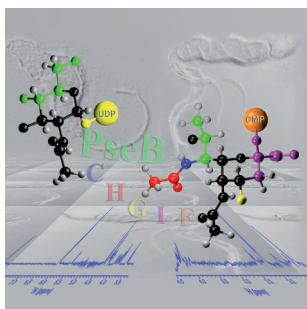


COVER PICTURE



The cover picture shows the six enzymes (PseB, C, H, G, I, F) responsible for producing CMP-pseudaminic acid (CMP-Pse) starting from UDP-GlcNAc in *Campylobacter jejuni* and *Helicobacter pylori*. These pathogens modify their flagella with sialic acid-like sugars such as pseudaminic acid (Pse) which are required for flagellar assembly, motility, and hence virulence. PseB plays a central role in Pse biosynthesis and is also thought to be implicated in other glycan pathways making it a prime therapeutic target. Saturation transfer difference nuclear magnetic resonance spectroscopy (STD NMR) was used to determine binding epitopes for PseB and to characterize PseB inhibition with CMP-Pse at the molecular level. Docking studies and CORCEMA calculations validated STD NMR results and revealed that CMP-Pse and UDP-GlcNAc adopt similar conformations within the PseB active site. These findings will guide the development of small-molecule inhibitors as a means to pharmaceutically control *C. jejuni* and *H. pylori* infections. For details, see the Communication by D. J. McNally, et al. on p. 55 ff.

NEWS

Spotlights on our sister journals

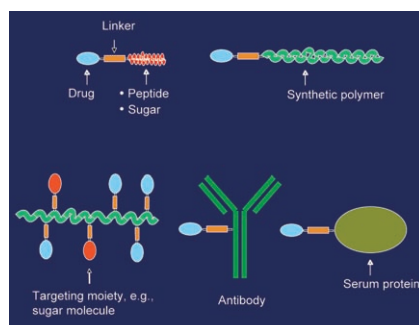
14 – 15

REVIEWS

F. Kratz,* I. A. Müller, C. Ryppa,
A. Warnecke

20 – 53

Prodrug Strategies in Anticancer
Chemotherapy



Targeted delivery: Many carrier-linked prodrugs have been developed over the past three decades with the goal of improving the therapeutic index of anticancer agents. In this review we elucidate the two main concepts that underlie the design of most anticancer prodrugs: drug targeting and controlled release of the drug at the tumor site.

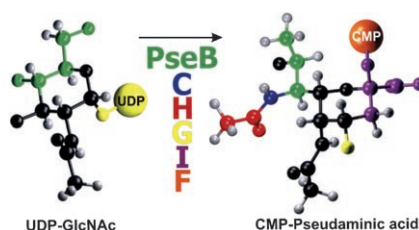
COMMUNICATIONS

D. J. McNally,* I. C. Schoenhofen,
R. S. Houlston, N. H. Khieu,
D. M. Whitfield, S. M. Logan, H. C. Jarrell,
J.-R. Brisson

55 – 59

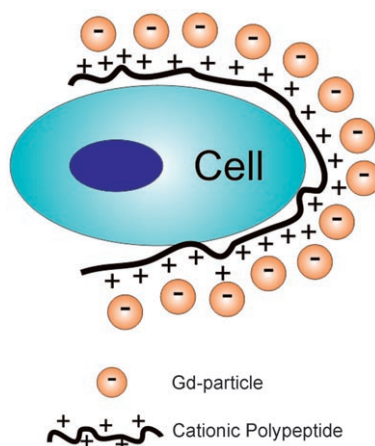


CMP-Pseudaminic Acid is a Natural Potent Inhibitor of PseB, the First Enzyme of the Pseudaminic Acid Pathway in *Campylobacter jejuni* and *Helicobacter pylori*



Deadly decorations. *Campylobacter jejuni* and *Helicobacter pylori* decorate their flagella, which are essential for virulence, with pseudaminic acid (Pse). Pse production is feedback-regulated in the bacterial cell by CMP-pseudaminic acid, a potent inhibitor of PseB, the first enzyme of the Pse pathway. Herein, STD NMR was used to map binding epitopes for PseB and to characterize the interaction between PseB and CMP-Pse.

