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# Bioorganic & Medicinal Chemistry

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## Bioorganic & Medicinal Chemistry Volume 18, Issue 21, 2010

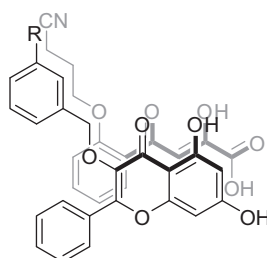
### Contents

#### ARTICLES

##### 3-O-Arylmethylgalangin, a novel isostere for anti-HCV 1,3-diketoacids (DKAs)

pp 7331–7337

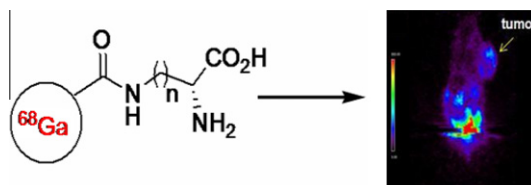
Hyo Seon Lee, Kwang-su Park, Bokhui Lee, Dong-Eun Kim, Youhoon Chong\*



##### Synthesis and evaluation of macrocyclic amino acid derivatives for tumor imaging by gallium-68 positron emission tomography

pp 7338–7347

Dinesh Shetty, Jae Min Jeong\*, Chang Hwan Ju, Young Ju Kim, Ji-Youn Lee, Yun-Sang Lee, Dong Soo Lee, June-Key Chung, Myung Chul Lee



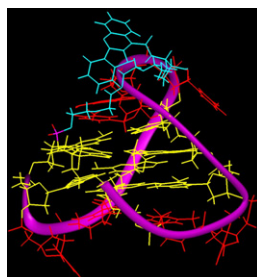
We have developed series of macrocyclic-amino acid derivatives for  $^{68}\text{Ga}$  labeling and evaluated for tumor PET imaging.



##### Synthesis and structural properties of oligonucleotides covalently linked to acridine and quindoline derivatives through a threoninol linker

pp 7348–7356

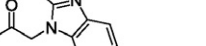
Anna Aviñó, Stefania Mazzini\*, Rubén Ferreira, Ramon Eritja\*



Acridine and quindoline derivatives linked to DNA stabilize duplex and quadruplex structures.

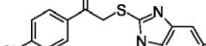


## pp 7357–7364




**3a-k**

**a:** R=H;  
**b:** R=Me;  
**c:** R=CH<sub>2</sub>OH;  
**d:** CH<sub>2</sub>Ph;  
**e:** CH<sub>2</sub>Me;  
**f:** (CH<sub>2</sub>)<sub>3</sub>Me;




**3l-n**

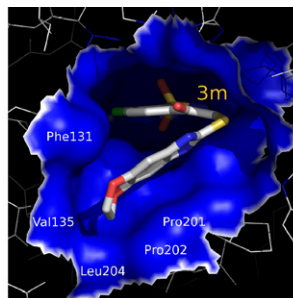
**l:** R' = H  
**m:** R' + R' = OCH<sub>2</sub>CH<sub>2</sub>O  
**n:** R' = Br, R' = H



**3o**

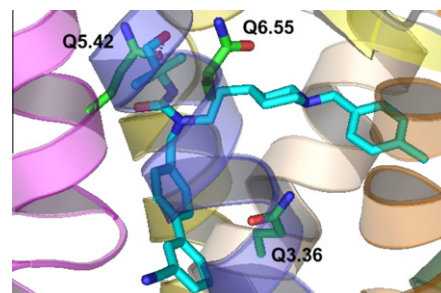
**g:** R=(CH<sub>2</sub>)<sub>3</sub>Me;  
**h:** R=CHMe<sub>2</sub>;  
**i:** R=CH<sub>2</sub>CHMe<sub>2</sub>;  
**j:** CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O;  
**k:** SMe





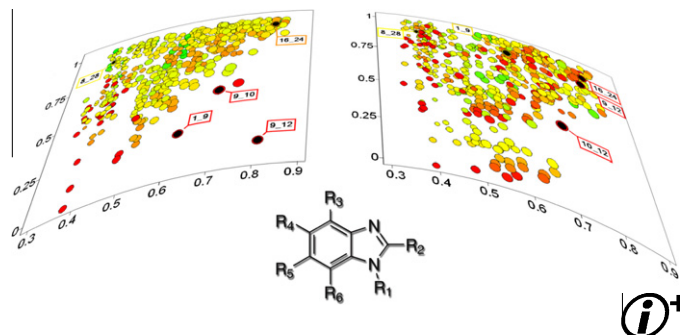
**pp 7365–7379**

Molecular modeling and docking studies of two new series of MCHR1 antagonists to the receptor suggest an important role for two glutamines (Gln5.42 and Gln6.55) in the affinity and selectivity to the MCHR1 receptor.



