5-(Tryptophyl)amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine-Based Potent and Selective CCK_1 Receptor Antagonists: Structure−Activity Relationship Studies on the Substituent at N2-Position

José M. Bartolomé-Nebreda,[§] Rosario Patiño-Molina,[§] Mercedes Martín-Martínez,[§] Isabel Gómez-Monterrey,[§] M. Teresa García-López,[§] Rosario González-Muñiz,[§] Edurne Cenarruzabeitia,[#] Miriam Latorre,[#] Joaquín Del Río,[#] and Rosario Herranz*[,§]

Instituto de Química Médica (CSIC), Juan de la Cierva 3, E-28006 Madrid, Spain, and Departamento de Farmacología, Universidad de Navarra, Irunlarrea 1, E-31080 Pamplona, Spain

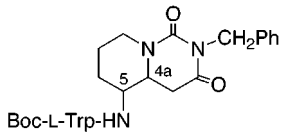
Received January 10, 2001

To establish structure−activity relationships a new series of analogues of the highly potent and selective CCK_1 receptor antagonist (4a*S*,5*R*)-2-benzyl-5-(*N*-Boc-tryptophyl)amino-1,3-dioxoperhydropyrido[1,2-*c*]-pyrimidine (**1a**) modified at N2-position of the central scaffold has been prepared and evaluated as CCK receptor ligands. With this aim the N2-benzyl group has been replaced by methyl, cyclohexyl, aromatic groups, 1-phenylethyl, and 1-carboxy-2-phenylethyl group. Then, substituents with different electronic and steric properties were introduced into different positions of the phenyl group of analogues **19a** and **19b**. The results of the CCK receptor binding and in vitro functional activity evaluation suggest the importance of the lipophilic character and an appropriate spatial orientation of the moiety linked at the N2-position of the 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine template for potent and selective binding and antagonist activity at CCK_1 receptor subtype. The 2-cyclohexyl and (2*S*)-1-naphthyl derivatives **18a** and **(2*S*)-20a** have emerged as more potent and selective CCK_1 receptor antagonists than the lead compound **1a**. Additionally, the results confirm the (4a*S*,5*R*)-stereochemistry at the central bicyclic skeleton as an essential structural requirement for potent binding to this receptor subtype.

Introduction

Cholecystokinin (CCK) is a regulatory peptide hormone, found predominantly in localized endocrine cells of the gastrointestinal tract, and a neurotransmitter present throughout the nervous system.[1] In the gastrointestinal system CCK regulates motility, pancreatic enzyme secretion, gastric emptying, and inhibition of gastric acid secretion.[1,2] In the nervous system CCK is involved in anxiogenesis,[1,3,4] satiety,[1,5] nociception,[1,6] memory and learning processes,[3,6−8] and regulation of dopamine release.[1,6] These biological effects are mediated by two specific G protein coupled receptor subtypes, termed CCK_1 and CCK_2.[6,9]

The variety of physiological effects of CCK and its possible role in some pathological disorders have stimulated research in this area and, over the past decade, a number of potent and selective non-peptide CCK_1 and CCK_2 receptor agonists and antagonists have been reported.[6,10−12] Some of these ligands have been useful tools for characterizing both CCK receptor subtypes and for gaining further insight into the functional significance of CCK in the periphery and in the central nervous system (CNS). However, the physiological effects of CCK mediated by CCK_1 or CCK_2 receptors are not completely established.[1,6] Therefore, the development of CCK receptor antagonists with higher selectivity for both receptor subtypes is of interest in order to shed further light on their functional roles. In this regard, we reported the design, synthesis,[13] and pharmacological properties[14] of the 5-(tryptophyl)amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine derivative **1a** (IQM-95,333), which is one of the most selective CCK_1 receptor antagonists described.[6] Thus, this compound showed a CCK_1 receptor affinity in the nanomolar range, but it was devoid of affinity at brain CCK_2 receptors.[14] In accordance with this CCK_1 receptor affinity, compound **1a** was a potent inhibitor of the CCK-8-stimulated amylase release from isolated pancreatic acini and blocked the CCK-8-induced hypophagia and hypolocomotion in rats.[14] Furthermore, despite the predominant role attributed to CCK_2 receptors in the anxiogenic effects of CCK,[3,6] this CCK_1 antagonist also showed a marked anxiolytic-like activity in animal models.[14] These results supported the suggestion of some authors that CCK_1 receptors may be involved also in anxiogenesis.[15−17] Previous structure−activity relationship studies on these 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine-based CCK_1 antagonists showed the importance of the 4a,5-*trans* stereochemistry at the 1,3-dioxoperhy-



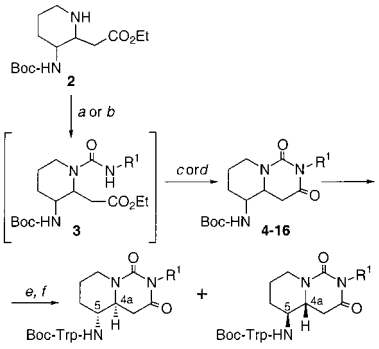
1a: (4a*S*,5*R*)

1b: (4a*R*,5*S*)

* To whom correspondence should be addressed. Tel: 34-91-5622900. Fax: 34-91-5644853. E-mail: rosario@iqm.csic.es.
[§] Instituto de Química Médica (CSIC).
[#] Departamento de Farmacología.

10.1021/jm010813d CCC: $20.00
Published on Web 05/25/2001

Scheme 1[a]



Nº	R^1	Nº	R^1
4, 17	Me	**11, 24**	2-(Me)Ph
5, 18	Cyclohexyl	**12, 25**	3-(Me)Ph
6, 19	Ph	**13, 26**	4-(Me)Ph
7, 20	1-Naphthyl	**14, 27**	3-(NO_2)Ph
8, 21	4-Pyridyl	**15, 28**	4-(NO_2)Ph
9, 22	(*R*)-CH-(Me)Ph	**16, 29**	4-(OMe)Ph
10, 23	(*S*)-CH-(Me)Ph		

[a] Reagents: (*a*) R^1-NCO, THF; (*b*) R^1-NH_2, $(CCl_3O)_2CO$, Et_3N, THF; (*c*) NaH, THF; (*d*) DBU, THF; (*e*) TFA, CH_2Cl_2; (*f*) Boc-L-Trp-OH, BOP, Et_3N.

dropyrido[1,2-*c*]pyrimidine skeleton[13] and the presence of the Boc-L-Trp residue[13,18] as essential features for CCK_1 binding affinity and subtype receptor selectivity. Replacement of the acid labile group Boc with the 3,3-dimethylbutyryl or the *tert*-butylaminocarbonyl groups led to acid-stable compounds with enhanced oral bioavailability.[18] Now, to further define the pharmacophore of this new family of CCK_1 antagonists, a structure−activity relationship study on the nature of the substituent at N2-position has been carried out. First, we have explored the replacement of the benzyl group at this position by methyl, cyclohexyl, aromatic groups (Ph, naphthyl, and pyridyl), 1-phenylethyl, and the phenylalanine derived 1-carboxy-2-phenylethyl group. Then, we have studied the effect of introducing substituents with different electronic and steric properties into different positions of the N2-phenyl group. These include the following: a methyl group, electron-withdrawing groups (NO_2 and CO_2H), and electron-donating groups [OMe, OAc, OH, and $N(Me)_2$]. The present paper deals with the synthesis and CCK receptor binding profile of this new series of 5-(Boc-tryptophyl)amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine derivatives.

Chemistry

As indicated in Scheme 1, the new 1,3-dioxoperhydropyrido-[1,2-*c*]pyrimidine derivatives **17a**−**29a** and **17b**−**29b** were prepared applying a synthetic route similar to that used for the lead compounds **1**. In general, this route involved reaction of the 2,3-*trans*-3-amino-2-piperidineacetic acid derivative **2** [obtained as a (5:1) racemic mixture of (2*S*,3*R*)- and (2*R*,3*S*)-isomers from Boc-D-Orn(Z)-OH[13]] with the corresponding isocyanate, followed by in situ base catalyzed cyclization of the resulting *N*-substituted carbamoylpiperidines of general formula **3** to their respective 5-Boc-amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine derivatives **4**−**16**.

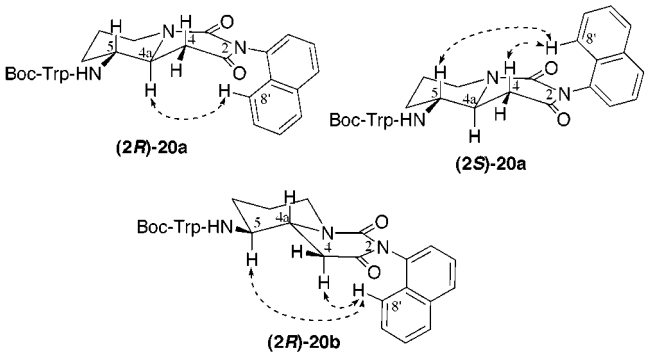
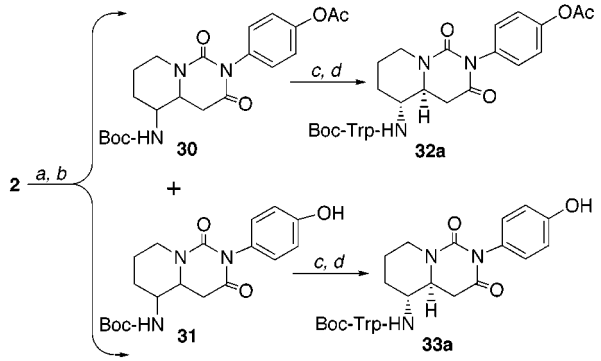


Figure 1. NOE relationships observed between the 2,3-dioxoperhydropyrido[1,2-*c*]pyrimidine skeleton and the naphthyl protons in the DPFGSE-NOE spectra of compounds **20**.

