

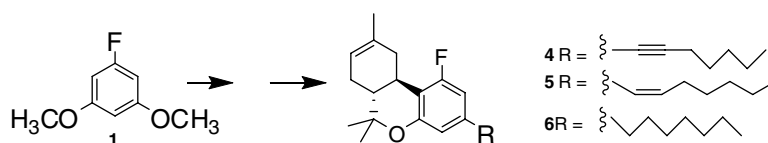
Contents

ARTICLES

- Synthesis of a coumarin-based europium complex for bioanalyte labeling** pp 1499–1503
Clémentine Féau, Emmanuel Klein, Paul Kerth and Luc Lebeau*

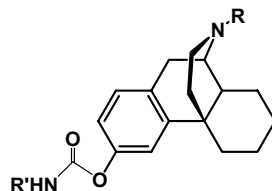
The synthesis and preliminary evaluation of a labeling compound designed for HTRF measurements with excitation at 370 nm by UV-LEDs is reported.

- The role of fluorine substitution in the structure–activity relationships (SAR) of classical cannabinoids** pp 1504–1507
Peter J. Crocker, Anu Mahadevan, Jenny L. Wiley, Billy R. Martin and Raj K. Razdan*



Substitution of the phenolic hydroxyl group of THC_s by a fluorine (**4**, **5**, **6**) has a significant detrimental effect on CB1 binding affinity.

- High-affinity carbamate analogues of morphinan at opioid receptors** pp 1508–1511
Xuemei Peng, Brian I. Knapp, Jean M. Bidlack and John L. Neumeyer*

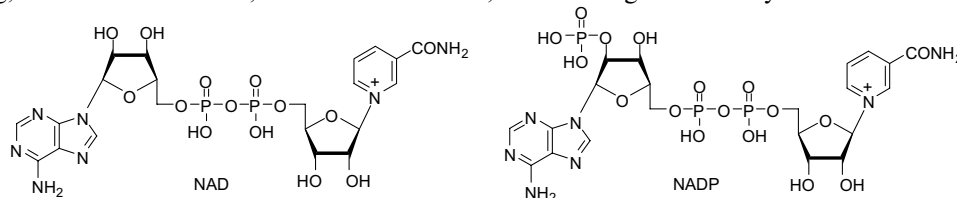


A series of novel carbamate analogues were synthesized and evaluated at opioid receptors. Functional activities of these compounds were measured in the [³⁵S]GTPγS binding assay. Phenyl carbamate derivatives showed the highest binding affinity for κ receptor ($K_i = 0.046$ and 0.051 nM) and for μ receptor ($K_i = 0.11$ and 0.12 nM).

Probing binding requirements of NAD kinase with modified substrate (NAD) analogues

pp 1512–1515

Laurent Bonnac, Liqiang Chen, Rashmi Pathak, Guangyao Gao, Qian Ming, Eric Bennett, Krzysztof Felczak, Martin Kullberg, Steven E. Patterson, Francesca Mazzola, Giulio Magni and Krzysztof W. Pankiewicz*

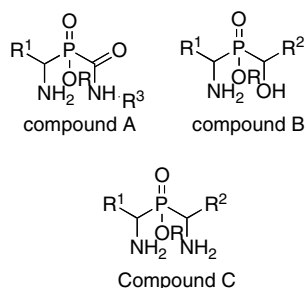


Synthesis of novel nicotinamide adenine dinucleotides (NAD⁺ analogues) containing 2'-fluorine in the *ribo* or *arabino* configuration of the adenosine ribose moiety, or the 2'-OH group in the *arabino* configuration, is reported. These compounds as well benzamide adenine dinucleotide (BAD) were evaluated as potential inhibitors of human and *Mycobacterium tuberculosis* NAD kinase, which converts NAD to NADP.

Novel hydroxamic acid-related phosphinates: Inhibition of neutral aminopeptidase N (APN)

pp 1516–1519

Marcin Drag,* Renata Grzywa and Jozef Oleksyszyn*



New phosphinate inhibitors of aminopeptidase N are reported.

Quinuclidines as selective agonists for alpha-7 nicotinic acetylcholine receptors

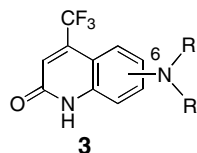
pp 1520–1522

Fedra M. Leonik, Roger L. Papke and Nicole A. Horenstein*

Discovery of an androgen receptor modulator pharmacophore based on 2-quinolinones

pp 1523–1526

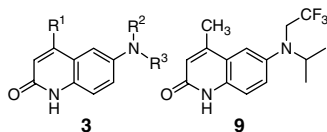
Arjan van Oeveren, Barbara A. Pio, Christopher M. Tegley, Robert I. Higuchi, Min Wu, Todd K. Jones, Keith B. Marschke, Andrés Negro-Vilar and Lin Zhi*



A series of alkylamino-2-quinolinone compounds (**3**) was discovered as androgen receptor modulators based on an early linear tricyclic quinoline pharmacophore (**1**). The series demonstrated selective high binding affinity to androgen receptor and potent receptor modulating activities in the cotransfection assays.

Novel selective androgen receptor modulators: SAR studies on 6-bisalkylamino-2-quinolinones pp 1527–1531

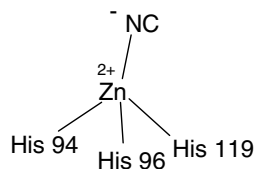
Arjan van Oeveren, Mehrnoush Motamedi, Esther Martinborough, Shuo Zhao, Yixing Shen, Sarah West, William Chang, Adam Kallel, Keith B. Marschke, Francisco J. López, Andrés Negro-Vilar and Lin Zhi*



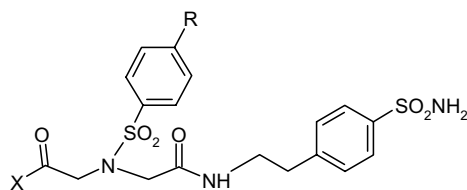
A series of selective androgen receptor modulators (SARMs) with a wide spectrum of receptor modulating activities was developed based on optimization of the 4-substituted 6-bisalkylamino-2-quinolinones (**3**). Significance of the trifluoromethyl group on the side chains and its interactions with amino acid residues within the androgen receptor (AR) ligand binding domain are discussed. A representative analog (**9**) was tested orally in a rodent model of hypogonadism and demonstrated desirable tissue selectivity.

