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THE SYNTHESIS AND CCK RECEPTOR AFFINITIES OF SELECTED CARBOXYLIC ACID MIMICS OF CI-988 – A POTENT AND SELECTIVE CCK-B ANTAGONIST

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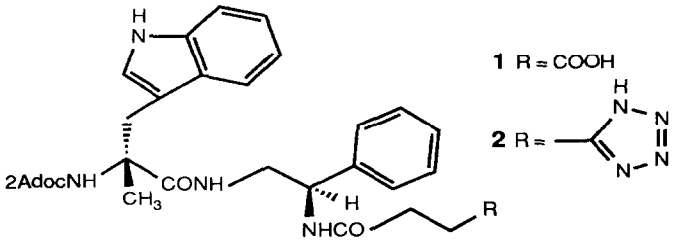
Abstract: Syntheses of selected acid mimics of the CCK-B selective receptor antagonist CI-988 (**1**) are described. The relationship between pK_a and CCK-B binding affinities of these compounds are discussed.

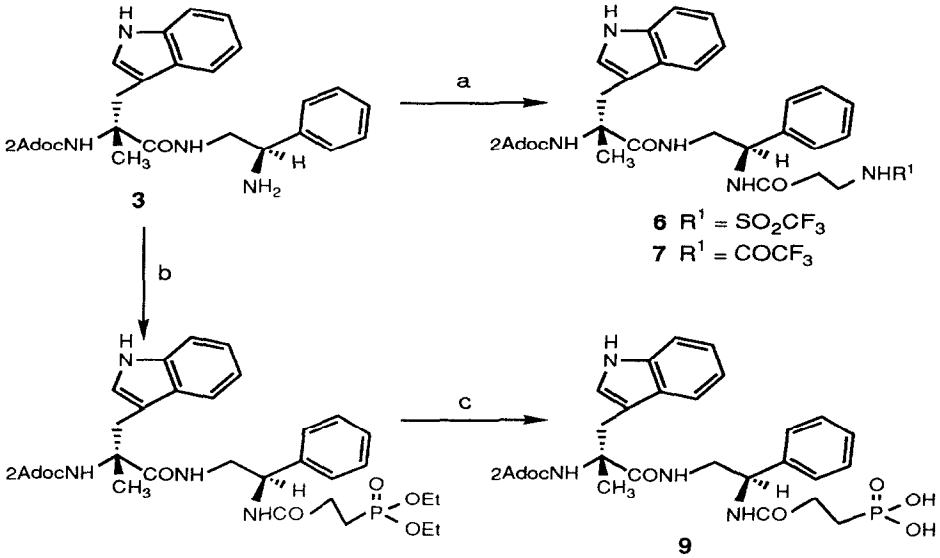
The C-terminal octapeptide of cholecystokinin, CCK-26-33(sulphated), is a hormonal regulator of various gut functions[1-3] which is also found in high concentrations in the CNS, where it seems to play a neurotransmitter or neuromodulatory role[4-6]. We have previously published[7,8] on 'dipeptoid' compounds,eg. **1** (CI-988), rationally designed from the endogenous neuropeptide CCK-26-33(sulphated). These compounds were shown to be potent and selective CCK-B receptor antagonists displaying antianxiety[9] and antigastrin[10] properties.It has also been shown that the presence of a carboxylic acid moiety in R enhances both affinity and selectivity for the CCK-B receptor[8]. The carboxylic acid group has been proposed to mimic the side chain of Asp32 in CCK-26-33(sulphated)[8]. In this publication the synthesis of some selected mimics of the carboxylic acid in compound **1** are described and the relationship between pK_a and CCK-B binding affinity is discussed.



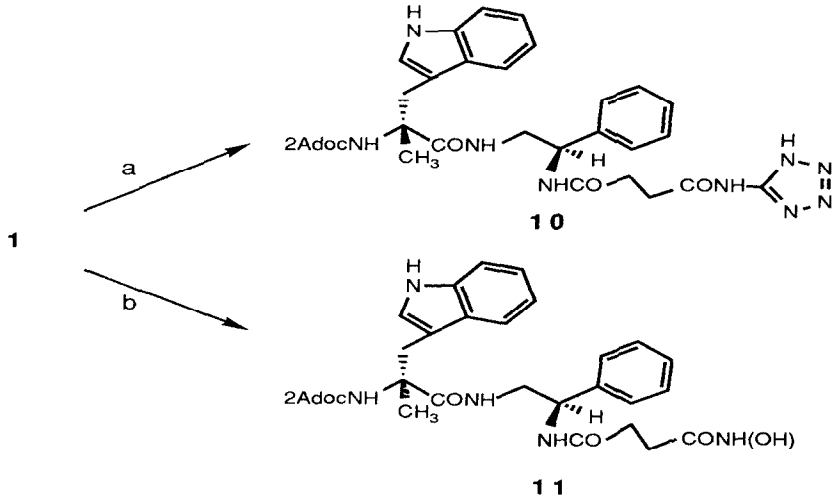
The target acid mimics were all prepared by coupling the previously described amine **3**[7] to a carboxylic acid containing the requisite acid moiety in free or protected form. The synthesis of **1**[7] and **2**[8] are described elsewhere.

