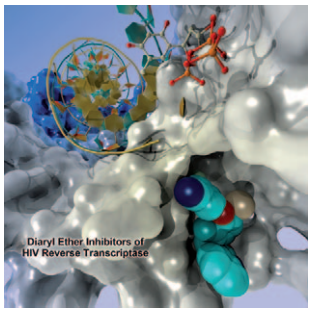
COVER PICTURE

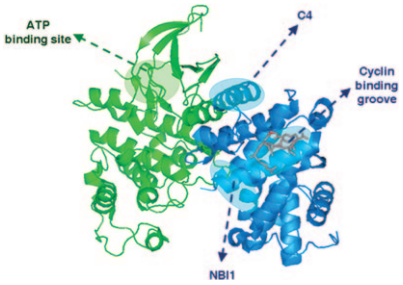


The cover picture shows a cut-away view of a diaryl ether non-nucleoside reverse transcriptase inhibitor (cyan) bound to HIV reverse transcriptase. The cartoon representation of the DNA template (teal) and primer (gold) strands, as well as the incoming nucleotide molecule, are shown as landmarks and aligned from a separate structure (PDB code 1RTD). Binding of the non-nucleoside inhibitor interferes with the precise alignment and dynamics of the growing strand and the polymerase catalytic center. For more details, see the Full Paper by Z. K. Sweeney et al. on p. 88 ff.

NEWS

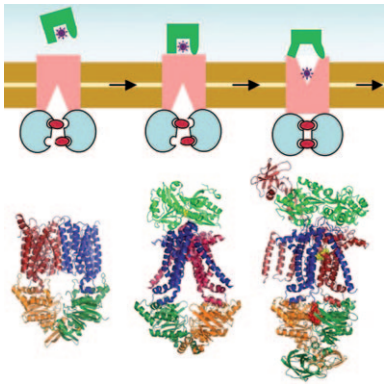
MINIREVIEWS

Deregulation of the cell cycle mechanism is implicated in many degenerative diseases and tumor development. Progression through the cell division cycle is controlled by a family of cyclin-dependent kinases (CDKs). Information regarding the activation of CDKs benefits new research strategies aimed at discovering more effective and selective drugs. This Minireview outlines the progress made in developing ATP-noncompetitive CDK–cyclin inhibitors.

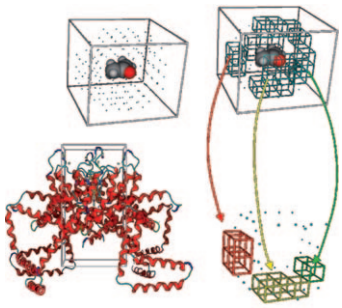


HIGHLIGHTS

Learning your ABC: ATP-binding cassette (ABC) transporters play key roles in the transport of solutes into, and out of cells. These transmembrane proteins are discussed in the context of their importance as targets for both antitumor and antimicrobial agents, due to the crucial role in drug resistance. The structural differences of ABC systems, arising from the need of various classes of solutes, are described and pieced together with functional data to suggest a common mechanism.

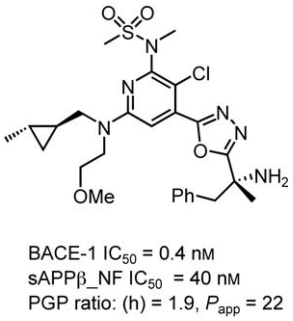


CONCEPTS

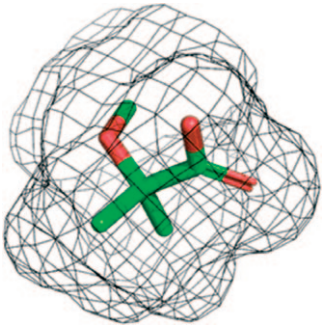


Bridging the gap: The challenge of multidisciplinarity calls for bridges between chemistry and biosciences; this paper shows that it is possible to extend the use of existing computational tools from their traditional application field (e.g. chemistry) to culturally-related research areas by the implementation of simple but well-designed utilities.

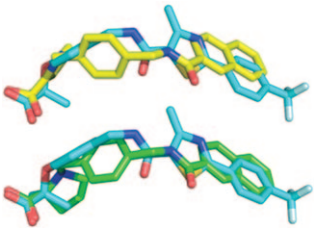
COMMUNICATIONS



Turning up the BACE: Incorporation of an isonicotinic core into oxadiazolyl tertiary carbinamine-based inhibitors of BACE-1 has led to the identification of an exquisitely potent inhibitor, which displays good P_{app} and low susceptibility to the P-gp efflux pump. Upon twice daily oral administration to monkeys, co-dosed with ritonavir, this inhibitor was shown to penetrate the CNS and lower $A\beta_{42}$ levels in the CSF by $>40\%$ over the 3 day course of the experiment.



