

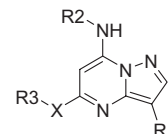
Contents

COMMUNICATIONS

Structure-guided design of pyrazolo[1,5-*a*]pyrimidines as inhibitors of human cyclin-dependent kinase 2 pp 863–867

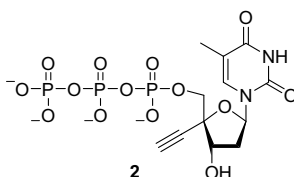
Douglas S. Williamson,* Martin J. Parratt, Justin F. Bower, Jonathan D. Moore, Christine M. Richardson, Pawel Dokurno, Andrew D. Cansfield, Geraint L. Francis, Richard J. Hebdon, Rob Howes, Philip S. Jackson, Andrea M. Lockie, James B. Murray, Claire L. Nunns, Jenifer Powles, Alan Robertson, Allan E. Surgenor and Christopher J. Torrance

The protein structure guided design of a series of pyrazolo[1,5-*a*]pyrimidines with high potency for human cyclin-dependent kinase 2 (CDK2) is described. Some examples were shown to inhibit the growth of human colon tumour cells, were equipotent for CDK1 and were selective against GSK-3 β and other kinases.



4'-C-Ethynyl-thymidine acts as a chain terminator during DNA-synthesis catalyzed by HIV-1 reverse transcriptase pp 869–871

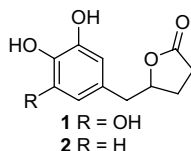
Daniel Summerer and Andreas Marx*



The synthesis and action on HIV-1 RT of 4'-C-ethynyl thymidine-5'-*O*-triphosphate **2** is reported.

Synthesis and biological activity of the tea catechin metabolites, M4 and M6 and their methoxy-derivatives pp 873–876

Joshua D. Lambert, Joseph E. Rice,* Jungil Hong, Zhe Hou and Chung S. Yang

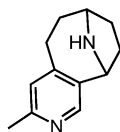


The synthesis of **1** and **2** and several methoxy-derivatives, and an evaluation of their growth inhibitory and antiinflammatory activity are reported.

6'-Methylpyrido[3,4-*b*]norhomotropane: synthesis and outstanding potency in relation to the $\alpha 4\beta 2$ nicotinic receptor pharmacophore model

pp 877–881

David B. Kanne, Motohiro Tomizawa, Kathleen A. Durkin and John E. Casida*

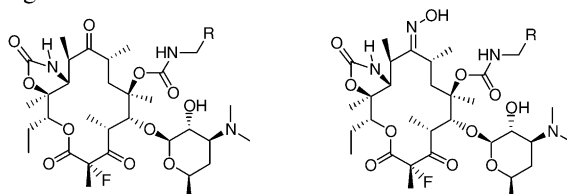


The racemic (\pm) compound is more potent at the $\alpha 4\beta 2$ nicotinic receptor ($K_i = 0.39$ nM) than any previously reported bridged nicotinoid, establishing an important role of the 6'-methyl substituent in this pharmacophore model.


Synthesis and antibacterial activity of C2-fluoro, C6-carbamate ketolides, and their C9-oximes

pp 883–887

Xiaodong Xu,* Todd Henninger, Darren Abbanat, Karen Bush, Barbara Folen, Jamease Hilliard and Mark Macielag

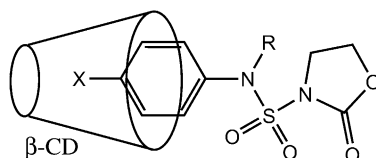


A series of C6-carbamate ketolides with C2-fluorination and C9-oximation was synthesized and shown to have in vitro activity that is superior to erythromycin and comparable to telithromycin. In vivo activity was adversely affected by fluorination, possibly as a result of increased serum protein binding.

Inclusion complexes of N-sulfamoyloxazolidinones with β -cyclodextrin

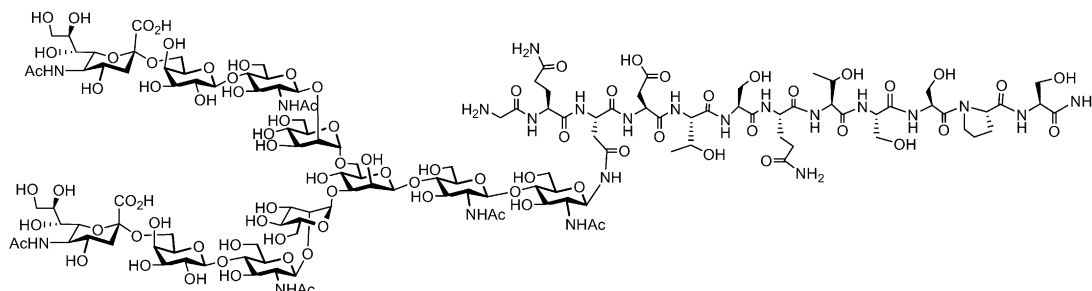
pp 889–894

Mekki Kadri,* Rayenne Djemil, Mohamed Abdaoui, Jean-Yves Winum, Frédéric Coutrot and Jean-Louis Montero*


Chemoenzymatic synthesis of CD52 glycoproteins carrying native N-glycans

pp 895–898

Hengguang Li, Suddham Singh, Ying Zeng, Haijing Song and Lai-Xi Wang*



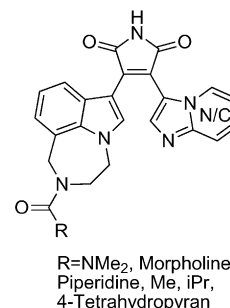
The synthesis of the CD52 glycoproteins was achieved using endoglycosidase-catalyzed oligosaccharide transfer as the key step.

The development of potent and selective bisarylmaleimide GSK3 inhibitors

pp 899–903

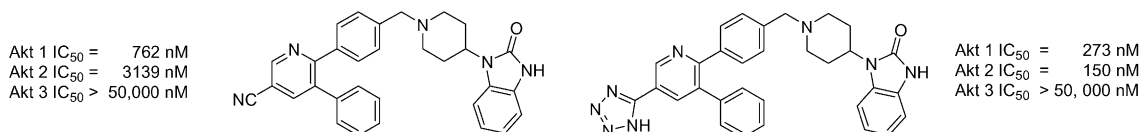
Thomas A. Engler,* Sushant Malhotra, Timothy P. Burkholder, James R. Henry, David Mendel, Warren J. Porter, Kelly Furness, Clive Diefenbacher, Angela Marquart, Jon K. Reel, Yihong Li, Joshua Clayton, Brian Cunningham, Johnathan McLean, John C. O'Toole, Joseph Brozinick, Eric Hawkins, Elizabeth Misener, Daniel Briere, Richard A. Brier, Jill R. Wagner, Robert M. Campbell, Bryan D. Anderson, Renee Vaughn, Donald B. Bennett, Timothy I. Meier and James A. Cook

3-(Imidazo[1,2-*a*]pyridin-3-yl)-, its aza-analogs, and 3-(pyrazolo[1,5-*a*]pyridin-3-yl)-4-(2-acyl-(1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-7-yl))maleimides are very potent inhibitors of GSK3 (≤ 5 nM) with >160 to >10,000-fold selectivity versus CDK2/4 and PKC β II.

