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Synthesis of 5-Alkyl-4-oxazoleacetic Acid Derivatives with Hypolipidemic Activities[1)]

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A series of 2-aryl and 2-alkyl derivatives of 5-alkyl-4-oxazoleacetic acids was synthesized and tested for hypolipidemic activity. Among them, 5-isopropyl-2-(4-fluorophenyl)-4-oxazoleacetates exhibited potent activities, being more active than clofibrate [ethyl 2-(4-chlorophenoxy)isobutyrate].

Keywords——hypolipidemic agent; 5-alkyl-4-oxazoleacetic acid; hypocholesterolemic activity; hypotriglyceridemic activity; platelet aggregation inhibition; aspartic acid azlactone; Dakin–West reaction

In the course of our studies on the development of hypolipidemic agents, a series of 2,5-disubstituted 4-oxazoleacetic acid derivatives was previously prepared and screened for hypolipidemic activity. Among them, some derivatives carrying thienyl[2)] and furyl[3)] groups at C-5 on the oxazole ring showed moderate to high activities. Above all, ethyl 2-(4-chlorophenyl)-5-(2-furyl)-4-oxazoleacetate has been found to be the most promising candidate for development with reduction of serum cholesterol and triglyceride in normal rats and especially in THLR/1 rats, a model of hereditary hyperlipidemia developed in our laboratory.[4)]

Meanwhile, several research groups have also prepared 4-oxazoleacetic acid derivatives with various pharmaceutical activities. Brown reported that 2,5-diaryl and 2-cycloalkyl-4-oxazoleacetic acids were effective antiinflammatory agents.[5)] Yamanaka *et al.* showed ethyl 2-(4-chlorophenyl)-5-ethoxy-4-oxazoleacetate to be hypolipidemic.[6)] Recently, Meguro *et al.* reported 5-alkyl-2-cycloalkyl-4-oxazoleacetic acid derivatives as hypoglycemic agents.[7)] Thus, the substituents on the oxazole ring of 4-oxazoleacetic acid derivatives were considered to play an important role in the various physiological activities. Consequently, the relationships between structure and physiological properties are of much interest.

The present study was undertaken to obtain a further insight into the hypolipidemic activity–structure relationships of 4-oxazoleacetic acid derivatives carrying 5-alkyl substituents.

Chemistry

Ethyl 4-oxazoleacetates (**17**—**25**) and the acids (**26**—**31**) were synthesized (as outlined in Chart 1) according to our previously reported method.[2,3)] The key intermediates, ethyl 3-(*N*-acylamino)-4-oxobutyrates (**8**—**16**), were prepared in two ways: by introduction of an acetic

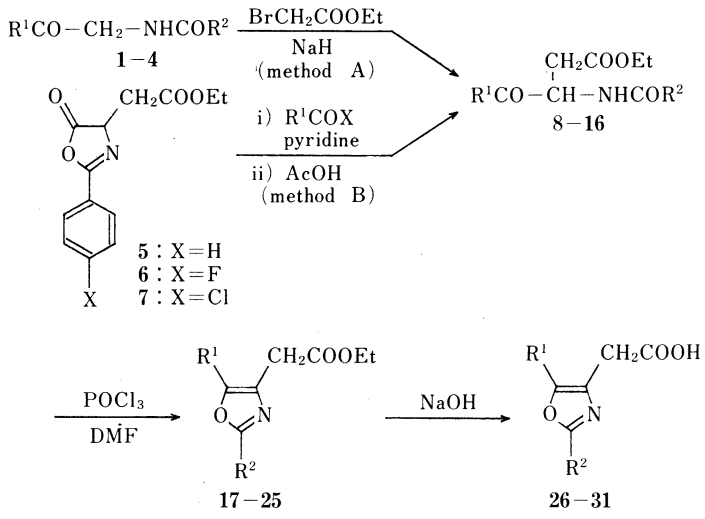
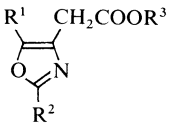


Chart 1

TABLE I. Physicochemical Properties and Physiological Activities of Ethyl 4-Oxazoleacetates and the Acids



