−67° (c = 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.37 (m, 5 H, 2″,3″,4″,5″,6″-H), 6.71 (s, 1 H, 5-H), 6.56 (s, 1 H, 8-H), 6.26 (s, 2 H, 2′,6′-H), 6.99 (s, 1 H, OCHO), 6.97 (s, 1 H, OCHO), 5.40 (s, 1 H, OH), 4.60 (m, 4 H, 4-H, 1-H, OCH_2), 4.45 (m, 2 H, 11-H), 3.76 (s, 6 H, 3′,5′-OCH_3), 3.46 (dd, 1 H, J = 5.2, 14.0, 2-H), and 2.92 (m, 1 H, 3-H); IR (KBr) 3440 (OH), 2900 (aliphatic C—H), 1750 (lactone), 1600, 1500, and 1480 (aromatic C=C) cm^{-1}. Anal. ($C_{28}H_{26}O_8$) C, H.

4′-*O*-Demethyl-4β-(3″-nitrobenzyl)podophyllotoxin (24). Yield 65%; crystals from ethyl acetate–chloroform; mp 209–210 °C; $[\alpha]^{25}_D$ −66° (c = 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.18 (m, 2 H, 2″,4″-H), 7.65 (d, 1 H, 6″-H), 7.56 (t, 1 H, 5″-H), 6.77 (s, 1 H, 5-H), 6.60 (s, 1 H, 8-H), 6.27 (s, 2 H, 2′,6′-H), 6.04 (s, 1 H, OCHO), 6.00 (s, 1 H, OCHO), 5.41 (s, 1 H, OH), 4.71 (m, 4 H, 4-H, 11-H, CH_2O), 4.41 (m, 2 H, 1-H, 11-H), 3.78 (s, 6 H, 3″,5″-OCH_3), 3.50 (dd, 1 H, J = 5.4, 14.0, 2-H), and 2.97 (m, 1 H, 3-H) IR (KBr) 3380 (OH), 2900 (aliphatic C—H), 1755 (lactone), 1600, 1500, and 1480 (aromatic C=C), 1520, and 1350 (NO_2) cm^{-1}. Anal. ($C_{28}H_{25}O_{10}N$) C, H, N.

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Registry No. **2**, 6559-91-7; **3**, 117604-05-4; **4**, 117507-84-3; **5**, 16477-16-0; **6**, 127882-73-9; **7**, 125830-36-6; **8**, 127882-79-5; **9**, 136794-70-2; **10**, 136794-71-3; **11**, 136794-72-4; **12**, 136794-73-5; **13**, 136794-74-6; **14**, 136794-75-7; **15**, 136794-76-8; **16**, 136794-77-9; **17**, 136794-78-0; **18**, 136794-79-1; **19**, 136794-80-4; **20**, 136794-81-5; **21**, 136794-82-6; **22**, 136794-83-7; **23**, 136794-84-8; **24**, 136794-85-9; $PhCH_2Br$, 100-39-0; p-$NO_2C_6H_4CH_2Br$, 100-11-8; m-$NO_2C_6H_4CH_2Br$, 3958-57-4; o-$NO_2C_6H_4CH_2Br$, 3958-60-9; o-$FC_6H_4CH_2Br$, 446-48-0; m-$FC_6H_4CH_2Br$, 456-41-7; p-$FC_6H_4CH_2Br$, 459-46-1; m-$CNC_6H_4CH_2Br$, 28188-41-2; p-$CNC_6H_4CH_2Br$, 17201-43-3; p-$CF_3C_6H_4CH_2Br$, 402-49-3; m-$ClC_6H_4CH_2Br$, 766-80-3; 3,5-$(MeO)_2C_6H_3CH_2Br$, 877-88-3; $PhCH_2OH$, 100-51-6; p-$NO_2C_6H_4CH_2OH$, 619-73-8.

Cholecystokinin Antagonists: (*R*)-Tryptophan-Based Hybrid Antagonists of High Affinity and Selectivity for CCK-A Receptors

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The intriguing structural similarities of glutamic acid based cholecystokinin (CCK) antagonists (A-64718 and A-65186) and the benzodiazepine CCK antagonist MK-329 (L-364,718) have been reported. Efforts to include the weak CCK antagonist benzotript into this construct utilizing a similar approach have resulted in a novel series of benzotript-based hybrid antagonists N^{α}-(3′-quinolylcarbonyl)-(*R*)-tryptophan di-*n*-pentylamide (**9**, A-67396), N^{α}-(4′,8′-dihydroxy-2′-quinolylcarbonyl)-(*R*)-tryptophan di-*n*-pentylamide (**23**, A-70276), and N^{α}-(3′-quinolylcarbonyl)-(*R*)-5′-hydroxytryptophan di-*n*-pentylamide (**36**, A-71134) which possess respectively binding affinities of 23, 21, and 11 nM for the pancreatic CCK-A receptor and which inhibit CCK_8-induced amylase secretion. Compound **9** possesses a selectivity of >500-fold for the pancreatic CCK-A receptor over the CCK-B receptor.[1]

Introduction

Within the past few years considerable research has been directed toward the development of cholecystokinin (CCK) antagonists as potential therapeutic agents for appetitive disorders, anxiety, potentiation of opiate analgesia, and treatment of gastrointestinal, pancreatic, and possibly psychiatric disorders.[2] As a result of these studies a number of potent and selective CCK antagonists have been reported and are currently being investigated.[3] Prior to these advances only a few, weak nonselective CCK antagonists were available including proglumide (Milid), benzotript, and dibutyryl-cyclic-GMP.[4] The development of CR 1409 and CR 1505 by Makovec and co-workers[5] and the development of the benzodiazepine MK-329 (devazepide) by Evans and co-workers[6] were significant in that they produced the first potent, non-peptide-based CCK antagonists (Figure 1) exhibiting high affinity and selectivity for the CCK-A receptors, which are found predominantly in the periphery and typically characterized in the pancreas, gallbladder, and ileum. The selectivity of such agents for CCK-A receptors over CCK-B receptors that predominant in brain has provided pharmacological tools both for central nervous system (CNS) receptor mapping studies and for the delineation of the functional roles for CCK-A receptors.[7] Thus, investigations with MK-329 have confirmed the existence of CCK-A receptors, albeit in low abundance, in several brain regions including the

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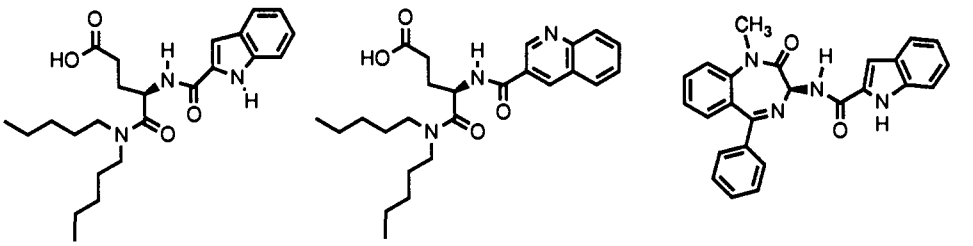
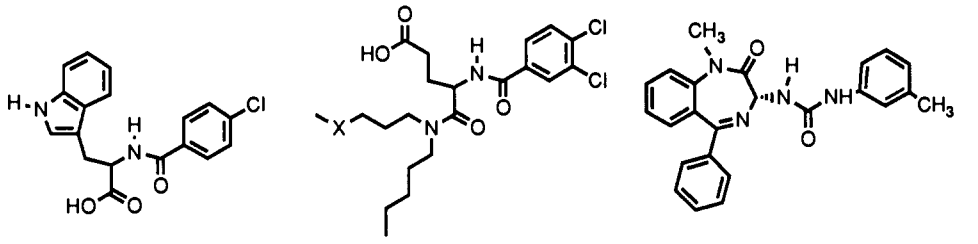
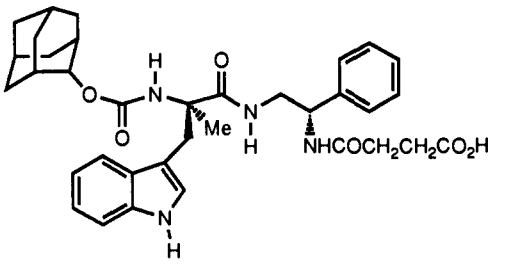
0022-2623/91/1834-3350$02.50/0



