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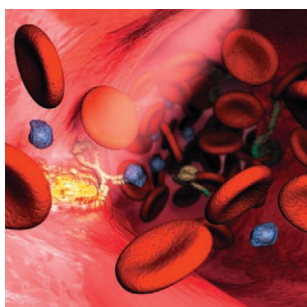
Full text:



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 under EarlyView®

COVER PICTURE



The cover picture shows an impression of a photoactivatable bispecific antibody bound to a tumour. Only the antitumour portion is initially active, allowing tumour cell binding. On irradiation with UV light the T-cell binding site is reactivated, allowing T-cell binding and activation. As anti-T-cell activity is not reactivated outside of the illuminated treatment area, immune activation is highly specific targeted to tumour tissues. For details, see the two back-to-back Communications by C. H. Self, S. Thompson, et al. on pp. 1587 and 1591 ff. (BioTransformations Ltd. Image courtesy of the Centre for Design Research.)

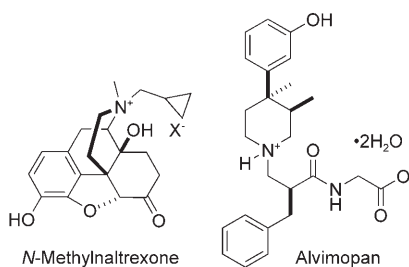
NEWS

Spotlights on our sister journals

1550 – 1551

REVIEWS

Modifying morphine. There has been an extensive amount of research performed during the last ten years on mu opioid receptor antagonists. The positive clinical data generated with *N*-methylnaltrexone and alvimopan has greatly contributed to a renewed interest in this field. In this article we review various chemical classes of mu opioid receptor antagonists and the clinical applications for this class of agents.



A. J. Goodman,* B. Le Bourdonnec,
R. E. Dolle

1552 – 1570

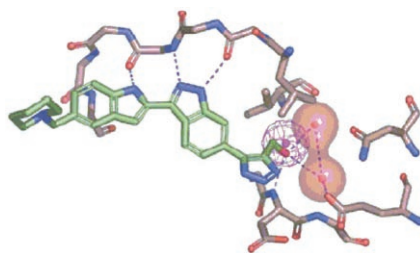
**Mu Opioid Receptor Antagonists:
Recent Developments**

MINIREVIEWS

K. L. Arrington,* V. Y. Dudkin

1571 – 1585

Novel Inhibitors of Checkpoint Kinase 1



Inhibition of Chk1 kinase has garnered attention as a possible complement to DNA-damaging chemotherapeutic agents, widening their therapeutic window. As a result, several distinct classes of Chk1 inhibitors have been recently identified with selected compound advancing to clinical trials stage. This review focuses on the challenges and recent progress achieved in this area from a medicinal chemistry perspective.

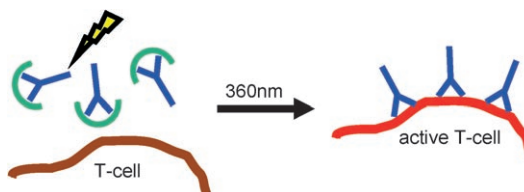
COMMUNICATIONS

C. H. Self,* A. C. Self, J. A. Smith, D. J. Self, S. Thompson*

1587 – 1590



Light-Directed Activation of Human T-Cells



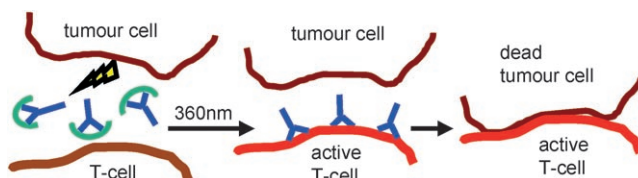
Anti-human CD3 antibodies are rendered inert with a coating of photolabile 2-nitrobenzyl groups until their activity is restored by irradiation with UVA light, at which point the antibodies are free to bind and activate T-cells. Such

antibodies should enable the regulation of cytotoxic T-cell activity at required times and locations in the body. This would have widespread medical application, particularly in the treatment of cancer.

