

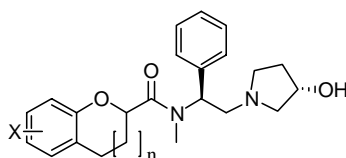
Contents

ARTICLES

Potent and highly selective kappa opioid receptor agonists incorporating chroman- and 2,3-dihydrobenzofuran-based constraints

pp 5114–5119

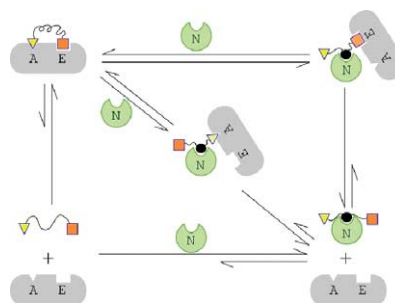
Guo-Hua Chu,* Minghua Gu, Joel A. Cassel, Serge Belanger, Thomas M. Graczyk, Robert N. DeHaven, Nathalie Conway-James, Mike Koblish, Patrick J. Little, Diane L. DeHaven-Hudkins and Roland E. Dolle



Transforming bivalent ligands into retractable enzyme inhibitors through polypeptide–protein interactions

pp 5120–5123

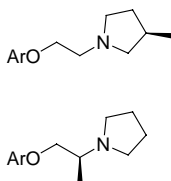
Dmitri Tolkathev, Anna Vinogradova and Feng Ni*



Estrogen receptor ligands. Part 14: Application of novel antagonist side chains to existing platforms

pp 5124–5128

Timothy A. Blizzard,* Jerry D. Morgan, II, Wanda Chan, Elizabeth T. Birzin, Lee-Yuh Pai, Edward C. Hayes, Carolyn A. DaSilva, Ralph T. Mosley, Yi Tien Yang, Susan P. Rohrer, Frank DiNinno and Milton L. Hammond



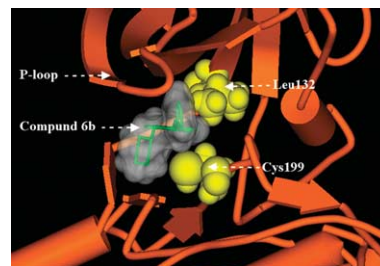
Two novel side chains which had previously been found to enhance antagonist activity in the dihydrobenzoxathiin SERM series were applied to three existing platforms. The novel side chains did not improve the antagonist activity of the existing platforms.

Structural basis for the GSK-3 β binding affinity and selectivity against CDK-2 of 1-(4-aminofurazan-3-yl)-5-dialkylaminomethyl-1*H*-[1,2,3] triazole-4-carboxylic acid derivatives

pp 5129–5135

Vineet Pande and Maria J. Ramos*

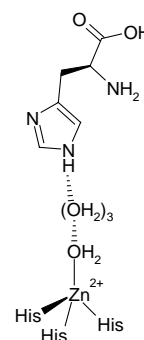
A novel structural class of glycogen synthase kinase-3 β inhibitors is modeled. The proposed binding modes justify the observed structure–activity relationships and provide a structural basis for the high selectivity of these inhibitors against cyclin dependent kinase-2.



Carbonic anhydrase activators: X-ray crystal structure of the adduct of human isozyme II with L-histidine as a platform for the design of stronger activators

pp 5136–5141

Claudia Temperini, Andrea Scozzafava, Luca Puccetti and Claudiu T. Supuran*

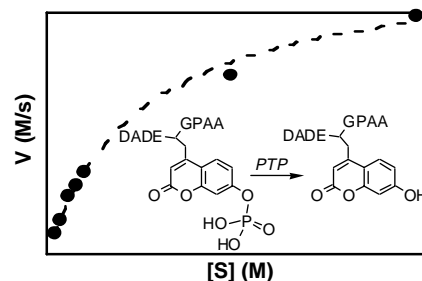


Highly sensitive peptide-based probes for protein tyrosine phosphatase activity utilizing a fluorogenic mimic of phosphotyrosine

pp 5142–5145

Sayantan Mitra and Amy M. Barrios*

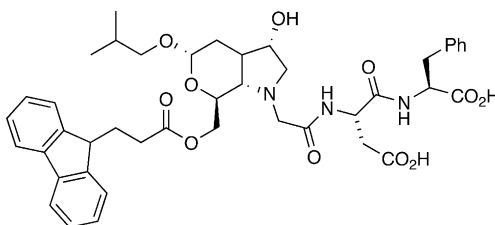
The high-yielding synthesis of an enantiomerically pure phosphocoumarin-based amino acid and its incorporation into peptides are reported. Peptides containing this new amino acid serve as sensitive fluorogenic probes for PTP activity.



