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Bioorganic & Medicinal Chemistry Vol. 17, No. 20, 2009

Contents

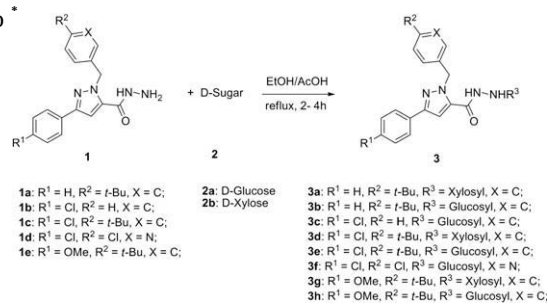
ARTICLES

Synthesis and discovery of pyrazole-5-carbohydrazide N-glycosides as inducer of autophagy in A549 lung cancer cells

pp 7085–7092

Song Lian, Hua Su, Bao-Xiang Zhao^{*}, Wei-Yong Liu, Liang-Wen Zheng, Jun-Ying Miao^{*}

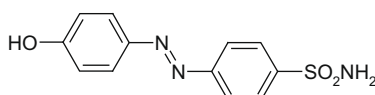
A series of novel 3-aryl-1-arylmethyl-1H-pyrazole-5-carbohydrazide N-β-glycoside derivatives was synthesized and the effects on A549 cell growth were investigated. Compound **3d** possessed the highest growth inhibitory effect and induced autophagy of A549 lung cancer cells.



Carbonic anhydrase inhibitors. Diazenylbenzenesulfonamides are potent and selective inhibitors of the tumor-associated isozymes IX and XII over the cytosolic isoforms I and II

pp 7093–7099

Fabrizio Carta, Alfonso Maresca, Andrea Scozzafava, Daniela Vullo, Claudiu T. Supuran^{*}

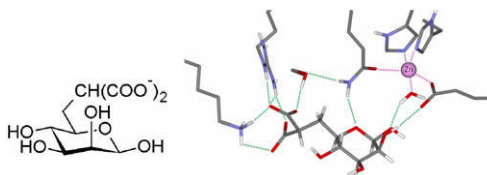


K_i (hCA I) = 393 nM, K_i (hCA II) = 665 nM, K_i (hCA IX) = 6.4 nM, K_i (hCA XII) = 5.0 nM.

Synthesis and evaluation of non-hydrolyzable D-mannose 6-phosphate surrogates reveal 6-deoxy-6-dicarboxymethyl-D-mannose as a new strong inhibitor of phosphomannose isomerases

pp 7100–7107

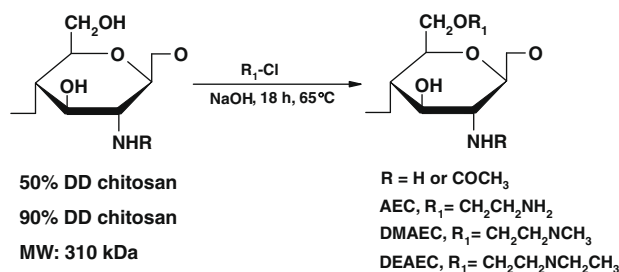
Johanna Foret, Benoit de Courcy, Nohad Gresh, Jean-Philip Piquemal, Laurent Salmon^{*}



Antibacterial activity of aminoderivatized chitosans against methicillin-resistant *Staphylococcus aureus* (MRSA)

pp 7108–7112

Dae-Sung Lee, Seong-Yun Jeong, Young-Mog Kim, Myung-Suk Lee, Chang-Bum Ahn, Jae-Young Je *

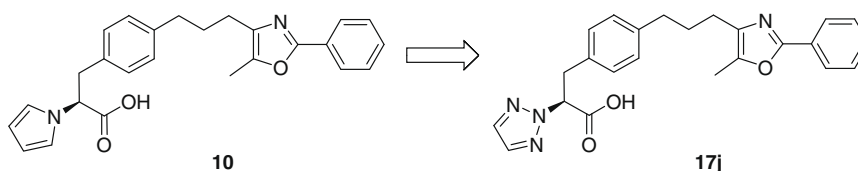


Two kinds of aminoethyl-chitosans (AEC), AEC90 and AEC50, having degrees of deacetylation of 90% and 50%, exhibited the strongest anti-MRSA activities by presenting MICs of 16–64 $\mu\text{g/mL}$ against two standard strains and twelve clinical isolates.

