

CHEMICAL & MEDICINAL CHEMISTRY

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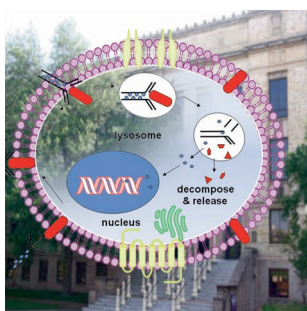
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COVER PICTURE



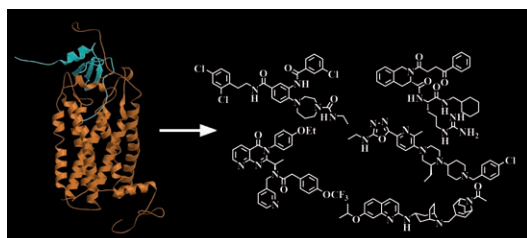
The cover picture shows a schematic representation of the Herceptin–platinum(II) binding complex, which recognizes Her2/neu on the surface of SK-BR-3 cancer cells. The novel platinum(II)-based agents achieve their high binding affinity through Herceptin, which retains its capacity to recognize Her2/neu. The investigated binding complex, Her-*n*LPt^{II}, shows remarkable cancer-cell-specific cytotoxicity toward SK-BR-3 and SK-OV-3 cancer cells. This study highlights an approach that is more practical than the preparation of mAb–drug conjugates, which can be more complex and difficult to develop as drugs. These findings will guide the development of mAb–metal-based drug-targeting entities as a means to treat human cancers and other diseases. For details, see the Full Paper by J. Gao and R. A. Zingaro, et al. on p. 954 ff.

NEWS

Spotlights on our sister journals

858 – 859

MINIREVIEWS



This minireview highlights the postulated therapeutic roles of the CXCR3 chemokine receptor and the nonpeptidic CXCR3 antagonists and agonists that have been developed in recent

years. The use of these molecules in exploring the (patho)physiological roles and putative clinical applications of CXCR3 are discussed.

M. Wijtmans,* D. Verzijl, R. Leurs,
I. J. P. de Esch, M. J. Smit


861 – 872

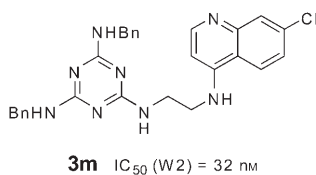
Towards Small-Molecule CXCR3
Ligands with Clinical Potential

COMMUNICATIONS

S. Melato, D. Prosperi, P. Coghi,
N. Basilico, D. Monti*

873 – 876


 **A Combinatorial Approach to 2,4,6-Trisubstituted Triazines with Potent Antimalarial Activity: Combining Conventional Synthesis and Microwave-Assistance**

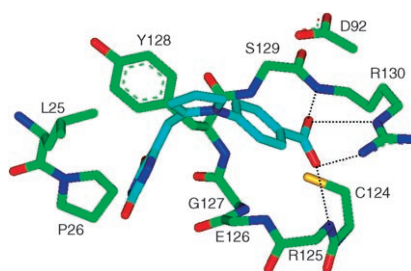


Managing malaria. Malaria is responsible for two million deaths per year particularly in developing countries, therefore there is great need for the development of cost effective treatment. The synthesis of a library of trisubstituted triazines with potent antimalarial in vitro activity is reported. Among them, five products may be developed as potential leads in the search for new drugs against plasmodial chloroquine-resistant strains.

H. Park,* S.-K. Jung, D. G. Jeong, S. E. Ryu,
S. J. Kim*

877 – 880


 **Discovery of VHR Phosphatase Inhibitors with Micromolar Activity based on Structure-Based Virtual Screening**

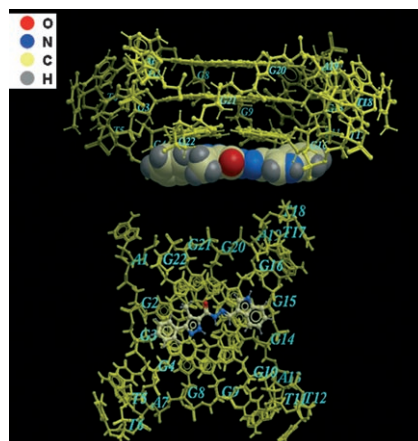


Human VHR phosphatase has been shown to be involved in the regulation of cell-cycle progression and is itself modulated during the cell cycle, indicating that VHR can serve as a therapeutic target for cancer. In the present study, we identify new VHR inhibitors by means of a structure-based drug design protocol involving the virtual screening with docking simulations and in vitro enzyme assay.

