POLYCYCLIC *N*-HETEROCYCLIC COMPOUNDS. 47 SYNTHESIS AND EVALUATION OF ANTI-PLATELET AGGREGATION ACTIVITY OF 11,13,15-TRIAZASTEROID AND RELATED COMPOUNDS

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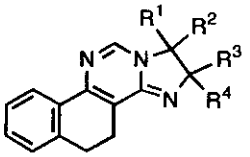
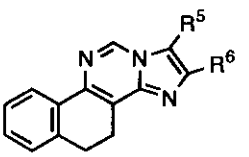
Abstract - Synthesis and separation of *cis*- and *trans*-1,2,4,5,5a,6,7,8,9,9a-decahydrobenz[*h*]imidazo[1,2-*c*]quinazolines and its precursors are described. Inhibitory activity against collagen-induced platelet aggregation for rabbit blood of these compounds and their benzologues at A ring is also evaluated.

In our earlier study, derivatives of 5,6-dihydrobenzo[*h*]quinazoline,[1] 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine,[2] and 5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]imidazo[1,2-*c*]pyrimidine[3] were reported to exhibit inhibitory activities against collagen-induced platelet aggregation for rabbit blood. Many benz[*h*]imidazo[1,2-*c*]quinazoline derivatives (**1** and **2**),[4-7] corresponding to 11,13,15-tri-



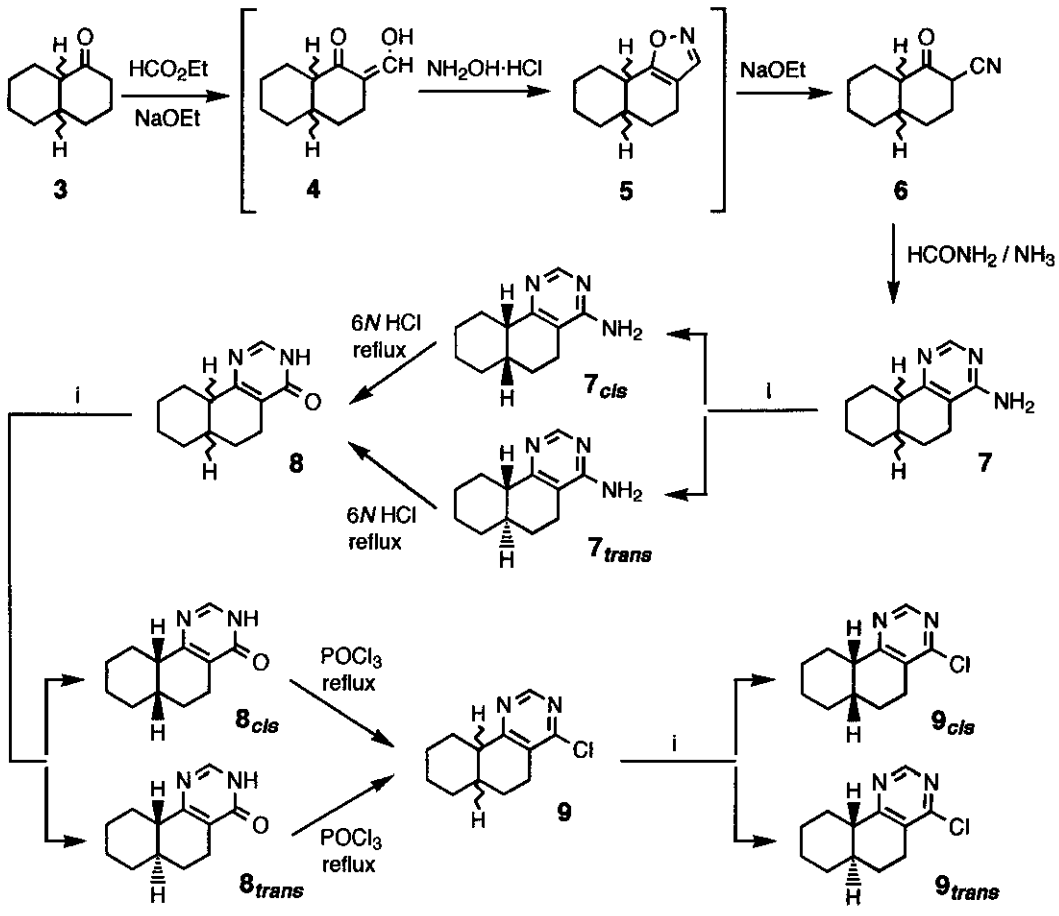
1a; $R^1 = R^2 = R^3 = R^4 = H$
1b; $R^1 = Me$, $R^2 = R^3 = R^4 = H$
1c; $R^1 = Et$, $R^2 = R^3 = R^4 = H$
1d; $R^1 = R^2 = R^3 = H$, $R^4 = Me$
1e; $R^1 = R^2 = R^3 = H$, $R^4 = Et$
1f; R^1 = R^2 = O, R^3 = R^4 = $CHNMe_2$



