (deuterochloroform): δ 2.71–3.88 (m, 3H, H5 and one of H6), 4.07–4.37 (m, 1H, one of H6), 7.02–7.31 (m, 2H, H3′ and 5′), 7.73–8.15 (m, 4H, H8, 9, 10, and 11), 8.40–8.64 (m, 2H, H2′ and 6′); FAB MS *m/z*: 359 (MH^+), 361 ($MH^+ + 2$). *Anal*. Calcd. for $H_{18}H_{12}ClFN_2OS$: C, 60.25; H, 3.37; N, 7.81. Found: C, 60.12; H, 3.51; N, 7.74.

4-Chloro-2-(4-chlorophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7-oxide (10f). The reaction was stirred for 6 h, and

the product was recrystallized from benzene-cyclohexane to give **10f** (79%) as colorless needles, mp 216–218 °C; IR (potassium bromide) cm^{-1}: 1035 (SO); ^1H NMR (deuterochloroform): δ 2.83–3.53 (m, 3H, H5 and one of H6), 4.25–4.44 (m, 1H, one of H6), 7.46 (d, 2H, *J* = 8.8 Hz, H3′ and 5′), 7.69–8.15 (m, 4H, H8, 9, 10, and 11), 8.45 (d, 2H, *J* = 8.8 Hz, H2′ and 6′); FAB MS *m/z*: 375 (MH^+), 377 ($MH^+ + 2$), 379 ($MH^+ + 4$). *Anal*. Calcd. for $C_{18}H_{12}Cl_2N_2OS$: C, 57.61; H, 3.22; N, 7.46. Found: C, 57.38; H, 3.34; N, 7.48.

4-Chloro-2-(4-methylphenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7-oxide (10g). The reaction was stirred for 9 h, and the product was recrystallized from benzene-cyclohexane to give **10g** (80%) as colorless needles, mp 213–214 °C; IR (potassium bromide) cm^{-1}: 1035 (SO); ^1H NMR (deuterochloroform): δ 2.43 (s, 3H, CH_3), 2.66–3.52 (m, 3H, H5 and one of H6), 4.07–4.45 (m, 1H, one of H6), 7.30 (d, 2H, *J* = 8.2 Hz, H3′ and 5′), 7.70–8.10 (m, 4H, H8, 9, 10, and 11), 8.39 (d, 2H, *J* = 8.2 Hz, H2′ and 6′); FAB MS *m/z*: 355 (MH^+), 357 ($MH^+ + 2$). *Anal*. Calcd. for $C_{19}H_{15}ClN_2OS$: C, 64.31; H, 4.26; N, 7.89. Found: C, 64.26; H, 4.30; N, 7.79.

4-Chloro-2-(4-methoxyphenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7-oxide (10h). The reaction was stirred for 5 h, and the product was recrystallized from benzene-cyclohexane to give **10h** (77%) as colorless needles, mp 203–205 °C; IR (potassium bromide) cm^{-1}: 1035 (SO); ^1H NMR (deuterochloroform): δ 2.97–3.51 (m, 3H, H5 and one of H6), 3.89 (s, 3H, OCH_3), 4.07–4.38 (m, 1H, one of H6), 6.98 (d, 2H, *J* = 9.0 Hz, H3′ and 5′), 7.67–8.15 (m, 4H, H8, 9, 10, and 11), 8.45 (d, 2H, *J* = 9.0 Hz, H2′ and 6′); FAB MS *m/z*: 371 (MH^+), 373 ($MH^+ + 2$). *Anal*. Calcd. for $C_{19}H_{15}ClN_2O_2S$: C, 61.53; H, 4.08; N, 7.55. Found: C, 61.42; H, 4.15; N, 7.52.

