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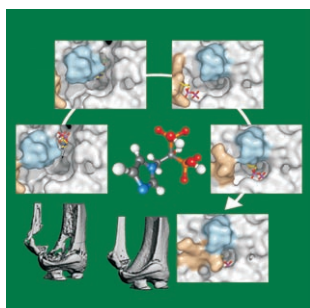
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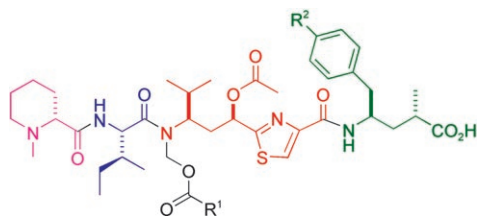
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COVER PICTURE



The cover picture shows micro computer tomography images that demonstrate the effect of zoledronate in the prevention of the tumor osteolytic response caused by local injection of human 4T1 mammary carcinoma cells into the tibia of nude mice. The circular arrangement shows interpolations between structural snapshots of farnesyl pyrophosphate synthase (FPPS), the molecular target of zoledronate and other bisphosphonates, upon inhibition by zoledronate and further complexation by IPP. It illustrates the structural basis for bisphosphonate treatment of bone metastasis, Paget's disease, osteoporosis, and other diseases. (Bone images courtesy of Dr. Jürg A. Gasser, Novartis Pharma AG). For more details, see the full paper by J.-M. Rondeau, W. Jahnke, et al. on p. 267 ff.

MINIREVIEWS



Tubulysins are potent cytotoxic natural tetrapeptides that have attracted great interest as potential drug payloads coupled with monoclonal antibodies for the targeting of tumors. Five years after the

publication of their isolation from myxobacteria species, tubulysins (shown) remain a challenge for total synthesis efforts, as published reports of synthesized tubulysin have yet to appear.

D. Neri,* G. Fossati, M. Zanda*

175 – 180

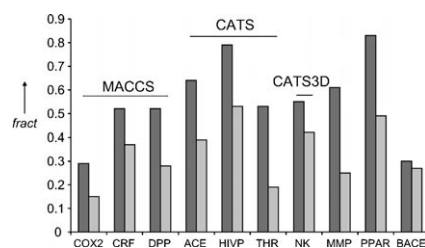
Efforts toward the Total Synthesis of Tubulysins: New Hopes for a More Effective Targeted Drug Delivery to Tumors

COMMUNICATIONS

S. Renner, G. Schneider*

181 – 185

Scaffold-Hopping Potential of Ligand-Based Similarity Concepts

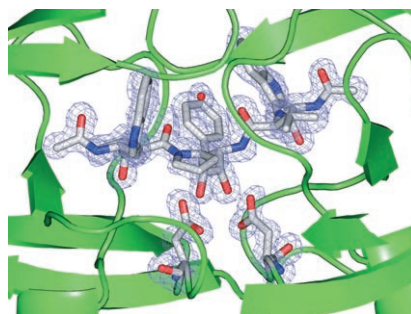


Virtual screening: Different similarity searching descriptors were compared for scaffold hopping. The pharmacophore pair CATS descriptor performed best for ligand classes with a high fraction (*fract*) of different scaffolds, MACCS fingerprints were best for classes with low scaffold diversity. The methods complemented each other in retrieving scaffolds.

S. Geremia,* N. Demitri, J. Wuerges, F. Benedetti, F. Berti, G. Tell, L. Randaccio

186 – 188

A Potent HIV Protease Inhibitor Identified in an Epimeric Mixture by High-Resolution Protein Crystallography

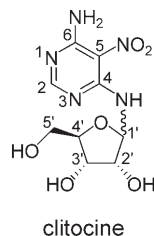


Discovery by co-crystallization: High-resolution electron-density maps of HIV-1 aspartyl protease complexed with a potent Phe-Pro isostere-based inhibitor (shown) allowed the determination of the stereochemistry of the inhibitor and an initial assessment of the inhibition properties of this compound without its purification from the epimeric mixture.

