# Polycyclic *N*-Hetero Compounds. XLIII. Syntheses and Properties of 2-Substituted 1-Acetoxy-6-acetyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]-pyrimido[5,4-*d*][1]benzazepines *via* *N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*]-[1]benzazepin-4-yl)amino Acids and Their Analogous Mesoionic Compounds, and Their Related Compounds as a Series of Potential Blood Platelet Aggregation Inhibitors

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A study of the cyclization method by heating of *N*-(6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)amino acids **3a-h**, **6**, and **9a,b** with excess acetic anhydride for the preparation of 2-substituted 1-acetoxy-6-acetyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepines **4a-h** and tetra- and penta-cyclic mesoionic compounds **7** and **10a,b** has been made. In addition, a tetracyclic mesoionic compound having a sulfur atom on the skeleton, 5,6-dihydro-4*H*-thiazolo[3′,2′:1,6]pyrimido[5,4-*d*][1]benzazepinium-1-one (**12**) was similarly prepared by treatment of 2-(6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-ylthio)acetic acid (**11**) with excess acetic anhydride. Their inhibitory activities against collagen-induced aggregation of rabbit blood platelets *in vitro* were also investigated, and some heterocycles exhibited from a two- to a four-fold more potent activity as compared with aspirin.

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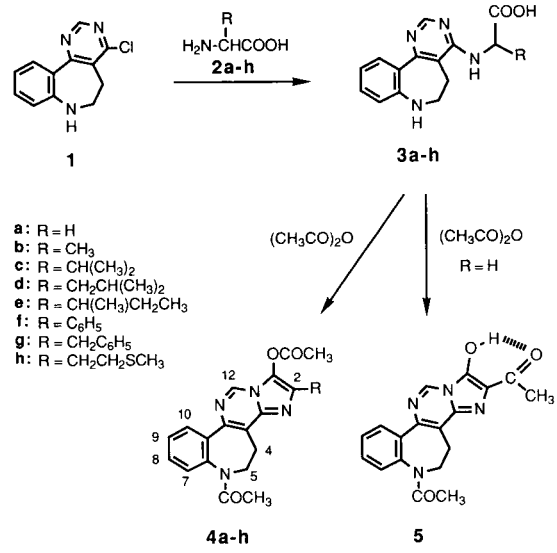
In the course of our work on novel antiplatelet aggregation agents, it became of interest to design and synthesize polycyclic hetero compounds with a new ring system. Actually a number of tri- and tetra-cyclic hetero compounds have recently been discovered as potential inhibitory active agents against collagen-induced aggregation of rabbit blood platelet [1]. Since the discovery of potential inhibitory activity of the compounds having a 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine ring system [2], our attention has focused on this tricyclic ring system. This paper deals with the syntheses of its derivatives and tetracyclic hetero compounds derived from it, and the evaluation of their inhibitory activities against rabbit platelet aggregation induced by collagen.

The synthetic method for 2-substituted 1-acetoxy-6-acetyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]-benzazepines **4a-h** is outlined in Scheme 1. The key compound, 4-chloro-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**1**) was prepared according to the method previously reported [3]. Heating of **1** with the appropriate amino acids **2a-h** in the presence of potassium carbonate in 50% aqueous 2-methoxyethanol or dioxane under reflux for several hours followed by acidification of the reaction mixture yielded the corresponding *N*-(6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)amino acids **3a-h** in good yields. The subsequent reaction of the tricyclic amino acid derivatives **3a-h** with excess acetic anhydride at 90° or room temperature led to the corresponding tetracyclic compounds **4a-h** with acetylations of both the hydroxyl group at the 1-position and secondary amine at the 6-position, in which the carbonyl stretching vibration bands around 1785 ($OCOCH_3$) and 1650 $cm^{-1}$ ($NCOCH_3$) in their ir (potassium bromide) spectra were observed.

Scheme 1



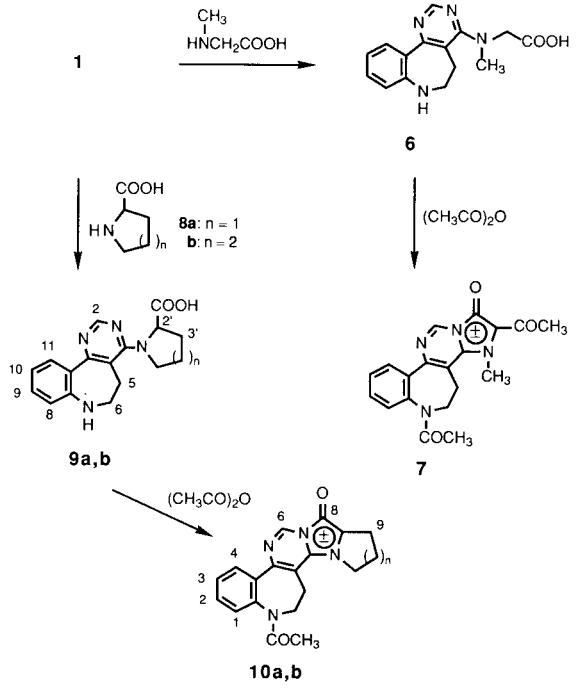

In the case of the dehydrative cyclization of **3a** by acetic anhydride, the reaction afforded the corresponding compound **4a** together with 2,6-diacetyl-1-hydroxy-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepine (**5**), which was not acetylated at the hydroxy group but acetylated at the 2-position and on the secondary amine. It

can therefore be presumed that when the acetylation occurred at the 2-position at first after the cyclization, the strong hydrogen bonding between the hydroxyl group and the acetyl group at the 2-position prevented further acetylation at the hydroxy group. Namely, the stretching vibration bands due to the hydroxyl group and the carbonyl group of **5** were observed at 2630 and 1600 $cm^{-1}$, respectively, at a lower wave number region than those usually observed. The stretching band due to the carbonyl group at the 1-position of **4a** was observed at 1780 $cm^{-1}$ in the ir (potassium bromide) spectra. The $^1$H-nmr spectrum of compound **5** also supported this assumption. That is to say, the signal of the pyrimidine ring proton at the 12-position was located further downfield ($\delta$ 10.33, DMSO-$d_6$) compared with that of compound **4a** ($\delta$ 8.77, deuteriochloroform) or **3a** ($\delta$ 8.57, DMSO-$d_6$) at the 2-position.

The structure of compounds **3a-h** showed preferentially a zwitterion form due to the presence of a protonated secondary amine referred to as ammonium bands in the 2200-2800 $cm^{-1}$ region and asymmetric and symmetric stretching vibrations of carboxylate in the 1617-1630 and 1360-1396 $cm^{-1}$ regions, respectively, in the ir (potassium bromide) spectra. However the structure of **3a-h** except for **3f** in the $^1$H-nmr (DMSO-$d_6$) spectra showed less zwitterion form because of the presence of a proton singlet arising from the carboxylic acid in the $\delta$ 12.5-12.8 region.

