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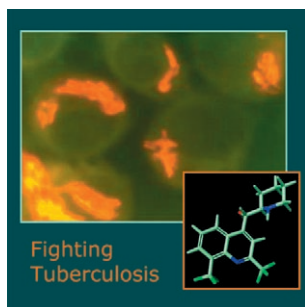
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Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE



The cover picture shows the structure of (+)-erythro-mefloquine atop a fluorescence photomicrograph of *Mycobacterium tuberculosis* H₃₇Rv (orange) residing within a macrophage cell culture. *M. tuberculosis* is able to grow both within macrophages and extracellularly. The strain shown was transformed with a red fluorescent protein gene, which enables easy visualization by fluorescence microscopy and assessment of viability. Mefloquine is an established antimalarial agent. See the Communication by A. P. Kozikowski et al. on p. 593 ff. for details on the activity of mefloquine and mefloquine analogues against both replicating and nonreplicating *M. tuberculosis*.

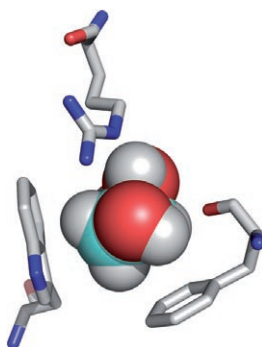
NEWS

From our sister journals

584 – 585

MINIREVIEWS

The treatment of malaria and other such diseases, which are caused by protozoa, is faced with problems from the rapid spread of resistant parasites. Aquaporins, cellular water and solute channels of the parasite–host interface, are potential novel drug targets. Research on protozoan aquaporin physiology and protein structure and function is currently taking up speed.



E. Beitz*

587 – 592

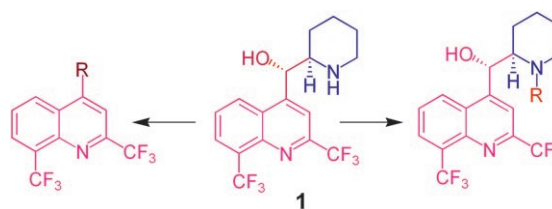
Aquaporin Water and Solute Channels from Malaria Parasites and Other Pathogenic Protozoa

COMMUNICATIONS

S. Jayaprakash, Y. Iso, B. Wan,
S. G. Franzblau, A. P. Kozikowski*

593 – 597

Design, Synthesis, and SAR Studies of Mefloquine-Based Ligands as Potential Antituberculosis Agents



Potential new tuberculosis treatment:

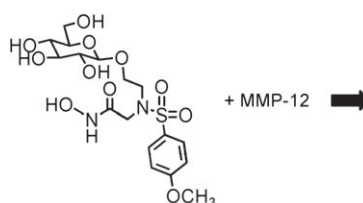
Mefloquine (1), an antimalarial drug with simple, yet interesting structural features has been found to be active against *Mycobacterium tuberculosis*. Thus, this molecule is a good candidate

as a lead compound in the search for new TB drugs. The design and synthesis of mefloquine analogues is described, and biological data against the TB organism are also presented.

V. Calderone, M. Fragai, C. Luchinat,*
C. Nativi,* B. Richichi, S. Roelens

598 – 601

A High-Affinity Carbohydrate-Containing Inhibitor of Matrix Metalloproteinases



Matrix metalloproteinases (MMPs) are a class of Zn-containing hydrolases that participate in a variety of biological processes, and aberrant activity of MMPs has been implicated in a number of diseases including cancer. A new glyco-

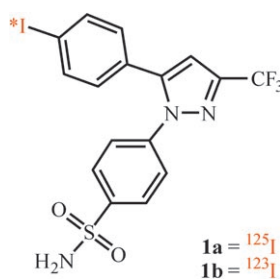
side-containing inhibitor of MMPs, unprecedented among the inhibitors of this family of enzymes, is reported. This inhibitor is water soluble, and displays nanomolar affinity toward several MMPs.

FULL PAPERS

H. M. Schuller,* G. Kabalka, G. Smith,
A. Mereddy, M. Akula, M. Cekanova

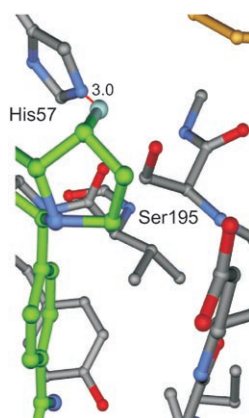
603 – 610

Detection of Overexpressed COX-2 in Precancerous Lesions of Hamster Pancreas and Lungs by Molecular Imaging: Implications for Early Diagnosis and Prevention



Cyclooxygenase-2 (COX-2) is overexpressed in many disease states, including cancer. The potential use of COX-2 inhibitors as a clinical tool is in doubt, as long-term use significantly increases cardiovascular mortality. We hypothesize that elevated COX-2 levels in target organs can be detected by planar nuclear medicine imaging prior to the development of overt cancer, so that susceptible individuals may be targeted for treatment.

