Piperazinealkanol Ester Derivatives of Indomethacin as Dual Inhibitors of 5-Lipoxygenase and Cyclooxygenase

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Piperazinealkanol ester derivatives of indomethacin were prepared and tested for inhibitory activities against 5-lipoxygenase (5-LO) and cyclooxygenase (CO). They inhibited 5-hydroxyeicosatetraenoic acid (5-HETE) formation by the cytosol of guinea pig polymorphonuclear leukocytes and thromboxane B_2 (TXB_2) formation by washed rabit platelet suspension. Of the test compounds, 2-[4-(2-hydroxyethyl)-1-piperazinyl]-1-phenylethyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetate dimaleate (II-8) was found to be the most active dual inhibitor of 5-LO and CO, and its inhibitory potency was higher than that of 2-[4-(3-hydroxypropyl)-1-piperazinyl]-ethyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl]-3-indolylacetate (CR-1015) (I), the lead compound.

Keywords piperazinealkanol ester derivative; indomethacin; dual inhibitor; 5-lipoxygenase; cyclooxygenase; 2-[4-(3-hydroxypropyl)-1-piperazinyl]-ethyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl]-3-indolylacetate

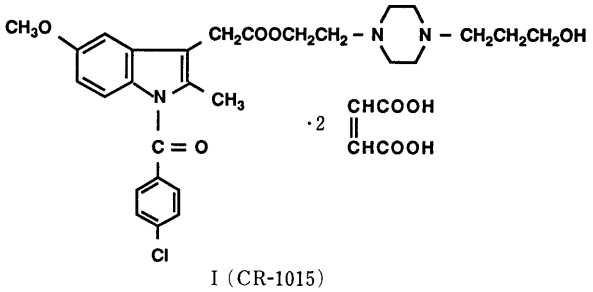
Non-steroidal anti-inflammatory drugs (NAIDs) are used in the treatment of a number of arthritic conditions, including rheumatoid arthritis and osteoarthritis. NAIDs reduce the pain and swelling associated with arthritis by blocking the production of prostaglandins from arachidonic acid by cyclooxygenase (CO).[1] Since prostaglandins are cytoprotective, their decreased production is implicated in the formation of gastric ulcers, an undesirable side effect of the chronic use of NAIDs.[2] Inhibiting CO may also increase the conversion of arachidonic acid to proinflammatory leukotrienes catalyzed by 5-lipoxygenase (5-LO). Leukotrienes are implicated in the pathogenesis of inflammatory disease[3] and also of the acute gastric ulceration induced by NAIDs.[4] It has been postulated that dual inhibitors possessing inhibitory activity on both CO and 5-LO would have improved efficacy and reduced side effects in comparison with selective CO inhibitors, so this approach could be valuable in the development of safer second-generation NAIDs.[5]

We found that 2-[4-(3-hydroxypropyl)-1-piperazinyl]-ethyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl]-3-indolylacetate (CR-1015) (I), which was identified in a biotransformation study of 3-[4-[2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetoxy]etyl]-1-piperazinyl]-propyl 4-benzamido-*N*,*N*-dipropylglutaramate dimaleate (CR-604), developed as an anti-inflammatory drug, inhibits 5-HETE formation by cytosol of guinea pig polymorphonuclear leukocytes and thromboxane B_2 (TXB_2) formation by washed rabbit platelet suspension.[6] We thus continued chemical modification studies of CR-1015 in order to find a more effective dual inhibitor of 5-LO and CO. Among the compounds tested, II-8 is the most active dual inhibitor of 5-LO and CO, and its potency was higher than that of I (CR-1015), the lead compound.

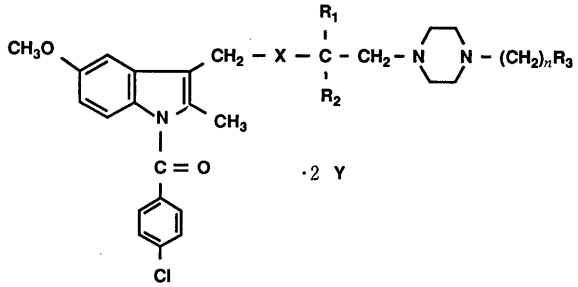
In this article, we report on the synthesis and biological activities of piperadinealkanol ester derivatives of indomethacin.

Synthesis

Compounds II-1—7 were prepared as shown in Chart 1. Monosubstituted piperazines III-1—3 were alkylated with chloride compounds to afford disubstituted piper-



I (CR-1015)



X : COO ; R_3 : OH ; Y : maleic acid
II-1 : $R_1=CH_3$; $R_2=H$; $n=5$
II-2 : $R_1=CH_3$; $R_2=H$; $n=6$
II-3 : R_1, $R_2=CH_3$; $n=3$
II-4 : $R_1=C_6H_5$; $R_2=H$; $n=10$
II-8 : $R_1=C_6H_5$; $R_2=H$; $n=2$
II-9 : $R_1=C_6H_5$; $R_2=H$; $n=3$
II-10 : $R_1=CH_3$; $R_2=H$; $n=3$
X : COO ; R_3 : $COOC(CH_3)_3$; Y : maleic acid
II-5 : $R_1=CH_3$; $R_2=H$; $n=2$
X : COO ; R_3 : $CH=CHCH_3$; Y : maleic acid
II-6 : $R_1=CH_3$; $R_2=H$; $n=1$
X : COO ; R_3 : COOH ; Y : HCl
II-7 : $R_1=CH_3$; $R_2=H$; $n=2$
X : CONH ; $R_3=OH$; Y : maleic acid
II-11 : R_1, $R_2=H$; $n=3$

