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CHEMISTRY ENABLING DRUG DISCOVERY

04/2007

CHEMICAL & MEDICINAL CHEMISTRY

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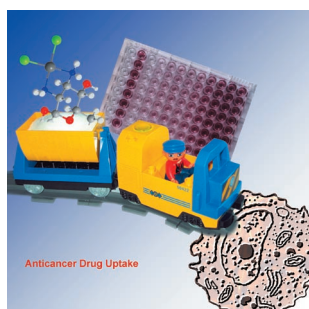
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Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE



The cover picture shows a train charged with sugar driving into a tumor cell, representing the concept of a targeted transfer of a platinum—carbohydrate complex. The coupling of the sugar to the platinum moiety was carried out in the quest for more selective tumor-inhibiting drugs. For details, see the Full Paper by A. A. Nazarov, B. K. Keppler, et al. on p. 505 ff. (LEGO® DUPLO® train used with special permission. ©2007 The LEGO Group.)

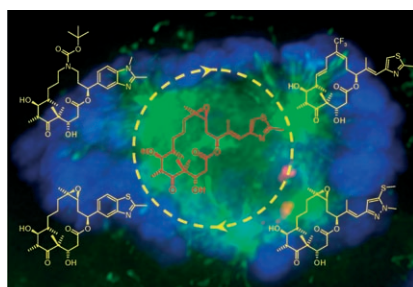
NEWS

Spotlights on our Sister Journals

394 – 395

REVIEWS

Epothilones have captured the attention of chemists, biologists, and drug researchers ever since they were found to inhibit human cancer cell growth through a "taxol-like" mechanism over ten years ago. Today, at least seven epothilone-derived agents have entered clinical trials. However, additional new and exciting analogues have emerged in recent years, suggesting that the potential of these natural products to serve as leads for new anticancer drugs is far from exhausted.



K.-H. Altmann,* B. Pfeiffer, S. Arseniyadis, B. A. Pratt, K. C. Nicolaou*

396 – 423

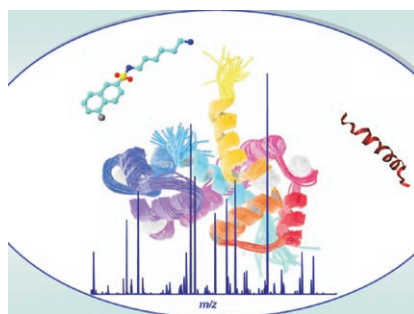
The Chemistry and Biology of Epothilones—The Wheel Keeps Turning

MINIREVIEWS

A. Sinz*

425–431

Investigation of Protein–Ligand Interactions by Mass Spectrometry



Mass spectrometry represents a versatile method, which allows screening for protein–ligand interactions from minute sample amounts within a short time. Methods comprise the analysis of intact noncovalent protein–ligand complexes in the gas phase, hydrogen/deuterium exchange of protein backbone amide hydrogens, and photoaffinity labeling.

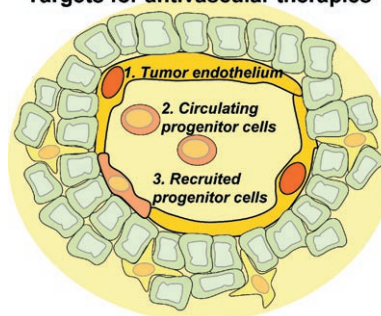
HIGHLIGHTS

K. Temming,* R. J. Kok

433–435

Antivascular Therapies: Targets Beyond the Vessel Wall

Targets for antivascular therapies


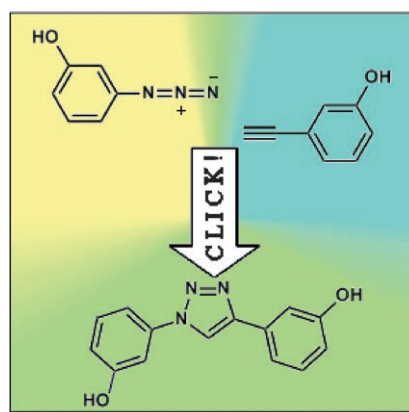


Unravelling the involvement of multiple cell types in angiogenesis yields more and more cells and pathways as druggable targets. It was recently demonstrated that blockade of circulating endothelial progenitor cell (CEP) recruitment improved therapeutic outcome of treatment with vascular disrupting agents (VDA). This knowledge paves the way for novel drugs and drug combinations in cancer therapy.

