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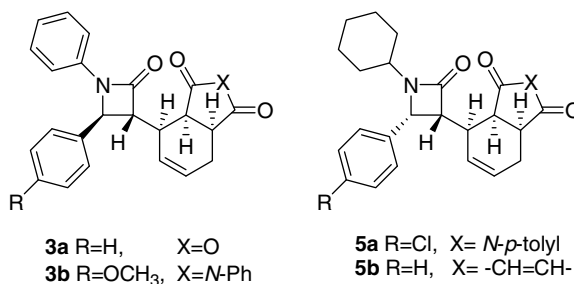
Contents

ARTICLES

PASS-assisted exploration of antidepressant activity of 1,3,4-trisubstituted- β -lactam derivatives

pp 5347–5349

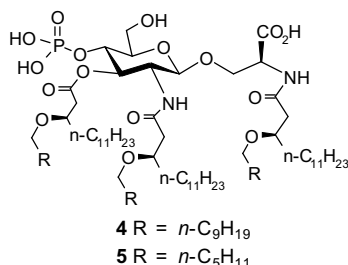
Munish Mittal, Rajesh K. Goel*, Gaurav Bhargava, Mohinder P. Mahajan*



The 'Ethereal' nature of TLR4 agonism and antagonism in the AGP class of lipid A mimetics

pp 5350–5354

Hélène G. Bazin, Tim J. Murray, William S. Bowen, Afsaneh Mozaffarian, Steven P. Fling, Laura S. Bess, Mark T. Livesay, Jeffrey S. Arnold, Craig L. Johnson, Kendal T. Ryter, Christopher W. Cluff, Jay T. Evans, David A. Johnson*

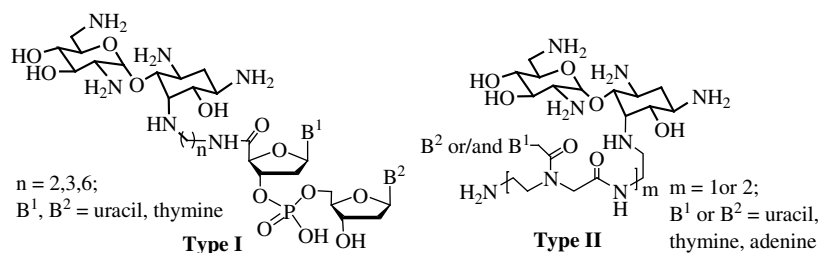


The novel ether lipid AGPs **4** and **5** were synthesized by a highly convergent method and evaluated along with their ester counterparts for TLR4 activity in both in vitro and in vivo models. Unlike agonist **4**, compound **5** showed species-specific agonist/antagonist activity.

Studies on the synthesis of neamine-dinucleosides and neamine-PNA conjugates and their interaction with RNA

pp 5355–5358

Hui Mei, Lei Xing, Li Cai, Hong-Wei Jin, Peng Zhao, Zhen-Jun Yang*, Liang-Ren Zhang, Li-He Zhang

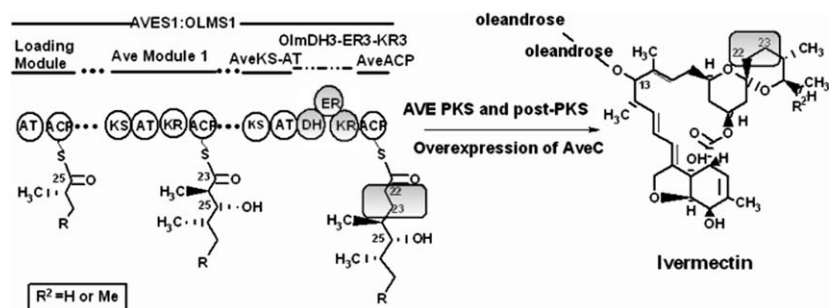


Two types of neamine derivatives were synthesized. Their binding affinities towards RNA were evaluated by SPR and the binding modes with RNA were elucidated by computer modelling.



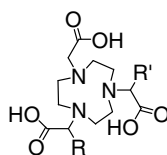
Engineering of avermectin biosynthetic genes to improve production of ivermectin in *Streptomyces avermitilis* pp 5359–5363

Meng Li, Zhi Chen, Xiuping Lin, Xuan Zhang, Yuan Song, Ying Wen, Jilun Li*



NODAPA-OH and NODAPA-(NCS)_n: Synthesis, ⁶⁸Ga-radiolabelling and in vitro characterisation of novel versatile bifunctional chelators for molecular imaging pp 5364–5367

Patrick J. Riss*, Carsten Kroll, Verena Nagel, Frank Rösch

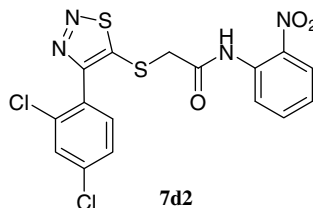


R = 4-PhOH, 4-PhNCS
R' = H, 4-PhNCS

Synthesis, ⁶⁸Ga-radiolabelling and stability data of three powerful novel chelators for molecular imaging is reported.

1,2,3-Thiadiazole thioacetanilides as a novel class of potent HIV-1 non-nucleoside reverse transcriptase inhibitors pp 5368–5371

Peng Zhan, Xinyong Liu*, Yuan Cao, Yan Wang, Christophe Pannecouque, Erik De Clercq*

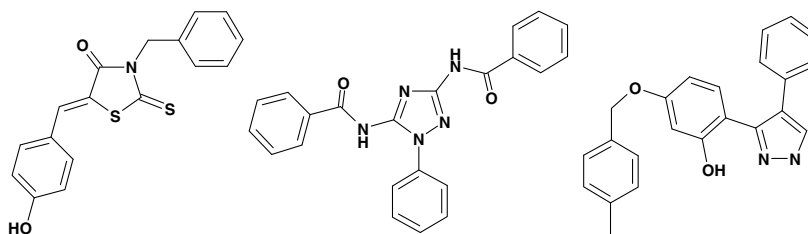


EC₅₀ = 0.059 ± 0.02 μM, SI>4883

A novel series of 1,2,3-thiadiazole thioacetanilide (TTA) derivatives have been designed, synthesized and evaluated for their anti-HIV activities in MT-4 cells. Some derivatives proved to be highly effective in inhibiting HIV-1 replication at nanomolar concentrations. The structure–activity relationship (SAR) is discussed.

Identification of novel inhibitors of extracellular signal-regulated kinase 2 based on the structure-based virtual screening pp 5372–5376

Hwangseo Park*, Young Jae Bahn, Dae Gwin Jeong, Eui Jeon Woo, Jung Sun Kwon, Seong Eon Ryu*



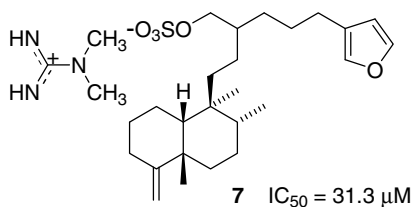
We have discovered three novel inhibitor scaffolds for extracellular signal-regulated kinase 2 (ERK2) by means of a drug design protocol involving the virtual screening with docking simulations and in vitro enzyme assay.



Inhibition of *Candida albicans* isocitrate lyase activity by sesterterpene sulfates from the tropical sponge *Dysidea* sp.

pp 5377–5380

Dongha Lee, Jongheon Shin*, Kyung-Mi Yoon, Tae-Im Kim, So-Hyoung Lee, Hyi-Seung Lee, Ki-Bong Oh*



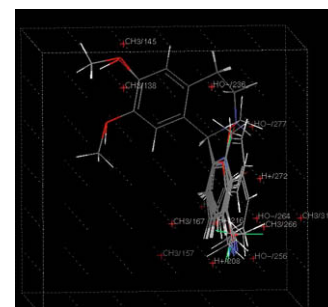
The isolation and bioactivity of seven sesterterpene sulfates are described.

Quantitative structure–activity relationship studies on 1-aryl-tetrahydroisoquinoline analogs as active anti-HIV agents

pp 5381–5386

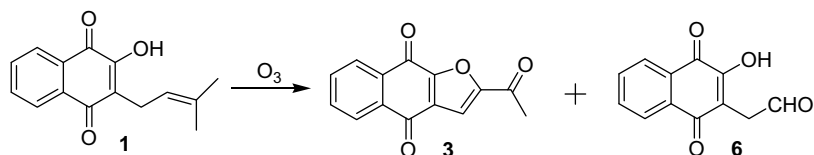
Ke-xian Chen, Hai-ying Xie, Zu-guang Li*, Jian-rong Gao

Statistically significant QSAR models have been developed for anti-HIV 1-aryl-tetrahydroisoquinoline analogs using GFA, stepwise-MLR, and MFA-G/PLS techniques. The results obtained by combining these methodologies gain insights into the structural requirements for anti-HIV activity of this class.

