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Design of potent, orally effective, nonpeptidal antagonists of the peptide hormone cholecystokinin

(neuropeptide/benzodiazepine)

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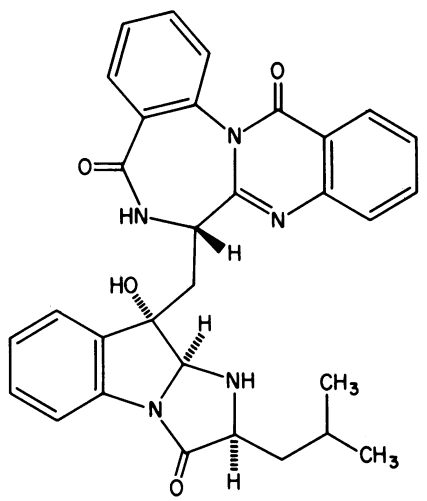
ABSTRACT **We describe the design and synthesis of nonpeptidal antagonists of the peptide hormone cholecystokinin. Several of these compounds have high specificity and nanomolar binding affinity and are active after oral administration. To our knowledge, the design of such agents has not previously been accomplished for any peptide hormone. The structural similarities between these synthetic compounds and the anxiolytic 1,4-benzodiazepines are noted, and the potential of this structural feature for future design of ligands for other peptide hormone receptors is discussed.**

Long-acting orally effective agents that interact competitively at peptide receptors are essential for the optimal development of important discoveries in the neuropeptide field. Such compounds represent unique biological reagents for determining unambiguously the role of the parent neurotransmitter or neurohormone in normal physiology and for assessing its contribution to pathophysiology. They are also of considerable importance in their own right as potential therapeutic agents.

Advances have been made in the design of metabolically stable peptide analogs (1), but the problem of achieving good oral bioavailability with such compounds remains unsolved. Nonpeptidal analogs could offer a broader range of possible solutions to this problem. Unfortunately, the design of biologically equivalent nonpeptidal analogs of bioactive peptides has not yet been achieved (2). The only previously known examples of effective nonpeptidal ligands for peptide hormone receptors are the enkephalin agonist, morphine (2, 3), and the recently reported cholecystokinin (CCK) antagonist, asperlicin (4–7). Both are complex natural products having poor oral bioavailability. In this paper, we describe the design and synthesis of 3-substituted-1,4-benzodiazepines, which are selective high-affinity antagonists of CCK, having good oral activity of long duration.

CCK [active core (CCK-8), H-Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2 (8)] is a gastrointestinal peptide hormone implicated in the control of pancreatic and biliary secretion, gall bladder contraction, and gut motility (9–12). Recent studies have suggested a key role for CCK in the central nervous system as well, perhaps as a neurotransmitter or neurohormone (11–15). Until now, there have been no known agents ideally suited to elucidate the physiologic role of CCK (16). The most widely used antagonists, proglumide and benzotript, are weakly potent amino acid-derived compounds (17) (Table 1) of poor specificity. Recently, another type of CCK antagonist was isolated from a fermentation broth (4, 6) based on identification of its binding properties to CCK receptors by using a radioreceptor assay (7). This compound, asperlicin (Compound **1**) (5), proved to be a selective nonpeptidal antagonist of CCK *in vitro* and *in vivo* (7). However, asperlicin has liabilities as a pharmacological or potential therapeutic agent, including lack of oral bioavailability, modest potency, and poor water solubility (7, 42).

Many important drugs such as ivermectin (18) and cefoxitin (19) are semisynthetic derivatives of natural products, suggesting that derivatization of asperlicin might generate improved CCK antagonists. Unfortunately, our efforts utilizing this approach failed to overcome the key defects of asperlicin discussed above (42).



1

With a lead structure such as morphine, very high affinity for the target receptor (3) justifies use of the intricate parent structure as an accurate template for identifying design directions for synthetic analogs. With asperlicin, this is not the case. While asperlicin has improved CCK receptor binding affinity by some 2 orders of magnitude over previously described antagonists (Table 1), it is still >4 orders of magnitude less avidly bound than the natural ligand CCK-8 (K_d, 0.11 nM) (7). These factors prompted us to consider major departures from the asperlicin structure and to seek an alternative lead for synthesis of improved CCK antagonists.

