

CHEM MED CHEM

CHEMISTRY ENABLING DRUG DISCOVERY

02/2008

CHEMICAL & MEDICINAL CHEMISTRY

<http://www.chemmedchem.org>

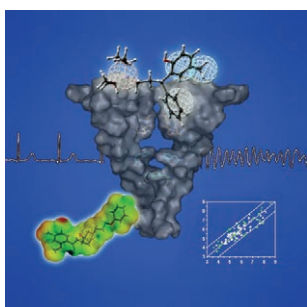
Full text:

WILEY
InterScience®
DISCOVER SOMETHING GREAT
<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

Spotlights on our sister journals

204 – 205

REVIEWS

Dyslipidemia is a pathological increase of lipid and lipoprotein levels in the blood. Most prominent among these are the hyperlipidemic diseases, hypercholesterolemia and hypertriglyceridemia. New therapeutic approaches include subtype-selective, dual, and pan-

agonists of the PPAR, and inhibitors of CETP, acyl-CoA-cholesterol-acyltransferase, and squalene synthase amongst others. Clinical implications of new drugs under investigation are discussed in this review.

O. Rau,* H. Zettl, L. Popescu,
D. Steinhilber, M. Schubert-Zsilavecz

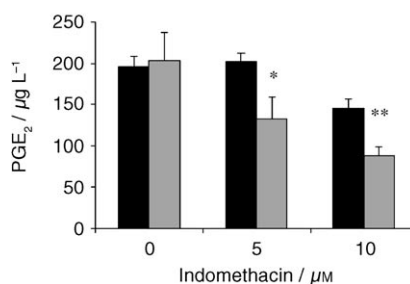
206 – 211

**The Treatment of Dyslipidemia—
What's Left in the Pipeline?**

S. Nagano, A. I. Bush*

223 – 225

Sensitive, Selective, and Irreversible Inhibition of Cyclooxygenase-2 Activity by Copper

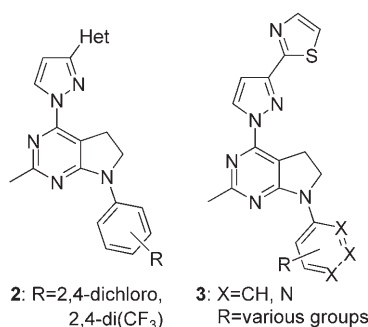


Copper bracelet. We analyzed prostaglandin E₂ (PGE₂) production by cyclooxygenase 2 (COX-2) after exposure to biomaterials. Cu²⁺ was the only metal ion that decreased PGE₂ production. These effects may explain the anti-inflammatory benefits of Cu²⁺ and the Cu²⁺-indomethacin complex reported previously.

F. M. Sabbatini,* R. Di Fabio,* Y. St-Denis, A.-M. Capelli, E. Castiglioni, S. Contini, D. Donati, E. Fazzolari, G. Gentile, F. Micheli, F. Pavone, M. Rinaldi, A. Pasquarello, M. G. Zampori, P. Di Felice, P. Zarantonello, R. Arban, B. Perini, G. Vitulli, R. Benedetti, B. Oliosi, A. Worby

226 – 229

Heteroaryl-Substituted 4-(1*H*-pyrazol-1-yl)-5,6-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidine Derivatives as Potent and Selective Corticotropin-Releasing Factor Receptor-1 Antagonists



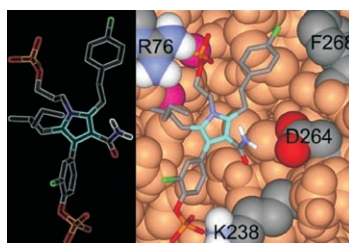
Potent and selective CRF₁ receptor antagonists based on the 5,6-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidines **2** were discovered and characterized. Identification of two complementary synthetic pathways allowed an efficient SAR exploration, which was facilitated by computational methods that allowed the rational design of target compounds within a defined drug-like physicochemical space.

