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0960-894X(20100415)20:8;1-5

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BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

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Publication information: *Bioorganic & Medicinal Chemistry Letters* (ISSN 0960-894X) is published semimonthly by Elsevier (Radarweg 29, 1043 NX Amsterdam, the Netherlands). Further information on this journal is available from the Publisher or from the Elsevier Customer Service Department nearest you or from this journal's website (http://www.elsevier.com/locate/bmcl). Information on other Elsevier products is available through Elsevier's website (http://www.elsevier.com). Periodicals Postage Paid at Rahway, NJ, and at additional mailing offices. USA POSTMASTER: Send change of address to *Bioorganic & Medicinal Chemistry Letters*, Elsevier Customer Service Department, 3251 Riverport Lane, Maryland Heights, MO 63043, USA.

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Bioorganic & Medicinal Chemistry Letters 20 (2010) 2391–2407

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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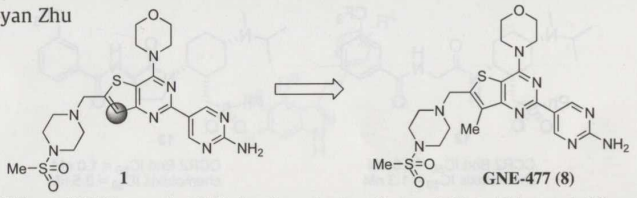
ARTICLES

Identification of GNE-477, a potent and efficacious dual PI3K/mTOR inhibitor pp 2408–2411

Timothy P. Heffron*, Megan Berry, Georgette Castanedo, Christine Chang, Irina Chuckowree, Jennafer Dotson, Adrian Folkes, Janet Gunzner, John D. Lesnick, Cristina Lewis, Simon Mathieu, Jim Nonomiya, Alan Olivero, Jodie Pang, David Peterson, Laurent Salphati, Deepak Sampath, Steve Sideris, Daniel P. Sutherlin, Vickie Tsui, Nan Chi Wan, Shumei Wang, Susan Wong, Bing-yan Zhu

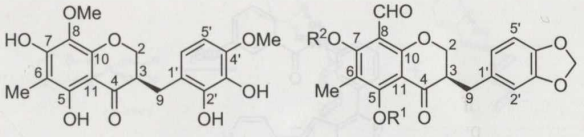


1 GNE-477 (8)

Efforts to identify potent small molecule inhibitors of PI3 kinase and mTOR led to the evaluation of tetrasubstituted thienopyrimidines. These molecules generally have reduced in vivo clearance relative to the trisubstituted thienopyrimidines culminating in the identification of **GNE-477** (**8**).

Homoisoflavonoid derivatives from the roots of *Ophiopogon japonicus* and their in vitro anti-inflammation activity pp 2412–2416

Tran Manh Hung, Cao Van Thu, Nguyen Tien Dat, Sung-Woo Ryoo, Jeong Hyung Lee, Jin Cheol Kim, Minkyun Na, Hyun-Ju Jung, KiHwan Bae*, Byung Sun Min*



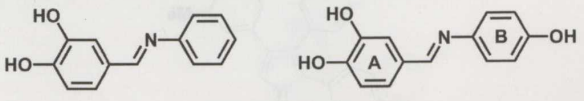
1

	R^1	R^2
2	H	Glc
3	Me	Glc

Three new homoisoflavonoids (**1**–**3**) were isolated from the roots of *Ophiopogon japonicus* (Liliaceae) and investigated by their effects on the release of the inflammatory chemokine eotaxin, stimulated by IL-4 and the combination of IL-4 and TNF-α in BEAS-2B cells.

Antioxidant and antiproliferative activities of hydroxyl-substituted Schiff bases pp 2417–2420

Li-Xia Cheng, Jiang-Jiang Tang, Hui Luo, Xiao-Ling Jin, Fang Dai, Jie Yang, Yi-Ping Qian, Xiu-Zhuang Li, Bo Zhou*



Eight hydroxyl-substituted Schiff bases were synthesized and bio-evaluated for their antioxidant and antiproliferative activities. Structure–activity relationship analysis indicates that *o*-diphenolic groups and 4-hydroxyl group attached to the aromatic B ring contribute critically to the activities.

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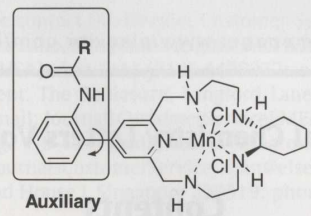
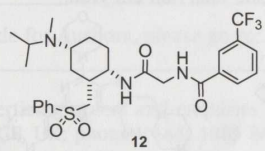
Synthesis and SOD activity of manganese complexes of substituted pyridino pentaaza macrocycles that contain axial auxiliary pp 2421–2424
Hakyoung Lee, Wonchoul Park, Dongyeol Lim*

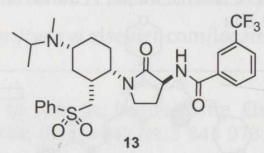


The synthesis and SOD-like activity of new manganese(II) complex of substituted pyridino pentaaza macrocyclic ligands are reported.

γ-Lactams as glycinamide replacements in cyclohexane-based CC chemokine receptor 2 (CCR2) antagonists pp 2425–2430
Robert J. Cherney*, Ruowei Mo, Dayton T. Meyer, Matthew E. Voss, Michael G. Yang, Joseph B. Santella III, John V. Duncia, Yvonne C. Lo, Gengjie Yang, Persymphonie B. Miller, Peggy A. Scherle, Qihong Zhao, Sandhya Mandlekar, Mary Ellen Cvijic, Joel C. Barrish, Carl P. Decicco, Percy H. Carter



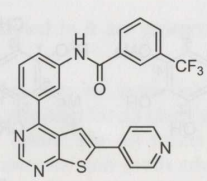
12
CCR2 Bnd IC_{50} = 0.8 nM
chemotaxis IC_{50} = 1.3 nM



13
CCR2 Bnd IC_{50} = 1.0 nM
chemotaxis IC_{50} = 0.5 nM

We describe the design, synthesis, and evaluation, of γ-lactams as glycinamide replacements within a series of di- and trisubstituted cyclohexane CCR2 antagonists.

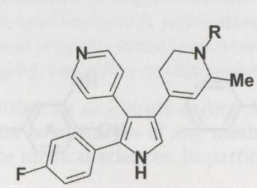
B-Raf kinase inhibitors: Hit enrichment through scaffold hopping pp 2431–2434
Ariamala Gopalsamy*, Mengxiao Shi, Yongbo Hu, Frederick Lee, Larry Feldberg, Eileen Frommer, Steven Kim, Karen Collins, Donald Wojciechowicz, Robert Mallon



11b

Scaffold hopping strategy was employed to replace the HTS hit scaffold pyrazolo[1,5-*a*]pyrimidine. This strategy led to the identification of additional lead compound **11b** with enhanced enzyme and cellular potency, while maintaining good selectivity over a number of kinases.

Tetrahydropyridine derivatives with inhibitory activity on the production of proinflammatory cytokines: Part 2 pp 2435–2437
Akira Nakao*, Nobuyuki Ohkawa, Takayoshi Nagasaki, Takashi Kagari, Hiromi Doi, Takaichi Shimozato, Shigeru Ushiyama, Kazumasa Aoki



3j: R = Me
3o: R = *n*-Pr

The synthesis of the proinflammatory cytokine production inhibitor **3o** (TNFα IC_{50} = 0.44 μM) and **3j** (TNFα ID_{50} = 1.42 mg/kg) are reported.

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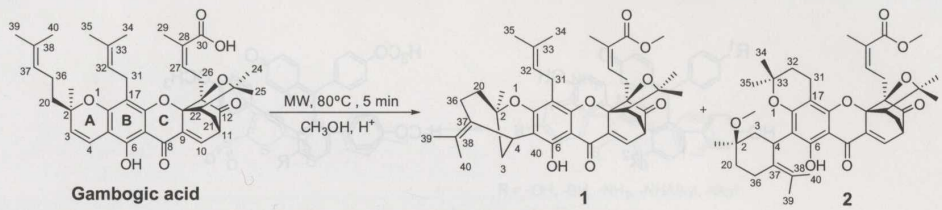
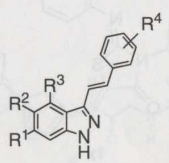
Spectacular modification of Gambogic acid on microwave irradiation in methanol: Isolation and structure identification of two products with potent anti-tumor activity pp 2438–2442
Xiaojian Wang, Na Lu, Qian Yang, Qinsheng Dai, Lei Tao, Xiaoke Guo, Qinglong Guo*, Qidong You*



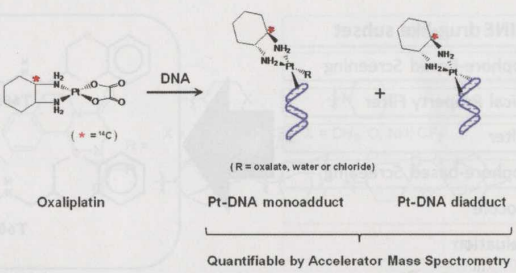
Treatment of gambogic acid with methanol in acidic condition under microwave irradiation led to the formation of two new products bearing spectacular A ring systems with promising anti-tumor effect.