Design, synthesis, and evaluation of octahydropyranopyrrole-based inhibitors of mammalian ribonucleotide reductase

pp 5146–5149

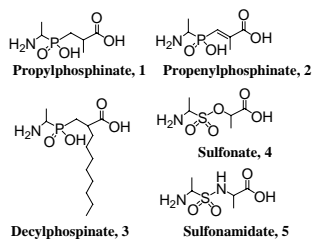
Michael J. Fuertes, Jaskiran Kaur, Prasant Deb, Barry S. Cooperman and Amos B. Smith, III*



Phosphinate, sulfonate, and sulfonamidate dipeptides as potential inhibitors of *Escherichia coli* aminopeptidase N

pp 5150–5153

Ke-Wu Yang, Frank C. Golich, Tara K. Sigdel and Michael W. Crowder*

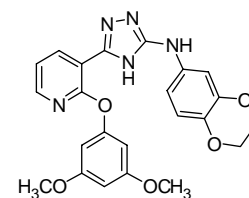


Synthesis and structure–activity relationships of 1,2,4-triazoles as a novel class of potent tubulin polymerization inhibitors

pp 5154–5159

Xiaohu Ouyang,* Xiaoling Chen, Evgueni L. Piatnitski, Alexander S. Kiselyov, Hai-Ying He, Yunyu Mao, Vatee Pattaropong, Yang Yu, Ki H. Kim, John Kincaid, Leon Smith, II, Wai C. Wong, Sui Ping Lee, Daniel L. Milligan, Asra Malikzay, James Fleming, Jason Gerlak, Dhanvanthri Deevi, Jacqueline F. Doody, Hui-Hsien Chiang, Sheetal N. Patel, Ying Wang, Robin L. Rolser, Paul Kussie, Marc Labelle and M. Carolina Tuma

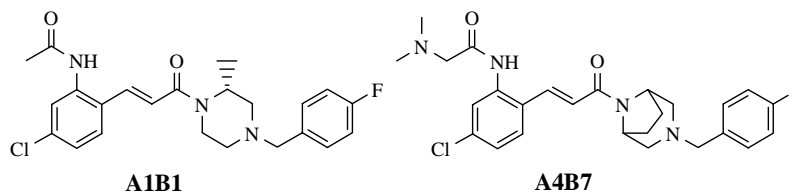
The synthesis and SAR studies on triazole-containing tubulin inhibitor class are reported.

30 EC₅₀ = 3.6 nM

Novel CCR1 antagonists with oral activity in the mouse collagen induced arthritis

pp 5160–5164

Laszlo Revesz,* Birgit Bollbuck, Thomas Buhl, Joerg Eder, Ronald Esser, Roland Feifel, Richard Heng, Peter Hiestand, Benedicte Jachez-Demange, Pius Loetscher, Helmut Sparrer, Achim Schlapbach and Rudolf Waelchli



A1B1 and A4B7 showed oral activity in the mouse collagen induced arthritis.

Quantitative structure–activity relationship studies of vitamin D receptor affinity for analogues of 1 α ,25-dihydroxyvitamin D₃. 1: WHIM descriptors

pp 5165–5169

Maykel Pérez González,* Pedro Lois Suárez, Yagamare Fall and Generosa Gómez

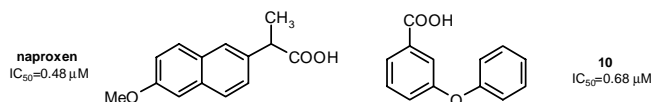
The WHIM approach has been applied to the study of the VDR affinity of 86 vitamin D analogues with excellent results. Three different approaches failed to give satisfactory models for this property.



Nonsteroidal anti-inflammatory drugs and their analogues as inhibitors of aldo-keto reductase AKR1C3: New lead compounds for the development of anticancer agents

pp 5170–5175

Stanislav Gobec,* Petra Brožič and Tea Lanišnik Rižner

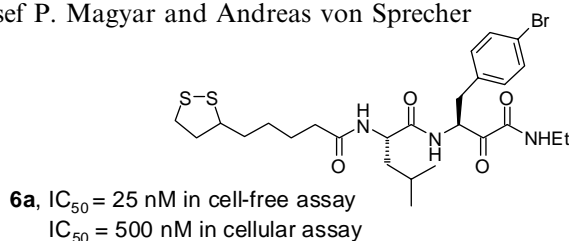


New inhibitors of human recombinant AKR1C3 are reported. Some compounds inhibited the enzyme in submicromolar range.

Novel cell-penetrating α -keto-amide calpain inhibitors as potential treatment for muscular dystrophy

pp 5176–5181

Cyrille Lescop,* Holger Herzner, Hervé Siendt, Reto Bolliger, Marco Henneböhle, Philipp Weyermann, Alexandre Briguët, Isabelle Courdier-Fruh, Michael Erb, Mark Foster, Thomas Meier, Josef P. Magyar and Andreas von Sprecher



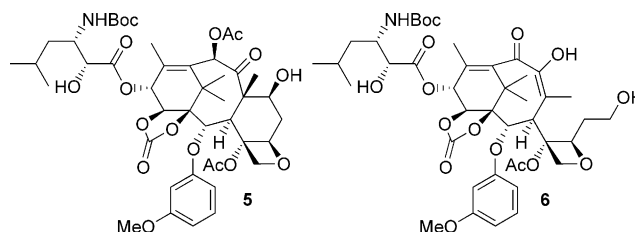
The synthesis of novel α -keto-amide calpain inhibitors bearing a lipoyl residue is reported. They demonstrated an improved activity in muscle cells compared to MDL28170, referring to increased cell membrane permeability.

