New Monocyclic and Acyclic hNK-2 Antagonists Retaining the β-turn Feature

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The human tachykinin NK-2 receptor is a promising target for important pathologies at respiratory, gastrointestinal and genitourinary level, where this receptor is mainly localized. Several peptidic and non-peptidic antagonists to this receptor are known, and a few of them are undergoing clinical studies. The bicyclic peptide MEN10627 [1] is one of the most potent antagonists for the neurokinin NK-2 receptor. However its low bioavailability prevents it to be used as a drug. We have already shown how, by selecting a proper part of its structure, i.e. that featuring the β-turn, it is possible to obtain simpler peptides still retaining their activity. The monocyclic series which originated was designed on the basis of theoretical assumptions with the support of modeling [2]. In the present contribution we show how subsequently that rationale has been experimentally validated through X-ray structure determination of a novel monocyclic hNK-2 antagonist (MEN13365). Moreover the same structural features have been retained in MEN15596, which belongs to a new non cyclic series of hNK-2 antagonists developed to circumvent the low oral bioavailability. Antagonists from this last series are presently undergoing preclinical development.

[1] Pavone, V.; Lombardi, A.; Nastri, F.; Saviano, M.; Maglio, O.; D'Auria, G.; Quartara, L.; Maggi, C.A.; Pedone, C. *J. Chem. Soc. Perkin Trans. 2* 1995, 987 and references therein. [2] Fedi, V.; Altamura, M.; Balacco, G.; Canfarini, F.; Criscuoli, M.; Giannotti, D.; Giolitti, A.; Giuliani, S.; Guidi, A.; Harmat, N.J.S.; Nannicini, R.; Pasqui, F,; Patacchini, R.; Perrotta, E.; Tramontana, M.; Triolo, A.; Maggi, C.A. *J. Med. Chem.* 2004, **47**, 6935 and references therein.

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