4-Chloro-2-(4-nitrophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7-oxide (10i). The reaction was stirred for 5 h, and the product was recrystallized from benzene to give **11i** (64%) as yellow needles, mp 236–238 °C; IR (potassium bromide) cm^{-1}: 1035 (SO); ^1H NMR (deuterochloroform): δ 2.78–3.60 (m, 3H, H5 and one of H6), 4.07–4.57 (m, 1H, one of H6), 7.72–8.15 (m, 4H, H8, 9, 10, and 11), 8.32 (d, 2H, *J* = 9.0 Hz, H3′ and 5′), 8.71 (d, 2H, *J* = 9.0 Hz, H2′ and 6′); FAB MS *m/z*: 386 (MH^+), 388 ($MH^+ + 2$). *Anal*. Calcd. for $C_{18}H_{12}ClN_3O_3S$: C, 56.03; H, 3.13; N, 10.89. Found: C, 55.86; H, 3.27; N, 10.78.

2-Substituted 4-chloro-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7,7-dioxide (11a–i). General procedure. To a solution of potassium permanganate (2.7 eq. of **6a–i**) in acetic acid (6.0 mL) and water (1.0 mL) was added **6a–i** (100 mg), and the reaction mixture was stirred at room temperature for the appropriate time. Sat. sodium hydrogen sulfite aq. was added to the reaction mixture under cooling to dissolve generated manganese dioxide. The crystalline precipitate was collected by filtration and recrystallized from a suitable solvent to give **11a–i**.

4-Chloro-2-methyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7,7-dioxide (11a). The reaction was stirred for 2 h, and the product was recrystallized from ethanol to give **11a** (62%) as colorless plates, mp 219–221 °C; IR (potassium bromide) cm^{-1}: 1308, 1151 (SO_2); ^1H NMR (deuterochloroform): δ 2.78 (s, 3H, CH_3), 3.16 (t, 2H, *J* = 5.8 Hz, H5), 3.84 (t, 2H, *J* = 5.8 Hz, H6), 7.75–7.96 (m, 3H, H8, 9, and 10), 8.11–8.22 (m, 1H, H11); FAB MS *m/z*: 295 (MH^+), 297 ($MH^+ + 2$). *Anal*. Calcd. for $C_{13}H_{11}ClN_2O_2S$: C, 52.97; H, 3.76; N, 9.50. Found: C, 53.13; H, 3.80; N, 9.50.

4-Chloro-2-ethyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7,7-dioxide (11b). The reaction was stirred for 2 h, and the product was recrystallized from ethanol to give **11b** (54%) as colorless plates, mp 158–159 °C; IR (potassium bromide) cm^{-1}: 1305, 1150 (SO_2); ^1H NMR (deuterochloroform): δ 1.41 (t, 3H, *J* = 7.7 Hz, CH_3), 3.04 (q, 2H, *J* = 7.7 Hz, CH_2CH_3), 3.18 (t, 2H, *J* = 6.6 Hz, H5), 3.84 (t, 2H, *J* = 6.6 Hz, H6), 7.72 (ddd, 1H, *J* = 7.5, 7.4, 1.6 Hz, H10), 7.85 (ddd, 1H, *J* = 7.6, 7.5, 1.4 Hz, H9), 7.94 (dd, 1H, *J* = 7.6, 1.6 Hz, H8), 8.16 (dd, 1H, *J* = 7.4, 1.4 Hz, H11); FAB MS *m/z*: 309 (MH^+), 311 ($MH^+ + 2$). *Anal*. Calcd. for $C_{14}H_{13}ClN_2O_2S$: C, 54.46; H, 4.24; N, 9.07. Found: C, 54.64; H, 4.26; N, 9.10.

4-Chloro-2-cyclohexyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7,7-dioxide (11c). The reaction was stirred for 2 h, and the product was recrystallized from ethanol to give **11c** (37%) as colorless plates, mp 185–187 °C; IR (potassium bromide) cm^{-1}: 1310, 1150 (SO_2); ^1H NMR (deuterochloroform): δ 1.26–2.28 (m, 10H, cyclohexyl-H), 2.70–3.38 (m, 3H, H5 and 1′), 3.83 (t, 2H, *J* = 7.0 Hz, H6), 7.77–8.00 (m, 3H, H8, 9, and 10), 8.09–8.24 (m, 1H, H11); FAB MS *m/z*: 363 (MH^+), 365 ($MH^+ + 2$). *Anal*. Calcd. for $C_{18}H_{19}ClN_2O_2S$: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.74; H, 5.30; N, 7.73.

