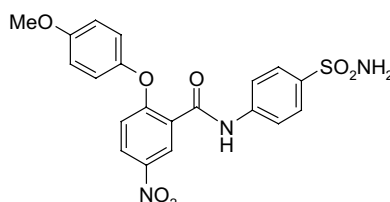


## Contents

### COMMUNICATIONS

**2-(4-Methoxyphenoxy)-5-nitro-*N*-(4-sulfamoylphenyl)benzamide activates Kir6.2/SUR1 K<sub>ATP</sub> channels** pp 5727–5730

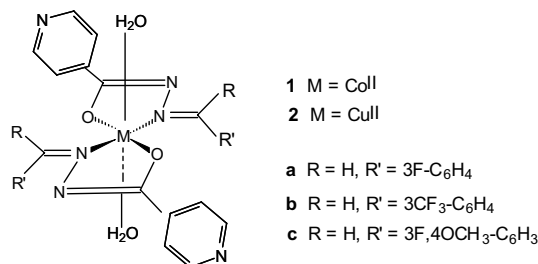
Flemming E. Nielsen, Palle Jacobsen, Anne Worsaae, Per O. G. Arkhammar, Philip Wahl and John Bondo Hansen\*



**In vitro advanced antimycobacterial screening of cobalt(II) and copper(II) complexes of fluorinated isonicotinoylhydrazones**

pp 5731–5733

Rosanna Maccari,\* Rosaria Ottanà, Bruno Bottari, Enrico Rotondo and Maria Gabriella Vigorita

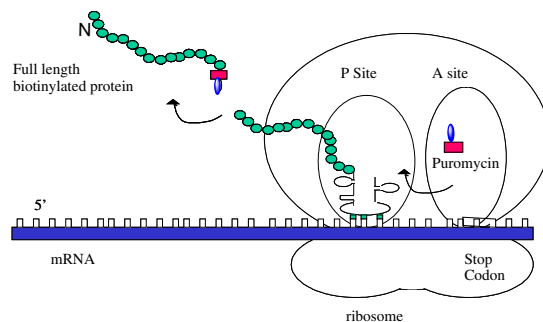


The in vitro antimycobacterial activities of metalcomplexes **1**, **2** are reported.

**Expanding the scope of site-specific protein biotinylation strategies using small molecules**

pp 5735–5738

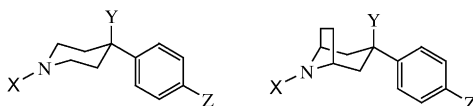
Lay-Pheng Tan, Grace Y. J. Chen and Shao Q. Yao\*



### Haloperidol: towards further understanding of the structural contributions of its pharmacophoric elements at D2-like receptors

pp 5739–5742

Donald M. N. Sikazwe, Shouming Li, Leroy Mardenborough, Vivian Cody, Brian L. Roth and Seth Y. Ablordeppey\*



### Site-specific PEGylation of proteins containing unnatural amino acids

pp 5743–5745

Alexander Deiters, T. Ashton Cropp, Daniel Summerer, Mridul Mukherji and Peter G. Schultz\*



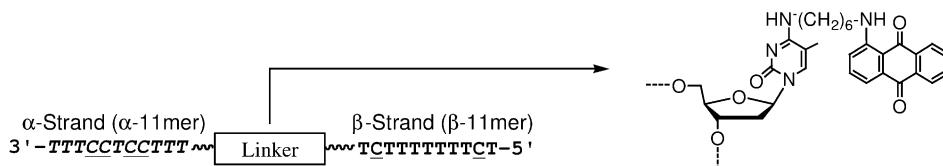
We report a generally applicable PEGylation methodology based on the site-specific incorporation of *para*-azidophenylalanine into proteins in yeast. The azido group was used in a mild [3+2] cycloaddition reaction with an alkyne derivatized PEG reagent to afford selectively PEGylated protein. This strategy should be useful for the generation of selectively PEGylated proteins for therapeutic applications.