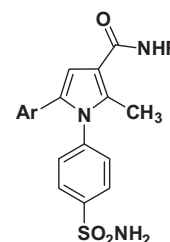
**pp 7380–7391**

Herein we present a quantitative description of the structure–activity relationships of several benzimidazoles tested against *Trichomonas vaginalis* and *Giardia intestinalis* using the emerging concept of activity landscape.



**pp 7392-7401**

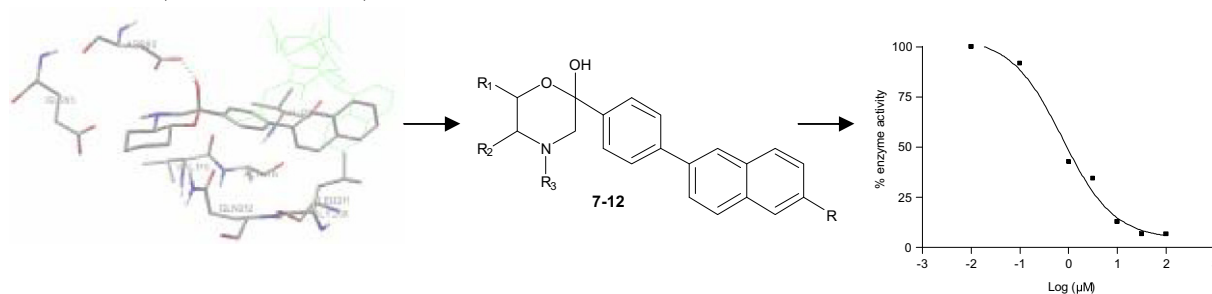
We report the synthesis and the pharmacological evaluation of a new class of human carbonic anhydrase (hCA) inhibitors, 1,5-diarylpyrrole-3-carboxamides. A molecular modeling study was conducted in order to simulate the binding mode of this new family of enzyme inhibitors within the active site of hCA IX.



**Design of more potent squalene synthase inhibitors with multiple activities**

pp 7402–7412

Angeliki P. Kourounakis\*, Alexios N. Matralis, Anastasios Nikitakis

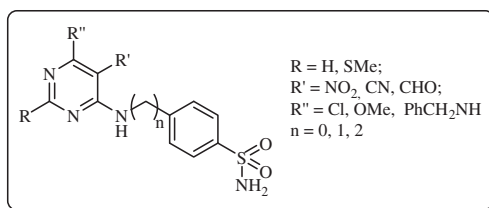


Antihyperlipidemic morpholine derivatives (**1–6**), combining several pharmacophore moieties, were evaluated in vitro and in vivo and optimized towards more active SQS inhibitors (**7–12**).

**4-[N-(Substituted 4-pyrimidinyl)amino]benzenesulfonamides as inhibitors of carbonic anhydrase isozymes I, II, VII, and XIII**

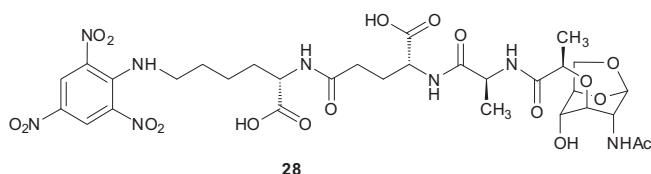
pp 7413–7421

Jurgis Sūdžius, Lina Baranauskienė, Dmitriy Golovenko, Jurgita Matulienė, Vilma Michailovienė, Jolanta Torresan, Jelena Jachno, Rasa Sukackaitė, Elena Manakova, Saulius Gražulis, Sigita Tumkevičius, Daumantas Matulis\*

**1,6-AnhMurNAc derivatives for assay development of amidase AmiD**

pp 7422–7431

Frédéric Mercier, Astrid Zervosen, Nathalie Teller, Jean-Marie Frère, Raphaël Herman, Anne Pennartz, Bernard Joris, André Luxen\*

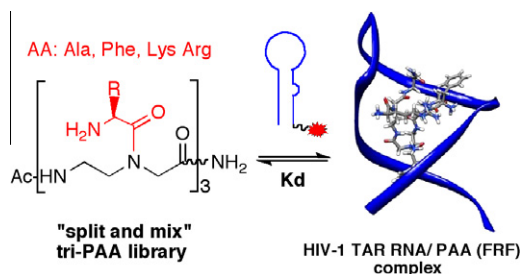


Peptide 1,6-anhMurNAc derivatives were obtained easily in good yield using a solid support synthesis. Biological studies with sAmiD showed that anhMurNAc-L-Ala-γ-D-Glu-L-Lys **28** with TNB as chromophoric group on the ε-amino group of L-Lys is a good candidate for the development of a sensitive enzyme assay of sAmiD.