**Semisynthesis and antitumoral activity of 2-acetylfuranonaphthoquinone and other naphthoquinone derivatives from lapachol**

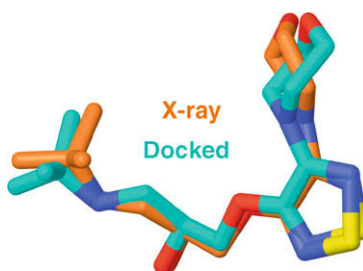
pp 5387–5390

Kenneth O. Eyang, Ponminor S. Kumar, Victor Kuete, Gabriel N. Folefoc*, Ephriam A. Nkengfack, Sundarababu Baskaran*

**Use of the X-ray structure of the β_2 -adrenergic receptor for drug discovery. Part 2: Identification of active compounds**

pp 5391–5395

Michael Sabio, Kenneth Jones, Sid Topiol*

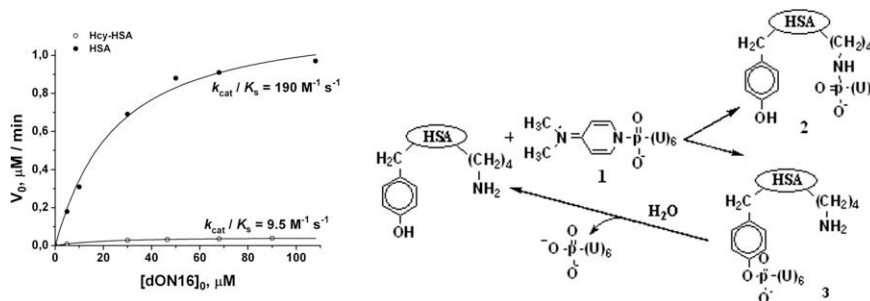


The previous use of a β_2 -adrenergic receptor's X-ray in docking studies is now validated with binding data and a recently published X-ray structure with Timolol.

Human serum albumin as a catalyst of RNA cleavage: N-Homocysteinylation and N-phosphorylation by oligonucleotide affinity reagent alter the reactivity of the protein

pp 5396–5398

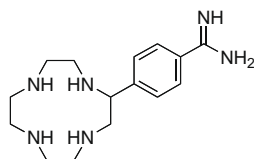
Yuliya V. Gerasimova, Dmitry D. Knorre, Makhmut M. Shakirov, Tatyana S. Godovikova *



Synthesis of novel benzamidine- and guanidine-derived polyazamacrocycles: Selective anti-protozoal activity for human African trypanosomiasis

pp 5399–5401

Caroline M. Reid, Charles Ebikeme, Michael P. Barrett, Eva-Maria Patzewitz, Sylke Müller, David J. Robins, Andrew Sutherland *



Biological testing of two novel polyazamacrocycles tagged with structural motifs recognized by the P2 aminopurine transporter show these compounds to be selectively toxic for trypanosomes.

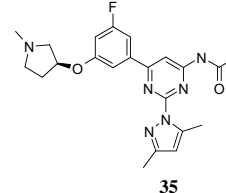


2,6-Diaryl-4-acylaminopyrimidines as potent and selective adenosine A_{2A} antagonists with improved solubility and metabolic stability

pp 5402–5405

Manisha Moorjani *, Zhiyong Luo, Emily Lin, Binh G. Vong, Yongsheng Chen, Xiaohu Zhang, Jaimie K. Rueter, Raymond S. Gross, Marion C. Lanier, John E. Tellew, John P. Williams, Sandra M. Lechner, Siobhan Malany, Mark Santos, María I. Crespo, José-Luis Díaz, John Saunders, Deborah H. Slee

The strategy for improving solubility and metabolic stability of a series of pyrimidine-based adenosine A_{2A} antagonists is described.

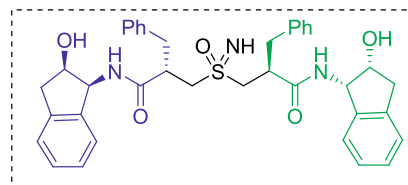
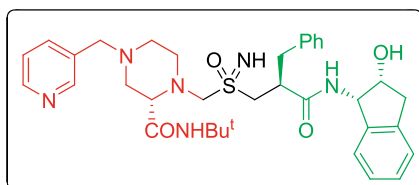


35
 K_i (nM) hA_{2A} 1
 hA₁/hA_{2A} 218
 CL_{int} (HLM) (mL/min/kg) 3
 Aqueous solubility (mg/mL) > 4 @ pH 8.0

Design and synthesis of sulfoximine based inhibitors for HIV-1 protease

pp 5406–5410

Abbas Raza, Yuk Yin Sham, Robert Vince *

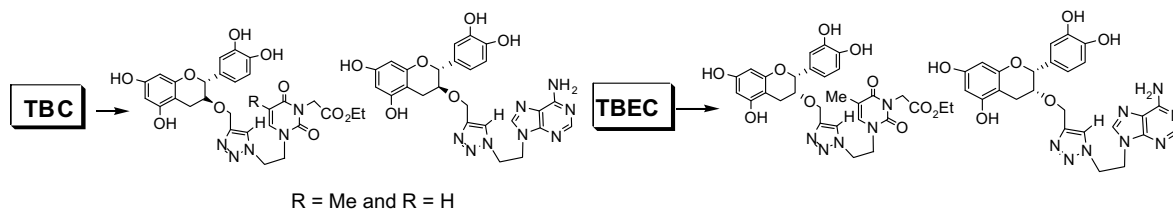


The design and synthesis of protease inhibitors featuring a sulfoximine moiety have been disclosed and the effect of sulfoximine group has been carefully studied and compared using docking models.

Design, synthesis and RNase A inhibition activity of catechin and epicatechin and nucleobase chimeric molecules

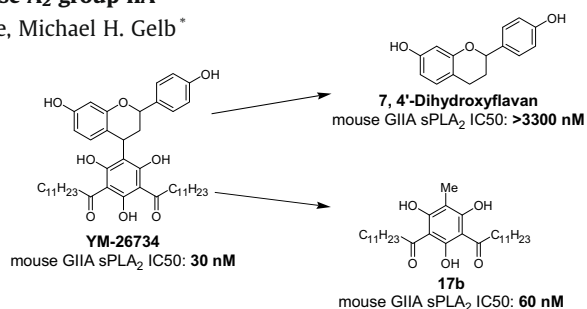
pp 5411–5414

Basab Roy, Sansa Dutta, Anupma Chowdhary, Amit Basak*, Swagata Dasgupta

**Simplified YM-26734 inhibitors of secreted phospholipase A₂ group IIA**

pp 5415–5419

Rob C. Oslund, Nathan Cermak, Christophe L. M. J. Verlinde, Michael H. Gelb*

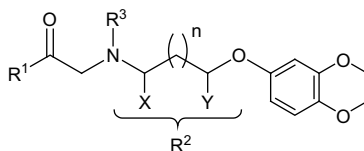


Modeling of YM-26734 in the active site of secreted phospholipase A₂ group IIA led to the design and synthesis of simplified analogs retaining nanomolar potency.

**Synthesis of (3,4-dimethoxyphenoxy)alkylamino acetamides as orexin-2 receptor antagonists**

pp 5420–5423

Andrew G. Cole*, Ilana L. Stroke, Lan-Ying Qin, Zahid Hussain, Srilatha Simhadri, Marc-Raleigh Brescia, Frank S. Waksmunski, Barbara Strohl, John E. Tellew, John P. Williams, John Saunders, Kenneth C. Appell, Ian Henderson, Maria L. Webb

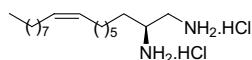


The synthesis and evaluation of (dimethoxyphenoxy)alkylamino acetamides as orexin-2 receptor antagonists are reported.

A novel monoacylglycerol lipase inhibitor with analgesic and anti-inflammatory activity

pp 5424–5427

Victoria Magrioti, George Naxakis, Dimitra Hadjipavlou-Litina, Alexandros Makriyannis, George Kokotos*

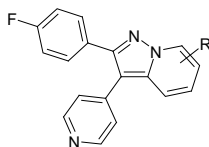


The synthesis of a selective MGL inhibitor presenting analgesic and anti-inflammatory activity is reported.

The identification of pyrazolo[1,5-*a*]pyridines as potent p38 kinase inhibitors

pp 5428–5430

Mui Cheung*, Philip A. Harris, Jennifer G. Badiang, Gregory E. Peckham, Stanley D. Chamberlain, Michael J. Alberti, David K. Jung, Stephanie S. Harris, Neal H. Bramson, Andrea H. Epperly, Stephen A. Stimpson, Michael R. Peel

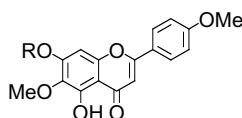


A series of pyrazolo[1,5-*a*]pyridine derivatives was designed and synthesized as novel potent p38 kinase inhibitors. Our approaches towards improving in vitro metabolism and in vivo pharmacokinetic properties of the series are described.

In vitro biological evaluation of novel 7-*O*-dialkylaminoalkyl cytotoxic pectolinarigenin derivatives against a panel of human cancer cell lines

pp 5431–5434

Marco Bonesi, Rosa Tundis*, Brigitte Deguin*, Monica R. Loizzo, Federica Menichini, François Tillequin, Francesco Menichini



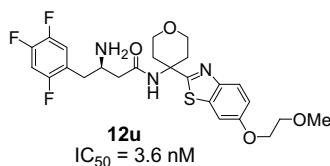
2 R = H IC₅₀ 5.3 μM on Caco-2
3 R = (CH₂)₃N(CH₃)₂ IC₅₀ 7.2 μM on COR-L23

The synthesis of the 7-*O*-dialkylaminoalkyl cytotoxic pectolinarigenin derivatives is reported.

