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# Bioorganic & Medicinal Chemistry

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## Bioorganic & Medicinal Chemistry Vol. 17, No. 5, 2009

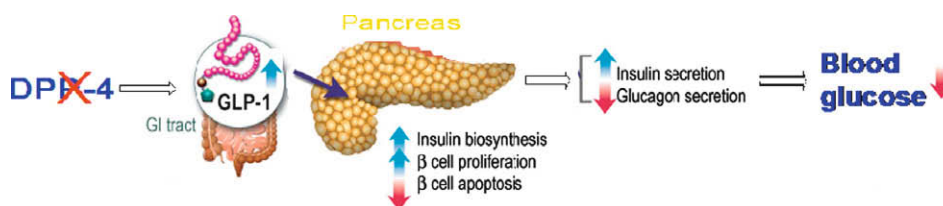
### Contents

#### REVIEW

#### Medicinal chemistry approaches to the inhibition of dipeptidyl peptidase-4 for the treatment of type 2 diabetes

pp 1783–1802

Shrikanth H. Havale, Manojit Pal \*

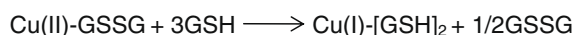
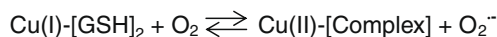


#### ARTICLES

#### Generation of superoxide radicals by copper–glutathione complexes: Redox-consequences associated with their interaction with reduced glutathione

pp 1803–1810

Hernán Speisky \*, Maritza Gómez, Francesca Burgos-Bravo, Camilo López-Alarcón, Carolina Jullian, Claudio Olea-Azar, Margarita E. Aliaga

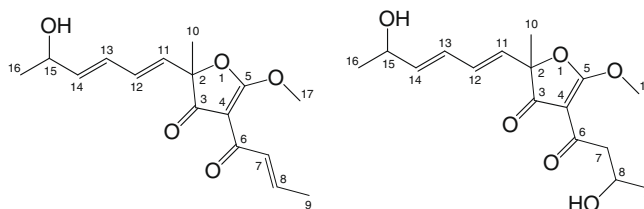


Cu(I)–[GSH]<sub>2</sub> reacts with oxygen forming superoxide radicals. Upon removal of such radicals Cu(II)–GSSG is formed. Subsequent addition of GSH regenerates the Cu(I)–[GSH]<sub>2</sub> complex. Redox implications of these interactions are discussed.

#### Penicillliols A and B, novel inhibitors specific to mammalian Y-family DNA polymerases

pp 1811–1816

Takuma Kimura, Toshifumi Takeuchi, Yuko Kumamoto-Yonezawa, Eiji Ohashi, Haruo Ohmori, Chikahide Masutani, Fumio Hanaoka, Fumio Sugawara, Hiromi Yoshida, Yoshiyuki Mizushima \*



Penicillliol A (1)

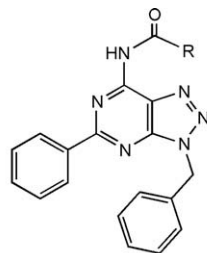
Penicillliol B (2)

Penicillliols A (1) and B (2) are novel 5-methoxy-3(2H)-furanones isolated from cultures of a fungus (*Penicillium daleae* K.M. Zalesky) derived from a sea moss, and these compounds selectively inhibited activities mammalian Y-family DNA polymerases.

### Synthesis, biological assays and QSAR studies of *N*-(9-benzyl-2-phenyl-8-azapurin-6-yl)-amides as ligands for A<sub>1</sub> adenosine receptors

pp 1817–1830

Irene Giorgi\*, Michele Leonardi, Daniele Pietra, Giuliana Biagi, Alice Borghini, Ilaria Massarelli, Osele Ciampi, Anna Maria Bianucci

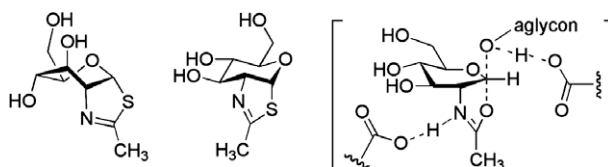


R = phenyl, substituted phenyl, cycloalkyl, heterocyclic ring

### GlcNAc-Thiazoline conformations

pp 1831–1836

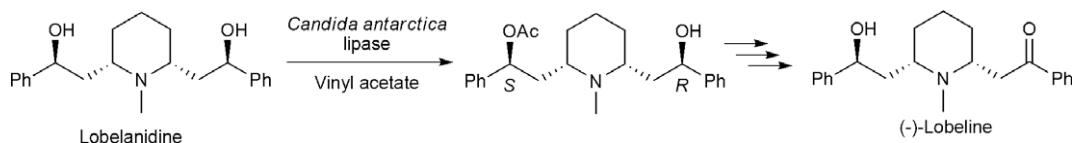
Spencer Knapp\*, David Fash, Mohannad Abdo, Thomas J. Emge, Paul R. Rablen\*



