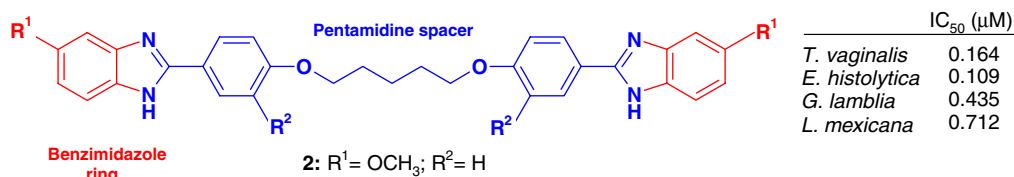


## Contents

### ARTICLES

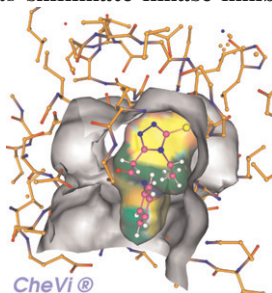
#### Design, synthesis and in vitro antiprotozoal activity of benzimidazole-pentamidine hybrids pp 3147–3151

Héctor Torres-Gómez, Emanuel Hernández-Núñez, Ismael León-Rivera, Jorge Guerrero-Alvarez, Roberto Cedillo-Rivera, Rosa Moo-Puc, Rocío Argotte-Ramos, María del Carmen Rodríguez-Gutiérrez, Manuel Jesús Chan-Bacab and Gabriel Navarrete-Vázquez\*



#### Structure-based prediction of *Mycobacterium tuberculosis* shikimate kinase inhibitors by high-throughput virtual screening pp 3152–3157

Aldo Segura-Cabrera\* and Mario A. Rodríguez-Pérez

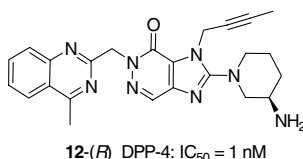


A structure-based virtual screening protocol was used to predict *Mycobacterium tuberculosis* shikimate kinase (MtSk) inhibitors. Forty-two percent of such inhibitors had a structural relationship to a triazole or a tetrazole heteroaromatic system.



#### 3,5-Dihydro-imidazo[4,5-*d*]pyridazin-4-ones: A class of potent DPP-4 inhibitors pp 3158–3162

Matthias Eckhardt,\* Norbert Hael, Frank Himmelsbach, Elke Langkopf, Herbert Nar, Michael Mark, Moh Tadayyon, Leo Thomas, Brian Guth and Ralf Lotz

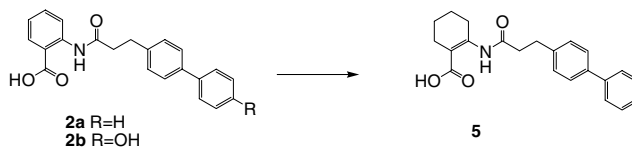


Systematic variations of the xanthine scaffold in **BI 1356** leading to the potent DPP-4 inhibitor **12-(*R*)** are reported.

**Tetrahydro anthranilic acid as a surrogate for anthranilic acid: Application to the discovery of potent niacin receptor agonists**

pp 3163–3167

Subharekha Raghavan,\* G. Scott Tria, Hong C. Shen, Fa-Xiang Ding, Andrew K. Taggart, Ning Ren, Larrisa C. Wilsie, Mihajlo L. Krsmanovic, Tom G. Holt, Michael S. Wolff, M. Gerard Waters, Milton L. Hammond, James R. Tata and Steven L. Colletti

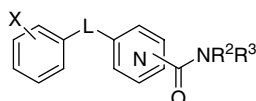


A series of cycloalkene acid-based niacin receptor agonists were designed and synthesized. Several compounds that were potent against the niacin receptor, with enhanced cytochrome P450 selectivity against subtypes CYP2C8 and CYP2C9 and had improved oral exposure in mice were identified.

**Pyridine amides as potent and selective inhibitors of 11 $\beta$ -hydroxysteroid dehydrogenase type 1**

pp 3168–3172

Haixia Wang,\* Zheming Ruan,\* James J. Li, Ligaya M. Simpkins, Rebecca A. Smirk, Shung C. Wu, Robert D. Hutchins, David S. Nirschl, Katy Van Kirk, Christopher B. Cooper, James C. Sutton, Zhengping Ma, Rajasree Golla, Ramakrishna Seethala, Mary Ellen K. Salyan, Akbar Nayeem, Stanley R. Krystek, Jr., Steven Sheriff, Daniel M. Camac, Paul E. Morin, Brian Carpenter, Jeffrey A. Robl, Robert Zahler, David A. Gordon and Lawrence G. Hamann



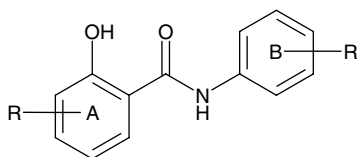
L = CH<sub>2</sub>SO<sub>2</sub>, CH<sub>2</sub>S, CH<sub>2</sub>O, S, O, N, bond

The synthesis and biological evaluation of a series of potent and selective pyridine amide 11 $\beta$ -HSD1 inhibitors is reported.

**Identification of halosalicylamide derivatives as a novel class of allosteric inhibitors of HCV NS5B polymerase**

pp 3173–3177

Yaya Liu,\* Pamela L. Donner, John K. Pratt, Wen W. Jiang, Teresa Ng, Vijaya Gracias, Steve Baumeister, Paul E. Wiedeman, Linda Traphagen, Usha Warrior, Clarence Maring, Warren M. Kati, Stevan W. Djuric and Akhteruzzaman Molla

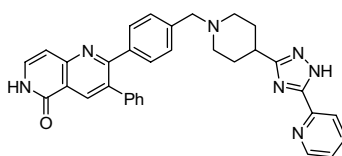


Halosalicylamide derivatives were evaluated as broad genotype inhibitors of HCV polymerase.


**Allosteric inhibitors of Akt1 and Akt2: A naphthyridinone with efficacy in an A2780 tumor xenograft model**

pp 3178–3182

Mark T. Bilodeau,\* Adrienne E. Balitza, Jacob M. Hoffman, Peter J. Manley, Stanley F. Barnett, Deborah Defeo-Jones, Kathleen Haskell, Raymond E. Jones, Karen Leander, Ronald G. Robinson, Anthony M. Smith, Hans E. Huber and George D. Hartman

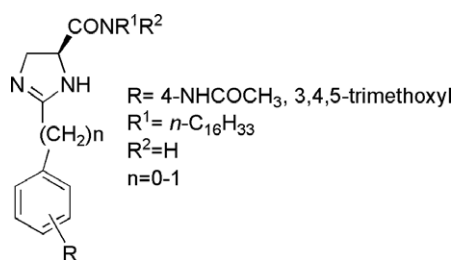


Akt1 IC<sub>50</sub> = 3.5 nM  
 Akt2 IC<sub>50</sub> = 42 nM  
 Cell Akt1 IC<sub>50</sub> = 16 nM  
 Cell Akt2 IC<sub>50</sub> = 266 nM

