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CHEMISTRY ENABLING DRUG DISCOVERY

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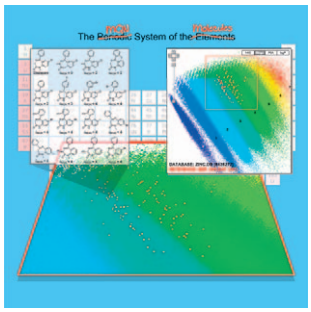
COVER PICTURE



The cover picture shows the classification, using the MQN system, of 8.4 million molecules in the public database of drug-like molecules ZINC. In analogy to the Periodic System of the Elements, in which atoms are classified by their atomic and main quantum numbers, the MQN system classifies molecules according to 42 molecular quantum numbers (MQN), defined as counts for structural features such as atoms, bonds, polar groups, and ring types. The 42-dimensional MQN space is represented as a projection in two dimensions along the first two principal components, the surface of which is color-coded by the number of cycles per molecule (blue to orange, 0 to 7 cycles). The red dots represent a family of known benzodiazepine receptor ligands. Related molecules are grouped closely in MQN space, as illustrated for diazepam and its nearest neighbors (structural formulae, MQN distance is indicated below each molecule). The MQN system provides a general and unifying concept for classifying large databases of organic molecules. For more details, see the Communication by J.-L. Reymond et al. on p. 1803 ff.

CLUSTER: Computational Medicinal Chemistry

As computer power has increased, so have the potential computational applications to practical problems. This is particularly true in the fields of pharmaceutical science and drug discovery where computational methods are used for hit and lead identification and refinement. The scope and importance of this research are exemplified in this issue's cluster. For more details, see Communications from p. 1803 to 1809 and Full Papers from p. 1859 to 1911.

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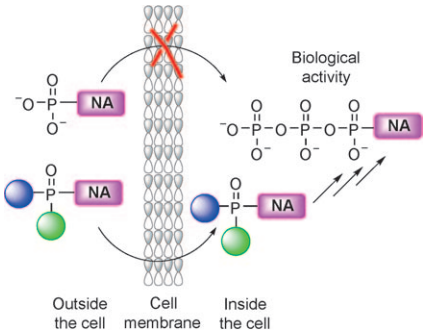
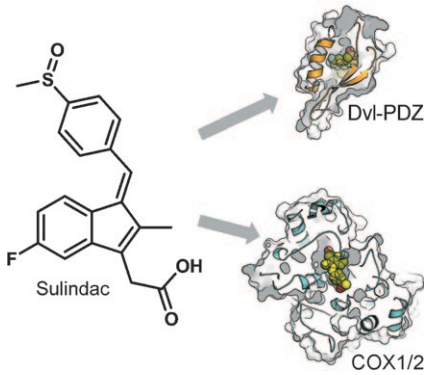
NEWS

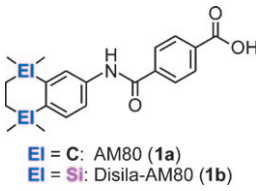
MINIREVIEWS



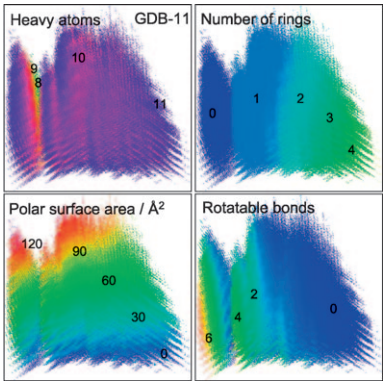
HIGHLIGHTS



COMMUNICATIONS

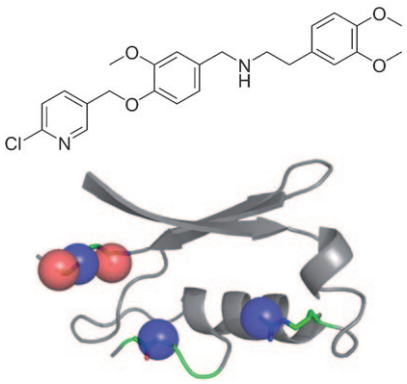


*K. T. Nguyen, L. C. Blum, R. van Deursen, J.-L. Reymond**



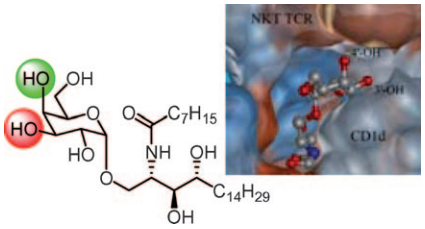
Classifying organic molecules using counts for simple structural features, such as atom, bond and ring types, called molecular quantum numbers (MQNs), defines a universal chemical space for analyzing large molecular databases such as ZINC and GDB. The organization of MQN space is revealed by principal component analysis (PCA), as shown for the GDB-11 database (26.4 million structures, up to 11 atoms of C, N, O, F).

