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Studies on 2-Oxoquinoline Derivatives as Blood Platelet Aggregation Inhibitors. IV.[1] Synthesis and Biological Activity of the Metabolites of 6-[4-(1-Cyclohexyl-1*H*-5-tetrazolyl)butoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (OPC-13013)

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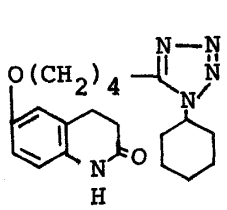
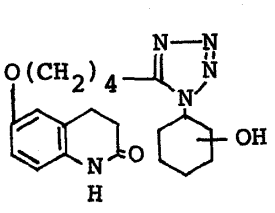
The metabolites of 6-[4-(1-cyclohexyl-1*H*-5-tetrazolyl)butoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (OPC-13013) (**1**), which has a potent inhibitory activity toward blood platelet aggregation and a cerebral vasodilating activity, were synthesized to confirm their structures and to examine their inhibitory activity. The structures of four major metabolites (**2a**—**c** and **3**) and a specific metabolite (**4**) found only in man were identified unequivocally by means of comparisons with the synthetic compounds. The inhibitory activity of 3,4-dehydro-OPC-13013 (**3**) was about three times higher than that of **1**, whereas two metabolites (**2a** and **2c**) had activity almost equal to that of **1**.

Keywords——6-[4-(1-cyclohexyl-1*H*-5-tetrazolyl)butoxy]-2-oxo-1,2,3,4-tetrahydroquinoline; metabolite; 1-(hydroxycyclohexyl)-5-(4-chlorobutyl)-1*H*-tetrazole; 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline; blood platelet aggregation inhibition

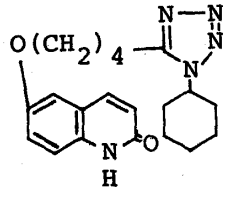
In the previous paper,[2] we described the synthesis and the inhibitory activity toward collagen- and adenosine diphosphate (ADP)- induced aggregation of rabbit platelets of 2-oxoquinoline derivatives having a tetrazole ring. After examination of the pharmacological and toxicological properties of these compounds, 6-[4-(1-cyclohexyl-1*H*-5-tetrazolyl)butoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (OPC-13013) (**1**) was selected as the most promising compounds, and is now under clinical trial. In metabolic studies, four major metabolites, OPC-13013 analogues (**2a**—**c**) hydroxylated on the cyclohexyl ring and 6-[4-(1-cyclohexyl-1*H*-5-tetrazolyl)butoxy]-1,2-dihydro-2-oxoquinoline (3,4-dehydro-OPC-13013) (**3**), were isolated from the biological fluids of rat, dog and man. 6-[4-(1-Cyclohexyl-1*H*-5-tetrazolyl)butoxy]-4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline (4-hydroxy-OPC-13013) (**4**) was also isolated as a minor but specific metabolite in man (Chart 1). In order to confirm the structures unequivocally, four metabolites (**2a**—**c** and **4**) were synthesized as described below. At the same time, all stereoisomers (**2d**—**f**) of **2a**—**c** were also synthesized, and these compounds were examined



1 (OPC-13013)



2a—**c** **a**: *cis*-4-OH **b**: *trans*-4-OH **c**: *cis*-3-OH



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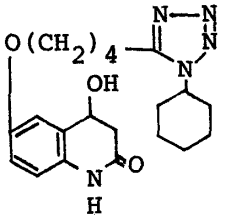