D.-L. Ma,* T.-S. Lai, F.-Y. Chan,
W.-H. Chung, R. Abagyan, Y.-C. Leung,
K.-Y. Wong*

881 – 884

 **Discovery of a Drug-Like G-Quadruplex Binding Ligand by High-Throughput Docking**




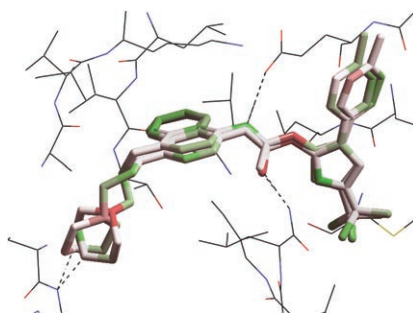
A new G-quadruplex binding ligand, namely 1*H*-pyrazole-3-carboxy-4-methyl-5-phenyl-(1*H*-indol-3-ylmethylene)hydrazide, was identified from a database of 100 000 drug-like compounds by in silico high-throughput docking. This compound was demonstrated experimentally to be an effective stabilizer of G-quadruplex DNA; it exhibits high selectivity for G-quadruplex over duplex DNA.

FULL PAPERS

I. Reulecke, G. Lange, J. Albrecht, R. Klein,
M. Rarey*

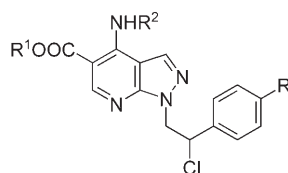
885 – 897

 **Towards an Integrated Description of Hydrogen Bonding and Dehydration: Decreasing False Positives in Virtual Screening with the HYDE Scoring Function**



HYDE is a new empirical scoring function for the evaluation of protein–ligand complexes that estimates binding free energy based on two terms for dehydration and hydrogen bonding only. In contrast to other scoring functions, HYDE accounts for destabilizing dehydration effects in a consistent manner, thereby decreasing the rate of false positive hits in virtual screening.

Healthy antagonism: A₁ adenosine receptor (A₁AR) affinity evaluations of purified enantiomers of the most active compound among the series reported (scaffold shown) indicate that the absolute stereochemical configuration affects the species-subtype selectivity of these antagonists, in agreement with a hypothesized larger cavity for bovine A₁AR with respect to the human A₁AR receptor.



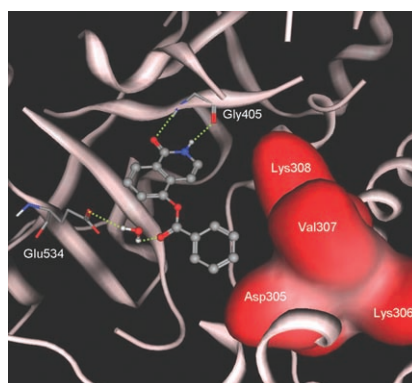
T. Tuccinardi, S. Schenone,* F. Bondavalli, C. Brullo, O. Bruno, L. Mosti, A. T. Zizzari, C. Tintori, F. Manetti, O. Ciampi, M. L. Trincavelli, C. Martini, A. Martinelli, M. Botta

898 – 913

Substituted Pyrazolo[3,4-*b*]pyridines as Potent A₁ Adenosine Antagonists: Synthesis, Biological Evaluation, and Development of an A₁ Bovine Receptor Model



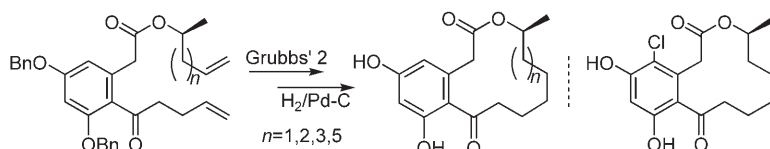
Selective PARP-2 inhibitors: A series of isoquinolinone derivatives were synthesized and pharmacologically evaluated as PARP-1/PARP-2 inhibitors. Among them, we identified the 5-benzoyloxy-isoquinolin-1(2*H*)-one derivative (shown here) as the most selective PARP-2 inhibitor reported so far, with a PARP-2/PARP-1 selectivity index greater than 60.