A-64718 A-65186 MK-329



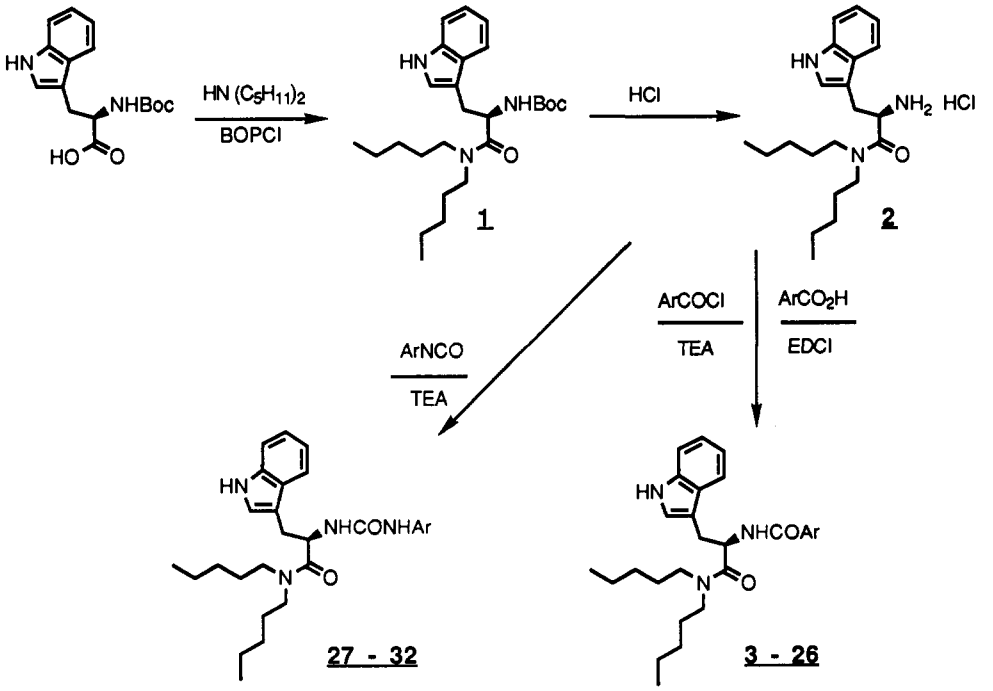
Benzotript CR 1409 X = CH_2 CR 1505 X = O L-365,260



PD-134308

Figure 1.

Scheme I. Synthesis of *N*-(Arylacyl)-(*R*)-tryptophan Di-*n*-pentylamides



nucleus tractus solitarius, interpeduncular nucleus, area postrema, and nucleus accumbens.[8] Several of these brain loci have been linked to dopamine modulation and/or dopamine mediated behavior;[9] however, the functional

significance of CCK and CCK-A receptors in neuronal systems remains an area of intense investigation.

The recent development of highly potent and selective antagonists for CCK-B receptors, such as L-365,260[10] and

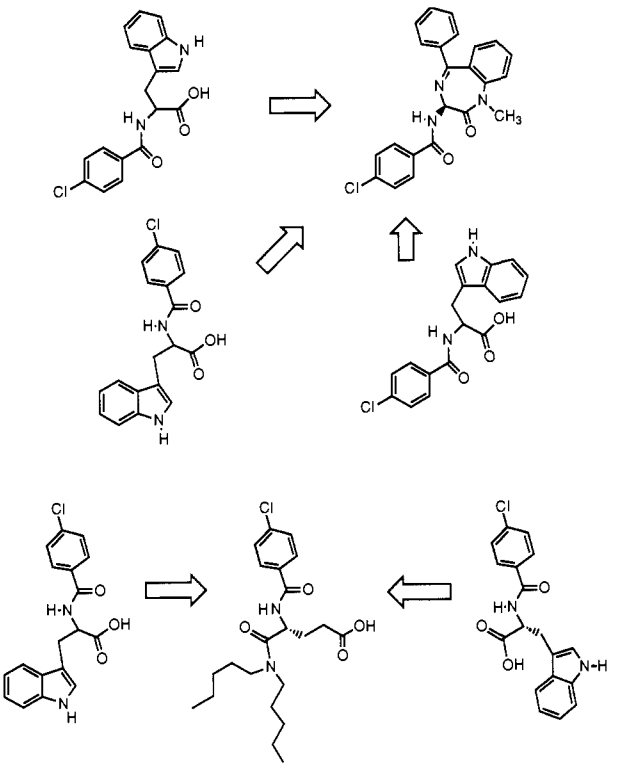


Figure 2.

PD-134308 (CI-988),[11] has shed further light on the functional roles of CCK-B receptors in the CNS. It appears that such agents exhibit both anxiolytic and analgesic activities,[12] although similar actions have been reported for the CCK-A selective antagonist MK-329.[13] Moreover, both MK-329 and L-365,260 have been reported to exert effects on food intake in rodents, with the CCK-B selective antagonists being more effective than the CCK-A selective antagonist.[14] These latter studies are highly controversial,

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Table I. Physical Data of Compounds 3–45

compd	formula[a]	mp (°C)	$[\alpha]_D$, deg	MS molecular ion	anal.
3	$C_{28}H_{36}ClN_3O_2$	b	−19.9 (c = 1.31, MeOH)	482 (M + H)	C,H,N
4	$C_{28}H_{36}ClN_3O_2 \cdot 0.25H_2O$	b	+20.3 (c = 1.11, MeOH)	482 (M + H)	C,H,N
5	$C_{28}H_{35}Cl_2N_3O_2 \cdot 0.25H_2O$	c	−16.7 (c = 1.19, MeOH)	516 (M + H)	C,H,N
6	$C_{28}H_{35}Cl_2N_3O_2$	b	+16.9 (c = 1.32, MeOH)	516 (M + H)	C,H,N
7	$C_{30}H_{38}N_4O_2 \cdot 0.5H_2O$	75–78	−16.2 (c = 0.105, MeOH)	487 (M + H)	C,H,N
8	$C_{30}H_{38}N_4O_2 \cdot H_2O$	89–92	+19.0 (c = 0.715, MeOH)	487 (M + H)	C,H,N
9	$C_{31}H_{38}N_4O_2 \cdot 0.25H_2O$	67–72	−20.8 (c = 1.08, MeOH)	499 (M + H)	C,H,N
10	$C_{31}H_{38}N_4O_2 \cdot 0.5H_2O$	c	+18.6 (c = 1.23, MeOH)	499 (M + H)	C,H,N
11	$C_{31}H_{38}N_4O_2$	c	−108.3 (c = 1.07, MeOH)	499 (M + H)	C,H,N
12	$C_{26}H_{36}N_4O_2$	108–110	−2.4 (c = 1.0, MeOH)	437 (M + H)	C,H,N
13	$C_{27}H_{36}N_4O_2 \cdot 0.75H_2O$	c	−19.7 (c = 0.7, MeOH)	499 (M + H)	C,H,N
14	$C_{29}H_{38}N_4O_2 \cdot 0.5H_2O$	c	+14.2 (c = 0.85, MeOH)	475 (M + H)	C,H,N
15	$C_{32}H_{39}N_3O_2 \cdot 0.25H_2O$	87–89	−21.2 (c = 1.24, MeOH)	498 (M + H)	C,H,N
16	$C_{32}H_{39}N_3O_2$	c	−3.4 (c = 1.76, MeOH)	498 (M + H)	C,H,N
17	$C_{31}H_{38}N_4O_2 \cdot 0.5H_2O$	65–70	−16.4 (c = 1.22, MeOH)	499 (M + H)	C,H,N
18	$C_{31}H_{38}N_4O_2$	87.5–89	+16.7 (c = 0.5, MeOH)	499 (M + H)	C,H,N
19	$C_{31}H_{38}N_4O_2 \cdot H_2O$	c	+17.9 (c = 1.08, MeOH)	499 (M + H)	C,H,N
20	$C_{32}H_{39}N_3O_3$	b	−20.6 (c = 1.02, MeOH)	514 (M + H)	C,H,N
21	$C_{31}H_{38}N_4O_3 \cdot 0.5H_2O$	149–51	+15.7 (c = 1.16, MeOH)	515 (M + H)	C,H[d]
22	$C_{31}H_{38}N_4O_3$	111–13	−53.6 (c = 1.04, MeOH)	515 (M + H)	C,H,N
23	$C_{31}H_{38}N_4O_4 \cdot 0.5H_2O$	144–50	−25.7 (c = 1.01, MeOH)	531 (M + H)	C,H,N
24	$C_{30}H_{38}N_4O_2 \cdot 0.25H_2O$	b	−11.1 (c = 1.14, MeOH)	487 (M + H)	C,H,N
25	$C_{30}H_{37}FN_4O_2 \cdot 1.5H_2O$	b	−16.7 (c = 1.32, MeOH)	505 (M + H)	C,H[e]
26	$C_{27}H_{36}N_3O_3S$	117–19	−51.9 (c = 1.24, MeOH)	518 (M + H)	C,H,N
27	$C_{28}H_{37}ClN_4O_2 \cdot 0.25H_2O$	73–75	−0.93 (c = 1.08, MeOH)	497 (M + H)	C,H,N
28	$C_{28}H_{37}ClN_4O_2 \cdot 0.25H_2O$	87–88	+1.39 (c = 1.01, MeOH)	497 (M + H)	C,H,N
29	$C_{29}H_{40}N_4O_2 \cdot 0.25H_2O$	136–8	−7.11 (c = 1.14, MeOH)	477 (M + H)	C,H,N
30	$C_{29}H_{40}N_4O_2 \cdot 0.25H_2O$	140–41	+7.6 (c = 1.19, MeOH)	477 (M + H)	C,H,N
31	$C_{29}H_{40}N_4O_2 \cdot 0.25H_2O$	155–56	−7.64 (c = 1.06, MeOH)	477 (M + H)	C,H,N
32	$C_{29}H_{40}N_4O_2$	158–9	+8.18 (c = 1.10, MeOH)	477 (M + H)	C,H,N
33	$C_{25}H_{35}N_3O_6 \cdot H_2O \cdot HOAc$	c	−5.5 (c = 0.8, MeOH)	564 (M + H)	C,N[f]
34	$C_{31}H_{37}FN_4O_2$	62–5	na	517 (M + H)	C,H,N
35	$C_{38}H_{44}N_4O_3 \cdot 1.5H_2O$	b	na	605 (M + H)	C,H,N
36	$C_{31}H_{38}N_4O_3$	78–90	−43.9 (c = 1.14, MeOH)	515 (M + H)	C,H,N
37	$C_{31}H_{38}N_4O_3 \cdot 0.25H_2O$	b	+28.4 (c = 1.10, MeOH)	515 (M + H)	C,H,N
38	$C_{37}H_{41}N_5O_4S$	128–30	+33.8 (c = 1.0, MeOH)	652 (M + H)	C,H,N
39	$C_{28}H_{24}N_4O_2$	211–12	+45.5 (c = 0.09, DMF–MeOH)[g]	449 (M + H)	C,H,N
40	$C_{29}H_{26}N_4O_2 \cdot 0.5H_2O$	110–14	−5.6 (c = 0.55, DMF)	463 (M + H)	C,H,N
41	$C_{32}H_{30}N_4O_4 \cdot 1.1CHCl_3$	82–85	+37.0 (c = 0.5, DMF)	535 (M + H)	C,H,N
42	$C_{29}H_{26}N_4O_2 \cdot 0.75H_2O$	114–19	+37.8 (c = 1.15, DMF–MeOH)[g]	463 (M + H)	C,H,N
43	$C_{29}H_{26}N_4O_2 \cdot 0.25H_2O$	246–9	+15.3 (c = 0.59, DMF–MeOH)[g]	463 (M + H)	C,H,N
44	$C_{31}H_{28}N_4O_4$	214–16	+38.9 (c = 0.19, $CHCl_3$–MeOH)[g]	521 (M + H)	C,H,N
45	$C_{31}H_{28}N_4O_4 \cdot 0.75H_2O$	214–16	−44.4 (c = 0.75, MeOH)	521 (M + H)	C,H,N

