Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

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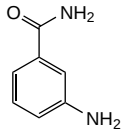
Novel antitumour molecules

Poly(ADP-ribose) polymerase 1 inhibitors with potent chemopotentiating activity

Poly(ADP-ribose) polymerase 1 (PARP-1) is the most abundant and well-characterized member of the constitutively expressed PARP nuclear protein family, which are crucial components of the cellular response to DNA damage. Upon activation, PARP-1 binds to DNA single-strand breaks and initiates the synthesis of long, branched polymers of ADP-ribose from nicotinamide adenine dinucleotide (NAD^+). These polymers are then transferred to a set of nuclear proteins involved in genome repair, the main acceptor being PARP-1 itself. Automodification of PARP-1 results in a decrease in its affinity for damaged DNA, allowing repair enzymes access to the strand break.

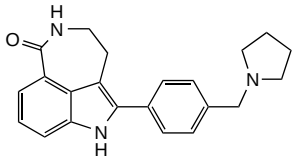
DNA repair processes mediated by PARP enzymes following cancer therapy using cytotoxic drugs or irradiation are important factors in anticancer drug resistance mechanisms. Cytotoxic agents can induce the activation of PARP-1, and potentiation of the DNA-damaging and cytotoxic effects of chemotherapy has been demonstrated using inhibitors of PARP-1. However, the early PARP-1 inhibitors [analogues of 3-aminobenzamide (**i**)] lacked specificity and potency.

Canan Koch and co-workers have described the characterization of two new

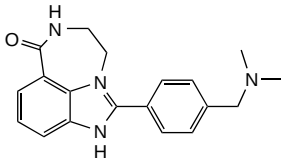


(i)

structural classes of PARP-1 inhibitor with conformationally locked benzamide cores (tricyclic lactam indoles) [1]. These new classes of PARP-1 inhibitor are potent *in vitro* inhibitors of PARP-1 enzyme activity and are potent enhancers of cellular growth inhibition. Most notably, compound **ii** was found to enhance the cytotoxicity of topotecan in three cancer cell lines (A549 lung, LoVo and SW620 colon) by approximately twofold, and temozolomide-mediated growth inhibition in LoVo cells by 7.8-fold. The tricyclic PARP-1 inhibitors were found to inhibit the formation of ADP-ribose polymer and to prevent depletion of NAD^+ after treatment with a DNA-damaging agent.



(ii)



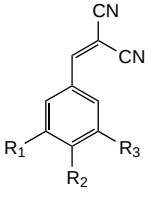
(iii)

A recent related study by the same researchers has identified the tricyclic benzimidazole **iii** as a lead PARP-1 inhibitor in preclinical development [2]. Compound **iii** (0.4 μM) was found to potentiate the cytotoxicity of both temozolomide and topotecan in the LoVo cell line (5.4- and 1.7-fold, respectively).

1 Canan Koch, S.S. *et al.* (2002) Novel tricyclic poly(ADP-ribose) polymerase-1 inhibitors with potent anticancer chemopotentiating activity: design, synthesis, and X-ray cocrystal structure. *J. Med. Chem.* 45, 4961–4974
2 Skalitzky, D.J. *et al.* (2003) Tricyclic benzimidazoles as potent poly(ADP-ribose) polymerase-1 inhibitors. *J. Med. Chem.* 46, 210–213

Antitumour quinols with selective activities in colon and renal cancer cell lines

Phenolic xenobiotics can be modified by cellular systems in several ways (e.g. by oxidation or glucuronidation) and the instability of certain antitumour protein tyrosine kinase (PTK) inhibitors has been documented. For example, di- and triphenolic tyrphostins (**iv**) decompose in solution to more active PTK inhibitors,



R_1, R_2, R_3 = H or OH

(iv)

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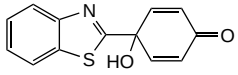
whereas tyrphostins devoid of hydroxy groups have a rapid onset of cellular activity, implicating metabolic oxidation as a potential bioactivating event.

Wells and co-workers reported the synthesis and antitumour evaluation of a series of heteroaromatic- and aromatic-substituted hydroxycyclohexadienones ('quinols') and their imine counterparts [3]. When the aromatic portion of the molecule was a fused heterobicyclic structure (e.g. the benzothiazole derivative **v**), potent *in vitro* activity was observed in HCT 116 [concentration giving 50% growth inhibition (GI_{50}) = 40 nM] and HT 29 (GI_{50} = 380 nM) human colon cancer cell lines. When examined in the 60 cell lines of the National Cancer Institute's *in vitro* anticancer drug screening program, active compounds in the series consistently displayed a highly unusual pattern of selectivity; cytotoxicity (LC_{50}) was concentrated in certain colon and renal cell lines only. Compound **v** also showed *in vivo* activity against human RXF 944XL renal xenografts and is the focus of further studies.

