



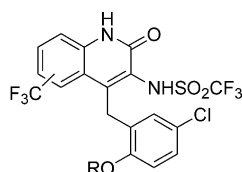
Contents

COMMUNICATIONS

The synthesis and structure–activity relationships of 3-amino-4-benzylquinolin-2-ones: discovery of novel KCNQ2 channel openers

pp 1615–1618

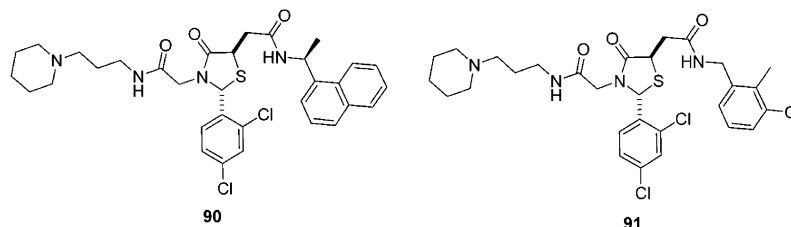
Piyasena Hewawasam,* Nathan Chen, Min Ding, Joanne T. Natale, Christopher G. Boissard, Sarita Yeola, Valentin K. Gribkoff, John Starrett and Steven I. Dworketzky



Discovery and SAR of trisubstituted thiazolidinones as CCR4 antagonists

pp 1619–1624

Shelley Allen, Bradley Newhouse, Aaron S. Anderson, Benjamin Fauber, Andrew Allen, David Chantry, Christine Eberhardt, Joshua Odingo and Laurence E. Burgess*



Substituted thiazolidinones were identified as CCR4 antagonists from high throughput screening. Subsequent lead optimization efforts resulted in defined structure–activity relationships and the identification of potent antagonists (compounds **90** and **91**) that inhibited the chemotaxis of Th2 T-cells in vitro.

Evidences for the formation of bisbenzamidine–heme complexes in cell-free systems

pp 1625–1628

Annie Mayence, Jean Jacques Vanden Eynde and Tien L. Huang*



IR spectra and colorimetry data indicated that bisbenzamidines readily interact with heme in cell-free systems at pH 5.0 and 7.0.

Femtosecond time-resolved guanine oxidation in acridine modified alanyl peptide nucleic acids

pp 1629–1632

D. Weicherding, W. B. Davis, S. Hess, T. von Feilitzsch, M. E. Michel-Beyerle* and U. Diederichsen*



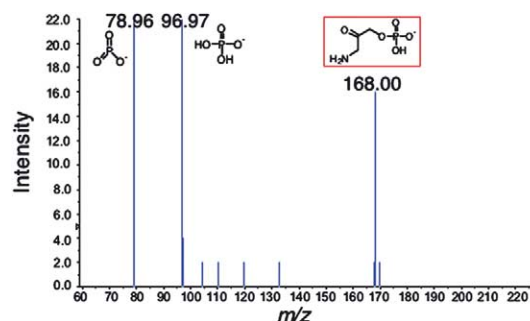
Femtosecond time resolved electron transfer dynamics of alanyl-PNA double strands where both strands contain an intercalated 9-amino-6-chloro-2-methoxy-acridine in its protonated state are investigated.

Biosynthesis of vitamin B₆: direct identification of the product of the PdxA-catalyzed oxidation of 4-hydroxy-L-threonine-4-phosphate using electrospray ionization mass spectrometry

pp 1633–1636

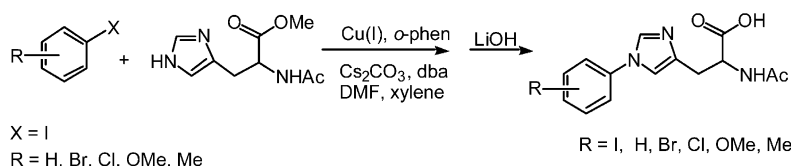
Jerel Banks and David E. Cane*

Negative ion electrospray ionization mass spectrometry (ESI-MS) and tandem mass spectrometric analysis (MS-MS) confirms that 3-amino-1-hydroxyacetone 1-phosphate (AHAP) is the product of the reaction catalyzed by 4-hydroxy-L-threonine-4-phosphate dehydrogenase (PdxA).

