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CHEMISTRY ENABLING DRUG DISCOVERY

03/2007

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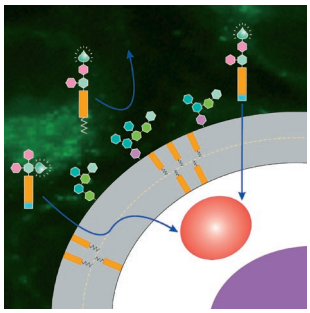
Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE



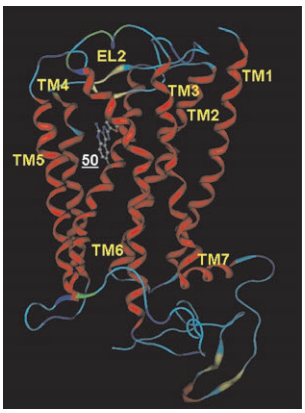
The cover picture shows three structurally similar steroid glycosides bearing fluorescent tags. One crosses the cell membrane faster (top, straight arrow) than the other (left, curved path) to localize in the lysosome (red sphere). The third (middle), with a cholesterol aglycone moiety, does not enter into the cell at all. Steroid glycosides are abundant natural surfactants known as saponins, which have membrane-disrupting properties. However, the three saponins represented here are not found in the cell membrane, where cholesterol and carbohydrate chains are abundant. For details, see the Communication by B. Yu et al. on p. 288 ff.

NEWS

From our sister journals ***258 – 259***

REVIEWS

Adenosine modulates a variety of physiological and pathophysiological processes through the interaction with four subtypes of a family of cell-surface G-protein-coupled receptors. This review presents an update of medicinal chemistry and molecular recognition of A_{2A} adenosine receptor agonists and antagonists and stresses the strong need for more selective ligands at the A_{2A} human subtype.



G. Cristalli, B. Cacciari, D. Dal Ben, C. Lambertucci, S. Moro, G. Spalluto, R. Volpini*

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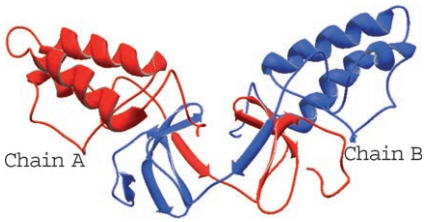
Highlights on the Development of A_{2A} Adenosine Receptor Agonists and Antagonists

HIGHLIGHTS

Z. Suo, M. A. F. Abdullah

283 – 284

Unique Composite Active Site of the Hepatitis C Virus NS2-3 Protease: a New Opportunity for Antiviral Drug Design



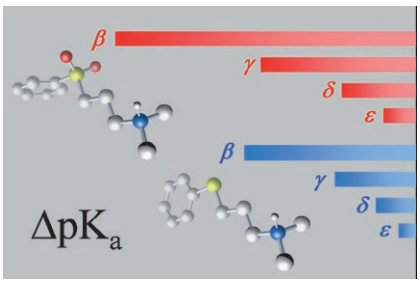
The crystal structure of the catalytic domain of hepatitis C virus NS2-3 protease reveals a unique composite active site. Information from the structure may lead to the design of new antiviral drugs to control liver disease.

COMMUNICATIONS

*R. E. Martin, B. Plancq, O. Gavelle, B. Wagner, H. Fischer, S. Bendels, K. Müller**

285 – 287

Remote Modulation of Amine Basicity by a Phenylsulfone and a Phenylthio Group

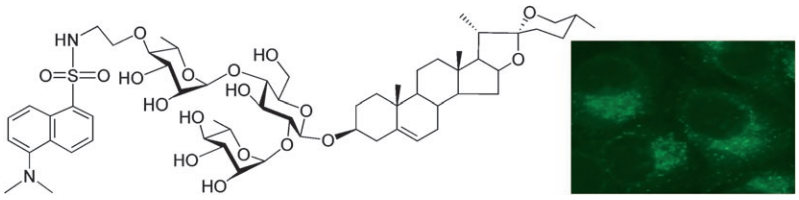


Marked basicity-lowering effects by a sulfone unit are documented in a series of phenylsulfone amines in which the sulfone unit is placed at different topological distances to an aliphatic amine group. An exponential attenuation of basicity shifts by increasing distance is observed. Smaller effects are exerted by a phenylthio group, in each case corresponding to those of a phenylsulfone unit one σ-bond further away from the amino function.

