



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc



Bioorganic & Medicinal Chemistry Vol. 16, No. 19, 2008

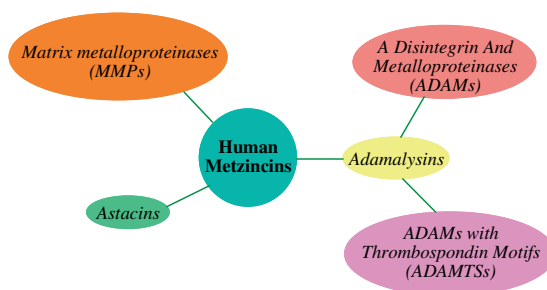
Contents

REVIEW

Specific targeting of metzincin family members with small-molecule inhibitors: Progress toward a multifarious challenge

pp 8781–8794

Dimitris Georgiadis*, Athanasios Yiotakis

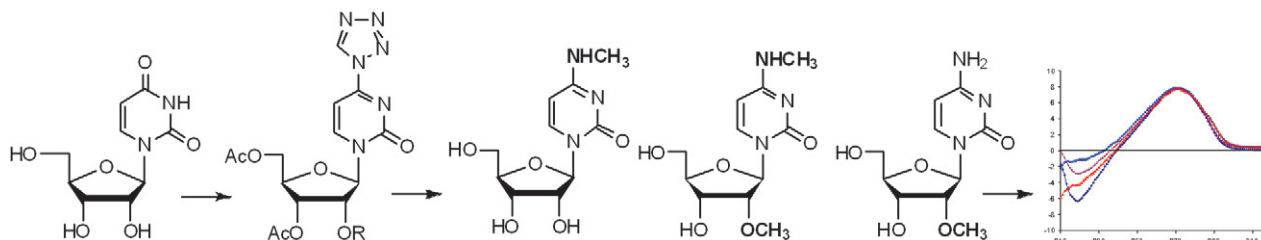


ARTICLES

Synthesis and solution conformation studies of the modified nucleoside *N*⁴,2'-*O*-dimethylcytidine (*m*⁴Cm) and its analogues

pp 8795–8800

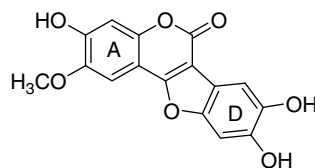
Santosh K. Mahto, Christine S. Chow*



Insights into the mechanism of Na⁺,K⁺-ATPase inhibition by 2-methoxy-3,8,9-trihydroxy coumestan

pp 8801–8805

Elisa S. C. Pôças, Natália A. Touza, Paulo H. C. Pimenta, Fernanda B. Leitão, Chaquip D. Neto, Alcides J. M. da Silva, Paulo R. R. Costa*, François Noël*



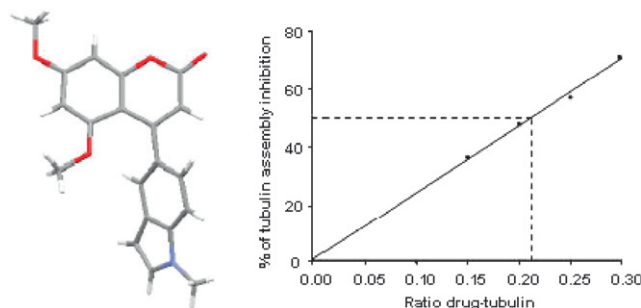
PCALC 36

The molecular mechanism involved in Na⁺,K⁺-ATPase inhibition by 2-methoxy-3,8,9-trihydroxy coumestan (PCALC36) was investigated. The results suggest that this compound irreversibly oxidizes important sulfhydryl groups of the enzyme, explaining its poor selectivity toward other P-type ATPases.

Synthesis and biological evaluation of polymethoxylated 4-heteroarylcoumarins as tubulin assembly inhibitor

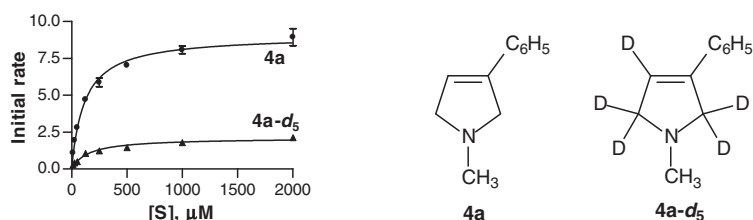
pp 8806–8812

Olga G. Ganina, Etienne Daras, Véronique Bourgarel-Rey, Vincent Peyrot, Alexey N. Andresyuk, Jean-Pierre Finet, Alexey Yu. Fedorov, Irina P. Beletskaya*, Sébastien Combes*