S. Thompson,* R. Stewart, J. A. Smith, C. H. Self*

1591 – 1593

Light Activation of Anti-CD3 in vivo Reduces the Growth of an Aggressive Ovarian Carcinoma



A photoactivatable anti-murine CD3 antibody was constructed. When reactivated in vivo in the presence of tumour pieces it markedly reduces the growth of ovarian carcinoma. Such antibodies

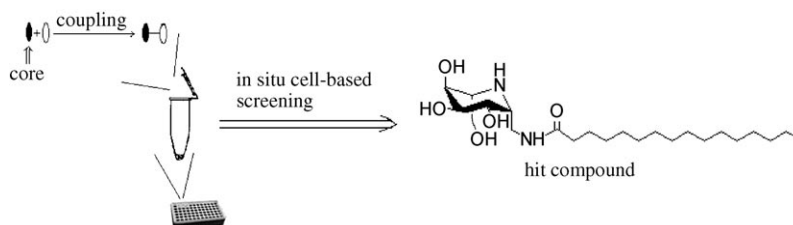
provide a means to target T-cells with a much higher degree of specificity to tumours, whilst minimising side effects in other non-illuminated areas of the body.

L. Zhang, F. Sun, Y. Li, X. Sun, X. Liu, Y. Huang, L.-H. Zhang, X.-S. Ye,* J. Xiao*

1594 – 1597



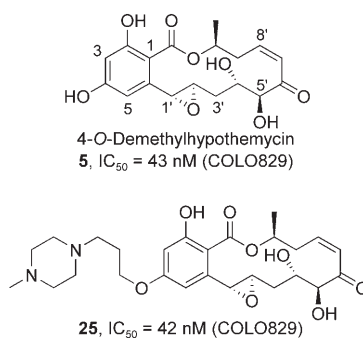
Rapid Synthesis of Iminosugar Derivatives for Cell-Based In Situ Screening: Discovery of "Hit" Compounds with Anticancer Activity



Effective and efficacious drug screening methods are imperative in the drug discovery process. A library has been constructed efficiently and followed by

in situ cell-based screening without product purification. This method led to discovery of several iminosugar derivatives with anticancer activity.

Evaluation of the hypothemycin cytotoxicity SAR identifies the C4'–C8' region of the macrocyclic lactone as relatively intolerant of structural modifications. Manipulation of the 4-position of the resorcylic acid, however, provides new opportunities to improve solubility and pharmacokinetic properties as this site may be modified without negatively impacting cytotoxicity.



B. R. Hearn,* K. Sundermann, J. Cannoy, D. V. Santi

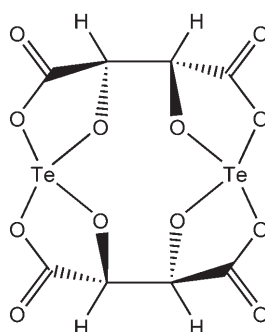
1598 – 1600

Semisynthesis and Cytotoxicity of Hypothemycin Analogues



FULL PAPERS

Synthetic tellurium compounds have protective effects in models of parasitic and viral diseases, autoimmune diseases, kidney diseases, and in protecting dopaminergic neurons and enhancing their function in animal models of Parkinson's disease. This wealth of biological activities prompted us to further develop additional organotellurium compounds with different activity profiles, such as Octa-O-bis-(*R,R*)-tartarate ditellurane (SAS) described herein.

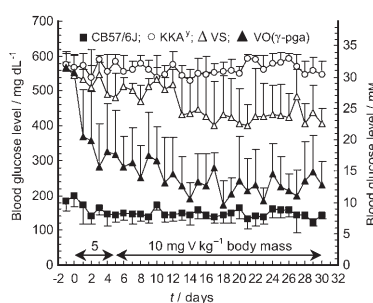


S. Yosef, M. Brodsky, B. Sredni, A. Albeck,* M. Albeck*

1601 – 1606

Octa-O-bis-(*R,R*)-Tartarate Ditellurane (SAS)—a Novel Bioactive Organotellurium(IV) Compound: Synthesis, Characterization, and Protease Inhibitory Activity

Dodging diabetes. Poly(γ -glutamic acid)oxovanadium(IV) complex (VO(γ -pga)) is the first example of orally active oxovanadium(IV)-polymer complex with a VO(O₄) coordination environment that is efficacious in the treatment of type 2 diabetes in mice. It has also holds promise for improved treatment of a range of other metabolic disorders.

