Polycyclic *N*-Heterocyclic Compounds. XLI. Synthesis of 4-Substituted 6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines, 1,2,5,6-Tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepines and Their Related Compounds as a Series of Potential Blood Platelet Aggregation Inhibitors

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As a series of polyheterocyclic compounds for exploitation as anti-platelet agents, tricyclic heterocyclic compounds, 4-substituted 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines **3-6**, **9**, **12-14**, and **16-26**, having nitrogen, oxygen, or sulfur containing functional groups at the 4-position, were prepared. In addition, tetracyclic heterocyclic compounds, 3-methyl-1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepinium chloride (**7**), 1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepines **10a-e**, 2,3,6,7-tetrahydro-1*H*,5*H*-pyrimido[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepine (**11**), and 1,2,5,6-tetrahydro-4*H*-thiazolo-[3′,2′:1,6]pyrimido[5,4-*d*][1]benzazepinium chloride (**15**) *via* ring closure of 4-(hydroxyalkylamino)- **6**, **9a-e**, and **3c**, and 4-(2-hydroxyethylthio)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**14**) with phosphoryl chloride or thionyl chloride, respectively, were also prepared. Their inhibitory activities against collagen-induced aggregation of rabbit blood platelets *in vitro* were investigated. Among them, compound **5** having a morpholino group at the 4-position on the tricyclic nucleus, which enhanced the activity more than 14-fold as compared with aspirin, was found to have the most satisfactory in inhibitory activity.

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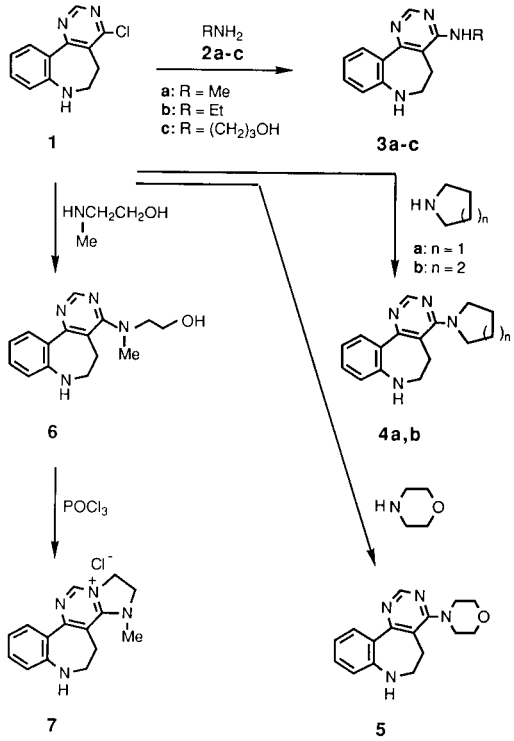
As part of our ongoing study in the design and synthesis of novel poly-heterocyclic compounds, we have recently reported the convenient syntheses and potential inhibitory activities against collagen-induced aggregation of rabbit blood platelets as compared with that of aspirin, which was well known as an anti-platelet agent [1], for 5,6-dihydrobenzo[*h*]quinazolines [2], 6,7-dihydro-5*H*-benzo[6,7]-cyclohepta[1,2-*d*]pyrimidines [3], 5,6-dihydro-4*H*-benzo-[3,4]cyclohept[1,2-*e*]imidazo[1,2-*c*]pyrimidines [4], 1,2,4,5-tetrahydro[1]benzothiepino[4,5-*e*]imidazo[1,2-*c*]pyrimidines [5], 5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidines [5], 1,2,4,5-tetrahydro[1]benzoxepino[4,5-*e*]imidazo[1,2-*c*]-pyrimidines [6], and 5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidines [6]. These findings of potent anti-platelet aggregation activity in such polyheterocyclic compounds have stimulated our further interest to develop general and simple methods for the synthesis of novel ring systems of polyheterocyclic compounds. In the previous paper [7] we reported the total synthesis of unsubstituted 1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepine (**10a**) as a novel ring system. In this paper we describe the preparation of its derivatives **10b-c** and tricyclic heterocyclic compounds such as 4-substituted 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines **3-6**, **9**, **12-14**, and **16-26** having nitrogen, oxygen, or sulfur containing functional groups at the 4-position. In addition, tetracyclic heterocyclic compounds such as 3-methyl-1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepinium chloride (**7**), 2,3,6,7-tetrahydro-1*H*,5*H*-pyrimido[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepine (**11**), and 1,2,5,6-tetrahydro-4*H*-thiazolo[3′,2′:1,6]pyrimido[5,4-*d*][1]benzazepinium chloride (**15**) *via* ring closure of 4-(*N*-methyl-2-hydroxyethylamino)- **6**, 4-(3-hydroxypropylamino)- **3c**, and 4-(2-hydroxyethylthio)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines (**14**) by heating with phosphoryl chloride or thionyl chloride, respectively, are also reported. Moreover the evaluation of inhibitory activity against rabbit blood platelet aggregation induced by collagen for them is discussed.

Synthesis.

4-Substituted 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines **3-6** having a nitrogen functional group at the 4-position are outlined in Scheme 1 and were synthesized from the key intermediate, 4-chloro-6,7-dihydro-5*H*-pyrimido-[5,4-*d*][1]benzazepine (**1**) [7]. Thus, treatment of **1** with an appropriate amine such as 40% methanolic methylamine, 70% aqueous ethylamine, 3-amino-1-propanol, pyrrolidine, piperidine, morpholine, and *N*-methylethanolamine at room temperature or 60-80° gave the corresponding 4-alkylamino derivatives **3a-c**, **4a,b**, **5**, and **6** in good yield. Further heating of 4-(*N*-methyl-2-hydroxyethylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**6**) with phosphoryl chloride afforded the cyclized compound, 3-methyl-1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]-benzazepinium chloride (**7**) in 30% yield. The structures of compounds **3-7** were fully supported by analytical and spectral data. In particular, the ^{1}H-nmr spectrum of **6**

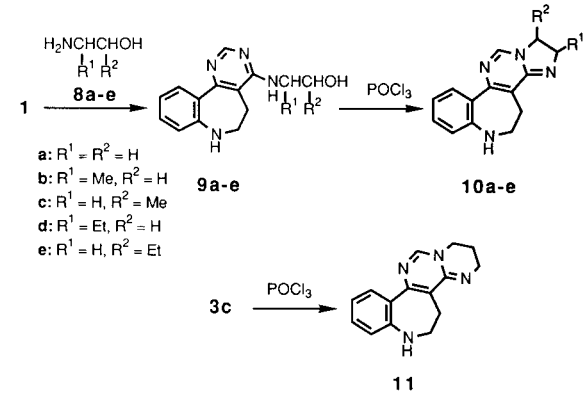
showed the pyrimidine ring proton as a singlet signal at 8.57 ppm (deuteriochloroform), while the spectrum of **7** shifted downfield the pyrimidine ring proton (δ 8.86 in DMSO-d_6) due to the quarternary nitrogen at the 12a-position.

Scheme 1



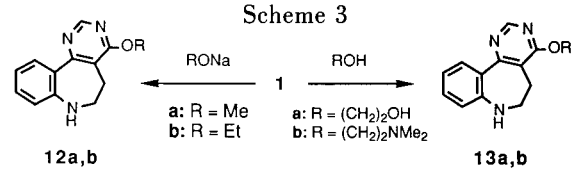
In the same manner, heating of **1** with excess aminoalcohols afforded the corresponding 4-(hydroxyalkylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines **9a-e** (Scheme 2). The subsequent dehydration of **9a-e** and **3c** by heating with phosphoryl chloride gave the corresponding tetracyclic compounds **10a-e** and **11** in 70-90% yields. Their structures were verified by elemental analyses and spectral data as shown in the Experimental.

Scheme 2



Next, 4-substituted derivatives **12a,b** and **13a,b** having an oxygen functional group at the 4-position are outlined in Scheme 3 and were synthesized from the reaction of **1** with an appropriate alcohol in the presence of base. Namely, a stirred solution of **1** with an excess of methanol or ethanol in the presence of sodium at room temperature yielded the corresponding 4-methoxy **12a** (88%) and 4-ethoxy derivative **12b** (71%). Similar treatment of **1** with excess ethylene glycol and triethylamine at 80° or with 2-dimethylaminoethanol and sodium hydride in dioxane at room temperature gave the corresponding 4-(2-hydroxyethoxy) **13a** (78%) and 4-(2-dimethylaminoethoxy) derivative **13b** (74%).

Scheme 3



Meanwhile, 4-substituted derivatives **14**, **16**, **18**, **19** and **20** having a sulfur functional group at the 4-position are outlined in Scheme 3 and were synthesized from **1** or **17**. Heating of **1** with 2-mercaptoethanol in pyridine afforded the 4-(2-hydroxyethylthio) derivative **14** (74%) which was easily cyclized by heating with thionyl chloride in chloroform to give the tetracyclic heterocyclic compound **15** (53%). Similar heating of **1** with 2-dimethylaminoethanethiol hydrochloride in the presence of sodium hydride in dioxane afforded the 4-dimethylaminoethylthio derivative **16** (68%). On the other hand, methylation of **1** by heating with excess methyl iodide and potassium carbonate in dry acetone gave the 7-methyl derivative **17** (51%) which was converted to the desired 4-thioxo derivative **18** (75%) by heating with excess thiourea in methyl cellosolve. Further ethylation of **18** by shaking with excess ethyl iodide in 1*N* potassium hydroxide at 4° afforded the 4-ethylthio derivatives **19** in 89% yield. Whereas heating **18** with 3-bromopropanol in the presence of triethylamine in methyl cellosolve at 80° afforded the 4-(3-hydroxypropylthio) derivative **20** in 40% yield.

