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The Design and Synthesis of the High Efficacy, Non-peptide CCK_1 Receptor Agonist PD 170292

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Abstract—The design, synthesis and biological actions of a novel, non-peptide CCK_1 receptor agonist (PD 170292) which exhibits a similar pharmacological profile to the CCK analogue JMV180 is reported. PD 170292 was designed based on a consideration of the structures of a peptide based CCK_1 receptor selective agonist and a peptoid CCK_2 receptor selective antagonist.

Introduction

We have devoted considerable effort toward the development of non-peptide ligands that act at receptors which selectively bind, and are activated by, the neuropeptide cholecystokinin (CCK). This research effort has led to the discovery of a variety of non-peptide ligands which differentially bind both the CCK_1 and CCK_2 receptor types.[1] One particular area of interest to us has been the identification of non-peptide agonists for the CCK_1 receptor type, a potential utility for which would be in the treatment of obesity.[2] Our approach to the design of such non-peptide CCK_1 agonists has principally relied upon appending a key feature of the peptide CCK_1 receptor selective agonist A-71623 (**1**) onto a "peptoid" motif which selectively binds the CCK_2 receptor (**2**).[3] This methodology has led to the development of non-peptide, full efficacy CCK_1 receptor selective agonists although with only mediocre potencies e.g. **3** (see Fig. 1).[4]

In this paper we report on the design and synthesis of a derivative of **3** with significantly improved affinity and potency for the CCK_1 receptor type. The target compound PD 170292 (**6**) behaves as an agonist at the high-affinity and as an antagonist at the low-affinity CCK_1 binding sites. It has a pharmacological profile similar to that of the CCK analogue JMV-180.[5] We believe PD 170292 (**6**) to be the first non-peptide derivative to present such a pharmacological profile.

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Chemistry

The starting point in the design of **3** was the phenethylamide derivative **2**. Although this peptoid ligand was one of our preferred CCK receptor ligands at that point in the research programme, it was a sub-optimal selection in that it exhibited only mediocre affinity for the CCK_1 receptor in addition to being selective for the CCK_2 receptor type.[6] Clearly the likelihood of developing a high affinity/high potency CCK_1 receptor agonist would be increased by selecting a starting template with greater affinity for the CCK_1 receptor. To this end we selected compound **4** (PD 149164) as our starting point/template since, although this compound was a CCK_2 receptor selective antagonist, it exhibited ~10-fold improved CCK_1 receptor affinity when compared to **2** in addition to being a full efficacy CCK_1 receptor agonist.[7]

Our strategy for improving CCK_1 receptor recognition essentially remained that of appending the aryl urea substituted Lys side chain in A-71623 (**1**) (thought to be key for imparting CCK_1 receptor affinity/efficacy) onto an appropriate point on the peptoid template. In contrast to our original lead in this research area (**3**), the point of attachment of the substituted Lys was to be the α-carbon of the C-terminal homologated Phe derivative in **4** (see Fig. 2). Thus, the substituted Lys group effectively replaces the 4-fluorophenyl group in **4** to give target compound PD 170292 (**6**). PD 170292 (**6**) was deemed to be structurally more closely related to A-71623 (**1**) than was the case with **3** and, in addition, the compound exhibited obvious structural similarities to a previously

