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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 21, 2010

### Contents

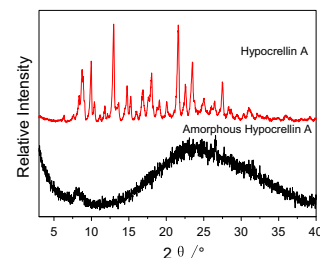
#### ARTICLES

##### Delivering a hydrophobic anticancer drug for photodynamic therapy by amorphous formulation

pp 6172–6174

Lin Zhou, Wei Wang, Yuying Feng, Shaohua Wei, Jiahong Zhou\*, Boyang Yu\*, Jian Shen

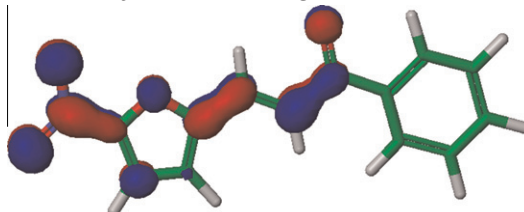
We have synthesized and characterized a water-soluble hypocrellin A (HA) by making its amorphous formulation (AM-HA) with excellent water-solubility and photosensitizing properties. In vitro, AM-HA retains high light-toxicity and reduces dark-toxicity simultaneously compared to traditional delivery vehicles [Tween-80 micelle embedded hypocrellin A (TW-HA)]. These properties of AM-HA could make it a promising candidate to be used in photodynamic therapy.



##### Design, synthesis, and biological evaluation of 4-(5-nitrofuran-2-yl)prop-2-en-1-one derivatives as potent antitubercular agents

pp 6175–6178

Nilesh R. Tawari, Ranjeet Bairwa, M. K. Ray, M. G. R. Rajan, Mariam S. Degani\*



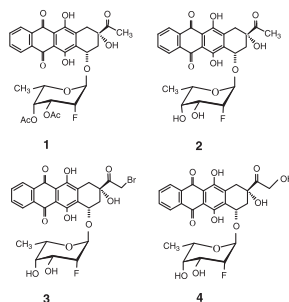
LUMO map for one of the synthesized compound

Based on stereoelectronic feature analysis using density functional theory (DFT) at B3LYP/3-21+G level, a series 4-(5-nitrofuran-2-yl)prop-2-en-1-one derivatives were envisaged as potential antitubercular agents. As expected, synthesis and biological evaluation showed that target compounds were potent inhibitors of *Mycobacterium tuberculosis*. Thus, this study shows the potential of stereoelectronic property analysis in developing improved nitroaromatics as antitubercular agents.

##### Inhibitory activity of four demethoxy fluorinated anthracycline analogs against five human-tumor cell lines

pp 6179–6181

Derek Horton\*, Anakshi Khare

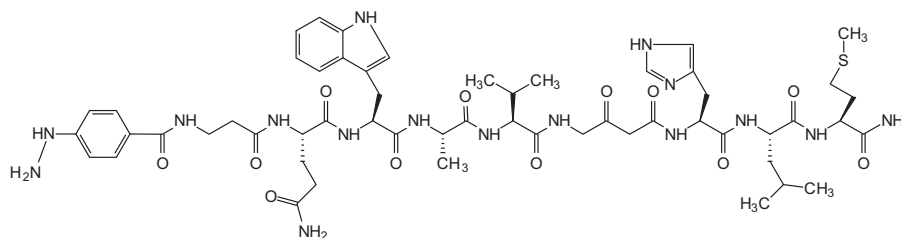


Four 4-demethoxy-3'-deamino-2'-fluoro-3'-hydroxy anthracycline analogs (**1–4**) were compared with adriamycin (doxorubicin) for their growth-inhibitory effects against five human-tumor cell lines.

**Bombesin derivative radiolabeled with technetium-99m as agent for tumor identification**

pp 6182–6184

André Luís Branco de Barros, Luciene das Graças Mota, Carolina de Aguiar Ferreira, Mônica Cristina de Oliveira, Alfredo Miranda de Góes, Valbert Nascimento Cardoso\*

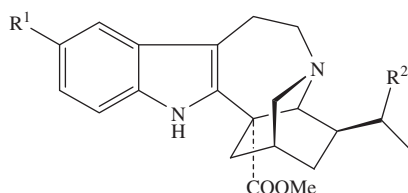


Preparation of technetium-labeled bombesin derivative for tumor identification.

