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## COVER PICTURE



The cover picture shows the best docking result of a new noncompetitive NMDA receptor antagonist, 2-(4-benzylpiperidin-1-yl)-1-(1*H*-indol-3-yl)ethan-1-one, in the NR2B ifenprodil-like binding site model. For details, see the Full Paper by A. Chimirri et al. on p. 1539 ff.

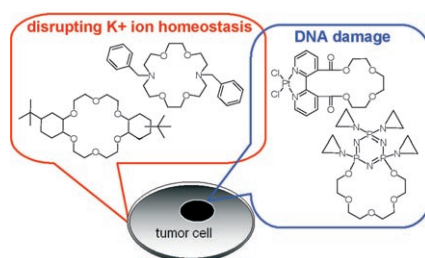
## NEWS

Spotlights on our sister journals

1474 – 1475

## REVIEWS

**Crown ethers and related compounds** are of enormous interest and importance in chemistry. The central feature of these compounds is their ability to form stable and selective complexes with various inorganic and organic cations. This review presents additional applications and the ever-increasing biomedical potential of crown ethers, with particular emphasis on their relevance as promising anticancer compounds.



M. Kralj,\* L. Tušek-Božić, L. Frkanec

1478 – 1492

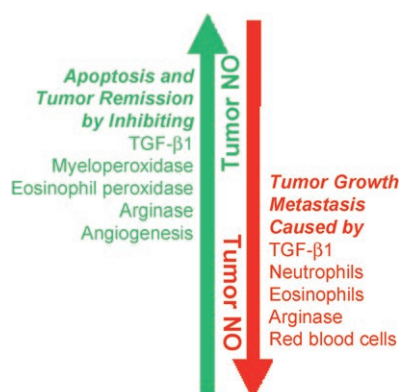
**Biomedical Potentials of Crown Ethers: Prospective Antitumor Agents**

## ESSAYS

A. Heller\*

1493 – 1499

**Apoptosis-Inducing High  $\cdot\text{NO}$  Concentrations Are Not Sustained Either in Nascent or in Developed Cancers**



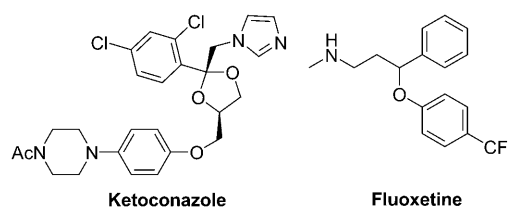
**Saying  $\cdot\text{NO}$  to cancer:** According to the analysis presented, nascent neoplasms are recognized by the immune system and are attacked through maintenance of an apoptosis-inducing high nitric oxide concentration. Increasing the  $\cdot\text{NO}$  concentration requires inhibition of the cytokine TGF- $\beta$ 1 in some cases, and inhibition of myeloperoxidase, eosinophil peroxidase, or arginase in others. In all tumors, it requires the prevention of angiogenesis.

## HIGHLIGHTS

K.-S. Yeung,\* N. A. Meanwell

1501 – 1502

**Inhibition of hERG Channel Trafficking: An Under-Explored Mechanism for Drug-Induced QT Prolongation**



**hERG channel trafficking inhibition leads to QT prolongation:** Drugs that cause long QT syndrome usually do so by directly blocking the hERG channel through binding in the pore domain. However, an increasing number of

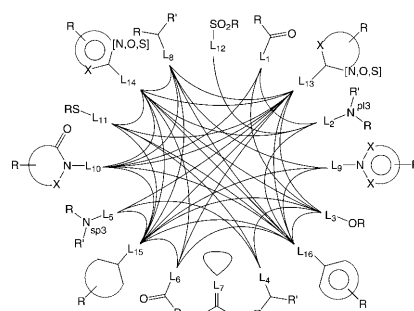
drugs, including the widely prescribed antifungal ketoconazole and the anti-depressant fluoxetine, can induce long QT syndrome by an indirect effect in which hERG channel expression at the cell surface is reduced.

