Polycyclic *N*-Heterocyclic Compounds. **51**. Synthesis of Novel 12-Substituted 11,13,15-Triazasteroidal Compounds and Their Inhibitory Activity on Platelet Aggregation

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Synthesis of 11-substituted 1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]quinazolines corresponding to 12-substituted 11,13,15-triazasteroid is described. Evaluation on inhibitory activity against collagen-induced platelet aggregation of these compounds and their precursors was also investigated.

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During the course of our studies on polycyclic *N*-heterocyclic compounds many 11,13,15-triazasteroidal compounds have been synthesized [2] and evaluated of their biological activities, for example, antidepressive activity [3] or inhibitory activity on platelet aggregation [4]. However, all of these triazasteroids have no substituent at 12-position. From the view of the structure-activity relationship of these compounds, we were interested in evaluating the bioactivity of 12-substituted 11,13,15-triazasteroids.

In this paper, we describe the syntheses of 12-substituted 11,13,15-triazasteroidal compounds and their precursors, 2,4-disubstituted 5,6-dihydrobenzo[*h*]quinazolines and anti-platelet activity of these compounds.

As shown in the Scheme, 2-cyano-1-tetralone **1** [5] was converted to 3-amino-4,5-dihydronaphtho[1,2-*c*]isoxazole **2** with hydroxylamine hydrochloride. The reduction of **2** with Zn powder in 1-propanol under reflux, which was modified from the method of Taylor *et al.* [6], gave the key intermediate, 1-amino-3,4-dihydro-2-naphthalenecar-

Table

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

Compound	Max. inhibit. rate [a]	IC_{50} [b]	Compound	Max. inhibit. rate [a]	IC_{50} [b]
4 [c]	64.9 ±6.5 [e]	21.5 (16.2-36.1)	**6f** [d]	24.8 ±2.6	
5a [d]	3.1 ±0.4		**6g** [d]	7.4 ±3.9	
5b [d]	8.7 ±0.5		**6h** [d]	2.0 ±0.6	
5c [d]	17.8 ±1.4		**6i** [d]	5.0 ±0.8	
5d [d]	21.1 ±0.5		**7a** [c]	6.8 ±0.8	
5e [d]	17.7 ±2.9		**7b** [c]	18.0 ±4.5	
5f [d]	46.2 ±8.5 [e]	6.0 (4.8-11.8)	**7c** [c]	3.2 ±1.8	
5g [d]	30.8 ±6.5		**7d** [c]	11.9 ±0.6	
5h [d]	47.6 ±10.0 [e]	2.3 (1.8-3.1)	**7e** [d]	2.8 ±2.7	
5i [c]	64.9 ±6.5 [e]	21.5 (16.2-36.1)	**7f** [c]	25.8 ±15.2	
6a [c]	34.1 ±11.8 [e]	24.7 (12.7-70.8)	**7g** [c]	3.2 ±3.1	
6b [c]	44.6 ±2.6 [e]	21.7 (15.0-32.4)	**7h** [d]	9.9 ±1.1	
6c [d]	67.1 ±13.4 [e]	1.7 (1.2-2.2)	**7i** [c]	3.5 ±3.4	
6d [d]	3.0 ±1.4		aspirin [c]	15.7 ±1.0	44.6 (37.6-55.0)
6e [d]	18.8 ±2.2		aspirin [d]	20.4 ±2.5	10.4 (7.0-34.7)

[a] Value is expressed as % and the mean ± S.E. of at least three experiments at final concentration of 25 μmol/l (in the case of 10% DMSO) or 2.5 μmol/l (in the case of 60% DMF). [b] Figures in upper lines and lower lines for each compound represent the IC_{50} value (μmol/l) and 95% confidence limits (μmol/l-μmol/l), respectively. Experiments were repeated at least each three times at final concentrations of 5, 25, 50 μmol/l (in the case of 10% DMSO), 1.0, 2.5, 5.0 μmol/l (in the case of 60% DMF), or 25, 50, 100 μmol/l (in the case of aspirin). [c] Measured in 10% DMSO. [d] Measured in 60% DMF. [e] Significantly different from aspirin at $p < 0.01$. [f] Not measured because of its solubility.

boxamide **3**. The structure of **3** was assisted with the presences of amino and amide groups in ir (3400, 3290, and 1650 cm^{-1}) and ^1H nmr spectra (δ 5.20 and 6.90 ppm, each two proton broad absorption).