Bioisosteric substitution of functional groups is a well-established strategy in medicinal chemistry. Tricyclic thrombin inhibitors were prepared with the terminal pyrrolidine ring systematically substituted to explore the potential bioisosteric behavior of C–F, C–OH, and C–OMe residues pointing into the catalytic center of the enzyme (shown). The effects on biological activity and physico-chemical properties were investigated.

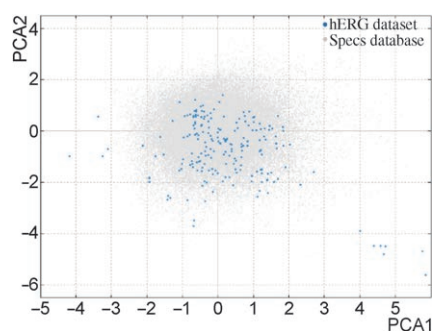


*E. Schweizer, A. Hoffmann-Röder, K. Schärer, J. A. Olsen, C. Fäh, P. Seiler, U. Obst-Sander, B. Wagner, M. Kansy, F. Diederich**

611 – 621

A Fluorine Scan at the Catalytic Center of Thrombin: C–F, C–OH, and C–OMe Bioisosterism and Fluorine Effects on pK_a and $\log D$ Values

Drug-induced QT interval prolongation can lead to serious arrhythmias which can evolve to be fatal, and hERG cardiac channel blockage is associated with this adverse side effect. Recursive partitioning models have been successfully developed to predict hERG blockage using diverse datasets (the chemical space covered is shown). This fast virtual screening approach could be used as an early tool in the drug-discovery process.

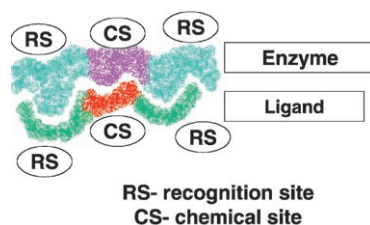


E. Dubus, I. Ijjaali, F. Petitet, A. Michel*

622 – 630

In Silico Classification of hERG Channel Blockers: a Knowledge-Based Strategy

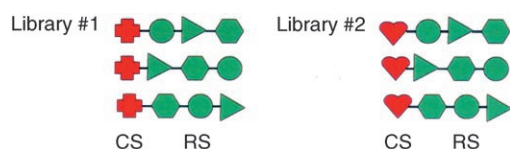
The binding trend of isoselective inhibitors with identical recognition sites (RS) and different reactive chemical sites (CS) depends mainly on their CS sites. A combined experimental/theoretical methodology is presented for expert analysis of the binding trend of CS fragments. Potential applications of the methodology include virtual screening of inhibitor libraries and the design of new inhibitors.



R. Ozeri, N. Khazanov, N. Perlman, M. Shokhen, A. Albeck**

631 – 638

Enzyme Iseoselective Inhibitors: A Tool for Binding-Trend Analysis



Iseoselective inhibition trend analysis is applied to predict the binding affinities of transition-state analogue inhibitors of medically important enzymes. The ra-

tional design of CS fragments (red) followed by conventional optimization of RS fragments (green) could be used as a novel approach to drug design.

M. Shokhen, N. Khazanov, A. Albeck**

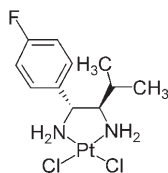
639 – 643

Enzyme Iseoselective Inhibitors: Application to Drug Design

A. Dullin, F. Dufrasne, M. Gelbcke,
R. Gust*

644 – 653

Synthesis and Cytotoxicity of Enantiomerically Pure [1,2-Diamino-1-(4-fluorophenyl)-3-methylbutane]-platinum(II) Complexes



A series of leaving group derivatives of enantiomerically pure [1,2-diamino-1-(4-fluorophenyl)-3-methylbutane]platinum(II) complexes were synthesized and tested for cytotoxicity on the hormone-dependent MCF-7 and the hormone-independent MDA-MB 231 breast cancer cell lines, as well as the LNCaP/FGC prostate cancer cell line. (*R,R*)-4F-Ph/*i*Prop-PtCl₂ was identified as the most active platinum(II) complex. The configuration and the C2-alkyl group determined the antiproliferative effects.

BOOKS

- | | | |
|---|----------------------|-----|
| DNA Pharmaceuticals: Formulation and Delivery in Gene Therapy, DNA Vaccination and Immunotherapy · M. Schleef (Ed.) | A. Kirby | 654 |
| Methods in Molecular Biology, Vol. 316: Bioinformatics and Drug Discovery · R. S. Larson (Ed.) | M. P. Jacobson | 654 |
| Directory of Therapeutic Enzymes · B. McGrath, G. Walsh (Eds.) | G. Jung | 655 |

SERVICE

- Author Index 657 Preview 658
- Keyword Index 657

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