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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.

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Molecules

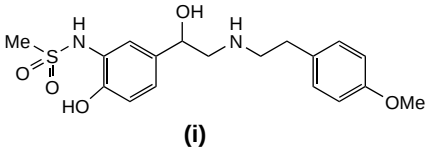
Identification of full agonists of the human β_3 adrenoceptor

There is a rapidly increasing incidence of obesity and non-insulin dependent diabetes mellitus (NIDDM) in the western world. Animal studies with diabetic rodents have shown that agonists of the β_3-adrenoceptor cause lipolysis in white adipose tissue and thermogenesis through proliferation of brown adipose tissue. The increased activity of brown adipose tissue proteins, such as thermogenin, uncouples the oxidation of free fatty acids to ATP generation with a concomitant increase in energy expenditure.

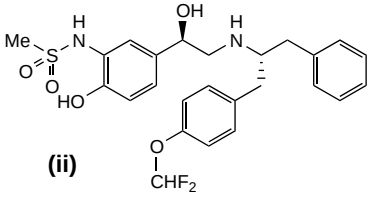
The lack of defined brown adipose tissue depots in humans defined the strategy of a group from Bristol-Myers Squibb (Princeton, NJ, USA) to seek to identify full agonists of the human β_3 adrenoceptor [1]. Compound screening identified several full agonists including compound **(i)**, which had a K_i value of 480 nM and intrinsic activity of 93%. The observed full agonism is attributed to the bioisosteric relationship of the methylsulphonamide substituted phenol and the natural ligands adrenaline and noradrenaline.

Following an extensive structure–activity relationship (SAR) investigation compound **(ii)** was identified as a potent full agonist of the β_3 adrenoceptor ($K_i = 21$ nM, intrinsic activity = 95%) with reasonable selectivity over the β_1 and β_2 subtypes 36- and 5-fold, respectively [2]. Compound **(ii)** exhibits a high volume of distribution (10 ± 5 l kg^{-1}) and a half-life of 7.3 ± 1.9 h after intravenous administration. However, extensive glucuronidation of the phenolic and benzylic hydroxyl groups caused low (<5%) oral bioavailability.

Chronic subcutaneous administration caused a dose-dependent reduction of plasma-glucose levels in a murine model of obesity induced diabetes. A clinical proof-of-concept study with a continuous intravenous infusion of compound **(ii)** failed to produce significant changes in the resting metabolic rate.



(i)



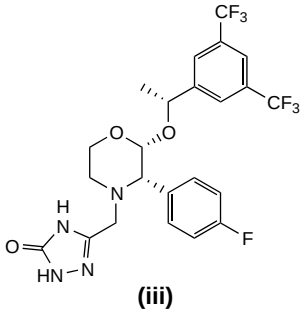
(ii)

1 Washburn, W.N. *et al.* (2001) β_3 Agonists. Part 1: evolution from inception to BMS194449. *Bioorg. Med. Chem. Lett.* 11, 3035–3039

2 Gavai, A.V. *et al.* (2001) BMS196085: a potent and selective full agonist of the human β_3 adrenoceptor. *Bioorg. Med. Chem. Lett.* 11, 3041–3044

Neurokinin-1 antagonist suitable for intravenous and oral clinical administration

The blockade of human neurokinin-1 receptors (h-NK$_1$, also known as substance P receptors) within the CNS is of interest for preventing emesis and treating depression. Compound **(iii)** is an orally active antagonist for h-NK$_1$ that displays a potent anti-emetic effect in the ferret [3]. However, **(iii)** has low aqueous solubility precluding its direct use by intravenous administration. A group from the Merck, Sharp and Dohme neuroscience research centre (Harlow, UK) sought to improve the aqueous solubility of **(iii)** to provide maximum flexibility in clinical use [4].



(iii)

The morpholine acetal core had previously been optimized for potency, selectivity and duration of action. The group thus focused on varying the pendant heterocycle and ultimately identified compound **(iv)**. This compound is a potent h-NK$_1$ antagonist ($IC_{50} = 0.19$ nM), with high aqueous solubility (>100 mg

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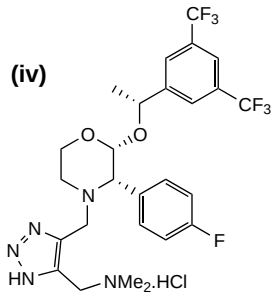
ml^{-1}) and >3000-fold selectivity against h-NK_2, h-NK_3 and 100 other receptors, ion channels and enzymes.