[a] NMR spectra are in agreement with the assigned structures. [b] Compound was obtained as a foam. [c] Compound was obtained as an oil. [d] N: calculated 10.70; found 10.14. [e] N: calculated 10.54; found 10.11. [f] H: calculated 7.49; found 7.04. [g] Solvent ratios are 1:1.

and the role of CCK and CCK receptors in the central regulation of food intake remains an active area of investigation.[15]

Our own interest in CCK antagonists is driven in part by the implications for modulating and/or potentiating neurotransmitter systems, particularly dopaminergic pathways, within the CNS. We also are interested in identifying novel CCK antagonists to structurally relate them with the known classes of CCK antagonists and, if possible, relate them to their peptide agonist counterparts. As part of our continuing research toward novel CCK antagonists, we initiated a study of benzotript and related derivatives to identify potent and selective antagonists of this class for both structural and pharmacological studies.

Discussion

We have already reported[16] on an interesting correlation between the potent benzodiazepine MK-329 (L-364,718) and the glutamic acid based antagonists represented by CR 1409, A-64718, and A-65186 and wished to extent our construct, if possible, to include benzotript. Initially we reasoned that one of the aryl groups in benzotript (indolyl or *p*-chlorophenyl) may be binding in a similar fashion to the heterocyclic portions of our hybrid compounds (A-64718, indolyl and A-65186, quinolyl; refer to Figure 1). We started by examining benzotript and its enantiomeric forms to derive some hint of enantioselectivity. We were

(15) Dourish, C. T.; Ruckert, A. C.; Tattersall, F. D.; Iversen, S. D. Evidence that Decreased Feeding Induced by Systemic Injection of Cholecystokinin is Mediated by CCK-A Receptors. *Eur. J. Pharmacol.* **1989**, *173*, 233–234. Hewson, G.; Leighton, G. E.; Hill, R. G.; Hughes, J. The cholecystokinin receptor antagonist L364,718 increases food intake in the rat by attenuation of the action of endogenous cholecystokinin. *Br. J. Pharmacol.* **1988**, *93*, 79–84. Khosla, S.; Crawley, J. N. Potency of L-364,718 as an antagonist of the behavioural effects of peripherally administered cholecystokinin. *Life Sci.* **1988**, *42*, 153–9.

(16) (a) Nadzan, A. M.; Kerwin, J. F., Jr.; Kopecka, H.; Lin, C. W.; Miller, T.; Witte, D.; Burt, S. Structural and Functional Relationships Among CCK Antagonists. In *Cholecystokinin Antagonists, Neurology and Neurobiology*; Wang, R. Y., Schoenfeld, R., Eds.; Alan R. Liss, Inc.: New York, 1988; Vol. 47, pp 93–103. Freidinger, R. M.; Whitter, W. L.; Gould, N. P.; Holloway, M. K.; Chang, R. S. L.; Lotti, V. J. Novel Glutamic Acid Derived Cholecystokinin Receptor Ligands. *J. Med. Chem.* **1990**, *33*, 591–95. (b) Kerwin, J. F., Jr.; Nadzan, A. M.; Kopecka, H.; Lin, C. W.; Miller, T.; Witte, D.; Burt, S. Hybrid Cholecystokinin (CCK) Antagonists: New Implications in the Design and Modification of CCK Antagonists. *J. Med. Chem.* **1989**, *32*, 739–42.

unable to differentiate the *R* and *S* enantiomers of benzotript in our binding assay, since both compounds were very weak inhibitors ($\sim 10^{-4}$ M) of [^{125}I]Bolton-Hunter CCK_8 binding in guinea pig pancreatic acinar membranes.[17] In envisioning possible correspondence between benzotript and other CCK antagonists, many potential overlaps can exist, some of which are represented in Figure 2. Substitution of the carboxylic acid moiety in benzotript by a di-*n*-pentylamide moiety was expected to provide a neutral analogue that might demonstrate this enantioselective differentiation in the binding assay. We reasoned that benzotript itself contained only two important hydrophobic recognition sites and that the pentyl groups may add an additional binding site.

Synthesis of the *R* and *S* enantiomers of the above analogues (**3** and **4**) was achieved as outlined in Scheme I. Boc-tryptophan of the desired optical enantiomer was coupled with di-*n*-pentylamine using BOPCl[18] at 0 °C. The Boc group was then removed by the action of HCl in dioxane to yield the hydrochloride salt **2**. The salt **2** (either the *R* or the *S* enantiomer) was reacted with *p*-chlorobenzoyl chloride to provide the desired compounds **3** (*R*) and **4** (*S*). Physical properties of compounds **3** and **4** and subsequent compounds are compiled in Table I. The integrity of the α center was assessed by preparing the Mosher's amides of the *R* and *S* hydrochloride salts **2**. Examination of the Mosher amides by ^{19}F NMR utilizing spiking techniques indicated that both enantiomers were greater than 99.5% pure.

Enantiomers **3** and **4** proved to be more potent CCK antagonists when compared to their parent benzotript (Table II). However, the two enantiomers did not demonstrate any substantial enantiopreference in the pancreatic binding assay. Continuing along this path, we replaced the *p*-chlorobenzoyl group with the 3,4-dichlorobenzoyl group to derive compounds **5** (*R*) and **6** (*S*). The binding of these two compounds demonstrated a slight stereopreference, although the overall binding affinity was not greatly improved from that of **3** and **4**. Since the di-*n*-pentylamide substitution greatly enhanced the potency, replacement of the *p*-chlorophenyl with 2-indolyl (**7** and **8**) and 3-quinolyl (**9** and **10**) groups was examined due to the fact that these substitutions were shown to increase potency and selectivity in the glutamate-based series.[16] These compounds were synthesized as in Scheme I utilizing the appropriate carboxylic acid or acid chloride. Compound **7** possessed an IC_{50} = 51 nM for pancreatic binding and a 160-fold preference for CCK-A (pancreas) over CCK-B (cortex) receptors. Compound **9** (A-67396), one of the most potent compounds (IC_{50} = 23 nM), had a selectivity of >500-fold for CCK-A receptors. In addition, compounds **7**/**8** possessed a eudismic ratio of $\sim$10, while compounds **9**/**10** exhibited a eudismic ratio of 48. Not only had the affinities and potencies increased dramatically but also a strong preference for the *R* enantiomer was displayed. In addition compound **9** proved to be a potent antagonist (IC_{50} = 43 nM) in the inhibition of CCK_8-induced amylase release. The finding that the *R* enantiomer was significantly more potent and selective for CCK-A receptors paralleled our findings in the glutamate derived series. These facts prompted us to examine the structure–activity relationship of the aryl group even further as we had done previously for the glutamate-based hybrids.