*Y. Wang, Y. Zhang, B. Yu**

288 – 291

The Cytotoxicity of Saponins Correlates with Their Cellular Internalization

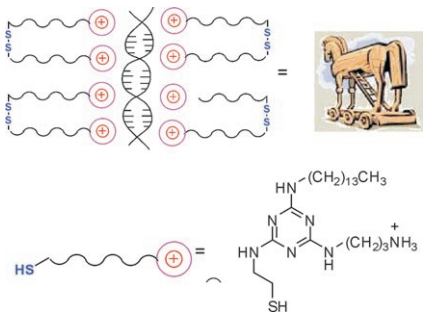


Sneaking in unexpectedly: Saponins are a broad class of plant-derived compounds that are commonly used as a tool to disrupt cell membranes. Some saponins such as that shown above, however, do not anchor themselves to the cell membrane, but are instead internalized. They localize specifically to acidic organelles such as lysosomes, and inhibit the growth of tumor cells.

*G. Candiani, M. Frigerio, F. Viani, C. Verpelli, C. Sala, L. Chiamenti, N. Zaffaroni, M. Folini, M. Sani, W. Panzeri, M. Zanda**

292 – 296

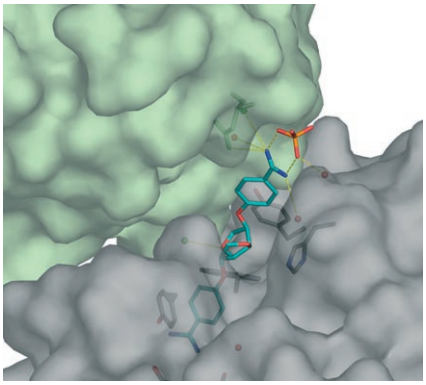
Dimerizable Redox-Sensitive Triazine-Based Cationic Lipids for in vitro Gene Delivery



The "Trojan Horse" trick works again. Conceptually new melamine-based cationic lipids show excellent transfection efficiency and low cytotoxicity in delivering a DNA plasmid payload to different types of cells, deceiving the natural mechanism of defense toward exogeneous DNA.

FULL PAPERS

Changing identity: The binding site residues of trypsin were gradually substituted to match those of the factor Xa binding site. Crystallographic analysis of the resulting mutant proteins complexed with bis-benzamidine inhibitors having a dianhydrosugar isosorbide scaffold in common has shown that aromatic interactions play a key role in determining substrate selectivity in these serine proteases.



*A. Di Fenza, A. Heine, U. Koert, G. Klebe**

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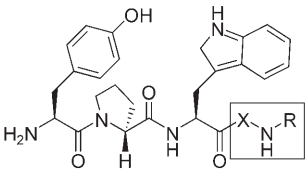
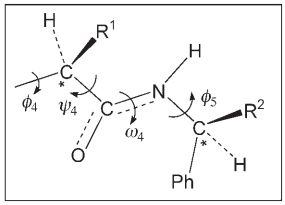
Understanding Binding Selectivity toward Trypsin and Factor Xa: the Role of Aromatic Interactions



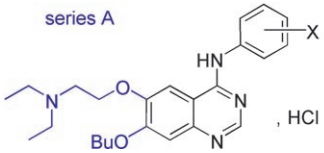


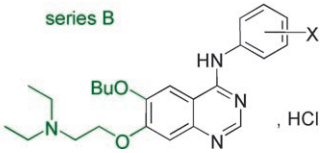
The C termini of endomorphin analogues, [Xaa^4-R]EMs, modified by substitution of Phe^4 with nonaromatic residues and terminated with benzyl groups, were designed to generate conformational constrains of the third aromatic ring by amide bond and torsion angles (ϕ_4 and ψ_4) of Xaa^4.

