

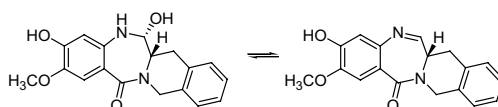
Contents

COMMUNICATIONS

Synthesis of a novel tetrahydroisoquinolino[2,1-*c*][1,4]benzodiazepine ring system with DNA recognition potential

pp 4371–4373

Kiran Kumar Kothakonda* and D. Subhas Bose

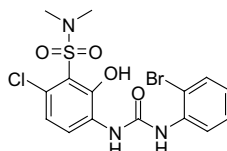


The first stereospecific synthesis of a novel tetrahydroisoquinolino[2,1-*c*][1,4]benzodiazepine ring system with DNA recognition potential starting from (*S*)-1,2,3,4-tetrahydroisoquinoline carboxylic acid has been reported.

Discovery of potent and orally bioavailable *N,N'*-diarylhurea antagonists for the CXCR2 chemokine receptor

pp 4375–4378

Qi Jin,* Hong Nie, Brent W. McClelland, Katherine L. Widdowson, Michael R. Palovich, John D. Elliott, Richard M. Goodman, Miriam Burman, Henry M. Sarau, Keith W. Ward, Melanie Nord, Bonnie M. Orr, Peter D. Gorycki and Jakob Busch-Petersen*

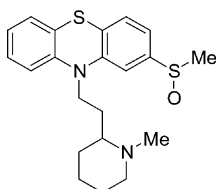


A series of 3-substituted *N,N'*-diarylhureas was prepared and CXCR2 receptor affinities as well as pharmacokinetic properties were examined.

Synthesis, receptor binding and functional studies of mesoridazine stereoisomers

pp 4379–4382

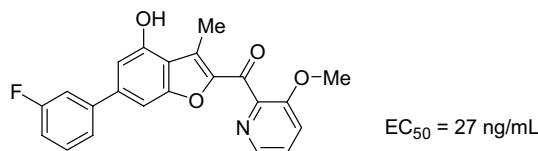
Sungwoon Choi, Deborah Haggart, Lawrence Toll and Gregory D. Cuny*



A library synthesis of 4-hydroxy-3-methyl-6-phenylbenzofuran-2-carboxylic acid ethyl ester derivatives as anti-tumor agents

pp 4383–4387

Ichiro Hayakawa, Rieko Shioya, Toshinori Agatsuma, Hidehiko Furukawa, Shunji Naruto and Yuichi Sugano*

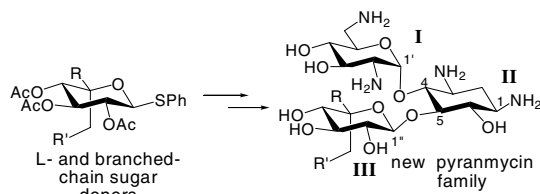


A compound library for structure optimization was synthesized employing solution-phase parallel synthesis to find highly potent derivatives.

Synthesis of an unusual branched-chain sugar, 5-C-methyl-L-idopyranose for SAR studies of pyranmycins: implication for the future design of aminoglycoside antibiotics

pp 4389–4393

Jinhua Wang, Jie Li, Przemyslaw G. Czyryca, Huiwen Chang, Jeff Kao and Cheng-Wei Tom Chang*

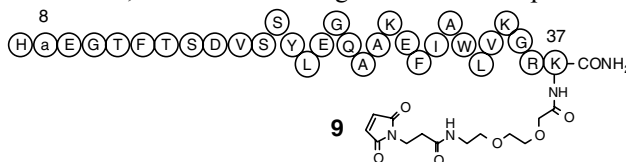


The syntheses of a challenging branched-chain sugar and several L-sugars have been accomplished. Their application in the studies of the antibacterial activity of pyranmycins is reported, which could provide new strategies for the future design of aminoglycoside antibiotics.

