

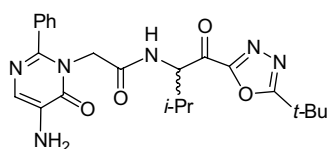
## Contents

### REVIEW

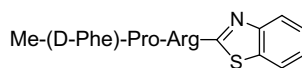
#### Inhibitors of proteases and amide hydrolases that employ an $\alpha$ -ketoheterocycle as a key enabling functionality

pp 1562–1595

Bruce E. Maryanoff\* and Michael J. Costanzo

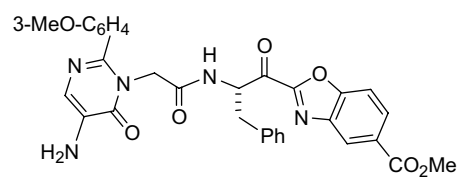


**6f**  $K_i$  (HNE) = 12 nM



**8a**

$K_i$  (human thrombin) = 0.2 nM



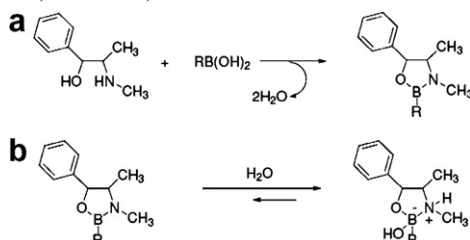
**52h**  $K_i$  (human chymase) = 4.8 nM

### ARTICLES

#### Oxazaborolidine derivatives inducing autoinducer-2 signal transduction in *Vibrio harveyi*

pp 1596–1604

R. Aharoni, M. Bronstheyn, A. Jabbour, B. Zaks, M. Srebnik and D. Steinberg\*

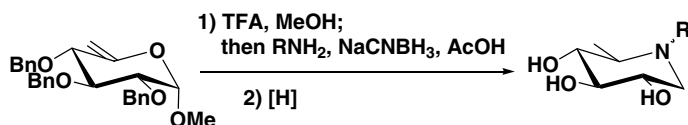


Five oxazaborolidine derivatives were synthesized as described. BNO-1 (R = phenyl) and BNO-5 (R = butyl) were found to have a strong positive effect on luminescence of *Vibrio harveyi* via AI-2 quorum sensing mechanism.

#### An expeditious one-pot synthesis of 1,6-dideoxy-*N*-alkylated nojirimycin derivatives and their inhibitory effects on the secretion of IFN- $\gamma$ and IL-4

pp 1605–1612

Jian Zhou, Yongmin Zhang, Xia Zhou, Jing Zhou, Li-He Zhang, Xin-Shan Ye\* and Xiao-Lian Zhang\*



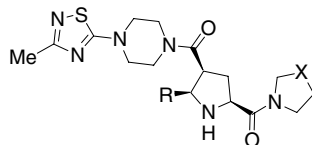
R = H, various alkyl groups

An efficient 'one-pot' approach to the synthesis of 1,6-dideoxy-*N*-alkylated nojirimycin derivatives in good yields and with high stereoselectivity was developed. The synthetic *N*-alkylated iminosugars showed inhibitory effects on the release of the cytokines IFN- $\gamma$  and IL-4 from the mouse splenocytes.

**Design and synthesis of DPP-IV inhibitors lacking the electrophilic nitrile group**

pp 1613–1631

Takashi Kondo\*, Takahiro Nekado, Isamu Sugimoto, Kenya Ochi, Shigeyuki Takai, Atsushi Kinoshita, Akira Hatayama, Susumu Yamamoto, Katsuya Kishikawa, Hisao Nakai and Masaaki Toda

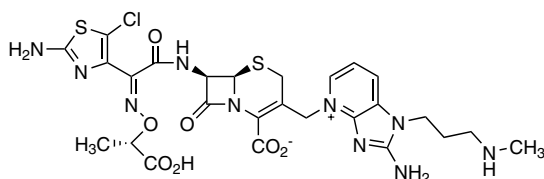


A series of 4β-[1-*N*-(sulfur-containing hetero-aryl)piperazin-4-ylcarbonyl]-L-prolylpyrrolidine analogs were synthesized as dipeptidyl peptidase IV (DPP-IV) inhibitor. The duration of ex vivo activity and the effect on the plasma glucose level were evaluated.

**A novel series of parenteral cephalosporins exhibiting potent activities against both *Pseudomonas aeruginosa* and other Gram-negative pathogens. Part 2: Synthesis and structure–activity relationships**

pp 1632–1647

Kenji Yamawaki,\* Takashi Nomura, Tatsuro Yasukata, Norihiko Tanimoto, Koichi Uotani, Hideaki Miwa, Yoshinori Yamano, Kei Takeda and Yasuhiro Nishitani

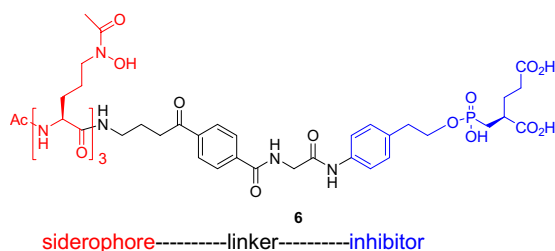


A novel series of 7β-[2-(2-amino-5-chloro-thiazol-4-yl)-2(Z)-((S)-1-carboxyethoxyimino)acetamido]cephalosporins bearing various pyridinium groups at the C-3' position were prepared, and their antibacterial activities were evaluated.

