chromatography (hexane/EtOAc, 1/1) gave a white solid (**95**, R = H, 2.36 g, 30.7%): mp 175–177 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.64 (s, 3 H, CO_2CH_3), 5.08 (s, 2 H, $-NCH_2-$), 7.02 (t, J = 7.2 Hz, 1 H, Ar*H*), 7.37 (t, J = 7.4 Hz, 1 H, Ar*H*), 7.44 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.66 (d, J = 7.6 Hz, 1 H, Ar*H*), 10.75 (br s, 1 H, $-NH-$); IR (KBr, cm^{-1}) 3000 (NH); 1765 (C=O), 1625 (C=O); MS (*m/e*) 206 (30, M$^+$). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-3-oxo-1*H*-indazole-1-acetic Acid Methyl Ester (96, R = H, R^1 = 4-Br,2-FC$_6$H$_3$CH$_2$). To a solution of 2,3-dihydro-3-oxo-1*H*-indazole-1-acetic acid methyl ester (**95**, R = H, 0.8 g, 3.88 mmol) in DMF (30 mL) was added NaH (80%, 140 mg, 4.65 mmol) and the mixture was stirred for 2 h. 4-Bromo-2-fluorobenzyl bromide (1.55 g, 5.82 mmol) was added, and the mixture was stirred for 1 h, poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 4/1) gave a white solid (1.35 g, 88.8%): mp 109–111 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.66 (s, 3 H, CO_2CH_3), 5.21 (s, 2 H, NCH_2CO_2Me), 5.39 (s, 2 H, $-NCH_2-$), 7.09 (t, J = 7.0 Hz, 1 H, Ar*H*), 7.4–7.65 (m, 6 H, Ar*H*); IR (KBr, cm^{-1}) 1745 (C=O), 1625 (C=O); MS (*m/e*) 392 (7, M$^+$). Anal. ($C_{17}H_{14}BrFN_2O_3$) C, H, N.

2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-3-oxo-1*H*-indazole-1-acetic Acid (64). To a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-2,3-dihydro-3-oxo-1*H*-indazole-1-acetic acid methyl ester (**96**, R = H, R^1 = 4-Br,2-FC$_6$H$_3$CH$_2$, 1.2 g, 3.05 mmol), THF (30 mL), and MeOH (30 mL) was added aqueous NaOH (2.5 N, 5 mL). After stirring for 30 min the mixture was neutralized with HCl (2 N), and most of the volatiles were removed in vacuo. The precipitated solid was filtered, washed with H_2O, and dried to give a white solid (**64**, 0.79 g, 69.3%): mp 134–136 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) d 5.05 (s, 2 H, NCH_2CO_2H), 5.37 (s, 2 H, $-NCH_2-$), 7.0 (t, J = 7.42 Hz, 1 H, Ar*H*), 7.36 (t, J = 7.82 Hz, 1 H, Ar*H*), 7.45 (dd, J = 8.2 Hz, 1.86 Hz, 1 H, Ar*H*), 7.5 (d, J = 8.51 Hz, 1 H, Ar*H*), 7.58–7.63 (m, 3 H, Ar*H*), 12.15 (br s, 1 H, CO_2H); IR (KBr, cm^{-1}) 3450 (OH), 3200–2700 (CO_2H), 1720 (C=O), 1620 (C=O); MS (CI) (*m/e*) 379 (78, M$^+$ + H). Anal. ($C_{10}H_{12}BrFN_2O_3$) C, H, N.

Preparation of 16. Compound **16** was synthesized according to the following procedures.

1-[(3,4-Dichlorophenyl)methyl]-1*H*-perimidin-2(3*H*)-one (102). To a suspension of 1,8-diaminonaphthalene (4.8 g, 30.38 mmol) in DMF (100 mL) were added α,3,4-trichlorotoluene (4.21 mL, 30.38 mmol) and Et_3N (4.23 mL, 30.38 mmol). After stirring at 65 °C for 15 h the mixture was poured into H_2O and extracted with EtOAc, and the organic extracts were dried over $MgSO_4$. Evaporation gave a brown solid (6.2 g), which was dissolved in dioxane (100 mL) and treated with phosgene (20% w/w in toluene, 14.05 g) at 100 °C for 2.5 h. The mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Crystallization from acetone/hexane/Et_2O (after cooling to −20 °C) gave a brown solid (**102**, 4.5 g, 43.2%): mp 263–265 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 5.14 (s, 2 H, $-NCH_2-$), 6.5 (t, J = 7.2 Hz, 1 H, Ar*H*) 6.65 (d, J = 7.4 Hz, 1 H, Ar*H*), 7.28 (m, 5 H, Ar*H*), 7.57 (d, J = 8.2 Hz, 1 H, Ar*H*), 7.67 (d, 1.8 Hz, 1 H, Ar*H*), 10.64 (s, 1 H, $-NHCO-$); IR (KBr, cm^{-1}) 3200 (NH), 1690 (C=O); MS (*m/e*) (29, M$^+$). Anal. ($C_{18}H_{12}Cl_2N_2O$) C, H, N.

