

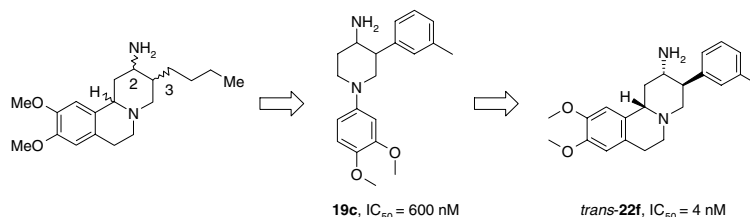
## Contents

## ARTICLES

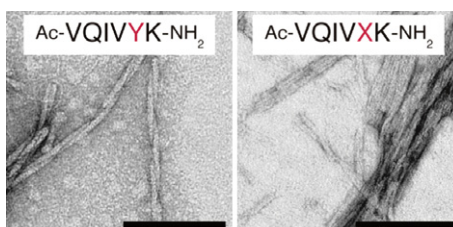
**1,3-Disubstituted 4-aminopiperidines as useful tools in the optimization of the 2-aminobenzo[a]-quinolizine dipeptidyl peptidase IV inhibitors** pp 2966–2970

Thomas Lübbers,\* Markus Böhringer, Luca Gobbi, Michael Hennig, Daniel Hunziker, Bernd Kuhn, Bernd Löffler, Patrizio Mattei, Robert Narquizian, Jens-Uwe Peters, Yves Ruff, Hans Peter Wessel and Pierre Wyss

In a search for novel DPP-IV inhibitors, 2-aminobenzo[a]-quinolizines were identified as submicromolar HTS hits. Due to the difficult synthetic access to this compound class, 1,3-disubstituted 4-aminopiperidines were used as model compounds for optimization. The developed synthetic methodology and the SAR could be transferred to the 2-aminobenzo[a]quinolizine series, leading to highly active DPP-IV inhibitors.


**Amyloid-forming propensity of the hydrophobic non-natural amino acid on the fibril-forming core peptide of human tau** pp 2971–2974

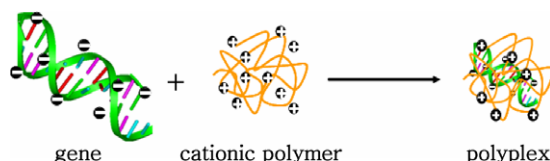
Akiyoshi Hirata, Kenji Sugimoto, Takashi Konno and Takashi Morii\*



TEM images of amyloid-type fibers formed from PHF6 (left) and phenyl-substituted PHF6Ph (right). Scale bar: 100 nm. The tyrosine residue (Y) corresponds to the native Tyr-310 residue of tau.


**A tetra(L-lysine)-grafted poly(organophosphazene) for gene delivery** pp 2975–2978

Yong Joo Jun, Jung Hee Kim, Su Jin Choi, Hwa Jeong Lee, Moo Jin Jun and Youn Soo Sohn\*



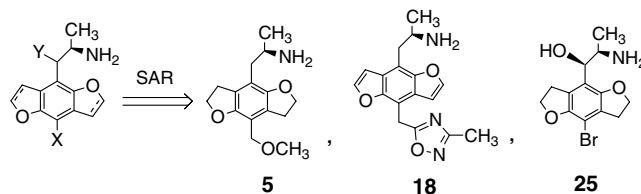
A novel cationic poly(organophosphazene) bearing a branched tetralysine and a poly(ethylene glycol) as side groups was synthesized and studied for gene delivery.



**Novel benzodifuran analogs as potent 5-HT<sub>2A</sub> receptor agonists with ocular hypotensive activity**

pp 2998–3002

Zixia Feng, Suchismita Mohapatra,\* Peter G. Klimko, Mark R. Hellberg, Jesse A. May, Curtis Kelly, Gary Williams, Marsha A. McLaughlin and Najam A. Sharif

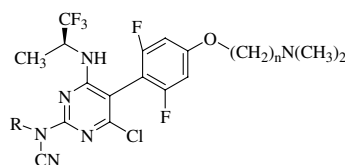


A series of benzodifuran analogs with reduced lipophilicity were designed and synthesized as novel 5-HT<sub>2A</sub> agonists. The selected compounds **5**, **18**, and **25** exhibited potent and efficacious ocular hypotensive activity in cynomolgus monkey eye, affording maximum IOP reductions of 37%, 27%, and 24%, respectively, at 300 µg doses.

**2-Cyanoaminopyrimidines as a class of antitumor agents that promote tubulin polymerization**

pp 3003–3005

Nan Zhang,\* Semiramis Ayral-Kaloustian, Thai Nguyen, Richard Hernandez and Carl Beyer



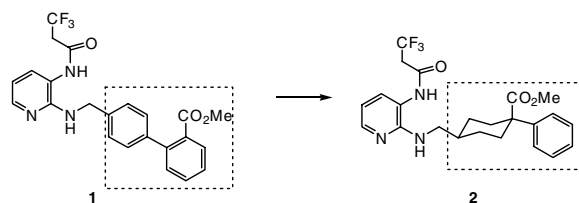
The synthesis, SAR, and mechanism of action studies for a series of 2-cyanoaminopyrimidines as anticancer agents is reported.

**Potent bradykinin B<sub>1</sub> receptor antagonists: 4-Substituted phenyl cyclohexanes**

pp 3006–3009

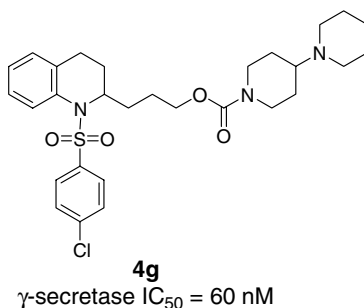
Dai-Shi Su,\* John L. Lim, M. Kristine Markowitz, Bang-Lin Wan, Kathy L. Murphy, Duane R. Reiss, C. Meacham Harrell, Stacy S. O'Malley, Rick W. Ransom, Raymond S. L. Chang, Douglas J. Pettibone, Cuyue Tang, Thomayant Prueksaritanont, Roger M. Freidinger and Mark G. Bock

4-Substituted phenyl cyclohexanes were identified as alternative isosteres for the biphenyl moiety of the lead compound **1**. The syntheses, SAR optimization, and pharmacokinetic profiles of these compounds are described.