**Discovery of 2,3,5-trisubstituted pyridine derivatives as potent Akt1 and Akt2 dual inhibitors**

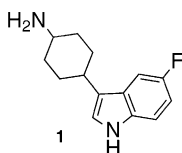
pp 905–909

Zhijian Zhao,* William H. Leister, Ronald G. Robinson, Stanley F. Barnett, Deborah Defeo-Jones, Raymond E. Jones, George D. Hartman, Joel R. Huff, Hans E. Huber, Mark E. Duggan and Craig W. Lindsley

**Studies towards the next generation of antidepressants. Part 4: Derivatives of 4-(5-fluoro-1*H*-indol-3-yl)cyclohexylamine with affinity for the serotonin transporter and the 5-HT_{1A} receptor**

pp 911–914

Deborah A. Evrard,* Ping Zhou, Soo Y. Yi, Dahui Zhou, Deborah L. Smith, Kelly M. Sullivan, Geoffrey A. Hornby, Lee E. Schechter, Terrance H. Andree and Richard E. Mewshaw*

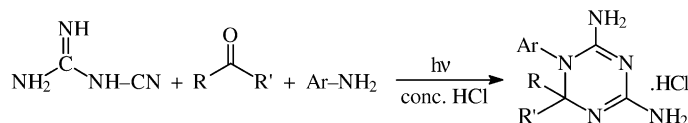


Derivatives of the serotonin reuptake inhibitor (**1**) that also have affinity for the 5-HT_{1A} receptor are reported.

1-Aryl-4,6-diamino-1,2-dihydrotriazine as antimalarial agent: a new synthetic route

pp 915–917

M. Kidwai,* P. Mothsra, R. Mohan and S. Biswas

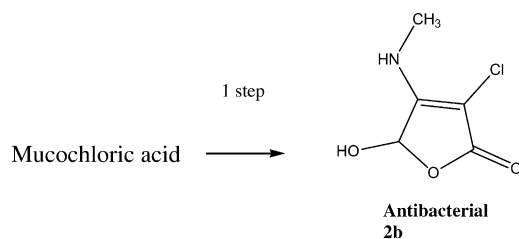


Some novel derivatives of 1-aryl-4,6-diamino-1,2-dihydrotriazines have been synthesized using neat technology under microwave. These were tested in vitro against both sensitive and resistant *Plasmodium falciparum* strains for antimalarial activity.

Synthesis and antibacterial activities of 5-hydroxy-4-amino-2(5H)-furanones

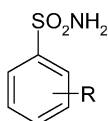
pp 919–921

Eric Lattmann,* Simon Dunn, Suwanna Niamsanit and Nison Sattayasai

**QSAR studies on benzene sulfonamide carbonic anhydrase inhibitors: need of hydrophobic parameter for topological modeling of binding constants of sulfonamides to human CA-II**

pp 923–930

Padmakar V. Khadikar,* Vimukta Sharma, Sneha Karmarkar and Claudiu T. Supuran

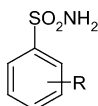


The binding constants ($\log K$) of benzene sulfonamides to human CA-II have been modeled using a large series of distance-based topological indices. The need or otherwise of the hydrophobic parameter ($\log P$) for such topological modeling of $\log K$ has been examined critically. In both the cases excellent results have been obtained. In multiparametric models involving indicator parameters we observed that introduction of hydrophobic parameter ($\log P$) yields much improved statistics. The results are discussed on the basis of statistical parameters and also by using cross-validation method.

Novel use of chemical shift in NMR as molecular descriptor: a first report on modeling carbonic anhydrase inhibitory activity and related parameters

pp 931–936

Padmakar V. Khadikar,* Vimukta Sharma, Sneha Karmarkar and Claudiu T. Supuran



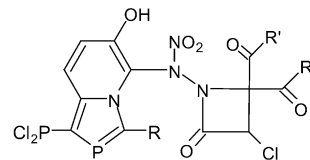
A novel use of NMR chemical shift of the SO_2NH_2 protons (in dioxane as solvent) as a molecular descriptor is described for modeling the inhibition constant for benzene sulfonamides against the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1). The methodology is extended to model diuretic activity and lipophilicity of benzene sulfonamide derivatives. The regression analysis of the data has shown that the NMR chemical shift is incapable of modeling lipophilicity. However, it is quite useful for modeling the diuretic activity of these derivatives. The results are compared with those obtained using distance-based topological indices: Wiener (W)-, Szeged (Sz)-, and PI (Padmakar-Ivan) indices.

Studies on synthesis and evaluation of quantitative structure–activity relationship of 5-[(3'-chloro-4',4'-disubstituted-2-oxoazetidinyl)(N-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]-azaphospholo[1,5-a]pyridin-1-yl-phosphorus dichlorides

pp 937–943

Pratibha Sharma,* Ashok Kumar, Shikha Sharma and Nilesh Rane

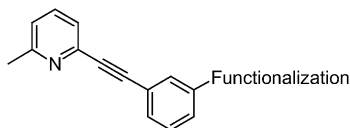
A new series of 5-[(3'-chloro-4',4'-disubstituted-2-oxoazetidinyl)(N-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-a]pyridin-1-yl-phosphorus dichlorides has been synthesized and subjected to acute antibacterial and antifungal screening studies. All the derivatives belonging to this series delineated remarkable activity as compared to standard drugs (ampicillin and clotrimazole). Compounds are quantitatively analyzed in relation to their different physicochemical parameters. Significant correlations were obtained between biological activity and polarizability parameter MR. Apart from this, indicator variables had also played a significant role.



Functionalization at position 3 of the phenyl ring of the potent mGluR5 noncompetitive antagonists MPEP

pp 945–949

David Alagille, Ronald M. Baldwin, Bryan L. Roth, Jarda T. Wroblewski, Ewa Grajkowska and Gilles D. Tamagnan*

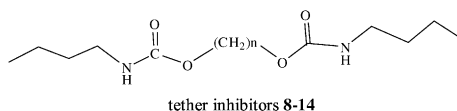


We described the synthesis and biological evaluation of MPEP analogs functionalized at the position 3 of the phenyl ring. The results point out the limitation in the choice of a functional group at this position; the only substituents leading to retention of activity are NO₂ (IC₅₀ = 13 nM) and CN (IC₅₀ = 8 nM).

A rate determining step change in the pre-steady state of acetylcholinesterase inhibitions by 1,*n*-alkane-di-*N*-butylcarbamates

pp 951–955

Gialih Lin,* Hsin-Chang Tseng, Ai-Chi Chio, Tsao-Ming Tseng and Bo-Yi Tsai

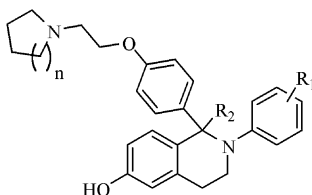


A discontinuity of the pre-steady state $-\log K_s$ values for the acetylcholinesterase inhibitions by tether inhibitors **8–14** versus the tether lengths plot, concave downwards, is indicative of a rate determining change in the K_s step.

QSAR of estrogen receptor modulators: exploring selectivity requirements for ER α versus ER β binding of tetrahydroisoquinoline derivatives using E-state and physicochemical parameters

pp 957–961

Subhendu Mukherjee, Achintya Saha and Kunal Roy*

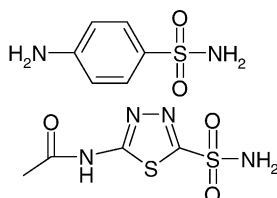


Considering importance of developing selective estrogen receptor modulators (SERMs), the present paper explores selectivity requirements of tetrahydroisoquinoline derivatives for binding with ER α versus ER β receptors using E-state index and physicochemical parameters.

