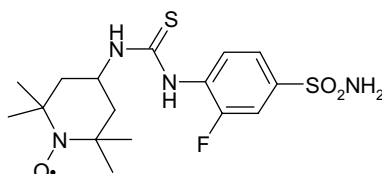


Contents

ARTICLES

- Carbonic anhydrase inhibitors: Design of spin-labeled sulfonamides incorporating TEMPO moieties as probes for cytosolic or transmembrane isozymes** pp 3475–3480

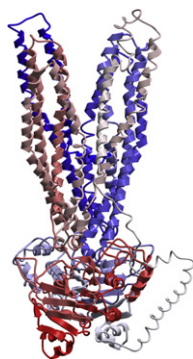
Alessandro Cecchi, Laura Ciani, Jean-Yves Winum, Jean-Louis Montero, Andrea Scozzafava, Sandra Ristori*, Claudiu T. Supuran*



K_i = 128 nM (hCA I), 12 nM (hCA II), 14 nM (hCA IX)

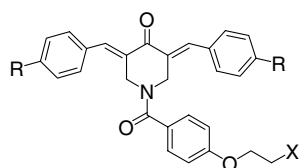
- Molecular model of the outward facing state of the human multidrug resistance protein 4 (MRP4/ABCC4)** pp 3481–3483

Aina Westrheim Ravna*, Georg Sager



- 1-[4-(2-Aminoethoxy)phenylcarbonyl]-3,5-bis-(benzylidene)-4-oxopiperidines: A novel series of highly potent revertants of P-glycoprotein associated multidrug resistance** pp 3484–3487

Umashankar Das, Joseph Molnár, Zoltán Baráth, Zsuzsanna Bata, Jonathan R. Dimmock*



R = H, CH₃, Cl, NO₂

X = -N(CH₃)₂ HCl, -N(C₂H₅)₂ HCl,

piperidine HCl, morpholine HCl, -N(CH₃)(C₂H₅)₂⁺ I⁻

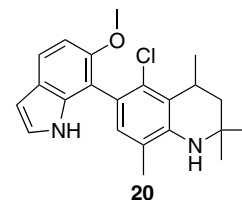
Optimal activity is shown when R is a methyl or chloro group and X is a 1-piperidyl substituent.

Discovery of nonsteroidal glucocorticoid receptor ligands based on 6-indole-1,2,3,4-tetrahydroquinolines

pp 3504–3508

Steven L. Roach*, Robert I. Higuchi, Mark E. Adams, Yan Liu,
Donald S. Karanewsky, Keith B. Marschke, Dale E. Mais,
Jeffrey N. Miner, Lin Zhi

A series of nonsteroidal glucocorticoid receptor (GR) ligands based on a 6-indole-1,2,3,4-tetrahydroquinoline scaffold are reported. Structure–activity relationship (SAR) of the pendent indole group identified compound **20** exhibiting good GR binding affinity, receptor selectivity and E-selectin repression activity.

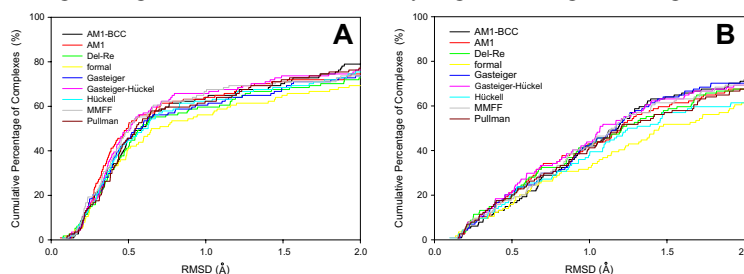


20
GR ($K_i = 1.5 \pm 0.2$ nM)
PR ($K_i = 1400 \pm 100$ nM)
MR ($K_i = 155 \pm 80$ nM)
AR ($K_i = 1500$ nM)

The effect of different electrostatic potentials on docking accuracy: A case study using DOCK5.4

pp 3509–3512

Keng-Chang Tsai, Sheng-Hung Wang, Nai-Wan Hsiao, Minyong Li*, Binghe Wang*

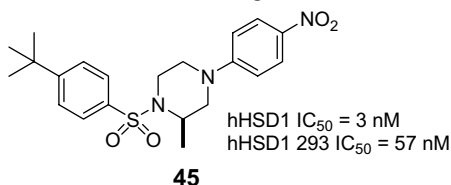


Nine different semi-empirical and empirical charges were compared their performance on the prediction of docking poses using DOCK5.4 program.

