

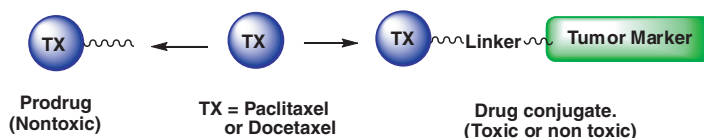
## Contents

## REVIEW

## Improved biochemical strategies for targeted delivery of taxoids

pp 3597–3623

Thota Ganesh\*



Paclitaxel (Taxol®) and docetaxel (Taxotere®) are very important anti-tumor drugs in clinical use for cancer. However, their clinical utility is limited due to systemic toxicity, low solubility, and inactivity against drug resistant tumors. To improve chemotherapeutic levels of these drugs, it would be highly desirable to design strategies which bypass the above limitations. In this respect various prodrug and drug targeting strategies have been envisioned either to improve oral bioavailability or tumor specific delivery of taxoids. Abnormal properties of cancer cells with respect to normal cells have guided in designing of these protocols. This review article records the designed biochemical strategies and their biological efficacies as potential taxoid chemotherapeutics.

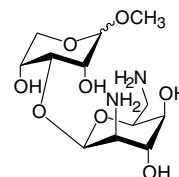
## ARTICLES

## Aminoglycoside antibiotic derivatives: Preparation and evaluation of toxicity on cochlea and vestibular tissues and antimicrobial activity

pp 3624–3634

Julierme G. da Silva, Miguel A. Hyppolito, José Antônio A. de Oliveira, Alexandre P. Corrado, Izabel Y. Ito and Ivone Carvalho\*

Neomycin derivatives such as neamine, methyl neobiosaminide B, 2-deoxystreptamine, tetra-azidoneamine, tetra-*N*-acetylneamine, tetra-*N*-carboxy-benzylneamine, tetra-*N*-carboxy-methylneamine and tetra-*p*-methoxy-benzyliminoneamine were prepared and evaluated in cochlear and vestibular tissues and antibacterial screening. Methyl neobiosaminide B has shown the most selective vestibular activity suggesting its potential use in Ménière's disease.

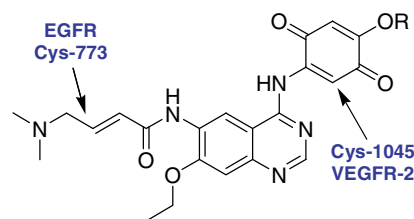


## Dual irreversible kinase inhibitors: Quinazoline-based inhibitors incorporating two independent reactive centers with each targeting different cysteine residues in the kinase domains of EGFR and VEGFR-2

pp 3635–3648

Allan Wissner,\* Heidi L. Fraser, Charles L. Ingalls, Russell G. Dushin, M. Brawner Floyd, Kinwang Cheung, Thomas Nittoli, Malini R. Ravi, Xingzhi Tan and Frank Loganzo

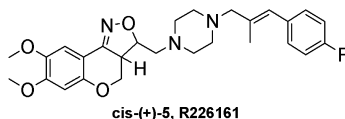
Compounds with two independent reactive centers were designed to function as dual irreversible inhibitors of the kinase domains of EGFR and VEGFR-2 where each reactive center targets a different, non-conserved, cysteine residue located in the ATP binding pocket of these enzymes.



**Tricyclic isoxazolines: Identification of R226161 as a potential new antidepressant that combines potent serotonin reuptake inhibition and  $\alpha_2$ -adrenoceptor antagonism**

pp 3649–3660

J. Ignacio Andrés,\* Jesús Alcázar, José M. Alonso, Rosa M. Alvarez, Margot H. Bakker, Ilse Biesmans, José M. Cid, Ana I. De Lucas, Wilhelmus Drinkenburg, Javier Fernández, Luis M. Font, Laura Iturrino, Xavier Langlois, Ilse Lenaerts, Sonia Martínez, Anton A. Megens, Joaquín Pastor, Shirley Pullan and Thomas Steckler

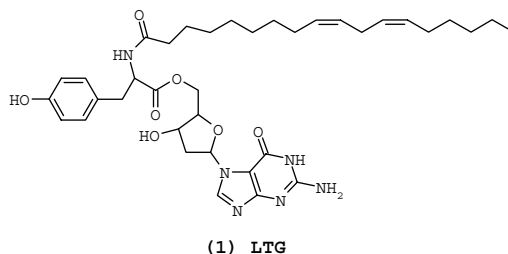


We report on the synthesis, in vitro binding and in vivo activity of R226161, identified within our series of tricyclic isoxazolines as a potential antidepressant combining 5-HT reuptake inhibition and  $\alpha_2$  antagonism.


