Highly Selective Inhibitors of Thromboxane Synthetase. 1. Imidazole Derivatives

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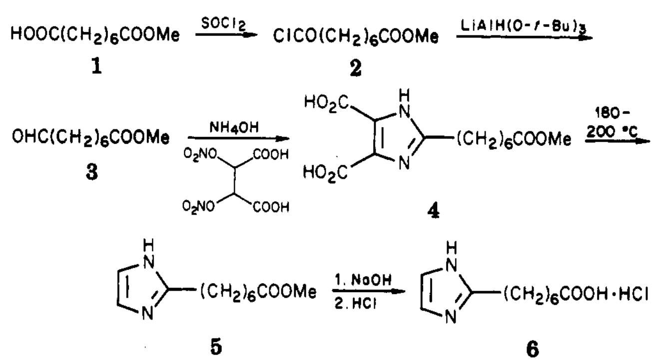
The structure–activity relationships of imidazole derivatives as inhibitors of thromboxane (TX) synthetase were investigated. Introduction of various substituents (e.g., one or two methyl groups, a halogen atom, a methylidene group, unsaturated bonds, or a phenylene group) into the α position or other positions in the carboxy-bearing side chain of 1-(7-carboxyheptyl)imidazole (15) was found to increase the inhibitory potency. The length of the side chains with the phenylene group was optimum for the inhibitory potency on TX synthetase in the region of 8.5–9.0 Å. Among the tested imidazole derivatives, 1-(7-carboxy-7-methyl-2-octynyl)imidazole (47), 4-[3-(1-imidazolyl)-propyl]benzoic acid (50), and (*E*)-4-(1-imidazolylmethyl)cinnamic acid (54) and its α-methyl analogue (57) showed the highest potency with an IC_{50} in the range of 10^{-8} to 10^{-9} M. Inhibition by these derivatives was highly selective for the TX synthetase, since other enzymes such as fatty acid cyclo-oxygenase and prostacyclin synthetase were not affected.

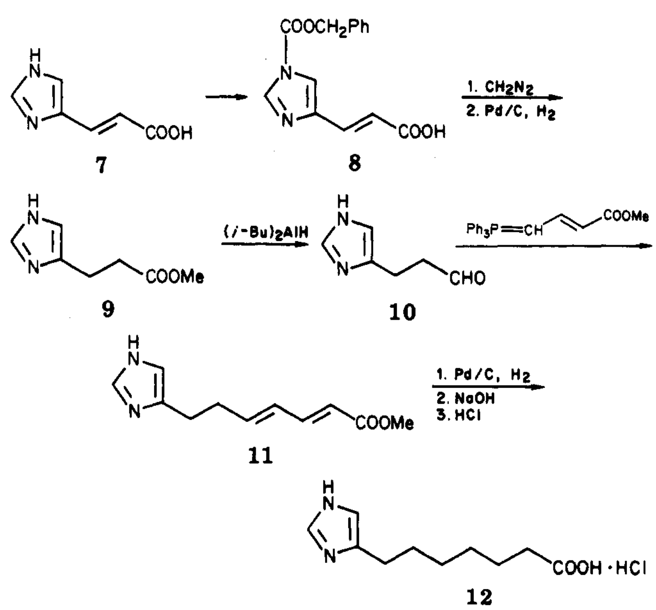
Thromboxane A_2 (TXA_2) was discovered by Hamberg et al.[1] as a highly unstable and biologically active compound produced from prostaglandin (PG) endoperoxide. In human blood platelets, the synthesis of TXA_2 from prostaglandin H_2 (PGH_2) is catalyzed by TX synthetase and is the main product in PG endoperoxide metabolism. Therefore, TXA_2 is considered to play an important role in the physiology and pathology of platelets.

Several inhibitors of TX synthetase, including *p*-benzyl-4-[1-oxo-2-(4-chlorobenzyl)-3-phenylpropyl]-phenylphosphonate (N-0164),[2] 2-isopropyl-3-nicotinoyl-indole (L-8027),[3] PG endoperoxide analogues,[4,5] and imidazole derivatives,[6,7] have already been reported. In particular, since it was discovered that imidazole is a selective inhibitor of human platelet TX synthetase by Needleman et al.[6] and Moncada et al.,[7] a variety of imidazole derivatives have been screened for inhibitory effects. Tai et al.[8] reported that 1-alkyl- and 1-aralkylimidazole derivatives were more selective and stronger inhibitors of TX synthetase than imidazole. Furthermore, they discovered that 1-substituted imidazoles retained inhibitory activity while imidazoles substituted at the other positions were inactive; therefore, it appears that the nitrogen atom at the 3 position must be sterically unhindered for inhibitory activity. Yoshimoto et al.[9] found that the 1-(ω-carboxyalkyl)imidazoles were more selective and stronger inhibitors of TX synthetase than the 1-alkylimidazoles, and these derivatives were more potent than the other (ω-substituted alkyl)imidazoles with methyl, amino, hydroxyl, ethoxycarbonyl, or carbamoyl groups. In view of these reports, we synthesized numerous imidazole derivatives with various substituents and investigated the relationships between the inhibitory activity for TX synthetase and the chemical structure of the side chain, e.g., modification of the terminal functional group, introduction of various substituents, unsaturated bonds, or a

Scheme I



Scheme II



(1) M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994–2998 (1975).
(2) P. S. Kulkarni and K. E. Eakins, *Prostaglandins*, **12**, 465–469 (1976).
(3) R. J. Gryglewski, A. Zmuda, R. Korbut, E. Krecioch, and K. Bieron, *Nature (London)*, **267**, 627–628 (1977).
(4) F. F. Sun, *Biochem. Biophys. Res. Commun.*, **74**, 1432–1440 (1977).
(5) R. R. Gorman, G. L. Bundy, D. C. Peterson, F. F. Sun, O. V. Miller, and F. A. Fitzpatrick, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 4007–4011 (1977).
(6) P. Needleman, A. Raz, J. A. Ferrendelli, and M. Minkes, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 1716–1720 (1977).
(7) S. Moncada, S. Bunting, K. Mullane, P. Thorogood, J. R. Vane, A. Raz, and P. Needleman, *Prostaglandins*, **13**, 611–618 (1977).
(8) H. H. Tai and B. Yuan, *Biochem. Biophys. Res. Commun.*, **80**, 236–242 (1978).
(9) T. Yoshimoto, S. Yamamoto, and O. Hayaishi, *Prostaglandins*, **16**, 529–540 (1978).

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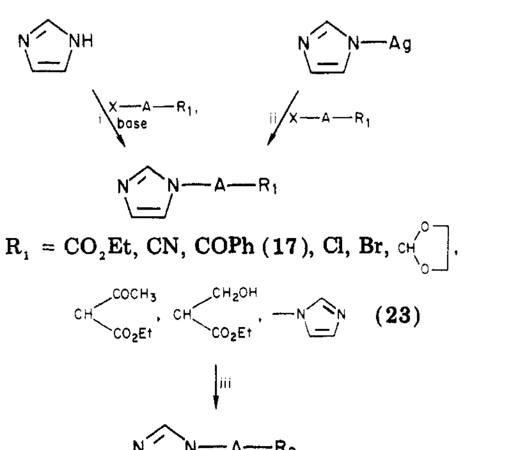
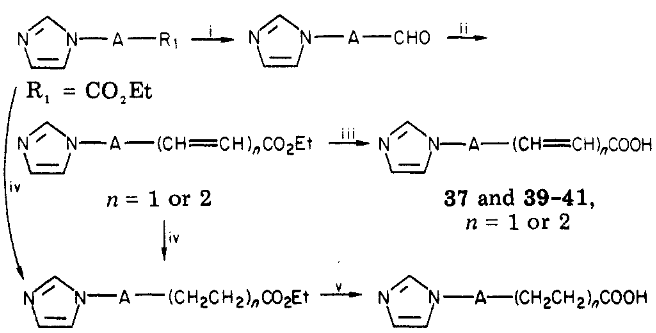
Scheme III[a]



R_2 = COOH (13, 15, 25, 26, 28, 42, 44, 46, 47, 49, 51, 53-64), CHO, CH_2COCH_3 (16), CH(OH)COOH (30), $CH(CH_2OH)COOH$ (32), $C(=CH_2)COOH$ (34)

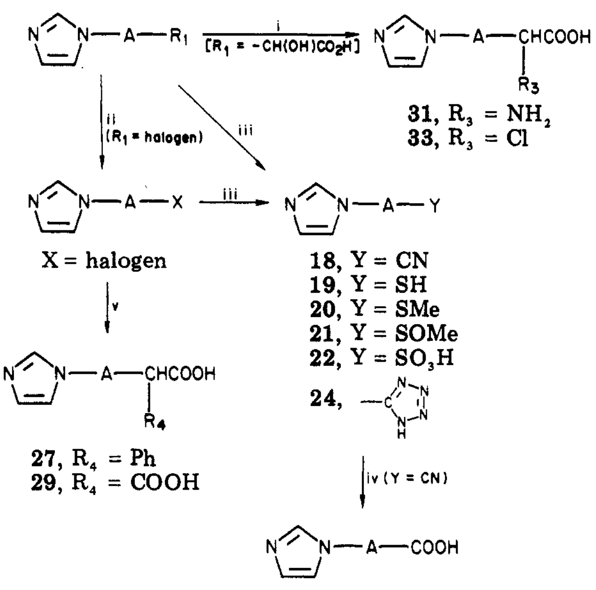
[a] X = halogen, TsO, etc. A = branched or nonbranched alkylene, alkenylene, alkynylene, aralkylene, aralkenylene, (aryloxy)alkylene, (aryloxy)alkenylene, (arylthio)-alkylene, etc. Method A-1 to A-4: (i) N-alkylation or N-arylation. Method A-5: (ii) N-alkylation. Method B: (iii) hydrolysis (H^+ or OH^-) or dehydration.

