POLYCYCLIC N-HETERO COMPOUNDS. XXV[1].
SYNTHESIS OF NOVEL D-HOMO-11,13,15-TRIAZASTEROIDAL SKELETON AND INVESTIGATION OF ITS ANTIDEPRESSIVE ACTIVITY

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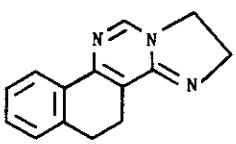
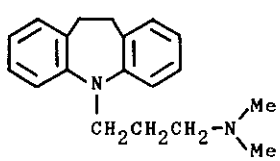
Abstract - A synthesis of D-homo-11,13,15-triazasteroidal skeleton, corresponding to benzo[h]pyrimido[1,2-c]quinazoline as a novel ring system is described.
Antidepressive activity of these compounds was screened by inhibitory action of reserpine-induced hypothermia. Compounds VIIc and XVI exhibited antireserpine action.

We have recently reported the synthesis of benz[h]imidazo[1,2-c]quinazoline ring system, corresponding to 11,13,15-triazasteroidal skeleton[2], and investigation of its antidepressive activity[3]. In the paper, we have carried out the modification of 1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazoline (I)[2] as a lead compound, because it exhibited antidepressive activity[3] as strong as imipramine (II) which was widely used as a tricyclic antidepressant. In the course of this work, synthesis of D-homo-11,13,15-triazasteroidal analogue, possessing benzo[h]pyrimido[1,2-c]quinazoline ring system, was designed. Furthermore, since there are no reports in literatures about this ring system, additional interest prompted us to synthesize its derivatives and to investigate their biological activities.



I



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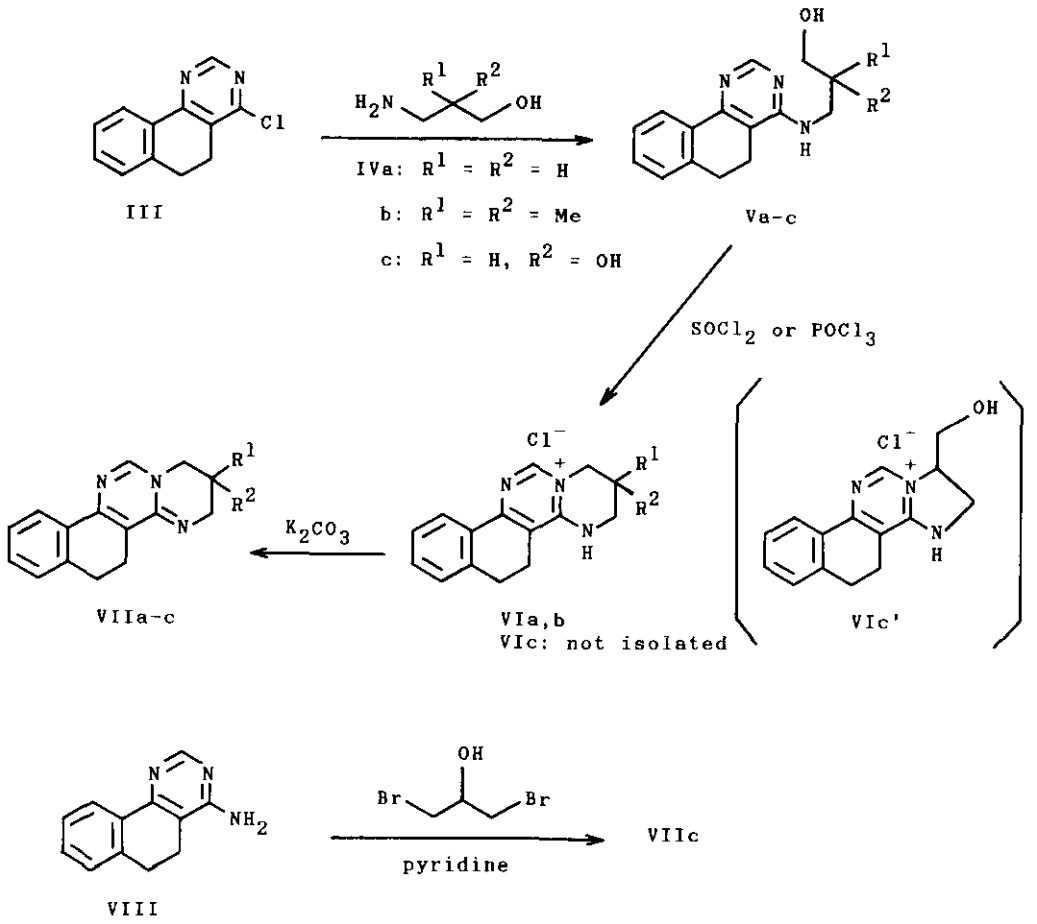
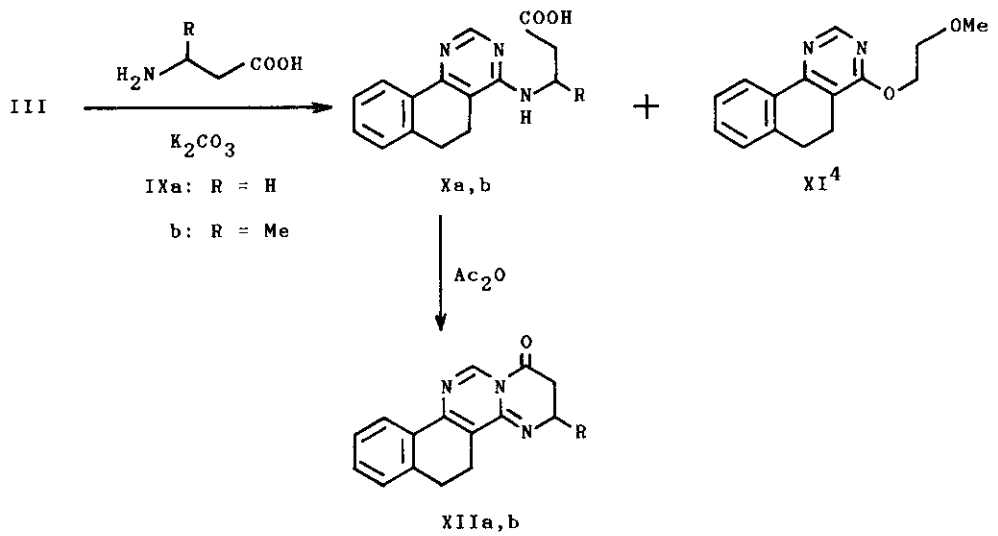


