CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY

02/2008

http://www.chemmedchem.org

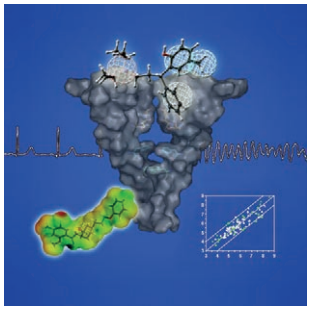
Full text:

http://www.interscience.wiley.com

ChemMedChem, European in origin but international in scope, deals with all aspects of drug discovery. It is co-owned by a group of European chemical societies and is published by Wiley-VCH. Contributions in *ChemMedChem* cover medicinal and pharmaceutical sciences, drug design, drug development and delivery, molecular modeling, combinatorial chemistry, target validation, lead generation, and ADMET studies, that is, research from the overlapping areas between biology, chemistry, and medicine. *ChemMedChem* publishes Communications and Full Papers, as well as Reviews, Minireviews, Highlights, Concepts, Essays, Book Reviews, and occasionally Conference Reports. Authors can submit manuscripts to *ChemMedChem* online through our homepage (see left) by clicking on "Online Submission" and following the simple instructions.

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

COVER PICTURE

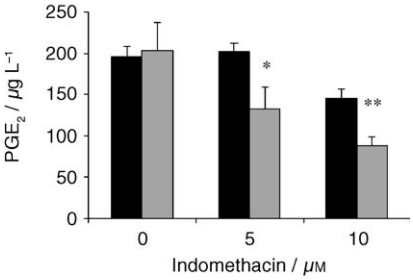


The cover picture shows a schematic representation of the hERG-encoded potassium channel together with one pharmacophore for potent hERG inhibitors, the MEP surface of cisapride, a potent hERG inhibitor, and a plot of measured versus predicted hERG IC_{50} values. Blockade of the hERG channel leads to a prolongation of the QT interval, which might lead to torsades des pointes, an uncontrolled excitation of heartbeats. On the cover picture, an ECG plot of normal heartbeats (middle left side) and an ECG plot of torsades des pointes (middle right side) is shown in white. Torsades des pointes might lead to lethal ventricular fibrillation. Therefore the inhibition of hERG is one of the major toxicological endpoints addressed in preclinical drug development. The combination of different hERG pharmacophores, derived from highly potent structurally diverse inhibitors together with specific QSAR models, offers a novel approach to predict hERG blockade. For details, see the Full Paper by B. Beck, T. Clark, et al. on p. 254 ff.

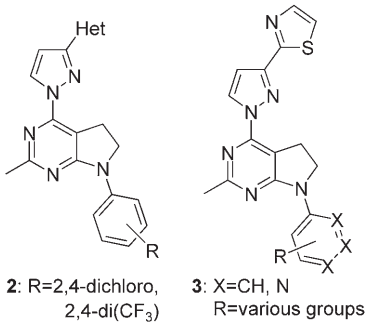
NEWS

REVIEWS

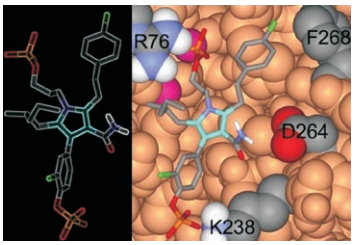
COMMUNICATIONS



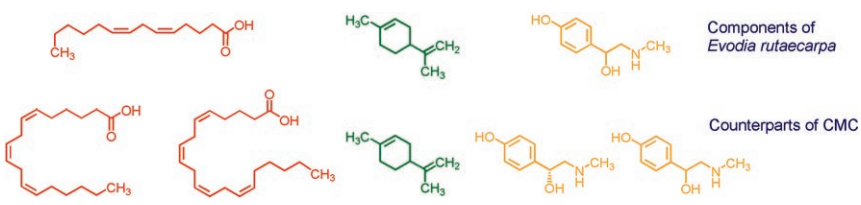
Copper bracelet. We analyzed prostaglandin E_2 (PGE_2) production by cyclooxygenase 2 (COX-2) after exposure to biometals. Cu^{2+} was the only metal ion that decreased PGE_2 production. These effects may explain the anti-inflammatory benefits of Cu^{2+} and the Cu^{2+}–indomethacin complex reported previously.



Potent and selective CRF_1 receptor antagonists based on the 5,6-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidines **2** were discovered and characterized. Identification of two complementary synthetic pathways allowed an efficient SAR exploration, which was facilitated by computational methods that allowed the rational design of target compounds within a defined drug-like physicochemical space.

