

over a large range; this was consistent with modelling and crystallographic studies and suggests that the affinity is modulated by the aryl side chain. In addition, these studies showed that, because the boronic acids thus far investigated are small molecules, much of the binding site of the enzyme was not involved. Consequently, Shoichet and colleagues⁶ synthesized a series of larger boronic acid derivatives, to determine which functionality would best complement the binding site of the enzyme, using structure-guided in-parallel synthesis. The known inhibitor (vi) ($K_i = 7.3 \mu\text{M}$; Ref. 5) was used as the lead because it is well suited to derivatization. Based on modelling studies, the researchers hypothesized that amide and sulfonamide derivatives of (vi,a) would fit the binding site well. Several derivatives were prepared using polymer-assisted in-parallel chemistry. Of these, several inhibitors showed K_i s in the 100 nM range, the most significant being (vi,b) ($K_i = 0.08 \mu\text{M}$). Modelling studies on (vi,b) led to a second focused library of 12 compounds, with improved solubility and, potentially, better interactions than the first series. The most potent was compound (vi,c) ($K_i = 0.06 \mu\text{M}$). Compounds (vi,b) and (vi,c) were tested in bacterial culture for their ability to reverse the resistance of β -lactamase-expressing bacteria to penicillins: they were found active in Gram-positive bacteria. In fact, these compounds reduced the minimum inhibitory concentration (MIC) of amoxicillin by 8–32-fold at a concentration of

4–16 $\mu\text{g ml}^{-1}$. On the contrary, they were much less effective against β -lactam-resistant Gram-negative bacteria.

Finally, the crystal structure of compound (vi,b), in complex with the group I β -lactamase AmpC, was obtained. This structure could serve as a template for future inhibitors.

- 4 Davies, J. (1994) Inactivation of antibiotics and the dissemination of resistance genes. *Science* 264, 375–382
- 5 Beesley, T. *et al.* (1983) The inhibition of class C beta-lactamases by boronic acids. *Biochem. J.* 209, 229–233
- 6 Tondi, D. *et al.* (2001) Structure-based design and in-parallel synthesis of inhibitors of AmpC β -lactamase. *Chem. Biol.* 8, 593–610

Daniela Barlocco

University of Milan,

Viale Abruzzi 42

Milano-20131, Italy

tel: +39 02 2950 2223

fax: +39 02 2951 4197

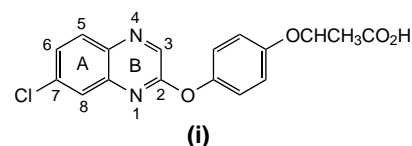
e-mail: daniela.barlocco@unimi.it

Novel antitumour molecules

Evaluation of analogues of the antitumour agent XK469

The compound 2-{4-[(7-Chloro-2-quinoxalinyloxy)phenoxy]propionyloxy}propionic acid [XK469; (i)], displays potent, broad-spectrum antitumour activity, most notably against transplanted tumours. As a result of these preclinical observations, XK469 has been scheduled to enter clinical trials later this year, even though the mechanism of action of this agent remains to be elucidated. Recently, Horwitz and coworkers at the Wayne State University School of

Medicine (Detroit, MI, USA) reported the results of an extensive SAR study to delineate the structure of the active site¹. The structure of the parent compound was dissected into three regions – (1) ring A of quinoxaline; (2) the hydroquinone connector linkage; and (3) the lactic acid moiety – to determine the resultant *in vitro* and *in vivo* effects of chemical alterations in each region. A halogen atom located at the 7-position generated the most highly- and broadly-active antitumour agents, whereas other 7-position substituents, substitution at other A and/or B ring positions, and changing the connector linkage to resorcinol or catechol derivatives, all produced markedly less-active structures.

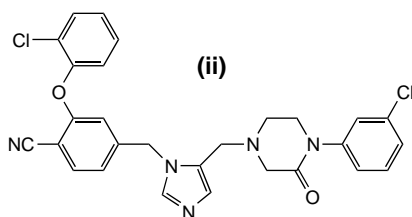


- 1 Hazeldine, S.T. *et al.* (2001) Design, synthesis and biological evaluation of analogues of the antitumor agent, 2-{4-[(7-chloro-2-quinoxalinyloxy)phenoxy]propionyloxy}propionic acid (XK469). *J. Med. Chem.* 44, 1758–1776