## COMMUNICATIONS

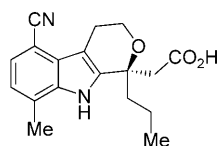
J. Degen, C. Wegscheid-Gerlach, A. Zaliani, M. Rarey\*

1503 – 1507

**On the Art of Compiling and Using 'Drug-Like' Chemical Fragment Spaces**



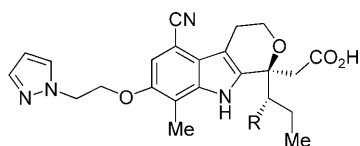
**To improve current methods** for the decomposition of molecules into fragments, we compiled a new and more elaborate set of rules for the breaking of retrosynthetically interesting chemical substructures (BRICS). We also incorporated further medicinal chemistry concepts and compiled differently sized sets of diverse high-quality fragments. Relative to existing methods, BRICS performs much better in retrieving compounds from various large and diverse query sets.



HCV-371 (1)

### Antiviral agents against hepatitis C:

The discovery and synthesis of pyrano[3,4-*b*]indole based inhibitors of HCV NS5B polymerase is described. These compounds effectively inhibit HCV NS5B polymerase and display



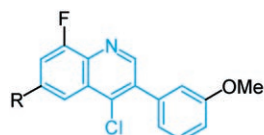
2 R=Me  
19 R=H

potent activities in a subgenomic HCV replicon assay. In particular, a *sec*-butyl-analogue of HCV-371 demonstrates in vivo antiviral activity in the chimeric mouse model of HCV infection.

M. G. LaPorte,\* R. W. Jackson, T. L. Draper, J. A. Gaboury, K. Galie, T. Herbertz, A. R. Hussey, S. R. Rippin, C. A. Benetatos, S. K. Chunduru, J. S. Christensen, G. A. Coburn, C. J. Rizzo, G. Rhodes, J. O'Connell, A. Y. M. Howe, T. S. Mansour, M. S. Collett, D. C. Pevear, D. C. Young, T. Gao, D. L. J. Tyrrell, N. M. Kneteman, C. J. Burns, S. M. Condon\*

1508 – 1515

### The Discovery of Pyrano[3,4-*b*]indole-Based Allosteric Inhibitors of HCV NS5B Polymerase with In Vivo Activity



3-aryl-4-chloroquinoline scaffold

**The cytotoxicity of substituted 3-aryl-4-chloroquinolines:** A series of 3-arylquinolines were designed, synthesized and evaluated as antitumor agents. While the majority of the 34 compounds evaluated exhibited potent cytotoxicity in one or more of the human tumor cell lines tested, two compounds

IC <sub>50</sub> (μM)	K562	Hep-G2	KB	L02
R = F	0.56±0.20	0.43±0.29	0.7±0.7	245±56
R = H	0.38±0.28	0.21±0.07	0.59±0.28	>300
5-fluorouracil	35±7	2.46±0.31	2.31±0.69	50±16

were identified as potential leads, with high activity against human hepatocellular liver carcinoma (Hep-G2), human erythromyeloblastoid leukemia (K562) and human oral epidermoid carcinoma (KB) cell lines, and lacking significant cytotoxicity against the normal human liver cell line (L02).

Z.-P. Xiao, P.-c. Lv, S.-P. Xu, T.-T. Zhu, H.-L. Zhu\*

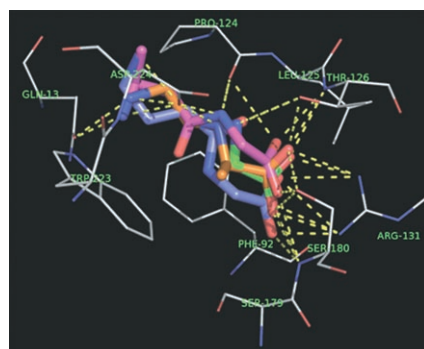
1516 – 1519

### Synthesis, Antiproliferative Evaluation, and Structure–Activity Relationships of 3-Arylquinolines



### The first virtual screening search

through the entire chemical space of small organic ligands has identified promising ligands as inhibitors of the *N*-methyl-D-aspartic acid (NMDA) receptor glycine site. This receptor is an important drug target implicated in synaptic plasticity, neuronal development, learning, and memory. Inhibiting the NMDA receptor may help prevent neuronal cell death caused by glutamate excitotoxicity in acute and chronic neurodegenerative disorders.



