

CHEMICAL & MEDICINAL CHEMISTRY

<http://www.chemmedchem.org>

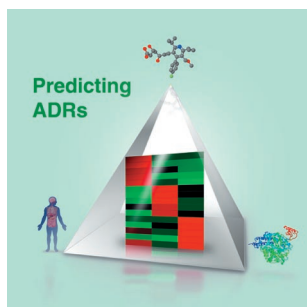
Full text:

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 the relation of a chemical structure (here the statin Cerivastatin) to a protein target and phenotypic observations (symbolized by a human). Statistical models for both links can be applied independently, predicting target activity and adverse reactions. Furthermore, they can also be linked, giving clues as to which targets are associated with particular adverse reactions. This knowledge can be used for optimizing panels used in preclinical profiling (where targets selected are those which give the most information about adverse reactions of particular concern); in the long run, those models will also facilitate more efficient progression of promising compounds into the clinic. For details, see the Full Paper by A. Bender et al. on p. 861 ff. (Cover design by Alan Abrams, Novartis.)

NEWS

Spotlights on our sister journals

742 – 743

REVIEWS

Good nicotine! Selective modulators for the nicotinic receptors may be developed as drugs for several disorders of the CNS such as Alzheimer's and Parkinson's disease, for pain control, and for smoking cessation. The importance of this research field is proved by the high number of ligands which constantly appear in the literature, and by the number of compounds undergoing pre-clinical and clinical trials.



M. N. Romanelli,* P. Gratteri,
L. Guandalini, E. Martini, C. Bonaccini,
F. Gualtieri

746 – 767

Central Nicotinic Receptors: Structure, Function, Ligands, and Therapeutic Potential

ESSAYS

I. R. Baxendale, J. J. Hayward, S. V. Ley,*
G. K. Tranmer

768 – 788

Pharmaceutical Strategy and
Innovation: An Academics Perspective



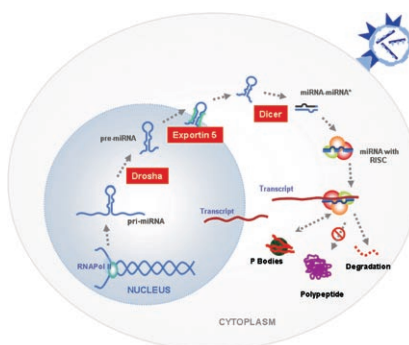
The challenges ahead: In this essay we describe and discuss issues facing the global pharmaceutical market, investigating the basis for many of these issues and highlighting the hurdles the industry needs to overcome, especially as they relate to the chemical sciences.

HIGHLIGHTS

V. Scaria, M. Hariharan,
S. K. Brahmachari, S. Maiti, B. Pillai*

789 – 792

microRNA: an Emerging Therapeutic



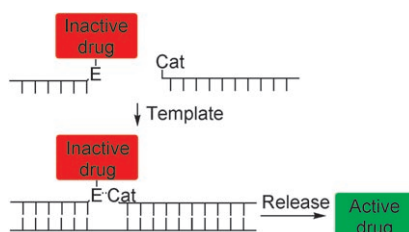
microRNAs are a recently discovered class of small noncoding RNAs which have been shown to regulate critical biological processes in higher eukaryotes. The regulatory impacts of microRNAs are now shown to encompass biological processes ranging from growth and development to oncogenesis and host–pathogen interaction. In this paper, we highlight the opportunities in developing novel diagnostics and therapeutics based on the microRNA regulatory mechanism.

CONCEPTS

M. F. Jacobsen, E. Cló, A. Mokhir,
K. V. Gothelf*

793 – 799

Model Systems for Activation of
Nucleic Acid Encoded Prodrugs



Nucleic acid controlled drug release.

