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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 6, 2011

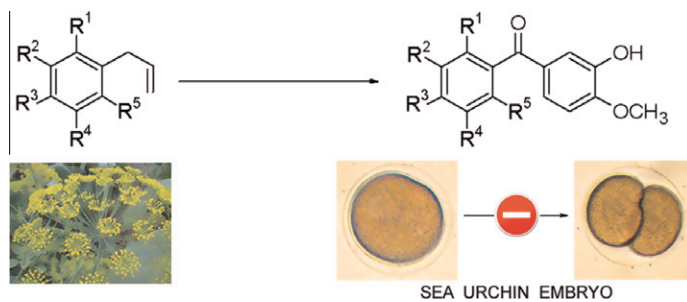
### Contents

#### ARTICLES

##### Application of plant allylpolyalkoxybenzenes in synthesis of antimetabolic phenstatin analogues

pp 1578–1581

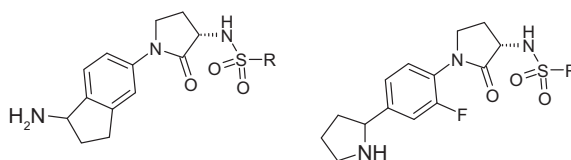
Iliya Y. Titov, Irina K. Sagamanova, Roman T. Gritsenko, Irina B. Karmanova, Olga P. Atamanenko, Marina N. Semenova\*, Victor V. Semenov



##### Structure and property based design of factor Xa inhibitors: Pyrrolidin-2-ones with aminoindane and phenylpyrrolidine P4 motifs

pp 1582–1587

Robert J. Young\*, Carl Adams, Mike Blows, David Brown, Cynthia L. Burns-Kurtis, Chuen Chan, Laiq Chaudry, Máire A. Convery, David E. Davies, Anne M. Exall, Graham Foster, John D. Harling, Eric Hortense, Stephanie Irvine, Wendy R. Irving, Steve Jackson, Savvas Kleanthous, Anthony J. Pateman, Angela N. Patikis, Theresa J. Roethka, Stefan Senger, Gary J. Stelman, John R. Toomey, Robert I. West, Caroline Whittaker, Ping Zhou, Nigel S. Watson

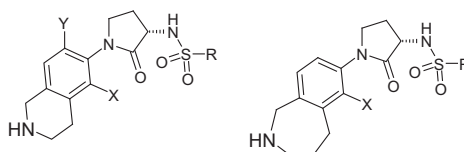


The discovery of potent series of orally available factor Xa inhibitors with aminoindane and phenylpyrrolidine motifs is described.

##### The discovery of potent and long-acting oral factor Xa inhibitors with tetrahydroisoquinoline and benzazepine P4 motifs

pp 1588–1592

Nigel S. Watson, Carl Adams, David Belton, David Brown, Cynthia L. Burns-Kurtis, Laiq Chaudry, Chuen Chan, Máire A. Convery, David E. Davies, Anne M. Exall, John D. Harling, Stephanie Irvine, Wendy R. Irving, Savvas Kleanthous, Iain M. McLay, Anthony J. Pateman, Angela N. Patikis, Theresa J. Roethke, Stefan Senger, Gary J. Stelman, John R. Toomey, Robert I. West, Caroline Whittaker, Ping Zhou, Robert J. Young\*

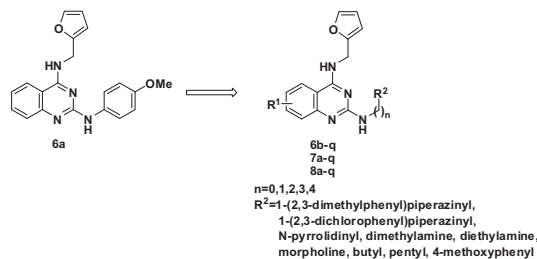


The discovery of potent and long-acting series of orally available factor Xa inhibitors with tetrahydroisoquinoline and benzazepine motifs is described.

### Synthesis and biological evaluation of 2,4-diaminoquinazoline derivatives as novel heat shock protein 90 inhibitors

pp 1593–1597

Dhanaji Achyut Rao Thorat, Munikumar Reddy Doddareddy, Seon Hee Seo, Tae-Joon Hong, Yong Seo Cho, Ji-Sook Hahn, Ae Nim Pae\*

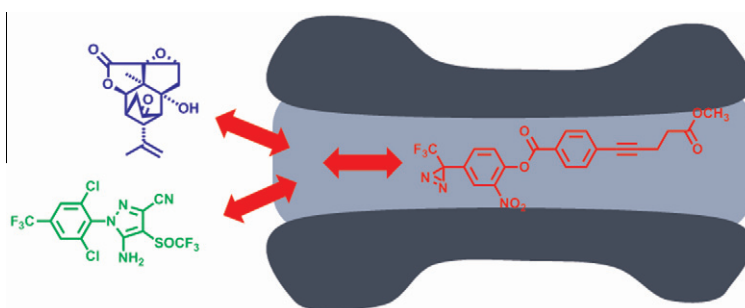


A novel series of 2,4-diaminoquinazoline derivatives were designed, synthesized and biologically evaluated as heat shock protein 90 inhibitors.

### A photoreactive probe that differentiates the binding sites of noncompetitive GABA receptor antagonists

pp 1598–1600

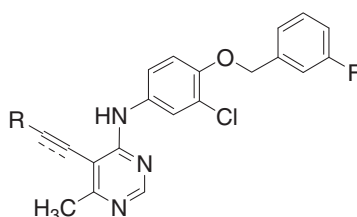
Hiroshi Shimotahira, Sayaka Fusazaki, Izumi Ikeda, Yoshihisa Ozoe\*



### Synthesis and evaluation of novel pyrimidine-based dual EGFR/Her-2 inhibitors

pp 1601–1606

Naoyuki Suzuki\*, Takeshi Shiota, Fumihiko Watanabe, Norihiro Haga, Takami Murashi, Takafumi Ohara, Kenji Matsuo, Naoki Oomori, Hiroshi Yari, Keiji Dohi, Makiko Inoue, Motofumi Iguchi, Jyunko Sentou, Tooru Wada

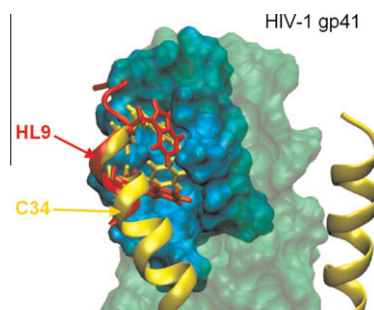


A structure–activity relationship study of 4-anilino-6-methylpyrimidines for dual EGFR/Her-2 inhibitor has resulted in the identification of 4-anilino-5-alkenyl or 5-alkynyl-6-methylpyrimidine derivatives that have exhibited effective inhibitory activity against both enzymes. The presence of 5-alkenyl or 5-alkynyl moiety with terminal hydrophilic group played important role for inhibition of these enzymes. Selected compounds in the series demonstrated some activity against Her-2 dependent cell line (BT474).

