

08/2006



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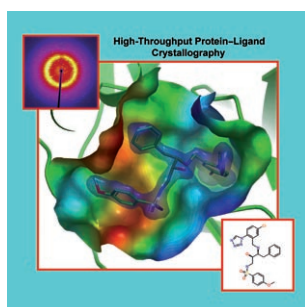
Full text:



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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 a compound bound to thrombin, as determined by automated protein-ligand crystallography. The picture illustrates how a diffraction pattern can be automatically analysed to reveal the binding mode of a compound given a 2D chemical structure and a known 3D structure for the protein. The compound shown was developed by means of fragment-based drug discovery, in which the binding of small, low-affinity molecules is determined by crystallography. This approach to drug discovery is enabled by the automation of protein-ligand crystallography. For details, see the full paper by W. T. M. Mooij et al. on p. 827 ff.

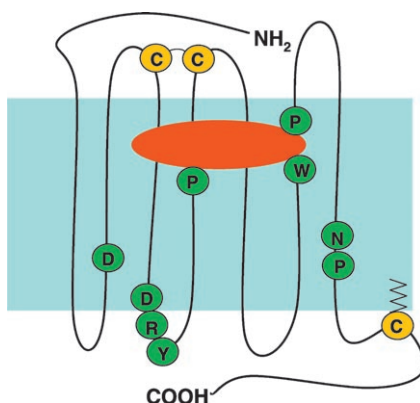
NEWS

From our sister journals

756 – 757

REVIEWS

GPCR-directed drug discovery is pursued today with modern approaches including combinatorial library design, structural biology, molecular informatics, and advanced screening technologies for the identification of new compounds that specifically activate or inhibit GPCRs. This Review outlines future progress that may relate today's discoveries to the development of new medicines.



E. Jacoby,* R. Bouhelal, M. Gerspacher, K. Seuwen

760 – 782

The 7TM G-Protein-Coupled Receptor Target Family

B. Marshall*

783 – 802

Helicobacter Connections



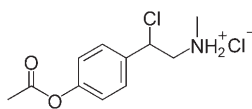
Devotion: In 1984 Barry Marshall performed a risky self experiment. Against a backdrop of skepticism from the mainstream in gastroenterology, the only way he was able to demonstrate that peptic ulcers are caused by bacterial infection was to drink a culture of *H. pylori*. For this discovery and the ensuing improvements in the treatment of ulcers, Marshall and J. Robin Warren shared the 2005 Nobel Prize for Physiology or Medicine.

HIGHLIGHTS

H. Rehwinkel,* H. Schäcke

803 – 805

GR Ligands: Can We Improve the Established Drugs?



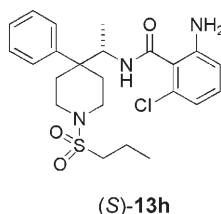
Glucocorticoids (GCs) represent the most effective therapy for acute and chronic inflammatory disorders, yet they can elicit severe side effects. New classes of GC receptor ligands appear to have all of the benefits and fewer side effects and have prompted new research into an old drug target. Compound A (shown) is the latest addition to this exciting development.

COMMUNICATIONS

C. W. Lindsley,* Z. Zhao, W. H. Leister, J. O'Brien, W. Lemaire, D. L. Williams Jr., T.-B. Chen, R. S. L. Chang, M. Burno, M. A. Jacobson, C. Sur, G. G. Kinney, D. J. Pettibone, P. R. Tiller, S. Smith, N. N. Tsou, M. E. Duggan, P. J. Conn, G. D. Hartman

807 – 811

Design, Synthesis, and In Vivo Efficacy of Glycine Transporter-1 (GlyT1) Inhibitors Derived from a Series of [4-Phenyl-1-(propylsulfonyl)piperidin-4-yl]methyl Benzamides

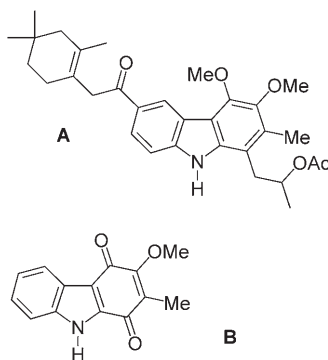


An iterative analogue library synthesis approach rapidly delivered (S)-13h, a potent, reversible, and selective GlyT1 inhibitor. (S)-13h selectively increased glycine levels in the prefrontal cortex to 340% of basal levels and significantly enhanced prepulse inhibition in mice. Thereby, providing strong support for the development of novel antipsychotics based on the NMDA hypofunction hypothesis of schizophrenia.