**An exogenous marker: A novel approach for the characterization of oxidative stress**

pp 3661–3666

Soliman Khatib, Ramadan Musa and Jacob Vaya\*

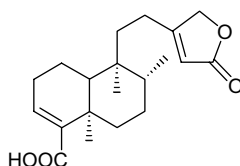


A novel marker was designed and synthesized for the characterization of oxidative stress in cells and organs. Analytical tools were developed to analyze products formed under its exposure to ROS.

**The isolation of secondary metabolites and in vitro potent anti-cancer activity of clerodermic acid from *Encisanthum membranifolium***

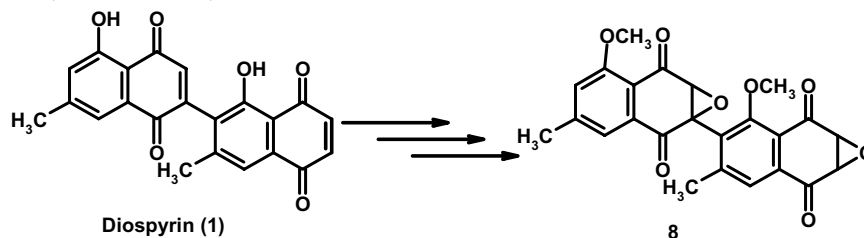
pp 3667–3671

Mai Efdi, Tomohiro Itoh, Yukihiro Akao, Yoshinori Nozawa, Mamoru Koketsu\* and Hideharu Ishihara


**Synthesis and antiproliferative activity of some novel derivatives of diospyrin, a plant-derived naphthoquinonoid**

pp 3672–3677

Madhushree Das Sarma, Rina Ghosh, Amarendra Patra and Banasri Hazra\*

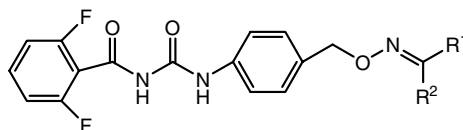


Novel quinonoids were produced through synthetic modification of diospyrin, a naturally occurring bioactive compound. The epoxide, **8**, proved to be the most potent derivative against three types of tumor cells, murine as well as human.

### Synthesis and bioassay evaluation of 1-(4-substitutedideneaminooxymethyl)-phenyl-3-(2,6-difluorobenzoyl)ureas

pp 3678–3683

Li Chen, Xiao-Ming Ou, Chun-Hui Mao, Jian Shang, Run-Qiu Huang, Fu-Chun Bi and Qing-Min Wang\*



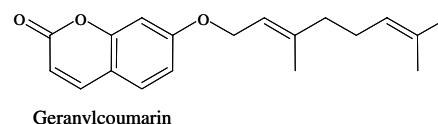
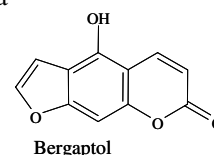
A variety of novel 1-(4-substitutedideneaminooxymethyl)-phenyl-3-(2,6-difluorobenzoyl)ureas were designed and synthesized by the reaction of 4-substitutedideneaminooxymethyl aniline with 2,6-difluorobenzoyl isocyanates in good yields. The title compounds were soluble in most organic solvents, which should make them easier to use. The preliminary bioassay showed that some of the title compounds show excellent insecticidal activity against *Mythimna separata* at the dosage of 25 mg kg<sup>-1</sup> and moderate insecticidal activity against *Nephotettix cincticeps* at the dosage of 500 mg kg<sup>-1</sup>. One title compound exhibited acaricidal activity against *Tetranychus urticae*.