Fig. 1. Piperazinealkanol Ester and Amido Derivatives of Indomethacin

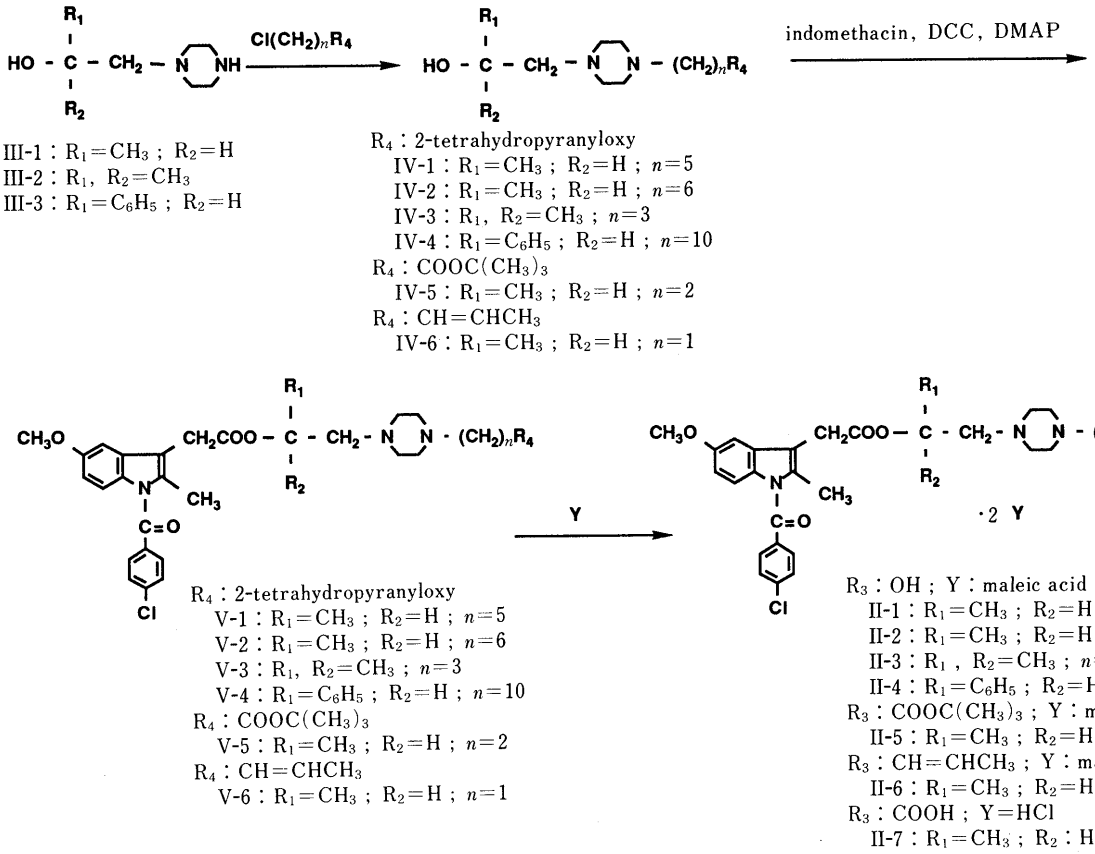


Chart 1

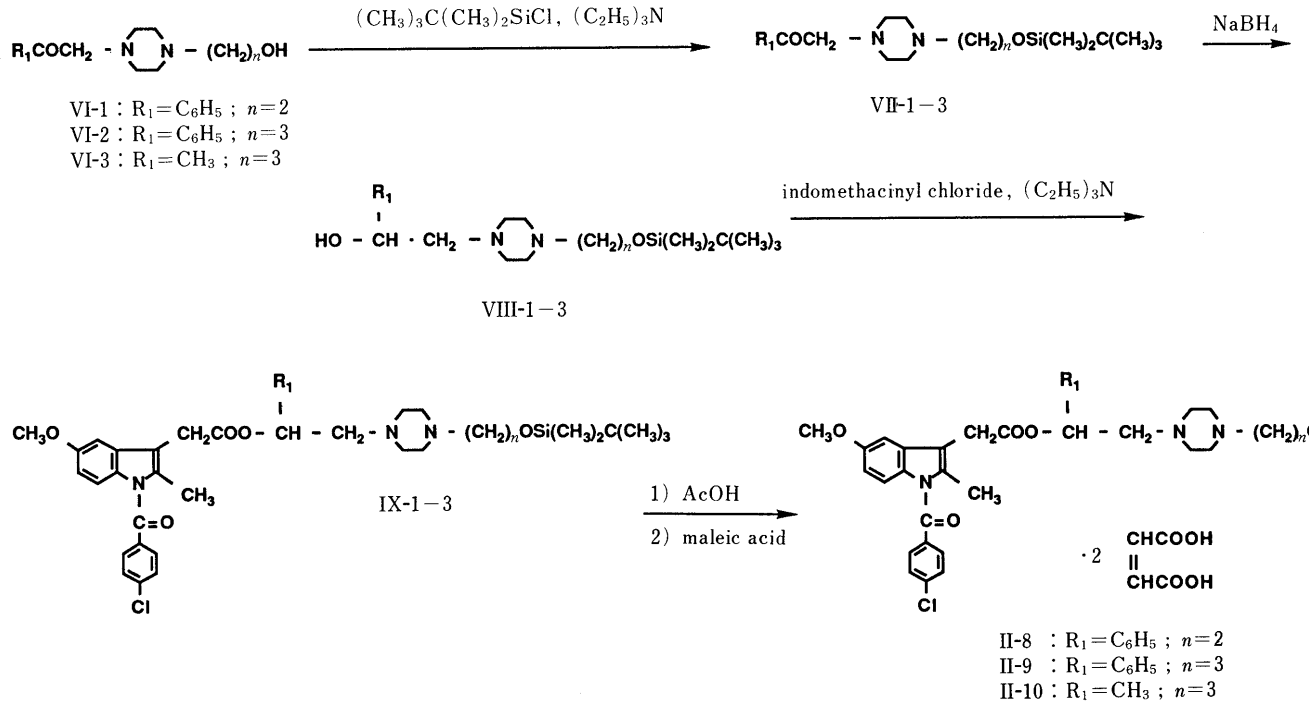
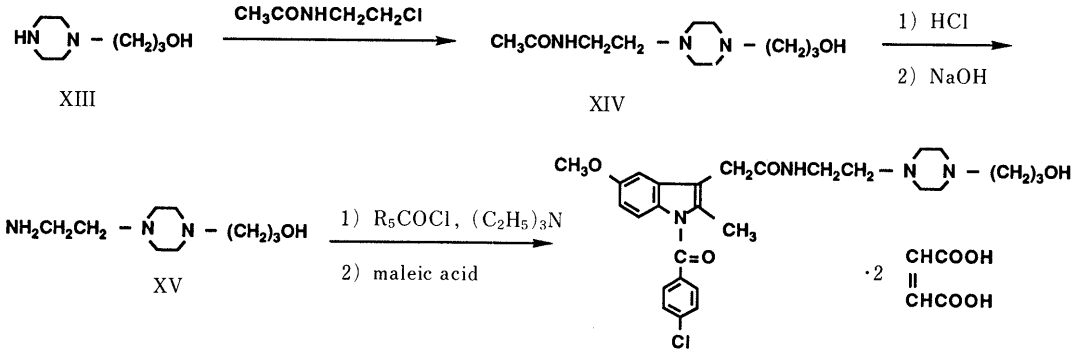


Chart 2

azines IV-1—6. Compounds IV-1—6 were treated with 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid (indomethacin) and 1,3-dicyclohexylcarbodiimide (DCC) in the presence of a catalytic amount of dimethylaminopyridine (DMAP) according to the method of Neises and Steglich[7] to give the esters V-1—6. Compounds V-1—4 were deprotected with maleic acid to give II-1—4 as the dimaleates. Compound V-5 was deprotected with concentrated HCl to give II-7 as the dihydrochloride . On the other hand, compounds V-5,6

were converted to the dimaleates II-5,6.

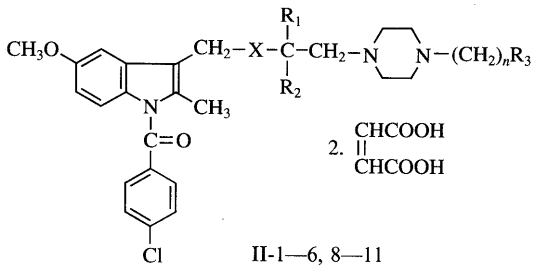
Compounds II-8—10 were prepared as shown in Chart 2. Disubstituted piperazines having a hydroxy moiety (VI-1—3) were treated with *tert*-butyldimethylsilyl chloride and triethylamine according to a modification of the method of Chaudhary and Hernandez[8] to give the silyl ethers VII-1—3. Compounds VII-1—3 were reduced with sodium borohydride to give secondary alcohol derivatives VIII-1—3. Compounds VIII-1—3 were treated with 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetyl chloride (indomethacinyl chloride) and triethylamine to give esters protected as the silyl ethers IX-1—3. Compounds



