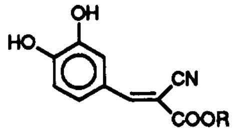
J. Med. Chem. 1991, 34, 1505–1508

Table II. Caffeic Acid Derivatives by Knoevenagel Condensation



14–27

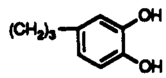
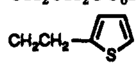
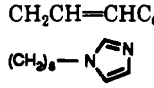
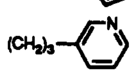
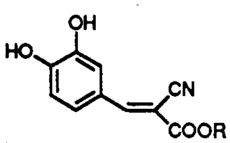
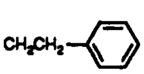
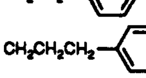
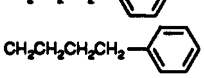
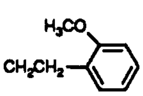
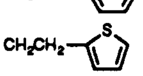
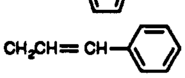
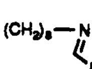
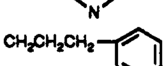
compd	R	compd	R
14	Me	21	$CH_2CH_2C_6H_4$-*p*-OH
15		22	
16		23	$CH_2CH_2OC_6H_5$
17	$CH_2CH_2C_6H_5$	24	
18	$(CH_2)_3C_6H_5$	25	$CH_2CH{=}CHC_6H_5$
19	$(CH_2)_4C_6H_5$	26	
20	$CH_2CH_2C_6H_4$-*o*-OMe	27	

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*-$NCCH_2CO_2(CH_2)_5(CH{=}CHCH_2)_4(CH_2)_4H$, 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; $NCCH_2CO_2(CH_2)_3C_6H_3$-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; $NCCH_2CO_2CH_2CH{=}CHC_6H_5$, 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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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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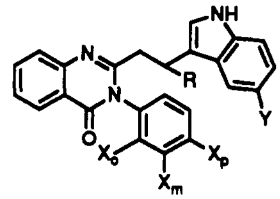
0022-2623/91/1834-1505$02.50/0

Table I. CCK-B Receptor Binding Data



no.	X_o	X_m	X_p	Y	R	CCK-B[a]
1	H	H	H	H	H	0.67 ± 0.15 (n = 3)
2	F	H	H	H	H	75%[b]
3	Cl	H	H	H	H	44%[b]
4	MeO	H	H	H	H	74%[b]
5	CF_3	H	H	H	H	35%[b]
6	H	F	H	H	H	0.73 ± 0.17 (n = 3)
7	H	Cl	H	H	H	0.69 ± 0.16 (n = 3)
8	H	Br	H	H	H	0.37 ± 0.03 (n = 3)
9	H	Me	H	H	H	0.15 ± 0.01 (n = 3)
10	H	Et	H	H	H	0.072 ± 0.001 (n = 3)
11	H	MeO	H	H	H	0.16 ± 0.03 (n = 3)
12	H	i-PrO	H	H	H	0.026 ± 0.0003 (n = 3)
13	H	CF_3	H	H	H	0.48 ± 0.20 (n = 4)
14	H	$-OCH_2O-$		H	H	0.19 ± 0.04 (n = 3)
15	H	MeO	H	Me	H	0.055 ± 0.003 (n = 3)
16	H	MeO	H	MeO	H	0.067 ± 0.005 (n = 3)
17	H	MeO	H	F	H	0.11 ± 0.01 (n = 3)
18	H	MeO	H	Cl	H	0.047 ± 0.003 (n = 3)
19	H	MeO	H	Br	H	0.038 ± 0.003 (n = 3)
20	H	MeO	H	Br	H	0.034 ± 0.007 (n = 3)
21	H	n-PrO	H	Br	H	0.058 ± 0.007 (n = 3)
22	H	i-PrO	H	Br	H	0.0093 ± 0.0015 (n = 3)
23	H	CpO[c]	H	Br	H	0.067 ± 0.006 (n = 5)
24	H	Et	H	Br	H	0.046 ± 0.01 (n = 3)
25	H	Et	H	Br	Me	0.10 ± 0.01 (n = 3)
26	H	MeS	H	Br	H	0.046 ± 0.008 (n = 3)
27	H	CF_3	H	Br	H	0.23 ± 0.03 (n = 3)
28	H	NMe_2	H	Br	H	0.016 ± 0.001 (n = 3)
29	H	MeO	MeO	Br	H	0.13 ± 0.03 (n = 3)
30	H	H	MeO	Br	H	0.031 ± 0.006 (n = 3)
31	H	H	EtO	Br	H	0.088 ± 0.010 (n = 3)
32	H	H	i-PrO	Br	H	0.11 ± 0.02 (n = 3)
33	H	H	Et	Br	H	0.028 ± 0.004 (n = 3)
34	H	H	i-Pr	Br	H	0.037 ± 0.013 (n = 3)
35	H	H	MeS	Br	H	0.037 ± 0.01 (n = 3)
36	H	H	NMe_2	Br	H	0.033 ± 0.006 (n = 4)

