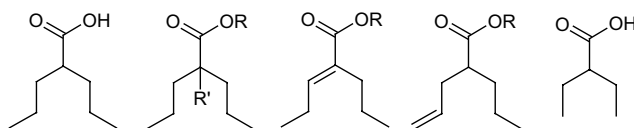


Contents

COMMUNICATIONS

- Examining the correlations between GSK-3 inhibitory properties and anti-convulsant efficacy of valproate and valproate-related compounds** pp 5465–5467

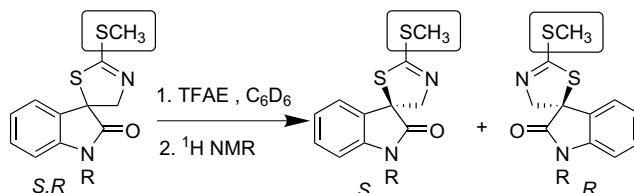
Geoff H. Werstuck,* Anna J. Kim, Timothy Brenstrum, Stephan A. Ohnmacht, Ella Panna and Alfredo Capretta*



A family of compounds based upon the chemical structure of valproate were synthesized and assayed for their ability to inhibit glycogen synthase kinase (GSK)-3 α and β activity in vitro.

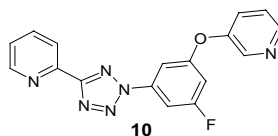
- Determination of the enantiomeric purity of the phytoalexins spirobrassinins by ^1H NMR using chiral solvation** pp 5469–5471

M. S. C. Pedras,* M. Hossain, M. G. Sarwar and S. Montaut



- 2-{2-[3-(Pyridin-3-yloxy)phenyl]-2H-tetrazol-5-yl}pyridine: a highly potent, orally active, metabotropic glutamate subtype 5 (mGlu5) receptor antagonist** pp 5473–5476

Dehua Huang,* Steve F. Poon, Deborah F. Chapman, Janice Chung, Merryl Cramer, Thomas S. Reger, Jeffrey R. Roppe, Lida Tehrani, Nicholas D. P. Cosford and Nicholas D. Smith



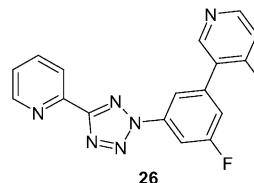
Structure–activity relationship studies on 3-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile **2** led to the discovery of 2-{2-[3-(pyridin-3-yloxy)phenyl]-2H-tetrazol-5-yl}pyridine (**10**)—a highly potent and selective mGlu5 receptor antagonist with good brain penetration and in vivo receptor occupancy in rat and cross-species oral bioavailability.

3-[3-Fluoro-5-(5-pyridin-2-yl-2H-tetrazol-2-yl)phenyl]-4-methylpyridine: a highly potent and orally bioavailable metabotropic glutamate subtype 5 (mGlu5) receptor antagonist

pp 5477–5480

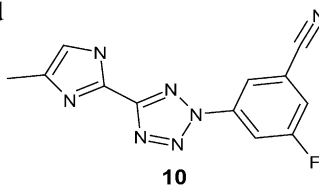
Steve F. Poon,* Brian W. Eastman, Deborah F. Chapman, Janice Chung, Merryl Cramer, Gregory Holtz, Nicholas D. P. Cosford and Nicholas D. Smith

Structure–activity relationship studies performed around 3-fluoro-5-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile for the purposes of developing novel mGlu5 receptor antagonists are described. Synthesis of a series of four-ring tetrazoles led to the discovery of 3-[3-fluoro-5-(5-pyridin-2-yl-2H-tetrazol-2-yl)phenyl]-4-methylpyridine (**26**), a highly potent, brain penetrant, tetrazole-based mGlu5 receptor antagonist.

**Discovery of highly potent, selective, orally bioavailable, metabotropic glutamate subtype 5 (mGlu5) receptor antagonists devoid of cytochrome P450 1A2 inhibitory activity**

pp 5481–5484

Nicholas D. Smith,* Steve F. Poon, Dehua Huang, Mitchell Green, Christopher King, Lida Tehrani, Jeffrey R. Roppe, Janice Chung, Deborah P. Chapman, Merryl Cramer and Nicholas D. P. Cosford

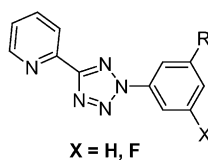


Structure–activity relationship studies focused on bio-isosteric replacements of 2-pyridyl resulted in mGlu5 receptor antagonists with reduced inhibition of cytochrome P450 1A2. This led to highly potent, selective and orally bioavailable 2-imidazolyl tetrazoles such as **10** that are devoid of cytochrome P450 inhibitory activity.