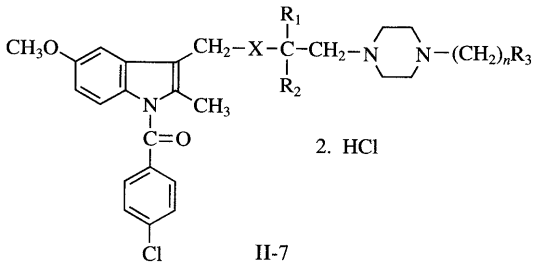
XIII XIV XV II-11

Chart 3

TABLE I. Physical and Biological Data for II-1—11



II-1—6, 8—11



II-7

Compd. No.	R_1	R_2	n	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibitory activities, IC_{50} (μM) 5-LO	CO
X: COO, R_3: OH											
II-1	CH_3	H	5	18[a]	168—170	$C_{39}H_{48}ClN_3O_{13}$	58.39 (57.92)	6.03 5.95	5.24 5.21)	6.2	22.8
II-2	CH_3	H	6	25[a]	158—159	$C_{40}H_{50}ClN_3O_{13}$	58.86 (58.73)	6.17 6.23	5.15 5.10)	4.7	41.2
II-3	CH_3	CH_3	3	34[a]	132—136	$C_{38}H_{46}ClN_3O_{13}$	57.90 (57.62)	5.88 6.09	5.33 4.98)	4.7	22.3
II-4	C_6H_5	H	10	28[a]	149—151	$C_{49}H_{60}ClN_3O_{13}$	62.98 (62.77	6.47 6.61	4.50 4.36)	0.9	100
II-8	C_6H_5	H	2	33[b]	158—159	$C_{41}H_{44}ClN_3O_{13}$ ·1/2H_2O	59.24 (59.19	5.46 5.52	5.05 4.81)	1.7	9.2
II-9	C_6H_5	H	3	38[b]	152—153	$C_{42}H_{46}ClN_3O_{13}$	60.17 (60.10	5.50 5.50	4.78 5.03)	1.6	20.4
II-10	CH_3	H	3	38[b]	164—166	$C_{37}H_{44}ClN_3O_{13}$	57.40 (57.11	5.73 5.76	5.43 5.57)	6.9	30.6
X: COO, R_3: $COOC(CH_3)_3$											
II-5	CH_3	H	2	72[a]	179—181	$C_{41}H_{50}ClN_3O_{14}$	58.33 (58.37	5.97 5.90	4.98 4.99)	6.1	36.9
X: COO, R_3: COOH											
II-7	CH_3	H	2	70[a]	194—198	$C_{29}H_{36}Cl_3N_3O_6$	55.38 (55.49	5.77 5.87	6.68 6.70)	49.6	107.4
X: COO, R_3: $CH=CHCH_3$											
II-6	CH_3	H	1	56[c]	173—177	$C_{38}H_{44}ClN_3O_{12}$	59.26 (59.38	5.76 5.66	5.46 5.38)	5.0	15.8
X: CONH, R_3: OH											
II-11	H	H	3	25[d]	146—147	$C_{36}H_{43}ClN_4O_{12}$ ·1/2H_2O	56.29 (56.38	5.77 5.56	7.29 7.38)	41.3	16.7
I (CR-1015)										17.3	38.5

a) Based on V. *b*) Based on IX. *c*) Based on IV. *d*) Based on XV.

TABLE II. NMR Data for II-1—11

Compd. No	^{1}H-NMR (DMSO-d_6) δ ppm
II-1	1.1—1.8 (6H, m, 3×CH_2), 1.17 (3H, d, J=6 Hz, CH_3), 2.1—3.3 (12H, m, 2×N–CH_2 and piperazine protons), 2.25 (3H, s, CH_3), 3.35 (2H, t, J=7 Hz, CH_2O), 3.47 (1H, br s, OH), 3.78 (5H, s, CH_3O and CH_2COO), 4.8—5.2 (1H, m, CHO), 6.17 (4H, s, 2×COCH=CHCO), 6.6—7.1 (3H, m, ArH), 7.67 (4H, s, ArH), 10.1 (4H, br s, 4×COOH)
II-2	1.17 (3H, d, J=6 Hz, CH_3), 1.0—1.8 (8H, m, 4×CH_2), 2.26 (3H, s, CH_3), 2.2—3.2 (12H, m, 2×N–CH_2 and piperazine protons), 3.41 (2H, t, J=6 Hz, CH_2O), 3.41 (1H, br s, OH), 3.78 (5H, s, CH_3O and CH_2COO), 4.8—5.2 (1H, m, CHO), 6.18 (4H, s, 2×COCH=CHCO), 6.5—7.1 (3H, m, ArH), 7.67 (4H, s, ArH), 10.2 (4H, br s, 4×COOH)
II-3	1.40 (6H, s, 2×CH_3), 1.5—1.9 (2H, m, CH_2), 2.0—3.4 (12H, m, 2×N–CH_2 and piperazine protons), 2.23 (3H, s, CH_3), 3.49 (2H, t, J= 6 Hz, CH_2O), 3.68 (2H, s, CH_2COO), 3.78 (3H, s, CH_3O), 6.18 (4H, s, 2×COCH=CHCO), 6.6—7.1 (3H, m, ArH), 7.67 (4H, s, ArH)
II-4	1.0—1.7 (16H, m, 8×CH_2), 2.27 (3H, s, CH_3), 2.3—3.2 (12H, m, 2×N–CH_2 and piperazine protons), 3.38 (2H, t, J=6 Hz, CH_2O), 3.74 (3H, s, CH_3O), 3.85 (2H, s, CH_2COO), 5.8—6.0 (1H, m, CHO), 6.17 (4H, s, 2×COCH=CHCO), 6.5—7.1 (3H, m, ArH), 7.33 (5H, s, ArH), 7.67 (4H, s, ArH)
II-8	2.26 (3H, s, CH_3), 2.4—3.3 (12H, m, 2×N–CH_2 and piperazine protons), 3.5—3.9 (2H, m, CH_2O), 3.74 (3H, s, CH_3O), 3.86 (2H, s, CH_2COO), 5.7—6.0 (1H, m, CHO), 6.18 (4H, s, 2×COCH=CHCO), 6.6—7.1 (3H, m, ArH), 7.33 (5H, s, ArH), 7.66 (4H, s, ArH), 10.6 (4H, br s, 4×COOH)
II-9	1.5—2.0 (2H, m, CH_2), 2.26 (3H, s, CH_3), 2.3—3.3 (12H, m, 2×N–CH_2 and piperazine protons), 3.47 (2H, t, J=6 Hz, CH_2O), 3.74 (3H, s, CH_3O), 3.85 (2H, m, CH_2COO), 5.8—6.0 (1H, m, CHO), 6.16 (4H, s, 2×COCH=CHCO), 6.6—7.2 (3H, m, ArH), 7.33 (5H, s, ArH), 7.67 (4H, s, ArH)
II-10	1.17 (3H, d, J=6 Hz, CH_3), 1.6—1.9 (2H, m, CH_2), 2.25 (3H, s, CH3), 2.3—3.2 (12H, m, 2×N–CH_2 and piperazine protons), 3.47 (2H, t, J=6 Hz, CH_2O), 3.77 (5H, s, CH_3O and CH_2COO), 4.8—5.1 (1H, m, CHO), 6.16 (4H, s, 2×COCH=CHCO), 6.6—7.2 (3H, m, ArH), 7.67 (4H, s, ArH)
II-5	1.17 (3H, d, J=6 Hz, CH_3), 1.42 (9H, s, $C(CH_3)_3$), 2.25 (3H, s, CH_3), 2.2—3.2 (12H, m, 2×N–CH_2 and piperazine protons), 3.77 (5H, s, CH_3O and CH_2COO), 4.8—5.1 (1H, m, CHO), 6.17 (4H, s, 2×COCH=CHCO), 6.5—7.1 (3H, m, ArH), 7.67 (4H, s, ArH)
II-7	1.21 (3H, d, J=6 Hz, CH_3), 2.24 (3H, s, CH_3), 2.85 (2H, t, J=7 Hz, N–CH_2), 3.0—4.4 (12H, m, N–CH_2 and piperazine protons), 3.78 (5H, s, CH_3O and CH_2COO), 5.0—5.4 (1H, m, CHO), 6.5—7.2 (3H, m, ArH), 7.67 (4H, s, ArH)
II-6	1.17 (3H, d, J=6 Hz, CH_3), 1.68, 1.73 (total 3H, each d, J=5, 6 Hz, =C–CH_3), 2.24 (3H, s, CH_3), 2.3—3.2 (10H, m, N–CH_2 and piperazine protons), 3.4—3.6 (2H, m, N–CH_2–C=), 3.77 (5H, s, CH_3O and CH_2COO), 4.8—5.2 (1H, m, CHO), 5.2—5.6 (1H, m, CH=), 5.6—6.1 (1H, m, CH=), 6.16 (4H, s, 2×COCH=CHCO), 6.6—7.1 (3H, m, ArH), 7.67 (4H, s, ArH)
II-11	1.5—1.9 (2H, m, CH_2), 2.24 (3H, s, CH_3), 2.5—2.8 (2H, m, CH_2), 2.8—3.4 (12H, m, 2×N–CH_2 and piperazine protons), 3.48 (2H, t, J=7 Hz, CH_2O), 3.51 (2H, s, CH_2CON), 3.77 (3H, s, CH_3O), 6.16 (4H, s, 2×COCH=CHCO), 6.6—7.2 (3H, m, ArH), 7.67 (4H, s, ArH), 8.01 (1H, t, J=6 Hz, CONH)

IX-1—3 were deprotected according to the method of Corey and Venkateswarlu[9] and isolated as the dimaleates II-8—10.

