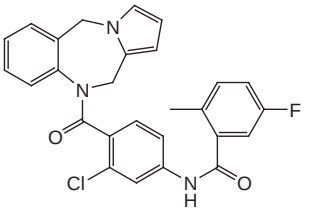
Monitor: molecules and profiles

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.

Molecules

Orally active arginine vasopressin-receptor antagonists

Increases in plasma osmolarity or decreases in blood volume and/or blood pressure causes the release of the antidiuretic hormone vasopressin from the posterior pituitary. The hormone exerts its pharmacological effects through interaction with two well-characterized receptor subtypes, the vascular V_{1a} receptor and the renal epithelial V_2 receptor. The hormone arginine vasopressin plays a key role in the regulation of sodium chloride balance in the body. Selective V_2-receptor antagonists might therefore have a role in the treatment of conditions in which excess renal absorption of water contributes to fluid retention in diseases such as congestive heart failure and liver cirrhosis. 5-Fluoro-2-methyl-*N*-[4-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ylcarbonyl)-3-chlorophenyl]-benzamide (**1**), (VPA985) has been developed as a nonpeptide vasopressin antagonist and is currently in Phase II clinical trials. Aranapakam, V. and coworkers have recently published two papers describing novel orally active arginine vasopressin-receptor antagonists based on the VPA985 template.



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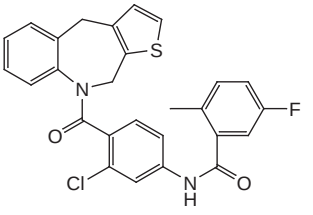
The first paper [*Bioorg. Med. Chem. Lett.* (1999) 9, 1733–1736] describes the synthesis and structure–activity relationships of compounds in which the 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine moiety in VPA985 is replaced with the 4,10-dihydro-5*H*-thieno[3,2-*c*][1]benzazepine and 9,10-dihydro-4*H*-thieno[2,3-*c*][1]benzazepine moieties. *In vitro* binding studies were conducted using a murine fibroblast cell line expressing human V_2 receptors or membrane-bound V_{1a} receptors from human platelets. *In vivo* studies monitored urine output from a water-loaded rat model.

Replacement of the 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine moiety in VPA985 with 9,10-dihydro-4*H*-thieno[2,3-*c*][1]benzazepine gave a series of derivatives with potent V_{1a}- and V_2-binding affinities. Compound (**2**) was found to be a particularly potent (IC_{50} = 6.8 nM), selective and orally active V_2-receptor antagonist.



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The second paper [*Bioorg. Med. Chem. Lett.* (1999) 9, 1737–1740] by the same group describes the synthesis and evaluation of a series of compounds in which one of the phenyl rings is replaced with a 3-pyridinyl moiety. In these studies, *in vitro* assays were conducted using receptors isolated from rat liver (V_{1a}) and rat kidney (V_2) while *in vivo* assays were conducted as described above.

Replacement of the phenyl ring with a 3-pyridinyl group provided a series of compounds with potent V_{1a}- and V_2-receptor activity. Three compounds were found to have *in vitro* selectivity for the V_2 receptor over the V_{1a} receptor and good oral activity, the most potent orally active compound in rats being compound (**3**) (CL385004).

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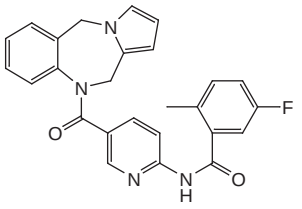

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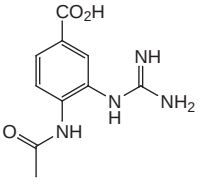
Influenza sialidase inhibitor

Influenza affects a vast percentage of the population each year. Attempts to vaccinate people against the disease are limited by the virus' ability to mutate to avoid the immune system. At present, therapeutic intervention is limited to the treatment of influenza A using amantadine and rimantadine that act at the M2 protein ion channel. However, even the use of these agents is limited by the emergence of resistant strains. Influenza is an RNA virus containing two key surface glycoproteins, sialidase and hemagglutinin, which are essential for infection.

The sialidase mediates two main activities. Firstly, it controls the release of the virus from the infected cell surface by cleavage of α-glycosidic bonds between the cell surface sialic acids and the virus. This then prevents viral aggregation and the release of viral progeny from host cells in the respiratory tract. Secondly, sialidase facilitates viral mobility through the mucus layer overlying the respiratory cells. This surface-bound enzyme is therefore a potential therapeutic target for the treatment of influenza infections.

Atigadda, V.R. and coworkers have recently described the synthesis of several novel aromatic inhibitors of influenza sialidase based on the lead compound 4-(*N*-acetylamino)-3-guanidinobenzoic acid (**4**) (BANA113) [*J. Med. Chem.* (1999) 42, 2332–2343]. Replacement of the *N*-acetyl group with a 2-pyrrolidinone ring and subsequent structure optimization led to the identification of an inhibitor (**5**) with an



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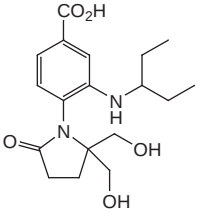

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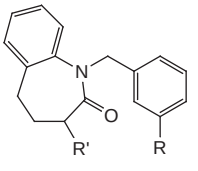
IC_{50} of 50 nM against influenza A sialidase. Although this inhibitor is 3000-fold less active against influenza B sialidase, it represents the first reported example of a simple achiral benzoic acid derivative with potent activity as an inhibitor of influenza sialidase.

Neuropeptide Y Y_1-receptor antagonists

Neuropeptide Y has a role in numerous physiological regulatory systems including regulation of cardiovascular function, food intake, pain and anxiety through stimulation of specific receptors. Four receptor subtypes have been identified in humans that belong to the seven-transmembrane receptor superfamily. The Y_1 receptor is present on the smooth muscle and has been suggested to mediate long-term vasoconstriction. In the gastrointestinal tract, the Y_1 receptor appears to inhibit gastric secretion, pancreatic exocrine secretion and gastrointestinal mobility whilst, in the CNS, this receptor subtype appears to have a role in anxiety. Selective inhibitors of this receptor subtype might therefore have uses in the treatment of a variety of disorders including congestive heart failure, digestive disorders and obesity.

Murakami, Y. and coworkers have recently reported the design, synthesis and evaluation of a novel series of potent and selective non-peptide neuropeptide Y Y_1-receptor antagonists based on a benzazepine template [*J. Med. Chem.* (1999) 42, 2621–2632]. Substitution and optimization of the template (**6**) led to the identification of the potent subset-selective neuropeptide Y Y_1-receptor antagonist 3-(3-(benzothiazol-6-yl)ureido)-1-*N*-(3-(*N*′-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**7**).

This compound competitively inhibited radiolabelled peptide YY binding to Y_1 receptors and inhibited Y_1 receptor-mediated increases in cytosolic free Ca^{2+} in human neuroblastoma SK-N-MC cells. Furthermore, this compound reduced the Y_1 receptor-mediated inhibitory effect of peptide YY on gastrin-induced histamine release from rat enterochromaffin-like cells. In addition, this compound showed no affinity for 17 other receptors including the Y_2, Y_4 and Y_5 receptors. Although highly potent and selective, several issues relating to the solubility and bioavailability of these compounds still remain to be resolved. However, these compounds should provide useful lead compounds for the future development of clinically effective NPY Y_1-receptor antagonists.



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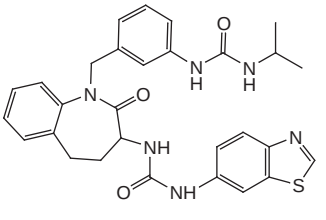

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