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Chart 1

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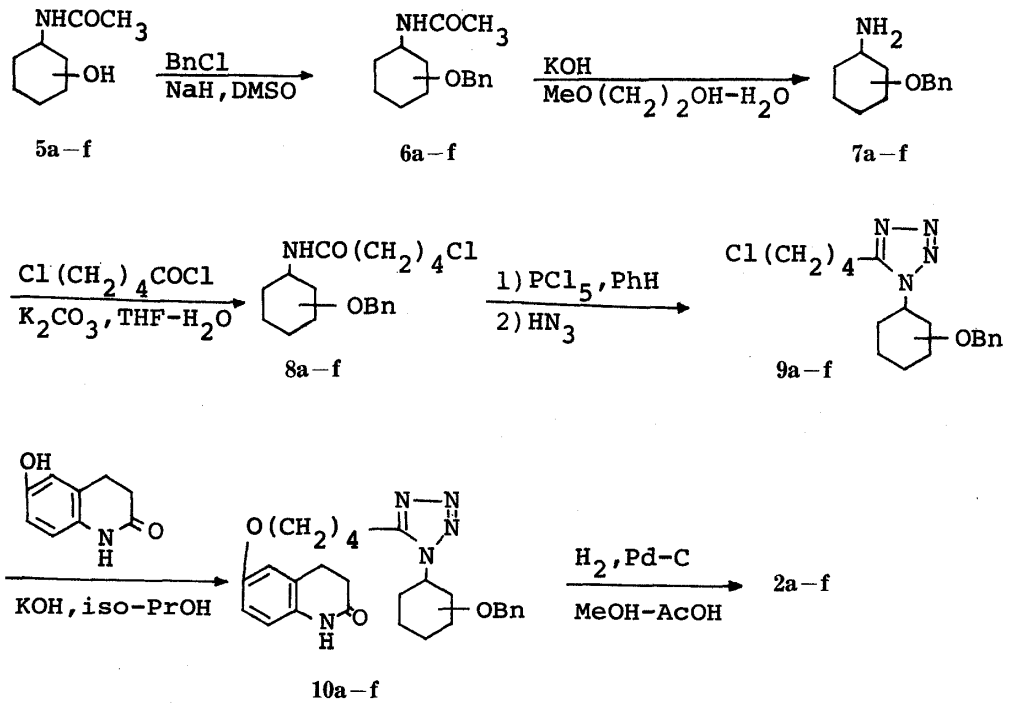
for inhibitory activity toward rabbit blood platelet aggregation. 3,4-Dehydro-OPC-13013 (**3**) was reported in the previous paper.[2]

Synthesis

For the confirmation of the structures of the metabolites (**2a**—**c**) hydroxylated on the cyclohexyl ring, six possible stereoisomers (**2a**—**f**) were synthesized as shown in Chart 2.

The hydroxy groups of the *N*-(hydroxycyclohexyl)acetamides (**5a**—**f**)[4] were selectively protected by benzylation as follows: **5a**—**f** were treated with benzyl chloride–barium oxide–barium hydroxide octahydrate[5] in *N*,*N*-dimethylformamide (DMF) at room temperature. However, the yields varied widely (3—81%) because the reactions were carried out under heterogeneous conditions and deacetylation occurred during prolonged treatment. Therefore, homogeneous and anhydrous reaction conditions using dimsyl sodium in dimethyl sulfoxide (DMSO) were applied. Benzylation with benzyl chloride (1—1.1 eq) and dimsyl sodium (1—1.1 eq) in DMSO at room temperature proceeded quite smoothly to give the benzyl ethers (**6a**—**f**) in good yields (Table I). Deacetylation of **6a**—**f** with potassium hydroxide gave the oily amino compounds (**7a**—**f**), which were converted into the valeramides (**8a**—**f**) by means of the Schotten–Baumann reaction in high yields (Tables II and III).

A benzen solution of **8a**—**f** was treated with phosphorus pentachloride (1—1.1 eq), followed by addition of hydrogen azide (*ca.* 2 eq). The solution was allowed to stand at room temperature overnight to give the tetrazoles (**9a**—**f**).[6] Among them, the oily compounds (**9c** and **d**) could not be distilled because of their thermal instability, but their structures were confirmed unambiguously by their nuclear magnetic resonance (NMR) spectra and mass spectra (MS) (Tables IV-1 and -2). Condensation of **9a**—**f** with 6-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline[7] in the presence of potassium hydroxide gave the 2-oxoquinolines (**10a**—**f**), followed by hydrogenolysis of the benzyl protecting group using 10% palladium charcoal



a : *cis*-4-OH
b : *trans*-4-OH
c : *cis*-3-OH
d : *trans*-3-OH
e : *cis*-2-OH
f : *trans*-2-OH

Bn=benzyl

Chart 2

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TABLE I. *N*-(Benzyloxycyclohexyl)acetamides