Scheme 1

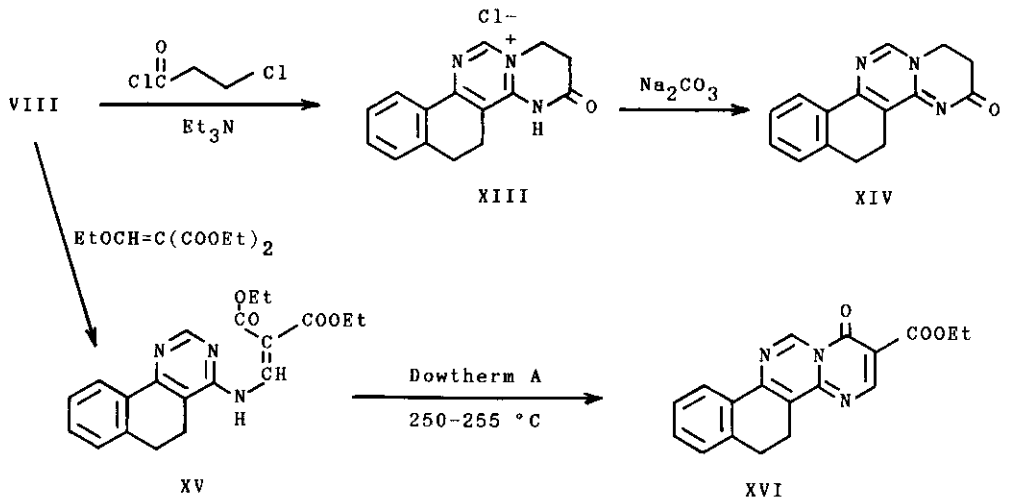
4-Chloro-5,6-dihydrobenzo[h]quinazoline (III)[2b] was used as a starting material. As shown in Scheme 1, the reaction of III with 3-hydroxypropylamine derivatives (IVa-c) afforded the corresponding 4-(3-hydroxypropylamino)-5,6-dihydrobenzo-[h]quinazolines (Va-c). Cyclization of V with thionyl chloride or phosphoryl chloride gave 2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazolinium chloride (VIa,b). Compound VIc could not be isolated because it was difficult to purify, however, the purification was successful in the next step. Treatment

of VIa,b and impure VIc with potassium carbonate gave free bases (VIIa-c). In the case of cyclization of Vc, formation of five-membered ring (imidazole type) could be also considered (VIc'). To confirm the type of the ring formation, reaction of 4-amino-5,6-dihydrobenzo[h]quinazoline (VIII)[2] with 1,3-dibromo-2-propanol in the presence of triethylamine was carried out and yielded VIIc. Therefore, our obtained compound from Vc was VIc, not VIc'.