Identification of CJC-1131-albumin bioconjugate as a stable and bioactive GLP-1(7–36) analog

pp 4395–4398

Roger Léger,* Karen Thibaudeau, Martin Robitaille, Omar Quraishi, Pieter van Wyk, Nathalie Bousquet-Gagnon, Julie Carette, Jean-Paul Castaigne and Dominique P. Bridon

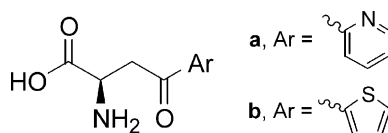


A series of analogs of GLP-1(7–36) amide containing a *N*ε-(2-{2-[2-(3-maleimidopropylamido)ethoxy]ethoxy}acetyl)-lysine has been synthesized and the resulting derivatives were bioconjugated to Cys34 of human serum albumin (HSA). The GLP-1-HSA bioconjugates were analyzed in vitro to assess the stabilizing effect of bioconjugation in the presence of DPP-IV as well as GLP-1 receptor binding and activation. Compound **9** (CJC-1131) having the point of attachment to albumin at the C-terminal of GLP-1 and a D-alanine substitution at position 8 was identified as having the best combination of stability and bioactivity.

Stereoselective synthesis and preliminary evaluation of new D-3-heteroarylcarbonylalanines as ligands of the NMDA receptor

pp 4399–4403

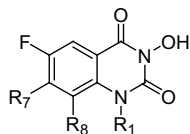
Paulo G. Lima, Rodrigo R. B. Caruso, Simone O. Alves, Renata F. Pessôa, Dayde L. Mendonça-Silva, Ricardo J. Nunes, François Noël, Newton G. Castro* and Paulo R. R. Costa*



New *N*-heteroarylcarbonylalanines of the D-series were stereoselectively prepared from enoates derived from D-mannitol. Their activities in binding and functional assays for the NMDA sub-type of glutamate receptors are described.

Synthesis and structural–activity relationships of 3-hydroxyquinazoline-2,4-dione antibacterial agents pp 4405–4409

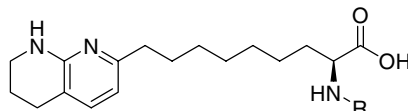
Tuan P. Tran,* Edmund L. Ellsworth, Michael A. Stier, John M. Domagala, H. D. Hollis Showalter, Stephen J. Gracheck, Martin A. Shapiro, Themis E. Joannides and Rajeshwar Singh



The synthesis and SAR of the 3-hydroxyquinazoline diones, a novel class of bacterial topoisomerase inhibitors, is reported.

Nonpeptide $\alpha_v\beta_3$ antagonists. Part 9: Improved pharmacokinetic profile through the use of an aliphatic, des-amide backbone pp 4411–4415

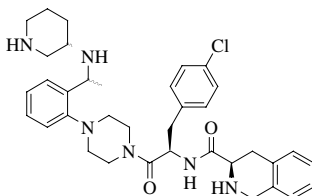
David B. Whitman,* Ben C. Askew, Le T. Duong, Carmen Fernandez-Metzler, Wasyl Halczenko, George D. Hartman, John H. Hutchinson, Chih-Tai Leu, Thomayant Prueksaritanont, Gideon A. Rodan, Sevgi B. Rodan and Mark E. Duggan



A series of $\alpha_v\beta_3$ receptor antagonists lacking the amide bond of previously-reported 'chain-shortened' compounds is described. Replacement of the lone amide bond with two methylene groups in this series yields more lipophilic compounds that have longer half-lives, lower clearance, and greater oral bioavailability when administered to dogs.

Structure–activity relationships of piperazinebenzylamines as potent and selective agonists of the human melanocortin-4 receptor pp 4417–4423

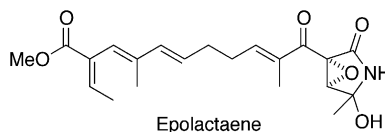
Joseph Pontillo, Joseph A. Tran, Melissa Arellano, Beth A. Fleck, Rajesh Huntley, Dragan Marinkovic, Marion Lanier, Jodie Nelson, Jessica Parker, John Saunders, Fabio C. Tucci, Wanlong Jiang, Caroline W. Chen, Nicole S. White, Alan C. Foster and Chen Chen*



