

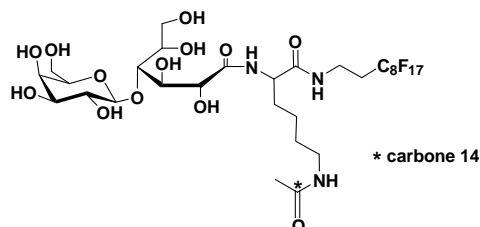
Contents

ARTICLES

Design, synthesis and preliminary biological evaluations of novel amphiphilic drug carriers

pp 1111–1114

Sandrine Périno, Christiane Contino-Pépin,* Sylvain Jasseron, Maryse Rapp,
Jean-Claude Maurizis and Bernard Pucci*



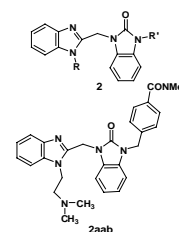
Synthesis and follow-up in mice of a new molecular amphiphilic drug carrier radiolabelled with ^{14}C .

Respiratory syncytial virus fusion inhibitors. Part 3: Water-soluble benzimidazol-2-one derivatives with antiviral activity in vivo

pp 1115–1122

Kuo-Long Yu, Xiangdong Alan Wang, Rita L. Civiello, Ashok K. Trehan,
Bradley C. Pearce, Zhiwei Yin, Keith D. Combrink, H. Belgin Gulgeze, Yi Zhang,
Kathleen F. Kadow, Christopher W. Cianci, Junius Clarke, Eugene V. Genovesi,
Ivette Medina, Lucinda Lamb, Philip R. Wyde, Mark Krystal and Nicholas A. Meanwell*

The introduction of acidic and basic functionality into the side chains R and R' of respiratory syncytial virus (RSV) fusion inhibitors **2** was examined in an effort to identify compounds suitable for evaluation in vivo in the cotton rat model of RSV infection following administration as a small particle aerosol. Several acid-containing compounds demonstrated potent antiviral activity in cell culture and exhibited efficacy in the cotton rat comparable to ribavirin. In a BALB/c mouse model, the amide **2aab** reduced virus titers following oral dosing, establishing the potential of this class of RSV fusion inhibitors to interfere with infection in vivo following topical or systemic administration.

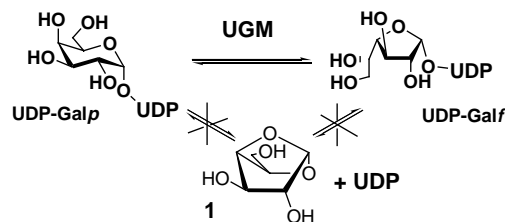


1,4-Anhydrogalactopyranose is not an intermediate of the mutase catalyzed UDP-galactopyranose/furanose interconversion

pp 1123–1125

Audrey Caravano, Pierre Sinaÿ* and Stéphane P. Vincent*

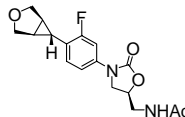
UDP-galactopyranose mutase catalyzes the isomerization of UDP-Galp into UDP-Galf. The involvement of 1,4-anhydrogalactose **1** as intermediate of this ring contraction has been proposed. Our study shows that this hypothesis is not correct.



Conformational constraint in oxazolidinone antibacterials. Part 2: Synthesis and structure–activity studies of oxa-, aza-, and thiabicyclo[3.1.0]hexylphenyl oxazolidinones

pp 1126–1129

Adam R. Renslo,* Hongwu Gao, Priyadarshini Jaishankar, Revathy Venkatachalam, Marcela Gómez, Johanne Blais, Michael Huband, J. V. N. Vara Prasad and Mikhail F. Gordeev

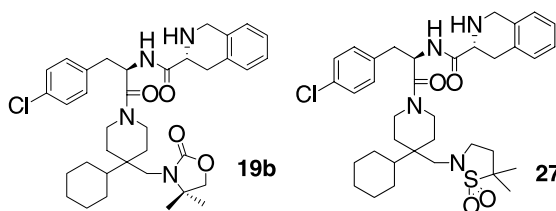


The synthesis and biological activities of novel conformationally constrained oxazolidinone antibacterials are described.

Optimization of a privileged structure leading to potent and selective human melanocortin subtype-4 receptor ligands

pp 1130–1133

Raman K. Bakshi,* Qingmei Hong, Rui Tang, Rubana N. Kalyani, Tanya MacNeil, David H. Weinberg, Lex H. T. Van der Ploeg, Arthur A. Patchett and Ravi P. Nargund

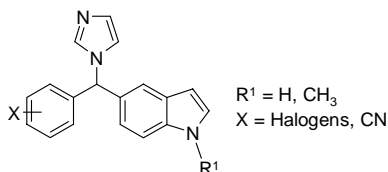


The design and synthesis of potent MC4 agonists **19b** and **27** are reported.

Synthesis and biological evaluation of 5-[(aryl)(1*H*-imidazol-1-yl)methyl]-1*H*-indoles: Potent and selective aromatase inhibitors

pp 1134–1137

Marie-Pierre Lézé,* Marc Le Borgne, Patricia Pinson, Anja Paluszczak, Muriel Duflos, Guillaume Le Baut and Rolf W. Hartmann

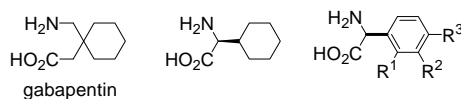


The synthesis and the aromatase (CYP19) inhibitory activity of 5-[(aryl)(imidazol-1-yl)methyl]-1*H*-indoles were reported. Among racemate compounds tested, 5-[(4-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-indole **8b** emerged as potent CYP19 inhibitor (IC₅₀ = 15.3 nM). And one of its enantiomers **8b2** was found to be more active (IC₅₀ = 9 nM).

Structure–activity relationships of α -amino acid ligands for the $\alpha_2\delta$ subunit of voltage-gated calcium channels

pp 1138–1141

Kathleen H. Mortell,* David J. Anderson, James J. Lynch, III, Sherry L. Nelson, Kathy Sarris, Heath McDonald, Reza Sabet, Scott Baker, Prisca Honore, Chih-Hung Lee, Michael F. Jarvis and Murali Gopalakrishnan

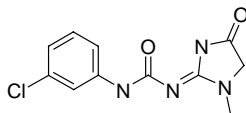


Phenyl ureas of creatinine as mGluR5 antagonists.

pp 1142–1145

A structure–activity relationship study of fenobam analogues

Andreas Wällberg,* Karolina Nilsson, Krister Österlund, Alecia Peterson, Susanne Elg, Patrick Raboisson, Udo Bauer, Lance G. Hammerland and Jan P. Mattsson

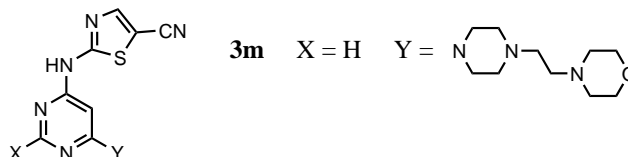


Structure–activity relationship of the mGluR5 antagonist fenobam is reported.

