



<http://www.chemmedchem.org>

Full text:

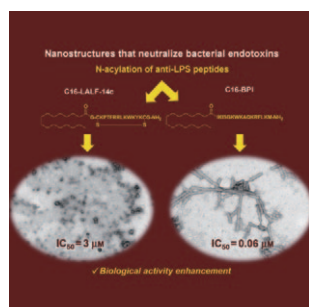


<http://www.interscience.wiley.com>

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



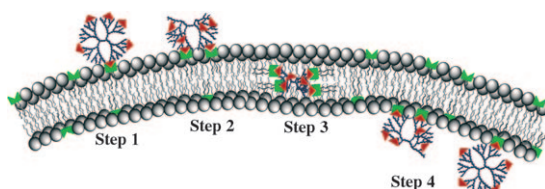
The cover picture shows how the N-acylation (i.e. palmitoylation) of LPS-neutralizing peptides, LALF-14c and BPI, promotes the formation of well-defined nanostructures, such as micelles or fibrils. These peptides show greater biological activities than their nonacylated counterparts. For details, see the Full Paper by F. Albericio et al. on p. 1748 ff.

NEWS

Spotlights on our sister journals

1632 – 1633

MINIREVIEWS



Intracellular delivery of therapeutic molecules is an issue of significant scientific and practical interest, especially in drug and gene delivery. Molecular transporters encompass a diversity of structures and aggregates that enable or enhance transport across biological

membranes. In the present review the transport of guanidinylated dendritic polymers through model liposomal and cell membranes is addressed and the elucidation of their transport mechanism is also discussed.

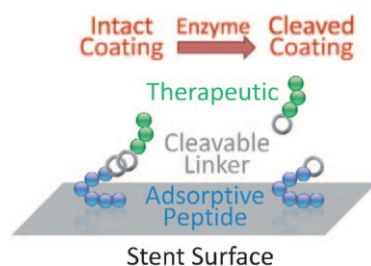
T. A. Theodossiou, A. Pantos, I. Tsogas, C. M. Paleos*

1635 – 1643

Guanidinylated Dendritic Molecular Transporters: Prospective Drug Delivery Systems and Application in Cell Transfection

S. R. Meyers, D. J. Kenan,* M. W. Grinstaff*

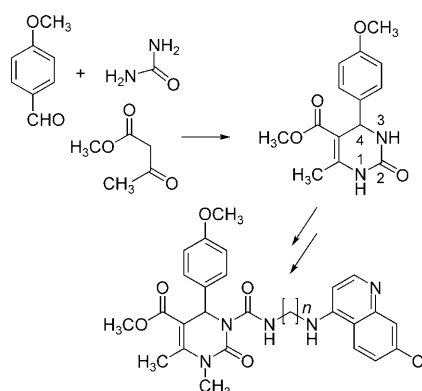
1645 – 1648

**Enzymatic Release of a Surface-Adsorbed RGD Therapeutic from a Cleavable Peptide Anchor**

Implanted medical devices inevitably promote inflammation of the surrounding tissue. A method for enzymatically triggered localized drug delivery would have marked benefits in dealing with this response. Herein we present a rationally designed peptide coating for use with medical devices such as stents, that contains three distinct domains: 1) an implant-adsorptive sequence, 2) an enzymatically cleavable release mechanism, and 3) a therapeutic to be delivered.

N. October, N. D. Watermeyer, V. Yardley, T. J. Egan, K. Ncokazi, K. Chibale*

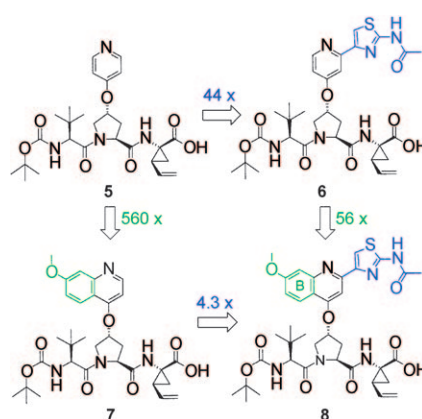
1649 – 1653

**Reversed Chloroquinines Based on the 3,4-Dihydropyrimidin-2(1H)-one Scaffold: Synthesis and Evaluation for Antimalarial, β -Haematin Inhibition, and Cytotoxic Activity**

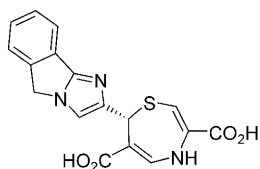
The synthesis, cytotoxicity, and anti-malarial activity of resistance-reversing bifunctional dihydropyrimidone–chloroquinoline conjugates are reported herein. In vitro assay results indicate this class of compounds is highly active against both chloroquine-resistant and chloroquine-sensitive strains of *P. falciparum*.

