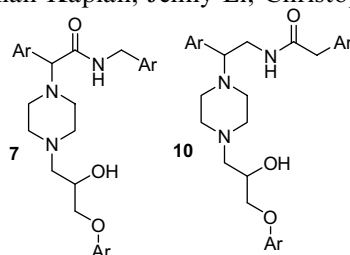


Contents

COMMUNICATIONS

The design, preparation and SAR of novel small molecule sodium (Na^+) channel blockers pp 2025–2030

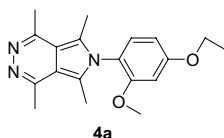
Mark A. Ashwell,* Jean-Marc Lapierre, Alan Kaplan, Jenny Li, Christopher Marr and Jin Yuan



A parallel strategy incorporating predictive modeling and parallel chemistry has led to the identification of two new structural motifs (**7** and **10**) with potent sodium both sodium site **2** blocking activity and favorable eADME profile.

Synthesis and biological evaluation of 6-aryl-6*H*-pyrrolo[3,4-*d*]pyridazine derivatives as high-affinity ligands of the $\alpha_2\delta$ subunit of voltage-gated calcium channels pp 2031–2034

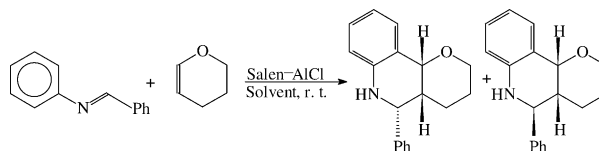
Tao Hu,* Brian A. Stearns, Brian T. Campbell, Jeannie M. Arruda, Chixu Chen, Jayashree Aiyar, Robert E. Bezverkov, Angelina Santini, Hervé Schaffhauser, Wensheng Liu, Shankar Venkatraman and Benito Munoz



Compounds such as **4a** ($\text{IC}_{50} = 4 \text{ nM}$) are high-affinity ligands of the $\alpha_2\delta$ subunit of voltage-gated calcium channels.

Highly diastereoselective inverse electron demand (IED) Diels–Alder reaction mediated by chiral salen–AlCl complex: the first, target-oriented synthesis of pyranoquinolines as potential antibacterial agents pp 2035–2040

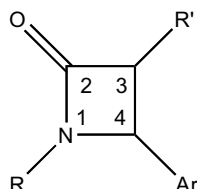
Chinnian J. Magesh, Sarasu V. Magesh and Paramasivan T. Perumal*



Examination of the 1,4-disubstituted azetidinone ring system as a template for combretastatin A-4 conformationally restricted analogue design

pp 2041–2046

Lichun Sun, Natalya I. Vasilevich, Joseph A. Fuselier,* Simon J. Hocart and David H. Coy

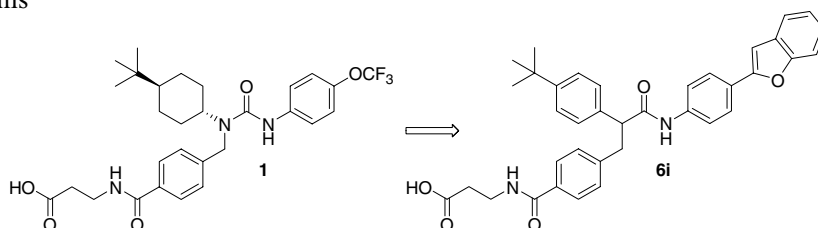


Synthesis, cytotoxicity, tubulin polymerization inhibition, anti-tumor activity, and serum and buffer stability of new 1,4-diaryl-2-azetidinones are reported.

Biaryl amide glucagon receptor antagonists

pp 2047–2050

Ravi Kurukulasuriya,* Bryan K. Sorensen, James T. Link, Jyoti R. Patel, Hwan-Soo Jae, Marty X. Winn, Jeffrey R. Rohde, Nelson D. Grihalde, Chun W. Lin, Christopher A. Ogiela, Andrew L. Adler and Christine A. Collins

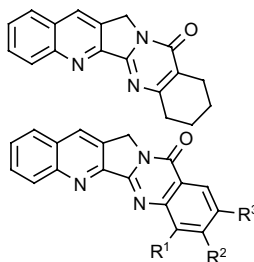


Biaryl amides derived from a reported series of ureas **1** were evaluated and found to be potent human glucagon receptor antagonists. The benzofuran analogue **6i** was administered in Sprague–Dawley rats and blocked the effects of an exogenous glucagon challenge.

Synthesis and biochemical properties of E-ring modified luotonin A derivatives

pp 2051–2054

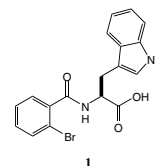
Ali Cagir, Shannon H. Jones, Brian M. Eisenhauer, Rong Gao and Sidney M. Hecht*

**N-Benzoyl amino acids as ICAM/LFA-1 inhibitors. Part 2: Structure–activity relationship of the benzoyl moiety**

pp 2055–2059

Daniel J. Burdick,* James C. Marsters, Jr., Ignacio Aliagas-Martin, Mark Stanley, Maureen Beresini, Kevin Clark, Robert S. McDowell and Thomas R. Gadek

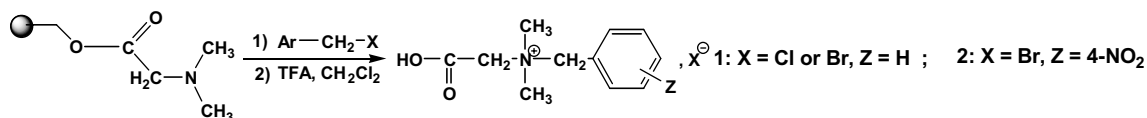
o-Bromobenzoyl L-tryptophan **1** inhibits the association of LFA-1 with ICAM-1 with an IC₅₀ of 1.7 μM. Evaluation of the structure–activity relationship of the benzoyl moiety shows that 2,6-di-substitutions greatly enhance potency of this class of inhibitors. Electronegative substitutions that favor a 90° angle between the benzoyl ring and the amide bond yield the most potent compounds. There is a strong correlation between the potency of the compounds and the difference between the ab initio energy at 90° and the global minima energy for given compounds. Combining the favored benzoyl substitutions with L-histidine and L-asparagine resulted in a 15-fold increase in potency over compound **1**.



Antibacterial activity of glycine betaine analogues: involvement of osmoporters

pp 2061–2065

Anne Cosquer, Morgane Ficamos, Mohamed Jebbar, Jean-Charles Corbel, Gwénaëlle Choquet, Catherine Fontenelle, Philippe Uriac and Théophile Bernard*

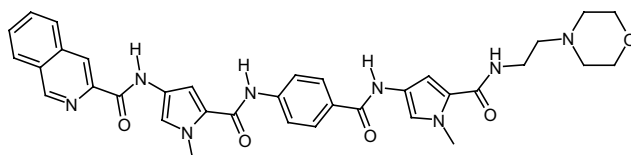


Glycine betaine (GB) analogues were obtained by SPOS using Wang resin and assayed for their toxic activity against 15 Gram positive and Gram negative bacteria. Four benzyl derivatives of GB were selected to determine their effect on bacterial growth. Bacteriostatic and lethal effects were observed for compound **1** and compound **2**, respectively. The importation of the two GB analogues into bacterial cells appeared strictly dependent on the powerful betaine membrane osmoporters; their capacity to be amassed intracellularly at molar levels from extremely diluted solutions might constitute a basis to design a new class of antimicrobial agents.

