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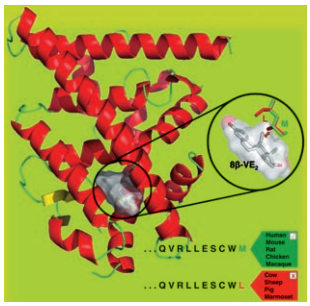
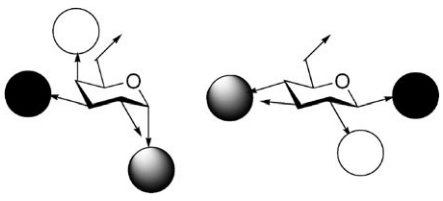
COVER PICTURE



The cover picture shows a model of the binding pocket of the estrogen receptor (ER) occupied by 8β-VE_2, 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-VE_2. 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

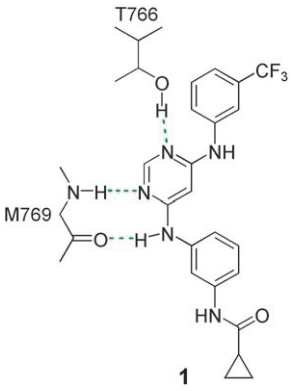
REVIEWS



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.

HIGHLIGHTS

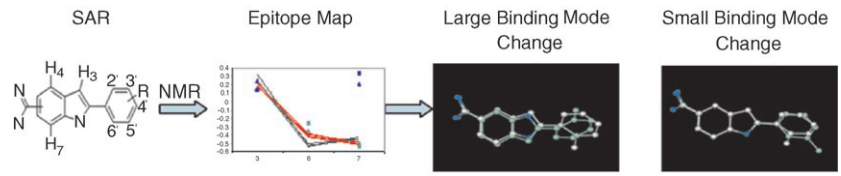
*O. Prien**



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.

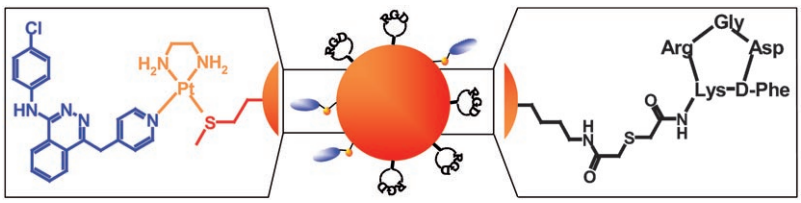
COMMUNICATIONS

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



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.

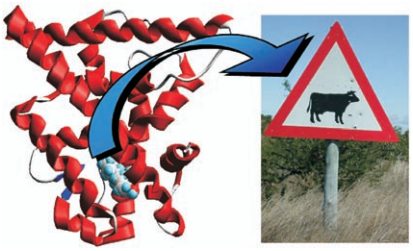
K. Temming, M. Lacombe, R. Q. J. Schaapveld, L. Orfi, G. Kéri, K. Poelstra, G. Molema, R. J. Kok*



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 inhibitor 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.

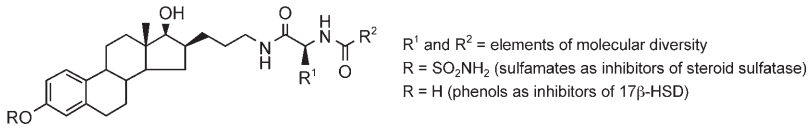
FULL PAPERS

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



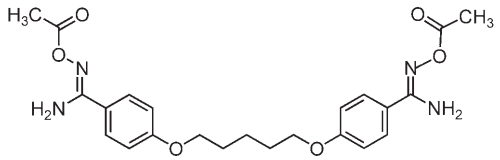
From homology model to animal model. Using homology modeling it has been demonstrated that a single amino acid in the ligand-binding pocket of human estrogen receptor β (hERβ) confers selectivity to a class of estradiol-derivative compounds. This observation is confirmed in functional cell-based assays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

*L. C. Ciobanu, D. Poirier**



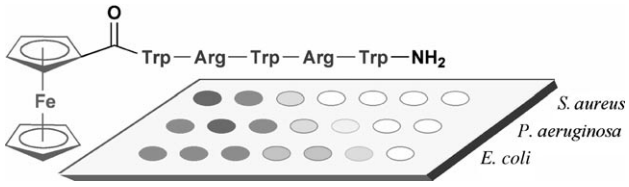
Two libraries of 16β-aminopropyl estradiol derivatives, phenols and sulfamates, were synthesized by solid-phase parallel chemistry using the sulfamate linker and trityl chloride resin. Our aim was to rapidly identify potential inhibitors of steroid biosynthesis for the hormonal therapy of estrogen-dependent diseases, and also to demonstrate the versatility and efficiency of the recently developed sulfamate linker.

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



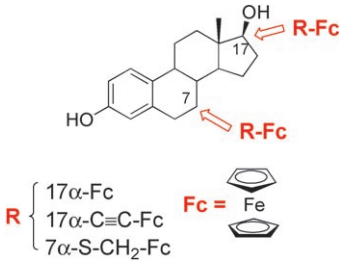
An oral form of pentamidine: The diacetyldiamidoximeester shown was synthesized by a very efficient and simple method. The prodrug is easily transformed into its active metabolite by several enzyme systems by sequential ester cleavage and N-dehydroxylation reactions with four intermediates formed.

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



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–pentapeptide 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} = 13.4–18.8μM). Their low cytotoxicity suggests that electronic communication between the ferrocenyl and phenol moieties is important in the generation of cytotoxic effects.



BOOKS

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