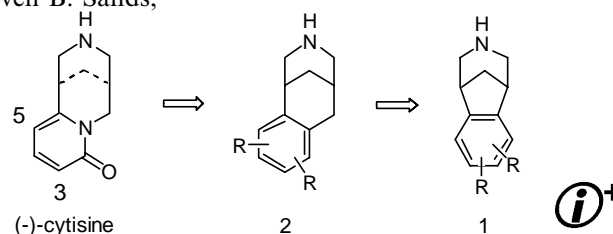


Contents

ARTICLES

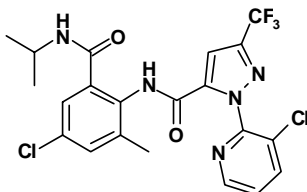
- 3,5-Bicyclic aryl piperidines: A novel class of $\alpha 4\beta 2$ neuronal nicotinic receptor partial agonists for smoking cessation** pp 4889–4897

Jotham W. Coe,* Paige R. Brooks, Michael C. Wirtz, Crystal G. Bashore, Krista E. Bianco, Michael G. Vetelino, Eric P. Arnold, Lorraine A. Lebel, Carol B. Fox, F. David Tingley, III, David W. Schulz, Thomas I. Davis, Steven B. Sands, Robert S. Mansbach, Hans Rollema and Brian T. O'Neill



- Insecticidal anthranilic diamides: A new class of potent ryanodine receptor activators** pp 4898–4906

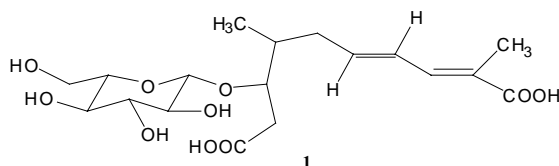
George P. Lahm,* Thomas P. Selby, John H. Freudenberger, Thomas M. Stevenson, Brian J. Myers, Gilles Seburyamo, Ben K. Smith, Lindsey Flexner, Christopher E. Clark and Daniel Cordova



This paper describes a novel class of anthranilic diamides with exceptional activity on insects of the order Lepidoptera. These compounds have been found to exhibit their action by release of intracellular Ca^{2+} stores mediated by the ryanodine receptor.

- A new antitumor compound from the plant *Oryctanthus* sp. as a VEGF receptor binding inhibitor** pp 4907–4909

Vinod R. Hegde,* Haiyan Pu, Mahesh Patel, Adrian Jachens, Vincent P. Gullo and Tze-Ming Chan

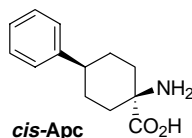


The 70% aqueous methanolic extract of the Peruvian plant *Oryctanthus* sp. was found to contain a novel saccharide of a diene α,ω -diacid. Compound **1** was identified as inhibitor of the VEGF receptor. The structure of this compound was established based on NMR studies. Compound **1** inhibited ligand binding to the VEGF receptor with an IC_{50} of 5.0 μM .

Discovery of 1-amino-4-phenylcyclohexane-1-carboxylic acid and its influence on agonist selectivity between human melanocortin-4 and -1 receptors in linear pentapeptides

pp 4910–4914

Xin-Jie Chu,* David Bartkovitz, Waleed Danho, Joseph Swistok, Adrian Wai-Hing Cheung, Grazyna Kurylko, Karen Rowan, Mitch Yeon, Lucia Franco, Lida Qi, Li Chen and Keith Yagaloff



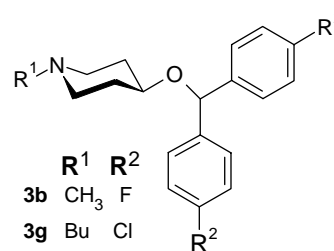
A design and synthesis of *cis*-Apc as new histidine surrogate and its incorporation into linear pentapeptides (Penta-*cis*-Apc-DPhe-Arg-Trp-Gly-NH₂) and related analogs leading to potent and selective hMC4R agonists are reported.

The synthesis and biological evaluation of dopamine transporter inhibiting activity of substituted diphenylmethoxypiperidines

pp 4915–4918

Gennady B. Lapa, Gary D. Byrd, Alla A. Lapa, Evgeny A. Budygin, Steven R. Childers, Sara R. Jones* and Jill J. Harp

