Polycyclic *N*-Heterocyclic Compounds. Part 85: Synthesis and Evaluation of Antiplatelet Aggregation Activity of 2,4-Disubstituted 5,6-Dihydro[1]benzazepino[5,4-*d*]pyrimidine and Related Compounds

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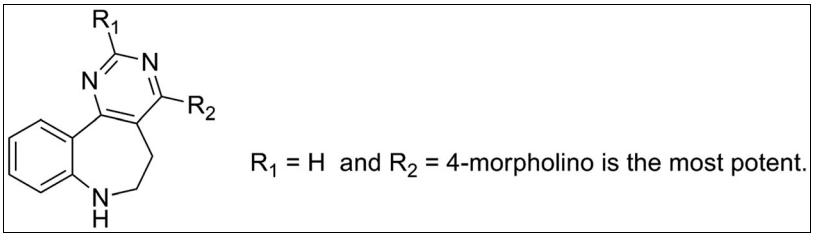

We have synthesized a large number of tricyclic 2-substituted 4-alkylamino-5,6-dihydro[1]benzazepino [5,4-*d*]pyrimidines as part of our research to develop new effective antiplatelet drugs. A variety of alkyl and aryl groups were used as substituents at the 2-position. Evaluation of the effects of the newly synthesized compounds on collagen-induced platelet aggregation revealed several promising antiplatelet 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 antiplatelet aggregation activity of these compounds, we discovered that 2-substituted 4-(2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinaozlines (**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 antiplatelet agent (Fig. 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 antiplatelet 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]. 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]benzazepino[5,4-*d*]pyrimidines (**3**), the aza-analogues of **1** and **2**. In this report, we describe in detail the synthesis and evaluation of these compounds.

RESULTS AND DISCUSSION

Chemistry. We synthesized the target molecules by the following method. First, 2-aminobenzonitrile (**4**) was tosylated with tosyl chloride in pyridine to afford *N*-tosyl-2-aminobenzonitrile (**5**) (87%) (Scheme 1). The functionality required for the construction of the benzazepine structure was introduced by alkylation of **5** with 4-chlorobutyronitrile and potassium iodide in the presence of potassium carbonate in acetone to give 2-(*N*-tosyl-3-cyanopropylamino) benzonitrile (**6**) (93%). Treatment of **6** with sodium hydride in THF triggered a Thrope–Ziegler cyclization to give 5-amino-1-tosyl-2,3-dihydro-1*H*-[1]benzazepine-4-carbonitrile (**7**) (82%). Next, **7** was allowed to react with Vilsmeier reagents prepared from a series of *N*,*N*-dimethylamides and phosphoryl chloride to give 4-chloro-7-tosyl-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benazepines (**8a–d**). Structures of **8a–d** were supported by the disappearance of the enamine and nitrile groups and the appearance of chlorine atoms in their IR and MS spectra. In addition, the NMR spectra and elemental analyses provided confirmation of these structures. Next, intermediates **8a–d** were hydrolyzed with concd HCl and acetic acid to give 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1] benazepin-4(3*H*)-ones (**9a–d**). Concomitant hydrolysis at 4-position and removal of *N*-tosyl protecting group were apparent by the disappearance of chlorine atoms and tosyl group in their IR and MS spectra. In addition, the NMR spectra provided confirmation of these structures. Compounds **9a–d** were converted to **10a–d** by treatment with phosphoryl chloride.

Next, we employed 2-aminoethanol to carry out nucleophilic substitution at the 4-position of **10a–d** to give **3a–d** (63–75%, Scheme 2) as analogues of **1** and **2**. Because we also expected the 2-hydroxyethylamino substituent to influence

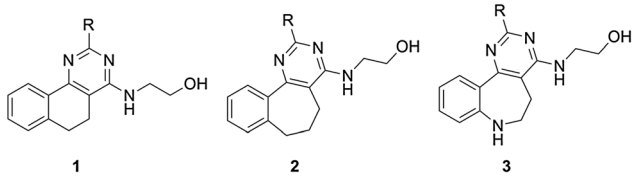
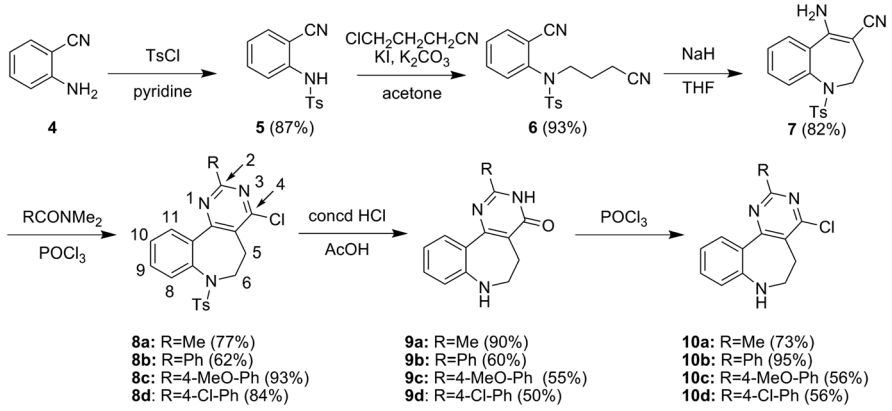


Figure 1. Previous hit compounds (**1** and **2**) as antiplatelet agents and their analogues (**3**) prepared here.

Scheme 1. Preparation of **10**.



8a: R=Me (77%)
8b: R=Ph (62%)
8c: R=4-MeO-Ph (93%)
8d: R=4-Cl-Ph (84%)

9a: R=Me (90%)
9b: R=Ph (60%)
9c: R=4-MeO-Ph (55%)
9d: R=4-Cl-Ph (50%)

10a: R=Me (73%)
10b: R=Ph (95%)
10c: R=4-MeO-Ph (56%)
10d: R=4-Cl-Ph (56%)

bioactivity, to eliminate the hydrogen donor ability of amino group, *N*-methyl-2-aminoethanol was also chosen to react with **10a–d** to give **11a–d** (67–91%). Similarly, the reaction of morpholine with **10a–d** was carried out to give **12a–d** (61–89%), thus simultaneously eliminating the hydrogen donor ability of the amino and hydroxy groups of the 2-hydroxyethylamino substituent. Finally, the reaction of piperidine with **10a–d** gave **13a–d** (70–78%) thereby eliminating the influence of the hydrogen acceptor ability of the ether group in the morpholine moiety. We had also prepared each corresponding 2-unsubsituted derivatives (R=H) (**3e** [14], **10e** [14], **11e** [15], **12e** [15], and **13e** [15]). All derivatives **3** and **10–13** satisfy the Lipinski's rule of five, and thus, they are expected to have drug-like properties [16].

