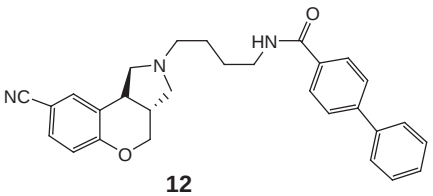
there are two groups of dopamine receptors: a D2-group comprises the D2, D3 and D4 receptors and the D1-group comprises the D1 and D5 receptors. Antipsychotic agents are believed to exert their therapeutic effects through antagonism of mesolimbic D2 receptors. However, interactions with D2 receptors located at other sites appear to contribute to the side effects of these agents. The D3 receptors are localized primarily in the limbic areas of the brain and have an affinity for many antipsychotic agents that interact with D2 receptors. Specific D3-receptor antagonists might therefore possess antipsychotic properties without the D2-receptor-associated neurological and endocrine side effects. To investigate this hypothesis, Dubuffet, T. and coworkers synthesized a novel series of benzopyrano[3,4-c]pyrrole derivatives and evaluated the antagonist activity of these agents at D3 and D2 receptors [*Bioorg. Med. Chem. Lett.* (1999) 9, 2059–2064].

These studies identified (**12**) as a potent (pK_i = 9.5) and selective D3-receptor antagonist. The therapeutic potential of this compound, which has also been



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shown to have adequate brain penetration and *in vivo* antagonistic properties, is presently under evaluation.

Emerging molecular targets

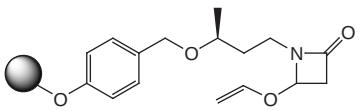
Apoptotic protease activating factor-1

As caspase activation is important in apoptotic cell death, various pharmaceutical and biotechnological companies are interested in agents that inhibit proximal caspase activation as potential treatments for a range of disorders. A recent Genetech patent (WO9855615) describes the first mammalian homologue of the *Caenorhabditis elegans* cell death gene *CED-4*, apoptotic protease activating factor-1A (Apaf-1). The role of this protein in the modulation of caspase activation and associated apoptotic cell death is described in detail in a recent patent evaluation that also highlights the therapeutic potential of this molecular target [*Exp. Opin. Ther. Patents* (1999) 9, 1139–1142]. However, as it is an increasingly common problem, this patent might serve to restrict methods of gene expression, protein production and compound screening available to those wishing to use Apaf-1 as a therapeutic target for the inhibition of proximal caspase activity. This might therefore hinder the short-term development of novel therapeutic agents for the treatment of certain diseases.

Combinatorial chemistry

Synthesis of β-lactams

The β-lactam ring is the key reactive functionality of all penicillin and cephalosporin antibiotics, and has subsequently attracted attention as a target for combinatorial chemistry. However, there have been few reports of solid-phase synthetic approaches to these molecules that might permit the synthesis of a library of analogues. Furman, B. and coworkers have recently described a resin-supported approach to the synthesis of 1-oxacephams that might offer potential biological activity [*Angew. Chem. Int. Ed.* (1999) 38, 1121–1123].



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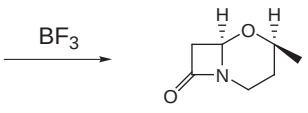

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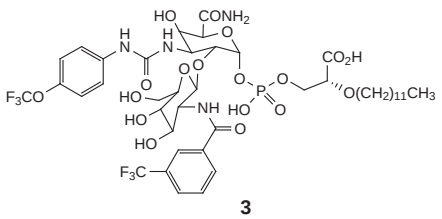
This synthesis is dependent on the final cyclization/cleavage step, where the oxazine ring is formed and proceeds with simultaneous cleavage from the solid support. Commencing with Wang resin, the intermediate (**1**), when treated with boron trifluoride, is converted to the 1-oxacepham (**2**) with a good yield and high diastereomeric purity.

Antibacterial disaccharides

Synthesis of the bacterial cell wall continues to be an attractive target for the discovery of novel antibacterial agents. The transglycolase enzyme is essential for the lengthening of peptidoglycan polymers and might be required to initiate chain growth. The moenomycin family of natural products contain naturally occurring antibacterials that act through inhibition of transglycolase. As moenomycin A is a complex pentasaccharide with a long lipid side-chain, Sofia, M.J. and coworkers have used combinatorial chemistry to identify novel disaccharides that might possess cell-wall inhibitory activity [*J. Med. Chem.* (1999) 42, 3193–3198].

