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CHEMISTRY ENABLING DRUG DISCOVERY

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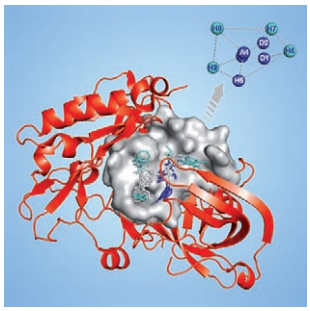
Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

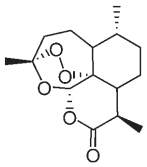
COVER PICTURE



The cover picture shows a model of the BACE-1 enzyme represented in ribbon mode with the catalytic site highlighted as a grey Connolly surface. The binding site is filled with six BACE-1 inhibitors in their docked conformations and coloured according to conserved interaction points. Theoretical studies of inhibitor binding allowed us to delineate an exhaustive nine-point pharmacophore model (upper right), which captures both the common geometric and the electronic features essential for enzyme inhibition. Interestingly, five of these points are present in all the inspected ligands (blue spheres), thus they can be referred to as essential features for inhibitor recognition and binding, whereas the other four points (light-blue spheres) contribute to BACE-1 selective inhibition. For more details, see the Full Paper by L. Marinelli et al. on p. 667 ff.

NEWS

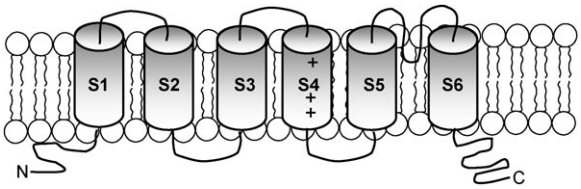
REVIEWS



Artemisinin

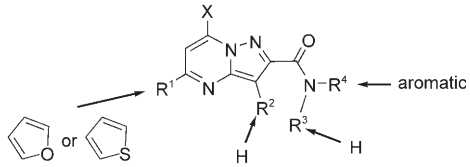
Fluoroartemisinins. Malaria continues to be one of the most important infectious diseases in the world. The increasing resistance of malaria parasites and resulting dramatic decline in the efficacy of the most affordable antimalarial drugs leads to a broad consensus on the need to develop new antimalarial drugs Artemisinin provides a crucial molecular framework from which medicinal chemists have prepared more efficacious antimalarial drugs.

HIGHLIGHTS

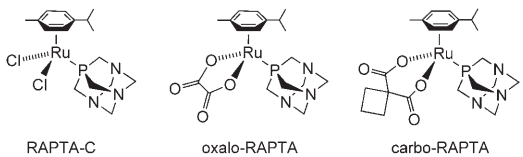


A novel mechanism of opening K^+ channels by the phospholipase, sphingomyelinase D (SmaseD) has been recently described. By testing various fractions of venom from the brown recluse spider, Ramu et al., (*Nature* **2006**, *442*, 696–699) found that SMaseD induced robust outward current through a voltage gated K^+ channel $K_v1.2$.

COMMUNICATIONS



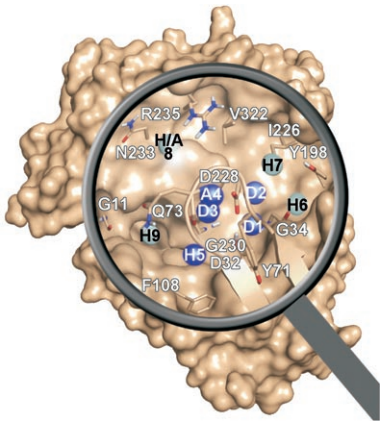
c-Myc/Max Dimerization. The interaction between the oncoprotein c-Myc and its activation partner Max is considered to be a desirable target for cancer drug development. However, the interaction is mediated by large α-helical interfaces without obvious binding sites for small molecule inhibitors. This paper describes the identification of a substitution pattern for pyrazolopyrimidines which appears to be associated with activity against this challenging target.



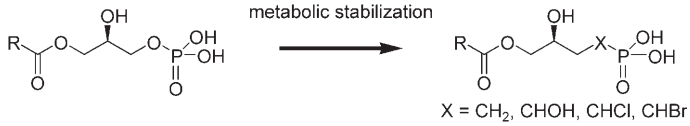
RAPTA-C oxalo-RAPTA carbo-RAPTA

Electrospray ionization mass spectrometry allows a rapid characterisation of the adducts formed between three novel anticancer ruthenium(II)-arene PTA compounds and horse heart cytochrome c or hen egg white lysozyme. Specific information on the nature of the protein-bound metallic fragments and the extent of protein metallation was readily obtained.

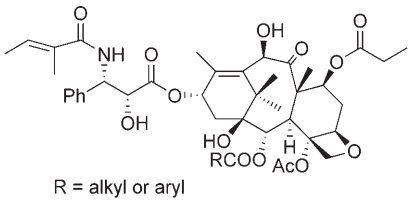
FULL PAPERS



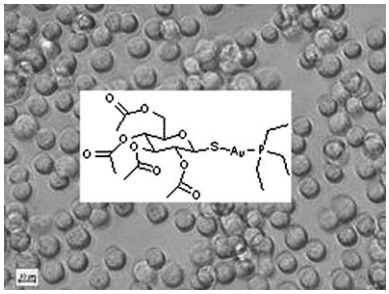
Based on the docking results of a series of BACE-1 inhibitors an exhaustive pharmacophore model, which captures both the common geometric and electronic features essential for enzyme inhibition, is presented providing a valuable tool for rational drug design.



Metabolically stabilized: We present the total synthesis and pharmacological characterization of α-substituted phosphonate analogues of LPA. The compounds include isoform-selective agonists and antagonists for the LPA GPCRs, and also include potent inhibitors of lysophospholipase D, a key enzyme involved in LPA biosynthesis.



Potent taxanes: A series of C2-modified 10-deacetyl-7-propionylcephalomannine derivatives were prepared and biologically evaluated. Some C2 *meta*-substituted benzoate analogues showed potent activity against both drug-sensitive and drug-resistant tumor cells.



Going for gold. This paper describes a method for the determination of the gold content in tumour cells exposed to gold drugs such as auranofin. The method allows the measurement of molar cellular concentrations, which offers the advantage of facilitating the comparison of data obtained from different experimental setups. The effectiveness of the method is demonstrated by means of the gold antitumour drug auranofin.

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

* Author to whom correspondence should be addressed.

BOOKS

SERVICE

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