**Deuterium isotope effects for the oxidation of 1-methyl-3-phenyl-3-pyrrolinyl analogues by monoamine oxidase B**

pp 8813–8817

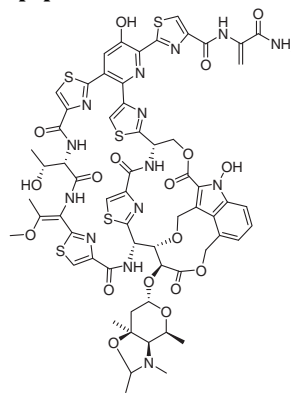
Anél Pretorius, Modupe O. Ogunrombi, Gisella Terre'Blanche, Neal Castagnoli Jr., Jacobus J. Bergh, Jacobus P. Petzer*

**Isolation, structure, and antibacterial activity of thiazomycin A, a potent thiazolyl peptide antibiotic from *Amycolatopsis fastidiosa***

pp 8818–8823

Chaowei Zhang, Deborah L. Zink, Misti Ushio, Bruce Burgess, Russell Onishi, Prakash Masurekar, John F. Barrett, Sheo B. Singh*

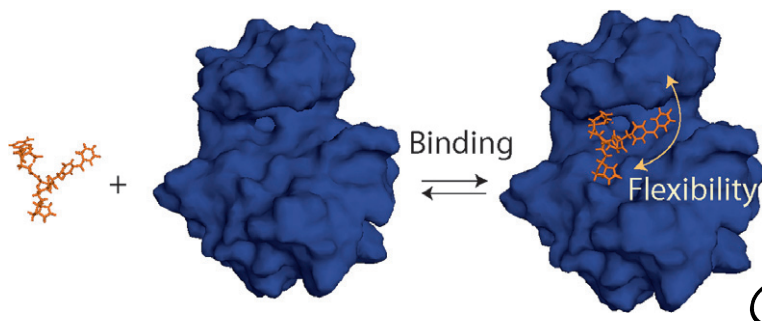
Isolation, structure, and antibacterial activities of thiazomycin A are described.

**Binding is not enough: Flexibility is needed for photocrosslinking of Lck kinase by benzophenone photoligands**

pp 8824–8829

Akira Kawamura*, Sagit Hindi, Doina M. Mihai, Laurence James, Olga Aminova

Target-binding is necessary for photoaffinity-labeling, but it does not guarantee successful photocrosslinking. In fact, it is not binding-affinity but conformational flexibility that determines labeling efficiency of our Lck photoprobes.

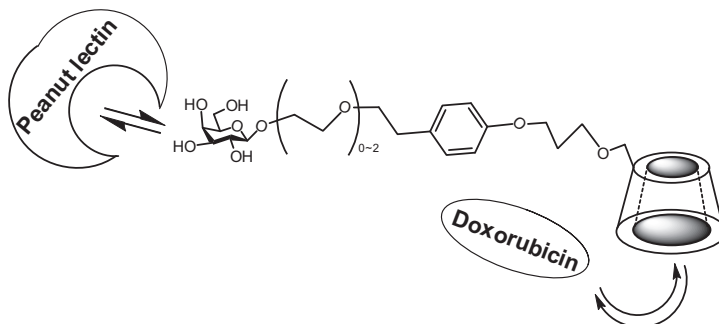


Design, synthesis and evaluation of D-galactose-β-cyclodextrin conjugates as drug-carrying molecules

pp 8830–8840

Yoshiki Oda, Hironari Yanagisawa, Machiko Maruyama, Kenjiro Hattori, Takashi Yamanoi*

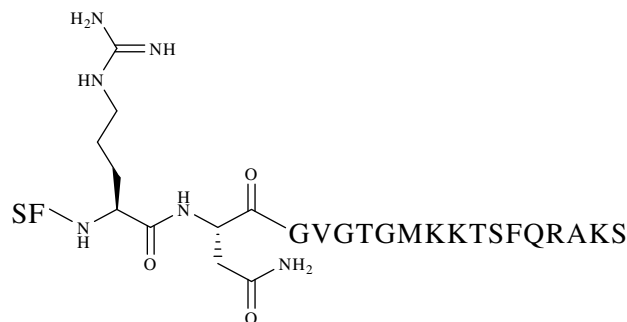
Several kinds of D-galactose-β-cyclodextrin conjugates were designed and synthesized as drug-carrying molecules. These conjugates had remarkably high inclusion associations of $10^5 \sim 10^7 \text{ M}^{-1}$ levels for the immobilized doxorubicin.