In searching for such a lead, we attempted to identify those elements of the asperlicin structure that might be responsible for its modest CCK antagonist activity and that might suggest more promising alternative leads. In this vein, our attention was drawn to the structural features highlighted in Scheme I.

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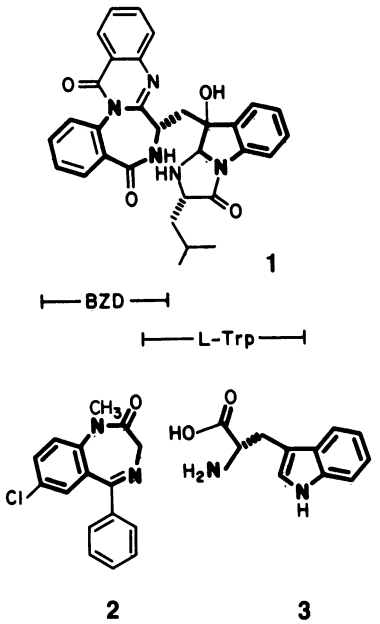
Abbreviations: CCK, cholecystokinin; ^{125}I-CCK, ^{125}I-labeled CCK.

Scheme I



1 2 3

As shown in boldface in the reoriented structure **1**, asperlicin contains elements of the 1,4-benzodiazepine (BZD) ring system found in such anti-anxiety agents as diazepam (**2**). Recent reports (20, 21) support the concept that the natural ligand for the anti-anxiety benzodiazepine receptor is a peptide, suggesting that the 5-phenyl-1,4-benzodiazepine ring (e.g., **2**) is in fact a very effective peptide receptor ligand. The existence of common features of structure and conformation among portions of many peptides suggested to us that this ring system might have a correspondingly broader utility in the construction of ligands for other peptide receptors, including the CCK receptor. We therefore adopted the 5-phenyl-1,4-benzodiazepine ring as the basis for design of improved CCK antagonists.

The 3-hydroxyindoline embedded in the right half of **1** is a distant molecular analog of the side chain of L-tryptophan (**3**). L-Tryptophan is one of the key amino acids of the required carboxyl-terminal sequence of CCK (22), and this observation provided a rationale for one possible approach to elaboration of the basic ring **2**—i.e., fusion with L-tryptophan (**3**).

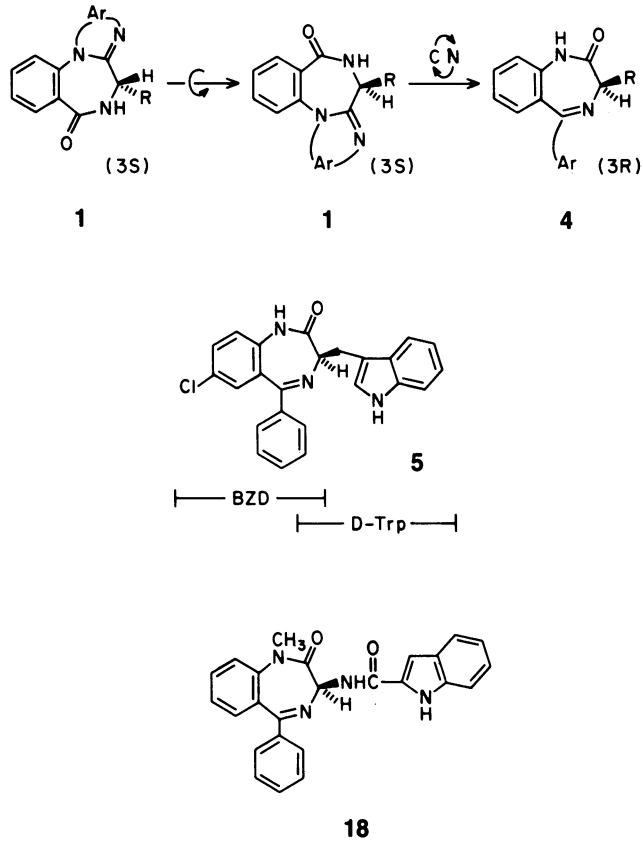
Examination of Scheme I reveals that asperlicin is not a particularly close analog of the ring system exemplified by **2**. Specifically, the 5-phenyl substituent in **2** is absent in **1**, which contains instead a quinazoline ring fused to the opposite (1, 2) side of the seven-membered ring. For modeling purposes, these two substituents can be approximately superimposed by rotation of **1** 180° about the horizontal in-plane axis as shown in Scheme II. However, as illustrated,

