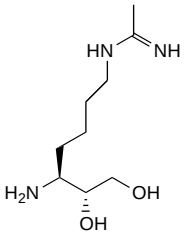
Monitor: molecules and profiles

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.

Selective inhibitor of human inducible nitric oxide synthase

Nitric oxide (NO) is involved in a variety of cellular processes including platelet aggregation, neurotransmission and immune activation. NO is generated by NO synthase (NOS) from arginine. Several isoforms of NOS have been identified and characterized, each producing NO for distinctly different physiological roles. As overproduction of NO has been associated with several disease states, various groups have focused on the identification selective inhibitors of the various isoforms of NOS as potential therapeutic agents. Hallinan, E.A. and coworkers have recently reported the identification of *N*-[5(S)-amino-6,7-dihydroxyheptyl]ethanimidamide dihydrochloride (**1**) as a highly selective inhibitor of the inducible NOS (iNOS) (IC_{50} = 12 μM) [*J. Med. Chem.* (1998) 41, 775–777].



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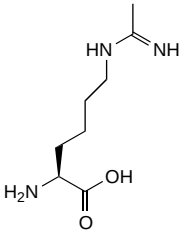

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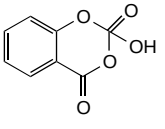
Although this compound is slightly less potent than the previously reported iNOS inhibitor ε-*N*-(iminoethyl)-L-lysine (**2**, IC_{50} = 5 μM), **1** is 700-times more selective for iNOS than for the endothelial NOS (eNOS) isoform, whereas **2** is only 30-times more selective for the iNOS.

β-Lactamase inhibitor

The resistance of bacteria to currently available antibiotics is of increasing public concern. The bacterial evolution of β-lactamases, which inactivate β-lactam antibiotics, has made a significant contribution to antibiotic resistance over recent years. This has led to the search for more effective β-lactamase inhibitors that may be used in combination with existing β-lactam antibiotics for combating bacterial infections. Pratt, R.F. and Hammar, N.J. have recently reported the use of salicyloyl cyclic phosphate (**3**) as a 'penicillin-like' inhibitor of β-lactamase [*J. Am. Chem. Soc.* (1998) 120, 3004–3006].



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The compound was shown to inhibit transiently the class C β-lactamase of *Enterobacter cloacae* P99, the class A TEM β-lactamase and the DD-dipeptidase of *Streptomyces* R61. Nucleophilic attack on this cyclic molecule by these β-lactamase enzymes results in the leaving group being linked to the molecule; this obstructs the hydrolysis of the covalent intermediate leading to enzyme–complex half-lives of 14, 140 and 340 minutes, respectively. The slower regeneration of the free enzyme is a very effective means of enzyme inhibition.

Potent, selective α_{1b}-adrenergic receptor antagonist

Recent identification of a range of α_1-adrenergic receptor subtypes has led to the need to synthesize compounds selective for each of the three subtypes in order to assist in the identification of their individual physiological roles. A recent communication describes the identification of a series of novel, potent, selective α_{1b}-adrenergic receptor antagonists related to the nonselective α_1-receptor antagonist prozosin (**4**) [Pantane, M.A. *et al. J. Med. Chem.* (1998) 41, 1205–1208].

The most potent compound of this series was 4-amino-2-(4-{1-(benzyloxycarbonyl)-2(S)-[(1,1 dimethylethyl)amino] carbonyl}-piperazinyl)-6,7-dimethoxyquinazoline (L765314; **5**), which had binding affinities for the rat and human α_{1b}-adrenergic receptors of 5.4 and 2 nM, respectively, and a 200-fold selectivity for the human α_{1b} over α_{1a} receptors.

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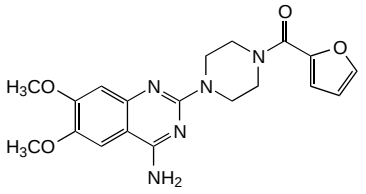

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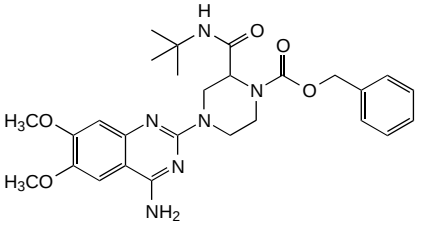

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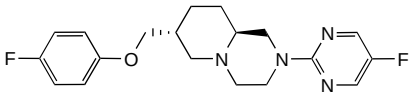
Dopamine D4 receptor antagonist