**Synthesis and antiproliferative activity of imidazole and imidazoline analogs for melanoma**

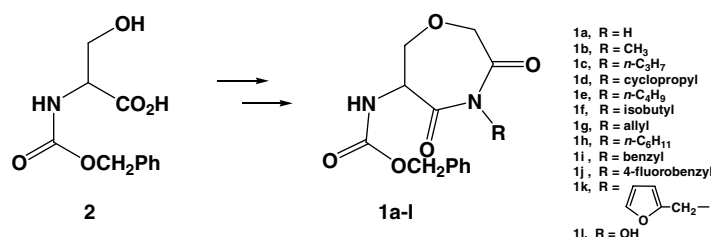
pp 3183–3187

Jianjun Chen, Zhao Wang, Yan Lu, James T. Dalton, Duane D. Miller and Wei Li\*

**Design and synthesis of 6-amino-1,4-oxazepane-3,5-dione derivatives as novel broad spectrum anticonvulsants**

pp 3188–3191

Gitalee Sharma, Jin Yup Park and Min Soo Park\*



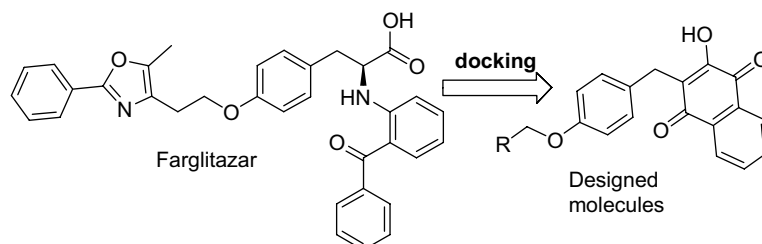
A series of 6-amino-1,4-oxazepane-3,5-dione derivatives, which are 7-membered heterocyclic imides and have N-CO-C-N group in their structures, were designed, synthesized, and their anticonvulsant activities were evaluated by both the MES and PTZ tests.

**New PPAR $\gamma$  ligands based on 2-hydroxy-1,4-naphthoquinone: Computer-aided design, synthesis, and receptor-binding studies**

pp 3192–3195

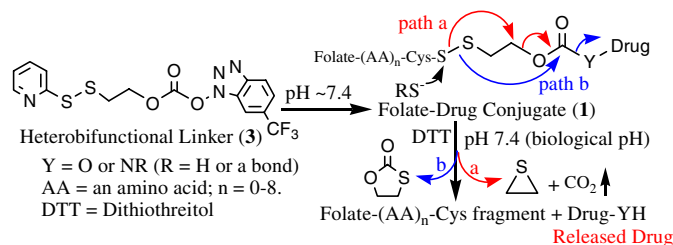
Sandeep Sundriyal, Bhoomi Viswanad, Elumalai Bharathy, Poduri Ramarao, Asit K. Chakraborti and Prasad V. Bharatam\*

2-Hydroxy-1,4-naphthoquinone was identified as a novel 'acidic head group' for the design of new series PPAR $\gamma$  ligands using docking studies. Synthesis and receptor-binding studies were used to validate the concept.

**Design and synthesis of releasable folate–drug conjugates using a novel heterobifunctional disulfide-containing linker**

pp 3196–3199

Apparao Satyam\*



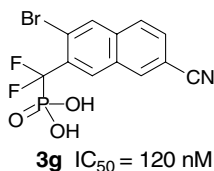
A novel heterobifunctional disulfide-containing linker **3** was synthesized and utilized to create targetable folate–drug conjugates **1** that were shown to release free drugs under biologically relevant pH via sulfhydryl-assisted cleavage.



**Discovery of [(3-bromo-7-cyano-2-naphthyl)(difluoro)methyl]phosphonic acid, a potent and orally active small molecule PTP1B inhibitor**

pp 3200–3205

Yongxin Han,\* Michel Belley, Christopher I. Bayly, John Colucci, Claude Dufresne, Andre Giroux, Cheuk K. Lau, Yves Leblanc, Daniel McKay, Michel Therien, Marie-Claire Wilson, Kathryn Skorey, Chi-Chung Chan, Giovana Scapin and Brian P. Kennedy

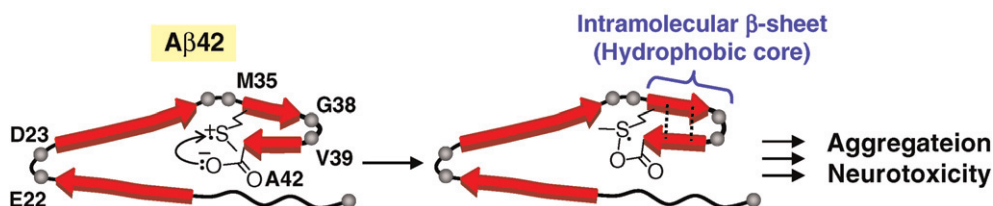


The discovery of the potent and orally active PTP1B inhibitor **3g** ( $IC_{50} = 120$  nM,  $ED_{50} = 0.8$  mg/kg in oGTT) is reported.

**Verification of the C-terminal intramolecular  $\beta$ -sheet in A $\beta$ 42 aggregates using solid-state NMR: Implications for potent neurotoxicity through the formation of radicals**

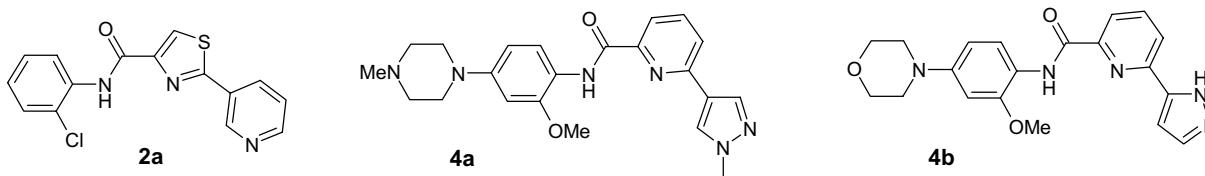
pp 3206–3210

Yuichi Masuda, Satoko Uemura, Azusa Nakanishi, Ryutaro Ohashi, K. Takegoshi, Takahiko Shimizu, Takuji Shirasawa and Kazuhiro Irie\*


**IRAK-4 inhibitors. Part 1: A series of amides**

pp 3211–3214

George M. Buckley, Lewis Gowers, Alicia Perez Higuieruelo, Kerry Jenkins, Stephen R. Mack, Trevor Morgan, David M. Parry, William R. Pitt, Oliver Rausch, Marianna D. Richard, Verity Sabin\* and Joanne L. Fraser

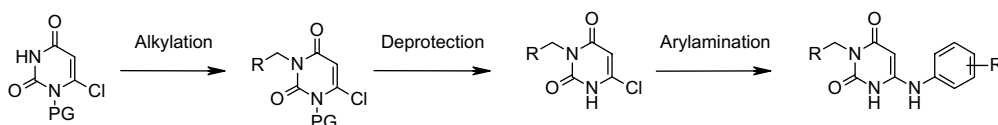


A series of amides, based on the screening hit **2a**, were prepared and profiled. Some potent IRAK-4-inhibitors were identified and two examples, **4a** and **4b**, were progressed into an in vivo PK study.

