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Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 10, 2011

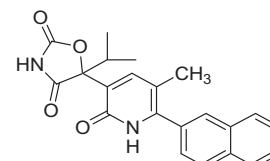
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Structure–activity relationship studies of novel 3-oxazolidinedione-6-naphthyl-2-pyridinones as potent and orally bioavailable EP₃ receptor antagonists pp 2806–2811

Ángel I. Morales-Ramos*, Yue H. Li, Mark Hilfiker*, John S. Mecom, Patrick Eidam, Dongchuan Shi, Pei-San Tseng, Carl Brooks, David Zhang, Ning Wang, Jon-Paul Jaworski, Dwight Morrow, Harvey Fries, Richard Edwards, Jian Jin*

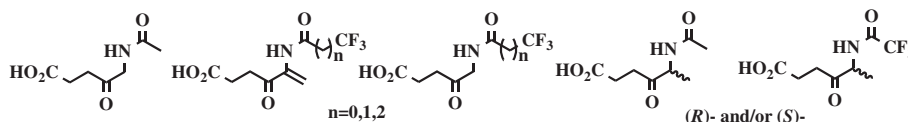
3-Oxazolidinedione-6-naphthyl-2-pyridinones are presented as novel and subtype selective EP₃ antagonists. The synthesis and extensive SAR that led to the discovery of compound **29** are described.



29, hEP₃ FLIPR fpK_i = 8.2
Cl (mL/min/kg) = 1.4
T_{1/2} (h) = 6.6
Oral F (%) = 100

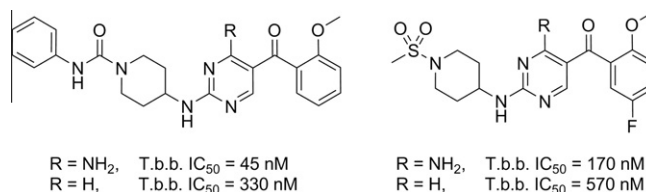
Synthesis and antibacterial activity of alaremycin derivatives for the porphobilinogen synthase pp 2812–2815

Noritaka Iwai*, Kyosuke Nakayama, Jumpei Oku, Tomoya Kitazume*



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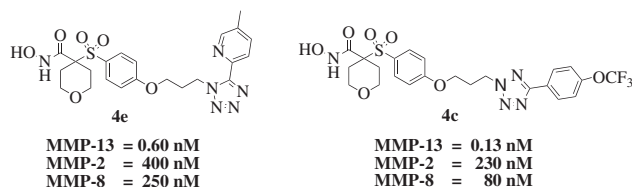
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MMP-13 selective α -sulfone hydroxamates: A survey of P1' heterocyclic amide isosteres

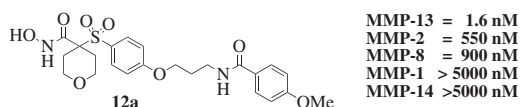
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Thomas E. Barta*, Daniel P. Becker, Louis J. Bedell, Alan M. Easton, Susan L. Hockerman, James Kiefer, Grace E. Munie, Karl J. Mathis, Madeleine H. Li, Joseph G. Rico, Clara I. Villamil, Jennifer M. Williams

**MMP-13 selective alpha-sulfone hydroxamates: Identification of selective P1' amides**

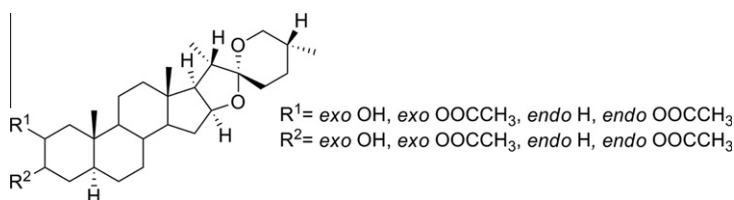
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Yvette M. Fobian, John N. Freskos, Thomas E. Barta*, Louis J. Bedell, Robert Heintz, Darren J. Kassab, James R. Kiefer, Brent V. Mischke, John M. Molyneaux, Patrick Mullins, Grace E. Munie, Daniel P. Becker

**Synthesis and antifungal activity of functionalized 2,3-spirosterane isomers**

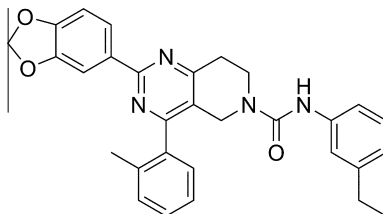
pp 2826–2831

Sunil Kumar Upadhyay, Clinton C. Creech, Katharine L. Bowdy, Edwin D. Stevens, Branko S. Jursic, Donna M. Neumann*

**Synthesis and SAR of pyrimidine-based, non-nucleotide P2Y₁₄ receptor antagonists**

pp 2832–2835

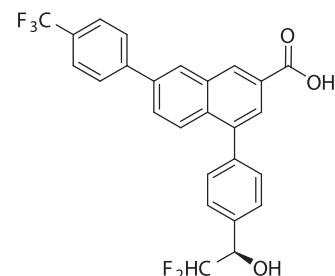
Daniel Guay, Christian Beaulieu, Michel Belley, Sheldon N. Crane, Jeancarlo DeLuca, Yves Gareau, Martine Hamel, Martin Henault, Huda Hyjazie, Stacia Kargman, Chi Chung Chan, Lijing Xu, Robert Gordon, Lianhai Li, Yael Mamane, Nicolas Morin, Joseph Mancini, Michel Thérien, Geoffrey Tranmer, Vouy Linh Truong, Zhaoyin Wang, W. Cameron Black*



The identification of 4,7-disubstituted naphthoic acid derivatives as UDP-competitive antagonists of P2Y₁₄

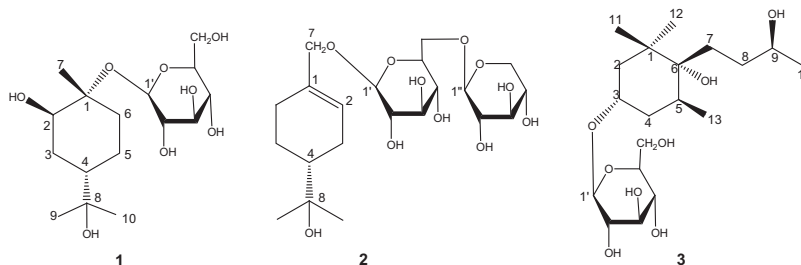
pp 2836–2839

Jacques Yves Gauthier, Michel Belley, Denis Deschênes, Jean-François Fournier, Sébastien Gagné, Yves Gareau, Martine Hamel, Martin Hénault, Huda Hyjazie, Stacia Kargman, Geneviève Lavallée, Jean-François Levesque, Lianhai Li, Yaël Mamane, Joseph Mancini, Nicolas Morin, Erin Mulrooney, Joël Robichaud, Michel Thérien, Geoffrey Tranmer, Zhaoyin Wang, Jin Wu, W. Cameron Black*

**New monoterpene glycosides and phenolic compounds from *Distylium racemosum* and their inhibitory activity against ribonuclease H**

pp 2840–2844

Jeong Ah Kim, Seo Young Yang, Anthony Wamiru, James B. McMahon, Stuart F. J. Le Grice, John A. Beutler, Young Ho Kim*



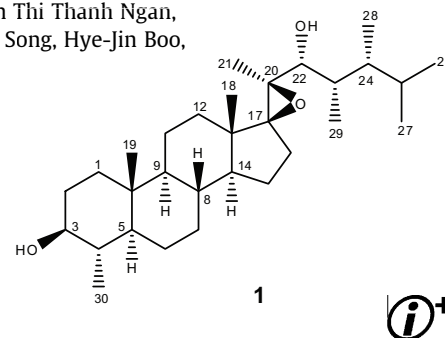
Two new monoterpene glycosides, distyloside A–B (**1–2**), and a new megastigmane glucoside, iso-dihydrodendranthemside A (**3**) were isolated from twigs and leaves of *Distylium racemosum* Siebold & Zucc. (Hamamelidaceae).

Cytotoxic and PPARs transcriptional activities of sterols from the Vietnamese soft coral *Lobophytum laevigatum*

pp 2845–2849

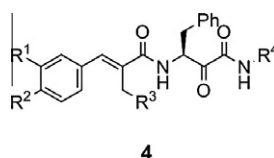
Tran Hong Quang, Tran Thu Ha, Chau Van Minh, Phan Van Kiem, Hoang Thanh Huong, Nguyen Thi Thanh Ngan, Nguyen Xuan Nhiem, Nguyen Huu Tung, Nguyen Phuong Thao, Dinh Thi Thu Thuy, Seok Bean Song, Hye-Jin Boo, Hee-Kyoung Kang, Young Ho Kim*

A new unusual sterol, named lobophytosterol (**1**), and five known metabolites (**2–6**) were isolated from the methanol extract of the soft coral *Lobophytum laevigatum*. Compounds **1–3** showed cytotoxic activity against selected human cancer cell lines. Treatment of these cells with compound **1** resulted in an induction of apoptosis evident by chromatin condensation in treated cells. Besides, compounds **2**, **4**, and **6** significantly upregulated PPARs transcriptional activity dose-dependently in Hep-G2 cells.

**Synthesis of cinnamoyl ketoamides as hybrid structures of antioxidants and calpain inhibitors**

pp 2850–2854

Yeong Jae Yoo, Dong Hyuk Nam, Seo Yun Jung, Jae Wan Jang, Hyoung Ja Kim, Changbae Jin, Ae Nim Pae, Yong Sup Lee*

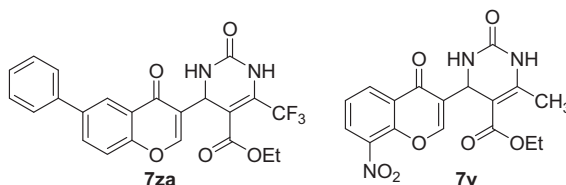


The excessive calpain activation causes serious cellular damage or even cell death in neurological disorders. Oxidative stress has also been implicated in the initiation or progression of neurodegenerative diseases. In the present study, a series of cinnamoyl ketoamides **4a–4j** were synthesized as hybrid structures of antioxidants and calpain inhibitors. Among synthesized, compound **4e** was the most potent inhibitor of μ -calpain ($IC_{50} = 0.13 \mu M$) and also exhibited strong antioxidant activities in three assay systems.