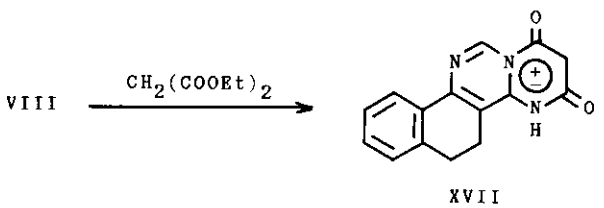
Scheme 2

Next, an introduction of carbonyl group in D-ring was designed. As shown in Scheme 2, the reaction of III with β-alanine derivatives (IXa,b) in the presence of potassium carbonate afforded N-(5,6-dihydrobenzo[h]quinazolin-4-yl)-β-alanines (Xa,b). In the case of transformation of III to Xa, 4-(2-methoxyethyloxy)-5,6-dihydrobenzo[h]quinazoline (XI) was yielded as by-product when aqueous 2-methoxyethanol was used as a solvent. The trouble was dissolved by using aqueous dioxane as a solvent. Although the cyclization of X with phosphoryl chloride in the presence of pyridine afforded many products (on tlc), treatment of X with acetic anhydride gave 1-oxo-2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazolines (XIIa,b) in good yield.



Scheme 3

As shown in Scheme 3, condensation of VIII with 3-chloropropionyl chloride in the presence of an equimolar amount of triethylamine afforded 3-oxo-2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazolinium chloride (XIII), which was converted to free base (XIV) by using aqueous potassium carbonate. On the other hand, heating of VIII with diethyl ethoxymethylenemalonate gave diethyl amino-methylenemalonate derivative (XV), which was transformed to ethyl 1-oxo-5,6-dihydro-1H-benzo[h]pyrimido[1,2-c]quinazoline-2-carboxylate (XVI).



Scheme 4

Katritzky[5] and Dvorsak[6] gave the mesomeric betaine structure for malonyl-α-aminopyridine, which was obtained by heating α-aminopyridine with diethyl malonate. As shown in Scheme 4, mesomeric betaine (XVII) was obtained from VIII by application of this method.

The antidepressive activity of these D-homotriazasteroids was screened by the inhibitory action against reserpine-induced hypothermia in mice and compared with that of control[7]. Compounds VIIc and XVI exhibited antireserpine action, however, other compounds did not.

Further studies of this series are in progress.

EXPERIMENTAL

Mps were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were obtained with a Japan Spectroscopic A-102 diffraction grating infrared spectrophotometer in KBr pellet. The nmr spectra were measured on a Hitachi R-22FTS FT-NMR spectrometer (90 MHz). The chemical shifts (δ) in ppm are measured relative to tetramethylsilane as an internal standard. The ms spectra were taken with a Shimadzu LKB-9000 instrument at 70eV. The uv spectra were taken on a Hitachi ESP-2 spectrophotometer in ethanol. IUPAC nomenclature is used in experimental section (not a steroid numbering).

4-(3-Hydoxypropylamino)-5,6-dihydrobenzo[h]quinaloline (Va)

A mixture of 1.5 g (6.9 mM) of III[2b] and 4.5 g of 3-amino-1-propanol (IVa) was stirred at 60 °C for 1.5 h. After cooling, 30 ml of water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The crystalline residue was recrystallized from benzene to give 1.26 g (71%) of Va as colorless needles, mp 122-124 °C. Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.29; H, 6.73; N, 16.37. Ms m/z: 255 (M^+); ir ν max: 3400, 3350 (O-H, N-H) cm^{-1}; nmr ($CDCl_3$): 1.89 (2H, quin, J = 6 Hz, CH_2-CH_2-CH_2), 2.63, 3.00 (each 2H, br t, J = 6 Hz, 5 and 6-H), 3.70 (4H, m, NCH_2 and OCH_2), 4.29, 5.26 (each 1H, br, D_2O exchangeable, OH and NH), 7.28 (3H, m, 7, 8, and 9-H), 8.29 (1H, dd, J = 8 Hz, 2 Hz, 10-H), 8.60 (1H, s, 2-H).