(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)-*N*-{4-[6-(2-methoxyethoxy)benzothiazol-2-yl]tetrahydropyran-4-yl}butanamide as a potent dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes

pp 5435–5438

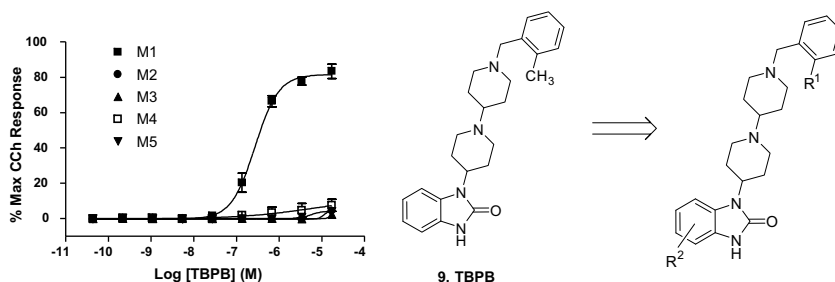
Aiko Nitta*, Hideaki Fujii, Satoshi Sakami, Yutaka Nishimura, Tomofumi Ohyama, Mikiya Satoh, Junko Nakaki, Shiho Satoh, Chifumi Inada, Hideki Kozono, Hiroki Kumagai, Masahiro Shimamura, Tominaga Fukazawa, Hideki Kawai

**Synthesis and SAR of analogues of the M1 allosteric agonist TBPB. Part I: Exploration of alternative benzyl and privileged structure moieties**

pp 5439–5442

Thomas M. Bridges, Ashley E. Brady, J. Phillip Kennedy, R. Nathan Daniels, Nicole R. Miller, Kwango Kim, Micah L. Breining, Patrick R. Gentry, John T. Brogan, Carrie K. Jones, P. Jeffrey Conn, Craig W. Lindsley*

The synthesis and SAR of analogues of the M1 allosteric agonist TBPB is described. With slight structural changes, mAChR selectivity was maintained, but the degree of partial agonism varied considerably.

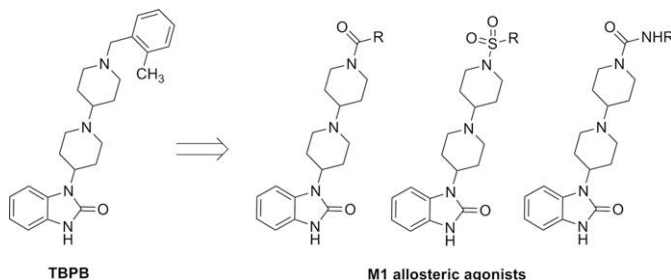


Synthesis and SAR of analogs of the M1 allosteric agonist TBPB. Part II: Amides, sulfonamides and ureas—The effect of capping the distal basic piperidine nitrogen

pp 5443–5447

Nicole R. Miller, R. Nathan Daniels, Thomas M. Bridges, Ashley E. Brady, P. Jeffrey Conn, Craig W. Lindsley*

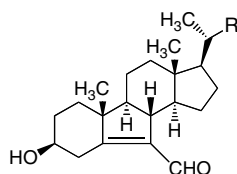
This letter describes the further synthesis and SAR, developed through an iterative analog library approach, of analogs of the highly selective M1 allosteric agonist TBPB by deletion of the distal basic piperidine nitrogen by the formation of amides, sulfonamides and ureas. Despite the large change in basicity and topology, M1 selectivity was maintained.



Synthesis and in vitro biological evaluation of ring B abeo-sterols as novel inhibitors of *Mycobacterium tuberculosis*

pp 5448–5450

Xiaomei Wei, Abimael D. Rodríguez*, Yuehong Wang, Scott G. Franzblau

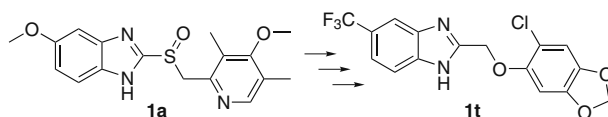


The synthesis of a small library of 5(6 → 7) abeo-sterols with strong anti-TB properties is reported.

Discovery of small molecule agonists for the bombesin receptor subtype 3 (BRS-3) based on an omeprazole lead

pp 5451–5455

David L. Carlton, Lissa J. Collin-Smith, Alejandro J. Daniels, David N. Deaton*, Aaron S. Goetz, Christopher P. Laudeman, Thomas R. Littleton, David L. Musso, Ronda J. Ott Morgan, Jerzy R. Szewczyk, Cunyu Zhang

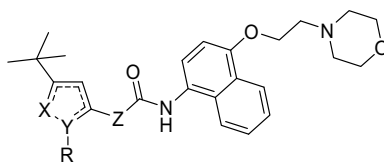


Starting from a weak omeprazole screening hit, replacement of the pyridine with a 1,3-benzodioxole moiety, modification of the thioether linkage, and substitution of the benzimidazole pharmacophore led to the discovery of nanomolar BRS-3 agonists.

'Reverse' α -ketoamide-based p38 MAP kinase inhibitors

pp 5456–5459

Antonio Garrido Montalban*, Erik Boman, Chau-Dung Chang, Susana Conde Ceide, Russell Dahl, David Dalesandro, Nancy G. J. Delaet, Eric Erb, Andrew Gibbs, Jeff Kahl, Linda Kessler, Jan Lundström, Stephen Miller, Hiroshi Nakanishi, Ed Roberts, Eddine Saiah, Robert Sullivan, Zhijun Wang, Christopher J. Larson

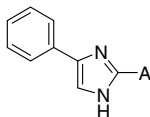


The design and synthesis of novel reverse α -ketoamide-based p38 inhibitors is reported.

2,4(5)-Diarylimidazoles: Synthesis and biological evaluation of a new class of sodium channel blockers against hNa_v1.2

pp 5460–5462

Mirko Rivara, Aparna R. Baheti, Marco Fantini, Giuseppe Cocconcelli, Chiara Ghiron, Christopher L. Kalmar, Natasha Singh, Ellen C. Merrick, Manoj K. Patel, Valentina Zuliani*



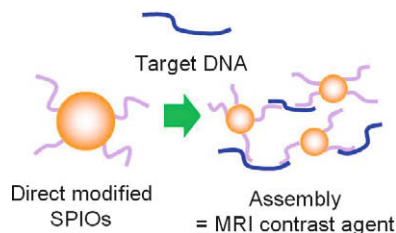
A: phenyl, 3-pyridine, 4-pyridine, cyclohexyl, 2-furan, 3-furan, 2-benzofuran, 3-thiophene

A small family of novel 2,4(5)-diarylimidazoles were prepared through a simple and efficient synthesis and evaluated as potential inhibitors of hNa_v1.2 sodium channel currents.

Assembly system of direct modified superparamagnetic iron oxide nanoparticles for target-specific MRI contrast agents

pp 5463–5465

Kazuo Tanaka, Narufumi Kitamura, Masahito Morita, Toshiro Inubushi, Yoshiki Chujo*

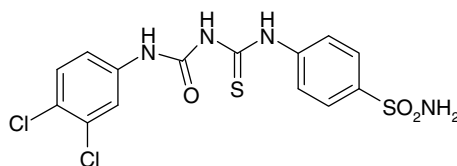


We report the direct modification of SPIOs with a biomolecule and the target-specific assembly system of these modified SPIOs for using MRI contrast agents.


Carbonic anhydrase inhibitors: Inhibition of *Plasmodium falciparum* carbonic anhydrase with aromatic/heterocyclic sulfonamides—in vitro and in vivo studies

pp 5466–5471

Jerapan Krungkrai*, Sudaratana R. Krungkrai, Claudiu T. Supuran*

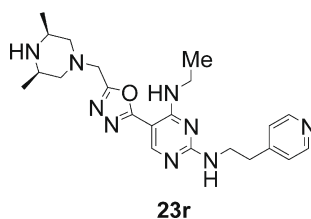


K_I (pfCA) = 180 nM; IC₅₀ = 1 μM; ID₅₀ = 10 mg/kg

Novel and orally active 5-(1,3,4-oxadiazol-2-yl)pyrimidine derivatives as selective FLT3 inhibitors

pp 5472–5477

Hiroshi Ishida*, Shoichi Isami, Tsutomu Matsumura, Hiroshi Umehara, Yoshinori Yamashita, Jiro Kajita, Eiichi Fuse, Hitoshi Kiyoi, Tomoki Naoe, Shiro Akinaga, Yukimasa Shiotsu, Hitoshi Arai



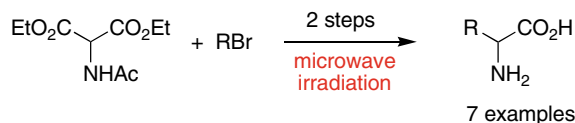
The synthesis and structure–activity relationship studies of a novel series of FLT3 inhibitors are described. Compound **23r** possesses best efficacy against tumor xenograft model by oral administration.



