Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 15, pp. 2037-2042, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00353-3

1,4-BENZODIAZEPIN-2-ONE DERIVED NEUROKININ-1 RECEPTOR ANTAGONISTS.

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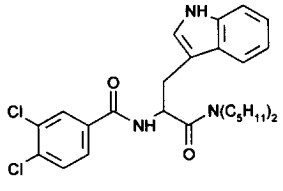
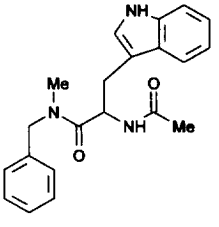
Abstract The identification of a series of 1,4-benzodiazepin-2-one derived NK_1 receptor antagonists is described and a bioactive conformation is proposed. © 1997 Elsevier Science Ltd.

The structural similarities between G-protein coupled 7-transmembrane receptors have been the focus of a great deal of research. The advent of site-directed mutagenesis, used in tandem with photoaffinity labelling studies, has begun to provide the means of studying the key interactions between receptors and their ligands.[1] Intriguingly, the structural similarities between receptors appears to have a corollary with the structural similarities between non-peptide agonists/antagonists that have been discovered for these systems.[1b] This has led to the concept of so-called "privileged structures" which occur repeatedly in pharmacologically active compounds.[2] Hence, these key motifs, such as diphenylmethane and 1,4-benzodiazepine, are increasingly being incorporated into combinatorial libraries directed at medicinal targets.[3]

We have been fascinated for some time by the structural similarities between the gastrin/cholecystokinin (CCK) and neurokinin (NK) receptors and their ligands. Both families have peptide agonists as their natural ligands and both, according to initial evidence, bind non-peptide ligands in a common pocket between the transmembrane helices, at a site distinct from the natural agonist binding site.[1b] Furthermore, at the simplest level the peptidic antagonists reported for these systems are also highly similar e.g. **(1)** and **(2)**.[4]



CCK_A IC_{50} 190nM[4a]
(1)



NK_1 IC_{50} 750nM[4b]
(2)

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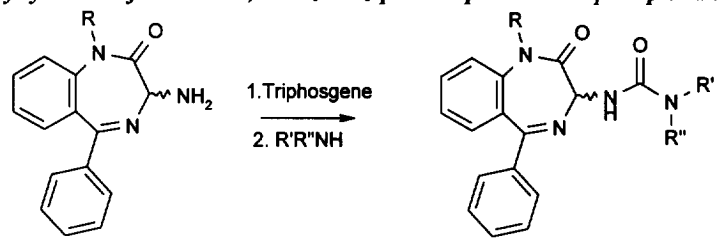
The classical non-peptide antagonists for the CCK receptors were developed by Freidinger *et al.* by simplifying and refining the structure of the natural product asperlicin to give the 1,4-benzodiazepines L-364,178 and L-365,260, selective antagonists of the CCK_A and CCK_B receptor subtypes respectively.[5] The benzodiazepine template has subsequently been used by many workers in other fields.[6] Herein we report the identification of benzodiazepine-derived NK_1 receptor antagonists, NMR studies on these compounds and initial structure-activity relationships around this novel series.

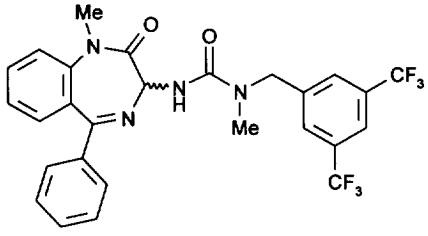
Results and Discussion.

At the outset of our programme the precise structural requirements of the NK_1 receptor were unclear. We therefore screened a wide variety of benzodiazepines which had been previously prepared for our gastrin/CCK programmes but failed to identify any active compounds. Similarly a small library of 50 compounds weighted towards aromatic derivatives (Figure 1) did not produce any active leads ($pK_i > 7$).[7]

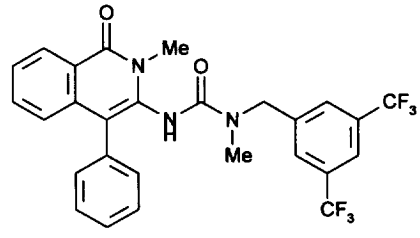
Figure 1. ***Array synthesis of 3-ureido-1,4-benzodiazepines as potential NK_1 receptor antagonists***



Although libraries of such size and diversity are limited, this set included compound **(3)** which incorporates the 3,5-bis(trifluoromethyl)benzyl side-chain, a common structural feature in NK_1 receptor antagonists from Merck[8] and, more recently, in compounds from Takeda such as **(4)**.[9] The Takeda compound was developed using a strategy which also looked to derive ligands for the NK_1 receptor based on the perceived similarities between the gastrin/CCK and NK_1 receptor antagonists.



(3)

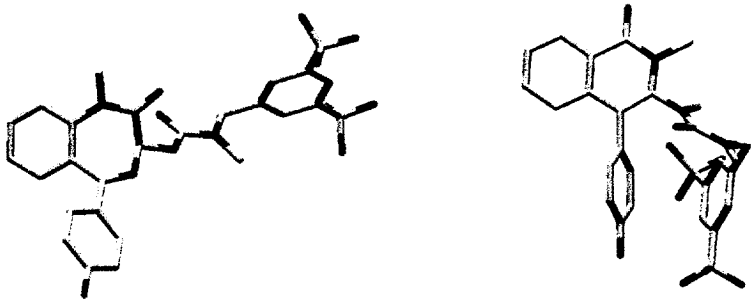


(4)