The reaction of compound **1** with appropriate secondary amino acids worked up in a similar manner as above yielded the corresponding *N*-(6,7-dihydro-5*H*-pyrimido[5,4-*d*]-[1]benzazepin-4-yl)amino acids **6** and **9a,b** as outlined in Scheme 2. Next, treatment of compound **6** with excess acetic anhydride at room temperature afforded the mesoionic 2,6-diacetyl-3-methyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepinium-1-one (**7**) as reasonably stable orange needles. The structure of **7** was assigned on the basis of following facts. The ir (potassium bromide) spectrum showed the characteristic C=O bands at 1690, 1655, and 1608 $cm^{-1}$ attributable to $C_2$-acetyl, $N_6$-acetyl, and $C_1$-oxo groups, respectively. The absorption of the $C_1$-oxo group is due to the polarized mesoionic character and appeared particularly at a lower wave number than that of a normal carbonyl group. In addition, the structure was supported by the $^1$H-nmr (DMSO-$d_6$) spectrum, which showed the disappearance of an $\alpha$-methylene signal of the *N*-methylglycine moiety of **6** and the appearance of two acetyl signals at $\delta$ 1.52 and 2.44 attributable to $N_6$-acetyl and $C_2$-acetyl, respectively. The $N_3$-methyl and $C_{12}$-proton signals of **7** particularly are located more downfield at $\delta$ 4.18 and 9.17, while the corresponding protons of **6** were at $\delta$ 3.12 ($C_4$-*N*-methyl) and 8.44 ($C_2$-proton), respectively. Moreover, in the uv (ethanol) spectrum the absorptions of **7** [$\lambda$ max nm (log $\epsilon$) 262 (3.99), 329 (3.55), and 418 (3.87)] indicated a bathochromic shift in all absorptions except 237 nm resulting from the basic aromatic character of the mesoionic ring compared to those of **6** [$\lambda$ max nm (log $\epsilon$) 237 (4.32), 259 (4.13) sh, 308 (3.72), and 357 (3.33) sh]. The above facts were qualitatively similar to those of analogous mesoionic compounds reported previously at all points [4].

Scheme 2

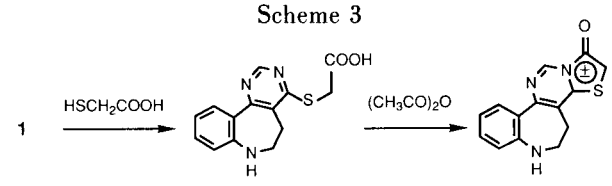



Similarly the pentacyclic mesoionic compounds **10a,b** were also prepared *via* the intermediates **9a,b** which were produced from the reaction of **1** with DL-proline (**8a**) or DL-pipecolic acid (**8b**), and the structures were fully supported by spectral and microanalytical data in similar observations as above. These compounds **7** and **10a,b** were reasonably stable in the refrigerator without a solvent but fairly unstable in a solvent at room temperature. For example, the hypsochromic shift in the uv absorptions of **10a** [$\lambda$ max nm (log $\epsilon$) 222 (4.35) sh, 246 (4.13), 360 (3.99), and 410 (4.05)] in ethanol at room temperature was gradually observed after several hours, which probably accounted for the decomposition of the mesoionic ring. Namely, the spectrum exhibited absorptions of [$\lambda$ max nm (log $\epsilon$) 227 (4.30), 249 (4.26), and 286 (3.79)] after 3 days.

On the other hand, similar treatment of **1** with mercaptoacetic acid in the presence of potassium carbonate in dimethylformamide at 90° afforded 2-(6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-ylthio)acetic acid (**11**) as shown in Scheme 3. Then dehydrative ring-closure of **11** was achieved by treatment of **11** in pyridine with excess acetic anhydride in dry benzene at room temperature to yield the mesoionic 5,6-dihydro-4*H*-thiazolo[3′,2′:1,6]py-

rimido[5,4-*d*][1]benzazepinium-1-one (**12**). The properties of this compound were very similar to those of other mesoionic compounds described above, and the structure was assigned on the basis of the ir (potassium bromide) spectrum (presence of a stretching vibration band at 1618 $cm^{-1}$ attributable to $C_1$-oxo group), the $^1$H-nmr (methanol-$d_4$) spectrum (disappearance of an α-methylene signal of the mercaptoacetic acid), the uv (ethanol) spectrum [λ max nm (log ε) 239 (4.14), 260 (3.98) sh, 298 (3.69), 395 (3.63), and 466 (3.98); the solution after 3 days at room temperature: 240 (4.30), 295 (3.78) sh, and 375 (3.54)], and the satisfactory microanalytical data.

Scheme 3




Biological Evaluation.

The compounds synthesized here were screened for inhibitory effect on rabbit blood platelet aggregation induced by collagen by a turbidimetric method [5]. The preparation of the platelets and the measurement of platelet aggregation were performed exactly according to the previously described procedure [2]. The extent of aggregation was expressed in terms of the maximum change of transmission which was designated 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, which is well known as an anti-platelet agent [6], 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 $p < 0.01$ or $p < 0.05$ on statistical analysis using Student's *t*-test, the amount

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** | 60.5 ± 4.0 [c] | 16.2 (11.7-21.4) | **3b** | 43.0 ± 2.8 [d] | 21.8 (16.3-30.2) |
| **3c** | 40.5 ± 5.6 [d] | 32.3 (19.5-91.6) | **3d** | 21.5 ± 3.5 | |
| **3e** | 26.5 ± 3.5 | | **3f** | 57.1 ± 1.3 [c] | 14.5 (11.6-17.8) |
| **3g** | 53.3 ± 4.0 [c] | 22.4 (18.8-28.3) | **3h** | 41.6 ± 4.1 [d] | 30.5 (24.7-39.4) |
| **4a** | 14.3 ± 2.5 | | **4b** | 13.2 ± 2.6 | |
| **4c** | 12.3 ± 3.2 | | **4d** | 31.3 ± 3.2 | |
| **4e** | 9.1 ± 2.8 | | **4f** | 12.3 ± 4.0 | |
| **4g** | 25.7 ± 2.6 | | **4h** | 15.7 ± 6.3 | |
| **5** | 76.3 ± 5.3 [c] | 10.9 (7.8-14.8) | **6** | 52.1 ± 6.7 [c] | 20.5 (15.6-27.1) |
| **7** | 16.4 ± 0.4 | | **9a** | 20.7 ± 11.7 | |
| **9b** | 7.1 ± 2.7 | | **10a** | 17.6 ± 1.5 | |
| **10b** | 50.3 ± 7.7 [d] | 24.3 (18.0-41.4) | **11** | 27.2 ± 6.3 | |
| **12** | 23.1 ± 4.5 | | Asprin | 35.5 ± 2.2 [c] | 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. [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). [c] Significantly different from asprin at $p < 0.01$. [d] Significantly different from aspirin at $p < 0.05$.

(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 listed in Table I.

As can be seen from the maximum inhibition rates in Table I, all tricyclic and tetracyclic compounds exhibited potent and dose-dependent inhibitions against rabbit platelet aggregation induced by collagen. Especially, most of the tricyclic heterocycles **3a-h** and **6**, which were substituted by an amino acid at the 4-position, manifested inhibitory activity which differed positively from that of aspirin at the final concentration of 25 μmol/l. Whereas the tetracyclic heterocycles **4a-h**, arising from the ring-closure of the tricyclic heterocycles **3a-h**, exhibited less activity except for compound **5** which showed a four-fold greater activity than aspirin in terms of $IC_{50}$. Among tricyclic heterocycles, compound **3f** manifested a three-fold stronger inhibitory activity than aspirin, followed by **3a**, **6**, **3b**, **3g**, **3h**, and **3c** exhibiting 2.8, 2.2, 2.0, 2.0, 1.5, and 1.4 times, respectively. On the other hand, the mesoionic heterocycles **7**, **10a**, and **12** were less active than aspirin except for **10b** which showed about a two-fold activity in terms of $IC_{50}$. The other 4-substituted tricyclic heterocycles **9a,b** and **11** also exhibited less activity. It may be concluded that the tricyclic compounds have a tendency to be more beneficial than the tetracyclic compounds for the inhibitory activity in this series.

## 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 Varian VXR-200 (200 MHz) instrument with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) and signals are quoted as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; dd, double doublet; dt, double triplet; ddd, double double doublet; sex, sextet; sep, septet. The FAB-ms spectra were measured on a VG-70SE instrument. Column chromatography was carried out with Kiesel gel 60 (70-230 mesh ASTM, Merk).

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)glycine (**3a**).

