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Bioorganic & Medicinal Chemistry Letters

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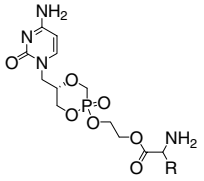
Contents

ARTICLES

Synthesis and biological activation of an ethylene glycol-linked amino acid conjugate of cyclic cidofovir pp 583–586
Ulrika Eriksson, John M. Hilfinger, Jae-Seung Kim, Stefanie Mitchell, Paul Kijek, Katherine Z. Borysko, Julie M. Breitenbach, John C. Drach, Boris A. Kashemirov and Charles E. McKenna*

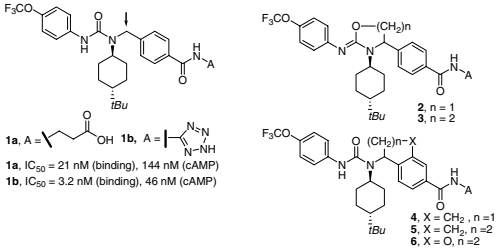


3 R=CH(CH$_3$)$_2$

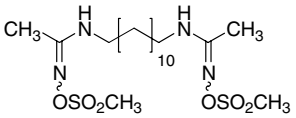
The synthesis, biological activation and oral bioavailability of an ethylene glycol-linked L-valyl ester conjugate of cyclic cidofovir (**3**) is reported.

Design and synthesis of conformationally constrained tri-substituted ureas as potent antagonists of the human glucagon receptor pp 587–592
Rui Liang,* Lauren Abrardo, Edward J. Brady, Mari Rios Candelore, Victor Ding, Richard Saperstein, Laurie M. Tota, Michael Wright, Steve Mock, Constantin Tamvakopolous, Sharon Tong, Song Zheng, Bei B. Zhang, James R. Tata and Emma R. Parmee

A series of conformationally constrained tri-substituted ureas (arrow indicates the position for conformation constraint in the Figure) were synthesized and their potential as the human glucagon receptor antagonists was evaluated. This effort resulted in the identification of compound **4a**, which had a binding IC$_{50}$ of 4.0 nM and was shown to reduce blood glucose levels at 3 mg/kg in glucagon-challenged mice which contain a humanized glucagon receptor. Compound **4a** was also efficacious in correcting hyperglycemia induced by a high fat diet in transgenic mice at doses as low as 3 mg/kg.



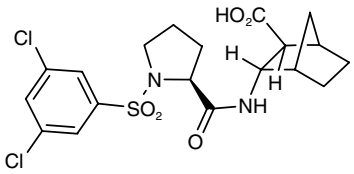
Synthesis and antimalarial activity of new 1,12-bis(*N*,*N*′-acetamidinyl)dodecane derivatives pp 593–596
Mahama Ouattara, Sharon Wein, Michèle Calas, Yen Vo Hoang, Henri Vial and Roger Escale*



Amidoxime and O-substituted derivatives of the bis-alkylamidine 1,12-bis(*N*,*N*′-acetamidinyl)dodecane were synthesized and evaluated as in vitro and in vivo antimalarial prodrugs. Among our compounds, the derivative bis-*O*-methylsulfonylamidoxime constitutes the best prodrug active on *Plasmodium* in vivo after oral administration.

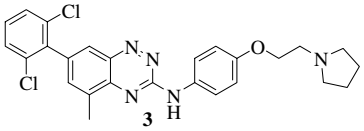
Highly constrained bicyclic VLA-4 antagonists **pp 597–601**
Linda L. Chang,* Quang Truong, George A. Doss, Malcolm MacCoss, Kathryn Lyons, Ermengilda McCauley, Richard Mumford, Gail Forrest, Stella Vincent, John A. Schmidt and William K. Hagmann

VLA-4 antagonists containing a bicyclic β-amino acid were studied. Activity was found to be related to the P_3-amino-carboxy dihedral angle in the bicycle. The best compound, **5m**, had VLA-4 IC_{50} of 54 nM and a 49% bioavailability in the rat at 2 mpk.



5m

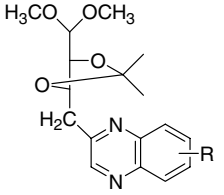
Discovery of [7-(2,6-dichlorophenyl)-5-methylbenzo[1,2,4]triazin-3-yl]-[4-(2-pyrrolidin-1-ylethoxy)-phenyl]amine—a potent, orally active Src kinase inhibitor with anti-tumor activity in preclinical assays **pp 602–608**
Glenn Noronha,* Kathy Barrett, Antonio Boccia, Tessa Brodhag, Jianguo Cao, Chun P. Chow, Elena Dneprovskaia, John Doukas, Richard Fine, Xianchang Gong, Colleen Gritzen, Hong Gu, Ehab Hanna, John D. Hood, Steven Hu, Xinshan Kang, Jann Key, Boris Klebansky, Ahmed Kousba, Ge Li, Dan Lohse, Chi Ching Mak, Andrew McPherson, Moorthy S. S. Palanki, Ved P. Pathak, Joel Renick, Feng Shi, Richard Soll, Ute Splittgerber, Silva Stoughton, Suhan Tang, Shiyin Yee, Binqi Zeng, Ningning Zhao and Hong Zhu



3

We describe the identification of benzotriazine **3**, a potent and orally active Src inhibitor with desirable pharmacokinetic properties and anti-tumor activity in preclinical assays.

