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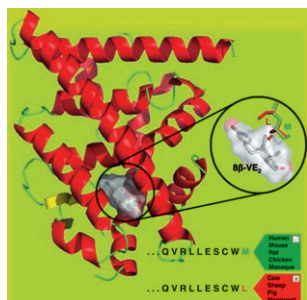
Full text:



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Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE



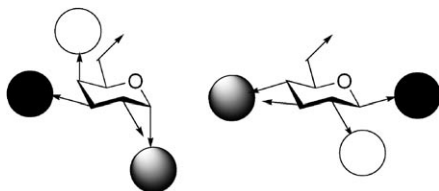
The cover picture shows a model of the binding pocket of the estrogen receptor (ER) occupied by 8β-VE₂, a steroidal ERβ-selective agonist. As illustrated by the model, a single amino acid, methionine, accounts for the ERβ selectivity of this compound class. An exchange to leucine at this position in some animal species, depicted in the sequence alignment, generates unfavorable interactions with 8β-VE₂. Therefore, knowledge about the structure of the protein–ligand complex can be used to predict suitable animal models for in vivo pharmacological studies with this ligand class. For more details, see the Full Paper by L. Toschi et al. on p. 1237 ff.

NEWS

From our sister journals

1160 – 1161

REVIEWS



One of the major challenges in drug discovery is to achieve the necessary spatial orientation of pharmacophores to interact with a given target in a selective and specific way. Carbohydrates offer a selection of rigid small-molecule

scaffolds to display pharmacophore groups in a sterically defined way, and this review highlights the achievements in the use of carbohydrate scaffolds in the drug-discovery process.

W. Meutermans, G. T. Le, B. Becker*

1164 – 1194

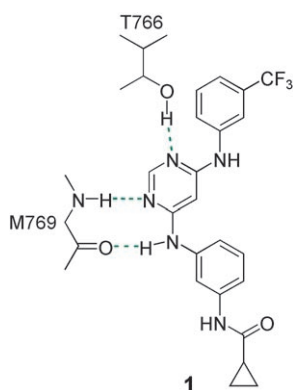
Carbohydrates as Scaffolds in Drug Discovery

HIGHLIGHTS

O. Prien*

1195 – 1196

The Gatekeeper: Friend or Foe in Identifying the Next Generation of Kinase Inhibitors



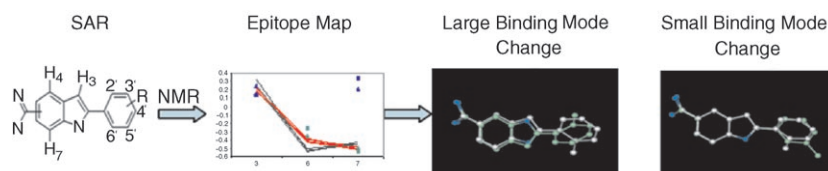
Fighting cancer: The next generation of small-molecule kinase inhibitors might be designed against distinct mutational forms of certain kinases. Current antitumor drugs display remarkable efficacy, but relapse is frequently observed during treatment due to acquired mutation. The gatekeeper plays an important role in this context, and compounds such as **1** that interact with it might be a starting point to design future inhibitors.

COMMUNICATIONS

S. Subramaniam, S. L. Briggs, A. D. Kline*

1197 – 1199

Monitoring the Ligand Binding Mode by Proton NMR Chemical Shift Differences



The ligand free-bound shift difference is established as a valuable binding mode monitor. Using bovine pancreatic trypsin, an indole inhibitor series and CLEANEX spectroscopy, exchange peaks identified the bound ligand resonances

from the free shift positions. The method requires no protein labeling or assignments and is sufficiently fast to be integrated in the drug-design process.

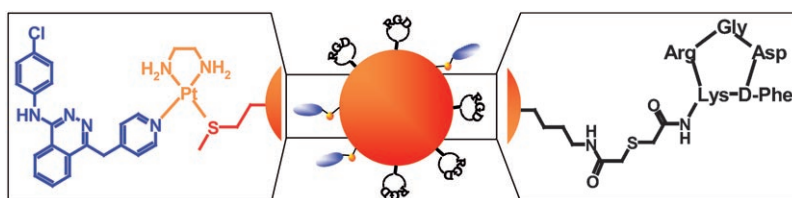
K. Temming,* M. Lacombe,
R. Q. J. Schaapveld, L. Orfi, G. Kéri,
K. Poelstra, G. Molema, R. J. Kok

1200 – 1203

Rational Design of RGD–Albumin Conjugates for Targeted Delivery of the VEGF-R Kinase Inhibitor PTK787 to Angiogenic Endothelium




