

## Contents

### Publisher's Announcement

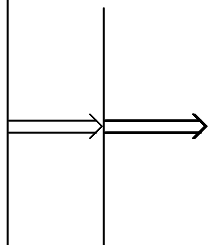
p 604

### REVIEW

#### Vascular disrupting agents

John W. Lippert, III

The review highlights six small molecule vascular disrupting agents namely DMXAA, ZD6126, TZT1027, CA4P, AVE8062, and Oxi4503. Their chemistry, modes of action, and current clinical trial status are discussed.

DMXAA		Introduction
ZD6126		Vascular Disrupting Agents
TZT1027		Synthetic Chemistry
CA4P		Biology
AVE8062		Clinical Trial Status
Oxi4503		

pp 605–615

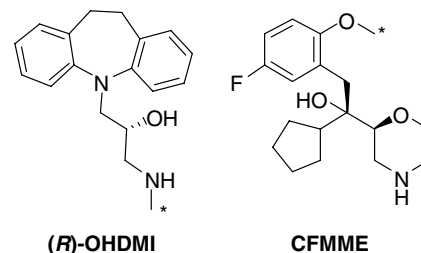
### ARTICLES

#### Synthesis of <sup>11</sup>C-labelled (*R*)-OHDMI and CFMME and their evaluation as candidate radioligands for imaging central norepinephrine transporters with PET

pp 616–625

Magnus Schou,\* Victor W. Pike, Judit Sóvágó, Balázs Gulyás, Peter T. Gallagher, David R. Dobson, Magnus W. Walter, Helene Rudyk, Lars Farde and Christer Halldin

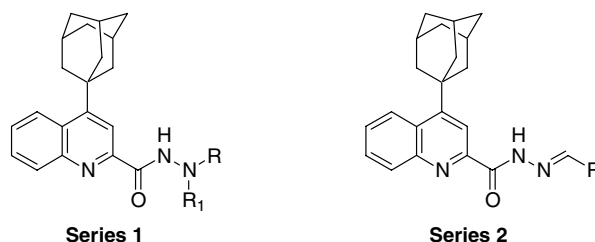
(*R*)-OHDMI and CFMME were synthesized and found to be potent NET inhibitors. Each was labelled with carbon-11 ( $t_{1/2} = 20.4$  min) as a prospective radioligand for imaging brain NETs with PET.



#### Synthesis, anti-tuberculosis activity, and 3D-QSAR study of 4-(adamantan-1-yl)-2-substituted quinolines

pp 626–640

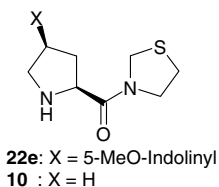
Amit Nayyar, Vikramdeep Monga, Alpeshkumar Malde, Evans Coutinho\* and Rahul Jain\*



### Lead optimization of [(S)- $\gamma$ -(arylamino)prolyl]thiazolidine focused on $\gamma$ -substituent: Indoline compounds as potent DPP-IV inhibitors

pp 641–655

Hiroshi Sakashita, Fumihiko Akahoshi,\* Tomohiro Yoshida, Hiroshi Kitajima, Yoshiharu Hayashi, Shinichi Ishii, Yoko Takashina, Reiko Tsutsumiuchi and Satoshi Ono

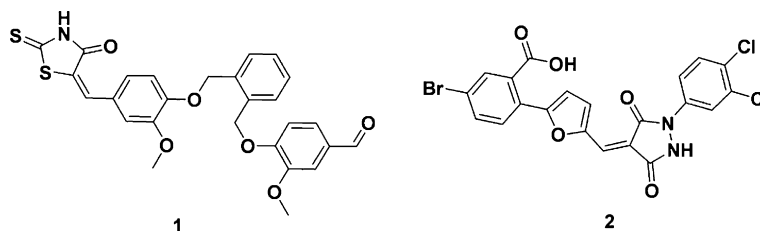


Lead optimization of the DPP-IV inhibitor [(S)- $\gamma$ -(arylamino)prolyl]thiazolidine was conducted with focus on the  $\gamma$ -substituent. Compounds with an indoline structure at the  $\gamma$ -position showed potent activity, with the representative compound **22e** 100-fold more potent than the prolylthiazolidine **10** and comparable to NVP-DPP728 despite its lack of an electrophilic group.

### Discovery of *Helicobacter pylori* shikimate kinase inhibitors: Bioassay and molecular modeling

pp 656–662

Cong Han, Jian Zhang, Lili Chen, Kaixian Chen, Xu Shen\* and Hualiang Jiang\*

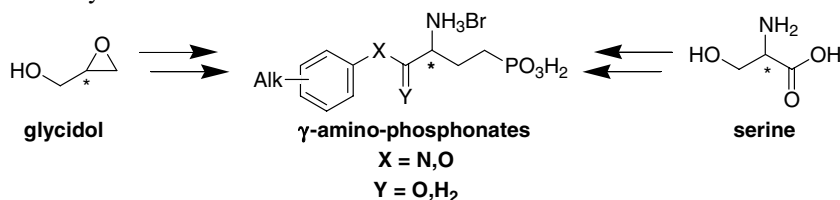


After high-throughput screening against our chemical library, compounds **1** and **2** were identified as *Helicobacter pylori* shikimate kinase inhibitors with IC<sub>50</sub> values of 5.5 and 6.4  $\mu$ M, respectively.

### Synthesis and biological evaluation of $\gamma$ -aminophosphonates as potent, subtype-selective sphingosine 1-phosphate receptor agonists and antagonists

pp 663–677

Frank W. Foss, Jr., Ashley H. Snyder, Michael D. Davis, Michael Rouse, Mark D. Okusa, Kevin R. Lynch and Timothy L. Macdonald\*

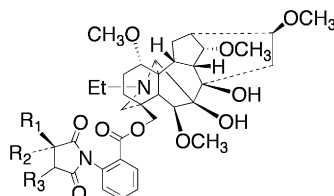


Arylamide, aryether, and arylamine containing  $\gamma$ -aminophosphonates provided potent, subtype-selective agonists and antagonists of the sphingosine 1-phosphate receptors. These phosphate mimetics displayed binding affinities comparable with previously reported phosphate precursors. Two pathways, from glycidol and serine, were pursued for the synthesis of the intermediate phosphoserine.

