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Cyclic Guanidines. XVI.[1] Synthesis and Biological Activities of Tetracyclic Imidazo[2,1-*b*]quinazolinone Derivatives[2]

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Tetracyclic imidazo[2,1-*b*]quinazolinone derivatives (**18**) with a modified or unmodified alkylene chain were prepared and evaluated for their ability to inhibit platelet aggregation. Most of the compounds were very potent except for some compounds substituted with an amino or a hydroxy group. The structure–activity relationships are discussed.

Keywords——cyclic guanidine; benzo[*f*]imidazo[2,1-*b*]quinazoline; benzo[*g*]imidazo[2,1-*b*]quinazoline; cyclopenta[*f*]imidazo[2,1-*b*]quinazoline; cyclopenta[*g*]imidazo[2,1-*b*]quinazoline; imidazo[2,1-*b*]pyrido[2,3-*f*]quinazoline; imidazo[2,1-*b*]pyrido[3,4-*f*]quinazoline; imidazo[2,1-*b*]pyrido[3,2-*f*]quinazoline; platelet-aggregation inhibitor; structure–activity relationship

The synthesis and platelet aggregation inhibitory effect of imidazothienopyrimidinones were reported in a previous paper.[3] Among the compounds tested, 1,2,3,5,6,7,8,9-octahydro[1]benzothieno[2,3-*d*]imidazo[1,2-*a*]pyrimidin-2-one, DH-6471, having alkylene chain in the molecule, was the most active. However, the compounds in this series are chemically unstable. Beverung and Partyka[4] reported that imidazo[2,1-*b*]quinazolinones were potent and stable compounds, so we next tried to synthesize tetracyclic imidazo[2,1-*b*]quinazolinones having an alkylene chain at the 6- and 7- or 7- and 8-positions of the imidazo[2,1-*b*]quinazoline ring.

The low water-solubility of the compounds in these series limits their clinical use. However, the introduction of a hydrophilic moiety, such as a hydroxy, amino, or imino function, into the compounds may improve the poor solubility. Furthermore, the 9-oxo derivative of DH-6471 is a very potent inhibitor.[5] It is thus of interest to prepare such oxo derivatives of the imidazo[2,1-*b*]quinazoline. This paper reports the preparation and biological properties of tetracyclic imidazo[2,1-*b*]quinazolinones having a modified or unmodified alkylene chain.

Chemistry

The compounds prepared for this study are shown in Table I and their syntheses are outlined in Charts 1 and 2.

A novel and facile synthetic route to the imidazo[2,1-*b*]quinazolin-2-ones was reported in our previous paper.[6] A key point of the route is the preparation of 2,4-dichloroquinazoline derivatives (**1**), which can be easily converted to the target molecules (**18**) *via* 2-chloro-3,4-dihydroquinazoline derivatives (**15**).

By the method described by Crenshow *et al.*,[7] 5-aminoindan was converted to phenoxycarbonylurea (**2a**), which was reacted with phosphoryl chloride to give a mixture of linear (**1a**) and angular cyclized compounds (**1c**). Each isomer was isolated by silica gel chromatography. Similar reaction of **2b** gave a similar mixture, but the isolation procedure afforded only the linear isomer (**1b**). The 1-benzoyloxy ureido derivative (**3**) obtained from 7-nitrotetralone was treated with phosphoryl chloride to give a debenzoylated product (**1o**) in poor yield. The direct conversion of the ureide compounds (**2**) and (**3**) to 2,4-dichloroquinazolines (**1**) was not appropriate for preparative-scale synthesis because of the tedious procedures and low yield. The another stepwise synthesis of **1** was tried.

Heating of 5-ethoxycarbonylamino-4-indancarbonitrile (**4c**), prepared by cyanation of the 4-bromo analog, with urea gave the **6c**, from which **1c** was obtained by chlorination with phosphoryl chloride in good yield. Similarly **4d**, and quinoline or isoquinoline derivatives (**5t**—**v**), synthesized by a method similar to that described by Tomioka *et al.*,[8] were converted into **1d**, **t**—**v** *via* **6d**, **t**—**v**, respectively.

Attempts to directly oxidize the final products, for example **18d**, to the compounds containing an oxo group in the alkylene chain were unsuccessful. The introduction of the oxo group was required before chlorination of the quinazoline-2,4-dione derivatives. The preparation was carried out by a route similar to that used for the synthesis of an active metabolite of DH-6471.[9] Vicinal amino-nitro compounds (**7**)[10] were cyanated, hydrolyzed, and then esterified by use of Meerwein reagent in the presence of diisopropylethylamine to give the corresponding esters (**8**). Reduction of **8** followed by acetylation afforded acetylamino derivatives (**10**). Introduction of the oxo group to **10** was achieved by treatment with chromic anhydride to give the key intermediates (**11**) in good yield. Deacetylation of **11** followed by thioketalization, and then reaction with benzoyl isocyanate afforded benzoyl ureas (**14**). The ureas (**14**) were treated with base to give easily **6e**, **f**, from which **1e**, **f** were derived in good yield.

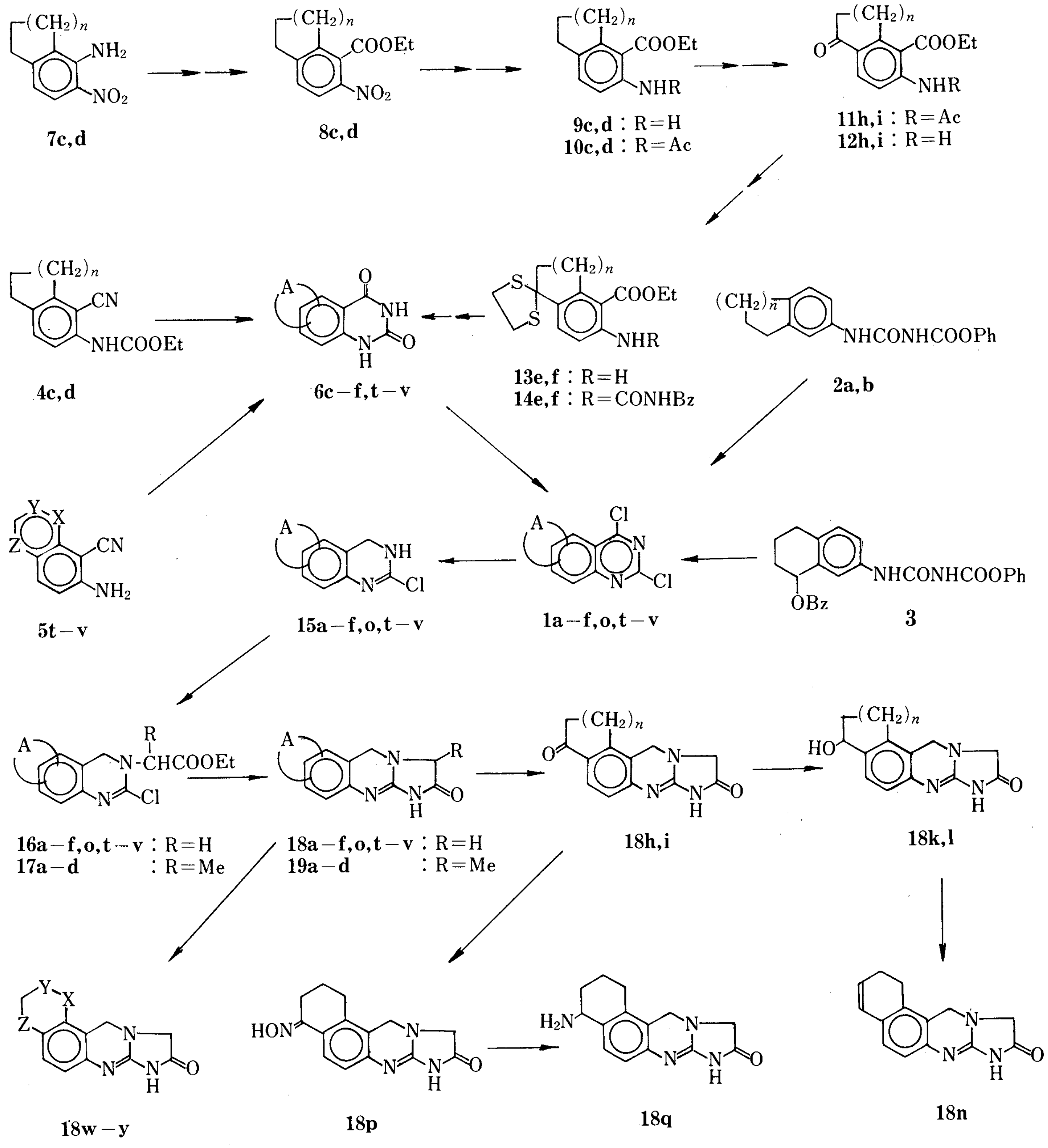
Reaction of the 2,4-dichloroquinazoline derivatives (**1a**—**f**, **o**, **t**—**v**) obtained here with sodium borohydride, followed by treatment with ethyl bromoacetate and base in the presence of a phase transfer catalyst easily gave the 3-acetates (**16a**—**f**, **o**, **t**—**v**). However, reaction of **15a**—**d** with ethyl 2-bromopropionate did not proceed under the same conditions. The 3-propionates (**17a**—**d**) were obtained by heating of **15a**—**d** with potassium carbonate in methyl ethyl ketone in poor yield. The acetates (**16**) and propionates (**17**) were heated with ethanolic ammonia in a sealed tube to give the desired compounds (**18a**—**f**, **o**, **t**—**v**) and **19**(**a**—**d**), respectively.