**Polyamide Amino Acids trimers as TAR RNA ligands and anti-HIV agents**

pp 7432–7438

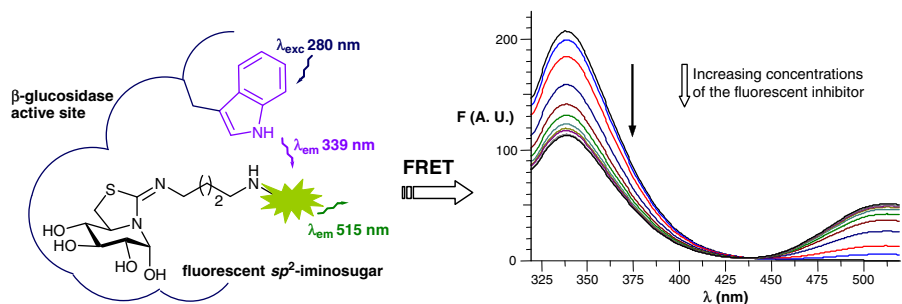
Vanessa Bonnard, Lise Pascale, Stéphane Azoulay, Audrey Di Giorgio, Christine Rogez-Kreuz, Karine Storck, Pascal Clayette, Nadia Patino\*



### Fluorescent-tagged $sp^2$ -iminosugars with potent $\beta$ -glucosidase inhibitory activity

pp 7439–7445

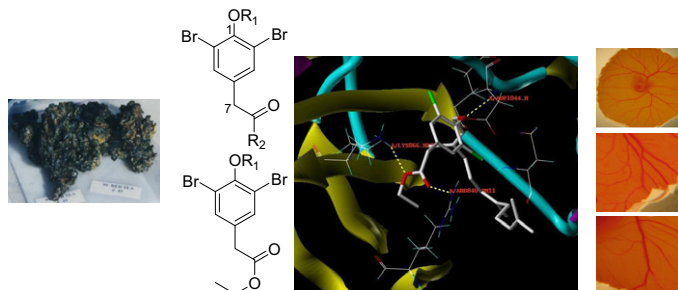
Matilde Aguilar-Moncayo, M. Isabel García-Moreno, Arnold E. Stütz, José M. García Fernández, Tanja M. Wrodnigg\*, Carmen Ortiz Mellet\*



### Design, synthesis, and biological evaluation of dibromotyrosine analogues inspired by marine natural products as inhibitors of human prostate cancer proliferation, invasion, and migration

pp 7446–7457

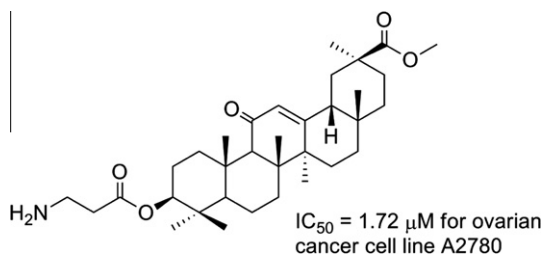
Asmaa A. Sallam, Sindhura Ramasahayam, Sharon A. Meyer, Khalid A. El Sayed\*



### Synthesis and antitumour activity of glycyrrhetic acid derivatives

pp 7458–7474

Stefan Schwarz, René Csuk\*

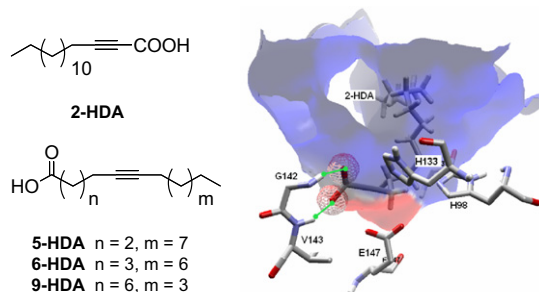


### 2-Hexadecynoic acid inhibits plasmodial FAS-II enzymes and arrests erythrocytic and liver stage *Plasmodium* infections

pp 7475–7485

Deniz Tasdemir\*, David Sanabria, Ina L. Lauinger, Alice Tarun, Rob Herman, Remo Perozzo, Mire Zloh, Stefan H. Kappe, Reto Brun, Néstor M. Carballeira\*