13g, EC₅₀ = 3.8 nM

Structure–activity relationships of epolactaene derivatives: structural requirements for inhibition of Hsp60 chaperone activity pp 4425–4429

Yoko Nagumo, Hideaki Kakeya, Junichiro Yamaguchi, Takao Uno, Mitsuru Shoji, Yujiro Hayashi and Hiroyuki Osada*

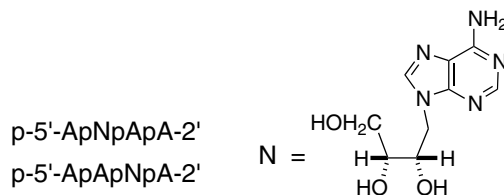


Epolactaene derivatives were synthesized and their ability to inhibit the growth of human cancer cell lines was tested. These derivatives were further analyzed for their ability to affect human heat shock protein 60 (Hsp60). We discovered the structural characteristics important for the ability to bind to Hsp60 and the fundamental role of α,β -unsaturated ketone in inhibiting Hsp60 chaperone activity.

Synthesis of 2',5'-oligoadenylate analogs containing an adenine acyclonucleoside and their ability to activate human RNase L

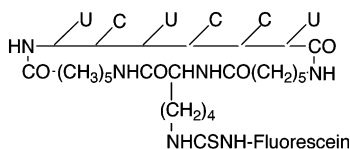
pp 4431–4434

Yoshihito Ueno, Shinji Ishihara, Yasutomo Ito and Yukio Kitade*


Synthesis and cellular uptake of a fluorescently labeled cyclic PNA-based compound

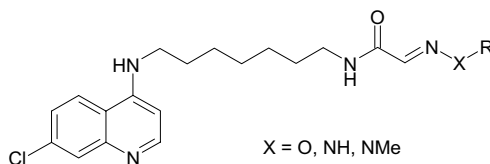
pp 4435–4438

Sergio Caldarelli, Geoffrey Depecker, Nadia Patino, Audrey Di Giorgio, Thibault Barouillet, Alain Doglio and Roger Condom*


Design, synthesis and antimalarial activity of a glyoxylylhydrazone library

pp 4439–4443

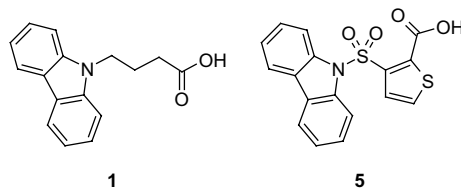
A. Ryckebusch, J.-S. Fruchart, L. Cattiaux, P. Rousselot-Paillet, V. Leroux, O. Melnyk, P. Grellier, E. Mouray, C. Sergheraert and P. Melnyk*


Discovery of inhibitors of human adipocyte fatty acid-binding protein, a potential type 2 diabetes target

pp 4445–4448

Fredrik Lehmann, Saba Haile, Eva Axen, Carmen Medina, Jonas Uppenberg, Stefan Svensson, Thomas Lundbäck, Lena Rondahl and Tjeerd Barf*

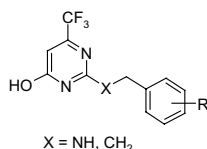
Low micromolar human A-FABP inhibitors were found by utilizing a fluorescence polarization assay, X-ray crystallography and modeling. The carbazole- and indole-based inhibitors displayed approximately 10-fold preferences over human H-FABP and E-FABP, and are highly selective against I-FABP. This communication describes the SAR for drug-like synthetic inhibitors of human A-FABP.



Substituted benzylamino-6-(trifluoromethyl)pyrimidin-4(1*H*)-ones: a novel class of selective human A-FABP inhibitors

pp 4449–4452

Rune Ringom, Eva Axen, Jonas Uppenberg, Thomas Lundbäck,
Lena Rondahl and Tjeerd Barf*

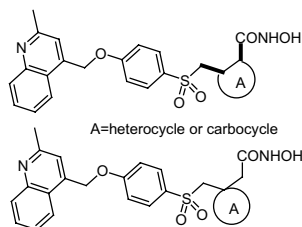


The synthesis and evaluation of novel human A-FABP inhibitors based on the 6-(trifluoromethyl)pyrimidine-4(1*H*)-one scaffold is described. Two series of compounds, bearing either an amino or carbon substituent in the 2-position of the pyrimidine ring were investigated. Modification of substituents and chain length optimization led to novel compounds with low micromolar activity and good selectivity for human A-FABP.

