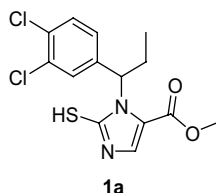


## Contents

## COMMUNICATIONS

**2-Mercaptoimidazoles, a new class of potent CCR2 antagonists**

pp 497–500

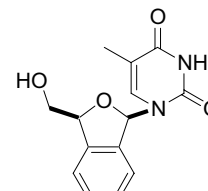
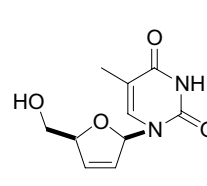
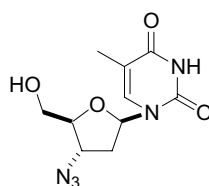
 Guy Van Lommen,\* Julien Doyon, Erwin Coesemans, Staf Boeckx, Marina Cools,  
 Mieke Buntinx, Bart Hermans and Jean VanWauwe

 The synthesis and SAR of a new class of CCR2 antagonists based on the lead compound **1a** are described. The optimization of the initial lead delivered nanomolar inhibitors of the MCP-1 induced Ca-flux in human THP-1 cells.

**Enantiomeric excess determination, purification and biological evaluation of (3S) and (3R)  $\alpha,\beta$ -butenolide analogues of isobenzofuranone**

pp 501–504

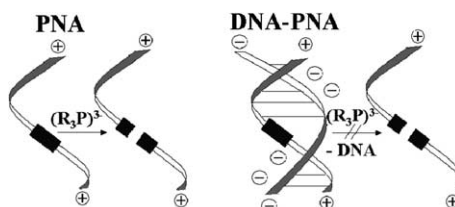
Emmanuelle Lipka, Marie-Pierre Vaccher, Claude Vaccher\* and Christophe Len

The asymmetric synthesis of isobenzofurane analogues, new potential antiviral agents, is reported. High performance liquid chromatography (HPLC) was the technique chosen to separate the enantiomers. We describe this chiral separation and then determine the enantiomeric excess. The biological results of each tested enantiomer are given.


**Hybridization dependent cleavage of internally modified disulfide–peptide nucleic acids**

pp 505–509

Iris Boll, Roland Krämer and Andriy Mokhir\*



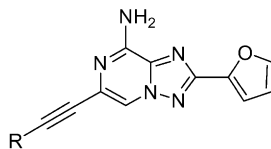
Cleavage of disulfide modified PNA by tris-(carboxyethyl)-phosphine is slowed down 33 times by a complementary DNA.



**Synthesis of alkyne derivatives of a novel triazolopyrazine as A<sub>2A</sub> adenosine receptor antagonists**

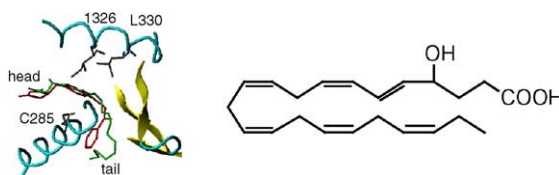
pp 511–515

Gang Yao,\* Serajul Haque, Li Sha, Gnanasambandam Kumaravel, Joy Wang, Thomas M. Engber, Eric T. Whalley, Patrick R. Conlon, Hexi Chang, William F. Kiesman and Russell C. Petter

**Identification of putative metabolites of docosahexaenoic acid as potent PPAR $\gamma$  agonists and antidiabetic agents**

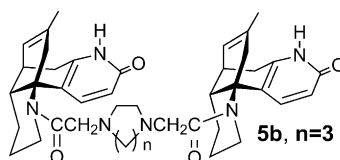
pp 517–522

Keiko Yamamoto,\* Toshimasa Itoh, Daijiro Abe, Masato Shimizu, Tomoatsu Kanda, Takatoshi Koyama, Masazumi Nishikawa, Tadakazu Tamai, Hiroshi Ooizumi and Sachiko Yamada\*

**Synthesis and acetylcholinesterase inhibition of derivatives of huperzine B**

pp 523–526

Song Feng, Yu Xia, Dongmei Han, Chunyan Zheng, Xuchang He, Xican Tang and Donglu Bai\*

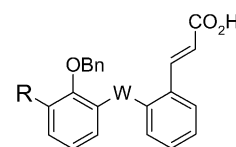


A number of new derivatives of HupB, including bis-HupB, have been synthesized. Among them bis-HupB 5b is 72-fold more potent in inhibition of AChE and 79-fold more selective for AChE versus BChE than HupB.

**Structure–activity relationship studies on *ortho*-substituted cinnamic acids, a new class of selective EP<sub>3</sub> antagonists**

pp 527–530

Michel Belley,\* Michel Gallant, Bruno Roy, Karine Houde, Nicolas Lachance, Marc Labelle, Laird A. Trimble, Nathalie Charet, Chun Li, Nicole Sawyer, Nathalie Tremblay, Sonia Lamontagne, Marie-Claude Carrière, Danielle Denis, Gillian M. Greig, Deborah Slipetz, Kathleen M. Metters, Robert Gordon, Chi Chung Chan and Robert J. Zamboni



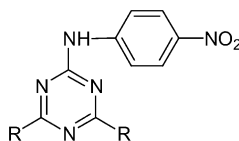
The synthesis, biological activity and the metabolism in vitro of a novel series of EP<sub>3</sub> antagonists have been evaluated. The very potent and selective EP<sub>2</sub> agonist **9** is also reported.

- 2a** R = Me W = CH<sub>2</sub>CH=CH  
**3a** R = Me W = CH=CHCH<sub>2</sub>  
**9** R = H W = CH=CH

**Syntheses of 2,4,6-trisubstituted triazines as antimalarial agents**

pp 531–533

Anu Agarwal, Kumkum Srivastava, S. K. Puri and Prem M. S. Chauhan\*

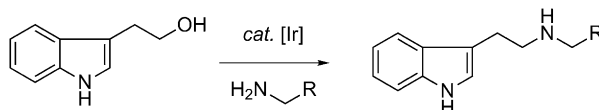


A series of 2,4,6-trisubstituted-1,3,5-triazines were synthesized and evaluated for their in vitro antimalarial activity against *P. falciparum*.

**N-Alkylation of phenethylamine and tryptamine**

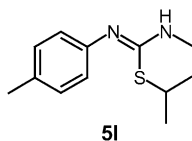
pp 535–537

Gerta Cami-Kobeci, Paul A. Slatford, Michael K. Whittlesey and Jonathan M. J. Williams\*

**Synthesis and biological evaluation of 3-benzyl-1-methyl- and 1-methyl-3-phenyl-isothioureas as potential inhibitors of iNOS**

pp 539–543

Nicola Paesano, Stefania Marzocco, Caterina Vicidomini, Carmela Saturnino, Giuseppina Autore, Giovanni De Martino and Gianluca Sbardella\*

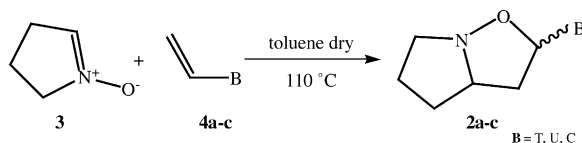


Novel benzyl- and phenyl-isothioureidic derivatives have been synthesised and tested as inhibitors of nitric oxide synthesis induced in lipopolysaccharide (LPS)-activated J774.A1 macrophage cell line.