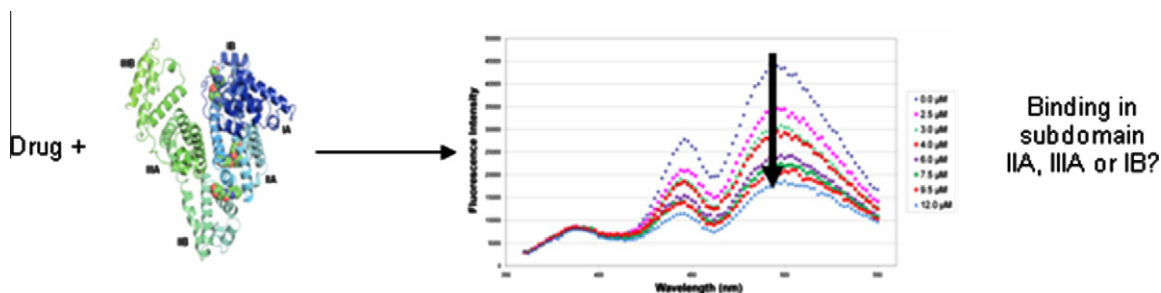
2-, 5-, 6-, and 9-hexadecynoic acids (HDAs) were synthesized and evaluated in vitro against various parasitic protozoa. 2-HDA inhibited both liver and blood stage *Plasmodium* infections and multiple plasmodial FAS-II target enzymes. 2-HDA was further studied through enzyme kinetics, docking studies and for pharmacokinetic properties.



**A combined spectroscopic and crystallographic approach to probing drug–human serum albumin interactions**

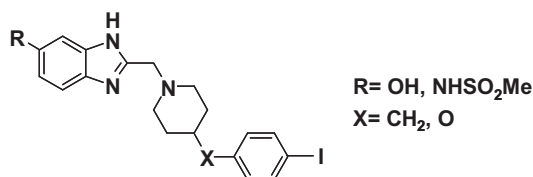
pp 7486–7496

David Buttar, Nicola Colclough, Stefan Gerhardt, Philip A. MacFaul\*, Scott D. Phillips, Alleyn Plowright, Paul Whittamore, Kin Tam, Klaus Maskos, Stefan Steinbacher, Holger Steuber

**Synthesis and biological evaluation of radio-iodinated benzimidazoles as SPECT imaging agents for NR2B subtype of NMDA receptor**

pp 7497–7506

Takeshi Fuchigami, Hiroshi Yamaguchi, Mikako Ogawa, Le Biao, Morio Nakayama, Mamoru Haratake, Yasuhiro Magata\*

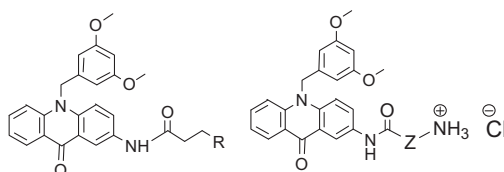


A series of radio-iodinated benzimidazole derivatives have been synthesized and evaluated in vitro and in vivo as potential SPECT tracers for imaging of the NR2B subtype of the NMDA receptor.

**Novel synthetic 2-amino-10-(3,5-dimethoxy)benzyl-9(10H)-acridinone derivatives as potent DNA-binding antiproliferative agents**

pp 7507–7514

Chunmei Gao, Feng Liu, Xudong Luan, Chunyan Tan, Hongxia Liu, Yonghua Xie, Yibao Jin, Yuyang Jiang\*

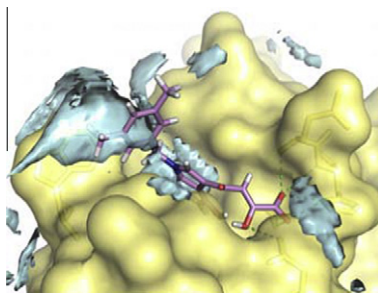


A novel series of 9(10H)-acridinone derivatives with terminal amino substituents at C2 position on the acridinone ring were designed and synthesized to studied for their antiproliferative activity and underlying mechanisms.