S. H. Kawai,* M. D. Bailey, T. Halmos, P. Forgione, S. R. LaPlante, M. Llinàs-Brunet, J. Naud, N. Goudreau

1654 – 1657

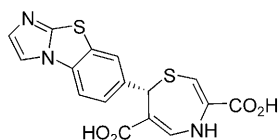
**The Use of Chemical Double-Mutant Cycles in Biomolecular Recognition Studies: Application to HCV NS3 Protease Inhibitors**

Things don't always add up: Our understanding of biomolecular recognition processes is often complicated by the fact that the binding contributions of individual ligand–protein subcontacts do not add up in a linear fashion. Chemical double-mutant cycles are useful analyses to quantify the degree of nonadditivity in such binding phenomena, and peptidyl inhibitors of hepatitis C virus NS3 protease are used to exemplify this.



Compound 23

New interactions of β -lactamases inhibitors: Using computational methods, tricyclic 6-methylidene penems **9a–e** were designed based on their 1,4-dihydrothiazepines rearrangement products as potent and broad spectrum in-



Compound 24

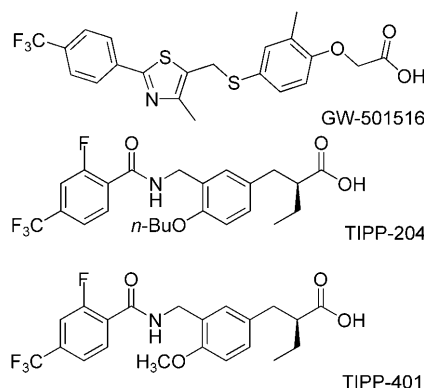
hibitors of β -lactamases. Both dihydrothiazepines **23** and **24** were found to form a new interaction with Val216 in SHV-1, which was not predicted based on initial docking studies.

A. Venkatesan, A. Agarwal, T. Abe, H. Ushiroguchi, T. Takasaki, A. Mihira, T. S. Mansour*

1658 – 1661

Targeting Val 216 in Class A β -Lactamases with Tricyclic 6-Methylidene Penems

Phenylpropanoic acid-derived PPAR agonist TIPP-204, shows high selectivity for human (h)PPAR δ while structurally related TIPP-401 is a hPPAR α/δ dual agonist. Computational docking of TIPP-401 in the ligand binding domain (LBD) of hPPAR α and hPPAR δ , and inspection of the TIPP-204–hPPAR δ LBD co-crystal structure identified key amino acids responsible for the differences in selectivity of the two analogues. These results were confirmed using mutagenesis assays. The amino acids determining the potency and selectivity of TIPP-204 are different to those of the PPAR δ -selective agonist GW-501516, which belongs to a different chemical class.

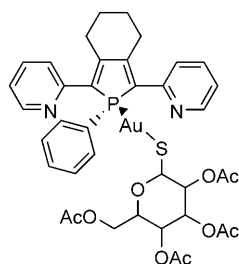


J. Kasuga, T. Oyama, I. Nakagome, M. Makishima, S. Hirono, K. Morikawa, Y. Hashimoto, H. Miyachi*

1662 – 1666

Determination of the Critical Amino Acids Involved in the Peroxisome Proliferator-Activated Receptor (PPAR) δ Selectivity of Phenylpropanoic Acid-Derived Agonists

A phosphine-coordinated gold(I) thio-sugar complex was found to exert potent cytotoxic and antiproliferative effects through thioredoxin reductase inhibition in MCF-7 cells.



