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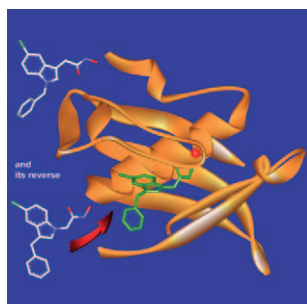
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Most of the articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®.

COVER PICTURE



The cover picture shows a "reverse" indole derivative in complex with *Bacillus stearothermophilus* peptide deformylase (PDF). This compound was selected from a structure–activity relationship study as a potent inhibitor of bacterial PDFs and shows antibacterial activity toward *Bacillus subtilis* as well as other pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus*. For more details, see the Full Paper by I. Artaud et al. on p. 261 ff.

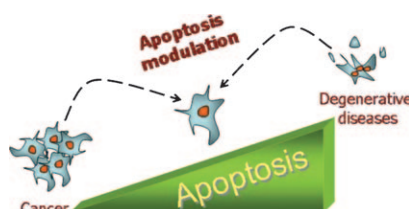
NEWS

Spotlights on our sister journals

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REVIEWS

Cells in the balance: Programmed cell death is an important and stringently controlled process. Aberrancies in its control mechanisms can lead to disease; overactive apoptosis can cause neuro-degenerative disorders, whereas deficient apoptotic activity can lead to cancer. Therefore, controlling apoptotic pathways with peptides is showing increasing promise as a strategy in drug development.



M. Orzáez, A. Gortat, L. Mondragón, E. Pérez-Payá*

146 – 160

Peptides and Peptide Mimics as Modulators of Apoptotic Pathways



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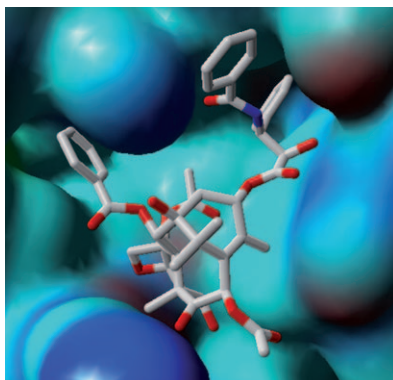
12 issues in 2009

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Further masthead information follows directly
 after the Table of Contents.

CONCEPTS

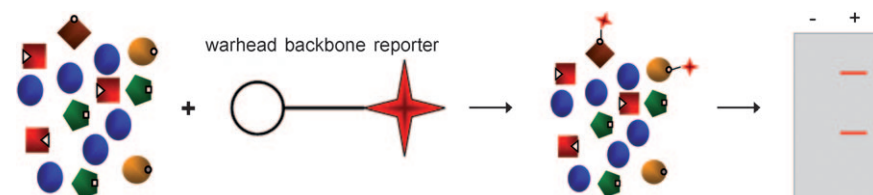
Docking-based virtual screening: Flexible docking, scoring, and virtual screening of ligand databases are on the way to fulfilling the promise. Docking-based virtual screening that targets taxane and colchicine binding sites will certainly provide new antitubulin agents.



L. Soullère*

161 – 163

Toward Docking-Based Virtual Screening for Discovering Antitubulin Agents by Targeting Taxane and Colchicine Binding Sites



Zinc-dependent metalloproteinases such as matrix metalloproteinases (MMPs) and A disintegrin and metalloproteinases (ADAMs) are potential therapeutic targets in many diseases. To better understand their complex role in

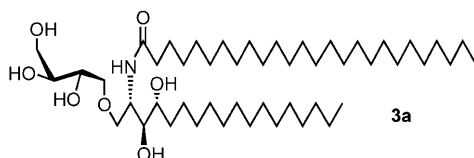
health and disease, new methodology for activity determination is under development. This concept gives an overview of the available methods for activity-based proteomic research on these enzymes.

T. Klein, P. P. Geurink, H. S. Overkleeft, H. K. Kauffman, R. Bischoff*

164 – 170

Functional Proteomics on Zinc-Dependent Metalloproteinases using Inhibitor Probes

COMMUNICATIONS



Based on the crystal structures of human α -GalCer-CD1d and i NKT- α -GalCer-CD1d complexes, nonglycosidic analogues of α -GalCer were synthesized. They activate i NKT cells resulting in den-

dratic cell maturation and the priming of antigen-specific T and B cells. Therefore, they are attractive adjuvants in vaccination strategies for cancer and infectious diseases.