2,3,5,6-Tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazolinium Chloride (VIa)

To a solution of 1.02 g (4 mM) of Va in 15 ml of alcohol-free, dry $CHCl_3$, was added 0.45 ml (6 mM) of $SOCl_2$ and the mixture was refluxed for 3 h. After evaporation of the solvent, crystalline residue was recrystallized from MeOH-dioxane to give 718 mg (66%) of VIa as colorless fine needles, mp 285-287 °C (dec.). Anal. Calcd. for $C_{15}H_{16}ClN_3 \cdot 1/2H_2O$: C, 63.71; H, 6.05; N, 14.86. Found: C, 63.39; H, 5.98; N, 14.59. Ms m/z: 237 (M - HCl); nmr (DMSO-d_6): 2.20 (2H, m, 2-H), 2.96 (4H, br s, 5 and 6-H), 3.56 (2H, m, the signal changed to broad triplet after addition of D_2O, J = 5 Hz, 3-H), 4.36 (2H, br t, J = 5 Hz, 1-H), 7.43 (3H, m, 7, 8, and 9-H), 8.17 (1H, dd, J = 7.5 Hz, 3 Hz, 10-H), 8.72 (1H, s, 12-H), 10.06 (1H, br, D_2O exchangeable, NH); uv λ max nm (log ε): 220 (3.78), 256 (4.02), 303 (3.63), 318 (3.68), 329 (3.73), 343 (3.53).

2,3,5,6-Tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazoline (VIIa)

To a solution of 136 mg (0.5 mM) of VIa in a 20 ml of H_2O, was added 10% K_2CO_3 to make alkali and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from benzene-cyclohexane to give 101 mg (84%) of VIIa as yellow needles, mp 220-223 °C. Anal. Calcd. for $C_{15}H_{15}N_3$: C, 65.93; H, 6.32; N, 17.72. Found: C, 65.75; H, 6.54; N, 17.73. Ms m/z: 237 (M^+); nmr ($CDCl_3$): 2.03 (2H, m, 2-H), 2.83 (4H, m, 5 and 6-H), 4.66, 4.87 (each 2H, t, J = 6 Hz, 1 and 3-H), 7.30 (3H, m, 7, 8, and 9-H), 7.53 (1H, s, 12-H), 8.68 (1H, m, 10-H); uv λ max nm (log ε): 258 (4.22), 303 (3.73), 318 (3.77), 330 (4.83), 345 (3.71).

4-(2,2-Dimethyl-3-hydroxypropylamino)-5,6-dihydrobenzo[h]quinazoline (Vb)

A soluiton of 648 mg (3 mM) of III, 618 mg (6 mM) of 3-amino-2,2-dimethyl-1-propanol (IVb), and 1 ml of triethylamine (3 mM) in 10 ml of dioxane was refluxed for 3 days. After cooling, the deposited crystals ($Et_3N \cdot HCl$) were filtered off and the filtrate was evaporated. The residue was recrystallized from EtOH to give 409 mg (51%) of Vb as colorless scales, mp 193-195 °C. Anal. Calcd. for $C_{17}H_{21}N_3O$: C, 72.05; H, 7.46; N, 14.82. Found: C, 71.94; H, 7.55; N, 14.80. Ms m/z: 283 (M^+); ir ν max: 3350, 3200 (O-H, N-H) cm^{-1}; nmr (DMSO-d_6): 0.85 (6H, s, 2 x Me), 2.83 (4H, m, 5 and 6-H), 3.18, 3.38 (each 2H, d, J = 4 Hz, J = 4.5 Hz, each signal changed to singlet after addition of D_2O, OCH_2 and NCH_2), 4.96, 6.82 (each 1H, br, D_2O exchangeable, OH and NH), 7.34 (3H, m, 7, 8, and 9-H), 8.15 (1H, m, 10-H), 8.40 (1H, s, 2-H).