Potent 2-[(pyrimidin-4-yl)amine]-1,3-thiazole-5-carbonitrile-based inhibitors of VEGFR-2 (KDR) kinase pp 1146–1150

John T. Sisko,* Thomas J. Tucker, Mark T. Bilodeau, Carolyn A. Buser, Patrice A. Ciecko, Kathleen E. Coll, Christine Fernandes, Jackson B. Gibbs, Timothy J. Koester, Nancy Kohl, Joseph J. Lynch, Xianzhi Mao, Debra McLoughlin, Cynthia M. Miller-Stein, Leonard D. Rodman, Keith W. Rickert, Laura Sepp-Lorenzino, Jennifer M. Shipman, Kenneth A. Thomas, Bradley K. Wong and George D. Hartman

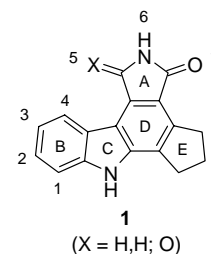
Pyrimidino-thiazolyl carbonitriles were prepared that are potent VEGFR-2 (KDR) kinase inhibitors. The modification of lead structures resulted in **3m** which exhibited the best overall profile in KDR inhibitory activity, iv/po pharmacokinetics, and reduced hERG affinity.

**Synthesis and structure–activity relationships of novel pyrrolo-carbazole lactam analogs as potent and cell-permeable inhibitors of poly(ADP-ribose)polymerase-1 (PARP-1)**

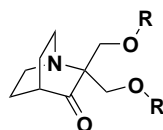
pp 1151–1155

Gregory J. Wells,* Ron Bihovsky, Robert L. Hudkins, Mark A. Ator and Jean Husten

A series of novel pyrrolo-carbazole lactams was identified as potent PARP-1 inhibitors in vitro and in a PC12 cellular NAD⁺ depletion assay. The SAR trends of substituents at the 3-position, as well as the effect of blocking the indole or lactam NH-groups of the template by methylation or formylation, are discussed in relation to molecular modeling studies.

**Structure–activity studies of quinuclidinone analogs as anti-proliferative agents in lung cancer cell lines** pp 1156–1159

Ahmed Malki, Aravinda B. Pulipaka, Susan C. Evans and Stephen C. Bergmeier*

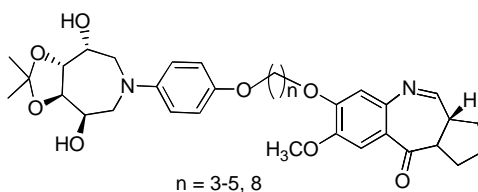


Several 2,2-disubstituted quinuclidinone analogs were prepared and evaluated as anti-proliferative agents.

Synthesis and DNA-binding ability of pyrrolo[2,1-c][1,4]benzodiazepine-azepane conjugates

pp 1160–1163

Ahmed Kamal,* D. Rajasekhar Reddy and P. S. Murali Mohan Reddy, Rajendar

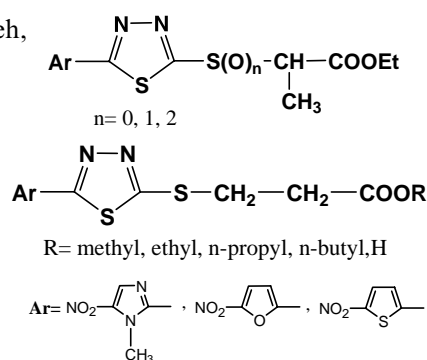
**Synthesis and antimycobacterial activity of some alkyl**

pp 1164–1167

[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio]propionates

Alireza Foroumadi,* Zahra Kargar, Amirhossein Sakhteman, Zahra Sharifzadeh, Robabeh Feyzmohammadi, Mahnoush Kazemi and Abbas Shafiee

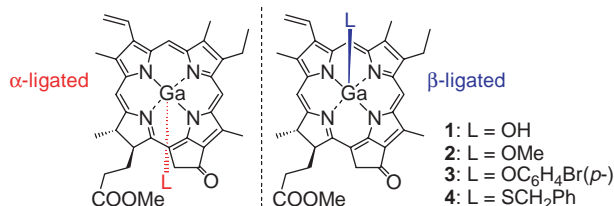
Two series of 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl, and sulfonyl] propionic acid alkyl esters were synthesized and screened for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv, among which compound **7i** was the most active ($MIC = 1.56 \mu g ml^{-1}$).

**Gallium(III) complexes of methyl pyropheophorbide-*a* as synthetic models for investigation of diastereomerically controlled axial ligation towards chlorophylls**

pp 1168–1171

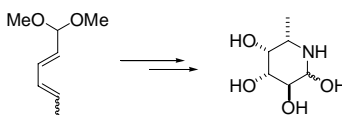
Shin-ichi Sasaki, Tadashi Mizoguchi and Hitoshi Tamiaki*

A pair of diastereomeric Ga(III) chlorophyll derivatives **1–4** arising from the fifth axial coordination onto the asymmetric chlorin π -macrocycle could be discriminated by NMR spectroscopy in solution.

**Asymmetric synthesis of the L-fuco-nojirimycin, a nanomolar α -L-fucosidase inhibitor**

pp 1172–1174

Mathieu Dubernet, Albert Defoin* and Céline Tarnus

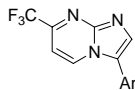


The L-fuco-nojirimycin was synthesised starting from asymmetric hetero-Diels–Alder reaction with chiral D-ribose nitroso-dienophiles. It appears as a very potent α -L-fucosidase inhibitor ($K_i = 1 \text{ nM}$).

Imidazo[1,2-*a*]pyrimidines as functionally selective GABA_A ligands

pp 1175–1179

Wesley P. Blackaby,* John R. Atack, Frances Bromidge, José L. Castro, Simon C. Goodacre, David J. Hallett, Richard T. Lewis, George R. Marshall, Andrew Pike, Alison J. Smith, Leslie J. Street, David F. D. Tattersall and Keith A. Wafford

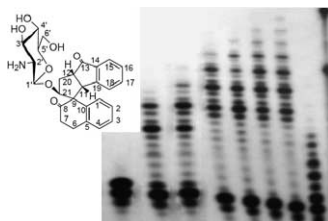


Imidazo[1,2-*a*]pyrimidines are GABA_A receptor benzodiazepine binding site ligands which can exhibit functional selectivity for the α_3 subtype over the α_1 subtype. SAR studies to optimize this functional selectivity are described.

Stimulation on DNA triplet repeat strand slippage synthesis by the designed spirocycles

pp 1180–1184

Zhen Xi,* Di Ouyang and Hong-Tao Mu



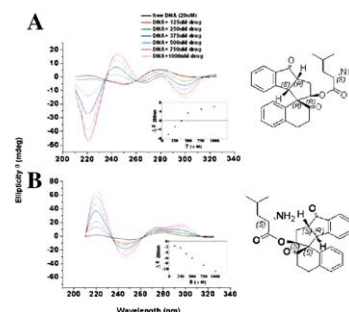
The designed chiral spirocyclic helical compounds have been found to have strong stimulation effect on DNA triplet repeat strand slippage synthesis. Their stimulation activities on DNA strand slippage show that they may bind to or induce the formation of a bulge or related structure during in vitro replication of DNA triplet repeats.

**Interaction of bulged DNA with leucine-containing mimics of NCSi-chrom**

pp 1185–1190

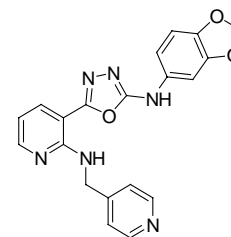
Zhen Xi,* Di Ouyang and Hong-Tao Mu

Synthesis of chiral spirocyclic helical compounds containing leucine that mimic the core of DNA bulge binder NCSi-gb has been described. The interaction between the compounds and DNA was studied by circular dichroism (CD). The results suggested that the two synthetic diastereoisomers **7** and **8** specifically targeted the bulge site of DNA and induced conformational change of bulged DNA greatly.