Carbonic anhydrase inhibitors. Inhibition of the transmembrane isozyme XII with sulfonamides—a new target for the design of antitumor and antiglaucoma drugs?

pp 963–969

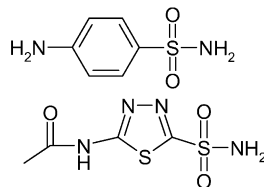
Daniela Vullo, Alessio Innocenti, Isao Nishimori, Jaromír Pastorek, Andrea Scozzafava, Silvia Pastoreková and Claudiu T. Supuran*



Carbonic anhydrase inhibitors. Inhibition of the human cytosolic isozyme VII with aromatic and heterocyclic sulfonamides

pp 971–976

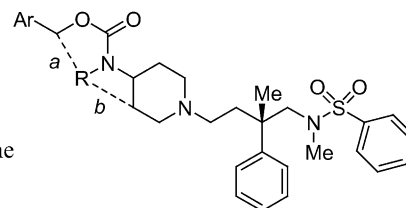
Daniela Vullo, Juha Voipio, Alessio Innocenti, Claudio Rivera, Harri Ranki, Andrea Scozzafava, Kai Kaila and Claudiu T. Supuran*


Synthesis and evaluation of CCR5 antagonists containing modified 4-piperidiny-2-phenyl-1-(phenylsulfonylamino)-butane

pp 977–982

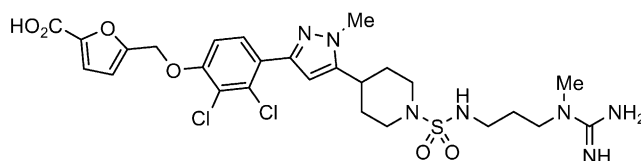
Shrenik K. Shah,* Natalie Chen, Ravindra N. Guthikonda, Sander G. Mills, Lorraine Malkowitz, Martin S. Springer, Sandra L. Gould, Julie A. DeMartino, Anthony Carella, Gwen Carver, Karen Holmes, William A. Schleif, Renee Danzeisen, Daria Hazuda, Joseph Kessler, Janet Lineberger, Michael Miller, Emilio A. Emini and Malcolm MacCoss

Synthesis, CCR5 affinity and anti-HIV activity of analogs containing bicyclic piperidine replacements for 4-aminopiperidine moiety of the lead are described.


Identification of nonpeptidic small-molecule inhibitors of interleukin-2

pp 983–987

Nathan D. Waal,* Wenjin Yang, Johan D. Oslob, Michelle R. Arkin, Jennifer Hyde, Wanli Lu, Robert S. McDowell, Chul H. Yu and Brian C. Raimundo

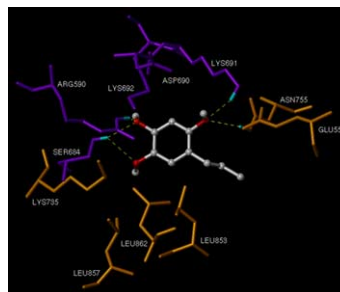


The identification, design, and synthesis of a series of novel sulfamide- and urea-based small-molecule antagonists of the protein–protein interaction IL-2/IL-2R α are described. Installation of a furan carboxylic acid fragment onto a low-micromolar sulfamide resulted in a 23-fold improvement in activity, providing a sub-micromolar, nonpeptidic IL-2 inhibitor ($IC_{50} = 0.60 \mu M$).

Molecular docking of the highly hypolipidemic agent α -asarone with the catalytic portion of HMG-CoA reductase

pp 989–994

José Luis Medina-Franco, Fabián López-Vallejo, Sergio Rodríguez-Morales, Rafael Castillo,* Germán Chamorro and Joaquín Tamariz*

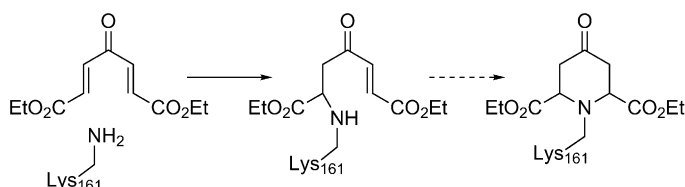


Docking experiments using a number of published crystal structures of HMG-CoA reductase with the potent hypocholesterolemic agent α -asarone are described. The docking results will be valuable for the structure-based design novel hypolipidemic agents.

Two new irreversible inhibitors of dihydrodipicolinate synthase: diethyl (*E,E*)-4-oxo-2,5-heptadienedioate and diethyl (*E*)-4-oxo-2-heptenedioate

pp 995–998

Jennifer J. Turner, Jackie P. Healy, Renwick C. J. Dobson, Juliet A. Gerrard and Craig A. Hutton*

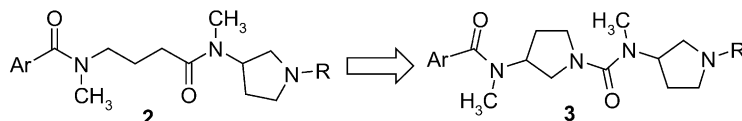


Two new irreversible inhibitors of dihydrodipicolinate synthase, a key enzyme in lysine biosynthesis and an important antibiotic target, are reported.

Bis(aminopyrrolidine)-derived ureas (APUs) as potent MCH₁ receptor antagonists

pp 999–1004

Jonathan Grey, Brian Dyck,* Martin W. Rowbottom, Junko Tamiya, Troy D. Vickers, Mingzhu Zhang, Liren Zhao, Christopher E. Heise, David Schwarz, John Saunders and Val S. Goodfellow

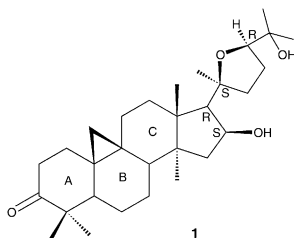


Ureas derived from two substituted 3-aminopyrrolidine subunits were prepared as constrained analogs of a linear lead compound and tested as antagonists of the MCH₁ receptor.

Synthesis of argentatin A derivatives as growth inhibitors of human cancer cell lines in vitro

pp 1005–1008

Hortensia Parra-Delgado, Teresa Ramírez-Apan and Mariano Martínez-Vázquez*

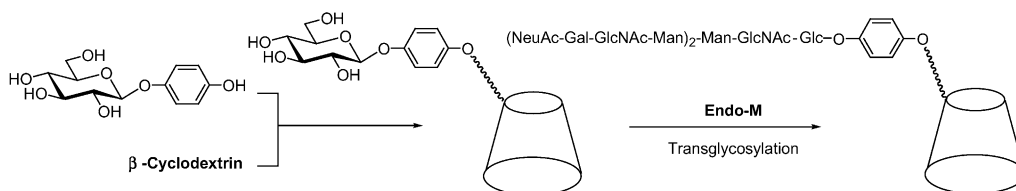


The syntheses of nine argentatin A (1) analogs are described. These compounds were assessed for their ability to inhibit growth in vitro in four human cancer cell lines. In addition, an X-ray study of (16*S*,17*R*,20*S*,24*R*)-3-oxime-20,24-epoxy-16,25-dihydroxycycloartan-3-one led to the determination of the correct stereochemistry of argentatin A.

