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Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 10, 2010

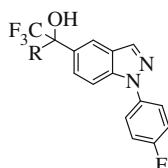
Contents

ARTICLES

5-Functionalized indazoles as glucocorticoid receptor agonists

pp 3017–3020

Mei Bai, Grant Carr, Russell J. DeOrazio, Thomas D. Friedrich, Svetlana Dobritsa, Kevin Fitzpatrick, Peter R. Guzzo, Douglas B. Kitchen, Michael A. Lynch, Denise Peace, Mohammed Sajad, Alexander Usyatinsky, Mark A. Wolf*

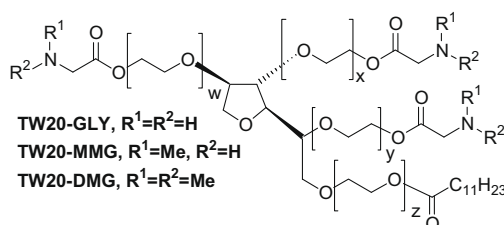


An indazole based series of glucocorticoid receptor (GR) agonists is reported and the SAR disclosed. The series yielded potent compounds for the GR with indications of selectivity for the preferred transrepression mechanism.

Novel Tween® 20 derivatives enable the formation of efficient pH-sensitive drug delivery vehicles for human hepatoblastoma

pp 3021–3025

Andrea Masotti*, Paola Vicennati, Anna Alisi, Carlotta Marianecchi, Federica Rinaldi, Maria Carafa, Giancarlo Ortaggi

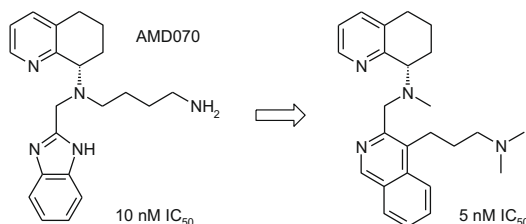


Novel pH-sensitive Tween® 20 derivatives give niosomes and deliver small molecules into human hepatoblastoma cells.

Synthesis and SAR of novel isoquinoline CXCR4 antagonists with potent anti-HIV activity

pp 3026–3030

John F. Miller*, Kristjan S. Gudmundsson, Leah D'Aurora Richardson, Stephen Jenkinson, Andrew Spaltenstein, Michael Thomson, Pat Wheelan

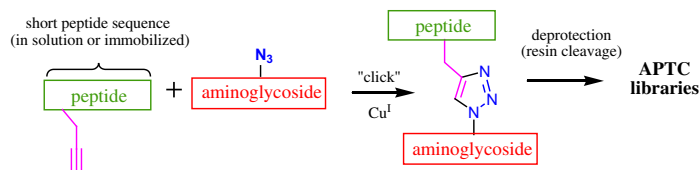


Using AMD070 as a starting point for structural modification, a novel series of isoquinoline CXCR4 antagonists was developed. A structure–activity scan of alternate lower heterocycles led to the 3-isoquinolyl moiety as an attractive replacement for benzimidazole. Side chain optimization in the isoquinoline series led to a number of compounds with low nanomolar anti-HIV activities and promising rat PK properties.

Evaluation of amphiphilic aminoglycoside–peptide triazole conjugates as antibacterial agents

pp 3031–3035

Smritilekha Bera, George G. Zhanel, Frank Schweizer*

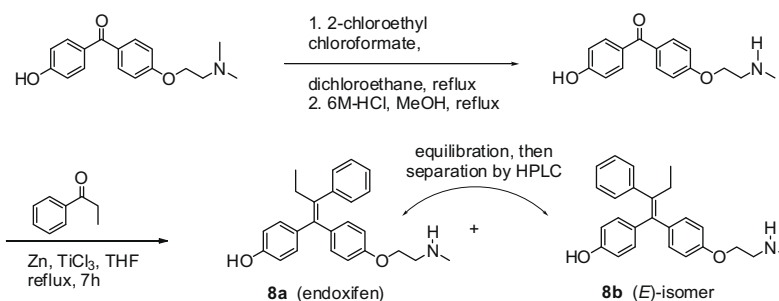


Synthesis of aminoglycoside–peptide triazole conjugates (APTCs) and their antibacterial evaluation is reported.