**Design and synthesis of a siderophore conjugate as a potent PSMA inhibitor and potential diagnostic agent for prostate cancer**

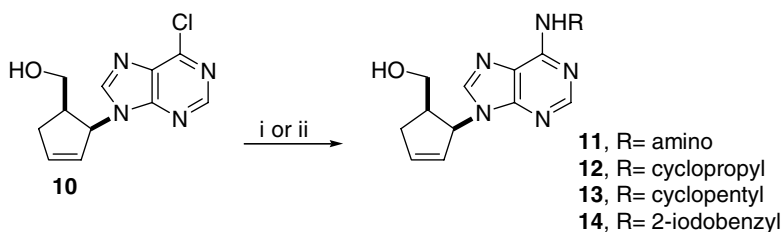
pp 1648–1657

Pingyu Ding, Paul Helquist and Marvin J. Miller\*

**New QSAR combined strategy for the design of A<sub>1</sub> adenosine receptor agonists**

pp 1658–1675

Maykel Pérez González,\* Pedro Besada, Maria José González Moa, Marta Teijeira and Carmen Terán\*

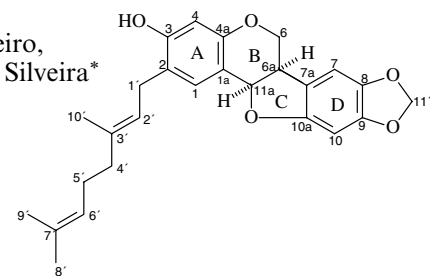


### Trypanocidal activity of a new pterocarpan and other secondary metabolites of plants from Northeastern Brazil flora

pp 1676–1682

Nashira Campos Vieira, Laila Salmen Espíndola,\* Jaime Martins Santana, Maria Leopoldina Veras, Otília Deusdênia Loiola Pessoa, Sávio Moita Pinheiro, Renata Mendonça de Araújo, Mary Anne Sousa Lima and Edilberto Rocha Silveira\*

This novel pterocarpan showed activity in vitro against epimastigote forms of *Trypanosoma cruzi* using the tetrazolium salt MTT as an alternative method.

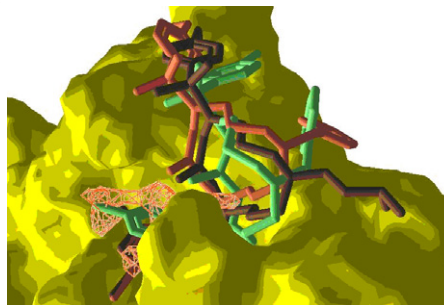


(-)-2-geranyl-3-hydroxy-8,9-methylenedioxypterocarpan

### Novel anti-HIV cyclotriazadisulfonamide derivatives as modeled by ligand- and receptor-based approaches

pp 1683–1690

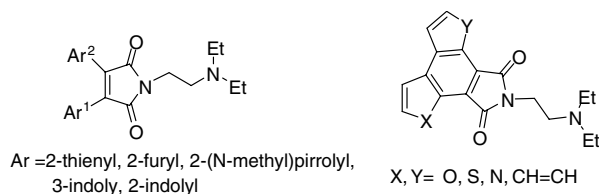
Júlia R. Pinheiro, Michelle Bitencourt, Elaine F. F. da Cunha,\* Teodorico C. Ramalho\* and Matheus P. Freitas\*



### Antiproliferative effects on human tumor cells and rat aortic smooth muscular cells of 2,3-heteroarylmaleimides and heterofused imides

pp 1691–1701

Nicola Ferri, Egle Maria Beccalli, Alessandro Contini, Alberto Corsini,\* Manuela Antonino, Tiziano Radice, Graziella Pratesi,\* Stella Tinelli, Franco Zunino and Maria Luisa Gelmi\*



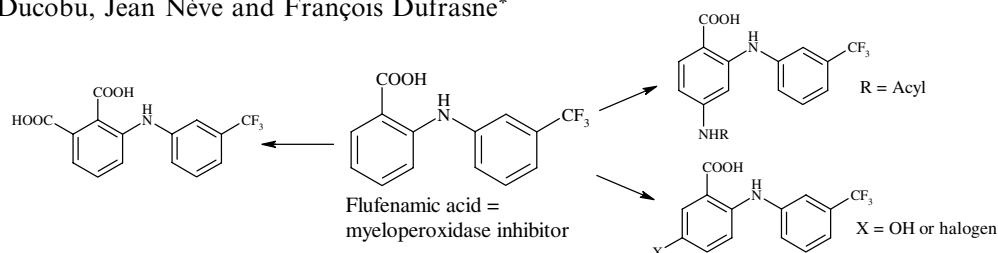
A series of 2,3-heteroarylmaleimides and polyheterocondensed imides were prepared and their antiproliferative activity was tested against human tumor cells (NCI-H460 lung carcinoma) and rat SMCs.

