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.

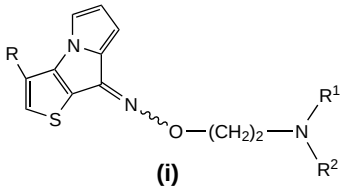
Molecules

Tricyclic oximino derivatives as novel 5-HT$_3$ ligands

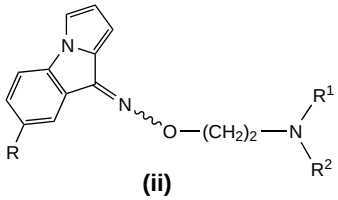
Since the identification of 5-hydroxytryptamine (5-HT), seven families of mammalian 5-HT receptors (5-HT$_{1-7}$), comprising 14 structurally and pharmacologically distinct subtypes, have been described.

Among them, the 5-HT$_3$ subtype has a peculiar characteristic, because it is the only ligand-gated ion channel. The interest for this receptor has constantly increased since the discovery that its antagonists could be used as anti-emetic agents associated with anticancer chemotherapy. In addition, it is currently being investigated for the treatment of anxiety, dementia, Alzheimer's disease, cognitive disfunction, depression and psychosis.

As an extension of their studies in this field, Rault and coworkers[1] have recently synthesized a series of *O*-substituted-oximino-pyrrolizines, **(i)** and **(ii)**. Compounds were tested for their 5-HT$_3$ receptor affinity by binding studies on NG 108-15 cell membranes in the presence of [^{3}H]granisetron. Initially they were used as an 50:50 *E* and *Z* mixture. The most interesting derivative of **i** was that in which all alkyl groups were methyl groups (R, R$_1$, R$_2$ = CH$_3$), which had a –log IC$_{50}$ value of 9.10 and good selectivity with respect to the other subtypes. In the same assay, the reference compound, S21178, had a value of 8.34 (Ref. 2). Attempts to separate the two isomeric forms of **ie** by fractional crystallization led to the isolation of a pure sample of the *Z* form. When tested in a binding study, it showed a greater affinity than the mixture (–log IC$_{50}$ = 9.96). This seems to suggest that the sulfur atom could be involved in the binding to the receptor. Compound **i**, with all three alkyl groups as methyl and in its *Z* form, was eventually tested on the guinea-pig isolated colon, and it was found to be a partial agonist of the 5-HT$_3$ receptor.



(i)



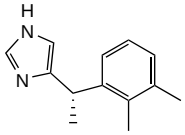
(ii)

1 Baglin, I. *et al.* (2001) First tricyclic oximino derivatives as novel 5-HT$_3$ ligands. *Bioorg. Med. Chem. Lett.* 11, 453–457

2 Rault, S. *et al.* (1996) Novel selective and partial agonists of 5-HT$_3$ receptors. Part 1. Synthesis and biological evaluation of piperazinopyrrolothienopyrazines. *J. Med. Chem.* 39, 2068–2080

Imidazolylmethylthiophenes as potential analgesic agents

Adrenergic receptors belong to the superfamily of seven-transmembrane G-protein-coupled receptors (GPCR) and are implicated in a variety of pharmacological functions. Recently, the α_2 adrenoceptor has been divided into the α_{2A}, α_{2B}, and α_{2C} receptor subtypes. A fourth subtype, the α_{2D} receptor, is believed to be a rat homologue of the α_{2A} receptor. At present, it is accepted that the α_{2A} receptor subtype is primarily responsible for antinociception, whereas the α_{2B} receptor mediates the antihypertensive effects and the α_{2C} receptor is involved in several other CNS responses. It is well known that the α_2 adrenoceptor agonist dexmedetomidine **(iii)** has good oral activity in the mouse and rat antinociception models (ED$_{50}$ = 0.05 and 0.1 mg kg^{-1}, respectively).



(iii)

Thiophene has long been known to be an effective isostere for benzene, with evident differences between the 2- and 3-positional substituents. On these bases, Boyd and coworkers have recently described several imidazolylalkylthiophenes[3], which were evaluated for their α_{2D} receptor-binding and antinociceptive activity

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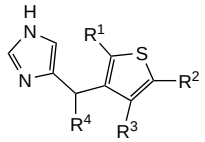
in the mouse abdominal irritant test (MAIT). Compounds with >80% inhibition in this model were then evaluated in the rat abdominal irritant test (RAIT). Because α_2-receptor agonists often produce problematic cardiovascular side-effects, the most potent compounds were also evaluated by means of electrocardiograph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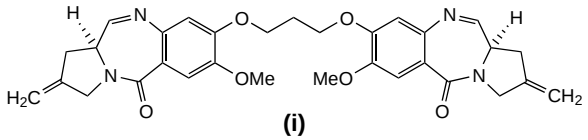
Novel antitumour molecules

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.

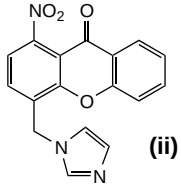


(i)

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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