**Indole alkaloids from *Ervatamia hainanensis* with potent acetylcholinesterase inhibition activities**

pp 6185–6187

Zha-Jun Zhan, Qi Yu, Zhan-Li Wang, Wei-Guang Shan\*

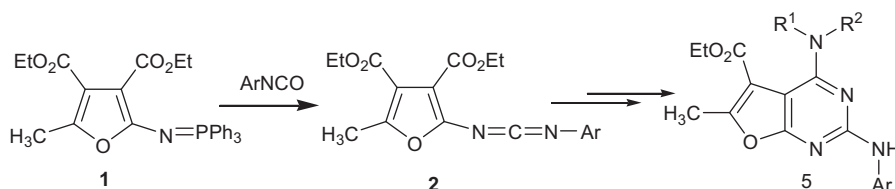


Eight indole alkaloids were isolated from the stems of *Ervatamia hainanensis*, in which compounds **1** and **3** exhibited the same level of activities as galantamine, a marketed cholinesterase inhibitor for the treatment of Alzheimer's disease.

**Efficient synthesis and biological evaluation of some 2,4-diamino-furo[2,3-d]pyrimidine derivatives**

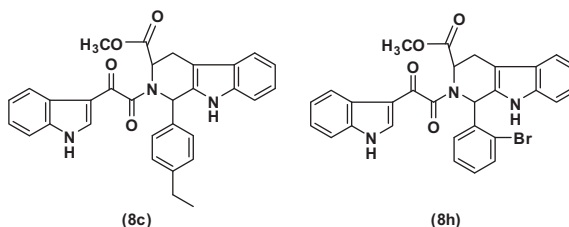
pp 6188–6190

Yang-Gen Hu\*, Yan Wang, Shi-Ming Du, Xiao-Bao Chen, Ming-Wu Ding\*

**Synthesis and biological evaluation of indolyl glyoxylamides as a new class of antileishmanial agents**

pp 6191–6194

Shikha S. Chauhan, Leena Gupta, Monika Mittal, Preeti Vishwakarma, Suman Gupta, Prem M. S. Chauhan\*



Antiamastigote activity:  
IC<sub>50</sub> = 5.17 μM,  
Selectivity index = 31.48.

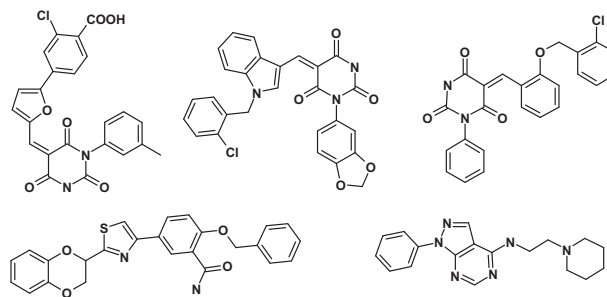
Antiamastigote activity:  
IC<sub>50</sub> = 3.79 μM,  
Selectivity index = 7.94.

A series of indolylglyoxylamide derivatives have been synthesized and screened for their in vitro antileishmanial activity against *Leishmania donovani*.

**Discovery of the inhibitors of tumor necrosis factor alpha with structure-based virtual screening**

pp 6195–6198

Hwanho Choi, Youngseop Lee, Hwangseo Park\*, Dal-Seok Oh\*

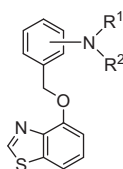


We have discovered five novel inhibitors of TNF- $\alpha$  based on the structure-based virtual screening and in vitro cell-based immunoassay.

**Design, synthesis and activity of benzothiazole-based inhibitors of NO production in LPS-activated macrophages**

pp 6199–6202

Guo Hua Jin, Hua Li, Semi An, Jae-Ha Ryu, Raok Jeon\*



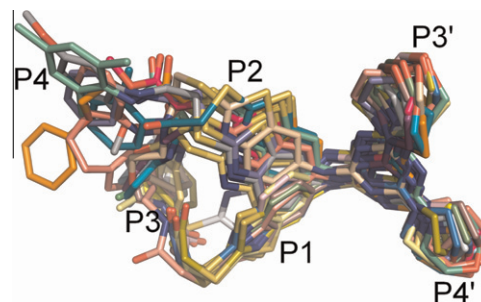
Synthesis of series of benzothiazole derivatives and their inhibitory activities on the NO production in lipopolysaccharide-activated macrophages are reported.