4-Chloro-2-phenyl-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7,7-dioxide (11d). The reaction was stirred for 1 h, and the product was recrystallized from ethanol to give **11d** (47%) as colorless needles, mp 223–225 °C; IR (potassium bromide) cm^{-1}: 1312, 1155 (SO_2); ^1H NMR (deuterochloroform): δ 3.21 (t, 2H, *J* = 6.4 Hz, H5), 3.87 (t, 2H, *J* = 6.4 Hz, H6), 7.50–8.23 (m, 7H, H8, 9, 10, 11, and 3′, 4′, 5′), 8.44–8.56 (m, 2H, H2′ and 6′); FAB MS *m/z*: 357 (MH^+), 359 ($MH^+ + 2$). *Anal*. Calcd. for $C_{18}H_{13}ClN_2O_2S$: C, 60.59; H, 3.67; N, 7.85. Found: C, 60.82; H, 3.77; N; 7.86.

4-Chloro-2-(4-fluorophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7,7-dioxide (11e). The reaction was stirred for 4 h, and the product was recrystallized from ethanol to give **11e** (64%) as colorless needles, mp 237–239 °C; IR (potassium bromide) cm^{-1}: 1312, 1150 (SO_2); ^1H NMR (deuterochloroform): δ 3.22 (t, 2H, *J* = 6.5 Hz, H5), 3.87 (t, 2H, *J* = 6.5 Hz, H6), 7.01–7.31 (m, 2H, H3′ and 5′), 7.73–7.98 (m, 3H, H8, 9, and 10), 8.12–8.22 (m, 1H, H11), 8.41–8.65 (m, 2H, H2′ and 6′); FAB MS *m/z*: 375 (MH^+), 377 ($MH^+ + 2$). *Anal*. Calcd. for $C_{18}H_{12}ClFN_2O_2S$: C, 57.68; H, 3.23; N, 7.47. Found: C, 57.64; H, 3.48; N, 7.39.

4-Chloro-2-(4-chlorophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7,7-dioxide (11f). The reaction was stirred for 12 h, and the product was recrystallized from ethyl acetate to give **11f** (55%) as colorless prisms, mp 100–102 °C; IR (potassium bromide) cm^{-1}: 1312, 1152 (SO_2); ^1H NMR (deuterochloroform): δ 3.24 (t, 2H, *J* = 6.6 Hz, H5), 3.88 (t, 2H, *J* = 6.6 Hz, H6), 7.46 (d, 2H, *J* = 9.0 Hz, H3′ and 5′), 7.76 (ddd, 1H, *J* = 7.8, 7.7, 1.5 Hz, H10), 7.89 (ddd, 1H, *J* = 7.8, 7.4, 1.4 Hz, H9), 8.04 (dd, 1H, *J* = 7.4, 1.5 Hz, H8), 8.19 (dd, 1H, *J* = 7.7, 1.4 Hz, H11), 8.46 (d, 2H, *J* = 9.0 Hz, H2′ and 6′); FAB MS *m/z*: 391 (MH^+), 393 ($MH^+ + 2$), 395 ($MH^+ + 4$). *Anal*. Calcd. for $C_{18}H_{12}Cl_2N_2O_2S$: C, 55.25; H, 3.09; N, 7.16. Found: C, 55.31; H, 3.22; N, 7.16.