3-[(3,4-Dichlorophenyl)methyl]-2,3-dihydro-2-oxo-1*H*-perimidine-1-acetic Acid Methyl Ester (103). To a mixture of 1-[(3,4-dichlorophenyl)methyl]-1*H*-perimidin-2(3*H*)-one (**102**, 3.2 g, 9.33 mmol), K_2CO_3 (1.54 g, 11.19 mmol), and DMF (50 mL) was added methyl bromoacetate (1.06 mL), 11.19 mmol). After stirring at 75 °C for 36 h, the mixture was poured into H_2O and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 3/1) gave a brown solid (**103**, 2.19, 54.2%): mp 129–131 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.73 (s, 3 H, CO_2CH_3), 4.88 (s, 2 H, NCH_2CO_2Me), 5.23 (s, 2 H, $-NCH_2-$), 6.7 (m, 2 H, Ar*H*), 7.37 (m, 5 H, Ar*H*), 7.63 (m, 2 H, Ar*H*); IR (KBr, cm^{-1}) 1750 (C=O), 1665 (C=O); MS (*m/e*) 414 (27, M$^+$). Anal. ($C_{21}H_{16}Cl_2N_2O_3$) C, H, N.

3-[(3,4-Dichlorophenyl)methyl]-2,3-dihydro-2-oxo-1*H*-perimidine-1-acetic Acid (16). To a solution of 3-[(3,4-dichlorophenyl)methyl]-2,3-dihydro-2-oxo-1*H*-perimidine-1-acetic acid methyl ester (**103**, 2.0 g, 4.82 mmol) in MeOH (30 mL) and THF (30 mL) was added aqueous NaOH (2.5 N, 10 mL). After stirring for 30 min the mixture was neutralized with HCl (2 N), and the volatiles were removed in vacuo. The residue was acidified with HCl (2 N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on acid-washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc, 1/1) gave a white solid (**16**, 1.3 g, 67.3%): mp 230–231 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.75 (s, 2 H, NCH_2CO_2H), 5.22 (s, 2 H, $-NCH_2-$), 6.6 (dd, J = 7.1 Hz, 1.44 Hz, 1 H, Ar*H*), 6.7 (d, J = 7.1 Hz, 1 H, Ar*H*), 7.28–7.41 (m, 5 H, Ar*H*), 7.62 (d, J = 8.33 Hz, 1 H, Ar*H*), 7.63 (d, J = 1.83 Hz, 1 H, Ar*H*). 11.99 (br s, 1 H, CO_2H); IR (KBr, cm^{-1}) 3200–2700 (CO_2H), 1710 (C=O), 1680 (C=O); MS (*m/e*) 400 (14, M$^+$). Anal. ($C_{20}H_{14}Cl_2N_2O_3$) C, H, N.

Acknowledgment. We gratefully acknowledge Dr. K. Sestanj for helpful discussions and suggestions; Dr. T. Hohman for his assistance in the preparation of the manuscript; Mr. A. Verwijs and his staff for the analytical data; Ms. M. Harrison for the in vitro and in vivo studies; and Ms. C. Delfino for typing the manuscript.

