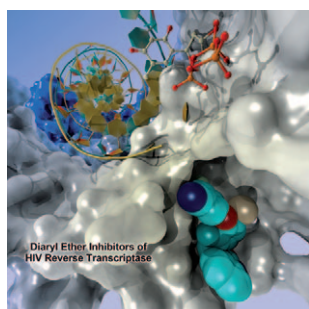


COVER PICTURE



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.

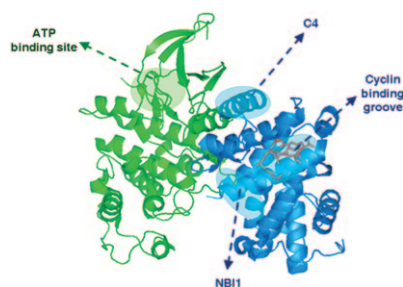
NEWS

Spotlights on our sister journals

14 – 15

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-non-competitive CDK–cyclin inhibitors.



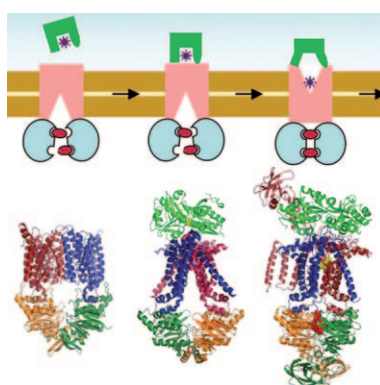
M. Orzáez, A. Gortat, L. Mondragón, O. Bachs, E. Pérez-Payá*

19 – 24

ATP-Noncompetitive Inhibitors of CDK–Cyclin Complexes

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.



*D. Parcej, R. Tampé**


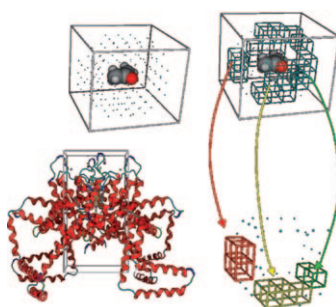
25 – 28

Solute-Binding Sites in ABC Transporters for Recognition, Occlusion and Trans-Inhibition

CONCEPTS

G. Caron, A. Nurisso, G. Ermondi*

29–36


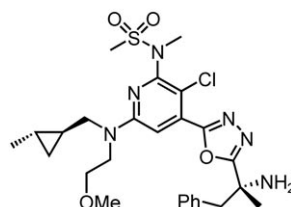

How to Extend the Use of Grid-Based Interaction Energy Maps from Chemistry to Biotics


Bridging the gap: The challenge of multidisciplinary 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

P. G. Nantermet,* H. A. Rajapakse, M. G. Stanton, S. R. Stauffer, J. C. Barrow, A. R. Gregro, K. P. Moore, M. A. Steinbeiser, J. Swestock, H. G. Selnick, S. L. Graham, G. B. McGaughey, D. Colussi, M.-T. Lai, S. Sankaranarayanan, A. J. Simon, S. Munshi, J. J. Cook, M. A. Holahan, M. S. Michener, J. P. Vacca

37–40


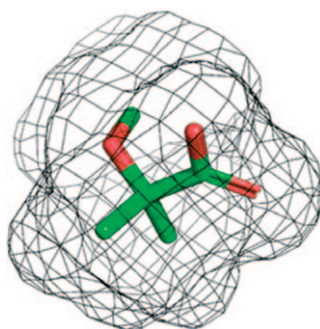

Evolution of Tertiary Carbinamine BACE-1 Inhibitors: A β Reduction in Rhesus CSF upon Oral Dosing


BACE-1 IC_{50} = 0.4 nM
 sAPP β _NF IC_{50} = 40 nM
 PGP ratio: (h) = 1.9, P_{app} = 22

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 β_{42} levels in the CSF by >40% over the 3 day course of the experiment.

E. Proschak, H. Zettl, Y. Tanrikulu, M. Weisel, J. M. Kriegl, O. Rau, M. Schubert-Zsilavecz, G. Schneider*


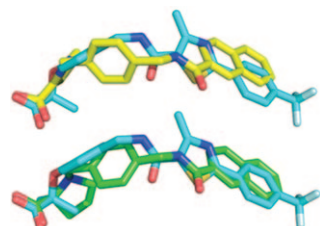
41–44


From Molecular Shape to Potent Bioactive Agents I: Bioisosteric Replacement of Molecular Fragments


Ligand-based virtual screening: By means of shape- and pharmacophore-based virtual screening, a potent PPAR α -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.