**Small molecules targeting the interaction between HIV-1 integrase and LEDGF/p75 cofactor**

pp 7515–7521

Laura De Luca\*, Stefania Ferro, Rosaria Gitto, Maria Letizia Barreca, Stefano Agnello, Frauke Christ, Zeger Debyser, Alba Chimirri

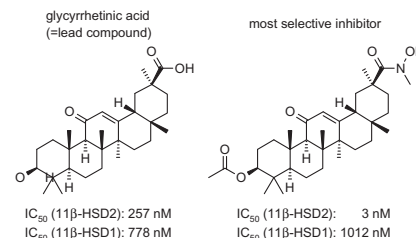


GRID approach was used to decipher structural requirements helpful to design and synthesize new inhibitors able to disrupt LEDGF/p75-IN binding.

## Synthesis of novel 3-amino and 29-hydroxamic acid derivatives of glycyrrhetic acid as selective 11 $\beta$ -hydroxysteroid dehydrogenase 2 inhibitors pp 7522–7541

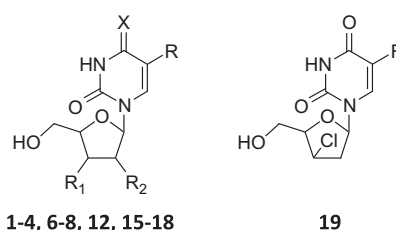
Christian Stanetty, Laszlo Czollner, Iris Koller, Priti Shah, Rawindra Gaware, Thierry Da Cunha, Alex Odermatt, Ulrich Joridis, Paul Kosma, Dirk Claßen-Houben\*

Starting from the natural compound glycyrrhetic acid a set of 11 $\beta$ -HSD2 selective inhibitors was prepared. The most potent and most selective compound is active against human 11 $\beta$ -HSD2 in the low nanomolar range with a 350-fold selectivity over human 11 $\beta$ -HSD1.



## Synthesis and in vitro antiviral activities of 3'-fluoro (or chloro) and 2',3'-difluoro 2',3'-dideoxynucleoside analogs against hepatitis B and C viruses pp 7542–7547

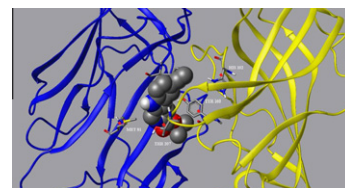
Naveen C. Srivastav, Neeraj Shakya, Michelle Mak, Chao Liang, D. Lorne J. Tyrrell, Babita Agrawal, Rakesh Kumar\*



## Design, synthesis, and subtype selectivity of 3,6-disubstituted $\beta$ -carbolines at Bz/GABA(A)ergic receptors. SAR and studies directed toward agents for treatment of alcohol abuse pp 7548–7564

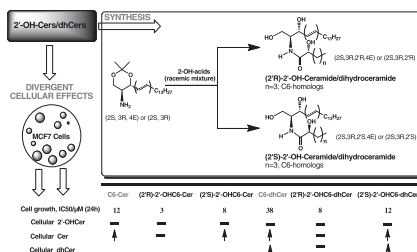
Wenyuan Yin, Samarpan Majumder, Terry Clayton, Steven Petrou, Michael L. VanLinn, Ojas A. Namjoshi, Chunrong Ma, Brett A. Cromer, Bryan L. Roth, Donna M. Platt, James M. Cook\*

A series of 3,6-disubstituted  $\beta$ -carbolines was synthesized and evaluated for their in vitro affinities at  $\alpha_4\beta_3\gamma_2$  GABA<sub>A</sub>/benzodiazepine receptor subtypes by radioligand binding assays in search of  $\alpha_1$  subtype selective ligands to treat alcohol abuse. Analogues of  $\beta$ -carboline-3-carboxylate-*t*-butyl ester ( $\beta$ CCT, **1**) were synthesized via a CDI-mediated process and the related 6-substituted  $\beta$ -carboline-3-carboxylates **6** including WYS8 (**7**) were synthesized via a Sonogashira or Stille coupling processes from 6-iodo- $\beta$ CCT (**5**). The bivalent ligands of  $\beta$ CCT (**32** and **33**) were also designed and prepared via a palladium-catalyzed homocoupling process to expand the structure–activity relationships (SAR) to larger ligands. Based on the pharmacophore/receptor model, a preliminary SAR study on 34 analogues illustrated that large substituents at position-6 of the  $\beta$ -carbolines were well tolerated. As expected, these groups are proposed to project into the extracellular domain (L<sub>DI</sub> region) of GABA<sub>A</sub>/Bz receptors (see **32** and **33**). Moreover, substituents located at position-3 of the  $\beta$ -carboline nucleus exhibited a conserved stereo interaction in lipophilic pocket L<sub>1</sub>, while N(2) presumably underwent a hydrogen bonding interaction with H<sub>1</sub>. Three novel  $\beta$ -carboline ligands ( $\beta$ CCT, 3PBC and WYS8), which preferentially bound to  $\alpha_1$  BzR subtypes permitted a comparison of the pharmacological efficacies with a range of classical BzR antagonists (flumazenil, ZK93426) from several different structural groups and indicated these  $\beta$ -carbolines were 'near GABA neutral antagonists'. Based on the SAR, the most potent (in vitro) selective ligand was the 6-substituted acetylenyl  $\beta$ CCT (WYS8, **7**). Earlier both  $\beta$ CCT and 3PBC had been shown to reduce alcohol self-administration in alcohol preferring (P) and high alcohol drinking (HAD) rats but had little or no effect on sucrose self-administration.<sup>1–3</sup> Moreover, these two  $\beta$ -carbolines were orally active, and in addition, were anxiolytic in P rats but were only weakly anxiolytic in rodents. These data prompted the synthesis of the  $\beta$ -carbolines presented here.



