

07/2006



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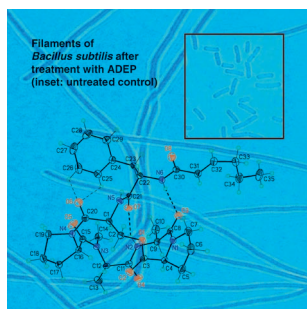
Full text:



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Some articles in this issue have already appeared online in Wiley InterScience. See [www.chemmedchem.org](http://www.chemmedchem.org) under EarlyView®

## COVER PICTURE



The cover picture shows an electron micrograph of *Bacillus subtilis* before (inset) and after treatment with an acyldepsipeptide (ADEP, structure shown), which blocks cell division to produce filamented cell structures. Exploration of the synthesis of enopeptin-type acyldepsipeptide antibiotics has led to new compounds with improved in vitro antibiotic activity against Gram-positive pathogens and in vivo activity in mouse models of lethal infection. For details, see the Communication by B. Hinzen et al. on p. 689 ff.

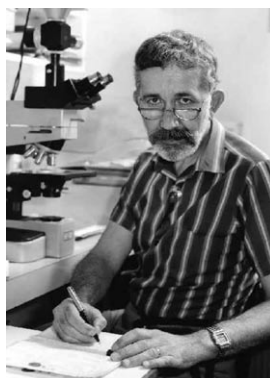
## NEWS

From our sister journals

668 – 669

## REVIEWS

When J. Robin Warren noticed small curved and spiral bacilli closely applied to the epithelial surface of a patient with severe chronic gastritis, it was a "fact" that bacteria could not live in the acidic environment of the stomach. In collaboration with Barry J. Marshall, Warren went on to confirm that *Helicobacter pylori* is a pathogenic bacterium associated with ulcers and chronic gastritis. In 2005, they were awarded the Nobel Prize for Physiology or Medicine.



J. R. Warren\*

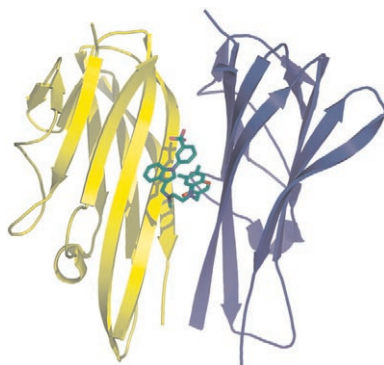
672 – 685

**Helicobacter: The Ease and Difficulty of a New Discovery (Nobel Lecture)**

## HIGHLIGHTS

T. Berg\*

687–688

Inhibition of TNF- $\alpha$  Signaling: Divide and Conquer**Invasion of the little green molecules.**

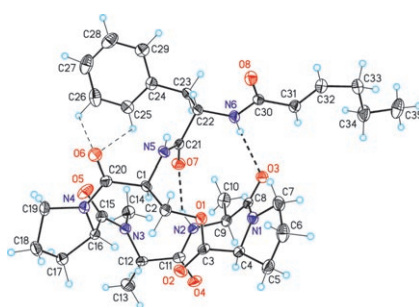
A small molecule was identified that inhibits binding between the trimeric cytokine tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and its receptors by an unusual mechanism. This molecule actively displaces one of the TNF- $\alpha$  polypeptides to form a stable complex with the remaining two protein subunits. (Graphic reprinted with permission; Copyright 2005, AAAS.)

## COMMUNICATIONS

B. Hinzen,\* S. Raddatz, H. Paulsen,  
T. Lampe, A. Schumacher, D. Häbich,  
V. Hellwig, J. Benet-Buchholz,  
R. Endermann, H. Labischinski,  
H. Brötz-Oesterhelt

689–693

## Medicinal Chemistry Optimization of Acyldepsipeptides of the Enopeptin Class Antibiotics

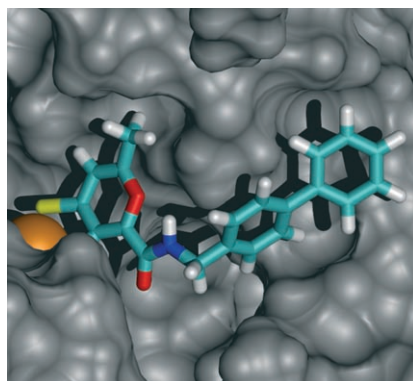


**The therapy of life-threatening infections** is significantly weakened by the global spread of antibiotic resistance. Synthetic exploration of enopeptin type acyldepsipeptide antibiotics revealed a remarkable structure–activity relationship. New compounds with improved in vitro antibiotic activity against Gram-positive pathogens (including multi-resistant strains) and in vivo activity in mouse models of lethal infection are described.