### Computational study of bindings of HL9, a nonapeptide fragment of human lysozyme, to HIV-1 fusion protein gp41

pp 1607–1611

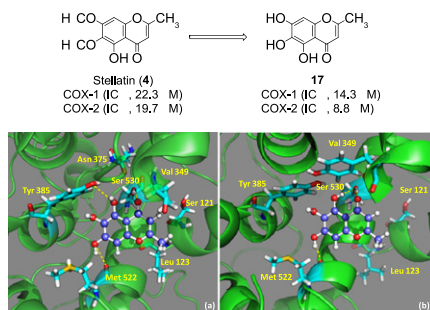
Yossa Dwi Hartono, Angelina Noviani Lee, Sylvia Lee-Huang, Dawei Zhang\*



**Synthesis, biological evaluation and molecular docking studies of stellatin derivatives as cyclooxygenase (COX-1, COX-2) inhibitors and anti-inflammatory agents**

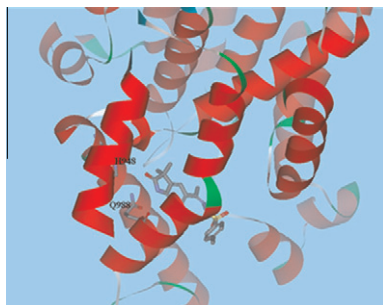
pp 1612–1616

Raju Gautam, Sanjay M. Jachak\*, Vivek Kumar, C. Gopi Mohan

**Discovery of new inhibitor for PDE3 by virtual screening**

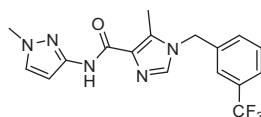
pp 1617–1620

Ki Young Kim, Hyuk Lee, Sung-Eun Yoo, Seong Hwan Kim\*, Nam Sook Kang\*

**N-Benzylimidazole carboxamides as potent, orally active stearylCoA desaturase-1 inhibitors**

pp 1621–1625

Karen A. Atkinson, Elena E. Beretta, Janice A. Brown, Mayda Castrodad, Yue Chen, Judith M. Cosgrove, Ping Du, John Litchfield, Michael Makowski, Kelly Martin, Thomas J. McLellan, Constantin Neagu, David A. Perry, David W. Piotrowski\*, Claire M. Steppan, Richard Trilles

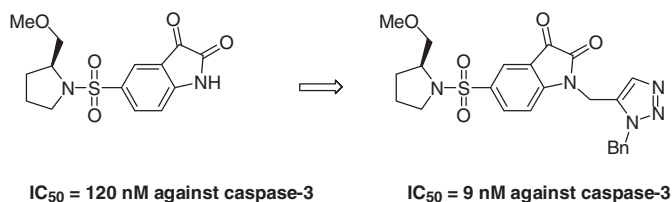


A potent, small molecule inhibitor with a favorable pharmacokinetic profile to allow for sustained SCD inhibition in vivo was identified. Biological evaluation of a SCD inhibitor (5b) included in vitro potency at SCD-1 and in vivo modulation of the plasma desaturation index (DI) in rats on a low essential fatty acid (LEFA) diet.

**Isatin 1,2,3-triazoles as potent inhibitors against caspase-3**

pp 1626–1629

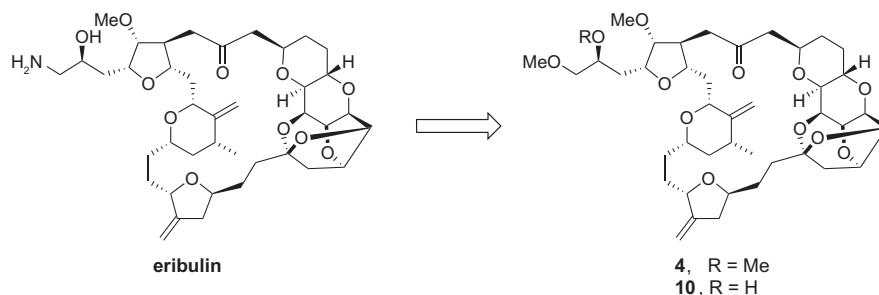
Yang Jiang\*, Trond Vidar Hansen



**Novel second generation analogs of eribulin. Part I: Compounds containing a lipophilic C32 side chain overcome P-glycoprotein susceptibility**

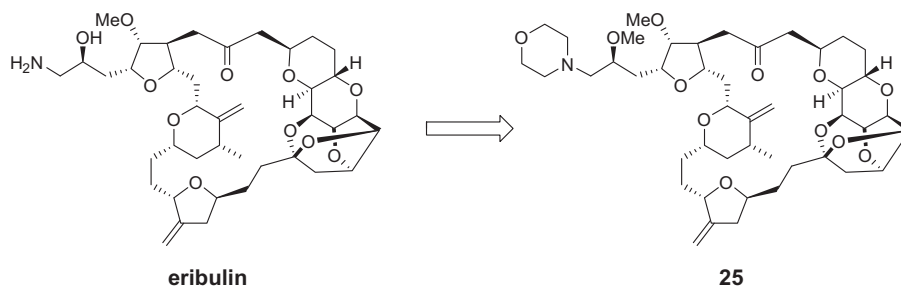
pp 1630–1633

Sridhar Narayan\*, Eric M. Carlson, Hongsheng Cheng, Hong Du, Yongbo Hu, Yimin Jiang, Bryan M. Lewis, Boris M. Seletsky, Karen Tendyke, Huiming Zhang, Wanjun Zheng, Bruce A. Littlefield, Murray J. Towle, Melvin J. Yu

**Novel second generation analogs of eribulin. Part II: Orally available and active against resistant tumors in vivo**

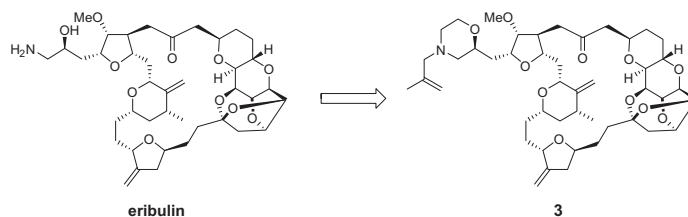
pp 1634–1638

Sridhar Narayan\*, Eric M. Carlson, Hongsheng Cheng, Krista Condon, Hong Du, Sean Eckley, Yongbo Hu, Yimin Jiang, Vipul Kumar, Bryan M. Lewis, Philip Saxton, Edgar Schuck, Boris M. Seletsky, Karen Tendyke, Huiming Zhang, Wanjun Zheng, Bruce A. Littlefield, Murray J. Towle, Melvin J. Yu

**Novel second generation analogs of eribulin. Part III: Blood–brain barrier permeability and in vivo activity in a brain tumor model**

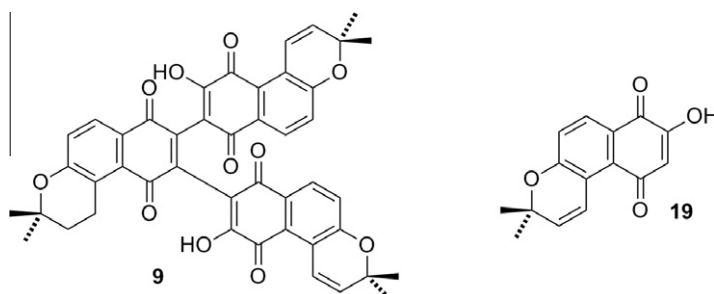
pp 1639–1643

Sridhar Narayan\*, Eric M. Carlson, Hongsheng Cheng, Krista Condon, Hong Du, Sean Eckley, Yongbo Hu, Yimin Jiang, Vipul Kumar, Bryan M. Lewis, Philip Saxton, Edgar Schuck, Boris M. Seletsky, Karen Tendyke, Huiming Zhang, Wanjun Zheng, Bruce A. Littlefield, Murray J. Towle, Melvin J. Yu

**Antiviral agents 3. Discovery of a novel small molecule non-nucleoside inhibitor of Hepatitis B Virus (HBV)**

pp 1644–1648

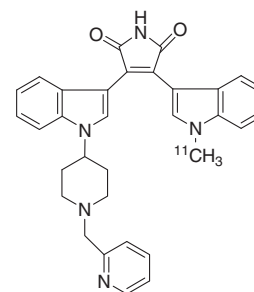
Ian T. Crosby\*, David G. Bourke, Eric D. Jones, Tyrone P. Jeynes, Susan Cox, Jonathan A. V. Coates, Alan D. Robertson



