Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2259–2262

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

L-TRYPTOPHAN UREA AMIDES AS NK_1/ NK_2 DUAL ANTAGONISTS

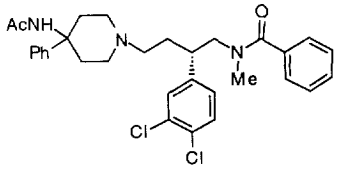
Hongbo Qi,* Shrenik K. Shah, Margaret A. Cascieri,† Sharon J. Sadowski,† and Malcolm MaCcoss

Department of Medicinal Chemistry and Department of Molecular Pharmacology & Biochemistry†
Merck Research Laboratories, Rahway, New Jersey, 07065, U.S.A.

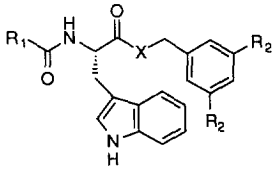
Received 24 February 1998; accepted 21 July 1998

Abstract: We report that a systematic modification of an NK_1 receptor selective antagonist resulted in the identification of novel compounds, **4c** and **4d**, with high affinity for both NK_1 and NK_2 receptors.

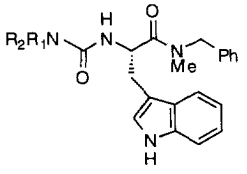
The neuropeptides, Substance P (SP) and Neurokinin A (NKA), function as neurotransmitters in the peripheral and central nervous system, where they predominantly interact with the Neurokinin 1 (NK_1) and Neurokinin 2 (NK_2) receptors, respectively.[1] The release of SP and NKA stored in afferent nerves in the airways by various stimuli has been shown to cause excessive mucus secretion, airway constriction, and plasma extravasation. Since these effects are very similar to the typical clinical symptoms of asthma, it has been suggested that both SP and NKA might be involved in the pathology of asthma.[2] Thus, a dual NK_1/NK_2 antagonist might offer a novel method for the treatment of asthma. When this work was initiated, a macrocyclic peptide FK-224, a dual antagonist of the NK_1 and NK_2 receptors (NK_1 IC_{50} = 37 nM, NK_2 IC_{50} = 72 nM), was reported to provide some protection against bradykinin induced bronchoconstriction in asthmatic patients.[3] Recently, dual NK_1 and NK_2 antagonists were obtained by modification of the NK_2 selective compound SR48968.[4] In this paper, we report on the design and synthesis of L-tryptophan based NK_1/NK_2 dual antagonists derived from the NK_1 selective L-tryptophan benzyl ester **1** reported previously from these laboratories.[5]



SR 48968
NK_1 IC_{50} = 800 nM
NK_2 IC_{50} = 0.13 nM



1: R_1 = Me, R_2 = CF_3, X = O
2: R_1 = NHMe, R_2 = Me, X = O
3: R_1 = Ph, R_2 = Me, X = NMe



4

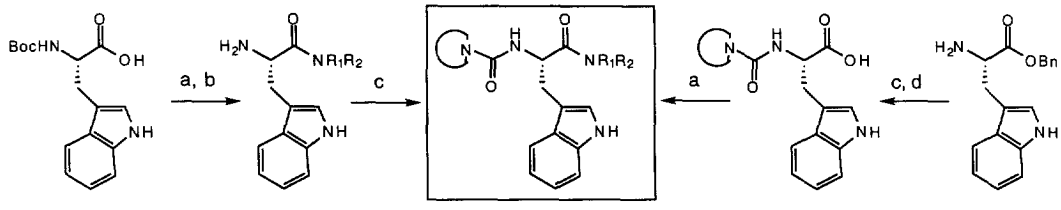
L-Tryptophan benzyl esters have been reported to be selective NK_1 antagonists. 3,5-Disubstitutions on the benzyl group, especially by CF_3 (**1**, NK_1 IC_{50} = 1.6 nM, NK_2 IC_{50}>5 μM), can markedly enhance the activity for NK_1 receptors. It was also found that a variety of substituents on the amino acid nitrogen were tolerated for high NK_1 receptor affinity, for example, the acetamide, methyl carbamate and *N*-methyl urea (**2**, NK_1 IC_{50} = 103 nM, NK_2 IC_{50} > 5 μM) were all NK_1 antagonists.[5] However, on the C-terminus of the molecule, replacement of the benzyl ester with the tertiary benzyl amide (**3**, NK_1 IC_{50} > 1.1 μM, NK_2 IC_{50} > 5

0960-894X/98/$ - see front matter
PII: S0960-894X(98)00395-3

μM) resulted in compounds with poor affinity for NK_1 and NK_2 receptors. In comparing **1** with the NK_2 selective antagonist SR48968,[6] it occurred to us that the 3,4-dichloro phenyl and the indolymethyl moieties might interact with the receptors in a similar fashion. Also, the phenyl group of the amide in compound **2** and the phenyl group of benzamide in SR48968 are connected by four single bonds to the indolylmethyl or 3,4-dichloro phenyl. Because of the flexibility of the substituents on the nitrogen for NK_1 activity in the tryptophan ester series, we rationalized that by incorporating the piperidine type functionality of SR48968 into the tryptophan ester or amide system to form an urea might result in compounds possessing both NK_1 and NK_2 receptors affinity .