Expedited SAR study of an mGluR5 antagonists: generation of a focused library using a solution-phase Suzuki coupling methodology

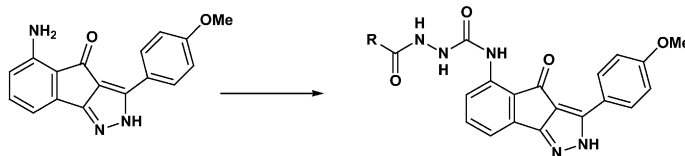
pp 5485–5488

Brian Eastman,* Chixu Chen, Nicholas D. Smith, Steven Poon, Janice Chung, Grace Reyes-Manalo, Nicholas D. P. Cosford and Benito Munoz

**Parallel synthesis of acylsemicarbazide libraries: preparation of potent cyclin dependent kinase (cdk) inhibitors**

pp 5489–5491

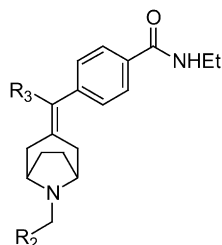
David A. Nugiel,* Anup Vidwans and Carolyn D. Dzierba



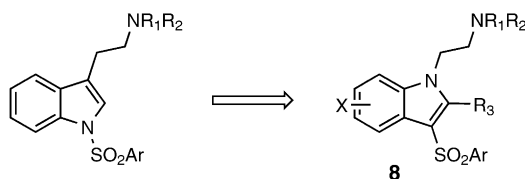
Potent cyclin dependent kinase inhibitors were prepared using parallel synthesis methodology. Treating advanced intermediate **2** with a variety of hydrazides in DMSO at 80 °C for 30 min gave the desired acylsemicarbazides in good to excellent yield. Several compounds were active against cdk4/D1 and cdk2/E in the low nanomolar range. The SAR indicates a wide variety of substituents are tolerated at the acylsemicarbazide moiety.

Parallel methods for the preparation and SAR exploration of *N*-ethyl-4-[(8-alkyl-8-aza-bicyclo[3.2.1]-oct-3-ylidene)-aryl-methyl]-benzamides, powerful μ and δ opioid agonists pp 5493–5498

Steven J. Coats,* Mark J. Schulz, John R. Carson, Ellen E. Codd, Dennis J. Hlasta, Philip M. Pitis, Dennis J. Stone, Jr., Sui-Po Zhang, Ray W. Colburn and Scott L. Dax

**1-(2-Aminoethyl)-3-(arylsulfonyl)-1*H*-indoles as novel 5-HT₆ receptor ligands** pp 5499–5502

Ronald Bernotas,* Steven Lenicek, Schuyler Antane, Guo Ming Zhang, Deborah Smith, Joseph Coupet, Boyd Harrison and Lee E. Schechter



Novel 1-(2-aminoethyl)-3-(arylsulfonyl)-1*H*-indoles were prepared. Binding assays indicated they are 5-HT₆ receptor ligands, among which *N,N*-dimethyl-*N*-{2-[3-(1-naphthylsulfonyl)-1*H*-indol-1-yl]ethyl}amine **8t** and *N*-methyl-*N*-{2-[3-(1-naphthylsulfonyl)-1*H*-indol-1-yl]ethyl}amine **8u** showed high affinity for 5-HT₆ receptors with $K_i = 3.7$ and 5.7 nM, respectively.

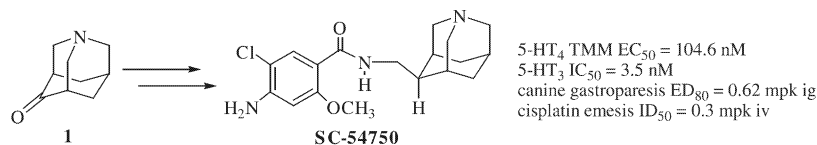
A ¹³C NMR approach to categorizing potential limitations of α,β -unsaturated carbonyl systems in drug-like molecules pp 5503–5507

Kevin P. Cusack,* Lee D. Arnold, Claude E. Barberis, Haipeng Chen, Anna M. Ericsson, Georgeen S. Gaza-Bulseco, Thomas D. Gordon, Christine M. Grinnell, Andreas Harsch, Maria Pellegrini and Edit Tarcsa

Compounds that contain an α,β -unsaturated carbonyl moiety are often flagged as potential Michael acceptors. All α,β -unsaturated carbonyl moieties are not equivalent, however, and we sought to better understand this system and its potential implications in drug-like molecules. Measurement of the ¹³C NMR shift of the β -carbon and correlation to in vitro results allowed compounds in our collection to be categorized as potential Michael acceptors, potential substrates for NADPH, or as photoisomerizable.

Azaadamantane benzamide 5-HT₄ agonists: gastrointestinal prokinetic SC-54750 pp 5509–5512

Daniel P. Becker,* Daniel L. Flynn, Robert L. Shone and Gary Gullikson

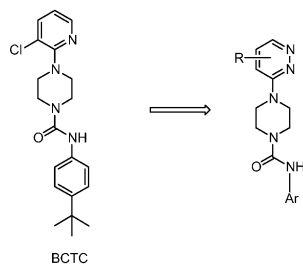


Azaadamantanone **1** was converted to a series of aminoazaadamantane benzamides **9a–d**, which were profiled for serotonin receptor activity. Aminomethylazaadamantane **SC-54750** is a potent 5-HT₄ agonist and 5-HT₃ antagonist with in vivo efficacy in gastroparesis models and also inhibits cisplatin-induced emesis.

Synthesis and evaluation of pyridazinylpiperazines as vanilloid receptor 1 antagonists

pp 5513–5519

Laykea Tafesse,* Qun Sun, Lori Schmid, Kenneth J. Valenzano, Yakov Rotshteyn, Xin Su and Donald J. Kyle

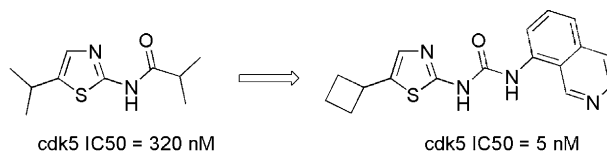


A series of pyridazinylpiperazines were synthesized and evaluated for VR1 antagonist activity in order to improve upon the pharmaceutical and pharmacological properties of BCTC.