2,2-Dimethyl-2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazolinium Chloride (VIb)

A solution of 403 mg (1.4 mM) of Vb and 1.14 ml (1.65 mM) of $SOCl_2$ in 15 ml of alcohol-free, dry $CHCl_3$ was stirred at room temperature for 3 days. After evaporation of the solvent, the residue was triturated with H_2O and the resulting mixture was evaporated to dryness. The crystalline residue was recrystallized from EtOH-acetone to give 295 mg (70%) of VIb as colorless needles, mp 263-265 °C. Anal. Calcd. for $C_{17}H_{20}N_3Cl \cdot H_2O$: C, 63.84; H, 6.93; N, 13.13. Found: C, 64.28; H, 6.63; N, 13.06. Ms m/z: 265 (M - HCl); nmr (DMSO-d_6): 1.10 (6H, s, 2 x Me), 2.98 (4H, s, 5 and 6-H), 3.30 (2H, s, 3-H), 4.10 (2H, s, 1-H), 7.50 (3H, m, 7, 8, and 9-H), 8.20 (1H, m, 10-H), 8.70 (1H, s, 12-H), 10.15 (1H, br, D_2O exchangeable, NH); uv λ max nm (log ε): 258 (3.63), 304 (3.19), 318 (3.23), 350 (3.12).

2,2-Dimethyl-2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazoline (VIIb)

A solution of 150 mg (0.5 mM) of VIb in 25 ml of H_2O was basified with 10% K_2CO_3 and the solution was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from acetone-benzene to give 115 mg (87%) of VIIb as pale yellow granules, mp 165-166 °C. Anal. Calcd. for $C_{17}H_{19}N_3$: C, 76.94; H, 7.22; N, 15.84. Found: C, 76.73; H, 7.20; N, 15.64. Ms m/z: 265 (M^+); nmr ($CDCl_3$): 1.03 (6H, s, 2 x Me), 2.82 (4H, m, 5 and 6-H), 3.36, 3.53 (each 2H, s, 1 and 3-H), 7.26 (3H, m, 7, 8, and 9-H), 7.50 (1H, s, 12-H), 8.00 (1H, m, 10-H); uv λ max nm (log ε): 230 (3.22), 258 (3.70), 290 (3.27), 304 (3.28), 318 (3.31), 331 (3.38), 345 (3.22).

4-(2,3-Dihydroxypropylamino)-5,6-dihydrobenzo[h]quinazoline (Vc)

A mixture of 324 mg (1.5 mM) of III and 350 mg (3.8 mM) of 3-amino-1,2-propandiol was heated at 100 °C for 1.5 days. After addition of ice water to the reaction mixture, the precipitated crystals were collected on a filter and recrystallized from dil. EtOH to give 310 mg (76%) of Vc as colorless needles, mp 183-185 °C. Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.14; H, 6.29; N, 15.54. Ms m/z: 271 (M^+); ir ν max: 3410, 3350 (O-H, N-H) cm^{-1}; nmr (DMSO-d_6): 2.80 (4H, m, 5 and 6-H), 3.32 (4H, m, the signal changed to two doublets after addition of D_2O, J = 6 Hz, NCH_2 and OCH_2), 3.67 (1H, m, =CH(OH)), 4.57, 4.85, 6.80 (each 1H, br, D_2O exchangeable, 2 x OH and NH), 7.33 (3H, m, 7, 8, and 9-H), 8.13 (1H, m, 10-H), 8.30 (1H, s, 2-H).

2-Hydroxy-2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazoline (VIIc)

Method A: A solution of 370 mg (1.36 mM) of Vc and 0.14 ml (1.49 mM) of $POCl_3$

in 10 ml of dry DMF was heated at 80-90 °C for 2 days. After evaporation of DMF, the residue was triturated with H_2O and the mixture was dried up. Since the purification of the residue was unsuccessful in this stage, the aqueous solution of the residue was basified with K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from acetone to give 190 mg (55%) of VIIc as pale yellow fine needles, mp 230-231 °C (dec.). Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.12; H, 5.96; N, 16.58. Found: C, 70.98; H, 5.90; N, 16.48. Ms m/z: 253 (M^+); ir ν max: 3350 (O-H) cm^{-1}; nmr ($CDCl_3$); 2.72 (4H, m, 5 and 6-H), 3.40-4.20 (5H, m, 1, 2, and 3-H), 5.17 (1H, br, D_2O exchangeable, OH), 7.25 (3H, m, 7, 8, and 9-H), 7.80 (1H, s, 12-H), 7.95 (1H, m, 10-H); uv λ max nm (log ε): 258 (4.15), 305 (3.78), 318 (3.81), 331 (3.86), 345 (3.69).