Then, sequential *N*-Boc removal and coupling with Boc-L-Trp-OH, using BOP as coupling reagent, provided the (5:1) diastereoisomeric mixtures of 5-(Boc-tryptophyl)-amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine derivatives **17a,b**−**29a,b**, which were chromatographically resolved in most cases. The 2-methyl derivatives **4** and **17** were prepared using Boc-L-Orn(Z)-OH as starting material for the piperidine **2**, isolating in this case only the major final diastereoisomer **17b**. The noncommercial 4-pyridylisocyanate was generated in situ from 4-aminopyridine, by reaction with bis-(trichloromethyl)carbonate in the presence of Et_3N.[19] NaH was used as base for the cyclization reaction of *N*-carbamoylpiperidines **3**, except for the 4-pyridyl and the 4-nitrophenyl derivatives where, due to the lower nucleophily of their carbamoyl NH,[20,21] this cyclization was slower than the saponification of the ethyl acetate group, by hydroxide generated from humidity traces in the reaction medium, and the respective bicyclic compounds **8** and **15** were not obtained. In both cases, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base, no saponification was observed, although the cyclization required longer reaction times (7 h at room temperature for **15** and 4 days at 60 °C for **8**, while in the other cases, using NaH at room temperature, the reaction was complete in 30 min).

In the synthesis of the 1-naphthyl derivatives **7**, two atropoisomeric pairs of racemic 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidines **(2*R**,4a*R**,5*S**)-7** and **(2*R**,-4a*S**,5*R**)-7** were obtained in a (1:2) ratio, due to the restricted rotation about the N2-naphthyl bond. After the coupling with Boc-L-Trp-OH, each one of the two resulting diastereoisomeric pairs was chromatographically resolved into **(2*R*)-20a** and (2*S*)-**20b** and **(2*S*)-20a** and (2*R*)-**20b**, respectively, in an **a**:**b** ratio of (5:1). We tried to establish the absolute configuration of these four diastereoisomers by X-ray diffraction. However, it was not possible to obtain good crystals for this analysis. Furthermore, when we tried to crystallize them from hot MeOH, partial stereomutation was observed. Due to these problems, the configuration was tentatively assigned by ^1H NMR, on the basis of the NOEs observed in the double pulsed field gradient spin−echo NOE sequence (DPFGSE-NOE) spectra of compounds **(2*R*)-20a**, (**2*S*)-20a,** and **(2*R*)-20b**. Thus, as shown in Figure 1, weak NOE enhancements were observed between the 8′-H proton of the naphthyl group and the 4-H and 5-H protons of the 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine

Scheme 2[a]



[a] Reagents: (*a*) 4-(NH_2)-Ph-OAc, $(CCl_3O)_2CO$, Et_3N, THF; (*b*) DBU, THF; (*c*) TFA, CH_2Cl_2; (*d*) Boc-L-Trp-OH, BOP, Et_3N, CH_2Cl_2.

skeleton in diastereoisomers (**2*S*)-20a** and **(2*R*)-20b**, while in **(2*R*)-20a** the naphthyl 8′-H proton showed weak NOE with the 4a-H proton.

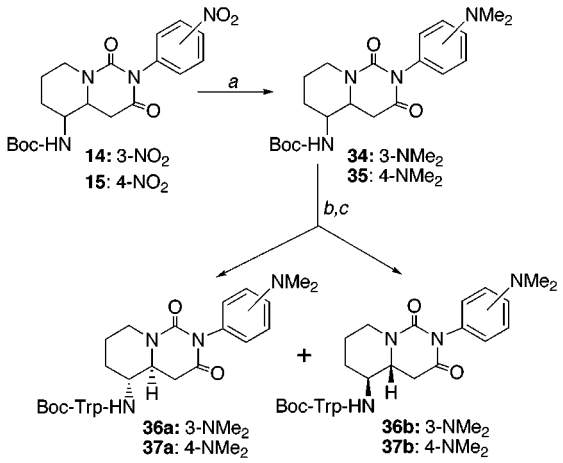
Similarly, due to restricted rotation, the 2-(2-methylphenyl)-1,3-dioxoperhydropyrido-[1,2-*c*]pyrimidines **11** were also obtained as a mixture of atropoisomers at position 2 in a (1.5:1) ^{1}H NMR estimated ratio. After *N*-Boc removing and coupling with Boc-L-Trp-OH, this mixture was chromatographically resolved in the two atropoisomers **(2*R*)-** and (**2*S*)-24a**, and the mixture **(2*RS*)-24b**, in a (**a**:**b** = 5:1) ratio. In this case, the stereomutation at N2 in each epimeric pair was faster than in compounds **20**, and, after the chromatographic resolution process, each isomer **(2*R*)-** and (**2*S*)-24a** was obtained with, at least, 10% of its corresponding epimer. This stereomutation was studied in the pair **(2*R*)-** and (**2*S*)-20a**, at room temperature and acetonitrile solution, by RP-HPLC. In these conditions the equilibrium was reached in 3 days in a (2:3) (2*R*)/(2*S*) epimeric ratio. The absolute configuration at N2 in this epimeric pair was tentatively assigned on the basis of the NOE observed in the NOESY spectrum of **(2*R*)-24a** between the methyl protons of the 2-methylphenyl group and the 4-H oriented toward the same face that the Boc-Trp moiety.

As indicated in Scheme 2, partial deacetylation took place in the synthesis of the 2-(4-acetoxyphenyl)-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine derivative **30**, obtaining a 15% of the phenolic derivative **31**. After *N*-Boc-removal and coupling with Boc-L-Trp-OH, only the major diastereoisomers of the tryptophyl derivatives **32a** and **33a** could be isolated.

Compounds incorporating the 3- or 4-(dimethylamino)phenyl moiety at position 2 of the perhydropyrido-[1,2-*c*]pyrimidine skeleton **36a**,**b** and **37a**,**b** were obtained from the corresponding nitro derivatives **14** and **15**, by catalytic hydrogenation in the presence of formaldehyde, followed by *N*-Boc-removal and coupling with Boc-L-Trp-OH (Scheme 3).

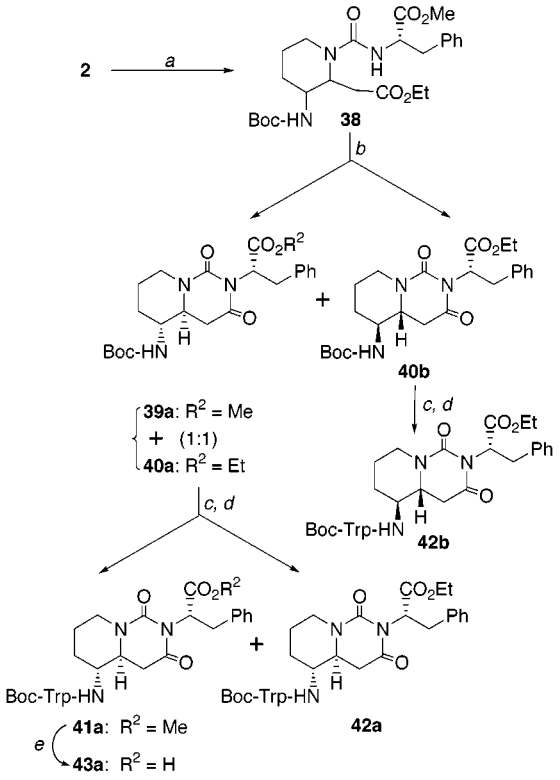
Applying a similar synthetic pathway, the reaction of the 2,3-*trans*-3-amino-2-piperidineacetic acid derivative **2** with the hydrochloride of phenylalanine methyl ester and bis(trichloromethyl)carbonate in the presence of Et_3N gave the corresponding 1-substituted-carbamoylpiperidine derivative **38** (Scheme 4). In the following NaH catalyzed cyclization the ethoxide, generated from the 2-ethoxycarbonylmethyl group, produced a partial

Scheme 3



[a] Reagents: (*a*) H_2, Pd(C), HCHO, MeOH; (*b*) TFA, CH_2Cl_2; (*c*) Boc-L-Trp-OH, BOP, Et_3N, CH_2Cl_2.