### Radical scavenging and cytochrome P450 3A4 inhibitory activity of bergaptol and geranylcoumarin from grapefruit

pp 3684–3691

Basavaraj Girennavar, G. K. Jayaprakasha, Y. Jadegoud, G. A. Nagana Gowda and Bhimanagouda S. Patil\*

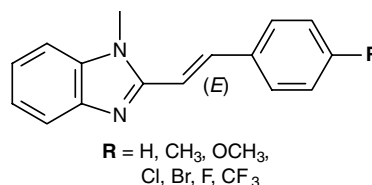
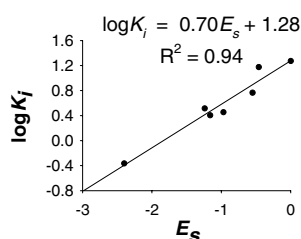
Bergaptol and geranylcoumarin were isolated from grapefruit and characterized using MS and NMR studies. Both the compounds were tested for their radical scavenging property using ABTS and DPPH methods. Bergaptol showed very good antioxidant potential and geranylcoumarin showed least activity. Further, these compounds were evaluated for cytochrome P450 CYP3A4 inhibition potential. Bergaptol and geranylcoumarin found to be potent inhibition of debenzylolation activity of CYP3A4 enzyme with IC<sub>50</sub> value of 24.92 and 42.93 μM, respectively.



### Inhibition of monoamine oxidase B by selected benzimidazole and caffeine analogues

pp 3692–3702

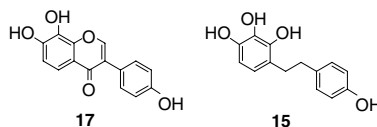
Deidré van den Berg, Kevin R. Zoellner, Modupe O. Ogunrombi, Sarel F. Malan, Gisella Terre'Blanche, Neal Castagnoli, Jr., Jacobus J. Bergh and Jacobus P. Petzer\*



### Polyphenols based on isoflavones as inhibitors of *Helicobacter pylori* urease

pp 3703–3710

Zhu-Ping Xiao, Da-Hua Shi, Huan-Qiu Li, Li-Na Zhang, Chen Xu and Hai-Liang Zhu\*

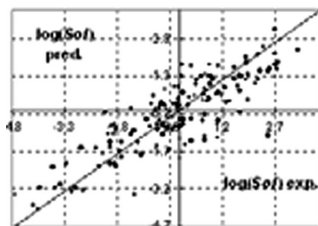


A series of polyphenols were synthesized and evaluated for inhibitory activity against *Helicobacter pylori* urease. Compounds **15** and **17** were the potent inhibitors with IC<sub>50</sub> = 0.03 and 0.14 mM, respectively.

**Application of descriptors based on Lipinski's rules in the QSPR study of aqueous solubilities**

pp 3711–3719

Pablo R. Duchowicz,\* Alan Talevi, Carolina Bellera, Luis E. Bruno-Blanch and Eduardo A. Castro

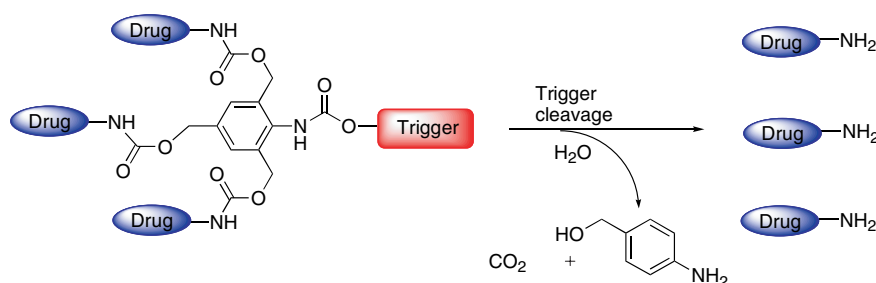


QSPR analysis for 148 drug-like compounds based on linear combinations of novel indices derived from Lipinski's 'rule of five' and Dragon-type of descriptor is described. Final solubility model is interpreted in structural terms.