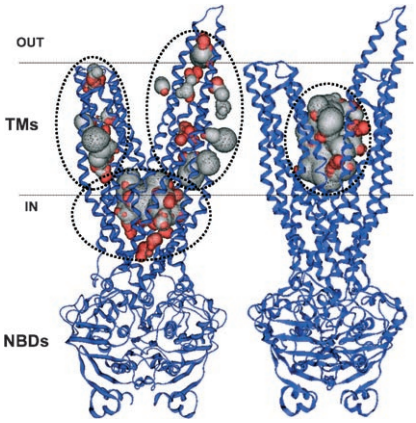


Inhibiting Wip1. Using a pyrrole-based scaffold, we developed a series of small molecules that mimic the three-dimensional arrangement of the polar and hydrophobic functional groups of the best cyclic peptide inhibitor. Iterative optimization cycles of design, synthesis, and kinetic testing has lead to a selective inhibitor of Wip1. The picture shows the structure of the best inhibitor bound to the active site of the enzyme.

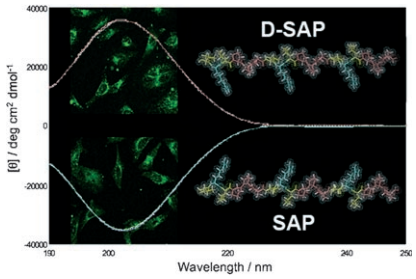


Merging east and west. Through a global structural comparison between traditional Chinese medicine (TCM) components and modern Western drugs, it is revealed that a certain part of TCM components have been recognized by modern Western medicine, which suggests that TCM, at least in part, has a scientific basis.

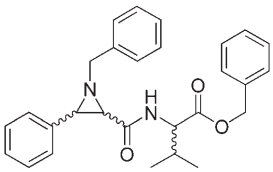
FULL PAPERS



Binding regions of P-glycoprotein. In recent years significant progress has been made towards understanding of the multidrug resistance transport proteins, particularly P-glycoprotein, whose substrates cover a broad spectrum of compounds including antibiotics, HIV protease inhibitors, steroids, chemotherapeutic, and immunosuppressive drugs. Herein, multiple binding sites that may bind and/or release substrates in multiple pathways are discussed.



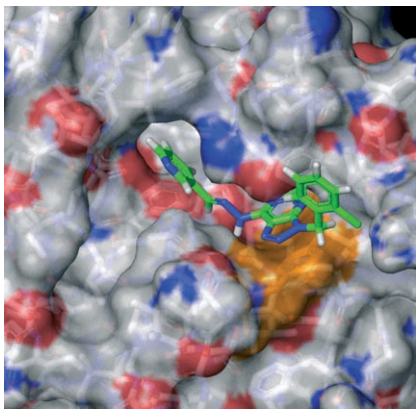
Penetrating particles. Given that most potential biomolecular drugs (for example, DNA, RNA, peptides, and proteins) are very often directed at intracellular targets, intracellular drug delivery is a focal point in drug development. SAP is an efficient and noncytotoxic cell-penetrating peptide. However, it is labile to proteases. Herein, its enantiomeric version, D-SAP, is reported to retain the properties of SAP, and is shown to be fully protease resistant.



11, **17**

k_2 = 56–121 x 10^3 M^{-1} min^{-1}

The *cis*-configured *N*-benzyl-substituted aziridine-2-carboxylic acid derivative **11** and its diastereomer **17** with an *R*-configured Val residue were developed according to docking studies and are shown to be potent pseudo-irreversible dual-mode inhibitors of the *C. albicans* aspartic protease SAP2. The compounds inhibit the growth of *C. albicans* without exhibiting nonspecific toxicity.



Erm methyltransferases are the major resistance factor to MLS_B antibiotics. We used a structure-based virtual screening approach to identify several new ErmC′ inhibitors. The analysis of docking models of the ErmC′ inhibitors identified herein and comparison with a compound previously identified by high-throughput screening suggests a strategy to generate potent leads.

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.

COMMENTARY

BOOKS

SERVICE

All the Tables of Contents may be found on the WWW under: http://www.chemmedchem.org

Issue 1, 2008, was published online on January 3, 2008.

CORRIGENDA

Dr. Yuko Fujiwara [Department of Physiology and University of Tennessee Cancer Institute, University of Tennessee Health Science Center, Memphis, TN 38163 (USA)] was unintentionally omitted from the author list for this manuscript. The correct author list is shown at right.

*J. Gajewiak, R. Tsukahara, T. Tsukahara, Y. Fujiwara, S. Yu, Y. Lu, M. Murph, G. B. Mills, G. Tigyi, G. D. Prestwich**

Alkoxymethylenephosphonate Analogues of (Lyso)phosphatidic Acid Stimulate Signaling Networks Coupled to the LPA_2 Receptor

ChemMedChem **2007**, *2*, 1789–1798

DOI 10.1002/cmdc.200700111

For compounds **5**, **9**, **14**, **18**, **22**, and **26** in Scheme 1, as well as the structure shown in the graphical abstract, $R = C_9H_{21}$ is incorrect; it should be $R = C_9H_{19}$.

*K. Chegaev, L. Lazzarato, B. Rolando, E. Marini, G. V. Lopez, M. Bertinaria, A. Di Stilo, R. Fruttero, A. Gasco**

Amphiphilic NO-Donor Antioxidants

ChemMedChem **2007**, *2*, 234–240

DOI 10.1002/cmdc.200600248