Finally, treatment of 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]-benzazepin-4(3*H*)-one (**21**) [7] with appropriate alkyl halides in the presence of base yielded the corresponding 3-alkyl-4-oxo derivatives **22-26**. Thus refluxing of **21** with 1.5 or 5 equivalents of methyl iodide in the presence of potassium carbonate in dry acetone afforded the 3-methyl-4-oxo derivative **22** (56%) and the 3,7-dimethyl-4-oxo derivative **23** (53%), respectively. Moreover refluxing of **21** with methyl bromoacetate, benzyl chloride, or bromoacetonitrile in the presence of triethylamine in dry acetone yielded the corresponding 3-methoxycarbonylmethyl-4-oxo **24** (42%), 3-benzyl-4-oxo **25** (40%), and 3-cyanomethyl-4-oxo derivative **26** (40%).

Biological Evaluation.

The compounds prepared here were screened for inhibitory effect on rabbit blood platelet aggregation by a turbidimetric method developed by Born and Cross [8] using an aggregometer. Details of the test procedures are reported in the Experimental. The extent of aggregation was expressed in terms of the maximum change of transmission which was expressed as a percentage for the difference of light transmission between the platelet rich plasma (PRP) and the platelet poor plasma (PPP) as 100%. The maximum aggregation rate (MAR) was calculated from an aggregation response curve obtained by equation 1, where A, B, and X are optical transmission of PRP, optical transmission of PPP, and maximum optical transmission on the aggregation response curve, respectively. Then the inhibition rate of the test compound at each concentration was calculated by equation 2, where Y and Z are MAR of test compound-treated PRP and MAR of vehicle-treated PRP, respectively.

Equation 1:

$$MAR = \frac{X - A}{B - A} \times 100$$

Equation 2:

$$\text{Inhibition rate} = \frac{Z - Y}{Z} \times 100$$

The inhibitory activity of aspirin against blood platelet aggregation was also examined as a positive control. When the inhibition rate of the test compound was significantly different from that of aspirin at $p < 0.01$ on statistical analysis using Student's *t*-test, the amount (μmol/l) for the 50% inhibition concentration against blood platelet aggregation induced by collagen (IC_{50}) was calculated by a probit method. The results of the maximum inhibition rates and IC_{50} values with 95% confidence limits for the test compounds and aspirin are recorded in Table I.

An examination of these results reveals the structure-activity relationships of the compounds prepared here in the following manner. The maximum inhibition rates of the tricyclic and tetracyclic compounds listed in Table I appeared to differ benefically from that of aspirin at the final concentration of 25 μmol/l, whereas the compounds without listed in the Table exhibited similar or less activity to aspirin. Next, a detailed comparison of the inhibitory activity in terms of IC_{50} of the compounds with that of aspirin clarified that many of such tri and tetracyclic compounds had more inhibitory activity than aspirin. Among them, compound **5** having a morpholino group at the 4-position on the tricyclic nucleus was found to have the greatest inhibitory activity. Namely, compound **5** exhibited 14.4 times stronger inhibitory activity than aspirin, followed by **10c**, **3b**, **4a**, **12a**, **12b**, **9c**, and **4b** exhibited 4.6, 4.1, 3.7, 3.7, 3.4, 3.3, and 3.1 times, respectively. The other compounds were less than 3-fold as active. It may be concluded that the tricyclic compounds have a tendency to be more satisfactory than the tetracyclic compounds for

Table I

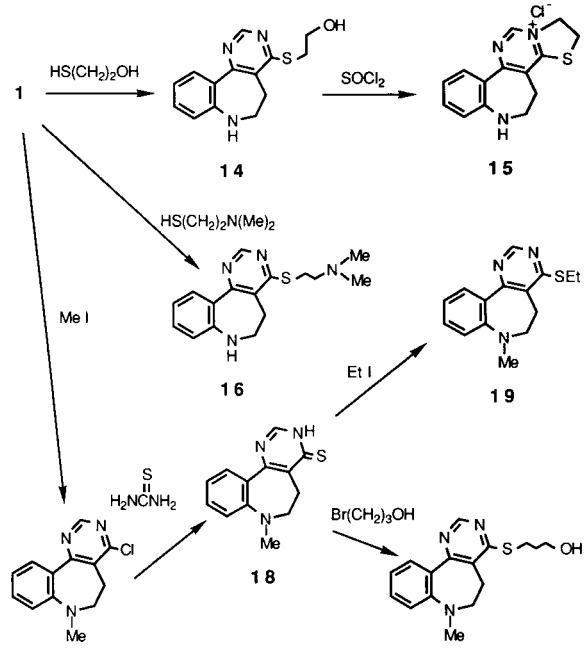
Maximum Inhibition Rate and IC_{50} on Blood Platelet Aggregation Induced by Collagen

Compound	Maximum inhibition rate [a]	IC_{50} [b] (μmol/ℓ)	Compound	Maximum inhibition rate [a]	IC_{50} [b] (μmol/ℓ)
3a	55.6 ± 5.2	20.8 (17.5-24.9)	**3b**	83.8 ± 6.9	10.9 (8.4-13.8)
3c	76.1± 4.0	17.4 (13.4-22.3)	**4a**	91.1 ± 1.5	12.2 (10.8-14.0)
4b	72.3 ± 7.4	14.3 (11.0-21.4)	**5**	83.9 ± 4.4	3.1 (1.1-5.6)
9b	63.7 ± 4.4	16.0 (8.9-24.9)	**9c**	72.5 ± 1.6	13.5 (7.9-18.6)
9d	63.6± 9.9	17.7 (12.1-24.2)	**9e**	46.6 ± 3.9	36.9 (23.0-89.7)
10c	70.7 ± 5.1	9.8 (7.0-12.6)	**11**	34.5 ± 1.4	28.0 (19.7-47.3)
12a	78.4 ± 3.6	12.1 (10.1-14.2)	**12b**	86.8 ± 1.4	13.0 (11.5-14.9)
13a	47.1 ± 5.1	29.8 (20.7-64.0)	**16**	54.0 ± 5.3	23.3 (17.4-32.7)
18	47.8 ± 7.8	24.5 (17.7-21.4)	**23**	37.4 ± 2.8	32.1 (24.1-47.7)
25	37.1 ± 3.8	34.2 (24.6-57.5)	Asprin	35.5 ± 2.2	44.6 (37.6-55.0)

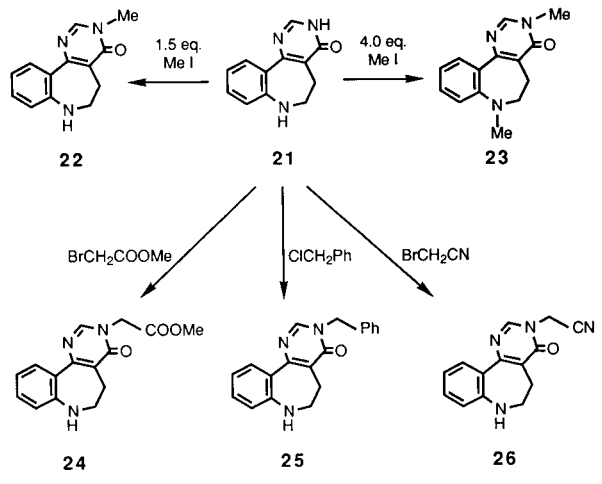
[a] The values are expressed as % and the mean ± S.E. of at least three different experiments at final concentration of 25 μmol/ℓ. Significantly different from aspirin at $p < 0.01$. [b] The values in parentheses represent 95% confidence limits. Experiments were repeated at least each 3 times at three different final concentrations of 1-100 μmol/ℓ (in the case of aspirin, the final concentrations were 25, 50 and 100 μmol/ℓ).

the inhibitory activity except for the compound **10c**. Especially, the tetracyclic benzazepinium chlorides **7** and **15**, which exhibited the maximum inhibition rates of 11.9 ± 6.6 and 33.1 ± 8.2, respectively, were less active than aspirin. However the relationship between chemical structure and the inhibitory activity against collagen-induced aggregation of rabbit blood platelet was not clear in this series.

Scheme 4



Scheme 5



EXPERIMENTAL

Melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. Infrared (ir) and ultraviolet (uv) spectra were recorded with Japan Spectroscopic IRA-102 diffraction grating infrared and Hitachi Model 200-10 spectrometers, respectively. Nuclear magnetic resonance (^{1}H-nmr) spectra were obtained with a Hitachi R-22 FTS FT-NMR (90 MHz), Varian VXR-200 (200 MHz) or a Varian VXR-500 (500 MHz) instrument with tetramethylsilane as an internal standard. The FAB-ms spectra were measured on a VG-70SE instrument and EI-ms spectra on a Shimadzu LKB-9000. Column chromatography was carried out with Kiesel gel 60 (70-230 mesh ASTM, Merck).

4-Chloro- (**1**), 4-(3-hydroxypropylamino)- (**3c**), and 4-(2-hydroxyethylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**9a**), and 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4(3*H*)-one (**21**) were prepared by the previously reported procedures [7,9].

4-Methylamino-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**3a**).

