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CHEMISTRY ENABLING DRUG DISCOVERY

11/2009

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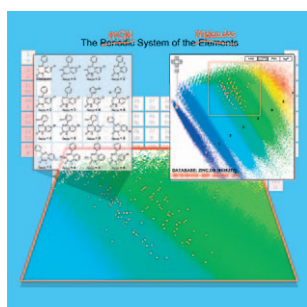
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COVER PICTURE



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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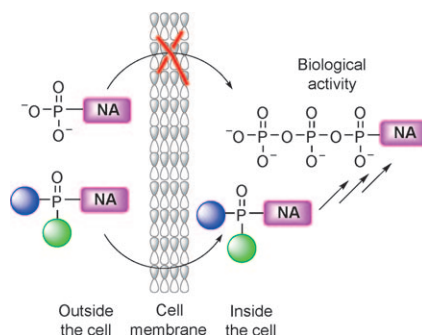
NEWS

Spotlights on our sister journals

1776 – 1778

MINIREVIEWS

Prodrug technologies aimed at delivering nucleoside monophosphates into cells (protides) have proved to be effective in improving the therapeutic potential of antiviral and anticancer nucleosides. In the phosphoramidate protide method, developed in our laboratories, the charges of the phosphate group are fully masked to provide efficient passive cell membrane penetration, and upon entering the cell, the masking groups are enzymatically cleaved to release the phosphorylated biomolecule. This Mini-review discusses the development and applications of phosphoramidate technology.



Y. Mehellou, J. Balzarini, C. McGuigan*

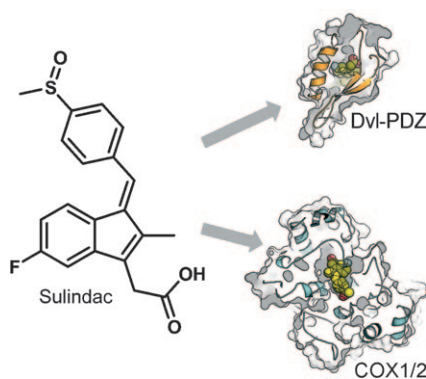
1779 – 1791

Aryloxy Phosphoramidate Triesters: a Technology for Delivering Monophosphorylated Nucleosides and Sugars into Cells

HIGHLIGHTS

Chemical biology for medicinal chemistry:

The nonsteroidal anti-inflammatory drug sulindac was originally developed to inhibit cyclooxygenase enzymes (COX1/2) to treat inflammation and pain. Recent studies have shown that sulindac also acts on the Wnt signaling pathway, a target relevant to cancer.



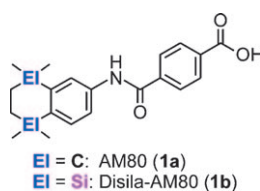
J. R. Simard, D. Rauh*

1793 – 1795

Chemical and Structural Biology to Direct the Repurposing of Sulindac

COMMUNICATIONS

C/Si switch: Twofold sila-substitution (C/Si exchange) in the RAR α -selective retinoids **1a** (AM80) and **2a** (AM580) leads to **1b** (disila-AM80) and **2b** (disila-AM580), respectively. The chemistry and biology of the C/Si pairs are reported.



R. Tacke,* V. Müller, M. W. Büttner, W. P. Lippert, R. Bertermann, J. O. Daiß, H. Khanwalkar, A. Furst, C. Gaudon, H. Gronemeyer

1797 – 1802

Synthesis and Pharmacological Characterization of Disila-AM80 (Disila-tamibarotene) and Disila-AM580, Silicon Analogues of the RAR α -Selective Retinoid Agonists AM80 (Tamibarotene) and AM580

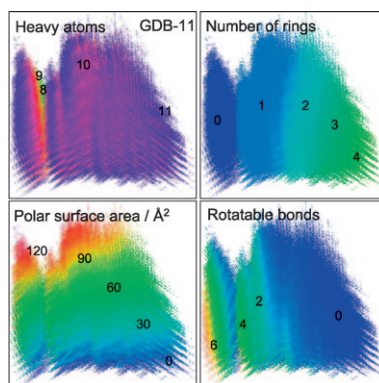


K. T. Nguyen, L. C. Blum, R. van Deursen,
J.-L. Reymond*

1803 – 1805



Classification of Organic Molecules by Molecular Quantum Numbers



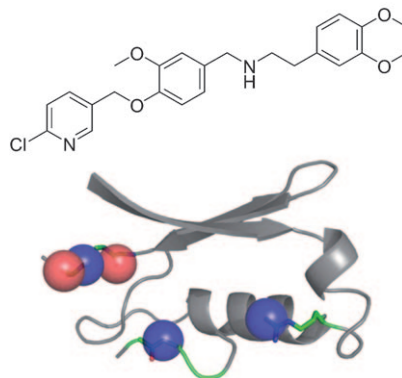
Classifying organic molecules using counts for simple structural features, such as atom, bond and ring types, called molecular quantum numbers (MQNs), defines a universal chemical space for analyzing large molecular databases such as ZINC and GDB. The organization of MQN space is revealed by principal 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*