Compd. No.	R^1	R^2	R^3	Yield[a] (%)	mp (°C)	IR[b] (cm^{-1}) $\nu_{C=O}$	Formula[c]	Reduction[d] Cho	Reduction[d] TG	Inhibition of platelet aggregation[f]
17	Me	4-Cl-Ph	Et	71	69—70	1725	$C_{14}H_{14}ClNO_3$	19[g]	36	−
18	iso-Pro	4-Cl-Ph	Et	79	70—71	1725	$C_{16}H_{18}ClNO_3$	18	55	+
19	cyclo-Pro	4-Cl-Ph	Et	64	66—67	1725	$C_{16}H_{16}ClNO_3$	12	34[g]	−
20	iso-Bu	4-Cl-Ph	Et	63	56—57	1730	$C_{17}H_{20}ClNO_3$	13	22	+
21	*n*-Pen	4-Cl-Ph	Et	84	52—53	1725	$C_{18}H_{22}ClNO_3$	15	52[g]	−
22	cyclo-Pen	4-Cl-Ph	Et	50	63—64	1730	$C_{18}H_{20}ClNO_3$	12	30[g]	++
23	iso-Pro	iso-Pro	Et	82	Syrup	1740	$C_{13}H_{21}NO_3$	e)	e)	e)
24	iso-Pro	Ph	Et	81	37—38	1730	$C_{16}H_{19}NO_3$	8	8	+
25	iso-Pro	4-F-Ph	Et	61	59—60	1725	$C_{16}H_{18}FNO_3$	23[g]	33	+
26	Me	4-Cl-Ph	H	83	160—161	1695	$C_{12}H_{10}ClNO_3$	14	48[g]	−
27	iso-Pro	4-Cl-Ph	H	92	171—172	1720	$C_{14}H_{14}ClNO_3$	12	39	+
28	*n*-Pen	4-Cl-Ph	H	87	136—137	1705	$C_{16}H_{18}ClNO_3$	19[g]	59[h]	−
29	iso-Pro	iso-Pro	H	57	85—86	1725	$C_{11}H_{17}NO_3$	5	14	−
30	iso-Pro	Ph	H	97	141—143	1725	$C_{14}H_{15}NO_3$	11	23	+
31	iso-Pro	4-F-Ph	H	83	137—138	1725	$C_{14}H_{14}FNO_3$	21[g]	42[g]	+
33	H	4-Cl-Ph	Et	52	65—66	1740	$C_{13}H_{12}FNO_3$	22[h]	−10	e)
34	H	4-Cl-Ph	H	56	186—188	1720	$C_{11}H_8ClNO_3$	19[g]	−16	e)
Clofibrate								15±1[i]	30±2[i]	

a) Yields of the ethyl 4-oxazoleacetates (**17**—**25**) and the acids (**26**—**31** and **34**) were calculated based on the corresponding ethyl 3-(*N*-acylamino)-4-oxocarboxylates (**8**—**16**) and ethyl oxazoleacetates (**17**—**25** and **33**). *b*) In Nujol mull. *c*) All compounds were analyzed for C, H, Cl, F and N and the results were within ±0.4% of theory. *d*) Male S.D. rats. Dosing at 0.05% in the diet for 7 d. Cho, cholesterol; TG, triglyceride. *e*) No evaluation. *f*) *In vitro* data (100 μg/ml); (+) indicates ≥10% but <aspirin (34—96%); (++) indicates inhibition ≥aspirin (see Experimental). *g*) Significant depression with $p<0.05$ by Student's *t*-test. *h*) Significant depression with $p<0.01$ by Student's *t*-test. *i*) Means±S.E. ($N=33$).

