

## Contents

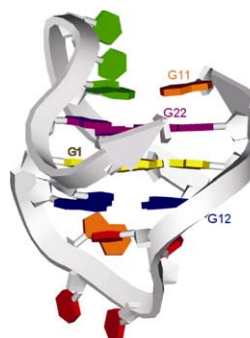
### ARTICLES

**d(G<sub>3</sub>T<sub>4</sub>G<sub>4</sub>) forms unusual dimeric G-quadruplex structure with the same general fold in the presence of K<sup>+</sup>, Na<sup>+</sup> or NH<sub>4</sub><sup>+</sup> ions**

Primož Šket, Martin Črnugelj and Janez Plavec\*

pp 5735–5744

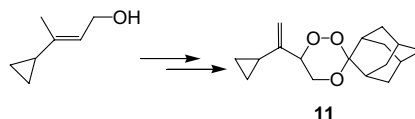
d(G<sub>3</sub>T<sub>4</sub>G<sub>4</sub>) oligonucleotide forms a dimeric G-quadruplex structure with a number of unique structural features. The comparative examination of several key interquartet and intraquartet H8–H8, NH–H8 and NH–NH NOE cross-peaks in the presence of K<sup>+</sup>, Na<sup>+</sup> and NH<sub>4</sub><sup>+</sup> ions showed only subtle structural differences while the same general fold is retained.



**Synthesis and antimalarial activity of 6-cycloalkylvinyl substituted 1,2,4-trioxanes**

Chandan Singh,\* Naveen Chandra Srivastav and Sunil K. Puri

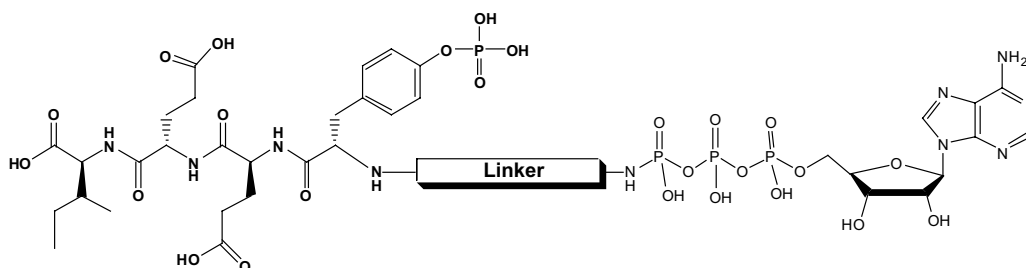
pp 5745–5752



**ATP-phosphopeptide conjugates as inhibitors of Src tyrosine kinases**

Nguyen-Hai Nam, Sungsoo Lee, Guofeng Ye, Gongqin Sun and Keykavous Parang\*

pp 5753–5766

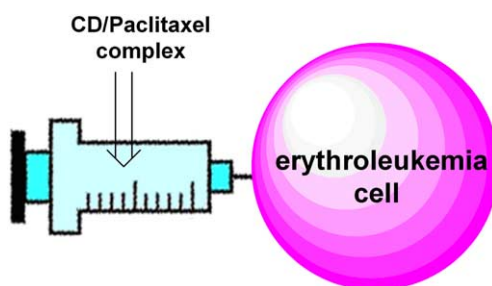


ATP-phosphopeptide conjugates were synthesized and evaluated in vitro against c-Src and Lck.

**Inclusion complexes of paclitaxel and oligo(ethylenediamino) bridged bis( $\beta$ -cyclodextrin)s: solubilization and antitumor activity**

