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CHEMISTRY ENABLING DRUG DISCOVERY

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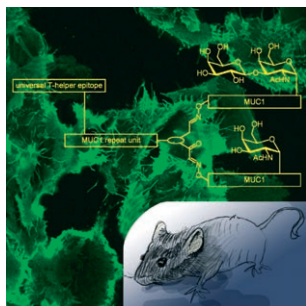
Full text:



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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 human MCF7 mammary adenocarcinoma cells, a cell line which has been used extensively to characterize tumor-associated MUC1 glycoprotein. Cells were analysed by fluorescence-activated cell sorting after being labelled with antibodies induced in mice by a synthetic glycopeptide construct (structure shown) in association with a mild adjuvant suitable for human therapy. This construct, composed of a universal T-helper and three diversely glycosylated tumor-related epitopes, was assembled using a convergent strategy based on two successive oxime ligations. It is the most immunogenic synthetic construct reported to date and is able to elicit antibodies that recognize tumor-related MUC1 on MCF7 cells. (Thanks to T. Cantalupo for the image.) For more details, see the Communication by A. F. Delmas et al. on p. 965 ff.

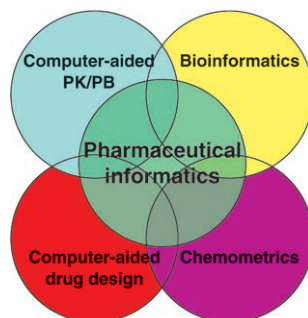
NEWS

From our sister journals

916 – 917

REVIEWS

The power of prediction: Herein some of the approaches and techniques used today to derive in silico models for the prediction of ADMET properties are described. This Review also discusses some of the fundamental requirements for deriving statistically sound and predictive ADMET relationships as well as some of the pitfalls and problems encountered during these investigations.



U. Norinder,* C. A. S. Bergström

920 – 937

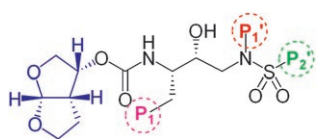
Prediction of ADMET Properties

MINIREVIEWS

A. K. Ghosh,* P. Ramu Sridhar,
N. Kumaragurubaran, Y. Koh, I. T. Weber,
H. Mitsuya

939 – 950

**Bis-Tetrahydrofuran: a Privileged
Ligand for Darunavir and a New
Generation of HIV Protease Inhibitors
That Combat Drug Resistance**



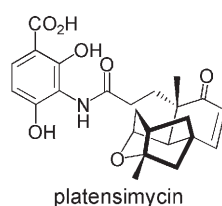
Two inhibitors that incorporate bis-THF as an effective high-affinity P₂ ligand for the HIV-1 protease substrate binding site maintain impressive potency against mutant strains resistant to currently approved protease inhibitors. Crystallographic structures of protein–ligand complexes help to explain the superior antiviral property of these inhibitors and their potency against a wide spectrum of HIV-1 strains.

HIGHLIGHTS

D. Häbich,* F. von Nussbaum*

951 – 954

**Platensimycin, a New Antibiotic and
“Superbug Challenger” from Nature**



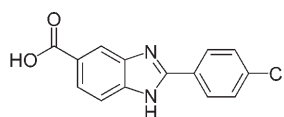
Natural products have once again proven their value as guideposts for unexplored targets. “Old-fashioned” extract screening integrated into an innovative assay set-up has opened a new playground for medicinal chemists. Platensimycin is the first member of a novel class of antibiotics that acts through a clinically unexploited target.

COMMUNICATIONS

C. Dubois, B. Hengerer, H. Mattes*

955 – 958

**Identification of a Potent Agonist of
the Orphan Nuclear Receptor Nurr1**

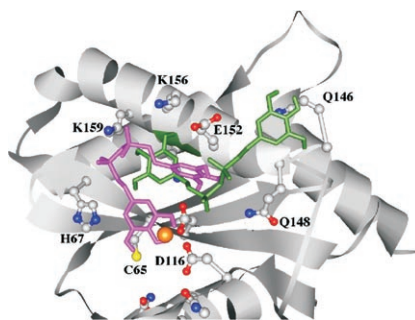


Benzimidazole-based Nurr1 agonists: Combinatorial chemistry and structure-based design were joined together to produce a lead-finding library of compounds focused on the nuclear receptor target family. A second-generation library directed against Nurr1, a specific orphan member of this family, was also prepared. This protocol allowed the discovery of a Nurr1 agonist with an EC₅₀ value of 8 nM.