Synthesis and evaluation of novel α -heteroaryl-phenylpropanoic acid derivatives as PPAR α/γ dual agonists

pp 7113–7125

Agustin Casimiro-Garcia *, Christopher F. Bigge, Jo Ann Davis, Teresa Padalino, James Pulaski, Jeffrey F. Ohren, Patrick McConnell, Christopher D. Kane, Lori J. Royer, Kimberly A. Stevens, Bruce Auerbach, Wendy Collard, Christine McGregor, Kun Song



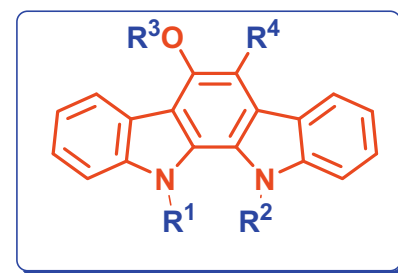
Replacement of the pyrrole group of **10** with a variety of five-membered ring heterocycles led to the identification of **17j** as a potent human PPAR α/γ dual agonist with demonstrated oral bioavailability and excellent activity in animal models of diabetes and dyslipidemia.

**Natural product leads for drug discovery: Isolation, synthesis and biological evaluation of 6-cyano-5-methoxyindolo[2,3-a]carbazole based ligands as antibacterial agents**

pp 7126–7130

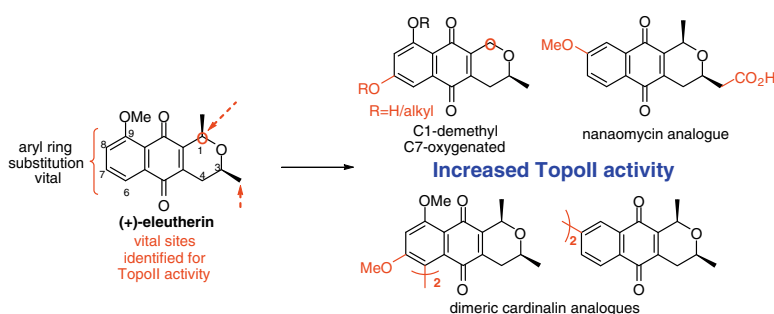
Songpo Guo, Suresh K. Tipparaju, Scott D. Pegan, Baojie Wan, Shunyan Mo, Jimmy Orjala, Andrew D. Mesecar, Scott G. Franzblau, Alan P. Kozikowski *

Indolo[2,3-a]carbazole based inhibitors synthesized starting from indigo displayed moderate inhibitory activities toward *Bacillus anthracis* and *Mycobacterium tuberculosis*.

**Pyranonaphthoquinone derivatives of eleutherin, ventiloquinone L, thysanone and nanaomycin A possessing a diverse topoisomerase II inhibition and cytotoxicity spectrum**

pp 7131–7137

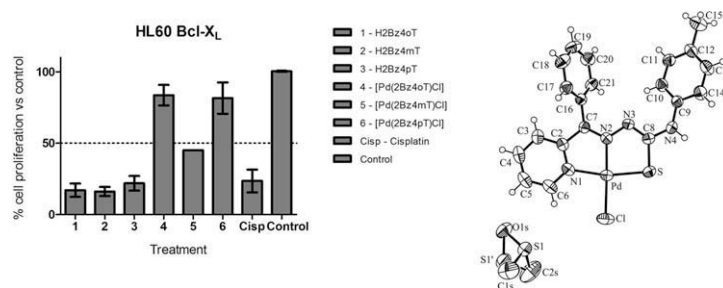
Jonathan Sperry, Isabel Lorenzo-Castrillejo, Margaret A. Brimble *, Felix Machín *