2a; $R^5 = OH$, $R^6 = COMe$
2b; $R^5 = OCOMe$, $R^6 = Me$
2c; $R^5 = OCOMe$, $R^6 = CHMe_2$
2d; $R^5 = OCOMe$, $R^6 = CH_2CHMe_2$
2e; $R^5 = OCOMe$, $R^6 = CHEt$ (Me)
2f; $R^5 = OCOMe$, $R^6 = C_6H_5$
2g; $R^5 = OCOMe$, $R^6 = CH_2C_6H_5$

azasteroid, had been also synthesized in our laboratory to investigate antidepressive activity. These triazasteroidal analogues were also evaluated for anti-platelet aggregation activity and some derivatives exhibited positive action. Our interest for this structure-activity relationship prompted us to synthesize 1,2,4,5,5a,6,7,8,9,9a-decahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (**11**), which corresponds to a hydrogenated compound at a benzene moiety (A-ring) of **1a** and more closely resembles steroidal skeleton. In this paper we now report the synthesis of *cis*- and *trans*-1,2,4,5,5a,6,7,8,9,9a-decahydrobenz[*h*]imidazo-[1,2-*c*]quinazolines and inhibitory activities against collagen-induced platelet aggregation of these compounds and their precursors. Evaluation for the same activity of **1** and **2** is also described because the result of the evaluation has not been published up to now.

As shown in Scheme 1, the commercially available *cis*/*trans* mixture of 1-decalone (**3**) was used as the starting material. 2-Cyano-1-decalone (**6**) was obtained as a *cis*/*trans* mixture by Boatmann's[8] and



Scheme 1

Johnson's[9] methods from **3**. This *cis/trans* mixture of **6** indicated characteristic cyano and carbonyl bands at 2240 cm^{-1} and 1710 cm^{-1} in ir spectrum, respectively. Hydroxymethylene ketone (**4**) and isoxazole (**5**) derivatives were used as crude materials without further purification. Heating the *cis/trans* mixture of compound (**6**) with formamide under ammonia stream afforded a *cis/trans* mixture of 4-amino-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline (**7**). Thin-layer chromatography (tlc) of **7** on silica gel showed two major spots (developing solvent system; ethyl acetate-methanol, 1 : 1, v/v, R*f* value; 0.57 and 0.50). This *cis/trans* mixture (**7**) could be separated by column chromatography on silica gel with ethyl acetate, to give successively the *trans*-isomer of **7** (**7*trans***) and the *cis*-form of **7** (**7*cis***). The molecular formula $C_{12}H_{17}N_3$ of **7*cis*** and **7*trans*** by elemental analyses, FAB-ms measurements [m/z: 204 (MH^+)], and ir spectra [cm^{-1}: 3400, 3350 (N-H)] consisted with their structures apart from their stereochemistry. The discrimination of the structure of **7*cis*** from that of **7*trans*** was performed by the aid of two dimensional (2D) techniques such as ^1H-^1H and one-bond and long-range ^1H-^{13}C shift-correlated (COSY) nmr spectroscopy, and all protons and carbons were assigned as shown in Tables 1 - 3. In the ^1H-nmr spectra, the signal of the H-10a of the **7*cis*** appeared at δ 2.54 ppm as a triplet of doublet with coupling constants of 6.8 and 4.9 Hz, while that of the corresponding **7*trans*** appeared at δ 2.04 ppm as a broad triplet with coupling constant of 11.1 Hz which was a typical diaxial coupling constant. These facts indicated that **7*trans*** was a *trans*-isomer and **7*cis*** which showed smaller coupling constant caused from equatorial-equatorial or equatorial-axial relationship was *cis*-isomer.