**A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen)**

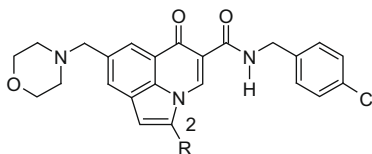
pp 3036–3038

Abdul H. Fauq*, Ghulam M. Maharvi, Dola Sinha

**Modifications of C-2 on the pyrroloquinoline template aimed at the development of potent herpesvirus antivirals with improved aqueous solubility**

pp 3039–3042

James A. Nieman*, Sajiv K. Nair, Steven E. Heasley, Brenda L. Schultz, Herbert M. Zerth, Richard A. Nugent, Ke Chen, Kevin J. Stephanski, Todd A. Hopkins, Mary L. Knechtel, Nancee L. Oien, Janet L. Wieber, Michael W. Wathen

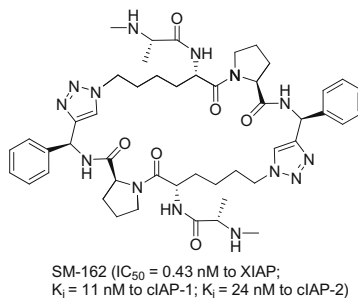


The synthesis of pyrroloquinoline analogs at C-2 with broad-spectrum anti-herpetic activity and improved solubility are reported.

**Cyclopeptide Smac mimetics as antagonists of IAP proteins**

pp 3043–3046

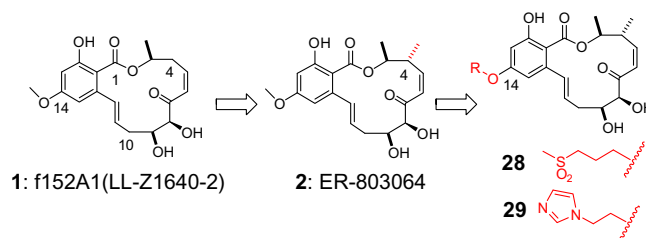
Haiying Sun, Liu Liu, Jianfeng Lu, Su Qiu, Chao-Yie Yang, Han Yi, Shaomeng Wang*



Discovery of an in vitro and in vivo potent resorcylic lactone analog of LL-Z1640-2 as anti-inflammatory lead, II

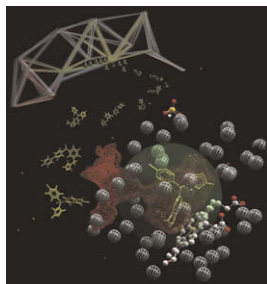
pp 3047–3049

Yongchun Shen, Hong Du, Makoto Kotake, Tomohiro Matsushima, Masaki Goto, Hiroshi Shirota, Fabian Gusovsky, Xiangyi Li, Yimin Jiang, Shawn Schiller, Mark Spyvee, Heather Davis, Zhiyi Zhang, Robert Pelletier, Megumi Ikemori-Kawada, Yoshiyuki Kawakami, Atsushi Inoue, Yuan Wang*

**Pharmacophore modeling strategies for the development of novel nonsteroidal inhibitors of human aromatase (CYP19)**

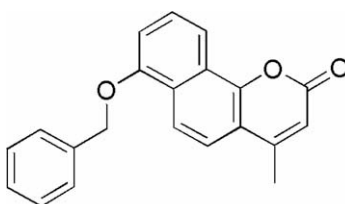
pp 3050–3064

Yagmur Muftuoglu, Gabriela Mustata*

**Synthesis of novel benzocoumarin derivatives as lipid lowering agents**

pp 3065–3069

Koneni V. Sashidhara*, Jammikuntla N. Rosaiah, Abdhesh Kumar, Gitika Bhatia, A.K. Khanna

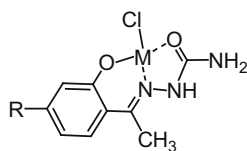


Novel benzocoumarin derivatives were synthesized and their hypolipidemic activity was evaluated resulting in identification of a potential lead.