### Conception of myeloperoxidase inhibitors derived from flufenamic acid by computational docking and structure modification

pp 1702–1720

Pierre Van Antwerpen, Martine Prévost, Karim Zouaoui-Boudjeltia, Sajida Babar, I. Legssyer, Patrick Moreau, Nicole Moguilevsky, Michel Vanhaeverbeek, Jean Ducobu, Jean Nève and François Dufrasne\*

Improving myeloperoxidase inhibition by modification of the chemical structure of flufenamic acid was attempted, leading to slightly more active compounds in the halogen-substituted series.

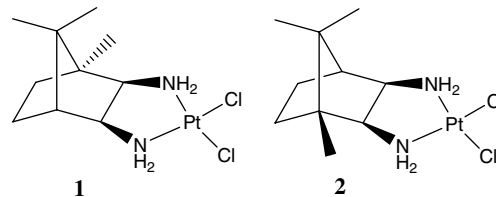


### Synthesis, characterization and antiproliferative studies of the enantiomers of *cis*-[(1,2-camphordiamine)dichloro]platinum(II) complexes

pp 1721–1737

Ángel M. Montaña,\* Francisco J. Bernal, Julia Lorenzo, Carlos Farnós, Consuelo Batalla, Maria J. Prieto, Virtudes Moreno, Francesc X. Avilés, Juan M. Mesas and María-Teresa Alegre

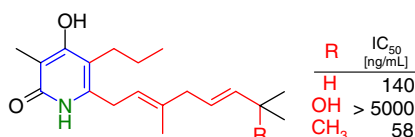
The platinum(II) complex (**1**) and its enantiomer (**2**) have been synthesized in four steps, starting from (1*S*)- and (1*R*)-camphorquinone, respectively. The interaction of the Pt(II) complexes with DNA was studied by circular dichroism, electrophoresis on agarose gel and atomic force microscopy. An important difference of cytotoxicity (IC<sub>50</sub>) in front of the HL-60 cell line was found between both enantiomers after 24 h of incubation.



### Iromycins from *Streptomyces* sp. and from synthesis: New inhibitors of the mitochondrial electron transport chain

pp 1738–1746

Frank Surup, Heydar Shojaei, Paultheo von Zezschwitz,\* Brigitte Kunze\* and Stephanie Grond\*



The iromycins reveal inhibitory activity on the mitochondrial electron transport chain at the site of complex I with only marginal cytotoxicity. Both, natural and synthetic derivatives were used for detailed SAR studies.

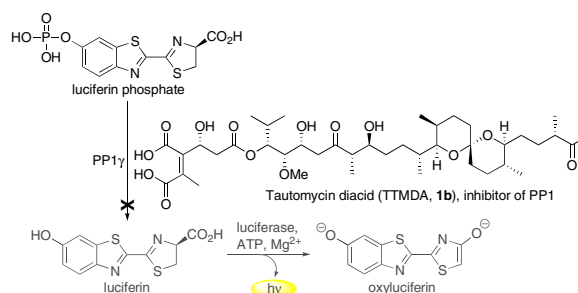


### Protein phosphatase inhibitory activity of tautomycin photoaffinity probes evaluated at femto-molar level

pp 1747–1755

Magne O. Sydnés, Masaki Kuse, Masakuni Kurono, Aya Shimomura, Hiroshi Ohinata, Akira Takai and Minoru Isobe\*

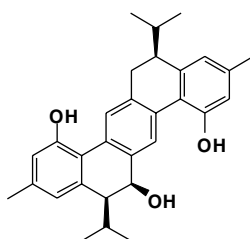
Development of a highly sensitive firefly bioluminescence assay system was, in fact, applied to ten tautomycin analogs having photoaffinity probes to obtain the *K<sub>i</sub>* values in the range of 3.4–213 nM, and one of them showed slightly higher activity than the natural tautomycin diacid derivative.