Discovery and SAR of 2-aminothiazole inhibitors of cyclin-dependent kinase 5/p25 as a potential treatment for Alzheimer's disease

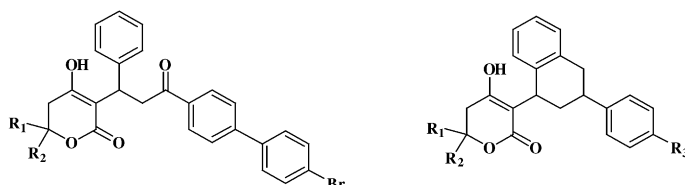
pp 5521–5525

Christopher J. Helal,* Mark A. Sanner, Christopher B. Cooper, Thomas Gant, Mavis Adam, John C. Lucas, Zhijun Kang, Stanley Kupchinsky, Michael K. Ahljanian, Bonnie Tate, Frank S. Menniti, Kristin Kelly and Marcia Peterson

**Synthesis and antitumor activity of 4-hydroxycoumarin derivatives**

pp 5527–5531

Jae-Chul Jung, Ji-Ho Lee, Seikwan Oh, Jae-Gon Lee and Oee-Sook Park*

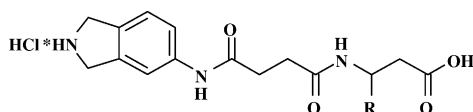


A series of 4-hydroxycoumarin derivatives was prepared and evaluated for antitumor activity against five human tumor cell lines.

Novel fibrinogen receptor antagonists. RGDF mimetics, derivatives of 4-(isoindoline-5-yl)amino-4-oxobutyric acid

pp 5533–5535

Andrei A. Krysko,* Boris M. Chugunov, Olga L. Malovichko, Sergei A. Andronati, Tatyana A. Kabanova, Tamara L. Karaseva and Anna V. Kiriya



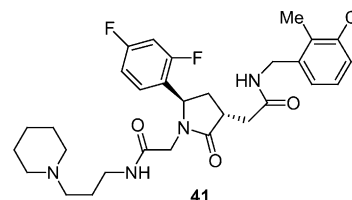
The novel RGDF mimetics **9a** and **9b** were synthesized with the use of 4-(isoindoline-5-yl)amino-4-oxobutyric acid as a surrogate of Arg-Gly motif. The synthesized compounds have demonstrated a high potency to inhibit platelet aggregation in vitro and to block FITC-Fg binding to $\alpha_{IIb}\beta_3$ on washed human platelets.

Racemic and chiral lactams as potent, selective and functionally active CCR4 antagonists

pp 5537–5542

Bradley Newhouse, Shelley Allen, Benjamin Fauber,
Aaron S. Anderson, C. Todd Eary, Joshua D. Hansen,
Justin Schiro, John J. Gaudino, Ellen Laird, David Chantry,
Christine Eberhardt and Laurence E. Burgess*

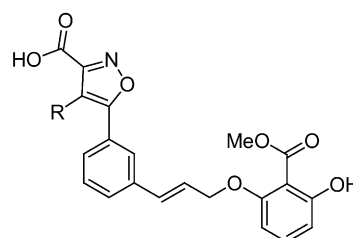
A series of racemic and chiral, nonracemic lactams that display high binding affinities, functional chemotaxis antagonism, and selectivity toward CCR4 are described. Compound **41**, which provides reasonably high blood levels in mice when dosed intraperitoneally, was identified as a useful pharmacological tool to explore the role of CCR4 antagonism in animal models of allergic disease.

**Isoxazole carboxylic acids as protein tyrosine phosphatase 1B (PTP1B) inhibitors**

pp 5543–5546

Hongyu Zhao,* Gang Liu, Zhili Xin, Michael D. Serby, Zhonghua Pei,
Bruce G. Szczepankiewicz, Philip J. Hajduk, Cele Abad-Zapatero,
Charles W. Hutchins, Thomas H. Lubben, Stephen J. Ballaron,
Deanna L. Haasch, Wiweka Kaszubska, Cristina M. Rondinone,
James M. Trevillyan and Michael R. Jirousek

Guided by X-ray crystallography, we have extended the structure–activity relationship (SAR) study on an isoxazole carboxylic acid-based PTP1B inhibitor (**1**) and more potent and equally selective (>20-fold selectivity over the highly homologous T-cell PTPase, TCPTP) PTP1B inhibitors were identified. Inhibitor **7** demonstrated good cellular activity against PTP1B in COS 7 cells.



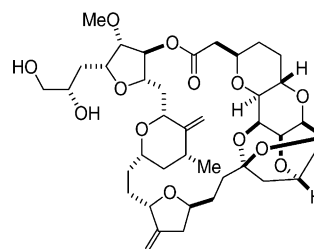
7 R=NH₂, K_i 2.1 μM (PTP1B), K_i >30 μM (TCPTP), cellular activity
8 R=CH₂OH, K_i 0.92 μM (PTP1B), K_i 19.2 μM (TCPTP)

Structurally simplified macrolactone analogues of halichondrin B

pp 5547–5550

Boris M. Seletsky, Yuan Wang, Lynn D. Hawkins, Monica H. Palme, Gregory J. Habgood,
Lucian V. DiPietro, Murray J. Towle, Kathleen A. Salvato, Bruce F. Wels, Kimberley K. Aalfs,
Yoshito Kishi, Bruce A. Littlefield and Melvin J. Yu*

Structurally simplified macrolactone analogues of halichondrin B (e.g., **47**, IC₅₀ = 0.67 nM) were identified that retain the potent cell growth inhibitory activity of the natural product in vitro.