Method B: A solution of 1.50 g (7.61 mM) of 4-amino-5,6-dihydrobenzo[h]-quinazoline (VIII)[2], 4.12 g (19 mM) of 1,3-dibromo-2-propanol, and 5 ml of pyridine in 20 ml of dioxane was refluxed for 3 days. After evaporation of organic solvents, the dark brown residue was triturated with 5% aqueous K_2CO_3 and extracted with $CHCl_3$. The organic layer was throughly washed with H_2O, dried over Na_2SO_4, and evaporated. The tarry residue was repeatedly recrystallized from acetone to give 241 mg (12.5%) of colorless fine needles, mp 229-231 °C, which was identical with the product, VIIc, described in method A (mixed mp, tlc, and ir).

N-(5,6-Dihydrobenzo[h]quinazoline-4-yl)-β-alanine (Xa) and 4-(2-Methoxyethyloxy)-5,6-dihydrobenzo[h]quinazoline (XI)

In 2-Methoxyethanol: A mixture of 216 mg (1 mM) of III, 178 mg (2 mM) of β-alanine, and 207 mg (1.5 mM) of K_2CO_3 in 10 ml of 2-methoxyethanol-H_2O (1 : 1) was refluxed for 10 h. After evaporation of the solvent, the residue was dissolved in H_2O. The remained insoluble crystals were collected on a filter and recrystallized from dil. EtOH to give 83 mg (32%) of XI as colorless fine needles, mp 30-31 °C. Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.31; H, 6.25; N, 16.40. Found: C, 70.47; H, 6.27; N; 16.42. Ms m/z: 256 (M^+); nmr ($CDCl_3$): 2.93 (4H, s, 5 and 6-H), 3.46 (3H, s, OMe), 3.80, 4.56 (each 2H, t, J = 5 Hz, OCH_2CH_2), 7.33 (3H, m, 7, 8, and 9-H), 8.30 (1H, m, 10-H), 8.72 (1H, s, 2-H). The above K_2CO_3-soluble filtrate was acidified with AcOH and the precipitated crystals were recrystallized from EtOH to give 15 mg (6%) of Xa as colorless needles, mp 192-194 °C. Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N,

15.61. Found: C, 66.68; H, 5.62; N, 15.55. Ms m/z: 269 (M^+); ir λ max: 3360 (N-H), 1700 (C=O) cm^{-1}; nmr (DMSO-d_6): 2.66 (2H, t, J = 7 Hz, CH_2CO), 2.82 (4H, m, 5 and 6-H), 3.65 (2H, m, the signal changed to triplet after addition of D_2O, J = 7 Hz, NCH_2), 7.02 (1H, t, J = 5 Hz, D_2O exchangeable, NH), 7.33 (3H, m, 7, 8, and 9-H), 8.16 (1H, m, 10-H), 8.49 (1H, s, 2-H).

In Dioxane: A mixture of 1.5 g (6.94 mM) of III, 1.8 g (21 mM) of IXa, and 1.9 g (13.7 mM) of K_2CO_3 in 30 ml of dioxane-H_2O (1 : 1) was refluxed for 15 h. After evaporation of the solvent, the residue was dissolved in small amount of H_2O and acidified with AcOH. The precipitated crystals were recrystallized from EtOH to give 1.20 g (65%) of Xa as colorless needles, mp 192-194 °C, which was identical with the above product (mixed mp, tlc, and ir).

1-Oxo-2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazoline (XIIa)

To a solution of 269 mg (1 mM) of Xa in 5 ml of pyridine, was added 0.3 ml (3 mM) of Ac_2O. The mixture was stirred at room temperature for 40 h. After evaporation of the solvent, the crystalline residue was recrystallized from EtOH to give 150 mg (60%) of XIIa as pale yellow needles, mp 272-275 °C. Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.45; H, 5.03; N, 16.51. Ms m/z: 251 (M^+); ir ν max: 1660 (C=O) cm^{-1}; nmr (CD_3OD): 2.80 (2H, t, J = 7.5 Hz, 2-H), 3.00 (4H, s, 5 and 6-H), 4.46 (2H, t, J = 7.5 Hz, 3-H), 7.41 (3H, m, 7, 8, and 9-H), 8.19 (1H, m, 10-H), 8.42 (1H, s, 12-H); uv λ max nm (log ε): 264 (4.05), 290 (3.72), 312 (3.41), 330 (3.63), 345 (3.85), 362 (3.92), 379 (3.72).