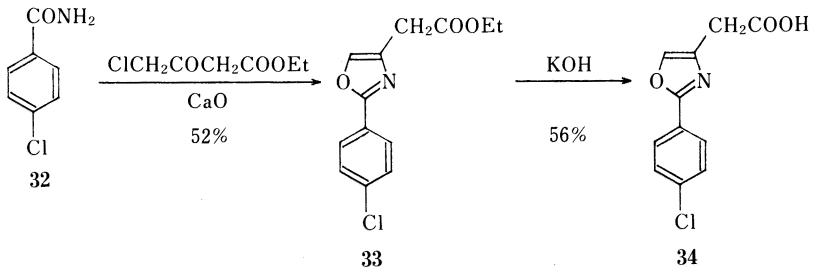


Chart 2

acid moiety into (*N*-acylamino)methyl ketones (**1**—**4**) (method A) and by Dakin–West reaction of aspartic acid azlactones (**5**—**7**) (method B).[8] Dehydrative cyclization of the intermediates (**8**—**16**) to ethyl 4-oxazoleacetates (**17**—**25**) and subsequent saponification to the corresponding acids (**26**—**31**) were carried out with Vilsmeier–Haack reagent and aqueous sodium hydroxide, respectively, and the results are listed in Table I. Ethyl 2-(4-chlorophenyl)-4-oxazoleacetate (**33**) was directly prepared in a good yield as shown in Chart 2 by the reaction of 4-chlorobenzamide (**32**) with ethyl γ-chloroacetoacetate instead of Brown's rather indirect method.[5]

Biological Results and Discussion

Hypolipidemic activity and inhibitory effect on platelet aggregation were assayed according to the method previously described.[2] The reductions of serum cholesterol and serum triglyceride were calculated after dosing male Sprague-Dawley (SD) rats for 5 d at 0.05% in the diet in comparison to the control group, and the results are listed in Table I. At first we examined the effect of the substituent at the 5-position of 2-(4-chlorophenyl)-4-oxazoleacetates. The ester (**33**) and the carboxylic acid (**34**), which are unsubstituted at C-5 on the oxazole ring, lowered the level of serum cholesterol. However, they also produced an unfavorable elevation of the level of serum triglyceride. On the other hand, the compounds substituted with an alkyl group at the 5-position generally decreased both serum cholesterol and triglyceride (see compounds **17**—**22** and **26**—**28**). As for the 5-substituted derivatives, acyclic compounds were more active than their cyclic counterparts (**18** and **21** were more potent than **19** and **22**, respectively).

We then examined the effect of the substituents at C-2 of 5-isopropyl-4-oxazoleacetates, since the isopropyl group is regarded as one of the most effective substituents at C-5. As was the case with the derivatives carrying a thienyl group at the 5-position,[2] the following tendencies were observed. The derivatives with an alkyl group at the 2-position (**29**) showed lower activities than those having an aryl group. On the other hand, the compounds having a 4-halogenophenyl group (**18**, **25**, **27** and **31**) showed relatively potent activities. As regards aromatic substituents at C-2 on the oxazole ring, activities were augmented in the order of phenyl, 4-chlorophenyl and 4-fluorophenyl (**24** < **18** < **25**, **30** < **27** < **31**). It was noted that 5-isopropyl-2-(4-fluorophenyl)-4-oxazoleacetates (**25**, **31**) were more potent than clofibrate, which was used as an active control for hypolipidemic activity.

Moreover, the series of these compounds having an aryl group at the 2-position inhibited platelet aggregation, which would be a good associated activity for hypolipidemic agents for the prevention of coronary heart disease. For example, compound **30** inhibited platelet aggregation by 97±2% after a single oral administration of 100 mg/kg *ex vivo* in rats.

Interestingly, these compounds showed neither antiinflammatory nor hypoglycemic activities.

Experimental

Melting points were measured on a Yamato melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained using Hitachi Perkin-Elmer R-20A high-resolution NMR spectrometer with tetramethylsilane as the internal standard. Mass spectra (MS) were taken on a Hitachi RMU-3M spectrometer at an ionizing potential of 30 eV.

Materials——α-Amino ketone hydrochlorides were prepared from 4-oxazolecarboxylates by acid hydrolysis using the reported method.[9] Ethyl 3-(4-chlorobenzoylamino)-5-methyl-4-oxohexanoate (**11**) and ethyl 3-(4-chlorobenzoylamino)-4-cyclopentyl-4-oxobutanoate (**16**) were prepared by our previous procedure.[8]