Microwave-assisted synthesis of unnatural amino acids

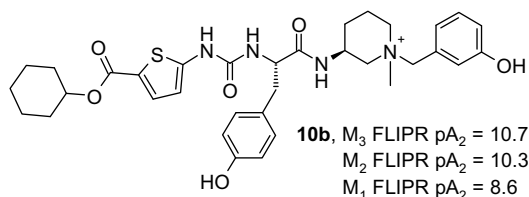
pp 5478–5480

Douglas D. Young, Jessica Torres-Kolbus, Alexander Deiters*

**Muscarinic acetylcholine receptor antagonists: SAR and optimization of tyrosine ureas**

pp 5481–5486

Jian Jin*, Yonghui Wang*, Dongchuan Shi, Feng Wang, Wei Fu, Roderick S. Davis, Qi Jin, James J. Foley, Henry M. Sarau, Dwight M. Morrow, Michael L. Moore, Ralph A. Rivero, Michael Palovich, Michael Salmon, Kristen E. Belmonte, Jakob Busch-Petersen

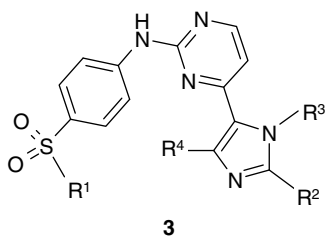


SAR exploration of multiple regions of a tyrosine urea template led to the identification of very potent muscarinic acetylcholine receptor antagonists such as **10b** with good sub-type selectivity for M₃ over M₁. The structure–activity relationships (SAR) and optimization of the tyrosine urea series are described.

Imidazoles: SAR and development of a potent class of cyclin-dependent kinase inhibitors

pp 5487–5492

Malcolm Anderson, David M. Andrews, Andy J. Barker, Claire A. Brassington, Jason Breed, Kate F. Byth, Janet D. Culshaw, M. Raymond V. Finlay, Eric Fisher, Helen H. J. McMiken, Clive P. Green*, Dave W. Heaton, Ian A. Nash, Nicholas J. Newcombe, Sandra E. Oakes, Richard A. Pauptit, Andrew Roberts, Judith J. Stanway, Andrew P. Thomas, Julie A. Tucker, Mike Walker, Hazel M. Weir

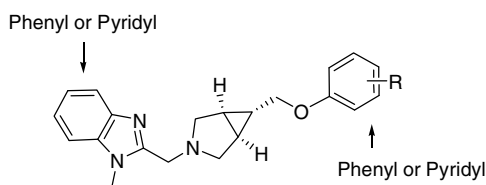


The SAR and development of an imidazole series (**3**) of CDK inhibitors are reported.

3-(Imidazolyl methyl)-3-aza-bicyclo[3.1.0]hexan-6-yl)methyl ethers: A novel series of mGluR2 positive allosteric modulators

pp 5493–5496

Lei Zhang*, Bruce N. Rogers, Allen J. Duplantier, Stanley F. McHardy, Ivan Efremov, Helen Berke, Weimin Qian, Andy Q. Zhang, Noha Maklad, John Candler, Angela C. Doran, John T. Lazzaro Jr., Alan H. Ganong

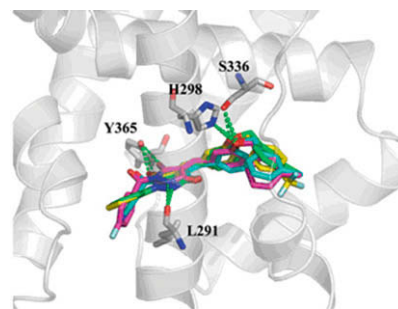


A novel series of mGluR2 positive allosteric modulators, 3-(imidazolyl methyl)-3-aza-bicyclo[3.1.0]hexan-6-yl)methyl ethers, is disclosed.

Pyrazolidine-3,5-dione derivatives as potent non-steroidal agonists of farnesoid X receptor: Virtual screening, synthesis, and biological evaluation

pp 5497–5502

Guanghai Deng, Weihua Li, Jianhua Shen*, Hualiang Jiang, Kaixian Chen, Hong Liu*



A series of novel non-steroidal compounds as FXR agonists and partial agonists was discovered by means of virtual screen and chemical synthesis.

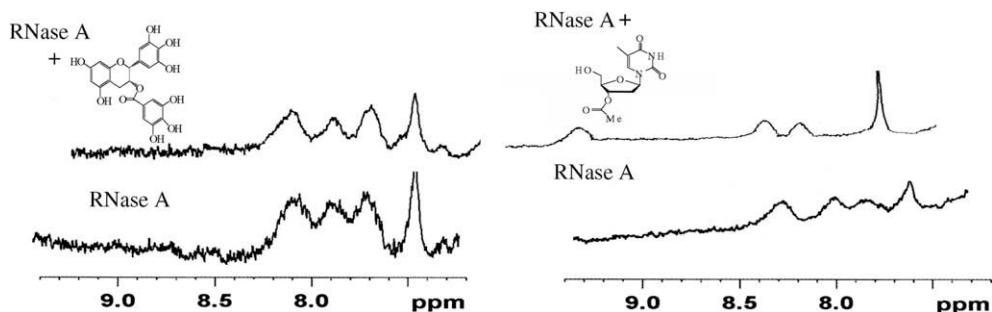


Using proton nuclear magnetic resonance to study the mode of ribonuclease A inhibition by competitive and noncompetitive inhibitors

pp 5503–5506

Kalyan Sundar Ghosh, Joy Debnath, Tanmaya Pathak, Swagata Dasgupta*

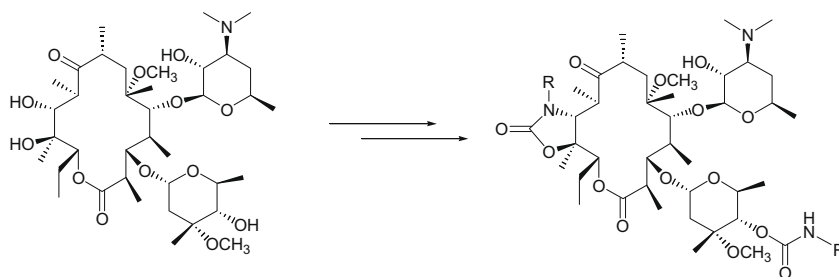
¹H NMR of C(2)-H of histidine residues of RNase A and its complexes with noncompetitive (left) and competitive (right) inhibitors.



Synthesis and antibacterial activity of 4-O-heteroarylcarbamoyl derivatives of macrolide

pp 5507–5511

Peng Xu, Lu Liu, Zhi-ping Jin, Guang-qiang Wang, Jian Liu, Yun Li, Ping-sheng Lei*



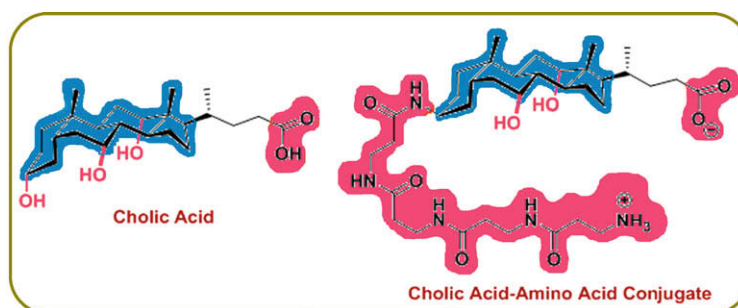
A series of novel 4''-position modified macrolide derivatives has been synthesized via a facile procedure. Their antibacterial activities were reported.



Synthesis of chimeric tetrapeptide-linked cholic acid derivatives: Impending synergistic agents

pp 5512–5517

Sudhir N. Bavikar, Deepak B. Salunke, Braja G. Hazra*, Vandana S. Pore*, Robert H. Dodd, Josiane Thierry, Fazal Shirazi, Mukund V. Deshpande, Sreenath Kadreppa, Samit Chattopadhyay

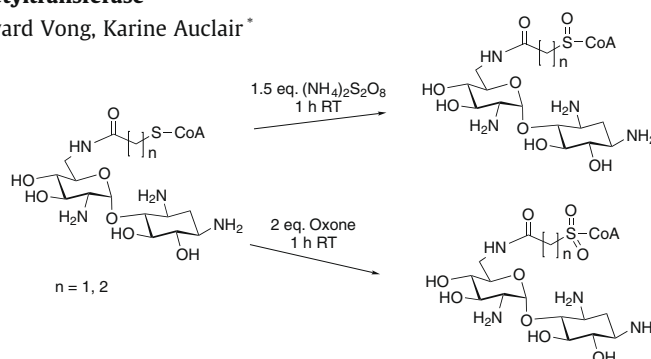


Synthesis and use of sulfonamide-, sulfoxide-, or sulfone-containing aminoglycoside–CoA bisubstrates as mechanistic probes for aminoglycoside N-6'-acetyltransferase

pp 5518–5522

Feng Gao, Xuxu Yan, Omar Zahr, Aaron Larsen, Kenward Vong, Karine Auclair*

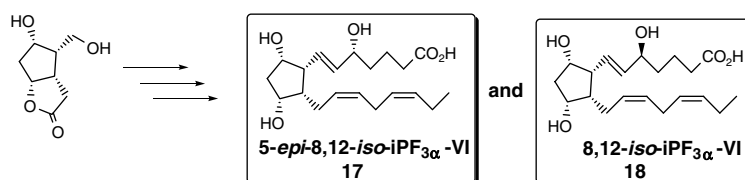
Selective oxidation of water-soluble sulfides to sulfoxides or sulfones in the presence of multiple functional groups. The aminoglycoside–CoA conjugates, prepared in two steps, are potent inhibitors of aminoglycoside N-6'-acetyltransferase.



