

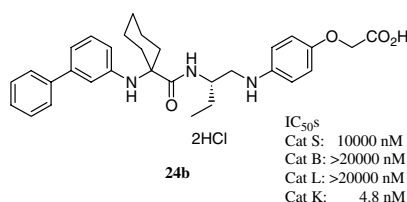
## Contents

### ARTICLES

#### Potent and selective cathepsin K inhibitors

pp 6789–6806

Tsuyoshi Shinozuka,\* Kousei Shimada, Satoshi Matsui, Takahiro Yamane, Mayumi Ama, Takeshi Fukuda, Motohiko Taki, Yuko Takeda, Eri Otsuka, Michiko Yamato, Shin-ichi Mochizuki, Keiko Ohhata and Satoru Naito

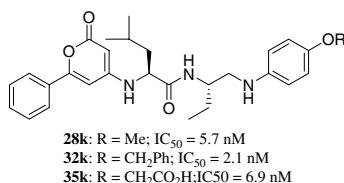


The synthesis, SARs, selectivity over other human cathepsins, pharmacokinetics, and in vivo evaluation of **24b** are reported.

#### Arylamine based cathepsin K inhibitors: Investigating P3 heterocyclic substituents

pp 6807–6819

Tsuyoshi Shinozuka,\* Kousei Shimada, Satoshi Matsui, Takahiro Yamane, Mayumi Ama, Takeshi Fukuda, Motohiko Taki, Yuko Takeda, Eri Otsuka, Michiko Yamato and Satoru Naito

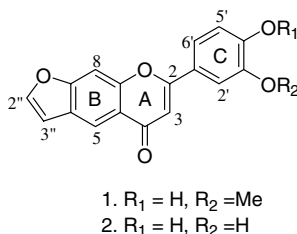


The synthesis, SARs, selectivity over other human cathepsins, and pharmacokinetics of heterocyclic substituted cathepsin K inhibitors are reported.

#### Isolation and synthesis of analgesic and anti-inflammatory compounds from *Ochna squarrosa* L.

pp 6820–6826

V. Anuradha, Pullela V. Srinivas, R. Ranga Rao, K. Manjulatha, Muralidhar G. Purohit and J. Madhusudana Rao\*

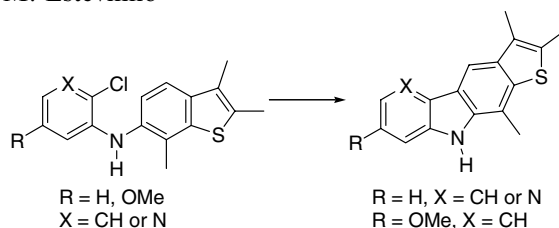


Two new furanoflavones and a new chalcone dimer were isolated from *Ochna squarrosa*. The new furanoflavones were synthesized using a new methodology for benzyl deprotection. All the new compounds displayed good analgesic and anti-inflammatory activities.

### Synthesis and antimicrobial activity studies of *ortho*-chlorodiarylamines and heteroaromatic tetracyclic systems in the benzo[*b*]thiophene series

pp 6827–6831

Maria-João R. P. Queiroz,\* Isabel C. F. R. Ferreira, Yannick De Gaetano, Gilbert Kirsch, Ricardo C. Calhella and Leticia M. Estevinho

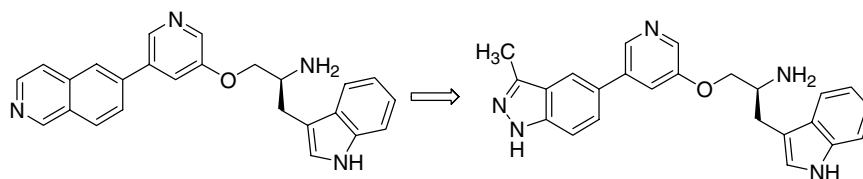


Synthesis and in vitro antimicrobial activity against Gram-positive and Gram-negative bacteria and *Candida albicans* are presented.