### Synthesis of (–)-lobeline via enzymatic desymmetrization of lobelanidine

pp 1837–1839

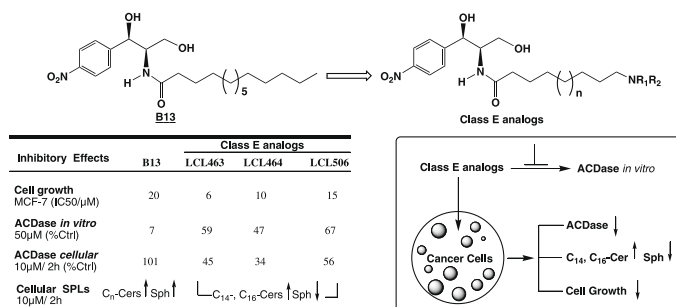
Robert Chênevert\*, Pierre Morin



### Synthesis and bioevaluation of ω-*N*-amino analogs of B13

pp 1840–1848

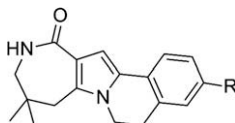
Aiping Bai, Zdzisław M. Szulc, Jacek Bielawski, Nalini Mayroo, Xiang Liu, James Norris, Yusuf A. Hannun, Alicja Bielawska\*



**Synthesis and cytotoxic activity of new azepino[3',4':4,5]pyrrolo[2,1-*a*]isoquinolin-12-ones**

pp 1849–1856

Roberto Martínez\*, Martha Menes Arzate, Ma. Teresa Ramírez-Apan

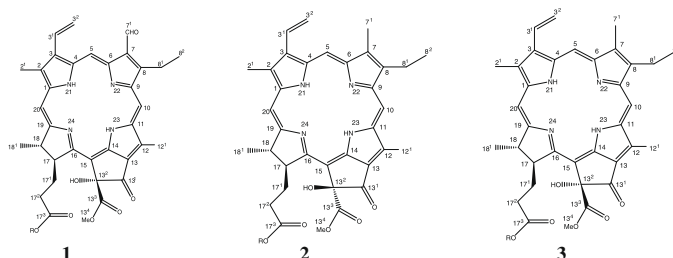


A series of new azepinopyrroloisoquinolinones were designed as potential cytotoxic compounds and were synthesized using a radical oxidative aromatic substitution reaction as the key step.

**Bioactive constituents from the leaves of *Clinacanthus nutans* Lindau**

pp 1857–1860

Santi Sakdarat\*, Aussavashai Shuypprom, Chamsai Pientong, Tipaya Ekalaksananan, Sasithorn Thongchai

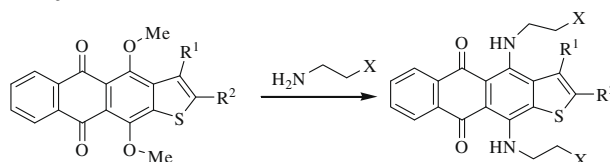


Three chlorophyll derivatives (phaeophytins) were isolated from the chloroform extract of *Clinacanthus nutans* Lindau leaves by means of chromatographic techniques and bioactivity-guided fractionation to give three pure compounds. They exhibited anti-HSV-1F activity at subtoxic concentrations. Their inhibitory activity affected the virus before viral entry to the host cells. This effect might be virucidal and interfering viral adsorption or penetration.

**Synthesis and cytotoxic properties of 4,11-bis[(aminoethyl)amino]anthra[2,3-*b*]thiophene-5,10-diones, novel analogues of antitumor anthracene-9,10-diones**

pp 1861–1869

Andrey E. Shchekotikhin\*, Valeria A. Glazunova, Lyubov G. Dezhenkova, Yuri N. Luzikov, Yuri B. Sinkevich, Leonid V. Kovalenko, Vladimir N. Buyanov, Jan Balzarini, Fong-Chun Huang, Jing-Jer Lin, Hsu-Shan Huang, Alexander A. Shtil, Maria N. Preobrazhenskaya

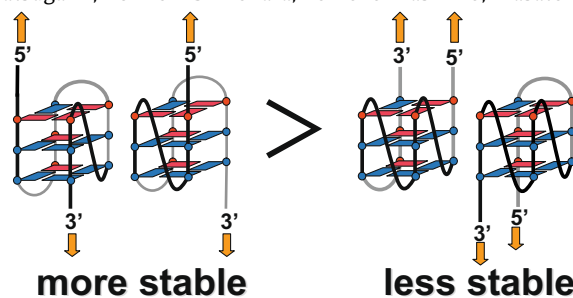


The preparation and cytotoxic properties of novel series of 4,11-bis[(aminoethyl)amino]anthra[2,3-*b*]thiophene-5,10-diones are described. The anthra[2,3-*b*]thiophene-5,10-diones carrying *N*-methyl- or *N,N*-dimethylamino groups at the side chains demonstrated a remarkable activity against drug resistant tumor cells. The derivatives with guanidine groups in the side chains were identified as potent inhibitors of telomerase activity.

