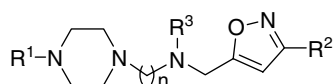


## Contents

### ARTICLES

**Synthesis and biological evaluation of novel T-type  $\text{Ca}^{2+}$  channel blockers** pp 3965–3970

Hee Kyung Jung, Munikumar Reddy Doddareddy, Joo Hwan Cha, Hyewhon Rhim,  
Yong Seo Cho, Hun Yeong Koh, Bong Young Jung and Ae Nim Pae\*



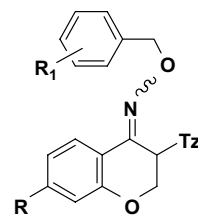
$\text{R}^1, \text{R}^2$  = aromatic substituents  
 $\text{R}^3$  = H, alkyl  $n = 2, 3$

A small molecule library of piperazinylalkylisoxazole derivatives containing about 600 compounds was designed, synthesized and evaluated for blocking effects on T-type  $\text{Ca}^{2+}$  channel.

**(E)- and (Z)-1,2,4-Triazolylchromanone oxime ethers as conformationally constrained antifungals** pp 3971–3976

Saeed Emami, Mehraban Falahati, Ali Banifatemi, Massoud Amanlou and Abbas Shafiee\*

A series of 1,2,4-triazolylchromanone oxime ethers were synthesized and tested for in vitro antifungal activity. Many of these derivatives exhibit high activity against *Candida albicans*, *Saccharomyces cerevisiae*, *Aspergillus niger* and *Microsporum gypseum*.

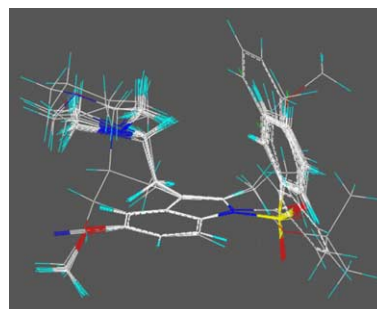


Tz = 1,2,4-Triazol-1-yl;  
1,2,4-Triazol-4-yl  
R = H; Cl  
R<sub>1</sub> = H; Cl; F; Br; di-Cl

**CoMFA and CoMSIA 3D QSAR analysis on  $N_1$ -arylsulfonylindole compounds as 5-HT<sub>6</sub> antagonists** pp 3977–3985

Munikumar Reddy Doddareddy, Yong Seo Cho, Hun Yeong Koh and Ae Nim Pae\*

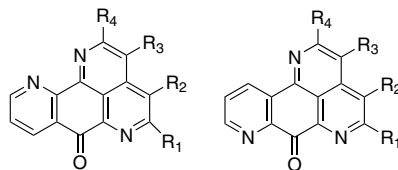
Comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) three-dimensional quantitative structure–activity relationship (3D-QSAR) studies were conducted on a series of  $N_1$ -arylsulfonylindole compounds as 5-HT<sub>6</sub> antagonists.



### Synthesis and in vitro antitumor activity of ring C and D-substituted phenanthroline-7-one derivatives, analogues of the marine pyridoacridine alkaloids ascididemin and meridine

pp 3987–3994

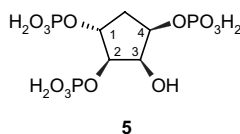
Evelyn Delfourne,\* Robert Kiss, Laurent Le Corre, Frederic Dujols, Jean Bastide, Françoise Collignon, Brigitte Lesur, Armand Frydman and Francis Darro



### Synthesis and binding properties of cyclopentane analogues of *myo*-inositol 1,4,5-tris(phosphate)

pp 3995–4001

Marc-Antoine Moris, Annabelle Z. Caron, Gaétan Guillemette and Gilbert Schlewer\*

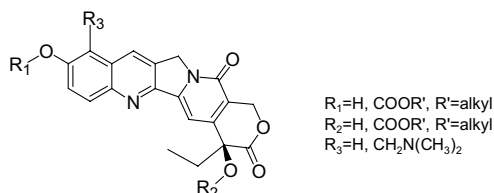


Cyclopentanic analogues of *myo*-inositol 1,4,5-tris(phosphate) were synthesised starting from cyclopentadiene, and their affinities for the Ins(1,4,5)P<sub>3</sub> receptors were tested.