2-Benzoylpyridine-*N*(4)-tolyl thiosemicarbazones and their palladium(II) complexes: Cytotoxicity against leukemia cells

pp 7138–7144

Karina S. O. Ferraz, Lucas Fernandes, Diego Carrilho, Mauro C. X. Pinto, Maria de Fátima Leite, Elaine M. Souza-Fagundes, Nivaldo L. Speziali, Isolda C. Mendes, Heloisa Beraldo *

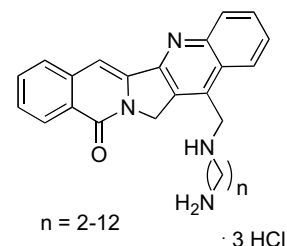
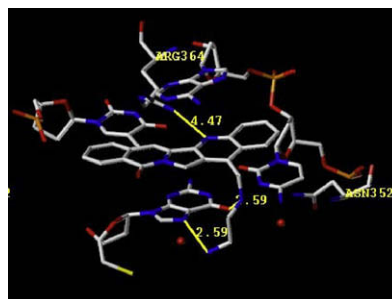


Synthesis and biological evaluation of 14-(aminoalkyl-aminomethyl)aromathecins as topoisomerase I inhibitors: Investigating the hypothesis of shared structure–activity relationships

pp 7145–7155

Maris A. Cinelli, Brenda Cordero, Thomas S. Dexheimer, Yves Pommier, Mark Cushman *

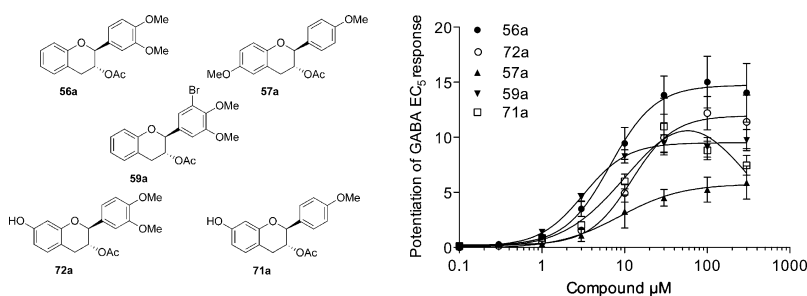
A series of novel 14-(aminoalkyl-aminomethyl)aromathecins were synthesized and evaluated against top1 and human cancer cell lines. These compounds display modest cytotoxic activity and behave similar to indenisoquinolines, indicating SAR overlap.



Synthesis and biological evaluation of flavan-3-ol derivatives as positive modulators of GABA_A receptors

pp 7156–7173

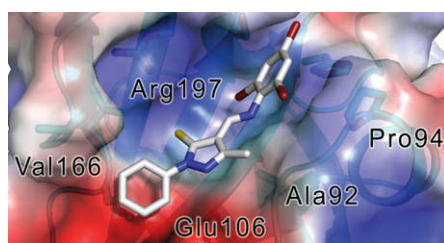
Kenneth N. Mewett, Sebastian P. Fernandez, Anmol K. Pasricha, Alice Pong, Steven O. Devenish, David E. Hibbs, Mary Chebib, Graham A. R. Johnston, Jane R. Hanrahan *



Discovery and structure–activity relationship analysis of *Staphylococcus aureus* sortase A inhibitors

pp 7174–7185

Nuttee Suree, Sung Wook Yi, William Thieu, Melanie Marohn, Robert Damoiseaux, Albert Chan, Michael E. Jung *, Robert T. Clubb *



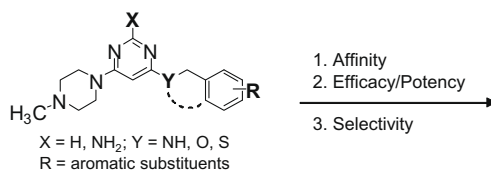
Model of the *Staphylococcus aureus* sortase enzyme bound to a small molecule.