J. Bang, H. Yamaguchi, S. R. Durell, E. Appella, D. H. Appella*

230 – 232



A Small Molecular Scaffold for Selective Inhibition of Wip1 Phosphatase



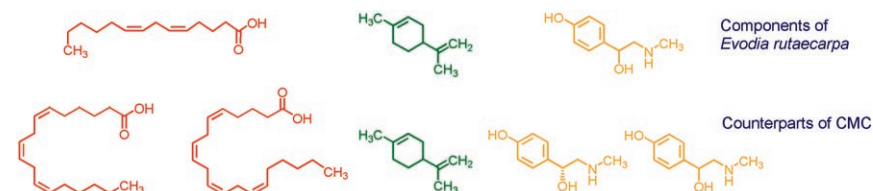
Inhibiting Wip1. Using a pyrrole-based scaffold, we developed a series of small molecules that mimic the three-dimensional arrangement of the polar and hydrophobic functional groups of the best cyclic peptide inhibitor. Iterative optimization cycles of design, synthesis, and kinetic testing has led to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

D.-X. Kong, X.-J. Li, G.-Y. Tang, H.-Y. Zhang*

233 – 236



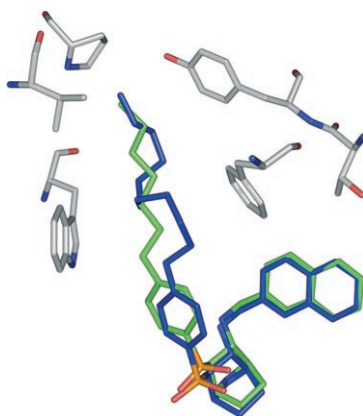
How Many Traditional Chinese Medicine Components Have Been Recognized by Modern Western Medicine? A Chemoinformatic Analysis and Implications for Finding Multicomponent Drugs



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.

The flap pocket of plasmepsin II was examined in terms of molecular recognition properties. It was found that *n*-alkyl chains of different length bind best to this cavity when the packing coefficient is around 0.55, and it is suggested that the chains adopt their conformation in order to fill the available space properly. The concept of ideal volume occupancy previously demonstrated for synthetic guest–host systems has been applied to an enzyme environment.



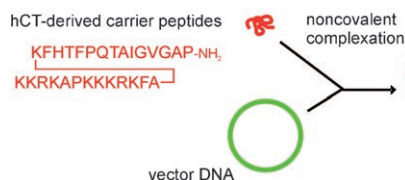
*M. Zürcher, T. Gottschalk, S. Meyer, D. Bur, F. Diederich**

237 – 240

Exploring the Flap Pocket of the Antimalarial Target Plasmepsin II: The “55% Rule” Applied to Enzymes



FULL PAPERS



Novel branched hCT-derived carrier peptides were synthesised, noncovalently complexed with vector DNA encoding fluorescent proteins, and shown

to efficiently transfect cell lines as well as primary rat hippocampal neurons and chicken cardiomyocytes, as shown in the micrograph image.

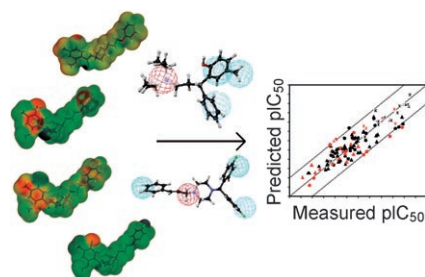


*R. Rennert, I. Neundorf, H.-G. Jahnke, P. Suchowerskyj, P. Dournaud, A. Robitzki, A. G. Beck-Sickinger**

241 – 253

Generation of Carrier Peptides for the Delivery of Nucleic Acid Drugs in Primary Cells

hERG blockade is one of the major toxicological problems in lead structure optimization. We present a predictive QSAR model for hERG blockade that differentiates between specific and non-specific binding by preliminary pharmacophore scanning. While PLS and SVR models reach competitive R^2 values, the mixture of interpretable quantum mechanically derived descriptors and pharmacophore-based splits of the datasets offers a novel approach toward the understanding of hERG blockade.



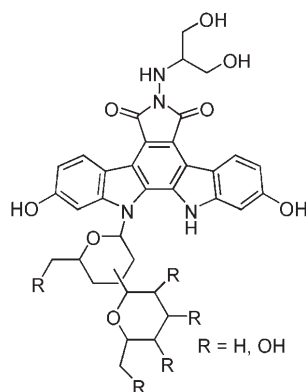
C. Kramer, B. Beck, J. M. Kriegl, T. Clark**

254 – 265

A Composite Model for hERG Blockade



Indolocarbazole glycosides represent an important class of antitumor agents. A series of derivatives bearing structurally varied disaccharides linked to the indolocarbazole core were synthesized and studied. The structural features of the disaccharides strongly influence the biological activity of these compounds. Molecular modeling by MD simulations provide a plausible explanation for the biological mechanism of these compounds.



