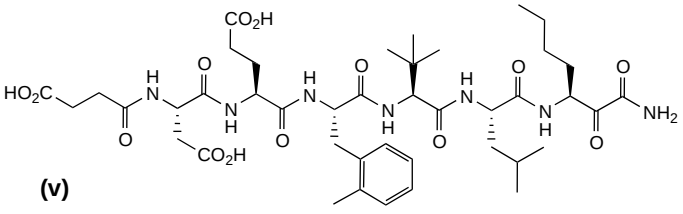
allyloxycarbonyl (alloc) groups, followed by regioselective amidation of the eight-acid residue using benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate (PyBOP) as the coupling reagent, afforded the 8-amide derivatives in moderate to excellent yields with a regioselectivity of >5:1 in all cases examined. The minor products were the corresponding 3-amide derivatives. Standard deprotection conditions afforded the final compounds. Compound **(iv)** displayed potent *in vitro* antifungal activity, however, the *in vivo* effect in a model of murine systemic candidiasis was somewhat weak. The reduced-tail vein irritation for **(iv)** suggests a possible strategy for further improving the profile of this series of compounds.

A potent inhibitor of hepatitis C virus NS3-4A proteinase

Infection by hepatitis C virus (HCV) is responsible for a large number of the worldwide cases of community-acquired hepatitis infection. If it is left untreated, HCV infection can lead to several potentially serious and life-threatening conditions, such as cirrhosis and hepatocellular cancer. Current treatment for this infection employs interferon-α as a part of a combination with ribavirin but new, more effective treatments are urgently needed.

HCV NS3-4A proteinase is a serine protease complex responsible for processing viral polyprotein by cleavage at the NS3-4A junction, and is a target of much interest for the development of new anti-HCV drugs. Recently, researchers at Roche (Welwyn, UK) have reported a series of peptide-based inhibitors of the NS3-4A proteinase, and the discovery of compound **(v)** bearing an α-ketoamide moiety that potently inhibits HCV NS3-4A proteinase (IC_{50} = 11 nM)[3]. Furthermore, this compound also displays excellent selectivity relative to human serine proteinases such as elastase (IC_{50} = 12,000 nM), chymotrypsin (IC_{50} = 300 nM) and trypsin (IC_{50} = >200,000 nM)



(v)

1 Yu, X.Y. *et al.* (2001) A series of quinoline analogues as potent inhibitors of *C. albicans* prolyl tRNA synthetase. *Bioorg. Med. Chem. Lett.* 11, 541–544.

2 Zhang, Y-Z. *et al.* (2001) 8-Amido-bearing pseudomycin B (PSB) analogue: novel antifungal agents. *Bioorg. Med. Chem. Lett.* 11, 123–126

3 Bennett, J.M. *et al.* (2001) The identification of α-ketoamides as potent inhibitors of hepatitis C virus NS3-4A proteinase. *Bioorg. Med. Chem. Lett.* 11, 355–357

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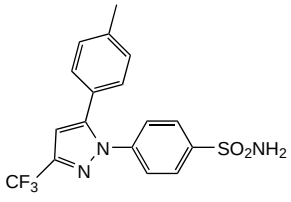
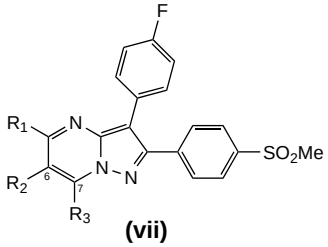
Pyrazolo[1,5-*a*]pyrimidines as novel COX-2 selective inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) exert their anti-inflammatory action mainly through inhibition of the enzyme cyclooxygenase (COX), of which two isoforms are known (COX-1 and COX-2). COX-1 is constitutively present in many tissues, such as the stomach, kidney and platelets, whereas COX-2 is cytokine inducible and expressed in a wide range of inflammatory cells. It is generally accepted that selective COX-2 inhibitors could provide anti-inflammatory agents devoid of the undesirable effects associated with non-selective NSAIDs. Based on the structure of early known anti-inflammatory agents, several diarylheterocycles have been prepared as selective COX-2 inhibitors. Amongst others, celecoxib **(vi)** is in the market for the treatment of acute pain, osteoarthritis and rheumatoid arthritis. Recently, Almansa and coworkers reported on a series of pyrazolo[1,5-*a*]pyrimidines **(vii)**, which were tested *in vitro* for their ability to inhibit COX-1 and COX-2 activity in a human whole blood (HWB) assay[4]. In addition, the compounds that showed > 60% inhibition at 10 μM were tested *in vivo* at 30 mg kg^{-1} in the rat carrageenan-induced paw edema assay. Finally, some of them were tested at 1 mg kg^{-1} in the carrageenan-induced air-pouch model, to evaluate prostaglandin production. SAR studies indicated that 6,7-disubstitution provided the best activity. The most potent and selective compound was **(vii)f** (R_1 = H; R_2,R_3=CH_3), which had the following IC_{50} values in HWB: COX-1 >10 μM, COX-2 = 0.08 μM. In this respect, **(vii)f** compares well with celecoxib, which, in the same test, had the following IC_{50} values: COX-1 = 13 μM, COX-2 = 0.6 μM. However, **(vii)f** was less active *in vivo*, owing to low oral bioavailability; several attempts to improve it have been unsuccessful until now.



(vi)



(vii)

4 Almansa, C. *et al.* (2001) Synthesis and SAR of a new series of COX-2 selective inhibitors: Pyrazolo[1,5-*a*]pyrimidines. *J. Med. Chem.* 44, 350–361

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