The thioketal moiety of **18e**, **f** was cleaved by heating with hydrochloric acid, giving the 8- or 9-oxo derivatives (**18h**, **i**). Reduction of **18h**, **i** with sodium borohydride gave the corresponding hydroxy products (**18k**, **l**). The 9-hydroxy derivative (**18l**) was treated with methanolic hydrochloric acid to give the dehydro compound (**18n**).

The linear hexahydro derivative (**18o**) containing a double bond in the alkylene chain was reacted with *N*-bromosuccinimide by a method similar to that described by Sugihara *et al.*[11] to give the 9-bromo-10-hydroxy derivative (**20**). The bromohydrin (**20**) was converted to the epoxide (**21**) by treatment with sodium methoxide. The structure of the epoxide (**21**) was confirmed by the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. Signals of two methine protons at the 11b- and 1a-position and two methylene protons at the 2-position were observed as four independent signals. The signal pattern was similar to that of tetrahydronaphthalene expoxide, described by Imuta and Ziffer.[12]

The epoxide (**21**) was heated with sulfuric acid to give the 9,10-dihydroxy derivative (**18r**). The 10-amino-9-hydroxy compound (**18s**) was obtained by heating **21** with ethanolic ammonia in a sealed tube. Sugihara *et al.*[11] reported that amination of tetrahydronaphthalene expoxide proceeded at the 1-position, and in this case the amino substitution also occurred at the same position.

Synthesis of the compound (**18j**) having an oxo group at the β-position in the indan ring was tried. Since β-indanone derivatives are relatively unstable, the chlorination of the quinazoline-2,4-dione derivative may be unsuccessful because of the requirement for severe



a, c, e, h, k: $n=1$; **b, d, f, i, l**: $n=2$; **t**: X=N, Y=Z=CH; **u**: X=Z=CH, Y=N;
v: X=Y=CH, Z=N; **w**: X=NH, Y=Z=CH_2; **x**: X=Z=CH_2, Y=NH; **y**: X=Y=CH_2, Z=NH

Chart 1

conditions. An alternative pathway used for the preparation was shown in Chart 2.

Diazotization of the starting material (**22**), followed by reaction with ethyl acrylate, tin–acetic acid reduction, chlorination, and then intramolecular Friedel–Crafts reaction gave 4,7-dibromo-1-indanone (**23**). The 1-indanone derivative (**23**) was reduced with sodium borohydride to give the hydroxy product, which was successively treated with potassium hydrogen sulfate, *m*-chloroperbenzoic acid, and silica gel to give 4,7-dibromo-2-indanone (**24**) in good yield. Nitration of **24** under mild conditions followed by ketalization then cyanation afforded the 5-cyano derivative (**27**). In the subsequent reduction of **27** with diborane, the reaction

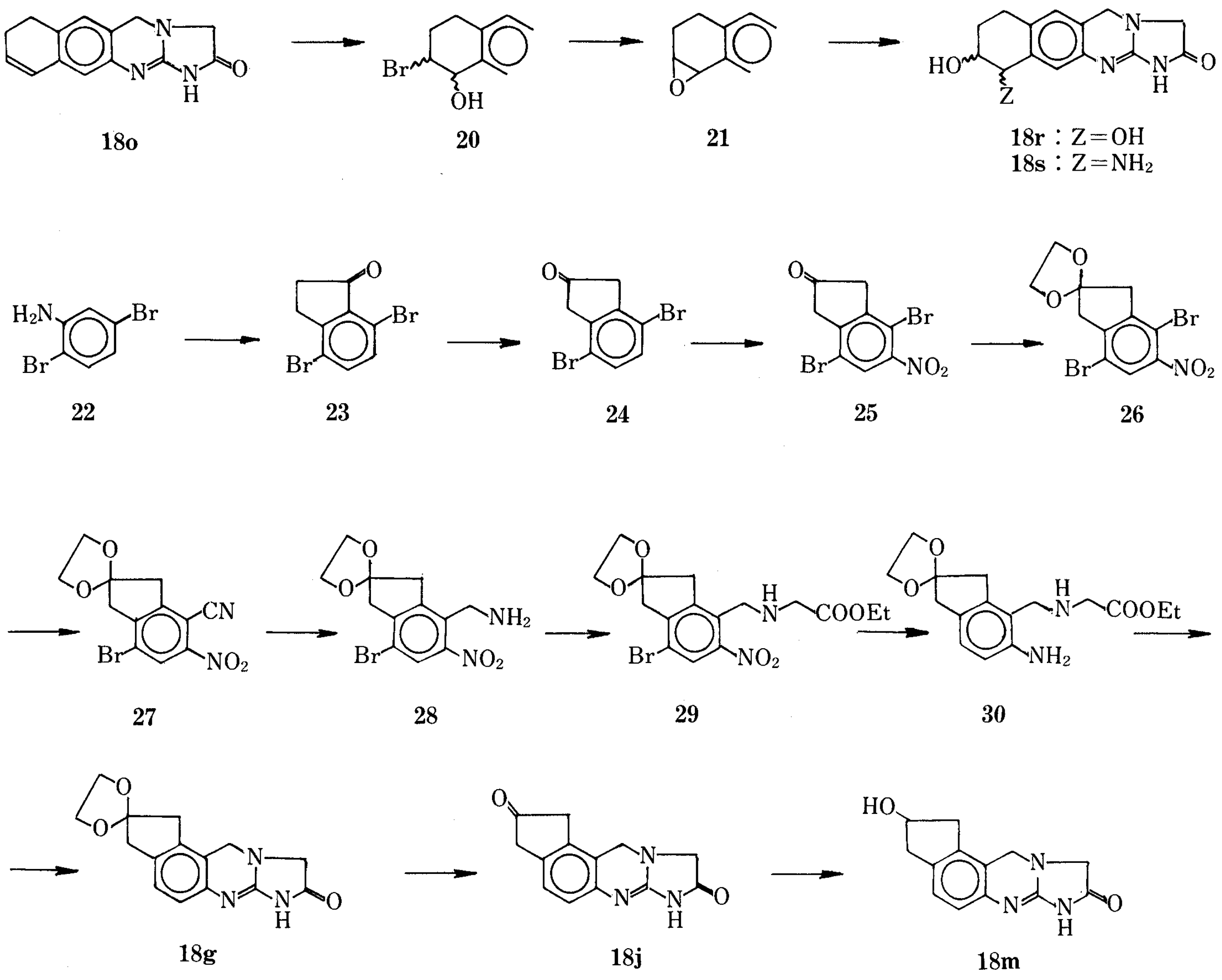


Chart 2

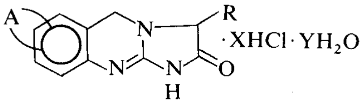
complex was treated with hydrochloric acid at room temperature to give **28** without cleavage of the ketal moiety. Heating of **28** with ethyl bromoacetate in the presence of sodium carbonate followed by catalytic reduction, then treatment with cyanogen bromide afforded the β-ketal derivative (**18g**), which was treated with 10% hydrochloric acid at room temperature for a long time to give the desired product (**18j**) in moderate yield. The final cleavage of the ketal function under heating resulted in complete decomposition. Reduction of **18j** with sodium borohydride gave the corresponding hydroxy derivative (**18m**).

The hydrochlorides of the compounds (**18q**, **r**, **w**—**y**) having an amino or imino moiety in the alkylene chain were soluble in water. However, the water solubilities of the compounds (**18h**—**m**, **r**) having an oxo or a hydroxy group were very poor.

