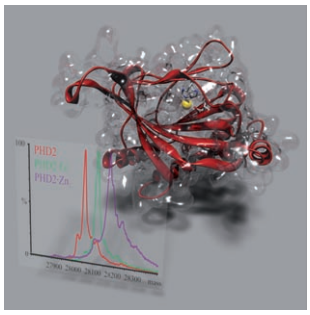
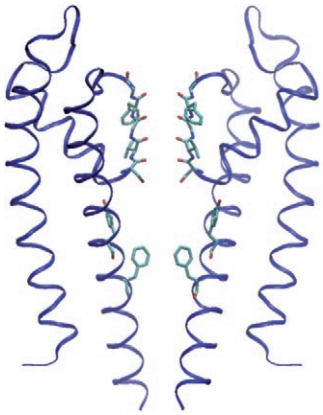
COVER PICTURE



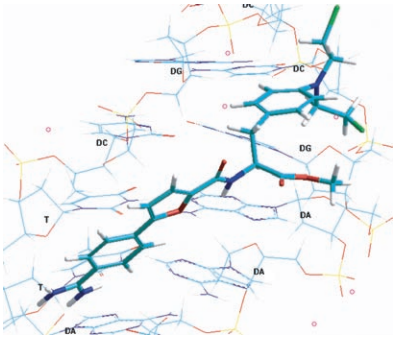
The cover picture shows a view from a crystal structure of prolyl hydroxylase domain 2 (PHD2), which is the major PHD that catalyses HIF-α hydroxylation under normoxic conditions. The hypoxic response in animals is mediated by the transcription factor hypoxia inducible factor (HIF). Levels of the HIF-α subunit are regulated by PHD-catalysed prolyl hydroxylation, which signals for the degradation of HIF-α under normoxic conditions. The requirement of the PHDs for molecular oxygen enables them to act as oxygen sensors. Inhibition of the PHDs in order to activate the hypoxic response is of interest for therapeutic benefit. Alongside the PHD2 structure are shown electrospray ionisation mass spectrometric data, described in the Communication by C. J. Schofield et al. on p. 569 ff., that reveal a second metal binding site on the enzyme.

NEWS

MINIREVIEWS



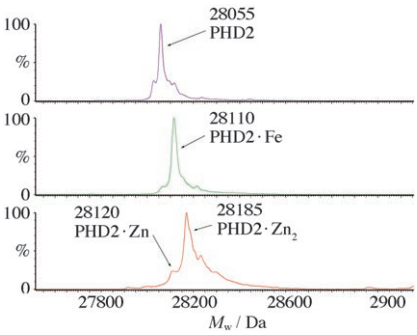
Solving hERG structure. hERG is a well established antitarget and an emerging pharmacological target. In the last years, several attempts have been performed to model its 3D structure, but only recently have sound and truly informative models appeared that can be compared with the classical simulations of K^+ channels.



Alkylating analogues. Herein, we report the synthesis and structure–activity studies of amidine analogues of alkylating antineoplastic compounds, a possible new class of cytotoxic minor groove binders and topoisomerase II inhibitors. Overexpression of prolidase in some neoplastic cells suggests that proline analogues of alkylating agents may serve as prolidase convertible prodrugs. The picture shows the $d(CGCGAATTCGCG)_2$–amidine analogue of melphalan complex.

CONFERENCE REPORTS

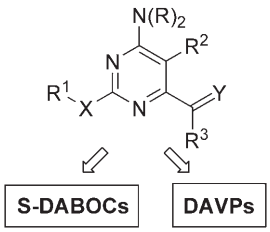
COMMUNICATIONS



Mild ionisation: Combined ESI-MS and mutagenesis analyses were used in metal binding studies on a human oxygen-sensing enzyme. The approach revealed a new metal binding site.

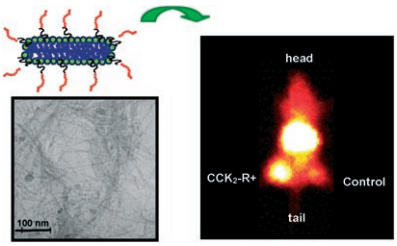
JMMC 2007

FULL PAPERS

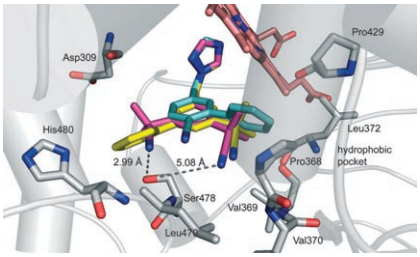


Targeting HIV. A systematic functionalization of the pyrimidine scaffold has been conducted to identify the minimal required structural features for RT inhibition. Herein, we describe how the combination of synthetic, biological, and molecular modeling studies allowed the identification of two novel classes of S-DABO analogues: S-DABO cytosine analogues (S-DABOCs) and 4-dimethyamino-6-vinylpyrimidines (DAVPs).

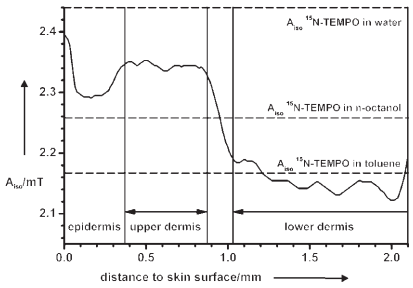
JMMC 2007



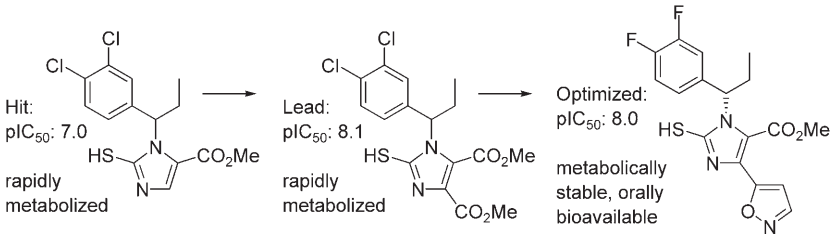
Supramolecular anticancer drugs: In the last decade, supramolecular aggregates such as micelles and vesicles have attracted much attention for their potential application as carriers in drug delivery. Supramolecular aggregates, obtained by mixing two amphiphilic monomers, one containing a radioactive indium complex, and the other the CCK8 peptide, are used to selectively deliver anticancer drugs to tumor cells.



New weapons for the fight against breast cancer: Compounds built from a biphenyl scaffold potently block the activity of a key enzyme involved in the final step of oestrogen biosynthesis. Attenuating the supply of this hormone is a viable anticancer strategy, as tumours require oestrogen for growth and development. The compound shown in cyan is one of several promising candidates reported herein.



Electron spin resonance imaging was used as a nondestructive spectroscopic method for establishing a polarity map of the upper skin layers and based on this, the spatial distribution of model drugs in the skin. Polarity was described by means of the changes of the ESR hyperfine splitting constant, A_{iso}, which in turn reflects interactions at a molecular level. The effect of polarity on the spatial distribution of spin probes as model drugs was studied.



The synthesis of small-molecule CCR2 receptor inhibitors is presented. The initial lead, although quite potent, was metabolically unstable both in vitro and in vivo. Isosteric replacement of one of the ester functions with small heterocycles led to highly potent, orally bioavailable and metabolically stable compounds.

Supporting information on the WWW (see article for access details).

A video clip is available as Supporting Information on the WWW (see article for access details).

* Author to whom correspondence should be addressed.

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BOOKS

SERVICE

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