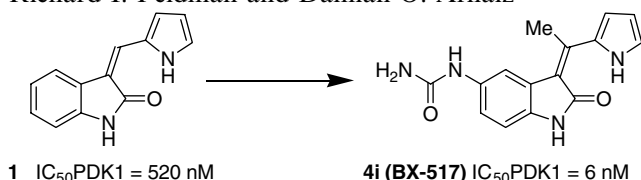


Contents

ARTICLES

Indolinone based phosphoinositide-dependent kinase-1 (PDK1) inhibitors. Part 1: Design, synthesis and biological activity pp 3814–3818

Imadul Islam, Judi Bryant, Yuo-Ling Chou, Monica J. Kochanny, Wheeseong Lee, Gary B. Phillips, Hongyi Yu, Marc Adler, Marc Whitlow, Elena Ho, Dao Lentz, Mark A. Polokoff, Babu Subramanyam, James M. Wu, Daguang Zhu, Richard I. Feldman and Damian O. Arnaiz*

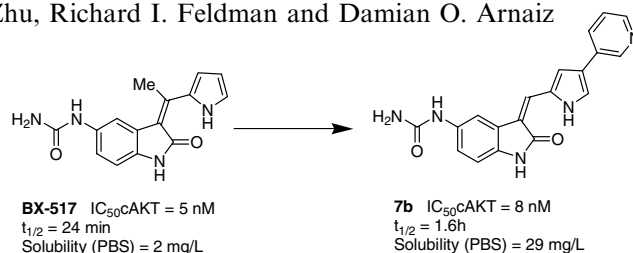


Optimization of **1** afforded **4i (BX-517)**, a potent and selective inhibitor of PDK1.

Indolinone based phosphoinositide-dependent kinase-1 (PDK1) inhibitors. Part 2: Optimization of BX-517 pp 3819–3825

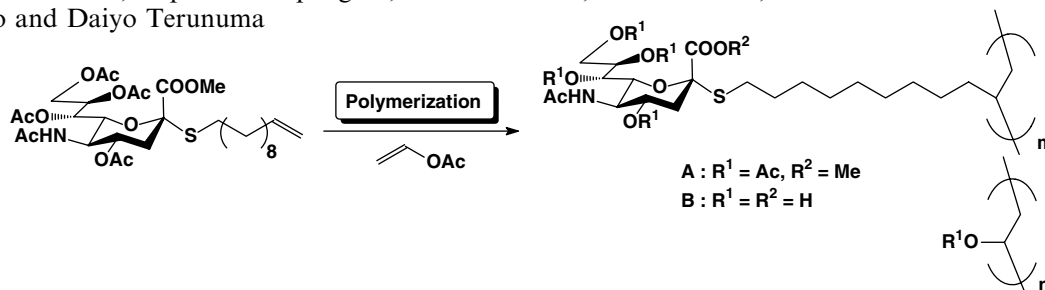
Imadul Islam,* Greg Brown, Judi Bryant, Paul Hrvatin, Monica J. Kochanny, Gary B. Phillips, Shendong Yuan, Marc Adler, Marc Whitlow, Dao Lentz, Mark A. Polokoff, James Wu, Jun Shen, Janette Walters, Elena Ho, Babu Subramanyam, Daguang Zhu, Richard I. Feldman and Damian O. Arnaiz

Optimization of **BX-517** afforded **7b**, an inhibitor of PDK1 with improved physicochemical properties.



Novel linear polymers bearing thiosialosides as pendant-type epitopes for influenza neuraminidase inhibitors pp 3826–3830

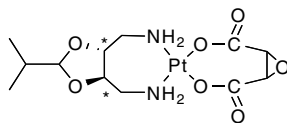
Koji Matsuoka,* Chiharu Takita, Tetsuo Koyama, Daisei Miyamoto, Sangchai Yingsakmongkon, Kazuya I. P. J. Hidari, Wipawee Jampangern, Takashi Suzuki, Yasuo Suzuki, Ken Hatano and Daiyo Terunuma



In vitro cytotoxicity study on platinum (II) complexes with epoxysuccinates as leaving groups

pp 3831–3834

Xia Liu, Hong Shen, Haibin Zhu, Kai Cui and Shaohua Gou*

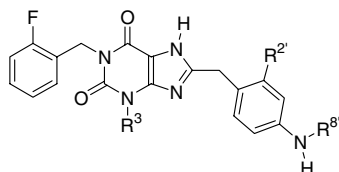


Ten new cisplatin-type platinum complexes with epoxysuccinates as leaving groups have been synthesized and structurally characterized. The in vitro cytotoxic activities of compounds toward SPC-A1 human lung adenocarcinoma cell line and BGC823 human stomach adenocarcinoma cell line have been determined.

C-8 Modifications of 3-alkyl-1,8-dibenzylxanthines as inhibitors of human cytosolic phosphoenolpyruvate carboxykinase

pp 3835–3839

Sherrie L. Pietranico, Louise H. Foley,* Nicholas Huby, Weiya Yun, Pete Dunten, John Vermeulen, Ping Wang, Katherine Toth, Gwendolyn Ramsey, Mary-Lou Gubler and Stanley J. Wertheimer

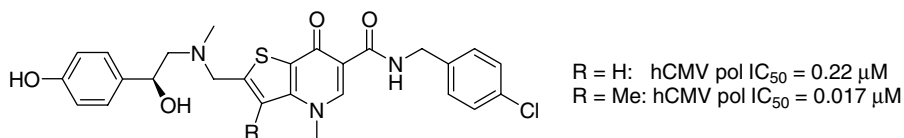


Enzyme and cellular assay results for a number of new modifications on the C-8 aminobenzyl unit are reported. Pyrazole sulfonic acid amide analogs are shown to provide improved inhibitors of cPEPCK and a new π - π interaction with the protein.