**Discovery and Initial SAR of Arylsulfonylpiperazine Inhibitors of 11 β -Hydroxysteroid Dehydrogenase Type 1 (11 β -HSD1)**

pp 3513–3516

Daqing Sun*, Zhulun Wang, Yongmei Di, Juan C. Jaen, Marc Labelle, Ji Ma, Shichang Miao, Athena Sudom,
Liang Tang, Craig S. Tomooka, Hua Tu, Stefania Ursu, Nigel Walker, Xuelei Yan, Qiuping Ye, Jay P. Powers*

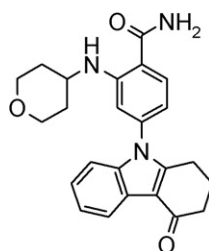


High-throughput screening of a small-molecule compound library resulted in the identification of a series of arylsulfonylpiperazines that are potent and selective inhibitors of human 11 β -Hydroxysteroid Dehydrogenase Type 1 (11 β -HSD1). Optimization of the initial lead resulted in the discovery of compound (*R*)-**45** (11 β -HSD1 $IC_{50} = 3$ nM).

Discovery of benzamide tetrahydro-4*H*-carbazol-4-ones as novel small molecule inhibitors of Hsp90

pp 3517–3521

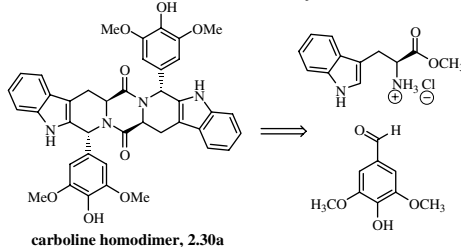
Thomas E. Barta, James M. Veal*, John W. Rice, Jeffrey M. Partridge, R. Patrick Fadden, Wei Ma,
Matthew Jenks, Lifeng Geng, Gunnar J. Hanson, Kenneth H. Huang, Amy F. Barabasz, Briana E. Foley,
James Otto, Steven E. Hall



Synthesis of diketopiperazine-based carboline homodimers and in vitro growth inhibition of human carcinomas

pp 3522–3525

Amy M. Deveau*, Nancy E. Costa, Elizabeth M. Joshi, Timothy L. Macdonald



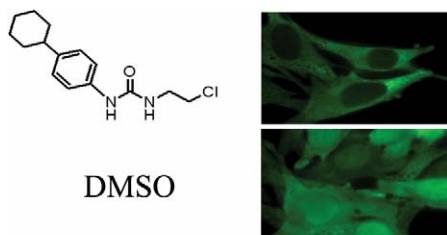
Carboline homodimers like **2.30a** were synthesized starting from D- or L-Trp-OCH₃ and shown to inhibit the in vitro growth of PC-3 and NCI-H520 human cancers.



Cycloalkyl-substituted aryl chloroethylureas inhibiting cell cycle progression in G₀/G₁ phase and thioredoxin-1 nuclear translocation

pp 3526–3531

Jessica S. Fortin*, Marie-France Côté, Jacques Lacroix, Alexandre Patenaude, Éric Petitclerc, René C.-Gaudreault*



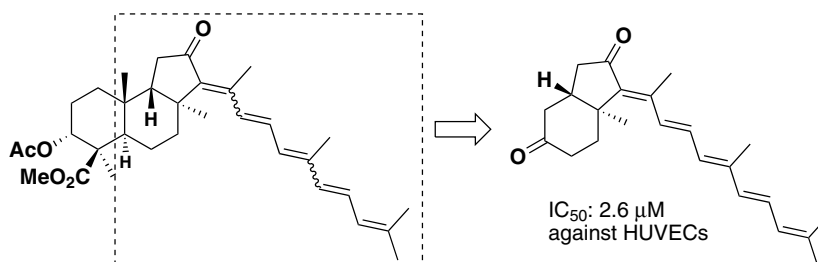
Green fluorescence = thioredoxin-1



Synthesis of BC-ring model of globostellatic acid X methyl ester, an anti-angiogenic substance from marine sponge