Carbonic anhydrase inhibitors. Inhibition of transmembrane isozymes XII (cancer-associated) and XIV with anions pp 1532–1537

Alessio Innocenti, Daniela Vullo, Jaromir Pastorek, Andrea Scozzafava, Silvia Pastorekova, Isao Nishimori and Claudiu T. Supuran*

**Carbonic anhydrase inhibitors: Inhibition of cytosolic/tumor-associated isoforms I, II, and IX with iminodiacetic carboxylates/hydroxamates also incorporating benzenesulfonamide moieties** pp 1538–1543

M. Amelia Santos,* Sergio Marques, Daniela Vullo, Alessio Innocenti, Andrea Scozzafava and Claudiu T. Supuran*

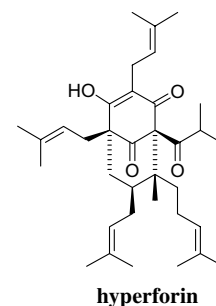


R = OMe, OPhe, Ph; X = OH, NHOH

In vitro antimalarial activity of hyperforin, a prenylated acylphloroglucinol. A structure–activity study pp 1544–1548

Luisella Verotta,* Giovanni Appendino, Ezio Bombardelli and Reto Brun

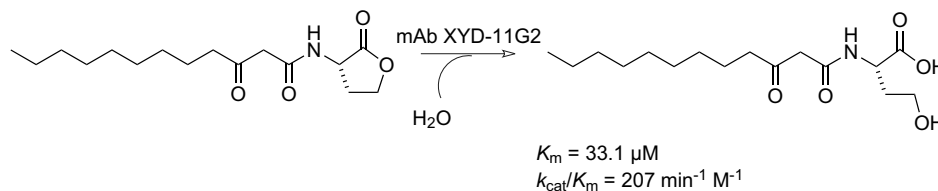
The antimalarial activity of hyperforin and a series of derivatives variously modified on the cyclohexatrienone system was investigated. Hyperforin was active against *Plasmodium falciparum* with an IC₅₀ value in the micromolar range, and the activity was not critically dependent on either its phenol-like sensitivity to autooxidation or the presence of unsaturation on the prenyl residues.



Antibody catalyzed hydrolysis of a quorum sensing signal found in Gram-negative bacteria

pp 1549–1552

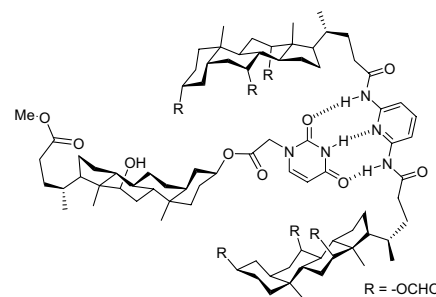
Sandra De Lamo Marin, Yang Xu, Michael M. Meijler* and Kim D. Janda*

**Bile acid-based receptors containing 2,6-bis(acylamino)pyridine for recognition of uracil derivatives**

pp 1553–1557

Prosenjit Chattopadhyay and Pramod S. Pandey*

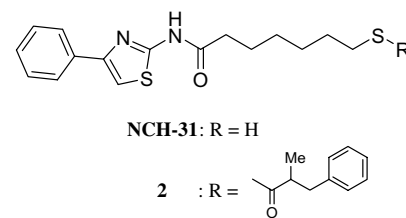
The binding ability of acyclic and cyclic bile acid-based receptors containing 2,6-bis(acylamino)pyridine for different uracil derivatives has been studied.

**Identification of a potent and stable antiproliferative agent by the prodrug formation of a thiolate histone deacetylase inhibitor**

pp 1558–1561

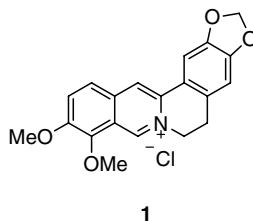
Takayoshi Suzuki,* Shinya Hisakawa, Yukihiro Itoh, Sakiko Maruyama, Mineko Kurotaki, Hidehiko Nakagawa and Naoki Miyata*

To identify prodrugs of a thiolate histone deacetylase inhibitor NCH-31 that show potent antiproliferative activity and are stable in human plasma, we synthesized several *S*-acyl derivatives of NCH-31. Among these compounds, *S*-2-methyl-3-phenylpropanoyl compound **2** showed potent antiproliferative activity and high stability in human plasma.

**Antiviral activity of berberine and related compounds against human cytomegalovirus**

pp 1562–1564

Kyoko Hayashi, Kazuki Minoda, Yasuo Nagaoka, Toshimitsu Hayashi and Shinichi Uesato*

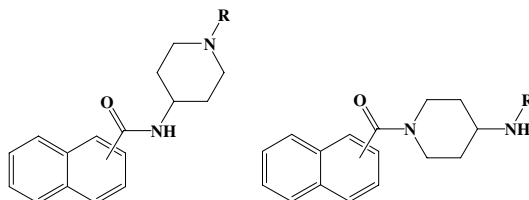


Berberine chloride (**1**) inhibited the human cytomegalovirus replication at IC_{50} 0.68 μM , which was equivalent to that (0.91 μM) for ganciclovir. The selectivity index of **1**, the ratio of 50% cytotoxic concentration to IC_{50} , was 110.

Synthesis and in vitro binding studies of substituted piperidine naphthamides. Part I: Influence of the substitution on the basic nitrogen and the position of the amide on the affinity for D_{2L}, D_{4.2}, and 5-HT_{2A} receptors

pp 1565–1569

Pascal Carato, Amaury Graulich, Niels Jensen, Bryan L. Roth and Jean-François Liégeois*

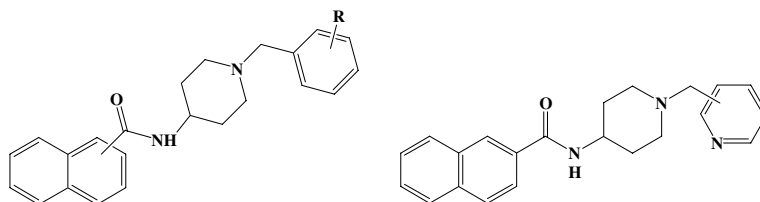


R = benzyl, 2-phenethyl, 1-phenethyl, 3-phenylpropyl, (S)-3-(1-hydroxy-1-phenyl)propyl, (R)-3-(1-hydroxy-1-phenyl)propyl, 4-phenylbutyl.