An efficient synthesis of quinoxaline derivatives from 4-chloro-4-deoxy-α-D-galactose and their cytotoxic activities **pp 609–612**
Lin Yan, Feng-Wu Liu, Gui-Fu Dai and Hong-Min Liu*



R = H, 7-NO_2, 6-Cl, 7-Cl, 6-COC_6H_5, 7-COC_6H_5

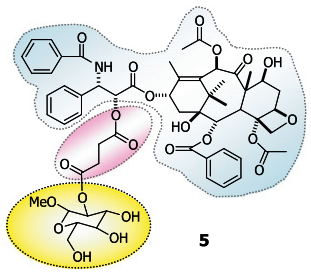
Novel synthesis and preliminary SAR study of some new quinoxaline derivatives were carried out.

Remarkable immunostimulation effects of hybrid liposomes on human peripheral blood mononuclear cells in vitro **pp 613–616**
Yuji Komizu, Yuka Tomonaga, Koichi Goto and Ryuichi Ueoka*

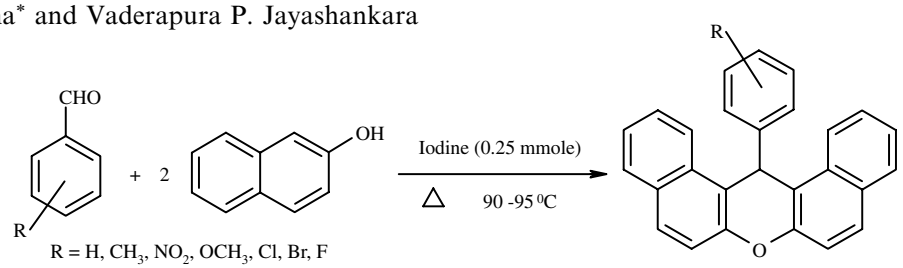
Hybrid liposomes composed of 90 mol% L-α-dimyristoylphosphatidylcholine (DMPC) and 10 mol% polyoxyethylene(25)dodecyl ether ($C_{12}(EO)_{25}$) markedly increased the production of cytokines (IFN-γ, IL-12) secreted by human peripheral blood mononuclear cells in vitro.

Synthesis of 2′-paclitaxel methyl 2-glucopyranosyl succinate for specific targeted delivery to cancer cells **pp 617–620**
Der-Zen Liu, Supachok Sinchaikul, Peddiahgari Vasu Govardhana Reddy, Meng-Yang Chang and Shui-Tein Chen*

The synthesis of novel glucose-conjugated paclitaxel **5** for improving its property and specific targeted delivery to cancer cells is reported.



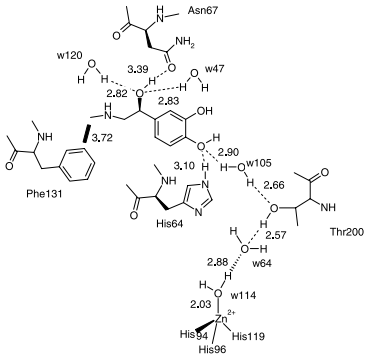
Molecular iodine catalyzed synthesis of aryl-14*H*-dibenzo[*a*, *j*]xanthenes under solvent-free condition **pp 621–623**
Mohamed A. Pasha* and Vaderapura P. Jayashankara



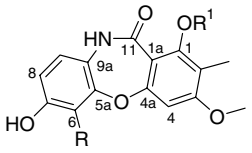
Molecular iodine efficiently catalyzes the reaction of β-naphthol and araldehydes on a preheated hot plate at 90–95 °C to give biologically active aryl-14*H*-dibenzo[*a*, *j*]xanthenes under solvent-free condition. The yields are excellent and the reactions go to completion within 15–20 min.

Identification of the benzodiazepines as a new class of antileishmanial agent **pp 624–627**
Rachel L. Clark, Katharine C. Carter, Alexander B. Mullen, Geoffrey D. Coxon, George Owusu-Dapaah, Emma McFarlane, M. Dao Duong Thi, M. Helen Grant, Justice N. A. Tettey and Simon P. Mackay*

Carbonic anhydrase activators: L-Adrenaline plugs the active site entrance of isozyme II, activating better isoforms I, IV, VA, VII, and XIV **pp 628–635**
Claudia Temperini, Alessio Innocenti, Andrea Scozzafava, Antonio Mastrolorenzo and Claudiu T. Supuran*



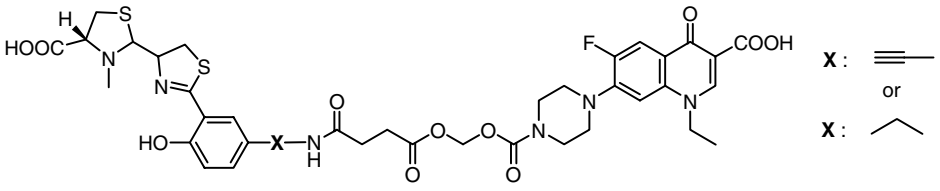
Natural dibenzoxazepinones from leaves of *Carex distachya*: Structural elucidation and radical scavenging activity pp 636–639
Antonio Fiorentino,* Brigida D'Abrosca, Severina Pacifico, Giuseppe Cefarelli, Piera Uzzo and Pietro Monaco



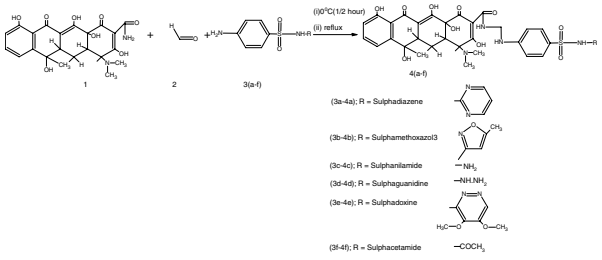
1 R = R^1 = Me
2 R = R^1 =H

Two new dibenzoxazepinones have been isolated and characterized from leaves of *Carex distachya*.