T. A. Choi, R. Czerwonka, W. Fröhner, M. P. Krah, K. R. Reddy, S. G. Franzblau,* H.-J. Knölker*

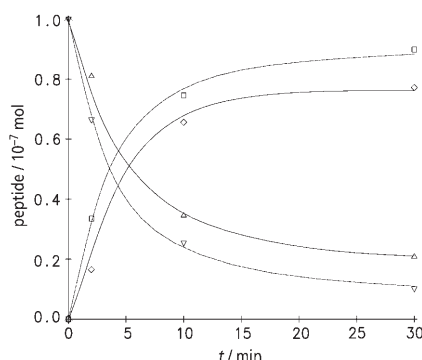
812 – 815

Synthesis and Activity of Carbazole Derivatives Against *Mycobacterium tuberculosis*



A series of carbazole derivatives was tested for inhibition of *Mycobacterium tuberculosis* growth and a mammalian cell line. Among several compounds with anti-TB activity, carbazoles A and B showed MIC values of $4.0 \mu\text{g mL}^{-1}$ ($8 \mu\text{M}$) and $2.2 \mu\text{g mL}^{-1}$ ($9 \mu\text{M}$) respectively, against *M. tuberculosis* and were relatively nontoxic for the mammalian cell line.

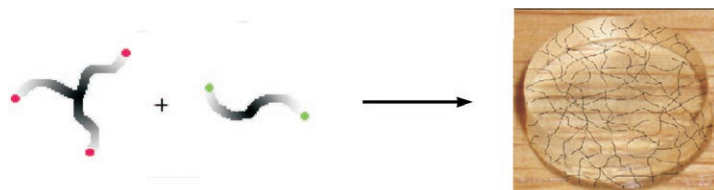
The permeability of phospholipid vesicles to a class I-restricted epitope derived from the melanoma-associated protein, gp100_{280–288}, and its possible effects on epitope degradation by fibroblast-expressed proteolytic enzymes were studied. The results indicate that the majority of the peptide may not be contained within the lipid vesicles when administered for vaccination.




A. Cavazza, M. Marini, G. C. Spagnoli, M. Adamina, L. G. Roda*

816 – 820

Permeability of Phospholipid Vesicles to the Tumor Antigen Epitope gp100_{280–288}



 **New lysine-based dendrimers** which upon reaction with a poly(ethylene glycol) di-activated ester afford a soft flexible hydrogel that can be used to seal a wound in the sclerotomy. These wounds are made during the common

ophthalmic procedure of a vitrectomy. The rheological and swelling properties of the hydrogel can be tuned by either changing the concentration, the type, and/or the generation of the dendrimers.

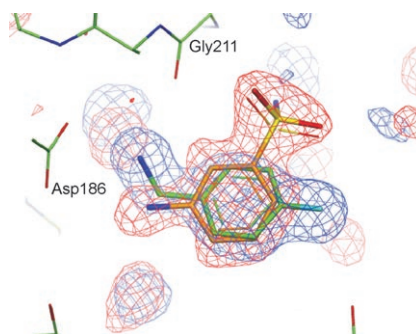
M. Wathier, M. S. Johnson, M. A. Carnahan, C. Baer, B. W. McCuen, T. Kim, M. W. Grinstaff*

821 – 825

In Situ Polymerized Hydrogels for Repairing Scleral Incisions Used in Pars Plana Vitrectomy Procedures

FULL PAPERS


An approach to automate protein–ligand crystallography is presented, featuring a novel ligand placement procedure that seeks solutions with sensible protein–ligand interactions and ligand geometries. The methods described significantly increase the number of structures available to structure-based drug design, and enable fragment-based drug design by crystallography.

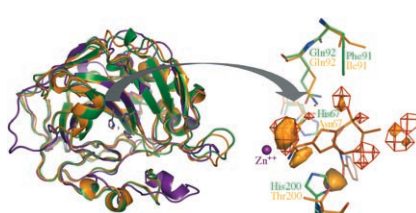


W. T. M. Mooij, M. J. Hartshorn, I. J. Tickle,* A. J. Sharff, M. L. Verdonk, H. Jhoti

827 – 838

Automated Protein–Ligand Crystallography for Structure-Based Drug Design

 **Elucidation of selectivity-determining features:** several 3D QSAR methods were applied to a set of about 140 ligands to identify features which determine selectivity towards carbonic anhydrases I, II, and IV. This study describes how protein and ligand information may be exploited simultaneously and provides a synopsis of the approaches used therein.