Dual inhibitors of farnesyltransferase and geranylgeranyltransferase-I

The search for selective anticancer agents against the oncogenic Ras protein, a key component of important intracellular-signalling pathways governing cell growth and differentiation, which is frequently mutated in cancer cells, has focused largely on the inhibition of the farnesyl-protein transferase enzyme (FTPase). FTPase catalyzes the S-farnesylation of a cysteine residue in the C-terminal tetrapeptide sequence of Ras, a post-translational modification required for Ras activation. Several FTPase inhibitors (FTIs) have shown outstanding preclinical promise with selective activity for FTPase over the analogous prenyltransferase, geranylgeranyl-protein transferase-I (GGPT-I), and early clinical trials are under way in some cases. However, one potential difficulty with using these

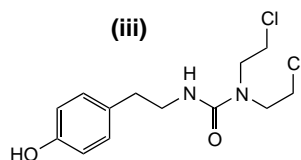
agents is that, in the case of Ki-Ras (Kirsten-Ras), activation through geranylgeranylation with resultant downstream signalling can occur when farnesylation is blocked. Thus, dual FTPase-GGPTase inhibitors should prevent prenylation of Ki-Ras and could have significant potential as anti-Ras agents. With this in mind, Bergman and coworkers at the Merck Research Laboratories (West Point, PA, USA) have reported the use of aryloxy substituted *N*-arylpiperazinones as dual inhibitors of the FTPase and GGPTase enzymes². For example, compound (ii) was found to inhibit both FPTase and GGPTase *in vitro* with IC₅₀ values in the low nanomolar region.



- 2 Bergman, J.M. *et al.* (2001) Aryloxy substituted *N*-arylpiperazinones as dual inhibitors of farnesyltransferase and geranylgeranyltransferase-I. *Bioorg. Med. Chem. Lett.* 11, 1411–1415

Melanocyte-directed enzyme prodrug therapy

Melanocyte-directed enzyme prodrug therapy (MDEPT) represents a possible selective strategy towards the treatment of malignant melanoma because of the unique occurrence of tyrosinase enzyme expression in melanocytes. MDEPT, therefore, offers a highly selective drug-delivery system, with increased selectivity for delivery of cytotoxic agents and minimization of side effects. Osborn and coworkers at the University of Reading (Reading, UK) have described the synthesis and evaluation of several MDEPT prodrugs incorporating a dopamine moiety as tyrosinase substrate, a drug such as phenyl mustard as the cytotoxic agent and a carbamate linker function³. In particular, the sterically undemanding prodrug *bis*-(2-chloroethyl)amino-4-hydroxyphenylaminomethanone (iii),

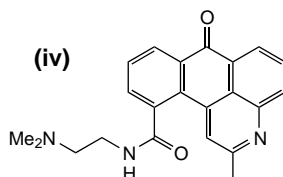


synthesized in one-pot, is oxidized by mushroom tyrosinase at a superior rate to tyrosine methyl ester, the carboxylic acid of which is the natural substrate for tyrosinase.

- 3 Jordan, A.M. *et al.* (2001) Melanocyte-directed enzyme prodrug therapy (MDEPT): development of second generation prodrugs for targeted treatment of malignant melanoma. *Bioorg. Med. Chem.* 9, 1549–1558

New cytotoxic 'fused' tetracyclic systems

A new class of 'fused' tetracyclic antitumour agents, the 7-oxo-7*H*-dibenz[*f,i*]isoquinolines, has been reported by Denny and coworkers at the University of Auckland, New Zealand⁴. Members of this class are topologically related to the DNA-intercalating tricyclic clinical drug amonafide. A series of carboxamide-linked compounds was prepared, from which the 11-carboxamide derivative (iv) emerged as the most promising agent, having curative *in vivo* activity in the refractive subcutaneous colon 38 mouse model.

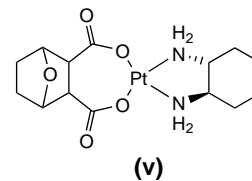


- 4 Bu, X. *et al.* (2001) Synthesis and cytotoxic activity of 7-oxo-7*H*-dibenz[*f,i*]isoquinoline and 7-oxo-7*H*-benzo[*e*]perimidine derivatives. *J. Med. Chem.* 44, 2004–2014

New antitumour agents from modified traditional Chinese medicine with a platinum moiety

Ho and coworkers at the Chinese University of Hong Kong (Hong Kong, China) have used a combination of demethylcantharidin, a modified component of traditional Chinese medicine (TCM) used in the treatment of liver, lung,