pp 3532–3535

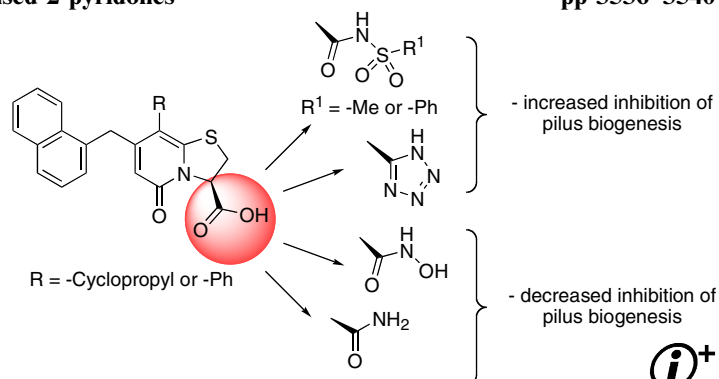
Naoyuki Kotoku, Nao Tamada, Asami Hayashi, Motomasa Kobayashi*



Carboxylic acid isosteres improve the activity of ring-fused 2-pyridones that inhibit pilus biogenesis in *E. coli*

pp 3536–3540

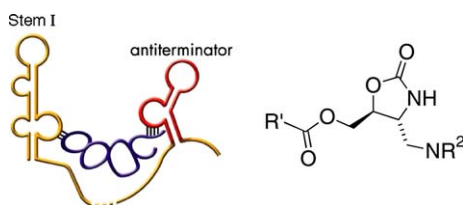
Veronica Åberg, Pralay Das, Erik Chorell, Mattias Hedenström, Jerome S. Pinkner, Scott J. Hultgren, Fredrik Almqvist*



4,5-Disubstituted oxazolidinones: High affinity molecular effectors of RNA function

pp 3541–3544

Rajaneesh Anupam, Abhijit Nayek, Nicholas J. Green, Frank J. Grundy, Tina M. Henkin, John A. Means, Stephen C. Bergmeier, Jennifer V. Hines*

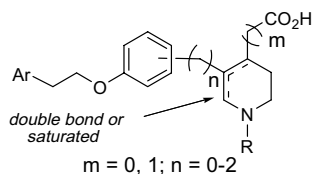


Novel oxazolidinone RNA ligands that modulate T box riboswitch function are reported.

**Design, synthesis, and structure–activity relationships of piperidine and dehydropiperidine carboxylic acids as novel, potent dual PPAR α/γ agonists**

pp 3545–3550

Xiang-Yang Ye*, Yi-Xin Li, Dennis Farrelly, Neil Flynn, Liquan Gu, Kenneth T. Locke, Jonathan Lippy, Kevin O'Malley, Celeste Twamley, Litao Zhang, Denis E. Ryono, Robert Zahler, Narayanan Hariharan, Peter T. W. Cheng*



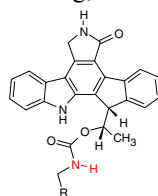
Piperidine and dehydropiperidine acid

The SAR of substituted dehydropiperidine and piperidine-4-carboxylic acid analogs as novel, potent dual PPAR α/γ agonists is discussed. A rare double bond migration in dehydropiperidine series has been observed and is discussed.

**TrkA kinase inhibitors from a library of modified and isosteric Staurosporine aglycone**

pp 3551–3555

Rabindranath Tripathy*, Thelma S. Angeles, Shi X. Yang, John P. Mallamo



12a, R = Me
IC₅₀ = 8 nM
Cell IC₅₀ = 18 nM

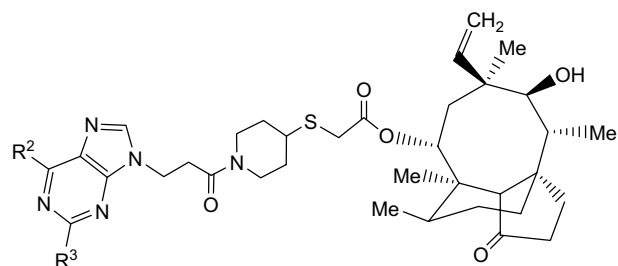
Discovery of TrkA kinase inhibitors from a library of a modified Staurosporine aglycone along with their potency, cellular data, selectivity profile and anti-tumor properties are discussed.