A mixture of 4-chloro-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (**1**) [3] (463 mg, 2 mmoles), glycine (300 mg, 4 mmoles), and potassium carbonate (828 mg, 6 mmoles) in 50% aqueous 2-methoxyethanol (10 ml) was heated under reflux with stirring for 2 hours. The reaction solution was then concentrated to dryness *in vacuo*, and the residue was dissolved in as little water as possible. The resulting solution was extracted with ethyl acetate (3 x 5 ml) to remove the by-product, 6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]-benzazepin-4(3*H*)-one [3]. Acidification of the water layer with acetic acid gave crystals which were collected by filtration, washed with cold water, and recrystallized from water to afford **3a** (370 mg, 69%) as yellow needles, mp 269-270°; ir (potassium bromide): ν 3260 (NH), ν 2800-2200 (broad, $NH_2^+$), $\nu_{as}$ 1630 and $\nu_s$ 1375 ($CO_2^-$) cm$^{-1}$; FAB-ms: m/z 271 ($MH^+$); $^1$H-nmr (DMSO-d$_6$): δ 2.86 (br t, J = 4.8 Hz, 2H, 5-H), 3.40 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.59 (br t, J = 4.8 Hz, 2H, 6-H), 4.11 (d, J = 5.6 Hz, changed to singlet after addition of deuterium oxide, 2H, 4-NHC$H_2$), 6.77 (dt, $J_{8,10}$ = 1.0 Hz, $J_{9,10}$ = 7.1 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 10-H), 6.87 (dd, $J_{8,9}$ = 8.1 Hz, $J_{8,10}$ = 1.0 Hz, 1H, 8-H), 7.23 (ddd, $J_{8,9}$ = 8.1 Hz, $J_{9,10}$ = 7.1 Hz, $J_{9,11}$ = 1.5 Hz, 1H, 9-H), 7.62 (dd, $J_{9,11}$ = 1.5 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 11-H), 8.57 (s, 1H, 2-H), 8.68 (br s, exchangeable with deuterium oxide, 1H, 4-NH), 12.78 (br, 1H, COOH); uv (ethanol): λ max nm (log ε) 235 (4.58), 298 (3.78), 342 (3.47).

*Anal.* Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.89; H, 5.03; N, 20.51.

The above procedure after the reaction was carried out as a usual work-up for the preparation of *N*-(6,7-dihydro-5*H*-pyrimido-[5,4-*d*][1]benzazepin-4-yl)amino acids **3b-h**.

*N*-(6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-DL-alanine (**3b**).

A mixture of **1** (463 mg, 2 mmoles), DL-alanine (712 mg, 8 mmoles), and potassium carbonate (552 mg, 4 mmoles) in 50% aqueous 2-methoxyethanol (12 ml) was heated under reflux with stirring for 2 hours. After the same work-up as noted above, recrystallization of the crude crystals from water afforded **3b** (450 mg, 79%) as yellow prisms, mp 251-252°; ir (potassium bromide): ν 3340 and 3300 (NH), ν 2770-2200 (broad, $NH_2^+$), $\nu_{as}$ 1620 and $\nu_s$ 1396 ($CO_2^-$) cm$^{-1}$; FAB-ms: m/z 285 ($MH^+$); $^1$H-nmr (DMSO-d$_6$): δ 1.48 (d, J = 7.5 Hz, 3H, $CH_3$), 2.88 (m, 2H, 5-H), 3.40 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.56 (m, 2H, 6-H), 4.62 (m, 1H, C*H*COOH), 6.75 (br t, J = 7.1 and 7.8 Hz, 1H, 10-H), 6.84 (br d, J = 8.1 Hz, 1H, 8-H), 7.20 (ddd, $J_{8,9}$ = 8.1 Hz, $J_{9,10}$ = 7.1 Hz, $J_{9,11}$ = 1.5 Hz, 1H, 9-H), 7.67 (br d, J = 8.1 Hz, 1H, 11-H), 7.95 (br s, exchangeable with deuterium oxide, 1H, 4-NH), 8.52 (s, 1H, 2-H), 12.65 (br, 1H, COOH); uv (ethanol): λ max nm (log ε) 235 (4.42), 295 (4.12), 325 (3.98) sh.

*Anal.* Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.08; H, 5.71; N, 19.57.

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-DL-valine (**3c**).

A mixture of **1** (463 mg, 2 mmoles), DL-valine (938 mg, 8 mmoles), and potassium carbonate (552 mg, 4 mmoles) in 50% aqueous 2-methoxyethanol (12 ml) was heated under reflux with stirring for 7 hours. After the same work-up as noted above, recrystallization of the crude crystals from ethanol afforded **3c** (460 mg, 74%) as yellow prisms, mp 242-244°; ir (potassium bromide): ν 3360 and 3300 (NH), ν 2800-2200 (broad, $NH_2^+$), $\nu_{as}$ 1618 and $\nu_s$ 1386 ($CO_2^-$) cm$^{-1}$; FAB-ms: m/z 313 ($MH^+$); $^1$H-nmr (DMSO-d$_6$): δ 0.97 (d, J = 5.9 Hz, 3H, $CH_3$), 1.00 (d, J = 6.4 Hz, 3H, $CH_3$), 2.20 [sex, J = 6.8 Hz, 1H, C*H*($CH_3$)$_2$], 2.81 (m, 2H, 5-H), 3.20 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.53 (m, 2H, 6-H), 4.37 [t, J = 7.3 Hz, changed to doublet (J = 7.3 Hz) after addition of deuterium oxide, 1H, C*H*COOH], 6.70 (br t, J = 7.0 and 7.6 Hz, 2H, 10-H and 4-NH), 6.75 (br d, J = 8.1 Hz, 1H, 8-H), 7.12 (ddd, $J_{8,9}$ = 8.1 Hz, $J_{9,10}$ = 7.1 Hz, $J_{9,11}$ = 1.5 Hz, 1H, 9-H), 7.88 (dd, $J_{9,11}$ = 1.5 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 11-H), 8.36 (s, 1H,

2-H), 12.50 (br, 1H, COOH); uv (ethanol): λ max nm (log ε) 235 (4.57), 300 (3.86), 340 (3.54) sh.

*Anal.* Calcd. for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94. Found: C, 65.35; H, 6.58; N, 17.65.

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-DL-leucine (**3d**).

A mixture of **1** (463 mg, 2 mmoles), DL-leucine (1.05 g, 8 mmoles), and potassium carbonate (552 mg, 4 mmoles) in 50% aqueous dioxane (12 ml) was heated under reflux with stirring for 24 hours. After the same work-up as noted above, recrystallization of the crude crystals from ethanol afforded **3d** (310 mg, 47%) as yellow needles, mp 199-200°; ir (potassium bromide): ν 3350 and 3310 (NH), ν 2750-2250 (broad, $NH_2^+$), $\nu_{as}$ 1620 and $\nu_s$ 1390 ($CO_2^-$) $cm^{-1}$; FAB-ms: m/z 327 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): δ 0.87 (d, J = 5.9 Hz, 3H, $CH_3$), 0.93 (d, J = 6.3 Hz, 3H, $CH_3$), 1.75 [m, 3H, $CH_2CH(CH_3)_2$], 2.86 (br m, 2H, 5-H), 3.38 (br s, exchangeable with deuterium oxide, 1H, 7-NH), 3.57 (br m, 2H, 6-H), 4.65 (m, 1H, CHCOOH), 6.30 (br, exchangeable with deuterium oxide, 1H, 4-NH), 6.75 (br t, J = 7.1 and 7.9 Hz, 1H, 10-H), 6.83 (br d, J = 8.3 Hz, 1H, 8-H), 7.19 (ddd, $J_{8,9}$ = 8.3 Hz, $J_{9,10}$ = 7.1 Hz, $J_{9,11}$ = 1.5 Hz, 1H, 9-H), 7.70 (br d, J = 8.0 Hz, 1H, 11-H), 8.48 (s, 1H, 2-H), 12.62 (br, 1H, COOH); uv (ethanol): λ max nm (log ε) 235 (4.97), 301 (4.26), 341 (3.96) sh.

*Anal.* Calcd. for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16. Found: C, 65.94; H, 6.85; N, 16.94.

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-DL-isoleucine (**3e**).