Table 1. Inhibition of binding of ^{125}I-labeled-CCK (^{125}I-CCK) to rat pancreatic CCK receptors by reported CCK antagonists

Antagonist	IC_{50}, μM*
Proglumide	600
Benzotript	102
Dibutyryl-cGMP	87
Benzyloxycarbonyl CCK(27–32)NH_2	3.5
Asperlicin	1.4
Diazepam (**2**)	>100†

*IC_{50} (μM) for half-maximal inhibition of binding of ^{125}I-CCK-33 to CCK receptors in rat pancreatic tissue (data from ref. 7).
†R. S. L. Chang and V. J. Lotti, personal communication.

Scheme II



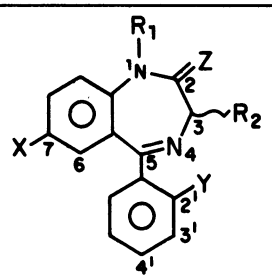
this operation disrupts the coincidence of the seven-membered ring nitrogen atoms. This coincidence can be restored by interchange of the NC and CN linkages in this ring, but such an operation results in inversion of the contained stereocenter (see **4**).

The ultimate aim of such an exercise, of course, is to design a hypothetical structure based on **2** and **3**, analogy to which might be considered the source of the CCK receptor affinity of **1**. Such a structure is **5** (cf. **4**), derived not from the naturally occurring L-tryptophan but, in accord with the rationale presented, from the unnatural isomer, D-tryptophan (Scheme II). Compound **5** was the first of a series of new CCK antagonists synthesized based on this rationale. The properties of **5** and a number of its analogs are summarized in Table 2.

MATERIALS AND METHODS

Compound **5** and the other 3-alkylbenzodiazepines shown in Table 2 (compounds **6**, **8**, **9**, and **10**) were prepared by base-mediated cyclization of α-aminoamides using published methods (25). The α-aminoamides were obtained either by acylation of the appropriate 2-aminobenzophenone with D- or L-tryptophan acid chloride, or by coupling with Boc-D- or -L-tryptophan followed by acid-catalyzed N-deprotection. 3-Amidobenzodiazepines (compounds **14–16**, **18**, **19**, and **21**) were obtained by acylation of the 3-amino derivatives. The latter were prepared from the 3-hydroxy compounds using published procedures (26–28). 3-Aminobenzodiazepines were resolved where indicated (compounds **18** and **19**) by separation of the L- or D-phenylalanine amide followed by Edman degradation for removal of phenylalanine. N^1 substituents (R_1, compounds **7**, **11**, **13**, **17–20**, **22**) were attached by alkylation of the unsubstituted compounds using sodium hydride and either iodomethane or ethyl bromoacetate. The acids **13** and **20** were obtained by saponification

Table 2. Inhibition of binding of ^{125}I-CCK to rat pancreatic CCK receptors by synthetic CCK antagonists



Compound	X	Y	Z	R_1	R_2	3-Stereo	CCK*	BZD
2	Cl	H	O	CH_3	H	—	>100	0.007 (40)
5	Cl	H	O	H	CH_2-3-indolyl	*R*	3.4	>100†
6	Cl	H	O	H	CH_2-3-indolyl	*S*	32	5.6†
7	Cl	H	O	CH_3	CH_2-3-indolyl	*R*	1.4	—
8	H	H	O	H	CH_2-3-indolyl	*R*	1.2	>100†
9	H	F	O	H	CH_2-3-indolyl	*R*	0.5	>100‡
10	H	F	O	H	CH_2-3-indolyl	*S*	10.6	—
11	H	F	O	CH_3	CH_2-3-indolyl	*R*	0.27	>100‡
12	H	F	=N—N=C(CH_3)—		CH_2-3-indolyl	*R*	0.3	0.8‡
13	H	F	O	CH_2COOH	CH_2-3-indolyl	*R*	0.3	>100‡
14	H	H	O	H	NHC(=O)-2-indolyl	*RS*	0.0047	>100†
15	H	H	O	H	NHC(=O)-3-indolyl	*RS*	1.1	—
16	H	F	O	H	$NHCCH_3$ (=O)	*RS*	40	—
17	H	H	O	CH_3	NHC(=O)-2-indolyl	*RS*	0.0011	>100‡
18	H	H	O	CH_3	NHC(=O)-2-indolyl	*S*	0.0008§	>100‡
19	H	H	O	CH_3	NHC(=O)-2-indolyl	*R*	0.065	>100‡
20	H	H	O	CH_2COOH	NHC(=O)-2-indolyl	*RS*	0.0014	>100‡
21	H	F	O	H	NHC(=O)-2-indolyl	*RS*	0.0021	3.0‡
22	H	F	O	CH_3	NHC(=O)-2-indolyl	*RS*	0.0014	7.8‡