Synthesis of *mono*-glucose-branched cyclodextrins with a high inclusion ability for doxorubicin and their efficient glycosylation using *Mucor hiemalis* endo- β -*N*-acetylglucosaminidase

pp 1009–1013

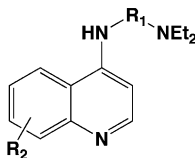
Takashi Yamanoi,* Naomichi Yoshida, Yoshiki Oda, Eri Akaike, Maki Tsutsumida, Natsumi Kobayashi, Kenji Osumi, Kenji Yamamoto, Kiyotaka Fujita, Keiko Takahashi and Kenjiro Hattori



Synthesis of ring-substituted 4-aminoquinolines and evaluation of their antimalarial activities

pp 1015–1018

Peter B. Madrid, John Sherrill, Ally P. Liou, Jennifer L. Weisman, Joseph L. DeRisi and R. Kiplin Guy*



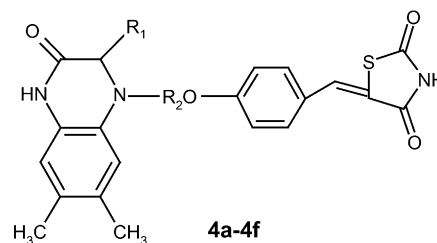
A simple two-step synthesis method was used to make 51 B-ring-substituted 4-hydroxyquinolines allowing analysis of the effect of ring substitutions on inhibition of growth of chloroquine sensitive and resistant strains of *Plasmodium falciparum*. Substituted quinoline rings other than the 7-chloroquinoline ring found in chloroquine were found to have significant activity against the drug-resistant strain of *Plasmodium falciparum* W2.

**Synthesis and pharmacological evaluation of substituted 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxaliny)ethoxy]phenyl]methylene]thiazolidine-2,4-dione derivatives as potent euglycemic and hypolipidemic agents**

pp 1019–1022

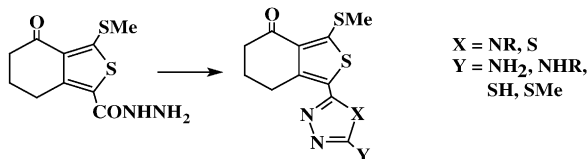
Dipti Gupta, Narendra Nath Ghosh and Ramesh Chandra*

A series of substituted 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxaliny)ethoxy]phenyl]methylene]thiazolidine-2,4-diones has been synthesized, which possesses euglycemic and hypolipidemic activities in Wistar male rats.

**Synthesis and antibacterial activity of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl]-3-methylthio-6,7-dihydrobenzo[c]thiophen-4(5H)ones**

pp 1023–1025

Sara Tehranchian, Tahmineh Akbarzadeh, Mohammad Reza Fazeli, Hossein Jamalifar and Abbas Shafiee*

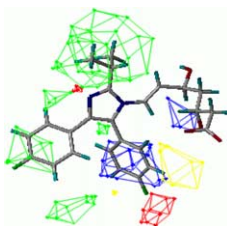


1,2,4-Triazole and 1,3,4-thiadiazole derivatives of benzo[c]thiophene were prepared and tested for in vitro antimicrobial activity. Some of these compounds exhibited high activity against *Staphylococcus aureus*, *S. epidermidis*, *Bacillus subtilis*.

Three-dimensional quantitative structure (3-D QSAR) activity relationship studies on imidazolyl and N-pyrrolyl heptenoates as 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) inhibitors by comparative molecular similarity indices analysis (CoMSIA)

pp 1027–1032

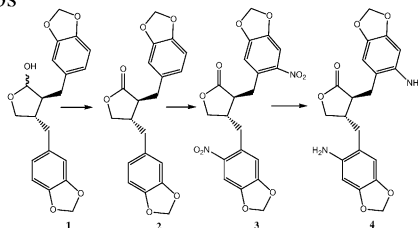
Ramasamy Thilagavathi, Raj Kumar, Vema Aparna, M. Elizabeth Sobhia, Bulusu Gopalakrishnan and Asit K. Chakraborti*



Synthesis and biological activity evaluation of lignan lactones derived from (–)-cubebin

pp 1033–1037

Rosangela da Silva,* Gustavo H. B. de Souza, Ademar A. da Silva, Vanessa A. de Souza, Ana C. Pereira, Vanesa de A. Royo, Marcio L. A. e Silva, Paulo M. Donate, Ana L. S. de Matos Araújo, José C. T. Carvalho and Jairo K. Bastos

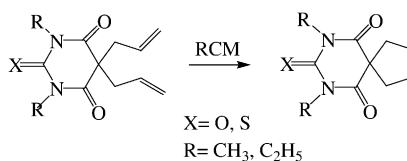


The anti-inflammatory and analgesic activities of three dibenzylbutyrolactone lignans obtained by partial synthesis starting from (–)-cubebin (**1**), which was isolated from the seeds of *Piper cubeba*, were evaluated using different animal models.

Spiro-annulation of barbituric acid derivatives and its analogs by ring-closing metathesis reaction

pp 1039–1043

Sambasivarao Kotha,* Ashoke Chandra Deb and Ramanatham Vinod Kumar

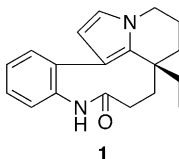


Barbituric acid **1** and related β -dicarbonyl compounds were dialkenylated under the phase-transfer catalyst [e.g., benzyltriethylammonium chloride (BTEAC)] conditions to generate the diallylated products. These diallylated products were subjected to the ring-closing metathesis (RCM) reaction to deliver the corresponding spiro-annulated derivatives.

Conformational analysis of rhazinilam and three-dimensional quantitative structure–activity relationships of rhazinilam analogues

pp 1045–1050

Hiroshi Morita,* Khalijah Awang, A. Hamid A. Hadi, Koichi Takeya, Hideji Itokawa and Jun'ichi Kobayashi



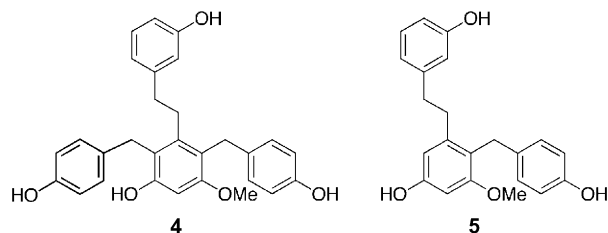
Most probable conformation in solution of rhazinilam (**1**) was analyzed and CoMFA results have been applied successfully to rationalize the inhibitory activities of tubulin disassembly of rhazinilam and its analogues in terms of their steric and electrostatic properties.

Antimitotic activity and reversal of breast cancer resistance protein-mediated drug resistance by stilbenoids from *Bletilla striata*

pp 1051–1054

Hiroshi Morita, Koichiro Koyama, Yoshikazu Sugimoto and Jun'ichi Kobayashi*

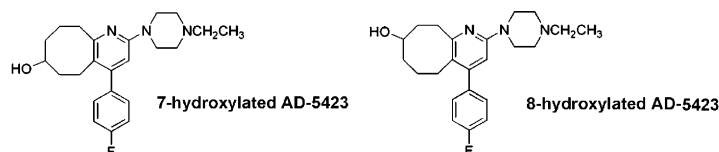
Eight stilbenoids **1–8** have been isolated by the guidance of inhibitory effect of tubulin polymerization from the tubers of *Bletilla striata* (Orchidaceae). Among them, both of bisbenzyls **4** and **5** inhibited the polymerization of tubulin at IC_{50} of 10 μ M, while bisbenzyl **4** potentiated the cytotoxicity of SN-38 in BCRP-transduced K562 (K562/BCRP) cells.