Thus separated **7*cis*** and **7*trans*** were hydrolyzed with hydrochloric acid, independently. Unexpectedly, a *cis/trans* mixture of 3,4,5,6,6a,7,8,9,10,10a-decahydrobenzo[*h*]quinazolin-4(3*H*)-one (**8**) was obtained in each case. Thus, acid-catalyzed epimerization occurred and the same two spots were detected on each tlc. The above mixture (**8**) could be separated to pure **8*cis*** and **8*trans*** by column chromatography on silica gel. Chlorination of each **8*cis*** and **8*trans*** with boiling phosphoryl chloride gave a *cis/trans* mixture of 4-chloro-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline (**9**), in each case. This mixture showed two spots on tlc and was separated to pure *cis*- and *trans*-isomers (**9*cis*** and **9*trans***) by column chromatography on silica gel. As shown in Scheme 2, the reaction of each isomer with ethanolamine in the presence of potassium carbonate gave 4-hydroxyethylamino derivatives (**10*cis*** and **10*trans***) without epimerization, respectively. Further cyclization of each **10*cis*** and **10*trans*** with phosphoryl chloride in chloroform afforded the corresponding *cis*- and *trans*-1,2,4,5,5a,6,7,8,9,9a-decahydro-benz[*h*]imidazo[1,2-*c*]quinazolines (**11*cis*** and **11*trans***). During the course from **9** to **11**, no

Table 1. ^{1}H-Nmr Data (500 MHz) for **7*cis*** (in $CDCl_3$)

Proton	δ_H[a)]		
H-2	8.14	s	
H-5eq	2.27	dt	$J_{5ax,5eq}$ = 17.0, $J_{5ax,6ax,6eq}$ = 7.8
H-5ax	2.40	dt	$J_{5eq,5ax}$ = 17.0, $J_{5eq,6ax,6eq}$ = 5.8
H-6ax[c)]	1.60[b)]	m	overlapped partially with H-7eq
H-6eq	1.87	dtd	$J_{6eq,6ax}$ = 12.8, $J_{6eq,6a,5eq}$ = 5.8, $J_{6eq,5ax}$ = 7.8
H-6a	1.94[b)]	m	overlapped partially with H-6eq
H-7ax[d)]	1.50[b)]	m	overlapped partially with H-8eq
H-7eq[c)]	1.57[b)]	m	overlapped partially with H-6ax
H-8ax[e)]	1.42[b)]	m	overlapped partially with H-8eq and H-9eq
H-8eq[d), e)]	1.45[b)]	m	overlapped partially with H-7ax and H-8ax
H-9ax	1.32[b)]	m	
H-9eq[e)]	1.41[b)]	m	overlapped partially with H-8ax
H-10ax[f)]	1.71[b)]	m	overlapped almost completely with H-10eq
H-10eq[f)]	1.71[b)]	m	overlapped almost completely with H-10ax
H-10a	2.54	td	$J_{10a,6a,10ax}$ = 6.8, $J_{10a,10eq}$ = 4.9
NH_2	6.35	br s	D_2O exchangeable

a) Chemical shifts are in δ values from internal TMS and are followed by multiplicities and *J* values (in Hz). b) Center of multiplet. c,d,e,f) Assignments with the same superscripts may be interchangeable.