Synthesis and in vitro binding studies of substituted piperidine naphthamides. Part II: Influence of the substitution on the benzyl moiety on the affinity for D_{2L}, D_{4.2}, and 5-HT_{2A} receptors

pp 1570–1574

Pascal Carato, Amaury Graulich, Niels Jensen, Bryan L. Roth and Jean-François Liégeois*

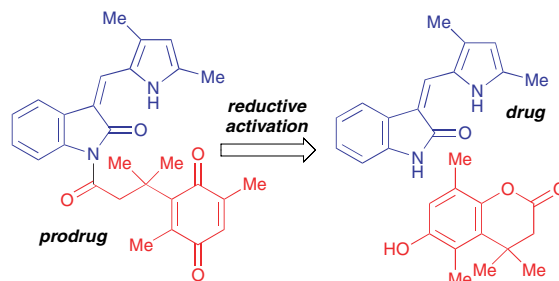


1- and 2-Naphthamide derivatives: R = H, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 3-CF₃, 4-CF₃, 2,3,4,5,6-F, 4-NO₂, 3-MeO, 4-MeO, 2-Me, 3-Me, 4-Me.

Synthesis and evaluation of prodrugs for anti-angiogenic pyrrolylmethylidanyl oxindoles

pp 1575–1578

Lesley Maskell, Emilie A. Blanche, Marie A. Colucci, Jacqueline L. Whatmore and Christopher J. Moody*

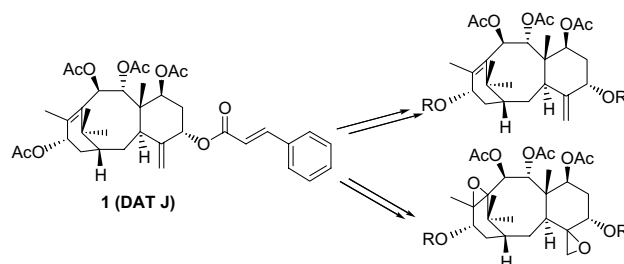


Synthesis and biological evaluation of new taxoids derived from 2-deacetoxytaxinine J

pp 1579–1583

Maurizio Botta,* Silvia Armaroli, Daniele Castagnolo, Gabriele Fontana, Paula Pera and Ezio Bombardelli

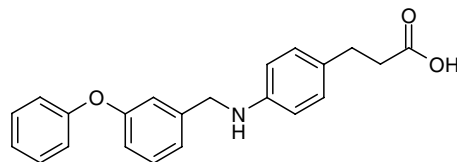
A small library of 2-deacetoxytaxinine J (DAT-J) **1** derivatives was synthesised and tested in vitro for their reversal activity in human mammary carcinoma MDR cell line MCF7-R. One of the new taxoids showed to be active at 0.1 μ M when tested in combination with paclitaxel.



Solid phase synthesis and SAR of small molecule agonists for the GPR40 receptor

pp 1584–1589

Stephen C. McKeown,* David F. Corbett, Aaron S. Goetz, Thomas R. Littleton, Eric Bigham, Celia P. Briscoe, Andrew J. Peat, Steve P Watson and Deirdre M. B. Hickey

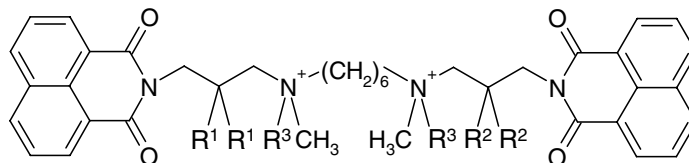
GPR40 pEC₅₀ = 7.3

The discovery, solid phase synthesis and structure–activity relationships of novel carboxylic acid agonists for the GPR40 receptor are described.

Antitrypanosomal activity of quaternary naphthalimide derivatives

pp 1590–1593

Mathias Muth, Verena Hoerr, Melanie Glaser, Alicia Ponte-Sucre, Heidrun Moll, August Stich and Ulrike Holzgrabe*

**i**⁺**Pharmacophore mapping of diverse classes of farnesyltransferase inhibitors**

pp 1594–1600

Tabish Equbal, Om Silakari,* Gundla Rambabu and Muttineni Ravikumar

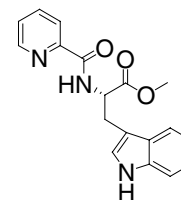
Pharmacophore mapping has been performed on farnesyltransferase inhibitors (FTIs) to quantitatively explore common chemical features among a considerable number of structures with great diversity.

i⁺**Synthesis of pseudopeptides based L-tryptophan as a potential antimicrobial agent**

pp 1601–1607

Jian Lv, Liang Yin, Tingting Liu and Yongmei Wang*

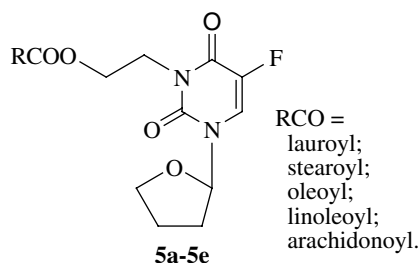
Synthesis and biological activity of pseudopeptides based L-tryptophan are described. L-*o*-TrpPA being less toxic could be an effective antimicrobial broad-spectrum drug, and has a good activity against methicillin-resistant *Staphylococcus aureus* and fluconazole-resistant *Candida* spp. from clinical isolates.

**L-*o*-TrpPA (82%)**

Immunomodulatory effects of two saponinins 1 and 2 isolated from *Luffa cylindrica* in Balb/C mice pp 1608–1612
Anamika Khajuria,* Amit Gupta, Saraswati Garai and Basanti Purinima Wakhloo



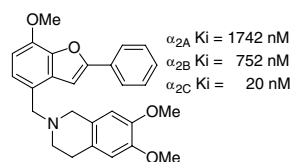
Synthesis and cytotoxicity of novel fatty acid-nucleoside conjugates pp 1613–1615
Yun-Xiao Zhang, Gui-Fu Dai, Le Wang and Jing-Chao Tao*



Syntheses and structure-activity relationships of novel fatty acid-nucleoside conjugates **5a-5e** are reported.

Novel 4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)methylbenzofuran derivatives as selective α_{2C} -adrenergic receptor antagonists pp 1616–1621

Koji Hagihara,* Hajime Kashima, Kyoichiro Iida, Junichi Enokizono, Shin-ichi Uchida, Hiromi Nonaka, Masako Kurokawa and Junichi Shimada

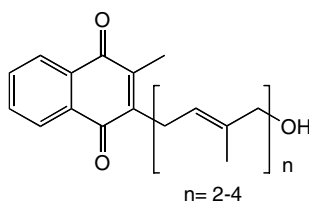


The synthesis and SAR studies of a series of novel 4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)methylbenzofuran derivatives as highly selective α_{2C} -adrenergic receptor antagonists are reported.



Efficient synthesis and biological evaluation of ω -oxygenated analogues of vitamin K_2 : Study of modification and structure-activity relationship of vitamin K_2 metabolites pp 1622–1625

Yoshitomo Suhara, Aya Murakami, Maya Kamao, Shino Mimatsu, Kimie Nakagawa, Naoko Tsugawa and Toshio Okano*



Novel ω -oxygenated vitamin K_2 analogues, which were candidates for metabolites of vitamin K_2 homologues, were efficiently synthesized and their apoptosis-inducing activity was evaluated.

