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# 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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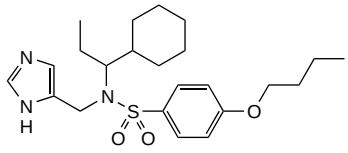
## Molecules

### Novel antifungals based on 4-substituted imidazole

There are few effective antifungal drugs available for use in humans, the polyene macrolide amphotericin B and the azole compounds, such as fluconazole and itraconazole, being the most widely used compounds. However, the emergence of new pathogenic fungi, as well as the development of resistance to established agents, has led to the requirement for new drugs with different modes of action and superior antifungal activity. Accordingly, many efforts to discover new lead compounds have been reported in recent years. Recently, A. Saha and co-workers[1] have described a combinatorial chemistry approach based upon the synthesis of focused libraries designed around a 1-*H*-imidazole-4-methylamino-sulfonamide structure, by which they identified imidazole **(i)** as the most potent inhibitor of growth of several *Candida* strains.



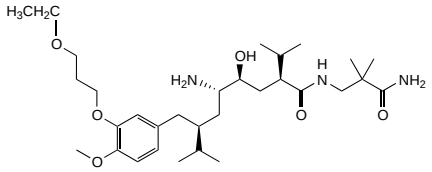
**(i)**

Solid-phase techniques were employed to prepare various exploratory and lead-optimization libraries and screening compounds were shown to be >90% pure by HPLC after cleavage from the resin. HPLC purification was employed to increase the purity to >90% when required. Antifungal screening revealed that **(i)** is a potent inhibitor of *Candida* activity and has a mode of action similar to the classical azole compounds, in that it inhibits 14-α-demethylase, an enzyme involved in the synthesis of a key component in fungi, ergosterol.

**1** Saha, A.K. *et al.* (2000) Novel antifungals based on 4-substituted imidazole: a combinatorial chemistry approach to lead discovery and optimization. *Bioorg. Med. Chem. Lett.* 10, 2175–2178

### Orally active non-peptide inhibitors of human renin

Human renin is an aspartic proteinase that has an important role in the regulation of blood pressure, attributed to its position at the first, rate-limiting step in the synthesis of angiotensin. Because renin alone can catalyze the cleavage reaction that generates angiotensin I from angiotensinogen, inhibitors of this enzyme offer potential improvements over angiotensin-converting enzyme (ACE) inhibitors. In spite of this, all known inhibitors of renin have failed in the drug development process owing to poor oral bioavailability and/or short duration of action. These drawbacks led to the requirement for high and/or frequent dosing. Recently, J. Rahuel and co-workers[2] have described an interesting new approach to the structure-based design of novel non-peptide renin inhibitors, and the identification of compound **(ii)** as a sub-nanomolar inhibitor with excellent oral *in vivo* activity in a primate model.



**(ii)**

The design process involved crystal-structure analysis of renin-inhibitor complexes, combined with molecular modelling, and revealed that the binding pocket for human renin can readily accommodate binding by more lipophilic substrates compared with the classical peptide inhibitors. Compound **(ii)** displayed potent inhibition of purified human renin ($IC_{50}$ = 0.6 nM).

**2** Rahuel, J. *et al.* (2000) Structure-based drug design: the discovery of novel non-peptide orally active inhibitors of human renin. *Chem. Biol.* 7, 493–504

### Potent and selective inhibitors of lck

The Src-family tyrosine kinase, lck, is mainly expressed in T lymphocytes and has an important role in the immune response. Catalytic activation of the syk family ZAP-70 kinase by lck is involved in T cell activation, hence inhibition of the activity of lck represents a potential approach to the discovery of new



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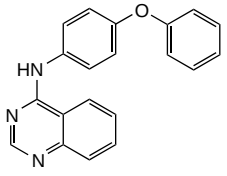
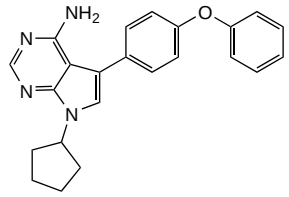
therapeutic entities for various autoimmune and inflammatory diseases. Because lck is only one of the members of the Src family of kinases, and all members share considerable amino acid sequence homology, it is crucial in any discovery effort to obtain good lck-specific selectivity. Scientists at BASF (Ludwigshafen, Germany) have recently discovered a series of pyrrolo[2,3-*d*]pyrimidines that display good selectivity for lck over other Src kinases[3,4].