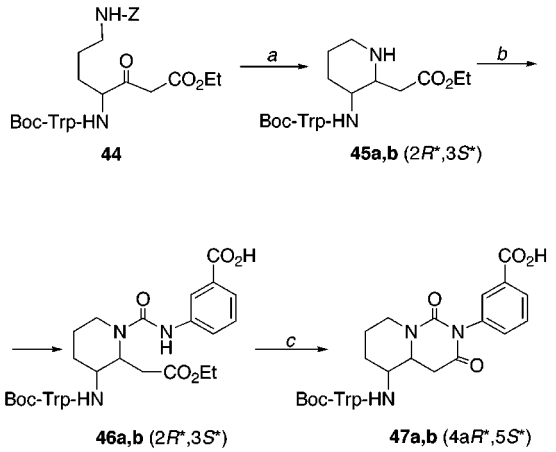
Scheme 4



[a] Reagents: (*a*) H-L-Phe-OMe·HCl, $(CCl_3O)_2CO$, Et_3N, THF; (*b*) NaH, THF; (*c*) TFA, CH_2Cl_2; (*d*) Boc-L-Trp-OH, BOP, Et_3N, CH_2Cl_2; (e) NaOH, MeOH, H_2O.

transesterification of the methyl ester group of **38**, obtaining a (1:1) mixture of methyl and ethyl esters of the (4a*S*,5*R*)-5-(Boc-amino)-1,3-dioxoperhydropyrido-[1,2-*c*]pyrimidines **39a** and **40a** (38%), along with the ethyl ester of the (4a*R*,5*S*)-diastereoisomer **40b** (10%). After *N*-Boc-removing, and coupling with Boc-L-Trp-OH, the methyl and ethyl ester mixture **39a** and **40a** was chromatographically resolved into the corresponding Boc-tryptophyl derivatives **41a** and **42a**, respectively. The saponification of the methyl ester in compound **41a** gave the 1-carboxy-2-phenylethyl derivative **43a**. In the ^{1}H-NMR spectra of compounds **39**−**43** some signals appeared duplicated (methyl or ethyl protons, indolic 4-H and phenylalanine α-H), indicating the presence of

Scheme 5



[a] Reagents: (a) H_2, Pd (C), EtOH; (*b*) 3-(NH_2)-Ph-CO_2H, $(CCl_3O)_2CO$, Et_3N, THF; (*c*) NaH, THF.

two rotamers, probably due to restricted rotation about the N2−C bond. None of these pairs of rotamers could be resolved.

Finally, in the synthesis of the 3-carboxyphenyl derivatives **47** (Scheme 5) the construction of the perhydropyrido[1,2-*c*]pyrimidine skeleton was posterior to the coupling with Boc-L-Trp-OH, to avoid the protection and final deprotection of the carboxyl group. Thus, (2*R**,3*S**)-2-ethoxycarbonylmethyl-3-(Boc-tryptophyl)-aminopiperidine (**45a,b**) [obtained from the Boc-L-Trp-D-Orn(Z)-OH derived *β*-ketoester **44** as a (2:1) diastereoisomeric mixture of (2*S*,3*R*)- and (2*R*,3*S*)-isomers, which could not be resolved[22]] was used as starting material for the reaction with 3-carboxyphenyl isocyanate, generated in situ from the 3-aminobenzoic acid. The chromatographic resolution of the diastereoisomeric pairs **45**−**47** was not possible.

Biological Results and Discussion

As shown in Table 1, the affinity of all new 5-(Boc-tryptophyl)amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine derivatives at CCK_1 and CCK_2 receptors was determined by measuring the displacement of [^{3}H]-propionyl-CCK-8 binding to rat pancreatic and cerebral cortex homogenates, respectively, as previously described.[23] Subsequently, those compounds which showed a significant affinity at CCK_1 receptors at concentrations below 10^{-7} M were tested for their antagonism of the CCK-8-stimulated amylase release from pancreatic acinar cells.[24] For comparative purposes CCK-8 and the model compounds **1a** and **1b** were also included in the assays. From the results, it can be deduced that, in general, the new N2-modified compounds with a (4a*S*,5*R*)-stereochemistry (compounds **a**) keep the high potency and selectivity in their binding to the CCK_1 receptor subtype versus the CCK_2 as well as the in vitro functional antagonistic activity.

The replacement of the N2-benzyl group of the model compound **1a** by a cyclohexyl or phenyl group had no significant effect on the binding potency and selectivity of **18a** and **19a** for CCK_1, while in **1b**, this change led to a decrease of an order of magnitude in the affinities of **18b** and **19b**. A higher decrease in the CCK_1 binding potency of **1b**, of at least 2 orders of magnitude, resulted when its benzyl group was replaced by a methyl in **17b**. These initial results indicated the preference for lipophilic groups at the N2-position.

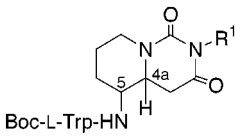
With respect to the introduction of additional substituents into the N2-phenyl group of **19a** this change led, in general, to slight or moderate decreases in the CCK_1 binding affinity and antagonist potency, independently of their electronic and steric properties. Thus, as an example, the effect of introducing the electron-withdrawing nitro group (**27a** and **28a**) was similar to that of introducing the electron-donating dimethylamino group (**36a** and **37a**). The decrease in affinity was higher when the group was introduced into a *meta*- than into a *para*-position. However, the CCK_1 binding profile of compound **19a** was slightly improved when a methyl group was introduced into *ortho*-position of the phenyl group (**24a**), or when this group was replaced by a 1-naphthyl group in a (2*S*)-configuration [**(2*S*)-20a**]. In both cases the rotation about the N2-aryl bond is restricted. The difference between both atropoisomers **(2*S*)-20a** and **(2*R*)-20a** in binding affinities and antagonistic activities (25- and 127-fold, respectively) show the importance of the aryl group orientation. On the other hand, it is interesting to note the important decrease in affinity, by more than 2 orders of magnitude, which resulted from the replacement of the phenyl group with the 4-pyridyl in **21a,b** as well as the complete loss of binding affinity with the introduction of the hydroxy or carboxy acid groups into the phenyl moiety (**33a** or **47a,b**).

Finally, the replacement of both prochiral protons of the benzyl group of the model compound **1a** with a methyl group led to the ten- and 4-fold less potent compounds **22a** and **23a**, respectively. The influence of the configuration at the additional chiral center of these two compounds shows again the importance of the aryl group orientation. On the other hand, the phenylalanine derivatives **41**−**43** were completely inactive. The absence of binding affinity in these compounds could be due to an unfavorable interaction of the additional alcoxycarbonyl or carboxy groups into the pocket of accommodation of the N2-substituent within the CCK_1 receptor or to an excessive lengthening of the linker chain between the phenyl group and the central scaffold.

In general, a quite good correlation was observed between the binding potency of the best compounds to CCK_1 receptors and the values for inhibition of CCK-8-stimulated amylase release from pancreatic acinar cells. Like the model compounds **1a** and **1b**, the new analogues did not show any intrinsic effect on the amylase release at a 10 μM concentration.

In conclusion, the biological results herein reported show that the group linked to the N2-position of the 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine skeleton is an essential element of the pharmacophore of this CCK_1 receptor antagonist family and suggest the importance of the lipophilic character and spatial orientation of that group for a potent interaction with the CCK_1 receptor. On the other hand, these results confirm, again, the (4a*S*,5*R*)-stereochemistry at the central scaffold as a highly strict structural requirement for the selective and potent binding to this receptor. Ligands **18a**, **(2*S*)-20a**, and **24a**, endowed with subnanomolar affinity, have emerged as more potent and selective CCK_1 antagonists than the lead compound **1a** and could serve to fine-tune

Table 1. Inhibition of [^{3}H]pCCK-8 Specific Binding to Rat Pancreas (CCK$_1$) and Cerebral Cortex Membranes (CCK$_2$) and Inhibition of Amylase Release from Dispersed Pancreatic Acini