**Improved synthesis of antibacterial 3-substituted 6-anilinouracils**

pp 3215–3218

Niels Svenstrup,\* Alexander Kuhl, Kerstin Ehlert and Dieter Häbich

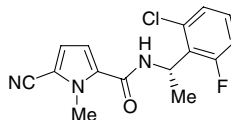


3-Substituted 6-anilinouracils, presently the most promising class of inhibitors of the bacterial DNA polymerase in Gram-positive bacteria, have been prepared by a general and straightforward three-step procedure starting from a readily available 1-benzoyloxymethyl-protected derivative of 6-chlorouracil.

**Structure–activity relationship and liver microsome stability studies of pyrrole necroptosis inhibitors**

pp 3219–3223

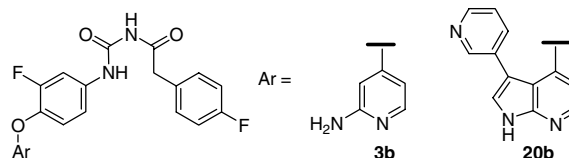
Xin Teng, Heather Keys, Junying Yuan, Alexei Degterev and Gregory D. Cuny\*

**Discovery of orally active pyrrolopyridine- and aminopyridine-based Met kinase inhibitors**

pp 3224–3229

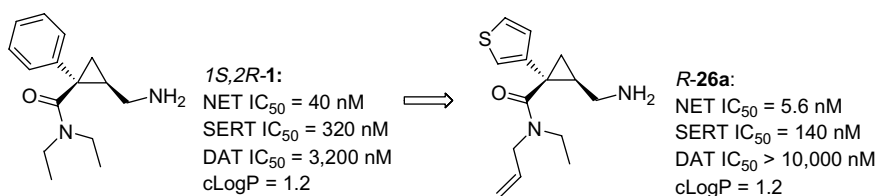
Zhen-Wei Cai,\* Donna Wei, Gretchen M. Schroeder, Lyndon A. M. Cornelius, Kyoung Kim, Xiao-Tao Chen, Robert J. Schmidt, David K. Williams, John S. Tokarski, Yongmi An, John S. Sack, Veeraswamy Manne, Amrita Kamath, Yueping Zhang, Punit Marathe, John T. Hunt, Louis J. Lombardo, Joseph Fargnoli and Robert M. Borzilleri

A series of acylurea analogs derived from pyrrolopyridine and aminopyridine scaffolds were identified as potent inhibitors of Met kinase activity. The SAR studies led to the discovery of compounds **3b** and **20b**, which demonstrated significant antitumor activity in a human gastric carcinoma xenograft model.

**Studies on a series of milnacipran analogs containing a heteroaromatic group as potent norepinephrine and serotonin transporter inhibitors**

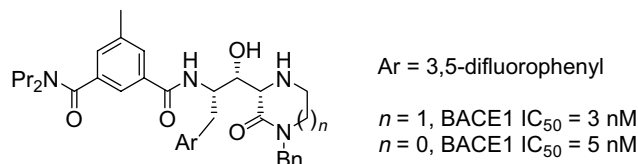
pp 3230–3235

Troy Vickers, Brian Dyck, Junko Tamiya, Mingzhu Zhang, Florence Jovic, Jonathan Grey, Beth A. Fleck, Anna Aparicio, Michael Johns, Liping Jin, Hui Tang, Alan C. Foster and Chen Chen\*

**Rational design of novel, potent piperazinone and imidazolidinone BACE1 inhibitors**

pp 3236–3241

J. N. Cumming,\* T. X. Le,\* S. Babu, C. Carroll, X. Chen, L. Favreau, P. Gaspari, T. Guo, D. W. Hobbs, Y. Huang, U. Iserloh, M. E. Kennedy, R. Kuvelkar, G. Li, J. Lowrie, N. A. McHugh, L. Ozgur, J. Pan, E. M. Parker, K. Saionz, A. W. Stamford, C. Strickland, D. Tadesse, J. Voigt, L. Wang, Y. Wu, L. Zhang and Q. Zhang



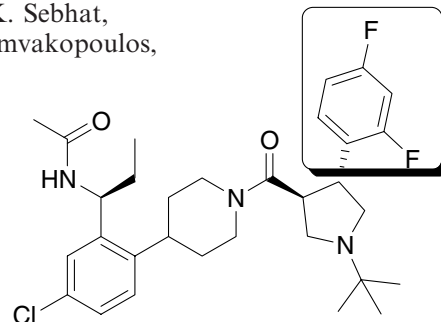
Two novel, potent cyclic amine motifs for BACE1 inhibitors are described, along with their SAR in both the non-prime and prime subsites.

### Synthesis and SAR of potent and orally bioavailable *tert*-butylpyrrolidine archetype derived melanocortin subtype-4 receptor modulators

pp 3242–3247

Liangqin Guo,\* Zhixiong Ye, Feroze Ujjainwalla, Heather L. Sings, Iyassu K. Sebhat, John Huber, David H. Weinberg, Rui Tang, Tanya MacNeil, Constantin Tamvakopoulos, Qianping Peng, Euan MacIntyre, Lex H. T. van der Ploeg, Mark T. Goulet, Matthew J. Wyvratt and Ravi P. Nargund

Discovery of a series of *tert*-butyl pyrrolidine derived, potent and orally bioavailable melanocortin receptor subtype-4 (MC4R) selective modulators is disclosed.

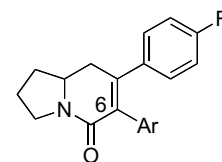


### Synthesis and evaluation of heteroaromatic 6,7-diaryl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ones for cytotoxicity against the HCT-116 colon cancer cell line

pp 3248–3250

F. Scott Kimball, Richard H. Himes and Gunda I. Georg\*

A heteroaromatic 6,7-diaryl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one library was prepared and tested for cytotoxic properties against the HCT-116 colon cancer cell line, thus providing information pertaining to structure–activity relationships for this class of compounds. The most active of the new analogs proved to be the C6 2-thiophene and 3-thiophene analogs with an  $IC_{50}$  values of 0.27  $\mu$ M and 0.60  $\mu$ M, respectively.



**14-Membered heteroaromatic analog library**

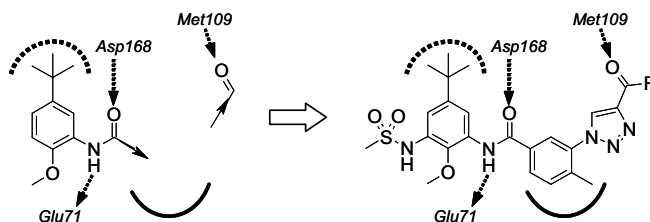
R = SMe, Ar = 2-thiophene;  $IC_{50}$  = 0.27  $\mu$ M

R = SMe, Ar = 3-thiophene;  $IC_{50}$  = 0.60  $\mu$ M

### Structure-based design and subsequent optimization of 2-tolyl-(1,2,3-triazol-1-yl-4-carboxamide) inhibitors of p38 MAP kinase

pp 3251–3255

D. A. Cogan,\* R. Aungst, E. C. Breinlinger, T. Fadra, D. R. Goldberg, M. H. Hao, R. Kroe, N. Moss, C. Pargellis, K. C. Qian and A. D. Swinamer

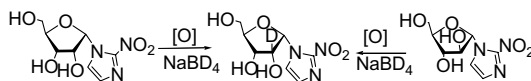


The de novo design and synthesis of a novel class of potent and selective p38 MAPK inhibitors is described.