Typical Procedure for the Preparation of (*N*-Acylamino)methyl Ketones (1—4)——[*N*-(4-Chlorobenzoyl)amino]-methyl Isobutyl Ketone (**3**): 4-Chlorobenzoyl chloride (4.9 g, 0.028 mol) was added dropwise to a mixture of aminomethyl isobutyl ketone hydrochloride (3.8 g, 0.025 mol), sodium bicarbonate (5.04 g, 0.060 mol), ethyl acetate (200 ml) and water (100 ml) at 5—10 °C with stirring. The mixture was further stirred at room temperature for 3 h. The ethyl acetate layer was washed with water, dried over magnesium sulfate and then evaporated. The residue was crystallized from a mixed solvent of diisopropyl ether and *n*-hexane to afford colorless crystals of **3** (6.2 g, 97.5%). mp 125—126 °C. IR (Nujol): 3320, 1718, 1635 cm^{-1}. NMR ($CDCl_3$) δ: 7.34 and 7.71 (2H each, $A'_2B'_2$, $J=9$ Hz), 6.87 (1H, br d, $J=5$ Hz), 4.27 (2H, d, $J=5$ Hz), 1.90—2.60 (3H, m), 0.97 (6H, d, $J=6$ Hz). MS *m/z*: 253 (M^+).

A similar procedure was followed for other acylaminomethyl ketones (**1**, **2** and **4**) starting from the corresponding aminomethyl ketone hydrochlorides. The yields and physicochemical data are shown in Table II.

Typical Procedure for the Synthesis of Ethyl 3-*N*-Acylamino-4-oxocarboxylates (8—10 and 12—15)——Method

TABLE II. Synthesis of (*N*-Acylamino)methyl Ketones

R^1–CO–CH_2–NH–COR^2

Compd. No.	R^1	R^2	Yield[a] (%)	mp (°C)	IR[b] (cm^{-1}) ν_{NH}	$\nu_{C=O}$ (ketone)	$\nu_{C=O}$ (amide)
1	iso-Pro	iso-Pro	56	45—46	3260	1718	1635
2	cyclo-Pro	4-Cl-Ph	84	175—176	3330	1720	1640
3	iso-Bu	4-Cl-Ph	78	125—126	3320	1718	1635
4	*n*-Pen	4-Cl-Ph	70	120—121	3300	1715	1640

a) Isolation yields based on the aminomethyl ketones. *b*) In Nujol mull.

TABLE III. Synthesis of Ethyl 3-Acylamino-4-oxobutyrates

R^1–CO–CH(CH_2–COOEt)–NH–COR^2

Compd.[c] No.	R^1	R^2	Method[d]	Yield[a] (%)	mp (°C)	IR[b] (cm^{-1}) ν_{NH}	$\nu_{C=O}$ (ketone)	$\nu_{C=O}$ (amide)
8	Me	4-Cl-Ph	B	65	57—59	3290	1720	1635
9	iso-Pro	Ph	B	68	44—46	3270	1720	1640
10	iso-Pro	4-F-Ph	B	90	Syrup	3330	1720	1645
12	iso-Pro	iso-Pro	A	84	Syrup	3300	1720	1650
13	cyclo-Pro	4-Cl-Ph	A	69	Syrup	3300	1730	1650
14	iso-Bu	4-Cl-Ph	A	74	61—63	3290	1728	1640
15	*n*-Pen	4-Cl-Ph	A	56	67—69	3280	1720	1635

a) Isolation yields based on the (*N*-acylamino)methyl ketones (method A) and aspartic acid azlactones (method B). *b*) In Nujol mull. *c*) Compounds **11** (R^1=iso-Pro, R^2=4-Cl-Ph) and **16** (R^1=cyclo-Pen, R^2=4-Cl-Ph) were prepared according to ref. 8. *d*) A: Ethoxycarbonylmethylation of (*N*-acylamino)methyl ketones. B: Dakin-West reaction of aspartic acid azlactones.