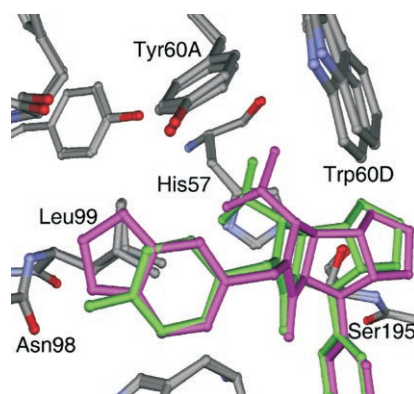
Linking the unlinkable: Many new chemical entities lack reactive groups for use in the formation of reversible bonds, for example, to conjugate them for targeted drug delivery purposes. We succeeded with the noncovalent coupling of a potent signal transduction in-



hibitor to a protein backbone by applying the platinum-based universal linkage system. The resulting drug-targeting conjugates offer new potential for cancer treatment with minimal side effects.

FULL PAPERS

 **Tricyclic inhibitors directing fluoro-alkyl groups** into the proximal (P) pocket at the active site of thrombin were synthesized. A comparison with corresponding alkylated and alkenylated inhibitors shows that the P pocket is both hydrophobic and fluorophilic. The exact positioning of a CHF₂ substituent in this pocket was revealed by X-ray crystal structure of a protein–ligand co-crystal.

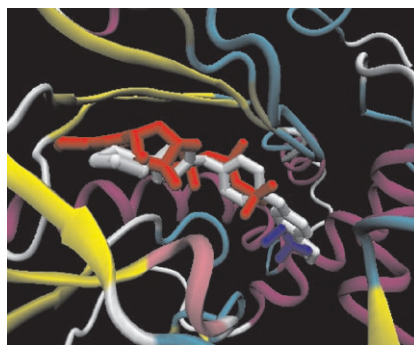


A. Hoffmann-Röder, E. Schweizer, J. Egger, P. Seiler, U. Obst-Sander, B. Wagner, M. Kansy, D. W. Banner, F. Diederich*

1205 – 1215

Mapping the Fluorophilicity of a Hydrophobic Pocket: Synthesis and Biological Evaluation of Tricyclic Thrombin Inhibitors Directing Fluorinated Alkyl Groups into the P Pocket

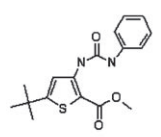
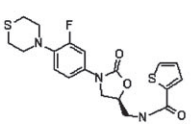
A homology model of human choline kinase (CK- α) is presented. Molecular dynamics simulations confirm its quality and support the putative ATP (red) and choline (green) binding sites. MD results are concordant with reported *C. elegans* choline kinase (CKA-2) mutagenesis. Preliminary docking studies indicate that inhibitors (white) can bind into both binding sites.




L. Milanese, A. Espinosa, J. M. Campos, M. A. Gallo, A. Entrena*

1216 – 1228

Insight into the Inhibition of Human Choline Kinase: Homology Modeling and Molecular Dynamics Simulations

Structure	Oral PhysChem Score	TL Solubility [mg L ⁻¹]	TL CLOGP	TL MWcorr	TL PSA [Å ²]	TL Rot Bonds
	4	<10	5.1	332.4	67.4	5
	2	10-50	2.6	407.7	61.9	5

 **In silico ADMET traffic lights** and the in silico oral PhysChem score are introduced as part of a data-driven hit-selection process. The output of these in silico

tools is easy to interpret due to the intuitive traffic light color scheme (shown) and a scoring system in the convenient range of 0–10.

M. Lobell,* M. Hendrix, B. Hinzen, J. Keldenich, H. Meier, C. Schmeck, R. Schohe-Loop, T. Wunberg, A. Hillisch

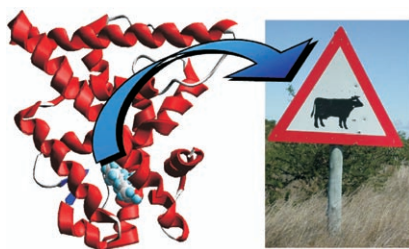
1229 – 1236

In Silico ADMET Traffic Lights as a Tool for the Prioritization of HTS Hits

L. Toschi,* J. Hilbig, T. Wintermantel,
A. Engelhaupt, A. Walter, K.-H. Fritzemeier,
A. Hillisch

1237 – 1248

Protein-Structure-Based Prediction of Animal Model Suitability for Pharmacodynamic Studies of Subtype-Selective Estrogens

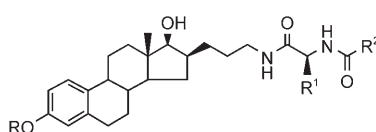


From homology model to animal model. Using homology modeling it has been demonstrated that a single amino acid in the ligand-binding pocket of human estrogen receptor β (hER β) confers selectivity to a class of estradiol-derivative compounds. This observation is confirmed in functional cell-based assays on hER α and hER β , and their respective mutants can be used to predict the suitability of animal models for pharmacological studies.