### Synthesis and biological evaluation of bis and monocarbonate prodrugs of 10-hydroxycamptothecins

pp 4003–4008

Xungui He, Wei Lu,\* Xiqun Jiang, Junchao Cai, Xiongwen Zhang and Jian Ding



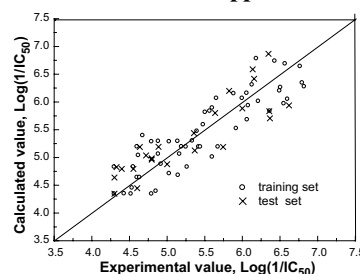
The bis and mono-alkyl carbonates of 10-hydroxycamptothecins were synthesized and their chemical and enzymatical stability as well as antitumor activity were studied.

### A QSAR study on inhibitory activities of 1-phenylbenzimidazoles against the platelet-derived growth factor receptor

pp 4009–4015

Chongli Zhong,\* Jingtao He, Chunyu Xue and Yajun Li

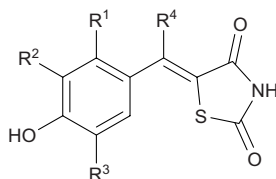
1-Phenylbenzimidazoles were reported by Palmer et al. (*J. Med. Chem.*, **1998**, 41, 5457; **1999**, 42, 2373) as a new class of inhibitors of the platelet-derived growth factor receptor (PDGFR), which are also of interest as potential anticancer drugs. Since the existing quantitative structure–activity relationship (QSAR) models for inhibitory activities of 1-phenylbenzimidazoles are less than satisfying, we performed a QSAR study in this work and developed a QSAR model using variable connectivity indices as input parameters. The new model was developed based on the analysis of a training set of 55 active compounds, and was validated with a test set of 24 active compounds and 44 inactive compounds. The results show that the new model gives good predictions, both for active and inactive compounds, and the effects the structure of the compounds on the inhibitory activity can be represented well by the model. This work not only presents a QSAR model for inhibitory activities of 1-phenylbenzimidazoles, but also demonstrates that the variable connectivity indices, a class of not widely recognized structural descriptors, are quite useful in the QSAR studies in the fields of pharmaceutics and biochemistry, which should play a more important role in the QSAR studies in these fields.



**Inhibitory effects of multi-substituted benzylidenethiazolidine-2,4-diones on LDL oxidation**

pp 4017–4023

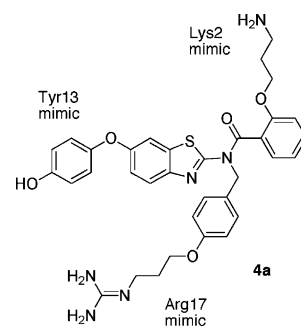
Tae-Sook Jeong, Ju-Ryoung Kim, Kyung Soon Kim, Kyung-Hyun Cho, Ki-Hwan Bae and Woo Song Lee\*

Benzylidenethiazolidine-2,4-diones **3a–h** were synthesized and evaluated for LDL-antioxidant activities.**Synthesis and biological evaluation of nonpeptide mimetics of  $\omega$ -conotoxin GVIA**

pp 4025–4037

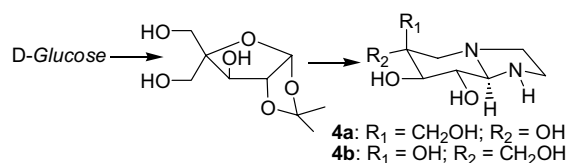
Jonathan B. Baell,\* Peter J. Duggan,\* Stewart A. Forsyth, Richard J. Lewis, Y. Phei Lok and Christina I. Schroeder

Nonpeptide mimetics possessing fragments that mimic Lys2, Tyr13 and Arg17 in  $\omega$ -conotoxin GVIA have been prepared. The lead compound (**4a**) and three analogues were assayed for rat brain N- and P/Q-type VGCC binding, with **4a** exhibiting low  $\mu$ M binding to the N-type channel, and two compounds demonstrating promising selectivity for the N-type over the P/Q-type channel.