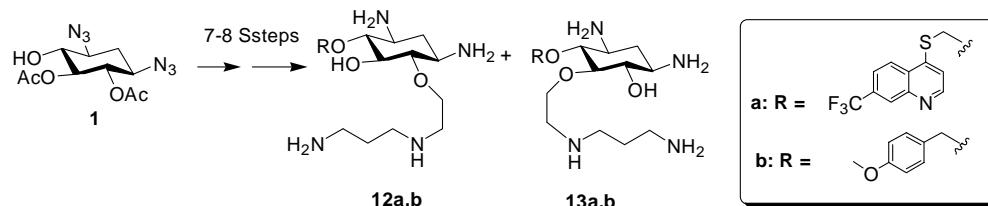
The development of potent 4-(arylmethoxy)-1-alkylpiperidine inhibitors of the dopamine transporter is described. Symmetrical *para* substituents of the benzene rings are important for high potency in binding to the dopamine transporter. **3b** has an IC₅₀ = 22.1±5.73 nM and elevates locomotor activity in mice, and **3g** has an IC₅₀ = 12.1±7.51 nM and is inactive in this test.



The synthesis and 16S A-site rRNA recognition of carbohydrate-free aminoglycosides

pp 4919–4922

Xiaojing Wang, Michael T. Migawa,* Kristin A. Sannes-Lowery and Eric E. Swayze



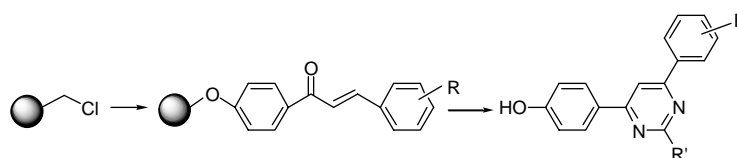
The first carbohydrate-free aminoglycoside analogs bearing the 2-deoxystreptamine moiety were synthesized from asymmetrically protected 2-deoxystreptamine and subsequently demonstrated to have significant binding to the 16S A-site rRNA target and moderate functional activity.



Solid support synthesis of 6-aryl-2-substituted pyrimidin-4-yl phenols as anti-infective agents

pp 4923–4926

Anu Agarwal, Kumkum Srivastava, S. K. Puri, S. Sinha and Prem M. S. Chauhan*

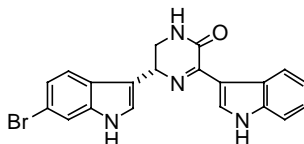


Out of the 30 compounds synthesized, 23 compounds have shown in vitro antimalarial activities against *Plasmodium falciparum* in the range of 0.25–2 µg/mL and 16 compounds have shown antitubercular activity against *Mycobacterium tuberculosis* H₃₇Ra, at a concentration of 25 µg/mL.

Bis(indole) alkaloids as sortase A inhibitors from the sponge *Spongisorites* sp.

pp 4927–4931

Ki-Bong Oh, Woongchon Mar, Sanghee Kim, Ji-Yun Kim, Mi-Na Oh,
Jae-Gyu Kim, Daehyun Shin, Chung J. Sim and Jongheon Shin*

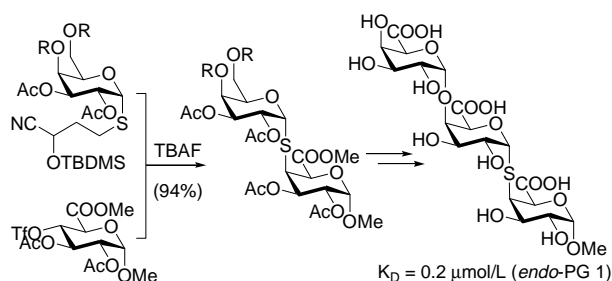


The isolation, structure identification, and bioactivity of nine bis(indole) alkaloids are described.

Design, synthesis, and enzymatic property of a sulfur-substituted analogue of trigalacturonic acid

pp 4932–4935

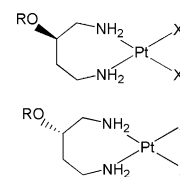
Kazunori Yamamoto, Naoki Watanabe, Hiroko Matsuda, Keiichiro Oohara,
Tomoyuki Araya, Masaru Hashimoto,* Kazuo Miyairi, Isao Okazaki, Minoru Saito,
Tetsuya Shimizu, Hiroaki Kato and Toshikatsu Okuno

**Synthesis and in vitro cytotoxicity of novel hydrophilic chiral 2-alkoxy-1,4-butanediamine platinum (II) complexes**

pp 4936–4943

Haibin Zhu, Kai Cui, Lianhong Wang and Shaohua Gou*

Twenty-six new hydrophilic chiral 2-alkoxy-1,4-butanediamine platinum (II) complexes have been synthesized and most of them were evaluated for their in vitro cytotoxicity toward two human tumor cell lines. The cytotoxicities of platinum complexes are related to the nature of the carrier ligand and leaving group. Complex **5b** exhibits the greatest potency among those 21 tested platinum complexes in both cell lines.