**[<sup>11</sup>C]Enzastaurin, the first design and radiosynthesis of a new potential PET agent for imaging of protein kinase C**

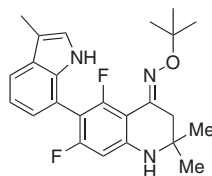
pp 1649–1653

Min Wang, Lu Xu, Mingzhang Gao, Kathy D. Miller, George W. Sledge, Qi-Huang Zheng\*

Radiosynthesis of [<sup>11</sup>C]Enzastaurin, a new potential PET agent for imaging of protein kinase C (PKC), is first reported.**[<sup>11</sup>C]Enzastaurin****Nonsteroidal 2,3-dihydroquinoline glucocorticoid receptor agonists with reduced PEPCK activation**

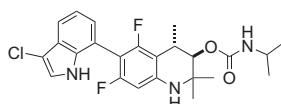
pp 1654–1657

Andrew R. Hudson\*, Robert I. Higuchi, Steven L. Roach, Lino J. Valdez, Mark E. Adams, Angie Vassar, Deepa Rungta, Peter M. Syka, Dale E. Mais, Keith B. Marschke, Lin Zhi

**Tetrahydroquinolin-3-yl carbamate glucocorticoid receptor agonists with reduced PEPCK activation**

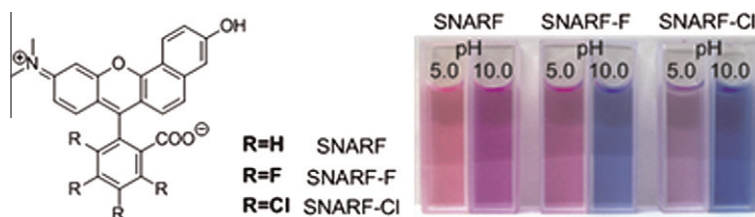
pp 1658–1662

Steven L. Roach\*, Robert I. Higuchi, Andrew R. Hudson, Angie Vassar, Virginia H. S. Grant, Ryan Lamer, Charlene Hooper, Deepa Rungta, Peter M. Syka, Dale E. Mais, Keith B. Marschke, Lin Zhi

**Synthesis and photophysical properties of new SNARF derivatives as dual emission pH sensors**

pp 1663–1666

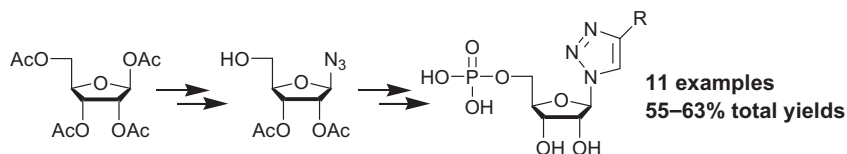
Eiji Nakata\*, Yoshijiyo Nazumi, Yoshihiro Yukimachi, Yoshihiro Uto, Hiroshi Maezawa, Toshihiro Hashimoto, Yasuko Okamoto, Hitoshi Hori\*



## Efficient synthesis of triazole moiety-containing nucleotide analogs and their inhibitory effects on a malic enzyme

pp 1667–1669

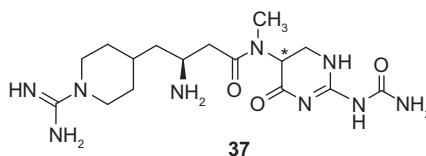
Shuhua Hou, Wujun Liu, Debin Ji, Zongbao (Kent) Zhao\*



## SAR studies on dihydropyrimidinone antibiotics

pp 1670–1674

Lianhong Xu\*, Lijun Zhang, Robert Jones, Clifford Bryant, Nina Boddeker, Eric Mabery, Gina Bahador, Julia Watson, Jeffery Clough, Murty Arimilli, Wendy Gillette, Dorothy Colagiovanni, Keyu Wang, Craig Gibbs, Choung U. Kim

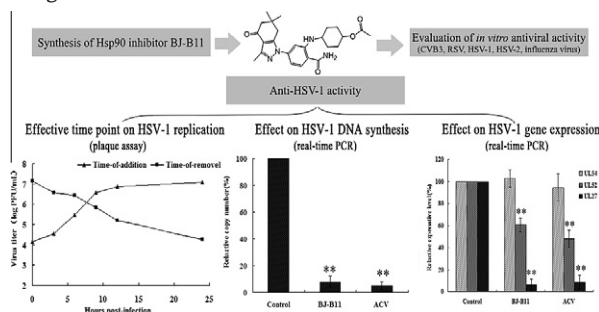


There is an urgent need for the development of novel antimicrobial agents that offer effective treatment against MRSA. Using a new class of dipeptide antibiotic TAN-1057A/B as lead, we designed, synthesized and evaluated analogs of TAN-1057A/B. Several novel dihydropyrimidinone antibiotics demonstrating comparable antibiotic efficacy while possessing favorable selectivity were identified.

## Synthesis and in vitro anti-HSV-1 activity of a novel Hsp90 inhibitor BJ-B11

pp 1675–1677

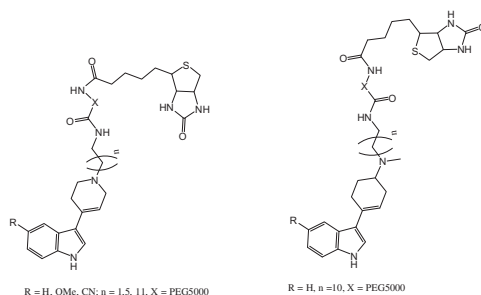
Huai-Qiang Ju, Yang-Fei Xiang, Bao-Juan Xin, Ying Pei, Jia-Xin Lu, Qiao-Li Wang, Min Xia, Chui-Wen Qian, Zhe Ren, Sha-Yan Wang, Yi-Fei Wang\*, Guo-Wen Xing\*



## Biotin tethered homotryptamine derivatives: High affinity probes of the human serotonin transporter (hSERT)

pp 1678–1682


Ian D. Tomlinson, Hideki Iwamoto, Randy D. Blakely, Sandra J. Rosenthal\*



**pp 1683–1686**

Chemical reaction scheme showing the synthesis of a quinuclidine derivative. The starting material is a quinuclidine core with a 2-bromoethoxy group. It reacts with an "Aminoquinoline entity" in DMF at 70 - 80°C for 4 - 6 h. The product is the same quinuclidine core where the bromine atom has been replaced by the aminoquinoline entity via an SN2 reaction.

pp 1687–1691


  
**7e**  
 CK2 Ki = 0.42 nM

## pp 1692-1696



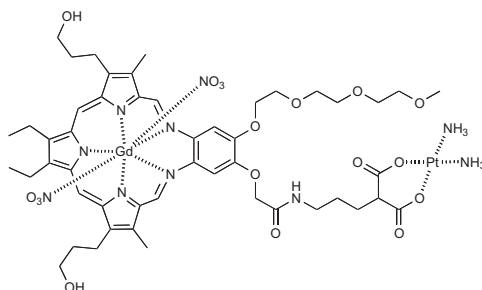
## pp 1697–1700

Chemical reaction scheme showing the conversion of compound **3** to compound **31**. Compound **3** is a complex molecule with a benzene ring substituted with a chlorine atom and a methyl group, and a pyrrole ring. It is linked to a six-membered ring containing a nitrogen atom and two methyl groups, and a hydroxyl group. Compound **31** is the same as compound **3**, but the chlorine atom has been replaced by a fluorine atom.

