analogues were selected from >70,000 screened compounds, yielding rich information on mechanisms of drug action and drug resistance. The average pairwise Pearson correlation coefficient within the CPT set was found to be 0.70 (indicating similar patterns of antitumour activity across the 60 cell lines) and coherence between structures and their activity patterns was observed. QSAR studies on 58 compounds using GI_{50} values for 60 cell lines as the dependent variables were performed. The application of various statistical methods to construct QSAR models indicated that the fully cross-validated genetic function approximation (GFA) method performed best in terms of correlation coefficients and cross-validation analysis. Several molecular descriptors, including partial atomic charges and three interatomic distances that refine the relative spatial dispositions of three significant atoms were correlated with antitumour activity. The cross-validated r^2 for the final GFA model was 0.783, indicating a predictive QSAR model.

6 Dallavalle, S. *et al.* (2001) Novel 7-oxyiminomethyl derivatives of camptothecin with potent *in vitro* and *in vivo* antitumor activity. *J. Med. Chem.* 44, 3264–3274

7 Fan, Y. *et al.* (2001) Quantitative structure-antitumor activity relationships of camptothecin analogues: cluster analysis and genetic algorithm-based studies. *J. Med. Chem.* 44, 3254–3263

Andrew D. Westwell
Cancer Research Laboratories
University of Nottingham
Nottingham
UK NG7 2RD
tel: +44 115 951 3419
fax: +44 115 951 3412
e-mail: andrew.westwell@nottingham.ac.uk

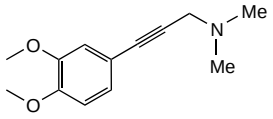
Combinatorial chemistry

Semicarbazide-sensitive amino oxidase inhibitors

The semicarbazide-sensitive amine oxidases (SSAOs) are a widespread group of enzymes found in plants and animals, which possess a copper atom and an oxidized tyrosine residue (topaquinone) in their active site. Although they appear to be involved in the oxidative deamination of endogenous amines, their precise function is unknown. In humans, SSAOs have been implicated in the physiopathology of diabetes.

Elevated levels of SSAOs have been reported in diabetics and it is believed that vascular damage could result from the toxicity of formaldehyde and hydrogen peroxide formed by the action of SSAOs on endogenous methylamine. Drugs that inhibit SSAOs could thus prove useful as prophylactics that prevent the long-term retinal damage associated with diabetes mellitus [1].

A small library of 20 single aryl propargyl amines was synthesized in solution. Testing the compounds in this library for their ability to inhibit bovine plasma SSAO identified several potent compounds. One of the most potent isolated was **(i)**, which possessed a K_i value of 2.9 μM.



(i)

The structure–activity relationship (SAR) obtained from studying this library of compounds suggests that binding to the active site occurs by coordination of the amine to the proximal copper (II) and formation of a π-complex between topaquinone and the electron-rich aryl group of the inhibitor. Further putative inhibitors are currently being synthesized, their design based on the SAR obtained from the small library discussed here, to test this hypothesis.

1 Conn, C. *et al.* (2001) Combinatorial synthesis of SSAO inhibitors using Sonogashira coupling: SAR of aryl propargylic amines. *Bioorg. Med. Chem. Lett.* 11, 2565–2568

Tyrosine and dual-specificity protein phosphatase inhibitors

Tyrosine phosphorylation of proteins is a fundamental mechanism of intracellular signal transduction involved in important cellular events such as cell growth and differentiation. The phosphorylation states of proteins are strictly controlled by various protein tyrosine-kinases (PTKs) and protein tyrosine-phosphatases (PTPs). PTPs represent a diverse family of enzymes that exist as integral membrane and non-receptor forms. Disorders of PTPs are likely to be related to several diseases such as cancer, autoimmune diseases and diabetes, and the characterization of PTPs are, therefore, expected to be not only useful tools for clarifying the biological functions of the PTPs themselves, but also candidates for novel therapeutics.

Recently, a subgroup of PTP enzymes that dephosphorylate both phosphotyrosine and phosphoserine/threonine have attracted attention. In particular, CDC25 phosphatases (CDC25-A, -B, and -C) are considered important members of a family of dual-specificity phosphatases (DSPs) that are known to be key enzymes in cell-cycle progression. CDC25 dephosphorylates and activates cyclin-dependent kinases. To find a selective inhibitor of CDC25, as well as other biologically important PTPs or DSPs, a focussed library was synthesized that used the structural features of PTPs and DSPs for its design [2].

A small library of 32 single compounds was synthesized in solution. Screening assays were performed against a recombinant vaccinia virus (VH-1)-related phosphatase (VHR) protein, using *p*-nitrophenyl phosphate as a substrate to determine the compounds' ability to act as VHR inhibitors. VHR is itself is a DSP that has been found to dephosphorylate and inactivate members of the mitogen-activated protein-kinase (MAPK) family. Additionally, compounds were tested for their ability to inhibit a recombinant CDC25B protein, using

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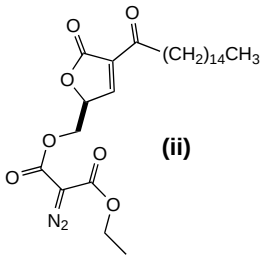
3-*O*-methylfluorescein phosphatate as substrate.

One of the most active compounds obtained was **(ii)**, which inhibited CDC25B with an IC_{50} value of 400 nM, and possessed 30-fold selectivity over the closely related DSP, VHR. This work indicates that synthesis of the tetronic acid library has been useful in the search for a PTP- or DSP-selective inhibitor. Expansion of this library to find more powerful and



(ii)

highly selective inhibitors of CDC25, and several other therapeutically important PTPs and DSPs, is thus warranted.

2 Sodeoka, M. *et al.* (2001) Synthesis of a tetronic acid library focused on inhibition of tyrosine and dual-specificity protein phosphatases and its evaluation regarding VHR and CDC25 inhibition. *J. Med. Chem.* 44, 3216–3222

Paul Edwards
Lead Discovery Technologies
Pfizer Global Research and Development
Sandwich
Kent, UK
fax: +44 1304 643555
e-mail: paul_edwards@sandwich.pfizer.com

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