## Synthesis, NMR characterization and divergent biological actions of 2'-hydroxy-ceramide/dihydroceramide stereoisomers in MCF7 cells pp 7565–7579

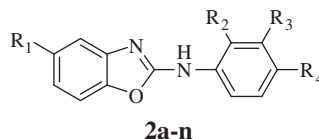
Zdzislaw M. Szulc, Aiping Bai, Jacek Bielawski, Nalini Mayroo, Doreen E. Miller, Hanna Gracz, Yusuf A. Hannun, Alicja Bielawska\*



**Synthesis and evaluation of benzoxazole derivatives as 5-lipoxygenase inhibitors**

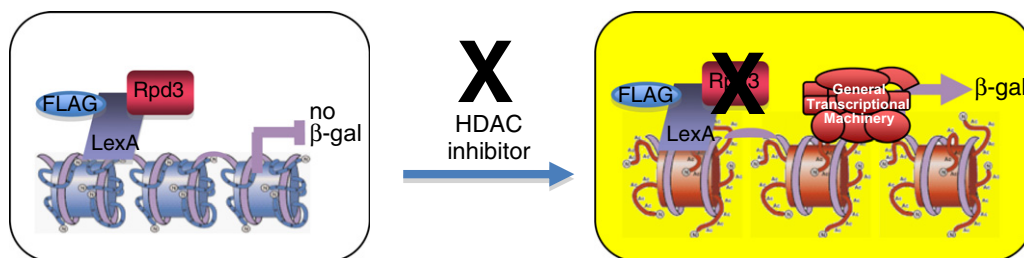
pp 7580–7585

Hyunmin Song, Sei-Ryang Oh, Hyeong-Kyu Lee, Gyoonee Han, Joo-Heon Kim, Hyeun Wook Chang, Kyung-Eun Doh, Hee-Kyung Rhee, Hea-Young Park Choo\*

**A histone deacetylase-dependent screen in yeast**

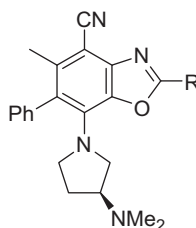
pp 7586–7592

Sujith V. W. Weerasinghe, Magdalene Wambua, Mary Kay H. Pflum\*

**1,3-Benzoxazole-4-carbonitrile as a novel antifungal scaffold of β-1,6-glucan synthesis inhibitors**

pp 7593–7606

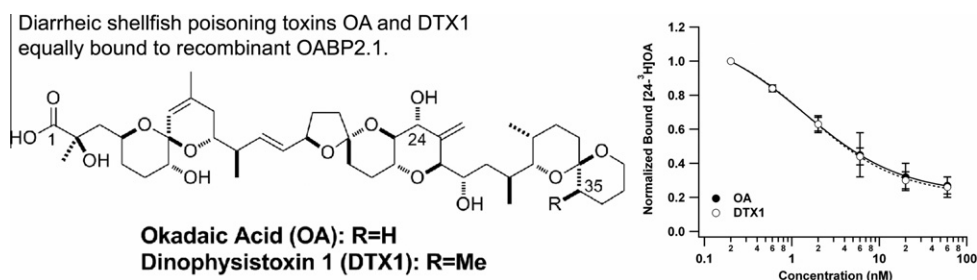
Jun-ichi Kuroyanagi\*, Kazuo Kanai, Yuuichi Sugimoto, Takao Horiuchi, Issei Achiwa, Hiroshi Takeshita, Katsuhiro Kawakami