Compd. No.	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
					C	H	N
6a	61 (11)[a]	65.5—67	CH_2Cl_2–hexane	$C_{15}H_{21}NO_2$	72.84	8.56	5.66
					(72.85	8.47	5.71)
6b	74 (23)	147—147.5	EtOAc–iso-PrOH	$C_{15}H_{21}NO_2$	72.84	8.56	5.66
					(72.73	8.43	5.63)
6c	69 (24)	104—105	$CHCl_3$–petr.ether	$C_{15}H_{21}NO_2$	72.84	8.56	5.66
					(73.19	8.49	5.74)
6d	81 (3)	80—82	$CHCl_3$–petr.ether	$C_{15}H_{21}NO_2$	72.84	8.56	5.66
					(72.80	8.52	5.70)
6e	84 (30)	97.5—99	$CHCl_3$–petr.ether	$C_{15}H_{21}NO_2$	72.84	8.56	5.66
					(73.17	8.37	5.62)
6f	79 (81)	85—85.5	$(iso\text{-}Pr)_2O$	$C_{15}H_{21}NO_2$	72.84	8.56	5.66
					(72.69	8.47	5.81)

a) Yields in parentheses are values obtained using BaO–$Ba(OH)_2 \cdot 8H_2O$ as a base.

TABLE II. *O*-Benzyl-aminocyclohexanols

Compd. No.	Yield (%)	bp (°C) (mmHg)
7a	89	123—125 (1)
7b	83	140—142 (3)
7c	88	144—146 (3)
7d	89	124—126 (4)
7e	76	115—118 (1)
7f	84	155—157 (13)

TABLE III. *N*-(Benzyloxycyclohexyl)-5-chlorovaleramides

Compd. No.	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
					C	H	N
8a	94	67—68	$CHCl_3$–petr.ether	$C_{18}H_{26}ClNO_2$	66.75	8.10	4.33
					(66.49	8.10	4.24)
8b	80	108—109.5	$CHCl_3$–petr.ether	$C_{18}H_{26}ClNO_2$	66.75	8.10	4.33
					(66.41	8.07	4.31)
8c	93	86—86.5	CH_2Cl_2–hexane	$C_{18}H_{26}ClNO_2$	66.75	8.10	4.33
					(66.80	8.19	4.26)
8d	98	65.5—68.5	Ether–hexane	$C_{18}H_{26}ClNO_2$	66.75	8.10	4.33
					(66.45	7.91	4.43)
8e	90	68—69	$CHCl_3$–petr.ether	$C_{18}H_{26}ClNO_2$	66.75	8.10	4.33
					(66.70	7.91	4.36)
8f	92	125—126.5	$CHCl_3$–petr.ether	$C_{18}H_{26}ClNO_2$	66.75	8.10	4.33
					(66.53	7.96	4.32)

in methanol–acetic acid at 60—70 °C to give the six hydroxylated isomers (**2a**—**f**) (Tables V and VI).

4-Hydroxy-OPC-13013 (**4**), hydroxylated at the 4-position on the 2-oxoquinoline ring,

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TABLE IV-1. 1-(Benzyloxycyclohexyl)-5-(4-chlorobutyl)-1*H*-tetrazoles

Compd. No.	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
					C	H	N
9a	94	80.5—81.5	CH_2Cl_2–hexane	$C_{18}H_{25}ClN_4O$	61.97	7.22	16.06
					(61.83	7.19	16.20)
9b	94	102.5—103.5	iso-PrOH	$C_{18}H_{25}ClN_4O$	61.97	7.22	16.06
					(61.82	7.17	16.39)
9e	96	76—78	$CHCl_3$–petr.ether	$C_{18}H_{25}ClN_4O$	61.97	7.22	16.06
					(61.86	7.19	16.02)
9f	53	78.5—79.5	$CHCl_3$–petr.ether	$C_{18}H_{25}ClN_4O$	61.97	7.22	16.06
					(61.86	7.08	16.04)

TABLE IV-2. 1-(Benzyloxycyclohexyl)-5-(4-chlorobutyl)-1*H*-tetrazoles

Compd. No.	Yield (%)	^{1}H-NMR $\delta^{a)}$ ($CDCl_3$)
9c	94	1.20—2.52 (12H, m), 2.86 (2H, t, 7.0), 3.52 (1H, m), 3.60 (2H, t, 6.0), 4.16 (1H, m), 4.59 (2H, s), 7.33 (5H, s)
9d	96	1.22—2.22 (12H, m), 2.83 (2H, t, 7.0), 3.55 (2H, t, 6.0), 3.99 (1H, m), 4.56 (1H, m), 4.49 and 4.61 (1H each, ABq, 12.0), 7.35 (5H, s)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in parentheses. Tetramethylsilane was used as an internal standard.

