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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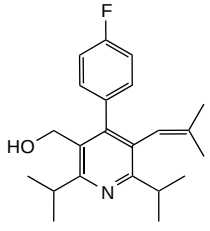
Molecules

Small-molecule glucagon antagonists to treat diabetes

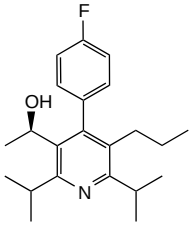
Glucagon is a peptide hormone that stimulates glycogenolysis and gluconeogenesis within the liver, increasing the levels of plasma glucose. In patients with diabetes it is the sustained high levels of glucagon that lead to excessive hepatic glucose production. Peptide antagonists of glucagon have been shown to decrease blood-glucose levels in diabetic animal models when administered intravenously.



(i)

Peptides have poor oral bioavailability and scientists from the Bayer Research Center (West Haven, CT, USA) conducted an HTS program to identify lead small-molecule glucagon antagonists resulting in the identification of compound **i** (IC_{50} = 7.0 μM for inhibition of peptide binding and IC_{50} = 2.0 μM, for inhibition of cAMP production) [1].

Isopropyl groups were found to be optimal at the 2- and 6-positions with only symmetrical pyridines being investigated at these positions to avoid regio-isomers. The hydroxyl group was found to act as a key hydrogen bond donator and conversion to a secondary alcohol gave improved binding. One enantiomer was more active and the absolute configuration was determined, by X-ray analysis of the Mosher ester, to be the *R*-isomer as shown in compound **ii**. Compound **ii** has an IC_{50} value of 0.11 μM of in a binding assay and an IC_{50} value of 0.065 μM in a functional assay. It will be interesting to see further optimization of this novel series.



(ii)

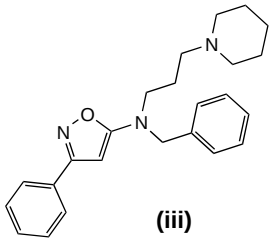
1 Ladouceur, G.H. (2002) Discovery of 5-hydroxyalkyl-4-phenylpyridines as a new class of glucagon receptor antagonists. *Bioorg. Med. Chem. Lett.* 12, 461–464

Small-molecule antagonists of the platelet thrombin receptor

The key role that the serine protease, thrombin, plays in the coagulation cascade has been known for some time. What has come to light only recently is how thrombin is able to activate cells such as platelets via the G-protein-coupled receptor – platelet thrombin receptor (PAR) – of which several subtypes have now been identified (PAR-1–PAR-4).

The novel mechanism of activation by thrombin involves proteolytic cleavage of the receptor's extracellular domain exposing a new N-terminus that binds intramolecularly to the receptor causing activation and thus acting as a tethered agonist.

Selective blockade of this activation might result in moderation of platelet aggregation without interfering with the enzymatic activity of thrombin and could provide a new mode of treatment for thrombotic disorders. Directed screening by a group from the Merck Research Laboratories (West Point, PA, USA) identified compound **iii** as a PAR-1 antagonist of moderate potency (IC_{50} = 9.0 μM) [2].



(iii)

Structure–activity relationship (SAR) studies were conducted by first optimizing the substituents on the exocyclic amino group followed by modifying the phenyl group. PAR-1 antagonist activity was determined by measuring the inhibition of the release of tritiated serotonin from washed platelets, stimulated by the peptide TRAP (thrombin receptor activating peptide), or by the more

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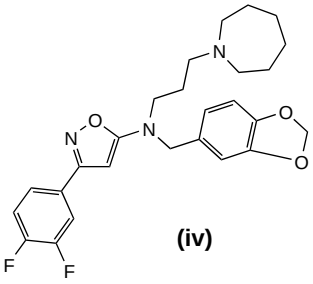
physiologically relevant thrombin. Some differences in SAR were observed depending upon the stimulus, with compound **iv** being identified as a potent antagonist in both assays (IC_{50} = 0.09 μM with TRAP as the agonist, 0.51 μM with thrombin and a binding IC_{50} of 0.15 μM measured by displacement of a radiolabeled peptide).



(iv)

Compound **iv** is not an inhibitor of the catalytic activity of thrombin, nor does it inhibit platelet aggregation induced by ADP. However, it does inhibit platelet aggregation induced by 1 nM thrombin for 10 min at a concentration of 4 μM and for 5–6 min at 1 μM.

