The front cover picture shows the structure of NVP-LEQ506, a new and potent inhibitor of the transmembrane receptor Smoothened. This compound, currently in clinical trials, binds to Smoothened, resulting in inhibition of the Hedgehog signaling pathway and thus preventing cell proliferation mediated by Gli transcription factors. The identification of this low-nanomolar inhibitor was achieved through systematic structure–property relationship studies in which potency, solubility, and off-target effects were optimized. This discovery opens new treatment options for patients with cancers driven by Hedgehog pathway mutations such as medulloblastoma, a malignant brain tumor. For more details, see the Communication by Stefan Peukert et al. on p. 1261 ff.

Inside Cover
For more details, see the Full Paper by R. Löser et al. on p. 1330 ff.

Back Cover
For more details, see the Communication by R. Wang et al. on p. 1270 ff.
MINIREVIEWS

Vital analogues: The use of 1,25(OH)₂D₃ for the treatment of a wide variety of diseases was limited by the parallel induction of hypercalcemic effects. There is an urgent need to find novel agents with greater selectivity. This review highlights recent advances in the research of 19-nor-1,25-dihydroxyvitamin D₃ analogues, paying special attention to their activities and structure–activity relationships.

COMMUNICATIONS

First disclosure: Continued optimization provided a novel type of Smoothened (Smo) antagonist based on a pyridazine core. The compound, NVP-LEQ506, currently in phase I clinical trials, combines high intrinsic potency and good pharmacokinetic properties resulting in excellent efficacy in rodent tumor models of medulloblastoma. Activity against a Smo mutant conferring resistance observed in a previous clinical trial with a competitor compound suggests additional therapeutic potential.

Better by benzylthio: A series of 6-substituted 9H-purin-9-yl-pyridinium derivatives was synthesized and evaluated for their antitumor activity. Compounds included in this study elicit variations in cell-cycle progression and an increase of apoptotic cells in a caspase-3-dependent process.
Probing the Key Interactions between Human Atg5 and Atg16 Proteins: A Prospective Application of Molecular Modeling

**Breaking things down:** Disruption of the Atg5–Atg16 protein–protein interaction is a potential strategy for the development of effective inhibitors of autophagy. Using a structural model of the human Atg5–Atg16 complex, a total of 30 Atg16-based peptides were designed and tested for their binding affinity to Atg5. A number of these peptides exhibited binding affinities in the low micromolar range. Furthermore, three Atg16 residues were identified as the key factors in Atg5 binding.

The Bivalent Ligand Approach as a Tool for Improving the in vitro Anti-Alzheimer Multitarget Profile of Dimebon

**Inspired by the concept** of bivalent ligands, we prepared a small set of analogues of the drug candidate dimebon. They were shown to inhibit AChE, Aβ aggregation, and NMDA receptor activation to a greater extent than dimebon. Some of these compounds also enhanced the survival of chicken neurons under apoptosis-inducing conditions.

Design of a Highly Selective and Potent Class of Non-planar Estrogen Receptor β Agonists

**Nothing flat about it:** A T-shaped trans-SS diastereomer of 4-(3-fluoro-8-oxatricyclo[7.5.0.0²,7]tetradeca-2,4,6-trien-1-yl)phenol (10) was found to be 1000-fold selective for ERβ over ERα. This compound exhibits ~10 nM potency and appears to be the first to take advantage of both conservative amino acid differences found in the α- and β-faces of the binding cavities of ERα and ERβ.
**Gets into your head:** By using a structure-guided drug discovery approach, highly selective brain-penetrant Plk-2 inhibitors were designed with the use of an interesting aromatic edge–face interaction as a potency–selectivity determinant. An analogue from this work lowered phosphorylated α-synuclein levels in vivo on oral dosing, demonstrating successful target engagement in the rat brain and paving the way for proof-of-concept studies in rodent models of Parkinson’s disease.

**Hitting the spot!** Converting the carboxylic acid function of (2S,3S)-trans-epoxysuccinyl-L-leucylamido-3-methylbutane (E-64c), a synthetic broad-spectrum cysteine peptidase inhibitor, into the corresponding alkylhydrazide was identified as a key step to obtain potent irreversible cathepsin C inhibitors.

**Fruct-o so good!** Using a structure-based approach, potential small-molecule regulators of phosphofructokinase-2, a bifunctional enzyme and regulator of glycolytic flux, were discovered. The most potent inhibitors of kinase activity in the series also inhibited the proliferation of HeLa, lung adenocarcinoma, colon adenocarcinoma, and breast cancer cells at concentrations in the low micromolar range.

