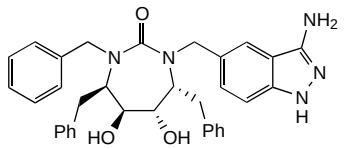
Monitor: molecules and profiles

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.

Cyclic urea protease inhibitors

HIV protease inhibitors have been shown to be effective in the treatment of AIDS. However, to avoid the development of resistance, these inhibitors are administered in combination with other antiviral agents. The ability of this virus to generate resistant mutants has driven the search for novel HIV protease inhibitors with improved therapeutic profiles. Rodgers, J.D. and coworkers have recently described the development of cyclic urea HIV protease inhibitors which has led to compounds with optimized potency, resistance profile, protein binding and oral bioavailability [*Chem. Biol.* (1998) 5, 597–608].

Nonsymmetrical cyclic ureas containing a 3-aminoindazole P2 group were found to be potent HIV protease inhibitors with good oral bioavailability. On the basis of bioavailability studies in dogs and an analysis of the resistance profiles of candidate compounds, DMP850 (**1**, K_i = 31 pM) and DMP851 (**2**, K_i = 21 pM) have been selected as the company's next generation of HIV protease inhibitors.



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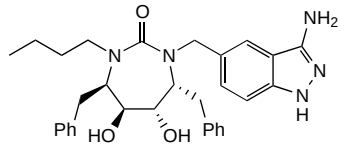

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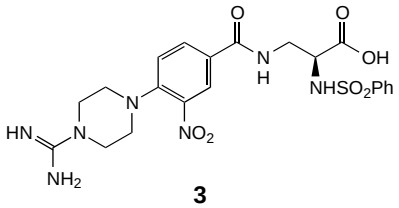
Nonpeptide integrin antagonists

The integrins are a group of cell surface proteins involved in cell–cell and cell–matrix adhesion. The individual integrins comprise a unique combination of α and β heterodimeric glycoprotein subunits. The most extensively studied members of this family are the $\alpha_{IIb}\beta_3$, $\alpha_5\beta_1$, $\alpha_v\beta_3$ and $\alpha_v\beta_5$. Various natural ligands including fibrinogen, fibronectin and vitronectin have common peptide sequences that bind to these ligands. Recent studies have shown that peptides and antibody antagonists of integrin $\alpha_v\beta_3$ inhibit angiogenesis and tumour growth. Furthermore, this integrin has been shown to play a major role in the adhesion of osteoclasts to bone matrix and in the migration of vascular smooth muscle cells. Integrin $\alpha_v\beta_3$ antagonists may therefore have therapeutic use in the treatment of cancer, osteoporosis and restenosis.

Nicolaou, K.C. and coworkers have described the design, synthesis and biological evaluation of a series of nitroaryl ether-based nonpeptide mimetics as potential $\alpha_v\beta_3$ antagonists [*Bioorg. Med. Chem.* (1998) 6, 1185–1208]. The ability of the compounds to bind to various integrins and inhibit cell adhesion was evaluated *in vitro*. Selected compounds were also tested *in vivo* in the chick chorioallantoic membrane (CAM) assay to assess their ability to inhibit angiogenesis. Compounds **3** and **4** were shown to be the most potent and selective inhibitors



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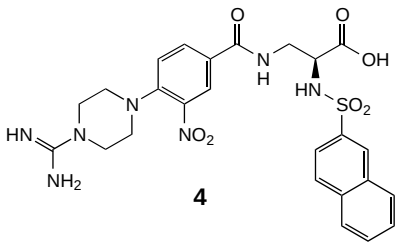

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Monitor Editor: **Andrew W. Lloyd**, School of Pharmacy and Biomolecular Sciences, University of Brighton, Cockcroft Building, Moulsecoomb, Brighton, UK BN2 4GJ. tel: +44 1273 642049, fax: +44 1273 679333, e-mail: a.w.lloyd@brighton.ac.uk

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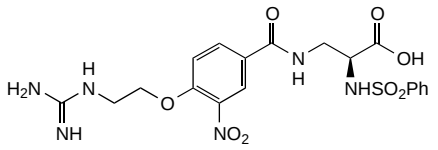
of $\alpha_{IIb}\beta_3$, while **5** was found to be highly effective at inhibiting angiogenesis *in vivo*.