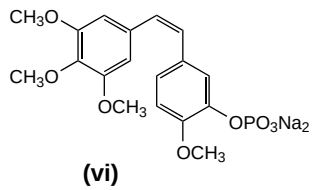


(v)

3 Wells, G. *et al.* (2003) 4-Substituted 4-hydroxycyclohexa-2,5-dien-1-ones with selective activities against colon and renal cancer cell lines. *J. Med. Chem.* 46, 532–541

Combretastatin A-4 analogues

The combretastatins (A-1 to A-6), isolated from the South African bush willow tree, are a series of important antineoplastic and cancer vasculature-targeting stilbenes. Several combretastatin analogues have been developed and the sodium combretastatin A-4 phosphate prodrug (CA4P; **vi**), has been evaluated in early clinical trials. Of the numerous structural variations of combretastatin A-4 that have been synthesized, one of the most important in terms of antitumour activity involves the replacement of the 3′-hydroxyl of the B-ring with an amine, and the subsequent preparation of a water-soluble hydrochloride salt or amino acid amide derivative.



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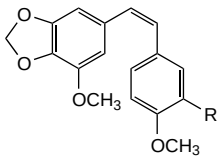
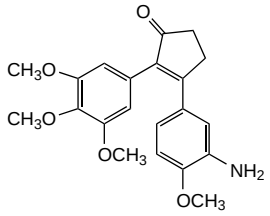


(vii) R = OH
(viii) R = NH_2

Pettit and co-workers have now reported the extension of the combretastatin A-4 3′-amino derivatives series to combretastatin A-2 (**vii**) and have described the synthesis and antitumour evaluation of 3,4-methylenedioxy-5,4′-dimethoxy-3′-amino-*Z*-stilbene (**viii**) and a selection of amino acid amide derivatives [4]. Compound **viii**, its hydrochloride salt, and the glycine and tyrosine amide derivatives, showed the highest level of growth inhibitory activity against a panel of six human and one murine cell lines (mean $GI_{50} = 10^{-2} - 10^{-3}$ μg ml^{-1}). The amine **viii** and its hydrochloride salt were also found to be potent inhibitors of tubulin polymerization (IC_{50} = 3.1 μM for inhibition of tubulin assembly) through binding at the colchicine site.

Nam and co-workers have reported the potent cytotoxicity (low nanomolar IC_{50}) of the antitumour agent 3-[(3-amino-4-methoxy)phenyl]-2-(3,4,5-trimethoxyphenyl)cyclopent-2-ene-1-one (**ix**) against a variety of tumour cell lines [5]. Because only modest antitumour activity was observed for compound **ix** administered intraperitoneally to BDF1 mice bearing Lewis lung carcinoma (3LL) cells, 14 prodrugs of **ix** (including α-amino acid, aliphatic amino acid, phosphoramidate and phosphate derivatives) were prepared to improve its water solubility and *in vivo* potency [6]. All of the new prodrugs showed improved water solubility, and several amino acid prodrugs and the phosphate prodrug (**x**) showed more potent *in vivo* activity (3LL cells implanted subcutaneously in mice) compared with the parent compound **ix**. None of the prodrugs was found to exhibit significant toxicities in mice.



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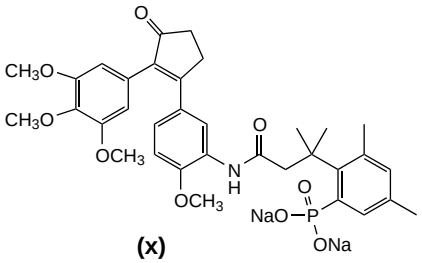

(x)

4 Pettit, G.R. *et al.* (2003) Antineoplastic agents. 487. Synthesis and biological evaluation of the antineoplastic agent 3,4-methylenedioxy-5,4′-dimethoxy-3′-amino-Z-stilbene and derived amino acid amides. *J. Med. Chem.* 46, 525–531

5 Nam, N-H. *et al.* (2002) Synthesis and antitumour activity of novel combretastatins: combretocyclopentenones and related analogues. *Bioorg. & Med. Chem.* 12, 1955–1958

6 Nam, N-H. *et al.* (2003) Water soluble prodrugs of the antitumour agent 3-[(3-amino-4-methoxy)phenyl]-2-(3,4,5-trimethoxyphenyl)cyclopent-2-ene-1-one. *Bioorg. & Med. Chem.* 11, 1021–1029

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