### Overcoming biochemical pharmacologic mechanisms of platinum resistance with a texaphyrin–platinum conjugate

pp 1701–1705

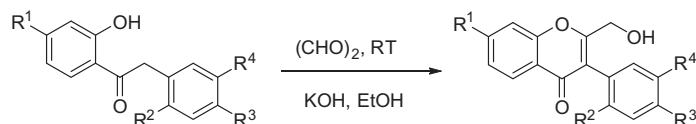
Jonathan F. Arambula, Jonathan L. Sessler\*, Zahid H. Siddik\*



### One step synthesis of 2-hydroxymethylisoflavone and their osteogenic activity

pp 1706–1709

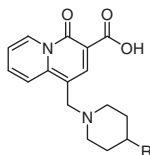
Manmeet Kumar, Preeti Rawat, Jyoti Kureel, Anuj Kumar Singh, Divya Singh, Rakesh Maurya\*



### Quinolizidinone carboxylic acid selective M1 allosteric modulators: SAR in the piperidine series

pp 1710–1715

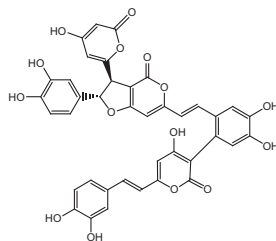
Scott D. Kuduk\*, Ronald K. Chang, Christina N. Di Marco, William J. Ray, Lei Ma, Marion Wittmann, Matthew A. Seager, Kenneth A. Koeplinger, Charles D. Thompson, George D. Hartman, Mark T. Bilodeau

SAR study of the piperidine moiety in a series of quinolizidinone carboxylic acid M<sub>1</sub> positive allosteric modulators was examined.

### Phellinstatin, a new inhibitor of enoyl-ACP reductase produced by the medicinal fungus *Phellinus linteus*

pp 1716–1718

Jun-Young Cho, Yun-Ju Kwon, Mi-Jin Sohn, Soon-Ja Seok, Won-Gon Kim\*

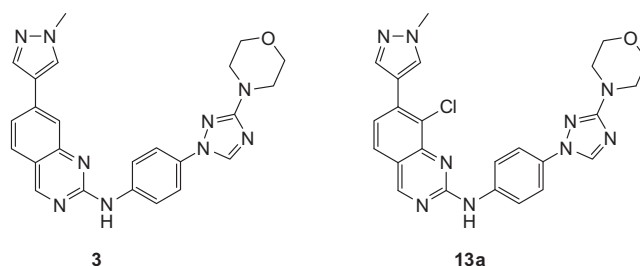


A new trimeric hispidin derivative, phellinstatin, was isolated from a culture broth of the medicinal fungus *Phellinus linteus* and its structure was established by various spectral analysis. Phellinstatin strongly inhibited *Staphylococcus aureus* enoyl-ACP reductase with an IC<sub>50</sub> of 6 M and also showed antibacterial activity against *S. aureus* and MRSA.

**Synthesis and SAR of novel quinazolines as potent and brain-penetrant c-jun N-terminal kinase (JNK) Inhibitors** pp 1719–1723

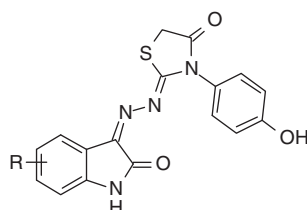
Yuanjun He, Theodore M. Kamenecka, Youseung Shin, Xinyi Song, Rong Jiang, Romain Noel, Derek Duckett, Weimin Chen, Yuan Yuan Ling, Michael D. Cameron, Li Lin, Susan Khan, Marcel Koenig\*, Philip V. LoGrasso\*

Quinazolines **3** and **13a** were discovered as novel c-jun N-terminal kinase (JNK) inhibitors with good brain penetration and pharmacokinetic (PK) properties. Compound **13a** is considered a potential candidate for in vivo evaluation.

**Oxindole derivatives as inhibitors of TAK1 kinase**

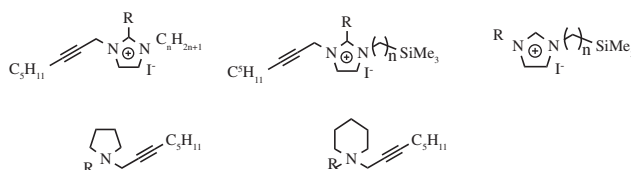
pp 1724–1727

Jeffrey W. Lockman\*, Matthew D. Reeder, Rosann Robinson, Patricia A. Ormonde, Daniel M. Cimbara, Brandi L. Williams, J. Adam Willardsen

**Antibacterial activities of imidazolium, pyrrolidinium and piperidinium salts**

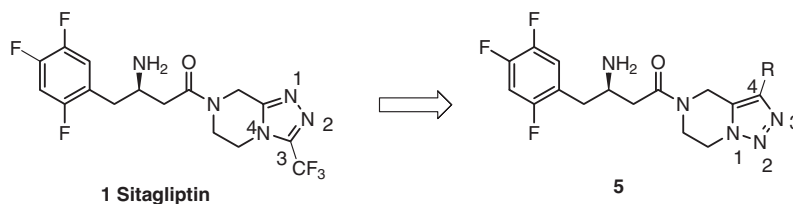
pp 1728–1730

Noritaka Iwai\*, Kyosuke Nakayama, Tomoya Kitazume\*

**Discovery of potent dipeptidyl peptidase IV inhibitors derived from  $\beta$ -aminoamides bearing substituted [1,2,3]-triazolopiperidines for the treatment of type 2 diabetes**

pp 1731–1735

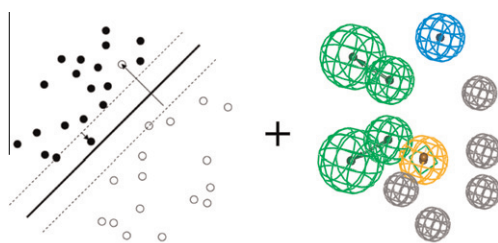
Zhenwei Shan, Min Peng, Houxing Fan, Qingtao Lu, Peng Lu, Chuansheng Zhao, Yilang Chen\*



**Discovery of novel mGluR1 antagonists: A multistep virtual screening approach based on an SVM model and a pharmacophore hypothesis significantly increases the hit rate and enrichment factor**

pp 1736–1740

Guo-Bo Li, Ling-Ling Yang, Shan Feng, Jian-Ping Zhou, Qi Huang, Huan-Zhang Xie, Lin-Li Li, Sheng-Yong Yang\*

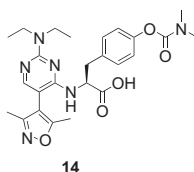


A multistep VS approach based on SVM and pharmacophore models of mGluR1 antagonists

**Discovery of a potent, orally bioavailable pyrimidine VLA-4 antagonist effective in a sheep asthma model**

pp 1741–1743

Christopher M. Semko\*, Linda Chen, Darren B. Dressen, Mark L. Dreyer, Whitney Dunn, Francine S. Farouz, Stephen B. Freedman, Elizabeth J. Holsztynska, Michael Jefferies, Andrei W. Konradi, Anna Liao, Judevin Lugar, Linda Mutter, Michael A. Pleiss, Kevin P. Quinn, Thomas Thompson, Eugene D. Thorsett, Christopher Vandever, Ying-Zi Xu, Ted A. Yednock



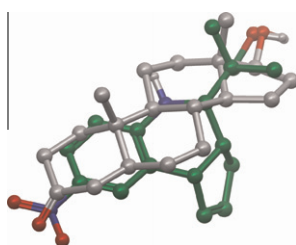
14

A series of N-(pyrimidin-4-yl)-phenylalanine VLA-4 antagonists is described. Optimization of substituents at the 2 and 5 positions of the pyrimidine ring gave **14**, a very potent VLA-4 inhibitor which is orally active in a sheep asthma model.

