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SAR STUDY OF THE INDOLE MOIETY OF CI-988, A POTENT AND SELECTIVE CCK-B ANTAGONIST

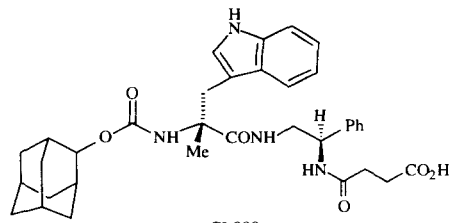
Corinne E. Augelli-Szafran,*[†a] Terri S. Purchase,[†a] Bruce D. Roth,[†a] Bradley Tait,[†a] Bharat K. Trivedi,[†a] Michael Wilson,[†a] Nirmala Suman-Chauhan,[‡b] and Louise Webdale,[‡b]

Departments of Medicinal Chemistry† and Pharmacology‡, [a]Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor Michigan, 48105, U.S.A. and [b]Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Hills Road, Cambridge CB2 2QB, UK

Abstract: Due to the interesting pharmacological activity observed for CI-988, a potent and selective CCK-B receptor antagonist, we have continued to study the SAR of this antagonist. This particular study examines the importance of the indole moiety for binding affinity. The synthesis and receptor binding affinity for analogs containing functionalized indole derivatives and replacing the indole with various heterocycles are reported.

Two receptor subtypes for cholecystokinin (CCK), a 33 residue polypeptide, are presently known.[1] CCK-A receptors are distributed mainly in peripheral tissue such as gall bladder and pancreas, while CCK-B receptors are located mainly in the central nervous system. The role of CCK in anxiety/panic disorders, acting via interactions with the CCK-B receptors, has been explored. Selective antagonists of this receptor are known to produce anxiolytic-like effects in both animal models[2] and humans.[3] Thus, it has been postulated that CCK-B receptor antagonists could represent a novel treatment for CNS disorders such as anxiety and panic attacks. Recently, the pharamcological profiles of a number of diverse antagonists have been described.[4]

Previous work in our laboratories[5] led to the development of dipeptoid CCK-B receptor antagonist, CI-988, which exhibits potent and selective antagonism at the CCK-B receptor.[5a] Due to the encouraging biological results of CI-988, we felt that SAR studies at both the C- and N- terminus might expand our understanding of the structural requirements for potency and selectivity. It was determined that the optimal moiety for potent CCK-B receptor binding at the N-terminus is [(2-adamantyloxy)carbonyl]-α-methyl-(*R*)-tryptophan.[5a,6] SAR studies at the C-terminus examined various side chains of CI-988.[5,6b,7] In this particular study, the effect of replacing the indole moiety of CI-988 with heterocycles and the effect of substituents on the indole ring were examined.



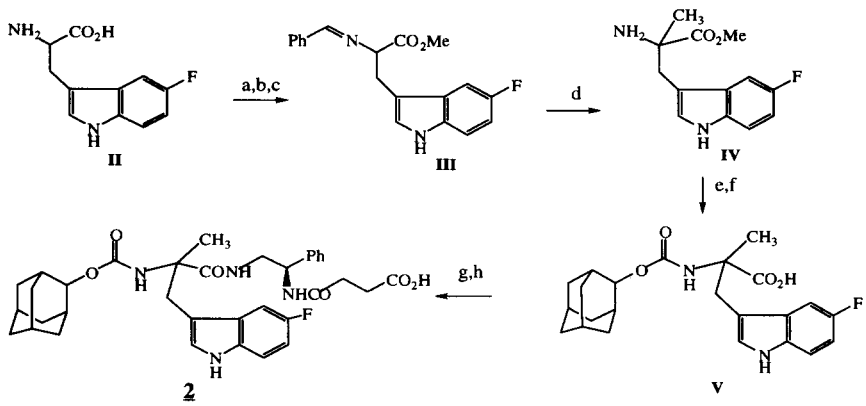
CI-988

Chemistry

Examples **1–5** (Table 1) were synthesized from 5-fluoro-D,L-tryptophan (**II**) via the route illustrated in Scheme 1. Methyl ester (**IV**) was obtained by condensation of ester (**II**) with benzaldehyde, followed by subsequent alkylation of **III** with methyl iodide[8a]. Treatment of **IV** with 2-adamantyl chloroformate,[5a] followed by hydrolysis yielded acid (**V**). Coupling of **V** with N-(2-amino-1-phenylethyl)succinamide benzyl ester[8b] gave

example **1**. Hydrogenation (20% Pd/C, H_2) of **1** gave **2**. Example **3** was isolated by chromatography of **2** (silica gel, 65% EtOAc/hexane). Examples **4** and **5** were synthesized via this same route, excluding alkylation with methyl iodide. For examples **7** and **19**, the appropriate indole analog of acid (**V**) was coupled with phenethylamine and 2-(*S*)-amino-1-(*S*)-1,3-propanediol, respectively.