Pleuromutilin derivatives having a purine ring. Part 1: New compounds with promising antibacterial activity against resistant Gram-positive pathogens

pp 3556–3561

Yoshimi Hirokawa, Hironori Kinoshita*, Tomoyuki Tanaka, Takanori Nakamura, Koichi Fujimoto, Shigeki Kashimoto, Tsuyoshi Kojima, Shiro Kato

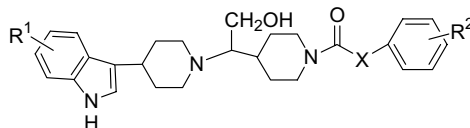
In the course of our research aimed at the discovery of the metabolically stable pleuromutilin analogues with potent antibacterial activity against Gram-positive pathogens, we have found two promising compounds, bearing a purine ring and having potential as novel antibacterial agents for use in human.



Substituted dipiperidine alcohols as potent CCR2 antagonists

pp 3562–3564

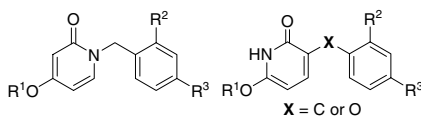
Mingde Xia*, Cuifen Hou, Duane DeMong, Scott Pollack, Meng Pan, James Brackley, Monica Singer, Michele Matheis, Druie Cavender, Michael Wachter



Structure–activity relationship studies led to the discovery of substituted dipiperidine alcohols as potent CCR2 antagonists displaying IC₅₀ values in the nanomolar or subnanomolar range.

Design and synthesis of 2-pyridones as novel inhibitors of the *Bacillus anthracis* enoyl-ACP reductase pp 3565–3569

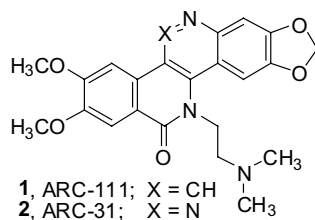
Suresh K. Tipparaju, Sipak Joyasawal, Sara Forrester, Debbie C. Mulhearn, Scott Pegan, Michael E. Johnson*, Andrew D. Mesecar*, Alan P. Kozikowski*



Novel 2-pyridone derivatives were synthesized and shown to be potent inhibitors of enoyl-ACP reductase from *Bacillus anthracis*.

**Facile formation of hydrophilic derivatives of 5*H*-8,9-dimethoxy-5-[2-(*N,N*-dimethylamino)ethyl]-2,3-methylenedioxydibenzo[*c,h*] [1,6]naphthyridin-6-one (ARC-111) and its 12-aza analog via quaternary ammonium intermediates** pp 3570–3572

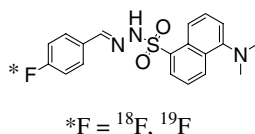
Wei Feng, Mavurapu Satyanarayana, Yuan-chin Tsai, Angela A. Liu, Leroy F. Liu, Edmond J. LaVoie*



Several new TOP1-targeting agents were prepared using the *N,N,N*-trimethyl quaternary ammonium salts of either **1** or **2**.

Synthesis, biological evaluation and radiochemical labeling of a dansylhydrazone derivative as a potential imaging agent for apoptosis pp 3573–3577

Wenbin Zeng, Min-liang Yao, David Townsend, George Kabalka, Jonathan Wall, Michael Le Puil, John Biggerstaff, Weimin Miao*

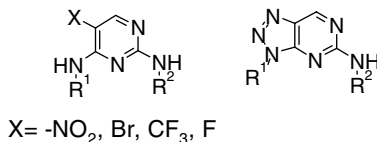


Design, synthesis, and biological evaluation of dansylhydrazones were reported.



2,5-Diaminopyrimidines and 3,5-disubstituted azapurines as inhibitors of glycogen synthase kinase-3 (GSK-3) pp 3578–3581

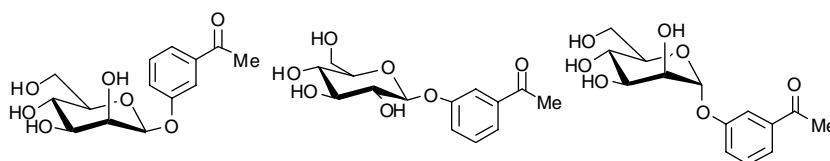
Christopher Lum*, Jeff Kahl, Linda Kessler, Jeff Kucharski, Jan Lundström, Stephen Miller, Hiroshi Nakanishi, Yazhong Pei, Kent Pryor, Edward Roberts, Lubomir Sebo, Robert Sullivan, Jan Urban, Zhijun Wang



The structure–activity relationships of potent and selective pyrimidine- and azapurine-based inhibitors of glycogen synthase kinase-3 (GSK-3) are reported.