Scheme IV[a]



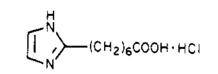
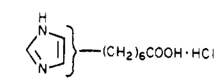
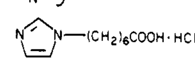
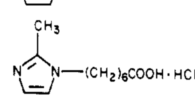
[a] Method C: (i) reduction; (ii) Wittig reaction; (III) hydrolysis. Method D: (iv) catalytic hydrogenation; (v) hydrolysis.

Scheme V[a]



[a] Method E: (i) halogenation and/or amination. Method F: (ii) reduction and halogenation. Method G: (iii) substitution or oxidation; (iv) hydrolysis. Method H: (v) C-alkylation.

Table I. Inhibitory Potencies of (ω-Carboxyalkyl)imidazoles on TX Synthetase

no.	structure	IC_{50},[a] nM
6		20 000
12		20 000
13		39
14		>>1 000

[a] Inhibitory potency on TX synthetase. All IC_{50} values were obtained graphically by measuring at three different concentrations of each inhibitor.

phenylene group into the side chain, and length of the side chain.

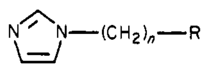
Chemistry. Three positional isomers of substituted imidazoles [1, 2, and 4(5) positions of the imidazole ring] were synthesized. The 2-substituted imidazole, 2-(6-carboxyhexyl)imidazole (6), was prepared from the half-ester 1 by the route shown in Scheme I. Treatment of 1 with thionyl chloride and reduction of the resulting chlorocarbonyl group gave aldehyde 3, which was treated with dinitrotartaric acid in 30% ammonia–water to produce imidazoledicarboxylic acid 4. Decarboxylation of 4 and hydrolysis of ester 5 gave compound 6.

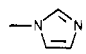
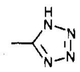
4(5)-(6-Carboxyhexyl)imidazole (12) was prepared from urocanic acid (7) by the route shown in Scheme II. Urocanic acid (7) was converted to aldehyde 10 via 8 and 9, and 10 led to the diene compound 11 by the Wittig reaction. The diene 11 was hydrogenated and hydrolyzed to give 12. On the other hand, 1-substituted imidazoles, e.g., 1-(6-carboxyhexyl)imidazole (13), and various imidazole derivatives (14–64) were prepared by various synthetic methods (Schemes III–V). Generally, the 1-substituted imidazole derivatives were prepared from imidazole and X-A-R_1 [X = Cl, Br, I, TsO; A = alkylene, aralkylene, (aryloxy)alkylene, (arylthio)alkylene, etc; R_1 = ester, nitrile, ketone, etc.] in the presence of a base, such as sodium hydride, potassium *tert*-butoxide, pyridine, diisopropylethylamine, potassium carbonate, or sodium methoxide (method A-1 to A-4), or from the silver salt of imidazole and X-A-R_1 (method A-5). The terminal functional groups were further converted to other groups by hydrolysis and/or dehydration (method B), the Wittig reaction (method C), hydrogenation (method D), and various substitution reactions (methods E–H).

Enzyme Assay. Since TXA_2 is extremely short-lived and readily converted into thromboxane B_2 (TXB_2) in aqueous medium, the enzyme (TX synthetase) activity was assayed by measuring the formation of TXB_2 from the substrate PGH_2.[10] The activities of prostacycline synthetase and fatty acid cyclo-oxygenase were assayed according to the previously described methods[11] (see Experimental Section).

(10) T. Yoshimoto, S. Yamamoto, M. Okuma, and O. Hayaishi, *J. Biol. Chem.*, 252, 5871–5874 (1977).
(11) T. Miyamoto, N. Ogino, S. Yamamoto, and O. Hayaishi, *J. Biol. Chem.*, 251, 2629–2636 (1976).

Table II. Inhibitory Potencies of 1-(ω-Substituted-alkyl)imidazoles on TX Synthetase



no	*n*	R	IC_{50}, nM	% inhibn at 25 nM
a	8	CH_3	400	
15	7	COOH·HCl	32	
16	7	$COCH_3$	>1000	
17	7	COPh	134	
18	7	CN		0.0 (19.0)[b]
19	8	SH		17.5 (52.4)
20	8	SCH_3		11.4 (52.4)
21	8	$SOCH_3$	3300	9.0 (52.4)
22	6	SO_3H		8.8 (36.8)
23	7		2000	13.4 (35.3)
24	7		2100	

[a] Inhibitory potency of 1-nonylimidazole which was assayed by Tai et al. was 10 nM (IC_{50}). See ref 8.
[b] Inhibitory potencies of compound **15** at the same concentration (25 nM) and under the same conditions are designated in parentheses.

Pharmacological Results and Discussion

(A) Position of the Side Chain on the Imidazole Ring. The inhibitory potency on TX synthetase of three positional isomers of the (ω-carboxyhexyl)imidazoles are shown in Table I. 1-Substituted imidazole **13** showed the highest potency among the three positional isomers **6**, **12**, and **13**, with IC_{50} values lower by two or three orders of magnitude than that of isomers **6** and **12**. Furthermore, the introduction of a methyl group into the 2 position of the imidazole ring (**14**) rendered the compound inactive.

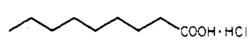
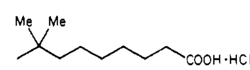
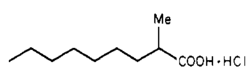
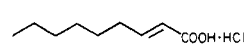
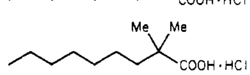
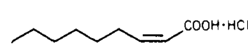
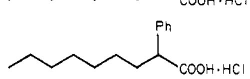
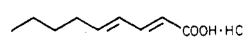
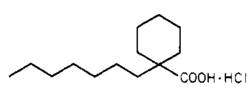
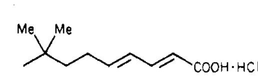
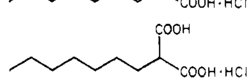
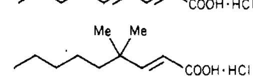
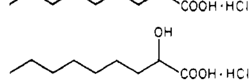
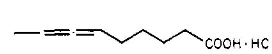
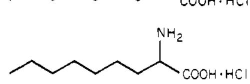
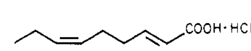
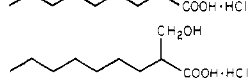
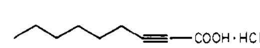
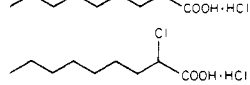
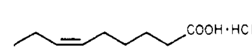
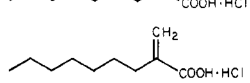
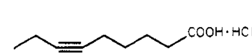
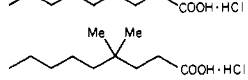
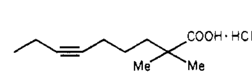
These results strongly suggest that the nitrogen atom at the 3 position in the imidazole ring must be sterically unhindered in order to maintain inhibitory activity, as reported by Tai et al.[8]

(B) Modification of the Terminal Functional Group. Table II shows the inhibitory potency of the 1-substituted imidazoles with various terminal functional groups, except for methyl, ethoxycarbonyl, hydroxyl, carbamoyl, and amino groups which were reported by Yoshimoto et al.[9]

These data suggest that a carboxyl group is the most preferable as the terminal functional group of 1-substituted imidazoles.

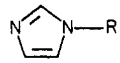
(C) Introduction of Substituents or Unsaturated Bonds into the Side Chain. Since the 1-(ω-carboxyalkyl)imidazoles with 6–9 methylene groups exhibited higher inhibitory activity,[9] we selected 1-(7-carboxyheptyl)imidazole (**15**) as the standard compound and investigated the change in the inhibitory activity by introduction of various substituents, such as alkyl, phenyl, carboxyl, amino, hydroxyl, and halogen, or unsaturated bonds into the side chain (Table III). Introduction of a methyl (**25**), *gem*-dimethyl (**26**), phenyl (**27**), or cyclohexyl group (**28**) into the α position of the carboxy-bearing side chain retained the inhibitory potency of compound **15**.

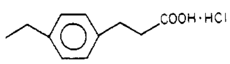
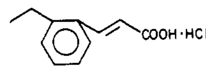
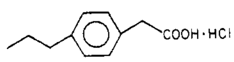
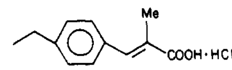
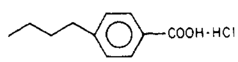
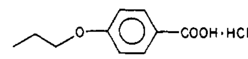
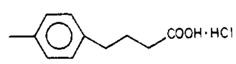
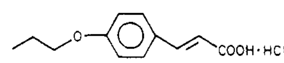
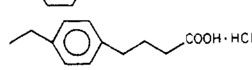
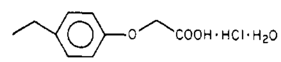
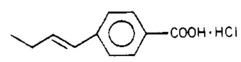
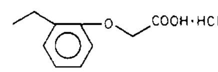
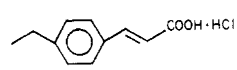
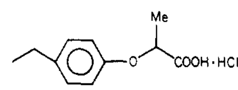
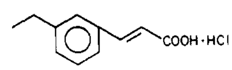
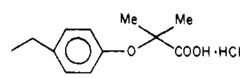
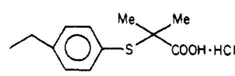
Table III. Modification of Compound 5

no.	R	IC_{50},[a] nM	no.	R	IC_{50},[a] nM
15		32	**36**		90
25[b]		30	**37**		70
26		30	**38**		16
27[b]		38	**39**		40
28		46	**40**		450
29		550	**41**		53
30[b]		140	**42**		42
31[b]		>1000	**43**		180
32[b]		250	**44**		42
33[b]		25	**45**		56
34		16	**46**		30
35		71	**47**		9

[a] Inhibitory potency on TX synthetase. [b] Racemic compound.

