Monitor: molecules and profiles

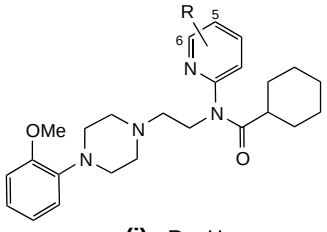
Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and 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

New analogues of WAY-100635 as potent 5-HT$_{1A}$ receptor antagonists

WAY-100635 [compound **(i)]** is a potent antagonist of the 5-HT$_{1A}$ serotoninergic receptor, which is involved in neuropsychiatric disorders (e.g. anxiety, depression and schizophrenia)[1]. The carbonyl-[^{11}C]-labelled WAY-100635 ($t_{1/2}$ = 20.3 min) provided the first radioligand for imaging the 5-HT$_{1A}$ receptor in the living human brain, by positron emission tomography (PET; Ref. 2). However, although it is an effective radioligand, it is rapidly metabolized. Therefore, a similarly effective radioligand that could easily be labelled with a longer-lived radionuclide (e.g. ^{18}F, $t_{1/2}$ = 109.7 min and ^{76}Br, $t_{1/2}$ = 16.1 h) is highly desirable. Furthermore, labelling with γ-emitting ^{123}I ($t_{1/2}$ = 13.2 h) would allow studies with single photon emission tomography (SPET), which is a widely used technique.

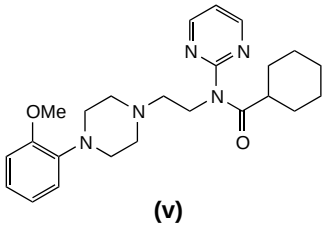
On these bases, Marchais and coworkers[3] synthesized new halogenated analogues of WAY-100635 **(ii–iv)**. In addition, a non-halogenated derivative **(v)**, which has an extra nitrogen atom, was prepared; this could possibly have higher affinity for the receptor. All the compounds were tested for their ability to inhibit the binding of [^{3}H]-5-CT to human cloned 5-HT$_{1A}$ receptors *in vitro*. Their intrinsic efficacy was determined in human cloned 5-HT$_{1A}$ receptors, by measuring



(i) R = H
(ii) R = 6-Br
(iii) R = 6-F
(iv) R = 5-Br

the production of cAMP (in the presence of forskolin) at a concentration up to 10 μM. All the new compounds showed significant affinity for the 5-HT$_{1A}$ receptor. Compound **(iv)** (K_i = 6.30 nM) was less potent than **(ii)** (K_i = 0.51 nM), suggesting that the position of the halogen has a role in the interaction with the receptor. Substitution of bromine in **(ii)** by fluorine [**(iii)**, K_i = 0.33 nM) had a positive effect. By contrast, the insertion of an additional nitrogen atom [**(v)**, K_i = 1.00 nM) did not enhance the affinity for the receptor. In the same experiment WAY-100635 had a K_i value of 0.17 nM. All the compounds were found to be full antagonists of the 5-HT$_{1A}$ receptor.

The lipophilicity of all compounds was calculated as log D at pH 7.4, to ascertain if they could penetrate the blood–brain barrier. The log D values resulted in a range of 2.30 to 4.16, and for WAY-100635 the log D value in the same experiment was 2.88. Therefore, all the compounds are expected to pass into the brain and, when labelled, can be studied using PET.



(v)

1 Fletcher, A. *et al.* (1993) WAY-100135: a novel, selective antagonist at presynaptic and postsynaptic 5-HT1A receptors. *Eur. J. Pharmacol.* 237, 283–291
2 Pike, V.W. *et al.* (1995) First delineation of 5-HT1A receptors in human brain with PET and [^{11}C]WAY-100635. *Eur. J. Pharmacol.* 283, R1–3
3 Marchais, S. *et al.* (2001) Short and efficient synthesis of analogues of WAY-100635: new and potent 5-HT$_{1A}$ receptor antagonists. *Bioorg. Med. Chem.* 9, 695–702

Novel boronic acid derivatives as inhibitors of the AmpC β-lactamase

β-Lactamases are the most common cause of widespread resistance to drugs of the penicillin and cephalosporin families. To overcome this problem, both β-lactam-based inhibitors (e.g. clavulanic acid) and β-lactamase-resistant β-lactams (e.g. aztreonam), were introduced. However, bacteria can rapidly acquire resistance to these compounds[4]. A completely different class of β-lactamase inhibitors is represented by the boronic acids[5]. They act competitively, forming reversible adducts with the catalytic serine of the enzymes. Their affinity varies