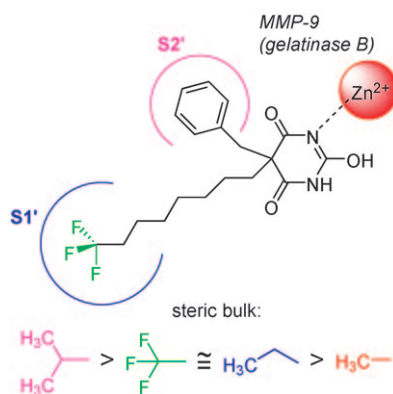
E. Proschak, K. Sander, H. Zettl, Y. Tanrikulu, O. Rau, P. Schneider, M. Schubert-Zsilavecz, H. Stark, G. Schneider*

45–48


From Molecular Shape to Potent Bioactive Agents II: Fragment-Based de novo Design


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.

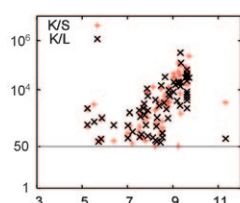
The controversial bioisosterism of the trifluoromethyl group has been re-assessed by measuring the inhibitory potency of a set of barbiturates having CF_3 , CH_3 , CH_3CH_2 , and $(\text{CH}_3)_2\text{CH}$ groups as remote substituents occupying the bottom of the tight lipophilic tunnel-like $\text{S1}'$ pocket of collagenase B as a steric probe. The results support the recent hypothesis that the CF_3 group is, in terms of bioisosterism, "smaller" than the isopropyl, larger than the methyl, and rather similar to the ethyl group.



M. Jagodzinska, F. Huguenot, G. Candiani, M. Zanda*

49 – 51

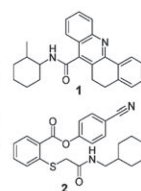
Assessing the Bioisosterism of the Trifluoromethyl Group with a Protease Probe



Reference molecules

In silico selectivity searching

Inhibitors with selective tendency



D. Stumpfe, M. Frizler, M. T. Sisay, J. Batista, I. Vogt, M. Gütschow, J. Bajorath*

52 – 54

Hit Expansion through Computational Selectivity Searching

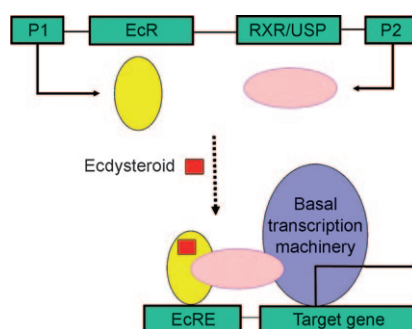


Finding small molecules that are selective for individual target proteins within target families is an important task. Thus far, computational screening methods have contributed very little to the identification of such molecules. We introduce in silico selectivity searching for the identification of cathepsin K inhibitors.

By computational analysis, 16 candidates out of 3.7 million database compounds were selected and tested, and two inhibitors were identified that showed on average fivefold selectivity for cathepsin K over cathepsins S and L. One of these inhibitors represents a previously unobserved chemotype.

FULL PAPERS

Modulating gene behaviour: In a ligand-inducible gene-expression (gene-switch) system, a small-molecule drug modulates the expression level of the target gene. The strategy of alkylation of natural ecdysteroid receptor (EcR) ligands points the way to improved ecdysteroidal actuators for switch-activated gene therapy.



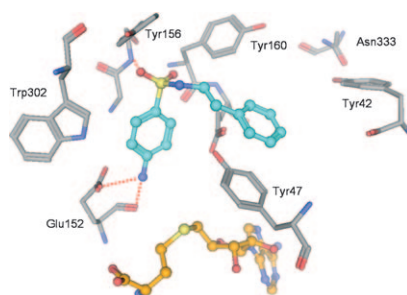
S. Lapenna,* L. Dinan, J. Friz, A. J. Hopfinger, J. Liu, R. E. Hormann

55 – 68

Semi-Synthetic Ecdysteroids as Gene-Switch Actuators: Synthesis, Structure–Activity Relationships, and Prospective ADME Properties



Novel PRMT1 inhibitors were discovered by applying a combination of structure-based virtual screening and in vitro experimental testing of Chembridge compound selection. Nine inhibitors were identified from the top-scored docking solutions and experimentally tested using human PRMT1 and an antibody-based assay with a time-resolved fluorescence readout.



