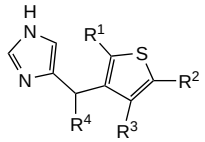
in the mouse abdominal irritant test (MAIT). Compounds with >80% inhibition in this model were then evaluated in the rat abdominal irritant test (RAIT). Because α_2-receptor agonists often produce problematic cardiovascular side-effects, the most potent compounds were also evaluated by means of electrocardiograph (ECG) in an anesthetized rat model.

The 3-substituted thiophenes **(iv)** were generally more potent than the 2-substituted analogues. In particular, the 4-bromo derivative (**iv**, R^3 = Br) and its α-methyl analogue [(–)**iv**, R^3 = Br, R^4 = Me] had the most interesting profile. (RAIT ED_{50} = 0.38 and 0.19 mg kg^{-1}, respectively, accompanied by low cardiovascular side-effect potential), compared with compound **(iii)** which had an ED_{50} value of 0.12 mg kg^{-1}. Based on the biological activity of this series, **(iii)**, and several restrained analogues, a pharmacophore model has been hypothesized.



(iv)

3 Boyd, E.B. *et al.* (2001) α-2 Adrenoceptor agonists as potential analgesic agents. 3. Imidazolylmethylyhiophenes. *J. Med. Chem.* 44, 863–872

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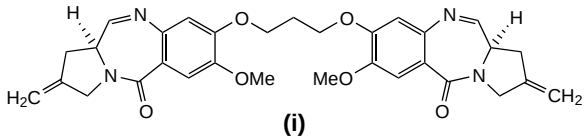
Novel antitumour molecules

A novel pyrrolobenzodiazepine DNA-interactive agent

The design of antitumour DNA-interactive agents with sequence specificity beyond two or three base-pairs is an area of intense research interest. The ultimate goal in this field is the design and synthesis of agents capable of specifically inhibiting the expression of particular proteins that are crucial for tumour cell proliferation, metastasis or drug resistance. The pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) are a family of antitumour antibiotics derived from various *Streptomyces* species, which exert their biological activity by binding covalently to the C2-amino position of guanine within the minor groove of DNA. These monomeric PBDs span three base-pairs with a preference for Pu-G-Pu (Pu = purine). Thurston and coworkers at the University of Nottingham (Nottingham, UK) have reported the synthesis and antitumour evaluation of a novel symmetrical PBD dimer, SJG136, **(i)**[1]. Compound **(i)** is an efficient inter-strand DNA cross-linking agent and thermal denaturation studies (5:1 calf thymus DNA:ligand ratio) give an increase in the T_m value of 33.6°C, the highest value recorded in this assay. In addition **(i)** is highly cytotoxic in several human ovarian cancer cell lines (e.g. IC_{50} value of 0.0225 nM in A2780 cells) and retains full potency in the cisplatin-resistant cell line, A2780*cis*R.

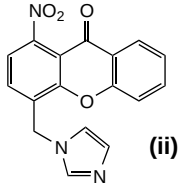


(i)

1 Thurston, D.E. *et al.* (2001) Design, synthesis and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient cross-linking ability and potent cytotoxicity. *J. Med. Chem.* 44, 737–748

Nonsteroidal aromatase inhibitors

Endogenous oestrogens are well known for their role in the development of hormone-dependent breast cancer. The two main approaches used to block their action are antagonists of the oestrogen receptor (e.g. tamoxifen) and of the biosynthesis of the hormones. Research efforts towards the second strategy have been largely focused on aromatase, a cytochrome P450 enzyme that catalyzes the conversion of androgens into oestrogens by aromatization of the steroid A-ring. Several non-steroidal aromatase inhibitors are either currently marketed (e.g. fadrozole, anastrozole and letrozole), or are in advanced clinical trials (e.g. vorozole). The design, synthesis and biological evaluation of a new class of aromatase inhibitors has been reported by Recanatini and coworkers at the Universities of Bologna, (Italy) and Saarlandes (Germany)[2]. Compound design was based on (*S*)-fadrozole as reference compound and used comparative molecular field analysis (CoMFA) of structure–activity relationships of large series of non-steroidal aromatase inhibitors. Chromone and xanthone nuclei were chosen as molecular skeletons and functionalities deemed crucial for aromatase binding, that is, a heterocyclic ring (imidazole or 1,3,4-triazole) linked via a methylene unit and H-bond accepting function (CN, NO_2, Br), were attached. The xanthone derivative **(ii)** was found to be a more potent inhibitor of aromatase than fadrozole (IC_{50} = 40 nM). In addition, several analogues were found to be fairly potent inhibitors of 17α-hydroxylase/C17,20-lyase (P450 17), an enzyme of therapeutic interest for the treatment of prostatic diseases.