Scheme 1

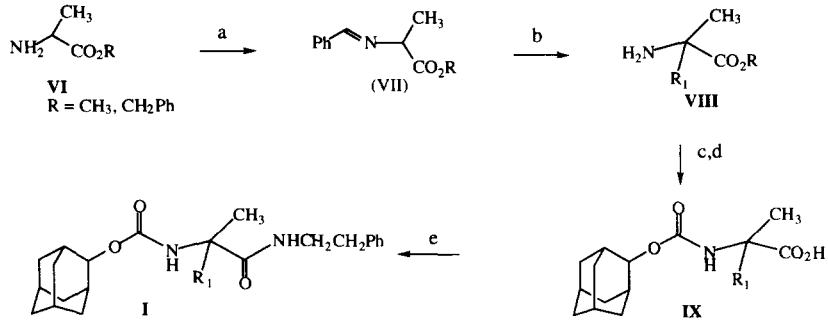


(a) MeOH/HCl; (b) 1 M K_2CO_3/Et_2O; (c) PhCHO, $MgSO_4$, THF, 25 °C; (d) LDA, CH_3I, 0.6 M citric acid, 1.35 M K_2CO_3, 0 °C to 25 °C; (e) 2-adamantyl chloroformate, NEt_3, THF, 25 °C; (f) LiOH, dioxane/H_2O, 25 °C; (g) N-(2-amino-1-phenylethyl)succinamide benzyl ester, HOBt, DCC, EtOAc, 25 °C; (h) 20%Pd/C, H_2, THF, 25 °C.

Examples **8–16** (Table 1) were synthesized via the route illustrated in Scheme 2. Condensation of amine (**VI**) with benzaldehyde, followed by alkylation with various halides (R_1X)[8a] yielded ester **VIII**. Treatment of **VIII** with 2-adamantyl chloroformate, then hydrogenation (20% Pd/C, H_2) or hydrolysis (LiOH) yielded acid (**IX**). Coupling of **IX** with phenethyl amine gave analogs of **I**, in which the indole moiety is replaced with various heterocycles. The alkyl halides used in the synthesis of **8**, **10**, **11**, **14**, **16**, **23**, and **24** were commercially available. (For **23** and **24**, acid (**IX**) was coupled with 2-(*S*)-amino-1-(*S*)-phenyl-1,3-propanediol.[8b]) Example **9** was isolated by the removal of the phthalimide of **8** with hydrazine/EtOH. Formation of the primary alcohol of benzotriazole with 36% CH_2O/H_2O, followed by treatment with thionyl chloride, gave the desired alkyl halide needed for the synthesis of **12**. The bromide for **13** was synthesized by treating 3-methylbenzofuran-2-carboxylic acid with dimethylamine, followed by NBS. For example **15**, intermediate **VIII** of **13** was coupled with the adamantyl chloroformate and treated with borane to give the desired intermediate **IX**. The appropriate bromides for **6**, **16**, and **17** were synthesized by alkylating benzyl methyl malonate with either α, α′-dibromo-*o*-xylene or 1,8-bis(bromomethyl)-naphthalene in the presence of NaH. Reduction of the benzyl ester (20% Pd/H_2), followed by coupling with 2-adamantanol using diphenylphosphoryl azide and triethylamine, followed by hydrolysis (LiOH) gave acid **IX**.

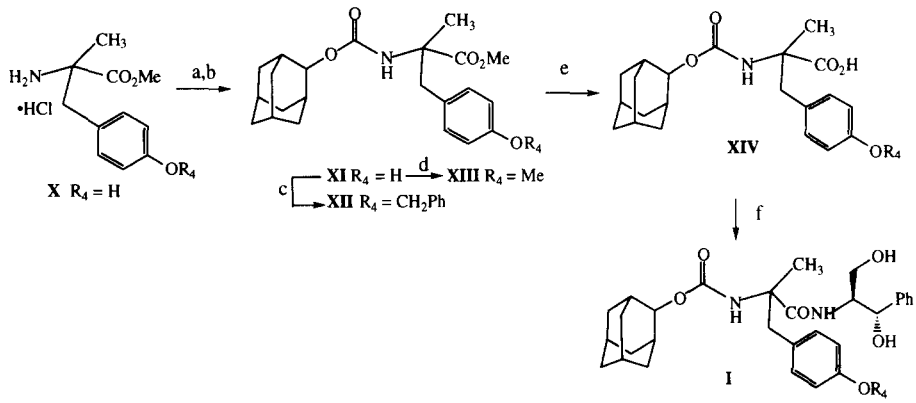
Scheme 3 illustrates the synthesis of **20–22**. Coupling of α-methyl-D,L-tyrosine methyl ester (**X**) with 2-adamantyl chloroformate gave **XI**. Acid (**XIV**) was obtained by treatment of **XI** with benzyl chloride or methyl iodide to give **XII** and **XIII**, respectively,and then hydrolysis (LiOH). Coupling of **XIV** with 2-(*S*)-amino-1-(*S*)-1,3-propanediol yielded the corresponding amide (**I**) (R_4 = OPh, OH, OMe, examples **20–22**, respectively).

