Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 7, pp. 805-810, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00108-X

DESIGN AND SYNTHESIS OF NOVEL NONPEPTIDE CCK-B RECEPTOR ANTAGONISTS

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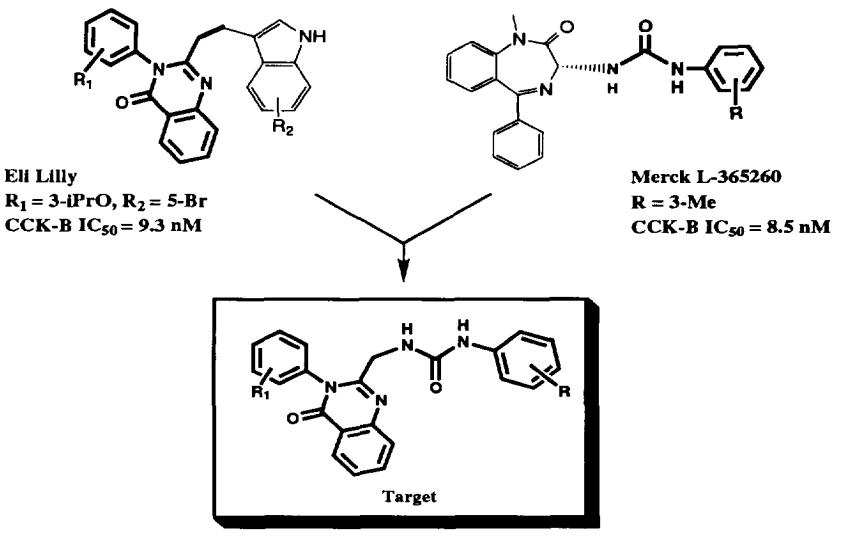
Abstract: A novel hybrid series of nonpeptide CCK-B receptor antagonists has been designed from two known series derived from asperlicin. An efficient synthesis of 2-aminoquinazolinone, an intermediate for the synthesis of a targeted analog, has been developed. © 1997 Elsevier Science Ltd.

The identification of cholecystokinin-B receptor subtype (CCK-B receptor) in mammalian brain and its putative role in nociception and anxiety has provided impetus for the discovery and development of potent and selective CCK-B receptor antagonists.[1,2] Several series of CCK-B antagonists have been disclosed from different structural classes including peptide, peptoid, and nonpeptide.[3] Earlier we disclosed a series of peptoid antagonists from which CI-988 was identified as a clinical candidate.[4] Further optimization of this series of compounds led to the identification of PD-145942 having an improved profile.[5] Due to our ongoing efforts in this area and interest to develop compounds from different structural classes, we focused our attention towards the development of a nonpeptide series of antagonists.

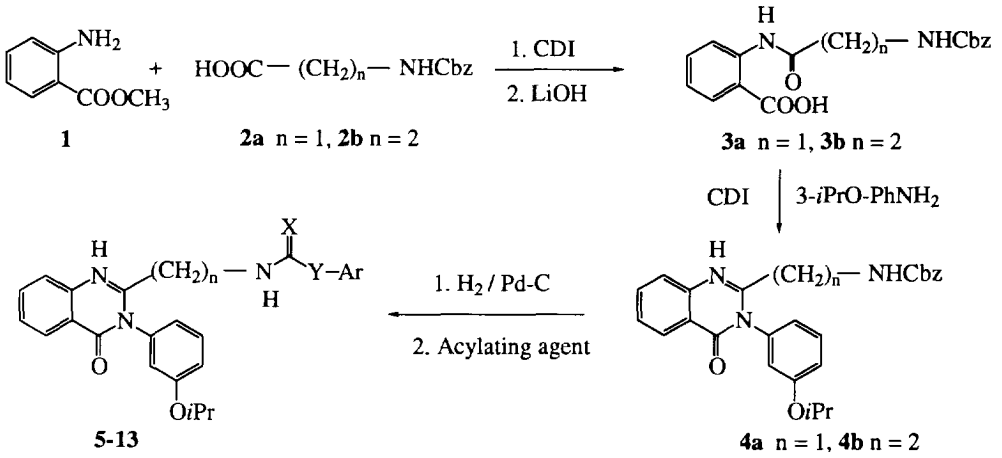
The discovery of asperlicin as a CCK ligand[6] provided a template for many research groups to design CCK-B receptor ligands. Merck scientists disclosed L-365260, which is derived from the benzodiazepine core of asperlicin.[7] Furthermore, Lilly researchers developed a series of quinazolinone derivatives by a bond disconnection approach.[8] On the basis of these observations, we designed a target (Figure 1) in which we combined key fragments of the Lilly and Merck series. Since 3-isopropoxyphenyl was the optimal substitution on the quinazolinone ring in the Lilly series, we initiated our investigation with this substitution on the quinazolinone ring and focused our initial efforts on substituting the phenyl ring, replacing the urea functionality and optimizing the linker in our target.