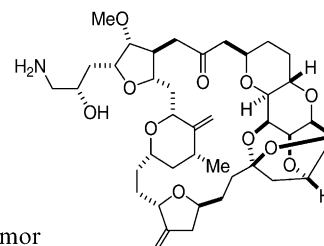
47 IC₅₀ = 0.67 nM

Macrocyclic ketone analogues of halichondrin B

pp 5551–5554

Wanjun Zheng, Boris M. Seletsky, Monica H. Palme, Paul J. Lydon, Lori A. Singer, Charles E. Chase,
Charles A. Lemelin, Yongchun Shen, Heather Davis, Lynda Tremblay, Murray J. Towle, Kathleen A. Salvato,
Bruce F. Wels, Kimberley K. Aalfs, Yoshito Kishi, Bruce A. Littlefield and Melvin J. Yu*

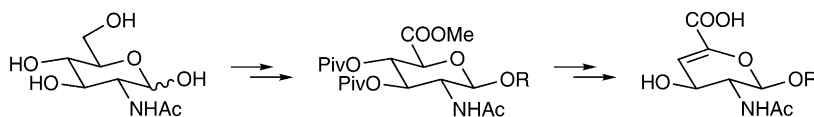
Synthesis and SAR studies of structurally simplified analogues of marine natural product halichondrin B resulted in the discovery of E7389, a new potential antitumor agent currently undergoing Phase I clinical trials.



E7389

An efficient approach to *N*-acetyl-D-glucosaminuronic acid-based sialylmimetics as potential sialidase inhibitors pp 5555–5558

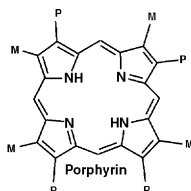
Maretta C. Mann, Robin J. Thomson and Mark von Itzstein*



The synthesis of Neu5Ac2en mimetics as inhibitors of *Vibrio cholerae* sialidase is reported.

An effective chromatographic separation of chicken red blood cell coproporphyrinogen oxidase and uroporphyrinogen decarboxylase, two enzymes in heme biosynthesis pp 5559–5564

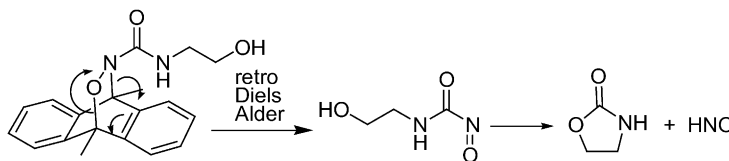
Marjorie A. Jones,* Munish Taneja, Yan Xu, Wen Chung, Christian M. Stob and Timothy D. Lash



A porphyrin-resin rapidly and effectively separates coproporphyrinogen oxidase from uroporphyrinogen decarboxylase as well as the majority of hemoglobin.

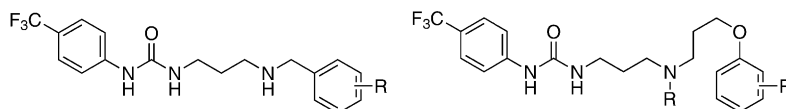
Nitroxyl (HNO) release from new functionalized *N*-hydroxyurea-derived acyl nitroso-9,10-dimethylantracene cycloadducts pp 5565–5568

Bu-Bing Zeng, Jinming Huang, Marcus W. Wright and S. Bruce King*



Aryl urea analogs with broad-spectrum antibacterial activity pp 5569–5572

Punit P. Seth,* Ray Ranken, Dale E. Robinson, Stephen A. Osgood, Lisa M. Risen, Elizabeth L. Rodgers, Michael T. Migawa, Elizabeth A. Jefferson and Eric E. Swayze



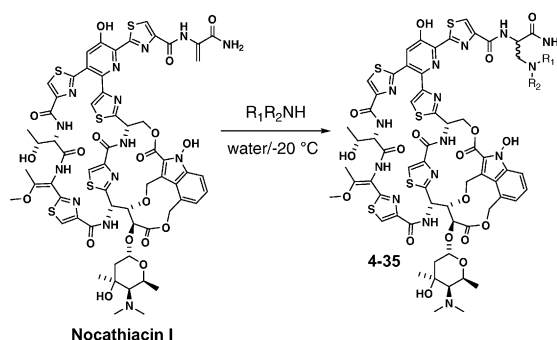
The synthesis and evaluation of aryl urea analogs as broad-spectrum antibacterial agents is described.

Nocathiacin I analogues: synthesis, in vitro and in vivo biological activity of novel semi-synthetic thiazolyl peptide antibiotics

pp 5573–5577

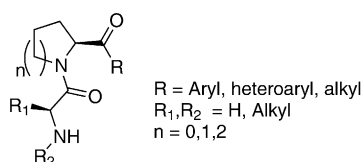
B. Narasimhulu Naidu,* Margaret E. Sorenson, Yunhui Zhang, Oak K. Kim, John D. Matiskella, John A. Wichtowski, Timothy P. Connolly, Wenying Li, Kin S. Lam, Joanne J. Bronson, Michael J. Pucci, Junius M. Clark and Yasutsugu Ueda

The synthesis and antibacterial activity of nocathiacin I analogues is described.