Table 2. ^{1}H-Nmr Data (500 MHz) for **7*trans*** (in $CDCl_3$)

Proton	δ_H[a)]		
H-2	8.17	s	
H-5ax	2.34	ddd	$J_{5ax,5eq}$ = 17.1, $J_{5ax,6ax}$ = 11.7, $J_{5ax,6eq}$ = 5.9
H-5eq	2.40	dd	$J_{5eq,5ax}$ = 17.1, $J_{5eq,6ax}$ = 5.9
H-6ax	1.36	dddd	$J_{6ax,6eq}$ = 13.0, $J_{6ax,6a}$ = 12.3, $J_{6ax,5ax}$ = 11.7, $J_{6ax,5eq}$ = 5.9
H-6eq	1.79	ddd	$J_{6eq,6ax}$ = 13.0, $J_{6eq,6a}$ = 6.4, $J_{6eq,5ax}$ = 5.9 overlapped partially with H-9eq
H-6a[c)]	1.25[b)]	m	overlapped partially with H-8ax
H-7ax	1.10	qd	$J_{7ax,8ax,6a,7eq}$ = 11.8, $J_{7ax,8eq}$ = 3.0
H-7eq[d)]	1.71	br d	$J_{7eq,7ax}$ = 11.8, overlapped almost completely with H-8eq
H-8ax[c)]	1.27[b)]	m	overlapped partially with H-6a and H-9ax
H-8eq[d)]	1.71	br d	$J_{8eq,8ax}$ = 10.5, overlapped almost completely with H-7eq
H-9ax[c)]	1.30[b)]	m	overlapped partially with H-6a and H-8ax
H-9eq	1.81	br d	$J_{9eq,9ax}$ = 12.8, overlapped partially with H-6eq
H-10ax	0.915	dddd	$J_{10ax,10eq}$ = 12.7, $J_{10ax,9ax}$ = 12.2, $J_{10ax,10a}$ = 11.1, $J_{10ax,9eq}$ = 3.2
H-10eq	2.64	br dd	$J_{10eq,10ax}$ = 12.7, $J_{10eq,9eq}$ = 2.4
H-10a	2.04	br t	$J_{10a,6a,10ax}$ = 11.1
NH_2	6.42	br s	D_2O exchangeable

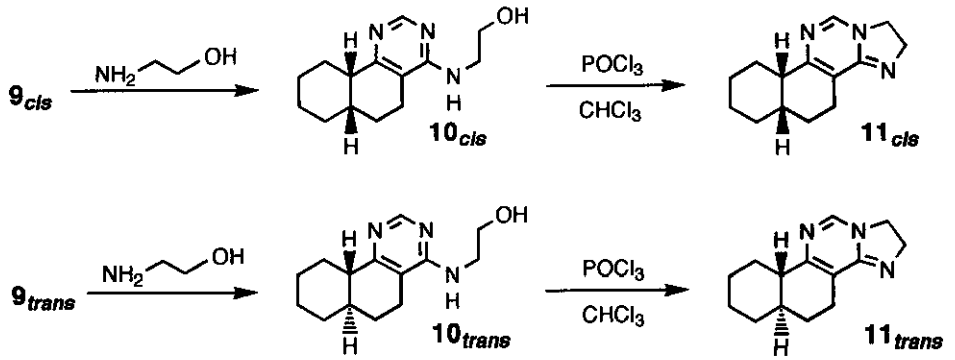
a) Chemical shifts are in δ values from internal TMS and are followed by multiplicities and *J* values (in Hz). b) Center of multiplet. c,d) Assignments with the same superscripts may be interchangeable.

Table 3. ^{13}C-Nmr Data (126 MHz) for **7*cis*** and **7*trans*** (in $CDCl_3$)

Carbon	**7*cis*** $\delta C^{a)}$	**7*trans*** $\delta C^{a)}$
C-2	155.09	154.68
C-4	161.84	161.95
C-4a	110.32	110.79
C-5	21.72[b)]	22.63
C-6	23.15	28.83[b)]
C-6a	32.70	39.41
C-7	29.52	33.49
C-8	24.87	25.76
C-9	21.89[b)]	26.35
C-10	28.13	28.84[b)]
C-10a	41.04	45.57
C-10b	164.29	162.76

a) Chemical shifts are in δ values. b) Assignments with the same superscripts in each column may be interchangeable.

epimerization was observed. In both cases of syntheses of **8** and **9**, refluxing hydrochloric acid (13 h) or refluxing phosphoryl chloride (5 h) was used, however, the reaction progressed under mild condition using refluxing chloroform (2 h) in the case of the synthesis of **11**. It seems this is the reason why the epimerization did not occur. The discriminations of the structures of *cis*- and *trans*-isomers of compounds (**8** - **11**) were also achieved by ^{1}H-nmr spectra, that is, chemical shifts and splitting pattern of H-10a were characteristic as described above.



