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SELECTIVE LIGANDS FOR CHOLECYSTOKININ RECEPTOR SUBTYPES CCK-A AND CCK-B WITHIN A SINGLE STRUCTURAL CLASS

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INTRODUCTION

Cholecystokinin (CCK) is one of a number of peptides which has been found in the central nervous system (CNS) as well as in the gastro intestinal (GI) tract. Receptors for CCK have been divided into two distinct subtypes, CCK-A and CCK-B. CCK-A receptors are found predominantly in the periphery but are also found in discrete areas of the brain.[1] This receptor subtype is selective for the C-terminal sulphated octapeptide of CCK (CCK-8S), and for the selective antagonist Devazepide (formerly MK 329, L364,718).[2] CCK-B receptors are found exclusively in the CNS, but have striking similarity to the peripheral gastrin receptor.[1] CCK-B receptors are selective for the C-terminal tetrapeptide of CCK (CCK-4) and BC 264,[6] and the selective antagonists CI-988 (formerly PD 134308) and L365,260.

CONCEPT AND RESULTS

The two selective antagonists Devazepide and L365,260 are benzodiazepines derived from the fungal metabolite asperlicin.[4] They differ only in the nature and stereochemistry of the side-chain. Devazepide has the 2-indole carboxamide side-chain and the S-configuration, whilst L365,260 has the meta-methyl phenyl urea side-chain and the R-configuration. The relationship between absolute configuration and receptor selectivity of these benzodiazepines is intriguing. One isomer being selective for CCK-A receptor subtypes and the opposite enantiomer selective for CCK-B receptor subtypes.[2,3b]

The importance of absolute stereochemistry on binding and selectivity for CI-988 and other compounds in the same and a similar series is shown in Table 1.[3a] Changing the R-α-methyl tryptophan centre in CI-988 and PD 135118 to the corresponding S-diastereoisomer results in a 40-fold decrease in CCK-B receptor affinity but has no significant effect upon CCK-A receptor binding.

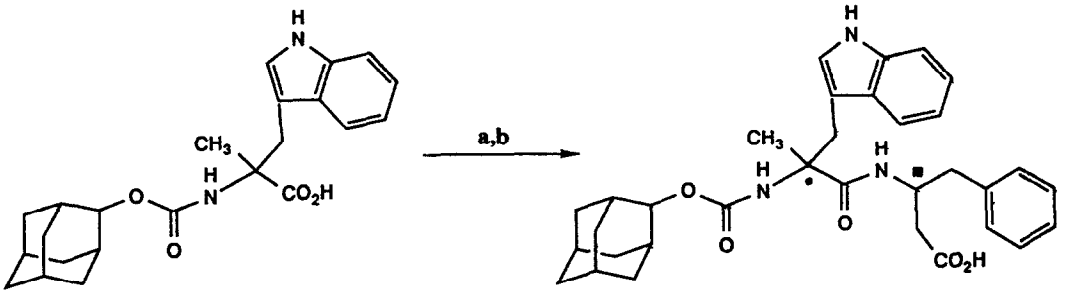
The effect of inverting the optical centre at the α-carbon of the phenethylamine moiety of PD 135118 or the ß-carbon of CI-988 has little effect on the CCK-A receptor binding and the CCK-B receptor affinity is reduced by 5-fold and 25-fold respectively, thus all the isomers of CI-988 and PD 135118 are CCK-B selective albeit with greatly reduced affinity and selectivity.

Significantly different from the above compounds is PD 135666 (Table 2). This compound shows

sub-nanomolar affinity for the CCK-B receptor (IC_{50} =0.15 nM), but differs from the other series in having relatively high affinity for the CCK-A receptor (IC_{50} = 25.5 nM). From the structure activity relationships (SAR) for the two series of compounds in Table 1 described above, the concept that we could significantly reduce CCK-B binding affinity without affecting CCK-A affinity was promising. Also, as the carboxylic acid in PD 135666 attributed more binding affinity to the CCK-A receptor compared with that of CI-988 and PD 135118, changing the stereochemistry on the substituted phenethylamine of PD 135666 may enhance CCK-A binding. This was indeed the case and the results are shown in Table 2.