**Complexes of 2-hydroxyacetophenone semicarbazones: A novel series of superoxide dismutase mimetics**

pp 3070–3073

Maliheh Safavi, Alireza Foroumadi, Maryam Nakhjiri, Mohammad Abdollahi, Abbas Shafiee, Hoda Ilkhani, Mohammad Reza Ganjali, Seyed Jalal Hosseinimehr, Saeed Emami*



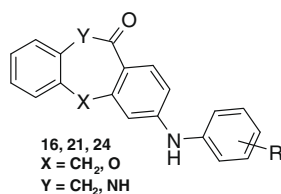
M = Cu (II), Zn
R = H, OH, MeO

A series of copper(II) and zinc complexes of 2-hydroxyacetophenone semicarbazones have been prepared and evaluated as superoxide dismutase (SOD) mimetics.

Design, synthesis and SAR of phenylamino-substituted 5,11-dihydro-dibenzo[*a,d*]cyclohepten-10-ones and 11*H*-dibenzo[*b,f*]oxepin-10-ones as p38 MAP kinase inhibitors

pp 3074–3077

Angelika Dorn, Verena Schattel, Stefan Laufer*



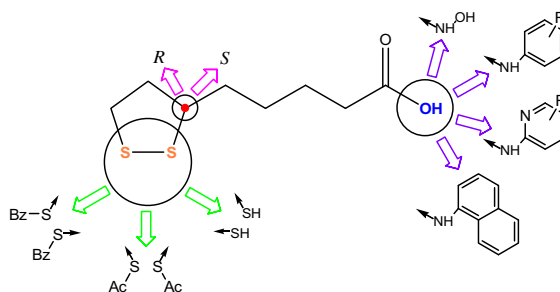
p38 MAP Kinase is an attractive and promising drug target for novel anti-inflammatory therapeutics. In this paper we present a novel, efficient synthesis route to obtain chloro-substituted 5,11-dihydro-dibenzo[*a,d*]cyclohepten-10-ones. Investigations of the inhibitory activities and structure–activity relationship of tricyclic inhibitors for p38 MAP kinase were accomplished.



Synthesis and anticancer evaluation of α -lipoic acid derivatives

pp 3078–3083

Shi-Jie Zhang, Qiu-Fu Ge, Dian-Wu Guo, Wei-Xiao Hu*, Hua-Zhang Liu



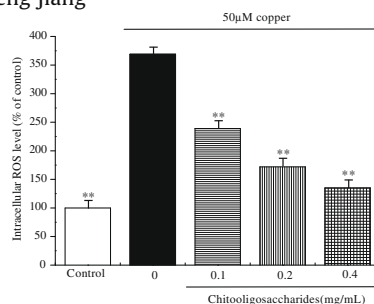
α -Lipoic acid derivatives were synthesized and their anticancer activities were evaluated.



Chitoooligosaccharides protect rat cortical neurons against copper induced damage by attenuating intracellular level of reactive oxygen species

pp 3084–3088

Wei Xu, Han-chang Huang, Chang-jun Lin, Zhao-Feng Jiang*

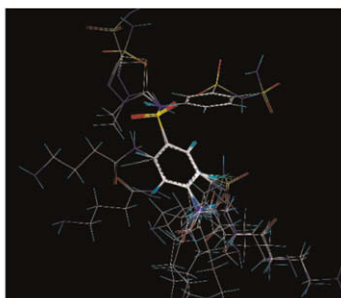
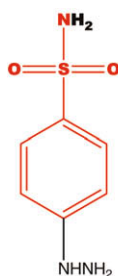


Chitoooligosaccharides attenuating intracellular reactive oxygen species level induced by copper.

3D-QSAR study of benzene sulfonamide analogs as carbonic anhydrase II inhibitors

pp 3089–3093

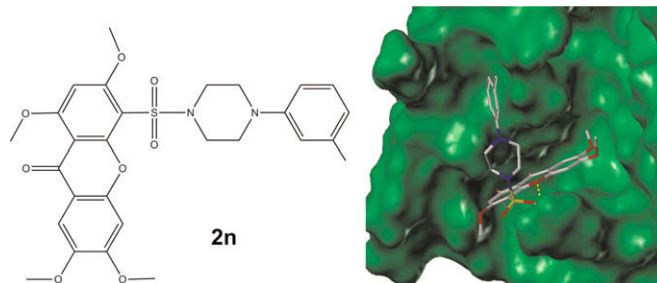
Kalyan K. Sethi*, Saurabh M. Verma, Naru Prasanthi, Suvendu K. Sahoo, Rabi N. Parhi, P. Suresh



