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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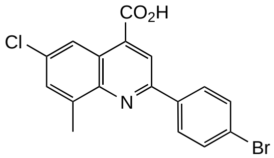
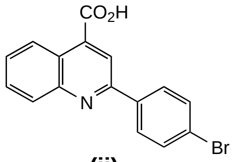
Molecules

Potent inhibitors of *Candida albicans* prolyl tRNA synthetase

The search for novel antifungal agents is a field of intense activity owing to the incidence of serious, life-threatening, fungal infections. Aminoacyl-tRNA synthetases (aaRSs) have been the subject of interest as possible targets for novel antibacterial drugs but the corresponding fungal enzymes have so far not attracted the same level of interest. Recently, researchers at Cubist (Cambridge, MA, USA) discovered a novel quinoline derivative **(i)** and showed it to be a potent inhibitor of *Candida albicans* prolyl tRNA synthetase, by optimization of seed compound **(ii)**, which was discovered using high-throughput screening[1].



(i)

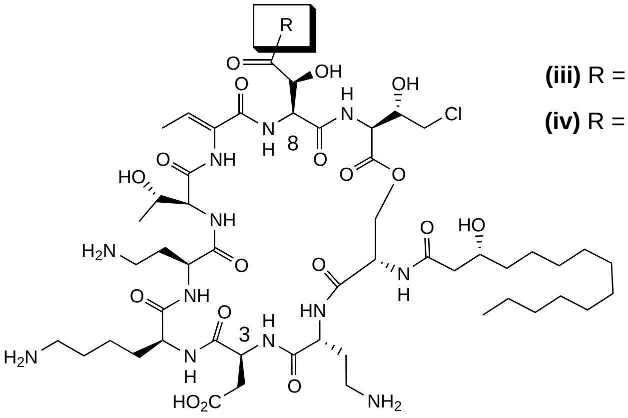


(ii)

Variation of the substituents on the basic quinoline skeleton of **(ii)** was performed to improve activity and selectivity relative to the corresponding human enzyme. As a result, the 4-bromophenyl substituent at position 2 of the quinoline was shown to be crucial for potent enzyme activity. Furthermore, introduction of substituents to the benzene ring of the quinoline moiety led to significant improvement in *in vitro* enzyme activity. Compound **(i)** was shown to possess excellent activity against *C. albicans* prolyl tRNA synthetase (IC_{50} = 5 nM) and only weak activity against the human enzyme (IC_{50} >100µM). Further studies demonstrated that **(i)** is a non-competitive inhibitor of the fungal enzyme relative to proline and a competitive inhibitor relative to ATP.

Pseudomycin analogues as potent antifungal agents

Pseudomycin B (PSB) **(iii)** is a novel depsipeptide natural product with potent antifungal activity, isolated from *Pseudomonas syringea* in plants. This compound has excellent activity against most of the main human fungal pathogens, especially *Candida* and *Cryptococcus*, although activity against *Aspergillus* strains is somewhat weak. Owing to this broad spectrum of activity, PSB is a candidate for development of a new approach to treatment of fungal infections, however, irritation potential at the site of injection is a side effect that prevents use of the natural product itself. Recently, researchers at Lilly (Indianapolis, USA) described a novel chemical transformation of PSB whereby the ‘northern’ acid residue (position 8) can be selectively functionalized as an amide derivative. The researchers found that one of the prepared analogues, compound **(iv)**, has more potent activity than PSB against *C albicans* and no tail-vein irritation after injection into mice[2].



(iii) R = H

(iv) R = NH_2

Protection of the three amino groups in PSB as benzyloxycarbonyl (cbz) or

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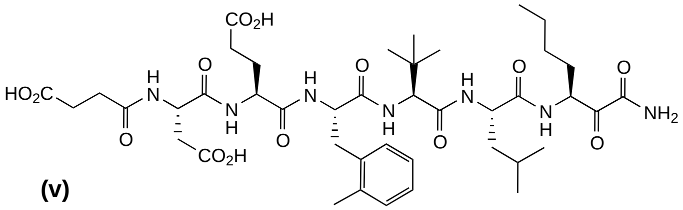
allyloxycarbonyl (alloc) groups, followed by regioselective amidation of the eight-acid residue using benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate (PyBOP) as the coupling reagent, afforded the 8-amide derivatives in moderate to excellent yields with a regioselectivity of >5:1 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)

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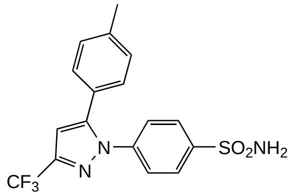
Pyrazolo[1,5-*a*]pyrimidines as novel COX-2 selective inhibitors

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.



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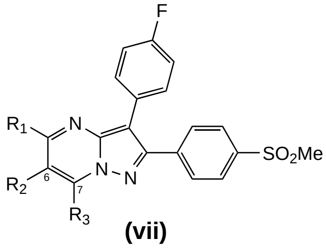

(vii)

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