### A novel sesquiterpenoid dimer parviflorene F induces apoptosis by up-regulating the expression of TRAIL-R2 and a caspase-dependent mechanism

pp 1756–1763

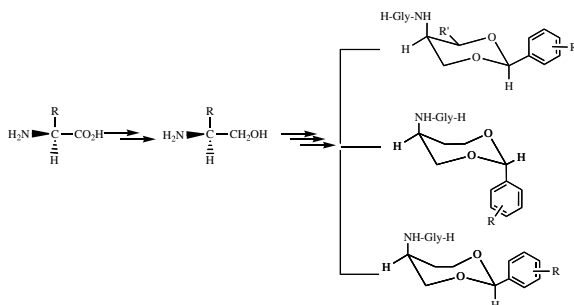
Takashi Ohtsuki, Mayu Tamaki, Kazuhumi Toume and Masami Ishibashi\*



**Toward the development of chemoprevention agents (III): Synthesis and anti-inflammatory activities of a new class of 5-glycylamino-2-substituted-phenyl-1,3-dioxacycloalkanes**

pp 1764–1774

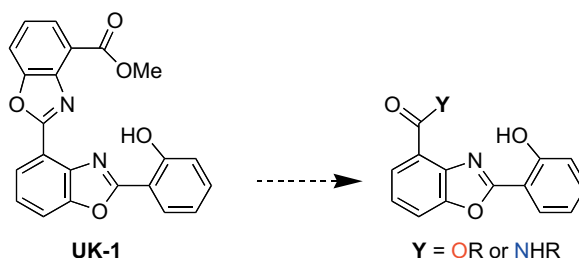
Lanrong Bi, Ming Zhao,\* Keli Gu, Chao Wang, Jingfang Ju\* and Shiqi Peng\*



**Synthesis, metal ion binding, and biological evaluation of new anticancer 2-(2'-hydroxyphenyl)benzoxazole analogs of UK-1**

pp 1775–1783

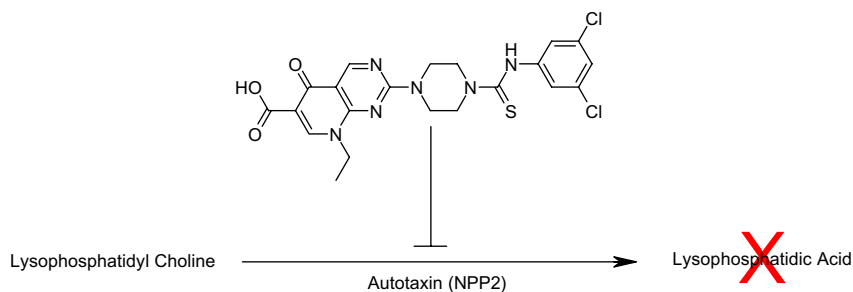
Mireya L. McKee and Sean M. Kerwin\*



**Virtual screening approaches for the identification of non-lipid autotaxin inhibitors**

pp 1784–1795

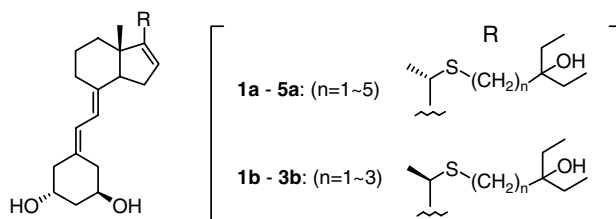
Abby L. Parrill,\* Uniqua Echols, Tran Nguyen, Truc-Chi T. Pham, Adrienne Hoeglund and Daniel L. Baker\*



**Synthesis and structure–activity relationships of 16-ene-22-thia-1 $\alpha$ ,25-dihydroxy-26,27-dimethyl-19-norvitamin D<sub>3</sub> analogs having side chains of different sizes**

pp 1796–1815

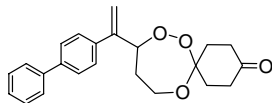
Hajime Takaku, Yukiko Miyamoto, Shiori Asami, Mika Shimazaki, Sachiko Yamada, Keiko Yamamoto, Nobuyuki Udagawa, Hector F. DeLuca and Masato Shimizu\*



**Orally active 1,2,4-trioxepanes: Synthesis and antimalarial activity of a series of 7-arylvinyl-1,2,4-trioxepanes against multidrug-resistant *Plasmodium yoelii* in Swiss mice**

pp 1816–1821

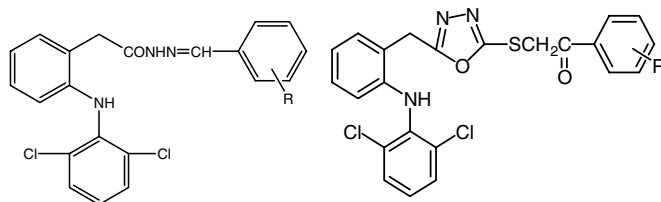
Chandan Singh,\* Shilpi Pandey, Malvika Sharma and Sunil K. Puri



**Design, Synthesis and Evaluation of Antiinflammatory, Analgesic and Ulcerogenicity studies of Novel S-Substituted phenacyl-1,3,4-oxadiazole-2-thiol and Schiff bases of Diclofenac acid as Nonulcerogenic Derivatives**

pp 1822–1831

Shashikant V. Bhandari,\* Kailash G. Bothara, Mayuresh K. Raut, Ajit A. Patil, Aniket P. Sarkate and Vinod J. Mokale

