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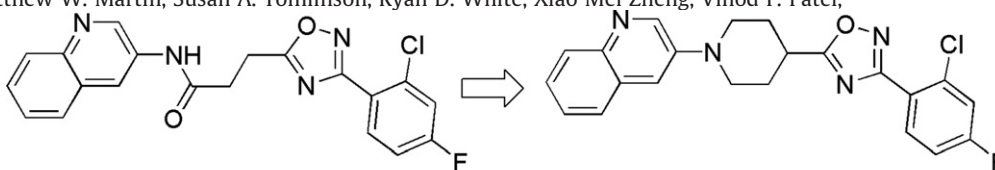
Contents

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Structural modifications of *N*-arylamide oxadiazoles: Identification of *N*-arylpiperidine oxadiazoles as potent and selective agonists of CB₂

pp 4267–4274

Erin F. DiMauro*, John L. Buchanan, Alan Cheng, Renee Emkey, Stephen A. Hitchcock, Liyue Huang, Ming Y. Huang, Brett Janosky, Josie H. Lee, Xingwen Li, Matthew W. Martin, Susan A. Tomlinson, Ryan D. White, Xiao Mei Zheng, Vinod F. Patel, Robert T. Freneau Jr.



hCB₂ EC₅₀ = 0.002 μM (E_{max} = 115%)

hCB₁ EC₅₀ = 0.403 μM (E_{max} = 51%)

Rat IV CL = 5.7 L/h/kg

hCB₂ EC₅₀ = 0.007 μM (E_{max} = 120%)

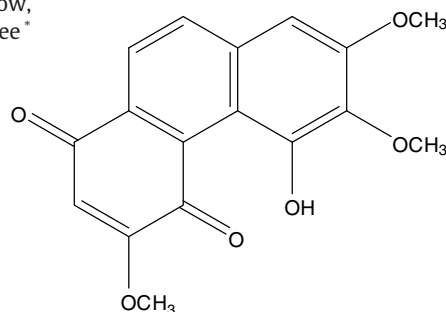
hCB₁ EC₅₀ = 1.43 μM (E_{max} = 55%)

Rat IV CL = 0.039 L/h/kg

Cytotoxic calanquinone A from *Calanthe arisanensis* and its first total synthesis

pp 4275–4277

Chia-Lin Lee, Kyoko Nakagawa-Goto, Donglei Yu, Yi-Nan Liu, Kenneth F. Bastow, Susan L. Morris-Natschke, Fang-Rong Chang, Yang-Chang Wu*, Kuo-Hsiung Lee*



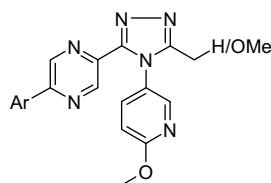
1, Calanquinone A



Design and optimization of potent, selective antagonists of Oxytocin

pp 4278–4281

Alan Brown*, Lindsay Brown, Dave Ellis, Nicholas Puhalo, Chris R. Smith, Olga Wallace, Lesa Watson

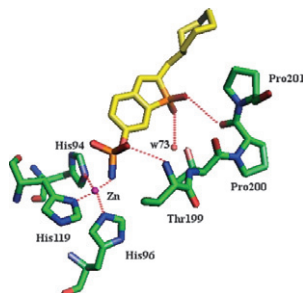


(X)

Pharmacophoric overlap of a high throughput screening hit and published OT antagonists followed by subsequent optimization led to a series of potent, selective Oxytocin antagonists (X). Several of these analogues showed oral bioavailability in vivo.

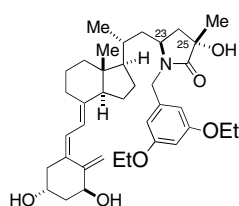
Carbonic anhydrase inhibitors. Interaction of the antitumor sulfamate EMD 486019 with twelve mammalian carbonic anhydrase isoforms: Kinetic and X-ray crystallographic studies pp 4282–4286

Claudia Temperini, Alessio Innocenti, Andrea Scozzafava, Claudiu T. Supuran *



Structure–activity relationship studies on vitamin D lactam derivatives as vitamin D receptor antagonist pp 4287–4290

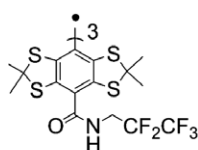
Kaori Cho, Fumito Uneuchi, Yuko Kato-Nakamura, Jun-ichi Namekawa, Seiichi Ishizuka, Kazuya Takenouchi, Kazuo Nagasawa *



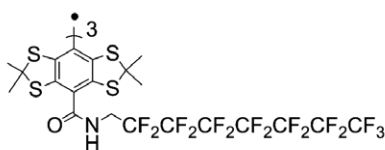
(23S,25S)-DLAM-1P-3,5(OEt)₂

Synthesis of two persistent fluorinated tetrathiatriarylmethyl (TAM) radicals for biomedical EPR applications pp 4291–4293

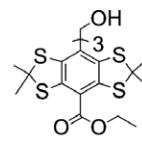
Benoît Driesschaert, Nicolas Charlier, Bernard Gallez, Jacqueline Marchand-Brynaert *



F15T-03



F45T-03

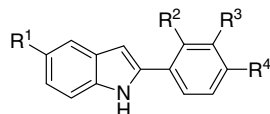


1

The synthesis of two new persistent fluorinated tetrathiatriarylmethyl (TAM) radicals (**F15T-03** and **F45T-03**) in two steps from ester precursor **1** (95% and 66%, respectively), and preliminary evaluation of their EPR properties are reported.