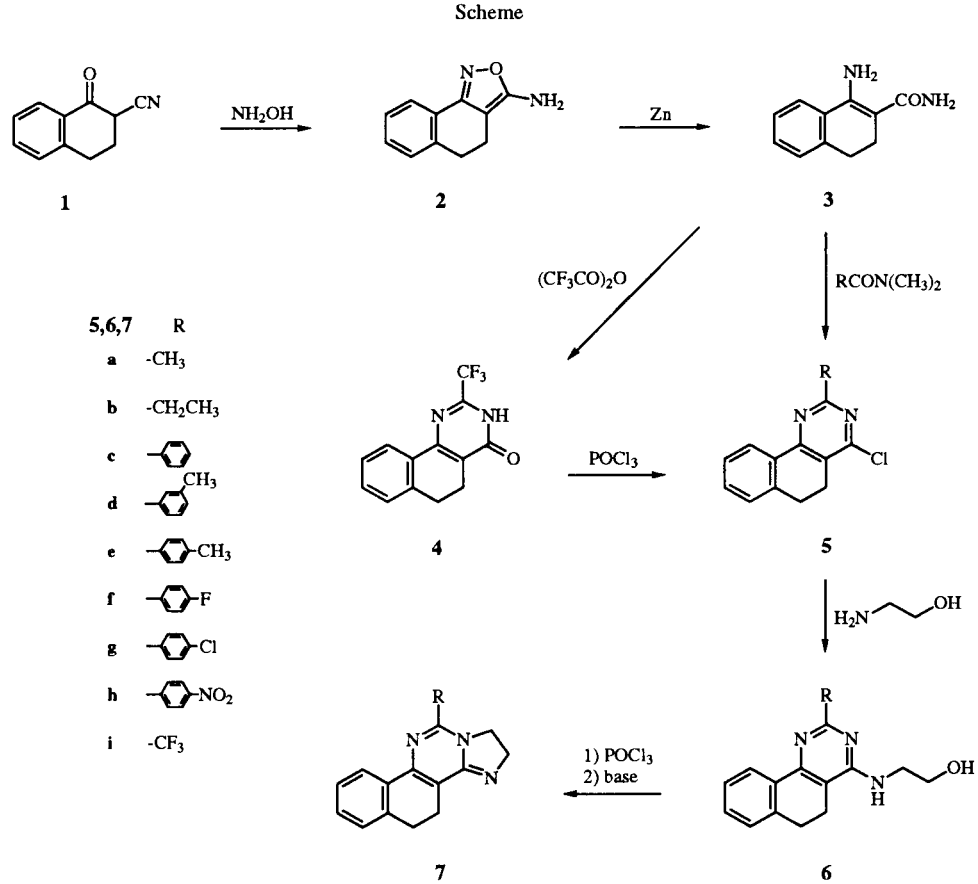
Next, we employed two strategies for preparing 2-substituted 4-chloro-5,6-dihydrobenzo[*h*]quinazolines **5**. One of them is the method *via* the Vilsmeier type reaction, and in this case eight *N,N*-dimethylamides bearing different substituent (R, methyl, ethyl, phenyl, *m*-tolyl, *p*-tolyl, 4-fluorophenyl, 4-chlorophenyl, or 4-nitrophenyl) were used as a starting material. These starting materials were prepared by the reaction of dimethylamine and the corresponding acid chloride in diethyl ether except for commercial available amides. Desired 2-substituted compounds **5a-h** were obtained by the refluxing **3** with the Vilsmeier reagent which was in advance prepared by mixing the corresponding amide with phosphorus oxychloride under ice-cooling in alcohol-free chloroform. The alternative route was employed for the synthesis of **5i**. In this case, trifluoroacetic anhydride was used as a cyclizing material and reacted with **3** in refluxing chloroform to afford 2-trifluoromethyl-5,6-dihydrobenzo[*h*]quinazolin-4(3*H*)-one **4**, at first. Then the quinazolinone **4** was converted to the chloro derivative **5i** by refluxing with phosphorus oxychloride in dioxane.

The structure of the quinazolinone **4** was consisted with the absorption of lactam (3450 and 1660 cm^{-1}) in ir spectrum and the presence of the one proton broad singlet (NH) at 7.11 ppm and the low-field shifted proton (H10) at 8.26 ppm which was caused by the anisotropic effect of newly formed pyrimidine ring in ^1H nmr spectrum. The structures of nine chloro derivatives **5a-i** were conformed by the observation of the isotope fragment peak of the parent peak in their mass spectra, that is, the ratio of the isotope fragment peak ($M^+ + 2$) to the parent peak (M^+) is about 1:3 (except for **5g**). In the case of **5g**, the presence of two chloro groups was indicated. The nmr data and elemental analyses also supported these structures.

As the next stage, hydroxyethylamino group was introduced into the 4 position of 5,6-dihydrobenzo[*h*]quinazolines. Instrumental data supported the structures of 4-(2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazolines **6** unambiguously.

Finally, the compounds **6** were cyclized to the desired 11-substituted 1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]-quinazolines corresponding to a 12-substituted 11,13,15-triazasteroid by refluxing **6** with phosphorus oxychloride followed by treatment with base. Low-field shift of two two-proton multiplets supported the cyclized structure, that is, one of them was shifted from *ca.* 3.9 ppm to *ca.*

Scheme



4.5 ppm and the other was from *ca.* 3.9 ppm to *ca.* 5.1 ppm and these signals were assigned as H1 and H2 of **7**.

Evaluation of the activity against platelet aggregation of the newly synthesized tetracyclic compound and their precursors was screened by a turbidimetric method developed by Born and Cross [7] using an aggregometer. Preparation of platelets, measurement of platelet aggregation, the calculation of the inhibition rate and the estimation method using aspirin as a standard were performed in the same manner described previously [5a]. Many compounds in this paper produced a dose-dependent inhibition against rabbit platelet aggregation induced by collagen. As shown in Table, three derivatives **5f**, **5h**, and **5i**, had the most potent activity among all compounds **5a-i**, and it seems that the electron-withdrawing group at the 2 position works more effectively than an electron-releasing group at the same position for appearance of the activity. In this series, **5h** was the most potent compound. Although the number of the derivative is only one, 2-trifluoromethylbenzoquinazolinone **4** showed the most potent activity. In the series of 4-hydroxyethylamino derivatives **6**, one-third of them, **6a**, **6b**, and **6c**, had potent activity. Especially, **6c** was the most potent derivative among all compounds determined in this report. The electron-releasing or withdrawing property of the substituent at the 2 position of these potent derivatives **6a**, **6b**, and **6c**, is opposite in comparison with that of **5**. That is, the compounds with an electron-releasing group at the 2 position seem to be more effective than the compounds with an electron-withdrawing group in the series of compounds **6**. None of tetracyclic compounds **7** showed any effective activity. The cyclization of compounds **6** was not effective in producing activity into tetracycles **7**.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The EI-ms spectra were measured on a Shimadzu LKB-9000 instrument. The FAB-ms were recorded on a VG 70-SE mass spectrometer, using glycerol as the matrix agent. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer as potassium bromide pellets and frequencies are expressed in cm^{-1}. The ^1H nmr spectra were recorded on a Hitachi R-22 FTS FT-NMR spectrometer (90-MHz) or Varian VXR-200 instrument (200-MHz) in the solvent indicated with tetramethylsilane as the internal standard and, unless otherwise stated, spectra were recorded on the Hitachi 90-MHz instrument. The chemical shifts are reported in ppm (δ) and the J values in Hz. The signals are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