Synthesis and evaluation of alkenyl indazoles as selective Aurora kinase inhibitors pp 2443–2447
Stéphanie Blanchard*, Anthony D. William, Angeline C.-H. Lee, Anders Poulsen, Ee Ling Teo, Weiping Deng, Noah Tu, Evelyn Tan, Kay Lin Goh, Wai Chung Ong, Chee Pang Ng, Kee Chuan Goh, Zahid Bonday, Eric T. Sun

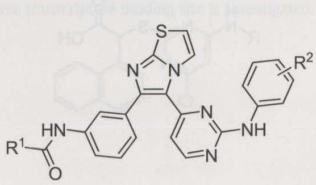


A series of alkenyl indazole derivatives were prepared and evaluated as selective Aurora inhibitors.

Towards biomarker-dependent individualized chemotherapy: Exploring cell-specific differences in oxaliplatin–DNA adduct distribution using accelerator mass spectrometry pp 2448–2451
Sang Soo Hah*, Paul T. Henderson, Kenneth W. Turteltaub



Imidazo[2,1-*b*]thiazoles: Multitargeted inhibitors of both the insulin-like growth factor receptor and members of the epidermal growth factor family of receptor tyrosine kinases pp 2452–2455
Steve D. Fidanze*, Scott A. Erickson, Gary T. Wang, Robert Mantei, Richard F. Clark, Bryan K. Sorensen, Nwe Y. Bamaung, Peter Kovar, Eric F. Johnson, Kerren K. Swinger, Kent D. Stewart, Qian Zhang, Lora A. Tucker, William N. Pappano, Julie L. Wilsbacher, Jieyi Wang, George S. Sheppard, Randy L. Bell, Steven K. Davidsen, Robert D. Hubbard



The design and enzyme activities of a novel class of imidazo[2,1-*b*]thiazoles is presented.

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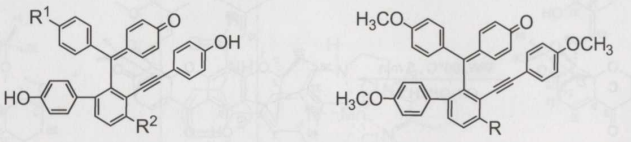
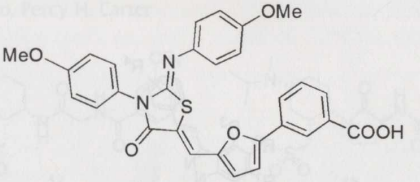
Antimicrobial selaginellin derivatives from *Selaginella pulvinata* **pp 2456–2460**
Yuan Cao, Ji-Jun Chen, Ning-Hua Tan, Lukas Oberer, Trixie Wagner, Yong-Ping Wu, Guang-Zhi Zeng, He Yan, Qiang Wang*



Selaginellin derivatives from *Selaginella pulvinata* with good antimicrobial activity.

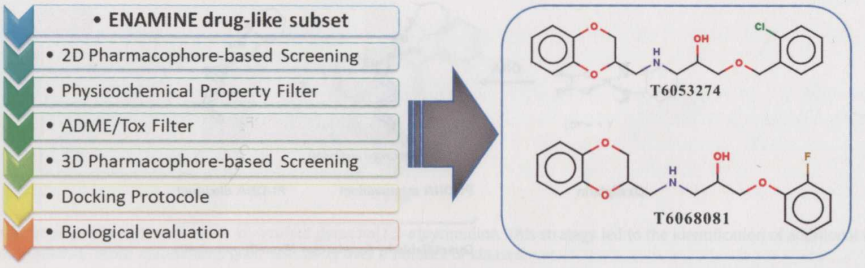
Design, synthesis, and antibiofilm activity of 2-arylimino-3-aryl-thiazolidine-4-ones **pp 2461–2464**
Bin Pan, Ren-Zheng Huang, Shi-Qing Han*, Di Qu, Ming-Li Zhu, Ping Wei, Han-Jie Ying



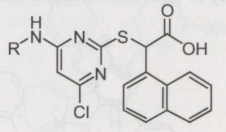
1x

The minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) and antibiofilm concentration assay of **1x** were 6.25 μM, 25 μM and 6.25 μM against *Staphylococcus epidermidis*, respectively.

The development and validation of a novel virtual screening cascade protocol to identify potential serotonin 5-HT$_7$R antagonists **pp 2465–2468**
Rafał Kurczab, Mateusz Nowak, Zdzisław Chilmonczyk, Ingebrigt Sylte, Andrzej J. Bojarski*



Rational design of a pirinixic acid derivative that acts as subtype-selective PPARγ modulator **pp 2469–2473**
Theresa M. Thieme, Ramona Steri, Ewgenij Proschak, Alexander Paulke, Gisbert Schneider, Manfred Schubert-Zsilavecz*



A series of pirinixic acid derivatives were synthesized and evaluated as subtype-selective peroxisome proliferator-activated receptor (PPARγ) agonists and modulator by in vitro transactivation of human PPARs.

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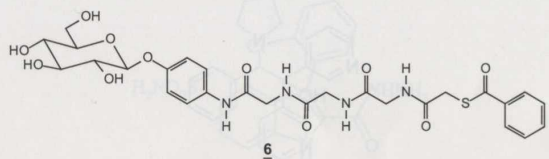
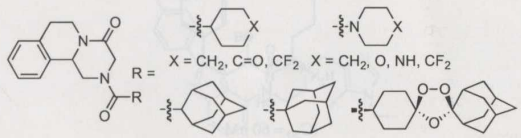
A-ring modifications on the triazafluorenone core structure and their mGluR1 antagonist properties pp 2474–2477
T. K. Sasikumar*, Li Qiang, Duane A. Burnett, William J. Greenlee, Cheng Li, Mariagrazia Grilli, Rosalia Bertorelli, Gianluca Lozza, Angelo Reggiani

A novel D-glucose derivative radiolabeled with technetium-99m: Synthesis, biodistribution studies and scintigraphic images in an experimental model of Ehrlich tumor pp 2478–2480
André Luís Branco de Barros, Valbert Nascimento Cardoso, Luciene das Graças Mota, Elaine Amaral Leite, Mônica Cristina de Oliveira, Ricardo José Alves*



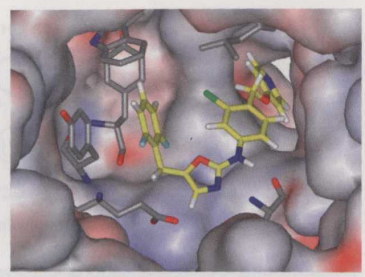
A D-glucose analogue was synthesized; its biodistribution studies and scintigraphic imagens were performed.

Praziquantel analogs with activity against juvenile *Schistosoma mansoni* pp 2481–2484
Yuxiang Dong, Jacques Chollet, Mireille Vargas, Nuha R. Mansour, Quentin Bickle, Yazen Alnouti, Jiangeng Huang, Jennifer Keiser, Jonathan L. Vennerstrom*



Eastern extension of azoles as non-nucleoside inhibitors of HIV-1 reverse transcriptase; cyano group alternatives pp 2485–2488
Cheryl S. Leung, Jacob G. Zeevaart, Robert A. Domaoal, Mariela Bollini, Vinay V. Thakur, Krasimir A. Spasov, Karen S. Anderson*, William L. Jorgensen*

Synthesis, assaying, and computational results are reported for new anti-HIV agents that exhibit high potency and low cytotoxicity. Extension into an eastern channel in the HIV-1 reverse transcriptase binding site is investigated.