Compound II-11 having a carboxamide moiety was prepared as shown in Chart 3. The monosubstituted piperazine XIII was alkylated with acetoamidoethyl chloride to afford the disubstituted piperazine XIV. Compound XIV was hydrolyzed with concentrated HCl to afford an aminoalcohol derivative of piperazine XV, which was acylated with indomethacinyl chloride and triethylamine, followed by treatment with maleic acid to afford compound II-11.

Results and Discussion

The test compounds were evaluted for *in vitro* inhibitory activity on 5-LO and CO. The biological data are summarized in Table I.

5-LO-Inhibitory Activity Introduction of a phenyl group on the carbon bonded to oxygen of the aminoalkoxy functionality increased the activity (I *vs.* II-9). Changing the phenyl group for a methyl group or introduction of another methyl group decreased the activity (II-9 *vs.* II-3, II-10). Increase of the chain length of the alkanol moiety had little effect on the activity (II-8 *vs.* II-4, II-9 and II-10 *vs.* II-1, II-2). Changing the hydroxypropyl moiety to a 2-butenyl or *tert*-butoxycarbonylethyl moiety had little effect (II-10 *vs.* II-5, II-6), and changing to a carboxyethyl moiety resulted in a loss of activity (II-10 *vs.* II-7). Compound II-11, with an amido bond, did not show higher activity.

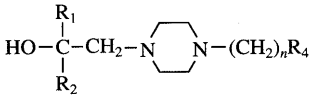
CO-Inhibitory Activity Introduction of a phenyl group on the carbon bonded to oxygen of the aminoalkoxy functionality increased the activity (I *vs.* II-9). Changing the phenyl group for a methyl group or introduction of another methyl group did not increase the activity (II-9 *vs.* II-3, II-10). Although increasing the chain length of the alkanol resulted in a loss of activity in the compound bearing a phenyl group (II-8 *vs.* II-4, II-9), the activity increased with increase in the chain length of the alcohol, reached a maximum with a five-carbon chain, and then decreased with further increase in chain length, including a methyl group (II-10 *vs.* II-1, II-2). Changing the hydroxypropyl moiety to a 2-butenyl group increased the activity (II-10 *vs.* II-6), but changing to a *tert*-butoxycarbonylethyl or carboxyethyl moiety did not (II-10 *vs.* II-5, II-7). Compound II-11, with an amido bond, had moderate activity among the test compounds.

In conclusion, compound II-8 was the most potent inhibitor of 5-LO and CO among the tested compounds, and the inhibitory potency of II-8 was higher than that of I, the initial lead compound.

Experimental

All melting points were recorded with a Yanagimoto micromelting point apparatus, and are uncorrected. ^{1}H-NMR spectra were determined in the cited solvent on a JEOL JMN-FX100 (100 MHz) spectrometer with tetramethylsilane as the internal standard. The chemical shifts are

TABLE III. NMR Data for IV-1—6



IV-1—6

Compd. No.	R_1	R_2	n	Solvent	^{1}H-NMR δ ppm
R_4: 2-tetrahydropyranyloxy					
IV-1	CH_3	H	5	C	1.13 (3H, d, J=6 Hz, CH_3), 1.2—2.0 (12H, m, 3×CH_2 and tetrahydropyran protons), 2.1—2.9 (12, m, 2×N–CH_2 and piperazine protons), 3.0—4.1 (5H, m, CHO, CH_2O and tetrahydropyran protons), 4.5—4.7 (1H, m, tetrahydropyran proton)
IV-2	CH_3	H	6	C	1.13 (3H, d, J=6 Hz, CH_3), 1.2—2.0 (14H, m, 4×CH_2 and tetrahydropyran protons), 2.1—2.9 (12H, m, 2×N–CH_2 and piperazine protons), 3.0—4.0 (5H, m, CH_2O, CHO and tetrahydropyran protons), 4.5—4.7 (1H, m, tetrahydropyran proton)
IV-3	CH_3	CH_3	3	C	1.16 (6H, s, 2×CH_3), 1.4—2.0 (8H, m, CH_2 and tetrahydropyran protons), 2.3—2.8 (12H, m, 2×N–CH_2 and tetrahydropyran protons), 3.2—4.0 (4H, m, CH_2O and tetrahydropyran protons), 4.5—4.6 (1H, m, tetrahydropyran proton)
IV-4	C_6H_5	H	10	C	1.0—2.0 (22H, m, 8×CH_2 and tetrahydropyran protons), 2.2—3.0 (12H, m, 2×N–CH_2 and piperazine protons), 3.2—4.1 (4H, m, CH_2O and tetrahydropyran protons), 4.5—4.6 (1H, m, tetrahydropyran proton), 4.5—4.8 (1H, m, CHO), 7.1—7.4 (5H, m, ArH)
R_4: $COOC(CH_3)_3$					
IV-5	CH_3	H	2	D	1.01 (3H, d, J=6 Hz, CH_3), 1.39 (9H, s, $SiC(CH_3)_3$), 2.0—2.6 (14H, m, N–CH_2, N–CH_2CH_2COO and piperizine protons), 3.5—3.9 (1H, m, CHO), 4.20 (1H, br s, OH)
R_4: $CH=CHCH_3$					
IV-6	CH_3	H	1	D	1.02 (3H, d, J=6 Hz, CH_3), 1.60, 1.65 (total 3H, each d, each J=5 Hz, CH_3), 2.1—2.5 (10H, m, N–CH_2 and piperazine protons), 2.7—3.0 (2H, m, N–CH_2), 3.5—3.9 (1H, m, CHO), 4.2 (1H, br s, OH), 5.2—5.7 (2H, m, CH=CH)

Measurement solvents: C, $CDCl_3$; D, DMSO-d_6.

given in ppm and the coupling constants in hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Elemental analyses (C, H, N) were performed on a Yanagimoto MT-2 CHN corder. Column chromatography and thin layer chromatography were carried out on Kieselgel 60 (70—230 mesh) and Kieselgel 60 F_{254} (E. Merck). Visualization was accomplished with UV light and/or iodine vapor.

1-(2-Hydroxypropyl)-4-[5-(2-tetrahydropyranyloxy)pentyl]piperazine (IV-1) A mixture of 1-(2-hydroxypropyl)piperazine[10] (III-1, 6.00 g, 41.6 mmol) and 5-(2-tetrahydropyranyloxy)pentyl chloride[11] (8.60 g, 41.6 mmol) in benzene (20 ml) was heated under reflux for 24 h. After concentration, the residue was purified by column chromatography (silica gel 500 g; eluent, EtOH : $CHCl_3$ = 1 : 5) to give IV-1 (2.65 g, 20%) as a pale brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=6 Hz, CH_3), 1.2—2.0 (12H, m, 3×CH_2 and tetrahydropyran protons), 2.1—2.9 (12H, m, 2×N-CH_2 and piperazine protons), 3.0—4.1 (5H, m, CHO, CH_2O and tetrahydropyran protons), 4.5—4.7 (1H, m, tetrahydropyran proton).