Synthesis of new UV-B light absorbents: (Acetylphenyl)glycosides with antioxidant activities pp 3582–3584

Takashi Otani, Tetsu Tsubogo, Naoki Furukawa, Takao Saito*, Katsumi Uchida, Kanako Iwama, Yuki Kanai, Hirofumi Yajima*

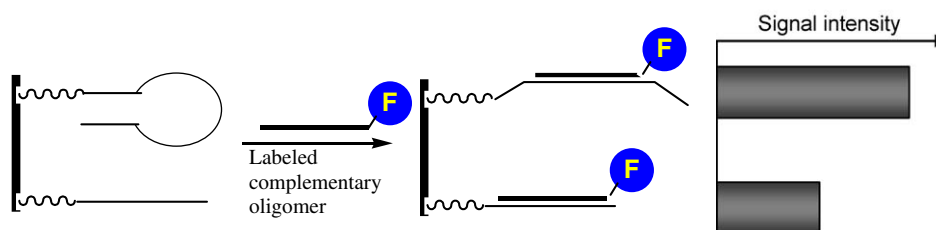


Synthesis of (acetylphenyl)glycosides, new UV-B light absorbents with antioxidant, was reported.



Oligonucleotide microarrays with stem–loop probes: Enhancing the hybridization of nucleic acids for sensitive analysis pp 3585–3588

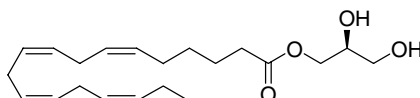
Shweta Mahajan, Archana Swami, Dalip Sethi, P. Kumar, K.C. Gupta*



Here, we have demonstrated that the dynamics of nucleic acid hybridization in microarrays depend on the physical structure of the immobilized species.

Monoglycerides from the brown alga *Sargassum sagamianum*: Isolation, synthesis, and biological activity pp 3589–3592

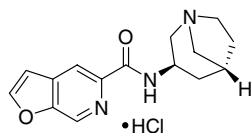
Hyeun Wook Chang, Kyoung Hwa Jang, Doohyun Lee, Hee Ryong Kang, Tae-Yoon Kim, Bong Ho Lee, Byoung Wook Choi, Sanghee Kim*, Jongheon Shin*



The isolation, synthesis, and bioactivity of fatty acid-derived monoglycerides are described.

Discovery of *N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]furo[2,3-*c*]pyridine-5-carboxamide as an agonist of the $\alpha 7$ nicotinic acetylcholine receptor: In vitro and in vivo activity pp 3611–3615

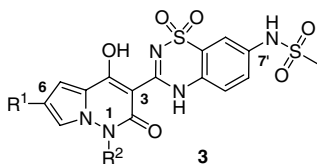
Brad A. Acker, E. Jon Jacobsen, Bruce N. Rogers, Donn G. Wishka, Steven C. Reitz, David W. Piotrowski, Jason K. Myers, Mark L. Wolfe, Vincent E. Groppi, Bruce A. Thornburgh, Paula M. Tinholt, Rodney R. Walters, Barbara A. Olson, Laura Fitzgerald, Brian A. Staton, Thomas J. Raub, Michael Krause, Kai S. Li, William E. Hoffmann, Mihaly Hajos, Raymond S. Hurst and Daniel P. Walker*

**PHA-709829**

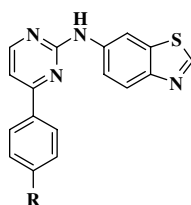
K_i ($\alpha 7$ nAChR) = 3.4 nM
 EC_{50} ($\alpha 7$ -5HT₃ chimera) = 46 nM

Pyrrolo[1,2-*b*]pyridazin-2-ones as potent inhibitors of HCV NS5B polymerase pp 3616–3621

