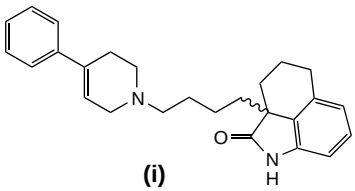
Monitor: molecules and profiles

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.

Molecules

Novel selective ligands for the 5-HT$_7$ receptor

The neurotransmitter serotonin (5-HT) has important roles in a variety of physiological and pathophysiological processes through the activation of seven types of 5-HT receptors (5HT$_1$–5HT$_7$). The biological functions of 5-HT$_7$, the most recent addition to the family, are still poorly understood [1]. Early data suggested that it could be involved in the vasodilation of blood vessels [2]. High levels of 5-HT$_7$ receptor mRNA have also been observed in the brain and the receptor appears to be involved in disturbance of circadian rhythms [3]. In previous papers [4,5], Kikuchi and collaborators reported on the affinity of a series of tetrahydrobenzindoles for the 5-HT$_7$ receptor. In particular, compounds **i** (DR4004) and **ii** (DR4365) were described as highly potent antagonists for the 5-HT$_7$ receptor. In addition, **ii** was found to show high selectivity with respect to 5-HT$_2$ receptor. On these bases, the same group has extended their investigations to other fused-ring tetrahydropyridine derivatives (**iiia–i**) [6].



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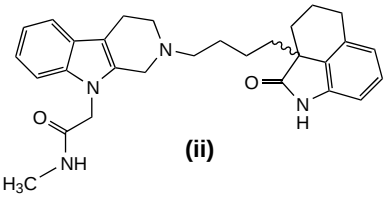

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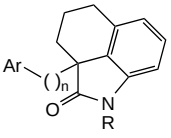

(iii a-i)

The compounds were evaluated for their affinity towards the 5-HT$_7$ and 5-HT$_2$ receptors. In particular, the affinity for the 5-HT$_7$ receptor was assayed in terms of their ability to displace the radioligand [^{3}H]5-carboxyamidotryptamine ([^{3}H]5-CT) from cloned human 5-HT$_7$ receptor expressed in COS-7 cells. Preliminary results indicated that, as for the previously described compounds, the optimum carbon chain length of this new series was n = 4. Several fused heterocycles were then considered. The thienopyridine (**iiid**, pK_i = 8.19 ± 0.15 for 5-HT$_7$ and pK_i = 6.08 ± 0.04 for 5-HT$_2$) and the isoquinoline derivative (**iiib**, pK_i = 8.35 ± 0.05 for 5-HT$_7$ and pK_i = 6.21 ± 0.16 for 5-HT$_2$) showed both high affinity and selectivity for the 5-HT$_7$ receptor. The furopyridine derivative (**iiie**, pK_i = 7.80 ± 0.21 for 5-HT$_7$ and pK_i <6 for 5-HT$_2$) had only moderate affinity. This could be a result of its reduced aromaticity. The imidazopyridine (**iiif**) and the pyrazolopyridine derivative (**iiig**) showed a low affinity. The *N*-methyl derivative of **iiid** (compound **iiih**, pK_i = 8.01 ± 0.09 for 5-HT$_7$ and pK_i = 6.02 ± 0.05 for 5-HT$_2$) retained both the affinity and selectivity of the parent compound. By contrast, the *N*-ethyl derivative of **iiid** [compound **iii(i)**, pK_i = 6.76 ± 0.16 for 5-HT$_7$ and pK_i = 6.31 ± 0.10 for 5-HT$_2$] showed low affinity for the 5-HT$_7$ receptor. This seems to indicate that the size of R in compound series **iii** strongly influences their binding to 5-HT$_7$ receptor. Further studies on compounds **iiid** and **iiih** showed their selectivity over the 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2C}$, 5-HT$_3$, 5-HT$_4$ and 5-HT$_6$ receptors. Finally, functional studies indicated **iiid** to be a 5-HT$_7$ receptor antagonist.

1 Tsou, A.P. *et al.* (1994) Cloning and expression of a 5-hydroxytryptamine7 receptor positively coupled to adenylyl cyclase. *J. Neurochem.* 63, 456–464
2 Leung, E. *et al.* (1996) Characterization of putative 5-HT$_7$ receptors mediating direct relaxation in Cynomolgus monkey isolated jugular vein. *Br. J. Pharmacol.* 117, 926–930
3 Schwartz, W.J. (1993) A clinician's primer on the circadian clock: its localization, function and resetting. *Adv. Int. Med.* 38, 81–106
4 Kikuchi, C. et al. (1999) Tetrahydrobenzindoles: selective antagonists of the 5-HT7 receptor. *J. Med. Chem.* 42, 533–535
5 Kikuchi, C. et al. (2002) 2a-[4-(Tetrahydropyridoindol-2-yl)butyl]tetrahydrobenzindole derivatives: new selective antagonists of the 5-hydroxytryptamine7 receptor. *J. Med. Chem.* 45, 2197–2206
6 Kikuchi, C. et al. (2002) Tetrahydrothienopyridylbutyl-tetrahydrobenzindoles: new selective ligands

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of the 5-HT7 receptor. *Biorg. Med. Chem. Lett.* 12, 2549–2552