**Synthesis of *N*^τ-arylhistidine derivatives via direct *N*-arylation**

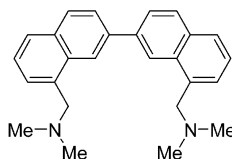
pp 1637–1640

Weimin Yue, Stefanie I. Lewis, Yakov M. Koen and Robert P. Hanzlik*

**Synthesis of a novel intercalator based on 2,2'-binaphthalene bearing dimethylammonium groups**

pp 1641–1643

Shin-ichi Kondo,* Tomoko Kinjo and Yumihiko Yano

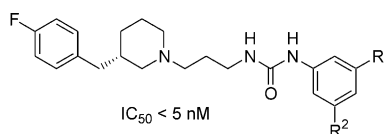


A novel type of DNA intercalator, 8,8'-bis(dimethylaminomethyl)-2,2'-binaphthalene based on 2,2'-binaphthalene skeleton, was prepared and the binding ability for calf thymus (CT) DNA was evaluated by UV-vis and fluorescence spectroscopic titrations and the melting temperature of CT DNA.

Discovery of *N*-propylurea 3-benzylpiperidines as selective CC chemokine receptor-3 (CCR3) antagonists

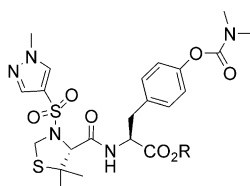
pp 1645–1649

Jeffrey G. Varnes, Daniel S. Gardner, Joseph B. Santella, III, John V. Duncia, Melissa Estrella, Paul S. Watson, Cheryl M. Clark, Soo S. Ko, Patricia Welch, Maryanne Covington, Nicole Stowell, Eric Wadman, Paul Davies, Kimberley Solomon, Robert C. Newton, George L. Trainor, Carl P. Decicco and Dean A. Wacker*

**Synthesis, characterization and evaluation of pro-drugs of VLA-4 antagonists**

pp 1651–1654

Donna M. Huryn,* Susan Ashwell, Reinhardt Baudy, Darren B. Dressen, William Gallaway, Francine S. Grant, Andrei Konradi, Robert W. Ley, Susan Petusky, Michael A. Pleiss, Dimitri Sarantakis, Christopher M. Semko, Mary M. Sherman, Cesar Tio and Lu Zhang



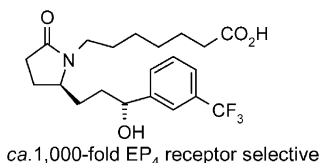
A pro-drug strategy to identify orally efficacious VLA-4 antagonists is described.

Lactams as EP₄ prostanoid receptor subtype selective agonists.

pp 1655–1659

Part 1: 2-Pyrrolidinones-stereochemical and lower side-chain optimization

Todd R. Elworthy,* Denis J. Kertesz, Woongki Kim, Michael G. Roepel, Lina Quattrocchio-Setti, David B. Smith, Jahari Laurant Tracy, Audrey Chow, Fujun Li, Emma R. Brill, Leang K. Lach, Daren McGee, Diana S. Yang and San-San Chiou

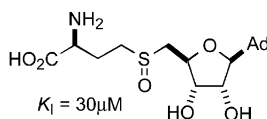


A series of 7-[(5*R*)-substituted 2-oxo-1-pyrrolidinyl]-heptanoic acids were prepared, isomeric purity determined, and pharmacologically evaluated. Ligands with affinity at the EP₄ receptor displayed agonist activity as well as high subtype selectivity.

