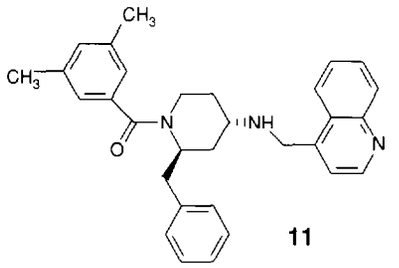
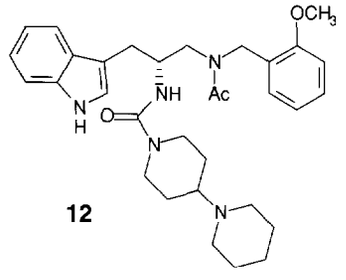
The key structural changes that confer increased affinity for the human NK_1 receptor appear to be replacement of the amidine linking group by an amide, and the modification of the ketone functionality in which a fourth aryl ring has been introduced to afford the tertiary alcohol **10** RPR 100893. Interestingly, it is the opposite enantiomer of this compound that has the highest affinity. In IM9 cells, RPR 100893 has been shown to have an affinity for the hNK_1 receptor of 30 nM [Tabart, M. and Peyronel, J.F. *Bioorg. Med. Chem. Lett.* (1994) 4, 673–676]. RPR 100893 was active in models of analgesia (formalin paw ED_{50} = 3.1 mg/kg subcutaneous dose) and migraine (ED_{50} = 2.5 ng/kg intravenous dose; ED_{50} = 0.5 mg/kg by mouth), and is reported to be in Phase II trials for the treatment of pain and migraine.

Scientists at Ciba-Geigy have described a series of 4-aminopiperidine amides as potential NK_1 receptor antagonists. A compound from this series **11** CGP 49823 that has relatively modest affinity of 11 nM [Subramanian, N. *et al. J. Physiol. Pharmacol.* (1994) 72, Suppl. 1P] is reported to be in Phase I trials as a potential treatment for anxiety disorders.



11

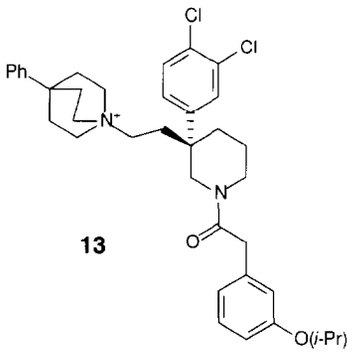
Recently workers at Lilly have reported the discovery and *in vivo* evaluation of LY 303870 **12**, a potent NK_1 receptor antagonist (hNK_1, K_i = 0.2 nM) [Gitter B.D. *et al. J. Pharm. Exp. Ther.* (1995) 275, 737–744]. In a new model of dural extravasation in guinea-pigs, LY 303870 was shown to be equipotent with the 5-HT_{1D} agonist sumatriptan when given intravenously and more potent than sumatriptan when given orally (ID_{50} = 0.1 μg/kg *vs* ID_{50} = 3 μg/kg).



12

Doses of up to 30 mg/kg were required to inhibit NK_1 agonist-induced hyperalgesia and formalin-induced nociception in rats, and even higher doses (up to 60 mg/kg) were needed to inhibit amphetamine-induced locomotor activity in mice. LY 303870 has completed Phase I studies.

Sanofi scientists have identified a novel *N*-acylated 3-(3,4-dichlorophenyl)piperidine **13** SR 140333 [Emonds-Alt, X. *et al. Eur. J. Pharmacol.* (1993) 250, 403–413] that displays high affinity (NK_1, K_i = 0.01 nM). This compound is structurally related to NK_2 and NK_3 antagonists that have been disclosed by the same company but shows excellent selectivity for the NK_1 receptor. In the rat SR 140333, given intravenously, potently inhibited the plasma extravasation induced by sciatic nerve stimulation, mustard oil application and substance P. SR 140333 is reported to be in Phase I trials for inflammation and migraine.



13

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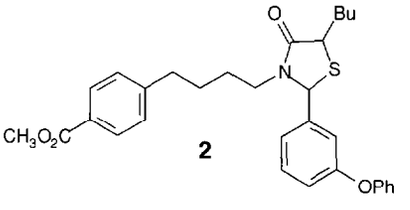
Combinatorial chemistry

Synthetic receptors

Combinatorial libraries are being constructed and used primarily for the discovery of novel ligands for biological receptors. However, this relationship can be reversed – preparing a large library to search for a synthetic receptor for a specific peptide ligand. Still, W.C. and coworkers have recently described a library of peptides that yielded a potent synthetic receptor of *N*-acyl Leu-enkephalin methyl ester [*J. Am. Chem. Soc.* (1996) 118, 1813–1814]. The tagged library was constructed by varying the four amino acid residues in two peptide arms of the A,B-*trans*-steroidal structure **1**. By attaching a dye molecule to the enkephalin, beads carrying an efficient receptor could be selected by their colour. The authors describe how the use of such receptors with decreased flexibility leads to increased receptor selectivity.

COX-1 inhibitors from a 4-thiazolidinone library

A combinatorial library of 4-thiazolidinones has been prepared and tested against the enzyme cyclooxygenase-1 (COX-1). Look, G.C. and coworkers at Affymax [*Bioorg. Med. Chem. Lett.* (1996) 6, 707–712] have made three libraries (carboxylic acid, carboxamide and methyl ester), each of 540 compounds, *via* the solid-phase condensation of a thioacetic acid plus an imine. Iterative deconvolution of the most active mixture from the ester library ultimately revealed the best compound **2** to be a micromolar COX-1 inhibitor.



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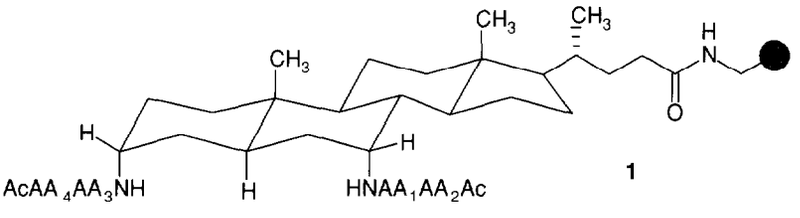

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1359-6446/96/$15.00. PII: S1359-6446(96)30046-9