Synthesis, structure–activity relationship of novel substituted 4H-chromen-1,2,3,4-tetrahydropyrimidine-5-carboxylates as potential anti-mycobacterial and anticancer agents

pp 2855–2859

B. China Raju*, R. Nageswara Rao, P. Suman, P. Yogeeswari, D. Sriram*, Thokhir Basha Shaik, Shasi Vardhan Kalivendi



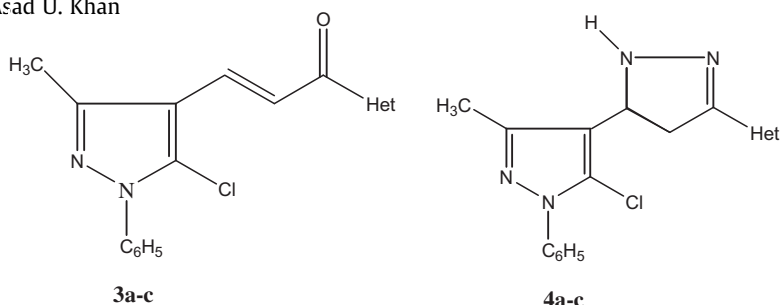
Series of 4H-chromen-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives were synthesized, screened for their anti-mycobacterial and anticancer activities, among them compound **7za** is more potent anti-mycobacterial, **7v** more potent anticancer agents compared to standard drugs and are being reported in this study for the first time to serve as a model compounds for design and development of therapeutic based anti-mycobacterial and anticancer activity.



Thermal solvent-free synthesis of novel pyrazolyl chalcones and pyrazolines as potential antimicrobial agents

pp 2860–2865

Zeba N. Siddiqui*, T. N. Mohammed Musthafa, Anis Ahmad, Asad U. Khan

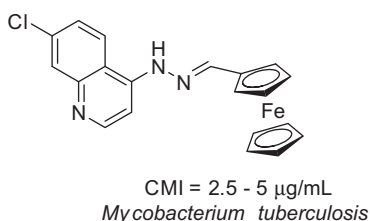


A novel series of pyrazolyl chalcones (**3a–c**) and pyrazolines (**4a–c**) were synthesized under thermal solvent-free condition and were screened for their in vitro antibacterial and antifungal activities.

Synthesis and in vitro antitubercular activity of ferrocene-based hydrazones

pp 2866–2868

Aman Mahajan, Laurent Kremer, Stefan Louw, Yann Guéradel, Kelly Chibale, Christophe Biot*

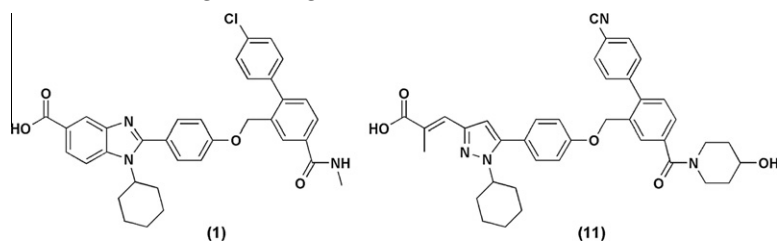


The Synthesis and evaluation of a novel class of (E)-3-(1-cyclohexyl-1H-pyrazol-3-yl)-2-methylacrylic acid Hepatitis C virus polymerase NS5B inhibitors

pp 2869–2872

Scott W. Martin*, Peter Glunz*, Brett R. Beno, Carl Bergstrom, Jeffrey L. Romine, E. Scott Priestley, Makenzie Newman, Min Gao, Susan Roberts, Karen Rigat, Robert Fridell, Dike Qiu, Galina Knobloch, Ying-Kai Wang

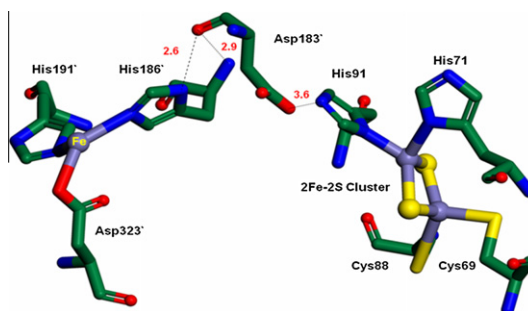
Presented is the identification and evaluation of a novel series of (E)-3-(1-cyclohexyl-1H-pyrazol-3-yl)-2-methylacrylic acid derivatives identified from a deannulation study performed on the reported benzimidazole NS5B inhibitor, **1**. This resulted in the identification of (E)-3-(2-(4-((4'-cyano-4-(4-hydroxypiperidine-1-carbonyl)biphenyl-2-yl)-methoxy)phenyl)-1-cyclohexyl-1H-imidazol-4-yl)-2-methylacrylic acid (**11**) as a potent inhibitor of NS5B. Potential pathways for the further optimization of this series are suggested.



Further biochemical studies on aminopyrrolnitrin oxygenase (PrnD)

pp 2873–2876

Manish Kumar Tiwari, Jung-Kul Lee*, Hee-Jung Moon, Huimin Zhao*

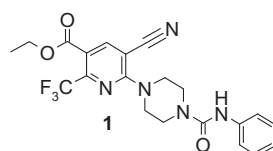


The electron in the PrnD Rieske oxygenase can be transferred by either of two pathways, one involving Asp183' and the other involving Asn180'.

**A novel series of piperazinyl-pyridine ureas as antagonists of the purinergic P2Y₁₂ receptor**

pp 2877–2881

Peter Bach*, Jonas Boström, Kay Brickmann, J. J. J. van Giezen, Ragnar Hovland, Annika U. Petersson, Asim Ray, Fredrik Zetterberg

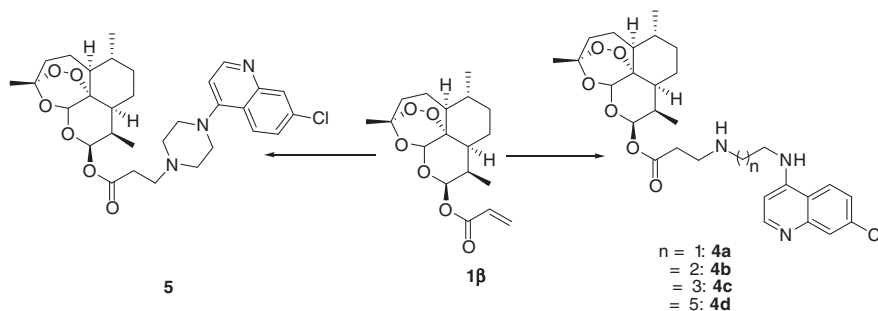


A novel series of piperazinyl-pyridine ureas, exemplified by **1**, was discovered to be P2Y₁₂ antagonists. SAR investigations presented several compounds with potencies in the sub-micromolar range. The pyridine 3-ethoxycarbonyl substituent, the urea *N*-H of the linker, and the right-hand aromatic ring all contributed significantly to potency. Solubility could be increased by shifting from 2-CF₃/5-CN to 2-H/5-Cl pyridines.

**Antiplasmodial and antitumor activity of dihydroartemisinin analogs derived via the aza-Michael addition reaction**

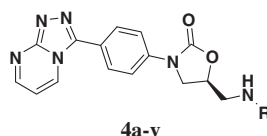
pp 2882–2886

Tzu-Shean Feng, Eric M. Guantai, Margo J. Nell, Constance E. J. van Rensburg, Heinrich C. Hoppe, Kelly Chibale*

**Synthesis and in vitro activity of novel 1,2,4-triazolo[4,3-a]pyrimidine oxazolidinone antibacterial agents**

pp 2887–2889

Manoj K. Khera*, Ian A. Cliffe, Tarun Mathur, Om Prakash

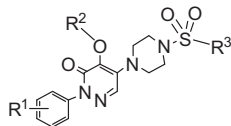


The synthesis and antibacterial activity of 3-(4-([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)-phenyl)oxazolidin-2-ones is reported.

SAR studies of pyridazinone derivatives as novel glucan synthase inhibitors

pp 2890–2893

Gang Zhou*, Pauline C. Ting, Robert Aslanian, Jianhua Cao, David W. Kim, Rongze Kuang, Joe F. Lee, John Schwerdt, Heping Wu, R. Jason Herr, Andrew J. Zych, Jinhai Yang, Sang Lam, Samuel Wainhaus, Todd A. Black, Paul M. McNicholas, Yiming Xu, Scott S. Walker

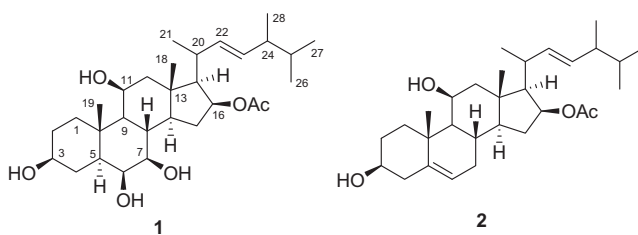


A series of small molecular pyridazinone analogs has been studied as potent β -1,3-glucan synthase inhibitors.