1-(2-Hydroxypropyl)-4-[6-(2-tetrahydropyranyloxy)hexyl]piperazine (IV-2) Compound IV-2 (3.08 g, 17%, a pale brown oil) was prepared in the same way as described for IV-1 using III-1 (8.00 g, 55.5 mmol) and 6-(2-tetrahydropyranyloxy)hexyl chloride[11] (12.3 g, 55.7 mmol) in benzene (10 ml).

1-(2-Hydroxy-2-methylpropyl)-4-[3-(2-tetrahydropyranyloxy)propyl]-piperazine (IV-3) Compound IV-3 (4.10 g, 25%, a pale brown oil) was prepared in the same way as described for IV-1 using 1-(2-hydroxy-2-methylpropyl)piperazine[10] (III-2, 11.8 g, 74.6 mmol) and 3-(2-tetrahydropyranyloxy)propyl chloride[12] (9.61 g, 53.8 mmol) in benzene (100 ml).

1-(2-Hydroxy-2-phenylethyl)-4-[10-(2-tetrahydropyranyloxy)decyl]-piperazine (IV-4) Compound IV-4 (5.40 g, 34%, a pale brown oil) was prepared in the same way as described for IV-1 using 1-(2-hydroxy-2-phenylethyl)piperazine[13] (III-3, 7.45 g, 36.1 mmol) and 10-(2-tetrahydropyranyloxy)decyl chloride[14] (10.0 g, 36.1 mmol) in benzene (100 ml).

1-(2-*tert*-Butoxycarbonylethyl)-4-(2-hydroxypropyl)piperazine (IV-5) Compound IV-5 (5.04 g, 45%, a pale brown oil) was prepared in the same way as described for IV-1 using III-1 (6.00 g, 41.6 mmol) and *tert*-butyl 3-chloropropionate[15] (6.84 g, 41.5 mmol) in benzene (40 ml).

1-(2-Butenyl)-4-(2-hydroxypropyl)piperazine (IV-6) Compound IV-6 (1.24 g, 30%, a pale brown oil) was prepared in the same way as described for IV-1 using III-1 (3.00 g, 20.8 mmol) and 2-butenyl chloride (1.88 g, 20.8 mmol) in benzene (50 ml).

NMR data for these compounds are summarized in Table III.

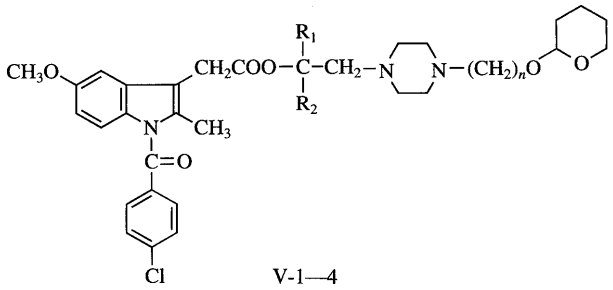
1-Methyl-2-[4-[5-(2-tetrahydropyranyloxy)pentyl]-1-piperazinyl]ethyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetate (V-1) A solution of DCC (2.61 g, 12.6 mmol) in dry dichloromethane (CH_2Cl_2, 20 ml) was added to a solution of IV-1 (2.65 g, 8.43 mmol), indomethacin (3.02 g, 8.44 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (30 ml) under ice cooling. The mixture was stirred overnight at room temperature. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica gel 450 g; eluent, MeOH : $CHCl_3$ = 1 : 20) to give V-1 (3.73 g, 68 %) as a pale brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J=6 Hz, CH_3), 1.2—2.0 (12H, m, 3×CH_2 and tetrahydropyran protons), 2.0—2.7 (12H, m, 2×N-CH_2 and piperazine protons), 2.38 (3H, s, CH_3), 3.2—4.0 (4H, m, CH_2O and tetrahydropyran protons), 3.64 (2H, s, CH_2COO), 3.83 (3H, s, CH_3O), 4.4—4.6 (1H, m, tetrahydropyran proton), 4.9—5.2 (1H, m, CHO), 6.5—7.0 (3H, m, ArH), 7.3—7.7 (4H, m, ArH).

Compounds V-2—4 were prepared in a similar manner to that described above. NMR data for these compounds are summarized in Table IV.

2-[4-(2-*tert*-Butoxycarbonylethyl)-1-piperazinyl]-1-methylethyl 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetate (V-5) A solution of DCC (5.16 g, 25.0 mmol) in dry CH_2Cl_2 (40 ml) was added to a solution of indomethacin (5.96 g, 16.7 mmol), IV-5 (4.54 g, 16.7 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (40 ml) under ice cooling. The mixture was stirred overnight under water cooling. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica gel 700 g; eluent, EtOH : $CHCl_3$ = 1 : 10) to give V-5 (6.00 g, 59%) as a pale brown oil.

1-Methyl-2-[4-(5-hydroxypentyl)-1-piperazinyl]ethyl 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetate Dimaleate (II-1) A solution of maleic acid (2.16 g, 18.6 mmol) in MeOH (50 ml) was added to a solution of V-1 (3.70 g, 5.66 mmol) in MeOH (100 ml). The mixture was heated under reflux for 3 h, then concentrated, and a mixture of $NaHCO_3$ (1.90 g, 22.6 mmol), H_2O (30 ml) and $CHCl_3$ (500 ml) was added to the residue. The organic layer was washed with water and concentrated, to afford a residue, which was purified by column chromatography (silica gel 450 g; eluent, MeOH : $CHCl_3$ = 1 : 5). The eluate was concentrated and the residue was dissolved in ether (50 ml) containing a small amount

TABLE IV. NMR Data for V-1—4



V-1—4

Compd. No.	R_1	R_2	n	^{1}H-NMR ($CDCl_3$) δ ppm
V-1	CH_3	H	5	1.21 (3H, d, J=6 Hz, CH_3), 1.2—2.0 (12H, m, 3×CH_2 and tetrahydropyran protons), 2.0—2.7 (12H, m, 2×N–CH_2 and piperazine protons), 2.38 (3H, s, CH_3), 3.2—4.0 (4H, m, CH_2O and tetrahydropyran protons), 3.64 (2H, s, CH_2COO), 3.83 (3H, s, CH_3O), 4.4—4.6 (1H, m, tetrahydropyran proton), 4.9—5.2 (1H, m, CHO), 6.5—7.0 (3H, m, ArH), 7.3—7.7 (4H, m, ArH)
V-2	CH_3	H	6	1.22 (3H, d, J=6 Hz, CH_3), 1.2—2.0 (14H, m, 4×CH_2 and tetrahydropyran protons), 2.1—2.7 (12H, m, 2×N–CH_2 and piperazine protons), 2.38 (3H, s, CH_3), 3.2—4.0 (4H, m, CH_2O and tetrahydropyran protons), 3.64 (3H, s, CH_3O), 3.83 (2H, s, CH_2COO), 4.4—4.7 (1H, m, tetrahydropyran protons), 4.9—5.3 (1H, m, CHO), 6.5—7.0 (3H, m, ArH), 7.3—7.7 (4H, m, ArH)
V-3	CH_3	CH_3	3	1.44 (6H, s, 2×CH_3), 1.4—1.9 (8H, m, CH_2 and tetrahydropyran protons), 2.1—2.6 (12H, m, 2×N–CH_2 and piperazine protons), 2.36 (3H, s, CH_3), 3.2—4.0 (4H, m, CH_2O and tetrahydropyran protons), 3.56 (2H, s, CH_2COO), 3.84 (3H, s, CH_3O), 4.5—4.6 (1H, m, tetrahydropyran proton), 6.5—7.0 (3H, m, ArH), 7.3—7.7 (4H, m, ArH)
V-4	C_6H_5	H	10	1.0—2.0 (22H, m, 8×CH_2 and tetrahydropyran protons), 2.1—3.0 (12H, m, 2×N–CH_2 and piperazine protons), 2.38 (3H, s, CH_3), 3.2—4.0 (4H, m, CH_2O and tetrahydropyran protons), 3.70 (2H, s, CH_2COO), 3.77 (3H, s, CH_3O), 4.5—4.6 (1H, m, tetrahydropyran proton), 5.8—6.0 (1H, m, CHO), 6.5—7.0 (3H, m, ArH), 7.1—7.3 (5H, m, ArH), 7.3—7.7 (4H, m, ArH)