**Design, synthesis, and evaluation of tetrahydroquinoline and pyrrolidine sulfonamide carbamates as γ-secretase inhibitors**

pp 3010–3013

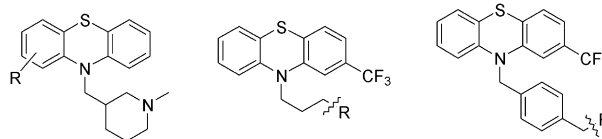
Tao Guo,\* Huizhong Gu, Doug W. Hobbs, Laura L. Rokosz, Tara M. Stauffer, Bijl Jacob and John W. Clader



### Synthesis and antitubercular activity of phenothiazines with reduced binding to dopamine and serotonin receptors

pp 3014–3017

Peter B. Madrid,\* Willma E. Polgar, Lawrence Toll and Mary J. Tanga



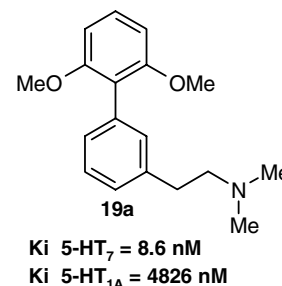
A series of phenothiazines were synthesized and evaluated for activity against *Mycobacterium tuberculosis*. The compounds were subsequently counter-screened for binding to dopamine and serotonin receptors to determine the in vitro selectivity of the compounds for antitubercular activity over psychotropic effects.

### Novel aminoethylbiphenyls as 5-HT<sub>7</sub> receptor ligands

pp 3018–3022

Magalie Paillet-Loilier, Frédéric Fabis,\* Alban Lepailleur, Ronan Bureau, Sabrina Butt-Gueulle, François Dauphin, Aurélien Lesnard, Catherine Delarue, Hubert Vaudry and Sylvain Rault

The synthesis of novel aminoethylbiphenyls with high affinity for the 5-HT<sub>7</sub> receptors and good selectivity towards 5-HT<sub>1A</sub> receptors is reported.

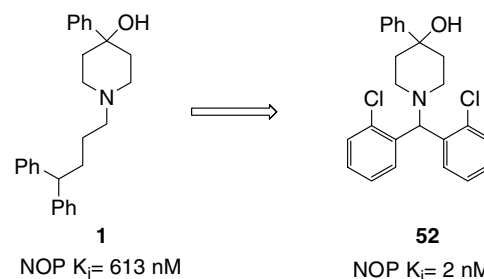


### Synthesis and structure–activity relationships of 4-hydroxy-4-phenylpiperidines as nociceptin receptor ligands: Part 1

pp 3023–3027

Ginny D. Ho,\* Ana Bercovici, Deen Tulshian, William J. Greenlee, Ahmad Fawzi, April Smith Torhan and Hongtao Zhang

A series of 4-hydroxy-4-phenylpiperidines have been synthesized and bind to the nociceptin receptor with high affinity. The synthesis and structure–activity relationships at the N-1 and C-4 hydroxy are described.

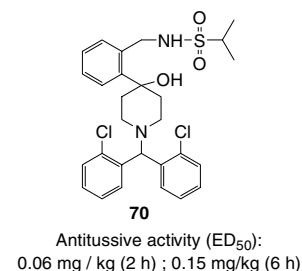


### Synthesis and structure–activity relationships of 4-hydroxy-4-phenylpiperidines as nociceptin receptor ligands: Part 2

pp 3028–3033

Ginny D. Ho,\* Ana Bercovici, Deen Tulshian, William J. Greenlee, Ahmad Fawzi, Xiomara Fernandez, Robbie L. McLeod, April Smith Torhan and Hongtao Zhang

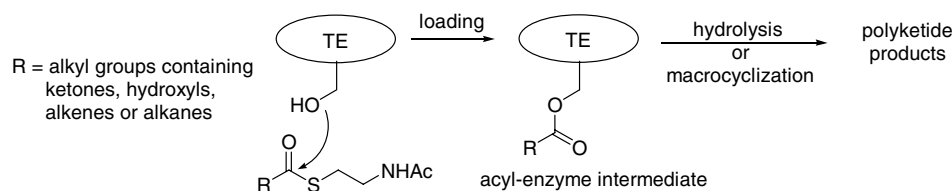
A series of 4-[2-(aminomethyl)phenyl]-1-[bis(2-chlorophenyl)methyl]-4-hydroxypiperidine analogs has been identified as nociceptin receptor ligands. These compounds display high affinity and functional activity at the nociceptin receptor. The synthesis and structure–activity relationships at the C-4 phenyl and N-1 positions are described and the antitussive activity of a selected compound is reported.



**The thioesterase domain from the pimarinin and erythromycin biosynthetic pathways can catalyze hydrolysis of simple thioester substrates**

pp 3034–3037

Krishna K. Sharma and Christopher N. Boddy\*

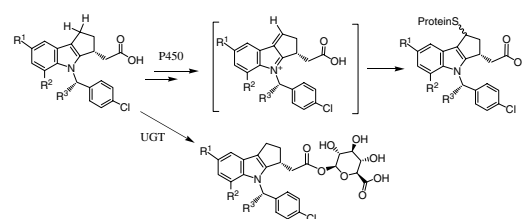


Thioesterase domains exhibit low substrate specificity for loading and can generate the acyl-enzyme intermediates, required for hydrolysis or macrocyclization, from a number of structurally different thioesters.

