

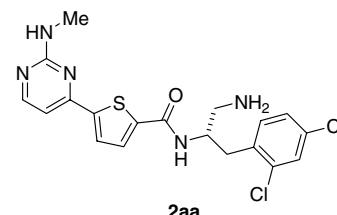
Contents

ARTICLES

Discovery of 2-pyrimidyl-5-amidothiophenes as potent inhibitors for AKT: Synthesis and SAR studies pp 4163–4168

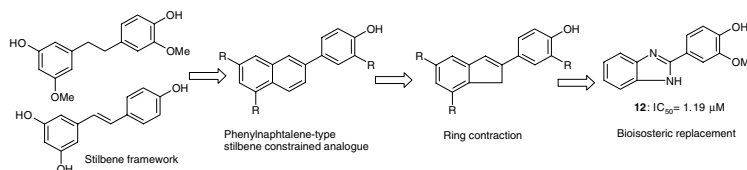
Xiaodong Lin,* Jeremy M. Murray, Alice C. Rico, Michael X. Wang, Daniel T. Chu, Yasheen Zhou, Merci Del Rosario, Susan Kaufman, Sylvia Ma, Eric Fang, Kenneth Crawford and A. B. Jefferson

A series of 2-pyrimidyl-5-amidothiophenes has been synthesized and evaluated for AKT inhibition. Compound **2aa** is a potent AKT inhibitor and showed cellular activity including antiproliferation and downstream target modulation. Selectivity profile is described. A co-crystal of **2aa** with PKA is determined and discussed.



Design, microwave-assisted synthesis, and spasmolytic activity of 2-(alkyloxyaryl)-1*H*-benzimidazole derivatives as constrained stilbene bioisosteres pp 4169–4173

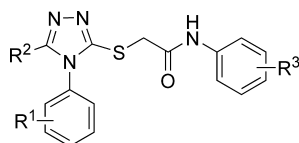
Gabriel Navarrete-Vázquez,* Hermenegilda Moreno-Díaz, Francisco Aguirre-Crespo, Ismael León-Rivera, Rafael Villalobos-Molina, Omar Muñoz-Muñoz and Samuel Estrada-Soto



The design of compounds explores the hypothesis that the stilbenoid framework could be mimicked with an appropriate 2-(Alkyloxyphenyl)benzimidazole scaffold. This framework has a similar structural motif as the 6-phenyl-naphthalene and behaves like stilbene bioisosteres. Compounds were synthesized through a rapid one-pot three component reaction via microwave irradiation.

Synthesis and biological evaluations of sulfanyltriazoles as novel HIV-1 non-nucleoside reverse transcriptase inhibitors pp 4174–4177

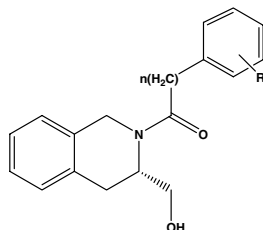
Zhiwei Wang, Baogen Wu, Kelli L. Kuhen, Badry Bursulaya, Truc N. Nguyen, Deborah G. Nguyen and Yun He*



Novel HIV-1 inhibitors

Identification of a lead pharmacophore for the development of potent nuclear receptor modulators as anticancer and X syndrome disease therapeutic agents pp 4178–4183

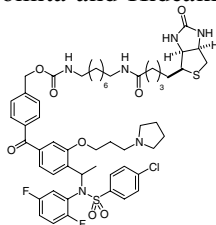
Hsiang-Ru Lin and Donald J. Abraham*



The synthesis and evaluation of 1, 2, 3, 4-tetrahydroisoquinoline-*N*-phenylamide derivatives as androgen receptor and farnesoid x receptor modulators are reported.

Synthesis of biotinylated photoaffinity probes based on arylsulfonamide γ -secretase inhibitors pp 4184–4189

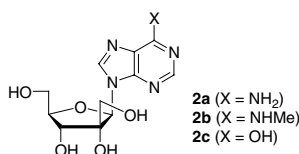
Haruhiko Fuwa,* Kenichi Hiromoto, Yasuko Takahashi, Satoshi Yokoshima, Toshiyuki Kan, Tohru Fukuyama, Takeshi Iwatsubo, Taisuke Tomita and Hideaki Natsugari*



Synthesis and biological evaluation of an arylsulfonamide class of γ -secretase inhibitors are described. Design, synthesis, and biological evaluation of multifunctional molecular probes harboring a benzophenone photophore as a cross-linking group and a biotin tag are also reported.

Synthesis of 2'-C-hydroxymethylribofuranosylpurines as potent anti-hepatitis C virus (HCV) agents pp 4190–4194

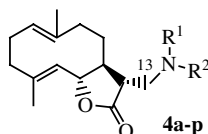
Byul Nae Yoo, Hea Ok Kim, Hyung Ryong Moon, Su Kyung Seol, Sung Key Jang, Kang Man Lee and Lak Shin Jeong*



On the basis of potent anti-HCV activity of 2'-*C*-methyladenosine, novel 2'-*C*-hydroxymethyladenosine analogues **2a–c** were synthesized from D-ribose in order to lead to favorable interaction with HCV polymerase.