of MeOH. To this solution, a solution of maleic acid (0.73 g, 6.29 mmol) in ether (50 ml) was added. Insoluble material was collected on a filter and washed with ether to give II-1 (0.80 g, 18%) as a white solid, mp 168—170 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.1—1.8 (6H, m, 3×CH_2), 1.17 (3H, d, J=6 Hz, CH_3), 2.1—3.3 (12H, m, 2×N-CH_2 and piperazine protons), 2.25 (3H, s, CH_3), 3.35 (2H, t, J=7 Hz, CH_2O), 3.47 (1H, br s, OH), 3.78 (5H, s, CH_3O and CH_2COO), 4.8—5.2 (1H, m, CHO), 6.17 (4H, s, 2×COCH=CHCO), 6.6—7.1 (3H, m, ArH), 7.67 (4H, s, ArH), 10.1 (4H, br s, 4×COOH). *Anal.* Calcd for $C_{39}H_{48}ClN_3O_{13}$: C, 58.39; H, 6.03; N, 5.24. Found: C, 57.92; H, 5.95; N, 5.21.

Compounds II-2—4 were prepared in a similar manner to that described above.

2-[4-(2-*tert*-Butoxycarbonylethyl)-1-piperazinyl]-1-methylethyl 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetate Dimaleate (II-5) A solution of maleic acid (0.835 g, 7.19 mmol) in ether (200 ml) was added to a solution of V-5 (2.00 g, 3.27 mmol) in ether (100 ml). Insoluble material was collected on a filter and washed with ether to give II-5 (1.99 g, 72%) as a white solid, mp 179—181 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, d, J=6 Hz, CH_3), 1.42 (9H, s, $C(CH_3)_3$), 2.25 (3H, s, CH_3), 2.2—3.2 (12H, m, 2×N-CH_2 and piperazine protons), 3.77 (5H, s, CH_3O and CH_2COO), 4.8—5.1 (1H, m, CHO), 6.17 (4H, s, 2×COCH=CHCO), 6.5—7.1 (3H, m, ArH), 7.67 (4H, s, ArH). *Anal.* Calcd for $C_{41}H_{50}ClN_3O_{14}$: C, 58.33; H, 5.97; N, 4.98. Found: C, 58.37; H, 5.90; N, 4.99.

2-[4-(2-Butenyl)-1-piperazinyl]-1-methylethyl 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetate Dimaleate (II-6) A solution of DCC (1.93 g, 9.35 mmol) in dry CH_2Cl_2 (8 ml) was added to a solution of IV-6 (1.24 g, 6.25 mmol), indomethacin (2.24 g, 6.26 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (10 ml) below 0 °C, followed by stirring overnight at room temperature. The reaction mixture was filtered and the filtrate was concentrated below 25 °C. The residue was purified by column chromatography (silica gel 300 g; eluent, EtOH : $CHCl_3$ = 1 : 10). The eluate was concentrated, and the residue was dissolved in ether (100 ml). A solution of maleic acid (1.45 g, 12.5 mmol) in ether (100 ml) was added, and the insoluble material was collected on a filter and washed with ether to give II-6 (2.70 g, 56%) as a white solid, mp 173—177 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, d, J=6 Hz, CH_3), 1.68, 1.73, (total 3H, each d, J=5, 6 Hz, =C-CH_3), 2.24 (3H, s, CH_3), 2.3—3.2 (10H, m, N–CH_2 and piperazine protons), 3.4—3.6 (2H, m, N–CH_2–C=), 3.77 (5H, s, CH_3O and CH_2COO), 4.8—5.2 (1H, m, CHO), 5.2—5.6 (1H, m, CH=), 5.6—6.1 (1H, m, CH=), 6.16 (4H, s, 2×COCH=CHCO), 6.6—7.1 (3H, m, ArH), 7.67 (4H, s, ArH). *Anal.* Calcd for $C_{38}H_{44}ClN_3O_{12}$: C, 59.26; H, 5.76; N, 5.46. Found: C, 59.38; H, 5.66; N, 5.38.

3-[4-[2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetoxy]-2-methylethyl]-1-piperazinyl]propionic Acid Dihydrochloride (II-7) A solution of 3 N HCl in dioxane (30 ml) was added to V-5 (3 g, 4.90 mmol) under ice cooling, followed by stirring overnight under water cooling. After concentration, ether was added to the residue, and the insoluble material was collected on a filter and washed with ether to give II-7 (2.16 g, 70%) as a white solid, mp 194—198 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (3H, d, J=6 Hz, CH_3), 2.24 (3H, s, CH_3), 2.85 (2H, t, J=7 Hz, N–CH_2), 3.0—4.4 (12H, m, N–CH_2 and piperazine protons), 3.78 (5H, s, CH_3O and CH_2COO), 5.0—5.4 (1H, m, CHO), 6.5—7.2 (3H, m, ArH), 7.67 (4H, s, ArH). *Anal.* Calcd for $C_{29}H_{36}Cl_3N_3O_6$: C, 55.38; H, 5.77; N, 6.68. Found: C, 55.49; H, 5.87; N, 6.70.

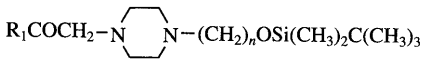
Physical data for these compounds are summarized in Tables I and II.

1-(2-*tert*-Butyldimethylsilyloxyethyl)-4-phenacylpiperazine (VII-1) A solution of *tert*-butyldimethylsilyl chloride (5.00 g, 33.2 mmol) in dry CH_2Cl_2 (20 ml) was added to a solution of 1-(2-hydroxyethyl)-4-phenacylpiperazine[16] (VI-1, 8.24 g, 33.2 mmol) and triethylamine (4.00 g, 39.5 mmol) in dry CH_2Cl_2 (50 ml) below 20 °C. The reaction mixture was stirred at room temperature for 2 h. After concentration, the residue was purified by column chromatography (silica gel 400 g; eluent, MeOH : $CHCl_3$ = 1 : 5) to give VII-1 (9.23 g, 77%) as a pale brown oil. ^{1}H-NMR (DMSO-d_6) δ: 0.07 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 2.2—2.7 (10H, m, N–CH_2 and piperazine protons), 3.70 (2H, t, J=6 Hz, CH_2O), 3.83 (2H, s, $COCH_2N$), 7.4—8.1 (5H, m, ArH).

1-(3-*tert*-Butyldimethylsilyloxypropyl)-4-phenacylpiperazine (VII-2) Compound VII-2 (5.30 g, 71%, a pale brown oil) was prepared in the same way as described for VII-1 using 1-(3-hydroxypropyl)-4-phenacylpiperazine[16] (VI-2, 5.20 g, 19.8 mmol), *tert*-butyldimethylsilyl chloride (3.60 g, 23.9 mmol) and triethylamine (3.7 ml, 26.5 mmol) in CH_2Cl_2 (80 ml).