Penicisteroids A and B, antifungal and cytotoxic polyoxygenated steroids from the marine alga-derived endophytic fungus *Penicillium chrysogenum* QEN-24S

pp 2894–2897

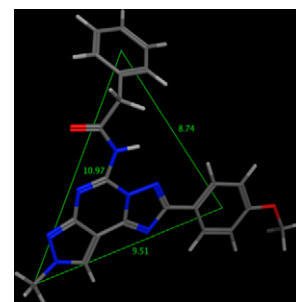
Shu-Shan Gao, Xiao-Ming Li, Chun-Shun Li, Peter Proksch, Bin-Gui Wang*

**Pharmacophore elucidation for a new series of 2-aryl-pyrazolo-triazolo-pyrimidines as potent human A₃ adenosine receptor antagonists**

pp 2898–2905

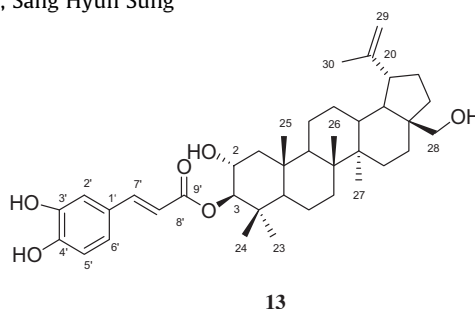
Siew Lee Cheong, Stephanie Federico, Gopalakrishnan Venkatesan, Priyanka Paira, Yi-Ming Shao, Giampiero Spalluto, Chun Wei Yap*, Giorgia Pastorin*

The ligand-based pharmacophore elucidation performed on 2-aryl-pyrazolo-triazolo-pyrimidines as potent hA₃ adenosine receptor antagonists has provided new insights on the structural characteristics deemed critical for the affinity at the hA₃ adenosine receptor.

**Antifibrotic constituents of *Alnus firma* on hepatic stellate cells**

pp 2906–2910

Mina Lee, Mi Kyeong Lee, Young Choong Kim, Sang Hyun Sung*



13

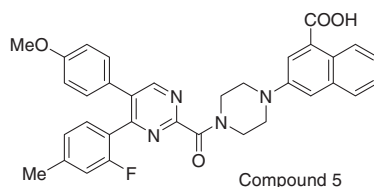
A new triterpenoid characterized as lup-20(29) en-2,28-diol-3-yl caffeate was isolated with 12 known diarylheptanoids from the barks of *Alnus firma*. Antifibrotic constituents of *A. firma* on HSCs might suggest the therapeutic potentials against liver fibrosis.



Discovery of pyrimidine carboxamides as potent and selective CCK1 receptor agonists

pp 2911–2915

Liping Wang*, James A. Hubert, Susan J. Lee, Jie Pan, Su Qian, Marc L. Reitman, Alison M. Strack, Drew T. Weingarh, Douglas J. MacNeil, Ann E. Weber, Scott D. Edmondson



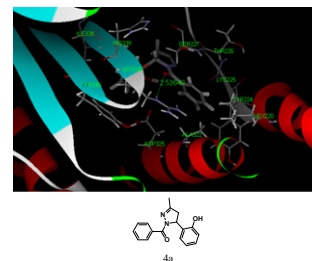
A series of six-membered heterocycle carboxamides were synthesized and evaluated as cholecystokinin 1 receptor (CCK1R) agonists. A pyrimidine core proved to be the best heterocycle, and SAR studies resulted in the discovery of analog **5**, a potent and structurally diverse CCK1R agonist.

**Design and synthesis of *N*-phenylacetyl (sulfonyl) 4,5-dihydropyrazole derivatives as potential antitumor agents**

pp 2916–2920

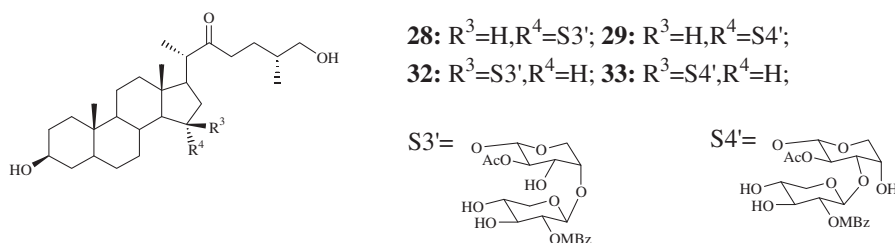
Xin-Hua Liu, Ban-Feng Ruan, Jing-Xin Liu, Bao-An Song, Ling-Hong Jing, Jun Li*, Yang Yang, Hai-Liang Zhu*, Xing-Bao Qi

Novel 5-(2-hydroxyphenyl)-3-methyl-4,5-dihydropyrazol-1-yl-anone as potential telomerase inhibitors were synthesized. The bioassay tests show that compound **4a** exhibited high activity against human gastric cancer cell SGC-7901, Hep-G2 and PC-3 cell lines. All title compounds were assayed for telomerase inhibition, the results show that compound **4a** can inhibit telomerase. Docking simulation was performed to position compound **4a** into the telomerase (3DU6) active site to determine the probable binding model.

**Synthesis of 5(6)-dihydro-OSW-1 analogs bearing three kinds of disaccharides linking at 15-hydroxy and their antitumor activities**

pp 2921–2924

Yuyao Guan, Dan Zheng, Liang Zhou, Haixing Wang, Zheng Yan, Nan Wang, Hong Chang, Pingping She, Pingsheng Lei*



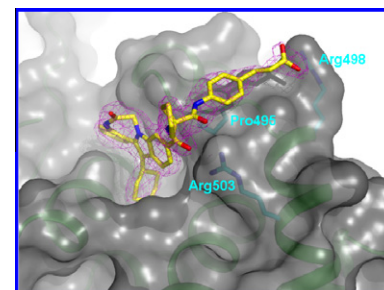
Eight 15(α)-O-glycosyl 5(6)-dihydro-OSW-1 analogs bearing three kinds of disaccharide side chains were synthesized and evaluated for their antitumor activities.

**Syntheses and initial evaluation of a series of indolo-fused heterocyclic inhibitors of the polymerase enzyme (NS5B) of the hepatitis C virus**

pp 2925–2929

Xiaofan Zheng*, Thomas W. Hudyma, Scott W. Martin, Carl Bergstrom, Min Ding, Feng He, Jeffrey Romine, Michael A. Poss, John F. Kadow, Chong-Hwan Chang, John Wan, Mark R. Witmer, Paul Morin, Daniel M. Camac, Steven Sheriff, Brett R. Beno, Karen L. Rigat, Ying-Kai Wang, Robert Fridell, Julie Lemm, Dike Qiu, Mengping Liu, Stacey Voss, Lenore Pelosi, Susan B. Roberts, Min Gao, Jay Knipe, Robert G. Gentles

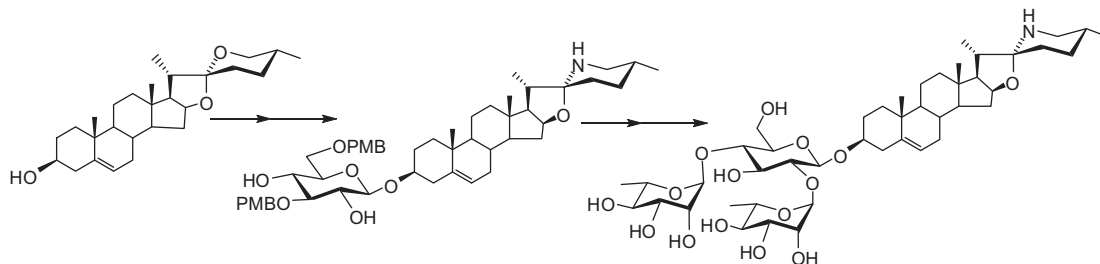
Presented are initial SAR studies on a series of bridged 2-arylindole-based NS5B inhibitors. The introduction of bridging elements between the indole N1 and the *ortho*-position of the 2-aryl moiety results in conformationally constrained heterocycles that possess multiple additional vectors for further exploration. The binding mode and pharmacokinetic (PK) properties of select examples are reported.



Total synthesis of solamargine

pp 2930–2933

Guohua Wei, Jing Wang, Yuguo Du*

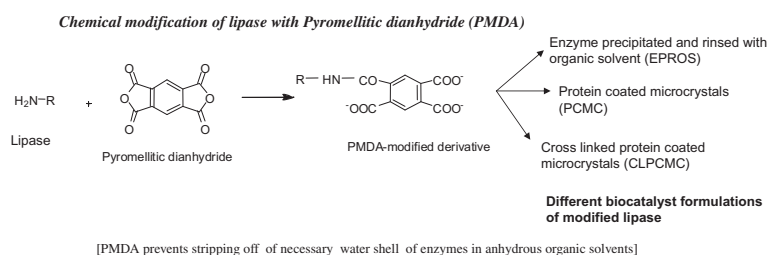


Solamargine has been synthesized in 13 steps and 10.5% overall yield from the natural abundant diosgenin.