We discovered 1,3-benzoxazole-4-carbonitrile as a novel scaffold of β-1,6-glucan synthesis inhibitors with potent antifungal activity against *Candida* species.**Binding of diarrhetic shellfish poisoning toxins to okadaic acid binding proteins purified from the sponge**

pp 7607–7610

***Halichondria okadae***

Keiichi Konoki\*, Kaori Saito, Hiroki Matsuura, Naoyuki Sugiyama, Yuko Cho, Mari Yotsu-Yamashita, Kazuo Tachibana

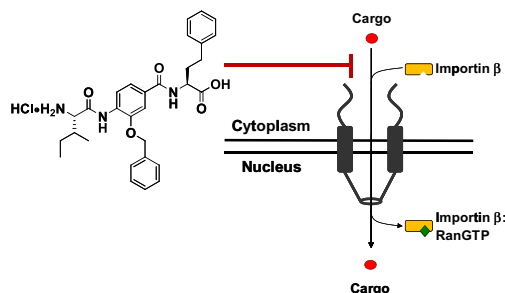




### Small molecule peptidomimetic inhibitors of importin $\alpha/\beta$ mediated nuclear transport

pp 7611–7620

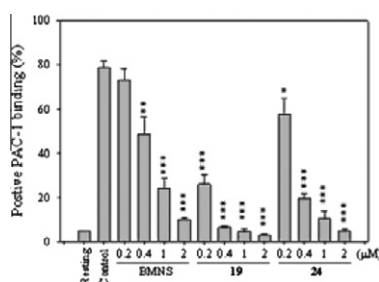
Géza Ambrus, Landon R. Whitby, Eric L. Singer, Oleg Trott, Euna Choi, Arthur J. Olson, Dale L. Boger, Larry Gerace\*



### The synthesis and biologic evaluation of anti-platelet and cytotoxic $\beta$ -nitrostyrenes

pp 7621–7627

Pei-Wen Hsieh\*, Yu-Ting Chang, Wen Yin Chuang, Hsin-Chu Shih, Shin-Zan Chiang, Chin-Chung Wu\*



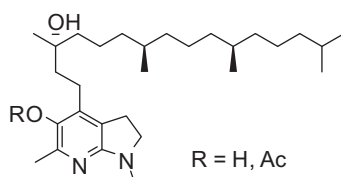
A series of  $\beta$ -nitrostyrenes were synthesized and subjected to anti-platelet aggregation assay and cytotoxicity assay. Most of them exhibited the most potent inhibitory effects on thrombin- and collagen-induced platelet aggregation.



### Design, synthesis, and evaluation of an $\alpha$ -tocopherol analogue as a mitochondrial antioxidant

pp 7628–7638

Jun Lu, Omar M. Khodour, Jeffrey S. Armstrong, Sidney M. Hecht\*

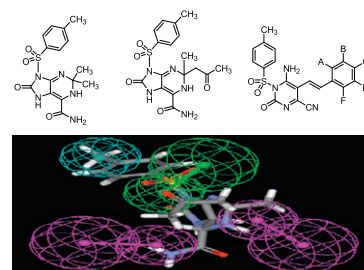


### A convenient synthesis and molecular modeling study of novel purine and pyrimidine derivatives as CDK2/cyclin A3 inhibitors

pp 7639–7650

Abdel-Sattar S. Hamad Elgazwy\*, Nasser S. M. Ismail, Heba S. A. Elzahabi

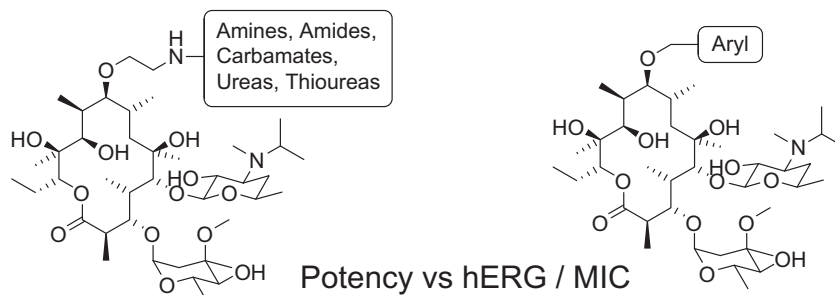
The manuscript describes the investigation of a series of novel purine and pyrimidine derivatives, which were prepared in good yield by using diaminomaleonitrile and tosylisocyanate in acetonitrile. Molecular modeling studies, including fitting to a 3D-pharmacophore model their docking into cyclin-dependent kinase2 (CDK2) active site were performed to understand the structural features of CDK2 inhibitors. Biological evaluation for both in vitro CDK2/cyclinA3 inhibition activity and antitumor activity in Ehrlich ascites carcinoma (EAC) cell based assay were also carried out.





