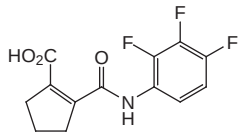
(MIC) values below 25 μg mL^{-1}.

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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flammation[8,9] might open an interesting new field of research on H_3-receptor agonists. These compounds could reduce the release of inflammatory mediators from mast cells and reduce the vascular component of neurogenic inflammation by inhibiting neuropeptide release from sensory nerves. In this connection, it should be noted that these agents could represent very unusual anti-inflammatory drugs, displaying gastroprotective properties. This could be of potential interest, considering that the major disadvantage of nonsteroidal anti-inflammatory drugs and steroids is a high incidence of GI adverse effects.

Intestinal mobility

As for GI motility, the effect mediated by H_3 receptors is less promising in terms of therapeutic application. Activation of this receptor subtype inhibits neurogenic contractions, without any direct alteration of muscle contractility. H_3 receptors are mainly located on the nerve terminals of the myenteric plexus, on pre- and post-ganglionic cholinergic and NANC fibres, where they negatively modulate the release of excitatory neurotransmitters, such as acetylcholine and substance P. However, unlike other prejunctional receptor systems (such as the α_2-adrenoceptor and adenosine A_1 receptor), H_3 receptors do not play a major role in the regulation of intestinal peristalsis, at least in experimental models from rabbits and guinea pigs[10].

Other visceral functions

Finally, there is scarce information concerning the involvement of H_3 receptors in the regulation of other visceral functions. H_3 receptors have been involved in the regulation of the mesenteric circulation[11], in the reduction of 5-hydroxytryptamine from ECL cells[12] and in the modulation of intestinal chloride-ion secretion[13].

Despite the large quantity of information concerning the GI effects of H_3-receptor ligands that has been accumulated in recent years using animal models, there are still few human studies. It would therefore be premature to assess the therapeutic potential of H_3-receptor ligands in GI-tract disorders. However, it is evident that they will make an important contribution to clarifying the role of histamine in the regulation of GI function.

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