Synthesis of 13-amino costunolide derivatives as anticancer agents pp 4195–4199

Sanjay K. Srivastava,* Aji Abraham, Beena Bhat, Manu Jaggi,* Anu T. Singh, Vinod K. Sanna, Gurvinder Singh, Shiv K. Agarwal, Rama Mukherjee and Anand C. Burman

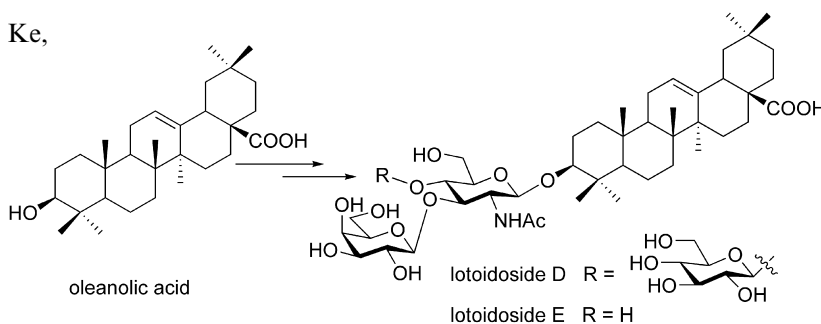


A number of 13-amino costunolide derivatives (**4a–p**) have synthesized and several of them have shown better cytotoxicity with better safety index as compared to costunolide.

Synthesis and antitumor activity of two natural *N*-acetylglucosamine-bearing triterpenoid saponins: Lotoidoside D and E pp 4200–4204

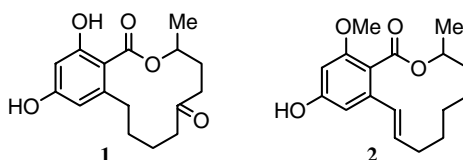
Mao-Cai Yan, Yang Liu, Hong Chen, Ying Ke, Qing-Chun Xu and Mao-Sheng Cheng*

Two antiproliferative triterpenoid saponins bearing *N*-acetylglucosamine were facilely synthesized. Antitumor activity was preliminarily investigated (IC_{50} = 2.74 μ M against HeLa cell).



Lactones from a brown alga endophytic fungus (No. ZZF36) from the South China Sea and their antimicrobial activities pp 4205–4208

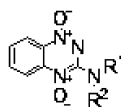
Rui-yun Yang, Chun-yuan Li, Yong-cheng Lin,* Guang-tian Peng, Zhi-gang She and Shi-ning Zhou



Two new metabolites named 6-oxo-de-*O*-methylasiodiplodin (**1**) and (*E*)-9-etheno-lasiodiplodin (**2**), with three known compounds, were isolated from a brown alga endophytic fungus (No. ZZF36). Their antimicrobial activity had been tested and compared for the first time.

Synthesis and hypoxic–cytotoxic activity of some 3-amino-1,2,4-benzotriazine-1,4-dioxide derivatives pp 4209–4213

Faqin Jiang, Bo Yang, Lingling Fan, Qiaojun He and Yongzhou Hu*

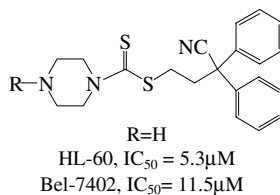


The synthesis and hypoxic–cytotoxic activity of 3-amino-1,2,4-benzotriazine-1,4-dioxide derivatives are reported.



Dithiocarbamic acid esters as anticancer agent. Part 1: 4-Substituted-piperazine-1-carbodithioic acid 3-cyano-3,3-diphenyl-propyl esters pp 4214–4219

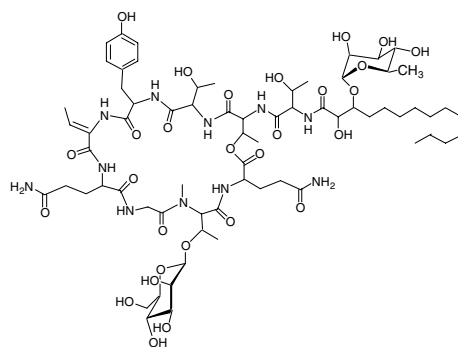
Xueling Hou, Zemei Ge, Tingmin Wang, Wei Guo, Jingrong Cui,* Tieming Cheng, Chingshan Lai and Runtao Li*



Hassallidin B—Second antifungal member of the Hassallidin family

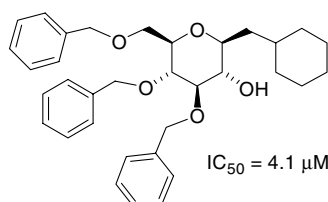
pp 4220–4222

Torsten Neuhoof, Peter Schmieder, Michael Seibold, Karina Preussel and Hans von Döhren*

**Antiproliferation and apoptosis induced by C-glycosides in human leukemia cancer cells**

pp 4223–4227

Carlos A. Sanhueza, Carlos Mayato, María García-Chicano, Raquel Díaz-Peñate, Rosa L. Dorta and Jesús T. Vázquez*

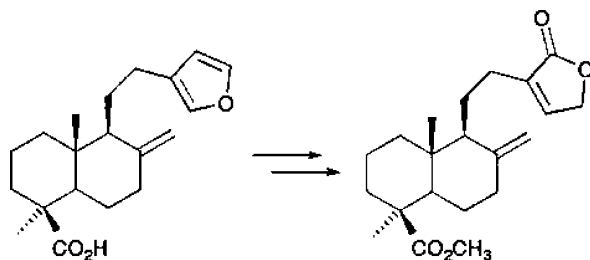


A large series of alkyl C-glycosides was synthesized and screened against the human promyelocytic leukemia cell line (HL60), showing significant activity and apoptosis.