Cellular labeling. MR visualization of cells has been attained by anchoring negatively charged Gd-loaded nanoparticles at the cellular membrane by a polycationic linker. Each nanoparticle contains approximately 800 Gd-chelates and each cell has been loaded with approximately 5×10^6 particles. In this way only 15% of the negative charges on the membrane has been used. The method has been validated by confocal microscopy.



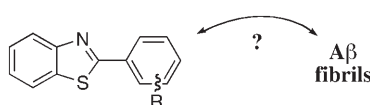
*E. Gianolio, G. B. Giovanzana, A. Ciampa, S. Lanzardo, D. Imperio, S. Aime**

60–62

A Novel Method of Cellular Labeling: Anchoring MR-Imaging Reporter Particles on the Outer Cell Surface



How do we go together? Structural variations have been used to obtain information regarding the interaction of thioflavin-derived markers and amyloid- β fibril targets. Affinity variations of up to three orders of magnitude were observed, revealing some structural requirements for these markers at the molecular level.



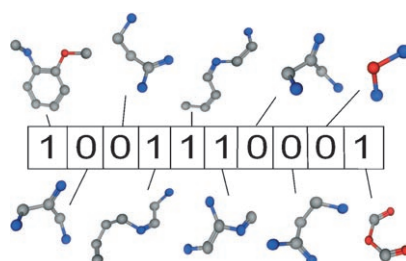
R. Leuma Yona, S. Mazères, P. Faller, E. Gras**

63–66

Thioflavin Derivatives as Markers for Amyloid- β Fibrils: Insights into Structural Features Important for High-Affinity Binding



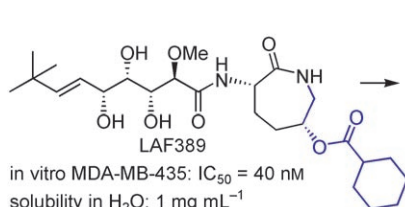
Fine fingerprints. Herein, we show that combinations of randomly generated fragments are signatures of active molecules. Small sets of such fragments are encoded as bit string representations and used for similarity searching. These fingerprints are successfully applied to mine high-throughput screening data sets. Shown are randomly generated substructures encoded as a small fingerprint that were extracted from a fragment pathway specific for cathepsin B inhibitors.



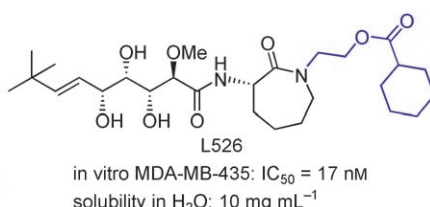
*J. Batista, J. Bajorath**

67–73

Similarity Searching using Compound Class-Specific Combinations of Substructures Found in Randomly Generated Molecular Fragment Populations



in vitro MDA-MB-435: $IC_{50} = 40$ nM
solubility in H_2O : 1 mg mL^{-1}



in vitro MDA-MB-435: $IC_{50} = 17$ nM
solubility in H_2O : 10 mg mL^{-1}

A series of potent, water-soluble N-substituted bengamide analogues were discovered through diverse derivatives of the caprolactam unit of bengamide. Important SAR information was also

gathered, and is different from previously reported SARs of this compound class. We therefore present a new view of bengamide natural products.

G. Liu, Y.-M. Ma, W.-Y. Tai, C.-M. Xie, Y.-L. Li, J. Li, F.-J. Nan**

74–78

Design, Synthesis, and Biological Evaluation of Caprolactam-Modified Bengamide Analogues



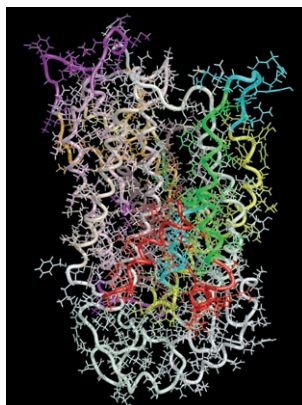
FULL PAPERS

A. Pedretti, L. De Luca, C. Sciarrillo,
G. Vistoli*

79 – 90



**Fragmental Modeling of Human
Glutamate Transporter EAAT1 and
Analysis of its Binding Modes by
Docking and Pharmacophore Mapping**