### Stereospecific deuteration of $\alpha$ -furanosyl azomycin nucleosides: A model reaction for tritium radiolabeling

pp 3256–3260

Piyush Kumar,\* Saeed Emami, Alexander J. B. McEwan and Leonard I. Wiebe

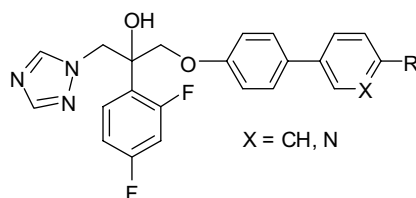


Stereospecific synthesis of 1- $\alpha$ -D-(2'-deuteroribofuranosyl)-2-nitroimidazole **7** starting from 1- $\alpha$ -D-(3',5'-O,O-tetraisopropylidisilyl-oxyribo/arabinofuranosyl)-2-nitroimidazole (**2** and **4**) is reported. This isotopic deuteration was independent of the configuration of –OH group at C-2' position of sugar moiety in the parent molecules.

**Synthesis and SAR studies of biaryloxy-substituted triazoles as antifungal agents**

pp 3261–3265

Ping Liu, Shaolong Zhu, Peng Li, Weijie Xie, Yongsheng Jin, Qingyan Sun, Qiuye Wu, Peng Sun, Yingjun Zhang, Xiaohong Yang,\* Yuanying Jiang\* and Dazhi Zhang\*

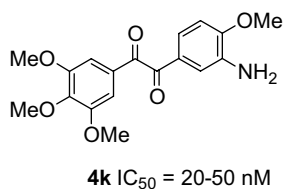


A series of novel biaryloxy-substituted triazole derivatives were synthesized and evaluated for their antifungal activity against eight human pathogenic fungi in vitro. Seventeen compounds showed higher activity than voriconazole against *Candida albicans*.

**Synthesis and antitumor activity of benzils related to combretastatin A-4**

pp 3266–3271

Céline Mousset, Anne Giraud, Olivier Provot, Abdallah Hamze, Jérôme Bignon, Jian-Miao Liu, Sylviane Thoret, Joëlle Dubois, Jean-Daniel Brion and Mouâd Alami\*

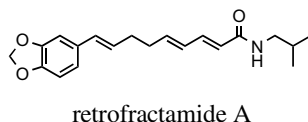


Benzil derivatives related to combretastatin A-4 exhibit excellent antiproliferative and antimitotic activities by arresting the cell cycle in G2/M phase.

**Effects of amide constituents from pepper on adipogenesis in 3T3-L1 cells**

pp 3272–3277

Hailong Zhang, Hisashi Matsuda, Seikou Nakamura and Masayuki Yoshikawa\*

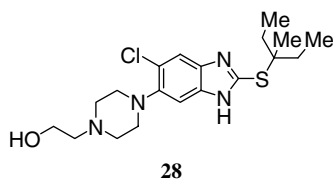


Several amide constituents (piperlonguminine and retrofractamides A, B, and C) from the fruit of *Piper chaba* promoted adipogenesis of 3T3-L1 cells. Among them, retrofractamide A was the most active and significantly increased the amount of adiponectin released into the medium and the uptake of 2-deoxyglucose into the cells. Retrofractamide A also increased mRNA levels of adiponectin, peroxisome proliferator-activated receptor  $\gamma$ 2 (PPAR $\gamma$ 2), glucose transporter 4 (GLUT4), and insulin receptor substrate 1 (IRS-1), but did not act as a PPAR $\gamma$  agonist different from troglitazone.

**Identification of novel benzimidazole series of potent and selective ORL1 antagonists**

pp 3278–3281

Osamu Okamoto,\* Kensuke Kobayashi, Hiroshi Kawamoto, Satoru Ito, Atsushi Satoh, Tetsuya Kato, Izumi Yamamoto, Sayaka Mizutani, Masaya Hashimoto, Atsushi Shimizu, Hiroki Sakoh, Yasushi Nagatomi, Yoshikazu Iwasawa, Hiroyuki Takahashi, Yasuyuki Ishii, Satoshi Ozaki and Hisashi Ohta

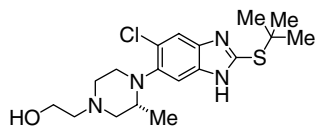


A structurally novel ORL1 selective antagonist with a (piperazin-1-yl)benzimidazole scaffold was identified. Among them, an analogue **28** exhibited sub-nanomolar antagonistic activity.

**Novel ORL1-selective antagonists with oral bioavailability and brain penetrability**

pp 3282–3285

Osamu Okamoto,\* Kensuke Kobayashi, Hiroshi Kawamoto, Satoru Ito, Takashi Yoshizumi, Izumi Yamamoto, Masaya Hashimoto, Atsushi Shimizu, Hiroyuki Takahashi, Yasuyuki Ishii, Satoshi Ozaki and Hisashi Ohta

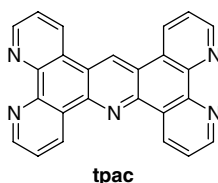


A novel ORL1-selective antagonist with oral bioavailability and brain penetrability, 2-(*tert*-butylthio)-5-chloro-6-[(2*R*)-4-(2-hydroxyethyl)-2-methylpiperazin-1-yl]-1*H*-benzimidazole, was identified in a 5-chloro-6-[piperazin-1-yl]-1*H*-benzimidazole series.

**Copper-mediated DNA photocleavage by a tetrapyridoacridine (tpac) ligand**

pp 3286–3290

Marta González-Álvarez, María-Selma Arias, María-José Fernández, Lourdes Gude, Antonio Lorente,\* Gloria Alzuet and Joaquín Borrás\*



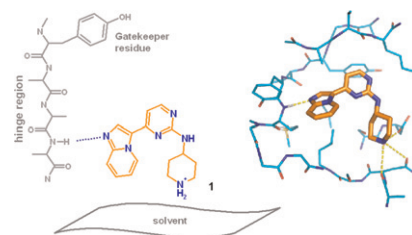
The nuclease activity of the copper(II)–tpac system induced by visible light is reported.