The synthesis of the L-tryptophan urea amides was straightforward and is shown in **Scheme I**. For easy modification of the N-terminal urea, Method A was used. N-Boc-L-Trp was coupled with the appropriate amine under the standard coupling conditions (EDC/HOBT) and the Boc was removed by treatment with trifluoroacetic acid. The resulting amine was sequentially reacted with 1,1'-carbonyldiimidazole (CDI) and then selected substituted piperidines to afford the urea analogs. Alternatively, the process was reversed for more convenient C- terminal modification (Method B). Thus, urea formation between L-Trp-OBn and the piperidines, followed by deprotection of the benzyl ester via catalytic hydrogenation afforded the common carboxylic acid intermediate, which was converted to the desired products by coupling with various amines under standard conditions.

Scheme I

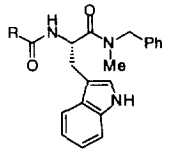


Reagents: (a) EDC, HOBt, NMM, R_1R_2NH, CH_2Cl_2; (b) TFA, Anisole; (c) CDI, Azacycles, THF; (d) H_2, Pd/C, EtOH

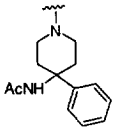
Binding affinities for these compounds on NK_1 were determined using ^{125}I-Tyr^8-SP at a concentration equivalent to its K_d (0.1 nM) on the human NK_1 receptor, stably expressed in CHO cell as previously described.[7] A similar protocol was used for NK_2 activity where cloned human NK_2 receptors expressed in CHO cells and ^{125}I -NKA as ligand were employed. A series of compounds with various substituted piperidines on the urea portion was prepared while the *N*-methyl benzyl amide moiety was retained at the C-terminus of the molecules (**Table I**). Incorporation of the piperidine moiety from SR48968 into the L-Trp urea provided a compound (**4a**) with moderate affinity for NK_1 and NK_2 receptors (IC_{50} NK_1/NK_2 = 77/928 nM respectively). Further modification of the piperidine with a 4- spiroindeno or 4-spiroindano piperidine resulted in **4b** (68/18 nM) and **4c** (56/27 nM) with improved NK_2 binding while still retaining NK_1 activity of **4a**. Compound **4d,** incorporating a 4-spiroindolinosulfonamide piperidine in the urea portion, was the most potent

and balanced antagonist in this series with an IC_{50} of 14 nM on NK_1 and 24 nM on NK_2. The R-enantiomer of **4d**, (**4d'**), (164/577 nM) was prepared from D-Trp and it was found to have substantially less affinity for both NK_1 and NK_2 receptors. Thus, the *S*-stereochemistry was preferred.

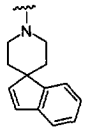
Table I Affinity of L-Trp Ureas **4** for the Cloned Human NK_1 and NK_2 Receptors.[8]



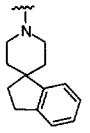
4



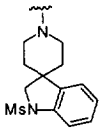
Ra



Rb



Rc

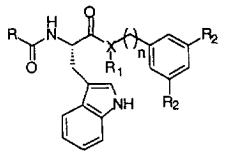


Rd

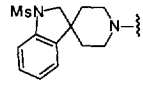
Compound	R	IC_{50} (nM) hNK_1	hNK_2	Compounds	R	IC_{50} (nM) hNK_1	hNK_2
4a	Ra	77	928	**4d**	Rd	14	24
4b	Rb	68	18	**4d'** (*R*)	Rd	164	577
4c	Rc	56	27				

After modification of the urea portion, the SAR on the amide portion was studied (**Table II**). To test whether an amide was necessary for dual activities, two esters, **5a** and **5b**, were prepared. With no substitutions on the benzyl group, **5a** (23/4500 nM) maintained affinity on the NK_1 receptor but lost NK_2 activity compared to the amide **4d** (14/24 nM). As expected, inclusion of the 3,5-di-CF_3 substituents as in **5b** (0.58/>1000 nM) resulted in a much higher affinity at NK_1 receptor but poorer affinity at NK_2 receptor. In the amide series, **5c** (10/1400 nM) with 3,5-diMe substituents and **5d** (1.0/4200 nM) with 3,5-diCF_3 substituents also showed enhanced NK_1 receptor affinity and diminished activity at NK_2 receptor compared with **4d**.