TABLE V. 6-{4-[1-(Benzyloxycyclohexyl)-1*H*-5-tetrazolyl]butoxy}-2-oxo-1,2,3,4-tetrahydroquinolines

Compd. No.	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
					C	H	N
10a	66	149—151	$CHCl_3$–petr.ether	$C_{27}H_{33}N_5O_3$	68.19	6.99	14.73
					(68.14	6.74	14.92)
10b	74	146.5—148	$CHCl_3$–ether	$C_{27}H_{33}N_5O_3$	68.19	6.99	14.73
					(68.06	6.86	14.79)
10c	64	148—151	CH_2Cl_2–EtOAc	$C_{27}H_{33}N_5O_3$	68.19	6.99	14.73
					(68.14	7.12	14.66)
10d	41	94—96	$CHCl_3$–hexane	$C_{27}H_{33}N_5O_3$	68.19	6.99	14.73
					(68.00	7.06	14.80)
10e	36	133—135	$CHCl_3$–petr.ether	$C_{27}H_{33}N_5O_3$	68.19	6.99	14.73
					(67.89	6.96	14.53)
10f	51	117—118	$CHCl_3$–ether	$C_{27}H_{33}N_5O_3$	68.19	6.99	14.73
					(68.19	7.01	14.70)

was next synthesized by the pathway shown in Chart 3. The parent compound, 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline, has already been synthesized by Einhorn,[8)] but it was reported to be easily dehydrated at high temperature, or under acidic or basic conditions to afford 1,2-dihydro-2-oxoquinoline. Therefore, in our synthesis of **4**, construction of the pyridine ring was carried out in the final step. 5-Hydroxy-2-nitrobenzaldehyde (**11**) was

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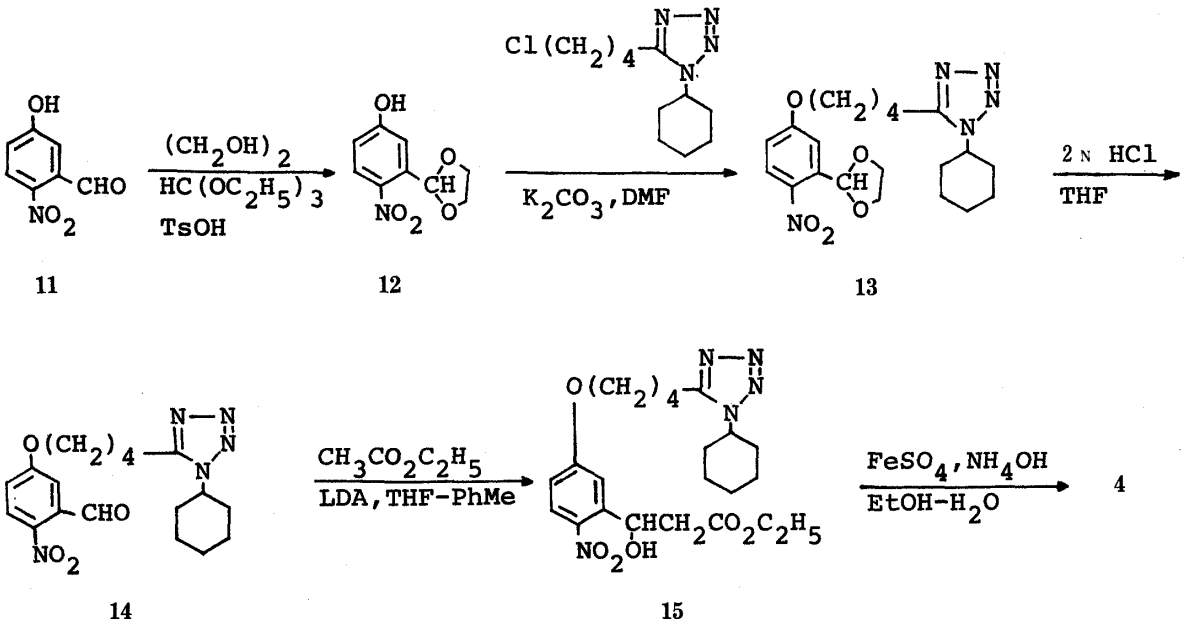
TABLE VI. 6-{4-[1-(Hydroxycyclohexyl)-1*H*-5-tetrazolyl]butoxy}-2-oxo-1,2,3,4-tetrahydroquinolines

