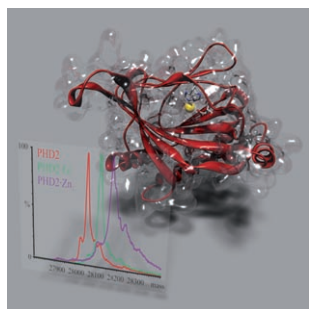


COVER PICTURE



The cover picture shows a view from a crystal structure of prolyl hydroxylase domain 2 (PHD2), which is the major PHD that catalyses HIF- α hydroxylation under normoxic conditions. The hypoxic response in animals is mediated by the transcription factor hypoxia inducible factor (HIF). Levels of the HIF- α subunit are regulated by PHD-catalysed prolyl hydroxylation, which signals for the degradation of HIF- α under normoxic conditions. The requirement of the PHDs for molecular oxygen enables them to act as oxygen sensors. Inhibition of the PHDs in order to activate the hypoxic response is of interest for therapeutic benefit. Alongside the PHD2 structure are shown electrospray ionisation mass spectrometric data, described in the Communication by C. J. Schofield et al. on p. 569 ff., that reveal a second metal binding site on the enzyme.

NEWS

Spotlights on our sister journals

520 – 521

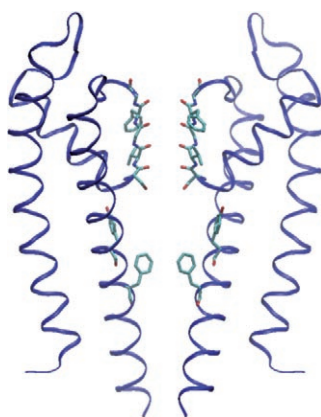
MINIREVIEWS

M. Recanatini, A. Cavalli, M. Masetti*

523 – 535

Modeling hERG and its Interactions with Drugs: Recent Advances in Light of Current Potassium Channel Simulations

JMMC
2007



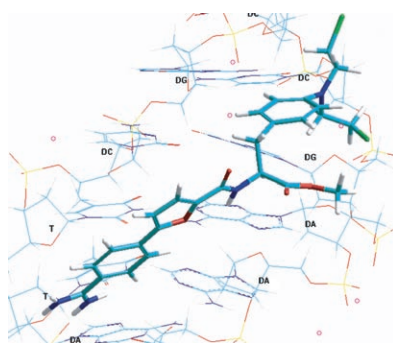
Solving hERG structure. hERG is a well established antitarget and an emerging pharmacological target. In the last years, several attempts have been performed to model its 3D structure, but only recently have sound and truly informative models appeared that can be compared with the classical simulations of K⁺ channels.

K. Bielawski, A. Bielawska*

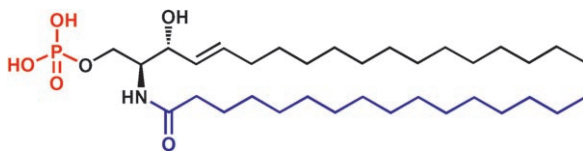
536 – 542

Small-Molecule based Delivery Systems for Alkylating Antineoplastic Compounds

JMMC
2007



Alkylating analogues. Herein, we report the synthesis and structure–activity studies of amidine analogues of alkylating antineoplastic compounds, a possible new class of cytotoxic minor groove binders and topoisomerase II inhibitors. Overexpression of prolidase in some neoplastic cells suggests that proline analogues of alkylating agents may serve as prolidase convertible prodrugs. The picture shows the d(CGCGAATTCGCG)₂–amidine analogue of melphalan complex.



Solving the sphinx. The sphingolipid ceramide and its metabolites are important signalling mediators, and a number of hypotheses for therapeutic opportunities in the sphingolipid field have

emerged. The focus of this review is on enzyme targets in sphingolipid metabolism addressing target validation, specific issues, and available tool compounds.

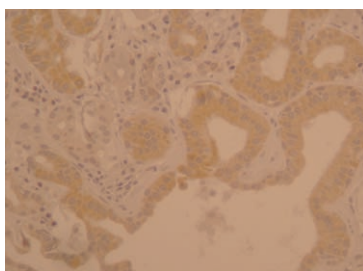
*P. Nussbaumer**

543 – 551

Medicinal Chemistry Aspects of Drug Targets in Sphingolipid Metabolism

JMMC
2007

Getting to grips with GERD. Proton pumps and bacteria have been identified in nongastric tissues of the human upper aerodigestive tract. Herein, we discuss how using proton pump inhibitors to treat GERD might be adversely affecting these acid-producing tissues and the bacteria themselves.