1-Acetonyl-4-(3-*tert*-butyldimethylsilyloxyproyl)piperazine (VII-3) Compound VII-3 (3.40 g, 64%, a pale brown oil) was prepared in the same way as described for VII-1 using triethylamine (2.9 ml, 20.8 mmol), 1-acetonyl-4-(3-hydroxypropyl)piperazine[17] (VI-3, 3.40 g, 17.0 mmol) and *tert*-butyldimethylsilyl chloride (2.80 g, 18.6 mmol) in CH_2Cl_2

TABLE V. NMR Data for VII-1—3

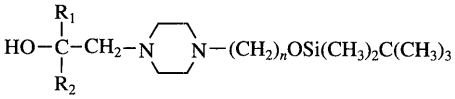


VII-1—3

Compd. No.	R_1	n	Solvent	^{1}H-NMR δ ppm
VII-1	C_6H_5	2	D	0.07 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 2.2—2.7 (10H, m, N–CH_2 and piperazine protons), 3.70 (2H, t, J=6 Hz, CH_2O), 3.83 (2H, s, $COCH_2N$), 7.4—8.1 (5H, m, ArH)
VII-2	C_6H_5	3	C	0.01 (6H, s, $Si(CH_3)_2$), 0.82 (9H, s, $SiC(CH_3)_3$), 1.5—2.0 (2H, m, CH_2), 2.2—2.6 (10H, m, N–CH_2 and piperizine protons), 3.54 (2H, t, J=6 Hz, CH_2O), 3.63 (2H, s, $COCH_2$), 7.2—8.0 (5H, m, ArH)
VII-3	CH_3	3	C	0.01 (6H, s, $Si(CH_3)_2$), 0.83 (9H, s, $SiC(CH_3)_3$), 1.4—1.9 (2H, m, CH_2), 2.07 (3H, s, CH_3CO), 2.2—2.6 (10H, m, N–CH_2 and piperazine protons), 3.10 (2H, s, $COCH_2N$), 3.55 (2H, t, J=6 Hz, CH_2O)

Measurement solvents: C, $CDCl_3$; D, DMSO-d_6.

TABLE VI. NMR Data for VIII-1—3



VIII-1—3

Compd. No.	R_1	R_2	n	Solvent	^{1}H-NMR δ ppm
VIII-1	C_6H_5	H	2	D	0.03 (6H, s, $Si(CH_3)_2$), 0.86 (9H, s, $SiC(CH_3)_3$), 2.2—2.7 (12H, m, 2 × N–CH_2 and piperazine protons), 3.65 (2H, t, J=6 Hz, CH_2O), 4.5—4.8 (1H, m, CHO), 4.94 (1H, d, J=4 Hz, OH), 7.0—7.4 (5H, m, ArH)
VIII-2	C_6H_5	H	3	C	0.01 (6H, s, $Si(CH_3)_2$, 0.85 (9H, s, $SiC(CH_3)_3$), 1.5—1.9 (2H, m, CH_2), 2.2—2.8 (10H, m, N–CH_2 and piperazine protons), 3.56 (2H, t, J=6 Hz, CH_2O), 3.80 (1H, s, OH), 4.60 (1H, t, J=7 Hz, CH), 7.17 (5H, s, ArH)
VIII-3	CH_3	H	3	C	0.01 (6H, s, $Si(CH_3)_2$), 0.83 (9H, s, $SiC(CH_3)_3$), 1.10 (3H, d, J=6 Hz, CH_3), 1.5—2.0 (2H, m, CH_2), 2.1—2.9 (12H, m, 2 × N–CH_2 and piperazine protons), 3.25 (1H, s, OH), 3.5—4.0 (3H, m, CHO and CH_2O)

Measurement solvents: C, $CDCl_3$; D, DMSO-d_6.

(60 ml).

NMR data for these compounds are summarized in Table V.

1-(2-*tert*-Butyldimethylsilyloxyethyl)-4-(2-hydroxy-2-phenyl)ethylpiperazine (VIII-1) Sodium borohydride (1.40 g, 37.0 mmol) was added to a solution of VII-1 (9.00 g, 24.8 mmol) in EtOH (50 ml) under ice cooling. The mixture was stirred at room temperature for 2 h, then concentrated. Water was added to the residue and the whole was extracted with $CHCl_3$. The organic layer was concentrated and the residue was purified by column chromatography (silica gel 400 g; eluent, MeOH : $CHCl_3$ = 1 : 20) to give VIII-1 (5.30 g, 59%) as a pale brown oil. ^{1}H-NMR (DMSO-d_6) δ: 0.03 (6H, s, $Si(CH_3)_2$), 0.86 (9H, s, $SiC(CH_3)_3$), 2.2—2.7 (12H, m, 2 × N–CH_2 and piperazine protons), 3.65 (2H, t, J=6 Hz, CH_2O), 4.5—4.8 (1H, m, CHO), 4.94 (1H, d, J=4 Hz, OH), 7.0—7.4 (5H, m, ArH).

Compounds VIII-2,3 were prepared in a similar manner to that described above. NMR data for these compounds are summarized in Table VI.

2-[4-(2-*tert*-Butyldimethylsilyloxyethyl)-1-piperazinyl]-1-phenylethyl 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetate (IX-1) Triethylamine (2.0 ml, 14.3 mmol) was added to a solution of VIII-1 (5.16 g, 14.4 mmol) and indomethacinyl chloride[18] (5.42 g, 14.4 mmol) in CH_2Cl_2 (100 ml) under ice cooling. The mixture was stirred for 3 h under ice cooling. The reaction mixture was washed with water and concentrated. The residue was purified by column chromatography (silica gel 450 g; eluent, MeOH : $CHCl_3$ = 1 : 20) to give IX-1 (5.18 g, 61%) as a pale brown oil. ^{1}H-NMR (DMSO-d_6) δ: 0.01 (6H, s, $Si(CH_3)_2$), 0.84 (9H, s, $SiC(CH_3)_3$), 2.0—2.8 (12H, m, 2 × N–CH_2 and piperazine protons), 2.24 (3H, s, CH_3), 3.60 (2H, t, J=6 Hz, CH_2O), 3.73 (3H, s, CH_3O), 3.81 (2H, s, CH_2COO), 5.7—6.0 (1H, m, CHO), 6.5—7.1 (3H, m, ArH), 7.31 (5H, s, ArH), 7.65 (4H, s, ArH).

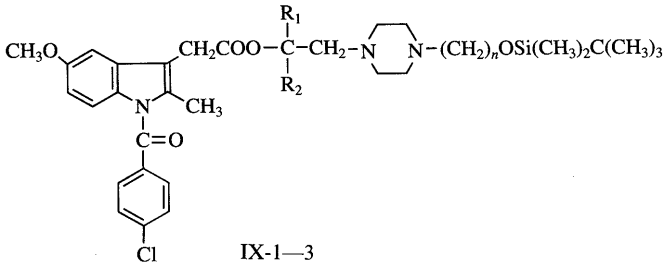
Compounds IX-2,3 were prepared in a similar manner to that described above. NMR data for these compounds are summarized in Table VII.

2-[4-(2-Hydroxyethyl)-1-piperazinyl]-1-phenylethyl 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetate Dimaleate (II-8) A mixture of IX-1 (5.18 g, 7.35 mmol) and tetrahydrofuran–water–acetic acid (1 : 1 : 3, 40 ml) was stirred at room temperature for 40 h, then concentrated below 60 °C. A mixture of water, $NaHCO_3$ and $CHCl_3$ was added to the residue, and the organic layer was separated, and concentrated. The residue was purified by column chromatography (silica gel 300 g; eluent, MeOH : $CHCl_3$ = 1 : 10). The eluent was concentrated, the residue was dissolved in ether (100 ml) and the solution was filtered. A solution of maleic acid (1.14 g, 9.82 mmol) in ether (100 ml) was added to the filtrate and the mixture was stirred at room temperature for 5 min. Insoluble material was collected on a filter and washed with ether to give II-8 (2.00 g, 33%) as a white solid, mp 158—159 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.26 (3H, s, CH_3), 2.4—3.3 (12H, m, 2 × N–CH_2 and piperazine protons), 3.5—3.9 (2H, m, CH_2O), 3.74 (3H, s, CH_3O), 3.86 (2H, s, CH_2COO), 5.7—6.0 (1H, m, CHO), 6.18 (4H, s, 2 × COCH=CHCO), 6.6—7.1 (3H, m, ArH), 7.33 (5H, s, ArH), 7.66 (4H, s, ArH), 10.6 (4H, br s, 4 × COOH). *Anal.* Calcd for $C_{41}H_{44}ClN_3O_{13}\cdot 1/2H_2O$: C, 59.24; H, 5.46; N, 5.05. Found: C, 59.19; H, 5.52; N, 4.81.