L. C. Ciobanu, D. Poirier*

1249 – 1259

Synthesis of Libraries of 16 β -Aminopropyl Estradiol Derivatives for Targeting Two Key Steroidogenic Enzymes



Two libraries of 16 β -aminopropyl estradiol derivatives, phenols and sulfamates, were synthesized by solid-phase parallel chemistry using the sulfamate linker and trityl chloride resin. Our aim was to rapidly identify potential inhibi-

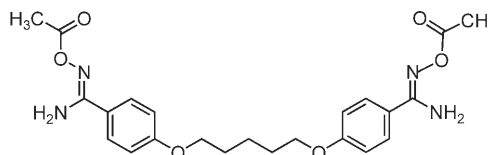
R^1 and R^2 = elements of molecular diversity
 R = SO_2NH_2 (sulfamates as inhibitors of steroid sulfatase)
 R = H (phenols as inhibitors of 17 β -HSD)

tors of steroid biosynthesis for the hormonal therapy of estrogen-dependent diseases, and also to demonstrate the versatility and efficiency of the recently developed sulfamate linker.

B. Clement,* A. Bürenheide, W. Rieckert,
J. Schwarz

1260 – 1267

Diacetyldiamidoximeester of Pentamidine, a Prodrug for Treatment of Protozoal Diseases: Synthesis, in vitro and in vivo Biotransformation



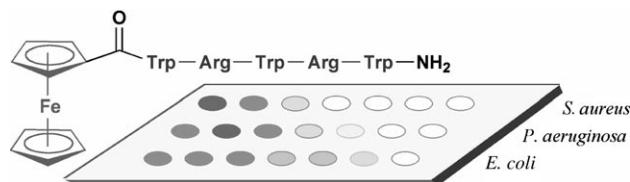
An oral form of pentamidine: The diacetyldiamidoximeester shown was synthesized by a very efficient and simple method. The prodrug is easily trans-

formed into its active metabolite by several enzyme systems by sequential ester cleavage and N-dehydroxylation reactions with four intermediates formed.

J. T. Chantson,* M. Vittoria Verga Falzacappa, S. Crovella, N. Metzler-Nolte*


1268 – 1274

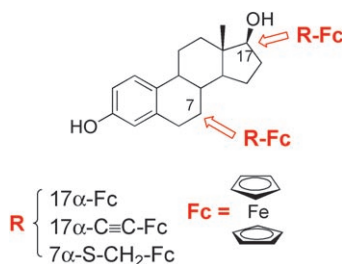
Solid-Phase Synthesis, Characterization, and Antibacterial Activities of Metallocene–Peptide Bioconjugates



The metal matters! Attaching an organometallic group to the N terminus of peptides changes not only the antibacterial activity, it also changes specificity against Gram-positive or Gram-negative bacteria. The ferrocene–pentapep-

tide conjugate shown here has an activity against the Gram-positive *S. aureus* which is even better than a naturally occurring antibiotic, the 20 amino acid peptide, pilosulin 2.

 **Ferrocenyl estradiol derivatives** retain satisfactory affinity for the estrogen receptor. These complexes are strongly estrogenic at submicromolar concentrations, and some of them become cytotoxic at high concentrations (IC_{50} = 13.4–18.8 μ M). Their low cytotoxicity suggests that electronic communication between the ferrocenyl and phenol moieties is important in the generation of cytotoxic effects.



A. Vessières,* D. Spera, S. Top,
B. Misterkiewicz, J.-M. Heldt, E. Hillard,
M. Huché, M.-A. Plamont, E. Napolitano,
R. Fiaschi, G. Jaouen

1275 – 1281

The Presence of a Ferrocenyl Unit on an Estrogenic Molecule is Not Always Sufficient to Generate in vitro Cytotoxicity

BOOKS

Methods in Molecular Medicine 114: Microarrays in Clinical Diagnostics ·

T. O. Joos, P. Fortina (Eds.)

Blood–Brain Barriers: From Ontogeny to Artificial Interfaces · R. Dermietzel,

D. C. Spray, M. Nedergaard (Eds.)

Analogue-based Drug Discovery · J. Fischer, C. R. Ganellin (Eds.)

Neurobiology of DOPA as a Neurotransmitter · Y. Misu, Y. Goshima

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K. Gademann 1284

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