GoPI-sugar

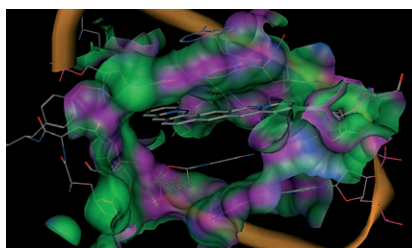
Cytotoxic to MCF-7 cells

E. Viry, E. Battaglia, V. Deborde, T. Müller, R. Réau, E. Davioud-Charvet, D. Bagrel*

1667 – 1670

A Sugar-Modified Phosphole Gold Complex with Antiproliferative Properties Acting as a Thioredoxin Reductase Inhibitor in MCF-7 Cells

Unsubstituted polyaromatic dications exhibit a significant influence on the activity of topoisomerase I, as shown by plasmid relaxation assays and molecular modeling studies. Moreover, these compounds inhibit the growth of selected human tumor cell lines.



S. Basili, G. Basso, A. Faccio, A. Granzhan, H. Ihmels,* S. Moro, G. Viola*

1671 – 1676

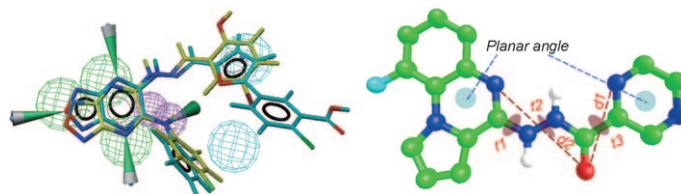
Diazoniapolycyclic Ions Inhibit the Activity of Topoisomerase I and the Growth of Certain Tumor Cell Lines

FULL PAPERS

J. Deng, L. Taheri, F. Grande, F. Aiello,
A. Garofalo, N. Neamati*

1677 – 1686

Discovery of Novel Anticancer Compounds Based on a Quinoxalinehydrazine Pharmacophore



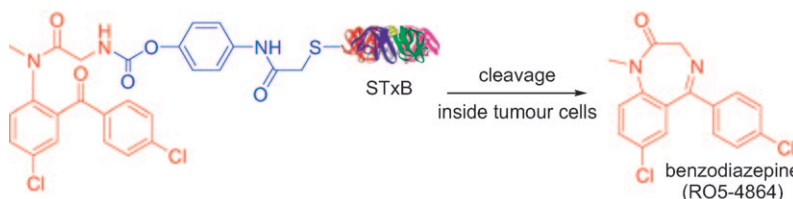
Predictive pharmacophores: Conformational sampling of a small lead molecule followed by representative pharmacophore model development is shown to be an efficient approach to the rational

design of novel antitumor agents with similar or better potency over the original lead compound, but with different physicochemical properties.

A. El Alaoui, F. Schmidt,* M. Sarr,
D. Decaudin, J.-C. Florent, L. Johannes

1687 – 1695

Synthesis and Properties of a Mitochondrial Peripheral Benzodiazepine Receptor Conjugate



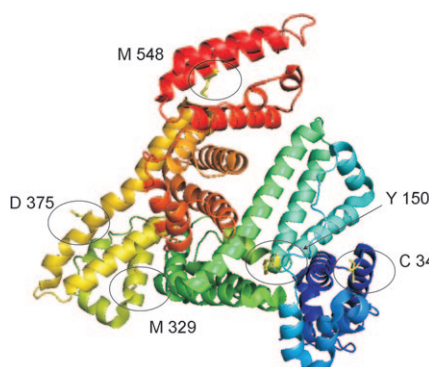
A water-soluble benzodiazepine: RO5-4864, a pro-apoptotic benzodiazepine, was solubilised by conjugation with STxB (B-subunit of Shiga toxin). After

receptor recognition and internalisation of the prodrug, the active principle is released and kills tumour cells.