Synthesis and structure–activity relationship of a novel sulfone series of TNF- α converting enzyme inhibitors

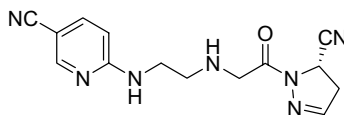
pp 4453–4459

Chu-Biao Xue,* Xiao-Tao Chen,* Xiaohua He, John Roderick, Ronald L. Corbett,
Bahman Ghavimi, Rui-Qin Liu, Maryanne B. Covington, Mingxin Qian, Maria D. Ribadeneira,
Krishna Vaddi, James M. Trzaskos, Robert C. Newton, James J.-W. Duan and Carl P. Decicco

**Synthesis and DP-IV inhibition of cyano-pyrazoline derivatives as potent anti-diabetic agents**

pp 4461–4465

Jin Hee Ahn,* Hye-Min Kim, Sun Ho Jung, Seung Kyu Kang, Kwang Rok Kim, Sang Dal Rhee,
Sung-Don Yang, Hyae Gyeong Cheon and Sung Soo Kim



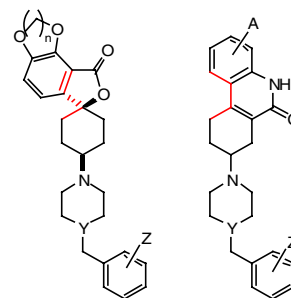
A new series of cyano-pyrazoline derivatives with a secondary amine at P-2 site was synthesized through achiral and chiral synthetic methods and evaluated for their ability to inhibit dipeptidyl peptidase IV (DP-IV).

Ligand conformation has a definitive effect on 5-HT_{1A} and serotonin reuptake affinity

pp 4467–4470

Kenneth M. Boy,* Michael Dee, Joseph Yevich,
John Torrente, Qi Gao, Lawrence Iben, Arlene Stark and
Ronald J. Mattson

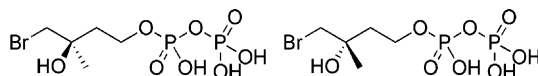
Conformationally constrained cyclohexanes and cyclohexenes were prepared and tested for 5-HT_{1A} and SSRI activity. The conformation of the dioxyaryl ring with respect to the cyclohexane ring is a key factor for selecting the relative potency of the compounds at the two receptors studied.



Synthesis of chiral phosphoantigens and their activity in $\gamma\delta$ T cell stimulation

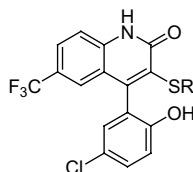
pp 4471–4477

Yongcheng Song, Yonghui Zhang, Hong Wang, Amy M. Raker, John M. Sanders, Erin Broderick, Allen Clark, Craig T. Morita and Eric Oldfield*

**4-Aryl-3-(mercapto)quinolin-2-ones: novel maxi-K channel opening relaxants of corporal smooth muscle**

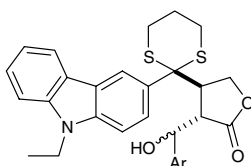
pp 4479–4482

Piyasena Hewawasam,* Wenhong Fan, Deborah A. Cook, Kimberly S. Newberry, Christopher G. Boissard, Valentin K. Gribkoff, John Starrett and Nicholas J. Lodge

**Anti-HIV activity of some synthetic lignanolides and intermediates**

pp 4483–4486

Rocío Sancho, Manuel Medarde,* Sonsoles Sánchez-Palomino, Blanca M. Madrigal, José Alcamí, Eduardo Muñoz* and Arturo San Feliciano



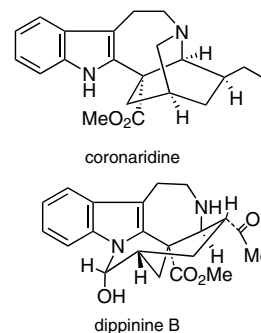
The inhibitory activity of lignanolides and intermediates on HIV replication, NF- κ B and Tat dependent HIV-LTR activation is evaluated.