IUPAC nomenclature is used for all compounds in the Experimental (not a steroidal numbering).

3-Amino-4,5-dihydronaphtho[1,2-*c*]isoxazole (**2**).

A solution of 2-cyano-1-tetralone (**1**, 10.4 g, 61 mmoles) and hydroxylamine hydrochloride (4.21 g, 61 mmoles) in 0.5 *N* aqueous sodium hydroxide (364 ml, 180 mmoles) was stirred at room temperature for 2 days. After the reaction completed, the reaction mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from benzene to give **2** (9.89 g, 87%) as a pale yellow powder, mp 126-128°; ir: 3430 (N-H); ^1H nmr (deuteriochloroform): 2.50 (m, 2H, H4), 2.90 (m, 2H, H5), 4.70 (br, deuterium oxide exchangeable, 2H, NH_2), 7.30 (m, 3H, H6, 7, and 8), 7.80 (m, 1H, H9); EI-ms: m/z 186 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.18; H, 5.26; N, 15.20.

1-Amino-3,4-dihydro-2-naphthalenecarboxamide (**3**).

A mixture of **2** (5.4 g, 29 mmoles) and powdered zinc (5.8 g, 90 mmoles) in *n*-propyl alcohol (300 ml) was refluxed for 36 hours. After removement of zinc by filtration the filtrate was evaporated *in vacuo* and water (200 ml) was poured onto the residue. The resulting mixture was extracted with chloroform and the organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from benzene to afford **3** (2.7 g, 49%) as pale yellow needles, mp 150-152°; ir: 3290, 3400 (N-H), 1650 (C=O); ^1H nmr (deuteriochloroform): 2.30 (m, 2H, H3), 2.80 (m, 2H, H4), 5.20 and 6.90 (each br, deuterium oxide exchangeable, each 2H, NH_2 x 2), 7.30 (m, 4H, H5, 6, 7, and 8); EI-ms: m/z 188 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.22; H, 6.40; N, 14.89.

4-Chloro-2-methyl-5,6-dihydrobenzo[*h*]quinazoline (**5a**).

A mixture of *N,N*-dimethylacetamide (139 mg, 1.60 mmoles) and phosphorus oxychloride (0.15 ml, 1.60 mmoles) in dry chloroform (2 ml) was stirred with ice-cooling for 30 minutes. To the above mixture was added **3** (100 mg, 0.53 mmole) and the resulting mixture was refluxed for 48 hours. Water (50 ml) was added to the reaction mixture, which was basified with aqueous sodium hydrogen carbonate and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from methanol to give **5a** (100 mg, 81%) as pale yellow needles, mp 133-135°; ^1H nmr (deuteriochloroform): 2.73 (s, 3H, CH_3), 3.01 (br s, 4H, H5 and 6), 7.37 (m, 3H, H7, 8, and 9), 8.40 (m, 1H, H10); FAB-ms: m/z 231 (MH^+), 233 ($MH^+ + 2$), intensity ratio of the parent peak at 231 to 233 is 3 to 1.

Anal. Calcd. for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81; N, 12.14. Found: C, 67.58; H, 4.79; N, 12.07.

4-Chloro-2-ethyl-5,6-dihydrobenzo[*h*]quinazoline (**5b**).

This compound was synthesized from *N,N*-dimethylpropionamide (162 mg, 1.60 mmoles), phosphorus oxychloride (0.15 ml, 1.60 mmoles) and **3** (100 mg, 0.53 mmole) in dry chloroform (refluxed for 24 hours) in a manner similar to the preparation of **5a**, and was obtained as colorless needles (from methanol) in 84% (108 mg) yield, mp 70-72°; ^1H nmr (deuteriochloroform): 1.38 (t, J = 8, 3H, CH_2CH_3), 2.97 (q, J = 8, 2H, CH_2CH_3), 3.01 (br s, 4H, H5 and 6), 7.33 (m, 3H, H7, 8, and 9), 8.43 (m, 1H, H10); FAB ms: m/z 245 (MH^+), 247 ($MH^+ + 2$), intensity ratio of the parent peak at 245 to 247 is 3 to 1.

Anal. Calcd. for $C_{14}H_{13}ClN_2$: C, 68.71; H, 5.35; N, 11.45. Found: C, 68.32; H, 5.33; N, 11.30.

4-Chloro-2-phenyl-5,6-dihydrobenzo[*h*]quinazoline (**5c**).