### Synthesis, nicotinic acetylcholine receptor binding, antinociceptive and seizure properties of methyllycaconitine analogs

pp 678–685

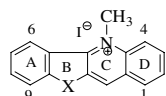
F. Ivy Carroll,\* Wei Ma, Hernán A. Navarro, Philip Abraham, Scott A. Wolckenhauer, M. I. Damaj and Billy R. Martin



### Synthesis and evaluation of isosteres of *N*-methyl indolo[3,2-*b*]-quinoline (cryptolepine) as new anti-infective agents

pp 686–695

Xue Y. Zhu, Leroy G. Mardenborough, Shouming Li, Abdul Khan, Wang Zhang, Pincheng Fan, Melissa Jacob, Shabana Khan, Larry Walker and Seth Y. Ablordeppey\*



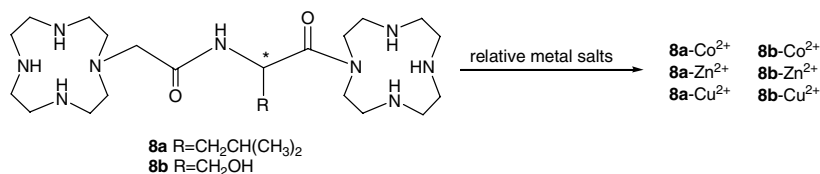
Compd 1; 5-Methyl indolo[3,2-*b*]quinolinium iodide; X = NH

Compd 5b; 5-Methyl benzothieno[3,2-*b*]quinolinium iodide; X = S

### Chiral multinuclear macrocyclic polyamine complexes: Synthesis, characterization and their interaction with plasmid DNA

pp 696–701

Yu-Guo Fang, Ji Zhang, Shan-Yong Chen, Ning Jiang, Hong-Hui Lin,\* Yu Zhang and Xiao-Qi Yu\*



### Design, synthesis, and antiproliferative and CDK2-cyclin A inhibitory activity of novel flavopiridol analogues

pp 702–713

Yu Mi Ahn, Lakshminarayana Voleti, Chun-Jing Liu, Hari K. R. Santhapuram, Jonathan M. White, Veena Vasandani, Lester A. Mitscher, Gerald H. Lushington, Paul R. Hanson, Douglas R. Powell, Richard H. Himes, Katherine F. Roby, Qizhuang Ye and Gunda I. Georg\*

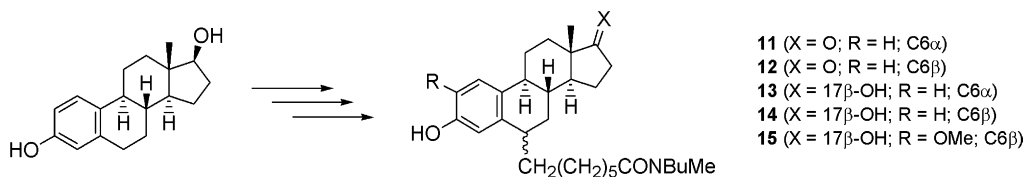
The design and synthesis of a small library of 8-amidoflavone, 8-sulfonamidoflavone, 8-amido-7-hydroxyflavone, and heterocyclic analogues of flavopiridol is reported. The potential activity of these compounds as kinase inhibitors was evaluated by cytotoxicity studies in MCF-7, ID-8 cancer cell lines, and inhibition of CDK2-Cyclin A enzyme activity in vitro. The antiproliferative and CDK2-Cyclin A inhibitory activity of these analogues was significantly lower than the activity of flavopiridol. Molecular docking simulations were carried out and these studies suggested a different binding orientation inside the CDK2 binding pocket for these analogues compared to flavopiridol.



### C6-(*N,N*-butyl-methyl-heptanamide) derivatives of estrone and estradiol as inhibitors of type 1 17 $\beta$ -hydroxysteroid dehydrogenase: Chemical synthesis and biological evaluation

pp 714–726

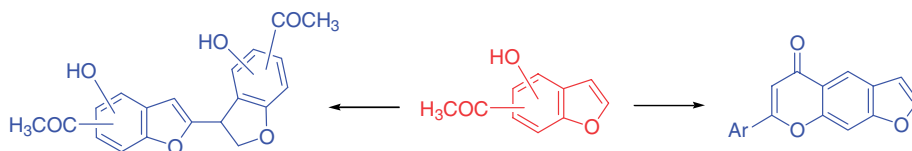
Christine Cadot, Yannick Laplante, Fatima Kamal, Van Luu-The and Donald Poirier\*



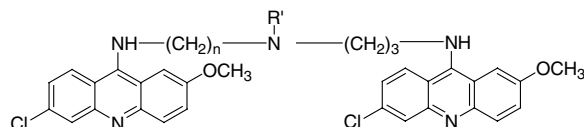
**Synthesis of benzofuran scaffold-based potential PTP-1B inhibitors**

pp 727–734

Manish Dixit, Brajendra K. Tripathi, Akhilesh K. Tamrakar,  
Arvind K. Srivastava, Brijesh Kumar and Atul Goel\*

**Linker-modified triamine-linked acridine dimers: Synthesis and cytotoxicity properties in vitro and in vivo** pp 735–748

Shan-Shue Wang,\* Yi-Jen Lee, Shih-Chung Hsu, Hsueh-O Chang, Wei-Kung Yin,  
Lien-Shange Chang and Shan-Yen Chou\*

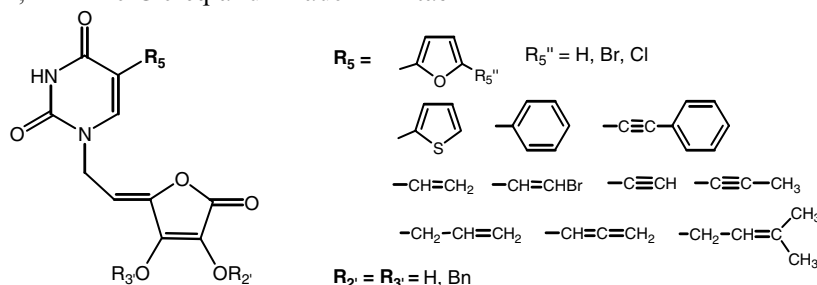


A series of N<sup>6</sup>-substituted 6 or 7 carbons of triamine-linked acridine dimers were synthesized and their biological activity was determined. Most acridine dimer derivatives reveal highly potent cancer cell killing activity with COLO205, HAT22T, SK-BR-3 and MOLT-4 human cancer cell lines by in vitro cytotoxicity assays and DNA binding activity. Some acridine dimers also demonstrated various anti-COLO 205 solid tumor activities in vivo. Compound 1 has shown the most potent solid tumor inhibition.