7-Oxo-4,7-dihydrothieno[3,2-*b*]pyridine-6-carboxamides: Synthesis and biological activity of a new class of highly potent inhibitors of human cytomegalovirus DNA polymerase

pp 3840–3844

Scott D. Larsen,* Zhijun Zhang, Brian A. DiPaolo, Peter R. Manninen, Douglas C. Rohrer, Michael J. Hageman, Todd A. Hopkins, Mary L. Knechtel, Nancee L. Oien, Bob D. Rush, Francis J. Schwende, Kevin J. Stefanski, Janet L. Wieber, Karen F. Wilkinson, Kathryn M. Zamora, Michael W. Wathen and Roger J. Brideau

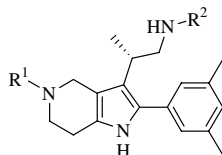


A new class of non-nucleoside antivirals is reported, wherein a C-3 methyl group confers dramatic improvement in potency, perhaps due to conformational restriction of the C-2 sidechain.

Identification of 2-(4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridin-3-yl)-ethylamine derivatives as novel GnRH receptor antagonists

pp 3845–3850

Mi Chen, Zhiqiang Guo, Marion C. Lanier, Liren Zhao, Stephen F. Betz, Charles Q. Huang, Colin J. Loweth, Neil J. Ashweek, Xin-Jun Liu, R. Scott Struthers, Margaret J. Bradbury, James W. Behan, Jenny Wen, Zhihong O'Brien, John Saunders and Yun-Fei Zhu*

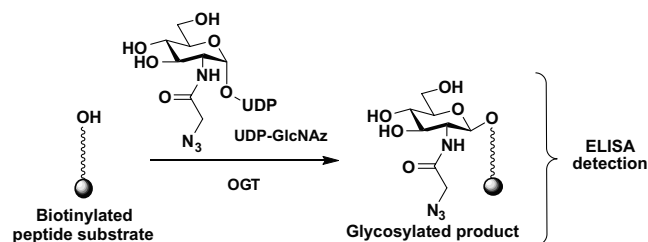


SAR of a series of novel and potent non-peptide GnRH receptor antagonists is disclosed.

A high-throughput assay for *O*-GlcNAc transferase detects primary sequence preferences in peptide substrates

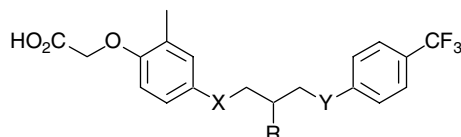
pp 3851–3854

Tanya M. Leavy and Carolyn R. Bertozzi*

**Discovery of *para*-alkylthiophenoxyacetic acids as a novel series of potent and selective PPAR δ agonists**

pp 3855–3859

Rui Zhang,* Aihua Wang, Alan DeAngelis, Patricia Pelton, Jun Xu, Peifang Zhu, Lubing Zhou, Keith Demarest, William V. Murray and Gee-Hong Kuo

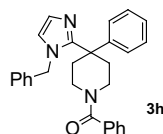


A series of *para*-alkylthiophenoxyacetic acids was prepared and found to be potent and selective PPAR δ agonists.

4-Phenyl-4-[1*H*-imidazol-2-yl]-piperidine derivatives as non-peptidic selective δ -opioid agonists with potential anxiolytic/antidepressant properties. Part 2

pp 3860–3863

Andrés A. Trabanco,* Nancy Aerts, Rosa M. Alvarez, José I. Andrés, Inge Boeckx, Javier Fernández, Antonio Gómez, Frans E. Janssens, Joseph E. Leenaerts, Ana I. De Lucas, Encarna Matesanz, Thomas Steckler and Shirley Pullan

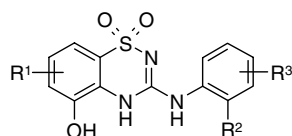


Selective δ -opioid agonists based on the 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine scaffold are reported. Compound **3h** has shown anxiolytic-/antidepressant-like effects in two mouse animal models.

3-Arylamino-2*H*-1,2,4-benzothiadiazin-5-ol 1,1-dioxides as novel and selective CXCR2 antagonists

pp 3864–3867

Yonghui Wang,* Jakob Busch-Petersen, Feng Wang, Lanping Ma, Wei Fu, Jeffrey K. Kerns, Jian Jin, Michael R. Palovich, Jing-Kang Shen, Miriam Burman, James J. Foley, Dulcie B. Schmidt, Gerald E. Hunsberger, Henry M. Sarau and Katherine L. Widdowson

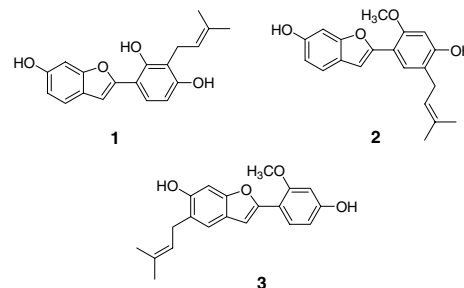


Synthesis, structure and activity relationships, selectivity and developability properties for a new class of CXCR2 receptor antagonists are described.

Inhibitory effect of 2-arylbenzofurans from *Erythrina addisoniae* on protein tyrosine phosphatase-1B pp 3868–3871

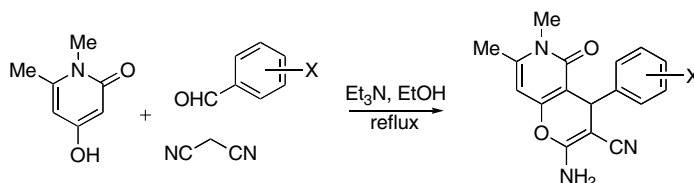
MinKyun Na, Duc Manh Hoang, Dieudonné Njamen, Joseph Tanyi Mbafor, Zacharias Tanee Fomum, Phuong Thien Thuong, Jong Seog Ahn and Won Keun Oh*

Three new (**1–3**) and three known (**4–6**) 2-arylbenzofuran derivatives were isolated from the stem bark of *Erythrina addisoniae*. The new compounds **1–3** were found to strongly inhibit PTP1B activity in vitro.