Cytotoxic effects and reversal of multidrug resistance by ibogan and related indole alkaloids

pp 4487–4489

Toh-Seok Kam,* Kooi-Mow Sim, Huey-Shen Pang, Takashi Koyano, Masahiko Hayashi and Kanki Komiyama*

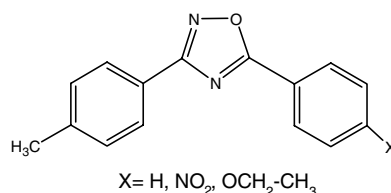
Five ibogan alkaloids (coronaridine, heyneanine, 19-*epi*-heyneanine, dippinine B, and dippinine C), out of a total of 25 tested, showed appreciable activity in reversing resistance in vincristine-resistant KB cells.



A suitable 1,2,4-oxadiazoles synthesis by microwave irradiation

pp 4491–4493

Vincenzo Santagada,* Francesco Frecentese, Elisa Perissutti, Donatella Cirillo, Sara Terracciano and Giuseppe Caliendo

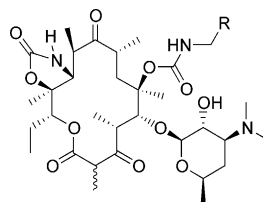


A novel and convenient microwave-assisted synthesis of 1,2,4-oxadiazoles is described. Conventional heating and microwave irradiation of the reactions are compared. Moreover, the importance of some coupling reagents was evaluated.

Synthesis and antibacterial activity of C-6 carbamate ketolides, a novel series of orally active ketolide antibiotics

pp 4495–4499

Todd C. Henninger,* Xiaodong Xu, Darren Abbanat, Ellen Z. Baum, Barbara D. Foleno, James J. Hilliard, Karen Bush, Dennis J. Hlasta and Mark J. Macielag

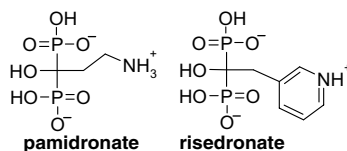


A new series of ketolides is reported, which features the use of a C-6 carbamate for tethering the arylalkyl sidechain to the macrolide core. The best members of this series display in vitro and in vivo activity comparable to telithromycin.

**The purine transferase from *Trypanosoma cruzi* as a potential target for bisphosphonate-based chemotherapeutic compounds**

pp 4501–4504

Daniel Fernández, Mary Anne Wenck, Sydney P. Craig, III and José M. Delfino*

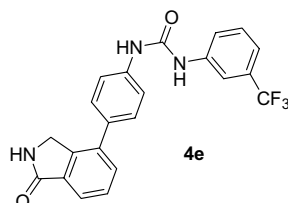


Bisphosphonates were tested as inhibitors of *Trypanosoma cruzi* hypoxanthine-guanine phosphoribosyltransferase by computational modeling and enzymatic assays. The two most potent inhibitors were **pamidronate** and **risedronate** with K_i values of 50.6 and 23.2 μ M, respectively.

Isoindolinone ureas: a novel class of KDR kinase inhibitors

pp 4505–4509

Michael L. Curtin,* Robin R. Frey, H. Robin Heyman, Kathy A. Sarris, Douglas H. Steinman, James H. Holmes, Peter F. Bousquet, George A. Cunha, Maria D. Moskey, Asma A. Ahmed, Lori J. Pease, Keith B. Glaser, Kent D. Stewart, Steven K. Davidsen and Michael R. Michaelides

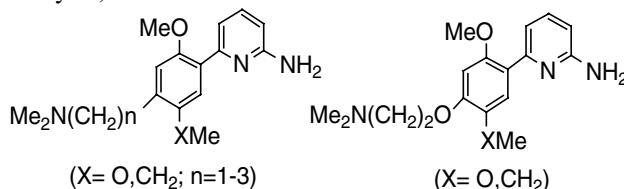


The evaluation of KDR kinase inhibitor **4e** (IC₅₀ 7 nM) and related analogs is reported.