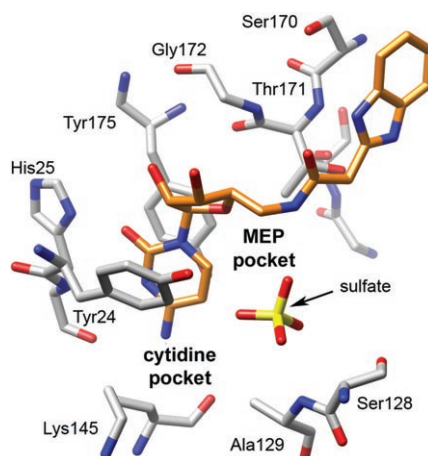
The glutamate transporters EAATs are involved in many neurodegenerative diseases. The aim of this study was to generate a model for the human EAAT1 in its homotrimeric structure using a fragmental approach. The model was validated by docking analyses and pharmacophore mapping using a set of 32 known ligands.

C. M. Crane, A. K. H. Hirsch, M. S. Alphey,
T. Sgraja, S. Lauw, V. Illarionova,
F. Rohdich,* W. Eisenreich, W. N. Hunter,*
A. Bacher, F. Diederich*

91 – 101



**Synthesis and Characterization of
Cytidine Derivatives that Inhibit the
Kinase IspE of the Non-Mevalonate
Pathway for Isoprenoid Biosynthesis**



The binding modes of two water-soluble, cytidine-based inhibitors in complex with the *A. aeolicus* kinase IspE were elucidated by co-crystal structure analysis. Because key active site residues in *A. aeolicus* IspE are identical to those of the corresponding enzymes of *M. tuberculosis* and *P. falciparum*, useful structural information was gained for future structure-based development of inhibitors of the parasite enzymes.

J. Winkler, M. Gilbert, A. Kocourková,
M. Stessl, C. R. Noe*

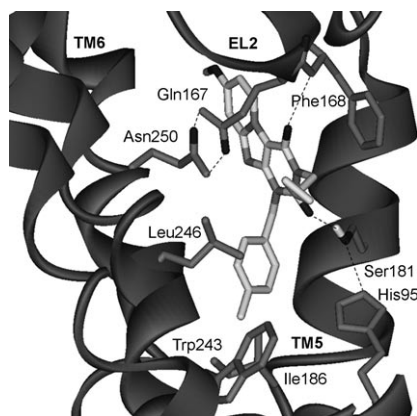
102 – 110

**2'-O-Lysylaminohexyl
Oligonucleotides: Modifications for
Antisense and siRNA**



Cationic nucleotides consisting of lysine tethered by a 2'-O-aminohexyl linker to uridine incorporated into siRNA increase target affinity and can be used in functional oligonucleotides for effective gene silencing in vitro. In DNA-based antisense oligonucleotides, affinity to the RNA complement was decreased, but the in vitro activity increased with a greater number of modifications.

Antagonizing adenosine. Novel compounds based on 1*H*,3*H*-pyrido[2,1-*f*]-purine-2,4-diones are described as potent and selective human adenosine A₃ antagonists with *K_i* values in the low-nanomolar range. Molecular modeling studies have been performed to explain the selectivity for the hA₃ receptor.



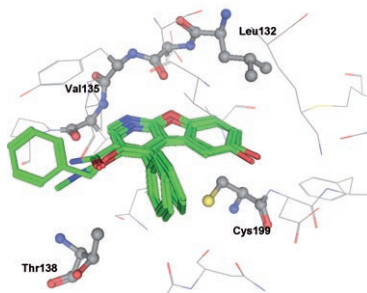
*E.-M. Priego, M.-J. Pérez-Pérez, J. K. von Frijtag Drabbe Kuenzel, H. de Vries, A. P. IJzerman, M.-J. Camarasa, S. Martín-Santamaría**

111 – 119

Selective Human Adenosine A₃ Antagonists based on Pyrido[2,1-*f*]-purine-2,4-diones: Novel Features of hA₃ Antagonist Binding



Glycogen synthase kinase 3β (GSK-3β) is of great importance for the phosphorylation of tau protein, which in turn is important as it forms the basis of neurofibrillary tangles in Alzheimer's disease. To better understand the pathophysiological process highly selective inhibitors of this kinase are of great value. Novel 1-aza-9-oxafluorenes show high selectivity as GSK-3β inhibitors and may prove useful as a tool to probe the role of GSK-3β in tangle formation.