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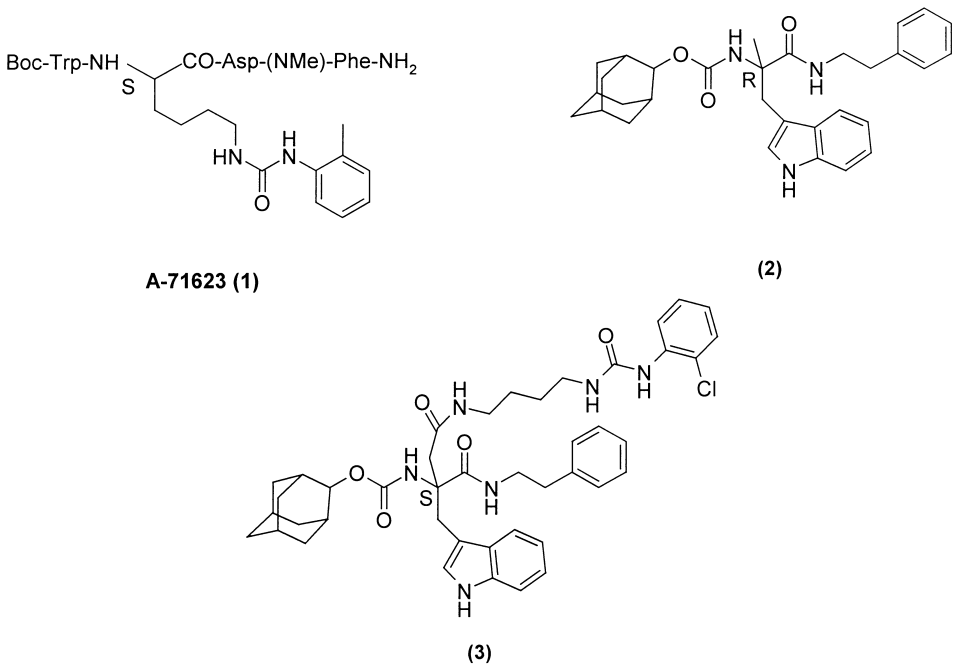


Figure 1.

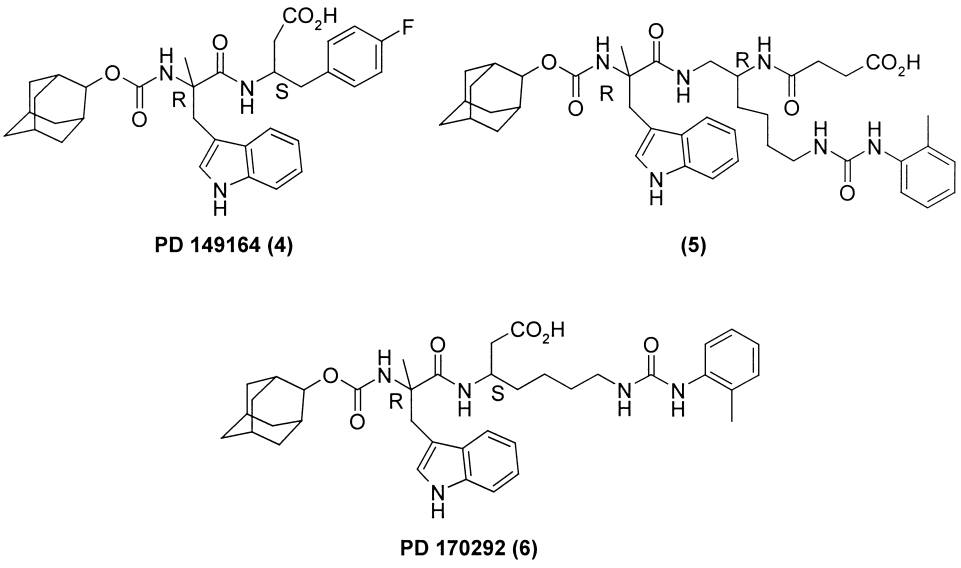


Figure 2.