**Remarkable drug-release enhancement with an elimination-based AB<sub>3</sub> self-immolative dendritic amplifier**

pp 3720–3727

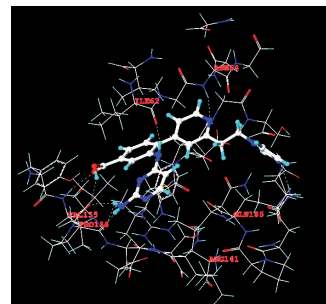
Amit Sagi, Ehud Segal, Ronit Satchi-Fainaro\* and Doron Shabat\*

**Structure based de novo design of novel glycogen synthase kinase 3 inhibitors**

pp 3728–3736

Nigus Dessalew\* and Prasad V. Bharatam

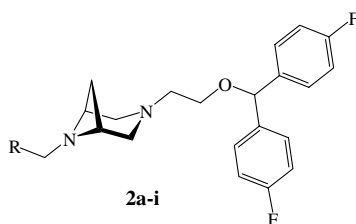
Structure based design has been successfully carried out to find a novel class of GSK-3 inhibitors using the Ludi de novo ligand design program. A total of 15 potential validated leads are suggested from the study.



**3-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-6-substituted-3,6-diazabicyclo[3.1.1]heptanes as novel potent dopamine uptake inhibitors**

pp 3748–3755

Giovanni Loriga, Stefania Ruiu, Ilaria Manca, Gabriele Murineddu, Christian Dessi, Luca Pani and Gérard A. Pinna\*



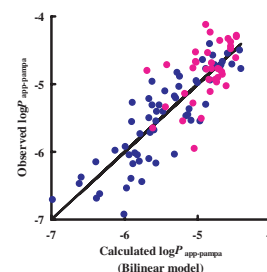
Some 3-{2-[bis-(4-fluorophenyl)methoxy]ethyl}-3,6-diazabicyclo[3.1.1]heptane derivatives (**2a-i**) have been synthesized and evaluated for their DA-uptake inhibition activity.

**QSAR study on permeability of hydrophobic compounds with artificial membranes**

pp 3756–3767

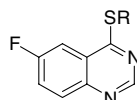
Masaaki Fujikawa, Kazuya Nakao, Ryo Shimizu and Miki Akamatsu\*

To investigate PAMPA permeability of hydrophobic compounds, we experimentally measured the  $P_{app-pampa}$  of compounds with high hydrophobicity, including several pesticides, and compared the measured  $P_{app-pampa}$  values with those calculated from the QSAR equation derived in our previous study. The new bilinear QSAR model explained the PAMPA permeability of the whole dataset of compounds, whether they were hydrophilic or hydrophobic, with the same parameters as the equation in the previous study. In addition, the PAMPA permeability coefficients correlated well with Caco-2 cell permeability coefficients.

**Synthesis and antifungal activity of novel s-substituted 6-fluoro-4-alkyl(aryl)thioquinazoline derivatives**

pp 3768–3774

Guang-Fang Xu, Bao-An Song,\* Pinaki S. Bhadury, Song Yang, Pei-Quan Zhang, Lin-Hong Jin, Wei Xue, De-Yu Hu and Ping Lu



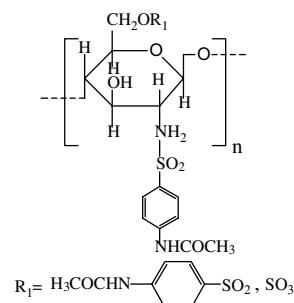
6-Fluoro-4-quinazolinol is prepared by the cyclization reaction of 2-amino-5-fluorobenzoic acid and formamide. The resulting thiol obtained by treatment of hydroxyl group with phosphorus (V) sulfide is converted under phase transfer condition to 4-substituted 4-alkylthio-6-fluoro quinazoline derivatives by reaction with halide. Title compounds **3a**, **3g**, and **3h** are found to possess good antifungal activities. Using the mycelial growth rate method in the laboratory, the mechanism of action of **3g** against *Fusarium oxysporum* in vitro is studied. The results indicate that **3a**, **3g**, and **3h** have high inhibitory effect on the growth of most of the fungi with  $EC_{50}$  values ranging from 8.3 to 64.2  $\mu\text{g/mL}$ .