A new class of anti-MRSA and anti-VRE agents: Preparation and antibacterial activities of indole-containing compounds

pp 1626–1628

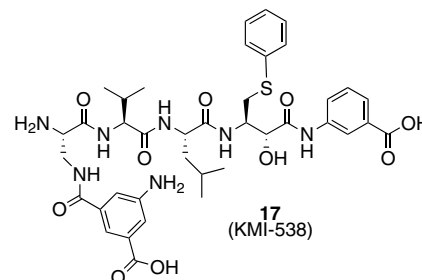
Yasuo Yamamoto* and Mizuyo Kurazono

Design and synthesis of BACE1 inhibitors containing a novel norstatine derivative (2R,3R)-3-amino-2-hydroxy-4-(phenylthio)butyric acid

pp 1629–1633

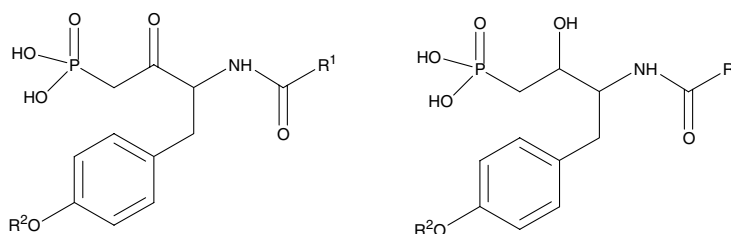
Zyta Ziora, Soko Kasai, Koushi Hidaka, Ayaka Nagamine, Tooru Kimura, Yoshio Hayashi and Yoshiaki Kiso*

A novel norstatine derivative, phenylthionorstatine [(2R,3R)-3-amino-2-hydroxy-4-(phenylthio)butyric acid; Ptns], was designed and synthesized. Then, Ptns was introduced into the structure of designed BACE1 inhibitors at the P₁ position.


Synthesis and biological evaluation of phosphonate derivatives as autotaxin (ATX) inhibitors

pp 1634–1640

Peng Cui,* Jose L. Tomsig, William F. McCalmont, Sangderk Lee, Christopher J. Becker, Kevin R. Lynch and Timothy L. Macdonald

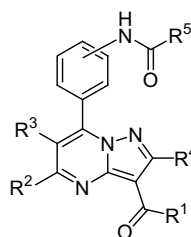


A series of β -keto and β -hydroxy phosphonate derivatives were synthesized. They were tested for autotaxin (ATX) inhibition.

Pyrazolo[1,5-*a*]pyrimidin-7-yl phenyl amides as novel antiproliferative agents: Exploration of core and headpiece structure–activity relationships

pp 1641–1645

Dennis Powell,* Ariamala Gopalsamy, Yanong D. Wang, Nan Zhang, Miriam Miranda, John P. McGinnis and Sridhar K. Rabindran

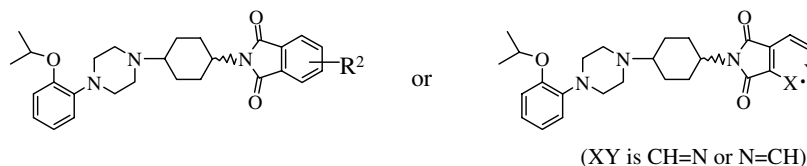


A novel series of antiproliferative agents containing a pyrazolo[1,5-*a*]pyrimidine scaffold and the structure–activity relationship studies of the headpiece, core are described.

1-Arylpiperazinyl-4-cyclohexylamine derived isoindole-1,3-diones as potent and selective α -1a/1d adrenergic receptor ligands

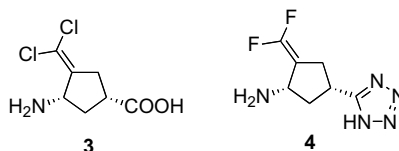
pp 1646–1650

Shengjian Li,* George Chiu, Virginia L. Pulito, Jingchun Liu, Peter J. Connolly and Steven A. Middleton

 $K_i(\alpha_{1a}), K_i(\alpha_{1d})$ values in the range of 0.09 nM ~ 38 nM; $K_i(\alpha_{1b})/K_i(\alpha_{1a})$ up to 401; $K_i(\alpha_{1b})/K_i(\alpha_{1d})$ up to 3607.**Structural modifications of (1*S*,3*S*)-3-amino-4-difluoromethylenecyclopentanecarboxylic acid, a potent irreversible inhibitor of GABA aminotransferase**

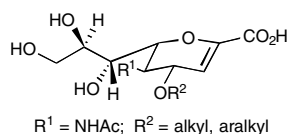
pp 1651–1654

Hai Yuan and Richard B. Silverman*

**Synthesis and evaluation of 4-*O*-alkylated 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid derivatives as inhibitors of human parainfluenza virus type-3 sialidase activity**

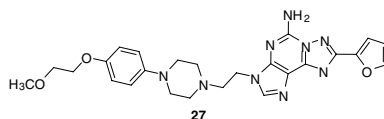
pp 1655–1658

David J. Tindal, Jeffrey C. Dyason, Robin J. Thomson, Takashi Suzuki, Hiroo Ueyama, Yohta Kuwahara, Naoyoshi Maki, Yasuo Suzuki and Mark von Itzstein*

4-*O*-Alkylated Neu5Ac2en derivatives display micromolar inhibition of hPIV-3 sialidase activity.**3*H*-[1,2,4]-Triazolo[5,1-*i*]purin-5-amine derivatives as adenosine A_{2A} antagonists**

pp 1659–1662

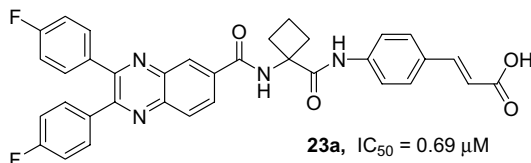
Lisa S. Silverman, John P. Caldwell,* William J. Greenlee, Eugenia Kiselgof, Julius J. Matasi, Deen B. Tulshian, Leyla Arik, Carolyn Foster, Rosalia Bertorelli, Angela Monopoli and Ennio Ongini



A novel series of 3-substituted-8-aryl-[1,2,4]-triazolo[5,1-*i*]purin-5-amine analogs related to Sch 58261 was synthesized in order to identify potent adenosine A_{2A} receptor antagonists with improved selectivity over the A_1 receptor, physicochemical properties, and pharmacokinetic profiles as compared to those of Sch 58261. As a result of structural modifications, numerous analogs with excellent in vitro binding affinities and selectivities were identified. Moreover, compound **27** displayed both superior in vitro and highly promising in vivo profiles.