**Structure–activity study at positions 3 and 4 of human neuropeptide S**

pp 8841–8845

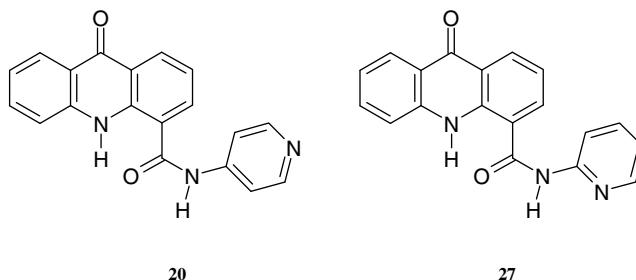
Valeria Camarda, Claudio Trapella, Girolamo Calo', Remo Guerrini*, Anna Rizzi, Chiara Ruzza, Stella Fiorini, Erika Marzola, Rainer K. Reinscheid, Domenico Regoli, Severo Salvadori

Thirty-eight novel hNPS analogues were synthesized and evaluated biologically. Basicity in position 3 is not crucial while the presence of Asn in position 4 is highly important for bioactivity.

**New acridone-4-carboxylic acid derivatives as potential inhibitors of Hepatitis C virus infection**

pp 8846–8852

Anna Stankiewicz-Drogon, Larisa G. Palchykovska*, Valentina G. Kostina, Inna V. Alexeeva, Anatoly D. Shved, Anna M. Boguszevska-Chachulska*



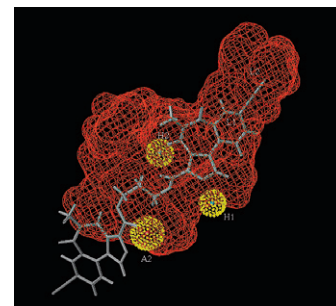
A series of N-substituted acridone-4-carboxamides have been synthesized and their anti-HCV and anti-T7 polymerase activity tested. Two compounds were efficient inhibitors of HCV RNA replication in a human hepatoma cell line.

A study of the structure–activity relationship of GABA_A–benzodiazepine receptor bivalent ligands by conformational analysis with low temperature NMR and X-ray analysis

pp 8853–8862

Dongmei Han, F. Holger Försterling, Xiaoyan Li, Jeffrey R. Deschamps, Damon Parrish, Hui Cao, Sundari Rallapalli, Terry Clayton, Yun Teng, Samarpan Majumder, Subramaniam Sankar, Bryan L. Roth, Werner Sieghart, Roman Furtmüller, James K. Rowlett, Michael R. Weed, James M. Cook*

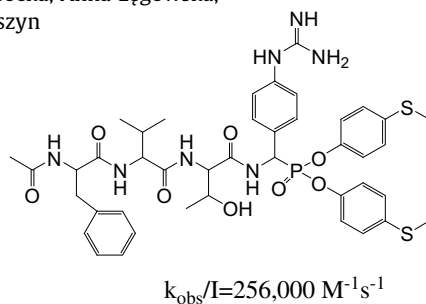
Linear conformation is important for subtype selective benzodiazepine dimers to access the Bz binding site and exhibit potent in vitro affinity.



New potent cathepsin G phosphonate inhibitors

pp 8863–8867

Marcin Sieńczyk, Adam Lesner*, Magdalena Wysocka, Anna Łęgowska,
Ewa Pietrusewicz, Krzysztof Rolka, Józef Oleksyszyn

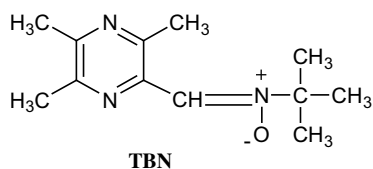


Structure–activity relationship (SAR) studies of phosphonate cathepsin G inhibitors.

Antioxidative and thrombolytic TMP nitron for treatment of ischemic stroke

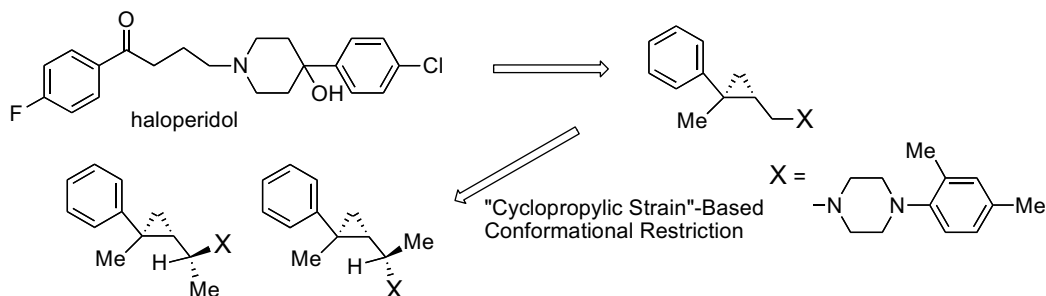
pp 8868–8874

Yewei Sun, Jie Jiang*, Zaijun Zhang, Pei Yu, Linda Wang, Changlin Xu, Wei Liu, Yuqiang Wang*