1806 – 1809



Identification and Validation of a Potent Type II Inhibitor of Inactive Polo-like Kinase 1

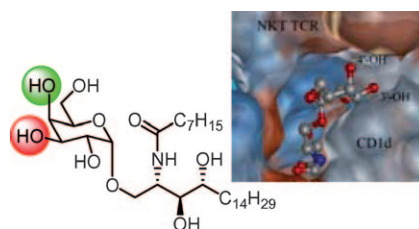


Virtual screening using a homology model of human polo-like kinase 1 (Plk1) in an inactive conformation led to the identification of a selective Plk1 inhibitor that decreases proliferation and induces apoptosis. This suggests that type II Plk1 inhibitors may be considered for the development of cancer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

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

1810 – 1815

The Roles of 3' and 4' Hydroxy Groups in α -Galactosylceramide Stimulation of Invariant Natural Killer T Cells



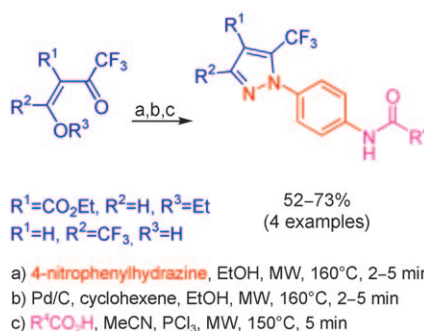
NKT cell stimulation: C3'- and C4'-modified α -galactosylceramide (α -GalCer) analogues show that the 3'-OH group is crucial for maintaining α -GalCer immunogenicity; any modifications at this position lead to loss of activity. However, the C4' position is less sensitive and tolerates minor modifications. Moreover, C4'-substituted analogues can induce the release of biased T_H2 cytokines.

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

1816 – 1818



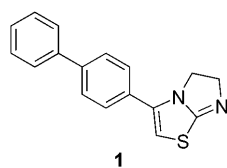
High-Speed Microwave-Assisted Synthesis of the Trifluoromethylpyrazol-Derived Canonical Transient Receptor Potential (TRPC) Channel Inhibitor Pyr3



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

No exit: Forty analogues of 3-biphenyl-5,6-dihydroimidazo[2,1-*b*]thiazole **1** were synthesized and their activities as iodide efflux inhibitors were evaluated in rat thyroid-derived cells. This study not only provided important SAR data, but has also identified a new compound with enhanced potency.



40 analogues

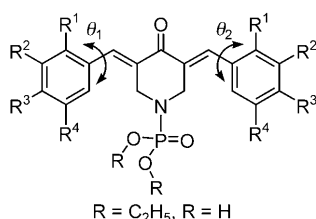
*N. Lecat-Guillet, Y. Ambroise**

1819 – 1830

Synthesis and Evaluation of Imidazo[2,1-*b*]thiazoles as Iodide Efflux Inhibitors in Thyrocytes



N-Phosphono derivatives and corresponding diethyl esters of 3,5-bis(benzylidene)-4-piperidones are disclosed as potent cytotoxic agents capable of reversing multi-drug resistance. As a handful of these compounds represent excellent lead structures, a number of guidelines for expanding this project have been made.



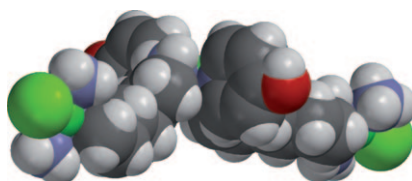
*S. Das, U. Das, P. Selvakumar, R. K. Sharma, J. Balzarini, E. De Clercq, J. Molnár, J. Serly, Z. Baráth, G. Schatte, B. Bandy, D. K. J. Gorecki, J. R. Dimmock**

1831 – 1840

3,5-Bis(benzylidene)-4-oxo-1-phosphonopiperidines and Related Diethyl Esters: Potent Cytotoxins with Multi-Drug-Resistance Reverting Properties



Organometallic drugs: Significant anti-tumor activity can be introduced in trinuclear palladium complexes when their reactivity is lowered by the presence of sterically hindered ligands such as 2-hydroxypyridine, 3-hydroxypyridine and 4-hydroxypyridine bound to the central palladium ion. This hypothesis was tested by the synthesis and evaluation of three novel tripalladium complexes containing planaramine ligands against ovarian cancer cell lines.

