

CHEMICAL & MEDICINAL CHEMISTRY

<http://www.chemmedchem.org>

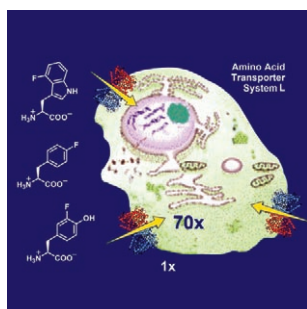
Full text:

WILEY
InterScience®
DISCOVER SOMETHING GREAT
<http://www.interscience.wiley.com>

ChemMedChem, European in origin but international in scope, deals with all aspects of drug discovery. It is co-owned by Chemistry Publishing Society Europe (ChemPubSoc Europe) and is published by Wiley-VCH. Contributions in *ChemMedChem* cover medicinal and pharmaceutical sciences, drug design, drug development and delivery, molecular modeling, combinatorial chemistry, target validation, lead generation, and ADMET studies, that is, research from the overlapping areas between biology, chemistry, and medicine. *ChemMedChem* publishes Communications and Full Papers, as well as Reviews, Minireviews, Highlights, Concepts, Essays, Book Reviews, and occasionally Conference Reports. Authors can submit manuscripts to *ChemMedChem* online through our homepage (see left) by clicking on "Online Submission" and following the simple instructions.

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 fluorinated aromatic amino acids that exhibit cytostatic activity on tumor cells. These amino acid derivatives are taken up by the cells via the amino acid transport system L. This active process results in a 70-fold accumulation of the fluorinated aromatic amino acids within the cell relative to the surrounding media, which explains why they are biologically active with quite low EC_{50} values. For details, see the Full Paper by N. Budisa, H. Lilie, et al. on p. 1449 ff.

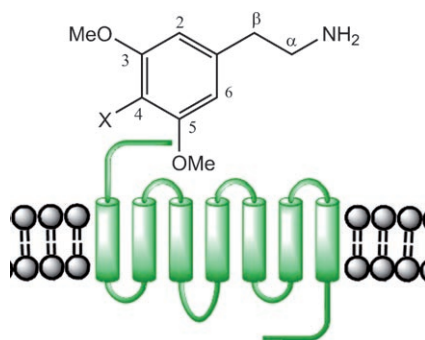
NEWS

Spotlights on our sister journals

1296 – 1297

MINIREVIEWS

Agonist activation of 5-HT_{2A} receptors has become therapeutically interesting. Substituted phenylalkylamines are the most suitable agonists for the study of 5-HT_{2A} receptor activation. This minireview summarizes the structure–activity relationships of phenylalkylamines as agonist ligands for the 5-HT_{2A} receptor.



A. R. Blaazer,* P. Smid, C. G. Kruse*

1299 – 1309

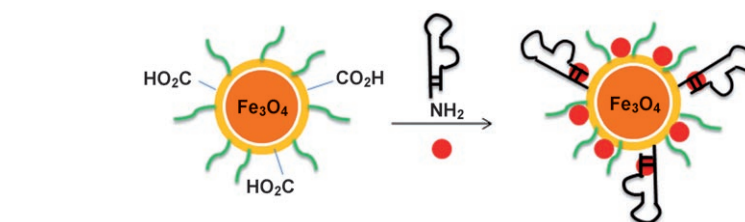
Structure–Activity Relationships of Phenylalkylamines as Agonist Ligands for 5-HT_{2A} Receptors

COMMUNICATIONS

A. Z. Wang, V. Bagalkot, C. C. Vasilliou, F. Gu, F. Alexis, L. Zhang, M. Shaikh, K. Yuet, M. J. Cima, R. Langer, P. W. Kantoff, N. H. Bander, S. Jon,* O. C. Farokhzad*

1311 – 1315

Superparamagnetic Iron Oxide Nanoparticle–Aptamer Bioconjugates for Combined Prostate Cancer Imaging and Therapy



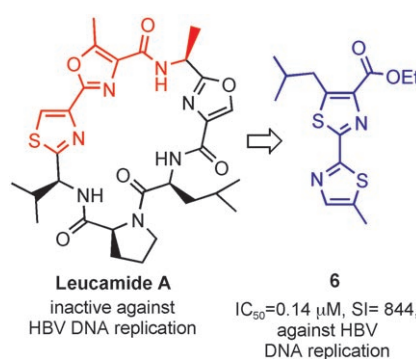
Multifunctional superparamagnetic iron oxide nanoparticles: Herein we report a novel, targeted, iron oxide nanoparticle for combined prostate cancer imaging and therapy. By conjugating an aptamer to a thermally stable

iron oxide nanoparticle, we have demonstrated that bioconjugates can detect prostate cancer cells with high sensitivity and specificity. Furthermore, the bioconjugates can be used to deliver targeted chemotherapy.

