The cover picture shows the statistically predominant binding mode of a fluorinated biphenyl methylene imidazole in the homology model of human cytochrome P540-17 (CYP17). This enzyme is a promising target for the treatment of prostate carcinoma, since it is crucial in the biosynthesis of androgens, which stimulate the proliferation of cancer cells. Fluorine not only interacts directly with nearby amino acid residues (Arg 109, Lys 231 and His 235) in a multipolar manner, but also influences the molecular electrostatic potentials of the molecule. This leads to improved T-stacking between the A-ring and Phe 114 and strengthens the sp2 N–Fe coordination. For more information, see the Full Paper by R. W. Hartmann et al. on p. 899 ff.

CLUSTER: Cancer Chemotherapy

Selectivity is paramount when treating cancer of any kind. Whether it is selectivity for neoplastic over healthy cells or targeting a specific cancer type, such as prostate or breast cancer, the end result is improved therapeutic efficacy. The means by which selectivity can be achieved are the focus of this issue’s cluster. For more details, see Full Papers from p. 881 to 920.

NEWS

Spotlights on our sister journals
MINIREVIEWS

Multidrug resistance (MDR) is the cause of increasing problems in the treatment of cancers and bacterial infections. The active efflux of drugs contributes significantly to this phenomenon. Herein we summarize recent advances in combating MDR, with particular emphasis on natural and synthetic efflux pump inhibitors of P-glycoprotein in resistant tumor cells (such as the cage dimeric compound shown) and of the NorA MDR pump in *S. aureus*.

COMMUNICATIONS

Guarding the grey matter: This paper reports the discovery of sulfonamide derivatives as carbonic anhydrase inhibitors that selectively act against the hCA VII over the hCA II isoform. These compounds represent potentially useful lead structures for the further development of neuroprotective agents targeting the hCA VII isoform.

Sodium glucose co-transporter 2 (SGLT2) is an emerging target for the treatment of type 2 diabetes mellitus (DM2). Here, the synthesis and preliminary biological evaluation of a series of potent, selective SGLT2 inhibitors, derived from a rigid spiro C-arylglucoside scaffold, is described.

Argyrin F unfolds its promising anti-tumor activity twice: First through stabilization of the tumor suppressor protein p27 and second by vascular damage.
Antiviral agents: A series of CN-CH₂-DAPY analogues were identified as novel non-nucleoside reverse transcriptase inhibitors (NNRTIs) against HIV-1. Most of the newly synthesized compounds exhibited strong activity against wild-type HIV-1.

Labeling the living! New synthetic chemistry allows living cells to be labeled for 10 min at extremely low concentrations without deactivating cell functions; lymphocyte trafficking was visualized with high-contrast fluorescence imaging at the whole-body level.

Selectivity: A computational methodology is presented for the analysis of multi-target structure–activity relationships of compound series that ultimately aims at the identification of selectivity determinants. The approach provides a basis for the formulation of intuitive rules for the design of target-selective compounds. Shown is the derivation of preference orders of pharmacophore features at a defined substitution site in an analogue series.

Molecular complexity and size effects are known to complicate virtual screening with fingerprints. A methodology is introduced to render standard fingerprints independent of molecular complexity effects by merging a fingerprint with its complement. The resulting fingerprints show increased similarity search performance for optimized reference compounds, which is highly relevant for many practical virtual screening applications.
Reactions between thiol-containing enzymes and Michael systems were studied to investigate new agents against viral proteases and to analyze the excess toxicity of Michael systems. Our results explain the trends in inhibition and toxicity and explain why some Michael systems are irreversible inhibitors of the SARS coronavirus main protease, whereas others are only reversible.

Octahedral Pt IV complexes with cyclohexyl group functionalized edda-type ligands kill tumor cells via oxidative stress-mediated caspase-independent necrosis-like cell death associated with massive cytoplasmic vacuolization.

A new unsymmetrical zinc phthalocyanine photosensitizer (pentalyse β-carbonylphthalocyanine zinc, ZnPc-(Lys) 5) was prepared in large quantity and high purity. This water-soluble cationic photosensitizer shows high tumor phototoxicity and significant inhibition of tumor growth.

