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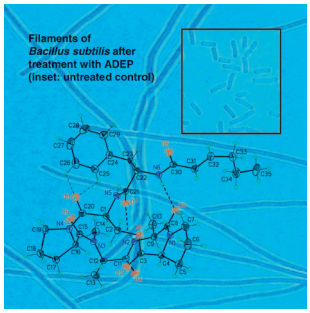
Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

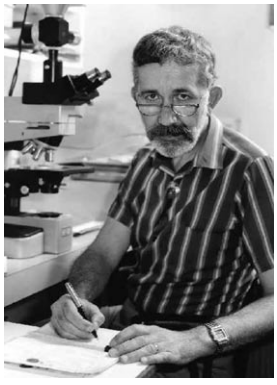
COVER PICTURE



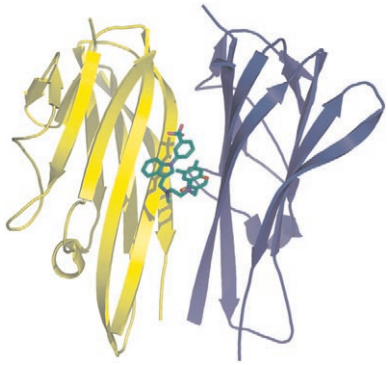
The cover picture shows an electron micrograph of *Bacillus subtilis* before (inset) and after treatment with an acyldepsipeptide (ADEP, structure shown), which blocks cell division to produce filamented cell structures. Exploration of the synthesis of enopeptin-type acyldepsipeptide antibiotics has 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

REVIEWS

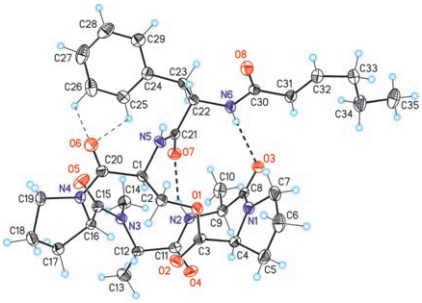


HIGHLIGHTS

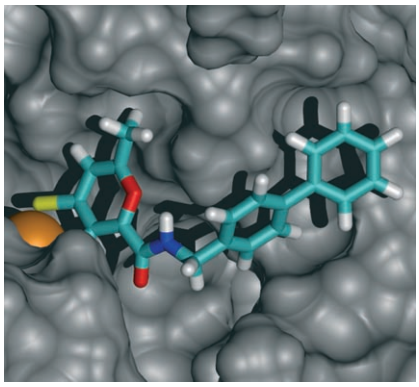


Invasion of the little green molecules. A small molecule was identified that inhibits binding between the trimeric cytokine tumor necrosis factor α (TNF-α) and its receptors by an unusual mechanism. This molecule actively displaces one of the TNF-α polypeptides to form a stable complex with the remaining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

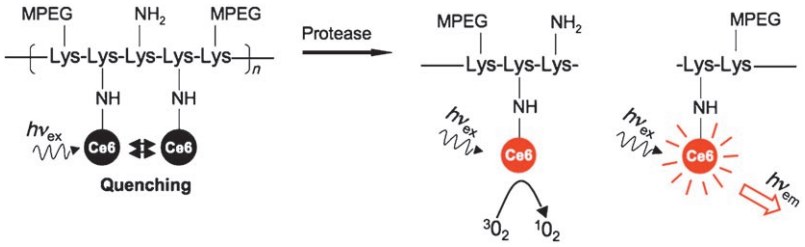
COMMUNICATIONS



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.

