

and mutational analysis of resistant virus are consistent with the notion that this protein is targeted by CL253824 and WAY1500138. The exact mode of action on the protein has not yet been determined.

- 4 Van Zeijl, M. (2000) Novel class of thiourea compounds that inhibit herpes simplex virus type 1 DNA cleavage and encapsidation: resistance maps to the UL6 gene. *J. Virol.* 74, 9054–9061

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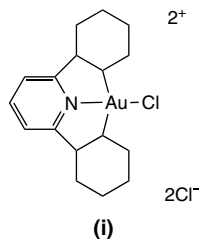
## Novel antitumour molecules

### Novel antitumour metal complexes related to cisplatin

Cisplatin and carboplatin, which are platinum-based drugs, play a leading role as cancer chemotherapeutic agents. Recently there has been a growing interest in the development of structurally related complexes of other metals (e.g. Ti, Au, Cu, Sn and Rh) as potential antitumour drugs. Two recent reports highlight such developments. Orioli and coworkers (University of Florence, Florence, Italy) have reported results on the use of gold (III) complexes with multidentate ligands as potential antitumour agents<sup>1</sup>. The use of multidentate ligands was found to impart a high degree of stability under physiological conditions, a problem that has hampered the development of gold (III) complexes previously. The *in vitro* cytotoxic properties were tested against the human ovarian tumour cell line A2780, either wild-type or cisplatin resistant. Typically, the investigated compounds had IC<sub>50</sub> values in the 0.2–10 µM range and were able to overcome cisplatin resistance when tested on the relevant cell line. However, in the most potent complexes tested, the free terpyridine (i) and phenanthroline

ligands were found to be more cytotoxic than the gold (III) complexes, rendering the interpretation of the cytotoxicity data complicated.

A related report by Caruso and coworkers (Consiglio Nazionale delle Ricerche, Rome, Italy and University of Camerino, Camerino, Italy) describes the characterization and biological testing of the coordination complex cyclo-tetrakis[bis(1-phenyl-3-methyl-4-benzoylpyrazolon-5-ato)µ-oxotitanium (IV)] as a potential antitumour drug<sup>2</sup>. The authors conclude, on the basis of both *in vitro* and *in vivo* results in CF-1 and A/J mice, that a Ti complex–liposome system might be a promising drug candidate.

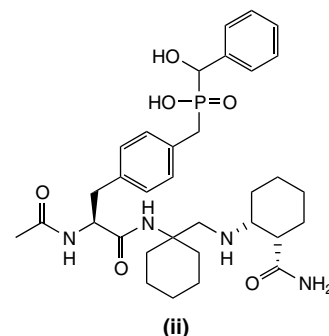


- 1 Messori, L. *et al.* (2000) Gold (III) complexes as potential antitumor agents: solution chemistry and cytotoxic properties of some selected gold (III) compounds. *J. Med. Chem.* 43, 3541–3548
- 2 Caruso, F. *et al.* (2000) Synthesis, structure and antitumor activity of a novel tetranuclear titanium complex. *J. Med. Chem.* 43, 3665–3670

### Phosphinate isosteres of phosphotyrosine for incorporation in Grb2-SH2 inhibitors

The signal transduction processes mediated by Grb2 (growth factor receptor-bound protein 2) are essential for the activity of growth factors involved in cell proliferation and differentiation. Deregulation of the pathways mediated by Grb2 can lead to uncontrolled cellular proliferation and ultimately tumour formation. Inhibiting the binding interactions between tyrosine kinase growth factor receptors and the Src homology 2 (SH2) domain of Grb2 therefore constitutes an attractive strategy in the search for new anticancer drugs. Recent

research by Furet and colleagues<sup>3</sup> (Novartis, Basel, Switzerland) and Walker and coworkers<sup>4</sup> (Novartis, Horsham, UK) describe the structure-based design and synthesis of a series of phosphinate isosteres of phosphotyrosine and their incorporation into a short inhibitory peptide sequence of the Grb2-SH2 domain. The phosphinate isosteres were designed as less charged and phosphatase-resistant pTyr replacements without the loss of binding affinity for the Grb2-SH2 domain. The resulting compounds, most notably (ii), were found to inhibit binding to Grb2-SH2 as potently as the corresponding doubly charged (phosphonomethyl)phenylalanine analogue.

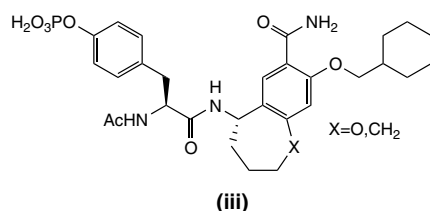


- 3 Furet, P. *et al.* (2000) Structure-based design and synthesis of phosphinate isosteres of phosphotyrosine for incorporation in Grb2-SH2 domain inhibitors. Part 1. *Bioorg. Med. Chem. Lett.* 10, 2337–2341
- 4 Walker, C.V. *et al.* (2000) Structure-based design and synthesis of phosphinate isosteres of phosphotyrosine for incorporation in Grb2-SH2 domain inhibitors. Part 2. *Bioorg. Med. Chem. Lett.* 10, 2343–2346

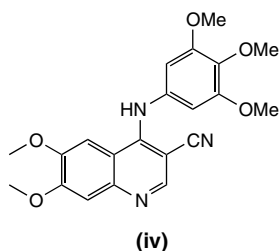
### Inhibitors of the Src SH2 domain and Src tyrosine kinase as potential anticancer drugs