A chemically modified lipase preparation for catalyzing the transesterification reaction in even highly polar organic solvents

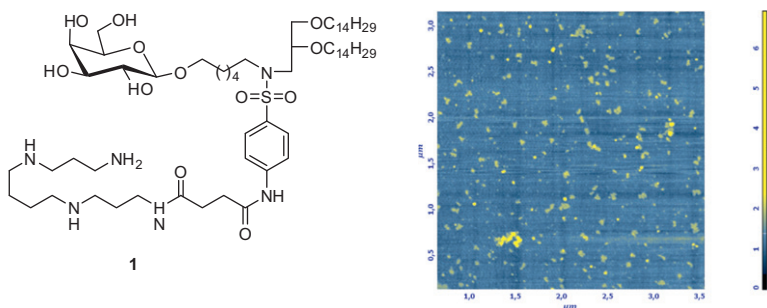
pp 2934–2936

Kusum Solanki, Munishwar Nath Gupta*

**Synthesis and transfection activity of novel galactosylated polycationic lipid**

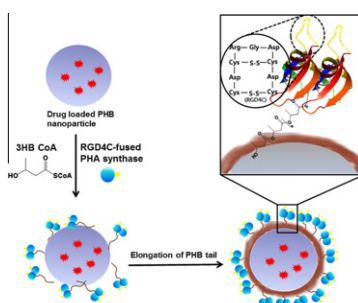
pp 2937–2940

M. A. Maslov*, D. A. Medvedeva, D. A. Rapoport, R. N. Serikov, N. G. Morozova, G. A. Serebrennikova, V. V. Vlassov, M. A. Zenkova

**Tumor-specific hybrid polyhydroxybutyrate nanoparticle: Surface modification of nanoparticle by enzymatically synthesized functional block copolymer**

pp 2941–2944

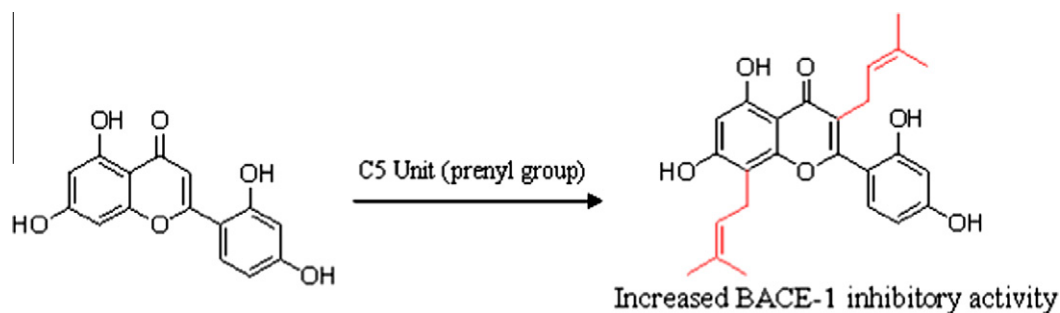
Jin Lee, Sung-Geun Jung, Cheon-Seok Park, Hae-Yeong Kim, Carl A. Batt, Young-Rok Kim*



Inhibition and structural reliability of prenylated flavones from the stem bark of *Morus lhou* on β -secretase (BACE-1)

pp 2945–2948

Jung Keun Cho, Young Bae Ryu,
 Marcus J. Curtis-Long,
 Ji Young Kim, Doman Kim,
 Sun Lee, Woo Song Lee,
 Ki Hun Park*



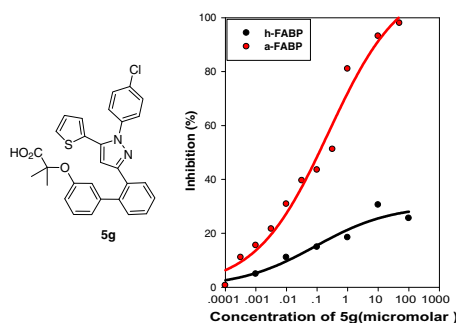
A series of prenylated flavones (1–8) were isolated and evaluated for their BACE-1 inhibitory activities. The inhibition and structural reliability of these analogs are described.



New aromatic substituted pyrazoles as selective inhibitors of human adipocyte fatty acid-binding protein

pp 2949–2952

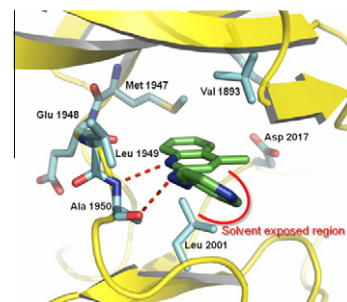
Xiujie Liu, Xiaoli Huang, Wanhua Lin, Dongye Wang, Yanyan Diao, Honglin Li, Xiaoyan Hui, Yu Wang, Aimin Xu,
 Donghai Wu*, Ding Ke*



Identification of chemicals to inhibit the kinase activity of leucine-rich repeat kinase 2 (LRRK2), a Parkinson's disease-associated protein

pp 2953–2957

Hyejin Yun, Hye Young Heo, Hyun Ha Kim, Nam DooKim*, Wongi Seol*

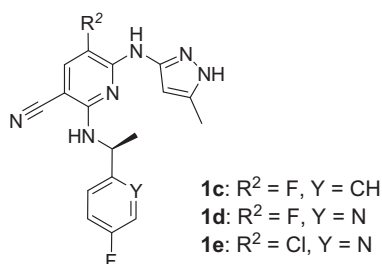


Novel inhibitors of LRRK2 kinase have been identified.

In vitro and in vivo evaluation of 6-aminopyrazolyl-pyridine-3-carbonitriles as JAK2 kinase inhibitors

pp 2958–2961

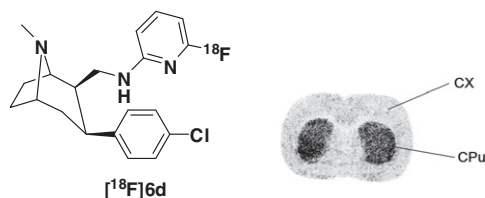
Tao Wang*, Stephanos Ioannidis, Lynsie Almeida, Michael H. Block, Audrey M. Davies, Michelle L. Lamb, David A. Scott,
 Mei Su, Hai-Jun Zhang, Marat Alimzhanov, Geraldine Beberitz, Kirsten Bell, Michael Zinda



Synthesis and evaluation of novel *N*-fluoropyridyl derivatives of tropane as potential PET imaging agents for the dopamine transporter

pp 2962–2965

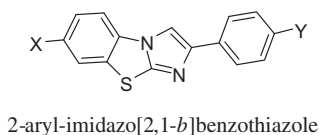
Jingying Liu, Lin Zhu, Karl Plössl, Brian P. Lieberman, Hank F. Kung*



2-Arylimidazo[2,1-*b*]benzothiazoles: A new family of amyloid binding agents with potential for PET and SPECT imaging of Alzheimer's brain

pp 2966–2968

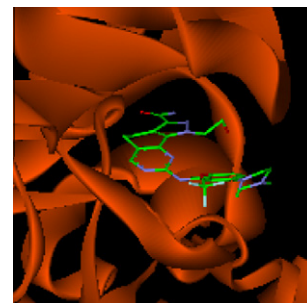
David Alagille*, Herve DaCosta, Ronald M. Baldwin, Gilles D. Tamagnan



NMS-P937, a 4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline derivative as potent and selective Polo-like kinase 1 inhibitor

pp 2969–2974

Italo Beria*, Roberto T. Bossi, Maria Gabriella Brasca, Michele Caruso, Walter Ceccarelli, Gabriele Fachin, Marina Fasolini, Barbara Forte, Francesco Fiorentini, Enrico Pesenti, Daniele Pezzetta, Helena Posterl, Alessandra Scolaro, Stefania Re Depaolini, Barbara Valsasina



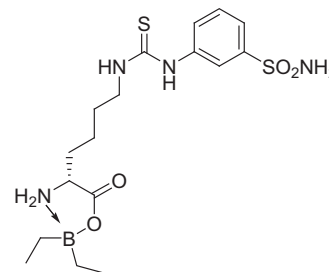
Lead optimization work on the 4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline series led to identification of NMS-P937. Crystal structure of NMS-P937 with PLK1 was obtained and discussed. NMS-P937 is a potent, selective and orally available PLK1 inhibitor that is presently in Phase I clinical trials.



Sulfonamides incorporating boroxazolidone moieties are potent inhibitors of the transmembrane, tumor-associated carbonic anhydrase isoforms IX and XII

pp 2975–2979

Marouan Rami, Alfonso Maresca, Fatma-Zhora Smaine, Jean-Louis Montero, Andrea Scozzafava, Jean-Yves Winum*, Claudiu T. Supuran*

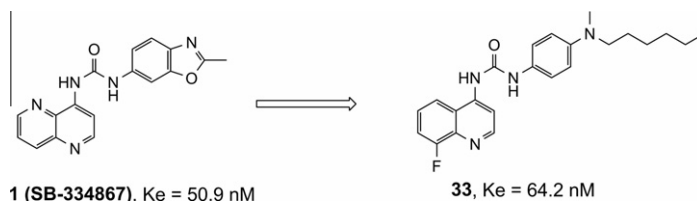


K_i (hCA I) = 3870 nM; K_i (hCA II) = 88 nM; K_i (hCA IX) = 9.5 nM; K_i (hCA XII) = 7.1 nM.

Diaryl urea analogues of SB-334867 as orexin-1 receptor antagonists

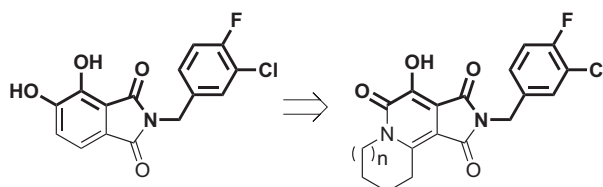
pp 2980–2985

David A. Perrey, Brian P. Gilmour, Scott P. Runyon, Brian F. Thomas*, Yanan Zhang*

**Development of tricyclic hydroxy-1H-pyrrolopyridine-trione containing HIV-1 integrase inhibitors**

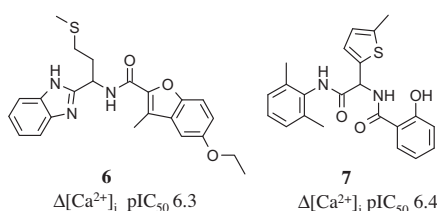
pp 2986–2990

Xue Zhi Zhao*, Kasthuraiah Maddali, Mathieu Metifiot, Steven J. Smith, B. Christie Vu, Christophe Marchand, Stephen H. Hughes, Yves Pommier, Terrence R. Burke Jr.*

**Discovery of small molecule human FPR1 receptor antagonists**

pp 2991–2997

John Unitt*, Malbinder Fagura, Tim Phillips, Sarah King, Matthew Perry, Andrew Morley*, Cathy MacDonald, Richard Weaver, Jadeen Christie, Simon Barber, Rukhsana Mohammed, Melanie Paul, Andrew Cook, Andrew Baxter

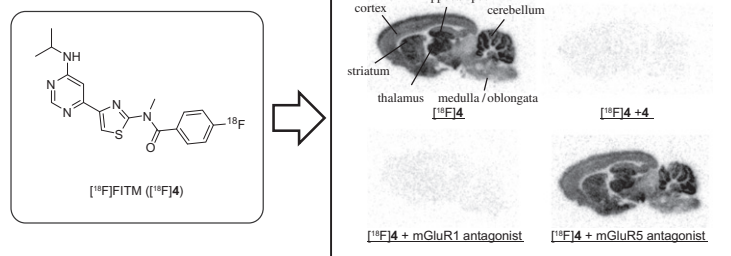


The identification of two novel series of formyl peptide receptor 1 (FPR1) antagonists are reported, represented by methionine benzimidazole **6** and diamide **7**. Both series specifically inhibited the binding of labelled fMLF to hrFPR1 and selectively antagonized FPR1 function in human neutrophils, making them useful in vitro validation tools for the target.