Synthesis and evaluation of analogues of *S*-adenosyl-L-methionine, as inhibitors of the *E. coli* cyclopropane fatty acid synthase

pp 1661–1664

Christine Guérard, Maud Bréard, Fabienne Courtois, Thierry Drujon and Olivier Ploux*



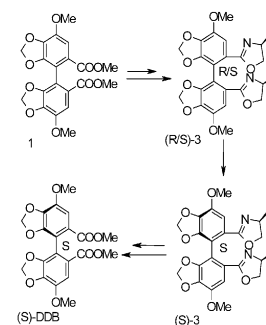
Analogues of *S*-adenosyl-L-methionine were synthesized and evaluated as inhibitors of the *E. coli* cyclopropane synthase. *S*-Adenosyl-L-homocysteine and its sulfoxides were the most potent inhibitors.

New synthesis of (*S*)-dimethyl-4,4'-dimethoxy-5,6,5',6'-dimethenedioxy-biphenyl-2,2'-dicarboxylate by configuration transform

Sen-Xiang Cheng, Jun-Biao Chang, Ling-Bo Qu and Rong-Feng Chen*

pp 1665–1667

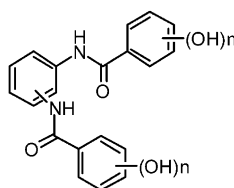
(*R/S*)-**3** has been synthesized from **1** and then the diastereoisomer mixture (*R/S*)-**3** was almost fully converted to single diastereoisomer (*S*)-**3** through the key configuration transform promoted by CuI. The C₂-symmetric biphenyl, (*S*)-dimethyl-4,4'-dimethoxy-5,6,5',6'-dimethenedioxy-biphenyl-2,2'-dicarboxylate was prepared easily through hydrolysis and ester exchange of (*S*)-**3**.



Inhibitory activities against topoisomerase I & II by polyhydroxybenzoyl amide derivatives and their structure–activity relationship

pp 1669–1672

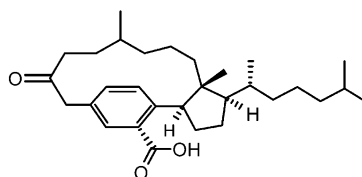
Mohamed Abdel-Aziz, Kazuya Matsuda, Masami Otsuka, Masaru Uyeda, Tadashi Okawara and Keitarou Suzuki*



Design and synthesis of macrocyclic inhibitors of phosphatase Cdc25B

pp 1673–1677

Stefan Bährle,* Thorsten Blume, Judith Günther, Daniela Henschel, Roman C. Hillig, Manfred Husemann, Anne Mengel, Christian Parchmann, Elke Schmid and Werner Skuballa

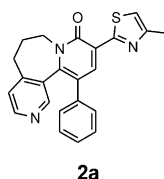


Based on molecular modeling studies, macrocyclic inhibitors of phosphatase cdc25B in the low micromolar range were synthetically derived from steroids.

Tricyclic pyridones as functionally selective human GABA_Aα_{2/3} receptor-ion channel ligands

pp 1679–1682

James Crawford,* John R. Atack, Susan M. Cook, Karl R. Gibson, Alan Nadin, Andrew P. Owens, Andrew Pike, Michael Rowley, Alison J. Smith, Bindi Sohal, Francine Sternfeld, Keith Wafford and Leslie J. Street

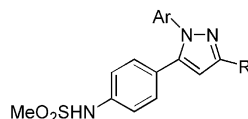


The synthesis of tricyclic 2-pyridones as high affinity functionally selective, orally bioavailable benzodiazepine site ligands that demonstrate activity in rodent anxiolysis models and reduced sedation relative to diazepam is described.

Methanesulfonamide group at position-4 of the C-5-phenyl ring of 1,5-diarylpyrazole affords a potent class of cyclooxygenase-2 (COX-2) inhibitors

pp 1683–1688

Sunil Kumar Singh,* Saibaba Vobbalareddy, Samala Shivaramakrishna, A. Krishnamraju, Shaikh Abdul Rajjak, Seshagiri Rao Casturi, Vangoori Akhila and Yeleswarapu Koteswar Rao*

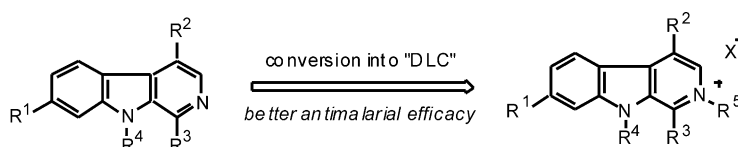


The effect of methanesulfonamide (MeSO₂NH) group on COX-2 inhibitory activity of 1,5-diarylpyrazole is described.