Structure–activity relationships of 2-aryl-1H-indole inhibitors of the NorA efflux pump in *Staphylococcus aureus* pp 4294–4297

Joseph I. Ambrus, Michael J. Kelso, John B. Bremner*, Anthony R. Ball, Gabriele Casadei, Kim Lewis

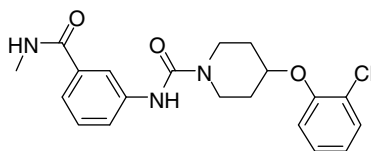


Three new potent indole NorA pump inhibitors and an antibacterial lead compound for *Staphylococcus aureus* are described.

Discovery of piperidine-aryl urea-based stearyl-CoA desaturase 1 inhibitors

pp 4298–4302

Zhili Xin*, Hongyu Zhao, Michael D. Serby, Bo Liu, Mei Liu, Bruce G. Szczepankiewicz, Lissa T. J. Nelson, Harriet T. Smith, Tom S. Suhar, Rich S. Janis, Ning Cao, Heidi S. Camp, Christine A. Collins, Hing L. Sham, Teresa K. Surowy, Gang Liu



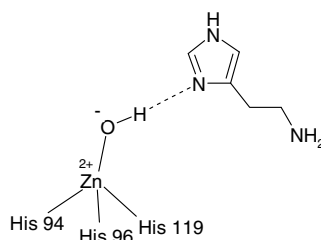
4c $IC_{50} < 4$ nM (mSCD1)

The discovery of potent, selective, orally bioavailable SCD1 inhibitors is reported.

**Carbonic anhydrase activators: Activation of the human cytosolic isozyme III and membrane-associated isoform IV with amino acids and amines**

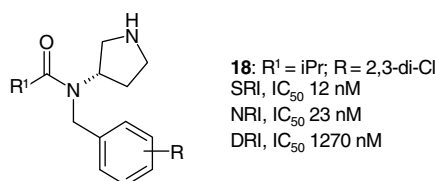
pp 4303–4307

Daniela Vullo, Isao Nishimori, Andrea Scozzafava, Claudiu T. Supuran*

**N-Benzyl-N-(pyrrolidin-3-yl)carboxamides as a new class of selective dual serotonin/noradrenaline reuptake inhibitors**

pp 4308–4311

Florian Wakenhut*, Paul V. Fish, M. Jonathan Fray, Ian Gurrell, James E. Mills, Alan Stobie, Gavin A. Whitlock

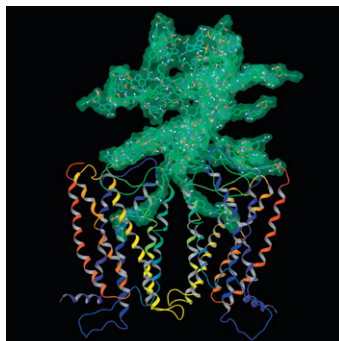


The structure–activity relationship and the synthesis of novel *N*-benzyl-*N*-(pyrrolidin-3-yl)carboxamides as dual serotonin (5-HT) and noradrenaline (NA) monoamine reuptake inhibitors are described. Compounds such as **18** exhibited dual 5-HT and NA-reuptake inhibition, good selectivity over dopamine (DA)-reuptake inhibition and drug-like physicochemical properties consistent with CNS target space. Compound **18** was selected for further preclinical evaluation.

Molecular modeling of a PAMAM-CGS21680 dendrimer bound to an A_{2A} adenosine receptor homodimer

pp 4312–4315

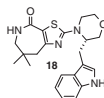
Andrei A. Ivanov, Kenneth A. Jacobson*



4-(1,3-Thiazol-2-yl)morpholine derivatives as inhibitors of phosphoinositide 3-kinase

pp 4316–4320

Rikki Alexander*, Ahrani Balasundaram, Mark Batchelor, Daniel Brookings, Karen Crépy, Tom Crabbe, Marie-France Deltent, Frank Driessens, Andrew Gill, Sue Harris, Gillian Hutchinson, Claire Kulisa, Mark Merriman, Prakash Mistry, Ted Parton, James Turner, Ian Whitcombe, Sara Wright



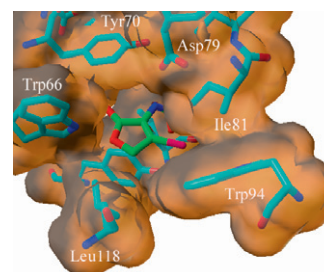
4-(1,3-Thiazol-2-yl)morpholine derivatives have been identified as potent and selective inhibitors of phosphoinositide 3-kinase, compound **18** is shown to demonstrate the utility of this class of compounds in xenograft models of tumor growth.