Structure–activity relationship (SAR) studies of quinoxalines as novel HCV NS5B RNA-dependent RNA polymerase inhibitors pp 1663–1666

Frank Rong,* Suetying Chow, Shunqi Yan, Gary Larson, Zhi Hong and Jim Wu



A novel quinoxaline amide was found to be active against HCV NS5B RNA-dependent RNA polymerase through SAR studies.

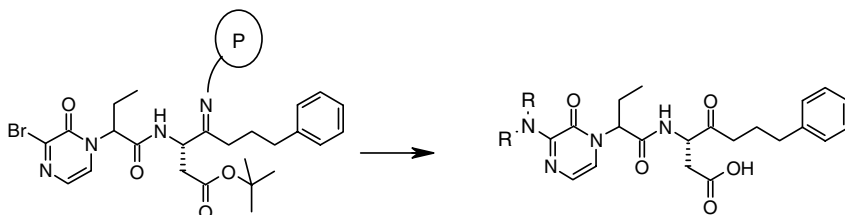
Inhibition of the mitochondrial F_1F_0 -ATPase by ligands of the peripheral benzodiazepine receptor pp 1667–1670

Joanne Cleary, Kathryn M. Johnson, Anthony W. Opipari, and Gary D. Glick*

PBR-ligand PK-11195 inhibits F_1F_0 -ATPase activity in an OSCP-dependent manner, similar to the pro-apoptotic benzodiazepine Bz-423.

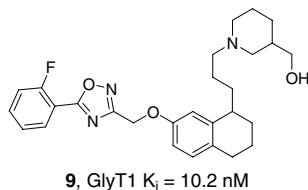
Solid-phase analogue synthesis of caspase-3 inhibitors via palladium-catalyzed amination of 3-bromopyrazinones pp 1671–1674

Elise Isabel,* Renee Aspiotis, W. Cameron Black, John Colucci, Réjean Fortin, André Giroux, Erich L. Grimm, Yongxin Han, Christophe Mellon, Donald W. Nicholson, Dita M. Rasper, Johanne Renaud, Sophie Roy, John Tam, Paul Tawa, John P. Vaillancourt, Steven Xanthoudakis and Robert J. Zamboni



A novel, non-substrate-based series of glycine type 1 transporter inhibitors derived from high-throughput screening pp 1675–1678

J. Lowe,* S. Drozda, W. Qian, M.-C. Peakman, J. Liu, J. Gibbs, J. Harms, C. Schmidt, K. Fisher, C. Strick, A. Schmidt, M. Vanase and L. Lebel

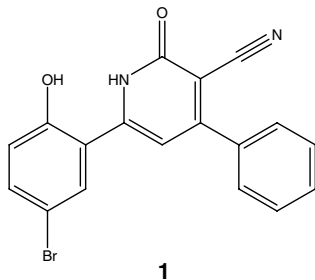


The synthesis and structure-activity relationships (SAR) of a series of indane and tetralin inhibitors of the type 1 glycine transporter, derived from a high-throughput screening (HTS) hit, are described.



Identification and structure–activity relationships of substituted pyridones as inhibitors of Pim-1 kinase pp 1679–1683

I. Wayne Cheney,* Shunqi Yan, Todd Appleby, Heli Walker, Todd Vo, Nanhua Yao, Robert Hamatake, Zhi Hong and Jim Z. Wu

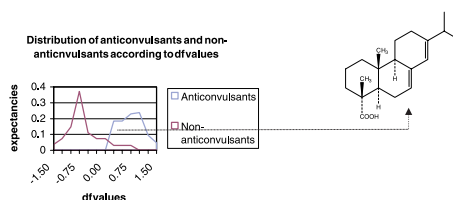


A novel class of pyridone-based inhibitors of Pim-1 kinase is reported. A complex crystal structure of Pim-1/compound **1** (IC_{50} of **1** = 50 nM) defined an inhibitory mechanism of action.

Discovery of anticonvulsant activity of abietic acid through application of linear discriminant analysis pp 1684–1690

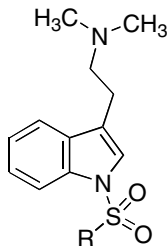
Alan Talevi, Mariana Sella Cravero, Eduardo A. Castro and Luis E. Bruno-Blanch*

Anticonvulsant activity of abietic acid at 30 mg/kg in the Maximal Electroshock test was rationally discovered through application of a Discriminant Function based on 2D descriptors in virtual screening of a 10,000 compounds database.

**Further studies on the binding of N_1 -substituted tryptamines at $h5-HT_6$ receptors**

pp 1691–1694

Abner Nyandegge, Renata Kolanos, Bryan L. Roth and Richard A. Glennon*

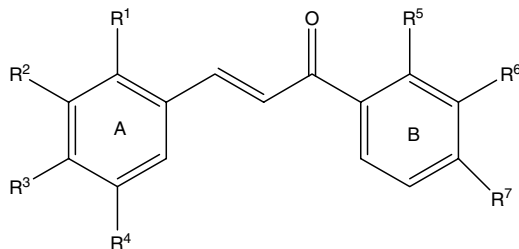


N_1 -Alkylsulfonyl- (R = alkyl) and N_1 -arylsulfonyltryptamines (R = aryl) bind at $h5-HT_6$ serotonin receptors. The latter bind with higher affinity than their N_1 -benzyltryptamine counterparts, and evidence suggests they might bind in a different manner at $h5-HT_6$ receptors.

Synthesis, antimycobacterial activity evaluation, and QSAR studies of chalcone derivatives

pp 1695–1700

P. M. Sivakumar, S. Prabu Seenivasan, Vanaja Kumar and Mukesh Doble*



Twenty-five chalcones were synthesized, and their activity was evaluated by luciferase reporter phage (LRP) assay, and quantitative structure–activity relationship (QSAR) was developed.



A spectroscopic and molecular modeling study of sinomenine binding to transferrin

pp 1701–1704

Hongyan Du, Junfeng Xiang, Yazhou Zhang and Yalin Tang*

The binding of sinomenine to human transferrin via non-covalent bonds has been first characterized. Our research may be potentially applied in sinomenine transport and delivery to targeted sites by transferrin.