Synthesis and biological evaluation of methoxylated analogs of the newer generation taxoids IDN5109 and IDN5390

pp 5182–5186

Luciano Barboni,* Roberto Ballini, Guido Giarlo, Giovanni Appendino, Gabriele Fontana and Ezio Bombardelli

Starting from 10-deacetylbaccatin III, the 2-debenzoyl-2-*m*-methoxybenzoyl analogs of the newer generation taxoids IDN5109 and IDN5390 were synthesized. The biological evaluation of these compounds (**5** and **6**, respectively) showed a general increase of cytotoxicity, as observed in first-generation anticancer taxanes.

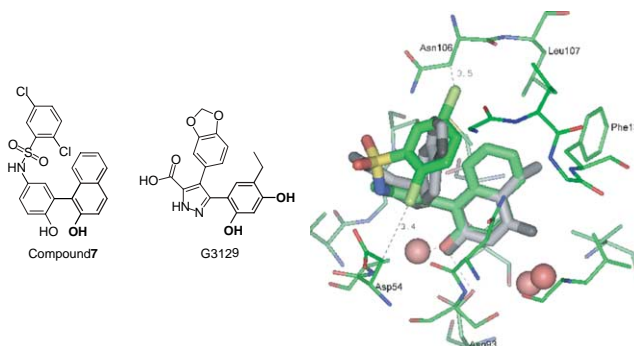


Structure-based discovery of a new class of Hsp90 inhibitors

pp 5187–5191

Xavier Barril,* Paul Brough, Martin Drysdale, Roderick E. Hubbard, Andrew Massey, Allan Surgenor and Lisa Wright

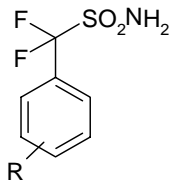
Docking-based virtual screening identified 1-(2-phenol)-2-naphthol compounds as a new class of Hsp90 inhibitors of low to sub-micromolar potency. Here we report the binding affinities and cellular activities of several members of this class. A high resolution crystal structure of the most potent compound reveals its binding mode in the ATP binding site of Hsp90, providing a rationale for the observed activity of the series and suggesting strategies for developing compounds with improved properties.



Carbonic anhydrase inhibitors: Inhibition of the human isozymes I, II, VA, and IX with a library of substituted difluoromethanesulfonamides

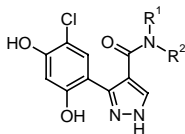
pp 5192–5196

Alessandro Cecchi, Scott D. Taylor, Yong Liu, Bryan Hill, Daniela Vullo, Andrea Scozzafava and Claudiu T. Supuran*

**3-(5-chloro-2,4-dihydroxyphenyl)-Pyrazole-4-carboxamides as inhibitors of the Hsp90 molecular chaperone**

pp 5197–5201

Paul A. Brough,* Xavier Barril, Mandy Beswick, Brian W. Dymock, Martin J. Drysdale, Lisa Wright, Kate Grant, Andrew Massey, Allan Surgenor and Paul Workman

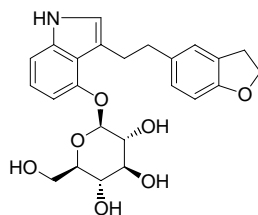


Structure-based drug design using information from X-ray structures of ligands bound to the molecular chaperone Hsp90 has been used to assist in the design of 3-(5-chloro-2,4-dihydroxyphenyl)-pyrazole-4-carboxamides, several of which can make a hydrogen bond to Phe138 of the protein, affording increased binding potency.

**Heteroaryl-*O*-glucosides as novel sodium glucose co-transporter 2 inhibitors. Part 1**

pp 5202–5206

Xiaoyan Zhang,* Maud Urbanski, Mona Patel, Roxanne E. Zeck, Geoffrey G. Cox, Haiyan Bian, Bruce R. Conway, Mary Pat Beavers, Philip J. Rybczynski and Keith T. Demarest

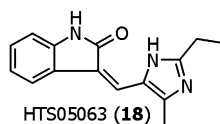


A series of benzo-fused heteroaryl-*O*-glucosides was synthesized and evaluated in SGLT1 and 2 cell-based functional assays. Indole-*O*-glucoside **10a** and benzimidazole-*O*-glucoside **18** exhibited potent in vitro SGLT2 inhibitory activity.