**Synthesis of 1-arylpiperazyl-2-phenylcyclopropanes designed as antidopaminergic agents: Cyclopropane-based conformationally restricted analogs of haloperidol**

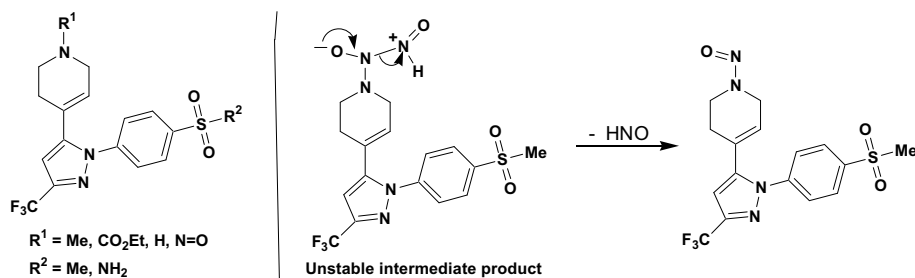
pp 8875–8881

Kazuya Yamaguchi, Yuji Kazuta, Kazufumi Hirano, Shizuo Yamada, Akira Matsuda, Satoshi Shuto*

**Synthesis of new 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2H-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines: A search for novel nitric oxide donor anti-inflammatory agents**

pp 8882–8888

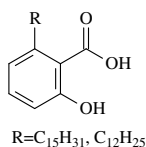
Morshed Alam Chowdhury, Khaled R. A. Abdellatif, Ying Dong, Edward E. Knaus*



Anacardic acid derivatives as inhibitors of glyceraldehyde-3-phosphate dehydrogenase from *Trypanosoma cruzi*

pp 8889–8895

Junia M. Pereira, Richele P. Severino, Paulo C. Vieira, João B. Fernandes, M. Fátima G. F. da Silva, Aderson Zottis, Adriano D. Andricopulo*, Glaucius Oliva, Arlene G. Corrêa *

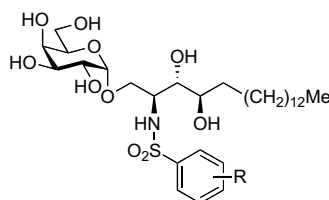


In this work, we describe the inhibitory effects of a small library of natural and synthetic anacardic acid derivatives against the enzyme glyceraldehyde-3-phosphate dehydrogenase from *Trypanosoma cruzi*. The most potent inhibitors, 6-*n*-pentadecyl- (1) and 6-*n*-dodecylsalicylic acids (10e), have IC_{50} values of 28 and 55 μ M, respectively, and mechanistic studies showed noncompetitive inhibition with respect to both substrate and cofactor.

RCAI-17, 22, 24–26, 29, 31, 34–36, 38–40, and 88, the analogs of KRN7000 with a sulfonamide linkage: Their synthesis and bioactivity for mouse natural killer T cells to produce Th2-biased cytokines

pp 8896–8906

Takuya Tashiro, Naomi Hongo, Ryusuke Nakagawa, Ken-ichiro Seino, Hiroshi Watarai, Yasuyuki Ishii, Masaru Taniguchi, Kenji Mori *

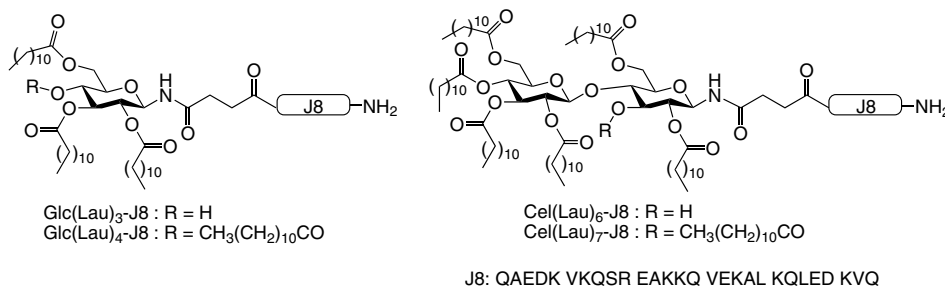


The sulfonamide analogues of KRN7000 induce NKT cells to produce Th2-biased cytokine production.