### $\alpha$ - $\beta$ Chimeric oligo-DNA bearing intercalator-conjugated nucleobase inside the linker sequence remarkably improves thermal stability of an alternate-stranded triple helix

pp 5747–5750

A. T. M. Zafrul Azam, Minoru Hasegawa, Tomohisa Moriguchi and Kazuo Shinozuka\*

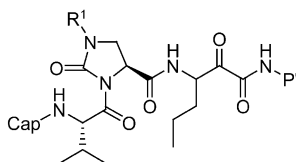


The triple helical DNA formed between the novel  $\alpha$ - $\beta$  chimeric oligodeoxynucleotides bearing an intercalator-conjugated nucleobase located at the internal 4-nt linker region and double-stranded DNA exhibited remarkable thermal stability.

### Novel 2-oxoimidazolidine-4-carboxylic acid derivatives as Hepatitis C virus NS3-4A serine protease inhibitors: synthesis, activity, and X-ray crystal structure of an enzyme inhibitor complex

pp 5751–5755

Ashok Arasappan,\* F. George Njoroge, Tejal N. Parekh, Xiaozheng Yang, John Pichardo, Nancy Butkiewicz, Andrew Prongay, Nanhua Yao and Viyyoor Girijavallabhan

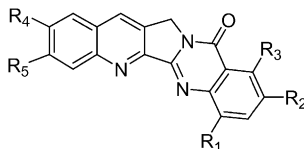


Synthesis and HCV NS3 serine protease inhibitory activity of some novel 2-oxoimidazolidine-4-carboxylic acid derivatives are reported. X-ray structure of an inhibitor, **15c** bound to the protease is presented.

**Synthesis and cytotoxic activity of substituted Luotonin A derivatives**

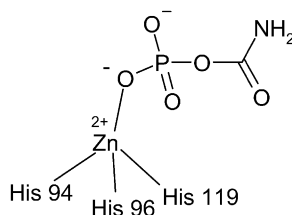
pp 5757–5761

Sabrina Dallavalle,\* Lucio Merlini, Giovanni Luca Beretta, Stella Tinelli and Franco Zunino

**Carbonic anhydrase inhibitors. Interaction of isozymes I, II, IV, V, and IX with phosphates, carbamoyl phosphate, and the phosphonate antiviral drug foscarnet**

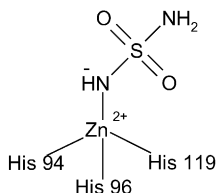
pp 5763–5767

Stefano Rusconi, Alessio Innocenti, Daniela Vullo, Antonio Mastrolorenzo, Andrea Scozzafava and Claudiu T. Supuran\*

**Carbonic anhydrase inhibitors: inhibition of the membrane-bound human isozyme IV with anions**

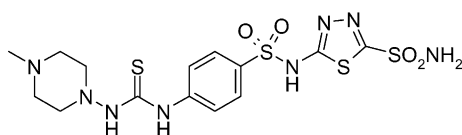
pp 5769–5773

Alessio Innocenti, Michael A. Firnges, Jochen Antel,\* Michael Wurl, Andrea Scozzafava and Claudiu T. Supuran\*

**Carbonic anhydrase inhibitors: synthesis and inhibition of cytosolic/tumor-associated carbonic anhydrase isozymes I, II, and IX with sulfonamides derived from 4-isothiocyanto-benzolamide**

pp 5775–5780

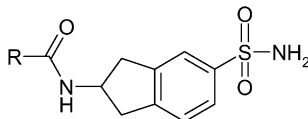
Alessandro Cecchi, Jean-Yves Winum, Alessio Innocenti, Daniela Vullo, Jean-Louis Montero, Andrea Scozzafava and Claudiu T. Supuran\*



**Carbonic anhydrase inhibitors. Design of anticonvulsant sulfonamides incorporating indane moieties**

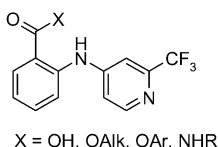
pp 5781–5786

Celine Chazallete, Bernard Masereel,\* Stéphanie Rolin, Anne Thiry, Andrea Scozzafava, Alessio Innocenti and Claudiu T. Supuran\*