This compound was synthesized from *N,N*-dimethylbenzamide (239 mg, 1.60 mmoles), phosphorus oxychloride (0.15 ml, 1.60 mmoles) and **3** (100 mg, 0.53 mmole) in dry chloroform (refluxed for 36 hours) in a manner similar to the preparation of **5a**, and was obtained as colorless needles (from methanol) in 50% (77 mg) yield, mp 130-132°; ^{1}H nmr (deuteriochloroform): 3.08 (br s, 4H, H5 and 6), 7.45 (m, 6H, H7, 8, and 9 and phenyl-H3', 4', and 5'), 8.60 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 293 (MH^+), 295 ($MH^+ + 2$), intensity ratio of the parent peak at 293 to 295 is 3 to 1.

Anal. Calcd. for $C_{18}H_{13}ClN_2$: C, 73.85; H, 4.48; N, 9.57. Found: C, 73.79; H, 4.43; N, 9.79.

4-Chloro-2-(*m*-tolyl)-5,6-dihydrobenzo[*h*]quinazoline (**5d**).

This compound was synthesized from *N,N*-dimethyl-3-methylbenzamide (261 mg, 1.60 mmoles), phosphorus oxychloride (0.15 ml, 1.60 mmoles) and **3** (100 mg, 0.53 mmole) in dry chloroform (refluxed for 33 hours) in a manner similar to the preparation of **5a**, and was obtained as pale yellow needles (from methanol) in 95% (154 mg) yield, mp 135-138°; ^{1}H nmr (deuteriochloroform): 2.47 (s, 3H, CH_3), 3.07 (br s, 4H, H5 and 6), 7.40 (m, 5H, H7, 8, and 9 and phenyl-H4' and 5'), 8.45 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 307 (MH^+), 309 ($MH^+ + 2$), intensity ratio of the parent peak at 307 to 309 is 3 to 1.

Anal. Calcd. for $C_{19}H_{15}ClN_2$: C, 74.39; H, 4.93; N, 9.13. Found: C, 74.51; H, 4.79; N, 9.22.

4-Chloro-2-(*p*-tolyl)-5,6-dihydrobenzo[*h*]quinazoline (**5e**).

This compound was synthesized from *N,N*-dimethyl-4-methylbenzamide (261 mg, 1.60 mmole), phosphorus oxychloride (0.15 ml, 1.60 mmoles) and **3** (100 mg, 0.53 mmole) in dry chloroform (refluxed for 23 hours) in a manner similar to the preparation of **5a**, and was obtained as colorless needles (from methanol) in 55% (89 mg) yield, mp 132-134°; ^{1}H nmr (deuteriochloroform): 2.43 (s, 3H, CH_3), 3.05 (br s, 4H, H5 and 6), 7.39 (m, 5H, H7, 8, and 9 and phenyl-H3' and 5'), 8.45 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 307 (MH^+), 309 ($MH^+ + 2$), intensity ratio of the parent peak at 307 to 309 is 3 to 1.

Anal. Calcd. for $C_{19}H_{15}ClN_2$: C, 74.39; H, 4.93; N, 9.13. Found: C, 74.42; H, 4.73; N, 9.28.

4-Chloro-2-(4-fluorophenyl)-5,6-dihydrobenzo[*h*]quinazoline (**5f**).

This compound was synthesized from *N,N*-dimethyl-4-fluorobenzamide (267 mg, 1.60 mmoles), phosphorus oxychloride (0.15 ml, 1.60 mmoles) and **3** (100 mg, 0.53 mmole) in dry chloroform (refluxed for 13 hours) in a manner similar to the preparation of **5a**, and was obtained as colorless needles (from methanol) in 80% (132 mg) yield, mp 144-147°; ^{1}H nmr (deuteriochloroform): 3.07 (br s, 4H, H5 and 6), 7.23 (m, 5H, H7, 8, and 9 and phenyl-H3' and 5'), 8.54 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 311 (MH^+), 313 ($MH^+ + 2$), intensity ratio of the parent peak at 311 to 313 is 3 to 1.

Anal. Calcd. for $C_{18}H_{12}ClFN_2$: C, 69.57; H, 3.89; N, 9.02. Found: C, 69.57; H, 3.86; N, 8.65.

4-Chloro-2-(4-chlorophenyl)-5,6-dihydrobenzo[*h*]quinazoline (**5g**).

This compound was synthesized from *N,N*-dimethyl-4-chlorobenzamide (294 mg, 1.60 mmoles), phosphorus oxychloride (0.15 ml, 1.60 mmoles) and **3** (100 mg, 0.53 mmole) in dry chloroform (refluxed for 8 hours) in a manner similar to the preparation of **5a**, and was obtained as colorless needles (from ethanol) in 66% (114 mg) yield, mp 137-139°; ^{1}H nmr (deuteriochloroform): 3.07 (br s, 4H, H5 and 6), 7.41 (m, 5H, H7, 8, and 9 and phenyl-H3' and 5'), 8.54 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 327 (MH^+), 329 ($MH^+ + 2$), 331 ($MH^+ + 4$), intensity ratio of the parent peak at 327 to 329 and 331 is 9 to 6 to 1.

Anal. Calcd. for $C_{18}H_{12}Cl_2N_2$: C, 66.07; H, 3.70; N, 8.56. Found: C, 66.01; H, 3.83; N, 8.35.

4-Chloro-2-(4-nitrophenyl)-5,6-dihydrobenzo[*h*]quinazoline (**5h**).