Biological Properties

Table I shows the inhibitory activity of the above compounds on platelet aggregation *in vitro* and *ex vivo* in rats. Most of the compounds were as active or more active than DH-6471[3] *in vitro*. As regards the bonding position of the alkylene chain, the compounds with the alkylene linkage between the 6- and 7-position (angular type) were more active than those linked between the 7- and 8-position (linear type) [**18c**, **d** > **18a**, **b**; **18n** ≫ **18o**]. The effects of the six-membered ring compounds were almost equal to those of five-membered ones [**18a** = **18b**; **18c** = **18d**; *etc*.]. The compounds (**19a**—**d**) substituted with a methyl group at the 3-position on the imidazo[2,1-*b*]quinazoline ring showed about one-tenth of the activity of the

TABLE I. Tetracyclic Imidazo[2,1-*b*]quinazolinone Derivatives (**18** and **19**) and Their Inhibition of Platelet Aggregation



18: R=H **19**: R=Me

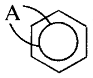
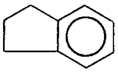
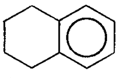
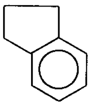
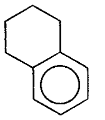
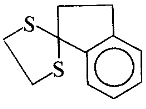
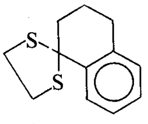
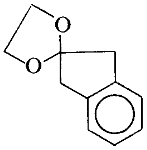
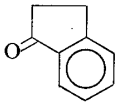
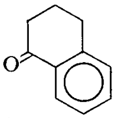
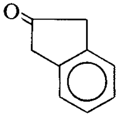
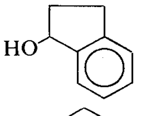
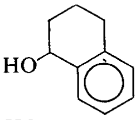
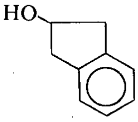
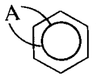
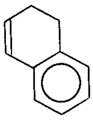
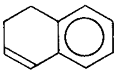
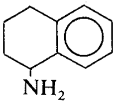
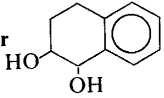
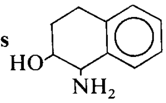
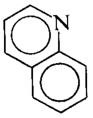
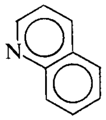
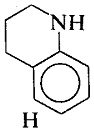
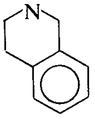
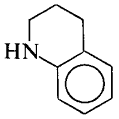
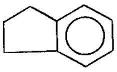
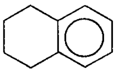
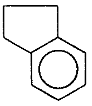
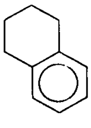
Compd.		Yield (%)	mp[a] (°C)	IR (cm⁻¹)	¹H-NMR[b] (δ)	Formula Calcd (Found)			Inhibn. of platelet aggregation			
									in vitro (μM)[e]		*ex vivo* (%)[f]	
						C	H	N	Collagen	ADP	Collagen	ADP
18a		51	220—222	1785	4.50[c]	$C_{13}H_{14}ClN_3O\cdot H_2O$			1.4	3.2		
			(dec.)	1680	4.85	55.42	5.72	14.92				
						(55.53	5.64	14.57)				
18b		67	219—221	1785	4.52[c]	$C_{14}H_{16}ClN_3O\cdot 0.5H_2O$			1.3	5.0	55.3[g]	11.8
			(dec.)	1680	4.85	58.63	5.98	14.65				
						(58.87	6.26	14.26)				
18c		59	>280	1790	4.56[c]	$C_{13}H_{14}ClN_3O$			0.062	0.25	80.7[h]	60.0[h]
				1680	4.86	59.20	5.35	15.93				
						(59.31	5.68	16.08)				
18d		65	>280	1780	4.51[c]	$C_{14}H_{16}ClN_3O$			0.042	0.64	50.4[g]	40.5[g]
				1690	4.68	60.54	5.81	15.13				
						(60.52	6.04	14.99)				
18e		83	Unclear	1785	4.53[c]	$C_{15}H_{16}ClN_3OS_2\cdot 2H_2O$			0.052	2.4	24.6	15.4
			(dec.)	1670	4.73	46.20	5.17	10.78				
						(46.25	5.27	10.75)				
18f		74	>280	1790	4.25	$C_{16}H_{18}ClN_3OS_2\cdot 2H_2O$			0.19	2.1	0.5	−12
				1680	4.57	47.58	5.49	10.40				
						(47.44	5.61	10.25)				
18g		66	Unclear	1790	4.22	$C_{15}H_{16}ClN_3O_3$			0.18	1.6	18.7	20.2
			(dec.)	1680	4.61	55.99	5.01	13.06				
						(55.99	5.33	12.92)				
18h		80	>280	1800	4.71[c]	$C_{13}H_{12}ClN_3O_2\cdot H_2O$			0.064	0.076	27.7	28
				1670	5.12	52.80	4.77	14.21				
						(52.52	4.67	14.07)				
18i		81	>280	1790	4.42[c]	$C_{14}H_{14}ClN_3O_2\cdot H_2O$			0.054	0.06	46.8[g]	46.5[g]
				1660	4.84	54.28	5.21	13.57				
						(54.28	5.09	13.48)				
18j		59	Unclear	1750	4.23	$C_{13}H_{12}ClN_3O_2\cdot H_2O$			0.25	2.5	34.3	9.4
			(dec.)	1680	4.63	52.80	4.77	14.21				
						(52.46	4.79	13.93)				
18k		74	>280	1790	4.20	$C_{13}H_{14}ClN_3O_2$			0.3	2.5	13.8	27.0
				1670	4.63	55.82	5.22	14.86				
						(55.64	5.22	14.86)				
18l		90	>280	1790	4.23	$C_{14}H_{16}ClN_3O_2\cdot 0.5H_2O$			0.37	1.1	43.0[g]	27.7
				1685	4.56	55.54	5.66	13.88				
						(55.41	5.84	13.58)				
18m		75	>280	1800	4.21	$C_{13}H_{14}ClN_3O_2\cdot H_2O$			2.75	13		
				1680	4.61	52.44	5.42	14.11				
						(52.53	5.08	14.09)				

TABLE I. (continued)

Compd.	 A	Yield (%)	mp[a] (°C)	IR (cm^{-1})	^{1}H-NMR[b] (δ)	Formula Calcd (Found)			Inhibn. of platelet aggregation in vitro (μM)[e]		ex vivo (%)[f]	
						C	H	N	Collagen	ADP	Collagen	ADP
18n		95	>280	1795	4.26	$C_{14}H_{14}ClN_3O \cdot H_2O$			0.03	0.12	77.2[h]	82.1[h]
				1685	4.66	57.24	5.49	14.31				
						(57.39	5.55	14.16)				
18o		49	258—259	1770	4.29[c]	$C_{14}H_{14}ClN_3O \cdot 0.5H_2O$			5.8	24		
			(dec.)	1610	4.70	59.05	5.31	14.75				
						(59.03	5.30	14.50)				
18q		68	254—257	1795	4.23	$C_{14}H_{18}Cl_2N_3O \cdot 0.5H_2O$			13.5	70	15.4	13.6
			(dec.)	1670	4.43	49.71	5.55	16.57				
						(49.58	5.39	16.48)				
18r		80	>280	1780	4.23	$C_{14}H_{16}ClN_3O_3 \cdot H_2O$			1.5	360		
				1680	4.66	51.30	5.53	12.82				
						(50.96	5.46	12.67)				
18s		70	230—240	1790	4.24	$C_{14}H_{18}Cl_2N_4O_2 \cdot H_2O$			110	220		
			(dec.)	1680	4.66	46.29	5.55	15.43				
						(46.67	5.48	15.00)				
18t		85	>280	1800	4.75[c]	$C_{13}H_{12}Cl_2N_4O \cdot H_2O$			0.07	0.25	8.2	14.5
				1690	5.62	47.43	4.29	17.02				
						(47.76	4.43	16.86)				
18v		72	>280	1780	4.77[c]	$C_{13}H_{12}Cl_2N_4O \cdot 0.5H_2O$			0.16	0.36	5.5	3.9
				1685	5.58	48.76	4.09	17.50				
						(48.82	4.32	17.52)				
18w		87	>280	1780	4.45[d]	$C_{13}H_{16}Cl_2N_4O \cdot 2H_2O$			0.70	0.75	31	29[g]
				1680	4.86	44.45	5.74	15.95				
						(44.24	5.34	15.88)				
18x		49	>280	1790	4.28[d]	$C_{13}H_{16}Cl_2N_4O \cdot 2H_2O$			1.20	8.5	−14	−8
				1680	4.63	44.45	5.74	15.95				
						(44.39	5.43	15.96)				
18y		82	220—225	1800	4.33[d]	$C_{13}H_{16}Cl_2N_4O \cdot 2H_2O$			0.70	2.80	31.6[g]	35.4[g]
			(dec.)	1670	4.70	44.45	5.74	15.92				
						(44.41	5.68	15.92)				
19a		13	210—215	1775	4.65 (q)[c]	$C_{14}H_{16}ClN_3O \cdot 0.5H_2O$			3.6	30		
			(dec.)	1680	4.86 (dd)	58.64	5.98	14.66				
						(58.38	6.36	14.64)				
19b		8	162—164	1780	4.28 (q)	$C_{15}H_{18}ClN_3O \cdot H_2O$			17.0	34		
			(dec.)	1680	4.56 (dd)	58.15	6.51	13.57				
						(57.85	6.44	13.41)				
19c		5	245—248	1775	4.28 (q)	$C_{14}H_{16}ClN_3O \cdot H_2O$			0.8	3.5		
			(dec.)	1675	4.59 (dd)	56.84	6.13	14.20				
						(56.25	5.92	14.02)				
19d		5	270—272	1780	4.28 (q)	$C_{15}H_{18}ClN_3O \cdot H_2O$			0.75	1.7		
			(dec.)	1680	4.54 (dd)	58.15	6.51	13.57				
						(58.14	6.43	13.66)				
DH-6471									0.1	2.0	29[g]	60[g]

a) Compounds were recrystallized from MeOH–EtOH. b) Chemical shifts of methylene protons at the 3- and 5-position of the imidazoquinazolin ring in DMSO-d_6. c) In trifluoroacetic acid. d) In D_2O. e) Effective concentration required for 50% inhibition of platelet aggregation. f) Percent inhibition of platelet aggregation at an oral dose of 10 mg/kg given 1 h before the test. g) $p<0.05$. h) $p<0.01$ (vs. control).