*F. Animati, M. Berettoni, M. Bigioni, M. Binaschi, P. Felicetti, L. Gontrani, O. Incani, A. Madami, E. Monteagudo, L. Olivieri, S. Resta, C. Rossi, A. Cipollone**


266 – 279

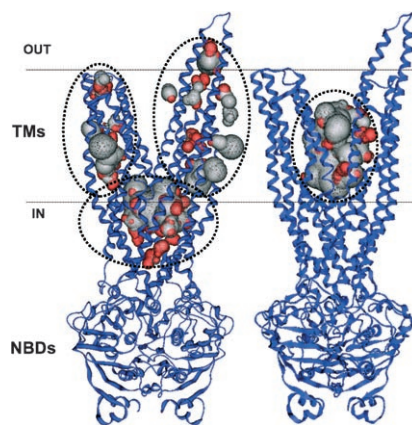
Synthesis, Biological Evaluation, and Molecular Modeling Studies of Rebecamycin Analogues Modified in the Carbohydrate Moiety



C. Globisch, I. K. Pajeva, M. Wiese*

280 – 295


 **Identification of Putative Binding Sites of P-glycoprotein Based on its Homology Model**

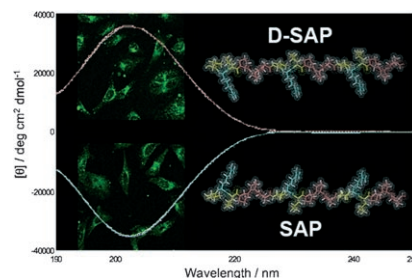


Binding regions of P-glycoprotein. In recent years significant progress has been made towards understanding of the multidrug resistance transport proteins, particularly P-glycoprotein, whose substrates cover a broad spectrum of compounds including antibiotics, HIV protease inhibitors, steroids, chemotherapeutic,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

S. Pujals, J. Fernández-Carneado, M. D. Ludevid, E. Giralto*

296 – 301


 **D-SAP: A New, Noncytotoxic, and Fully Protease Resistant Cell-Penetrating Peptide**

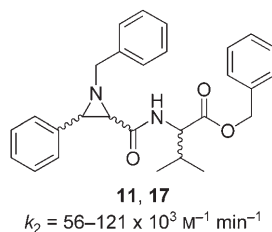


Penetrating particles. Given that most potential biomolecular drugs (for example, DNA, RNA, peptides, and proteins) are very often directed at intracellular targets, intracellular drug delivery is a focal point in drug development. SAP is an efficient and noncytotoxic cell-penetrating peptide. However, 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.

B. Degel, P. Staib, S. Rohrer, J. Scheiber, E. Martina, C. Büchold, K. Baumann, J. Morschhäuser, T. Schirmeister*

302 – 315

 **Cis-Configured Aziridines Are New Pseudo-Irreversible Dual-Mode Inhibitors of *Candida albicans* Secreted Aspartic Protease 2**

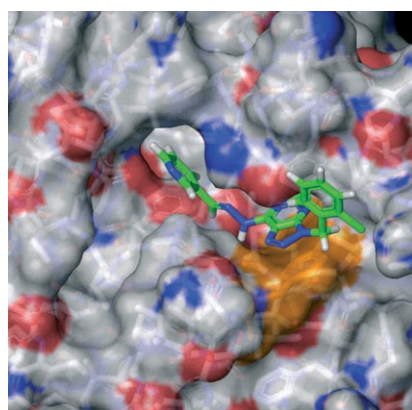


The cis-configured N-benzyl-substituted aziridine-2-carboxylic acid derivative 11 and its diastereomer 17 with an R-configured Val residue were developed according to docking studies and are shown to be potent pseudo-irreversible dual-mode inhibitors of the *C. albicans* aspartic protease SAP2. The compounds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

M. Feder,* E. Purta, L. Kosciński, S. Čubrilo, G. Maravic Vlahovicek, J. M. Bujnicki

316 – 322

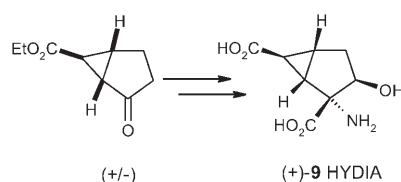
Virtual Screening and Experimental Verification to Identify Potential Inhibitors of the ErmC Methyltransferase Responsible for Bacterial Resistance against Macrolide Antibiotics



ErmC 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.