First identification of xanthone sulfonamides as potent acyl-CoA:cholesterol acyltransferase (ACAT) inhibitors

pp 3094–3097

Honggang Hu, Hongli Liao, Jun Zhang, Weifeng Wu, Jufang Yan, Yonghong Yan, Qingjie Zhao, Yan Zou, Xiaoyun Chai, Shichong Yu, Qiuye Wu*

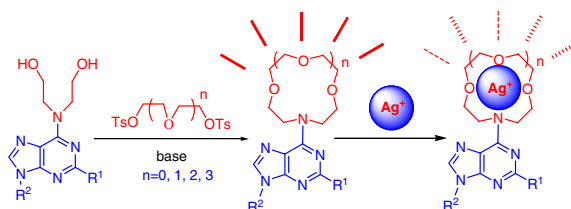


A series of xanthone sulfonamides were identified by HTS as inhibitors of the ACAT. Compound **2n** shows 64.8% inhibition to ACAT at 10 $\mu\text{g/mL}$ concentration.

**The synthesis of novel fluorescent purine analogues modified by azacrown ether at C6**

pp 3098–3102

Hai-Ming Guo*, Jing Wu, Hong-Ying Niu, Dong-Chao Wang, Feng Zhang, Gui-Rong Qu*

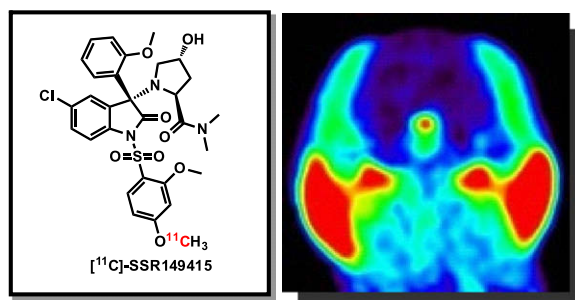


The synthesis and fluorescence properties of novel purine analogues linked azacrown ether at C6 position were investigated. These new purine analogues could be prepared from a series of 6-chloropurines and showed selective and efficient signaling behaviors toward micromolar concentration of Ag^+ ion over other common metal ions in an aqueous environment.

**Synthesis of [^{11}C]SSR149415 and preliminary imaging studies using positron emission tomography**

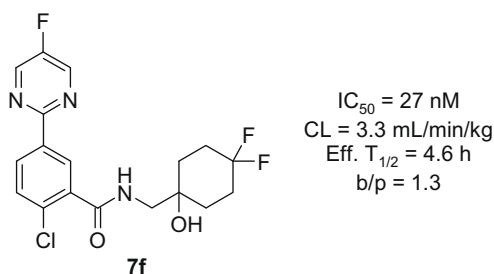
pp 3103–3106

Matthias Schönberger, Carmine Leggett, Sung Won Kim, Jacob M. Hooker*

**Discovery of 2-chloro-N-((4,4-difluoro-1-hydroxycyclohexyl)methyl)-5-(5-fluoropyrimidin-2-yl)benzamide as a potent and CNS penetrable P2X₇ receptor antagonist**

pp 3107–3111

Xiangyang Chen*, Betsy Pierce, Win Naing, Margaret L. Grapperhaus, Dennis P. Phillion

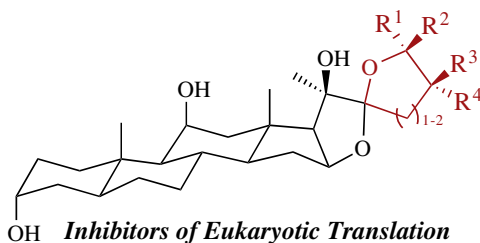


The discovery of a potent P2X₇ receptor antagonist, **7f**, with excellent CNS exposure and PK profile is reported.