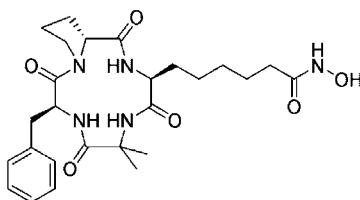
pp 5767–5775

Yu Liu,\* Guo-Song Chen, Yong Chen, Dong-Xu Cao, Zhi-Qiang Ge and Ying-Jin Yuan


**Chlamydocin–hydroxamic acid analogues as histone deacetylase inhibitors**

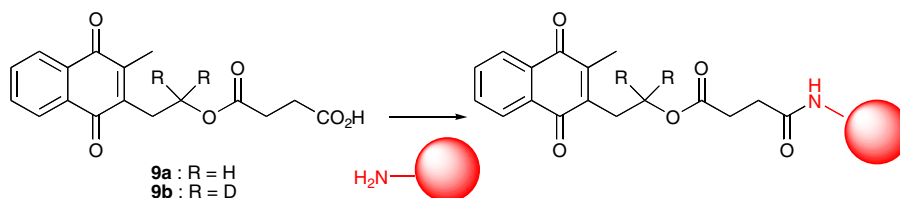
pp 5777–5784

Norikazu Nishino,\* Binoy Jose, Ryuzo Shinta, Tamaki Kato, Yasuhiko Komatsu and Minoru Yoshida


**Synthesis and protein conjugation studies of vitamin K analogues**

pp 5785–5791

Richard J. Payne, Alison M. Daines, Bruce M. Clark and Andrew D. Abell\*

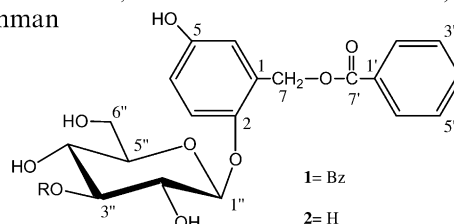


Two vitamin K analogues bearing a carboxylic acid side chain (**9a** and **9b**) have been synthesised and coupled to *N*-acetyl-Gly-L-Lys methyl ester, lysozyme and bovine serum albumin (BSA) as a first step to the development of an ELISA-based method for the detection of vitamin K. The protein conjugates have been characterised by ESMS and LC–MS.

**Phenolic glycosides, a new class of human recombinant nucleotide pyrophosphatase phosphodiesterase-1 inhibitors**

pp 5793–5798

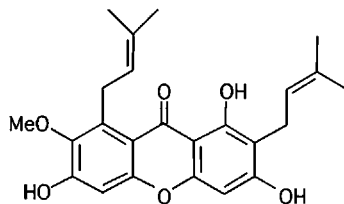
Muhammad Iqbal Choudhary,\* Naheed Fatima, Muhammad Athar Abbasi, Saima Jalil, Viqar Uddin Ahmad and Atta-ur-Rahman



Cytotoxicity and kinetic studies of phenolic glycosides, benzoyl salireposide (**1**) and salireposide (**2**), were performed against phosphodiesterase I enzyme from snake venom phosphodiesterase and human nucleotide pyrophosphatase phosphodiesterase-1. These compounds are potential candidates for the therapy of arthritis.

**Preferential target is mitochondria in  $\alpha$ -mangostin-induced apoptosis in human leukemia HL60 cells** pp 5799–5806

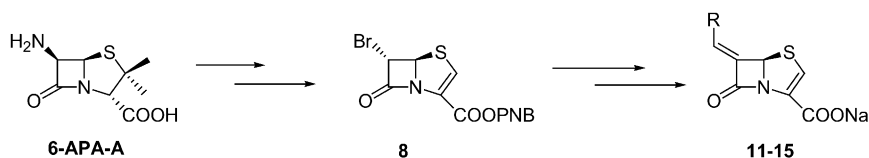
Kenji Matsumoto,\* Yukihiro Akao, Hong Yi, Kenji Ohguchi, Tetsuro Ito, Toshiyuki Tanaka, Emi Kobayashi, Munekazu Iinuma and Yoshinori Nozawa



$\alpha$ -Mangostin, xanthone derivative from the pericarps of mangosteen, preferentially targets mitochondria, resulting in induction of apoptosis in human leukemia HL60 cells.