J. Will, D. A. Wolters, W. S. Sheldrick*

1696 – 1707

Characterisation of Cisplatin Binding Sites in Human Serum Proteins Using Hyphenated Multidimensional Liquid Chromatography and ESI Tandem Mass Spectrometry

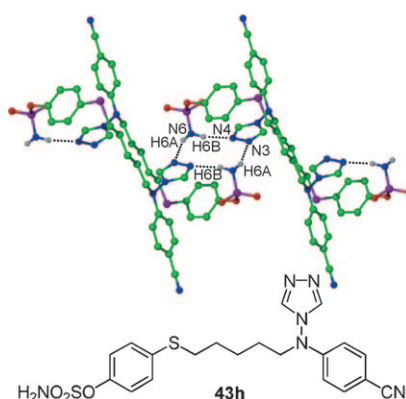


First oxygen, then sulfur: Combined biphasic liquid chromatography and ESI tandem mass spectrometry have been employed to identify specific cisplatin binding sites in blood serum proteins. Five coordinating residues were characterised for both human serum albumin (HSA) and serotransferrin (Trfe), including C34, M329 and M548 for the former, and M256 for the latter protein. The remaining residues all contain O-donor sites (D, E, T, Y), which also dominate for other abundant serum proteins.

C. Bubert, L. W. L. Woo, O. B. Sutcliffe,
M. F. Mahon, S. K. Chander, A. Purohit,
M. J. Reed, B. V. L. Potter*

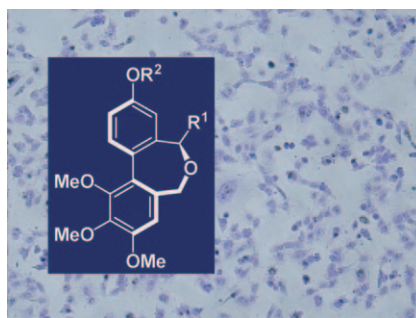
1708 – 1730

Synthesis of Aromatase Inhibitors and Dual Aromatase Steroid Sulfatase Inhibitors by Linking an Arylsulfamate Motif to 4-(4H-1,2,4-triazol-4-yl-amino)benzonitrile: SAR, Crystal Structures, in vitro and in vivo Activities



Linking an aryl alcohol and aryl sulfamate motif to 4-(4H-1,2,4-triazol-4-yl-amino)benzonitrile generates novel aromatase and dual aromatase–sulfatase inhibitors, respectively, some of which are amenable to X-ray crystallography. SAR using in vitro evaluation in JEG-3 cells shows that some aromatase inhibitors are remarkably potent, with IC_{50} values as low as 0.26 nM. A dual inhibitor shows potent in vivo oral activity and > 90% inhibition of both enzymes.

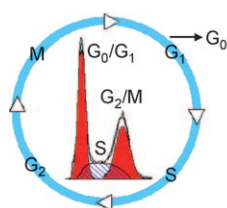
Fast and reversible: A new series of dibenzoxepines (see structure) show promising activities as potential vascular-disrupting agents (VDAs). In particular, they induce a fast and reversible change in the morphology of endothelial cells (in background) at subtoxic doses.



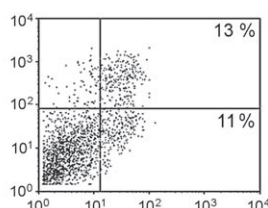
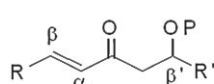
A. Joncour, J.-M. Liu, A. Décor, S. Thoret, J. Wdziejczak-Bakala, J. Bignon*, O. Baudoin*

1731 – 1739

Synthesis of Anti-Microtubule Biaryls and Preliminary Evaluation as Vascular-Disrupting Agents



An iron(III)-catalyzed multicomponent domino process is the key step in the synthesis of β' -acyloxy- α,β -unsaturated ketones. These novel compounds arrest the cell cycle and trigger apoptosis by



irreparably damaging cancer cells. The biological activity of these compounds seem parallel to those observed with the antitumor natural product, persin.

L. G. León, R. M. Carballo, M. C. Vega-Hernández, P. O. Miranda, V. S. Martín, J. I. Padrón, J. M. Padrón*

1740 – 1747

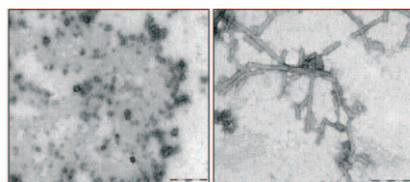
β' -Hydroxy- α,β -unsaturated ketones: A new pharmacophore for the design of anticancer drugs. Part 2.