Synthesis of pyochelin–norfloxacin conjugates pp 640–644
Freddy Rivault, Clémence Liébert, Alain Burger, Françoise Hoegy, Mohamed A. Abdallah, Isabelle J. Schalk and Gaëtan L. A. Mislin*



Synthesis and biological study of medicinally important Mannich bases derived from 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a pentahydroxy naphthacene carboxamide pp 645–648
Sheela Joshi, Anju Das Manikpuri* and Prapti Tiwari



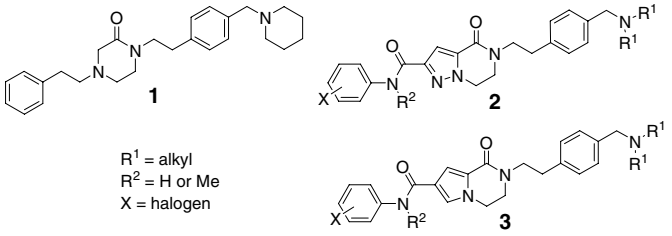
Design of cell-permeable, fluorescent activity-based probes for the lysosomal cysteine protease asparaginyl endopeptidase (AEP)/legumain pp 649–653
Kelly B. Sexton, Martin D. Witte, Galia Blum and Matthew Bogyo*

The synthesis of a highly selective, cell-permeable fluorescent label of the lysosomal cysteine protease legumain is reported.

Solid-phase synthesis of Stat3 inhibitors incorporating *O*-carbamoylserine and *O*-carbamoylthreonine as glutamine mimics **pp 654–656**
Pijus K. Mandal, Patricia A. Heard, Zhiyong Ren, Xiaomin Chen and John S. McMurray*

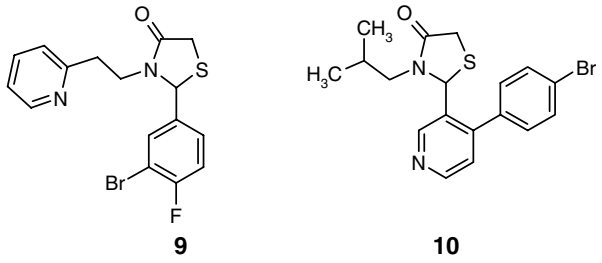
Novel pyrazolopiperazinone- and pyrrolopiperazinone-based MCH-R1 antagonists **pp 657–661**
Kenneth M. Meyers, José Méndez-Andino,* Anny-Odile Colson, X. Eric Hu, John A. Wos, Maria C. Mitchell, Karen Hodge, Jeremy Howard, Jennifer L. Paris, Martin E. Dowty, Cindy M. Obringer and Ofer Reizes

The synthesis and biological testing of novel classes of potent melanin-concentrating hormone (MCH-R1) antagonists based on pyrazolopiperazinone and pyrrolopiperazinone scaffolds are described.

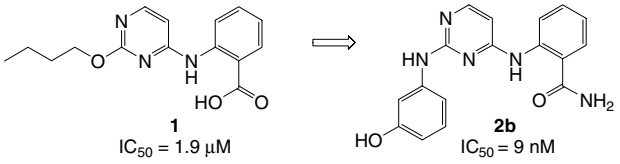


Synthesis and SAR of novel 2-arylthiazolidinones as selective analgesic N-type calcium channel blockers **pp 662–667**
Lars J. S. Knutsen,* Christopher J. Hobbs, Christopher G. Earnshaw, Andrea Fiumana, Jenny Gilbert, Sarah L. Mellor, Fleur Radford, Nichola J. Smith, Philip J. Birch, J. Russell Burley, Stuart D. C. Ward and Iain F. James

A series of new N-type ($Ca_v2.2$) calcium channel blockers derived from the 'hit' structures **9** and **10** is described. Extensive SAR studies using a range of synthetic approaches resulted in novel, patented compounds with IC_{50} values of up to 0.2 μM in an in vitro IMR32 assay, and selectivities for N/L of up to 30-fold. The new compounds described have potential in treatment of neuropathic pain.



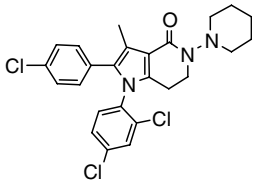
Discovery of a new class of 4-anilinopyrimidines as potent c-Jun N-terminal kinase inhibitors: Synthesis and SAR studies **pp 668–672**
Mei Liu,* Sanyi Wang, Jill E. Clampit, Rebecca J. Gum, Deanna L. Haasch, Cristina M. Rondinone, James M. Trevillyan, Cele Abad-Zapatero, Elizabeth H. Fry, Hing L. Sham and Gang Liu



A new series of 4-anilinopyrimidines has been synthesized and evaluated as JNK1 inhibitors. SAR studies led to the discovery of potent JNK1 inhibitors with good enzymatic activity as well as cellular potency represented by compound **2b**. Kinase selectivity profile and the crystal structure of **2b** are also described.

Constrained analogs of CB-1 antagonists: 1,5,6,7-Tetrahydro-4H-pyrrolo[3,2-c]pyridine-4-one derivatives **pp 673–678**
Roger A. Smith,* Zahra Fathi, Su-Ellen Brown, Soongyu Choi, Jianmei Fan, Susan Jenkins, Harold C. E. Kluender, Anish Konkar, Rico Lavoie, Ronald Mays, Jennifer Natoli, Stephen J. O'Connor, Astrid A. Ortiz, Brent Podlogar, Christy Taing, Susan Tomlinson, Theresa Tritto and Zhonghua Zhang

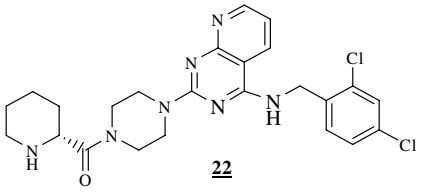
Pyrrolopyridinones were designed and established as potent constrained analogs of the pyrazole CB-1 receptor antagonist/inverse agonist rimonabant. A representative analog was also demonstrated to cause significant appetite suppression and reduction in body weight gain in rodent models.



