ELSEVIER

Bioorganic & Medicinal Chemistry Letters Vol. 14, No. 3, 2004

Bioorganic & Medicinal Chemistry Letters

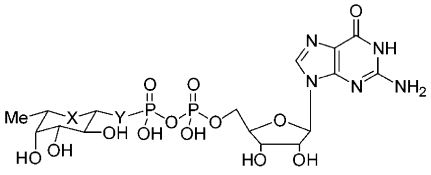
Contents

Publisher's Announcement p 569

COMMUNICATIONS

Inhibition kinetics of carba- and *C*-fucosyl analogues of GDP-fucose against fucosyltransferase V: implication for the reaction mechanism pp 571–573

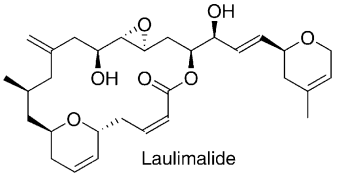
Andrew J. Norris, Julian P. Whitelegge, M. Jane Strouse, Kym F. Faull and Tatsushi Toyokuni*



1 X = CH_2, Y = O K_i = 67.1μM
2 X = O, Y = CH_2 K_i = 889 μM

Synthesis and biological evaluation of (−)-laulimalide analogues pp 575–579

Brian M. Gallagher, Jr.,* Francis G. Fang, Charles W. Johannes, Marc Pesant, Martin R. Tremblay, Hongjuan Zhao, Kozo Akasaka, Xiang-yi Li, Junke Liu and Bruce A. Littlefield

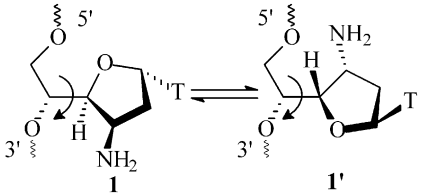


Laulimalide

Analogues of the marine natural product (−)-laulimalide were prepared by total synthesis and evaluated in vitro for anticancer activity.

Synthesis and incorporation of an α-hexofuranosyl thymidine into oligodeoxynucleotides via its two exocyclic OH-groups pp 581–584

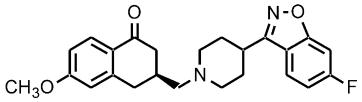
Vyacheslav V. Filichev and Erik B. Pedersen*



We describe the synthesis and incorporation into oligodeoxynucleotides (ODN) of a new type of modified nucleotide **1** which is considered as an acyclic nucleotide restricted by the furanose ring. The thermal stability of ODN/DNA and ODN/RNA duplexes was studied by UV experiments.

Chemoenzymatic synthesis and binding affinity of novel (*R*)- and (*S*)-3-aminomethyl-1-tetralones, potential atypical antipsychotics **pp 585–589**

Yolanda Caro, María Torrado, Christian F. Masaguer, Enrique Raviña,* Fernando Padín, José Brea and María I. Loza

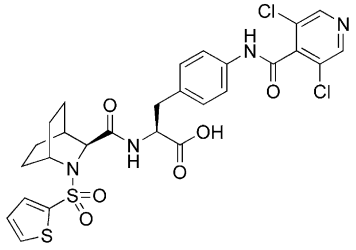


(*S*)-(+)-8d

The chemoenzymatic preparation and the binding affinities of new (*R*)- and (*S*)-3-aminomethyl-1-tetralones is described. Some of these compounds [e.g., (*S*)-(+)-**8d**] showed potential atypical antipsychotic profiles with Meltzer's ratio higher than 1:30.

Aza-bicyclic amino acid sulfonamides as $\alpha_4\beta_1/\alpha_4\beta_7$ integrin antagonists **pp 591–596**

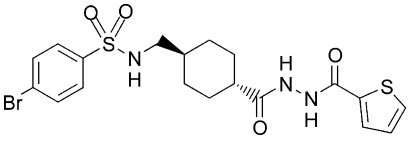
Alexey B. Dyatkin,* William J. Hoekstra, William A. Kinney, Maria Kontoyianni, Rosemary J. Santulli, Edward S. Kimball, M. Carolyn Fisher, Stephen M. Prouty, William M. Abraham, Patricia Andrade-Gordon, Dennis J. Hlasta, Wei He, Pamela J. Hornby, Bruce P. Damiano and Bruce E. Maryanoff*



The design, synthesis and biological activity of novel $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin antagonists containing a bridged azabicyclic nucleus, are reported. Selected compounds were evaluated in the antigen-sensitized sheep model of asthma.

Synthesis of new thiophene and benzo[*b*]thiophene hydrazide derivatives as human NPY Y_5 antagonists **pp 597–599**

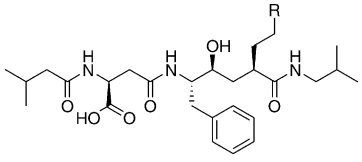
Silvia Galiano, Oihana Erviti, Silvia Pérez, Antonio Moreno, Laura Juanenea, Ignacio Aldana* and Antonio Monge



Neuropeptide Y is one of the most potent appetite stimulating hormones known. Novel thiophene and benzo[*b*]thiophene hydrazide derivatives were synthetized and evaluated biologically as NPY Y_1 and Y_5 receptor subtype antagonists. They were found to have nanomolar binding affinities for human NPY Y_5 receptor, obtaining the lead compound, *trans*-*N*-4-[*N*′-(thiophene-2-carbonyl)hydrazinocarbonyl]cyclohexylmethyl-4-bromobenzenesulfonamide, which binds with a 7.70 nM IC_{50} to the hY_5 receptor.