Communications to the Editor

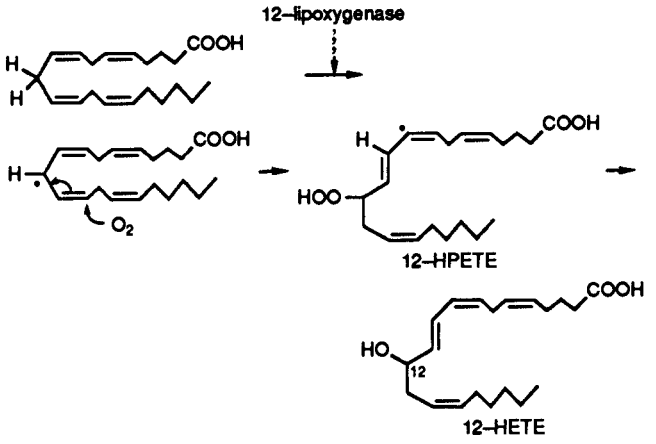
Novel Caffeic Acid Derivatives: Extremely Potent Inhibitors of 12-Lipoxygenase

12-Hydroxy-5,8,14-*cis*-10-*trans*-eicosatetraenoic acid (12-HETE) is known to be produced from arachidonic acid by 12-lipoxygenase present in platelets,[1] leukocytes,[2] macrophages,[3] etc. 12-HETE has been reported to cause increase in leukocyte chemotaxis,[4] platelet aggregation,[5] vascular smooth muscle cell migration, etc.[6,7] Especially, the specific activity of 12-HETE to elicit vascular smooth muscle cell migration is extremely high (ED = 10^{-14}–10^{-11} M).[6] Together with the fact that 12-HETE is the most abundant metabolite of arachidonic acid produced by platelets in aggregation,[8] an important role of 12-HETE in the process of intima thickness in atherogenesis is suggested.[4] Therefore, it is urgent to search for some inhibitors of 12-lipoxygenase for the prevention against the

(1) Nugteren, D. H. *Biochim. Biophys. Acta* **1975**, *380*, 299.
(2) Yoshimoto, T.; Miyamoto, T.; Ochi, K.; Yamamoto, S. *Biochim. Biophys. Acta* **1982**, *713*, 638.
(3) Rigaud, M.; Durand, J.; Breton, J. C. *Biochim. Biophys. Acta* **1979**, *573*, 408.
(4) Turner, S. R.; Tainer, J. A.; Lynn, W. S. *Nature* **1975**, *257*, 680.
(5) Morita, I.; Murota, S. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1987**, *17*, 219.
(6) Nakao, J.; Ooyama, T.; Ito, H.; Chang, W. C.; Murota, S. *Atherosclerosis* **1982**, *44*, 339.
(7) Nakao, J.; Koshihara, Y.; Ito, H.; Murota, S.; Chang, W. C. *Life Sci.* **1985**, *37*, 1435.
(8) Lapetina, E. G.; Cuatrecasas, P. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 121.

0022-2623/91/1834-1503$02.50/0

Scheme I. Biosynthesis of 12-HETE from Arachidonic Acid



Scheme II. General Synthetic Method of Caffeic Acid Derivatives

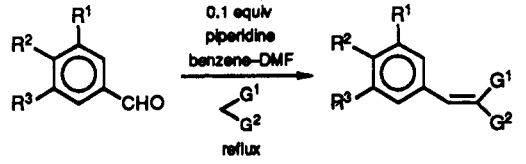
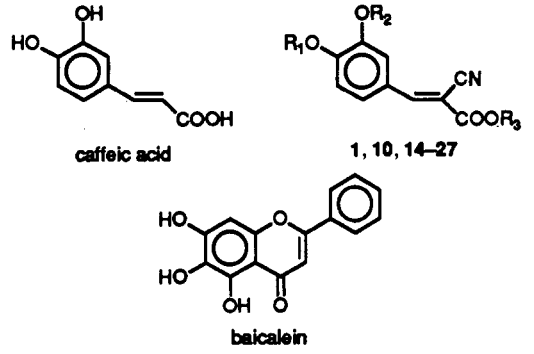


Chart I

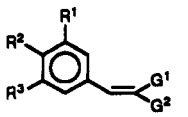


development of atheroscrelosis. On the other hand, caffeic acid has been reported to inhibit 5-lipoxygenase.[9] Thus, TMK-688[10] (one of the caffeic acid derivatives) has been developed as an orally active antiallergic agent. However, none of these caffeic acid derivatives so far reported inhibits 12-lipoxygenase (Chart I, Scheme I).

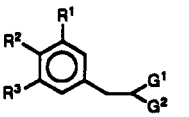
During the course of investigation, we found that a series of novel caffeic acid derivatives, which were synthesized by the condensation of benzaldehyde derivatives and cyanoacetate derivatives, exhibited extremely potent inhibitory activities on 12-lipoxygenase (IC_{50} = 0.013–0.47 μM, R^1 = H, R^2 = alkyl, aralkyl, and aryl).[11] Moreover, they had more selective inhibition to 12-lipoxygenase than to 5- and 15-lipoxygenase (Scheme II).