Syntheses and properties of the major hydroxy metabolites in humans of blonanserin AD-5423, a novel antipsychotic agent

pp 1055–1059

Takeshi Ochi,* Masato Sakamoto, Akira Minamida, Kenji Suzuki, Tomohiko Ueda, Teruaki Une, Hiroshi Toda, Kazuya Matsumoto and Yoshiaki Terauchi

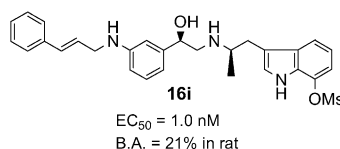


Two hydroxy metabolites in humans of blonanserin was synthesized. The optical resolution, structure, and biological results of these metabolites were also reported.

Tryptamine-based human β_3 -adrenergic receptor agonists. Part 3: Improved oral bioavailability via modification of the sulfonamide moiety

pp 1061–1064

Masaaki Sawa,* Kazuhiro Mizuno, Hiroshi Harada, Hirotaka Tateishi, Yukiyo Arai, Shinya Suzuki, Mayumi Oue, Hiroshi Tsujiuchi, Yasuji Furutani and Shiro Kato

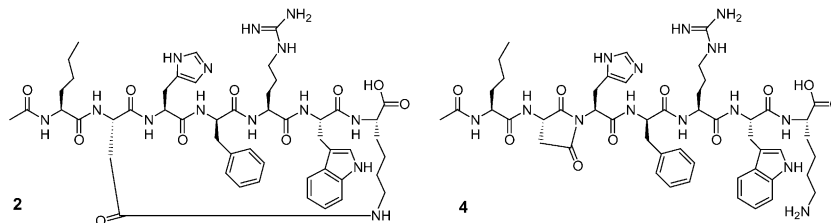


A series of tryptamine-based human β_3 -adrenergic receptor (AR) agonists were synthesized in an effort to improve oral bioavailability. Cinnamylamine analog **16i** exhibited an excellent agonistic profile in vitro and good oral bioavailability in rats.

Detection and control of aspartimide formation in the synthesis of cyclic peptides

pp 1065–1068

David Flora, Huaping Mo, John P. Mayer, M. Amin Khan and Liang Z. Yan*



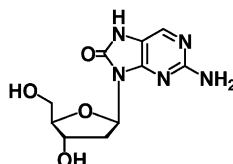
A method was developed to diagnose and minimize aspartimide formation during the synthesis of cyclic peptides on solid phase. Peptide **2** was prepared with minimal byproduct **4**.



Synthesis and incorporation into DNA fragments of the artificial nucleobase, 2-amino-8-oxopurine

pp 1069–1073

Claudio Cadena-Amaro, Muriel Delepierre and Sylvie Pochet*



The synthesis of 2-amino-9-(2-deoxy- β -D-ribofuranosyl)-7,8-dihydro-8-oxo-purine (dJ) and its incorporation into DNA via a convertible phosphoramidite are reported. The thermal stability of heteroduplexes containing J has been studied by UV thermal-denaturation experiments.

Design, synthesis, and evaluation of oxazole transthyretin amyloidogenesis inhibitors

pp 1075–1078

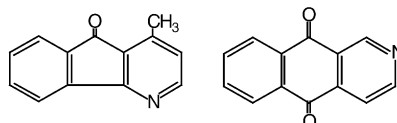
Hossein Razavi, Evan T. Powers, Hans E. Purkey, Sara L. Adamski-Werner, Kyle P. Chiang, Maria T. A. Dendle and Jeffery W. Kelly*

The C(2) 3,5-dichlorophenyl-, C(4) carboxyl-, C(5) alkyl-substituted oxazole derivatives synthesized in this study exhibit substantial transthyretin fibril formation inhibition activity in vitro and acceptable binding selectivity in human plasma making them appealing drug candidates against neuropathologies associated with transthyretin amyloidogenesis.

**Structure–activity relations of azafluorenone and azaanthraquinone as antimicrobial compounds**

pp 1079–1082

Junko Koyama,* Izumi Morita, Norihiro Kobayashi, Toshiyuki Osakai, Yoshinosuke Usuki and Makoto Taniguchi



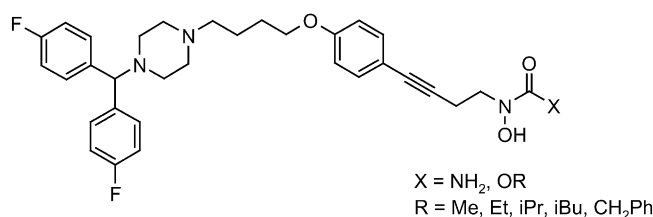
Antimicrobial activities of azafluorenones, 1-azaanthraquinones, and 2-azaanthraquinones were tested.

5-Lipoxygenase inhibition by *N*-hydroxycarbamates in dual-function compounds

pp 1083–1085

Timothy A. Lewis,* Lynn Bayless, Alan J. DiPesa, Joseph B. Eckman, Michel Gillard, Lyn Libertine, Ralph T. Scannell, Donna M. Wypij and Michelle A. Young

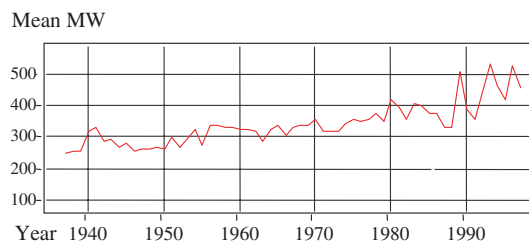
A series of *N*-hydroxycarbamates containing a histaminergic H₁ receptor antagonist pharmacophore was synthesized. The compounds possessed both antihistaminergic and 5-lipoxygenase inhibiting activities in vitro comparable to the corresponding *N*-hydroxyurea analog. Both activities were demonstrated in animal models with selected *N*-hydroxycarbamates.

**The evolution of synthetic oral drug properties**

pp 1087–1090

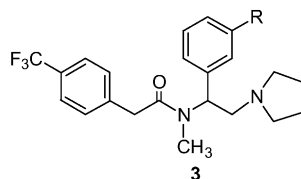
John R. Proudfoot*

The mean molecular weight of synthetic oral drugs has increased substantially over the past 60 years. Fewer than 5% of oral drugs approved or marketed since 1937 have more than 4-H bond donors and only 2% have MW > 500 and >3 H-bond donors.



Synthesis and evaluation of novel peripherally restricted κ -opioid receptor agonists**pp 1091–1095**

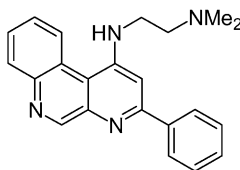
Virendra Kumar,* Deqi Guo, Joel A. Cassel, Jeffrey D. Daubert, Robert N. DeHaven, Diane L. DeHaven-Hudkins, Erin K. Gauntner, Susan L. Gottshall, Susan L. Greiner, Michael Koblish, Patrick J. Little, Erik Mansson and Alan L. Maycock



Analogs (**3**) of parent compound **1** ($R = H$) were prepared as novel potent kappa receptor agonists with improved peripheral restriction indices (platform sedation ED_{50} /writhing ED_{50}).

New triple-helix DNA stabilizing agents**pp 1097–1100**

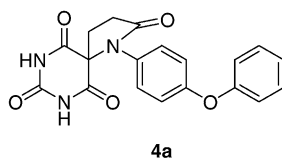
Lucjan Strekowski,* Maryam Hojjat, Ewa Wolinska, Alesia N. Parker, Ekaterina Paliakov, Tadeusz Gorecki, Farial A. Tanious and W. David Wilson*



$\Delta T_m = 27.5\text{ }^{\circ}\text{C}$ for polydA·2polydT; $\Delta T_m = 0.0\text{ }^{\circ}\text{C}$ for polydA·polydT.