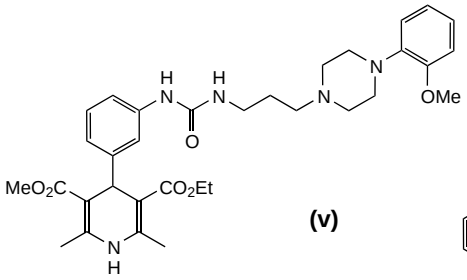
2 Nantermet, P.G. (2002) Discovery of a nonpeptidic small-molecule antagonist of the human platelet receptor (PAR-1). *Bioorg. Med. Chem. Lett.* 12, 319–323

Small-molecule neuropeptide Y receptor antagonist

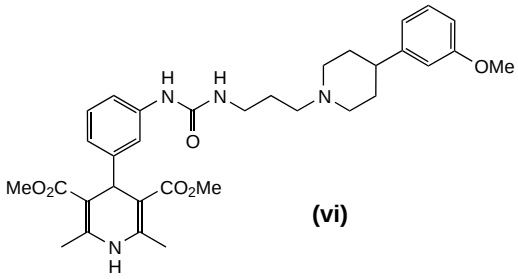
Obesity is a growing public health concern in the Western world. There are many factors that cause obesity, however, it is clear that its progression is closely associated with an imbalance between food intake and energy expenditure.

Neuropeptide Y (NPY) is a 36 amino acid peptide that is prevalent in the peripheral and central nervous systems, has been implicated in the regulation of feeding behavior and is the most potent stimulant of feeding known, to date.

There are six known NPY receptor subtypes with Y_1 and Y_5 being involved in the feeding response. HTS at the Bristol-Myers Squibb Pharmaceutical Research Institute (Wallingford, CT, USA) identified the dihydropyridine **v** as a



(v)



(vi)

competitive Y1 receptor antagonist with a K_i value of 109 nM [3]. The propyl side chain was found to be the optimum length and a piperidine ring could replace the piperazine. Replacing the ethyl ester with the smaller methyl ester improved binding and also had the advantage of rendering the dihydropyridine achiral. Compound **vi** was identified as competitive, full-functional antagonist with a K_i value of 3.3 nM at the Y_1 receptor and no affinity for the other NPY receptors. Intraperitoneal administration of **vi** at 10 and 30 mg kg^{-1} antagonized the increase in food consumption (33% ± 15% and 57% ± 11%, respectively) induced by ICV infusion of NPY in satiated rats. Compound **vi** was also shown to decrease spontaneous nocturnal feeding in the rat. The compound highlights the potential of Y_1 antagonists to treat obesity.

3 Poindexter, G.S. (2002) Dihydropyridine neuropeptide Y Y1 receptor antagonists. *Bioorg. Med. Chem. Lett.* 12, 379–382

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Combinatorial chemistry

Nucleoside phosphoramidates

Compounds that have phosphoramidate functionality have a range of biological activities. Well known examples include the anticancer drug cyclophosphamide and the cardioprotective agent phosphocreatine. As phosphoric and carboxylic equivalents, phosphoramidates have been evaluated as analogues of nucleosides and oligonucleotides. For example, 5′-phosphoramidates have been synthesized as 'prodrug' derivatives of antiviral nucleosides, such as 3′-azidothymidine (AZT), reported to possess anti-HIV activity. Oligonucleotides with primary, secondary and tertiary phosphoramidate internucleotidic linkages have been evaluated as antisense agents. However, only a few nucleoside phosphoramidates have been prepared and evaluated for antiviral activity.

The clinically useful antiviral drugs target mainly viral reverse-transcriptase (RT), DNA polymerase and protease. However, two crucial issues have emerged from their therapeutic use: (1) the rapid development of drug resistance; and (2) side effects such as mitochondrial and bone-marrow toxicity associated with most polymerase and RT inhibitors. Newer strategies are, therefore, needed to combat viral infections.

Combinatorial synthesis and HTS has stimulated efforts to assemble novel libraries of compounds for evaluation against biological targets. This strategy, combinatorial synthesis combined with the screening of biologically relevant libraries for their ability to modulate biological pathways, with or without regard to specific molecular targets, is appropriate in the context of antiviral lead discovery. This approach enables the

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