B. G. Reddy, J. D. Silk, M. Salio, R. Balamurugan, D. Shepherd, G. Ritter, V. Cerundolo, R. R. Schmidt*

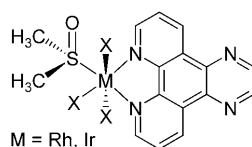
171 – 175

Nonglycosidic Agonists of Invariant NKT Cells for Use as Vaccine Adjuvants



FULL PAPERS

Whereas the cytostatic agents mer -[RhX₃(DMSO)(pp)] (X = Cl, Br; pp = phen, dpq) are considerably more potent than their facial isomers, this order is reversed for the analogous kinetically more inert Ir^{III} polypyridyl complexes. The complexes induce specific apoptotic cell death in leukemia and lymphoma cells via the intrinsic mitochondrial pathway and cause negligible necrotic damage.



M. Dobroschke, Y. Geldmacher, I. Ott, M. Harlos, L. Kater, L. Wagner, R. Gust, W. S. Sheldrick,* A. Prokop

177 – 187

Cytotoxic Rhodium(III) and Iridium(III) Polypyridyl Complexes: Structure–Activity Relationships, Antileukemic Activity, and Apoptosis Induction

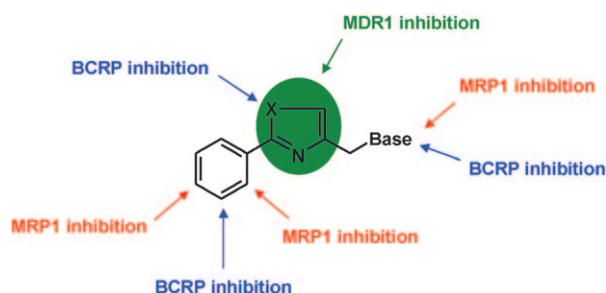


N. A. Colabufo,* F. Berardi, M. G. Perrone,
M. Cantore, M. Contino, C. Inglese,
M. Niso, R. Perrone

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Multi-Drug-Resistance-Reverting Agents: 2-Aryloxazole and 2-Arylthiazole Derivatives as Potent BCRP or MRP1 Inhibitors



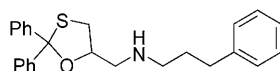
The 2-aryloxazole and 2-arylthiazole scaffolds were used for generating compounds that we characterized for their inhibitory activity toward ATP binding cassette transporters involved in multi-drug resistance, such as BCRP and

MRP1, by using tumor cell lines overexpressing each transporter. These SAR studies are a significant step toward improving the inhibitory potency against P-glycoprotein, BCRP, and MRP1.

S. Franchini, A. Tait, A. Prandi, C. Sorbi,
R. Gallesi, M. Buccioni, G. Marucci,
C. De Stefani, A. Cilia, L. Brasili*

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(2,2-Diphenyl-[1,3]oxathiolan-5-ylmethyl)-(3-phenyl-propyl)-amine: a Potent and Selective 5-HT_{1A} Receptor Agonist

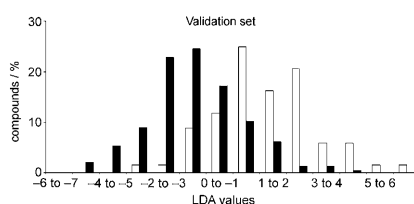


A selective 5-HT_{1A} receptor agonist: A new series of ligands acting at 5-HT_{1A} serotonin receptor were identified. Among them (2,2-diphenyl-[1,3]oxathiolan-5-ylmethyl)-(3-phenyl-propyl)amine (shown) possesses outstanding activity ($pK_i = 8.72$, $pD_2 = 7.67$, $E_{max} = 85$) and selectivity ($5-HT_{1A}/\alpha_{1D} > 150$), and represents a new 5-HT_{1A} agonist chemotype.

R. Gozalbes,* F. Barbosa, E. Nicolai,
D. Horvath, N. Froloff

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Development and Validation of a Pharmacophore-Based QSAR Model for the Prediction of CNS Activity

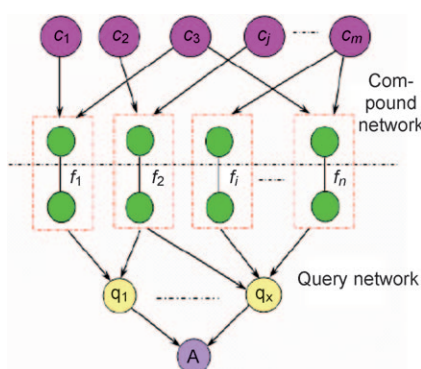


A QSAR model for the prediction of CNS activity was developed and validated based on data from an in-house database of “drug-like” compounds. The model has demonstrated its applicability for novel chemical structures and its usefulness for the design of CNS-focused compound libraries.