**Design and synthesis of tricyclic tetrahydroquinolines as a new series of nonsteroidal selective androgen receptor modulators (SARMs)**

pp 1744–1747

Naoya Nagata\*, Motonori Miyakawa, Seiji Amano, Kazuyuki Furuya, Noriko Yamamoto, Kiyoshi Inoguchi

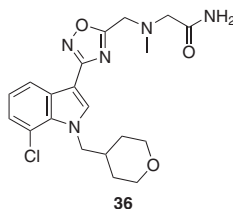


We report design and synthesis of tricyclic tetrahydroquinolines by a four-point pharmacophore method as new SARMs. This compound has a decreased virilizing effect with retention of the anabolic effect as compared with DHT in vivo.

**Discovery of potent and orally bioavailable heterocycle-based cannabinoid CB1 receptor agonists**

pp 1748–1753

Takao Kiyoi, Julia M. Adam\*, John K. Clark, Keneth Davies, Anna-Marie Easson, Darren Edwards, Helen Feilden, Ruth Fields, Stuart Francis, Fiona Jeremiah, Duncan McArthur, Angus J. Morrison, Alan Prosser, Paul D. Ratcliffe, Jurgen Schulz, Grant Wishart, James Baker, Robert Campbell, Jean E. Cottney, Maureen Deehan, Ola Epemolu, Louise Evans

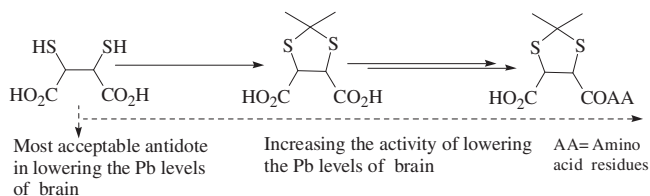


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**Lead detoxification activities and ADMET hepatotoxicities of a class of novel 5-(1-carboxyl-L-amino-acid)-2,2-dimethyl-[1,3]dithiolane-4-carboxylic acids**

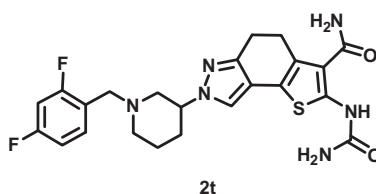
pp 1754–1757

Yanxia Xu, Yuji Wang, Ming Zhao\*, Baoguang Hou, Li Peng, Meiqing Zheng, Jianhui Wu, Shiqi Peng\*

**Novel dihydrothieno[2,3-*e*]indazole derivatives as I $\kappa$ B kinase inhibitors**

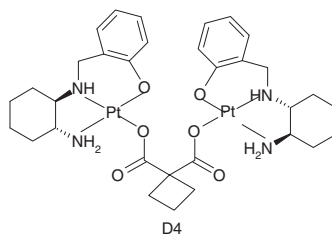
pp 1758–1762

Hiroyasu Takahashi\*, Mariko Shinoyama, Takashi Komine, Muneki Nagao, Masashi Suzuki, Hisatoshi Tsuchida, Koichi Katsuyama

IKK- $\beta$  inhibitors characterized by a dihydrothieno [2,3-*e*] indazole core are reported. Compound **2t** was efficacious in a mouse model of LPS-stimulated TNF- $\alpha$  production.**Design, synthesis and in vitro cytotoxicity of novel dinuclear platinum(II) complexes**

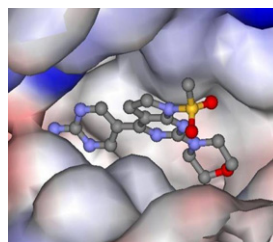
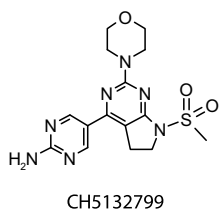
pp 1763–1766

Chuanzhu Gao, Shaohua Gou\*, Lei Fang, Jian Zhao

Novel dinuclear platinum(II) complexes were designed, prepared and biologically evaluated. Results indicated that compound **D4** showed better antitumor activity than carboplatin against two selected human cell lines.**Discovery and biological activity of a novel class I PI3K inhibitor, CH5132799**

pp 1767–1772

Jun Ohwada\*, Hirosato Ebiike, Hatsuo Kawada, Masao Tsukazaki, Mitsuaki Nakamura, Takuya Miyazaki, Kenji Morikami, Kiyoshi Yoshinari, Miyuki Yoshida, Osamu Kondoh, Shino Kuramoto, Kotaro Ogawa, Yuko Aoki, Nobuo Shimma

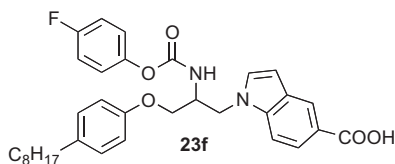


An orally available, potent class I PI3K inhibitor, CH5132799, was discovered by structure-based drug design.

## Structure–activity relationship studies on 1-(5-carboxyindol-1-yl)-propan-2-one inhibitors of human cytosolic phospholipase A<sub>2</sub>: Variation of the activated ketone moiety

pp 1773–1776

Martina Kaptur, Alwine Schulze Elfringhoff, Matthias Lehr\*

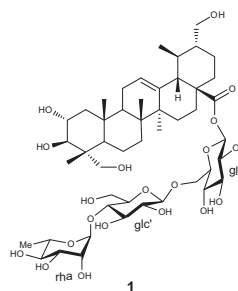


## A new ursane-type triterpenoid glycoside from *Centella asiatica* leaves modulates the production of nitric oxide and secretion of TNF- $\alpha$ in activated RAW 264.7 cells

pp 1777–1781

Nguyen Xuan Nhiem, Bui Huu Tai, Tran Hong Quang, Phan Van Kiem, Chau Van Minh, Nguyen Hoai Nam, Jun-Ho Kim, Lee-Rang Im, Young-Mi Lee, Young Ho Kim\*

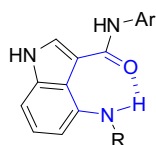
Phytochemical investigation resulted in isolation of one new ursane-type triterpene glycoside, asiaticoside G (**1**) and nine known compounds from the leaves of *Centella asiatica*. The anti-inflammatory activities of the isolated compounds were investigated on lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. Asiaticoside G (**1**) potently inhibited the production of nitric oxide and tumor necrosis factor- $\alpha$  with inhibition rates of 77.3% and 69.0%, respectively, at the concentration of 100  $\mu$ M.