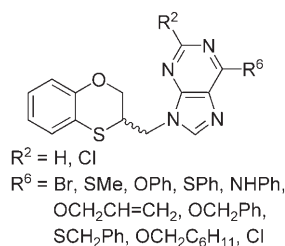


*B. Voigt, M. Krug, C. Schächtele, F. Totzke, A. Hilgeroth**

120 – 126

Probing Novel 1-Aza-9-oxafluorenes as Selective GSK-3β Inhibitors

New therapeutic structures against the human breast cancer cell line MCF-7: a series of 2- and 6-substituted (*R,S*)-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine derivatives represent a new compound structure class. For some of these compounds, anticancer activity is correlated with the capacity to induce apoptosis.

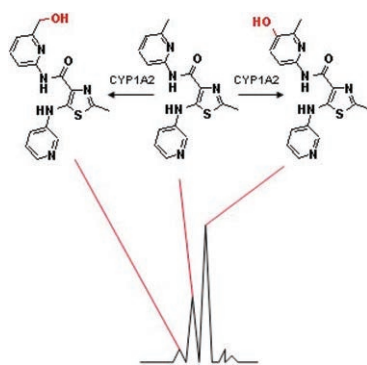


*M. Díaz-Gavilán, A. Conejo-García, O. Cruz-López, M. C. Núñez, D. Choquesillo-Lazarte, J. M. González-Pérez, F. Rodríguez-Serrano, J. A. Marchal, A. Aránega, M. A. Gallo, A. Espinosa, J. M. Campos**

127 – 135

Synthesis and Anticancer Activity of (*R,S*)-9-(2,3-Dihydro-1,4-Benzoxathiin-3-ylmethyl)-9*H*-Purines

LC-SPE-NMR-MS. The combination of high performance liquid chromatography, on-line solid-phase extraction, NMR and MS spectroscopy into an integrated LC-SPE-NMR-MS system has been used to give comprehensive structural data on the major metabolites of a lead metabotropic glutamate receptor 5 (mGlu5) allosteric antagonist.



S. M. Ceccarelli, G. Schlotterbeck,* P. Boissin, M. Binder, B. Buettelmann, S. Hanlon, G. Jaeschke, S. Kolczewski, E. Kupfer, J.-U. Peters, R. H. P. Porter, E. P. Prinssen, M. Rueher, I. Ruf, W. Spooren, A. Stämpfli, E. Vieira*

136 – 144

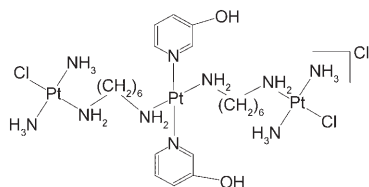
Metabolite Identification via LC-SPE-NMR-MS of the In vitro Biooxidation Products of a Lead mGlu5 Allosteric Antagonist and Impact on the Improvement of Metabolic Stability in the Series



H. Tayyem, F. Huq,* J. Q. Yu, P. Beale, K. Fisher

145 – 151


Synthesis and Activity of a Trinuclear Platinum Complex: $[\{\text{trans-PtCl}(\text{NH}_3)_2\}_2\mu\text{-}\{\text{trans-Pt}(3\text{-hydroxypyridine})_2(\text{H}_2\text{N}(\text{CH}_2)_6\text{NH}_2)_2\}]\text{Cl}_4$ in Ovarian Cancer Cell Lines

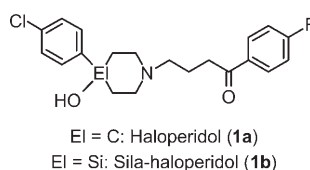


Anticancerous complexes. Although highly effective against testicular and ovarian cancers, cisplatin and its analogues have a limited spectrum of activity, numerous side effects, and the problem of intrinsic and/or acquired resistance. This paper describes the synthesis, characterisation, and cytotoxicity of a novel trinuclear platinum complex TH1 (shown) which has the potential to become a highly active anticancer drug.