Eicosapentaenoic-acid-derived isoprostanes: Synthesis and discovery of two major isoprostanes

pp 5523–5527

Chih-Tsung Chang, Pranav Patel, Namin Kang, John A. Lawson, Wen-Liang Song, William S. Powell, Garret A. FitzGerald, Joshua Rokach*

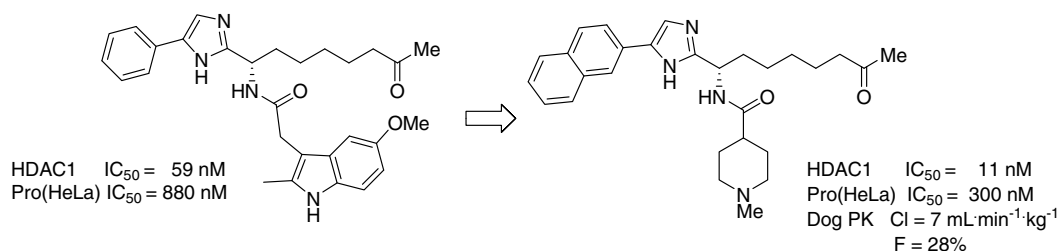


5-*epi*-8,12-*iso*-iPF_{3α}-VI **17** and 8,12-*iso*-iPF_{3α}-VI **18** were prepared by stereospecific synthesis and used to discover the corresponding novel iPs in human urine.

Optimization of a series of potent and selective ketone histone deacetylase inhibitors

pp 5528–5532

Giovanna Pescatore*, Olaf Kinzel, Barbara Attenni, Ottavia Cecchetti, Fabrizio Fiore, Massimiliano Fonsi, Michael Rowley, Carsten Schultz-Fademrecht, Sergio Serafini, Christian Steinkühler, Philip Jones

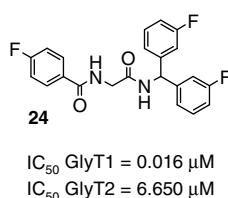


The optimization of a series of ketone small molecule HDAC inhibitors leading to potent and selective class I HDAC inhibitors with good dog PK is reported.

Design, synthesis and structure–activity relationship of simple bis-amides as potent inhibitors of GlyT1

pp 5533–5536

Synèse Jolidon*, Daniela Alberati, Adam Dowle, Holger Fischer, Dominik Hainzl, Robert Narquizian, Roger Norcross, Emmanuel Pinard



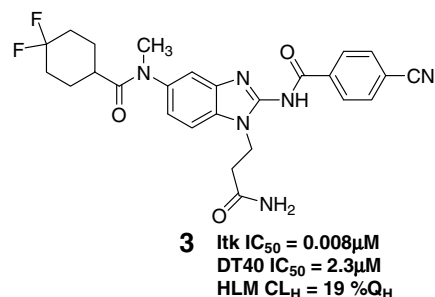
Novel classes of potent and small bis-amide type inhibitors of GlyT1 were developed through simplification of a benzodiazepinone-lead structure identified from high-throughput screening.

Itk kinase inhibitors: Initial efforts to improve the metabolic stability and the cell activity of the benzimidazole lead

pp 5537–5540

Kevin J. Moriarty, Michael Winters, Lei Qiao, Declan Ryan, Renee DesJarlis, Darius Robinson, Brian N. Cook, Mohammed A. Kashem, Paul V. Kaplita, Lisa H. Liu, Thomas M. Farrell, Hnin Hnin Khine, Josephine King, Steven S. Pullen, Gregory P. Roth, Ronald Magolda, Hidenori Takahashi *

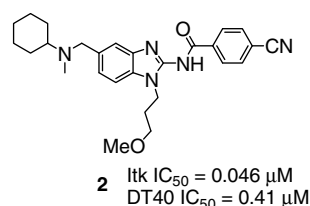
The SAR study and metabolically stabilized benzimidazole class Itk inhibitors are discussed.



5-Aminomethyl-1H-benzimidazoles as orally active inhibitors of inducible T-cell kinase (Itk)

pp 5541–5544

Michael P. Winters, Darius J. Robinson, Hnin Hnin Khine, Steven S. Pullen, Joseph R. Woska Jr., Ernest L. Raymond, Rosemarie Sellati, Charles L. Cywin, Roger J. Snow, Mohammed A. Kashem, John P. Wolak, Josephine King, Paul V. Kaplita, Lisa H. Liu, Thomas M. Farrell, Renee DesJarlais, Gregory P. Roth, Hidenori Takahashi *, Kevin J. Moriarty

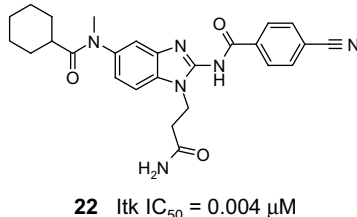


The SAR of this 5-aminomethyl-benzimidazole class of Itk inhibitors is discussed, along with in vivo efficacy in a mouse model.

Discovery, SAR and X-ray structure of 1H-benzimidazole-5-carboxylic acid cyclohexyl-methyl-amides as inhibitors of inducible T-cell kinase (Itk)

pp 5545–5549

Kevin J. Moriarty, Hidenori Takahashi *, Steven S. Pullen, Hnin Hnin Khine, Rosemarie H. Sallati, Ernest L. Raymond, Joseph R. Woska Jr., Deborah D. Jeanfavre, Gregory P. Roth, Michael P. Winters, Lei Qiao, Declan Ryan, Renee DesJarlais, Darius Robinson, Matthew Wilson, Mark Bobko, Brian N. Cook, Ho Yin Lo, Peter A. Nemoto, Mohammed A. Kashem, John P. Wolak, André White, Ronald L. Magolda, Bruce Tomczuk

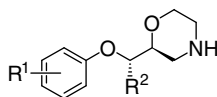


The SAR study of novel class of Itk inhibitors is discussed.

Design and synthesis of reboxetine analogs morpholine derivatives as selective norepinephrine reuptake inhibitors

pp 5550–5553

Wenjian Xu *, David L. Gray *, Shelly A. Glase, Nancy S. Barta

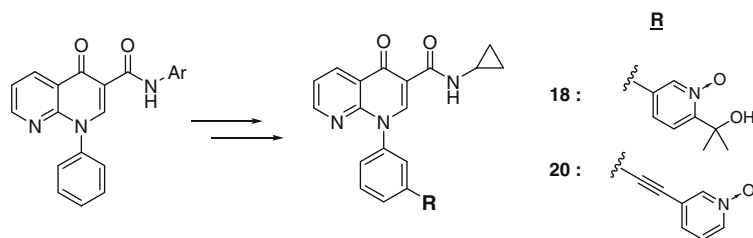


The design and synthesis of morpholine compounds with binding affinity for the norepinephrine reuptake transporter are reported. Effective chemical routes allowed access to compounds with varied physicochemical properties.

Optimization and structure–activity relationship of a series of 1-phenyl-1,8-naphthyridin-4-one-3-carboxamides: Identification of MK-0873, a potent and effective PDE4 inhibitor

pp 5554–5558

Daniel Guay*, Louise Boulet, Richard W. Friesen, Mario Girard, Pierre Hamel, Zheng Huang, France Laliberté, Sébastien Laliberté, Joseph A. Mancini, Eric Muise, Doug Pon, Angela Styhler

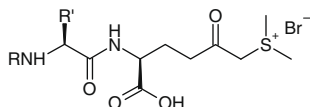


Discovery of the potent and orally active PDE4 inhibitors **18** and **20** (PDE4A IC_{50} = 6 and 7 nM; HWB IC_{50} = 0.12 and 0.18 μ M) is reported.

Synthesis of potent water-soluble tissue transglutaminase inhibitors

pp 5559–5562

Martin Griffin*, Alexandre Mongeot, Russell Collighan, Robert E. Saint, Richard A. Jones, Ian G. C. Coutts, Daniel L. Rathbone

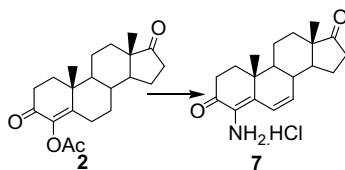


Dipeptide-based sulfonium peptidylmethylketones derived from 6-diazo-5-oxo-L-norleucine (DON) have been investigated as potential water-soluble inhibitors of extracellular transglutaminase. The lead compounds were prepared in four steps and exhibited potent activity against tissue transglutaminase.

Synthesis and evaluation of novel 4-amino-4,6-androstadiene-3,17-dione: An analog of formestane

pp 5563–5566

Sanjay K. Sharma*, Weizhong Zheng, Alummoottil V. Joshua, Douglas N. Abrams, Alexander J. B. McEwan

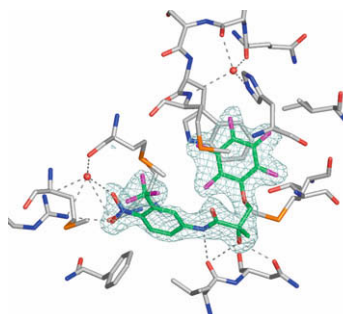


Synthesis of 4-amino-4,6-androstadiene-3,17-dione **7**, an analog of formestane used in breast cancer therapy as an aromatase inhibitor, from 4-acetoxy-4-androstene-3,17-dione **2** is described. This is the first report of a 4-amino diene (4,6) system in this series of molecules. The new and reported molecules were screened by the National Cancer Institute (NCI, Bethesda, USA) for in vitro antitumor activity against 60 human cancer cell lines. Compound **7** showed best activity against breast cancer cell line (MCF-7).