Synthesis and immunological evaluation of self-adjuvanting glycolipopeptide vaccine candidates

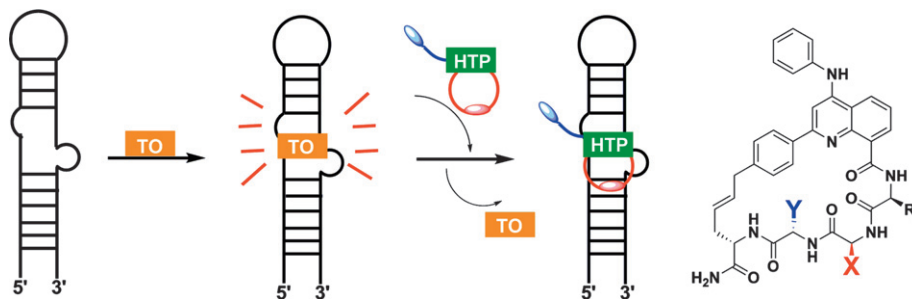
pp 8907–8913

Yoshio Fujita, Abu-Baker M. Abdel-Aal, Norbert Wimmer, Michael R. Batzloff, Michael F. Good, Istvan Toth *

**Screening helix-threading peptides for RNA binding using a thiazole orange displacement assay**

pp 8914–8921

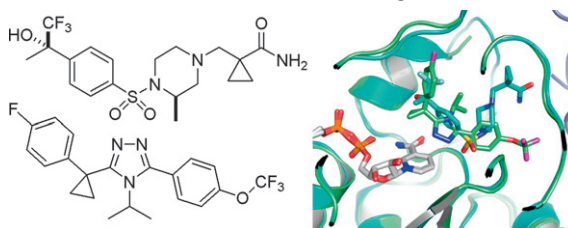
Malathy Krishnamurthy, Nicole T. Schirle, Peter A. Beal *



Distinctive molecular inhibition mechanisms for selective inhibitors of human 11 β -hydroxysteroid dehydrogenase type 1

pp 8922–8931

Hua Tu, Jay P. Powers*, Jinsong Liu, Stefania Ursu, Athena Sudom, Xuelei Yan, Haoda Xu, David Meininger, Michael DeGraffenreid, Xiao He, Juan C. Jaen, Daqing Sun, Marc Labelle, Hiroshi Yamamoto, Bei Shan, Nigel P. C. Walker, Zhulun Wang*

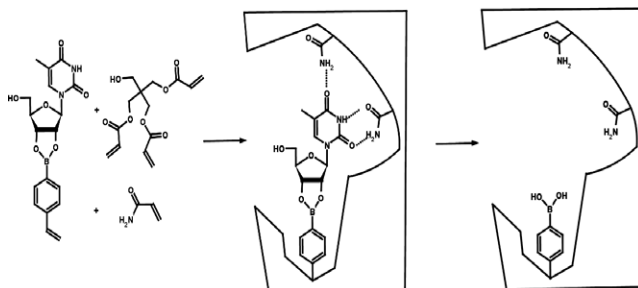


The synthesis, X-ray co-crystal structures and kinetic analysis of two novel and potent small molecule inhibitors of 11 β -HSD1 are reported. Structural and kinetic analyses demonstrate two distinctive molecular inhibition mechanisms for the two classes of inhibitors.

Molecularly imprinted polymer of 5-methyluridine for solid-phase extraction of pyrimidine nucleoside cancer markers in urine

pp 8932–8939

Damien Jégourel, Raphaël Delépée*, Florent Breton, Antoine Rolland, Richard Vidal, Luigi A. Agrofoglio*

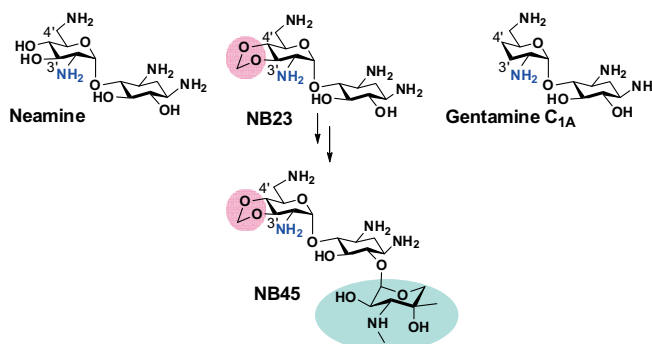


Structure–toxicity relationship of aminoglycosides: Correlation of 2'-amine basicity with acute toxicity in pseudo-disaccharide scaffolds

pp 8940–8951

Lilach Chen, Mariana Hainrichson, Dmitry Bourdetsky, Amram Mor, Sima Yaron, Timor Baasov*

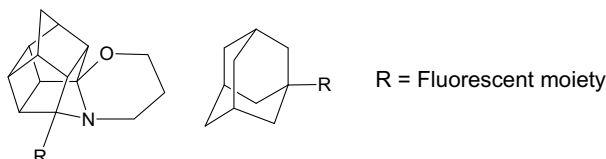
A new pseudo-disaccharide NB23 with a 3',4'-methylidene protection was designed and its properties were evaluated in comparison to other two structurally related pseudo-disaccharides. The basicity of the 2'-amine was found to be well correlated to acute toxicity data in mice: the increase in the basicity is associated with the toxicity increase. Based on these data, a new pseudo-trisaccharide NB45 was constructed. NB45 exhibited significant antibacterial activity while at the same time retained low acute toxicity.



