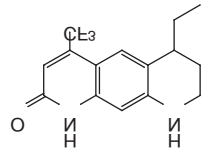
both agonists and antagonists of sex steroid hormone receptors.



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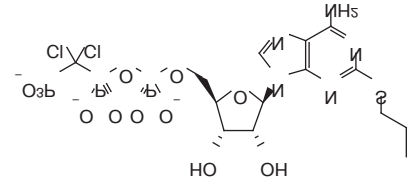
Novel antithrombotic therapy

Platelet adhesion and aggregation is critical in the process of arterial thrombosis. Although platelet aggregation is important in normal haemostasis to arrest bleeding following traumatic transection of blood vessels, it may lead to occlusive arterial thrombosis following aggregation at the site of an atherosclerotic plaque. The P_{2T} receptor plays an important role in the process of platelet aggregation and it has been suggested that antagonists for this receptor may therefore be useful antithrombotic agents.

Adenosine triphosphate (ATP) is a weak, nonselective but competitive P_{2T} receptor antagonist. Screening of structural analogues of ATP by workers from Astra Charnwood (Loughborough, UK) has led to the identification of ARC67085MX (**4**) having an IC_{50} of 2.5 nM against ADP-induced human platelet aggregation and greater than 1000-fold selectivity for the P_{2T} receptor



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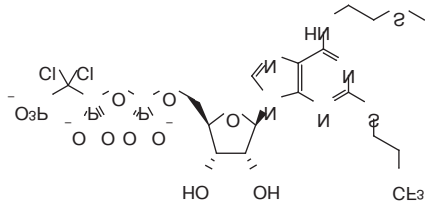

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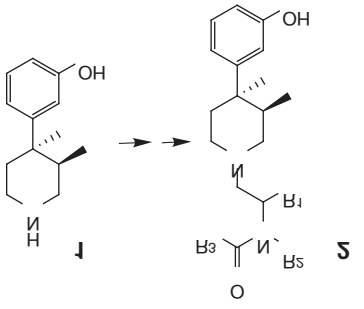
[Ingall, A.H. *et al.* (1999) *J. Med. Chem.* 42, 213–220]. Further lead optimization has led to the identification of ARC69931MX (**5**) with an IC_{50} of 0.4 nM. In marked contrast to GPIIb/IIIa antagonists, these compounds were shown to cause only minor increases in bleeding time at maximally effective antithrombotic doses. The P_{2T} receptor antagonists may therefore provide a major advancement in the development of treatments for thrombotic disease.

Combinatorial chemistry

κ-Opioid antagonist libraries

A combinatorial library has been applied to the discovery of ligands for the κ-opioid receptor [Thomas, J.B. *et al.* (1998) *J. Med. Chem.* 41, 5188–5197]. Whereas μ-opioid antagonists have been used for many years in the treatment of drug abuse, κ antagonists might provide a more effective and longer-lasting treatment, and novel agents provide an attractive target for drug discovery. The library described in this publication was based on 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**1**), a pharmacophore known to give non-selective opioid activity, and two other components, an N-substituted or unsubstituted Boc-protected amino acid and a range of substituted aryl carboxylic acids in a parallel solution-phase approach.

The 288 products contained within the library were screened in competitive binding against a known selective κ-opioid ligand, and it was apparent that a few compounds demonstrated significant inhibition of binding at 100 nM. Of these, (**3**) was the most potent with a K_i value of 6.9 nM. This compound further demonstrated 57-fold selectivity over the μ-opioid receptor and >824-fold selectivity over the δ-receptor. The authors speculate that the potency and selectivity is dependent on the optimum size of the lipophilic isopropyl group, and that the 4-hydroxy substituent is also essential for receptor affinity.



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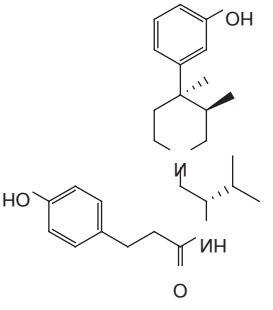

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Optimization of PPARγ agonists

Type 2 diabetes, defined by high plasma-glucose levels, peripheral insulin resistance and insufficient insulin secretion, is a widespread, debilitating disease. Recently, a group at Glaxo identified the receptor for the thiazolidinedione class of antidiabetics. One example, the drug rosiglitazone, binds to the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), and for other analogues there is a correlation between the potency of binding to the PPARγ receptor and *in vivo* antiglycemic activity.

