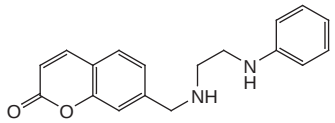
Monitor: molecules and profiles

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

Human dopamine D4-receptor antagonists

Recent evidence suggests that dopamine D4-receptor antagonists might have antipyschotic activity without the neurological side effects associated with D2-receptor antagonists. This has stimulated the search for potent, highly specific D4-receptor antagonists. A series of chromen-2-ones have recently been identified with selective affinity for this receptor subclass[1].



(i)

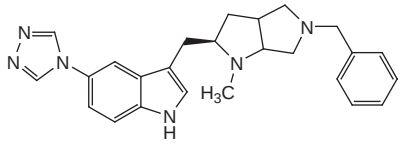
The compounds were screened for binding to cloned human, D2L-, D3- and D4.2-receptor subtypes expressed in Chinese hamster ovary K1 cells. Several compounds were found to have high affinity (K_i <20 nM) and more than 100-fold selectivity for the D4.2 receptor over the D2L receptor. A functional assay monitoring ^{3}H-thymidine uptake was used to demonstrate the antagonistic effects of these compounds at D4.2 receptors. On oral administration of 7-[(2-phenylaminoethylamino)methyl]chromen-2-one (**i**) to rats at 20 mg kg^{-1}, an increase in accumulation of 3,4-dihydroxyphenylalanine (DOPA) was observed in the hippocampus and striatum. Other studies examining the behavioural effects of this compound in mice and rats have indicated that this compound might have antipsychotic activity without the associated extrapyramidal side effects.

1 Kesten, S.R. *et al.* (1999) Design, synthesis, and evaluation of chromen-2-ones as potent and selective dopamine D4 antagonists. *J. Med. Chem.* 42, 3718–3725

Human 5-HT$_{1D}$-receptor agonists

The discovery that 5-HT$_{1B/1D}$-receptor agonists such as sumatriptan are effective treatments for migraine has led to extensive research in this field. Studies with h5-HT$_{1B}$ and h5-HT$_{1D}$-receptor antibodies suggests that the ability of these agonists to block peptide release in the peripheral meningeal arteries, inhibit neurotransmitter release in the brain stem and interrupt central pain transmission is mediated by the h5-HT$_{1D}$ receptor. Meanwhile, the h5-HT$_{1B}$-receptor subclass is associated with direct vasoconstriction.

Although various compounds have either now reached the market or are



(ii)

in late-stage clinical trials, none of the existing agents demonstrates selectivity for either receptor subclass. As selective h5-HT$_{1D}$-receptor agonists might reduce pain without the associated vasoconstriction, these compounds could be of greater therapeutic value than existing agents. As part of a programme to identify selective h5-HT$_{1D}$-receptor agonists to confirm the target tissue for antimigraine drugs, a series of conformationally restricted (benzylamino)methyl-substituted pyrrolidines have been produced, exemplified by (**ii**), with high h5-HT$_{1D}$-receptor binding and improved oral bioavailability over existing compounds[2]. Although these compounds have high h5-HT$_{1D}$-receptor binding affinities, none of the compounds showed any significant selectivity for the h5-HT$_{1D}$ over the h5-HT$_{1B}$ receptor.

2 Russell, M.G.N. *et al.* (1999) 2,7-Diazabicyclo[3.3.0]octanes as novel h5-HT$_{1D}$ receptor antagonists. *Bioorg. Med. Chem. Lett.* 9, 2491–2496

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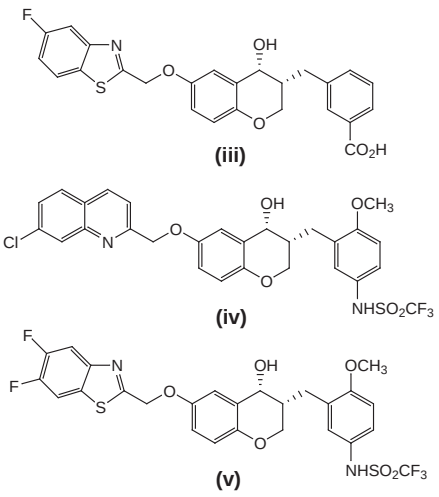
Cysteinyl LT_1-receptor antagonists

The cysteinyl leukotrienes (cysLT) have been implicated as key mediators in asthma through an action at the $cysLT_1$ receptor. Recent studies at Pfizer (Groton, CT, USA) have identified CP85958 (**iii**) as a potent $cysLT_1$-receptor antagonist. However, this agent has unacceptable liver toxicity in monkeys. Following analysis of the metabolic pathway, compounds have been synthesized that incorporate functional groups to increase potency, and are metabolically labile to enable metabolism by an alternative pathway[3].