**Synthesis and evaluation of glycosidase inhibitory activity of octahydro-2H-pyrido[1,2-a]pyrimidine and octahydro-imidazo[1,2-a]pyridine bicyclic diazasugars**

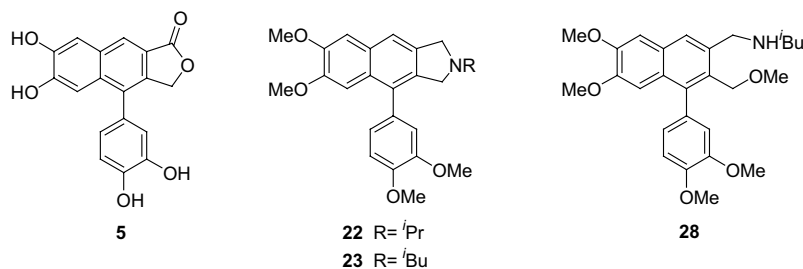
pp 4039–4044

Dilip D. Dhavale,\* Mohammed M. Matin, Tarun Sharma and Sushma G. Sabharwal

**Preparation and anti-HIV activities of retrojusticidin B analogs and azalignans**

pp 4045–4054

Kadali S. Sagar, Chia-Chuan Chang, Wei-Kung Wang, Jung-Yaw Lin and Shoei-Sheng Lee\*

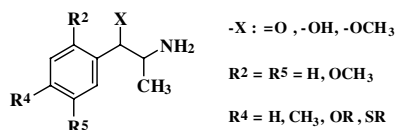


Ten lignans and nine azalignans, structurally related to two anti-HIV RT retrojusticidin B and phyllamycin A, were prepared. Of them, compounds **5**, **22**, **23**, and **28** showed good anti-HIV activity with  $IC_{50}$  value of 0.25, 1.07, 0.01, 0.32  $\mu$ g/mL, respectively.

**MAO inhibition by arylisopropylamines: the effect of oxygen substituents at the  $\beta$ -position**

pp 4055–4066

Mauricio Osorio-Olivares, Marcos Caroli Rezende,\* Silvia Sepúlveda-Boza, Bruce K. Cassels and Angélica Fierro

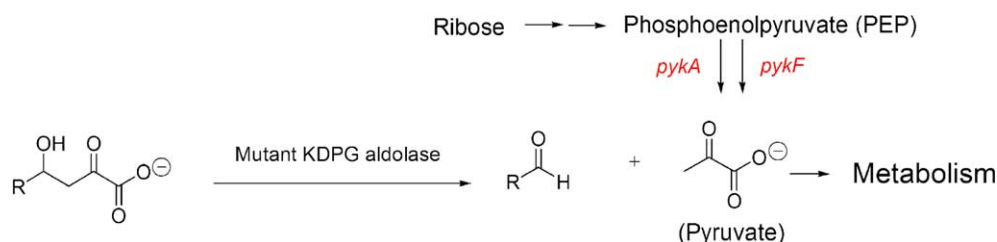


Twenty-nine arylisopropylamines with an oxo, hydroxy, or methoxy side-chain  $\beta$ -substituent were prepared and evaluated in vitro as MAO-A and MAO-B inhibitors.

**A bacterial selection for the directed evolution of pyruvate aldolases**

pp 4067–4074

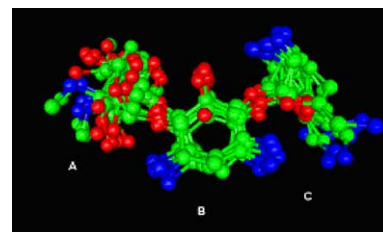
Jennifer S. Griffiths, Manoj Cheriyan, Jayme B. Corbell, Luka Pocivavsek, Carol A. Fierke\* and Eric J. Toone\*

**Acid–base versus structural properties of an aminoglycoside antibiotic—sisomicin: NMR and potentiometric approach**

pp 4075–4080

Artur Krężel, Wojciech Szczepanik, Magdalena Świątek and Małgorzata Jeżowska-Bojczuk\*

$^1\text{H}$  NMR, potentiometry and molecular modeling study were applied due to characterize precisely the acid–base properties of an aminoglycoside antibiotic—sisomicin. The group protonation constants of this drug were determined, as well as the summary stability constants of six representatives of aminoglycosides.