**Molecular docking and structure–activity relationship studies on benzothiazole based non-peptidic BACE-1 inhibitors**

pp 6203–6207

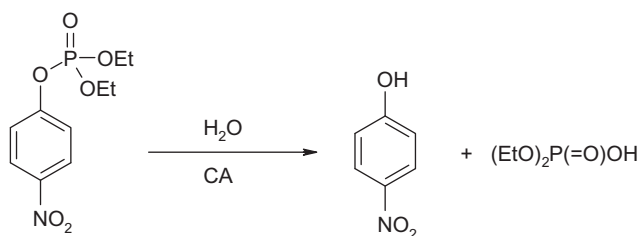
Weijun Xu, Gang Chen, Weiliang Zhu\*, Zhili Zuo\*

Twenty-two compounds derived from compound **1** were studied via in silico and in vitro approaches against BACE-1. Compound **5** bearing pyrrolidinyls at 4- and 6-positions on triazine and a P4 phenyl acetamide group showed IC<sub>50</sub> of 0.12  $\mu$ M.

**Paraoxon, 4-nitrophenyl phosphate and acetate are substrates of  $\alpha$ - but not of  $\beta$ -,  $\gamma$ - and  $\zeta$ -carbonic anhydrases**

pp 6208–6212

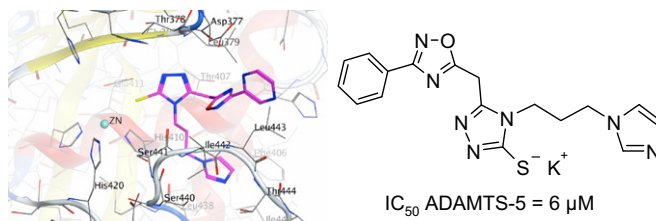
Alessio Innocenti, Claudiu T. Supuran\*



**New non-hydroxamic ADAMTS-5 inhibitors based on the 1,2,4-triazole-3-thiol scaffold**

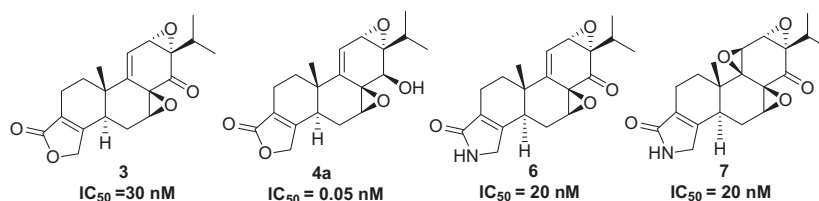
pp 6213–6216

Lucie Maingot, Florence Leroux, Valérie Landry, Julie Dumont, Hideaki Nagase, Bruno Villoutreix, Olivier Sperandio, Rebecca Deprez-Poulain\*, Benoit Deprez\*

**Synthesis and biological evaluation of novel triptolide analogues for anticancer activity**

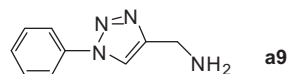
pp 6217–6221

Bing Zhou, Zehong Miao, Gang Deng, Jian Ding, Yaxi Yang, Huijin Feng, Yuanchao Li\*

**‘Click’ assembly of selective inhibitors for MAO-A**

pp 6222–6225

Zhao Jia, Qing Zhu\*



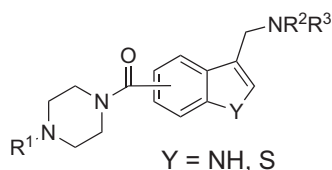
MAO-A: IC<sub>50</sub> = 0.97 μM  
SI = 526.33

An efficient strategy for the fast construction of 108 compounds library was developed using click chemistry. The fingerprint of inhibitory activity toward MAO-A/B against this library was obtained, and four hit compounds were identified as selective inhibitors toward MAO-A. Docking study was carried out to demonstrate the binding mode between **a9** and MAO-A/B, and the result reveals that **a9** localized in the ‘aromatic cage’ and oriented to establish π–π stacking interactions with Tyr407, Tyr444 and FAD in MAO-A rather than in MAO-B.

**Indole- and benzothiophene-based histamine H<sub>3</sub> antagonists**

pp 6226–6230

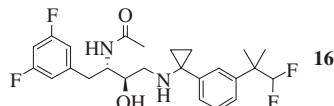
Alejandro Santillan Jr., Kelly J. McClure, Brett D. Allison, Brian Lord, Jamin D. Boggs, Kirsten L. Morton, Anita M. Everson, Diane Nepomuceno, Michael A. Letavic, Alice Lee-Dutra, Timothy W. Lovenberg, Nicholas I. Carruthers, Cheryl A. Grice\*