Antiproliferative and apoptosis inducing properties of pyrano[3,2-c]pyridones accessible by a one-step multicomponent synthesis pp 3872–3876

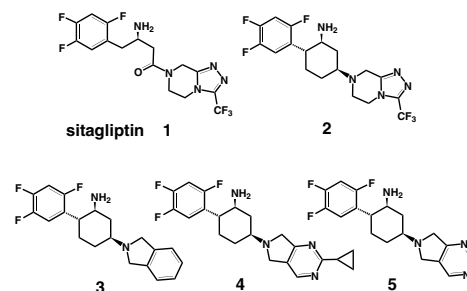
Igor V. Magedov,* Madhuri Manpadi, Nikolai M. Evdokimov, Eerik M. Elias, Elena Rozhkova, Marcia A. Ogasawara, Jennifer D. Bettale, Nikolai M. Przheval'skii, Snezna Rogelj and Alexander Kornienko*



Modeling assisted rational design of novel, potent, and selective pyrrolopyrimidine DPP-4 inhibitors pp 3877–3879

Ying-Duo Gao,* Dennis Feng, Robert P. Sheridan, Giovanna Scapin, Sangita B. Patel, Joseph K. Wu, Xiaoping Zhang, Ranabir Sinha-Roy, Nancy A. Thornberry, Ann E. Weber and Tesfaye Biftu

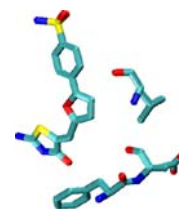
Molecular modeling was used to improve potency of the cyclohexylamine series. In addition, a 3-D QSAR method was used to gain insight for reducing off-target DPP-8/9 activities. Compounds **3**, **4**, and **5** were synthesized and found to be potent DPP-4 inhibitors, in particular **4** and **5** are designed to be highly selective against off-target DASH enzymes while maintaining potency on DPP-4.



Discovery of a potent CDK2 inhibitor with a novel binding mode, using virtual screening and initial, structure-guided lead scoping pp 3880–3885

Christine M. Richardson,* Claire L. Nunns, Douglas S. Williamson, Martin J. Parratt, Pawel Dokurno, Rob Howes, Jenifer Borgognoni, Martin J. Drysdale, Harry Finch, Roderick E. Hubbard, Philip S. Jackson, Peter Kierstan, Georg Lentzen, Jonathan D. Moore, James B. Murray, Heather Simmonite, Allan E. Surgenor and Christopher J. Torrance

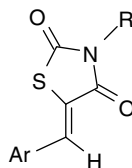
Virtual screening identified a potent CDK2 inhibitor with a novel binding mode.



Evaluation of in vitro aldose reductase inhibitory activity of 5-arylidene-2,4-thiazolidinediones

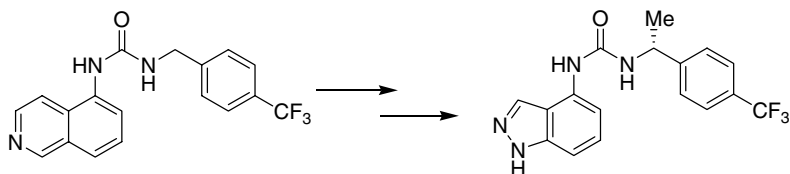
pp 3886–3893

Rosanna Maccari,* Rosaria Ottanà, Rosella Ciurleo, Maria Gabriella Vigorita,
Dietmar Rakowitz, Theodora Steindl and Thierry Langer

 **α -Methylation at benzylic fragment of *N*-aryl-*N'*-benzyl ureas provides TRPV1 antagonists with better pharmacokinetic properties and higher efficacy in inflammatory pain model**

pp 3894–3899

Arthur Gomtsyan,* Erol K. Bayburt, Ryan Keddy, Sean C. Turner, Tammie K. Jinkerson,
Stanley Didomenico, Richard J. Perner, John R. Koenig, Irene Drizin, Heath A. McDonald, Carol S. Surowy,
Prisca Honore, Joe Mikusa, Kennan C. Marsh, Jill M. Wetter, Connie R. Faltynek and Chih-Hung Lee



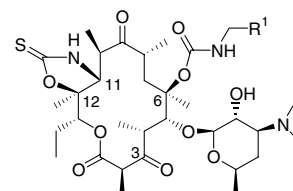
Better PK and higher efficacy in animal model of
inflammatory pain

Synthesis and antibacterial activity of 3-keto-6-*O*-carbamoyl-11,12-cyclic thiocarbamate erythromycin A derivatives

pp 3900–3904

Bin Zhu,* Brett A. Marinelli, Darren Abbanat, Barbara D. Foleno, Karen Bush and Mark J. Macielag

A series of 3-keto-6-*O*-carbamoyl-11,12-cyclic thiocarbamate erythromycin A derivatives has been synthesized. The best compounds in this series possess potent in vitro antibacterial activity against erythromycin-susceptible and erythromycin-resistant bacteria.

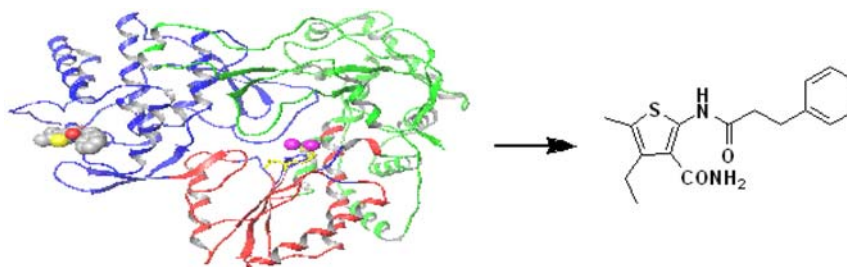


6-*O*-Carbamoyl-11,12-Cyclic
Thiocarbamate Ketolides

Discovery of novel dialkyl substituted thiophene inhibitors of HCV by in silico screening of the NS5B RdRp

pp 3905–3909

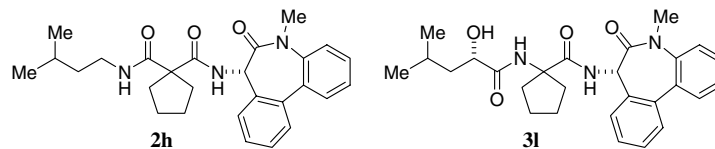
Shirley Louise-May, Wengang Yang, Xingtie Nie, Dongmei Liu, Milind S. Deshpande,
Avinash S. Phadke, Mingjun Huang* and Atul Agarwal*



Design and synthesis of benzoazepinone-derived cyclic malonamides and aminoamides as potent γ -secretase inhibitors

pp 3910–3915

Michael G. Yang,* Jian-Liang Shi, Dilip P. Modi, Jennifer Wells, Brian M. Cochran, Mark A. Wolf, Lorin A. Thompson, Mercy M. Ramanjulu, Arthur H. Roach, Robert Zaczek, David W. Robertson, Ruth R. Wexler and Richard E. Olson

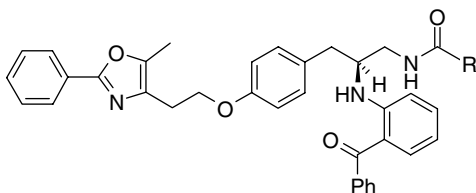


Compounds such as **2h** (APP IC₅₀ = 5.8 nM) and **3l** (APP IC₅₀ = 4.2 nM) are potent γ -secretase inhibitors.