2,4-Diaminopyrimidines as histamine H₄ receptor ligands—Scaffold optimization and pharmacological characterization

pp 7186–7196

Kerstin Sander, Tim Kottke, Yusuf Tanrikulu, Ewgenij Proschak, Lilia Weizel, Erich H. Schneider, Roland Seifert, Gisbert Schneider, Holger Stark *



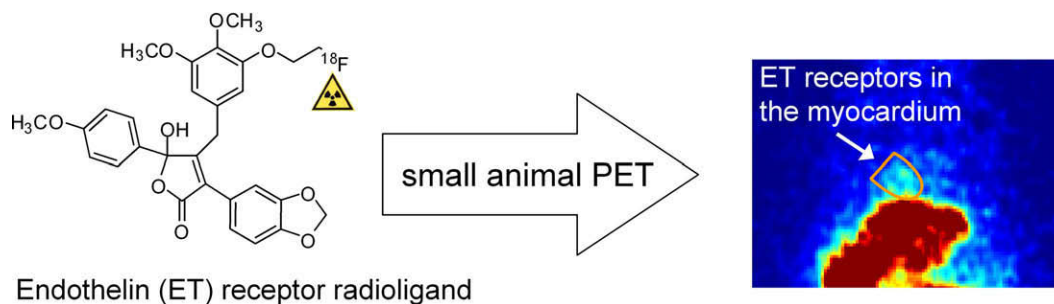
A combination of modern and classical approaches in bioinformatics and medicinal chemistry was applied to develop and investigate a 2,4-diaminopyrimidine scaffold as a pharmacophore of histamine H₄ receptor ligands. Ligands were characterized regarding their affinity, efficacy and selectivity on the human histamine H₄ receptor.



PET-compatible endothelin receptor radioligands: Synthesis and first in vitro and in vivo studies

pp 7197–7208

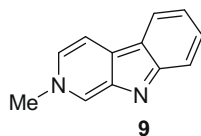
Carsten Höltke *, Marilyn P. Law, Stefan Wagner, Klaus Kopka, Andreas Faust, Hans-Jörg Breyholz, Otmar Schober, Christoph Bremer, Burkhard Riemann, Michael Schäfers



Structure–activity relationship of antiparasitic and cytotoxic indoloquinoline alkaloids, and their tricyclic and bicyclic analogues

pp 7209–7217

Gitte Van Baelen, Steven Hostyn, Liene Dhooghe, Pál Tapolcsányi, Péter Mátyus, Guy Lemièr, Roger Dommissie, Marcel Kaiser, Reto Brun, Paul Cos, Louis Maes, György Hajós, Zsuzsanna Riedl, Ildikó Nagy, Bert U. W. Maes, Luc Pieters *



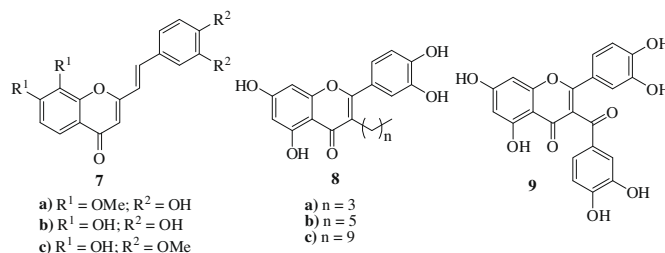
In a series of carbolines, azaindoles and pyrrolo(iso)quinolines, 2-methyl-β-carboline (9) showed the highest in vitro activity (IC₅₀ = 0.45 μM) against *Plasmodium falciparum* K1, without apparent cytotoxicity against L6 cells (SI > 1000).



Synthesis and antioxidant properties of new chromone derivatives

pp 7218–7226

Ana Gomes, Ondrej Neuwirth, Marisa Freitas, Diana Couto, Daniela Ribeiro, Andrea G. P. R. Figueiredo, Artur M. S. Silva, Raquel S. G. R. Seixas, Diana C. G. A. Pinto, Augusto C. Tomé, José A. S. Cavaleiro, Eduarda Fernandes *, José L. F. C. Lima



Several 2-styrylchromones and 3-substituted flavones were tested for their scavenging activity against ROS and RNS, their reducing activity and metal chelating capacity. Structure–activity relationship analysis was performed.

pp 7227–7238

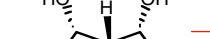
Chemical structures of Dehydroaltenusin (1) and Desmethyldehydroaltenusin (2) are shown. Dehydroaltenusin (1) is a coumarin derivative with a methoxy group (OCH₃) and a hydroxyl group (OH) on the benzene ring, and a carboxylic acid group (COOH) and a hydroxyl group (OH) on the pyrone ring. Desmethyldehydroaltenusin (2) is a coumarin derivative with two hydroxyl groups (OH) on the benzene ring, and a carboxylic acid group (COOH) and a hydroxyl group (OH) on the pyrone ring.

pp 7239–7247

Chemical reaction scheme showing the conversion of Clioquinol to compound 11.