TABLE II. Duration of Inhibition of Platelet Aggregation in Rats after a Single Oral Dose of **18c, d, n**[a]

Compd.	Dose (mg/kg)	Collagen (%)[b] Time after dose (h)				ADP (%)[b] Time after dose (h)			
		1	2	3	6	1	2	3	6
18c	3	41	34[d]	41[c]	18	26	67[d]	38	23
18d	3	36[c]	50[e]	53[c]	6	22	44[c]	24	18
18n	10	31[c]	41[d]	32[c]	7	41[c]	39[d]	14[c]	5

a) Five animals were used in each group. Data are given as mean values. *b*) Percent inhibition of platelet aggregation. *c*) $p<0.05$. *d*) $p<0.01$. *e*) $p<0.001$.

unsubstituted ones (**18a**—**d**).

The most active derivatives *in vitro* were angular 8- or 9-oxo compounds (**18h**, **i**) which inhibited platelet aggregation by about 50% at 10^{-2} μM. Very potent activity was retained in the corresponding hydroxy derivatives (**18k**, **l**). However, other compounds (**18m**, **r**) substituted with a hydroxy group at different positions showed relatively weak activity. Among the compounds containing the basic function in the alkylene chain, **18q** (with an amino group) and **18x** (replacing a methylene moiety by an imino one at the phenethyl position) were very weakly active. On the other hand, the imino function at the benzyl position had little effect on the high potency [**18w**, **y**]. Strong basicity resulted in loss of the activity.

The synthetic intermediates, thioketals (**18e**, **f**), ketal (**18g**), and pyridine-condensed derivatives (**18t**, **v**) were also potent. Very high activity was also retained in the angular compound (**18n**) with a double bond in the alkylene chain.

Most of the active compounds were examined *ex vivo* after a single oral administration at 10 mg/kg of body weight to rats, and the results are shown in Table I. Although many compounds were very potent *in vitro* as described above, only eight compounds (**18b**—**d**, **i**, **l**, **n**, **w**, **y**) showed significant activity *ex vivo*. The introduction of a hydrophilic function resulted in loss of the activity. Marked potency was found in the compounds (**18c**, **d**, **n**) with a simple alkylene linkage. These compounds were also tested for the duration of their action *ex vivo* after a single oral administration of 10 mg/kg. As shown in Table II, the compounds were relatively short-acting.

It was found that the compounds of a related series containing imidazothienopyrimidinones were very potent inhibitors of low K_m cyclic adenosine monophosphate phosphodiesterase (low K_m cAMP : PDE) in rat platelets, and their inhibitory potency was closely correlated to the inhibitory activity towards platelet aggregation. Therefore, the antiplatelet action of these compounds may result from their inhibition of low K_m cAMP : PDE in platelets. These results will be discussed elsewhere.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were taken on a Hitachi 285 spectrometer. ^{1}H-NMR spectra were recorded with Hitachi R-40 and JEOL JNM-FX 90Q spectrometers (Me_4Si as an internal standard, δ value). For column chromatography, silica gel (Merck, 0.05—0.2 mm) was used.

Reaction of 1-(5-Indanyl)-3-phenoxycarbonylurea (2a) with Phosphoryl Chloride——A mixture of $POCl_3$ (150 ml) and **2a** (15 g, 50 mmol) (prepared from 5-indanamine and phenoxycarbonylisocyanate[13] in quantitative yield) was heated under gentle reflux for 10 h and concentrated to dryness. The residue was poured into ice-water and then extracted with $CHCl_3$. The organic layer was washed with water, dried, and evaporated. The residue was purified by chromatography on silica gel (150 g) with $CHCl_3$ to give a mixture of 2,4-dichloro-7,8-dihydro-6*H*-cyclopenta[*g*]quinazoline (**1a**) and 7,9-dichloro-2,3-dihydro-1*H*-cyclopenta[*f*]quinazoline (**1c**) (3.2 g, 27%). The mixture was purified again on silica gel (200 g) to give **1a** (1.3 g, 9.1%) and **1c** (0.77 g, 6.4%).

1a: mp 141—144 °C (acetone). IR (KBr): 1550, 1400 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.77 (1H, s), 8.02 (1H, s). *Anal.* Calcd for $C_{11}H_8Cl_2N_2$: C, 55.26; H, 3.37; N, 11.72. Found: C, 54.92; H, 3.31; N, 11.66.

1c: mp 144—145 °C (acetone). IR (KBr): 1530, 1480 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.80 (2H, s). *Anal.* Calcd for $C_{11}H_8Cl_2N_2$: C, 55.26; H, 3.37; N, 11.72. Found: C, 55.55; H, 3.44; N, 11.88.

2,4-Dichloro-6,7,8,9-tetrahydrobenzo[*g*]quinazoline (1b)——A mixture of POCl$_3$ (100 ml) and **2b** (8.05 g, 26 mmol) was refluxed for 10 h and worked up as described above for **1a** and **1c** to yield pure **1b** (0.62 g, 9%), mp 157—158 °C (acetone). IR (KBr): 1530, 1190 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.63 (1H, s), 7.85 (1H, s). *Anal.* Calcd for $C_{12}H_{10}Cl_2N_2$: C, 56.94; H, 3.98; N, 11.07. Found: C, 57.16; H, 4.01; N, 10.87.

1,3-Dichloro-7,8,9,10-tetrahydrobenzo[*f*]quinazoline (1d)——A mixture of **6d** (3.0 g, 14 mmol), POCl$_3$ (90 ml), and iso-Pr$_2$NEt (9 ml) was refluxed overnight and worked up as described above to give **1d** (2.95 g, 86%), mp 132—134 °C (Et$_2$O). IR (KBr): 1520, 1245 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.67 (2H, s). *Anal.* Calcd for $C_{12}H_{10}Cl_2N_2$: C, 56.94; H, 3.98; N, 11.07. Found: C, 57.59; H, 4.18; N, 10.93.

Compounds **1c, e, f, t—v** were prepared from **6c, e, f, t—v**, respectively, in a fashion analogous to that used for **1d**.

1c: Yield 78%, mp 144—145 °C (acetone). IR (KBr): 1530, 1480 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.8 (2H, s). *Anal.* Calcd for $C_{11}H_8Cl_2N_2$: C, 55.25; H, 3.37; N, 11.72. Found: C, 55.55; H, 3.44; N, 11.88.

1e: Yield 88%, mp 169—170 °C (acetone). IR (KBr): 1530, 1470 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 3.53 (4H, s), 7.84 (1H, d, J=9 Hz), 8.16 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{13}H_{10}Cl_2N_2S_2$: C, 47.42; H, 3.06: N, 8.51. Found: C, 47.65; H, 3.11; N, 8.46.

1f: Yield 73%, mp 175—177 °C (acetone). IR (KBr): 1520, 1470 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 3.6 (4H, m), 7.76 (1H, d, J=9 Hz), 8.46 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{14}H_{12}Cl_2N_2S_2$: C, 48.98; H, 3.53; N, 8.16. Found: C, 49.11; H, 3.53; N, 8.28.

1t: Yield 65%, mp unclear (dec.). IR (KBr): 1530, 1210 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.94 (1H, d, J=9.5 Hz), 8.21 (1H, d, J=9.5 Hz). *Anal.* Calcd for $C_{11}H_{15}Cl_2N_3$: C, 52.83; H, 2.02; N, 16.80. Found: C, 52.45; H, 2.17; N, 16.68.

1u: Yield 12%, mp 231—235 °C (dec.). IR (KBr): 1520, 1350 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 8.06 (1H, d, J=9.5 Hz), 8.25 (1H, d, J=9.5 Hz). *Anal.* Calcd for $C_{11}H_{15}Cl_2N_3$: C, 52.83; H, 2.02; N, 16.80. Found: C, 52.69; H, 2.26; N, 16.58.

1v: Yield 49%, mp 189—191 °C (acetone). IR (KBr): 1520, 1340 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 8.14 (1H, d, J=9 Hz), 8.55 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{11}H_{15}Cl_2N_3$: C, 52.83; H, 2.02; N, 16.80. Found: C, 52.53; H, 2.28; N, 16.63.