H.-J. Chen, W.-L. Wang, G.-F. Wang, L.-P. Shi, M. Gu, Y.-D. Ren, L.-F. Hou, P.-L. He, F.-H. Zhu, X.-G. Zhong, W. Tang, J.-P. Zuo,* F.-J. Nan*

1316 – 1321

Rational Design and Synthesis of 2,2-Bisheterocycle Tandem Derivatives as Non-Nucleoside Hepatitis B Virus Inhibitors



Non-nucleoside tandem derivatives:

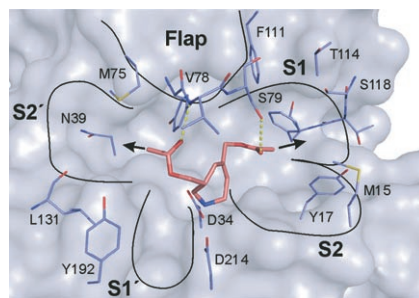
Potent hepatitis B antiviral activity is established for 2,2'-bisthiazole heterocyclic derivatives. The core structure of these compounds differs from those of known non-nucleoside hepatitis B antiviral agents, constituting a new direction in hepatitis B virus drug development.

FULL PAPERS

T. Luksch, N.-S. Chan, S. Brass, C. A. Sotriffer, G. Klebe, W. E. Diederich*

1323 – 1336

Computer-Aided Design and Synthesis of Nonpeptidic Plasmepsin II and IV Inhibitors

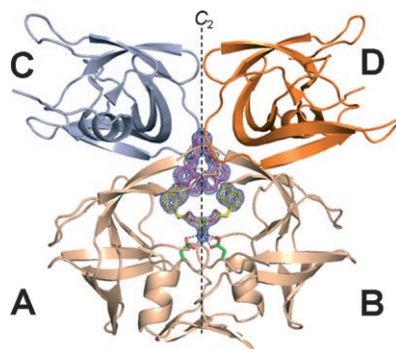


Computer-aided inhibitor design: Non-peptidic inhibitors of the aspartic proteases plasmepsin II and IV were developed that bear a tetrahydro-1*H*-azepine scaffold. Structural modifications of the initial lead in a consecutive design cycle led to inhibitors with affinities in the nanomolar range. The K_i values are generally in good agreement with the design hypothesis, thus supporting the predicted binding mode for both plasmepsins.

J. Böttcher, A. Blum, S. Dörr, A. Heine, W. E. Diederich, G. Klebe*

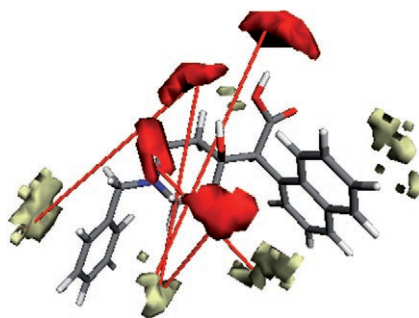
1337 – 1344

Targeting the Open-Flap Conformation of HIV-1 Protease with Pyrrolidine-Based Inhibitors



Although HIV-1 protease exhibits high flexibility, all approved drugs target virtually the same protein conformation. Herein we report novel symmetric pyrrolidine-based inhibitors addressing the open-flap conformation of the protease. The co-crystal structure of one derivative provides a valuable starting point for further development of HIV protease inhibitors.

The synthesis of a series of adrenomedullin (AM) modulators was carried out. A competitive AM monoclonal antibody assay and SPR measurements were used to evaluate the affinity of these compounds toward AM. A 3D-QSAR study highlighted essential features for AM binding, and the derived model is a valuable tool in the design of new derivatives.



V. Roldós, S. Martín-Santamaría, M. Julián, A. Martínez, L. Choulier, D. Altschuh, B. de Pascual-Teresa,* A. Ramos*

1345 – 1355

Small-Molecule Negative Modulators of Adrenomedullin: Design, Synthesis, and 3D-QSAR Study



Attachment of ligands to DNA or RNA delivery systems is a promising strategy for targeted applications. We report the conjugation of a ligand directly onto lipid–nucleic acid complexes using

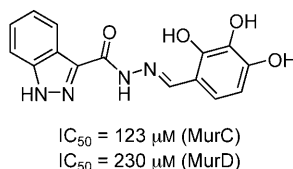
an oximation approach. Simple incubation of DMDK lipoplexes with an aminoxy reagent labeled the lipoplexes without sacrificing transfection efficiency.