FULL PAPERS

H. Fortin, S. Tomasi,* J.-G. Delcros, J.-Y. Bansard, J. Boustie

189 – 196

In Vivo Antitumor Activity of Clitocine, an Exocyclic Amino Nucleoside Isolated from *Lepista inversa*

From the forest floor: Clitocine, a nucleoside produced by the Basidiomycete mushroom *Lepista inversa*, was isolated, synthesized, and its stability was studied. Clitocine has potent in vitro activity toward cancer cell lines (with IC_{50} values in the nanomolar range), and apoptotic effects were observed. Potent in vivo antitumor activity was also observed in mouse models.

S. A. Laufer,* S. Margutti, M. D. Fritz

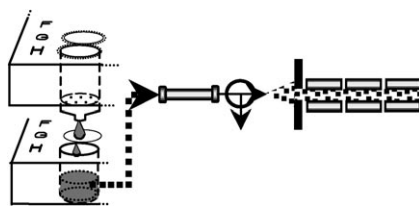
197 – 207

Substituted Isoxazoles as Potent Inhibitors of p38 MAP Kinase



Leaving cytochromes alone: The inhibitory potency of the isoxazole compound (shown) toward p38 MAP kinase supports the important role of hydrogen bonding in the interaction between p38 inhibitors and Lys 53 of the kinase. A further advantage of the isoxazole scaffold is a decreased interaction with cytochrome isoenzymes.

No need to label: A new kind of MS-binding assay allows the amount of a nonlabeled marker bound to the target to be determined by LC-ESI-MS-MS instead of by quantitation of nonbound marker, as done in previous studies. The new MS-binding assay is methodologically similar to classical radioligand-binding studies, but is free of the major drawbacks inherent in the latter.

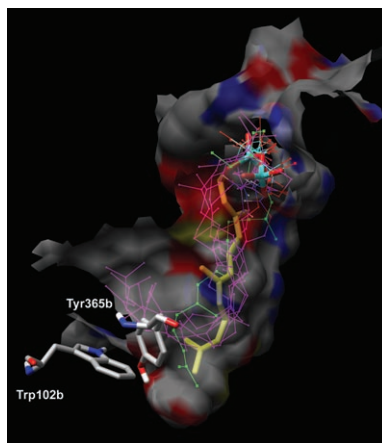


C. Zepperitz, G. Höfner, K. T. Wanner*

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MS-Binding Assays: Kinetic, Saturation, and Competitive Experiments Based on Quantitation of Bound Marker as Exemplified by the GABA Transporter mGAT1

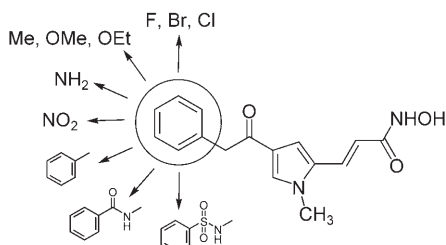
New stable analogues of geranylgeranyl diphosphate with a *Z,E,E* side chain in place of the “natural” *E,E,E* portion were prepared and assayed for prenyltransferase (GGTase I and FTase) inhibition. A docking analysis (shown) of the molecules within the enzymes was conducted to rationalize the biological results and to explain the inverse selectivity exhibited by one of the derivatives.



F. Minutolo, S. Bertini, L. Betti, R. Danesi, G. Gervasi, G. Giannaccini, A. Martinelli, A. M. Papini, E. Peroni, G. Placanica, S. Rapposelli, T. Tuccinardi, M. Macchia*

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Synthesis of Stable Analogues of Geranylgeranyl Diphosphate Possessing a (*Z,E,E*)-Geranylgeranyl Side Chain, Docking Analysis, and Biological Assays for Prenyl Protein Transferase Inhibition



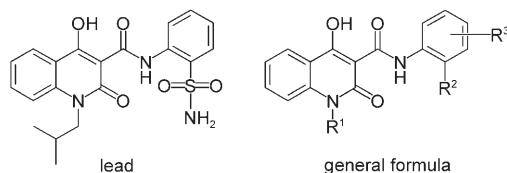
A. Mai,* S. Massa, S. Valente, S. Simeoni, R. Ragno, P. Bottoni, R. Scatena, G. Brosch*

225 – 237

Aroyl-Pyrryl Hydroxyamides: Influence of Pyrrole C4-Phenylacetyl Substitution on Histone Deacetylase Inhibition

Targeting histone deacetylation: Novel aroyl-pyrryl hydroxyamides have been shown to be HDAC inhibitors. Compounds substituted at the 3'-aroyl position (3'-chloro and 3'-methyl pyrroles)

are the most potent derivatives, and have interesting antiproliferative and cytodifferentiation actions toward HL-60 leukemia cells.