**Radiosynthesis and preliminary evaluation of 4-[¹⁸F]fluoro-N-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-N-methylbenzamide as a new positron emission tomography ligand for metabotropic glutamate receptor subtype 1**

pp 2998–3001

Tomoteru Yamasaki, Masayuki Fujinaga, Yuichiro Yoshida, Katsushi Kumata, Joji Yui, Kazunori Kawamura, Akiko Hatori, Toshimitsu Fukumura, Ming-Rong Zhang*



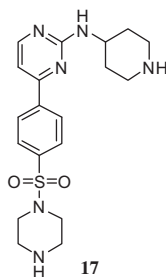
In vitro autoradiography using the rat brain section



Discovery of piperidinyl aminopyrimidine derivatives as IKK-2 inhibitors

pp 3002–3006

Sora Kim, Jin Kyo Jung, Hyo Seon Lee, Youngjae Kim, Jiyeon Kim, Kihang Choi, Du-Jong Baek, Bongjin Moon, Kwang-Seok Oh, Byung Ho Lee, Kye Jung Shin, Ae Nim Pae, Ghilsoo Nam, Eun Joo Roh, Yong Seo Cho, Hyunah Choo*

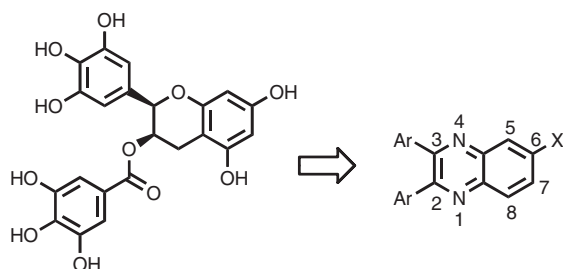


Piperidinyl aminopyrimidine derivatives as IKK-2 inhibitors were synthesized and their biological results were reported.

Synthesis and evaluation of quinoxaline derivatives as potential influenza NS1A protein inhibitors

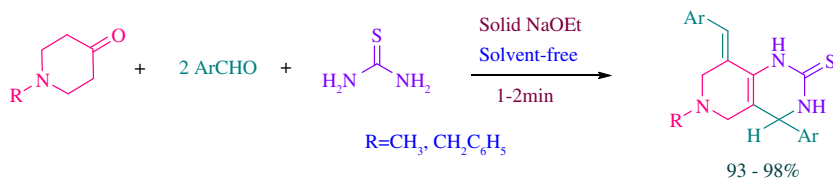
pp 3007–3011

Lei You, Eun Jeong Cho, John Leavitt, Li-Chung Ma, Gaetano T. Montelione, Eric V. Anslyn*, Robert M. Krug*, Andrew Ellington, Jon D. Robertus

**A green expedient synthesis of pyridopyrimidine-2-thiones and their antitubercular activity**

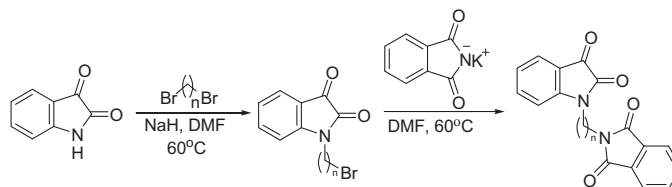
pp 3012–3016

Stephen Michael Rajesh, Raju Suresh Kumar, Lawzer Arun Libertsen, Subbu Perumal*, Perumal Yogeeswari, Dharmarajan Sriram

**Synthesis and in vitro cytotoxic evaluation of N-alkylbromo and N-alkylphthalimido-isatins**

pp 3017–3020

Pardeep Singh, Sharanjeet Kaur, Vipan Kumar, P. M. S. Bedi, M. P. Mahajan*, Irum Sehar, Harish Chandra Pal, Ajit Kumar Saxena

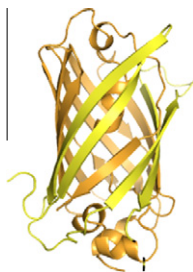


The manuscript pertains to the synthesis and in vitro cytotoxic evaluation of a series of *N*-alkylbromo and *N*-alkylphthalimido-isatins against four different human cancer cell lines. The active analogue **IS-4** exhibited IC₅₀ values of 4.57, 10.90, 11.75, 12.40 and 54.20 μM against HeLa, PC-3, HCT-15, THP-1 and Colo-205, respectively.

Structure and characteristics of reassembled fluorescent protein, a new insight into the reassembly mechanisms

pp 3021–3024

Masami Isogai, Yoshihiro Kawamoto, Kazuto Inahata, Harumi Fukada, Kenji Sugimoto, Toshiji Tada*

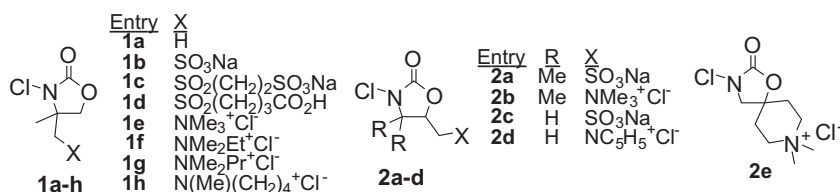


The crystal structure of reassembled fluorescent protein, Venus.

**Novel 3-chlorooxazolidin-2-ones as antimicrobial agents**

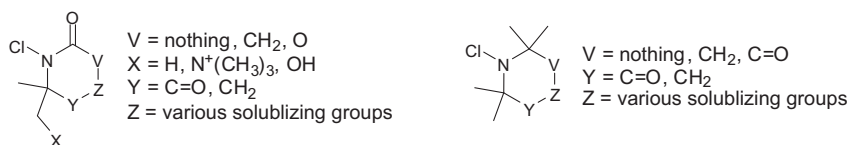
pp 3025–3028

Timothy P. Shiau, Eric D. Turtle, Charles Francavilla, Nichole J. Alvarez, Meghan Zuck, Lisa Friedman, Donogh J. R. O'Mahony, Eddy Low, Mark B. Anderson, Ramin (Ron) Najafi, Rakesh K. Jain*

**Novel N-chloroheterocyclic antimicrobials**

pp 3029–3033

Charles Francavilla, Eric D. Turtle, Bum Kim, Donogh J. R. O'Mahony, Timothy P. Shiau, Eddy Low, Nichole J. Alvarez, Chris E. Celeri, Louisa D'Lima, Lisa C. Friedman, Francis S. Ruado, Ping Xu, Meghan E. Zuck, Mark B. Anderson, Ramin (Ron) Najafi, Rakesh K. Jain*

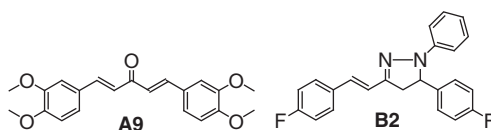


A novel series of N-chloroheterocycles has been prepared and the biological properties are reported.

Dibenzylideneacetone analogues as novel Plasmodium falciparum inhibitors

pp 3034–3036

Rahul Balasaheb Aher*, Gajanan Wanare, Neha Kawathekar, Ravi Ranjan Kumar, Naveen Kumar Kaushik, Dinkar Sahal, Virander Singh Chauhan



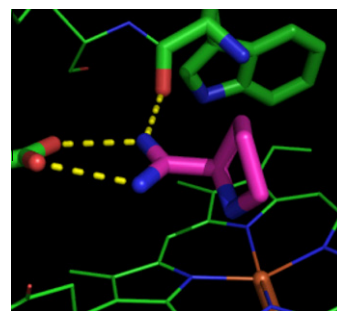
A9: IC₅₀^{3D7} = 1.97 μM, IC₅₀^{RK19} = 1.69 μM; **B2**: IC₅₀^{3D7} = 9.10 μM, IC₅₀^{RK19} = 11.09 μM. The synthesis and antimalarial activity of a series of dibenzylideneacetones and their pyrazolines are discussed.



Heteroalicyclic carboxamides as inhibitors of inducible nitric oxide synthase; the identification of (2R)-2-pyrrolidinecarboxamide as a potent and selective haem-co-ordinating inhibitor

pp 3037–3040

Robert J. Young*, Wendy Alderton, Anthony D. R. Angell, Paul J. Beswick, David Brown, C. Lynn Chambers, Miriam C. Crowe, John Dawson, Christopher C. F. Hamlett, Simon T. Hodgson, Savvas Kleanthous, Richard G. Knowles, Linda J. Russell, Richard Stocker, James M. Woolven

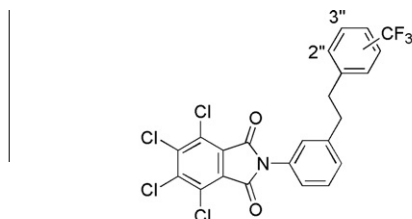


The exploration of heterocyclic carboxamides as iNOS inhibitors led to the identification of (2R)-2-pyrrolidinecarboxamide as a potent and selective haem-co-ordinating inhibitor.