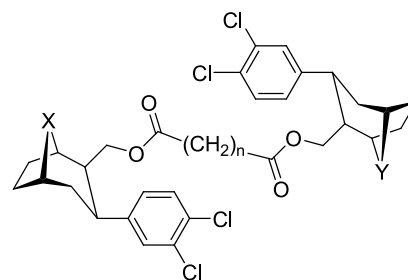


**The synthesis of bivalent 2β-carbomethoxy-3β-(3,4-dichlorophenyl)-8-heterobicyclo[3.2.1]octanes as probes for proximal binding sites on the dopamine and serotonin transporters**

pp 1832–1841

Peter C. Meltzer,\* Olga Kryatova, Duy-Phong Pham-Huu, Patrick Donovan and Aaron Janowsky

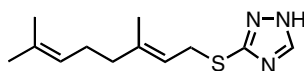
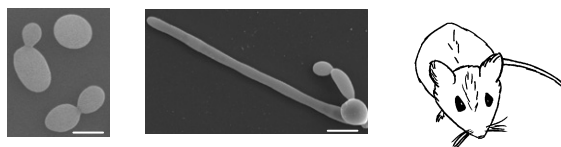
Bivalent tropane ligands do not yield evidence for the existence of proximal binding sites on the dopamine or serotonin transporters.



**Influence of heterocyclic and oxime-containing farnesol analogs on quorum sensing and pathogenicity in *Candida albicans***

pp 1842–1848

Roman Shchepin, Dhammika H. M. L. P. Navarathna, Raluca Dumitru, Shane Lippold, Kenneth W. Nickerson and Patrick H. Dussault\*

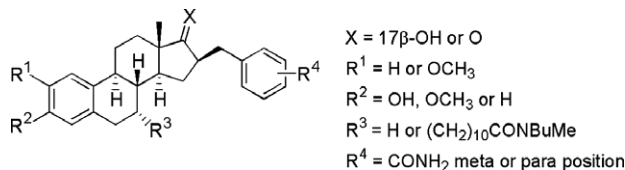


A series of farnesol analogs are potent quorum-sensing molecules for the human pathogen *Candida albicans*. Two of the most potent analogs display very different effects in a mammalian model of systemic candidiasis.

**Estradiol and estrone C-16 derivatives as inhibitors of type 1 17 $\beta$ -hydroxysteroid dehydrogenase: Blocking of ER<sup>+</sup> breast cancer cell proliferation induced by estrone**

pp 1849–1860

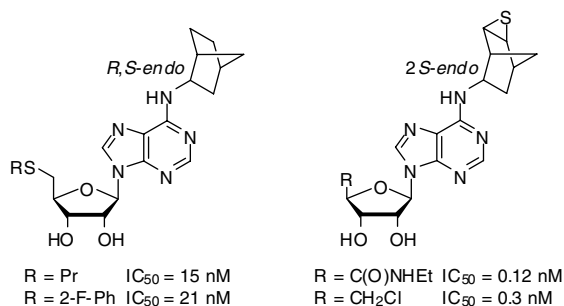
Yannick Laplante, Christine Cadot, Michelle-Audrey Fournier and Donald Poirier\*

**N<sup>6</sup>-substituted C5'-modified adenosines as A<sub>1</sub> adenosine receptor agonists**

pp 1861–1873

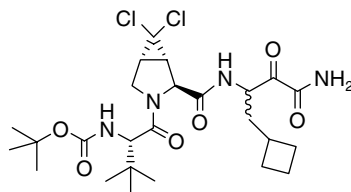
T. D. Ashton, Stephen P. Baker, Sally A. Hutchinson and Peter J. Scammells\*

Two series of 5'-modified ENBA analogues were synthesised and evaluated as A<sub>1</sub> adenosine receptor agonists. The ultimate goal of this research was to identify novel and potent partial agonists. However, in an unanticipated outcome, a number of highly potent full agonists were discovered.

**Potent and selective small molecule NS3 serine protease inhibitors of Hepatitis C virus with dichlorocyclopropylproline as P2 residue**

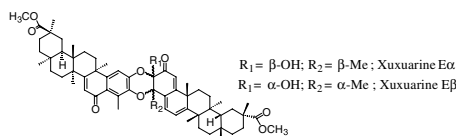
pp 1874–1883

Kevin X. Chen,\* Bantha Vibulbhan, Weiyang Yang, Kuo-Chi Cheng, Rong Liu, John Pichardo, Nancy Butkiewicz and F. George Njoroge

**Biomimetic synthesis of xuxuarines E $\alpha$  and E $\beta$ : Structure revision of *Rzedowskia* bistriterpenoids**

pp 1884–1889

Neil E. Jacobsen, E. M. Kithsiri Wijeratne, Joaquim Corsino, Maysa Furlan, Vanderlan da S. Bolzani and A. A. Leslie Gunatilaka\*

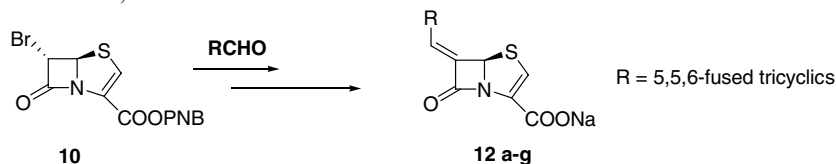


Biomimetic synthesis of the biscelastrols, xuxuarine E $\alpha$  and E $\beta$ , from pristimerin is reported leading to the revision of structures proposed for *Rzedowskia* bistriterpenoids I and II.