hCB-1 Ki = 2.2 nM

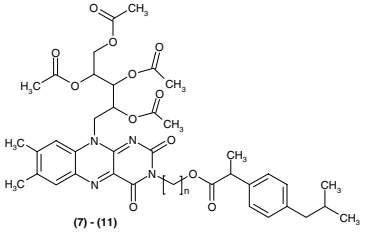
Core exploration in optimization of chemokine receptor CCR4 antagonists **pp 679–682**
Ashok V. Purandare,* Honghe Wan, John E. Somerville, Christine Burke, Wayne Vaccaro, XiaoXia Yang, Kim W. McIntyre and Michael A. Poss

The design, synthesis, and SAR studies of 'core' variations led to identification of novel, selective, and potent small molecule antagonist (**22**) of the CC chemokine receptor-4 (CCR4) with improved in vitro activity and liability profile. Compound **22** was efficacious in a murine allergic inflammation model (ED_{50} 10 mg/kg).



22

Synthesis and biological activities of novel dexibuprofen tetraacetylriboflavin conjugates **pp 683–687**
Christian Banekovich, Ingo Ott,* Thao Koch, Barbara Matuszczak* and Ronald Gust

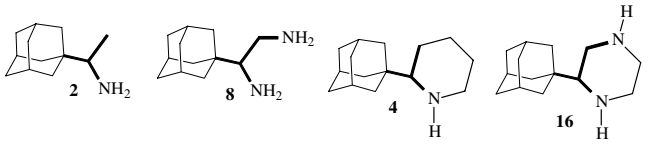


(7) - (11)

Structural basis for the inhibition of Aurora A kinase by a novel class of high affinity disubstituted pyrimidine inhibitors **pp 688–691**
Leslie W. Tari, Isaac D. Hoffman, Daniel C. Bensen, Michael J. Hunter, Jay Nix, Kirk J. Nelson, Duncan E. McRee and Ronald V. Swanson*

We have characterized a novel binding mode for a newly discovered 2,4-disubstituted pyrimidine inhibitor of AIK, using X-ray crystallography. This structure provides an excellent basis for the design of specific and potent compounds with potential therapeutic value in the treatment of cancer.

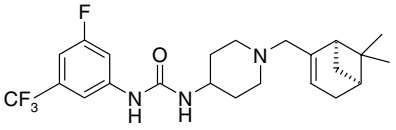
Influence of an additional 2-amino substituent of the 1-aminoethyl pharmacophore group on the potency of rimantadine against influenza virus A pp 692–696
Dimitrios Tataridis, George Fytas,* Antonios Kolocouris, Christos Fytas, Nicolas Kolocouris, George B. Foscolos, Elizaveta Padalko, Johan Neyts and Erik De Clercq



The anti-influenza A (H3N2) virus potency of the diamino rimantadine analogues **8** and **16** compared to the activities of the rimantadine **2** and the heterocyclic rimantadine **4** is probably due to additional hydrogen bonding interactions with the M2 protein receptor.

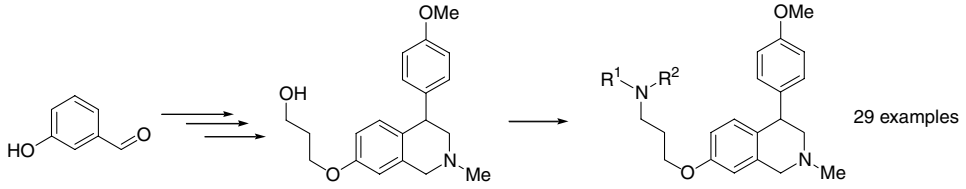
Identification and structure–activity relationships of 1-aryl-3-piperidin-4-yl-urea derivatives as CXCR3 receptor antagonists pp 697–701
Daniel R. Allen, Amanda Bolt, Gayle A. Chapman, Roland L. Knight, Johannes W. G. Meissner,* David A. Owen and Robert J. Watson

The synthesis and biological evaluation of a series of 1-aryl-3-piperidin-4-yl-urea derivatives as small-molecule CXCR3 antagonists is described. SAR studies resulted in significant improvement of potency and physicochemical properties and established the key pharmacophore of the series, and led to the identification of **9t**, which exhibits an IC_{50} of 16 nM in the GTPγS^{35} functional assay.



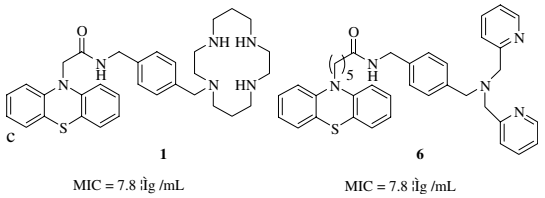
9t, hCXCR3 IC_{50} 16 nM

Dual serotonin transporter/histamine H_3 ligands: Optimization of the H_3 pharmacophore pp 702–706
John M. Keith,* Leslie A. Gomez, Michael A. Letavic, Kiev S. Ly, Jill A. Jablonowski, Mark Seierstad, Ann J. Barbier, Sandy J. Wilson, Jamin D. Boggs, Ian C. Fraser, Curt Mazur, Timothy W. Lovenberg and Nicholas I. Carruthers



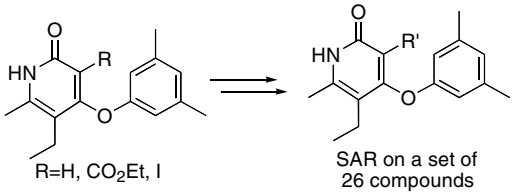
A series of tetrahydroisoquinolines acting as dual histamine H_3/serotonin transporter ligands is described. A highly regio-selective synthesis of the tetrahydroisoquinoline core involving acid mediated ring-closure of an acetophenone intermediate followed by reduction with $NaCNBH_3$ was developed. In vitro and in vivo data are discussed.