**IRAK-4 inhibitors. Part II: A structure-based assessment of imidazo[1,2-*a*]pyridine binding**

pp 3291–3295

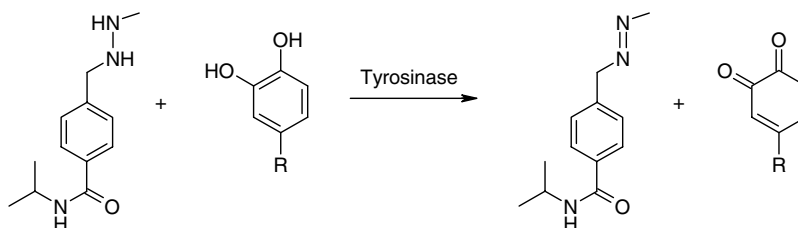
George M. Buckley, Thomas A. Ceska, Joanne L. Fraser, Lewis Gowers, Colin R. Groom, Alicia Perez Higuero,\*, Kerry Jenkins,\* Stephen R. Mack, Trevor Morgan, David M. Parry, William R. Pitt, Oliver Rausch, Marianna D. Richard and Verity Sabin

The binding mode of a series of IRAK-4 inhibitors derived screening hit **1** was inferred using a combination of in silico docking into a homology model, surrogate crystal structure analysis and analogue SAR.

**Indirect oxidation of the antitumor agent procarbazine by tyrosinase—Possible application in designing anti-melanoma prodrugs**

pp 3296–3300

Beata Gąsowska-Bajger and Hubert Wojtasek\*

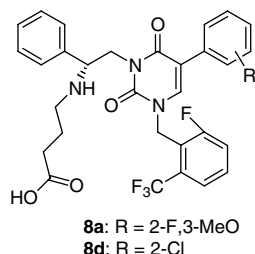




**Potent and orally bioavailable zwitterion GnRH antagonists with low CYP3A4 inhibitory activity**

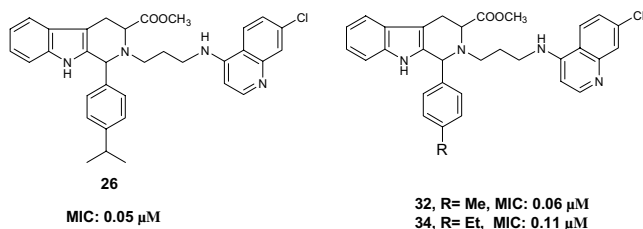
pp 3301–3305

Chen Chen,\* Yongsheng Chen, Joseph Pontillo, Zhiqiang Guo, Charles Q. Huang, Dongpei Wu, Ajay Madan, Takung Chen, Jenny Wen, Qiu Xie, Fabio C. Tucci, Martin Rowbottom, Yun-Fei Zhu, Warren Wade, John Saunders, Haig Bozigian and R. Scott Struthers

**Synthesis of 2-[3-(7-Chloro-quinolin-4-ylamino)-alkyl]-1-(substituted phenyl)-2,3,4,9-tetrahydro-1H-β-carbolines as a new class of antimalarial agents**

pp 3306–3309

Leena Gupta, Kumkum Srivastava, Shubhra Singh, S. K. Puri and Prem M. S. Chauhan\*



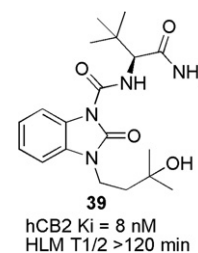
A series of hybrid molecules 2-[3-(7-Chloro-quinolin-4-ylamino)-alkyl]-1-(substituted phenyl)-2,3,4,9-tetrahydro-1H-β-carbolines have been synthesized and screened for their in vitro antimalarial activity against *Plasmodium falciparum*.

**The SAR studies of novel CB2 selective agonists, benzimidazolone derivatives**

pp 3310–3314

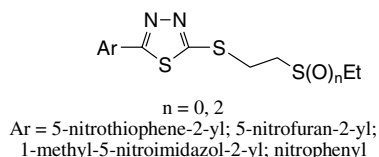
Hirofumi Omura,\* Makoto Kawai, Akiko Shima, Yasuhiro Iwata, Fumitaka Ito, Tsutomu Masuda, Atsuko Ohta, Naoya Makita, Kiyoyuki Omoto, Hiromi Sugimoto, Akira Kikuchi, Hiroshi Iwata and Kazuo Ando

Benzimidazolone derivatives as novel CB2 selective agonists are reported. Compound **39** exhibited excellent metabolic stability and significant attenuation of the visceral allodynia in a rat model by oral administration.

**Synthesis and anti-*Helicobacter pylori* activity of 5-(nitroaryl)-1,3,4-thiadiazoles with certain sulfur containing alkyl side chain**

pp 3315–3320

Alireza Foroumadi, Ardeshir Rineh, Saeed Emami, Farideh Siavoshi, Sadegh Massarrat, Fatemeh Safari, Saeed Rajabalian, Mehraban Falahati, Ensieh Lotfali and Abbas Shafiee\*

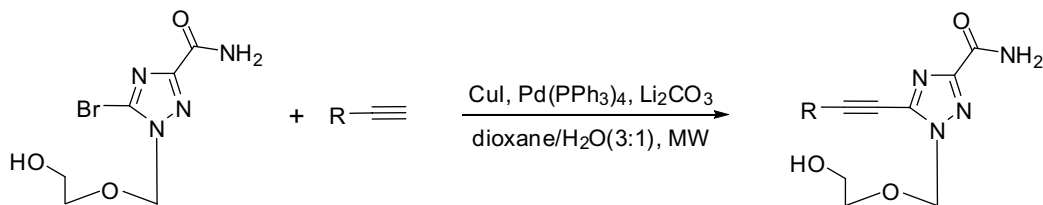


The synthesis and anti-*Helicobacter pylori* activity of 2-[2-(ethylthio)ethylthio]-5-(nitroaryl)-1,3,4-thiadiazoles and 2-[2-(ethylsulfonyl)ethylthio]-5-(nitroaryl)-1,3,4-thiadiazoles were described.

**Arylethynyltriazole acyclonucleosides inhibit hepatitis C virus replication**

pp 3321–3327

Ruizhi Zhu, Menghua Wang, Yi Xia, Fanqi Qu, Johan Neyts and Ling Peng\*

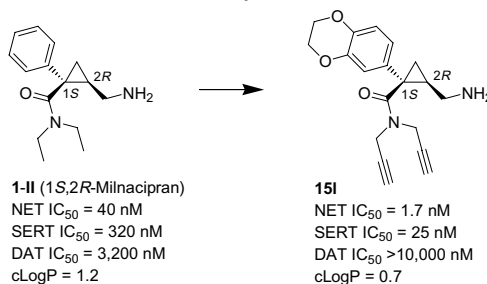


Novel ethynyltriazole acyclonucleosides were synthesized efficiently via a one-step Sonogashira reaction in aqueous solution and under microwave irradiation. Some of them elicit potent antiviral activity against hepatitis C virus, and constitute therefore an interesting structural lead in the search for novel antiviral candidates.