Structural and stereochemical requirements of the spiroketal group of hippuristanol for antiproliferative activity

pp 3112–3115

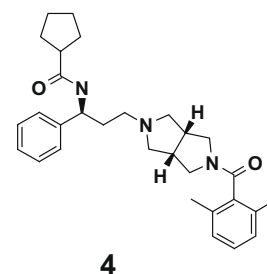
Wei Li, Yongjun Dang, Jun O. Liu*, Biao Yu*

**Novel hexahydropyrrolo[3,4-c]pyrrole CCR5 antagonists**

pp 3116–3119

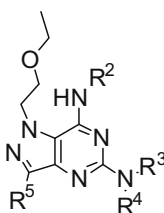
David M. Rotstein*, Chris R. Melville, Fernando Padilla, Dick Cournoyer, Eun K. Lee, Remy Lemoine, Ann C. Petersen, Lina Q. Setti, Jutta Wanner, Lijing Chen, Lubov Filonova, David G. Loughhead, Jason Manka, Xiao-Fa Lin, Shelley Gleason, Surya Sankuratri, Changhua Ji, Andre deRosier, Marianna Dioszegi, Gabrielle Heilek, Andreas Jekle, Pamela Berry, Cheng-I Mau, Paul Weller

Utilizing a high-throughput screening lead as a starting point, an information-based approach led to the discovery of a novel series of CCR5 antagonists, exemplified by compound **4**. Improvement of pharmacokinetic properties for the series was pursued by SAR exploration of the lead template. The synthesis, SAR and biological profiles of the series are described.

**1-(2-Ethoxyethyl)-1H-pyrazolo[4,3-d]pyrimidines as potent phosphodiesterase 5 (PDE5) inhibitors**

pp 3120–3124

Michael B. Tollefson*, Brad A. Acker, E.J. Jacobsen, Robert O. Hughes, John K. Walker, David N.A. Fox, Michael J. Palmer, Sandra K. Freeman, Ying Yu, Brian R. Bond

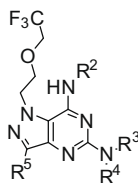


This work explores the potency, selectivity and efficacy of 1-(2-ethoxyethyl)-1H-pyrazolo[4,3-d]pyrimidines as PDE5 inhibitors resulting in the advancement of a clinical candidate.

1-(2-(2,2,2-Trifluoroethoxy)ethyl)-1H-pyrazolo[4,3-d]pyrimidines as potent phosphodiesterase 5 (PDE5) inhibitors

pp 3125–3128

Michael B. Tollefson*, Brad A. Acker, E.J. Jacobsen, Robert O. Hughes, John K. Walker, David N. A. Fox, Michael J. Palmer, Sandra K. Freeman, Ying Yu, Brian R. Bond



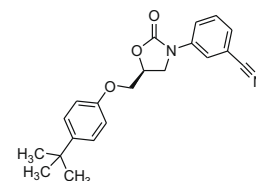
This work explores the advancement of more selective and potent PDE5 inhibitors resulting from the substitution of 2-(2,2,2-trifluoroethoxy)ethyl at the 1-position of 1H-pyrazolo[4,3-d]pyrimidines.

3-Aryl-5-phenoxyethyl-1,3-oxazolidin-2-ones as positive allosteric modulators of mGluR2 for the treatment of schizophrenia: Hit-to-lead efforts

pp 3129–3133

Edward J. Brnardic*, Mark E. Fraley, Robert M. Garbaccio, Mark E. Layton, John M. Sanders, Chris Culberson, Marlene A. Jacobson, Brian C. Magliaro, Pete H. Hutson, Julie A. O'Brien, Sarah L. Huszar, Jason M. Uslaner, Kerry L. Fillgrove, Cuyue Tang, Yuhsin Kuo, Sylvie M. Sur, George D. Hartman

Hit to lead optimization of oxazolidinones as positive allosteric modulators of mGluR2 is described. An optimized lead compound was found to be brain penetrant and active in a rat ketamine-induced hyperlocomotion model for antipsychotic activity.



