DDT Vol. 7, No. 10 May 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.

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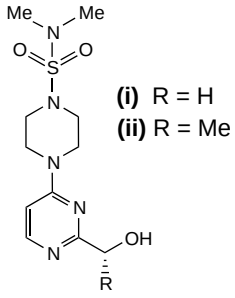
## Molecules

### Orally effective sorbitol dehydrogenase inhibitors to treat diabetes

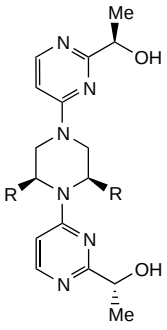
In patients with diabetes, prolonged elevated levels of blood glucose leads to tissue degeneration manifested as neuropathy, retinopathy and other diseases. A recent hypothesis proposes that excess glucose flux through the polyol pathway gives rise to an imbalance in the NADH: $NAD^+$ ratio, and that this reductive stress could be the underlying cause of the observed tissue degeneration. The polyol pathway involves the conversion of glucose to sorbitol and the oxidation of sorbitol to fructose catalyzed by sorbitol dehydrogenase with the concomitant conversion of $NAD^+$ to NADH.

A recent publication from Pfizer (Department of Cardiovascular and Metabolic Disease, Groton, CT, USA) described the improvement of *in vitro* and *in vivo* potency for the known sorbitol dehydrogenase inhibitor **(i)** (R = H, $IC_{50}$ = 0.24 μM, $ED_{50}$ = 14 mg $kg^{-1}$) on incorporation of a methyl group to give compound **(ii)** (R = H, $IC_{50}$ = 0.027 μM, $ED_{50}$ = 1.6 mg $kg^{-1}$) [1]. However, compound **(ii)** has a short half-life resulting from *N*-demethylation of the sulfamoyl group and, therefore, the group sought to improve the pharmacokinetic and pharmacodynamic properties by replacing the *N*,*N*-dimethyl sulfamoyl group with a variety of heterocycles [2]. For example, compound **(iii)** (R = H) was identified with a prolonged half-life and improved *in vivo* potency ($IC_{50}$ = 0.04 μM, $ED_{90}$ = 5 mg $kg^{-1}$).

The biological targets for these inhibitors are the peripheral nerves that are wrapped in a fatty myelin sheath. In an effort to further improve *in vivo* potency the lipophilicity of the molecule was increased by incorporating additional methyl groups to give compound **(iv)** (R = Me). This compound has an improved *in vitro* and *in vivo* potency ($IC_{50}$ = 0.01 μM, $ED_{90}$ = 0.3 mg $kg^{-1}$) and demonstrated normalization of sciatic-nerve fructose concentration in a chronically diabetic rat model for ~17 h with a single oral dose of 2 mg $kg^{-1}$.




**(i)** R = H
**(ii)** R = Me




**(iii)** R = H
**(iv)** R = Me

1 Myalari, B.L. (2001) Sorbitol dehydrogenase inhibitors (SDIs): A new potent, enantiomeric SDI, 4-[2-(1*R*-hydroxy-ethyl)-pyrimidin-4-yl]-piperazine-1-sulfonic acid dimethylamide. *J. Med. Chem.* 44, 2695–2700

2 Chu-Moyer, M.Y. (2002) Orally-effective, long-acting sorbitol dehydrogenase inhibitors: Synthesis, structure–activity relationships and *in vivo* evaluation of novel heterocycle-substituted piperazino-pyrimidines. *J. Med. Chem.* 45, 511–528

### Orally active inhibitors of lipoprotein-associated phospholipase $A_2$

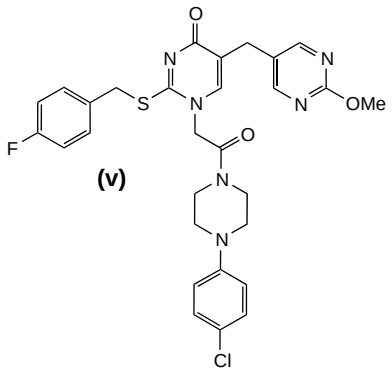
Atherosclerosis is widely regarded as an inflammatory disease. Treatments that target this inflammation and influence the formation and stability of atherosclerotic plaques represent a new opportunity to treat the population who are at risk.

A group from GlaxoSmithKline (GSK; Harlow, UK and Stevenage, UK) have focused attention on lipoprotein-associated phospholipase $A_2$ (Lp-$PLA_2$) that has been shown to hydrolyze oxidatively modified phosphatidylcholines to release the pro-inflammatory mediators lysophosphatidyl choline and oxidized fatty acids. There is also a positive correlation between Lp-$PLA_2$ levels and coronary events in asymptomatic hypercholesterolaemic men. A recent publication from the GSK group described molecule

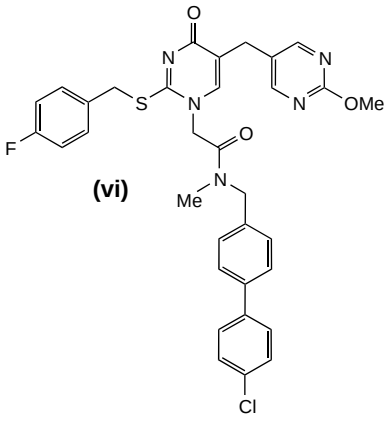


PII: S1359-6446(02)02254-7

**(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.

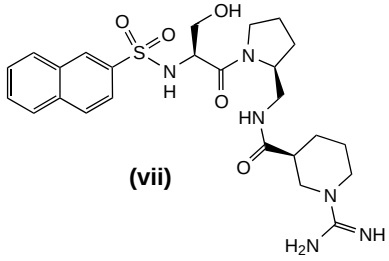
**3** Smith, S.A. (2001) 1-(Arylpiperazinyl-amidoalkyl)-pyrimidones; orally active inhibitors of lipoprotein-associated phospholipase $A_2$. *Bioorg. Med. Chem. Lett.* 11, 1925–1929

**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

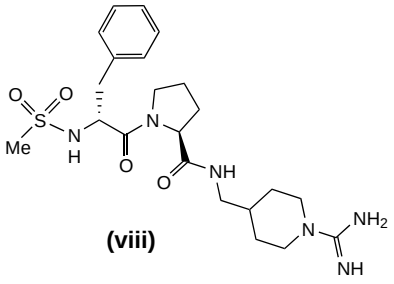
Thrombotic diseases such as stroke and arterial or venous thrombosis are a major cause of mortality. There has been great research efforts to supplement current therapies such as heparin and warfarin with safer and more effective therapies. Thrombin is the ultimate serine protease in the coagulation 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

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## 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

  PII: S1359-6446(02)02287-0 