**The orientation of the ends of G-quadruplex structures investigated using end-extended oligonucleotides**

pp 1870–1875

Yuta Sannohe, Kyosuke Sato, Akimasa Matsugami, Ken-ichi Shinohara, Tomoko Mashimo, Masato Katahira, Hiroshi Sugiyama\*

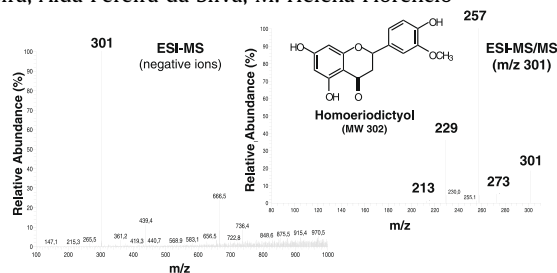


We found that the ends of stable G-quadruplex structures point in opposite directions. This result indicates that the human telomere DNA is likely to form compact higher-order structures.

## Plant extracts with anti-inflammatory properties—A new approach for characterization of their bioactive compounds and establishment of structure–antioxidant activity relationships

pp 1876–1883

Sónia Amaral, Lurdes Mira, J. M. F. Nogueira, Alda Pereira da Silva, M. Helena Florêncio\*



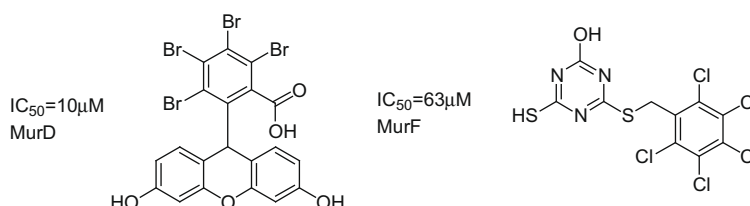
The ESI-MS/MS methodology proposed can be used as a model procedure for identification and characterization of unknowns without the prerequisite for standard compounds analysis.



## Discovery of new inhibitors of the bacterial peptidoglycan biosynthesis enzymes MurD and MurF by structure-based virtual screening

pp 1884–1889

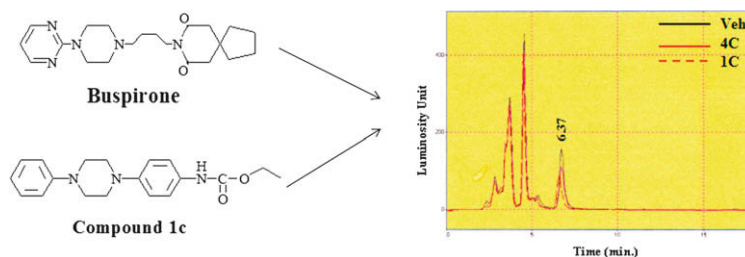
Samo Turk, Andreja Kovač, Audrey Boniface, Julieanne M. Bostock, Ian Chopra, Didier Blanot, Stanislav Gobec\*



## Synthesis and pharmacological evaluation of new arylpiperazines *N*-{4-[4-(aryl) piperazine-1-yl]-phenyl}-amine derivatives: Putative role of 5-HT<sub>1A</sub> receptors

pp 1890–1897

Manisha Khatri, Santosh Kumar Rai, Sameena Alam, Anjana Vij, Manisha Tiwari\*

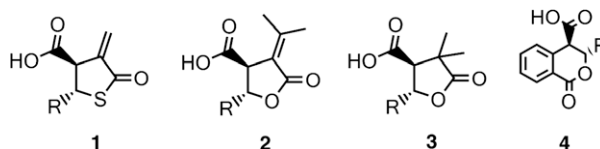


A series of *N*-{4-[4-(aryl)piperazine-1-yl]-phenyl}-amine derivatives (**1c–4e**) were synthesized and evaluated for their anxiolytic activity. Serotonin levels were also determined by HPLC for possible involvement of 5-HT<sub>1A</sub> receptors. Compounds **1c** and **4c** were found to be good anxiolytics.

