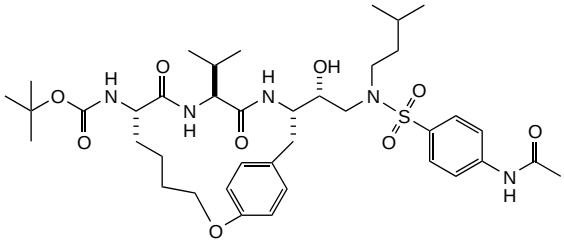
An interesting feature of this chemotype is that the ribose sugar is required for activity: the 2′-deoxy analogue has no activity against HBV. Finally, compound **(iii)** was found to be selective for HBV over other viruses, such as HIV, HSV, CMV (cytomegalovirus), VZV (varicella zoster virus) and EBV (Epstein-Barr virus), and was minimally toxic to non-infected cells.

2 Sood, R.K. *et al.* (2002) Novel ring-expanded nucleoside analogs exhibit potent and selective inhibition of hepatitis B virus replication in cultured human hepatoblastoma cells *Antiviral Res.* 53, 159–164

Cyclic-peptide based HIV-protease inhibitors

Proteases usually bind their substrate peptides in β-sheet structures. HIV-protease is no exception and this principle can be used in the design of peptomimetic inhibitors of the enzyme. As such, these inhibitors can potentially serve as antiviral therapeutics against AIDS.

Cyclic peptide based inhibitors of HIV protease are the focus of a report from the Center for Drug Design and Development at the University of Queensland, Australia [3]. An example is compound **(iv)** with a K_i value of 2.0 nM against the enzyme and a IC_{50} value of 177 nM against HIV in cell culture. The macrocycle of this peptidomimetic holds the inhibitor in the β-sheet form, mimicking the substrate and thus reducing the entropy loss associated with binding to the active site. Because the entropic energy price is paid before binding it is assumed that there is more tolerance for side-chain fit. The cyclic peptides also have the advantage of being more resistant to *in vivo* degradation and more easily absorbed into the cell than their linear peptide counter parts.



(iv)

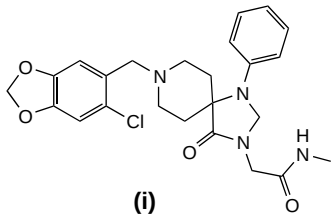
3 Glenn, M.P. *et al.* (2002) β-Strand mimicking macrocyclic amino acids: Templates for protease inhibitors with antiviral activity *J. Med. Chem.* 45, 371–381

Michael A. Walker
Bristol-Myers Squibb
Pharmaceutical Research Institute
Wallingford, CT 06492, USA
tel: +1 203 677 6686
fax: +1 203 677 7702
e-mail: walkerma@bms.com

Combinatorial chemistry

μ Opiate ligands

Parallel synthesis and HTS, which rely to varying degrees on molecular modelling for library management, description, similarity evaluation and quantitative SARs, have led to a dramatic increase in throughput in the primary stages of drug discovery. A generic hit-to-lead strategy, relying on the systematic generation and evaluation of analogues around the parent hit compound, has been reported [1]. The strategy makes use of two different analoging methods to cover efficiently the structural space around hits. The first method is classical exploratory analoging based on similar topology. The second method relies on algorithms for rapid generation of 3D molecular fingerprints based on multi-conformational models of candidate compounds, in combination with similarity evaluation tools for the comparison of 3D fingerprints. To validate this strategy experimentally, the authors have applied this to the search for potent μ opiate ligands. A library of 294 single compounds was synthesized in solution. The library compounds were screened at 10 μM for binding at the μ opiate human receptor. One of the most potent compounds found was **(i)**, (IC_{50} = 0.9 nM against the human μ-opiate ligand). This work has shown that the two design methods indicated could be used in parallel for the elucidation of SARs, and the potent compounds discovered here could be important in further work in this area.



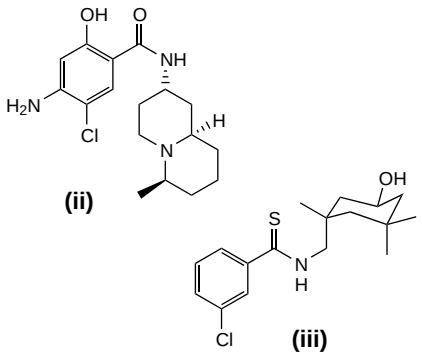
(i)

1 Poulain, R. *et. al.* (2001) From hit to lead. Combining two complementary methods for focused library design. Application to μ opiate ligands. *J. Med. Chem.* 44, 3378–3390

Influenza virus fusion inhibitors

Problematic annual outbreaks of influenza continue to emerge and are associated with significant morbidity and, in certain populations, mortality. These annual epidemics are driven by antigenic drift, a consequence of the poor fidelity of the influenza virus RNA polymerase. The more insidious pandemics, which occur less frequently but impose a much greater disease burden, result from antigenic shift, the production of reassortant viruses. Recently, a strategy of prophylaxis that depends upon vaccination campaigns conducted immediately before the onset of the influenza season has been implemented. However, the success of this approach is dependent upon an ability to accurately predict the anticipated circulating virus several months in advance, to produce an appropriately effective vaccine. As part of an overall effort towards further defining the fusion-inhibiting pharmacophore and identifying compounds with both increased potency and inhibition of H3 influenza subtypes, exploration of SARs associated with the amine element of literature compound **(ii)** (BMY27709 [2], identified as an effective and potent inhibitor of the H1 and H2 subtypes of influenza A virus strain [3]) were performed. Two libraries, giving a total of 418 single compounds, were synthesized

  PII: S1359-6446(02)02269-9



in solution. The libraries were screened for inhibition of the H1 subtype of influenza A viruses that act by preventing the pH-induced fusion process, thereby blocking viral entry into host cells. In a plaque-reduction assay, the most potent inhibitor found from both libraries synthesized was compound **(iii)**, which possessed an EC_{50} value of 0.02 μg ml^{-1}. This work has identified highly potent inhibitors of H1 influenza fusion based on the lead BMY27709 **(ii)** and could lay the foundation for further work to improve potency in this series.