Effect of B-ring substitution pattern on binding mode of propionamide selective androgen receptor modulators

pp 5567–5570

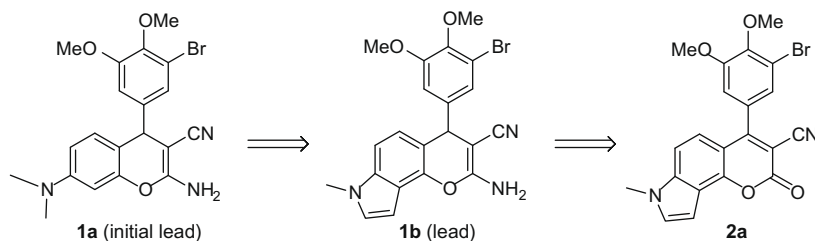
Casey E. Bohl, Zengru Wu, Jiyun Chen, Michael L. Mohler, Jun Yang, Dong Jin Hwang, Suni Mustafa, Duane D. Miller, Charles E. Bell, James T. Dalton*



Discovery of 4-aryl-2-oxo-2H-chromenes as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay

pp 5571–5575

William Kemnitzer, Songchun Jiang, Hong Zhang, Shailaja Kasibhatla, Candace Crogan-Grundy, Charles Blais, Giorgio Attardo, Real Denis, Serge Lamothe, Henriette Gourdeau, Ben Tseng, John Drewe, Sui Xiong Cai *



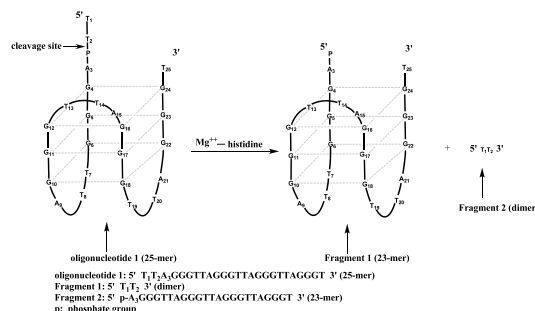
The synthesis and SAR of a group of apoptosis inducing 4-aryl-2-oxo-2H-chromenes with modifications at the 4-aryl, 7- and 8-positions is reported.

Site-specific self-cleavage of G-quadruplexes formed by human telomeric repeats

pp 5576–5580

Xinming Li, Magdelaine Tao Ng, Yifan Wang, Tianyan Zhou, Sock Teng Chua, Weixing Yuan, Tianhu Li *

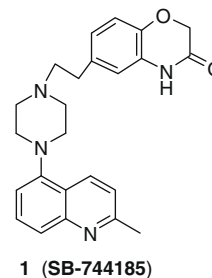
It is demonstrated that certain G-quadruplex structures formed by human telomeric repeats could perform site-specific self-cleaving actions.



Novel 5-HT_{1A/1B/1D} receptors antagonists with potent 5-HT reuptake inhibitory activity

pp 5581–5585

Halina T. Serafinowska *, Frank E. Blaney, Peter J. Lovell, Giancarlo G. Merlo, Claire M. Scott, Paul W. Smith, Kathryn R. Starr, Jeannette M. Watson

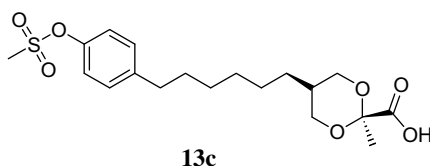


Novel 2-methyl-5-quinolinyl-1-piperazinylalkyl-3,4-dihydro-2H-1,4-benzoxazin-3-ones showing high affinities for the 5-HT_{1A/1B/1D} receptors coupled with potent 5-HT reuptake inhibitory activity have been discovered. Their synthesis, SAR as well as docking of compound **1** into the 5HT_{1A} receptor model and a model of the 5-HT transporter are discussed.

Discovery of a highly orally bioavailable c-5-[6-(4-Methanesulfonyloxyphenyl)hexyl]-2-methyl-1,3-dioxane-r-2-carboxylic acid as a potent hypoglycemic and hypolipidemic agent

pp 5586–5590

Harikishore Pingali *, Mukul Jain, Shailesh Shah, Sujay Basu, Pankaj Makadia, Amitgiri Goswami, Pandurang Zaware, Pravin Patil, Atul Godha, Suresh Giri, Ashish Goel, Megha Patel, Harilal Patel, Pankaj Patel

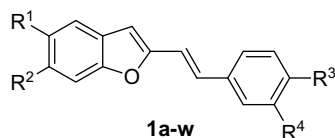


A series of novel 1,3-dioxane-2-carboxylic acid derivatives have been reported as PPAR α and γ agonists. Compound **13c** exhibited potent hypoglycemic and lipid lowering activity and high oral bioavailability.

Aminostyrylbenzofuran derivatives as potent inhibitors for A β fibril formation

pp 5591–5593

Ji Hun Byun, HyeYun Kim, YoungSoo Kim, Inhee Mook-Jung, Dong Jin Kim, Won Koo Lee*, Kyung Ho Yoo*

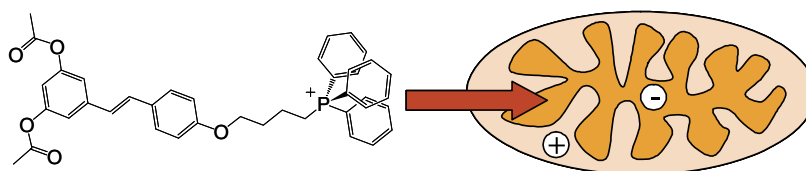


The synthesis of a novel series of aminostyrylbenzofuran derivatives **1a-w** and their inhibitory activities for A β fibril formation by thioflavin T (ThT) assay were described. Among them, compounds **1i** and **1q** exhibited excellent inhibitory activities (IC_{50} = 0.07 and 0.08 μ M, respectively) than those of Curcumin (IC_{50} = 0.80 μ M) and IMSB (IC_{50} = 8.00 μ M) as reference compounds. Both compounds were selected as promising candidates for further biological evaluation.

Development of mitochondria-targeted derivatives of resveratrol

pp 5594–5597

Lucia Biasutto, Andrea Mattarei, Ester Marotta, Alice Bradaschia, Nicola Sassi, Spiridione Garbisa, Mario Zoratti*, Cristina Paradisi

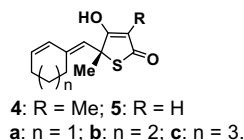


Synthesis, mitochondriotropic behavior, and cytotoxicity of resveratrol-triphenylphosphonium conjugates.

**Synthesis and biological activity of enantiomeric pairs of 5-[(E)-cycloalk-2-enylidenemethyl]thiolactomycin congeners**

pp 5598–5600

Kohei Ohata*, Shiro Terashima

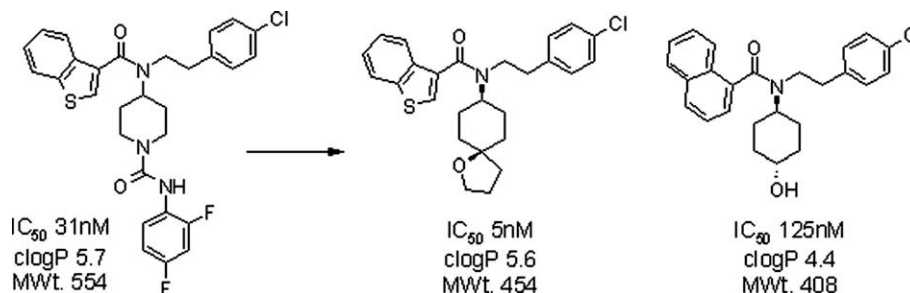


While all the synthesized congeners lacked in vitro antibacterial activity, some of the congeners (*ent*-**4b**, **5b** and *ent*-**4c**) were found to exhibit more potent mammalian type I FAS inhibitory activity than (*S*)-3-demethylthiolactomycin (*ent*-**2**) having an unnatural configuration.

Small, non-peptide C5a receptor antagonists: Part 1

pp 5601–5604

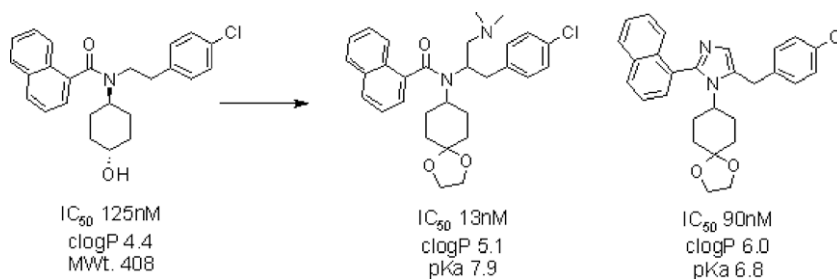
Julian Blagg, Charles Mowbray, David C. Pryde*, Gary Salmon, Esther Schmid, David Fairman, Kevin Beaumont



Small, non-peptide C5a receptor antagonists: Part 2

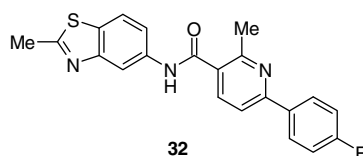
pp 5605–5608

Julian Blagg, Charles Mowbray, David Pryde*, Gary Salmon, David Fairman, Esther Schmid, Kevin Beaumont

**Design and synthesis of 6-phenylnicotinamide derivatives as antagonists of TRPV1**

pp 5609–5613

Susan M. Westaway*, Mervyn Thompson, Harshad K. Rami, Geoffrey Stemp, Leontine S. Trouw, Darren J. Mitchell, Jon T. Seal, Stephen J. Medhurst, Sarah C. Lappin, James Biggs, James Wright, Sandra Arpino, Jeffrey C. Jerman, Jennifer E. Cryan, Vicky Holland, Kim Y. Winborn, Tanya Coleman, Alexander J. Stevens, John B. Davis, Martin J. Gunthorpe

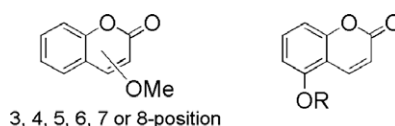


N-Quinolin-7-yl-6-phenylnicotinamide (**2**) was previously identified as a potent TRPV1 antagonist with activity in an in vivo model of inflammatory pain. Optimization of this lead through modification of both the biaryl and heteroaryl components has resulted in the discovery of 6-(4-fluorophenyl)-2-methyl-*N*-(2-methylbenzothiazol-5-yl)nicotinamide (**32**; SB-782443) which possesses an excellent overall profile and has been progressed into pre-clinical development.