**Metabolic activation of indole-containing prostaglandin D2 receptor 1 antagonists: Impacts of glutathione trapping and glucuronide conjugation on covalent binding**

pp 3038–3043

Jean-François Lévesque,\* Stephen H. Day, Nathalie Chauret, Carmai Seto, Laird Trimble, Kevin P. Bateman, José M. Silva, Carl Berthelette, Nicolas Lachance, Michael Boyd, Lianhai Li, Claudio F. Sturino, Zhaoyin Wang, Robert Zamboni, Robert N. Young and Deborah A. Nicoll-Griffith

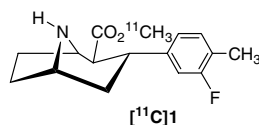


Impacts of substituents on the indole-core of DP1 receptor antagonists on reactive metabolite formation and in vitro and in vivo covalent binding to liver proteins.

**Synthesis and biological evaluation of 2β,3α-(substituted phenyl)nortropanes as potential norepinephrine transporter imaging agents**

pp 3044–3047

Fanxing Zeng, Jeffrey S. Stehouwer, Nachwa Jarkas, Ronald J. Voll, Larry Williams, Vernon M. Camp, John R. Votaw, Michael J. Owens, Clinton D. Kilts, Charles B. Nemeroff and Mark M. Goodman\*

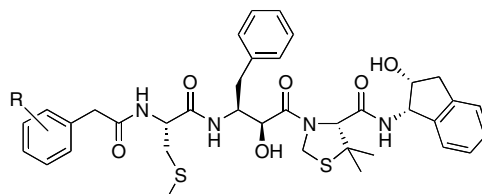


A series of 2β,3α-(substituted phenyl)nortropanes was synthesized and evaluated in vitro for human monoamine transporters. Radiolabeling and nonhuman primate microPET brain imaging studies were performed with the most promising compound, [<sup>11</sup>C]1, to determine its utility as a NET imaging agent.

**Additional interaction of allophenylnorstatine-containing tripeptidomimetics with malarial aspartic protease plasmepsin II**

pp 3048–3052

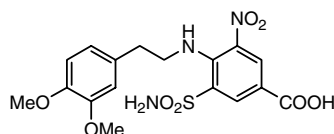
Koushi Hidaka, Tooru Kimura, Yumi Tsuchiya, Mami Kamiya, Adam J. Ruben, Ernesto Freire, Yoshio Hayashi and Yoshiaki Kiso\*



A series of allophenylnorstatine-containing tripeptidic compounds were synthesized with various N-terminal phenylacetyl moieties. Certain derivatives exhibited extremely potent inhibitory activity against plasmepsin II.

### Ligand based virtual screening and biological evaluation of inhibitors of chorismate mutase (Rv1885c) from *Mycobacterium tuberculosis* H37Rv pp 3053–3058

Himanshu Agrawal, Ashutosh Kumar, Naresh Chandra Bal, Mohammad Imran Siddiqi and Ashish Arora\*



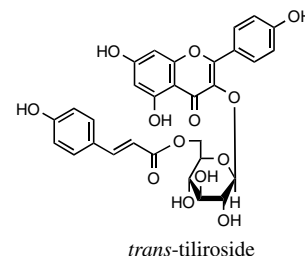
We have identified new lead candidates, which showed inhibition against *Mycobacterium tuberculosis* Chorismate Mutase, by a combination of ligand-based virtual screening and biological assays.



### Potent anti-obese principle from *Rosa canina*: Structural requirements and mode of action of *trans*-tiliroside pp 3059–3064

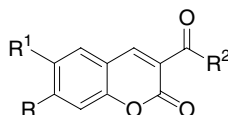
Kiyofumi Ninomiya, Hisashi Matsuda, Mizuho Kubo, Toshio Morikawa, Norihisa Nishida and Masayuki Yoshikawa\*

*trans*-Tiliroside (0.1–10 mg/kg/d) from the seeds of *Rosa canina* potently inhibited the gain of body weight, especially visceral fat weight, and significantly reduced blood glucose levels after loading of glucose (1 g/kg, ip) in mice. On the other hand, kaempferol and *p*-coumaric acid lacked such effect and kaempferol 3-*O*-β-D-glucopyranoside tended to reduce the gain of body weight and visceral fat weight, but not significantly, at a dose of 10 mg/kg/d. These results indicate the importance of both kaempferol 3-*O*-β-D-glucopyranoside and *p*-coumaroyl moieties for anti-obese effects. Furthermore, a single oral administration of *trans*-tiliroside at a dose of 10 mg/kg increased the expression of PPAR-α mRNA of liver tissue in mice.



### A novel class of selective anti-*Helicobacter pylori* agents 2-oxo-2*H*-chromene-3-carboxamide derivatives pp 3065–3071

Franco Chimenti, Bruna Bizzarri,\* Adriana Bolasco, Daniela Secci, Paola Chimenti, Simone Carradori, Arianna Granese, Daniela Rivanera, Daniela Lilli, Alessandra Zicari, M. Maddalena Scaltrito and Francesca Sisto

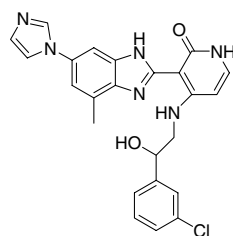


A novel class of selective anti-*Helicobacter pylori* agents, 2-oxo-2*H*-chromene-3-carboxamide derivatives, were prepared and evaluated for their anti-bacterial activity. Some of them exhibited a potent and specific inhibitory effect on the growth of *H. pylori*.

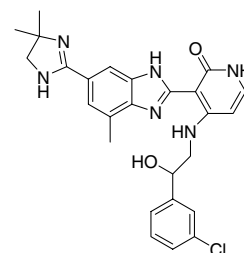
### Imidazole moiety replacements in the 3-(1*H*-benzo[d]imidazol-2-yl)pyridin-2(1*H*)-one inhibitors of insulin-like growth factor receptor-1 (IGF-1R) to improve cytochrome P450 profile pp 3072–3076

Upender Velaparthy,\* Peiying Liu, Balu Balasubramanian, Joan Carboni, Ricardo Attar, Marco Gottardis, Aixin Li, Ann Greer, Mary Zoeckler, Mark D. Wittman and Dolatrai Vyas

A series of 3-(1*H*-benzo[d]imidazol-2-yl)pyridin-2(1*H*)-one inhibitors of insulin-like growth factor receptor-1 (IGF-1R) were examined in which the pendant imidazole moiety was replaced to improve selectivity for IGF-1R inhibition over cytochrome P450 (CYP). Synthesis and SAR of these compounds is presented.