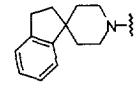
Table II Affinity of L-Trp Ureas **5** and **6** for the Cloned Human NK_1 and NK_2 Receptors



5: R=



6: R=

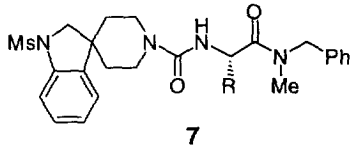


Compound	X	R_1	R_2	n	IC_{50} (nM) hNK_1	hNK_2
5a	O		H	1	23	4500
5b	O		CF_3	1	0.58	>1000
4d	N	Me	H	1	14	24
5c	N	Me	Me	1	10	1400
5d	N	Me	CF_3	1	1.0	4200
6a	N	H	H	0	39%@3000	2100
6b	N	H	H	1	227	14
6c	N	H	H	2	332	211
4c	N	Me	H	1	56	27
6d	N	Et	H	1	242	139

Since an unsubstituted benzyl amide was required for dual affinity, we then investigated the distance between the phenyl and the amide nitrogen as well as the substitutions on the nitrogen in the spiroindane series (**6**). Among the N-H derivatives, a single methylene was found to be optimal (compare **6b** with **6a** and **6c**, **Table II**). The preferred nitrogen substitution was found to be R_1 = Me (compare **4c** with **6b** and **6d**, **Table II**).

We also studied the replacement of the indolylmethyl group with a phenethyl or benzyloxy methyl by starting with L-homophenylalanine or *O*-benzyl-L-serine, respectively, using a similar synthetic route. These replacements resulted in the loss of affinity at both receptors.

Table III Affinity of Ureas **7** for the Cloned Human NK_1 and NK_2 Receptors.



7

Compounds	R	IC_{50} (nM) hNK_1	hNK_2
7a	$PhCH_2CH_2$-	1100	166
7b	$PhCH_2OCH_2$-	480	258

In conclusion, systematic modification of an NK_1 receptor selective antagonist resulted in the identification of novel compounds, **4c** and **4d**, with high affinity for both NK_1 and NK_2 receptors.

Acknowledgment. We would like to thank Amy Bernick for mass spectrometry support.

References and Notes

1. For reviews of neurokinin receptors and neurokinin receptors antagonists see: (a) Maggi, C. A.; Manzini, S. *Drugs and the Lung* **1994**, 507. (b) Rees, D. *Annu. Rep. Med. Chem.* **1993**, *28*, 59. (c) Longmore, J.; Swain, C. J.; Hill, R. G. *Drug News and Perspectives* **1995**, *8*, 5. (d) Regoli, D.; Boudon, A.; Fauchere, J. *Pharmacol. Rev.* **1994**, *46*, 551.
2. For reviews of the role of the neurokinins in the airway functions see: (a) Lowe, III J. A.; Snider, R. M.; *Annu. Rep. Med. Chem.* **1993**, *28*, 99. (b) Lundberg, J. M.; *Can. J. Physiol. Pharmacol.* **1995**, *73*, 908. (c) Maggi, C. A.; Giachetti, A.; Dey, R. D.; Said, S. I. *Physiological Reviews* **1995**, *75*, 277. (d). Piedimonte, G. *Exp. Lung Res.* **1995**, *21*, 809.
3. Ichinose, M.; Nakajima, N.; Takahashi, T.; Yamauchi, H.; Inoue, H.; Takishima, T. *Lancet* **1992**, *340*, 1248. However, later clinical trials do not seem to confirm these results. Schmidt, D.; Jorres, R. A.; Rabe, K. F; Magnussen, H. *Eur. J. Clin. Pharmacol.*, **1996**, *50*, 269
4. Burkholder, T. P.; Kudlacz, E. M.; Le, T.; Knippenberg, R. W.; Shatzer, S. A.; Maynard, G. D.; Webster, M. E.; Horgan, S. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 951.
5. Macleod, A. M.; Merchant, K. J.; Brookfield, F.; Kelleher, F.; Stevenson, G.; Owens, A. P.; Swain, C. J.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Strader, C. D.; MacIntyre, D. E.; MetzgerJ. M.; Ball, R. G.; Baker, R. *J. Med. Chem.* **1994**, *37*, 1269
6. Advenier, C.; Rouissi, N.; Nguyen, Q. T.; Emonds-Alt, X.; Breliere, J.; Neliat, G.; Naline, E.; Regoli, D. *Biochem. Phys. Res. Commun.* **1992**, *184*, 1418.
7. Cascieri, M. A.; Ber, E.; Fong, T. M.; Sadowski, S.; Bansal, A.; Swain, C.; Seward, E.; Frances, B.; Burns, D. Strader, C. D. *Mol. Pharmacol.* **1992**, *42*, 458.
8. Each reported IC_{50}s is the average of three independent determinations.