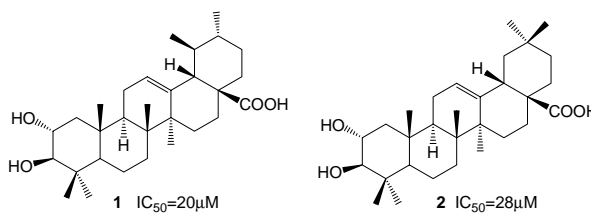


R = Me, Et
2X = dichloro, oxalato, malonato,
cyclobutane-1,1-dicarboxylato, etc

Pentacyclic triterpenes. Part 1: The first examples of naturally occurring pentacyclic triterpenes as a new class of inhibitors of glycogen phosphorylases

pp 4944–4948

Xiaoan Wen, Hongbin Sun,* Jun Liu, Guanzhong Wu, Luyong Zhang, Xiaoming Wu and Peizhou Ni

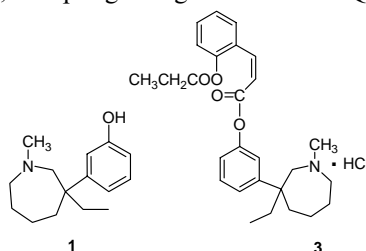


The semi-synthesis, in vitro and in vivo biological evaluation of corosolic acid (**1**) and maslinic acid (**2**) are described. Compounds **1** and **2** represent a new class of inhibitors of glycogen phosphorylases.

Insecticidal activity of proteinous venom from tentacle of jellyfish *Rhopilema esculentum* Kishinouye pp 4949–4952
Huahua Yu, Xiguang Liu, Xiangli Dong, Cuiping Li, Rong Xing, Song Liu and Pengcheng Li*

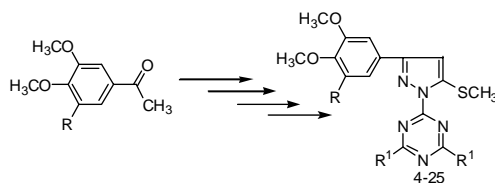
Insecticidal activity of proteinous venom from tentacle of jellyfish *Rhopilema esculentum* Kishinouye was determined against three pest species, *Stephanitis pyri* Fabriciusa, *Aphis medicaginis* Koch, and *Myzus persicae* Sulzer.

Design, synthesis, and bioavailability evaluation of coumarin-based prodrug of meptazinol pp 4953–4956
Qiong Xie, Xiaolin Wang, Xinghai Wang, Zhiqiang Jiang and Zhuibai Qiu*



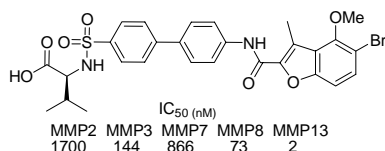
A coumarin-based esterase-sensitive prodrug (**3**) of meptazinol (**1**) was designed and synthesized to minimize the first-pass effect of meptazinol. Biological evaluation results in rats indicated that there was a 4-fold increase in oral bioavailability of this prodrug compared to the parent drug meptazinol.

Synthesis of 2-[3,5-substituted pyrazol-1-yl]-4,6-trisubstituted triazine derivatives as antimalarial agents pp 4957–4960
Sanjay Babu Katiyar, Kumkum Srivastava, S. K. Puri and Prem M. S. Chauhan*



A series of 22 compounds were synthesized and screened against *Plasmodium falciparum* NF-54 strain. Of the screened compounds, 6 compounds showed MIC in the range between 1 and 2 $\mu\text{g/mL}$. These compounds are 32 times more potent than the cycloguanil which was used as the standard drug.

Synthesis and SAR of highly selective MMP-13 inhibitors pp 4961–4966
Jianchang Li,* Thomas S. Rush, III, Wei Li, Dianne DeVincentis, Xuemei Du, Yonghan Hu, Jennifer R. Thomason, Jason S. Xiang, Jerauld S. Skotnicki, Steve Tam, Kristina M. Cunningham, Priya S. Chockalingam, Elisabeth A. Morris and Jeremy I. Levin

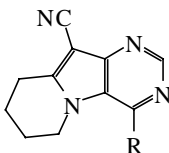


The structure-based design and synthesis of a series of novel biphenyl sulfonamide carboxylic acids as potent MMP-13 inhibitors with selectivity over MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-14, Aggrecanase 1, and TACE are described.