**Synthesis of new *N*-(2-(trifluoromethyl)pyridin-4-yl)anthranilic acid derivatives and their evaluation as anticancer agents**

pp 5787–5791

Maria T. Cocco, Cenzo Congiu,\* Valentina Lilliu and Valentina Onnis

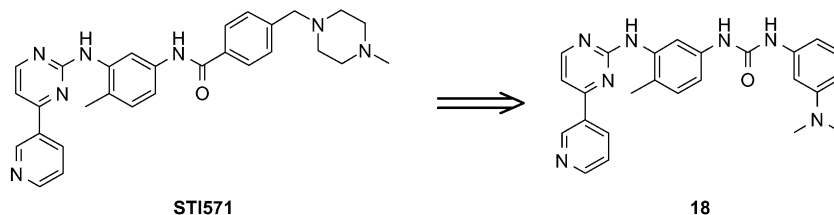


A series of *N*-(2-(trifluoromethyl)pyridin-4-yl)anthranilic acid derivatives was prepared and tested for the in vitro cytotoxic activity against human cancer cell lines. Some aryl esters exhibit antiproliferative activity with GI<sub>50</sub> values at nanomolar concentrations.

**Urea derivatives of STI571 as inhibitors of Bcr-Abl and PDGFR kinases**

pp 5793–5797

Paul W. Manley,\* Werner Breitenstein, Josef Brüggem, Sandra W. Cowan-Jacob, Pascal Furet, Jürgen Mestan and Thomas Meyer

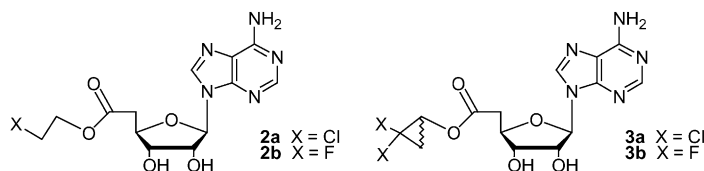


Urea-based analogues of STI571 are described possessing structural features which can differentiate between Abl/Bcr-Abl and PDGFR kinase inhibition.

**Inactivation of *S*-adenosylhomocysteine hydrolase with haloethyl and dihalocyclopropyl esters derived from homoadenosine-6'-carboxylic acid**

pp 5799–5802

Georges Guillerme, Murielle Muzard\* and Cédric Glapski

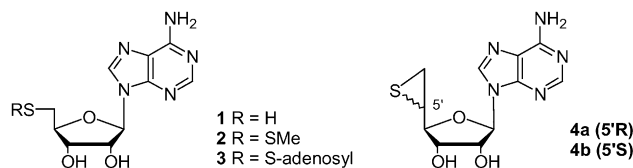


Inactivation of AdoHcy hydrolase with 2–3 resulted in time-dependent loss of enzyme activity. The mechanism of inactivation is discussed.

**Inactivation of human S-adenosylhomocysteine hydrolase by covalent labeling of cysteine 195 with thionucleoside derivatives**

pp 5803–5807

Georges Guillermin, Murielle Muzard,\* Cédric Glapski and Serge Pilard

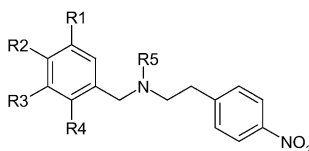


Thionucleosides **1–4** were synthesized for selectively targeting  $^{195}\text{Cys}$  of human placental AdoHcy hydrolase.

**Synthesis of small molecule CDC25 phosphatases inhibitors**

pp 5809–5812

Marie-Odile Contour-Galcéra,\* Olivier Lavergne, Marie-Christine Brezak, Bernard Ducommun and Grégoire Prévost

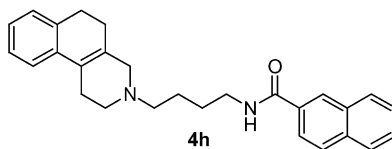


A targeted library of 2-(4-nitrophenyl)ethylbenzylamines has been prepared to optimize the biological activity of BN82002, our initial lead compound, recently described as an original inhibitor of CDC25 phosphatases. The most potent of these compounds inhibit CDC25 in the micromolar range.