N-(5,6-Dihydrobenzo[h]quinazolin-4-yl)-3-amino-n-butyric Acid (Xb)

A mixture of 432 mg (3 mM) of III, 515 mg (5 mM) of 3-amino-n-butyric acid, and 552 mg (4 mM) of K_2CO_3 in 20 ml of dioxane-H_2O (1 : 1) was refluxed for 3 days. After evaporation of the solvent, the residue was dissolved in small amount of H_2O. The solution was acidified with AcOH and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The crystalline residue was recrystallized from EtOH-benzene to give 414 mg (49%) of Xb as a pale yellow powder, mp 169-170 °C. Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.55; H, 6.05; N, 14.68. Ms m/z: 283 (M^+); ir ν max: 3420 (N-H), 1700 (C=O) cm^{-1}; nmr (DMSO-d_6): 1.21 (3H, d, J = 6 Hz, Me), 2.60 (2H, m, CH_2CO), 2.79 (4H, m, 5 and 6-H), 4.63 (1H, m, N-CH), 6.70 (1H, br d, J = 6 Hz, D_2O exchangeable, NH), 7.32 (3H, m, 7, 8, and 9-H), 8.15 (1H, m, 10-H), 8.46 (1H, s, 2-H), 12.15 (1H, br, D_2O exchangeable, OH).

3-Methyl-1-oxo-2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazoline (XIIb)

A mixture of 300 mg (1.06 mM) of Xb, 1 ml of Ac_2O, and 1 ml of pyridine was heated at 90 °C for 1 day. After evaporation of the solvent, 5 ml of xylene was added to the residue and evaporated. The residue was recrystallized from benzene-acetone to give 126 mg (45%) of XIIb as pale brown needles, mp 248-250 °C. Anal. Calcd. for $C_{16}H_{15}N_3O \cdot 1/2H_2O$: C, 70.05; H, 5.87; N, 15.31. Found: C, 70.08; H, 5.59; N, 15.37. Ms m/z: 265 (M^+); ir ν max: 1655 (C=O) cm^{-1}; nmr ($CDCl_3$): 1.54 (3H, d, J = 6 Hz, Me), 2.88 (2H, d, J = 6 Hz, 2-H), 3.00 (4H, m, 5 and 6-H), 4.56 (1H, m, 3-H), 7.33 (3H, m, 7, 8, and 9-H), 8.12 (1H, s, 12- H), 8.20 (1H, m, 10-H); uv λ max nm (log ε): 228 (3.79), 234 (3.75), 268 (4.23), 280 (4.02), 310 (3.65), 325 (3.82), 342 (4.03), 354 (4.12), 370 (3.97).

3-Oxo-2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazolinium Chloride (XIII)

To a solution of 591 mg (3 mM) of VIII and 0.5 ml (3.6 mM) of Et_3N in 15 ml of dry, alcohol-free $CHCl_3$, was added 378 mg (3 mM) of 3-chloropropionyl chloride in 5 ml of dry $CHCl_3$ and the solution was stirred at room temperature for 1 day. The precipitated crystals were collected on a filter. Since the starting material still remained in the filtrate, the solution was refluxed for additional 10 h. After evaporation of the solvent, the residue was combined with the above crystals and recrystallized from EtOH to give 241 mg (28%) as yellow granules, mp 274-276 °C. Anal. Calcd. for $C_{15}H_{14}ClN_3O \cdot 1/2H_2O$: C, 60.71; H, 5.09; N, 14.15. Found: C, 60.94; H, 5.08; N, 14.07. Ms m/z: 251 (M - HCl); ir ν max: 1730 (C=O) cm^{-1}; nmr (DMSO-d_6): 3.07 (6H, m, 2, 5, and 6-H), 4.80 (2H, t, J = 7 Hz, 1-H), 7.52 (3H, m, 7, 8, and 9-H), 8.27 (1H, m, 10-H), 9.31 (1H, s, 12-H); uv λ max nm (log ε): 228 (3.47), 260 (3.59), 268 (3.64), 280 (3.50), 314 (3.46), 345 (3.68), 370 (3.35).