Topological model for the prediction of MRP1 inhibitory activity of pyrrolopyrimidines and templates derived from pyrrolopyrimidine

pp 4967–4972

Viney Lather and Anil K. Madan*



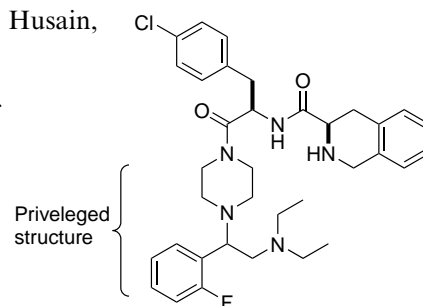
Wiener's index—a distance-based topological descriptor has been successfully employed for development of a model for prediction of MRP1 inhibitory activity of pyrrolopyrimidines and their derivatives. Active range of the proposed model possesses vast potential for providing lead structures for development of potent inhibitors of MRP1.

Privileged structure based ligands for melanocortin receptors—Substituted benzylic piperazine derivatives

pp 4973–4978

Matthew J. Fisher,* Ryan T. Backer, Iván Collado, Óscar de Frutos, Saba Husain, Hansen M. Hsiung, Steve L. Kuklish, Ana I. Mateo, Jeffrey T. Mullaney, Paul L. Ornstein, Cristina García Paredes, Thomas P. O'Brian, Timothy I. Richardson, Jikesh Shah, John M. Zgombick and Karin Briner

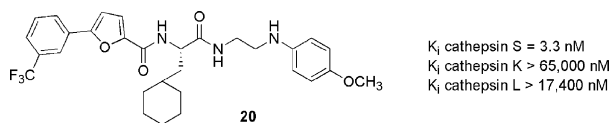
A variety of substituted benzylic piperazines provide useful privileged structures for the construction of ligands with affinity for melanocortin 4 receptors.



Design and synthesis of arylaminoethyl amides as noncovalent inhibitors of cathepsin S. Part 1

pp 4979–4984

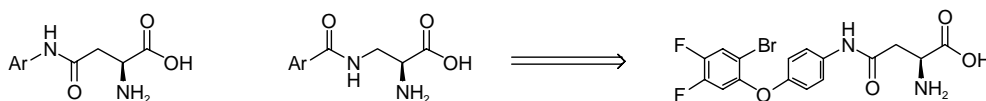
Hong Liu,* David C. Tully, Robert Epple, Badry Bursulaya, Jun Li, Jennifer L. Harris, Jennifer A. Williams, Ross Russo, Christine Tumanut, Michael J. Roberts, Phil B. Alper, Yun He and Donald S. Karanewsky



Synthesis and biological activities of aryl-ether-, biaryl-, and fluorene-aspartic acid and diaminopropionic acid analogs as potent inhibitors of the high-affinity glutamate transporter EAAT-2

pp 4985–4988

Alexander Greenfield,* Cristina Grosanu, John Dunlop, Beal McIlvain, Tikva Carrick, Brian Jow, Qiang Lu, Dianne Kowal, John Williams and John Butera

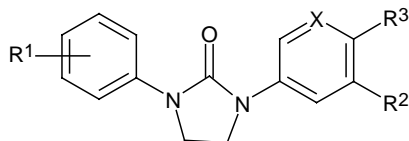


An extensive SAR study of a series of aspartic and 2,3-diaminopropionic acid amides led to the discovery of 2-bromo-4,5-difluorophenoxyphenyl-L-asparagine—one of the most potent, selective, competitive non-substrate inhibitors of EAAT-2 identified to date.

A series of bisaryl imidazolidin-2-ones has shown to be selective and orally active 5-HT_{2C} receptor antagonists

pp 4989–4993

Caroline J. Goodacre,* Steven M. Bromidge, David Clapham, Frank D. King, Peter J. Lovell, Mike Allen, Lorraine P. Campbell, Vicky Holland, Graham J. Riley, Kathryn R. Starr, Brenda K. Trail and Martyn D. Wood

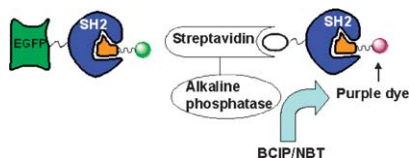


A series of novel bisaryl imidazolidinones have been prepared and evaluated both in vitro and in vivo for their 5-HT_{2C} receptor antagonist activity.

Solid-phase binding assays of peptides using EGFP-Src SH2 domain fusion protein and biotinylated Src SH2 domain

pp 4994–4997

Guofeng Ye, Marina Ayrapetov, Nguyen-Hai Nam, Gongqin Sun and Keykavous Parang*

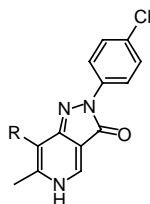


Two solid-phase binding assays were evaluated for potential use in the screening of peptides as the Src SH2 domain inhibitors.

