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Most of the articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

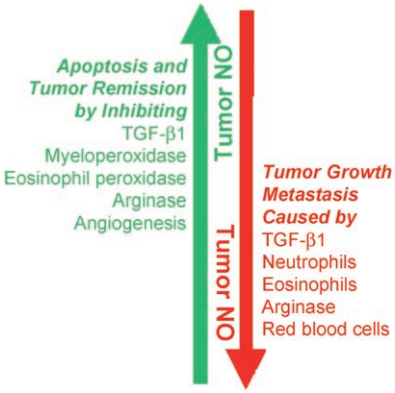
COVER PICTURE

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

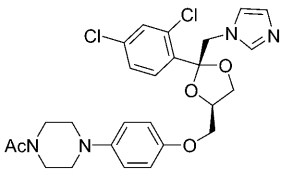
REVIEWS

ESSAYS

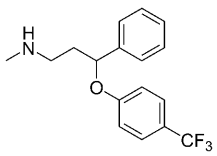


Saying ·NO to cancer: According to the analysis presented, nascent neoplasms are recognized by the immune system and are attacked through maintenance of an apoptosis-inducing high nitric oxide concentration. Increasing the ·NO concentration requires inhibition of the cytokine TGF-β1 in some cases, and inhibition of myeloperoxidase, eosinophil peroxidase, or arginase in others. In all tumors, it requires the prevention of angiogenesis.

HIGHLIGHTS



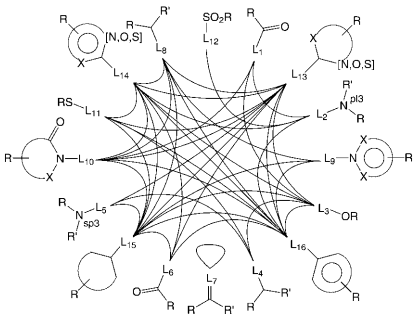
Ketoconazole



Fluoxetine

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 antidepressant fluoxetine, can induce long QT syndrome by an indirect effect in which hERG channel expression at the cell surface is reduced.

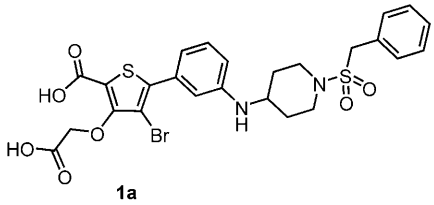
COMMUNICATIONS



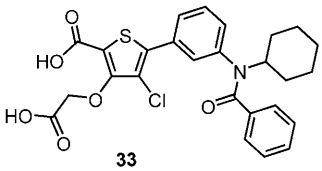
To improve current methods for the decomposition of molecules into fragments, we compiled a new and more elaborate set of rules for the breaking of retrosynthetically interesting chemical substructures (BRICS). We also incorporated further medicinal chemistry concepts and compiled differently sized sets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

CONTENTS

*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**



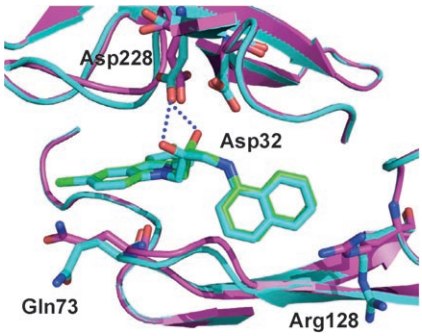
1a



33

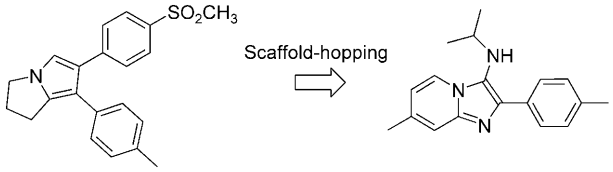
Further optimization efforts on the previously disclosed PTP-1B inhibitor **1 a** led to the discovery of a new series of potent compounds, for example derivative **33**, which targeted the second phosphotyrosine binding pocket near the catalytic site. In the new series, the *N*-sulfonylpiperidine group of **1 a** 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 **1 a** 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. Digiacomo, C. Granchi, F. Minutolo, S. Rapposelli, A. Bortolato, S. Moro, M. Macchia**



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.

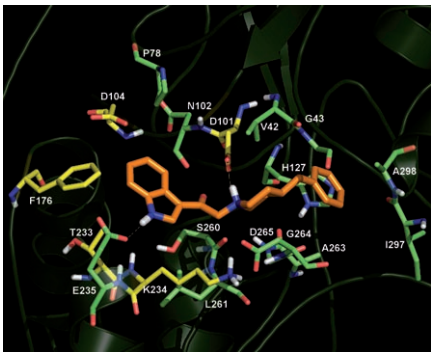
*B. Hofmann, L. Franke, E. Proschak, Y. Tanrikulu, P. Schneider, D. Steinhilber, G. Schneider**



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**



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.

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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