Non-competitive and selective dipeptidyl peptidase IV inhibitors with phenethylphenylphthalimide skeleton derived from thalidomide-related α -glucosidase inhibitors and liver X receptor antagonists

pp 3041–3045

Kazunori Motoshima, Kazuyuki Sugita, Yuichi Hashimoto*, Minoru Ishikawa



non-competitive and selective DPP-IV inhibitors

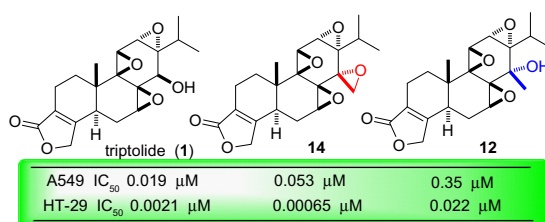
28a (3''-substituted) : DPP-IV IC₅₀ = 3.1 μ M, DPP-8 IC₅₀ >30 μ M
28b (2''-substituted) : DPP-IV IC₅₀ = 4.0 μ M, DPP-8 IC₅₀ = 11 μ M



Semisynthesis of triptolide analogues: Effect of γ -lactone and C-14 substituents on cytotoxic activities

pp 3046–3049

Yutaka Aoyagi, Yukio Hitotsuyanagi, Tomoyo Hasuda, Haruhiko Fukaya, Koichi Takeya*, Ritsuo Aiyama, Takeshi Matsuzaki, Shusuke Hashimoto



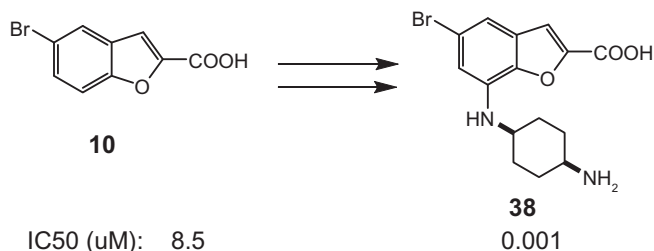
Triptolide γ -lactone and C-14 analogues were prepared and evaluated cytotoxicity against A549 and HT-29 cells.

The discovery of novel benzofuran-2-carboxylic acids as potent Pim-1 inhibitors

pp 3050–3056

Yibin Xiang*, Bradford Hirth, Gary Asmussen, Hans-Peter Biemann, Kimberly A. Bishop, Andrew Good, Maria Fitzgerald, Tatiana Gladysheva, Annuradha Jain, Katherine Jancsics, Jinyu Liu, Markus Metz, Andrew Papoulis, Renato Skerlj, J. David Stepp, Ronnie R. Wei

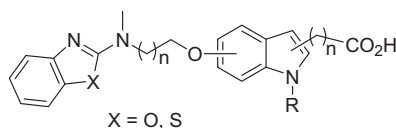
Fragment based screening using Surface Plasmon Resonance (SPR) followed by Pim-1 biochemical assay identified hit **10**. A X-ray structure of the bound complex of **10** to the Pim-1 protein revealed that **10** binds in the ATP binding site with the 5-bromo group sitting in the hydrophobic pocket near the hinge region. Guided by the X-ray structures, a potent Pim-1 inhibitor **38** was identified by adding an aminocyclohexylamino group at the 7-position of the benzofuran core. X-ray structure of the bound complex of **38** indicated that the terminal amino group forms salt-bridge interacts with D128 and E171 of the ribose binding site.



Design and synthesis of benzoxazole containing indole analogs as peroxisome proliferator-activated receptor- γ/δ dual agonists

pp 3057–3061

Hyo Jin Gim, Ye-Jin Cheon, Jae-Ha Ryu, Raok Jeon*

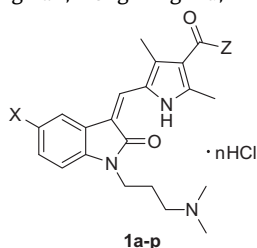


Synthesis of series of benzoxazole or benzothiazole containing indole-based analogs, 6-alkoxyindole-2-carboxylic acids and 5-alkoxy-3-indolylacetic acids, and their PPAR γ/δ transactivation activities are reported.

**Synthesis and antitumor activity of 5-[1-(3-(dimethylamino)propyl)-5-halogenated-2-oxindolin-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxamides**

pp 3062–3065

Kai Lv, Li-Li Wang, Ming-Liang Liu*, Xin-Bo Zhou, Shi-Yong Fan, Hong-Ying Liu, Zhi-Bing Zheng*, Song Li

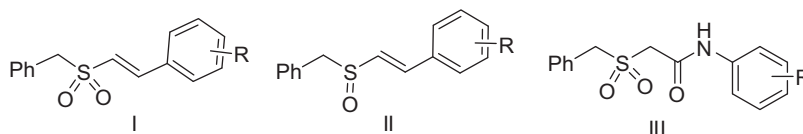


We report herein a series of novel 1-[3-(dimethylamino)propyl]indolin-2-one derivatives. Results revealed that all compounds show potent antitumor activity, compounds **1e–h** (IC₅₀'s: 0.45–5.08 μ M) are more active than Sunitinib (IC₅₀'s: 1.35–6.61 μ M), and the most active compound **1h** (IC₅₀: 0.47–3.11 μ M) is 2.1–4.6-fold more potent than Sunitinib against all five cancer cell lines. In addition, **1a–p** have higher selectivity on VEGF-stimulated HUVEC other than bFGF-stimulated HUVEC.

Synthesis and biological evaluation of benzyl styrylsulfonyl derivatives as potent anticancer mitotic inhibitors

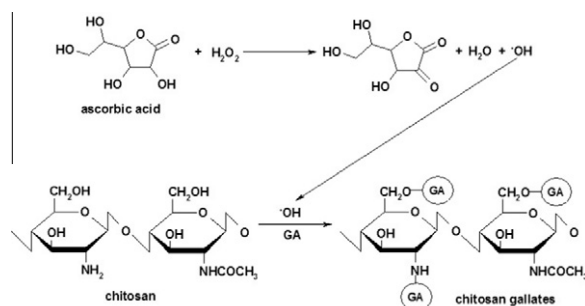
pp 3066–3069

Osama Chahrour, Ashraf Abdalla, Frankie Lam, Carol Midgley, Shudong Wang*

**Chitosan gallate as potential antioxidant biomaterial**

pp 3070–3073

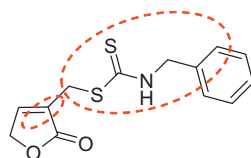
Young-Sook Cho, Se-Kwon Kim*, Jae-Young Je*



Synthesis and in vitro antitumor activity of new butenolide-containing dithiocarbamates

pp 3074–3077

Xiao-Juan Wang, Hai-Wei Xu, Lin-Lin Guo, Jia-Xin Zheng, Bo Xu, Xiao Guo, Chen-Xin Zheng, Hong-Min Liu*



I-14

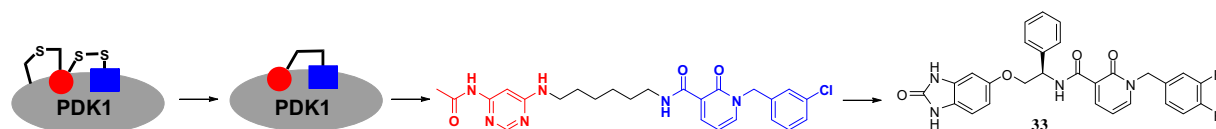
Broad spectrum anti-cancer activity $IC_{50} < 10 \mu\text{g/mL}$.

Three series of butenolide-containing dithiocarbamates were designed and synthesized. Their anti-tumor activity in vitro was evaluated. Among them compound I-14 exhibited excellent anti-cancer activity against five human cancer cell lines with $IC_{50} < 10 \mu\text{g/mL}$. Structure–activity relationship analysis showed that the introduction of dithiocarbamate side chains on the C-3 position of butenolide was crucial for anti-tumor activity.

Discovery of a potent and highly selective PDK1 inhibitor via fragment-based drug discovery

pp 3078–3083

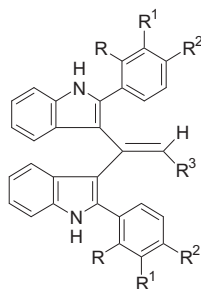
Daniel A. Erlanson*, Joseph W. Arndt, Mark T. Cancilla, Kathy Cao, Robert A. Elling, Nicki English, Jessica Friedman, Stig K. Hansen, Cathy Hession, Ingrid Joseph, Gnanasambandam Kumaravel, Wen-Cherng Lee, Ken E. Lind, Robert S. McDowell, Konrad Miatkowski, Christine Nguyen, Thinh B. Nguyen, Sophia Park, Nuzhat Pathan, David M. Penny, Michael J. Romanowski, Daniel Scott, Laura Silvian, Robert L. Simmons, Bradley T. Tangonan, Wenjin Yang, Lihong Sun*



Regioselective one pot synthesis of 3,3'-diindolylethylene derivatives and study of their cytotoxic activity

pp 3084–3087

Madhumita Mandal, Deepak Kumar, Rajneeta Roy, Rupashree Sen, Padma Das, Mitali Chatterjee, Parasuraman Jaisankar*



Synthesis and study of cytotoxic activity of 2,2'-diphenyl-3,3'-diindolylethylene derivatives are reported.