Co-crystal structure guided array synthesis of PPAR γ inverse agonists

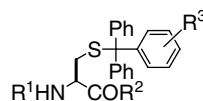
pp 3916–3920

Ryan P. Trump, Jeffrey E. Cobb, Barry G. Shearer, Millard H. Lambert, Robert T. Nolte, Timothy M. Willson, Richard G. Buckholz, Sumin M. Zhao, Lisa M. Leesnitzer, Marie A. Iannone, Kenneth H. Pearce, Andrew N. Billin and William J. Hoekstra*


Synthesis and biological evaluation of L-cysteine derivatives as mitotic kinesin Eg5 inhibitors

pp 3921–3924

Naohisa Ogo, Shinya Oishi, Kenji Matsuno, Jun-ichi Sawada, Nobutaka Fujii and Akira Asai*



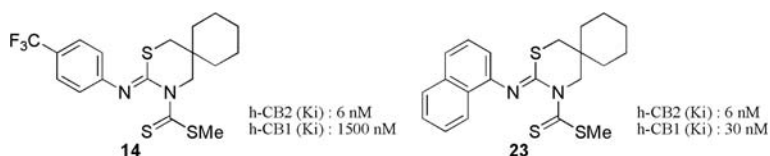
The synthesis and evaluation for Eg5 inhibitory activity of *S*-substituted-L-cysteine derivatives are reported. Derivative **4f** (R¹ = H, R² = OH, R³ = 4-OMe) demonstrated potent and selective inhibitory activity against Eg5 and induced mitotic arrest with characteristic monoastral spindles in HeLa cells.

2-Arylimino-5,6-dihydro-4H-1,3-thiazines as a new class of cannabinoid receptor agonists.

pp 3925–3929

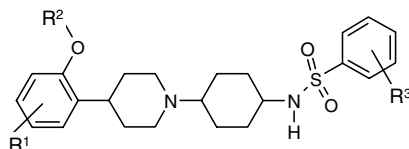
Part 2: Orally bioavailable compounds

Hiroyuki Kai,* Yasuhide Morioka, Minoru Tomida, Tadashi Takahashi, Maki Hattori, Kohji Hanasaki, Katsumi Koike, Hiroki Chiba, Shunji Shinohara, Toshiyuki Kanemasa, Yuka Iwamoto, Kohji Takahashi, Yoshitaka Yamaguchi, Takahiko Baba, Takayoshi Yoshikawa and Hideyuki Takenaka



(Phenylpiperidiny)cyclohexylsulfonamides: Development of $\alpha_{1A/1D}$ -selective adrenergic receptor antagonists for the treatment of benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS) pp 3930–3934

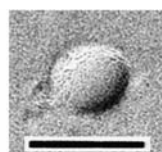
George Chiu,* Shengjian Li, Peter J. Connolly, Virginia Pulito, Jingchun Liu and Steven A. Middleton



A series of (phenylpiperidinyl)cyclohexylsulfonamides that show selectivity to human $\alpha_{1a/1d}$ adrenergic receptors were developed. These compounds have potential for the treatment of BPH/LUTS.

RNAi gene silencing using cerasome as a viral-size siRNA-carrier free from fusion and cross-linking pp 3935–3938

Kazuki Matsui, Yoshihiro Sasaki, Takayoshi Komatsu, Masaru Mukai,
Jun-ichi Kikuchi* and Yasuhiro Aoyama*



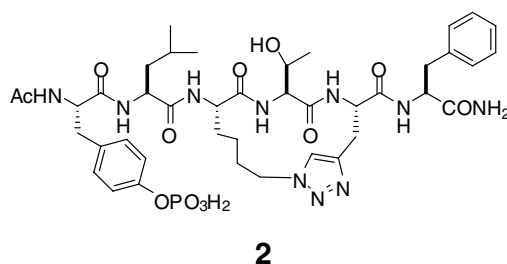
scale bar = 100 nm

Cerasome can be used as a viral-size siRNA-carrier for RNAi silencing of exogenous and endogenous genes.



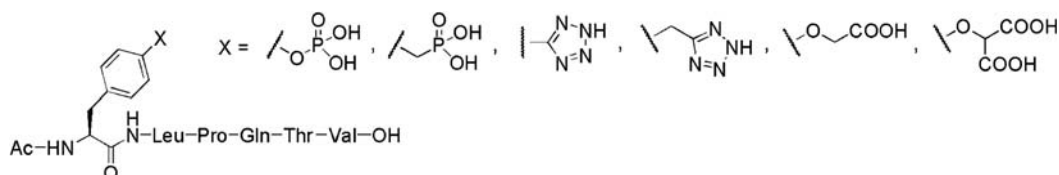
Design and synthesis of a new, conformationally constrained, macrocyclic small-molecule inhibitor of STAT3 via ‘click chemistry’ pp 3939–3942

Jiayong Chen, Zaneta Nikolovska-Coleska, Chao-Yie Yang, Cindy Gomez, Wei Gao, Krzysztof Krajewski, Sheng Jiang, Peter Roller and Shaomeng Wang*



New syntheses of tetrazolylmethylphenylalanine and *O*-malonyltyrosine as pTyr mimetics for the design of STAT3 dimerization inhibitors pp 3943–3946

Jennifer Dourlat, Bruno Valentin, Wang-Qing Liu and Christiane Garbay*



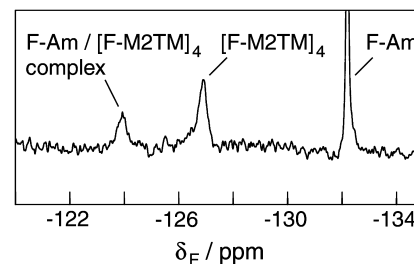
The novel syntheses of two pTyr mimetics, L-tetrazolylmethylphenylalanine (L-Tmp) and L-*O*-malonyltyrosine (L-OMT) are reported. Incorporation into a high affinity ligand of the STAT3 SH2 domain identified L-OMT as the first non-phosphorus pTyr mimetic reported so far against the STAT3 SH2 domain.