**Substrate variants versus transition state analogues as noncovalent, reversible enzyme inhibitors**

pp 4081–4088

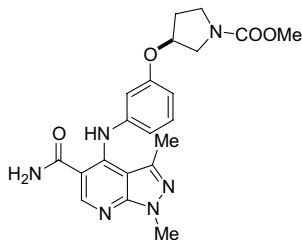
Timothy P. Smyth

Transition-state-analogue structures and substrate variants provide two discrete paradigms for the design of reversible enzyme inhibitors; these are contrasted here and the case of substrate variants is delineated with a well-defined set of structures.

**New orally active PDE4 inhibitors with therapeutic potential**

pp 4089–4100

Hiroshi Ochiai, Akiharu Ishida, Tazumi Ohtani, Kensuke Kusumi, Katuya Kishikawa, Susumu Yamamoto, Hiroshi Takeda, Takaaki Obata, Hisao Nakai\* and Masaaki Toda

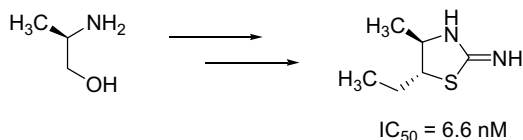


The discovery of an orally active pyrazolopyridine derivatives as a structually new PDE4 inhibitor is reported.

**4,5-Dialkylsubstituted 2-imino-1,3-thiazolidine derivatives as potent inducible nitric oxide synthase inhibitors**

pp 4101–4116

Shigeo Ueda,\* Hideo Terauchi, Akihiro Yano, Masashi Matsumoto, Taeko Kubo, Yoko Kyoya, Kenji Suzuki, Motoharu Ido and Motoji Kawasaki

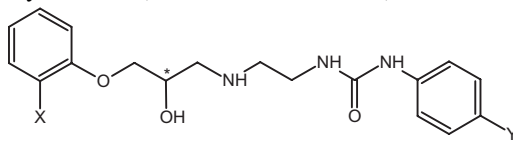


A series of 2-imino-1,3-thiazolidine derivatives have been synthesized and their inhibitory activity against iNOS and selectivity for iNOS both in vitro and in vivo was described.

**Synthesis and first in vivo evaluation of new selective high affinity  $\beta_1$ -adrenoceptor radioligands for SPECT based on ICI 89,406**

pp 4117–4132

Stefan Wagner,\* Klaus Kopka, Marilyn P. Law, Burkhard Riemann, Victor W. Pike, Otmar Schober and Michael Schäfers

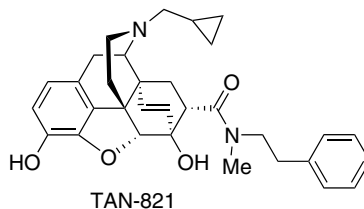


Six pairs of new compounds with the 3-aryloxy-2-propanolamine core of the selective  $\beta_1$ -adrenoceptor ligand, ICI 89,406 (X: CN, Y: H), were synthesized. Each pair consisted of the racemic and the (*S*)-aryloxypropanolamine derivatives. The comparison of racemic (11a: X: I, 11b: X:  $^{125}$ I, 11c: X:  $^{123}$ I, Y: COOH) and (*S*)- (15a: X: I, 15b: X:  $^{125}$ I, 15c: X:  $^{123}$ I, Y: COOH) compounds indicates that the (*S*)-enantiomer should improve the feasibility of imaging  $\beta_1$ -adrenoceptor density noninvasively in vivo in the human heart using the molecular imaging technique of single photon emission computed tomography (SPECT) in patients suffering from cardiac diseases like ventricular arrhythmias and heart failure.

**Drug design and synthesis of  $\epsilon$  opioid receptor agonist: 17-(cyclopropylmethyl)-4,5 $\alpha$ -epoxy-3,6 $\beta$ -dihydroxy-6,14-endoethenomorphinan-7 $\alpha$ -(*N*-methyl-*N*-phenethyl)carboxamide (TAN-821) inducing antinociception mediated by putative  $\epsilon$  opioid receptor**

pp 4133–4145

Hideaki Fujii,\* Minoru Narita, Hirokazu Mizoguchi, Miho Murachi, Toshiaki Tanaka, Koji Kawai, Leon F. Tseng and Hiroshi Nagase\*



