CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY

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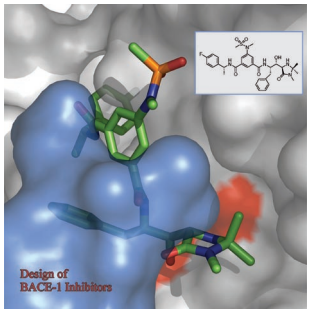
Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE



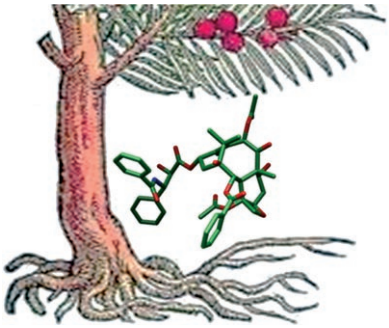
The cover picture shows a close-up view of a modified hydroxyethylamine aspartyl protease inhibitor bound in the BACE-1 active site. The imidazolidinone ring serves as a rigid scaffold for orienting substituents into the S1′ and S2′ sites of the enzyme while making hydrogen bond contacts to the catalytic aspartate groups (highlighted in red) and the flap (colored in blue). Based on this X-ray crystal structure, additional analogues were designed to exploit the imidazolidinone heterocycle as a template for potent BACE-1 inhibitors. For details, see the Communication by J. Barrow et al. on p. 995 ff.

NEWS

Spotlights on our sister journals ***918 – 919***

REVIEWS

Emergence of resistance represents a major limitation to the clinical use of paclitaxel and docetaxel as anticancer agents, and many efforts have been made during the years to overcome this phenomenon; as a result, several distinct mechanisms have been described and new generation taxanes potentially useful for the treatment of resistant tumors have been identified.



*E. Galletti, M. Magnani, M. L. Renzulli, M. Botta**

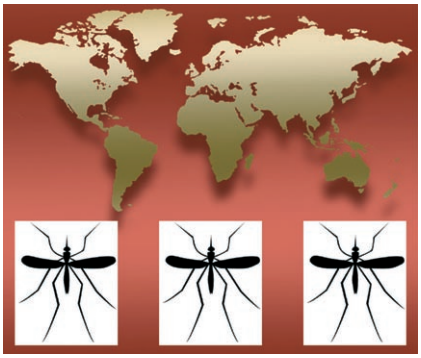
920 – 942

Paclitaxel And Docetaxel Resistance: Molecular Mechanisms and Development of New Generation Taxanes

*M. Schlitzer**

944 – 986

Malaria Chemotherapeutics Part I: History of Antimalarial Drug Development, Currently Used Therapeutics, and Drugs in Clinical Development



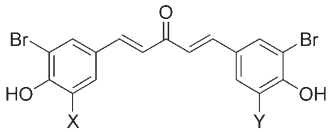
Malaria is the most important tropical infectious disease, yet the arsenal to combat this ancient plague is rather limited. This review briefly describes the history of antimalarial drug development and focuses on therapeutics in current use, their mechanisms of action, resistance against them, as well as drugs in clinical development.

COMMUNICATIONS

A. Mai, S. Valente, D. Cheng, A. Perrone, R. Ragno, S. Simeoni, G. Sbardella, G. Brosch, A. Nebbioso, M. Conte, L. Altucci,* M. T. Bedford**

987 – 991

Synthesis and Biological Validation of Novel Synthetic Histone/Protein Methyltransferase Inhibitors



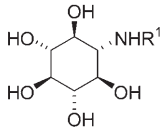
X = Y = H, Br

Coding control: Protein arginine methyltransferases (PRMTs) and histone lysine methyltransferases (HKMTs) are epigenetic enzymes involved in regulation of gene expression and cellular processes. A new series of histone/protein methyltransferase inhibitors based on the 1,5-diphenyl-1,4-pentadien-3-one scaffold is reported. The described compounds showed various degrees of selectivity against the tested PRMTs (PRMT1 and CARM1) and HKMT (SET7).