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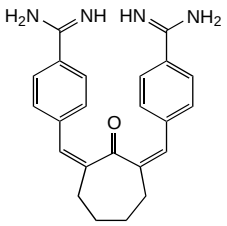
Potent inhibitor of Factor Xa

The trypsin-like serine protease Factor Xa plays an important role in the blood coagulation cascade. The primary role of this enzyme is in the formation of the prothrombinase complex by combining with factor Va and calcium on a phospholipid membrane. This complex is responsible for the proteolytic activation of thrombin, which in turn promotes clot formation by catalysing the conversion of fibrinogen to polymerizable fibrin and activating platelets. Although various anticoagulants such as warfarin and heparin are widely used in the clinic, the slow onset of action and the need for extensive monitoring of patients on warfarin has led to the need to develop direct-acting anticoagulants, such as thrombin inhibitors. Studies of proteinaceous Factor Xa inhibitors in preclinical models of venous and arterial thrombosis have indicated that selective inhibitors of Factor Xa will also have therapeutic efficacy.

As part of a programme to identify orally active Factor Xa inhibitors, Shaw, K.J. and coworkers have investigated the activity of the geometric isomers of a previously reported conformationally restricted bisamidine inhibitor [*J. Med. Chem.* (1998) 41, 3551–3556]. These studies have identified (Z,Z)-2,7-bis(4-amidinobenzylidene)cycloheptan-1-one (**6**) as a highly active inhibitor of Factor Xa [K_i (Factor Xa) = 0.66 nM; K_i (thrombin) = 530 nM; K_i (trypsin) = 33 nM]. Despite the potent Factor Xa inhibition, this compound suffers from the inherent photochemically induced olefin isomerization and bisamidine instability. To overcome these problems, the group has investigated the potential



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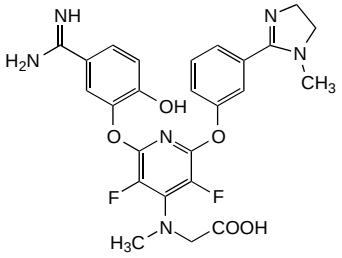
use of several isosteric scaffolds to develop photochemically inert and synthetically feasible pharmacophores. In a subsequent publication, the group has reported the use of these scaffolds for the transformation of **6** into ZK807834 (**7**) – a highly potent [K_i (Factor Xa) = 0.11 nM], selective [K_i (Factor IIa) = 2 mM; K_i (trypsin) = 280 nM] and orally active Factor Xa inhibitor [Phillips, G.B. *et al. J. Med. Chem.* (1998) 41, 3557–3562].



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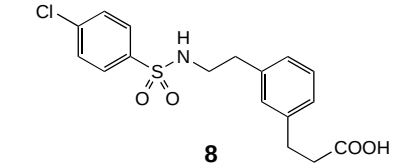
Thromboxane receptor antagonists

Thromboxane A_2 (TxA_2) causes both vasoconstriction and platelet aggregation and is therefore a potential therapeutic target for several disease states. Several groups have recently described dual acting TxA_2 synthease inhibitors and TxA_2 receptor antagonists. Such compounds prevent both the biosynthesis of TxA_2 from its precursor PGH_2 and the action of PGH_2 (also a potent agonist) on TxA_2 receptors. Workers from Pfizer Central Research (Sandwich, UK) have recently described the design, synthesis and evaluation of a series of thromboxane receptor antagonists based on 3-{2-[(4-chlorophenyl)sulfonyl]amino}ethyl benzene propanoic acid (**8**) [Dack, K.N. *et al. Bioorg. Med. Chem. Lett.* (1998) 8, 2061–2066].

Modification of **8** with an arylmethyl group gave a series of compounds with potent *in vitro* and *in vivo* activities. These compounds are exemplified by **9** (UK147535) which gave >12 h inhibition of TxA_2 in dogs following oral administration of 0.1 mg kg^{-1}.



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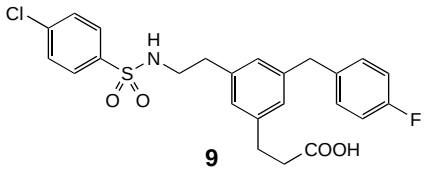

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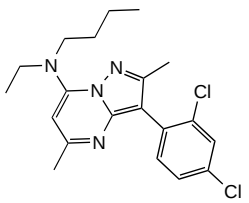
Corticotrophin-releasing factor 1 receptor antagonists

The binding of corticotrophin-releasing factor (CRF) to CRF-1 receptors in the hypothalamus is responsible for the elevation of ACTH and other peptides associated with the psychological effects of stress that lead to anxiety and depression. CRF-1 antagonists may therefore be useful agents for the treatment of these disorders. Wustrow, D.J. and coworkers have identified a series of 3-phenylpyrazolo[1,5-a]pyrimidines with affinity for the CRF-1 receptor [*Bioorg. Med. Chem. Lett.* (1998) 8, 2067–2070].

The most potent compound in this series (**10**) had a K_i of 5 nM. This compound has been used in subsequent X-ray crystallograpic studies to elucidate the spatial requirements of more-potent CRF-1 antagonists.



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