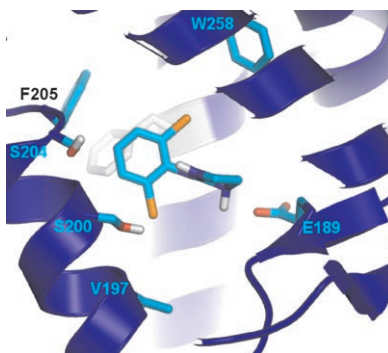
The concept of applying oligonucleotide conjugates for the templated release of prodrugs has been demonstrated in model systems. Recent developments in this area concerning actual applications are discussed.

COMMUNICATIONS

B. Balogh, C. Hetényi,* M. G. Keserű,
P. Mátyus*

801 – 805

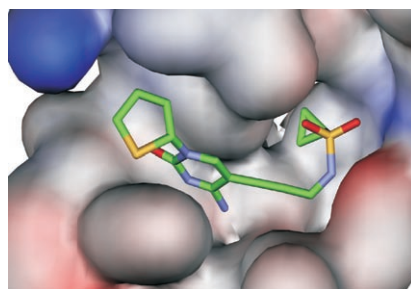
Structure-Based Calculation of Binding
Affinities of α_{2A} -Adrenoceptor
Agonists



An atomic resolution structure of α_{2A} -adrenoceptor was constructed and 15 known agonists were docked into the optimized model and experimental binding free energies were estimated.

The figure shows the binding of the agonist clonidine (sticks) to the core binding pocket of the adrenoceptor (blue cartoon, key residues are marked with sticks).

IspE kinase inhibitors. The first inhibitors for the kinase IspE, an enzyme of the non-mevalonate pathway, are presented. The nonphosphate based inhibitors avoid binding to the ATP site but instead occupy the substrate site and a small, newly detected hydrophobic sub-pocket at the active site of IspE. With appropriate filling of this pocket, competitive inhibition constants K_{ic} in the upper nanomolar range are measured.



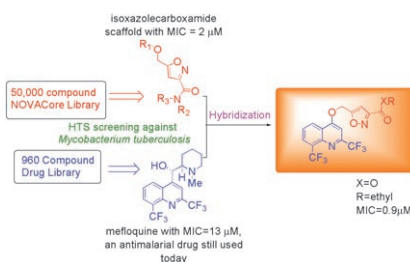
A. K. H. Hirsch, S. Lauw, P. Gersbach, W. B. Schweizer, F. Rohdich, W. Eisenreich,* A. Bacher, F. Diederich*

806 – 810

Nonphosphate Inhibitors of IspE Protein, a Kinase in the Non-Mevalonate Pathway for Isoprenoid Biosynthesis and a Potential Target for Antimalarial Therapy



The high throughput screening of two chemical libraries against *Mycobacterium tuberculosis* led to the design of hybrid compounds by using nitrile oxide cycloaddition chemistry. One of the hybrids shows an excellent MIC against *M. tuberculosis* H37Rv. As this molecule shows no CYP3A4 inhibition and a maximum tolerated dose of $\geq 200 \text{ mg kg}^{-1}$ po in mice, it represents a potential drug candidate for TB therapy.



J. Mao, B. Wan, Y. Wang, S. G. Franzblau,* A. P. Kozikowski*

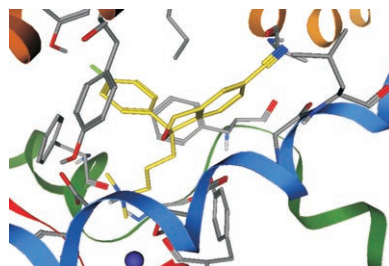
811 – 813

HTS, Chemical Hybridization, and Drug Design Identify a Chemically Unique Antituberculosis Agent—Coupling Serendipity and Rational Approaches to Drug Discovery



FULL PAPERS

Insights into the serotonin transporter–escitalopram complex. A three-dimensional molecular model for the serotonin transporter in complex with the allosteric serotonin reuptake inhibitor escitalopram was constructed. The model explains various protein–ligand interactions in the high-affinity ligand-binding site.

