DDT Vol. 7, No. 3 February 2002

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.

Monitor Editor: Debbie Tranter

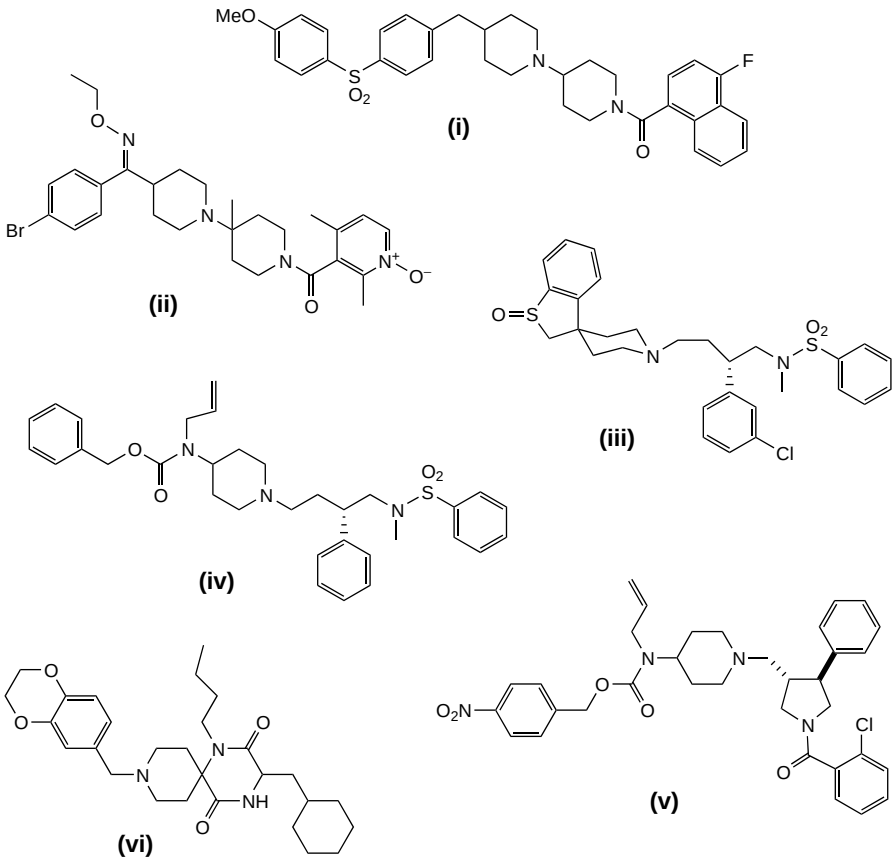
Monitor Contributors:
David Barrett, *Fujisawa Pharmaceutical Company*
Steven Langston, *Millennium Pharmaceuticals*
Paul Edwards, *Pfizer*
Michael Walker, *Bristol-Myers Squibb*
Andrew Westwell, *Nottingham University*
John Weidner, *Emisphere*
Daniela Barlocco, *University of Milan*
David Gurwitz, *Tel Aviv University*

Molecules

New CCR5 antagonists as anti-HIV agents

Blocking the entry of HIV into cells has emerged as a relatively new target in developing an effective treatment for AIDS. Viral binding to the host-cell CCR5 chemokine receptor, in addition to binding of CD4, is a necessary step for infection by macrophage-tropic (M-tropic) HIV strains. This is significant because it is this strain that is the most commonly transmitted form of HIV. Several laboratories have recently disclosed antagonists of the CCR5 receptor that are capable of inhibiting infection by HIV [1].

For example, a screen of the Schering-Plough (Kenilworth, NJ, USA) proprietary compound collection yielded a piperazine-based chemotype, such as compound **(i)** [2,3]. This analogue showed reasonable affinity for the CCR5 receptor (K_i = 1 μM) but showed no selectivity for CCR5 over the muscarinic M_2 receptor (K_i = 1.3 nM). Nonetheless, this initial hit was optimized, and compound **(ii)** (SCH 351125, previously SCH-C) was identified as a lead compound for further development with excellent selectivity for the CCR5 receptor (K_i = 2.1 nM) [2,3]. With a mean EC_{50} value of 2 nM against a wide number of clinical strains and optimal pharmacokinetics, this compound has been advanced into Phase I clinical trails [4].



Merck (Rahway, NJ, USA) has disclosed a series of antagonists of [^{125}I]-MIP-1α (macrophage inflammatory protein) that bind to CCR5 and are related to compound **(iii)**. An SAR study of the spiro-fused piperidine revealed that the spiro-ring fusion was not required for activity but could be replaced by acyclic linkers [5]. Based on this observation, a potent series of carbamates, represented by compound **(iv)**, were identified. Compound **(iv)** is a potent antagonist (IC_{50} = 1.5 nM) and it is also active as an antiviral in cell culture (IC_{95} = 0.8 μM). These results were applied to a pyrrolidine-based chemotype, yielding compound **(v)**. This is a potent inhibitor of MIP-1α binding to CCR5 (IC_{50} = 0.8 nM) and is active against HIV in normal human donor PBMCs (peripheral blood mononuclear cells), possessing a cellular IC_{95} value of 31 nM [6].

PII: 1359-6446(02)02132-8

Finally, a report of a spirodiketopiperazine-based CCR5 antagonist, E913, has appeared [7]. Like the previous compounds, E913 **(vi)** is a potent inhibitor of MIP-1α binding to CCR5 expressing cells (IC_{50} = 0.002 μM). It is capable of inhibiting laboratory, clinical and drug-resistant strains with an IC_{50} value of 0.03–0.06 μM. As expected, the anti-HIV activity of the compound was specific for M-tropic, but not T-cell tropic, virus.