In silico fragment-based discovery of indolin-2-one analogues as potent DNA gyrase inhibitors

pp 5207–5210

Marko Oblak, Simona Goljč Grdadolnik, Miha Kotnik, Roman Jerala, Metka Filipič and Tomaž Šolmajer*

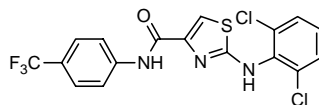


We report here compounds with indolin-2-one scaffold as potent DNA gyrase inhibitors. Using the tools of virtual screening and NMR spectroscopy indolin-2-one analogue HTS05063 (**18**) that inhibits the DNA gyrase supercoiling activity in the low micromolar range was discovered.

Synthesis and evaluation of thiazole carboxamides as vanilloid receptor 1 (TRPV1) antagonists

pp 5211–5217

Ning Xi,* Yunxin Bo, Elizabeth M. Doherty, Christopher Fotsch, Narender R. Gavva, Nianhe Han, Randall W. Hungate, Lana Klionsky, Qingyian Liu, Rami Tamir, Shimin Xu, James J. S. Treanor and Mark H. Norman

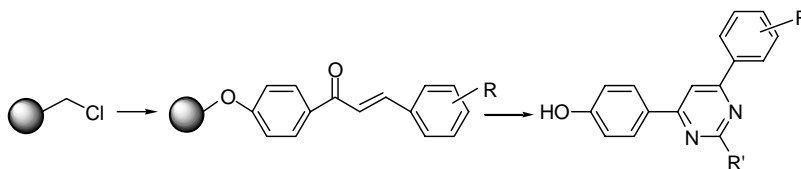


A series of thiazole carboxamides was prepared and evaluated as TRPV1 receptor antagonists. IC₅₀ values of ca. 0.050 mM were achieved in either capsaicin- or acid-mediated calcium influx assays in TRPV1-expressing CHO cells.

A small library of trisubstituted pyrimidines as antimalarial and antitubercular agents

pp 5218–5221

Anu Agarwal, Kumkum Srivastava, S. K. Puri, S. Sinha and Prem M. S. Chauhan*

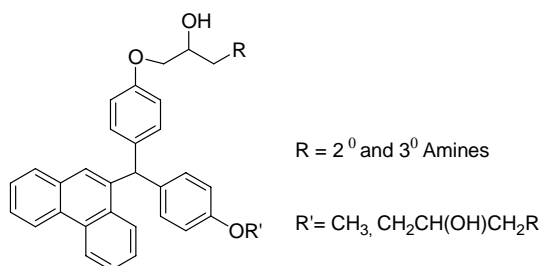


Out of the 20 compounds synthesized, 16 compounds have shown in vitro antimalarial activity against *Plasmodium falciparum* in the range of 0.25–2 µg/mL and 8 compounds have shown antitubercular activity against *Mycobacterium tuberculosis* H₃₇Ra, at a concentration of 12.5 µg/mL.

Synthesis and antitubercular activity of 2-hydroxy-aminoalkyl derivatives of diaryloxy methano phenanthrenes

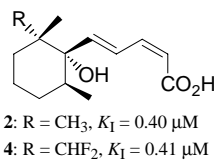
pp 5222–5225

Gautam Panda,* Shagufta, Anil K. Srivastava and Sudhir Sinha

**A lead compound for the development of ABA 8'-hydroxylase inhibitors**

pp 5226–5229

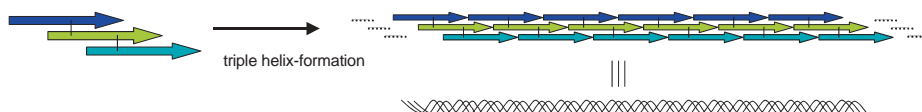
Kotomi Ueno, Hidetaka Yoneyama, Shigeki Saito, Masaharu Mizutani, Kanzo Sakata, Nobuhiro Hirai and Yasushi Todoroki*



Self-complementary peptides for the formation of collagen-like triple helical supramolecules

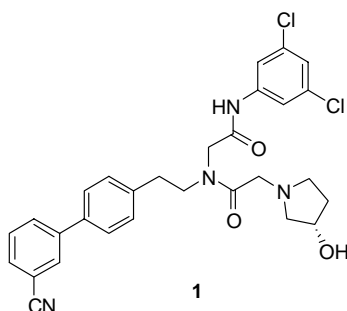
pp 5230–5233

Takaki Koide,* Daisuke L. Homma, Shinichi Asada and Kouki Kitagawa

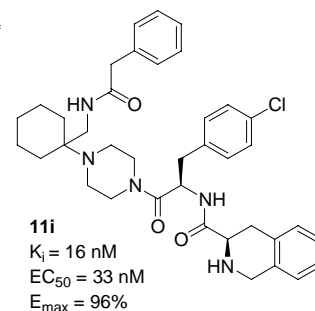
**Biaryl diamides as potent melanin concentrating hormone receptor 1 antagonists**

pp 5234–5236

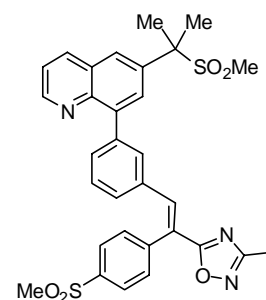
Anandan Palani,* Sherry Shapiro, Mark D. McBriar, John W. Clader, William J. Greenlee, Kim O'Neill and Brian Hawes