N-Acyl-3-amino-5H-furanone derivatives as new inhibitors of LuxR-dependent quorum sensing: Synthesis, biological evaluation and binding mode study

pp 4321–4324

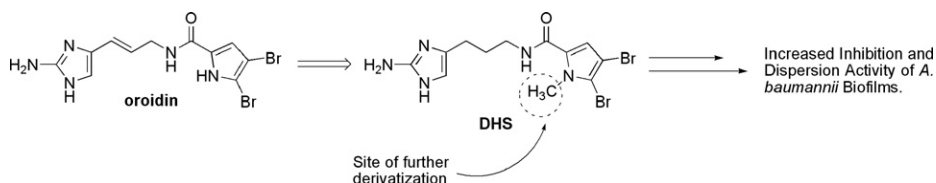
Jane Estephane, Julien Dauvergne, Laurent Soullère*, Sylvie Reverchon, Yves Queneau, Alain Doutheau*

Amongst some *N*-acyl-3-amino-5H-furanone derivatives tested as LuxR-dependent quorum sensing inhibitors, 4-halogenated compounds were found to be the most active. Molecular modelling showed that the presence of the halogen atom could enhance the fitting of the lactone ring through specific interactions with conserved or conservatively replaceable residues in the LuxR protein family.

**Effects of N-pyrrole substitution on the anti-biofilm activities of oroidin derivatives against *Acinetobacter baumannii***

pp 4325–4327

Justin J. Richards, Catherine S. Reed, Christian Melander*

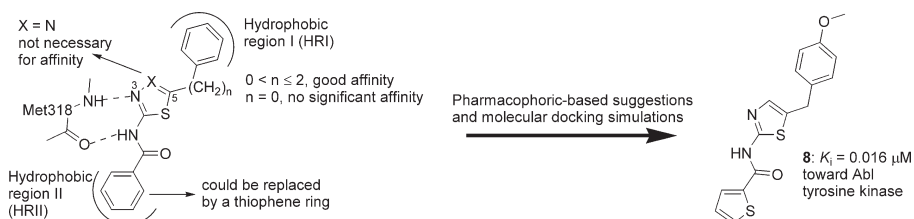


Modification of the alkyl substituent on the pyrrole-based nitrogen of the oroidin template has resulted in derivatives that display more potent anti-biofilm activities than the previous lead compound, DHS.

**N-(thiazol-2-yl)-2-thiophene carboxamide derivatives as Abl inhibitors identified by a pharmacophore-based database screening of commercially available compounds**

pp 4328–4331

Fabrizio Manetti, Federico Falchi, Emmanuele Crespan, Silvia Schenone, Giovanni Maga, Maurizio Botta*

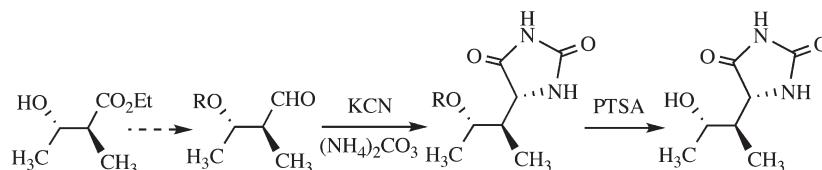


Affinity optimization of thiazole or thiadiazole Abl inhibitors. From 2-benzamido thia(dia)zole compounds to *N*-(thiazol-2-yl)-2-thiophene carboxamide derivatives.

Synthesis of hydantoin analogues of (2S,3R,4S)-4-hydroxyisoleucine with insulinotropic properties

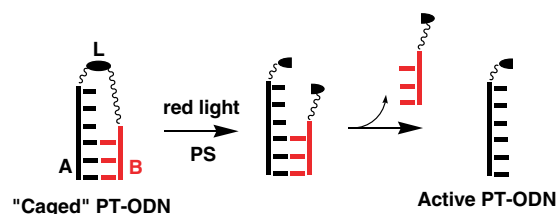
pp 4332–4335

Didier Sergent, Qian Wang, N. André Sasaki, Jamal Ouazzani *

**Red light-activated phosphorothioate oligodeoxyribonucleotides**

pp 4336–4338

Alexandru Rotaru, János Kovács, Andriy Mokhir *



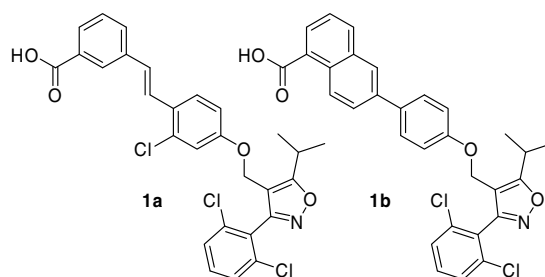
'Caged' phosphothioate oligodeoxyribonucleotides are reported. These compounds do not bind complementary nucleic acids in the dark. Upon irradiation with red light in the presence of chlorine e6 they become efficient binders.