**Oxadiazole derivatives as a novel class of antimetabolic agents: Synthesis, inhibition of tubulin polymerization, and activity in tumor cell lines**

pp 1191–1196

Xiaohu Ouyang,* Evgueni L. Piatnitski, Vatee Pattaropong, Xiaoling Chen, Hai-Ying He, Alexander S. Kiselyov, Avdhoot Velankar, Joel Kawakami, Marc Labelle, Leon Smith II, Julia Lohman, Sui Ping Lee, Asra Malikzay, James Fleming, Jason Gerlak, Ying Wang, Robin L. Rosler, Kai Zhou, Stan Mitelman, Margarita Camara, David Surguladze, Jacqueline F. Doody and M. Carolina Tuma



EC₅₀ (MDR cell line) = 7.8 nM

The synthesis, SAR studies, and pharmacokinetic properties of oxadiazole based tubulin inhibitor class are reported. This class of compounds binds to the colchicine site on tubulin and has antimetabolic activity with nanomolar potency against tumor cell lines including cells with MDR phenotype.

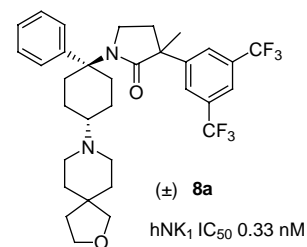


Novel lactam NK₁ antagonists with anti-emetic activity

pp 1197–1201

Gregory J. Hollingworth,* Emma J. Carlson, José L. Castro, Gary G. Chicchi, Natalie Clark, Laura C. Cooper, Olivier Dirat, Jerry Di Salvo, Jason M. Elliott, Ruth Kilburn, Marc M. Kurtz, Wayne Rycroft, F. David Tattersall, Kwei-Lan Tsao and Christopher J. Swain

The discovery of potent NK₁ antagonists such as **8a** is reported. Compound **8a** displays good activity in a ferret emesis model.

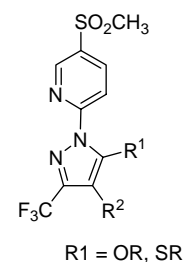
**5-Heteroatom-substituted pyrazoles as canine COX-2 inhibitors:**

pp 1202–1206

Part 2. Structure–activity relationship studies of 5-alkylethers and 5-thioethers

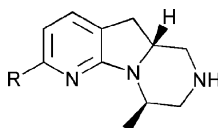
Subas M. Sakya,* Hengmiao Cheng, Kristin M. Lundy DeMello, Andrei Shavnya, Martha L. Minich, Bryson Rast, Jason Dutra, Chao Li, Robert J. Rafka, David A. Koss, Jin Li, Burton H. Jaynes, Carl B. Ziegler, Donald W. Mann, Carol F. Petras, Scott B. Seibel, Annette M. Silvia, David M. George, Anne Hickman, Michelle L. Haven and Michael P. Lynch

Structure–activity relationship (SAR) studies of novel 2-[3-trifluoromethyl-5-alkyl(thio)ether pyrazo-1-yl]-5-methanesulfonyl pyridine derivatives for canine COX enzymes are described. The 4-cyano-5-alkyl ethers were found to have excellent potency and selectivity, whereas the 5-thioethers were potent but less selective than the ether analogs in a canine whole blood (CWB) COX-2 assay.

**Synthesis and biological evaluation of novel hexahydro-pyrido[3',2':4,5]pyrrolo[1,2-a]pyrazines as potent and selective 5-HT_{2C} receptor agonists**

pp 1207–1211

Hans G. F. Richter,* D. R. Adams, A. Benardeau, M. J. Bickerdike, J. M. Bentley, T. J. Blench, I. A. Cliffe, C. Dourish, P. Hebeisen, G. A. Kennett, A. R. Knight, C. S. Malcolm, P. Mattei, A. Misra, J. Mizrahi, N. J. T. Monck, J.-M. Plancher, S. Roever, J. R. A. Roffey, S. Taylor and S. P. Vickers

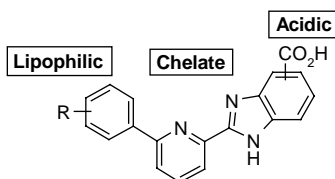


A novel series of chiral 5,5a,6,7,8,9-hexahydro-9-methyl-pyrido[3',2':4,5]pyrrolo[1,2-a]pyrazines as potent and selective 5-HT_{2C} receptor agonists has been discovered. Several analogues had low potential to induce phospholipidosis in vitro and showed low affinity for the hERG potassium channel.

New benzimidazoles as thrombopoietin receptor agonists

pp 1212–1216

Igor G. Safonov,* Dirk A. Heerding, Richard M. Keenan, Alan T. Price, Connie L. Erickson-Miller, Christopher B. Hopson, Jenna L. Levin, Kenneth A. Lord and Peter M. Tapley

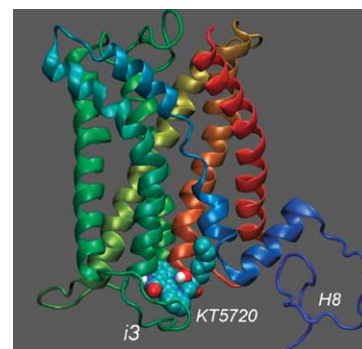


The synthesis and SAR of a novel, rationally designed series of benzimidazole TPO receptor agonists are reported.

The existence of a second allosteric site on the M₁ muscarinic acetylcholine receptor and its implications for drug design

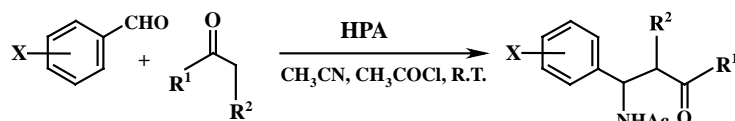
L. Michel Espinoza-Fonseca* and José G. Trujillo-Ferrara

pp 1217–1220

**Heteropoly acids as solid green Brønsted acids for a one-pot synthesis of β-acetamido ketones by Dakin–West reaction**

Ezzat Rafiee,* Fariba Tork and M. Joshaghani

pp 1221–1226

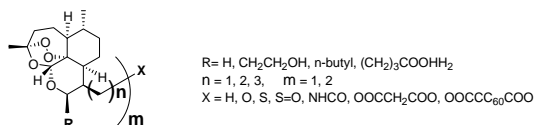


A new and important catalytic activity of HPAs (cheap, commercially available, noncorrosive, and environmentally benign compounds) has been studied for the synthesis of β-acetamido ketones in excellent yields under mild reaction conditions.

Antiangiogenic activity of deoxoartemisinin derivatives on chorioallantoic membrane

Mankil Jung,* Jungae Tak, Won-Yoon Chung and Kwang-Kyun Park

pp 1227–1230

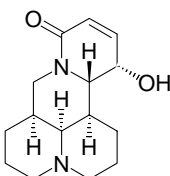


Nonacetal-type derivatives of artemisinin and their novel dimers were synthesized and some of them showed potent in vivo antiangiogenic activity on chorioallantoic membrane higher than or comparable to those of fumagillin and thalidomide.

(+)-12α-Hydroxysophocarpine, a new quinolizidine alkaloid and related anti-HBV alkaloids from *Sophora flavescens*

Pei-Lan Ding, Zhi-Xin Liao, Hai Huang, Pei Zhou and Dao-Feng Chen*

pp 1231–1235



(+)-12α-Hydroxysophocarpine, a new quinolizidine alkaloid was isolated from the roots of *Sophora flavescens*, together with 10 known quinolizidine alkaloids. (+)-Oxysophocarpine, (–)-sophocarpine, (+)-lehmannine and (–)-13,14-dehydrosophoridine showed significant anti-HBV activity in vitro.