The Src homology 2 (SH2) domain of proteins recognizing phosphotyrosine (pTyr) sequences of tyrosine kinases play a crucial role in many intracellular signalling cascades. The non-receptor tyrosine kinase, Src, is involved in signalling pathways controlling cell proliferation, migration and angiogenesis. Elevated levels of kinase activity have been associated with several different cancers including breast and colon. Using

structure-based design and synthesis, Shakespeare and coworkers (ARIAD Pharmaceuticals, Cambridge, MA, USA) have identified a short series of bicyclic non-peptide inhibitors for the Src SH2 domain<sup>5</sup>. The resulting compounds, (iii), represent some of the strongest binding inhibitors known for this target SH2 domain, and have promise for



future inhibitors with increased cell penetration and *in vivo* activity. In related studies, the preparation and SARs of a series of Src tyrosine kinase inhibitors has been reported by Wang and coworkers<sup>6</sup> (Wyeth-Ayerst Research, Pearl-River, NY, USA). A series of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines were prepared and tested for inhibition of Src kinase activity, from which compound (iv) emerged as the most potent (ATP competitive) inhibitor ( $IC_{50} = 35$  nM).



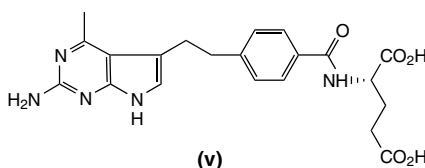
5 Shakespeare, W.C. *et al.* (2000) Structure-based design of novel bicyclic nonpeptide inhibitors for the Src-SH2 domain. *J. Med. Chem.* 43, 3815–3819

6 Wang, Y.D. *et al.* (2000) Inhibitors of Src tyrosine kinase: the preparation and structure-activity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines. *Bioorg. Med. Chem. Lett.* 10, 2477–2480

#### A potent dual inhibitor of thymidylate synthase and dihydrofolate reductase

Inhibitors of folate metabolism, such as thymidylate synthase (TS) and dihydrofolate reductase (DHFR) inhibitors, have provided important clinical agents for cancer chemotherapy owing to their

inhibition of the biosynthesis of nucleic acid precursors. Gangjee and coworkers have reported the design and synthesis of a potent dual inhibitor of TS and DHFR [(v); Ref. 7]; evaluation of compound (v) in the National Cancer Institute (Bethesda, MD, USA) *in vitro* preclinical screening program afforded  $GI_{50}$  values in the nanomolar range against several human tumour cell lines (of leukaemic, non-small cell lung, colon, CNS and renal origin).



7 Gangjee, A. *et al.* (2000) Design, synthesis, and X-ray crystal structure of a potent dual inhibitor of thymidylate synthase and dihydrofolate reductase as an antitumor agent. *J. Med. Chem.* 43, 3837–3851

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## Drug delivery

### PEG-anhydride prodrugs and mucoadhesive polymers

Mucoadhesive polymer drug-delivery systems adhere to mucosal surfaces, such as the surface of the eye, and facilitate localized drug delivery. Mucoadhesion is thought to occur by hydrogen bonding of the mucoadhesive polymer to mucin, a glycoprotein that coats the mucosal surface. Several polymers have been used as mucoadhesive carriers, including poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA), with PAA being used the most extensively. Polyethylene glycol (PEG) and PAA at low pH form hydrogen-bonded complexes between the carboxylic acid groups of PAA and the ether oxygens of

PEG. These formulations have higher viscosities than PAA itself, and it has been shown that this higher viscosity retards the removal of the polymer from the mucosal surface.

Another use of PEG in drug delivery is its covalent attachment to drugs to yield a prodrug conjugate. PEGylated drugs provide reduced toxicity and immunogenicity, low uptake by the reticuloendothelial system, and prolonged blood circulation. Drug molecules are usually conjugated to PEG via ester or amide bonds. A PEG prodrug will not be readily absorbed via the gastrointestinal mucosa, and PEG ester and amide bonds hydrolyze relatively slowly under physiological conditions. Given that mucin turnover times at various mucosal sites are ~1–4 h, the typical PEG prodrug strategy cannot be used for mucosal delivery.

Indomethacin is a non-steroidal anti-inflammatory that is being evaluated as an ocular anti-inflammatory. Lele and colleagues have recently reported the potential for mucosal drug delivery using hydrogen-bonded complexes of PAA and PEGylated indomethacin. In place of the usual ester or amide bond, the drug was conjugated, via the carboxyl group, to the PEG by a relatively easily hydrolyzable anhydride bond, the first known example of a PEG-anhydride-drug linkage<sup>1</sup>. Upon mixing acidic solutions of PEG-indomethacin and PAA, a hydrogen-bonded complex precipitated as a gummy mass, which was lyophilized before further study. Several different molecular weights of PAA were examined. The release of indomethacin within dialysis tubing (MW cutoff of 3500 Da) from these complexes was compared with the release of free drug from PEG-indomethacin alone. Greater than 60% of the total drug was released from PEG-indomethacin in 50 min, compared with 80 min when PEG-indomethacin was complexed with PAA (250 kDa). The release rate of indomethacin decreased with an increase in the MW of PAA in the complex. Thus, although 60% of the