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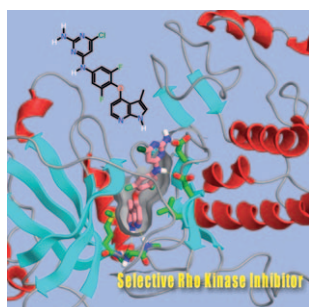
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Most of the articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE



The cover picture shows the 2D chemical structure of Bayer Schering's azaindole-based Rho kinase (ROCK) inhibitor, and also its 3D tube model docked into the ATP binding site of ROCK-1 (X-ray crystallographic structure). The kinase protein is mostly shown as a ribbon diagram with the β -sheet lobe on the left, the hinge region at the bottom, and the α -helical lobe on the right. The gatekeeper methionine and some additional key residues are also shown in tube representation. The depicted inhibitor was identified as a highly selective and orally available ROCK inhibitor, which leads to sustained blood pressure reduction in vivo. For more details, see the Full Paper by H. Schirok et al. on p. 1893 ff.

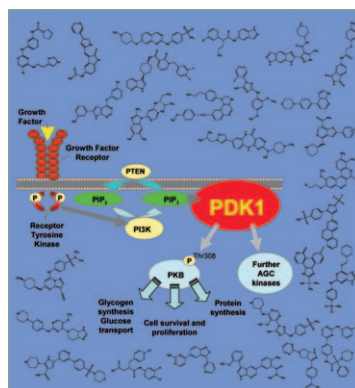
NEWS

Spotlights on our sister journals

1808 – 1809

REVIEWS

The master regulator: In this review we present a comprehensive collection of small molecules reported to interact with 3-phosphoinositide-dependent protein kinase-1 (PDK1) and their biological characterisation towards activity and selectivity for PDK1.



C. Peifer,* D. R. Alessi

1810 – 1838

Small-Molecule Inhibitors of PDK1

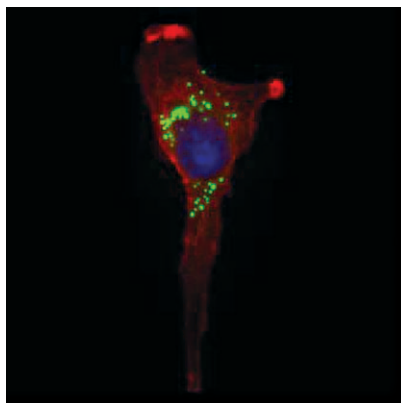
COMMUNICATIONS

F. Alexis, P. Basto, E. Levy-Nissenbaum,
A. F. Radovic-Moreno, L. Zhang,
E. Pridgen, A. Z. Wang, S. L. Marein,
K. Westerhof, L. K. Molnar,
O. C. Farokhzad*

1839 – 1843



HER-2-Targeted Nanoparticle–Affibody Bioconjugates for Cancer Therapy

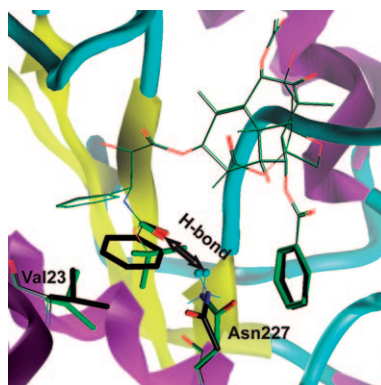


Affibodies are a class of polypeptide ligand that are potential candidates for tissue-specific targeting of drug-encapsulated controlled release polymeric nanoparticles (NPs). We developed drug delivery vehicles composed of polymeric NPs surface modified with affibody ligands that bind the extracellular domain of the human epidermal growth factor receptor 2 (HER-2) for targeted delivery to cells that over-express the HER-2 antigen.

