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.

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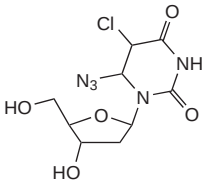
Novel antiviral molecules

Nucleoside analogue inhibitors of herpes viruses

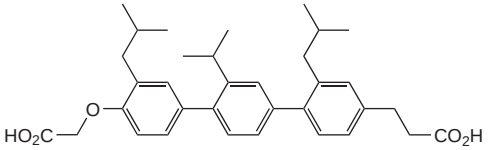
The viruses belonging to the herpes family – herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), human cytomegalovirus (HCMV) and Varicella–Zoster virus (VZV) – are often associated with mild illnesses. However, infection with these viruses can lead to severe illness, especially in immunocompromised people, such as AIDS patients. Acyclovir is currently used against HSV infections, whereas ganciclovir is used against HCMV. Unfortunately, virus strains resistant to these drugs have been observed in the clinic, necessitating the discovery of new agents [1].

Nucleotide analogues of 2′-deoxyuridine, wherein the 5- and 6-positions are modified by a halogen atom and an azido-group, have recently been discovered as novel inhibitors of several viruses from the herpes family [2]. Thus **i** was found to inhibit HSV-1, HSV-2, HCMV and VZV (EC_{50} = 0.33–28.9 μM) in cell culture. At the same time, this compound was found to be minimally cytotoxic to the host cell (IC_{50} = >327 μM).



(i)

1 Freeman, S. and Gardiner, J.M. (1996) Acyclic nucleosides as antiviral compounds. *Mol. Biotechnol.* 5, 125–137
2 Kumar, R. (2002) 5-Bromo (or Chloro)-6-azido-5,6-dihydro-2′-deoxyuridine and -thymidine derivatives with potent antiviral activity. *Bioorg. Med. Chem. Lett.* 12, 275–278



(ii)

Rationally designed inhibitor of HIV gp41 assembly

The HIV fusion protein gp41 contains two helical regions called the N- and C-helical domains, which denote their relative positions on the protein. Association between these two regions into a six-helix bundle is a necessary event in the fusion of the virus with the host cell. Known inhibitors of helix-bundle formation and, therefore, of HIV infection have been constructed from peptides with sequences corresponding to the C-helical domain. These inhibitors presumably act by binding to the N-terminal helical domain, thus preventing the formation of the six-helix bundle.

An interesting report from Andrew Hamilton's laboratory at Yale University (New Haven, CT, USA) describes the rational design of a small-molecule inhibitor of gp41 assembly [3]. The molecule, **ii**, is called a proteomimetic because it mimics the α-helical seven-amino-acid domain of the N- and C-helical regions. The alkyl groups attached to the terphenyl template correspond to the side chains of the *i*, *i* + 4 and *i* + 7 amino acid residues of the helix. Compound **ii** was found to disrupt the formation of the six-helix bundle and inhibit gp41-mediated fusion with an IC_{50} value of 15.7 μg ml^{-1}.

3 Ernst, J.T. *et al.* (2002) Design of a protein surface antagonist based on α-helix mimicry: inhibition of gp41 assembly and viral fusion. *Angew. Chem. Int. Ed. Engl.* 41, 278–281

Combinatorial chemistry to optimize activity and pharmacokinetics of indinavir

One of the most important advances in AIDS therapy was the discovery and clinical application of HIV-protease inhibitors. Although these compounds are potent and add to the overall reduction of mortality and morbidity associated with HIV infection, there is still room for further improvement. As with most antiviral agents, viral resistance develops from prolonged treatment. In addition, some protease inhibitors suffer from poor *in vivo* half lives and complicated dosing regimens. For example, the highly potent protease inhibitor indinavir **(iii)** is affected by significant first pass metabolism. Therefore, to realize improvements in anti-HIV therapy involving HIV-protease

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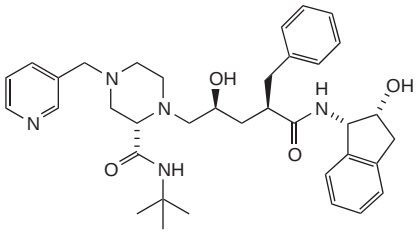

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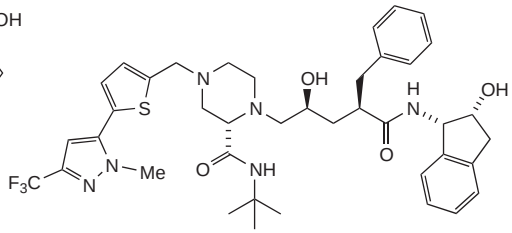

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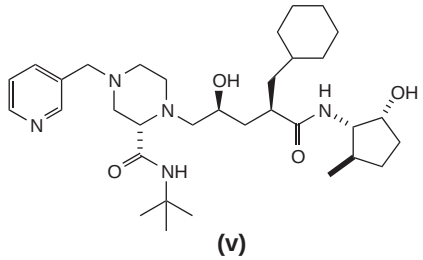


(v)

inhibitors, compounds need to be developed that have improved pharmacokinetics and potency against drug-resistant strains.