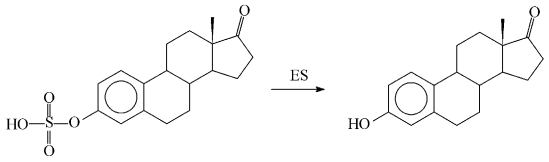
Rational design and synthesis of selective BACE-1 inhibitors **pp 601–604**

Stephen F. Brady, Satendra Singh, Ming-Chih Crouthamel, M. Katharine Holloway, Craig A. Coburn, Victor M. Garsky, Michael Bogusky, Michael W. Pennington, Joseph P. Vacca, Daria Hazuda and Ming-Tain Lai*



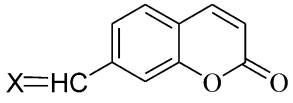
A series of selective BACE 1 inhibitors less than 600 MW were synthesized based on the unique features of the S1′ pocket.

Inhibition of estrone sulfatase (ES) by alkyl and cycloalkyl ester derivatives of 4-[(aminosulfonyl)oxy] benzoic acid **pp 605–609**
Chirag K. Patel, Caroline P. Owen and Sabbir Ahmed*



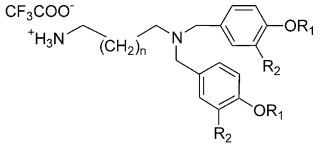
The inhibition of estrone sulfatase is investigated using esters of 4-aminosulfonated derivatives of benzoic acid.

Synthesis and biological evaluation of novel coumarin derivatives with a 7-azomethine linkage **pp 611–614**
Christos A. Kontogiorgis and Dimitra J. Hadjipavlou-Litina*



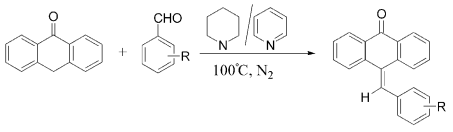
Synthesis of several novel coumarin derivatives with anti-inflammatory and antioxidant activity.

Diamine derivatives with antiparasitic activities **pp 615–619**
Guillermo R. Labadie, Seoung-Ryoung Choi and Mitchell A. Avery*



The synthesis of libraries of diamines with antileishmanial and antimalarial activity is reported.

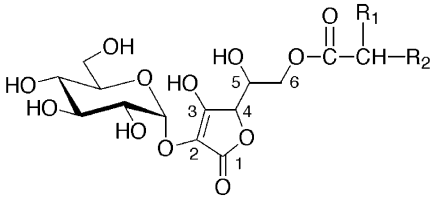
Synthesis and antitumor activity of 10-substituted benzylidene anthrone **pp 621–622**
Weixiao Hu* and Wei Zhou



Fifteen compounds were prepared. Their antitumor activities in vitro were evaluated. It was found that the substitutes have a significant effect R: H, m-NO_2, p-F, o-OH, p-OH, o-CH_3, m-CH_3, on the activity and there are 6 compounds p-CH_3, o-OCH_3, m-OCH_3, p-OCH_3, o-Cl, m-Cl, which appear as strong effective inhibition.

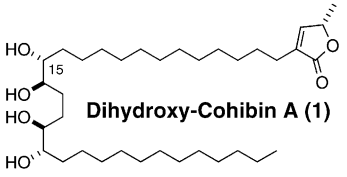
Permeation and metabolism of a series of novel lipophilic ascorbic acid derivatives, 6-*O*-acyl-2-*O*-α-D-glucopyranosyl-L-ascorbic acids with a branched-acyl chain, in a human living skin equivalent model **pp 623–627**

Akihiro Tai, Satomi Goto, Yutaka Ishiguro, Kazuko Suzuki, Teruhiko Nitoda and Itaru Yamamoto*



Synthesis and mitochondrial complex I inhibition of dihydroxy-cohibin A, non-THF annonaceous acetogenin analogue **pp 629–632**

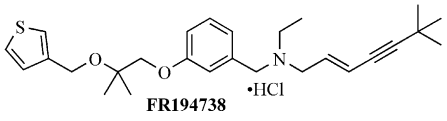
Hiroyuki Konno,* Naoki Hiura, Hidefumi Makabe, Masato Abe and Hideto Miyoshi*



Synthesis and activity of dihydroxy-cohibin A (**1**) are described.

Synthesis and biological activity of a novel squalene epoxidase inhibitor, FR194738 **pp 633–637**

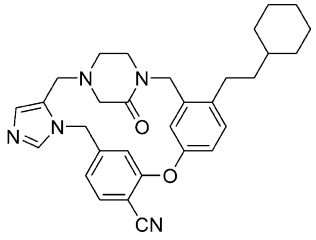
Masae Sawada,* Ken-ichi Washizuka and Hiroyuki Okumura



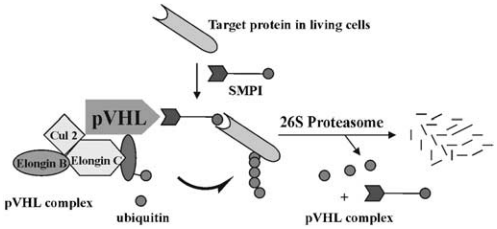
The synthesis and biological properties of a novel squalene epoxidase inhibitor, FR194738, are described. This compound displayed potent in vitro inhibitory activities against squalene epoxidase and cholesterol synthesis, and lowered plasma cholesterol and triglyceride levels in dogs.

