Monitor

Our new look ***Monitor*** provides an insight into the latest developments in the pharmaceutical and biotechnology industries. ***Chemistry*** examines and summarises recent presentations and publications in medicinal chemistry in the form of expert overviews of their biological and chemical significance, whereas ***Profiles*** provides commentaries on promising lines of research, new molecular targets and technologies. ***Biology*** reports on new significant breakthroughs in the field of biology and their relevance to drug discovery. ***Business*** reports on the latest patents and collaborations, and ***People*** provides information on the most recent personnel changes within the drug discovery industry.

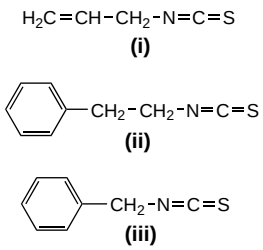
Chemistry

Novel antitumour molecules

Plant-derived isothiocyanates as rapid inducers of cancer cell growth inhibition

A variety of organic isothiocyanates (ITCs) present in edible vegetables such as mustard, garden cress, watercress and broccoli have been shown to inhibit chemical carcinogenesis. In addition, the *in vivo* inhibition of carcinogen-induced tumorigenesis in the lung, stomach, colon, liver, oesophagus, bladder and mammary glands has been demonstrated for a number of ITCs [1]. The chemopreventative properties of ITCs result from the ability to disrupt multiple steps in the carcinogenic process such as the inhibition of carcinogen-activating enzymes, the induction of carcinogen-detoxifying enzymes and the induction of apoptosis and cell-cycle arrest in malignant cells.

In addition to blocking chemical carcinogenesis, ITCs have potential as cancer therapeutic agents owing to their ability to induce apoptosis and cell cycle arrest in cultured human cancer cell lines. Allyl-ITC (AITC, **i**), administered i.p., inhibited the growth of human prostate cancer xenografts in mice [1]. Interestingly, exposure of human leukaemia cells to either phenethyl-ITC (PEITC, **ii**) or its cysteine conjugate for only three hours was long enough for a maximum inhibition of cell growth, indicative of fast interaction with cellular targets. Thus, the anticancer activity of PEITC *in vivo* could be largely unaffected by the rapid disposal kinetics associated with this compound [2]. Zhang and co-workers now report that exposure of a range of cancer cells, including blood (HL60/S and 8226/s), breast (MCF-7), liver (HepG2), colon (HT-29) and skin (HaCaT), to **i**, **ii** or benzyl-ITC (BITC, **iii**) inhibits proliferation in a time-independent manner [3]. This finding is significant because ITCs that enter the human body are rapidly cleared through urinary excretion. In leukaemic HL60/S cells, **i** and **iii** were found to modulate multiple cellular targets involved in proliferation, including disruption of mitochondrial membrane potential, activation of multiple caspases, arrest of cell cycle progression and induction of differentiation. These findings suggest that selected ITCs can rapidly initiate growth inhibition of cancer cells by simultaneously modulating multiple cellular targets, and that their growth inhibitory activity might be largely unaffected by *in vivo* metabolism and disposition factors.

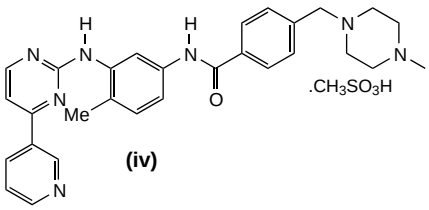


1 Conaway, C.C. *et al.* (2002) Isothiocyanates as cancer chemopreventative agents: their biological activities and metabolism in rodents and humans. *Curr. Drug Metab.* 3, 233–255
2 Adesida, A. *et al.* (1996) Inhibition of human leukaemia 60 cell growth by mercapturic acid metabolites of phenylethyl isothiocyanate. *Food Chem. Toxicol.* 34, 385–392
3 Zhang, Y. *et al.* (2003) Selected isothiocyanates rapidly induce growth inhibition of cancer cells. *Mol. Cancer Therap.* 2, 1045–1052

Small molecule inhibitors of both wild-type and mutant Bcr-Abl kinase

The Philadelphia chromosome (Ph) is a reciprocal genetic translocation between chromosomes 9 and 22, giving rise to the Bcr-Abl fusion protein, a constitutively active oncogenic tyrosine kinase present in about 95% of chronic myeloid leukaemia (CML) cases and up to 20% of adult acute lymphoblastic leukaemia (ALL) cases. Because transformation is strictly dependent on BCR-ABL tyrosine kinase activity *in vivo*, this oncoprotein represents an attractive target for CML therapy.

Imatinib mesylate (STI571, Gleevec®, **iv**) is a 2-phenylaminopyrimidine ATP-competitive Bcr-Abl kinase inhibitor. Impressive clinical trial data [4], particularly for chronic-phase CML, has resulted in the rapid approval of imatinib for clinical use. Response rates in advanced-phase CML (accelerated phase and blast crisis) were initially also encouraging; however, the majority of patients suffering from advanced-phase CML and Ph+ ALL experience a relapse of their disease, despite continued treatment with the drug. The major



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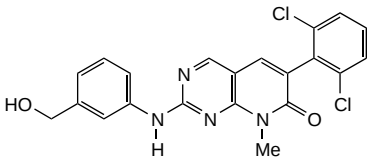