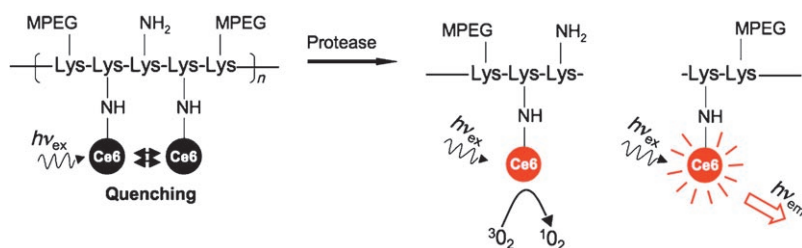
J. A. Lewis, J. Mongan, J. A. McCammon,\*  
S. M. Cohen\*

694–697

## Evaluation and Binding-Mode Prediction of Thiopyrone-Based Inhibitors of Anthrax Lethal Factor



**Lethal weapon:** Heterocyclic chelators have been identified for use in anthrax lethal factor inhibitors (LFI). A complete LFI (AM-2S, shown), which consists of a thiopyrone chelator and a simple biphenyl backbone, has an  $IC_{50}$  value in the low micromolar range. Potential binding modes for AM-2S were computationally examined, and the importance of a molecular surface solvent–solute boundary in such studies was demonstrated.



**Photodynamic therapy with a molecular switch:** Both singlet oxygen generation and near-infrared fluorescence from a photosensitizer were markedly decreased by conjugating multiple chlor-

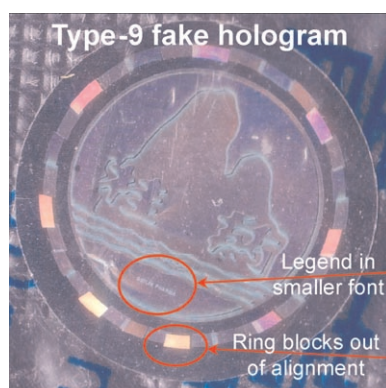
$\text{in}_{\text{e6}}$  photosensitizers onto a polypeptide backbone. Protease-mediated cleavage of the backbone results in the formation of degraded probes, which are highly phototoxic and fluorescent.

Y. Choi, R. Weissleder,  
C.-H. Tung\*

698 – 701

**Protease-Mediated Phototoxicity of a Polylysine-Chlorin<sub>e6</sub> Conjugate**

**Vacuum is not the limit:** direct analysis in real time (DART), a new MS ionization method, allows probing of pharmaceuticals under atmospheric pressure, thus bypassing lengthy sample preparation steps and enhancing throughput. DART allows rapid screening of solid drugs at almost constant temperature which decreases errors in mass measurement and improves the identification of potentially harmful unknowns. This is important for identifying counterfeit drugs (fake hologram shown).

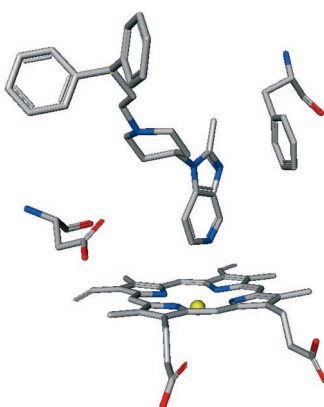


F. M. Fernández,\* R. B. Cody, M. D. Green,  
C. Y. Hampton, R. McGready,  
S. Sengaloundeth, N. J. White,  
P. N. Newton

702 – 705

**Characterization of Solid Counterfeit Drug Samples by Desorption Electrospray Ionization and Direct-analysis-in-real-time Coupled to Time-of-flight Mass Spectrometry**

**The discovery of UK-374,503** started from a high-throughput screening hit that was a potent Type II P450 2D6 inhibitor and which displayed no antiviral activity. The optimisation of affinity for the CCR5 receptor while reducing concerns about P450 inhibition and the subsequent introduction of antiviral effects were key milestones for the project.

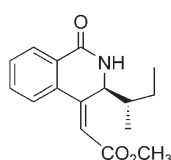


D. Armour, M. J. de Groot, M. Edwards,  
M. Perros, D. A. Price,\* B. L. Stammen,  
A. Wood

706 – 709

**The Discovery of CCR5 Receptor Antagonists for the Treatment of HIV Infection: Hit-to-Lead Studies**

**A protein destroyer is blocked:** (*S,S,Z*)-methyl-2-(3-*sec*-butyl-1-oxo-2,3-dihydroisoquinolin-4(1*H*)-ylidene)acetate is a potent low-molecular-weight inhibitor of  $\mu$ -calpain ( $\text{IC}_{50} = 25 \text{ nM}$ ). Several derivatives of this compound were synthesized and tested as inhibitors of the calpain protease to gain insight into their structure-activity relationships.