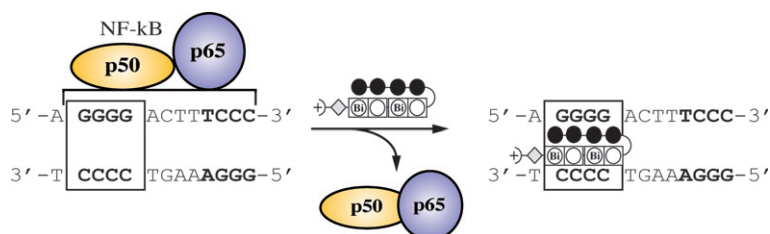
**The novel C-5 aryl, alkenyl, and alkynyl substituted uracil derivatives of L-ascorbic acid: Synthesis, cytostatic, and antiviral activity evaluations**

pp 749–758

Tatjana Gazivoda, Silvana Raić-Malić, Marko Marjanović, Marijeta Kralj,  
Krešimir Pavelić, Jan Balzarini, Erik De Clercq and Mladen Mintas\*

**Programmable oligomers targeting 5'-GGGG-3' in the minor groove of DNA and NF- $\kappa$ B binding inhibition** pp 759–770

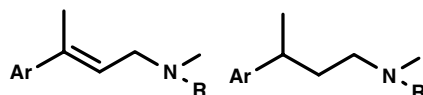
David M. Chenoweth, Julie A. Poposki, Michael A. Marques and Peter B. Dervan\*



**Design, synthesis, and SAR analysis of novel selective  $\sigma_1$  ligands**

pp 771–783

Simona Collina,\* Guya Loddo, Mariangela Urbano, Laura Linati,  
Athos Callegari, Francesco Ortuso, Stefano Alcaro, Christian Laggner,  
Thierry Langer, Orazio Prezzavento, Giuseppe Ronsisvalle and Ornella Azzolina



**11** Ar=biphen-4-yl, R=CH<sub>3</sub>, K<sub>i</sub> $\sigma_1$  = 1.02±0.2, K<sub>i</sub> $\sigma_2$ / K<sub>i</sub> $\sigma_1$  = 157.8

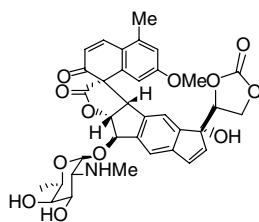
**12** Ar=naphth-2-yl, R=CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, K<sub>i</sub> $\sigma_1$  = 7.88±0.3, K<sub>i</sub> $\sigma_2$ / K<sub>i</sub> $\sigma_1$  = 110.8

The synthesis, SARs, and molecular modeling studies are reported.

**Molecular probes of DNA bulges: Functional assay and spectroscopic analysis**

pp 784–790

Graham B. Jones,\* Yiqing Lin, Ziwei Xiao, Lizzy Kappen and Irving H. Goldberg

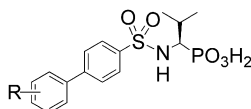


A mimic of the natural product derived DNA bulge-binding agent NCSi-gb was prepared from an accessible compound using an  $\alpha$ -fucosylation strategy. The congener shows pronounced affinity for two-base DNA bulges and is active in a functional DNA slippage assay. Fluorescence patterns induced between the agent and synthetic oligos suggest fingerprinting assays may be developed for the detection of bulged sites in DNA.

 **$\alpha$ -Biphenylsulfonylamino 2-methylpropyl phosphonates: Enantioselective synthesis and selective inhibition of MMPs**

pp 791–799

Alessandro Biasone, Paolo Tortorella, Cristina Campestre, Mariangela Agamennone,  
Serena Preziuso, Marika Chiappini, Elisa Nuti, Paolo Carelli, Armando Rossello,  
Fernando Mazza and Carlo Gallina\*

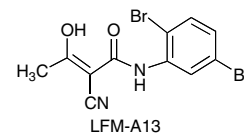


(*R*)- $\alpha$ -Biphenylsulfonylamino 2-methylpropyl phosphonates were synthesized starting from enantiopure (*S*)-*N*-isobutylidene-*p*-bromobenzenesulfinamide as common intermediate. Screening of the new phosphonate inhibitors on MMP-1, -2, -3, -7, -8, -9, -13 and -14 showed IC<sub>50</sub> in the range of nM in most cases.

**Anti-breast cancer activity of LFM-A13, a potent inhibitor of Polo-like kinase (PLK)**

pp 800–814

Fatih M. Uckun,\* Ilker Dibirdik, Sanjive Qazi, Alexei Vassilev, Hong Ma, Chen Mao,  
Alexey Benyumov and Katayoon H. Emami



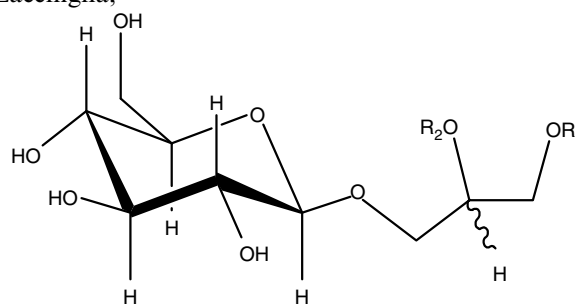
Molecular modeling studies led to the identification of LFM-A13 ( $\alpha$ -cyano- $\beta$ -hydroxy- $\beta$ -methyl-*N*-(2,5-dibromophenyl)propenamide) as a potent inhibitor of Polo-like kinase (Plk). LFM-A13 inhibited recombinant purified Plx1, the *Xenopus* homolog of Plk, in a concentration-dependent fashion, as measured by autophosphorylation and phosphorylation of a substrate Cdc25 peptide. LFM-A13 was a selective Plk inhibitor. While the human PLK3 kinase was also inhibited by LFM-A13 with an IC<sub>50</sub> value of 6  $\mu$ M, none of the 7 other serine-threonine kinases, including CDK1, CDK2, CDK3, CHK1, IKK, MAPK1 or SAPK2a, none of the 10 tyrosine kinases, including ABL, BRK, BMX, c-KIT, FYN, IGF1R, PDGFR, JAK2, MET, or YES, or the lipid kinase PI3K $\gamma$  were inhibited (IC<sub>50</sub> values > 200–500  $\mu$ M). The mode of Plk3 inhibition by LFM-A13 was competitive with respect to ATP with a K<sub>i</sub> value of 7.2  $\mu$ M from Dixon plots. Notably, LFM-A13 delayed tumor progression in the MMTV/*neu* transgenic mouse model of HER2 positive breast cancer at least as effectively as paclitaxel and gemcitabine. These results establish LFM-A13 as a small molecule inhibitor of Plk with in vitro and in vivo anti-proliferative activity against human breast cancer.