*B. J. Vesper, K. W. Altman, K. M. Elseth, G. K. Haines III, S. I. Pavlova, L. Tao, G. Tarjan, J. A. Radosevich**

552 – 559

Gastroesophageal Reflux Disease (GERD): Is There More to the Story?

JMMC
2007

CONFERENCE REPORTS

European Medicinal Chemistry Education and Training was the subject of a round table discussion at the 5th Joint Meeting on Medicinal Chemistry. This report emphasises the importance of such regular periodic forums to focus education and training towards the principal goal of medicinal chemistry (and medicinal chemists), which is to get better drugs, to cure diseases, and/or (at least) to improve the quality of life of patients.



G. Cristalli, P. Mátyus, P. Mohr, G. Ronsisvalle, N. J. de Souza, A. Tsantili-Kakoulidou*

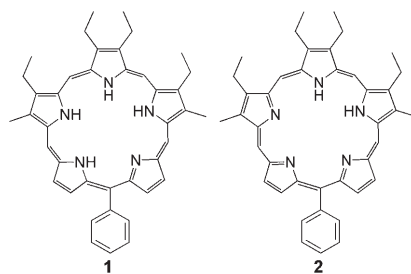
561 – 563

European Medicinal Chemistry Education: The Transformational Accomplishments and Challenges

JMMC
2007

COMMUNICATIONS

Photodynamic therapy (PDT) uses non-toxic photosensitizers and visible light to produce reactive oxygen species that kill malignant cells by apoptosis or necrosis. Silencing the antioxidant *GSTA1-1* gene by siRNA sensitizes hepatic HepG2 cells to PDT with pentaphyrins. The study is a proof-of-concept for combining PDT with antigene molecules that decrease cellular response to oxidative stress.



*V. Rapozzi, C. Lombardo, S. Cogoi, C. Comuzzi, L. Xodo**

565 – 568

Small Interfering RNA-Mediated Silencing of Glutathione-S-Transferase A1 Sensitizes Hepatic Carcinoma Cells to Photodynamic Therapy with Pentaphyrins

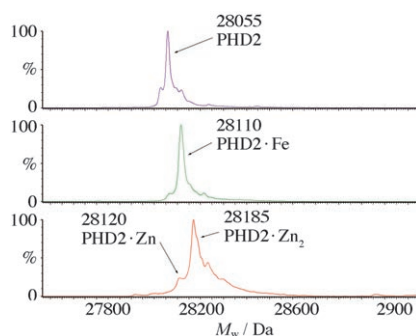


J. Mecinović, R. Chowdhury,
B. M. R. Liénard, E. Flashman,
M. R. G. Buck, N. J. Oldham,
C. J. Schofield*

569 – 572

ESI-MS Studies on Prolyl Hydroxylase
Domain 2 Reveal a New Metal Binding
Site

JMMC
2007



Mild ionisation: Combined ESI-MS and mutagenesis analyses were used in metal binding studies on a human oxygen-sensing enzyme. The approach revealed a new metal binding site.

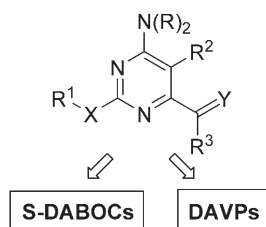
FULL PAPERS

M. Radi, C. Falciani, L. Contemori,
E. Petricci, G. Maga, A. Samuele, S. Zanolì,
M. Terrazas, M. Castria, A. Togninelli,
J. A. Esté, I. Clotet-Codina,
M. Armand-Ugón, M. Botta*

573 – 593

A Multidisciplinary Approach for the
Identification of Novel HIV-1 Non-
Nucleoside Reverse Transcriptase
Inhibitors: S-DABOCs and DAVPs

JMMC
2007

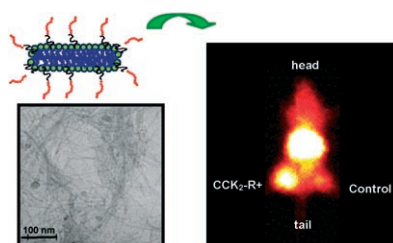


Targeting HIV. A systematic functionalization of the pyrimidine scaffold has been conducted to identify the minimal required structural features for RT inhibition. Herein, we describe how the combination of synthetic, biological, and molecular modeling studies allowed the identification of two novel classes of S-DABO analogues: S-DABO cytosine analogues (S-DABOCs) and 4-dimethylamino-6-vinylpyrimidines (DAVPs).