**The preparation and antioxidant activity of the sulfanilamide derivatives of chitosan and chitosan sulfates**

pp 3775–3782

Zhimei Zhong, Xia Ji, Rong Xing, Song Liu, Zhanyong Guo, Xiaolin Chen and Pengcheng Li\*

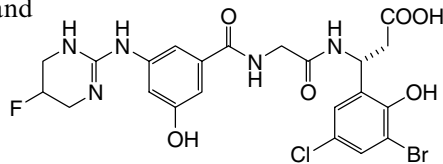
New sulfanilamide derivatives of chitosan and chitosan sulfates were synthesized and their antioxidant activity was reported.



**R-Isomers of Arg-Gly-Asp (RGD) mimics as potent  $\alpha_3\beta_3$  inhibitors**

pp 3783–3800

Srinivasan R. Nagarajan,\* Balekudru Devadas, James W. Malecha, Hwang-Fun Lu, Peter G. Ruminski, Joseph G. Rico, Thomas E. Rogers, Laura D. Marrufo, Joe T. Collins, H. Peter Kleine, Melissa K. Lantz, Jun Zhu, Nawasa F. ;Green, Mark A. Russell, Bryan H. Landis, Lawrence M. Miller, Debra M. Meyer, Tiffany D. Duffin, V. Wayne Engleman, Mary B. Finn, Sandra K. Freeman, David W. Griggs, Melanie L. Williams, Maureen A. Nickols, Jodi A. Pegg, Kristen E. Shannon, Christina Steininger, Marisa M. Westlin, G. Alan Nickols and Jeffery L. Keene

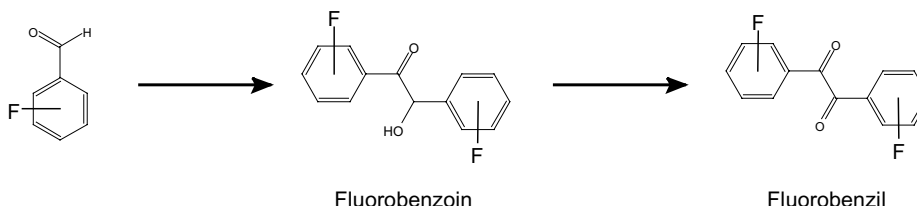


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**Analysis of the inhibition of mammalian carboxylesterases by novel fluorobenzoin and fluorobenzils**

pp 3801–3817

Latorya D. Hicks, Janice L. Hyatt, Teri Moak, Carol C. Edwards, Lyudmila Tsurkan, Monika Wierdl, Antonio M. Ferreira, Randy M. Wadkins and Philip M. Potter\*



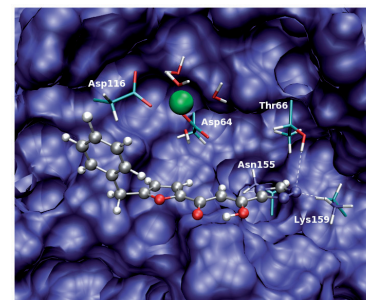
The inhibition of mammalian carboxylesterases by fluorobenzoin and fluorobenzils has been evaluated. These studies demonstrated that the electronic charge on the central atoms impacts the biological activity of these molecules.

**Calculation of binding energy using BLYP/MM for the HIV-1 integrase complexed with the S-1360 and two analogues**

pp 3818–3824

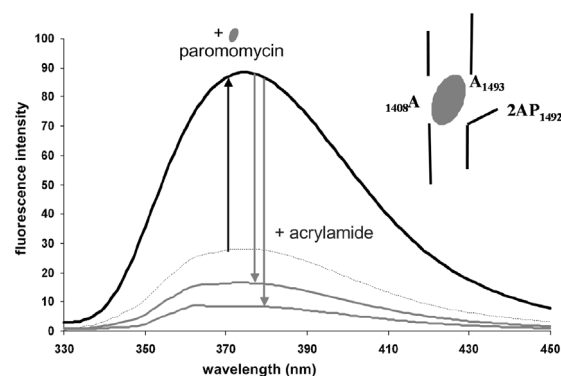
Cláudio N. Alves,\* Sergio Martí, Raquel Castillo, Juan Andrés, Vicent Moliner,\* Iñaki Tuñón and Estanislao Silla

Representation of the most important interactions between the S-1360 and HIV-1 integrase.