A mixture of **1** (463 mg, 2 mmoles), DL-isoleucine (1.05 g, 8 mmoles), and potassium carbonate (552 mg, 4 mmoles) in 50% aqueous dioxane (12 ml) was heated under reflux with stirring for 35 hours. After the same work-up as noted above, recrystallization of the crude crystals from ethanol afforded **3e** (420 mg, 64%) as yellow prisms, mp 221-222°; ir (potassium bromide): ν 3340 and 3300 (NH), ν 2750-2200 (broad, $NH_2^+$), $\nu_{as}$ 1617 and $\nu_s$ 1384 ($CO_2^-$) $cm^{-1}$; FAB-ms: m/z 327 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): δ 0.87 (t, J = 7.3 Hz, 3H, $CH_2CH_3$), 0.94 (d, J = 6.6 Hz, 3H, $CHCH_3$), 1.30 (m, 1H, one of $CH_2CH_3$), 1.52 (m, 1H, one of $CH_2CH_3$), 1.99 (m, 1H, $CHCH_3$), 2.81 (br s, 2H, 5-H), 3.28 (br s, exchangeable with deuterium oxide, 1H, 7-NH), 3.53 (br t, J = 4.5 Hz, 2H, 6-H), 4.43 (t, J = 7.3 Hz, changed to doublet (J = 7.3 Hz) after addition of deuterium oxide, 1H, CHCOOH), 6.71 (br t, J = 7.1 and 7.9 Hz, 2H, 10-H and 4-NH), 6.76 (br d, J = 8.0 Hz, 1H, 8-H), 7.12 (br t, J = 7.1 and 8.1 Hz, 1H, 9-H), 7.88 (br d, J = 7.9 Hz, 1H, 11-H), 8.36 (s, 1H, 2-H), 12.49 (br, 1H, COOH); uv (ethanol): λ max nm (log ε) 235 (4.68), 298 (3.98), 341 (3.66).

*Anal.* Calcd. for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16. Found: C, 65.98; H, 6.85; N, 16.93.

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-DL-phenylglycine (**3f**).

A mixture of **1** (463 mg, 2 mmoles), DL-phenylglycine (604 mg, 4 mmoles), and potassium carbonate (552 mg, 4 mmoles) in 50% aqueous dioxane (18 ml) was heated under reflux with stirring for 40 hours. After the same work-up as noted above, recrystallization of the crude crystals from ethanol afforded **3f** (520 mg, 73%) as yellow prisms, mp 181-182°; ir (potassium bromide): ν 3320 (NH), ν 2750-2250 (broad, $NH_2^+$), $\nu_{as}$ 1620 and $\nu_s$ 1370 ($CO_2^-$) $cm^{-1}$; FAB-ms: m/z 347 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): δ 2.85 (m, 2H, 5-H), 3.51 (m, 2H, 6-H), 3.60 (br, exchangeable with deuterium oxide, 1H, 7-NH), 5.66 (d, J = 5.7 Hz, changed to singlet after addition of deuterium oxide, 1H, CHCOOH), 6.71 (br t, J = 7.1 and 7.9 Hz, 1H, 10-H), 6.76 (br d, J = 8.1 Hz, 1H, 8-H), 7.13 (br t, J = 7.1 and 8.1 Hz, 1H, 9-H), 7.26-7.54 (m, 5H, Ph), 7.90 (br d, J = 7.9 Hz, 1H, 11-H), 8.41 (s, 1H, 2-H); uv (ethanol): λ max nm (log ε) 233 (4.45), 298 (3.74), 340 (3.39) sh.

*Anal.* Calcd. for $C_{20}H_{18}N_4O_2 \cdot 2/3H_2O$: C, 67.03; H, 5.44; N, 15.63. Found: C, 67.08; H, 5.25; N, 15.46.

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-DL-phenylalanine (**3g**).

A mixture of **1** (463 mg, 2 mmoles), DL-phenylalanine (660 mg, 4 mmoles), and potassium carbonate (552 mg, 4 mmoles) in 50% aqueous dioxane (12 ml) was heated under reflux with stirring for 40 hours. After the same work-up as noted above, recrystallization of the crude crystals from ethanol afforded **3g** (530 mg, 74%) as yellow needles, mp 245-246°; ir (potassium bromide): ν 3390 and 3345 (NH), ν 2750-2225 (broad, $NH_2^+$), $\nu_{as}$ 1620 and $\nu_s$ 1360 ($CO_2^-$) $cm^{-1}$; FAB-ms: m/z 361 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): δ 2.73 (m, 2H, 5-H), 3.15 (m, 2H, $CH_2C_6H_5$), 3.34 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.50 (m, 2H, 6-H), 4.72 (m, 1H, CHCOOH), 5.91 (br s, exchangeable with deuterium oxide, 1H, 4-NH), 6.69 (br t, J = 7.1 and 7.9 Hz, 1H, 10-H), 6.75 (br d, J = 8.1 Hz, 1H, 8-H), 7.05-7.33 (m, 6H, 9-H and Ph), 7.84 (br d, J = 8.0 Hz, 1H, 11-H), 8.30 (s, 1H, 2-H), 12.66 (br, 1H, COOH); uv (ethanol): λ max nm (log ε) 236 (4.52), 295 (3.93), 340 (3.52) sh.

*Anal.* Calcd. for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.88. Found: C, 69.70; H, 5.79; N, 15.77.

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-DL-methionine (**3h**).

A mixture of **1** (926 mg, 4 mmoles), DL-methionine (2.38 g, 16 mmoles), and potassium carbonate (1.14 g, 8 mmoles) in 50% aqueous dioxane (24 ml) was heated under reflux with stirring for 44 hours. After the same work-up as noted above, recrystallization of the crude crystals from 70% ethanol afforded **3h** (1.05 g, 76%) as yellow prisms, mp 228-230°; ir (potassium bromide): ν 3270 (NH), ν 2750-2230 (broad, $NH_2^+$), $\nu_{as}$ 1625 and $\nu_s$ 1360 ($CO_2^-$) $cm^{-1}$; FAB-ms: m/z 345 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): δ 2.04 (s, 3H, $SCH_3$), 2.11 (m, 2H, $CH_2SCH_3$), 2.59 (m, 2H, $CH_2CH_2S$), 2.79 (br t, J = 4.6 Hz, 2H, 5-H), 3.35 (br, exchangeable with deuterium oxide, 1H, 7-NH), 3.54 (br t, J = 4.6 Hz, 2H, 6-H), 4.64 (m, 1H, CHCOOH), 5.94 (br, exchangeable with deuterium oxide, 1H, 4-NH), 6.71 (br t, J = 7.1 and 7.8 Hz, 1H, 10-H), 6.77 (br d, J = 8.0 Hz, 1H, 8-H), 7.13 (ddd, $J_{8,9}$ = 8.1 Hz, $J_{9,10}$ = 7.0 Hz, $J_{9,11}$ = 1.5 Hz, 1H, 9-H), 7.88 (dd, $J_{9,11}$ = 1.5 Hz, $J_{10,11}$ = 8.0 Hz, 1H, 11-H), 8.36 (s, 1H, 2-H), 12.55 (br, 1H, COOH); uv (ethanol): λ max nm (log ε) 235 (4.48), 299 (3.79), 3.40 (3.46) sh.

*Anal.* Calcd. for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.85; N, 16.27. Found: C, 59.44; H, 6.07; N, 15.98.

1-Acetoxy-6-acetyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepine (**4a**) and 2,6-Diacetyl-1-hydroxy-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepine (**5**).