Scheme 2

The inhibitory activities against platelet aggregation of **1**, **2**, and **7 - 11** were screened by a turbidimetric method developed by Born and Cross[10] using an aggregometer. Preparation of platelet, measurement of platelet aggregation, the calculation of the inhibition rate, and estimation of the test compounds were performed in the same manner described previously.[3] Many compounds in this paper produced a dose-dependent inhibition (not so strong) against rabbit platelet aggregation induced by collagen. As shown in Table 4, the comparison of the inhibition rate of test compounds at the final concentration of 25 mmol/l with that of aspirin showed that **1f**, **2a**, **2b**, **2d** and **2f** were more potent than aspirin at $p<0.01$ on statistical analysis. From this finding that only the compounds which have a hydroxyl group or acetoxy group at position 1 showed more potent activity than aspirin, it seems that oxygen function attached on position 1 plays some positive roles in the activity. The most potent rate of the compounds described in Table 4 was about three times of that of aspirin. Many tricyclic compounds synthesized in our laboratory showed more than 3 times of potent rate of aspirin,[1-3] therefore, tetracyclic derivatives like a types of **1** and **2** seemed not to have so strong activity. The substitution effect at position 2 was rather ambiguous. Among new synthesized products (**7 - 11**), **7*cis***, **7*trans***, and **10*cis*** showed more potent activity than aspirin as shown in Table 5. However, theseactivities were not strong. With regard to the geometry

Table 4. Maximum Inhibition Rate and IC_{50} on Collagen-Induced Platelet Aggregation of **1** and **2**

Compd	Max. inhibit. rate[a)]	IC_{50}[b)]	Compd	Max. inhibit. rate[a)]	IC_{50}[b)]
1a	13.7±2.7		**2a**	25.1±1.3[c)]	25.8 (22.8-29.6)
1b	8.7±1.1		**2b**	31.3±5.0[c)]	13.7 (6.2-21.8)
1c	10.3±0.4		**2c**	10.3±1.4	
1d	6.2±3.5		**2d**	38.6±2.4[c)]	14.1 (9.2-19.7)
1e	12.1±2.8		**2e**	14.7±5.8	
1f	23.9±1.5[c)]	20.1 (14.5-28.6)	**2f**	26.9±3.4[c)]	17.3 (12.2-25.1)
aspirin	15.7±1.0	48.0 (44.1-53.3)	**2g**	19.1±5.7	

a) Value is expressed as % and the mean ± SE of at least 3 experiments at final concentration of 25 mmol/l. b) Figures in upper lines and lower lines for each compound represent the IC_{50} value (mmol/l) and 95% confidence limits (mmol/l-mmol/l), respectively. Experiments were repeated at least each 3 times at final concentrations of 5, 25, 50 mmol/l (in the case of aspirin, final concentrations were 10, 25, 100 mmol/l). c) Significantly different from aspirin at $p<0.01$.

Table 5. Maximum Inhibition Rate and IC_{50} on Collagen-Induced Platelet Aggregation of **7 - 11**

Compd	Max. inhibit. rate[a]	IC_{50}[b]	Compd	Max. inhibit. rate[a]	IC_{50}[b]
7*cis*	23.9±2.5[c]	52.8 (56.6-133.6)	**10*cis***	24.4±1.0[c]	43.5 (31.1-76.1)
7*trans*	24.6±3.8[c]	79.9 (37.2-93.3)	**10*trans***	10.5±0.4	
8*cis*	5.8±2.1		**11*cis***	16.7±1.9	
8*trans*	6.0±1.0		**11*trans***	11.2±0.2	
9*cis*	9.0±0.4		**aspirin**	15.7±1.0	48.0 (44.1-53.3)
9*trans*	11.9±2.5				

a) Value is expressed as % and the mean ± SE of at least 3 experiments at final concentration of 25 mmol/l. b) Figures in upper lines and lower lines for each compound represent the IC_{50} value (mmol/l) and 95% confidence limits (mmol/l-mmol/l), respectively. Experiments were repeated at least each 3 times at final concentrations of 5, 25, 50 mmol/l (in the case of aspirin, final concentrations were 10, 25, 100 mmol/l). c) Significantly different from aspirin at $p<0.01$.