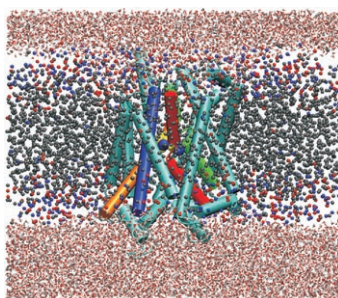


A. M. Jørgensen, L. Tagmose, A. M. M. Jørgensen, S. Topiol, M. Sabio, K. Gundertoft, K. P. Bøgesø, G. H. Peters*

815 – 826

Homology Modeling of the Serotonin Transporter: Insights into the Primary Escitalopram-binding Site

Characterizing transporters. The dynamic properties of the bacterial leucine transporter and the human serotonin transporter were investigated using molecular dynamics simulations. The properties include overall protein flexibility, binding pocket flexibility, and stability of key interactions between protein and ligand.



A. M. Jørgensen, L. Tagmose, A. M. M. Jørgensen, K. P. Bøgesø, G. H. Peters*

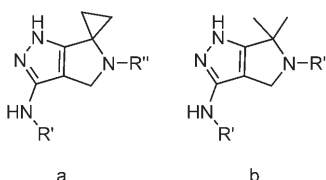
827 – 840

Molecular Dynamics Simulations of Na^+/Cl^- -Dependent Neurotransmitter Transporters in a Membrane-Aqueous System

M. G. Brasca,* C. Albanese, R. Amici, D. Ballinari, L. Corti, V. Croci, D. Fancelli, F. Fiorentini, M. Nesi, P. Orsini, F. Orzi, W. Pastori, E. Perrone, E. Pesenti, P. Pevarello, F. Riccardi-Sirtori, F. Roletto, P. Roussel, M. Varasi, A. Vulpetti, C. Mercurio

841 – 852

6-Substituted Pyrrolo[3,4-c]pyrazoles: An Improved Class of CDK2 Inhibitors

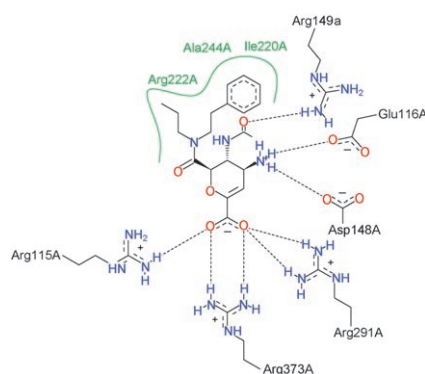


An improved class of CDK2/cyclin A inhibitors based on a bicyclic pyrrolo[3,4-c]pyrazole scaffold is presented. Conventional and polymer-assisted solution phase chemistry provided a way of generating compounds with interesting biochemical and cellular characteristics. Optimization of the physical properties and pharmacokinetic profile led to a compound, which exhibited good efficacy in vivo on A2780 human ovarian carcinoma.

K. Stierand, M. Rarey*

853 – 860

From Modeling to Medicinal Chemistry: Automatic Generation of Two-Dimensional Complex Diagrams



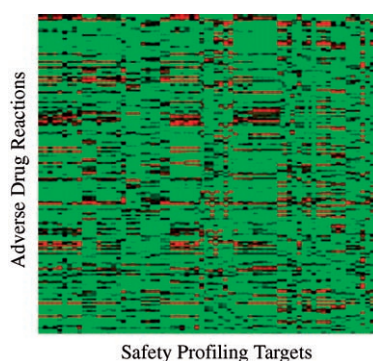
The visualization of protein ligand complexes is an important medium in the discussion of (structure-based) drug design results between the modeler and the medicinal chemist. The new software tool POSEVIEW automatically generates 2D diagrams of given complexes, containing the ligand and the amino acids of the receptor, which are connected to the ligand by hydrogen bonds or hydrophobic contacts.