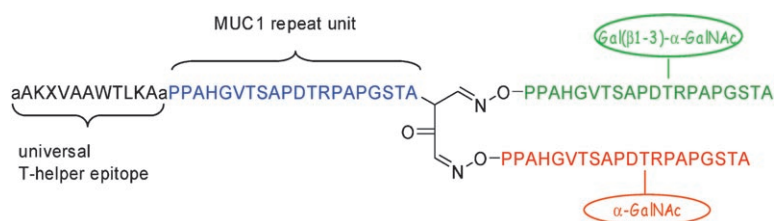
D. C. Meadows, D. J. Tantillo,
J. Gervay-Hague*

959 – 964

**Correlation of Biological Activity with
Active Site Binding Modes of Geminal
Disulfone HIV-1 Integrase Inhibitors**



Binding modes of a series of potent geminal disulfone-containing HIV-1 integrase inhibitors were investigated using AutoDock 3.0. Two major conformations were shared for this series of compounds: a “U-shaped” conformation and an “L-shaped” conformation. The data presented suggest that the U-shaped conformer may be the more biologically relevant conformation and that the design of molecules that are structurally biased in that conformation could lead to more potent analogues.



The glycopeptide construct shown was synthesized using a convergent strategy based on oxime chemical ligation. It is composed of a universal T-helper and three tumor-related epitopes from the human mucin MUC1, a non-glycosylated repeat unit, and two units

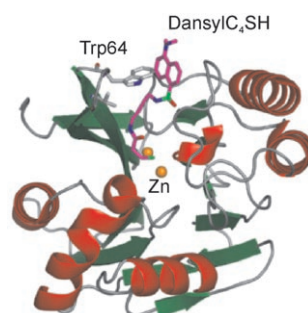
glycosylated with the Tn and TF epitopes, respectively. In association with a mild adjuvant suitable for human therapy, this construct elicited a strong specific immune response in mice, directed against natural tumor-associated structures.

G.-A. Cremer, N. Bureaud, V. Piller, H. Kunz, F. Piller, A. F. Delmas*

965 – 968

Synthesis and Biological Evaluation of a Multiantigenic Tn/TF-Containing Glycopeptide Mimic of the Tumor-Related MUC1 Glycoprotein

A series of fluorescent probes, *N*-(5-(dimethylamino)-1-naphthalenesulfonamido(alkyl)_n)-3-thiopropionamide (DansylC_nSHs), were rationally designed to detect and inhibit metallo-β-lactamase (IMP-1). These compounds were shown to function as fluorescent probes for and inhibitors of metallo-β-lactamases. The X-ray crystallographic structure shown indicates the potential of these agents for use as a new fluorescent probes for metallo-β-lactamases.

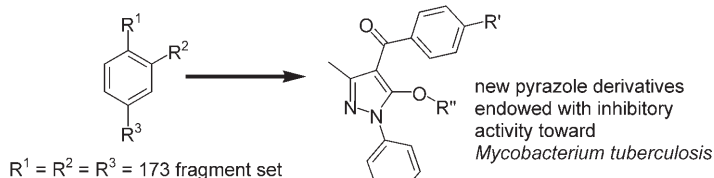


H. Kurosaki,* Y. Yamaguchi,* H. Yasuzawa, W. Jin, Y. Yamagata, Y. Arakawa

969 – 972

Probing, Inhibition, and Crystallographic Characterization of Metallo-β-lactamase (IMP-1) with Fluorescent Agents Containing Dansyl and Thiol Groups

FULL PAPERS



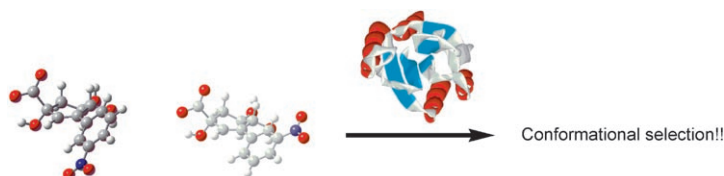
Step by step: Ligand-based virtual screening was applied toward the identification of new compounds targeting *Mycobacterium tuberculosis*. After generating a large virtual library, a realistic

number of hits was selected through a series of filtering steps, leading to the identification of two leads. These were used to synthesize a small series of analogues.

F. Manetti, M. Magnani, D. Castagnolo, L. Passalacqua, M. Botta,* F. Corelli, M. Saddi, D. Deidda, A. De Logu

973 – 989

Ligand-Based Virtual Screening, Parallel Solution-Phase and Microwave-Assisted Synthesis as Tools to Identify and Synthesize New Inhibitors of *Mycobacterium tuberculosis*



Saturation transfer difference (STD) and transferred NOESY experiments were carried out to deduce the bound conformation of a nanomolar inhibitor of *M. tuberculosis* type II dehydroquinase, the third enzyme of the shikimic

acid pathway. One conformation of those present in solution for the competitive 3-nitrophenyl derivative inhibitor is selected when it is bound to the active site of the enzyme.