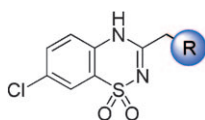


*M. Farhad, J. Q. Yu, P. Beale, K. Fisher, F. Huq**

1841 – 1849

Studies on the Synthesis and Activity of Three Tripalladium Complexes Containing Planaramine Ligands

Open sesame: Enhanced activity as K_{ATP} channel openers was found in benzo-thiadiazine-1,1-dioxides with cycloaliphatic side chains in the position 3, relative to the parent compound, diazoxide ($R=H$). High selectivity was reached with nonpolar globular substituents ($R=1$ -adamantyl): the affinity for the SUR2B/Kir6.1 ion channel surpasses that for SUR/Kir6.2 receptor by more than two orders of magnitude.



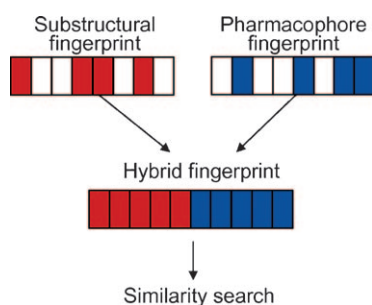
*S. Lachenicht, A. Fischer, C. Schmidt, M. Winkler, A. Rood, H. Lemoine, M. Braun**

1850 – 1858

Synthesis of Modified 4*H*-1,2,4-Benzothiadiazine-1,1-dioxides and Determination of their Affinity and Selectivity for Different Types of K_{ATP} Channels

B. Nisius, J. Bajorath*

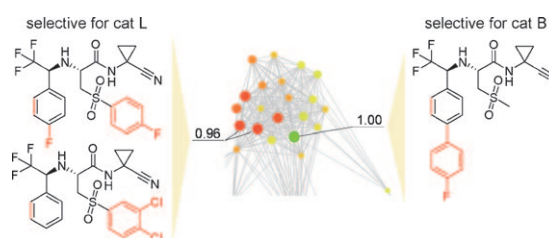
1859 – 1863

**Molecular Fingerprint Recombination: Generating Hybrid Fingerprints for Similarity Searching from Different Fingerprint Types**

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*

1864 – 1873

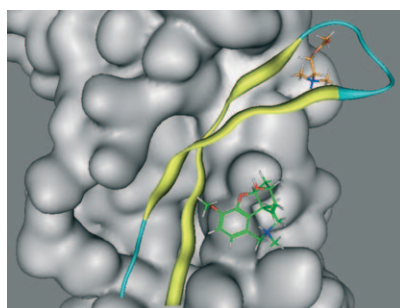
From Structure–Activity to Structure–Selectivity Relationships: Quantitative Assessment, Selectivity Cliffs, and Key Compounds

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*

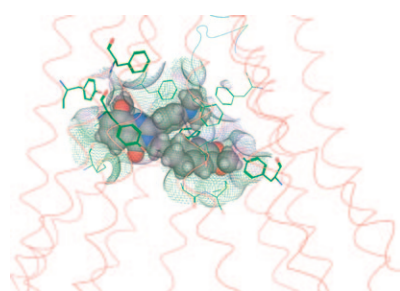
1874 – 1882

**Structural Model for the Binding Sites of Allosterically Potentiating Ligands on Nicotinic Acetylcholine Receptors**

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.

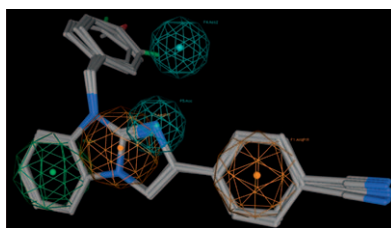
I. K. Pajeva, C. Globisch, M. Wiese*

1883 – 1896

**Combined Pharmacophore Modeling, Docking, and 3D QSAR Studies of ABCB1 and ABCC1 Transporter Inhibitors**

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.

A series of small-molecule activators of P-glycoprotein (P-gp) based on an imidazo[1,2-*a*]benzimidazole lead structure were synthesized and characterized with various functional assays. Although all these compounds are structurally related, a small subset inhibited P-gp.