Substituted 6-phenyl-pyridin-2-ylamines: selective and potent inhibitors of neuronal nitric oxide synthase

pp 4511–4514

Deane M. Nason, Steven D. Heck, Mathew S. Bodenstein, John A. Lowe, III, Robert B. Nelson, Dane R. Liston, Charles E. Nolan, Lorraine F. Lanyon, Karen M. Ward and Robert A. Volkmann*

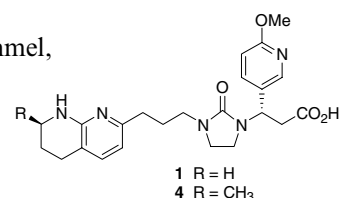


The synthesis and nNOS/eNOS activity of 6-(4-(dimethylaminoalkyl))-4-(dimethylaminoalkoxy)-5-ethyl-2-methoxyphenyl-pyridin-2-ylamines and 6-(4-(dimethylaminoalkyl))-4-(dimethylaminoalkoxy)-2,5-dimethoxyphenyl-pyridin-2-ylamines **1–8** are described. These compounds are potent inhibitors of the human nNOS isoform.

Nonpeptide $\alpha_v\beta_3$ antagonists. Part 10: In vitro and in vivo evaluation of a potent 7-methyl substituted tetrahydro-[1,8]naphthyridine derivative

pp 4515–4518

Michael J. Breslin,* Mark E. Duggan, Wasyl Halczenko, George D. Hartman, Le T. Duong, Carmen Fernandez-Metzler, Michael A. Gentile, Donald B. Kimmel, Chih-Tai Leu, Kara Merkle, Thomayant Prueksaritanont, Gideon A. Rodan, Sevgi B. Rodan and John H. Hutchinson



Subtle modifications were incorporated into the structure of clinical candidate **1**. These changes were designed to maintain potency and selectivity while inducing changes in physical properties leading to improved pharmacokinetics in three species. This approach led to the identification of **4** as a potent, selective $\alpha_v\beta_3$ receptor antagonist that was selected for clinical development based on an improved PK profile and efficacy demonstrated in an in vivo model of bone turnover.

Syntheses and anti-MRSA activities of the C3 analogs of mansonone F, a potent anti-bacterial sesquiterpenoid: insights into its structural requirements for anti-MRSA activity

pp 4519–4523

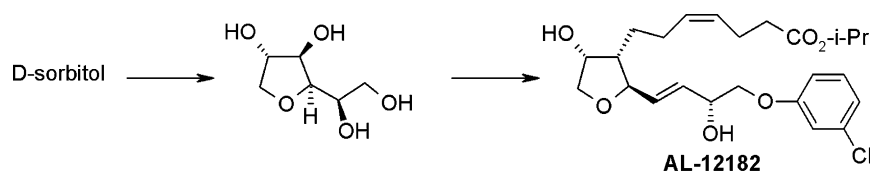
Dong-Yun Shin, Sun Nam Kim, Jung-Hyun Chae, Soon-Sil Hyun, Seung-Yong Seo, Yong-Sil Lee, Kwang-Ok Lee, Seok-Ho Kim, Yun-Sang Lee, Jae Min Jeong, Nam-Song Choi and Young-Ger Suh*

Syntheses and excellent anti-MRSA activities of the mansonone F analogs are reported. In addition, the minimal structural requirements for its anti-MRSA activities as well as its structure–activity relationship including the C3 substituents effects on anti-MRSA activity are also described.