A mixture of 4-chloro-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**1**) (463 mg, 2 mmoles) and 40% methanolic methylamine (10 ml, 116 mmoles) was stirred at room temperature for 6 hours. After the solution was concentrated to dryness *in vacuo*, the residue was purified by column chromatography on silica gel (chloroform/acetone, 1:1 v/v) and recrystallized from benzene to afford **3a** (400 mg, 89%) as pale brown prisms, mp 180-181°; ir (chloroform): ν max 3480, 3380 (NH) cm^{-1}; ms: FAB m/z 227 (MH^+); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 2.63 (t, J = 5.4 Hz, 2H, 5-H), 3.08 (d, J = 5.4 Hz, changed to singlet after addition of deuterium oxide, 3H, NCH_3), 3.56 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.70 (t, J = 5.4 Hz, 2H, 6-H), 4.88 (br, exchangeable with deuterium oxide, 1H, 4-NH), 6.65-7.43 (m, 3H, 8-, 9-, and 10-H), 8.12 (dd, $J_{9,11}$ = 1.8 Hz, $J_{10,11}$ = 7.2 Hz, 1H, 11-H), 8.70 (s, 1H, 2-H).

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.31; H, 6.22; N, 24.45.

4-Ethylamino-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**3b**).

A mixture of **1** (463 mg, 2 mmoles) and 70% aqueous ethylamine (11.6 ml, 143 mmoles) in dry dioxane (30 ml) was stirred at room temperature for 96 hours. After the solution was concentrated to dryness *in vacuo*, the residue was purified by column chromatography on silica gel (chloroform/acetone, 5:1 v/v) and recrystallized from benzene to afford **3b** (290 mg, 60%) as yellow needles, mp 142-143°; ir (chloroform): ν max 3460, 3370 (NH) cm^{-1}; ms: FAB m/z 241 (MH^+); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 1.27 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.64 (t, J = 5.7 Hz, 2H, 5-H), 3.54 (dq, J = 5.3, 7.2 Hz, 2H, CH_2CH_3), 3.69 (t, J = 5.7 Hz, 2H, 6-H), 3.90 (br, exchangeable with deuterium oxide, 1H, 7-NH), 4.77 (br t, J = 5.3 Hz, exchangeable with deuterium oxide, 1H, 4-NH), 6.68 (dd, $J_{8,10}$ = 1.1 Hz, $J_{8,9}$ = 7.9 Hz, 1H, 8-H), 6.96 (dt, $J_{8,10}$ = 1.1 Hz, $J_{9,10}$ = 7.2 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 10-H), 7.20 (dt, $J_{9,11}$ = 1.5 Hz, $J_{9,10}$ = 7.2 Hz, $J_{8,9}$ = 7.9 Hz, 1H, 9-H), 8.01 (dd, $J_{9,11}$ = 1.5 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 11-H), 8.58 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.87; H, 6.77; N, 23.22.

4-(1-Pyrrolidinyl)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**4a**).

A mixture of **1** (463 mg, 2 mmoles) and pyrrolidine (1.32 ml, 16

mmoles) was stirred at 70° for 1 hour. After the solution was concentrated to dryness *in vacuo*, the residue dissolved in water (5 ml) was extracted with chloroform (2 x 5 ml). The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The yellowish oily residue was purified by column chromatography on silica gel (chloroform/acetone, 1:1 v/v), and the isolated crystals were recrystallized from benzene to afford **4a** (500 mg, 94%) as colorless needles, mp 195-196°; ir (potassium bromide): ν max 3250 (NH) cm^{-1}; ms: EI m/z 266 (M^+, 95%), 251 (M^+ -NH, 17%), 237 (M^+ -$NHCH_2$, 48%), 223 (M^+ -$NHCH_2CH_2$, 100%); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 1.97 (m, 4H, $NCH_2(CH_2)_2CH_2$), 2.82 (t, J = 6.1 Hz, 2H, 5-H), 3.66 (m, 4H, $N(CH_2)_2$), 3.72 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.84 (t, J = 6.1 Hz, 2H, 6-H), 6.80 (dd, $J_{8,10}$ = 1.2 Hz, $J_{8,9}$ = 7.8 Hz, 1H, 8-H), 7.07 (dt, $J_{8,10}$ = 1.2 Hz, $J_{9,10}$ = 7.3 Hz, $J_{10,11}$ = 7.8 Hz, 1H, 10-H), 7.28 (dt, $J_{9,11}$ = 1.7 Hz, $J_{9,10}$ = 7.3 Hz, $J_{8,9}$ = 7.8 Hz, 1H, 9-H), 7.95 (dd, $J_{9,11}$ = 1.7 Hz, $J_{10,11}$ = 7.8 Hz, 1H, 11-H), 8.60 (s, 1H, 2-H).

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.39; H, 6.98; N, 21.05.

4-Piperidino-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**4b**).

A mixture of **1** (231 mg, 1 mmole) and piperidine (0.79 ml, 8 mmoles) was heated at 70° with stirring for 2 hours. After the same work-up as noted above, the resulting oily residue was purified by column chromatography on silica gel (chloroform/acetone, 2:1 v/v) and recrystallized from benzene-cyclohexane to afford **4b** (200 mg, 71%) as yellow needles, mp 148-150°; ir (potassium bromide): ν max 3260 (NH) cm^{-1}; ms: EI m/z 280 (M^+, 100%), 265 (M^+ -NH, 59%), 251 (M^+, -$NHCH_2$, 25%), 237 (M^+ -$NHCH_2CH_2$, 23%); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 1.68 (br m, 6H, $NCH_2(CH_2)_3CH_2$), 2.85 (t, J = 5.6 Hz, 2H, 5-H), 3.32 (m, 4H, $N(CH_2)_2$), 3.76 (t, J = 5.6 Hz, 2H, 6-H), 4.00 (br, exchangeable with deuterium oxide, 1H, 7-NH), 6.73 (dd, $J_{8,10}$ = 1.0 Hz, $J_{8,9}$ = 9.0 Hz, 1H, 8-H), 6.96 (ddd, $J_{8,10}$ = 1.0 Hz, $J_{9,10}$ = 7.2 Hz, $J_{10,11}$ = 8.0 Hz, 1H, 10-H), 7.24 (ddd, $J_{9,11}$ = 1.7 Hz, $J_{9,10}$ = 7.2 Hz, $J_{8,9}$ = 9.0 Hz, 1H, 9-H), 7.98 (dd, $J_{9,11}$ = 1.7 Hz, $J_{10,11}$ = 8.0 Hz, 1H, 11-H), 8.72 (s, 1H, 2-H).

Anal. Calcd. for $C_{17}H_{20}N_4$: C, 72.82; H, 7.19; N, 19.99. Found: C, 73.12; H, 7.43; N, 19.71.

4-Morpholino-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**5**).

A mixture of **1** (463 mg, 2 mmoles), morpholine (0.7 ml, 8 mmoles), and potassium carbonate (552 mg, 4 mmoles) in dry DMF (10 ml) was heated at 80° with stirring for 16 hours. After the solution was concentrated to dryness *in vacuo*, the residue in water (10 ml) was basified (*p*H *ca.* 9) with 2*N* sodium hydroxide and extracted with ethyl acetate (3 x 7 ml). After the usual work-up, the resulting yellowish oily residue was purified by column chromatography on silica gel (chloroform/acetone, 1:1 v/v) and recrystallized from benzene-cyclohexane to afford **5** (360 mg, 64%) as yellow needles, mp 131-132°; ir (chloroform): ν max 3440 (NH) cm^{-1}; ms: FAB m/z 283 (MH^+); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 2.87 (t, J = 5.5 Hz, 2H, 5-H), 3.36 (t, J = 4.7 Hz, 4H, $N(CH_2)_2$), 3.73 (t, J = 5.5 Hz, 2H, 6-H), 3.84 (t, J = 4.7 Hz, 4H, $O(CH_2)_2$), 4.04 (br, exchangeable with deuterium oxide, 1H, 7-NH), 6.72 (dd, $J_{8,10}$ = 1.0 Hz, $J_{8,9}$ = 8.0 Hz, 1H, 8-H), 6.95 (ddd, $J_{8,10}$ = 1.0 Hz, $J_{9,10}$ = 7.2 Hz, $J_{10,11}$ = 8.0 Hz, 1H, 10-H), 7.24 (ddd, $J_{9,11}$ = 1.5 Hz, $J_{9,10}$ = 7.2 Hz, $J_{8,9}$ = 8.0 Hz, 1H, 9-H), 7.97 (dd, $J_{9,11}$ = 1.5 Hz, $J_{10,11}$ = 8.0 Hz, 1H, 11-H), 8.74 (s, 1H, 2-H).

Anal. Calcd. for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.85. Found: C, 67.73; H, 6.39; N, 19.96.

4-(*N*-Methyl-2-hydroxyethylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**6**).

A mixture of **1** (926 mg, 4 mmoles) and *N*-methylethanolamine (1.2 g, 16 mmoles) was heated at 60° with stirring for 30 minutes. The solution cooled and diluted with water (15 ml) was extracted with ethyl acetate (3 x 10 ml). After the usual work-up, the solid residue was recrystallized from ethyl acetate to afford **6** (795 mg, 74%) as colorless plates, mp 130-131°; ir (potassium bromide): ν max 3290 (OH), 3250 (NH), 1040 (COH) cm^{-1}; ms: FAB m/z 271 (MH^+); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 2.85 (t, J = 5.9 Hz, 2H, 5-H), 3.15 (s, 3H, NMe), 3.18 (br, exchangeable with deuterium oxide, 1H, OH), 3.67 (t, J = 4.5 Hz, 2H, $NMeCH_2$), 3.81 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.83 (t, J = 5.9 Hz, 2H, 6-H), 3.91 (t, J = 4.5 Hz, 2H, CH_2OH), 6.78 (dd, $J_{8,10}$ = 1.0 Hz, $J_{8,9}$ = 8.0 Hz, 1H, 8-H), 7.05 (ddd, $J_{8,10}$ = 1.0 Hz, $J_{9,10}$ = 7.2 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 10-H), 7.29 (ddd, $J_{9,11}$ = 1.5 Hz, $J_{9,10}$ = 7.2 Hz, $J_{8,9}$ = 8.0 Hz, 1H, 9-H), 7.95 (dd, $J_{9,11}$ = 1.5 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 11-H), 8.57 (s, 1H, 2-H); uv: λ max nm (log ϵ) 237 (4.78), 260 (4.59) sh, 310 (4.18), 370 (3.77) sh.