**Ketopyrrolidines and ketoazetidines as potent dipeptidyl peptidase IV (DPP IV) inhibitors**

pp 5579–5583

Dana Ferraris,* Yao-Sen Ko, David Calvin, Tiffany Chiou, Susan Lautar, Bert Thomas, Krystyna Wozniak, Camilo Rojas, Vincent Kalish and Sergei Belyakov

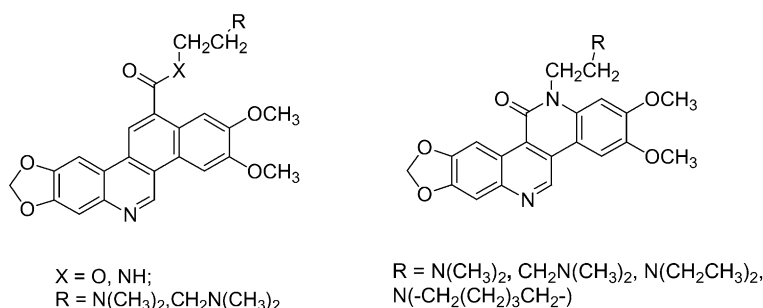


In this paper the synthesis and structure–activity relationships of two classes of electrophile-based DPP IV inhibitors, the ketopyrrolidines and ketoazetidines, is discussed. The in vitro potency, stability and ex vivo experiments were performed on select compounds within these series to determine their inhibitory capacity in plasma.

**Dimethoxybenzo[*l*]phenanthridine-12-carboxylic acid derivatives and 6*H*-dibenzo[*c,h*][2,6]naphthyridin-5-ones with potent topoisomerase I-targeting activity and cytotoxicity**

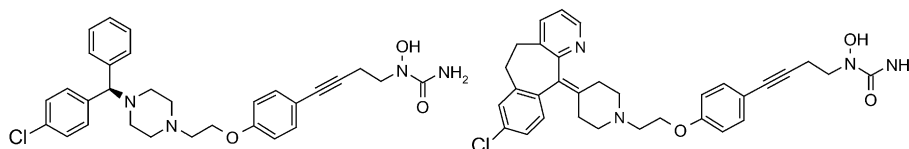
pp 5585–5589

Alexander L. Ruchelman, Shejin Zhu, Nai Zhou, Angela Liu, Leroy F. Liu and Edmond J. LaVoie*

**Cetirizine and loratadine-based antihistamines with 5-lipoxygenase inhibitory activity**

pp 5591–5594

Timothy A. Lewis,* Michelle A. Young, Mark P. Arrington, Lynn Bayless, Xiong Cai, Philippe Collart, Joseph B. Eckman, James L. Ellis, Doina G. Ene, Lyn Libertine, Jean-Marie Nicolas, Ralph T. Scannell, Bruce F. Wels, Karen Wenberg and Donna M. Wypij

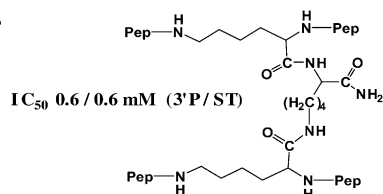
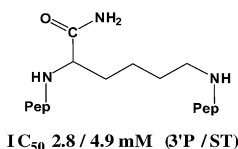


Three different histaminergic H₁ scaffolds were attached by various linkers to a single 5-LO scaffold. Both activities were observed in vitro. Pharmacokinetic properties of the compounds were evaluated and both a cetirizine-based compound and a loratadine-based analog were evaluated in vivo.

Synthesis and HIV-1 integrase inhibitory activity of dimeric and tetrameric analogs of indolicidin

pp 5595–5598

Krzysztof Krajewski, Christophe Marchand, Ya-Qiu Long, Yves Pommier and Peter P. Roller*

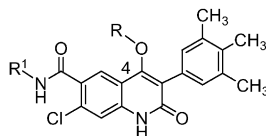
Indolicidin = ILPWKWPWWPWRR-NH₂**IC₅₀ 60 / 57 mM (3'P/ST)****ILPWKWPWWPWPP-NH₂****IC₅₀ 16 / 13 mM (3'P/ST)****Pep = ILPWKWPWWPWPP**

The HIV-1 integrase inhibitory activity of indolicidin and its analogs (including dimeric and tetrameric) are reported.

Identification of neutral 4-O-alkyl quinolone nonpeptide GnRH receptor antagonists

pp 5599–5603

Robert J. DeVita,* Mamta Parikh, Jinlong Jiang, Jason A. Fair, Jonathan R. Young, Thomas F. Walsh, Mark T. Goulet, Jane-L. Lo, Ning Ren, Joel B. Yudkovitz, Jisong Cui, Yi T. Yang, Kang Cheng, Susan P. Rohrer and Matthew J. Wyvratt

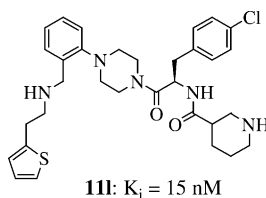


Potent neutral replacements of the basic amine at the 4-position of quinolone non-peptide GnRH antagonists are reported.