*IC_{50} (μM) for half-maximal inhibition of binding of ^{125}I-CCK-33 to CCK receptors in rat pancreatic tissue.
†IC_{50} (μM) for half-maximal displacement of [^{3}H]diazepam from benzodiazepine (BZD) receptors in rat cerebral cortical membranes.
‡IC_{50} (μM) for half-maximal displacement of [^{3}H]flunitrazepam from guinea pig brain benzodiazepine receptors.
§Refined assay of Chang and Lotti gives IC_{50} = 0.08 nM, K_i = 0.1 nM for **18** (24).

of the corresponding ethyl esters. The triazole ring (compound **12**) was fused to **9** using published procedures (29). All compounds were characterized by satisfactory elemental analyses and by consistent ^{1}H NMR and mass spectra.

IC_{50} values (μM) for half-maximal inhibition of binding of ^{125}I-CCK-33 to CCK receptors in rat pancreatic tissue were obtained by using the procedure described by Innis and Snyder (30). IC_{50} values (μM) for half-maximal displacement of [^{3}H]diazepam from benzodiazepine receptors in rat cerebral cortical membranes or [^{3}H]flunitrazepam from guinea pig brain benzodiazepine receptors were obtained by the procedure described by Braestrup and Squires (31). For detailed study of compound **18**, a refined CCK binding assay using ^{125}I-CCK-8 in place of ^{125}I-CCK-33 as radioligand and using lower receptor concentrations was developed. This improved method yielded an IC_{50} of 0.08 nM and a K_i of 0.1 nM for compound **18**. These studies are described in the accompanying paper (24).

RESULTS AND DISCUSSION

The critical structure in our new approach to the synthesis of effective antagonists of CCK was the prototype, compound **5**. Biological evaluation of this compound demonstrated the validity of our approach. Although much simplified, compound **5** proved nearly as potent a ligand for pancreatic CCK receptors as **1** (Table 2). Equally important, **5**, unlike **1**, was well-absorbed after oral administration and was found to be

an orally effective antagonist of CCK (V. J. Lotti and R. S. L. Chang, personal communication). Consistent with our rationale, compound **5** was nearly 10-fold more potent than the known 3*S* enantiomer **6** (Table 2), which had been reported earlier (32) to be a weak anti-anxiety agent. This low anxiolytic activity is not unexpected in view of the known deleterious effect of most 3-alkyl substituents on anti-anxiety activity in the benzodiazepine series (33, 34), and it is a desirable feature in our compounds, given our analog design objectives.

The success of compound **5** prompted us to undertake extensive structure/activity studies, the key findings from which may be illustrated by using the selected analogs listed in Table 2. These studies showed the CCK antagonist potencies of compounds derived from **5** to be highly sensitive to the nature of the group attached to the 3-position of the benzodiazepine ring and to the linkage forming the attachment (see Table 2). The 3-amidobenzodiazepine group (e.g., **14–22**) in particular provided a series of superior CCK antagonists, exemplified by the (3*S*)-2-indole amide **18** (L-364,718), the most potent competitive antagonist of CCK yet described (24). This compound is 3 orders of magnitude more potent than the lead structures **1** and **5**, at least 80-fold more potent than its own 3*R* enantiomer **19**, and some 6 orders of magnitude more potent than the much studied CCK antagonist, proglumide (Table 1). Its affinity for the CCK receptor is comparable to that of CCK-8 (24). Compound **18** is selective for pancreatic CCK receptors versus brain CCK and gastric gland gastrin receptors, and is orally effective as an antagonist of CCK-8-induced gastric emptying (24). A detailed account of the biochemical and pharmacological properties of compound **18** is given in the accompanying paper (24).