Conformationally constrained farnesoid X receptor (FXR) agonists: Naphthoic acid-based analogs of GW 4064

pp 4339–4343

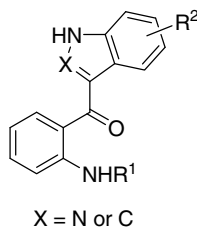
Adwoa Akwabi-Ameyaw, Jonathan Y. Bass, Richard D. Caldwell, Justin A. Caravella, Lihong Chen, Katrina L. Creech, David N. Deaton*, Stacey A. Jones, Istvan Kaldor, Yaping Liu, Kevin P. Madauss, Harry B. Marr, Robert B. McFadyen, Aaron B. Miller, Frank Navas III, Derek J. Parks, Paul K. Spearing, Dan Todd, Shawn P. Williams, G. Bruce Wisely

Starting from the known FXR agonist GW 4064 **1a**, a series of stilbene replacements were prepared. The 6-substituted 1-naphthoic acid **1b** was an equipotent FXR agonist with improved developability parameters relative to **1a**. Analog **1b** also reduced the severity of cholestasis in the ANIT acute cholestatic rat model.

**Synthesis and evaluation of heteroaryl-ketone derivatives as a novel class of VEGFR-2 inhibitors**

pp 4344–4347

Eugene L. Piatnitski Chekler*, Reeti Katoch-Rouse, Alexander S. Kiselyov, Dan Sherman, Xiaohu Ouyang, Ki Kim, Ying Wang, Yaron R. Hadari, Jacqueline F. Doody



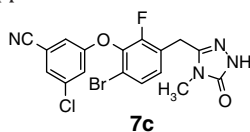
A novel series of potent heteroaryl-ketone derivatives active against VEGFR-2 kinase is described. The best compounds were demonstrated to be inactive against a panel of tyrosine and serine/threonine kinases with the exception of VEGFR-1 kinase. Selected representatives displayed acceptable exposure levels when administered orally to mice.



Discovery of triazolinone non-nucleoside inhibitors of HIV reverse transcriptase

pp 4348–4351

Zachary K. Sweeney*, Sahaja Acharya, Andrew Briggs, James P. Dunn, Todd R. Elworthy, Jennifer Fretland, Anthony M. Giannetti, Gabrielle Heilek, Yu Li, Ann C. Kaiser, Michael Martin, Y. David Saito, Mark Smith, Judy M. Suh, Steven Swallow, Jeffrey Wu, Julie Q. Hang, Amy S. Zhou, Klaus Klumpp



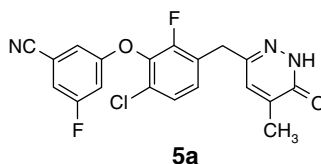
EC_{50} (WT) = 2 nM
 PO (2 mg/kg): AUC = 38.4 μ M·h
 F = 74%

Novel diaryl ether HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) were prepared. Triazolinone compounds that strongly inhibit wild-type and NNRTI-resistant viruses and display excellent pharmacokinetic properties were identified.

Discovery and optimization of pyridazinone non-nucleoside inhibitors of HIV-1 reverse transcriptase

pp 4352–4354

Zachary K. Sweeney*, James P. Dunn, Yu Li, Gabrielle Heilek, Pete Dunten, Todd R. Elworthy, Xiaochun Han, Seth F. Harris, Donald R. Hirschfeld, J. Heather Hogg, Walter Huber, Ann C. Kaiser, Denis J. Kertesz, Woongki Kim, Taraneh Mirzadegan, Michael G. Roepel, Y. David Saito, Tania M. P. C. Silva, Steven Swallow, Jahari L. Tracy, Armando Villasenor, Harit Vora, Amy S. Zhou, Klaus Klumpp

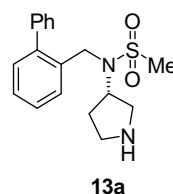
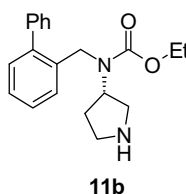
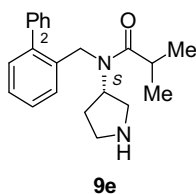


A number of pyridazinones were evaluated as HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). These compounds strongly inhibited the wild-type virus and NNRTI-resistant viruses.