**Structure–activity relationship studies on a series of cyclohexylpiperazines bearing a phenylacetamide as ligands of the human melanocortin-4 receptor** pp 5237–5240

Joseph Pontillo, Joe A. Tran, Nicole S. White, Melissa Arellano, Beth A. Fleck, Dragan Marinkovic, Fabio C. Tucci, John Saunders, Alan C. Foster and Chen Chen*

**Discovery of a substituted 8-arylquinoline series of PDE4 inhibitors: Structure–activity relationship, optimization, and identification of a highly potent, well tolerated, PDE4 inhibitor** pp 5241–5246

Dwight Macdonald,* Anthony Mastracchio, Hélène Perrier, Daniel Dubé, Michel Gallant, Patrick Lacombe, Denis Deschênes, Bruno Roy, John Scheigetz, Kevin Bateman, Chun Li, Laird A. Trimble, Stephen Day, Nathalie Chauret, Deborah A. Nicoll-Griffith, Jose M. Silva, Zheng Huang, France Laliberté, Susana Liu, Diane Ethier, Doug Pon, Eric Muise, Louise Boulet, Chi Chung Chan, Angela Styhler, Stella Charleson, Joseph Mancini, Paul Masson, David Claveau, Donald Nicholson, Mervyn Turner, Robert N. Young and Yves Girard



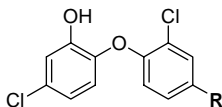
The discovery and SAR of a new series of substituted 8-arylquinoline PDE4 inhibitors are described. From this series of compounds, the development candidate L-454,560 was selected.

L-454,560

Synthesis, biological activity, and X-ray crystal structural analysis of diaryl ether inhibitors of malarial enoyl acyl carrier protein reductase. Part 1: 4'-Substituted triclosan derivatives

pp 5247–5252

Joel S. Freundlich,* John W. Anderson, Dimitri Sarantakis, Hong-Ming Shieh, Min Yu, Juan-Carlos Valderramos, Edinson Lucumi, Mack Kuo, William R. Jacobs, Jr., David A. Fidock, Guy A. Schiehsler, David P. Jacobus and James C. Sacchettini

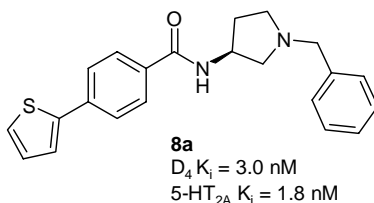


Nanomolar inhibitors of *P. falciparum* enoyl acyl carrier protein reductase are presented that demonstrate potent anti-parasitic efficacy.

***N*-[(3*S*)-1-Benzylpyrrolidin-3-yl]-(2-thienyl)benzamides: Human dopamine D₄ ligands with high affinity for the 5-HT_{2A} receptor**

pp 5253–5256

Jalaj Arora, Michel Bordeleau, Laurence Dube, Keith Jarvie, Lucy Mazzocco, Jack Peragine, Ashok Tehim and Ian Egle*

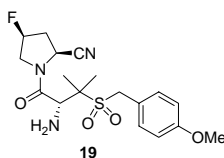


A series of *N*-[(3*S*)-1-benzylpyrrolidin-3-yl]-(2-thienyl)benzamides **8** has been prepared and found to bind with high affinity to the human D₄ (hD₄) and 5-HT_{2A} receptors. Several compounds displayed selectivity for these receptors versus hD₂ and α₁ adrenergic receptors of over 500-fold.

2-Cyano-4-fluoro-1-thiovalylpyrrolidine analogues as potent inhibitors of DPP-IV

pp 5257–5261

Curt D. Haffner,* Darryl L. McDougald, Steven M. Reister, Brian D. Thompson, Christopher Conlee, Jing Fang, Jonathan Bass, James M. Lenhard, Dallas Croom, Melissa B. Secosky-Chang, Thaddeus Tomaszek, Donavon McConn, Kevin Wells-Knecht and Paul R. Johnson

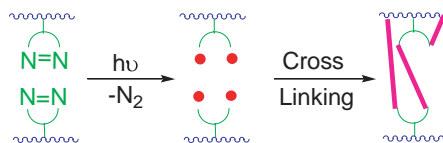


We report the synthesis and biological activity of a series of 2-cyano-4-fluoro-1-thiovalylpyrrolidine inhibitors of DPP-IV. Within this series, compound **19** provided a potent, selective, and orally active DPP-IV inhibitor which demonstrated a very long duration of action in both rat and dog.

Photocurable hard and porous biomaterials from ROMP precursors cross-linked with diyl radicals

pp 5262–5265

Eric Enholm,* Aarti Joshi and Dennis L. Wright



A combination of (ROMP) ring-opening metathesis polymerization and diradical (diyl) cross-linking provides a new access to hard biomaterials and potential artificial bone replacements.