**Design of an orally efficacious hydroxyethylamine (HEA) BACE-1 inhibitor in a preclinical animal model**

pp 6231–6236

Anh P. Truong, Gergely Tóth, Gary D. Probst\*, Jennifer M. Sealy, Simeon Bowers, David W. G. Wone, Darren Dressen, Roy K. Hom, Andrei W. Konradi, Hing L. Sham, Jing Wu, Brian T. Peterson, Lany Ruslim, Michael P. Bova, Dora Kholodenko, Ruth N. Motter, Frédérique Bard, Pamela Santiago, Huifang Ni, David Chian, Ferdie Soriano, Tracy Cole, Elizabeth F. Brigham, Karina Wong, Wes Zmolek, Erich Goldbach, Bhushan Samant, Linda Chen, Hongbing Zhang, David F. Nakamura, Kevin P. Quinn, Ted A. Yednock, John-Michael Sauer



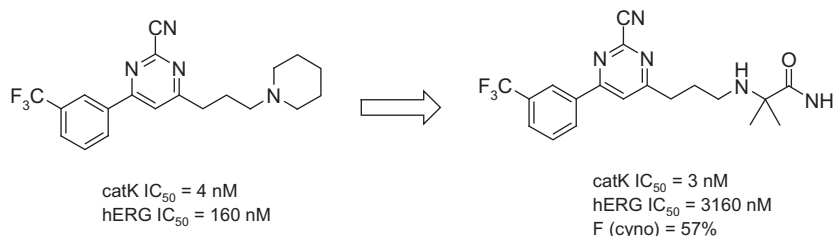
In this Letter, we describe our efforts to design HEA BACE-1 inhibitors that are highly permeable coupled with negligible levels of permeability-glycoprotein activity. These efforts culminate in producing **16** which lowers A $\beta$  by 28% and 32% in the cortex and CSF, respectively, in the *wild type* preclinical Hartley guinea pig animal model when dosed orally at 30 mpk BID for 2.5 days.

**Optimisation of 2-cyano-pyrimidine inhibitors of cathepsin K: Improving selectivity over hERG**

pp 6237–6241

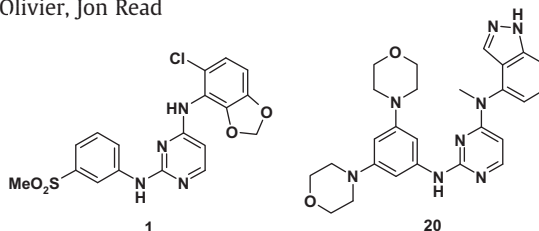
Zoran Rankovic\*, Jiaqiang Cai, Jennifer Kerr, Xavier Fradera, John Robinson, Ashvin Mistry, William Finlay, George McGarry, Fiona Andrews, Wilson Caulfield, Iain Cumming, Maureen Dempster, John Waller, Wullie Arbuckle, Mark Anderson, Iain Martin, Ann Mitchell, Clive Long, Mark Baugh, Paul Westwood, Emma Kinghorn, Phil Jones, Joost C. M. Uitdehaag, Mario van Zeeland, Dominique Potin, Laurent Saniere, Andre Fouquet, François Chevallier, Hortense Deronzier, Cecile Dorleans, Eric Nicolai

Structure-guided optimisation strategies which led to a successful attenuation of hERG block in 2-cyano-pyrimidine series of catK inhibitors are described.

**Inhibitors of the tyrosine kinase EphB4. Part 3: Identification of non-benzodioxole-based kinase inhibitors**

pp 6242–6245

Catherine Bardelle, Bernard Barlaam\*, Nigel Brooks, Tanya Coleman, Darren Cross, Richard Ducray, Isabelle Green, Christine Lambert-van der Brempt, Annie Olivier, Jon Read

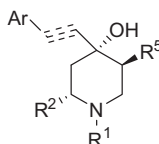


Starting from the initial bis-anilinopyrimidine **1**, good potency against EphB4 was retained when the benzodioxole at C-4 was replaced by an indazole. The key interactions of the indazole with the protein were characterised by crystallographic studies. Further optimisation led to compound **20**, a potent inhibitor of the EphB4 and Src kinases with good pharmacokinetics in various preclinical species and high fraction unbound in plasma. Compound **20** may be used as a tool for evaluating the potential of EphB4 kinase inhibitors in vivo.