R. Pellicciari,* E. Camaioni, G. Costantino, L. Formentini, P. Sabbatini, F. Venturoni, G. Eren, D. Bellocchi, A. Chiarugi, F. Moroni

914 – 923

On the Way to Selective PARP-2 Inhibitors. Design, Synthesis, and Preliminary Evaluation of a Series of Isoquinolinone Derivatives



Nonsteroidal anti-inflammatory drugs: (*S*)-Curvularin and its 13-, 14-, and 16-membered homologues were synthesized by a uniform strategy based on Kochi oxidative decarboxylation and ring-closing metathesis. The 5,7-di-*O*-

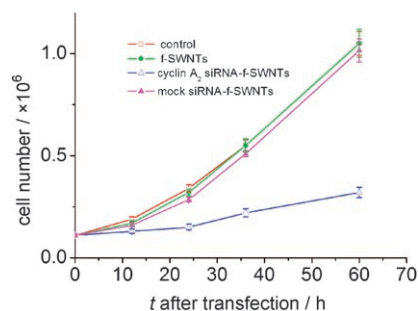
acetyl and 4-chloro derivatives of (*S*)-curvularin show improved downregulation of iNOS expression and almost no negative effects on eNOS expression, as is desirable for anti-inflammatory drugs.

S. Elzner, D. Schmidt, D. Schollmeyer, G. Erkel, T. Anke, H. Kleinert, U. Förstermann, H. Kunz*

924 – 939

Inhibitors of Inducible NO Synthase Expression: Total Synthesis of (*S*)-Curvularin and Its Ring Homologues

Carbon-nanotube vectors. Cyclin A₂ plays critical role in DNA replication, transcription, and cell cycle regulation. SWNTs can facilitate the coupling of siRNA specifically targeting human cyclin A₂ in chronic myelogenous leukemia K562 cells. Depletion of cyclin A₂ in this manner inhibits cell proliferation and promotes apoptosis demonstrating that cyclin A₂ can serve as a novel therapeutic target.



X. Wang, J. Ren, X. Qu*

940 – 945

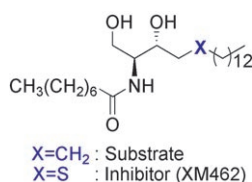
Targeted RNA Interference of Cyclin A₂ Mediated by Functionalized Single-Walled Carbon Nanotubes Induces Proliferation Arrest and Apoptosis in Chronic Myelogenous Leukemia K562 Cells



J. M. Munoz-Olaya, X. Matabosch,
C. Bedia, M. Egido-Gabás, J. Casas,
A. Llebaria, A. Delgado, G. Fabriàs*

946 – 953

Synthesis and Biological Activity of a Novel Inhibitor of Dihydroceramide Desaturase

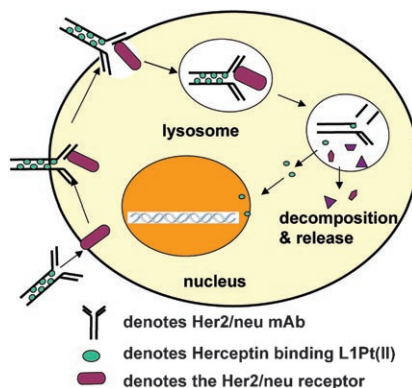


Rational design considering both mechanistic aspects of enzymatic desaturation and structural features of reported fatty acyl-CoA desaturase inhibitors led to the dihydroceramide desaturase inhibitor XM462. The design, synthesis, and biological activity of this compound both in vitro and in Jurkat A3 human leukemia cells are reported.

J. Gao,* Y. G. Liu, R. Liu, R. A. Zingaro*

954 – 962

Herceptin–Platinum(II) Binding Complexes: Novel Cancer-Cell-Specific Agents

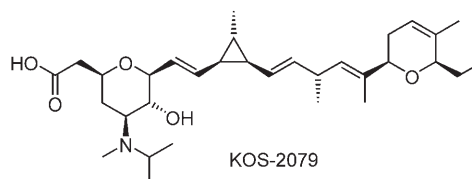


Specificity and toxicity. A new series of Herceptin–platinum(II) binding complexes, Her-*n*LPT^{II}, were investigated and show remarkable cancer-cell-specific cytotoxicity toward Her2/neu-overexpressing cancer cells (SK-BR-3 and SK-OV-3). This study suggests a new approach for the development of mAb–platinum(II)-based targeting agents for the treatment of human cancers.

Z.-Q. Tian, Z. Wang, Y. Xu, C. Q. Tran,
D. C. Myles, Z. Zhong, J. Simmons,
L. Vetcher, L. Katz, Y. Li, S. J. Shaw*

963 – 969

Investigating Amine Derivatives of Ambruticin VS-5 and VS-4



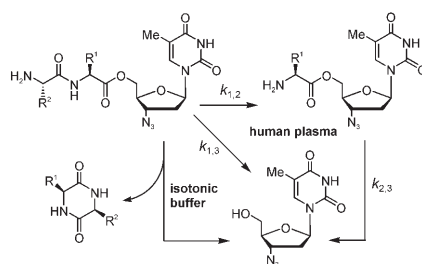
Potent antifungals: A study of the amine region of the ambruticin VS series resulted in compound KOS-2079,

which has excellent potency and oral bioavailability, and which showed efficacy in an in vivo mouse model.