Compounds II-9,10 were prepared in a similar manner to that described above. Physical data for these compounds are summerized in Tables I and II.

1-(2-Acetylaminoethyl)-4-(3-hydroxypropyl)piperazine (XIV) A mixture of 1-(3-hydroxypropyl)piperazine[19] (XIII, 10.0 g, 69.3 mmol) and acetylaminoethyl chloride[20] (8.40 g, 69.1 mmol) in dry benzene (50 ml) was heated under reflux for 12 h, then concentrated. The residue was extracted with concentrated NH_3–MeOH–$CHCl_3$ (3 : 25 : 75). The organic layer was concentrated and purified by column chromatography (silica gel 400 g; eluent, concentrated NH_3 : MeOH : $CHCl_3$ = 3 : 25 : 75) to give XIV (5.30 g, 34%) as a colorless oil. ^{1}H-NMR (DMSO-d_6) δ: 1.3—1.8 (2H, m, CH_2), 1.78 (3H, s, CH_3CO), 1.9—2.6 (12H, m, 2 × N–CH_2 and piperazine protons), 2.9—3.3 (2H, m, CH_2), 3.42 (2H,

TABLE VII. NMR Data for IX-1—3



IX-1—3

Compd. No.	R_1	R_2	n	Solvent	^{1}H-NMR δ ppm
IX-1	C_6H_5	H	2	D	0.01 (6H, s, $Si(CH_3)_2$), 0.84 (9H, s, $SiC(CH_3)_3$), 2.0—2.8 (12H, m, 2 × N–CH_2 and piperazine protons), 2.24 (3H, s, CH_3), 3.60 (2H, t, J=6 Hz, CH_2O), 3.73 (3H, s, CH_3O), 3.81 (2H, s, CH_2COO), 5.7—6.0 (1H, m, CHO), 6.5—7.1 (3H, m, ArH), 7.31 (5H, s, ArH), 7.65 (4H, s, ArH)
IX-2	C_6H_5	H	3	C	0.01 (6H, s, $Si(CH_3)_2$), 0.85 (9H, s, $SiC(CH_3)_3$), 1.5—1.8 (2H, m, CH_2), 2.0—2.8 (15H, m, CH_3, 2 × N–CH_2 and piperazine protons), 3.3—3.8 (6H, m, OCH_3, CHO and CH_2O), 5.8—6.0 (2H, m, CH_2COO), 6.4—7.8 (12H, m, ArH)
IX-3	CH_3	H	3	C	0.01 (6H, s, $Si(CH_3)_2$), 0.83 (9H, s, $SiC(CH_3)_3$), 1.0—1.9 (5H, m, CH_3 and CH_2), 2.0—2.7 (15H, m, CH_3, 2 × N–CH_2 and piperazine protons), 3.4—3.9 (6H, m, OCH_3, CHO and CH_2O), 4.8—5.2 (2H, m, CH_2COO), 6.3—7.7 (7H, m, ArH)

Measurement solvents: C, $CDCl_3$; D, DMSO-d_6.

t, J=6 Hz, CH_2O), 7.65 (1H, t, J=6 Hz, CONH).

1-(2-Aminoethyl)-4-(3-hydroxypropyl)piperazine (XV) A mixture of XIV (4.00 g, 17.4 mmol) and concentrated HCl (20 ml) was heated at 80 °C for 4 h. After cooling, the reaction mixture was basified with diluted NaOH solution, and concentrated. The residue was extracted with MeOH and the organic layer was concentrated. The residue was purified by column chromatography (silica gel 200 g; eluent, concentrated NH_3 : MeOH : $CHCl_3$ = 0.5 : 3 : 5) to give XV (2.98 g, 91%) as a pale brown oil. ^{1}H-NMR (DMSO-d_6) δ: 1.3—1.7 (2H, m, CH_2), 2.1—2.5 (12H, m, 2 × N–CH_2 and piperazine protons), 2.61 (2H, t, J=6 Hz, CH_2), 3.22 (3H, br s, NH_2, OH), 3.42 (2H, t, J=6 Hz, CH_2O).

***N*-[2-[4-(3-Hydroxypropyl)-1-piperazinyl]ethyl]-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetamide Dimaleate (II—11)** Indomethacinyl chloride[18] (3.00 g, 7.97 mmol) was added to a solution of XV (1.49 g, 7.96 mmol) and triethylamine (1.34 ml, 9.61 mmol) in dry CH_2Cl_2 (50 ml) under ice cooling. The mixture was stirred at room temperature for 2 h, then concentrated. The residue was purified by column chromatography (silica gel 400 g; eluent, MeOH : $CHCl_3$ = 5 : 1). The eluate was concentrated, and a solution of maleic acid (1.11 g, 9.56 mmol) in EtOH (50 ml) was added. The mixture was stirred at room temperature for 30 min, then insoluble material was collected on a filter and recrystallized from EtOH to give II-11 (1.50 g, 25%) as a white solid, mp 146—147 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.5—1.9 (2H, m, CH_2), 2.24 (3H, s, CH_3), 2.5—2.8 (2H, m, CH_2), 2.8—3.4 (12H, m, 2 × N–CH_2 and piperazine protons), 3.48 (2H, t, J=7 Hz, CH_2O), 3.51 (2H, s, CH_2CON), 3.77 (3H, s, CH_3O), 6.16 (4H, s, 2 × COCH=CHCO), 6.6—7.2 (3H, m, ArH), 7.67 (4H, s, ArH), 8.01 (1H, t, J=6 Hz, CONH). *Anal.* Calcd for $C_{36}H_{43}ClN_4O_{12} \cdot 1/2H_2O$: C, 56.29; H, 5.77 ; N, 7.29. Found: C, 56.38; H, 5.56; N,7.38.

Biological Methods The assays were carried out based on the methods of Ono *et al.*[6]

5-Lipoxygenase Inhibition Assay The cytosol fraction of guinea pig polymorphonuclear leukocytes (500 μl) was preincubated with test drugs in the presence of $CaCl_2$ (1 mM) and GSH (1 mM) at 37 °C for 3 min and then incubated with [1-^{14}C]arachidonic acid (0.1 μCi) at 37 °C for 5 min. The reaction was terminated by precipitating the proteins with acetone (1 ml) and adding ice-cold saline (0.5 ml). The mixture was adjusted to about pH 3 with 2 N formic acid (150 μl) and extracted with $CHCl_3$ (2 × 2 ml). The organic layer was evaporated under an N_2 gas stream. The residue was redissolved in $CHCl_3$, applied quantitatively to TLC plates and developed with petroleum ether–ether–acetic acid (50 : 50 : 1, v/v) for separation of 5-lipoxygenase metabolites. Radioactivity on the plate were detected with a scanner (JTC-601, Aloka). The radioactivity in the position corresponding to that of authentic 5-[^{3}H]-hydroxyeicosatetraenoic acid (HETE) was determined in a liquid scintillation counter (Mark-III, Tracor Analytic). Each experiment was done in duplicate.

Cyclooxygenase Inhibition Assay Washed rabbit platelet suspension (1 ml) was preincubated with test drugs in the presence of GSH (1 mM) at 37 °C for 3 min, and then incubated with [1-^{14}C]arachidonic acid (0.1 μCi) at 37 °C for 5 min. The reaction was terminated, and the mixture was extracted by addition of a mixture (3 ml) of ethyl acetate–MeOH–1 M citric acid (30 : 4 : 1, v/v). Radioactive metabolites from [1-^{14}C]-arachidonic acid were separated by TLC in $CHCl_3$–MeOH–acetic acid–H_2O (90 : 8 : 1 : 0.8, v/v). The radioactivity at the position of authentic thromboxane B_2 was counted in a liquid scintillation counter. Each experiment was done in duplicate.

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