**Identification of 1*S*,2*R*-milnacipran analogs as potent norepinephrine and serotonin transporter inhibitors**

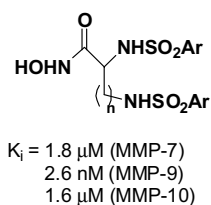
pp 3328–3332

Junko Tamiya, Brian Dyck, Mingzhu Zhang, Kasey Phan, Beth A. Fleck, Anna Aparicio, Florence Jovic, Joe A. Tran, Troy Vickers, Jonathan Grey, Alan C. Foster and Chen Chen\*

**Novel bis-(arylsulfonamide) hydroxamate-based selective MMP inhibitors**

pp 3333–3337

Rajesh Subramaniam, Manas K. Haldar, Shakila Tobwala, Bratati Ganguly, D. K. Srivastava\* and Sanku Mallik\*

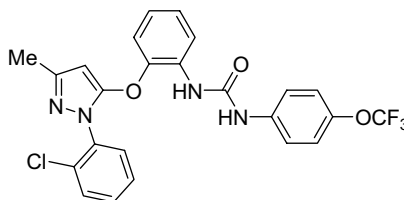


The syntheses of a series of selective MMP inhibitors are described.

**P2Y<sub>1</sub> receptor antagonists as novel antithrombotic agents**

pp 3338–3343

Jeffrey A. Pfefferkorn,\* Chulho Choi, Thomas Winters, Robert Kennedy, Liguang Chi, Lisa A. Perrin, Gina Lu, Yun-Wen Ping, Tom McClanahan, Richard Schroeder, Michael T. Leininger, Andrew Geyer, Sabine Schefzick and James Atherton

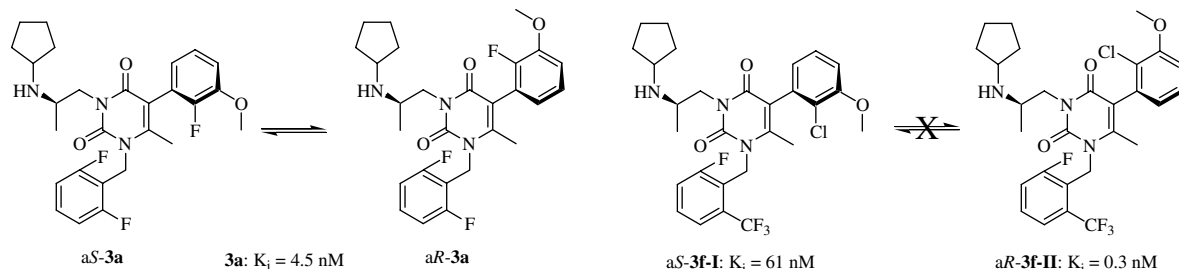


This manuscript describes the synthesis and evaluation of a series of P2Y<sub>1</sub> receptor antagonists for the treatment of platelet aggregation disorders.

**5-Aryluracils as potent GnRH antagonists—Characterization of atropisomers**

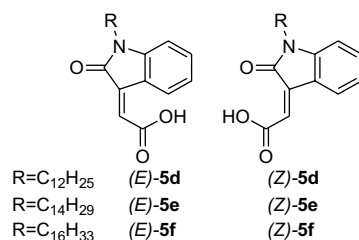
pp 3344–3349

Liren Zhao, Zhiqiang Guo, Yongsheng Chen, Tao Hu, Dongpei Wu, Yun-Fei Zhu, Martin Rowbottom, Timothy D. Gross, Fabio C. Tucci, R. Scott Struthers, Qiu Xie and Chen Chen\*

**Design and synthesis of *N*-alkyl oxindolylidene acetic acids as a new class of potent Cdc25A inhibitors**

pp 3350–3353

Rumiko Shimazawa,\* Masami Kuriyama and Ryuichi Shirai\*

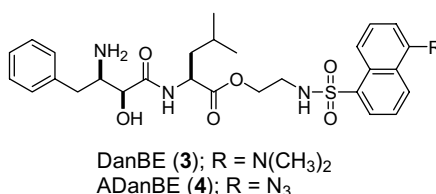


*N*-Alkyl oxindolylidene acetic acids (E)-5d–f and (Z)-5d–f were designed and synthesized, and were found to show strong inhibitory activity towards Cdc25A ( $IC_{50} = 1.6$ – $2.9$   $\mu$ M).

**Demonstration of direct binding of cIAP1 degradation-promoting bestatin analogs to BIR3 domain: Synthesis and application of fluorescent bestatin ester analogs**

pp 3354–3358

Shinichi Sato, Hiroshi Aoyama,\* Hiroyuki Miyachi, Mikihiko Naito and Yuichi Hashimoto



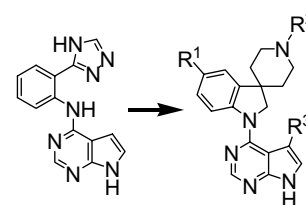
Fluorescent bestatin ester analogs 3 and 4 were designed and synthesized. Direct binding of cIAP1-BIR3 domain protein and these probes was observed in fluorescence polarization assay and photoaffinity labeling assay.

**Synthesis and structure based optimization of novel Akt inhibitors**

pp 3359–3363

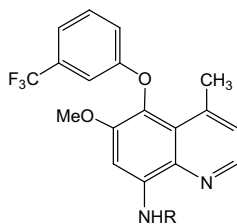
Blaise Lippa,\* Gonghua Pan, Matthew Corbett, Chao Li, Goss S. Kauffman, Jayvardhan Pandit, Shaughnessy Robinson, Liuqing Wei, Ekaterina Kozina, Eric S. Marr, Gary Borzillo, Elisabeth Knauth, Elsa G. Barbacci-Tobin, Patrick Vincent, Merin Troutman, Deborah Baker, Francis Rajamohan, Shefali Kakar, Tracey Clark and Joel Morris\*

Akt1 X-ray co-crystal structures are utilized to optimize the potency of an HTS hit to a spiroindoline pyrrolopyrimidine. The synthesis and SAR of multiple inhibitor classes, along with the efficacy of one lead compound in a tumor model are presented.



**Synthesis and anti-breast cancer activities of substituted quinolines**

pp 3364–3368

Aibin Shi, Thu A. Nguyen, Srinivas K. Battina, Sandeep Rana,  
Dolores J. Takemoto, Peter K. Chiang and Duy H. Hua\*1: R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>2: R = CH<sub>2</sub>CH<sub>2</sub>CN3: R = CH<sub>2</sub>CH<sub>2</sub>C(=NH)OCH<sub>2</sub>CH<sub>3</sub>4: R = CH<sub>2</sub>CH<sub>2</sub>C(=NH)NH<sub>2</sub>

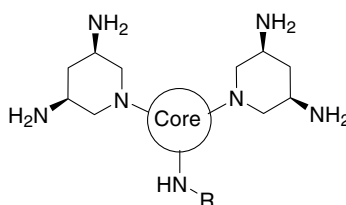
5: R =

6: R =

7: R =

**Antibacterial activity in serum of the 3,5-diamino-piperidine translation inhibitors**

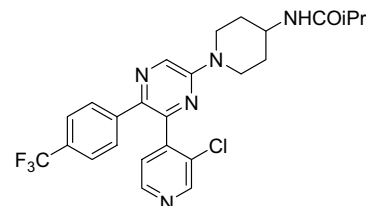
pp 3369–3375

Yuefen Zhou, Chun Chow, Douglas E. Murphy, Zhongxiang Sun, Thomas Bertolini,  
Jamie M. Froelich, Stephen E. Webber, Thomas Hermann and Daniel Wall\*