**Monitoring aminoglycoside-induced conformational changes in 16S rRNA through acrylamide quenching**

pp 3825–3831

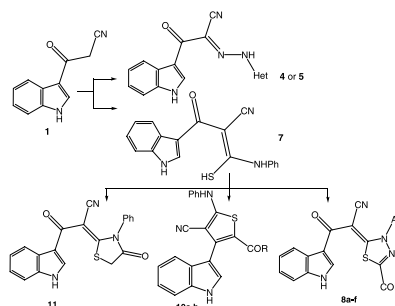
Pei-Wen Chao and Christine S. Chow\*



**Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents**

pp 3832–3841

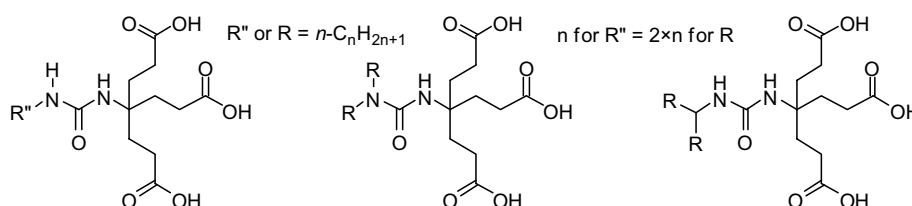
Mohamed A. A. Radwan,\* Eman A. Ragab, Nermien M. Sabry and Siham M. El-Shenawy



**Synthesis and antimicrobial activity of symmetrical two-tailed dendritic tricarboxylato amphiphiles**

pp 3842–3853

Eko W. Sugandhi, Joseph O. Falkinham, III and Richard D. Gandour\*

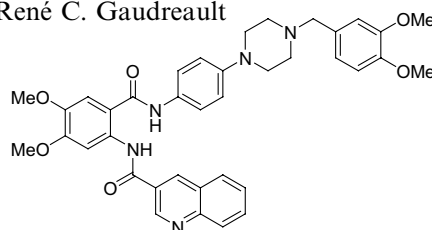


Antimicrobial activity of the water-soluble, dendritic tricarboxylato amphiphiles varies by microorganism as whether one or two tails or hydrophobicity or length predicts inhibition of growth.

**In vitro activity of novel dual action MDR anthranilamide modulators with inhibitory activity on CYP-450 (Part 2)**

pp 3854–3868

Philippe Labrie,\* Shawn P. Maddaford, Jacques Lacroix, Concettina Catalano, David K. H. Lee, Suman Rakhit and René C. Gaudreault

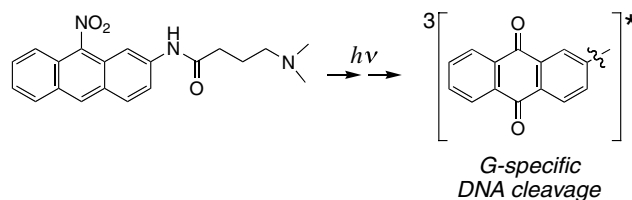


Synthesis and in vitro cytotoxicity assays of new anthranilamide MDR modulators have been performed to assess their potency of inhibition of P-glycoprotein (P-gp) and their effect on CYP450.

**9-Nitroanthracene derivative as a precursor of anthraquinone for photodynamic therapy**

pp 3869–3873

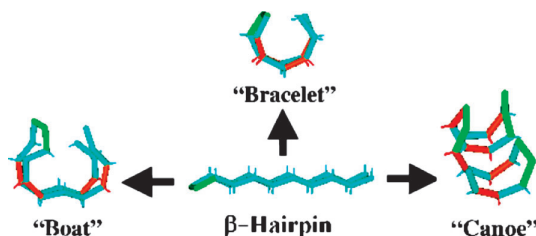
Kiyoshi Fukuhara,\* Shinji Oikawa, Nana Hakoda, Yasunori Sakai, Yusuke Hiraku, Takuji Shoda, Shinichi Saito, Naoki Miyata, Shosuke Kawanishi and Haruhiro Okuda



