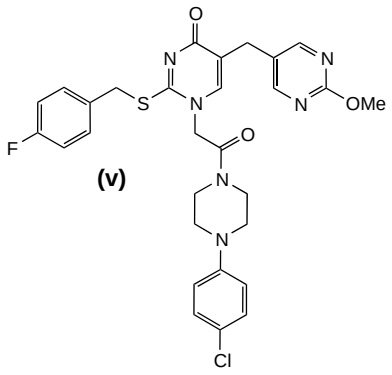
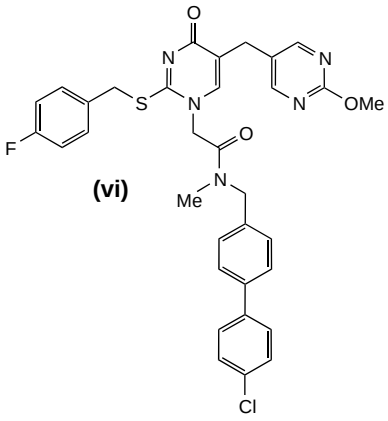
(v) as an improved inhibitor of Lp-PLA_2 (IC_{50} = 0.02 μM) compared with the previously reported highly lipophilic inhibitors [3]. Compound **(v)** displayed oral activity in a hyperlipidaemic rabbit model (WHHL rabbit) with plasma inhibition of Lp-PLA_2 occurring for 5 h at a peroral dose of 10 mg kg^{-1}.



(v)



(vi)

To improve the oral activity of **(v)** the group investigated replacement of the piperidine N-1 substituent with biarylamides and identified molecule **(vi)** [4]. This compound was found to be a potent Lp-PLA_2 inhibitor *in vitro* (IC_{50} = 0.02 nM) and *ex vivo* (53% inhibition of Lp-PLA_2 at 10 nM and 93% at 100 nM concentrations) in human plasma, compared with 77% at 100 nM for compound **(v)**. Molecule **(vi)** also shows extended activity for >8 h in WHHL rabbits when dosed orally at 10 mg kg^{-1}. Such molecules will be important in assessing the role of Lp-PLA_2 in atherosclerosis.

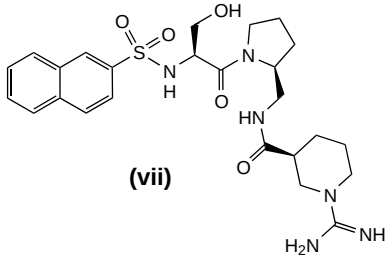
3 Smith, S.A. (2001) 1-(Arylpiperazinyl-amidoalkyl)-pyrimidones; orally active inhibitors of lipoprotein-associated phospholipase A_2. *Bioorg. Med. Chem. Lett.* 11, 1925–1929

4 Smith, S.A. (2002) Potent orally active inhibitors of lipoprotein-associated phospholipase A_2: 1-(biphenylmethyl-amidoalkyl)-pyrimidones. *Bioorg. Med. Chem. Lett.* 12, 51–55

Orally active thrombin active-site inhibitors

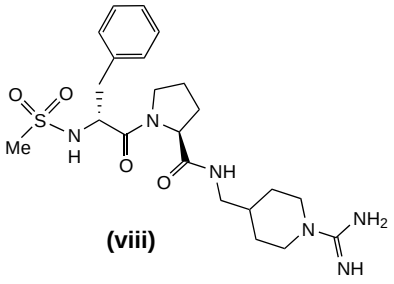
Thrombotic diseases such as stroke and arterial or venous thrombosis are a major cause of mortality. There has been great research efforts to supplement current therapies such as heparin and warfarin with safer and more effective therapies. Thrombin is the ultimate serine protease in the coagulation cascade and catalyzes the cleavage of fibrinogen to fibrin that is polymerized by thrombin-activated Factor XIIIa to form a fibrin clot.

A group from Bristol-Myers Squibb (Princeton, NJ, USA) set out to discover reversible, non-electrophilic, direct thrombin inhibitors. Starting from a series of tripeptide inhibitors and crystallographic data, compounds **(vii)** (BMS189090) and **(viii)** (BMS189664) were identified [5,6].



(vii)

Both molecules are potent reversible inhibitors that do not show time-dependent kinetics (K_i = 3 nM and 8 nM for **vii** and **viii**, respectively). The compounds show good selectivity for related trypsin-like serine proteases (40-fold over trypsin) and show similar activity at doubling the thrombin time in protein-rich plasma (61 and 59 nM for **vii** and **viii**, respectively). Both compounds exhibit efficacy in venous and arterial thrombosis models at levels below those required to significantly increase bleeding time. Compound **(viii)** shows a greater potency in a mouse thrombin-induced lethality model (ID_{50} = 29 mg kg^{-1} and 8.8 mg kg^{-1} perorally for **vii** and **viii**, respectively).



(viii)

The pharmacokinetic properties of compound **(viii)** were evaluated and it was found to exhibit an oral bioavailability of 15% and 17% in dogs and monkeys, respectively, with an elimination half-life of >6 h. The compound has been chosen for further development.