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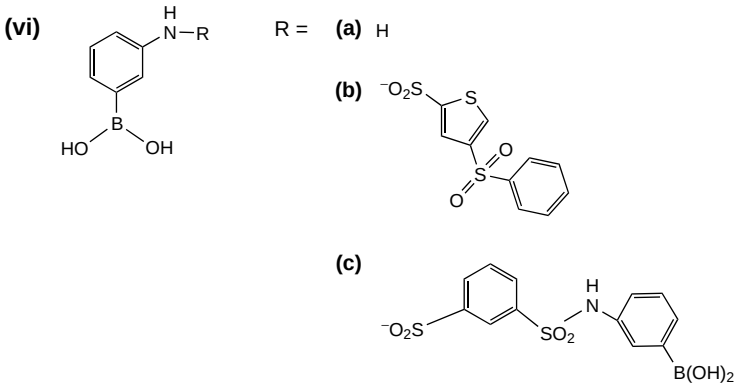


over a large range; this was consistent with modelling and crystallographic studies and suggests that the affinity is modulated by the aryl side chain. In addition, these studies showed that, because the boronic acids thus far investigated are small molecules, much of the binding site of the enzyme was not involved. Consequently, Shoichet and colleagues[6] synthesized a series of larger boronic acid derivatives, to determine which functionality would best complement the binding site of the enzyme, using structure-guided in-parallel synthesis. The known inhibitor **(vi)** (K_i = 7.3 μM; Ref. 5) was used as the lead because it is well suited to derivatization. Based on modelling studies, the researchers hypothesized that amide and sulfonamide derivatives of **(vi,a)** would fit the binding site well. Several derivatives were prepared using polymer-assisted in-parallel chemistry. Of these, several inhibitors showed K_is in the 100 nM range, the most significant being **(vi,b)** (K_i = 0.08 μM). Modelling studies on **(vi,b)** led to a second focused library of 12 compounds, with improved solubility and, potentially, better interactions than the first series. The most potent was compound **(vi,c)** (K_i = 0.06 μM). Compounds **(vi,b)** and **(vi,c)** were tested in bacterial culture for their ability to reverse the resistance of β-lactamase-expressing bacteria to penicillins: they were found active in Gram-positive bacteria. In fact, these compounds reduced the minimum inhibitory concentration (MIC) of amoxicillin by 8–32-fold at a concentration of 4–16 μg ml^{-1}. On the contrary, they were much less effective against β-lactam-resistant Gram-negative bacteria.

Finally, the crystal structure of compound **(vi,b)**, in complex with the group I β-lactamase AmpC, was obtained. This structure could serve as a template for future inhibitors.

4 Davies, J. (1994) Inactivation of antibiotics and the dissemination of resistance genes. *Science* 264, 375–382

5 Beesley, T. *et al.* (1983) The inhibition of class C beta-lactamases by boronic acids. *Biochem. J.* 209, 229–233

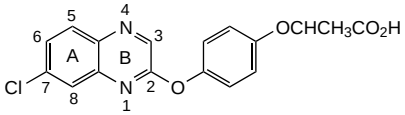
6 Tondi, D. *et al.* (2001) Structure-based design and in-parallel synthesis of inhibitors of AmpC β-lactamase. *Chem. Biol.* 8, 593–610

Daniela Barlocco
University of Milan,
Viale Abruzzi 42
Milano-20131, Italy
tel: +39 02 2950 2223
fax: +39 02 2951 4197
e-mail: daniela.barlocco@unimi.it

Novel antitumour molecules

Evaluation of analogues of the antitumour agent XK469

The compound 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid [XK469; **(i)**], displays potent, broad-spectrum antitumour activity, most notably against transplanted tumours. As a result of these preclinical observations, XK469 has been scheduled to enter clinical trials later this year, even though the mechanism of action of this agent remains to be elucidated. Recently, Horwitz and coworkers at the Wayne State University School of Medicine (Detroit, MI, USA) reported the results of an extensive SAR study to delineate the structure of the active site[1]. The structure of the parent compound was dissected into three regions – (1) ring A of quinoxaline; (2) the hydroquinone connector linkage; and (3) the lactic acid moiety – to determine the resultant *in vitro* and *in vivo* effects of chemical alterations in each region. A halogen atom located at the 7-position generated the most highly- and broadly-active antitumour agents, whereas other 7-position substituents, substitution at other A and/or B ring positions, and changing the connector linkage to resorcinol or catechol derivatives, all produced markedly less-active structures.



(i)

1 Hazeldine, S.T. *et al.* (2001) Design, synthesis and biological evaluation of analogues of the antitumor agent, 2-{4-[7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (XK469). *J. Med. Chem.* 44, 1758–1776

Dual inhibitors of farnesyltransferase and geranylgeranyltransferase-I

The search for selective anticancer agents against the oncogenic Ras protein, a key component of important intracellular-signalling pathways governing cell growth and differentiation, which is frequently mutated in cancer cells, has focused largely on the inhibition of the farnesyl-protein transferase enzyme (FTPase). FTPase catalyzes the *S*-farnesylation of a cysteine residue in the C-terminal tetrapeptide sequence of Ras, a post-translational modification required for Ras activation. Several FTPase inhibitors (FTIs) have shown outstanding preclinical promise with selective activity for FTPase over the analogous prenyltransferase, geranylgeranyl-protein transferase-I (GGPT-I), and early clinical trials are under way in some cases. However, one potential difficulty with using these

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