Anal. Calcd. for $C_{15}H_{18}N_4O$: C, 66.66; H, 6.71; N, 20.73. Found: C, 66.33; H, 6.74; N, 20.55.

3-Methyl-1,2,5,6-tetrahydro-4*H*-imidazo[1',2':1,6]pyrimido[5,4-*d*]-[1]benzazepinium Chloride (**7**).

A mixture of **6** (270 mg, 1 mmole) and phosphoryl chloride (1.5 ml, 16 mmoles) was refluxed for 2 hours. The reaction mixture was concentrated to syrup *in vacuo*, and cold water (10 ml) was poured at once to the residue. After the resulting solution was concentrated again to dryness *in vacuo*, the residue was purified by column chromatography on silica gel (ethanol). The isolated crystals were recrystallized from ethanol-diethyl ether to afford **7** (90 mg, 31%) as yellow prisms, mp 251-253°; ir (potassium bromide): ν max 3220 (NH) cm^{-1}; ms: FAB molecular ion peak was not observed, m/z 253 (MH^+ -Cl); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 2.93 (t, J = 5.6 Hz, 2H, 4-H), 3.37 (s, 3H, NMe), 3.80 (t, J = 5.6 Hz, 2H, 5-H), 4.05 (t, J = 9.9 Hz, 2H, 2-H), 4.38 (br, exchangeable with deuterium oxide, 1H, 6-NH), 4.60 (t, J = 9.9 Hz, 2H, 1-H), 7.17 (br dd, $J_{8,9}$ = 7.1 Hz, $J_{9,10}$ = 8.0 Hz, 1H, 9-H), 7.32 (br d, J = 8.3 Hz, 1H, 7-H), 7.48 (ddd, $J_{8,10}$ = 1.5 Hz, $J_{8,9}$ = 7.1 Hz, $J_{7,8}$ = 8.3 Hz, 1H, 8-H), 7.89 (dd, $J_{8,10}$ = 1.5 Hz, $J_{9,10}$ = 8.0 Hz, 1H, 10-H), 8.86 (s, 1H, 12-H); uv: λ max nm (log ϵ) 255 (4.65), 288 (4.13), 331 (4.00), 425 (3.85).

Anal. Calcd. for $C_{15}H_{17}ClN_4 \cdot 3H_2O$: C, 52.55; H, 6.76; N, 16.34. Found: C, 52.64; H, 6.70; N, 16.21.

4-(2-Hydroxy-1-methylethylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**9b**).

A mixture of **1** (2 g, 8.66 mmoles) with *DL*-2-amino-1-propanol (**8b**) (4 g, 53.3 mmoles) was heated at 150° with stirring for 2 hours. The solution was diluted with water (20 ml) and extracted with ethyl acetate (3 x 10 ml). After the usual work-up, the residue was recrystallized from ethanol-ethyl acetate to yield **9b** (1.9 g, 81%) as colorless prisms, mp 87-88°; ir (potassium bromide): ν max 3320 (sh) (OH), 3260, 3150 (sh) (NH), 1040 (COH) cm^{-1}; ms: FAB m/z 271 (MH^+); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 1.15 (d, J = 6.64 Hz, 3H, Me), 2.70 (br t, J = 5.32 Hz, 2H, 5-H), 3.27-3.52 (m, 4H, CH_2OH and 6-H), 4.23 (quin, J = 6.60 Hz, 1H, $NHCH(CH_3)$-CH_2), 4.72 (t, J = 5.81 Hz, exchangeable with deuterium oxide,

1H, OH), 5.88 (br t, J = 2.80 Hz, exchangeable with deuterium oxide, 1H, 7-NH), 6.48 (d, J = 7.63 Hz, exchangeable with deuterium oxide, 1H, 4-NH), 6.68 (dd, $J_{8,9}$ = 8.00 Hz, $J_{8,10}$ = 1.00 Hz, 1H, 8-H), 6.73 (ddd, $J_{8,10}$ = 1.00 Hz, $J_{9,10}$ = 7.10 Hz, $J_{10,11}$ = 7.95 Hz, 1H, 10-H), 7.11 (ddd, $J_{8,9}$ = 8.00 Hz, $J_{9,10}$ = 7.10 Hz, $J_{9,11}$ = 1.60 Hz, 1H, 9-H), 7.87 (dd, $J_{9,11}$ = 1.60 Hz, $J_{10,11}$ = 7.95 Hz, 1H, 11-H), 8.34 (s, 1H, 2-H).

Anal. Calcd. for $C_{15}H_{18}N_4O \cdot H_2O$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.22; H, 7.17; N, 19.23.

4-(2-Hydroxypropylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**9c**).

A mixture of **1** (2 g, 8.66 mmoles) with *DL*-1-amino-2-propanol (**8c**) (5 g, 66.6 mmoles) was heated at 95° with stirring for 1.5 hours. Treatment of the resulting solution with water gave the precipitate, which was filtered by suction, washed with cold water, and recrystallized from ethanol-ethyl acetate to yield **9c** (1.95 g, 83%) as colorless prisms, mp 191-193°; ir (potassium bromide): ν max 3320 (OH), 3150 (NH), 1062 (COH) cm^{-1}; ms: FAB m/z 271 (MH^+); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 1.06 (d, J = 6.10 Hz, 3H, Me), 2.70 (br t, J = 5.37 Hz, 2H, 5-H), 3.30 (m, 2H, 6-H), 3.51 (m, 2H, NHCH_2CH), 3.86 (quin, J = 5.81 Hz, 1H, C*H*(OH)-CH_3), 4.80 (d, J = 4.39 Hz, exchangeable with deuterium oxide, 1H, OH), 5.90 (br t, J = 3.66 Hz, exchangeable with deuterium oxide, 1H, 7-H), 6.68 (dd, $J_{8,9}$ = 8.08 Hz, $J_{8,10}$ = 1.17 Hz, 1H, 8-H), 6.74 (ddd, $J_{8,10}$ = 1.17 Hz, $J_{9,10}$ = 7.00 Hz, $J_{10,11}$ = 7.90 Hz, 1H, 10-H), 7.11 (ddd, $J_{8,9}$ = 8.08 Hz, $J_{9,10}$ = 7.00 Hz, $J_{9,11}$ = 1.59 Hz, 1H, 9-H), 6.95 (br t, J = 5.52 Hz, exchangeable with deuterium oxide, 1H, 4-NH), 7.89 (dd, $J_{9,11}$ = 1.59 Hz, $J_{10,11}$ = 7.90 Hz, 1H, 11-H), 8.34 (s, 1H, 2-H).

Anal. Calcd. for $C_{15}H_{18}N_4O$: C, 66.66; H, 6.71; N, 20.73. Found: C, 66.44; H, 6.83; N, 20.43.

4-(1-Hydroxymethylpropylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**9d**).

A mixture of **1** (2 g, 8.66 mmoles) with *DL*-2-amino-1-butanol (**8d**) (4 g, 44.9 mmoles) was heated at 150° for 1.5 hours. Treatment of the resulting solution with water gave the precipitate, which was filtered by suction, washed with cold water, and recrystallized from ethyl acetate to yield **9d** (1.99 g, 81%) as colorless prisms, mp 174-176°; ir (potassium bromide): ν max 3330 (OH), 3140 (NH), 1070 (COH) cm^{-1}; ms: FAB m/z 285 (MH^+); ^{1}H-nmr (500 MHz, deuteriochloroform): δ 1.03 (t, J = 7.49 Hz, 3H, Me), 1.64 (m, 1H, one of CHCH_2CH$_3$), 1.68 (br, exchangeable with deuterium oxide, 2H, OH and 7-NH), 1.73 (m, 1H, one of CHCH_2-CH_3), 2.69 (t, J = 5.81 Hz, 2H, 5-H), 3.68 (dd, J = 6.41, 11.01 Hz, 1H, one of CHCH_2OH), 3.74 (br t, J = 5.81 Hz, 2H, 6-H), 3.83 (dd, J = 2.90, 11.01 Hz, 1H, one of CHCH_2OH), 4.11 (m, 1H, 4-NHC*H*), 4.83 (d, J = 6.46 Hz, exchangeable with deuterium oxide, 1H, 4-NH), 6.73 (dd, $J_{8,9}$ = 7.80 Hz, $J_{8,10}$ = 1.10 Hz, 1H, 8-H), 7.00 (dt, $J_{8,10}$ = 1.10 Hz, $J_{9,10}$ = 7.10 Hz, $J_{10,11}$ = 7.90 Hz, 1H, 10-H), 7.24 (dt, $J_{8,9}$ = 7.80 Hz, $J_{9,10}$ = 7.10 Hz, $J_{9,11}$ = 1.58 Hz, 1H, 9-H), 8.02 (dd, $J_{9,11}$ = 1.58 Hz, $J_{10,11}$ = 7.90 Hz, 1H, 11-H), 8.54 (s, 1H, 2-H).