A solution of **3a** (135 mg, 0.5 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was heated at 90° with stirring for 10 minutes. The excess acetic anhydride was then taken off *in vacuo*, and the residue treated with small amount of xylene was concentrated to dryness again. The two products, which existed in the residue, were separated by column chromatography on silica gel (chloroform/acetone, 3:1 v/v) to afford **4a** (72 mg, 43%) as the first product. The second product **5** (54 mg, 32%) was eluted with the sol-

vent system (chloroform/acetone, 1:1 v/v). Recrystallization of **4a** from benzene-cyclohexane gave pale brown needles, mp 190-192°; ir (potassium bromide): $\nu$ 1780 and 1660 (C=O), $\nu_{as}$ 1207 and $\nu_s$ 1042 (C-O-C) $cm^{-1}$; FAB-ms: m/z 337 ($MH^+$); $^1$H-nmr (deuteriochloroform): $\delta$ 1.67 (s, 3H, $NCOCH_3$), 2.48 (s, 3H, $OCOCH_3$), 2.67 (dt, J = 6.4, 13.8, and 14.0 Hz, 1H, 4-Ha), 3.72 (m, 2H, 4-Hb and 5-Ha), 5.07 (dt, J = 5.6, 13.2, and 13.3 Hz, 1H, 5-Hb), 7.28 (dd, $J_{7,8}$ = 7.6 Hz, $J_{7,9}$ = 1.5 Hz, 1H, 7-H), 7.51 (m, 2H, 8-H and 9-H), 7.58 (s, 1H, 2-H), 7.84 (dd, $J_{8,10}$ = 1.7 Hz, $J_{9,10}$ = 7.4 Hz, 1H, 10-H), 8.77 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 231 (4.46), 292 (4.18), 329 (3.92) sh.

*Anal.* Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.40; H, 4.92; N, 16.90.

Recrystallization of **5** from ethanol gave green needles, mp >300°; ir (potassium bromide): $\nu$ 2630 (OH), $\nu$ 1650 and 1600 (C=O) $cm^{-1}$; FAB-ms: m/z 337 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): $\delta$ 1.51 (s, 3H, $NCOCH_3$), 2.41 (s, 3H, 2-$COCH_3$), 2.56 (m, 1H, 4-Ha), 3.57 (m, 2H, 4-Hb and 5-Ha), 4.78 (m, 1H, 5-Hb), 7.51 (m, 1H, 7-H), 7.60-7.66 (m, 2H, 8-H and 9-H), 7.87 (m, 1H, 10-H), 10.33 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 230 (4.69), 262 (4.65), 368 (4.54).

*Anal.* Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.39; H, 4.90; N, 16.88.

1-Acetoxy-6-acetyl-2-methyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]-pyrimido[5,4-*d*][1]benzazepine (**4b**).

A solution of **3b** (142 mg, 0.5 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was stirred at room temperature for 30 minutes. The excess acetic anhydride was then taken off *in vacuo*, and the residue treated with small amount of xylene was concentrated to dryness again. The residue was recrystallized from benzene-cyclohexane to give **4b** (100 mg, 57%) as colorless needles, mp 176-178°; ir (potassium bromide): $\nu$ 1780 and 1650 (C=O), $\nu_{as}$ 1185 and $\nu_s$ 1030 (C-O-C) $cm^{-1}$; FAB-ms: m/z 351 ($MH^+$); $^1$H-nmr (deuteriochloroform): $\delta$ 1.66 (s, 3H, $NCOCH_3$), 2.40 (s, 3H, 2-$CH_3$), 2.51 (s, 3H, $OCOCH_3$), 2.67 (dt, J = 6.7, 13.9, and 14.0 Hz, 1H, 4-Ha), 3.76 (m, 2H, 4-Hb and 5-Ha), 5.09 (dt, J = 5.7, 13.0, and 13.8 Hz, 1H, 5-Hb), 7.28 (dd, $J_{7,8}$ = 7.5 Hz, $J_{7,9}$ = 1.6 Hz, 1H, 7-H), 7.48 (dt, $J_{7,9}$ = 1.6 Hz, $J_{8,9}$ = 7.1 Hz, $J_{9,10}$ = 7.4 Hz, 1H, 8-H), 7.56 (dt, $J_{7,8}$ = 7.5 Hz, $J_{8,9}$ = 7.1 Hz, $J_{8,10}$ = 1.9 Hz, 1H, 9-H), 7.83 (dd, $J_{8,10}$ = 1.9 Hz, $J_{9,10}$ = 7.4 Hz, 1H, 10-H), 8.62 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 236 (4.49), 298 (4.10), 349 (3.85).

*Anal.* Calcd. for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 64.97; H, 5.04; N, 15.83.

1-Acetoxy-6-acetyl-2-isopropyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]-pyrimido[5,4-*d*][1]benzazepine (**4c**).

A solution of **3c** (156 mg, 0.5 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was heated at 90° with stirring for 10 minutes. After the same work-up as noted in the procedure of **4b**, the residue was recrystallized from benzene-petroleum ether to give **4c** (110 mg, 58%) as pale green prisms, mp 168°; ir (potassium bromide): $\nu$ 1785 and 1655 (C=O), $\nu_{as}$ 1170 and $\nu_s$ 1015 (C-O-C) $cm^{-1}$; FAB-ms: m/z 379 ($MH^+$); $^1$H-nmr (deuteriochloroform): $\delta$ 1.34 [d, J = 7.0 Hz, 6H, $CH(CH_3)_2$], 1.68 (s, 3H, $NCOCH_3$), 2.49 (s, 3H, $OCOCH_3$), 2.62 (dt, J = 6.0, 13.6, and 14.0 Hz, 1H, 4-Ha), 3.07 [sep, J = 7.0 Hz, 1H, $CH(CH_3)_2$], 3.76 (m, 2H, 4-Hb and 5-Ha), 5.08 (dt, J = 6.0, 13.0, and 13.6 Hz, 1H, 5-Hb), 7.27 (dd, $J_{7,8}$ = 7.5 Hz, $J_{7,9}$ = 1.6 Hz, 1H, 7-H), 7.46 (dt, $J_{7,9}$ = 1.6 Hz, $J_{8,9}$ = 7.4 Hz, $J_{9,10}$ = 7.4 Hz, 1H, 8-H), 7.54 (dt, $J_{7,8}$ = 7.5 Hz, $J_{8,9}$ = 7.4 Hz, $J_{8,10}$ = 1.8 Hz, 1H, 9-H), 7.81 (dd, $J_{8,10}$ = 1.8 Hz, $J_{9,10}$ = 7.4 Hz, 1H, 10-H), 8.53 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 239 (4.41), 295 (4.15), 332 (4.01) sh.

*Anal.* Calcd. for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.80. Found: C, 66.61; H, 5.81; N, 14.79.

1-Acetoxy-6-acetyl-2-isobutyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]-pyrimido[5,4-*d*][1]benzazepine (**4d**).

A solution of **3d** (163 mg, 0.5 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was stirred at room temperature for 10 minutes. After the same work-up as noted in the procedure of **4b**, the residue was recrystallized from benzene-*n*-hexane to give **4d** (80 mg, 40%) as yellow plates, mp 139-141°; ir (potassium bromide): $\nu$ 1785 and 1655 (C=O), $\nu_{as}$ 1160 and $\nu_s$ 1012 (C-O-C) $cm^{-1}$; FAB-ms: m/z 393 ($MH^+$); $^1$H-nmr (deuteriochloroform): $\delta$ 0.94 and 0.95 [each 3H, each d, each J = 6.6 Hz, $CH(CH_3)_2$], 1.68 (s, 3H, $NCOCH_3$), 2.10 [m, 1H, $CH(CH_3)_2$], 2.49 (s, 3H, $OCOCH_3$), 2.55 (d, J = 7.3 Hz, 2H, $CH_2CH$), 2.65 (dt, J = 6.0, 13.8, and 14.0 Hz, 1H, 4-Ha), 3.72 (m, 2H, 4-Hb and 5-Ha), 5.03 (dt, J = 5.4, 13.1, and 13.4 Hz, 1H, 5-Hb), 7.23 (dd, $J_{7,8}$ = 7.4 Hz, $J_{7,9}$ = 1.5 Hz, 1H, 7-H), 7.46 (dt, $J_{7,8}$ = 7.4 Hz, $J_{8,9}$ = 7.2 Hz, $J_{8,10}$ = 1.8 Hz, 1H, 8-H), 7.54 (dt, $J_{7,9}$ = 1.5 Hz, $J_{8,9}$ = 7.2 Hz, $J_{9,10}$ = 7.3 Hz, 1H, 9-H), 7.82 (dd, $J_{8,10}$ = 1.8 Hz, $J_{9,10}$ = 7.3 Hz, 1H, 10-H), 8.54 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 240 (4.47), 296 (4.20), 320 (4.07) sh.