Thus, Knoevenagel condensation reactions of the aldehydes with ethyl cyanoacetate, cyanoacetic acid, diethyl malonate, malononitrile, 2-cyanoacetamide, methyl (phenylsulfonyl)acetate, and diethyl cyano methylphosphonate (0.1 equiv of piperidine, benzene–DMF, reflux 2–3 h) afforded a series of compounds 1–12 in good yields, respectively.[12,13] In order to determine the role of a double bond, reduction of 1 with $NaBH_4$ in EtOH was carried out to give compound 13 (Table I).

Table I. Caffeic Acid Derivatives by Knoevenagel Condensation



1–12



13

compd	G^1	G^2	R^1	R^2	R^3
1	CN	COOEt	OH	OH	H
2	CN	COOEt	OMe	OMe	H
3	CN	COOEt	OMe	OH	H
4	CN	CN	OH	OH	H
5	CN	$CONH_2$	OH	OH	H
6	CN	COOH	OH	OH	H
7	CN	$PO(OEt)_2$	OH	OH	H
8	COOEt	COOEt	OH	OH	H
9	COOMe	$SO_2C_6H_5$	OH	OH	H
10	CN	COOEt	OH	OH	OH
11	CN	COOH	OH	OH	OH
12	CN	$COOCH_2CH_2C_6H_5$	OH	H	H
13	CN	COOEt	OH	OH	H

The inhibitory effects of these caffeic acid derivatives on 12-lipoxygenase, cyclooxygenase, and thromboxane synthetase (with rat platelet-rich plasma)[14] and on 5- and 15-lipoxygenase (with rat polymorphonuclear leukocytes)[15]

(9) Koshihara, Y.; Neichi, T.; Murota, S.; Lao, A. N.; Fujimoto, Y.; Tatsuno, T. *Biochim. Biophys. Acta* **1984**, *792*, 92.

(10) Murota, S.; Tomioka, H.; Ozawa, S.; Suzuki, T.; Wakabayashi, T. *Leukotrienes and Prostanoids in Health and Disease*; Zor, U. Ed.; Kargel: Basel, 1989, p 56.

(11) (a) Japan Patent S63-106274, 1988. (b) Japan Patent H1-055867, 1989. (c) 7th International Conference on Prostaglandins and Related Compounds, Florence, Italy, May, 1990, Abstract 179.

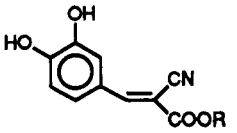
(12) All new compounds reported herein exhibit ^1H, ^{13}C NMR, IR, and mass spectra and elemental analysis in agreement with the assigned structures. Compound **24**: mp 168–170 °C (EtOH–H_2O); yellow crystals; IR (Nujol) 1680, 2220 cm^{-1}; ^1H NMR (CD_3OD) δ 3.27 (2 H, t, J = 7 Hz), 4.45 (2 H, t, J = 7 Hz), 6.83 (1 H, d, J = 9 Hz), 6.88–6.99 (2 H, m), 7.18–7.27 (1 H, m), 7.35 (1 H, dd, J = 8, 2 Hz), 7.65 (1 H, d, J = 2 Hz), 8.08 (1 H, s).

(13) The stereochemistry (*E* and *Z*) of the Knoevenagel condensation was determined as shown in the figure by X-ray crystallographic analysis and NMR data. The details will be published in a separate paper.

(14) Assay method for the inhibitory activity of 12-lipoxygenase, cyclooxygenase, thromboxane synthetase using rat platelet homogenate: Citrated blood was collected from the rat abdominal vein and platelet-rich plasma was prepared in the usual way. The plasma was washed twice with isotonic buffer solution A [134 mM NaCl, 5 mM D-glucose, 1 mM EDTA, 1 mM EGTA, 15 mM Tris-HCl (pH = 7.4)] stored at −80 °C until use. The washed plasma was thawed and sonicated in ice water and used as the enzyme solution. To the isotonic buffer solution A were added 1 mM GSH, the sample compound, and the enzyme solution (300–500 μg of protein). The mixture was preincubated for 5 min at 37 °C, then [^{14}C]arachidonic acid (0.05 μCi) was further added to the solution and reacted for 5 min. After the reaction had been quenched, the reaction mixture was developed on a silica gel thin-layer plate and 12-HETE, TXB_2, and HHT were identified by autoradiography.[16] The reduction in each arachidonic acid metabolite production was used as the index of inhibitory activity of compounds.