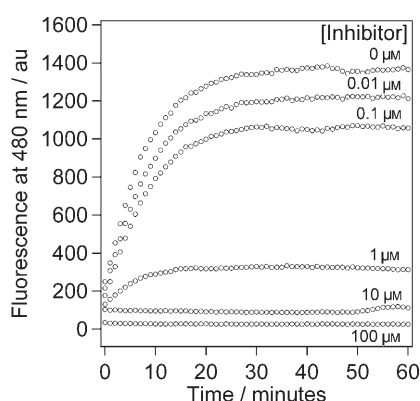


S. Karmaker, T. K. Saha,* Y. Yoshikawa, H. Sakurai

1607 – 1612

Amelioration of Hyperglycemia and Metabolic Syndromes in Type 2 Diabetic KKA^y Mice by Poly(γ -glutamic acid)oxovanadium(IV) Complex

An engineered fibril model associated with Alzheimer's disease, comprising a covalent assembly of four amyloid β peptide (A β) fragments, displays important properties for high-throughput screening of compounds that inhibit A β fibril formation. With this tool, screening studies are complete within one hour instead of a matter of days, as with native A β .



G. T. Dolphin, M. Oubrai, P. Dumy,* J. Garcia*

1613 – 1623

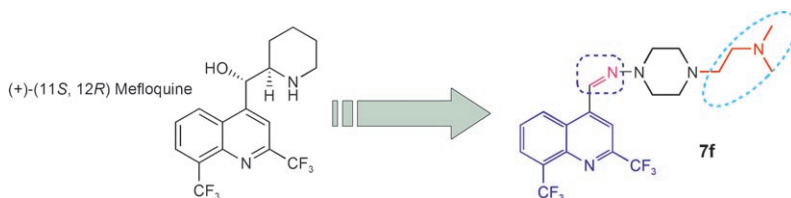
Designed Amyloid β Peptide Fibril—A Tool for High-Throughput Screening of Fibril Inhibitors



J. Mao, Y. Wang, B. Wan,
A. P. Kozikowski,* S. G. Franzblau*

1624 – 1630

Design, Synthesis, and Pharmacological Evaluation of Mefloquine-Based Ligands as Novel Antituberculosis Agents



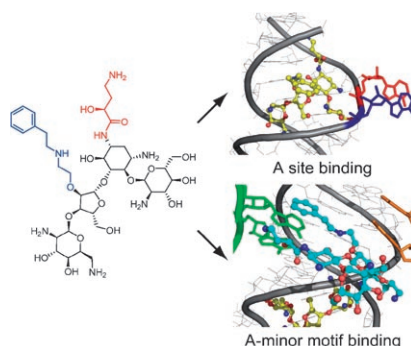
Tuberculosis is among the top five deadly diseases in developing countries. The current TB chemotherapy regimen requires patients to take three to four drugs for a minimum of six months. The key to shortening the current long regi-

men lies in effectively targeting this NRP-TB. To this end, we report herein the design and synthesis of mefloquine-based analogues and the evaluation of their activity against R-TB and NRP-TB.

J. Kondo, K. Pachamuthu, B. François,
J. Szychoński, S. Hanessian,* E. Westhof*

1631 – 1638

Crystal Structure of the Bacterial Ribosomal Decoding Site Complexed with a Synthetic Doubly Functionalized Paromomycin Derivative: a New Specific Binding Mode to an A-Minor Motif Enhances in vitro Antibacterial Activity

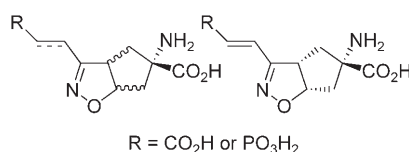


The synthetic paromomycin analogue with the L-haba group and an ether chain with an O-phenethylaminoethyl group could specifically bind to ribosomes in two different modes: 1) the classical binding to the A site and 2) binding to an A-minor motif participating in the recognition of the codon-anticodon helix or in the intersubunit bridges.

