



Contents lists available at ScienceDirect

# Bioorganic & Medicinal Chemistry

journal homepage: [www.elsevier.com/locate/bmc](http://www.elsevier.com/locate/bmc)


## Bioorganic & Medicinal Chemistry Volume 18, Issue 18, 2010

### Contents

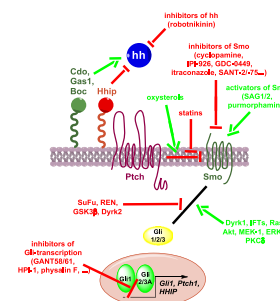
#### REVIEW

##### Modulators of the hedgehog signaling pathway

Philipp Heretsch, Lito Tzagkaroulaki, Athanassios Giannis\*

The hedgehog (hh) pathway is the basis of an important new class of therapeutic agents with far-reaching implications in oncology. In this review, we trace the story of cyclopamine, the first reported inhibitor of hh signaling, give an overview on the biological modes of this pathway, and finally present potent modulators—many of them already in clinical studies.

pp 6613–6624

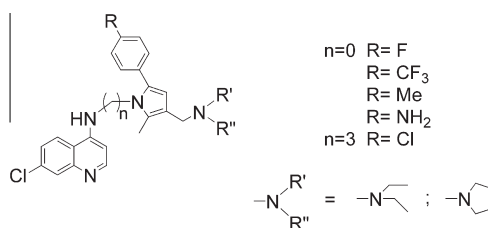


#### ARTICLES

##### Synthesis, antimalarial activity, and cellular toxicity of new arylpyrrolylaminoquinolines

Manolo Casagrande, Nicoletta Basilico, Chiara Rusconi, Donatella Taramelli, Anna Sparatore\*

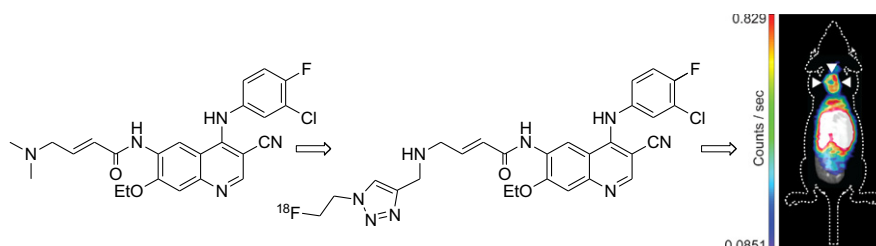
pp 6625–6633



##### Development of a new epidermal growth factor receptor positron emission tomography imaging agent based on the 3-cyanoquinoline core: Synthesis and biological evaluation

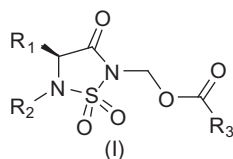
Federica Pisaneschi\*, Quang-De Nguyen, Elham Shamsaei, Matthias Glaser, Edward Robins, Maciej Kaliszczak, Graham Smith, Alan C. Spivey, Eric O. Aboagye\*

pp 6634–6645



## Effects of structure on inhibitory activity in a series of mechanism-based inhibitors of human neutrophil elastase pp 6646–6650

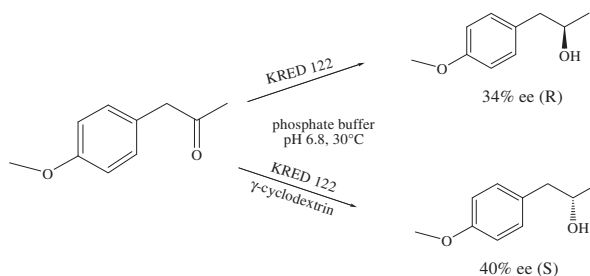
Dengfeng Dou, Guijia He, Rongze Kuang, Qingfong Fu, Radhika Venkataraman, William C. Groutas\*



A series of compounds based on the 1,2,5-thiadiazolidin-3-one 1,1-dioxide scaffold were synthesized and used to probe the S' subsites of human neutrophil elastase and proteinase 3.