**New conformationally locked bicyclic N,O-nucleoside analogues of antiviral drugs**

pp 545–550

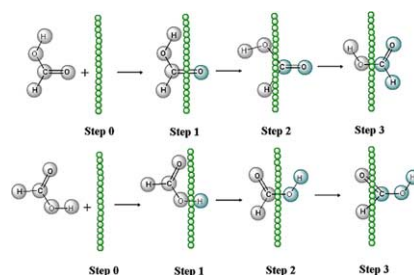
Antonio Procopio,\* Stefano Alcaro, Antonio De Nino, Loredana Maiuolo, Francesco Ortuso and Giovanni Sindona



The bicyclic pyrimidine derivatives of *N,O*-isoxazolidines were designed and synthesized by using 1,3-dipolar cycloaddition of pyrrolidine *N*-oxide and the appropriate vinyl-nucleobases.

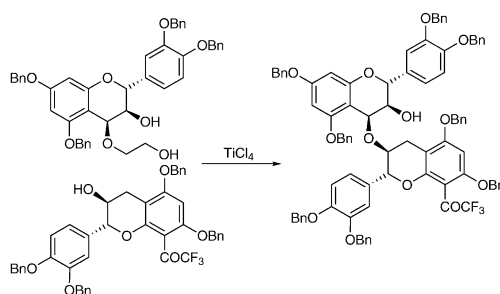
**Unified Markov thermodynamics based on stochastic forms to classify drugs considering molecular structure, partition system, and biological species: distribution of the antimicrobial G1 on rat tissues**

pp 551–557

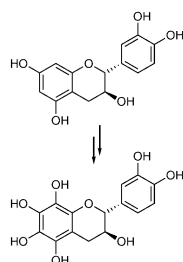
 Humberto González-Díaz,\* Guillermin Agüero, Miguel A. Cabrera, Reinaldo Molina,  
 Lourdes Santana, Eugenio Uriarte, Giovanna Delogu and Nilo Castañedo

**Synthesis of modified proanthocyanidins: introduction of acyl substituents at C-8 of catechin.**

pp 559–562

**Selective synthesis of a C-4 → O → C-3 ether-linked procyanidin-like dimer**

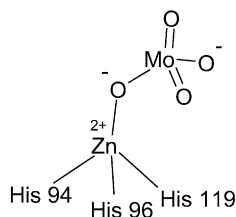
 Josiane Beauhaire, Nour-Eddine Es-Safi, François-Didier Boyer, Lucien Kerhoas, Christine le Guernevé  
 and Paul-Henri Ducrot\*

**Synthesis of modified proanthocyanidins: easy and general introduction of a hydroxy group at C-6 of catechin; efficient synthesis of elephantorrhizol**

pp 563–566

 François-Didier Boyer, Nour-Eddine Es-Safi, Josiane Beauhaire, Christine Le Guernevé  
 and Paul-Henri Ducrot\*

**Carbonic anhydrase inhibitors. Inhibition of isozymes I, II, IV, V, and IX with anions isosteric and isoelectronic with sulfate, nitrate, and carbonate**

pp 567–571

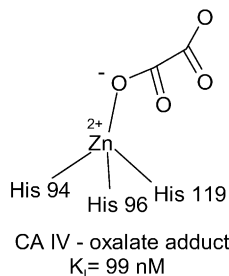
Alessio Innocenti, Daniela Vullo, Andrea Scozzafava and Claudiu T. Supuran\*



**Carbonic anhydrase inhibitors. Interaction of isozymes I, II, IV, V, and IX with carboxylates**

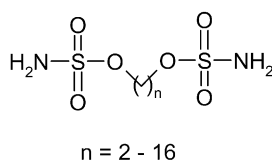
pp 573–578

Alessio Innocenti, Daniela Vullo, Andrea Scozzafava, Joseph R. Casey and Claudiu T. Supuran\*

**Carbonic anhydrase inhibitors: synthesis and inhibition of cytosolic/tumor-associated carbonic anhydrase isozymes I, II, and IX with bis-sulfamates**

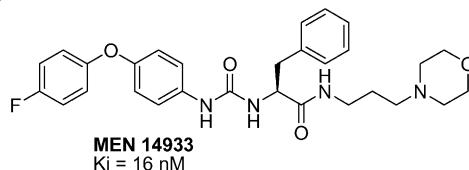
pp 579–584

Jean-Yves Winum, Silvia Pastorekova, Lydia Jakubickova, Jean-Louis Montero, Andrea Scozzafava, Jaromir Pastorek, Daniela Vullo, Alessio Innocenti and Claudiu T. Supuran\*

**Generation of a new class of hNK<sub>2</sub> receptor ligands using the ‘fragment approach’**

pp 585–588

Piero D’Andrea, Marina Porcelloni, Andrea Madami, Riccardo Patacchini, Maria Altamura and Daniela Fattori\*

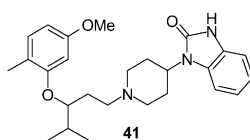


The so-called ‘fragment approach’ was applied in the search for new leads as selective hNK<sub>2</sub> antagonists. A first round of structural space exploration through the use of bond rigidity as scaffold to support the fragments, afforded **27a** as 200 nM hNK<sub>2</sub> ligand. Further refinement gave **MEN 14933** as a 16 nM hNK<sub>2</sub> ligand, selective versus hNK<sub>1</sub>, of a novel class. Conformational analysis was used to study results and plan future work.

**Synthesis and SAR studies of 3-phenoxypropyl piperidine analogues as ORL1 (NOP) receptor agonists**

pp 589–593

Ronald Palin,\* David R. Barn, John K. Clark, Jean E. Cottney, Phillip M. Cowley, Marc Crockatt, Louise Evans, Helen Feilden, Richard R. Goodwin, Frank Griekspoor, Simon J. A. Grove, Andrea K. Houghton, Philip S. Jones, Richard J. Morphy, Alasdair R. C. Smith, Hardy Sundaram, David Vrolijk, Mark A. Weston, Grant Wishart and Paul Wren



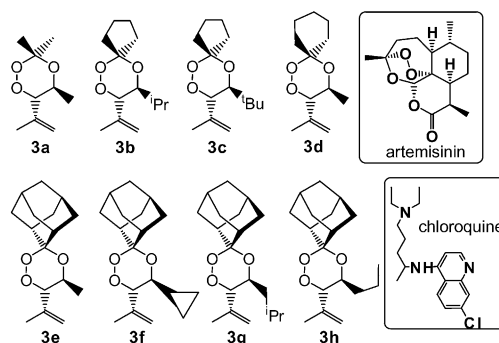
A series of potent and soluble ORL1 agonists was prepared and evaluated. Compound **41** showed antinociceptive properties in mouse formalin paw test (ED<sub>50</sub> = 1.07 μmol/kg).