(*cis*/*trans*), *trans*-form showed more potent activity than that of *cis*-form except for **10**, however, the difference was very small.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The EI- and FAB-ms spectra were recorded on a VG 70-SE mass spectrometer, using glycerol or *m*-nitrobenzyl alcohol as the matrix agent. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer in potassium bromide and frequencies are expressed in cm^{-1}. The ^1H- and ^{13}C-nmr spectra were recorded on a Hitachi R-22 FTS FT-NMR spectrometer working at 90 MHz (^1H-nmr), Varian VXR-200 instrument working at 200 MHz (^1H-nmr), or Varian VXR-500 instrument working at 500 MHz (^1H-nmr) and 126 MHz (^{13}C-nmr) in the solvent indicated with tetramethylsilane(for ^1H) and the solvent ($CDCl_3$, for ^{13}C) as the internal standard. Chemical shifts are given in ppm (δ) and *J* values in Hz, and the signals are designated as follows; s, singlet; d, doublet; dd, double of doublet; dt, double of triplet; t, triplet; m, multiplet; br, broad.

Synthesis and Separation of 4-Amino-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline (7)

A solution of a *cis/trans* mixture of 2-cyano-1-decalone (**6**, 2.75 g, 15.5 mmol) in formamide (110 ml, 2.77 mol) was heated at 165-175 °C under NH_3 stream for 10 h. After cooling of the reaction mixture, water (1 l) was added to the solution and the resulting mixture was extracted with ethyl acetate (200 ml x 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate to give successively 1.26 g of **7*trans*** which was recrystallized from ethyl acetate as colorless needles and 0.84 g of **7*cis*** which was recrystallized from ethanol as colorless plates. The total yield of **7*trans*** and **7*cis*** was 67%.

7*cis*; mp 229-231 °C; ir: 3400, 3350 (N-H); FAB-ms m/z: 204 (MH^+). *Anal*. Calcd for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.80; H, 8.64; N, 20.43.

7trans; mp 181-183 °C; ir: 3400, 3350 (N-H); FAB-ms m/z: 204 (MH^+). *Anal*. Calcd for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.68; H, 8.69; N, 20.60.

Synthesis and Separation of 3,4,5,6,6a,7,8,9,10,10a-Decahydrobenzo[*h*]quinazolin-4(3*H*)-one (8)

Method A (from **7*cis***): A mixture of **7*cis*** (406 mg, 2 mmol) and 6*N* HCl (12 ml) was refluxed for 13 h. After cooling of the reaction mixture, water was added to the mixture. The resulting mixture was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (20 ml x 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel to give 94 mg of **8*trans*** which was eluted with ethyl acetate and recrystallized from benzene as colorless needles and 220 mg of **8*cis*** which was eluted with ethyl acetate-acetone (4 : 1 - 1 : 1, v/v) and recrystallized from benzene as colorless plates. The total yield of **8*cis*** and **8*trans*** was 77%. Formation ratio of **8*cis*** to **8*trans*** was 7 to 3.

Method B (from **7*trans***): The reaction for **7*trans*** was carried out in the same amount and under the same reaction conditions as described in Method A. Chromatographic separation of the residue afforded 73 mg of **8*cis*** and 294 mg of **8*trans***. The total yield of **8*cis*** and **8*trans*** was 90%. Formation ratio of **8*cis*** to **8*trans*** was 1 to 4.

8*cis*; mp 224-226 °C; ir: 3150 (N-H), 1645 (C=O); FAB-ms m/z: 205 (MH^+); ^1H nmr ($CDCl_3$): 1.55, 1.96, 2.43, and 2.69 (8H, 3H, 1H, and 1H, each m, H-5, -6, -6a, -7, -8, -9, and -10), 2.61 (1H, dt,

$J_{d(ax\text{-}ax)}$ = 10.2, $J_{t(ax\text{-}eq)}$ = 4.1, H-10a), 8.05 (1H, s, H-2), 12.95 (1H, br, D_2O exchangeable, NH). *Anal.* Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.73; H, 7.84; N, 13.61.