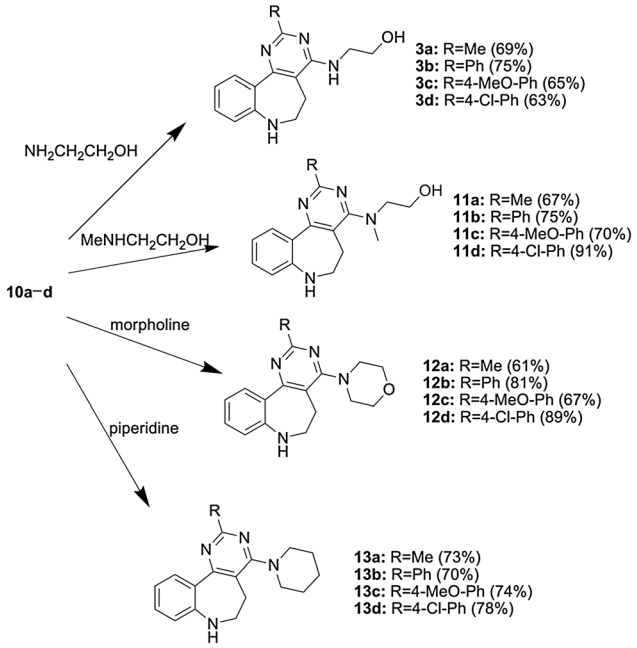
Biology. The products prepared as described earlier were screened for inhibitory activity against rabbit platelet aggregation by a turbidimetric method using an aggregometer as described by Born and Cross [17]. Platelet aggregation was induced by the addition of collagen (final concentration 14.3 μg/mL). A 10% solution of DMSO (final concentration 0.71%) or 60% 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 **3** showed any significant improvement in potency over aspirin. Compound **10** did not show any superior potency to aspirin either (data not shown). However, certain of the substituted tricyclic compounds **11–13** showed a bioactivity superior to that of aspirin. A detailed comparison of the inhibitory activity (IC_{50}) of the compounds that showed significant difference ($P < 0.05$) from the activity of aspirin at the same concentration was determined. Among them, **12e** with the 2-unsusbituted 4-morpholino substituent is the most potent, having 15 times more activity than aspirin and having greater potency than the most potent **1** (R=Ph) [1] and most potent **2** (R=4-Cl-Ph) [2]. The difference in the potency observed for series **3** and **11** is quite interesting because the only difference in the structures is the presence of NH in the less active **3** and NMe in the more active **11**. A 2-methyl substituent is preferable for **11–13** in general. Because our results suggest that the presence of a secondary amino group of **3** decreases activity in this series, we prepared compounds **14a–d** (67–83%) by dehydration of **3a–d** and **14e** (R=H) [14] from **3e** to examine the effects of an imine on activity (Scheme 3). However, none of **14** showed any significant improvement in potency over aspirin (data not shown). More detailed examination will be needed to clarify structure–activity relationships in this series of compounds.

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

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 EI-mass and FAB-mass (*m*-nitrobenzyl alcohol was used as the matrix) were

Scheme 2. Preparation of **3** and **11–13**.



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 TMS 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 TLC to determine the appropriate time for termination.

***N*-Tosyl-2-aminobenzonitrile (5).** To a solution of 2-aminobenzonitrile (**4**, 25.0 g, 0.212 mol) in 150 mL of pyridine was added tosyl chloride (50.0 g, 0.262 mol) at 0°C, and the reaction mixture was stirred at rt for 2 days. After the evaporation of solvent *in vacuo*, ice water (400 mL) was added, and the resulting precipitate was filtered off then washed with water. The solid was recrystallized from ethanol to give **5** (50.0 g, 87%) as colorless plates, mp 133–135°C; IR (potassium bromide) cm^{-1}: 3160 (NH), 2200 (CN), 1320, 1145 (SO); ^1H NMR (DMSO-d_6): δ 2.38 (s, 3H, Me), 6.98–7.98 (m, 8H, Ar-H), 10.5 (br, 1H, deuterium oxide exchangeable, NH); FAB-mass *m/z* 273 (MH^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.74; H, 4.51; N, 10.21.

2-(*N*-Tosyl-3-cyanopropylamino)benzonitrile (6). A mixture of **5** (50.0 g, 0.184 mol), 4-chlorobutyronitrile (19.1 g, 0.184 mmol), potassium carbonate (76.0 g, 0.550 mol), and potassium iodide (10.0 g, 60.2 mmol) in dry acetone (500 mL) was refluxed for 1 week. After the removal of solvent *in vacuo*, ice water (500 mL) was added to the resulting oily residue, and the mixture was stirred for a couple of hours. The resulting precipitate was filtered off, washed with water, and recrystallized from methanol to give **6** (58.0 g, 93%) as colorless plates, mp 86–88°C; IR (potassium bromide) cm^{-1}: 2250 (CN), 1350, 1160 (SO); ^1H NMR (DMSO-d_6): δ 1.50–1.92 (m, 2H, $NCH_2CH_2CH_2$), 2.43 (s, 3H, Me), 2.61 (br t, 2H, $J = 8.0$ Hz, CH_2CN), 3.65 (br t, 2H, $J = 8.0$ Hz, NCH_2), 6.95–8.10 (m, 8H, Ar-H); FAB-mass *m/z* 340 (MH^+). *Anal.* Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.70; H, 5.14; N, 12.45.