## Novel fatty acid synthase (FAS) inhibitors: Design, synthesis, biological evaluation, and molecular docking studies

pp 1898–1904

Xiaokui Wang, Jian Lin, Yao Chen, Wu Zhong, Guoming Zhao, Hongying Liu, Site Li, Lili Wang, Song Li\*



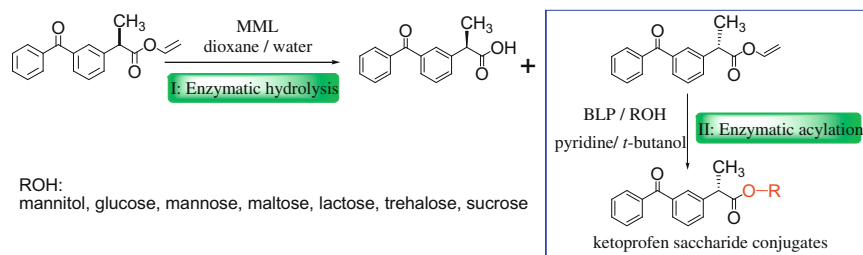
The synthesis, biological evaluation, and molecular docking studies of several novel series of **C75** derivatives are described.



**Two-step enzymatic selective synthesis of water-soluble ketoprofen-saccharide conjugates in organic media**

pp 1905–1910

Hai-Yang Wang, Chao Li, Na Wang\*, Kun Li, Xing-Wen Feng, Ting He, Xiao-Qi Yu\*

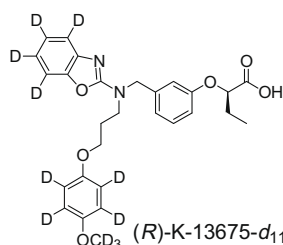


Ketoprofen-saccharide conjugates were synthesized by selectively enzymatic hydrolysis and acylation. The products have better water solubility than parent ketoprofen and thus suitable for potentially pharmaceutical application.

**Synthesis of highly deuterium-labeled (R)-K-13675, PPAR  $\alpha$  agonist, for use as an internal standard for low-level quantification of drugs in plasma**

pp 1911–1917

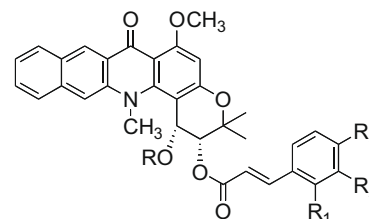
Yukiyoshi Yamazaki, Shin-ichiro Ogawa, Kimiyuki Shibuya\*

**Synthesis, cytotoxic activity, and DNA binding properties of antitumor *cis*-1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine cinnamoyl esters**

pp 1918–1927

Quynh Do, Wen Tian, Rodrigue Yougnia, Thomas Gaslonde, Bruno Pfeiffer, Alain Pierré, Stéphane Léonce, Laurence Kraus-Berthier, Marie-Hélène David-Cordonnier, Sabine Depauw, Amélie Lansiaux, Romain Mazinghien, Michel Koch, François Tillequin\*, Sylvie Michel, Hanh Dufat

Cinnamoyl esters of ( $\pm$ )-*cis*-1,2-dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7H-benzo[*b*]pyrano[3,2-*h*]acridin-7-one are slower DNA alkylators than the corresponding diacetate S23906-1, and are significantly active against C-38 adenocarcinoma implanted in mice.

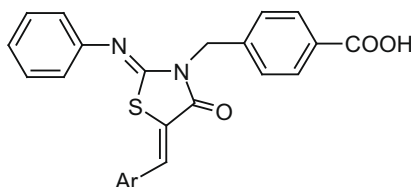


R = H, COCH<sub>3</sub>  
 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = H, Cl, Br, OCH<sub>3</sub>, CF<sub>3</sub>, NO<sub>2</sub>

**5-Arylidene-2-phenylimino-4-thiazolidinones as PTP1B and LMW-PTP inhibitors**

pp 1928–1937

Rosaria Ottanà\*, Rosanna Maccari, Rosella Ciurleo, Paolo Paoli, Michela Jacomelli, Giampaolo Manao, Guido Camici, Christian Laggner, Thierry Langer

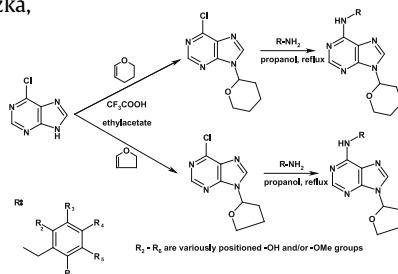


## Synthesis, characterization and biological activity of ring-substituted 6-benzylamino-9-tetrahydropyran-2-yl and 9-tetrahydrofuran-2-ylpurine derivatives

pp 1938–1947

Lucie Szüčová\*, Lukáš Spíchal, Karel Doležal, Marek Zatloukal, Jarmila Greplová, Petr Galuszka, Vladimír Kryštof, Jiří Voller, Igor Popa, Frank J. Massino, Jan-Elo Jørgensen, Miroslav Strnad

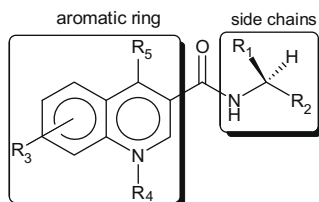
Synthesis of 9-tetrahydropyran-2-yl and 9-tetrahydrofuran-2-yl benzylaminopurines, their stability, cytokinin activity, perception by cytokinin receptors, degradation by cytokinin oxidase/dehydrogenase and cytotoxicity against human diploid fibroblasts and selected human cancer cell lines in vitro are described.