The discovery that the atypical antipsychotic agent clozapine has a higher affinity for the dopamine D_4 receptor than the D_2 receptor has led to widespread interest in the potential use of selective D_4 receptor antagonists as potential therapeutic agents for the treatment of schizophrenia. A group from Pfizer Central Research (Groton, CT, USA) has recently reported studies into the synthesis, structure–activity relationships and pharmacology of a series of novel, potent and selective pyrido [1,2-a]pyrazine dopamine D_4 receptor antagonists [Sanner, M.A. *et al. Bioorg. Med. Chem. Lett.* (1998) 8, 725–730]. These studies led to the identification of particularly potent (K_i = 3.4 nM) and selective (D_4/D_2 binding = 1,000) compound CP239019 (**6**) that was also shown to inhibit apomorphine-induced hyperlocomotion in rats following oral administration.



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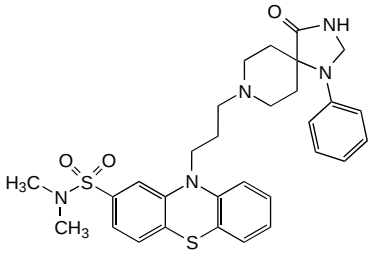
Nonpeptidic RANTES antagonist

The chemokine RANTES (regulated on activation normal T-cell expressed and secreted) has been shown to be a potent chemoattractant for various leukocytes *in vitro* and has been found to have high affinity for the CCR1, CCR3 and CCR5 chemokine receptors. The expression of RANTES in a variety of inflammatory diseases, such as asthma, arthritis and atherosclerosis, has led to the synthesis and evaluation of various compounds as potential RANTES inhibitors and as possible therapeutic agents for the treatment of these disease states. Bright, C. and coworkers from Rhône-Poulenc Rorer (Dagenham, UK) have described the identification of a series of phenothiazines that inhibit RANTES binding to THP-1 cell membranes following the screening of a collection of compounds from their corporate database [*Bioorg. Med. Chem. Lett.* (1998) 8, 771–774]. The lead compound RP23618 (**7**) was shown to inhibit binding of radiolabelled RANTES to the THP-1 cell membranes specifically and to antagonize RANTES-induced chemotaxis of the THP-1 cells.



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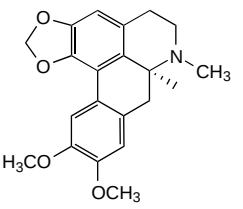
Natural antitumour agent

Various Chinese medicinal herbs have been previously reported to have antitumour activity. Huang, R-L. and coworkers have recently described the isolation of *d*-dicentrine (**8**), a naturally occurring isoquinoline alkaloid, from the root of Lindera megaphylla Hemsl. (Lauraceae) [*Planta Med.* (1998) 64, 212–215]. Various *in vitro* and *in vivo* assays were employed to evaluate the antitumour activity of this compound. Analysis of the compound's activity against 21 tumour cell lines showed that the compound was most effective against the esophageal carcinoma HCE-6, the lymphoma cell lines Molt-4 and



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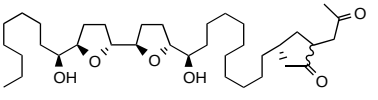
CESS, the leukemia cell lines HL60 and K562 and the hepatoma cell line MS-G2. Intraperitoneal administration of 100 μg of *d*-dicentrine twice weekly for four weeks was also shown to significantly reduce the occurrence of leukemia cell lines in Severe Combined Immunodeficiency (SCID) mice.

Bioactive acetogenins

Annona squamosa Rich. (Annonaceae) has also been purported to possess antitumour activity. Fractionation of the Bark of this fruit tree has led to the recent identification of three new acetogenins, (2,4-*cis* and *trans*)-squamolinone (**9**), (2,4-*cis* and *trans*)-9-oxo-asimicinone (**10**) and bullacin B (**11**) [Hopp, D.C. *et al. Bioorg. Med. Chem.* (1998) 6, 569–575]. All these compounds showed significant cytotoxic activity against six human cell lines (A-549, MCF-7, HT-29, A-498, PC-3



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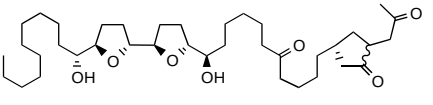

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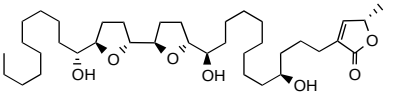

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and PACA-2). Bullacin B was found to be the most potent having a million-times greater activity against the human breast adenocarcinoma cell line MCF-7 than adriamycin.