This compound was synthesized from *N,N*-dimethyl-4-nitrobenzamide (310 mg, 1.60 mmoles), phosphorus oxychloride (0.15 ml, 1.60 mmoles) and **3** (100 mg, 0.53 mmole) in dry chloroform (refluxed for 8 hours) in a manner similar to the preparation of **5a**, and was obtained as pale yellow needles (from ethanol) in 64% (114 mg) yield, mp 179-181°; ir: 1350 and 1530 (NO_2); ^{1}H nmr (DMSO-d_6): 3.05 (br s, 4H, H5 and 6), 7.50 (m, 3H, H7, 8, and 9), 7.96 (m, 1H, H10), 8.56 (m, 4H, phenyl-H2', 3', 5', and 6'); FAB-ms: m/z 338 (MH^+), 340 ($MH^+ + 2$), intensity ratio of the parent peak at 338 to 340 is 3 to 1.

Anal. Calcd. for $C_{18}H_{12}ClN_3O_2$: C, 64.01; H, 3.58; N, 12.44. Found: C, 63.87; H, 3.83; N, 12.21.

2-Trifluoromethyl-5,6-dihydrobenzo[*h*]quinazolin-4(3*H*)-one (**4**).

A solution of **3** (100 mg, 0.53 mmole) and trifluoroacetic anhydride (336 mg, 1.6 mmoles) in dry chloroform (2 ml) was refluxed for 3 hours. Water (50 ml) was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from methanol to give **4** (131 mg, 93%) as colorless needles, mp 240-242°; ir: 3450 (N-H), 1660 (C=O); ^{1}H nmr (deuteriochloroform): 2.96 (br s, 4H, H5 and 6), 7.11 (br, deuterium oxide exchangeable, 1H, NH), 7.39 (m, 3H, H7, 8, and 9), 8.26 (m, 1H, H10); FAB-ms: m/z 267 (MH^+).

Anal. Calcd. for $C_{13}H_9F_3N_2O$: C, 58.65; H, 3.41; N, 10.52. Found: C, 58.86; H, 3.32; N, 10.44.

4-Chloro-2-trifluoromethyl-5,6-dihydrobenzo[*h*]quinazoline (**5i**).

A solution of **4** (232 mg, 0.87 mmole) and phosphorus oxychloride (2.1 ml, 22.5 mmoles) in dry dioxane (6 ml) was refluxed for 14 hours. After evaporation of the excess phosphorus oxychloride and the solvent, water (100 ml) was cautiously poured onto the residue under cooling. The mixture was basified with aqueous sodium hydrogen carbonate and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from ethanol to give **5i** (203 mg, 82%) as colorless needles, mp 158-161°; ^{1}H nmr (deuteriochloroform): 3.10 (br s, 4H, H5 and 6), 7.39 (m, 3H, H7, 8, and 9), 8.43 (m, 1H, H10); FAB-ms: m/z 285 (MH^+), 287 ($MH^+ + 2$), intensity ratio of the parent peak at 285 to 287 is 3 to 1.

Anal. Calcd. for $C_{13}H_8ClF_3N_2$: C, 54.85; H, 2.83; N, 9.84. Found: C, 54.96; H, 2.74; N, 9.59.

4-(2-Hydroxyethylamino)-2-methyl-5,6-dihydrobenzo[*h*]quinazoline (**6a**).

A solution of **5a** (100 mg, 0.43 mmole) and ethanolamine (265 mg, 4.34 mmoles) in dioxane (2 ml) was stirred at 70° for 24 hours. After evaporation of the reaction mixture, water (50 ml) was added to the residue and the mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from benzene to give **6a** (102 mg, 93%) as colorless needles, mp 144-146°; ir: 3340 (N-H, O-H); ^{1}H nmr (200-MHz, deuteriochloroform): 2.57 (s, 3H, CH_3), 2.60 (t, J = 8.0, 2H, H5), 2.96 (t, J = 8.0, 2H, H6), 3.69 and 3.86 (each m, each 2H, NCH_2CH_2O), 5.17 (br, deuterium oxide exchangeable, 1H, NH or OH), 7.28 (m, 3H, H7, 8, and 9), 8.23 (m, 1H, H10); FAB-ms: m/z 256 (MH^+).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.57; H, 6.71; N, 16.46. Found: C, 70.32; H, 6.82; N, 16.41.

2-Ethyl-4-(2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazoline (**6b**).

A solution of **5b** (100 mg, 0.41 mmole) and ethanolamine (250 mg, 4.09 mmoles) in dioxane (2 ml) was stirred at 70° for 23 hours. The post-treatment was performed in a manner similar to that of **6a**, and **6b** was obtained as colorless plates (from benzene) in 94% (104 mg) yield, mp 117-119°; ir: 3330 (N-H, O-H); ^{1}H nmr (200-MHz, deuteriochloroform): 1.37 (t, J = 7.8, 3H, CH_2CH_3), 2.60 (t, J = 7.6, 2H, H5), 2.84 (q, J = 7.8, 2H, CH_2CH_3), 2.96 (t, J = 7.6, 2H, H6), 3.71 and 3.85 (each m, each 2H, NCH_2CH_2O), 5.17 (br, deuterium oxide exchangeable, 1H, NH or OH), 7.27 (m, 3H, H7, 8, and 9), 8.30 (m, 1H, H10); FAB-ms: m/z 270 (MH^+).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.57; H, 7.07; N, 15.53.

4-(2-Hydroxyethylamino)-2-phenyl-5,6-dihydrobenzo[*h*]quinazoline (**6c**).