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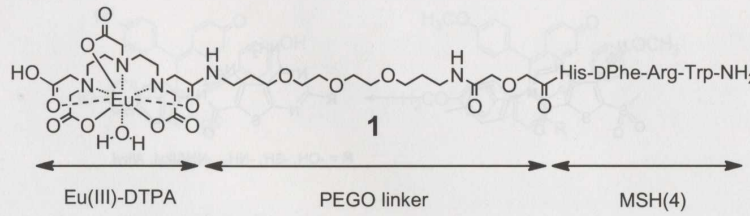
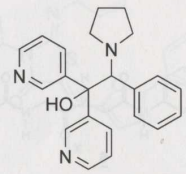
Synthesis and characterization of a Eu-DTPA-PEGO-MSH(4) derivative for evaluation of binding of multivalent molecules to melanocortin receptors pp 2489–2492
Liping Xu, Josef Vagner, Ramesh Alleti, Venkataramanarao Rao, Bhumasamudram Jagadish, David L. Morse, Victor J. Hruby, Robert J. Gillies, Eugene A. Mash*

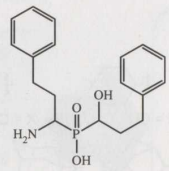


Discovery of triarylethanolamine inhibitors of the Kv1.5 potassium channel pp 2493–2496
Douglas C. Beshore*, Nigel J. Liverton, Charles J. McIntyre, Christopher F. Claiborne, Brian Libby, J. Christopher Culberson, Joseph J. Salata, Christopher P. Regan, Joseph J. Lynch, Laszlo Kiss, Robert H. Spencer, Stephanie A. Kane, Rebecca B. White, Suzie Yeh, George D. Hartman, Christopher J. Dinsmore



TAEA (7j)

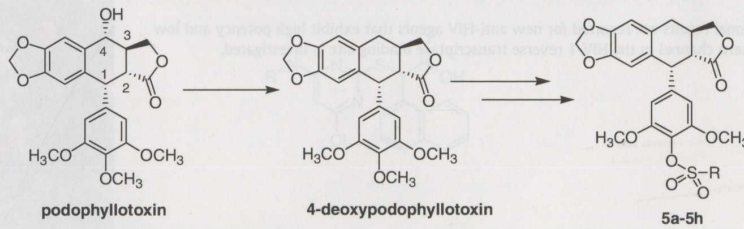
Identification of very potent inhibitor of human aminopeptidase N (CD13) pp 2497–2499
Renata Grzywa, Józef Oleksyszyn, Guy S. Salvesen, Marcin Drąg*



IC_{50} = 60 nM

New potent human aminopeptidase N (CD13) inhibitor (IC_{50} = 60 nM) is reported.

Natural products-based insecticidal agents 5. Design, semisynthesis and insecticidal activity of novel 4′-substituted benzenesulfonate derivatives of 4-deoxypodophyllotoxin against *Mythimna separata* Walker in vivo pp 2500–2502
Hui Xu*, Juan-Juan Wang



Some 4′-substituted benzenesulfonates of 4-deoxypodophyllotoxin exhibited the potent insecticidal activity.

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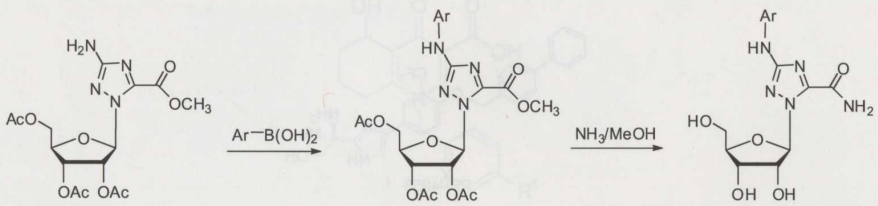
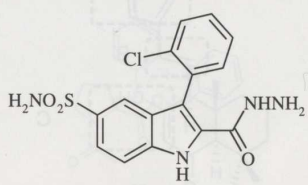
N-Aryltriazole ribonucleosides with potent antiproliferative activity against drug-resistant pancreatic cancer pp 2503–2507
Yang Liu, Yi Xia, Yuting Fan, Alain Maggiani, Palma Rocchi, Fanqi Qu, Juan L. Iovanna, Ling Peng*

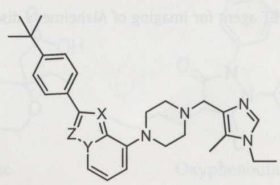


Carbonic anhydrase inhibitors. The β-carbonic anhydrases from the fungal pathogens *Cryptococcus neoformans* and *Candida albicans* are strongly inhibited by substituted-phenyl-1*H*-indole-5-sulfonamides pp 2508–2511
Özlen Güzel, Alfonso Maresca, Rebecca A. Hall, Andrea Scozzafava, Antonio Mastrolorenzo, Fritz A. Mühlschlegel, Claudiu T. Supuran*



K_I = 640 nM (hCA I); K_I = 38.8 nM (hCA II); K_I = 8.0 nM (Can2); K_I = 45 nM (CaNce103).

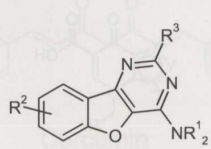
Synthesis and biological evaluation of piperazinyl heterocyclic antagonists of the gonadotropin releasing hormone (GnRH) receptor pp 2512–2515
Matthew D. Vera, Joseph T. Lundquist IV, Murty V. Chengalvala, Joshua E. Cottom, Irene B. Feingold, Lloyd M. Garrick, Daniel M. Green, Diane B. Hauze, Charles W. Mann, John F. Mehlmann, John F. Rogers, Linda Shanno, Jay E. Wrobel, Jeffrey C. Pelletier*



X = N(H), O, S; Y = C, N; Z = N(H), O, S

A series of bicycloheterocyclic replacements for the previously described benzimidazole template were prepared and tested for GnRH activity.

Identification and hit-to-lead exploration of a novel series of histamine H4 receptor inverse agonists pp 2516–2519
Sue Cramp*, Hazel J. Dyke, Christopher Higgs, David E. Clark, Matthew Gill, Pascal Savy, Neil Jennings, Steve Price, Peter M. Lockey, Dennis Norman, Soraya Porres, Francis Wilson, Alison Jones, Nigel Ramsden, Raffaella Mangano, Dan Leggate, Marie Andersson, Richard Hale



The hit-to-lead exploration of a series of novel, potent and selective series of histamine H4 receptor inverse agonists originating from a virtual screening approach is described.

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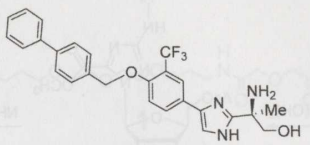
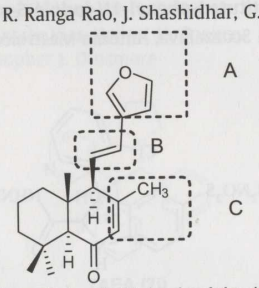
Exploration of amino alcohol derivatives as novel, potent, and highly selective sphingosine-1-phosphate receptor subtype-1 agonists pp 2520–2524
Ghotas Evindar*, Sylvie G. Bernier, Elisabeth Doyle, Malcolm J. Kavarana, Alexander L. Satz, Jeanine Lorusso, Heather S. Blanchette, Ashis K. Saha, Gerhard Hannig, Barry A. Morgan, William F. Westlin



PPI-4955

Identification of a selectivity enhancing moiety has allowed for discovery of pro-drug PPI-4955 (**21b**), a potent and selective sphingosine-1-phosphate receptor-1 agonist, with excellent dose responsiveness and pharmacodynamic properties.

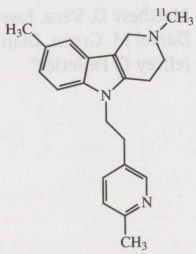
Synthesis, cytotoxic activity and structure–activity relationships of hedychenone analogues pp 2525–2528
P. Prabhakar Reddy, Aditya G. Lavekar, K. Suresh Babu, R. Ranga Rao, J. Shashidhar, G. Shashikiran, J. Madhusudana Rao*



A series of analogues have been synthesized by modification of the furanoid ring, double bond and the vinylic methyl functionality of this natural product lead. All the compounds were tested for their in vitro cytotoxic activity against human cancer cell lines.

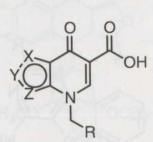
[^{11}C]Dimebon, radiosynthesis and lipophilicity of a new potential PET agent for imaging of Alzheimer's disease and Huntington's disease pp 2529–2532
Mingzhang Gao, Min Wang, Gary D. Hutchins, Qi-Huang Zheng*

Radiosynthesis and lipophilicity of [^{11}C]Dimebon, a new potential PET agent for imaging of Alzheimer's disease and Huntington's disease, are first reported.