**Design, synthesis, and evaluation of hexahydrobenz[*f*]isoquinolines as a novel class of dopamine 3 receptor ligands**

pp 5813–5816

Xihan Wu, Jianyong Chen, Min Ji, Judith Varady, Beth Levant and Shaomeng Wang\*

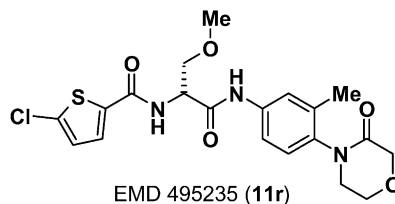


$K_i = 6.1 \text{ nM}$  to the  $D_3$  receptor  
Selectivity of 163 and 133-fold over the  $D_1$  and  $D_2$  receptors

**Chlorothiophenecarboxamides as P1 surrogates of inhibitors of blood coagulation factor Xa**

pp 5817–5822

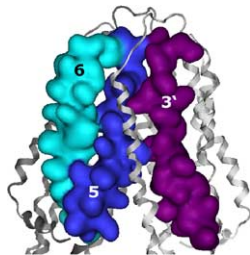
Werner W. K. R. Mederski,\* Bertram Cezanne,\* Christoph van Amsterdam, Karl-Ulrich Bühring, Dieter Dorsch, Johannes Gleitz, Joachim März and Christos Tsaklakidis



**Homology model of the multidrug transporter LmrA from *Lactococcus lactis***

pp 5823–5826

Karin Pleban, Antonio Macchiarulo, Gabriele Costantino, Roberto Pellicciari, Peter Chiba\* and Gerhard F. Ecker\*

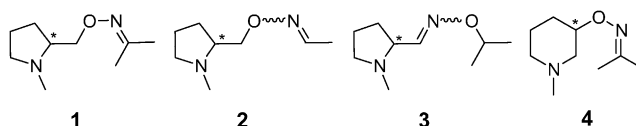


Starting from the dimeric crystal structure of *Vibrio cholerae* MsbA, two homology models of the ATP-dependent multidrug transporter LmrA were generated.

**Synthesis and  $\alpha 4\beta 2$  nicotinic affinity of 2-pyrrolidinylmethoxyimines and prolinal oxime ethers**

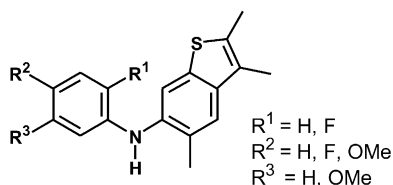
pp 5827–5830

Marco Pallavicini,\* Barbara Moroni, Cristiano Bolchi, Francesco Clementi, Laura Fumagalli, Cecilia Gotti, Silvia Vailati, Ermanno Valoti and Luigi Villa

**Screening of antimicrobial activity of diarylamines in the 2,3,5-trimethylbenzo[b]thiophene series: a structure–activity evaluation study**

pp 5831–5833

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

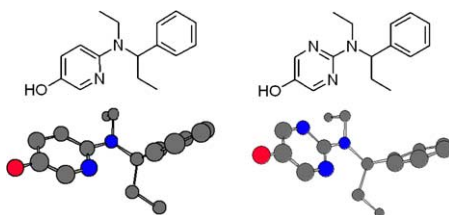


In vitro antimicrobial data against Gram positive, Gram negative bacteria, and *Candida albicans* are presented.

**Ring nitrogen-substituted non-steroidal estrogens: pyridine and pyrimidine analogs of the phenol in deoxyhexestrol experience resonance constraints on preferred ligand conformation**

pp 5835–5839

Meri De Angelis and John A. Katzenellenbogen\*

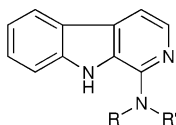


Pyridine and pyrimidine analogs of the nonsteroidal estrogen deoxyhexestrol were synthesized. Their low affinity for the estrogen receptor is ascribed, in part, to resonance enforcement of a conformation unfavorable for binding.

**Synthesis and biological studies of 1-amino  $\beta$ -carbolines**

pp 5841–5844

Yohan Boursereau and Iain Coldham\*

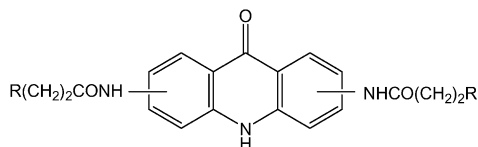


A selection of amino-substituted  $\beta$ -carbolines have been prepared and show anticancer and antimalarial activities.