Gram-scale synthesis of pinusolide and evaluation of its antileukemic potential

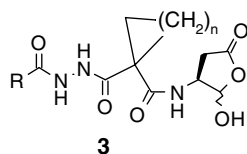
pp 4228–4232

E. E. Shults,* J. Velder, H.-G. Schmalz,* S. V. Chernov, T. V. Rubalova, Y. V. Gatilov, G. Henze, G. A. Tolstikov and A. Prokop*

**Synthesis and evaluation of novel 1-(2-acylhydrazinocarbonyl)-cycloalkyl carboxamides as interleukin-1 β converting enzyme (ICE) inhibitors**

pp 4233–4236

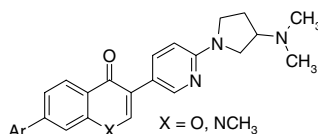
David L. Soper, Justin Sheville, Steven V. O'Neil, Yili Wang, Michael C. Lauferweiler, Kofi A. Oppong, John A. Vos, Christopher D. Ellis, Amy N. Fancher, Wei Lu, Maureen K. Suchanek, Richard L. Wang, Biswanath De and Thomas P. Demuth, Jr.*



Novel 1-(2-acylhydrazinocarbonyl)cycloalkyl carboxamides were designed and synthesized as selective peptidomimetic inhibitors of interleukin-1 β converting enzyme (ICE IC₅₀ values <100 nM).

Substituted chromones and quinolones as potent melanin-concentrating hormone receptor 1 antagonists pp 4237–4242

Brian Dyck,* Liren Zhao, Junko Tamiya, Joseph Pontillo, Sarah Hudson, Brett Ching, Christopher E. Heise, Jenny Wen, Christi Norton, Ajay Madan, David Schwarz, Warren Wade and Val S. Goodfellow

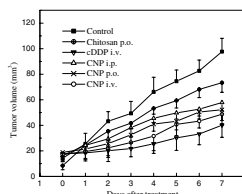


A series of substituted chromones were designed, synthesized, and evaluated for their ability to bind melanin-concentrating hormone receptor 1. Compounds with subnanomolar binding affinity and 66% oral bioavailability in rats were discovered.

In vivo antitumor activity of chitosan nanoparticles

pp 4243–4245

Lifeng Qi* and Zirong Xu

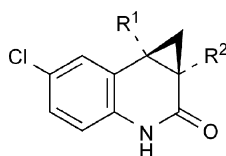


Effects of administration routes on antitumor efficacy of chitosan nanoparticles (CNP) against Sarcoma-180 subcutaneous tumor formation and growth in ICR mice.

Design, synthesis, and biological evaluations of novel quinolones as HIV-1 non-nucleoside reverse transcriptase inhibitors

pp 4246–4251

David Ellis, Kelli L. Kuhen, Beth Anaclerio, Baogen Wu, Karen Wolff, Hong Yin, Badry Bursulaya, Jeremy Caldwell, Donald Karanewsky and Yun He*

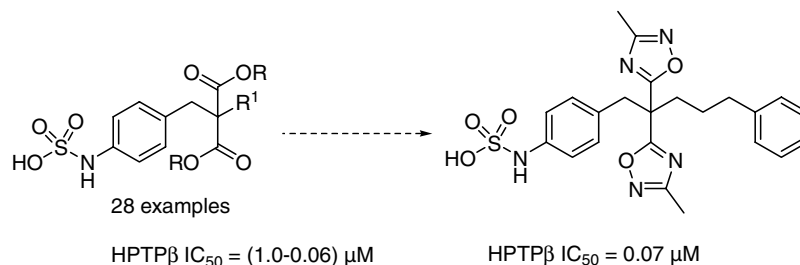


Novel HIV-1 non-nucleoside reverse transcriptase inhibitors

Design and synthesis of potent, non-peptidic inhibitors of HPTPβ

pp 4252–4256

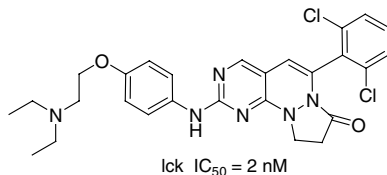
Kande K. D. Amarasinghe,* Artem G. Evidokimov, Kevin Xu, Cynthia M. Clark, Matthew B. Maier, Anil Srivastava, Anny-Odile Colson, Gina S. Gerwe, George E. Stake, Brian W. Howard, Matthew E. Pokross, Jeffrey L. Gray and Kevin G. Peters



The development of novel 1,2-dihydro-pyrimido[4,5-c]pyridazine based inhibitors of lymphocyte specific kinase (Lck)

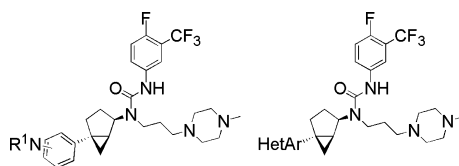
pp 4257–4261

Mark Sabat,* John C. VanRens, Todd A. Brugel, Jennifer Maier, Matthew J. Laufersweiler, Adam Golebiowski, Biswanath De, Vijayasurian Easwaran, Lily C. Hsieh, Jeff Rosegen, Steve Berberich, Eric Suchanek and Michael J. Janusz

**Bicyclo[3.1.0]hexyl urea melanin concentrating hormone (MCH) receptor-1 antagonists: Impacting hERG liability via aryl modifications**

pp 4262–4265

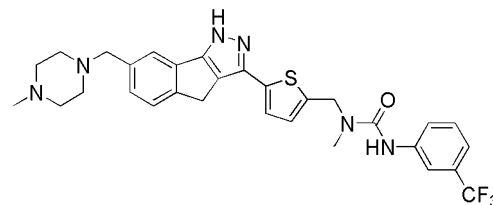
Mark D. McBriar,* Henry Guzik, Sherry Shapiro, Ruo Xu, Jaroslava Paruchova, John W. Clader, Kim O'Neill, Brian Hawes, Steve Sorota, Michael Margulis, Kristal Tucker, Daniel J. Weston and Kathleen Cox