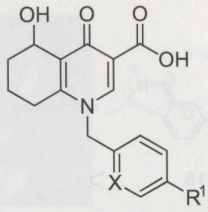
[^{11}C]Dimebon, [^{11}C]**7b**

Heterocyclic fused pyridone carboxylic acid M_1 positive allosteric modulators pp 2533–2537
Scott D. Kuduk*, Christina N. Di Marco, Ronald K. Chang, William J. Ray, Lei Ma, Marion Wittmann, Matthew A. Seager, Kenneth A. Koeplinger, Charles D. Thompson, George D. Hartman, Mark T. Bilodeau



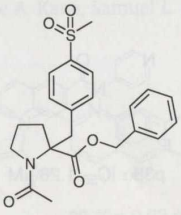
The phenyl ring in a series of quinolone carboxylic acid M_1 positive allosteric modulators was replaced with a variety of heterocycles in order to reduce protein plasma binding and enhance CNS exposure.

Hydroxy cycloalkyl fused pyridone carboxylic acid M_1 positive allosteric modulators pp 2538–2541
Scott D. Kuduk*, Robert M. DiPardo, Douglas C. Beshore, William J. Ray, Lei Ma, Marion Wittmann, Matthew A. Seager, Kenneth A. Koeplinger, Charles D. Thompson, George D. Hartman, Mark T. Bilodeau



Incorporation of hydroxycycloalkyl fused pyridone carboxylic acids in lieu of quinolone carboxylic acids enhance free fraction without increased susceptibility to P-glycoprotein transport.

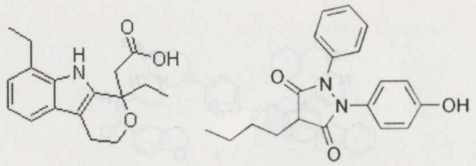
Benzyl prolinate derivatives as novel selective KCC2 blockers pp 2542–2545
Cécile Pégurier*, Nathalie Bosman, Philippe Collart, Marie-Laure Delporte, Karine Leclercq, Sébastien Lengelé, Ananda Kumar Kanduluru, Stéphane Meunier, Nathalie Pacico, Lakshmana Rao Vadali, Alain Wagner, Christian Wolff, Laurent Provins



13

The benzyl prolinate **13** has been identified as a potent KCC2 blocker with selectivity versus NKCC1 and favorable ADME properties. It was evaluated in an in vivo model of epilepsy, the audiogenic mouse seizure test.

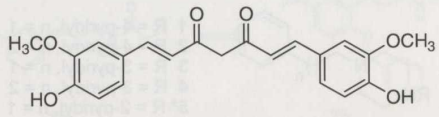
Chemopreventive activities of etodolac and oxyphenbutazone against mouse skin carcinogenesis pp 2546–2548
Govind J. Kapadia*, Magnus A. Azuine, Yuuko Shigeta, Nobutaka Suzuki, Harukuni Tokuda



Etodolac Oxyphenbutazone

Inhibition of mouse skin cancer by non-steroidal anti-inflammatory drugs, etodolac and oxyphenbutazone is reported.

Curcumin derivatives inhibit testicular 17β-hydroxysteroid dehydrogenase 3 pp 2549–2551
Guo-Xin Hu, Guang Liang, Yanhui Chu, Xiaokun Li, Qing-Quang Lian*, Han Lin, Yi He, Yadong Huang, Dianne O. Hardy, Ren-Shan Ge*



Curcumin

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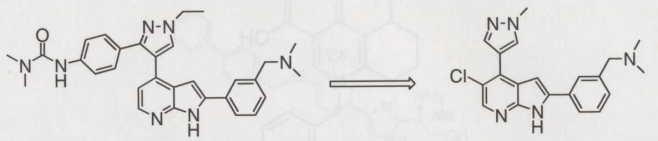
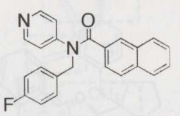
Discovery of a new series of Aurora inhibitors through truncation of GSK1070916 pp 2552–2555
Jesus R. Medina*, Seth W. Grant, Jeffrey M. Axten, William H. Miller, Carla A. Donatelli, Mary Ann Hardwicke, Catherine A. Oleykowski, Qiaoyin Liao, Ramona Plant, Hong Xiang



GSK1070916 14

The SAR results from this investigation will be presented with an emphasis on the impact structural changes have on the cellular phenotype.

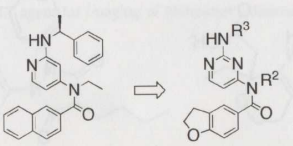
Amide-based inhibitors of p38α MAP kinase. Part 1: Discovery of novel *N*-pyridyl amide lead molecules pp 2556–2559
Gregory R. Luedtke, Kurt Schinzel, Xuefei Tan*, Richland W. Tester, Imad Nashashibi, Yong-jin Xu, Sundeep Dugar, Daniel E. Levy*, Joon Jung



p38α IC_{50} 1.26 μM

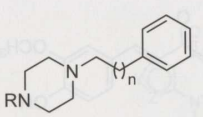
A novel series of *N*-pyridyl amide p38α kinase inhibitors is described. The proposed binding modes of the initial hits were evaluated against SAR findings to provide rationale for further development of this structural class.

Amide-based inhibitors of p38α MAP kinase. Part 2: Design, synthesis and SAR of potent *N*-pyrimidyl amides pp 2560–2563
Richland Tester, Xuefei Tan*, Gregory R. Luedtke, Imad Nashashibi, Kurt Schinzel, Weiling Liang, Joon Jung, Sundeep Dugar, Albert Liclican, Jocelyn Tabora, Daniel E. Levy*, Steven Do



Identification and optimization of a new class of *N*-pyrimidyl amide based p38α MAP kinase inhibitors is described. The lead structure was derived from a previously reported class of pyridine-based amides. p38α activity (enzymatic/cellular) and CYP3A4 data for the new series are presented.

The effect of the pyridyl nitrogen position in pyridylpiperazine sigma ligands pp 2564–2565
Lidiya Stavitskaya, Michael J. Seminerio, Marilyn M. Matthews-Tsourounis, Rae R. Matsumoto, Andrew Coop*



1 R = 4-pyridyl, n = 1
2 R = 4-pyridyl, n = 2
3 R = 3-pyridyl, n = 1
4 R = 3-pyridyl, n = 2
5* R = 2-pyridyl, n = 1
6* R = 2-pyridyl, n = 2

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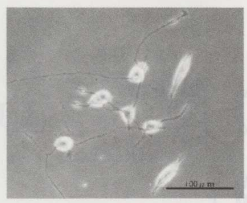
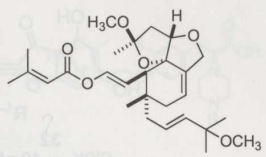
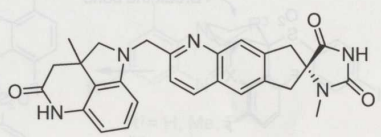
NGF-potentiating vibsane-type diterpenoids from *Viburnum sieboldii* **pp 2566–2571**
Miwa Kubo, Yoshiko Kishimoto, Kenichi Harada, Hideaki Hioki, Yoshiyasu Fukuyama*



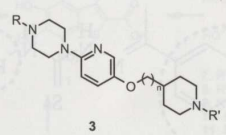


Identification of potent, highly constrained CGRP receptor antagonists **pp 2572–2576**
Craig A. Stump*, Ian M. Bell, Rodney A. Bednar, John F. Fay, Steven N. Gallicchio, James C. Hershey, Richard Jelley, Constantine Kreatsoulas, Eric L. Moore, Scott D. Mosser, Amy G. Quigley, Shane A. Roller, Christopher A. Salvatore, Steven S. Sharik, Cory R. Theberge, C. Blair Zartman, Stefanie A. Kane, Samuel L. Graham, Harold G. Selnick, Joseph P. Vacca, Theresa M. Williams



19 K_i = 0.52 nM

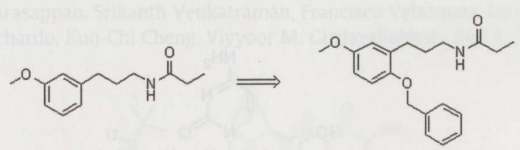
2,5-Disubstituted pyridines as potent GPR119 agonists **pp 2577–2581**
Yulin Wu*, Judith D. Kuntz, Andrew J. Carpenter*, Jing Fang, Howard R. Sauls, Daniel J. Gomez, Carina Ammala, Yun Xu, Shane Hart, Sarva Tadepalli



3

A series of 2-piperazinyl-5-alkoxypyridines (**3**) were synthesized and screened against human GPR119 receptor. Through SAR analysis, compounds containing 2-alkylsulfonylpiperazinyl-5-alkoxypyridines were discovered and found to be potent agonists of the human GPR119 receptor.

