ethyl-acetate soluble portion a new flavanone glucoside called myrciacitrin III (**iii**) and two new acylated flavanone glucosides called myrciacitrins IV (**iv**) and V (**v**) [5]. Their structures were attributed on the basis of chemical (mainly acidic and enzymatic hydrolysis) and spectroscopic (MS, IR, UV, NMR) data.

Their inhibitory activity was then tested on AR extracted from the lenses of Wistar rats. AR catalyzes the reduction of glucose to sorbitol in the polyol patway and is thought to be related to chronic diabetic complications such as peripheral neuropathy, retinopathy, and cataracts.

Myrciacitrins I–V were found to inhibit AR with IC_{50} values ranging from 1.6×10^{-5} M to 7.9×10^{-7} M, the most potent compound being Myrciacitrin II (ii). In the same assay, epalrestat, a commercial synthetic AR inhibitor, had an IC_{50} value of 7.2×10^{-8} M.

3 Matsuda, H. *et al.* (1999) Antidiabetic principles of natural medicines. IV. Aldose reductase and α-glucosidase inhibitors from the roots of *Salacia oblonga* Wall. (*Celastraceae*): structure of a new friedelane-type triterpene, kotalagenin 16-acetate. *Chem. Pharm. Bull.* 57, 1725–1729

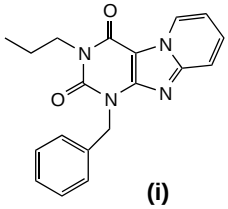
4 Yoshikawa, M. *et al.* (1998) Antidiabetic principles of natural medicines. II. Aldose reductase and α-glucosidase inhibitors from Brazilian natural medicine, the leaves of *Myrcia multiflora* DC. (*Myrtaceae*): structures of myrciacitrins I and II and myrciaphenones A and B. *Chem. Pharm. Bull.* 46, 113–119

5 Matsuda, H. *et al.* Antidiabetic principles of natural medicines. V. Aldose-reductase inhbitors from *Myrcia multiflora* DC. (2): Structures of myrcyacitrins III, IV, and V. *Chem. Pharm. Bull.* 50, 429–431

Novel human A_3 adenosine receptor antagonists

Adenosine exerts its physiological effects by activating specific cell membrane receptors. To date, four different adenosine receptor subtypes have been identified: A_1, A_{2A}, A_{2B} and A_3. The A_3 subtype has been investigated in recent years and antagonists for this receptor are potentially useful for the treatment of inflammation and the regulation of cell growth. The xanthine core structure has served as the basis for numerous selective antagonists for adenosine A_1, A_{2A} and A_{2B} receptors; however, xanthine-derived compounds are much less potent antagonists of the A_3 subtype.

A novel synthetic procedure has enabled the identification of a series of xanthine-fused structures – 1*H*,3*H*-pyrido[2,1-*f*]purine-2,4-diones – which show moderate antagonist effects at A_1 receptors, low or negligible activity at A_{2A} receptors and significant affinity at the A_3 receptor [6]. Several compounds in this series show affinities in the low nanomolar range. In particular, the 1-benzyl-3-propyl-*1*H,*3*H-pyrido[2,1-*f*]purine-2,4-dione derivative (**i**), which can be considered a lead compound in this series, exhibited a K_i value of 4.0 ± 0.3 nM against the hA_3 receptor. Because xanthine derivatives have traditionally been considered poor A_3 antagonists, the described pyrido[2,1-*f*]purine-2,4-dione derivatives represent a new family of adenosine receptor antagonists that deserve further exploration.



(i)

6 Priego, E.M. *et al.* (2002). Pyrido[2,1-*f*]purine-2,4-dione derivatives as a novel class of highly potent human A_3 adenosine receptor antagonists. *J. Med. Chem.* 45, 3337–3344

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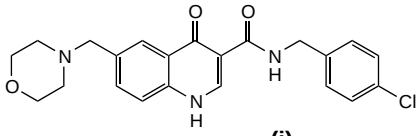
Novel antiviral molecules

A new antiviral compound active against herpes viruses

PNU183792 (**i**), a 4-oxo-dihydroquinoline, has been identified as an antiviral



(i)

agent with activity against members of the herpes virus family [1]. This includes human cytomegalovirus (hCMV), Varicella–Zoster virus (VZV) and herpes simplex viruses. A novel chemotype, PNU183792 is believed to act as a non-nucleoside viral polymerase inhibitor with an IC_{50} value of 0.4–0.7 μM.

Furthermore, in cell culture, compound **i** is able to inhibit hCMV ($IC_{50} = 0.3$ μM), VZV ($IC_{50} = 0.1$ μM), HSV-1 ($IC_{50} = 3.3$ μM) and HSV-2 ($IC_{50} = 4.6$ μM). In a mouse model of CMV infection, PNU183792 reduced mortality when dosed orally (25–100 mg kg^{-1}), before or at 48 h post-infection with virus.