J. G. Hecker, G. O. Berger, K. A. Scarfo, S. Zou, M. H. Nantz*

1356 – 1361

A Flexible Method for the Conjugation of Aminoxy Ligands to Preformed Complexes of Nucleic Acids and Lipids

Targeting pathogen resistance: There is an urgent need to improve existing compounds and to develop new antimicrobial drugs in the battle against infectious diseases because of the increase in multidrug-resistant bacteria. As Mur ligases have an essential role in the intracellular biosynthesis of bacterial peptidoglycan, they represent attractive targets for the design of novel antibacterials.

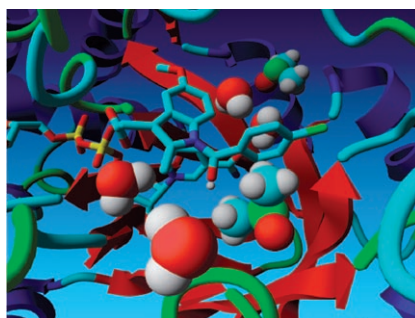


R. Šink, A. Kovač, T. Tomašić, V. Rupnik, A. Boniface, J. Bostock, I. Chopra, D. Blanot, L. P. Mašič, S. Gobec, A. Zega*

1362 – 1370

Synthesis and Biological Evaluation of N-Acylhydrazones as Inhibitors of MurC and MurD Ligases

Solvent accessibility mapping can be used to characterize protein–ligand interactions. Herein, we critically evaluate the applicability of solvent accessibility mapping to derive binding orientations for ligands of two dehydrogenases (AKR1C3 and HSD17β1) with very different binding pockets, including complexes in which the ligand is buried more deeply inside the protein.



C. Ludwig, P. J. A. Michiels, A. Lodi, J. Ride, C. Bunce, U. L. Günther*

1371 – 1376

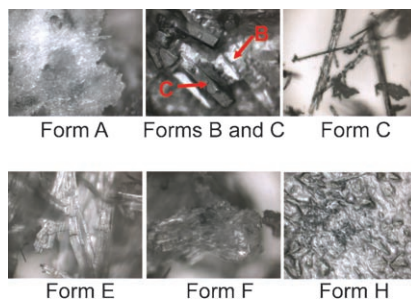
Evaluation of Solvent Accessibility Epitopes for Different Dehydrogenase Inhibitors

G. Petruševski, P. Naumov,* G. Jovanovski,
G. Bogoeva-Gaceva, S. W. Ng

1377 – 1386



Solid-State Forms of Sodium Valproate, Active Component of the Anticonvulsant Drug Epilim



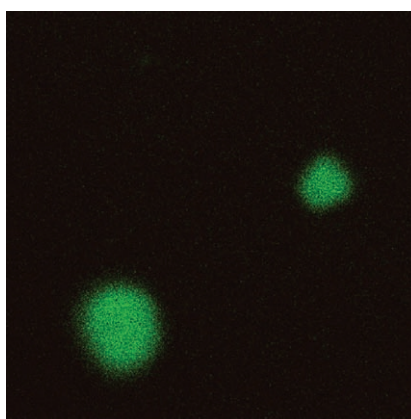
Sodium valproate, the active ingredient of a group of valproate-based anticonvulsants, can be present in eight forms in the solid state, including four solvates with valproic acid. The pronounced hygroscopicity of some of the forms is inherent to the loose crystal packing, which is directed by the symmetric shape of the compound. Partial or complete stabilization can be achieved by thermal/evacuation treatment and crystallization with valproic acid.

N. Viola-Villegas, A. E. Rabideau,
J. Cesnavicius, J. Zubieta, R. P. Doyle*

1387 – 1394



Targeting the Folate Receptor (FR): Imaging and Cytotoxicity of Re¹ Conjugates in FR-Overexpressing Cancer Cells

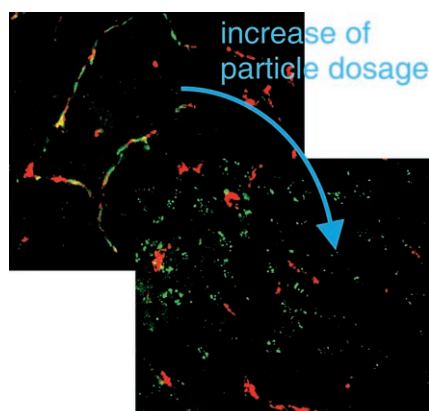


Lighting the way: A new folic acid based bioconjugate selectively delivers Re¹ to the folate-receptor-positive ovarian tumor cell line A2780/AD (shown). The compounds have significant cytotoxicity, and this is explored in terms of DNA interactions and is contrasted with cisplatin controls.