Compd. No.	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
					C	H	N
2a	88	195—196.5	MeOH–H_2O	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17
					(62.06	7.08	18.40)
2b	93	202.5—204	MeOH–H_2O	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17
					(62.28	7.14	18.35)
2c	87	154.5—156.5	MeOH–H_2O	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17
					(62.32	7.16	18.15)
2d	86	157.5—158.5	$CHCl_3$–ether	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17
					(62.52	7.19	18.20)
2e	80	158—160	EtOH–H_2O	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17
					(62.34	7.06	17.84)
2f	82	176—177	EtOH–H_2O	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17
					(61.93	6.80	17.82)

protected as the acetal (**12**) in the usual manner, and **12** was condenced with 5-(4-chlorobutyl)-1-cyclohexyl-1*H*-tetrazole[2] in the presence of potassium carbonate in DMF, followed by removal of the acetal group with 2 N hydrochloric acid to give the aldehyde (**14**) in a good yield. The cross aldol reaction of **14** with the lithium enolate of ethyl acetate readily gave the *β*-hydroxy ester (**15**). Finally, **15** was reduced with ferrous sulfate in ammonia water–ethanol at 50—60 °C for 1.5 h according to Einhorn's method, followed by purification on a silica gel column to give 4-hydroxy-OPC-13013 (**4**) in 48% yield.



11 12 13

14 15

Chart 3

The structures of the metabolites (**2a—c**, **3** and **4**) were identical with those of the corresponding synthetic compounds on the basis of NMR, MS and high performance liquid chromatographic comparisons.

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TABLE VII. Inhibitory Activities of the OPC-13013 Metabolites

Compd. No.	Inhibition (IC_{50}, μM) ADP	Collagen
1 (OPC-13013)	24	32
2a	23	33
2b	59	78
2c	25	37
2d	56	107
2e	25	44
2f	23	38
3	9.7	7.3
4	59	100

Biological Results

The inhibitory activity toward blood platelet aggregation was measured *in vitro* by the same method as described in a previous paper[9] using rabbit citrated platelet-rich plasma. The results are shown in Table VII. 3,4-Dehydro-OPC-13013 (**3**) was about three times more active than the mother compound (OPC-13013) (**1**). However, 4-hydroxy-OPC-13013 (**4**) was less active. Among the hydroxylated metabolites on the cyclohexyl ring, the *cis*-isomers (**2a** and **2c**) had activity almost equal to that of **1**.

Experimental

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were measured on a Hitachi 215 spectrophotometer. NMR spectra were recorded on Varian EM-390 or Bruker WH-400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. MS spectra were obtained on a Varian MAT-312 instrument.

Preparation of 6a—f. *N*-(*trans*-4-Benzyloxycyclohexyl)acetamide (6b)——**5b** (1.2 g, 7.6 mmol) was added to a stirred dimsyl sodium solution prepared from 60% NaH (0.32 g, 8.0 mmol) and DMSO (13 ml) at room temperature under argon. After 1.5 h, benzyl chloride (0.95 ml, 7.6 mmol) was added. The stirring was continued for an additional 1 h, and then the pale brown solution was poured into ice-water. The solid collected by filtration was washed with H_2O and recrystallized from EtOAc–isopropyl ether to give colorless plates of **6b** (1.4 g, 74%), mp 147—147.5 °C. NMR δ: 0.88—1.65 (4H, m), 1.90 (3H, s), 1.80—2.21 (4H, m), 3.30 (1H, m), 3.73 (1H, m), 4.51 (2H, s), 5.97 (1H, d, J=8.0 Hz), 7.28 (5H, s). IR ν(KBr): 3320, 2945, 2860, 1640, 1558 cm^{-1}. The elemental analysis data are shown in Table I.

Compounds **6a** and **6c—f** were obtained by the same procedure as described for **6b**; the yields and physical data are listed in Table I.

Preparation of 7a—f. *trans*-*O*-Benzyl-4-aminocyclohexanol (7b)——A mixture of **6b** (1.4 g, 5.7 mmol), 85% KOH (2.4 g, 43 mmol), 2-methoxyethanol (14 ml) and H_2O (1.5 ml) was refluxed for 20 h. After evaporation of the solvent, CH_2Cl_2 and H_2O were added to the residue. The CH_2Cl_2 layer was washed with H_2O and dried over Na_2SO_4, and the solvent was removed. The brown residue was distilled *in vacuo* to afford **7b** as a colorless oil (0.96 g, 83%), bp 140—142 °C (3 mmHg). NMR δ: 0.70—2.15 (10H, m), 2.59 (1H, m), 3.24 (1H, m), 4.42 (2H, s), 7.21 (5H, s). MS *m/e*: 205 (M^+, 2%), 188 (2), 149 (9), 114 (7), 91 (100), 56 (75).