A. Accardo, D. Tesauro, L. Aloj, L. Tarallo,
C. Arra, G. Mangiapia, M. Vaccaro,
C. Pedone, L. Paduano,* G. Morelli*

594 – 602

Peptide-Containing Aggregates as
Selective Nanocarriers for
Therapeutics

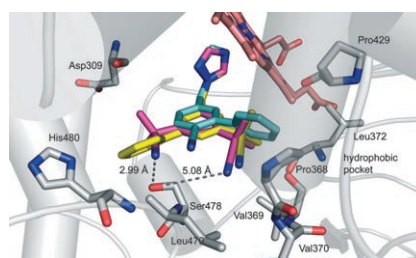


Supramolecular anticancer drugs: In the last decade, supramolecular aggregates such as micelles and vesicles have attracted much attention for their potential application as carriers in drug delivery. Supramolecular aggregates, obtained by mixing two amphiphilic monomers, one containing a radioactive indium complex, and the other the CCK8 peptide, are used to selectively deliver anticancer drugs to tumor cells.

T. Jackson, L. W. L. Woo, M. N. Trusselle,
A. Purohit, M. J. Reed, B. V. L. Potter*

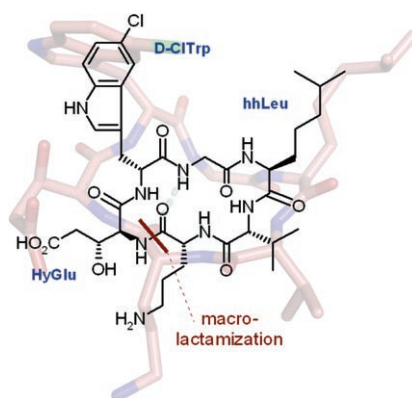
603 – 618

Non-Steroidal Aromatase Inhibitors
Based on a Biphenyl Scaffold:
Synthesis, in vitro SAR, and Molecular
Modelling



New weapons for the fight against breast cancer: Compounds built from a biphenyl scaffold potently block the activity of a key enzyme involved in the final step of oestrogen biosynthesis. Attenuating the supply of this hormone is a viable anticancer strategy, as tumours require oestrogen for growth and development. The compound shown in cyan is one of several promising candidates reported herein.

What is the active principle of the "S-520 longicatenamycin antibiotic complex"? Longicatenamycin A (shown) is the first defined longicatenamycin congener that has been totally synthesized and tested in pure form.



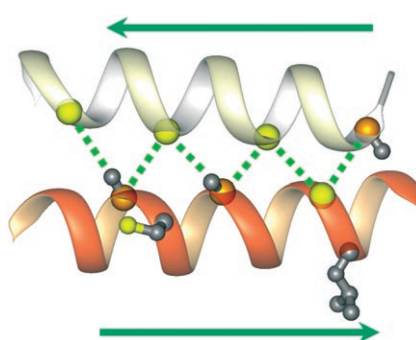
F. von Nussbaum, S. Anlauf, C. Freiberg, J. Benet-Buchholz, J. Schamberger, T. Henkel, G. Schiffer, D. Häbich*

619–626

Total Synthesis and Initial Structure–Activity Relationships of Longicatenamycin A



The interface shown is based on a highly conserved GxxxGxxxG motif in the APH-1 protein (top helix) and a small-residue AxxxAxxxG motif in presenilin (bottom helix). The model was constructed by homology modeling based on the structure of aquaporin. This model can be used for further structural characterization of γ -secretase and its components.