**Evaluation of by disubstituted acridone derivatives as telomerase inhibitors: the importance of G-quadruplex binding**

pp 5845–5849

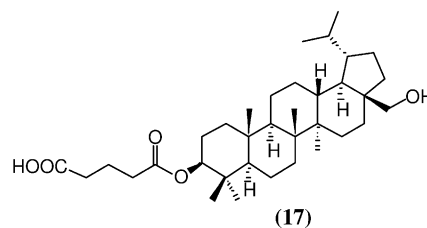
R. John Harrison, Anthony P. Reszka, Shozeb M. Haider, Barbara Romagnoli, James Morrell, Martin A. Read, Sharon M. Gowan, Christopher M. Incles, Lloyd R. Kelland and Stephen Neidle\*

**3-*O*-Glutaryl-dihydrobetulin and related monoacyl derivatives as potent anti-HIV agents**

pp 5851–5853

Yoshiki Kashiwada,\* Michiko Sekiya, Yasumasa Ikeshiro, Toshihiro Fujioka, Nicole R. Kilgore, Carl T. Wild, Graham P. Allaway and Kuo-Hsiung Lee\*

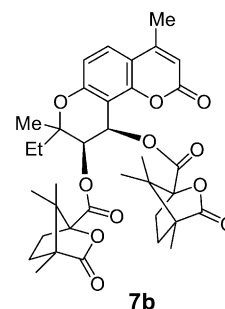
3-*O*-Glutaryl-dihydrobetulin (**17**) demonstrated extremely potent anti-HIV activity with an  $EC_{50}$  value of  $2 \times 10^{-5} \mu M$  and a TI value of  $1.12 \times 10^6$ . 3-*O*-(3',3'-Dimethylsuccinyl)- and 3-*O*-(3',3'-dimethylglutaryl)-dihydrobetulins (**15**, **16**) were also potent anti-HIV compounds with  $EC_{50}$  values of 0.0017 and 0.0013  $\mu M$ , respectively, and TI values of 16,160 and 19,530, respectively.

**Anti-AIDS agents. Part 62: anti-HIV activity of 2'-substituted 4-methyl-3',4'-di-*O*-(–)-camphanoyl-(+)-*cis*-khellactone (4-methyl DCK) analogs**

pp 5855–5857

Qian Zhang, Ying Chen, Peng Xia,\* Yi Xia, Zheng-Yu Yang, Donglei Yu, Susan L. Morris-Natschke and Kuo-Hsiung Lee\*

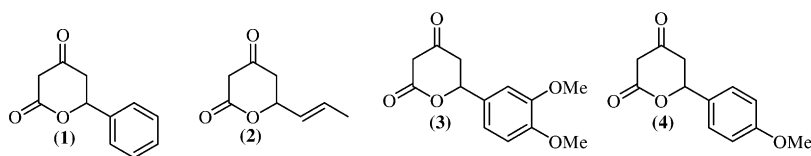
Four 4-methyl-3',4'-di-*O*-(–)-camphanoyl-(+)-*cis*-khellactone (4-methyl DCK) analogs (**7a–d**) with different alkyl substituents at the 2'-position were synthesized and evaluated for inhibition of HIV-1 replication in H9 lymphocytes. 2'-Methyl-2'-ethyl-4-methyl DCK (**7b**) was more potent ( $EC_{50} = 0.22 \mu M$ , TI > 175) than the other three compounds (**7a**, **7c**, and **7d**), but significantly less potent than 4-methyl DCK (**2**,  $EC_{50} = 0.0059 \mu M$ , TI > 6600).



**Determination of the free radical scavenging activity of dihydropyran-2,4-diones**

pp 5859–5861

Laura Cristiane de Souza, Stella Maris Soares de Araújo and Dennis de Oliveira Imbroisi\*

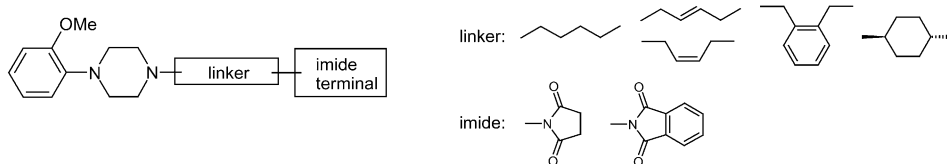


The capacities of the dihydropyran-2,4-diones **1–4** to inhibit the stable free radical DPPH have been determined. All four compounds exhibited high inhibition percentages but 6-phenyl-dihydropyran-2,4-dione (**1**) was the most active. The antioxidant activity for this class of compound is reported for the first time.