R. Tacke,* F. Popp, B. Müller, B. Theis, C. Burschka, A. Hamacher, M. U. Kassack, D. Schepmann, B. Wünsch, U. Jurva, E. Wellner

152 – 164

 **Sila-Haloperidol, a Silicon Analogue of the Dopamine (D₂) Receptor Antagonist Haloperidol: Synthesis, Pharmacological Properties, and Metabolic Fate**

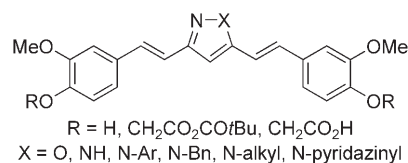


Sila-haloperidol (1b), a silicon analogue of the dopamine (D₂) antagonist haloperidol (1a), was synthesized. As shown in receptor binding studies, sila-haloperidol (1b) shows a higher potency at hD₂ receptors than the parent carbon compound 1a and exhibits higher subtype selectivity at dopamine receptors and at σ receptors as well. The metabolic fates of the C/Si analogues 1a and 1b are totally different.

R. Narlawar, M. Pickhardt, S. Leuchtenberger, K. Baumann, S. Krause, T. Dyrks, S. Weggen, E. Mandelkow, B. Schmidt*

165 – 172


Curcumin-Derived Pyrazoles and Isoxazoles: Swiss Army Knives or Blunt Tools for Alzheimer's Disease?

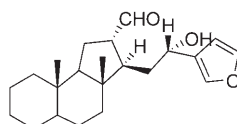


Curcumin-derived isoxazoles and pyrazoles minimize the metal chelation properties of curcumin. Replacement of the 1,3-dicarbonyl moiety with isosteric heterocycles turns curcumin analogue isoxazoles and pyrazoles into potent ligands of fibrillar A β ₄₂ aggregates. Additionally, several compounds are potent inhibitors of tau protein aggregation and depolymerized tau protein aggregates at low micromolar concentrations.

L. Du, L. Shen, Z. Yu, J. Chen, Y. Guo,* Y. Tang,* X. Shen,* H. Jiang

173 – 180

 **Hyrtilial, from the Marine Sponge *Hyrtilios erectus*, Inhibits HIV-1 Integrase Binding to Viral DNA by a New Inhibitor Binding Site**




HIV-1 integrase mediates the integration of reverse-transcribed viral cDNA into the host genome and presents an attractive target for anti-HIV drug development. We report that hyrtiosal, a natural product from the marine sponge *Hyrtilios erectus*, known to be a PTP1B inhibitor, could competitively inhibit HIV-1 integrase binding to the viral DNA by a new inhibitor binding site.

CONFERENCE REPORTS

Highlighting the New Advances in Drug Discovery and Development

S. Taliani, F. Da Settimo*

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

* Author to whom correspondence should be addressed.

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Structural Genomics on Membrane Proteins · K. H. Lundstrom (Ed.)	L. Schmitt	185
Structural Genomics and High Throughput Structural Biology · M. Sundström, M. Norin, A. Edwards (Eds.)	K. Lundstrom	186

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GESELLSCHAFT DEUTSCHER CHEMIKER

Call for Nominations for the Klaus Grohe Prize 2008

The Klaus Grohe Foundation, administered by the German Chemical Society (GDCh), awards the Klaus Grohe Prize to outstanding young scientists (post graduate students and postdoctoral researchers up to three years after having completed the doctorate) working in the field of medicinal chemistry and drug research at research institutes in Germany or other European countries.

Contact

Gesellschaft
Deutscher Chemiker
Abt. Preise und Auszeichnungen
P.O.Box 90 04 40
60444 Frankfurt a. M.

E-Mail: b.koehler@gdch.de
Tel. 069 79 17-323
Fax: 069 79 17-307

In general, the prize winners should have some connection to medicinal chemistry/drug research in Germany.

Two prizes, each endowed with € 2000, will be awarded at the 125th Conference of the GDNÄ (Association of German Natural Scientists and Physicians) in September 2008. The prize winners will give a lecture on their scientific work.

Proposals should consist of a letter in support of the nomination (self-nominations are welcome), a curriculum vitae, and a list of publications.

Please submit your nomination by **March 15, 2008** to

Gesellschaft Deutscher Chemiker, Barbara Köhler, Awards,
Varrentrappstraße 40 - 42, 60486 Frankfurt am Main, Germany.