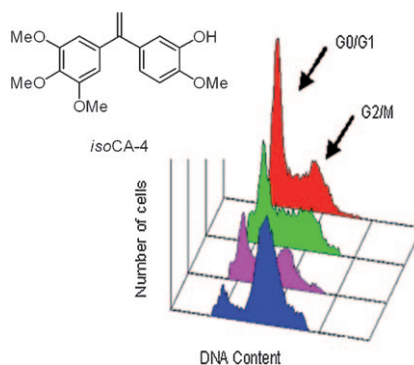


K. Sterz, L. Möllmann, A. Jacobs, D. Baumert, M. Wiese*

1897 – 1911

Activators of P-glycoprotein: Structure–Activity Relationships and Investigation of their Mode of Action

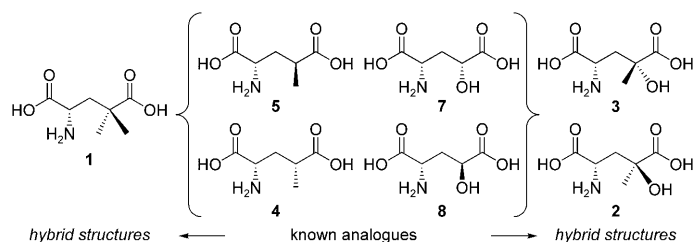
A disruptive influence: We studied the antimitotic activity of a series of new isocombreastatin derivatives with B-ring modifications. We selected isocombreastatin analogues *isoCA-4*, *isoNH₂CA-4* and *isoFCA-4* as lead compounds for their high antitumor activity.



A. Hamze, A. Giraud, S. Messaoudi, O. Provot, J.-F. Peyrat, J. Bignon, J.-M. Liu, J. Wdzieczak-Bakala, S. Thoret, J. Dubois, J.-D. Brion, M. Alami*

1912 – 1924

Synthesis, Biological Evaluation of 1,1-Diarylethylenes as a Novel Class of Antimitotic Agents



Glutamate analogues 1–3 are hybrid structures of the previously reported analogues 4–8. These three analogues were investigated at the iGluRs and EAAT1–3, and results of our *in silico*

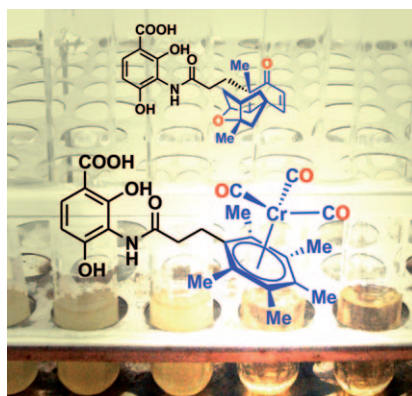
studies explain the differences in their pharmacological profiles, providing further insight into the SAR for iGluR and EAAT ligands.

L. Bunch,* D. S. Pickering, T. Gefflaut, V. Vinatier, V. Helaine, A. Amir, B. Nielsen, A. A. Jensen

1925 – 1929

4,4-Dimethyl- and Diastereomeric 4-Hydroxy-4-methyl- (2S)-Glutamate Analogues Display Distinct Pharmacological Profiles at Ionotropic Glutamate Receptors and Excitatory Amino Acid Transporters

Bioorganometallic antibacterial agents: The synthesis of Cr organometallics based on the lead structure of the new antibiotic platensimycin is described. Compounds containing a (η^6 -pentamethylbenzene)Cr(CO)₃ moiety are significantly more active than other metal-containing analogues and also the metal-free derivatives, and exhibited antibacterial activity against the Gram-positive *B. subtilis* but not against Gram-negative *E. coli*.



M. Patra, G. Gasser, A. Pinto, K. Merz, I. Ott, J. E. Bandow, N. Metzler-Nolte*

1930 – 1938

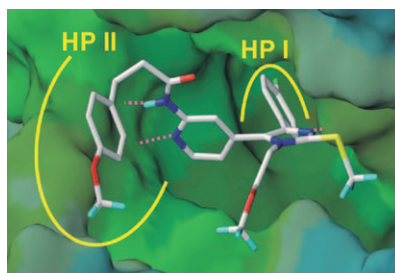
Synthesis and Biological Evaluation of Chromium Bioorganometallics Based on the Antibiotic Platensimycin Lead Structure

K. Ziegler, D. R. J. Hauser, A. Unger,
W. Albrecht, S. A. Laufer*

1939 – 1948



2-Acylaminopyridin-4-ylimidazoles as p38 MAP Kinase Inhibitors: Design, Synthesis, and Biological and Metabolic Evaluations



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).

* Author to whom correspondence should be addressed.

BOOKS

The Cannabinoid Receptors · P. H. Reggio (Ed.)
Cancer Proteomics: From Bench to Bedside · S. S. Daoud (Ed.)

D. Selwood 1949
L. Prokai 1950

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