5 Jagabandhu, D. (2002) Thrombin active site inhibitors: chemical synthesis, *in vitro* and *in vivo* pharmacological profile of a novel and selective agent BMS-189090 and analogues. *Bioorg. Med. Chem. Lett.* 12, 41–44

6 Jagabandhu, D. (2002) Molecular design and structure–activity relationships leading to the potent, selective, and orally active thrombin active site inhibitor BMS-189664. *Bioorg. Med. Chem. Lett.* 12, 45–49

Steven Langston
Millennium Pharmaceuticals
Merrifield Centre
Rosemary Lane
Cambridge, UK CB1 3LQ
tel: +44 (0)1223 722400
e-mail: steve.langston@mpi.com

Novel antiviral molecules

New uracil-based nucleosides active against herpes simplex virus (HSV)

A recent study by Kumar *et al.* [1] has uncovered a new series of 2′-deoxyuridines substituted at the 5-position of the nucleobase that are active against HSV-1 and HSV-2. One of the most potent compounds identified was **(i)**.

This analogue contains the unusual cyanamido group attached to C-5 of the

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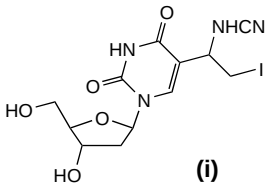
uracil nucleobase. It is active against HSV-1 (EC_{50} = 1.6–9.4 μM) with potency similar to that of acyclovir (EC_{50} = 2.2–4.4 μM). In addition, it was active against thymidine-kinase deficient HSV-1 (EC_{50} = 2.3–15.3 μM) suggesting that the nucleoside can be activated by cellular kinases.

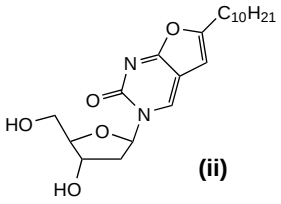


(i)

1 Kumar, R. *et al.* (2001) Synthesis and antiviral activity of novel 5-(1-cyanamido-2-haloethyl) and 5-(1-hydroxy(or methoxy)-2-azidoethyl) analogues of uracil nucleosides. *J. Med. Chem.* 44, 3531–3538

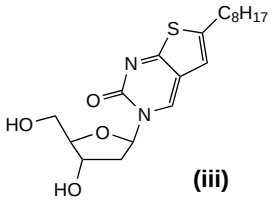
Bicyclic anti-Voricella-Zoster virus (VZV) nucleosides

Bicyclic 2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one nucleosides such as **(ii)** have been reported to be potent inhibitors of Voricella-Zoster virus (VZV) [2]. Further modifications of this chemotype have been pursued and a recent paper discloses thieno-analogues of this series.



(ii)

Compound **(iii)** was identified as a highly potent inhibitor of VZV in human embryonic lung cells (EC_{50} = 0.002–0.005 μM) [3]. Its activity was dependent on VZV thymidine-kinase expression, as demonstrated by the fact that **(iii)** was found to be inactive against VZV strains 07/1 and YS/R, which are thymidine-kinase deficient. This suggests that phosphorylation of the nucleoside by VZV thymidine-kinase is necessary for activation of the inhibitor in cell culture.



(iii)

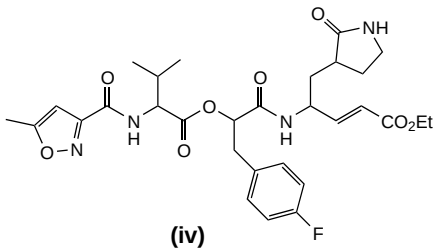
The structure–activity relationship (SAR) with respect to the substituent attached to the thieno-ring of this new chemotype parallels that of the furo-pyrimidine series with optimal activity being observed for alkyl side chains 8–10 carbon atoms in length.

2 McGuigan, C. *et al.* (1999) Potent and selective inhibition of Voricella-Zoster virus (VZV) by nucleoside analogues with an unusual bicyclic base. *J. Med. Chem.* 42, 4479–4484

3 Brancale, A. *et al.* (2001) Bicyclic anti-VZV nucleosides: Thieno analogues retain full antiviral activity. *Bioorg. Med. Chem. Lett.* 11, 2507–2510

Irreversible depsipeptidyl human rhinovirus 3C protease inhibitors

Human rhinoviruses (HRVs) belong to the picornaviridea family and are responsible for causing the common cold. HRV



(iv)

depends on a virally expressed protease called the 3C protease for viral maturation and replication. The 3C protease is a cysteine protease which resembles trypsin-like serine proteases in structure.

A group at Pfizer (San Diego, CA, USA) has taken advantage of this fact by designing inhibitors of HRV that target this enzyme [4]. A recent example of their efforts has been disclosed [5]. Compound **(iv)** irreversibly inhibits the 3C protease with a k_{obs}/[I] value of 270,000 $M^{-1}\,s^{-1}$ and is active against the virus in cell culture with an EC_{50} value of 0.007 μM.

4 Matthews, D.A. *et al.* (1999) Structure-assisted design of mechanism-based irreversible inhibitors of human rhinovirus 3C protease with potent antiviral activity against multiple rhinovirus serotypes. *Proc. Natl. Acad. Sci. U. S. A.* 96, 11000–11007

5 Webber, S.E. *et al.* (2001) Design and synthesis of irreversible depsipeptidyl human rhinovirus 3C protease inhibitors. *Bioorg. Med. Chem. Lett.* 11, 2683–2686

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

Contributions to *Monitor*

We welcome recommendations of papers for review within *Monitor*, in the fields of combinatorial chemistry, pharmacogenomics, pharmacoproteomics, bioinformatics, new therapeutic targets, high throughput screening, new drug delivery technologies and other promising lines of research.

Details of recent papers or those *in press* should be directed to Dr Debbie Tranter, Editor, Drug Discovery Today, Elsevier Science London, 84 Theobald's Road, London, UK WC1X 8RR. tel: +44 (0) 20 7611 4132, fax: +44 (0) 7611 4485, e-mail: deborah.tranter@drugdiscoverytoday.com