**Novel spiroanellated 1,2,4-trioxanes with high in vitro antimalarial activities**

pp 595–597

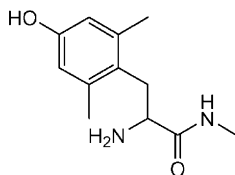
Axel G. Griesbeck,\* Tamer T. El-Idreesy, Lars-Oliver Höinck, Johann Lex and Reto Brun

A remarkable increase in antimalarial in vitro activity was achieved by integration of spiroadamantane motifs in 6-alkylidene 1,2,4-trioxanes **3a–h** via diastereoselective photooxygenation of allylic alcohols and subsequent  $\text{BF}_3$ -catalyzed peroxyacetalization with adamantanone.

**Studies on the structure–activity relationship of 2',6'-dimethyl-L-tyrosine (Dmt) derivatives: bioactivity profile of H-Dmt–NH–CH<sub>3</sub>**

pp 599–602

Yoshio Fujita, Yuko Tsuda, Takashi Motoyama, Tingyou Li, Anna Miyazaki, Toshio Yokoi, Yusuke Sasaki, Akihiro Ambo, Hideko Niizuma, Yunden Jinsmaa, Sharon D. Bryant, Lawrence H. Lazarus and Yoshio Okada\*

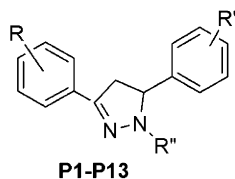


H-Dmt–NH–CH<sub>3</sub> showed the highest affinity ( $K_i\mu = 7.45$  nM) equal to that of morphine, partial  $\mu$ -opioid agonism ( $E_{\text{max}} = 66.6\%$ ) in vitro and a moderate antinociception in mice.

**Synthesis and in vitro selective anti-*Helicobacter pylori* activity of pyrazoline derivatives**

pp 603–607

F. Chimenti, B. Bizzarri,\* F. Manna, A. Bolasco, D. Secci, P. Chimenti, A. Granese, D. Rivanera, D. Lilli, M. M. Scaltrito and M. I. Brenciaglia

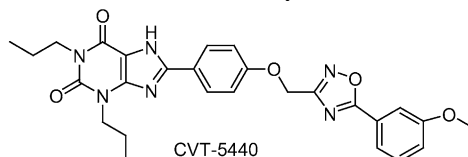


The synthesis of a series of N1-substituted 3,5-diphenyl pyrazolines and their activity against *Helicobacter pylori* is reported.

**The discovery of a selective, high affinity A<sub>2B</sub> adenosine receptor antagonist for the potential treatment of asthma**

pp 609–612

Jeff Zablocki,\* Rao Kalla, Thao Perry, Venkata Palle, Vaibhav Varkhedkar, Dengming Xiao, Anthony Piscopio, Tenning Maa, Art Gimbel, Jia Hao, Nancy Chu, Kwan Leung and Dewan Zeng

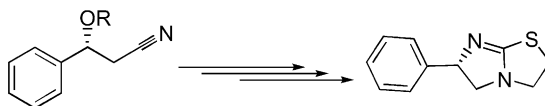


Adenosine has been suggested to play a role in asthma, possibly via activation of A<sub>2B</sub> adenosine receptors on mast cells and other pulmonary cells. We describe our initial efforts to discover a xanthine based selective A<sub>2B</sub> AdoR antagonist that resulted in the discovery of CVT-5440, a high affinity A<sub>2B</sub> AdoR antagonist with good selectivity (A<sub>2B</sub> AdoR  $K_i = 50$  nM, selectivity A<sub>1</sub> > 200: A<sub>2A</sub> > 200: A<sub>3</sub> > 167).

**A new facile chemoenzymatic synthesis of levamisole**

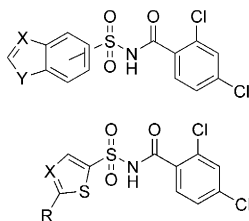
pp 613–615

Ahmed Kamal,\* G. B. Ramesh Khanna, T. Krishnaji and R. Ramu

**Acyl sulfonamide anti-proliferatives. Part 2: Activity of heterocyclic sulfonamide derivatives**

pp 617–620

Mary M. Mader,\* Chuan Shih, Eileen Considine, Alfonso De Dios, Cora Sue Grossman, Philip A. Hipskind, Ho-Shen Lin, Karen L. Lobb, Beatriz Lopez, José E. Lopez, Luisa M. Martin Cabrejas, Michael E. Richett, Wesley T. White, Yiu-Yin Cheung, Zhongping Huang, John E. Reilly and Sean R. Dinn

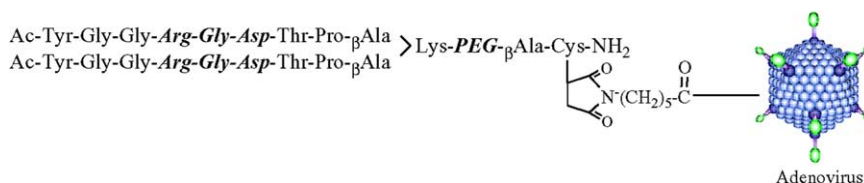


The cytotoxic and oncolytic activity of heterocyclic and fused bicyclic sulfonamide analogs is described.

**Design and synthesis of a peptide-PEG transporter tool for carrying adenovirus vector into cells**

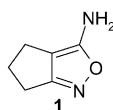
pp 621–624

Mitsuko Maeda, Shinya Kida, Keiko Hojo, Yusuke Eto, Jian-Qing Gaob, Shinnosuke Kurachi, Fumiko Sekiguchi, Hiroyuki Mizuguchi, Takao Hayakawa, Tadanori Mayumi, Shinsaku Nakagawa and Koichi Kawasaki\*

**A new bactericidal lead structure for the protection of materials**

pp 625–629

Erasmus Vogl,\* Rainer Bruns, Oliver Kretschik, Hermann Uhr, Johannes Kaulen, Martin Kugler, Peter Wachtler, Wolfgang Kreiss and Günther Eberz

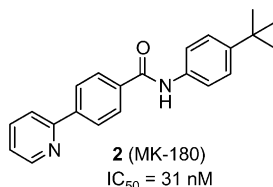


The bicyclic amine **1** represents a new lead structure for broad spectrum bactericides. Extensive activity screening as well as toxicity investigations have been carried out for **1** and its derivatives.

**Biarylcarboxybenzamide derivatives as potent vanilloid receptor (VR1) antagonistic ligands**

pp 631–634

Hyeung-geun Park,\* Ji-yeon Choi, Mi-hyun Kim, Sea-hoon Choi, Mi-kyung Park, Jihye Lee, Young-Ger Suh, Hawon Cho, Uhtaek Oh, Hee-Doo Kim, Yung Hyup Joo, Song Seok Shin, Jin Kwan Kim, Yeon Su Jeong, Hyun-Ju Koh, Young-Ho Park and Sang-sup Jew\*



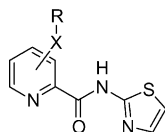
A series of biarylcarboxybenzamide derivatives were prepared and the structure–activity relationship studies on the antagonistic activity on VR1 were performed.