8*trans*; mp 228-229°C; ir: 3150 (N-H), 1645 (C=O); FAB-ms m/z: 205 (MH^+); ^1H nmr ($CDCl_3$): 1.05 (1H, m, H-10_{ax}), 1.12-1.94 (9H, m, H-5, -6, -6a, -7, and -9), 2.15 (1H, br t, $J_{ax\text{-}ax}$ = 11.5, H-10a), 2.40-2.65 (3H, m, H-8 and H-10_{eq}), 8.06 (1H, s, H-2), 13.05 (1H, br, D_2O exchangeable, NH). *Anal.* Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.52; H, 7.87; N, 13.71.

Synthesis and Separation of 4-Chloro-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline (9)

Method A (from **8*cis***): A mixture of **8*cis*** (980 mg, 4.8 mmol) and $POCl_3$ (30 ml, 0.32 mol) was refluxed for 5 h. After evaporation of $POCl_3$ *in vacuo*, water (100 ml) was cautiously added to the residue. The resulting solution was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was chromatographed on silica gel with *n*-hexane-ethyl acetate (95 : 5, v/v) to give successively 295 mg of **9*trans*** which was recrystallized from *n*-hexane as colorless prisms and 688 mg of **9*cis*** which was recrystallized from *n*-hexane-petroleum ether (1 : 1, v/v) as colorless prisms. The total yield of **9*cis*** and **9*trans*** was 92%. Formation ratio of **9*cis*** to **9*trans*** was 7 to 3.

Method B (from **8*trans***): The reaction for **8*trans*** was carried out in the same amount and under the same reaction conditions described in Method A. Chromatographic separation of the residue afforded 298 mg of **9*cis*** and 695 mg of **9*trans***. The total yield of **9*cis*** and **9*trans*** was 92%. Formation ratio of **9*cis*** to **9*trans*** was 3 to 7.

9*cis*; mp 62-63 °C; FAB-ms m/z: 223 (MH^+); ^1H nmr ($CDCl_3$): 1.60, 1.97, 2.68, and 2.87 (8H, 3H, 1H, and 2H, each m, H-5, -6, -6a, -7, -8, -9, and -10), 2.91 (1H, dt, $J_{d(ax\text{-}ax)}$ = 10.2, $J_{t(ax\text{-}eq)}$ = 4.1, H-10a), 8.72 (1H, s, H-2). *Anal.* Calcd for $C_{12}H_{15}N_2Cl$: C, 64.71; H, 6.79; N, 12.58. Found: C, 64.89; H, 6.87; N, 12.34.

9*trans*; mp 59-60 °C; FAB-ms m/z: 223 (MH^+); ^1H nmr ($CDCl_3$): 1.34, 1.77, 2.72, and 2.90 (6H, 4H, 2H, and 1H, each m, H-5, -6, -6a, -7, -8, -9, and -10), 2.30 (1H, br t, $J_{ax\text{-}ax}$ = 11.7, H-10a), 8.73 (1H, s, H-2). *Anal.* Calcd for $C_{12}H_{15}N_2Cl$: C, 64.71; H, 6.79; N, 12.58. Found: C, 65.01; H, 6.95; N, 12.35.

Synthesis of *cis*-4-(2-Hydroxyethylamino)-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline (10*cis*)

A mixture of **9*cis*** (222 mg, 1 mmol), ethanolamine (305 mg, 5 mmol), K_2CO_3 (414 mg, 3 mmol), and dry dioxane (3 ml) was refluxed for 9 h. After cooling the reaction mixture, water (80 ml) was added. The resulting mixture was extracted with ethyl acetate (25 ml x 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was recrystallized from benzene to give 232 mg (94%) of **10*cis*** as colorless plates, mp 136-138 °C; ir: 3250 (N-H and O-H); FAB-ms m/z: 248 (MH^+); ^1H nmr ($CDCl_3$): 1.50, 1.92, and 2.34 (8H, 3H, and 2H, each m, H-5, -6, -6a, -7, -8, -9, and -10), 2.62 (1H, dt, $J_{d(ax\text{-}ax)}$ = 10.4, $J_{t(ax\text{-}eq)}$ = 5.1, H-10a), 3.72 (4H, m, NCH_2CH_2), 5.13 (1H, br, D_2O exchangeable, NH), 8.37 (1H, s, H-2). *Anal.* Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 67.65 H, 8.76; N, 16.86.