1 Blair, W.S. *et al.* (2000) HIV-1 entry – an expanding portal for drug discovery. *Drug Discov. Today* 5, 183–194

2 Tagat, J.R. *et al.* (2001) Piperazine-based CCR5 antagonists as HIV-1 inhibitors. II Discovery of 1-[2,4-dimethyl-3-pyridinyl)carbonyl]-4-methyl-4-[3(*S*)-methyl-4-[1(*S*)-[4-trifluoro-methyl)phenyl]ethyl]-1-piperazinyl]-piperidine *N*1-oxide (Sch-350634), an orally bioavailable, potent CCR5 antagonist. *J. Med. Chem.* 44, 3343–3346

3 Palani, A. *et al.* (2001) Discovery of 4-[(*Z*)-(4-bromophenyl)-(ethoxyimino)methyl]-1′-[(2,4-dimethyl-3-pyridinyl)carbonyl]-4′-methyl-1,4′-bipoperidine *N*-oxide (SCH 351125): An orally bioavailable human CCR5 antagonist for the treatment of HIV infection. *J. Med. Chem.* 44, 3339–3342

4 Strizki, J.M. *et al.* (2001) SCH-C (SCH 351125), an orally bioavailable, small-molecule antagonist of the chemokine receptor CCR5, is a potent inhibitor of HIV-1 infection *in vitro* and *in vivo*. *Proc. Natl. Acad. Sci. U. S. A.* 98, 12718–12723

5 Finke, P.E. *et al.* (2001) Antagonists of human CCR5 receptor as anti-HIV-1 agents. Part 3: A proposed pharmacophore model for 1-[*N*-(methyl)-*N*-(phenylsulfonyl)amino]-2-(phenyl)-4-[4-(substituted)piperidin-1-yl]butanes. *Bioorg. Med. Chem. Lett.* 11, 2469–2473

6 Hale, J.J. *et al.* (2001) 1,3,4-trisubstitued pyrrolidine CCR5 receptor antagonists. Part 2: Lead optimization affording selective, oral bioavailable compounds with potent anti-HIV activity. *Bioorg. Med. Chem. Lett.* 11, 2741–2745

7 Maeda, K. *et al.* (2001) Novel low molecular weight spirodiketopiperazine derivatives potently inhibit R5 HIV-1 infection through their antagonistic effects on CCR5. *J. Biol. Chem.* 276, 35194–35200

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

Drug Delivery

A once-a-day dosing formulation of Cyclosporin A

A common problem in organ transplantation is subsequent organ rejection. This problem is alleviated by the administration of immunosuppressive agents. One of the most important immunosuppressive agents in use is Cyclosporin A (CsA), a highly lipophilic cyclic peptide. CsA is an immunosuppressant of choice because of its lack of myelotoxicity when compared with other immunosuppressive agents [1,2]. A drawback of CsA is the need for careful blood-level monitoring; levels above the therapeutic window cause serious adverse effects, such as nephrotoxicity and neurotoxicity, whereas levels below the therapeutic window cause episodes of organ rejection.

Disadvantages of current formulation

CsA is currently marketed as a pre-microemulsion concentrate (NEORAL®; Novartis AG, Basel, Switzerland), which is administered every 12 h. Within the dosing interval, CsA blood levels drop to a point where high episodes of organ rejection occur. It is crucial, therefore, that patients comply with this twice-a-day dosing schedule to achieve success. A once-a-day dosing regimen that maintains sufficient blood levels throughout the 24 h dosing interval would potentially increase patient compliance and, at the same time, decrease episodes of organ rejection. The premicroemulsion concentrate formulation alone cannot be used for a once-a-day formulation because CsA would be released at too high a level during part of the dosing interval, resulting in serious toxicity. To achieve a once-a-day CsA formulation, it will probably be necessary to develop a controlled release formulation that will maintain blood levels of CsA within the therapeutic window for the entire 24 h period.

Kim and coworkers have recently reported on the design of a once-a-day dosing regimen of CsA [1]. Their strategy was to combine a new formulation of CsA premicroemulsion concentrates (preME) and a novel technology for enteric-coated solid-state premicroemulsion concentrates of CsA (sME). The co-administration of preME and sME, containing a total of 200 mg of CsA, provided blood levels of CsA above the minimum therapeutic level for ~24 h with a peak level comparable to that of preME.

New formulations of CsA

Enteric-coated sME were prepared by coating preME with enteric carrier-polymers, such as sodium alginate (AL), EUDRAGIT® L100 (EuD; Rohm GmbH, Darmstadt, Germany), and cellulose acetate phthalate (CAP). PreME consisted of CsA, medium-chain triglyceride, and a mixture of surfactants and cosurfactants. Medium-chain triglycerides were selected as oil because they have been reported to improve the intestinal absorption of various active compounds. Propylene carbonate (ProC) was used as a cosurfactant to solubilize CsA. The surfactants consisted of a mixture of Polyoxol 40 [hydrogenated castor oil 40, CREMOPHOR 40® (Cre); BASF, Ludwigschafen, Germany], mono- and diglyceride (Gly), and poloxamer 124 (Pol) in a 5:1:1 weight ratio. Cre was chosen as the major surfactant because it has been reported to enhance the intestinal permeability of drugs. Pol and Gly were added in equal amounts to improve the stability of the microemulsions. The composite mixture of all these surfactants and cosurfactants (Smix) was considered in ternary phase diagrams with water and oil.

A ternary phase diagram of Smix, water and oil was constructed to help develop an optimal formulation of preME. Various proportions of oil, Smix and water were tested and the phase of each mixture was determined visually. The composition of CsA:oil:Smix (10:18.5:71.5%) formed microemulsions regardless of the amount of water, according to the constructed phase

  PII: 1359-6446(02)02107-9