**Chemoenzymatic synthesis and antimicrobial activity evaluation of monoglucosyl diglycerides**

pp 815–826

Francesca Cateni,\* Paolo Bonivento, Giuseppe Procida, Marina Zacchigna, Luciana Gabrielli Favretto, Giuditta Scialino and Elena Banfi

Monoglucosyl diglycerides with medium-long length fatty acid acyl chains were prepared and examined for antimicrobial activity against Gram-positive, Gram-negative bacteria and fungi.

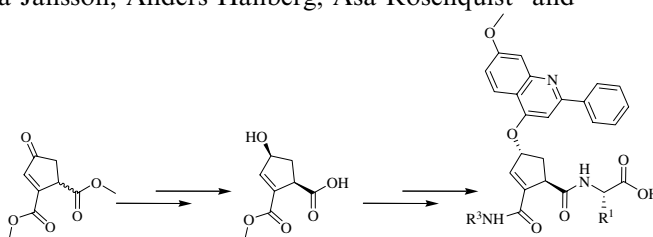


$R_1, R_2 = \text{Fatty acids}$

**Synthesis of novel potent hepatitis C virus NS3 protease inhibitors: Discovery of 4-hydroxy-cyclopent-2-ene-1,2-dicarboxylic acid as a *N*-acyl-L-hydroxyproline bioisostere**

pp 827–838

Fredrik Thorstensson, Fredrik Wångsell, Ingemar Kvarnström, Lotta Vrang, Elizabeth Hamelink, Katarina Jansson, Anders Hallberg, Åsa Rosenquist\* and Bertil Samuelsson\*

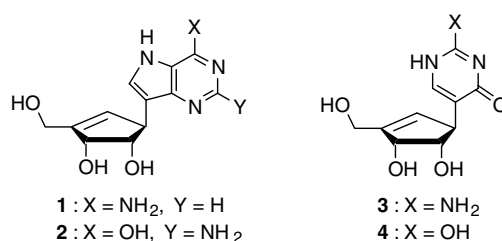


HCV NS3 protease inhibitors incorporating 4-hydroxy-cyclopent-2-ene-1,2-dicarboxylic acid as a new *N*-acyl-L-hydroxyproline mimic are described. The most promising exhibiting a  $K_i$  value of 1.1 nM.

**Enantioselective synthesis and antiviral activity of purine and pyrimidine cyclopentenyl C-nucleosides**

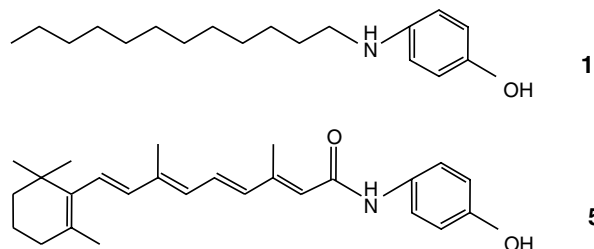
pp 839–846

Jagadeeshwar R. Rao, Raymond F. Schinazi and Chung K. Chu\*

**Potent anticancer activities of novel aminophenol analogues against various cancer cell lines**

pp 847–853

Toshihiro Ohba, Takayasu Yamauch, Kimio Higashiyama and Noriko Takahashi\*

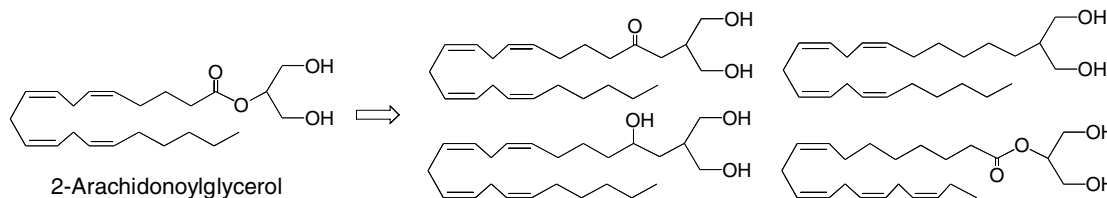


A novel **1** designed from **5**, was a potent anticancer agent greater than **5**.

### Synthesis and biological evaluation of several structural analogs of 2-arachidonoylglycerol, an endogenous cannabinoid receptor ligand

pp 854–867

Yoshitomo Suhara, Saori Oka, Atsushi Kittaka, Hiroaki Takayama, Keizo Waku and Takayuki Sugiura\*

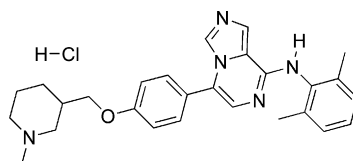


Several structural analogs of 2-arachidonoylglycerol were synthesized and their biological activities as CB1 receptor agonists and CB2 receptor agonists were evaluated.

### Synthesis and c-Src inhibitory activity of imidazo[1,5-a]pyrazine derivatives as an agent for treatment of acute ischemic stroke

pp 868–885

Harunobu Mukaiyama,\* Toshihiro Nishimura, Satoko Kobayashi, Tomonaga Ozawa, Noboru Kamada, Yoshimitsu Komatsu, Shinji Kikuchi, Hideki Oonota and Hiroshi Kusama



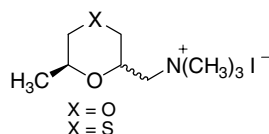
14c·HCl

We studied novel c-Src inhibitors as potential therapeutic agents for acute ischemic stroke. Compound **14c·HCl** demonstrated potent c-Src inhibitory activity, remarkable central nervous system (CNS) penetration, and significant neuroprotective efficacy in vivo in rat models.

### Dioxane and oxathiane nuclei: Suitable substructures for muscarinic agonists

pp 886–896

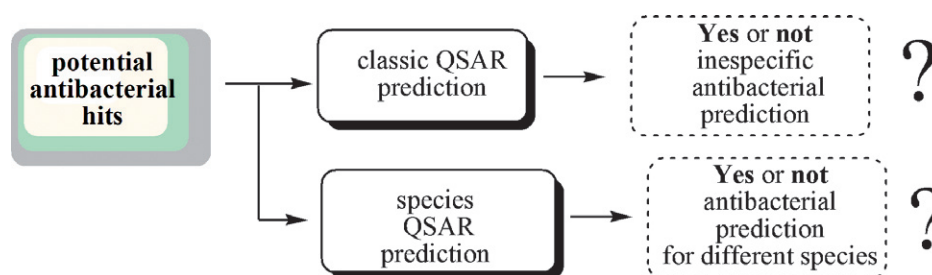
Alessandro Piergentili,\* Wilma Quaglia, Mario Giannella, Fabio Del Bello, Bruno Bruni, Michela Buccioni, Antonio Carrieri and Samuele Ciattini



