Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

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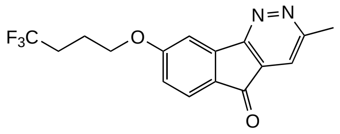
Molecules

Rational design of a novel indenopyridazinone derivative as a MAO-B inhibitor

Monoamine oxidase (MAO; E.C. 1.4.3.4), which exists in two forms, namely MAO-A and MAO-B [1], catalyses the oxidative deamination of biogenic and xenobiotic amines to the corresponding aldehyde and ammonia, both in the periphery and in the CNS [2]. Inhibitors of MAO represent useful tools for the treatment of several psychiatric and neurological diseases. In particular, reversible and selective MAO-B inhibitors are under investigation for the treatment of Parkinson's disease and Alzheimer's disease [3].

Based on the general MAO-B pharmacophore proposed previously by Ooms and colleagues [4], these same researchers have now designed and synthesized 3-methyl-8-(4,4,4-trifluorobutoxy)-indeno[1,2-*c*]pyridazin-5-one (compound **i**) as a possible potent and selective reversible MAO-B inhibitor [5]. The compound was tested using intact mitochondria prepared from human placenta and baboon liver as sources for MAO-A and MAO-B, respectively [6]. The nonselective substrate 1-methyl-4-(1-methylpyrrol-2-yl)-1,2,3,4-tetrahydropyridine (MMTP) was incubated with compound **i** and the mitochondrial homogenates. Compound **i** inhibited both enzymes with K_i values of 14 nM for MAO-B and 100 μM for MAO-A, indicating that compound **i** is one of the most potent and selective reversible MAO-B inhibitors.

Finally, compound **i** was docked to the active site of human MAO-B using the recently reported X-ray crystal structure of the enzyme [7]. This study revealed that the compound docks in the vicinity of the FAD-cofactor and that the carbonyl and the pyridazine moieties form H-bonds with Tyr188, Tyr398, and Tyr345. These data are in accordance with the MAO-B pharmacophore previously proposed by Ooms and colleagues.



(i)

1 Grimsby, J. *et al.* (1990) Tissue distribution of human monoamine oxidase A and B mRNA. *J. Neurochem.* 55, 1166–1169
2 Weyler, W. *et al.* (1990) Biochemistry and genetics of monoamine oxidase. *Pharmacol. Ther.* 47, 391–417
3 Wouters, J. *et al.* (1998) Structural aspects of monoamine oxidase and its reversible inhibition. *Curr. Med. Chem.* 5, 137–162
4 Wouters, J. *et al.* (1997) Reversible inhibition of type B monoamine oxidase. Theoretical study of model diazo heterocyclic compounds. *Eur. J. Med. Chem.* 32, 721–730
5 Ooms, F. *et al.* (2003) Rational approaches towards reversible inhibition of type B monoamine oxidase. Design and evaluation of a novel 5*H*-indeno[1,2-*c*]pyridazin-5-one derivative. *Bioorg. Med. Chem. Lett.* 13, 69–73
6 Salach, J.I. *et al.* (1987) Preparation of the flavin-containing aromatic amine oxidases of human placenta and beef liver. *Methods Enzymol.* 142, 627–637
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Sesquiterpene derivatives from the leaves of artichoke (*Cynara scolymus* L.)

The leaves of artichoke are used in European traditional medicine for the treatment of several pathologies, including hepatitis and hyperlipidemia. To verify the anti-hyperlipidemic effect of the artichoke, Shimoda and collaborators [8] recently examined the effect of a methanolic extract obtained from the dried leaves of artichoke cultivated in Peru. Preliminary results showed that the extract was able to significantly suppress serum triglyceride (TG) levels in olive oil-loaded mice. The methanolic extract was subsequently partitioned into ethyl acetate and water. Although the ethyl acetate soluble fraction (250 mg kg^{-1}, p.o.) significantly suppressed the increase in serum TG levels (63%, compared with control, $P<0.05$) two hours following its administration, the water soluble fraction was inactive at the same dose.

Reversed-phase column chromatography and HPLC of the organic fraction of the extract was used to isolate the known sesquiterpenes (compounds **ii**–**iv**) [9–11] in addition to luteolin-7-*O*-β-D-glucopyranoside [12] and other minor

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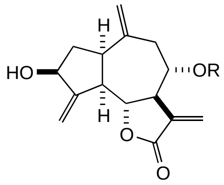
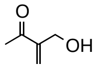
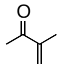
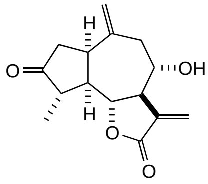


Cynaropicrin **(ii)** R = 

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.

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

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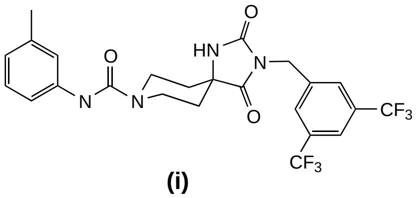
Combinatorial chemistry

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)

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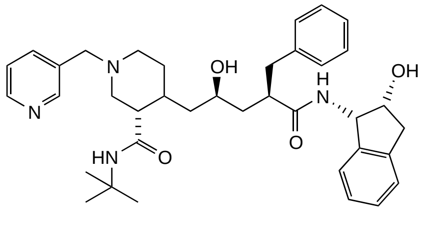
HIV protease inhibitors

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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