polyvinylidene fluoride hollow fibres containing various cancer cell cultures were implanted intraperitoneally (ip) and subcutaneously (sc) into mice and compounds were administered by the ip route (the so-called hollow fibre assay). Compound **(xa)** was found to be potent in the hollow fibre assay, despite the fact that its cytotoxicity in *in vitro* cancer cell cultures was relatively unimpressive. This result emphasizes the fact that *in vitro* cytotoxicity studies are not always accurate indicators of how well a compound will perform in *in vivo* efficacy models.

7 Jayaraman, M. *et al.* (2002) Synthesis of new dihydroindeno[1,2-*c*]isoquinoline and indenoisoquinolinium chloride topoisomerase inhibitors having high *in vivo* anticancer activity in the hollow fiber animal model. *J. Med. Chem.* 45, 242–249

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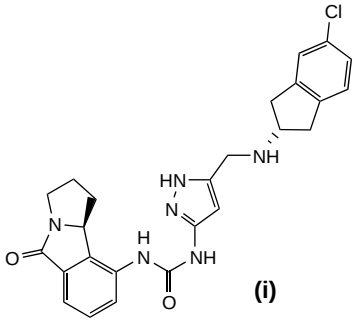
Combinatorial chemistry

Selective Cdk4 inhibitors

Cyclins and cyclin-dependent kinases (Cdks) have important roles in regulating the cell cycle. In particular, D-type cyclins, which are amplified or overexpressed in several tumour cells, associate with Cdk4/6 to activate their phosphorylation activity. Cyclin D-Cdk4/6 complexes phosphorylate the retinoblastoma protein (pRB) and regulate the cell cycle during the G_1–S transition. Loss of function or deletion of $p16^{ink4a}$ (an endogenous Cdk4/6 specific inhibitor protein) frequently occurs in clinical cancer cells. Thus, selective Cdk4/6 inhibitors should be useful as a new class of cytostatic antitumour agents.

To overcome the problem of selectivity for Cdk4/6 over the hundreds of homologous kinases in the superfamily, specific amino acid residues were identified around the ATP-binding pocket of Cdk4 by comparing the amino acid sequences of 390 representative kinases. Subsequently, a chemical library was designed using this information about the locations of these amino acid residues [1] and 64 single analogues were prepared in solution. Evaluation of the library compounds' ability to inhibit Cdk4 was undertaken. One of the most potent compounds isolated was **(i)**, which displayed an IC_{50} value of 2.3 nM against D-Cdk4 and had excellent selectivity over Cdk1/2 (780-fold and 190-fold, respectively) and >430-fold selectivity over a range of kinases investigated. This library design, based on the locations of amino acids around the ATP-binding pocket and an analysis of the binding mode of lead compounds, has enabled the authors to develop potent and selective inhibitors of Cdk4 efficiently. The kinase superfamily consists of numerous kinases that have a common folding pattern. Therefore, in general it is difficult to improve target kinase selectivity with respect to all other kinases simultaneously. The approach described here should be useful for the development of specific kinase inhibitors more systematically and efficiently.

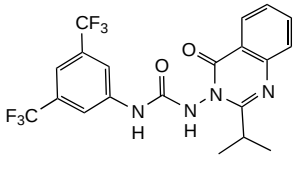


(i)

1 Honma, T. *et al.* (2001) A novel approach for the development of selective Cdk4 inhibitors: library design based on locations of Cdk4 specific amino acid residues. *J. Med. Chem.* 44, 4628–4640

Antibacterial agents

The rapid emergence of drug resistant pathogens emphasizes the need for new classes of antibacterial agents. Historically, new types of compounds have been identified from the diverse pool of natural products, for which there are many clinically proven efficacious agents. Many existing antibacterial drugs, such as the β-lactams penicillin and methicillin, act by direct inhibition of one or more key steps in the metabolic pathway for the synthesis of the bacterial cell wall constituent peptidoglycan. Efforts have been made to identify cell-wall active agents through screening and deconvolution of mixture-based combinatorial libraries [2]. A library of 10,000 semi-carbazone compounds in mixtures of 100 was synthesized in solution. The library was screened for inhibition of growth, bacterial histidine kinases and peptidoglycan biosynthesis in whole cells of *Staphylococcus aureus*. Active mixtures were deconvoluted and resynthesized as single compounds. These were tested in a cell-wall-synthesis assay in *S. aureus* (MI246) and against a panel of six Gram-positive pathogens. One of the most potent compounds isolated was **(ii)**, which displayed an IC_{50} value of 66 μM against cell wall and an arithmetic mean MIC of 1.5 μM against the panel of six Gram-positive organisms. This work has provided new structural classes of compounds with antibacterial activity and could provide a basis for future work in this area.



(ii)

2 Wilson, L.J. *et al.* (2001) The identification and characterization of hydrazinyl urea-based antibacterial agents through combinatorial chemistry. *Bioorg. Med. Chem. Lett.* 11, 1149–1152

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