**The impact of spacer structure on 5-HT<sub>7</sub> and 5-HT<sub>1A</sub> receptor affinity in the group of long-chain arylpiperazine ligands**

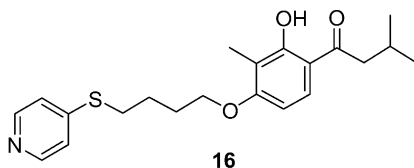
pp 5863–5866

Andrzej J. Bojarski,\* Beata Duszyńska, Marcin Kołaczkowski, Piotr Kowalski and Teresa Kowalska

**Allosteric potentiators of the metabotropic glutamate receptor 2 (mGlu2). Part 2: 4-Thiopyridyl acetophenones as non-tetrazole containing mGlu2 receptor potentiators**

pp 5867–5872

Anthony B. Pinkerton,\* Rowena V. Cube, John H. Hutchinson, Joyce K. James, Michael F. Gardner, Hervé Schaffhauser, Blake A. Rowe, Lorrie P. Daggett and Jean-Michel Vernier



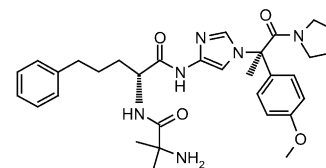
We have identified and synthesized a series of 4-thiopyridyl acetophenones as positive allosteric potentiators of the metabotropic glutamate receptor 2. Structure–activity relationship studies directed toward replacement of the tetrazole in the initial lead led to the discovery of **16** (EC<sub>50</sub> = 340 nM), which showed improved brain penetration over the initial lead.

**Synthesis and biological evaluation of an orally active ghrelin agonist that stimulates food consumption and adiposity in rats**

pp 5873–5876

Charles W. Lugar, Michael P. Clay, Terry D. Lindstrom, Andrea L. Woodson, David Smiley, Mark L. Heiman and Jeffrey A. Dodge\*

LY444711 is an orally active ghrelin agonist that binds with good affinity and is a potent activator of the growth hormone secretagogue receptor 1a (GHS-R1a) receptor. In rat models of feeding behavior and pharmacology, LY444711 creates a positive energy balance and induces adiposity by stimulating food consumption and sparing fat utilization.

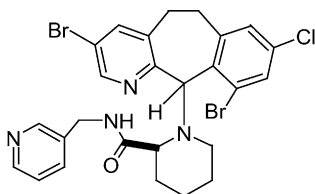




**Farnesyl protein transferase inhibitors targeting the catalytic zinc for enhanced binding**

pp 5877–5880

F. George Njoroge,\* Bancha Vibulbhan, Patrick Pinto, Corey Strickland, Paul Kirschmeier, W. Robert Bishop and V. Girijavallabhan

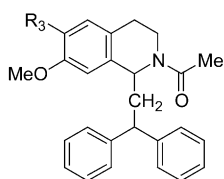


Design and synthesis of farnesyl protein transferase inhibitors, targeting catalytic zinc are reported.

**Tetrahydroisoquinoline derivatives as melatonin MT<sub>2</sub> receptor antagonists**

pp 5881–5884

George N. Karageorge,\* Stephen Bertenshaw, Lawrence Iben, Cen Xu, Nathan Sarbin, Anthony Gentile and Gene M. Dubowchik



**1a** (R3= -OMe) MT<sub>2</sub> IC<sub>50</sub> = 9.7 nM

**1z** (R3= -H) MT<sub>2</sub> IC<sub>50</sub> = 5.5 nM

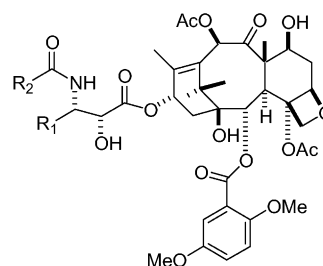
A series of tetrahydroisoquinolines has yielded potent MT<sub>2</sub> receptor antagonists, which are selective versus the MT<sub>1</sub> receptor.