The results of these studies are shown in Table II. A few trends can be seen in the binding data presented. The presence of a second aromatic ring is preferred by comparing compounds **7** vs **12** and **9** vs **13** and even by examining the difference between compound **5** and **15**. The position of the aryl group also appears to play a role in the overall binding affinity, since compounds **16**, **18**, and **24** display lower affinity than their respective counterparts **15**, **19**, and **7**. Among a number of quinolyl and isoquinolyl compounds, positioning of the nitrogen or its effect on the local aryl electrostatic potential appeared to confer lower binding affinity. For example, the isoquinolyl isomer **19** was very poor in comparison to **9**, **11**, or even **17**. There did not appear to be a great difference in binding affinity between compounds **9** and **15**. These trends paralleled closely the trends in the SAR of the glutamate-based hybrids. The rank order affinities of various aryl substitutions was 3-quinolyl > 2-naphthyl > 2-indolyl > 2-quinolyl > 3,4-dichlorobenzoyl > 1-naphthyl, the same order as seen within the glutamate-derived antagonists[16b] (Table III). Taken together the data suggested that these two distinct antagonist series may be occupying the same or overlapping sites at the CCK receptor. Furthermore, if a strict interpretation of our previous model was enforced, then the indolylmethyl group in the (*R*)-tryptophan series and the carboxylic acid side chain in the glutamate series were occupying the same relative position in the receptor–ligand complex. This interpretation may have ramifications for comparison of the non-peptide antagonists with their selective peptide agonist counterparts.[19]

With these new lead compounds we sought to broaden our knowledge of the SAR in this series. The possibility of replacing the amide bond with a sulfonamide was examined by preparing **26** in direct analogy to compound **3**. The binding of **26** was clearly 2 orders of magnitude worse than its parent, and this substitution was not pursued further.

Substitution of the indolyl function in MK-329 with an arylamino group and inversion of the related chiral center has been reported to provide arylureas with enhanced affinity for CCK-B receptors as present in the CNS (e.g. L-365,260 in Figure 1).[10] In an effort to mimic this transformation of CCK-A selective into CCK-B selective compounds, a number of arylureas were prepared from the corresponding isocyanates (Scheme I) and assayed (Table II). Compounds **27**–**32** all demonstrated a clear loss in affinity for the CCK-A receptor (pancreas) but displayed very little if any improvement for CCK-B sites (cortex). While these modifications did not accomplish a similar reversal of selectivity, they evidenced a loss of CCK-A binding affinity as reported for the benzodiazepine-based class.

In order to examine other possibilities for improving our CCK-A selective lead, a number of substituted quinolyl and naphthyl analogues were synthesized, concentrating on hydroxyl substituents in the hope of inducing hydrogen-bonding interactions within the receptor complex. For the most part, the various changes decreased binding affinity (e.g. compounds **20** and **22**). One exception was compound **21** with a 4-hydroxy-2-quinolyl moiety, wherein the affinity remained unchanged from its parent compound **11**. Addition of an 8-hydroxyl group to **21** provided compound **23** (A-70276), which was equipotent with the

(17) Also refer to: Jensen, R. T.; Jones, S. W.; Gardner, J. D. Studies of N-Acyl Derivatives of Tryptophan that Function as Specific Cholecystokinin Receptor Antagonists. *Biochim. Biophys. Acta* **1983**, *761*, 269–77.

(18) Tung, R. D.; Rich, D. H. Bis(2-oxo-3-oxazolidinyl)phosphinic Chloride as a Coupling Reagent for N-Alkyl Amino Acids. *J. Am. Chem. Soc.* **1985**, *107*, 4342–3.

(19) Coats, E. A.; Knittel, J. J. Correlation Analysis and Molecular Modeling of Cholecystokinin Inhibitors. *Quant. Structure–Act. Relat.* **1990**, *9* (2), 94–101.

lead **9** (A-67396). This result was surprising since the 8-hydroxyl substituent was shown to be poor (compound **22**). The role that the hydroxyl groups of **23** play in receptor recognition and binding is unclear and currently is an area for further investigation.

In order to verify that the SAR between the glutamate- and benzotript-based series was indeed parallel, the 4,8-dihydroxy-2-(quinolylcarbonyl)-(*R*)-glutamic acid di-*n*-pentylamide (**33**) was prepared. The binding affinity of **33** (Table III) was comparable to that of A-65186 just as the binding affinity of compound **23** was comparable to that of compound **9**. A number of other analogues in the tryptophan and glutamate series[1b] are shown in Table III as well. A qualitative rank order of potency is evident as one moves down the table. This order is preserved both in the glutamate- and tryptophan-based series' binding affinities and is mirrored for most of these compounds in the amylase release IC_{50} data. However, whereas the more potent aryl groups such as 3-quinolyl (**9**) demonstrate a 2–3-fold difference between the binding IC_{50} and the amylase IC_{50}, this correlation dissipates with the aryl group substitution for the tryptophan series, falling to a 10-fold difference between the two IC_{50} values. The origin of this loss in functional activity is not known at this time, but the trend in rank order potency remains relatively consistent through both series.

To explore the antagonist side chain which may be interacting in the receptor complex, a limited number of substituted tryptophan analogues were synthesized. In some cases (e.g. **34** and **35**) racemic mixtures of the appropriate 5-substituted tryptophan derivatives were employed. Synthesis followed a standard course of preparing the N^{α}-Boc derivatives: coupling with di-*n*-pentylamine, deprotection, and acylation in a fashion analogous to that in Scheme I. The data in Table IV suggest that the binding of the indole moiety of the tryptophan is relatively insensitive to changes in substitution at the remote 5-position but that proximal substitution can be detrimental if sterically demanding (e.g. (*o*-nitrophenyl)thio, **38**). Certain 5-indolyl substitutions can improve affinity and potency although only by small factors. The most interesting compound was the 5-hydroxyl compound **36** (A-71134), which demonstrated a slight improvement in binding potency (IC_{50} = 11 nM) relative to **9**.

The two lead compounds **9** and **36** were further evaluated against CCK_8-stimulated amylase release in guinea pig pancreatic acini (Figure 3). Compound **9** at 200 nM and compound **36** at 100 nM both produced a rightward shift in the dose–response curve for CCK_8, thus demonstrating that both antagonists **9** and **36** function as competitive CCK-A receptor antagonists. The EC_{50} for CCK_8 without antagonist present was 0.052 ± 0.0093 nM. With compound **9** the EC_{50} was shifted to 0.96 ± 0.024 nM and with compound **36** the EC_{50} was 2.0 ± 0.2 nM. Both concentrations of antagonist reduced basal amylase release by approximately 30%.

We next turned our attention to the di-*n*-pentylamide function and examined two points of interest: (1) could the hydrophobic pentyl chain(s) be replaced by aromatic functions as our model would suggest and (2) could a second stereogenic center be introduced to enhance the construct. A limited series of benzylamides were prepared in standard fashion and are shown in Table V. The benzylamide **39** demonstrated 1 order of magnitude decrease in affinity as compared to compound **9**. Further substitution of the amide, even with methyl to give **40** or with carbethoxymethyl to give **41**, was also detrimental. However, substitution of the benzylic methylene with methyl did provide a measurable preference for the *R* stereocenter (compare **42** vs **43**). This effect was also evident when the methyl group was replaced with an ethoxycarbonyl moiety wherein a 10-fold preference for the *R,S* diastereomer **44** over the *R,R* diastereomer **45** was evidenced. The two compounds **42** and **44** suggest that one pentyl group in this series of antagonists is replacing the phenyl moiety in the benzodiazepine antagonists in its interaction with the CCK receptor. In addition, the second stereocenter provides new information with which to refine the antagonist model.

Summary

Investigation of the possible relationship between benzotript- and glutamate-based CCK antagonists has resulted in a number of potent and selective antagonists for the CCK-A receptor. Examples of these are compounds **9**, **23**, **36**, **42**, and **44**. These compounds suggest the structural homology between benzotript and proglumide-like antagonists that is required for receptor recognition. The parallel SAR evidenced between these two series strongly suggested that these antagonists are interacting with the same sites on the CCK-A receptor. The parallel nature of this SAR demonstrated that certain structural features may be transferable between the two series without great loss in binding affinities. Furthermore, the (*R*)-tryptophan-based template has provided sites for further substitution such as the hydroxylated quinolyl nucleus and the substituted indole of tryptophan, and the introduction of a second stereogenic center α to the amide nitrogen. With subtle structural differences in antagonist design, the identification of further subtypes of the CCK-A receptor may be possible.