DNA binding ligands with in vivo efficacy in murine models of bacterial infection: optimization of internal aromatic amino acids

pp 2067–2072

Roland W. Bürli, Jacob A. Kaizerman, Jian-Xin Duan, Peter Jones, Kirk W. Johnson, Mari Iwamoto, Kiet Truong, Wenhao Hu, Timothy Stanton, Alfred Chen, Sofia Touami, Matthew Gross, Vernon Jiang, Yigong Ge and Heinz E. Moser*

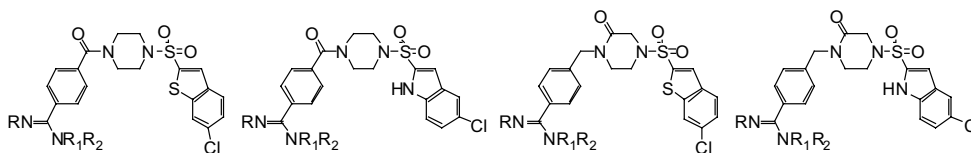


DNA binding ligands with potent antimicrobial activity against Gram-positive bacteria were further optimized by variation of the internal aromatic amino acids to successfully achieve in vivo efficacy in murine models of bacterial infection with methicillin-resistant *S. aureus* (MRSA).

N,N-Dialkylated 4-(4-arylsulfonylpiperazine-1-carbonyl)-benzamidines and 4-((4-arylsulfonyl)-2-oxo-piperazin-1-ylmethyl)-benzamidines as potent factor Xa inhibitors

pp 2073–2078

Zhaozhong J. Jia,* Ting Su, Jingmei F. Zuckett, Yanhong Wu, Erick A. Goldman, Wenhao Li, Penglie Zhang, Lane A. Clizbe, Yonghong Song, Shawn M. Bauer, Wenrong Huang, John Woolfrey, Uma Sinha, Ann E. Arfsten, Athiwat Hutchaleelaha, Stanley J. Hollenbach, Joseph L. Lambing, Robert M. Scarborough and Bing-Yan Zhu*

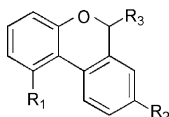


A class of N,N-dialkylated 4-(4-arylsulfonylpiperazine-1-carbonyl)-benzamidines and 4-((4-arylsulfonyl)-2-oxo-piperazin-1-ylmethyl)-benzamidines has been discovered as potent factor Xa inhibitors with desirable in vitro and in vivo anticoagulant activity, but with low oral bioavailability. The 5-chloroindole and 6-chlorobenzo[b]thiophene groups are optimal as the factor Xa S1 binding elements.

Synthesis and biological evaluation of novel, selective, nonsteroidal glucocorticoid receptor antagonists

pp 2079–2082

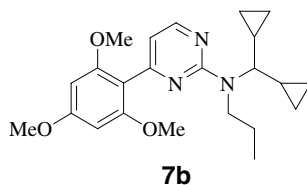
Irini Akritopoulou-Zanze,* Jyoti R. Patel, Kresna Hartandi, Jehrod Brenneman, Martin Winn, John K. Pratt, Marlene Grynfarb, Annika Goos-Nisson, Thomas W. von Geldern and Philip R. Kym



We report the discovery of a novel class of glucocorticoid receptor (GR) antagonists based on the chromene molecular scaffold. The compounds exhibit good functional potency and an improved receptor selectivity profile for GR over other steroid receptors when compared to the classical steroidal GR-antagonist, RU-486.

Design, synthesis, and SAR of 2-dialkylamino-4-arylpyrimidines as potent and selective corticotropin-releasing factor₁ (CRF₁) receptor antagonists pp 2083–2086

Charles Q. Huang,* Dimitri E. Grigoriadis, Zhengyu Liu, James R. McCarthy, John Ramphal, Thomas Webb, Jeffrey P. Whitten, Michael Y. Xie and Chen Chen*


Macrocyclic proteoglycan mimics. Potent inhibition of cell adhesion by a bundle of chondroitin sulfate chains assembled on the calix[4]resorcarene platform pp 2087–2090

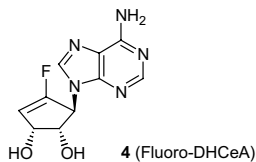
Naotoshi Tomita, Shinsuke Sando, Takashi Sera and Yasuhiro Aoyama*



The adhesion of baby hamster kidney cells on a fibronectin-coated plastic plate is effectively inhibited by a calix[4]resorcarene-based macrocyclic proteoglycan mimic having four chondroitin sulfate (CS) chains (**1d**) but not by a singly CS-functionalized analog.

Synthesis of fluorinated cyclopentenyladenine as potent inhibitor of *S*-adenosylhomocysteine hydrolase pp 2091–2093

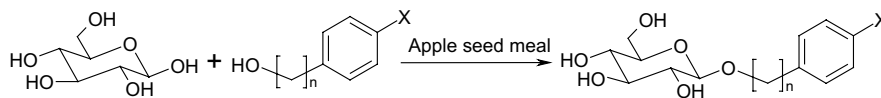
Hea Ok Kim, Su Jeong Yoo, Hee Sung Ahn, Won Jun Choi, Hyung Ryong Moon, Kang Man Lee, Moon Woo Chun and Lak Shin Jeong*



Fluoro-DHCeA (**4**), a potent inhibitor of *S*-adenosylhomocysteine hydrolase was efficiently synthesized from *D*-cyclopentenone derivative **5** using electrophilic fluorination as a key step.

Use of apple seed meal as a new source of β -glucosidase for enzymatic glucosylation of 4-substituted benzyl alcohols and tyrosol in monophasic aqueous-dioxane medium pp 2095–2097

Ai Min Tong, Wen Ya Lu, Jian He Xu* and Guo Qiang Lin

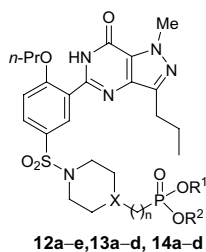


A facile method for enzymatic glucosylation of 4-substituted benzyl alcohols and tyrosol with glucose in a monophasic aqueous-dioxane medium was reported, using a crude meal of apple seed as a new catalyst. The corresponding β -D-glucosides were synthesized in moderate yields (13.1–23.1%), among which the salidroside was obtained in 15.8% yield.

