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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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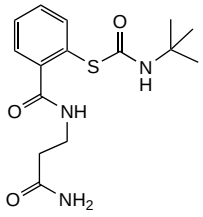
Novel antiviral molecules

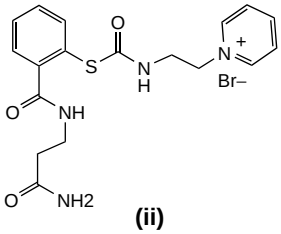
HIV-1 nucleocapsid (NCp7) zinc finger inhibitors

The nucleocapsid p7 protein (NCp7) of HIV-1 is a 55 amino acid protein and is crucial to several viral functions, such as reverse transcription, integration and protease processing, in addition to its role in packaging the viral RNA. Therefore, this protein makes an ideal target for the development of anti-viral agents. The Achilles heal to NCp7 appears to be zinc finger motifs comprised of the Cys-$(Xaa)_2$-Cys-$(Xaa)_4$-His-$(Xaa)_4$-Cys(CHCC) sequence, without which the virus is rendered noninfectious.

Recent research has identified agents that are designed to react with the CHCC cysteine residues thereby inactivating NCp7 [1]. Examples of these compounds are **i** and **ii**, which have EC_{50} values of 0.37 and 0.95 μM, respectively, against HIV-1_{RF} infected CEM-SS cells. Mechanistic studies are still in progress, but it is suggested that these compounds react with NCp7 via transacylation of the carbamoyl moiety onto the thiol side chain of one of the cysteine residues.



(i)



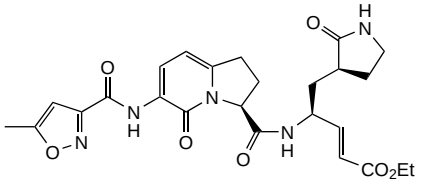
(ii)

1 Goel, A. (2002) Benzamide-based thiolcarbamates: a new class of HIV-1 NCp7 inhibitors. *Bioorg. Med. Chem. Lett.* 12, 767–770

New rhinovirus 3C protease inhibitors

Like most RNA viruses, the rhinovirus is dependent on a virally expressed protease, the 3C protease, to process the viral polyprotein following cellular translation. The 3C protease is a cysteine protease that is structurally similar to the trypsin serine protease family but has little homology with prevalent mammalian enzymes. As such, this enzyme is an ideal antiviral target.

Dragovich *et al.* have identified **iii** as a peptidomimetic inhibitor of this enzyme [2]. The compound acts by interacting with the substrate binding domain and forming an irreversible covalent bond to the active site cysteine residue via the Michael acceptor α,β-unsaturated ester moiety. Computational chemistry based on an inhibitor-bound X-ray crystal structure of the 3C protease was used to design **iii**. The compound is an active irreversible inhibitor of the enzyme



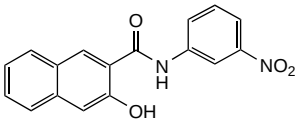
(iii)

($k_{obs}/[I]$ = 177,000 $M^{-1}s^{-1}$) and a potent antiviral agent against several HRV strains in cell culture (EC_{50} = 0.02–0.16 μM).

2 Dragovich, P.S. (2002) Structure-based design, synthesis and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. Part 7: Structure-activity studies of bicyclic 2-pyridone-containing peptidomimetics. *Bioorg. Med. Chem. Lett.* 12, 733–738

A novel class of herpesvirus polymerase inhibitors

A new class of inhibitors that are active against several viruses in the herpes family has been discovered using broad screening of the Pharmacia (http://www.pharmacia.com) compound collection against the viral polymerase expressed by human cytomegalovirus (HCMV) [3]. Thus, PNU26370 (compound **iv**) was found to be a promising lead compound that inhibited the viral polymerase. Subsequent evolution of this lead



(iv)

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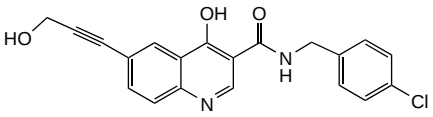

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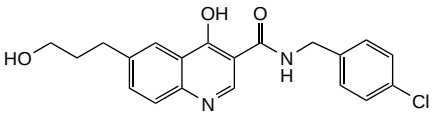

(vi)

yielded the hydroxyquinoline chemotype, represented by PNU181128 (**v**) and PNU181465 (**vi**).

Both **iv** and **v** inhibited the viral DNA polymerases from HCMV, herpes simplex virus type 1 (HSV1) and varicella-zoster virus (VZV) with K_i values of 0.07–0.95 μM. In addition, the compounds expressed potent antiviral activity against laboratory and clinical isolates of HCMV, VZV and HSV in several plaque reduction assays. Mechanistic studies correlated the antiviral activity with the observed polymerase inhibition. The compounds were found to inhibit viral polymerase by competing with nucleoside binding.