Effects of α -tocopherol and related compounds on reactions involving various organic radicals

pp 1236–1239

V. N. Povalishev, G. I. Polozov and O. I. Shadyro*

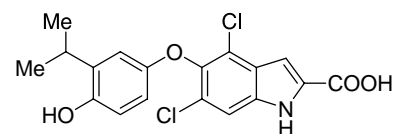
The interaction of various organic radicals with sulfur-containing analogues of α -tocopherol is reported.

Thyroid receptor ligands. Part 5: Novel bicyclic agonist ligands selective for the thyroid hormone receptor β

pp 1240–1244

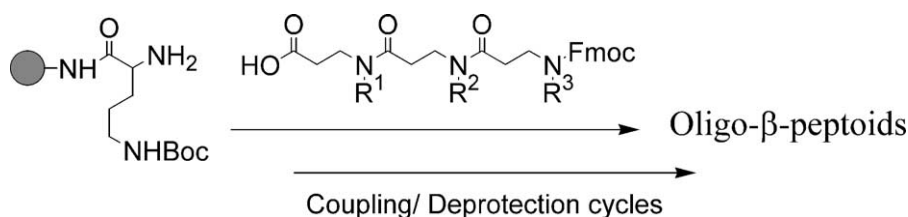
Ana-Maria Garcia Collazo, Konrad F. Koehler, Neeraj Garg, Mathias Färnegårdh, Bolette Husman, Liu Ye, Jan Ljunggren, Karin Mellström, Johnny Sandberg, Marlena Grynfarb, Harri Ahola and Johan Malm*

Based on the examination of the crystal structure of rat TR β complexed with 3,5,3'-triiodo-L-thyronine (**2**), a novel TR β -selective indole derivative **6b** was prepared and tested in vitro. Its β -selectivity could be rationalized through the comparison of the X-ray crystallographic structures of **6b** complexed with TR α and TR β .

**6b** TR α /TR β = 14**Antimicrobial β -peptoids by a block synthesis approach**

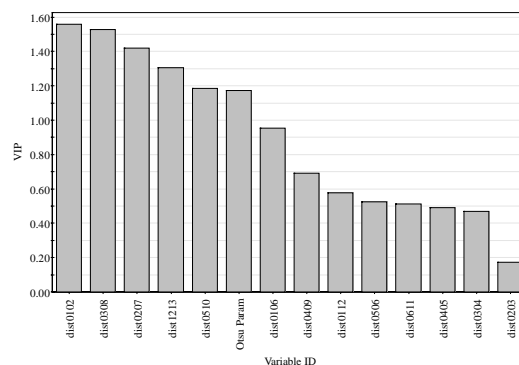
pp 1245–1248

Steven W. Shuey,* William J. Delaney, Mukesh C. Shah and Mark A. Scialdone

**The cytotoxicity of ortho alkyl substituted 4-X-phenols: A QSAR based on theoretical bond lengths and electron densities**

pp 1249–1254

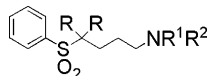
R. J. Loader, N. Singh, P. J. O'Malley and P. L. A. Popelier *



Aminoalkyl phenyl sulfones—a novel series of 5-HT₇ receptor ligands

pp 1255–1258

Piotr Raubo,* Margaret S. Beer, Peter A. Hunt, Ian T. Huscroft, Clare London, Josephine A. Stanton and Janusz J. Kulagowski

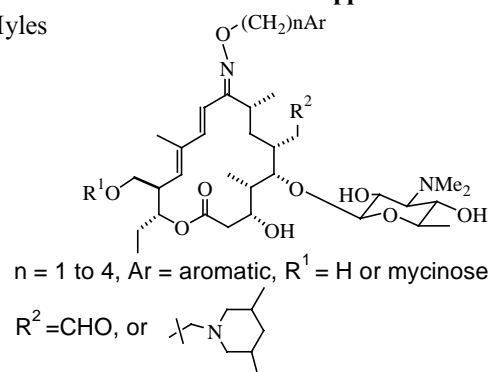


A novel series of 5-HT₇ receptor ligands has been identified and evaluated, providing compounds showing a broad spectrum of functional activities and good selectivity over selected receptors and ion channels.

Synthesis and in vitro antibiotic activity of 16-membered 9-O-arylalkyloxime macrolides

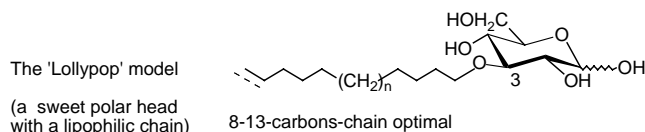
pp 1259–1266

Hong Fu,* Saul Marquez, Xiangrong Gu, Leonard Katz and David C. Myles

**Probing structure/affinity relationships for the *Plasmodium falciparum* hexose transporter with glucose derivatives**

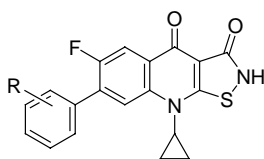
pp 1267–1271

Martine Fayolle, Marina Ionita, Sanjeev Krishna, Christophe Morin* and Asha Parbhu Patel

**Isothiazoloquinolones containing functionalized aromatic hydrocarbons at the 7-position: Synthesis and in vitro activity of a series of potent antibacterial agents with diminished cytotoxicity in human cells**

pp 1272–1276

Jason A. Wiles,* Qiuping Wang, Edlaine Lucien, Akihiro Hashimoto, Yongsheng Song, Jijun Cheng, Christopher W. Marlor, Yangsi Ou, Steven D. Podos, Jane A. Thanassi, Christy L. Thoma, Milind Deshpande, Michael J. Pucci and Barton J. Bradbury*



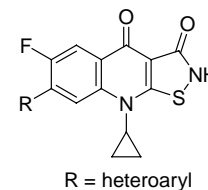
We describe a novel series of isothiazoloquinolones that demonstrate strong antibacterial activity against methicillin-resistant *Staphylococcus aureus* and low cytotoxic activity against a human cell line.

**Biological evaluation of isothiazoloquinolones containing aromatic heterocycles at the 7-position:
In vitro activity of a series of potent antibacterial agents that are effective against
methicillin-resistant *Staphylococcus aureus***

pp 1277–1281

Jason A. Wiles,* Yongsheng Song, Qiuping Wang, Edlaine Lucien, Akihiro Hashimoto,
Jijun Cheng, Christopher W. Marlor, Yangsi Ou, Steven D. Podos, Jane A. Thanassi,
Christy L. Thoma, Milind Deshpande, Michael J. Pucci and Barton J. Bradbury*

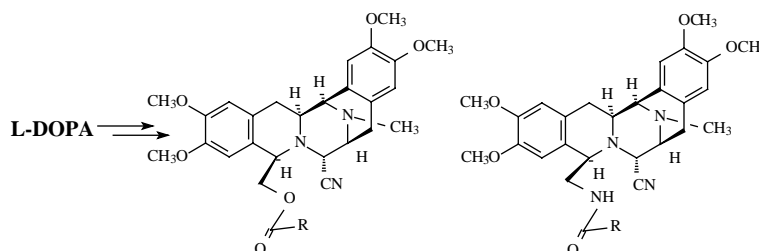
Several of the reported analogues demonstrate strong in vitro antistaphylococcal activity,
particularly against MRSA, and low cytotoxicity.



