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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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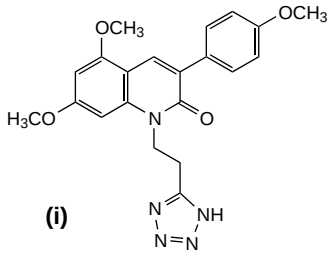
Novel anticancer molecules

Non-cytotoxic 3-aryl-2-quinolone derivatives with additive effects in combination regimens

The vast majority of clinically used anticancer drugs can be classified as being toxic to highly toxic, limiting their clinical use to a relatively low number of administrations per patient. For this reason, (alongside the common problem of drug resistance) anticancer drug combinations, where the two (or more) drugs possess differing mechanisms-of-action, are frequently employed to increase the treatment efficacy. For example, the use of antitubulin compounds, such as vincristine or paclitaxel, which in part target the ability of cancer cells to migrate and invade neighbouring tissue, can have an additive antitumour effect alongside cytotoxic agents. An interesting new application of this philosophy has been reported by Joseph and co-workers [1]. The authors synthesized a series of non-toxic (IC_{50} >10^{-5} M in 12 distinct human cancer cell lines) 3-aryl-2-quinolone derivatives, then quantitatively determined *in vitro* the level of migration of living MCF-7 human breast cancer cells through the use of a computer-assisted phase-contrast videomicroscopy system. At 10^{-7} M, certain compounds studied (e.g. compound **i**) markedly decreased the migration level of these MCF-7 cells. The new antimigratory agents were then



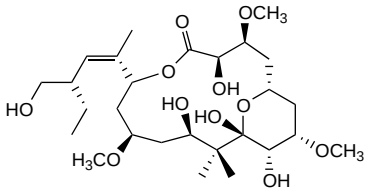
(i)

tested *in vivo* in an MXT mouse mammary adenocarcinoma model. Although compound **i** alone was found to be non-toxic *in vivo*, in combination with either doxorubicin or etoposide (clinically used topoisomerase inhibitors), additive benefits were observed, demonstrating that non-toxic antimigratory compounds can actually improve the efficacy of antitumour treatment when combined with conventional cytotoxic agents.

1 Joseph, B. *et al.* (2002) 3-Aryl-2-quinolone derivatives: synthesis and characterization of *in vitro* and *in vivo* antitumour effects with emphasis on a new therapeutical target connected with cell migration. *J. Med. Chem.* 45, 2543–2555

Novel antimitotic agents

The microtubule system of eukaryotic cells is an important anticancer drug target, and antimitotic compounds that interfere with the microtubule–tubulin equilibria have proven useful agents in the clinic. Notably, many leading agents in this class are derived from natural sources, for example, paclitaxel from the bark of the Pacific yew tree and the epothilones isolated from the bacterium *Sorangium cellulosum*. One important problem driving much of the research effort in this area is that of drug resistance through overexpression of P-glycoprotein leading to drug efflux, most notably in the case of the hydrophobic paclitaxel but less so for the epothilones, laulimalides and discodermolides.



(ii)

Peloruside A (**ii**), isolated from the New Zealand marine sponge *Mycale hentscheli*, is an example of a recently discovered novel agent in this class, exhibiting potent paclitaxel-like microtubule-stabilizing activity and cytoxicity at nanomolar concentrations [2]. Miller and co-workers have now reported further on the antitumour features of this novel agent [3]. Like paclitaxel, peloruside A arrests H441 human lung adenocarcinoma cells in the G_2–M phase of the cell cycle and induces apoptosis. The relatively simple structure of peloruside A makes it suitable for the design and synthesis of analogues with improved tumour targeting and reduced tumour cross-resistance, and should assist in the further elucidation of a common

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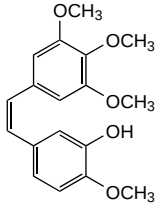
pharmacophore for this intriguing class of agent.

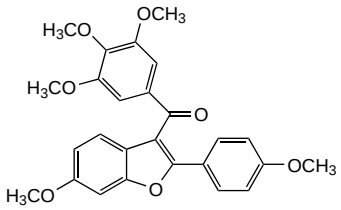
More recent studies have established that some tubulin-binding drugs selectively target the vascular system of tumours, inducing morphological changes in the endothelial cells of tumour blood vessels to occlude flow and resulting in virtually complete vascular shutdown within minutes. An example of an agent acting in this manner is combretastatin A-4 (CA4; compound **iii**), a powerful inhibitor of tubulin polymerization and a potent cytotoxin isolated from the stem wood of the South African tree *Combretum caffrum*. The disodium phosphate prodrug form of CA4 is currently undergoing clinical trials as a tumour vascular targeting agent. Two recent publications on antitumour agents structurally related to CA4, giving rise to new potent tubulin inhibitors and antimitotic agents, have appeared.