AL-12182, a novel 11-oxa prostaglandin analog with topical ocular hypotensive activity in the monkey

pp 4525–4528

Robert D. Selliah, Mark R. Hellberg, Najam A. Sharif, Marsha A. McLaughlin, Gary W. Williams, Daniel A. Scott, David Earnest, Karen S. Haggard, W. Dennis Dean, Pete Delgado, Michael S. Gaines, Raymond E. Conrow and Peter G. Klimko*



3 μ g dose, 40% drop in monkey IOP

pp 4529–4532

Hepatitis C virus E1 192-205

192 205

Tyr-Glu-Val-Arg-Asn-Val-Ser-Gly-Val-Tyr-His-Val-Thr-Asn

Antibody light chain from a multiple myeloma patient

pp 4533–4537

(S)-5: $R^1 = F$, $R^2 = H$; $X = CH_2$; $Y = NH$

The synthesis and the KCNQ2 opener activity of a novel series of acrylamides are described.

pp 4539–4544

$$\begin{array}{c} \text{R}_2 \\ \diagup \\ \text{X} \\ \diagdown \\ \text{R}_3 \end{array} \begin{array}{c} \text{C} \\ \diagup \\ \text{N} \\ \diagdown \\ \text{H} \end{array} = \text{NH}$$

$\text{X} = \text{S}, \text{CHR}_1$

Chemical structures of the compounds are shown below. The top structure is a bis-phenol derivative with a long flexible linker, showing an IC_{50} of 500 nM. The bottom structure is a bis-phenol derivative with a rigid linker, showing an IC_{50} of 2-3 nM.

Top structure: $IC_{50} = 500 \text{ nM}$

Bottom structure: $IC_{50} = 2-3 \text{ nM}$

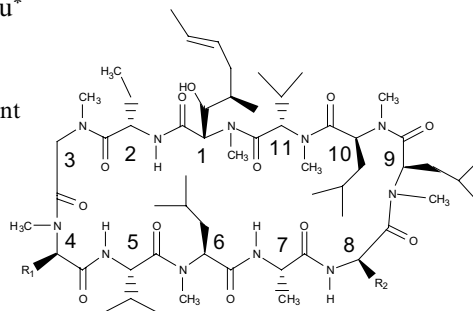
Modifications of the linker between the benzamidine moieties led to the discovery of several new highly potent anti-*Pneumocystis carinii* agents.

Synthesis and neurotrophic activity of nonimmunosuppressant cyclosporin A derivatives

pp 4549–4551

Ling Wei, Joseph P. Steiner, Gregory S. Hamilton and Yong-Qian Wu*

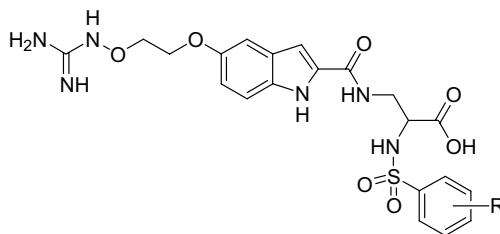
In order to exploit cyclophilin as a potential target for neurological drug design, we demonstrate in this presentation that several nonimmunosuppressant analogues of cyclosporin A, modified at the various positions in the 'effector' domain, are equipotent nerve growth agents compared to cyclosporin A. Our results suggest that neurotrophic activity of cyclosporin A and its derivatives resides in the binding domain, and binding to cyclophilin and/or inhibiting rotamase activity may be a necessity for neurotrophic effects of cyclophilin ligands.



Design, synthesis, and biochemical evaluation of novel $\alpha_v\beta_3$ integrin ligands

pp 4553–4555

Juan Jose Marugan,* Kristin D. Haslow and Carl Crysler

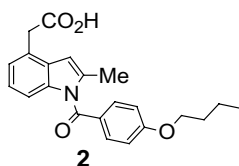


Synthesis and activity of oxyguanidine-indoles as $\alpha_v\beta_3$ ligands is reported.

Discovery of new chemical leads for prostaglandin D₂ receptor antagonists

pp 4557–4562

Kazuhiko Torisu,* Kaoru Kobayashi, Maki Iwahashi, Hiromu Egashira, Yoshihiko Nakai, Yutaka Okada, Fumio Nanbu, Shuichi Ohuchida, Hisao Nakai and Masaaki Toda

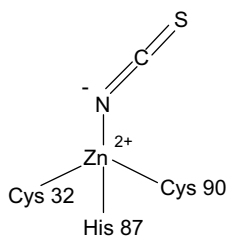


A new chemical lead **2** for DP receptor antagonist was discovered starting from chemical modification of Indomethacin analogs.