Scheme 2



(a) PhCHO, $MgSO_4$, THF, 25 °C; (b) LDA, R_1X, 0.6 M citric acid, 1.35 M K_2CO_3, 0 °C to 25 °C; (c) 2-adamantyl chlorformate, NEt_3, THF, 25 °C; (d) 20%Pd/C, H_2, THF, 25 °C or LiOH, dioxane/H_2O, 25 °C; (e) $NH_2CH_2CH_2Ph$, HOBt, DCC or EDCI, EtOAc or CH_2Cl_2, NEt_3, 25 °C.

Scheme 3



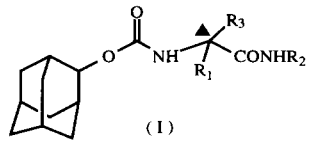
(a) 0.001 M K_2CO_3/EtOAc; (b) 2-adamanyl chloroformate, NEt_3, THF, 25 °C; (c) $PhCH_2Cl$, K_2CO_3, CH_3CN, Δ; (d) CH_3I, K_2CO_3, CH_3CN, Δ; (e) LiOH, dioxane/H_2O; (f) 2-(*S*)-amino-1-(*S*)-1,3-propanediol, HOBt, DCC, EtOAc, 25 °C.

Results and Discussion

It had previously been shown that the N-terminal carbamate alkyl moiety required a cycloalkyl or a bulky substituent rather than a straight chain or aromatic hydrocarbon to achieve micromolar CCK-B receptor affinity.[6a] A study of bulky, fused C-10 cyclic systems led to the 2-adamantyl group which has been shown to be the optimal N-terminus necessary for potent CCK-B binding. However, a variety of side chains at the C-terminus were utilized. Examples **1–6** have the same side chain as CI-988, whereas **7–18** and **19–24** utilize phenethyl amine and 2-(*S*)-amino-1-(*S*)-1,3-propanediol, respectively, side chains that could be synthesized more easily. Since the parent compounds (**7**[5a] and **19**[8b]) both showed good affinity for the CCK-B receptor (IC_{50} = 32 nM and 6.1 nM, respectively), we felt that **7** and **19** would be reasonable reference compounds for this SAR study.

Previous efforts in our laboratories focused on optimizing the C- and N-terminal regions of CI-988. This study focused on modifying the central α-methyl tryptophan moiety. Based on this SAR study, very little

TABLE 1.



(I)