Synthesis and phosphodiesterase 5 inhibitory activity of new sildenafil analogues containing a phosphonate group in the 5'-sulfonamide moiety of phenyl ring

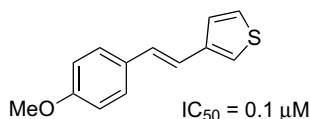
pp 2099–2103

Dae-Kee Kim,* Ju Young Lee, Hyun-Ju Park and Khac Minh Thai

**Styrylheterocycles as a novel class inhibitor of cyclooxygenase-2-mediated prostaglandin E₂ production**

pp 2105–2108

Sang Kook Lee, Eun-Jung Park, Eunjung Lee, Hye-Young Min, Eun-Young Kim, Taeho Lee and Sanghee Kim*

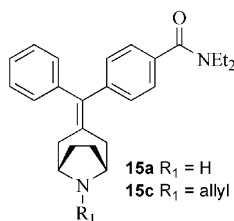


The inhibitory effects of a series of styrylheterocycles on the production of COX-2 mediated PGE₂ were evaluated in a cell culture system. A new series of potential inhibitors, including 3-[2-(4-methoxy-phenyl)-vinyl]-thiophene, have been identified.

N,N-Dialkyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamides, potent, selective δ opioid agonists

pp 2109–2112

John R. Carson,* Steven J. Coats, Ellen E. Codd, Scott L. Dax, Jung Lee, Rebecca P. Martinez, Lou Anne Neilson, Philip M. Pitis and Sui-Po Zhang

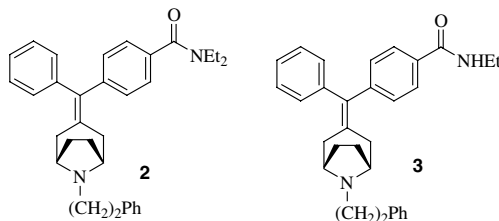


Compounds such as **15a** and **15c** are potent and selective δ opioid agonists.

N-Alkyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamides, μ and δ opioid agonists: a μ address

pp 2113–2116

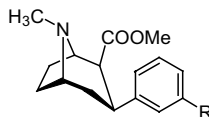
John R. Carson,* Steven J. Coats, Ellen E. Codd, Scott L. Dax, Jung Lee, Rebecca P. Martinez, Linda A. McKown, Lou Anne Neilson, Philip M. Pitis, Wu-Nan Wu and Sui-Po Zhang



Compound **2**, a potent and selective δ opioid agonist is metabolically converted to **3**, a potent and selective μ opioid agonist.

Synthesis and monoamine transporter affinity of 3'-analogs of 2- β -carbomethoxy-3- β -(4'-iodophenyl)-tropane (β -CIT) pp 2117–2120

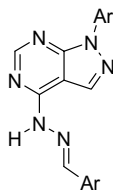
Frederic Bois, Ronald M. Baldwin, Nora S. Kula, Ross J. Baldessarini, Robert B. Innis and Gilles Tamagnan*



A series of novel 3 β -substituted 3'-substituted phenyltropanes was synthesized and evaluated by selective radioligand binding assays for affinity to monoamine transporters.

Novel pyrazolopyrimidine derivatives as GSK-3 inhibitors pp 2121–2125

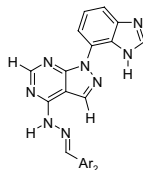
Andrew J. Peat, Joyce A. Boucheron, Scott H. Dickerson, Dulce Garrido, Wendy Mills, Jennifer Peckham, Frank Preugschat, Terrence Smalley, Stephanie L. Schweiker, Jayme R. Wilson, Tony Y. Wang, Huiqiang Q. Zhou and Stephen A. Thomson*



A series of [1-aryl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]arylhydrazones were discovered as novel inhibitors glycogen synthase kinase-3 (GSK-3).

Novel GSK-3 inhibitors with improved cellular activity pp 2127–2130

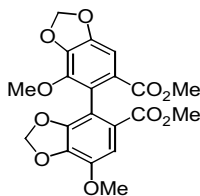
Andrew J. Peat,* Dulce Garrido, Joyce A. Boucheron, Stephanie L. Schweiker, Scott H. Dickerson, Jayme R. Wilson, Tony Y. Wang and Stephen A. Thomson



A novel series of [1-(1*H*-benzimidazol-7-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl] arylhydrazones was synthesized and shown to potently inhibit glycogen synthase kinase-3 (GSK-3). In light of detailed structure–activity relationships and structural knowledge of the GSK-3 binding pocket, a benzimidazole substituent was incorporated onto the pyrazolopyrimidine core resulting in improved potency over previous analogs. More importantly, these derivatives show low nanomolar efficacy for stimulating glycogen synthesis *in vitro* and therefore may be useful in the treatment of type 2 diabetes mellitus.

Efficient synthesis of γ -DDB pp 2131–2136

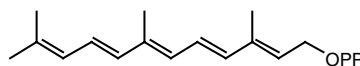
Junbiao Chang,* Xiaohu Guo, Senxiang Cheng, Ruiyun Guo, Rongfeng Chen and Kang Zhao*



Didehydrofarnesyl diphosphate: an intrinsically fluorescent inhibitor of protein farnesyltransferase

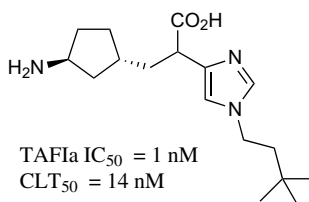
pp 2137–2140

Xiao-hui Liu and Glenn D. Prestwich*

All-trans $\Delta\Delta$ FPP**Imidazole acetic acid TAFIa inhibitors: SAR studies centered around the basic P₁' group**

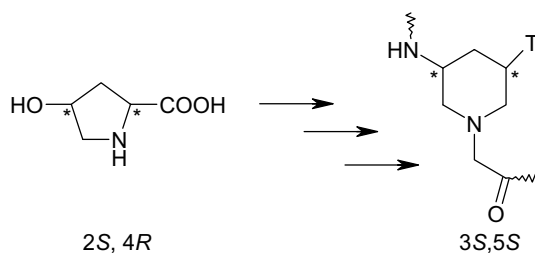
pp 2141–2145

Philippe G. Nantermet,* James C. Barrow, Stacey R. Lindsley, MaryBeth Young, Shi-Shan Mao, Steven Carroll, Carolyn Bailey, Michele Bosserman, Dennis Colussi, Daniel R. McMasters, Joseph P. Vacca and Harold G. Selnick

TAFIa IC₅₀ = 1 nM
CLT₅₀ = 14 nM**Design and synthesis of conformationally frozen peptide nucleic acid backbone: chiral piperidine PNA as a hexitol nucleic acid surrogate**

pp 2147–2149

Pallavi S. Lonkar and Vijayanti A. Kumar*



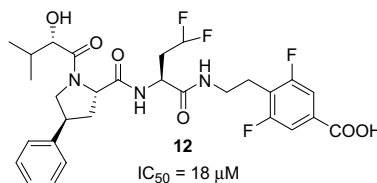
2S, 4R

3S,5S

**Capped dipeptide phenethylamide inhibitors of the HCV NS3 protease**

pp 2151–2154

Emanuela Nizi, Uwe Koch, Jesus M. Ontoria, Antonella Marchetti, Frank Narjes, Savina Malancona, Victor G. Matassa and Cristina Gardelli*



12

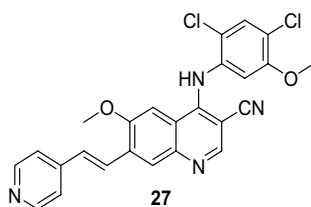
IC₅₀ = 18 μ M

The N-terminal amino acid of phenethylamide tripeptide inhibitors of the hepatitis C virus NS3 protease can be replaced with an α -hydroxy acid to obtain more drug like inhibitors with low micromolar activity. The highest affinity of the capping residue with S-configuration has been explained by molecular modeling studies.