**1,4-Dihydroindeno[1,2-c]pyrazoles as novel multitargeted receptor tyrosine kinase inhibitors**

pp 4266–4271

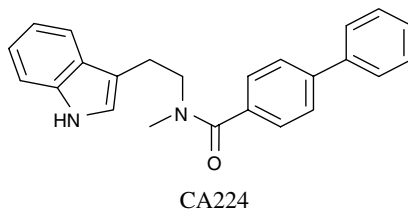
Jürgen Dinges,* Kimba L. Ashworth, Irini Akritopolou-Zanze, Lee D. Arnold, Steven A. Baumeister, Peter F. Bousquet, George A. Cunha, Steven K. Davidsen, Stevan W. Djuric, Vijaya J. Gracias, Michael R. Michaelides, Paul Rafferty, Thomas J. Sowin, Kent D. Stewart, Zhiren Xia and Henry Q. Zhang

A series of 1,4-dihydroindeno[1,2-c]pyrazoles with urea-type side chains was identified as potent multitargeted (VEGFR and PDGFR families) receptor tyrosine kinase inhibitors. A KDR homology model suggested that the urea moiety is able to interact with a recognition motif in the hydrophobic specificity pocket of the enzyme.

**CA224, a non-planar analogue of fascaplysin, inhibits Cdk4 but not Cdk2 and arrests cells at G₀/G₁ inhibiting pRB phosphorylation**

pp 4272–4278

Sachin Mahale, Carine Aubry, A. James Wilson, Paul R. Jenkins, Jean-Didier Maréchal, Michael J. Sutcliffe and Bhabatosh Chaudhuri*



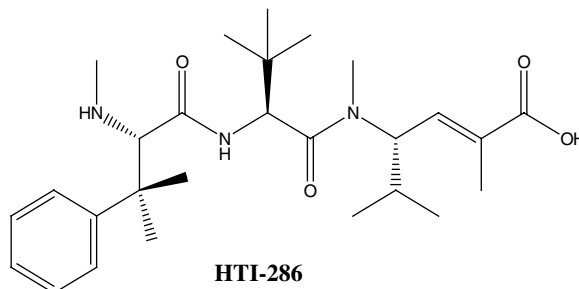
CA224, a tryptamine analogue of fascaplysin, is a specific inhibitor of Cdk4-D1 against Cdk2-A in enzyme assays, blocks cancer cells at G₀/G₁ and prevents pRB hyperphosphorylation, but does not bind or intercalate DNA like fascaplysin.

Mapping the bound conformation and protein interactions of microtubule destabilizing peptides by STD–NMR spectroscopy

pp 4279–4282

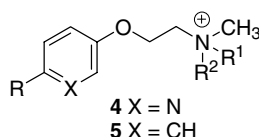
Mark J. Milton, R. Thomas Williamson and Frank E. Koehn*

Using HTI-286 as a model we demonstrate that relaxation-compensated STD–NMR can be an effective tool to provide a qualitative epitope map for microtubule destabilizing peptides. It was essential to collect STD with short saturation times to render an accurate picture of the binding interaction.

**Aryloxyethylamines: Binding at $\alpha 7$ nicotinic acetylcholine receptors**

pp 4283–4286

Hanan M. Ragab, Jin Sung Kim, Małgorzata Dukat, Hernán Navarro and Richard A. Glennon*



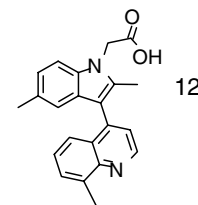
An examination of several aryloxyalkylamine analogs **4** and **5** was undertaken to determine the role of various structural features for binding at homomeric $\alpha 7$ nicotinic acetylcholine receptors. In general, the ring N atom might contribute to affinity but is not essential. In contrast, the *N,N,N*-trimethyl quaternary amine is a major contributor to $\alpha 7$ binding.

Discovery of potent CRTh2 (DP₂) receptor antagonists

pp 4287–4290

Timothy N. Birkinshaw,* Simon J. Teague,* Claire Beech, Roger V. Bonnert, Stephen Hill, Anil Patel, Sara Reakes, Hitesh Sangane, Iain G. Dougall, Tim T. Phillips, Sylvia Salter, Jerzy Schmidt, Elizabeth C. Arrowsmith, Juan J. Carrillo, Fiona M. Bell, Stuart W. Paine and Richard Weaver

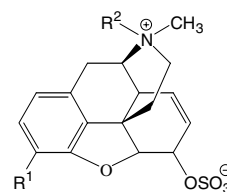
The discovery and optimisation of potent antagonists of the CRTh2 receptor is described culminating in the synthesis of **12**, a novel, potent, selective and metabolically stable lead compound.

**Opiate receptor binding properties of morphine-, dihydromorphine-, and codeine 6-*O*-sulfate ester congeners**

pp 4291–4295

Peter A. Crooks,* Santosh G. Kottayil, Abeer M. Al-Ghananeem, Stephen R. Byrn and D. Allan Butterfield

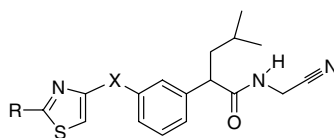
A series of 3-*O*-acyl-6-*O*-sulfate esters of morphine, dihydromorphine, *N*-methylmorphinium iodide, codeine, and dihydrocodeine were prepared and evaluated for their ability to bind to μ -, δ -, κ_1 -, κ_2 -, and κ_3 -opiate receptors. Several compounds exhibited good affinity for the μ -opiate receptor. Morphine-3-*O*-propionyl-6-*O*-sulfate had four times greater affinity than morphine at the μ -opiate receptor and was the most selective compound at this receptor subtype.