Derivatives of (3S)-N-(biphenyl-2-ylmethyl)pyrrolidin-3-amine as selective noradrenaline reuptake inhibitors: Reducing P-gp mediated efflux by modulation of H-bond acceptor capacity

pp 4355–4359

Paul V. Fish*, Nancy S. Barta, David L. F. Gray, Thomas Ryckmans, Alan Stobie, Florian Wakenhut, Gavin A. Whitlock

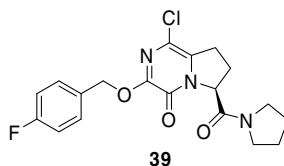


Carboxamide **9e**, carbamate **11b** and sulfonamide **13a** were identified as potent NRIs with excellent selectivity over SRI and DRI, good in vitro metabolic stability and weak CYP inhibition. Carbamate **11b** demonstrated superior transit performance in MDCK-mdr1 cell lines with minimal P-gp efflux, which was attributed to reduced HBA capacity. Evaluation in vivo, in rat microdialysis experiments, showed **11b** increased NA levels by 400% over pre-drug levels confirming good CNS penetration.

Pyrrolidinyl pyridone and pyrazinone analogues as potent inhibitors of prolyl oligopeptidase (POP)

pp 4360–4363

Curt D. Haffner*, Caroline J. Diaz, Aaron B. Miller, Robert A. Reid, Kevin P. Madauss, Annie Hassell, Mary H. Hanlon, David J. T. Porter, J. David Becherer, Luke H. Carter

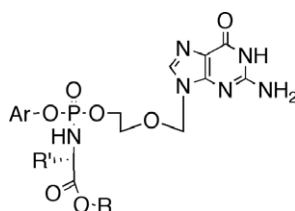


We report the synthesis and in vitro activity of a series of novel pyrrolidinyl pyridones and pyrazinones as potent inhibitors of prolyl oligopeptidase (POP). Within this series, compound **39** was co-crystallized within the catalytic site of a human chimeric POP protein which provided a more detailed understanding of how these inhibitors interacted with key residues within the catalytic pocket.

Successful kinase bypass with new acyclovir phosphoramidate prodrugs

pp 4364–4367

Christopher McGuigan*, Marco Derudas, Joachim J. Bugert, Graciela Andrei, Robert Snoeck, Jan Balzarini

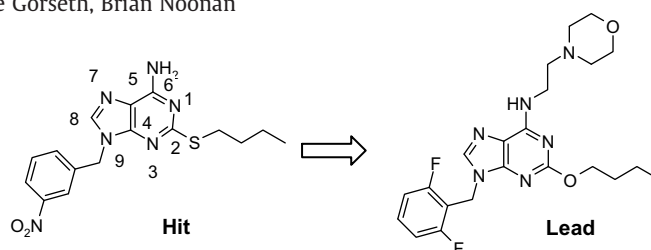


Low or sub- μ M versus HSV-1 and -2 and VZV. Retain full activity versus thymidine kinase mutants proving intracellular phosphate delivery.

Exploring 9-benzyl purines as inhibitors of glutamate racemase (Murl) in Gram-positive bacteria

pp 4368–4372

Bolin Geng*, Gloria Breault, Janelle Comita-Prevoir, Randy Petrichko, Charles Eyermann, Tomas Lundqvist, Peter Doig, Elise Gorseth, Brian Noonan

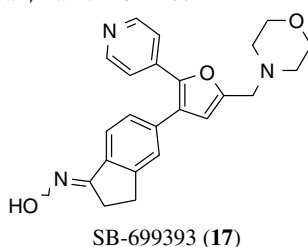


An early SAR study of a screening hit series has generated a series of 9-benzyl purines as inhibitors of bacterial glutamate racemase (Murl) with micromolar enzyme potency and improved physical properties. X-ray co-crystal EI structures were obtained.

The identification of potent, selective and CNS penetrant furan-based inhibitors of B-Raf kinase

pp 4373–4376

Andrew K. Takle*, Mark J. Bamford, Susannah Davies, Robert P. Davis, David K. Dean, Alessandra Gaiba, Elaine A. Irving, Frank D. King, Antoinette Naylor, Christopher A. Parr, Alison M. Ray, Alastair D. Reith, Beverley B. Smith, Penelope C. Staton, Jon G. A. Steadman, Tania O. Stean, David M. Wilson

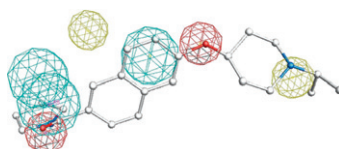


Modification of the potent imidazole-based B-Raf inhibitor SB-590885 resulted in the identification of a series of furan-based derivatives with enhanced CNS penetration. One such compound, SB-699393 (17), was examined in vivo to challenge the hypothesis that selective B-Raf inhibitors may be of value in the treatment of stroke.