*M. Egido-Gabás, D. Canals, J. Casas, A. Llebaria, A. Delgado**

992 – 994

Aminocyclitols as Pharmacological Chaperones for Glucocerebrosidase, a Defective Enzyme in Gaucher Disease



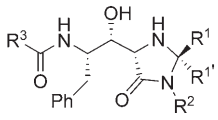
R^1: alkyl or arylalkyl

New therapeutic strategies against sphingolipidoses: a series of aminocyclitols described herein represent new structural types of compounds with promising chaperone-like properties on GlcCerase, a defective enzyme associated with Gaucher disease.

J. C. Barrow, K. E. Rittle, P. L. Ngo, H. G. Selnick, S. L. Graham, S. M. Pitzenberger, G. B. McGaughey, D. Colussi, M.-T. Lai, Q. Huang, K. Tugusheva, A. S. Espeseth, A. J. Simon, S. K. Munshi, J. P. Vacca*

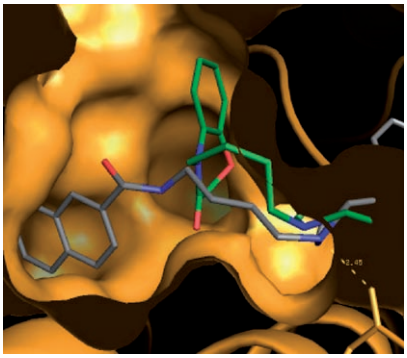
995 – 999

Design and Synthesis of 2,3,5-Substituted Imidazolidin-4-one Inhibitors of BACE-1



Structure-based drug design was used to incorporate the traditional hydroxyethyl amine aspartyl protease inhibitor motif into 2,3,5-substituted imidazolidin-4-one structures with good BACE-1 enzyme inhibitory potency. These compounds represent a promising drug target for Alzheimer's disease-modifying therapy and are therefore of interest to the medicinal chemistry community.

GPCR-focused compound libraries were designed by strategic iterative virtual screening. The most potent ligands yielded K_i values of 65 nM at the dopamine D_3 receptor subtype. Two potential binding modes were observed for receptor antagonists in a homology-based model of the dopamine D_3 receptor. Results demonstrate opportunities for a combination of different virtual screening methods in early stages of GPCR drug discovery for new lead finding.

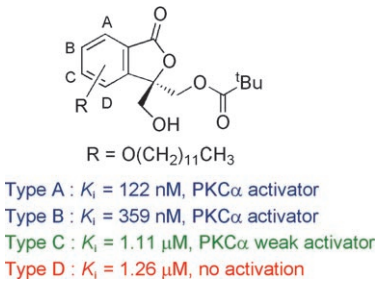


*A. Böcker, B. C. Sasse , M. Nietert, H. Stark, G. Schneider**

1000 – 1005

GPCR Targeted Library Design: Novel Dopamine D_3 Receptor Ligands

Substituent direction is important: Type A–D isobenzofuranone derivatives were synthesized with differently directed hydrophobic alkyl side chains. These ligands bind in a similar conformation to protein kinase Cα but have contrasting activation abilities, possibly owing to different interaction of the side chain with the membrane lipid.

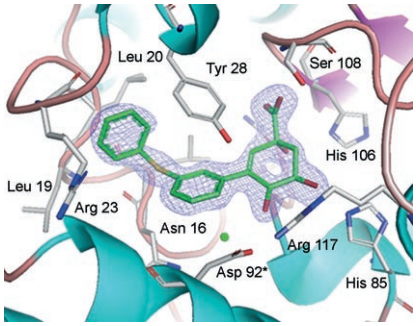


*G. Hirai, T. Shimizu, T. Watanabe, Y. Ogoshi, M. Ohkubo, M. Sodeoka**

1006 – 1009

Importance of Interaction between C1 Domain and Lipids in Protein Kinase Cα Activation: Hydrophobic Side Chain Direction in Isobenzofuranone Ligands Controls Enzyme Activation Level

Filling the pocket: Biaryl inhibitors of type II dehydroquinase are described, designed to bind to both the active site and a subsidiary pocket. Compounds exhibited nanomolar inhibition of the enzyme, which is rationalised by molecular docking and protein crystallographic studies.