Clioquinol (8-chloro-6-iodo-2-naphthol) is converted to **11** (2-hydroxy-6-(4-(4-methylphenyl)sulfonylpiperidin-1-ylmethyl)-8-nitroquinoline).

pp 7248–7253



Inhibition GlcNAcase

No-inhibition Chitinase
β-Glucosidase
α-Glucosidase



pp 7254–7264

The reaction scheme shows the conversion of a substituted sugar to a nucleoside derivative. On the left, a sugar molecule is shown in its cyclic form, with a substituent labeled 'AcHN' at the C2 position. An arrow points to the right, where the product is shown. The product is a nucleoside derivative, specifically a 2'-deoxyribose sugar linked to a pyrimidine base. The pyrimidine base is substituted with a cyano group (NC) at the 5-position and a 4-oxo group (O=) at the 2-position. The sugar is shown in its cyclic form, with the pyrimidine base attached to the C1 position.

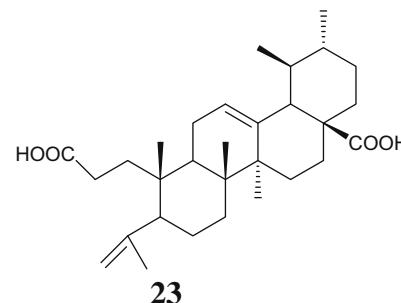


Ursolic acid derivatives induce cell cycle arrest and apoptosis in NTUB1 cells associated with reactive oxygen species

pp 7265–7274

Huang-Yao Tu, A-Mei Huang, Bai-Luh Wei, Kim-Hong Gan, Tzyh-Chyuan Hour, Shyh-Chyun Yang^{*}, Yeong-Shiau Pu, Chun-Nan Lin^{*}

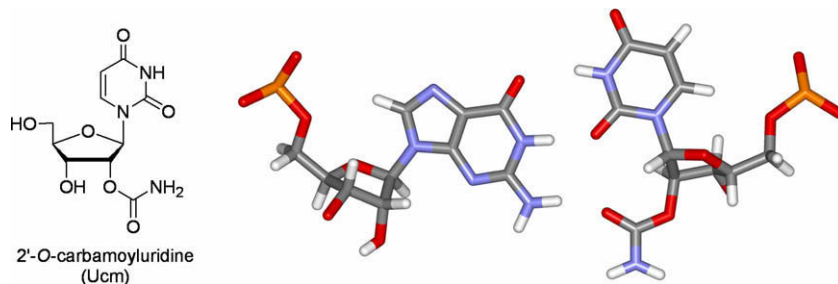
Twenty-three ursolic acid (**1**) derivatives **2–24** including nine new **1** derivatives **5, 7–11, 20–22** were synthesized and evaluated for cytotoxicities against NTUB1 cells (human bladder cancer cell line).



Synthesis and hybridization of 2'-O-methyl-RNAs incorporating 2'-O-carbamoyluridine and unique participation of the carbamoyl group in U–G base pair

pp 7275–7280

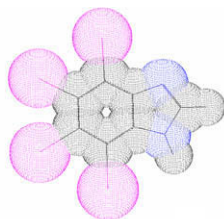
Kohji Seio^{*}, Ryuya Tawarada, Takeshi Sasami, Masashi Serizawa, Misako Ise, Akihiro Ohkubo, Mitsuo Sekine^{*}



Tetraiodobenzimidazoles are potent inhibitors of protein kinase CK2

pp 7281–7289

Alessandra Gianoncelli, Giorgio Cozza, Andrzej Orzeszko, Flavio Meggio, Zygmunt Kazimierczuk^{*}, Lorenzo A. Pinna^{*}