These studies have led to the identification of CP199330 (**iv**) and CP199331 (**v**) $cysLT_1$-receptor antagonists, which



are equipotent with currently marketed $cysLT_1$-receptor antagonists, have good pharmacokinetic profiles in rats and monkeys, and are devoid of the liver toxicity observed with CP85958.

3 Chambers, R.J. *et al.* (1999) Discovery of CP-199,330 and CP-199,331: Two potent and orally efficacious cysteinyl LT_1 receptor antagonists devoid of liver toxicity. *Bioorg. Med. Chem. Lett.* 9, 2773–2778

Marine natural products as therapeutic agents

The marine environment provides a wealth of diverse chemical structures with biological activities. The increasing number of patents in this field in recent years provides an indication of the industrial growth of this field. A recent analysis of the patent literature provides a useful reference source for workers in this field[4].

This minireview focuses on the patent literature from 1996 to April 1999, during which time almost 100 patents have been issued in this field. The review covers the isolation and characterization of potential active agents from marine bacteria, marine algae, sponges, cnidaria, bryozoans, molluscs and tunicates. The paper also highlights the challenges of obtaining adequate quantities of these complex marine-derived metabolites for commercialization, emphasizing the importance and challenges of total chemical syntheses and the possible use of aquaculture and cell culture to provide strategies for marine natural product production. The author rightly highlights that the ultimate elucidation of the biosynthesis of these compounds might enable the use of biotechnology to develop recombinant systems for product manufacture.

4 Kerr, R.G. and Kerr, S.S. (1999) Marine natural products as therapeutic agents. *Exp. Opin. Ther. Patents* 9, 1207–1222

Combinatorial chemistry

Fourier-transform screening

Many different materials have been suggested as solid supports for combinatorial chemistry, but cotton threads have only occasionally been used. Using a one-dimensional support necessitates clever methods for the generation of a library, and a recent publication describes an ingenious method for both the synthesis and testing of a library[5].

To prepare this library, the cotton thread was wrapped around a cylinder of specified diameter, and zones marked on the side of the cylinder using wax lines. The cylinders could then be dipped into reagent solutions to attach various monomeric building blocks. After derivatizing the cotton with the first set of monomers, the cotton was unwound and rewound onto a cylinder of different diameter. In this way, subsequent steps of functionalization were staggered along the cotton thread with a different repeat frequency, thereby permitting the preparation of every monomer combination. A peptide library of the sequence Ac-X-X1-Pro-Gln-Phe-Ala-Ala-Ala-linker was constructed where X and X1 were chosen from seven and five alternatives, respectively. The compounds, designed to include the known streptavidin-binding motif, were screened for their ability to bind to fluorescein-conjugated streptavidin by passing the thread through a spectrometer cell using a modified audiotape cassette.

The variation of fluorescence along the thread, resulting from the differing peptide sequences bound along the cotton, gave a signal that could be Fourier-transformed to generate a library spectrum. The peaks in this spectrum represent the cylinder frequencies and their harmonics, with the magnitude of the signal indicating the significance of the activity averaged over the library. From this analysis, it was readily possible to discern the general features that were important for binding and helped to define trends in activity within the library.

5 Schwabacher, A.W. *et al.* (1999) Fourier transform combinatorial chemistry. *J. Am. Chem. Soc.* 121, 8669–8670

Erm methyltransferase inhibitors

Significant resistance to the macrolide–lincosamide–streptogramin (MLS)-type antibiotics in pathogenic bacteria stems from the bacteria's ability to selectively methylate ribosomal RNA near to, or within, the macrocycle binding site. The enzymes responsible for this

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