^{19}F NMR detection of the complex between amantadine and the receptor portion of the influenza A M2 ion channel in DPC micelles

pp 3947–3952

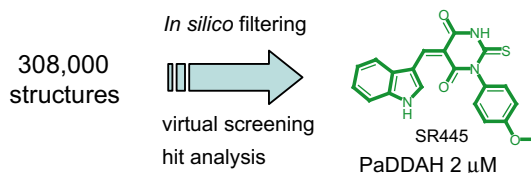
Antonios Kolocouris, Christos Zikos and R. William Broadhurst*

A signal corresponding to the complex formed between amantadine analogue **2** and the transmembrane fragment of the influenza A M2 proton channel receptor in dodecylphosphocholine micelles is detected for the first time using ^{19}F NMR spectroscopy.


Discovery of inhibitors of the pentain superfamily protein dimethylarginine dimethylaminohydrolase (DDAH), by virtual screening and hit analysis

pp 3953–3956

Basil Hartzoulakis, Sharon Rossiter, Herpreet Gill, Bernard O'Hara, Emily Steinke, Paul J. Gane, Ramon Hurtado-Guerrero, James M. Leiper, Patrick Vallance, Judith Murray Rust and David L. Selwood*

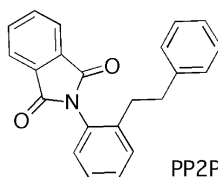


Physicochemical filtering of a 308,000 library produced a representative subset of 35,000 compounds. Virtual screening on a dual processor PC using FlexX, identified two hit series. Similarity searches around the actives and chemical re-synthesis of pure compounds resulted in SR445 as an inhibitor of *Pseudomonas aeruginosa* DDAH at 2 μM .


Liver X receptor antagonists with a phthalimide skeleton derived from thalidomide-related glucosidase inhibitors

pp 3957–3961

Tomomi Noguchi-Yachide, Atsushi Aoyama, Makoto Makishima, Hiroyuki Miyachi and Yuichi Hashimoto*

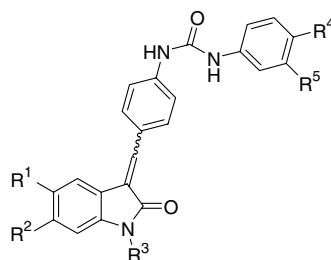


Novel LXR antagonists with a 2'-substituted phenylphthalimide skeleton were obtained by structural development of glucosidase inhibitors derived from thalidomide.

Synthesis and RET protein kinase inhibitory activity of 3-arylureidobenzylidene-indolin-2-ones

pp 3962–3968

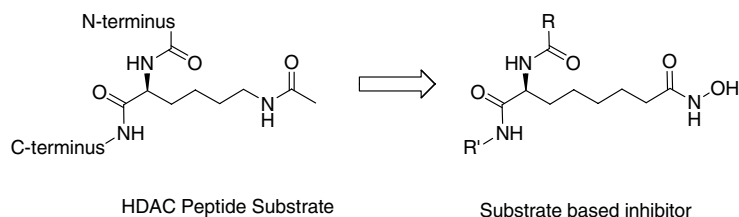
Eleonora Rizzi, Giuliana Cassinelli,* Sabrina Dallavalle,* Cinzia Lanzi, Raffaella Cincinelli, Raffaella Nannei, Giuditta Cuccuru and Franco Zunino



Aminosuberoyl hydroxamic acids (ASHAs): A potent new class of HDAC inhibitors

pp 3969–3971

Sandro Belvedere, David J. Witter,* Jiaming Yan, J. Paul Secrist, Victoria Richon and Thomas A. Miller



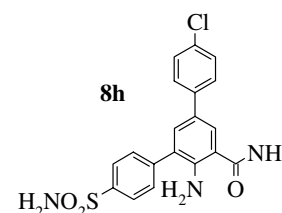
Exploring branched substrate-like HDAC inhibitors, mimicking the peptide substrate, lead to a series of aminosuberoyl hydroxamic acids (ASHAs) with remarkable HDAC inhibitory activity.

The discovery of 2-amino-3,5-diarylbenzamide inhibitors of IKK- α and IKK- β kinases

pp 3972–3977

John A. Christopher,* Barbara G. Avitabile, Paul Bamborough, Aurelie C. Champigny, Geoffrey J. Cutler, Susan L. Dyos, Ken G. Grace, Jeffrey K. Kerns, Jeremy D. Kitson, Geoffrey W. Mellor, James V. Morey, Mary A. Morse, Carolyn F. O'Malley, Champa B. Patel, Nicholas Probst, William Rumsey, Clive A. Smith and Michael J. Wilson

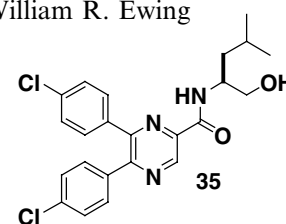
A potent and selective series of 2-amino-3,5-diarylbenzamide inhibitors of IKK- α and IKK- β is described. The most potent compounds are **8h**, **8r** and **8v**, with IKK- β inhibitory potencies of pIC_{50} 7.0, 6.8 and 6.8, respectively. The series has excellent selectivity, both within the IKK family over IKK- ϵ , and across a wide variety of kinase assays. The potency of **8h** in the IKK- α and IKK- β enzyme assay translates to significant cellular activity (pIC_{50} 5.7–6.1) in assays of functional and mechanistic relevance.