LPS-neutralizing peptides

LALF
BPI
SAP

Acyl chain incorporation



Nanostructure formation and enhancement of activity

N-acylated LPS-neutralizing peptides derived from the anti-LPS peptides LALF-14c, BPI, and SAP are presented herein. The N-acylated peptides showed greater activities than their original counterparts. Structural analysis of

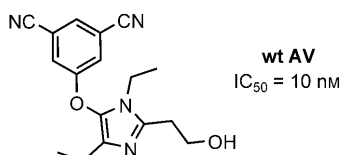
these peptides reveals that N-acylation promotes the formation of micellar or fibril-like structures. The correlation between anti-LPS activity and nanostructure formation is discussed.

C. Mas-Moruno, L. Cascales, L. J. Cruz, P. Mora, E. Pérez-Payá, F. Albericio*

1748 – 1755

Nanostructure Formation Enhances the Activity of LPS-Neutralizing Peptides

Balancing potency and metabolic stability: A series of 5-aryloxy imidazoles were developed as potent and metabolically stable non-nucleoside reverse transcriptase inhibitors for the treatment of HIV. These derivatives possess excellent activity against clinically relevant mutations of the enzyme.



L. H. Jones,* G. Allan, R. Corbau, D. Hay, D. S. Middleton, C. E. Mowbray, S. D. Newman, M. Perros, A. Randall, H. Vuong, R. Webster, M. Westby, D. Williams

1756 – 1762

Optimization of 5-Aryloxyimidazole Non-Nucleoside Reverse Transcriptase Inhibitors

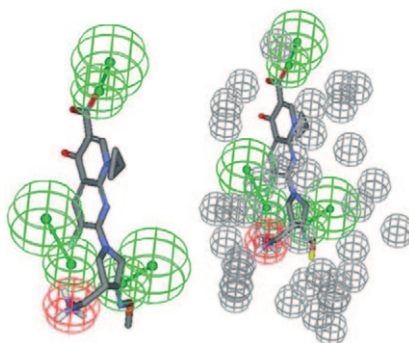


I. M. Al-masri, M. K. Mohammad,
M. O. Taha*

1763 – 1779



Discovery of DPP IV Inhibitors by Pharmacophore Modeling and QSAR Analysis followed by in silico Screening

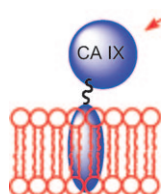


Designing drugs for diabetes: Dipeptidyl peptidase deactivates the natural hypoglycemic incretin hormones. Inhibition of this enzyme should restore glucose homeostasis in diabetic patients making it an attractive target for the development of new antidiabetic drugs. Herein, the pharmacophoric space of DPP IV was explored using a set of 358 known inhibitors with the aiming of identifying possible lead compounds.

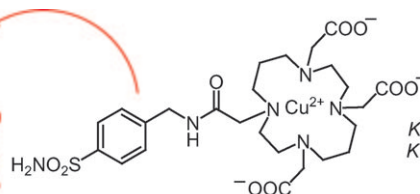
M. Rami, A. Cecchi, J.-L. Montero,
A. Innocenti, D. Vullo, A. Scozzafava,
J.-Y. Winum,* C. T. Supuran*

1780 – 1788

Carbonic Anhydrase Inhibitors: Design of Membrane-Impermeant Copper(II) Complexes of DTPA-, DOTA-, and TETA-Tailed Sulfonamides Targeting the Tumor-Associated Transmembrane Isoform IX



Copper carbonic anhydrase inhibitors: The synthesis of carbonic anhydrase inhibitors incorporating metal-complexing moieties was carried out. Complexation with copper gave impermeable inhibi-



K_i hCA IX = 17 nM
 K_i (hCA II) / K_i (hCA IX) = 20.8

tors, which can target the transmembrane tumor associated CA IX. Incorporation of radioactive copper isotopes may lead to interesting diagnostic/therapeutic applications.



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

Adenosine Receptors: Therapeutic Aspects for Inflammatory and Immune Diseases • G. Hasko, B. N. Cronstein and C. Szabo (Eds.)

C. E. Müller 1789

SERVICE

Author Index 1792 Preview 1794

Keyword Index 1793

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

Issue 10, 2008, was published online on October 10, 2008.