Monitor: molecules and profiles

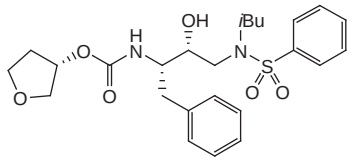
Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and 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 HIV protease inhibitors

The treatment of HIV involves the use of combination therapy against at least two therapeutic targets. Although combined drug therapies that exclusively target the viral reverse transcriptase have become available in recent years, protease inhibitors are still widely used in combination with these agents. These combination therapies have significantly reduced AIDS-related complications and death. However, the present generation of protease inhibitors still requires large doses for complete viral suppression. This often leads to side effects and poor patient compliance. Recently, various groups have therefore focussed on developing new-generation protease inhibitors with increased potency and resistance profile.

Spaltenstein, A. and coworkers have recently reported the synthesis of a series of HIV protease inhibitors that combine novel cyclic P1/P2 scaffolds based on the hydroxyethylene isostere of amprenavir (**i**) with a P1′-P3′ indanolamine-based



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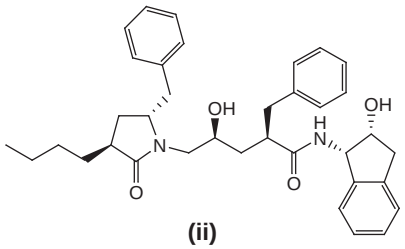


(ii)

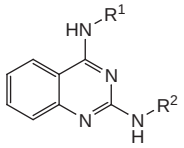
arrangement[1]. These studies have led to the identification of compound (**ii**), a 50 pM HIV protease inhibitor that showed comparable activity to currently available drugs in the MT-4 cell-based antiviral assay.

1 Spaltenstein, A. *et al.* (2000) Novel inhibitors of HIV protease: design, synthesis and biological evaluation of picomolar inhibitors containing cyclic P1/P2 scaffolds. *Bioorg. Med. Chem. Lett.* 10, 1159–1162

Neuropeptide Y Y_5-receptor antagonists

The 36 amino acid neuropeptide Y is found in high abundance in both the central and peripheral nervous systems. This peptide has been implicated in several physiological responses, including the stimulation of feeding, and in the pathophysiology of various disorders. Two receptor subtypes, Y_1 and Y_5, appear to be responsible for the centrally mediated neuropeptide Y feeding response, with compounds that act as antagonists of neuropeptide Y at Y_5 receptors being shown to reduce food intake in animal models. There is therefore an interest in developing novel Y_5-receptor antagonists as potential therapeutic treatments for eating disorders and obesity.

Workers from Novartis Pharma AG (Basel, Switzerland) and Synaptic Pharmaceutical Corporation (Paramus, NJ, USA) have recently reported a novel series of potent and selective Y_5-receptor antagonists[2]. A combination of combinatorial chemistry and database mining led to the identification of the quinazoline scaffold (**iii**). Lead opti-



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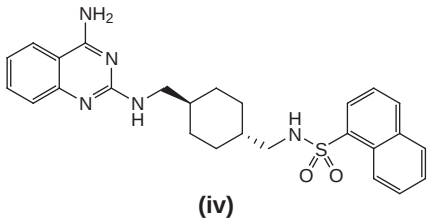

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mization led to the discovery of CGP71683A (**iv**), the first selective, nanomolar Y_5-receptor antagonist (IC_{50} = 2.9 nM). This compound has

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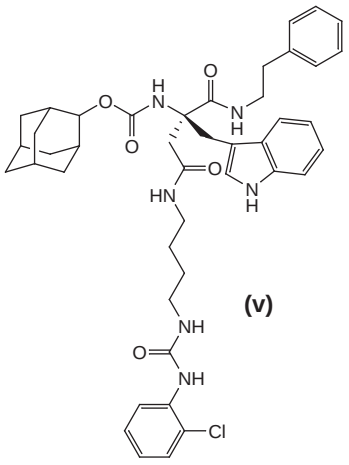
been subsequently employed in the elucidation of the involvement of the Y_5-receptor subtype in mediating food uptake induced by neuropeptide Y.

2 Rueeger, H. *et al.* (2000) Design, synthesis and SAR of a series of 2-substitutied 4-amino-quinazoline neuropeptide Y Y_5 receptor antagonists. *Bioorg. Med. Chem. Lett.* 10, 1175–1179

Non-peptide receptor agonist

The neuropeptide cholecystokinin (CCK) binds to two receptor subtypes, CCK_1 and CCK_2. Considerable research has recently focussed on the development of non-peptide ligands that will bind selectively to these receptor subtypes. In particular, various groups have been interested in developing selective CCK_1 agonists as these might have therapeutic use in the treatment of obesity.