Table IV. Modification of Compound 5



no.	R	IC_{50},[a] nM	no.	R	IC_{50},[a] nM
48		54	56		1600
49		1500	57		4
50		5	58		14
51		120	59		250
52		1200	60		40
53		44	61		210
54		11	62[b]		38
55		32	63		25
			64		95

[a] Inhibitory potency on TX synthetase. [b] Racemic compound.

These results suggest that the steric effect in the neighborhood of the terminal carboxyl group does not affect the inhibitory activity on the interaction between the enzyme and the side-chain moiety of the imidazole derivatives. On the other hand, introduction of a polar group, such as a carboxyl (**29**), hydroxyl (**30**), amino (**31**), or hydroxymethyl (**32**), into the α position of the terminal carboxyl group of compound **15** decreased the inhibitory activity, but introduction of a chlorine atom (**33**) or methylidene group (**34**) increased the inhibitory potency above that of compound **15**. Thus, introduction of polar functional groups, which are able to form intramolecular hydrogen bonds with the terminal carboxyl group, may cause a decrease in the inhibitory activity of the compounds. When an unsaturated bond was introduced into the 2 position of the carboxy-bearing side chain of compound **15**, the cis double bond (**38**) increased the potency by 2-fold and the triple bond (**44**) slightly decreased the potency. On the other hand, introduction of a triple bond into the 6 position and a *gem*-dimethyl group into the α position of the carboxy-bearing side chain (**47**) increased the potency by 3.5-fold when compared with compound **15**. Introduction of a *gem*-dimethyl group at the carbon atom adjacent to the imidazole ring (**36**, **40**) decreased the inhibitory potency. These results also suggest that the steric effect in the neighborhood of the imidazole ring greatly affected the inhibitory activity on the interaction between the enzyme and the imidazoles.

(D) Introduction of a Phenylene Group into the Side Chain. The introduction of a phenylene group into the alkylene side chain can be expected to increase the rigidity and hydrophobicity of the side chain. Introduction of the phenylene group into the position adjacent to the terminal carboxyl group (**50**) remarkably increased the potency by 6-fold when compared with compound **15**, and the shift of the phenylene group only one carbon atom toward the imidazole ring (**49**) decreased the potency by 300-fold when compared with compound **50** (Table IV). Elongation by only one carbon atom (**52**) in the side chain of compound **48** decreased the potency by 20-fold. These results clearly show that the distance between the imidazole ring and the terminal carboxyl group remarkably affects the potency of the inhibitors. When the double bond was introduced into the side chain, the potency of compound **53** was much less than that of the saturated compound **50**; on the contrary, the potency of the cinnamic acid type compound **54** was increased by 5-fold compared with that of the saturated compound **48**. The shift of the position of the substituents in the phenylene ring [para (**54**) to meta (**55**) to ortho (**56**)] greatly decreased the potency. Furthermore, introduction of a methyl group (**57**) into the α position of the terminal carboxyl group of compound **54** increased the potency by 3-fold. In addition, replacement of the carbon atom by an oxygen or sulfur atom generally decreased the potency. Introduction of methyl (**62**) and *gem*-dimethyl groups (**63**) into the α position of the carboxy-bearing side chain slightly increased the potency over that of compound **60**.

(E) Length of the Side Chain. The 1-(ω-carboxyalkyl)imidazoles markedly inhibited TX synthetase in the broad region of the side chain with 6–9 methylene groups as reported by Yoshimoto et al.[9] The distances between the imidazole ring and the terminal carboxyl group were estimated to be 10–14 Å. We examined the relationship between the length of the side chain and the inhibitory activity of compounds **48**–**64**. As shown in Figure 1, the length of side chain of the potent compounds concentrated in a very limited region (8.5–9.0 Å) in contrast with that of the 1-(ω-carboxyalkyl)imidazoles. The extent of the effective length may be limited because the side chains with a phenylene group are structurally rigid as compared with the alkylene side chains.

In conclusion, the inhibitory potency of the imidazole derivatives on TX synthetase was influenced by the position of the substituent in the imidazole ring, the kind of terminal functional group, the combination and order of

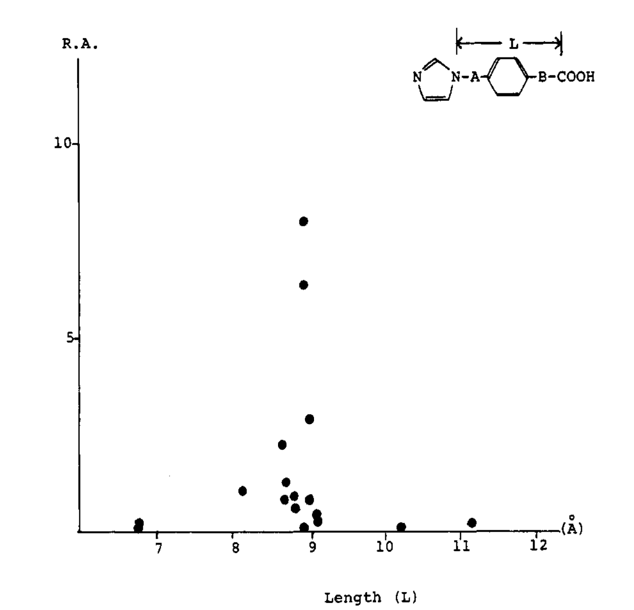


Figure 1. The relationship between the inhibitory activity and length of the side chains (48–64): R.A. = relative inhibitory activity for compound **15**; the length (L) was estimated using Dreiding stereomodels.

the substituents, and length of the side chain.

The compound with the highest inhibitory activity was (*E*)-4-(1-imidazolylmethyl)-α-methylcinnamic acid hydrochloride (**57**), which was 10^4 times as active as imidazole. The potent compounds (**15**, **47**, **54**, and **57**) did not show any effects on other enzymes involved in PG biosynthesis, such as fatty acid cyclo-oxygenase ($IC_{50} \gg 100$ μM) and prostacyclin synthetase ($IC_{50} \gg 100$ μM), and they inhibited TX synthetase very selectively.

Tai et al.[8] have suggested that the hydrophobic binding of the side chain to the receptor site of TX synthetase plays as important role in the inhibition of TX synthetase by 1-alkylimidazoles.

We will report in a future paper the results of studies on quantitative structure–activity relationships in terms of hydrophobicity and other factors of the side chains.

Experimental Section

Biological Method. Materials. [1-^{14}C]Arachidonic acid (AA; 51 mCi/mmol) was purchased from New England Nuclear. Sheep vesicular gland microsomes were obtained from Ran Biochemicals (Tel Aviv). [1-^{14}C]PGH_2 was prepared by the method of Yoshimoto et al.[9]

Preparation of Platelets. Freshly citrated rabbit blood was centrifuged at 200*g* for 10 min. The platelet-rich plasma was removed and recentrifuged at 2000*g* for 10 min. The pellets were suspended in 0.1 M potassium phosphate at pH 7.4.

Enzyme Assay. Reaction A (0.2 mL) containing sheep vesicular gland microsomes (4 mg), [1-^{14}C]AA (0.12 μmol, 0.8 μCi), tryptophan (10 μmol), beef hemoglobin (0.2 μmol), and potassium phosphate at pH 7.4 (20 μmol) was carried out at 24 °C for 90 s and was terminated by the addition of indomethacin (20 μM at final concentration), and then the mixture was immersed immediately in an ice bath (70–80% of AA was converted to PGH_2). Reaction B (0.1 mL) containing rabbit platelet (4×10^7 cells), potassium phosphate at pH 7.4 (10 μmol), and tested compound was started by the addition of a 10-μL aliquot of reaction mixture A as mentioned above or the purified [1-^{14}C]PGH_2 (5 nmol, 5×10^4 cpm) and then incubated at 24 °C for 1 min. Reaction B was stopped by the addition of 0.3 mL of a mixture of EtOAc/MeOH/0.2 M citric acid (30:4:1), and Na_2SO_4 (0.5 g) was added to the mixture. A 50- to 100-μL aliquot of the organic layer was removed and placed on a silica gel plate (Merck, silica gel 60 F-254). Thin-layer chromatography was carried out to a height of 15 cm with $CHCl_3$/EtOAc/MeOH/AcOH/H_2O (70:30:8:1:0.5). The measurement of the radioactivity on silica gel plates was performed as described previously.[9]

Chemistry. The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Microanalyses were performed with Yanaco CHN CORDER Model MT2. The NMR spectra were taken with a Hitachi Model R-22 high-resolution nuclear magnetic resonance spectrometer with tetramethylsilane as the internal standard. The IR spectra were obtained with a Hitachi Model 260-10 infrared spectrophotometer. Mass spectra (MS) were obtained on a JMSOISG double-focusing mass spectrometer and are reported as mass/charge ratio (relative intensity).