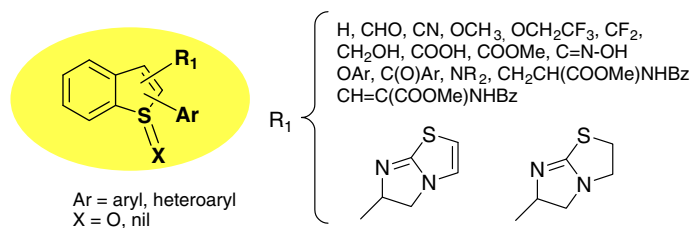
4,5,6,7-tetraiodo-1H-benzimidazole (TIBI)

$K_i = 0.023 \mu\text{M}$

Synthesis and evaluation of benzo[b]thiophene derivatives as inhibitors of alkaline phosphatases

pp 7290–7300

Lina Li, Lei Chang, Stéphane Pellet-Rostaing^{*}, François Liger, Marc Lemaire^{*}, René Buchet^{*}, Yuqing Wu

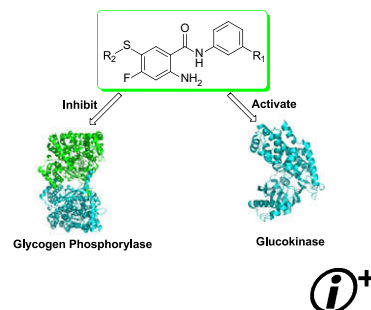


Benzamide derivatives as dual-action hypoglycemic agents that inhibit glycogen phosphorylase and activate glucokinase

pp 7301–7312

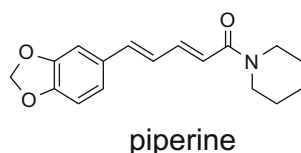
Lei Zhang, Honglin Li, Qingzhang Zhu, Jun Liu, Ling Chen, Ying Leng^{*}, Hualiang Jiang, Hong Liu^{*}

A series of benzamide derivatives which can simultaneously inhibit glycogen phosphorylase (GP) and activate glucokinase (GK) were prepared and evaluated. These dual actions towards GK and GP represent a 'double whammy' on the hyperglycemia associated with Type 2 diabetes (T2D) and provide a new methodology to design anti-diabetic agents.



Hepatoprotective amide constituents from the fruit of *Piper chaba*: Structural requirements, mode of action, and new amides

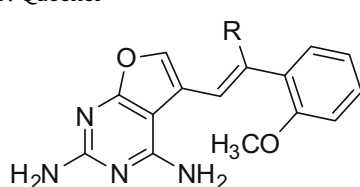
pp 7313–7323

Hisashi Matsuda, Kiyofumi Ninomiya, Toshio Morikawa, Daisuke Yasuda, Itadaki Yamaguchi, Masayuki Yoshikawa^{*}

The 80% aqueous acetone extract from the fruit of *Piper chaba* (Piperaceae) was found to have hepatoprotective effects on D-GalN/LPS-induced liver injury in mice. From the ethyl acetate-soluble fraction, three new amides, piperchabamides E, G, and H, 33 amides, and four aromatic constituents were isolated. Among the isolates, several amide constituents inhibited D-GalN/TNF- α -induced death of hepatocytes, and the following structural requirements were suggested: (i) the amide moiety is essential for strong activity; and (ii) the 1,9-decadiene structure between the benzene ring and the amide moiety tended to enhance the activity. Moreover, a principal constituent, piperine, exhibited strong in vivo hepatoprotective effects at doses of 5 and 10 mg/kg, po and its mode of action was suggested to depend on the reduced sensitivity of hepatocytes to TNF- α .