Synthesis and biological evaluation of alkoxy coumarins as novel nematocidal constituents

pp 5614–5617

Kazuto Takaishi*, Minoru Izumi, Naomichi Baba, Kazuyoshi Kawazu, Shuhei Nakajima

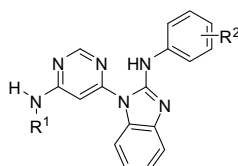


All monomethoxycoumarins and several 5-alkoxycoumarins were examined nematocidal activity and environment safety using crustacean and fish. Among them 5-alkoxycoumarins produced an excellent result even though their simple skeletons.

**Discovery of pyrimidine benzimidazoles as Lck inhibitors: Part I**

pp 5618–5621

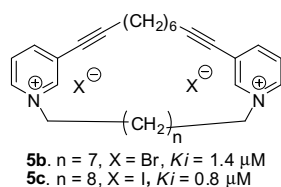
Guobao Zhang*, Pingda Ren, Nathanael S. Gray, Taebo Sim, Yi Liu, Xia Wang, Jianwei Che, Shin-Shay Tian, Mark L. Sandberg, Tracy A. Spalding, Russell Romeo, Maya Iskandar, Donald Chow, H. Martin Seidel, Donald S. Karanewsky, Yun He*



A series of 4-amino-6-benzimidazole-pyrimidines were designed and synthesized as potent Lck inhibitors.

bis-Pyridinium cyclophanes: Novel ligands with high affinity for the blood–brain barrier choline transporter pp 5622–5625

Zhenfa Zhang, Paul R. Lockman, Rajendar K. Mittapalli, David D. Allen, Linda P. Dwoskin, Peter A. Crooks*



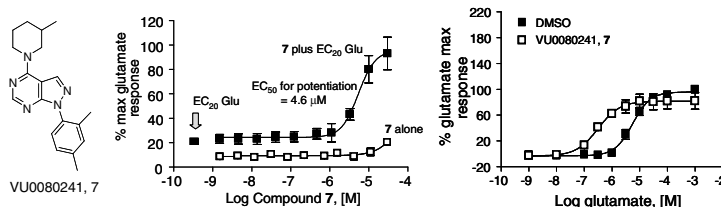
bis-Pyridinium cyclophanes (**5**) designed as conformationally restricted *bis*-quaternary ammonium compounds exhibited high affinity for the blood–brain barrier choline transporter; **5c** and **5b** ($K_i = 0.8$ and $1.4 \mu\text{M}$, respectively) represent two of the most potent blood–brain barrier choline transporter ligands known.

Positive allosteric modulators of the metabotropic glutamate receptor subtype 4 (mGluR4): Part I.

pp 5626–5630

Discovery of pyrazolo[3,4-*d*]pyrimidines as novel mGluR4 positive allosteric modulators

Colleen M. Niswender, Evan P. Lebois, Qingwei Luo, Kwangho Kim, Hubert Muchalski, Huiyong Yin, P. Jeffrey Conn, Craig W. Lindsley*

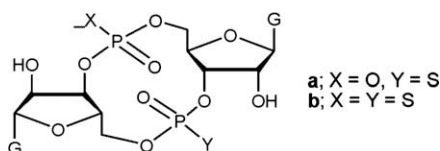


The synthesis and SAR of a novel mGluR4 positive allosteric modulator **7**, VU0080241, is described. VU0080241 displayed an EC_{50} of $4.6 \mu\text{M}$ and shifted the glutamate response curve 11.8- to 27-fold to the left.

Synthesis and immunostimulatory properties of the phosphorothioate analogues of cdiGMP

pp 5631–5634

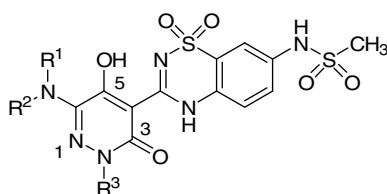
Hongbin Yan*, Xiaolu Wang, Rhonda KuoLee, Wangxue Chen



The phosphorothioate analogues of cdiGMP were synthesized and their immunostimulatory properties were compared.

Novel HCV NS5B polymerase inhibitors derived from 4-(1',1'-dioxo-1',4'-dihydro-1' λ^6 -benzo[1',2',4']thiadiazin-3'-yl)-5-hydroxy-2H-pyridazin-3-ones. Part 5: Exploration of pyridazinones containing 6-amino-substituents pp 5635–5639

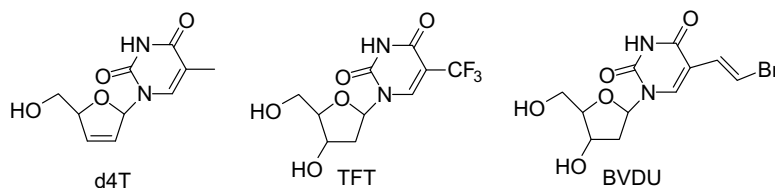
Peter S. Dragovich*, Julie K. Blazel, David A. Ellis, Qing Han, Ruhi Kamran, Charles R. Kissinger, Laurie A. LeBrun, Lian-Sheng Li, Douglas E. Murphy, Michael Noble, Rupal A. Patel, Frank Ruebsam, Maria V. Sergeeva, Amit M. Shah, Richard E. Showalter, Chinh V. Tran, Mei Tsan, Stephen E. Webber, Leo Kirkovsky, Yuefen Zhou



Synthesis of nucleoside-based antiviral drugs in ionic liquids

pp 5640–5642

Vineet Kumar, Sanjay V. Malhotra *



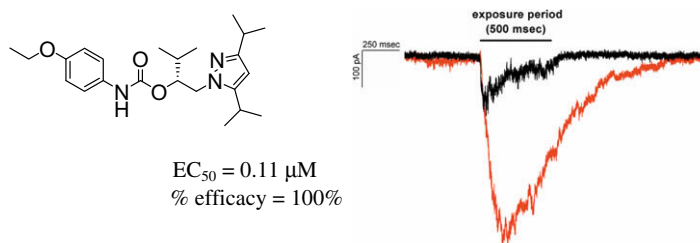
Nucleoside-based antiviral drugs have been synthesized using imidazolium-based ionic liquids as reaction medium. The ionic liquids were proved to be better solvents for all the nucleoside in terms of solubility and reaction medium as compared to conventional molecular solvents.



Synthesis and activity of substituted carbamates as potentiators of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor

pp 5643–5647

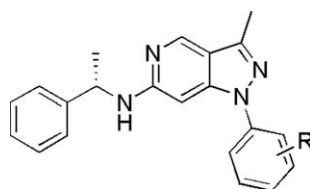
Stephanie K. Springer *, Katrina S. Woodin, Virginia Berry, Alessandro A. Boezio, Lei Cao, Kristie Clarkin, Jean-Christophe Harmange, Markus Hierl, Johannes Knop, Annika B. Malmberg, Jeff S. McDermott, Hung Q. Nguyen, Daniel Waldon, Brian K. Albrecht, Stefan I. McDonough



Design and synthesis of 2-amino-pyrazolopyridines as Polo-like kinase 1 inhibitors

pp 5648–5652

Raymond V. Fucini *, Emily J. Hanan, Michael J. Romanowski, Robert A. Elling, Willard Lew, Kenneth J. Barr, Jiang Zhu, Joshua C. Yoburn, Yang Liu, Bruce T. Fahr, Junfa Fan, Yafan Lu, Phuongly Pham, Ingrid C. Choong, Erica C. VanderPorten, Minna Bui, Hans E. Purkey, Marc J. Evanchik, Wenjin Yang



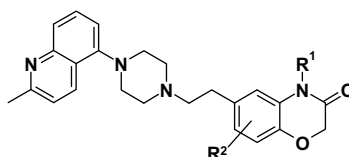
A series of 2-amino-pyrazolopyridine analogs was identified as inhibitors of Polo-like kinase 1 (Plk1). The SAR studies led to the discovery of several compounds demonstrating Plk1 inhibition in cell based assays. Co-crystal structures of inhibitors with zPlk1 demonstrate key binding motifs.