 π -Delocalized β -carbolinium cations as potential antimalarials

pp 1689–1692

Kiyosei Takasu,* Tsubasa Shimogama, Chalerm Saiin, Hye-Sook Kim, Yusuke Wataya and Masataka Ihara*

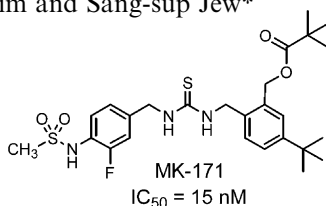


The synthesis and evaluation for antimalarial potency of β -carbolinium salts are reported.

***N*-4-Methansulfonamidobenzyl-*N'*-2-substituted-4-*tert*-butyl-benzyl thioureas as potent vanilloid receptor antagonistic ligands**

pp 1693–1696

Hyeung-geun Park,* Ji-yeon Choi, Sea-hoon Choi, Mi-kyung Park, Jihye Lee, Young-Ger Suh, Hawon Cho, Uhtaek Oh, Hee-Doo Kim, Yung Hyup Joo, Sun-Young Kim, Young-Ho Park, Yeon Su Jeong, Jin Kyu Choi, Jin Kwan Kim and Sang-sup Jew*

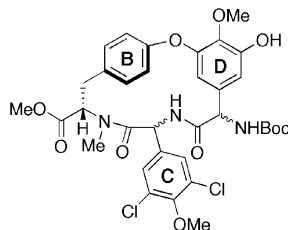


A series of *N*-4-methansulfonamidobenzyl-*N'*-2-substituted-4-*tert*-butylbenzylthioureas were prepared and the structure–activity relationship studies on the antagonistic activity against VR1 were performed.

Complestatin synthetic studies: the effect of the amino acid configuration on peptide backbone conformation in the common western BCD macrocycle

pp 1697–1702

Amos B. Smith, III,* Jason J. Chruma, Qiang Han and Joseph Barbosa

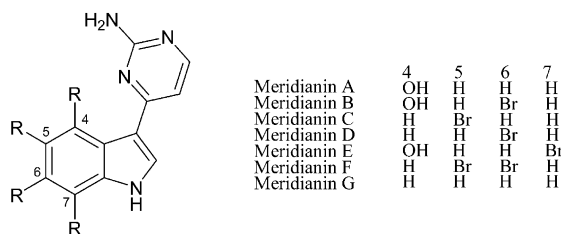


Four diastereomers of the complestatin western macrocycle were prepared and their individual conformations determined by X-ray, NMR, and computational analysis.

Meridianins, a new family of protein kinase inhibitors isolated from the Ascidian *Aplidium meridianum*

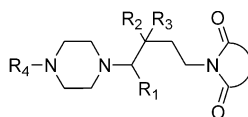
pp 1703–1707

Marie Gompel, Maryse Leost, Elisa Bal De Kier Joffe, Lydia Puricelli,
Laura Hernandez Franco, Jorge Palermo and Laurent Meijer*


The design and preparation of metabolically protected new arylpiperazine 5-HT_{1A} ligands

pp 1709–1712

Manish Tandon, Mary-Margaret O'Donnell, Alex Porte, David Vensel, Donglai Yang,
Rocio Palma, Alan Beresford and Mark A. Ashwell*

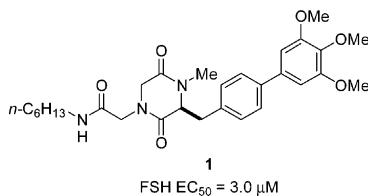


An in silico cytochrome CYP3A4 metabolism model was combined with a pharmacophore affinity model to design new metabolically protected 5-HT_{1A} ligands. New molecules were prepared using parallel chemistry and screened in vitro.