**Inhibitors of type I MetAPs containing pyridine-2-carboxylic acid thiazol-2-ylamide.**

pp 635–638

**Part 1: SAR studies on the determination of the key scaffold**

Qun-Li Luo, Jing-Ya Li, Zhi-Ying Liu, Ling-Ling Chen, Jia Li, Qi-Zhuang Ye\* and Fa-Jun Nan\*



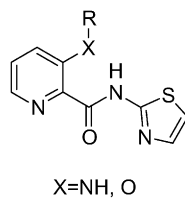
Systematic SAR studies on the HTS hit pyridine-2-carboxylic acid thiazol-2-ylamide (PACT) analogues revealed that the scaffold of PCAT is indispensable for the inhibition of type I MetAP.

**Inhibitors of type I MetAPs containing pyridine-2-carboxylic acid thiazol-2-ylamide.**

pp 639–644

**Part 2: SAR studies on the pyridine ring 3-substituent**

Qun-Li Luo, Jing-Ya Li, Ling-Ling Chen, Jia Li, Qi-Zhuang Ye\* and Fa-Jun Nan\*

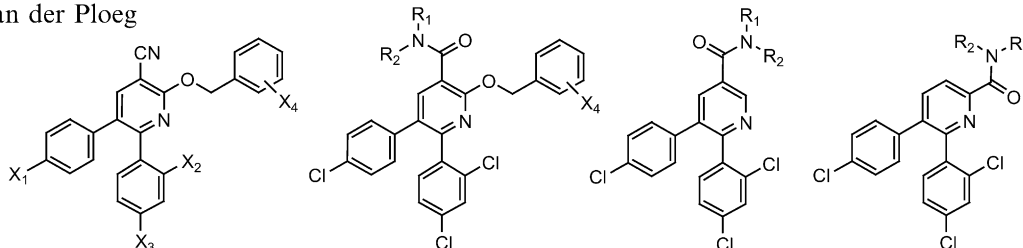


SAR studies on the pyridine ring 3-substituent of PCAT inhibitor of *Ec*MetAP1 and *Sc*MetAP1, revealed that 3-substituents have different selectivity for *Ec*MetAP1 and *Sc*MetAP1.

**Synthesis and SAR of 5,6-diarylpyridines as human CB1 inverse agonists**

pp 645–651

Laura C. Meurer,\* Paul E. Finke, Sander G. Mills, Thomas F. Walsh, Richard B. Toupence, Mark T. Goulet, Junying Wang, Xinchun Tong, Tung M. Fong, Julie Lao, Marie-Therese Schaeffer, Jing Chen, Chun-Pyn Shen, D. Sloan Stribling, Lauren P. Shearman, Alison M. Strack and Lex H. T. Van der Ploeg



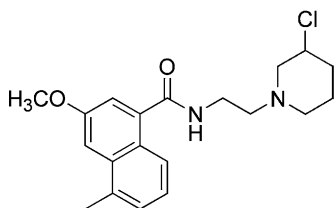
The synthesis and structure–activity relationships for four series of pyridine-based human CB1 inverse agonists are described.



**Truncated azinomycin analogues intercalate into DNA**

pp 653–656

Maxwell A. Casely-Hayford, Klaus Pors, Laurence H. Patterson, Clive Gerner, Stephen Neidle and Mark Searcey\*



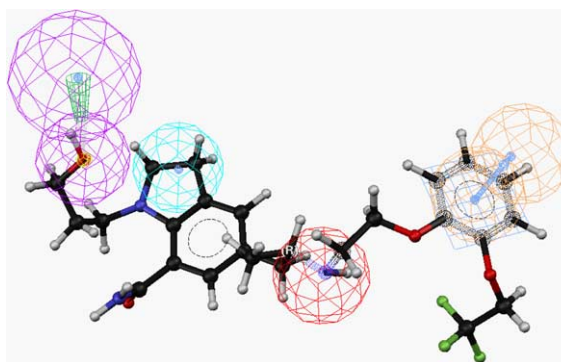
A designed analogue of the left half of azinomycin has been synthesized and unwinds supercoiled DNA.

**Pharmacophore identification of  $\alpha_{1A}$ -adrenoceptor antagonists**

pp 657–664

Min-Yong Li, Keng-Chang Tsai and Lin Xia\*

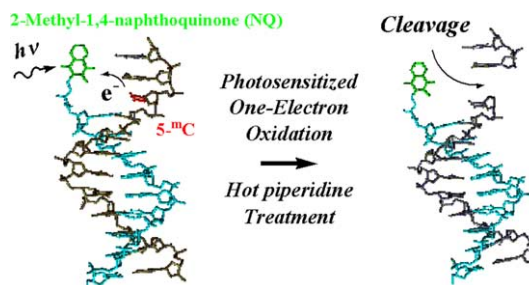
In this paper three-dimensional pharmacophore hypotheses were built from a training set of 30  $\alpha_{1A}$ -adrenoceptor antagonists. The best pharmacophore is considered to be used in designing new leads for hopefully more active compounds.

**Cleavage at 5-methylcytosine in DNA by photosensitized oxidation with 2-methyl-1,4-naphthoquinone tethered oligodeoxynucleotides**

pp 665–668

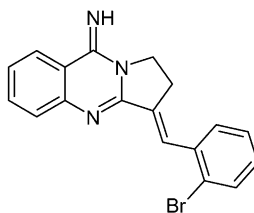
Hisatsugu Yamada, Kazuhito Tanabe\* and Sei-ichi Nishimoto\*

Photosensitized one-electron oxidation of 5-methylcytosine in DNA by 2-methyl-1,4-naphthoquinone, attached to 5'-end of an oligodeoxynucleotide strand, produced 5-formylcytosine and led to selective DNA strand cleavage at the original 5-methylcytosine configuration. This specified photoreaction is useful for positive display of 5-methylcytosine in DNA on a sequencing gel.

**Pyrrolidinoquinazolines—a novel class of CCR3 modulators**

pp 669–673

Ralf Anderskewitz,\* Rolf Bauer, Gisela Bodenbach, Dirk Gester, Bernd Gramlich, Gerd Morschhäuser and Franz W. Birke

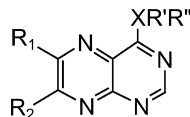


A novel class of CCR3 modulators is described. Optimization led to compound **8b** ( $K_i$ : 28 nM), which surprisingly proved to be an agonist.