Synthesis and inhibition of Src kinase activity by 7-ethenyl and 7-ethynyl-4-anilino-3-quinolinecarbonitriles

pp 2155–2158

Ana Carolina Barrios Sosa,* Diane H. Boschelli, Fei Ye, Jennifer M. Golas and Frank Boschelli

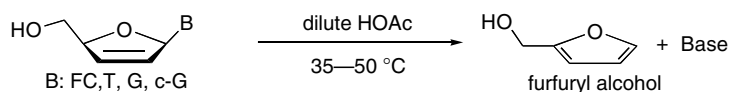


A series of 7-ethynyl and 7-ethenyl-4-anilino-3-quinolinecarbonitriles was synthesized and tested for Src inhibition. The 7-(4-ethenylpyridine) derivative **27** was the most potent inhibitor tested in this series.

2',3'-Didehydro-2',3'-dideoxynucleosides are degraded to furfuryl alcohol under acidic conditions

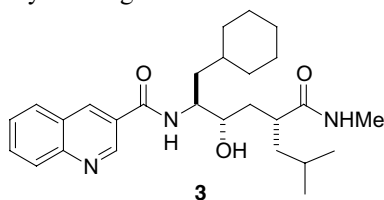
pp 2159–2162

Junxing Shi, Adrian S. Ray, Judy S. Mathew, Karen S. Anderson, Chung K. Chu and Raymond F. Schinazi*

**The discovery of structurally novel CCR1 antagonists derived from a hydroxyethylene peptide isostere template**

pp 2163–2167

John C. Kath,* Amy P. DiRico, Ronald P. Gladue, William H. Martin, Eric B. McElroy, Ingrid A. Stock, Laurie A. Tylaska and Deye Zheng

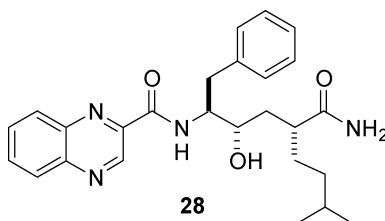


This manuscript details fundamental SAR work around compound **3**, a micromolar inhibitor of CCL3 binding to its receptor CCR1.

Potent small molecule CCR1 antagonists

pp 2169–2173

John C. Kath,* William H. Brissette, Matthew F. Brown, Maryrose Conklyn, Amy P. DiRico, Peter Dorff, Ronald P. Gladue, Brett M. Lillie, Paul D. Lira, Erin N. Mairs, William H. Martin, Eric B. McElroy, Molly A. McGlynn, Timothy J. Paradis, Christopher S. Poss, Ingrid A. Stock, Laurie A. Tylaska and Deye Zheng

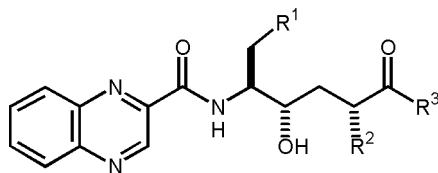


This manuscript details the discovery of potent CCR1 antagonists.

Novel CCR1 antagonists with improved metabolic stability

pp 2175–2179

Matthew F. Brown,* Mike Avery, William H. Brissette, J. H. Chang, Kevin Colizza, Maryrose Conklyn, Amy P. DiRico, Ronald P. Gladue, John C. Kath, Suzanne S. Krueger, Paul D. Lira, Brett M. Lillie, Greg D. Lundquist, Erin N. Mairs, Eric B. McElroy, Molly A. McGlynn, Timothy J. Paradis, Christopher S. Poss, Michelle I. Rossulek, Richard M. Shepard, Jeff Sims, Timothy J. Strelevitz, Susan Truesdell, Laurie A. Tylaska, Kwansik Yoon and Deye Zheng

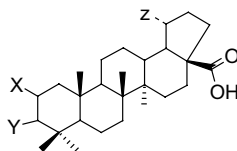


The synthesis, biological activity and pharmacokinetic profile of novel CCR1 antagonists are described.

Betulinic acid and its derivatives as anti-angiogenic agents

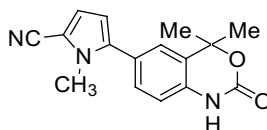
pp 2181–2184

Rama Mukherjee, Manu Jaggi,* Praveen Rajendran, Mohammad J. A. Siddiqui, Sanjay K. Srivastava,* Anand Vardhan and Anand C. Burman

**Novel pyrrole-containing progesterone receptor modulators**

pp 2185–2189

Mark A. Collins, Valerie Hudak, Reinhold Bender, Andrew Fensome, Puwen Zhang, Lori Miller, Richard C. Winneker, Zhiming Zhang, Yuan Zhu, Jeffrey Cohen, Rayomond J. Unwalla and Jay Wrobel*

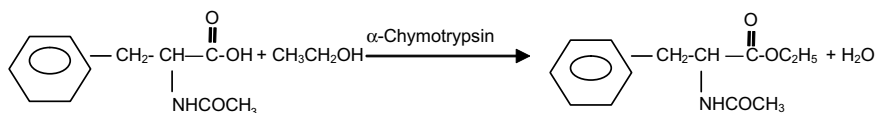


A series of 1,4-dihydro-2*H*-[*d*][3,1]-benzoxazin-2-one and 1,3-dihydro-[3*H*]-indol-2-one containing 6- or 5-, respectively, appended substituted pyrrole moieties were synthesized and evaluated for their ability to modulate the activity of the progesterone receptor (PR).

Preparation of highly active α -chymotrypsin for catalysis in organic media

pp 2191–2193

Ipsita Roy and Munishwar N. Gupta*

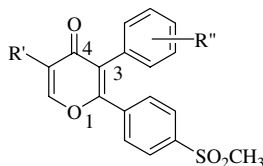


The increase in reaction rates of free α -chymotrypsin-catalyzed esterification was achieved by precipitation of the enzyme from an aqueous solution.

