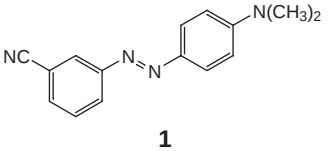
Monitor: molecules and profiles

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.

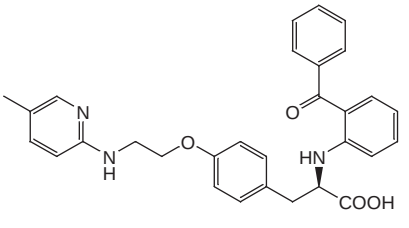
Cholesterol and plasma lipid modifying agents

Although many recent clinical trials have demonstrated that 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors, which block cholesterol synthesis, are effective at reducing coronary heart disease-associated mortality, it is widely recognized that hypercholesterolaemia is not the only dyslipidaemia contributing to this disease. A recent review of the patent literature provides a useful overview of the other approaches that are being adopted by various groups in attempts to develop drugs to normalize plasma lipid profiles [Suckling, K.E. *Exp. Opin. Ther. Patents* (1998) 8, 1415–1424]. The review covers approaches to lowering plasma triglyceride or lipoprotein A and raising plasma concentrations of high-density lipoprotein (HDL) using various agents including some unusual compounds such as **1**. However, despite their effects in animal and cell models, many of these compounds do not appear to have defined molecular targets.



1

The author identifies the peroxisome proliferator-activated receptors (PPARs) as the molecular targets with greatest potential. PPARs are nuclear hormone receptors that regulate expression of genes associated with lipoprotein metabolism. For example, PPARα inhibits the synthesis of apoC-III, an endogenous inhibitor of lipoprotein lipase, and stimulates the synthesis of apoA-I, which promotes an increase in plasma HDL. Thiazolidinediones have been classically recognized as PPARγ agonists. One of these agents, troglitazone – presently in clinical use for the treatment of high plasma glucose concentrations associated with type 2 diabetes, has been shown to reduce plasma triglycerides. Over recent years there have been several patent disclosures of thiazolidinediones and oxazolidinediones, but perhaps more interesting is the disclosure by Glaxo Wellcome of PPARγ activators from a different structural class exemplified by **2**.



2

Endothelin ET_B receptor antagonists

The endothelins (ET-1, ET-2 and ET-3) have a range of biological effects including vasodilation, inotropism, modulation of nervous function and mitogenesis, as well as being regarded as the most potent vasoconstrictors reported to date. The endothelins have been implicated in the pathophysiology of a variety of diseases including acute renal failure, acute hypertensive crisis, immunosuppressant-induced renal failure and pulmonary hypertension. The biological effects of the endothelins are mediated by the cell-surface endothelin receptors, which have been classified into two subtypes: ET_A and ET_B. Although endothelin receptor antagonists have been reported, they are either ETA-selective or non-selective. Chan, M.F. and coworkers have recently described a systematic modification of the ET_A-selective *N*-(5-isoxazolyl)benezenesul-phonamide endothelin antagonists (**3**) to give ET_B-selective antagonists [*Bioorg. Med. Chem.* (1998) 6, 2301–2316].

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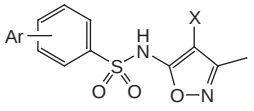
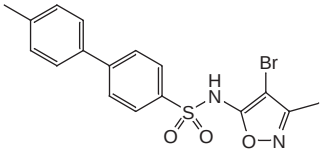


3

The difference in selectivity was achieved by substitution of the 4-position with aryl or substituted aryl groups. The *para*-tolyl group gave rise to the most active and selective ET_B antagonist, with **4** having an IC_{50} of 17 nM and 290-fold selectivity for the ET_B receptor over the ET_A receptor



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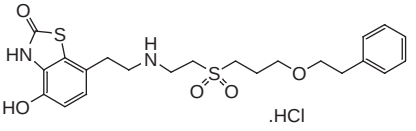
Dual D_2-receptor and β_2-adrenoceptor agonists