6-[2-(4-Aryl-1-piperazinyl)ethyl]-2H-1,4-benzoxazin-3(4H)-ones: Dual-acting 5-HT₁ receptor antagonists and serotonin reuptake inhibitors

pp 5653–5656

Steven M. Bromidge *, Barbara Bertani, Manuela Borriello, Stefania Faedo, Laurie J. Gordon, Enrica Granci, Matthew Hill, Howard R. Marshall, Luigi P. Stasi, Valeria Zucchelli, Giancarlo Merlo, Alessia Vesentini, Jeannette M. Watson, Laura Zonzini



Investigation of a series 6-[2-(4-aryl-1-piperazinyl)ethyl]-2H-1,4-benzoxazin-3(4H)-ones has led to the discovery of potent 5-HT_{1A/1B/1D} receptor antagonists with and without additional SerT affinity. Modulation of the different target activities gave compounds with a range of profiles suitable for further in vivo characterization.

pp 5657–5659

The chemical structure shows a central imidazole-2-one ring. At position 4, there is a vinyl group (-CH=CH-) connected to a 4-hydroxyphenyl ring. At position 5, there is a carbonyl group (=O). At position 2, there is a methylene group (-CH2-) connected to another 4-hydroxyphenyl ring. The structure is symmetrical with respect to the central imidazole ring.

Dehydrocoelenterazine

pp 5660–5663



pp 5664–5667

Substrate

ATP → ADP, P_i

Biotin-DIFO

Streptavidin



pp 5668–5671

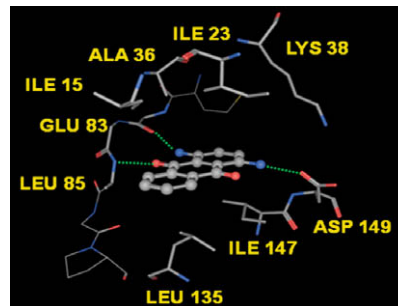
CN1C=CC=C2C(=C1)C(=C(C=C2)C(=O)NCCCCCC(=O)NC(C)C(=O)NC(C)C(=O)OC(=O)C3=CC=CC=C3)N[C@@H]4C[C@H](C)[C@@H](C)C(=O)N4

Identification of novel protein kinase CK1 delta (CK1 δ) inhibitors through structure-based virtual screening

pp 5672–5675

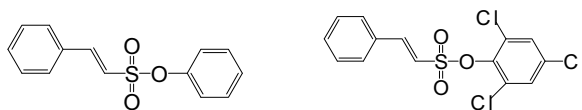
Giorgio Cozza, Alessandra Gianoncelli, Monica Montopoli, Laura Caparrotta, Andrea Venerando, Flavio Meggio, Lorenzo A. Pinna, Giuseppe Zagotto, Stefano Moro*

Using a structure-based virtual screening (SBVS) approach we have identified two anthraquinones as novel CK1 δ inhibitors. These compounds are among the most potent and selective CK1 δ inhibitors known today (IC_{50} = 0.3 and 0.6 μ M, respectively).

**Analogues of 2-phenyl-ethenesulfonic acid phenyl ester have dual functions of inhibiting expression of inducible nitric oxide synthase and activating peroxisome proliferator-activated receptor γ**

pp 5676–5679

Yue-Zhi Lee, Cheng-Wei Yang, Iou-Jiun Kang, Ssu-Hui Wu, Yu-Sheng Chao, Jyh-Haur Chern, Shiow-Ju Lee*

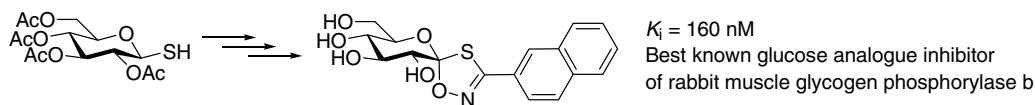


Dual functions of 2-phenyl-ethenesulfonic acid phenyl ester analogues inhibit expression of inducible nitric oxide synthase and activate peroxisome proliferator-activated receptor γ .

Novel design principle validated: Glucopyranosylidene-spiro-oxathiazole as new nanomolar inhibitor of glycogen phosphorylase, potential antidiabetic agent

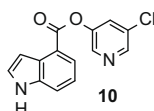
pp 5680–5683

László Somsák*, Veronika Nagy, Sébastien Vidal, Katalin Czifrák, Eszter Berzsényi, Jean-Pierre Praly*

**Design, synthesis and antiviral efficacy of a series of potent chloropyridyl ester-derived SARS-CoV 3CLpro inhibitors**

pp 5684–5688

Arun K. Ghosh*, Gangli Gong, Valerie Grum-Tokars, Debbie C. Mulhearn, Susan C. Baker, Melissa Coughlin, Bellur S. Prabhakar, Katrina Sleeman, Michael E. Johnson, Andrew D. Mesecar

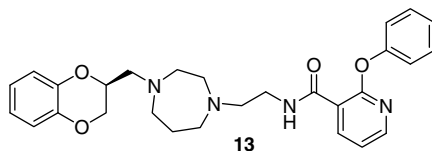


SARS 3CLpro IC_{50} = 30 nM; antiviral EC_{50} = 6.9 μ M

Design, synthesis and biological evaluation of a series of chloropyridyl ester-derived SARS-CoV 3CLpro Inhibitors are described. Inhibitor **10** has shown potent activity in both enzyme inhibitory and antiviral assays.

Identification and SAR around *N*-[2-[4-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-[1,4]diazepan-1-yl]-ethyl]-2-phenoxy-nicotinamide, a selective α_{2C} adrenergic receptor antagonist pp 5689–5693

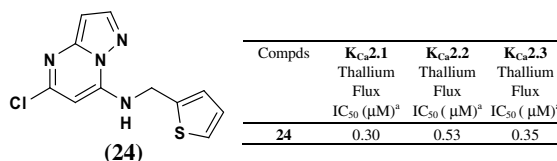
Snahel D. Patel, Wendy M. Habeski, Hyunsuk Min, Jiansu Zhang, Robin Roof, Bradley Snyder, Gary Bora, Brian Campbell, Cheryl Li, Debra Hidayetoglu, Douglas S. Johnson, Archana Chaudhry, Maura E. Charlton, Natasha M. Kablaoui*



The discovery of CNS-penetrant and selective α_{2C} adrenergic receptor antagonist *N*-[2-[4-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-[1,4]diazepan-1-yl]-ethyl]-2-phenoxy-nicotinamide, **13**, is described. Structure–activity studies demonstrate the requirements for binding affinity, functional activity, and selectivity over other α_2 -AR subtypes.

Preliminary SAR studies on non-apamin-displacing 4-(aminomethylaryl)pyrazolopyrimidine K_{Ca} channel blockers pp 5694–5697

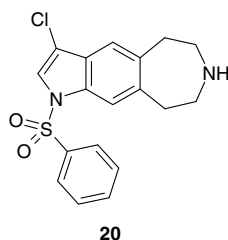
Robert G. Gentles*, Shuanghua Hu, Yazhong Huang, Katherine Grant-Young, Michael A. Poss, Charles Andres, Tracey Fiedler, Ronald Knox, Nicholas Lodge, C. David Weaver, David G. Harden



An exploratory SAR study on a series of non-apamin-displacing 4-(aminomethylaryl)pyrazolopyrimidine K_{Ca} channel blockers is described, and their selectivity against K_{Ca} channel subtypes is reported. The aminomethylthiophene derivative **24**, was the most potent analog identified in the series.

Tricyclic azepine derivatives as selective brain penetrant 5-HT₆ receptor antagonists pp 5698–5700

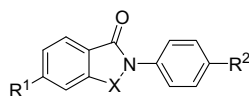
Giancarlo Trani*, Stuart M. Baddeley, Michael A. Briggs, Tsu T. Chuang, Nigel J. Deeks, Christopher N. Johnson, Abir A. Khazragi, Tania L. Mead, Andrew D. Medhurst, Peter H. Milner, Leann P. Quinn, Alison M. Ray, Dean A. Rivers, Tania O. Stean, Geoffrey Stemp, Brenda K. Trail, David R. Witty



The syntheses of novel, highly brain penetrant 5-HT₆ receptor antagonists such as **20** are described.

[¹⁸F]-labeled isoindol-1-one and isoindol-1,3-dione derivatives as potential PET imaging agents for detection of β -amyloid fibrils pp 5701–5704

Ji Hoon Lee, Seong Rim Byeon, YoungSoo Kim, Soo Jeong Lim, Seung Jun Oh, Dae Hyuk Moon, Kyung Ho Yoo, Bong Young Chung*, Dong Jin Kim*



X = CH₂, CO
 R¹ = O(CH₂)₂F, O(CH₂)₃F, O(CH₂)₂F¹⁸
 R² = NH₂, NHCH₃, N(CH₃)₂


Novel series of isoindol-1-one and isoindol-1,3-dione derivatives for β -amyloid-specific binding agents were synthesized and evaluated by a competitive binding assay with [¹²⁵I]TZDM against A β 42 aggregates. Two new [¹⁸F]-labeled isoindole derivatives were synthesized and evaluated as potential β -amyloid imaging probes based on the in vivo pharmacokinetic profiles. In conclusion, these compounds are promising PET imaging probes for studying accumulation of A β fibrils in the brains of AD patients.

OTHER CONTENTS

Summary of instructions to authors

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* 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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