Design and synthesis of tetracyclic nonpeptidic biaryl nitrile inhibitors of cathepsin K

pp 4296–4299

Eduardo L. Setti,* Shankar Venkatraman, James T. Palmer, Xiaoming Xie, Harry Cheung, Walter Yu, Gregg Wesolowski and Joel Robichaud



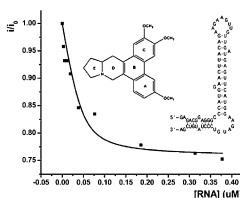
X: phenyl ring

A novel series of potent and selective inhibitors of cysteine protease cathepsin K is described.

The interaction between tylophorine B and TMV RNA

pp 4300–4304

Zhen Xi,* Ruoyu Zhang, Zhihong Yu and Di Ouyang



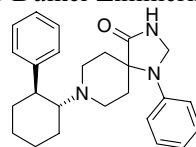
Tobacco mosaic virus (TMV) inhibitor tylophorine B binds to TMV RNA in multiple binding sites with IC_{50} of 2.4 nM. It also binds to assembly origin of TMV RNA with one binding site of K_d of 9 nM. We speculate that tylophorine B likely exerts its virus inhibition by binding to assembly origin, and interfering with virus assembly initiation.

Design and synthesis of 4-substituted-8-(2-phenyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one as a novel class of GlyT1 inhibitors: Achieving selectivity against the μ opioid and nociceptin/orphanin FQ peptide (NOP) receptors

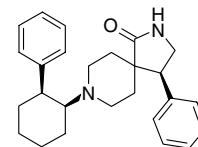
pp 4305–4310

Daniela Alberati, Simona M. Ceccarelli, Synèse Jolidon, Eva A. Krafft, Anke Kurt, Axel Maier, Emmanuel Pinard, Henri Stalder, Deborah Studer, Andrew W. Thomas* and Daniel Zimmerli

A novel class of 4-substituted-8-(2-phenyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-ones have been discovered and developed as potent and selective GlyT1 inhibitors. The molecules display excellent selectivities (when compared to their triazaspiropiperidine analogues) against the μ opioid receptor as well as the nociceptin/orphanin FQ peptide (NOP) receptor.



GlyT1 EC_{50} (μ M): 0.073
NOP IC_{50} (μ M): 0.310
 μ IC_{50} (μ M): 0.520



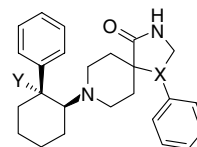
GlyT1 EC_{50} (μ M): 0.246
NOP IC_{50} (μ M): >10
 μ IC_{50} (μ M): >10

Discovery of 4-substituted-8-(2-hydroxy-2-phenyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one as a novel class of highly selective GlyT1 inhibitors with improved metabolic stability

pp 4311–4315

Daniela Alberati, Dominik Hainzl, Synèse Jolidon, Eva A. Krafft, Anke Kurt, Axel Maier, Emmanuel Pinard, Andrew W. Thomas* and Daniel Zimmerli

A novel class of 2,8-diaza-spiro[4.5]decan-1-ones have been discovered and developed as potent and selective GlyT1 inhibitors. In general, the diaspiropiperidine series show improved metabolic stability (when compared to the triazaspiropiperidine series) and we have also identified a key relationship between reducing basicity of the piperidine nitrogen and reducing hERG affinity.

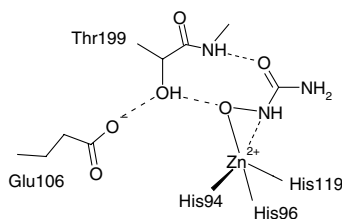


X = N; Y = H: CL_{int} (μ L/min/mg protein): 240
X = N; Y = OH: CL_{int} (μ L/min/mg protein): 499
X = CH; Y = H: CL_{int} (μ L/min/mg protein): 36
X = CH; Y = OH: CL_{int} (μ L/min/mg protein): 13

N-Hydroxyurea—A versatile zinc binding function in the design of metalloenzyme inhibitors

pp 4316–4320

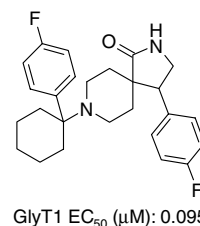
Claudia Temperini, Alessio Innocenti, Andrea Scozzafava and Claudiu T. Supuran*

**4-Substituted-8-(1-phenyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one as a novel class of highly selective GlyT1 inhibitors with superior pharmacological and pharmacokinetic parameters**

pp 4321–4325

Daniela Alberati, Dominik Hainzl, Synèse Jolidon, Anke Kurt, Emmanuel Pinard, Andrew W. Thomas* and Daniel Zimmerli

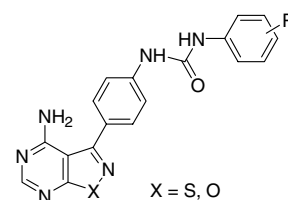
A novel class of 4-substituted-8-(1-phenyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-ones have been discovered and developed as potent and selective GlyT1 inhibitors. These molecules also exhibit superior pharmacological and pharmacokinetic parameters, relative to all GlyT1 inhibitors of the spiro-piperidine family, culminating in the identification of **16b** with an oral bioavailability of ~60%. A straightforward two-step procedure for the assembly of the target molecules is also presented.