*S. Keppner, E. Proschak, G. Schneider, B. Spänkuch**



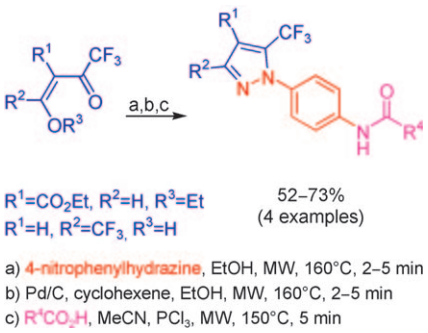
Virtual screening using a homology model of human polo-like kinase 1 (Plk1) in an inactive conformation led to the identification of a selective Plk1 inhibitor that decreases proliferation and induces apoptosis. This suggests that type II Plk1 inhibitors may be considered for the development of cancer therapeutics.

C. Xia, W. Zhang, Y. Zhang, W. Chen, J. Nadas, R. Severin, R. Woodward, B. Wang, X. Wang, M. Kronenberg, P. G. Wang**



NKT cell stimulation: C3′- and C4′-modified α-galactosylceramide (α-GalCer) analogues show that the 3′-OH group is crucial for maintaining α-GalCer immunogenicity; any modifications at this position lead to loss of activity. However, the C4′ position is less sensitive and tolerates minor modifications. Moreover, C4′-substituted analogues can induce the release of biased T_h2 cytokines.

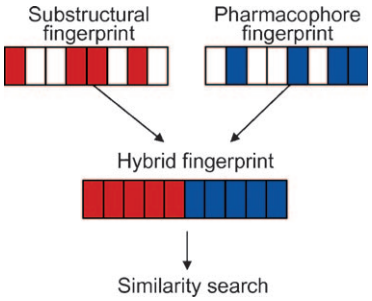
*T. N. Glasnov, K. Groschner, C. O. Kappe**



Process intensification using controlled microwave heating allows an efficient three-step synthesis of pyrazole-based inhibitors of TRPC3 and related NFAT transcription factor regulators. Compared to the conventional protocol, a dramatic reduction in overall processing time from ~2 days to 40 min was achieved, accompanied by significantly improved product yields.

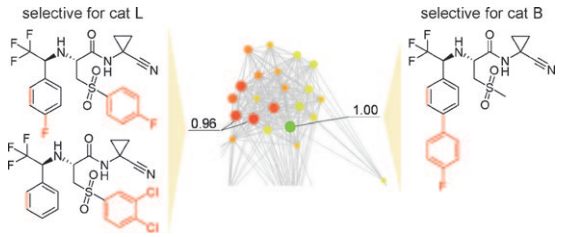
FULL PAPERS

*B. Nisius, J. Bajorath**



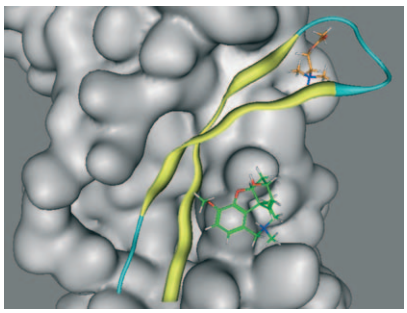
Fingerprint recombination is introduced as a methodology to generate hybrid fingerprints from original fingerprints of distinct design. Hybrid fingerprints combine preferred bit subsets from their parental fingerprints and emphasize compound class-specific features during similarity searching, which leads to consistent improvements in search performance. This new fingerprint design strategy is generally applicable to fingerprint representations where individual bit positions are associated with defined chemical information.

*L. Peltason, Y. Hu, J. Bajorath**



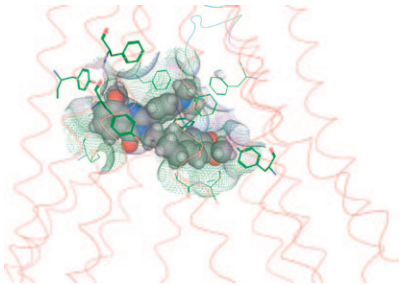
Selectivity cliffs: Network-like similarity graphs are used to organize similarity relationships and selectivity distributions within collections of compounds that are active against multiple targets. Shown here is a network region that contains compounds with different selectivities that are selectivity cliff markers (identified by red and green nodes) and highlights substituents that determine selectivity.

*E. Luttmann, J. Ludwig, A. Höffle-Maas, M. Samochocki, A. Maelicke, G. Fels**

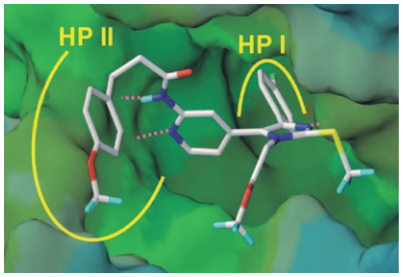


Galanthamine acts as an allosteric potentiating ligand at nicotinic acetylcholine receptors, thereby opening a new approach for the symptomatic treatment of Alzheimer's disease. Amino acids essential for the allosteric effect of galanthamine were identified by molecular modeling and verified by site-directed mutagenesis and electrophysiological experiments.

*I. K. Pajeva, C. Globisch, M. Wiese**



Selective and dual inhibitors of the ABCB1 (P-gp) and ABCC1 (MRP1) transporters were studied by pharmacophore modeling, docking into the P-gp binding cavity, and 3D QSAR to describe the binding preferences of the proteins and to identify the similarities and differences in their interactions.



Novel 1,2,4,5-tetrasubstituted imidazole derivatives were prepared. They were characterized not only for their ability to inhibit p38 MAP kinase and to modulate cytokine release in human whole blood, but also for their metabolic stability.

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).

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BOOKS

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