**Novel imidazole substituted 6-methylidene-penems as broad-spectrum  $\beta$ -lactamase inhibitors** pp 5807–5817

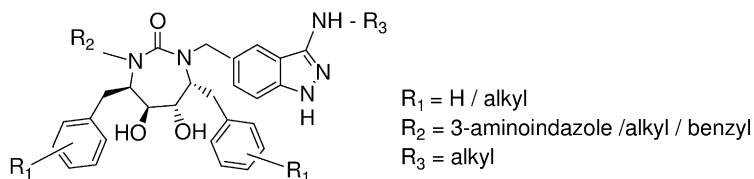
Aranapakam M. Venkatesan,\* Atul Agarwal, Takao Abe, Hideki Ushiroguchi, Itsuki Yamamura, Toshio Kumagai, Peter J. Petersen, William J. Weiss, Eileen Lenoy, Youjun Yang, David M. Shlaes, John L. Ryan and Tarek S. Mansour



A series of novel imidazole substituted 6-methylidene-penems has been synthesized ( $R$  = heterocycle) and was shown to be potent, broad-spectrum  $\beta$ -lactamase inhibitors against class-A and class-C enzymes. The present paper deals with the design, synthesis, and structure–activity relationships (SAR) of compounds **11–15**.

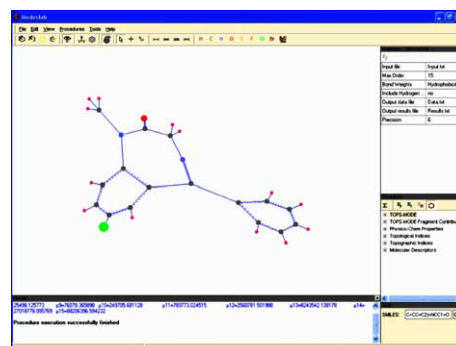
**A mechanistic study of 3-aminoindazole cyclic urea HIV-1 protease inhibitors using comparative QSAR** pp 5819–5831

Rajni Garg\* and Barun Bhattacharai

**In silico prediction of central nervous system activity of compounds. Identification of potential pharmacophores by the TOPS–MODE approach** pp 5833–5843

Miguel Angel Cabrera Pérez\* and Marival Bermejo Sanz

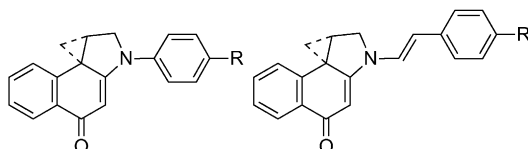
The central nervous system (CNS) activity was investigated by the TOPS–MODE approach. The discriminant model to classify CNS and non-CNS drugs explained more than 81% of the variance and it was assessed by a *leave-n-out* cross-validation procedure, an external prediction set and a 5-fold *full* cross-validation. With this methodology was demonstrated that the hydrophobicity increase the CNS activity, while the dipole moment and the polar surface area decrease it; evidencing the capacity of the TOPS–MODE descriptors to estimate CNS activity for new drug candidates. The model has also been able to identify potential structural pharmacophore, showing its possibilities in the lead generation and optimization processes.



**Synthesis and evaluation of *N*-aryl and *N*-alkenyl CBI derivatives**

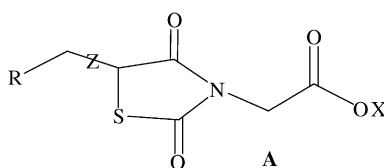
pp 5845–5856

Jay P. Parrish, John D. Trzupek, Terry V. Hughes, Inkyu Hwang and Dale L. Boger\*

**Synthesis and antihyperglycemic activity profiles of novel thiazolidinedione derivatives**

pp 5857–5864

Bashir A. Bhat, Shashikanth Ponnala, Devi Prasad Sahu,\* Priti Tiwari, Brajendra K. Tripathi and Arvind K. Srivastava

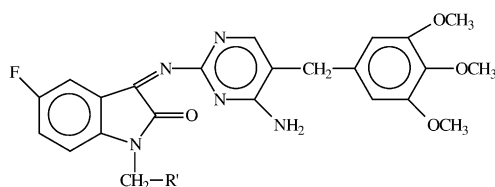


A number of thiazolidine-2,4-diones derivatives having carboxylic ester appendage at N-3 were synthesized and their antihyperglycemic activity was evaluated. Many of these derivatives as well as their corresponding carboxylic acid showed significant improvement on post-prandial hyperglycemia in normal rats, in contrast to their poor agonist activity at PPAR $\gamma$ .