**A double catgrip mixed L and D mini protein only 20 residues long**

pp 3874–3882

Soumendra Rana, Bijoy Kundu and Susheel Durani\*



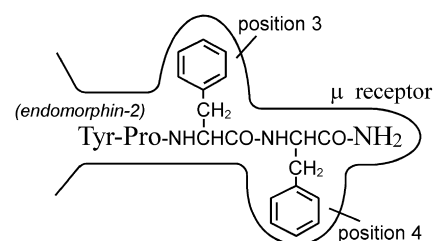
Proteins stereochemically customizable in form and function.

**Differential receptor binding characteristics of consecutive phenylalanines in  $\mu$ -opioid specific peptide ligand endomorphin-2**

pp 3883–3888

Takeshi Honda, Naoto Shirasu, Kaname Isozaki, Michiaki Kawano, Daiki Shigehiro, Yoshiro Chuman, Tsugumi Fujita, Takeru Nose and Yasuyuki Shimohigashi\*

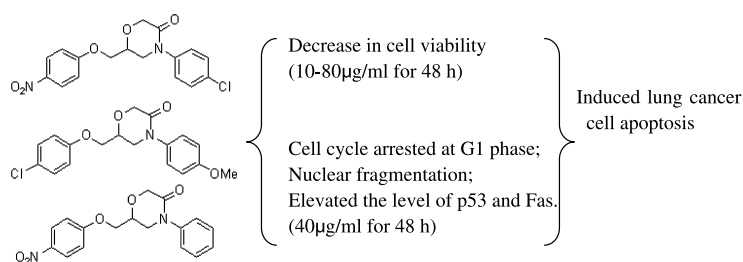
Endomorphin-2 is a unique opioid peptide possessing the two Phe residues at positions 3 and 4. It was evidenced these residues provide the receptor binding abilities with different interaction profiles.

**Novel morpholin-3-one derivatives induced apoptosis and elevated the level of P53 and Fas in A549 lung cancer cells**

pp 3889–3895

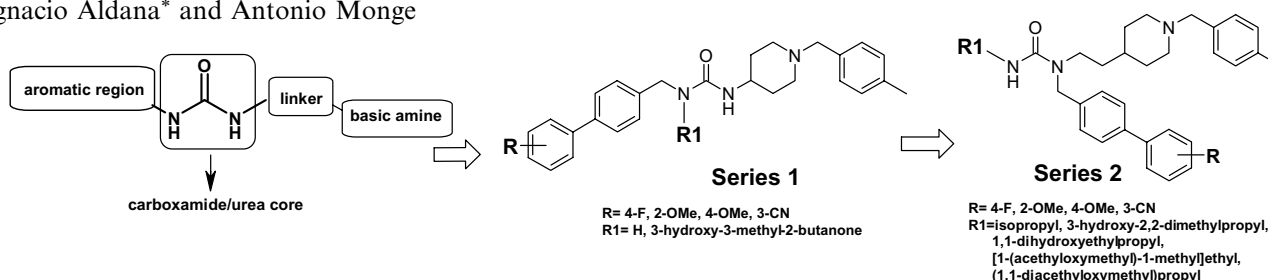
Qiuxia He, Xingshang Zhu, Mei Shi, Baoxiang Zhao,\* Jing Zhao, Shangli Zhang and Junying Miao\*

Morpholin-3-one derivatives arrested cell cycle partly at G1 phase, elevated the levels of P53 and Fas, and induced A549 cell apoptosis.