## Design, synthesis, and biological evaluation of novel quinoline derivatives as HIV-1 Tat-TAR interaction inhibitors

pp 1948–1956

Shuguang Chen, Ran Chen, Meizi He, Ruifang Pang, Zhiwu Tan, Ming Yang\*



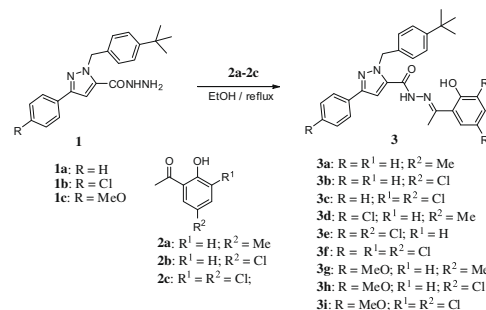
A series of novel quinoline derivatives bearing an aromatic ring and two side chains were designed and synthesized, most of which showed high inhibitions to HIV-1 Tat-TAR interaction and antiviral activities with low cytotoxicities.

## Synthesis of novel substituted pyrazole-5-carbohydrazone hydrazone derivatives and discovery of a potent apoptosis inducer in A549 lung cancer cells

pp 1957–1962

Liang-Wen Zheng, Ling-Ling Wu, Bao-Xiang Zhao\*, Wen-Liang Dong, Jun-Ying Miao\*

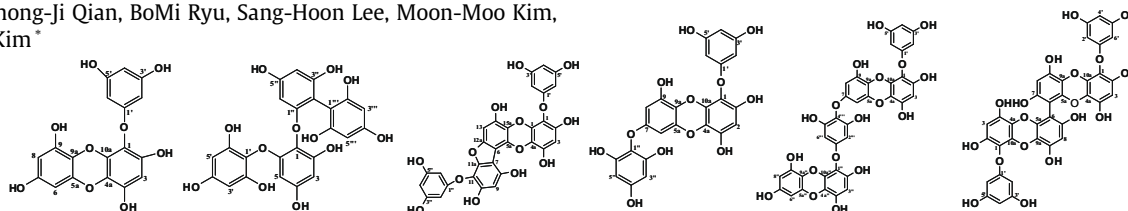
A series of novel 3-aryl-1-(4-*tert*-butylbenzyl)-1H-pyrazole-5-carbohydrazone hydrazone derivatives were synthesized and the effects of all the compounds on A549 cell growth were investigated. The results showed that all compounds had inhibitory effects on the growth of A549 lung cancer cells and compound **3e** showed the highest growth inhibitory effect and induced apoptosis of A549 lung cancer cells.



## Chemical components and its antioxidant properties in vitro: An edible marine brown alga, *Ecklonia cava*

pp 1963–1973

Yong Li, Zhong-Ji Qian, BoMi Ryu, Sang-Hoon Lee, Moon-Moo Kim, Se-Kwon Kim\*

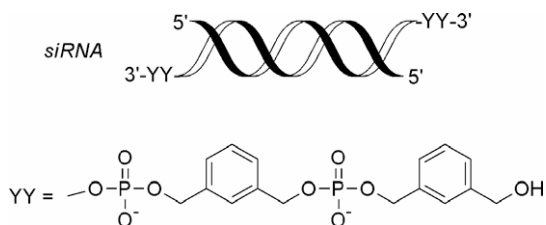


Seven phlorotannins were isolated and characterized from an edible marine brown alga *Ecklonia cava* (EC), along with three common sterol derivatives (fucosterol, ergosterol, and cholesterol) according to the comprehensive spectral analysis of MS and NMR data. Compounds **5** (7-phloro Eckol) and **7** (6,6'-bieckol) in phlorotannin derivatives were obtained for the first time with the high yields respectively. Any bioactive reports of compound **3** (Fucodiphloretol G) was found nowhere up to date. The antioxidant properties of all phlorotannins were assessed by total antioxidant activity in a linoleic model, free radicals scavenging assay using electron spin resonance spectrometry (ESR) technique; cellular reactive oxygen species (ROS) assay by DCFH-DA, membrane protein oxidation, cellular glutathione (GSH) level in RAW264.7 cell line; and myeloperoxidase (MPO) assay in HL-60 cell line. The results revealed that phlorotannins have noteworthy antioxidant properties in vitro, especially, compounds **7** (6,6'-bieckol), **6**, and **3** showed the significant activities comparing to the other phlorotannins in general. Furthermore, the structure-activity relationship (SAR) was discussed according to structural differences of the tested phlorotannins with diverse skeletons and linkages polymerized by phloroglucinol units. It implied that phlorotannins from this genus could be more potential candidates to develop unique natural antioxidants for further industrial application as functional food, cosmetic industry and pharmaceutical exploration, as well as it makes clear to understand why EC have been used as traditional folk herb for a long history.