Pyrazolopyridinones as functionally selective GABA_A ligands

pp 4998–5002

Wesley P. Blackaby,* John R. Atack, Frances Bromidge, Richard Lewis, Michael G. N. Russell, Alison Smith, Keith Wafford, Ruth M. McKernan, Leslie J. Street and José L. Castro

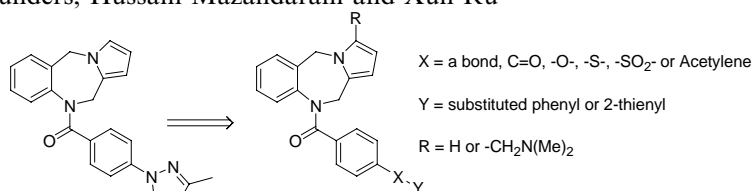


2,5-Dihydro-3H-pyrazolo[4,3-c]pyridin-3-ones are GABA_A receptor benzodiazepine binding site ligands, which can exhibit functional selectivity for the α_3 subtype over the α_1 subtype. SAR studies to optimize this functional selectivity are described.

(4-Substituted-phenyl)-(5H-10,11-dihydro-pyrrolo [2,1-c][1,4] benzodiazepin-10-yl)-methanone derivatives as vasopressin receptor modulators

pp 5003–5006

Aranapakam M. Venkatesan,* George T. Grosu, Amedeo A. Failli, Peter S. Chan, Joseph Coupet, Trina Saunders, Hussain Mazandarani and Xun Ru



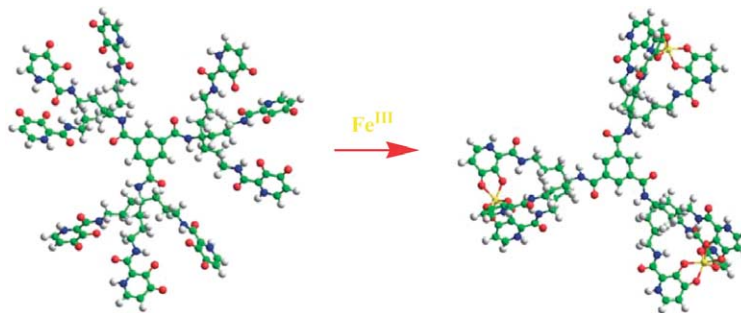
2b-VNA-932

Synthesis and structure–activity relationships (SAR) of arginine vasopressin (AVP) receptor modulators are described.

High affinity iron(III) scavenging by a novel hexadentate 3-hydroxypyridin-4-one-based dendrimer: Synthesis and characterization

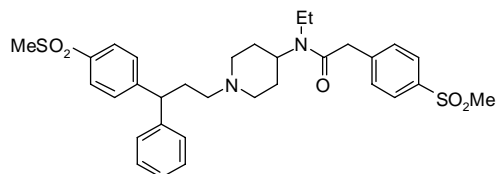
pp 5007–5011

Tao Zhou, Zu Dong Liu, Hendrik Neubert, Xiao Le Kong, Yong Min Ma and Robert C. Hider*

**Modulators of the human CCR5 receptor. Part 2: SAR of substituted 1-(3,3-diphenylpropyl)-piperidinyl phenylacetamides**

pp 5012–5015

John G. Cumming,* Anne E. Cooper, Ken Grime, Chris J. Logan, Sharon McLaughlin, John Oldfield, John S. Shaw, Howard Tucker, Jon Winter and David Whittaker



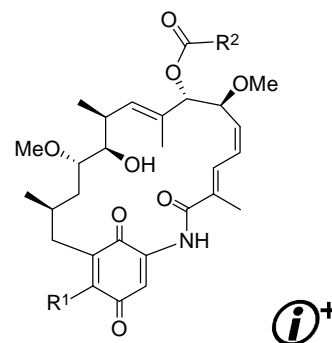
SAR and DMPK studies led to the identification of substituted *N*-alkyl-*N*-[1-(3,3-diphenylpropyl)piperidin-4-yl]-2-phenylacetamides as potent and orally bioavailable ligands for the human CCR5 receptor.

Structure-based design of 7-carbamate analogs of geldanamycin

pp 5016–5021

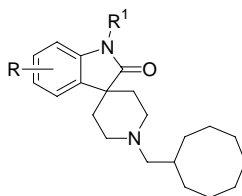
Giulio Rastelli, Zong-Qiang Tian, Zhan Wang, David Myles and Yaoquan Liu*

The structure-based design, synthesis, Hsp90 inhibitions, and cytotoxicity of a series of 7-derivatives of 17-alkyl geldanamycins are described.