Synthesis and antitumor activity of simplified ecteinascidin–saframycin analogs

pp 1282–1285

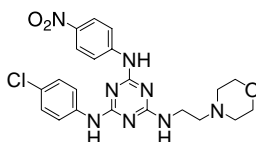
Zhan-Zhu Liu,* Ye Wang, Ye-Feng Tang, Shi-Zhi Chen,
Xiao-Guang Chen and Hong-Yan Li



Triaminotriazine DNA helicase inhibitors with antibacterial activity

pp 1286–1290

Geoffrey A. McKay, Ranga Reddy, Francis Arhin, Adam Belley, Dario Lehoux, Greg Moeck,
Ingrid Sarmiento, Thomas R. Parr, Philippe Gros, Jerry Pelletier and Adel Rafai Far *



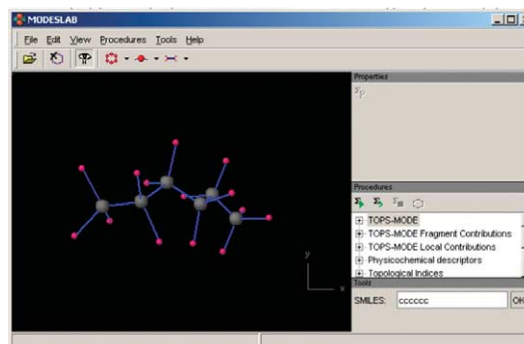
The structure–activity relationships around a *Pseudomonas aeruginosa* DNA helicase triaminotriazine inhibitor in terms of inhibitory and antibacterial activities as well as cytotoxicity toward mammalian cells are presented. Several features of this class of compounds as antibacterials are highlighted.

A topological function based on spectral moments for predicting affinity toward A₃ adenosine receptors

pp 1291–1296

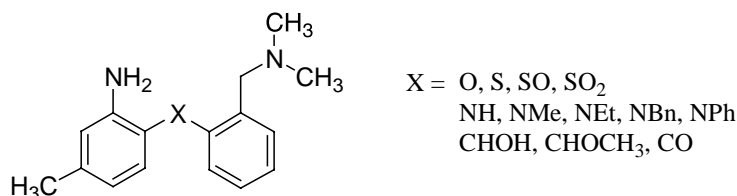
Maykel Pérez González,* Carmen Terán and Marta Teijeira

The spectral moment descriptors have been applied to the study of affinity for A₃ adenosine receptors with excellent results. The fragment contribution shows alert structures that permit the synthesis of new analogues with desirable properties.



Synthesis and in vitro evaluation of novel derivatives of diphenylsulfide as serotonin transporter ligands pp 1297–1300

Johnny Vercoillie, Sylvie Mavel, Laurent Galineau, Tiziana Ragusa, Robert Innis, Michael Kassiou, Sylvie Chalon, Frédéric Dollé, Jean-Claude Besnard, Denis Guilloteau and Patrick Emond*



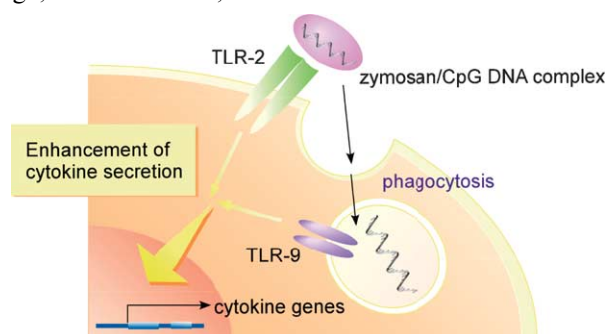
A series of diphenylsulfide derivatives was prepared and their binding affinities for monoamine transporters (SERT, DAT, and NET) are reported.

**CpG DNA/zymosan complex to enhance cytokine secretion owing to the cocktail effect**

pp 1301–1304

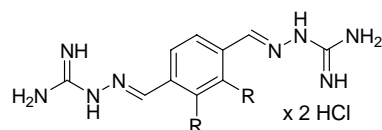
Takahisa Anada,* Naoko Okada, Jusaku Minari, Ryouji Karinaga, Masami Mizu, Kazuya Koumoto, Seiji Shinkai and Kazuo Sakurai

This report presents a new strategy to construct a delivering vehicle for CpG DNA and to enhance its activity with the cocktail effect of the two immunostimulants.

**Novel endotoxin-sequestering compounds with terephthalaldehyde-bis-guanylhydrazone scaffolds**

pp 1305–1308

Kriangsak Khownum, Stewart J. Wood, Kelly A. Miller, Rajalakshmi Balakrishna, Thuan B. Nguyen, Matthew R. Kimbrell, Gunda I. Georg* and Sunil A. David*

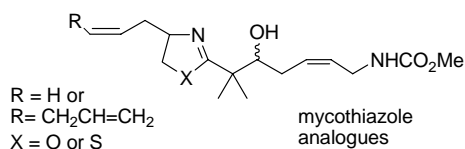


A homologous series of bis-guanylhydrazone compounds decorated with hydrophobic functionalities bind and neutralize lipopolysaccharide (LPS) with a potency comparable to that of polymyxin B, a peptide antibiotic known to sequester LPS.

**Synthesis and biological evaluation of simplified mycothiazole analogues**

pp 1309–1311

Graciela Mahler, Gloria Serra, Sylvia Dematteis, Jenny Saldaña, Laura Domínguez and Eduardo Manta*



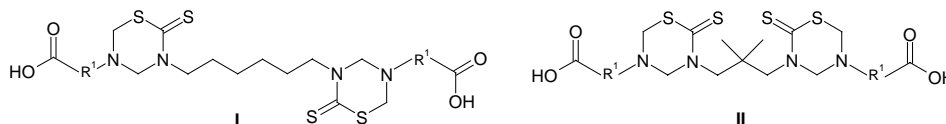
New structurally mycothiazole analogues were synthesized and evaluated against HCT-15 colon tumor cells and L₄ larvae of *Nippostrongylus brasiliensis*.



Alkyl-linked bis-THTT derivatives as potent in vitro trypanocidal agents

pp 1312–1315

Julieta Coro, Richard Atherton, Susan Little, Hayley Wharton, Vanessa Yardley, Amaury Alvarez, Jr., Margarita Suárez, Rolando Pérez* and Hortensia Rodríguez

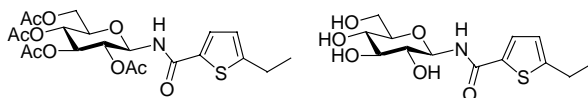


The potent in vitro anti-trypanosomal activity of alkyl-linked bis tetrahydro (2*H*) 1,3,5 thiadiazine 2-thiones (THTT) **I** and **II** is reported.

***N*-Glycosyl-thiophene-2-carboxamides: Effects on endothelial cell growth in the presence and absence of bFGF—A significant increase in potency using per-*O*-acetylated sugar analogues**

pp 1316–1319

Sarah L. Rawe, Violeta Zaric, Kathy M. O' Boyle* and Paul V. Murphy*



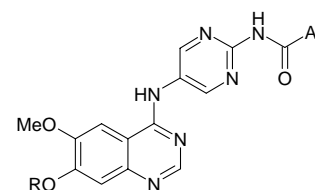
Per-*O*-acetylated-*N*-glucosyl-thiophene-2-carboxamides showed significant inhibition of both serum and bFGF stimulated uptake of [³H]thymidine, when compared to the unprotected analogues.

SAR and inhibitor complex structure determination of a novel class of potent and specific Aurora kinase inhibitors

pp 1320–1323

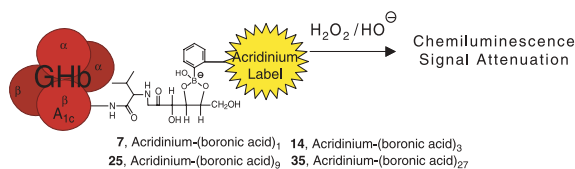
Nicola M. Heron,* Malcolm Anderson, David P. Blowers, Jason Breed, Jonathan M. Eden, Stephen Green, George B. Hill, Trevor Johnson, Frederic H. Jung, Helen H. J. McMiken, Andrew A. Mortlock, Andrew D. Pannifer, Richard A. Pauptit, Jennifer Pink, Nicola J. Roberts and Siân Rowsell

The discovery, optimisation and subsequent structural determination of a novel class of Aurora kinase inhibitors are described.