**Isothiazolopyrimidines and isoxazolopyrimidines as novel multi-targeted inhibitors of receptor tyrosine kinases**

pp 4326–4330

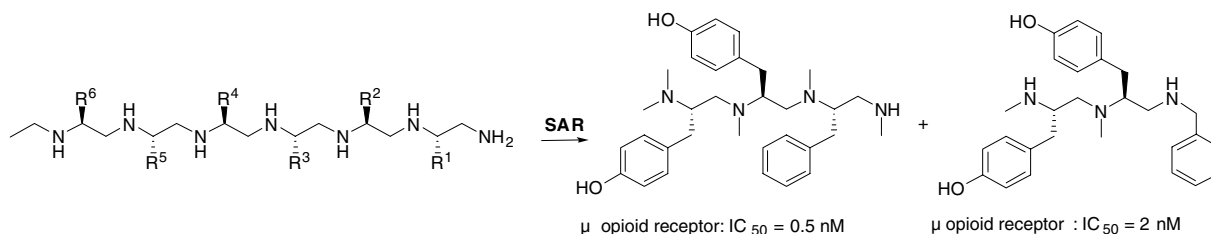
Zhiqin Ji,* Asma A. Ahmed, Daniel H. Albert, Jennifer J. Bouska, Peter F. Bousquet, George A. Cunha, Keith B. Glaser, Jun Guo, Junling Li, Patrick A. Marcotte, Maria D. Moskey, Lori J. Pease, Kent D. Stewart, Melinda Yates, Steven K. Davidsen and Michael R. Michaelides

A series of isothiazolopyrimidines and isoxazolopyrimidines were synthesized and identified as potent RTK inhibitors. SAR studies led to isothiazolopyrimidine urea analogs that potently inhibit VEGFR tyrosine kinases (KDR enzymatic and cellular IC₅₀ values below 10 nM) as well as cKIT and TIE2.

**Identification of potent and highly selective chiral tri-amine and tetra-amine μ opioid receptors ligands: An example of lead optimization using mixture-based libraries**

pp 4331–4338

Adel Nefzi, John M. Ostresh, Jon R. Appel, Jean Bidlack, Colette T. Dooley and Richard A. Houghten*

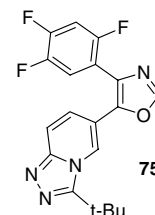


Screening of a mixture based heptaamine library (34,012,170 compounds) against μ opioid receptor and identification of highly active heptaamine compounds.

Structure–activity relationships of triazolopyridine oxazole p38 inhibitors: Identification of candidates for clinical development

pp 4339–4344

Kim F. McClure,* Michael A. Letavic, Amit S. Kalgutkar, Christopher A. Gabel, Laurent Audoly, John T. Barberia, John F. Braganza, Demetrius Carter, Thomas J. Carty, Santo R. Cortina, Mark A. Dombroski, Kathleen M. Donahue, Nancy C. Elliott, Colleen P. Gibbons, Crystal K. Jordan, Alexander V. Kuperman, Jeff M. Labasi, Ronald E. LaLiberte, Jennifer M. McCoy, Brian M. Naiman, Kendra L. Nelson, Hang T. Nguyen, Kevin M. Peese, Francis J. Sweeney, Timothy J. Taylor, Catherine E. Trebino, Yuriy A. Abramov, Ellen R. Laird, Walter A. Volberg, Jun Zhou, Justin Bach and Franco Lombardo



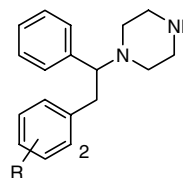
p38 α IC₅₀ = 1.8 nM
HWB IC₅₀ = 63 nM

N-(1,2-Diphenylethyl)piperazines: A new class of dual serotonin/noradrenaline reuptake inhibitor

pp 4345–4348

M. Jonathan Fray,* Gerwyn Bish, Alan D. Brown, Paul V. Fish, Alan Stobie, Florian Wakenhut and Gavin A. Whitlock

The synthesis and structure–activity relationships are described for a series of 20 mono-substituted *N*-(1,2-diphenylethyl)piperazines as dual serotonin/noradrenaline reuptake inhibitors. Compound **14** possessed a similar in vitro potency selectivity profile to duloxetine.



human amine transporter IC₅₀ (nM)

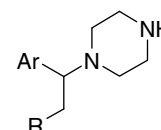
14 R = 2-Cl 5.4 (5-HT); 22 (NA); 1300 (DA)
R = 2-OEt 13 (5-HT); 16 (NA); >4000 (DA)

Structure–activity relationships of N-substituted piperazine amine reuptake inhibitors

pp 4349–4353

M. Jonathan Fray,* Gerwyn Bish, Paul V. Fish, Alan Stobie, Florian Wakenhut and Gavin A. Whitlock

The synthesis and structure–activity relationships are described for 26 variously N-substituted piperazines as dual serotonin/noradrenaline reuptake inhibitors. Compound (*R*)(–)-**2** was a potent, balanced 5-HT/NA reuptake inhibitor with high selectivity over a wide range of GPCRs and demonstrated only weak inhibitory activity versus cytochromes P₄₅₀.

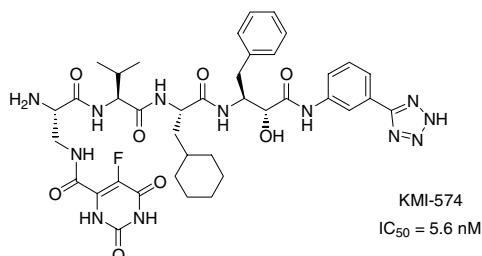


Ar = Ph, C₆H₄F, 3-pyridyl,
2-thiazolyl, 5-thiazolyl
R = pyridyl, naphthyl, *o*-C₆H₄Cl,
o-C₆H₄OEt