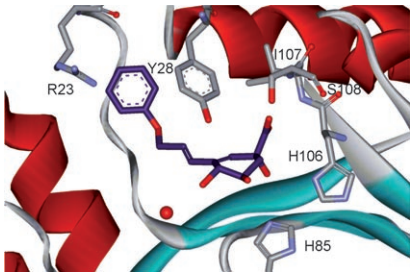
*R. J. Payne, A. Riboldi-Tunnicliffe, O. Kerbarh, A. D. Abell, A. J. Lapthorn, C. Abell**

1010 – 1013

Design, Synthesis, and Structural Studies on Potent Biaryl Inhibitors of Type II Dehydroquinases

FULL PAPERS

Closing the lid: A range of potent type II dehydroquinase inhibitors are described. All incorporate an anhydroquinate core, designed to mimic the reaction intermediate. Linkers of various length and rigidity were attached at C3 to place a phenyl substituent into an adjacent binding pocket where it can interact with residues on a mobile loop which closes the active site.



*R. J. Payne, F. Peyrot, O. Kerbarh, A. D. Abell, C. Abell**

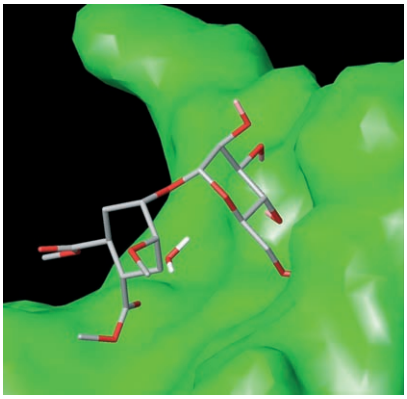
1015 – 1029

Rational Design, Synthesis, and Evaluation of Nanomolar Type II Dehydroquinase Inhibitors

J. J. Reina, S. Sattin, D. Invernizzi, S. Mari, L. Martínez-Prats, G. Tabarani, F. Fieschi, R. Delgado, P. M. Nieto, J. Rojo, A. Bernardi**

1030 – 1036

1,2-Mannobioside Mimic: Synthesis, DC-SIGN Interaction by NMR and Docking, and Antiviral Activity

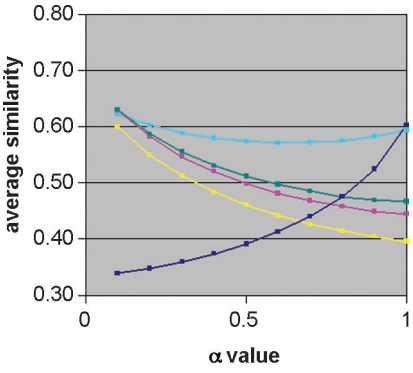


Copy carbos: DC-SIGN specifically recognizes highly glycosylated structures on the surface of several pathogens such as viruses, bacteria, yeasts, and parasites. A new sort of carbohydrate mimic is described representing promising ligands for the DC-SIGN receptor and therefore, potential antiviral drugs. Their binding properties based on NMR and docking studies are described. An infection assay in an Ebola virus model confirms their biological activity.

*Y. Wang, H. Eckert, J. Bajorath**

1037 – 1042

Apparent Asymmetry in Fingerprint Similarity Searching is a Direct Consequence of Differences in Bit Densities and Molecular Size

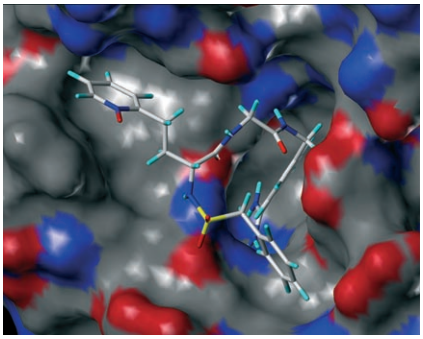


Molecular size effects: Application of the Tversky similarity measure makes it possible to calculate molecular fingerprint similarity in a symmetrical and asymmetrical fashion. The graph shows average pairwise Tversky similarity values of five different compound classes as a function of the alpha parameter of the Tversky coefficient. The different curves that are observed and their slopes are the result of molecular size effects.