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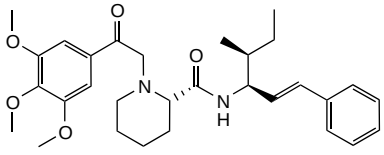
Combinatorial chemistry

Cathepsin K inhibitors

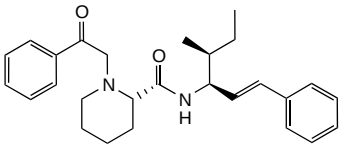
Cathepsin K, a cysteine protease that is predominantly expressed in osteoclasts, has been implicated in bone resorption through the use of selective peptide inhibitors, antisense oligonucleotides and the existence of a human genetic disorder, pycnodysostosis. These observations provide a rationale for the use of cathepsin K inhibitors as a treatment for diseases characterized by excessive bone loss, such as osteoporosis.

Recently, the first indication that inhibition of cathepsin K leads to a reduction in bone resorption in primates was achieved. Workers at Bayer (http://www.bayer.com) performed HTS of their compound collection, which provided the micromolar hit **i** [1]. The presence of an electrophilic carbonyl group (aminomethyl ketone moiety) in this molecule suggested the possibility for reversible formation of a covalent tetrahedral adduct with the active-site Cys25 similar to the case with other reported ketone inhibitors.

A small library of 26 compounds was synthesized in solution in an attempt to elucidate SAR based on the lead compound (**i**) found from HTS screening.



(i)



(ii)

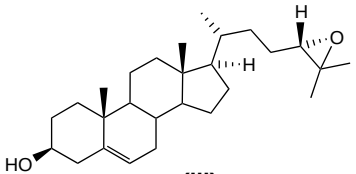
The library compounds were evaluated in a cathepsin K inhibition assay. One of the most potent compounds found was **ii**, which possessed a cathepsin K inhibition IC_{50} value of 230 nM. This work has produced a novel and useful template for cathepsin K inhibitor design and holds promise for further optimization.

1 Smith, R.A. et al. (2001) Discovery and parallel synthesis of a new class of cathepsin K inhibitors. *Bioorg. Med. Chem. Lett.* 11, 2951–2954

Liver X receptor agonists

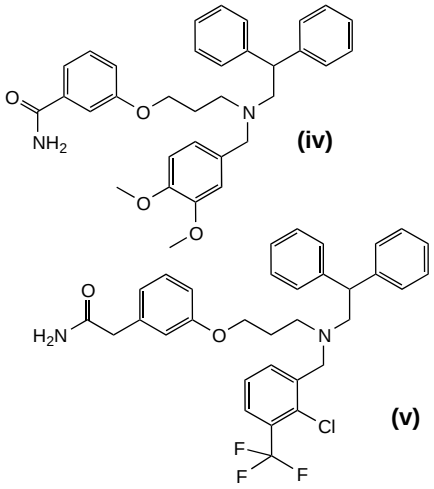
The increased incidence of cardiovascular disease (CVD) in westernized nations has been linked to increased dietary intake of cholesterol and saturated fats and an increase in low-density lipoprotein (LDL) particles. Accumulation of small, dense LDL particles in the arterial wall leads to the formation of cholesterol-laden foam cells, which are the hallmark of coronary atherosclerosis, and activation of the immune system. Although cholesterol-lowering drugs, such as statins, reduce the incidence of CVD in patients with high circulating levels of LDL cholesterol (LDLc), atherosclerosis also afflicts individuals with relatively normal LDLc levels. In contrast to LDL, the levels of high-density lipoprotein (HDL) particles are inversely related to the incidence of CVD. The protective role of HDL might result from its role in mediating 'reverse cholesterol transport' whereby cholesterol is transported from peripheral cells back to the liver. Thus, agents that promote reverse cholesterol transport by raising circulating levels of HDL could provide an alternative therapeutic option for the prevention of atherosclerotic CVD.

The liver X receptors, LXRα (NR1H3) and LXRβ (NR1H2) are oxysterol-activated transcripted factors that belong to the nuclear hormone receptor superfamily. It has been proposed that compound **iii** is an endogenous ligand for LXRα in the liver. Upon cholesterol feeding, the hepatic levels of **iii** in rats are raised to levels consistent with its putative role as a natural LXRα agonist.



(iii)

The identification of a novel chemical series of LXR agonists through solid-phase parallel synthesis of tertiary amines has recently been reported [2]. A library of 1280 compounds was synthesised on Rink amide solid phase resin, the design of which was based on the GlaxoSmithKline (http://www.gsk.com) HTS hit **iv**. The library compounds were screened for activity in the cell-free ligand-sensing assay (LiSA) for human LXRα. The LXRα LiSA measures the ligand-dependent recruitment of a 24 amino acid fragment of the steroid receptor coactivator 1 (SRC1) to the ligand-binding domain of the receptor. One of the most potent compounds isolated was compound **v**, which possessed an EC_{50} value of 45 nM in the LXRα–SRC1 LiSA. This work has provided a novel, potent lead for the development of drugs to increase reverse cholesterol transport and further work in this area is warranted.



(iv)

(v)

2 Collins, J.L. *et al.* (2002) Identification of a nonsteroidal liver X receptor agonist through parallel array synthesis of tertiary amines. *J. Med. Chem.* 45, 1963–1966

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