A. Abdo,* N. Salim

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Similarity-Based Virtual Screening with a Bayesian Inference Network



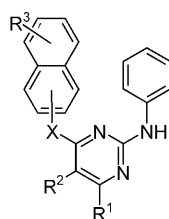
An inference network model for molecular similarity searching: The similarity search problem is modeled using inference or evidential reasoning under uncertainty. The inference network model treats similarity searching as an evidential reasoning process in which multiple sources of evidence about compounds and reference structures are combined to estimate resemblance probabilities.

X.-Q. Feng, Y.-H. Liang, Z.-S. Zeng,
F.-E. Chen,* J. Balzarini, C. Pannecouque,
E. De Clercq

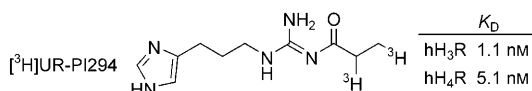
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Structural Modifications of DAPY Analogues with Potent Anti-HIV-1 Activity



A novel series of diarylpyrimidine analogues (DAPYs) featuring a naphthyl moiety at the C4 position were designed, with all compounds exhibiting strong activity against wild-type HIV-1.



Histamine mediates its various functions through four histamine receptor subtypes. The H₃ subtype is mainly found in the central nervous system, where it modulates the release of histamine and other neurotransmitters, whereas the H₄ subtype plays a crucial

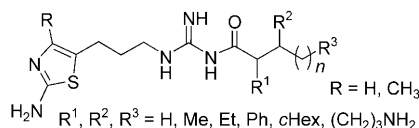
role in inflammatory and immunological processes. Herein, the synthesis and characterization of a conveniently accessible tritiated radioligand is reported that proved to be a versatile pharmacological probe.

P. Igel, D. Schnell, G. Bernhardt, R. Seifert, A. Buschauer*

225 – 231

Tritium-Labeled N¹-[3-(1H-imidazol-4-yl)propyl]-N²-propionylguanidine ([³H]UR-PI294), a High-Affinity Histamine H₃ and H₄ Receptor Radioligand

Bioisosteric replacement of the guanidino group in arpromidine-like histamine H₂ receptor (H₂R) agonists by an acylguanidine moiety is useful for obtaining potent H₂R agonists with improved oral bioavailability and blood-brain barrier penetration. We show that bioisosteric replacement of the imidazole ring in N^G-acylated imidazolylpropylguanidines by a 2-aminothiazol-5-yl group resulted in potent H₂R agonists with much greater selectivity for the human H₂R over H₃ and H₄ receptors.



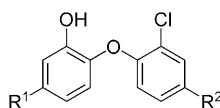
A. Kraus, P. Ghorai, T. Birnkammer, D. Schnell, S. Elz, R. Seifert, S. Dove, G. Bernhardt, A. Buschauer*

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N^G-Acylated Amino-thiazolylpropyl-guanidines as Potent and Selective Histamine H₂ Receptor Agonists



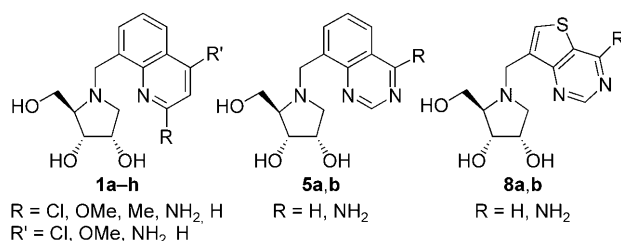
Overcoming resistance: Isoniazid (INH) is a frontline antitubercular drug that inhibits the enoyl acyl carrier protein reductase InhA. Novel inhibitors of InhA that are not cross-resistant to INH represent a significant goal in antitubercular chemotherapy. The design, synthesis, and biological activity of a series of triclosan-based inhibitors is reported, including their promising efficacy against INH-resistant strains of *M. tuberculosis*.



J. S. Freundlich, F. Wang, C. Vilchèze, G. Gulten, R. Langley, G. A. Schiehsler, D. P. Jacobus, W. R. Jacobs Jr., J. C. Sacchettini*

241 – 248

Triclosan Derivatives: Towards Potent Inhibitors of Drug-Sensitive and Drug-Resistant *Mycobacterium tuberculosis*



A series of bicyclic N-arylmethyl-substituted iminoribitols were synthesised and evaluated in vitro against *T. vivax* nucleoside hydrolase. The importance of the N-Asp40 interaction was confirmed and depends on an optimal pK_a

value, which can be influenced by substituents. The compounds were active inhibitors of nucleoside hydrolase (IAG-NH) and are inactive against human purine nucleoside phosphorylase.