### Unified QSAR approach to antimicrobials. Part 2: Predicting activity against more than 90 different species in order to halt antibacterial resistance

pp 897–902

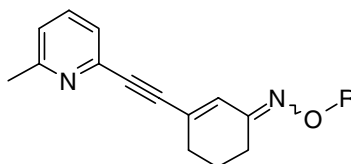
Francisco J. Prado-Prado, Humberto González-Díaz,\* Lourdes Santana and Eugenio Uriarte



**ABP688, a novel selective and high affinity ligand for the labeling of mGlu5 receptors: Identification, in vitro pharmacology, pharmacokinetic and biodistribution studies**

pp 903–914

Samuel Hintermann, Ivo Vranesic, Hans Allgeier, Armin Brülisauer, Daniel Hoyer, Michel Lemaire, Thomas Moenius, Stephan Urwyler, Steven Whitebread, Fabrizio Gasparini\* and Yves P. Auberson

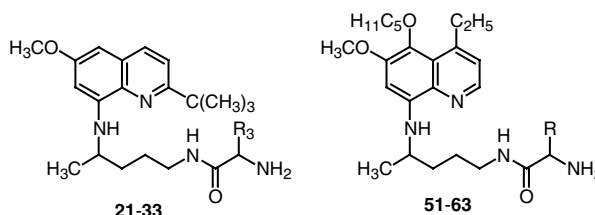


**2**, ABP688 R = -CH<sub>3</sub>  
 [<sup>3</sup>H]-ABP688, R = -CT<sub>3</sub>


**Synthesis, antimalarial, antileishmanial, antimicrobial, cytotoxicity, and methemoglobin (MetHB) formation activities of new 8-quinolinamines**

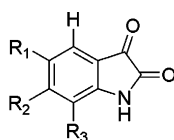
pp 915–930

Kirandeep Kaur, Sanjay R. Patel, Premanand Patil, Meenakshi Jain, Shabana I. Khan, Melissa R. Jacob, Shobana Ganesan, Babu L. Tekwani and Rahul Jain\*


**In vitro cytotoxicity evaluation of some substituted isatin derivatives**

pp 931–938

Kara L. Vine,\* Julie M. Locke, Marie Ranson, Stephen G. Pyne and John B. Bremner



**2p** R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = Br

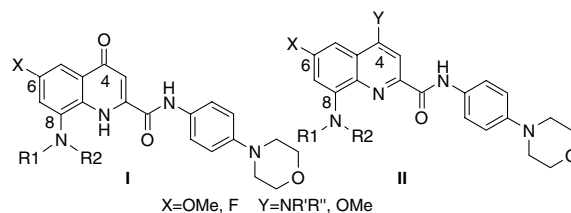
IC <sub>50</sub> (μM)	U937	Jurkat
	6.67	5.80

**Synthesis of novel quinolone and quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amides: A late-stage diversification approach to potent 5HT<sub>1B</sub> antagonists**

pp 939–950

Carey L. Horschler,\* John P. McCauley, James E. Hall, Dean H. Snyder, W. Craig Moore, Thomas J. Hudzik and Marc J. Chapdelaine

MPS amenable syntheses of novel potent 5HT<sub>1B</sub> antagonists, 6-methoxy-8-amino-4-oxo-1,4-dihydroquinoline-2-carboxylic acid-(4-morpholin-4-yl-phenyl)amides (**I**) and 4-amino-6-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid-(4-morpholin-4-yl-phenyl)amides (**II**), are described.



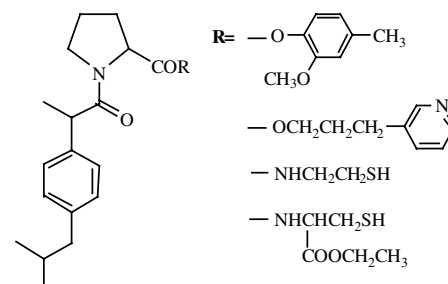


**Design and study of some novel ibuprofen derivatives with potential nootropic and neuroprotective properties**

pp 951–961

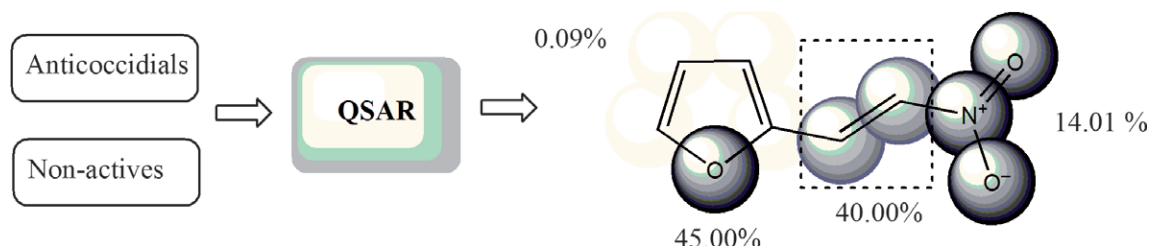
Ioanna C. Siskou, Eleni A. Rekka,\* Angeliki P. Kourounakis, Michael C. Chrysoselis, Kariofyllis Tsiakitzis and Panos N. Kourounakis

Ibuprofen derivatives incorporating a proline moiety are designed and studied as potentially active agents in neurodegenerative disorders.

**QSAR study of anticoccidial activity for diverse chemical compounds: Prediction and experimental assay of *trans*-2-(2-nitrovinyl)furan**

pp 962–968

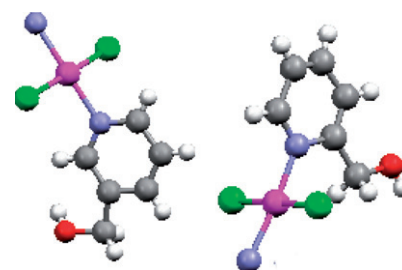
Humberto González-Díaz,\* Ervelio Olazábal, Lourdes Santana, Eugenio Uriarte, Yenny González-Díaz and Nilo Castañedo

**Influence of the position of substituents in the cytotoxic activity of *trans* platinum complexes with hydroxymethyl pyridines**

pp 969–979

Alberto Martínez, Júlia Lorenzo, María J. Prieto, Mercè Font-Bardia, Xavier Solans, Francesc X. Avilés and Virtudes Moreno\*

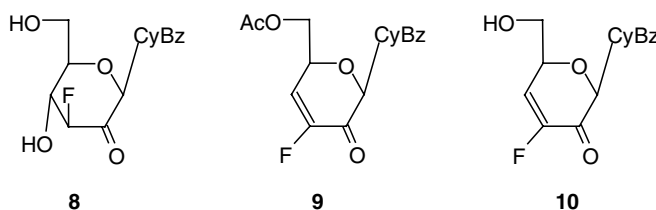
The synthesis, chemical characterization, interaction with DNA and cytotoxic activity of two *trans* platinum complexes, (Complex-1) *trans*-[PtCl<sub>2</sub>NH<sub>3</sub>(3-hydroxymethylpyridine)] and (Complex-2) *trans*-[PtCl<sub>2</sub>NH<sub>3</sub>(2-hydroxymethylpyridine)], are described. We have probed that the different position of the hydroxymethyl substituent is crucial in their activity.

