

12/2006



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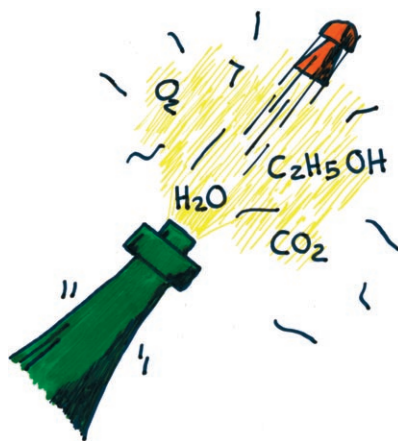
Full text:



<http://www.interscience.wiley.com>

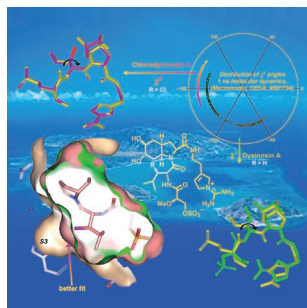
*ChemMedChem*, European in origin but international in scope, deals with all aspects of drug discovery. It is co-owned by a group of European chemical societies and is published by Wiley-VCH. Contributions in *ChemMedChem* cover medicinal and pharmaceutical sciences, drug design, drug development and 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](http://www.chemmedchem.org) under EarlyView®



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## COVER PICTURE



**The cover picture shows** the cyanobacterial linear peptides dysinosin A ( $R=H$ ) and chlorodysinosin A ( $R=Cl$ ), members of the aeruginosin family of cyanobacterial linear peptides. Their structures and absolute configurations were determined by total synthesis and X-ray co-crystallization with the enzyme thrombin. The presence of one chlorine atom in the D-leucine residue of chlorodysinosin A remarkably increases the inhibition potency against thrombin and Factor VIIa relative to dysinosin A. Molecular mechanics simulations starting from the bound conformations of dysinosin A and its chloro analogue suggest a more restricted sampling of conformations for the latter around the  $\chi^1$  dihedral angle. The chlorine atom in chlorodysinosin A may also contribute to lipophilicity, leading to a better fit in the hydrophobic  $S_3$  pocket, as illustrated in the partial X-ray co-crystal structure. The background of the picture shows Lizard Island in North Queensland, Australia, where dysinosin A was isolated from the Dysideidae family of marine sponges. For details, see the Review by S. Hanessian on p. 1300 ff.

## NEWS

From our sister journals

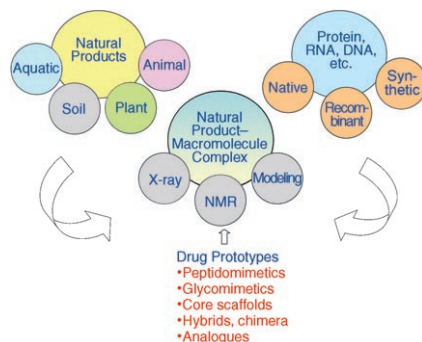
1296 – 1297

## REVIEWS

S. Hanessian\*

1300 – 1330

## Structure-Based Organic Synthesis of Drug Prototypes: A Personal Odyssey



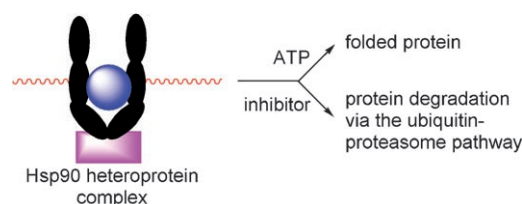
A “reorientation” of the concept of total synthesis of natural products emphasizes a biology-inspired, chemistry-driven approach without compromising the sanctity of basic research and the noble objectives of co-worker training in an academic setting. Structure-based organic synthesis provides a unique framework to capitalize on data gleaned from the bioactivity of natural products in conjunction with X-ray crystallography, molecular modeling, and NMR spectroscopy for the design and synthesis of new drug prototypes.