Macrocyclic piperazinones as potent dual inhibitors of farnesyltransferase and geranylgeranyltransferase-I **pp 639–643**

Christopher J. Dinsmore,* C. Blair Zartman, Jeffrey M. Bergman, Marc T. Abrams, Carolyn A. Buser, J. Christopher Culberson, Joseph P. Davide, Michelle Ellis-Hutchings, Christine Fernandes, Samuel L. Graham, George D. Hartman, Hans E. Huber, Robert B. Lobell, Scott D. Mosser, Ronald G. Robinson and Theresa M. Williams

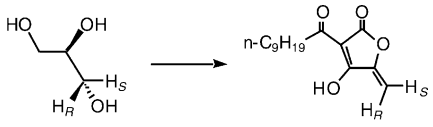


Degradation of target protein in living cells by small-molecule proteolysis inducer **pp 645–648**
Dong Zhang, Sun-Hee Baek, Abby Ho and Kyungbo Kim*



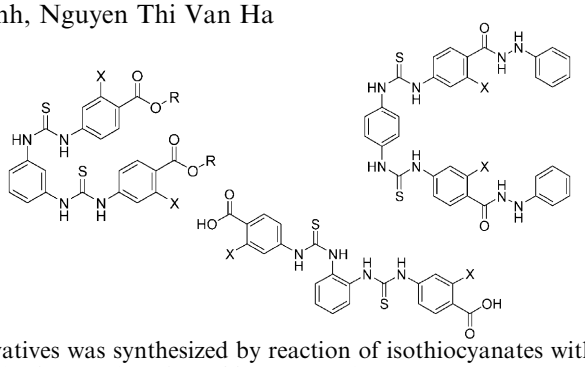
Development of cell-permeable small molecule that recruits a target protein for ubiquitination and degradation is described, using the E3 ubiquitin ligase–substrate interaction.

Biosynthesis of agglomerin A: stereospecific incorporation of pro-*R*- and pro-*S*-hydrogens at *sn*-C-3 of glycerol into the branched C_3 moiety **pp 649–651**
Youichi Mashimo, Yasuyo Sekiyama, Hiroshi Araya and Yoshinori Fujimoto*



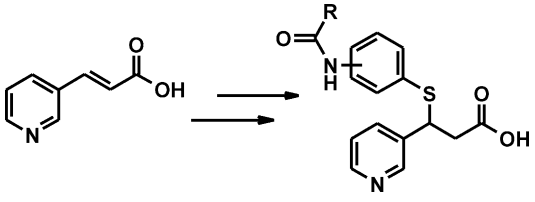
Feeding experiments of *sn*-(3*R*)-[3-^{2}H]- and *sn*-(3*S*)-[3-^{2}H]-glycerols, followed by ^{2}H NMR analysis of the biosynthesized agglomerin A, revealed that the immediate precursor of the branched C_3 unit of, agglomerin A is glyceric acid or its biological equivalent.

Synthesis and antifungal activities of phenylenedithioureas **pp 653–656**
Truong Phuong,* Thai Khac-Minh, Nguyen Thi Van Ha and Huynh Thi Ngoc Phuong



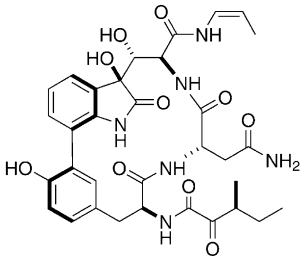
A series of phenylenedithiourea derivatives was synthesized by reaction of isothiocyanates with aromatic amines. Some of them have MIC values for antifungi activities be equal to that of ketoconazole.

Solid-phase synthesis of a small library of 3-phenylthio-3-nicotinyl propionic acid derivatives acting as antagonists of the integrin $\alpha V\beta 3$ **pp 657–661**
Paola Vianello,* Paolo Cozzi, Arturo Galvani, Maurizio Meroni, Mario Varasi, Daniele Volpi and Tiziano Bandiera



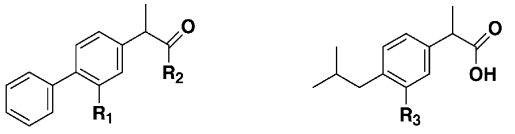
The solid-phase synthesis and the pharmacological evaluation of new nicotinyl propionic acid derivatives is reported.