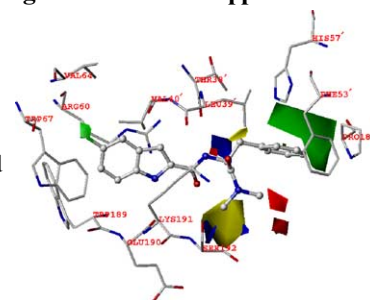
The drug design and synthesis of a series of 6,14-endoethenomorphinan-7 $\alpha$ -carboxamide derivatives as a putative  $\epsilon$  opioid receptor agonist are described. One of the derivatives, TAN-821, was the putative  $\epsilon$  opioid receptor agonist.

### Inhibitory mode of indole-2-carboxamide derivatives against HLGPα: molecular docking and 3D-QSAR analyses

pp 4147–4157

Guixia Liu, Zhenshan Zhang, Xiaomin Luo,\* Jianhua Shen, Hong Liu, Xu Shen, Kaixian Chen and Hualiang Jiang\*

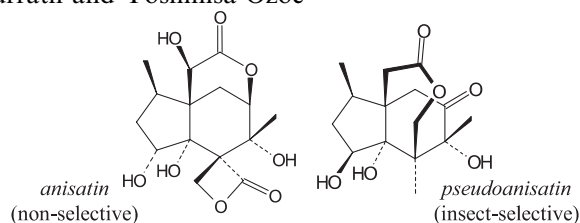
The interaction of a series of indole-2-carboxamides with target protein HLGPα was studied using molecular docking and 3D-QSAR approaches. Structure-based investigations and the final 3D-QSAR results provide clear guidelines and accurate activity predictions for novel inhibitor design.



### Structure–activity relationships of *seco*-prezizaane and picrotoxane/picrodendrane terpenoids by *Quasar* receptor-surface modeling

pp 4159–4167

Thomas J. Schmidt,\* Marion Gurrath and Yoshihisa Ozoe

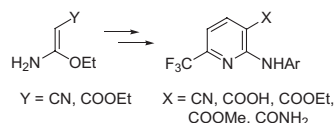


A 4D-QSAR study based on binding data for 30 terpenoid antagonists at *Musca domestica* and *Rattus norvegicus* GABA-gated chloride channels provided insights into the different properties of the binding sites. Structural features important for insect selectivity are identified.

### Synthesis of new 2-arylamino-6-trifluoromethylpyridine-3-carboxylic acid derivatives and investigation of their analgesic activity

pp 4169–4177

Maria T. Cocco,\* Cenzo Congiu, Valentina Onnis, Micaela Morelli, Vicente Felipe and Omar Cauli

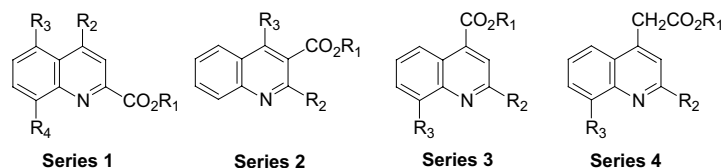


New 2-arylamino-6-trifluoromethylpyridine-3-carboxylic acid derivatives were synthesized. When compared to aspirin, ibuprofen and flufenamic acid some of the new compounds exhibited a comparable or improved analgesic activity and a lower ulcerogenic effect.

### Synthesis and antimycobacterial activities of ring-substituted quinolinecarboxylic acid/ester analogues. Part 1

pp 4179–4188

Balasubramanian Vaitilingam, Amit Nayyar, Prakash B. Palde, Vikramdeep Monga, Rahul Jain,\* Sukhraj Kaur and Prati Pal Singh

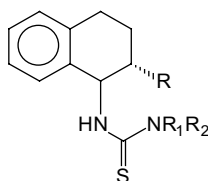


The antimycobacterial activities of ring-substituted quinolinecarboxylic acids/esters (Series 1–4) against *M. tuberculosis* H37Rv strains are described. The most effective analogue has exhibited excellent antimycobacterial efficacy (MIC = 1.0 µg/mL).