R. D. Winefield, R. A. Entwistle,
T. B. Foland, G. H. Lushington,
R. H. Himes*

1844 – 1847

Differences in Paclitaxel and Docetaxel Interactions with Tubulin Detected by Mutagenesis of Yeast Tubulin



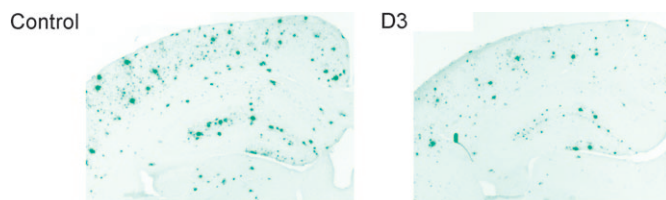
A molecular model showing the yeast tubulin–paclitaxel and tubulin–docetaxel complexes in a mutated form of the protein that contains Asn at position 227 instead of His. The side chain of Asn 227 is able to form an H-bond with the carbonyl oxygen of the paclitaxel benzamide and the docetaxel carbamate groups.

T. van Groen, K. Wiesehan, S. A. Funke,
I. Kadish, L. Nagel-Steger, D. Willbold*

1848 – 1852



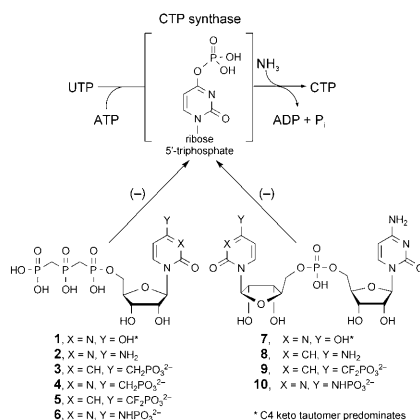
Reduction of Alzheimer's Disease Amyloid Plaque Load in Transgenic Mice by D3, a D-Enantiomeric Peptide Identified by Mirror Image Phage Display



Alzheimer's disease (AD) is a progressive neurodegenerative disorder, affecting more than 20 million people worldwide. Only palliative therapies are available today. We identified a novel D-enantiomeric amino acid peptide "D3" with significant A β disaggregation and A β aggregation inhibiting properties in

vitro and in vivo. It inhibits cytotoxicity in cell culture and reduces amyloid plaque load and cerebral damage of transgenic AD mouse models. D3 might be a tool for further research approaches on the origin of AD and might provide a novel basis for therapeutic and preventive approaches to AD.

CTP synthase (CTPS) catalyzes the conversion of UTP to CTP and is a recognized target for the development of anticancer, antiviral, and antiprotozoal agents. We show that phosphonate and phosphoramidate 5'-bismethylene triphosphate intermediate analogues **3–6** inhibit CTPS activity, as do the multivalent nucleotide inhibitors **7–10**. These results support the further development of these two classes of compounds as CTPS inhibitors.



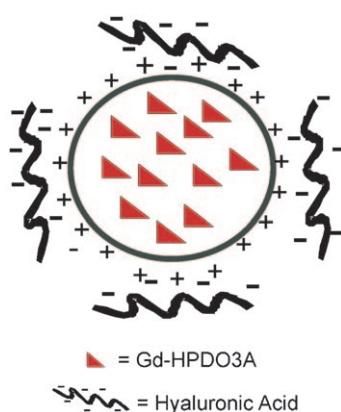
S. D. Taylor, F. A. Lunn, S. L. Bearne**

1853 – 1857

Ground State, Intermediate, and Multivalent Nucleotide Analogue Inhibitors of Cytidine 5'-Triphosphate Synthase



The supramolecular adducts of negatively charged hyaluronic acid polymers and cationic Gd-liposomes were used for labeling cells that overexpress CD44 receptors. This cellular labeling methodology is very efficient and allows the internalization of a large payload of soluble Gd complexes in a very short time-frame.

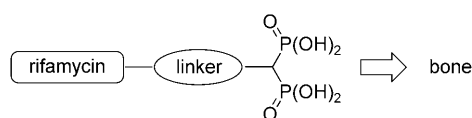


*G. Esposito, S. Geninatti Crich, S. Aime**

1858 – 1862

Efficient Cellular Labeling by CD44 Receptor-Mediated Uptake of Cationic Liposomes Functionalized with Hyaluronic Acid and Loaded with MRI Contrast Agents

Benzoxaziorifamycins are potent antibacterial agents currently in development. Tethering these antibiotics to a bisphosphonate functional group by a cleavable linker allows the delivery of these agents to osseous tissues, where



they can be released over time to treat bone infections. Various linker strategies are presented herein to develop osteotropic prodrugs, the activities of which are examined in vitro and in vivo.