2-(6-Carboxyhexyl)imidazole Hydrochloride (6). A mixture of 7-(methoxycarbonyl)heptanoic acid (**1**; 10.5 g, 56 mmol) and $SOCl_2$ (5 mL, 69 mmol) was refluxed for 6 h. The reaction mixture was concentrated and distilled under vacuum [148–150 °C (12 mmHg)] to give **2** (10.5 g, 91%): IR (film) 1800 (COCl), 1740 (COOMe) cm^{-1}.

t-BuOH (13.3 mL, 140 mmol) was added slowly to a suspension of $LiAlH_4$ (1.81 g, 47 mmol) in dry diglyme (40 mL) at 0 °C and stirred for 2 h at room temperature. The mixture was cooled to −60 °C, and the acid chloride **2** was added slowly and stirred for 1 h. The solution was poured into a mixture of concentrated HCl (2 mL) and ice–water (100 mL) and extracted with Et_2O. The extract was concentrated and the residue was distilled under vacuum [95–97 °C (0.15 mmHg)] to give **3** (2.1 g, 24%): IR (film) 1740 (COOMe), 1730 (CHO) cm^{-1}. To a solution of dinitrotartaric acid (obtained from 4 g of tartaric acid)[12] in H_2O (60 mL) was added 30% NH_4OH (15 mL) and then a solution of **3** (2.1 g, 12 mmol) in MeOH (40 mL) at 5 °C. After warming slowly to room temperature, the mixture was stirred overnight. The solution was washed with Et_2O and adjusted to pH 3 with concentrated HCl. The resulting colorless crystals were filtered and dried in vacuo to give crude **4** (1.89 g, 52%): IR (film) 1720 (COOMe and COOH) cm^{-1}. A mixture of crude **4** (1.0 g, 3.4 mmol) and powdered copper (1.0 g, 15.7 mmol) was heated at 180–200 °C for 1 h. The crude product was chromatographed on silica gel using MeOH–$CHCl_3$ (1:99) as eluent. The eluate was concentrated and the residual crystals were recrystallized from *i*-Pr_2O to give **5** (200 mg, 28%): mp 55.5–56.5 °C; IR (KBr) 1740 (COOMe) cm^{-1}; MS, *m/e* 210 (M^+, 17), 179 (18), 137 (23), 95 (100), 82 (74), 81 (76).

A solution of **5** (105 mg, 0.5 mmol) and 1 N NaOH (0.55 mL, 0.55 mmol) in MeOH (1.2 mL) was stirred for 1 h at room temperature. After concentration in vacuo, H_2O (10 mL) was added to the residue, and the aqueous solution was washed with Et_2O. The solution was adjusted to pH 1 with 1 N HCl and evaporated under reduced pressure to remove the excess of the HCl completely. The residue was dissolved in absolute EtOH, filtered, and evaporated in vacuo to give **6** (95 mg, 82%): IR (KBr) 1705 (COOH) cm^{-1}.

4(5)-(6-Carboxyhexyl)imidazole Hydrochloride (12). Carbobenzoxy chloride (30% toluene solution; 4.36 mL, 7.5 mmol) was added slowly at 20 °C to a solution of urocanic acid (**7**; 2.0 g, 14.5 mmol) and $NaHCO_3$ (3.04 g, 36 mmol) in H_2O (28 mL) and stirred for 30 min. Additionally, $NaHCO_3$ (3.04 g, 36 mmol) and carbobenzoxy chloride (4.36 mL, 7.5 mmol) were added to the solution and stirred for 1 h. The reaction mixture was washed with Et_2O and adjusted to pH 3 with 6 N HCl, extracted with EtOAc, and dried ($MgSO_4$) to give **8** as an EtOAc solution. An excess of CH_2N_2 in Et_2O was added to the solution at 0 °C, stirred for 10 min, and concentrated in vacuo to give 4(5)-[2-(methoxycarbonyl)ethenyl]-*N*-carbobenzoxyimidazole (3.8 g). Then a solution of the methyl ester in EtOH (65 mL) was hydrogenated over 5% Pd/C (1.0 g) under a hydrogen atmosphere at room temperature. After filtration, the solution was evaporated under reduced pressure to give **9** (1.95 g, 87% from **7**). Diisobutylaluminum hydride (DIBAL; 25% toluene solution; 17 mL, 30 mmol) was added dropwise at −60 °C under a nitrogen atmosphere to a solution of **9** (1.34 g, 8.7 mmol) in CH_2Cl_2 (65 mL) and stirred for 20 min at the same temperature. After the mixture was quenched with MeOH, H_2O was added to the mixture, the mixture was filtered, and the filtrate was concentrated in vacuo to give crude **10** (1.04 g, 96%): mp 80–86 °C (crude); MS, *m/e* 124 (M^+,

(12) H. R. Snyder, R. G. Handrick, and L. A. Brooks, "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1955, p 471.

18), 96 (36), 95 (100), 81 (50), 68 (32), 54 (15).

A mixture of **10** (245 mg, 2 mmol), 3-(methoxycarbonyl)-2-propenylidenetriphenylphosphorane[13] (1.08 g, 3 mmol) and $CHCl_3$ (30 mL) was stirred for 3 h at room temperature. After the mixture was concentrated in vacuo, the residue was chromatographed on silica gel using MeOH–$CHCl_3$ (1:24) as eluent to give **11** (280 mg, 69%). A solution of **11** (280 mg, 1.4 mmol) in MeOH (4 mL) was hydrogenated over 5% Pd/C (180 mg) under a hydrogen atmosphere at room temperature. After the solution was filtered, the filtrate was evaporated in vacuo, and the residue was chromatographed on silica gel using $CHCl_3$–MeOH (24:1) as eluent to give 4(5)-[6-(methoxycarbonyl)hexyl]imidazole (230 mg, 81%): MS, *m/e* 210 (M^+, 17), 179 (18), 137 (23), 95 (100), 82 (74), 81 (76).

A solution of 4(5)-[6-(methoxycarbonyl)hexyl]imidazole (220 mg, 1 mmol) and 1 N NaOH (1.1 mL, 1.1 mmol) in MeOH (2 mL) was stirred at room temperature for 1 h. After the solution was evaporated under reduced pressure, H_2O (10 mL) was added to the residue, and the aqueous solution was washed with Et_2O, adjusted to pH 1 with 1 N HCl, and concentrated in vacuo to dryness. The residual solid was dissolved in EtOH and filtered. The filtrate was evaporated and the residual crystals were recrystallized from EtOH–Et_2O to give **12** (150 mg, 62%): IR (KBr) 1695 (COOH) cm^{-1}; NMR (Me_2SO-d_6) δ 1.1–1.7 (m, 8 H), 2.20 (t, 2 H), 2.65 (t, 2 H), 7.40 (s, 1 H), 9.05 (s, 1 H).

Method A-1. 1-[7-(Methoxycarbonyl)heptyl]imidazole. Imidazole (13 g, 190 mmol) was added slowly to a suspension of NaH (4.6 g, 190 mmol) in dry DMF (400 mL) at room temperature and heated at 90 °C for 1 h. A solution of methyl 8-bromooctanoate (43 g, 180 mmol) in dry DMF (50 mL) was added to the mixture during 1 h and heated at 90 °C for another hour. After the solution was concentrated in vacuo, the residual oil was dissolved in Et_2O (500 mL), washed with H_2O, dried ($MgSO_4$), and evaporated. The residual oil was distilled in vacuo [165–170 °C (1 mmHg)] to give 1-[7-(methoxycarbonyl)heptyl]imidazole (32 g, 79%) as a pale yellow oil: IR (film) 1730 (COOMe) cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.0 (m, 10 H), 2.29 (t, 2 H), 3.64 (s, 3 H), 3.92 (t, 2 H), 6.87 (t, 1 H), 6.98 (br s, 1 H), 7.40 (br s, 1 H).

Method A-2. 1-[7-(Methoxycarbonyl)-1,2-heptadienyl]imidazole. Imidazole (500 mg, 7.4 mmol) was added to a suspension of NaH (182 mg, 7.6 mmol) in dry DMF (20 mL) at room temperature under a nitrogen atmosphere. A solution of methyl 8-bromo-6-octynoate (1.55 g, 6.7 mmol) in dry DMF (1 mL) was added to the mixture and heated at 110 °C for 50 min. After the solution was concentrated in vacuo, the residual oil was dissolved in Et_2O, washed with H_2O, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ as eluent to give 1-[7-(methoxycarbonyl)-1,2-heptadienyl]imidazole (300 mg, 20%): MS, *m/e* 220 (M^+, 50), 189 (17), 161 (23.5), 119 (100), 93 (22), 69 (29.5).

Method A-3. Ethyl 4-[4-(1-Imidazolyl)phenyl]butyrate. A mixture of imidazole (3.4 g, 50 mmol), ethyl 4-(4-bromophenyl)butyrate (12.7 g, 47 mmol), anhydrous K_2CO_3 (6.5 g, 47 mmol), and CuBr (300 mg) in nitrobenzene (20 mL) was heated at 170–180 °C for 30 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and filtered, and the filtrate was concentrated under reduced pressure. The residual dark brown oil was chromatographed on silica gel using benzene (to remove the nitrobenzene), followed by $CHCl_3$ to give ethyl 4-[4-(1-imidazolyl)phenyl]butyrate (4.8 g, 40%) as a pale brown oil: IR (film) 1720 (COOEt) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H), 1.85–2.15 (m, 2 H), 2.25–2.5 (m, 2 H), 2.71 (t, 2 H), 4.14 (q, 2 H), 7.15 (br s, 1 H), 7.2–7.35 (m, 5 H), 7.78 (br s, 1 H).

Method A-4. 1-(6-Chlorohexyl)-2-methylimidazole. 2-Methylimidazole (5 g, 61 mmol) was added slowly to a suspension of NaH (1.46 g, 61 mmol) in dry DMF (100 mL) at room temperature and stirred at 80 °C for 30 min. After the mixture was cooled, 1,6-dichlorohexane (20 g, 130 mmol) was added, and the mixture was heated at 80 °C for 2 h. The mixture was evaporated, extracted with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2–EtOH (20:1) to give 1-(6-chlorohexyl)-2-methylimidazole (4.19 g, 34%) as a colorless oil: NMR ($CDCl_3$) δ 1.2–1.9 (m, 8 H), 2.35 (s, 3 H), 3.52 (t, 2 H), 3.84 (t, 2 H), 6.80 (d, 1 H), 6.90 (d, 1 H).