5-Amino-1-tosyl-2,3-dihydro-1*H*-[1]-benzazepine-4-carbonitrile (7). A mixture of **6** (10.0 g, 29.5 mmol) and NaH (60%, 3.54 g, 88.5 mmol, washed twice with ligroin) in dry THF (200 mL) was heated at 45°C for 14 h under a nitrogen atmosphere. After the removal of solvent *in vacuo*, ice water (150 mL) was added to the residue slowly, and the resulting white precipitate was filtered off, washed with water, and recrystallized from ethanol–ethyl acetate to give **7** (8.20 g, 82%) as pale yellow needles, mp 226–227.5°C; IR (potassium bromide) cm^{-1}: 3450, 3350, 3250 (NH), 2190 (CN), 1340, 1150 (SO); ^1H NMR (DMSO-d_6): δ 1.96 (br t, 2H, $J = 7.0$ Hz, H3), 2.41 (s, 3H, Me), 3.87 (br t, 2H, $J = 7.0$ Hz, H2), 6.21 (s, 2H, deuterium oxide exchangeable, NH_2), 7.27–7.64 (m, 8H, Ar-H); FAB-mass *m/z* 340 (MH^+). *Anal.* Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 64.09; H, 5.05; N, 12.41.

General procedure for the synthesis of 2-substituted 4-chloro-7-tosyl-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (8a–d). The Vilsmeier reagent was prepared by the reaction of the corresponding *N*,*N*-dimethylamide [18] (67.9 mmol) and phosphoryl chloride (60 mL) under ice cooling for 1 h. The enaminonitrile **7** (10.0 g, 29.5 mmol) was added, and the reaction was stirred at 75°C for 4 h. After the removal of excess phosphoryl chloride, ice water (300 mL) was poured into the residue, and the mixture was basified to pH 9 with sodium carbonate. The resulting white solid precipitate was washed with water and recrystallized from the appropriate solvent to give **8**.

4-Chloro-2-methyl-7-tosyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (8a). Recrystallization of the solid from methanol gave **8a** (77%) as colorless prisms, mp 200–202°C;

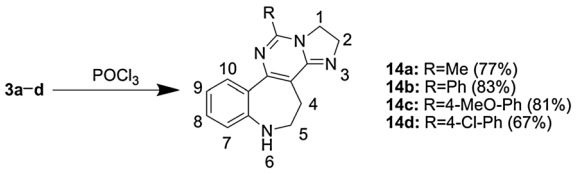
Table 1

Effects of compounds **3** and **11–13** on rabbit platelet aggregation *in vitro* induced by collagen.

Compound	% inhibition[a]	IC_{50} (μM)[b]
3a[c]	20.4 ± 0.2	—
3b[d]	29.9 ± 3.5	—
3c[d]	26.7 ± 7.1	—
3d[d]	17.5 ± 5.1	—
3e[c]	11.8 ± 2.2	—
11a[c]	95.8 ± 3.3*	4.5 (1.1–7.1)
11b[d]	56.5 ± 11.3*	2.1 (1.3–3.0)
11c[d]	38.2 ± 9.9	—
11d[d]	58.6 ± 10.7*	2.5 (1.9–3.5)
11e[c]	39.2 ± 9.2	—
12a[c]	92.7 ± 4.1*	8.9 (3.9–13.3)
12b[d]	67.4 ± 8.4*	2.3 (1.4–3.7)
12c[d]	24.2 ± 1.5	—
12d[d]	11.7 ± 8.1	—
12e[c]	83.9 ± 4.4*	3.1 (1.1–5.6)
13a[c]	92.5 ± 1.7*	4.4 (0.5–7.7)
13b[d]	19.5 ± 1.7	—
13c[d]	10.3 ± 2.7	—
13d[d]	29.6 ± 4.4	—
13e[c]	72.3 ± 7.4*	14.3 (11.0–21.4)
Aspirin[c]	15.7 ± 1.0	48.0 (44.1–53.3)
Aspirin[d]	26.1 ± 1.7	6.5 (5.3–8.8)

*Means significantly different from aspirin at $P < 0.05$.
[a]Data represent the % inhibition of the vehicle control group (mean ± SE of three experiments at least) at final concentration of 25 μM (in the case of 10% DMSO) or 2.5 μM (in the case of 60% DMF).
[b]Experiments were repeated at least three times each at final concentrations of 5.0, 25, and 50 μM in the case of 10% DMSO; 25, 50, and 100 μM aspirin in the case of 10% DMSO; 1.0, 2.5, and 5.0 μM in the case of 60% DMF; or 2.5, 5.0, and 10 μM aspirin in the case of 60% DMF. Figures in parentheses represent the 95% confidence limits of IC_{50}.
[c]10% DMSO was used as a cosolvent.
[d]60% DMF was used as a cosolvent.

Scheme 3. Preparation of **14**.



IR (potassium bromide) cm^{-1}: 1327, 1160 (SO); ^1H NMR (deuterochloroform): δ 2.36, 2.55 (each s, each 3H, 2 × Me), 2.82 (t, 2H, $J = 6.0$ Hz, H5), 4.34 (t, 2H, $J = 6.0$ Hz, H6), 6.85–7.81 (m, 8H, Ar-H); FAB-mass *m/z* 400 (MH^+), 402 ($MH^+ + 2$). *Anal*. Calcd for $C_{20}H_{18}ClN_3O_2S$: C, 60.07; H, 4.54; N, 10.51. Found: C, 60.20; H, 4.55; N, 10.49.

4-Chloro-2-phenyl-7-tosyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (8b). Recrystallization of the solid from benzene gave **8b** (62%) as colorless prisms, mp 139–141°C; IR (potassium bromide) cm^{-1}: 1346, 1162 (SO); ^1H NMR (deuterochloroform): δ 1.66 (s, 3H, Me), 2.87 (t, 2H, $J = 6.0$ Hz, H5), 4.40 (t, 2H, $J = 6.0$ Hz, H6), 6.65–7.82 (m, 11H, Ar-H), 8.23–8.47 (m, 2H, H2′ and 6′); FAB-mass *m/z* 462 (MH^+), 464 ($MH^+ + 2$). *Anal*. Calcd for $C_{25}H_{20}ClN_3O_2S$: C, 65.00; H, 4.36; N, 9.10. Found: C, 65.37; H, 4.53; N, 9.00.