*Anal.* Calcd. for $C_{22}H_{24}N_4O_3 \cdot 1/2H_2O$: C, 65.82; H, 6.28; N, 13.95. Found: C, 65.53; H, 6.10; N, 14.24.

1-Acetoxy-6-acetyl-2-*sec*-butyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]-pyrimido[5,4-*d*][1]benzazepine (**4e**).

A solution of **3e** (163 mg, 0.5 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was heated at 90° with stirring for 10 minutes. After the same work-up as noted in the procedure of **4b**, the resulting oily residue was purified by column chromatography on silica gel (chloroform/acetone, 3:1 v/v) to afford **4e** (150 mg, 76%) as yellowish oil; ir (chloroform): $\nu$ 1788 and 1640 (C=O), $\nu_{as}$ 1175 and $\nu_s$ 1030 (C-O-C) $cm^{-1}$; FAB-ms: m/z 393 ($MH^+$); $^1$H-nmr (deuteriochloroform): $\delta$ 1.06 (t, J = 7.3 Hz, 3H, $CH_2CH_3$), 1.51 (d, J = 7.1 Hz, 3H, $CHCH_3$), 1.89 (s, 3H, $NCOCH_3$), 1.95 (m, 2H, $CHCH_2$-$CH_3$), 2.68 (s, 3H, $OCOCH_3$), 2.85 (m, 1H, $CHCH_2CH_3$), 3.00 (dt, J = 6.0, 13.8, and 13.9 Hz, 1H, 4-Ha), 3.94 (m, 2H, 4-Hb and 5-Ha), 5.27 (dt, J = 5.4, 12.9, and 13.5 Hz, 1H, 5-Hb), 7.47 (dd, $J_{7,8}$ = 7.5 Hz, $J_{7,9}$ = 1.5 Hz, 1H, 7-H), 7.66 (dt, $J_{7,8}$ = 7.5 Hz, $J_{8,9}$ = 7.3 Hz, $J_{8,10}$ = 1.8 Hz, 1H, 8-H), 7.74 (dt, $J_{7,9}$ = 1.5 Hz, $J_{8,9}$ = 7.3 Hz, $J_{9,10}$ = 7.4 Hz, 1H, 9-H), 8.02 (dd, $J_{8,10}$ = 1.8 Hz, $J_{9,10}$ = 7.4 Hz, 1H, 10-H), 8.73 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 239 (4.28), 295 (4.02), 328 (3.87) sh.

1-Acetoxy-6-acetyl-2-phenyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]-pyrimido[5,4-*d*][1]benzazepine (**4f**).

A solution of **3f** (173 mg, 0.48 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was heated at 90° with stirring for 10 minutes. After the same work-up as noted in the procedure of **4b**, the residue was recrystallized from benzene to give **4f** (90 mg, 44%) as colorless prisms, mp 220-222°; ir (potassium bromide): $\nu$ 1785 and 1635 (C=O), $\nu_{as}$ 1160 and $\nu_s$ 1015 (C-O-C) $cm^{-1}$; FAB-ms: m/z 413 ($MH^+$); $^1$H-nmr (methanol-$d_4$): $\delta$ 1.69 (s, 3H, $NCOCH_3$), 2.60 (s, 3H, $OCOCH_3$), 2.77 (dt, J = 6.2, 13.6, and 14.0 Hz, 1H, 4-Ha), 3.82 (m, 2H, 4-Hb and 5-Ha), 5.12 (dt, J = 6.0, 13.1, and 13.4 Hz, 1H, 5-Hb), 7.38-7.67 (m, 6H, 7-H, 8-H, 9-H, and Ph), 7.87-8.01 (m, 3H, 10-H and Ph), 9.15 (s, 1H, 12-H); uv (ethanol): $\lambda$

max nm (log $\epsilon$) 242 (4.54), 253 (4.54), 305 (4.07), 345 (4.12).

*Anal.* Calcd. for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.60; H, 4.90; N, 13.31.

1-Acetoxy-6-acetyl-2-benzyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]-pyrimido[5,4-*d*][1]benzazepine (**4g**).

A solution of **3g** (180 mg, 0.5 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was heated at 90° with stirring for 15 minutes. After the same work-up as noted in the procedure of **4b**, the residue was recrystallized from benzene-petroleum ether to give **4g** (102 mg, 48%) as colorless needles, mp 147-149°; ir (potassium bromide): $\nu$ 1790 and 1655 (C=O), $\nu_{as}$ 1170 and $\nu_s$ 1030 (C-O-C) $cm^{-1}$; FAB-ms: m/z 427 ($MH^+$); $^1$H-nmr (deuteriochloroform): $\delta$ 1.68 (s, 3H, $NCOCH_3$), 2.16 (s, 3H, $OCOCH_3$), 2.65 (dt, J = 6.4, 13.8, and 14.1 Hz, 1H, 4-Ha), 3.74 (m, 2H, 4-Hb and 5-Ha), 4.13 (s, 2H, $CH_2C_6H_5$), 5.08 (dt, J = 5.5, 13.2, and 13.3 Hz, 1H, 5-Hb), 7.22-7.32 (m, 6H, 7-H and Ph), 7.47 (dt, $J_{7,8}$ = 7.4 Hz, $J_{8,9}$ = 7.2 Hz, $J_{8,10}$ = 1.8 Hz, 1H, 8-H), 7.55 (dt, $J_{7,9}$ = 1.6 Hz, $J_{8,9}$ = 7.2 Hz, $J_{9,10}$ = 7.5 Hz, 1H, 9-H), 7.82 (dd, $J_{8,10}$ = 1.8 Hz, $J_{9,10}$ = 7.5 Hz, 10-H), 8.53 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 240 (4.69) sh, 295 (4.43), 329 (4.29) sh.

*Anal.* Calcd. for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14. Found: C, 70.73; H, 5.33; N, 13.41.

1-Acetoxy-6-acetyl-2-(2-methylthioethyl)-5,6-dihydro-4*H*-imidazo-[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepine (**4h**).

A solution of **3h** (172 mg, 0.5 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was heated at 90° with stirring for 10 minutes. After the same work-up as noted in the procedure of **4b**, the resulting oily residue was purified by column chromatography on silica gel (chloroform/acetone, 3:1 v/v) and recrystallized from ethanol to afford **4h** (82 mg, 40%) as colorless needles, mp 133-135°; ir (potassium bromide): $\nu$ 1785 and 1635 (C=O), $\nu_{as}$ 1170 and $\nu_s$ 1020 (C-O-C) $cm^{-1}$; FAB-ms: m/z 411 ($MH^+$); $^1$H-nmr (deuteriochloroform): $\delta$ 1.68 (s, 3H, $NCOCH_3$), 2.15 (s, 3H, $SCH_3$), 2.50 (s, 3H, $OCOCH_3$), 2.65 (dt, J = 6.4, 13.7, and 14.2 Hz, 1H, 4-Ha), 2.94 (m, 4H, $CH_2CH_2S$), 3.72 (m, 2H, 4-Hb and 5-Ha), 5.07 (dt, J = 5.4, 12.9, and 13.5 Hz, 1H, 5-Hb), 7.27 (dd, $J_{7,8}$ = 7.5 Hz, $J_{7,9}$ = 1.5 Hz, 1H, 7-H), 7.47 (dt, $J_{7,8}$ = 7.5 Hz, $J_{8,9}$ = 7.2 Hz, $J_{8,10}$ = 1.8 Hz, 1H, 8-H), 7.55 (dt, $J_{7,9}$ = 1.5 Hz, $J_{8,9}$ = 7.2 Hz, $J_{9,10}$ = 7.3 Hz, 1H, 9-H), 7.82 (dd, $J_{8,10}$ = 1.8 Hz, $J_{9,10}$ = 7.3 Hz, 1H, 10-H), 8.57 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 238 (4.65) sh, 295 (4.39), 328 (4.26) sh.