2,4-Dichloro-6,7-dihydrobenzo[*g*]quinazoline (1o)——A mixture of POCl$_3$ (50 ml) and **3** (4.3 g, 10 mmol) (prepared 7-amino-1,2,3,4-tetrahydronaphthalen-1-yl benzoate and phenoxycarbonylisocyanate in quantitative yield) was refluxed with stirring overnight and worked up as described above for **1a** to yield **1o** (1.0 g, 40%), mp 156—157 °C (acetone). IR (KBr): 1540 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 6.3—6.6 (1H, m), 6.73 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{12}H_8Cl_2N_2$: C, 57.40; H, 3.21; N, 11.15. Found: C, 57.25; H, 3.21; N, 11.02.

2,3,6,7,8,9-Hexahydro-1*H*-cyclopenta[*f*]quinazolin-7,9-dione (6c)——A mixture of **4c** (27.8 g, 120 mmol) and urea was heated at 200—210 °C for 1.5 h. The reaction mass was crushed, and washed with water and then acetone. The wet product was refluxed overnight in a mixture of conc. HCl (180 ml) and water (250 ml). The precipitate was collected by filtration, washed with water, and dried to give crude **6c** (21.4 g, 88%), mp >280 °C. IR(KBr): 1710, 1670, 1610 cm^{-1}. The crude product was used for the next reaction without further purification.

Compounds **6d, t—v** were also obtained from **4d, t—v**, respectively, in the same manner as described above for **6c**.

6d: Yield 75%, mp >280 °C. IR (KBr): 1700, 1600 cm^{-1}.

6t: Yield 95%, mp >280 °C. IR (KBr): 1710, 1620 cm^{-1}.

6u: Yield 79%, mp >280 °C. IR (KBr): 1680, 1605 cm^{-1}.

6v: Yield 95%, mp >280 °C. IR (KBr): 1710, 1605 cm^{-1}.

2,3,6,7,8,9-Hexahydro-1*H*-spiro[cyclopenta[*f*]quinazolin-3,2′-[1,3]dithiolane]-7,9-dione (6e)——A mixture of **14e** (8.2 g, 18.5 mmol) and NaOEt (13 g, 190 mmol) in EtOH (300 ml) was refluxed for 3 h. The precipitate was collected by filtration, washed with EtOH, and dissolved in water (200 ml). The solution was warmed at 50—60 °C and adjusted to pH 4—5 with conc. HCl. The precipitate was collected, washed with water, and dried to give **6e** (4.5 g, 84%), mp >280 °C. IR (KBr): 1720, 1680, 1660, 1610 cm^{-1}. *Anal.* Calcd for $C_{13}H_{12}N_2O_2S_2$: C, 53.40; H, 4.14; N, 9.58. Found: 53.37; H, 4.15; N, 9.40.

Compound **6f** was also prepared in the same manner as described above for **6e**.

6f: Yield 86%, mp >280 °C. IR (KBr): 1720, 1600 cm^{-1}. *Anal.* Calcd for $C_{14}H_{14}N_2O_2S_2$: C, 54.88; H, 4.61; N, 9.14. Found: C, 54.87; H, 4.84; N, 9.19.

Ethyl 5-Nitro-4-indancarboxylate (8c)——A solution of NaNO$_2$ (3.1 g, 45 mmol) in water (15 ml) was added to a mixture of **7c**[10a] (8.0 g, 45 mmol), conc. HCl (8.5 ml, 90 mmol), and water (100 ml) with stirring. The reaction mixture was stirred for 1 h, and insoluble material was filtered off. The filtrate was added to a solution of CuCN [prepared from CuSO$_4$·5H$_2$O (11.2 g, 45 mmol) and KCN (12.2 g, 220 mmol)] in water (70 ml) at 70—80 °C with vigorous stirring. The mixture was further heated for 10 min, cooled and extracted with CHCl$_3$. The extract was washed with water, dried, and evaporated. The residue was purified by silica gel (100 g) chromatography using $CHCl_3$ as an eluent to give the 5-nitro-4-carbonitrile (6.6 g, 77%) [mp 94—95 °C (Et_2O). IR (KBr): 2220 cm^{-1}. *Anal.* Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.76; H, 4.37; N, 14.80].

A mixture of the nitro–carbonitrile (6.6 g, 35 mmol), conc. H_2SO_4 (29 ml), AcOH (58 ml) and water (115 ml) was heated at 120 °C for 1 h, then a solution of $NaNO_2$ (4.0 g) in water (30 ml) was added at 90—100 °C. After the mixture had been heated for 1 h, NaCl (40 g) was added to the hot mixture and the whole was cooled in an ice-bath. The precipitate was collected to give the crude free acid (6.2 g, 62%) [mp 170—172 °C, IR (KBr): 1715, 1515, 1340 cm^{-1}].

iso-Pr_2NEt (7.9 g, 72.5 mmol) was added portionwise to a solution of the free acid (6.2 g) and the Meerwein reagent [prepared from epichlorhydrin (6.7 g) and $BF_3 \cdot Et_2O$ (15.5 g) in the usual manner] in CH_2Cl_2 (180 ml). The solution was washed with dil. HCl and then water, dried and concentrated to dryness to give **8c** as an oil (6.8 g, 87%). IR (Neat): 1750, 1350 cm^{-1}.

Compound **8d** was prepared from **7d**[10b] in a fashion analogous to that used for **8c**.

8d: Yield 48% (overall yield from **7d**), mp 53—54 °C (benzene–hexane). IR (KBr): 1730, 1340 cm^{-1}. *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.60; H, 5.94; N, 5.51.

Ethyl 5-Amino-4-indancarboxylate (9c)——A solution of **8c** (6.8 g, 29 mmol) in EtOH (70 ml) was treated with hydrogen in the presence of PtO_2 (0.2 g). The catalyst was removed and the filtrate was concentrated to give **9c** (5.9 g, quant.), mp 68—69 °C (Et_2O). IR (KBr): 1660, 1610 cm^{-1}. *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.35; H, 7.36; N, 6.80.

Compound **8d** was also hydrogenated and worked up as described above for **9c** to give crude **9d** (quant.) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 6.40 (1H, d, $J=9$ Hz), 6.93 (1H, d, $J=9$ Hz).

Ethyl 5-Acetylamino-4-indancarboxylate (10c)——Ac_2O (3.2 g, 31 mmol) was added to a solution of **9c** (5.75 g, 28 mmol) in benzene (10 ml). The mixture was allowed to stand for 1 h, then washed with aqueous $NaHCO_3$ solution and water, dried, and concentrated to dryness to give **10c** (6.5 g, 93%), mp 101—102 °C (Et_2O). IR (KBr): 3250, 1690, 1670 cm^{-1}. *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.98; H, 6.93; N, 5.69.

Compound **10d** was also obtained from **9d** in the same manner as described above for **10c**.

10d: Yield 94%, mp 92—94 °C (EtOH). IR (KBr): 3250, 1715, 1650 cm^{-1}. *Anal.* Calcd for $C_{15}N_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.17; H, 7.40; N, 5.40.

Ethyl 5-Acetylamino-1-oxo-4-indancarboxylate (11h)——A solution of CrO_3 (12.3 g, 130 mmol) in water (12 ml) was added to a solution of **10c** (6.4 g, 26 mmol) in glacial AcOH (40 ml) with stirring. After being stirred for 1 h, the mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to dryness to give **11h** (5.8 g, 86%), mp 171—173 °C (benzene). IR (KBr): 1700, 1670, 1600, 1580 cm^{-1}. *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 63.94; H, 5.69; N, 5.26.

Compound **11i** was prepared from **10d** in the same manner as described above for **11h**.

11i: Yield 83%, mp 154—155 °C (benzene). IR (KBr): 1720, 1680, 1660 cm^{-1}. *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.40; H, 6.24; N, 5.08.

Ethyl 5-Amino-1-oxo-4-indancarboxylate (12h)——A mixture of **11h** (5.5 g, 21 mmol) and conc. HCl (11 ml) in EtOH (110 ml) was refluxed with stirring for 1 h. The mixture was neutralized with dil. NaOH solution, and the solvent was evaporated off. The aqueous residue was extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to dryness to give **12h** (4.6 g, quant.), mp 167—169 °C (EtOH). IR (KBr): 1660, 1570 cm^{-1}. *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.50; H, 5.84; N, 6.31.

Compound **12i** was also obtained from **11i** in the same manner as described above for **12h**.

12i: Yield 95%, mp 113—114 °C (EtOH). IR (KBr): 1690, 1660, 1610 cm^{-1}. *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.90; H, 6.59; N, 5.84.

Ethyl 5-Aminospiro[[1,3]dithiolane-2,1′-indan]-4′-carboxylate (13e)——A solution of **12h** (4.4 g, 20 mmol), ethanedithiol (9.4 g, 100 mmol), and *p*-TsOH (4.5 g, 24 mmol) in benzene (80 ml) was refluxed under a nitrogen atmosphere for 1 h. The reaction mixture was washed with dil. NaOH solution and water, then dried and concentrated to dryness to give **13e** (5.9 g, quant.), mp 87—89 °C (Et_2O). IR (KBr): 1670, 1605, 1250 cm^{-1}. *Anal.* Calcd for $C_{14}H_{17}NO_2S_2$: C, 56.92; H, 5.80; N, 4.74. Found: C, 57.23; H, 5.77; N, 4.76.