Frank Ruebsam,* Stephen E. Webber, Martin T. Tran, Chinh V. Tran, Douglas E. Murphy, Jingjing Zhao, Peter S. Dragovich, Sun Hee Kim, Lian-Sheng Li, Yuefen Zhou, Qing Han, Charles R. Kissinger, Richard E. Showalter, Matthew Lardy, Amit M. Shah, Mei Tsan, Rupal Patel, Laurie A. LeBrun, Ruhi Kamran, Maria V. Sergeeva, Darian M. Bartkowski, Thomas G. Nolan, Daniel A. Norris and Leo Kirkovsky

**3**
Synthesis and structure–activity relationship of aminopyrimidine IKK2 inhibitors pp 3622–3627

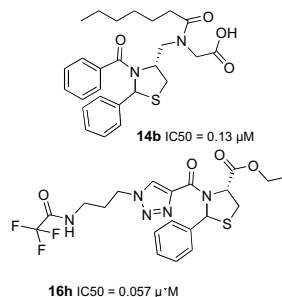
Alistair H. Bingham, Richard J. Davenport,* Richard Fosbeary, Lewis Gowers, Roland L. Knight, Christopher Lowe, David A. Owen, David M. Parry and Will R. Pitt

**R**

The synthesis and structure–activity relationship of a novel series of aminopyrimidines is exemplified. Results of key compounds from within this series in the E-selectin reporter cell assay are also reported.

Design, synthesis and evaluation of potent thymidylate synthase X inhibitors pp 3628–3631

F. Esra Önen, Yap Boum, Claire Jacquement, Maria Vittoria Spanedda, Nada Jaber, Daniel Scherman, Hannu Myllykallio*, Jean Herscovici*

**16h** IC_{50} = 0.057 μ M

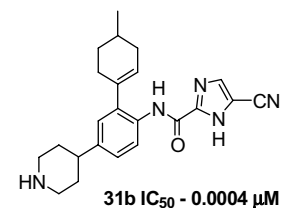
The synthesis of potent thymidylate synthase X inhibitors is reported.

Structure-based optimization of a potent class of arylamide FMS inhibitors

pp 3632–3637

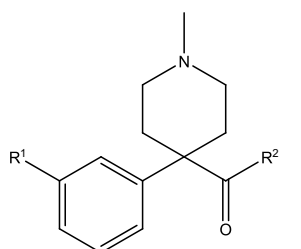
Sanath K. Meegalla, Mark J. Wall, Jinsheng Chen, Kenneth J. Wilson, Shelley K. Ballentine, Renee L. DesJarlais, Carsten Schubert, Carl S. Crysler, Yanmin Chen, Christopher J. Molloy, Margery A. Chaikin, Carl L. Manthey, Mark R. Player, Bruce E. Tomczuk and Carl R. Illig*

Potent FMS inhibitors possessing a 1,2,4-phenylenetriamine core structure were optimized with the aid of structure-based modeling to alleviate the potential for quinonediimine reactive intermediate formation and to obtain equally potent FMS inhibitors with no detectable IDR liability.

**Opioids and efflux transporters. Part 3: P-glycoprotein substrate activity of 3-hydroxyl addition to meperidine analogs**

pp 3638–3640

Susan L. Mercer, Christopher W. Cunningham, Natalie D. Eddington and Andrew Coop*

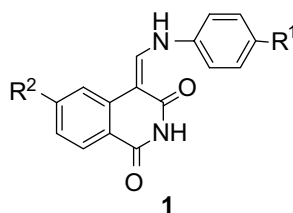


Compound	R ¹	R ²
Meperidine	H	OCH ₂ CH ₃
Ketone analog	H	CH ₂ CH ₃
Bemidone	OH	OCH ₂ CH ₃
Ketobemidone	OH	CH ₂ CH ₃

**Lead identification to generate isoquinolinedione inhibitors of insulin-like growth factor receptor (IGF-1R) for potential use in cancer treatment**

pp 3641–3645

Scott C. Mayer,* Annette L. Banker, Frank Boschelli, Li Di, Mark Johnson, Cynthia Hess Kenny, Girija Krishnamurthy, Kristina Kutterer, Franklin Moy, Susan Petusky, Malini Ravi, Diane Tkach, Hwei-Ru Tsou and Weixin Xu

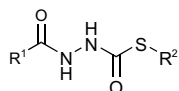


The strategies, synthesis, and SAR behind novel isoquinolinedione IGFR inhibitors (**1**) are reported.