*A. Stürzebecher, D. Dönnecke, A. Schweinitz, O. Schuster, P. Steinmetzer, U. Stürzebecher, J. Kotthaus, B. Clement, J. Stürzebecher, T. Steinmetzer**

1043 – 1053

Highly Potent and Selective Substrate Analogue Factor Xa Inhibitors Containing D-Homophenylalanine Analogues as P3 Residue: Part 2

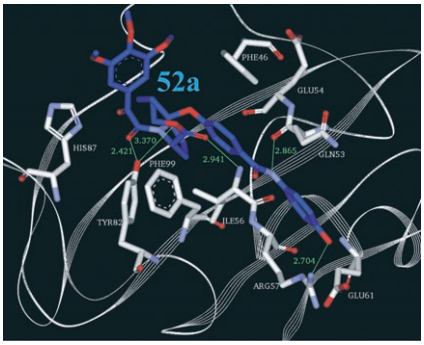


Factor Xa inhibitors: Thromboembolic diseases are a major cause of death and morbidity worldwide. Therefore, anticoagulants are routinely used for the treatment and prevention of thrombotic complications in high risk patients. A series of highly potent substrate-analogue factor Xa inhibitors containing D-homophenylalanine analogues has been identified and shown to be highly potent factor Xa inhibitors with excellent anticoagulant activity.

C. H. Röhrig, C. Loch, J.-Y. Guan, G. Siegal, M. Overhand**

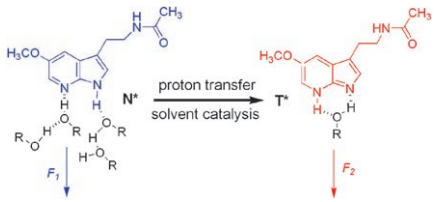
1054 – 1070

Fragment-Based Synthesis and SAR of Modified FKBP Ligands: Influence of Different Linking on Binding Affinity



A flexible fragment-linking approach towards modified FKBP ligands is described. The effects of six different linkers of similar length were determined by using a fluorescence-based assay, and molecular details were obtained with docking studies (an example of which is shown). Novel high-affinity binding ligands were obtained.

7-azamelatonin is an analogue of melatonin and therefore a putative pharmacological agent for the treatment of diverse disorders including circadian rhythm disturbances, migraine headaches, and seasonal depression. Efficient synthetic routes toward 7-azamelatonin are reported. 7-azamelatonin reveals unique excited-state proton transfer properties in water, which may find biochemical applications in the future.

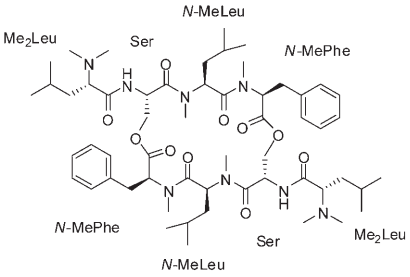


*P.-W. Wu, Y.-M. Cheng, W.-T. Hsieh, Y.-H. Wang, C.-Y. Wei, P.-T. Chou**

1071 – 1075

7-Azamelatonin: Efficient Synthetic Routes, Excited-State Double Proton Transfer Properties and Biomedical Implications

Sea solutions: The structurally complex, water-soluble natural products used by marine organisms for functions as diverse as defense and prey capture are extremely potent, and drugs derived from marine organisms have recently inspired a new era in human therapy, offering vast potential for the treatment of myriad diseases for which new, alternative therapies are desperately needed such as cancer.



L. J. Cruz, A. Francesch, C. Cuevas, F. Albericio**

1076 – 1084

Synthesis and Structure–Activity Relationship of Cytotoxic Marine Cyclodepsipeptide IB-01212 Analogues

Supporting information on the WWW (see article for access details).

* Author to whom correspondence should be addressed.

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