Core = triazine, pyridine, pyrimidine or purine

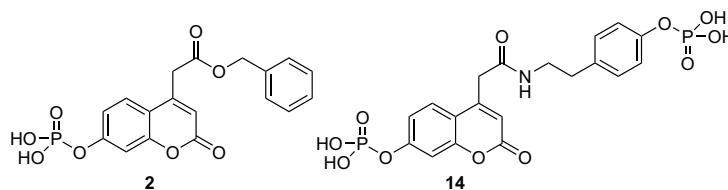
**Aminopyrazine CB1 receptor inverse agonists**

pp 3376–3381

David J. Wustrow,\* George D. Maynard, Jun Yuan, He Zhao, Jianmin Mao, Qin Guo,  
Mark Kershaw, Jack Hammer, Robbin M. Brodbeck, Kristen E. Near, Dan Zhou,  
David S. Beers, Bertrand L. Chenard, James E. Krause and Alan J. HutchisonA series of 5,6-diaryl-2-amino-pyrazines with potent CB1 antagonist-like activity were  
discovered and shown to have robust effects on food intake in vivo.18c, hCB1 K<sub>i</sub> = 0.24 nM**Designing better coumarin-based fluorogenic substrates for PTP1B**

pp 3382–3385

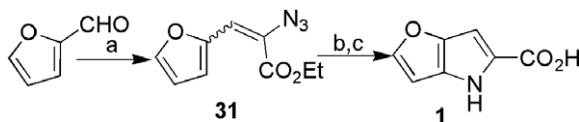
Christopher P. Holmes,\* Natalie Macher, J. Russell Grove, Larry Jang and Jennifer D. Irvine

We have prepared and evaluated nine novel analogs of 4-methylumbelliferone phosphate (MUP) with a variety of additional groups  
occupying the second phosphate binding pocket of PTP1B. Surprisingly, the simple benzyl ester **2** was an equivalent substrate for  
the enzyme as phosphotyrosine mimic **14**.

**The discovery of fused pyrrole carboxylic acids as novel, potent D-amino acid oxidase (DAO) inhibitors**

pp 3386–3391

Tim Sparey,\* Pravien Abeywickrema, Sarah Almond, Nick Brandon, Noel Byrne, Alister Campbell, Pete H. Hutson, Marlene Jacobson, Brian Jones, Sanjeev Munshi, Danette Pascarella, Andrew Pike, G. Sridhar Prasad, Nancy Sachs, Melanie Sakatis, Vinod Sardana, Shankar Venkatraman and Mary Beth Young



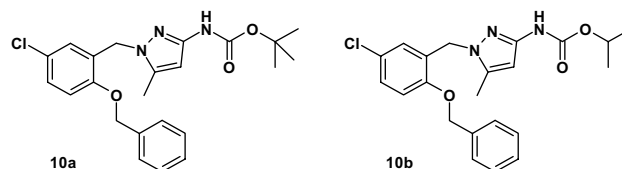
Novel inhibitors of D-amino acid oxidase (DAO) were discovered. In vivo data for compound **1** showed central and peripheral DAO inhibition and increased peripheral D-serine levels.

**Non-acidic pyrazole EP<sub>1</sub> receptor antagonists with in vivo analgesic efficacy**

pp 3392–3399

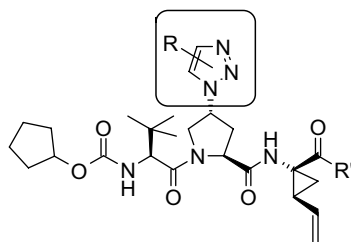
Adrian Hall,\* Andy Billinton, Susan H. Brown, Nicholas M. Clayton, Anita Chowdhury, Gerard M. P. Giblin, Paul Goldsmith, Thomas G. Hayhow, David N. Hurst, Ian R. Kilford, Alan Naylor, Barry Passingham and Lisa Winyard

This paper details the characterization of a series of amides, reversed amides and carbamates as EP<sub>1</sub> antagonists which culminated in the identification of the two carbamate derivatives **10a** and **10b**. Both compounds were found to display potent analgesic activity in vivo and to penetrate the central nervous system.

**Potent triazolyl-proline-based inhibitors of HCV NS3 protease**

pp 3400–3404

Julie Naud, Christopher Lemke, Nathalie Goudreau, Eric Beaulieu, Peter D. White, Montse Llinàs-Brunet and Pat Forgione\*

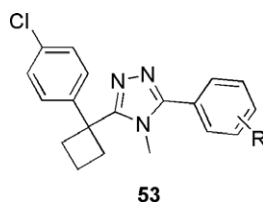


The SAR studies of a series of triazolyl substituted proline as potent inhibitors of the HCV NS3 protease is reported.

**4-Methyl-5-phenyl triazoles as selective inhibitors of 11β-hydroxysteroid dehydrogenase type I**

pp 3405–3411

Yuping Zhu,\* Steven H. Olson, Anne Hermanowski-Vosatka, Steven Mundt, Kashmira Shah, Marty Springer, Rolf Thieringer, Samuel Wright, Jianying Xiao, Hratch Zokian and James M. Balkovec

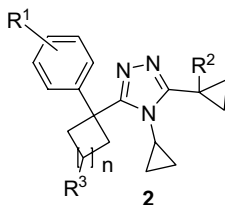


The synthesis and biological activity of selective inhibitors of 11β-hydroxysteroid dehydrogenase type I are reported.

**Phenylcyclobutyl triazoles as selective inhibitors of 11 $\beta$ -hydroxysteroid dehydrogenase type I**

pp 3412–3416

Yuping Zhu,\* Steven H. Olson, Donald Graham, Gool Patel, Anne Hermanowski-Vosatka, Steven Mundt, Kashmira Shah, Marty Springer, Rolf Thieringer, Samuel Wright, Jianying Xiao, Hratch Zokian, Jasminka Dragovic and James M. Balkovec



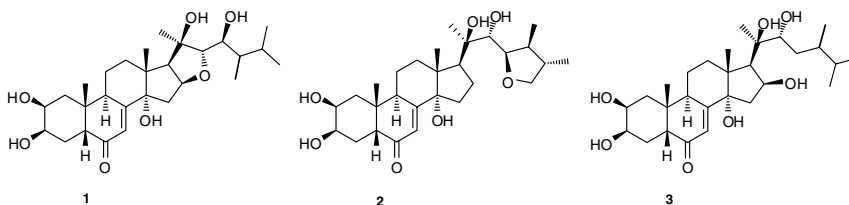
The synthesis and biological activity of selective inhibitors of 11 $\beta$ -hydroxysteroid dehydrogenase type I are reported.

**New anti-inflammatory ergostane-type ecdysteroids from the sclerotium of *Polyporus umbellatus***

pp 3417–3420

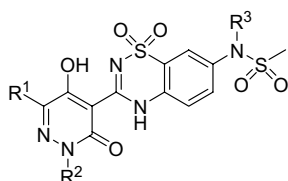
Yi Sun and Ken Yasukawa\*

Three new ergostane-type ecdysteroids along with five known ecdysteroids were isolated from the sclerotium of *Polyporus umbellatus* under bioassay-guided purification. All compounds exhibited potent anti-inflammatory activity in the test of TPA-induced inflammation in mice.