Anal. Calcd. for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.71. Found: C, 67.25; H, 7.16; N, 19.49.

4-(2-Hydroxybutylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**9e**).

A mixture of **1** (2 g, 8.66 mmoles) with *DL*-1-amino-2-butanol (**8e**) (5 g, 56.1 mmoles) was heated at 150° with stirring for 3 hours. The resulting solution was diluted with water (20 ml) and extracted with ethyl acetate (3 x 15 ml). After the usual work-up, the residue was recrystallized form ethyl acetate to yield **9e** (1.86 g, 76%) as colorless prisms, mp 138-139°; ir (potassium bromide): ν max 3330 (sh) (OH), 3250, 3140 (sh) (NH), 1070 (COH) cm^{-1}; ms: FAB m/z 285 (MH^+); ^{1}H-nmr (500 MHz, deuteriochloroform): δ 1.00 (t, J = 7.50 Hz, 3H, Me), 1.56 (quin, J = 7.50 Hz, 2H, CHCH_2CH$_3$), 1.71 (br s, exchangeable with deuterium oxide, 2H, OH and 7-NH), 2.69 (t, J = 5.76 Hz, 2H, 5-H), 3.42 (m, 1H, 4-NHCH$_2$C*H*), 3.74 (m, 4H, 4-NHCH_2CH and 6-H), 5.26 (br t, J = 5.08 Hz, exchangeable with deuterium oxide, 1H, 4-NH), 6.72 (dd, $J_{8,9}$ = 8.00 Hz, $J_{8,10}$ = 1.20 Hz, 1H, 8-H), 6.98 (ddd, $J_{8,10}$ = 1.20 Hz, $J_{9,10}$ = 7.00 Hz, $J_{10,11}$ = 7.90 Hz, 1H, 10-H), 7.23 (ddd, $J_{8,9}$ = 8.00 Hz, $J_{9,10}$ = 7.00 Hz, $J_{9,11}$ = 1.52 Hz, 1H, 9-H), 8.03 (dd, $J_{9,11}$ = 1.52 Hz, $J_{10,11}$ = 7.90 Hz, 1H, 11-H), 8.55 (s, 1H, 2-H).

Anal. Calcd. for $C_{16}H_{20}N_4O \cdot H_2O$: C, 63.55; H, 7.30; N, 18.53. Found: C, 63.71; H, 7.26; N, 18.28.

General Cyclization Procedure for 1,2,5,6-Tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepines **10a-e** and 2,3,6,7-Tetrahydro-1*H*,5*H*-pyrimido[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepine (**11**).

A mixture of the dihydropyrimidobenzazepines **9a-e**, **3c** (2 g) with phosphoryl chloride (20 ml) was heated under reflux for 2-3 hours, respectively. The phosphoryl chloride was then taken off *in vacuo*, and ice-water was added to the residue. The resulting solution was adjusted with 10% aqueous sodium hydroxide to *p*H 10-11 and extracted with ethyl acetate. After the usual work-up, the residue was recrystallized from an appropriate organic solvent to yield the pure product. By using the above procedure, the following results were obtained.

2-Methyl-1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*]-[1]benzazepine (**10b**).

From 4-(2-hydroxy-1-methylethylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**9b**) gave the product **10b** (90%) as yellow needles, mp 237-239° (from dioxane-ethanol); ir (potassium bromide): ν max 3280 cm^{-1} (NH); ms: FAB m/z 253 (MH^+); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 1.17 (d, J = 6.19 Hz, Me), 2.65 (m, 2H, 4-H), 3.41 (m, 2H, 5-H), 3.60 (m, 1H, 2-H), 4.16 (m, 2H, 1-H), 6.21 (t, J = 4.20 Hz, exchangeable with deuterium oxide, 1H, 6-NH), 6.59 (ddd, $J_{7,9}$ = 1.25 Hz, $J_{8,9}$ = 6.89 Hz, $J_{9,10}$ = 8.14 Hz, 1H, 9 -H), 6.69 (dd, $J_{7,8}$ = 8.27 Hz, $J_{7,9}$ = 1.25 Hz, 1H, 7-H), 7.04 (ddd, $J_{7,8}$ = 8.27 Hz, $J_{8,9}$ = 6.89 Hz, $J_{8,10}$ = 1.68 Hz, 1H, 8-H), 7.92 (dd, $J_{8,10}$ = 1.68 Hz, $J_{9,10}$ = 8.14 Hz, 1H, 10-H), 7.95 (s, 1H, 12-H).

Anal. Calcd. for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 71.68; H, 6.31; N, 22.50.

1-Methyl-1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*]-[1]benzazepine (**10c**).

From 4-(2-hydroxypropylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**9c**) gave the product **10c** (84%) as yellow needles, mp 222-223° (from benzene-ethanol); ir (potassium bromide): ν max 3260 cm^{-1} (NH); ms: FAB m/z 253 (MH^+); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 1.39 (d, J = 6.35 Hz, 3H, Me), 2.67 (m, 2H, 4-H), 3.38 (dd, $J_{2,2}$ = 13.97 Hz, $J_{1,2}$ = 7.03 Hz, 1H, one of 2-H), 3.43 (m, 2H, 5-H), 3.99 (dd, $J_{2,2}$ = 13.97 Hz, $J_{1,2}$ = 10.35 Hz, 1H, one of 2-H), 4.50 (m, 1H, 1-H), 6.27 (t, J = 4.40

Hz, exchangeable with deuterium oxide, 1H, 6-NH), 6.60 (ddd, $J_{7,9}$ = 1.20 Hz, $J_{8,9}$ = 6.90 Hz, $J_{9,10}$ = 8.11 Hz, 1H, 9-H), 6.71 (dd, $J_{7,8}$ = 8.20 Hz, $J_{7,9}$ = 1.20 Hz, 1H, 7-H), 7.05 (ddd, $J_{7,8}$ = 8.20 Hz, $J_{8,9}$ = 6.90 Hz, $J_{8,10}$ = 1.59 Hz, 1H, 8-H), 7.94 (dd, $J_{8,10}$ = 1.59 Hz, $J_{9,10}$ = 8.11 Hz, 1H, 10-H), 8.09 (s, 1H, 12-H).

Anal. Calcd. for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 71.66; H, 6.18; N, 22.20.

2-Ethyl-1,2,5,6-tetrahydro-4*H*-imidazo[1',2':1,6]pyrimido[5,4-*d*][1]-benzazepine (**10d**).

From 4-(1-hydroxymethylpropylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**9d**) gave the product **10d** as yellow needles (71%), mp 132° (from ethyl acetate-ethanol); ir (potassium bromide): ν max 3250 cm^{-1} (NH); ms: FAB m/z 267 (MH^+); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 0.88 (t, J = 7.33 Hz, 3H, CH_2CH_3), 1.50 (m, 2H, CH_2CH_3), 2.66 (m, 2H, 4-H), 3.41 (m, 2H, 5-H), 3.69 (dd, $J_{2,2}$ = 10.25 Hz, $J_{1,2}$ = 7.33 Hz, 1H, 1-H), 3.99 (m, 1H, 2-H), 4.16 (t, J = 10.25 Hz, 1H, 1-H), 6.22 (t, J = 4.00 Hz, exchangeable with deuterium oxide, 1H, 6-NH), 6.59 (ddd, $J_{7,9}$ = 1.17 Hz, $J_{8,9}$ = 6.97 Hz, $J_{9,10}$ = 8.12 Hz, 1H, 9-H), 6.70 (dd, $J_{7,8}$ = 8.35 Hz, $J_{7,9}$ = 1.17 Hz, 1H, 7-H), 7.04 (ddd, $J_{7,8}$ = 8.35 Hz, $J_{8,9}$ = 6.97 Hz, $J_{8,10}$ = 1.65 Hz, 1H, 8-H), 7.91 (dd, $J_{8,10}$ = 1.65 Hz, $J_{9,10}$ = 8.12 Hz, 1H, 10-H), 7.95 (s, 1H, 12-H).

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 71.85; H, 6.76; N, 20.73.

1-Ethyl-1,2,5,6-tetrahydro-4*H*-imidazo[1',2':1,6]pyrimido[5,4-*d*][1]-benzazepine (**10e**).

From 4-(2-hydroxybutylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*]-[1]benzazepine (**9e**) gave the product **10e** (94%) as yellow plates, mp 159-160° (from ethyl acetate); ir (potassium bromide): ν max 3300 cm^{-1} (NH); ms: FAB m/z 267 (MH^+); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 0.85 (t, J = 7.35 Hz, 3H, CH_2CH_3), 1.57-1.86 (m, 2H, CH_2CH_3), 2.65 (m, 2H, 4-H), 3.41 (m, 2H, 5-H), 3.49 (dd, $J_{2,2}$ = 14.46 Hz, $J_{1,2}$ = 6.54 Hz, 1H, one of 2-H), 3.92 (dd, $J_{2,2}$ = 14.46 Hz, $J_{1,2}$ = 10.37 Hz, 1H, one of 2-H), 4.33 (m, 1H, 1-H), 6.21 (t, J = 4.03 Hz, exchangeable with deuterium oxide, 6-NH), 6.60 (ddd, $J_{7,9}$ =1.20 Hz, $H_{8,9}$ = 6.90 Hz, $J_{9,10}$ = 8.11 Hz, 1H, 9-H), 6.69 (dd, $J_{7,8}$ = 8.36 Hz, $J_{7,9}$ = 1.20 Hz, 1H, 7-H), 7.04 (ddd, $J_{7,8}$ = 8.36 Hz, $J_{8,9}$ = 6.90 Hz, $J_{8,10}$ = 1.68 Hz, 1H, 8-H), 7.93 (dd, $J_{8,10}$ = 1.68 Hz, $J_{9,10}$ = 8.11 Hz, 1H, 10-H), 8.00 (s, 1H, 12-H).

