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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.

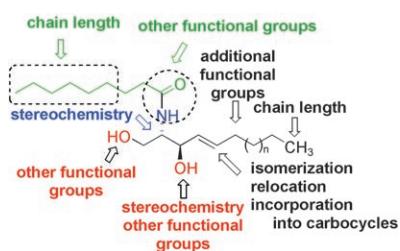
NEWS

From our sister journals

578 – 579

REVIEWS

Working out sphingolipids. Sphingolipids are 2-amino-1,3-diol derivatives that play important roles in the regulation of many cell functions. The design of synthetic analogues as chemical tools for the study of sphingolipid metabolism and functions offers new insights into this intriguing kind of lipids.



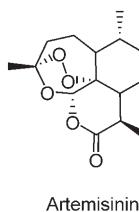
A. Delgado,* J. Casas, A. Llebaria,
J. L. Abad, G. Fabriás

580 – 606

Chemical Tools to Investigate Sphingolipid Metabolism and Functions

J.-P. Bégué, D. Bonnet-Delpont*

608–624

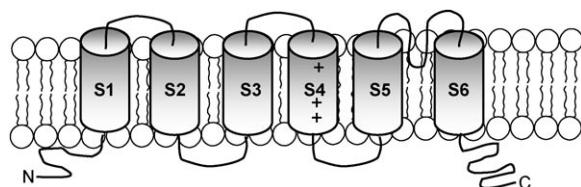
Fluoroartemisinins: Metabolically More Stable Antimalarial Artemisinin Derivatives

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

J. Chen,* M. Gopalakrishnan*

625–626

Opening Ion Channels: Enzyme at the Gate

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

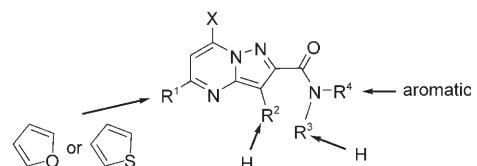
spider, Ramu et al., (*Nature* 2006, 442, 696–699) found that SmaseD induced robust outward current through a voltage gated K^+ channel $K_v1.2$.

COMMUNICATIONS

A. Kiessling, R. Wiesinger, B. Sperl, T. Berg*

627–630

Selective Inhibition of c-Myc/Max Dimerization by a Pyrazolo[1,5-*a*]-pyrimidine



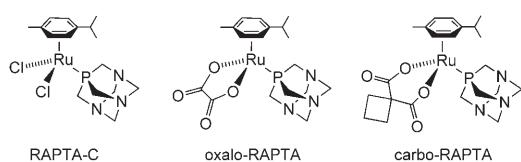
c-Myc/Max Dimerization. The interaction between the oncoprotein c-Myc and its activation partner Max is considered to be a desirable target for cancer drug development. However, the interaction is mediated by large α -helical in-

terfaces 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.

A. Casini, G. Mastrobuoni, W. H. Ang, C. Gabbiani, G. Pieraccini, G. Moneti, P. J. Dyson, L. Messori*

631–635

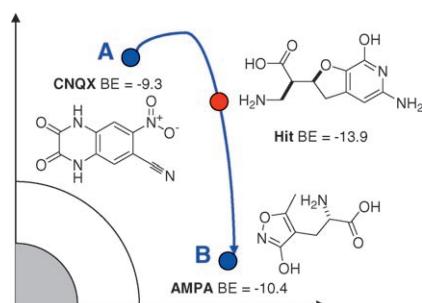
ESI-MS Characterisation of Protein Adducts of Anticancer Ruthenium(II)-Arene PTA (RAPTA) Complexes



Electrospray ionization mass spectrometry allows a rapid characterisation of the adducts formed between three novel anticancer ruthenium(II)-arene PTA compounds and horse heart cyto-

chrome 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.

Space the final frontier! Modern medicine depends on the discovery of new drugs however, detailed knowledge of all possible organic molecules is not available. To travel in this so-called chemical space and discover new compounds, we wrote a spaceship program combining a point mutation generator with a selection module for target similarity. Thus, allowing travel from a starting molecule A to a target molecule B through a continuum of structural mutations.