COMMUNICATIONS

T. Pirali, S. Gatti, R. Di Brisco, S. Tacchi, R. Zaninetti, E. Brunelli, A. Massarotti, G. Sorba, P. L. Canonico, L. Moro, A. A. Genazzani, G. C. Tron,* R. A. Billington

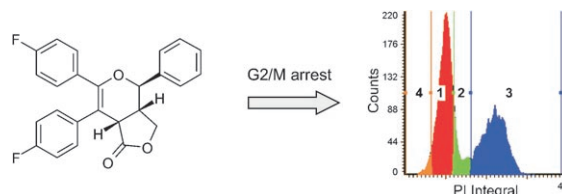
437–440

 Estrogenic Analogues Synthesized by Click Chemistry


Fast and simple: the complexity of steroids can be mimicked by two phenol rings linked together by the easiest of reactions: the click [3+2] azide-alkyne cycloaddition.

C. A. Fuhrer, E. Grüter, S. Ruetz, R. Häner*

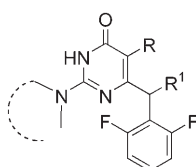
441–444

 *Cis*-Stilbene Derived Furopyranones Show Potent Antiproliferative Activity by Inducing G2/M Arrest


Bicyclic furopyranones containing the *cis*-stilbene motif are described. The derivatives show antiproliferative activity in A549 and KB31 cells. The presence of

the *cis*-stilbene motif is critical for biological activity. The compounds induce cell cycle arrest at the G2/M transition.

A new series of dihydro-alkylamino-benzyl-oxypyrimidines (N,N-DABOs) showing a broad activity spectrum against NNRTI-resistant mutants have been reported. Such compounds display a slow, tight binding to HIV-1 RT.



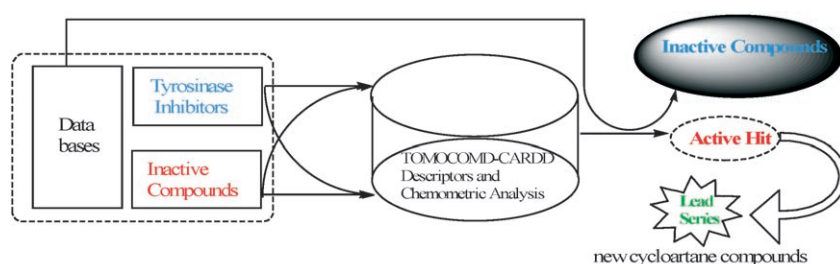
R. Cancio, A. Mai,* D. Rotili, M. Artico, G. Sbardella, I. Clotet-Codina, J. A. Esté, E. Crespan, S. Zanolli, U. Hübscher, S. Spadari, G. Maga*

445 – 448

Slow-, Tight-Binding HIV-1 Reverse Transcriptase Non-Nucleoside Inhibitors Highly Active against Drug-Resistant Mutants



FULL PAPERS



Y. Marrero-Ponce,* M. T. H. Khan, G. M. Casañola Martín, A. Ather, M. N. Sultankhodzhaev, F. Torrens, R. Rotondo

449 – 478

Prediction of Tyrosinase Inhibition Activity Using Atom-Based Bilinear Indices

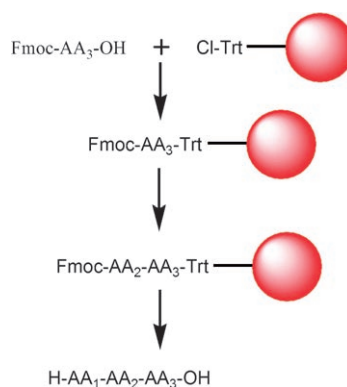


Putting the descriptors to work: Molecular parametrization is easily calculated from 2D molecular information, thus improving the chances of an in silico discovery of viable leads and minimizing the use of resources. Having demon-

strated success with a training data set of compounds with considerable structural variation, this method decreases the degree of uncertainty in virtual screening.

The human intestinal transporter

hPEPT1 facilitates the cellular uptake of dipeptides and tripeptides arising from degradation of proteins present in the diet. Many small, biologically active substances display low bioavailability due to low permeability or low solubility, but linking such drugs to a peptidic promoiety recognized by hPEPT1, can result in a prodrug complex that can be transported into the systemic circulation.