Piperazinebenzylamines as potent and selective antagonists of the human melanocortin-4 receptor

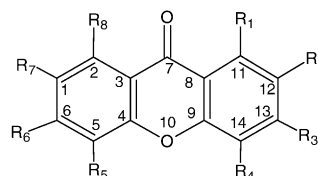
pp 5605–5609

Joseph Pontillo, Joseph A. Tran, Beth A. Fleck, Dragan Marinkovic, Melissa Arellano, Fabio C. Tucci, Marion Lanier, Jodie Nelson, Jessica Parker, John Saunders, Brian Murphy, Alan C. Foster and Chen Chen*

**QSAR modeling of the MAO inhibitory activity of xanthenes derivatives**

pp 5611–5617

M. B. Núñez, F. P. Maguna, N. B. Okulik and E. A. Castro*

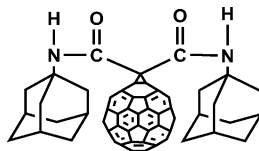


This work presents a QSAR study of the MAO A inhibitory activity (IMAO A) of a set of xanthenes resorting to the molecular descriptors E-state index (S_i), molecular connectivity (χ) and shape (k). The xanthenes group (9-H-xanton-9-onas), of natural or synthetic origin, present eight positions for the substitution and their IMAO A was reported previously by Gnerre et al. The descriptors included in the adjusted model were selected to describe the molecular structure of the compounds. The model was selected using the leave-one-out method and the cross-validation statistics shows the model is useful for prediction since: $r^2 = 0.847$, $s = 8.069$ and $F = 9.72$, calculated by multiple linear regression.

Synthesis of 61-bis(1-adamantylcarbamoyl)-1,2-methano[60]fullerene and its antagonistic effect on haloperidol-induced catalepsy in mice

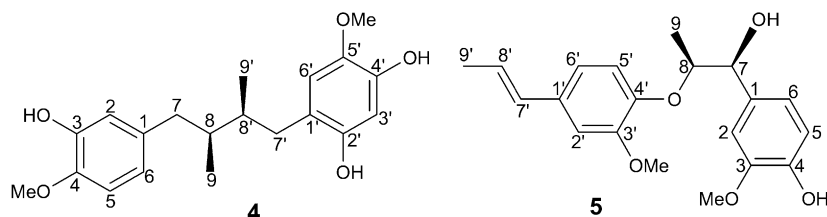
pp 5619–5621

Manabu Nakazono, Shigeo Hasegawa, Tsuneyuki Yamamoto and Kiyoshi Zaitse*

**Antioxidant activities of a new lignan and a neolignan from *Saururus chinensis***

pp 5623–5628

Woo Song Lee, Young-Il Baek, Ju-Ryoung Kim, Kyung-Hyun Cho, Dai-Eun Sok and Tae-Sook Jeong*

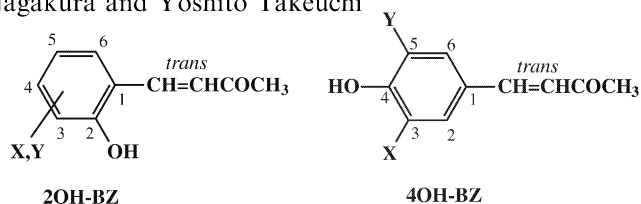


A new diarylbutane lignan, 2'-hydroxy dihydroguaiaretic acid (**4**), and a known 8-O-4'-type neolignan, machilin D (**5**) were isolated from the ethyl acetate extracts of *Saururus chinensis* root and exhibited low-density lipoprotein (LDL)-antioxidant activity and radical DPPH scavenging activity.

Quantitative structure–activity relationship analyses of antioxidant and free radical scavenging activities for hydroxybenzalacetones

pp 5629–5633

Chisako Yamagami,* Noriko Motohashi, Tatsuhiko Emoto, Akira Hamasaki, Takao Tanahashi, Naotaka Nagakura and Yoshito Takeuchi

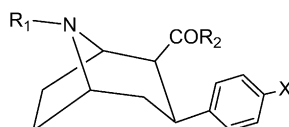


Antioxidant activities for a series of hydroxybenzalacetones, **OH-BZ**, were evaluated by measuring inhibitory potencies of **OH-BZ** against lipid peroxidation induced by *t*-BuOOH or γ -irradiation. Their quantitative structure–activity relationship (QSAR) studies indicated that the activities are mainly governed by electronic and steric factors.

Synthesis and amine transporter affinities of novel phenyltropane derivatives as potential positron emission tomography (PET) imaging agents

pp 5635–5639

Xuemei Peng, Ao Zhang, Nora S. Kula, Ross J. Baldessarini and John L. Neumeyer*

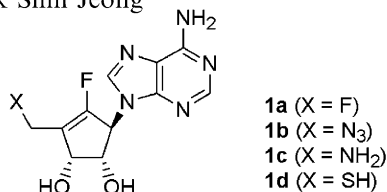


A series of novel fluoroalkyl-containing tropane derivatives were synthesized from cocaine. The binding affinities for DAT, SERT, and NET were determined via competitive binding assays.

Synthesis of 5'-substituted fluoro-neplanocin A analogues: importance of a hydrogen bonding donor at 5'-position for the inhibitory activity of S-adenosylhomocysteine hydrolase

pp 5641–5644

Hyung Ryong Moon, Hyun Joo Lee, Kyung Ran Kim, Kang Man Lee, Sang Kook Lee, Hea Ok Kim, Moon Woo Chun and Lak Shin Jeong*

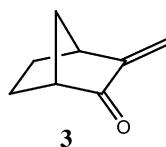


Four 5'-substituted fluoro-neplanocin A analogues **1a–d** were designed and synthesized to study structure–activity relationship against SAH. The inhibitory activity against SAH was in the following order: NH₂ > SH > F, N₃, indicating a hydrogen bonding donor such as OH or NH₂ was essential for inhibitory activity.