**Synthesis of nuclease-resistant siRNAs possessing universal overhangs**

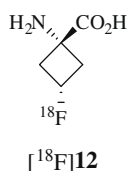
pp 1974–1981

Yoshihito Ueno\*, Yuuji Watanabe, Aya Shibata, Kayo Yoshikawa, Takashi Takano, Michinori Kohara, Yukio Kitade\*

**Stereoselective synthesis and biological evaluation of *syn*-1-amino-3-[<sup>18</sup>F]fluorocyclobutyl-1-carboxylic acid as a potential positron emission tomography brain tumor imaging agent**

pp 1982–1990

Weiping Yu, Larry Williams, Vernon M. Camp, Eugene Malveaux, Jeffrey J. Olson, Mark M. Goodman\*

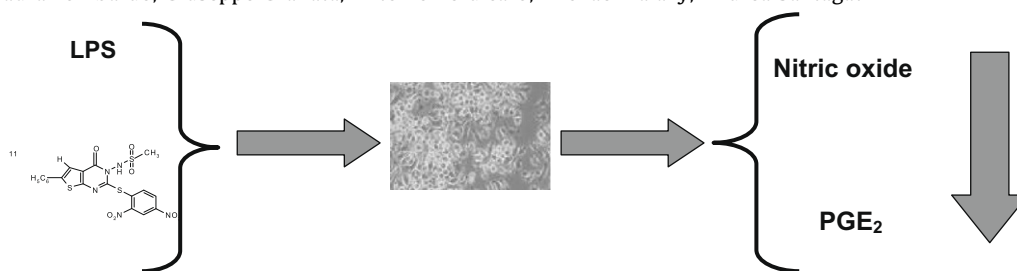


*syn*-FACBC 12, the isomer of *anti*-FACBC, has been stereoselectively synthesized and [<sup>18</sup>F] radiofluorinated in 52% decay-corrected yield. Biological evaluation using rat 9L gliosarcoma model showed that this tracer entered tumor cells via L-type amino acid transport in vitro with high tumor to brain ratio of 12:1 at 30 min post injection in vivo.

**Inhibition of iNOS and COX-2 in human whole blood ex vivo and monocyte-macrophage J774 cells by a new group of aminothiopyrimidone derivatives**

pp 1991–1996

Venera Cardile\*, Laura Lombardo, Giuseppe Granata, Antonio Perdicaro, Michael Balazy, Andrea Santagati

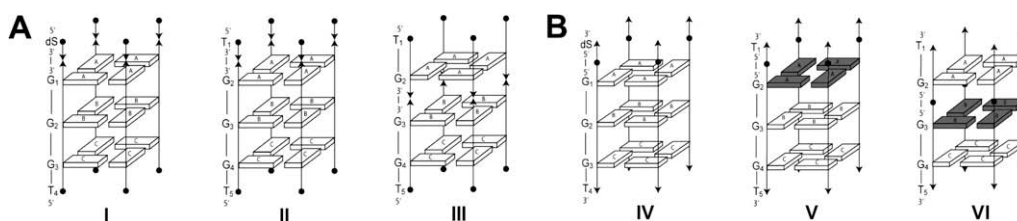


*N*-[2-[(2,4-Dinitrophenyl)thio]-4-oxo-6-phenylthieno[2,3-*d*]pyrimidin-3(4*H*)-*y*]methanesulfonamide inhibits LPS-stimulated formation of nitric oxide and PGE<sub>2</sub>.

**Effects of the introduction of inversion of polarity sites in the quadruplex forming oligonucleotide TGGGT**

pp 1997–2001

Veronica Esposito, Antonella Virgilio, Antonietta Pepe, Giorgia Oliviero, Luciano Mayol, Aldo Galeone\*

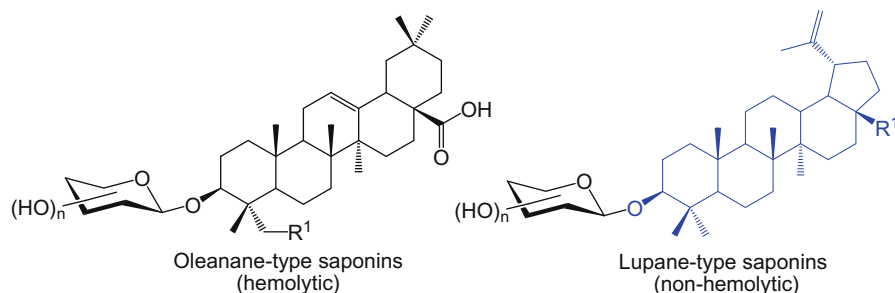


NMR and CD studies concerning quadruplexes based on sequence TGGGT and containing 3'–3' or 5'–5' inversion of polarity sites were reported.