IGF1R IC<sub>50</sub> = 0.18 μM  
CYP3A4 IC<sub>50</sub> = <0.046 μM

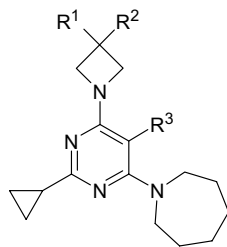


IGF1R IC<sub>50</sub> = 0.046 μM  
CYP3A4 IC<sub>50</sub> = >5.1 μM

**Dual M<sub>3</sub> antagonists-PDE4 inhibitors. Part 2: Synthesis and SAR of 3-substituted azetidiny derivatives**

pp 3077–3080

Laurent Provins,\* Bernard Christophe, Pierre Danhaive, Jacques Dulieu,  
Michel Gillard, Luc Quéré and Karin Stebbins

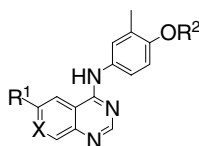


The SAR around 3-substituted azetidiny pyrimidine derivatives as potent dual M<sub>3</sub> antagonists and PDE4 inhibitors is reported.

**The discovery of highly selective erbB2 (Her2) inhibitors for the treatment of cancer**

pp 3081–3086

Blaise Lippa,\* Goss S. Kauffman, Joel Arcari, Tricia Kwan, Jinshan Chen, William Hungerford,  
Samit Bhattacharya, Xumiao Zhao, Courtney Williams, Jun Xiao, Leslie Pustilnik, Chunyan Su,  
James D. Moyer, Ling Ma, Mary Campbell and Stefanus Steyn

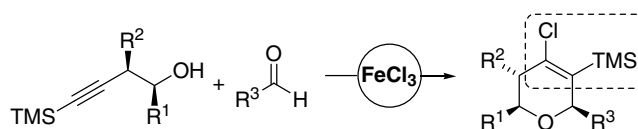


The synthesis and biological evaluation of potent and selective inhibitors of the erbB2 kinase is presented. The vast majority of these compounds are found to be >100× selective over the closely related EGFR kinase. Two lead compounds are further shown to have low clearance and moderate bioavailability in rat.

**Antiproliferative activity of 4-chloro-5,6-dihydro-2H-pyrans. Part 2: Enhancement of drug cytotoxicity**

pp 3087–3090

Leticia G. León, Pedro O. Miranda, Víctor S. Martín, Juan I. Padrón and José M. Padrón\*

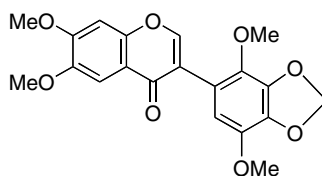


The inexpensive, stable and environmentally friendly FeCl<sub>3</sub> promotes the Prins cyclization to synthesize functionalized alkyl chlorodihydropyrans. The method represents an efficient and regioselective manner to obtain in a single step chlorovinyl-TMS oxacycles with enhanced cytotoxicity against human solid tumor cells.

**Glaziovianin A, a new isoflavone, from the leaves of *Ateleia glazioviana* and its cytotoxic activity against human cancer cells**

pp 3091–3094

Akihito Yokosuka,\* Mitsue Haraguchi, Takeo Usui, Sayaka Kazami, Hiroyuki Osada,  
Takao Yamori and Yoshihiro Mimaki\*



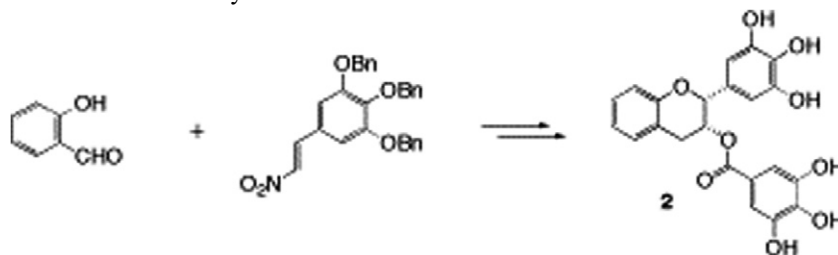
Glaziovianin A (1)

### Concise synthesis of dideoxy-epigallocatechin gallate (DO-EGCG) and evaluation of its anti-influenza virus activity

pp 3095–3098

Takumi Furuta,\* Yasuo Hirooka, Ayako Abe, Yusuke Sugata, Mitsuru Ueda, Kouki Murakami, Takashi Suzuki, Kiyoshi Tanaka and Toshiyuki Kan\*

Dideoxy-epigallocatechin gallate (DO-EGCG) (**2**), a simplified analog of naturally occurring EGCG, was efficiently prepared. Compound **2** showed potent anti-influenza virus activity.

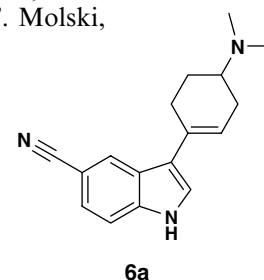


### Conformationally restricted homotryptamines **3**. Indole tetrahydropyridines and cyclohexenylamines as selective serotonin reuptake inhibitors

pp 3099–3104

Jeffrey A. Deskus,\* James R. Epperson, Charles P. Sloan, Joseph A. Cipollina, Pierre Dextraze, Jingfang Qian-Cutrone, Qi Gao, Baoqing Ma, Brett R. Beno, Gail K. Mattson, Thaddeus F. Molski, Rudolph G. Krause, Matthew T. Taber, Nicholas J. Lodge and Ronald J. Mattson

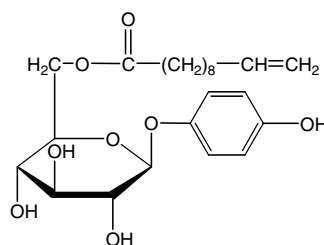
A series of indole tetrahydropyridine and indole cyclohexenylamines was prepared, and their binding affinities at the human serotonin transporter (SERT) were determined. In particular, compound **6a** gave potent SERT activity. The enantiomers of **6a** were energy minimized and compared to other known conformationally restricted SSRIs. Compound **6a** was also found to give a dose–response similar to the SSRI fluoxetine in microdialysis studies in rats.