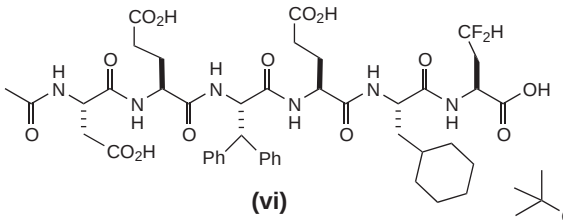
A group from Merck (Rahway, NJ and West Point, PA, USA) has accomplished this by using combinatorial chemistry as a means of rapidly finding molecules with the desired properties [4]. Three regions of indinavir **(iii)** were examined using solid-phase chemistry to synthesize the library. Compounds were assayed for activity and pharmacokinetic properties as mixtures of 24 compounds. The best mixtures were then evaluated and re-tested to yield the optimized compounds. For example, **iv** was found to be more potent than **iii** against wildtype and drug-resistant HIV-protease, with IC_{50} values of <0.1 and <0.6 nM, respectively. Compound **v** ($t_{1/2}$ = 49 min) has an improved half-life in dogs (dose = 10 mg kg^{-1}) compared with indinavir ($t_{1/2}$ = 39 min).

4 Cheng, Y. *et al.* (2002) A combinatorial library of Indinavir analogues and its *in vitro* and *in vivo* studies. *Bioorg. Med. Chem. Lett.* 12, 529–532

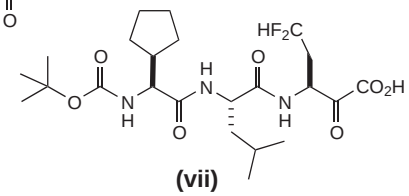
Design of tripeptide HCV-protease inhibitors

The serine protease (NS3-protease) expressed by hepatitis C virus (HCV) has emerged as a key target in the development of agents to be used in the treatment HCV infection. The enzyme is required for processing of the non-structural elements of the viral proteome and is crucial in the HCV lifecycle. For this reason, several groups are currently involved in the discovery of potent inhibitors.

It is known that the NS3-protease is susceptible to product-based inhibition. In fact, the peptidomimetic compound **vi**, which was designed based on this knowledge, is a highly potent inhibitor of the protease, with a K_i value of 40 nM. Unfortunately, **vi** suffers from several structural features that make it unattractive as a potential drug; namely, the large size of the molecule and the potentially reactive cysteine residue at the C-terminus. Two recent publications offer solutions to both problems [5,6].



(vi)



(vii)

It was found that a CF_2H group could replace the cysteine thiol (SH) group of the peptide because it has similar steric and electrostatic properties. Furthermore, changing the C-terminal carboxylic acid into an α-ketoacid converts it into a reversible covalent inhibitor. This enables the N-terminus to be trimmed, yielding tripeptide **vii** with an IC_{50} value of 0.4 μM after additional optimization of the other amino acid side chains.

5 Narjes, F. *et al.* (2002) A designed P_1 cysteine mimetic for covalent and non-covalent inhibitors of HCV protease. *Bioorg. Med. Chem. Lett.* 12, 701–704

6 Colarusso, S. *et al.* (2002) Evolution, synthesis and SAR of tripeptide α-ketoacid inhibitors of the hepatitis C virus NS3/NS4A serine protease. *Bioorg. Med. Chem. Lett.* 12, 705–708

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Novel antitumour molecules

Non-genotoxic enediynes as potential anticancer therapeutics

Adduct formation between anticancer agents and non-genotoxic species such as proteins, glutathione (GSH) and water often does not have profound genetic and cytotoxic consequences compared with the formation of direct DNA adducts, and is often regarded as a detoxification process. GSH is the most prevalent intracellular thiol known to function in many biological phenomena, such as the suppression of apoptosis. In addition, GSH and glutaredoxin reductase combine

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