P. Conti,* A. Pinto, L. Tamborini,
G. Grazioso, G. De Sarro,
H. Bräuner-Osborne, G. Szabo,
L. Gábor Hársing, C. De Micheli

1639 – 1647

Synthesis of Conformationally Constrained Glutamic Acid Homologues and Investigation of Their Pharmacological Profiles

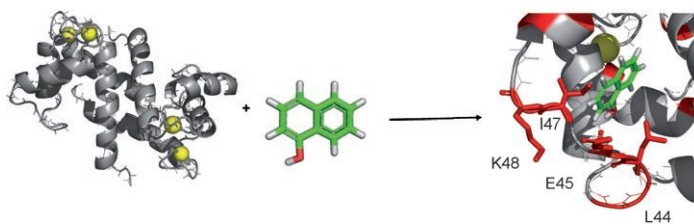


Structurally constrained homologues of glutamic acid were prepared and tested against iGluRs and mGluRs. Amino acid (±)-5 (shown at right, R = CO₂H) emerged as a selective group I mGluR antagonist capable of protecting DBA/2 mice from audiogenic seizures after i.c.v. administration.

Y. Arendt, A. Bhaumik, R. Del Conte,
C. Luchinat,* M. Mori, M. Porcu

1648 – 1654

Fragment Docking to S100 Proteins Reveals a Wide Diversity of Weak Interaction Sites



NMR screening of two S100 proteins which are potential drug targets has been performed with a fragment library. A relatively large variety of interaction regions for various ligands for the two S100 proteins were identified even ap-

plying computer-aided drug design. Our results show that they have only few ligands in common, suggesting that selective leads could be developed starting from the different hits identified in the present work.

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

* Author to whom correspondence should be addressed.

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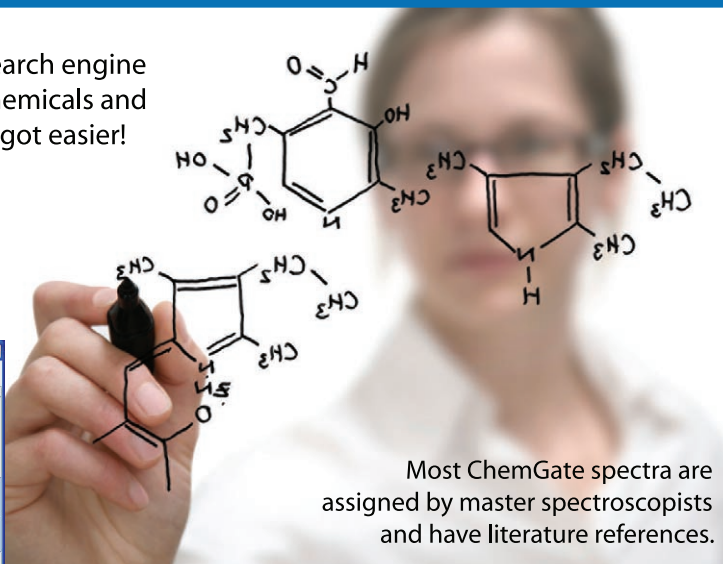
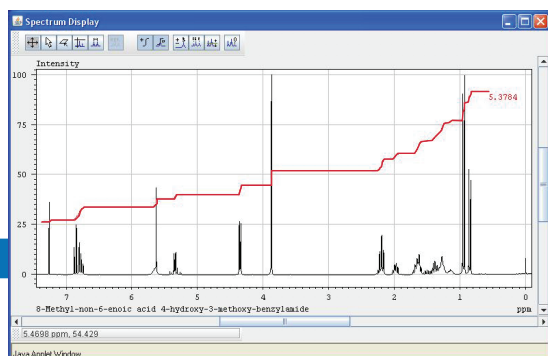
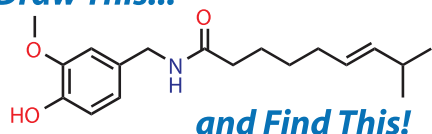
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