Experimental Section

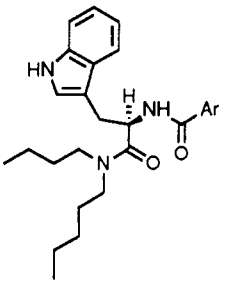
Biology. The guinea pig cerebral cortical and pancreatic membrane preparations and binding assays were performed using the modified protocol of Lin et al.[20] IC_{50}s were determined from the Hill analysis. The CCK_8-stimulated amylase release assay was also performed using published procedures.[20] The reference concentration for CCK_8 in determining the IC_{50}s of the compounds in the CCK_8-stimulated amylase release assay was 3×10^{-10} M.

Chemistry. Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting point apparatus or a Büchi 510 capillary melting point apparatus. TLC was performed on Merck precoated silica gel 60 F_{254} plates. Silica gel (E. Merck; 230–400 mesh) was used for flash chromatography eluting with 5–10 psi of air pressure. Optical rotations were determined in a Perkin-Elmer 241 polarimeter. Proton NMR spectra were obtained at 300 MHz in $CDCl_3$ at room temperature unless otherwise indicated. Solvents and other reagents were reagent grade and were used without further purification unless otherwise noted.

***N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-(*R*)-tryptophan Di-*n*-pentylamide (1).** *N*-Boc-(*R*)-tryptophan (10 g, 33 mmol) was stirred at 0 °C in 160 mL of CH_2Cl_2 with bis(2-oxo-3-oxazolidinyl)phosphinic chloride[18] (BOPCl; 8.6 g, 34 mmol) and 4.5 mL (32 mmol) of triethylamine (TEA). To this reaction mixture was added di-*n*-pentylamine (18 mL, 89 mmol), and the mixture was

(20) Lin, C. W.; Miller, T. Characterization of cholecystokinin receptor sites in guinea pig cortical membranes using [^{125}I]Bolton Hunter-cholecystokinin octapeptide. *J. Pharmacol. Exp. Ther.* **1985**, *232*, 775–780. Lin, C. W.; Bianchi, B. R.; Grant, D. T.; Miller, T.; Danaher, E. A.; Tufano, M. D.; Kopecka, H.; Nadzan, A. M. Cholecystokinin receptors: relationships among phosphotidyllinositol turnover, amylase release and receptor affinity in pancreas. *J. Pharmacol. Exp. Ther.* **1986**, *236*, 729–34. Lin, C. W.; Holladay, M. W.; Barrett, R.; Miller, T.; Witte, D.; Wolfram, C.; Kerwin, J. F., Jr.; Wagenaar, F.; Nadzan, A. M. Distinct Requirements for Activation at CCK-A and CCK-B Receptors: Studies with a C-terminal Hydrazide Analogue of CCK_4. *Mol. Pharmacol.* **1989**, *36*, 881–86.

Table II. Binding Affinities of *N*-(Arylacyl)tryptophan Dipentylamides



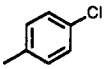
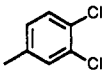
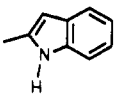
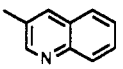
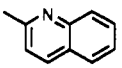
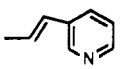
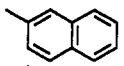
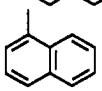
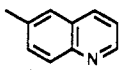
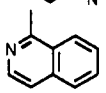
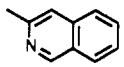
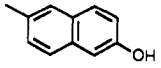
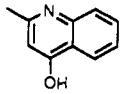
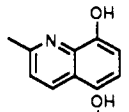
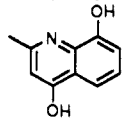
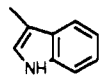
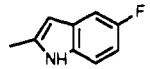
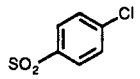
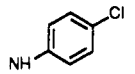
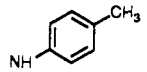
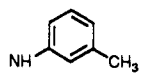
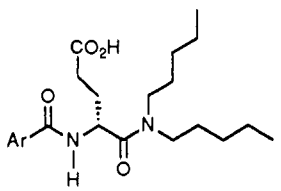
compd[b]	Ar	binding:[a] IC_{50} (nM) pancrease	binding:[a] IC_{50} (nM) cortex	IC_{50} (nM)[a,c] amylase
benzotript		>100000	nd	nd
3R		370 (2)	>10000	<10000
4S		475 ± 58 (3)	27000	<30000
5R		190 ± 69 (3)	>10000	2500 ± 790 (3)
6S		670 (2)	>10000	>30000
7R		51 ± 13 (5)	8000 ± 850 (3)	670 (2)
8S		520 ± 86 (3)	3100	<30000
9R		23 ± 5.4 (6)	12000 (2)	43 ± 3.2 (3)
10S		1130 ± 270 (3)	7400 (2)	<100000
11R		120 ± 34 (3)	~100000	1300 (2)
12R		5650 ± 820 (3)	>10000	>100000
13R		14600 ± 2200 (3)	>10000	>100000
14R		>1000	>10000	<100000
15R		29 ± 3.8 (3)	11000 (2)	360 ± 74 (3)
16R		500 ± 120 (3)	9700	<30000
17R		239 ± 25 (4)	>10000	<10000
18R		5800	>10000	>100000
19R		880 ± 130 (3)	>10000	<100000
20R		5200 ± 900 (4)	>10000	~100000
21R		51 ± 14 (4)	3300 (2)	110
22R		390 ± 150 (4)	>10000	<100000
23R		21 ± 3.4 (6)	4200	46 ± 12 (3)

Table II (Continued)

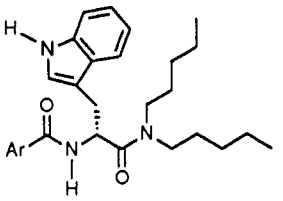
compd[b]	Ar	binding:[a] IC_{50} (nM) pancrease	binding:[a] IC_{50} (nM) cortex	IC_{50} (nM)[a,c] amylase
24*R*		430 ± 140 (3)	20000	<10000
25*R*		155 ± 27 (4)	~10000	<100000
26*R*		22000 ± 8100 (3)	>10000	>100000
27*R*		4200	5600	nd
28*S*		>10000	>10000	nd
29*R*		2500 ± 770 (3)	1900 (2)	nd
30*S*		>10000	9250	nd
31*R*		1100 ± 310 (4)	>10000	>30000
32*S*		1500 ± 290 (3)	>10000	<100000

[a] Standard deviations shown when available; number of determinations in parentheses. [b] *R* or *S* enantiomers designated for clarity. [c] Compounds listed at inhibitions of <10000 nM inhibited CCK_8-induced amylase release by 75% or greater. Concentrations above 10000 nM demonstrated 60% inhibition or greater.

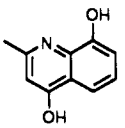
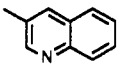
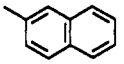
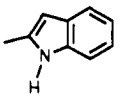
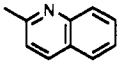
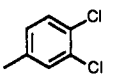
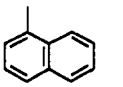
Table III. Comparison of (*R*)-Glutamate and (*R*)-Tryptophan CCK Antagonists



(*R*)-Glu analogues



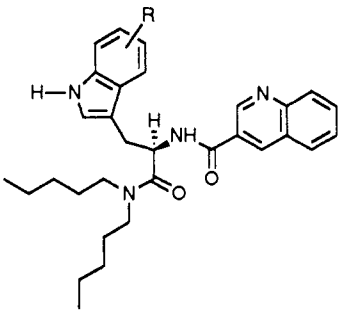
(*R*)-Trp analogues

compd	analogue	IC_{50} (nM)[a] aryl group	IC_{50} (nM)[a] pancrease	inhibition of amylase release
23	Trp		21 ± 3.4 (6)	46 ± 12 (3)
33	Glu		7 ± 0.5 (3)	106 (2)
9	Trp		23.4 ± 5.4 (6)	43 ± 3.2 (3)
A-65186	Glu		5.1 ± 1.7 (7)	16 ± 3.6 (3)
15	Trp		29 ± 3.8 (3)	360 ± 74 (3)
	Glu		12 ± 6.6 (4)	36 ± 9 (3)
7	Trp		51 ± 13 (5)	670 (2)
A-64718	Glu		19 ± 2.6 (4)	36 (2)
11	Trp		120 ± 34 (3)	1300 (2)
	Glu		63 ± 31 (5)	110 ± 3.7 (3)
5	Trp		190 ± 69 (3)	2500 ± 790 (3)
	Glu		66 ± 30 (5)	180 ± 10 (3)
16	Trp		530 (2)	nd
	Glu		320 ± 260 (3)	280 ± 50 (3)

[a] Standard deviations shown when available; number of determinations in parentheses.

stirred overnight and allowed to warm to room temperature. An additional equivalent of BOPCl was added after 18 h and the reaction stirred an additional day. Solvent was evaporated in vacuo, the residue was taken up in EtOAc and washed with H_2O,

Table IV. Indole Substitutions of Compound **9** (A-67396)



compd[b]	R	binding:[a] IC_{50} (nM) pancreas	binding:[a] IC_{50} (nM) cortex	IC_{50} (nM)[a,c] CCK_8-stimulated amylase release
34*RS*	5-fluoro	48 ± 7.6 (3)	7600	>100000
35*RS*	5-benzyloxy	67 ± 7.1 (3)	6300	<100000
36*R*	5-hydroxy	11 ± 2.9 (4)	<10000	27 ± 5.9 (3)
37*R*	2-oxo-(3*H*)	46 ± 13 (4)	4100	62
38*R*	2-*o*-NPS	1500	>10000	<100000

[a] Standard deviations shown when available; number of determinations in parentheses. [b] Enantiomeric composition shown for clarity. [c] Compounds listed at concentrations <100000 nM demonstrated 60% inhibition or greater.