(15) Assay method for the inhibitory activity of 5- and 15-lipoxygenase using rat polymorphonuclear leukocytes (PMNLs): Heparinized blood was withdrawn from a rat, and PMNLs were obtained with Ficoll/Hypaque gradient centrifugation and hypotonic hemolysis. PMNLs were washed three times in Hanks' balanced salt solution and finally resuspended into a concentration of 2×10^7 cells/mL in $^1/_{15}$ M phosphate buffer (pH = 8.2). The final cell suspension contained more than 94% neutrophils (vs total cells) and the platelet contamination was below 1%. Isolated PMNLs were sonicated at 4 °C and incubated with [^{14}C]arachidonic acid (0.2 μCi) for 20 min at 37 °C after the addition of 1 mM $CaCl_2$. The reaction was stopped by the acidification with HCl to pH 3. Arachidonic acid metabolites were extracted with ethyl acetate and developed on a silica gel thin-layer plate. 5- and 15-HETEs were detected and quantified by autoradiography.[16]

Table II. Caffeic Acid Derivatives by Knoevenagel Condensation



14–27

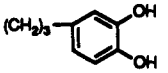
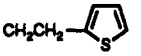
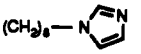
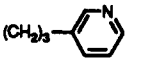
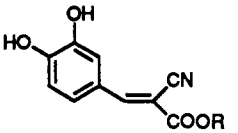
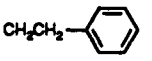
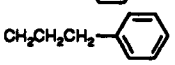
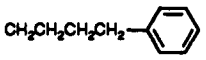
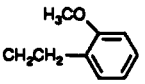
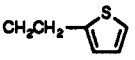
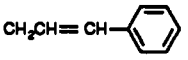
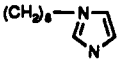
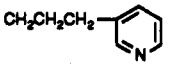
compd	R	compd	R
14	Me	21	$CH_2CH_2C_6H_4$-*p*-OH
15		22	
16		23	$CH_2CH_2OC_6H_5$
17	$CH_2CH_2C_6H_5$	24	
18	$(CH_2)_3C_6H_5$		
19	$(CH_2)_4C_6H_5$	25	$CH_2CH{=}CHC_6H_5$
20	$CH_2CH_2C_6H_4$-*o*-OMe	26	
		27	

Table III. 12-, 15-, and 5-Lipoxygenase Inhibitory Effects of Caffeic Acids Derivatives



no.	mol formula mol weight	R	IC_{50},[a] μM 12-lipo	15-lipo	5-lipo
1	$C_{12}H_{11}NO_4$ 233.23	C_2H_5	0.033	0.33	>10
17	$C_{18}H_{15}NO_4$ 309.32		0.051	0.43	0.16
18	$C_{19}H_{17}NO_4$ 323.35		0.053	1.40	0.16
19	$C_{19}H_{19}NO_4$ 325.37		0.47	3.59	0.22
20	$C_{19}H_{17}NO_5$ 339.35		0.064	1.62	0.14
24	$C_{16}H_{13}NOS$ 315.35		0.013	0.50	0.09
25	$C_{19}H_{15}NO_4$ 321.33		0.063	3.33	1.89
26	$C_{21}H_{25}N_3O_4$ 383.45		0.18	>10	>10
27	$C_{18}H_{16}N_2O_4$ 324.34		0.47	3.93	>10
baicalein			0.015	0.26	>10

[a] n = 3. No inhibition was observed on cyclooxygenase and thromboxane synthetase in all compounds tested at the concentration below 10^{-6} M.

were investigated. These assay tests revealed that compound 1 had very potent 12- and 15-lipoxygenase inhibitory activities (12-lipoxygenase, IC_{50} = 0.033 μM; 15-lipoxygenase, IC_{50} = 0.33 μM), but did not inhibit cyclooxygenase and thromboxane synthetase in the concentration below 10^{-6} M. However, 12-lipoxygenase inhibitory effects of compound 13 (with single bond) and compounds 12, 10, 3, 2 (with mono- or tri-OH group and mono- or di-OMe group on the benzene ring) were weak or inactive in the concentration of 10^{-6} M.