[a] IC_{50} (μM, mean ± SEM) for inhibition of ^{125}I-labeled CCK-8 sulfate binding with mouse brain membranes. [b] Percent inhibition (10 μM) of ^{125}I-labeled CCK-8 sulfate binding with mouse brain membranes. [c] Cyclopentyloxyl.

two receptor subtypes designated CCK-A and CCK-B[3] with the latter exhibiting ligand specificities similar to the stomach gastrin receptor.[4,5] Previously reported synthetic studies in other laboratories using the benzodiazepine core of the natural product asperlicin[6] have yielded the highly potent CCK-A antagonist MK-329[7,8] and the CCK-B/gastrin antagonist L-365,260.[9,10] However, since the asperlicin structure is comprised of several heterocyclic

Table II. Receptor Selectivity

no.	CCK-B[a]	CCK-B[b]	CCK-A[c]	gastrin[d]
13	0.48 ± 0.2	–	6%	8.2 ± 1.7
19	0.038 ± 0.003	0.36 ± 0.03	5%	1.3 ± 0.4
22	0.0093 ± 0.0015	0.081 ± 0.004	–6%	0.16 ± 0.04
24	0.046 ± 0.01	0.33 ± 0.05	–5%	1.1 ± 0.2
25	0.10 ± 0.01	–	–18%	1.6 ± 0.1
L-365,260	0.0073 ± 0.0004	0.0053 ± 0.0006	–	0.0029 ± 0.0003

[a] IC_{50} (μM, mean ± SEM) for inhibition of ^{125}I-labeled CCK-8 sulfate binding with mouse brain membranes (n = 3–5). [b] IC_{50} (μM, mean ± SEM) for inhibition of ^{125}I-labeled CCK-8 sulfate binding with guinea pig brain membranes (n = 3–5). [c] Percent inhibition (10 μM) of ^{3}H-labeled L-364,718 binding with rat pancreas. [d] IC_{50} (μM, mean ± SEM) for inhibition of ^{125}I-labeled gastrin binding with guinea pig stomach mucosal membranes (n = 3).

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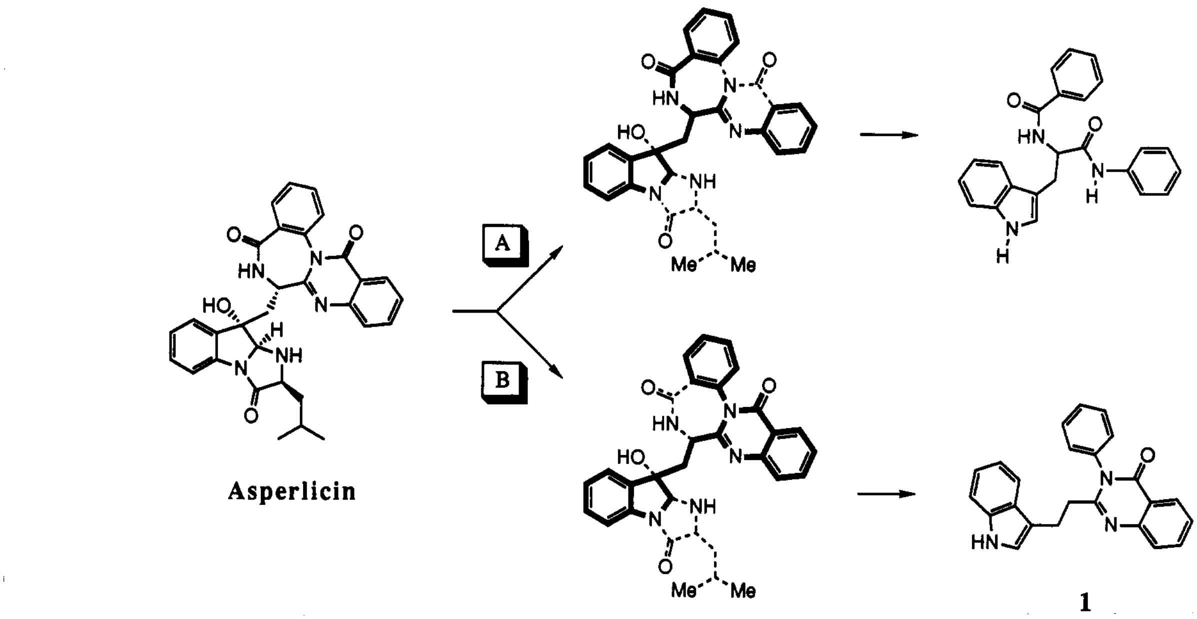
Scheme I



systems, we hypothesized that alternative substructures embedded within the molecular framework of this natural product may provide a rational starting point for our efforts to design a structurally novel series of nonpeptide CCK receptor ligands.[11]