**Synthesis of tetrahydronaphthyl thioureas as potent appetite suppressants**

pp 4189–4196

Kalpana Bhandari,\* Shipra Srivastava and Girija Shankar

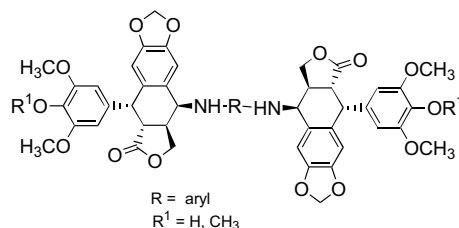


A series of thiourea derivatives of 1-aminotetrahydronaphthalene and 1-amino-2-hydroxytetrahydronaphthalene were synthesized in single pot in 48–90% yield and evaluated for their anorexigenic activity.

**Design, synthesis, biological evaluation and QSAR studies of novel bisepipodophyllotoxins as cytotoxic agents**

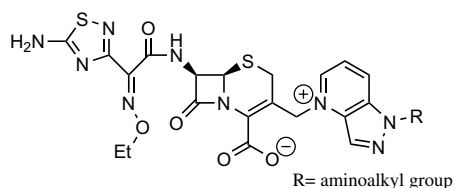
pp 4197–4209

Ahmed Kamal,\* E. Laxman, G. B. Ramesh Khanna, P. S. M. M. Reddy, Tasneem Rehana, M. Arifuddin, K. Neelima, Anand K. Kondapi and Sunanda G. Dastidar

**New broad-spectrum parenteral cephalosporins exhibiting potent activity against both methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. Part 2: Synthesis and structure–activity relationships in the S-3578 series**

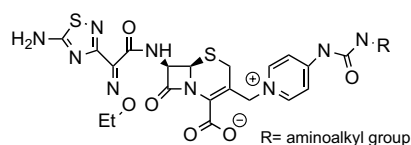
pp 4211–4219

Hidenori Yoshizawa,\* Tadatoshii Kubota, Hikaru Itani, Hiroyuki Ishitobi, Hideaki Miwa and Yasuhiro Nishitani

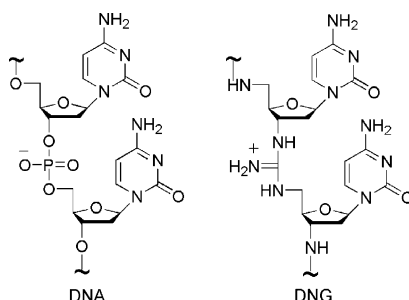
**New broad-spectrum parenteral cephalosporins exhibiting potent activity against both methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. Part 3: 7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-ethoxyiminoacetamido] cephalosporins bearing 4-[3-(aminoalkyl)-ureido]-1-pyridinium at C-3'**

pp 4221–4231

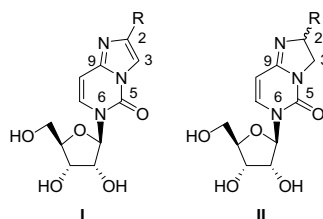
Hidenori Yoshizawa,\* Tadatoshii Kubota, Hikaru Itani, Kyoji Minami, Hideaki Miwa and Yasuhiro Nishitani



**DNG cytidine: synthesis and binding properties of octameric guanidinium-linked deoxycytidine oligomer** pp 4233–4244  
Istvan E. Szabo and Thomas C. Bruice\*

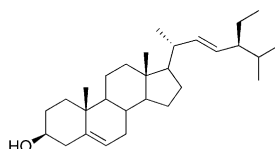


**Novel imidazo[1,2-*c*]pyrimidine base-modified nucleosides: synthesis and antiviral evaluation** pp 4245–4252  
Nurolaini Kifli, Erik De Clercq, Jan Balzarini and Claire Simons\*



Novel 6-(β-D-ribofuranosyl)-2-alkyl/aryl-6*H*-imidazo[1,2-*c*]pyrimidin-5-one and 6-(β-D-ribofuranosyl)-5-oxo-5,6-dihydro- and 2,3,5,6-tetrahydro-imidazo[1,2-*c*]pyrimidine-2-carbonitrile nucleosides were prepared and evaluated against a wide range of viral types and strains in cell culture.