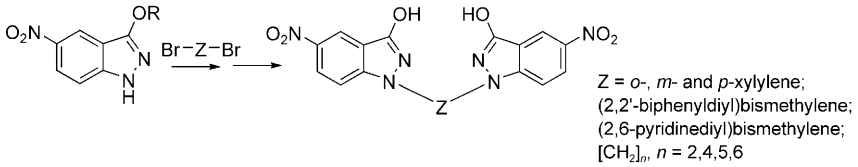
Ligand-based virtual screening: By means of shape- and pharmacophore-based virtual screening, a potent PPARα-selective activator was identified from a large compound collection with minimal experimental effort. This compound represents a scaffold-hop from known PPAR agonists and provides proof-of-concept for a novel ligand-based virtual screening approach.



Fragment-based drug design: Computer-assisted molecular design has emerged as a valuable tool for lead discovery. We present the successful de novo design, synthesis, and testing of a PPAR agonist using a novel fragment-based compound assembly strategy.

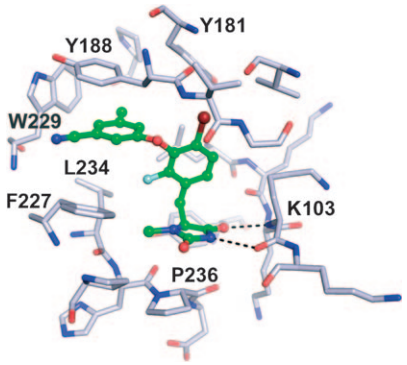
FULL PAPERS

M. Martins Alho, R. N. García-Sánchez, J. J. Nogal-Ruiz, J. A. Escario, A. Gómez-Barrio, A. R. Martínez-Fernández, V. J. Arán**



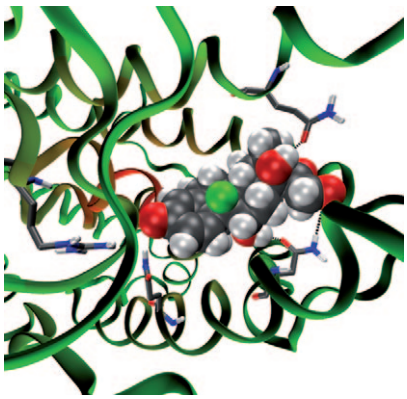
1,1′-Hydrocarbylenebis(5-nitroindazol-3-ols) are inhibitors of biocrystallization of heme to hemozoin, a *Plasmodium* specific detoxification process and therefore they are good leads for the development of new antimalarial drugs. Acidic OH groups with adequate pK_a values provided by NO_2 substituents seem to be essential for activity.

Z. K. Sweeney, J. J. Kennedy-Smith, J. Wu, N. Arora, J. R. Billedeau, J. P. Davidson, J. Fretland, J. Q. Hang, G. M. Heilek, S. F. Harris, D. Hirschfeld, P. Inbar, H. Javanbakht, J. A. Jernelius, Q. Jin, Y. Li, W. Liang, R. Roetz, K. Sarma, M. Smith, D. Stefanidis, G. Su, J. M. Suh, A. G. Villaseñor, M. Welch, F.-J. Zhang, K. Klumpp*



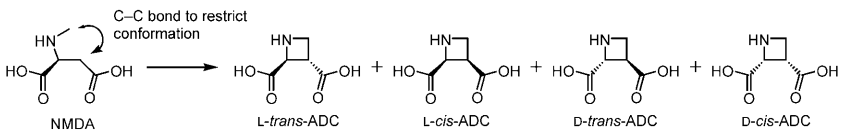
As part of a program focused on the discovery of NNRTIs for the treatment of HIV infection, we concentrated on the optimization of a series of diaryl ether compounds. The structure–activity relationships observed in this series of compounds provide insight into the structural features required for inhibiting the replication of a wide range of mutant viruses.

*M. Spreafico, B. Ernst, M. A. Lill, M. Smiesko, A. Vedani**



A multidimensional QSAR (mQSAR) study was performed on the glucocorticoid receptor. Based on 118 compounds a family of receptor models was generated and validated using consensus scoring. The model was then employed to quantify adverse effects triggered by a series of 24 psychotropic drugs.

M. Sivaprakasam, K. B. Hansen, O. David, B. Nielsen, S. F. Traynelis, R. P. Clausen, F. Couty, L. Bunch**



Subtype selective: The four stereoisomers of azetidine-2,3-dicaroxylic acid were synthesized. Most notable was L-*trans*-ADC, which showed the highest potency toward the NR1/NR2D NMDA receptor subtype and a significant preference for this over the other subtypes. Docking studies suggest an unusual binding mode for these amino acids in the agonist binding site.

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

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

* Author to whom correspondence should be addressed.

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