Fluorescent polycyclic ligands for nitric oxide synthase (NOS) inhibition

pp 8952–8958

Jacques Joubert, Sandra van Dyk, Sarel F. Malan*

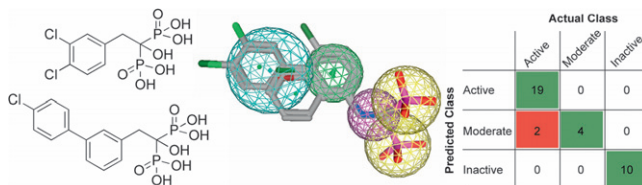


Indazole, isoindole and other fluorescent structures conjugated to polycyclic moieties inhibited NOS in low μ M concentrations and Stokes shifts of 29–80 nm were observed.

Bisphosphonate inhibitors of ATP-mediated HIV-1 reverse transcriptase catalyzed excision of chain-terminating 3'-azido, 3'-deoxythymidine: A QSAR investigation

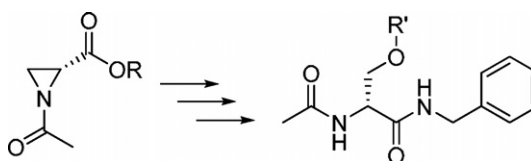
pp 8959–8967

Yongcheng Song, Julian M. W. Chan, Zev Tovian, Aaron Secrest, Eva Nagy, Kilannin Krysiak, Kyle Bergan, Michael A. Parniak, Eric Oldfield*

**Synthesis and anticonvulsant activities of *N*-benzyl (2*R*)-2-acetamido-3-oxysubstituted propionamide derivatives**

pp 8968–8975

Pierre Morieux, James P. Stables, Harold Kohn*

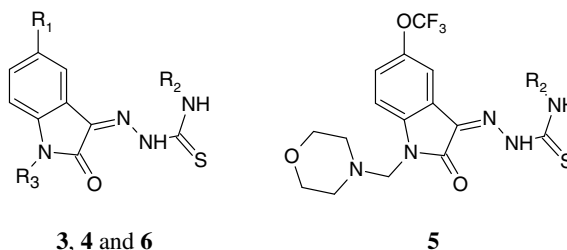


An expedient, stereospecific route to 3-oxysubstituted analogs of the neurological agent lacosamide has been developed.

Synthesis and antituberculosis activity of 5-methyl/trifluoromethoxy-1*H*-indole-2,3-dione 3-thiosemicarbazone derivatives

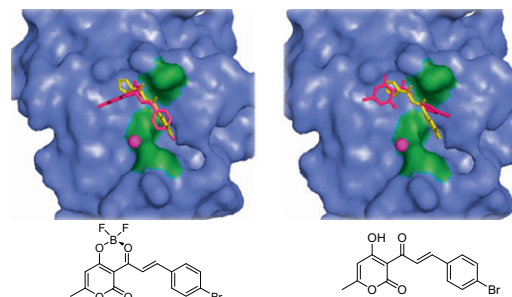
pp 8976–8987

Özlen Güzel, Nilgün Karalı*, Aydın Salman

R₁ = CH₃, OCF₃R₂ = alkyl, cycloalkyl, (non)substituted phenylR₃ = H, CH₃**Discovery of 3-acetyl-4-hydroxy-2-pyranone derivatives and their difluoridoborate complexes as a novel class of HIV-1 integrase Inhibitors**

pp 8988–8998

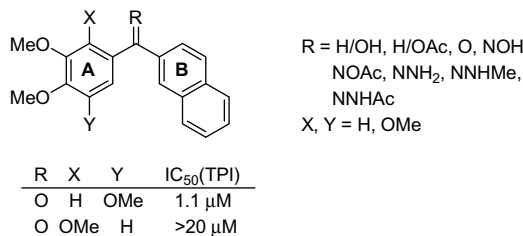
Kavya Ramkumar, Konstantin V. Tambov, Rambabu Gundla, Alexandr V. Manaev, Vladimir Yarovenko, Valery F. Traven, Nouri Neamati*



Naphthylphenstatins as tubulin ligands: Synthesis and biological evaluation

pp 8999–9008

Concepción Álvarez, Raquel Álvarez, Purificación Corchete, Concepción Pérez-Melero, Rafael Peláez*, Manuel Medarde*



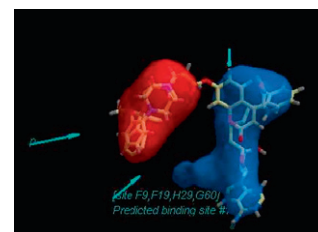
The synthesis and biological evaluation of naphthylphenstatins, modified on the bridge, are described.