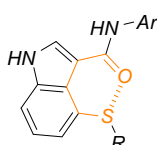
## KDR inhibitor with the intramolecular non-bonded interaction: Conformation–activity relationships of novel indole-3-carboxamide derivatives

pp 1782–1785

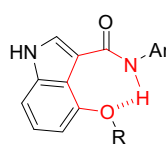
Takahiro Honda\*, Hironori Nagahara, Hiroyuki Mogi, Masakazu Ban, Hiroyuki Aono



**pseudo 7-membered ring**  
KDR 25% inhi. @10 $\mu$ M



**pseudo 6-membered ring**  
KDR 92% inhi. @10 $\mu$ M



**pseudo 7-membered ring**  
KDR 4% inhi. @10 $\mu$ M

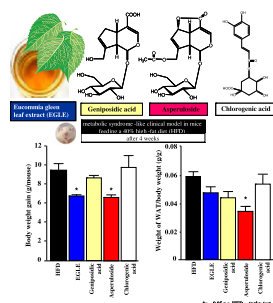
Ar = -3-CF<sub>3</sub>-Ph  
R = -CH<sub>2</sub>-4-Py



## Anti-obesity compounds in green leaves of *Eucommia ulmoides*

pp 1786–1791

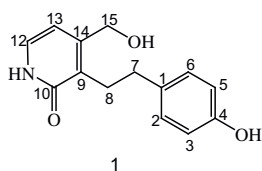
T. Hirata\*, T. Kobayashi, A. Wada, T. Ueda, T. Fujikawa, H. Miyashita, T. Ikeda\*, S. Tsukamoto, T. Nohara



**A novel alkaloid, aristopyridinone A and anti-inflammatory phenanthrenes isolated from *Aristolochia manshuriensis***

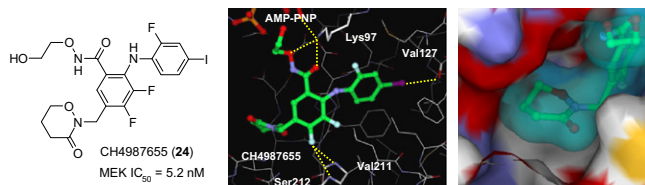
pp 1792–1794

Yu-Ming Chung, Fang-Rong Chang, Tseng-Fu Tseng, Tsong-Long Hwang, Lei-Chin Chen, Shou-Fang Wu, Chia-Lin Lee, Zu-Yau Lin, Li-Yeh Chuang, Jinu-Huang Su\*, Yang-Chang Wu\*

**Design and synthesis of novel allosteric MEK inhibitor CH4987655 as an orally available anticancer agent**

pp 1795–1801

Yoshiaki Isshiki\*, Yasunori Kohchi, Hitoshi Ikura, Yasuaki Matsubara, Kohsuke Asoh, Takeshi Murata, Masami Kohchi, Eisaku Mizuguchi, Shinji Tsujii, Kazuo Hattori, Takaaki Miura, Yasushi Yoshimura, Satoshi Aida, Masanori Miwa, Ryoichi Saitoh, Naoaki Murao, Hisafumi Okabe, Charles Belunis, Cheryl Janson, Christine Lukacs, Verena Schück, Nobuo Shimma



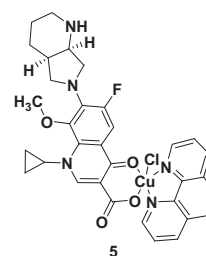
Novel allosteric MEK inhibitor CH4987655 (**24**) possessing unique 3-oxo-[1,2]oxazinan substructure was designed and synthesized. CH4987655 shows slow dissociation from the target enzyme and high metabolic stability together with strong oral antitumor efficacy.

**Synthesis, characterization and anti-tumor activity of moxifloxacin–Copper complexes against breast cancer cell lines**

pp 1802–1806

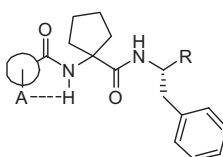
Sommai Patitungkho, Shreelekha Adsule, Prasad Dandawate, Subhash Padhye\*, Aamir Ahmad\*, Fazlul H. Sarkar

Novel moxifloxacin–copper complexes were synthesized, characterized and screened for anti-proliferative and apoptosis-inducing activity against hormone dependent (MCF-7 and T47D) and hormone independent (MDA-MB-231 and BT-20) breast cancer cell lines and was compared against non-tumorigenic breast epithelial cell line (MCF-10A). The results indicated that copper conjugate **2** and its nitrogen adducts **3–5** exert significant growth inhibition of cancer cell lines and apoptosis-induction, compared to parent moxifloxacin (**1**) without any significant effect on non-tumorigenic MCF-10A cells. Interestingly, compound **5** was found to be very active against multiple cell lines.

**hNK<sub>2</sub> receptor antagonists. The use of intramolecular hydrogen bonding to increase solubility and membrane permeability**

pp 1807–1809

Alessandro Ettorre, Piero D'Andrea, Sandro Mauro, Marina Porcelloni, Cristina Rossi, Maria Altamura, Rose M. Catalioto, Sandro Giuliani, Carlo Alberto Maggi, Daniela Fattori\*

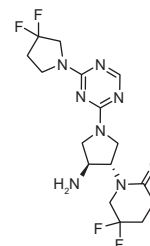


### 1-((3*S*,4*S*)-4-Amino-1-(4-substituted-1,3,5-triazin-2-yl) pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one inhibitors of DPP-4 for the treatment of type 2 diabetes

pp 1810–1814

Kim M. Andrews, David A. Beebe, John W. Benbow\*, David A. Boyer, Shawn D. Doran, Yu Hui, Shenping Liu, R. Kirk McPherson, Constantin Neagu, Janice C. Parker, David W. Piotrowski\*, Steven R. Schneider, Judith L. Treadway, Maria A. VanVolkenberg, William J. Zembrowski

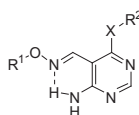
A 3-amino-4-substituted pyrrolidine series of dipeptidyl peptidase IV (DPP-4) inhibitors was rapidly developed into a candidate series by identification of a polar valerolactam replacement for the lipophilic 2,4,5-trifluorophenyl pharmacophore. The addition of a *gem*-difluoro substituent to the lactam improved overall DPP-4 inhibition and an efficient asymmetric route to 3,4-diaminopyrrolidines was developed. Advanced profiling of a subset of analogs identified **5o** with an acceptable human DPP-4 inhibition profile based on a rat PK/PD model and a projected human dose that was suitable for clinical development.



### 4-Aminopyrimidine-5-carbaldehyde oximes as potent VEGFR-2 inhibitors. Part II

pp 1815–1818

Shenlin Huang\*, Ronghua Li, Kenneth R. LaMontagne, Lee M. Greenberger, Peter J. Connolly

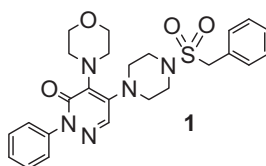


A series of 4-aminopyrimidine-5-carbaldehyde oximes was discovered to have potent VEGFR-2 inhibitory activities. Described here are the chemistry for analogue synthesis and SAR study results. The PK properties, kinase profiling, and in vivo efficacy study for compound **4b** are also discussed.

### The synthesis and structure–activity relationship of pyridazinones as glucan synthase inhibitors

pp 1819–1822

Pauline C. Ting\*, Rongze Kuang, Heping Wu, Robert G. Aslanian, Jianhua Cao, David W. Kim, Joe F. Lee, John Schwerdt, Gang Zhou, Samuel Wainhaus, Todd A. Black, Anthony Cacciapuoti, Paul M. McNicholas, Yiming Xu, Scott S. Walker

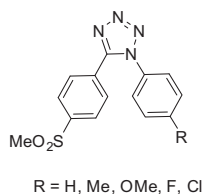


A structure–activity relationship study of the lead 5-[4-(benzylsulfonyl)piperazin-1-yl]-4-morpholino-2-phenyl-pyridazin-3(2*H*)-one **1** has resulted in the identification of 2-(3,5-difluorophenyl)-4-(3-fluorocyclopentyloxy)-5-[4-(isopropylsulfonyl)piperazin-1-yl]-pyridazin-3(2*H*)-one **11c** as a  $\beta$ -1,3-glucan synthase inhibitor. Compound **11c** exhibited significant efficacy in an in vivo mouse model of *Candida glabrata* infection.