**Design, synthesis and biological evaluation of novel non-nucleoside HIV-1 reverse transcriptase inhibitors with broad-spectrum chemotherapeutic properties**

pp 5865–5873

Dharmarajan Sriram,\* Tanushree Ratan Bal and Perumal Yogeeswari

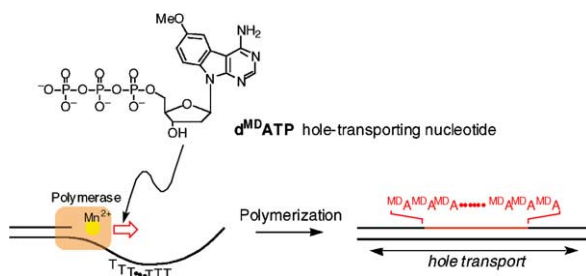


Aminopyrimidinimino-5-fluoroisatin compounds were designed as a novel non-nucleoside reverse transcriptase inhibitor with broad-spectrum chemotherapeutic properties that include anti-HIV, anti-HCV, anti-tuberculous and anti-bacterial activities.

**Synthesis of an artificial hole-transporting nucleoside triphosphate, d<sup>MD</sup>ATP, and its enzymatic incorporation into DNA**

pp 5875–5880

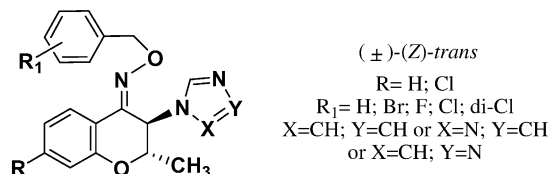
Akimitsu Okamoto,\* Kazuo Tanaka, Ken-ichiro Nishiza and Isao Saito\*



**Stereoselective synthesis and antifungal activity of (Z)-trans-3-azolyl-2-methylchromanone oxime ethers**

pp 5881–5889

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



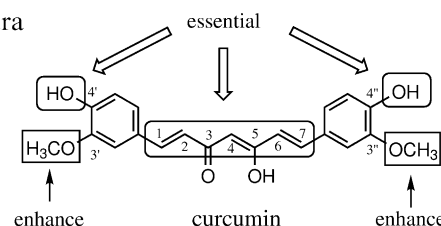
A series of (Z)-trans-3-azolyl-2-methylchromanone oxime ethers were stereoselectively synthesized and tested for in vitro antifungal activity. Many of these derivatives exhibit high activity against *Candida albicans*, *Saccharomyces cerevisiae*, *Aspergillus niger*, and *Microsporium gypseum*.

**Anti-allergic principles from Thai zedoary: structural requirements of curcuminoids for inhibition of degranulation and effect on the release of TNF- $\alpha$  and IL-4 in RBL-2H3 cells**

pp 5891–5898

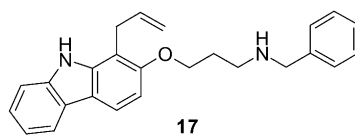
Hisashi Matsuda, Supinya Tewtrakul, Toshio Morikawa, Akihiko Nakamura and Masayuki Yoshikawa\*

The 80% aqueous acetone extract of the rhizomes of *Curcuma zedoaria* cultivated in Thailand (Thai zedoary) was found to inhibit release of  $\beta$ -hexosaminidase, as a marker of antigen-IgE-mediated degranulation, in RBL-2H3 cells and passive cutaneous anaphylaxis reaction in mice. Effects of four curcuminoids from Thai zedoary and several related compounds on the degranulation were examined. Among them, curcumin showed the highest activity against  $\beta$ -hexosaminidase release with IC<sub>50</sub> of 5.3  $\mu$ M, followed by bisdemethoxycurcumin (IC<sub>50</sub> = 11  $\mu$ M). With regard to the structural requirements of curcuminoids for the activity, the conjugated olefins at the 1–7 positions and the 4'- or 4''-hydroxyl groups of curcuminoids were suggested to be essential for the strong activity, whereas the 3'- or 3''-methoxyl group only enhanced the activity. Furthermore, effects of curcumin and bisdemethoxycurcumin on calcium ionophores (A23187 and ionomycin)-induced degranulation and antigen-induced release of TNF- $\alpha$  and IL-4 were examined.