**Novel series of substituted biphenylmethyl urea derivatives as MCH-R1 antagonists for the treatment of obesity**

pp 3896–3911

Silvia Galiano, Javier Ceras, Nuria Cirauqui, Silvia Pérez, Laura Juanenea, Gildardo Rivera, Ignacio Aldana\* and Antonio Monge

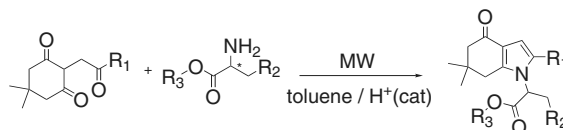




### Synthesis and cytotoxic evaluation of new (4,5,6,7-tetrahydro-indol-1-yl)-3-*R*-propionic acids and propionic acid ethyl esters generated by molecular mimicry

pp 3912–3918

Roberto Martínez,\* Angel Clara-Sosa and Ma. Teresa Ramírez Apan



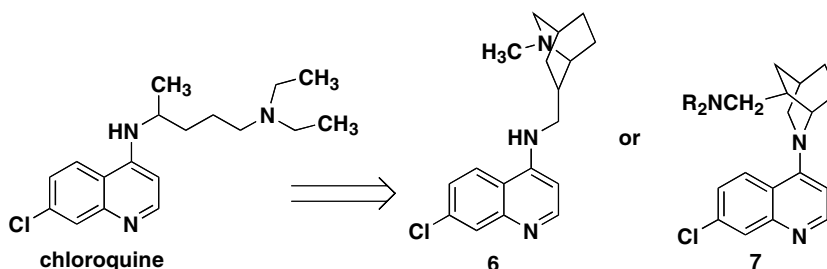
The new cytotoxic compounds with aminoacids residues incorporated were synthesized using the microwave technology. The *N*-(L)-cysteine ethyl ester derivatives inhibited the proliferation of all cancer cell lines tested.

### Synthesis of isoquinuclidine analogs of chloroquine: Antimalarial and antileishmanial activity

pp 3919–3925

M. O. Faruk Khan, Mark S. Levi, Babu L. Tekwani, Norman H. Wilson and Ronald F. Borne\*

The synthesis of new chloroquine analogs is reported. Some analogs showed good anti-malarial activity against both chloroquine susceptible D6 and the resistant W2 strains of *Plasmodium falciparum*. All analogs also demonstrated significant antileishmanial activity.

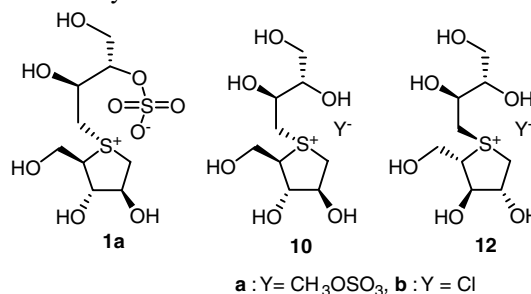


### Biological evaluation of de-O-sulfonated analogs of salacinol, the role of sulfate anion in the side chain on the $\alpha$ -glucosidase inhibitory activity

pp 3926–3937

Genzoh Tanabe, Kazuya Yoshikai, Takanori Hatanaka, Mizuho Yamamoto, Ying Shao, Toshie Minematsu, Osamu Muraoka,\* Tao Wang, Hisashi Matsuda and Masayuki Yoshikawa

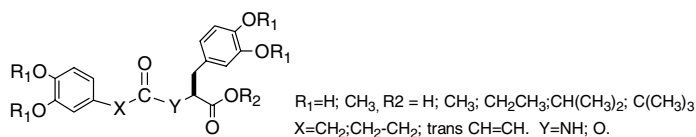
Two de-O-sulfonated salacinols (**10a** and **10b**) and the diastereomer (**12a**) were synthesized and their inhibitory activity against intestinal  $\alpha$ -glucosidase was examined. A potent inhibitory activity of **10a** and **10b** equal to that of **1a** against  $\alpha$ -glucosidase indicated that the *O*-sulfonate anion moiety of **1a** is not essential for the inhibitory activity.



### The structure–activity relationship of the series of non-peptide small antagonists for p56lck SH2 domain

pp 3938–3950


See-Hyoung Park, Hyun-Sik Oh, Mi-Ae Kang, Hyeongjin Cho, Joshi Bishnu Prasad, Jonghwa Won\* and Keun-Hyeung Lee\*



A series of non-peptide small antagonists for p56lck SH2 domain was synthesized and the binding affinity for the domain and in vitro T-cell inhibitory activity were measured.

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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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