Compounds **7a** and **7c—f** were obtained by the same procedure as described for **7b**; the yields and boiling points are shown in Table II.

Preparation of 8a—f. *N*-(*trans*-4-Benzyloxycyclohexyl)-5-chlorovaleramide (8b)——5-Chlorovaleryl chloride (3.72 g, 24 mmol) was added in portions to a stirred mixture of **7b** (5.0 g, 24 mmol), K_2CO_3 (4.14 g, 30 mmol), tetrahydrofuran (THF) (50 ml) and H_2O (30 ml) with ice-cooling, and the reaction mixture was stirred at room temperature for 0.5 h. After evaporation of the THF, the residue was extracted with CH_2Cl_2. The extract was washed with H_2O and 1 N HCl, and dried over Na_2SO_4. After evaporation of the solvent *in vacuo*, the solid was recrystallized from $CHCl_3$–petr. ether to give **8b** as colorless needles (6.4 g, 80%), mp 108—109.5 °C. NMR δ: 0.94—2.24 (14H, m), 3.32 (1H, m), 3.55 (2H, t, J=6.5 Hz), 3.78 (1H, m), 4.54 (2H, s), 5.24 (1H, d, J=7.5 Hz), 7.33 (5H, s). IR ν(KBr): 3325, 2940, 2860, 1630, 1550 cm^{-1}. The elemental analysis data are shown in Table III.

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Compounds **8a** and **8c**—**f** were obtained by the same procedure as described for **8b**; the yields and physical data are listed in Table III.

Preparation of 9a—f. 1-(*trans*-4-Benzyloxycyclohexyl)-5-(4-chlorobutyl)-1*H*-tetrazole (9b)——PCl_5 (4.2 g, 20 mmol) was added in three portions to a stirred solution of **8b** (6.3 g, 19 mmol) in benzene (60 ml) keeping the temperature below 30 °C with water-cooling, and the clear solution was stirred at 30 °C for 1 h, followed by the addition of a 1.6 M benzene solution (25 ml, 40 mmol) of HN_3. The resulting solution was allowed to stand overnight. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed sufficiently with H_2O, and dried over Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue was recrystallized from iso-PrOH to give **9b** as colorless needles (6.3 g, 94%), mp 102.5—103.5 °C. NMR δ: 1.20—2.50 (12H, m), 2.86 (2H, t, J=6.5 Hz), 3.50 (1H, m), 3.56 (2H, t, J=5.5 Hz), 4.18 (1H, m), 4.56 (2H, s), 7.31 (5H, s). IR ν(KBr): 2945, 2870, 1515, 1500 cm^{-1}. The elemental analysis data are shown in Table IV-1.

Compounds **9a** and **9c**—**f** were obtained by the same procedure as described for **9b**; the yields and physical data are listed in Tables IV-1 and -2.

Preparation of 10a—f. 6-{4-[1-(*trans*-4-Benzyloxycyclohexyl)-1*H*-5-tetrazolyl]butoxy}-2-oxo-1,2,3,4-tetrahydroquinoline (10b)——A mixture of 6-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline (3.3 g, 20 mmol), **9b** (7.5 g, 22 mmol), and 85% KOH (1.6 g, 24 mmol) in iso-PrOH (100 ml) was refluxed with stirring for 18 h, then cooled to room temperature. The yellowish solid collected by filtration was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with aqueous NaOH and H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The pale brown residue was purified on a silica gel column eluting with $CHCl_3$–MeOH (50 : 1) to give **10b** as a colorless solid (7.0 g, 73%), which was recrystallized from $CHCl_3$–ether to afford colorless needles, mp 146.5—148 °C. NMR δ: 1.30—2.38 (12H, m), 2.59 (2H, br t, J=7.5 Hz), 2.93 (4H, br t, J=7.5 Hz), 3.53 (1H, m), 3.98 (2H, t, J=7.0 Hz), 4.17 (1H, m), 4.59 (2H, s), 6.66—6.76 (3H, m), 7.35 (5H, s), 9.08 (1H, s). IR ν(KBr): 3201, 3068, 2955, 2875, 1668, 1506 cm^{-1}. The elemental analysis data are shown in Table V.

Compounds **10a** and **10c**—**f** were obtained by the same procedure as described for **10b**; the yields and physical data are listed in Table V.