**Visualising cathepsins in tumours:** Cysteine cathepsins are key players in tumour pathology. An azadipeptide nitrile with high affinity for cathepsins L, S, B, and K was labelled with fluorine-18 and investigated for its pharmacokinetic properties. PET imaging studies with tumour-bearing mice indicate the tumour accumulation of the probe and the potential of tumour targeting for this inhibitor class.
Characterization of the Stereochemical Structures of 2H-Thiazolo[3,2-a]pyrimidine Compounds and Their Binding Affinities for Anti-apoptotic Bcl-2 Family Proteins

Ambidexterity! The compounds reported herein were characterized as inhibitors of anti-apoptotic Bcl-2 family proteins. Structures in this compound class contain a chiral center (C4 atom) on the pyrimidine ring. Interestingly, our study revealed that the R and S enantiomers of this compound class have similar binding affinities for Bcl-xL, Bcl-2, and Mcl-1.

Identification of Hck Inhibitors As Hits for the Development of Antileukemia and Anti-HIV Agents

Rational design: Virtual screening by cross-docking identified various small molecules as hematopoietic cell kinase (Hck) inhibitors. Evaluation of the virtual hits in a cell-free assay revealed that some compounds inhibit Hck at sub-micromolar concentrations. Simulations allowed the identification of key interactions in the inhibitor–kinase complexes.

Synergistic Inhibitor Binding to the Papain-Like Protease of Human SARS Coronavirus: Mechanistic and Inhibitor Design Implications

Synergistic fragment merging: To improve the potency of previously developed SARS-PLpro inhibitors, synergistic small fragments were identified by enzymatic assay and confirmed by SPR. Merged compounds are proposed based on enzymatic mode of inhibition, mutual exclusivity, computational solvent mapping, and molecular docking studies.

Discovery of an Acyclic Nucleoside Phosphonate that Inhibits Mycobacterium tuberculosis ThyX Based on the Binding Mode of a 5-Alkynyl Substrate Analogue

Rational design: The selective ThyX inhibitor 5-alkynyl 2′-deoxyuridine 5′-monophosphate was modeled in its target active site, and NMR was used to support the predicted binding mode. To increase the stability of the lead compound, some acyclic nucleoside phosphonate (ANP) derivatives were synthesized and tested in vitro for ThyX inhibition. A modestly active inhibitor was identified, further optimization of which could lead to antibacterial thymidylate synthase inhibitors.
Design, Synthesis and Biological Evaluation of Rose Bengal Analogues as SecA Inhibitors

To be or not to be active: A cyclic lipopeptide and its amide analogue can depolarize the cytoplasmic membranes of Gram-positive bacteria, whereas the N-methylamide analogue is inactive. Membrane depolarization does not correlate with bacterial cell lethality, suggesting that membrane-targeting activity is not the main mode of action for this class of antibacterial peptides.

Immediate, early effects: >The quinolone scaffold of the potent and selective anti-HCMV compound WCS was investigated in depth, furnishing new SAR insight and identifying novel potent analogues, the anti-HCMV activity of which is brought about by inhibition of IE2-mediated transactivation. These quinolone derivatives are therefore particularly well suited for treating patients that do not respond to the DNA polymerase inhibitors in current use.

Design, Synthesis, and Evaluation of WCS Analogues as Inhibitors of Human Cytomegalovirus Immediate-Early 2 Protein, a Promising Target for Anti-HCMV Treatment

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

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BOOKS

Understanding Diabetes: A Biochemical Perspective · R. F. Dods (Au.)
New Therapeutic Strategies for Type 2 Diabetes · R. M. Jones (Ed.)
Drug Discovery from Natural Products · O. Genilloud, F. Vicente (Ed.)
Efficient Preparations of Fluorine Compounds · H. W. Roesky (Ed.)
CORRIGENDUM

There is an additional source of support that was inadvertently omitted in the
Acknowledgments. In particular, co-funding by FEDER through the COMPETE pro-
gram (ref. FCOMP-01-0124-FEDER-020963) was not mentioned.

Therefore, the Acknowledgments text should have read as follows: This project was
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Cinnamic Acid/Chloroquinoline
Conjugates as Potent Agents against
Chloroquine-Resistant Plasmodium falciparum

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Due to a typesetting error, Scheme 1 was incorrectly printed. The correct scheme is given below. On behalf of the typesetters, we apologize for this printing error.

Scheme 1. Reagents and conditions: a) LDA, THF, −78 °C; then 13k,l, 25 °C (14k, 89%; 14l, 73%); b) LDA, THF, −78 °C; then 15, −78−25 °C (16k, 31%; 16l, 39%); c) NaOH, MeOH, 70 °C (6k, 73%; 6l, 80%).