## MINIREVIEWS

S. Chaudhury, T. R. Welch, B. S. J. Blagg\*

1331 – 1340

## Hsp90 as a Target for Drug Development



**Blocking the chaperones:** Heat shock protein 90 (Hsp90) has emerged as a promising target for the treatment of cancer, Alzheimer's and Parkinson's dis-

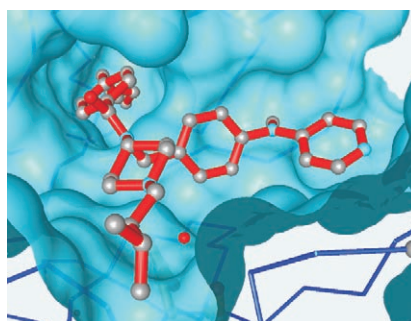
eases, motor impairments, multiple sclerosis, and other disorders. Progress toward the development of both N- and C-terminal inhibitors is described.

## COMMUNICATIONS


C. Boss, O. Corminboeuf, C. Grisostomi, S. Meyer, A. F. Jones, L. Prade, C. Binkert, W. Fischli, T. Weller, D. Bur\*

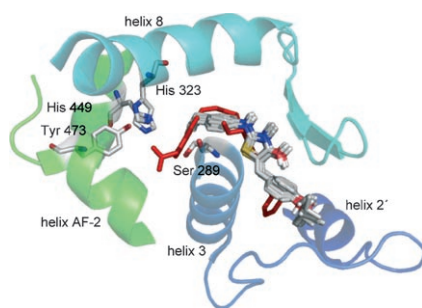
1341 – 1345

## Achiral, Cheap, and Potent Inhibitors of Plasmepsins I, II, and IV



**A novel class of molecules** targeting aspartic proteinases from *P. falciparum* is described. Synthesis of these easily available, achiral, and highly potent molecules was supported by structural information and eventually allowed the identification of compounds highly active against three vacuolar aspartic proteinases. In a red blood cell assay, the growth of *P. falciparum* (strain K1) could be effectively prevented.

 **Probabilistic Neural Networks (PNNs)** were used for the retrieval of peroxisome proliferator-activated receptor (PPAR) modulators from a large compound collection. Four out of nine compounds tested in cell-based assays exhibited an agonistic effect toward PPAR $\gamma$ , one toward PPAR $\alpha$ . The experimental binding mode of a potent ligand (red) of PPAR $\gamma$  is compared with the predicted orientation of another ligand shown by the superposition of several high-ranking docking solutions.

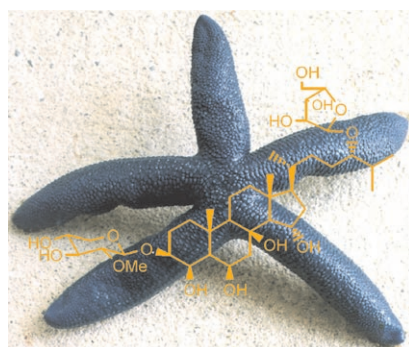


*S. Derksen, O. Rau, P. Schneider, M. Schubert-Zsilavecz, G. Schneider\**

**1346 – 1350**

**Virtual Screening for PPAR Modulators Using a Probabilistic Neural Network**

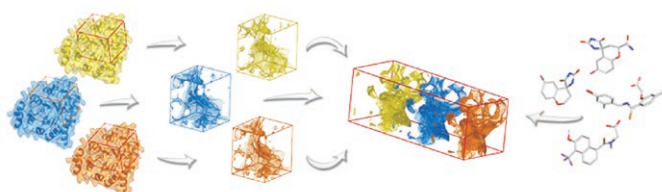
**Improving NGF:** Granuloside A was rediscovered from a different starfish and found to enhance the neuritogenic activity of nerve growth factor up to 40-fold. The glycoside at the side chain seemed to be important for its activity. This effect is attributable to both enhancement and maintenance of the phosphorylation of MAP kinase ERK1/2.