Scheme I outlines two possible bond disconnection strategies which preserve the three aromatic domains of asperlicin and reduce the chemical complexity of the natural product to two conceptually different classes of compounds. The first path (A) yields a substructure common to the tryptophan-derived CCK antagonists such as benzotript.[12] Of greater interest, however, is the second highlighted bond disconnection path (B) which yields a 3-phenyl-4(3*H*)-quinazolinone nucleus, a structural feature common to the sedative–hypnotics mecloqualone and methaqualone.[13] Although the benzodiazepine and quinazolinone nuclei differ structurally, they are related on the basis of atom pair descriptors.[14] Consequently, we investigated the possibility that an appropriately functionalized quinazolinone such as **1** may serve as a template for developing potent nonpeptide CCK receptor ligands. The lack of asymmetric centers in this heterocyclic system may also facilitate our structure optimization by reducing the number of variables for our structure–activity relationship (SAR) study and simplifying the synthesis of the final targets.

A series of compounds based upon this asperlicin substructure was prepared[15] and evaluated by using CCK and gastrin radioligand binding assays (Table I). Alkyl or alkoxyl substitution at either the meta or para positions of the pendant phenyl ring appeared optimal and provided congeners with reasonable affinity for CCK-B and gastrin

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(15) Satisfactory spectral and analytical data were obtained for all new compounds. Although several synthetic routes are available for preparing the described series, the following experimental procedure for synthesizing compound **22** is representative: 3-nitrophenol (50.0 g, 360 mmol), isopropyl iodide (76.19 g, 450 mmol), and K_2CO_3 (60 g) were combined and heated at reflux under N_2 overnight in acetone (400 mL). After solvent removal in vacuo, the residue was partitioned between EtOAc and H_2O. The separated organic layer was washed with 1 N NaOH, brine, dried over Na_2SO_4, and concentrated in vacuo to provide 56 g (86%) of 3-isopropoxynitrobenzene as a clear yellow oil.

A mixture of the above product (8.5 g, 50 mmol), PtO_2 (0.3 g), and EtOH (200 mL) was hydrogenated (40 psi H_2) at room temperature for 1.5 h in a Paar shaker. The mixture was filtered through Celite and concentrated in vacuo to furnish 7.08 g of the desired aniline. This material was combined with isatoic anhydride (7.35 g, 45 mmol) and heated at 90 °C for 2 h. Upon cooling and addition of hexanes, the product crystallized to give 10.19 g (83%) of 2-amino-*N*-(3-isopropoxyphenyl)benzamide as a white solid. An analytical sample was obtained by recrystallization from 20% EtOAc/hexanes: mp 79–86 °C; ^1H NMR ($CDCl_3$) δ 1.36 (6 H, d, J = 6.1 Hz), 4.59 (1 H, h, J = 6.1 Hz), 5.2 (2 H, bs), 6.6–6.8 (3 H, m), 7.0–7.1 (1 H, m), 7.2–7.4 (3 H, m), 7.47 (1 H, d, J = 7.7 Hz), 7.80 (1 H, bs); IR ($CHCl_3$) 1664, 1611, 1524, 1490 cm^{-1}; MS (FD) 270 (M^+). Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

A solution of 3-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-methyl]-5-bromoindole (4.12 g, 12 mmol) prepared according to the method of Farlow et al. (Farlow, D. S.; Flaugh, M. E.; Horvath, S. D.; Lavagnino, E. R.; Pranc, P. Two Efficient Syntheses of Indole-3-Propionic Esters and Acids. Further Applications of Meldrum's Acid. *Org. Prep. Proced. Int.* **1981**, *13*, 39–48), the above benzamide (3.48 g, 13 mmol) and pyridinium *p*-toluenesulfonate (1.64 g, 6.5 mmol) in 50 mL of pyridine was heated at reflux for 3.5 days. The reaction mixture was concentrated in vacuo, chromatographed (SiO_2, 30% EtOAc/hexanes), and crystallized to give 2.13 g (36%) of compound **22**: mp 179–181 °C; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, d, J = 6.0 Hz), 1.34 (3 H, d, J = 6.1 Hz), 2.8 (2 H, m), 3.2 (2 H, m), 4.53, (1 H, h, J = 6.0 Hz), 6.7–7.6 (9 H, m), 7.8 (2 H, m), 8.2–8.4 (2 H, m); IR (KBr) 1671 cm^{-1}; MS (FAB) 502, 504 (M^+ + H). Anal. ($C_{27}H_{24}N_3O_2Br$) C, H, N.