2,3-Diarylpyran-4-ones: a new series of selective cyclooxygenase-2 inhibitors

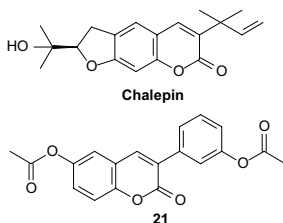
pp 2195–2198

Yung Hyup Joo,* Jin Kwan Kim, Seon-Hwa Kang, Min-Soo Noh, Jun-Yong Ha, Jin Kyu Choi, Kyung Min Lim and Shin Chung

**Structure–activity relationships of novel inhibitors of glyceraldehyde-3-phosphate dehydrogenase**

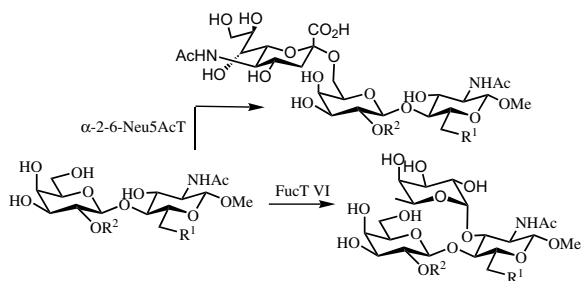
pp 2199–2204

Andrei Leitão, Adriano D. Andricopulo, Glaucius Oliva, Mônica T. Pupo, Anderson A. de Marchi, Paulo C. Vieira, Maria Fátima G. F. da Silva, Vitor F. Ferreira, Maria Cecília B. V. de Souza, Marcus M. Sá, Valéria R. S. Moraes and Carlos A. Montanari*

**Glycosyltransferase activity can be selectively modulated by chemical modifications of acceptor substrates**

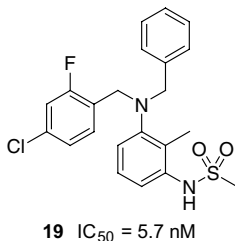
pp 2205–2208

M. Carmen Galan, Christopher S. Dodson, Andre P. Venot and Geert-Jan Boons*

**Discovery of novel nonsteroidal glucocorticoid receptor modulators**

pp 2209–2212

J. T. Link,* Bryan K. Sorensen, Jyoti Patel, Maurice Emery, Marlena Grynfarb and Annika Goos-Nilsson

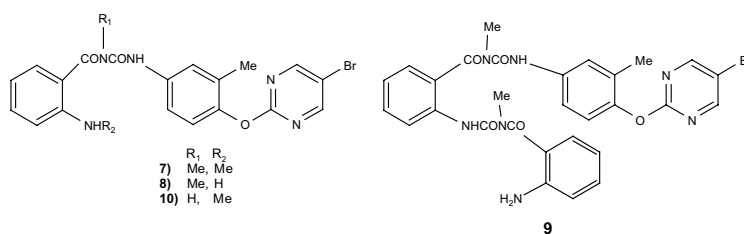


The discovery and synthesis of a novel series of selective glucocorticoid receptor modulators is reported, typified by sulfonamide **19** (h-GR binding IC₅₀ = 5.7 nm).

Synthesis and antitumor evaluation of benzoylphenylurea analogs

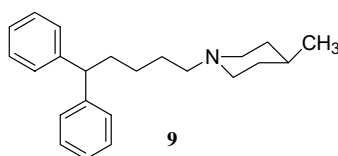
pp 2213–2216

Hallur Gurulingappa, Maria L. Amador, Ming Zhao, Michelle A. Rudek, Manuel Hidalgo and Saeed R. Khan*

**Thioxanthene-derived analogs as σ_1 receptor ligands**

pp 2217–2220

Richard A. Glennon,* Abd M. Ismaiel, Seth Ablordeppey, Mahmoud El-Ashmawy and James B. Fisher



Compound **9**, derived from a thioxanthene analog, binds with very high affinity ($K_i = 0.09$ nM) at σ_1 receptors and with about 190-fold selectivity versus σ_2 receptors. As such, it extends the SAR for σ_1 binding of phenylpentylamines to derivatives bearing a benzylic phenyl group.

Application of the four-component Ugi condensation for the preparation of sulfated glycoconjugate libraries

pp 2221–2226

Ligong Liu, Cai Ping Li, Siska Cochran and Vito Ferro*

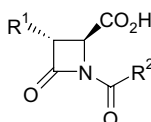


The synthesis, via the Ugi reaction, of a library of heparan sulfate mimetics is described. The compounds display micromolar affinities for the heparan sulfate-binding growth factors FGF-1 and FGF-2.

Synthesis of potent and highly selective nonguanidine azetidinone inhibitors of human tryptase

pp 2227–2231

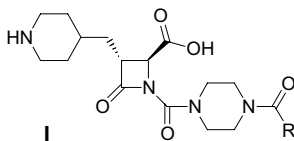
Gregory S. Bisacchi,* William A. Slusarchyk, Scott A. Bolton, Karen S. Hartl, Glenn Jacobs, Arvind Mathur, Wei Meng, Martin L. Ogletree, Zulan Pi, James C. Sutton, Uwe Treuner, Robert Zahler, Guohua Zhao and Steven M. Seiler



A series of potent azetidinone tryptase inhibitors with primary or secondary amine or aminopyridine functionality incorporated at the R^1 position is described. One analog (**4**, $IC_{50} = 1.8$ nM) was shown to be highly selective against trypsin and most other related serine proteases.

Solid-phase synthesis and SAR of 4-carboxy-2-azetidinone mechanism-based tryptase inhibitors pp 2233–2239

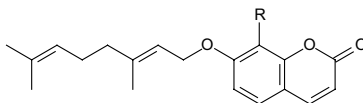
James C. Sutton,* Scott A. Bolton, Malcolm E. Davis, Karen S. Hartl, Bruce Jacobson, Arvind Mathur, Martin L. Ogletree, William A. Slusarchyk, Robert Zahler, Steven M. Seiler and Gregory S. Bisacchi



A parallel library based on structure **I** was prepared, which identified potent tryptase inhibitors with improved selectivity against trypsin. A crystal structure of one compound bound to trypsin is shown and a hypothesis is presented to account for the observed SAR.

Synthesis and anti-inflammatory activity of natural and semisynthetic geranyloxycoumarins pp 2241–2243

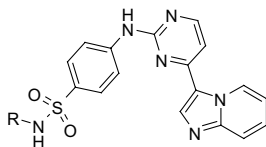
Massimo Curini,* Francesco Epifano, Federica Maltese, Maria C. Marcotullio, Aurelia Tubaro, Gianmario Altinier, Sylvia Prieto Gonzales and Juan C. Rodriguez



Synthesis and anti-inflammatory activity of some natural and semisynthetic 7-geranyloxy-8-substituted coumarins are described.

Imidazo[1,2-*a*]pyridines. Part 2: SAR and optimisation of a potent and selective class of cyclin-dependent kinase inhibitors pp 2245–2248

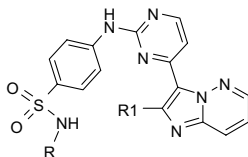
Kate F. Byth, Janet D. Culshaw, Stephen Green, Sandra E. Oakes and Andrew P. Thomas*



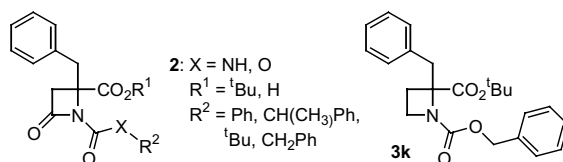
Investigation of detailed SAR and optimisation of imidazo[1,2-*a*]pyridine cyclin-dependent kinase inhibitors has led to the identification of potent and selective inhibitors of CDK2 and CDK1.