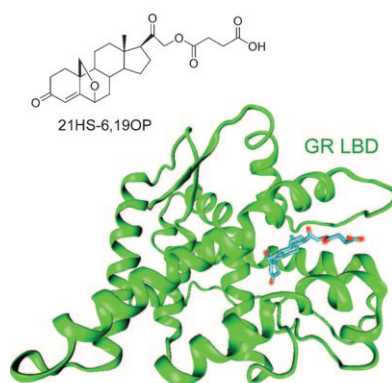
*R. Reddy, E. Dietrich, Y. Lafontaine, T. J. Houghton, O. Belanger, A. Dubois, F. F. Arhin, I. Sarmiento, I. Fadhil, K. Laquerre, V. Ostiguy, D. Lehoux, G. Moeck, T. R. Parr Jr., A. Rafai Far**

1863 – 1868

Bisphosphonated Benzoxaziorifamycin Prodrugs for the Prevention and Treatment of Osteomyelitis

FULL PAPERS

A pure agonist: The 21-hemisuccinate of 21-hydroxy-6,19-epoxyprogesterone (21HS-6,19OP) is a tissue-specific modulator of the glucocorticoid receptor (GR). Molecular dynamics simulations of the GR ligand binding domain (LBD) complexed with 21HS-6,19OP indicate that the hemisuccinate moiety may play a key role in stabilizing the active conformation of the receptor dimerization interface.



*L. D. Álvarez, M. A. Martí, A. S. Veleiro, R. I. Misico, D. A. Estrin, A. Pecci, G. Burton**

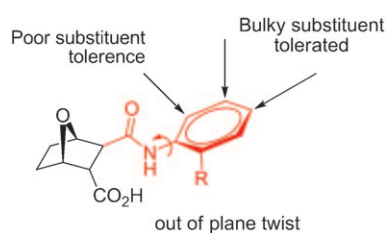
1869 – 1877

Hemisuccinate of 21-Hydroxy-6,19-Epoxyprogesterone: A Tissue-Specific Modulator of the Glucocorticoid Receptor

T. A. Hill, S. G. Stewart, C. P. Gordon,
S. P. Ackland, J. Gilbert, B. Sauer,
J. A. Sakoff, A. McCluskey*

1878 – 1892

Norcantharidin Analogues: Synthesis, Anticancer Activity and Protein Phosphatase 1 and 2A Inhibition

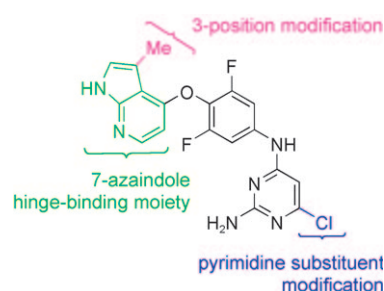


Norcantharidin analogues as potential anticancer agents: Aromatic substituted norcantharidin analogues were synthesised and evaluated for the protein phosphatase 1 and 2A and tumour cell line growth inhibition. While some derivatives possessed good inhibitory activity, bulky *ortho* substituents caused the aromatic ring to twist out of planarity of the amide functionality, leading to a loss of activity.

H. Schirok,* R. Kast, S. Figueroa-Pérez,
S. Bennabi, M. J. Gnoth, A. Feurer,
H. Heckroth, M. Thutewohl, H. Paulsen,
A. Knorr, J. Hütter, M. Lobell, K. Münter,
V. Geiß, H. Ehmke, D. Lang, M. Radtke,
J. Mittendorf, J.-P. Stasch

1893 – 1904

Design and Synthesis of Potent and Selective Azaindole-Based Rho Kinase (ROCK) Inhibitors

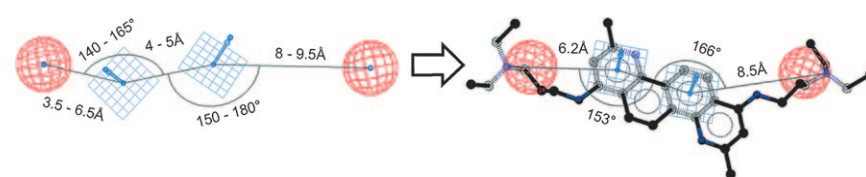


A new compound class of Rho kinase (ROCK) inhibitors containing a 7-azaindole hinge-binding moiety was discovered. The introduction of substituents at the 3-position of the bicyclic ring system led to a significant increase in activity and permitted the design of compounds with a favorable pharmacokinetic profile. The ROCK inhibitors are orally bioavailable and mediate a sustained blood pressure lowering effect *in vivo*.