Identification and structure–activity relationship studies of 3-methylene-2-norbornanone as potent anti-proliferative agents presumably working through p53 mediated apoptosis

pp 5645–5649

N. Laxma Reddy,* Jeanette Hill, Long Ye, Prabhavathi B. Fernandes and David M. Stout

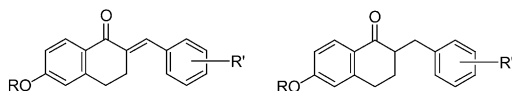


3-Methylene-2-norbornanone (**3**) showed potent activity (LC₅₀ = 3–8 μM) and selectivity for mutant p53 cell types in anti-proliferation assays. Structure–activity relationship (SAR) studies of compound **3** led to the generation of a series of compounds with high levels of anti-proliferative activities.

Synthesis and CYP24 inhibitory activity of 2-substituted-3,4-dihydro-2H-naphthalen-1-one (tetralone) derivatives

pp 5651–5654

Sook Wah Yee and Claire Simons*

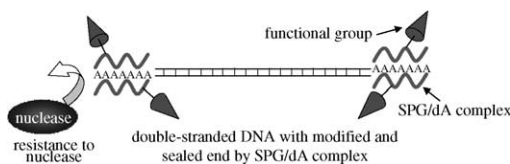


The synthesis of novel 2-benzyl- and 2-benzylidene-3,4-dihydro-2H-naphthalen-1-one derivatives and their inhibitory activity versus kidney mitochondrial 25-hydroxyvitamin D₃ 24-hydroxylase (CYP24) is described.

Proposal of new modification technique for linear double-stranded DNAs using the polysaccharide schizopyllan

pp 5655–5659

Takahisa Anada, Hideshi Matsunaga, Ryouji Karinaga, Kazuya Koumoto, Masami Mizu, Koji Nakano, Seiji Shinkai and Kazuo Sakurai*

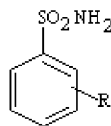


A poly(dA) tailed double-stranded DNA and its polysaccharide complexes are reported.

Topological modeling of lipophilicity, diuretic activity, and carbonic inhibition activity of benzene sulfonamides: a molecular connectivity approach

pp 5661–5666

Mona Jaiswal, Padmakar V. Khadikar* and Claudiu T. Supuran

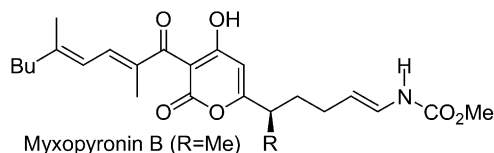


A large series of distance-based topological indices has been used for modeling lipophilicity, diuretic activity, and carbonic anhydrase inhibition activity of a library of simple substituted benzene sulfonamides. The results have shown that the topological approach used is quite useful for modeling carbonic anhydrase inhibition and the use of molecular connectivity is the best for this purpose. Excellent results are obtained in multiparametric regressions. The results are critically discussed on the basis of statistical parameters.

Myxopyronin B analogs as inhibitors of RNA polymerase, synthesis and biological evaluation

pp 5667–5672

Thomas Doundoulakis, Alan X. Xiang, Ricardo Lira, Konstantinos A. Agrios, Stephen E. Webber, Wes Sisson, Robert M. Aust, Amit M. Shah, Richard E. Showalter, James R. Appleman and Klaus B. Simonsen*

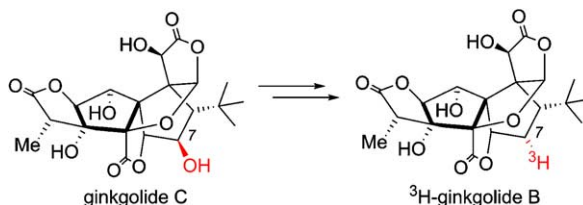


A series of myxopyronin B analogs has been prepared via a convergent synthetic route and were tested for in vitro inhibitory activity against DNA-dependent RNA polymerase and antibacterial activity against *E. coli* and *S. aureus*.

Preparation of a tritiated ginkgolide

pp 5673–5675

Kristian Strømgaard,* Makiko Suehiro and Koji Nakanishi*

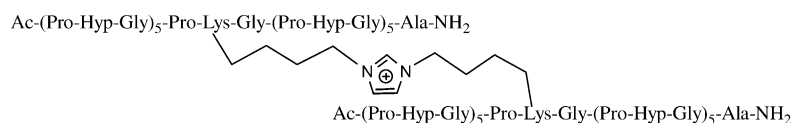


A radiolabeled constituent of *Ginkgo biloba*, [³H]-ginkgolide B, was prepared in high specific radioactivity, providing a tool for studying neuromodulatory properties of ginkgolides.

Intact glycation end products containing carboxymethyl-lysine and glyoxal lysine dimer obtained from synthetic collagen model peptide

pp 5677–5680

Hiroaki Yamada, Tomoko Sasaki, Sachiko Niwa, Tohru Oishi, Michio Murata,* Toru Kawakami and Saburo Aimoto

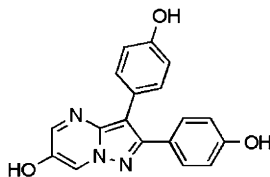


Glycation reactions using a model peptide of collagen and glucose or ribose resulted in detection of carboxymethyl-lysine in the peptide; and treatment with glyoxal provided a dimer of the peptide linked with glyoxal lysine dimer (GOLD).