### Enzymatic synthesis of arbutin undecylenic acid ester and its inhibitory effect on melanin synthesis

pp 3105–3108

Yutaka Tokiwa,\* Masaru Kitagawa, Takao Raku, Shusaku Yanagitani and Kenji Yoshino

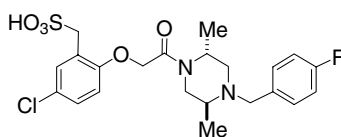


Transesterification of arbutin and undecylenic acid vinyl ester was catalyzed by protease to get arbutin derivative having undecylenic acid ester. The arbutin ester significantly suppressed melanin production in murine B16 melanoma cells.

### Piperazinyl CCR1 antagonists—optimization of human liver microsome stability

pp 3109–3112

Matthew F. Brown,\* Kevin B. Bahnck, Laura C. Blumberg, William H. Brissette, Sara A. Burrell, James P. Driscoll, Flavia Fedeles, Michael B. Fisher, Robert S. Foti, Ronald P. Gladue, Aikomari Guzman-Martinez, Matthew M. Hayward, Paul D. Lira, Brett M. Lillie, Yi Lu, Greg D. Lundquist, Eric B. McElroy, Molly A. McGlynn, Timothy J. Paradis, Christopher S. Poss, James H. Roache, Andrei Shavnya, Richard M. Shepard, Kristen A. Trevena and Laurie A. Tylaska

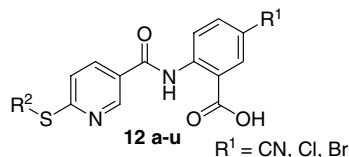


The synthesis, biological activity, and pharmacokinetic profile of CCR1 antagonists are described.



**Preparation of novel anthranilic acids as antibacterial agents: Extensive evaluation of structural and physical properties on antibacterial activity and human serum albumin affinity** pp 3113–3116

Atli Thorarensen,\* Jianke Li, Brian D. Wakefield, Donna L. Romero, Keith R. Marotti, Michael T. Sweeney, Gary E. Zurenko and Ronald W. Sarver

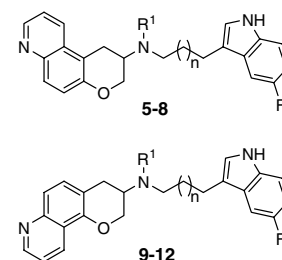


This paper describes the SAR in the anthranilic acids as antibacterial agents against Gram-positive organisms and how that activity relates to the compounds, affinity for human serum albumin (HSA).

**Novel pyridyl-fused 3-amino chroman derivatives with dual action at serotonin transporter and 5-HT<sub>1A</sub> receptor** pp 3117–3121

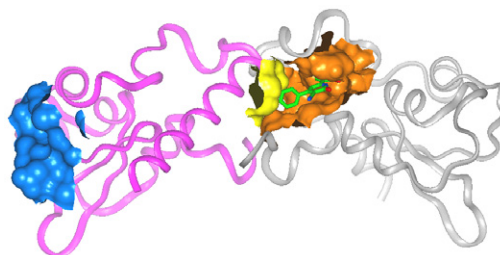
Dahui Zhou,\* Nicole T. Hatzenbuehler, Jonathan L. Gross, Boyd L. Harrison, Deborah A. Evrard, Michael Chlenov, Jeannette Golembieski, Geoffrey Hornby, Lee E. Schechter, Deborah L. Smith, Terrance H. Andree and Gary P. Stack

Structural modifications of the initial lead, 3-aminochroman (**4**), led to the identification of a novel series of pyridyl-fused amino chroman derivatives (**5–8**) and the structural isomers (**9–12**). The compounds described were evaluated for dual 5-HT transporter inhibitory and 5-HT<sub>1A</sub> receptor activities. The design strategy, synthesis, and in vitro biological characterization for these novel compounds are described.

**Discovery of a novel small molecule binding site of human survivin**

pp 3122–3129

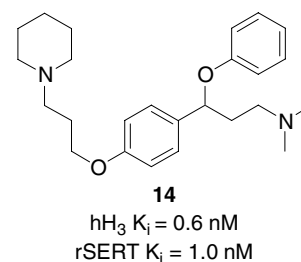
Michael D. Wendt,\* Chaohong Sun, Aaron Kunzer, Daryl Sauer, Kathy Sarris, Ethan Hoff, Liping Yu, David G. Nettesheim, Jun Chen, Sha Jin, Kenneth M. Comess, Yihong Fan, Steven N. Anderson, Binumol Isaac, Edward T. Olejniczak, Philip J. Hajduk, Saul H. Rosenberg and Steven W. Elmore

**Synthesis and biological evaluation of diamine-based histamine H<sub>3</sub> antagonists with serotonin reuptake inhibitor activity**

pp 3130–3135

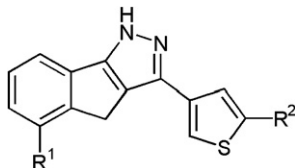
Emily M. Stocking,\* Jennifer M. Miller, Ann J. Barbier, Sandy J. Wilson, Jamin D. Boggs, Heather M. McAllister, Jiejun Wu, Timothy W. Lovenberg, Nicholas I. Carruthers and Ronald L. Wolin

The synthesis and structure–activity relationships of a series of novel phenoxyphenyl diamine derivatives with affinity for both the histamine H<sub>3</sub> receptor and the serotonin transporter is described.