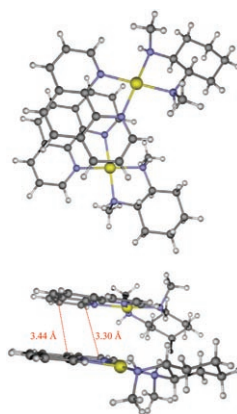
K. Thorn, R. Andersen, J. Christensen, P. Jakobsen, C. U. Nielsen, B. Steffansen, M. Begtrup*

479 – 487

Design, Synthesis, and Evaluation of Tripeptidic Promoiety Targeting the Intestinal Peptide Transporter hPEPT1

Four platinum(II) metallointercalating complexes

of 1,10-phenanthroline with the chiral ancillary ligands trans-(1*R*,2*R*)- and trans-(1*S*,2*S*)-1,2-diaminocyclohexane and *N,N'*-dimethyl-(1*R*,2*R*)- and *N,N'*-dimethyl-(1*S*,2*S*)-1,2-diaminocyclohexane have been synthesised and characterised. [Pt(*S,S*-dach)(phen)](ClO₄)₂ was more active than cisplatin in all cell lines tested and shows only partial cross-resistance to cisplatin in two cisplatin resistant cell lines.



D. M. Fisher, P. J. Bednarski, R. Grünert, P. Turner, R. R. Fenton,* J. R. Aldrich-Wright*

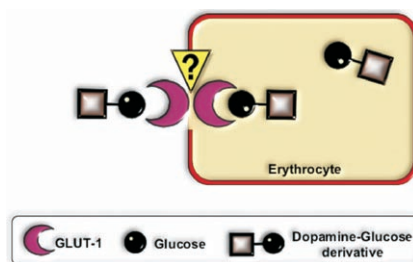
488 – 495

Chiral Platinum(II) Metallointercalators with Potent in vitro Cytotoxic Activity

I. García-Álvarez, L. Garrido,
A. Fernández-Mayoralas*

496 – 504

Studies on the Uptake of Glucose Derivatives by Red Blood Cells

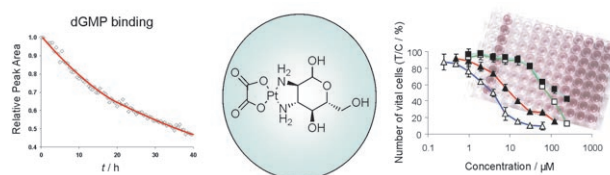


Drug uptake in the brain is strictly regulated by the blood-brain barrier. To test the viability of using the glucose carrier GLUT-1 to facilitate the transport of bioactive compounds across cell membranes, the uptake of several glucosyl dopamine derivatives by erythrocytes was studied using HPLC and ^1H MAS NMR techniques together with studies using specific GLUT-1 inhibitors.

I. Berger, A. A. Nazarov,* C. G. Hartinger,
M. Groessl, S.-M. Valiahd, M. A. Jakupec,
B. K. Keppler*

505 – 514

A glucose derivative as natural alternative to the cyclohexane-1,2-diamine ligand in the anticancer drug oxaliplatin?



Novel oxaliplatin analogues based on naturally available, enantiomerically pure 2,3-diaminoglucose were synthesized to exploit the glycolytic energy production of cells for selective cellular uptake. The new complexes were evalu-

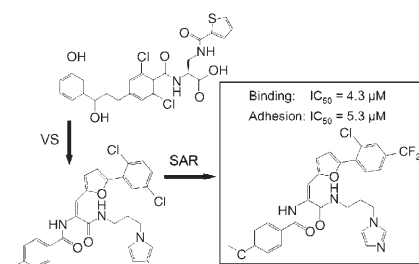
ated for their affinity toward dGMP by capillary electrophoresis and for their in vitro cytotoxicity by a colorimetric microculture assay in the human cancer cell lines HeLa, CH1, SW480, and U2OS.

M. Shoda, T. Harada, K. Yano,
F. L. Stahura, T. Himeno, S. Shiojiri,
Y. Kogami, H. Kouji, J. Bajorath*

515 – 521



Virtual Screening Leads to the Discovery of an Effective Antagonist of Lymphocyte Function-Associated Antigen-1

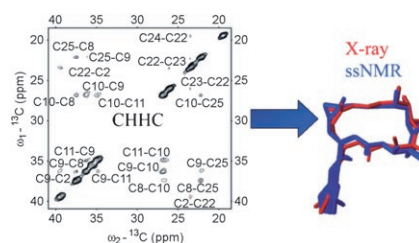


Antagonists of the LFA-1/ICAM-1 interaction: Computational screening identified a novel LFA-1 antagonist that could be transformed into a lead by structure-activity relationship analysis and analogue design. Shown are the template compound, a known LFA-1 antagonist (top left), the new antagonist identified by ligand-based virtual screening and substructure searching (bottom left), and a compound with further increased potency (boxed).