**Chemiluminescent acridinium-9-carboxamide boronic acid probes: Application to a homogeneous glycosylated hemoglobin assay**

pp 1324–1328

Maciej Adamczyk,* Yon-Yih Chen, Donald D. Johnson, Phillip G. Mattingly, Jeffrey A. Moore, You Pan and Rajarathnam E. Reddy



Antioxidant activity and cytoprotective effect of κ -carrageenan oligosaccharides and their different derivatives

pp 1329–1334

Huamao Yuan, Jinming Song,* Weiwei Zhang, Xuegang Li, Ning Li and Xuelu Gao

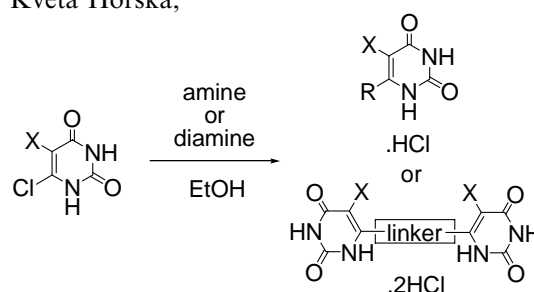
The antioxidant effect both in vitro and in cell-based systems of κ -carrageenan oligosaccharides and their chemically modified derivatives was studied in this paper.

Design and synthesis of novel 5,6-disubstituted uracil derivatives as potent inhibitors of thymidine phosphorylase

pp 1335–1337

Radim Nencka,* Ivan Votruba, Hubert Hřebabeký, Eva Tloušťová, Květa Horská, Milena Masojídková and Antonín Holý

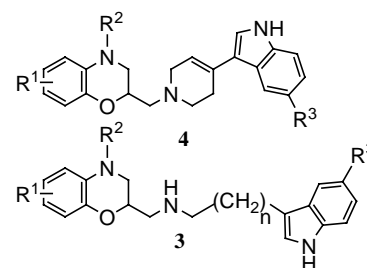
We report on a series of novel 5,6-disubstituted uracils with significant inhibitory activity against human and *Escherichia coli* thymidine phosphorylases.

**Studies toward the discovery of the next generation of antidepressants. Part 5: 3,4-Dihydro-2H-benzo[1,4]oxazine derivatives with dual 5-HT_{1A} receptor and serotonin transporter affinity**

pp 1338–1341

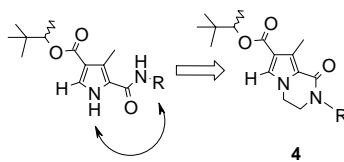
Dahui Zhou,* Boyd L. Harrison, Uresh Shah, Terrance H. Andree, Geoffrey A. Hornby, Rosemary Scerni, Lee E. Schechter, Deborah L. Smith, Kelly M. Sullivan and Richard E. Mewshaw*

The synthesis and structure–activity relationship of two new classes of benzoxazines with dual selective serotonin reuptake inhibitors and 5-HT_{1A} receptor activities are described.

**From pyrroles to pyrrolo[1,2-*a*]pyrazinones: A new class of mGluR1 antagonists**

pp 1342–1345

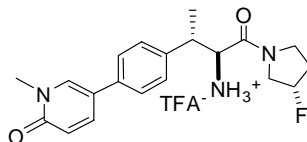
Fabrizio Micheli,* Paolo Cavanni, Romano Di Fabio, Carla Marchioro, Daniele Donati, Stefania Faedo, Micaela Maffei, Fabio Maria Sabbatini and Maria Elvira Tranquillini



A new class of mGluR1 noncompetitive antagonists is reported.

Discovery of potent, selective, and orally bioavailable pyridone-based dipeptidyl peptidase-4 inhibitors pp 1346–1349

Jinyou Xu,* Lan Wei, Robert Mathvink, Scott D. Edmondson, Anthony Mastracchio, George J. Eiermann, Huaibing He, Joseph F. Leone, Barbara Leiting, Kathryn A. Lyons, Frank Marsilio, Reshma A. Patel, Aleksandr Petrov, Joseph K. Wu, Nancy A. Thornberry and Ann E. Weber



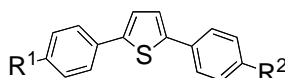
9, DPP-IV IC₅₀ = 34 nM

anti-Substituted biaryl β-methylphenylalanine derived amides have been shown to be potent DPP-4 inhibitors exhibiting excellent selectivity over both DPP8 and DPP9. The optimized compound **9** exhibited good pharmacokinetic profiles in three preclinical species.

Design, synthesis, and structure–activity relationship of novel thiophene derivatives for β-amyloid plaque imaging

pp 1350–1352

Rajesh Chandra, Mei-Ping Kung and Hank F. Kung*



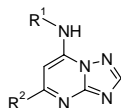
R¹, R² = NH₂, OH or
HN—CH₂—F

Synthesis and SAR of novel 2,5-diphenylthiophene derivatives as Aβ plaque imaging agents are reported. The inhibition constant (K_i) of potent compounds ranges from 3.9 to 10 nM.

Triazolo[1,5-*a*]pyrimidines as novel CDK2 inhibitors: Protein structure-guided design and SAR

pp 1353–1357

Christine M. Richardson,* Douglas S. Williamson, Martin J. Parratt, Jenifer Borgognoni, Andrew D. Cansfield, Pawel Dokurno, Geraint L. Francis, Rob Howes, Jonathan D. Moore, James B. Murray, Alan Robertson, Allan E. Surgenor and Christopher J. Torrance

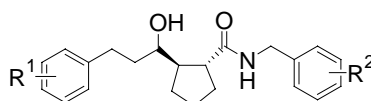


Crystallographic and modelling data, in conjunction with a medicinal chemistry template-hopping approach, led to the identification of a series of novel and potent inhibitors of human cyclin-dependent kinase 2 (CDK2), with selectivity over glycogen synthase kinase-3β (GSK-3β). One example had a CDK2 IC₅₀ of 120 nM and showed selectivity over GSK-3β of 167-fold.

Synthesis and SAR of 1,2-*trans*-(1-hydroxy-3-phenylprop-1-yl)cyclopentane carboxamide derivatives, a new class of sodium channel blockers

pp 1358–1361

Dong Ok,* Chunshi Li, Catherine Abbadie, John P. Felix, Michael H. Fisher, Maria L. Garcia, Gregory J. Kaczorowski, Kathryn A Lyons, William J. Martin, Birgit T. Priest, McHardy M. Smith, Brande S. Williams, Matthew J. Wyvratt and William H. Parsons



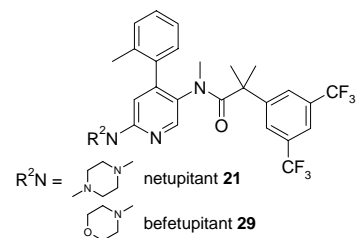
Novel cyclopentane-based 3-phenyl-1-hydroxypropyl compounds were evaluated for inhibitory activity against the peripheral nerve and sodium channel Na_v1.7 and off-target activity against the cardiac potassium channel hERG.

Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists

pp 1362–1365

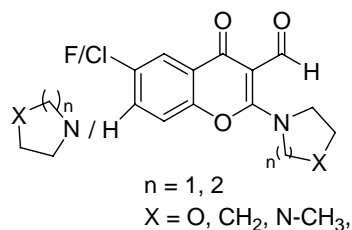
Torsten Hoffmann,* Michael Bös, Heinz Stadler, Patrick Schnider, Walter Hunkeler, Thierry Godel, Guido Galley, Theresa M. Ballard, Guy A. Higgins, Sonia M. Poli and Andrew J. Sleight

The discovery of netupitant **21** and befetupitant **29** is described.

**Design, synthesis, and evaluation of novel 6-chloro-/fluorochromone derivatives as potential topoisomerase inhibitor anticancer agents**

pp 1366–1370

M. P. S. Ishar,* Gurpinder Singh, Satyajit Singh, K. K. Sreenivasan and Gurmit Singh

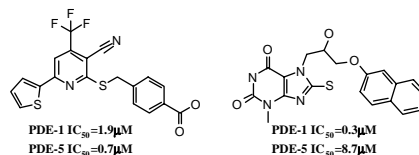


Novel chromone derivatives have been developed as potential DNA-topoisomerase inhibitors, which have displayed promising anticancer activity.

Identification of phosphodiesterase-1 and 5 dual inhibitors by a ligand-based virtual screening optimized for lead evolution

pp 1371–1379

Kazuto Yamazaki,* Naoto Kusunose, Katsuya Fujita, Hideshi Sato, Shigehiro Asano, Akihito Dan and Masaharu Kanaoka

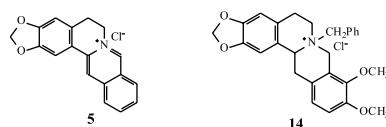


We identified new lead candidates which showed potent dual inhibition against phosphodiesterase-1 and 5 by a ligand-based virtual screening optimized for lead evolution. The obtained lead candidates were structurally diverse.

Synthesis and antihyperglycemic evaluation of various protoberberine derivatives

pp 1380–1383

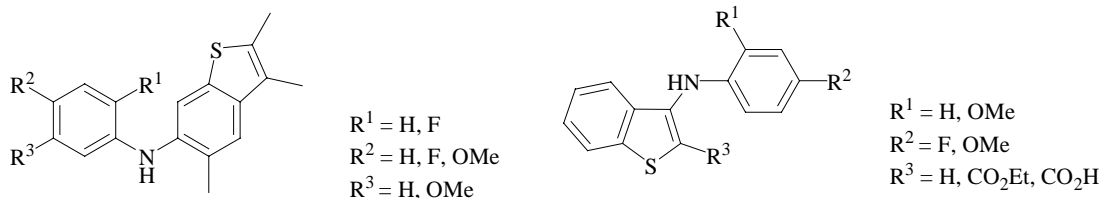
Xiaoli Bian, Langchong He* and Guangde Yang



Evaluation of the antioxidant properties of diarylamines in the benzo[*b*]thiophene series by free radical scavenging activity and reducing power

pp 1384–1387

Isabel C. F. R. Ferreira,* Maria-João R. P. Queiroz, Miguel Vilas-Boas, Leticia M. Estevinho, Agathe Begouin and Gilbert Kirsch

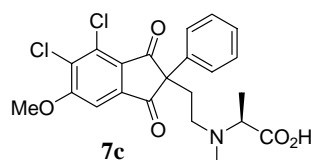


Chemical assays for the determination of the reducing power and free radical scavenging activity of the diarylamines are presented.

Sarcosine based indandione hGlyT1 inhibitors

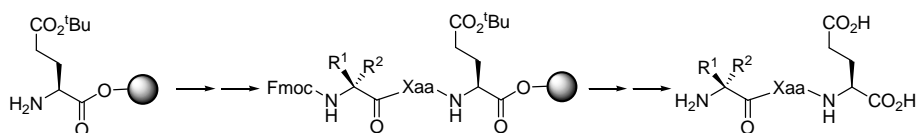
pp 1388–1391

Christopher G. Thomson,* Karen Duncan, Stephen R. Fletcher, Ian T. Huscroft, Gopalan Pillai, Piotr Raubo, Alison J. Smith and Darren Stead

A series of indandione sarcosine hGlyT1 inhibitors has been developed, leading to very potent compounds, selective over a number of counterscreen receptors. Substitution around the indandione ring and the amino acid has been explored leading to compound **7c** with an IC_{50} of 0.47 nM at hGlyT1.**New Gly-Pro-Glu (GPE) analogues: Expedite solid-phase synthesis and biological activity**

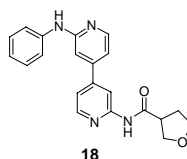
pp 1392–1396

Sergio A. Alonso De Diego, Marta Gutiérrez-Rodríguez, M. Jesús Pérez de Vega, Diego Casabona, Carlos Cativiela, Rosario González-Muñiz, Rosario Herranz, Eurne Cenarruzabeitia, Diana Frechilla, Joaquín Del Río, M. Luisa Jimeno and M. Teresa García-López*

**Design and synthesis of 2'-anilino-4,4'-bipyridines as selective inhibitors of c-Jun N-terminal kinase-3**

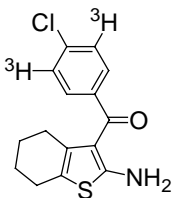
pp 1397–1401

Britt-Marie Swahn,* Yafeng Xue, Erwan Arzel, Elisabet Kallin, Angelika Magnus, Niklas Plobeck and Jenny Viklund

The design and synthesis of new c-Jun N-terminal kinase-3 inhibitors (JNK3) with selectivity against JNK1 and p38 α are reported. Compound **18** displayed the best selectivity against JNK1 within the series.

Synthesis and biological characterization of [³H] (2-amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chlorophenyl)-methanone, the first radiolabelled adenosine A₁ allosteric enhancer pp 1402–1404

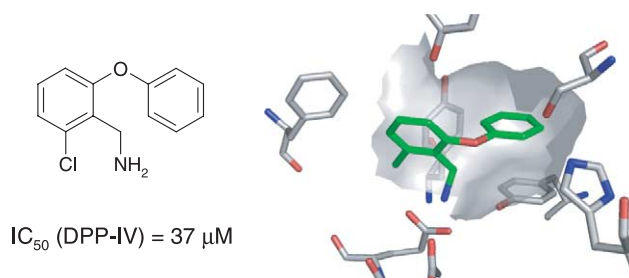
Pier Giovanni Baraldi,* Maria Giovanna Pavani, Edward Leung, Allan R. Moorman, Katia Varani, Fabrizio Vincenzi, Pier Andrea Borea and Romeo Romagnoli



In silico fragment-based discovery of DPP-IV S1 pocket binders pp 1405–1409

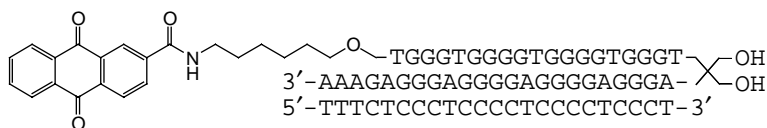
Christian Rummey, Sonja Nordhoff, Meinolf Thiemann and Günther Metz*

A virtual screening approach for S1-binding fragments of dipeptidyl peptidase IV using FlexX-Pharm docking confirmed substructures of known inhibitors and identified novel fragments with activities in the micromolar range suitable as starting points for structure-based design.