**Investigation of 4-piperidinols as novel H<sub>3</sub> antagonists**

pp 6246–6249

James T. Anderson\*, Michael Campbell, Jianmin Wang, Kurt R. Brunden, John J. Harrington, Alain Stricker-Krongrad, Jianping Song, Chris Doucette, Steven Murphy, Youssef L. Bennani

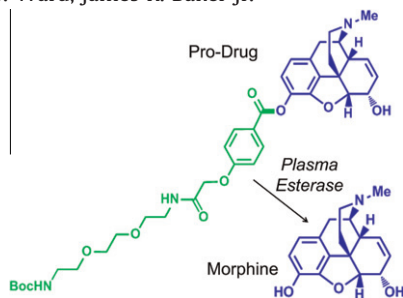


Compounds containing a substituted 4-piperidinol core have been found to be potent antagonists of the human H<sub>3</sub> receptor and showed a low binding affinity for the hERG channel.

**Plasma-mediated release of morphine from synthesized prodrugs**

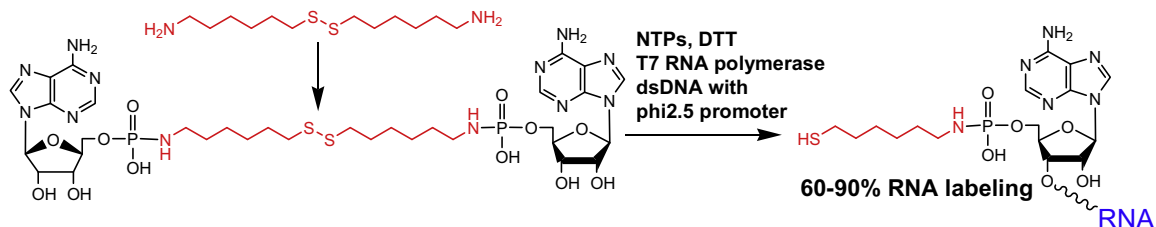
pp 6250–6253

Thommey P. Thomas\*, Baohua Huang, Ankur Desai, Hong Zong, Xue-min Cheng, Alina Kotlyar, Pascale R. Leroueil, Thomas Dunham, Abraham van der Spek, Brent B. Ward, James R. Baker Jr.\*

**Synthesis of symmetrical thiol-adenosine conjugate and 5' thiol-RNA preparation by efficient one-step transcription**

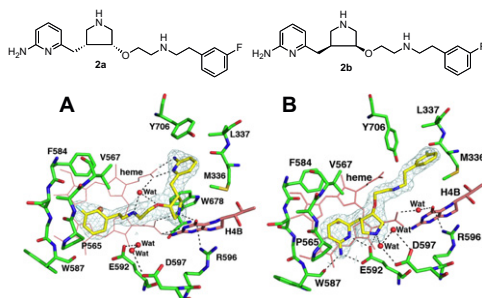
pp 6254–6257

Faqing Huang\*, Yongliang Shi

**Peripheral but crucial: A hydrophobic pocket (Tyr<sup>706</sup>, Leu<sup>337</sup>, and Met<sup>336</sup>) for potent and selective inhibition of neuronal nitric oxide synthase**

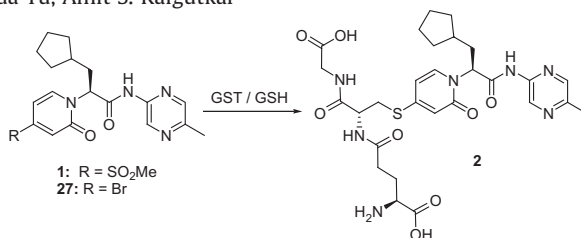
pp 6258–6261

Fengtian Xue, Huiying Li, Jianguo Fang, Linda J. Roman, Pavel Martásek, Thomas L. Poulos\*, Richard B. Silverman\*

**Intrinsic electrophilicity of the 4-methylsulfonyl-2-pyridone scaffold in glucokinase activators: Role of glutathione-S-transferases and in vivo quantitation of a glutathione conjugate in rats**

pp 6262–6267

John Litchfield, Raman Sharma, Karen Atkinson, Kevin J. Filipinski, Stephen W. Wright, Jeffrey A. Pfefferkorn, Beijing Tan, Rachel E. Kosa, Benjamin Stevens, Meihua Tu, Amit S. Kalgutkar\*

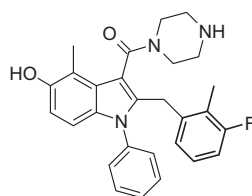


The role of glutathione-S-transferase in the nucleophilic displacement reaction on 4-substituted-2-pyridone derivatives by glutathione (GSH) was examined. The principal in vivo clearance mechanism of **1** in rats involved GSH conjugation leading to the formation of **2**.