C. K. Weiss,* M.-V. Kohnle, K. Landfester,
T. Hauk, D. Fischer, J. Schmitz-Wienke,
V. Mailänder

1395 – 1403

The First Step into the Brain: Uptake of NIO-PBCA Nanoparticles by Endothelial Cells *in vitro* and *in vivo*, and Direct Evidence for their Blood–Brain Barrier Permeation



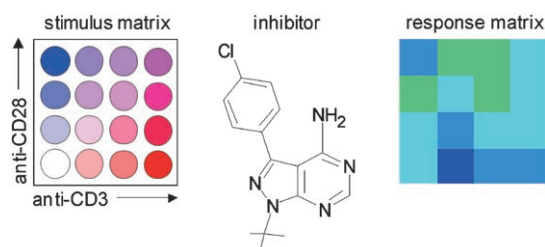
Enter the brain. Fluorescent polysorbate 80 coated PBCA nanoparticles, prepared in miniemulsion, were investigated for their capacity to permeate blood–tissue barriers *in vivo* and *in vitro*. Direct evidence for a concentration-dependent permeation of the blood–brain barrier as well as the blood–retina barrier was obtained.

K. Köhler, A. Ganser, T. André, G. Roth,
L. Grosse-Hovest, G. Jung, R. Brock*

1404 – 1411



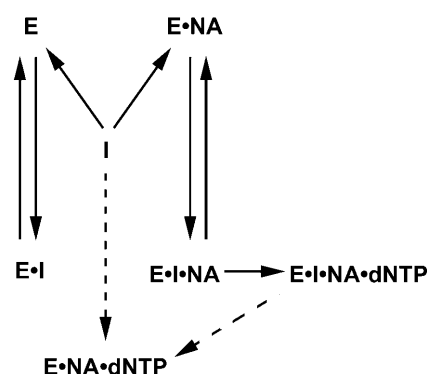
Stimulus Dependence of the Action of Small-Molecule Inhibitors in the CD3/CD28 Signalling Network



2+2 ≠ 4. Inside the body, cells are simultaneously exposed to a multitude of various stimuli. To address the relevance of cellular signalling networks for drug design, cells were exposed to a matrix

of combinations of two stimuli, and the cellular responses were recorded in the absence and presence of pharmacological inhibitors.

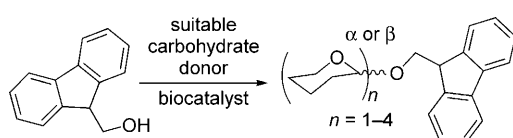
Fast on, slow off: In addition to their greatly improved association rates to HIV-1 RT wild-type and mutated forms, 2-Cl-6-F-*N,N*-DABOs preferentially associate with mutated RT forms in the unbound (free enzyme) state or in binary complex with the nucleic acid substrate. Their interaction with mutated RT is highly stabilized by nucleotide binding to the enzyme, resulting in very slow inhibitor dissociation rates. These unique properties can be exploited to design NNRTIs that specifically target drug-resistant forms of HIV-1 RT.



A. Samuele, M. Facchini, D. Rotili, A. Mai,*
M. Artico, M. Armand-Ugón, J. A. Esté,
G. Maga*

1412 – 1418

Substrate-Induced Stable Enzyme–Inhibitor Complex Formation Allows Tight Binding of Novel 2-Aminopyrimidin-4(3*H*)-ones to Drug-Resistant HIV-1 Reverse Transcriptase Mutants



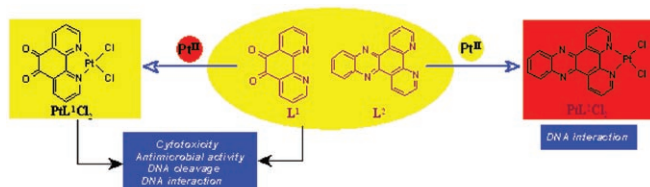
Biocatalytic routes that circumvent difficult chemical procedures for the production of a series of various polyglycosides using marine glycosidases from *A. fasciata* (α -glucosides) and *T. neapolitana* (β -xylosides) are described. Easy

access to these polyglycosides permits the discovery of antiviral activity, possibly exerted by influencing the balance of cytokines in the environment of peripheral blood mononuclear cells.

