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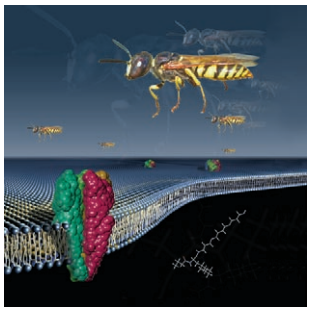
Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE

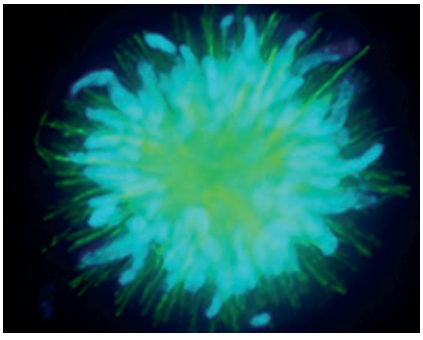


The cover picture shows an analogue of the natural wasp toxin PhTX-433 (lower right). The natural toxin is a noncompetitive antagonist of ionotropic receptors (depicted in the lipid bilayer as space-filling models). As PhTX-433 is relatively nonselective in its action, solid-phase synthetic methods have given access to analogues of this toxin that have potency toward the nicotine acetylcholine receptor in the nanomolar concentration range. For more details, see the communication by J. Jaroszewski et al. on p. 303 ff. (Thanks to Steen Drozd Lund, Flemming Steen Jørgensen, Christian Adam Olsen, Baysic Dsn, and Good Morning Technology for the graphics.)

NEWS

MINIREVIEWS

Turning the motors off: Mitotic kinesins are molecular motors that play a central role in cell division. Small molecules that block kinesin activity can lead to mitotic arrest, apparent in the formation of a monoaster within the cell (shown). Kinesin-targeted molecules hold great potential as an alternative strategy in cancer chemotherapy.



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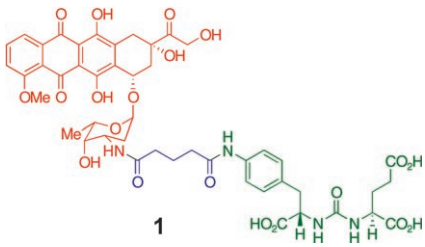
COMMUNICATIONS

*S. Jayaprakash, X. Wang, W. D. Heston, A. P. Kozikowski**

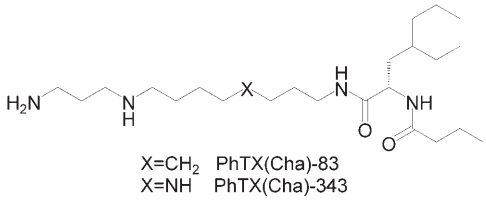
Design and Synthesis of a PSMA Inhibitor–Doxorubicin Conjugate for Targeted Prostate Cancer Therapy



Prostate-specific membrane antigen (PSMA) provides an attractive target for the development of targeted chemotherapeutics for prostate cancer. We have designed and synthesized a bioconjugate **1** that comprises the cytotoxic drug doxorubicin and one of our previously described urea-based PSMA inhibitors. While this bioconjugate retained high binding affinity for PSMA, it inhibited only 30% of C4-2 cell growth at a concentration of 5.0 μM.

*C. A. Olsen, I. R. Mellor, P. Wellendorph, P. N. R. Usherwood, M. Witt, H. Franzyk, J. W. Jaroszewski**

Tuning Wasp Toxin Structure for Nicotinic Receptor Antagonism: Cyclohexylalanine-Containing Analogues as Potent and Voltage-Dependent Blockers

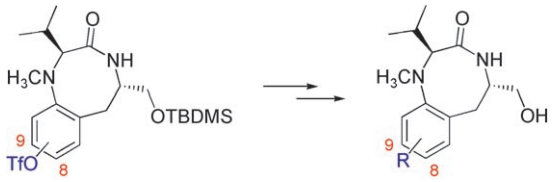


Receptor antagonists with sting: The natural wasp toxin PhTX-433, a noncompetitive antagonist of ionotropic receptors, is relatively nonselective in its action. Solid-phase synthetic methods gave rise to analogues (shown) with nanomolar potency toward the nicotine acetylcholine receptor. The inhibition was voltage-dependent, which suggests that the analogues bind deep inside the transmembrane pore.

FULL PAPERS

*U. R. Mach, N. E. Lewin, P. M. Blumberg, A. P. Kozikowski**

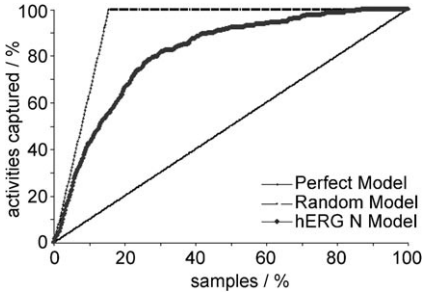
Synthesis and Pharmacological Evaluation of 8- and 9-Substituted Benzolactam-V8 Derivatives as Potent Ligands for Protein Kinase C, a Therapeutic Target for Alzheimer's Disease



A small library of benzolactam-V8-based activators of protein kinase C (PKC) was synthesized and all members were found to have binding affinity for PKCα in the nanomolar concentration range. As PKC activators are involved in the processing of the amyloid precursor protein, these compounds could be valuable in the treatment of Alzheimer's disease.

*H. Sun**

An Accurate and Interpretable Bayesian Classification Model for Prediction of hERG Liability



A naive Bayes classifier and an atom type-based molecular descriptor system were used to categorize hERG blockers into active and inactive classes. A training set of 1979 corporate compounds was used and the model was validated on an external test set of 66 drugs. The model offers extra information for the design of compounds free of undesirable hERG activity.

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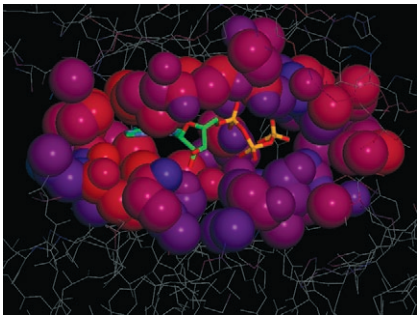
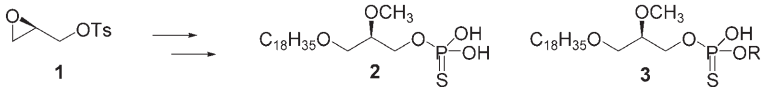


Time to prioritise: An analysis of the hydrophobic properties of the ATP binding site of cyclin-dependent kinase 2 (shown) reveals that the adenine binding region extends into an area unused by ATP. This region may be targeted by the addition of nonpolar groups to newly designed ligands to impart them with greater specificity.



Ligand stereochemistry: The conversion of glycidol **1** to enantiomerically pure phosphorothioate analogues **2** and **3** of lysophosphatidic acid (LPA) is presented. The availability of such alkyl LPA analogues has improved the understanding of ligand–receptor interactions for the endothelial differentiation gene family class of G-protein-coupled receptors.

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

* Author to whom correspondence should be addressed.

BOOKS

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