**Discovery of pyrazine carboxamide CB1 antagonists: The introduction of a hydroxyl group improves the pharmaceutical properties and in vivo efficacy of the series**

pp 3978–3982

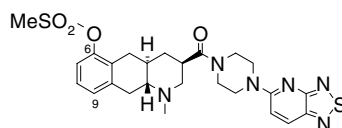
Bruce A. Ellsworth,* Ying Wang, Yeheng Zhu, Annapurna Pendri, Samuel W. Gerritz, Chongqing Sun, Kenneth E. Carlson, Liya Kang, Rose A. Baska, Yifan Yang, Qi Huang, Neil T. Burford, Mary Jane Cullen, Susan Johnghar, Kamelia Behnia, Mary Ann Pelleymounter, William N. Washburn and William R. Ewing

Structure–activity relationships for a series of pyrazine carboxamide CB1 antagonists are reported. Pharmaceutical properties of the series are improved via inclusion of hydroxyl-containing sidechains. This structural modification sufficiently improved ADME properties of an orally inactive series such that food intake reduction was achieved in rat feeding models. Compound **35** elicits a 46% reduction in food intake in ad libitum fed rats 4-h post-dose.

**Identification and SAR of potent and selective non-peptide obeline somatostatin sst_1 receptor antagonists**

pp 3983–3987

Thomas Troxler,* Daniel Hoyer, Daniel Langenegger, Peter Neumann, Paul Pfäffli, Philippe Schoeffter, Dieter Sorg, Robert Swoboda and Konstanze Hurth*



4g: pK_d (ss_{t1}) = 9.67, (ss_{t2}) = 5.29

The identification of a novel class of non-peptide somatostatin ss_{t1} receptor ligands is described. Optimization of positions 6 and 9 in these obeline-type compounds leads to functional antagonists with sub-nanomolar affinities to ss_{t1} and >10,000-fold selectivities over the ss_{t2} receptor subtype.

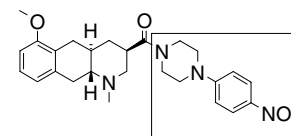


SAR of the arylpiperazine moiety of obeline somatostatin sst₁ receptor antagonists

pp 3988–3991

Konstanze Hurth,* Albert Enz, Philipp Floersheim, Conrad Gentsch, Daniel Hoyer, Daniel Langenegger, Peter Neumann, Paul Pfäffli, Dieter Sorg, Robert Swoboda, Annick Vassout and Thomas Troxler*

The optimization of the arylpiperazine moiety in obeline-type somatostatin sst₁ antagonists is presented, leading to compounds with subnanomolar sst₁ affinities and >10,000-fold selectivities over the sst₂ receptor subtype as well as promising pharmacokinetic properties.

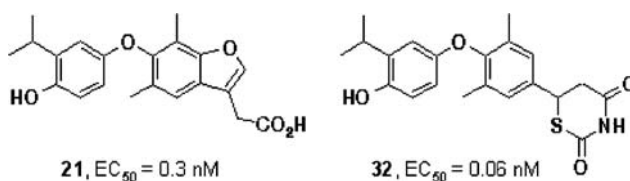


31: pK_d (sst₁) = 9.15, (sst₂) = 5.11

**Novel heterocyclic thyromimetics. Part 2**

pp 3992–3996

Helmut Haning,* Ulrich Mueller, Gunter Schmidt, Carsten Schmeck, Verena Voehringer, Axel Kretschmer and Hilmar Bischoff

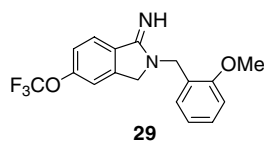


Novel heterocyclic thyromimetics are presented carrying carboxy-substituted benzofurans or sulfur containing heterocycles, as replacements for the amino acid side chain of T3. Potent agonists were identified in both series (e.g., **21** and **32**.)

Cyclic benzamidines as orally efficacious NR2B-selective NMDA receptor antagonists

pp 3997–4000

Kevin T. Nguyen,* Christopher F. Claiborne, John A. McCauley, Brian E. Libby, David A. Claremon, Rodney A. Bednar, Scott D. Mosser, Stanley L. Gaul, Thomas M. Connolly, Cindra L. Condra, Bohumil Bednar, Gary L. Stump, Joseph J. Lynch, Kenneth S. Koblan and Nigel J. Liverton

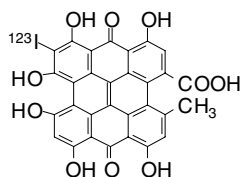


A novel series of cyclic benzamidines was synthesized and shown to exhibit NR2B-subtype selective NMDA antagonist activity. Compound **29** is orally active in a carrageenan-induced rat hyperalgesia model of pain.

Synthesis and preliminary evaluation of mono-[¹²³I]iodohypericin monocarboxylic acid as a necrosis avid imaging agent

pp 4001–4005

Humphrey Fonge, Lixin Jin, Huaijun Wang, Yicheng Ni, Guy Bormans and Alfons Verbruggen*

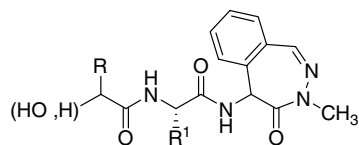


The study describes the synthesis and preliminary biological evaluation of mono-[¹²³I]iodohypericin monocarboxylic acid as a potential tracer agent for in vivo visualization of necrosis by SPECT.

Discovery of (*S*)-2-((*S*)-2-(3,5-difluorophenyl)-2-hydroxyacetamido)-*N*-((*S*,*Z*)-3-methyl-4-oxo-4,5-dihydro-3*H*-benzo[*d*][1,2]diazepin-5-yl)propanamide (BMS-433796): A γ -secretase inhibitor with A β lowering activity in a transgenic mouse model of Alzheimer's disease

pp 4006–4011

C. V. C. Prasad,* Ming Zheng, Shikha Vig, Carl Bergstrom, David W. Smith, Qi Gao, Suresh Yeola, Craig T. Polson, Jason A. Corsa, Valerie L. Guss, Alice Loo, Jian Wang, Bogdan G. Slecza, Charles Dangler, Barbara J. Robertson, Joseph P. Hendrick, Susan B. Roberts and Donna M. Barten*

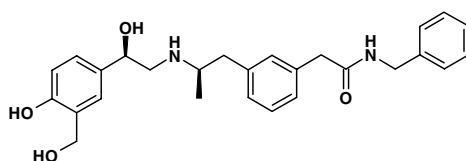


Potent and orally active benzodiazepinone-based γ -secretase inhibitors with a narrow therapeutic range were identified.