### Synthesis and evaluation of 1,5-diaryl-substituted tetrazoles as novel selective cyclooxygenase-2 (COX-2) inhibitors

pp 1823–1826

Baker Jawabrah Al-Hourani, Sai Kiran Sharma, Jonathan Y. Mane, Jack Tuszynski, Vickie Baracos, Torsten Kniess, Mavanur Suresh, Jens Pietzsch, Frank Wuest\*

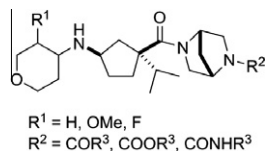


A series of 1,5-diaryl-substituted tetrazole derivatives was synthesized. All compounds were evaluated in in vitro cyclooxygenase (COX) assays to determine COX-1 and COX-2 inhibitory potency and selectivity.

**Design and synthesis of novel CCR2 antagonists: Investigation of non-aryl/heteroaryl binding motifs**

pp 1827–1831

John I. Trujillo\*, Wei Huang, Robert O. Hughes, D. Joseph Rogier, Steven R. Turner, Rajesh Devraj, Philip A. Morton, Chu-Biao Xue, Ganfeng Chao, Maryanne B. Covington, Robert C. Newton, Brian Metcalf

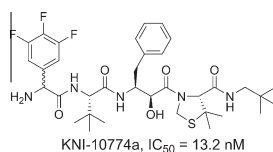


This report describes the design and synthesis of a series of CCR2 antagonists incorporating non-aryl/heteroaryl RHS motifs and a 2.2.1 ring system.

**Maintaining potent HTLV-I protease inhibition without the P<sub>3</sub>-cap moiety in small tetrapeptidic inhibitors**

pp 1832–1837

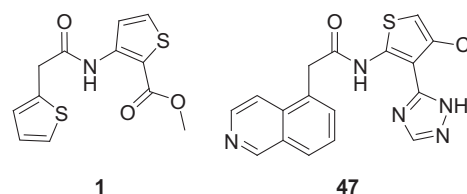
Jeffrey-Tri Nguyen, Keiko Kato, Henri-Obadja Kumada, Koushi Hidaka, Tooru Kimura, Yoshiaki Kiso\*

**Design and synthesis of a novel, orally active, brain penetrant, tri-substituted thiophene based JNK inhibitor**

pp 1838–1843

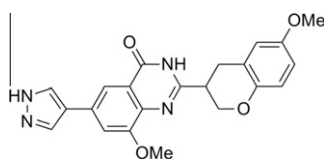
Simeon Bowers\*, Anh P. Truong\*, R. Jeffrey Neitz, Martin Neitzel, Gary D. Probst, Roy K. Hom, Brian Peterson, Robert A. Galembo Jr., Andrei W. Konradi, Hing L. Sham, Gergely Tóth, Hu Pan, Nanhua Yao, Dean R. Artis, Elizabeth F. Brigham, Kevin P. Quinn, John-Michael Sauer, Kyle Powell, Lany Ruslim, Zhao Ren, Frédérique Bard, Ted A. Yednock, Irene Griswold-Prenner

The SAR of a series of tri-substituted thiophene JNK3 inhibitors is described. By optimizing both the N-aryl acetamide region of the inhibitor and the 4-position of the thiophene we obtained single digit nanomolar compounds, such as **47**, which demonstrated an in vivo effect on JNK activity when dosed orally in our kainic acid mouse model as measured by phospho-c-jun reduction.

**Synthesis and biological evaluation of 4-quinazolinones as Rho kinase inhibitors**

pp 1844–1848

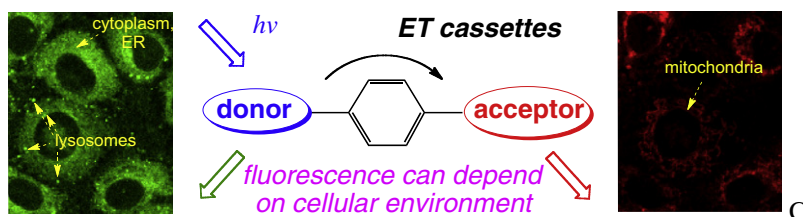
Xingang Fang, Yen Ting Chen\*, E. Hampton Sessions, Sarwat Chowdhury, Tomas Vojtkovsky, Yan Yin, Jennifer R. Pocas, Wayne Grant, Thomas Schröter, Li Lin, Claudia Ruiz, Michael D. Cameron, Philip LoGrasso, Thomas D. Bannister, Yangbo Feng\*



**Organelle-selective energy transfer: A fluorescent indicator of intracellular environment**

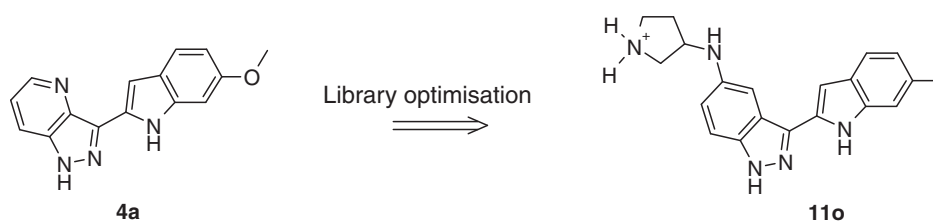
pp 1849–1851

Aurore Loudet, Yuichiro Ueno, Liangxing Wu, Jiney Jose, Rola Barhoumi, Robert Burghardt, Kevin Burgess\*

**Optimisation of ITK inhibitors through successive iterative design cycles**

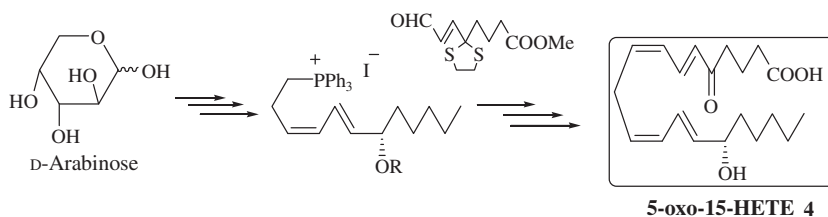
pp 1852–1856

Matthias Herdemann, Alexander Weber\*, Jérôme Jonveaux, Frank Schwoebel, Michael Stoeck, Isabelle Heit\*

**5-Oxo-15-HETE: Total synthesis and bioactivity**

pp 1857–1860

Pranav Patel, Jaganmohan R. Anumolu, William S. Powell, Joshua Rokach\*

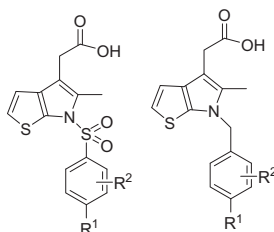


The first total synthesis of 6(E),8(Z),11(Z),13(E) 5-oxo-15-HETE **4** was accomplished. The synthetic material was evaluated in the calcium mobilization assay and compared with 5-oxo-EETE the natural ligand for the OXE receptor.