Compound **13f** was prepared from **12i** in a fashion analogous to that used for **13e**.

13f: Yield 95%, mp 97—98 °C (Et_2O). IR (KBr): 1690, 1620, 1270 cm^{-1}. *Anal.* Calcd for $C_{15}H_{19}NO_2S_2$: C, 58.22; H, 6.19; N, 4.53. Found: C, 58.37; H, 6.12; N, 4.55.

Ethyl 5′-Benzoylureidospiro[[1,3]dithiolane-2,1′-indan]-4′-carboxylate (14e)——Benzoyl isocyanate (3.1 g, 20 mmol) was added to a solution of **13e** (6.1 g, 20 mmol) in benzene (25 ml) wih stirring. The mixture was allowed to stand for 1 h and then concentrated to dryness. The residue was treated with Et_2O–MeOH (10 : 1) and collected to give **14e** (8.4 g, 95%), mp 185—187 °C (benzene). IR (KBr): 1690, 1260 cm^{-1}. *Anal.* Calcd for $C_{22}H_{22}N_2O_4S_2$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.83; H, 5.03; N, 6.24.

Compound **14f** was also obtained from **13f** in the same manner as described above for **14e**.

14f: Yield 92%, mp 186—187 °C (benzene). IR (KBr): 1720, 1690, 1270 cm^{-1}. *Anal.* Calcd for $C_{23}H_{24}N_2O_4S_2$: C, 60.51; H, 5.30; N, 6.13. Found: C, 60.22; H, 5.11; N, 6.12.

2-Chloro-7,8-dihydro-6*H*-cyclopenta[*g*]quinazoline (15a)——$NaBH_4$ (0.95 g, 25 mmol) was added portionwise to a solution of **1a** (1.2 g, 5 mmol) in a mixture of $CHCl_3$ (10 ml) and EtOH (10 ml). The mixture was stirred for 1 h and concentrated to dryness. The residue was treated with ice-water. Insoluble material was collected, washed with water, and dried to give **15a** (1.0 g, quant.), mp unclear (dec.). ^1H-NMR ($CDCl_3$) δ: 4.67 (2H, s). *Anal.* Calcd for $C_{11}H_{11}ClN_2$: C, 63.92; H, 5.37; N, 13.56. Found: C, 64.20; H, 5.50; N, 13.46.

Compounds **15b**—**f**, **o**, **t**—**v** were also obtained from **1b**—**f**, **o**, **t**—**v**, respectively, in the same manner as described above for **15a**.

15b: Yield 89%, mp 115—118 °C (acetone). ^1H-NMR ($CDCl_3$) δ: 4.65 (2H, s). *Anal.* Calcd for $C_{12}H_{13}ClN_2$: C, 65.30; H, 5.94; N, 12.69. Found: C, 65.63; H, 5.52; N, 12.61.

15c: Yield 94%, mp unclear (dec.). ^1H-NMR ($CDCl_3$) δ: 4.63 (2H, s). *Anal.* Calcd for $C_{11}H_{11}ClN_2$: C, 63.92; H, 5.37; N, 13.56. Found: C, 64.17; H, 5.44; N, 13.45.

15d: Yield 90%, mp unclear (dec.). ^1H-NMR ($CDCl_3$) δ: 4.67 (2H, s). *Anal.* Calcd for $C_{12}H_{13}ClN_2$: C, 65.30; H, 5.94; N, 12.69. Found: C, 65.55; H, 6.26; N, 12.67.

15e: Yield quant., mp unclear (dec.). ^1H-NMR ($CDCl_3$) δ: 4.77 (2H, s). *Anal.* Calcd for $C_{13}H_{13}ClN_2S_2\cdot0.5H_2O$: C, 51.05; H, 4.61; N, 9.16. Found: C, 51.31; H, 4.54; N, 9.03.

15f: Yield quant., mp unclear (dec.). ^1H-NMR ($CDCl_3$) δ: 4.64 (2H, s). *Anal.* Calcd for $C_{14}H_{15}ClN_2S_2$: C, 54.09; H, 4.86; N, 9.01. Found: C, 54.09; H, 4.77; N, 8.96.

15o: Yield 83%, mp unclear (dec.). ^1H-NMR ($CDCl_3$) δ: 4.56 (2H, s). *Anal.* Calcd for $C_{12}H_{11}ClN_2$: C, 65.91; H, 5.07; N, 12.81. Found: C, 65.22; H, 5.29; N, 12.53.

15t: Yield 84%, mp unclear (dec.). ^1H-NMR (DMSO-d_6) δ: 5.16 (2H, s). *Anal.* Calcd for $C_{11}H_8ClN_3\cdot0.5H_2O$: C, 58.29; H, 4.00; N, 18.54. Found: C, 58.69; H, 3.88; N, 18.44.

15u: Yield 72%, mp unclear (dec.). ^1H-NMR (DMSO-d_6) δ: 5.23 (2H, s). *Anal.* Calcd for $C_{11}H_8ClN_3\cdot1.5H_2O$: C, 54.00; H, 4.53; N, 17.17. Found: C, 54.33; H, 4.32; N, 17.10.

15v: Yield 84%, mp unclear (dec.). ^1H-NMR (DMSO-d_6) δ: 5.13 (2H, s). *Anal.* Calcd for $C_{11}H_8ClN_3\cdot1.5H_2O$: C, 54.00; H, 4.53; N, 17.17. Found: C, 54.17; H, 4.25; N, 17.30.

Ethyl 2-Chloro-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazoline-3-acetate (16a)——A mixture of **15a** (0.78 g, 3.8 mmol), tetrabutylammonium iodide (0.1 g), $BrCH_2COOEt$ (0.7 g, 4.2 mmol) and 10 N NaOH (3.8 ml) in CH_2Cl_2 (30 ml) was vigorously stirred for 30 min under a nitrogen atmosphere. The organic layer was separated, washed with water, dried, and evaporated to dryness to give **16a** (0.83 g, 95%), mp unclear (dec.). ^1H-NMR ($CDCl_3$) δ: 1.15 (3H, t, $J=7$ Hz), 4.13 (2H, s), 4.67 (2H, s). *Anal.* Calcd for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.88; N, 9.57. Found: C, 61.41; H, 6.00; N, 9.53.

Compounds **16b**—**f**, **o**, **t**—**v** were prepared from **15b**—**f**, **o**, **t**—**v**, respectively, in the same manner as described for **16a**.

16b: Yield quant., oil. ^1H-NMR ($CDCl_3$) δ: 1.28 (3H, t, $J=7$ Hz), 4.15 (2H, s), 4.62 (2H, s).

16c: Yield quant., mp 108—109 °C (acetone). ^1H-NMR ($CDCl_3$) δ: 1.30 (3H, t, $J=7$ Hz), 4.12 (2H, s), 4.65 (2H, s). *Anal.* Calcd for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 9.57. Found: C, 61.49; H, 5.76; N, 9.80.

16d: Yield quant., oil. ^1H-NMR ($CDCl_3$) δ: 1.30 (3H, t, $J=7$ Hz), 4.15 (2H, s), 4.62 (2H, s).

16e: Yield 95%, mp 165—167 °C (EtOH). ^1H-NMR ($CDCl_3$) δ: 1.32 (3H, t, $J=7$ Hz), 4.13 (2H, s), 4.63 (2H, s). *Anal.* Calcd for $C_{17}H_{19}ClN_2O_2S_2$: C, 53.32; H, 5.00; N, 7.32. Found: C, 53.54; H, 4.84; N, 7.31.

16f: Yield quant., mp 145—147 °C (EtOH). ^1H-NMR ($CDCl_3$) δ: 1.30 (3H, t, $J=7$ Hz), 4.12 (2H, s), 4.58 (2H, s). *Anal.* Calcd for $C_{18}H_{21}ClN_2O_2S_2$: C, 54.46; H, 5.33; N, 7.06. Found: C, 54.62; H, 5.20; N, 7.04.

16o: Yield 90%, oil. ^1H-NMR ($CDCl_3$) δ: 1.32 (3H, t, $J=7$ Hz), 4.20 (2H, s), 4.79 (2H, s).

16t: Yield 94%, mp 149—153 °C (acetone). ^1H-NMR ($CDCl_3$) δ: 1.32 (3H, t, $J=7$ Hz), 4.30 (2H, s), 5.33 (2H, s). *Anal.* Calcd for $C_{15}H_{14}ClN_3O_2\cdot0.5H_2O$: C, 57.60; H, 4.83; N, 13.44. Found: C, 58.00; H, 4.69; N, 13.53.

16u: Yield 95%, oil. ^1H-NMR ($CDCl_3$) δ: 1.35 (3H, t, $J=7$ Hz), 4.33 (2H, s), 5.27 (2H, s).