K. T. Nguyen, S. Syed, S. Urwyler, S. Bertrand, D. Bertrand, J.-L. Reymond\*

1520 – 1524

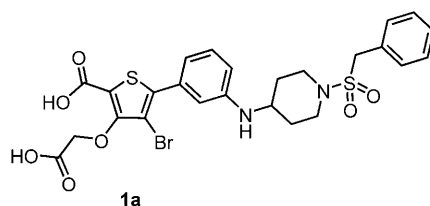
### Discovery of NMDA Glycine Site Inhibitors from the Chemical Universe Database GDB



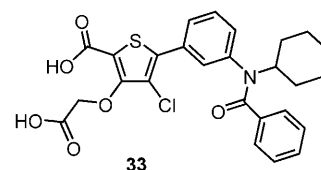
Z.-K. Wan, J. Lee, R. Hotchandani,  
A. Moretto, E. Binnun, D. P. Wilson,  
S. J. Kirincich, B. C. Follows, M. Ipek,  
W. Xu, D. Joseph-McCarthy, Y.-L. Zhang,  
M. Tam, D. V. Erbe, J. F. Tobin, W. Li,  
S. Y. Tam, T. S. Mansour, J. Wu\*

1525 – 1529

## Structure-Based Optimization of Protein Tyrosine Phosphatase-1 B Inhibitors: Capturing Interactions with Arginine 24



**Further optimization efforts** on the previously disclosed PTP-1B inhibitor **1a** led to the discovery of a new series of potent compounds, for example derivative **33**, which targeted the second phosphotyrosine binding pocket near the catalytic site. In the new series, the *N*-sulfonylpiperidine group of **1a** was

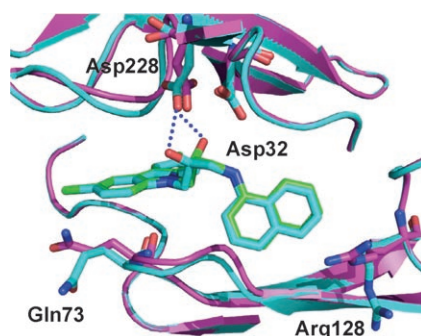


replaced with a smaller substituent, capable of forming a new hydrogen bond interaction with arginine 24. The series reported here maintains the binding mode of **1a** and has the added advantages of a lower molecular weight, smaller polar surface area, and fewer rotatable bonds.

V. Asso, E. Ghilardi, S. Bertini,  
M. Digiacoimo, C. Granchi, F. Minutolo,  
S. Rapposelli, A. Bortolato, S. Moro,  
M. Macchia\*

1530 – 1534

## $\alpha$ -Naphthylaminopropan-2-ol Derivatives as BACE1 Inhibitors

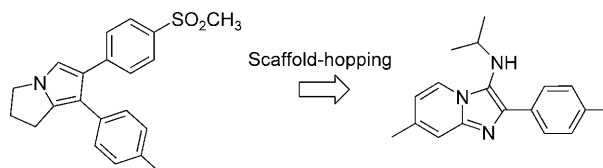


**Fast and healthy (molecular) weight loss!** A relatively large BACE1 inhibitor containing a hydroxyethylamine aspartyl protease inhibitor motif was identified by high-throughput screening, and has inspired the design of new “lighter”, biologically active derivatives, representing a promising new class anti-Alzheimer’s drugs.

B. Hofmann, L. Franke, E. Proschak,  
Y. Tanrikulu, P. Schneider, D. Steinhilber,  
G. Schneider\*

1535 – 1538

## Scaffold-Hopping Cascade Yields Potent Inhibitors of 5-Lipoxygenase



**A two-step iterative approach to virtual screening** can identify potent lead scaffolds as demonstrated for 5-lipoxygenase inhibition, a validated target for the treatment of inflammation and allergic reactions. Four cycles of virtual

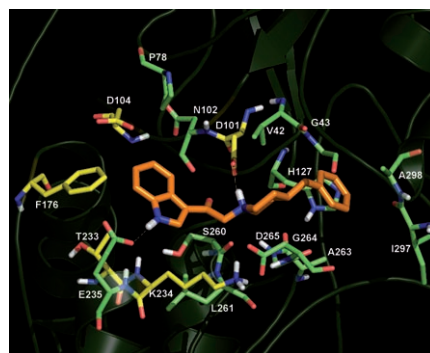
screening using both 3D- and 2D-based methods, and substructure searching were performed, and cell-based assays were used to further refine the lead selection at each stage of the process.