The 4-arylaminoquinazoline **(iii)** was identified as a potent inhibitor of lck and



**(iii)**

led to the hypothesis that the phenoxy group occupies a unique hydrophobic pocket on lck, which improves binding. Studies of the binding of known lck inhibitor PP1 (Ref. 5) suggest that a pyrrolo[2,3-*d*]pyrimidine skeleton with a phenoxy group attached at the appropriate site would result in improved lck inhibition. The resulting compound **(iv)** was shown to be a potent inhibitor of IL-2 production in Jurkat cells and in mice at low doses ($ED_{50}$ = 4 mg $kg^{-1}$) after intraperitoneal administration.



**(iv)**


**3** Arnold, L.D. *et al.* (2000) Pyrrolo[2,3-*d*]pyrimidines containing an extended 5-substituent as potent and selective inhibitors of lck I. *Bioorg. Med. Chem. Lett.* 10, 2167–2170

**4** Burchat, A.F. *et al.* (2000) Pyrrolo[2,3-*d*]pyrimidines containing an extended 5-substituent as potent and selective inhibitors of lck II. *Bioorg. Med. Chem. Lett.* 10, 2171–2174

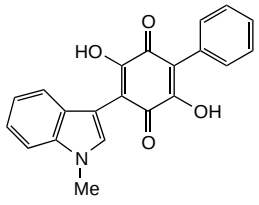
**5** Hanke, J.H. *et al.* (1996) Discovery of a novel, potent and Src family-selective tyrosine kinase inhibitor. *J. Biol. Chem.* 271, 695–701


## Small-molecule activator of the insulin receptor

Resistance to insulin is a feature of non-insulin dependent diabetes mellitus (NIDDM) and is also a contributing factor in other diseases such as atherosclerosis and hypertension.

Starting from a fungal metabolite shown to have anti-diabetic properties, the Merck group (Rahway, NJ, USA) has identified a series of diaryl-dihydroxybenzoquinones, represented by **(v)**, which are potent, selective and orally active insulin-receptor tyrosine-kinase (IRTK) activators, and thus antihyperglycaemic agents[6].

In animal model studies, molecule **(v)** is reported to reduce elevated glucose



**(v)**

levels in diabetic *db/db* mice and to reduce the insulin concentration in obese *ob/ob* mice. Significantly, **(v)** did not provoke hypoglycaemia with doses up to 10 mg $kg^{-1}$ in normal mice. A structurally related molecule with a similar pharmacokinetic profile to **(v)**, but inactive in the IRTK assay, did not reduce glucose levels in diabetic mice.

In attempting to address concerns over the quinone structure, molecule **(v)** has proven to be chemically stable and did not show overt toxicity at pharmacological doses.

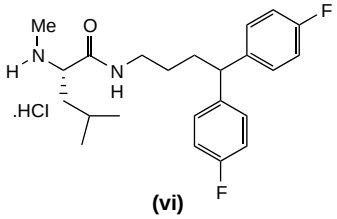

**6** Liu, K. *et al.* (2000) Discovery of a potent, highly selective, and orally efficacious small-molecule activator of the insulin receptor. *J. Med. Chem.* 43, 3487–3494


## Small-molecule calcium channel antagonist with potential for the treatment of pain

Voltage-dependent ion channels are attractive drug targets for the treatment of pain and inflammation. The synthetic version of the peptide ω-conotoxin, Ziconotide (SNX111), is a potent, selective N-type $Ca^{2+}$ channel blocker that has shown a marked analgesic effect in clinical trials.

The Pfizer group (Ann Arbor, MI, USA) has disclosed the small molecule **(vi)** as a balanced $Ca^{2+}$, $Na^{+}$ and $K^{+}$ channel antagonist ($ID_{50}$ = 1.3, 5.1 and 9.9 μM, respectively)[7]. Molecule **(vi)** is described as the first small-molecule N-type calcium channel antagonist to show potent analgesic activity in several animal models of different types of pain, such as post-operative, incisional and inflammatory pain. It also exhibited anti-convulsant activity in a mouse model, which indicates CNS bioavailability.

This molecule is much less potent than the peptide Ziconotide. However, it suggests that a more selective N-type calcium channel antagonist could be a useful analgesic with an alternative pharmacokinetic profile to a peptide.



**(vi)**


**7** Song, Y. *et al.* (2000) (*S*)-4-Methyl-2-(methylamino)pentanoic acid [4,4-bis(4-fluorophenyl)butyl]amide hydrochloride: a novel calcium channel antagonist, is efficacious in several animal models of pain. *J. Med. Chem.* 43, 3474–3477



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