**Novel HCV NS5B polymerase inhibitors derived from 4-(1',1'-dioxo-1',4'-dihydro-1<sup>6</sup>-benzo[1',2',4']-thiadiazin-3'-yl)-5-hydroxy-2H-pyridazin-3-ones: Part 4. Optimization of DMPK properties**

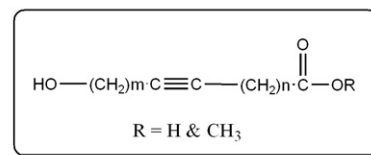
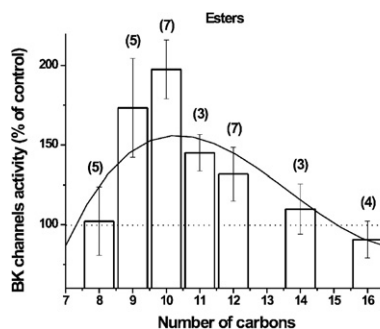
pp 3421–3426

Maria V. Sergeeva, Yuefen Zhou,\* Darian M. Bartkowski, Thomas G. Nolan, Daniel A. Norris, Ellen Okamoto, Leo Kirkovsky, Ruhi Kamran, Laurie A. LeBrun, Mei Tsan, Rupal Patel, Amit M. Shah, Matthew Lardy, Alberto Gobbi, Lian-Sheng Li, Jingjing Zhao, Thomas Bertolini, Nebojsa Stankovic, Zhongxiang Sun, Douglas E. Murphy, Stephen E. Webber and Peter S. Dragovich

**Design and synthesis of hydroxy-alkynoic acids and their methyl esters as novel activators of BK channels**

pp 3427–3430

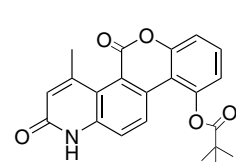
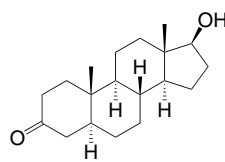
Shivaputra Patil, Anna N. Bukiya, Wei Li, Alejandro M. Dopico\* and Duane Miller\*



|      |       |       |
|------|-------|-------|
| C-8  | m = 2 | n = 3 |
| C-9  | m = 2 | n = 4 |
| C-10 | m = 3 | n = 4 |
| C-11 | m = 3 | n = 5 |
| C-12 | m = 4 | n = 5 |
| C-14 | m = 4 | n = 7 |
| C-16 | m = 4 | n = 9 |



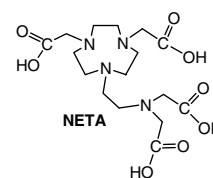
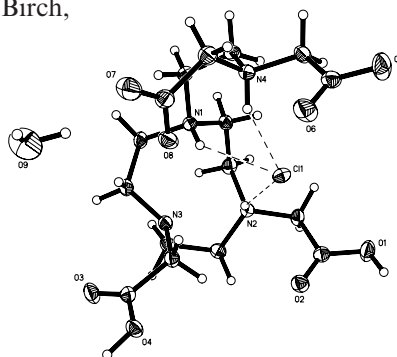
**Discovery of a novel series of nonsteroidal androgen receptor modulators: 5- or 6-oxachrysen-2-ones** pp 3431–3435  
 Shuo Zhao,\* Yixing Shen, Arjan van Oeveren, Keith B. Marschke and Lin Zhi\*

**5d**hAR EC<sub>50</sub> (Eff.) = 1.1 nM (132%)**DHT**hAR EC<sub>50</sub> (Eff.) = 5.1 nM (100%)

**Efficient synthesis and evaluation of bimodal ligand NETA**

pp 3436–3439

Hyun-Soon Chong,\* Hyun A. Song, Noah Birch,  
 Thien Le, Sooyoun Lim and Xiang Ma

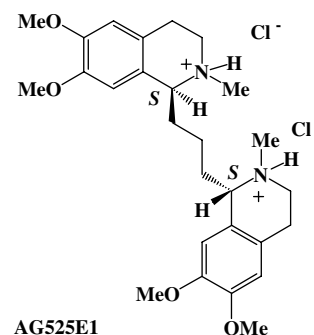


**Bis-tetrahydroisoquinoline derivatives: AG525E1, a new step in the search for non-quaternary non-peptidic small conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channel blockers**

pp 3440–3445

Amaury Graulich, Cédric Lamy, Livia Alleva, Sébastien Dilly, Philippe Chavatte,  
 Johan Wouters, Vincent Seutin and Jean-François Liégeois\*

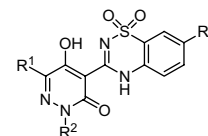
In parallel to the development of *N*-methyl-laudanosine derivatives, a chiral and bis-tertiary amine, AG525E1, shows an approximately 100-fold increase in affinity for apamin-sensitive sites than laudanosine. Physicochemical parameters support its ability to reach CNS targets.

**AG525E1**

**Novel HCV NS5B polymerase inhibitors derived from 4-(1',1'-dioxo-1',4'-dihydro-1''-benzo[1',2',4']-thiadiazin-3'-yl)-5-hydroxy-2*H*-pyridazin-3-ones. Part 3: Further optimization of the 2-, 6-, and 7'-substituents and initial pharmacokinetic assessments**

pp 3446–3455

Lian-Sheng Li, Yuefen Zhou,\* Douglas E. Murphy, Nebojsa Stankovic, Jingjing Zhao,  
 Peter S. Dragovich, Thomas Bertolini, Zhongxiang Sun, Benjamin Ayida, Chinh V. Tran,  
 Frank Ruebsam, Stephen E. Webber, Amit M. Shah, Mei Tsan, Richard E. Showalter,  
 Rupal Patel, Laurie A. LeBrun, Darian M. Bartkowski, Thomas G. Nolan, Daniel A. Norris,  
 Ruhi Kamran, Jennifer Brooks, Maria V. Sergeeva, Leo Kirkovsky,  
 Qiang Zhao and Charles R. Kissinger

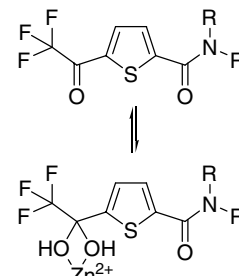


**2-Trifluoroacetylthiophenes, a novel series of potent and selective class II histone deacetylase inhibitors**

pp 3456–3461

Philip Jones,\* Matthew J. Bottomley, Andrea Carfi, Ottavia Cecchetti, Federica Ferrigno, Paola Lo Surdo, Jesus M. Ontoria, Michael Rowley, Rita Scarpelli, Carsten Schultz-Fademrecht and Christian Steinkühler


The development of a novel series of class II HDAC inhibitors is reported.

**OTHER CONTENTS**

Summary of instructions to authors

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\*Corresponding author

 Supplementary data available via ScienceDirect**COVER**

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5677.]

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