1 Brideau, R.J. *et al.* (2002) Broad-spectrum antiviral activity of PNU-183792, a 4-oxo-dihydroquinoline, against human and animal herpesviruses. *Antiviral Res.* 54, 19–28

Azapeptide inhibitors of the hepatitis C virus serine protease

The hepatitis C virus (HCV) genome encodes a polyprotein that requires processing by cellular and virally expressed proteases for the virus to propagate. One such protease, the NS3 protein, is expressed by the virus and is a chymotrypsin-like serine protease that is responsible for processing a significant portion of the non-structural proteins (from NS3 to NS5B). As such, this protease is an attractive target for the development of potential antiviral agents.

A paper from Schering-Plough (http://www.schering-plough.com) identifies azapeptides as inhibitors of the protease [2]. Because it is known that the NS3-protease is susceptible to strong product-based inhibition, these peptides were designed around the known sequence of the protease NS5A–NS5B cleavage substrate. In addition, an aza-amino acid analogue, wherein the α-carbon atom of the amino acid is replaced by nitrogen,

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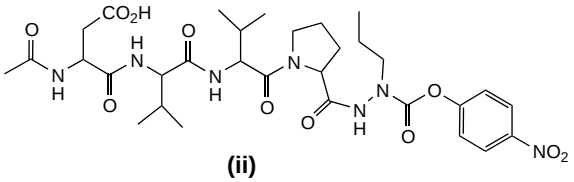


(ii)

was employed at the P1 position of the inhibitor.

A representative member of this series is **ii**, which has a K_i of 7 μM. Assays to uncover the mechanism of inhibition showed that the inhibitory activity was not time-dependent and that proteolytic processing of the azapeptides was slow, suggesting that the compounds reversibly compete with substrate.

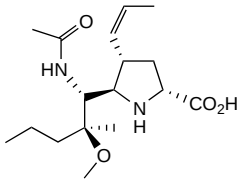
2 Zhang, R. *et al.* (2002) Azapeptides as inhibitors of hepatitis C virus NS3 serine protease. *Bioorg. Med. Chem. Lett.* 12, 1005–1008

A potent inhibitor of influenza A and B neuraminidases

Inhibition of the neuraminidase enzyme expressed by the influenza virus has been shown to yield clinically effective antiviral agents. However, the emergence of viral resistance is always an impending threat associated with antiviral therapy, making the search for new agents a continuous process. Towards that end, a recent report from Abbott laboratories (http://abbott.com) describes the *in vitro* characterization of a new, highly potent neuraminidase inhibitor, A315675 (**iii**) [3].

A315675 is derived from a pyrrolidine based template and is found to inhibit neuraminidases from a broad spectrum of viral strains. Thus neuraminidases derived from A/H1N1, A/H3N2, A/H1N9 and B strains of the virus are inhibited with K_i values between 0.02 and 0.31 nM. Moreover (**iii**) was found to be very active against laboratory and clinically isolated strains of the virus in cell culture plaque reduction assays.

An interesting feature of this compound is that it displays time-dependent reversible inhibition kinetics. Apparently, this is derived from a very slow inhibitor off-rate, having a calculated dissociation half life of 10–12 h. Although purely speculative at this time, this result suggests that A315675 might exert a prolonged duration of action *in vivo* leading to less frequent dosing.

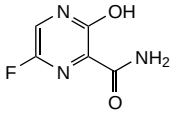


(iii)

3 Kati, W.M. *et al.* (2002) *In vitro* characterization of A315675, a highly potent inhibitor of A and B strain influenza virus neuraminidases and influenza virus replication. *Antimicrob. Agents Chemother.* 46, 1014–1021

A new anti-influenza compound

A novel inhibitor of the influenza virus has recently been disclosed [4]. Unlike clinically available anti-influenza agents, T705 (**iv**) was found to be active against influenza A, B and C in cell culture plaque reduction assays. In these experiments, **iv** was found to inhibit the formation of plaques by the virus with IC_{50} values ranging from 0.013 to 0.48 μg ml^{-1}.



(iv)

In addition, T705 dosed orally at 200 mg kg^{-1} four times daily for five days prevented death in mice infected with the A/PR/8/34 influenza strain of the virus for up to 21 days, compared with controls that showed only a 20% survival rate. Studies to determine the mechanism of action of this compound are currently in progress.

4 Furuta, Y. *et al.* (2002) *In vitro* and *in vivo* activities of anti-influenza virus compound T-705. *Antimicrob. Agents Chemother.* 46, 977–981

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