**Fluoro-ketopyranosyl nucleosides: Synthesis and biological evaluation of 3-fluoro-2-keto-β-D-glucopyranosyl derivatives of *N*<sup>4</sup>-benzoyl cytosine**

pp 980–987

Stella Manta, George Agelis, Tanja Botić, Avrelja Cencič and Dimitri Komiotis\*

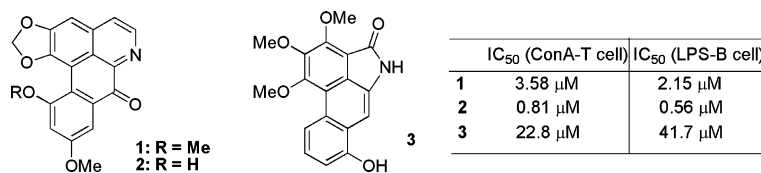
We report the synthesis of three novel fluoro-ketopyranosyl nucleosides (compounds 8–10). These novel synthesized compounds have a promising potential in combating the rotaviral infections and in the treatment of colon cancer. As compared to AZT, compound 10 showed to be more effective at lower concentrations in inhibition of rotavirus infection as well as in the same range of antitumor activity.



### Discovery and synthesis of new immunosuppressive alkaloids from the stem of *Fissistigma oldhamii* (Hemsl.) Merr.

pp 988–996

Yi-Nan Zhang, Xiang-Gen Zhong, Zong-Ping Zheng, Xu-Dong Hu, Jian-Ping Zuo\* and Li-Hong Hu\*

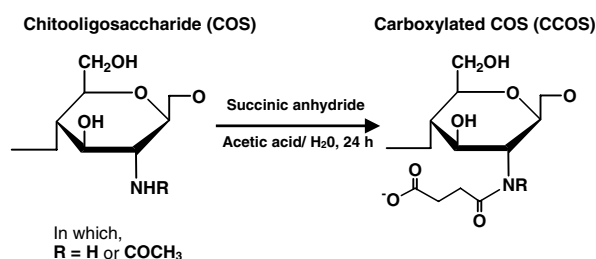


### Inhibition of free radical-mediated oxidation of cellular biomolecules by carboxylated chitoooligosaccharides

pp 997–1003

Niranjan Rajapakse, Moon-Moo Kim, Eresha Mendis and Se-Kwon Kim\*

Chitoooligosaccharides (COS) were chemically modified to improve proton donation by introducing  $-\text{COCH}_2\text{CH}_2\text{COO}^-$  group to the amino group at C2 position of pyranose unit. The new COS derivative, carboxylated chitoooligosaccharides (CCOS), was studied for its effects to inhibit free radical-mediated oxidation of biomolecules in human and mouse leukocytes.

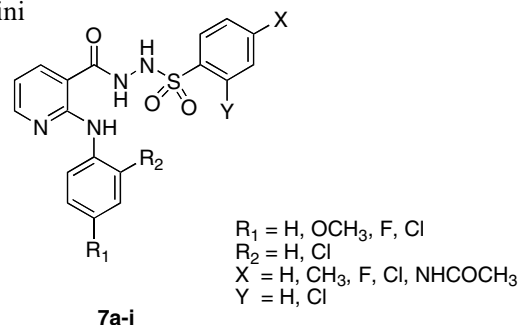


### Synthesis of a new class of 2-anilino substituted nicotinyl arylsulfonylhydrazides as potential anticancer and antibacterial agents

pp 1004–1013

Ahmed Kamal,\* M. Naseer A. Khan, K. Srinivasa Reddy and K. Rohini

Synthesis and evaluation of *N*'-1-[2-anilino-3-pyridyl]carbonyl 1-benzenesulfonylhydrazide derivatives (**7a-i**) as anticancer and antibacterial agents.

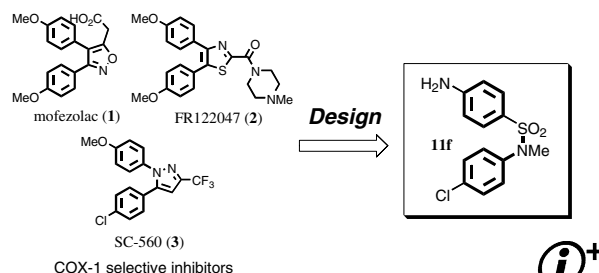


### Analgesic agents without gastric damage: Design and synthesis of structurally simple benzenesulfonanilide-type cyclooxygenase-1-selective inhibitors

pp 1014–1021

Xiaoxia Zheng, Hiroyuki Oda, Kayo Takamatsu, Yukio Sugimoto, Akihiro Tai, Eiichi Akaho, Hamed Ismail Ali, Toshiyuki Oshiki, Hiroki Kakuta\* and Kenji Sasaki

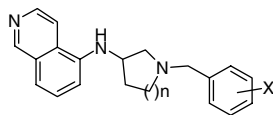
Design and synthesis of structurally simple benzenesulfonanilide-type cyclooxygenase-1 inhibitors as analgesic agents are reported.



**Design and synthesis of rho kinase inhibitors (III)**

pp 1022–1033

Masayuki Iwakubo, Atsuya Takami, Yuji Okada, Takehisa Kawata, Yoshimichi Tagami, Motoko Sato, Terumi Sugiyama, Kayoko Fukushima, Shinichiro Taya, Mutsuki Amano, Kozo Kaibuchi and Hiroshi Iijima\*

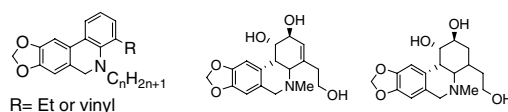


*N*-(1-benzyl-3-pyrrolidyl)-*N*-(5-isoquinolyl)amine analogues were optimized efficacy based on the in vitro Rho kinase inhibition, the cell-based chemotaxis inhibition, and the ex vivo test.

**Preparation of secolycorines against acetylcholinesterase**

pp 1034–1043

Shoei-Sheng Lee,\* Uppala Venkatesham, Chitneni Prasad Rao, Sio-Hong Lam and Jung-Hsin Lin



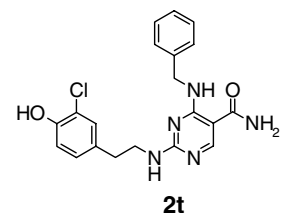
Secolycorines were facilely prepared from lycorine and some of them are more potent than galanthamine against acetylcholinesterase.