TMC-95A, a reversible proteasome inhibitor, induces neurite outgrowth in PC12 cells **pp 663–665**
Masayuki Inoue,* Haifeng Zhai, Hayato Sakazaki, Hidetomo Furuyama, Yoshiyasu Fukuyama* and Masahiro Hirama*



TMC-95A

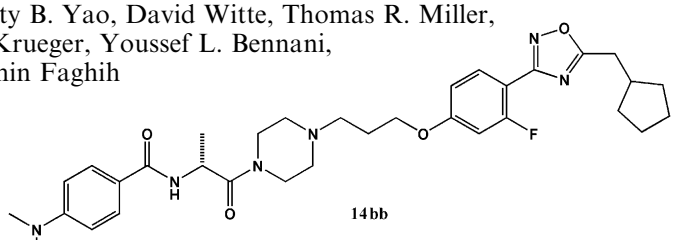
Manipulation of kinetic profiles in 2-aryl propionic acid cyclooxygenase inhibitors **pp 667–671**
Kushol Gupta, Carl J. Kaub, Kristen N. Carey, Eduard G. Casillas, Barry S. Selinsky and Patrick J. Loll*



R_1 = F or H
R_2 = OH, OCH_3, NH_2, $NH(CH_3)_2$, $N(CH_3)_2$
R_3 = H, NO_2, BR

Structure–activity relationships are reported for compounds derived from the cyclooxygenase inhibitors flurbiprofen and ibuprofen, focusing on their kinetic profiles for COX-1 inhibition.

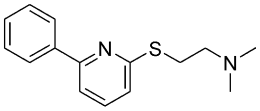
Structure–activity relationships of non-imidazole H_3 receptor ligands. Part 3: 5-Substituted 3-phenyl-1,2,4-oxadiazoles as potent antagonists **pp 673–676**
Gregory A. Gfesser,* Henry Zhang, Jurgen Dinges, Gerard B. Fox, Jia Bao Pan, Timothy A. Esbenshade, Betty B. Yao, David Witte, Thomas R. Miller, Chae-Hee Kang, Kathy M. Krueger, Youssef L. Bennani, Arthur A. Hancock and Ramin Faghih



14bb

Further structure–activity relationship studies on novel histamine-3 receptor antagonists are presented. Compound **14bb** is a potent antagonist of both the rat cortical and human clone receptors, and is demonstrated to act functionally as an antagonist in an in vivo mouse dipsogenia model.

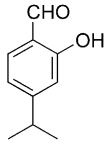
Thiazoles and thiopyridines: novel series of high affinity h5HT$_7$ ligands **pp 677–680**
Christopher G. Thomson,* Margaret S. Beer, Neil R. Curtis, Helen J. Diggle, Emma Handford and Janusz J. Kulagowski



3a K_i 0.6 nM

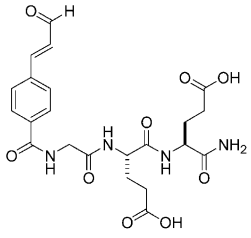
A series of thiazole based 5HT$_7$ ligands has been identified from screening. Optimization of the pendent aryl group and modification of the core gave a related series of high affinity, thiopyridine based 5HT$_7$ ligands, the most active of which (**3a**) behaves as a partial agonist.

2-Hydroxy-4-isopropylbenzaldehyde, a potent partial tyrosinase inhibitor **pp 681–683**
Ken-ichi Nihei, Yoshiro Yamagiwa, Tadao Kamikawa and Isao Kubo*



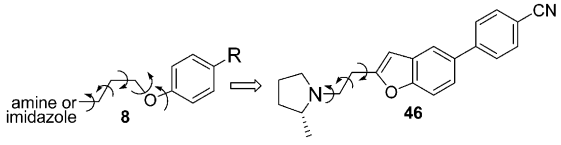
Chamaecin (2-hydroxy-4-isopropylbenzaldehyde) was synthesized and tested for its tyrosinase inhibitory activity. It partially inhibits the oxidation of L-3,4-dihydroxyphenylalanine (L-DOPA) catalyzed by mushroom tyrosinase with an IC_{50} of 2.3 μM.

Peptidyl aldehydes as slow-binding inhibitors of dual-specificity phosphatases **pp 685–687**
Junguk Park, Hua Fu and Dehua Pei*



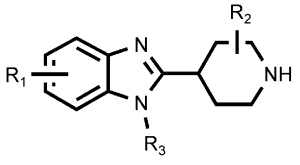
Peptidyl aldehydes are found as reversible covalent inhibitors of dual-specificity phosphatases, with the most potent one having K_I* values of 18 and 290 μM against phosphatases VH1 and VHR, respectively.

A new class of potent non-imidazole H_3 antagonists: 2-aminoethylbenzofurans **pp 689–693**
Marlon Cowart,* John K. Pratt, Andrew O. Stewart, Youssef L. Bennani, Timothy A. Esbenshade and Arthur A. Hancock

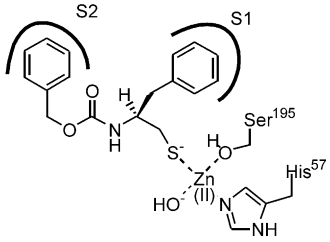


Benzofurans such as **46** are a new class of non-imidazole histamine H_3 antagonists that reduce the rotatable bond count from the known pharmacophore. **46**: rat cortex $K_i = 3.22$ nM, human $K_i = 0.45$ nM.