**Synthesis and biological evaluation of 5-substituted 1,4-dihydroindeno[1,2-*c*]pyrazoles as multitargeted receptor tyrosine kinase inhibitors** pp 3136–3140

Irini Akritopoulou-Zanze,\* Daniel H. Albert, Peter F. Bousquet, George A. Cunha, Christopher M. Harris, Maria Moskey, Jurgen Dinges, Kent D. Stewart and Thomas J. Sowin



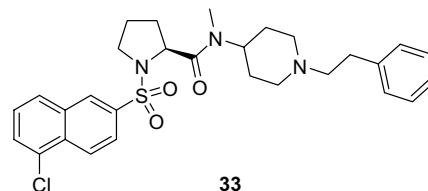
We report the synthesis and biological evaluation of 5-substituted 1,4-dihydroindeno[1,2-*c*]pyrazoles as multitargeted kinase inhibitors. Initial efforts focused on the development of selective KDR inhibitors, while later strategies involved the improvement of potency toward multiple kinase targets. Thus, several compounds were identified as potent KDR, Flt1, Flt3, and c-Kit inhibitors.

**Small molecule antagonists of the CC chemokine receptor 4 (CCR4)**

pp 3141–3145

Douglas F. Burdi,\* Shannon Chi, Karen Mattia, Celeste Harrington, Zhan Shi, Shaowu Chen, Swanee Jacutin-Porte, Robert Bennett, Kenneth Carson, Wei Yin, Vikram Kansra, Jose-Angel Gonzalo, Anthony Coyle, Bruce Jaffee, Timothy Ocain, Marty Hodge, Gregory LaRosa and Geraldine Harriman

The identification, optimization, and structure–activity relationship (SAR) of small-molecule CCR4 antagonists is described. An antagonist **33** was identified that showed good cross-reactivity against the mouse receptor and inhibited CCR4-based cell recruitment in dose-dependent fashion.

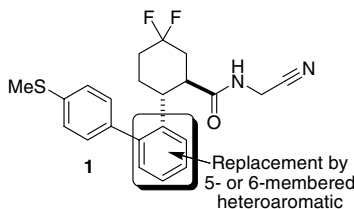


$K_i$  (hTARC/FLIPR) = 100 nM  
 $K_i$  (mMDC/FLIPR) = 150 nM

 **$\beta$ -Substituted cyclohexanecarboxamide cathepsin K inhibitors: Modification of the 1,2-disubstituted aromatic core**

pp 3146–3151

Joël Robichaud,\* Christopher I. Bayly, W. Cameron Black, Sylvie Desmarais, Serge Léger, Frédéric Massé, Daniel J. McKay, Renata M. Oballa, Julie Pâquet, M. David Percival, Jean-François Truchon, Gregg Wesolowski and Sheldon N. Crane

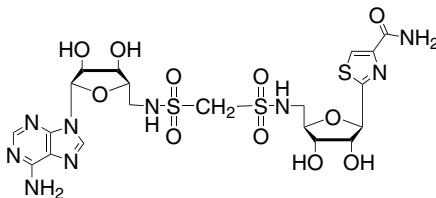


Further SAR around the central 1,2-disubstituted phenyl of the cathepsin K inhibitor **1** demonstrates that this phenyl P2–P3 linker can be replaced by various 5- or 6-membered heteroaromatic rings.

**Methylenebis(sulfonamide) linked nicotinamide adenine dinucleotide analogue as an inosine monophosphate dehydrogenase inhibitor**

pp 3152–3155

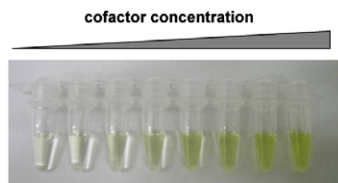
Liqiang Chen,\* Guangyao Gao, Laurent Bonnac, Daniel J. Wilson, Eric M. Bennett, Hiremagalur N. Jayaram and Krzysztof W. Pankiewicz\*



**Aptazyme-based riboswitches as label-free and detector-free sensors for cofactors**

pp 3156–3160

Atsushi Ogawa\* and Mizuo Maeda

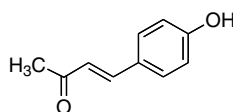


We constructed a label-free and detector-free aptazyme-based riboswitch sensor for detecting the cofactor of the aptazyme.

**Structure function analysis of benzalacetone synthase from *Rheum palmatum***

pp 3161–3166

Tsuyoshi Abe, Hiroyuki Morita, Hisashi Noma, Toshiyuki Kohno, Hiroshi Noguchi and Ikuro Abe\*



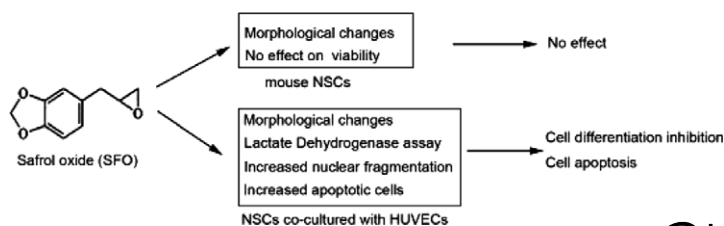
Structure function analysis of benzalacetone synthase from *Rheum palmatum* is reported.

**Safrole oxide is a useful tool for investigating the effect of apoptosis in vascular endothelial cells on neural stem cell survival and differentiation in vitro**

pp 3167–3171

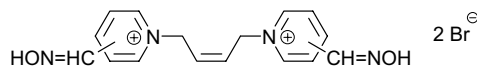
Le Su, BaoXiang Zhao,\* Xin Lv, Jing Zhao, ShangLi Zhang and JunYing Miao\*

Safrole oxide has no effect on the growth of mouse neural stem cells. But the apoptotic VECs triggered by safrole oxide induced NSC apoptosis in the co-culture system.