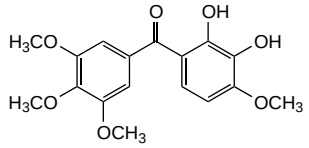
(iii)

Flynn and co-workers have described the one-pot preparation and antitumour activity of some benzo[*b*]furan and indole analogues of recently identified benzo[*b*]thiophene inhibitors of tubulin polymerization [4]. Several potent inhibitors of tubulin polymerization and colchicine binding, compared to CA4, were identified; for example, compound **iv** (IC_{50} for inhibition of tubulin polymerization = 0.41 μM, CA4 IC_{50} = 2.1 μM). In addition, tubulin inhibitors, such as **iv**, were found to be potent inhibitors of MCF-7 human breast carcinoma cell growth *in vitro* (IC_{50} = 34 nM).

Recent studies on the combretastatins have indicated the importance of the alkene *Z* geometry for inhibition of cancer-cell growth and tubulin polymerization. *Z*-Combretastatin analogues, however,

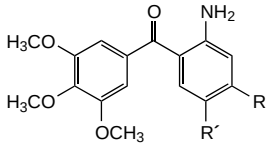


(iv)



(v)

are prone to isomerization during storage and administration; more recent studies have described the discovery of benzophenones (with the two aryl rings fixed in a quasi-*cis* orientation), such as hydroxyphenstatin (**v**), which display anticancer and antimitotic activities that are comparable to CA4 [5]. Liou and co-workers have now reported the synthesis and antitumour evaluation of related 2-aminobenzophenone derivatives [6]. Two lead compounds, **vi** and **vii**, from this new series were found with the following *in vitro* properties: inhibition of tubulin proliferation, inhibition of colchicine binding to tubulin and G_2–M phase arrest of cells. In addition, compounds **vi** and **vii** yielded 50- to 100-fold lower IC_{50} values than CA4 against Colo 205 (colon), NUGC3 (stomach) and HA22T (liver) human cancer cell lines *in vitro*.



(vi) R = OCH_3, R′ = H
(vii) R = H, R′ = OCH_3

2 West, L.M. and Northcote, P.T. (2000) Peloruside A: a potent cytotoxic macrolide isolated from the New Zealand marine sponge *Mycale sp. J. Org. Chem.* 65, 445–449

3 Hood, K.A. *et al.* (2002) Peloruside A, a novel antimitotic agent with paclitaxel-like microtubule-stabilising activity. *Cancer Res.* 62, 3356–3360

4 Flynn, B.L. *et al.* (2002) One-pot synthesis of benzo[*b*] furan and indole inhibitors of tubulin polymerisation. *J. Med. Chem.* 45, 2670–2673

5 Pettit, G.R. *et al.* (2000) Antineoplastic agents. 443. Synthesis of the cancer cell growth inhibitor hydroxyphenstatin and its sodium diphosphate prodrug. *J. Med. Chem.* 43, 2731–2737

6 Liou, J-P. *et al.* (2002) Synthesis and structure-activity relationship of 2-aminobenzophenone derivatives as antimitotic agents. *J. Med. Chem.* 45, 2556–2562

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Combinatorial chemistry

Antipsychotics sharing dopamine D_2- and serotonin 5-HT_{1A}-receptor affinities

Schizophrenia is a disease of which the etiology is unknown. The disease is characterized by positive and negative symptoms: positive symptoms include hallucinations and paranoia, and the most characteristic negative symptoms are social withdrawal and flattening of the personality. Also, cognitive as well as depressive symptoms can occur. ‘Neuroleptics’ have been developed that show antipsychotic activity in the clinic. These compounds predominantly alleviate the positive symptoms by attenuating the dopaminergic neurotransmission system in the mesolimbic area of the brain. Therapy with these types of compounds is frequently accompanied by extra-pyramidal side effects (EPS) resulting from a blockade of dopaminergic activity within the motor areas of the brain. Thus, ~20% of the treated patients suffer from EPS, of which Parkinson-like symptoms is most common. There is a need for compounds that induce fewer side effects and, equally importantly, also treat the other than positive symptoms