Amide **18** is one of a class of potent CCK antagonists that allows a clearer examination of the relationship between the CCK antagonist and anti-anxiety activities of benzodiazepines. This relationship is an important one, since recent reports (35–38) have suggested a CCK antagonist activity for anti-anxiety benzodiazepines themselves (i.e., diazepam; **2**). The data in Table 2 illustrate how substitution in the benzodiazepine ring affects CCK receptor binding potencies as compared with its influence on reported anti-anxiety activities. Thus, some substitutions such as 2′-fluoro (Y = F), N^1-methyl ($R_1 = CH_3$), and N^1-C^2-triazole fusion [ZR_1 = =N—N=C(CH_3)—] have effects on CCK receptor affinity similar to those reported in the anti-anxiety series (33, 39): they provide potent compounds in each case. N^1-carboxymethyl ($R_1 = CH_2COOH$), on the other hand, greatly reduces anti-anxiety potency (34), but gives potent CCK receptor ligands (**13** and **20**). Conversely, 7-substituents such as chloro (X = Cl) are, if anything, slightly detrimental to CCK receptor affinity but are vital for good anti-anxiety activity (33).

Most importantly in the present case, of course, are the effects of 3-substitution. 3-Alkyl and 3-amido substituents are reported (23, 32–34, 40) to be detrimental to anti-anxiety activity. Our results are consistent with these reports. Thus, as shown by the data in Table 2, our 3-alkyl and 3-amido substituents greatly enhance CCK antagonist potency but greatly diminish the anti-anxiety-related benzodiazepine receptor binding activity: selectivity changes from $>10^4$ in favor of benzodiazepine vs. CCK receptors to $>10^4$ in favor of CCK ($>10^8$-fold reversal) in the conversion of **2** to **18**. Furthermore, the stereochemical preference for anti-anxiety activity in the 3-alkyl enantiomers **5/6** is the same as that reported for 3-methylbenzodiazepines (3*S*) (32, 40), and it is opposite to that preferred for CCK antagonist potency (3*R*) (Table 2). While these results do not directly contradict or confirm the pharmacologically observed (35–38) CCK antagonist activity of benzodiazepines such as **2**, they do demonstrate that the ability of benzodiazepines to bind CCK receptors is a property separate and distinct from their affinity for benzodiazepine receptors.

It should be noted that for all the CCK antagonists reported here, the preferred orientation of the 3-substituent in space is the same. The apparent change in preferred stereochemistry from *R* to *S* between the alkyl (e.g., **5/6**) and amide (e.g., **18/19**) series is an artifact of the convention used to assign the stereochemical designator (41).

In retrospect, the development of the lead structure **5** to the much more effective **18** eclipsed the rationale by which the indole methyl side chain was chosen for compound **5**—namely, its resemblance to the side chain of L-tryptophan. More importantly, however, the outstanding success of **18** strengthened the central hypothesis of this work—that the 5-phenyl-1,4-benzodiazepine ring exemplified by **2**, **5**, and, especially, **18**, can provide a useful base for the design of peptide receptor ligands.

CONCLUSION

In summary, we report here the conception and development of the first specific nonpeptidal antagonist of CCK with nanomolar potency and good oral bioavailability. To the best of our knowledge, this is the first example of such a ligand deliberately designed for any peptide receptor. Studies of this compound **18**, and its analogs have already provided evidence for the distinction between CCK and benzodiazepine receptor binding activities of benzodiazepines and may add as well to the understanding of the mechanism of binding of anti-anxiety agents such as **2** to their receptors.

Whether the benzodiazepine ring in **2** and **18** serves as a conventional structural mimic for key portions of the respective natural ligands or whether it exploits some as yet unidentified feature common to peptide receptors remains unclear. What is clear is that this ring system has now provided very effective ligands for two different peptide receptors, suggesting a generality that could be of much use in the design of ligands for still other such receptors.

We are pleased to acknowledge the efforts of Dr. James Springer and Mr. Jordan Hirshfield, who established the absolute stereochemistry of the compounds reported here by x-ray crystallographic analysis of a derivative. We are also indebted to Drs. Raymond Chang and Victor Lotti for permission to publish the binding results in Tables 1 and 2. We are particularly grateful to Dr. Ralph Hirschmann for his thorough and incisive analyses, which gave focus and perspective to this written account. We also wish to thank Dr. Michael Rosenblatt for his careful review of the manuscript and Mrs. Mary Banker for her efforts in its preparation.

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