**Parallel synthesis of pteridine derivatives as potent inhibitors for hepatitis C virus NS5B RNA-dependent RNA polymerase**

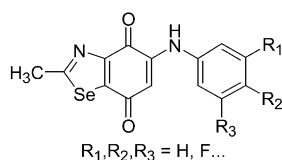
pp 675–678

Yili Ding,\* Jean-Luc Girardet, Kenneth L. Smith, Gary Larson, Brett Prigaro, Vicky C. H. Lai, Weidong Zhong and Jim Z. Wu


**Synthesis and antifungal activity of noble 5-arylamino- and 6-arylthio-4,7-dioxobenzoselenazoles**

pp 679–682

Chung-Kyu Ryu,\* Ja-Young Han, Ok-Jai Jung, Su-Kyung Lee, Jung Yoon Lee and Seong Hee Jeong



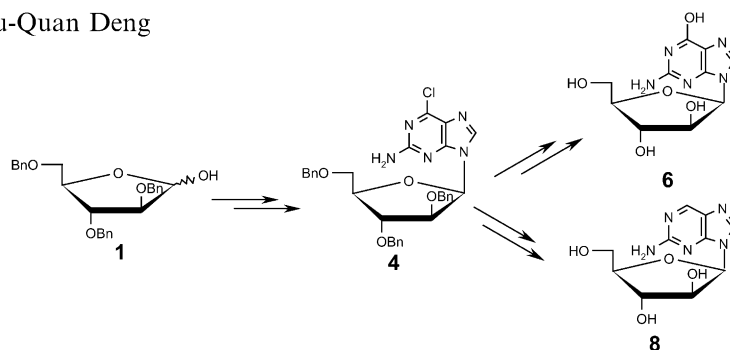
5-Arylamino- and 6-arylthio-4,7-dioxobenzoselenazoles were synthesized and tested for in vitro antifungal activity against pathogenic fungi. Among them, 5-arylamino-4,7-dioxobenzoselenazoles exhibited potent antifungal activity.

**Stereoselective synthesis of 9-β-D-arabianofuranosyl guanine and 2-amino-9-(β-D-arabianofuranosyl)purine**

pp 683–685

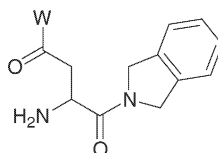
Xue-Jun Yu,\* Gai-Xia Li, Xiou-Xiang Qi and You-Quan Deng

A facile method was reported to synthesize 9-β-D-arabianofuranosyl guanine (**6**) and 2-amino-9-(β-D-arabianofuranosyl)purine (**8**) via the key intermediate, 2-amino-6-chloro-9-(2,3,5-triphenylmethoxyl-β-D-arabianofuranosyl)purine (**4**), which was stereoselectively prepared using activated molecular sieve as catalyst.


**Novel isoindoline compounds for potent and selective inhibition of prolyl dipeptidase DPP8**

pp 687–691

Weir-Torn Jiaang,\* Yuan-Shou Chen, Tsu Hsu, Ssu-Hui Wu, Chia-Hui Chien, Chung-Nien Chang, Sheng-Ping Chang, Shiow-Ju Lee and Xin Chen\*

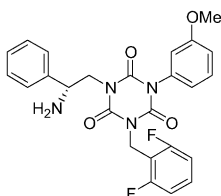


W=1,2,3,4-tetrahydroisoquinoline  
 W=6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline  
 W=1-(4,4'-difluor-benzhydryl)-piperazine



# A convenient one-pot synthesis of asymmetric 1,3,5-triazine-2,4,6-triones and its application towards a novel class of gonadotropin-releasing hormone receptor antagonists

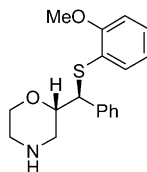
Zhiqiang Guo,\* Dongpei Wu, Yun-Fei Zhu, Fabio C. Tucci, Joseph Pontillo, John Saunders, Qiu Xie, R. Scott Struthers and Chen Chen\*



A convenient one-pot synthetic route was developed for the preparation of asymmetric 1,3-dialkyl-1,3,5-triazine-2,4,6-triones from isocyanates, primary amines and *N*-chlorocarbonyl isocyanate. This methodology was applied to the synthesis of a chemical library acting as antagonists of the *h*GnRH receptor.

## Discovery and structure–activity relationships of novel selective norepinephrine and dual serotonin/norepinephrine reuptake inhibitors

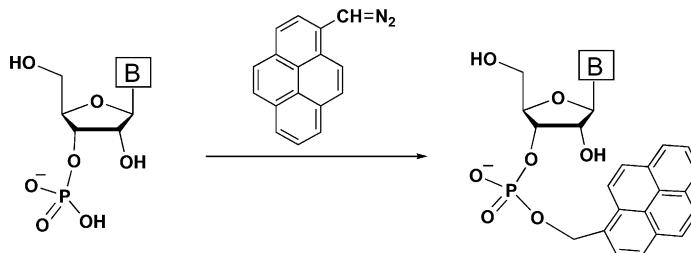
John Boot, Manuel Cases, Barry P. Clark, Jeremy Findlay, Peter T. Gallagher, Lorna Hayhurst, Teresa Man, Christian Montalbetti, Richard E. Rathmell, Hélène Rudyk, Magnus W. Walter,\* Maria Whatton and Virginia Wood



The preparation of novel arylthiomethyl morpholines using a stereochemically versatile route featuring an aldol condensation as the key step is described. Members of this series are demonstrated to be inhibitors of both serotonin and norepinephrine reuptake.

## Pyrenyldiazomethane, a versatile reagent for nucleotide phosphate alkylation

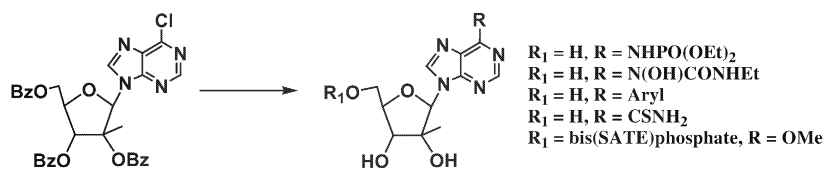
Mitsuharu Kotera,\* Marie-Louise Dheu, Anne Milet, Jean Lhomme and Ali Laayoun



Pyrenyldiazomethane was shown to react quantitatively and selectively at phosphate with 2', 3', and 5'-nucleotide phosphates incorporating the different nucleic bases.

## Synthesis of 9-(2-β-C-methyl-β-D-ribofuranosyl)-6-substituted purine derivatives as inhibitors of HCV RNA replication

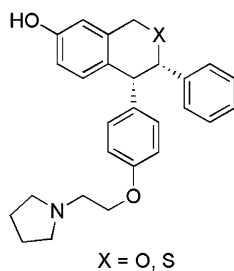
Yili Ding,\* Jean-Luc Girardet, Zhi Hong, Vicky C. H. Lai, Haoyun An, Yung-hyo Koh,  
Stephanie Z. Shaw and Weidong Zhong



**Estrogen receptor ligands. Part 11: Synthesis and activity of isochromans and isothiochromans**

pp 715–718

Jian Liu,\* Elizabeth T. Birzin, Wanda Chan, Yi Tien Yang, Lee-Yuh Pai, Carolyn DaSilva, Edward C. Hayes, Ralph T. Mosley, Frank DiNinno, Susan P. Rohrer, James M. Schaeffer and Milton L. Hammond

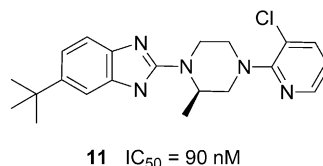


The isochroman and isothiochroman compounds were synthesized as potent estrogen receptor ligands.