A: Ethyl 3-(4-Chlorobenzoylamino)-6-methyl-4-oxoheptanoate (**14**): Compound **3** (2.5 g, 0.0099 mol) was added portionwise to a suspension of sodium hydride dispersion (61% in paraffine, 0.5 g, 0.0127 mol) in *N*,*N*-dimethylformamide (15 ml) at −40 to −50 °C. Then ethyl bromoacetate (1.8 g, 0.0111 mol) was added to the mixture at the same temperature. After gradual warming of the mixture to 10 °C during 30 min, the reaction was quenched with acetic acid. The mixture was poured into water and extracted three times with ethyl acetate. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate and then evaporated *in vacuo*. The residue was crystallized from a mixture of diisopropyl ether and *n*-hexane to afford colorless crystals of **14** (2.5 g, 74.4%). mp 61—63 °C (dec.). IR (Nujol): 3290, 1728, 1640 cm^{-1}. NMR ($CDCl_3$) δ: 7.34 and 7.70 (2H each, $A_2'B_2'$, J=9 Hz), 7.20—7.80 (1H, br), 4.65—5.13 (1H, m), 4.12 (2H, q, J=7 Hz), 2.95 (1H, d, J=2.0 Hz), 2.88 (1H, d, J=3.0 Hz), 1.90—2.60 (3H, m), 1.24 (3H, t, J=7 Hz), 0.92 (6H, d, J=6 Hz). MS *m/z*: 340 (M^+).

The ethyl acetate moiety was similarly introduced into the other (*N*-acylamino)methyl ketones to afford 3-(*N*-acylamino)-4-oxocarboxylates (**12**, **13** and **15**); the yields and physicochemical data are listed in Table III.

Method B: Ethyl 3-(4-Chlorobenzoylamino)-4-oxopentanoate (**8**): Acetic anhydride (2.86 g, 0.028 mol) was added dropwise to a solution of **7** (7.05 g, 0.025 mol) in pyridine (10 ml) under cooling with ice. The mixture was stirred at room temperature for 1 h and at 50—60 °C for 2 h. Then acetic acid (3.61 ml) was added at 55 °C and the mixture was poured into brine and extracted with ethyl acetate. The extracts were combined, washed successively with 5% hydrochloric acid, water, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and evaporated. The residue was crystallized from a mixed solvent of diisopropyl ether and *n*-hexane to afford colorless crystals of **8** (4.83 g, 65%). mp 57—59 °C. IR (KBr): 3290, 1720, 1635 cm^{-1}. NMR ($CDCl_3$) δ: 7.35 and 7.72 (2H each, $A_2'B_2'$, J=9 Hz), 7.10—7.90 (1H, br), 4.65—5.15 (1H, m), 4.15 (2H, q, J=7 Hz), 3.02 (1H, d, J=2 Hz), 2.93 (1H, d, J=3 Hz), 2.30 (3H, s), 1.26 (3H, t, J=7 Hz). MS *m/z*: 254 ($M^+ - Ac$).

Similarly, Dakin–West reaction of other aspartic acid azlactones (**5** and **6**) with 2-methylpropionic anhydride was carried out to afford the corresponding ethyl 3-*N*-acylamino-4-oxocarboxylates (**9** and **10**). The yields and physicochemical data are shown in Table III.

Typical Procedure for the Synthesis of Ethyl 4-Oxazoleacetates (17—25)——Ethyl 2-(4-Chlorophenyl)-5-isopropyl-4-oxazoleacetate (**18**): Phosphoryl chloride (7.1 g, 0.046 mol) was added dropwise to a solution of **11** (10 g, 0.031 mol) in *N*,*N*-dimethylformamide (30 ml) at 0—5 °C. The mixture was stirred at the same temperature for 3 h and then at room temperature for an additional 2 h. The reaction mixture was poured into ice-water, and neutralized with sodium bicarbonate. The aqueous mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The residue was crystallized from ethanol to afford colorless crystals of **18** (7.5 g, 79.4%). mp 70—71 °C. IR (Nujol): 1725, 1635 cm^{-1}. NMR (CDCl) δ: 7.88 and 7.33 (2H each, $A_2'B_2'$, J=8 Hz), 4.16 (2H, q, J=7 Hz), 3.57 (2H, s), 2.80—3.35 (1H, m), 1.34 (6H, d, J=7 Hz), 1.28 (3H, t, J=7 Hz). MS *m/z*: 307 (M^+).

In a similar manner, dehydrative cyclization of the other butyrates (**8**—**10** and **12**—**16**) was performed to give the corresponding oxazoleacetates (**17** and **19**—**25**). The yields and physicochemical data are listed in Table I.