4-Chloro-2-(4-methoxyphenyl)-7-tosyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (8c). Recrystallization of the solid from acetone gave **8c** (93%) as colorless prisms, mp 206–208°C; IR (potassium bromide) cm^{-1}: 1330, 1155 (SO); ^1H NMR (deuterochloroform): δ 1.73 (s, 3H, Me), 2.85 (t, 2H, $J = 6.5$ Hz, H5), 3.91 (s, 3H, OMe), 4.37 (t, 2H, $J = 6.5$ Hz, H6), 6.73–7.85 (m, 10H, Ar-H), 8.35 (d, 2H, $J = 8.0$ Hz, H2′ and 6′); EI-mass *m/z* 491 (M^+), 493 ($M^+ + 2$). *Anal*. Calcd for $C_{26}H_{22}ClN_3O_3S$: C, 63.47; H, 4.51; N, 8.54. Found: C, 63.47; H, 4.66; N, 8.62.

4-Chloro-2-(4-chlorophenyl)-7-tosyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (8d). Recrystallization of the solid from ethyl acetate gave **8d** (84%) as colorless prisms, mp 225–227°C; IR (potassium bromide) cm^{-1}: 1340, 1155 (SO); ^1H NMR (deuterochloroform): δ 1.72 (s, 3H, Me), 2.87 (t, 2H, $J = 6.5$ Hz, H5), 4.40 (t, 2H, $J = 6.5$ Hz, H6), 6.75–7.88 (m, 10H, Ar-H), 8.34 (d, 2H, $J = 8.5$ Hz, H2′ and 6′); FAB-mass *m/z* 496 (MH^+), 498 ($MH^+ + 2$). *Anal*. Calcd for $C_{25}H_{19}Cl_2N_3O_2S$: C, 60.49; H, 3.86; N, 8.46. Found: C, 60.60; H, 3.93; N, 8.36.

General procedure for the synthesis of 2-substituted 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4(3*H*)-one (9a–d). A mixture of **8a–d** (1.00 g) in concd hydrochloric acid (30 mL) and acetic acid (15 mL) was refluxed for an appropriate time. After the removal of volatile components *in vacuo*, ice water (50 mL) was poured into the residue, and the solution was adjusted to pH 9 with sodium carbonate. The precipitated solid was washed with water and recrystallized from a suitable solvent to give **9**.

2-Methyl-6,7-dihydro-5H-pyrimido[5.4-d][1]benzazepin-4(3H)-one (9a). The reaction was refluxed for 30 h, and the product was recrystallized from ethyl acetate to give **9a** (90%) as a yellow powder, mp 241–243°C; IR (potassium bromide) cm^{-1}: 3340 (NH), 1650 (CO); ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H, Me), 2.61–2.90 (m, 2H, H5), 3.20–3.51 (m, 3H, changed to 2H with addition of deuterium oxide, H6, and NH), 6.45–8.06 (m, 4H, Ar-H), 12.30 (br, 1H, deuterium oxide exchangeable, NH); FAB-mass *m/z* 228 (MH^+) [19].

2-Phenyl-6,7-dihydro-5H-pyrimido[5.4-d][1]benzazepin-4(3H)-one (9b). The reaction was refluxed for 24 h, and the product was recrystallized from 1,4-dioxane to give **9b** (60%) as yellow prisms, mp 239–241°C; IR (potassium bromide) cm^{-1}: 3450 (NH), 1630 (CO); ^1H NMR (DMSO-d_6): δ 2.73–2.98 (m, 2H, H5), 3.35–3.70 (m, 2H, H6), 6.35 (br, 1H, deuterium oxide exchangeable, NH), 6.62–8.39 (m, 9H, Ar-H), 12.4 (br, 1H, deuterium oxide exchangeable, NH); FAB-mass *m/z* 290 (MH^+). *Anal*. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.61; H, 5.47; N, 14.89.

2-(4-Methoxyphenyl)-6,7-dihydro-5H-pyrimido[5.4-d][1]benzazepin-4(3H)-one (9c). The reaction was refluxed for 36 h, and the product was recrystallized from 1,4-dioxane to give **9c** (55%) as yellow prisms, mp 282–283°C; IR (potassium bromide) cm^{-1}: 3420 (NH), 1610 (CO); ^1H NMR (DMSO-d_6): δ 2.75–2.93 (m, 2H, H5), 3.35–3.60 (m, 2H, H6), 3.85 (s, 3H, OMe), 6.64–8.28 (m, 9H, changed to 8H after addition of deuterium oxide, Ar-H, and NH), 12.4 (br, 1H, deuterium oxide exchangeable, NH); FAB-mass *m/z* 320 (MH^+). *Anal*. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.39; H, 5.46; N, 13.17.

2-(4-Chlorophenyl)-6,7-dihydro-5H-pyrimido[5.4-d][1]benzazepin-4(3H)-one (9d). The reaction was refluxed for 72 h, and the product was recrystallized from 1,4-dioxane to give **9d** (50%) as yellow prisms, mp 285–287°C; IR (potassium bromide) cm^{-1}: 3340 (NH), 1620 (CO); ^1H NMR (DMSO-d_6): δ 2.84

(t, 2H, $J = 7.1$ Hz, H5), 3.47 (t, 2H, $J = 7.1$ Hz, H6), 6.46 (br, 1H, deuterium oxide exchangeable, NH), 6.63–8.32 (m, 8H, Ar-H), 12.59 (br, 1H, deuterium oxide exchangeable, NH); FAB-mass *m/z* 324 (MH^+), 326 ($MH^+ + 2$). *Anal*. Calcd for $C_{18}H_{14}ClN_3O$: C, 66.77; H, 4.36; N, 12.98. Found: C, 66.57; H, 4.64; N, 13.05.

General procedure for the synthesis of 2-substituted 4-chloro-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (10a–d). Compounds **9a–d** (1.00 g) and phosphoryl chloride (10 mL) were heated at 100°C for an appropriate time with stirring. After the evaporation of excess phosphoryl chloride *in vacuo*, ice water (80 mL) was added to the residue, and the solution was adjusted to pH 10 with sodium carbonate to precipitate a yellow solid. The solid was purified by silica gel column chromatography using *n*-hexane-ethyl acetate as an eluent solvent and purified by recrystallization from 1,4-dioxane to give **10**.