			IC$_{50}$ (nM)[a]		
compd	stereochemistry	R^1	CCK$_1$	CCK$_2$	amylase release[b] IC$_{50}$ (nM)
CCK-8			1.04 ± 0.08	5.60 ± 0.30	
1a	(4a*S*,5*R*)	CH$_2$−Ph	1.59 ± 0.10	>10000	0.64 (0.4−0.9)
1b	(4a*R*,5*S*)	CH$_2$−Ph	22.70 ± 4.0	6153	77 (73−81)
17b	(4a*R*,5*S*)	Me	9162	>10000	ND[c]
18a	(4a*S*,5*R*)	cyclohexyl	0.60 ± 0.05	>10000	3.0 (1.8−3.7)
18b	(4a*R*,5*S*)	cyclohexyl	165 ± 36	7159	287 (205−325)
19a	(4a*S*,5*R*)	Ph	1.18 ± 0.72	>10000	3.5 (1.4−10.1)
19b	(4a*R*,5*S*)	Ph	628.0 ± 28	>10000	>1000
(2*R*)-20a	(2*R*,4a*S*,5*R*)	1-naphthyl	15.4 ± 7.3	>10000	93.0 (39−220)
(2*S*)-20a	(2*S*,4a*S*,5*R*)	1-naphthyl	0.59 ± 0.04	>10000	0.73 (0.4−2.1)
(2*R*)-20b	(2*R*,4a*R*,5*S*)	1-naphthyl	>1000	>10000	ND[c]
(2*S*)−20b	(2*S*,4a*R*,5*S*)	1-naphthyl	>1000	>10000	ND[c]
21a,b (5:1)	(4a*R**,5*S**)	4-pyridyl	386 ± 36.2	>10000	ND[c]
22a	(4a*S*,5*R*)	(*R*)-CH−(Me)Ph	15.0 ± 1.85	>10000	12.63 (5.2−23.8)
22b	(4a*R*,5*S*)	(*R*)-CH−(Me)Ph	>1000	>10000	ND[c]
23a	(4a*S*,5*R*)	(*S*)-CH−(Me)Ph	6.89 ± 1.1	>10000	112 (55−232)
23b	(4a*R*,5*S*)	(*S*)-CH−(Me)Ph	>1000	>10000	ND[c]
24a	(4a*S*,5*R*)	2-(Me)Ph	0.97 ± 0.43	>10000	1.89 (0.6−3.0)
24b	(4a*R*,5*S*)	2-(Me)Ph	>1000	>10000	ND[c]
25a	(4a*S*,5*R*)	3-(Me)Ph	3.98 ± 2.57	>10000	10.0 (5.7−24.3)
25b	(4a*R*,5*S*)	3-(Me)Ph	100	1320	ND[c]
26a	(4a*S*,5*R*)	4-(Me)Ph	2.90 ± 1.2	>10000	16.6 (9.1−23.4)
26b	(4a*R*,5*S*)	4-(Me)Ph	200	2320	ND[c]
27a	(4a*S*,5*R*)	3-(NO$_2$)Ph	44.0 ± 2.5	>10000	49.5 (20.8−57.1)
27b	(4a*R*,5*S*)	3-(NO$_2$)Ph	>1000	>10000	ND[c]
28a	(4a*S*,5*R*)	4-(NO$_2$)Ph	12.0 ± 2.8	>10000	64.0 (62.6−65.7)
28b	(4a*R*,5*S*)	4-(NO$_2$)Ph	>1000	>10000	ND[c]
29a	(4a*S*,5*R*)	4-(OMe)Ph	15.9 ± 2.9	>10000	38.1 (34.1−44.3)
32a	(4a*S*,5*R*)	3-(OAc)Ph	70.3 ± 4.7	>10000	ND[c]
33a	(4a*S*,5*R*)	3-(OH)Ph	>1000	>10000	ND[c]
36a	(4a*S*,5*R*)	3-[N(Me)$_2$]Ph	50.8 ± 15.5	>10000	ND[c]
36b	(4a*R*,5*S*)	3-[N(Me)$_2$]Ph	>1000	>10000	ND[c]
37a	(4a*S*,5*R*)	4-[N(Me)$_2$]Ph	4.3 ± 1.05	>10000	39.8 (32.3−54.5)
37b	(4a*R*,5*S*)	4-[N(Me)$_2$]Ph	>1000	2320	ND[c]
41a	(4a*S*,5*R*)	(*S*)-CH(CO$_2$Me)-CH$_2$−Ph	>1000	>10000	ND[c]
42a	(4a*S*,5*R*)	(*S*)-CH(CO$_2$Et)-CH$_2$−Ph	>1000	>10000	ND[c]
42b	(4a*R*,5*S*)	(*S*)-CH(CO$_2$Et)-CH$_2$−Ph	>1000	>10000	ND[c]
43a	(4a*S*,5*R*)	(*S*)-CH(CO$_2$H)-CH$_2$−Ph	>1000	>10000	ND[c]
47a,b (2:1)	(4a*R**,5*S**)	3-(CO$_2$H)Ph	>1000	>10000	ND[c]

[a] Values are the mean or mean± SEM of at least three experiments, performed with seven concentrations of test compounds in triplicate. [b] Inhibition of amylase release stimulated by CCK-8 (0.1 nM) in dispersed pancreatic acini. Data represent the mean of three to six independent experiments in duplicate (standard errors within ±15% of the mean). [c] ND = not determined.

interactions with this receptor by further structural modifications.

Experimental Section

Chemistry. All reagents were of commercial quality. Solvents were dried and purified by standard methods. Amino acid derivatives were obtained from Bachem Feinchemikalien AG. Analytical TLC was performed on aluminum sheets coated with a 0.2 mm layer of silica gel 60 F_{254}, Merck, and preparative TLC on 20 × 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} Merck. Silica gel 60 (230−400 mesh), Merck, was used for flash chromatography. Melting points were taken on a micro hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded with Varian Gemini-200, Varian INOVA-300, Varian INOVA-400, or Varian Unity-500 spectrometers, operating at 200, 300, 400, or 500 MHz, using TMS as reference. A relaxation time of 1.5 s and a mix time of 600 ms were used in the NOESY spectra, and 2 s and 500 ms, respectively, for the DPGSE-NOE spectra. Elemental analyses were obtained on a CH-O-RAPID apparatus. Analytical RP HPLC was performed on a Waters Nova-pak C_{18} (3.9 × 150 mm, 4 μm) column, with a flow rate of 1 mL/min, and using a tunable UV detector set at 214 nm. Mixtures of CH_3CN (solvent A) and 0.05% TFA in H_2O (solvent B) were used as mobile phase.

General Procedure for the Synthesis of the (4a*R,5*S**)-5-(*tert*-Butoxycarbonyl)amino-1,3-dioxoperhydropyrido-[1,2-*c*]pyrimidine Derivatives 4−7, 9−14, and 16. Method A.** The corresponding isocyanate, methyl isocyanate, cyclohexyl isocyanate, phenyl isocyanate, 1-naphthyl isocyanate, (1*R*)-1-phenylethyl isocyanate, (1*S*)-1-phenylethyl isocyanate, 2-, 3-, and 4-methylphenyl isocyanate, 3-nitrophenyl isocyanate, and 4-methoxyphenyl isocyanate (0.39 mmol), was added to a solution of (2*R**,3*S**)-3-(*tert*-butoxycarbonyl)amino-2-(ethoxycarbonyl)methylpiperidine[25] (**2**) (100 mg, 0.36 mmol) in dry THF (2.5 mL). After 1 h of stirring at room temperature, the reaction mixture was diluted with THF (2.5 mL). Then, NaH (10 mg of 60% dispersion in mineral oil, 0.39 mmol) was added, and the stirring was continued for 30 additional min. Afterward, a 0 °C cooled 1 N HCl solution (25 mL) was added, and the resulting reaction mixture was extracted with EtOAc (2 × 25 mL). The organic extracts were washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to

Table 2. Analytical Data of 5-(*tert*-Butoxycarbonyl)amino-1,3-dioxoperhydropyrido-[1,2-*c*]pyrimidines

compd	yield (%)	mp[a] (°C)	formula[b]
4	80	174−176	$C_{14}H_{23}N_3O_4$
5	78	foam	$C_{19}H_{31}N_3O_4$
6	85	210−212	$C_{19}H_{25}N_3O_4$
(2*R,4a*R**,5*S**)-7**	27	120−122	$C_{23}H_{27}N_3O_4$
(2*R,4a*S**,5*R**)-7**	48	119−121	$C_{23}H_{27}N_3O_4$
8	60	foam	$C_{18}H_{24}N_4O_4$
9	80	syrup	$C_{21}H_{29}N_3O_4$
10	71	67−69	$C_{21}H_{29}N_3O_4$
11	81	foam	$C_{20}H_{27}N_3O_4$
12	35	94−96	$C_{20}H_{27}N_3O_4$
13	48	209−211[c]	$C_{20}H_{27}N_3O_4$
14	61	100−102	$C_{19}H_{24}N_4O_6$
15	85	90−92	$C_{19}H_{24}N_4O_6$
16	40	95−97	$C_{20}H_{27}N_3O_5$
30	30	foam	$C_{21}H_{27}N_3O_6$
31	11	foam	$C_{19}H_{25}N_3O_5$
34	46	syrup	$C_{21}H_{30}N_4O_4$
35	80	foam	$C_{21}H_{30}N_4O_4$
39a + **40a** (1:1)	34		
40b	10	syrup	$C_{24}H_{33}N_3O_6$

[a] From EtOAc/hexane. [b] Satisfactory analyses for C, H, N. [c] Sublimation.

dryness. Except for the case of the naphthyl derivatives **7**, the residue was purified by flash chromatography using a (33−50%) gradient of EtOAc in hexane as eluant. The naphthyl derivatives **7** were purified by preparative TLC using a (1:1) EtOAc−hexane mixture as eluant. The higher R_f fraction corresponded to the minor atropoisomeric pair **(2*R**,4a*R**,5*S**)-7** (37 mg, 27%), while the lower R_f fraction corresponded to **(2*R**,4a*S**,5*R**)-7** (56 mg, 48%). Significant analytical and spectroscopic data of these compounds are summarized in Tables 2 and 3.

Synthesis of (4a*R,5*S**)-5-(*tert*-Butoxycarbonyl)amino-2-(4-pyridyl)-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine (8). Method B.** Bis(trichoromethyl)carbonate (123 mg, 0.42 mmol) was added to a solution of 4-aminopyridine (118 mg, 1.25 mmol) in dry THF (3 mL) cooled at 0 °C. Then, TEA (354 μL, 2.52 mmol) was added dropwise throughout 5 min, continuing the stirring at 0 °C for 5 additional min. Afterward, a solution of (2*R**,3*S**)-3-(*tert*-butoxycarbonyl)amino-2-(ethoxycarbonyl)methylpiperidine[25] (**2**) (175 mg, 0.63 mmol) in dry THF (3 mL) was added at room temperature, and the mixture was stirred at room temperature for 1 h. Then, the reaction mixture was diluted with EtOAc (50 mL), washed successively with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved into dry THF (7 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (96 μL, 0.69 mmol) was added to this solution. This reaction mixture was refluxed for 4 days, then a 0 °C cooled 1 N HCl solution (25 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 25 mL). The organic extracts were washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography using a (1−4%) gradient of MeOH in dichloromethane as eluant to give **8** (131 mg, 60%), whose significant analytical and spectroscopic data are shown in Tables 2 and 3.