Imidazo[1,2-*b*]pyridazines: a potent and selective class of cyclin-dependent kinase inhibitors pp 2249–2252

Kate F. Byth, Nicola Cooper, Janet D. Culshaw, David W. Heaton, Sandra E. Oakes, Claire A. Minshull, Richard A. Norman, Richard A. Pauptit, Julie A. Tucker, Jason Breed, Andrew Pannifer, Siân Rowsell, Judith J. Stanway, Anna L. Valentine and Andrew P. Thomas*

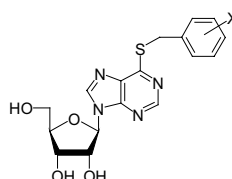


Imidazo[1,2-*b*]pyridazines have been identified and characterised as potent CDK inhibitors. The binding mode and SAR of these compounds has been elucidated and shown to differ from that of the structurally similar imidazo[1,2-*a*]pyridine series. Examples of this series show potent and selective CDK inhibition and give significant blood levels following oral dosing to mice.

Synthesis and anti-HCMV activity of 1-acyl- β -lactams and 1-acylazetidines derived from phenylalanine pp 2253–2256Guillermo Gerona-Navarro, M^a Jesús Pérez de Vega, M^a Teresa García-López, Graciela Andrei, Robert Snoeck, Jan Balzarini, Erik De Clercq and Rosario González-Muñiz***Novel halogenated nitrobenzylthioinosine analogs as *es* nucleoside transporter inhibitors**

pp 2257–2260

Amol Gupte and John K. Buolamwini*



Synthesis and structure–activity relationship of novel halogenated nitrobenzylthioinosine analogs as *es* nucleoside transporter inhibitors is reported.

Neuroprotective effects of flavones on hydrogen peroxide-induced apoptosis in SH-SY5Y neuroblastoma cells

pp 2261–2264

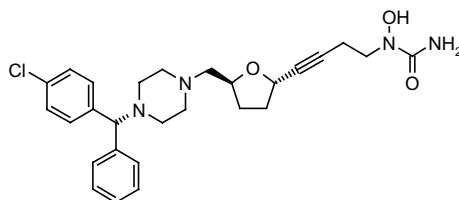
Sam Sik Kang, Ji Yeon Lee, Yoo Keum Choi, Gap Seok Kim and Byung Hee Han*

Neuroprotective effects of flavones were examined. Luteolin and apigenin exhibited neuroprotection against oxidative stress-induced cell death in SH-SY5Y cells. Free radical scavenging activity and neuroprotection assays revealed that flavones exerted their neuroprotective effects via the direct interaction with the apoptotic caspase pathway independently of their antioxidant activity.

5-Lipoxygenase inhibitors with histamine H₁ receptor antagonist activity

pp 2265–2268

Timothy A. Lewis,* Lynn Bayless, Joseph B. Eckman, James L. Ellis, Gurmit Grewal, Lyn Libertine, Jean Marie Nicolas, Ralph T. Scannell, Bruce F. Wels, Karen Wenberg and Donna M. Wypij

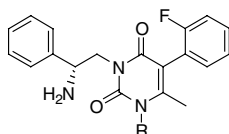


Compounds containing the pharmacophores of known antihistamines and known 5-lipoxygenase inhibitors show both activities in vitro and in animal models.

Synthesis and structure–activity relationships of (*R*)-1-alkyl-3-[2-(2-amino)phenethyl]-5-(2-fluorophenyl)-6-methyluracils as human GnRH receptor antagonists

pp 2269–2274

Martin W. Rowbottom,* Fabio C. Tucci, Yun-Fei Zhu, Zhiqiang Guo, Timothy D. Gross, Greg J. Reinhart, Qui Xie, R. Scott Struthers, John Saunders and Chen Chen*

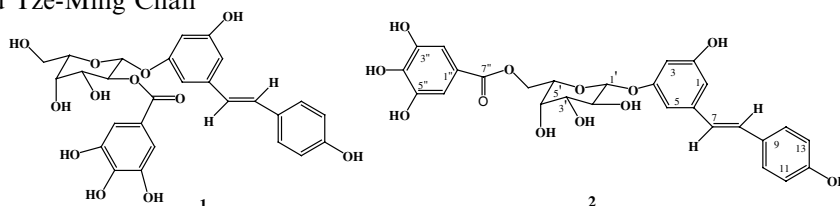


The design and synthesis of this novel class of GnRH receptor antagonists is described. Results from SAR studies carried out around N-1 of the uracil are summarized. The best compound showed $K_i = 0.7$ nM.

Two new bacterial DNA primase inhibitors from the plant *Polygonum cuspidatum*

pp 2275–2277

Vinod R. Hegde,* Haiyan Pu, Mahesh Patel, Todd Black, Aileen Soriano, Wenjun Zhao, Vincent P. Gullo and Tze-Ming Chan

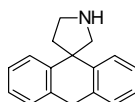


The 70% aqueous methanolic extract of the Peruvian plant *Polygonum cuspidatum* sp. was found to contain two novel phenolic saccharides **1** and **2**, which were identified as inhibitors of the bacterial DNA primase enzyme. Structures of these two compounds were established based on high resolution NMR studies. Compounds **1** and **2** inhibited the primase enzyme with an IC_{50} of 4 and 5 μ M, respectively.

Structural determinants for high 5-HT_{2A} receptor affinity of spiro[9,10-dihydroanthracene]-9,3'-pyrrolidine (SpAMDA)

pp 2279–2283

Srinivas Peddi, Bryan L. Roth, Richard A. Glennon and Richard B. Westkaemper*

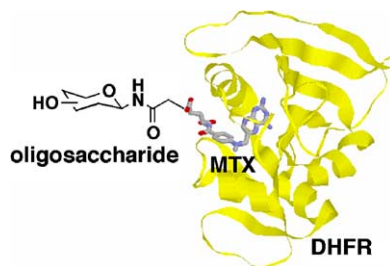


The 5-HT_{2A} receptor affinities of ring altered derivatives of spiro[9,10-dihydroanthracene]-9,3'-pyrrolidine (**4**), a structurally unique tetracyclic 5-HT_{2A} receptor antagonist, are described. Most characteristics of the parent compound prove to be necessary for optimal 5-HT_{2A} receptor affinity. In addition, the parent compound is shown to have high 5-HT₂ receptor selectivity.

Tight binding ligand approach to oligosaccharide-grafted protein

pp 2285–2289

Kiichiro Totani, Ichiro Matsuo and Yukishige Ito*

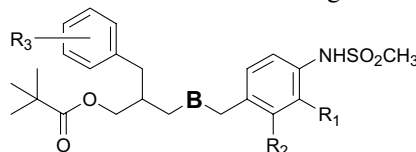


A novel type of artificial glycoprotein was developed, by using dihydrofolate reductase (DHFR) and oligosaccharide–methotrexate (MTX) as a protein–ligand pair.