A solution of **5c** (100 mg, 0.34 mmole) and ethanolamine (209 mg, 3.42 mmoles) in dioxane (2 ml) was stirred at 70° for 26 hours. The post-treatment was performed in a manner similar to that of **6a**, and **6c** was obtained as colorless needles (from benzene) in 91% (98 mg) yield, mp 126-129°; ir: 3350 (N-H, O-H); ^{1}H nmr (200-MHz, deuteriochloroform): 2.66 (t, J = 7.6, 2H, H5), 2.99 (t, J = 7.6, 2H, H6), 3.88 (m, 4H, NCH_2CH_2O), 5.21 (br, deuterium oxide exchangeable, 1H, NH or OH), 7.32 (m, 3H, H7, 8, and 9), 7.47 (m, 3H, phenyl-H3', 4', and 5'), 8.49 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 318 (MH^+).

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.79; H, 6.06; N, 13.19.

4-(2-Hydroxyethylamino)-2-(*m*-tolyl)-5,6-dihydrobenzo[*h*]-quinazoline (**6d**).

A solution of **5d** (100 mg, 0.33 mmole) and ethanolamine (199 mg, 3.27 mmoles) in dioxane (2 ml) was stirred at 70° for 48 hours. The post-treatment was performed in a manner similar to that of **6a**, and **6d** was obtained as pale yellow powder (from benzene) in 86% (94 mg) yield, mp 135-138°; ir: 3350 (N-H, O-H); ^{1}H nmr (deuteriochloroform): 2.46 (s, 3H, CH_3), 2.71 (m, 2H, H5), 2.95 (m, 2H, H6), 3.90 (br s, 4H, NCH_2CH_2O), 5.15 (br, deuterium oxide exchangeable, 1H, NH or OH), 7.39 (m, 5H, H7, 8, and 9 and phenyl-H4' and 5'), 8.39 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 332 (MH^+).

Anal. Calcd. for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N, 12.68. Found: C, 75.90; H, 6.23; N, 12.67.

4-(2-Hydroxyethylamino)-2-(*p*-tolyl)-5,6-dihydrobenzo[*h*]-quinazoline (**6e**).

A solution of **5e** (100 mg, 0.33 mmole) and ethanolamine (199 mg, 3.27 mmoles) in dioxane (2 ml) was stirred at 70° for 37 hours. The post-treatment was performed in a manner similar to that of **6a**, and **6e** was obtained as pale yellow powder (from benzene) in 88% (96 mg) yield, mp 131-134°; ir: 3330 (N-H, O-H); ^{1}H nmr (deuteriochloroform): 2.40 (s, 3H, CH_3), 2.69 (m, 2H, H5), 2.94 (m, 2H, H6), 3.88 (br s, 4H, NCH_2CH_2O), 5.18 (br, deuterium oxide exchangeable, 1H, NH or OH), 7.33 (m, 5H, H7, 8, and 9 and phenyl-H3' and 5'), 8.43 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 332 (MH^+).

Anal. Calcd. for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N, 12.68. Found: C, 75.95; H, 6.24; N, 12.46.

2-(4-Fluorophenyl)-4-(2-Hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazoline (**6f**).

A solution of **5f** (100 mg, 0.32 mmole) and ethanolamine (197 mg, 3.22 mmoles) in dioxane (2 ml) was stirred at 70° for 26 hours. The post-treatment was performed in a manner similar to that of **6a**, and **6f** was obtained as pale yellow plates (from benzene) in 95% (102 mg) yield, mp 111-114°; ir: 3330 (N-H, O-H); ^{1}H nmr (deuteriochloroform): 2.64 (m, 2H, H5), 2.96 (m, 2H, H6), 3.88 (br s, 4H, NCH_2CH_2O), 5.18 (br, deuterium oxide exchangeable, 1H, NH or OH), 7.31 (m, 5H, H7, 8, and 9 and phenyl-H3' and 5'), 8.47 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 336 (MH^+).

Anal. Calcd. for $C_{20}H_{18}FN_3O$: C, 71.63; H, 5.41; N, 12.53. Found: C, 71.64; H, 5.26; N, 12.57.

2-(4-Chlorophenyl)-4-(2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazoline (**6g**).

A solution of **5g** (100 mg, 0.31 mmole) and ethanolamine (187 mg, 3.06 mmoles) in dioxane (2 ml) was stirred at 70° for 20 hours. The post-treatment was performed in a manner similar to that of **6a**, and **6g** was obtained as colorless needles (from benzene) in 93% (101 mg) yield, mp 155-158°; ir: 3340 (N-H, O-H); ^{1}H nmr (deuteriochloroform): 2.63 (m, 2H, H5), 2.99 (m, 2H, H6), 3.90 (br s, 4H, NCH_2CH_2O), 5.17 (br, deuterium oxide exchangeable, 1H, NH or OH), 7.39 (m, 5H, H7, 8, and 9 and phenyl-H3' and 5'), 8.45 (m, 3H, H10 and phenyl-H2' and 6'); FAB-ms: m/z 352 (MH^+), 354 ($MH^+ + 2$), intensity ratio of the parent peak at 352 to 354 is 3 to 1.

Anal. Calcd. for $C_{20}H_{18}ClN_3O$: C, 68.28; H, 5.16; N, 11.94. Found: C, 68.00; H, 4.97; N, 12.22.

4-(2-Hydroxyethylamino)-2-(4-nitrophenyl)-5,6-dihydrobenzo-[*h*]quinazoline (**6h**).