Synthesis of substituted *N*-[3-(3-methoxyphenyl)propyl] amides as highly potent MT_2-selective melatonin ligands **pp 2582–2585**
Yueqing Hu, Maurice K. C. Ho, King H. Chan, David C. New, Yung H. Wong*



1b **2b**

MT_2 Ki = 7.07 nM MT_2 Ki = 0.55 pM

A benzyloxyl substituent incorporated at C6 position of the 3-methoxyphenyl ring dramatically enhanced the melatonin MT_2-binding affinity.

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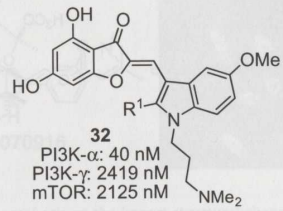
Novel benzofuran-3-one indole inhibitors of PI3 kinase-α and the mammalian target of rapamycin: Hit to lead studies pp 2586–2590

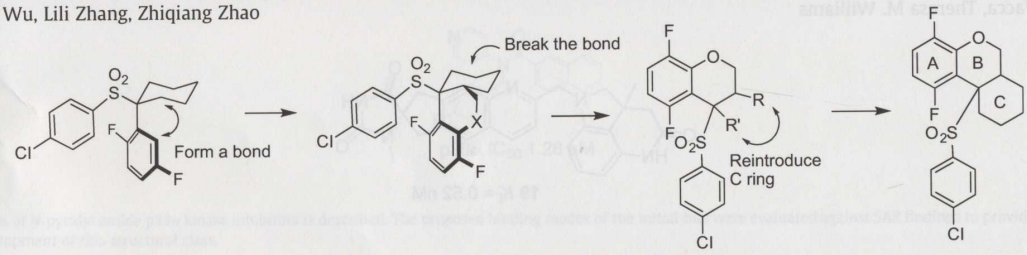
Matthew G. Bursavich, Natasja Brooijmans, Lawrence Feldberg, Irwin Hollander, Stephen Kim, Sabrina Lombardi, Kaapjoo Park, Robert Mallon, Adam M. Gilbert*



32
PI3K-α: 40 nM
PI3K-γ: 2419 nM
mTOR: 2125 nM

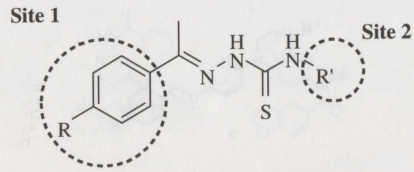
Design and synthesis of tricyclic sulfones as γ-secretase inhibitors with greatly reduced Notch toxicity pp 2591–2596

Ruo Xu*, David Cole, Ted Asberom, Tom Bara, Chad Bennett, Duane A. Burnett, John Clader, Martin Domalski, William Greenlee, Lynn Hyde, Hubert Josien, Hongmei Li, Mark McBriar, Brian McKittrick, Andrew T. McPhail, Dmitri Pissarnitski, Li Qiang, Murali Rajagopalan, Thavalakulamgar Sasikumar, Jing Su, Haiqun Tang, Wen-Lian Wu, Lili Zhang, Zhiqiang Zhao



Substituted hydrazinecarbothioamide as potent antitubercular agents: Synthesis and quantitative structure–activity relationship (QSAR) pp 2597–2600

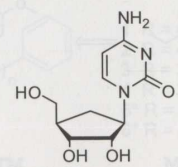
Supriya Singh, Pintu K. Mandal, Nagendra Singh, Anup K. Misra, Shubhra Singh, Vinita Chaturvedi, Sudhir Sinha, Anil K. Saxena*



A series of novel substituted hydrazinecarbothioamides was synthesized and evaluated for anti-TB activity. Three most active compounds viz. **1**, **6** and **12** were found to exhibit minimum inhibitory concentration (MIC) of 0.4 μg/mL whereas four compounds viz. **3**, **5**, **10** and **11** showed comparatively lesser activity with MIC value of 0.8 μg/mL against *Mycobacterium tuberculosis* strain. A highly significant QSAR equation explaining 81.8% variance is described.

(−)-Carbodine: Enantiomeric synthesis and in vitro antiviral activity against various strains of influenza virus including H5N1 (avian influenza) and novel 2009 H1N1 (swine flu) pp 2601–2604

Jagadeeshwar R. Rao, Ashok K. Jha, Ravindra K. Rawal, Ashoke Sharon, Craig W. Day, Dale L. Barnard, Donald F. Smee, Chung K. Chu*



(-)-Carbodine

Enantiomerically pure cyclopentyl cytosine [(−)-carbodine] exhibited potent antiviral activity against H5N1 (avian) and novel H1N1 (swine) flu.

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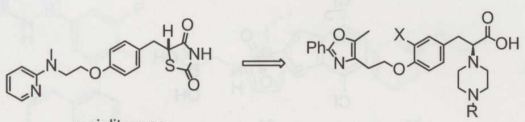
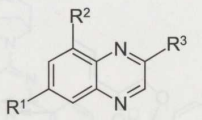
(*S*)-3-(4-(2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy)phenyl)-2-(piperazin-1-yl)propanoic acid compounds: Synthesis and biological evaluation of dual PPARα/γ agonists pp 2605–2608
Xinbo Zhou, Wei Chen, Cheng Xu, Shiyong Fan, Yunde Xie, Wu Zhong, Lili Wang, Song Li*

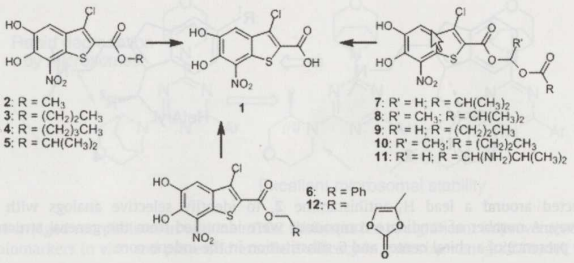


A series of novel, potent PPARα/γ dual agonists were synthesized and appraised. Compound **2b** was chosen for further in vivo evaluation in the *db/db* mice, rosiglitazone were used for comparison.

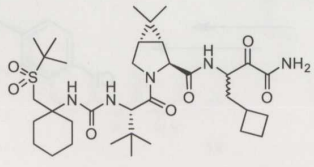
Discovery and SAR of potent, orally available 2,8-diaryl-quinoxalines as a new class of JAK2 inhibitors pp 2609–2613
Carole Pissot-Soldermann*, Marc Gerspacher, Pascal Furet, Christoph Gaul, Philipp Holzer, Clive McCarthy, Thomas Radimerski, Catherine H. Regnier, Fabienne Baffert, Peter Drueckes, Gisele A. Tavares, Eric Vangrevelinghe, Francesca Blasco, Giorgio Ottaviani, Flavio Ossola, Julien Scesa, Janitha Reetz



Design, synthesis and in vitro/in vivo evaluation of orally bioavailable prodrugs of a catechol-*O*-methyltransferase inhibitor pp 2614–2616
Jarkko Rautio*, Jukka Leppänen, Marko Lehtonen, Krista Laine, Mikko Koskinen, Jarmo Pystynen, Jouko Savolainen, Mikko Sairanen



The introduction of P4 substituted 1-methylcyclohexyl groups into Boceprevir®: A change in direction in the search for a second generation HCV NS3 protease inhibitor pp 2617–2621
Frank Bennett*, Yuhua Huang, Siska Hendrata, Raymond Lovey, Stephane L. Bogen, Weidong Pan, Zhuyan Guo, Andrew Prongay, Kevin X. Chen, Ashok Arasappan, Srikanth Venkatraman, Francisco Velazquez, Latha Nair, Mousumi Sannigrahi, Xiao Tong, John Pichardo, Kuo-Chi Cheng, Viyyoor M. Girijavallabhan, Anil K. Saksena, F. George Njoroge



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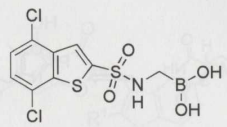
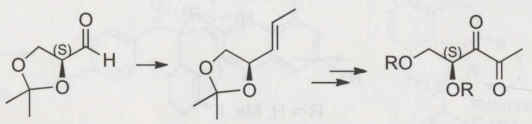
4,7-Dichloro benzothien-2-yl sulfonylaminomethyl boronic acid: First boronic acid-derived beta-lactamase inhibitor with class A, C, and D activity pp 2622–2624
Qiang Tan*, Aimie M. Ogawa, Ronald E. Painter, Young-Whan Park, Katherine Young, Frank P. DiNinno



DSABA

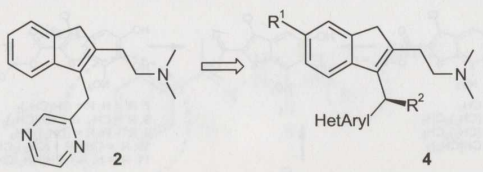
4,7-Dichloro-1-benzothien-2-yl sulfonylaminomethyl boronic acid (DSABA) is reported as the first boronic acid-based class D beta-lactamase inhibitor, also with class A and C activity.