Metabotropic glutamate receptor 2/3

ligands: An asymmetric synthesis of (1*S*,2*R*,3*R*,5*R*,6*S*)-2-amino-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid (+)-9 (HYDIA) and a few of its O-alkylated derivatives is described. These compounds are potent and selective competitive antagonists for the group II mGluRs.



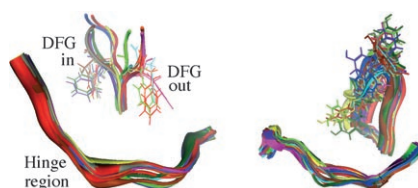
T. J. Woltering, G. Adam, P. Huguenin, J. Wichmann, S. Kolczewski, S. Gatti, A. Bourson, J. N. C. Kew, G. Richards, J. A. Kemp, V. Mutel, F. Knoflach*

323 – 335

Asymmetric Synthesis and Receptor Pharmacology of the Group II mGlu Receptor Ligand (1*S*,2*R*,3*R*,5*R*,6*S*)-2-Amino-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic Acid—HYDIA

Ligand-induced protein flexibility

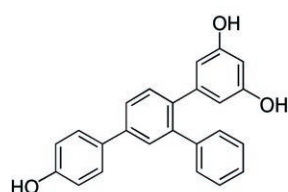
hampers structure-based drug design efforts. Superposition of crystal structures of p38MAPK bound to different ligands shows the range of conformational variation in the protein. We have attempted to develop a model correlating these variations to ligand properties. This model can be used to predict ligand-induced changes in the protein for novel query ligands and hence improve the reliability of inferences from docking.



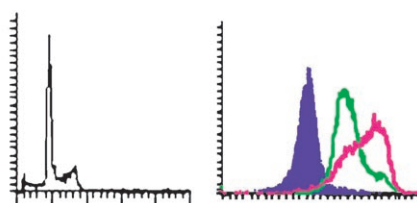
*J. Subramanian, S. Sharma, C. B-Rao**

336 – 344

Modeling and Selection of Flexible Proteins for Structure-Based Drug Design: Backbone and Side Chain Movements in p38 MAPK



Looking for small organic molecules that are able to interfere with cell-cycle regulation: a promising strategy for the

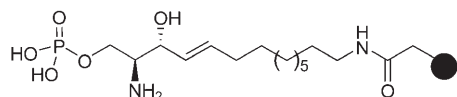


development of innovative antitumor agents.

D. Pizzirani, M. Roberti, A. Cavalli, S. Grimaudo, A. Di Cristina, R. M. Pipitone, N. Gebbia, M. Tolomeo, M. Recanatini*

345 – 355

Antiproliferative Agents That Interfere with the Cell Cycle at the G₁→S Transition: Further Development and Characterization of a Small Library of Stilbene-Derived Compounds



A sphingosine-1-phosphate analogue, synthesized via olefin cross-metathesis and subsequent phosphorylation, is regioselectively acylated at its N terminus in solution and shows biological activity.

The compound is immobilized on an affinity matrix, and the choice of a UV-active phosphate protecting group allows for quantification of resin loading after cleavage.

T. Ullrich, M. Ghobrial, C. Peters, A. Billich, D. Guerini, P. Nussbaumer*

356 – 360

Synthesis and Immobilization of erythro-C14- ω -Aminosphingosine-1-phosphate as a Potential Tool for Affinity Chromatography

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

Sport Doping—A Double Blind Proposal

C. Djerassi 361

BOOKS

Biochips as Pathways to Drug Discovery · A. Carmen, G. Hardiman (Eds.)

M. D. Disney 363

SERVICE

Author Index 364 Preview 366

Keyword Index 365

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 LPA₂ 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=C₉H₂₁ is incorrect; it should be R=C₉H₁₉.

*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