**Synthesis and biological evaluation of novel propylamine derivatives as orally active squalene synthase inhibitors**

pp 5899–5908

Tsukasa Ishihara,\* Hirotoshi Kakuta, Hiroshi Moritani, Tohru Ugawa and Isao Yanagisawa

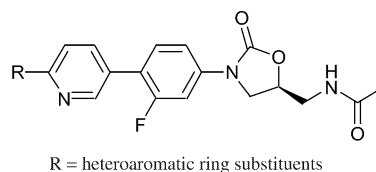


Propylamine derivatives with tricyclic systems were synthesized, and their inhibitory activities against squalene synthase and their effects on plasma lipid levels after oral dosing in rats were evaluated. Allyl-substituted 9H-carbazole derivative **17** demonstrated potent inhibition and good lipid-lowering effects with a reduced tendency to elevate plasma transaminase levels.

**Synthesis and antibacterial activity of oxazolidinones containing pyridine substituted with heteroaromatic ring**

pp 5909–5915

Yeong Woo Jo, Weon Bin Im, Jae Keol Rhee, Mi Ja Shim, Won Bae Kim and Eung Chil Choi\*



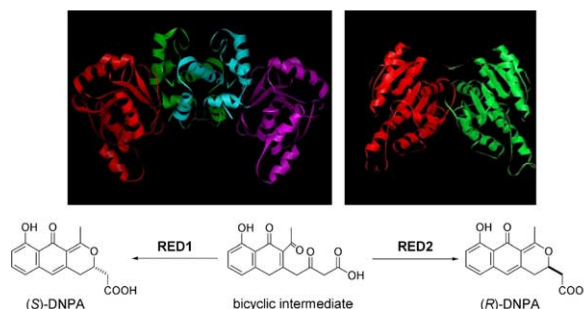
Oxazolidinone derivatives containing pyridine substituted with heteroaromatic ring were synthesized and exhibited potent in vitro and in vivo antibacterial activities against many antibiotic-resistant microbial strains.

### Remarkably different structures and reaction mechanisms of ketoreductases for the opposite stereochemical control in the biosynthesis of BIQ antibiotics

pp 5917–5927

Takaaki Taguchi, Kanako Kunieda, Mayuko Takeda-Shitaka, Daisuke Takaya, Noriaki Kawano, Meriel R. Kimberley, Kevin I. Booker-Milburn, G. Richard Stephenson, Hideaki Umeyama, Yutaka Ebizuka and Koji Ichinose\*

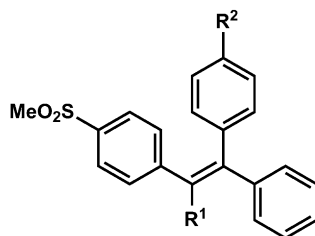
Remarkably different reduction mechanisms and structures of two stereospecific ketoreductases, RED1 and RED2, giving the opposite enantiomeric intermediates in the BIQ biosyntheses: new insights obtained by biochemical experiments and bioinformatics.



### Design and synthesis of acyclic triaryl (*Z*)-olefins: a novel class of cyclooxygenase-2 (COX-2) inhibitors

pp 5929–5940

Md. Jashim Uddin, P. N. Praveen Rao and Edward E. Knaus\*



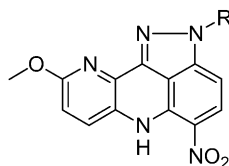
R<sup>1</sup> = H, Et, *n*-Butyl, *n*-Heptyl, *n*-Pentadecyl;

R<sup>2</sup> = H, OH, OAc

### Synthesis and biological evaluation of indazolo[4,3-*bc*][1,5]naphthyridines-(10-aza-pyrazolo[3,4,5-*k*]acridines): a new class of antitumor agents

pp 5941–5947

Amelia Magnano, Silvia Sparapani, Roberta Lucciarini, Mosca Michela, Consuelo Amantini, Giorgio Santoni and Ippolito Antonini\*