Analysis of structure–activity relationships for the ‘B-region’ of *N*-(3-acyloxy-2-benzylpropyl)-*N'*-[4-(methylsulfonylamino)benzyl]thiourea analogues as vanilloid receptor antagonists: discovery of an *N*-hydroxythiourea analogue with potent analgesic activity

pp 2291–2297

Jeewoo Lee,* Sang-Uk Kang, Hyun-Kyung Choi, Jiyoun Lee, Ju-Ok Lim, Min-Jung Kil, Mi-Kyung Jin, Kang-Pil Kim, Jong-Hyuk Sung, Suk-Jae Chung, Hee-Jin Ha, Young-Ho Kim, Larry V. Pearce, Richard Tran, Daniel J. Lundberg, Yun Wang, Attila Toth and Peter M. Blumberg

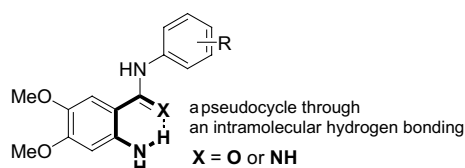


The structural modifications on the B-region of the potent and high affinity vanilloid receptor (VR1) lead ligand *N*-(3-acyloxy-2-benzylpropyl)-*N'*-[4-(methylsulfonylamino)benzyl]thiourea were investigated.

Synthesis and biological evaluation of benzamides and benzamidines: structural requirement of a pyrimidine ring for inhibition of EGFR tyrosine kinase

pp 2299–2302

Toru Asano, Tomohiro Yoshikawa, Hiroyuki Nakamura,* Yoshimasa Uehara and Yoshinori Yamamoto

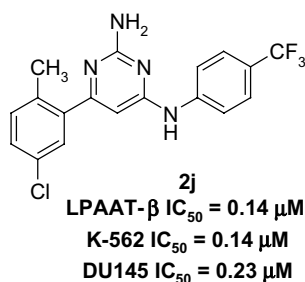


A series of benzamides and the benzamidines was synthesized as the mimics of 4-anilinoquinazolines, which possess inhibition of epidermal growth factor receptor (EGFR) tyrosine kinase, and tested for cytotoxicity toward A431 and inhibitory activity toward autophosphorylation by the enzyme assay.

Synthesis, SAR, and antitumor properties of diamino-*C,N*-diarylpyrimidine positional isomers: inhibitors of lysophosphatidic acid acyltransferase- β

pp 2303–2308

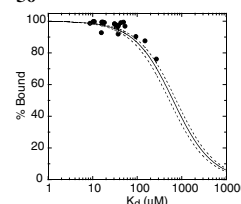
Baoqing Gong, Feng Hong, Cory Kohm, Scott Jenkins, John Tulinsky, Rama Bhatt, Peter de Vries, Jack W. Singer and Peter Klein*



A simple method for predicting serum protein binding of compounds from IC₅₀ shift analysis for in vitro assays

pp 2309–2312

David W. Rusnak, Zhihong Lai, Timothy J. Lansing, Nelson Rhodes, Tona M. Gilmer and Robert A. Copeland*

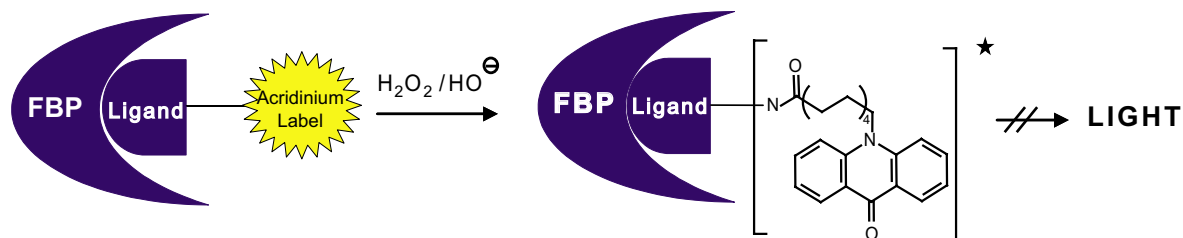


The shift in apparent IC₅₀ that attends addition of serum proteins to in vitro cellular, enzymatic, and receptor binding assays can be used to determine the dissociation constant for compound–serum protein complexes. We show here that a simple linear relationship exists between the apparent IC₅₀ in the presence of serum protein and the inverse of the apparent K_d for the compound–serum protein complex. Using a series of cell-active kinase inhibitors we demonstrate that the K_d value derived in this way can be used to predict the extent of protein binding in serum for various compounds. This method should provide a simple means of assessing the relative serum protein binding propensity of compounds early in the compound optimization phase of drug discovery campaigns.

Chemiluminescence quenching of pteronic acid–*N*-sulfonyl-acridinium-9-carboxamide conjugates by folate binding protein

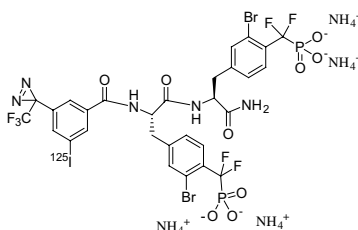
pp 2313–2317

Maciej Adamczyk,* James R. Fino, Phillip G. Mattingly, Jeffrey A. Moore and You Pan


Synthesis of a novel peptidic photoaffinity probe for the PTP-1B enzyme

pp 2319–2322

Michel Thérien,* Kathryn Skorey, Robert Zamboni, Chun Sing Li, Cheuk K. Lau, Tammy LeRiche, Vouy Linh Truong, Deena Waddleton and Chidambaram Ramachandran

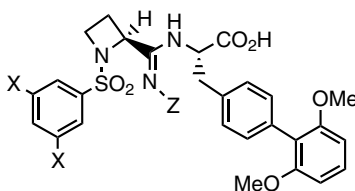


The synthesis of a novel radioactive peptidic photoaffinity probe for the PTP-1B enzyme as well as some SAR leading to the choice of this compound as a photoaffinity probe are presented.

Amidines as amide bond replacements in VLA-4 antagonists

pp 2323–2326

Theodore M. Kamenecka,* You-Jung Park, Linus S. Lin, Stephen de Laszlo, Ermengilda D. McCauley, Gail Van Riper, Linda Egger, Usha Kidambi, Richard A. Mumford, Sharon Tong, Wei Tang, Adria Colletti, Yohannes Teffera, Ralph Stearns, Malcolm MacCoss, John A. Schmidt and William K. Hagmann

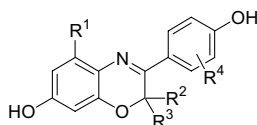


The preparation and SAR of amidines as small molecule antagonists of VLA-4 is discussed.

Synthesis and structure–activity relationship of 3-arylbenzoxazines as selective estrogen receptor β agonists

pp 2327–2330

Wu Yang,* Yufeng Wang, Zhengping Ma, Rajasree Golla, Terry Stouch, Ramakrishna Seethala, Susan Johnson, Rong Zhou, Timur Güngör, Jean H. M. Feyen and John K. Dickson, Jr.