Small molecule biaryl FSH receptor agonists. Part 1: Lead discovery via encoded combinatorial synthesis

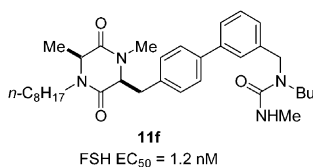
pp 1713–1716

Tao Guo,* Anton E. P. Adang, Roland E. Dolle, Guizhen Dong, Dan Fitzpatrick, Peng Geng,
Koc-Kan Ho, Steven G. Kultgen, Ruiyan Liu, Edward McDonald, Brian F. McGuinness,
Kurt W. Saionz, Kenneth J. Valenzano, Nicole C. R. van Straten, Dan Xie and Maria L. Webb


Small molecule biaryl FSH receptor agonists. Part 2: Lead optimization via parallel synthesis

pp 1717–1720

Tao Guo,* Anton E. P. Adang, Guizhen Dong, Dan Fitzpatrick, Peng Geng, Koc-Kan Ho,
Charles H. Jibilian, Steven G. Kultgen, Ruiyan Liu, Edward McDonald, Kurt W. Saionz,
Kenneth J. Valenzano, Nicole C. R. van Straten, Dan Xie and Maria L. Webb

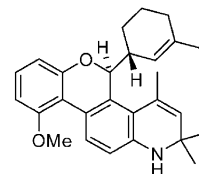


Differentiation of in vitro transcriptional repression and activation profiles of selective glucocorticoid modulators

pp 1721–1727

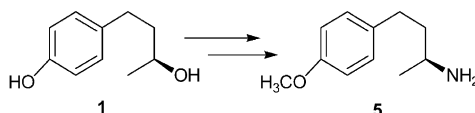
Steven W. Elmore,* John K. Pratt, Michael J. Coghlan, Yue Mao, Brian E. Green, David D. Anderson, Michael A. Stashko, Chun W. Lin, Douglas Falls, Masaki Nakane, Loan Miller, Curtis M. Tyree, Jeffrey N. Miner and Ben Lane

The SAR at C-5 of the 10-methoxy-2,2,4-trimethylbenzopyrano[3,4-f]quinoline core leading to identification of (–) anti 1-methylcyclohexen-3-yl as the optimum substituent that imparts minimal GR mediated in vitro transcriptional activation while maintaining full transcriptional repression is described. The in vitro profile of these candidates in human cell assays relevant to the therapeutic window of glucocorticoid modulators is outlined.

**Betuligenol derivative with growth inhibition and antifeedant activity**

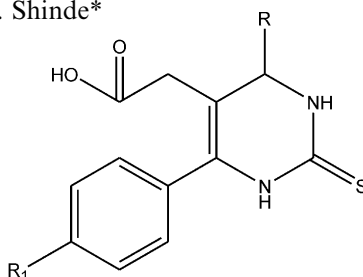
pp 1729–1731

Sunil K. Chattopadhyay,* Sachin Srivastava, Koneni V. Sashidhara, Arun K. Tripathi, Asish K. Bhattacharya and Arvind S. Negi

**Synthesis and anti-inflammatory activity of some [4,6-(4-substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid derivatives**

pp 1733–1736

Sushilkumar S. Bahekar and Devanand B. Shinde*

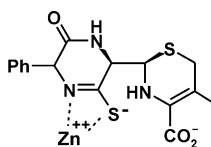


A series of [4,6-(substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid (**4a–r**) has been synthesized by the base catalyzed condensation anti-inflammatory activity in vivo were evaluated and compared with standard drug diclofenac sodium.

The inhibition of metallo-β-lactamase by thioxo-cephalosporin derivatives

pp 1737–1739

Wing Y. Tsang, Anupma Dhanda, Christopher J. Schofield, Jean-Marie Frère, Moreno Galleni and Michael I. Page*

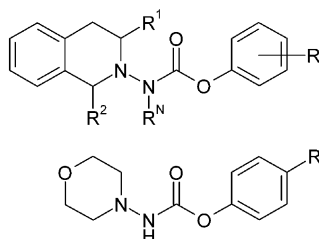


Thioxo derivatives of cephalosporins inhibit class B metallo-β-lactamase.

