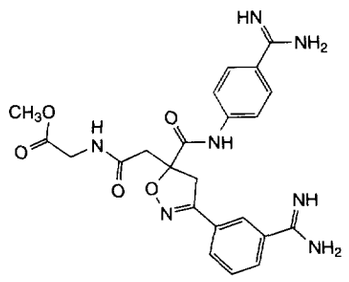
Monitor: molecules and profiles

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.

Factor Xa inhibitors

The serine protease Factor Xa links the intrinsic and extrinsic pathways in the blood coagulation cascade through its generation of thrombin from prothrombin. Inhibitors of this enzyme are therefore being investigated by several groups for potential use in the treatment of both arterial and venous thrombosis.

Quan, M.L. and coworkers have described the design and synthesis of a series of bisbenzamidine isoxazoline derivatives as Factor Xa inhibitors [*Bioorg. Med. Chem. Lett.* (1997) 7, 2813–2818]. The most potent of these compounds (**1**) has a K_i = 18 nM against Factor Xa. The authors also report that these compounds show efficacy in the rat vena cava thrombosis model.



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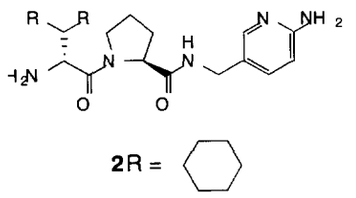
Novel thrombin inhibitor

An alternative approach to the inhibition of the blood coagulation cascade is through the inhibition of thrombin, which mediates the conversion of fibrinogen to fibrin and stimulates the activation of platelets. Although several companys have shown good inhibition of thrombin *in vitro* with agents based on fibrinogen-like sequences based on D-Phe-Pro-Arg, the subsequent development of these compounds has been limited by their poor oral bioavailability. Feng, D-M. and coworkers have recently reported the design and synthesis of a novel class of thrombin inhibitors incorporating neutral aminopyridyl moieties at the P1 position [*J. Med. Chem.* (1997) 40, 3726–3733].

The most potent of these compounds (**2**) showed nanomolar potency (K_i = 0.8 nM), 1,500-fold selectivity for thrombin over trypsin and good oral bioavailability (F = 76%) in rats.



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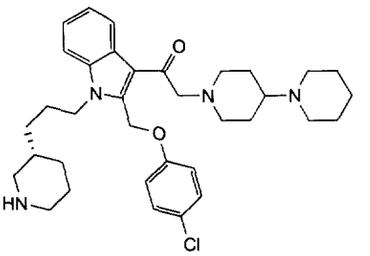
Neuropeptide Y antagonists

Neuropeptide Y (NPY) is the most abundant peptide neurotransmitter in the brain. NPY receptors occur in both the CNS and peripheral tissues. Although several NPY receptor subtypes (Y1, Y2, Y4, Y5 and Y6) have been characterized at the molecular level, the pharmacological role of each of these subtypes has yet to be fully elucidated. Despite the lack of pharmacological information on this class of receptor, physiological response and anatomical location have led to the implication of NPY in a variety of disorders including obesity and diabetes. The lack of specific ligands for the various receptor subtypes has hindered the pharmacological characterization of this receptor class.

A group from Lilly Research Laboratories (Indianapolis, IN, USA) has recently reported the use of biased library screening using cloned human NPY Y1 receptors and subsequent traditional medicinal chemistry approaches to identify a novel series of 1,2,3-trisubstituted indole NPY Y1 antagonists. Further structure–activity studies has led to the identification of **3** (LY357897) as the first selective, subnanamolar NPY Y1 antagonist (K_i = 0.75 nM).



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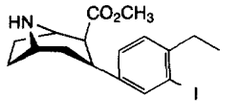
Serotonin reuptake inhibitor

Serotonin (5-HT) reuptake inhibitors have been widely used in the treatment of depression. Despite the lower incidence of side effects associated with this class of antidepressant, patients still suffer gastrointestinal, sleep disturbance and sexual dysfunction side effects.

Blough, B.E. and coworkers have described the synthesis and evaluation of 3β-(4-ethyl-3-iodophenyl)nortropane-2β-carboxylic acid methyl ester (**4**), which has high affinity for the 5-HT reuptake transporter (IC_{50} = 0.69 nM) and relatively low affinity for the dopamine and norephinephrine reuptake transporters (IC_{50} = 329 and 148 nM, respectively). *In vivo* competition binding studies in mice showed regional distribution of this compound and an EC_{50} comparable to that obtained for other 5-HT reuptake inhibitors. This compound may therefore be a useful antidepressant, and the authors suggest that a ^{123}I analogue may have use as a single-photon-emission computed tomography ligand for imaging 5-HT neurones in the brain.