Typical Procedure for Saponification of Ethyl 4-Oxazoleacetates (17, 18, 21 and 23—25 to 26—31)——2-(4-Chlorophenyl)-5-isopropyl-4-oxazoleacetic Acid (**27**): Potassium hydroxide (4.4 g, 0.078 mol) was added to a solution of **18** (6 g, 0.020 mol) in methanol (100 ml) and water (10 ml). The mixture was stirred at room temperature for 10 h, then evaporated *in vacuo*. Water was added to the residue and the aqueous solution was acidified (pH 2) with concentrated hydrochloric acid, and then extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and finally evaporated *in vacuo*. The residue was crystallized from ethanol to afford colorless crystals of **27** (5 g, 91.7%). mp 171—172 °C. IR (Nujol): 1720 cm^{-1}. NMR (DMSO-d_6) δ: 7.52 and 7.90 (2H each, $A_2'B_2'$, J=9 Hz), 3.55 (2H, s), 2.92—3.75 (1H, m), 1.27 (6H, d, J=7 Hz). MS *m/z*: 279 (M^+).

The esters (**17**, **21** and **23**—**25**) were saponified in a similar way. The yields and physicochemical data of the acids (**26** and **28**—**31**) obtained are listed in Table I.

Ethyl 2-(4-Chlorophenyl)-4-oxazoleacetate (33)——A mixture of 4-chlorobenzamide (10 g, 0.065 mol), ethyl γ-chloroacetoacetate (15 g, 0.091 mol) and calcium oxide (2.24 g, 0.04 mol) was heated at 130—140 °C for 6 h. After cooling of the mixture, chloroform was added and undissolved materials were removed by filtration. The filtrate was evaporated and the residue was chromatographed on silica-gel column ($CHCl_3$: AcOEt=10:1). The crude products were recrystallized from diisopropyl ether to afford colorless crystals of **33** (9.0 g, 52%). mp 65—66 °C. IR (Nujol): 3200, 1740, 1610 cm^{-1}. NMR ($CDCl_3$) δ: 7.38 and 7.93 (2H each, $A_2'B_2'$, J=9 Hz), 7.68 (1H, s), 4.21 (2H, q, J=7 Hz), 3.66 (2H, s), 1.27 (3H, t, J=7 Hz). MS *m/z*: 265 (M^+).

2-(4-Chlorophenyl)-4-oxazoleacetic Acid (34)——Aqueous sodium hydroxide (10%, 20 ml) was added to a solution of **33** (5.4 g, 0.020 mol) in methanol (50 ml) and the mixture was heated on steam bath for 30 min. After cooling, the mixture was acidified (pH 2) by adding concentrated hydrochloric acid and the crystals formed were collected and washed with ethyl acetate to afford **34** (2.8 g, 56%). mp 186—188 °C (dec.). IR (Nujol): 3150, 1720, 1610, 1550 cm^{-1}. NMR ($CDCl_3$ + DMSO-d_6) δ: 10.00—11.00 (1H, br), 7.42 and 7.96 (2H each, $A_2'B_2'$, J=9 Hz), 7.75 (1H, s), 3.66 (2H, s). MS *m/z*: 237 (M^+).

Hypolipidemic Activity——Commercial male SD rats (4 weeks old, five animals per group) were used. The concentration of a test compound in the diet was 50 mg/100 g. After 8 d of the experimental diet, the levels of serum

cholesterol and triglyceride were measured as previously described.[2,3]

The hypolipidemic activity of the test compound is expressed in Table I as percent depression of serum lipid levels compared to the control group. Clofibrate, used as a positive control drug, reduced serum cholesterol and triglyceride by $15 \pm 1\%$ and $30 \pm 2\%$ ($N = 33$), respectively, under these conditions.

Inhibitory Effect on Collagen-Induced Platelet Aggregation *in Vitro* ——Inhibition of platelet aggregation was measured using blood of commercial male SD rats according to the method previously described,[2,3] and calculated by means of the following equation:

inhibition of platelet aggregation =

[1 − (degree of platelet aggregation with test agent)/(degree of platelet aggregation without test agent)] × 100

The inhibitory effect of test compounds was expressed as (−) if the percent inhibition was less than 10%, (+) if the inhibition was equal to or above 10% but less than the inhibition (34—96%) concurrently obtained with aspirin (100 μg/ml), and (++) if the inhibition was equal to or above the inhibition by aspirin. The results are summarized in Table I.

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