16v: Yield quant., oil. ^1H-NMR ($CDCl_3$) δ: 1.34 (3H, t, $J=7$ Hz), 4.32 (2H, s), 5.08 (2H, s).

Ethyl 2-(2-Chloro-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-3-yl)propionate (17a)——A mixture of **15a** (1.03 g, 5 mmol), MeCHBrCOOEt (0.98 g, 5.5 mmol) and finely powdered K_2CO_3 (2.1 g, 15 mmol) in methyl ethyl ketone (MEK) (60 ml) was refluxed with vigorous stirring under a nitrogen atmosphere for 6 h. Insoluble material was filtered off and washed with MEK. The filtrate and washings were combined and evaporated to dryness. The residue was purified by silica gel (30 g) chromatography to give crude **17a** (0.28 g) as oil. ^1H-NMR ($CDCl_3$) δ: 1.27 (3H, t, $J=7$ Hz), 1.53 (3H, d, $J=7$ Hz), 4.50 (2H, s), 4.95 (1H, q, $J=7$ Hz).

Compounds **17b**—**d** were also obtained from **15b**—**d** in the same manner as described above for **17a**. These crude compounds (**17**) were used for the next reaction without further purification.

17b: Oil. ^1H-NMR ($CDCl_3$) δ: 1.27 (3H, t, $J=7$ Hz), 1.54 (3H, d, $J=7$ Hz), 4.51 (2H, s), 4.93 (1H, q, $J=7$ Hz).

17c: Oil. ^1H-NMR ($CDCl_3$) δ: 1.27 (3H, t, $J=7$ Hz), 1.56 (3H, d, $J=7$ Hz), 4.51 (2H, s), 4.93 (1H, q, $J=7$ Hz).

17d: Oil. ^1H-NMR ($CDCl_3$) δ: 1.27 (3H, t, $J=7$ Hz), 1.56 (3H, d, $J=7$ Hz), 4.51 (2H, s), 4.93 (1H, q, $J=7$ Hz).

2,3,5,7,8,9-Hexahydro-1*H*-cyclopenta[*g*]imidazo[2,1-*b*]quinazolin-2-one Hydrochloride (18a)——A suspension of **16a** (6.3 g, 21 mmol) in NH_3–EtOH solution (30 ml) was heated in a sealed tube at 120—130 °C for 5 h. The precipitate was collected, washed with EtOH and then water, and dried to give the free base of **18a** (2.5 g). The free base was treated with dil. HCl–MeOH solution and concentrated to dryness. The residue was recrystallized from

EtOH–MeOH to give the hydrochloride.

Compounds **18b**—**f**, **o**, **t**—**v** and **19a**—**d** were prepared from **16b**—**f**, **o**, **t**—**v** and **17a**—**d**, respectively, in a fashion analogous to that used for **18a**. These results are shown in Table I. Only compound **18u** was used for the next reaction without conversion to the hydrochloride.

1,2,3,8,9,11-Hexahydro-7*H*-spiro[cyclopenta[*f*]imidazo[2,1-*b*]quinazolin-2,2′-[1,3]dithiolan]-8-one Hydrochloride (18g)——A solution of **30** (1.0 g, 3.3 mmol) and BrCN (0.36 g, 3.3 mmol) in EtOH (40 ml) was stirred at 40 °C for 40 h. The mixture was treated with aqueous $NaHCO_3$ solution and the whole was stirred at room temperature for 1 h. The precipitate was collected, washed with water and dried to give the free base of **18g** (0.61 g), which was converted to the hydrochloride in the usual manner. The results are shown in Table I.

1,2,3,8,9,11-Hexahydro-7*H*-cyclopenta[*f*]imidazo[2,1-*b*]quinazoline-3,8-dione Hydrochloride (18h)——A suspension of **18e** (2.22 g, 7 mmol) in conc. HCl (80 ml) was refluxed for 8 h. After removal of trace insoluble material, the filtrate was washed with Et_2O and concentrated to dryness to give **18h**.

Compound **18i** was also obtained from **18f** in the same manner as described above for 18 h. The results are shown in Table I.

1,2,3,8,9,11-Hexahydro-7*H*-cyclopenta[*f*]imidazo[2,1-*b*]quinazoline-2,8-dione (18j)——A solution of the free base of **18g** (0.25 g, 0.88 mmol) in 10% HCl (15 ml) and MeOH (80 ml) was stirred at room temperature for 2.5 d and concentrated to half the initial volume *in vacuo* at under 15 °C. The precipitate was collected, washed with MeOH, and dried to give **18j**. The results are shown in Table I.

3-Hydroxy-1,2,3,8,9,11-hexahydro-7*H*-cyclopenta[*f*]imidazo[2,1-*b*]quinazolin-8-one Hydrochloride (18k)—— $NaBH_4$ (0.57 g, 15 mmol) was added portionwise to a suspension of **18h** (0.45 g, 1.5 mmol) in EtOH (100 ml). The mixture was stirred for 2 h and concentrated to dryness. The residue was treated with water and the precipitate was collected, washed with water, and dried to give the free base of **18k**, which was converted to the hydrochloride.

Compounds **18l**, **m** were also obtained from **18i**, **j** in the same manner as described above for **18k**. The results are shown in Table I.

1,2,3,9,10,12-Hexahydrobenzo[*f*]imidazo[2,1-*b*]quinazolin-9-one Hydrochloride (18n)——Compound **18l** (2.3 g, 8 mmol) was added to a mixture of conc. HCl (90 ml) and MeOH (180 ml) in ice-bath with stirring. The mixture was refluxed for 10 min. After removal of the MeOH, the residue was collected to give **18n**. The results are shown in Table I.

4-Hydroxyimino-1,2,3,4,8,9,10,12-octahydrobenzo[*f*]imidazo[2,1-*b*]quinazolin-9-one (18p)——A mixture of **18i** (0.6 g, 2 mmol) and $HONH_2 \cdot HCl$ (0.56 g, 8 mmol) in MeOH (100 ml) was refluxed overnight and concentrated to dryness *in vacuo*. The residue was treated with water and the precipitate was collected to give **18p** (0.42 g, 69%), mp >280 °C. IR (KBr): 1790, 1675, 1615 cm^{-1}. ^1H-NMR (DMSO-d_6/TFA) δ: 4.46 (2H, s), 4.89 (2H, s). *Anal.* Calcd for $C_{14}H_{14}ClN_2O_2 \cdot HCl$: C, 54.82; H, 4.93; N, 18.26. Found: C, 54.55; H, 4.91; N, 18.48.

4-Amino-1,2,3,4,8,9,10,12-octahydrobenzo[*f*]imidazo[2,1-*b*]quinazolin-9-one Dihydrochloride (18q)——A suspension of **18p** (0.2 g, 0.65 mmol) and conc. HCl (5 ml) in MeOH (150 ml) was treated with hydrogen in the presence of 10% Pd–charcoal (0.1 g) at 4.3 times atmospheric pressure. After complete reduction, the catalyst was removed and the filtrate was concentrated to give **18g**. The results are shown in Table I.

9,10-Dihydroxy-1,2,3,5,7,8,9,10-octahydrobenzo[*g*]imidazo[2,1-*b*]quinazolin-2-one Hydrochloride (18r)——A mixture of **21** (0.3 g, 1.2 mmol) and conc. H_2SO_4 (0.15 g, 1.5 mmol) in water (120 ml) was heated overnight at 80 °C and neutralized with $NaHCO_3$ solution. The precipitate was collected, washed with water, and dried to give the free base of **18r**, which was converted to the hydrochloride. The results are shown in Table I.

10-Amino-9-hydroxy-1,2,3,5,7,8,9,10-octahydrobenzo[*g*]imidazo[2,1-*b*]quinazolin-2-one (18s)——A mixture of **21** (0.3 g, 1.2 mmol) in 10% NH_3–EtOH solution (50 ml) was heated at 130 °C in a sealed tube and concentrated to dryness *in vacuo*. The residue was collected, washed with water, and dried to give the crude free base of **18s**, which was converted to the pure hydrochloride. The results are shown in Table I.

1,2,3,4,8,9,10,12-Octahydroimidazo[2,1-*b*]pyrido[2,3-*f*]quinazolin-9-one Dihydrochloride (18w)——A suspension of the free base of **18t** (1.19 g, 5 mmol) in MeOH (120 ml) and 10% HCl (24 ml) was treated with hydrogen in the presence of PtO_2 (0.12 g) for 4 h. The catalyst was filtered off, the filtrate was concentrated to dryness *in vacuo*, and the residue was collected to give **18w**.

Compounds **18x**, **y** were prepared from **18u**, **v**, respectively, in the same manner as described above for **18w**. The results are shown in Table I.