Structure–activity relationship studies on quorum sensing ComX_{RO-E-2} pheromone

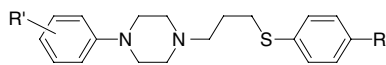
pp 1705–1707

Masahiro Okada,* Hisao Yamaguchi, Isao Sato, Soo Jeong Cho, David Dubnau and Youji Sakagami*

Synthesis and QSAR studies on hypotensive 1-[3-(4-substituted phenylthio) propyl]-4-(substituted phenyl) piperazines

pp 1708–1712

Anil K. Saxena,* Jyoti Rao, Ruchika Chakrabarty, Mridula Saxena and R. C. Srimal

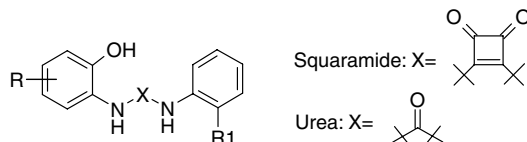


Synthesis and QSAR studies in a series of 1-[3-(4-substituted phenylthio) propyl]-4-(substituted phenyl) piperazines for their hypotensive and 5-HT_{2A} receptor binding affinities show that hydrophobicity and resonance parameters are important for the activities.

Comparison of *N,N'*-diarylsquaramides and *N,N'*-diarylureas as antagonists of the CXCR2 chemokine receptor

pp 1713–1717

Brent W. McClelland, Roderick S. Davis, Michael R. Palovich, Katherine L. Widdowson, Michelle L. Werner, Miriam Burman, James J. Foley, Dulcie B. Schmidt, Henry M. Sarau, Martin Rogers, Kevin L. Salyers, Peter D. Gorycki, Theresa J. Roethke, Gary J. Stelman, Leonard M. Azzarano, Keith W. Ward and Jakob Busch-Petersen*

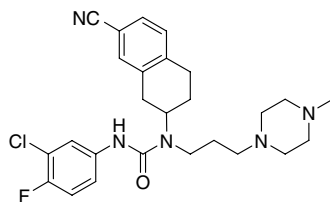


N,N'-diarylsquaramides were prepared and evaluated as antagonists of CXCR2. The compounds were found to be potent and selective antagonists of CXCR2. Significant differences in SAR were observed relative to the previously described *N,N'*-diarylurea series.

Discovery of tetralin ureas as potent melanin concentrating hormone 1 receptor antagonists

pp 1718–1721

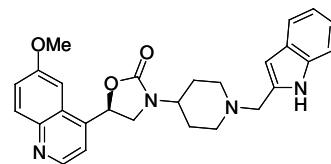
Tao Guo,* Huizhong Gu, Doug W. Hobbs, Dennis E. Busler and Laura L. Rokosz

**7o**MCH1R K_i = 8.5 nM**Oxazolidinones as novel human CCR8 antagonists**

pp 1722–1725

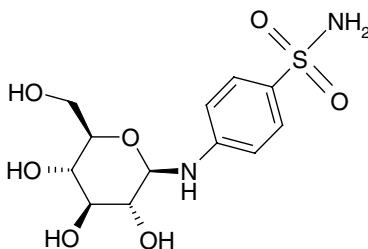
Jian Jin,* Yonghui Wang, Feng Wang, Jeffery K. Kerns, Victoria M. Vinader, Ashley P. Hancock, Matthew J. Lindon, Graeme I. Stevenson, Dwight M. Morrow, Parvathi Rao, Cuc Nguyen, Victoria J. Barrett, Chris Browning, Guido Hartmann, David P. Andrew, Henry M. Sarau, James J. Foley, Anthony J. Jurewicz, James A. Fornwald, Andy J. Harker, Michael L. Moore, Ralph A. Rivero, Kristen E. Belmonte and Helen E. Connor

High-throughput screening of the corporate compound collection led to the discovery of a novel series of N-substituted-5-aryl-oxazolidinones as potent human CCR8 antagonists. The synthesis, structure-activity relationships, and optimization of the series that led to the identification of SB-649701 (**1a**) are described.

SB-649701 (**1a**), hCCR8 FLIPR pIC_{50} = 7.7**Carbonic anhydrase inhibitors: Binding of an antiglaucoma glycosyl-sulfanilamide derivative to human isoform II and its consequences for the drug design of enzyme inhibitors incorporating sugar moieties**

pp 1726–1731

Anna Di Fiore, Andrea Scozzafava, Jean-Yves Winum, Jean-Louis Montero, Carlo Pedone, Claudiu T. Supuran* and Giuseppina De Simone*

**Design, synthesis, and biological evaluation of novel analogues of archazolid:**

pp 1732–1735

A highly potent simplified V-ATPase inhibitor

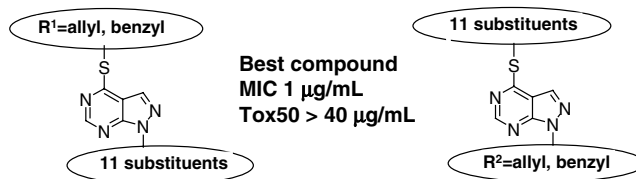
Dirk Menche,* Jorma Hassfeld, Florenz Sasse, Markus Huss and Helmut Wiczorek

Novel analogues of the V-ATPase inhibitors archazolid A and B with modifications of the free hydroxyl groups and the side chain were designed by molecular modeling, synthesized by derivatization of the parent natural product, and evaluated for V-ATPase inhibition and growth inhibition of murine connective tissue cells.

New thiopyrazolo[3,4-d]pyrimidine derivatives as anti-mycobacterial agents

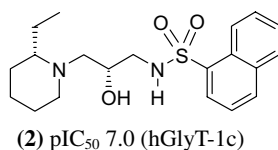
pp 1736–1740

Lluís Ballell,* Robert A. Field, Gavin A. C. Chung and Robert J. Young

**1,3-Diaminopropan-2-ol Sulfonamides as potent and selective inhibitors of the glycine transporter type 1**

pp 1741–1745

Shahzad S. Rahman,* Steven Coulton, Hugh J. Herdon, Graham F. Joiner, Jian Jin and Roderick A. Porter



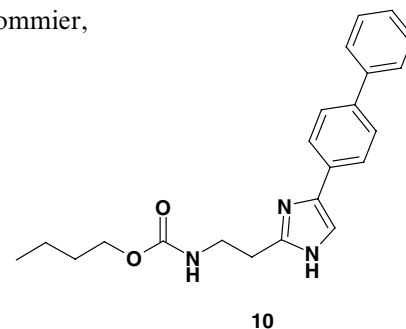
High throughput screening led to the discovery of a novel series of 1,3-diaminopropan-2-ol sulfonamides as selective GlyT-1 inhibitors. Structure–activity relationships of this novel series and optimisation of the initial hit that led to the identification of (2), a potent and selective GlyT-1 inhibitor, are also presented.