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 71.89; H, 6.83; N, 20.88.

2,3,6,7-Tetrahydro-1*H*,5*H*-pyrimido[1',2':1,6]pyrimido[5,4-*d*][1]-benzazepine (**11**).

From 4-(3-hydroxypropylamino)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**3c**) gave the product **11** (96%) as yellow needles, mp >290° (from ethanol); ir (potassium bromide): ν max 3230 cm^{-1} (NH); ms: FAB m/z 253 (MH^+); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 2.10 (m, 2H, 2-H), 2.85 (br t, J = 5.12 Hz, 2H, 5-H), 3.50 (m, 4H, 3-H and 6-H), 4.24 (br t, J = 5.50 Hz, 2H, 1-H), 6.68 (br t, J = 4.00 Hz, exchangeable with deuterium oxide, 7-NH), 6.72 (ddd, $J_{8,10}$ = 1.10 Hz, $J_{9,10}$ = 6.90 Hz, $J_{10,11}$ = 8.20 Hz, 1H, 10-H), 6.82 (dd, $J_{8,9}$ = 8.40 Hz, $J_{8,10}$ = 1.10 Hz, 1H, 8-H), 7.21 (ddd, $J_{8,9}$ = 8.40 Hz, $J_{9,10}$ = 6.90 Hz, $J_{9,11}$ = 1.60 Hz, 1H, 9-H), 7.98 (dd, $J_{9,11}$ = 1.60 Hz, $J_{10,11}$ = 8.20 Hz, 1H, 11-H), 8.55 (s, 1H, 13-H).

Anal. Calcd. for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 71.18; H, 6.14; N, 22.18.

4-Methoxy-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**12a**).

To a stirred solution of sodium (90 mg, 3.9 mmoles) in dry methanol (10 ml) was added the methanol solution (20 ml) of **1** (463 mg, 2 mmoles) by portions at room temperature and the stirring was continued for 6 hours. After the solution was concentrated to the 1/3 volume *in vacuo* and diluted with water (30 ml), the resulting solution was extracted with chloroform (3 x 15 ml). The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (chloroform/acetone, 1:1 v/v) and recrystallized from cyclohexane to afford **12a** (406 mg, 88%) as yellow needles, mp 120-121°; ir (chloroform): ν max 3440 (NH) cm^{-1}; ms: FAB m/z 228 (MH^+); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 2.94 (t, J = 5.6 Hz, 2H, 5-H), 3.70 (t, J = 5.6 Hz, 2H, 6-H), 3.81 (br, exchangeable with deuterium oxide, 1H, 7-NH), 4.01 (s, 3H, OMe), 6.82 (dd, $J_{8,10}$ = 1.2 Hz, $J_{8,9}$ = 8.1 Hz, 1H, 8-H), 6.94 (ddd, $J_{8,10}$ = 1.2 Hz, $J_{9,10}$ = 7.2 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 10-H), 7.23 (ddd, $J_{9,11}$ = 1.7 Hz, $J_{9,10}$ = 7.2 Hz, $J_{8,9}$ = 8.1 Hz, 1H, 9-H), 8.05 (dd, $J_{9,11}$ = 1.7 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 11-H), 8.71 (s, 1H, 2-H).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.82; H, 5.85; N, 18.60.

4-Ethoxy-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**12b**).

To a stirred solution of sodium (80 mg, 3.5 mmoles) in dry ethanol (2 ml) was added the ethanol solution (20 ml) of **1** (463 mg, 2 mmoles) by portions at room temperature and the solution was stirred for 1 hour. After the same work-up as noted in the procedure of **12a**, the resulting residue was purified by column chromatography on silica gel (benzene/ethyl acetate, 1:1 v/v) and recrystallized from cyclohexane to afford **12b** (390 mg, 81%) as colorless needles, mp 102-103°; ir (potassium bromide): ν max 3260 (NH) cm^{-1}; ms: FAB m/z 242 (MH^+); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 1.43 (t, J = 6.7 Hz, 3H, CH_2CH_3), 2.98 (t, J = 5.3 Hz, 2H, 5-H), 3.72 (t, J = 5.3 Hz, 2H, 6-H), 3.90 (br, exchangeable with deuterium oxide, 1H, 7-NH), 4.50 (q, J = 6.7 Hz, 2H, OCH_2), 6.72-7.40 (m, 3H, 8-, 9-, and 10-H), 8.13 (br d, J = 7.5 Hz, 1H, 11-H), 8.75 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.95; H, 6.32; N, 17.16.

4-(2-Hydroxyethoxy)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**13a**).

A mixture of **1** (463 mg, 2 mmoles), ethylene glycol (10 ml), and triethylamine (12 ml) was heated at 80° with stirring for 36 hours. After evaporation of excess triethylamine *in vacuo*, the solution diluted with water (60 ml) was extracted with chloroform (3 x 30 ml). After the usual work-up, the residue was purified by column chromatography on silica gel (chloroform/acetone, 2:1 v/v) and recrystallized from benzene to afford **13a** (400 mg, 78%) as yellow needles, mp 130-131°; ir (potassium bromide): ν max 3350 (OH), 3220 (NH), 1025 (COH) cm^{-1}; ms: FAB m/z 258 (MH^+); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 3.07 (t, J = 5.5 Hz, 2H, 5-H), 3.74 (t, J = 5.5 Hz, 2H, 6-H), 4.03 (m, 2H, CH_2OH), 4.20 (br, exchangeable with deuterium oxide, 1H, 7-NH), 4.63 (m, 2H, OCH_2), 4.80 (br, exchangeable with deuterium oxide, 1H, OH), 6.70-7.44 (m, 3H, 8-, 9-, and 10-H), 8.21 (dd, J = 2.0, 7.6 Hz, 1H, 11-H), 8.77 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.63; H, 5.93; N, 16.13.

4-(2-Dimethylaminoethoxy)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]-

benzazepine (**13b**).

To a stirred dry dioxane solution (10 ml) of 2-dimethylaminoethanol (267 mg, 3 mmoles) was added sodium hydride (120 mg, 3 mmoles) by portions at room temperature, and then the mixture was refluxed under an inert atmosphere of argon for 30 minutes. After cooling and addition of dry dioxane solution (20 ml) of **1** (463 mg, 2 mmoles), the reaction mixture was heated at 60-70° with stirring for 4 hours. The mixture was concentrated to dryness *in vacuo*, diluted with water (30 ml), and acidified by acetic acid. The resulting solution was extracted with ethyl acetate (3 x 15 ml) to remove the by-product of 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4(3*H*)-one (**21**). The water layer was adjusted to *p*H 9 with 5% aqueous sodium hydrogen carbonate, extracted with ethyl acetate, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to afford **13b** (420 mg, 74%) as yellowish oil; ir (chloroform): ν max 3440 (NH) cm^{-1}; ms: FAB m/z 285 (MH^+); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 2.33 (s, 6H, 2 x Me), 2.75 (t, J = 5.3 Hz, 2H, CH_2NMe_2), 2.93 (t, J = 5.0 Hz, 2H, 5-H), 3.62 (t, J = 5.0 Hz, 2H, 6-H), 4.25 (br, exchangeable with deuterium oxide, 1H, 7-NH), 4.54 (t, J = 5.3 Hz, 2H, OCH_2), 6.62-7.30 (m, 3H, 8-, 9-, and 10-H), 8.15 (br d, J = 7.7 Hz, 1H, 11-H), 8.75 (s, 1H, 2-H).

Anal. Calcd. for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.83; H, 6.94; N, 19.41.

4-(2-Hydroxyethylthio)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**14**).

A mixture of **1** (463 mg, 2 mmoles), 2-mercaptoethanol (3 ml, 43 mmoles), and dry pyridine (1 ml) was heated at 100° with stirring for 1 hour. After cooling, the solution diluted with water (25 ml) was extracted with ethyl acetate (3 x 15 ml). After the usual work-up, the residue was purified by column chromatography on silica gel (chloroform/acetone, 2:1 v/v) and recrystallized from benzene to afford **14** (400 mg, 74%) as yellowish needles, mp 155-157°; ir (potassium bromide): ν max 3340 (OH), 3270 (NH), 1030 (COH) cm^{-1}; ms: EI m/z 273 (M^+, 78%), 228 ($M^+ - CH_2CH_2OH$, 90%), 196 ($M^+ - SCH_2CH_2OH$, 28%); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 2.91 (s, exchangeable with deuterium oxide, 1H, OH), 3.00 (t, J = 5.5 Hz, 2H, 5-H), 3.46 (t, J = 5.3 Hz, 2H, SCH_2), 3.73 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.79 (t, J = 5.5 Hz, 2H, 6-H), 4.01 (t, J = 5.3 Hz, 2H, CH_2OH), 6.70-7.43 (m, 3H, 8-, 9-, and 10-H), 8.10 (dd, $J_{9,10}$ = 1.8 Hz, $J_{10,11}$ = 7.5 Hz, 1H, 11-H), 8.93 (s, 1H, 2-H); uv: λ max nm (log ϵ) 242 (4.54), 300 (4.39), 374 (3.59).

Anal. Calcd. for $C_{14}H_{15}N_3OS$: C, 61.51; H, 5.53; N, 15.37. Found: C, 61.77; H, 5.43; N, 15.10.