Through optimization of the known CCK_1-receptor agonist (**v**) that has limited potency, Bernad, N. and coworkers have identified a series of derivatives with enhanced affinity and potency for the CCK_1 receptor[3]. The optimal compound, PD170292 (**vi**), has a pharmacological profile similar to the CCK analogue JMV180, behaving as an agonist at the high-affinity CCK_1-receptor binding sites and as an antagonist at the low-affinity CCK_1 receptor binding sites. In addition to having nanomolar affinity for the rat pancreatic



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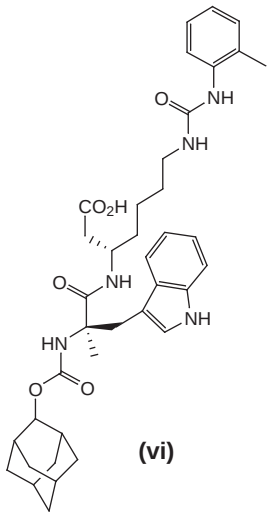


(vi)

CCK_1 receptor, this compound binds to CCK_2 receptors in guinea pig brain membranes where it was shown, like JMV180, to act as an antagonist.

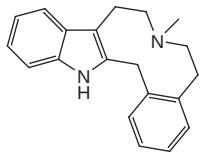
This compound is therefore the first non-peptide derivative to possess the same pharmacological profile as JMV180. Further optimization of this structure will undoubtedly lead to further selectivity and a better understanding of the structure–activity relationship (SAR) of the CCK receptors.

3 Bernad, N. *et al.* (2000) The design and synthesis of high efficacy, non-peptide CCK_1 receptor agonist PD 170292. *Bioorg. Med. Chem. Lett.* 10, 1245–1248

Dopamine-receptor antagonist

Various selective dopamine-receptor antagonists have previously been shown to be useful neuroleptic compounds. These agents tend to interact specifically with one or more of the dopamine-receptor subtypes D1, D3 and/or D4. A key approach to the development of new approaches is the modification of the endogeneous ligand, dopamine. Although rigidification of the arylalkyl amine chain tends to reduce substrate affinity, it might increase receptor-subtype selectivity.

Witt, T., Hock, F.J. and Lehmann, J. have recently reported the discovery of a new class of dopamine antagonists for future investigation based on the partially hydrogenated derivatives of the new heterocyclic ring system, benz[*d*]indolo[2,3-*g*]azecine[4]. Biological evaluation of these compounds identified 7-methyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine (**vii**) as



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having greater affinity for the D1-receptor binding site (K_i = 80 pM) than butaclamol and SCH23390 in a rat striatal binding assay. The compound shows good selectivity for the D1 receptor versus D2 and 5-HT_2 receptors and α_1-adrenoceptors, and characterization using a murine functional assay demonstrated that this compound was a D1-receptor antagonist. This compound offers potential as a useful lead candidate for the future development of a new class of dopamine-receptor antagonists.

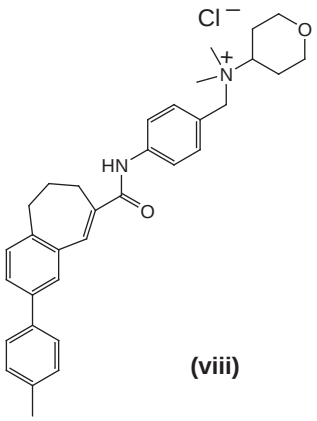
4 Witt, T. *et al.* (2000) 7-Methyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine: a new heterocyclic system and new lead compound for dopamine receptor antagonists. *J. Med. Chem.* 43, 2079–2081

CCR5 antagonists as anti-HIV agents

The fusion and entry of macrophage-tropic HIV-1 into host cells has been shown to involve the β-chemokine receptor CCR5. The natural ligands for CCR5 [regulated on activation, normal T-cell expressed and secreted (RANTES) and macrophage inflammatory protein] are known to block M-tropic HIV-1 infection. This suggests that nonpeptide CCR5 antagonists could be useful inhibitors of M-tropic HIV-1 replication.

Shiraishi, M. and coworkers have described the discovery of a series of novel, potent and selective small-molecule CCR5 antagonists following HTS of the

chemical library held by Takeda Chemical Industries Ltd (Osaka, Japan) using Chinese hamster ovary cells stably expressing CCR5 (Ref. 5). Lead optimization identified *N*,*N*-dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]-tetrahydro-2*H*-pyran-4-aminium chloride (**viii**) as a potent and selective CCR5 antagonist (IC_{50} = 1.4 nM). Further studies demonstrated that this compound also inhibited the replication of macrophage M-tropic HIV-1 (Ba-L strain) in both MAGI–CCR5 cells and peripheral blood mononuclear cells with EC_{50}s of 1.2 and 3.7 nM, respectively. This compound has subsequently been selected for clinical evaluation.