Design, synthesis, and evaluation of efflux substrate–metal chelator conjugates as potential antimicrobial agents pp 707–711
Yanling Zhang, C. Eric Ballard, Shi-Long Zheng, Xingming Gao, Ko-Chun Ko, Hsiuchin Yang, Gary Brandt, Xinhui Lou, Phang C. Tai, Chung-Dar Lu and Binghe Wang*

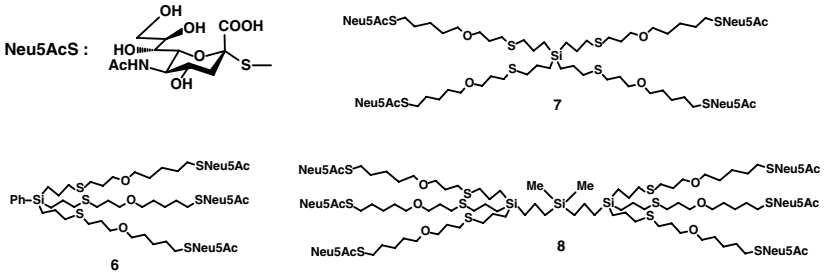


A series of efflux substrate–metal chelator conjugates was developed as potential antimicrobial agents.

Structure–activity relationship in the 3-iodo-4-phenoxypyridinone (IOPY) series: The nature of the C-3 substituent on anti-HIV activity pp 712–716
Abdellah Benjahad,* Said Oumouch, Jerôme Guillemont, Elisabeth Pasquier, Dominique Mabire, Koen Andries, Chi Hung Nguyen* and David S. Grierson



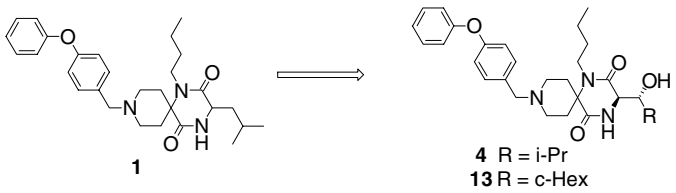
Thiosialoside clusters using carbosilane dendrimer core scaffolds as a new class of influenza neuraminidase inhibitors pp 717–721
Jun-Ichi Sakamoto, Tetsuo Koyama, Daisei Miyamoto, Sangchai Yingsakmongkon, Kazuya I. P. J. Hidari, Wipawee Jampangern, Takashi Suzuki, Yasuo Suzuki, Yasuaki Esumi, Ken Hatano, Daiyo Terunuma and Koji Matsuoka*



Pharmacophore identification of KSP inhibitors pp 722–726
Fei Liu, Qi-Dong You* and Ya-Dong Chen

A three-dimensional pharmacophore model was developed based on 25 currently available KSP inhibitors in Catalyst software package.

Spirodiketopiperazine-based CCR5 antagonists: Lead optimization from biologically active metabolite pp 727–731
Rena Nishizawa,* Toshihiko Nishiyama, Katsuya Hisaichi, Naoki Matsunaga, Chiaki Minamoto, Hiromu Habashita, Yoshikazu Takaoka, Masaaki Toda, Shiro Shibayama, Hideaki Tada, Kenji Sagawa, Daikichi Fukushima, Kenji Maeda and Hiroaki Mitsuya

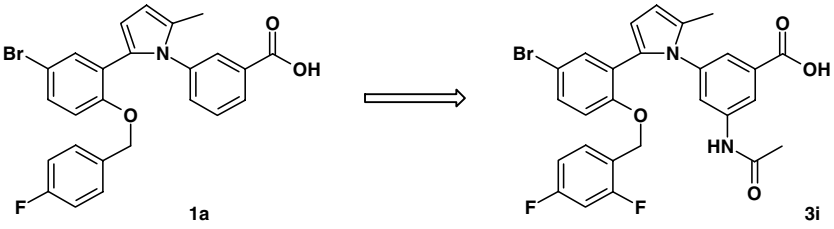


Key modification introducing a hydroxyl group on side chain to improve CCR5 antagonistic activity as well as in vitro anti-HIV activity by the application of the metabolite's information of **1**.

1,5-Biaryl pyrrole derivatives as EP_1 receptor antagonists: Structure–activity relationships of 4- and 5-substituted benzoic acid derivatives pp 732–735

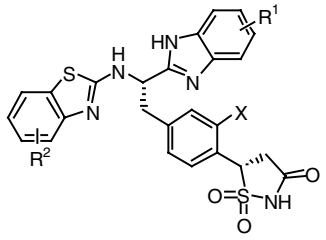
Adrian Hall,* Susan H. Brown, Iain P. Chessell, Anita Chowdhury, Nicholas M. Clayton, Tanya Coleman, Gerard M. P. Giblin, Beverley Hammond, Mark P. Healy, Matthew R. Johnson, Ann Metcalf, Anton D. Michel, Alan Naylor, Riccardo Novelli, David J. Spalding and Jennifer Sweeting

Substitution of the benzoic acid moiety of compounds such as **1a** led to the identification of **3i**, which was active in the established FCA model of inflammatory pain (ED_{50} = 1.1 mg/kg).