A. Bender,* J. Scheiber, M. Glick, J. W. Davies, K. Azzaoui, J. Hamon, L. Urban, S. Whitebread, J. L. Jenkins

861 – 873



Analysis of Pharmacology Data and the Prediction of Adverse Drug Reactions and Off-Target Effects from Chemical Structure

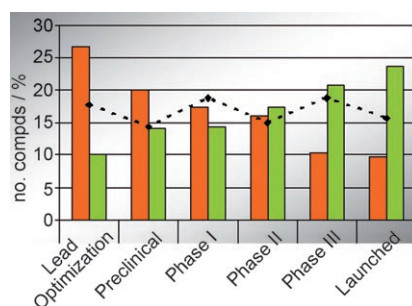


Preclinical Safety Pharmacology attempts to anticipate adverse drug reactions (ADRs) during early phases of drug discovery by testing compounds in simple, in vitro binding assays. In this paper we describe the successful application of cheminformatics methods to predict adverse side effects of drugs to accelerate drug discovery and decrease late stage attrition in drug discovery projects.

K. Azzaoui,* J. Hamon, B. Faller, S. Whitebread, E. Jacoby, A. Bender, J. L. Jenkins, L. Urban

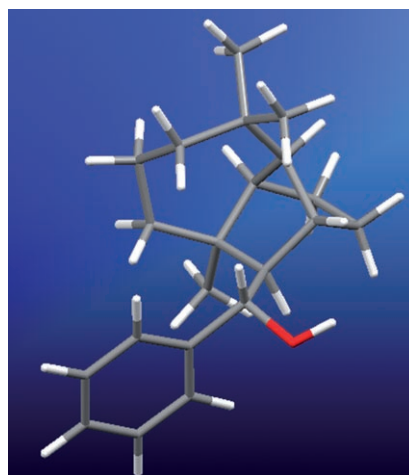
874 – 880

Modeling Promiscuity Based on in vitro Safety Pharmacology Profiling Data



A scoring model based on Bayesian classification for promiscuous and selective compounds has been developed. Such models were applied to a database of compounds at different phases of the drug-discovery process, and indeed lower promiscuity was predicted for marketed drugs than for compounds in early development or those which failed during clinical development.

The overlapping substrate selectivities of promiscuous metabolic enzymes such as UGTs make the design of selective inhibitors difficult. The results of this study indicate that the phenyl-substituted longifolol derivate (shown) is a potent and selective inhibitor of UGT2B7, the key enzyme involved in drug glucuronidation. The tricyclic framework is presumably responsible for isoform selectivity, the phenyl group prevents glucuronidation of the hydroxy group, which itself promotes solubility.



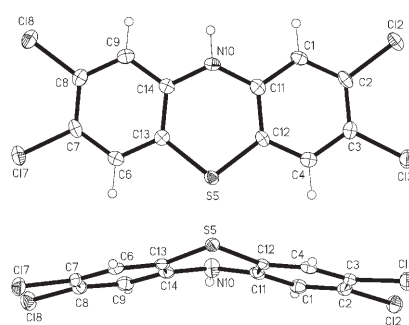
*I. Bichlmaier, M. Kurkela, T. Joshi, A. Siiskonen, T. Ruffer, H. Lang, M. Finel, J. Yli-Kauhaluoma**

881 – 889

Potent Inhibitors of the Human UDP-Glucuronosyltransferase 2B7 Derived from the Sesquiterpenoid Alcohol Longifolol



New Design for a Classical Pharmacophore. Structural similarities between dioxins and traditional phenothiazine drugs were exploited by synthesizing a new drug lead: 2,3,7,8-tetrachlorophenothiazine. Preliminary findings support the design of this compound, as it combines in vitro activity with favorable kinetics in two rodent models.