**Discovery and optimization of a new class of potent and non-chiral indole-3-carboxamide-based renin inhibitors**

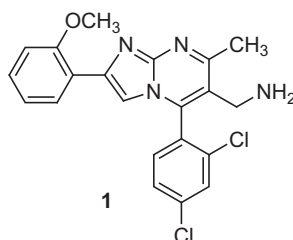
pp 6268–6272

Bodo Scheiper\*, Hans Matter, Henning Steinhagen, Ulrich Stolz, Zsolt Böcskei, Valérie Fleury, Gary McCort

Renin-Inhibitor ( $IC_{50} = 0.002 \mu M$ )**Synthesis, SAR, and atropisomerism of imidazopyrimidine DPP4 inhibitors**

pp 6273–6276

Stephen P. O'Connor\*, Ying Wang, Ligaya M. Simpkins, Robert P. Brigance, Wei Meng, Aiyang Wang, Mark S. Kirby, Carolyn A. Weigelt, Lawrence G. Hamann

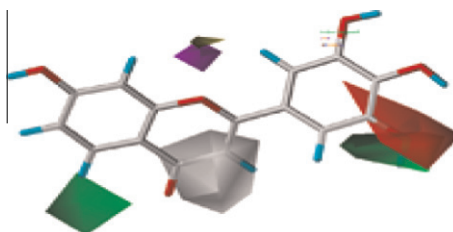


The synthesis and SAR of aminomethyl-substituted imidazopyrimidine DPP4 inhibitors bearing varied pendant aryl groups is described. Compound **1**, which exists as a separable mixture of non-interconvertible atropisomers was used as the starting point for investigation. The effects of substituent pattern and type as well as stereochemical effects on inhibitor potency are discussed.

**Isoflavone derivatives inhibit NF-κB-dependent transcriptional activity**

pp 6277–6281

Sunhee Lee, Kyung Chan Lim, Soon Young Shin, Young Han Lee\*

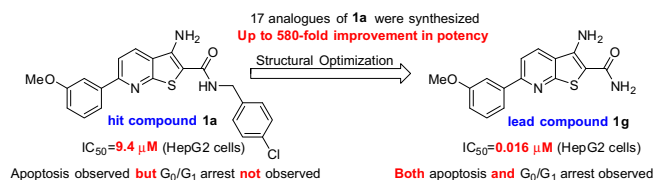


Isoflavones are known to have anti-inflammatory and anti-tumor activities, due, in part, to inhibition of NF-κB activity. However, the structural moiety of isoflavones responsible for the inhibition of NF-κB is not clearly understood. In this work, structure–activity relationships of isoflavone derivatives were examined with regard to NF-κB inhibition, using CoMFA and CoMSIA.

**Novel thienopyridine derivatives as specific anti-hepatocellular carcinoma (HCC) agents: Synthesis, preliminary structure–activity relationships, and in vitro biological evaluation**

pp 6282–6285

Xiu-Xiu Zeng, Ren-Lin Zheng, Tian Zhou, Hai-Yun He, Ji-Yan Liu, Yu Zheng, Ai-Ping Tong, Ming-Li Xiang, Xiang-Rong Song, Sheng-Yong Yang, Luo-Ting Yu, Yu-Quan Wei, Ying-Lan Zhao\*, Li Yang\*



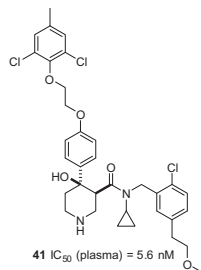
Among 17 analogues of **1a**, the most potent analog **1g** possesses hepatocellular carcinoma (HCC)-specific anticancer activity. It was inactive toward a panel of five different types of human cancer cell lines.



**Design and optimization of new piperidines as renin inhibitors**

pp 6286–6290

Olivier Corminboeuf, Olivier Bezençon\*, Corinna Grisostomi, Ľuboš Remeň, Sylvia Richard-Bildstein, Daniel Bur, Lars Prade, Patrick Hess, Panja Strickner, Walter Fischli, Beat Steiner, Alexander Treiber



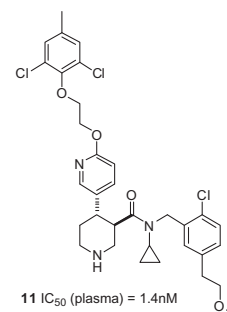
A novel series of piperidine-based renin inhibitors with improved efficacy in a double transgenic rat model is reported. Piperidines such as **41** ( $IC_{50}$  in plasma = 5.6 nM) showed high efficacy on blood pressure reduction (–36 mmHg) at low dose (3 mg/kg).