**4-(2-Pyridyl)piperazine-1-benzimidazoles as potent TRPV1 antagonists**

pp 719–723

Bin Shao,\* Jincheng Huang, Qun Sun, Kenneth J. Valenzano, Lori Schmid and Scott Nolan

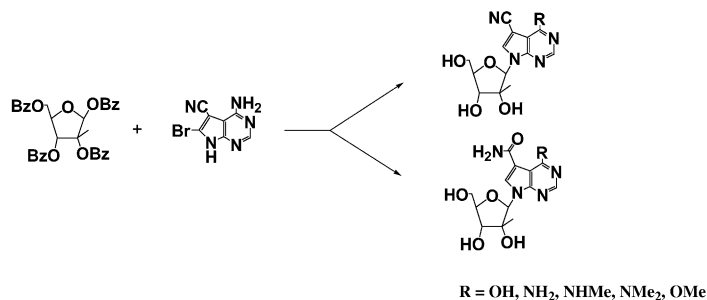


A series of 4-(2-pyridyl)piperazine-1-benzimidazole analogues were designed. Compound **11** was identified as a potent TRPV1 antagonist (IC<sub>50</sub> = 90 nM, F% = 19).

**Synthesis of 2'-β-C-methyl toyocamycin and sangivamycin analogues as potential HCV inhibitors**

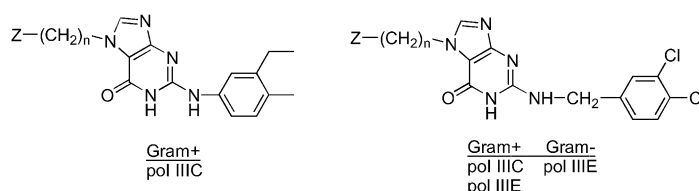
pp 725–727

Yili Ding,\* Haoyun An, Zhi Hong and Jean-Luc Girardet

**Active site directed inhibitors of replication-specific bacterial DNA polymerases**

pp 729–732

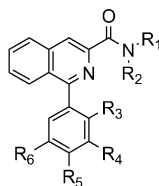
George E. Wright,\* Neal C. Brown, Wei-Chu Xu, Zheng-yu Long, Chengxin Zhi, Joseph J. Gambino, Marjorie H. Barnes and Michelle M. Butler



**1-(Phenyl)isoquinoline carboxamides: a novel class of subtype selective inhibitors of thyrotropin-releasing hormone (TRH) receptors**

pp 733–736

Jian-kang Jiang, Craig J. Thomas, Susanne Neumann, Xinping Lu, Kenner C. Rice and Marvin C. Gershengorn\*

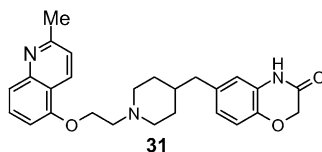


The synthesis and biological activity of several 1-(phenyl)isoquinoline carboxamide analogues is described. These are the first ligands reported that show selective binding to the TRH R2 receptors.

**3,4-Dihydro-2H-benzoxazinones are 5-HT<sub>1A</sub> receptor antagonists with potent 5-HT reuptake inhibitory activity**

pp 737–741

Peter J. Atkinson, Steven M. Bromidge, Mark S. Duxon, Laramie M. Gaster, Michael S. Hadley, Beverley Hammond, Christopher N. Johnson,\* Derek N. Middlemiss, Stephanie E. North, Gary W. Price, Harshad K. Rami, Graham J. Riley, Claire M. Scott, Tracey E. Shaw, Kathryn R. Starr, Geoffrey Stemp, Kevin M. Thewlis, David R. Thomas, Mervyn Thompson, Antonio K. K. Vong and Jeannette M. Watson

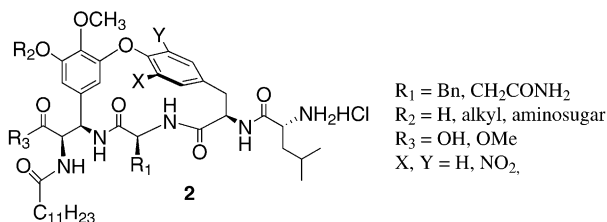


The discovery of the potent 5-HT<sub>1A</sub> receptor antagonist and 5-HT reuptake inhibitor **31** is reported.

**Design and synthesis of macrocycles active against vancomycin-resistant enterococci (VRE): the interplay between D-Ala-D-Lac binding and hydrophobic effect**

pp 743–746

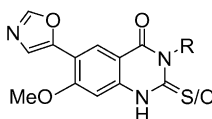
Nianchun Ma, Yanxing Jia, Zuosheng Liu, Eduardo Gonzalez-Zamora, Michèle Bois-Choussy, Adriano Malabarba, Cristina Brunati and Jieping Zhu\*



**Quinazolinethiones and quinazolinediones, novel inhibitors of inosine monophosphate dehydrogenase: synthesis and initial structure–activity relationships**

pp 751–754

George M. Buckley, Natasha Davies, Hazel J. Dyke, Philip J. Gilbert, Duncan R. Hannah, Alan F. Haughan,\* Caroline A. Hunt, William R. Pitt, Rachael H. Profit, Nicholas C. Ray, Marianna D. Richard, Andrew Sharpe, Alicia J. Taylor, Justine M. Whitworth and Sophie C. Williams

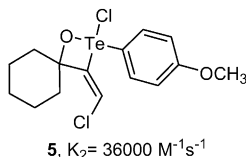


Novel quinazolinethiones and quinazolinediones are reported which exhibit IMPDH II inhibitory activity.

**Tellurium-based cysteine protease inhibitors: evaluation of novel organotellurium(IV) compounds as inhibitors of human cathepsin B**

pp 755–760

Rodrigo L. O. R. Cunha, Miriam E. Urano, Jair R. Chagas, Paulo C. Almeida, Cláudia Bincoletto, Ivarne L. S. Tersariol\* and João V. Comasseto\*

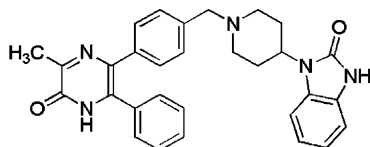


The inhibition of Cathepsin B by a sort of different classes of organotellurium(IV) compounds was described.