A. Tramice, A. Arena, A. De Gregorio,
R. Ottanà, R. Maccari, B. Pavone,
N. Arena, D. Iannello, M. G. Vigorita,
A. Trincone*

1419 – 1426

Facile Biocatalytic Access to 9-Fluorenylmethyl Polyglycosides: Evaluation of Antiviral Activity on Immunocompetent Cells



Leading a double life: The dual action of DNA-targeting drugs as both anti-neoplastic and antimicrobial agents is exemplified by the phenanthroline

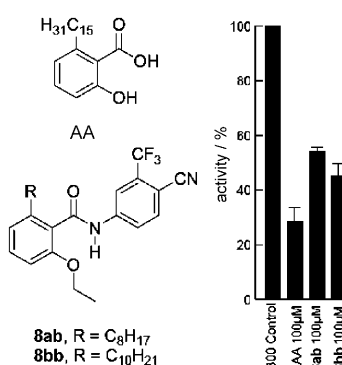
derivatives and then resolved through their complexation with Pt leading to greater specificity and hence improved therapeutic utility.

S. Roy, K. D. Hagen, P. U. Maheswari,
M. Lutz, A. L. Spek, J. Reedijk,*
G. P. van Wezel*

1427 – 1434

Phenanthroline Derivatives with Improved Selectivity as DNA-Targeting Anticancer or Antimicrobial Drugs

HATs off: 4-Cyano-3-trifluoromethylphenylbenzamides **8ab** and **8bb** exhibit activities similar to anacardic acid (AA) as human p300 inhibitors. They induce a decrease in histone acetylation levels in immortalized HEK cells and counteract the action of the HDAC inhibitor SAHA in MCF7 breast cancer cells.




J. A. Souto, M. Conte, R. Álvarez,
A. Nebbioso, V. Carafa, L. Altucci,*
A. R. de Lera*

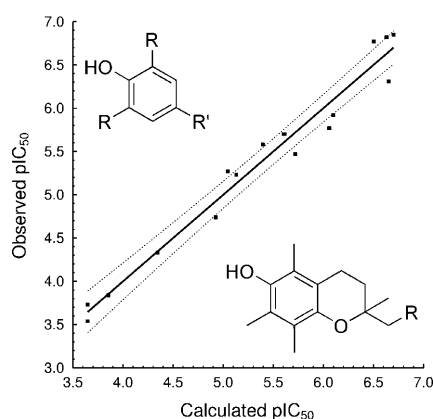
1435 – 1442

Synthesis of Benzamides Related to Anacardic Acid and Their Histone Acetyltransferase (HAT) Inhibitory Activities

P. Tosco, E. Marini, B. Rolando,
L. Lazzarato, C. Cena, M. Bertinaria,
R. Fruttero, M. Reist, P.-A. Carrupt,
A. Gasco*

1443 – 1448


 **Structure–Antioxidant Activity Relationships in a Series of NO-Donor Phenols**

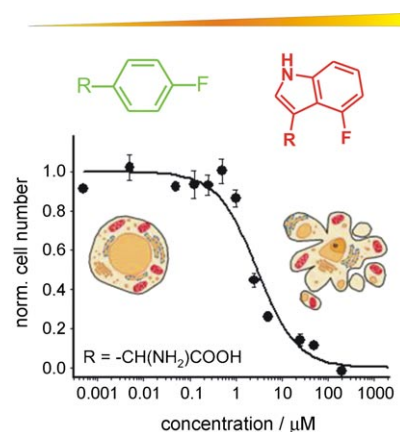


Antioxidants have attracted a great deal of attention as therapeutic agents for a number of pathologies. The relationships between reactivity descriptors, lipophilicity, and antioxidant activity have been explored on a recently reported series of NO-donor phenols. QSAR equations have been derived which shed light on the possible mechanisms of reaction with radicals in different environments.


C. Giese, S. Lepthien, L. Metzner,
M. Brandsch, N. Budisa,* H. Lillie*


1449 – 1456

 **Intracellular uptake and inhibitory activity of aromatic fluorinated amino acids in human breast cancer cells**



Fluorinated aromatic amino acids as antitumor agents: The cellular uptake of fluorinated derivatives of tryptophan, tyrosine and phenylalanine via the active amino acid transport system L resulted in a 70-fold intracellular accumulation. These analogues effectively and irreversibly inhibited MCF-7 tumor cell culture growth with IC_{50} values in the low micromolar range, indicating that these substances might represent new cytostatic drugs for certain tumor types.

 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

The Chemokine Receptors · J. K. Harrison and N. W. Lukacs (Eds.)

L. Gattegno 1457

SERVICE

Author Index 1460 Preview 1462

Keyword Index 1461

All the Tables of Contents may be found on the WWW under:
<http://www.chemmedchem.org>

Issue 8, 2008, was published online on August 11, 2008.