Refinement of histamine H3 ligands pharmacophore model leads to a new class of potent and selective naphthalene inverse agonists

pp 4377–4379

Olivier Roche, Matthias Nettekoven*, Walter Vifian, Rosa Maria Rodriguez Sarmiento



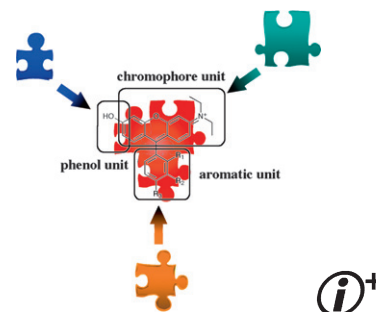
The refined histamine H3 ligand pharmacophore model guided successfully the selection process towards the identification of new, potent and selective naphthalene inverse agonists.

Design and synthesis of regioisomerically pure unsymmetrical xanthene derivatives for staining live cells and their photochemical properties

pp 4380–4384

Shinichiro Kamino, Hayato Ichikawa, Shun-ichi Wada, Yuka Horio, Yoshihide Usami, Takako Yamaguchi, Toshiki Koda, Aki Harada, Kazusa Shimanuki, Masao Arimoto, Mitsunobu Doi, Yoshikazu Fujita*

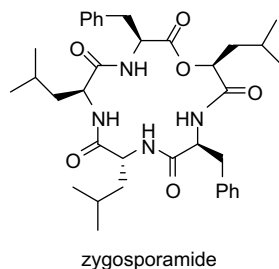
We show here the synthesis of regioisomerically pure unsymmetrical xanthene derivatives by combining three units, just like pieces of a jigsaw puzzle.



Synthesis and antitumor activity of cyclodepsipeptide zygosporamide and its analogues

pp 4385–4387

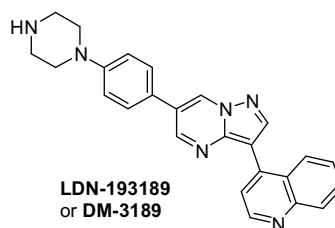
You Wang, Feiran Zhang, Yihua Zhang, Jun O. Liu*, Dawei Ma*



Structure–activity relationship study of bone morphogenetic protein (BMP) signaling inhibitors

pp 4388–4392

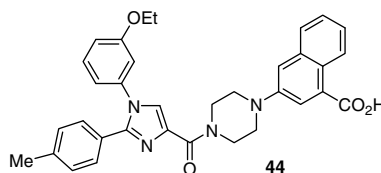
Gregory D. Cuny*, Paul B. Yu, Joydev K. Laha, Xuechao Xing, Ji-Feng Liu, Carol S. Lai, Donna Y. Deng, Chetana Sachidanandan, Kenneth D. Bloch, Randall T. Peterson



Discovery of imidazole carboxamides as potent and selective CCK1R agonists

pp 4393–4396

Cheng Zhu*, Alexa R. Hansen, Thomas Bateman, Zhesheng Chen, Tom G. Holt, James A. Hubert, Bindhu V. Karanam, Susan J. Lee, Jie Pan, Su Qian, Vijay B. G. Reddy, Marc L. Reitman, Alison M. Strack, Vincent Tong, Drew T. Weingarth, Michael S. Wolff, Doug J. MacNeil, Ann E. Weber, Joseph L. Duffy, Scott D. Edmondson

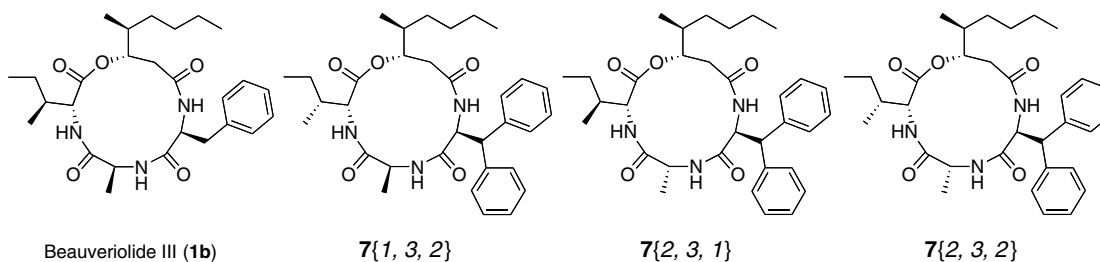


The discovery and optimization of a novel class of 1,2-diaryl imidazole carboxamides as CCK1R agonists are reported. Compound **44** exhibited excellent lean mouse overnight food intake reduction.