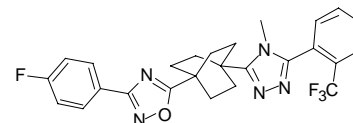


Discovery of 4-heteroaryl-bicyclo[2.2.2]octyltriazoles as potent and selective inhibitors of 11 β -HSD1: Novel therapeutic agents for the treatment of metabolic syndrome

pp 5266–5269

Xin Gu,* Jasminka Dragovic, Gloria C. Koo, Sam L. Koprak, Cheryl LeGrand, Steven S. Mundt, Kashmira Shah, Marty S. Springer, Eugene Y. Tan, Rolf Thieringer, Anne Hermanowski-Vosatka, Hratch J. Zokian, James M. Balkovec and Sherman T. Waddell

Heteroaryl substituted bicyclo[2.2.2]octyltriazoles have been shown to be potent and selective inhibitors of 11 β -hydroxysteroid dehydrogenase type I (11 β -HSD1) with excellent pharmacokinetic profiles. Compound **11** is a 2.2 nM inhibitor of human 11 β -HSD1 enzyme.

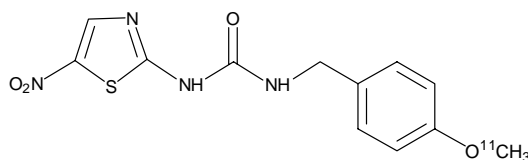


11 hHSD1 IC₅₀ = 2.2 nM
hHSD2 IC₅₀ > 2000 nM

Synthesis and ex vivo evaluation of carbon-11 labelled *N*-(4-methoxybenzyl)-*N'*-(5-nitro-1,3-thiazol-2-yl)urea ([¹¹C]AR-A014418): A radiolabelled glycogen synthase kinase-3 β specific inhibitor for PET studies

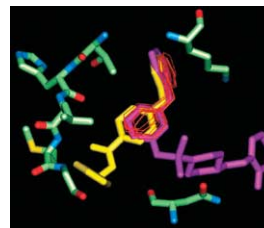
pp 5270–5273

Neil Vasdev,* Armando Garcia, Winston T. Stableford, Alex B. Young, Jeffrey H. Meyer, Sylvain Houle and Alan A. Wilson

**Two classes of p38 α MAP kinase inhibitors having a common diphenylether core but exhibiting divergent binding modes**

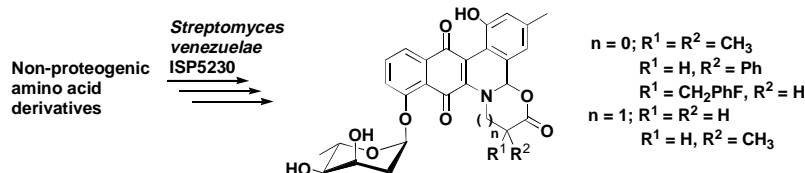
pp 5274–5279

Enrique L. Michelotti, Kristofer K. Moffett, Duyan Nguyen, Martha J. Kelly, Rupa Shetty, Xiaomei Chai, Katrina Northrop, Variketta Namboodiri, Brandon Campbell, Gary A. Flynn, Ted Fujimoto, Frank P. Hollinger, Marina Bukhtiyarova, Eric B. Springman and Michael Karpusas*

i⁺**Novel and expanded jadomycins incorporating non-proteogenic amino acids**

pp 5280–5283

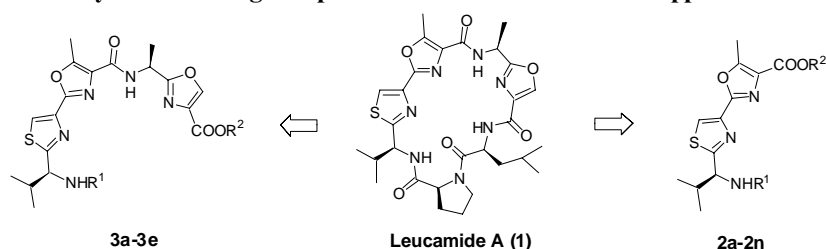
David L. Jakeman,* Cathy L. Graham and Taryn R. Reid

i⁺

Synthesis and biological evaluation of novel bisheterocycle-containing compounds as potential anti-influenza virus agents

Wen-Long Wang, De-Yong Yao, Min Gu,
Min-Zhi Fan, Jing-Ya Li,
Ya-Cheng Xing and Fa-Jun Nan*

pp 5284–5287



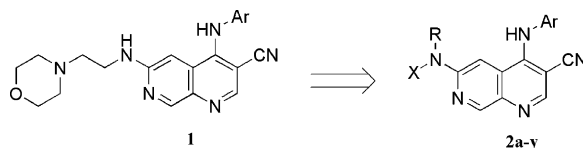
A series of novel 4,2-bisheterocycle tandem derivatives consisting of a methyloxazole and thiazole subunit were synthesized. Many compounds were found to inhibit human influenza A virus. Several analogues exhibited moderate biological activity and could serve as leads for further optimizations for antiviral research.