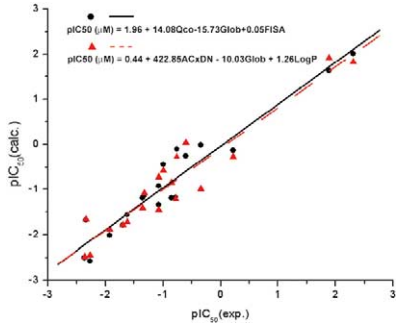
Synthesis and evaluation of novel bacterial *r*RNA-binding benzimidazoles by mass spectrometry **pp 695–699**
Yun He,* Jun Yang, Baogen Wu, Dale Robinson, Kelly Sprankle, Pei-Pei Kung, Kristin Lowery, V. Mohan, Steve Hofstadler, Eric E. Swayze and Rich Griffey



Inhibition of α-chymotrypsin with thiol-bearing substrate analogues in the presence of zinc ion **pp 701–705**
Min Su Han, Dong Ju Oh and Dong H. Kim*

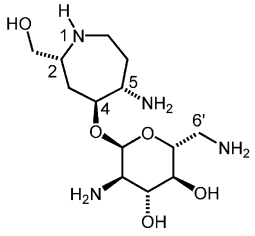


QSAR Studies of PC-3 cell line inhibition activity of TSA and SAHA-like hydroxamic acids **pp 707–711**
Di-Fei Wang, Olaf Wiest,* Paul Helquist, Hsuan-Yin Lan-Hargest and Norbert L. Wiech

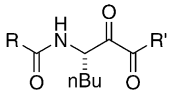


Quantitative structure–activity relationships (QSAR) for a series of new trichostatin A (TSA)-like hydroxamic acids for the inhibition of PC3 cell proliferation line have been developed.

Rational design of azepane-glycoside antibiotics targeting the bacterial ribosome **pp 713–718**
Sofia Barluenga,* Klaus B. Simonsen, Ethel S. Littlefield, Benjamin K. Ayida, Dionisios Vourloumis, Geoffrey C. Winters, Masayuki Takahashi, Sarah Shandrick, Qiang Zhao, Qing Han and Thomas Hermann*



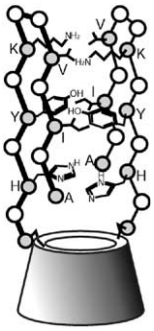
Design of small molecule ketoamide-based inhibitors of cathepsin K **pp 719–722**
John G. Catalano, David N. Deaton,* Stacey T. Long, Robert B. McFadyen, Larry R. Miller, J. Alan Payne, Kevin J. Wells-Knecht and Lois L. Wright



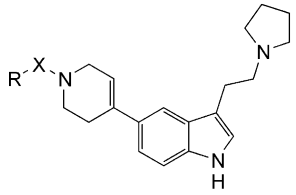
A novel series of ketoamide-based inhibitors of cathepsin K has been identified. Modifications to P^2 and P^3 elements were crucial to enhancing inhibitory activity. Although not optimized, a selected inhibitor was effective in attenuating type I collagen hydrolysis in a surrogate assay of bone resorption.

Enantioselective ester hydrolysis catalyzed by β-cyclodextrin conjugated with β-hairpin peptides **pp 723–726**
Hiroshi Tsutsumi, Hiroshi Ikeda, Hisakazu Mihara* and Akihiko Ueno*

Designed cyclodextrin–peptide conjugates, which have one or two β-hairpin peptides, have been synthesized as catalysts for ester hydrolysis. One or two β-hairpin peptides were located at the primary hydroxyl group side of β-cyclodextrin so as to arrange two histidine residues that act as a general acid and a general base catalysts and provide the substrate recognition subsite. Kinetic studies revealed that the two-β-hairpin peptide was more effective than that of the one-β-hairpin peptide for substrate recognition.



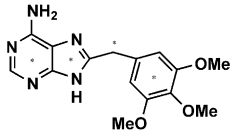
3-(2-Pyrrolidin-1-ylethyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole derivatives as high affinity human 5-$HT_{1B/1D}$ ligands **pp 727–729**
Ian Egle,* Neil MacLean, Lidia Demchyshyn, Louise Edwards, Abdelmalik Slassi and Ashok Tehim



2

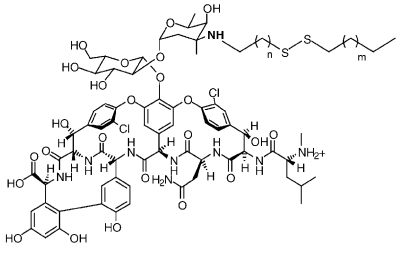
A series of 3-(2-pyrrolidin-1-ylethyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole derivatives (**2**) has been prepared using parallel synthesis techniques, and their structure–activity relationships studied. High affinity human 5-$HT_{1B/1D}$ (h5-$HT_{1B/1D}$) ligands have been identified.

3D-QSAR studies on PU3 analogues by comparative molecular field analysis **pp 731–734**
Hong-Chong Liu, Ping-Chiang Lyu, Max K. Leong, Keng-Chang Tsai and Ging-Ho Hsiue*



A CoMFA model of PU3 derivatives has been built with LOO cross-validation q^2 and conventional r^2 values of 0.513 and 0.947, respectively. The effects of the electrostatic and steric fields around on their activities are clarified by analyzing the CoMFA contour maps. The model provides the tools for predicting the affinity of related compounds, and for guiding further new potent Hsp90 inhibitors.