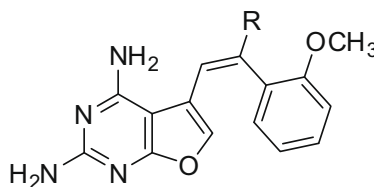
Design, synthesis, and X-ray crystal structures of 2,4-diaminofuro[2,3-d]pyrimidines as multireceptor tyrosine kinase and dihydrofolate reductase inhibitors

pp 7324–7336

Aleem Gangjee^{*}, Wei Li, Lu Lin, Yibin Zeng, Michael Ihnat, Linda A. Warnke, Dixy W. Green, Vivian Cody, Jim Pace, Sherry F. Queener

E-isomer

2-Amino-4-oxo DHFR Binding Mode

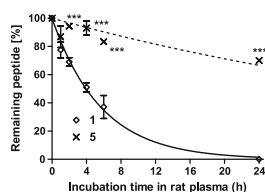


Z-isomer

2,4-Diaminopyrimidine DHFR Binding Mode

The biological activity and metabolic stability of peptidic bifunctional compounds that are opioid receptor agonists and neurokinin-1 receptor antagonists with a cystine moiety

pp 7337–7343

Takashi Yamamoto, Padma Nair, Shou-wu Ma, Peg Davis, Henry I. Yamamura, Todd W. Vanderah, Frank Porreca, Josephine Lai, Victor J. Hruby^{*}

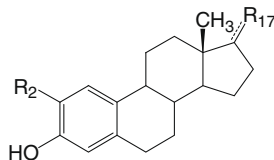
- 1: Tyr-DAla-Gly-Phe-Met-Pro-Leu-Trp-NH-[3',5'-(CF₃)₂Bzl]
- 2: Tyr-c[DCys-Gly-Phe-Cys]-Pro-Leu-Trp-NH-[3',5'-(CF₃)₂Bzl]
- 3: Tyr-c[DCys-Gly-Phe-DCys]-Pro-Leu-Trp-NH-[3',5'-(CF₃)₂Bzl]
- 4: Tyr-c[DCys-Gly-Phe-Nle-Pro-Cys]-Trp-NH-[3',5'-(CF₃)₂Bzl]
- 5: Tyr-c[DCys-Gly-Phe-Nle-Pro-DCys]-Trp-NH-[3',5'-(CF₃)₂Bzl]

The biological activities and metabolic stabilities of peptidic bifunctional compounds with a Cys-S-S-Cys disulfide bond, possessing opioid agonist and NK1 antagonist activities, were reported.

Synthesis of 2- and 17-substituted estrone analogs and their antiproliferative structure–activity relationships compared to 2-methoxyestradiol

pp 7344–7352

Jamshed H. Shah, Gregory E. Agoston, Lita Suwandi, Kimberly Hunsucker, Victor Pribluda, Xiaoguo H. Zhan, Glenn M. Swartz, Theresa M. LaVallee, Anthony M. Treston *

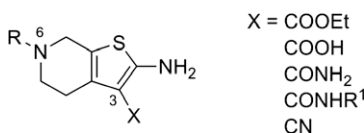


17-Modified and 2,17-modified 2-methoxyestradiol analogs were synthesized and evaluated for antitumor, antiangiogenic, and estrogenic activity in vitro. Selected analogs were evaluated against metabolism in ex vivo and in vivo models.

3- and 6-Substituted 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridines as A₁ adenosine receptor allosteric modulators and antagonists

pp 7353–7361

Luigi Aurelio, Celine Valant, Heidi Figler, Bernard L. Flynn, Joel Linden, Patrick M. Sexton, Arthur Christopoulos *, Peter J. Scammells *

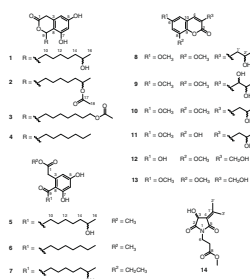


A number of 3- and 6-substituted 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridines were prepared and evaluated as potential allosteric modulators at the A₁ adenosine receptor. These modifications afforded compounds with the ability to recognize an allosteric site on the agonist-occupied A₁AR at relatively high concentrations, but ultimately favoured orthosteric antagonism over allosteric enhancement.