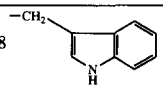
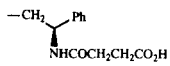
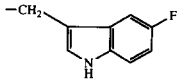
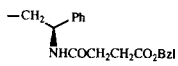
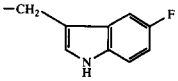
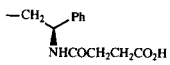
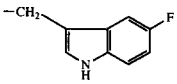
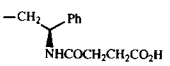
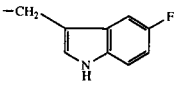
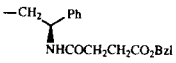
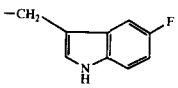
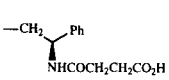
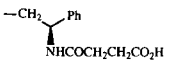
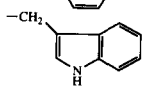
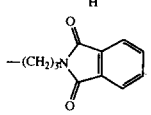
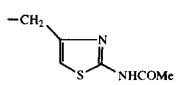
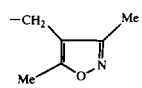
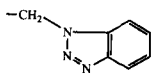
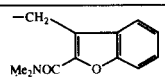
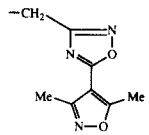
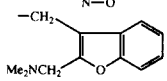
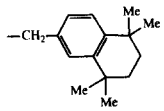
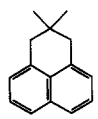
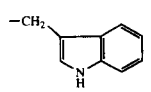
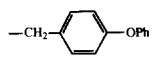
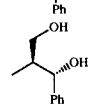
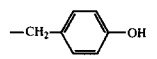
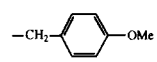
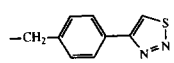
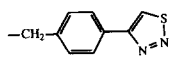
Example	R_1	R_2	R_3	▲	IC_{50}(nM)[a] CCK-A	IC_{50}(nM)[a] CCK-B	A/B Ratio
CI-988			CH_3	*R*	4300	1.7	2500
1			CH_3	*R*,*S* (1:1)[b]	2649	129	21
2			CH_3	*R*,*S* (1.2:1)[b]	2185	8.2	266
3			CH_3	*S*	2859	58	49
4			H	*R*,*S* (1:1)[b]	583	2820	0.20
5			H	*R*,*S* (1:1)[b]	1909	693	3
6			----	----	1350	1910	0.70
7[e]		-CH_2CH_2Ph	CH_3	*R*	650	32	20
8		-CH_2CH_2Ph	CH_3	*R*,*S*	c	8%@1 μM	d
9	-$(CH_2)_3NH_2$	-CH_2CH_2Ph	CH_3	*R*,*S*	c	3%@1 μM	d
10		-CH_2CH_2Ph	CH_3	*R*,*S*	5349	877	6
11		-CH_2CH_2Ph	CH_3	*R*,*S*	6939	2280	3
12		-CH_2CH_2Ph	CH_3	*R*,*S*	3620	2169	1.7

TABLE 1 (cont'd).

Example	R_1	R_2	R_3	▲	IC_{50}(nM)[a] CCK-A	IC_{50}(nM)[a] CCK-B	A/B Ratio
13		-CH_2CH_2Ph	CH_3	*R,S*	65	125	0.5
14		-CH_2CH_2Ph	CH_3	*R,S*	20%@10 μM	28%@10 μM	d
15		-CH_2CH_2Ph	CH_3	*R,S*	c	171	d
16		-CH_2CH_2Ph	CH_3	*R,S*	19800	1559	13
17		-CH_2CH_2Ph	---	---	22%@10 μM	20390	d
18		-CH_2CH_2Ph	---	---	7220	6780	1.1
19[f]			CH_3	*R*	681	6.1	117
20			CH_3	*R,S*	616	141	4
21			CH_3	*R,S* (1:1)[b]	c	200	d
22			CH_3	*R,S* (1:1)[b]	43%@1 μM	68	d
23			CH_3	*R* or *S*	c	342	d
24			CH_3	*R* or *S*	c	1540	d

[a]IC_{50} represents the concentration (nM) producing half maximal inhibition of specific binding of [^{125}I] Bolton-Hunter-labeled CCK-8 to CCK receptors in the mouse cerebral cortex (CCK-B) or the rat pancreas (CCK-A). For compounds tested more than once, the value given is the geometric mean. Complete protocol of both assays is described by Boden et al.[6b] [b]HPLC conditions: [Hypersil BDS, 250 x 4.6 mm, 5 μm column; 55:45 CH_3CN:buffer (0.5 M $NH_4H_2PO_4$, 0.5% TEA), pH 3.0]. [c]Not tested. [d]Not determined. [e]See ref 5a for preparation. [f]See ref 8b for preparation.

structural variation is tolerated in this region of the molecule. Remarkably, even the very conservative 5-fluoro-substituted indole analog (**2**) was five times less potent and ten times less selective than CI-988. Consistent with previous studies,[5d] analogs that lacked the α-methyl group in the tryptophan moiety (**5**, **6**, **17**, and **18**) also displayed reduced binding affinity. Not surprisingly, analogs possessing the N-terminus phenethyl amide moiety (**8–18**) were significantly less potent. Improved activity was obtained with the more optimal phenylpropanediol N-terminus (**19–24**).

In conclusion, "dipeptoids" in which the indole ring of CI-988 has been replaced with various heterocycles and substituted indole derivatives, have been synthesized and studied as potential CCK-B receptor ligands. The results from this study (Table 1) indicate that the binding site of the CCK-B receptor prefers the indole ring and does not tolerate the heterocycles.The only compound that maintained affinity for the CCK-B receptor similar to that of CI-988 was **2**. However, the 5-fluoro-substituent of **2** caused a ten-fold reduction in selectivity for the CCK-B vs CCK-A receptor.

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