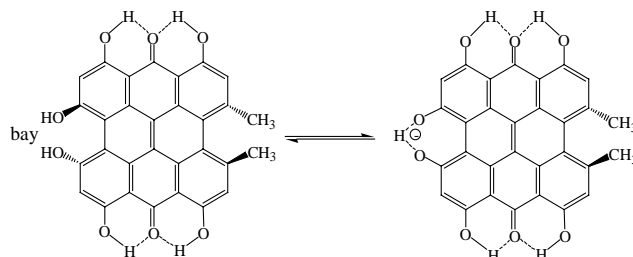
Synthesis of linked triple helical DNAs possessing high affinity to triple helical DNA binding protein pp 1410–1413

Aya Shibata, Yoshihito Ueno, Koichiro Shinbo, Masayuki Nakanishi, Akira Matsuda and Yukio Kitade*



Anion of hypericin is crucial to understanding the photosensitive features of the pigment pp 1414–1417

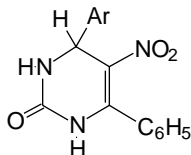
Liang Shen, Hong-Fang Ji and Hong-Yu Zhang*



By means of time-dependent density functional theory calculations, it is revealed that the anion of hypericin, derived from proton dissociation in the bay region, is responsible for the photosensitive features of the pigment.

Antiarrhythmic activity of 4,6-di(het)aryl-5-nitro-3,4-dihydropyrimidin-(1*H*)-2-ones and its effects on arterial pressure in rats

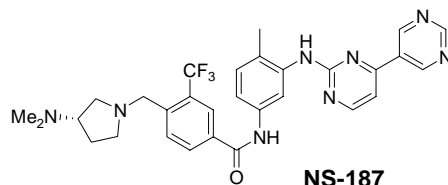
pp 1418–1420

Arkadiy O. Bryzgalov, Margarita P. Dolgikh, Irina V. Sorokina, Tatiana G. Tolstikova,*
Valentina F. Sedova and Oleg P. ShkurkoAr = C₆H₅, 4-HOC₆H₄,
3-FC₆H₄, 3-O₂NC₆H₄,
3-Py, 2-Th

The antiarrhythmic activity of title compounds toward two types of experimental rat arrhythmia has been studied.

Design and synthesis of 3-substituted benzamide derivatives as Bcr-Abl kinase inhibitors

pp 1421–1425

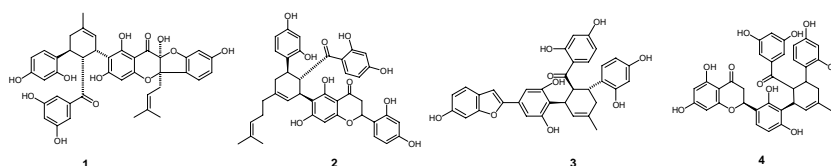
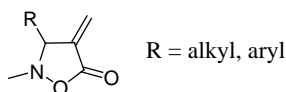
Tetsuo Asaki,* Yukiteru Sugiyama, Taisuke Hamamoto, Masaya Higashioka,
Masato Umehara, Haruna Naito and Tomoko Niwa

NS-187

A series of 3-substituted benzamide derivatives of STI-571 (imatinib mesylate) was prepared and evaluated for antiproliferative activity against the Bcr-Abl-positive leukemia cell line K562. Several 3-halogenated and 3-trifluoromethylated compounds, including NS-187, showed excellent potency.

Protein tyrosine phosphatase 1B inhibitors from *Morus* root bark

pp 1426–1429

Long Cui, MinKyun Na, Hyuncheol Oh, Eun Young Bae, Dae Gwin Jeong, Seong Eon Ryu,
Sohee Kim, Bo Yeon Kim, Won Keun Oh* and Jong Seog AhnAn organic layer prepared from the Chinese crude drug 'Sang-Bai-Pi' (*Morus* root bark) was studied in order to identify the inhibitory compounds for protein tyrosine phosphatase 1B (PTP1B). Bioassay-guided fractionation resulted in the isolation of sanggenon C (1), sanggenon G (2), mulberrofuran C (3), and kuwanon L (4) as PTP1B inhibitors, along with moracin O (5) and moracin P (6). Compounds 1–4 inhibited PTP1B with IC₅₀ values ranging from 1.6 ± 0.3 μM to 16.9 ± 1.1 μM.**4-Methylideneisoxazolidin-5-ones—A new class of α-methylidene-γ-lactones with high cytostatic activity** pp 1430–1433Tomasz Janecki,* Tomasz Wąsek, Marek Różalski, Urszula Krajewska,
Kazimierz Studzian and Anna Janecka

R = alkyl, aryl

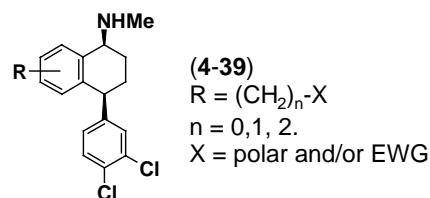
A series of 4-methylideneisoxazolidin-5-ones was synthesized and their cytostatic activity against L-1210, HL-60, and NALM-6 leukemia cell lines was evaluated. The most potent analogues had IC₅₀ < 1 μM.

Designing rapid onset selective serotonin re-uptake inhibitors. Part 1: Structure–activity relationships of substituted (1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydro-1-naphthaleneamine

pp 1434–1439

Donald S. Middleton,* Mark Andrews, Paul Glossop, Geoffrey Gymer, Alan Jessiman, Patrick S. Johnson, Malcolm MacKenny, Michael J. Pitcher, Tony Rooker, Alan Stobie, Kim Tang and Paul Morgan

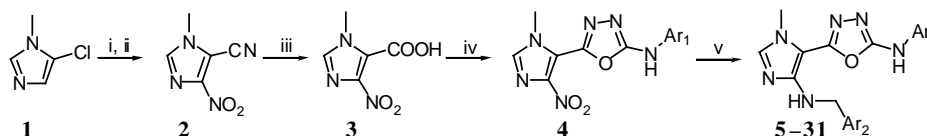
A series of sertraline analogues (**4–39**) which possess polar groups on the fused tetrahydronaphthalene ring, targeting reduced V_d as a strategy to reduce T_{max} and increase rate of elevation of central 5-HT levels, were prepared.



Hetaryl imidazoles: A novel dual inhibitors of VEGF receptors I and II

pp 1440–1444

Alexander S. Kiselyov,* Marina Semenova and Victor V. Semenov

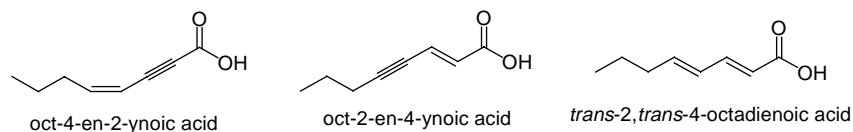


Novel potent derivatives of hetaryl imidazoles are described as inhibitors of vascular endothelial growth factor receptor II (VEGFR-2). Many compounds display VEGFR-2 inhibitory activity reaching $IC_{50} < 100$ nM in both enzymatic and cell-based assays. The compounds also inhibit the related tyrosine kinase, VEGFR-1, with similar potencies. By controlling the substitution pattern on the 5-carboxamido pharmacophore, both dual and specific VEGFR-2 thiazoles were identified.

Inactivation of medium-chain acyl-CoA dehydrogenase by oct-4-en-2-ynoic-CoA

pp 1445–1448

Jia Zeng, Guisheng Deng, Wenhua Yu and Ding Li*



OTHER CONTENTS


Erratum

p 1449

Summary of instructions to authors

p I

*Corresponding author

+ Supplementary data available via ScienceDirect

COVER

View of the crystal structure of the DB819-d(CGCGAATTCGCG)₂ complex, looking down the minor groove of the DNA (see Campbell, N.H.; Evans, D.A.; Lee, M.P.H.; Parkinson, G.N.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 15.). The DB819 molecule is shown in space-filling mode. Visualisation produced with the VMD program. [Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.]



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