A. Lange, T. Schupp, F. Petersen,
T. Carlomagno, M. Baldus*

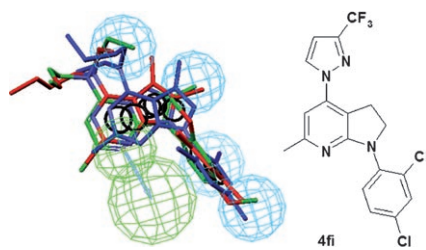
522 – 527

High-Resolution Solid-State NMR Structure of an Anticancer Agent



The 3D solid-state NMR structure of Epothilone B. Solid-state Nuclear Magnetic Resonance (ssNMR) has recently made significant progress in probing molecular structures. Epothilones are natural compounds produced by the myxobacterium *Sorangium cellulosum* and exhibit high cytotoxic activity against multiresistant tumor cells. Herein, we show that two 2D CHHC correlation experiments are sufficient to rapidly assemble a high-resolution structure of Epothilone B.

The structure–activity relationships of two new classes of potent and selective CRF₁ receptor antagonists is described. The metabolic stability of one of the two classes was dramatically improved by replacing the alkyl chains in the upper region of the antagonists. Several compounds (an example is shown) exhibited low plasma clearance, good oral bioavailability, high brain penetration, and a pharmacological response in an in vivo model.



R. Arban, R. Benedetti, G. Bonanomi, A.-M. Capelli, E. Castiglioni, S. Contini, F. Degiorgis, P. Di Felice, D. Donati, E. Fazzolari, G. Gentile, C. Marchionni, C. Marchioro, F. Messina, F. Micheli, B. Oliosi, F. Pavone, A. Pasquarello, B. Perini, M. Rinaldi, F. M. Sabbatini, G. Vitulli, P. Zarantonello, R. Di Fabio,* Y. St-Denis*

528 – 540

Cyclopenta[*d*]pyrimidines and Dihydropyrrolo[2,3-*d*]pyrimidines as Potent and Selective Corticotropin-Releasing Factor 1 Receptor Antagonists

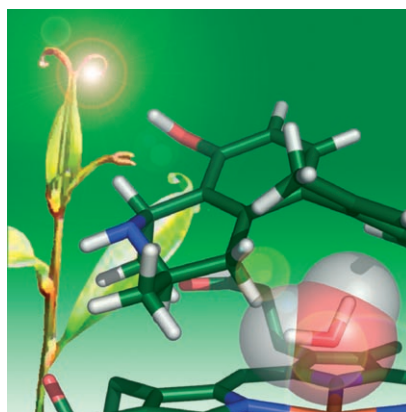
K. F. Schwedhelm, M. Horstmann, J. H. Faber, Y. Reichert, G. Bringmann, C. Faber*

541 – 548

The Novel Antimalarial Compound Dioncophylline C Forms a Complex with Heme in Solution



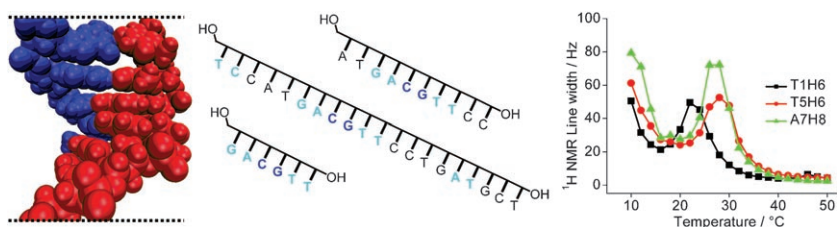
Dioncophylline C, a promising antimalarial agent derived from the tropical liana *Triphyophyllum peltatum* is investigated when binding to its presumed target, heme. Structures of the observed complex are calculated from NMR paramagnetic relaxation measurements and the possible mode of complex stabilization is discussed.



G. He, A. Patra, K. Siegmund, M. Peter, K. Heeg, A. Dalpke, C. Richert*

549 – 560

Immunostimulatory CpG Oligonucleotides Form Defined Three-Dimensional Structures: Results from an NMR Study



Structure matters. The innate immune response mediated by Toll-like receptors distinguishes foreign DNA from host DNA. One- and two-dimensional NMR studies show that immunostimulatory

sequences form an unusual 3D structure. Structure information occurs beyond the core hexamer GACGTT and appears to involve the 5' terminus.

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

* Author to whom correspondence should be addressed.

BOOKS

Fundamentals of Early Clinical Drug Development: From Synthesis Design to Formulation • A. F. Abdel-Magid, S. Caron (Eds.)
Protein–Carbohydrate Interactions in Infectious Diseases • C. A. Bewley (Ed.)
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Issue 3, 2007, was published online on March 1, 2007.

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