Benzothiazole benzimidazole (*S*)-isothiazolidinone derivatives as protein tyrosine phosphatase-1B inhibitors pp 736–740

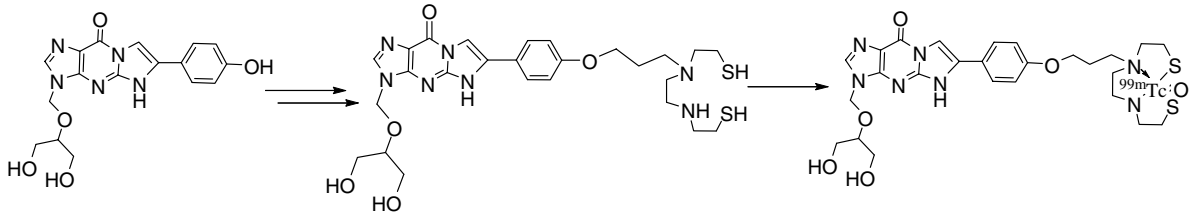
Richard B. Sparks,* Padmaja Polam, Wenyu Zhu, Matthew L. Crawley, Amy Takvorian, Erin McLaughlin, Min Wei, Paul J. Ala, Lucie Gonneville, Nancy Taylor, Yanlong Li, Richard Wynn, Timothy C. Burn, Phillip C. C. Liu and Andrew P. Combs



Benzothiazole Benzimidazole (*S*)-IZD's

Synthesis of a technetium-99m labeled tricyclic ganciclovir analog for non-invasive reporter gene expression imaging pp 741–744

Yi Zhang, Jing Lin and Dongfeng Pan*



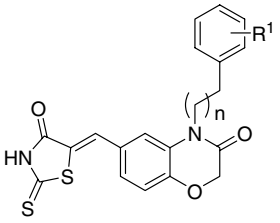
Analogues of the dopamine D2 receptor antagonist L741,626: Binding, function, and SAR pp 745–749

Peter Grundt, Sarah Little Jane Husband, Robert R. Luedtke, Michelle Taylor and Amy Hauck Newman*

Discovery of adamantane ethers as inhibitors of 11β-HSD-1: Synthesis and biological evaluation **pp 750–755**
Jyoti R. Patel,* Qi Shuai, Jurgen Dinges, Marty Winn, Marina Pliushchev, Steven Fung, Katina Monzon, William Chiou, Jiahong Wang, Liping Pan, Seble Wagaw, Kenneth Engstrom, Francis A. Kerdesky, Kenton Longenecker, Russell Judge, Wenying Qin, Hovis M. Imade, DeAnne Stolarik, David W. A. Beno, Michael Brune, Linda E. Chovan, Hing L. Sham, Peer Jacobson and J. T. Link

The synthesis and SAR of adamantane ethers are described as novel, potent and selective inhibitors of 11β-HSD-1. An X-ray crystal structure of one of these inhibitors bound to h-11β-HSD-1 is also described.

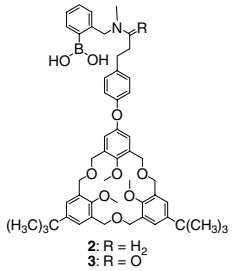
Design and synthesis of phenethyl benzo[1,4]oxazine-3-ones as potent inhibitors of PI3Kinaseγ **pp 756–760**
Thomas B. Lanni, Jr.,* Keri L. Greene, Christine N. Kolz, Kimberly S. Para, Melean Visnick, James L. Mobley, David T. Dudley, Theodore J. Baginski and Marya B. Liimatta



Molecular dynamics simulation of the $P2Y_{14}$ receptor. Ligand docking and identification of a putative binding site of the distal hexose moiety **pp 761–766**
Andrei A. Ivanov, Ingrid Fricks, T. Kendall Harden and Kenneth A. Jacobson*

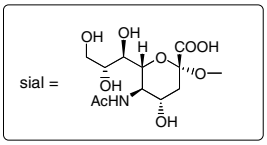
Dopamine-selective potentiometric responses by new ditopic sensory elements based on a hexahomotrioxacalix[3]arene **pp 767–771**
Ryosuke Saijo, Saori Tsunekawa, Hiroyuki Murakami, Naohiro Shirai, Shin-ichi Ikeda and Kazunori Odashima*

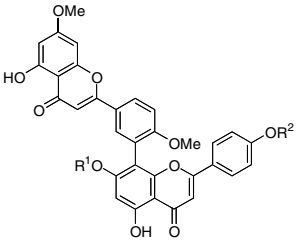
New ditopic sensory elements **2** and **3** for catecholamines were designed. Host **3** displayed high potentiometric selectivity for dopamine over other catecholamines (noradrenaline, adrenaline) and inorganic cations (Na^+, K^+, and NH_4^+).



Anti-influenza virus activity of biflavonoids **pp 772–775**
Kazuhiko Miki, Takayuki Nagai, Kazushige Suzuki, Ryo Tsujimura, Kiyotaka Koyama, Kaoru Kinoshita, Kimio Furuhata, Haruki Yamada and Kunio Takahashi*

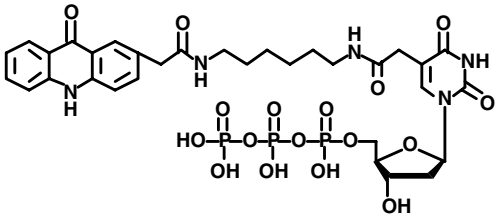
Ginkgetin was found to inhibit the influenza virus sialidase. Ginkgetin-sialic acid conjugates showed a significant survival effect in the influenza-virus-infected mice.