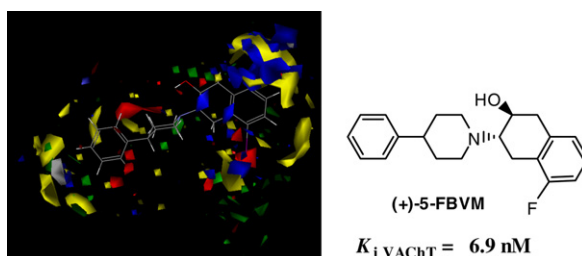
**9-Dihydroerythromycin ethers as motilin agonists—Developing structure–activity relationships for potency and safety** pp 7651–7658

Yaoquan Liu, Yong Li, David C. Myles, Mark Claypool, Christopher W. Carreras, Simon J. Shaw\*

**3D QSAR study, synthesis, and in vitro evaluation of (+)-5-FBVM as potential PET radioligand for the vesicular acetylcholine transporter (VACHT)**

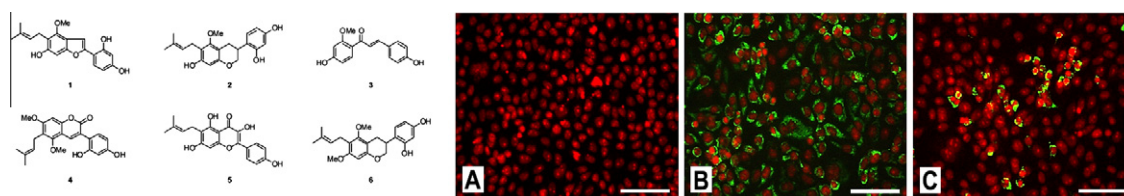
pp 7659–7667

Mitja Kovac, Sylvie Mavel\*, Winnie Deuther-Conrad, Nathalie Méheux, Jana Glöckner, Barbara Wenzel, Marko Anderluh, Peter Brust, Denis Guilloteau, Patrick Emond

**In vitro anti-rotavirus activity of polyphenol compounds isolated from the roots of *Glycyrrhiza uralensis***

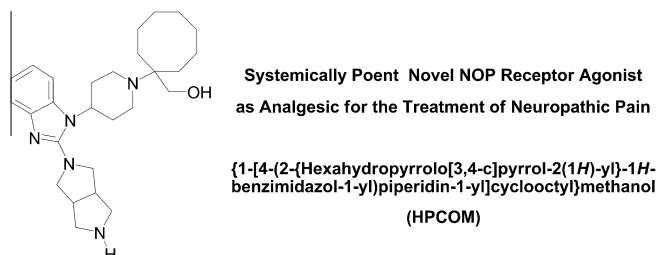
pp 7668–7674

Hyung-Jun Kwon, Ha-Hyun Kim, Young Bae Ryu, Jang Hoon Kim, Hyung Jae Jeong, Seung-Woong Lee, Jong Sun Chang, Kyoung-Oh Cho, Mun-Chual Rho, Su-Jin Park\*, Woo Song Lee\*

Polyphenols isolated from *Glycyrrhiza uralensis* have proven to be anti-rotavirus agents in vitro, acting by inhibiting both viral absorption and viral replication.**Discovery of {1-[4-(2-{hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-1H-benzimidazol-1-yl}piperidin-1-yl)-cyclooctyl}methanol, systemically potent novel non-peptide agonist of nociceptin/orphanin FQ receptor as analgesic for the treatment of neuropathic pain: Design, synthesis, and structure–activity relationships**


pp 7675–7699

Shigeo Hayashi\*, Eriko Nakata, Asato Morita, Kunihiro Mizuno, Kenzo Yamamura, Aki Kato, Katsuyo Ohashi



**OTHER CONTENT****Corrigendum****p 7700**

\*Corresponding author

\* Supplementary data available via ScienceDirect**COVER**

An insight into biologically relevant chemical space showing the scaffolds of potential natural-product based inhibitors orbiting their target, the protein structure of protein 11-beta steroid dehydrogenase (PDB code 1xu7). Graphic produced using Pymol (<http://www.pymol.org>). [M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, Charting biologically relevant chemical space: A structural classification of natural products (SCONP), *PNAS* **2005**, 102, 17272–17277 and S. Wetzel, H. Waldmann, Cheminformatic analysis of natural products and their chemical space, *Chimia* **2007**, 61(6), 355–360].

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