V. F. V. Prazeres, C. Sánchez-Sixto, L. Castedo, Á. Canales, F. J. Cañada, J. Jiménez-Barbero, H. Lamb, A. R. Hawkins, C. González-Bello*

990 – 996

Determination of the Bound Conformation of a Competitive Nanomolar Inhibitor of *Mycobacterium tuberculosis* Type II Dehydroquinase by NMR Spectroscopy

S. De Luca, M. Saviano, R. Della Moglie,
G. Digilio, C. Bracco, L. Aloj, L. Tarallo,
C. Pedone, G. Morelli*

997 – 1006

Conformationally Constrained CCK8 Analogues Obtained from a Rationally Designed Peptide Library as Ligands for Cholecystokinin Type B Receptor

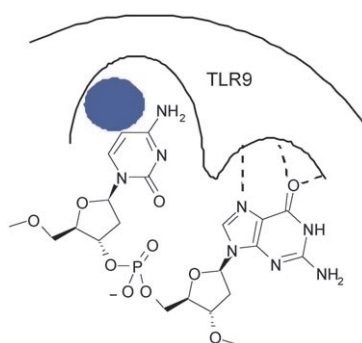


A rationally designed peptide library provided CCK8 analogues as new ligands (in red) for the cholecystokinin type B receptor (blue). In vitro cellular assays were used to determine the binding affinity of the ligands, and $IC_{50} \approx 10 \mu\text{M}$ for the best compounds. NMR structural data of the lead compound confirm that the structure is stabilized by both the cyclic constraint and by interaction with the micelle.

M. Jurk, A. Kritzler, H. Debelak, J. Vollmer,
A. M. Krieg, E. Uhlmann*

1007 – 1014

Structure–Activity Relationship Studies on the Immune Stimulatory Effects of Base-Modified CpG Toll-Like Receptor 9 Agonists

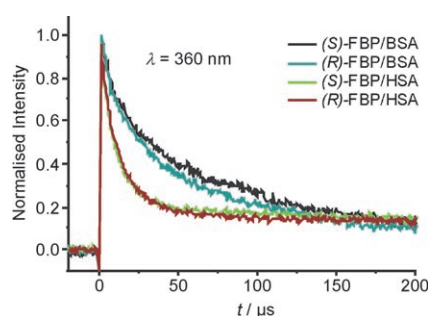


Activation of Toll-like receptors (TLRs) results in stimulation of the innate immune response, including secretion of proinflammatory cytokines, up-regulation of co-stimulatory molecules, and secretion of cytokines and chemokines. In our SAR model, the CpG dinucleotide motif of immune stimulatory oligodeoxynucleotides is recognized by TLR9 by the Hoogsteen site of guanine and the C5 corner of cytosine resulting in potent stimulation of the innate immune response.

I. Vayá, C. J. Bueno, M. C. Jiménez,*
M. A. Miranda*

1015 – 1020

Use of Triplet Excited States for the Study of Drug Binding to Human and Bovine Serum Albumins

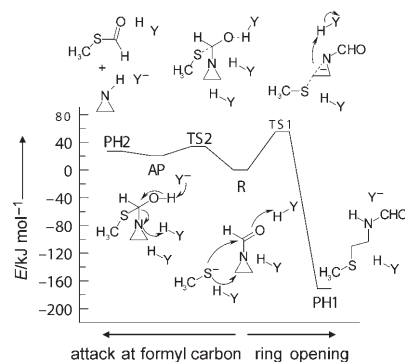


The triplet excited states of (*S*)- and (*R*)-flurbiprofen (FBP) were used as reporters for the microenvironments of the binding sites of serum albumins. Multiexponential fitting of the triplet decays ($\lambda = 360 \text{ nm}$) can be satisfactorily correlated with the distribution of the drug among the two protein binding sites and the bulk solution. Triplet lifetimes and site occupancy are both sensitive to the type of serum albumin used.

R. Vicik, H. Helten, T. Schirmeister,*
B. Engels*

1021 – 1028

Rational Design of Aziridine-Containing Cysteine Protease Inhibitors with Improved Potency: Studies on Inhibition Mechanism



Cysteine proteases are attractive targets for the development of new drugs, as they play pivotal roles in many diseases. Aziridine-containing cysteine protease inhibitors have been developed. To investigate the influence of the aziridine ring substituents on the kinetics and thermodynamics of the ring-opening reaction in detail, quantum chemical computations were performed. *N*-formylated aziridine was predicted to be much more effective than the nonformylated system.

SERVICE

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