A solution of **5h** (100 mg, 0.30 mmole) and ethanolamine (181 mg, 2.96 mmoles) in dioxane (2 ml) was stirred at 70° for 18 hours. The post-treatment was performed in a manner similar to that of **6a**, and **6 h** was obtained as pale yellow powder (from ethanol) in 90% (98 mg) yield, mp 166-168°; ir: 3350 (N-H, O-H), 1330, 1570 (NO_2); ^{1}H nmr (DMSO-d_6): 2.88 (m, 4H, H5 and 6), 3.67 (m, 4H, NCH_2CH_2O), 4.77 and 7.12 (each br, deuterium oxide exchangeable, each 1H, NH and OH), 7.35 (m, 3H, H7, 8, and 9), 8.34 (m, 3H, H10 and phenyl-H3' and 5'), 8.71 (m, 2H, phenyl-H2' and 6'); FAB-ms: m/z 363 (MH^+).

Anal. Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46. Found: C, 66.12; H, 4.93; N, 15.70.

2-Trifluoromethyl-4-(2-hydroxyethylamino)-5,6-dihydrobenzo-[*h*]quinazoline (**6i**).

A solution of **5i** (100 mg, 0.35 mmole) and ethanolamine (214 mg, 3.51 mmoles) in dioxane (2 ml) was stirred at 70° for 9 hours. The post-treatment was performed in a manner similar to that of **6a**, and **6i** was obtained as colorless plates (from benzene) in 82% (89 mg) yield, mp 176-180°; ir: 3340 (N-H, O-H); ^{1}H nmr (deuteriochloroform): 2.68 (m, 2H, H5), 2.95 (m, 2H, H6), 3.82 (br s, 4H, NCH_2CH_2O), 5.41 (br, deuterium oxide exchangeable, 1H, NH or OH), 7.36 (m, 3H, H7, 8, and 9), 8.30 (m, 1H, H10); FAB-ms: m/z 310 (MH^+).

Anal. Calcd for $C_{15}H_{14}F_3N_3O$: C, 58.25; H, 4.56; N, 13.59. Found: C, 58.41; H, 4.39; N, 13.47.

11-Methyl-1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]quinazoline (**7a**).

A solution of **6a** (150 mg, 0.59 mmole) in phosphorus oxychloride (2 ml, 21 mmoles) was refluxed for 5 hours. After evaporation of excess phosphorus oxychloride of the reaction mixture, water (50 ml) was added to the residue. The mixture was basified with potassium carbonate and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from ethanol to give **7a** (101 mg, 72%) as colorless needles, mp >300°; ^{1}H nmr (200-MHz, trifluoroacetic acid-d): 3.05 (m, 2H, H4), 3.20 (m, 2H, H5), 3.25 (s, 3H, CH_3), 4.59 (m, 2H, H1), 5.11 (m, 2H, H2), 7.56 (m, 2H, H6 and 8), 7.77 (m, 1H, H7), 8.06 (d, J = 7.2, 1H, H9); FAB-ms: m/z 238 (MH^+).

Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.05; H, 6.31; N, 17.52.

11-Ethyl-1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]quinazoline (**7b**).

A solution of **6b** (150 mg, 0.56 mmole) in phosphorus oxychloride (2 ml, 21 mmoles) was refluxed for 5 hours. The post-treatment was performed in a manner similar to that of **7a**, and **7b** was obtained as pale yellow powder (from a mixture of ethanol and ethyl acetate) in 76% (107 mg) yield, mp >300°; ^{1}H nmr (200-MHz, trifluoroacetic acid-d): 1.69 (t, J = 7.4, 3H, CH_2CH_3), 3.04 (m, 2H, H4), 3.18 (m, 2H, H5), 3.50 (q, J = 7.4, 2H, CH_2CH_3), 4.60 (m, 2H, H1), 5.15 (m, 2H, H2), 7.56 (m, 2H, H6 and 8), 7.77 (m, 1H, H7), 8.06 (d, J = 7.8, 1H, H9); FAB-ms: m/z 252 (MH^+).

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.54; H, 6.79; N, 16.62.

11-Phenyl-1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]quinazoline (**7c**).

A solution of **6c** (150 mg, 0.47 mmole) in phosphorus oxychloride (2 ml, 21 mmoles) was refluxed for 5 hours. The post-treatment was performed in a manner similar to that of **7a**, and **7c** was obtained as pale yellow powder (from a mixture of methanol and ethyl acetate) in 82% (115 mg) yield, mp >300°; ^{1}H nmr (deuteriochloroform): 2.86 (br s, 4H, H4 and 5), 4.01 (br s, 4H, H1 and 2), 7.22 (m, 3H, H6, 7, and 8), 7.53 (m, 5H, phenyl-H), 8.14 (m, 1H, H9); FAB-ms: m/z 300 (MH^+).

Anal. Calcd. for $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.41; H, 5.58; N, 14.12.

11-(*m*-Tolyl)-1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]quinazoline (**7d**).

A solution of **6d** (150 mg, 0.45 mmole) in phosphorus oxychloride (2 ml, 21 mmoles) was refluxed for 5 hours. The post-treatment was performed in a manner similar to that of **7a**, and **7d** was obtained as pale yellow powder (from ethyl acetate) in 81% (114 mg) yield, mp >300°; ^{1}H nmr (200-MHz, trifluoroacetic acid-d): 2.57 (s, 3H, CH_3), 3.08 (m, 2H, H4), 3.23 (m, 2H, H5), 4.52 (m, 2H, H1), 5.00 (m, 2H, H2), 7.56 (m, 2H, H6 and 8), 7.77 (m, 5H, H7 and phenyl-H), 8.07 (d, J = 8.4, 1H, H9); FAB-ms: m/z 314 (MH^+).