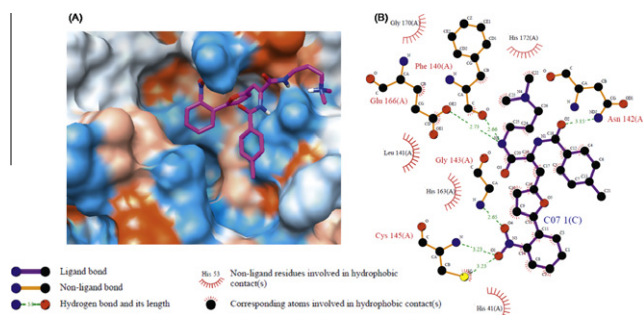


Virtual screening identification of novel severe acute respiratory syndrome 3C-like protease inhibitors and in vitro confirmation

pp 3088–3091

Thi Thanh Hanh Nguyen, Hwa-Ja Ryu, Se-Hoon Lee, Soonwook Hwang, Vincent Breton, Joon Haeng Rhee, Doman Kim*

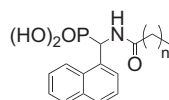
Novel potent inhibitors of 3C-like protease (3CL_{pro}) of severe acute respiratory syndrome associated coronavirus (SARS-CoV) were identified through structure-based virtual screening and validated the inhibitory activity in vitro.



Synthesis, modelling and kinetic assays of potent inhibitors of purple acid phosphatase

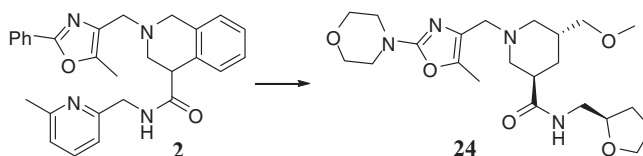
pp 3092–3094

Siti Hajar Mohd-Pahmi, Waleed M. Hussein, Gerhard Schenk, Ross P. McGeary*

n = 10: K_i (red kidney bean PAP) = 5 μM n = 12: K_i (pig PAP) = 8 μM **1,5-Substituted nipecotic amides: Selective PDE8 inhibitors displaying diastereomer-dependent microsomal stability**

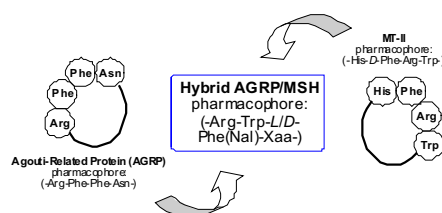
pp 3095–3098

Michael P. DeNinno*, Stephen W. Wright, Michael S. Visser, John B. Etienne, Dianna E. Moore, Thanh V. Olson, Benjamin N. Rocke, Melissa P. Andrews, Cynthia Zarbo, Michele L. Millham, Brian P. Boscoe, David D. Boyer, Shawn D. Doran, Karen L. Houseknecht

**Cyclic lactam hybrid α -MSH/Agouti-related protein (AGRP) analogues with nanomolar range binding affinities at the human melanocortin receptors**

pp 3099–3102

Alexander V. Mayorov, Mingyong Cai, Erin S. Palmer, Dustin K. Tanaka, James P. Cain, Matthew M. Dedek, Bahar Tan, Dev Trivedi, Victor J. Hruby*

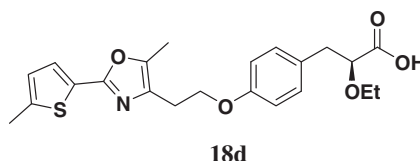


Design and synthesis of cyclic lactam hybrid α -MSH/Agouti-related protein (AGRP) analogues with high nanomolar range binding affinities at the hMC3–5R and nanomolar range partial agonist activity at the hMC1R is reported.

Revisiting glitazars: Thiophene substituted oxazole containing α -ethoxy phenylpropanoic acid derivatives as highly potent PPAR α/γ dual agonists devoid of adverse effects in rodents

pp 3103–3109

Preeti Raval*, Mukul Jain, Amitgiri Goswami, Sujay Basu, Archana Gite, Atul Godha, Harikishore Pingali, Saurin Raval, Suresh Giri, Dinesh Suthar, Maanan Shah, Pankaj Patel

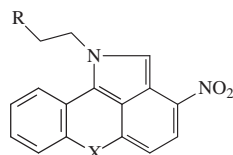


Design and synthesis of a novel thiophene substituted oxazole derivatives are reported and their PPAR α/γ agonistic activity has been evaluated. Lead compound **18d** has demonstrated potent antidiabetic and lipid lowering activity devoid of treatment related adverse effects and eventually emerged as very potent PPAR α/γ dual agonist.

Design, synthesis and antiproliferative activity of novel aminosubstituted benzothiopyranoisindoles

pp 3110–3112

Antonios Christodoulou, Ioannis K. Kostakis, Vassilios Kourafalos, Nicole Pouli, Panagiotis Marakos*, Ioannis P. Trougakos, Ourania E. Tsitsilonis



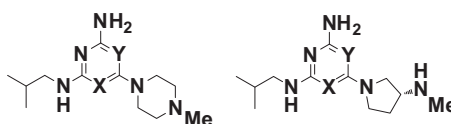
X = S, SO₂

R = N(CH₃)₂, N(CH₂CH₃)₂,
N(CH₂)₄, N(CH₂)₅

**Triamino pyrimidines and pyridines as histamine H₄ receptor modulators**

pp 3113–3116

Steven P. Meduna*, Brad M. Savall, Hui Cai, James P. Edwards, Robin L. Thurmond, Patricia M. McGovern



X = CH, Y = N

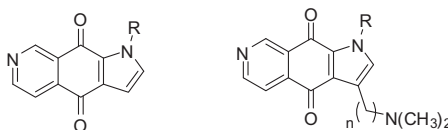
X = N, Y = CH

X = Y = CH

**Synthesis and antiproliferative activity of new cytotoxic azanaphthoquinone pyrrolo-annelated derivatives: Part II**

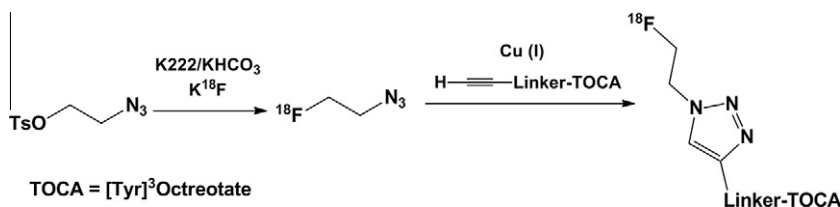
pp 3117–3121

Karem Shanab, Eva Schirmer, Eva Wulz, Barbara Weissenbacher, Sigrid Lassnig, Rita Slanz, Germana Fösleitner, Wolfgang Holzer, Helmut Spreitzer*, Peter Schmidt, Babette Aicher, Gilbert Müller, Eckhard Günther

**Synthesis and in vitro evaluation of [¹⁸F]fluoroethyl triazole labelled [Tyr³]octreotate analogues using click chemistry**

pp 3122–3127

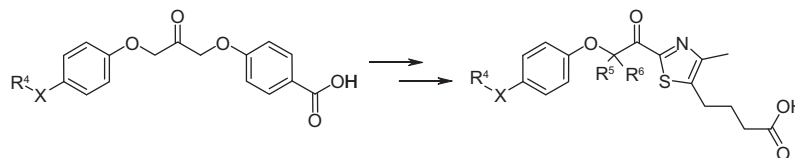
Lisa Iddon, Julius Leyton, Bård Indrevoll, Matthias Glaser, Edward G. Robins, Andrew J. T. George, Alan Cuthbertson, Sajinder Kaur Luthra, Eric O. Aboagye*



Design of novel and potent cPLA₂ inhibitors containing an α -methyl-2-ketothiazole as a metabolically stable serine trap

pp 3128–3133

Antonio Mete*, Glen Andrews, Mike Bernstein, Stephen Connolly, Paul Hartopp, Clive G. Jackson, Richard Lewis, Iain Martin, David Murray, Rob Riley, David H. Robinson, Gill M. Smith, Edward Wells, W. John Withnall



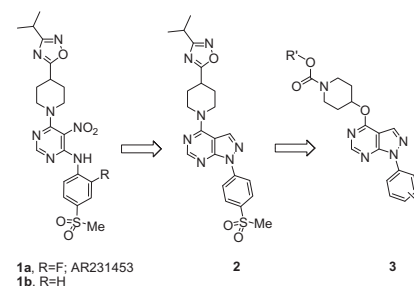
We report the design of novel, potent cPLA₂ inhibitors that possess an α -methyl-2-ketothiazole that acts as a serine-reactive moiety. We describe the optimization of the series for potency and metabolic stability towards ketone reduction. This was achieved by attenuating the reactivity of the ketone using a combination of electronic and steric effects.

Discovery of fused bicyclic agonists of the orphan G-protein coupled receptor GPR119 with in vivo activity in rodent models of glucose control

pp 3134–3141

Graeme Semple*, Albert Ren, Beatriz Fioravanti, Guilherme Pereira, Imelda Calderon, Karoline Choi, Yifeng Xiong, Young-Jun Shin, Tawfik Gharbaoui, Carleton R. Sage, Michael Morgan, Charles Xing, Zhi-Liang Chu, James N. Leonard, Andrew J. Grottick, Hussein Al-Shamma, Yin Liang, Keith T. Demarest, Robert M. Jones

The design of a new series of agonists of the orphan G-protein coupled receptor GPR119, starting from AR231453 is outlined. This resulted in the discovery of **3k** (APD668, JNJ-28630368), the first compound with this mechanism of action to be progressed into clinical development for the treatment of diabetes.

