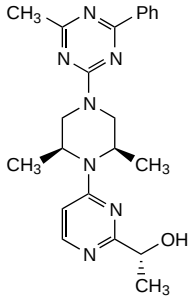
oxidation to the aldehyde, followed by reduction. The *RR*-isomer shown is the most active.

The group thus sought to identify improved inhibitors with the ability to reduce the elevation of fructose levels in the sciatic nerve for prolonged periods and only containing the one essential chiral hydroxyethylene group [7]. The ideal compound would have sufficient lipophilicity to partition from the blood to the nerve tissue and also a reduced basicity compared to compound **viii** (pKa = 6.8 and 6.0) to give a greater proportion of the molecule in a neutral form.

Compound **ix** was identified with good *in vitro* potency (IC_{50} = 5 nM) and a dramatic improvement in activity in the chronic rat model (ED_{90} = 0.05 mg kg^{-1}). The molecule has reduced basicity (pKa = 6.2 and 4.8) and increased lipophilicity, having a logP of 2.0 compared to 1.4 for compound **viii**. Compound **ix** appeared to be stable to the oxidoreduction of the chiral hydroxyethylene group by liver microsomes and exhibited a long half-life of 7 h and 10 h in dog and rat, respectively.

The compound is thus anticipated to provide a sustained inhibition of SDH and help clarify the significance of the polyol pathway in the development of diabetic complications.



(ix)

5 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

6 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

7 Myalari, B.L. (2002) A sorbitol dehydrogenase inhibitor of exceptional *in vivo* potency with along duration of action: 1-(*R*)-{4-[4-(4,6-dimethyl[1,3,5]triazin-2-yl)-2*R*,6*S*-dimethylpiperazin-1-yl]pyrimidin-2-yl}ethanol. *J. Med. Chem*. 45, 4398–4401

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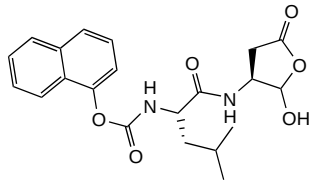
Combinatorial chemistry

Caspase inhibitors

Caspases are a family of cysteine proteases that are involved in both cytokine maturation and apoptosis. Caspase-1 [interleukin-1β (IL-1β) converting enzyme (ICE)] is involved in the induction of inflammation by catalyzing the cleavage of the pro-form of IL-1β. Other caspases have a role in the regulation of apoptosis, either as signalling molecules or as downstream effectors. Inhibition of caspases, either broad spectrum or caspase specific, could be of therapeutic value in the treatment of inflammatory and degenerative diseases, such as rheumatoid arthritis, Parkinson's disease and myocardial infarction. A series of novel, potent, broad spectrum inhibitors has been reported [1].

A library of 46 aspartyl aldehyde compounds was prepared on solid phase. Compounds were designed to probe the SAR in the S3 caspase subunit and were evaluated for their caspase inhibitory activity. Several potent compounds were obtained, one of the most potent being compound **i**, which possessed an IC_{50} value of 570 nM against Csp-1, 132 nM against Csp-3, 940 nM against Csp-6 and 770 nM against Csp-8. This work has produced potent compounds with broad spectrum affinity for caspases 1, 3, 6 and 8, and this class of compounds warrants further investigation.



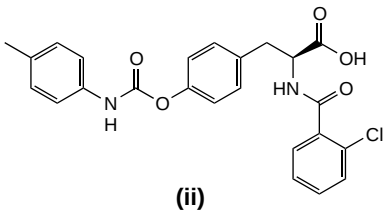
(i)

1 Linton, S. D. *et. al.* (2002) Acyl dipeptides as reversible caspase inhibitors. Part 1: Initial lead optimisation. *Bioorg. Med. Chem. Lett.* 12, 2969–2971

$\alpha_4\beta_1/\alpha_4\beta_7$ Integrin antagonists

Integrins are heterodimeric proteins, which, when expressed in leukocytes, mediate their recruitment to sites of inflammation in a tissue-specific manner. The binding of integrins to surface expressed endothelial proteins initiates cell–cell contacts, which eventually lead to the extravasation of the leukocyte into the tissue.

It has been proposed that improper control of integrin expression can result in pathologies that are directly attributable to the particular expression of the molecules involved. Interaction of the integrin $\alpha_4\beta_7$ with mucosal addressin cell adhesion molecule (MAdCAM) has been implicated in ulcerative colitis and inflammatory bowel disease. The interaction between $\alpha_4\beta_1$ and vascular cell adhesion molecule (VCAM) is thought to contribute to asthma, multiple sclerosis and other autoimmune diseases. Inhibition of these protein–protein interactions significantly effects animal models of disease. This biological connection to disease has increased the interest in the development of small-molecule antagonists for these integrins. Research has been conducted to identify potent inhibitors of a_4b_7 antagonists [2].



(ii)

PII: S1359-6446(03)02642-4

Two libraries providing over 180 compounds were synthesized on Wang resin. The library compounds were evaluated for their inhibition of the $\alpha_4\beta_7$–MAdCAM interaction in a protein-based ELISA. As a measure of selectivity for $\alpha_4\beta_7$, inhibition of the related $\alpha_4\beta_1$–VCAM interaction was also tested. One of the most potent compounds isolated was **ii**, which possessed an IC_{50} value for $\alpha_4\beta_7$ of 72 nM, with more than sixfold selectivity over the related $\alpha_4\beta_1$. This work has generated rapid SARs for these templates. Other structural analogues that maintain potency against these integrins could result, given further investigation.

2 Sutherlin, D. P. *et al.* (2002) Solid-phase synthesis of dual $\alpha_4\beta_1$/ $\alpha_4\beta_7$ integrin antagonists: Two scaffolds with overlapping pharmacophores. *Bioorg. Med. Chem. Lett.* 12, 2913–2917

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