Synthesis and bioluminescence-inducing properties of autoinducer (*S*)-4,5-dihydroxypentane-2,3-dione and its enantiomer pp 2625–2628
Manikandan Kadirvel, William T. Stimpson, Souad Moumene-Afifi, Biljana Arsic, Nicola Glynn, Nigel Halliday, Paul Williams, Peter Gilbert, Andrew J. McBain, Sally Freeman, John M. Gardiner*



Synthesis of both enantiomers of autoinducer DPD (shown (*S*), R = H) along with their ester bioprecursors (R = Bz, Ac) & biological assays.

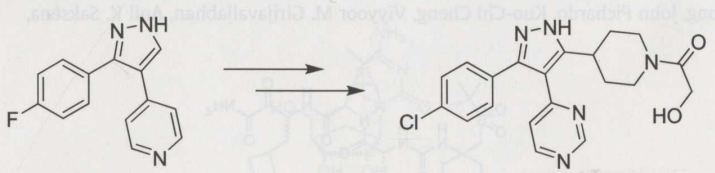
Selectivity profiling of novel indene H_1-antihistamines for the treatment of insomnia pp 2629–2633
Bin-Feng Li, Wilna J. Moree*, Jinghua Yu, Timothy Coon, Said Zamani-Kord, Siobhan Malany, Kayvon Jalali, Jianyun Wen, Hua Wang, Chun Yang, Samuel R. J. Hoare, Robert E. Petroski, Ajay Madan, Paul D. Crowe, Graham Beaton*



2 4

Structure–activity relationships were conducted around a lead H_1-antihistamine **2**, to identify selective analogs with the potential for reduced biotransformation through the CYP2D6 pathway. A number of candidate compounds were identified from the general structure **4** using the appropriate combination of electron rich heterocycles, the presence of a chiral center and 6-substitution in the indene core.

Identification of SD-0006, a potent diaryl pyrazole inhibitor of p38 MAP kinase pp 2634–2638
John K. Walker*, Shaun R. Selness, Rajesh V. Devraj, Michael E. Hepperle, Win Naing, Huey Shieh, Ravi Kurambail, Syaulan Yang, Daniel L. Flynn, Alan G. Benson, Dean M. Messing, Tom Dice, Tina Kim, R. J. Lindmark, Joseph B. Monahan, Joseph Portanova



SC-102 SD-0006

Starting from the novel screening lead, SC-102, synthesis and structure activity relationships are provided highlighting the progression to and identification of the potent p38 MAP kinase inhibitor SD-0006.

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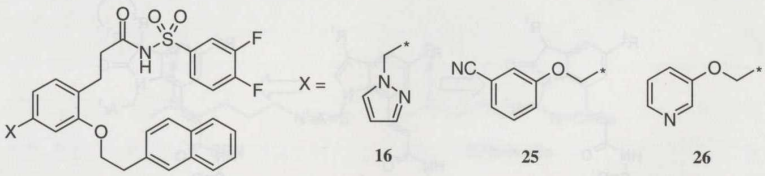
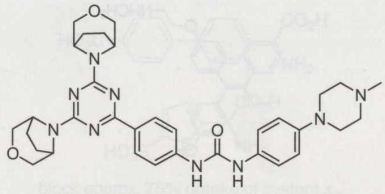
Discovery of novel *N*-acylsulfonamide analogs as potent and selective EP3 receptor antagonists pp 2639–2643
Masaki Asada*, Tetsuo Obitsu, Atsushi Kinoshita, Yoshihiko Nakai, Toshihiko Nagase, Isamu Sugimoto, Motoyuki Tanaka, Hiroya Takizawa, Ken Yoshikawa, Kazutoyo Sato, Masami Narita, Shuichi Ohuchida, Hisao Nakai, Masaaki Toda



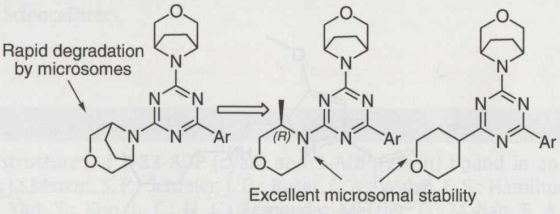
Identification of novel *N*-acyl 3,4-difluorobenzenesulfonamide analogs as potent and selective EP3 receptor antagonists and their in vivo efficacy with respect to the PGE_2-induced uterine contraction in pregnant rats are reported.

Discovery of 2-ureidophenyltriazines bearing bridged morpholines as potent and selective ATP-competitive mTOR inhibitors pp 2644–2647
Arie Zask*, Jeroen C. Verheijen, David J. Richard, Joshua Kaplan, Kevin Curran, Lourdes Toral-Barza, Judy Lucas, Irwin Hollander, Ker Yu



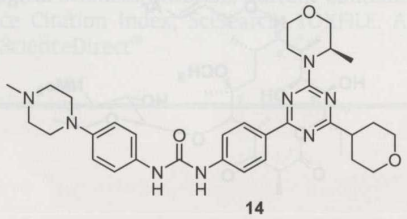
Incorporation of bridged morpholines in monocyclic triazine PI3K/mTOR inhibitors gave compounds with increased mTOR selectivity relative to the corresponding morpholine analogs leading to compounds which suppressed mTOR biomarkers in vivo and possessed excellent efficacy in a murine xenograft model.

2-Arylureidophenyl-4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)triazines as highly potent and selective ATP competitive mTOR inhibitors: Optimization of human microsomal stability pp 2648–2653
Jeroen C. Verheijen*, David J. Richard, Kevin Curran, Joshua Kaplan, Ker Yu, Arie Zask



Isosteric replacement of one of the 3,5-ethylene-bridged morpholines in triazine mTOR inhibitors led to significant improvements in human microsomal stability, resulting in a compound that selectively suppressed mTOR biomarkers in vivo and possessed excellent efficacy in a murine xenograft model.

Triazines incorporating (*R*)-3-methylmorpholine are potent inhibitors of the mammalian target of rapamycin (mTOR) with selectivity over PI3Kα pp 2654–2657
David J. Richard*, Jeroen C. Verheijen, Ker Yu, Arie Zask



Potent inhibitors of the mammalian target of rapamycin (mTOR) which contain the triazine scaffold and the (*R*)-3-methyl morpholine moiety have been identified. Such compounds also displayed excellent cellular activity and good selectivity over the related lipid kinase PI3Kα.

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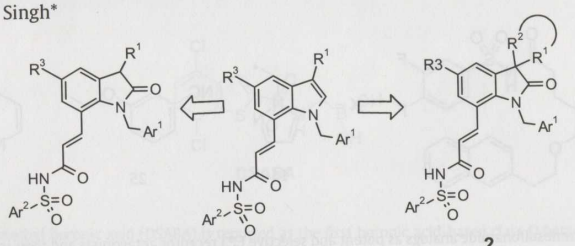
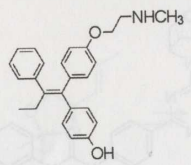
1,7-Disubstituted oxyindoles are potent and selective EP_3 receptor antagonists pp 2658–2664
Nian Zhou, Alexandre M. Polozov, Matthew O'Connell, James Burgeson, Peng Yu, Wayne Zeller, Jun Zhang, Emmanuel Onua, Jose Ramirez, Gudrun A. Palsdottir, Gudrun V. Halldorsdottir, Thorkell Andresson, Alex S. Kiselyov, Mark Gurney, Jasbir Singh*

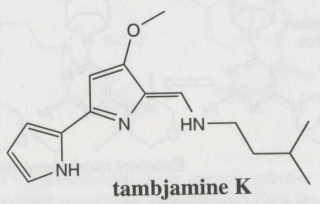


Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder pp 2665–2667
Shoukath M. Ali, Ateeq Ahmad, Syed Shahabuddin, Moghis U. Ahmad, Saifuddin Sheikh, Imran Ahmad*

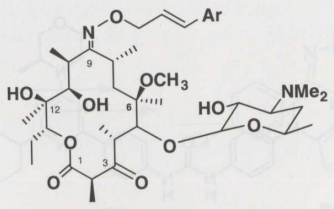


A novel synthesis of endoxifen and its PKC inhibitory activity is reported.