Figure 1



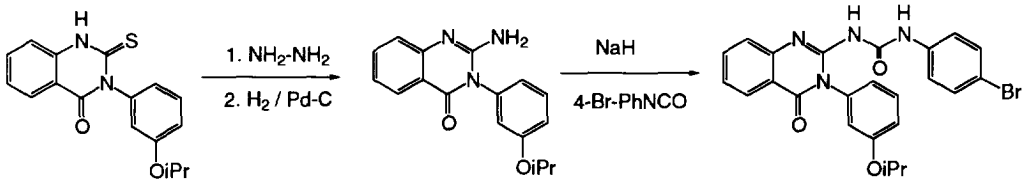
The synthesis of targeted compounds **5-13** (Table 1) is outlined in Scheme 1. Coupling of methyl anthranilate **1** with protected amino acids (**2a** and **2b**) followed by saponification yielded the corresponding acid derivatives **3a** and **3b**. Compounds **3a** and **3b** underwent coupling reaction with 3-isopropoxy aniline in presence of CDI and then insitu dehydrative cyclization to give the quinazolinone derivatives **4a** and **4b**, respectively. This one pot cyclization was unique since the reported procedure includes preparation of the bisamide derivative using CDI, and then treatment with a dehydrating agent such as pyridinium *p*-toluenesulfonate or *p*-toluenesulfonic acid to form

Scheme 1



the quinazolinone.[9] Deprotection of compounds **4a** and **4b** followed by acylation with an appropriate acylating agent provided the desired compounds **5-13** (Table 1). Attempts to prepare the requisite amine precursor **15** by literature procedures were unsuccessful.[10-12] However, it was synthesized by the treatment of the thioxoquinazolinone **14** with excess hydrazine in refluxing ethanol to yield the corresponding hydrazino derivative,[13] and the N-N bond was subsequently cleaved by hydrogenation using 10% palladium on carbon as a catalyst to provide the required amine **15**. Reaction of **15** with 4-bromophenyl isocyanate in the presence of sodium hydride gave urea **16** (Scheme 2).

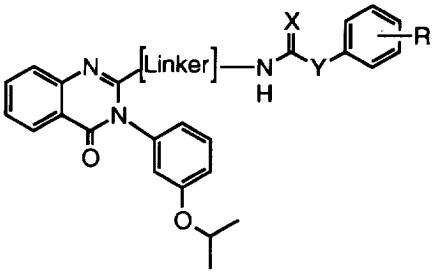
Scheme 2



14 **15** **16**

The CCK receptor binding affinities[4] of the compounds prepared[14] for this study are given in Table 1. The limited set of substitutions onto the phenyl of the urea moiety was selected on the basis of other urea series of CCK-B receptor ligands reported in the literature.[7,15] Incorporation of a 3-methyl substituent, an optimal substituent in Merck series[7], gave compound **5** with poor binding affinity for the CCK-B receptor. However, compound **6** with a 4-bromo substituent, a preferred substituent in Lilly's pyrazolidinone series,[14] produced moderate binding affinity (137 nM) for the CCK-B receptor. Compounds with other electron withdrawing substitutions such as 4-trifluoromethyl and 4-nitro (**7** and **8**) also showed modest and equipotent receptor binding affinity for both the receptors. However, compound **9** with 3-carbethoxy substitution showed 126 nM binding affinity for the CCK-B receptor. Attempts to replace the urea moiety with thiourea (**10**) or sulfonylurea (**12**) resulted in the loss of binding affinities at both the receptors. Introduction of a methylene group in between the urea moiety and the aryl ring decreased the binding affinity (**6** vs. **11**). In an attempt to determine the optimal spacing of aryl urea moiety from the quinazolinone moiety, we tested higher homolog **13** and lower homolog **16**, but both resulted in significant reduction in binding affinity for the CCK-B receptor suggesting that the spatial distance of the aryl urea functionality from the quinazolinone ring is a critical determinant of binding affinity. While the synthesis and SAR study were ongoing, we chose to establish functional activity of this novel series of ligands. Thus,

Table 1. CCK Receptor Binding Affinities[a]



Compound	Linker	X	Y	R	IC_{50} (nM) CCK-A	IC_{50} (nM) CCK-B
5	CH_2	O	NH	3-CH_3	1637	879
6	CH_2	O	NH	4-Br	984	137
7	CH_2	O	NH	4-CF_3	674	691
8	CH_2	O	NH	4-NO_2	385	212
9	CH_2	O	NH	3-COOEt	1465	126
10	CH_2	S	NH	4-Br	6929	8024
11	CH_2	O	$NHCH_2$	4-Br	3100	652
12	CH_2	O	$NHSO_2$	4-CH_3	>1 μM	>1 μM
13	CH_2CH_2	O	NH	4-Br	1630	585
16	-	O	NH	4-Br	>1000	>1000

[a] IC_{50} represents the concentration (nM) producing half-maximal inhibition of specific binding of [^{125}I] Bolton Hunter CCK-8 to CCK receptors in the mouse cerebral cortex (CCK-B) or the rat pancreas (CCK-A). The values given are the geometrical mean of at least three separate experiments. Statistical errors were 15% of the mean values.

compounds **6** and **9** were evaluated in an in vitro functional assay measuring intracellular calcium levels in the rat pancreatic acinar AR42J cell line[16]. Both compounds reversibly antagonized pentagastrin-evoked increases in intracellular calcium levels and showed no agonist activity. Although the CCK-B binding affinities of the two compounds were similar, compound **9** (Ke = 230 nM) was a more potent antagonist than compound **6** (Ke = 1330 nM) in this assay. The difference in binding affinities and antagonist potecies may be because of difference

in species of origin of CCK receptors.

In summary, we have designed a novel series of CCK-B receptor antagonists. We have demonstrated a one pot procedure to prepare quinazolinone derivatives **4a** and **4b** from the corresponding 2-amido benzoic acid derivatives **3a** and **3b** and requisite aniline. We have also developed an efficient method to prepare 2-amino quinazolinone **15** by hydrogenation of the corresponding hydrazine derivative. Binding data of this class of compounds suggest that the linker is a critical determent for CCK-B receptor binding affinity. These encouraging results have led us to further investigate SAR for this series of novel CCK-B receptor antagonists, which will be discussed in detail in a forthcoming full article.

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(*Received in USA* 26 *December* 1996; *accepted* 19 *February* 1997)