Method A-5. 1-[7-(Methoxycarbonyl)-6-heptynyl]imidazole. The silver salt of imidazole (for preparation, see following paragraph) (6.8 g, 39 mmol) was added to a solution of 7-(methoxycarbonyl)-6-heptynyl iodide (3.63 g, 13 mmol) in toluene (70 mL) and refluxed for 20 min. The reaction mixture was filtered and concentrated in vacuo, and the residue was chromatographed on silica gel using MeOH–$CHCl_3$ (3:97) as eluent to give 1-[7-(methoxycarbonyl)-6-heptynyl]imidazole (220 mg, 8%): IR (film) 2240 (C≡C), 1710 (COOMe) cm^{-1}; NMR ($CDCl_3$) δ 2.34 (t, 2 H), 3.77 (s, 3H), 3.96 (t, 2 H), 6.91 (m, 1 H), 7.05 (m, 1 H), 7.47 (m, 1 H); MS, *m/e* 220 (M^+, 39), 189 (42), 161 (31), 123 (26), 82 (100), 81 (52).

Preparation of the Silver Salt of Imidazole. To a solution of $AgNO_3$ (16.9 g, 100 mmol) in H_2O (680 mL) was added a solution of imidazole (6.8 g, 100 mmol) in H_2O (280 mL) at room temperature, and then a solution of NaOH (4.0 g, 100 mmol) in H_2O (20 mL) was added at 90 °C. The mixture was allowed to cool to 50 °C and stirred at the same temperature for 6 h. The resulting precipitates were filtered, washed with cold H_2O, EtOH, Me_2CO, and Et_2O, successively, and dried under reduced pressure to give the silver salt of imidazole (quantitatively).

By the same procedures (method A-1, -4, and -5), the following compounds were prepared, and these are summarized in the left column of Table V.

Method B-1. 1-(7-Carboxyheptyl)imidazole Hydrochloride (15). A mixture of 1-[7-(methoxycarbonyl)heptyl]imidazole (10.0 g, 45 mmol) (prepared by method A-1), NaOH (2,3 g, 57 mmol), and H_2O (30 mL) was stirred at room temperature for 1 h. After concentration in vacuo, an excess of dilute HCl was added to the residue and concentrated to dryness. The residual solid was dissolved in EtOH, filtered, and evaporated, and the residual crystals were recrystallized from EtOH to give **15** (8.7 g, 79%) as colorless leaflets: IR (KBr) 1710 (COOH) cm^{-1}; NMR (Me_2SO-d_6) δ 1.1–2.0 (m, 10 H), 2.19 (t, 2 H), 4.20 (t, 2 H), 7.63 (t, 1 H), 7.77 (t, 1 H), 9.24 (br s, 1 H), 10–12 (br, 2 H).

By the same procedure (method B-1), the following compounds were prepared, and these are summarized in the right column of Table V.

Method B-2. 1-(8-Oxononyl)imidazole (16). A solution of 1-[7-(ethoxycarbonyl)-8-oxononyl]imidazole (330 mg, 1.18 mmol) (prepared by method A-1) in 10% H_2SO_4 (15 mL) was refluxed for 5 h. The mixture was made alkaline with aqueous $NaHCO_3$ and extracted with Et_2O (300 mL). The extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (50:1) to give **16** (236 mg, 96%): IR (film) 1705 ($COCH_3$) cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.0 (m, 10 H), 2.12 (s, 3 H), 2.43 (t, 2 H), 3.95 (t, 2 H), 6.90 (m, 1 H), 7.02 (br s, 1 H), 7.46 (br s, 1 H).

Method B-3. 1-(7-Carboxy-7-octenyl)imidazole Hydrochloride (34). A few drops of H_3PO_4 were added to 1-[7-carboxy-7-(hydroxymethyl)heptyl]imidazole hydrochloride (**32**; 180 mg, 0.65 mmol) (prepared by method A-1) and heated at 160 °C for 5 h under reduced pressure (15 mmHg). The mixture was chromatographed on cellulose gel using *n*-BuOH–H_2O–AcOH (8:10:1), and the eluate was concentrated in vacuo. The residue was adjusted to pH 8 with 1 N NaOH and filtered, and the filtrate was purified again by column chromatography as described above to give **34** (78 mg, 46%): IR (film) 1700 (COOH), 1630 (C=C) cm^{-1}; NMR (D_2O) δ 1.2–2.1 (m, 8 H), 2.25–2.4 (m, 2 H), 4.26 (t, 2 H), 5.65–5.75 (m, 1 H), 6.1–6.2 (m, 1 H), 7.4–7.6 (m, 2 H), 8.65–8.8 (m, 1 H).

Method C. 1-[(4*E*,6*E*)-7-Carboxy-1,1-dimethyl-4,6-heptadienyl]imidazole Hydrochloride (40). DIBAL (25% toluene solution; 3.1 mL, 5.4 mmol) was added slowly at −78 °C under a nitrogen atmosphere to a solution of 1-[3-(ethoxycarbonyl)-1,1-dimethylpropyl]imidazole (570 mg, 2.7 mmol) (prepared by method A-1) in dry toluene (12 mL) and stirred for 30 min. To the mixture were added EtOH carefully at −78 °C and H_2O at 0 °C. After filtration, the filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel using $CHCl_3$–MeOH (24:1) as eluent to give 1-(3-formyl-1,1-dimethylpropyl)imidazole (340 mg, 76%): IR (film) 1750 (CHO) cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 6 H), 2.2 (m, 4 H), 7.0 (m, 2 H), 7.5 (m, 1 H), 9.5 (br s, 1 H); MS, *m/e* 166 (M^+, 55), 138 (39), 81 (91), 69 (100).

(13) E. Buchata and F. Andree, *Chem. Ber.*, 92, 3111 (1959).

Diethyl (*E*)-3-(ethoxycarbonyl)-2-propenylphosphonate (2.0 g, 8 mmol) was added dropwise at −78 °C under a nitrogen atmosphere to a solution of lithium diisopropylamide (LDA; 0.32 M THF solution; 25 mL, 8 mmol) and stirred at −70 °C for 30 min. Then, a solution of 1-(3-formyl-1,1-dimethylpropyl)imidazole (1.0 g, 6 mmol) in dry THF (2 mL) was added to the mixture at −70 °C and stirred at room temperature for 30 min. After quenching with AcOH (0.91 mL, 16 mmol), the mixture was evaporated, and the residue was dissolved in $CHCl_3$, washed with saturated $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$–EtOH (99:1) as eluent to give 1-[(4*E*,6*E*)-7-(ethoxycarbonyl)-1,1-dimethyl-4,6-heptadienyl]imidazole (850 mg, 54%): IR (film) 1710 (COOEt), 1640 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, 3 H), 1.57 (s, 6 H), 1.9 (m, 4 H), 4.20 (q, 2 H), 5.79 (d, 1 H), 5.9–6.3 (m, 2 H), 7.0–7.4 (m, 1 H), 7.03 (m, 1 H), 7.09 (m, 1 H), 7.6 (m, 1 H); MS, *m/e* 262 (M^+, 34), 261 (26), 233 (33), 217 (22), 189 (48), 149 (100), 119 (22), 69 (39), 67 (27).

The above ethyl ester (500 mg) was hydrolyzed as described in method B-1 to give **40** (450 mg, 87%): IR (KBr) 1705 (COOH), 1640 (C=C) cm^{-1}; NMR (D_2O) δ 1.71 (s, 6 H), 2.05–2.1 (m, 4 H), 5.86 (d, 1 H), 6.0–6.3 (m, 2 H), 7.0–7.4 (m, 1 H), 7.55 (m, 1 H), 7.75 (m, 1 H), 8.85 (m, 1 H).

By the same procedure, compounds **37**, **39**, and **41** were prepared, and these are summarized in Table VI.

Method D-1. 1-(7-Carboxy-1,1-dimethylheptyl)imidazole Hydrochloride (36). A solution of 1-[(4*E*,6*E*)-7-(ethoxycarbonyl)-1,1-dimethyl-4,6-heptadienyl]imidazole (850 mg, 3.2 mmol) (prepared by method C) in EtOH (10 mL) was hydrogenated over 5% Pd/C (400 mg) at room temperature under a hydrogen atmosphere. The mixture was filtered and evaporated in vacuo, and the residue was chromatographed on silica gel using $CHCl_3$–EtOH (99:1) to give 1-[7-(ethoxycarbonyl)-1,1-dimethylheptyl]imidazole (830 mg, 96%) as a colorless oil: IR (film) 1732 (COOEt) cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 3 H), 1.52 (s, 6 H), 2.26 (t, 2 H), 4.12 (q, 2 H), 7.01 (m, 1 H), 7.06 (m, 1 H), 7.59 (m, 1 H); MS, *m/e* 266 (M^+, 16), 265 (28), 221 (15), 110 (21), 109 (18), 69 (100).

The above ethyl ester was hydrolyzed as described in method B-1 to give **36** in 82% yield: IR (KBr) 1720 (COOH) cm^{-1}; NMR (D_2O) δ 1.0–2.1 (m, 16 H), 2.37 (t, 2 H), 7.57 (m, 1 H), 7.72 (m, 1 H), 8.83 (m, 1 H).

By the same procedure, **35** and **48** were prepared from 1-[(6*E*)-7-(ethoxycarbonyl)-5,5-dimethyl-6-heptenyl]imidazole (prepared by method C) and ethyl 4-(1-imidazolylmethyl)cinnamate (prepared by method A-1) in 88 and 63% yields, respectively.