A. R. Hermone, J. C. Burnett, J. E. Nuss,
L. E. Tressler, T. L. Nguyen, B. A. Šolaja,
J. L. Vennerstrom, J. J. Schmidt, P. Wipf,
S. Bavari,* R. Gussio*

1905 – 1912

Three-Dimensional Database Mining Identifies a Unique Chemotype that Unites Structurally Diverse Botulinum Neurotoxin Serotype A Inhibitors in a Three-Zone Pharmacophore



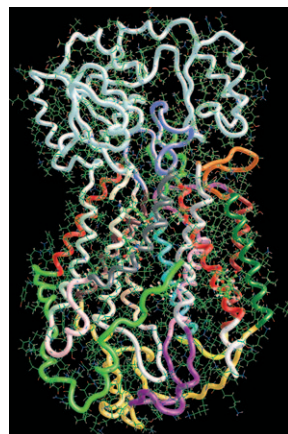
Three-dimensional database mining employing an internally consistent search query identified a novel botulinum neurotoxin serotype A metalloprotease inhibitor chemotype. This inhibitor served as the basis for uniting

different structural classes of previously identified inhibitors in a three-zone pharmacophore. Subsequently, this model was used to identify a novel three-zone inhibitor.

A. Pedretti, L. De Luca, C. Marconi,
G. Negrisoni, G. Aldini, G. Vistoli*

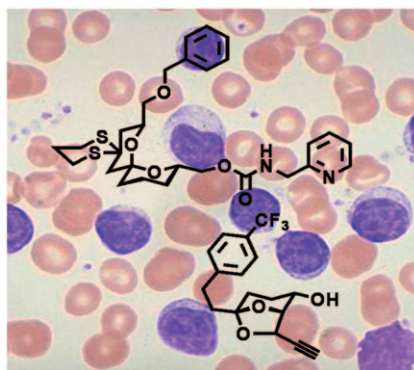
1913 – 1921

Modeling of the Intestinal Peptide Transporter hPepT1 and Analysis of Its Transport Capacities by Docking and Pharmacophore Mapping



The intestinal hPepT1 transporter is involved in the active absorption of dietary peptides and peptidomimetic drugs. The aim of this study was to generate a model for hPepT1 by fragments. The model was validated by docking analyses and pharmacophore mapping using a set of 50 known ligands. The results suggest that the model can be used to predict the transport of peptide-like molecules.

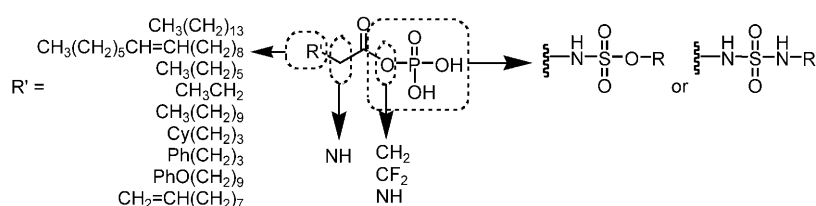
The guiding principle of natural products is applied with success to the rapid identification of a new series of small molecules with activity against chronic lymphocytic leukaemia. These compounds are shown to induce apoptosis via a classical intrinsic drug-induced pathway with superior activity to market leader chemotherapeutics in similar screens.



L.-G. Milroy, G. Zinzalla, F. Loiseau, Z. Qian, G. Prencipe, C. Pepper, C. Fegan, S. V. Ley*

1922 – 1935

Natural-Product-Like Spiroketal and Fused Bicyclic Acetals as Potential Therapeutic Agents for B-Cell Chronic Lymphocytic Leukaemia



