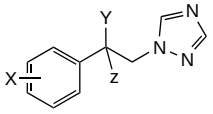
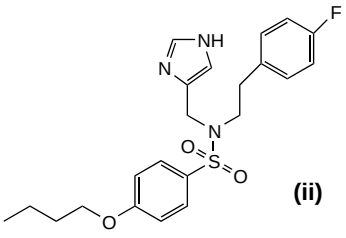
Combinatorial chemistry

Azole antifungals

Efforts to discover new antifungal agents continue because of the perceived threat of emerging new pathogenic fungi and the resistance of many strains to existing therapy. The triazole class of drugs remains the therapeutic mainstay for systemic life-threatening fungal infections. These drugs, known as azole antifungals, share a common mode of action, in that they inhibit cytochrome P450-dependent sterol 14-α-demethylase. Inhibition of this enzyme results in the depletion of ergosterol, an essential sterol for fungal cell-membrane synthesis. Nearly all azole antifungals are *N*-substituted azoles and share the azolyl phenethyl amine pharmacophore **(i)**. The synthesis of focused libraries containing the 1-*H*-imidazole-4-methylaminosulfonamide motif, with the aim of discovering potent new antifungal lead compounds, is described[1].



(i) X = Cl or F; Y, Z = O, O or O, C



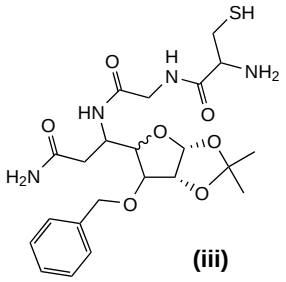
(ii)

A library of >1000 individual compounds was synthesized on a 1-*H*-imidazole-4-carboxaldehyde-immobilized, 2-chlorotrityl chloride polystyrene solid-phase resin. Screening of these compounds against eight isolates of *Candida* spp., for their *in vitro* antifungal activity, revealed several active compounds. One of the most potent compounds discovered was **(ii)**, which possessed an IC_{50} of 26 nM against ergosterol. This library has been successful in providing a novel series of antifungal imidazoles, some of which possessed potent anti-*Candida* activity. These active compounds inhibit fungal ergosterol synthesis. Future work could be directed at further optimization of this pharmacophore to achieve delivery of even more potent anti-*Candida* compounds.

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

DNA topoisomerase II inhibitors

Effective treatment regimens to decrease microfilaramia are the primary reason for the World Health Assembly's recent designation of lymphatic filariasis as a disease that is no longer a global public-health problem. Human lymphatic filariasis, which is caused by helminths *Wuchereria bancrofti* (90% of cases) and *Brugia malayi* (10% of cases), affects ~120 million people. In this case, the challenge of drug discovery lies in the identification of novel therapeutic targets from the myriad of parasite enzymes, receptors, genome data and metabolic pathways. The known potential antifilarials act either on the membrane receptors or on metabolic enzymes. DNA topoisomerases are cellular enzymes that are intricately involved in maintaining the topographic structure of DNA, transcription and mitosis. Topoisomerase has been identified as an important biochemical target in cancer chemotherapy and microbial infections. Intracellular bacteria have been detected in most filarial worms, and it is thought that by eradicating the endobacteria, filarial parasites might also die because of the disturbance in the endosymbiosis. Recently, DNA topoisomerase II (topo II) of the filarial parasites has been identified as a target for the development of antifilarial compounds, thus enabling the study of the effect of various inhibitors of topoisomerases and antifilarials[2]. A small library of 24 compounds was synthesized on solid phase from Sieber amide resin (Advanced ChemTech Europe, Cambridge, UK). One of the most potent compounds isolated was **(iii)**, which gave 95% inhibition of DNA topo II of the filarial parasite *Setaria cervi*. This library has provided a novel low molecular weight pharmacophore with potent DNA topo II-inhibitory activity. Because no satisfactory inhibitor for topo II of *S. cervi* is currently available, glycoconjugate **(iii)** lays the foundation for the design of more potent inhibitors.



(iii)

2 Tripathi, R.P. *et al.* (2001) Identification of inhibitors of DNA topoisomerase II from a synthetic library of glycoconjugates. *Combi. Chem. High Throughput Screen.* 4, 237–244

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