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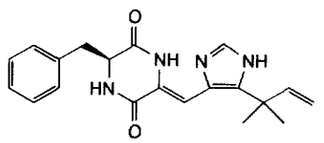
Mammalian cell-cycle inhibitor

Cell-cycle inhibitors are useful for studies investigating cell-cycle mechanism and control and may be used as potential anticancer agents. Kahoh, K. and coworkers have recently described the isolation and characterization of a novel mammalian cell-cycle inhibitor, termed phenylahistin (**5**), from culture broths of *Aspergillus ustus* NSC-F038 [*Bioorg. Med. Chem. Lett.* (1997) 7, 2847–2852].

Phenylahistin was isolated as a mixture of enantiomers (*R*:*S* = 3:1) but only the (−)-(*S*)-enantiomer was found to have cytotoxic and cell-cycle inhibitory activity against P388 murine leukaemia cells. The effect of phenylahistin on cell-cycle progression of P388 cells was



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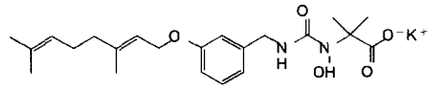
investigated using flow cytometry and was shown to inhibit cell-cycle progression in the G2/M phase at nanomolar concentrations.

Squalene synthase inhibitor

Squalene synthase is an attractive target for the pharmacological control of serum cholesterol, as inhibition of this enzyme blocks cholesterol biosynthesis without interfering in the biosynthesis of non-sterolmevalonate-derived products. Many experimental squalene synthase inhibitors are diphosphonate-containing compounds in which the negatively charged diphosphonate is essential for substrate binding. However, the oral bioavailability and stability of these compounds is limited by the highly charged diphosphonate moiety. Wattanasin, S., Boettcher, B.R. and Scallen, T. have described the development of a series of novel non-phosphorous-containing farnesyl diphosphonate mimics in which the diphosphate group has been replaced with an *N*-hydroxyglycinate moiety [*Bioorg. Med. Chem. Lett.* (1997) 7, 3039–3044].

This has led to the subsequent identification of compound **6** as a potent squalene synthase inhibitor (IC_{50} = 230 nM).



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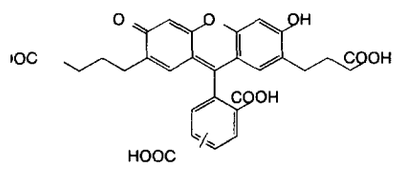
Intracellular pH indicator

Many cellular events involve changes in intracellular pH. These changes can be readily monitored using fluorescent spectroscopy. A wide range of compounds have been developed as fluorescent pH-sensitive probes. Liu, J., Diwu, Z. and Klaubert, D.H. from Molecular Probes (Eugene, OR, USA) have reported the synthesis and spectral properties of 2′,7′-bis-(3-carboxypropyl)-5-(and-6)-carboxyfluorescein (**7**) [*Bioorg. Med. Chem. Lett.* (1997) 7, 3069–3072].

This compound has excitation and emission maxima of 505 and 527 nm, respectively, with isobestic points of 454 and 504 nm, respectively. The pK_a was found to be 7.0, which makes the compound sensitive to pH changes in the physiological range. The dual spectral properties of this compound will permit its use as both an emission- and excitation-ratiometric pH indicator allowing rapid determination of intracellular pH, independent of dye concentration, path length, cellular leakage and photobleaching.



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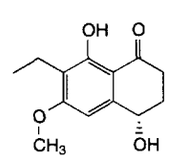
Serotonin ligands

There is considerable interest in the identification of novel serotonin ligands, because 5-HT_{2C} receptor agonists may be effective for the treatment of depression and obsessive–compulsive disorder, while antagonists may be used to treat anxiolytic conditions. Bös, M. and coworkers have recently reported the first nitrogen-free seratonin ligands (**8**, **9**) [*Bioorg. Med. Chem.* (1997) 5, 2165–2171].

O-Methylasparvenone (**8**) and asparvenone (**9**) were isolated from *Aspergillus parvulus* Smith broth as part of a screening programme for 5-HT_{2C} ligands and shown to be moderate 5-HT_{2C} antagonists (pK_i = 6.7 and 6.4, respectively).



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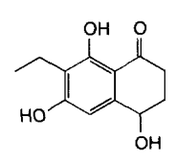

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