**Preparation of 3-spirocyclic indolin-2-ones as ligands for the ORL-1 receptor**

pp 5022–5026

Gilles C. Bignan,* Kathleen Battista, Peter J. Connolly, Michael J. Orsini, Jingchun Liu, Steven A. Middleton and Allen B. Reitz

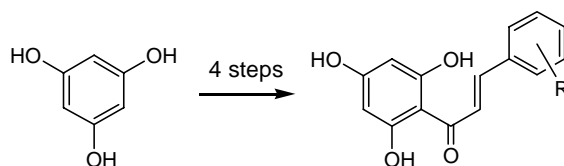


Synthesis and SAR of a series of indolin-2-ones provided compounds with high affinity for the ORL-1 receptor.

Synthesis and evaluation of antiplatelet activity of trihydroxychalcone derivatives

pp 5027–5029

Li-Ming Zhao, Hai-Shan Jin, Liang-Peng Sun, Hu-Ri Piao and Zhe-Shan Quan*



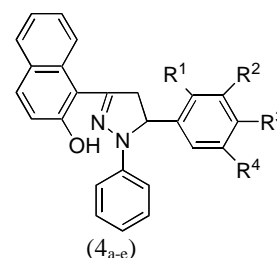
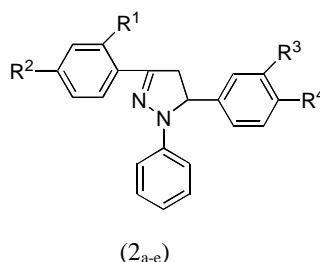
A series of trihydroxychalcones was synthesized and screened in vitro for their inhibitory effects on washed rabbit platelet aggregation induced by arachidonic acid (100 μ M) and collagen (10 μ g/ml). Compound **4e** exhibited a potent inhibitory effect on arachidonic acid- and collagen-induced platelet aggregation. The structure–activity relationships were also discussed in this paper.

Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2''-hydroxy naphthalen-1''-yl)-1,5-diphenyl-2-pyrazolines

pp 5030–5034

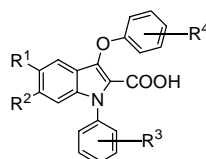
Y. Rajendra Prasad,* A. Lakshmana Rao, L. Prasanna, K. Murali and P. Ravi Kumar

The synthesis of different substituted 2-pyrazolines from the corresponding chalcones by condensation with phenyl hydrazine hydrochloride is reported. The chalcones employed in this reaction were prepared by condensing appropriate acetophenones with benzaldehyde derivatives in dilute ethanolic potassium hydroxide solution. The majority of the compounds synthesised possessed significant antidepressant activity in mice ($P < 0.05$) in the Porsolt behavioural despair test.

**Synthesis and biological activities of novel aryl indole-2-carboxylic acid analogs as PPAR γ partial agonists**

pp 5035–5038

James F. Dropinski,* Taro Akiyama, Monica Einstein, Bahanu Habulihaz, Tom Doebber, Joel P. Berger, Peter T. Meinke and Guo Q. Shi

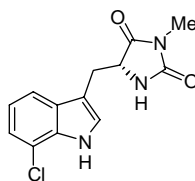


A series of novel aryl indole-2-carboxylic acids has been identified as potent selective PPAR γ modulators. Their chemical synthesis and in vitro activities are discussed. An optimized compound was efficacious in the *db/db* mouse model of type 2 diabetes.

Structure–activity relationship study of novel necroptosis inhibitors

pp 5039–5044

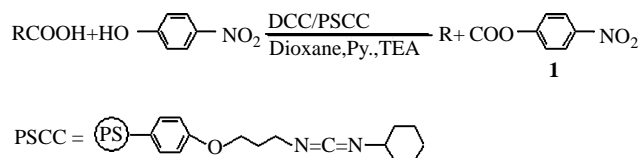
Xin Teng, Alexei Degterev, Prakash Jagtap, Xuechao Xing, Sungwoon Choi, Régine Denu, Junying Yuan and Gregory D. Cuny*



Polymer supported carbodiimide strategy for the synthesis of *N*-acylated derivatives of deoxy- and ribo purinenucleosides using active esters

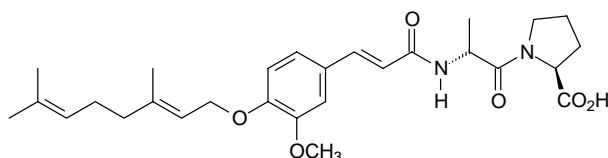
pp 5045–5048

Snehlata Tripathi,* Krishna Misra and Yogesh S. Sanghvi

**Synthesis of a novel prodrug of 3-(4'-geranyloxy-3'-methoxyphenyl)-2-*trans*-propenoic acid for colon delivery**

pp 5049–5052

Massimo Curini,* Francesco Epifano and Salvatore Genovese

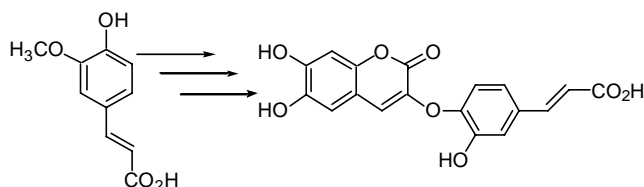


The synthesis of a novel colon ACE targeted prodrug of 3-(4'-geranyloxy-3'-methoxyphenyl)-2-*trans*-propenoic acid is described.