(viii)

5 Shiraishi, M. *et al.* (2000) Discovery of novel, potent, and selective small-molecule CCR5 antagonists as anti-HIV-1 agents: synthesis and biological evaluation of anilide derivatives with a quaternary ammonium moiety. *J. Med. Chem.* 43, 2049–2063

Andrew Lloyd

Pharmacogenomics

Qualitative gene profiling using differential analysis of transcripts with alternative splicing

RNA splicing is a tightly regulated process essential for gene expression. The process is cell-type specific and enables different cells to be characterized by their splicing potential or spliceome. The splicing profile might be modulated by both mutations and modifications of signaling pathways. As the deletion of exons or retention of introns within the coding sequence will modify the functional domains of proteins, the identification of changes in the spliceome provides a means of identifying functional domains that are specifically regulated at the level of RNA splicing. Comparisons of spliceomes from diseased cells could enable the identification of novel therapeutic targets. Similarly, spliceome profiling could provide an alternative means of assessing toxicity and efficacy of candidate drugs and the identification of information that will enable differentiation between responders and non-responders.

As part of a review of this field, Schweighhoffer, F. and coworkers have described a novel approach to systematically characterize RNA splicing alterations using differential analysis of transcripts with alternative splicing (DATAS)[1]. DATAS enables the systematic identification of spliced sequences that are differentially expressed in mRNA populations. Samples for comparison can be obtained from human or animal biopsies as well as cell culture. Cytosolic polyadenylated RNAs and their corresponding cDNAs are prepared using standard techniques from the samples under comparison. Heteroduplexes of RNA and DNA resulting from cross-hybridization of the different samples are then prepared and RNaseH used to release non-hybridized sequences (Fig. 1). These sequences represent splicing differences, translocations and deletions within the genes and are subsequently isolated, reverse transcribed and cloned to give libraries that can be examined using polyacrylamide gel electrophoresis (PAGE).

This alternative pharmacogenomic approach provides new tools for identifying potential therapeutic targets in

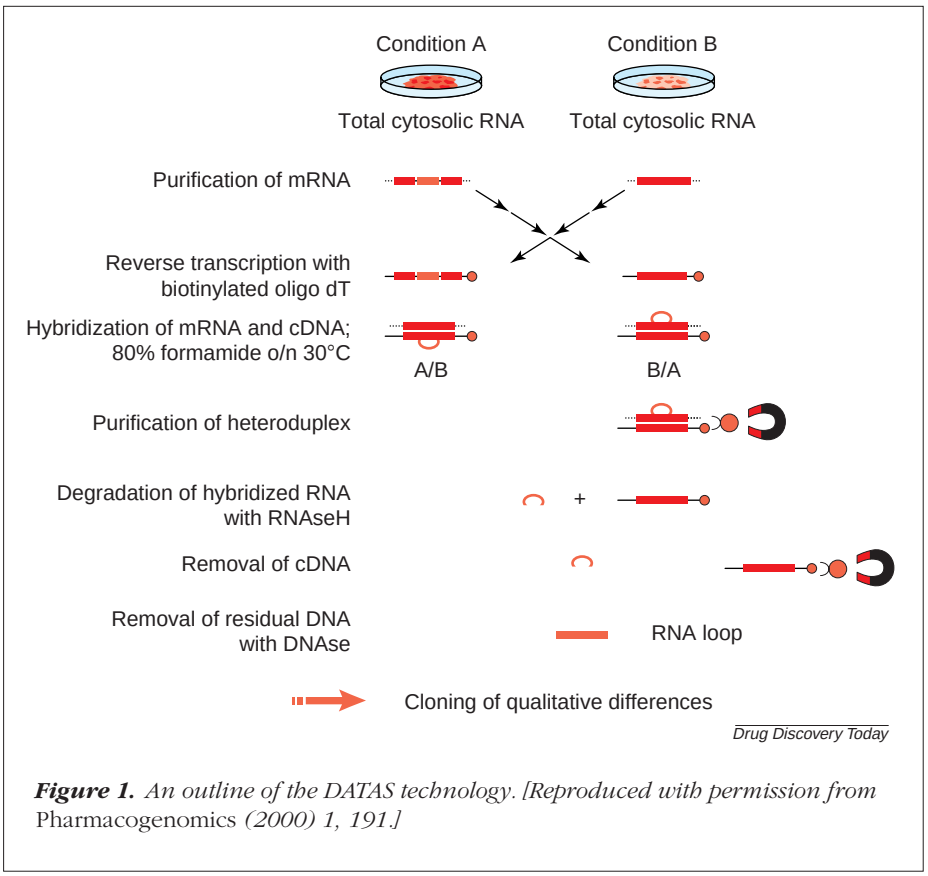


Figure 1. *An outline of the DATAS technology. [Reproduced with permission from* Pharmacogenomics *(2000) 1, 191.]*

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