### Synthesis and SAR of indazole-pyridine based protein kinase B/Akt inhibitors

pp 6832–6846

Keith W. Woods,\* John P. Fischer, Akiyo Claiborne, Tongmei Li, Sheela A. Thomas, Gui-Dong Zhu, Robert B. Diebold, Xuesong Liu, Yan Shi, Vered Klinghofer, Edward K. Han, Ran Guan, Shayna R. Magnone, Eric F. Johnson, Jennifer J. Bouska, Amanda M. Olson, Ron de Jong, Tilman Oltersdorf, Yan Luo, Saul H. Rosenberg, Vincent L. Giranda and Qun Li

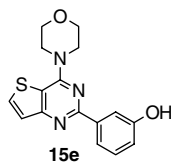


SAR studies leading from the isoquinoline analogue to the discovery of the indazole moiety are described.

### Synthesis and biological evaluation of 4-morpholino-2-phenylquinazolines and related derivatives as novel PI3 kinase p110 $\alpha$ inhibitors

pp 6847–6858

Masahiko Hayakawa,\* Hiroyuki Kaizawa, Hiroyuki Moritomo, Tomonobu Koizumi, Takahide Ohishi, Minoru Okada, Mitsuaki Ohta, Shin-ichi Tsukamoto, Peter Parker, Paul Workman and Mike Waterfield



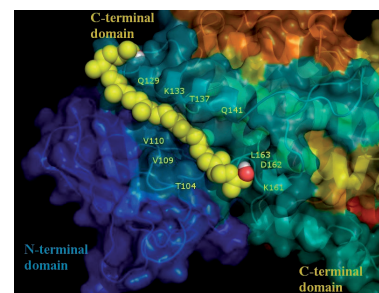
The thieno[3,2-*d*]pyrimidine derivative **15e** is a potent and selective p110 $\alpha$  inhibitor.

### Molecular modeling of the non-covalent binding of the dietary tomato carotenoids lycopene and lycophyll, and selected oxidative metabolites with 5-lipoxygenase

pp 6859–6867

Eszter Hazai, Zsolt Bikádi, Ferenc Zsila and Samuel F. Lockwood\*

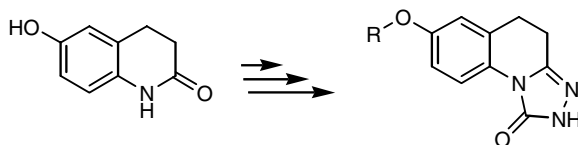
All-*trans*-lycophyll bound at the 'cleavage site' of 5-lipoxygenase, as revealed by molecular docking calculations. The long linear cleft is a putative allosteric binding site on 5-LOX.



**Anticonvulsant and toxicity evaluation of some 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1(2*H*)-ones**

pp 6868–6873

Hong-Guang Jin, Xian-Yu Sun, Kyu-Yun Chai, Hu-Ri Piao and Zhe-Shan Quan\*



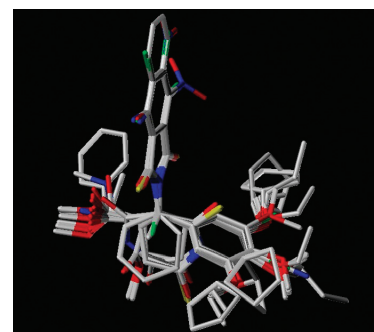
A series of 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1(2*H*)-one derivatives was synthesized starting from 7-hydroxyl-3,4-dihydro-2(1*H*)-quinoline. Compound 7-benzyloxy-4,5-dihydro-[1,2,4]thiazolo[4,3-*a*]quinoline-1(2*H*)-one (**3f**) was the most potent in all synthesized compounds.

**Development of new CoMFA and CoMSIA 3D-QSAR models for anti-inflammatory phthalimide-containing TNF $\alpha$  modulators**

pp 6874–6885

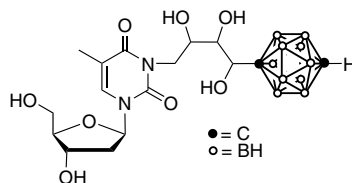
Carolina Martins Avila, Nelilma Correia Romeiro, Gilberto M. Sperandio da Silva, Carlos M. R. Sant'Anna, Eliezer J. Barreiro and Carlos A. M. Fraga\*

3D-QSAR studies using CoMFA and CoMSIA approaches were performed on a series of anti-inflammatory thalidomide-analogue TNF $\alpha$  modulators.