Inhibition of Tpl2 kinase and TNF- α production with 1,7-naphthyridine-3-carbonitriles:

pp 5288–5292

Synthesis and structure–activity relationships

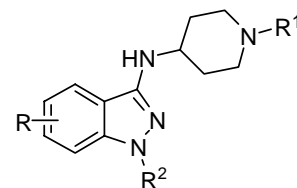
Lori Krim Gavrin, Neal Green,* Yonghan Hu, Kristin Janz, Neelu Kaila, Huan-Qiu Li,
Steve Y. Tam, Jennifer R. Thomason, Ariamala Gopalsamy, Greg Ciszewski, John W. Cuzzo,
J. Perry Hall, Sang Hsu, Jean-Baptiste Telliez and Lih-Ling Lin


Aminopiperidine indazoles as orally efficacious melanin concentrating hormone receptor-1 antagonists

pp 5293–5297

Anil Vasudevan,* Andrew J. Souers, Jennifer C. Freeman, Mary K. Verzal, Ju Gao,
Mathew M. Mulhern, Derek Wodka, John K. Lynch, Kenneth M. Engstrom,
Seble H. Wagaw, Sevan Brodjian, Brian Dayton, Doug H. Falls, Eugene Bush,
Michael Brune, Robin D. Shapiro, Kennan C. Marsh, Lisa E. Hernandez,
Christine A. Collins and Philip R. Kym

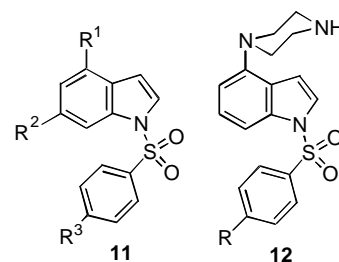
The synthesis and biological evaluation of novel 3-amino indazole melanin concentrating hormone receptor-1 antagonists are reported, several of which demonstrated functional activity of less than 100 nM. Compounds **19** and **28**, two of the more potent compounds identified in this study, were characterized by high exposure in the brain and demonstrated robust efficacy when dosed in diet-induced obese mice.


Binding of amine-substituted N₁-benzenesulfonylindoles at human 5-HT₆ serotonin receptors

pp 5298–5302

Manik Pullagurla, Uma Siripurapu, Renata Kolanos, Mikhail L. Bondarev,
Małgorzata Dukat, V. Setola, B. L. Roth and Richard A. Glennon*

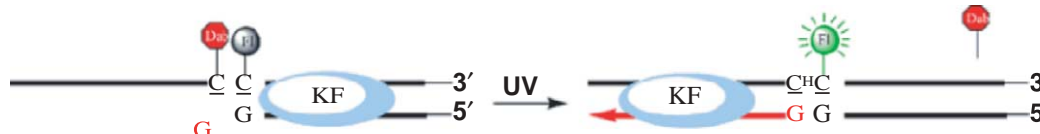
Indoles **11** and **12** (R¹ and/or R² = NHCH₃ or H; R and R³ = NH₂ or H) were examined to determine the influence of amine substituents on 5-HT₆ receptor affinity. Although all compounds displayed low nanomolar affinity, only a single aryl amine moiety is required for binding. It appears that multiple modes of binding are possible upon interaction of these types of compounds with 5-HT₆ receptors.



Photoregulation of DNA polymerase I (Klenow) with caged fluorescent oligodeoxynucleotides

pp 5303–5306

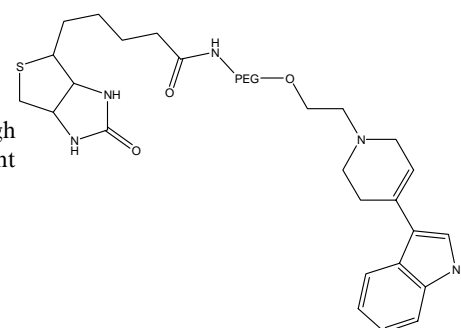
XinJing Tang, Julia L. Richards, Adam E. Peritz and Ivan J. Dmochowski*

**Inhibitors of the serotonin transporter protein (SERT): The design and synthesis of biotinylated derivatives of 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-indoles. High-affinity serotonergic ligands for conjugation with quantum dots**

pp 5307–5310

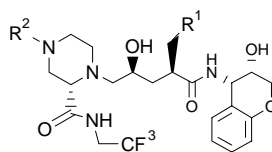
Ian D. Tomlinson, John N. Mason, Randy D. Blakely and Sandra J. Rosenthal*

Biotinylated derivatives of 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-indoles with high affinity for the serotonin transporter have been synthesized and attached to fluorescent quantum dots. These conjugates have been shown to retain biological activity.