Synthesis of (4a*R,5*S**)-5-(*tert*-Butoxycarbonyl)amino-2-(4-nitrophenyl)-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine (15). Method C.** 4-Nitrophenyl isocyanate (64 mg, 0.39 mmol) was added to a solution of (2*R**,3*S**)-3-(*tert*-butoxycarbonyl)amino-2-(ethoxycarbonyl)methylpiperidine[25] (**2**) (100 mg, 0.36 mmol) in dry THF (2.5 mL). After 1 h of stirring at room temperature, the reaction mixture was diluted with THF (2.5 mL). Then, 1,8-diazabicyclo[5.4.0]undec-7-ene (51 μL, 0.39 mmol) was added, and the stirring was continued for 7 additional h. Afterward, a 0 °C cooled 1 N HCl solution (25 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 25 mL). The organic extracts were washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography using a (17−66%) gradient of EtOAc in hexane as eluant to give **15** (123 mg, 85%), whose significant analytical and spectroscopic data are shown in Tables 2 and 3.

Synthesis of the (4a*R,5*S**)-2-[4-(Acethoxy- and Hydroxy)phenyl]-5-(*tert*-butoxycarbonyl)amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidines 30 and 31.** These compounds were prepared as above-mentioned in method B, from 4-aminophenol acetate [189 mg, 1.25 mmol; obtained from 4-nitrophenol acetate by catalytic hydrogenation in the presence of 10% Pd(C)[26]] and (2*R**,3*S**)-3-(*tert*-butoxycarbonyl)-amino-2-(ethoxycarbonyl)-methylpiperidine[25] (**2**) (175 mg, 0.63 mmol). The reaction products were purified by flash chromatography, using a (33−66%) gradient of EtOAc in hexane as eluant, obtaining the 4-acethoxyphenyl derivative **30** as major product (79 mg, 37%) with higher R_f and **31** (26 mg, 13%) in the lower R_f, fraction. The significant analytical and spectroscopic data of these compounds are indicated in Tables 2 and 3.

Synthesis of the (4a*R,5*S**)-5-(*tert*-Butoxycarbonyl)-amino-2-(3- and 4-dimethylaminophenyl)-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidines 34 and 35.** A solution of the (4a*R**,5*S**)-5-(*tert*-butoxycarbonyl)amino-2-(3- or 4-nitrophenyl)-1,3-dioxoperhydropyrido-[1,2-*c*]pyrimidines **14** or **15** (100 mg, 0.25 mmol) in MeOH (25 mL) was hydrogenated in the presence of 37% aqueous formaldehyde (75 μL, 1 mmol) and 10% Pd(C) (20 mg), at room temperature and 3 atm of H_2 pressure, for 2 and 3 days, respectively. Then, the catalyst was filtered off, washed with MeOH, and the resulting solution was evaporated to dryness. The residue was purified by flash chromatography, using a (50−75%) gradient of EtOAc in hexane as eluant, to give the pure compounds **34** and **35**, whose analytical and spectroscopic data are summarized in Tables 2 and 3.

Synthesis of the (4a*R,5*S**)-5-(*tert*-Butoxycarbonyl)-amino-2-[(1*S*)-1-(methoxycarbonyl)- and (ethoxycarbonyl)-2-phenylethyl]-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidines 39a, 40a, and 40b.** Bis(trichoromethyl)carbonate (123 mg, 0.42 mmol) was added to a suspension of H-L-Phe-OMe·HCl (226 mg, 1.25 mmol) and TEA (175 μL, 1.25 mmol) in dry THF (3 mL) cooled at 0 °C. Then, TEA (354 μL, 2.52 mmol) was added dropwise throughout 5 min, continuing the stirring at 0 °C for 5 additional min. Afterward, a solution of (2*R**,3*S**)-3-(*tert*-butoxycarbonyl)amino-2-(ethoxycarbonyl)-methylpiperidine[25] (**2**) (175 mg, 0.63 mmol) in dry THF (3 mL) was added at room temperature, and this mixture was stirred at room temperature for 1 h. Then, the reaction mixture was diluted with EtOAc (50 mL), washed successively with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved into dry THF (9 mL), and NaH (27 mg of 60% dispersion in mineral oil, 0.61 mmol) was added to this solution. This reaction mixture was stirred at room temperature for 30 min, then a 0 °C cooled 1 N HCl solution (25 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 25 mL). The organic extracts were washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by preparative TLC, using (1:1) EtOAc−hexane mixture as eluant, obtaining the unresolved mixture **39a** + **40a** (136 mg, 46%) as major fraction with higher R_f and **40b** (24 mg, 12%) as lower R_f fraction. Significant analytical and spectroscopic data of these compounds are summarized in Tables 2 and 3.

General Procedure for the Synthesis of the 5-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine Derivatives 17−29, 32, 33, 36, 37, 41, and 42. TFA (0.5 mL) was added to a solution of the corresponding *N*-Boc protected 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine derivative **4**−**16**, **30**, **31**, **34**, **35**, **39**, and **40**, (0.17 mmol) in dichloromethane (2 mL), and after 30 min at room temperature, the solvents were evaporated to dryness. The residue was dissolved in dry dichloromethane (2 mL), and Boc-L-Trp-OH (65 mg, 0.21 mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP, 94 mg, 0.21 mmol), and TEA (54 μL, 0.38 mmol) were added successively to that solution, and stirring was continued at room

Table 3. Significant ^{1}H NMR[a] Spectroscopic Data of 5-(*tert*-Butoxycarbonyl)amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidines

compd	4-H		4a−H	5-H	6-H		7-H		8-H		5-NH	R^1
4	2.69	2.91	3.10	3.40	1.56	2.05	1.56		2.69	4.36	4.52	3.20
5	2.65	2.86	3.05	3.38	1.20−1.85	2.07	1.20−1.85	2.23	2.65	4.25−4.60	4.25−4.60	4.25−4.60, 2.26, 1.20−1.85
6	2.89	3.09	3.22	3.50	1.72	2.16	1.72		2.70	4.35	4.58	7.10−7.40
(2*R,4a*R**,5*S**)-7**	2.97	3.17	3.36	3.57	1.34	2.08	1.56−1.83		2.70	4.35	4.62	7.36, 7.65, 7.92
(2*R,4a*S**,5*R**)-7**	3.09		3.15	3.60	1.35	2.07	1.67	1.81	2.66	4.35	4.67	7.72, 7.67, 7.92
8	2.95	3.11	3.28	3.58	1.31	2.15	1.68	1.88	2.76	4.38	4.47	7.14, 8.70
9	2.77	2.93	3.10	3.44	1.36	2.08	1.66	1.81	2.65	4.33	4.39	6.09[b]
10	2.70	2.93	3.07	3.41	1.35	2.07	1.59	1.79	2.56	4.30	4.38	6.07[b]
11	2.93, 2.94	3.10, 3.12	3.26	3.53, 3.55	1.41	2.13	1.69	1.83, 1.85	2.73, 2.74	4.38	4.51, 4.55	2.10, 2.16[c]
12	2.91	3.10	3.18	3.52	1.35	2.13	1.66	1.85	2.72	4.37	4.48	2.36[c]
13	2.90	3.10	3.24	3.50	1.40	2.11	1.56	1.85	2.71	4.36	4.48	2.37[c]
14	2.97	3.13	3.32	3.57	1.26	2.17	1.67	1.88	2.77	4.39	4.50	7.52, 7.62, 8.07, 8.26
15	2.72	2.91	3.41	3.41	1.48	1.86	1.72		2.72	4.09	7.10	7.48, 8.27
16	2.90	3.10	3.26	3.52	1.25	2.13	1.69	1.85	2.72	4.38	4.48	3.82[c]
30	2.87	3.05	3.20	3.49	1.25	2.06	1.64	1.79	2.68	4.33	4.68	2.28[c]
31	2.91	3.10	3.24	3.55	1.27	2.13	1.66−1.86		2.75	4.39	4.57	6.69, 6.92
34	2.94	3.11	3.25	3.50	1.71	2.12	1.60	1.80	2.76	4.41	4.41	2.94[c]
35	2.85	3.05	3.16	3.47	1.34	2.06	1.64−1.69		2.68	4.33	4.68	2.29[c]
39a + **40a** (1:1)	2.68		2.87	3.15	1.93	1.96	1.73		2.56	4.31	4.31	5.77, 5.66[b]
40b	2.50	2.79	2.93	2.93	1.32	1.94	1.56	1.71	2.44	4.22	4.22	5.60[b]

[a] Spectra registered at 300 MHz in $CDCl_3$, except for **15** which was registered in DMSO-d_6. [b] δ corresponding to the 1-H of R^1. [c] δ corresponding to CH_3.

temperature for 24 h. Afterward, the reaction mixture was diluted with dichloromethane (25 mL), washed successively with 10% citric acid (10 mL), 10% $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL), dried over Na_2SO_4, and evaporated. The resulting Boc-tryptophyl derivatives were purified and resolved into diastereoisomers **a** (4a*S*,5*R*) and **b** (4a*R*,5*S*) by preparative TLC, using 5% EtOAc in ethyl ether (**17**−**26**) or 1% MeOH in dichloromethane (**27**−**29**, **32, 33, 36, 37, 41**, and **42**) as eluants. In compounds **17**, only the major diastereoisomer **b** was isolated, and the diasteroisomeric resolution was not possible for the 4-pyridyl derivatives **21**. Significant analytical and ^{1}H NMR spectroscopic data of the resulting Boc-tryptophyl derivatives are summarized in Tables 4 and 5.