**Hydrophilically enhanced 3-carboranyl thymidine analogues (3CTAs) for boron neutron capture therapy (BNCT) of cancer**

pp 6886–6899

Sureshbabu Narayanasamy, B. T. S. Thirumamagal, Jayaseharan Johnsamuel, Youngjoo Byun, Ashraf S. Al-Madhoun, Elena Usova, Guirec Y. Cosquer, Junhua Yan, Achintya K. Bandyopadhyaya, Rohit Tiwari, Staffan Eriksson and Werner Tjarks\*

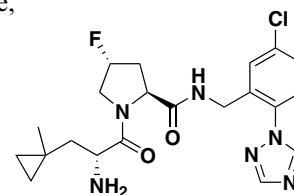


Several 3-carboranyl thymidine analogues (3CTAs), all of which are containing hydrophilicity-enhancing groups, were synthesized and their biochemical and physicochemical properties were evaluated.

**Discovery of potent, selective 4-fluoroproline-based thrombin inhibitors with improved metabolic stability**

pp 6900–6916

Donnette D. Staas,\* Kelly L. Savage, Vanessa L. Sherman, Heidi L. Shimp, Terry A. Lyle, Lekhanh O. Tran, Catherine M. Wiscourt, Daniel R. McMasters, Philip E. J. Sanderson, Peter D. Williams, Bobby J. Lucas, Jr., Julie A. Krueger, S. Dale Lewis, Rebecca B. White, Sean Yu, Bradley K. Wong, Christopher J. Kochansky, M. Reza Anari, Youwei Yan and Joseph P. Vacca



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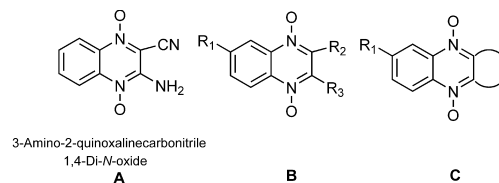
$K_i$  (thrombin) = 0.37 nM  
 $K_i$  (trypsin) = 3300 nM  
 2xAPTT = 190 nM

### New quinoxaline 1,4-di-*N*-oxides. Part 1: Hypoxia-selective cytotoxins and anticancer agents derived from quinoxaline 1,4-di-*N*-oxides

pp 6917–6923

Kamelia M. Amin, Magda M.F. Ismail,\* Eman Noaman, Dalia H. Soliman and Yousry A. Ammar

A new series of quinoxaline 1,4-di-*N*-oxides (**B**) and fused quinoxaline di-*N*-oxide (**C**) were synthesized and evaluated for antitumor activity against liver carcinoma (Hepg2) and brain tumor (U251), human cell lines. Compounds **9c** and **8a** demonstrated potent antitumor activity against Hepg2 with IC<sub>50</sub> 1.9 and 2.9 µg/mL, respectively, accompanied by lack of toxicity against U251. The hypoxic-cytotoxic activity was also evaluated for selected compounds. Compound **10a** was the most potent cytotoxin IC<sub>50</sub> 0.9 µg/mL, potency 75 µg/mL, and was 15 times more selective toward hypoxic cells (HCR > 111) than the standard (**A**) (HCR > 7.5). Enaminone **4**, enamine derivatives **3a,b** were more selective (HCR >10, >8.7, 9.4, respectively) than the standard in hypoxia.

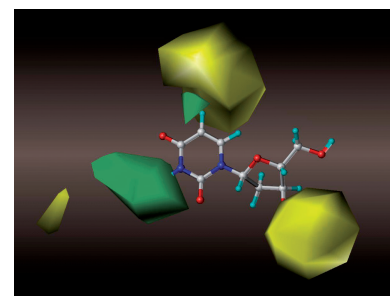


### Comparative molecular field analysis and comparative molecular similarity indices analysis of boron-containing human thymidine kinase 1 substrates

pp 6924–6932

Achintya K. Bandyopadhyaya,\* Rohit Tiwari and Werner Tjarks

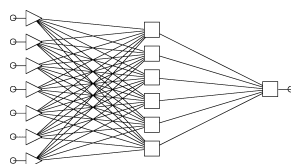
3D-QSAR using CoMFA and CoMSIA techniques has been applied to evaluate boronated and non-boronated pyrimidine nucleosides as substrates of human thymidine kinase 1 (hTK1). The derived CoMSIA model showed predictive capabilities and a high level of internal consistency. Contour maps obtained from the CoMSIA model correlated with the experimentally developed SAR.