8R R^1 = sial, R^2 = H
8S R^1 = sial, R^2 = H
9R R^1 = sial, R^2 = sial
9S R^1 = sial, R^2 = sial

Chemico-enzymatic synthesis of a new fluorescent-labeled DNA by PCR with a thymidine nucleotide analogue bearing an acridone derivative **pp 776–779**
Atsushi Shoji, Tomoya Hasegawa, Masayasu Kuwahara, Hiroaki Ozaki and Hiroaki Sawai*

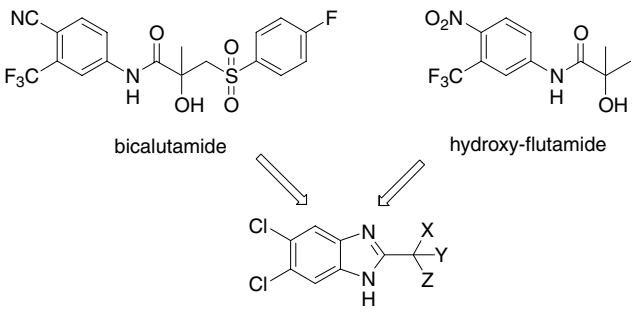


Triphosphate of acridone-tagged thymidine analogue was incorporated as a substrate for PCR using KOD Dash DNA polymerase forming a new fluorescent labeled DNA which is useful for a DNA probe.

Synthesis and antiproliferative activity of (2*R*,3*R*)-disubstituted tetrahydropyrans. Part 2: Effect of side chain homologation **pp 780–783**
Romen Carrillo, Leticia G. León, Tomás Martín,* Víctor S. Martín and José M. Padrón*

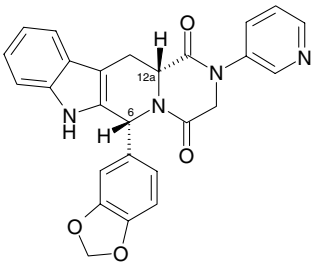
The in vitro antitumor activity of enantiomerically pure (2*R*,3*R*)-disubstituted tetrahydropyrans against three diverse human solid tumor cells is reported.

Synthesis and SAR of potent and selective androgen receptor antagonists: 5,6-Dichloro-benzimidazole derivatives **pp 784–788**
Raymond A. Ng, Jihua Guan, Vernon C. Alford, Jr., James C. Lanter, George F. Allan, Tifanie Sbriscia, Olivia Linton, Scott G. Lundeen and Zhihua Sui*



PDE5 inhibitors: An original access to novel potent arylated analogues of tadalafil **pp 789–792**
Terence Beghyn,* Candide Hounsou and Benoit P. Deprez

The synthesis of potent PDE5 inhibitors is reported. Some heteroarylated compounds (e.g., **14a**) display an improved aqueous solubility, when compared to tadalafil.

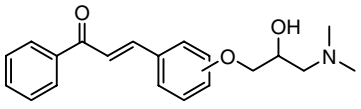


14a, EC_{50} (PDE5) = 28 nM± 5

Discovery of galectin ligands in fully randomized combinatorial one-bead-one-compound (glyco)peptide libraries **pp 793–798**
Sabine André, C. Elizabeth P. Maljaars, Koen M. Halkes, Hans-Joachim Gabius and Johannis P. Kamerling*

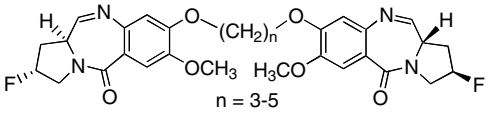
Human lectins (galectins) are emerging targets for drug design. Combinatorial one-bead-one-compound (glyco)peptide libraries were screened with galectin-1 and -3. Testing lead (glyco)peptides includes medically relevant inhibition assays with tumour cells.

Chalcone based aryloxypropanolamines as potential antihyperglycemic agents **pp 799–802**
Poonam Shukla, Amar Bahadur Singh, Arvind Kumar Srivastava and Ram Pratap*



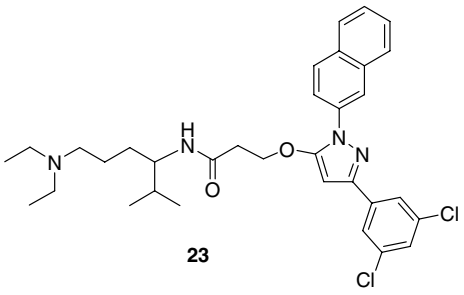
A series of chalcone based aryloxypropanolamines were synthesized which exhibited potent antihyperglycemic activity in SLM and STZ rat models.

Synthesis and DNA-binding ability of *C2R*-fluoro substituted DC-81 and its dimers **pp 803–806**
Ahmed Kamal,* D. Rajasekhar Reddy and P. S. Murali Mohan Reddy



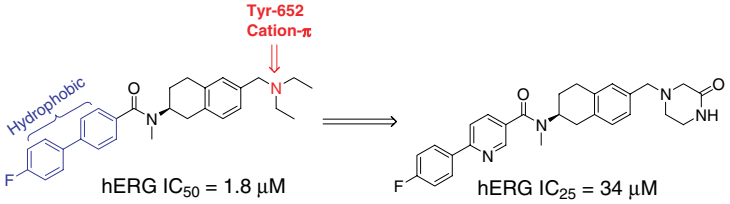
Diaryl substituted pyrazoles as potent CCR2 receptor antagonists **pp 807–813**
Anthony B. Pinkerton,* Dehua Huang, Rowena V. Cube, John H. Hutchinson, Mary Struthers, Julia M. Ayala, Pasquale P. Vicario, Sima R. Patel, Thomas Wisniewski, Julie A. DeMartino and Jean-Michel Vernier

We have identified and synthesized a series of diaryl substituted pyrazoles as potent antagonists of the chemokine receptor subtype 2b. Structure–activity relationship studies directed toward improving the potency led to the discovery of **23** (IC_{50} = 6 nM).