Design, synthesis, and evaluation of inhibitors of cathepsin L: Exploiting a unique thiocarbamate chemotype

pp 3646–3651

Michael C. Myers, Parag P. Shah, Mary Pat Beavers, Andrew D. Napper, Scott L. Diamond, Amos B. Smith, III* and Donna M. Huryn*



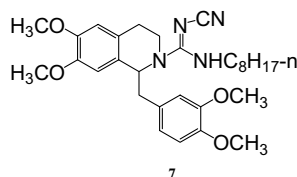
Cathepsin L Inhibitors

A novel series of thiocarbamates was designed and synthesized to probe the structural requirements for cathepsin L inhibitory activity. These studies were guided by molecular docking studies using coordinates of a papain–inhibitor complex as a model for cathepsin L, and led to an understanding of the specific binding interactions as well as appropriate carbonyl reactivity required for potent activity. Furthermore, a highly potent inhibitor of cathepsin L (IC₅₀ 7 nM) was identified a result of these studies.

Design and synthesis of tetrahydroisoquinoline derivatives as potential multidrug resistance reversal agents in cancer

pp 3652–3655

Yu Li, Hui-bin Zhang*, Wen-long Huang*, Yun-man Li



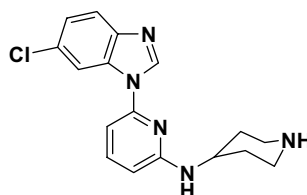
Synthesis and biological evaluation of potent MDR reversal agent **7** are reported.

IRAK-4 inhibitors. Part III: A series of imidazo[1,2-*a*]pyridines

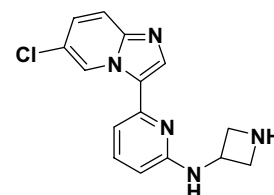
pp 3656–3660

George M. Buckley, Richard Fosbeary, Joanne L. Fraser, Lewis Gowers, Alicia P. Higuero, Lynwen A. James, Kerry Jenkins*, Stephen R. Mack, Trevor Morgan, David M. Parry, William R. Pitt, Oliver Rausch, Marianna D. Richard and Verity Sabin

Following the identification of a potent IRAK-4 inhibitor through routine project cross screening, a novel class of IRAK-4 inhibitor was established. The SAR of imidazo[1,2-*a*]pyridino-pyridines and benzimidazolo-pyridines was explored.



7, IRAK-4 IC₅₀ 3nM



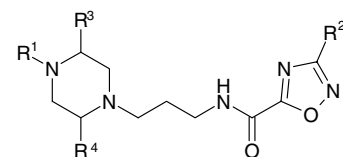
44, IRAK-4 IC₅₀ 6nM (LE ~0.52)
TNFα inhibition 54nM

Novel aryl and heteroaryl substituted *N*-[3-(4-phenylpiperazin-1-yl)propyl]-1,2,4-oxadiazole-5-carboxamides as selective GSK-3 inhibitors

pp 3661–3666

Angela G. Koryakova, Yan A. Ivanenkov, Elena A. Ryzhova, Elena A. Bulanova, Ruben N. Karapetian, Olga V. Mikitas, Eugeny A. Katrukha, Vasily I. Kazey, Ilya Okun, Dmitry V. Kravchenko, Yan V. Lavrovsky, Oleg M. Korzinov and Alexandre V. Ivachtchenko*

Synthesis, biological evaluation and structure-activity relationships for a series of novel nonpeptide small molecule inhibitors of GSK-3β kinase.



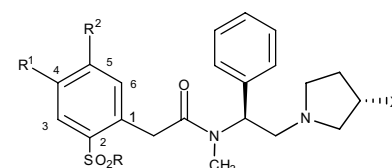
R¹ = substituted phenyl
R² = pyridyl, pyrimidyl, benzodioxolyl
R³, R⁴ = H, Me

**Use of receptor chimeras to identify small molecules with high affinity for the dynorphin A binding domain of the κ opioid receptor**

pp 3667–3671

Virendra Kumar*, Deqi Guo, Michael Marella, Joel A. Cassel, Robert N. DeHaven, Jeffrey D. Daubert and Erik Mansson


A series of 2-substituted sulfamoyl arylacetamides of general structure **2** were prepared as potent κ opioid receptor agonists for the dynorphin A binding domain.



2 (X = H, OH)

OTHER CONTENTS**Summary of instructions to authors****p I**

*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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