receptors. QSAR analysis of the meta-substituted analogues 1 and 6–14 suggested that the substituent steric descriptor, MR,[16] accounts for most of the variance observed in the CCK-B receptor binding data for the parent indole analogues:

$$-\log(IC_{50}) = 0.089\ (\pm 0.017)MR + 5.99\ (\pm 0.14)$$

$$n = 10,\ s = 0.24,\ r = 0.88,\ F_{(1,8)} = 27.3,\ p < 0.001$$

A substituent at C-5 of the indole nucleus also incrementally enhanced receptor-blocking activity and this increase was additive to the effects observed with phenyl ring substitution. However, whereas meta or para monosubstitution (i.e. **19** and **30**) provided approximately equipotent analogues, disubstitution (i.e. **29**) appeared to be detrimental. In addition, increasing the alkoxyl substituent size to give **23** as suggested by the above relationship reduced receptor-binding activity relative to compound **22**. Consequently, the isopropoxyl group may represent the maximum size for alkoxyl substituents on the pendant phenyl ring.

The CCK/gastrin receptor selectivity was subsequently investigated, and the data for a representative group of analogues appear in Table II. The compounds examined exhibit excellent selectivity for CCK-B over CCK-A receptors. Although the molecular basis for this observation is unclear, both the benzodiazepine and quinazolinone[17] antagonists possess structural features common to the quinazolino-1,4-benzodiazepine, asperlicin. These results are interesting since the natural product is a selective CCK-A receptor antagonist. The apparent modest selectivity between CCK-B and stomach gastrin receptors, on the other hand, is most likely attributable to a species difference. Since a species effect was not observed for L-365,260, the quinazolinone and benzodiazepine antagonists may interact with different regions and/or different amino acid residues associated with the CCK-B receptor. Nevertheless, these compounds, like other reported CCK-B antagonists,[9,18] do not discriminate between guinea pig CCK-B and gastrin receptors in vitro.

Since the methylene carbon attached to the quinazolinone ring of **1** is common to both the quinazolinone and benzodiazepine substructures in asperlicin (Scheme I),[19] we examined the effect of substitution at that position on CCK-B receptor binding and receptor subtype selectivity. However, only a minor difference in potency was observed for compound **25** relative to **24** with no apparent change in the receptor binding IC_{50} ratio (Table II).[20]

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(17) Compound **12** (10^{-6} M) noncompetitively blocked the CCK-8S and CCK-4 induced contractile response in isolated guinea pig ileal longitudinal smooth muscle. No agonist activity was observed over the concentration range of 10^{-10} to 10^{-5} M. Additional studies are in progress to further elucidate the pharmacological properties of this series.

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(20) Compound **25** was prepared and tested in racemic form.

The receptor-binding assays were conducted as described in literature procedures: CCK-B receptor binding was performed with mouse brain membranes according to the method of Chang and Lotti.[21] CCK-A receptor binding was determined in rat pancreas with ^{3}H-labeled L-364,718 by the procedure described by Chang et al.[22] Finally, a modified procedure of Takeuchi et al. was used to measure gastrin binding to guinea pig stomach mucosal membranes.[23]

Certain benzodiazepine anxiolytics have been reported to functionally antagonize some of the peripheral[24] and central effects of CCK.[25] In addition, the benzodiazepine κ-opioid agonist tifluadom has been reported to be a CCK-A receptor antagonist.[26] Although 3-phenyl-4-(3*H*)-quinazolinones such as methaqualone have not to our knowledge been reported as CCK antagonists, our study raises the possibility that quinazolinones may, like the benzodiazepines, be amenable to structural modifications to yield nonpeptidal ligands for a specific peptide receptor.

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Specific Anti-HIV-1 "Acyclonucleosides" Which Cannot Be Phosphorylated: Synthesis of Some Deoxy Analogues of 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine

Chemotherapy of AIDS (acquired immunodeficiency syndrome) is one of the most challenging scientific projects upon which much attention is currently focused. Although AZT (3′-azido-3′-deoxythymidine) is available as the sole compound formally approved for clinical use,[1,2] its serious

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