Cytosporones, coumarins, and an alkaloid from the endophytic fungus *Pestalotiopsis* sp. isolated from the Chinese mangrove plant *Rhizophora mucronata*

pp 7362–7367

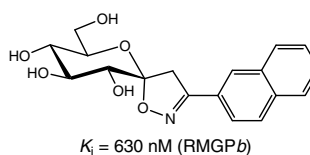
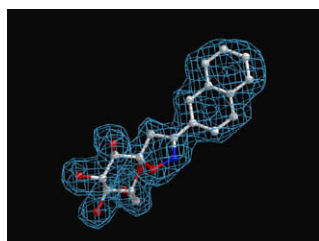
Jing Xu, Julia Kjer, Jandirk Sendker, Victor Wray, Huashi Guan, RuAngelie Edrada, Werner E. G. Müller, Mirko Bayer, Wenhan Lin *, Jun Wu *, Peter Proksch *



Glucose-based spiro-isoxazolines: A new family of potent glycogen phosphorylase inhibitors

pp 7368–7380

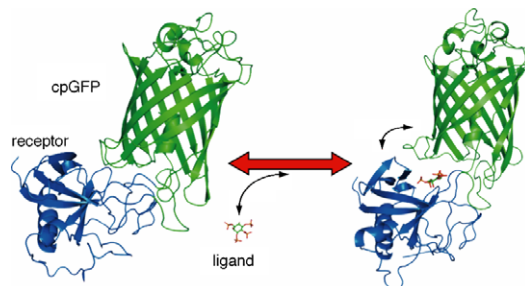
Mahmoud Bentifa, Joseph M. Hayes, Sébastien Vidal, David Gueyrard, Peter G. Goekjian, Jean-Pierre Praly *, Gregory Kizilis, Costas Tiraidis, Kyra-Melinda Alexacou, Evangelia D. Chrysina *, Spyros E. Zographos, Demetres D. Leonidas, Georgios Archontis, Nikos G. Oikonomakos



A single circularly permuted GFP sensor for inositol-1,3,4,5-tetrakisphosphate based on a split PH domain

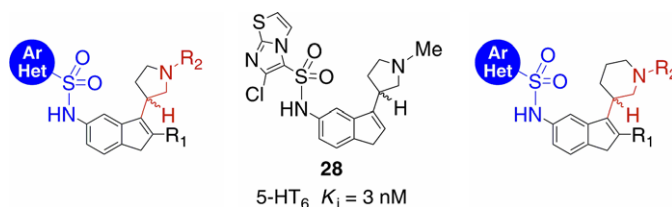
pp 7381–7386

Reiko Sakaguchi, Takashi Endoh, Seigo Yamamoto, Kazuki Tainaka, Kenji Sugimoto, Nobutaka Fujieda, Shigeki Kiyonaka, Yasuo Mori, Takashi Morii *

**Indene-based frameworks targeting the 5-HT₆ serotonin receptor: Ring constraint in indenylsulfonamides using cyclic amines and structurally abbreviated counterparts**

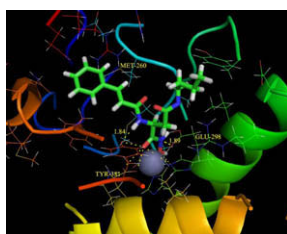
pp 7387–7397

Ermitas Alcalde *, Neus Mesquida *, Sara López-Pérez, Jordi Frigola, Ramon Mercè, Jörg Holenz, Marta Pujol, Enrique Hernández

Design and synthesis of indenylsulfonamides with a conformationally restricted aminoethyl side chain that exhibit high binding affinities for the 5-HT₆ serotonin receptor ($K_i \geq 3$ nM) and function as antagonists.**Design, synthesis, and preliminary studies of the activity of novel derivatives of *N*-cinnamoyl-L-aspartic acid as inhibitors of aminopeptidase N/CD13**

pp 7398–7404

Yingzi Liu, Luqing Shang, Hao Fang, Huawei Zhu, Jiajia Mu, Qiang Wang, Xuejian Wang, Yumei Yuan, Wenfang Xu *

The compound **8c** was built and docked into the active site of APN (PDB code: 2DQM) using Sybyl7.0. The docking result was showed by PyMOL.**OTHER CONTENTS****Instructions to contributors**

p I

*Corresponding author

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].

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