(iv)



In a guinea pig hind-foot-tapping model the compound displayed excellent CNS penetration and duration of action (ID_{50} = 0.3 mg kg^{-1} for 24 h intravenous pretreatment) for blockade of a centrally acting NK_1 receptor agonist. Compound **(iv)** was shown to inhibit retching and vomiting in the ferret induced by cytotoxic agents such as cisplatin and centrally acting agents such as morphine. The effect was observed both for intravenous dosing (ID_{90} = 0.1 mg kg^{-1}) and oral dosing as an aqueous solution (ID_{90} = 1 mg kg^{-1}).

Anti-depressant activity was observed in a guinea pig neonatal vocalization model (ID_{50} = 0.2 mg kg^{-1} perorally). The compound is thus highly effective in preclinical tests for emesis and depression.

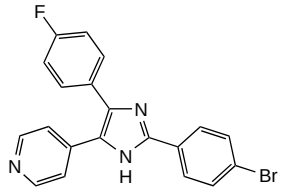
3 Hale, J.J. *et al.* (1998) Structural optimization affording 2-(*R*)-1(*R*)-3,5-*bis*(trifluoromethyl)phenylethoxy)-3-(*S*)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a potent orally active long-acting morpholine acetal human NK_1 receptor antagonist. *J. Med. Chem.* 41, 4607–4614

4 Harrison, T. *et al.* (2001) An orally active, water soluble neurokinin-1 receptor antagonist suitable for both intravenous and oral clinical administration. *J. Med. Chem.* 44, 4296–4299

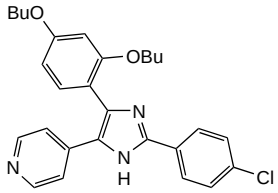
Imidazoles as glucagon receptor antagonists

The morbidity associated with non-insulin dependent diabetes (NIDDM) is in large part a result of prolonged elevated levels of plasma glucose. Glucagon is a peptide hormone that counters the effects of insulin to maintain glucose homeostasis. The hormone causes an increase in hepatic gluconeogenesis, glycogenolysis and reduces the ability of insulin to inhibit these processes. Antagonists of the glucagon receptor are thus anticipated to decrease the rate of glucose release from the liver and improve the response to insulin.

A group from the Merck research laboratories (Rahway, NJ, USA) undertook a screening effort to identify non-peptide antagonists of the human glucagon receptor (h-Glur) [5]. The triaryl imidazole **(v)** was identified (IC_{50} = 0.27 μM) but it is also an inhibitor of p38 mitogen-activated protein kinase (MAPK; IC_{50} = 0.16 μM).



(v)



(vi)

Investigation into the structure–activity relationships (SARs) showed the requirement for both the imidazole NH and the 4-pyridyl nitrogen atom for binding to the glucagon receptor. It was found that substitution of the 4-aryl group improved binding to the receptor and also conferred selectivity for the glucagon receptor over MAPK. Compound **(vi)** was identified (IC_{50} = 0.006 μM, h-Glur) and exhibited only 20% inhibition at 40 μM for p38 MAPK. In the presence of a physiological concentration of Mg^{2+} ions (5 mM) the activity of the compounds in the series dropped 2–25 fold for binding to h-Glur. In the presence of a physiological concentration of Mg^{2+} the activity of **(vi)** was 0.053 μM against h-Glur.

Thus by systematic SAR studies a selective small molecule was identified to help investigate the role of h-Glur antagonism in glucose homeostasis.

5 Chang, L.L. *et al.* (2001) Substuted imidazoles as glucagon receptor antagonists. *Bioorg. Med. Chem. Lett.* 11, 2549–2553

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Novel antitumour molecules

Potent inhibitors of src kinase activity

Tyrosine kinases (TKs) are enzymes that catalyze the specific phosphorylation of tyrosine residues on proteins. The highly homologous Src TK family are involved in several intracellular signalling pathways and are overexpressed in several human tumours, notably metastatic tumours. Src TKs are, therefore, a valid target for anticancer drug development. In addition, Src has been implicated in vascular endothelial growth factor (VEGF) signalling in endothelial cells, implying a possible anti-angiogenesis role for Src kinase. Src inhibitors might also have a role in the prevention of brain damage following stroke and in the treatment of osteoporosis.

Boschelli and coworkers at Wyeth-Ayerst Research (New York, NY, USA) have described the optimization of 4-phenylamino-3-quinolinecarbonitriles as potent inhibitors of Src activity [1]. Using the previously described Src kinase inhibitor 4-[(2,4-dichlorophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile [compound **(i)**; IC_{50} = 30 nM] as a starting point, several rounds of refinement of this lead compound through SAR studies led to the identification of compound