**Piperidine-based renin inhibitors: Upper chain optimization**

pp 6291–6296

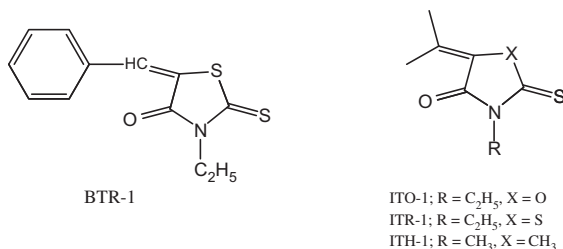
Olivier Corminboeuf, Olivier Bezençon\*, Ľuboš Remeň, Corinna Grisostomi, Sylvia Richard-Bildstein, Daniel Bur, Lars Prade, Panja Strickner, Patrick Hess, Walter Fischli, Beat Steiner, Alexander Treiber

The optimization of the 4-position of 3,4-disubstituted piperidine-based renin inhibitors is reported herein. This work culminated in the discovery of **11**, a renin inhibitor with a suitable profile for development.

**Novel rhodanine derivatives induce growth inhibition followed by apoptosis**

pp 6297–6301

Balaji T. Moorthy, Subban Ravi\*, Mrinal Srivastava, Kishore K. Chiruvella, H. Hemlal, Omana Joy, Sathees C. Raghavan\*

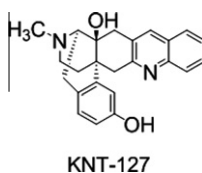


We have designed and synthesized three novel compounds, 5-isopropylidene derivatives of 3-dimethyl-2-thiohydantoin (ITH-1), 3-ethyl-2-thio-2,4-oxazolidinedione (ITO-1), and 5-benzylidene-3-ethyl rhodanine (BTR-1), and have tested their chemotherapeutic properties using different assays. We find that among the three compounds, BTR-1 is most potent.

**Design and synthesis of KNT-127, a  $\delta$ -opioid receptor agonist effective by systemic administration**

pp 6302–6305

Hiroshi Nagase\*, Toru Nemoto, Ayaka Matsubara, Manabu Saito, Naoshi Yamamoto, Yumiko Osa, Shigeto Hirayama, Mayumi Nakajima, Kaoru Nakao, Hidenori Mochizuki, Hideaki Fujii

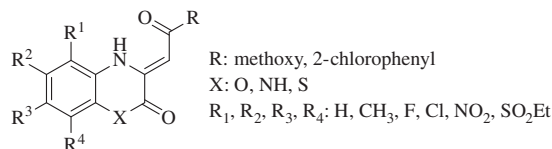


We designed novel  $\delta$ -agonists, effective in systemic administration. One of the agonists, KNT-127, is expected to be a useful tool to clarify the real pharmacological effects mediated via the  $\delta$ -receptor including analgesia and addiction.

## Synthesis and SAR studies of 1,4-benzoxazine MenB inhibitors: Novel antibacterial agents against *Mycobacterium tuberculosis*

pp 6306–6309

Xiaokai Li, Nina Liu, Huaning Zhang, Susan E. Knudson, Richard A. Slayden\*, Peter J. Tonge\*



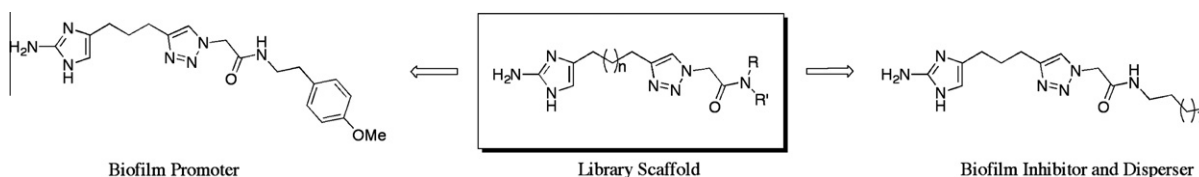
Several 1,4-benzoxazines were identified in a HTS directed at MenB, the 1,4-dihydroxy-2-naphthoyl-CoA synthase in the *Mycobacterium tuberculosis* menaquinone biosynthesis pathway. Subsequent SAR studies resulted in the discovery of compounds with MIC values as low as 0.6 µg/ml against H37Rv.