*Y. Yu, X. Shao, Y. Cui, H.-m. Liu, C.-l. Wang, Y.-z. Fan, J. Liu, S.-l. Dong, Y.-x. Cui, R. Wang**

309 – 317

Structure–Activity Study on the Spatial Arrangement of the Third Aromatic Ring of Endomorphins 1 and 2 Using an Atypical Constrained C Terminus



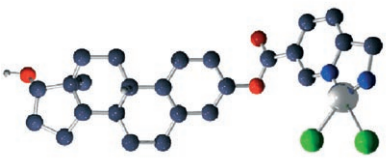


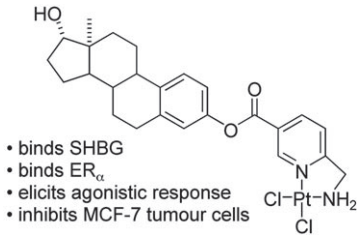
Synthesis and analysis of the in vitro properties of 4-anilinoquinazoline derivatives of Iressa, a specific EGFR inhibitor, were carried out. Different relationships are proposed, and the main data is represented by induction of apoptosis in hormone-independent PC3 cell line.

*A. Telliez, M. Desroses, N. Pommery, O. Briand, A. Farce, G. Laconde, A. Lemoine, P. Depreux, J.-P. Hénichart**

318 – 332

Derivatives of Iressa, a Specific Epidermal Growth Factor Receptor Inhibitor, are Powerful Apoptosis Inducers in PC3 Prostatic Cancer Cells





DNA binding isn't everything: The steroid tail of the platinum complex shown binds strongly to the carrier globulin SHBG, contrary to its isomer featuring a 17-O-linked estradiol. It also binds to the nuclear estrogen receptor, eliciting a distinct estrogenic response, and it inhibits the proliferation of MCF-7 breast cancer cells. Of all steroid conjugate complexes investigated, it interacted least with isolated plasmid DNA.

R. Schobert, G. Bernhardt, B. Biersack, S. Bollwein, M. Fallahi, A. Grotemeier, G. L. Hammond*

333 – 342

Steroid Conjugates of Dichloro(6-aminomethylnicotinate)platinum(II): Effects on DNA, Sex Hormone Binding Globulin, the Estrogen Receptor, and Various Breast Cancer Cell Lines

F. Manetti, A. Pucci, M. Magnani, G. A. Locatelli, C. Brullo, A. Naldini, S. Schenone, G. Maga, F. Carraro, M. Botta**

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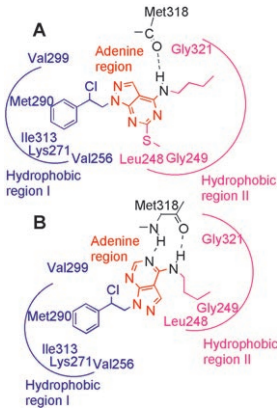
Inhibition of Bcr-Abl Phosphorylation and Induction of Apoptosis by Pyrazolo[3,4-*d*]pyrimidines in Human Leukemia Cells

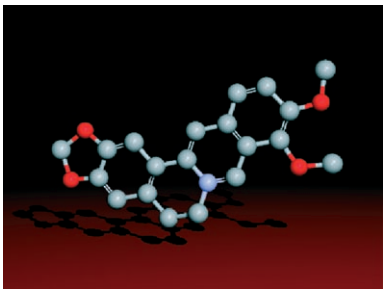


Dual Src/Abl inhibition. On the basis of the experimental evidence that various Src inhibitors are also active against Bcr-Abl kinase (the so called dual Src/Abl inhibitors), a series of pyrazolo-pyrimidines previously found as Src inhibitors, were also tested toward Abl and Bcr-Abl-expressing cell lines. Results showed an activity toward the isolated enzyme in the low micromolar range and micromolar activity toward a panel of three human leukemia cell lines.