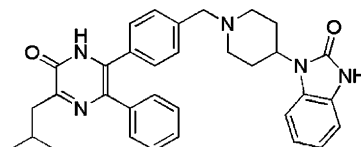
**Allosteric Akt (PKB) inhibitors: discovery and SAR of isozyme selective inhibitors**

pp 761–764

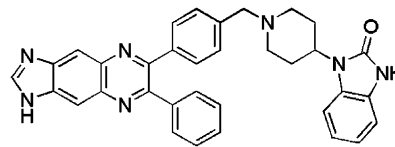
Craig W. Lindsley,\* Zhijian Zhao, William H. Leister, Ronald G. Robinson, Stanley F. Barnett, Deborah Defeo-Jones, Raymond E. Jones, George D. Hartman, Joel R. Huff, Hans E. Huber and Mark E. Duggan



Akt1 selective



Akt2 selective



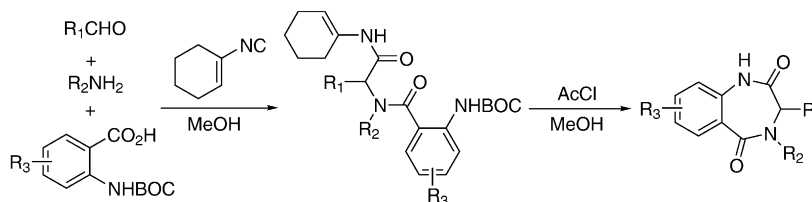
Dual Akt1/Akt2 selective

**1,4-Benzodiazepine-2,5-diones as small molecule antagonists of the HDM2–p53 interaction: discovery and SAR**

pp 765–770

Daniel J. Parks, Louis V. LaFrance, Raul R. Calvo, Karen L. Milkiewicz, Varsha Gupta, Jennifer Lattanze, Kannan Ramachandren, Theodore E. Carver, Eugene C. Petrella, Maxwell D. Cummings, Diane Maguire, Bruce L. Grasberger and Tianbao Lu\*

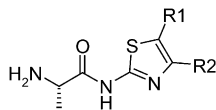
A library of 1,4-benzodiazepine-2,5-diones was screened for binding to the p53-binding domain of HDM2 using ThermoFluor®, a miniaturized thermal denaturation assay. The hits obtained were shown to bind to HDM2 in the p53-binding pocket using a fluorescence polarization (FP) peptide displacement assay. The potency of the series was optimized, leading to sub-micromolar antagonists of the p53–HDM2 interaction.



**Non-peptidic small molecule inhibitors of XIAP**

pp 771–775

Cheol-Min Park,\* Chaohong Sun, Edward T. Olejniczak, Alan E. Wilson, Robert P. Meadows, Stephen F. Betz, Steven W. Elmore and Stephen W. Fesik



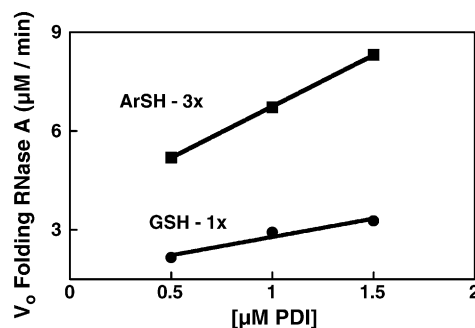
Non-peptidic small molecule SMAC mimetics were designed and synthesized that bind to the BIR3 domain of XIAP using structure-based design. Substituted five-membered heterocycles such as thiazoles and imidazoles were identified that serve as replacements for peptide fragments of the lead.

**Increased catalytic activity of protein disulfide isomerase using aromatic thiol based redox buffers**

pp 777–781

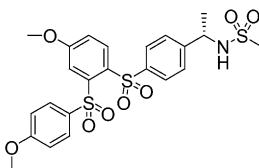
Jonathan D. Gough and Watson J. Lees\*

PDI is an enzyme that acts as a chaperone, shufflase, and oxidase during the folding of disulfide-containing proteins. The ability of aromatic thiols to increase the activity of PDI-catalyzed protein folding over that of the standard thiol glutathione (GSH) was measured. 4-Mercaptobenzoic acid (ArSH) increased the activity of PDI by a factor of three.

**Triaryl bis-sulfones as a new class of cannabinoid CB2 receptor inhibitors: identification of a lead and initial SAR studies**

pp 783–786

Brian J. Lavey,\* Joseph A. Kozlowski, R. William Hipkin, Waldemar Gonsiorek, Daniel J. Lundell, John J. Piwinski, Satwant Narula and Charles A. Lunn

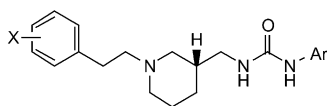


A novel class of cannabinoid CB2 receptor ligands is described. The compounds are nanomolar inhibitors of the CB2 receptor and can show high selectivity over the cannabinoid CB1 receptor. One compound is shown to be a CB2-selective inverse agonist.

**N-Arylalkylpiperidine urea derivatives as CC chemokine receptor-3 (CCR3) antagonists**

pp 787–791

Douglas G. Batt,\* Gregory C. Houghton, John Roderick, Joseph B. Santella, III, Dean A. Wacker, Patricia K. Welch, Yevgeniya I. Orlovsky, Eric A. Wadman, James M. Trzaskos, Paul Davies, Carl P. Decicco and Percy H. Carter

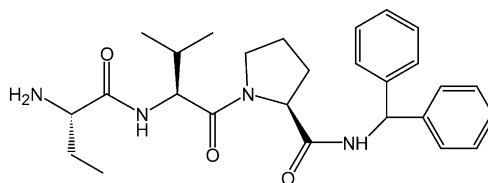


The synthesis and structure–activity relationships of *N*-arylalkylpiperidylmethyl ureas as antagonists of the CC chemokine receptor-3 (CCR3) are presented. These compounds displayed potent binding to the receptor as well as functional antagonism of eotaxin-elicited effects on eosinophils.

**Structure-based design, synthesis and biochemical testing of novel and potent Smac peptido-mimetics**

pp 793–797

Haiying Sun, Zaneta Nikolovska-Coleska, Jianyong Chen, Chao-Yie Yang, York Tomita, Hongguang Pan, Yoshiko Yoshioka, Krzysztof Krajewski, Peter P. Roller and Shaomeng Wang\*

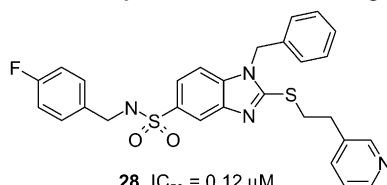


**6j** ( $K_i = 24$  nM to XIAP BIR3)

**Benzimidazole derivatives as novel nonpeptide luteinizing hormone-releasing hormone (LHRH) antagonists. Part 1: Benzimidazole-5-sulfonamides**

pp 799–803

Kentaro Hashimoto,\* Miyuki Tatsuta, Mikayo Kataoka, Kayo Yasoshima, Yuka Shogase, Makoto Shimazaki, Takeshi Yura, Yingfu Li, Noriyuki Yamamoto, Jang B. Gupta and Klaus Urbahns



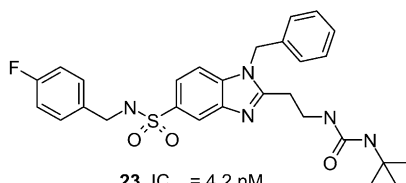
**28**,  $IC_{50} = 0.12$   $\mu$ M

A new class of benzimidazole-5-sulfonamides has been identified as nonpeptide luteinizing hormone-releasing hormone (LHRH) antagonists. Initial structure–activity relationships are presented resulting in compounds **19** and **28** with submicromolar dual functional activity on human and rat receptors.