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.39; H, 6.04; N, 13.28.

11-(*p*-Tolyl)-1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]quinazoline (**7e**).

A solution of **6e** (150 mg, 0.45 mmole) in phosphorus oxychloride (2 ml, 21 mmoles) was refluxed for 5 hours. The post-treatment was performed in a manner similar to that of **7a**, and **7e** was obtained as colorless needles (from a mixture of ethanol and ethyl acetate) in 78% (110 mg) yield, mp >300°; ^{1}H nmr (200-MHz, trifluoroacetic acid-d): 2.60 (s, 3H, CH_3), 3.08 (m, 2H, H4), 3.23 (m, 2H, H5), 4.53 (m, 2H, H1), 5.05 (m, 2H, H2), 7.55 (m, 2H, H6 and 8), 7.65 (d, J = 8.1, 2H, phenyl-H3' and 5'), 7.76 (m, 1H, H7), 7.89 (d, J = 8.1, 2H, phenyl-H2' and 6'), 8.07 (d, J = 7.8, 1H, H9); FAB-ms: m/z 314 (MH^+).

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.53; H, 6.02; N, 13.29.

11-(4-Fluorophenyl)-1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]-quinazoline (**7f**).

A solution of **6f** (150 mg, 0.45 mmole) in phosphorus oxychloride (2 ml, 21 mmoles) was refluxed for 5 hours. The post-treatment was performed in a manner similar to that of **7a**, and **7f** was obtained as colorless needles (from a mixture of methanol and ethyl acetate) in 75% (107 mg) yield, mp >300°; ^{1}H nmr (200-MHz, trifluoroacetic acid-d): 3.08 (m, 2H, H4), 3.22 (m, 2H, H5), 4.52 (m, 2H, H1), 5.01 (m, 2H, H2), 7.52 (m, 4H, H6 and 8 and phenyl-H3' and 5'), 7.76 (m, 1H, H7), 8.07 (m, 3H, H9 and phenyl-H2' and 6'); FAB-ms: m/z 318 (MH^+).

Anal. Calcd. for $C_{20}H_{16}FN_3$: C, 75.69; H, 5.08; N, 13.24. Found: C, 75.52; H, 5.14; N, 13.18.

11-(4-Chlorophenyl)-1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]-quinazoline (**7g**).

A solution of **6g** (150 mg, 0.43 mmole) in phosphorus oxychloride (2 ml, 21 mmoles) was refluxed for 5 hours. The post-treatment was performed in a manner similar to that of **7a**, and **7g** was obtained as pale yellow powder (from ethanol) in 75% (108 mg) yield, mp >300°; ^{1}H nmr (200-MHz, trifluoroacetic acid-d): 3.05 (m, 2H, H4), 3.21 (m, 2H, H5), 4.48 (m, 2H, H1), 4.98 (m, 2H, H2), 7.54 (m, 2H, H6 and 8), 7.81 (m, 3H, H7 and phenyl-H3' and 5'), 7.89 (m, 2H, phenyl-H2' and 6'), 8.08 (d, J = 7.8, 1H, H9); FAB-ms: m/z 334 (MH^+), 336 ($MH^+ + 2$), intensity ratio of the parent peak at 334 to 336 is 3 to 1.

Anal. Calcd. for $C_{20}H_{16}ClN_3$: C, 71.96; H, 4.83; N, 12.59. Found: C, 71.83; H, 4.74; N, 12.49.

11-(4-Nitrophenyl)-1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]-quinazoline (**7h**).

A solution of **6h** (150 mg, 0.41 mmole) in phosphorus oxychloride (2 ml, 21 mmoles) was refluxed for 5 hours. The post-treatment was performed in a manner similar to that of **7a**, and **7h** was obtained as pale brown powder (from a mixture of

ethanol and benzene) in 91% (129 mg) yield, mp 285-287°; ir: 1340, 1530 (NO_2); ^1H nmr (200-MHz, trifluoroacetic acid-d): 3.01 (m, 2H, H4), 3.18 (m, 2H, H5), 4.36 (m, 2H, H1), 4.87 (m, 2H, H2), 7.46 (m, 2H, H6 and 8), 7.64 (t, J = 7.5, 1H, H7), 8.19 (m, 3H, H9 and phenyl-H3' and 5'), 8.61 (d, J = 8.3, 2H, phenyl-H2' and 6'); FAB-ms: m/z 345 (MH^+).

Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.83; H, 4.53; N, 16.19.

11-Trifluoromethyl-1,2,4,5-tetrahydrobenzo[*h*]imidazo[1,2-*c*]-quinazoline (**7i**).

A solution of **6i** (150 mg, 0.49 mmole) in phosphorus oxychloride (2 ml, 21 mmoles) was refluxed for 5 hours. The post-treatment was performed in a manner similar to that of **7a**, and **7i** was obtained as colorless granules (from benzene) in 87% (125 mg) yield, mp 244-247°; ^1H nmr (deuteriochloroform): 2.85 (br s, 4H, H4 and 5), 4.16 (br s, 4H, H1 and 2), 7.32 (m, 3H, H6, 7 and 8), 8.06 (m, 1H, H9); FAB-ms: m/z 292 (MH^+).

Anal. Calcd. for $C_{15}H_{12}F_3N_3$: C, 61.85; H, 4.15; N, 14.43. Found: C, 61.92; H, 4.22; N, 14.28.

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