Synthesis of (4a*S*,5*R*)-5-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]amino-2-[(1*S*)-1-(carboxy)-2-phenylethyl]-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine (43a). Saponification of 41a. NaOH (0.5 N, 1.2 mL, 0.60 mmol) was added to a solution of (4a*S*,5*R*)-5-[*N*-(*tert*-butoxycarbonyl)tryptophyl]amino-2-[(1*S*)-1-(methoxycarbonyl)-2-phenylethyl]-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine (**41a**) (36 mg, 60 μmol) in MeOH (1 mL), and the reaction mixture was stirred a room temperature for 24 h. Then, it was evaporated to dryness, and the residue was successively dissolved with EtOAc (15 mL) and extracted with H_2O (10 mL). The aqueous phase was acidified with 1 N HCl to pH ≅ 2 and extracted with EtOAc (15 mL). The extract was washed with brine (5 mL), dried over Na_2SO_4, and evaporated, to yield **43a** (18 mg, 52%), whose analytical and spectroscopic data are shown in Tables 4 and 5.

Synthesis of the Dipeptide Boc-L-Trp-D-Orn-OH.[22] Boc-D-Orn(Z)-OH (5 g, 13.6 mmol) was added slowly to a solution of thionyl chloride (3.60 mL, 49.5 mmol) in dry MeOH (50 mL) cooled at −78 °C. Afterward, the reaction mixture was stirred at room temperature for 24 h. Then saturated $NaHCO_3$ solution was added dropwise until pH ≅ 8, and the MeOH was evaporated in vacuum. The resulting suspension was diluted with H_2O (100 mL) and extracted with dichloromethane (200 mL). The extract was washed with brine (150 mL), dried over Na_2SO_4, and evaporated. The resulting H-D-Orn(Z)-OMe (3.54 g, 13.3 mmol, 98%) was dissolved in dry dichloromethane (150 mL), and Boc-L-Trp-OH (5.15 g, 16.9 mmol), BOP (7.47 g, 16.9 mmol), and TEA (4.27 mL, 16.9 mmol) were added successively to the solution. After 6 h of stirring at room temperature, the reaction mixture was washed successively with 10% citric acid (100 mL), saturated $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography, using 50% of EtOAc in hexane, to give the dipeptide Boc-L-Trp-D-Orn-OMe (6.09 g, 80%) as white solid: mp = 137−139 °C; RP HPLC t_R = 23.45 (A:B = 50:50); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 [m,

Table 4. Analytical Data of 5-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidines

compd	yield	mp[a] (°C)	formula[b]	t_R (min) (A:B)[c]
17b	70	174−176	$C_{25}H_{33}N_5O_5$	8.23 (45:55)[d]
18a	63	180−182	$C_{30}H_{41}N_5O_5$	31.68 (37:63)
18b	16	128−130	$C_{30}H_{41}N_5O_5$	34.40 (37:63)
19a	46	143−145	$C_{30}H_{35}N_5O_5$	18.20 (33:67)
19b	9	180−182	$C_{30}H_{35}N_5O_5$	19.67 (33:67)
(2*R*)-20a	60	151−153	$C_{34}H_{37}N_5O_5$	45.93 (33:67)
(2*S*)-20a	65	148−150	$C_{34}H_{37}N_5O_5$	45.67 (33:67)
(2*R*)-20b	11	137−139	$C_{34}H_{37}N_5O_5$	41.87 (33:67)
(2*S*)-20b	10	139−141	$C_{34}H_{37}N_5O_5$	43.33 (33:67)
21a,b (5:1)	67	foam	$C_{29}H_{34}N_6O_5$	18.22, 18.28 (25:75)
22a	54	112−114	$C_{32}H_{39}N_5O_5$	34.13 (37:63)
22b	10	99−101	$C_{32}H_{39}N_5O_5$	29.80 (37:63)
23a	53	116−118	$C_{32}H_{39}N_5O_5$	19.53 (40:60)
23b	11	108−110	$C_{32}H_{39}N_5O_5$	19.00 (40:60)
(2*RS*)−24a[e]	73	131−132	$C_{31}H_{37}N_5O_5$	25.27, 27.27 (33:67)
(2*RS*)−24b[e]	15	120−122	$C_{31}H_{37}N_5O_5$	29.73, 31.80 (33:67)
25a	59	131−133	$C_{31}H_{37}N_5O_5$	30.80 (33:67)
25b	10	106−108	$C_{31}H_{37}N_5O_5$	33.87 (33:67)
26a	56	128−130	$C_{31}H_{37}N_5O_5$	31.74 (33:67)
26b	7	234−236[f]	$C_{31}H_{37}N_5O_5$	34.94 (33:67)
27a	70	foam	$C_{30}H_{34}N_6O_7$	49.53 (30:70)
27b	13	foam	$C_{30}H_{34}N_6O_7$	45.56 (30:70)
28a	68	foam	$C_{30}H_{34}N_6O_7$	34.78 (33:67)
28b	12	foam	$C_{30}H_{34}N_6O_7$	31.44 (33:67)
29a	64	foam	$C_{31}H_{37}N_5O_6$	49.53 (30:70)
32a	75	foam	$C_{32}H_{37}N_5O_7$	20.94 (25:75)
33a	48	foam	$C_{30}H_{35}N_5O_6$	21.89 (28:72)
36a	64	foam	$C_{32}H_{40}N_6O_5$	14.17 (28:72)
36b	12	foam	$C_{32}H_{40}N_6O_5$	13.00 (28:72)
37a	60	foam	$C_{32}H_{40}N_6O_5$	26.00 (25:75)
37b	10	foam	$C_{32}H_{40}N_6O_5$	22.83 (25:75)
41a	44	75−77	$C_{34}H_{41}N_5O_7$	18.20 (40:60)
42a	44	foam	$C_{35}H_{43}N_5O_7$	26.47 (40:60)
42b	77	94−96	$C_{35}H_{43}N_5O_7$	29.13 (40:60)
43a[e]	54	foam	$C_{33}H_{39}N_5O_7$	73.60, 70.60 (26:74)
47a,b (2:1)	41	foam	$C_{31}H_{35}N_5O_7$	16.20, 17.60 (30:70)

[a] From ethyl ether/hexane. [b] Satisfactory analyses for C, H, N. [c] Nova-pak C_{18}, A = CH_3CN, B = 0.05% TFA in H_2O. [d] μBondapak C_{18}. [e] (2:3) atropoisomeric pair. [f] Sublimation.

Table 5. Significant ^{1}H NMR[a] Spectroscopic Data of 5-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidines

compd	4-H	4a−H	5-H	6-H	7-H	8-H	α-H (Trp)	R^1
17b	2.48 3.68	2.95	3.49	1.20−1.70	1.20−1.70	3.68	4.09	4.09	3.33
18a	2.40 2.52	2.85	3.62	1.03 1.60	1.60	2.52	4.28	4.43	1.10−1.85, 2.18, 2.42, 4.40
18b	2.12 2.26	2.50	3.57	1.10−1.85	1.10−1.85	2.50	4.24	4.39	1.10−1.85, 2.12, 2.26, 4.49
19a	2.63	3.02	3.78	1.14 1.68	1.68	2.63	4.31	4.48	7.13, 7.38, 7.42
19b	2.22	2.69	3.72	1.18 1.89	1.67	2.57	4.27	4.42	7.12, 7.40, 7.45
(2*R*)-20a	2.70 2.80	3.20	3.89	1.19 1.75	1.65 1.75	2.70	4.33	4.51	7.38, 7.47, 7.55, 7.89, 7.90
(2*S*)-20a	2.75	3.10	3.92	1.17 1.58−1.80	1.58−1.80	2.64	4.32	4.50	7.56, 7.64. 7.89, 7.24, 7.48
(2*R*)-20b	2.22 2.47	2.70	3.83	1.20 1.90	1.57 1.70	2.58	4.25	4.42	7.32, 7.54, 7.56, 7.59, 7.91, 7.89
(2*S*)-20b	2.25 2.35	2.65	3.74	1.16 1.87	1.57 1.68	2.55	4.25	4.42	7.43, 7.52, 7.53, 7.89, 7.90
21a,b (5:1)	2.61, 2.43	3.03, 2.97	3.76, 3.65	1.07, 1.23	1.87, 1.54	1.55, 1.54	1.63, 1.54	2.67, 2.62	4.29, 4.11	4.43, 4.87	7.18, 7.15, 8.69, 8.71
22a	2.47	2.91	3.64	1.12 1.51−1.74	1.51−1.74	2.47	4.24	4.46	6.05[b]
22b	2.16	2.37	3.57	1.09 1.89	1.42 1.66	2.46	4.17	4.41	6.02[b]
23a	2.49	2.87	3.66	1.03 1.61	1.42 1.61	2.54	4.24	4.45	6.05[b]
23b	2.11	2.48	3.56	1.22 1.81	1.50 1.67	2.42	4.20	4.39	6.03[b]
(2*RS*)-24a	2.68, 2.70	3.05, 3.06	3.82	1.53−1.78	1.65, 1.73	2.59, 2.57	4.32, 4.33	4.49	2.08, 2.29[c]
(2*RS*)-24b	2.22, 2.23	2.67, 2.63	3.71	1.16, 1.18	1.94, 1.88	1.59, 1.55	1.94, 1.73	2.57, 2.51	4.27, 4.26	4.40	2.06, 2.15[c]
25a	2.64	3.04	3.82	1.15 1.69	1.69	2.64	4.33	4.51	2.38[c]
25b	2.26	2.69	3.70	1.17 1.87	1.59 1.69	2.64	4.26	4.40	2.37[c]
26a	2.61	3.06	3.82	1.13 1.67	1.67	2.61	4.31	4.46	2.37[c]
26b	2.27	2.65	3.70	1.19 1.88	1.56 1.68	2.56	4.26	4.41	2.37[c]
27a	2.64	3.12	3.81	1.16 1.83	1.66	2.64	4.30	4.45	7.49, 7.62, 8.26
27b	2.34	2.79	3.73	1.19 1.84	1.59 1.75	2.64	4.27	4.39	7.51, 7.60, 8.05, 8.26
28a	2.78 3.01	3.40	3.68	1.21 1.68	1.52 1.68	2.73	4.06	4.06	7.48, 8.26
28b	2.34	2.79	3.77	1.20 1.90	1.59 1.75	2.66	4.28	4.42	8.28, 8.31
29a	2.60	3.02	3.73	1.10 1.67	1.67	2.60	4.31	4.51	3.81[c]
32a	2.61	2.98	3.72	1.09 1.60	1.60	2.61	4.29	4.46	2.29[c]
33a	2.56	2.88	3.71	1.05 1.55	1.55	2.56	4.27	4.45	6.75, 6.91
36a	2.59	3.01	3.78	1.14 1.67	1.67	2.59	4.31	4.51	2.94[c]
36b	2.31	2.65	3.66	1.26 1.89	1.61 1.77	2.57	4.30	4.51	2.95[c]
37a	2.60	2.95	3.72	1.10 1.56	1.56	2.60	4.29	4.51	2.95[c]
37b	2.30	2.54	3.68	1.14 1.88	1.59 1.73	2.54	4.28	4.40	2.96[c]
41a	2.36	2.79	3.17	1.12 1.71	1.42−1.60	2.58	4.14	4.43	5.63[b]
42a	2.34	2.80	3.18	1.08 1.70	1.35−1.61	2.45	4.15	4.43	5.61[b]
42b	2.35	2.72	3.29	1.11 1.61	1.61	2.36	4.13	4.41	5.47[b]
43a[d]	2.63	4.37	3.88	0.90 1.25	1.25, 1.50	1.40, 1.67	2.75	3.77	4.31	4.42, 4.50[b]
47a,b (2:1)	2.59 3.97	3.45	3.74	1.39 1.45	1.60 1.74	2.59	4.09	4.09	7.92, 7.68, 7.32

[a] Spectra registered at 300, 400 or 500 MHz in $CDCl_3$ except for **28** and **47a,b**, which were registered in DMS0-d_6, and **35a** which was registered in $(CD_3)_2CO$. [b] δ corresponding to the 1-H of R^1. [c] δ corresponding to CH_3. [d] Data of the (1:1) atropoisomeric mixture assigned in the TOCSY spectrum.

2H, 4-H (Orn)], 1.37−1.59 [m, 2H, 3-H (Orn)], 1.48 (s, 9H, Boc), 3.05 [m, 2H, 5-H (Orn)], 3.13 [dd, 1H, J = 9 and 14 Hz, 3-H (Trp)], 3.34 [dd, 1H, J = 5 and 14 Hz, 3-H (Trp)], 3.67 (s, 3H, OMe), 4.51 [m, 2H, 2-H (Orn) and 2-H (Trp)], 4.82 [t, 1H, J = 6 Hz, 5-NH (Orn)], 5.18 [s, 2H, CH_2 (Z)], 5.28 [bs, 1H, 2-NH (Trp)], 6.04 [d, 1H, 2-NH (Orn)], 7.02 [d, 1H, J = 2 Hz, 2-H (In)], 7.11−7.25 [m, 2H, 5-H and 6-H (In)], 7.31−7.44 [m, 6H, 7-H (In) and Ph (Z)], 7.72 [d, 1H, J = 7.5 Hz, 4-H (In)], 8.46 [s, 1H, 1-H (In)]. Anal. ($C_{30}H_{38}N_4O_7$) C, H, N. This dipeptide methyl ester (5.84 g, 10.3 mmol) was dissolved into MeOH (75 mL), and 1 N NaOH (24 mL) and H_2O (8 mL) were added to the solution. After 15 min of stirring at room temperature, the MeOH was evaporated, and the resulting solution was diluted with H_2O (150 mL) and washed with EtOAc (100 mL). The aqueous phase was acidified to pH ≅ 5, by dropwise addition of 1 N HCl, and extracted with EtOAc (2 × 150 mL). The organic extracts were dried over Na_2SO_4 and evaporated to dryness to yield the dipeptide Boc-L-Trp-D-Orn-OH (5.69 g, 100%) as a syrup, which was used without further purification for the following step in the synthetic pathway. RP HPLC t_R = 21.45 (A:B = 50:50); ^{1}H NMR [200 MHz, $(CD_3)_2CO$] δ 1.24−1.50 [m, 2H, 4-H (Orn)], 1.35 (s, 9H, Boc), 1.52−1.85 [m, 2H, 3-H (Orn)], 3.11 [m, 3H, 5-H (Orn) and 3-H (Trp)], 3.27 [dd, 1H, J = 6.5 and 14 Hz, 3-H (Trp)], 4.43 [m, 2H, 2-H (Orn) and 2-H (Trp)], 5.06 [s, 2H, CH_2 (Z)], 6.02 [bs, 1H, 2-NH (Trp)], 6.31 [bs, 1H, 2-NH (Orn)], 7.00−7.12 [m, 2H, 5-H and 6-H (In)], 7.21 [d, 1H, J = 2 Hz, 2-H (In)], 7.31 [m, 7H, 2-NH (Orn), 7-H (In) and Ph (Z)], 7.65 [d, 1H, J = 7 Hz, 4-H (In)], 10.05 [s, 1H, 1-H (In)].

Synthesis of Ethyl (4*RS*)-7-Benzyloxycarbonylamino-4-[*N*-(*tert*-butoxycarbonyl)-L-tryptophyl]amino-3-oxoheptanoate (44).[22] 1,1-Dicarbonyldiimidazole (2.01 g, 12.4 mmol) was added to a solution of Boc-L-Trp-D-Orn-OH (5.69 g, 10.3 mmol) in dry THF (95 mL), and the mixture was stirred at room temperature for 2 h. Then, this reaction mixture was added dropwise, and under argon atmosphere, to a −78 °C cooled solution of the lithium enolate of ethyl acetate [obtained by dropwise addition of dry EtOAc (5.23 mL, 53.56 mmol), under argon atmosphere, to a 1 M solution of lithium bis-(trimethylsilyl)amide in hexane (53.56 mL, 53.56 mmol) cooled to −78 °C, followed by 15 min of stirring]. After 25 min of stirring at this temperature, 1 N HCl was added until pH ≅ 7, and the resulting mixture was extracted with EtOAc (2 × 150 mL). The organic extracts were successively washed with saturated $NaHCO_3$ (200 mL), H_2O (200 mL), and brine (200 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography using 25% of EtOAc in hexane as eluant, to yield the title compound (3.69 g, 63%) as a white solid. A 10% of epimerization at the C_2 of ornithine was observed in the ^{1}H NMR spectrum. Therefore, this Boc-L-Trp-D-Orn-OH derived β-ketoester **44** was obtained as a (9:1) (4*S*/4*R*)-epimeric pair, which could not be resolved. RP HPLC t_R = 24.93 (A:B = 50:50); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (m 2H, 6-H), 1.19 and 1.21 (2 t, 3 H, Et), 1.32−1.57 (m, 2H, 5-H), 1.39 and 1.43 (2 s, 9 H, Boc), 3.11 and 3.13 [2 d, 1 H, 3-H (Trp)], 3.29 and 3.39 [2 d, 1 H, 3-H (Trp)], 3.34 and 3.37 (2 s, 2 H, 2-H), 4.11 (c, 2 H, Et), 4.42 [m, 2 H, 2-H and 2-H (Trp)], 4.85 (m, 1 H, 7-NH), 5.13 [s, 2 H, CH_2 (Z)], 5.22 [d,

1H, 2-NH (Trp)], 5.82 and 6.29 (2 d, 1 H, 4-NH), 6.97 [s, 1 H, 2-H (In)], 7.06−7.24 [m, 2 H, 5-H and 6-H (In)], 7.25−7.34 [m, 6 H, 7-H (In) and Ph (Z)], 7.64 [d, 1 H, 4-H (In)], 8.59 [s, 1 H, 1-H (In)]. Anal. ($C_{33}H_{42}N_4O_8$) C, H, N.

