COVER FEATURES

The front cover picture shows the crystal structure of the active site of human hypoxanthine–guanine phosphoribosyltransferase (HGPRT) in complex with (S)-3-hydroxy-2-(phosphonoethoxy)propylguanine (HPEPG). HPEPG exhibits high potency for the hypoxanthine-guanine-xanthine phosphoribosyltransferase (HGXPRT) of Plasmodium falciparum ($K_i = 0.1 \mu M$), as well as for human HGPRT ($K_i = 0.6 \mu M$). The crystal structures of acyclic nucleoside phosphonates (ANPs), including HPEPG, in complex with human HGPR reveal the binding mode of novel inhibitors and show specific interactions with active site residues. Such information is important for future design of more potent inhibitors of plasmodial 6-oxopurine phosphoribosyltransferases. This approach may represent a viable strategy to treat malaria.

More details can be found in the Full Paper by Luke W. Guddat, Zlatko Janeba et al. on page 1707 in Issue 10, 2015. (DOI: 10.1002/cmdc.201500322).

The inside cover picture shows the historic development of a novel radiotracer. Originally, nitroglycerine found widespread application in dynamite production and then later in the treatment of ischemic heart disease. Its successor, 5-isosorbide mononitrate, is the basis for this study. By incorporating the radiolabel $^{18}$F into the bicyclic scaffold, we have made it possible to unravel the biodistribution of these popular drugs by dynamic positron emission tomography (PET).

More details can be found in the Full Paper by Michael Schäfers, Ryan Gilmour et al. on page 1724 in Issue 10, 2015. (DOI: 10.1002/cmdc.201500275).

The back cover picture shows the action of a vaccine candidate against hookworm. B-cell peptide epitopes derived from hookworm protease Na-APR-1 were incorporated into lipid core peptides (structure shown on the right). Proper epitope conformation ($\beta$-sheet and not $\alpha$-helix) was found to be crucial for pathogen protein recognition by the antibodies produced.

More details can be found in the Full Paper by Mariusz Skwarczynski et al. on page 1647 in Issue 10, 2015. (DOI: 10.1002/cmdc.201500227).
EDITOR’S PICK

Editor’s Pick... Positron emission tomography (PET) is an established method for obtaining functional, high-resolution whole-body images of soft tissues through the use of radionuclide tracer molecules. PET plays a key clinical role in the diagnosis of various cancers and also features prominently in neuroimaging. It’s also important in basic research: medicinal chemists use PET to visualize the tissue distributions of potential or existing drug molecules, and this is nicely illustrated in the Full Paper by Schäfers, Gilmour and colleagues on p. 1724 ff. (DOI: 10.1002/cmdc.201500275), who describe their synthesis of a fluorine-18-labeled analogue of the vasodilator drug isosorbide 5-mononitrate (IS-5MN). The researchers report the first in vivo observation of the biodistribution of this commonly prescribed medication to treat hypertension. In their Communication on p. 1635 ff. (DOI: 10.1002/cmdc.201500287), Wuest and co-workers present their work toward imaging the expression levels of cyclooxygenase-2 (COX-2) in colorectal cancer tissue by the use of fluorine-18-labeled COX-2-specific inhibitors. Such non-invasive monitoring of COX-2 expression levels would yield valuable information on the role of COX-2 in the progression of cancer and various other diseases.

As part of our Volume 10 celebrations, each month, our Editor selects two articles of particular interest or relevance, and highlights them in the Table of Contents. These articles are free to access for the month of the issue, so sign up for e-mail alerts or follow us on Facebook or Twitter to avoid missing out!

NEWS

Spotlights on our sister journals 1600 – 1603

REVIEWS

Making resistance futile: As the threat of antimicrobial resistance progresses, scientists need to look for alternative drugs. This review focuses on the progress of small-molecule membrane-active agents as possible drugs against various pathogenic microorganisms. Design strategies that have been undertaken toward development in this field are discussed in detail, along with possible solutions to yet-unanswered questions.

C. Ghosh, J. Haldar* 1606 – 1624

Membrane-Active Small Molecules: Designs Inspired by Antimicrobial Peptides

HIGHLIGHTS

Prodrugs enlarged: An unprecedented synthesis of enzymatically cleavable siRNA prodrugs (“siRNN”) has recently been reported. Targeting domain (TD)-functionalized siRNN released the parent siRNA after cellular uptake and triggered the RNA interference mechanism both in vitro and in vivo. The highlighted report could pave the way for prodrug-based approaches to overcome delivery-related limitations of nucleic acid therapeutics.

C. Ducho* 1625 – 1627

Enzymatically Cleavable siRNA Prodrugs: a New Paradigm for the Intracellular Delivery of RNA-Based Therapeutics
Pyrazolopyrimidines: Potent Inhibitors Targeting the Capsid of Rhino- and Enteroviruses

Curing the common cold! A cluster of pyrazolopyrimidines with potent broad-spectrum activity against enteroviruses was discovered. Extensive structure–property relationship analyses led to the identification of 3-(4-trifluoromethylphenyl)amino-6-phenylpyrazolo[3,4-d]pyrimidine-4-amine, shown to be a blocker of the viral capsid protein, as a lead compound for drug development with favorable physicochemical, pharmacokinetic, and toxicological properties.