*Anal.* Calcd. for $C_{21}H_{22}N_4O_3S$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.25; H, 5.45; N, 13.39.

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-*N*-methyl-glycine (**6**).

A mixture of **1** (1.15 g, 5 mmoles), *N*-methylglycine (1.78 g, 20 mmoles), and potassium carbonate (1.38 g, 10 mmoles) in 50% aqueous dioxane (30 ml) was heated under reflux with stirring for 2 hours. After the same work-up as noted in the procedure for **3a**, the crude crystals were recrystallized from water to give **6** (960 mg, 64%) as yellow plates, mp 150-152°; ir (potassium bromide): $\nu$ 3360 (NH), $\nu$ 3060-2400 (COOH), 1720 (C=O) $cm^{-1}$; FAB-ms: m/z 285 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): $\delta$ 2.79 (br t, J = 4.7 and 5.6 Hz, 2H, 5-H), 3.12 (s, 3H, $NCH_3$), 3.56 (br t, J = 4.7 and 5.6 Hz, 2H, 6-H), 4.07 (s, 2H, $CH_2COOH$), 6.75 (ddd, $J_{8,10}$ = 1.2 Hz, $J_{9,10}$ = 7.1 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 10-H), 6.81 (dd, $J_{8,9}$ = 8.1 Hz, $J_{8,10}$ = 1.2 Hz, 1H, 8-H), 7.16 (ddd, $J_{8,9}$ = 8.1 Hz, $J_{9,10}$ = 7.1 Hz, $J_{9,11}$ = 1.6 Hz, 1H, 9-H), 7.85 (dd, $J_{9,11}$ = 1.6 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 11-H), 8.44 (s, 1H, 2-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 237 (4.32), 259 (4.13) sh, 308 (3.72), 357 (3.33) sh.

*Anal.* Calcd. for $C_{15}H_{16}N_4O_2 \cdot H_2O$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.30; H, 6.06; N, 18.29.

2,6-Diacetyl-3-methyl-5,6-dihydro-4*H*-imidazo[1′,2′:1,6]pyrimido-[5,4-*d*][1]benzazepinium-1-one (**7**).

A solution of **6** (142 mg, 0.47 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was stirred at room temperature for 2 hours. After the same work-up as noted in the procedure of **4b**, the residue was purified by column chromatography on silica gel (ethanol) and recrystallized from ethanol to afford **7** (90 mg, 54%) as orange needles, mp >290° dec; ir (potassium bromide): $\nu$ 1690, 1655, and 1608 (C=O) $cm^{-1}$; FAB-ms: m/z 351 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): $\delta$ 1.52 (s, 3H, $NCOCH_3$), 2.44 (s, 3H, 2-$COCH_3$), 2.48 (m, 1H, 4-Ha), 3.44 (m, 1H, 4-Hb), 3.68 (m, 1H, 5-Ha), 4.18 (s, 3H, $NCH_3$), 4.93 (dt, J = 4.6, 12.9, and 14.4 Hz, 1H, 5-Hb), 7.46-7.90 (m, 4H, 7-H, 8-H, 9-H, and 10-H), 9.17 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 262 (3.99), 329 (3.55), 418 (3.87).

*Anal.* Calcd. for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.33; H, 5.20; N, 15.78.

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-DL-proline (**9a**).

A mixture of **1** (926 mg, 4 mmoles), DL-proline (1.82 g, 16 mmoles), and potassium carbonate (1.14 g, 8 mmoles) in 50% aqueous 2-methoxyethanol (24 ml) was heated under reflux with stirring for 2 hours. After the same work-up as noted in the procedure of **3a**, the crude crystals were recrystallized from 70% ethanol to give **9a** (790 mg, 64%) as yellow plates, mp 231-233°; ir (potassium bromide): $\nu$ 3350 (NH), $\nu$ 2970-2300 (COOH), 1720 (C=O) $cm^{-1}$; FAB-ms: m/z 311 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): $\delta$ 1.94 (m, 3H, 3′-Ha and 4′-H), 2.25 (m, 1H, 3′-Hb), 2.82 (m, 2H, 5-H), 3.33 (br s, exchangeable with deuterium oxide, 1H, 7-NH), 3.66 (m, 2H, 6-H), 3.76 (m, 2H, 5′-H), 4.56 (t, 1H, J = 6.6 Hz, 2′-H), 6.79 (ddd, $J_{8,10}$ = 1.1 Hz, $J_{9,10}$ = 7.1 Hz, $J_{10,11}$ = 8.0 Hz, 1H, 10-H), 6.84 (dd, $J_{8,9}$ = 8.1 Hz, $J_{8,10}$ = 1.1 Hz, 1H, 8-H), 7.18 (ddd, $J_{8,9}$ = 8.1 Hz, $J_{9,10}$ = 7.1 Hz, $J_{9,11}$ = 1.7 Hz, 1H, 9-H), 7.80 (dd, $J_{9,11}$ = 1.7 Hz, $J_{10,11}$ = 8.0 Hz, 1H, 11-H), 8.36 (s, 1H, 2-H), 12.18 (br, 1H, COOH); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 234 (4.39), 256 (4.22) sh, 308 (3.80).

*Anal.* Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.60; H, 5.98; N, 18.07.

*N*-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-yl)-DL-pipecolic Acid (**9b**).

A mixture of **1** (926 mg, 4 mmoles), DL-pipecolic acid (2.06 g, 16 mmoles), and potassium carbonate (1.14 g, 8 mmoles) in 50% aqueous dioxane (24 ml) was heated under reflux with stirring for 24 hours. After the same work-up as noted in the procedure for **3a**, the crude crystals were recrystallized from ethanol to give **9b** (1.10 g, 85%) as yellow plates, mp 181-182°; ir (potassium bromide): $\nu$ 3320 (NH), $\nu$ 2940-2300 (COOH), 1690 (C=O) $cm^{-1}$; FAB-ms: m/z 325 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): $\delta$ 1.61 (br m, 4H, 4′-H and 5′-H), 1.91 (br m, 2H, 3′-H), 2.82 (m, 2H, 5-H), 3.13-3.61 (m, 5H, 6′-H, 6-H, and 7-NH), 4.33 (br t, 1H, J = 4.6 Hz, 2′-H), 6.68 (br t, J = 7.4 and 7.6 Hz, 1H, 10-H), 6.77 (br d, J = 8.1 Hz, 1H, 8-H), 7.13 (br t, J = 7.3 and 7.6 Hz, 1H, 9-H), 7.90 (br d, J = 7.7 Hz, 1H, 11-H), 8.54 (s, 1H, 2-H), 12.45 (br, 1H, COOH); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 238 (4.35), 260 (4.07) sh, 308 (3.66), 355 (3.41) sh.

*Anal.* Calcd. for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.45; H, 6.18; N, 17.14.

15-Acetyl-10,11,14,15-tetrahydro-9*H*,13*H*-pyrrolo[1'',2'':3',4']imidazo[1',2':1,6]pyrimido[5,4-*d*][1]benzazepinium-8-one (**10a**).