β-Secretase inhibitors: Modification at the P₄ position and improvement of inhibitory activity in cultured cells

pp 4354–4359

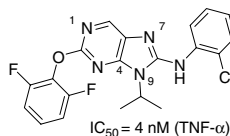
Yoshio Hamada, Naoto Igawa, Hayato Ikari, Zyta Ziora, Jeffrey-Tri Nguyen, Abdellah Yamani, Koushi Hidaka, Tooru Kimura, Kazuki Saito, Yoshio Hayashi, Maiko Ebina, Shoichi Ishiura and Yoshiaki Kiso*



KMI-574
IC₅₀ = 5.6 nM

The development of novel C-2, C-8, and N-9 trisubstituted purines as inhibitors of TNF- α production pp 4360–4365

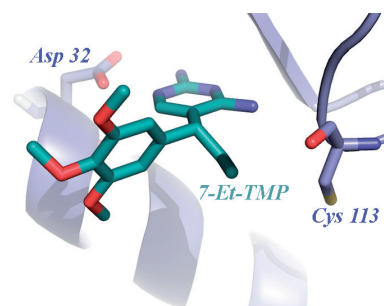
Mark Sabat,* John C. VanRens, Michael P. Clark, Todd A. Brugel, Jennifer Maier, Roger G. Bookland, Matthew J. Lauffersweiler, Steven K. Laughlin, Adam Golebiowski, Biswanath De, Lily C. Hsieh, Richard L. Walter, Marlene J. Mekel and Michael J. Janusz

**Analysis of complexes of inhibitors with *Cryptosporidium hominis* DHFR leads to a new trimethoprim derivative**

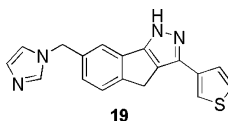
pp 4366–4370

Veljko M. Popov, David C. M. Chan, Yale A. Fillingham, W. Atom Yee, Dennis L. Wright and Amy C. Anderson*

A trimethoprim derivative with an ethyl substitution at the C7 position forms van der Waals contacts with Cys 113 and shows increased potency.

**Hit-to-lead optimization of 1,4-dihydroindeno[1,2-*c*]pyrazoles as a novel class of KDR kinase inhibitors** pp 4371–4375

Jürgen Dinges,* Irini Akritopoulou-Zanze, Lee D. Arnold, Teresa Barlozzari, Peter F. Bousquet, George A. Cunha, Anna M. Ericsson, Nobuhiko Iwasaki, Michael R. Michaelides, Nobuo Ogawa, Kathleen M. Phelan, Paul Rafferty, Thomas J. Sowin, Kent D. Stewart, Ryukou Tokuyama, Zhiren Xia and Henry Q. Zhang

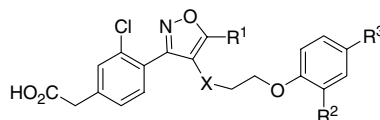


A series of 1,4-dihydroindeno[1,2-*c*]pyrazoles was evaluated as KDR kinase inhibitors. Hit-to-lead optimization studies led to **19**, a lead compound with an acceptable selectivity profile, activity in whole cells, and good oral efficacy in an estradiol-induced murine uterine edema model of VEGF activity.

3,4,5-Trisubstituted isoxazoles as novel PPAR δ agonists: Part 1

pp 4376–4380

Robert Epple,* Ross Russo, Mihai Azimioara, Christopher Cow, Yongping Xie, Xing Wang, John Wityak, Don Karanewsky, Andrea Gerken, Maya Iskandar, Enrique Saez, H. Martin Seidel and Shin-Shay Tian



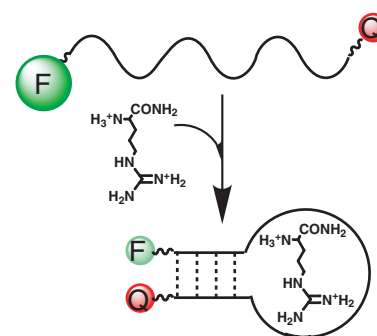
A structurally novel series of selective PPAR δ agonists is reported.

Biomolecular sensor based on fluorescence-labeled aptamer

pp 4381–4384

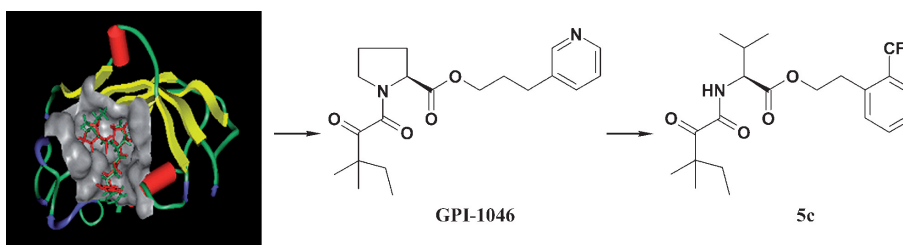
Hiroaki Ozaki,* Akifumi Nishihira, Masayuki Wakabayashi,
Masayasu Kuwahara and Hiroaki Sawai

Fluorescence-labeled aptamer for L-argininamide was developed by a combination of DNA aptamer and fluorophore–quencher pairs. The fluorescence intensity of the aptamer was reduced to about one-fifth by the addition of L-argininamide. The binding affinities of the modified aptamers were nearly equal to that of its original aptamer.