**Novel series of bispyridinium compounds bearing a (Z)-but-2-ene linker—Synthesis and evaluation of their reactivation activity against tabun and paraoxon-inhibited acetylcholinesterase**

pp 3172–3176

Kamil Musilek, Ondrej Holas, Kamil Kuca,\* Daniel Jun, Vlastimil Dohnal, Veronika Opletalova and Martin Dolezal

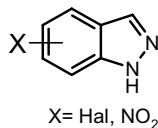


A series of bisquaternary reactivators of acetylcholinesterase (AChE) bearing (Z)-but-2-ene connecting linker was synthesized and evaluated on tabun and paraoxon-inhibited AChE with promising results.

**4-Substituted indazoles as new inhibitors of neuronal nitric oxide synthase**

pp 3177–3180

Michel Boulouard, Pascale Schumann-Bard, Sabrina Butt-Gueulle, Elodie Lohou, Silvia Stiebing, Valérie Collot\* and Sylvain Rault

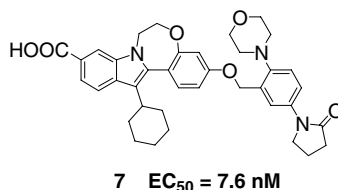


The synthesis and in vitro and in vivo pharmacological evaluation of a complete series of substituted indazoles as new inhibitors of nNOS are reported.

**Further studies on hepatitis C virus NS5B RNA-dependent RNA polymerase inhibitors toward improved replicon cell activities: Benzimidazole and structurally related compounds bearing the 2-morpholinophenyl moiety**

pp 3181–3186

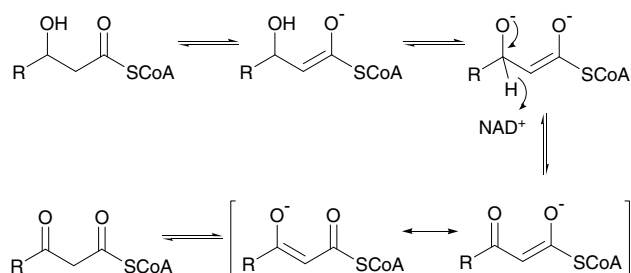
Shintaro Hirashima,\* Takahiro Oka, Kazutaka Ikegashira, Satoru Noji, Hiroshi Yamanaka, Yoshinori Hara, Hiroyuki Goto, Ryo Mizojiri, Yasushi Niwa, Toru Noguchi, Izuru Ando, Satoru Ikeda and Hiromasa Hashimoto\*


**Formation of an enolate intermediate is required for the reaction catalyzed by 3-hydroxyacyl-CoA dehydrogenase**

pp 3187–3190

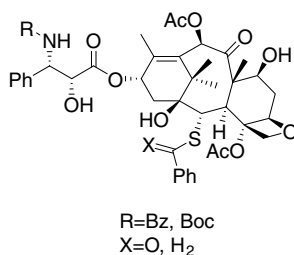
Xiaojun Liu, Guisheng Deng, Xiusheng Chu, Nan Li, Long Wu and Ding Li\*

Fluorinated substrate analogs were synthesized and incubated with rat liver 3-hydroxyacyl-CoA dehydrogenase, which reveals that the formation of an enolate intermediate is required for the enzymatic reaction.


**Synthesis, biological evaluations, and tubulin binding poses of C-2α sulfur linked taxol analogues**

pp 3191–3194

Lei Wang, Ana A. Alcaraz, Ruth Matesanz, Chun-Gang Yang, Isabel Barasoain, J. Fernando Díaz, Ye-Zhi Li, James P. Snyder and Wei-Shuo Fang\*

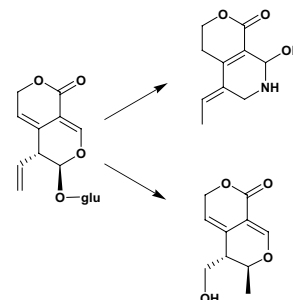


**Biotransformation of gentiopicroside by asexual mycelia of *Cordyceps sinensis***

pp 3195–3197

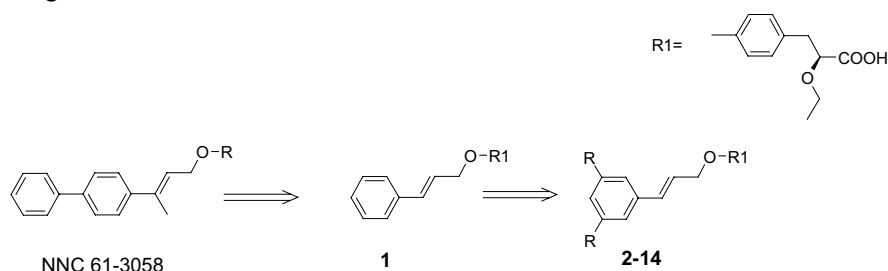
Dong Wang, Min Xu, Hong-Tao Zhu, Ke-Ke Chen, Ying-Jun Zhang\* and Chong-Ren Yang\*

The biotransformation of gentiopicroside by asexual mycelia of *Cordyceps sinensis* yielded two products, one of which was proved to be a new pyridine monoterpene alkaloid. The possible mechanisms were discussed.

**Design of potent PPAR $\alpha$  agonists**

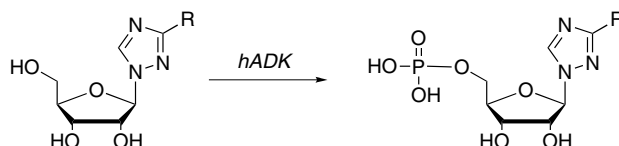
pp 3198–3202

Per Sauerberg,\* John P. Mogensen, Lone Jeppesen, Paul S. Bury, Jan Fleckner, Grith S. Olsen, Claus B. Jeppesen, Erik M. Wulff, Pavel Pihera, Miroslav Havranek, Zdenek Polivka and Ingrid Pettersson

**Structural effects on the phosphorylation of 3-substituted 1- $\beta$ -D-ribofuranosyl-1,2,4-triazoles by human adenosine kinase**

pp 3203–3207

Sidath C. Kumarapperuma, Yanjie Sun, Marjan Jeselnik, Kiwon Chung, William B. Parker, Colleen B. Jonsson and Jeffrey B. Arterburn\*



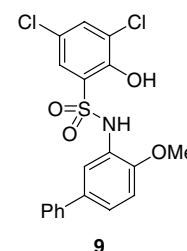
Variation of the 3-substituents in a series of bioisosteric and homologated 1- $\beta$ -D-ribofuranosyl-1,2,4-triazoles has marked effects on activity with the human adenosine kinase, and analysis of computational descriptors and binding models offers insight for the design of novel substrates.