Therefore, it was demonstrated that a 3,4-dihydroxycinnamoyl group was essential for the inhibition of 12-lipoxygenase. Furthermore, a cyano group was crucial since caffeic acid and compound 8 with an ethyl ester group instead of a cyano group did not show 12-lipoxygenase inhibition.

Thus, compounds 14–27 (R = alkyl, aralkyl) were synthesized to find more potent compounds (Table II). Interestingly, the pharmacological tests described above revealed that the compounds exhibited the very potent inhibitory activity of 12-lipoxygenase and were more selective to 12-lipoxygenase than to 5- and 15-lipoxygenase, namely, all compounds except 19 showed a lower value of IC_{50} with 12-lipoxygenase than with 5- and 15-lipoxygenase. Especially, compound 24 was the most potent 12-lipoxygenase inhibitor in the synthetic compounds reported so far and was comparable to baicalein (most potent 12-lipoxygenase inhibitor in natural products).

Registry No. 1, 132464-92-7; 2, 24393-47-3; 3, 132464-93-8; 4, 118409-57-7; 5, 122520-85-8; 6, 122520-79-0; 7, 132464-94-9; 8, 125562-44-9; 9, 132464-95-0; 10, 132464-96-1; 11, 132464-97-2; 12, 132464-98-3; 13, 132464-99-4; 14, 132465-00-0; 15, 132465-01-1; 16, 132465-02-2; 17, 132465-03-3; 18, 132465-04-4; 19, 132465-05-5; 20, 132465-06-6; 21, 132465-07-7; 22, 132465-08-8; 23, 132465-09-9; 24, 132465-10-2; 25, 132465-11-3; 26, 132465-12-4; 27, 132465-13-5; $NCCH_2CO_2Me$, 105-34-0; *Z,Z,Z,Z*-$NCCH_2CO_2(CH_2)_5(CH{=}CH\text{-}CH_2)_4(CH_2)_4H$, 132465-14-6; $NCCH_2CO_2(CH_2)_{21}H$, 132465-15-7; $NCCH_2CO_2(CH_2)_3C_6H_5$, 2046-18-6; $NCCH_2CO_2(CH_2)_4C_6H_5$, 132465-16-8; $NCCH_2CO_2(CH_2)_2C_6H_4$-*o*-OMe, 132465-17-9; $NCCH_2CO_2(CH_2)_2C_6H_4$-*p*-OH, 132465-18-0; $NCCH_2CO_2(CH_2)_3\text{-}C_6H_3$-3,4-$(OH)_2$, 132465-19-1; $NCCH_2CO_2(CH_2)_2OC_6H_5$, 32804-78-7; $NCCH_2CO_2(CH_2)$-c-C_4H_3S, 132465-20-4; $NCCH_2CO_2CH_2C\text{-}H{=}CHC_6H_5$, 132465-21-5; $NCCH_2CO_2Et$, 105-56-6; $CNCH_2CN$, 109-77-3; $CNCH_2CONH_2$, 107-91-5; $CNCH_2CO_2H$, 372-09-8; $CNCH_2PO(OEt)_2$, 2537-48-6; $EtOCOCH_2CO_2Et$, 105-53-3; $EtOCOCH_2SO_2C_6H_5$, 34097-60-4; $CNCH_2CO_2(CH_2)_2C_6H_5$, 99842-68-9; 3,4-dihydroxybenzaldehyde, 621-59-0; 3,4-dimethoxybenzaldehyde, 120-14-9; 4-hydroxy-3-methoxybenzaldehyde, 121-33-5; 3,4,5-trihydroxybenzaldehyde, 13677-79-7; 3-hydroxybenzaldehyde, 100-83-4; 1-(8-(imidazol-2-yl))octyl 2-cyanoacetate, 132465-22-6; 1-(3-(pyridin-3-yl))propyl 2-cyanoacetate, 132465-23-7; 12-lipoxygenase, 82391-43-3.

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Received December 11, 1990

Quinazolinone Cholecystokinin-B Receptor Ligands

Cholecystokinin (CCK) exerts a variety of actions on peripheral target tissues such as gall bladder contraction and pancreatic exocrine secretion and may function as a neutrotransmitter or neuromodulator in the central nervous system.[1,2] These effects are mediated by at least

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0022-2623/91/1834-1505$02.50/0