Synthesis and biological evaluation of a focused library of beauveriolides

pp 4397–4400

Kenichiro Nagai, Takayuki Doi, Taichi Ohshiro, Toshiaki Sunazuka, Hiroshi Tomoda, Takashi Takahashi, Satoshi Ōmura *

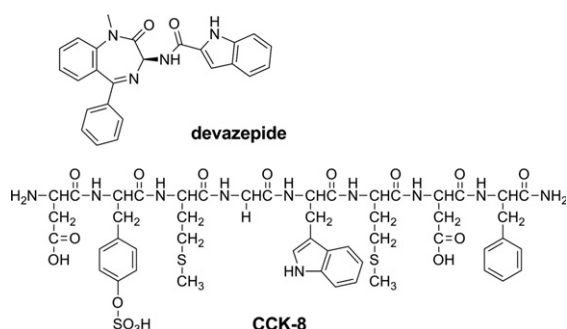


A library of beauveriolide analogues focusing on L-Ala and D-allo-Ile of beauveriolide III (**1b**) was synthesized by combinatorial synthesis and their inhibitory activity of CE synthesis in macrophage was tested. Cyclic compounds **7{1, 3, 2}**, **7{2, 3, 1}**, and **7{2, 3, 2}** were 20 times more potent than **1b**.

Benzodiazepine ligands can act as allosteric modulators of the Type 1 cholecystokinin receptor

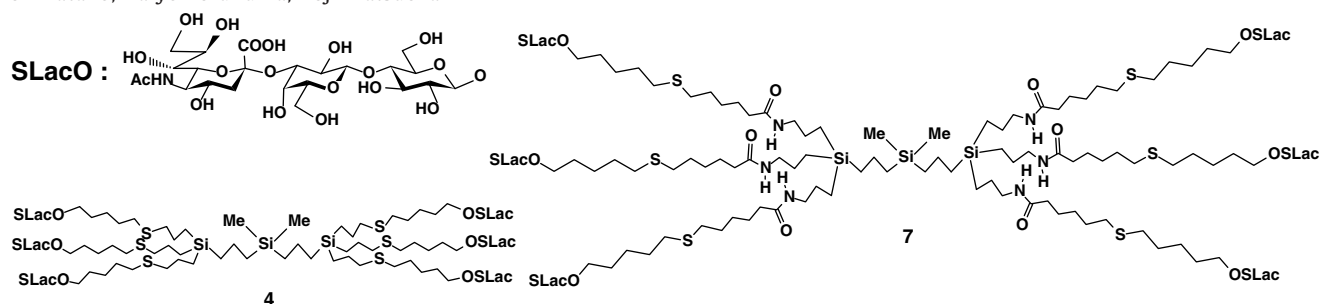
pp 4401–4404

Fan Gao, Patrick M. Sexton, Arthur Christopoulos, Laurence J. Miller *

Small molecule benzodiazepine ligands are allosteric modulators of the CCK₁ receptor.**Sialyl $\alpha(2 \rightarrow 3)$ lactose clusters using carbosilane dendrimer core scaffolds as influenza hemagglutinin blockers**

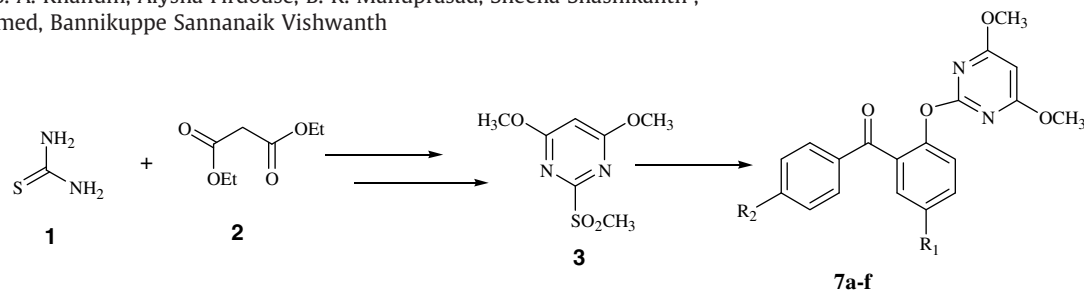
pp 4405–4408

Hiroyuki Oka, Tomotsune Onaga, Tetsuo Koyama, Chao-Tan Guo, Yasuo Suzuki, Yasuaki Esumi, Ken Hatano, Daiyo Terunuma, Koji Matsuoka *

**Synthesis and anti-inflammatory activity of 2-(2-aroxyloxy)-4,6-dimethoxy pyrimidines**

pp 4409–4412

T. D. Venu, S. A. Khanum, Aiysha Firdouse, B. K. Manuprasad, Sheena Shashikanth*, Riyaz Mohamed, Bannikuppe Sannanaik Vishwanth

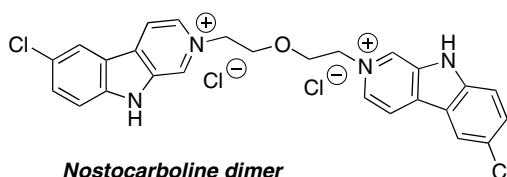


The newly synthesized compounds 2-(2-aroxyloxy)-4,6-dimethoxy pyrimidines **7a-f** were screened for their anti-inflammatory activity and compared with standard drugs.