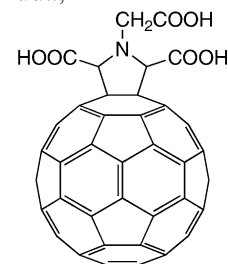
Structure-based design of potent and selective inhibitors of collagenase-3 (MMP-13)**pp 1101–1106**

Soong-Hoon Kim,* Andrew T. Pudzianowski, Kenneth J. Leavitt, Joseph Barbosa, Patricia A. McDonnell, William J. Metzler, Bruce M. Rankin, Richard Liu, Wayne Vaccaro and William Pitts

**Human immunodeficiency virus-reverse transcriptase inhibition and hepatitis C virus RNA-dependent RNA polymerase inhibition activities of fullerene derivatives****pp 1107–1109**

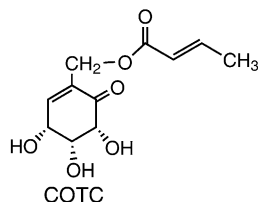
Tadahiko Mashino,* Kumiko Shimotohno, Noriko Ikegami, Dai Nishikawa, Kensuke Okuda, Kyoko Takahashi, Shigeo Nakamura and Masataka Mochizuki

We examined the human immunodeficiency virus-reverse transcriptase and hepatitis C virus RNA-dependent RNA polymerase inhibition activities of cationic, anionic, and amino acid-type fullerene derivatives. Among the fullerene derivatives, the amino acid-type fullerene derivative was the most efficient in human immunodeficiency virus-reverse transcriptase inhibition.



Reversal of anticancer drug resistance by COTC based on intracellular glutathione and glyoxalase I pp 1111–1114

Daisuke Kamiya, Yuki Uchihata, Eiko Ichikawa,* Kuniti Kato and Kazuo Umezawa

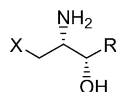


Inhibitor of Glyoxalase I

Synthesis and biological properties of novel sphingosine derivatives

pp 1115–1119

Teiichi Murakami,* Kiyotaka Furusawa, Tadakazu Tamai,* Kazuyoshi Yoshikai and Masazumi Nishikawa

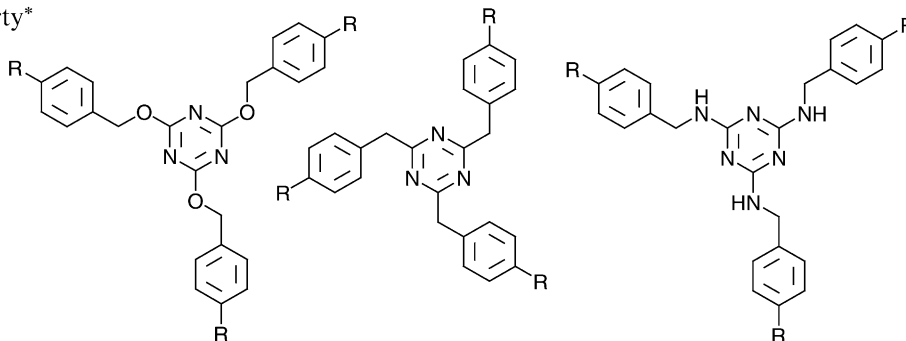
(R: *n*-alk-1-enyl, styryl, aryl; X: OPO₃H₂, Br)

Sphingosine-1-phosphate (S-1P) derivatives such as *threo*-(2*S*,3*S*)-S-1Ps and *threo*-(1*S*,2*R*)-2-amino-1-aryl-3-bromopropanols have been prepared. These *threo*-amino alcohols have shown potent inhibitory activity against Ca²⁺ ion increases in HL60 cells induced by natural *erythro*-S-1P.

Synthesis and antibacterial activity of 2,4,6-tri substituted *s*-triazines

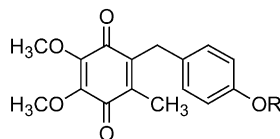
pp 1121–1123

K. Srinivas, U. Srinivas, V. Jayathirtha Rao,* K. Bhanuprakash,* K. Hara Kishore and U. S. N. Murty*

**2,3-Dimethoxy-5-methyl-1,4-benzoquinones and 2-methyl-1,4-naphthoquinones: glycation inhibitors with lipid peroxidation activity**

pp 1125–1129

Young-Sik Jung,* Bo-Young Joe, Sung Ju Cho and Yasuo Konishi

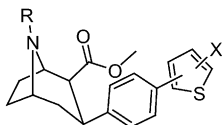


Anti-glycation activity of our anti-oxidant quinone library was measured and several 2,3-dimethoxy-5-methyl-1,4-benzoquinones and 2-methyl-1,4-naphthoquinones were identified as novel inhibitors of glycation.

Synthesis and monoamine transporter affinity of new 2 β -carbomethoxy-3 β -[4-(substituted thiophenyl)]phenyltropanes: discovery of a selective SERT antagonist with picomolar potency

pp 1131–1133

Gilles Tamagnan,* David Alagille, Xing Fu, Nora S. Kula, Ross J. Baldessarini, Robert B. Innis and Ronald M. Baldwin


4b: SERT K_i = 17 pM
 Selectivity DAT/SERT = 710

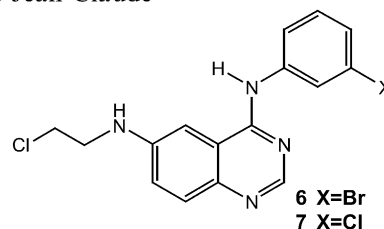
We report the synthesis and monoamine transporter affinity of 10 new 2 β -carbomethoxy-3 β -[4-(substituted thiophenyl)]phenyltropanes. Among these, compound **4b** exhibited very high affinity for the serotonin transporter (SERT: K_i = 17 pM).

Synthesis of half-mustard combi-molecules with fluorescence properties: correlation with EGFR status

pp 1135–1138

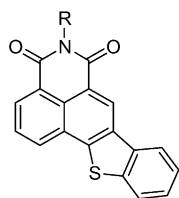
Zakaria Rachid, Fouad Brahimi, Juozas Domarkas and Bertrand Jacques Jean-Claude*

The synthesis of 6-(2-chloroethylamino)-4-anilinoquinazolines (ZR2002 and ZR2003) designed to block EGFR tyrosine kinase and to damage genomic DNA is described. These compounds present fluorescence properties that permitted the quantitation of their subcellular uptake by flow cytometry. Fluorescence intensities increased with increasing levels of EGFR in a panel of isogenic and established cell lines.


Five-member thio-heterocyclic fused naphthalimides with aminoalkyl side chains: intercalation and photocleavage to DNA

pp 1139–1142

Yufang Xu, Baoyuan Qu, Xuhong Qian* and Yonggang Li


B₁ R=CH₂CH₂N(CH₃)₂
B₂ R=CH₂CH₂CH₂N(CH₃)₂
B₃ R=CH₂CH₂N(CH₂)₄NH

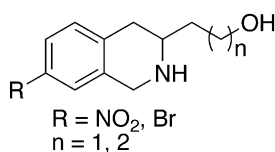
B₄ R=CH₂CH₂CH₂CH₃

Several photocleavers of five-member thio-heterocyclic fused naphthalimides are designed, synthesized and evaluated.