The preformed pentafluorophenol(PFP) esters of the β-alanine derived trifluoromethanesulphonyl and trifluoroacetyl derivatives **4** and **5** were treated with the amine **3** to give the sulphonamide **6** and acetamide **7** (Scheme 1). Similarly, coupling amine **3** to the PFP ester of diethylphosphono-3-propionic acid gave the diethyl phosphonate derivative **8**. The free phosphonic acid **9** was

liberated by subsequent treatment of **8** with bromotrimethylsilane (TMSBr) in dichloromethane followed by hydrolysis of the intermediate trimethylsilyl esters with aqueous methanol. The aminotetrazole **10** and hydroxamic acid **11** were prepared by the action of 5-aminotetrazole and hydroxylamine respectively on the PFP ester of the carboxylic acid **1** (Scheme 2).



Scheme 1 a) $HO_2CCH_2CH_2NHR^1$ (**4** R^1=SO_2CF_3, **5** R^1=$COCF_3$), DCC, PFP, EtOAc, **4** (64%), **5** (54%); b) $HO_2CCH_2CH_2P(O)(OEt)_2$, DCC, PFP, EtOAc, (65%); c) (i) TMSBr, CH_2Cl_2; (ii) $MeOH/H_2O$ (43%)



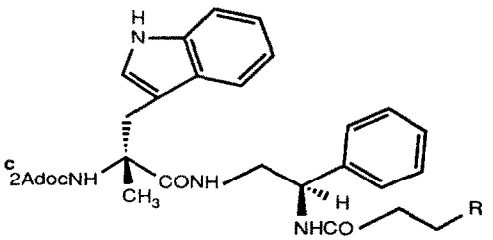
Scheme 2 a) (i) DCC, PFP, DMF; (ii) $H_2N(CHN_4)$ (8%); b) (i) DCC, PFP, DMF; (ii) $NH_2(OH).HCl$, Et_3N (35%)

The use of carboxylic acid mimics to improve the pharmacokinetic profile of drugs is well

known[11]. For each mimic described here, tetrazole **2**, **10**[12], trifluoromethanesulphonamide **6**[13], trifluroacetamide **7**[13], phosphonic acid **9**[14] and hydroxamic acid **11**[15], examples are known where replacement of a carboxylic acid by these groups in other drugs gives compounds of similar or enhanced activity.

In our case the use of the tetrazole moiety, **2**, **10**, which have similar pK_a values to that of the parent carboxylic acid **1**, yielded compounds of similar affinity to **1** but with reduced selectivity (Table 1). However with compounds either more acidic such as the phosphonic acid **9**, or less acidic (**6**, **7** or **11**), both affinity and CCK-B selectivity are reduced. There appears to be no direct correlation between pKa and biological activity in this series since the less acidic hydroxamic acid **11** (pK_a>9.5), has a higher affinity (5 fold) and is 18 fold more selective for the CCK-B receptor, than the more acidic trifluoromethanesulphonamide **6** (pK_a=7.9).

Table 1 CCK Receptor Binding Affinities[a] and pK_a Data[b]



		IC_{50}(nM)			
Compound	R	CCK-B	CCK-A	A/B ratio	pK_a
1	COOH	1.7(1.3-3.7)	4300(1200-8500)	2500	5.6
2	CHN_4[d]	5.6(3.0-8.1)	1070(1000-1100)	190	5.4
6	$NHSO_2CF_3$	77(62-98)	680(620-770)	8	7.9
7	$NHCOCF_3$	89(63-170)	800(680-970)	10	>9.5
9	$P(O)(OH)_2$	23(22-24)	2700(2300-3500)	20	3.4, 7.8
10	$CONH(CHN_4)$[d]	6.3(5.3-7.7)	1200(1100-1500)	190	5.2
11	CONH(OH)	14(8.6-32)	1800(900-1900)	130	>9.5

[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 3 separate experiments. [b] pK_a measurements are obtained by a titration method using a Radiometer VIT90 Video Titrator. The solvent used was 20% aqueous DMF. The values given are the arithmetic mean from at least 3 separate experiments. [c] 2Adoc refers to 2-adamantyloxycarbonyl. [d] CHN_4 represents tetrazole.

It appears therefore that in these carboxylic acid mimics a simple correlation between pK_a and biological activity cannot be drawn. It may be that the geometry (planar vs tetrahedral) and/or charge distribution (point charge vs delocalised charge) of the carboxylic acid mimics are the determining factors for binding affinity. Additional acid mimics are currently being prepared to further investigate the relationship between the geometry/charge distribution and binding affinity. The results will be published elsewhere in a full paper.

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