The Glaxo group has also described a number of studies through which high-affinity ligands for the PPARγ receptor have been discovered. Most recently, a paper describes the use of a combination of orthodox solution-phase chemistry and solid-phase combinatorial chemistry to explore SAR around the lead compound (**4**) [Collins, J.L. *et al.* (1998) *J. Med. Chem.* 41, 5037–5054].

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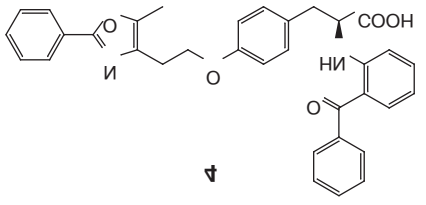
In the solid-phase SAR work, the caesium carboxylate (**5**, R = H) was attached to 2-chlorotrityl resin and Mitsunobu chemistry was employed to generate a range of aryl ethers. A total of 62 compounds were generated in parallel on solid-support, subsequently cleaved using 10% TFA in dichloromethane and were isolated with purities ranging from 16% to 98%. Of the products, six compounds demonstrated pK_i values greater than six, and these progressed to further biological assays.



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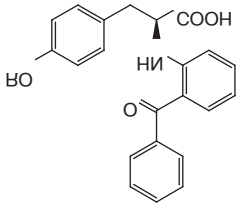

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Glycopeptide libraries

Many biological processes, including immune response, cellular adhesion, inflammation and cancer cell metastasis, are controlled by the recognition of glycoconjugates. In addition, many viral, bacterial and parasitic infections are also mediated by the interaction of glycoconjugates with protein receptors. As a result, compounds that mimic carbohydrates that can ameliorate these interactions have the potential for treating a range of diseases.

In the search for carbohydrate-based pharmaceuticals, a novel one bead–one compound library of glycopeptides has been prepared by using a novel encoding method [St Hilaire, P.M. *et al.* (1998) *J. Am. Chem. Soc.* 120, 13312–13320]. The method, named encoded ladder synthesis, is based on the ladder library method, in which in each round of synthesis a small proportion (10%) of the growing compound is capped with a carboxylic acid. This permits MALDI-TOF mass spectrometric identification of the product compounds by analysis of the unique mixture of terminated intermediates. This method has been extended by the use of a range of capping groups related to the monomers being added. Specifically, instead of adding an Fmoc-amino acid, the beads were also capped with a small proportion of the similarly reactive Boc-protected amino acid. Release of the glycopeptides from the resin support using a photolytic reaction generated 300,000 combinatorial library products tested as oligosaccharide mimics for the *Lathyrus odoratus* lectin.

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Bioinformatics: guide for evaluating bioinformatic software

There are hundreds of bioinformatic software programs available that serve a variety of applications. For someone new to bioinformatics there is a bewildering array of freeware, shareware, and commercial analytical programs, and it is difficult to make a decision between them. We are mainly influenced by what our peer group uses, but we still need a method to assess, or evaluate, the software to see if it fits our particular purpose. Established workers in bioinformatics also need some way to determine how best a particular software program integrates into the existing infrastructure. Software evaluation is an art, a science, and a business. It can be as casual as a 'let's have a play' approach or as formal as a rigorous, structured and systematic investigation. A large or networked organization would usually require detailed and specific criteria for evaluating software and also effective project management of the evaluation process. What follows, however, is a general guide for evaluating 'off-the-shelf' bioinformatics analysis software. Both an individual PC-user or a bioinformatics/IT manager, responsible for a suite of programs over a local or distributed network, may equally use these guidelines.

Why evaluate?

The first question that needs to be addressed is 'Does the software do the job it is supposed to do – is it fit for the purpose intended?' Evaluation also helps decisions to be made between competing products; to match software to the specific needs of the individual or organization; plan for integration within an existing infrastructure; ensure effectiveness, efficiency and quality; and finally to save time and money.

Who will evaluate?

The end-user is an obvious important evaluator. However, when organizational issues must be addressed then the information technology, bioinformatics and other appropriate departments need to be consulted for the evaluation process. A third party can also be consulted if necessary and this may be used to provide unbiased, independent advice and thus help to avoid internal politics or vested interests.

Software can also be used to evaluate software – although you'll then have the 'chicken and the egg' paradox of trying to evaluate the software which is evaluating the software!

How to evaluate?

Evaluation can be approached from several different perspectives encompassing scientific, business or procedural issues. Invariably, however, evaluation is based on a set of criteria

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