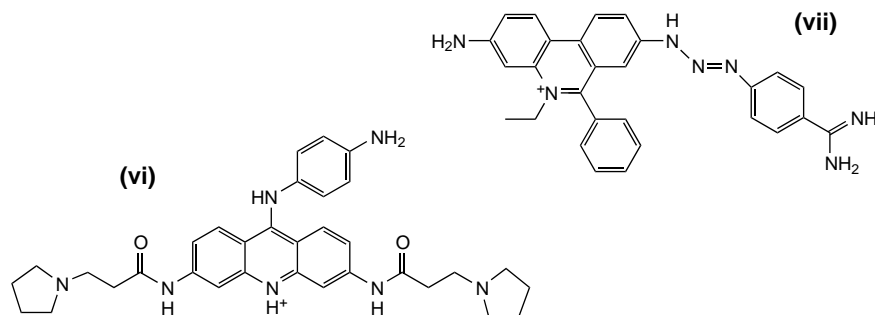
intestinal and digestive tract disorders, and a platinum moiety based on the clinically used cisplatin series, to produce a series of TCM-based platinum compounds⁵. The new agents [e.g. (v)] demonstrate dual mechanisms of antitumour activity, encompassing protein phosphatase (PP2A) inhibition and platination of DNA; the former mechanism could provide an explanation for the circumvention of cisplatin-induced resistance.



- 5 Ho, Y-P. *et al.* (2001) Potential new antitumor agents from an innovative combination of demethylcantharidin, a modified traditional Chinese medicine, with a platinum moiety. *J. Med. Chem.* 44, 2065–2068

Selective G-quadruplex-mediated telomerase inhibitors

The telomeric ends of eukaryotic chromosomes consist of TTAGGG repeat units, which progressively shorten with each replicative event until telomeres reach a critically short length and enter senescence. However, in most cancer cells the relatively short telomeres are stable in length, being maintained by the action of the telomerase enzyme complex. Because telomerase is activated in 80–90% of tumour cells, but undetectable in most normal somatic cells, inhibition of telomerase represents an attractive anti-cancer therapeutic strategy. Telomerase requires the 3' end of the DNA telomere primer to be single-stranded; folding of single-stranded telomeric DNA into a four-stranded guanine-quadruplex inhibits the enzyme from synthesizing further telomeric DNA repeats. Molecules that stabilize such quadruplex structures could, therefore, be effective telomerase inhibitors, and several tricyclic aromatic chromophores have been identified to fulfil this role. Niedle and coworkers at the Institute of Cancer Research (London, UK) have reported the design and



synthesis of a series of 3,6,9-trisubstituted acridine telomerase inhibitors⁶. Potent telomerase inhibitory activity, combined with low duplex DNA affinity, has been observed, for example compound (vi), which has an $^{tel}EC_{50}$ value of 60 nM.

In related work, Mergny and coworkers at the Muséum National d'Histoire Naturelle (Paris, France) have described the use of ethidium derivatives, such as (vii), in the stabilization of G-quadruplex structures and telomerase inhibition

*in vitro*⁷ [e.g. for compound (vii), the IC_{50} value for telomerase is 18 nM].

- 6 Read, M. *et al.* (2001) Structure-based design of selective and potent G quadruplex-mediated telomerase inhibitors. *Proc. Natl. Acad. Sci. U. S. A.* 98, 4844–4849
- 7 Koepfel, F. *et al.* (2001) Ethidium derivatives bind to G-quartets, inhibit telomerase and act as fluorescent probes for quadruplexes. *Nucleic Acids Res.* 29, 1087–1096

Andrew Westwell

Cancer Research Laboratories

University of Nottingham

Nottingham,

UK NG7 2RD

tel: +44 115 9513419

fax: +44 115 9513412

e-mail: andrew.westwell@nottingham.ac.uk

In the 15th September 2001 issue of *Drug Discovery Today*...

Editorial Proposed regulation on human cloning will pave the way for vital research into degenerative disease
by *Crispin Kirkman*

Update news and views

- A look at some novel training courses that are being launched focusing on chemoinformatics
- Discussions on how HTS can help the understanding of the physiology of life and the potential impact of phage display on modern biological research
- Conference report on RSC's *Combinatorial Approaches to Chemistry and Biology III*
- Book review of *The Outsourcing R&D Toolkit*

Reviews Effective decision making: progressing compounds through clinical development
by *Christine A. Shillingford and Colin W. Vose*

Lead optimization in 12 months? True confessions of a chemistry team
by *Simon J.F. MacDonald and Paul W. Smith*

Deformylase as a novel antibacterial target
by *Zhengyu Yuan, Joaquim Trias and Richard J. White*

Monitor Molecules and combinatorial chemistry