## Haemolytic activity, cytotoxicity and membrane cell permeabilization of semi-synthetic and natural lupane- and oleanane-type saponins

pp 2002-2008

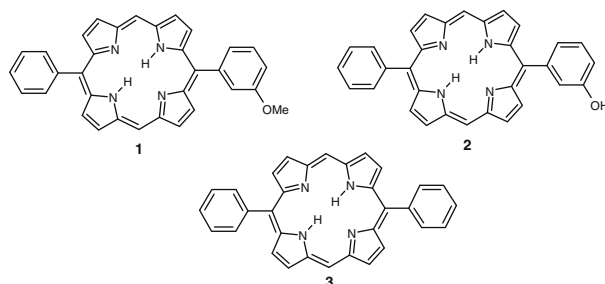
Charles Gauthier, Jean Legault, Karl Girard-Lalancette, Vakhtang Mshvildadze, André Pichette \*



## Photodynamic effects of novel 5,15-diaryl-tetrapyrrole derivatives on human colon carcinoma cells

pp 2009-2016

Marzia B. Gariboldi, Raffaella Ravizza, Peter Baranyai, Enrico Caruso, Stefano Banfi\*, Stefania Meschini, Elena Monti



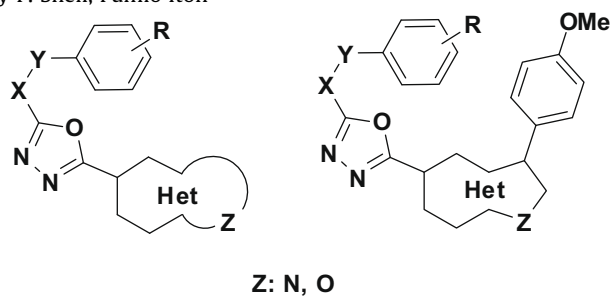
The investigation of some mechanistic aspects of the photodynamic action of three newly synthesized *meso* diaryl-substituted tetrapyrrole that have shown in vitro cytotoxicity on the human colon carcinoma cell line HCT116. The results were compared with those obtained with *m*-THPC.

# Design, synthesis and structure–activity relationships of 1,3,4-oxadiazole derivatives as novel inhibitors of glycogen synthase kinase-3β

pp 2017-2029

Morihiisa Saitoh\*, Jun Kunitomo, Eiji Kimura, Yoji Hayase, Hiromi Kobayashi, Noriko Uchiyama, Tomohiro Kawamoto, Toshimasa Tanaka, Clifford D. Mol, Douglas R. Dougan, Garret S. Textor, Gyorgy P. Snell, Fumio Itoh

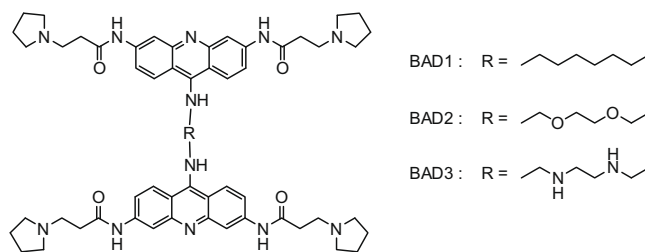
Design, synthesis and structure–activity relationships of novel oxadiazole derivatives as GSK-3 $\beta$  inhibitors are reported.



## BRACO19 analog dimers with improved inhibition of telomerase and hPot 1

pp 2030-2037

Yuan-Te Fu, Brian R. Keppler, Joana Soares, Michael B. Jarstfer\*



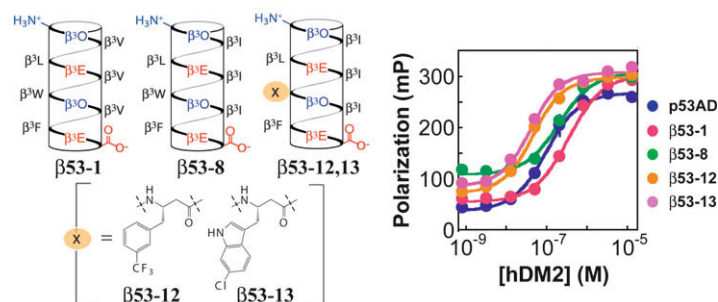
The ability of several acridine dimers designed based on the known telomerase inhibitor BRACO19 were prepared and tested for binding to G-quadruplex DNA and inhibition of telomerase and hPot1.