**Synthesis and evaluation of 2-{{2-(4-hydroxyphenyl)-ethyl}amino}pyrimidine-5-carboxamide derivatives as novel STAT6 inhibitors**

pp 1044–1055

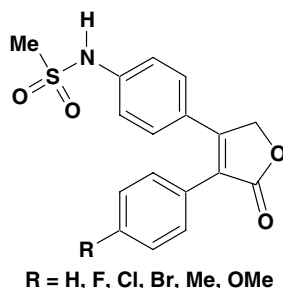
Shinya Nagashima,\* Masaki Yokota, Ei-ichi Nakai, Sadao Kuromitsu, Keiko Ohga, Makoto Takeuchi, Shin-ichi Tsukamoto and Mitsuaki Ohta

2-{{2-(4-Hydroxyphenyl)ethyl}amino}pyrimidine-5-carboxamide derivatives were prepared and their STAT6 inhibitory activities were evaluated. Compound **2t** (AS1517499) was an effective inhibitor of STAT6 activation and also inhibited IL-4-induced Th2 differentiation in mouse spleen T cells.

**Synthesis and biological evaluation of methanesulfonamide analogues of rofecoxib: Replacement of methanesulfonyl by methanesulfonamido decreases cyclooxygenase-2 selectivity**

pp 1056–1061

Afshin Zarghi, P. N. Praveen Rao and Edward E. Knaus\*

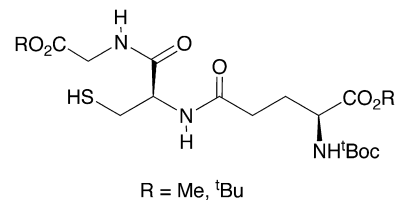


### Preparation of *N*-*t*Boc L-glutathione dimethyl and di-*tert*-butyl esters: Versatile synthetic building blocks

pp 1062–1066

J. R. Falck,\* Bhavani Sangras and Jorge H. Capdevila

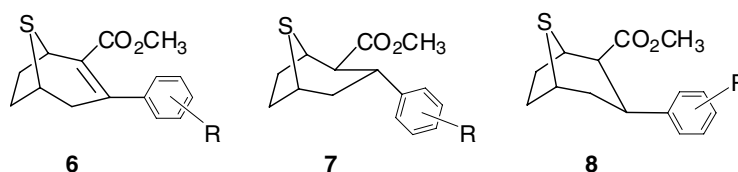
The title L-glutathione derivatives, containing acid- and base-labile esters, respectively, were obtained in good overall yields. *N*-*t*Boc L-glutathione dimethyl ester was prepared via Fischer esterification of L-glutathione disulfide (GSSG) using HCl in dry methanol, protection of the amine with *t*Boc<sub>2</sub>O, and tributylphosphine cleavage of the disulfide in wet isopropanol. Alternatively, Fischer esterification and *t*Boc-protection of L-glutathione (GSH) also furnished *N*-*t*Boc glutathione dimethyl ester accompanied by a small amount of *S*-*t*Boc that was removed chromatographically. The di-*tert*-butyl ester was obtained by S-palmitoylation of GSH in TFA as solvent, *N*-*t*Boc-protection, esterification using *t*BuOH mediated by diisopropylcarbodiimide/copper(I) chloride, and saponification of the thioester. These L-glutathione derivatives are versatile synthetic building blocks for the preparation of S-glutathione adducts.



### Synthesis of 8-thiabicyclo[3.2.1]octanes and their binding affinity for the dopamine and serotonin transporters

pp 1067–1082

Duy-Phong Pham-Huu, Jeffrey R. Deschamps, Shanghao Liu, Bertha K. Madras and Peter C. Meltzer\*

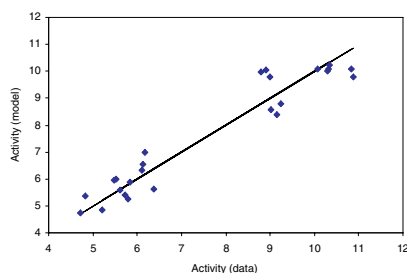


2-Carbomethoxy-3-aryl-8-thiabicyclo[3.2.1]octane analogues of cocaine provide potent and selective inhibitors of the dopamine and serotonin transporters.

### Antinociceptive and antiinflammatory activities and QSAR studies on 2-substituted-4,5-diphenyl-1*H*-imidazoles

pp 1083–1090

A. Puratchikody and Mukesh Doble\*



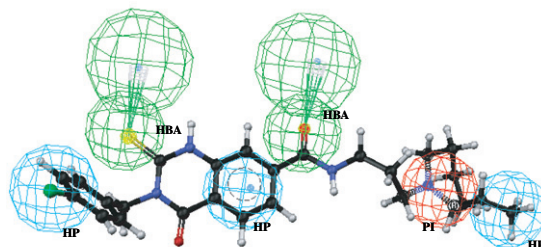
Parity plot of hot plate data (experiments carried out at 120 s).

### 3D pharmacophore based virtual screening of T-type calcium channel blockers

pp 1091–1105

Munikumar Reddy Doddareddy, Hyunah Choo, Yong Seo Cho, Hyewhon Rhim, Hun Yeong Koh, Jung-Ha Lee, Seong-Woo Jeong and Ae Nim Pae\*

Virtual screening of the commercial databases was done by using a three dimensional pharmacophore previously developed for T-type calcium channel blockers using CATALYST program. Screening yielded several hits with micro-molar IC<sub>50</sub> values and high T-type selectivity. This result shows a successful example of ligand based drug discovery of potent T-type calcium channel blockers.

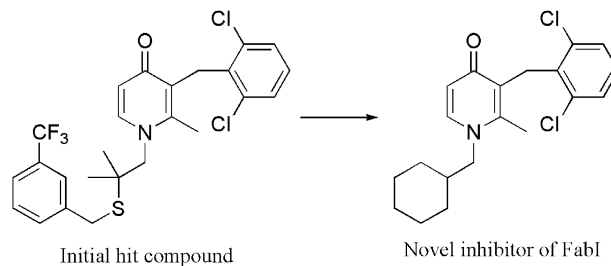


**4-Pyridone derivatives as new inhibitors of bacterial enoyl-ACP reductase FabI**

pp 1106–1116

Hideo Kitagawa,\* Ko Kumura, Sho Takahata, Maiko Iida and Kunio Atsumi

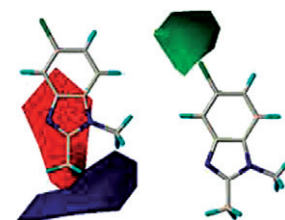
From structure optimization studies yielded 4-pyridone derivatives as novel FabI inhibitors with potent antibacterial activity against *Staphylococcus aureus*.