**Synthesis and HIV-1 integrase inhibitory activities of caffeic acid dimers derived from *Salvia officinalis***

pp 5053–5056

Fabrice Bailly,* Clémence Queffelec, Gladys Mbemba, Jean-François Mouscadet and Philippe Cotelle

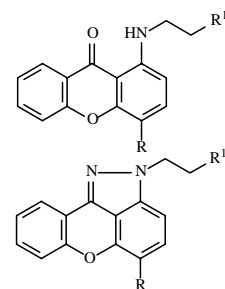


Two caffeoyl-coumarin conjugates derived from sagecoumarin were synthesized and exhibited potent micromolar inhibitory potencies against HIV-1 integrase in 3'-end processing reaction but were less effective against HIV-1 replication.

Design, synthesis, and antiproliferative activity of some novel aminosubstituted xanthenones, able to overcome multidrug resistance toward MES-SA/Dx5 cells

pp 5057–5060

Ioannis K. Kostakis, Roxane Tenta, Nicole Pouli, Panagiotis Marakos,* Alexios-Leandros Skaltsounis, Harris Pratsinis and Dimitris Kletsas

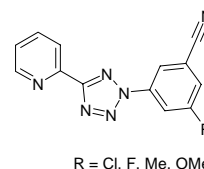
R = H, NO₂R¹ = N(CH₃)₂, N(CH₂)₄, N(CH₂)₅

3-[Substituted]-5-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitriles: Identification of highly potent and selective metabotropic glutamate subtype 5 receptor antagonists

pp 5061–5064

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

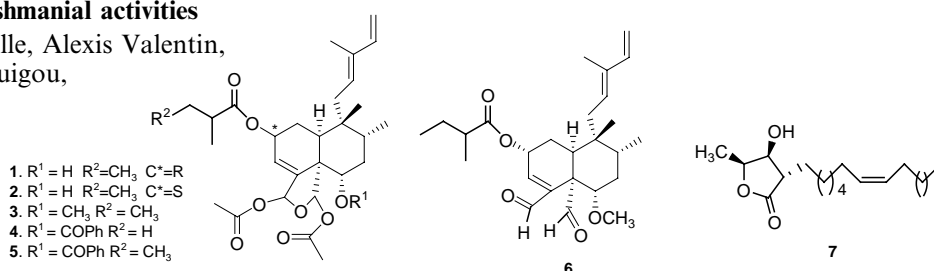
Structure–activity relationship studies on the phenyl ring of 3-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile **2** led to the discovery that small, non-hydrogen bond donor substituents at the 3-position led to a substantial increase in in vitro potency. In particular, 3-fluoro-5-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile (**7**) is a highly potent and selective mGlu5 receptor antagonist with good rat pharmacokinetics, brain penetration, and in vivo receptor occupancy.



New clerodane diterpenoids from *Laetia procera* (Poepp.) Eichler (Flacourtiaceae), with antiplasmodial and antileishmanial activities

pp 5065–5070

Valérie Jullian,* Colin Bonduelle, Alexis Valentin, Lucia Acebey, Anne-Gaëlle Duigou, Marie-Francoise Prévost and Michel Sauvain

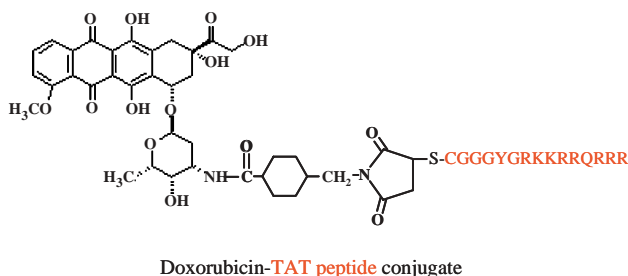


Together with two known compounds, Casearlucine A (**1**) and Casearmembrol B (**2**), four new clerodane diterpenoids and one new butanolide have been isolated from *Laetia procera* (Flacourtiaceae). The six clerodane diterpenoids displayed activities against *Plasmodium falciparum*, *Leishmania amazonensis*, and human tumor cell line MCF7.