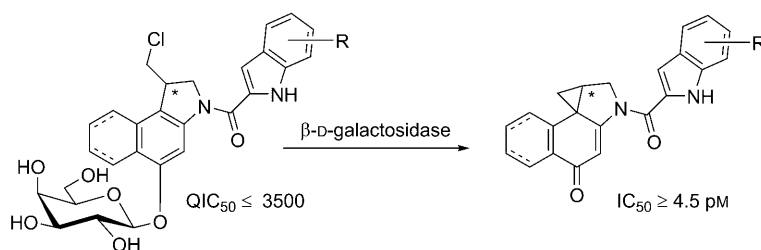
Targeting phospholipid biosynthesis: Novel inhibitors of the PlsX/PlsY pathway to phosphatidic acid, a key intermediate in the biosynthesis of phospholipids in Gram-positive bacteria have been discovered. Substrate mimics that

incorporate various bioisosteric replacement head groups and acyl chains were revealed that demonstrate good enzyme inhibition, good antimicrobial activity, and low cytotoxicity.

K. D. Grimes, Y.-J. Lu, Y.-M. Zhang, V. A. Luna, J. G. Hurdle, E. I. Carson, J. Qi, S. Kudrimoti, C. O. Rock, R. E. Lee*

1936 – 1945

Novel Acyl Phosphate Mimics that Target PlsY, an Essential Acyltransferase in Gram-Positive Bacteria



Cancer chemotherapy is often based on the difference in proliferation rates between normal and malignant cells. However, severe side effects are frequently observed, as the proliferation rates of several normal cell types are similar to those of tumor cells. We have

developed new glycosidic prodrugs of duocarmycin analogues showing excellent selectivities ($QIC_{50} \leq 3500$) and very high cytotoxicities of the corresponding drugs ($IC_{50} \geq 4.5 \mu\text{M}$) for use in antibody-directed enzyme prodrug therapy (ADEPT).

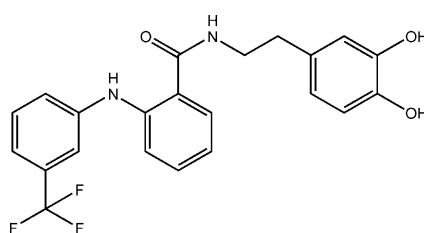
L. F. Tietze,* J. M. von Hof, B. Krewer, M. Müller, F. Major, H. J. Schuster, I. Schuberth, F. Alves

1946 – 1955

Asymmetric Synthesis and Biological Evaluation of Glycosidic Prodrugs for a Selective Cancer Therapy



Two-in-one: We generated potentially naturally occurring acid amides of several anti-inflammatory and analgesic drugs. Either the amine or acid components served as drug moieties. We found TRPV1 agonist activity in the nanomolar range with dopamine amides of fenamic acids, and TRPV1 antagonist activity with the arachidonyl amide of a dipyrone metabolite.



C. Sinning, B. Watzler, L. De Petrocellis, V. Di Marzo,* P. Imming*


1956 – 1964

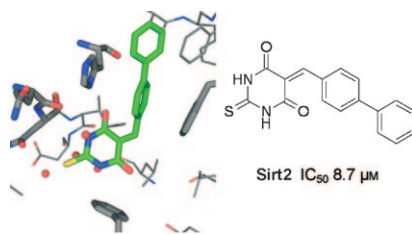
Dopamides, Vanillylamides, Ethanalamides, and Arachidonic Acid Amides of Anti-inflammatory and Analgesic Drug Substances as TRPV1 Ligands




U. Uciechowska, J. Schemies,
R. C. Neugebauer, E.-M. Huda,
M. L. Schmitt, R. Meier, E. Verdin,
M. Jung, W. Sippl*

1965 – 1976


 **Thiobarbiturates as Sirtuin Inhibitors: Virtual Screening, Free-Energy Calculations, and Biological Testing**



Thiobarbiturate inhibitors of Sirt2 were developed by applying a combination of virtual screening, free-energy calculation, and in vitro experimental testing. A significant correlation between calculated binding free energies and measured Sirt2 inhibitory activities was observed. The analyses suggested a molecular basis for the interaction of the identified thiobarbiturate derivatives with human Sirt2.

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

* Author to whom correspondence should be addressed.

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

BOOKS

The Handbook of Nanomedicine · Kewal K. Jain

M. M. Amiji 1977

SERVICE

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Keyword Index 1979 Index 1981

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The editorial staff and the publishers thank all readers, authors, referees, and advertisers for their interest and support over the past year and wish them all a happy new year.