The discovery of long acting β_2 -adrenoreceptor agonists

pp 4012–4015

Alan D. Brown, Mark E. Bunnage, Paul A. Glossop,* Kim James, Rhys Jones, Charlotte A. L. Lane, Russell A. Lewthwaite, Simon Mantell, Christelle Perros-Huguet, David A. Price,* Mike Trevethick and Rob Webster

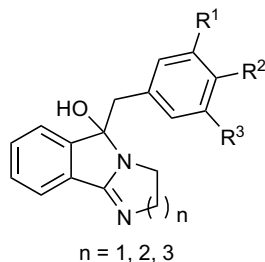


The design and profile of a series of saligenin containing long acting β_2 -adrenoreceptor agonists is described. Evaluation of these analogues using a guinea-pig tissue model demonstrates that analogues within this series have significantly longer durations of action than salmeterol and have the potential for a once daily profile in human.

[1,3]Diazaheterofused isoindolol derivatives displaying anxiolytic-like effects on mice

pp 4016–4021

Alejandro Zamilpa, Maribel Herrera-Ruiz, Esther Del Olmo,* José L. López-Pérez, Jaime Tortoriello* and Arturo San Feliciano

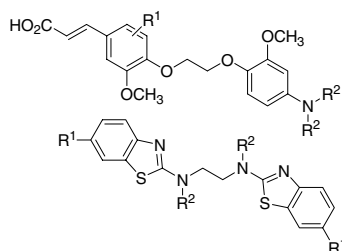


A number of imidazo[2,1-*a*], pyrimido[2,1-*a*] and [1,3]diazepino[2,1-*a*]isoindolols have been tested in the elevated plus-maze test, with significant anxiolytic-like results.

Ferulic acid and benzothiazole dimer derivatives with high binding affinity to β -amyloid fibrils

pp 4022–4025

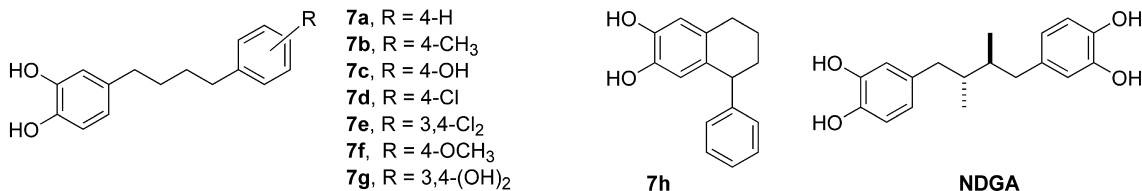
Seong Rim Byeon, Yun Jung Jin, Soo Jeong Lim, Ji Hoon Lee, Kyung Ho Yoo, Kye Jung Shin, Seung Jun Oh and Dong Jin Kim*



Inhibition of IGF-1R and lipoyxygenase by nordihydroguaiaretic acid (NDGA) analogs

pp 4026–4029

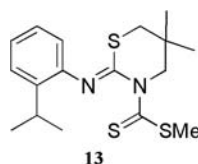
Joseph E. Blecha, Marc O. Anderson, Jennifer M. Chow, Christle C. Guevarra, Celia Pender, Cristina Penaranda, Marianna Zavodovskaya, Jack F. Youngren* and Clifford E. Berkman*

**2-Arylimino-5,6-dihydro-4H-1,3-thiazines as a new class of cannabinoid receptor agonists.**

pp 4030–4034

Part 1: Discovery of CB₂ receptor selective compounds

Hiroyuki Kai,* Yasuhide Morioka, Takami Murashi, Koichi Morita, Satomi Shinonome, Hitoshi Nakazato, Keiko Kawamoto, Kohji Hanasaki, Fumiyo Takahashi, Shin-ichi Mihara, Tohko Arai, Kohji Abe, Hiroshi Okabe, Takahiko Baba, Takayoshi Yoshikawa and Hideyuki Takenaka

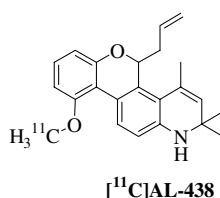


Among the 2-arylimino-5,6-dihydro-4H-1,3-thiazines, the most potent compound **13** displays K_i values of >5000 and 9 nM to CB₁ and CB₂ receptors, respectively.

Synthesis and radiopharmacological characterization of [¹¹C]AL-438 as a nonsteroidal ligand for imaging brain glucocorticoid receptors

pp 4035–4039

Frank Wuest,* Torsten Kniess, Ralf Bergmann, Brian Henry and Jens Pietzsch



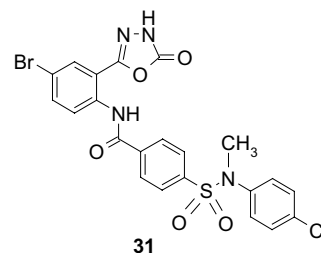
The radiosynthesis and the radiopharmacological characterization of [¹¹C]AL-438 as a nonsteroidal ligand for the glucocorticoid receptor (GR) is reported.

Structure–activity relationships of bioisosteres of a carboxylic acid in a novel class of bacterial translation inhibitors

pp 4040–4043

J. Craig Ruble, Brian D. Wakefield, Gregg M. Kamilar, Keith R. Marotti, Earline Melchior, Michael T. Sweeney, Gary E. Zurenko and Donna L. Romero*

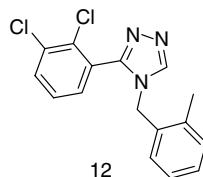
To improve potency and reduce protein binding in a novel series of antibacterial translation inhibitors, the SAR of carboxylic acid replacements and bioisosteres such as in compound **31** was explored.