1 N HCl solution, saturated $NaHCO_3$, and water, and then the organic solution was dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was purified by chromatography using EtOAc–hexane (1:4). The product was isolated as an oil in 57% yield (8.2 g): $[\alpha]_D = -28.4°$ (c = 1.08, MeOH); MS(CI) m/e 444 (m + H)$^+$, 326; ^{1}H NMR δ 0.78 (t, J = 7 Hz, 3 H), 0.88 (t, J = 6 Hz, 3 H), 0.9–1.2 (m, 8 H), 1.25 (m, 4 H), 1.45 (s, 9 H), 2.7–3.08 (m, 3 H), 3.1 (d, J = 9 Hz, 2 H), 3.33 (m, 1 H), 4.9 (q, J = 12 Hz, 1 H), 5.4 (d, J = 9 Hz, 1 H), 7.05 (s, 1 H), 7.15 (m, 2 H), 7.34 (d, J = 9 Hz, 1 H), 7.7 (d, J = 9 Hz, 1 H), 8.1 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.85, 13.96, 22.2, 22.4, 27.1, 28.3, 28.6, 28.7, 29.04, 30.1, 46.13, 47.62, 50.65, 79.34, 110.8, 111.0, 118.8, 119.5, 121.9, 122.8, 127.7, 136.1, 155.06, 171.8. *S* enantiomer: $[\alpha]_D = +28.6°$ (c = 1.75, MeOH).

(*R*)-Tryptophan Di-*n*-pentylamide Hydrochloride (2). The product 1 (2.0 g, 4.4 mmol) was dissolved in 4 N HCl in dioxane (12 mL) and stirred under inert atmosphere (N_2) for 1 h. When the reaction was complete by TLC, the solvent was evaporated in vacuo and hexane and Et_2O were added. The

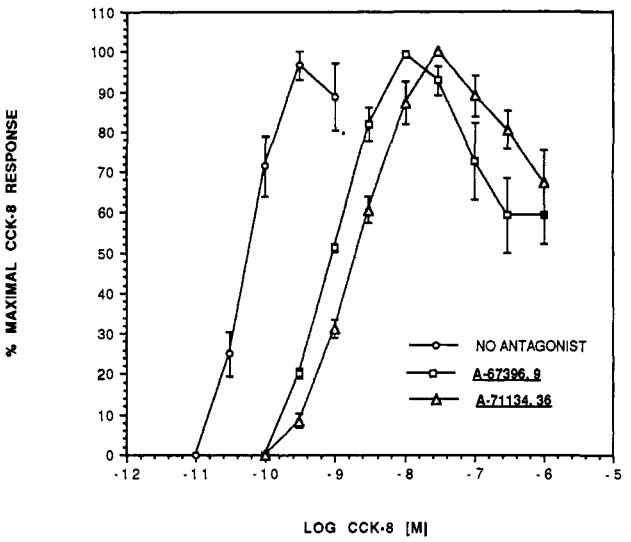
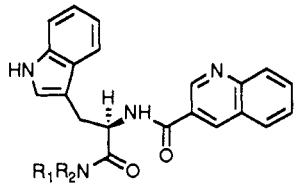
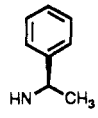
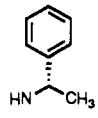
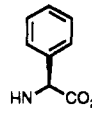
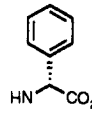


Figure 3. Effect of compounds **9** (200 nM) and **36** (100 nM) on the dose–response curves of CCK_8-stimulated amylase secretion in guinea pig pancreatic acinar cells. Results shown are from three experiments each conducted in triplicate.

Table V. Amide SAR of Compound **9** (A-67396)



compd	NR_1R_2	binding:[a] IC_{50} (nM) pancreas	cortex
9	$N(C_5H_{11})_2$	23.4 ± 5.4 (6)	15000
39	NHBzl	350	>10000
40	$N(CH_3)Bzl$	600 ± 57 (3)	~10000
41	$N(Bzl)CH_2CO_2Et$	400 ± 76 (6)	9200
42		180 ± 70 (3)	>10000
43		810 ± 270 (3)	>10000
44		165 ± 59 (3)	>10000
45		1700	nd

[a] Standard deviations shown when available; number of determinations in parentheses.

residue was triturated with these two solvents and the solvent again removed in vacuo. This procedure was repeated several times until the product was obtained as a glassy solid in quantitative yield: $[\alpha]_\Delta = -86.4°$ (c = 1.05, MeOH); MS(FAB$^+$) m/e 344 (m + 1)$^+$; ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J = 7 Hz, 3 H), 0.84 (t, J = 7 Hz, 3 H), 0.95–1.16 (m, 6 H), 1.19–1.30 (m, 6 H), 2.58–2.68 (m, 1 H), 2.72–2.83 (m, 1 H), 2.88–2.97 (m, 1 H), 3.11 (dd, J = 9, 14 Hz, 1 H), 3.24–3.33 (m, 2 H), 4.24–4.3 (m, 1 H), 7.01 (dt, J = 1, 7 Hz, 1 H), 7.10 (dt, J = 1, 7 Hz, 1 H), 7.18 (d, J = 2 Hz, 1 H), 7.37 (d, J = 8 Hz, 1 H), 7.60 (d, J = 8 Hz, 1 H), 8.42 (s, 1 H), 11.88 (d, J = 8 Hz, 1 H).

General Procedures for Coupling of 2. Method A. Coupling to Acid Chlorides. To a mixture of the hydrochloride **2** and TEA (2 equiv) stirred in CH_2Cl_2 at 0 °C was added 1 equiv of acid chloride. When TLC analysis indicated the complete consumption of starting material, the mixture was taken up in EtOAc and washed three times with portions of water. The organic extract was dried over $MgSO_4$ and then filtered. Concentration of the filtrate and silica gel chromatography (EtOAc–hexane) provided product.

Method B. Coupling to Carboxylic Acids. EDCI [1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride] (1.1 equiv) was added to a cooled (4 °C) solution of the carboxylic acid (1 equiv), **2**, HOBt (0.2 equiv), and TEA (triethylamine) (2 equiv, alternatively NMM; N-methylmorpholine) in CH_2Cl_2 (or alternatively DMF). The reaction was allowed to attain room temperature overnight and monitored by TLC for completion. The solvent was evaporated, the residue was dissolved in EtOAc, extracted with 0.1 M H_3PO_4 (3×, alternatively citric acid), 0.1 M Na_2CO_3 (3×), H_2O (3×), and brine (1×), dried over $MgSO_4$, and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica (EtOAc–hexane) to provide product.

Method C. Coupling to Aryl Isocyanates. Compound **2** was reacted with the isocyanate (1 equiv) and TEA (1 equiv) in THF for 1–3 h at ambient temperature. The reaction mixture was taken up into EtOAc and then extracted with 0.1% citric acid, H_2O, and 0.5 M $NaHCO_3$ and dried over $MgSO_4$. After filtration the EtOAc solution was diluted with 2 volumes of hexane and the resulting solid collected by filtration to yield product.