4-Chloro-2-methyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (10a). The reaction was heated for 2 h, and the product was eluted with *n*-hexane-ethyl acetate (5:2) to give **10a** (73%) as yellow fine crystals, mp 140–143°C; IR (potassium bromide) cm^{-1}: 3300 (NH); ^1H NMR (deuterochloroform): δ 2.73 (s, 3H, Me), 3.10 (t, 2H, $J = 6.0$ Hz, H5), 3.76 (t, 2H, $J = 6.0$ Hz, H6), 3.98 (br, 1H, deuterium oxide exchangeable, NH), 6.63–8.15 (m, 4H, Ar-H); FAB-mass *m/z* 246 (MH^+), 248 ($MH^+ + 2$). *Anal*. Calcd for $C_{13}H_{12}ClN_3$: C, 63.55; H, 4.92; N, 17.10. Found: C, 63.41; H, 5.18; N, 17.03.

4-Chloro-2-phenyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (10b). The reaction was heated for 15 min, and the product was eluted with *n*-hexane-ethyl acetate (5:1) to give **10b** (95%) as yellow fine crystals, mp 123–125°C; IR (potassium bromide) cm^{-1}: 3400 (NH); ^1H NMR (DMSO-d_6): δ 2.93–3.13 (m, 2H, H5), 3.70–3.91 (m, 2H, H6), 4.51 (br, 1H, deuterium oxide exchangeable, NH), 7.42–8.56 (m, 9H, Ar-H); FAB-mass *m/z* 308 (MH^+), 310 ($MH^+ + 2$). *Anal*. Calcd for $C_{18}H_{14}ClN_3$: C, 70.24; H, 4.58; N, 13.65. Found: C, 70.46; H, 4.78; N, 13.76.

4-Chloro-2-(4-methoxyphenyl)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (10c). The reaction was heated for 6 h, and the product was eluted with *n*-hexane-ethyl acetate (5:1) to give **10c** (56%) as yellow fine crystals, mp 109–110°C. IR (potassium bromide) cm^{-1}: 3420 (NH); ^1H NMR (DMSO-d_6): δ 2.85–3.14 (m, 2H, H5), 3.53–3.85 (m, 2H, H6), 3.86 (s, 3H, OMe), 4.05 (br, 1H, deuterium oxide exchangeable, NH), 6.95–8.49 (m, 8H, Ar-H); FAB ms *m/z* 338 (MH^+), 340 ($MH^+ + 2$) [19].

4-Chloro-2-(4-chlorophenyl)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (10d). The reaction was heated for 1 h, and the product was eluted with *n*-hexane-ethyl acetate (5:1) to give **10d** (56%) as yellow fine crystals, mp 120–122°C; IR (potassium bromide) cm^{-1}: 3420 (NH); ^1H NMR (DMDO-d_6): δ 2.95–3.15 (m, 2H, H5), 3.64–3.92 (m, 2H, H6), 4.16 (br, 1H, deuterium oxide exchangeable, NH), 7.18–8.53 (m, 8H, Ar-H); FAB-mass *m/z* 342 (MH^+), 344 ($MH^+ + 2$). *Anal*. Calcd for $C_{18}H_{13}Cl_2N_3$: C, 63.17; H, 3.83; N, 12.28. Found: C, 63.32; H, 4.10; N, 12.03.

General procedure for the synthesis of 2-substituted 4-(2-hydroxyethylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (3a–d). A mixture of **10a–d** (1.00 mmol) and 2-aminoethanol (611 mg, 10.0 mmol) in dry 1,4-dioxane (5.0 mL) was refluxed for an appropriate time. The reaction mixture was evaporated *in vacuo*, and ice water (5.0 mL) was added to the residue. The resulting solid was collected on a filter, washed with water, and recrystallized to give **3**.

4-(2-Hydroxyethylamino)-2-methyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (3a). The solution was refluxed for 7 h, and the solid was recrystallized from ethyl acetate to give **3a** (69%) as pale brown needles, mp 217–219°C; IR (potassium bromide) cm^{-1}: 3300, 3250, 3150 (NH, OH); ^1H NMR (DMSO-d_6): δ 2.52 (s, 3H, Me), 2.78–2.91 (m, 2H, H5), 3.25–3.70 (m, 6H, H6 and NCH_2CH_2O), 4.93, 6.31 (each br, each 1H, deuterium oxide exchangeable, NH or OH), 6.75–7.64 (m, 4H, Ar-H), 8.31 (br, 1H, deuterium oxide exchangeable, NH or OH); FAB-mass *m/z* 271 (MH^+). *Anal*. Calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.26; H, 6.73; N, 20.42.

4-(2-Hydroxyethylamino)-2-phenyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (3b). The solution was refluxed for 24 h, and the solid was recrystallized from ethyl acetate to give **3b** (75%) as colorless needles, mp 192–194°C; IR (potassium bromide) cm^{-1}: 3420, 3320, 3190 (NH, OH); ^1H NMR (DMSO-d_6): δ 2.80 (br t, 2H, $J = 5.5$ Hz, H5), 3.34–3.60 (m, 6H, H6, NCH_2CH_2O), 4.65, 6.20, 6.85 (each br, each 1H, deuterium oxide exchangeable, NH and OH), 7.01–8.45 (m, 9H, Ar-H); FAB-mass *m/z* 333 (MH^+); *Anal*. Calcd for $C_{20}H_{20}N_4O$: C, 72.27; H, 6.06; N, 16.86. Found: C, 72.25; H, 6.14; N, 16.67.

4-(2-Hydroxyethylamino)-2-(4-methoxyphenyl)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (3c). The solution was refluxed for 48 h, and the solid was recrystallized from benzene to give **3c** (65%) as a pale yellow powder, mp 152–153°C; IR (potassium bromide) cm^{-1}: 3380, 3300, 3180 (NH, OH); ^1H NMR (DMSO-d_6): δ 2.73 (br t, 2H, $J = 5.0$ Hz, H5), 3.40–3.75 (m, 6H, H6 and NCH_2CH_2O), 3.82 (s, 3H, OMe), 4.74, 5.89 (each br, each 1H, deuterium oxide exchangeable, NH or OH), 6.62–8.45 (m, 9H, changed to 8H with addition of deuterium oxide, Ar-H, and NH or OH); FAB-mass *m/z* 363 (MH^+); *Anal*. Calcd for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 6.12; N, 15.46. Found: C, 69.69; H, 6.23; N, 15.81.