Butyl 2-(4-[1.1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethylcarbamate, a potent sodium channel blocker for the treatment of neuropathic pain

pp 1746–1749

Anne-Marie Liberatore,* Jocelyne Schulz, Christine Favre-Guilmar, Jacques Pommier, Jacques Lannoy, Emilia Pawlowski, Marie-Anne Barthelemy, Marion Huchet, Michel Auguet, Pierre-Etienne Chabrier and Dennis Bigg

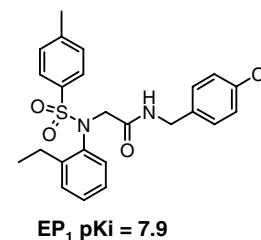
A series of 4-arylimidazole carbamates was synthesized and their binding affinities to the site-2 sodium (Na⁺) channel were determined. SAR studies led to the identification of compound 10, a potent Na⁺ channel blocker which was efficacious in pain models in vivo.

**Identification of novel glycine sulfonamide antagonists for the EP₁ receptor**

pp 1750–1754

Stephen C. McKeown,* Adrian Hall,* Richard Blunt, Susan H. Brown, Iain P. Chessell, Anita Chowdhury, Gerard M. P. Giblin, Mark P. Healy, Matthew R. Johnson, Olivier Lorthioir, Anton D. Michel, Alan Naylor, Xiao Lewell, Shilina Roman, Stephen P. Watson, Wendy J. Winchester and Richard J. Wilson

The discovery, synthesis, pharmacokinetic profile and structure–activity relationships of a novel series of non-acidic EP₁ receptor antagonists are described.



N-Caffeoylphenalkylamide derivatives as bacterial efflux pump inhibitors

pp 1755–1758

Serge Michalet,* Gilbert Cartier, Bruno David, Anne-Marie Mariotte, Marie-Geneviève Dijoux-franca, Glenn W. Kaatz, Michael Stavri and Simon Gibbons

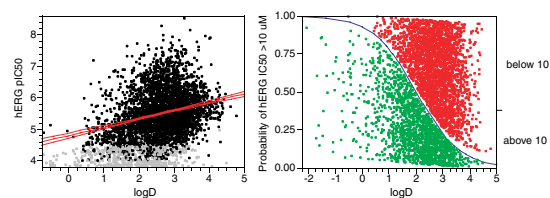
As part of an ongoing project to identify plant natural products as efflux pump inhibitors (EPIs), bioassay-guided fractionation of the methanolic extract of *Mirabilis jalapa* Linn. (Nyctaginaceae) led to the isolation of an active polyphenolic amide: *N-trans-feruloyl 4'-O-methyldopamine*. This compound showed moderate activity as an EPI against multidrug-resistant (MDR) *Staphylococcus aureus* overexpressing the multidrug efflux transporter NorA, causing an 8-fold reduction of norfloxacin MIC at 292 μM (100 $\mu\text{g/mL}$). This prompted us to synthesize derivatives in order to provide structure–activity relationships and to access more potent inhibitors. Among the synthetic compounds, some were more active than the natural compound and *N-trans-3,4-O-dimethylcaffeoyl tryptamine* showed potentiation of norfloxacin in MDR *S. aureus* comparable to that of the standard reserpine.

A quantitative assessment of hERG liability as a function of lipophilicity

pp 1759–1764

Michael J. Waring* and Craig Johnstone

The impact of lipophilicity as a factor contributing to hERG potency is assessed for a large dataset of compounds of differing ionisation type. This dataset is derived from compounds tested in the Ionworks™-based in vitro electrophysiology hERG assay at AstraZeneca. Using logistic regression, a quantification of the risk associated with increasing lipophilicity is presented. The anticipated differences between acidic, basic and neutral compounds are apparent in the data but lipophilicity is shown to be a stronger driver for hERG potency than might have been expected. Simple rules defining target lipophilicity values for minimizing hERG liability are derived.

**Discovery of non-covalent dipeptidyl peptidase IV inhibitors which induce a conformational change in the active site**

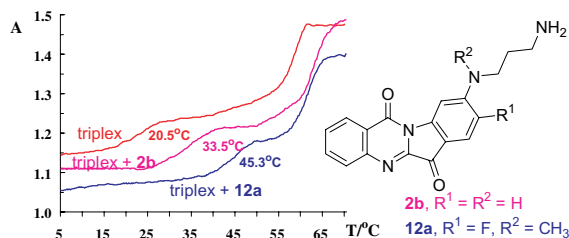
pp 1765–1768

Scott M. Sheehan,* Hans-Juergen Mest, Brian M. Watson, Valentine J. Klimkowski, David E. Timm, Annick Cauvin, Stephen H. Parsons, Qing Shi, Emily J. Canada, Michael R. Wiley, Gerd Ruehter, Britta Evers, Soenke Petersen, Larry C. Blaszcak, Shon R. Pulley, Brandon J. Margolis, Graham N. Wishart, Beatrice Renson, Dirk Hankotius, Michael Mohr, Johann-Christian Zechel, J. Michael Kalbfleisch, Elizabeth A. Dingess-Hammond, Andre Boelke and Andreas G. Weichert

Specific stabilization of DNA triple helices by indolo[2,1-b]quinazolin-6,12-dione derivatives

pp 1769–1772

Grace Shiahuy Chen, Bhalchandra V. Bhagwat, Pei-Yin Liao, Hui-Ting Chen, Shwu-Bin Lin and Ji-Wang Chern*

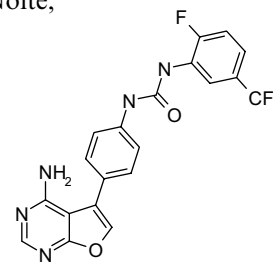


Slight structural modification with large triplex stabilizing effect. The position-8 F atom or a CH_3 group to the nitrogen adjacent to the planar core enhances triplex stability and the effect is additive.

Orally active 4-amino-5-diarylyurea-furo[2,3-*d*]pyrimidine derivatives as anti-angiogenic agent inhibiting VEGFR2 and Tie-2 pp 1773–1778

Yasushi Miyazaki,* Jun Tang, Yutaka Maeda, Masato Nakano, Liping Wang, Robert T. Nolte, Hideyuki Sato, Masaki Sugai, Yuji Okamoto, Anne T. Truesdale, Daniel F. Hassler, Eldridge N. Nartey, Denis R. Patrick, Maureen L. Ho and Kazunori Ozawa

Dual VEGFR2 and Tie-2 inhibitors as anti-angiogenic agents were identified. Compound **8a** exhibited strong inhibitory activities against VEGFR2 and Tie-2 in both enzyme and cellular assays, demonstrated high pharmacokinetic exposure through oral administration, and showed marked tumor growth inhibition and anti-angiogenic activity in mouse HT-29 xenograft model via once-daily oral administration.