## FULL PAPERS

R. Gitto, L. De Luca, S. Ferro, F. Occhiuto,  
S. Samperi, G. De Sarro, E. Russo,  
L. Ciranna, L. Costa, A. Chimirri\*

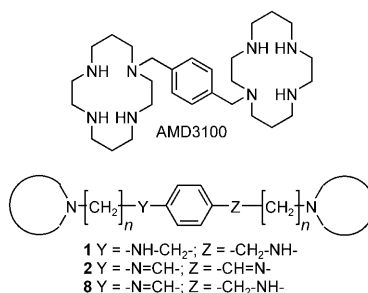
1539 – 1548

## Computational Studies to Discover a New NR2B/NMDA Receptor Antagonist and Evaluation of Pharmacological Profile



**Theory and practice:** A ligand-based and target-based approach were combined for the discovery of new ligands for the ionotropic glutamate NMDA/NR2B receptor. The identification of hits and evaluation of their neuroprotective effects in in vivo and in vitro experiments is reported.

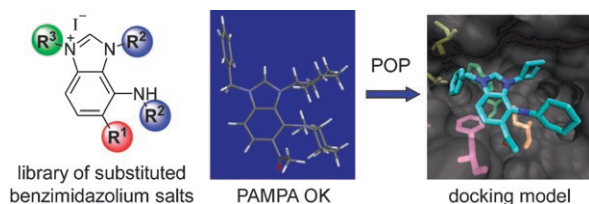
**Improving on a good thing:** A combinatorial library of non-cyclam polynitrogenated compounds was designed by preserving the main features of AMD3100. A selection of diverse compounds from this library were prepared, and their *in vitro* activity was tested in cell cultures against HIV strains. This led to the identification of novel potent CXCR4 coreceptor inhibitors without cytotoxicity at the tested concentrations.



S. Pettersson, V. I. Pérez-Nueno, L. Ros-Blanco, R. Puig de La Bellacasa, M. O. Rabal, X. Batllori, B. Clotet, I. Clotet-Codina, M. Armand-Ugón, J. Esté, J. I. Borrell, J. Teixidó\*

1549 – 1557

**Discovery of Novel Non-Cyclam Polynitrogenated CXCR4 Coreceptor Inhibitors**



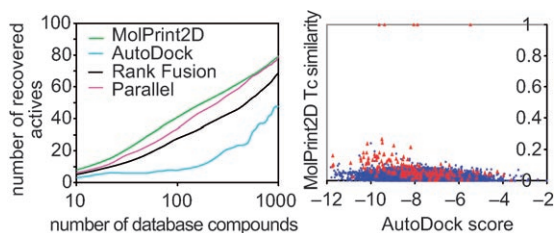
**POP off:** Benzimidazolium salts, representing a new family of prolyl oligopeptidase (POP) inhibitors, were identified from a library of compounds arising from multicomponent reactions. The new scaffolds have properties of solubil-

ity, specificity, and lipophilicity that may allow them to cross the blood–brain barrier by passive diffusion. The best scaffolds would be an excellent starting point for the synthesis of improved POP inhibitors.

T. Tarragó, C. Masdeu, E. Gómez, N. Isambert, R. Lavilla, E. Giralte\*

1558 – 1565

**Benzimidazolium Salts as Small, Nonpeptidic and BBB-Permeable Human Prolyl Oligopeptidase Inhibitors**



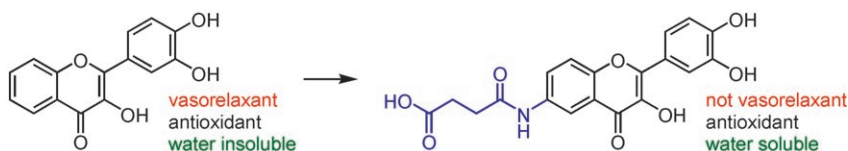
**Docking and similarity search** calculations using 2D fingerprints were carried out in parallel to identify inhibitors of nine target enzymes. By combining the results of docking and similarity searching, compound recall achieved by the individual methodologies was further

increased in several cases. As a compound selection scheme, parallel selection of candidate compounds from docking and similarity search rankings overall produced higher recall than rank fusion.