Carbonic anhydrase inhibitors. Inhibition of the beta-class enzyme from the methanoarchaeon *Methanobacterium thermoautotrophicum* (Cab) with anions

pp 4563–4567

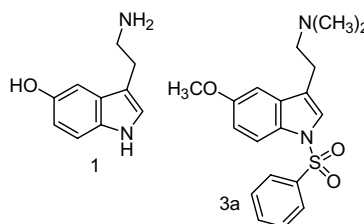
Alessio Innocenti, Sabrina Zimmerman, James G. Ferry, Andrea Scozzafava and Claudiu T. Supuran*



Possible differences in modes of agonist and antagonist binding at human 5-HT₆ receptors

pp 4569–4573

Manik R. Pullagurla, Richard B. Westkaemper and Richard A. Glennon*



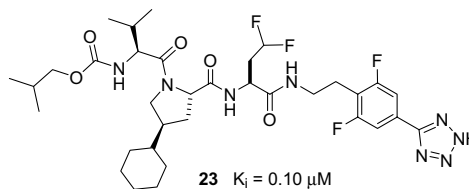
A homology model of human 5-HT₆ receptors was constructed and *N*₁-arylsulfonyltryptamines (e.g., **3a**) were found to bind in a different manner than the tryptamine agonist serotonin (**1**).

SAR and pharmacokinetic studies on phenethylamide inhibitors of the hepatitis C virus NS3/NS4A serine protease

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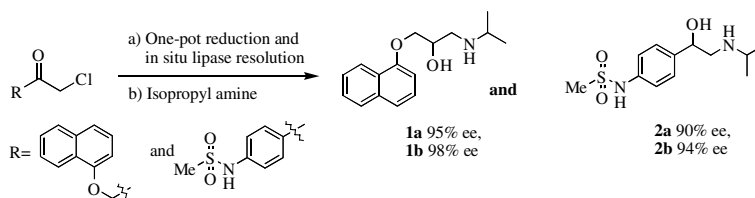
Savina Malancona, Stefania Colarusso, Jesus M. Ontoria, Antonella Marchetti, Marco Poma, Ian Stansfield, Ralph Laufer, Annalise Di Marco, Marina Taliani, Maria Verdirame, Odalys Gonzalez-Paz, Victor G. Matassa and Frank Narjes*

The development of phenethylamide **23** (*K_i* 0.1 μM) is described together with the pharmacokinetics behavior of this and related compounds.

**Chemoenzymatic synthesis of (*S*) and (*R*)-propranolol and sotalol employing one-pot lipase resolution protocol**

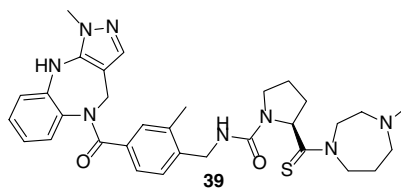
pp 4581–4583

Ahmed Kamal,* Mahendra Sandbhor and Ahmad Ali Shaik

**Non-peptide oxytocin agonists**

pp 4585–4589

Gary R. W. Pitt, Andrzej R. Batt, Robert M. Haigh, Andrew M. Penson, Peter A. Robson, David P. Rooker, André L. Tartar, Julie E. Trim, Christopher M. Yea and Michael B. Roe*




The first non-peptide, low molecular weight agonists of the hormone oxytocin (OT) are reported. The most potent compound, **39**, showed an EC₅₀ = 33 nM and was selective for the OT receptor.

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Contributors to this issue
Instructions to contributors

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*Corresponding author

+ Supplementary data available via ScienceDirect

COVER

Cover figure provided by **Indraneel Ghosh**, Department of Chemistry, University of Arizona. The cover depicts the **Dual Surface Selection** methodology developed by the author: the blue helix of htBl (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBl (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].



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