**Synthesis and biological evaluation of novel taxoids designed for targeted delivery to tumors**

pp 5885–5888

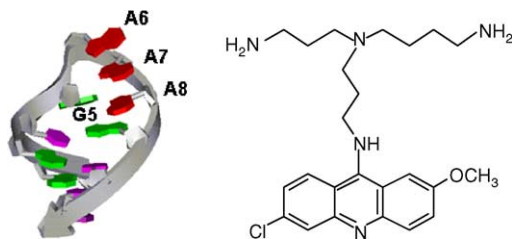
Erkan Baloglu,\* Michael L. Miller, Elizabeth E. Roller, Emily E. Cavanagh, Barbara A. Leece, Victor S. Goldmacher and Ravi V. J. Chari

The use of drug–antibody conjugates affords a method for the targeted delivery of anticancer drugs specifically to cancer cells. Monoclonal antibodies alone usually do not possess high therapeutic efficacy, however, they are capable of targeting tumor markers selectively. We have prepared taxoids with significantly higher cytotoxicity than paclitaxel and docetaxel. These taxoids now meet the high potency required for use in a targeted-delivery approach using monoclonal antibodies. The synthesis and biological evaluation of these taxoids are reported.

**Binding of an aminoacridine derivative to a GAAA RNA tetraloop**

pp 5889–5893

Zhaohui Yan and Anne M. Baranger\*

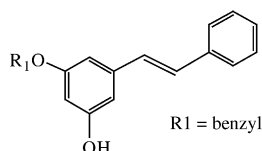


An aminoacridine derivative binds with low micromolar affinity and one to one stoichiometry to the junction between the stem and the loop of a GAAA tetraloop.

### Synthesis and inhibitory effects of pinosylvin derivatives on prostaglandin E<sub>2</sub> production in lipopolysaccharide-induced mouse macrophage cells

pp 5895–5898

Eun-Jung Park, Hye-Young Min, Yong-Hyun Ahn, Cheol-Man Bae, Jae-Ho Pyee and Sang Kook Lee\*



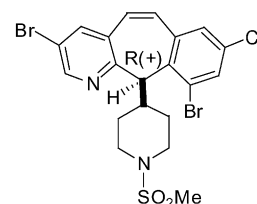
The inhibitory effects of pinosylvin analogues on the production of COX-2 mediated PGE<sub>2</sub> were evaluated in a cell culture system. A new series of potential inhibitors, including 3-hydroxy-5-benzyloxy-*trans*-stilbene and 3,5-dimethoxy-*trans*-stilbene, have been identified.

### Bridgehead modification of trihalocycloheptabenzopyridine lead to a potent farnesyl protein transferase inhibitor with improved oral metabolic stability

pp 5899–5902

F. George Njoroge,\* Bancha Vibulbhan, Xiongwei Shi, Corey Strickland, Paul Kirschmeier, Robert Bishop, Amin Nomeir and Viyyoor Girijavallabhan

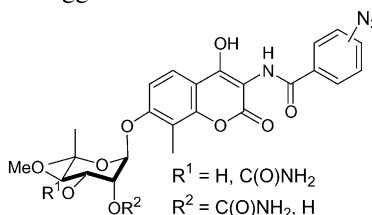
Modification of the ethano bridge of the core structure of the antitumor agent, SARASAR<sup>®</sup> (SCH66336) with concomitant introduction of a sulfonamide moiety off the distal piperidine afforded inhibitor **9-(S-)**, a compound with greatly improved PK profile.



### Syntheses of photolabile novobiocin analogues

pp 5903–5906

Gang Shen, Xiao ming Yu and Brian S. J. Blagg\*

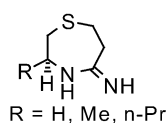


Novobiocin was recently shown to inhibit Hsp90 through a previously unrecognized C-terminal ATP binding site. Although the N-terminal region of Hsp90 has been solved by X-ray crystallography, the C-terminal region has not. In an effort to elucidate the C-terminal binding site of Hsp90, four photolabile analogues of novobiocin were prepared.

### Synthesis of analogs of (1,4)-3- and 5-imino oxazepane, thiazepane, and diazepane as inhibitors of nitric oxide synthases

pp 5907–5911

K. Shankaran,\* Karla L. Donnelly, Shrenik K. Shah, Charles G. Caldwell, Ping Chen, William K. Hagmann, Malcolm MacCoss, John L. Humes, Stephen G. Pacholok, Theresa M. Kelly, Stephan K. Grant and Kenny K. Wong

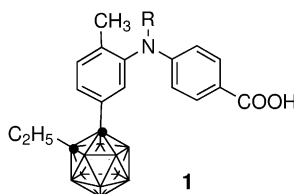


The preparation and SAR of a series of iNOS inhibitors leading to the most potent compound, incorporating a (1,4)-5-imino thiazepane (R = *n*-Pr) is disclosed.