Hyperactivity of the airways occurs in both chronic obstructive airways disease and asthma, and leads to many of the symptoms associated with these disease states, including bronchoconstriction, dyspnea, cough and mucus production. Evidence suggests that D_2-receptor agonist activity should reduce reflex bronchoconstriction, dyspnea, cough and mucus secretion. Moreover, commonly employed β_2-adrenoceptor agonists are effective at reducing the bronchoconstriction caused by locally released mediators. Therefore, workers from Astra Charnwood (Loughborough, UK) have focused on the development of dual D_2-receptor and β_2-adrenoceptor agonists [Bonnert, R.V. *et al. J. Med. Chem.* (1998) 41, 4915–4917].

A recent report from this group describes the discovery and biological evaluation of 7-(2-aminoethyl)-4-hydroxybenzothiazol-2(3*H*)-one derivatives that possess this dual activity. The most promising compound (**5**) shows good activity in several *in vivo* D_2-



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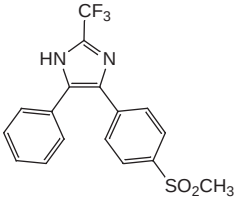
receptor and β_2-adrenoceptor models that are relevant to chronic obstructive airways disease and asthma, and has been selected for further development for the treatment of these diseases.

4,5-Diarylimidazoles as selective cyclooxygenase inhibitors

Following the discovery of at least two isoforms of cyclooxygenase (COX-1 and COX-2), there has been increasing interest in the development of selective inhibitors for these two isoforms. Barta, T.E. and coworkers have recently reported the synthesis and activity of a series of 4,5-diarylimidazole analogues [*Bioorg. Med. Chem. Lett.* (1998) 8, 3443–3448].

Of these compounds, **6** was found to have an IC_{50} of 80 nM and was 6750 times more selective for COX-1 than COX-2. This compound also showed *in vivo* potency in the mouse air pouch model and the rat adjuvant arthritis model.

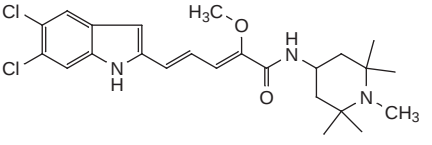


6

Osteoclast V-ATPase inhibitor

In postmenopausal osteoporosis the resorption of bone occurs more rapidly than bone formation, leading to net bone loss and a consequential increase in the likelihood of bone fracture. Bone resorption is reliant on the low pH in the extracellular microcompartments formed on osteoclast attachment to the bone. The lower pH causes dissolution of the mineralized matrix of the bone and allows the organic matrix to be degraded by proteolytic enzymes, which function optimally in this environment. The pH of this environment is maintained by a vacuolar-type proton ATPase (V-ATPase) that is present on the osteoclast ruffled border. Inhibitors of V-ATPase are therefore attractive targets for the inhibiton of osteoclast activity, bone resorption and hence osteoporosis.

The optimization of a novel series of osteoclast ATPase inhibitors by Nadler, G. and coworkers has led to the identification of (2*Z*,4*E*)-5-(5,6-dichloro-2-indolyl)-2-methoxy-*N*-(1,2,2,6,6-pentamethylpiperidin-4-yl)-2,4-pentadienamide (**7**) as a potent and selective inhibitor of osteoclast ATPase activity *in vitro*. This compound will be a useful tool for evaluating the potential use of osteoclast proton pump inhibitors for the treatment of osteopenic diseases such as osteoporosis.



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In short…

Small Molecule Therapeutics (SMT, Monmouth Junction, NJ, USA) has identified a novel class of antibacterial agents using their whole-cell screening technology, with two potential lead compounds that are active against multi-drug resistant *Staphylococcus aureus*. The compounds target the bacterial enzyme topoisomerase I, which maintains DNA in a form essential for growth.

Prabha Fernandes, CEO of SMT, believes that the compounds identified have great potential because they are the first known compounds to inhibit the topoisomerase I en-