R. van Deursen, J.-L. Reymond

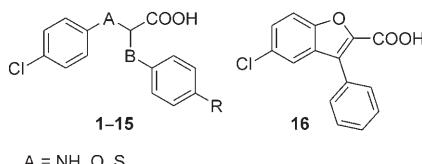
636 – 640

Chemical Space Travel



FULL PAPERS

A series of chiral 4-chlorophenoxyacetic acid analogues was synthesized and tested for activity toward both PPAR α and PPAR γ . Some derivatives were potent PPAR α agonists as well as PPAR γ agonists. Docking experiments were performed to explain the influence of the absolute configuration on PPAR α activity.



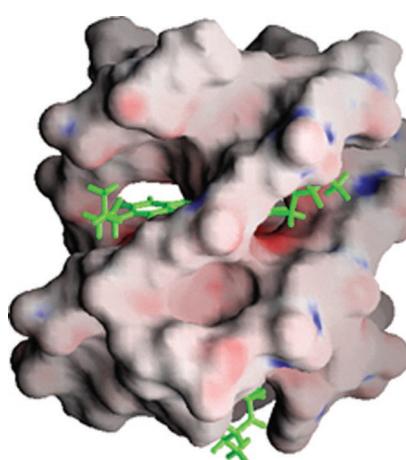
A = NH, O, S
B = alkyl or alkyloxy chain
R = H, Cl

*G. Fracchiolla, A. Laghezza,
L. Piemontese, G. Carbonara,
A. Lavecchia,* P. Tortorella, M. Crestani,
E. Novellino, F. Loiodice**

641 - 654

Synthesis, Biological Evaluation, and Molecular Modeling Investigation of Chiral Phenoxyacetic Acid Analogues with PPAR α and PPAR γ Agonist Activity

The synthesis and evaluation of G-quadruplex binding properties of a series of quinacridine-based ligands (MMQs) are described. Structure-activity relationship studies support a model of interaction of these compounds with G-quadruplex structures which is furthermore confirmed by the solution structure determined by 2D NMR experiments.



*C. Hounsou, L. Guittat, D. Monchaud,
M. Jourdan, N. Saettel, J.-L. Mergny,
M.-P. Teulade-Fichou**

655 – 666

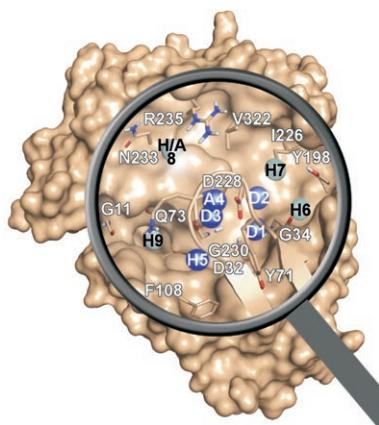
G-Quadruplex Recognition by Quinacridines: a SAR, NMR, and Biological Study



V. Limongelli, L. Marinelli,* S. Cosconati,
H. A. Braun, B. Schmidt, E. Novellino

667–678

Ensemble-Docking Approach on BACE-1: Pharmacophore Perception and Guidelines for Drug Design

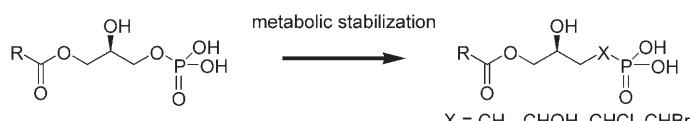


Based on the docking results of a series of BACE-1 inhibitors an exhaustive pharmacophore model, which captures both the common geometric and electronic features essential for enzyme inhibition, is presented providing a valuable tool for rational drug design.

G. Jiang, Y. Xu, Y. Fujiwara, T. Tsukahara,
R. Tsukahara, J. Gajewiak, G. Tigyi,
G. D. Prestwich*

679–690

α -Substituted Phosphonate Analogues of Lysophosphatidic Acid (LPA) Selectively Inhibit Production and Action of LPA



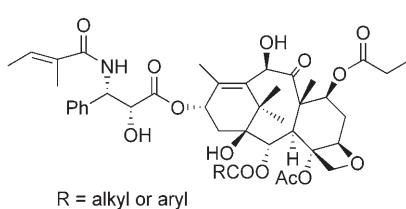
Metabolically stabilized: We present the total synthesis and pharmacological characterization of α -substituted phosphonate analogues of LPA. The compounds include isoform-selective ago-

nists and antagonists for the LPA GPCRs, and also include potent inhibitors of lysophospholipase D, a key enzyme involved in LPA biosynthesis.