### QSAR modeling of anti-invasive activity of organic compounds using structural descriptors

pp 6933–6939

Alan R. Katritzky,\* Minati Kuanar, Dimitar A. Dobchev, Barbara W. A. Vanhoecke,\* Mati Karelson, Virinder S. Parmar, Christian V. Stevens and Marc E. Bracke\*



The anti-invasive activity of 139 compounds was correlated by an artificial neural network approach with descriptors calculated solely from the molecular structures using CODESSA Pro. The resulting nonlinear (artificial neural network) QSAR model predicted the exact class for 66 (71%) of the training set of 93 compounds.

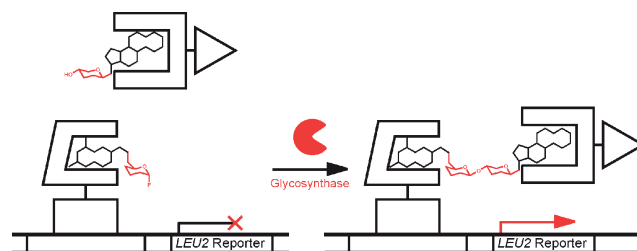


### Optimized design and synthesis of chemical dimerizer substrates for detection of glycosynthase activity via chemical complementation

pp 6940–6953

Haiyan Tao, Pamela Peralta-Yahya, Hening Lin and Virginia W. Cornish\*

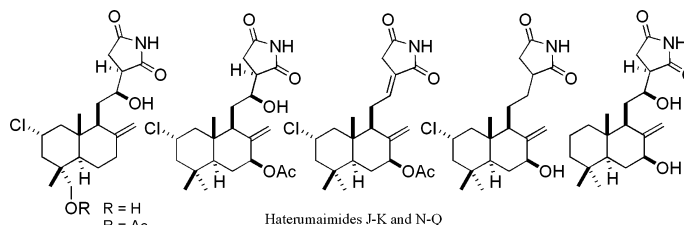
Using chemical complementation, glycosynthase activity is detected as covalent coupling between a small molecule disaccharide acceptor and a small molecule disaccharide  $\alpha$ -fluoro donor substrate. Here we report the optimized design and synthesis of these small molecule substrates and their activity in the chemical complementation assay.



### Cytotoxic labdane alkaloids from an ascidian *Lissoclinum* sp.: Isolation, structure elucidation, and structure–activity relationship

pp 6954–6961

Jasim Uddin, Katsuhiro Ueda,\* Eric R. O. Siwu, Masaki Kita and Daisuke Uemura

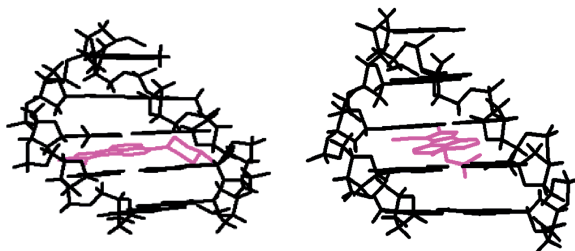


Four new cytotoxic labdane alkaloids, haterumaimides N–Q were isolated from the ascidian *Lissoclinum* sp. Their structures and SAR studies of this series of alkaloids are described.

### Acenaphtho[1,2-*b*]pyrrole derivatives as new family of intercalators: Various DNA binding geometry and interesting antitumor capacity

pp 6962–6970

Zhichao Zhang, Yuanyuan Yang, Danni Zhang, Yuanyuan Wang, Xuhong Qian\* and Fengyu Liu\*



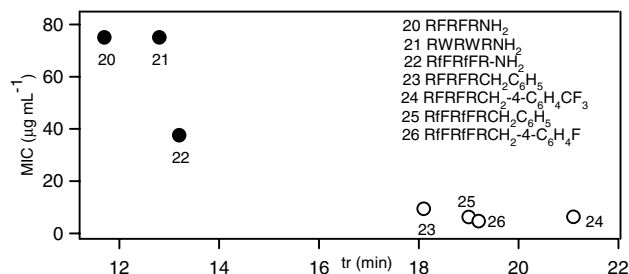
It contributes much more to the antitumor property for the geometry of intercalator–DNA complexes than the binding affinity.