## Modulating the development of *E. coli* biofilms with 2-aminoimidazoles

pp 6310–6312

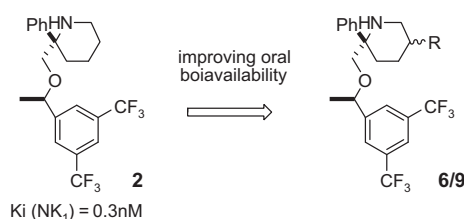
Catherine S. Reed, Robert W. Huigens III, Steven A. Rogers, Christian Melander\*



## Discovery of a series of potent, orally active $\alpha,\alpha$ -disubstituted piperidine NK<sub>1</sub> antagonists

pp 6313–6315

Dong Xiao\*, Cheng Wang, Anandan Palani, Hon-Chung Tsui, Gregory Reichard, Sunil Paliwal, Neng-Yang Shih, Robert Aslanian, Ruth Duffy, Jean Lachowicz, Geoffrey Varty, Cynthia Morgan, Fei Liu, Amin Nomeir

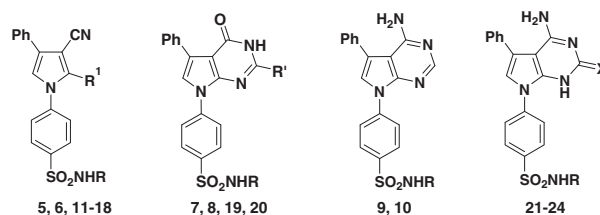


Modification of prototype NK<sub>1</sub> antagonist **2** resulted in the synthesis of a series of simple amides **6** and retroamides **9**. These compounds were shown to be potent and orally active NK<sub>1</sub> antagonists.

## Synthesis of novel pyrrole and pyrrolo[2,3-*d*]pyrimidine derivatives bearing sulfonamide moiety for evaluation as anticancer and radiosensitizing agents

pp 6316–6320

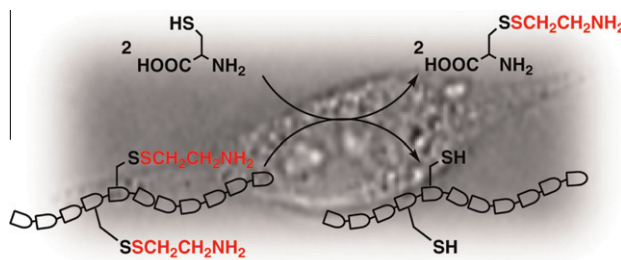
Mostafa M. Ghorab, Fatma A. Ragab, Helmy I. Heiba, Hanan A. Youssef, Marwa G. El-Gazzar\*



**A retro-inverso TAT-like peptide designed to deliver cysteamine to cells**

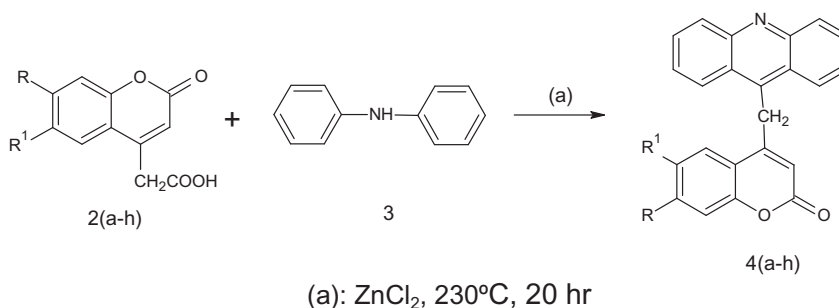
pp 6321–6323

Jongdoo Lim, Jean-Philippe Pellois, Eric E. Simanek\*

**Bernthsen synthesis, antimicrobial activities and cytotoxicity of acridine derivatives**

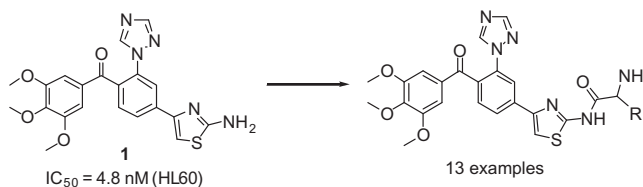
pp 6324–6326

Mehul M. Patel, Mimansha D. Mali, Saurabh K. Patel\*

**Discovery of a potent tubulin polymerization inhibitor: Synthesis and evaluation of water-soluble prodrugs of benzophenone analog**

pp 6327–6330

Jaekwang Lee, Suyeal Bae, Seo-hee Lee, Hojin Choi, Young Hoon Kim, Soo Jin Kim, Gyu Tae Park, Seung Kee Moon, Dal-Hyun Kim, Sungsook Lee, Soon Kil Ahn, Nam Song Choi, Kyung Joo Lee\*



Synthesis and evaluation of various amino acid prodrugs of **1** led to the discovery of **3-HCl** (R = (S)-isopropyl) which was shown to have potent antitumor efficacy in mouse xenografts. Pharmacokinetic study in rats was also described.

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\* 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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