### 5,5,6-Fused tricycles bearing imidazole and pyrazole 6-methylidene penems as broad-spectrum inhibitors of $\beta$ -lactamases

pp 1890–1902

Aranapakam M. Venkatesan,\* Atul Agarwal, Takao Abe, Hideki Ushiroguchi, Mihira Ado, Takasaki Tsuyoshi, Osvaldo Dos Santos, Zhong Li, Gerry Francisco, Yang I. Lin, Peter J. Petersen, Youjun Yang, William J. Weiss, David M. Shlaes and Tarek S. Mansour



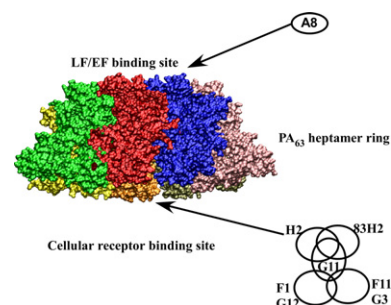
A series of novel 5,5,6-fused tricyclic-6-methylidene penems have been synthesized and were shown to be potent, broad spectrum  $\beta$ -lactamase inhibitors against class-A, class-B, and class-C enzymes. The present paper deals with the synthesis and structure–activity relationships of these derivatives.

### Selection and characterization of human antibodies neutralizing *Bacillus anthracis* toxin

pp 1903–1913

Bin Zhou, Charlotte Carney and Kim D. Janda\*

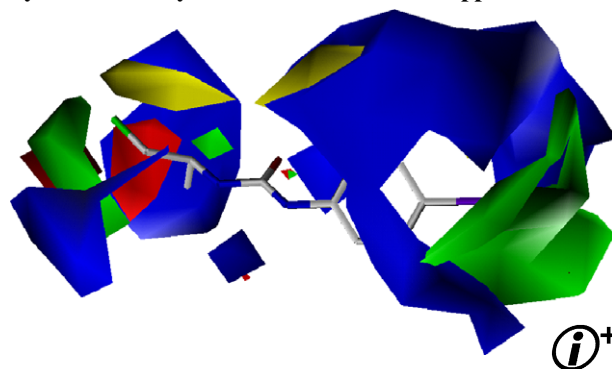
The selection and characterization of human monoclonal antibodies that can neutralize the toxicity of *B. anthracis* is described. The studies reported highlight each antibody's protection properties and potential neutralizing epitope(s).



### A comparative molecular field and comparative molecular similarity indices analyses (CoMFA and CoMSIA) of *N*-phenyl-*N'*-(2-chloroethyl)ureas targeting the colchicine-binding site as anticancer agents

pp 1914–1926

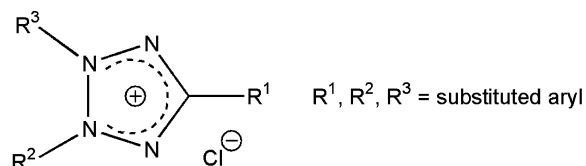
Sébastien Fortin,\* Philippe Labrie, Emmanuel Moreau, Lianhu Wei, Lakshmi P. Kotra and René C.-Gaudreault



### Anti-*Plasmodium* activity of tetrazolium salts

pp 1927–1947

Xilin Cui, Jason Z. Vlahakis, Ian E. Crandall and Walter A. Szarek\*



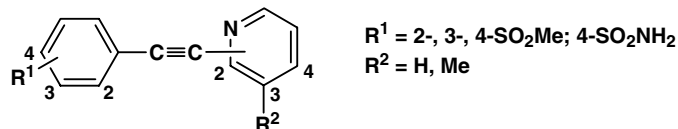
Novel tetrazolium salts have been synthesized that show potent and selective anti-*Plasmodium* activity.



**Synthesis and cyclooxygenase inhibitory activities of linear 1-(methanesulfonylphenyl or benzenesulfonamido)-2-(pyridyl)acetylene regioisomers**

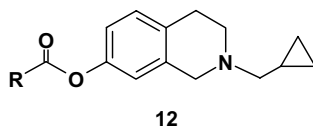
pp 1948–1956

Morshed Alam Chowdhury, Ying Dong, Qiao-Hong Chen,  
Khaled R. A. Abdellatif and Edward E. Knaus\*

**New 1,2,3,4-tetrahydroisoquinoline derivatives as modulators of proteolytic cleavage of amyloid precursor proteins**

pp 1957–1965

Ming-Kuan Hu,\* Yung-Feng Liao,\* Jung-Fang Chen, Bo-Jeng Wang,  
Ying-Tsen Tung, Hui-Ching Lin and Kang-Po Lee

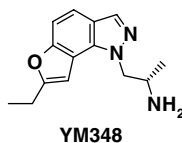


A type of *N*-cyclopropylmethyl-tetrahydroisoquinolines (**12**) was delicately synthesized and shown to possess both sAPP $\alpha$ -releasing stimulation and  $\gamma$ -secretase inhibitory potency in cell models.