Carbazates as potent inhibitors of hormone-sensitive lipase

pp 1741–1744

Johannes C. de Jong, Lotte G. Sørensen, Hans Tornqvist and Poul Jacobsen*

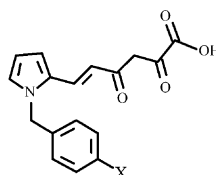


The synthesis of a new series of carbazates is presented. Modification of the phenolic 4-position in a series of 1,2,3,4-tetrahydroisoquinoline and morpholine derived carbazates, yielded HSL inhibitors with nanomolar potency.

6-Aryl-2,4-dioxo-5-hexenoic acids, novel integrase inhibitors active against HIV-1 multiplication in cell-based assays

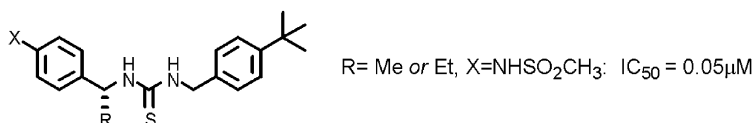
pp 1745–1749

Roberta Costi, Roberto Di Santo, Marino Artico,* Alessandra Roux, Rino Ragno, Silvio Massa, Enzo Tramontano, Massimiliano La Colla, Roberta Loddo, M. Elena Marongiu, Alessandra Pani and Paolo La Colla*

**Chain-branched 1,3-dibenzylthioureas as vanilloid receptor 1 antagonists**

pp 1751–1755

Chong Hyun Ryu, Mi Jung Jang, Jeong Wha Jung, Ju-Hyun Park, Hye Young Choi, Young-ger Suh, Uhtaek Oh, Hyeung-geun Park, Jeewoo Lee, Hyun-Joo Koh, Joo-Hyun Mo, Yung Hyup Joo, Young-Ho Park and Hee-Doo Kim*

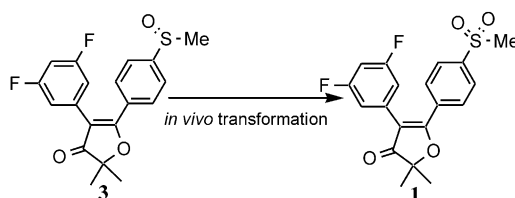


Chain-branching led to a significant change in the mode of action and the potency against vanilloid receptor 1.

A prodrug approach to COX-2 inhibitors with methylsulfone

pp 1757–1760

Joo Hyun Moh, Young Hoon Choi, Kyoung Min Lim, Ki-Wha Lee, Song Seok Shin, Jin Kyu Choi, Hyun Joo Koh and Shin Chung*

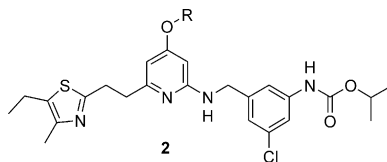


Sulfoxide prodrug **3** was effectively converted into the corresponding methyl sulfone COX-2 selective inhibitor **1** in rats.

Synthesis and evaluation of substituted 4-alkoxy-2-aminopyridines as novel neuropeptide Y1 receptor antagonists

pp 1761–1764

Nagaaki Sato,* Takunobu Shibata, Makoto Jitsuoka, Toshiyuki Ohno, Toshiyuki Takahashi, Tomoko Hirohashi, Tetsuya Kanno, Hisashi Iwaasa, Akio Kanatani and Takehiro Fukami



A series of substituted 4-alkoxy-2-aminopyridines **2** were synthesized and evaluated as neuropeptide Y Y1 receptor antagonists.