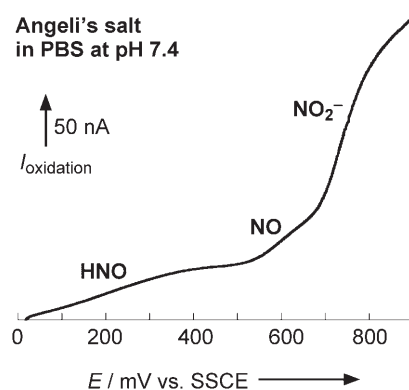


*K. W. Fried, C. M. Schneider, K.-W. Schramm, A. Datta, N. Chahbane, C. Corsten, D. R. Powell, D. Lenoir, A. Kettrup, P. Terranova, G. I. Georg, K. K. Rozman**

890 – 897

From Dioxin to Drug Lead—The Development of 2,3,7,8-Tetrachlorophenothiazine


Studying Angeli's salt decomposition: The nature of the reactive nitrogen species (HNO, NO, NO₂⁻) released by Angeli's salt, a potent pharmacological agent for the treatment of cardiovascular diseases, was determined by using combined electrochemical and spectrophotometric studies.



C. Amatore, S. Arbault, C. Ducrocq,* S. Hu, I. Tapsoba*

898 – 903

Angeli's Salt (Na₂N₂O₃) is a Precursor of HNO and NO: a Voltammetric Study of the Reactive Intermediates Released by Angeli's Salt Decomposition

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

* Author to whom correspondence should be addressed.

BOOKS

Apoptosis and Cancer Therapy: From Cutting-Edge Science to Novel Therapeutic Concepts · K. M. Debatin and S. Fulda (Eds.)

T. Wieder 904

Author Index 905 Preview 906

Keyword Index 905

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

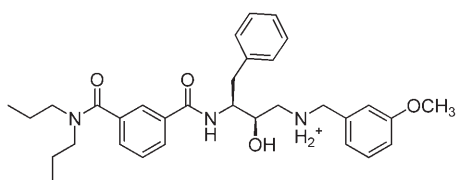
Issue 5, 2007, was published online on April 30, 2007.

CORRIGENDUM

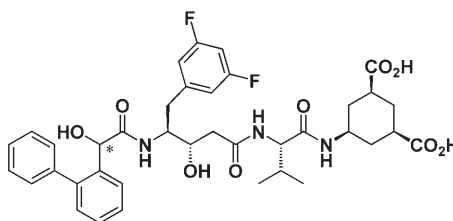
The structure of the docked ligands was omitted in error. The editorial office apologises for this.

V. Limongelli, L. Marinelli,* S. Cosconati,
H. A. Braun, B. Schmidt, E. Novellino**Ensemble-Docking Approach on
BACE-1: Pharmacophore Perception
and Guidelines for Drug Design***ChemMedChem* 2007, 2, 667–678

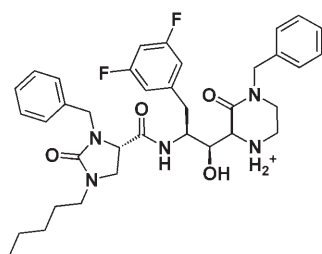
DOI 10.1002/cmdc.200600314



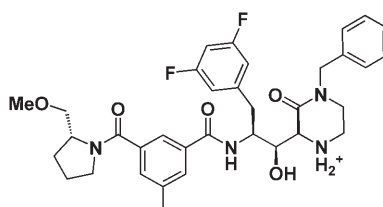
1
(IC₅₀ = 200 nM)



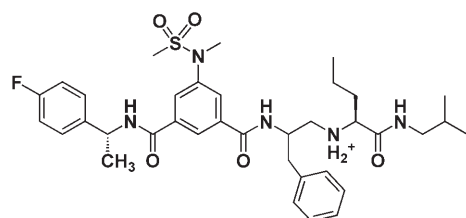
2
(IC₅₀ = 20 nM)



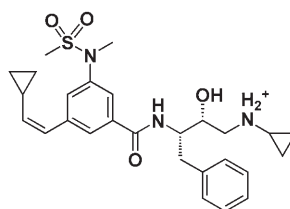
3
(IC₅₀ = 1 nM)



4
(IC₅₀ = 1.4 nM)



5
(IC₅₀ = 4 nM)



6
(IC₅₀ = 35 nM)