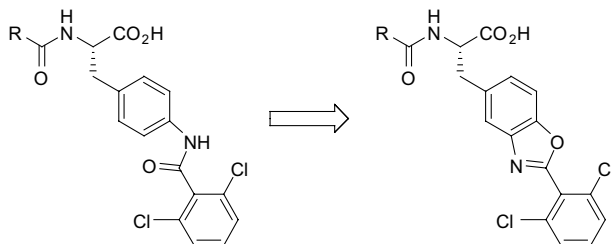


A series of 3-aryl-7-hydroxybenzoxazine analogues have been prepared and evaluated as ligands for the two estrogen receptor subtypes. Compounds with more than a 10-fold selectivity toward the ER β subtype have been identified in both binding and functional assays.

Bioisosteric replacement of anilide with benzoxazole: potent and orally bioavailable antagonists of VLA-4

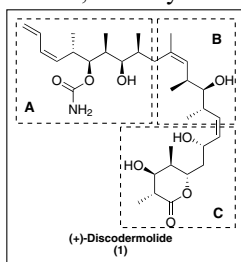
pp 2331–2334

Linus S. Lin,* Thomas J. Lanza, Jr., Laurie A. Castonguay, Theodore Kamenecka, Ermenegilda McCauley, Gail Van Riper, Linda A. Egger, Richard A. Mumford, Xinchun Tong, Malcolm MacCoss, John A. Schmidt and William K. Hagmann

**Design, synthesis and cytotoxicity of 7-deoxy aryl discodermolide analogues**

pp 2335–2338

Mark A. Burlingame,* Simon J. Shaw, Kurt F. Sundermann, Dan Zhang, Joseph Petryka, Esteban Mendoza, Fenghua Liu, David C. Myles, Matthew J. LaMarche, Tomoyasu Hirose, B. Scott Freeze and Amos B. Smith, III*

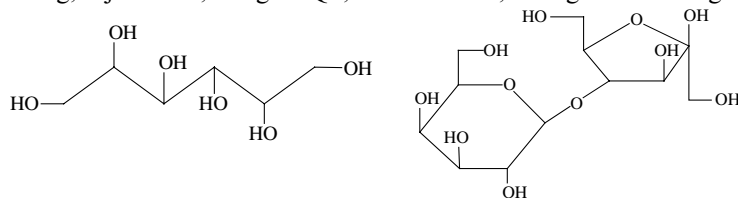


A series of 7-deoxy discodermolide analogues in which the lactone fragment 'C' was replaced by aryl substituents were designed, synthesized, and evaluated for cytotoxicity.

Studies on intestinal permeability of cirrhotic patients by analysis lactulose and mannitol in urine with HPLC/RID/MS

pp 2339–2344

Hongxia Liu,* Shusheng Zhang, Ajuan Yu, Lingbo Qu, Yufen Zhao, Hongchun Huang and Jichang Li*

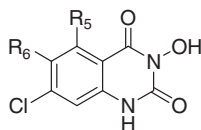
Mannitol (C₆H₁₄O₆, Mw 182.17)Lactulose (C₁₂H₂₂O₁₁, Mw 342.29)

The contents of mannitol (M), lactulose (L), and the L/M ratio in urine were determined by HPLC/RID/MS, and the ratios of L/M were used for evaluation of intestinal permeability for cirrhotic patients.

3-Hydroxy-quinazoline-2,4-dione as a useful scaffold to obtain selective Gly/NMDA and AMPA receptor antagonists

pp 2345–2349

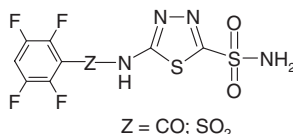
Vittoria Colotta,* Daniela Catarzi, Flavia Varano, Francesca Romana Calabri, Guido Filacchioni, Chiara Costagli and Alessandro Galli



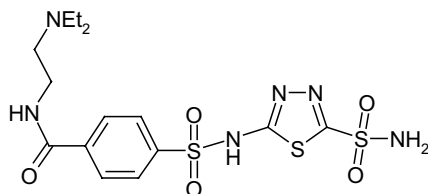
The synthesis and Gly/NMDA, AMPA and KA receptor binding activities of some 3-hydroxy-quinazoline-2,4-dione derivatives are reported. The binding data showed that introduction of chlorine atom(s) on precise position(s) of the benzofused moiety yielded Gly/NMDA selective antagonists, while the presence of the 6-(1,2,4-triazol-4-yl) group shifted the affinity and selectivity towards the AMPA receptor.

Carbonic anhydrase inhibitors: inhibition of the tumor-associated isozyme IX with fluorine-containing sulfonamides. The first subnanomolar CA IX inhibitor discovered pp 2351–2356

Daniela Vullo, Andrea Scozzafava, Silvia Pastorekova, Jaromir Pastorek and Claudiu T. Supuran*

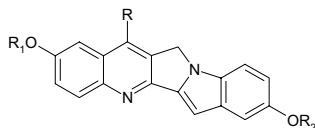
**Carbonic anhydrase inhibitors: X-ray crystallographic structure of the adduct of human isozyme II with a topically acting antiglaucoma sulfonamide** pp 2357–2361

Francesco Abbate, Angela Casini, Andrea Scozzafava and Claudiu T. Supuran*

**New benzo[5,6]pyrrolizino[1,2-*b*]quinolines as cytotoxic agents**

pp 2363–2365

Aurore Perzyna, Frédérique Klupsch, Raymond Houssin, Nicole Pommery, Amélie Lemoine and Jean-Pierre Hénichart*

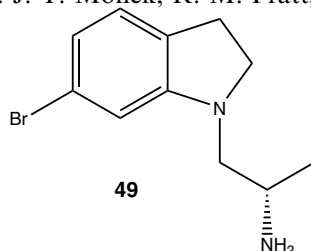


A series of ethers of the dihydroxybenzo[5,6]pyrrolizino[1,2-*b*]quinoline skeleton, a new heterocyclic pattern, was synthesised and evaluated for its cytotoxic activity against three cancer cell lines.

Indoline derivatives as 5-HT_{2C} receptor agonists

pp 2367–2370

J. M. Bentley,* D. R. Adams, D. Bebbington, K. R. Benwell, M. J. Bickerdike, J. E. P. Davidson, C. E. Dawson, C. T. Dourish, M. A. J. Duncton, S. Gaur, A. R. George, P. R. Giles, R. J. Hamlyn, G. A. Kennett, A. R. Knight, C. S. Malcolm, H. L. Mansell, A. Misra, N. J. T. Monck, R. M. Pratt, K. Quirk, J. R. A. Roffey, S. P. Vickers and I. A. Cliffe




A series of 1-(1-indolyl)-2-propylamines was synthesised and evaluated as 5-HT_{2C} receptor agonists for the treatment of obesity. A number of compounds, including **49**, were found to reduce food intake in rats after oral administration.

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*Corresponding author

 Supplementary data available via ScienceDirect

COVER

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



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