**Molecular modeling of some 1H-benzimidazole derivatives with biological activity against *Entamoeba histolytica*: A comparative molecular field analysis study**

pp 1117–1126

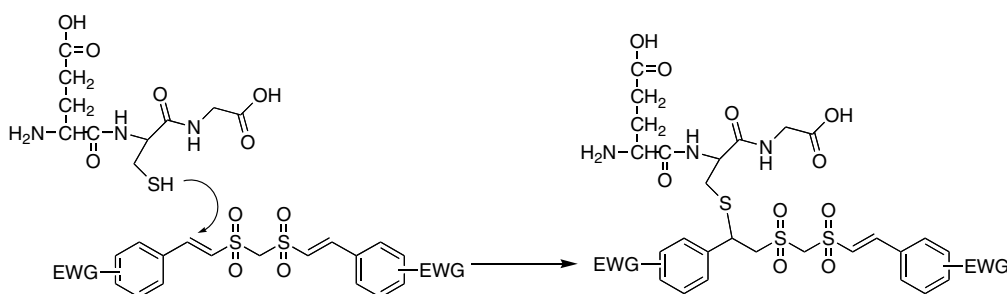
Fabian López-Vallejo, José Luis Medina-Franco, Alicia Hernández-Campos, Sergio Rodríguez-Morales, Lilián Yépez, Roberto Cedillo and Rafael Castillo\*

CoMFA models that explain the amoebicidal activity of tautomeric benzimidazole derivatives were developed.

**Ring substituent effects on biological activity of vinyl sulfones as inhibitors of HIV-1**

pp 1127–1137

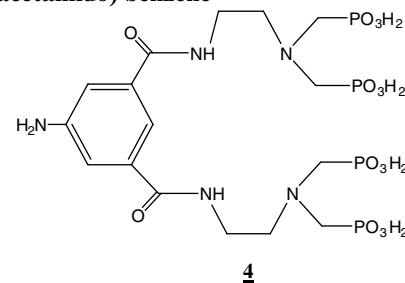
D. Christopher Meadows, Tino Sanchez, Nouri Neamati, Thomas W. North and Jacquelyn Gervay-Hague\*

**Synthesis, characterization, and in vivo skeletal localization of a new <sup>99m</sup>Tc-based multidentate phosphonate chelate: 5-Amino-1,3-bis(ethylamine-(*N,N* dimethyl diphosphonic acid) acetamido) benzene**

pp 1138–1145

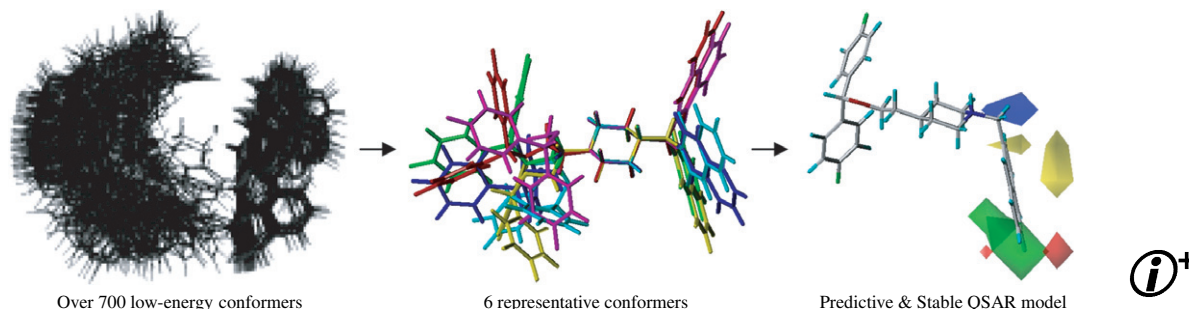
Puja Panwar, Sweta Singh, Nitin Kumar, Harish Rawat and Anil K. Mishra\*

The compound 5-amino-1, 3-bis(ethylamine-(*N,N*-dimethyl diphosphonic acid) acetamido) benzene (IPTMP), was synthesized from 5-nitroisophthalate dimethyl ester and ethylenediamine, a new synthetic route of preparation of phosphonate based chelating agent, is described to obtain a more stable agent for radiodiagnosis and radiotherapy.



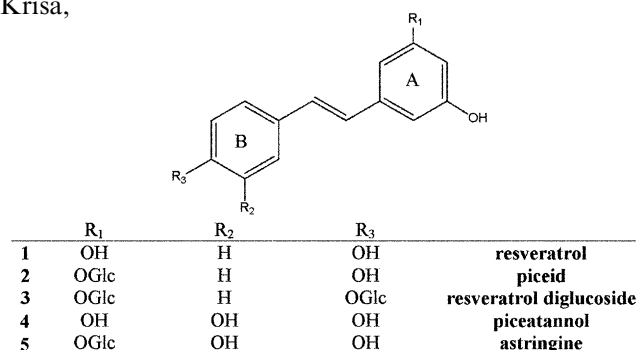
**DAT/SERT selectivity of flexible GBR 12909 analogs modeled using 3D-QSAR methods****pp 1146–1159**

Kathleen M. Gilbert, Terrence L. Boos, Christina M. Dersch, Elisabeth Greiner, Arthur E. Jacobson, David Lewis, Dorota Matecka, Thomas E. Prisinzano, Ying Zhang, Richard B. Rothman, Kenner C. Rice and Carol A. Venanzi

**Inhibitory activity of stilbenes on Alzheimer's  $\beta$ -amyloid fibrils in vitro****pp 1160–1167**

Céline Rivière, Tristan Richard, Lysiane Quentin, Stéphanie Krisa, Jean-Michel Mérillon and Jean-Pierre Monti\*

Polymerization of the amyloid  $\beta$ -peptide ( $A\beta$ ) has been identified as one of the major characteristics of Alzheimer's disease (AD). The inhibitory properties of stilbenes were characterized and compared. These results support the hypothesis that stilbenes could be of therapeutic value in AD.

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\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

Terfenadine (an antihistamine pulled from the market in 1997) bound to a model of an open form of the homo-tetrameric pore domain of hERG, produced using Schrödinger's "Induced Fit Docking" technology [Farid, R.; Day, T.; Friesner, R. A.; Pearlstein, R. A. *Bioorg. Med. Chem.* **2006**, *14*, 3160–3173].

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