Synthesis of the (2*R,3*S**)- and (2*R**,3*R**)-3-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]amino-2-(ethoxycarbonyl)methylpiperidines 45.**[22] A solution of the (9:1) epimeric mixture of *β*-ketoester **44** (400 mg, 0.64 mmol) in EtOH (40 mL) was hydrogenated at room temperature and 3 atm of H_2 pressure, in the presence of 10% Pd (C) (40 mg) for 7 days. Afterward, the catalyst was filtered off and washed with EtOH (10 mL), and the resulting solution was evaporated to dryness. The residue was purified by preparative TLC using 4% of MeOH in dichloromethane as eluant to isolate two fractions. The lower R_f and major fraction (90 mg, 30%) corresponded to a (2:1) epimeric mixture of the 2,3-*trans*-piperidines **45a,b**, and the higher R_f fraction corresponded to the (2:1) epimeric mixture of the 2,3-*cis*-piperidines **45c,d** (44 mg, 14%).

(2R*,3S*)-3-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]amino-2-(ethoxycarbonyl)methylpiperidine (45a,b). RP HPLC t_R = 18.89 (A:B = 25:75); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 and 1.05 (m, 1 H, 4-H), 1.22 and 1.25 (t, 3 H, Et), 1.44 (s, 9 H, Boc), 1.55 (m, 2 H, 5-H), 1.81 and 2.03 (m, 1 H, 4-H), 2.20 and 2.43 (m, 2 H, 2-CH_2), 2.45 (m, 1 H, 2-H), 2.45 and 2.91 (m, 2 H, 6-H), 3.13 and 3.30 [m, 2 H, 3-H (Trp)], 3.51 (m, 1 H, 3-H), 4.07 and 4.08 (c, 2 H, Et), 4.36 [dd, 1H, 2-H (Trp)], 5.18 [bs, 1 H, 2-NH (Trp)], 5.59 and 5.70 (d, 1 H, 3-NH), 7.05 [d, 1 H, J = 2 Hz, 2-H (In)], 7.08−7.22 [m, 2 H, 5-H and 6-H (In)], 7.35 [d, 1 H, J = 7.5 Hz, 7-H (In)], 7.66 [d, 1 H, J = 7.5 Hz, 4-H (In)], 8.27 [bs, 1 H, 1-H (In)]. Anal. ($C_{25}H_{36}N_4O_5$) C, H, N.

(2*R,3*R**)-3-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]amino-2-(ethoxycarbonyl)methylpiperidine (45c,d)**. RP HPLC t_R = 27.72 (A:B = 25:75); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 and 0.90 (m, 1 H, 5-H), 1.07 (m, 1 H, 4-H), 1.23 and 1.24 (t, 3 H, Et), 1.43 (s, 9 H, Boc), 1.32 (m, 1 H, 4-H), 2.00 and 2.45 (m, 1 H, 2-CH_2), 2.45 and 2.54 (m, 4 H, 6-H and 2-CH_2), 2.90 (m, 1 H, 2-H), 3.15 and 3.33 [m, 2 H, 3-H (Trp)], 3.83 and 3.92 (m, 1 H, 3-H), 4.09 and 4.14 (c, 2 H, Et), 4.43 [m, 1H, 2-H (Trp)], 5.19 [bs, 1 H, 2-NH (Trp)], 6.32 and 6.54 (bs and d, 1 H, 3-NH), 7.05 [d, 1 H, J = 2 Hz, 2-H (In)], 7.21−7.10 [m, 2 H, 5-H and 6-H (In)], 7.34 [d, 1 H, J = 7.5 Hz, 7-H (In)], 7.68 [d, 1 H, J = 7.5 Hz, 4-H (In)], 8.15 [bs, 1 H, 1-H (In)]. Anal. ($C_{25}H_{36}N_4O_5$) C, H, N.

Synthesis of (4a*R,5*S**)-5-[*N*-(*tert*-Butoxycarbonyl)-tryptophyl]amino-2-(3-carboxy)phenyl-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine (47a,b).** Bis(trichoromethyl)-carbonate (96 mg, 0.32 mmol) was added to a 0 °C cooled solution of 3-aminobenzoic acid (163 mg, 1.3 mmol). Afterward, TEA (0.60 mL, 4.28 mmol) was added dropwise throughout 5 min. After 5 min of stirring at 0 °C, a solution of (2*R**,3*S**)-3-[*N*-(*tert*-butoxycarbonyl)-L-tryptophyl]amino-2-(ethoxycarbonyl)methylpiperidine (**45a,b**) (200 mg, 0.43 mmol) in dry THF (3 mL) was added at room temperature, and the mixture was stirred at room temperature for 16 h. Then, the reaction mixture was diluted with EtOAc (50 mL), washed successively with H_2O (25 mL), 10% citric acid (25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography to give the piperidine derivative **46a,b** (60 mg, 0.1 mmol, 23%) as a syrup, which was dissolved into dry THF (2 mL). Then, NaH (12 mg of 60% dispersion in mineral oil, 0.30 mmol) was added to this solution. This reaction mixture was stirred at room temperature for 30 min, then a 0 °C cooled 1 N HCl solution (25 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 25 mL). The organic extracts were washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography using 10−50% gradient of MeOH in dichloromethane as eluant, to yield the (2:1) diastereoisomeric mixture of 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidines **47a,b** (40 mg, 67%), which could not be resolved. The significant analytical and spectroscopic data of these compounds are shown in Tables 4 and 5.

Binding Assays. CCK_1 and CCK_2 receptor binding assays were performed using rat pancreas and cerebral cortex homogenates, respectively, according to the method described by Daugé et al.[23] with minor modifications. Briefly, rat pancreas tissue was carefully cleaned and homogenized in Pipes HCl buffer, pH 6.5, containing 30 mM $MgCl_2$ (15 mL/g of wet tissue), and the homogenate was then centrifuged twice at 4 °C for 10 min at 50 000g. For displacement assays, pancreatic membranes (0.2 mg protein/tube) were incubated with 0.5 nM [^{3}H]pCCK-8 in Pipes HCl buffer, pH 6.5, containing $MgCl_2$ (30 mM), bacitracin (0.2 mg/mL) and Soybean Trypsin Inhibitor (SBTI, 0.2 mg/mL), for 120 min at 25 °C. Rat brain cortex was homogenized in 50 mM Tris-HCl buffer pH 7.4 containing 5 mM $MgCl_2$ (20 mL/g of wet tissue), and the homogenate was centrifuged twice at 4 °C for 35 min at 100 000g. Brain membranes (0.45 mg protein/tube) were incubated with 1 nM [^{3}H]pCCK-8 in 50 mM Tris-HCl buffer, pH 7.4, containing $MgCl_2$ (5 mM) and bacitracin (0.2 mg/mL) for 60 min at 25 °C. Final incubation volume was 0.5 mL in both cases. Nonspecific binding was determined using CCK-8 1 μM as the cold displacer. The inhibition constants (Ki) were calculated using the equation of Cheng &Prusoff from the displacement curves analyzed with the Receptor Fit Competition LUNDON program.

Amylase Release. Dispersed rat pancreatic acini were prepared by using a modification of the technique of Jensen et al.[24] The rat was decapitated, and the pancreas was carefully cleaned. Tissue was injected with 1 mL of a solution of collagenase (type V, Sigma) at a concentration of 1 mg/mL (in distilled water) and subjected to the digestion step consisting in two 6 min incubations at 37 °C and washing three times the tissue in buffer A (composition in mM: NaCl 140, KCl 4.87. $MgCl_2$ 1.13, $CaCl_2$ 1.10, Glucose 10 and Hepes 10, pH = 7.4) after each incubation. The tissue obtained after the last incubation was dispersed with the aid of a Pasteur pipet, and the homogenate was centrifuged twice (100 g, 1 min, 4 °C). The final pellet was resuspended in 100 mL of buffer B (NaCl 98 mM, KCl 6 mM, NaH_2PO_4 2.5 mM, $CaCl_2$ 0.5 mM, theophylline 5 mM, glucose 11.4 mM, L-glutamine 2 mM, L-glutaric acid 5 mM, fumaric acid 5 mM, pyruvic acid 5 mM, SBTI 0.01%, bovine serum albumin 1%, essential amino acid mixture 1%, and essential vitamin mixture 1%). Amylase release was measured using the procedure of Peikin et al.[27] Samples (2 mL) of acini suspension were placed in plastic tubes and incubated for 30 min at 37 °C in atmosphere of pure O_2 with agitation (70 cycles/min). Amylase activity was determined using the Amyl Kit Reagent (Boeringher Mannheim). Release (S) was calculated as the percentage of the amylase activity in the acini that was released into extracellular medium during the incubation period. The percentage of inhibition of amylase release elicited by a fixed CCK-8 concentration (0.1 nM) produced by the assayed compounds was calculated according to the formula

$$\% I = [(S_{CCK} - S_C) - (S_T - S_C)/(S_{CCK} - S_C)] \times 100$$

where S_C was control release (vehicle), S_{CCK} the release elicited by CCK-8, and S_T the release elicited by CCK-8 in the presence of increasing drug concentrations. Linear regression analysis was used in order to estimate the IC_{50} values of the compounds on the dose response curves.

Acknowledgment. This work has been supported by the CICYT (SAF 97-0030), Fundación La Caixa (97/022) and Consejeria de Educación y Cultura de la Comunidad de Madrid (CAM-08.5/0006/1998).

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JM010813D