**Synthesis and structure–activity relationships of a series of substituted 2-(1*H*-furo[2,3-*g*]indazol-1-yl)ethylamine derivatives as 5-HT<sub>2C</sub> receptor agonists**

pp 1966–1982

Itsuro Shimada,\* Kyoichi Maeno, Ken-ichi Kazuta, Hideki Kubota, Tetsuya Kimizuka,  
Yasuharu Kimura, Ken-ichi Hatanaka, Yuki Naitou, Fumikazu Wanibuchi,  
Shuichi Sakamoto and Shin-ichi Tsukamoto

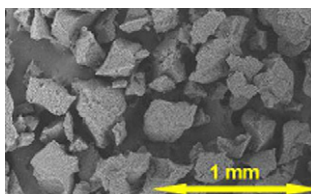


A novel series of indazole derivatives were prepared, and their binding affinities for 5-HT<sub>2C</sub> and 5-HT<sub>2A</sub> receptors were evaluated. Synthesis and structure–activity relationships, including in vivo evaluation, are discussed.

**Properties of flaky affinity resin with co-continuous structure**

pp 1983–1991

Tomoko Mori, Akito Tanaka, Takuya Kubo, Kunimitsu Kaya, Mari Sakamoto and Ken Hosoya\*



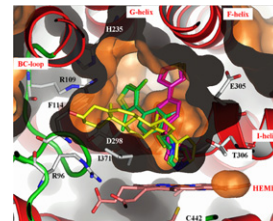
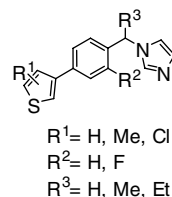
## Synthesis, biological evaluation and molecular modelling studies of methyleneimidazole substituted biaryls as inhibitors of human 17 $\alpha$ -hydroxylase-17,20-lyase (CYP17).

pp 1992–2010

### Part I: Heterocyclic modifications of the core structure

Carsten Jagusch, Matthias Negri, Ulrike E. Hille, Qingzhong Hu, Marc Bartels, Kerstin Jahn-Hoffmann, Mariano A. E. Pinto-Bazurco Mendieta, Barbara Rodenwaldt, Ursula Müller-Vieira, Dirk Schmidt, Thomas Lauterbach, Maurizio Recanatini, Andrea Cavalli and Rolf W. Hartmann\*

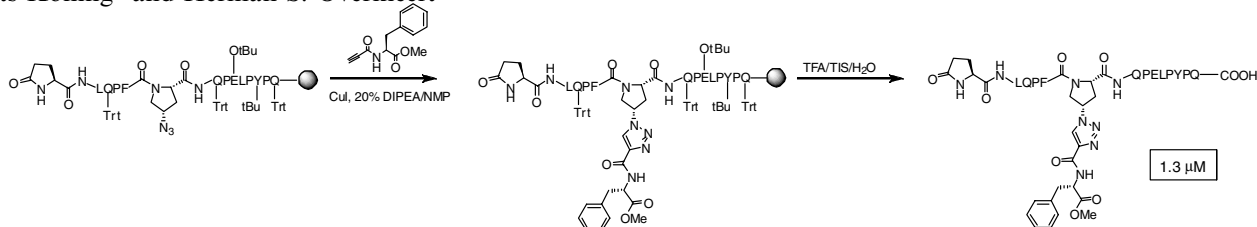
Some novel biaryl CYP17 inhibitors which are highly active in vitro and in vivo were discovered. Docking studies indicated two new binding modes different from steroidal inhibitors and substrates.



## Design of azidoproline containing gluten peptides to suppress CD4<sup>+</sup> T-cell responses associated with Celiac disease

pp 2053–2062

Varsha V. Kapoerchan, Martina Wiesner, Mark Overhand, Gijs A. van der Marel, Frits Koning\* and Herman S. Overkleeft\*



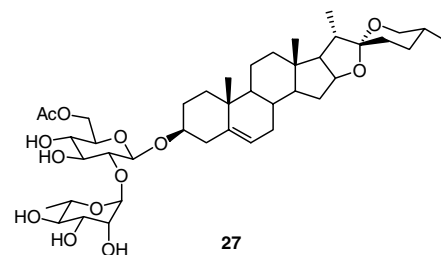
Natural gluten peptides were modified by 'click' chemistry to yield potential blockers for the HLA-DQ2 protein, which presents immunogenic gluten to T-cells inducing a gluten-specific T-cell response, and thus plays an important role in Celiac disease.