3-Oxo-2,3,5,6-tetrahydro-1H-benzo[h]pyrimido[1,2-c]quinazoline (XIV)

A solution of 143 mg (0.5 mM) of XIII in 15 ml of H_2O was basified with 10% K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The crystalline residue was recrystallized from benzene-acetone to give 75 mg (60%) of XIV as pale yelow needles, mp 197-200 °C. Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.47; H, 5.27; N, 16.61. Ms m/z: 251 (M^+); ir ν max: 1725 (C=O) cm^{-1}; nmr (DMSO-d_6): 2.87 (6H, m, 2, 5, and 6-H), 4.36 (2H, t, J = 6 Hz, 1-H), 7.39 (3H,

m, 7, 8, and 9-H), 8.14 (1H, m, 10-H), 8.51 (1H, s, 12-H); uv λ max nm (log ε): 251 (3.54), 274 (3.43), 302 (3.33), 323 (3.35), 338 (3.25).

Diethyl N-(5,6-Dihydrobenzo[h]quinazolin-4-yl)aminomethylenemalonate (XV)

A solution of 197 mg (1 mM) of VIII and 0.2 ml (1 mM) of diethyl ethoxymethylenemalonate in 20 ml of xylene was refluxed for 10 h. After evaporation of xylene, the crystalline residue was recrystallized from EtOH to give 227 mg (62%) of XV as pale brown needles, mp 110-112 °C. Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.09; H, 5.73; N, 11.18. Ms m/z: 367 (M^+); ir ν max: 1700 (C=O) cm^{-1}; nmr (acetone-d_6): 1.35, 1.38 (each 3H, t, J = 7.5 Hz, 2 x Me), 3.07 (4H, m, 5 and 6-H), 4.29, 4.35 (each 2H, q, J = 7.5 Hz, 2 x CH_2Me), 7.41 (3H, m, 7, 8, and 9-H), 8.31 (1H, m, 10-H), 8.82 (1H, s, 2-H), 9.25 (1H, d, J = 12 Hz, the signal changed to singlet after addition of D_2O, NCH), 11.28 (1H, br, D_2O exchangeable, NH).

Ethyl 1-Oxo-5,6-dihydro-1H-benzo[h]pyrimido[1,2-c]quinazoline-2-carboxylate (XVI)

A mixture of 330 mg (0.89 mM) of XV and 3 g of Dowtherm A was heated at 250-260 °C for 12 h. After cooling, the reaction mixture was washed with n-hexane to remove Dowtherm A. The residue was recrystallized from benzene-n-hexane to give 200 mg (75%) of XVI as yellowish brown needles, mp 234-235 °C. Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.70; N, 13.07. Found: C, 67.17; H, 4.57; N, 13.06. Ms m/z: 321 (M^+); ir ν max: 1720, 1700 (C=O) cm^{-1}; nmr ($CDCl_3$): 1.41 (3H, t, J = 7 Hz, Me), 3.20 (4H, m, 5 and 6-H), 4.43 (2H, q, J = 7 Hz, CH_2O), 7.36 (3H, m, 7, 8, and 9-H), 8.35 (1H, m, 10-H), 9.05 (1H, s, 3-H), 9.85 (1H, s, 12-H); uv λ max nm (log ε): 235 (3.54), 242 (3.57), 250 (3.51), 293 (3.35), 382 (3.99), 398 (4.02).

Mesomeric 5,6-Dihydrobenzo[h]pyrimido[1,2-c]quinazoline-1,3-dione (XVII)

A solution of 197 mg (1 mM) of VIII and 0.76 ml (5 mM) of diethyl malonate in 20 ml of xylene was refluxed for 30 h. After cooling, the precipitated solid was collected on a filter and recrystallized from diluted EtOH to give 187 mg (71%) of XVII as pale yellowish brown scales, mp 287-290 °C (dec.). Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.91; H, 4.18; N, 15.84. Found: C, 67.68; H, 4.10; N, 15.59. Ms m/z: 265 (M^+); ir ν max: 3090, 2900, 1715 (C=O), 1600 cm^{-1}; nmr (DMSO-d_6): 3.10 (4H, m, 5 and 6-H), 5.50 (1H, s, 2-H), 7.46 (3H, m, 7, 8, and 9-H), 8.23 (1H, m, 10-H), 9.53 (1H, s, 12-H); uv λ max nm (log ε): 230 (4.10), 239 (4.05), 254 (4.20), 264 (4.25), 289 (3.78), 320 (3.76), 330 (3.90), 345

(4.01).

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Five male ICR-JCL mice weighting 23 to 28 g were used in all experiments and test compounds (10 mg/kg, i.p.) were injected after the injection of reserpine (2 mg/kg, i.p.).

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