Pyrazolo[1,5-*a*]pyrimidines as estrogen receptor ligands: defining the orientation of a novel heterocyclic core

pp 5681–5684

Dennis R. Compton, Kathryn E. Carlson and John A. Katzenellenbogen*

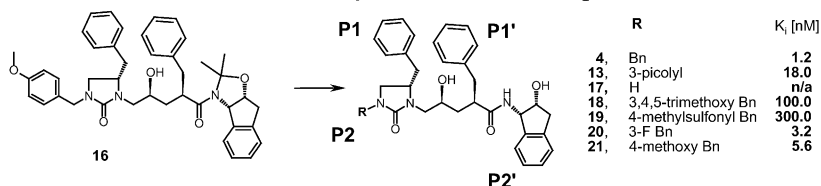


We investigated the pyrazolo[1,5-*a*]pyrimidine system as a novel heterocyclic scaffold for the development of estrogen receptor (ER) ligands. By altering the pattern of hydroxyl substitution, we established the orientation that is most favorable for ER binding, thus enabling further development of this ER ligand core.

Potent inhibitors of the HIV-1 protease incorporating cyclic urea P1–P2 scaffold

pp 5685–5687

Wieslaw M. Kazmierski,* Eric Furfine, Yolanda Gray-Nunez, Andrew Spaltenstein and Lois Wright

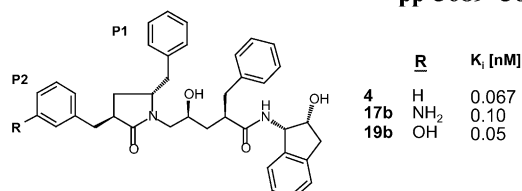


We have developed an efficient synthetic approach to analogues of potent HIV-protease inhibitor (PI) **4**. Key chemistry includes TFA-mediated deprotection of MOB-protected **16** to precursor **17**. Alkylation of **17** enabled the synthesis of many PIs, as exemplified here by **13**, **19–21**, in excellent yields and purity, and thus overcoming bottlenecks of our prior synthetic approach to these PIs. These results allowed to rapidly evaluate the SAR in P1–P2 cyclic urea-based HIV-1 PIs as well as provided a strong rationale towards P1–P2 pyrrolidone scaffold-based PIs, ultimately leading to subnanomolar PIs (follow-up communication).

Discovery of potent pyrrolidone-based HIV-1 protease inhibitors with enhanced drug-like properties

pp 5689–5692

Wieslaw M. Kazmierski,* Webb Andrews, Eric Furfine, Andrew Spaltenstein and Lois Wright

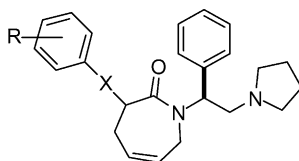


SAR around the HIV-1 protease inhibitor lead **4**, which utilizes the (3*S*,5*R*)-3,5-bis(phenylmethyl)-2-pyrrolidinone as P1–P2 scaffold, led to discovery of *meta*-amino- and *meta*-hydroxy inhibitors **17b** and **19b**, which while equipotent to **4**, in addition offered an improved aqueous solubility. The SAR was further rationalized with the aid of X-ray crystallography and suggested specific role assumed by the *meta*-substituent, which can uniquely support high enzyme potency and which can be utilized as a platform for further chemical manipulations to fine-tune other drug-like properties in this series. This finding enables additional chemistry manipulations in search for other potential HIV-1 protease inhibitor drug candidates.

Azepinone as a conformational constraint in the design of κ-opioid receptor agonists

pp 5693–5697

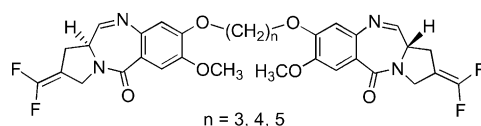
Paul A. Tuthill, Pamela R. Seida, William Barker, Joel A. Cassel, Serge Belanger, Robert N. DeHaven, Michael Koblish, Susan L. Gottshall, Patrick J. Little, Diane L. DeHaven-Hudkins and Roland E. Dolle*



Synthesis of fluorinated analogues of SJG-136 and their DNA-binding potential

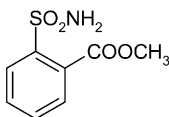
pp 5699–5702

Ahmed Kamal,* P. S. M. M. Reddy, D. Rajasekhar Reddy, E. Laxman and Y. L. N. Murthy

**Carbonic anhydrase inhibitors: inhibition of human cytosolic isozyme II and mitochondrial isozyme V with a series of benzene sulfonamide derivatives**

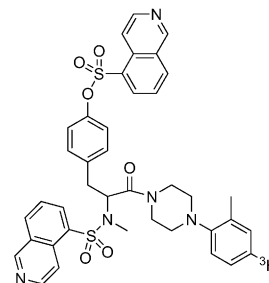
pp 5703–5707

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

**Synthesis, radiolabeling, and preliminary biological evaluation of [³H]-1-[(*S*)-*N*,*O*-bis-(isoquinolinesulfonyl)-*N*-methyl-tyrosyl]-4-(*o*-tolyl)-piperazine, a potent antagonist radioligand for the P2X₇ receptor**

pp 5709–5712

Romeo Romagnoli, Pier Giovanni Baraldi,* Maria Giovanna Pavani, Mojgan Aghazadeh Tabrizi, Allan R. Moorman, Francesco Di Virgilio, Elena Cattabriga, Cecilia Pancaldi, Stefania Gessi and Pier Andrea Borea




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*Corresponding author

* Supplementary data available via ScienceDirect

COVER

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



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