*T. Tarrago, N. Kichik, J. Seguí, E. Giralt**

354 – 359

The Natural Product Berberine is a Human Prolyl Oligopeptidase Inhibitor

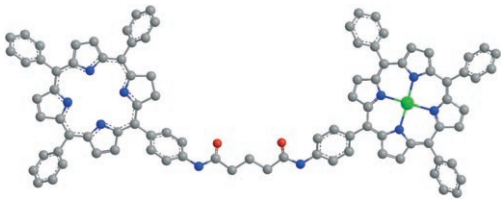


Chinese medicinal plants, a new source of prolyl oligopeptidase inhibitors: ^{19}F NMR spectroscopy screening was used to search for new prolyl oligopeptidase inhibitors in a library of traditional Chinese medicine plant extracts. Several extracts were identified as powerful inhibitors of this peptidase. The natural alkaloid berberine was isolated from *Rhizoma coptidis* extract and inhibited prolyl oligopeptidase in a dose-dependent manner.

J. R. McCarthy, R. Weissleder*

360 – 365

Model Systems for Fluorescence and Singlet Oxygen Quenching by Metalloporphyrins



Next-generation photodynamic therapy (PDT) agents will minimize extraneous phototoxicity by being active only at the target site. This can only occur if suitable photosensitizer excited-state quenching moieties are identified. A series of porphyrin–metalloporphyrin dimers were therefore investigated for potential application in activatable PDT agents.

*M. R. Nussio, M. J. Sykes, J. O. Miners, J. G. Shapter**

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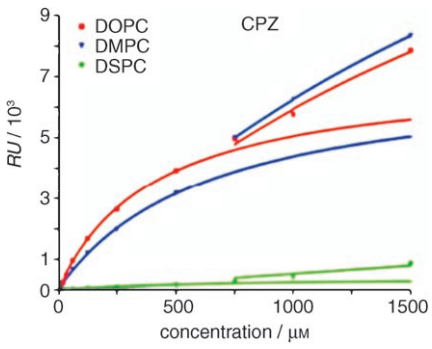
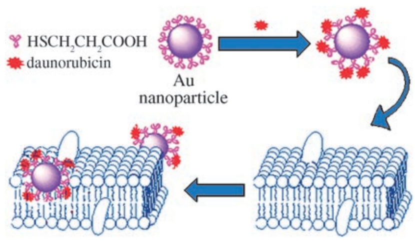
Characterisation of the Binding of Cationic Amphiphilic Drugs to Phospholipid Bilayers Using Surface Plasmon Resonance



The interactions of three cationic amphiphilic drugs (CADs) with phospholipid vesicles were investigated using surface plasmon resonance (SPR). High CAD concentrations provided evidence for a nonsaturable binding process, which may arise from intercalation of the drugs within the lipid bilayer. CAD binding was additionally shown to be dependent on membrane fluidity.

A golden opportunity: Functionalized gold nanoparticles (NPs) synergistically enhance the delivery of drugs to, and serve as biomarkers of drug-resistant leukemia cells. The combination of 3-mercaptopropionic acid capped Au NPs with anticancer drugs could be a new approach to the treatment of cancer.



J. Li, X. Wang, C. Wang, B. Chen, Y. Dai, R. Zhang, M. Song, G. Lv, D. Fu*

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The Enhancement Effect of Gold Nanoparticles in Drug Delivery and as Biomarkers of Drug-Resistant Cancer Cells

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

* Author to whom correspondence should be addressed.

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