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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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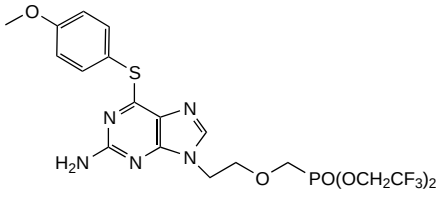
Molecules

Novel anti-hepatitis B agents

It is estimated that more than 400 million people worldwide are chronic carriers of hepatitis B virus (HBV). Infection by HBV is responsible for approximately 4 million deaths annually, making the discovery of anti-viral agents that are effective against this virus a high priority. Current treatments are limited to interferon-α, which appears to be effective in only 10–30% of patients, and the nucleoside analogue lamivudine. The corresponding triphosphate ester of lamivudine acts by inhibiting HBV polymerase. Given the potential for the development of viral resistance to polymerase inhibitors, new nucleoside analogues are continually being sought.

A recent paper by Sekiya *et al.* describes the discovery of a novel series of analogues based on 6-arylthio-substituted purine [1]. A representative member of this chemotype is compound **i**, which is a bis(2,2,2-trifluoroethyl) ester prodrug of the corresponding phosphonic acid. Anti-HBV activity (IC_{50} = 0.03 μM) and minimal cytotoxicity (CC_{50} > 1000 μM) were demonstrated in cell culture for this compound. Mice dosed orally at 100 mg kg^{-1} showed measurable concentrations of the corresponding hydrolyzed parent drug and the partially hydrolyzed monoester in plasma and liver, thus demonstrating absorption of the compound from the gut. Compounds such as **i** hold promise as potential clinically effective anti-HBV agents.

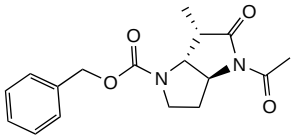


(i)

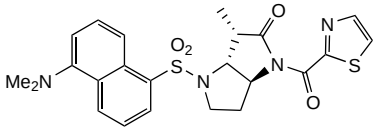
1 Sekiya, K. *et al.* (2002) 2-Amino-6-rythio-9-[2-(phosphonomethoxy)ethyl]purine bis(2,2,2-trifluoroethyl) esters as novel HBV-specefic antiviral reagents *J. Med. Chem.* 45, 3138–3142

Mechanism-based inhibitors of HCMV protease

The pyrrolidine-5,5-*trans*-lactam template, such as that found in compound **ii** (IC_{50} = 40 μM), has previously been disclosed as a useful template in the synthesis of inhibitors of the serine protease expressed by the human cytomegalovirus (HCMV) [2]. Compounds derived from this scaffold are mechanism-based inhibitors, wherein the active site serine residue of the protease is acylated by the lactam carbonyl group. Unfortunately, the reactive carbonyl group that yields the potent activity also makes the resulting inhibitors unstable in human plasma. For example, compound **ii** has a half-life of only 54 minutes in human plasma.



(ii)



(iii)

A group from GlaxoSmithKline (http://www.gsk.com) has fixed this problem through careful SAR work, optimizing the inhibitor for both activity and stability in human plasma [3]. First, it was discovered that replacement of the acetyl group that is attached to the lactam nitrogen, by a larger moiety, increased the plasma stability substantially but, unfortunately, eliminated inhibitory activity against the enzyme. However, activity against the enzyme was restored when a dansyl group was attached to the pyrroline ring, yielding compound **iii**, which has a IC_{50} value of 2.1 μM and a plasma half-life of >50 hours.

2 Borthwick, A. D. *et al.* (2002) Design and synthesis of pyrrolidine-5,5-trans-lactams (5-oxohexahydropyrrolo[3,2-b]pyrroles) as novel mechanism-based inhibitors of human cytomegalovirus protease. 2. Potency and chirality *J. Med. Chem.* 45, 1–18

3 Borthwick, A. D. (2002) Pyrrolidine-5,5-trans-lactams as novel mechanism-based inhibitors of human cytomegalovirus protease. Part 3: Potency and plasma stability. *Bioorg. Med. Chem. Lett.* 12, 1719–1722

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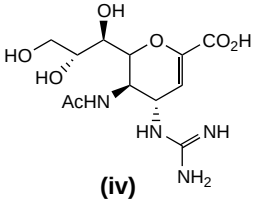
Inhibitors of influenza neuraminidase

Neuraminidase is one of two proteins that are expressed on the surface of the influenza virus and that have a role in virus-to-cell attachment. By virtue of its ability to remove sialic acid groups from cellular proteins, this enzyme reduces the affinity of influenza for target cells thus permitting mobility of the virus *in vivo*. Inhibitors of this enzyme have proven effective in preventing and treating viral infection, presumably by preventing the spread of the virus. In light of the success achieved by exploiting this target, efforts towards the discovery of new neuraminidase inhibitors continue.

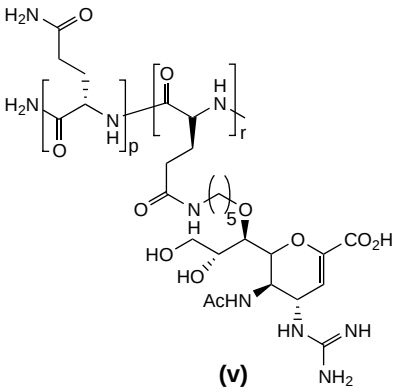
X-ray studies of sialic acid or zanamivir (**iv**) bound to neuraminidase have revealed that the 7-hydroxyl group does not form a hydrogen bond to the enzyme, suggesting that this position can be modified to form product-based inhibitors.



(iv)

Recently, a series of publications has appeared wherein this approach was pursued [4–6]. As predicted, replacement of the 7-hydroxyl group of zanamivir by F and N_3, or etherification of the hydroxyl, yielded little change in inhibitory activity against neuraminidase. However, it did result in a slight improvement in antiviral potency against the A/Yamagata/32/89 (H1N1) strain in a plaque reduction assay.

In further work, the 7-hydroxyl group was used as an attachment site for the synthesis of polyglutamic acid based polyvalent sialidase inhibitors, such as compound **v** (p/q = 10:1). The polyvalent inhibitor **v** was ~7-fold less active than zanamivir against the enzyme on a per-drug basis but was 100-fold more potent against the virus in the plaque reduction assay. Thus, the effect of polyvalent presentation of the inhibitor appears to be entropic. Furthermore, intranasal administration of compound **v** to mice, 24 hours before infection with the A/PR/8/3/34 (H1N1) strain of influenza resulted in a 100% survival rate after 20 days. By contrast, **iv** yielded 0% survival under the same conditions.



(v)

4 Honda, T. *et al.* (2002) Synthesis and anti-influenza virus activity of 4-guanidin-7-substituted Neu5Ac2en derivatives *Bioorg. Med. Chem. Lett.* 12, 1921–1924

5 Honda, T. *et al.* (2002) Synthesis and anti-influenza virus activity of 7-O-alkylated derivatives related to Zanamivir *Bioorg. Med. Chem. Lett.* 12, 1925–1928

6 Honda, T. *et al.* (2002) Synthesis and anti-influenza evaluation of polyvalent sialidase inhibitors bearing 4-guanidino-Neu5Ac2en derivatives *Bioorg. Med. Chem.* 12, 1929–1932

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