(ii)

2 Recanatini, M. *et al.* (2001) A new class of non-steroidal aromatase inhibitors: design and synthesis of chromone and xanthone derivatives and inhibition of the p450 enzymes aromatase and 17α-hydroxylase/c17,20-lyase. *J. Med. Chem.* 44, 672–680

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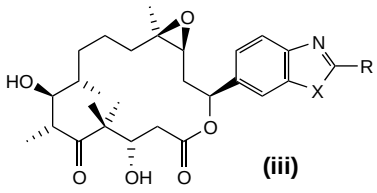
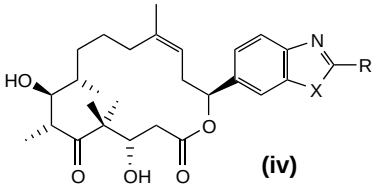
Highly potent analogues of epothilones B and D

In recent years, the natural product epothilones A, B, C and D have emerged as a new class of microtubule-stabilizing agents with potent *in vitro* and *in vivo* antitumour activity, resulting in a host of research activity directed at structure–activity relationship studies and the design and synthesis of novel, potent epothilone analogues. Altmann and coworkers at Novartis Pharma AG (Basel, Switzerland) report the synthesis of a new class of epothilone B and D analogues in which the natural (2-(2-methylthiazol-4-yl)-1-methyl)-ethenyl side-chain has been replaced with several benzoheterocyclic moieties **(iii)** and **(iv)**[3]. This new class of agents show more potent anti-proliferative activity than epothilones B and D in the human epidermoid cancer cell-line KB-31 and a P-glycoprotein-overexpressing, paclitaxel-resistant subline KB-8511.



(iii)



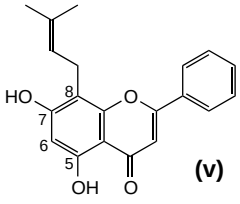
(iv)

R = CH_3; X = S
R = H; X = N(CH_3)
R = CH_3; X = N(CH_3)
R = H; X = CH = CH

3 Altmann, K-H. *et al.* (2000) Synthesis and biological evaluation of highly potent analogues of epothilones B and D. *Bioorg. Med. Chem. Lett.* 10, 2765–2768

Enhancement of binding affinity toward P-glycoprotein and modulation of cancer cell chemoresistance

Multidrug resistance (MDR) of cancer cells is often correlated with the overexpression of P-glycoprotein (P-gp), a membrane transporter protein that rejects several cytotoxic drugs (e.g. anthracyclines, vinca alkaloids, taxanes and epipodophyllotoxins) from cells. Flavonoids have been reported to act as P-gp modulators by mimicking the adenine moiety of ATP, the energy source for P-gp. Barron and coworkers in Lyon (France) have reported the synthesis of a series of *C*- or *O*-substituted hydrophobic derivatives of chrysin (5,7-dihydroxyflavone) to investigate the structural requirements and the effect of increasing the hydrophobicity of the A-ring toward P-gp modulation[4]. Increasing the hydrophobicity at either position 6, 7 or 8 increased the affinity of *in vitro* binding to a purified cytosolic domain of P-gp, but only benzyl and 3,3-dimethylallyl *C*-substitution produced a high maximal quenching of the protein intrinsic-fluorescence. Inhibition of membrane P-gp within leukaemic cells using 8-(3,3-dimethylallyl)chrysin **(v)** was found to be more efficient than for the commonly used cyclosporin A.



(v)

4 Barron, D. *et al.* (2001) *C*-Isoprenylation of flavonoids enhances binding affinity toward P-glycoprotein and modulation of cancer cell chemoresistance. *J. Med. Chem.* 44, 763–768

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Drug delivery

Bone-specific delivery of diclofenac

Prodrug strategies have considerable potential as site-specific drug delivery systems. There are many site-specific drug delivery strategies, but osseous tissues are still difficult to target because of the biological properties of bone. Osseous tissues consist mainly of the inorganic compound hydroxyapatite (HAP), and bones lack the efficient circulatory systems of other tissues, with blood-flow rates in bone of 0.05–0.2 ml min^{-1} g^{-1}. Bisphosphonates are a class of synthetic compounds that are structurally related to pyrophosphate and are clinically used to treat various bone disorders, including osteoporosis. Bisphosphonates are known to have high affinity for HAP, and osseous tissues are the main targets for the accumulation of bisphosphonates in the body after administration. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely employed as painkillers. However, NSAIDs have several undesirable side effects, in particular gastrointestinal (GI) toxicity. The NSAID diclofenac (DIC) is used clinically in the treatment of rheumatism, but to obtain therapeutic effects, large doses of DIC, which are known to cause GI damage, are required. The bone-specific delivery of NSAIDs, therefore, could be beneficial in the treatment of bone disease, while decreasing undesirable GI side effects.

Hirabayashi and colleagues have recently proposed a drug-delivery system that targets osseous tissues based on a bisphosphonic prodrug moiety[1]. This strategy was previously demonstrated using carboxyfluorescein as a model drug. The bisphosphonic prodrug of carboxyfluorescein (CF–BP) maintains the osteotropic property of the bisphosphonic moiety. CF–BP is rapidly taken up into osseous tissues after intravenous injection and disappears slowly, with a half-life of ~26 days. The successful use of this bisphosphonic prodrug strategy has now been reported for bone-specific delivery and sustained release of DIC. The bisphosphonic prodrug of DIC, disodium 2-(2,6-dichloroanilino)phenylacetoxyacetoaminomethylene bisphosphonate (DIC-BP) was synthesized by linking DIC to an aminomethylene

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