Method D-2. (1) 1-[(2*Z*)-7-Carboxy-2-heptenyl]imidazole Hydrochloride (45). A mixture of 1-[7-(methoxycarbonyl)-2-heptynyl)imidazole (220 mg, 1 mmol) (prepared by method A-5), quinoline (15 mg, 0.12 mmol), 5% Pd/$BaSO_4$ (16 mg), and MeOH (16 mL) was hydrogenated under a hydrogen atmosphere. After absorption of a theoretical amount (23 mL) of hydrogen, the mixture was filtered and evaporated in vacuo, and the residue was chromatographed on silica gel using $CHCl_3$ to give 1-[(2*Z*)-7-(methoxycarbonyl)-2-heptenyl]imidazole (192 mg, 86%) as a colorless oil: IR (film) 1740 (COOMe) cm^{-1}; MS, *m/e* 222 (M^+, 38.5), 191 (34), 154 (31), 81 (49.5), 80 (71), 69 (100).

The above methyl ester (89 mg) was hydrolyzed as described in method B-1 to give **45** (59 mg, 60%): IR (KBr) 1720 (COOH), 1640 (C=C) cm^{-1}; NMR (D_2O) δ 1.4–1.8 (m, 4 H), 2.1–2.3 (m, 4 H), 4.92 (d, 2 H), 5.5–6.1 (m, 2 H), 7.51 (m, 2 H), 8.74 (br s, 1 H).

(2) 1-[(2*Z*,6*E*)-7-Carboxy-2,6-heptadienyl]imidazole Hydrochloride (43). By the same procedure, **43** was prepared from 1-[(6*E*)-7-(methoxycarbonyl)-6-hepten-2-yl]imidazole (prepared by method A-5) in a 32% yield: IR (film) 1710 (COOH) 1650 (C=C) cm^{-1}; NMR (D_2O) δ 2.3–2.5 (m, 4 H), 4.8–5.0 (d, 2 H), 5.6–6.1 (m, 3 H), 6.85–7.2 (m, 1 H), 7.45–7.55 (m, 2 H), 8.65–8.8 (br s, 1 H).

Method E-1. 1-[(7*RS*)-7-Carboxy-7-chloroheptyl]imidazole Hydrochloride (33). A solution of 1-(7-carboxy-7-hydroxyheptyl)imidazole hydrochloride (**30**; 140 mg, 0.5 mmol) (prepared by method B-1) in $SOCl_2$ (0.19 mL, 2.5 mmol) was stirred overnight at room temperature. After the solution was evaporated, ice-water was added to the residue and stirred for 5 min. The solution was filtered and concentrated under reduced pressure to give **33** (149 mg, 99%): IR (film) 1740 (COOH) cm^{-1}; NMR (Me_2SO-d_6) δ 1.0–1.6 (m, 6 H), 1.6–2.0 (m, 4 H), 4.23 (t, 2 H), 4.48 (t, 1 H), 7.71 (m, 1 H), 7.84 (m, 1 H), 9.28 (br s, 1 H).

Method E-2. 1-[(7*RS*)-7-Carboxy-7-aminoheptyl]imidazole Hydrochloride (31). A mixture of **33** (515 mg, 1.8 mmol) (prepared by method E-1), 30% NH_4OH (60 mL), and MeOH (5 mL) was stirred at room temperature for 2 weeks. After the solution was evaporated in vacuo, the residue was dissolved in H_2O and washed with EtOAc. The aqueous solution was poured into an Amberlite IRA-400 column, followed by washing with H_2O until the eluent became neutral, and then eluted with 5% AcOH. The eluent was evaporated in vacuo, Amberlite IRC-120 B and a few drops of concentrated HCl in H_2O (5 mL) were added to the residue, and the solution was stirred at 90 °C for 6 h. The suspension was packed into a column, washed with H_2O until the eluent became neutral, and then eluted with 10% NH_4OH. The eluent was concentrated under reduced pressure, and the residue was dissolved in H_2O. The solution was poured into an Amberlite IRA-400 column, followed by washing with H_2O until the eluent became neutral, and then eluted with 2 N HCl. The eluent was evaporated in vacuo to give **31** (130 mg, 25%): IR (KBr) 1650 (COOH) cm^{-1}; NMR (CD_3OD) δ 1.2–2.2 (m, 10 H), 3.5–3.8 (m, 1 H), 4.0–4.5 (m, 2 H), 7.5–7.9 (m, 2 H), 9.0–9.2 (m, 1 H).

Method F. 1-(7-Chloroheptyl)imidazole. 1-[6-(Ethoxycarbonyl)hexyl]imidazole (14.0 g, 62 mmol) (prepared by method A-1) was added slowly at room temperature to a suspension of $LiAlH_4$ (3.4 g, 90 mmol) in dry THF (100 mL) and refluxed for 2 h. After cooling, the mixture was treated with 10% NaOH in the usual way and filtered. The filtrate was dried ($MgSO_4$) and evaporated, and the residual oil was distilled under vacuum [159–162 °C (1 mmHg)] to give 1-(7-hydroxyheptyl)imidazole (7.0 g, 62%) as a colorless oil. Then, thionyl chloride (30 g, 250 mmol) was added to a solution of the above alcohol (16.0 g, 90 mmol) in dry benzene (200 mL) at room temperature during 20 min and refluxed for 2 h. After the solution was evaporated, the residual oil was neutralized with saturated Na_2CO_3, extracted with CH_2Cl_2, and dried ($MgSO_4$), and the solution was evaporated under reduced pressure to give 1-(7-chloroheptyl)imidazole (17.4 g, 99%) as a pale brown oil: NMR ($CDCl_3$) δ 1.1–2.0 (m, 10 H), 3.51 (t, 2 H), 3.92 (t, 2 H), 6.86 (br s, 1 H), 7.0 (br s, 1 H), 7.43 (br s, 1 H).

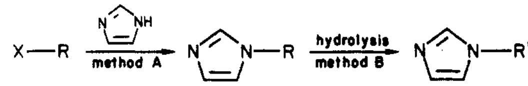
By the same procedure, 3-[4-(1-imidazolylmethyl)phenyl]propyl chloride and 1-(8-chlorooctyl)imidazole were prepared from ethyl 3-[4-(1-imidazolylmethyl)phenyl]propionate (prepared by method D-1) and 1-[7-(methoxycarbonyl)heptyl]imidazole (prepared by method A-1) in 69 and 97% yields, respectively.

Method G-1. 1-(7-Cyanoheptyl)imidazole (18). 1-(7-Chloroheptyl)imidazole (17.4 g, 87 mmol) (prepared by method F) was added at 40 °C during 20 min to a solution of NaCN (5.35 g, 110 mmol) in Me_2SO (50 mL) and heated at 100 °C for 5 h. After the solvent was removed under reduced pressure, the residue was diluted with H_2O (30 mL), extracted with CH_2Cl_2, and dried ($MgSO_4$). The solvent was evaporated and the residual oil was passed through a short column of silica gel using CH_2Cl_2. The eluate was distilled under vacuum [192–194 °C (1 mmHg)] to give **18** (14.6 g, 88%) as a colorless oil: IR (film) 2240 (CN) cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.0 (m, 10 H), 2.32 (t, 2 H), 3.92 (t, 2 H), 6.85 (t, 1 H), 7.00 (s, 1 H), 7.40 (s, 1 H).

Method G-2. 1-(7-Tetrazolylheptyl)imidazole (24). A mixture of **18** (1.4 g, 7.2 mmol) (prepared by method G-1), LiCl (314 mg, 7.4 mmol), NaN_3 (470 mg, 7.2 mmol), NH_4Cl (193 mg, 3.6 mmol), and DMF (5 mL) was stirred at 100–110 °C for 87 h. After the mixture was concentrated in vacuo, the residue was dissolved in EtOH, filtered, and evaporated. The residue was chromatographed on silica gel [eluent; $CHCl_3$–MeOH (97:3 to 93:7)] to give **24** (790 mg, 46%): NMR (CD_3OD) δ 1.2–1.5 (m, 6 H), 1.6–2.0 (m, 4 H), 2.91 (t, 2 H), 4.16 (t, 2 H), 7.27 (m, 2 H), 7.39 (m, 1 H), 8.33 (m, 1 H).

Method G-3. 1-(8-Mercaptooctyl)imidazole (19). A solution of 1-(8-chlorooctyl)imidazole (310 mg, 1.4 mmol) (prepared by method F) in degassed DMF (1 mL) was added at 0 °C to a solution of NaSH (120 mg, 2.1 mmol) in degassed DMF (20 mL) and stirred at room temperature for 1 h. The solution was diluted with H_2O (15 mL), extracted with Et_2O, washed with saturated NaCl, and dried (Na_2SO_4). After the solution was evaporated in vacuo, the residue was chromatographed on silica gel using