**Orally bioavailable highly potent HIV protease inhibitors against PI-resistant virus**

pp 5311–5314

Zhijian Lu,* Joann Bohn, Tom Rano, Carrie A. Rutkowski, Amy L. Simcoe, David B. Olsen, William A. Schleif, Anthony Carella, Lori Gabryelski, Lixia Jin, Jiunn H. Lin, Emilio Emini, Kevin Chapman and James R. Tata

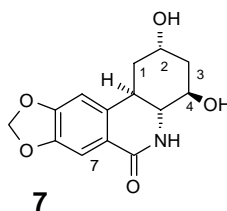


Efforts directed to identifying potent HIV protease inhibitors (PI) have yielded a class of compounds that are not only very active against wild-type (NL4-3) HIV virus but also very potent against a panel of PI-resistant viral isolates. Chemistry and biology are described.

A synthesis of 3-deoxydihydrolycoricidine: Refinement of a structurally minimum pancratistatin pharmacophore

pp 5315–5318

James McNulty,* Vladimir Larichev and Siyaram Pandey

**7**

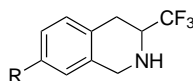
The synthesis and anticancer evaluation of 3-deoxydihydrolycoricidine **7** are reported.



Inhibitors of phenylethanolamine *N*-methyltransferase devoid of α_2 -adrenoceptor affinity

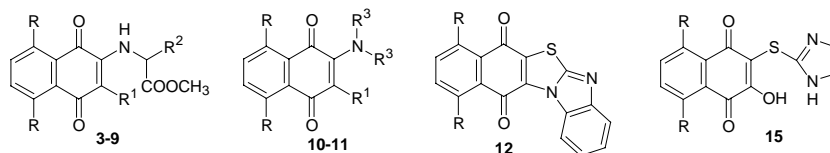
pp 5319–5323

Gary L. Grunewald,* Jian Lu, Kevin R. Criscione and Cosmas O. Okoro

**5c**, $K_i = 0.98 \mu\text{M}$ **Synthesis and biological evaluation of novel (L)- α -amino acid methyl ester, heteroalkyl, and aryl substituted 1,4-naphthoquinone derivatives as antifungal and antibacterial agents**

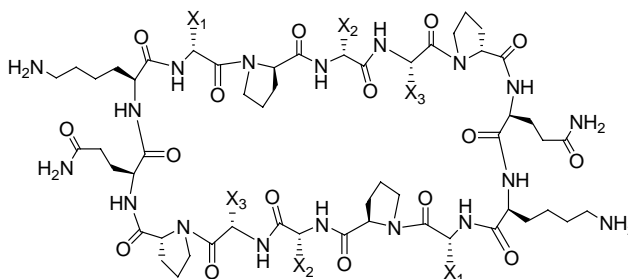
pp 5324–5328

Vishnu K. Tandon,* Dharmendra B. Yadav, Ravindra V. Singh, Ashok K. Chaturvedi and Praveen K. Shukla

The synthesis, antifungal, and antibacterial activities of **3–15** are described.**Geometric diversity through permutation of backbone configuration in cyclic peptide libraries**

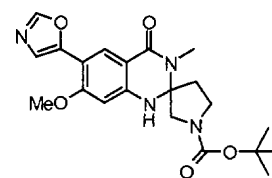
pp 5329–5334

Zachary E. Perlman, Jonathan E. Bock, Jeffrey R. Peterson and R. Scott Lokey*

**Novel 7-methoxy-6-oxazol-5-yl-2,3-dihydro-1*H*-quinazolin-4-ones as IMPDH inhibitors**

pp 5335–5339

Helen L. Birch, George M. Buckley, Natasha Davies, Hazel J. Dyke, Elizabeth J. Frost, Philip J. Gilbert, Duncan R. Hannah, Alan F. Haughan, Michael J. Madigan, Trevor Morgan, William R. Pitt, Andrew J. Ratcliffe, Nicholas C. Ray, Marianna D. Richard, Andrew Sharpe,* Alicia J. Taylor, Justine M. Whitworth and Sophie C. Williams

The synthesis and biological activity of a novel series of 7-methoxy-6-oxazol-5-yl-2,3-dihydro-1*H*-quinazolin-4-ones are described. Some of these compounds were found to be potent inhibitors of inosine 5'-monophosphate dehydrogenase type II (IMPDH II).

pp 5340–5343

Chemical reaction scheme showing the conversion of Rapamycin (6) to compound 3. Rapamycin (6) is a cyclohexane derivative with a methoxy group, a hydroxyl group, and a side chain. It is converted to compound 3, which has a triazole ring system. The reaction is reversible.

pp 5344–5352

COc1cc(OC)c(cc1C(=O)Nc2ccc(N)cc2)SC3OCCO3

K(VIIa) = 120 nM

COc1cc(OC)c(cc1C(=O)Nc2ccc(N)cc2)SC3OCCO3

F = 100% (rat)

COc1cc(OC)c(cc1C(=O)Nc2ccc(N)cc2)SC3OCCO3

F = 15% (rat)

OTHER CONTENTS

pp I–II

p III

 Supplementary data available via ScienceDirect

COVER

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