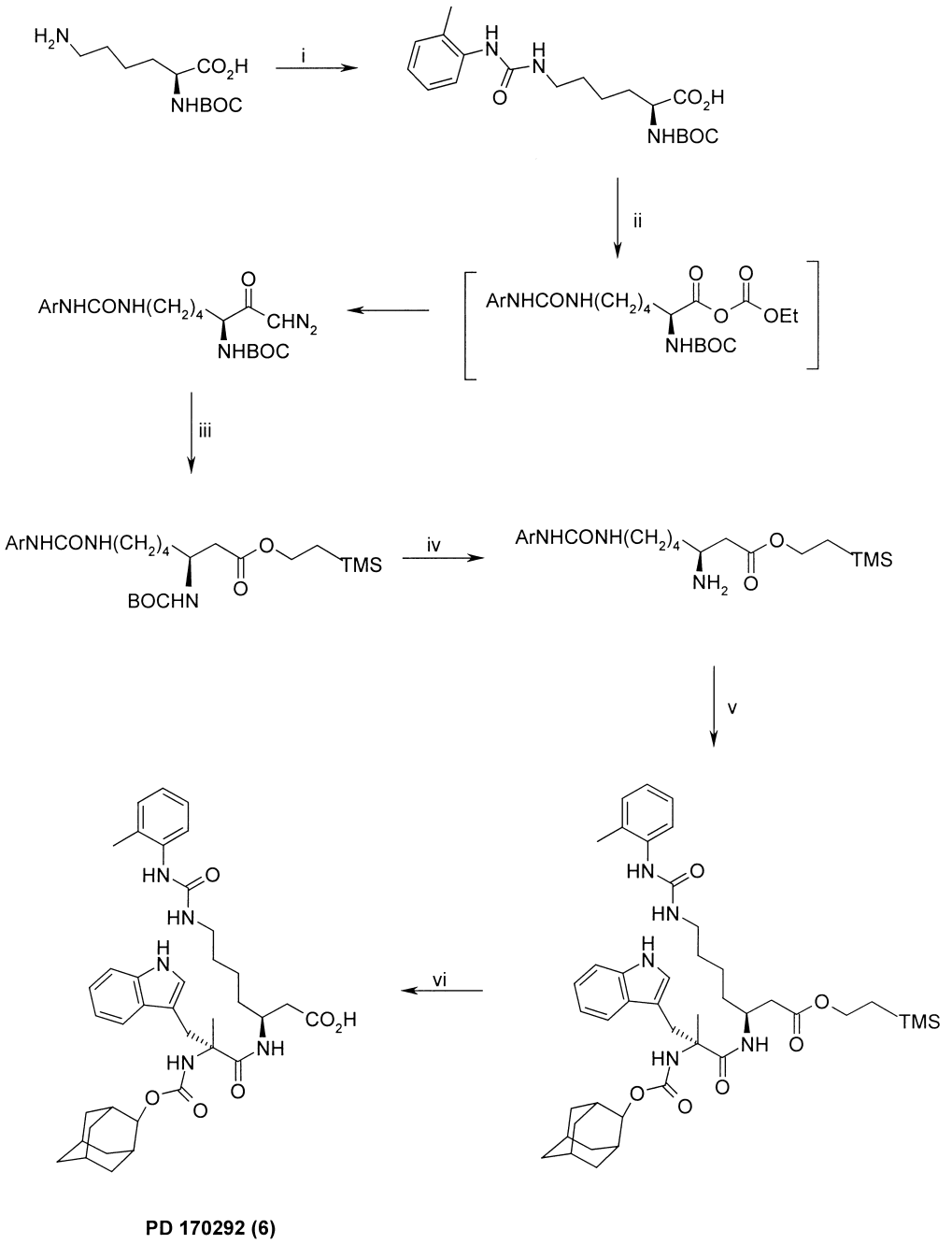
published series of "mixed" CCK_1/CCK_2 receptor agonists e.g., **5**.[8]

Biology

The CCK receptor affinities and functional activities of the target compound **6** are reported in Table 1.