CYP17 inhibition is a promising approach for the treatment of prostate cancer. Modification of biphenyl methylene imidazoles by fluorine substitution significantly increases the inhibitory potency of this compound class and prolongs plasma half-life. Compound 9 (ball-and-stick structure) was found to be a potent CYP17 inhibitor (IC 50 = 131 nM) with good pharmacokinetic properties.

Mechanistic Study of the Reaction of Thiol-Containing Enzymes with α,β-Unsaturated Carbonyl Substrates by Computation and Chemoassays

Octahedral Platinum(IV) complexes with cyclohexyl-functionalized ethylenediamine-N,N',N'-diacetate-type ligands

Pentalysine β-Carbonylphthalocyanine Zinc: An Effective Tumor-Targeting Photosensitizer for Photodynamic Therapy

The Role of Fluorine Substitution in Biphenyl Methylene Imidazole-Type CYP17 Inhibitors for the Treatment of Prostate Carcinoma
The Binding Mode of Side Chain- and C3-Modified Epothilones to Tubulin

Always similar to Epo A: The tubulin-bound conformation of a series of C3- and C15-modified epothilones was found to be similar to the NMR-derived structure of tubulin-bound Epo A, based on NMR spectroscopy and computational modeling. The results obtained for two isomeric quinoline-based Epo B analogues suggest that the aromatic side chain moieties contribute to tubulin binding through van der Waals interactions rather than hydrogen bonding.

Gene Therapy in HIV-Infected Cells to Decrease Viral Impact by Using an Alternative Delivery Method

The NN16 dendrimer is capable of transfecting genetic material to a wide array of cell types crucial for HIV infection, thereby resulting in low cytotoxicity. We monitored the cellular uptake of oligonucleotides transfected via NN16, identifying it as an efficient vector in gene therapy by its significant reduction of HIV protein release and specific inhibition of gene expression in HIV-infected cells.

Fragment-Based Lead Discovery: Screening and Optimizing Fragments for Thermolysin Inhibition

Virtual fragment-based screening has been applied to the metalloproteinase thermolysin. A protein-targeted library was screened by docking, and two fragments could be identified. For one, a crystal structure with the protein was determined. It was further optimized to improve affinity and keep its fragment-like properties. Redesign of the zinc coordination group revealed novel micromolar fragments as a good starting point for further lead design.

A Series of 18F-Labelled Pyridinylphenyl Amides as Subtype-Selective Radioligands for the Dopamine D3 Receptor

A series of D3 receptor ligands was developed based on 3D-QSAR models. The in vitro D3 affinities of the predicted biphenyl amide ligands revealed single-digit to sub-nanomolar potencies with substantial D3 selectivities. Ex vivo autoradiography of rat brain revealed high accumulation of two 18F-labeled D3 radioligand candidates in the ventricles.
Pushing back the frontiers of science: Conferences are an ideal way to share exciting and ground-breaking results with some of the world’s foremost medicinal chemists, and this meeting was no exception. The 7th international conference, organized jointly by the DPhG and GDCh and held earlier this year (March 14–17) in Münster (Germany), featured presentations on hot topics in drug discovery, including ion channels, nanotechnology, neglected diseases and anticancer drugs. Select presentations delivered at the conference are described.

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

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BOOKS

Dynamic Combinatorial Chemistry in Drug Discovery, Bioorganic Chemistry, and Material Science · B. L. Miller (Ed.)
Kinase Inhibitor Drugs · R. Li, J. A. Stafford (Eds.)
EGFR Signaling Networks in Cancer Therapy · J. D. Haley, W. J. Gullick (Eds.)
Antimicrobial Drug Resistance · D. L. Mayers (Ed.)
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CORRIGENDUM

L. Bülow, I. Nickeleit, A.-K. Girbig, T. Brodmann, A. Rentsch, U. Eggert, F. Sasse, H. Steinmetz, R. Frank, T. Carlomagno, N. P. Malek, M. Kalesse*

Synthesis and Biological Characterization of Argyrin F
ChemMedChem 2010, 5, 832–836

I.N. is not a corresponding author of this paper, rather L.B and I.N. contributed equally to this work.