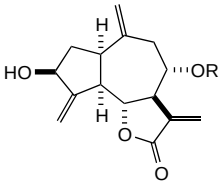
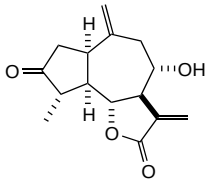


Cynaropicrin **(ii)** R =

Aguerin B **(iii)** R =



Grosheimin **(iv)**

components. When tested at lower doses (100 and 50 mg kg^{-1}, p.o.), compounds **ii–iv** retained their anti-hyperlipidemic activity, with compound **ii** being the most potent. A SAR study suggested that the oxygen functional group and the *exo*-methylene moiety in the α-methylene-γ-butyrolactone ring were essential for the activity of these sesquiterpene derivatives.

Finally, the effect of compounds **ii–iv** on gastric emptying (GE) in olive oil-loaded mice was examined. All the compounds were able to significantly suppress GE at doses of 50 and 100 mg kg^{-1}, p.o. In addition, none of the compounds showed any effect on pancreatic lipase activity and fatty acid translocation in Caco-2 cells *in vitro*. This suggests that suppression of GE could be involved in the anti-hyperlipidemic activity of these compounds.

8 Shimoda, H. *et al.* (2003) Anti-hyperlipidemic sesquiterpenes and new sesquiterpene glycosides from the leaves of artichoke (*Cynara scolymus* L.): structure requirement and mode of action. *Biorg. Med. Chem. Lett.* 13, 223–228

9 Samek, Z. *et al.* (1971) Terpenes. CCXIII. Sesquiterpenic lactones of the *Cynara scolymus* species. *Tetrahedron Lett.* 50, 4775–4778

10 Stevens, K. L. *et al.* (1982) Sesquiterpene lactones from *Centaurea repens*. *Phytochemistry* 21, 1093–1098

11 Toda, S. *et al.* (1985) Natural antioxidants. III. Antioxidative components isolated from rhizome of *Curcuma longa* L. *Chem. Pharm Bull.* 33, 1725–1728

12 Markham, K.R. *et al.* (1978) Carbon-13 NMR studies of flavonoids. III. Naturally occurring flavonoid glycosides and their acylated derivatives. *Tetrahedron* 34, 1389–1397

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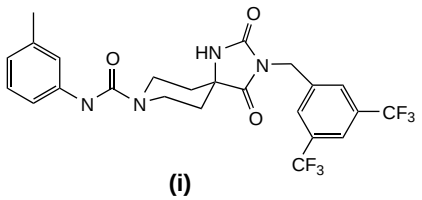
Combinatorial chemistry

NK_1 receptor ligands

The tachykinin receptors (NK_1, NK_2 and NK_3) belong to the target family of seven-transmembrane G-protein-coupled receptors. These receptors are expressed in both the periphery (mainly NK_2) and the CNS (NK_1 and NK_3). Hence, their therapeutic utility ranges from CNS indications to the potential treatment of respiratory and gastric diseases. The endogenous ligands for these receptors are the tachykinins, a group of vasoactive peptides that share a common C-terminal amino acid sequence, Phe-X-Gly-Leu-Met-NH_2, where X is either phenylalanine or valine. The most renowned member of this peptide family is the undecapeptide substance P (X=Phe), which shows highest affinity for the NK_1 receptor, whereas neurokinin A and neurokinin B (X=Val) are both decapeptides that bind preferentially to NK_2 and NK_3 receptors, respectively. Library design and synthesis was accomplished by searching for novel small-molecule ligands that target the NK_1 receptor [1]. Several libraries were synthesized on Merrifield solid-phase resin in an attempt to generate compounds with affinity for the human NK_1 (hNK_1) receptor. One of the most potent compounds found was compound **i**, which possessed a binding affinity (pK_i) against the hNK_1 receptor of 7.34. This work has produced modestly potent compounds with affinity for the hNK_1 receptor and thus this class of compounds warrants further investigation.



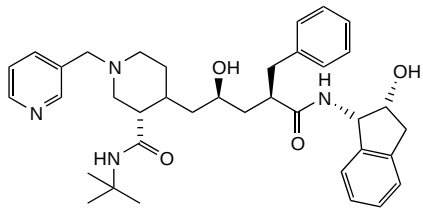
(i)

1 Bleicher, K.H. *et. al.* (2002) Parallel solution- and solid-phase synthesis of spirohydantoin derivatives as neurokinin-1 receptor ligands. *Bioorg. Med. Chem. Lett.* 12, 2519–2522

HIV protease inhibitors

The cleavage of Gag and Gag-Pol polyproteins by HIV protease is essential for the assembly of the mature, infectious virus. Inhibition of HIV protease results in immature virions that are incapable of replication. Disease progression in AIDS patients is slowed down by administering a combination of protease inhibitors (PIs) and reverse-transcriptase inhibitors. However, currently approved PIs suffer from various drawbacks, leading to patient non-compliance. Furthermore, the emergence of multi-drug-resistant viruses is jeopardising current PI therapies.

In an effort to improve the metabolic profile of indinavir (compound **ii**), a marketed PI, a replacement for the metabolically labile aminoindanol moiety was sought [2]. A library of 902 compounds was synthesized as 22 mixtures on Rapp TentaGel S-COOH resin. The library compounds were evaluated



(ii)

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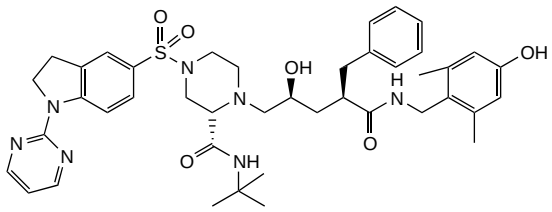

(iii)

for their ability to prevent cleavage of a substrate by the HIV protease wild-type enzyme and the mutant A-44 enzyme. Additionally, the mixtures were tested for their ability to inhibit the spread of viral infection in MT4 human T-lymphoid cells infected with the HIV-1 IIIb isolate, measured as CIC_{95}. Active mixtures were deconvoluted. One of the most potent compounds isolated was compound **iii,** which possessed an IC_{50} of 0.2 nM against the wild-type enzyme and a CIC_{95} (the concentration of test compound that inhibited virus antigen production by 95%, relative to untreated controls) of 31.3 nM. This work has provided novel, potent leads worthy of further investigation.

2 Raghavan, S. *et. al.* (2002) Combinatorial library of indinavir analogues: replacement for the aminoindanol at P_2. *Bioorg. Med. Chem. Lett.* 12, 2855–2858

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