*J. Qi, C. Han, Y. Sasayama, H. Nakahara, T. Shibata, K. Uchida, M. Ojika\**

**1351 – 1354**

**Granuloside A, a Starfish Steroid Glycoside, Enhances PC12 Cell Neuritogenesis Induced by Nerve Growth Factor through an Activation of MAP Kinase**



 **Multiple protein structures** can be addressed simultaneously in a single docking calculation with "in situ cross-docking". For ligands that interact with the flexible protein aldose reductase, the approach is able to identify the correct

protein conformer and reproduce the experimental binding mode. Ligands that inhibit two closely related enzymes with different  $K_i$  values can be investigated as well.

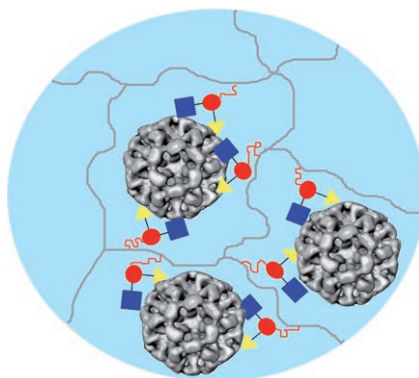
*M. Zentgraf, J. Fokkens, C. A. Sotriffer\**

**1355 – 1359**

**Addressing Protein Flexibility and Ligand Selectivity by "in situ Cross-Docking"**

## FULL PAPERS

**Trapped!** Hydrogels have potential for use as prophylactic drugs against norovirus infection, as they absorb virus particles with high affinity. Virus entrapped in the hydrogel would be rendered harmless as it is cleared from the body. This approach could be useful in the worldwide fight against viral gastroenteritis outbreaks.



*Y. Zhang, Q. Yao, C. Xia, X. Jiang, P. G. Wang\**

**1361 – 1366**

**Trapping Norovirus by Glycosylated Hydrogels: a Potential Oral Antiviral Drug**

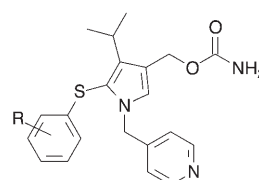
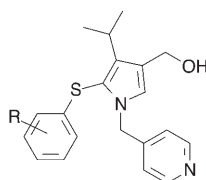
R. Di Santo,\* R. Costi, M. Artico, G. Miele,  
A. Lavecchia, E. Novellino, A. Bergamini,  
R. Cancio, G. Maga

1367–1378

**Arylthiopyrrole (AThP) Derivatives as Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors: Synthesis, Structure–Activity Relationships, and Docking Studies (Part 1)**



**AThPs are potent anti-HIV-1 agents** that target reverse transcriptase. Compounds such as those shown are highly active against HIV-1 in cell-based assays. Moreover, selected derivatives showed interesting activities against clinically



relevant, drug-resistant RT forms carrying K103N and Y181I mutations. Docking experiments were also performed to rationalize some SARs and resistance data.

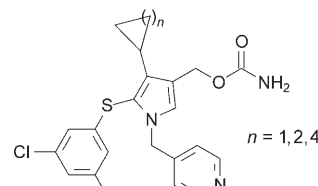
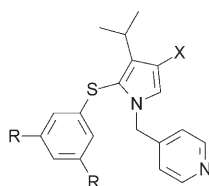
A. Lavecchia, R. Costi, M. Artico, G. Miele,  
E. Novellino, A. Bergamini, E. Crespan,  
G. Maga, R. Di Santo\*

1379–1390

**Arylthiopyrrole (AThP) Derivatives as Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors: Synthesis, Structure–Activity Relationships, and Docking Studies (Part 2)**



**AThPs are potent NNRTIs** endowed with antiviral activities in cell-based assays. The effect of substitution at positions 3 and 4 of the pyrrole ring (examples shown) toward biological properties was studied, and the most active



derivatives showed interesting activities against clinically relevant, drug-resistant RT forms (K103N, Y181I, and L100I). Docking simulations helped to explain some SAR and resistance data.



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

\* Author to whom correspondence should be addressed.

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