The NK_1 receptor has proven to be extremely promiscuous - a wide variety of effective templates have now been described.[10] To date, most of these templates contain two aryl rings which can adopt an orientation that will allow a π–π interaction in at least some of their accessible low-energy conformations;[11] for example Takeda have described modelling which shows that an analogue of **(4)** can lie in just such a conformation (Figure 2).[9] It has been proposed that this stacking of the two aryl rings is important in the bioactive conformation.[12]

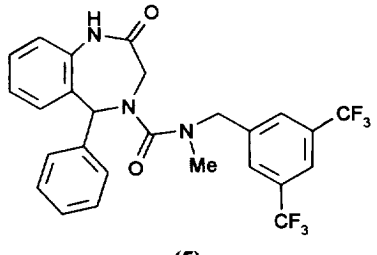
The data available from both X-ray analysis and NMR studies in solution suggest that the C-3 substituted 1,4-benzodiazepines such as **(3)** tend to adopt an extended conformation[2a] (Figure 2) keeping the aromatic rings some distance apart, and this may explain the failure to identify a NK_1 receptor antagonist from within this series.

Figure 2. ***Low energy conformations of (3) and (4).***



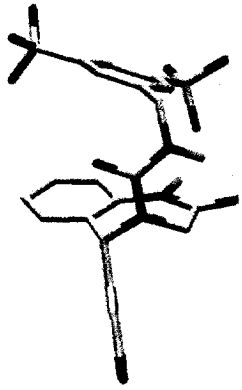
(3) **(4)**

Molecular modelling[13] of an alternative 1,4-benzodiazepine template **(5)** suggested that, of the available low energy conformations, **(5)** has two energetically accessible pseudo-boat conformations in which two of the aromatic rings can adopt an orientation which allows a π-π interaction (Figure 3). Upon chemical synthesis, compound **(5)** proved to have high affinity for the NK_1 receptor (pKi 8.0).

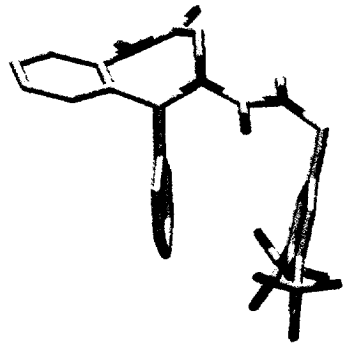


(5)

Figure 3. ***Low energy conformations of compound (5)***

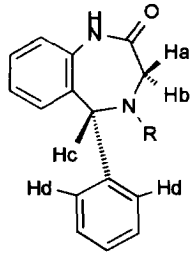


(5a)



(5b)

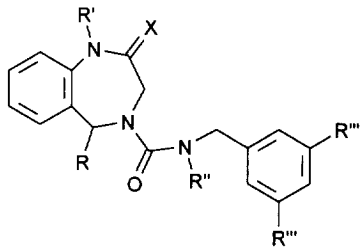
We were keen therefore to identify which of these conformations corresponded to the bioactive conformation. NMR studies on the solution conformation of **(5)** in $CDCl_3$ are not consistent with there being a substantial population of conformation **5b** - no n.O.e. is observed between protons Ha and Hc. Although the absence of a n.O.e. cannot be considered conclusive, these protons would be in a pseudo 1,3-diaxial relationship in conformation **5b**. Furthermore a n.O.e. between Hb and Hd strongly suggests that the compound resides predominantly in conformation **5a**. This would suggest that the 5-phenyl group is not essential for high binding affinity. The NMR studies cannot entirely rule out an alternative pseudo-chair conformation, however, modelling and X-ray studies by ourselves and others[14] would seem to make the pseudo-chair less likely.

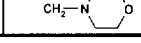


To confirm this theory we elected to synthesise compound **(6)** in which the 5-phenyl group is replaced by a 5-methyl group. Compound **(6)** is only marginally less potent than **(5)** (pKi 7.5) and appears to adopt a similar conformation in d_6-DMSO solution by NMR. This suggests that conformer **5a** may be the bioactive conformation.

A range of other simple derivatives were prepared and results are summarised in Table 1. Interestingly the benzodiazepine template is not acting as a passive scaffold - N-methylation of the amide **(7)** results in a reduction of activity suggesting that the N-1 amide is involved in receptor binding, presumably acting as a hydrogen bond donor. The tetra-substitution of the urea appears to be critical (compare compounds **(5)** and **(9)**) possibly by allowing the urea to twist out of a fully planar conformation or by allowing both *cis* and *trans* conformations about the urea.[15] The 3,5-bis(trifluoromethyl) substitution on the benzyl group contributes substantially to potency (compare compounds **(5)** and **(10)**).

Table 1 ***Structure-activity relationships in the 1,4-benzodiazepin-2-one series of NK_1 receptor antagonists***



Compound No.	R	R'	R''	R'''	X	pKi[7]	n	SEM
(5)	Ph	H	Me	CF_3	O	8.0	3	0.25
(6)	Me	H	Me	CF_3	O	7.5	4	0.21
(7)	Me	Me	Me	CF_3	O	6.0	4	0.06
(8)	Me	H	Me	CF_3	2H	7.4	3	0.04
(9)	Ph	H	H	CF_3	O	6.2	3	0.05
(10)	Ph	H	Me	H	O	6.0	4	0.06
(11)	CO_2Me	H	Me	CF_3	O	6.5	3	0.24
(12)		H	Me	CF_3	O	6.1	4	0.26

Conclusion

The 1,4-benzodiazepin-2-one derivative **(5)** represents the first example of a new class of potent NK_1 receptor antagonists, and provides another example of the use of the 1,4-benzodiazepine template for antagonists of G-protein coupled 7- transmembrane receptors.

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15. A similar observation was made regarding the importance of N-methylation in the related compounds of reference 9.

(*Received in Belgium* 5 *March* 1997; *accepted* 3 *July* 1997)