Table V. N-Alkylation of Imidazole and Its Hydrolysis



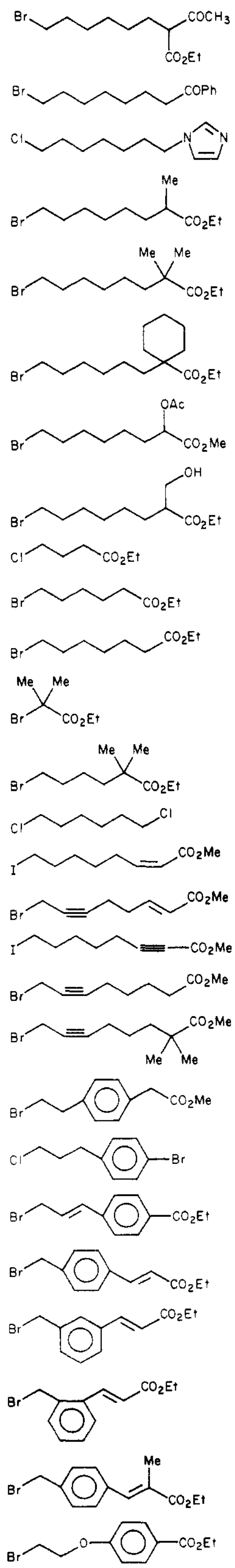
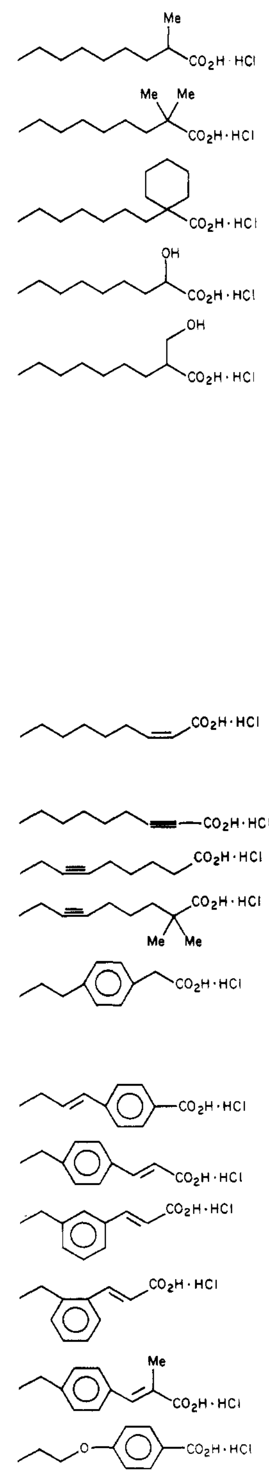
substrate: X-R	N-alkylated imidazoles: method	yield, %	compd	hydrolized product: method	yield, %	R'	compd
	A-1	60		B-3	96		16
	A-1	35	17				
	A-1	35	23				
	A-1	58		B-1	96		25
	A-1	87		B-1	95		26
	A-1	90		B-1	27		28
	A-1	59		B-1	90		30
	A-1	56		B-1	95		32
	A-1	45					
	A-1	56					
	A-1	70					
	A-1	34					
	A-1	78					
	A-4	36					
	A-5	57		B-1	95		38
	A-5	32					
	A-5	8		B-1	61		44
	A-5	48		B-1	95		46
	A-5	61		B-1	80		47
	A-1	40		B-1	71		49
	A-1	86					
	A-1	58		B-1	60		53
	A-1	50		B-1	68		54
	A-1	36		B-1	50		55
	A-1	45		B-1	60		56
	A-1	55		B-1	85		57
	A-1	55		B-1	87		58

Table V (*Continued*)

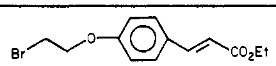
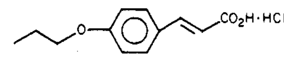
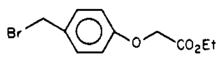
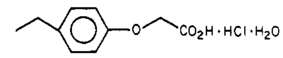
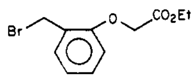
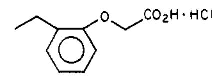
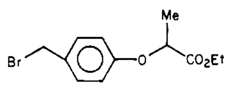
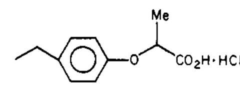
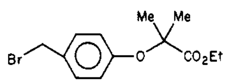
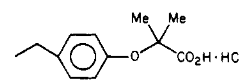
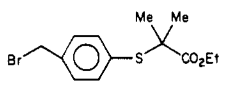
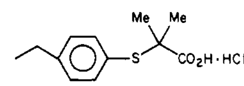
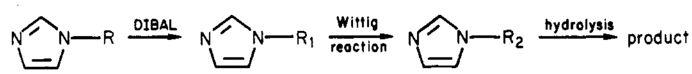
substrate: X-R	N-alkylated imidazoles: method	yield, %	compd	hydrolized product: method	yield, %	R′	compd
	A-1	52		B-1	78		**59**
	A-1	36		B-1	59		**60**
	A-1	35		B-1	82		**61**
	A-1	44		B-1	71		**62**
	A-1	57		B-1	72		**63**
	A-1	57		B-1	73		**64**

Table VI. Reduction, the Wittig Reaction, and Hydrolysis of 1-[(Ethoxycarbonyl)alkyl]imidazoles



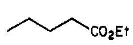
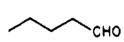
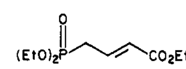
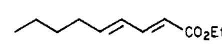
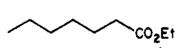
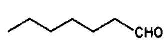
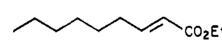
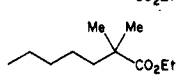
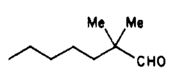
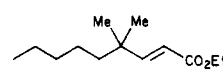
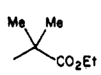
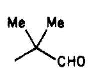
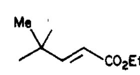
substrate (R)	reduction with DIBAL (R_1)	Wittig reaction: reagent	product (R_2)	hydrolysis	total yield, %
				**39**	39
		$(EtO)_2P(O)CH_2CO_2Et$		**37**	18
		$Ph_3P{=}CHCO_2Et$		**41**	43
		$Ph_3P{=}CHCO_2Et$			56

Table VII. Imidazole Derivatives

compd	mp, °C	formula[a]	recrystn solvent	compd	mp, °C	formula[a]	recrystn solvent
6	99-100.5	$C_{10}H_{16}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O	**38**	oil	$C_{11}H_{16}N_2O_2{\cdot}HCl$	
12	116.5-118	$C_{10}H_{16}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O	**39**	174-176	$C_{11}H_{14}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O
13	135-136.5	$C_{10}H_{16}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O	**40**	187-189	$C_{13}H_{18}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O
14	134-136	$C_{11}H_{18}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O	**41**	82-84	$C_{13}H_{20}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O
15	153-154	$C_{11}H_{18}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O	**42**	oil	$C_{11}H_{14}N_2O_2{\cdot}HCl$	
16	oil	$C_{12}H_{20}N_2O$		**43**	oil	$C_{11}H_{14}N_2O_2{\cdot}HCl$	
17	oil	$C_{17}H_{22}N_2O$		**44**	92-95	$C_{11}H_{14}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O
18	oil	$C_{11}H_{17}N_3$		**45**	81-83	$C_{11}H_{16}N_2O_2{\cdot}HCl$	EtOH
19	oil	$C_{11}H_{20}N_2S$		**46**	140-142	$C_{11}H_{14}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O
20	oil	$C_{12}H_{22}N_2S$		**47**	111-114	$C_{13}H_{18}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O
21	oil	$C_{12}H_{22}N_2OS$		**48**	165-167	$C_{13}H_{14}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O
22	236-240	$C_9H_{16}N_2O_3S$	EtOH-Et$_2$O	**49**	150-152	$C_{13}H_{14}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O
23	oil	$C_{13}H_{20}N_4$		**50**	200-203	$C_{13}H_{14}N_2O_2{\cdot}HCl$	EtOH
24	semicrystals	$C_{11}H_{18}N_6$		**51**	153-154	$C_{13}H_{14}N_2O_2{\cdot}HCl$	EtOH
25	oil	$C_{12}H_{20}N_2O_2{\cdot}HCl$		**52**	186-188.5	$C_{14}H_{16}N_2O_2{\cdot}HCl$	EtOH
26	oil	$C_{13}H_{22}N_2O_2{\cdot}HCl$		**53**	284-287	$C_{13}H_{12}N_2O_2{\cdot}HCl$	EtOH
27	oil	$C_{17}H_{22}N_2O_2{\cdot}HCl$		**54**	214-217	$C_{13}H_{12}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O
28	158-160	$C_{16}H_{26}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O	**55**	119-120	$C_{13}H_{12}N_2O_2{\cdot}HCl$	EtOH
29	oil	$C_{12}H_{18}N_2O_4{\cdot}HCl$		**56**	201-203.5	$C_{13}H_{12}N_2O_2{\cdot}HCl$	EtOH
30	oil	$C_{11}H_{18}N_2O_3{\cdot}HCl$		**57**	209-213	$C_{14}H_{14}N_2O_2{\cdot}HCl$	EtOH
31	semicrystals	$C_{11}H_{19}N_3O_2{\cdot}HCl$		**58**	230-235	$C_{12}H_{12}N_2O_3{\cdot}HCl$	EtOH-Et$_2$O
32	oil	$C_{12}H_{20}N_2O_3{\cdot}HCl$		**59**	214-217	$C_{14}H_{14}N_2O_3{\cdot}HCl$	EtOH
33	oil	$C_{11}H_{17}N_2O_2{\cdot}HCl$		**60**	92-96	$C_{12}H_{12}N_2O_3{\cdot}HCl{\cdot}H_2O$	EtOH-Et$_2$O-H$_2$O
34	oil	$C_{12}H_{18}N_2O_2{\cdot}HCl$		**61**	167-169	$C_{12}H_{12}N_2O_3{\cdot}HCl$	EtOH
35	oil	$C_{13}H_{22}N_2O_2{\cdot}HCl$		**62**	155-158	$C_{13}H_{14}N_2O_3{\cdot}HCl$	EtOH-CH$_3$CN-Et$_2$O
36	140-141	$C_{13}H_{22}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O	**63**	174-177	$C_{14}H_{16}N_2O_3{\cdot}HCl$	EtOH-Me$_2$CO-Et$_2$O
37	114-116	$C_{11}H_{16}N_2O_2{\cdot}HCl$	EtOH-Et$_2$O	**64**	169-171	$C_{14}H_{16}N_2O_2S{\cdot}HCl$	EtOH-Et$_2$O

[a] All compounds had C, H, and N analyses within ±0.4% of the theoretical values.