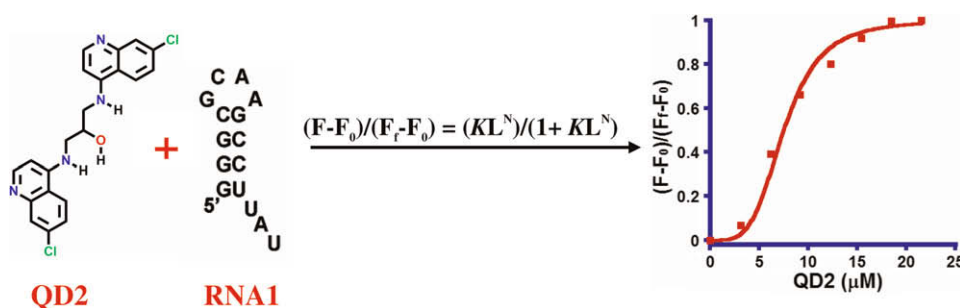
34

mGluR2 FLIPR EC₅₀ = 82 nM

Cooperative binding of a quinoline derivative to an RNA stem loop containing a dangling end

pp 3134–3137

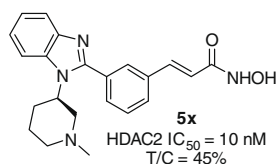
Sreenivasa Rao Ramisetty, Anne M. Baranger*



Benzimidazole and imidazole inhibitors of histone deacetylases: Synthesis and biological activity

pp 3138–3141

Jerome C. Bressi, Ron de Jong, Yiqin Wu, Andy J. Jennings, Jason W. Brown, Shawn O'Connell, Leslie W. Tari, Robert J. Skene, Phong Vu, Marc Navre, Xiaodong Cao, Anthony R. Gangloff*



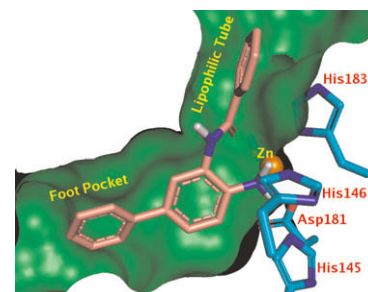
A series of imidazole and benzimidazole compounds were designed, synthesized, and found to be nanomolar inhibitors of human histone deacetylases, displaying activity in cellular and xenograft models.

Exploration of the HDAC2 foot pocket: Synthesis and SAR of substituted *N*-(2-aminophenyl)benzamides

pp 3142–3145

Jerome C. Bressi, Andy J. Jennings, Robert Skene, Yiqin Wu, Robert Melkus, Ron De Jong, Shawn O'Connell, Charles E. Grimshaw, Marc Navre, Anthony R. Gangloff*

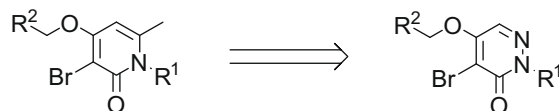
Substituted *N*-(2-aminophenyl)benzamides demonstrated time-dependent binding kinetics that is rationalized using a co-complex crystal structure of HDAC2 and *N*-(4-aminobiphenyl-3-yl)benzamide (6).



Discovery of 5-substituted-*N*-arylpyridazinones as inhibitors of p38 MAP kinase

pp 3146–3149

Kevin D. Jerome*, Michael E. Hepperle, John K. Walker, Li Xing, Rajesh V. Devraj, Alan G. Benson, John E. Baldus, Shaun R. Selness

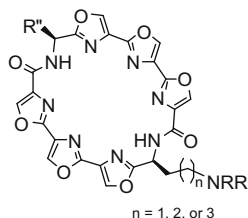


The synthesis, structure–activity relationship and modeling of a series of 5-substituted-*N*-aryl pyridazinone based p38 α inhibitors are described. In comparing the series to the similar *N*-aryl pyridinone series, it was found that the pyridazinones maintained a weaker interaction to the p38 enzyme, and therefore showed generally weaker binding than the pyridinones.