Potent and selective antiplasmodial activity of the cyanobacterial alkaloid nostocarboline and its dimers

pp 4413–4415

Damien Barbaras, Marcel Kaiser, Reto Brun, Karl Gademann *

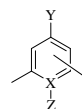
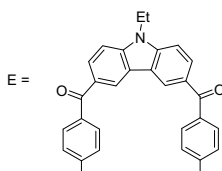
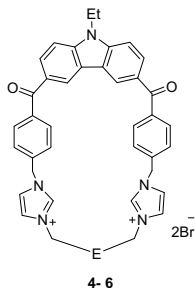
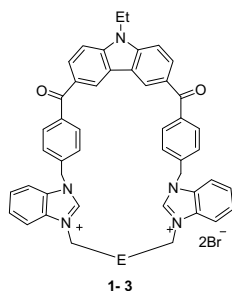
**Nostocarboline dimer**IC₅₀ = 18 nM, *Plasmodium falciparum* K1IC₅₀ = 47900 nM, rat myoblasts (L6)

> 2500 fold selectivity

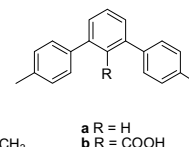
**Synthesis of some novel imidazole-based dicationic carbazolophanes as potential antibacterials**

pp 4416–4419

Perumal Rajakumar*, Karuppannan Sekar, Vellasamy Shanmugaiah, Narayanasamy Mathivanan



a meta X-Z = N, Y = H
 b para X = C, Z = OCH₃, Y = OCH₃
 c meta X = C, Z = OH, Y = NO₂

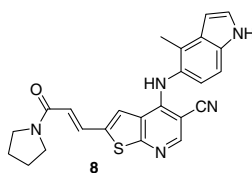


a R = H
 b R = COOH

2-Alkenylthieno[2,3-b]pyridine-5-carbonitriles: Potent and selective inhibitors of PKCθ

pp 4420–4423

L. Nathan Tumey*, Diane H. Boschelli, Julie Lee, Divya Chaudhary



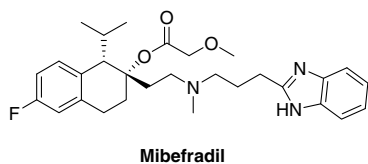
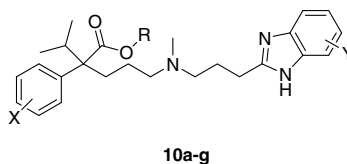
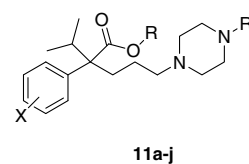
PKCθ = 3.8 nM
 PKCα, PKCβ, PKCδ, PKCε, PKCη, PKCζ > 1300 nM

A series of 2-alkenylamide thieno[2,3-b]pyridine inhibitors of PKCθ is described. SAR studies led to compound **8** which has excellent selectivity over a variety of PKC isoforms.

Synthesis and evaluation of α,α'-disubstituted phenylacetate derivatives for T-type calcium channel blockers

pp 4424–4427

Hyung Kook Lee, Yun Suk Lee, Eun Joo Roh, Hyewhon Rhim, Jae Yeol Lee, Kye Jung Shin *

**Mibefradil****10a-g****11a-j**

Novel series of α,α'-disubstituted phenylacetate derivatives (**10** and **11**) based on pharmacophore mapping study were prepared and evaluated for T-type calcium channel (α_{1C}) blockers by patch-clamp method. Among them, compound **10e** (X = *p*-Br, Y = H, R = Me) showed higher potency than Mibefradil and competitive PK profiles for further in vivo assay.

pp 4428–4432

pp 4433–4437

A 3D ribbon diagram of a protein structure, showing various colored loops and helices. The structure is composed of several distinct regions, each represented by a different color: orange, green, cyan, magenta, and blue. The orange and green regions form large, complex loops, while the cyan, magenta, and blue regions form more compact, helical structures. The overall shape is somewhat elongated and irregular, with the different colored regions interwoven. The diagram is set against a white background and is enclosed within an oval frame.

pp 4438–4441

N[C@@H](C)C(=O)NCc1ccc(cc1)C(=O)n2nc(F)(F)Fcc2

7b



pp 4442–4446

CC1=C(C)N2C(=C1)C(=CN2)C3=CC=CC=C3N4C=NC=CC=C4N5CCN(CC5)C(=O)O

A series of CDK inhibitors with a novel binding mode and good activity in clinically relevant disease models is reported.

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*Corresponding author

* Supplementary data available via ScienceDirect

COVER

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5677.]

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