Design, synthesis, and docking studies of novel benzopyrone derivatives as H₁-antihistaminic agents

pp 9009–9017

Nahla A. Farag*, Shadia. R. Mohamed, Gamal A. H. Soliman

Two new series of 2H-1-benzopyran-2-one derivatives substituted at C-6 and/or C-7 with propanolamines, and/or piperazine propanol derivatives have been synthesized and assayed for the H₁-histamine antagonist. Twelve of the 20 newly synthesized 4-substituted benzopyrones have shown potent antihistaminic H₁ activity. In addition, molecular modeling and docking of the tested compounds into high affinity histamine binding protein (HBP) and histamine N-methyltransferase (HNMT) active site in complex with its bound inhibitor (diphenhydramine) was performed in order to predict the affinity and orientation of these compounds at the active sites. The ICM score values show good agreement with predicted binding affinities obtained by molecular docking studies as verified by pharmacological screening. The results showed similar orientation of the target compounds at HBP, and HNMT active sites compared with reported histamine H₁ antagonist. Also, it was concluded that in order for the compounds to be active, they must bind with both active sites of HNMT enzyme (two pockets) to inhibit it. Compounds **8c**, **8i**, **11g**, **11i**, and **11k**; observe the maximum activities.

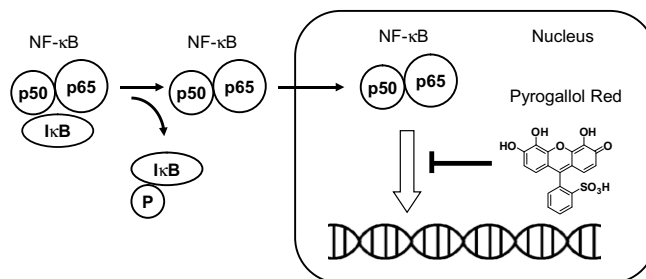


Studies on inhibition mechanism of transcription factor NF-κB and DNA binding by chelator pyrogallol red on the basis of its interaction with metal ions

pp 9018–9022

R. K. Sharma*, C. Chelladurai, A. D. Tiwari, H. K. Rajor, S. Mehta, M. Otsuka

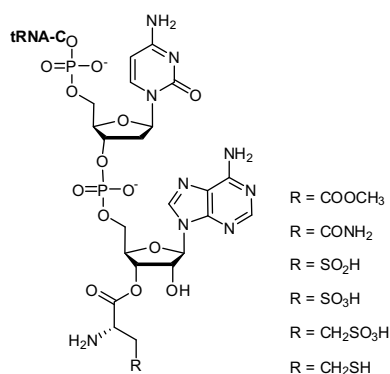
The interaction of pyrogallol red (PR) an inhibitor of NF-κB–DNA binding with zinc was studied by isolating the zinc–PR complex. The complex was characterized using IR, UV–visible, ¹H NMR, and thermal studies. Binding sites of PR were identified by molecular modeling using MM+ and PM3 methods and by generating molecular electrostatic map. These studies have confirmed the role of metal ion chelation in the inhibition of NF-κB–DNA binding.



Synthesis of pdCpAs and transfer RNAs activated with derivatives of aspartic acid and cysteine

pp 9023–9031

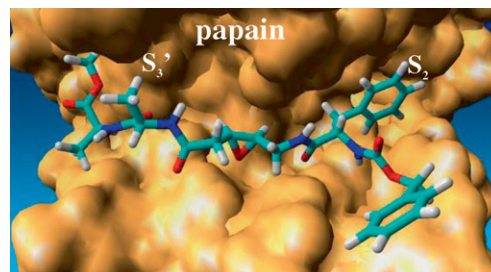
Shengxi Chen, Sidney M. Hecht*



Peptidyl epoxides extended in the P' direction as cysteine protease inhibitors: Effect on affinity and mechanism of inhibition

pp 9032–9039

Nurit Perlman, Maya Hazan, Michael Shokhen, Amnon Albeck*

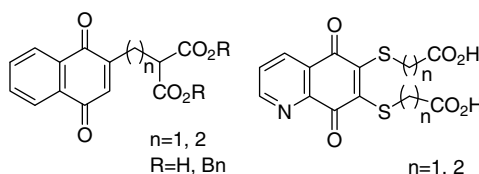


Extension of peptidyl epoxides in the C-terminal direction, to gain S'-P' interactions with a target enzyme, increased affinity to cysteine proteases but changed the mechanism to reversible competitive inhibition.