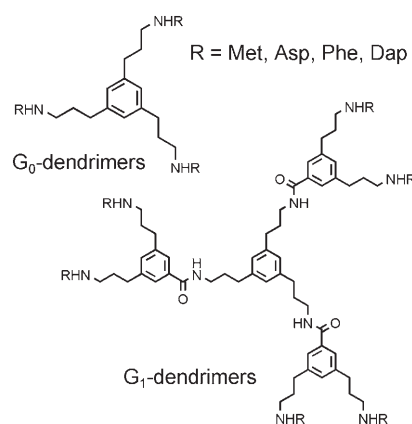
*K. Jozwiak, K. A. Krzysko, L. Bojarski, M. Gacia, S. Filipek**

627–634

Molecular Models of the Interface between Anterior Pharynx-Defective Protein 1 (APH-1) and Presenilin Involving GxxxG Motifs

JMMC
2007

Designing dendrimers. A series of G_0 and G_1 generation 1,3,5-tris(3-aminopropyl)benzene dendrimers surface-modified with the amino acids phenylalanine (Phe), methionine (Met), aspartic acid (Asp), and diaminopropionic acid (Dap) was investigated with regard to their stability against enzymatic hydrolysis with the model enzymes papain, chymotrypsin, trypsin, and pepsin as well as the cytosol of MCF-7 cells.

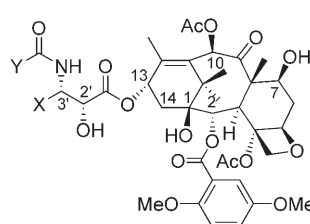


*T. Kapp, P. Francke, R. Gust**

635–641

Investigations on Surface Modified Dendrimers: Enzymatic Hydrolysis and Uptake into MCF-7 Breast Cancer Cells

Revealing relationships: Quantitative structure–activity relationships were developed for four series of taxane derivatives with respect to their inhibitory activities against breast cancer cells. The activities of these taxane derivatives are largely dependent either on their hydrophobicity or the hydrophobic/molar refractivity descriptor of their substituents.



R. P. Verma, C. Hansch*

642–652

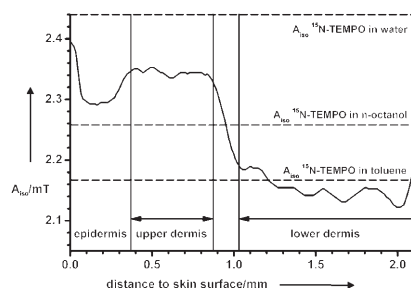
Taxane Analogues against Breast Cancer: A Quantitative Structure–Activity Relationship Study

K.-P. Moll, W. Herrmann,* R. Stößer,
H.-H. Borchert

653 – 659



Changes of the Properties in the Upper Layers of Human Skin on Treatment with Models of Different Pharmaceutical Formulations—An Ex vivo ESR Imaging Study

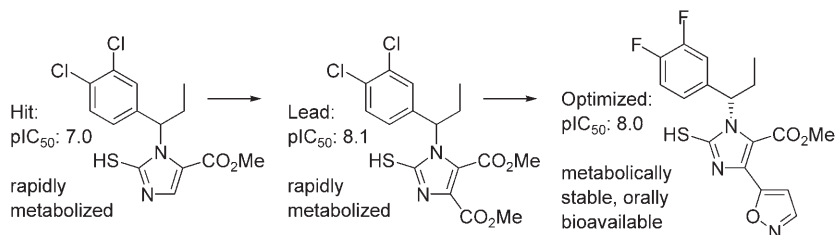


Electron spin resonance imaging was used as a nondestructive spectroscopic method for establishing a polarity map of the upper skin layers and based on this, the spatial distribution of model drugs in the skin. Polarity was described by means of the changes of the ESR hyperfine splitting constant, A_{iso} , which in turn reflects interactions at a molecular level. The effect of polarity on the spatial distribution of spin probes as model drugs was studied.

J. Doyon,* E. Coesemans, S. Boeckx,
M. Buntinx, B. Hermans, J. P. Van Wauwe,
R. A. H. J. Gilissen, A. H. J. De Groot,
D. Corens, G. Van Lommen*

660 – 669

Discovery of Potent, Orally Bioavailable Small-Molecule Inhibitors of the Human CCR2 Receptor



The synthesis of small-molecule CCR2 receptor inhibitors is presented. The initial lead, although quite potent, was metabolically unstable both in vitro and in vivo. Isosteric replacement of one of

the ester functions with small heterocycles led to highly potent, orally bioavailable and metabolically stable compounds.



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.

**JMMC
2007**

Participant in the Joint Meeting on Medicinal Chemistry, June 2007.

BOOKS

Molecules that Changed the World · K. C. Nicolaou and T. Montagnon (Ed.)

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<http://www.chemmedchem.org>

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