R. Heinke, A. Spannhoff, R. Meier, P. Trojer, I. Bauer, M. Jung, W. Sippl*

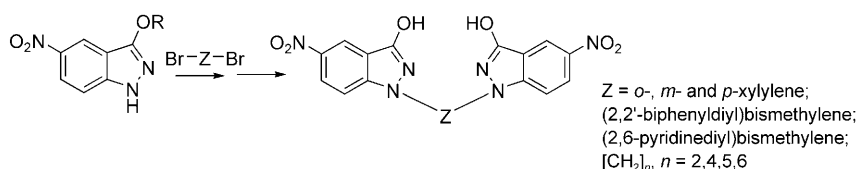
69 – 77

Virtual Screening and Biological Characterization of Novel Histone Arginine Methyltransferase PRMT1 Inhibitors

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

78 – 87

Synthesis and Evaluation of 1,1'-Hydrocarbylenebis(indazol-3-ols) as Potential Antimalarial Drugs



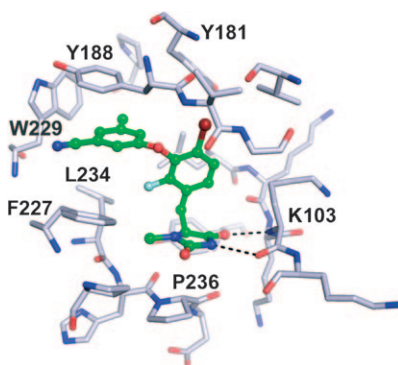
1,1'-Hydrocarbylenebis(5-nitroindazol-3-ols) are inhibitors of biocrystallization of heme to hemozoin, a *Plasmodium* specific detoxification process and therefore they are good leads for the

development of new antimalarial drugs. Acidic OH groups with adequate pK_a values provided by NO₂ 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

88 – 99

Diphenyl Ether Non-Nucleoside Reverse Transcriptase Inhibitors with Excellent Potency Against Resistant Mutant Viruses and Promising Pharmacokinetic Properties



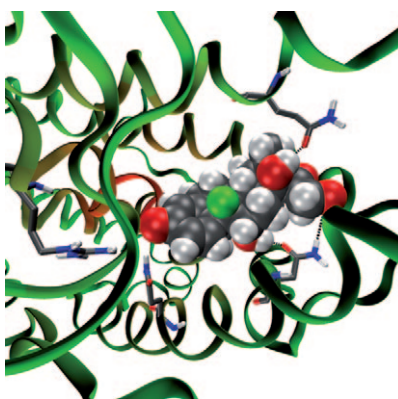
As part of a program focused on the discovery of NNRTIs for the treatment of HIV infection, we concentrated on the optimization of a series of diaryl ether compounds. The structure–activity relationships observed in this series of compounds provide insight into the structural features required for inhibiting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

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

100 – 109



Mixed-Model QSAR at the Glucocorticoid Receptor: Predicting the Binding Mode and Affinity of Psychotropic Drugs



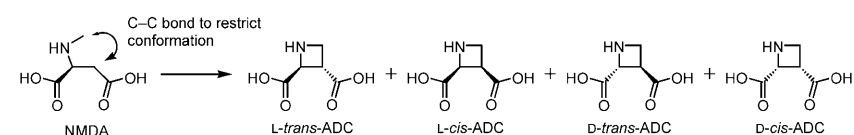
A multidimensional QSAR (mQSAR) study was performed on the glucocorticoid receptor. Based on 118 compounds a family of receptor models was generated and validated using consensus scoring. The model was then employed to quantify adverse effects triggered by a series of 24 psychotropic drugs.

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

110 – 117



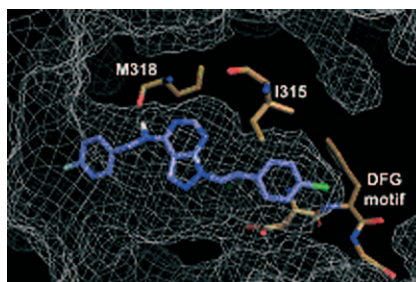
Stereocontrolled Synthesis and Pharmacological Evaluation of Azetidine-2,3-Dicarboxylic Acids at NMDA Receptors



Subtype selective: The four stereoisomers of azetidine-2,3-dicarboxylic 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.

Docking studies with the Bcr–Abl T315I mutant suggest that C6-unsubstituted pyrazolo[3,4-*d*]pyrimidines engage the Abl kinase domain in a manner that avoids steric clashes with the gatekeeper residue. The selected compounds affect the proliferation and survival of cells with the T315I mutation which do not respond to dual Src/Abl inhibitors.





M. A. Santucci, V. Corradi, M. Mancini, F. Manetti, M. Radi, S. Schenone, M. Botta*

118 – 126

C6-Unsubstituted Pyrazolo[3,4-*d*]pyrimidines Are Dual Src/Abl Inhibitors Effective against Imatinib Mesylate Resistant Chronic Myeloid Leukemia Cell Lines



 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.

SERVICE

Author Index 129 Preview 130

Keyword Index 129

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<http://www.chemmedchem.org>

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