**Novel naphthoquinone and quinolinedione inhibitors of CDC25 phosphatase activity with antiproliferative properties**

pp 9040–9049

Emmanuelle Braud, Mary-Lorène Goddard, Stéphanie Kolb, Marie-Priscille Brun, Odile Mondésert, Muriel Quaranta, Nohad Gresh, Bernard Ducommun, Christiane Garbay*

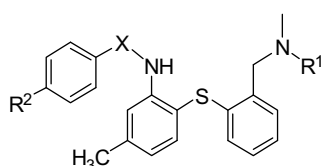


Novel naphthoquinone and quinolinedione derivatives were evaluated for their inhibitory activity toward CDC25 phosphatase activity. These compounds also display cytotoxic activity against HeLa cells.

Docking study, synthesis, and in vitro evaluation of fluoro-MADAM derivatives as SERT ligands for PET imaging

pp 9050–9055

Sylvie Mavel*, Johnny Vercouillie, Lucette Garreau, Tiziana Raguza, Aina Westrheim Ravna, Sylvie Chalon, Denis Guilloteau, Patrick Emond



X = C=O, CH₂; R¹ = H, CH₃; R² = NO₂, F

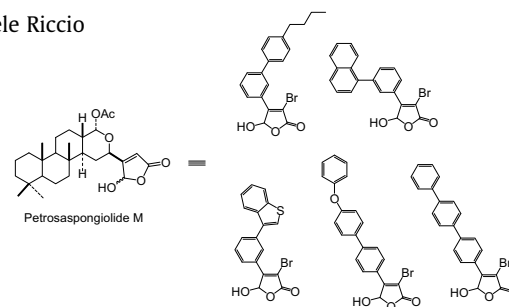
Fluorinated SERT ligands have been synthesized and they displayed good in vitro affinity for the SERT and good selectivity toward the other monoamine transporters as predicted by a docking study.

Development of a second generation of inhibitors of microsomal prostaglandin E synthase 1 expression bearing the γ-hydroxybutenolide scaffold

pp 9056–9064

Maurizio Aquino, Maria D. Guerrero, Ines Bruno*, María C. Terencio, Miguel Paya, Raffaele Riccio

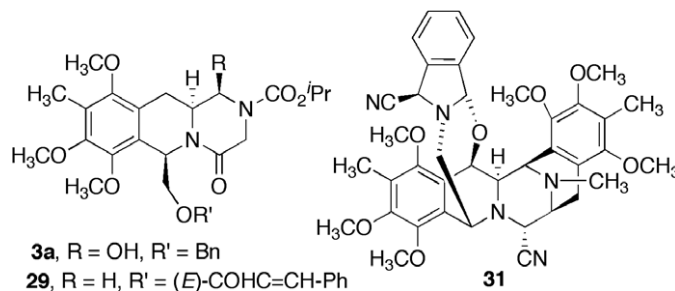
We report the synthesis of a new collection of potential anti-inflammatory agents, designed on the natural compound petrosaspongiolide M. Their pharmacological behavior was evaluated on PLA₂, COX-2, and mPGES-1 enzymes.



Pyrazino[1,2-*b*]isoquinolines: Synthesis and study of their cytostatic and cytotoxic properties

pp 9065–9078

Irene Ortín, Juan Francisco González, Elena de la Cuesta, Cristina Manguan-García, Rosario Perona, Carmen Avendaño *

**OTHER CONTENTS****Bioorganic & Medicinal Chemistry Reviews and Perspectives**

pp 9079–9081

Instructions to contributors

p I

*Corresponding author

i+ Supplementary data available via ScienceDirect

COVER

An insight into biologically relevant chemical space showing the scaffolds of potential natural-product based inhibitors orbiting their target, the protein structure of protein 11-beta steroid dehydrogenase (PDB code 1xu7). Graphic produced using Pymol (<http://www.pymol.org>). [M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, Charting biologically relevant chemical space: A structural classification of natural products (SCONP), *PNAS* **2005**, 102, 17272–17277 and S. Wetzel, H. Waldmann, Cheminformatic analysis of natural products and their chemical space, *Chimia* **2007**, 61(6), 355–360].

Available online at

ScienceDirect
www.sciencedirect.com

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE



ELSEVIER

ISSN 0968-0896