M. Berg, G. Bal, A. Goeminne, P. Van der Veken, W. Versées, J. Steyaert, A. Haemers, K. Augustyns*

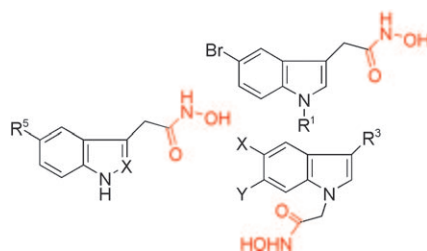
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Synthesis of Bicyclic N-Arylmethyl-Substituted Iminoribitol Derivatives as Selective Nucleoside Hydrolase Inhibitors

S. Petit, Y. Duroc, V. Larue, C. Giglione,
C. Léon, C. Soulama, A. Denis, F. Dardel,
T. Meinnel, I. Artaud*

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Structure–Activity Relationship Analysis of the Peptide Deformylase Inhibitor 5-Bromo-1*H*-indole-3- acetohydroxamic Acid

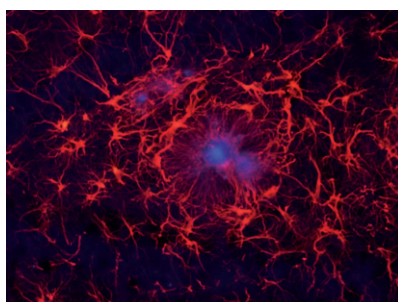


SAR by NMR: A series of indole compounds derived from 5-bromo-1*H*-indole-3-acetohydroxamic acid were synthesized. Their inhibitory activities were evaluated against purified peptide deformylases (PDFs), and their antibacterial activities against *B. subtilis*, *E. coli* (wild type and *tolC*), and a variety of pathogens were also determined. The potency of the best inhibitors was related to the NMR footprints of the respective acids with ¹⁵N-labeled *E. coli* Ni-PDF.

T. van Groen,* I. Kadish, K. Wiesehan,
S. A. Funke, D. Willbold

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In vitro and in vivo Staining Characteristics of Small, Fluorescent, Aβ42-Binding D-Enantiomeric Peptides in Transgenic AD Mouse Models



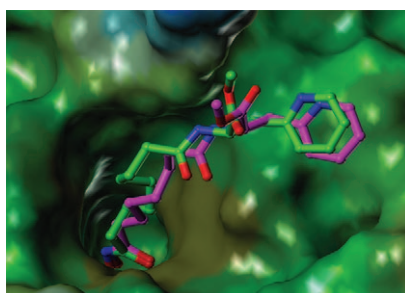
Plaque visualisation: We identified three different D-enantiomeric peptides that bind to Alzheimer's amyloid β (Aβ1-42). As there is currently no definitive pre-mortem diagnosis for Alzheimer's disease, we investigated the peptides' suitability as molecular probes for in vivo imaging in transgenic mouse models.

S. Schäfer, L. Saunders, S. Schlimme,
V. Valkov, J. M. Wagner, F. Kratz, W. Sippl,
E. Verdin, M. Jung*

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Pyridylalanine-Containing Hydroxamic Acids as Selective HDAC6 Inhibitors



Pyridylalanine inhibitors of histone deacetylase (HDAC) have been synthesized that show selectivity for the isoform HDAC6 over HDAC1 in vitro. This selectivity was also identified in cancer cells by analyzing tubulin versus histone acetylation. The compounds show decreased intrinsic cytotoxicity relative to pan-HDAC inhibitors, but show antiproliferative synergy with the proteasome inhibitor bortezomib.



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



A video clip is available as Supporting Information
on the WWW (see article for access details).

* Author to whom correspondence should be addressed.

BOOKS

Natural Compounds as Drugs, Volumes I and II • F. Petersen and R. Amstutz (Eds.)
Essential Concepts in Toxicogenomics • D. L. Mendrick and W. B. Mattes (Eds.)
New Antibiotic Targets • W. S. Champey (Ed.)

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Issue 1, 2009, was published online on January 7, 2009.

CORRIGENDUM

K.-S. Yeung,* N. A. Meanwell

Inhibition of hERG Channel Trafficking: An Under-Explored Mechanism for Drug-Induced QT Prolongation

ChemMedChem 2008, 3, 1501–1502

DOI 10.1002/cmdc.200800170

The first sentence, "Functional blockage of the human *ether-á-go-go-related gene* (hERG or KCNH2) encoded cardiac potassium channel is responsible for the rapidly activating component of the delayed rectifier K⁺ current (*I_{Kr}*), which can delay ventricular cell repolarization." should read "The human *ether-á-go-go-related gene* (hERG or KCNH2) encoded cardiac potassium channel is responsible for the rapidly activating component of the delayed rectifier K⁺ current (*I_{Kr}*). Functional blockage the hERG channel can delay ventricular cell repolarization."

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