***N*-(3′-Isoquinolylcarbonyl)-(*R*)-tryptophan Di-*n*-pentylamide (19).** 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (500 mg, 2.3 mmol) and Cbz-OSu (874 mg, 3.5 mmol) were dissolved in 30 mL of 1:1:1 dioxane–H_2O–MeOH. TEA (641 μL, 4.6 mmol) was added to the reaction mixture and stirring continued overnight. The mixture was concentrated, the residue was extracted with 0.1 M H_3PO_4 and H_2O, dried over $MgSO_4$, and filtered, and the filtrate was concentrated. The crude material (829 mg) was used directly without further purification: ^{1}H NMR δ 3.17 (d, J = 5 Hz, 2 H), 4.44–4.73 (m, 2 H), 4.86–4.94 (m, 1 H), 5.08–5.26 (m, 2 H), 7.16–7.24 (m, 4 H), 7.32–7.42 (m, 6 H). *N*-Cbz-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (400 mg, 1.29 mmol) and compound **2**(*R*) (464 mg, 1.29 mmol) were coupled according to general method B to provide N^α-(*N*-Cbz-1,2,3,4-tetrahydroisoquinolyl-3-carbonyl)-(*R*)-tryptophan di-*n*-pentylamide: R_f = 0.32 (18:1 CH_2Cl_2–EtOH); MS(CI) m/e 637 (m + H)$^+$, 508, 503, 478, 391, 326; ^{1}H NMR (DMSO-d_6, 145 °C) δ 0.84–0.88 (m, 3 H), 1.10–1.40 (m, 15 H), 2.82 (s, H_2O), 2.85–3.23 (m, 8 H), 4.53 (dd, J = 2, 15 Hz, 1 H), 4.76 (dd, J = 8, 15 Hz, 1 H), 4.87 (t, J = 5 Hz, 1 H), 4.93–5.02 (m, 1 H), 5.15–5.27 (m, 2 H), 6.96–7.03 (m, 2 H), 7.08–7.12 (m, 2 H), 7.17–7.22 (m, 4 H), 7.34–7.47 (m, 6 H), 7.55–7.58 (m, 1 H), 10.35 (s, 1 H). N^α-(*N*-Cbz-1,2,3,4-tetrahydroisoquinolyl-3-carbonyl)-(*R*)-tryptophan di-*n*-pentylamide (260 mg, 0.41 mmol) was dissolved in 25 mL of decalin and treated with 10 mg of 10% Pd/C at reflux for 5 h. The reaction was cooled and the mixture was filtered. After concentration of the filtrate, the residue was purified by chromatography on silica gel eluted with a 4:1 to 2:1 hexane–EtOAc step gradient to yield 121 mg (59%) of **19**: R_f = 0.5 (1:1 hexane–EtOAc); ^{1}H NMR δ 0.77 (t, J = 7 Hz, 3 H), 0.86 (t, J = 7 Hz, 3 H), 0.94–1.44 (m, 12 H), 2.86–3.10 (m, 3 H), 3.33–3.44 (m, 3 H), 5.47–5.54 (m, 1 H), 7.11–7.20 (m, 3 H), 7.32 (dd, J = 1, 7 Hz, 1 H), 7.67–7.78 (m, 2 H), 7.83 (dd, J = 1, 7 Hz, 1 H), 7.96 (d, J = 8 Hz, 1 H), 8.03 (d, J = 7 Hz, 1 H), 8.15 (s, 1 H), 8.59 (s, 1 H), 9.02 (d, J = 9 Hz, 1 H), 9.18 (s, 1 H).

***N*$^\alpha$-[(4′,8′-Dihydroxy-2′-quinolyl)carbonyl]-(*R*)-glutamic Acid Di-*n*-pentylamide (33).** NMM (0.55 mL, 5 mmol), HOBt (0.33 g, 2.42 mmol), 4,8-dihydroxyquinoline-2-carboxylic acid (0.5 g, 2.44 mmol), and DCC (0.55 g, 2.6 mmol) were added to a solution of (*R*)-glutamic acid di-*n*-pentylamide γ-benzyl ester (1.0 g, 2.42 mmol) in DMF (10 mL) at 0 °C. The reaction was allowed to proceed overnight with warming to ambient temperature. Standard workup as in method B above, followed by chromatography on silica gel ($CHCl_3$–MeOH, 18:1), provided *N*-[(4′,8′-dihydroxy-2′-quinolyl)carbonyl]-(*R*)-glutamic acid di-*n*-pentylamide γ-benzyl ester, a semisolid yellow oil in 55% yield (0.75 g): MS(CI) m/e 564 (m + H)$^+$; ^{1}H NMR δ 0.85–0.95 (m, 6 H),

1.22–1.42 (m, 8 H), 1.55–1.75 (m, 4 H), 1.75–2.0 (m, 2 H), 2.5–2.62 (m, 1 H), 2.65–2.80 (m, 1 H), 3.05–3.20 (m, 1 H), 3.30–3.52 (m, 2 H), 3.64–3.78 (m, 1 H), 5.0 (m, 1 H), 5.2 (s, 2 H), 6.95 (m, 2 H), 7.15 (m, 7 H), 7.6 (d, J = 9 Hz, 1 H), 8.1 (bs, 1 H), 9.2 (bs, 1 H). N-[(4',8'-Dihydroxy-2'-quinolyl)carbonyl]-(R)-glutamic acid di-n-pentylamide γ-benzyl ester (0.4 g, 0.71 mmol) was treated with 0.3 g of 10% Pd/C in 15 mL of MeOH and cyclohexadiene (2 mL) under N_2 atmosphere. After the reaction was complete, the mixture was filtered through Celite, the filtrate concentrated in vacuo, and the residue purified by chromatography (EtOAc–hexane–HOAc, 70:30:1) to provide 0.2 g of oily product (60%): ^{1}H NMR (DMSO-d_6) δ 0.75–0.88 (m, 6 H), 1.1–1.35 (m, 8 H), 1.4–1.65 (m, 4 H), 1.95–2.10 (m, 2 H), 2.35–2.42 (m, 2 H), 3.1 (m, 1 H), 3.2–3.4 (m, 3 H), 5.0 (m, 1 H), 7.10 (d, J = 9 Hz, 1 H), 7.42 (t, J = 10 Hz, 1 H), 7.49 (bs, 1 H), 7.55 (d, J = 9 Hz, 1 H), 9.6 (bd, J = 9 Hz, 1 H), 10.1 (bs, 1 H), 12.00 (bs, 1 H).

N^{α}-(3'-Quinolylcarbonyl)-(R)-(2,3-dihydro-2-oxoindol-3-yl)alanine Di-n-pentylamide (37). Compound **9** (2.5 g, 5.0 mmol) was dissolved in 50 mL of CH_2Cl_2 and cooled to 4 °C. TEA (2.8 mL, 20 mmol) was added in one portion followed by the addition of *tert*-butyl hypochlorite (0.57 mL, 5.0 mmol) over 10 min.[21] The reaction was allowed to attain room temperature overnight. The reaction solution was washed with water and then dried over $MgSO_4$. The solution was filtered and the filtrate concentrated. The residue was mixed with 4:1 hexane–EtOAc, and the resulting solid was filtered to provide 2(R)-(di-n-pentylcarbamoyl)-2,3-dihydro-1-(3'-quinolylcarbonyl)pyrrolo-[2,3-b]indole: 1.43 g, 2.9 mmol (58%); mp 145–53 °C; $[\alpha]_D$ = +172° (c = 1.04, CH_2Cl_2); MS(CI) m/e 497 (m + H)$^+$; ^{1}H NMR δ 0.74 (t, J = 7 Hz, 3 H), 0.78 (t, 7 Hz, 3 H), 0.85–1.13 (m, 12 H), 1.26–1.34 (m, 1 H), 2.85–2.94 (m, 3 H), 3.05–3.13 (m, 3 H), 5.50 (dd, J = 3, 10 Hz, 1 H), 7.11–7.13 (m, 2 H), 7.32–7.39 (m, 2 H), 7.52 (t, J = 7 Hz, 1 H), 7.8 (dt, J = 1, 7 Hz, 1 H), 7.86 (d, J = 7 Hz, 1 H), 8.13 (d, J = 8 Hz, 1 H), 8.35 (d, J = 2 Hz, 1 H), 9.06 (d, J = 2 Hz, 1 H), 9.38 (s, 1 H). The product [2(R)-(di-n-pentylcarbamoyl)-2,3-dihydro-1-(3'-quinolylcarbonyl)pyrrolo[2,3-b]-indole, 121 mg, 0.24 mmol] was dissolved in dioxane (10 mL) and treated with concentrated hydrochloric acid (1 mL). A red solution formed immediately, which bleached in 10–15 s to provide a colorless solution. After several hours, the reaction mixture was poured into EtOAc and washed with H_2O until neutral and then dried over $MgSO_4$. The crude product was purified by chromatography on silica eluted with a step gradient from 1 to 5% EtOH in CH_2Cl_2 to provide product 97 mg of the title compound (0.19 mmol, 79% yield): ^{1}H NMR δ 0.85–0.96 (m, 6 H), 1.24–1.38 (m, 8 H), 1.48–1.61 (m, 4 H), 1.69 (s, H_2O), 2.16 (ddd, J = 3, 8, 14 Hz, 0.6 H), 2.32 (ddd, J = 3, 8, 14 Hz, 0.4 H), 2.50–2.62 (m, 1 H), 3.03–3.16 (m, 0.6 H), 3.18–3.29 (m, 0.4 H), 3.34–3.45 (m, 1 H), 3.51–3.64 (m, 1.6 H), 3.92 (m, 1 H), 5.32 (dt, J = 2, 8 Hz, 0.4 H), 5.53 (dt, J = 2, 10 Hz, 0.6 H), 6.82 (d, J = 7 Hz, 0.6 H), 6.37 (d, J = 7 Hz, 0.4 H), 6.98–7.06 (m, 1 H), 7.12 (t, J = 7 Hz, 1 H), 7.20 (t, J = 8 Hz, 1 H), 7.45 (d, J = 7 Hz, 0.6 H), 7.52–7.58 (m, 0.4 H), 7.62 (t, J = 8 Hz, 1 H), 7.72–7.88 (m, 2 H), 8.02 (d, J = 8 Hz, 0.4 H), 8.08 (d, J = 8 Hz, 0.6 H), 8.12–8.15 (m, 1 H), 8.37 (s, 0.4 H), 8.42 (d, J = 2 Hz, 0.6 H), 8.62 (d, J = 2 Hz, 0.4 H), 9.20 (d, J = 2 Hz, 0.6 H), 9.34 (d, J = 2 Hz, 0.4 H).