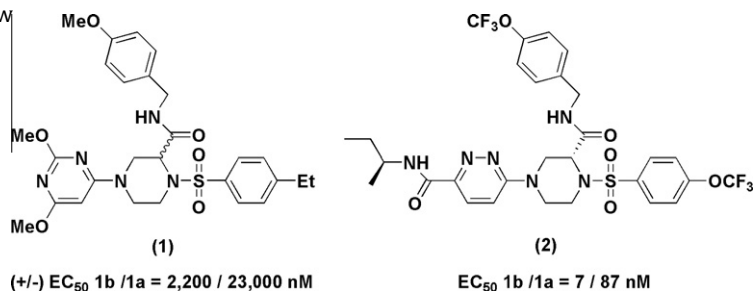


SAR studies on a series of *N*-benzyl-4-heteroaryl-1-(phenylsulfonyl)piperazine-2-carboxamides: Potent inhibitors of the polymerase enzyme (NS5B) of the hepatitis C virus

pp 3142–3147

Robert G. Gentles*, Min Ding, Xiaofan Zheng, Louis Chupak, Michael A. Poss, Brett R. Beno, Lenore Pelosi, Mengping Liu, Julie Lemm, Ying-Kai Wang, Susan Roberts, Min Gao, John Kadow

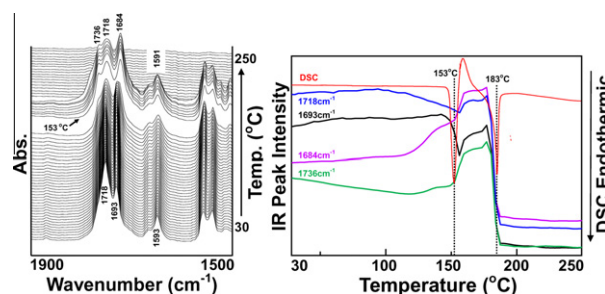
Described herein is the initial optimization of the screening hit (+/-) *N*-benzyl-4-heteroaryl-1-(phenylsulfonyl)-piperazine-2-carboxamide (**1**) that led to the discovery of the potent NS5B inhibitor (*S*)-*N*-sec-butyl-6-((*R*)-3-(4-(trifluoromethoxy)benzylcarbamoyl)-4-(4-(trifluoromethoxy)-phenylsulfonyl)-piperazin-1-yl)pyridazine-3-carboxamide (**2**).



Simultaneous DSC-FTIR microspectroscopy used to screen and detect the co-crystal formation in real time

pp 3148–3151

Tieh-kang Wu, Shan-Yang Lin*, Hong-Liang Lin, Yu-Ting Huang

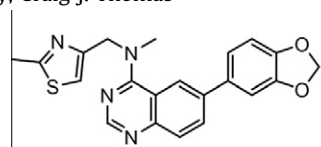


Thermal-dependent three-dimensional FTIR spectral plot of the physical mixture of IMC/SAC and its temperature-dependent changes in peak intensity of the specified IR bands.

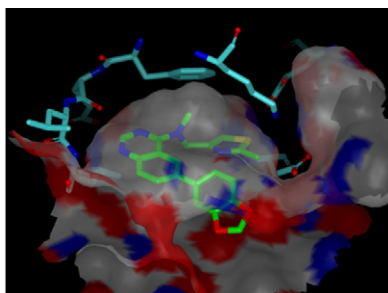
Potent and selective small molecule inhibitors of specific isoforms of Cdc2-like kinases (Clk) and dual specificity tyrosine-phosphorylation-regulated kinases (Dyrk)

pp 3152–3158

Andrew S. Rosenthal, Cordelle Tanega, Min Shen, Bryan T. Mott, James M. Bougie, Dac-Trung Nguyen, Tom Misteli, Douglas S. Auld, David J. Maloney, Craig J. Thomas*



Clk1 IC₅₀ = 20 nM
Clk4 IC₅₀ = 11 nM
Dyrk1A IC₅₀ = 14 nM
Dyrk1B IC₅₀ = 25 nM

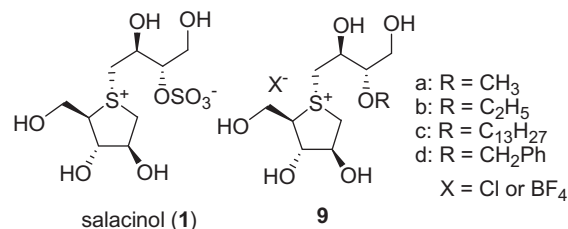


Biological evaluation of 3'-O-alkylated analogs of salacinol, the role of hydrophobic alkyl group at 3' position in the side chain on the α -glucosidase inhibitory activity

pp 3159–3162

Genzoh Tanabe, Tetsu Otani, Wenying Cong, Toshie Minematsu, Kiyofumi Ninomiya, Masayuki Yoshikawa, Osamu Muraoka*

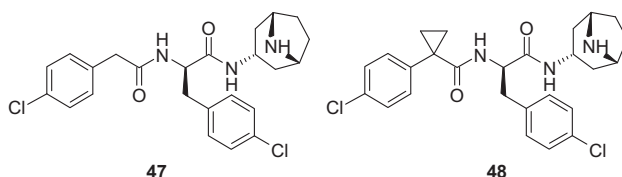
Four analogs (**9**) in which the 3'-O-sulfate anion of salacinol (**1**), a naturally occurring potent α -glucosidase inhibitor, was replaced by O-alkyl groups (a: OCH₃, b: OC₂H₅, c: OC₁₃H₂₇ or d: OCH₂Ph) were synthesized, and their α -glucosidase inhibitory activities were evaluated. All the analogues were found more potent than **1**, and one of them (**9d**) showed excellent inhibitory activity which surpassed those of the currently used antidiabetics, acarbose and voglibose, against rat small intestinal maltase. Thus, introduction of hydrophobic moieties to C3' position in this class of molecules was found beneficial for improvement of the inhibitory activity.



The discovery of novel 8-azabicyclo[3.2.1]octan-3-yl)-3-(4-chlorophenyl) propanamides as vasopressin V_{1A} receptor antagonists

pp 3163–3167

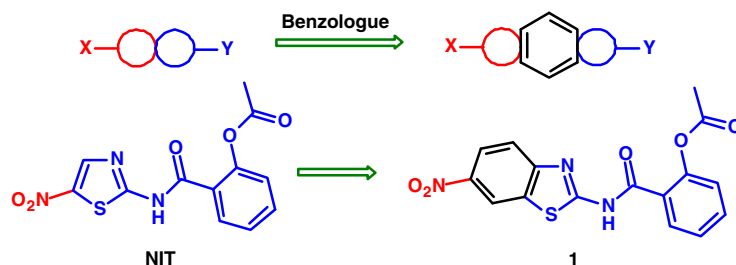
Susan Napier*, Grant Wishart*, William Arbuckle, James Baker, David Barn, Matilda Bingham, Angus Brown, Alan Byford, Chris Claxton, Mark Craighead, Kirsteen Buchanan, Lee Fielding, Lindsay Gibson, Richard Goodwin, Susan Goutcher, Nicholas Irving, Cliona MacSweeney, Rachel Milne, Chris Mort, Jeremy Presland, Hazel Sloan, Fiona Thomson, Zara Turnbull, Trevor Young



Synthesis of benzologues of Nitazoxanide and Tizoxanide: A comparative study of their in vitro broad-spectrum antiprotozoal activity

pp 3168–3171

Gabriel Navarrete-Vazquez*, Fabiola Chávez-Silva, Rocío Argotte-Ramos, María del Carmen Rodríguez-Gutiérrez, Manuel Jesús Chan-Bacab, Roberto Cedillo-Rivera, Rosa Moo-Puc, Emanuel Hernández-Nuñez



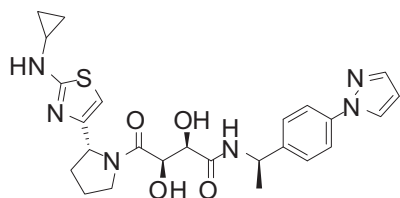
	IC ₅₀ (μM)	
	1	NIT
<i>G. intestinalis</i>	0.297	1.214
<i>T. vaginalis</i>	0.842	0.068
<i>E. histolytica</i>	3.515	0.504
<i>L. mexicana</i>	1.350	6.180
<i>T. cruzi</i>	4.890	18.73
<i>P. berghei</i>	2.420	3.890
CC ₅₀ VERO	833.0	683.0



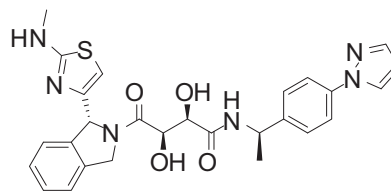
2-(2-Aminothiazol-4-yl)pyrrolidine-based tartrate diamides as potent, selective and orally bioavailable TACE inhibitors

pp 3172–3176

Chaoyang Dai*, Dansu Li, Janeta Popovici-Muller, Lianyun Zhao, Vinay M. Girijavallabhan, Kristin E. Rosner, Brian J. Lavey, Razia Rizvi, Bandarpalle B. Shankar, Michael K. C. Wong, Zhuyan Guo, Peter Orth, Corey O. Strickland, Jing Sun, Xiaoda Niu, Shiyang Chen, Joseph A. Kozlowski, Daniel J. Lundell, John J. Piwinski, Neng-Yang Shih, M. Arshad Siddiqui



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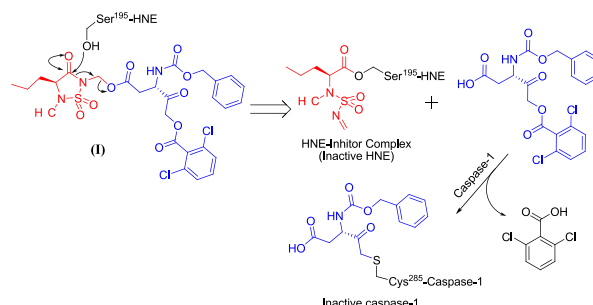


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Dual function inhibitors of relevance to chronic obstructive pulmonary disease

pp 3177–3180

Dengfeng Dou, Guijia He, Kevin R. Alliston, William C. Groutas*



*Corresponding author

Supplementary data available via ScienceDirect

COVER

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, 20, 206.]

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