Exploring the active site of phenylethanolamine *N*-methyltransferase with 3-hydroxyethyl- and 3-hydroxypropyl-7-substituted-1,2,3,4-tetrahydroisoquinolines

pp 1143–1147

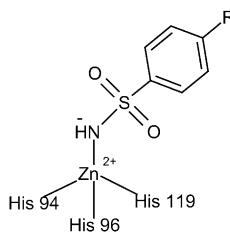
Gary L. Grunewald,* F. Anthony Romero, Mitchell R. Seim, Kevin R. Criscione, Jean D. Deupree, Christy C. Spackman and David B. Bylund



Carbonic anhydrase inhibitors. Inhibition of the membrane-bound human and bovine isozymes IV with sulfonamides

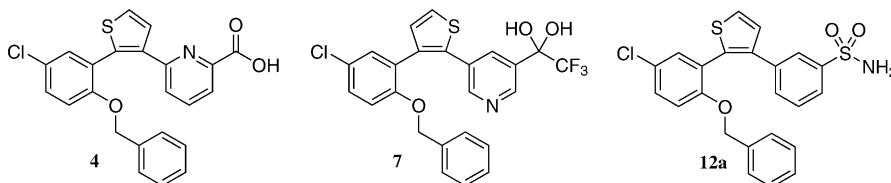
pp 1149–1154

Alessio Innocenti, Michael A. Firnges, Jochen Antel,* Michael Wurl, Andrea Scozzafava and Claudiu T. Supuran*

**2,3-Diarylthiophenes as selective EP₁ receptor antagonists**

pp 1155–1160

Yves Ducharme,* Marc Blouin, Marie-Claude Carrière, Anne Chateaufneuf, Bernard Côté, Danielle Denis, Richard Frenette, Gillian Greig, Stacia Kargman, Sonia Lamontagne, Evelyn Martins, François Nantel, Gary O'Neill, Nicole Sawyer, Kathleen M. Metters and Richard W. Friesen



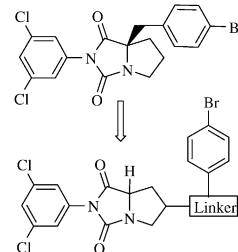
The synthesis and biological activity of a novel series of EP₁ receptor antagonists is reported. SAR studies in this series led to the identification of optimized inhibitors **4**, **7**, and **12a**.

De novo design, synthesis, and in vitro activity of LFA-1 antagonists based on a bicyclic[5.5]hydantoin scaffold

pp 1161–1164

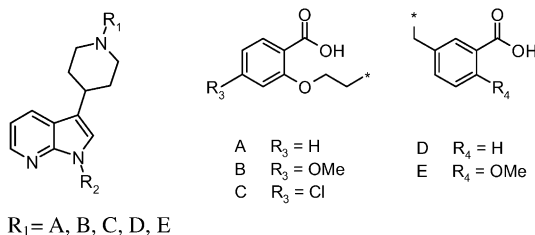
Dominique Potin, Michele Launay, Eric Nicolai, Maud Fabreguette, Patrice Malabre, François Caussade, Dominique Besse, Stacey Skala, Dawn K. Stetsko, Gordon Todderud, Brett R. Beno, Daniel L. Cheney, Chiehying J. Chang, Steven Sheriff, Diane L. Hollenbaugh, Joel C. Barrish, Edwin J. Iwanowicz, Suzanne J. Suchard and T. G. Murali Dhar*

LFA-1 is a member of the $\beta 2$ -integrin family and is expressed on all leukocytes. This paper describes the de novo design, synthesis, and in vitro activity of LFA-1 antagonists based on a bicyclic[5.5]hydantoin scaffold.

**Synthesis and structure–activity relationships of piperidinylpyrrolopyridine derivatives as potent and selective H₁ antagonists**

pp 1165–1167

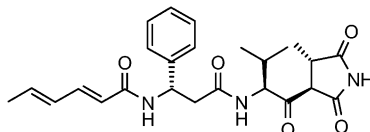
Silvia Fonquerna,* Montse Miralpeix,* Lluís Pagès, Carles Puig, Arantxa Cardús, Francisca Antón, Dolors Vilella, Mónica Aparici, José Prieto, Graham Warreallow, Jorge Beleta and Hamish Ryder



Pyrrolidinedione derivatives as antibacterial agents with a novel mode of action

pp 1189–1192

Jens Pohlmann, Thomas Lampe, Mitsuyuki Shimada, Peter G. Nell, Josef Pernerstorfer, Niels Svenstrup, Nina A. Brunner, Guido Schiffer and Christoph Freiberg*

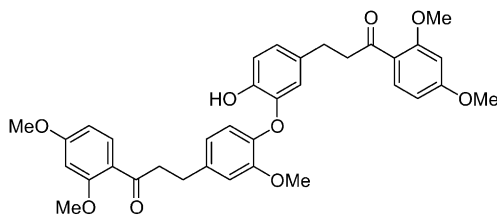


Pyrrolidinediones represent a new class of antibiotics that target bacterial fatty acid biosynthesis. Structure–activity relationships for the pyrrolidinedione group and the fatty acid side chain are described.

Effects of a verbenachalcone derivative on neurite outgrowth, inhibition of caspase induction and gene expression

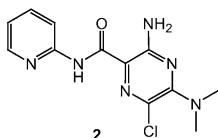
pp 1193–1196

Li-An Yeh, Deppa Padmanaban, Pei Ho, Xeuchao Xing, Patricia Rowley, Lee Jae Morse, Roderick V. Jensen and Gregory D. Cuny*

**Dipyridyl amides: potent metabotropic glutamate subtype 5 (mGlu5) receptor antagonists**

pp 1197–1200

Céline Bonnefous,* Jean-Michel Vernier, John H. Hutchinson, Janice Chung, Grace Reyes-Manalo and Theodore Kamenecka

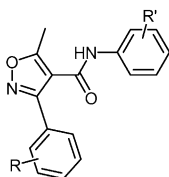


The mGlu5 receptor has been implicated in a number of CNS disorders. Herein, we report on the discovery, synthesis, and biological evaluation of dipyridyl amides as small molecules mGluR5 antagonists.

Synthesis and structure–activity relationships of isoxazole carboxamides as growth hormone secretagogue receptor antagonists

pp 1201–1204

Zhili Xin,* Hongyu Zhao, Michael D. Serby, Bo Liu, Verlyn G. Schaefer, Douglas H. Falls, Wiweka Kaszubska, Christine A. Colins, Hing L. Sham and Gang Liu



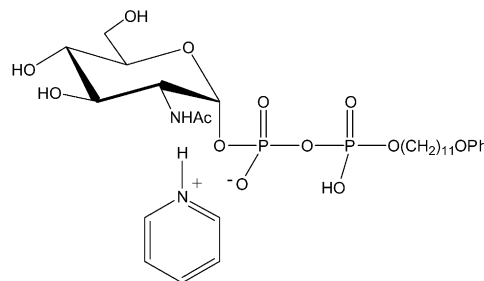
A series of isoxazole carboxamide derivatives has been developed as potent ghrelin receptor antagonists. The synthesis and structure–activity relationships (SAR) are described.

Identification of a UDP-Gal: GlcNAc-R galactosyltransferase activity in *Escherichia coli* VW187

pp 1205–1211

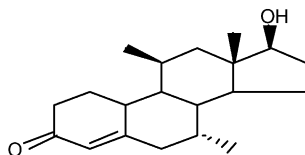
Pedro J. Montoya-Peleaz, John G. Riley, Walter A. Szarek, Miguel A. Valvano,
John S. Schutzbach and Inka Brockhausen*

The paper reports the synthesis of a GlcNAc α -pyrophosphate, covalently bound to a phenoxyundecyl moiety, and its use as an acceptor substrate in a novel assay for a galactosyltransferase from *Escherichia coli*.