1,2,5,6-Tetrahydro-4*H*-thiazolo[3',2':1,6]pyrimido[5,4-*d*][1]benzazepinium Chloride (**15**).

A mixture of **14** (504 mg, 1.84 mmoles) and thionyl chloride (0.36 ml, 5 mmoles) in alcohol-free dry chloroform (18 ml) was refluxed for 2 hours. The reaction mixture was concentrated to syrup *in vacuo*, and cold water (15 ml) was poured at once to the residue. After the resulting solution was concentrated again to dryness *in vacuo*, the residue was purified by column chromatography on silica gel (ethanol) and recrystallized from ethanol-diethyl ether to afford **15** (285 mg, 53%) as red needles, mp 261-263°; ir (potassium bromide): ν max 3220 (NH) cm^{-1}; ms: FAB molecular ion peak was not observed, m/z 256 ($MH^+ - Cl$); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 2.93 (m, 2H, 4-H), 3.53 (m, 2H, 5-H), 3.84 (t, J = 8.0 Hz, 2H, 2-H), 5.06 (t, J = 8.0 Hz, 2H, 1-H), 6.66 (ddd, $J_{7,9}$ = 1.2 Hz, $J_{8,9}$ = 6.8 Hz, $J_{9,10}$ = 8.2 Hz, 1H, 9-H), 6.88 (br dd, $J_{7,9}$ = 1.2 Hz, $J_{7,8}$ = 8.4 Hz, 1H, 7-H), 7.25 (ddd, $J_{8,10}$ = 1.5 Hz, $J_{8,9}$ = 6.8 Hz, $J_{7,8}$ = 8.4 Hz, 1H, 8-H), 7.90 (t, J = 4.8 Hz, exchangeable with deuterium oxide, 1H, 6-NH), 8.24 (dd, $J_{8,10}$ = 1.5 Hz, $J_{9,10}$ = 8.2 Hz, 1H, 10-H), 9.35 (s, 1H, 12-H); uv: λ max nm (log ϵ) 225 (4.75), 246 (4.88), 336 (4.85), 475 (4.54).

Anal. Calcd. for $C_{14}H_{14}ClN_3S \cdot 3/2H_2O$: C, 52.74; H, 5.37; N, 13.18. Found: C, 52.39; H, 5.16; N, 13.00.

4-Dimethylaminoethylthio-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]-benzazepine (**16**).

To a stirred dry dioxane solution (10 ml) of 2-dimethylaminoethanethiol hydrochloride (425 mg, 3 mmoles) was added sodium hydride (120 mg, 3 mmoles) by portions at room temperature, and then the mixture was refluxed under an inert atmosphere of argon for 30 minutes. After cooling and addition of dry dioxane solution (20 ml) of **1** (463 mg, 2 mmoles), the reaction mixture was heated at 60-70° with stirring for 1 hour. After the reaction, the mixture was worked up exactly according to the procedure of **13b** to afford **16** (410 mg, 68%) as yellowish oil; ir (chloroform): ν max 3440 (NH) cm^{-1}; ms: FAB m/z 301 (MH^+); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 2.36 (s, 6H, 2 x Me), 2.70 (t, J = 6.9 Hz, 2H, SCH_2), 2.95 (t, J = 4.5 Hz, 2H, 5-H), 3.43 (t, J = 6.9 Hz, 2H, CH_2NMe_2), 3.61 (t, J = 4.5 Hz, 2H, 6-H), 4.10 (br, exchangeable with deuterium oxide, 1H, 7-NH), 6.71-7.43 (m, 3H, 8-, 9-, and 10-H), 8.07 (br d, J = 7.3 Hz, 1H, 11-H), 8.95 (s, 1H, 2-H).

Anal. Calcd. for $C_{16}H_{20}N_4S$: C, 63.97; H, 6.71; N, 18.65. Found: C, 63.71; H, 6.98; N, 18.37.

4-Chloro-7-methyl-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**17**).

To a stirred solution of **1** (2 g, 8.64 mmoles) with potassium carbonate (10 g, 72.5 mmoles) in dry acetone (120 ml) was added methyl iodide (41 ml, 0.66 mole), and the mixture was refluxed for 17 hours. After the reaction, the solution filtered off the precipitate was concentrated to dryness *in vacuo* and diluted with water (80 ml). Then the resulting solution was adjusted to *p*H 8 with 10% aqueous sodium hydrogen carbonate and extracted with ethyl acetate (3 x 30 ml). After the usual work-up, the residue was purified by column chromatography on silica gel (chloroform/acetone, 2:1 v/v) to afford **17** (1.08 g, 51%) as yellowish oil. This compound was used to the next reaction without further purification because of the nature of highly lability.

7-Methyl-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine-4(3*H*)-thione (**18**).

A mixture of **17** (660 mg, 2.7 mmoles) with thiourea (1.02 g, 13.4 mmoles) in methyl cellosolve (20 ml) was refluxed with stirring for 25 hours. The reaction mixture was concentrated to dryness *in vacuo*, dissolved in 2*N* sodium hydroxide (30 ml), and stirred at room temperature for 2 hours. The mixture was acidified with acetic acid and extracted with ethyl acetate (3 x 15 ml). After the usual work-up, the residue was recrystallized from benzene to afford **18** (490 mg, 75%) as yellow needles, mp 204-205°; ir (potassium bromide): ν max 3120, 3050 (NH), 1178 (C=S) cm^{-1}; ms: FAB m/z 244 (MH^+); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 2.83 (s, 1H, NMe), 3.16 (t, J = 5.3 Hz, 2H, 5-H), 3.63 (t, J = 5.3 Hz, 2H, 6-H), 6.96-7.53 (m, 3H, 8-, 9-, and 10-H), 7.78 (br d, J = 7.5 Hz, 1H, 11-H), 8.20 (s, 1H, 2-H), 13.13 (br, exchangeable with deuterium oxide, 1H, 3-NH).

Anal. Calcd. for $C_{13}H_{13}N_3S$: C, 64.17; H, 5.39; N, 17.27. Found:

C, 64.20; H, 5.42; N, 16.98.

4-Ethylthio-7-methyl-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**19**).

To a solution of **18** (486 mg, 2 mmoles) in 1*N* potassium hydroxide (3 ml) at 4° was added ethyl iodide (0.48 ml, 6 mmoles), and the mixture was shaken for 30 hours. After the reaction mixture was adjusted to *p*H 5 with acetic acid, the solution was concentrated to syrup *in vacuo*, diluted with water (30 ml), and extracted with ethyl acetate (3 x 15 ml). After the usual work-up, the residue was purified by column chromatography on silica gel (chloroform/acetone, 6:1 v/v) to afford **19** (480 mg, 89%) as yellowish oil; ms: FAB m/z 272 (MH^+); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 1.36 (t, J = 6.8 Hz, 3H, SCH_2CH_3), 2.66 (m, 2H, SCH_2), 2.69 (s, 3H, NMe), 3.15 (t, J = 6.3 Hz, 2H, 5-H), 3.43 (t, J = 6.3 Hz, 2H, 6-H), 6.93-7.46 (m, 3H, 8-, 9-, and 10-H), 7.73 (br d, J = 7.5 Hz, 1H, 11-H), 8.92 (s, 1H, 2-H).

Anal. Calcd. for $C_{15}H_{17}N_3S$: C, 66.39; H, 6.31; N, 15.48. Found: C, 66.01; H, 6.63; N, 15.38.

4-(3-Hydroxypropylthio)-7-methyl-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**20**).

A solution of **18** (486 mg, 2 mmoles), 3-bromopropanol (0.72 ml, 8 mmoles), and triethylamine (1.12 ml, 8 mmoles) in methyl cellosolve (20 ml) was heated at 80° with stirring for 2 hours. After the reaction mixture was concentrated to syrup *in vacuo*, the residue was diluted with water (20 ml), adjusted to *p*H 8 with 1*N* sodium hydroxide, and extracted with chloroform (3 x 15 ml). After the usual work-up, the residue was purified by column chromatography on silica gel (chloroform/acetone, 1:1 v/v) to afford **20** (237 mg, 40%) as yellowish oil; ir (chloroform): ν max 3400 (OH) cm^{-1}; ms: FAB m/z 302 (MH^+); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 1.90 (m, 2H, $SCH_2CH_2CH_2O$), 2.71 (s, 3H, NCH_3), 2.74 (t, J = 6.4 Hz, 2H, 5-H), 3.32 (t, J = 6.7 Hz, 2H, SCH_2), 3.46 (t, J = 6.4 Hz, 2H, 6-H), 3.64 (t, J = 5.8 Hz, 2H, CH_2O), 5.36 (br, exchangeable with deuterium oxide, 1H, OH), 6.99 (dd, $J_{8,10}$ = 1.0 Hz, $J_{8,9}$ = 8.1 Hz, 1H, 8-H), 7.07 (dt, $J_{8,10}$ = 1.0 Hz, $J_{9,10}$ = 7.5 Hz, $J_{10,11}$ = 7.6 Hz, 1H, 10-H), 7.37 (dt, $J_{9,11}$ = 1.7 Hz, $J_{9,10}$ = 7.5 Hz, $J_{8,9}$ = 8.1 Hz, 1H, 9-H), 7.67 (dt, $J_{9,11}$ = 1.7 Hz, $J_{10,11}$ = 7.6 Hz, 1H, 11-H), 8.85 (s, 1H, 2-H).

Anal. Calcd. for $C_{16}H_{19}N_3OS$: C, 63.76; H, 6.35; N, 13.94. Found: C, 63.96; H, 6.60; N, 13.78.