Macrocyclic hexaoxazoles: Influence of aminoalkyl substituents on RNA and DNA G-quadruplex stabilization and cytotoxicity

pp 3150–3154

Mavurapu Satyanarayana, Young-Ah Kim, Suzanne G. Rzuczek, Daniel S. Pilch, Angela A. Liu, Leroy F. Liu, Joseph E. Rice, Edmond J. LaVoie*

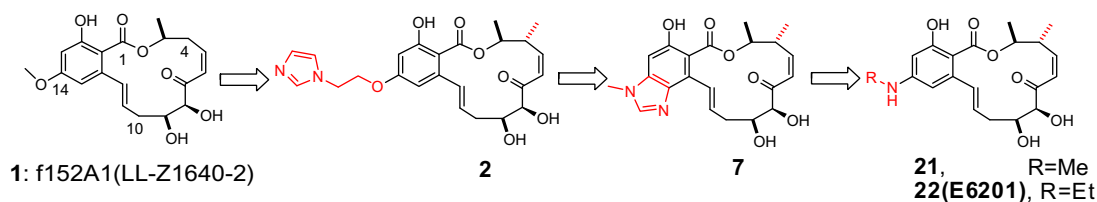


Several monoaminoalkyl derivatives with R'' being isopropyl and various bis-aminoalkyl substituted hexaoxazoles derivatives were evaluated for cytotoxicity and stabilization of G-quadruplex RNA and DNA. One of the more cytotoxic analogs (where $n = 1$, R'' is isopropyl and both R and R' are methyl substituents) inhibits human tumor growth in the athymic nude mouse xenograft model.

**Discovery of anti-inflammatory clinical candidate E6201, inspired from resorcylic lactone LL-Z1640-2, III**

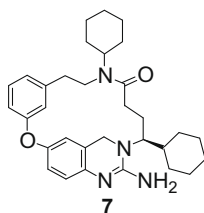
pp 3155–3157

Yongchun Shen, Roch Boivin, Naoki Yoneda, Hong Du, Shawn Schiller, Tomohiro Matsushima, Masaki Goto, Hiroshi Shirota, Fabian Gusovsky, Charles Lemelin, Yimin Jiang, Zhiyi Zhang, Robert Pelletier, Megumi Ikemori-Kawada, Yoshiyuki Kawakami, Atsushi Inoue, Matthew Schnaderbeck, Yuan Wang*

**Macrocyclic BACE inhibitors: Optimization of a micromolar hit to nanomolar leads**

pp 3158–3160

Yifang Huang, Eric D. Strobel, Chih Y. Ho, Charles H. Reynolds, Kelly A. Conway, Jennifer A. Piesvaux, Douglas E. Brenneman, George J. Yohrling, H. Moore Arnold, Daniel Rosenthal, Richard S. Alexander, Brett A. Tounge, Marc Mercken, Marc Vandermeeren, Michael H. Parker, Allen B. Reitz, Ellen W. Baxter*

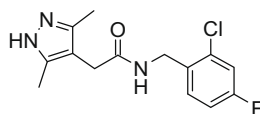


Structural biology allowed the identification of **7** as a potent BACE inhibitor ($IC_{50} = 5$ nM).

Synthesis and structure–activity relationships of a series of (1*H*-pyrazol-4-yl)acetamide antagonists of the P2X₇ receptor

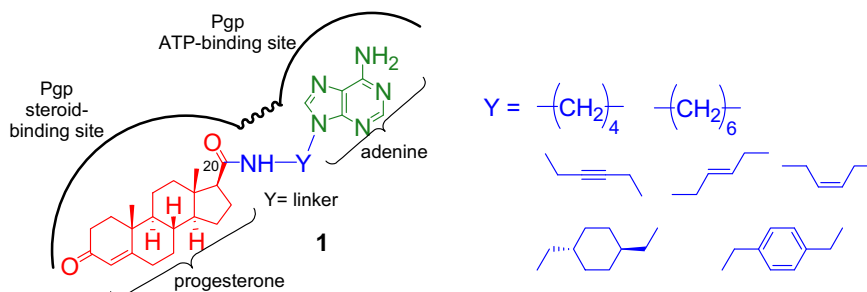
pp 3161–3164

Laura J. Chambers*, Alexander J. Stevens, Andrew P. Moses, Anton D. Michel, Daryl S. Walter, David J. Davies, David G. Livermore, Elena Fonfria, Emmanuel H. Demont, Mythily Vimal, Pam J. Theobald, Paul J. Beswick, Robert J. Gleave, Shilina A. Roman, Stefan Senger

**32**Human P2X₇ pIC₅₀ 7.7**Design, synthesis and evaluation of progesterone–adenine hybrids as bivalent inhibitors of P-glycoprotein-mediated multidrug efflux**