**Benzimidazole derivatives as novel nonpeptide luteinizing hormone-releasing hormone (LHRH) antagonists. Part 2: Benzimidazole-5-sulfonamides**

pp 805–807

Yingfu Li, Mikayo Kataoka, Miyuki Tatsuta, Kayo Yasoshima, Takeshi Yura, Klaus Urbahns, Atsushi Kiba, Noriyuki Yamamoto, Jang B. Gupta and Kentaro Hashimoto\*



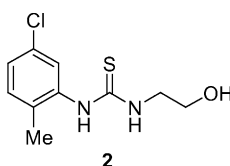
**23**,  $IC_{50} = 4.2$  nM

The 2-cyclopropyl substituted benzimidazole **2** has been used as a starting point for further optimization of an LHRH antagonist series. SAR studies reveal that a *tert*-butyl urea fragment connected through a simple carbon chain would improve activity. Further modification of the benzylsulfonamide moiety led to the discovery of **23** ( $IC_{50}$ : 4.2 nM).

**1-Hydroxyalkyl-3-phenylthioureas as novel HDL-elevating agents**

pp 809–812

Gary M. Coppola,\* Robert E. Damon, J. Bruce Eskesen, Dennis S. France and James R. Paterniti, Jr.



**2**

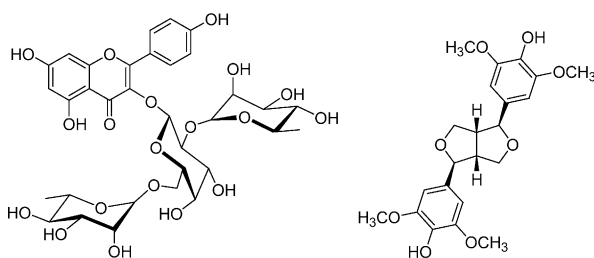
Thiourea **2** was identified as a potential HDL-elevating agent from a targeted database search. Structure–activity relationship of its analogs is described.



**DNA topoisomerase I inhibitors from *Rinorea anguifera***

pp 813–816

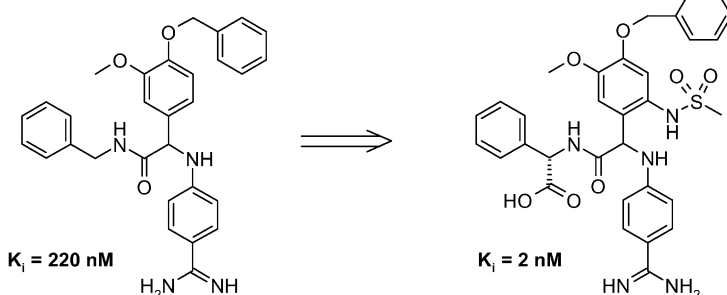
Ji Ma, Shannon H. Jones, Rebekah Marshall, Xihan Wu and Sidney M. Hecht\*

**Design of selective phenylglycine amide tissue factor/factor VIIa inhibitors**

pp 817–822

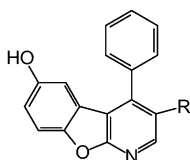
Katrin Groebke Zbinden,\* David W. Banner, Jean Ackermann, Allan D'Arcy, Daniel Kirchhofer, Yu-Hua Ji, Thomas B. Tschopp, Sabine Wallbaum and Lutz Weber

Proof of concept experiments have shown that tissue factor/factor VIIa inhibitors have antithrombotic activity without enhancing bleeding propensity. Starting from lead compounds generated by a biased combinatorial approach, phenylglycine amide tissue factor/factor VIIa inhibitors with low nanomolar affinity and good selectivity against other serine proteases of the coagulation cascade were designed.

**Novel CDK inhibition profiles of structurally varied 1-aza-9-oxafluorenes**

pp 823–825

Burkhardt Voigt, Laurent Meijer, Olivier Lozach, Christoph Schächtele, Frank Totzke and Andreas Hilgeroth\*



Structural variation of merely one substituent in novel 1-aza-9-oxafluorenes suggests that its hydrogen bond acceptor function might be essential for inhibitory activity and, furthermore, leads to unexpected shifts in the selectivity profile of CDK inhibition.

**Specific recognition of naphthyridine-based ligands toward guanine-containing bulges in RNA duplexes and RNA–DNA heteroduplexes**

pp 827–831

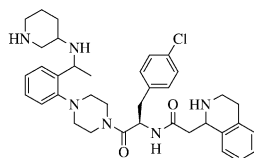
Jeffrey B.-H. Tok,\* Lanrong Bi and Max Saenz

Mismatched bulges in nucleic acid constructs are important in the recognition event between biological molecules. Herein, we report that naphthyridine dimer **2** is able to specifically bind G–G mismatches in all nucleic acid constructs comprising of RNA–RNA, RNA–DNA and DNA–DNA duplexes. This binding behavior suggests that the binding process primarily occurs between the guanine base pairs and the naphthyridine moiety, and is independent of the tertiary structure of the nucleic acid duplexes.

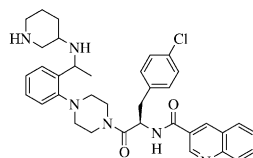
### Identification of agonists and antagonists of the human melanocortin-4 receptor from piperazinebenzylamines

pp 833–837

Joe A. Tran, Joseph Pontillo, Melissa Arellano, Nicole S. White, Beth A. Fleck, Dragan Marinkovic, Fabio C. Tucci, Marion Lanier, Jodie Nelson, John Saunders, Alan C. Foster and Chen Chen\*



**12e**,  $K_i = 6.3$  nM,  $EC_{50} = 31$  nM



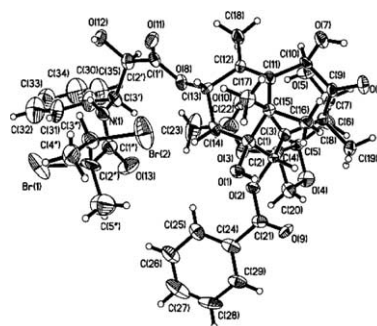
**12l**,  $K_i = 4.5$  nM,  $IC_{50} = 300$  nM

### Crystallographic determination of stereochemistry of biologically active 2'',3''-dibromo-7-*epi*-10-deacetylcephalomannine

pp 839–842

Yi Jiang, Hai-Xia Lin, Jian-Min Chen\* and Min-Qin Chen

Two dibrominated cephalomannine analogues were synthesized and evaluated to be biologically active compounds, the stereochemistry at C2'' and C3'' of the two diastereomers was assigned unambiguously by means of crystallographic study.




## OTHER CONTENTS

Contributors to this issue  
Instructions to contributors

pp I–III  
pp V–VIII

\*Corresponding author

 Supplementary data available via ScienceDirect

## COVER

Non-peptidic small molecules were discovered using structure-based design to mimic SMAC protein believed to trigger apoptosis by abrogating the inhibitory effects of XIAP on caspases. The picture depicts the NMR structure of the SMAC peptide mimetic, compound **20g** bound to BIR3 domain of XIAP indicating the key hydrogen bonds with dotted lines.

Indexed/Abstracted in: Adis LMS Drug Alerts, Beilstein, Biochemistry & Biophysics Citation Index, BIOSIS previews, CAB Abstracts, CAB Health, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/Elsevier BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE



ISSN 0960-894X