C. Santos, J. Morais, L. Gouveia,
E. de Clercq, C. Pannecouque,
C. U. Nielsen, B. Steffansen, R. Moreira,*
P. Gomes*

970 – 978

Dipeptide Derivatives of AZT: Synthesis, Chemical Stability, Activation in Human Plasma, hPEPT1 Affinity, and Antiviral Activity

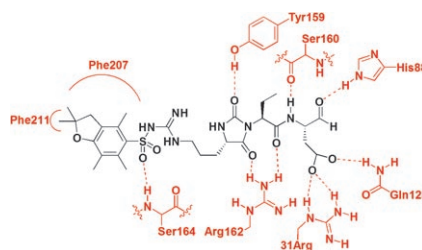


5'-O-Dipeptide ester prodrugs of AZT were prepared and found to be good substrates for hPEPT1. They exhibit anti-HIV activity similar to that of AZT, yet are less cytotoxic. The prodrugs release AZT through an elimination–cyclization pathway in aqueous buffer and by the action of amino- and diaminopeptidases in human plasma, as shown in the scheme.

J. Vázquez, A. García-Jareño,
L. Mondragón, J. Rubio-Martinez,
E. Pérez-Payá,* F. Albericio*

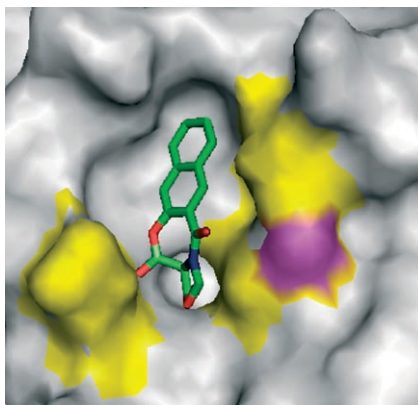
979 – 985

Conformationally Restricted Hydantoin-Based Peptidomimetics as Inhibitors of Caspase-3 with Basic Groups Allowed at the S₃ Enzyme Subsite



Apoptosis induction: Novel scaffold molecules for the inhibition of caspase-3 have been developed. These compounds have an overall attenuated negative charge and show similar IC₅₀ values for both recombinant and human endogenous caspase-3. This could provide the basis for a new strategy for the discovery of potent and more druglike inhibitors of caspase-3.

Taking IN out: Herein we report the preparation and preliminary biological evaluation of two series of tetracyclic analogues resulting from the fusion of a diversely annulated naphthoxazepine-dione system with 1,3-thiazole and 1,3-oxazole. To understand their mode of interaction with the HIV-1 integrase (IN) active site, we docked the compounds into the X-ray crystal structure of the core domain of IN.

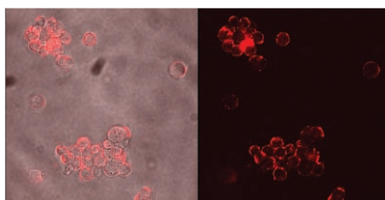


A. Garofalo,* F. Grande, A. Brizzi, F. Aiello, R. Dayam, N. Neamati

986 – 990

Naphthoxazepine Inhibitors of HIV-1 Integrase: Synthesis and Biological Evaluation

Early diagnosis is the key for lung cancer survival. Novel aptamer-based molecular probes were developed for the recognition of specific small-cell lung cancer (SCLC) cell-surface molecular markers. They show high affinity and specificity in various assay formats. This approach shows the potential for early lung cancer detection.





H. W. Chen, C. D. Medley, K. Sefah, D. Shangquan, Z. Tang, L. Meng, J. E. Smith, W. Tan*

991 – 1001

Molecular Recognition of Small-Cell Lung Cancer Cells Using Aptamers



 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 Art of Drug Synthesis · D. S. Johnson, J. J. Li (Eds.)

S. Peukert, B. Radetich 1002

Drug Discovery Research: New Frontiers in the Post-Genomic Era · Z. Huang (Ed.)

W. A. Barton 1003

Prodrugs: Challenges and Rewards. Parts 1 and 2 · V. J. Stella, R. T. Borchardt,

H. Kubinyi 1003

M. J. Hageman, R. Oliyai, H. Maag, J. W. Tilley (Eds.)

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