3-Methyl-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4(3*H*)-one (**22**).

A mixture of **21** (426 mg, 2 mmoles), potassium carbonate (829 mg, 6 mmoles), and methyl iodide (426 mg, 3 mmoles) in dry acetone (30 ml) was heated under reflux in a sealed tube for 4 hours. After removing the precipitated potassium carbonate by filtration, the filtrate was concentrated to syrup *in vacuo*. The residue diluted with water (30 ml) was adjusted to *p*H 9 with sodium hydrogen carbonate and extracted with ethyl acetate (3 x 15 ml). After the usual work-up, the residue was recrystallized from benzene to afford **22** (256 mg, 56%) as yellow needles, mp 185-187°; ir (potassium bromide): ν max 3350 (NH), 1640 (C=O) cm^{-1}; ms: EI m/z 227 (M^+, 67%), 212 ($M^+ - CH_3$, 81%); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 2.89 (t, J = 5.9 Hz, 2H, 5-H), 3.54 (s, 3H, Me), 3.57 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.76 (t, J = 5.9 Hz, 2H, 6-H), 7.11 (m, 2H, 9- and 10-H), 7.30 (m, 1H, 8-H), 7.90 (dd, $J_{9,11}$ = 1.5 Hz, $J_{10,11}$ = 8.2 Hz, 1H, 11-H), 8.11 (s, 1H, 2-H).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.62; H, 5.83; N, 18.38.

3,7-Dimethyl-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4(3*H*)-one (**23**).

A mixture of **21** (2 g, 9.39 mmoles), potassium carbonate (8 g, 57.9 mmoles), and methyl iodide (68.4 g, 482 mmoles) in dry acetone (120 ml) was refluxed for 7 hours. After removal of the precipitated potassium carbonate by filtration, the filtrate was concentrated to syrup *in vacuo*. The residue diluted with water (100 ml) was adjusted to *p*H 9 with sodium hydrogen carbonate and extracted with ethyl acetate (3 x 45 ml). After the usual work-up, the residue was purified by column chromatography on silica gel (chloroform/acetone, 2:1 v/v) and recrystallized from benzene-cyclohexane to afford **23** (1.2 g, 53%) as colorless needles, mp 130-132°; ir (potassium bromide): ν max 1650 (C=O) cm^{-1}; ms: FAB m/z 242 (MH^+); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 2.80 (t, J = 5.4 Hz, 2H, 5-H), 2.86 (s, 3H, 7-Me), 3.59 (t, 2H, J = 5.4 Hz, 6-H), 3.60 (s, 3H, 3-Me), 7.02-7.53 (m, 3H, 8-, 9-, and 10-H), 7.77 (br d, J = 7.2 Hz, 1H, 11-H), 8.19 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.80; H, 6.30; N, 17.14.

Methyl (4-Oxo-3,4,6,7-tetrahydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-3-yl)acetate (**24**).

A mixture of **21** (426 mg, 2 mmoles), methyl bromoacetate (0.284 ml, 3 mmoles), and triethylamine (0.4 g, 4 mmoles) in dry acetone (20 ml) was refluxed with stirring for 18 hours. After the mixture was concentrated to dryness *in vacuo*, the residue was purified by column chromatography on silica gel (chloroform/acetone, 1:1 v/v) and recrystallized from ethyl acetate to afford **24** (240 mg, 42%) as yellow needles, mp 203-204°; ir (potassium bromide): ν max 3360 (NH), 1758, 1742 (C=O) cm^{-1}; ms: FAB m/z 286 (MH^+); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 2.96 (t, J = 5.3 Hz, 2H, 5-H), 3.68 (t, J = 5.3 Hz, 2H, 6-H), 3.75 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.81 (s, 3H, COOMe), 4.64 (s, 2H, CH_2COOMe), 6.66 (dd, $J_{8,10}$ = 1.1 Hz, $J_{8,9}$ = 8.2 Hz, 1H, 8-H), 6.87 (ddd, $J_{8,10}$ = 1.1 Hz, $J_{9,10}$ = 7.1 Hz, $J_{10,11}$ = 8.1 Hz, 1H, 10-H), 7.20 (ddd, $J_{9,11}$ = 1.6 Hz, $J_{9,10}$ = 7.1 Hz, $J_{8,9}$ = 8.2 Hz, 1H, 9-H), 8.02 (s, 1H, 2-H), 8.03 (dd, $J_{9,11}$ = 1.6 Hz, $J_{10,11}$ = 8.1 Hz, 1H, 11-H).

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.93; H, 5.17; N, 14.58.

3-Benzyl-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4(3*H*)-one (**25**).

A mixture of **21** (426 mg, 2 mmoles), benzyl chloride (380 mg, 3 mmoles), and triethylamine (405 mg, 4 mmoles) in dry acetone (20 ml) was heated under reflux with stirring for 17 hours. The reaction was further refluxed with an additional amount of benzyl chloride (190 mg, 1.5 mmoles) for 24 hours. After the mixture was concentrated to dryness *in vacuo*, the residue was purified by column chromatography on silica gel (chloroform/acetone, 5:1 v/v) and recrystallized from ethyl acetate to afford **25** (240 mg, 40%) as colorless needles, mp 238-239°; ir (potassium bromide): ν max 3280 (NH), 1658 (C=O) cm^{-1}; ms: FAB m/z 304 (MH^+); ^{1}H-nmr (200 MHz, deuteriochloroform): δ 2.80 (t, J = 6.3 Hz, 2H, 5-H), 3.51 (t, J = 6.3 Hz, 2H, 6-H), 4.35 (s, 2H, CH_2Ph), 4.37 (br, exchangeable with deuterium oxide, 1H, 7-NH), 7.06 (dd, $J_{8,10}$ = 1.0 Hz, $J_{8,9}$ = 8.1 Hz, 1H, 8-H), 7.09 (ddd, $J_{8,10}$ = 1.0 Hz, $J_{9,10}$ = 7.1 Hz, $J_{10,11}$ = 8.0 Hz, 1H, 10-H), 7.16-7.27 (m, 5H, Ph), 7.34

(ddd, $J_{9,11}$ = 1.8 Hz, $J_{9,10}$ = 7.1 Hz, $J_{8,9}$ = 8.1 Hz, 1H, 9-H), 7.79 (dd, $J_{9,11}$ = 1.8 Hz, $J_{10,11}$ = 8.0 Hz, 1H, 11-H), 8.21 (s, 1H, 2-H).

Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.22; H, 5.65; N, 13.85. Found: C, 74.92; H, 5.60; N, 13.60.

(4-Oxo-3,4,6,7-tetrahydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-3-yl)-acetonitrile (**26**).

A mixture of **21** (426 mg, 2 mmoles), bromoacetonitrile (360 mg, 3 mmoles), and triethylamine (405 mg, 4 mmoles) in dry acetone (20 ml) was heated under reflux with stirring for 96 hours. After removal of the precipitate by filtration, the filtrate was concentrated to syrup *in vacuo*. The residue was purified by column chromatography on silica gel (chloroform/acetone, 1:1 v/v) and recrystallized from ethyl acetate to afford **26** (200 mg, 40%) as yellow prisms, mp 218-220°; ir (potassium bromide): ν max 3350 (NH), 2250 (C≡N), 1650 (C=O) cm^{-1}; ms: FAB m/z 253 (MH^+); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 2.97 (t, J = 5.4 Hz, 2H, 5-H), 3.72 (t, J = 5.4 Hz, 2H, 6-H), 4.20 (br, exchangeable with deuterium oxide, 1H, 7-NH), 4.83 (s, 2H, CH_2CN), 6.62-7.20 (m, 3H, 8-, 9-, and 10-H), 7.30 (s, 1H, 2-H), 8.03-8.20 (m, 1H, 11-H).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.49; H, 4.77; N, 21.90.

Inhibition of Blood Platelet Aggregation *in Vitro*.

Preparation of Platelets.

Nine volumes of blood (from auricular vein of male albino rabbit) were mixed with one volume of 3.8% aqueous sodium citrate as the anticoagulant at room temperature of 25°. Then, the mixture was immediately centrifuged at 160 g for 10 minutes to get the platelet rich plasma (PRP) without erythrocytes and leukocytes. The upper plasma (PRP) was transferred with a siliconed Pasteur pipette into a plastic test tube. The residual blood was further centrifuged at 2000 g for 10 minutes to get the platelet poor plasma (PPP). The PRP containing 4.5 x 10^5 - 5.0 x 10^5 platelets/μl and PPP thus obtained were used for the measurement of blood platelet aggregation.

Measurement of Blood Platelet Aggregation.

Platelet aggregation was measured by the turbidimetric method [8] with an aggregometer (Aggrecorder II PA-3220, Kyoto Daiichi Kagaku Co., Ltd., Kyoto). Aqueous dimethyl sulfoxide (10%) (25 μl) containing the inhibitory agent (aspirin) or test compound (final concentration of sample, 25 μmol/l) and 1 *M* tris-HCl buffer (*p*H 7.4) (25 μl) were added to the PRP (250 μl) in a siliconized glass cuvette. Continuous magnetic stirring was used to ensure adequate mixing. After incubation of the sample solution at 37° for 2 minutes, collagen diluted with SKF Horm buffer (50 μl) (Hormon-Chemie Co., West Germany) was added to the solution as an aggregation agent (final concentration of collagen, 14.3 μg/ml). Changes in the light transmission passed through the PRP in the sample solution at 650 nm were determined by continuous recording at 37°.

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