Changing the stereochemistry at the R-α-methyl tryptophan centre (PD 140547) reduced CCK-B binding by almost two orders of magnitude (IC_{50} = 13.2 nM), however, CCK-A binding was also reduced by some 20-fold. Similarly inverting the α-position of the phenethylamine group (PD 140723) gave a 60-fold reduction in CCK-B binding (IC_{50} = 9.3 nM). CCK-A binding was also reduced from 25.5 nM in PD 135666 to 186 nM in PD 140723. The acetic acid moiety clearly had a substantial effect, and when both centres were inverted (PD 140548) this compound became ~100-fold selective for the CCK-A receptor (IC_{50} at CCK-A = 2.8 nM; IC_{50} at CCK-B = 259 nM). Thus by inverting the two chiral centres in PD 135666 to give its enantiomer PD 140548, a compound that was selective for CCK-B, with a CCK-A/CCK-B ratio of 170 was transformed into a compound that was CCK-A selective (A/B ratio = 0.01) within a single structural type, without side-chain modifications.

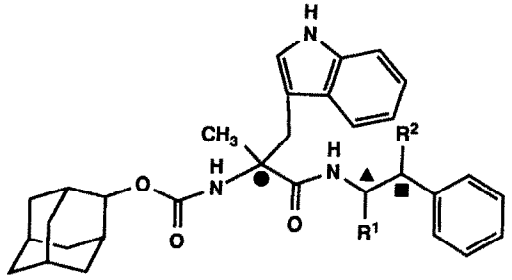
Scheme 1[a]



a a = PFP, DCC, benzyl-ß-aminobenzenebutanoate, EtOAc.
b = 10% Pd/C, H_2, EtOH

	•	■
PD 135666	R	S
PD 140723	R	R
PD 140547	S	S
PD 140548	S	R

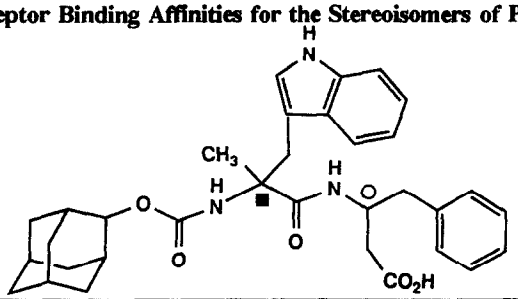
TABLE 1. CCK-Receptor Binding Affinities for the Stereoisomers of PD 135118 and CI-988



Compd	●	▲	■	R^1	R^2	IC_{50} (nM) CCK-B	CCK-A	A/B ratio
PD 138916	R	R	-	$CH_2NHCO(CH)_2CO_2H$	H	23(15-31)	850(800-1000)	37
PD 135118	R	S	-	$CH_2NHCO(CH_2)_2CO_2H$	H	4.2(2.9-6.3)	950(740-1100)	230
PD 138915	S	R	-	$CH_2NHCO(CH_2)_2CO_2H$	H	170(160-180)	580(430-890)	3.4
PD 138917	S	S	-	$CH_2NHCO(CH_2)_2CO_2H$	H	180(150-210)	>10000	>56
CI-988	R	-	R	H	$NHCO(CH_2)_2CO_2H$	1.7(1.3-2.7)	4300(1200-8500)	2500
PD 136621	R	-	S	H	$NHCO(CH_2)_2CO_2H$	43(34-50)	3100(2200-4600)	72
PD 137342	S	-	R	H	$NHCO(CH_2)_2CO_2H$	63(44-79)	18000(2500-72000)	290
PD 137337	S	-	S	H	$NHCO(CH_2)_2CO_2H$	160(120-190)	2500(1200-4400)	16

[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 geometric mean and the range from at least three experiments.

Table 2. CCK-Receptor Binding Affinities for the Stereoisomers of PD 135666.



Compd	■	○	IC_{50} (nM) CCK-A	CCK-B	A/B ratio
PD 135666	R	S	25.5(18.1-35.8)	0.15(0.09-0.21)	170
PD 140547	S	S	539(463-629)	13.2(10.4-16.9)	41
PD 140548	S	R	2.8(1.4-5.1)	259(208-292)	0.01
PD 140723	R	R	186(133-268)	9.3(8.4-10.5)	20

[a]Binding affinities defined in footnote a, Table 1

SYNTHESIS

The synthesis of all the compounds in Table 2 is outlined in Scheme 1.[5] 2-Adamantyloxycarbonyl-α-methyl tryptophan was prepared according to literature[3a] and was coupled to benzyl-ß-aminobenzenebutanoate via its pentafluorophenyl ester to give the benzyl ester. Hydrogenation of this ester using 10% Pd/C under an atmosphere of hydrogen gave the target compounds.

CONCLUSION

These studies have shown how a subset of a series of CCK-B selective ligands give rise to CCK-A selective compounds by inversion of two chiral centres simultaneously.

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