HIV-1 integrase inhibitors: The lead compound (left) was identified in a pharmacophore-guided database search. A systematic structural exploration

on the lead compound resulted in the identification of a novel class of HIV-1 integrase inhibitors exemplified by the general formula (right).

R. Dayam, T. Sanchez, N. Neamati*

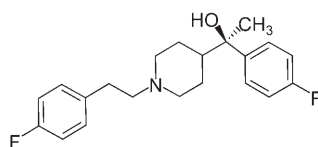
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Discovery and Structure-Activity Relationship Studies of a Unique Class of HIV-1 Integrase Inhibitors

T. Heinrich,* H. Böttcher, H. Prücher,
R. Gottschlich, K.-A. Ackermann,
C. van Amsterdam

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1-(1-Phenethylpiperidin-4-yl)-1-phenylethanol as Potent and Highly Selective 5-HT_{2A} Antagonists

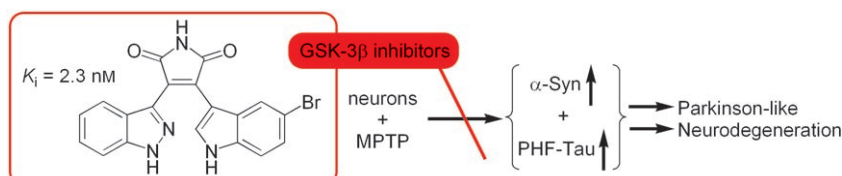


Mind your 'A's and 'C's: The *R* enantiomer of the tertiary alcohol (shown) is a highly potent antagonist of the serotonin receptor subtype 2A (5-HT_{2A}) and has greater than 1300-fold selectivity for 5-HT_{2A} over the 2C receptor subtype, 5-HT_{2C}. The affinity and selectivity of this compound toward 5-HT_{2A} versus other relevant receptors (domaminergic D₂ and adrenergic α₁) was also optimized.

A. P. Kozikowski,* I. N. Gaisina,
P. A. Petukhov, J. Sridhar, L. T. King,
S. Y. Blond, T. Duka, M. Rusnak, A. Sidhu

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Highly Potent and Specific GSK-3β Inhibitors That Block Tau Phosphorylation and Decrease α-Synuclein Protein Expression in a Cellular Model of Parkinson's Disease



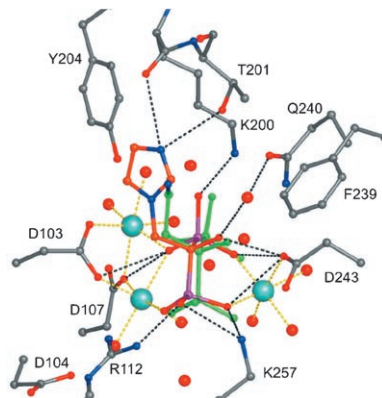
Analogue of the natural product staurosporine are able to inhibit Tau phosphorylation at a GSK-3β-specific site. Two members of this compound series can protect neuronal cells against cell death by decreasing the expression

of α-synuclein. This work provides the chemical and biological information relevant to the identification of new chemical entities for the treatment of Tau-related neurodegenerative disease states.

J.-M. Rondeau,* F. Bitsch, E. Bourcier,
M. Geiser, R. Hemmig, M. Kroemer,
S. Lehmann, P. Ramage, S. Rieffel,
A. Strauss, J. R. Green, W. Jahnke*

267 – 273

Structural Basis for the Exceptional in vivo Efficacy of Bisphosphonate Drugs



The structural basis for bisphosphonate therapy has been elucidated by solving the first crystal structures of human farnesyl pyrophosphate synthase (FPPS), the molecular target of bisphosphonates. The structures uncover a particularly interesting and efficient mode of enzyme inhibition, and suggest novel routes for the treatment of bone metastasis and soft-tissue cancer.

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

* Author to whom correspondence should be addressed.

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