3 Oien, N.L. *et al.* (2002) Broad-spectrum antiherpes activities of 4-hydroxyquinoline carboxamides, a novel class of herpesvirus polymerase inhibitors. *Antimicrob. Agents Chemother.* 46, 724–730

A potent inhibitor of respiratory syncytial virus

The respiratory syncytial virus (RSV) belongs to the paramyxoviridea family of viruses and is responsible for annual outbreaks of lower respiratory tract infections occurring from October to May each year. A recent report by Huntley *et al.* discloses the structure of a promising new inhibitor of this virus [4].

RFI641, **vii**, was discovered in a cell-based screen for potential inhibitors of the virus. Not only is the compound an effective inhibitor of the virus in cell culture but it is also active prophylactically in mice, cotton rats and African green monkeys. Additionally, therapeutic activity against the virus, 24 h post-infection, was seen in the monkey model. The compound appears to act by blocking fusion of the virus to the cell. IC_{50} values against various strains of RSV were between 0.02 and 0.06 μg ml^{-1}.

4 Huntley, C.C. (2002) RFI-641, a potent respiratory syncytial virus inhibitor. *Antimicrob. Agents Chemother.* 46, 841–847

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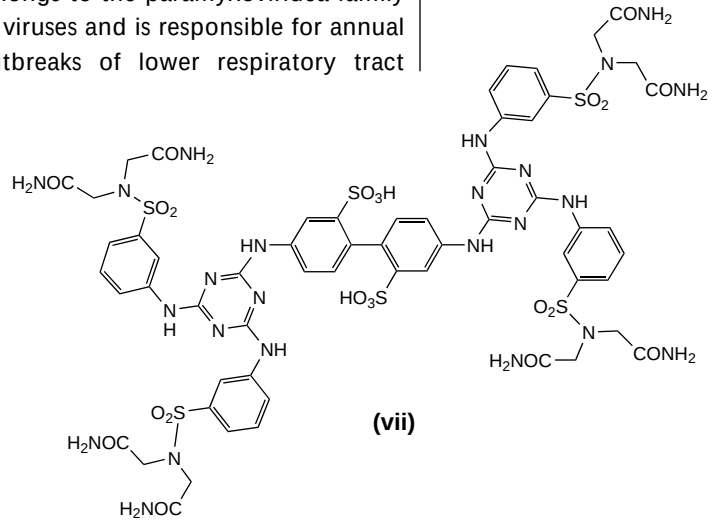
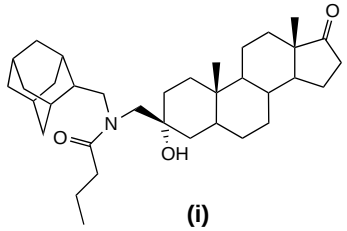
Combinatorial chemistry

17β-Hydroxysteroid dehydrogenase inhibitors

Type 3 17β-hydroxysteroid dehydrogenase (17β-HSD) is a steroidogenic enzyme that catalyzes the reduction of 4-androstene-3,17-one (Δ⁴-dione) to testosterone using reduced nicotinamide adenine dinucleotide phosphate (NADPH) as the cofactor. This third member of the 17β-HSD enzyme family is found almost exclusively in the testis and contributes to the production of ~60% of total active androgens in men. The inhibition in the testis of type 3 17β-HSD and the inhibition in peripheral tissues of other key enzymes, such as 5α-reductases, represent interesting strategies towards a complete blockade of the biosynthesis of androgens T and dihydrotestosterone (DHT). In the case of hormone sensitive diseases such as prostate cancer, obtaining a complete androgen blockade is crucial to counter the proliferation effect of androgens on prostate cancer cells. To achieve an optimal blockage of androgen formation, a potent inhibitor of type 3 17β-HSD was sought by parallel library synthesis [1]. A total of four libraries comprising 298 single compounds were synthesized in solution. The library compounds were screened for their ability to inhibit the type 3 17β-HSD activity in transfected human embryonic kidney (HEK)-293 cells. One of the most potent compounds found was **i**, which possessed an IC_{50} value of 35 nM; this is 18-fold higher than that of the natural substrate of the enzyme, Δ⁴-dione. This work has provided a library of steroid derivatives as a potential new class of inhibitors of type 3 17β-HSD.



(vii)



(i)

1 Poirier, D. *et. al.* (2002) Synthesis and optimization of a new family of type 3 17β-hydroxysteroid dehydrogenase inhibitors by parallel liquid-phase chemistry. *J. Med. Chem.* 45, 640–653

  PII: S1359-6446(02)02345-0