9-Bromo-10-hydroxy-1,2,3,5,7,8,9,10-octahydrobenzo[*g*]imidazo[2,1-*b*]quinazolin-2-one (20)——A mixture of **18o** (1.5 g, 6.3 mmol) and NBS (1.5 g, 8.4 mmol) in DMSO (20 ml) was stirred at room temperature overnight and poured into ice-water. $NaHCO_3$ (0.85 g, 8.4 mmol) was added and the reaction mixture was stirred for another 1 h. The precipitate was collected, washed with water, and dried to give **20** (1.4 g, 67%), mp 190—195 °C (dec.). IR (KBr): 3000—2400, 1725, 1645 cm^{-1}. ^1H-NMR (DMSO-d_6/TFA) δ: 4.25—4.45 (1H, m), 4.56 (3H, s, 5-H and 9- or 10-H). *Anal.* Calcd for $C_{14}H_{14}BrN_3O_2$: C, 50.01; H, 4.20; N, 12.50. Found: C, 49.67; H, 4.28; N, 12.22.

1a,2,3,5,7,8,9,11b-Octahydro[1]benzooxireno[3,2-*g*]imidazo[2,1-*b*]quinazolin-8-one (21)——A mixture of **20** (1.9 g, 5.65 mmol) and NaOMe (0.61 g, 11.3 mmol) in DMSO (20 ml) was stirred under a nitrogen atmosphere overnight. The precipitate was collected, washed with dil. NaOH solution and water, and dried to give **21** (1.25 g, 87%), mp >280 °C. IR (KBr): 1710, 1640, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.75 (1H, m, 1a-H), 3.90 (1H, d, $J=$ 4 Hz, 11b-H). *Anal.* Calcd for $C_{14}H_{13}N_3O_4$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.69; H, 5.48; N, 16.52.

4,7-Dibromo-1-indanone (23)——3-(2,5-Dibromophenyl)propionic acid [mp 75—78 °C (hexane)], obtained from **22** (70.8 g, 280 mmol) by a method similar to that described by Kaiser *et al.*[14] for the preparation of 3-(2,3-dichlorophenyl)propionic acid, was converted to the acid chloride in the usual manner. The acid chloride was treated with $AlCl_3$ (29 g, 220 mmol) in CS_2 (130 ml) at -10 °C and the mixture was worked up in the usual way to give **23** (44.2 g, 63%), mp 155—156 °C (EtOH). IR (KBr): 1700, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.90 (2H, m), 3.00 (2H, m). *Anal.* Calcd for $C_9H_6Br_2O$: C, 37.28; H, 2.09. Found: C, 37.48; H, 2.03.

4,7-Dibromo-2-indanone (24)——Compound **23** (93 g, 320 mmol) was treated with $NaBH_4$ (6.5 g) in EtOH (500 ml) at room temperature and the mixture was worked up as usual to give 4,7-dibromo-1-indanol [mp 70—71 °C (Et_2O–hexane). ^{1}H-NMR ($CDCl_3$) δ: 5.30 (1H, dd, $J=6.5$, 2.5 Hz)]. The alcohol was heated with $KHSO_4$ (10 g) at 210—220 °C for 30 min and distilled under pressure to give 4,7-dibromoindene [mp 45—48 °C, ^{1}H-NMR ($CDCl_3$) δ: 6.66 (1H, d, $J=7$ Hz), 6.97 (1H, d, $J=7$ Hz)]. The indene derivative was refluxed with *m*-chloroperbenzoic acid (46 g) in $CHCl_3$ (750 ml) for 5.5 h. The mixture was worked up as usual to give 3,6-dibromooxireno[2,3-*a*]indan [mp 101—110 °C (EtOH), ^{1}H-NMR ($CDCl_3$) δ: 4.09 (1H, t, $J=2.5$ Hz, 1a-H), 4.44 (1H, s, 6b-H)]. A solution of the epoxide in benzene was refluxed with silica gel (140 g) with vigorous stirring for 2 h. The silica gel was filtered off, and the filtrate was evaporated to give **24** (41.7 g, 50% from **23**), mp 166—168 °C (benzene). IR (KBr): 1740, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (4H, s). *Anal.* Calcd for $C_9H_6Br_2O$: C, 37.28; H, 2.09. Found: C, 37.22; H, 1.80.

4,7-Dibromo-5-nitro-2-indanone (25)——Compound **24** (10 g, 34.5 mmol) was added to cooled (-25 °C) fuming HNO_3 (50 ml) with stirring. The mixture was stirred at the same temperature for 15 min, then poured into ice-water and extracted with benzene. The extract was washed with water, dried, and evaporated to give **25** (10.7 g, 93%), mp 190—192 °C. IR (KBr): 1750, 1520, 1320 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.73 (2H s), 3.76 (2H, s), 8.0 (1H, s). *Anal.* Calcd for $C_9H_5Br_2NO_3$: C, 32.27; H, 1.50; N, 4.18. Found: C, 31.86; H, 1.57; N, 4.43.

4′,7′-Dibromo-5′-nitrospiro[[1.3]dioxolane-2,2′-indan] (26)——A mixture of **25** (3.0 g, 9 mmol), ethyleneglycol (1 ml, 18 mmol) and *p*-TsOH (50 mg) in benzene (20 ml) was refluxed for 1.5 h with removal of water by means of a Dean–Stark column, and worked up as usual to give **26** (2.7 g, 80%), mp 106—108 °C (EtOH–Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 4.03 (4H, s). *Anal.* Calcd for $C_{11}H_9Br_2NO_4$: C, 34.90; H, 2.39; N, 3.70. Found: 35.15; H, 2.50; N, 3.86.

7′-Bromo-5′-nitrospiro[[1.3]dioxolane-2,2′-indan]-4′-carbonitrile (27)——A mixture of **26** (23.7 g, 63 mmol) and CuCN (5.8 g, 65 mmol) in *N*-methylpyrrolidinone (60 ml) was heated at 105 °C with stirring for 1 h under a nitrogen atmosphere, and then poured into ice-water. Benzene was added to the mixture and the precipitate was filtered off. The filtrate was washed with water, dried, and concentrated to dryness. The residue was recrystallized from $CHCl_3$–Et_2O to give **27** (13.3 g, 66%), mp 145—147 °C. IR (KBr): 2210, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.08 (4H, s). *Anal.* Calcd for $C_{12}H_9BrN_2O_4$: C, 44.33; H, 2.79; N, 8.65. Found: C, 44.64; H, 2.86; N, 8.66.

4′-Aminomethyl-7′-bromo-5′-nitrospiro[[1.3]dioxolane-2,2′-indan] (28)——A 1 M BH_3–THF solution (100 ml) was added to a solution of **27** (14.5 g, 45 mmol) in anhydrous THF (100 ml) under a nitrogen atmosphere, and the mixture was stirred overnight. Water and then 10% HCl (60 ml) were added to the mixture in an ice-bath with stirring. Stirring was continued for 1 h, the THF was evaporated off, and the aqueous residue was washed with benzene, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to dryness. The residue was purified by silica gel (25 g) chromatography to give **28** (6.6 g, 45%), mp 105—106 °C (benzene–Et_2O). IR (KBr): 3400, 1520, 1350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.86 (2H, s), 4.06 (4H, s). *Anal.* Calcd for $C_{12}H_{13}BrN_2O_4$: C, 43.79; H, 3.98; N, 8.51. Found: C, 44.14; H, 3.91; N, 8.47.

Ethyl 7′-Bromo-5′-nitrospiro[[1.3]dioxolane-2,2′-indan]-4′-methylaminoacetate (29)——A solution of $BrCH_2COOEt$ (3.16 g, 19 mmol) in DMF (20 ml) was added to a mixture of **28** (6.2 g, 19 mmol) and Na_2CO_3 (1.0 g) in DMF (40 ml) at 80 °C with stirring. The mixture was stirred at the same temperature for 1 h and concentrated to dryness. The residue was treated with water and extracted with benzene. The extract was washed with water, dried, and concentrated to dryness. The residue was purified by silica gel (100 g) chromatography to give **29** (6.8 g, 87%), mp 63—65 °C (MeOH). IR (KBr): 1745, 1525, 1345 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, $J=7$ Hz), 3.24 (2H, s), 3.86 (4H, s), 4.03 (4H, s). *Anal.* Calcd for $C_{16}H_{19}BrN_2O_6$: C, 46.28; H, 4.61; N, 6.75. Found: C, 46.18; H, 4.66; N, 6.75.

Ethyl 5′-Aminospiro[[1.3]dioxolane-2,2′-indan]-4′-methylaminoacetate (30)——A solution of **29** (6.8 g, 16 mmol) in 1 N HCl (16 ml) and EtOH (300 ml) was treated with hydrogen in the presence of 10% Pd/charcoal (0.7 g). The catalyst was removed and the EtOH was evaporated off. The aqueous residue was washed with benzene, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to give **30** (5.2 g, quant.) as a pale brown oil, which was used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, $J=7$ Hz), 3.36 (2H, s), 3.73 (2H, s), 3.97 (4H, s).

Biological Method——Male Wistar-Imamichi rats weighing 250 g (8 weeks old) were used for the biological tests. The preparation of platelet-rich plasma and the platelet aggregation test *in vitro* and *ex vivo* were carried out by the methods described in the previous report.[3]

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