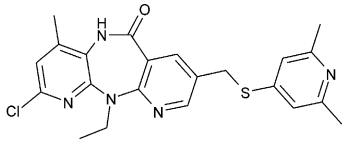
Vancomycin disulfide derivatives as antibacterial agents **pp 735–738**
YongQi Mu,* Matthew Nodwell, John L. Pace, Jeng-Pyng Shaw and J. Kevin Judice



The synthesis and biological activity of vancomycin disulfide derivatives are reported.

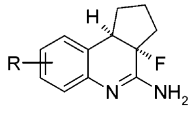
Novel nevirapine-like inhibitors with improved activity against NNRTI-resistant HIV: 8-heteroarylthiomethyldipyridodiazepinone derivatives **pp 739–742**

C. Yoakim,* P. R. Bonneau, R. Déziel, L. Doyon, J. Duan, I. Guse, S. Landry, E. Malenfant, J. Naud, W. W. Ogilvie, J. A. O'Meara, R. Plante, B. Simoneau, B. Thavonekham, M. Bös and M. G. Cordingley



Fluorinated dihydroquinolines as potent *n*-NOS inhibitors **pp 743–746**

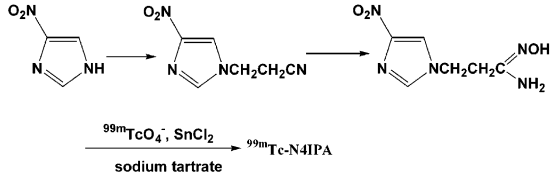
Stefan Jaroch,* Hartmut Rehwinkel, Peter Hölscher, Detlev Sülzle, Gerardine Burton, Margrit Hillmann, Fiona M. McDonald and Heribert Miklautz



Fluorinated dihydroquinolines showed reduced basicity of the amidine function. Their syntheses and potencies as neuronal nitric oxide synthase (*n*-NOS) inhibitors are reported.

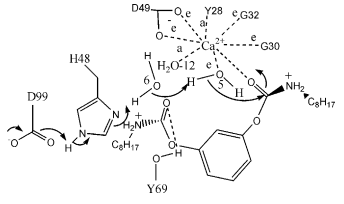
Synthesis and biological results of the technetium-99m-labeled 4-nitroimidazole for imaging tumor hypoxia **pp 747–749**

Taiwei Chu, Shaowen Hu, Bing Wei, Yi Wang, Xinqi Liu and Xiangyun Wang*



Benzene-di-*N*-octylcarbamates as conformationally constrained phospholipase A_2 inhibitors **pp 751–755**

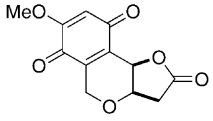
Gialih Lin,* Yan-Fu Lin, Mei-Ting Hwang and Yu-Zen Lin



Conformationally constrained 1,2-, 1,3-, and 1,4-benzene-di-*N*-octyl-carbamates are potent reversible competitive inhibitors of *Naji mocambique mocambique* phospholipase A_2 with the K_i values of 11, 4, and 15 μM, respectively.

Synthesis and antibiotic activity of the tricyclic furo[3,2-*c*] isochromen-2-trione unit of the pyranonaphthoquinones **pp 757–760**

Darío A. Bianchi, Emma G. Sutich and Teodoro S. Kaufman*

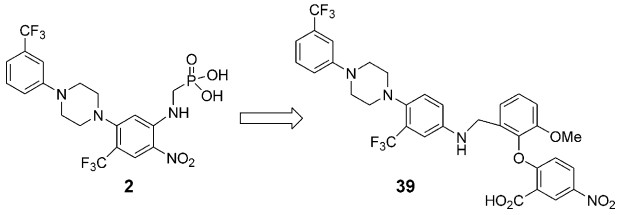


15

The synthesis of furo[3,2-*c*] isochromen-2-trione (**15**), which embodies the proposed pharmacophore for the antibiotic activity of the pyranonaphthoquinones, is reported. Compound **15** is active against *Staphylococcus aureus* and *Bacillus subtilis*.

Synthesis and biological evaluation of piperazine-based derivatives as inhibitors of plasminogen activator inhibitor-1 (PAI-1) **pp 761–765**

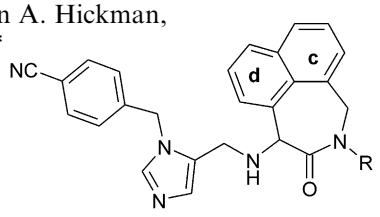
Bin Ye,* Yuo-Ling Chou, Rushad Karanjawala, Wheeseong Lee, Shou-Fu Lu, Kenneth J. Shaw, Steven Jones, Dao Lentz, Amy Liang, Jih-Lie Tseng, Qingyu Wu and Zuchun Zhao



Systematic optimization of lead **2** identified through HTS led to the discovery of a more potent PAI-1 inhibitor **39** with improved pharmacokinetic properties.