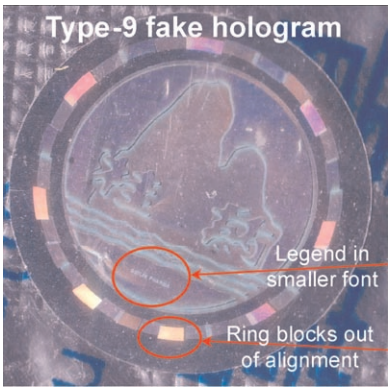


Lethal weapon: Heterocyclic chelators have been identified for use in anthrax lethal factor inhibitors (LFi). A complete LFi (AM-2S, shown), which consists of a thiopyrone chelator and a simple biphenyl backbone, has an IC_{50} value in the low micromolar range. Potential binding modes for AM-2S were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

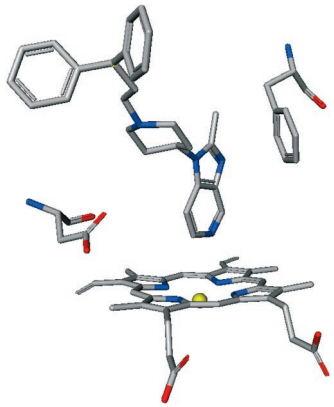


Photodynamic therapy with a molecular switch: Both singlet oxygen generation and near-infrared fluorescence from a photosensitizer were markedly decreased by conjugating multiple chlorin$_{e6}$ photosensitizers onto a polypeptide backbone. Protease-mediated cleavage of the backbone results in the formation of degraded probes, which are highly phototoxic and fluorescent.

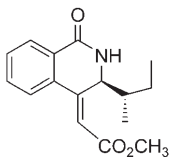
Vacuum is not the limit: direct analysis in real time (DART), a new MS ionization method, allows probing of pharmaceuticals under atmospheric pressure, thus bypassing lengthy sample preparation steps and enhancing throughput. DART allows rapid screening of solid drugs at almost constant temperature which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

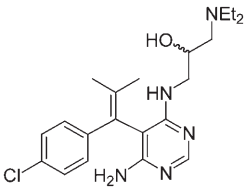


The discovery of UK-374,503 started from a high-throughput screening hit that was a potent Type II P450 2D6 inhibitor and which displayed no antiviral activity. The optimisation of affinity for the CCR5 receptor while reducing concerns about P450 inhibition and the subsequent introduction of antiviral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



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 μ-calpain (IC_{50} = 25 nM). Several derivatives of this compound were synthesized and tested as inhibitors of the calpain protease to gain insight into their structure–activity relationships.





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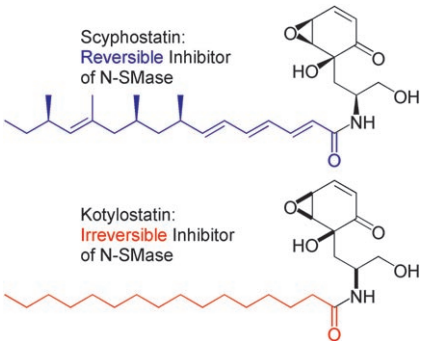
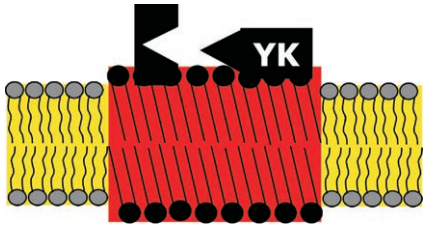
Do the two-step: A new convergent synthesis of the arenearylpyrimidylmethane (AAPM) scaffold requires only two steps, and subsequent derivatisation yielded the potent lead **1** against a multidrug-resistant malarial strain. The presence of atropisomerism with this class of compounds is also reported.

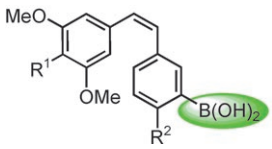


The combination of structural novelty and significant biological activity has made scyphostatin the focus of many synthetic efforts and the prototype for novel N-SMase inhibitors. Potent, specific inhibitors of these enzymes may be valuable in deciphering their biological role and lead to the development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

FULL PAPERS



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.



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

SERVICE

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

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CORRIGENDUM

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

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

ChemMedChem **2006**, *1*, 593–597

DOI 10.1002/cmdc.200600010

The IC_{50} value for mefloquine in Table 2 of this article is incorrectly reported as 128 μM; the correct value is 12 μM. The editorial office apologizes for this error.