L. Tan, H. Geppert, M. T. Sisay, M. Gütschow, J. Bajorath\*

1566 – 1571

**Integrating Structure- and Ligand-Based Virtual Screening: Comparison of Individual, Parallel, and Fused Molecular Docking and Similarity Search Calculations on Multiple Targets**



**Functional flavonols:** 3',4'-Dihydroxyflavonol has emerged as a promising agent for the treatment of cardiovascular disease, but possesses poor solubility in water. Addition of an ionisable succinic acid side chain confers water sol-

ubility, and pharmacological analysis revealed loss of vasorelaxant activity and retention of antioxidant activity. This marks the discovery of the first single-acting water-soluble antioxidant flavonol.

S. Yap, K. J. Loft, O. L. Woodman, S. J. Williams\*

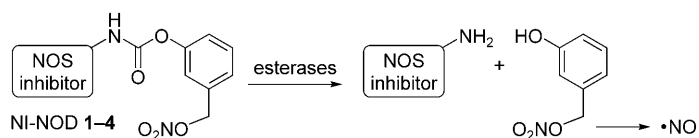
1572 – 1579

**Discovery of Water-Soluble Antioxidant Flavonols without Vasorelaxant Activity**

M. Botta,\* E. Distrutti, A. Mencarelli,  
M. C. Parlato, F. Raffi, S. Cipriani,  
S. Fiorucci\*

1580–1588

## Anti-Inflammatory Activity of a New Class of Nitric Oxide Synthase Inhibitors That Release Nitric Oxide



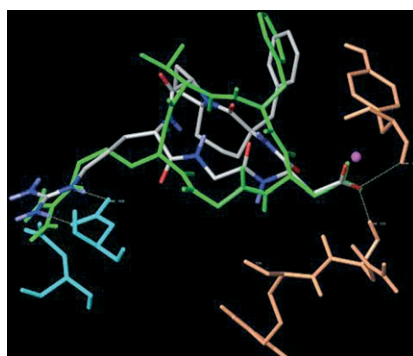
**Getting the balance right:** Nitric oxide (NO) is a gaseous mediator that exerts key regulatory functions in mammalian cells. Low levels of NO exert homeostatic functions and counteract inflammation, whereas high amounts of NO

cause tissue destruction and cell death. A new class of nitric oxide synthase (NOS) inhibitor NO-donating drugs (NI-NODs) is described. The efficacy of NI-NODs is shown both in vitro and in vivo.

D. Arosio, L. Belvisi,\* L. Colombo,  
M. Colombo, D. Invernizzi, L. Manzoni,\*  
D. Potenza, M. Serra, M. Castorina,  
C. Pisano, C. Scolastico

1589–1603

## A Potent Integrin Antagonist from a Small Library of Cyclic RGD Pentapeptide Mimics Including Benzyl-Substituted Azabicycloalkane Amino Acids

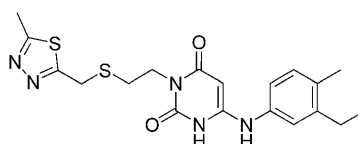


**Vitronectin receptors  $\alpha_v\beta_3$  and  $\alpha_v\beta_5$**  have received increasing attention as therapeutic targets because of their critical role in tumor-induced angiogenesis and formation of metastasis. A new potent integrin antagonist was synthesized, and herein we describe the solution-phase synthesis, in vitro screening, and determination of the conformational properties of the integrin ligands by spectroscopic and computational methods.

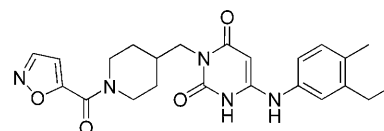
N. Svenstrup,\* K. Ehlert, C. Ladel, A. Kuhl,  
D. Häbich

1604–1615

## New DNA Polymerase III Inhibitors: 3-Substituted Anilinothiazoles with Potent Antibacterial Activity in vitro and in vivo



**Resistance is futile:** 6-Anilinothiazoles represent a promising lead structure. They target DNA polymerase III of Gram-positive bacteria, and exhibit a bactericidal mode of action with no cross-resist-



ance to marketed antibiotics. Herein we describe the synthesis of novel anilinothiazoles, some of which display potent in vivo efficacy in murine models of bacterial septicemia.

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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