Novel and potent 3-(2,3-dichlorophenyl)-4-(benzyl)-4H-1,2,4-triazole P2X₇ antagonists

pp 4044–4048

William A. Carroll,* Douglas M. Kalvin, Arturo Perez Medrano, Alan S. Florjancic, Ying Wang, Diana L. Donnelly-Roberts, Marian T. Namovic, George Grayson, Prisca Honoré and Michael F. Jarvis

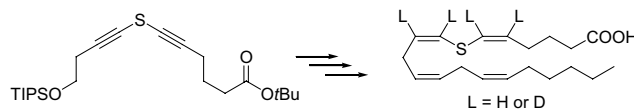


The synthesis and in vitro characterization of a series of phenyltriazole P2X₇ antagonists are described. Compound **12** was discovered to be active in a rat model of neuropathic pain.

Synthesis of 7-thiaarachidonic acid as a mechanistic probe of prostaglandin H synthase-2

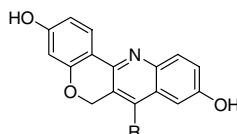
pp 4049–4052

Chris M. McGinley, Cyril Jacquot and Wilfred A. van der Donk*

**ERβ ligands. Part 6: 6H-Chromeno[4,3-b]quinolines as a new series of estrogen receptor β-selective ligands**

pp 4053–4056

An T. Vu,* Alison N. Campbell, Heather A. Harris, Rayomand J. Unwalla, Eric S. Manas and Richard E. Mewshaw



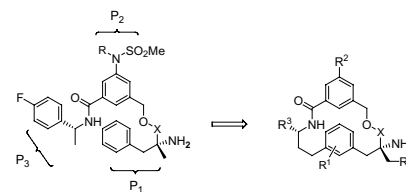
A series of 6H-chromeno[4,3-b]quinolines has been prepared and displayed high affinity and moderate selectivity for estrogen receptor beta.

Design, synthesis, and SAR of macrocyclic tertiary carbinamine BACE-1 inhibitors

pp 4057–4061

Stacey R. Lindsley,* Keith P. Moore, Hemaka A. Rajapakse, Harold G. Selnick, Mary Beth Young, Hong Zhu, Sanjeev Munshi, Lawrence Kuo, Georgia B. McGaughey, Dennis Colussi, Ming-Chih Crouthamel, Ming-Tain Lai, Beth Pietrak, Eric A. Price, Sethu Sankaranarayanan, Adam J. Simon, Guy R. Seabrook, Daria J. Hazuda, Nicole T. Pudvah, Jerome H. Hochman, Samuel L. Graham, Joseph P. Vacca and Philippe G. Nantermet*

This Letter describes the design and synthesis of tertiary carbinamine macrocyclic inhibitors of the β-secretase (BACE-1) enzyme. These macrocyclic inhibitors, some of which incorporate novel P2 substituents, display a 2- to 100-fold increase in potency relative to the previously described acyclic analogs while affording greater stability.

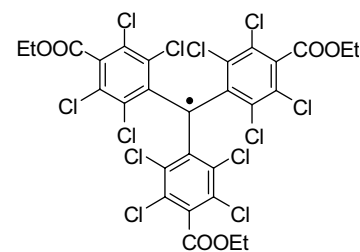


**Synthesis and characterization of a perchlorotriphenylmethyl (trityl) triester radical:
A potential sensor for superoxide and oxygen in biological systems**

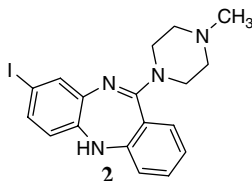
pp 4062–4065

 Vinh Dang, Jinhua Wang, Song Feng, Christophe Buron, Frederick A. Villamena,
Peng George Wang and Periannan Kuppusamy*

Perchlorotriphenylmethyl (trityl) triester radical: a potential sensor for superoxide and oxygen in biological systems.


Synthesis and biodistribution of 8-iodo-11-(4-methylpiperazino)-5H-dibenzo[b,e][1,4]-diazepine: Iozapine

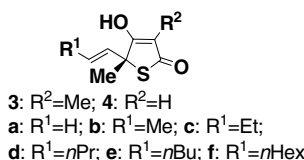
pp 4066–4069

 Alummoottil V. Joshua,* Sanjay K. Sharma, Alicia Strelkov, John R. Scott, Mathew T. Martin-Iverson,
Douglas N. Abrams, Peter H. Silverstone and Alexander J. B. McEwan

 8-Iodo-11-(4-methylpiperazino)-5H-dibenzo[b,e][1,4]-diazepine: Iozapine(**2**), a potential D4-receptor ligand was synthesized using oxidative iododestannylation reaction. The preliminary biodistribution studies of radioiodinated iozapine have shown that the compound is taken up in the brains of mice and rabbits.

Synthesis and biological activity of enantiomeric pairs of 5-vinylthiolactomycin congeners

pp 4070–4074

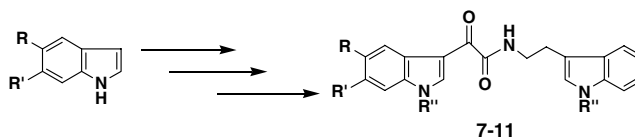
Kohei Ohata* and Shiro Terashima


 Among **3a–f**, *ent*-**3a–f**, **4a–f**, and *ent*-**4a–f** produced, (*S*)-3-demethyl-5-(pent-1-enyl)thiolactomycin derivative (*ent*-**4d**) exhibited mammalian type I FAS inhibitory activity equal to that of C75, the potent inhibitor so far reported, with complete loss of in vitro antibacterial activity.

Synthesis of marine alkaloid: 8,9-Dihydrococcinamide B and its analogues as Novel class of antileishmanial agents

pp 4075–4079


Leena Gupta, Archana Talwar, Nishi, Shraddha Palne, Suman Gupta and Prem M. S. Chauhan*



A series of 8,9-dihydrococcinamide B, its analogues and indolylglyoxylamide derivatives have been synthesized and screened for their in vitro antileishmanial activity profile in promastigote and amastigote models.

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

*Corresponding author

 Supplementary data available via ScienceDirect**COVER**

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, 16, 5664.]

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