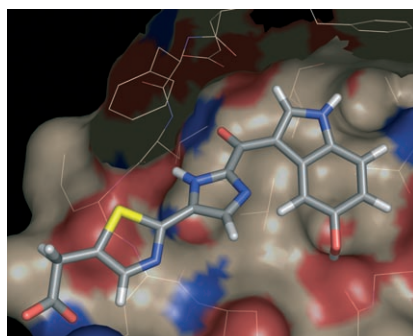
A. Hillebrecht, C. T. Supuran, G. Klebe*

839 – 853

Integrated Approach Using Protein and Ligand Information to Analyze Selectivity- and Affinity-Determining Features of Carbonic Anhydrase Isozymes

J. Degen, M. Rarey*

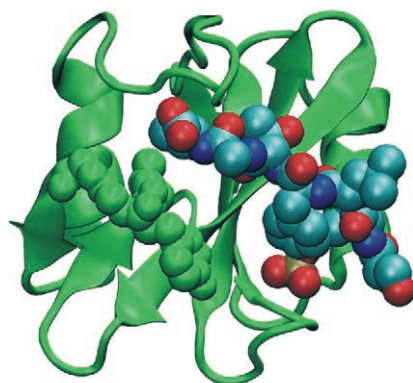
854 – 868

FLEXNovo: Structure-Based Searching in Large Fragment Spaces

Filtering through: A novel molecular design software package, FLEXNovo, based on the concept of chemical fragment spaces, has been applied to inhibitor design for four targets of pharmaceutical interest. FLEXNovo is shown to reproduce known structural motifs and binding modes. The results underline the importance of using target-specific (tailored) filter functions as well as pharmacophore-type constraints for guiding the search process.

K. Hampel, I. Kaufhold, M. Zacharias, F. D. Böhmer, D. Imhof*

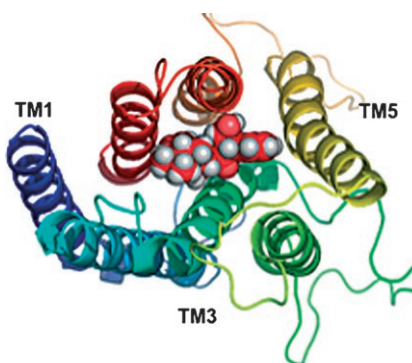
869 – 877

Phosphopeptide Ligands of the SHP-1 N-SH2 Domain: Effects on Binding and Stimulation of Phosphatase Activity

High-affinity peptides that target the N-terminal SH2 domain of SHP-1 were investigated for their ability to stimulate the phosphatase activity of both wild-type and mutant enzyme forms. This study is based on initial investigations of the structural requirements for the SHP-1 N-SH2 ligand binding of peptides derived from the natural interaction partner Ros EGLN-pY2267-MVL (image: PDB code 1aya).

J. Y.-c. Peng, N. Vaidehi,* S. E. Hall, W. A. Goddard III*

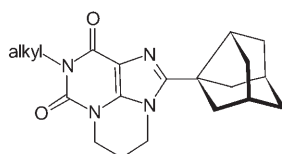
878 – 890

The Predicted 3D Structures of the Human M1 Muscarinic Acetylcholine Receptor with Agonist or Antagonist Bound

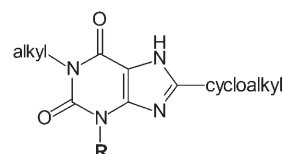
The power of prediction: The 3D structure of the human M1 muscarinic receptor and the binding sites of seven agonists and antagonists were predicted using the MembStruk and HierDock methods. The results correlate well with mutagenesis data and measured binding affinities. The predicted binding site provides structural insight that will aid structure-based drug design for better ligands.

S. Weyler, F. Fülle, M. Diekmann, B. Schumacher, S. Hinz, K.-N. Klotz, C. E. Müller*

891 – 902

Improving Potency, Selectivity, and Water Solubility of Adenosine A₁ Receptor Antagonists: Xanthines Modified at Position 3 and Related Pyrimido[1,2,3-*cd*]purinediones

The structure–activity relationships of 3-substituted xanthine derivatives were investigated. 1-Butyl-3-(3-hydroxypropyl)-8-(3-noradamantyl)xanthine exhibited sub-nanomolar K_i values for rat and human adenosine A₁ receptors and was



highly A₁-selective. 8-Alkyl-2-(3-noradamantyl)pyrimido[1,2,3-*cd*]purine-8,10-diones represent a new class of potent, selective adenosine A₁ receptor antagonists.

BOOKS

Modern Biopharmaceuticals: Design, Development and Optimization · J. Knäblein	G. Kauffmann	903
The Adrenergic Receptors in the 21st Century · D. M. Perez (Ed.)	B. Schmidt	904

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