Synthesis of *N*,*N*′-disubstituted 3-aminobenzo[*c*] and [*d*]azepin-2-ones as potent and specific farnesyl transferase inhibitors **pp 767–771**

Thierry Le Diguarher, Jean-Claude Ortuno, David Shanks, Nicolas Guilbaud, Alain Pierré, Eric Raimbaud, Jean-Luc Fauchère,* John A. Hickman, Gordon C. Tucker and Patrick J. Casara*

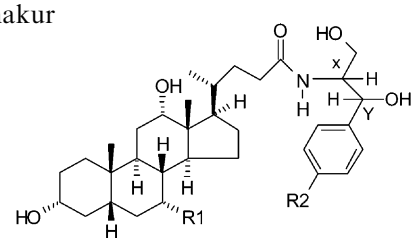


2 ring c
3 ring d

A structure–activity study was performed by synthesis on *N*,*N*′-disubstitution of 3-aminobenzo[*c*] and [*d*]azepin-2-one **2** and **3** to afford potent and specific farnesyl transferase inhibitors with low nM enzymatic and cellular activities.

Bile acid amides derived from chiral amino alcohols: novel antimicrobials and antifungals **pp 773–777**

Braja G. Hazra,* Vandana S. Pore,* Sanjeev Kumar Dey, Suchitra Datta, Mahendra P. Darokar, Dharmendra Saikia, S. P. S. Khanuja and Anup P. Thakur

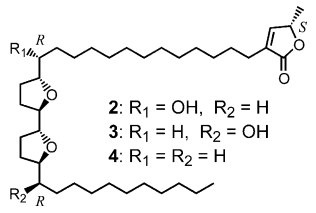


R_1 = H or OH; R_2 = H or NO_2

Asymmetric centres x and y have (R)-, (R)- or (S)-, (S)- configuration

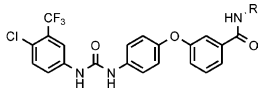
Synthesis and biological activity of eight new amides from bile acids and chiral aromatic amino alcohols are described.

Essential structural features of acetogenins: role of hydroxy groups adjacent to the bis-THF rings **pp 779–782**
Masato Abe, Atsushi Kenmochi, Naoya Ichimaru, Takeshi Hamada, Takaaki Nishioka and Hideto Miyoshi*



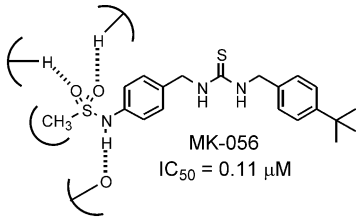
The role of each OH group adjacent to the bis-THF rings of acetogenin in the inhibitory action was examined with bovine heart mitochondrial complex I.

Omega-carboxypyridyl substituted ureas as Raf kinase inhibitors: SAR of the amide substituent **pp 783–786**
Uday R. Khire,* Donald Bankston, James Barbosa, David R. Brittelli, Yolanda Caringal, Robert Carlson, Jacques Dumas, Todd Gane, Sarah L. Heald, Barbara Hibner, Jeffrey S. Johnson, Michael E. Katz, Nancy Kennure, Jill Kingery-Wood, Wendy Lee, Xiao-Gao Liu, Timothy B. Lowinger, Ian McAlexander, Mary-Katherine Monahan, Reina Natero, Joel Renick, Bernd Riedl, Hong Rong, Robert N. Sibley, Roger A. Smith and Donald Wolanin



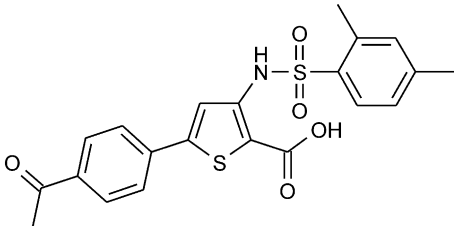
The carboxamide group of the urea class of Raf-1 kinase inhibitors is shown to be a suitable position for the introduction of water-solubilizing groups. This change led to improved aqueous solubility without significant impact on Raf-1 kinase potency.

***N*-4-Substituted-benzyl-*N′*-*tert*-butylbenzyl thioureas as vanilloid receptor ligands: investigation on the role of methanesulfonamido group in antagonistic activity** **pp 787–791**
Hyeung-geun Park,* Ji-yeon Choi, Sea-hoon Choi, Mi-kyung Park, Jihye Lee, Young-ger Suh, Hawon Cho, Uhtaek Oh, Jiyoun Lee, Sang-Uk Kang, Jeewoo Lee, Hee-Doo Kim, Young-Ho Park, Yeon Su Jeong, Jin Kyu Choi and Sang-sup Jew*



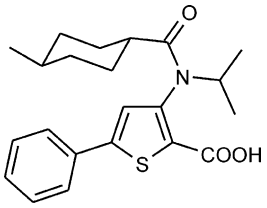
A series of *N*-4-substituted-benzyl-*N′*-*tert*-butylbenzyl thioureas were prepared and the structure–activity relationship studies on the antagonistic activity against VR1 were performed.