2-(4-Chlorophenyl)-4-(2-hydroxyethylamino)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (3d). The solution was refluxed for 24 h, and the solid was recrystallized from cyclohexane to give **3d** (63%) as colorless needles, mp 103–105°C; IR (potassium oxide) cm^{-1}: 3420, 3350, 3200 (NH, OH); ^1H NMR (deuterochloroform): δ 2.70 (t, 2H, $J = 6.0$ Hz, H5), 3.24 (br, 2H, deuterium oxide exchangeable, NH or OH), 3.53–3.99 (m, 6H, H6 and NCH_2CH_2O), 5.28 (br, 1H, deuterium oxide exchangeable, NH or OH), 6.62–8.52 (m, 8H, Ar-H); FAB-mass *m/z* 367 (MH^+); *Anal*. Calcd for $C_{20}H_{19}ClN_4O$: C, 65.48; H, 5.22; N, 15.27. Found: C, 65.44; H, 5.45; N, 15.39.

General procedure for the synthesis of 2-substituted 4-(*N*-methyl-2-hydroxyethylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (11a–d). A mixture of **10a–d** (1.00 mmol) and 2-(*N*-methylamino)ethanol (751 mg, 10.0 mmol) in dry 1,4-dioxane (5.0 mL) was refluxed for an appropriate time. The reaction mixture was evaporated to dryness *in vacuo*, ice water (50 mL) was added to the residue, and the precipitated solid was filtered off and washed with water. The solid was purified by column chromatography on silica gel and/or recrystallization to give **11**.

2-Methyl-4-(N-methyl-2-hydroxyethylamino)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (11a). The mixture was refluxed for 30 h, and the crude product was chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (1:1) was evaporated *in vacuo* to give **11a** (67%) as yellow needles, mp 176–178°C; IR (potassium bromide) cm^{-1}: 3260, 3180 (NH, OH); ^1H NMR (deuterochloroform): δ 2.58 (s, 3H, 2-Me), 2.81

(t, 2H, $J = 6.0$ Hz, H5), 3.14 (s, 3H, NMe), 3.50–4.22 (m, 7H, changed to 6H with addition of deuterium oxide, H6, NCH_2CH_2O, and NH or OH), 5.90 (br, 1H, deuterium oxide exchangeable, NH or OH), 6.65–8.08 (m, 4H, Ar-H); FAB-mass *m/z* 285 (MH^+). *Anal*. Calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.42; H, 7.18; N, 19.55.

4-(N-Methyl-2-hydroxyethylamino)-2-phenyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (11b). The mixture was refluxed for 25 h, and the crude product was chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (2:1) was evaporated *in vacuo*, and the product was recrystallized from *n*-hexane to give **11b** (75%) as yellow needles, mp 96–98°C; IR (potassium bromide) cm^{-1}: 3400, 3300 (NH, OH); ^1H NMR (deuterochloroform): δ 2.88 (t, 2H, $J = 6.0$ Hz, H5), 3.16 (s, 3H, NMe), 3.55–4.20 (m, 6H, H6 and NCH_2CH_2O), 5.90 (br, 1H, deuterium oxide exchangeable, NH or OH), 6.71–8.57 (m, 9H, Ar-H), 8.66 (br, 1H, deuterium oxide exchangeable, NH or OH); FAB-mass *m/z* 347 (MH^+). *Anal*. Calcd for $C_{21}H_{22}N_4O \cdot 1/2\ H_2O$: C, 70.96; H, 6.52; N, 15.76. Found: C, 71.28; H, 6.58; N, 15.61.

2-(4-Methoxyphenyl)-4-(N-methyl-2-hydroxyethylamino)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (11c). The mixture was refluxed for 34 h, and the product was recrystallized from ethyl acetate to give **11c** (70%) as yellow needles, mp 151–152°C; IR (potassium bromide) 3430, 3300 (NH, OH); ^1H NMR (deuterochloroform): δ 2.87 (t, 2H, $J = 6.5$ Hz, H5), 3.15 (s, 3H, NMe), 3.64–4.10 (m, 9H, OMe, H6, and NCH_2CH_2O), 5.30 (br, 1H, deuterium oxide exchangeable, NH or OH), 6.68–8.54 (m, 9H, changed to 8H with addition of deuterium oxide, Ar-H, NH or OH); FAB-mass *m/z* 377 (MH^+). *Anal*. Calcd for $C_{22}H_{24}N_4O_2 \cdot 1/3\ H_2O$: C, 69.09; H, 6.50; N, 14.65. Found: C, 69.01; H, 6.38; N, 14.63.

2-(4-Chlorophenyl)-4-(N-methyl-2-hydroxyethylamino)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (11d). The mixture was refluxed for 24 h, and the crude product was chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (2:1) was evaporated *in vacuo* to give **11d** (91%) as yellow needles, mp 115–117°C; IR (potassium bromide) cm^{-1}: 3420, 3300 (NH, OH); ^1H NMR (deuterochloroform): δ 2.89 (t, 2H, $J = 6.0$ Hz, H5), 3.17 (s, 3H, NMe), 3.61–4.06 (m, 7H, changed to 6H, with addition of deuterium oxide, H6, NCH_2CH_2O, and NH or OH), 4.68 (br, 1H, deuterium oxide exchangeable, NH or OH), 6.69–8.50 (m, 8H, Ar-H); FAB-mass *m/z* 381 (MH^+), 383 ($MH^+ + 2$). *Anal*. Calcd for $C_{21}H_{21}ClN_4O$: C, 66.22; H, 5.56; N, 14.71. Found: C, 66.02; H, 5.77; N, 14.51.

General procedure for the synthesis of 2-substituted 4-morpholino-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (12a–d). A mixture of **10a–d** (1.00 mmol) and morpholine (871 mg, 10.0 mmol) in dry 1,4-dioxane (5.0 mL) was refluxed for 1 day. After the evaporation of solvent *in vacuo*, ice water (60 mL) was poured into the residue. The precipitated solid was collected on a filter and was recrystallized from cyclohexane to give **12a–d**.