Preparation of 2a—f. 6-{4-[1-(*trans*-4-Hydroxycyclohexyl)-1*H*-5-tetrazolyl]-butoxy}-2-oxo-1,2,3,4-tetrahydroquinoline (2b)——A solution of **10b** (0.80 g) in 1 : 1 MeOH–AcOH (80 ml) was hydrogenated in the presence of 10% Pd–C (0.4 g) at 60—70 °C and 1.5—2.0 atm for 8 h. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* and passed through a short silica gel column eluting with $CHCl_3$–MeOH (15 : 1) to afford a colorless solid, which was recrystallized from EtOH–H_2O to give **2b** as colorless needles (0.60 g, 93%), mp 202.5—204 °C. NMR (400 MHz) δ: 1.47 (2H, m), 1.75—2.26 (10H, m), 2.60 (2H, br t, J=7.5 Hz), 2.92 (2H, t, J=7.5 Hz), 2.93 (2H, br t, J=7.5 Hz), 3.83 (1H, tt, J=10.5, 4.5 Hz), 3.98 (2H, t, J=6.0 Hz), 4.14 (1H, tt, J=10.5, 4.5 Hz), 6.62 (1H, d, J=8.5 Hz), 6.69 (1H, dd, J=8.5, 2.5 Hz), 6.72 (1H, d, J=2.5 Hz), 7.32 (1H, s). IR ν(KBr): 3400, 3208, 3060, 2952, 2875, 1660, 1508 cm^{-1}. MS *m/e*: 385 (M^+, 1%), 244 (1), 223 (16), 207 (3), 163 (7), 134 (7), 125 (100). The elemental analysis data are shown in Table VI.

Compounds **2a** and **2c**—**f** were obtained by the same procedure as described for **2b**; the yields and physical data are listed in Table VI.

5-Hydroxy-2-nitrobenzaldehyde Ethylene Acetal (12)——A mixture of **11** (10 g, 60 mmol), triethylorthoformate (11 g, 74 mmol), ethylene glycol (50 ml), and TsOH (1 g) was refluxed with stirring for 1 h. The solution was extracted with $CHCl_3$, and the extract was washed with brine. After evaporation of the solvent, purification on a silica gel column eluting with $CHCl_3$–MeOH (100 : 1) gave **12** as a yellow oil (8.3 g, 66%). NMR δ: 3.95 (4H, s), 6.52 (1H, s), 6.78 (1H, dd, J=9.0, 3.0 Hz), 7.16 (1H, d, J=3.0 Hz), 7.92 (1H, d, J=9.0 Hz). MS *m/e*: 210 ($M^+ - 1$, 4%), 194 (35), 164 (100), 120 (57), 107 (56), 73 (64).

5-[4-(1-Cyclohexy-1*H*-5-tetrazolyl)butoxy]-2-nitrobenzaldehyde Ethylene Acetal (13)——A solution of 5-(4-chlorobutyl)-1-cyclohexyltetrazole (2.5 g, 10 mmol) in DMF (30 ml) was added to a stirred mixture of **12** (2.1 g, 10 mmol) and K_2CO_3 (1.5 g, 11 mmol) in DMF (20 ml) at 120 °C. After 6 h, the solvent was removed *in vacuo*, the residue was extracted with $CHCl_3$, the extract was washed with brine, and then the solvent was evaporated off *in vacuo*. Chromatography on silica gel with $CHCl_3$ as an eluent gave **13** as a yellow oil (3.6 g, 87%). NMR δ: 1.10—2.20 (14H, m), 2.94 (2H, t, J=7.0 Hz), 4.06 (4H, s), 4.10 (1H, m), 4.13 (2H, t, J=6.0 Hz), 6.65 (1H, s), 6.90 (1H, dd, J=9.0, 3.0 Hz), 7.28 (1H, d, J=3.0 Hz), 8.02 (1H, d, J=3.0 Hz). MS *m/e*: 417 (M^+, 3%), 297 (9), 207 (10), 178 (13), 125 (100).