A library of 1300 disaccharides were prepared on solid-phase supports using acid, isocyanate and lipid building-blocks. The combinatorial library employed the IRORI radio-frequency tagging method for directed-sorting mix-and-split, and each compound was prepared as a discrete entity. The final products were screened for both inhibition of bacterial cell wall synthesis and inhibition of bacterial cell growth. The most active compounds, exemplified by (**3**) had IC_{50} values of bacterial cell wall



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synthesis inhibition below 15 μg mL^{-1} and minimum inhibitory concentration

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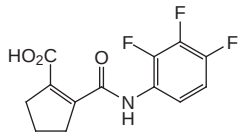
(MIC) values below 25 μg mL^{-1}.

Although moenomycin A is still a more potent inhibitor of cell wall synthesis, these structurally distinct and simpler compounds are equipotent with vancomycin and are active against *Enterococcus faecium*, a moenomycin-resistant strain.

Computational library screening

The advance of molecular modelling techniques now permits the computational screening of virtual combinatorial libraries. This approach has been successfully used by de Julián-Ortiz, J.V. and coworkers to identify novel anti-herpes compounds [*J. Med. Chem.* (1999) 42, 3308–3314]. Following the compilation of screening data from the literature, application of the Furnival–Wilson algorithm generated subsets of descriptors of the active compounds. Having generated a model of activity against the herpes simplex virus type 1 (HSV-1), a consideration of virtual library structures allowed the computational selection of likely antiviral compounds, chosen if they satisfy every discriminant equation in the model.

The two libraries, phenol esters and



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anilides, formed from two databases of building-blocks, yielded five new structures of which three had appreciable anti-HSV-1 activity. For example, compound (**4**) had an IC_{50} value of 0.9 μM. There were no obvious chemical or geometrical features of the newly discovered active compounds that were related to the structures in the training set, indicating that there must be a more subtle topological pattern underlying the biological activity. This study indicates that with a suitable set of active compounds, it might not be necessary to synthesize entire combinatorial libraries to discover novel leads.

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Histamine H_3 receptors and the gastrointestinal tract

Histamine H_3 receptors are prejunctional receptors that are widely distributed in central and peripheral tissues, and which reduce neurotransmitter release from different types of neurons[1]. These receptors have also been identified in the gastrointestinal (GI) tract, where they are located in several cell types including neurons [either cholinergic or nonadrenergic, noncholinergic (NANC)], enteric ganglia, histaminocytes and other paracrine cells (such as fundic somatostatin cells). In some species, these receptors are located postjunctionally on gastric parietal cells, and vascular and intestinal muscle cells[2]. Data available so far indicate that H_3 receptors might influence gastric acid secretion, intestinal motility and mucosal defense mechanisms.

Gastric secretion

The effects mediated by H_3 receptors on acid production are dependent on the species and the secretory stimulus considered. For example, H_3-receptor activation inhibits acid output in cats and dogs, where indirect stimuli, such as 2-deoxy-D-glucose, pentagastrin, bombesin and peptone meal, are markedly reduced. The mechanism underlying the gastric antisecretory effect is primarily related to an inhibition of the release of histamine from enterochromaffin-like (ECL) cells and a reduction in vagal input to the parietal cells, as there is no evidence of H_3 receptors on parietal cells[3]. Although a direct inhibitory effect on acid secretion has been postulated in rabbits[4], no effect was observed in rats despite H_3-receptor activation inhibiting histamine release from ECL cells. The concomitant reduction in somatostatin release from fundic D cells, which has the opposite effect on histamine release, might explain its lack of effect on acid production. By contrast, there is a predominant effect on somatostatin release in mice, as administration of H_3-receptor agonists increases acid secretion in this species[5].

The recent findings that *Helicobacter pylori* (*Hp*) is able to produce a histamine metabolite, N^{α}-methylhistamine (N^{α}-MHA)[6], which is a potent H_3-receptor agonist, has raised the possibility that H_3 receptors are responsible for the reduced somatostatin release, and consequent hypergastrinaemia, observed in *Hp*-positive patients. It must be considered, however, that H_3 receptors might also reduce histamine release. Furthermore, N^{α}-MHA is also a potent H_2-receptor agonist that can directly stimulate parietal cells to produce acid, and these multiple components make the relationship between *Hp* and acid production very complex.

The activation of H_3 receptors has proven to exert beneficial effects in the GI tract by enhancing gastric defence mechanisms, as selective H_3-receptor agonists provide significant protection against a variety of noxious stimuli including ethanol, acetylsalicylic acid and stress[7]. Histological study in the gastric mucosa of rats treated with the H_3-receptor agonist *R*-α-methylhistamine showed an increased restitution of surface epithelial cells and increased thickness of adherent mucus layer, together with an increase in the number and volume of mucous cells. The recent findings that H_3 receptors might also mediate anti-inflammatory effects in different experimental models of cutaneous in-

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