Protein-dynamics of the putative HCV receptor CD81 large extracellular loop

pp 1765–1769

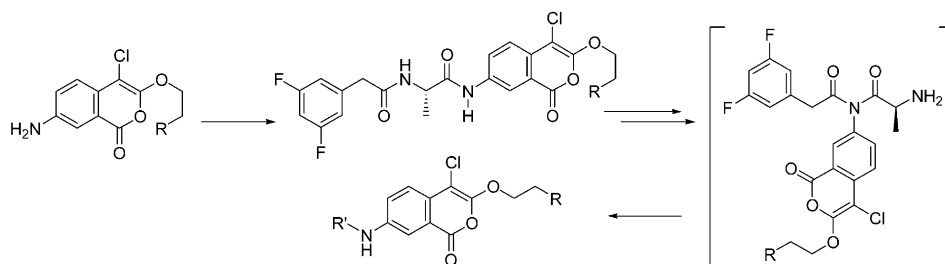
Alexander Neugebauer, Christian D. P. Klein and Rolf W. Hartmann*

Molecular dynamics simulations of the putative HCV receptor CD81 indicate that the conformation of the two helical regions in one of the published X-ray structures is affected by crystallographic contacts and most likely does not represent the native state of the protein. The implications of this result for drug design projects aimed at the CD81/E2 interaction are discussed.

**N-Acyl substituted 7-amino-4-chloroisocoumarin: A peptide degradation model via an imide mechanism**

pp 1771–1774

Cédrik Garino, Frédéric Bihel, Florence Souard, Gilles Quéléver and Jean-Louis Kraus*

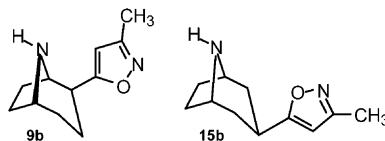


R = OMe; R' = 3,5-difluorophenylacetyl, alanyl.

Synthesis and nicotinic acetylcholine receptor binding affinities of 2- and 3-isoxazolyl-8-azabicyclo[3.2.1]octanes

pp 1775–1778

Jie Cheng, Sari Izenwasser, Chunming Zhang, Suhong Zhang, Dean Wade and Mark L. Trudell*



A series of epiboxidine homologues, 2- and 3-isoxazole substituted 8-azabicyclo[3.2.1]octane derivatives was synthesized and evaluated as potential ligands for neuronal nicotinic acetylcholine receptors in [³H]cytisine labeled rat brain. The 2β-isoxazolyl-8-azabicyclo[3.2.1]octane **9b** (K_i = 3 nM) was the most potent compound of the series with a binding affinity twice that of nicotine. The 3β-isoxazolyl-8-azabicyclo[3.2.1]octane **15b** (K_i = 148 nM) exhibited moderate affinity while the corresponding 2α- and 3α-isomers exhibited micromolar binding affinity.

Different hydroxyl radical scavenging activity of water-soluble β -alanine C_{60} adducts

pp 1779–1781

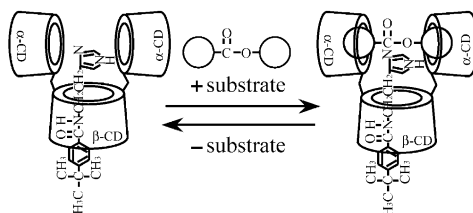
Tao Sun,* Zhishen Jia and Zhude Xu

Different hydroxyl radical scavenging effect of water-soluble β -alanine C_{60} adducts is closely related to the numbers of residual C=C bonds in C_{60} , steric effect and electron-withstanding effect of amino group especially.

Cyclodextrin trimers as receptors for arranging ester and catalyst at optimized location to achieve enhancement of hydrolytic activity

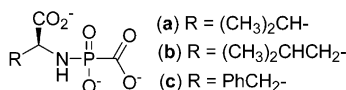
pp 1783–1786

Hiroki Nakajima, Yuzuru Sakabe, Hiroshi Ikeda* and Akihiko Ueno

**Synthesis and stability studies of phosphonoformate–amino acid conjugates: a new class of slowly releasing foscarnet prodrugs**

pp 1787–1790

Mong S. Marma, Boris A. Kashemirov and Charles E. McKenna*

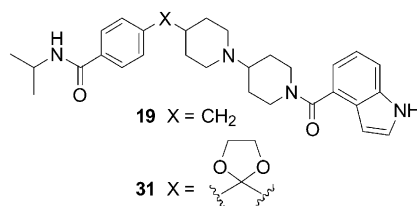


A new class of foscarnet prodrug has been prepared. The prodrugs slowly release foscarnet at physiological pH and temperature.