**Thienopyrrole acetic acids as antagonists of the CRTH2 receptor**

pp 1861–1864

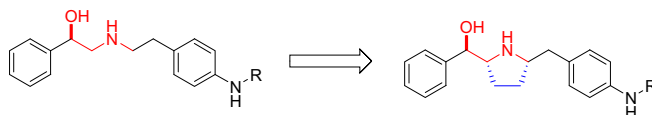
Dominique Bonafoux\*, Ayome Abibi, Brian Bettencourt, Andrew Burchat, Anna Ericsson, Christopher M. Harris, Tegest Kebede, Michael Morytko, Michael McPherson, Grier Wallace, Xiaoyun Wu



**Design of a novel pyrrolidine scaffold utilized in the discovery of potent and selective human  $\beta_3$  adrenergic receptor agonists**

pp 1865–1870

Gregori J. Morriello\*, Harvey R. Wendt, Alka Bansal, Jerry Di Salvo, Scott Feighner, Jiafang He, Amanda L. Hurley, Donna L. Hreniuk, Gino M. Salituro, Marat Vijay Reddy, Sheila M. Galloway, Katherine K. McGettigan, George Laws, Crystal McKnight, George A. Doss, Nancy N. Tsou, Regina M. Black, Judy Morris, Richard G. Ball, Anthony T. Sanfiz, Eric Streckfuss, Mary Struthers, Scott D. Edmondson



A novel class of human  $\beta_3$ -adrenergic receptor agonists was designed in effort to improve selectivity and metabolic stability versus previous disclosed  $\beta_3$ -AR agonists. As observed, many of the  $\beta_3$ -AR agonists seem to need the acyclic ethanolamine core for agonist activity. We have synthesized derivatives that constrained this moiety by introduction of a pyrrolidine. This unique modification maintains human  $\beta_3$  functional potency with improved selectivity versus ancillary targets and also eliminates the possibility of the same oxidative metabolites formed from cleavage of the N–C bond of the ethanolamine. Compound **39** exhibited excellent functional  $\beta_3$  agonist potency across species with good pharmacokinetic properties in rat, dog, and rhesus monkeys. Early de-risking of this novel pyrrolidine core (**44**) via full AMES study supports further research into various new  $\beta_3$ -AR agonists containing the pyrrolidine moiety.

**Synthesis and SAR studies of novel 2-(4-oxo-2-aryl-quinazolin-3(4H)-yl)acetamide vasopressin  $V_{1b}$  receptor antagonists**

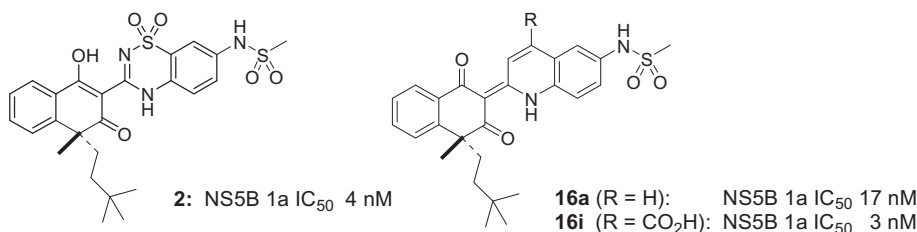
pp 1871–1875

Susan E. Napier\*, Jeffrey J. Letourneau\*, Nasrin Ansari, Douglas S. Auld, James Baker, Stuart Best, Leigh Campbell-Wan, Jui-Hsiang Chan, Mark Craighead, Hema Desai, Katharine A. Goan, Koc-Kan Ho, Ellen G. J. Hulskotte, Cliona P. MacSweeney, Rachel Milne, J. Richard Morphy, Irina Neagu, Michael H. J. Ohlmeyer, Ard W. M. M. Peeters, Jeremy Presland, Chris Riviello, Ge S. F. Ruigt, Fiona J. Thomson, Heather A. Zanetakos, Jiuqiao Zhao, Maria L. Webb

**Hepatitis C NS5B polymerase inhibitors: Functional equivalents for the benzothiadiazine moiety**

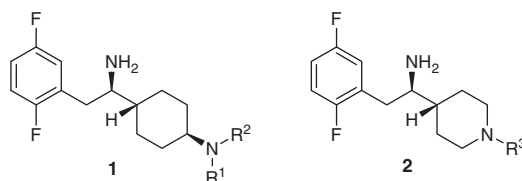
pp 1876–1879

Douglas K. Hutchinson\*, Charles A. Flentge, Pamela L. Donner, Rolf Wagner, Clarence J. Maring, Warren M. Kati, Yaya Liu, Sherie V. Masse, Tim Middleton, Hongmei Mo, Debra Montgomery, Wen W. Jiang, Gennadiy Koev, David W. A. Beno, Kent D. Stewart, Vincent S. Stoll, Akhteruzzaman Molla, Dale J. Kempf

**Synthesis and evaluation of [(1R)-1-amino-2-(2,5-difluorophenyl)ethyl]cyclohexanes and 4-[(1R)-1-amino-2-(2,5-difluorophenyl)ethyl]piperidines as DPP-4 inhibitors**

pp 1880–1886

Ping Chen\*, Charles G. Caldwell, Wallace Ashton, Joseph K. Wu, Huaibing He, Kathryn A. Lyons, Nancy A. Thornberry, Ann E. Weber

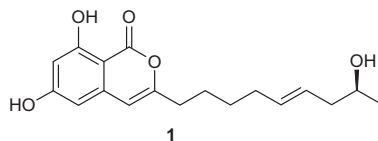


A novel series of 4-substituted-[(1R)-1-amino-2-(2,5-difluorophenyl)ethyl]cyclohexanes **1** and piperidines **2** were prepared and evaluated for inhibition of dipeptidyl dipeptidase IV (DPP-4) for treatment of type 2 diabetes.

**Toxic polyketides produced by *Fusarium* sp., an endophytic fungus isolated from *Melia azedarach***

pp 1887–1889

Sheng-Xiang Yang, Jin-Ming Gao\*, Qiang Zhang, Hartmut Laatsch\*

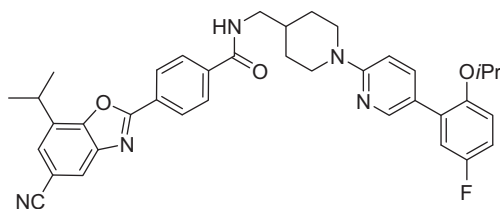


A new isocoumarin named fusariumin (**1**), together with two known resorcylic macrolides aigialomycin D (**2**) and pochonin N (**3**), has been isolated from the cultures of *Fusarium* sp., an endophytic fungus from *Melia azedarach*. The isolates displayed significant growth inhibitory activity against the brine shrimp (*Artemia salina*).

**2-(4-Carbonylphenyl)benzoxazole inhibitors of CETP: Scaffold design and advancement in HDLc-raising efficacy**

pp 1890–1895

Ramzi F. Sweis\*, Julianne A. Hunt, Florida Kallashi, Milton L. Hammond, Ying Chen, Suzanne S. Eveland, Qiu Guo, Sheryl A. Hyland, Denise P. Milot, Anne-Marie Cumiskey, Melanie Latham, Raymond Rosa, Larry Peterson, Carl P. Sparrow, Samuel D. Wright, Matt S. Anderson, Peter J. Sinclair

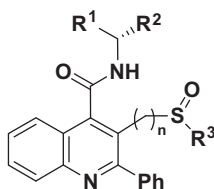


Compound **11v** was the first in its series found to be a potent inhibitor of CETP ( $IC_{50}$  = 16 nM), with robust in vivo efficacy ( $\Delta$ HDLc = 24 mg/dL) and absent of any potentially liable aniline-containing substructures.

**Synthesis and SAR of sulfoxide substituted carboxyquinolines as NK3 receptor antagonists**

pp 1896–1899

Hui Xiong, James Kang, James M. Woods, John P. McCauley Jr., Gerard M. Koether, Jeffrey S. Albert, Lindsay Hinkley, Yan Li, Reto A. Gadiant, Thomas R. Simpson\*



Synthesis and SAR of a series of C3-alkylsulfoxide substituted quinolines as potent NK3 receptor antagonists are reported. These compounds have excellent NK3 functional activity, good selectivity and drug-like properties. Several key compounds have good in vitro/in vivo DMPK characteristics, and are active in a gerbil locomotor activity model.

**OTHER CONTENTS****Corrigenda**

pp 1900–1902

\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

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

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