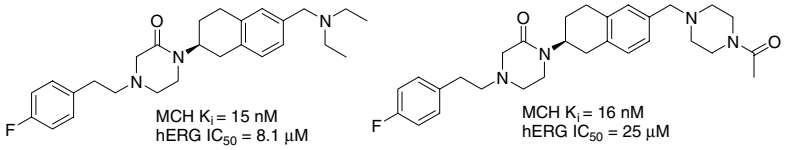


Aminomethyl tetrahydronaphthalene biphenyl carboxamide MCH-R1 antagonists—Increasing selectivity over hERG **pp 814–818**
Kenneth M. Meyers, Nicholas Kim, José L. Méndez-Andino,* X. Eric Hu, Rashid N. Mumin, Sean R. Klopfenstein, John A. Wos, Maria C. Mitchell, Jennifer L. Paris, David C. Ackley, Jerry K. Holbert, Scott W. Mittelstadt and Ofer Reizes

SAR studies addressing two distinct alternatives for structural modifications leading to improve hERG selectivity of a series of MCH-R1 antagonists are described.



Aminomethyl tetrahydronaphthalene ketopiperazine MCH-R1 antagonists—Increasing selectivity over hERG **pp 819–822**
Kenneth M. Meyers, José L. Méndez-Andino,* Anny-Odile Colson, Namal C. Warshakoon, John A. Wos, Maria C. Mitchell, Karen M. Hodge, Jeremy M. Howard, David C. Ackley, Jerry K. Holbert, Scott W. Mittelstadt, Martin E. Dowty, Cindy M. Obringer, Ofer Reizes and X. Eric Hu



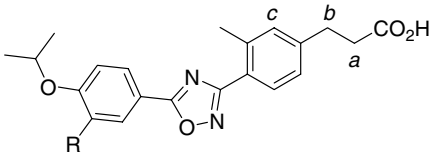
A direct correlation between hERG binding and QTc prolongation was established for this series of aminomethyl tetrahydronaphthalene ketopiperazine MCH-R1 antagonists.

Evaluating scoring functions for docking and designing β-secretase inhibitors **pp 823–827**
M. Katharine Holloway,* Georgia B. McGaughey, Craig A. Coburn, Shawn J. Stachel, Kristen G. Jones, Elizabeth L. Stanton, Alison R. Gregro, Ming-Tain Lai, Ming-Chih Crouthamel, Beth L. Pietrak and Sanjeev K. Munshi

Several simple scoring methods were examined for 2 series of β-secretase (BACE-1) inhibitors to identify a docking/scoring protocol which could be used to design BACE-1 inhibitors in a drug discovery program.

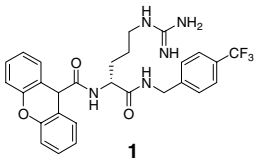
SAR studies of 3-arylpropionic acids as potent and selective agonists of sphingosine-1-phosphate receptor-1 ($S1P_1$) with enhanced pharmacokinetic properties pp 828–831
Lin Yan,* Pei Huo, Jeffrey J. Hale, Sander G. Mills, Richard Hajdu, Carol A. Keohane, Mark J. Rosenbach, James A. Milligan, Gan-Ju Shei, Gary Chrebet, James Bergstrom, Deborah Card and Suzanne M. Mandala

Structure–activity relationship (SAR) studies of 3-arylpropionic acids—a class of novel $S1P_1$ selective agonists—by introducing substitution to the propionic acid chain and replacing the adjacent phenyl ring with pyridine (indicated by alphabetic letters in the Figure) led to a series of modified 3-arylpropionic acids with enhanced half-life in rat. These analogs exhibited longer half-life in rat than did unmodified 3-arylpropionic acids, suggesting that metabolic oxidation on the propionic acid chain, particularly at the C3 benzylic position of 3-arylpropionic acids, is probably responsible for their short half-life in rodent.



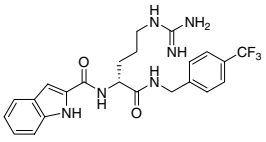
1a R = CF_3
1b R = CN

MCH-R1 antagonists based on an arginine scaffold: SAR studies on the amino-terminus pp 832–835
José Méndez-Andino,* Anny-Odile Colson, Daniel Denton, Maria C. Mitchell, Doreen Cross-Doersen and X. Eric Hu



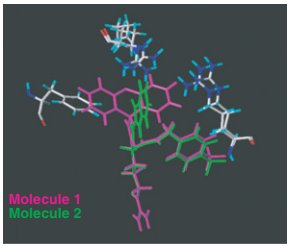
1

IC_{50} = 4 nM



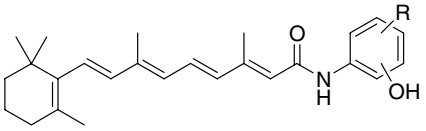
2

IC_{50} = 20 nM



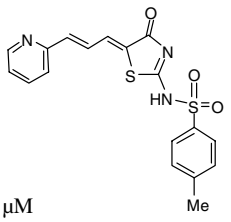
The MCH-R1 antagonist activity dependence on the π-electronic character of the aromatic systems corresponding to the amino-terminus of these arginine-based molecules is described.

Solid phase-assisted synthesis and screening of a small library of *N*-(4-hydroxyphenyl)retinamide (4-HPR) analogs pp 836–840
Serena M. Mershon, Allyson L. Anding, Jason S. Chapman, Margaret Clagett-Dame, Laura A. Stonerock and Robert W. Curley, Jr.*



Solid phase synthesis of a small retinamide library and screening for mammary tumor cell growth inhibition are reported.

Synthesis of thiazolone-based sulfonamides as inhibitors of HCV NS5B polymerase pp 841–845
Yili Ding,* Kenneth L. Smith, Chamakura V. N. S. Varaprasad, Eugene Chang, John Alexander and Nanhua Yao



IC_{50}: 0.6 μM
CC_{50}: >300 μM

OTHER CONTENTS

Summary of instructions to authors **p I**

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

The residue–residue bridges served to constrain the configuration of the EL2. [Ivanov, A. A.; Fricks, I.; Harden, T. K.; Jacobson, K. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 761.

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