5-[4-(1-Cyclohexyl-1*H*-5-tetrazolyl)butoxy]-2-nitrobenzaldehyde (14)——A stirred solution of **13** (9.0 g) in THF (70 ml) was treated with 2 N HCl (20 ml) at 50 °C. After 1 h, the solution was concentrated *in vacuo*. The residue was extracted with $CHCl_3$, the extract was washed with aqueous $NaHCO_3$, and the solvent was evaporated off *in vacuo*. Purification on a silica gel column eluting with EtOAc–hexane (1 : 1) gave **14** as a yellow solid (6.9 g, 86%), which was recrystallized from EtOAc–hexane to afford yellow needles, mp 92—94 °C. *Anal.* Calcd for $C_{18}H_{23}N_5O_4$: C, 57.90; H, 6.21; N, 18.76. Found: C, 57.56; H, 6.06; N, 18.76. NMR δ: 1.10—2.20 (14H, m), 2.94 (2H, t, J=7.0 Hz), 4.10 (1H, m), 4.18 (2H, t, J=6.0 Hz), 7.14 (1H, dd, J=9.0, 3.0 Hz), 7.30 (1H, d, J=3.0 Hz), 8.16 (1H, d, J=9.0 Hz), 10.50 (1H, s). IR ν(KBr): 2960, 1702, 1600 cm^{-1}.

Ethyl 3-{5-[4-(1-Cyclohexyl-1*H*-5-tetrazolyl)butoxy]-2-nitrophenyl}-3-hydroxypropionate (15)——A 1.4 M hexane solution (8.0 ml, 11 mmol) of *n*-BuLi was added to a solution of diisopropylamine (1.0 g, 10 mmol) in THF

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(20 ml) under argon while the temperature was kept below 20 °C by water-cooling. After 0.5 h, the solution was cooled to −60 °C, and EtOAc (1.0 ml, 10 mmol) was added at the same temperature. Then a solution of **14** (2.7 g, 7.2 mmol) in toluene (10 ml) was added, and the reaction mixture was allowed to warm to room temperature. After acidification of the mixture with 5% HCl, $CHCl_3$ was added. The $CHCl_3$ solution was washed with brine and aqueous $NaHCO_3$, dried over K_2CO_3, and then evaporated *in vacuo*. The residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (50 : 1) to give **15** as a yellow oil (3.0 g, 90%). NMR δ: 1.27 (3H, t, J=7.5 Hz), 1.20—2.26 14H, m), 2.56 (1H, dd, J=16.0, 9.0 Hz), 2.92 (1H, dd, J=16.0, 3.0 Hz), 2.93 (2H, t, J=7.0 Hz), 4.12 (2H, br s), 4.15 (2H, t, J=6.0 Hz), 4.22 (2H, q, J=7.5 Hz), 5.79 (1H, dd, J=9.0, 3.0 Hz), 6.83 (1H, dd, J=9.0, 3.0 Hz), 7.38 (1H, d, J=3.0 Hz), 8.05 (1H, d, J=9.0 Hz). MS *m/e*: 461 (M^+, 0.7%), 444 (20), 397 (2), 207 (17), 125 (100). IR ν (neat): 3420, 2960, 2880, 1742, 1621, 1615, 1598, 1588, 1522 cm^{-1}.

6-[4-(1-Cyclohexyl-1*H*-5-tetrazolyl)butoxy]-4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline (4)——A solution of **15** (3.0 g) in EtOH (50 ml) and 28% NH_4OH (12 ml) were added to a stirred solution of $FeSO_4 \cdot 7H_2O$ (28 g) in H_2O (150 ml) at room temperature. After being stirred at 50—60 °C for 1.5 h, the reaction mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was purified on a silica gel column eluting with $CHCl_3$–MeOH (30 : 1) to give a solid, which was recrystallized from $CHCl_3$–Et_2O to give **4** (1.2 g, 48%) as colorless needles, mp 109.5—112 °C. *Anal.* Calcd for $C_{20}H_{27}N_5O_3$: C, 62.32; H, 7.06; N, 18.17. Found: C, 62.01; H, 7.32; N, 17.89. NMR (400 MHz) δ: 1.18—2.10 (14H, m), 2.82 (1H, dd, J=17.0, 5.0 Hz), 2.86 (1H, dd, J=17.0, 5.0 Hz), 2.91 (2H, t, J=7.5 Hz), 4.00 (2H, t, J=6.0 Hz), 4.12 (1H, tt, J=10.5, 4.5 Hz), 4.92 (1H, t, J=5.0 Hz), 6.71 (1H, d, J=9.0 Hz), 6.77 (1H, dd, J=9.0, 3.0 Hz), 6.95 (1H, d, J=3.0 Hz), 8.08 (1H, br s). MS *m/e*: 367 ($M^+ - 18$, 2%), 243 (1), 207 (24), 161 (10), 125 (100). IR ν (KBr): 3355, 3250, 2915, 2848, 1664, 1503 cm^{-1}.

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