### The introduction of fluorine atoms or trifluoromethyl groups in short cationic peptides enhances their antimicrobial activity

pp 6971–6978

Diana Giménez, Cecilia Andreu,\* Marcel·lí del Olmo, Teresa Varea, Dolores Diaz and Gregorio Asensio

The effect of introducing fluorine atoms or trifluoromethyl groups in cationic pentapeptides is reported. An enhanced antimicrobial activity was found suggesting an increase in their hydrophobicity.

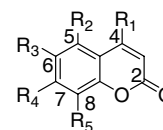


### Structure–activity relationship of natural and synthetic coumarins inhibiting the multidrug transporter P-glycoprotein

pp 6979–6987

Imad Raad, Raphael Terreux, Pascal Richomme, Eva-Laure Matera, Charles Dumontet, Jean Raynaud and David Guilet\*

The substitution of the basic structure of coumarin, by phenyl group on position C<sub>4</sub> and α-(hydroxyisopropyl)dihydrofuran moiety on position C<sub>5</sub>–C<sub>6</sub> or C<sub>7</sub>–C<sub>8</sub>, reduces the P-gp-mediated drug efflux of daunorubicin out of human leukemic cells (K562/R7).

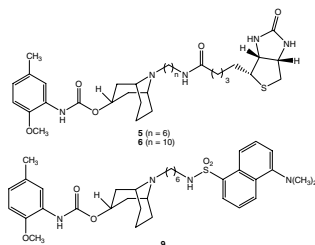


R<sub>1</sub> = H, picolinyl or phenyl  
 R<sub>2</sub> and R<sub>4</sub> = H, OH, O-prenyl  
 R<sub>3</sub> and R<sub>5</sub> = acyl, prenyl (cyclic or acyclic), ...

**Synthesis of *N*-substituted 9-azabicyclo[3.3.1]nonan-3 $\alpha$ -yl carbamate analogs as  $\sigma_2$  receptor ligands**

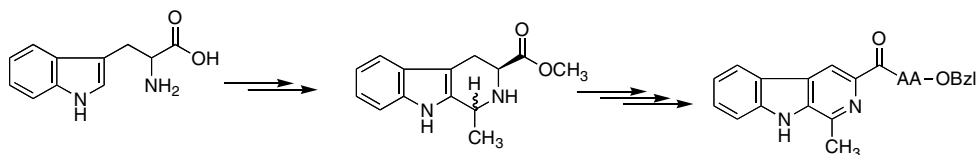
pp 6988–6997

Suwanna Vangveravong, Jinbin Xu, Chenbo Zeng and Robert H. Mach\*

Synthesis and in vitro binding of a series of molecular probes for studying the function of the  $\sigma_2$  receptor.**Synthesis and cytotoxic activities of  $\beta$ -carboline amino acid ester conjugates**

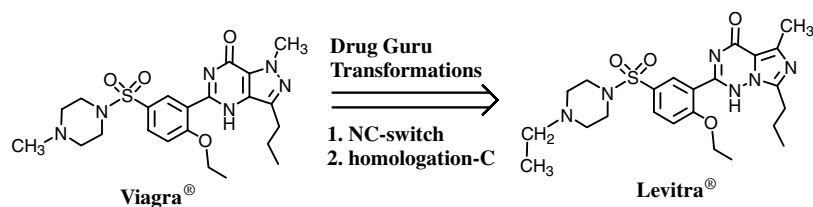
pp 6998–7010

Ming Zhao, Lanrong Bi, Wei Wang, Chao Wang, Michèle Baudy-Floc'h, Jingfang Ju\* and Shiqi Peng\*