2 Luo, G-X. *et al.* (1996) Characterization of a hemagglutinin-specific inhibitor of influenza A virus. *Virology* 226, 66–76

3 Deshpande, M.S. *et al.* (2001) An approach to the identification of potent inhibitors of influenza virus fusion using parallel synthesis methodology. *Bioorg. Med. Chem. Lett.* 11, 2393–2396

Paul Edwards
Lead Discovery Technologies
Pfizer Global Research and Development
Sandwich, Kent, UK
fax: +44 1304 643 555
e-mail: paul_edwards@sandwich.pfizer.com

Drug delivery

Zero-order release of nifedipine

Nifedipine is a calcium antagonist that is commonly prescribed as an antianginal and antihypertensive. Clinical studies have shown that the duration of the hypotensive effect has a direct correlation to the nifedipine plasma concentration. Nifedipine has poor aqueous solubility, rate-limiting absorption through the gastrointestinal (GI) tract and a biological half-life of ~2 h. Absorption of the drug is poor when orally administered via the currently available immediate-release dosage forms. Nifedipine is also available as an extended release formulation that consists of a tablet core surrounded by a slow-releasing layer composed of the drug and hydrophilic polymers, such as hydroxypropylcellulose and hydroxypropylmethylcellulose. The outer slow-release layer provides initial drug release followed by a rapid drug release from the tablet core. The overall drug release from such a formulation follows first-order kinetics. One of the most desirable characteristics in a controlled-release formulation of a drug such as nifedipine is to achieve zero-order kinetics, or constant drug release, thus maintaining a constant therapeutic level *in vivo*.

Mehta *et al.* have recently reported the development of a novel, multi-unit, erosion matrix-pellet system, with zero-order release *in vivo* [1]. The principal components of the formulation include nifedipine and two members of the Eudragit® (Rohm GmbH, Darmstadt, Germany) class of polymers, Eudragit L10055 and Eudragit S100. This erosion matrix formulation was extruded into small pellets, ~2mm in diameter, which were packed into capsules. The pellets erode slowly in the GI tract, thus releasing nifedipine. An *in vivo* study in beagle dogs demonstrated that the erosion matrix formulation releases nifedipine by zero-order kinetics.

The bioavailability of nifedipine from erosion matrix pellets was tested against a currently available immediate-release soft gelatin capsule formulation (Adalat®; Bayer Aktiengesellschaft, Leverkeusen–Bayerwerk, Germany) by dosing, in a randomized comparative cross-over study, the two formulations to four dogs. Capsules containing 30 mg nifedipine were dosed in each phase of the study. After a one-week washout period, dogs were dosed with the opposite formulation. Serial blood samples were drawn and the plasma analyzed by HPLC assay, the results of which were used for pharmacokinetic evaluation [C_{max}, T_{max}, $AUC_{0-24\,h}$ and mean residence time ($MRT_{0-24\,h}$)]. The mean T_{max} for nifedipine erosion matrix pellets was 15.5 h. By comparison, the T_{max} of the immediate-release formulation was 0.5 h. The $MRT_{0-24\,h}$ was 12.5 h for the erosion matrix pellets and 1.72 h for the immediate-release formulation, indicating a much longer residence time in the GI tract. The mean $AUC_{0-24\,h}$ for nifedipine from the erosion matrix pellet formulation was fourfold higher than the conventional immediate-release gelatin capsules.

Nifedipine release from the erosion matrix pellets is governed by the polymer-controlled surface erosion process. By this mechanism, drug release occurs in a constant fashion in the form of a microfine suspension in the GI tract and, thus, is readily available for a prolonged period. Overall, the release of nifedipine from the erosion matrix pellet formulation followed zero-order kinetics and a constant plasma level of nifedipine was observed. Nifedipine release from this erosion matrix formulation continued for >24 hours, at which point the observations were discontinued. It is also interesting to observe that a significant nifedipine plasma concentration was obtained 1 h after administration without any significant lag time. Thus, careful consideration of variables in a controlled-release formulation had a considerable effect on *in vivo* release parameters. In this case, it could lead to a formulation of nifedipine with therapeutic advantages over those currently available, and the same principles could potentially be applied to other poorly soluble drugs.

1 Mehta, K.A. *et al.* (2002) *In vivo* release performance of nifedipine in dogs from a novel Eudragit-based multi-unit erosion matrix. *Drug Deliv. Technol.* 2, 34–37

John Weidner
Scientist, Parallel Synthesis
Medicinal Chemistry, Emisphere Technologies
765 Old Saw Mill River Rd
Tarrytown, NY 10591, USA
tel: +1 914 785 4792
fax: +1 914 593 8250
e-mail: Jweidner@emisphere.com

  PII: S1359-6446(02)02270-5