CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY

06/2007

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http://www.interscience.wiley.com

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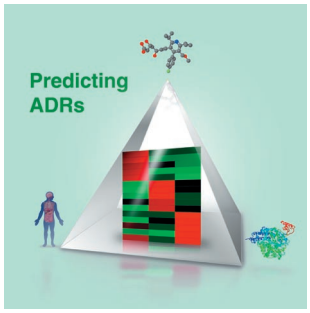
Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE



The cover picture shows the 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.)

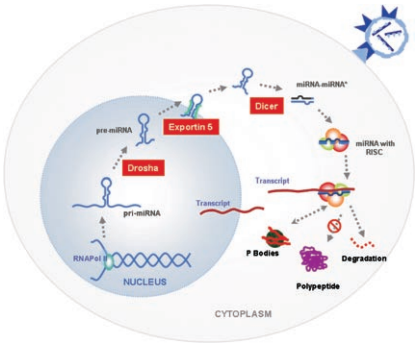
NEWS

REVIEWS

ESSAYS

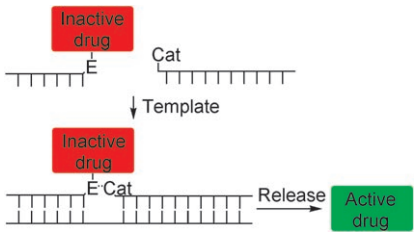
The challenges ahead: In this essay we describe and discuss issues facing the global pharmaceutical market, investigating the basis for many of these issues and highlighting the hurdles the industry needs to overcome, especially as they relate to the chemical sciences.

HIGHLIGHTS



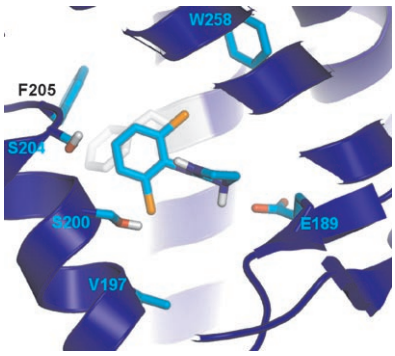
microRNAs are a recently discovered class of small noncoding RNAs which have been shown to regulate critical biological processes in higher eukaryotes. The regulatory impacts of microRNAs are now shown to encompass biological processes ranging from growth and development to oncogenesis and host–pathogen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

CONCEPTS



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.

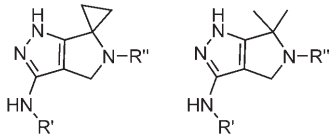
COMMUNICATIONS



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).

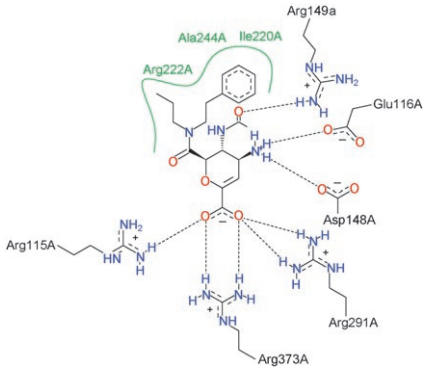
FULL PAPERS

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*



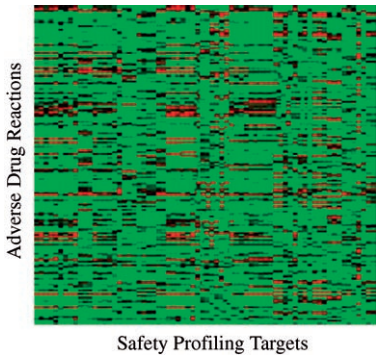
An improved class of CDK2/cyclin A inhibitors based on a bicyclic pyrrolo-[3,4-c]pyrazole scaffold is presented. Conventional and polymer-assisted solution phase chemistry provided a way of generating compounds with interesting biochemical and cellular characteristics. Optimization of the physical properties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

*K. Stierand, M. Rarey**



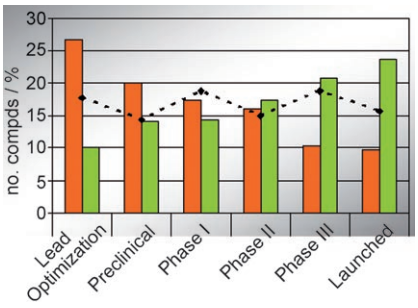
The visualization of protein ligand complexes is an important medium in the discussion of (structure-based) drug design results between the modeler and the medicinal chemist. The new software tool POSEVIEW automatically generates 2D diagrams of given complexes, containing the ligand and the amino acids 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*



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*



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.

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

* Author to whom correspondence should be addressed.

BOOKS

SERVICE

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

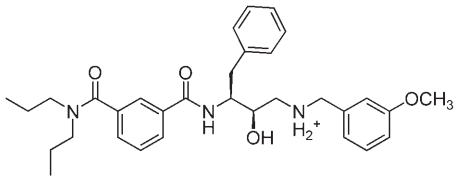
The structure of the docked ligands was omitted in error. The editorial office apologises for this.

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

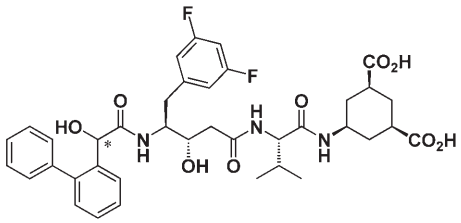
Ensemble-Docking Approach on BACE-1: Pharmacophore Perception and Guidelines for Drug Design

ChemMedChem **2007**, *2*, 667–678

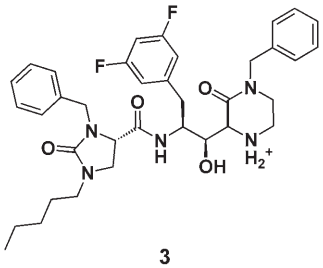
DOI 10.1002/cmdc.200600314



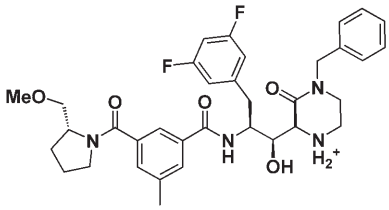
1
(IC_{50} = 200 nM)



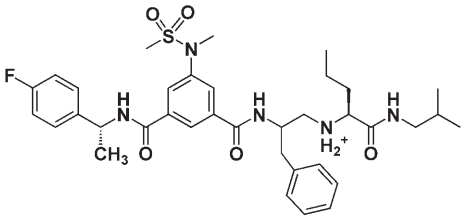
2
(IC_{50} = 20 nM)



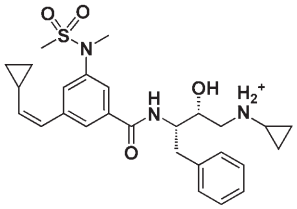
3
(IC_{50} = 1 nM)



4
(IC_{50} = 1.4 nM)



5
(IC_{50} = 4 nM)



6
(IC_{50} = 35 nM)