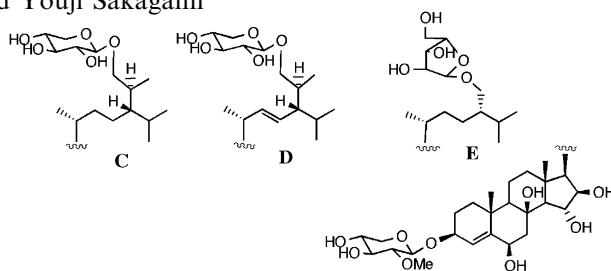
**Plant sterols as selective DNA polymerase β lyase inhibitors and potentiators of bleomycin cytotoxicity** pp 4253–4258  
Shi-Sheng Li, Zhijie Gao, Xizhi Feng, Shannon H. Jones and Sidney M. Hecht\*



Bioassay-guided fractionation of plant extracts led to the isolation and identification of three phytosterols, stigmasterol, β-sitosterol, and β-sitosterol-β-D-glucoside, as selective DNA polymerase β lyase inhibitors.

**Linckosides C–E, three new neuritogenic steroid glycosides from the Okinawan starfish *Linckia laevigata*** pp 4259–4265

Jianhua Qi, Makoto Ojika\* and Youji Sakagami



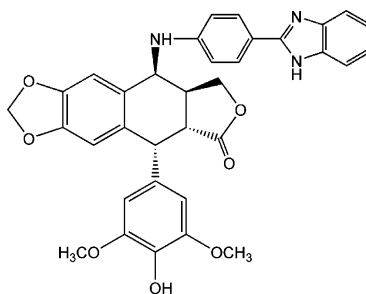
Three new steroid glycosides, linckosides C–E, were isolated from an Okinawan starfish as mimics and synergists for the neuritogenic activity of NGF.



**Anti-AIDS agents. Part 61: Anti-HIV activity of new podophyllotoxin derivatives**

pp 4267–4273

Xiao-Kang Zhu, Jian Guan, Zhiyan Xiao, L. Mark Cosentino and Kuo-Hsiung Lee\*

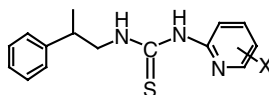


12

**Effect of stereochemistry on the anti-HIV activity of chiral thiourea compounds**

pp 4275–4284

T. K. Venkatachalam, C. Mao and Fatih M. Uckun\*

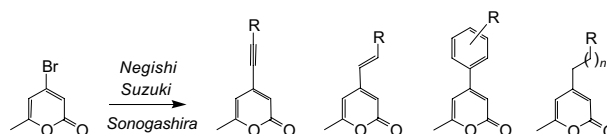


Chiral derivatives of several substituted halopyridyl and thiazolyl PETT compounds were synthesized as non-nucleoside inhibitors of the reverse transcriptase (RT) enzyme (NNRTI) of the human immunodeficiency virus (HIV-1). Molecular modeling studies indicated that because of the asymmetric geometry of the NNRTI binding pocket, the *R* stereoisomers would fit the NNRTI binding pocket of the HIV-1 RT much better than the corresponding *S* stereoisomers, as reflected by their  $10^4$ -fold lower  $K_i$  values.

**2-Pyrones possessing antimicrobial and cytotoxic activities**

pp 4285–4299

Ian J. S. Fairlamb,\* Lester R. Marrison, Julia M. Dickinson, Feng-Ju Lu and Jan Peter Schmidt



4-Bromo-6-methyl-2-pyrone is a versatile substrate for Negishi, Suzuki and Sonogashira cross-coupling reactions. The corresponding products are bioactive against a wide range of yeasts, bacteria and fungi. The alkynyl class of 2-pyrones demonstrate cytotoxic activities at the micromolar level.

**OTHER CONTENTS**

**Contributors to this issue**  
**Instructions to contributors**

**p I**  
**pp III–VII**

\*Corresponding author

**COVER**

2004: Overlaps of the eight known aldolase alpha-beta barrels in 2-deoxyribose-5-phosphate aldolase (DERA). Ribbon model for DERA is shown in green, with key Lys residues capable of Schiff base formation highlighted in stick figure. Reactive Lys167 is shown in yellow. DeSantis, G.; Liu, J.; Clark, D. P.; Heine, A.; Wilson, I. A.; and Wong, C.-H. *Bioorganic & Medicinal Chemistry* **2003**, *11*, 43–52.



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