2-Methyl-4-morpholino-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (12a). Compound **12a** (61%) was obtained as a white powder, mp 161–162°C; IR (potassium bromide) cm^{-1}: 3280 (NH); ^1H NMR (deuterochloroform): δ 2.63 (s, 3H, Me), 2.82 (t, 2H, $J = 5.0$ Hz, H5), 3.25–3.51 (m, 4H, 3′ and 4′), 3.60–4.02 (m, 6H, H6, 2′, and 6′), 4.14 (br, 1H, deuterium oxide exchangeable, NH), 6.62–8.16 (m, 4H, Ar-H); FAB ms *m/z* 297 (MH^+). *Anal*. Calcd for $C_{17}H_{20}N_4O$: C, 68.89; H, 6.80; N, 18.90. Found: C, 68.77; H, 6.87; N, 18.93.

4-Morpholino-2-phenyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (12b). Compound **12b** (81%) was obtained as a white powder, mp 175–176°C; IR (potassium bromide) cm^{-1}: 3340, 3400 (NH); ^1H NMR (deuterochloroform): δ 2.91 (br t, 2H, $J = 5.0$ Hz, H5), 3.32–4.02 (m, 10H, H6, 2′, 3′, 5′, and 6′), 4.80 (br, 1H, deuterium oxide exchangeable, NH), 6.64–8.65 (m, 9H, Ar-H); FAB-mass *m/z* 359 (MH^+). *Anal*. Calcd for $C_{22}H_{22}N_4O \cdot 1/2\ H_2O$: C, 71.91; H, 6.31; N, 15.25. Found: C, 71.62; H, 6.20; N, 15.61.

2-(4-Methoxyphenyl)-4-morpholino-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (12c). Compound **12c** (67%) was obtained as yellow plates, mp 163–164°C; IR (potassium bromide) cm^{-1}: 3360, 3440 (NH); ^1H NMR (deuterochloroform): δ 2.88 (br t, 2H, $J = 6.0$ Hz, H5), 3.27–4.02 (m, 10H, H6, 2′, 3′, 5′, and 6′), 3.87 (s, 3H, OMe), 4.30 (br, 1H, deuterium oxide exchangeable, NH), 6.60–8.60 (m, 8H, Ar-H); FAB-mass *m/z* 389 (MH^+). *Anal*. Calcd for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42. Found: C, 71.35; H, 6.37; N, 14.49.

2-(4-Chlorophenyl)-4-morpholino-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (12d). Compound **12d** (89%) was obtained as a white powder, mp 168–170°C; IR (potassium bromide) cm^{-1}: 3310, 3430 (NH); ^1H NMR (deuterochloroform): δ 2.91 (t, 2H, $J = 5.0$ Hz, H5), 3.34–4.04 (m, 10H, H6, 2′, 3′, 5′, and 6′), 4.24 (br, 1H, deuterium oxide exchangeable, NH), 6.62–8.60 (m, 8H, Ar-H); FAB-mass *m/z* 393 (MH^+), 395 ($MH^+ + 2$). *Anal*. Calcd for $C_{22}H_{21}ClN_4O$: C, 67.26; H, 5.39; N, 14.26. Found: C, 66.99; H, 5.47; N, 13.89.

General procedure for the synthesis of 2-substituted 4-piperidino-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (13a–d). A mixture of **10a–d** (1.00 mmol) and piperidine (852 mg, 10.0 mmol) in dry 1,4-dioxane (5.0 mL) was refluxed for 1 day. After the evaporation of solvent *in vacuo*, ice water (50 mL) was poured into the residue, and the mixture was extracted with ethyl acetate (25 mL × 3). The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The resulted yellow viscous oil was purified by recrystallization to give **13**.

2-Methyl-4-piperidino-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (13a). The residue was recrystallized from benzene to give **13a** (73%) as colorless needles, mp 176–178°C; IR (potassium bromide) cm^{-1}: 3280 (NH); ^1H NMR (deuterochloroform): δ 1.66 (br s, 6H, 3′, 4′, and 5′), 2.61 (s, 3H, Me), 2.79 (t, 2H, $J = 5.5$ Hz, H5), 3.05–3.43 (m, 4H, H2′ and 6′), 3.73 (t, 2H, $J = 5.5$ Hz, H6), 3.98 (br, 1H, deuterium oxide exchangeable, NH), 6.61–8.10 (m, 4H, Ar-H); EI-mass *m/z* 294 (M^+). *Anal*. Calcd for $C_{18}H_{22}N_4$: C, 73.44; H, 7.53; N, 19.03. Found: C, 73.30; H, 7.56; N, 18.75.

2-Phenyl-4-piperidino-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (13b). The residue was recrystallized from cyclohexane to give **13b** (70%) as yellow prisms, mp 150–151°C; IR (potassium bromide) cm^{-1}: 3420 (NH); ^1H NMR (deuterochloroform): δ 1.70 (br s, 6H, H3′, 4′, and 5′), 2.87 (t, 2H, $J = 5.5$ Hz, H5), 3.16–3.59 (m, 4H, H2′ and 6′), 3.74 (t, 2H, $J = 5.5$ Hz, H6), 4.21 (br, 1H, deuterium oxide exchangeable, NH), 6.65–8.76 (m, 9H, Ar-H); FAB-mass *m/z* 357 (MH^+). *Anal*. Calcd for $C_{23}H_{24}N_4$: C, 77.50; H, 6.79; N, 15.72. Found: C, 77.18; H, 6.79; N, 15.78.

2-(4-Methoxyphenyl)-4-piperidino-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (13c). The residue was recrystallized from cyclohexane to give **13c** (74%) as a white powder, mp

161–163°C; IR (potassium bromide) cm^{-1}: 3340 (NH); ^1H NMR (deuterochloroform): δ 1.50–1.94 (m, 6H, H3′, 4′, and 5′), 2.87 (br t, 2H, $J = 5.0$ Hz, H5), 3.18–3.55 (m, 4H, H2′ and 6′), 3.74 (br t, 2H, $J = 5.0$ Hz, H6), 3.87 (s, 3H, OMe), 4.23 (br, 1H, deuterium oxide exchangeable, NH), 6.62–8.63 (m, 8H, Ar-H); FAB-mass *m/z* 387 (MH^+). *Anal*. Calcd for $C_{24}H_{26}N_4O$; C, 74.58; H, 6.78; N, 14.50. Found: C, 74.83; H, 6.87; N, 14.70.