A new cytotoxic tambjamine alkaloid from the Azorean nudibranch *Tambja ceutae* pp 2668–2670
Marianna Carbone, Carlo Irace, Francesca Costagliola, Francesco Castelluccio, Guido Villani, Gonçalo Calado, Vinicius Padula, Guido Cimino, J. Lucas Cervera, Rita Santamaria, Margherita Gavagnin*



Synthesis and antibacterial activity of new 9-*O*-arylpropenyloxime ketolides pp 2671–2674
Ghilsoo Nam*, Yang Soo Kim, Kyung Il Choi



New 9-*O*-arylpropenyloxime ketolides were synthesized and evaluated their antibacterial activities against clinically isolated gram-positive strains. The SAR is discussed.

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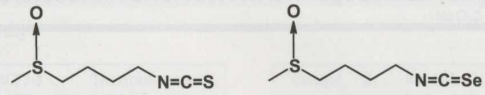
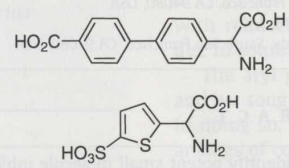
Enhanced Nrf2-dependent induction of glutathione in mouse embryonic fibroblasts by isoselenocyanate analog of sulforaphane pp 2675–2679
Sans W. Emmert, Dhimant Desai, Shantu Amin, John P. Richie Jr.*



SFN-isoSe, an isosteric selenium analog of naturally occurring sulforaphane (SFN), is a potent inducer of the Nrf2/ARE pathway and may represent a more effective chemoprotective agent in vivo.

Conformationally-restricted amino acid analogues bearing a distal sulfonic acid show selective inhibition of system x_c^- over the vesicular glutamate transporter pp 2680–2683
Jean-Louis G. Etoga, S. Kaleem Ahmed, Sarjubhai Patel, Richard J. Bridges, Charles M. Thompson*



block approx. 75% uptake of system x_c^-

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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.]

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

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Bioorganic & Medicinal Chemistry Letters 20 (2010) 2665–2667

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder

Shoukath M. Ali, Ateeq Ahmad, Syed Shahabuddin, Moghis U. Ahmad, Saifuddin Sheikh, Imran Ahmad *

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ARTICLE INFO

Article history:
Received 12 December 2009
Accepted 5 February 2010
Available online 23 February 2010

Keywords:
Endoxifen
PKC
Bipolar disorder
Chemical synthesis

ABSTRACT

Protein kinase C (PKC) plays a major role in regulation of both pre and postsynaptic neurotransmission. Excessive activation of PKC results in symptoms related to bipolar disorder. Tamoxifen, a widely used breast cancer drug is known to inhibit PKC and demonstrate antimanic properties in human. We describe herein the synthesis of endoxifen, a tamoxifen active metabolite and compared its PKC inhibitory activity with that of tamoxifen. Endoxifen exhibited fourfold higher potency compared to tamoxifen.

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Bipolar disorder (BPD) is a chronic debilitating illness characterized by drastic swings in mood, energy and functional ability, that affects adult population.[1] Until recently, not much was known about the molecular and cellular mechanisms of BPD. Recent data suggests that mania is associated with overactive protein kinase C (PKC) intracellular signaling which plays a major role in regulation of both pre and postsynaptic neurotransmission.[2] Interestingly, the current first line therapy of mania, lithium and valproate indirectly inhibit PKC.[3] In addition, recent preclinical and clinical studies with the relatively selective PKC inhibitor *Z*-tamoxifen add support to the relevance of the PKC target in BPD. Animal studies demonstrate that tamoxifen significantly reduced manic behavior in rodents.[4] Preliminary investigations of PKC inhibitor tamoxifen in the treatment of acute mania showed anti-manic effects compared to placebo.[5] Recently, two groups confirmed antimanic properties of tamoxifen in double-blind, placebo controlled clinical studies.[6] Thus, a growing body of work in both preclinical and clinical indicates that PKC signalling may play an important factor in the pathophysiology and treatment of BPD. The development of CNS-penetrant PKC inhibitors such as tamoxifen may have considerable benefit for this devastating illness.[7] However, there is a large inter-individual and ethnic variability in tamoxifen bioavailability and function due to CYP2D6 genetic polymorphism which extensively metabolizes tamoxifen into active metabolites, 4-hydroxy tamoxifen and 4-hydroxy-*N*-desmethyl tamoxifen (endoxifen).[8] Alternative PKC inhibitors that are independent of CYP2D6 action such as endoxifen may provide better opportunity for the treatment of BPD and other diseases. Here we have synthesized endoxifen (Fig. 1) and showed its PKC inhibitory activity in vitro for the first time. We have also compared its PKC activity with known PKC inhibitor tamoxifen.

Previously reported endoxifen synthesis involved demethylation of 4-hydroxytamoxifen.[9] However, there are no reports for its synthesis starting from commercially available starting materials. Here, we report the synthesis of endoxifen starting from commercially available 4-bromophenol, α-phenyl butyric acid and 2-chloroethoxybenzene. The synthetic scheme is depicted in Scheme 1. 1-[4-(2-Chlororethoxy)phenyl]-2-phenyl-butan-1-one **3** was synthesized by refluxing solution of 2-phenylbutyric acid **2** and thionyl chloride in 1,2-dichloroethane (EDC) for an hour before it was cooled to room temperature and added drop wise to a stirring solution of 2-chloroethoxybenzene **1** and anhydrous aluminum chloride in EDC at 0 °C. After the completion of reaction the workup was done by pouring the reaction solution in HCl/H_2O solution (1:1) and extracted with EDC. The crude product was purified by flash chromatography (hexane/ethyl acetate) yielding **3** in 88% yield. Alternatively, **3** was also synthesized in 96% yield by

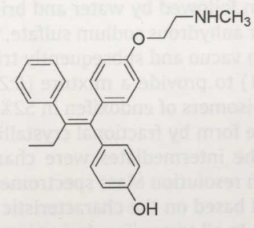

Figure 1. Structure of endoxifen.

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doi:10.1016/j.bmcl.2010.02.024

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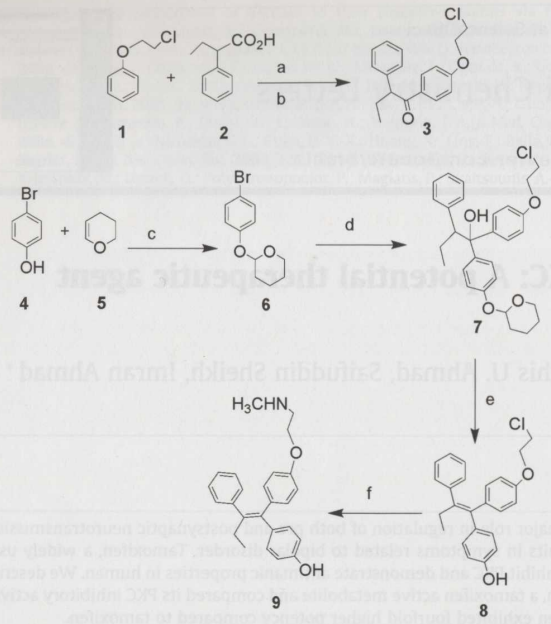

Scheme 1. Reagents and conditions: (a) method; (i) **2**, $SOCl_2$, EDC; **3**, $AlCl_3$, EDC; (b) method; (ii) TFAA, rt; (c) concd H_2SO_4, rt; (d) (i) **6**, Mg, THF; reflux→rt; (ii) add **3** in THF, reflux; (e) concd HCl, MeOH, reflux; (f) methylamine, 2-propanol, reflux.