**Novel retinoid X receptor (RXR) antagonists having a dicarba-*closo*-dodecaborane as a hydrophobic moiety**

pp 5913–5918

Kiminori Ohta, Toru Iijima, Emiko Kawachi, Hiroyuki Kagechika and Yasuyuki Endo\*

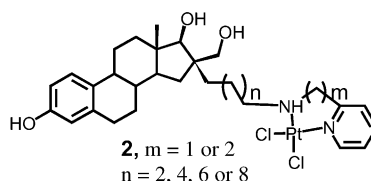


We designed and synthesized novel retinoid X receptor (RXR)-selective antagonists such as **1** bearing a carborane moiety.

**Biological evaluation of novel estrogen–platinum(II) hybrid molecules on uterine and ovarian cancers—molecular modeling studies**

pp 5919–5924

Véronique Gagnon, Marie-Ève St-Germain, Caroline Descôteaux, Josée Provencher-Mandeville, Sophie Parent, Sanat K. Mandal, Eric Asselin and Gervais Bérubé\*

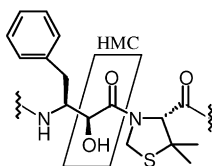


The biological activity of hybrids **2** was evaluated in vitro on human uterine and ovarian cancers. The molecules present high affinity for the estrogen receptor alpha. The cytotoxicity and the affinity of **2** are explained by molecular modeling analysis.

**Identification of peptidomimetic HTLV-I protease inhibitors containing hydroxymethylcarbonyl (HMC) isostere as the transition-state mimic**

pp 5925–5929

Hikoichiro Maegawa, Tooru Kimura, Yasuhiro Arai, Yasuko Matsui, Soko Kasai, Yoshio Hayashi and Yoshiaki Kiso\*

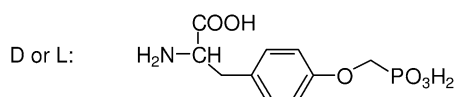


Towards the development of chemotherapy for the infection by human T-cell leukemia virus type I (HTLV-I), we have established evaluation systems for HTLV-I protease (PR) inhibitors using both recombinant and chemically synthesized HTLV-I PRs. Newly synthesized substrate-based inhibitors containing hydroxymethylcarbonyl (HMC) isostere showed potent anti-HTLV-I PR activity.

**A nonhydrolyzable analogue of phosphotyrosine, and related aryloxymethano- and aryloxyethano-phosphonic acids as motifs for inhibition of phosphatases**

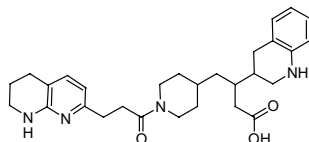
pp 5931–5935

Subashree Iyer, Jarod M. Younker, Przemyslaw G. Czyryca\* and Alvan C. Hengge\*



**1,2,3,4-Tetrahydroquinoline-containing  $\alpha_v\beta_3$  integrin antagonists with enhanced oral bioavailability** pp 5937–5941

Shyamali Ghosh, Rosemary J. Santulli, William A. Kinney,\* Bart L. DeCorte, Li Liu, Joan M. Lewis, Jef C. Proost, Gregory C. Leo, John Masucci, William E. Hageman, Andrew S. Thompson, Ian Chen, Reiko Kawahama, Robert W. Tuman, Robert A. Galembo, Jr., Dana L. Johnson, Bruce P. Damiano and Bruce E. Maryanoff

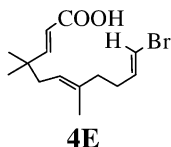


Selective reduction of the quinoline yielded potent  $\alpha_v\beta_3$  antagonists with improved oral bioavailability relative to the corresponding quinoline derivatives.

**Unprecedented olefin-dependent histidine-kinase inhibitory of zerumbone ring-opening material**

pp 5943–5946

Takashi Kitayama,\* Risa Iwabuchi, Shu Minagawa, Fumihiro Shiomi, John Cappiello, Seiji Sawada, Ryutaro Utsumi\* and Tadashi Okamoto



The synthesis and evaluation of **4E**, autophosphorylation inhibitor of YycG (histidine-kinase), are reported.

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\*Corresponding author

Supplementary data available via ScienceDirect

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