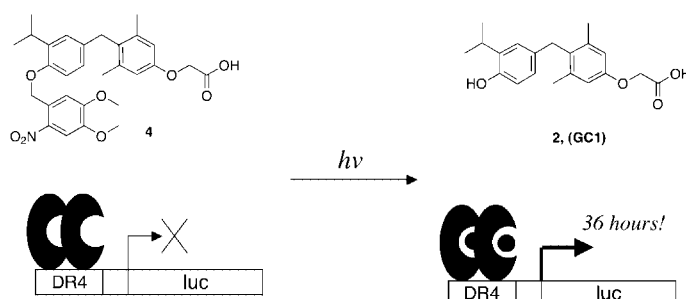
R = alkylaminoalkyl

Indazolo[4,3-*bc*][1,5]naphthyridines(10-aza-pyrazolo[3,4,5-*k*]acridines).

### Photo-caged agonists of the nuclear receptors RAR $\gamma$ and TR $\beta$ provide unique time-dependent gene expression profiles for light-activated gene patterning

pp 5949–5959

Kristian H. Link, Federico G. Cruz, Hai-Fen Ye, Kathryn E. O'Reilly, Sarah Dowdell and John T. Koh\*




## pp 5961–5971

pp 5973–5982

## pp 5983–5990

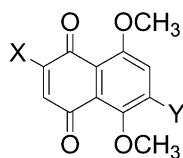
## pp 5991–5995

$R_1(O)CO$   
  
**(1a)**  $R_1 = R_2 = CH_3$   
**(1b)**  $R_1 = R_2 = C_3H_7$   
**(1c)**  $R_1 = CH_3, R_2 = C_3H_7$   
**(1d)**  $R_1 = CH_3, R_2 = C_5H_{11}$   
**(1f)**  $R_1 = C_3H_7, R_2 = C_5H_{11}$

### Elucidation of structure–activity relationships for 2- or 6-substituted-5,8-dimethoxy-1,4-naphthoquinones

pp 5997–6009

Rajeshwar P. Verma\* and Corwin Hansch

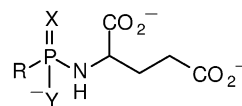


QSAR have been performed for different series of 2- or 6-substituted-5,8-dimethoxy-1,4-naphthoquinones with respect to their antiproliferative/cytotoxic activities against L1210. Activities of these compounds are found to be largely dependent on their hydrophobicity.

### Stereoselective inhibition of glutamate carboxypeptidase by organophosphorus derivatives of glutamic acid

pp 6011–6020

Jeremy P. Mallari, Cindy J. Choy, Ying Hu, Alicia R. Martinez, Mia Hosaka, Yoko Toriyabe, Jack Maung, Joseph E. Blecha, Stephen F. Pavkovic and Clifford E. Berkman\*



R = Et, *n*-Bu, Ph  
X = O, S  
Y = O, S

A series of phosphonyl, thiophosphonyl, and dithiophosphonyl derivatives of glutamic acid were prepared and examined for inhibitory potency against glutamate carboxypeptidase (carboxypeptidase G). Although varied in extent, stereoselective inhibition was dependent upon both carbon and phosphorus stereochemistry.

## OTHER CONTENTS

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Instructions to contributors

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\*Corresponding author

+ Supplementary data available via ScienceDirect

## COVER

Schematic presentation of the folding of DNA oligonucleotide d(G<sub>3</sub>T<sub>4</sub>G<sub>4</sub>) in the presence of K<sup>+</sup>, Na<sup>+</sup> or NH<sub>4</sub><sup>+</sup> ions into the dimeric G-quadruplex. The ribbon presentation on the right shows the lowest energy NMR structure in the presence of any of the three ions. Only subtle structural differences were found through detailed examination of NOEs, while the same general fold was retained. [Šket, P.; Črnigelj, M.; Plavec, J. *Bioorg. Med. Chem.* **2004**, *12*, 5735–5744].

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