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.

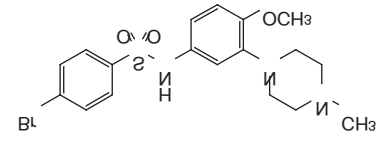
5-HT$_6$ receptor antagonist

The most recent addition to the 5-hydroxytryptamine receptor superfamily is the 5-HT$_6$ receptor, which was first cloned from rat striatal mRNA in 1993. This receptor is positively coupled to adenylyl cyclase and has been shown to have high affinity for a range of therapeutically important antipsychotic and antidepressant agents, suggesting that it may have a role in these disease states.

Other studies using antisense oligonucleotides directed towards the 5-HT$_6$ mRNA have suggested that these receptors may also be applied in modulating cholinergic neurotransmission. Therefore 5-HT$_6$ receptor antagonists may also have a role in the treatment of memory dysfunction. However, further evaluation of the pharmacological role of the 5-HT$_6$ receptor has been limited by the lack of selective ligands.

A recent report from workers at SmithKline Beecham Pharmaceuticals (Harlow, UK) describes the identification of **1** as a selective, high affinity 5-HT$_6$ ligand, following screening of the SmithKline Beecham Compound Bank against cloned human 5-HT$_6$ receptors in HeLa cell membranes [Bromidge, S.M. *et al.* (1999) *J. Med. Chem.* 42, 202–205].

Exploration of the structure–activity relationship and lead optimization ultimately led to the identification of 5-chloro-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfonamide (SB271046) (**2**) as a potent, selective and orally bioavailable 5-HT$_6$ receptor antagonist.



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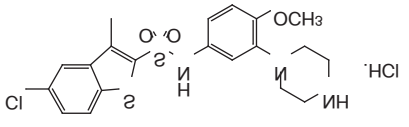

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Novel nonsteroidal androgen-receptor agonist

Androgen therapy has been used effectively in hormone replacement therapy for the treatment of hypogonadal men, and has also been investigated for cancer cachexia, male contraception and performance enhancement. The beneficial effects of these agents are limited by the side-effects associated with the metabolism of these agents.

Various strategies have been previously employed in attempts to overcome these problems, including the use of alternative routes of administration and the chemical modification of the androgenic steroids to reduce hepatic metabolism. Other approaches have involved the identification of more receptor- and tissue-selective compounds that may overcome the steroid-related side-effects. Although a number of non-steroidal structural templates are presently being investigated as potential androgen-receptor antagonists, there have been very few studies directed towards the development of non-steroidal androgen-receptor agonists.

A recent communication from Ligand Pharmaceuticals Inc. (San Diego, CA, USA) has described the identification of 4-ethyl-1,2,3,4-terahydro-6-(fluoromethyl)-8-pyridono[5,6-*g*]-quinoline (LG121071) **3** as a potent, orally active, nonsteroidal androgen-receptor agonist [Hamann, L.G. (1999) *J. Med. Chem.* 42, 210–212]. This study further supports the drug discovery approach using a common pharmacophore to develop

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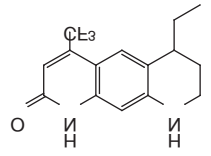
both agonists and antagonists of sex steroid hormone receptors.



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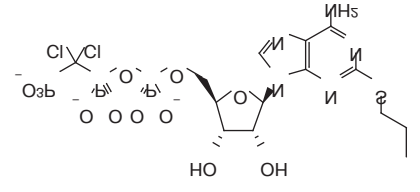
Novel antithrombotic therapy

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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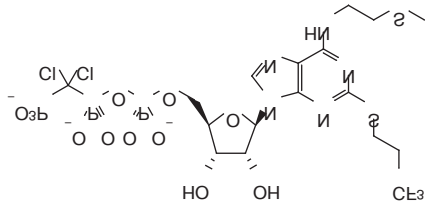

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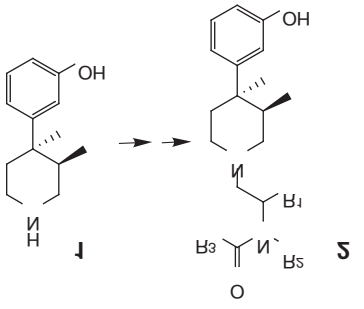
[Ingall, A.H. *et al.* (1999) *J. Med. Chem.* 42, 213–220]. Further lead optimization has led to the identification of ARC69931MX (**5**) with an IC_{50} of 0.4 nM. In marked contrast to GPIIb/IIIa antagonists, these compounds were shown to cause only minor increases in bleeding time at maximally effective 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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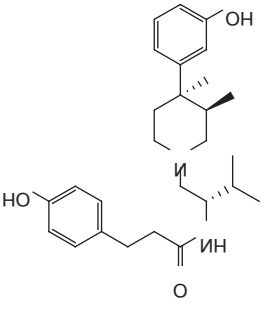

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Optimization of PPARγ agonists

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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