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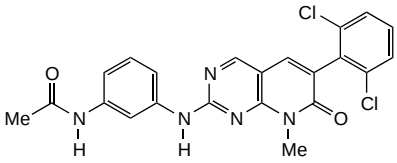

(vi)

mechanism of resistance to imatinib was subsequently found to be due to point mutations within the Bcr-Abl kinase domain at positions that determine specific contacts between imatinib and the ATP-binding site.

von Bubnoff and co-workers have now screened 13 different pyrido-pyrimidines (previously shown to be potent inhibitors of Bcr-Abl) with cells expressing wild-type and mutant Bcr-Abl [5]. All of the compounds examined were found to be more potent Bcr-Abl inhibitors than imatinib. Two of these compounds, PD166326 (**v**) and SKI DV-M016 (**vi**) , were found to be potent inhibitors of the Bcr-Abl activation loop mutant H396P (equipotent with wild-type Bcr-Abl) and the nucleotide-binding loop mutants (Y253H, E255K and E255V), but were not active against T315I, a mutant that makes a direct contact with imatinib. Because these compounds are active against frequently observed mutants of Bcr-Abl that are prevalent in imatinib resistance, they have great potential as a second-generation of agents that selectively target Bcr-Abl, and could overcome common resistance mechanisms for this class of agent.

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5 von Bubnoff, N. *et al.* (2003) Inhibition of wild-type and mutant Bcr-Abl by pyrido-pyrimidine-type small molecule kinase inhibitors. *Cancer Res.* 63, 6395–6404

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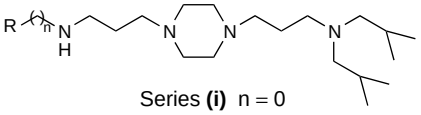
Anti-infectives

New piperazine derivatives as antimalarial agents

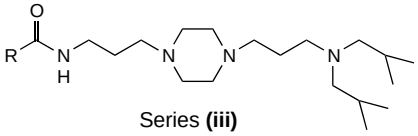
Chloroquine (CQ) exerts its antimalarial activity through different mechanisms [6,7] and several hypotheses have been proposed to explain CQ resistance [8,9]. However, it is generally accepted that CQ-resistant isolates accumulate less drug than their CQ-sensitive counterparts [10].

Although several studies have been performed on the 7-chloroquinoline moiety of many antimalarial agents, the effect of replacing the quinoline moiety as a whole has not been investigated. Sergheraert and collaborators have recently reported the results of their studies on 17 series of N^1,N^1-diisobutyl-1,4-bis(3-aminopropyl)piperazine derivatives bearing a variety of aromatic entities [11]. The compounds were designed on the basis of a previous study from the same group [12]. In particular, three different series (**i-iii**) were prepared and tested for the following parameters: antimalarial activity between 0.9 nM and 5.27 μM against the FcB1 strain, inhibition of b-hematin (synthetic equivalent of hemozoin) formation, and vacuolar accumulation ratio (VAR). In addition, their cytotoxicity was evaluated. The results indicated that the presence in series **iii** of an amide link resulted in compounds that were significantly less active than their analogues in series **i** and **ii**. The greatest antimalarial activity was found in compounds with the highest VAR values and the highest potencies as inhibitors of b-hematin formation. In particular, compounds **b** and **c** from series **ii**, although weaker inhibitors of b-hematin formation compared with CQ, were better inhibitors of Plasmodium growth. This could be because of their greater accumulation in the food vacuole. By contrast, the efficiency of b-hematin inhibition by compound **a** from series **i** counterbalanced a moderate VAR.

The cytotoxicity of the compounds against MRC-5 cells ranged from 6.5 μM to more than 100 μM. Compounds **a** and **b** displayed a selectivity index (given by the ratio of CC_{50}:IC_{50}) close to that of CQ (397).

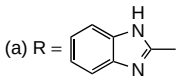


Series **(i)** n = 0
Series **(ii)** n = 1

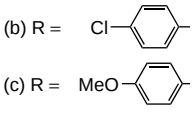


Series **(iii)**

For series **(i)**



For series **(ii)**



Because the resistance to CQ could be structure-dependent, compounds that do not have a quinoline moiety, such as the series of piperazine derivatives **i** and **ii**, could represent a valid alternative against CQ-resistant strains.

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8 Reed, M. B. *et al.* (2000) Pgh1 modulates sensitivity and resistance to multiple antimalarials in *Plasmodium falciparum*. *Nature*, 403, 906–9

9 Carlton, J. M. *et al.* (2001) Conservation of a novel vacuolar transporter in Plasmodium species and its central role in chloroquine resistance of *P. falciparum*. *Curr. Opin. Microbiol.* 4, 415–20

10 Bray, P. G. *et al.* (1998) A comparison of the phenomenology and genetics of multidrug resistance in cancer cells and quinoline resistance in *Plasmodium falciparum*. *Pharmacol. Ther.* 77, 1–28

11 Ryckebusch, A. *et al.* (2003) Synthesis and antimalarial evaluation of new 1,4-bis(3-aminopropyl)piperazine derivatives. *Bioorg. Med. Chem. Lett.* 13, 3783–3787

12 Ryckebusch, A. *et al.* (2003) Synthesis and *in vitro* and *in vivo* antimalarial activity of N1-(7-chloro-4-quinolyl)-1,4-bis(3-aminopropyl)piperazine derivatives. *J. Med. Chem.* 46, 542–57

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