**7 α ,11 β -Dimethyl-19-nortestosterone: a potent and selective androgen response modulator with prostate-sparing properties**

pp 1213–1216

C. Edgar Cook* and John A. Kepler*

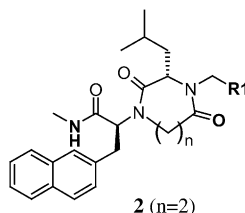


7 α ,11 β -Dimethyl-19-nortestosterone, made by 1,6-methyl addition to 17 β -acetoxy-11 β -methylestra-4,6-dien-3-one, was a highly potent and selective androgen response modulator. It had enhanced androgen receptor binding, androgenic activity, and anabolic:androgenic ratio over its two monomethyl homologs.

1,4-Diazepane-2,5-diones as novel inhibitors of LFA-1

pp 1217–1220

Sompong Wattanasin,* Joerg Kallen, Stewart Myers, Qin Guo, Michael Sabio, Claus Ehrhardt,
Rainer Albert, Ulrich Hommel, Gisbert Weckbecker, Karl Welzenbach and Gabriele Weitz-Schmidt

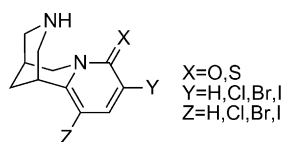


1,4-Diazepane-2,5-diones (**2**) are found to be a new class of potent LFA-1 inhibitors. The synthesis, structure, and biological evaluation of these 1,4-diazepine-2,5-diones and related derivatives are described.

Halogenated and isosteric cytosine derivatives with increased affinity and functional activity at nicotinic acetylcholine receptors

pp 1221–1224

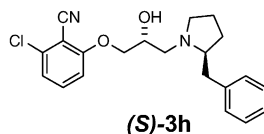
Richard W. Fitch, Yumika Kaneko, Paul Klaparski, John W. Daly,* Gunther Seitz and Daniela Gündisch



A series of derivatives of (7*R*,9*S*)-(–)-cytosine were evaluated for affinity and function at several subtypes of nicotinic receptors. Substitution-dependent changes in potency, efficacy, and selectivity were seen.

Discovery and structure–activity relationships of 2-benzylpyrrolidine-substituted aryloxypropanols as calcium-sensing receptor antagonists pp 1225–1228

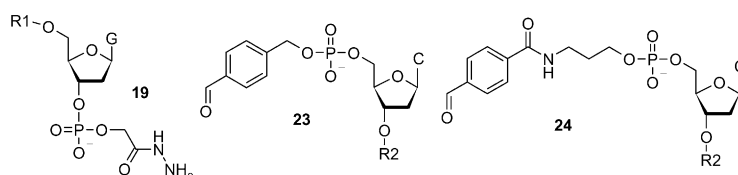
Wu Yang,* Yufeng Wang, Jacques Y. Roberge, Zhengping Ma, Yalei Liu, R. Michael Lawrence, David P. Rotella, Ramakrishna Seethala, Jean H. M. Feyen and John K. Dickson, Jr.



A novel series of calcium-sensing receptor antagonists was prepared as exemplified by (S)-3h. This new compound showed comparable potency to NPS-2143 as a calcium-sensing receptor antagonist but possessed reduced hERG blocking activity.

Kinetic model studies on the chemical ligation of oligonucleotides via hydrazone formation pp 1229–1233

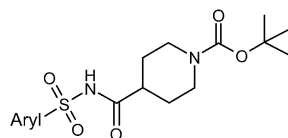
K. Achilles and G. v. Kiedrowski*



The synthesis of new 3'- and 5'-hydrazide- and aldehyde-modified oligonucleotides and the suitability of hydrazone formation for activator-free ligation of oligonucleotides is reported.

N-Acyl arylsulfonamides as novel, reversible inhibitors of human steroid sulfatase pp 1235–1238

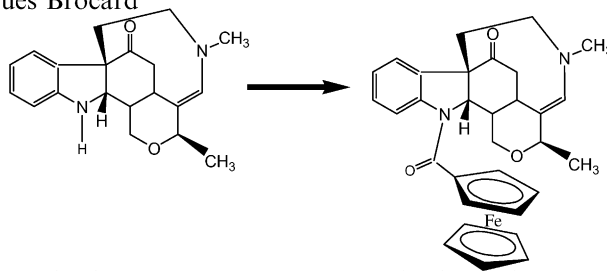
Philipp Lehr, Andreas Billich, Barbara Wolff and Peter Nussbaumer*



The discovery and structure–activity relationships for this novel class of STS inhibitors are presented.

Synthesis and chloroquine-enhancing activity of N_a-deacetyl-ferrocenoyl-strychnobrasiline pp 1239–1241

Dorothee Razafimahefa, Lydie Péliniski,* Marie-Thérèse Martin, David Ramanitrahasimbola, Philippe Rasoanaivo* and Jacques Brocard

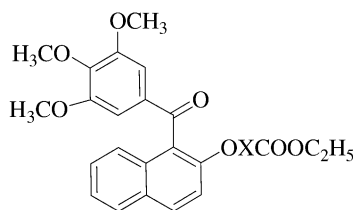


The synthesis (yield 22%) as well as the in vitro ($IC_{50} = 4.83 \mu\text{g/mL}$) and in vivo antiparasmodial and chemosensitizing activities of N_a-deacetyl-ferrocenoyl-strychnobrasiline are reported.

Synthesis of a novel plant growth promoter from gallic acid

pp 1243–1247

Arvind Singh Negi,* Mahinder P. Darokar, Sunil K. Chattopadhyay, Ankur Garg,
Asish K. Bhattacharya, Vandana Srivastava and Suman P. S. Khanuja

**QSAR studies on 1,2-dithiole-3-thiones: modeling of lipophilicity, quinone reductase specific activity, and production of growth hormone**

pp 1249–1255


Padmakar Khadikar,* Mona Jaiswal, Madhu Gupta, Dheeraj Mandloi and Raj Singh Sisodia

Quantitative structure–activity relationship (QSAR) studies on lipophilicity ($\log P$) for a series of 1,2-dithiole-3-thiones have been carried out using distance-based topological indices. In addition, we have also reported QSAR study on modeling quinone reductase specific activity ($\log \text{CDQR}$) and production of growth hormone ($\log \text{CDGH}$). The regression analysis of the data show that this set of compounds exhibit ‘familial’ relationships in that excellent results are obtained by dividing the data set into two classes (families).

OTHER CONTENTS

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Corrigendum	p 1259
Corrigendum	p 1261
Contributors to this issue	pp I–III
Instructions to contributors	pp V–VIII

*Corresponding author

 Supplementary data available via ScienceDirect

COVER

2005: The proteolytic enzyme memapsin 2 (β -secretase, BACE-1) is the protease that cleaves the β -amyloid precursor protein (APP) to produce the 40–42 residue amyloid- β peptide (A β) in the human brain, a key event in the progression of Alzheimer’s disease (AD). The X-ray crystal structure of memapsin 2 complexed with a peptidomimetic cyclic inhibitor is depicted. Inhibitor (green) is in the binding cleft of memapsin 2 shown as a ribbon diagram for the polypeptide backbone [Ghosh, A. K.; Devasamudram, T.; Hong, L.; DeZutter, C.; Xu, X.; Weerasena, V.; Koelsch, G.; Bilcer, G.; Tang, J. *Bioorg. Med. Chem. Lett.* **2005**, 15, 15].

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