**Drug Guru: A computer software program for drug design using medicinal chemistry rules**

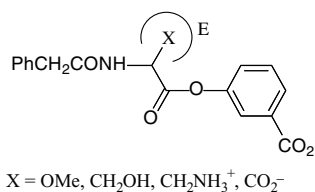
pp 7011–7022

Kent D. Stewart,\* Melisa Shiroda and Craig A. James

**Synthesis and  $\beta$ -lactamase reactivity of  $\alpha$ -substituted phenaceturates**

pp 7023–7033

S. A. Adediran, D. Cabaret, R. R. Flavell, J. A. Sammons, M. Wakselman\* and R. F. Pratt\*



**Biochemical and functional characterization of an L-amino acid oxidase isolated from *Bothrops pirajai* snake venom**

pp 7034–7043

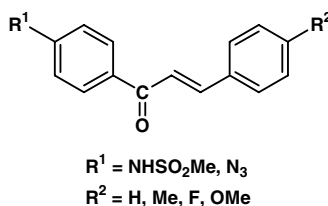
Luiz Fernando M. Izidoro, Marcela C. Ribeiro, Guilherme R. L. Souza, Carolina D. Sant'Ana, Amelia Hamaguchi, Maria I. Homs-Brandeburgo, Luiz R. Goulart, Rene O. Belebony, Auro Nomizo, Suely V. Sampaio, Andreimar M. Soares\* and Veridiana M. Rodrigues\*

N-terminal sequence is: ADDKNPLEEFRETNYEVFLEIAKNGLKATSNPKRVVIVG. The present investigation reports, the first time, the isolation and biochemical characterization of a new L-amino acid oxidase (BpirLAAO-I) from *Bothrops pirajai* venom, with special reference to its platelet aggregation effect and bactericidal, parasitocidal, and antitumoral activity.

**Synthesis and biological evaluation of 1,3-diphenylprop-2-en-1-ones possessing a methanesulfonamido or an azido pharmacophore as cyclooxygenase-1/2 inhibitors**

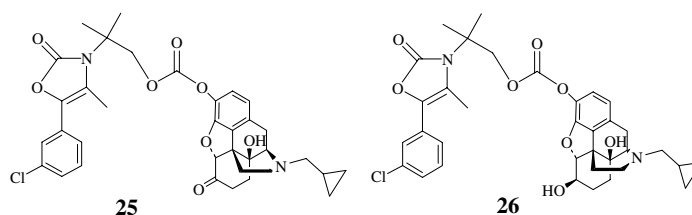
pp 7044–7050

Afshin Zarghi, Tannaz Zebardast, Farinaz Hakimion, Farshad H. Shirazi, P. N. Praveen Rao and Edward E. Knaus\*

**Synthesis and hydrolytic behavior of two novel tripartate codrugs of naltrexone and 6β-naltrexol with hydroxybupropion as potential alcohol abuse and smoking cessation agents**

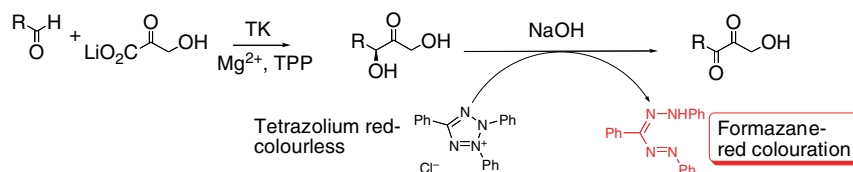
pp 7051–7061

Mohamed O. Hamad, Paul K. Kiptoo, Audra L. Stinchcomb and Peter A. Crooks\*

**A colorimetric assay for screening transketolase activity**


pp 7062–7065

Mark E. B. Smith, Ursula Kaulmann, John M. Ward and Helen C. Hailes\*



**OTHER CONTENTS****Summary of instructions to authors****p I**

\*Corresponding author

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

2006: The cover figure shows a synthetic multifunctional pore that is composed of rigid-rod staves (para-octiphenyls, tan) and beta-sheet hoops (arrows) and can be activated with external ligands (fullerenes, golden spheres) and closed with internal blockers (alpha-helix, red ribbon) [Gorteau, V.; Bollot, G.; Mareda, J.; Pasini, D.; Tran, D.-H.; Lazar, A. N.; Coleman, A. W.; Sakai, N.; Matile, S. *Bioorg. Med. Chem.* **2005**, 13, 5171–5180].

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