Design, Synthesis, and Evaluation of an 18F-Labeled Radiotracer Based on Celecoxib–NBD for Positron Emission Tomography (PET) Imaging of Cyclooxygenase-2 (COX-2)

From fluorescence to PET imaging: In line with the success of our fluorescent COX-2 imaging celecoxib–NBD probe, we extend our efforts to prepare an 18F-labeled PET imaging probe for in vivo detection of COX-2 expression in colorectal cancer. Herein we report the preparation of a series of COX-2 inhibitors, the radiosynthesis of an 18F-labeled radio-tracer, results of in vitro cell uptake studies in colorectal cancer HCA-7 cells, radiometabolite analysis, and in vivo PET imaging studies in HCA-7 tumor-bearing NIH-III mice.

A Bisbenzamidine Phosphonate as a Janus-faced Inhibitor for Trypsin-like Serine Proteases

Two fragments, two modes: We designed a Janus-faced serine protease inhibitor by merging two benzamidine fragments, which impart the molecule with either irreversible or reversible inhibitory activity. Unexpected differences in potency toward trypsin-like proteases were found; the compound exhibits remarkable inhibitory activity against human thrombin. This hybrid approach is a useful way to obtain potent and selective inhibitors.
FULL PAPERS

Hooked on a vaccine: B-cell peptide epitopes derived from hookworm protease were incorporated into lipid core peptides (LCPs). LCPs self-assembled into nanoparticles and induced strong humoral immune responses, without the help of any external adjuvants. Proper epitope conformation was found to be crucial for pathogen protein recognition by the antibodies produced.

Stop the pore: Prolonged Ca\(^{2+}\)-dependent opening of the mitochondrial permeability transition pore (mtPTP) causes cell death. Herein we describe the discovery of novel small-molecule mtPTP inhibitors with picomolar activity in vitro assays and high in vivo efficacy in a zebrafish model of muscular dystrophies.

Synergy from stereochemical complexity: An attempt to synthesize analogues of a known spiroindolinone led to a series of diastereomers. One spiroindolinone, termed synazo-1, was shown to exhibit potent activity (300 pm) against C. albicans in the presence of fluconazole. Synazo-1 is a true synergizer and was also highly active against some drug-resistant C. albicans strains.

Fighting the big C: We describe the synthesis of a new family of analogues based on the scaffold of the natural product (−)-tarchonanthuslaetone; these compounds were evaluated in vitro against tumor cell lines. We further conducted an initial investigation into the mechanism of action, including the inhibition of phosphatases and glutathione-S-transferase and the production of reactive oxygen species.
Discovery of Novel, Potent, and Specific Cell-Death Inducers in the Jurkat Acute Lymphoblastic Leukemia Cell Line

Successfully herding Jurkats: From ligand-based virtual screening we selected 31 hits for proliferation studies in leukemic Jurkat cells. Three compounds with (sub)micromolar potencies were discovered. Importantly, no or very low antiproliferative activity in peripheral blood mononuclear cells (PBMCs) demonstrates very high specificity. These findings may have significant clinical relevance in the therapy of malignant tumors.

Combating malaria: An efficient inhibition of plasmodial 6-oxopurine phosphoribosyltransferase, a key enzyme of the parasitic purine nucleotide salvage pathway, is a promising way to combat malaria. Novel acyclic nucleoside phosphonates were designed as potent inhibitors of phosphoribosyltransferases, and the mode of their binding in the enzyme active site was studied in detail.

Visualization breakthrough: Herein we disclose the synthesis of a fluorinated analogue of the commonly prescribed vasodilator isosorbide 5-mononitrate (IS-5MN). Radioisotope labeling of 2F-IS-5MN has, for the first time, allowed observation of the in vivo biodistribution of this organic nitrate by means of dynamic positron emission tomography (PET) in wild-type mice.

Safety check: We examined the issue of metalloprotein inhibitor (MPI) specificity by investigating the selectivity of a variety of MPI against a representative panel of metalloenzymes in the presence of competing metalloproteins. The results provide a framework for examining the selectivity of MPI and suggest that current MPI present no more risk for non-specific activity than small-molecule inhibitors of metal-independent enzymes.
**Change it out:** A series of disulfide esters of dithiocarbamic acid were synthesized to block free sulfhydryl groups present in sperm and *Trichomonas* for a safe dual-action spermicide. A majority of the compounds demonstrated multiple activities with good safety profiles, with the most promising compound exhibiting spermicidal activity 15-fold higher than that of the market-ed spermicide Nonoxynol-9.

**Stabilizers on display:** Bicyclic peptides that bind with high affinity to the negative regulatory region (NRR) of the Notch1 receptor were developed by phage display. The ligands were found to increase the melting temperature of the NRR, demonstrating that in-vitro-evolved bicyclic peptides can stabilize proteins.

**BOOKS**

*Successful Drug Discovery* · J. Fischer (Ed.)

*Antitargets and Drug Safety* · L. Urbán, V. F. Patel, R. J. Vaz (Eds.)

*Thermodynamics and Kinetics of Drug Binding* · G. M. Keseru, D. C. Swinney (Eds.)

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

*A video clip is available as Supporting Information on the WWW (see article for access details).*

Contributions labeled with this symbol have been judged as “Very Important Papers” by the referees.

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