When isolated rat pancreatic acini are incubated with increasing concentrations of CCK-8S, a typical biphasic dose–response curve for amylase secretion is obtained (Fig. 3), with a decrease in the response for supramaximal concentrations of CCK-8. It has been proposed that the occupancy of high affinity sites of receptors by low concentrations of CCK-8S (usually less than 100 pM) is closely related to amylase release while occupancy of low affinity sites by higher CCK-8S concentrations is correlated to the inhibition of amylase secretion.[9,10] PD 170292 (**6**) was able to stimulate amylase release from isolated rat pancreatic acini with similar maximal efficacy as CCK-8S but without causing any decrease of amylase release even at supramaximal concentrations. The present results illustrate that PD 170292 (**6**) behaves like the CCK-8 peptide analogue JMV-180[5,11] being a full agonist at the CCK_1 high affinity sites and an antagonist at the CCK_1 low affinity sites.

In addition to exhibiting high nanomolar affinity for the rat pancreatic CCK_1 receptor, PD 170292 (**6**) was also



Scheme 1. (i) 2-methylphenyl isocyanate, DMF, 60%; (ii) (a) EtO_2CCl, TEA, THF, (b) "CH_2N_2" quant.; (iii) $PhCO_2Ag$, TEA, $TMSCH_2CH_2OH$, 40%; (iv) HCO_2H, quant.; (v) 2-Adoc(R)αMeTrp,[6] HBTU, DIPEA, acid, DMF, 54%; (vi) TBAF, THF, 78%.

Table 1. CCK receptor affinities[13] and CCK_1/CCK_2 receptor functional activity[12, 14] of α,α-disubstituted tryptophan derivatives

Compound	CCK Binding IC_{50} (nM)		Amylase secretion	Calcium mobilisation
	CCK_1	CCK_2	EC_{50} (nM)	EC_{50} (nM)
CCK-8S	1.0	0.30	0.02	2
2	650	32	ND[a]	ND
3	150	3600	480	ND
4 PD 149164	75	0.083	(see ref 7)	ND
6 PD 170292	1.2	6.7	5	Antagonist $IC_{50} = 40$ nM

[a]ND, means value not determined.

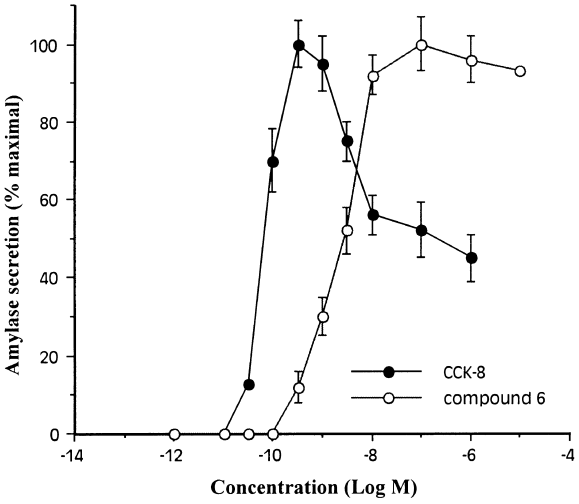


Figure 3. Effects of CCK-8S and PD 170292 (**6**) on amylase release from rat pancreatic acini.

able to recognise CCK_2 receptors in guinea pig brain membranes with similar affinity. Like JMV180, PD 170292 (**6**) acts as an antagonist at the CCK_2 receptor. It was unable to promote $[Ca^{2+}]_i$ mobilisation in Jurkat cells[12] even at a concentration as high as 1 μM. However, it was able to antagonise the effects of CCK-8S on $[Ca^{2+}]_i$ accumulation (IC_{50} 40±10 nM). Interestingly, these findings clearly contrast with those published for **5** which was found to be an agonist at both the CCK_1 and CCK_2 receptor types.[8]

Conclusions

In this paper we have demonstrated the design and synthesis of a novel, non-peptide CCK_1 receptor agonist. PD 170292 (**6**) behaves as a full agonist at the high affinity sites and as an antagonist at the low affinity sites of the CCK_1 receptor. In addition to demonstrating both high efficacy and potency for the CCK_1 receptor type, compound **6** [15] has also been shown to be a high affinity CCK_2 receptor antagonist.

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