Isopropyl amide derivatives of potent and selective muscarinic M_2 receptor antagonists

pp 1791–1794

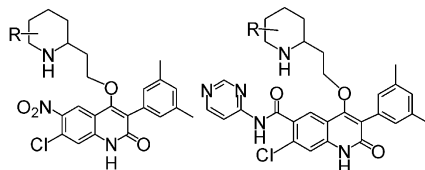
Anandan Palani,* Sundeep Dugar, John W. Clader, William J. Greenlee, Vilma Ruperto, Ruth A. Duffy and Jean E. Lachowicz



Syntheses and structure–activity relationship studies of piperidine-substituted quinolones as nonpeptide gonadotropin releasing hormone antagonists

pp 1795–1798

Jinlong Jiang,* Robert J. DeVita, Mark T. Goulet, Matthew J. Wyvratt, Jane-L. Lo, Ning Ren, Joel B. Yudkovitz, Jisong Cui, Yi T. Yang, Kang Cheng and Susan P. Rohrer

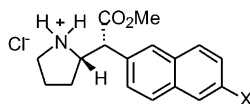


Synthesis and structure–activity relationships of piperidine-substituted quinolones as gonadotropin releasing hormone antagonists are described.

Synthesis of methylphenidate analogues and their binding affinities at dopamine and serotonin transport sites

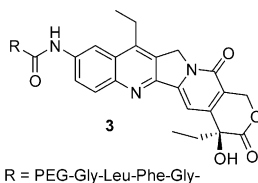
pp 1799–1802

Huw M. L. Davies,* Darrin W. Hopper, Tore Hansen, Quixu Liu and Steven R. Childers*

**Efficient and chemoselective *N*-acylation of 10-amino-7-ethyl camptothecin with poly(ethylene glycol)**

pp 1803–1805

Andrea Guiotto,* Mirta Canevari, Piero Orsolini, Olivier Lavanchy, Christine Deuschel, Norimasa Kaneda, Akinobu Kurita, Takeshi Matsuzaki, Takeshi Yaegashi, Seigo Sawada and Francesco M. Veronese*

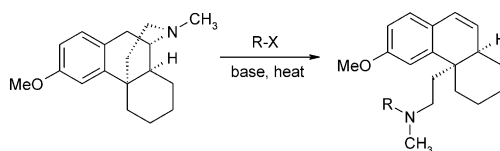


Chemoselective acylation of 10-amino-7-ethyl camptothecin with poly(ethylene glycol) using phenyl dichlorophosphate is reported. Preliminary in vivo antitumor tests for **3** show high activity against P388 murine leukemia.

Synthesis of potent sigma-1 receptor ligands via fragmentation of dextromethorphan

pp 1807–1809

Mark P. Arrington, Claire Brown and C. Eric Schwartz*

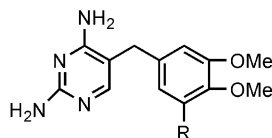


Treatment of dextromethorphan with various alkylating agents followed by base treatment led to Hoffman-type elimination reactions to produce tricyclic derivatives, characterized in vitro as potent sigma-1 receptor ligands.

Preliminary in vitro studies on two potent, water-soluble trimethoprim analogues with exceptional species selectivity against dihydrofolate reductase from *Pneumocystis carinii* and *Mycobacterium avium*

pp 1811–1815

Ronald A. Forsch, Sherry F. Queener and Andre Rosowsky*

R: $-\text{C}\equiv\text{C}(\text{CH}_2)_3\text{COOH}$, $-\text{C}\equiv\text{CC}_6\text{H}_4(4\text{-COOH})$

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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 htB1 (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htB1 (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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ISSN 0960-894X