N^{α}-(3'-Quinolylcarbonyl)-2-[(2'-nitrophenyl)thio]-(R)-tryptophan Di-n-pentylamide (38). 2-Nitrobenzenesulfenyl chloride (3.4 mg, 0.02 mmol) was added to **9** (10 mg, 0.02 mmol) in $CHCl_3$. After 3 h, the reaction mixture was purified by chromatography on silica gel and eluted with $CHCl_3$ to 1% EtOH in $CHCl_3$ to provide 13 mg (0.02 mmol; 100%) of yellow product: ^{1}H NMR δ 0.81–0.90 (m, 6 H), 1.04–1.37 (m, 9 H), 1.43–1.58 (m, 4 H), 3.12–3.25 (m, 2 H), 3.31–3.48 (m, 4 H), 5.38–5.45 (m, 1 H), 6.33 (dd, J = 1, 7 Hz, 1 H), 7.08–7.18 (m, 2 H), 7.21–7.36 (m, 4 H), 7.58 (dt, J = 1, 7 Hz, 1 H), 7.75–7.83 (m, 3 H), 8.10 (d, J = 8 Hz, 1 H), 8.13 (dd, J = 1, 8 Hz, 1 H), 8.33 (d, J = 2 Hz, 1 H), 8.38 (s, 1 H), 9.10 (d, J = 2 Hz, 1 H).

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Registry No. 1, 127369-12-4; **2**, 136631-67-9; **3**, 127368-39-2; **4**, 134018-97-6; **5**, 134018-98-7; **6**, 134018-99-8; **7**, 127368-38-1; **8**, 134019-00-4; **9**, 127368-51-8; **10**, 127368-94-9; **11**, 134019-02-6; **12**, 127368-43-8; **13**, 127368-60-9; **14**, 127368-54-1; **15**, 134019-03-7; **16**, 134019-04-8; **17**, 127368-93-8; **18**, 127368-44-9; **19**, 127368-92-7; **20**, 127368-91-6; **21**, 127368-98-3; **22**, 127368-89-2; **23**, 127387-81-9; **24**, 134019-01-5; **25**, 127369-00-0; **26**, 127368-75-6; **27**, 127369-08-8; **28**, 127369-07-7; **29**, 127369-06-6; **30**, 127369-05-5; **31**, 127369-04-4; **32**, 127369-03-3; **33**, 122668-07-9; **33** (γ-benzyl ester), 122668-06-8; **34**, 136631-68-0; **35**, 127368-52-9; **36**, 127368-83-6; **37**, 127368-77-8; **38**, 136631-69-1; **39**, 127368-41-6; **40**, 127368-59-6; **41**, 127368-56-3; **42**, 127368-63-2; **43**, 136675-73-5; **44**, 136631-70-4; **45**, 136631-71-5; CCK, 9011-97-6; *o*-NPS-Cl, 7669-54-7; Boc-D-Trp-OH, 5241-64-5; $HN(n\text{-}C_5H_{11})_2$, 2050-92-2; (S)-H-Trp-N(n-$C_5H_{11})_2$·HCl, 136675-74-6; 4-ClC_6H_4COCl, 122-01-0; 3,4-$Cl_2C_6H_3COCl$, 3024-72-4; 4-$ClC_6H_4SO_2Cl$, 98-60-2; 4-ClC_6H_4NCO, 104-12-1; 4-MeC_6H_4NCO, 622-58-2; 3-MeC_6H_4NCO, 621-29-4; H-D-Glu(OBzl)-N(n-$C_5H_{11})_2$, 136631-72-6; H-DL-Trp(5-F)-OH, 154-08-5; Boc-DL-Trp(5-F)-OH, 67337-05-7; Boc-DL-Trp(5-F)-N(n-$C_5H_{11})_2$, 127369-35-1; H-DL-Trp(5-F)-N(n-$C_5H_{11})_2$·HCl, 136631-73-7; H-DL-Trp(5-OBzl)-OH, 6383-70-6; Boc-DL-Trp(5-OBzl)-N(n-$C_5H_{11})_2$, 127369-33-9; H-DL-Trp(5-OBzl)-N(n-$C_5H_{11})_2$·HCl, 136631-74-8; H-D-Trp(5-OH)-OH, 4350-07-6; Boc-D-Trp(5-OH)-OH, 102838-87-9; Boc-D-Trp(5-OH)-N(n-$C_5H_{11})_2$, 127369-43-1; H-D-Trp(5-OH)-N(n-$C_5H_{11})_2$·HCl, 136631-75-9; $BzlNH_2$, 100-46-9; Boc-D-Trp-NHBzl, 127369-14-6; H-D-Trp-NHBzl·HCl, 136631-76-0; H-D-Trp-OMe, 22032-65-1; MeNHBzl, 103-67-3; Bzl-Gly-OEt, 6436-90-4; Boc-D-Trp-(*N*-Bzl)Gly-OEt, 127369-22-6; H-D-Trp-(*N*-Bzl)Gly-OEt·HCl, 136631-77-1; (*R*)-$PhCHMeNH_2$, 3886-69-9; Boc-D-Trp-(*R*)-NHCHMePh, 127369-26-0; H-D-Trp-(*R*)-NHCHMePh·HCl, 136658-53-2; (*S*)-$PhCHMeNH_2$, 2627-86-3; Boc-D-Trp-(*S*)-NHCHMePh, 127369-24-8; H-D-Trp-(*S*)-NHCHMePh·HCl, 136658-54-3; (*S*)-$H_2NCHPhCOOEt$, 15962-49-9; Boc-D-Trp-(*S*)-NHCHPhCOOEt, 136631-78-2; H-D-Trp-(*S*)-NHCHPhCOOEt·HCl, 136631-79-3; (*R*)-$H_2NCHPhCOOEt$, 39251-40-6; Boc-D-Trp-(*R*)-NHCHPhCOOEt, 136631-80-6; H-D-Trp-(*R*)-NHCHPhCOOEt·HCl, 136658-85-0; indole-2-carboxylic acid, 1477-50-5; quinoline-3-carboxylic acid, 6480-68-8; 2-quinaldic acid, 93-10-7; pyrrole-2-carboxylic acid, 634-97-9; nicotinic acid, 59-67-6; 3-(3'-pyridyl)acrylic acid, 1126-74-5; 2-naphthoic acid, 93-09-4; 1-naphthoic acid, 86-55-5; quinoline-6-carboxylic acid, 10349-57-2; isoquinoline-1-carboxylic acid, 486-73-7; 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 35186-99-3; *N*-Cbz-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 82716-88-9; N^{α}-(*N*-Cbz-1,2,3,4-tetrahydroisoquinolyl)-3-carbonyl-(*R*)-tryptophan di-*n*-pentylamide, 127387-82-0; 6-acetoxynaphthalene-2-carboxylic acid, 17295-26-0; *N*-(6'-acetoxy-2'-naphthoyl)-(*R*)-tryptophan di-*n*-pentylamide, 127368-90-5; 4-hydroxyquinoline-2-carboxylic acid, 492-27-3; 8-hydroxyquinoline-2-carboxylic acid, 1571-30-8; 4,8-dihydroxyquinoline-2-carboxylic acid, 59-00-7; indole-3-carboxylic acid, 771-50-6; 5-fluoroindole-2-carboxylic acid, 399-76-8; 2(*R*)-(di-*n*-pentylcarbamoyl)-2,3-dihydro-1-(3'-quinolylcarbonyl)pyrrolo[2,3-*b*]indole, 127368-80-3; methyl *N*-(3-quinolylcarbonyl)-(*R*)-tryptophanate, 127369-17-9; *N*-(3'-quinolylcarbonyl)-(*R*)-tryptophan, 127369-16-8; 3-quinolinecarboxylic acid *N*-hydroxysuccinimide ester, 127369-50-0.

Supplementary Material Available: Experimental, spectral, and chemical analysis data for compounds 1–45 (26 pages). Ordering information is given on any current masthead page.

(21) Cf. Ohne, M.; Spande, T. F.; Witkop, B. Cyclization of Tryptophan and Tryptamine Derivatives to Pyrrolo[2,3-*b*]indoles. *J. Am. Chem. Soc.* **1970**, *92* (2), 343–48.