Synthesis of doxorubicin–peptide conjugate with multidrug resistant tumor cell killing activity

pp 5071–5075

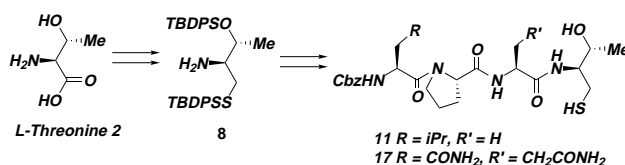
Jun F. Liang* and Victor C. Yang



Synthesis of (2R,3S) 3-amino-4-mercapto-2-butanol, a threonine analogue for covalent inhibition of sortases

pp 5076–5079

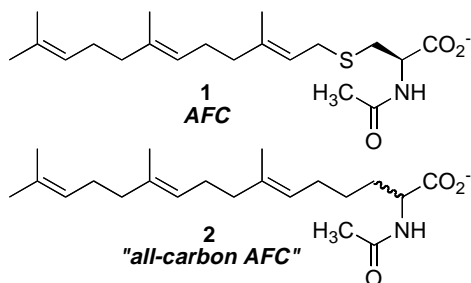
Michael E. Jung,* Jeremy J. Clemens, Nuttee Suree, Chu Kong Liew, Rosemarie Pilpa, Dean O. Campbell and Robert T. Clubb



Synthesis of desthio prenylcysteine analogs: Sulfur is important for biological activity

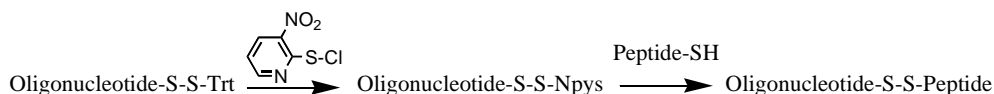
pp 5080–5083

Brian S. Henriksen, Jessica L. Anderson, Christine A. Hrycyna and Richard A. Gibbs*

**Toward high yield synthesis of peptide–oligonucleotide chimera through a disulfide bridge: A simplified method for oligonucleotide activation**

pp 5084–5087

Frédéric Maurel, Françoise Debart, Florine Cavelier, Alain R. Thierry, Bernard Lebleu, Jean-Jacques Vasseur and Eric Vivès*

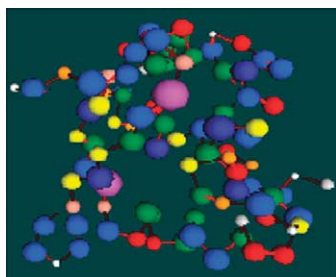


A straightforward method to attach an oligonucleotide to a cell penetrating peptide is developed.

Proteins QSAR with Markov average electrostatic potentials

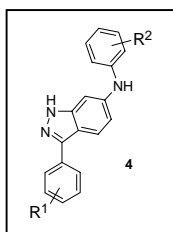
pp 5088–5094

Humberto González-Díaz* and Eugenio Uriarte*

**Design and synthesis of 6-anilinoindazoles as selective inhibitors of c-Jun N-terminal kinase-3**

pp 5095–5099

Britt-Marie Swahn,* Fernando Huerta, Elisabet Kallin, Jonas Malmström, Tatjana Weigelt, Jenny Viklund, Patrick Womack, Yafeng Xue and Liselotte Öhberg


The structure-based design and synthesis of a new series of c-Jun N-terminal kinase-3 inhibitors **4** with selectivity against JNK1 and p38 α is reported.

OTHER CONTENTS

Contributors to this issue
Summary of instructions to authors 2005

pp I–II
p III

*Corresponding author

+ Supplementary data available via ScienceDirect

COVER

Amerliorating transthyretin amyloidogenesis by native state kinetic stabilization mediated by small molecule binding. Small molecule binding to the amyloidogenic protein transthyretin kinetically stabilizes the native tetrameric state, preventing dissociation to folded monomers that misfold and misassemble into toxic intermediates, amorphous aggregates, and amyloid fibrils. The Kelly laboratory has developed several structurally distinct inhibitor families, depicted in the background, that are undergoing pharmacological evaluation. Created by Steven M. Johnson, graduate student in Professor Jeffery W. Kelly's laboratory, Department of Chemistry, The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA.



Full text of this journal is available, on-line from **ScienceDirect**. Visit www.sciencedirect.com for more information.



This journal is part of **ContentsDirect**, the *free* alerting service which sends tables of contents by e-mail for Elsevier books and journals. You can register for **ContentsDirect** online at: <http://contentsdirect.elsevier.com>

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIODISE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE



ISSN 0960-894X