A solution of **9a** (155 mg, 0.5 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was stirred at room temperature for 1.5 hours. The excess acetic anhydride was evaporated under an inert atmosphere of argon *in vacuo*, and the residue treated with small amount of xylene was again concentrated to dryness. The resulting solid was filtered off by suction and washed with cold benzene to afford **10a** [7] (80 mg, 48%) as orange powder, mp >192° dec; ir (potassium bromide): $\nu$ 1650 and 1630 sh (C=O) $cm^{-1}$; FAB-ms: m/z 335 ($MH^+$); $^1$H-nmr (deuteriochloroform): $\delta$ 1.67 (s, 3H, $NCOCH_3$), 2.61-2.87 (m, 3H, 10-H and 13-Ha), 3.02-3.24 (m, 3H, 9-H and 13-Hb), 3.73 (m, 1H, 14-Ha), 4.40 (t, J = 7.2 Hz, 2H, 11-H), 5.04 (dt, J = 5.4, 13.0, and 13.4 Hz, 1H, 14-Hb), 7.26 (dd, $J_{1,2}$ = 7.4 Hz, $J_{1,3}$ = 1.6 Hz, 1H, 1-H), 7.50 (dt, $J_{1,2}$ = 7.4 Hz, $J_{2,3}$ = 7.2 Hz, $J_{2,4}$ = 1.9 Hz, 1H, 2-H), 7.58 (dt, $J_{1,3}$ = 1.6 Hz, $J_{2,3}$ = 7.2 Hz, $J_{3,4}$ = 7.5 Hz, 1H, 3-H), 7.92 (dd, $J_{2,4}$ = 1.9 Hz, $J_{3,4}$ = 7.5 Hz, 1H, 4-H), 9.13 (s, 1H, 6-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 222 (4.35) sh, 246 (4.13), 360 (3.99), 410 (4.05); the solution after 3 days at room temperature had: 227 (4.30), 249 (4.26), 286 (3.79).

16-Acetyl-9,10,11,12,15,16-hexahydro-14*H*-piperidino[1'',2'':3',4']-imidazo[1',2':1,6]pyrimido[5,4-*d*][1]benzazepinium-8-one (**10b**).

A solution of **9b** (162 mg, 0.5 mmole) in acetic anhydride (0.94 ml, 10 mmoles) was stirred at room temperature for 2 hours. After the same work-up as noted in the procedure of **10a**, the crystals were filtered off by suction and washed with cold benzene to afford **10b** [7] (50 mg, 29%) as orange powder, mp >195° dec; ir (potassium bromide): $\nu$ 1640 and 1620 sh (C=O) $cm^{-1}$; FAB-ms: m/z 349 ($MH^+$); $^1$H-nmr (deuteriochloroform): $\delta$ 1.66 (s, 3H, $NCOCH_3$), 2.05 (m, 2H, 10-H), 2.50-3.12 (m, 5H, 9-H, 11-H, and 14-Ha), 3.34 (m, 1H, 14-Hb), 3.75 (m, 1H, 15-Ha), 4.41 (m, 2H, 12-H), 5.08 (ddd, J = 4.8, 12.8, and 14.4 Hz, 1H, 15-Hb), 7.26 (dd, $J_{1,2}$ = 7.5 Hz, $J_{1,3}$ = 1.5 Hz, 1H, 1-H), 7.51 (dt, $J_{1,2}$ = 7.5 Hz, $J_{2,3}$ = 7.3 Hz, $J_{2,4}$ = 1.9 Hz, 1H, 2-H), 7.59 (dt, $J_{1,3}$ = 1.5 Hz, $J_{2,3}$ = 7.3 Hz, $J_{3,4}$ = 7.5 Hz, 1H, 3-H), 7.92 (dd, $J_{2,4}$ = 1.9 Hz, $J_{3,4}$ = 7.5 Hz, 1H, 4-H), 9.17 (s, 1H, 6-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 222 (4.49) sh, 250 (4.27) sh, 370 (3.96), 417 (4.03); the solution after 3 days at room temperature had: 224 (4.48), 251 (4.34) sh, 284 (4.06) sh.

2-(6,7-Dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepin-4-ylthio)acetic Acid (**11**).

A mixture of **1** (926 mg, 4 mmoles), mercaptoacetic acid (0.56 ml, 8 mmoles), and potassium carbonate (1.65 g, 12 mmoles) in dimethylformamide (15 ml) was heated at 90° with stirring for 1.5 hours. After cooling, the precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue diluted with water (50 ml) was adjusted to *p*H 9 with sodium hydrogen carbonate. Then, the 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 [3]. After the water layer was acidified with acetic acid, the solution was extracted with ethyl acetate (3 x 20 ml). The combined organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was purified by recrystallization from benzene to afford **11** (712 mg, 62%) as pale yellow needles, mp 155-157°; ir (potassium bromide): $\nu$ 3320 (NH), $\nu$ 3030-2350 (COOH), $\nu$ 1708 (C=O) $cm^{-1}$; FAB-ms: m/z 288 ($MH^+$); $^1$H-nmr (DMSO-$d_6$): $\delta$ 2.92 (br t, J = 5.0 Hz, 2H, 5-H), 3.60 (br t, J = 5.0 Hz, 2H, 6-H), 4.05 (s, 2H, $SCH_2$), 6.80 (m, 2H, 8-H and 10-H), 7.25 (ddd, $J_{8,9}$ = 8.1 Hz, $J_{9,10}$ = 7.1 Hz, $J_{9,11}$ = 1.5 Hz, 1H, 9-H), 8.12 (dd, $J_{9,11}$ = 1.5 Hz, $J_{10,11}$ = 7.9 Hz, 1H, 11-H), 8.87 (s, 1H, 2-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 242 (4.42), 300 (3.90), 375 (3.65).

*Anal.* Calcd. for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.69; H, 4.64; N, 14.34.

5,6-Dihydro-4*H*-thiazolo[3',2':1,6]pyrimido[5,4-*d*][1]benzazepinium-1-one (**12**).

To a stirring solution of **11** (135 mg, 0.5 mmole) in pyridine (0.5 ml) was added a mixture of dry benzene (3.5 ml) and acetic anhydride (0.14 ml, 1.5 mmoles) at room temperature under an inert atmosphere of argon, and the stirring was continued for 1.5 hours. The precipitated crystals were filtered off by suction and washed with cold benzene to afford **12** [7] (100 mg, 79%) as brown powder, mp >186° dec; ir (potassium bromide): $\nu$ 3220 (NH), $\nu$ 1618 (C=O) $cm^{-1}$; FAB-ms: m/z 270 ($MH^+$); $^1$H-nmr (methanol-$d_4$): $\delta$ 2.99 (t, J = 5.5 Hz, 2H, 4-H), 3.72 (t, J = 5.5 Hz, 2H, 5-H), 6.86 (dd, $J_{7,8}$ = 8.0 Hz, $J_{7,9}$ = 1.2 Hz, 1H, 7-H), 6.90 (ddd, $J_{7,9}$ = 1.2 Hz, $J_{8,9}$ = 7.2 Hz, $J_{9,10}$ = 8.0 Hz, 1H, 9-H), 7.28 (ddd, $J_{7,8}$ = 8.0 Hz, $J_{8,9}$ = 7.2 Hz, $J_{8,10}$ = 1.5 Hz, 1H, 8-H), 7.37 (s, 1H, 2-H), 7.90 (dd, $J_{8,10}$ = 1.5 Hz, $J_{9,10}$ = 8.0 Hz, 1H, 10-H), 8.78 (s, 1H, 12-H); uv (ethanol): $\lambda$ max nm (log $\epsilon$) 239 (4.14), 260 (3.98) sh, 298 (3.69), 395 (3.63), 466 (3.98); the solution after 3 days at room temperature had: 240 (4.30), 295 (3.78) sh, 375 (3.54).

Measurement of Blood Platelet Aggregation.

The platelets such as platelet rich plasma (PRP) and platelet poor plasma (PPP) were prepared exactly according to the previously outlined procedure [2]. The measurement for the platelet aggregation in 10% aqueous dimethyl sulfoxide solution containing the inhibitory agent such as aspirin as a positive control or test compound with collagen as an aggregation agent and 1 *M* tris-HCl buffer by the turbidimetric method [5] with an aggregometer were also performed as stated in the previous paper [2].

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