2-(4-Chlorophenyl)-4-piperidino-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (13d). The residue was recrystallized from cyclohexane to give **13d** (78%) as a white powder, mp 170–172°C; IR (potassium bromide) cm^{-1}: 3410 (NH); ^1H NMR (deuterochloroform): δ 1.72 (br s, 6H, H3′, 4′, and 5′), 2.91 (br t, 2H, $J = 5.0$ Hz, H5), 3.25–4.59 (m, 4H, H2′ and 6′), 3.76 (br t, 2H, $J = 5.0$ Hz, H6), 3.94 (br, 1H, deuterium oxide exchangeable, NH), 6.62–8.61 (m, 8H, Ar-H); FAB-mass *m/z* 391 (MH^+), 393 ($MH^+ + 2$). *Anal*. Calcd for $C_{23}H_{23}ClN_4$: C, 70.67; H, 5.93; N, 14.33. Found: C, 71.02; H, 6.05; N, 14.01.

General procedure for the synthesis of 12-substituted 1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepine (14a–d). A mixture of **3a–d** (100 mg) and phosphoryl chloride (3.0 mL) was refluxed for 1 h, and ice water (50 mL) was added to the oily product. The solution was adjusted to pH 11–12 with aq 10% potassium hydroxide and then extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate to give crystalline **14** as a free base. As a free base, **14** did not give satisfactory elemental analytical data, possibly because of its hygroscopic nature, so an analytical sample for elemental analysis was prepared as the hydrochloride as follows: To a solution of **14** in ethanol (15 mL) was added concd hydrochloric acid (2.0 mL) to pH 1–2 followed by evaporation under reduced pressure. The resulting residue was recrystallized from ethanol–ethyl acetate to give **14** as the hydrochloride.

12-Methyl-1,2,5,6-tetrahydro-4H-imidazo[1′,2′:1,6]pyrimido[5,4-d][1]benzazepine (14a). According to the general procedure, free amine **14a** (77%) was obtained from **3a** as yellow prisms, mp 208–211°C; IR (potassium bromide) cm^{-1}: 3260, 3450 (sh) (NH); ^1H NMR (DMSO-d_6): δ 2.23 (s, 3H, Me), 2.63–2.82 (m, 2H, H4), 3.24–3.55 (m, 2H, H5), 3.78–4.12 (m, 4H, H1 and 2), 6.11 (br, 1H, deuterium oxide exchangeable, NH), 6.47–8.06 (m, 4H, Ar-H); FAB-mass *m/z* 253. Elemental analysis was performed for the hydrochloride prepared as described earlier; *Anal*. Calcd for $C_{15}H_{16}N_4 \cdot 2HCl \cdot H_2O$: C, 52.49; H, 5.87; N, 16.32. Found: C, 52.31; H, 5.74; N, 16.39.

12-Phenyl-1,2,5,6-tetrahydro-4H-imidazo[1′,2′:1,6]pyrimido[5,4-d][1]benzazepine (14b). According to the general procedure, free amine **14b** (83%) was obtained from **3b** as yellow prisms, mp 114–116°C; IR (potassium bromide) cm^{-1}: 3350 (NH); ^1H NMR (deuterochloroform): δ 2.89 (t, 2H, $J = 5.5$ Hz, H4), 3.73 (t, 2H, $J = 5.5$ Hz, H5), 4.04 (br s, 4H, H1 and 2), 6.60–8.23 (m, 10H, changed to 9H with addition of deuterium oxide, Ar-H, NH); FAB-mass *m/z* 315 (MH^+). Elemental analysis was performed for the hydrochloride prepared as described earlier; *Anal*. Calcd for $C_{20}H_{18}N_4 \cdot 2HCl \cdot 2/3H_2O$: 60.16; H, 5.38; N, 14.03. Found: C, 59.95; H, 5.43; N, 13.86.

12-(4-Methoxyphenyl)-1,2,5,6-tetrahydro-4H-imidazo[1′,2′:1,6]pyrimido[5,4-d][1]benzazepine (14c). According to the general procedure, free amine **14c** (81%) was obtained from **3c** as yellow needles, mp 127–130°C; IR (potassium bromide) cm^{-1}: 3400 (NH); ^1H NMR (deuterochloroform): δ 2.73–3.02 (m, 2H, H4), 3.56–4.37 (m, 9H, OMe, H1, 2, and 5), 6.60–8.32 (m, 9H, changed to 8H with addition of deuterium oxide, Ar-H, and NH); FAB-mass *m/z* 345 (MH^+). Elemental analysis was performed for the hydrochloride prepared as described earlier; *Anal*. Calcd for $C_{21}H_{20}N_4O \cdot 2HCl \cdot 2.5H_2O$: C, 54.55; H, 5.89; N, 12.12. Found: C, 54.33; H, 5.49; N, 12.11.

12-(4-Chlorophenyl)-1,2,5,6-tetrahydro-4H-imidazo[1′,2′:1,6]pyrimido[5,4-d][1]benzazepine (14d). According to the general procedure, free amine **14d** (67%) was obtained from **3d** as yellow needles, mp 201–203°C; IR (potassium bromide) cm^{-1}: 3340 (NH); ^1H NMR (DMSO-d_6): δ 2.74 (t, 2H, $J = 5.0$ Hz, H4), 3.30–3.56 (m, 2H, H5), 3.82, 4.10 (each t, each 2H, $J = 9.0$ Hz, H1 and 2), 6.28 (br s, 1H, deuterium oxide exchangeable, NH), 6.60–8.07 (m, 8H, Ar-H); FAB-mass *m/z* 349 (MH^+), 351 ($MH^+ + 2$). Elemental analysis was performed for the hydrochloride prepared as described earlier; *Anal*. Calcd for $C_{20}H_{17}ClN_4 \cdot 2HCl \cdot 8/3H_2O$: C, 51.35; H, 4.81; N, 11.98. Found: C, 50.98; H, 5.23; N, 11.90.

Measurement of platelet aggregation. Preparation of platelet-rich plasma was performed according to the method described previously [20]. The platelet-rich plasma described earlier, 250 μL, synthetic compounds **3** and **10–14**, 25 μL (10% DMSO solution or 60% DMF solution), and 1*M* Tris–HCl buffer (pH 7.4) 25 μL were mixed and preincubated at 37°C, followed 2 min later by addition of 50-μL aggregating agent (collagen, final concentration 14.3 μg/mL) with stirring (1000 rpm). 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 [20].

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