R. Chicharro, M. Alonso, M. T. Mazo,  
V. J. Arán, B. Herradón\*

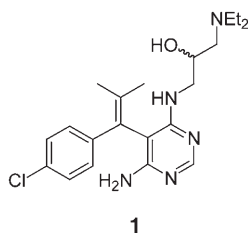
710 – 714

**Derivatives of 3-*sec*-Butyl-1-oxo-2,3-dihydroisoquinoline as Inhibitors of  $\mu$ -Calpain**

N. R. Yepuri, R. Haritakul, R. Griffith,  
S. P. Leach, P. A. Keller\*

715–717

### The Synthesis and Testing of Arenearylpyrimidylmethanes as Antimalarial Agents

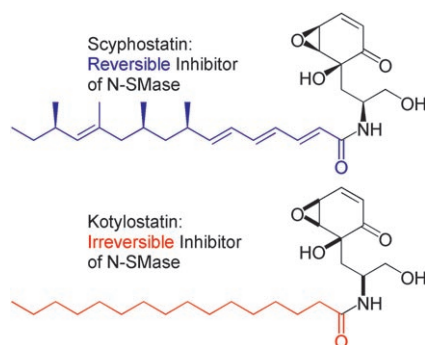


**Do the two-step:** A new convergent synthesis of the arenearylpyrimidylmethane (AAPM) scaffold requires only two steps, and subsequent derivatisation yielded the potent lead **1** against a multidrug-resistant malarial strain. The presence of atropisomerism with this class of compounds is also reported.

V. Wascholowski, A. Giannis,\*  
E. N. Pitsinos\*

718–721

### Influence of the Scyphostatin Side Chain on the Mode of Inhibition of Neutral Sphingomyelinase



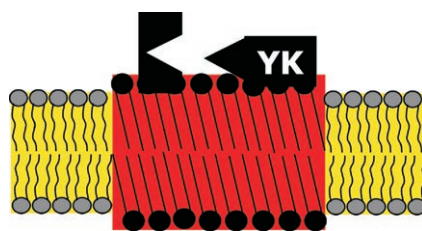
**The combination of structural novelty** and significant biological activity has made scyphostatin the focus of many synthetic efforts and the prototype for novel N-SMase inhibitors. Potent, specific inhibitors of these enzymes may be valuable in deciphering their biological role and lead to the development of novel therapeutics. Scyphostatin and kolylostatin, although structurally related, exhibit different modes of inhibition towards N-SMase.

## FULL PAPERS

S. C. D. N. Lopes, A. Fedorov,  
M. A. R. B. Castanho\*

723–728

### Chiral Recognition of D-Kyotorphin by Lipidic Membranes: Relevance Toward Improved Analgesic Efficiency

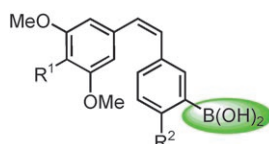


**A matter of preference:** The dipeptide YK (kyotorphin) has analgesic properties; the L,D enantiomer is more effective than its L,L counterpart. One property that contributes to this improved efficiency is the preference of D-kyotorphin for rigid patches in lipid membranes, where receptors are usually located.

H. Nakamura,\* H. Kuroda, H. Saito,  
R. Suzuki, T. Yamori, K. Maruyama,  
T. Haga

729–740

### Synthesis and Biological Evaluation of Boronic Acid Containing *cis*-Stilbenes as Apoptotic Tubulin Polymerization Inhibitors



**Is boronic acid** an alternative functional group for drug design? A series of boronic acid containing *cis*-stilbenes as potent inhibitors of tubulin polymerization was synthesized by the introduction of boronic acid as an acceptor-type functional group into the aromatic ring B of the combretastatin framework.

## BOOKS

Methods and Principles in Medicinal Chemistry, Vol. 24: G Protein-Coupled Receptors as Drug Targets: Analysis of Activation and Constitutive Activity • R. Seifert, T. Weiland (Eds.)

DNA Methylation: Approaches, Methods and Applications • M. Esteller (Ed.)

Metal-based Neurodegeneration: From Molecular Mechanisms to Therapeutic Strategies • R. R. Crichton, R. J. Ward

Immunodominance: The Choice of the Immune System • J. A. Frelinger (Ed.)

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Issue 6, 2006, was published online on May 31, 2006.

## CORRIGENDUM

S. Jayaprakash, Y. Iso, B. Wan,  
 S. G. Franzblau, A. P. Kozikowski\*

The IC<sub>50</sub> value for mefloquine in Table 2 of this article is incorrectly reported as 128  $\mu\text{M}$ ; the correct value is 12  $\mu\text{M}$ . The editorial office apologizes for this error.

**Design, Synthesis, and SAR Studies of Mefloquine-Based Ligands as Potential Antituberculosis Agents**

*ChemMedChem* **2006**, *1*, 593–597

DOI 10.1002/cmdc.200600010

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