**2-Hydroxy-*N*-arylbenzenesulfonamides as ATP-citrate lyase inhibitors**

pp 3208–3211

James J. Li,\* Haixia Wang, Joseph A. Tino, Jeffrey A. Robl, Timothy F. Herpin, R. Michael Lawrence, Scott Biller, Haris Jamil, Randy Ponticello, Luping Chen, Ching-hsuen Chu, Neil Flynn, Dong Cheng, Rulin Zhao, Bangchi Chen, Dora Schnur, Mary T. Obermeier, Vito Sasseville, Ramesh Padmanabha, Kristen Pike and Thomas Harrity

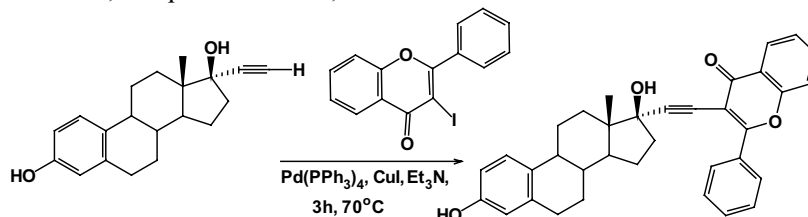
A novel series of 2-hydroxy-*N*-arylbenzenesulfonamides were identified to be ATP-citrate lyase (ACL) inhibitors with compound **9** displaying potent in vitro activity ( $IC_{50} = 0.13 \mu M$ ). Chronic oral dosing of compound **9** in high-fat fed mice lowered plasma cholesterol, triglyceride, and glucose, as well as inhibited weight gain.



### Synthesis, characterization, and estrogen receptor binding affinity of flavone-, indole-, and furan-estradiol conjugates

pp 3212–3216

Naseem Ahmed, Celena Dubuc, Jacques Rousseau, Francois B  nard and Johan E. van Lier\*

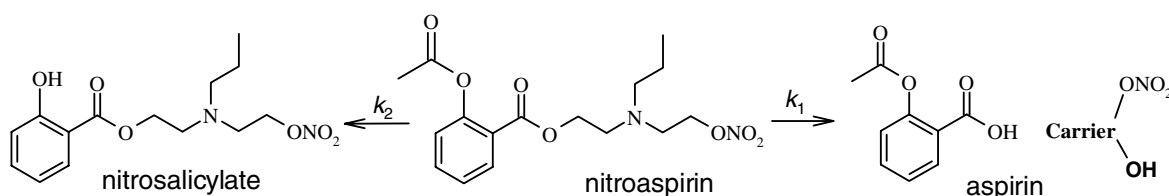


Flavone-, indole-, and furan-17  -estradiol conjugates with 2–8 carbon linker chains extending from the 17  -position of the estradiol were synthesized by Pd-catalyzed cross-coupling reactions. In vitro competitive binding assays for the estrogen receptor revealed that a two-carbon alkynyl linker combined with a flavone conjugate provided the highest binding affinity.

### Evaluation of nitrate-substituted pseudocholine esters of aspirin as potential nitro-aspirins

pp 3217–3220

John F. Gilmer,\* Louise M. Moriarty and John M. Clancy

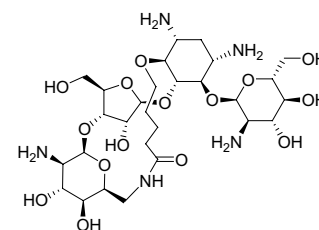


### 6-Hydroxy to 6'''-amino tethered ring-to-ring macrocyclic aminoglycosides as probes for APH(3')-IIIa kinase

pp 3221–3225

Stephen Hanessian,\* Janek Szychowski, Nathalie B. Campos-Reales Pineda, Alexandra Furtos and Jeffrey W. Keillor\*

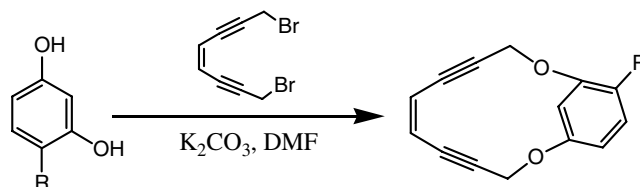
Based on molecular modeling and available X-ray structure data on aminoglycosides complexed with a bacterial ribosomal surrogate or with a kinase, two analogues of paromomycin were prepared by tethering the 6-OH and the 6'''-NH<sub>2</sub> group with a five-carbon bridge. Only one of two possible hydroxyl groups was phosphorylated by the kinase. The application of ring closure metathesis is presented for the first time to construct bridged macrocyclic analogues in the aminoglycoside series.



### Syntheses and antibacterial activity of phendioxy substituted cyclic enediynes

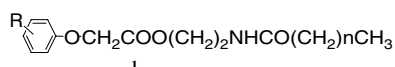
pp 3226–3230

Mukesh Chandra Joshi, Gopal Singh Bisht and Diwan S. Rawat\*




**Synthesis of new plant growth regulator: *N*-(Fatty acid) *O*-aryloxyacetyl ethanolamine****pp 3231–3234**

Liang Han, Jian-Rong Gao, Zheng-Ming Li,\* Yun Zhang and Wei-Ming Guo

The synthesis of the new plant growth regulator **1** is reported.**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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