$CHCl_3$–MeOH (97:3) as eluent to give **19** (93 mg, 30%): NMR ($CDCl_3$) δ 1.1–2.0 (m, 13 H), 2.53 (q, 2 H), 3.94 (t, 2 H), 6.9 (m, 1 H), 7.05 (m, 1 H), 7.46 (br s, 1 H).

Method G-4. 1-[8-(Methylthio)octyl]imidazole (20). MeSH (30% MeOH solution; 0.48 mL, 3 mmol) was added to a solution of MeONa (270 mg, 5 mmol) in MeOH (1 mL) and stirred for 5 min. The mixture was added to a solution of 1-(8-chlorooctyl)-imidazole (420 mg, 2 mmol) (prepared by method F) in MeOH (2 mL) at room temperature and refluxed for 3 h. Then the mixture was dissolved in Et_2O (60 mL), washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel [eluent Et_2O–EtOAc (49:1) to Et_2O–MeOH (19:1)] to give **20** (220 mg, 50%): NMR ($CDCl_3$) δ 1.2–2.0 (m, 12 H), 2.09 (s, 3 H), 2.48 (t, 2 H), 3.92 (t, 2 H), 6.88 (m, 1 H), 7.04 (m, 1 H), 7.45 (m, 1 H).

1-[8-(Methylsulfinyl)octyl]imidazole (21). A solution of *m*-chloroperbenzoic acid (71 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of **20** (88 mg, 0.4 mmol) in CH_2Cl_2 (1 mL) at −78 °C. After stirring at ambient temperature for 20 min, the reaction mixture was poured into aqueous Na_2SO_3, extracted with Et_2O, washed with aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). The solution was concentrated and chromatographed on silica gel using $CHCl_3$–MeOH (19:1) to give **21** (67 mg, 71%): NMR ($CDCl_3$) δ 1.1–1.6 (m, 8 H), 1.6–2.0 (m, 4 H), 2.56 (s, 3 H), 2.6–2.8 (m, 2 H), 3.93 (t, 2 H), 6.90 (m, 1 H), 7.04 (m, 1 H), 7.46 (m, 1 H).

Method G-5. 1-(6-Sulfohexyl)imidazole (22). A mixture of 1-(6-chlorohexyl)imidazole (1.8 g, 9.6 mmol) (prepared by method F), $Na_2SO_3 \cdot 7H_2O$ (3.02 g, 12 mmol), and 1 N HCl (10 mL) was heated to remove H_2O for 2 h and at 120–130 °C for an additional 2 h. After the mixture was cooled to room temperature, concentrated HCl (5 mL) was added to the mixture, and the resulting crystals were filtered off and washed with H_2O (2 mL × 5). The filtrate and washings were combined and evaporated in vacuo. The residue was dissolved in EtOH (5 mL), filtered, and evaporated, and the residual crystals were recrystalized to give **22** (740 mg, 32%): NMR (D_2O) δ 1.2–2.1 (m, 8 H), 2.7–3.0 (m, 2 H), 4.25 (t, 2 H), 7.4–7.6 (m, 2 H), 8.72 (m, 1 H).

Method G-6. 4-[3-(1-Imidazolyl)propyl]benzoic Acid Hydrochloride (50). A mixture of 4-[3-(1-imidazolyl)propyl]-phenyl bromide (4.0 g, 15 mmol) (prepared by method A-1), CuCN (2.2 g, 25 mmol), and dry DMF (15 mL) was refluxed for 6 h. The hot reaction mixture was poured into a warm solution of NaCN (3 g) in H_2O (3 mL), shaked vigorously, extracted with benzene, washed with 10% aqueous NaCN (20 mL) and H_2O, and dried ($MgSO_4$). After the solvent was removed, the residual oil was chromatographed on silica gel using $CHCl_3$ to give 4-[3-(1-imidazolyl)propyl]benzonitrile (2.0 g, 63%) as a pale brown oil: IR (film) 2230 (CN) cm^{-1}; NMR ($CDCl_3$) δ 2.0–2.4 (m, 2 H), 2.55–2.8 (m, 2 H), 3.97 (t, 2 H), 6.87 (m, 1 H), 7.03 (m, 1 H), 7.21 (d, 2 H), 7,41 (br s, 1 H), 7.53 (d, 2 H). A solution of the above nitrile (1.0 g, 4.7 mmol) in concentrated HCl (10 mL) was refluxed for 3 h. After the solution was evaporated, the residual solid was dissolved in EtOH, and the solution was filtered and evaporated in vacuo. The residual crystals were recrystallized to give 4-[3-(1-imidazolyl)propyl]benzoic acid hydrochloride (**50**; 700 mg, 55%): IR (KBr) 1700 (COOH) cm^{-1}; NMR (Me_2SO-d_6) δ 2.0–2.4 (m, 2 H), 2.45–2.85 (m, 2 H), 4.29 (t, 2 H), 7.31 (d, 2 H), 7.66 (m, 1 H), 7.75–7.95 (m, 3 H), 9.28 (br s, 1 H).

Method G-7. (1) 1-(6-Carboxyhexyl)-2-methylimidazole Hydrochloride (14). A solution of 1-(6-chlorohexyl)-2-methylimidazole (4.19 g, 21 mmol) (prepared by method A-4) in Me_2SO (4 mL) was added at 40 °C to a mixture of NaCN (1.2 g, 25 mmol) and Me_2SO (20 mL) and stirred at 100 °C for 5 h. After the solution was concentrated in vacuo, the residue was extracted with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and evaporated under reduced pressure to give 1-(6-cyanohexyl)-2-methylimidazole (3.14 g, 78%) as a pale yellow oil: IR (film) 2250 (CN) cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.0 (m, 10 H), 2.32 (t, 2 H), 2.35 (s, 3 H), 3.81 (t, 2 H), 6.75 (d, 1 H), 6.84 (d, 1 H). The above nitrile was hydrolyzed as described in method G-6 to give **14** (34%) as colorless leaflets: IR (KBr) 1720 (COOH) cm^{-1}; NMR (Me_2SO-d_6) δ 1.1–2.0 (m, 8 H), 2.22 (t, 2 H), 2.64 (s, 3 H), 4.10 (t, 2 H), 7.52 (d, 1 H), 7.69 (d, 1 H).

(2) 4-[4-(1-Imidazolylmethyl)phenyl]butyric Acid Hydrochloride (52). By the same procedure, **52** was prepared from 3-[4-(1-imidazolylmethyl)phenyl]propyl chloride (prepared by method F) in a 50% yield: IR (KBr) 1755 (COOH) cm^{-1}; NMR (Me_2SO-d_6) δ 1.6–2.0 (m, 2 H), 2.2 (t, 2 H), 2.60 (t, 2 H), 5.42 (s, 2 H), 7.18 (d, 2 H), 7.36 (d, 2 H), 7.62 (m, 1 H), 7.77 (m, 1 H), 9.41 (m, 1 H), 9.5–11.5 (br, 1 H).

Method H-1. 1-[(7*RS*)-7-Carboxy-7-phenylheptyl]-imidazole Hydrochloride (27). Ethyl phenylacetate (660 mg, 4 mmol) was added slowly to a mixture of LDA (0.32 M THF solution; 12.5 mL, 4 mmol) and THF (5 mL) at −78 °C and stirred at −50 °C for 30 min. A solution of 1-(6-chlorohexyl)imidazole (370 mg, 2 mmol) (prepared by method A-4) in THF (1.5 mL) was added to the solution at −50 °C. After warming slowly to −20 °C, the reaction mixture was allowed to stand for 2 days. After the mixture was cooled to −78 °C, H_2O–THF (2:1) (6 mL) was added slowly, extracted with Et_2O, washed with brine, and dried (Na_2SO_4). After concentration in vacuo, the residue was chromatographed on silica gel using MeOH–$CHCl_3$ (1:300) to give 1-[(7*RS*)-7-(ethoxycarbonyl)-7-phenylheptyl]imidazole (370 mg, 59%): IR (film) 1730 (COOEt) cm^{-1}; NMR ($CDCl_3$) δ 1.20 (t, 3 H), 3.51 (t, 1 H), 3.89 (t, 2 H), 4.12 (m, 2 H), 6.88 (m, 1 H), 7.04 (m, 1 H), 7.30 (s, 1 H), 7.44 (m, 1 H); MS, *m/e* 314 (M^+, 91), 313 (50), 241 (54), 151 (100), 138 (67), 137 (72), 95 (64), 91 (89), 82 (89). The above ester was hydrolyzed as described in method B-1 to give **27** in an 80% yield: IR (film) 1720 (COOH) cm^{-1}; NMR (D_2O) δ 1.1–1.5 (m, 6 H), 1.6–2.2 (m, 4 H), 3.7 (q, 1 H), 4.21 (t, 2 H), 7.3–7.6 (m, 7 H), 8.74 (m, 1 H).

Method H-2. 1-(7,7-Dicarboxyheptyl)imidazole Hydrochloride (29). Diethyl malonate (920 mg, 5.75 mmol) was added to a solution of Na (126 mg, 5.5 mmol) in EtOH (5 mL) at 60 °C and stirred for 15 min. Then a solution of 1-(6-chlorohexyl)-imidazole (930 mg, 5 mmol) (prepared by method A-4) in EtOH (3 mL) was added to the mixture and refluxed for 6 h. After cooling, the mixture was evaporated in vacuo, and the residue was dissolved in Et_2O (20 mL), washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo. The residue (crude diethyl ester; 820 mg) was hydrolyzed as described in method B-1 to give **29** (720 mg, 50%): IR (film) 1730 (COOH) cm^{-1}; NMR (D_2O) δ 1.0–2.2 (m, 10 H), 3.65 (t, 1 H), 4.28 (t, 2 H), 7.45–7.6 (m, 2 H), 8.78 (br s, 1 H).

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