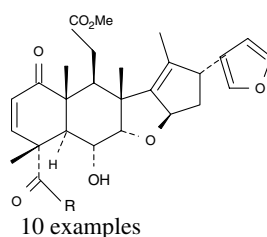
**Modeling and synthesis of non-cyclic derivatives of GPI-1046 as potential FKBP ligands with neurotrophic properties**

pp 4385–4390

Liqin Zhao,* Hongying Liu, Lili Wang and Song Li*

**Synthesis and biological activity of amide derivatives of nimbolide**

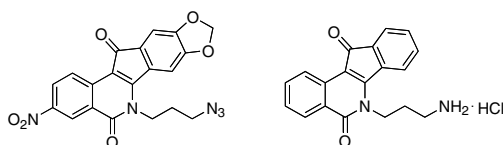
pp 4391–4394

B. S. Sastry, K. Suresh Babu, T. Hari Babu, S. Chandrasekhar, P. V. Srinivas,
A. K. Saxena and J. Madhusudana Rao*

A series of nimbolide derivatives have been synthesized and evaluated for in vitro cytotoxic activity against a panel of human cancer cell lines.

Evaluation of indenoisoquinoline topoisomerase I inhibitors using a hollow fiber assay

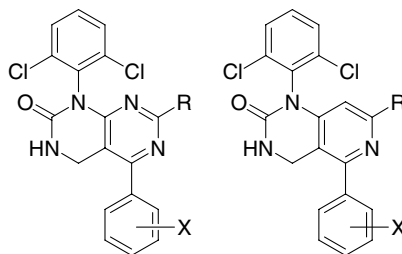
pp 4395–4399

Andrew Morrell, Muthusamy Jayaraman, Muthukaman Nagarajan, Brian M. Fox,
Marintha Rae Meckley, Alexandra Ioanoviciu, Yves Pommier, Smitha Antony,
Melinda Hollingshead and Mark Cushman*

p38 MAP kinase inhibitors. Part 3: SAR on 3,4-dihydropyrimido[4,5-*d*]pyrimidin-2-ones and 3,4-dihydropyrido[4,3-*d*]pyrimidin-2-ones

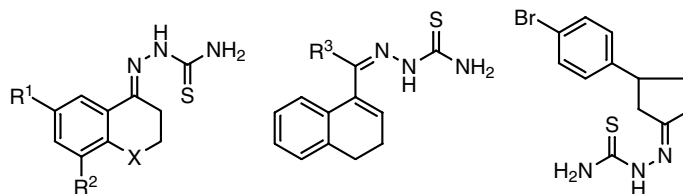
pp 4400–4404

Swaminathan R. Natarajan,* David D. Wisnoski, James E. Thompson, Edward A. O'Neill and Stephen J. O'Keefe

**Design, synthesis, and biochemical evaluation of novel cruzain inhibitors with potential application in the treatment of Chagas' disease**

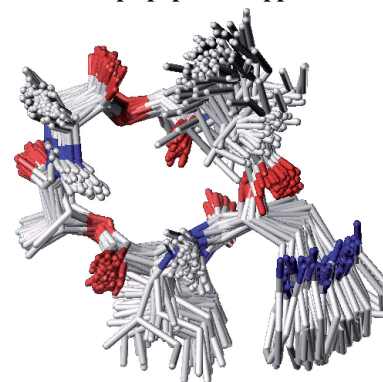
pp 4405–4409

Rogelio Siles, Shen-En Chen, Ming Zhou, Kevin G. Pinney and Mary Lynn Trawick*

**Synthesis and anthelmintic activity of substituted (*R*)-phenyllactic acid containing cyclohexadepsipeptides** pp 4410–4415

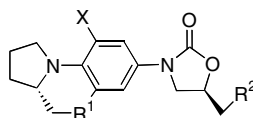
Peter Jeschke,* Jordi Benet-Buchholz, Achim Harder, Winfried Etzel, Michael Schindler, Wolfgang Gau and Hans-Christoph Weiss

The substituted (*R*)-phenyllactic acid containing cyclohexadepsipeptides (CHDPs) **3–7** represent novel enniatin derivatives with strong *in vivo* activities against the parasitic nematode *Haemonchus contortus* Rudolphi in sheep. 2D NMR spectroscopic analysis revealed for the substituted (*R*)-phenyllactic acid containing CHDPs one major conformer with an unsymmetrically folded conformation lacking a *cis*-amide bond. A correlation between the substitution pattern and its anthelmintic activity was found. Here we report on a simple total synthetic pathway of the precursor for this particular type of CHDPs and an efficient modification of the benzylic side chain (*R*-PhLac²).

**Synthesis of novel tricyclic oxazolidinones by a tandem SN₂ and SNAr reaction: SAR studies on conformationally constrained analogues of Linezolid**

pp 4416–4419

N. Selvakumar,* B. Yadi Reddy, G. Sunil Kumar, Manoj Kumar Khera, D. Srinivas, M. Sitaram Kumar, Jagattaran Das, Javed Iqbal and Sanjay Trehan

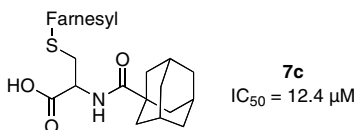


The synthesis of a series of tricyclic oxazolidinones employing a tandem SN₂ and SNAr reaction as the key step is disclosed. SAR studies on these novel compounds resulted in certain potent antibacterial compounds.

Amide-substituted farnesylcysteine analogs as inhibitors of human isoprenylcysteine carboxyl methyltransferase

pp 4420–4423

James L. Donelson, Heather B. Hodges, Daniel D. MacDougall, Brian S. Henriksen, Christine A. Hrycyna* and Richard A. Gibbs*

**OTHER CONTENTS**

Summary of instructions to authors

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*Corresponding author

i+ Supplementary data available via ScienceDirect

COVER

View of the crystal structure of the DB819-d(CGCGAATTCGCG)₂ complex, looking down the minor groove of the DNA (see Campbell, N.H.; Evans, D.A.; Lee, M.P.H.; Parkinson, G.N.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2006**, 16, 15). The DB819 molecule is shown in space-filling mode. Visualisation produced with the VMD program. [Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, 14, 33.]



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