Synthesis of *trans*-4-(2-Hydroxyethylamino)-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline (10*trans*)

The reaction for **9*trans*** was carried out in the same amount and under the same reaction conditions described in the synthesis of **10*cis*** except for the refluxing period (8 h). After same treatment, the resulting residue was recrystallized from benzene-cyclohexane to give 227 mg (92%) of **10*trans*** as colorless plates, mp 128-130 °C; ir: 3250 (N-H and O-H); FAB-ms m/z: 248 (MH^+); ^1H nmr ($CDCl_3$): 1.38, 1.85, 2.37, and 2.70 (6H, 4H, 2H, and 1H, each m, H-5, -6, -6a, -7, -8, -9, and -10), 2.18 (1H, br t, $J_{ax\text{-}ax}$ = 11.9, H-10a), 3.74 (4H, m, NCH_2CH_2), 4.97 (1H, br, D_2O exchangeable, NH), 8.43 (1H, s, H-2). *Anal.* Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 68.30 H, 8.81; N, 17.26.

Synthesis of *cis*-1,2,4,5,5a,6,7,8,9,9a-Decahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (11*cis*)

A mixture of **10*cis*** (120 mg, 0.49 mmol), $POCl_3$ (0.23 ml, 2.45 mmol), and dry chloroform (2 ml) was refluxed for 2 h. After evaporation of the reaction mixture to dryness, water (40 ml) was cautiously added to the residue. The mixture was basified with $NaHCO_3$ and extracted with chloroform (20 ml x 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The yellowish-brown residue was chromatographed on silica gel with ethanol to give 39 mg (35%) of **11*cis*** as pale yellow viscous oil. An aliquot of this oil was converted to hydrochloride with 1*N*-HCl-ethanol, which was recrystallized from ethanol-diethyl ether to give colorless plates, mp 241 °C (decomp); FAB-

ms of free base m/z: 230 (MH^+); ^1H nmr ($CDCl_3$) of free base: 1.40, 1.79, 2.26, and 2.45 (8H, 3H, 1H, and 1H, each m, H-4, -5, -5a, -6, -7, -8, and -9), 2.33 (1H, dt, $J_{d(ax\text{-}ax)}$ = 10.7, $J_{t(ax\text{-}eq)}$ = 5.0, H-9a), 3.95 (4H, m, H-1 and -2), 7.66 (1H, s, H-11). *Anal.* Calcd for $C_{14}H_{19}N_3 \cdot HCl$: C, 63.27; H, 7.21; N, 15.81. Found: C, 62.99; H, 7.45; N, 15.72.

Synthesis of *trans*-1,2,4,5,5a,6,7,8,9,9a-Decahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (11*trans*)

The reaction for **10*trans*** was carried out in the same amount and under the same reaction conditions described in the synthesis of **11*cis***. After same treatment, The eluate of ethanol on the chromatographic purification gave 46 mg (41%) of **11*trans*** as pale yellow viscous oil, an aliquot of which was converted to hydrochloride. Recrystallization of the salt from ethanol-ether afforded hydrochloride of **11*trans*** as colorless plates, mp 263 °C (decomp); FAB-ms of free base m/z: 230 (MH^+); ^1H nmr ($CDCl_3$) of free base: 0.86, 1.02, 1.20, 1.64, 1.75, 2.25, and 2.40 (1H, 1H, 4H, 3H, 1H, 1H, and 2H, each m, H-4, -5, -5a, -6, -7, -8, and -9), 1.86 (1H, br t, $J_{ax\text{-}ax}$ = 11.1, 9a-H), 3.91 (4H, m, 1- and 2-H), 7.63 (1H, s, 11-H). *Anal.* Calcd for $C_{14}H_{19}N_3 \cdot HCl$: C, 63.27; H, 7.21; N, 15.81. Found: C, 63.05; H, 7.41; N, 15.68.

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