mixing **1**, **2**, and trifluoroacetic anhydride (TFAA) and stirring for 10 h. The reaction solution was neutralized with saturated sodium bicarbonate solution before it was extracted with ethyl acetate and concentrated. The crude product after crystallization in hexane at 0 °C provided **3** in 96% yield. The tetrahydopyran (THP) protecting group was introduced into 4-bromophenol **4** by stirring with 3 M equiv of 3,4-dihydro-2*H*-pyran **5** and catalytic amount of concentrated sulfuric acid at 0 °C under nitrogen for 30 min. The reaction solution was diluted with hexane–water. After workup, the product was isolated in 91% yield by crystallization in small amount of cold hexane. Compounds **3** and **6** were reacted under Grignard's reaction conditions (Mg/THF) to provide an intermediate **7** which was heated under acidic condition (HCl and methanol) to undergo simultaneously dehydration and deprotection reaction. After conventional workup, the crude product was purified on silica gel column and eluted with dichloromethane–hexane mixture (1:1) to afford 1-[4-(2-chloroethoxy)phenyl-(4-hydroxyphenyl)-2-phenyl but-1-ene] **8** as *E*- and *Z*-geometric isomers in 86.5% yield. Compound **8** was then transformed into compound **9** by treatment with 40% methylamine (aqueous) in isopropyl alcohol and refluxed for 48 h. The solvent was removed and the residue was extracted with ethyl acetate and washed with 5% aq sodium bicarbonate solution followed by water and brine solution.

After drying over anhydrous sodium sulfate, the organic extract was concentrated in vacuo and subsequently triturated with ethyl acetate/hexane (1:1) to provide a mixture (*E*:*Z*, 5.8:4.2, HPLC) of geometric *E*- and *Z*-isomers of endoxifen in 52% yield. *Z*-Endoxifen was isolated in pure form by fractional crystallization in benzene. The product and the intermediates were characterized[10] by ^1H NMR, ^{13}C NMR, high resolution Mass spectrometry. The *Z*-configuration was assigned based on the characteristic chemical shift[9b,11] of OCH_2 in ^1H NMR. In all tamoxifen derivatives studies, the *Z*-isomers (*trans*), the OCH_2 protons of the side chain have a chemical shift (δ) less than 4.00 ppm owing to the through-space shielding influence of the vicinal 2-phenyl substituents. Based on this, the isomer having the triplet at δ 3.86 was assigned as *Z*-isomer and the isomer with δ 4.03 was identified as *E*-isomer.

Effect of synthesized endoxifen on PKC activity was evaluated in vitro and compared with that of tamoxifen using a PKC kinase activity ELISA assay kit (Assay Designs, Ann Arbor, MI) which contained a PKC Substrate Microtiter Plate, Active PKC, ATP, Phospho-specific Substrate Antibody, Anti-Rabbit IgG-HRP conjugate, TMB substrate, Stop solution, Wash and Dilution Buffer. The assay was carried out according to manufacturer's instructions. Briefly, 50 µl of a reaction mix containing Kinase Assay Dilution Buffer, 0.025, 0.05, 0.1, or 0.2 mM endoxifen and 10 ng PKC was added to each well of a presoaked PKC Substrate Microtiter Plate. To compare PKC inhibition activity with tamoxifen, 50 µl of the Dilution Buffer reaction mix containing 0.025, 0.05, 0.1, or 0.2 mM tamoxifen (Toronto Research Chemicals, North York, ON, Canada) and 10 ng PKC was added to another set of wells. Fifty microliter of Kinase Assay Dilution Buffer alone or with 10 ng PKC was used as negative and positive controls, respectively. The reaction was initiated by adding 10 µl of diluted ATP to each well. Following incubation at 30 °C for up to 90 min, the reaction was stopped by emptying contents of the plate. Forty microliters of Phosphospecific Substrate Antibody was added to each well followed by 60 min incubation at room temperature. All wells were washed four times with Wash Buffer and 40 µl of diluted Anti-Rabbit IgG: HRP Conjugate was added. After 30 min incubation at room temperature, wells were again washed and 60 µl of TMB Substrate was added. Following further incubation at room temperature for 30 min, 20 µl of Stop Solution was added and absorbance was read at 450 nm in a microplate reader (SpectraMax M2, Molecular Devices, Sunnyvale, CA). The results were analyzed using SoftMax® Pro 5 software.

Endoxifen inhibited PKC activity in concentration dependent manner. The percentage PKC inhibition ranged between 12% and 78% with endoxifen concentration between 0.025 and 0.2 mM, respectively. In comparison, tamoxifen was found less potent PKC inhibitor at 0.1 and 0.2 mM resulting 14% and 25% PKC inhibition, respectively; lower concentrations of tamoxifen (0.025 and 0.05 mM) showed negligible PKC inhibition. Figure 2 shows endoxifen and tamoxifen induced PKC inhibition at 0.2 mM. The study demonstrated that endoxifen is about fourfold more potent PKC inhibitor than tamoxifen, and suggests its pivotal role in BPD.

In summary, we have synthesized endoxifen that inhibited PKC significantly in comparison with tamoxifen. Preclinical and clinical evidence demonstrate that PKC is an important target-perhaps the first mechanistically distinct drug target for BPD and tamoxifen is a relatively selective PKC inhibitor. This is the first report demonstrating endoxifen to be potentially a superior candidate for BPD treatment especially for those with defects in activating enzymes

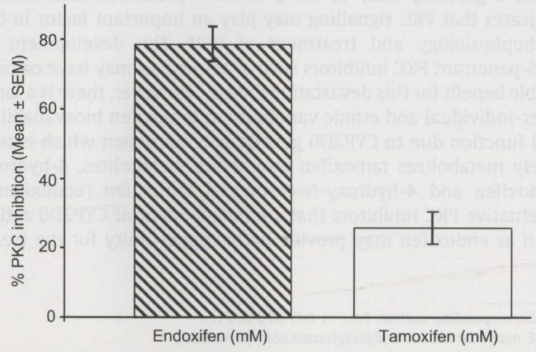

Figure 2. Percentage inhibition of PKC activity by 0.2 mM endoxifen and tamoxifen in vitro.

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for tamoxifen metabolism. Repeated daily oral administration of endoxifen up to 4 mg/kg and 8 mg/kg body weight in rats and mice, respectively, for 28 days showed no signs of toxicity (unpublished observation). Efficacy studies with endoxifen will be the subject of further investigation.

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10. *Compound* **6**: mp 56–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (m, 3H), 1.83 (m, 2H), 1.98 (m, 1H), 3.57 (m, 1H), 3.85 (m, 1H), 5.36 (t, J = 3.2 Hz, 1H), 6.93 (AB, J = 8.79, J = 2.14, 2H), 7.35 (AB, J = 8.79, J = 2.14 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 25.1, 30.2, 61.9, 96.5, 113.8, 118.3, 132.2, 156.2; HRMS (ESI), expected 278.991, observed 278.9984 ($M+Na^+$). *Compound* **3**: mp 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 3H), 1.85 (m, 1H), 2.18 (m, 1H), 3.78 (t, J = 5.9 Hz, 2H), 4.22 (t, J = 5.9 Hz, 2H,), 4.38 (t, J = 7.26 Hz, 1H), 6.86 (AB, J = 9 Hz, J = 2.14 Hz, 2H), 7.18 (m, 1H), 7.28 (m, 4H), 7.96 (AB, J = 8.78 Hz, J = 1.93 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 27.1, 41.5, 55.1, 67.9, 114.2, 126.8, 128.2, 128.8, 130.6, 130.9, 139.9, 161.7, 198.5. HRMS (ESI), expected 325.0966, observed 325.0976 ($M+Na^+$). *Compound* **9** (**Z-endoxifen**): mp 139–143 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (t, J = 7.24 Hz, 3H), 2.29 (s, 3H), 2.42 (q, J = 7.2 Hz, 2 H), 2.74 (t, J = 5.59 Hz, 3H), 3.86 (t, J = 5.56 Hz, 2H), 6.58 (d, J = 8.78 Hz, 2H), 6.71 (d, J = 8.56 Hz, 2H), 6.75 (d, J = 8.68 Hz, 2H), 6.98 (d, J = 8.2 Hz, 2H), 7.08–7.13 (m, 3H), 7.15–7.19 (m, 2H), 9.38 (br, 1H); HRMS (ESI), expected 374.2115, observed 374.2116 ($M+H^+$).
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