C.-G. Yang, I. Barasoain, X. Li,
R. Matesanz, R. Liu, F. J. Sharom, D.-L. Yin,
J. F. Diaz,* W.-S. Fang*

691–701

Overcoming Tumor Drug Resistance with High-Affinity Taxanes: A SAR Study of C2-Modified 7-Acyl-10-Deacetyl Cephalomannines

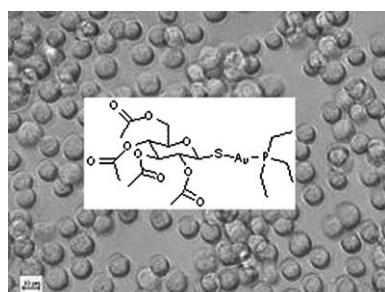


Potent taxanes: A series of C2-modified 10-deacetyl-7-propionylcephalomannine derivatives were prepared and biologically evaluated. Some C2 *meta*-substituted benzoate analogues showed potent activity against both drug-sensitive and drug-resistant tumor cells.

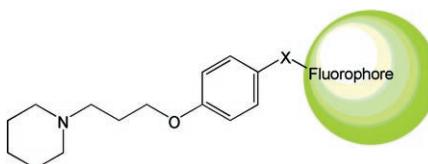
I. Ott,* H. Scheffler, R. Gust

702–707

Development of a Method for the Quantification of the Molar Gold Concentration in Tumour Cells Exposed to Gold-Containing Drugs



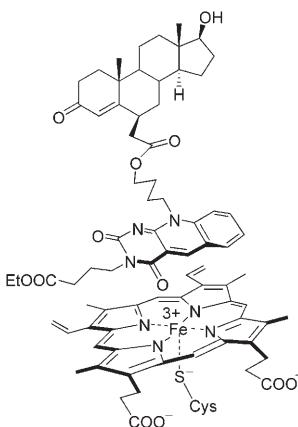
Going for gold. This paper describes a method for the determination of the gold content in tumour cells exposed to gold drugs such as auranofin. The method allows the measurement of molar cellular concentrations, which offers the advantage of facilitating the comparison of data obtained from different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



Small molecule ligands for aminergic GPCRs with fluorescent properties are rarely described in medicinal chemistry. Herein, novel compounds of high diversity concerning the fluorophores have been designed based on a (phenoxy-propyl)piperidine pharmacophore. They

presented in vitro affinities in a low nanomolar or subnanomolar concentration range at histamine H₃ receptors. Some compounds also showed a rather good in vivo potency as a H₃-receptor antagonist.

Drug–drug interactions related to cytochrome P450 3A4 (CYP3A4) are a serious problem in drug development. Several steroid-linked fluorophores were synthesized and are shown to be excellent CYP3A4 inhibitors. On binding to CYP3A4 their fluorescence is quenched; it is restored in the presence of compounds having higher affinity for CYP3A4. This method uses a simple fluorescence measurement to identify new drugs that could pose problematic drug–drug interactions.



M. Amon, X. Ligneau, J.-C. Camelin,
I. Berrebi-Bertrand, J.-C. Schwartz,
H. Stark*

708–716

Highly Potent Fluorescence-Tagged Nonimidazole Histamine H₃ Receptor Ligands



A. Chouquet, Y. Grinkova, D. Ricard,
S. Sligar, W.-D. Woggon*

717–724

Fluorescent Probes for Rapid Screening of Potential Drug–Drug Interactions at the CYP3A4 Level



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

* Author to whom correspondence should be addressed.

BOOKS

Pathogenomics: Genome Analysis of Pathogenic Microbes · J. Hacker,

U. Dobrindt (Eds.)

Bioorganometallics: Biomolecules, Labeling, Medicine · G. Jaouen (Ed.)

Chirality in Drug Research · E. Francotte, W. Lindner (Eds.)

J. Brannigan 725

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