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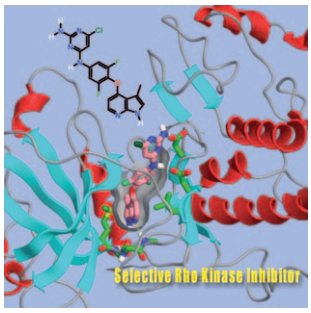
COVER PICTURE

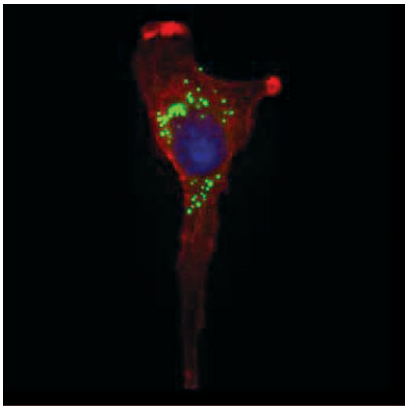


The cover picture shows the 2D chemical structure of Bayer Schering's azaindole-based Rho kinase (ROCK) inhibitor, and also its 3D tube model docked into the ATP binding site of ROCK-1 (X-ray crystallographic structure). The kinase protein is mostly shown as a ribbon diagram with the β-sheet lobe on 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.

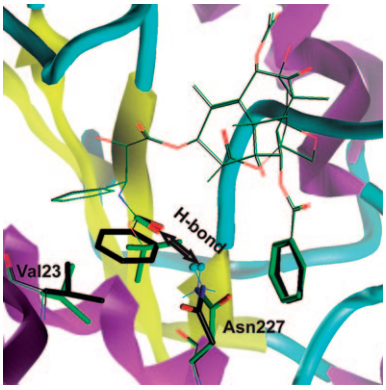
NEWS

REVIEWS

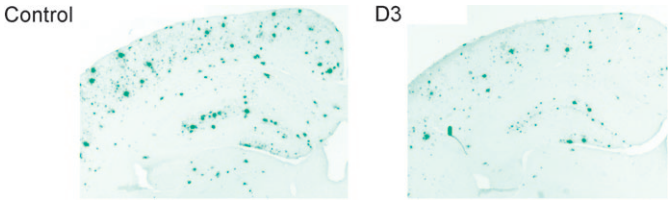
COMMUNICATIONS



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 overexpress the HER-2 antigen.



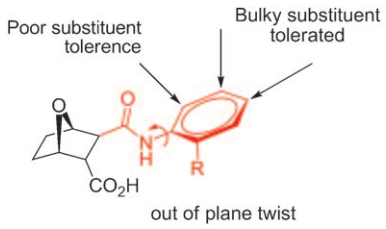
A molecular model showing the yeast tubulin–paclitaxel and tubulin–docetaxel complexes in a mutated form of the protein that contains Asn at position 227 instead of His. The side chain of Asn 227 is able to form an H-bond with the carbonyl oxygen of the paclitaxel benzamide and the docetaxel carbamate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



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 Aβ disaggregation and Aβ aggregation inhibiting properties in vitro an 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.

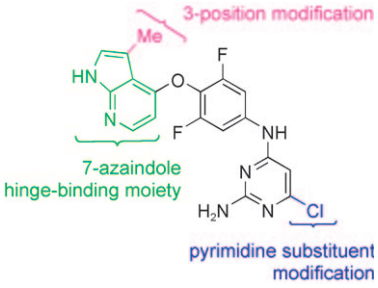
FULL PAPERS

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



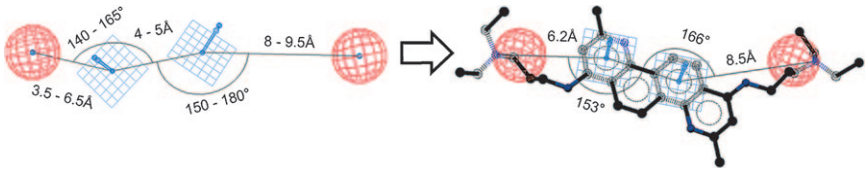
Norcantharidin analogues as potential anticancer agents: Aromatic substituted norcantharidin analogues were synthesised and evaluated for the protein phosphatase 1 and 2A and tumour cell line growth inhibition. While some derivatives possessed good inhibitory activity, bulky *ortho* substituents caused 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*



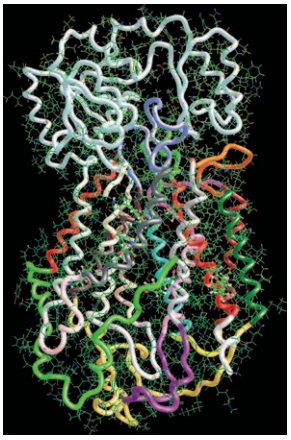
A new compound class of Rho kinase (ROCK) inhibitors containing a 7-azaindole hinge-binding moiety was discovered. The introduction of substituents at the 3-position of the bicyclic ring system led to a significant increase in activity and permitted the design of compounds with a favorable pharmacokinetic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



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. Negrisoli, G. Aldini, G. Vistoli**

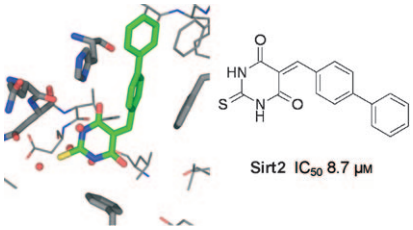


The intestinal hPepT1 transporter is involved in the active absorption of dietary peptides and peptidomimetic drugs. The aim of this study was to generate a model for hPepT1 by fragments. The model was validated by docking analyses and pharmacophore mapping using a set of 50 known ligands. The results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

*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).

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

* Author to whom correspondence should be addressed.

BOOKS

SERVICE

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