**$\beta$ -Peptides with improved affinity for hDM2 and hDMX**

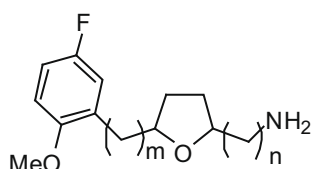
pp 2038–2046

Elizabeth A. Harker, Douglas S. Daniels, Danielle A. Guarracino, Alanna Schepartz \*

**2,5-Disubstituted tetrahydrofurans as selective serotonin re-uptake inhibitors**

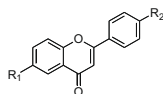
pp 2047–2068

Troy Voelker, Haiji Xia, Keith Fandrick, Robert Johnson, Aaron Janowsky, John R. Cashman \*

 **$^{18}F$ -labeled flavones for in vivo imaging of  $\beta$ -amyloid plaques in Alzheimer's brains**

pp 2069–2076

Masahiro Ono \*, Rumi Watanabe, Hidekazu Kawashima, Tomoki Kawai, Hiroyuki Watanabe, Mamoru Haratake, Hideo Saji, Morio Nakayama \*

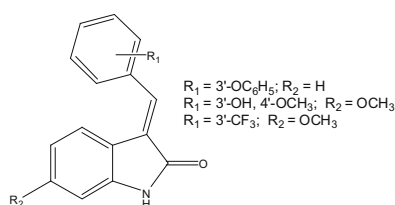


Compound	R <sub>1</sub>	R <sub>2</sub>
8a	FCH <sub>2</sub> CH <sub>2</sub> O	N(CH <sub>3</sub> ) <sub>2</sub>
8b	F(CH <sub>2</sub> CH <sub>2</sub> O) <sub>2</sub>	N(CH <sub>3</sub> ) <sub>2</sub>
8c	F(CH <sub>2</sub> CH <sub>2</sub> O) <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>
12	FCH <sub>2</sub> CH <sub>2</sub> O	NH <sub>2</sub>
13	FCH <sub>2</sub> CH <sub>2</sub> O	NHCH <sub>3</sub>
15b	F(CH <sub>2</sub> CH <sub>2</sub> O) <sub>2</sub>	NH <sub>2</sub>
15c	F(CH <sub>2</sub> CH <sub>2</sub> O) <sub>3</sub>	NH <sub>2</sub>
17b	F(CH <sub>2</sub> CH <sub>2</sub> O) <sub>2</sub>	NHCH <sub>3</sub>
17c	F(CH <sub>2</sub> CH <sub>2</sub> O) <sub>3</sub>	NHCH <sub>3</sub>
21	F	NH <sub>2</sub>
22	F	NHCH <sub>3</sub>
23	F	N(CH <sub>3</sub> ) <sub>2</sub>

**Functionalized 3-benzylidene-indolin-2-ones: Inducers of NAD(P)H-quinone oxidoreductase 1 (NQO1) with antiproliferative activity**

pp 2077–2090

Wei Zhang, Mei-Lin Go \*

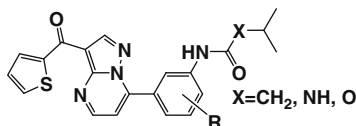


Functionalized 3-benzylidene-indolin-2-ones combine selective induction of NQO1 with potent antiproliferative activity. They can potentially protect normal cells by upregulation of NQO1 and other phase II enzymes as well as simultaneously targeting neoplastic cells.




**Synthesis, SAR study and biological evaluation of novel pyrazolo[1,5-*a*]pyrimidin-7-yl phenyl amides as anti-proliferative agents****pp 2091–2100**

Yanong D. Wang\*, Erick Honores, Biqi Wu, Steve Johnson, Dennis Powell, Miriam Miranda, John P. McGinnis, Carolyn Discafani, Sridhar K. Rabindran, Wendy Cheng, Girija Krishnamurthy

**OTHER CONTENTS****Bioorganic & Medicinal Chemistry Reviews and Perspectives  
Instructions to contributors****p 2101–2103  
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\*Corresponding author

\* Supplementary data available via ScienceDirect

**COVER**

An insight into biologically relevant chemical space showing the scaffolds of potential natural-product based inhibitors orbiting their target, the protein structure of protein 11-beta steroid dehydrogenase (PDB code 1xu7). Graphic produced using Pymol (<http://www.pymol.org>). [M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, Charting biologically relevant chemical space: A structural classification of natural products (SCONP), *PNAS* **2005**, 102, 17272–17277 and S. Wetzel, H. Waldmann, Cheminformatic analysis of natural products and their chemical space, *Chimia* **2007**, 61(6), 355–360].

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