Potential synergism and inhibitors to multiple target enzymes of Xuefu Zhuyu Decoction in cardiac disease therapeutics: A computational approach pp 1779–1783

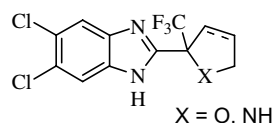
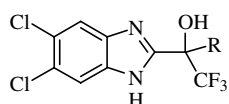
Qin Huang, Xuebin Qiao and Xiaojie Xu*

Comparison of chemical space distribution between Xuefu Zhuyu Decoction and drug/drug-like molecules curing cardiac system disease, and prediction of docking results and ADME in Xuefu Zhuyu Decoction.



Synthesis of potent and tissue-selective androgen receptor modulators (SARMs): 2-(2,2,2)-Trifluoroethyl-benzimidazole scaffold pp 1784–1787

Raymond A. Ng, James C. Lanter, Vernon C. Alford, George F. Allan, Tifanie Sbriscia, Scott G. Lundeen and Zhihua Sui*



Discovery and SAR of isonicotinamide BACE-1 inhibitors that bind β -secretase in a N-terminal 10s-loop down conformation pp 1788–1792

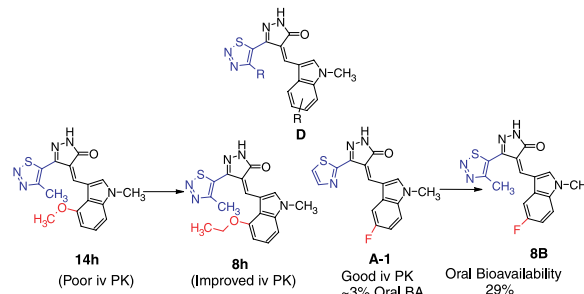
Shaun R. Stauffer,* Matthew G. Stanton, Alison R. Gregro, Melissa A. Steinbeiser, Jennifer R. Shaffer, Philippe G. Nantermet, James C. Barrow, Kenneth E. Rittle, Dennis Collusi, Amy S. Espeseth, Ming-Tain Lai, Beth L. Pietrak, M. Katharine Holloway, Georgia B. McGaughey, Sanjeev K. Munshi, Jerome H. Hochman, Adam J. Simon, Harold G. Selnick, Samuel L. Graham and Joseph P. Vacca

1,2,3-Thiadiazole substituted pyrazolones as potent KDR/VEGFR-2 kinase inhibitors

pp 1793–1798

Rabindranath Tripathy,* Arup Ghose, Jasbir Singh, Edward R. Bacon, Thelma S. Angeles, Shi X. Yang, Mark S. Albom, Lisa D. Aimone, Joseph L. Herman and John P. Mallamo

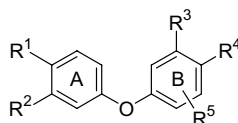
Discovery of 1,2,3-Thiadiazole substituted pyrazolones as potent KDR kinase inhibitors along with their potency, cellular data, improved PK profile, and modeling results is discussed.



Synthesis of novel diaryl ethers and their evaluation as antimitotic agents

pp 1799–1802

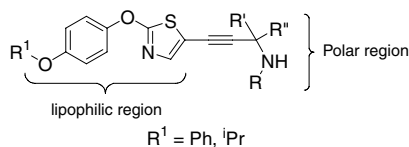
Jin-Kyung In, Mi-Sung Lee, Jung-Eun Yang, Jae-Hwan Kwak, Heesoon Lee, Shanthaveerappa K. Boovanahalli, Kyeong Lee,* Soo Jin Kim, Seung Kee Moon, Sungsook Lee, Nam Song Choi, Soon Kil Ahn and Jae-Kyung Jung*



The synthesis and structure–activity relationship studies of selective acetyl-CoA carboxylase inhibitors containing 4-(thiazol-5-yl)but-3-yn-2-amino motif: Polar region modifications

pp 1803–1807

Xiangdong Xu,* Moshe Weitzberg, Robert F. Keyes, Qun Li, Rongqi Wang, Xiaojun Wang, Xiaolin Zhang, Ernst U. Frevert, Heidi S. Camp, Bruce A. Beutel, Hing L. Sham and Yu Gui Gu

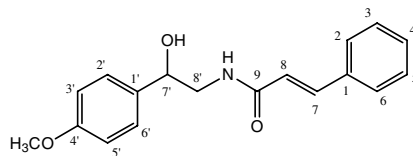


Potent and selective ACC2 inhibitors were synthesized by modifying the polar region of a HTS hit and the SAR suggests a compact and lipophilic binding pocket.

Antihyperglycemic and antidyslipidemic agent from *Aegle marmelos*

pp 1808–1811

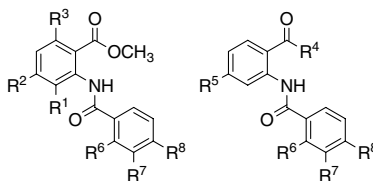
T. Narender,* S. Shweta, P. Tiwari, K. Papi Reddy, T. Khaliq, P. Prathipati, A. Puri, A. K. Srivastava, R. Chander, S. C. Agarwal and K. Raj



The evaluation and structure–activity relationships of 2-benzoylaminobenzoic esters and their analogues as anti-inflammatory and anti-platelet aggregation agents

pp 1812–1817

Pei-Wen Hsieh, Tsong-Long Hwang, Chin-Chung Wu, Shin-Zan Chiang, Chung-I Wu and Yang-Chang Wu*



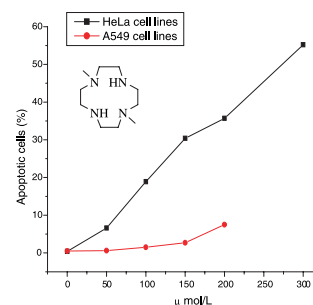
A series of 2-benzoylaminobenzoic esters were synthesized and subjected to anti-platelet aggregation, inhibition of superoxide anion generation, and inhibition of neutrophil elastase release assays.

HeLa cells apoptosis induced by 1,7-dimethyl-1,4,7,10-tetraazacyclododecane

pp 1818–1822

Li Yang, Feng Liang,* Min Liu, Congyi Zheng,* Shuhui Wan, Xiaoqin Xiong, Xiaolian Zhang, Chao Shen and Xiang Zhou*

The first apoptosis induction on human cancer cell lines of free macrocyclic polyamines is presented.



OTHER CONTENTS

Summary of instructions to authors

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*Corresponding author

Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domoaal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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