## Synthesis of novel spirostanoic saponins and their cytotoxic activity

pp 2063–2076

Juan C. Hernández, Francisco León, Ignacio Brouard, Fernando Torres, Sara Rubio, José Quintana, Francisco Estévez and Jaime Bermejo\*

To create your abstract, type over the instructions in the template box below. Fonts or abstract dimensions should not be changed or altered. This paper describes the cytotoxic effect induced by new synthetic spirostanoic saponins on human tumor cell lines (human myeloid leukemia and human melanoma cells).



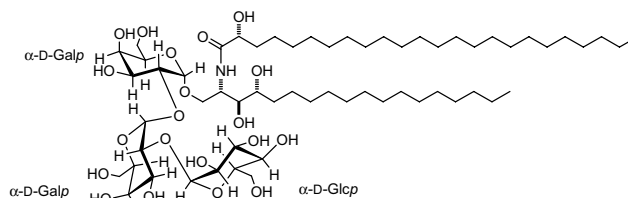
## Corrugoside, a new immunostimulatory $\alpha$ -galactoglycosphingolipid from the marine sponge *Axinella corrugata*

pp 2077–2085

Valeria Costantino, Ernesto Fattorusso, Concetta Imperatore, Alfonso Mangoni,\* Stefan Freigang and Luc Teyton



*Axinella corrugata*

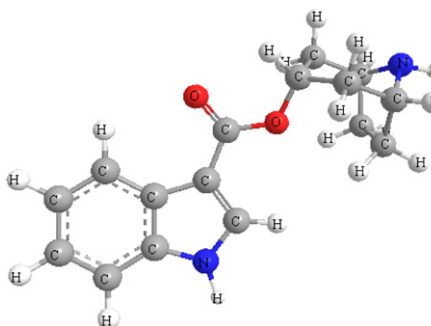
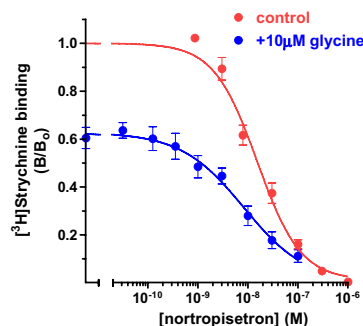


Corrugoside activates murine NKT cells

## Synthesis of (nor)tropeine (di)esters and allosteric modulation of glycine receptor binding

pp 2086–2092

Gábor Maksay,\* Péter Nemes, Zoltán Vincze and Timea Bíró



### Targeting the inverted CCAAT Box-2 of the topoisomerase II $\alpha$ gene: DNA sequence selective recognition by a polyamide–intercalator as a staggered dimer

pp 2093–2102

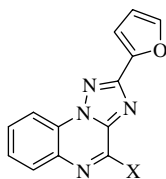
Hilary Mackay, Toni Brown, Jim S. Sexton, Minal Kotecha, Binh Nguyen, W. David Wilson, Jerome Kluza, Boris Savic, Caroline O'Hare, Daniel Hochhauser, Moses Lee\* and John A. Hartley



### Synthesis, adenosine receptor binding and 3D-QSAR of 4-substituted 2-(2'-furyl)-1,2,4-triazolo[1,5-a]quinoxalines

pp 2103–2113

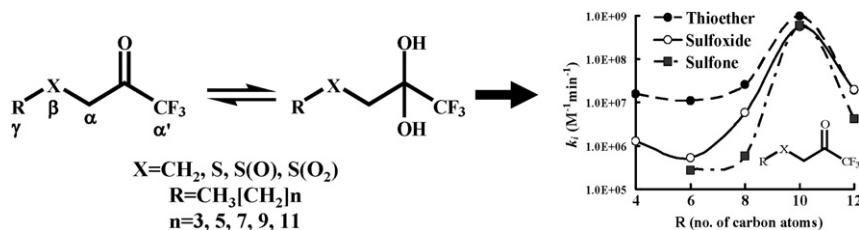
Ana Martínez, Hugo Gutiérrez-de-Terán, José Brea, Enrique Raviña,\* Maria Isabel Loza, Maria Isabel Cadavid, Ferran Sanz, Bernat Vidal, Victor Segarra and Eddy Sotelo\*



### Influence of sulfur oxidation state and steric bulk upon trifluoromethyl ketone (TFK) binding kinetics to carboxylesterases and fatty acid amide hydrolase (FAAH)

pp 2114–2130

Craig E. Wheelock, Kosuke Nishi, Andy Ying, Paul D. Jones, Michael E. Colvin, Marilyn M. Olmstead and Bruce D. Hammock\*



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\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

Trifluoromethyl ketone (TFK)-containing inhibitors exist in a dynamic equilibrium between the *gem*-diol and ketone forms prior to binding to the enzyme. The inhibitors form a transition state analog enzyme:inhibitor complex via a reversible covalent bond in which the alkyl chain length (**R**) and chemical moiety beta to the ketone (**X**) greatly affect the binding kinetics [Wheelock, C. E.; Nishi, K.; Ying, A.; Jones, P. D.; Colvin, M. E.; Olmstead, M. M.; Hammock, B. D. *Bioorg. Med. Chem.* **2008**, *16*, 2114–2130].

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