Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 2, pp. 165-166, 1996

0960-894X/96 $15.00 + 0.00

0960-894X(95)00582-X

THE DESIGN AND SYNTHESIS OF NON-PEPTIDE LIGANDS WITH AFFINITY AND SELECTIVITY FOR TACHYKININ RECEPTORS.

David C. Horwell, Andrew I. Morrell* and Edward Roberts

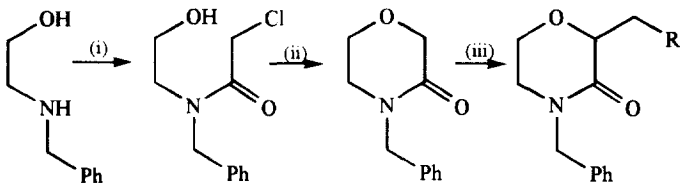
Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Hills Road, Cambridge, CB2 2QB, UK..

Abstract: 2,4-disubstituted morpholin-3-one based ligands which show affinity for tachykinin receptors have been designed and synthesised. Variation of the side chains attached to the central template gives rise to selectivity between receptor subtypes. This selectivity is directly analogous to that exhibited by dipeptide ligands for the same receptor subtypes.

The rational design of non-peptide ligands for membrane-bound peptide receptors is an active area of current research interest.[1] With a few notable exceptions, the majority of non-peptide ligands discovered to date have relied upon a broad screening approach to identify the initial chemical lead.[1c] The direct translation of a peptide epitope into a non-peptide structure is an attractive approach to the identification of lead compounds acting at peptide receptors. As part of our continuing strategy for the development of novel approaches to drug design and discovery[2] we have addressed the use of small, low molecular weight chemical templates to which peptidal side chains can be attached.[3]

We elected to prepare mimetics of two dipeptides which had proved to be valuable chemical leads in the development of ligands for both the tachykinin NK-1[4] and NK-3[5] receptors, and we now wish to report the application of the morpholin-3-one ring system as a template for a series of peptidomimetics, which show both affinity and selectivity for tachykinin receptor subtypes. The morpholin-3-one ring system provides a suitable template for the attachment of peptidal side chains, satisfying design criteria initially outlined by Farmer and Ariens.[6]

The substituted morpholinones were synthesised by treatment of N-benzylethanolamine with chloroacetyl chloride to afford the N-benzyl-N-chloroacetyl ethanolamine (2), and subsequent cyclisation of (2) to the morpholin-3-one (3) with potassium *tert*-butoxide.[7] Treatment of (3) with LDA in THF followed by addition of benzyl chloride afforded 2,4-dibenzyl morpholin-3-one (4) in 70% yield. Similarly (3) gave (5) in 26% yield upon treatment with LDA and addition of gramine methiodide (Scheme).[8]



Reagents and conditions (i) $ClCH_2COCl$, NEt_3, $PhCH_3$, reflux (ii) ^tBuOK, ^tBuOH, reflux(iii) LDA, RCH_2X, -78°C (X = Br, $N^+Me_3\Gamma$)

Scheme

Table 1 illustrates the binding affinities of the morpholin-3-one template based peptidomimetics (4) and (5) for the tachykinin NK-1 and NK-3 receptors, together with the binding affinities for the dipeptides Z-Trp-Phe-NH_2[4] Boc-Phe-Phe-NH_2[5] and the endogenous receptor ligands Substance P (SP) and Neurokinin B (NKB). The affinities of the morpholinone dipeptide mimetics (4) and (5) are clearly analogous to those of the dipeptides Z-Trp-Phe-NH_2 and Boc-Phe-Phe-NH_2.

Ligand	IC_{50} NK-1[a]	IC_{50} NK-3[b]
SP	0.26	717
BocPhePheNH$_2$	IA	1550
(4)	IA	4090
NKB	97.5	10
ZTrpPheNH$_2$	4200	IA
(5)	3500	IA

Table 1 IC_{50} (nM) represents the concentration of ligand producing half-maximal inhibition of specific binding of a) [^{125}I]-Bolton-Hunter SP to NK-1 receptors in human lymphoma IM9 cells; b) [^{125}I]-[MePhe7]NKB to NK-3 receptors in Guinea pig cortical membranes. Values are the geometric mean from at least three experiments. 'IA' indicates <10% inhibition at 10μM.

Thus the morpholin-3-one template-based peptidomimetics (4) and (5) represent prototypical examples of the direct translation of recognition sites from a peptidic to a non-peptidic structure, with retention of affinity for a membrane-bound receptor. It should therefore prove possible to apply this approach to additional dipeptide leads identified from rationally designed dipeptide libraries[2], thereby obtaining non-peptide ligands which are amenable to further optimisation using traditional medicinal chemistry techniques. The application of this particular approach to further neuropeptide targets and chemical optimisation of lead structures will be reported in due course.

Acknowledgement We would like to thank N. Suman-Chauhan and R. Franks for the receptor binding assays, and W. Howson and S. P. Langston for valuable discussions.

References and Notes

1. (a) Giannis, A; Kolter, T. *Angew. Chem. Intl. Ed. Engl.* **1993**, *32*, 1244-1267. (b) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bos, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039- 3049. (c) Rees, D. C. *Curr. Med. Chem.* **1994**, *1*, 145-158.
2. Horwell, D. C.; Howson, W.; Ratcliffe, G. S.; Rees, D. C. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 799.
3. Horwell, D. C.; Lennon, I. C.; Roberts, E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 525-530.
4. Boyle, S.; Guard, S.; Higginbottom, M.; Horwell, D. C.; Howson, W.; McKnight, A. T.; Martin, K.; Pritchard, M. C.; O'Toole, J.; Raphy, J.; Rees, D. C.; Roberts, E.; Watling, K. J.; Woodruff, G. N.; Hughes, J. *Bioorg. Med. Chem.* **1994**, *2*, 357-370.
5. Boden, P.; Eden, J. M.; Hodgson, J.; Horwell, D. C.; Howson, W.; Hughes, J.; McKnight, A. T.; Meacham, K.; Pritchard, M. C.; Raphy, J.; Ratcliffe, G. S.; Suman-Chauhan, N.; Woodruff, G. N. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1679-1684.
6. Farmer, P. S.; Ariens, E. J. *Trends in Pharmacol. Sci.* **1982**, *3*, 362.
7. Brown, G. R.; Foubister, A. J.; Stribling, D. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 547-551.
8. All compounds gave satisfactory spectra and analytical data.

(*Received in Belgium* 12 *September* 1995; *accepted* 7 *December* 1995)