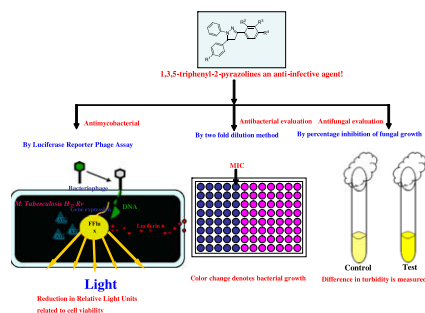
pp 3165–3168

Wael Zeinyeh, Ghina Alameh, Sylvie Radix*, Catherine Grenot, Charles Dumontet, Nadia Walchshofer*

**Novel 1,3,5-triphenyl-2-pyrazolines as anti-infective agents**

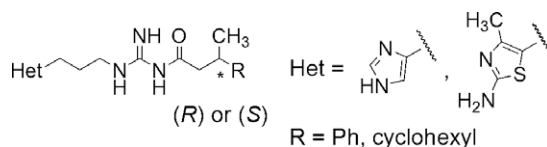
pp 3169–3172

P. M. Sivakumar, S. Prabhu Seenivasan, Vanaja Kumar, Mukesh Doble*

**Chiral N^C-acylated hetarylpropylguanidine-type histamine H₂ receptor agonists do not show significant stereoselectivity**

pp 3173–3176

Prasanta Ghorai, Anja Kraus, Tobias Birnkammer, Roland Geyer, Günther Bernhardt, Stefan Dove, Roland Seifert, Sigurd Elz, Armin Buschauer*



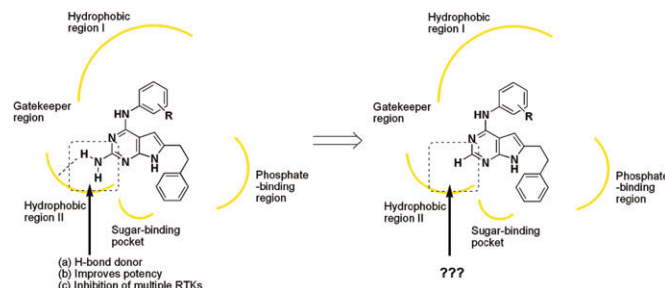
The synthesis and pharmacological characterisation of the enantiomers of the title compounds on recombinant histamine receptors (gpH₂R and hH₂R, hH₁R, hH₃R, hH₄R) and on the isolated guinea pig atrium is described.



The contribution of a 2-amino group on receptor tyrosine kinase inhibition and antiangiogenic activity in 4-anilinosubstituted pyrrolo[2,3-d]pyrimidines

pp 3177–3181

Aleem Gangjee*, Ojas A. Namjoshi, Michael A. Ihnat, Aaron Buchanan

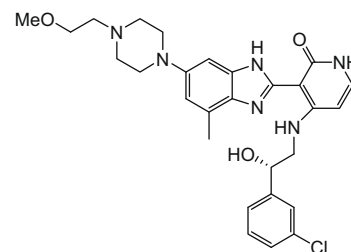


Insulin-like growth factor-1 receptor (IGF-1R) kinase inhibitors: SAR of a series of 3-[6-(4-substituted-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridine-2-one

pp 3182–3185

Upender Velaparthi*, Mark G. Saulnier*, Mark D. Wittman, Peiying Liu, David B. Frennesson, Kurt Zimmermann, Joan M. Carboni, Marco Gottardis, Aixin Li, Ann Greer, Wendy Clarke, Zheng Yang, Krista Menard, Francis Y. Lee, George Trainor, Dolatrai Vyas

A series of 3-[6-(4-substituted-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridine-2-one were synthesized to modulate CYP3A4 inhibition and improve aqueous solubility of our prototypical compound BMS-536924 (**1**), while maintaining potent IGF-1R inhibitory activity. Structure–activity and structure–solubility studies led to the identification of BMS-577098 (**27**), which demonstrates oral in vivo efficacy in animal models. The improvement was achieved by replacing morpholine with more polar bio-isoster piperazine and modulating the basicity of distal nitrogen with appropriate substitutions.



BMS-577098

OTHER CONTENT

Corrigendum

pp 3186–3187

*Corresponding author

i+ 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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