4-Chloro-2-(4-methylphenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7,7-dioxide (11g). The reaction was stirred for 2 h, and the product was recrystallized from ethanol to give **11g** (57%) as colorless needles, mp 272–274 °C; IR (potassium bromide) cm^{-1}: 1312, 1155 (SO_2); ^1H NMR (deuterochloroform): δ 2.43 (s, 3H, CH_3), 3.20–3.32 (m, 2H, H5), 3.76–4.03 (m, 2H, H6), 7.29

(d, 2H, $J = 7.6$ Hz, H3′ and 5′), 7.79–8.24 (m, 4H, H8, 9, 10, and 11), 8.40 (d, 2H, $J = 7.6$ Hz, H2′ and 6′); FAB MS *m/z*: 371 (MH^+), 373 ($MH^+ + 2$). *Anal*. Calcd. for $C_{19}H_{15}ClN_2O_2S$: C, 61.53; H, 4.08; N, 7.55. Found: C, 61.40; H, 4.14; N, 7.51.

4-Chloro-2-(4-methoxyphenyl)-5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine 7,7-dioxide (11h). The reaction was stirred for 1 h, and the product was recrystallized from ethanol to give **11h** (68%) as colorless needles, mp 235–237 °C; IR (potassium bromide) cm^{-1}: 1305, 1150 (SO_2); ^1H NMR (deuterochloroform): δ 3.15–3.28 (m, 2H, H5), 3.73–3.95 (m, 2H, H6), 3.89 (s, 3H, OCH_3), 6.99 (d, 2H, $J = 8.8$ Hz, H3′ and 5′), 7.86–8.16 (m, 4H, H8, 9, 10, and 11), 8.47 (d, 2H, $J = 8.8$ Hz, H2′ and 6′); FAB MS *m/z*: 387 (MH^+), 389 ($MH^+ + 2$). *Anal*. Calcd. for $C_{19}H_{15}ClN_2O_3S$: C, 58.99; H, 3.91; N, 7.24. Found: C, 58.70; H, 4.06; N, 7.33.

4-Chloro-2-(4-nitrophenyl)-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine 7,7-dioxide (11i). The reaction was stirred for 1 h, and the product was recrystallized from ethyl acetate to give **11i** (56%) as colorless needles, mp >300 °C; IR (potassium bromide) cm^{-1}: 1315, 1160 (SO_2); ^1H NMR (deuterochloroform): δ 3.28 (t, 2H, $J = 7.0$ Hz, H5), 3.90 (t, 2H, $J = 7.0$ Hz, H6), 7.79 (ddd, 1H, $J = 8.0$, 7.6, 1.5 Hz, H10), 7.92 (ddd, 1H, $J = 7.7$, 7.6, 1.4 Hz, H9), 8.05 (dd, 1H, $J = 7.7$, 1.5 Hz, H8), 8.21 (dd, 1H, $J = 8.0$, 1.4 Hz, H11), 8.34 (d, 2H, $J = 9.0$ Hz, H3′ and 5′), 8.71 (d, 2H, $J = 9.0$ Hz, H2′ and 6′); FAB MS *m/z*: 402 (MH^+), 404 ($MH^+ + 2$). *Anal*. Calcd. for $C_{18}H_{12}ClN_3O_4S$: C, 53.80; H, 3.01; N, 10.46. Found: C, 53.65; H, 3.13; N, 10.35.

Measurement of platelet aggregation. Preparation of platelet rich plasma was carried out according to the method described previously [21]. The platelet rich plasma described earlier, 250 μL, synthetic compounds **3** and **6–11**, 25 μL (10% DMSO solution or 60% DMF solution), and 1 M Tris–HCl buffer (pH 7.4) 25 μL were mixed and pre-incubated at 37 °C, followed 2 min later by addition of 50 μL aggregating agent (collagen, final concentration 14.3 μg/mL). Platelet aggregation was measured by continuous recording of light transmission at 650 nm through plasma for 10–15 min using an aggregometer (Aggrecoder II PA-3220, Kyoto Daiichi Kagaku Co. Ltd., Kyoto, Japan). Aspirin was used as a positive control. The inhibition rate was calculated from an aggregation response according to the method already described [21].

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