Discovery of thiophene-2-carboxylic acids as potent inhibitors of HCV NS5B polymerase and HCV subgenomic RNA replication. Part 1: Sulfonamides **pp 793–796**
Laval Chan,* Sanjoy K. Das, T. Jagadeeswar Reddy, Carl Poisson, Mélanie Proulx, Oswy Pereira, Marc Courchesne, Caroline Roy, Wuyi Wang, Arshad Siddiqui, Constantin G. Yannopoulos, Nghe Nguyen-Ba, Denis Labrecque, Richard Bethell, Martine Hamel, Philippe Courtemanche-Asselin, Lucille L'Heureux, Maud David, Olivier Nicolas, Stéphanie Brunette, Darius Bilimoria and Jean Bédard



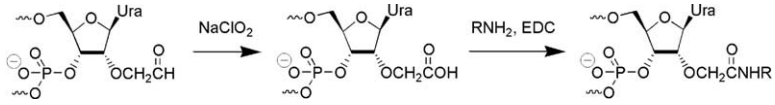
Discovery of thiophene-2-carboxylic acids as potent inhibitors of HCV NS5B polymerase and HCV subgenomic RNA replication. Part 2: Tertiary amides **pp 797–800**

Laval Chan,* Oswy Pereira, T. Jagadeeswar Reddy, Sanjoy K. Das, Carl Poisson, Marc Courchesne, Mélanie Proulx, Arshad Siddiqui, Constantin G. Yannopoulos, Nghe Nguyen-Ba, Caroline Roy, Daniel Nasturica, Christophe Moinet, Richard Bethell, Martine Hamel, Lucille L'Heureux, Maud David, Olivier Nicolas, Philippe Courtemanche-Asselin, Stéphanie Brunette, Darius Bilimoria and Jean Bédard



Synthesis of oligonucleotide 2′-conjugates via amide bond formation in solution **pp 801–804**

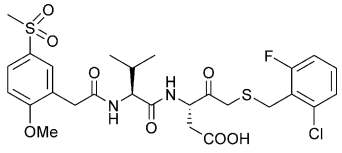
Anna V. Kachalova, Dmitry A. Stetsenko,* Michael J. Gait and Tatiana S. Oretskaya



Discovery of novel aspartyl ketone dipeptides as potent and selective caspase-3 inhibitors **pp 805–808**

Yongxin Han, André Giroux, Erich L. Grimm, Renée Aspiotis, Sébastien Francoeur, Christopher I. Bayly, Daniel J. Mckay, Sophie Roy, Steve Xanthoudakis, John P. Vaillancourt, Dita M. Rasper, John Tam, Paul Tawa, Nancy A. Thornberry, Erin P. Paterson, Margarita Garcia-Calvo, Joseph W. Becker, Jennifer Rotonda, Donald W. Nicholson and Robert J. Zamboni

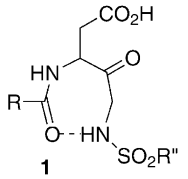
The discovery of a series of potent, selective and reversible caspase-3 inhibitors employing combinatorial chemistry, structural biology and molecular modeling is described. Compound **16**, for example, is a potent inhibitor against rh-caspase-3 with an IC_{50} of 5 nM, selective against rh-caspase-1 (IC_{50}: 1600 nM), rh-caspase-7 (IC_{50}: 120 nM) and rh-caspase-8 (IC_{50}: 490 nM), and active against camptothecin induced apoptosis in NT2 cells with an IC_{50} of 1 μM.



16

The design and synthesis of sulfonamides as caspase-1 inhibitors **pp 809–812**

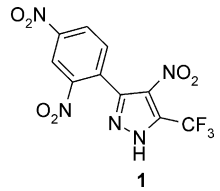
William G. Harter,* Hans Albrect, Kenneth Brady, Bradley Caprathe, James Dunbar, John Gilmore, Sheryl Hays, Catherine R. Kostlan, Beth Lunney and Nigel Walker



1

A series of sulfonamides has been prepared as inhibitors of interleukin-1β converting enzyme (ICE), also known as caspase 1. These compounds were designed to improve potency by rigidifying the enzyme bound molecule through an intramolecular hydrogen bond. An X-ray crystal structure of a representative member of this series bound to the active site of ICE, confirms the presence of the hydrogen bonding interaction.

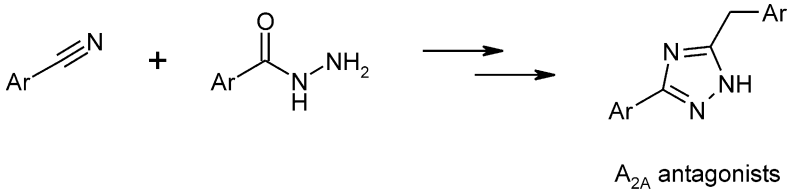
3-Trifluoromethyl-4-nitro-5-arylpyrazoles are novel K_{ATP} channel agonists **pp 813–816**
Andrew J. Peat, Claire Townsend, M. Craig McKay, Dulce Garrido, Christopher M. Terry, Jayme L. R. Wilson and Stephen A. Thomson*



1

The syntheses of a series of 3-trifluoromethyl-4-nitro-5-arylpyrazoles as potent K_{ATP} channel agonists are reported. The most potent compound reported is ca. 100-fold more potent than diazoxide and exhibits selectivity for the SUR1 K_{ATP} channel subtype.

Synthesis and SAR evaluation of 1,2,4-triazoles as A_{2A} receptor antagonists **pp 817–821**
Alexander Alanine, Lilli Anselm, Lucinda Steward, Stefan Thomi, Walter Vifian and Michael D. Groaning*



OTHER CONTENTS

Contributors to this issue **pp I–II**
Instructions to contributors **pp III–VI**

*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 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).

Indexed/Abstracted in: Adis LMS Drug Alerts, Beilstein, Biochemistry & Biophysics Citation Index, BIOSIS previews, CAB Abstracts, CAB Health, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/Elsevier BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0960-894X