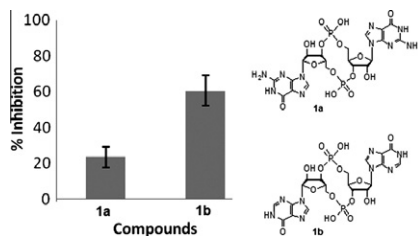
## Chiral switch of enzymatic ketone reduction by addition of $\gamma$ -cyclodextrin pp 6651–6656

Galina A. Petkova, Vladimír Král\*



## Synthesis of cyclic di-nucleotidic acids as potential inhibitors targeting diguanylate cyclase pp 6657–6665

Shi Min Ching, Wan Jun Tan, Kim Lee Chua, Yulin Lam\*

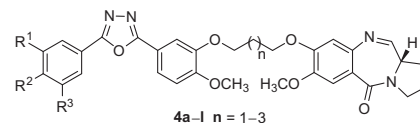


Cyclic di-inosinic acid demonstrates a stronger inhibition on Slr1143, a diguanylate cyclase of *Synechocystis* sp. than c-di-GMP and is a potential inhibitor for biofilm formation.



## Synthesis, anticancer activity and mitochondrial mediated apoptosis inducing ability of 2,5-diaryloxadiazole–pyrrolobenzodiazepine conjugates pp 6666–6677

Ahmed Kamal\*, D. Dastagiri, M. Janaki Ramaiah, E. Vijaya Bharathi, J. Surendranadha Reddy, G. Balakishan, Pranjali Sarma, S. N. C. V. L. Pushpavalli, Manika Pal-Bhadra\*, Aarti Juvekar, Subrata Sen, Surekha Zingde



4a–c R<sup>1</sup> = H; R<sup>2</sup> = F; R<sup>3</sup> = H

4d–f R<sup>1</sup> = H; R<sup>2</sup> = CF<sub>3</sub>; R<sup>3</sup> = H

4g–i R<sup>1</sup> = OCH<sub>3</sub>; R<sup>2</sup> = OCH<sub>3</sub>; R<sup>3</sup> = OCH<sub>3</sub>

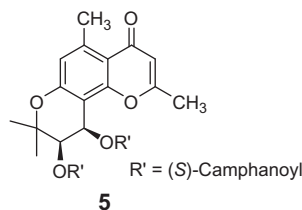
4j–l R<sup>1</sup> = H; R<sup>2</sup> = OCH<sub>3</sub>; R<sup>3</sup> = OCH<sub>3</sub>

New class of 2,5-diaryloxadiazole–pyrrolobenzodiazepine conjugates have been prepared and evaluated for their anticancer activity. Further, some of the biological assays related to mechanism aspects have also been carried out.

### Anti-AIDS agents 79. Design, synthesis, molecular modeling and structure–activity relationships of novel dicamphanoyl-2',2'-dimethyldihydropyranochromone (DCP) analogs as potent anti-HIV agents

pp 6678–6689

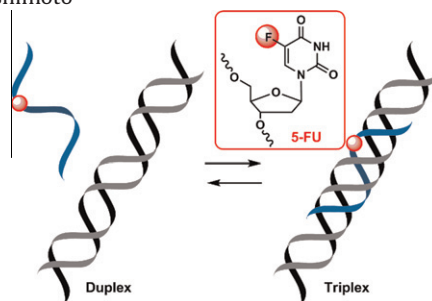
Ting Zhou, Qian Shi, Chin-Ho Chen, Hao Zhu, Li Huang, Phong Ho, Kuo-Hsiung Lee\*



### Monitoring of duplex and triplex formation by $^{19}\text{F}$ NMR using oligodeoxynucleotides possessing 5-fluorodeoxyuridine unit as $^{19}\text{F}$ signal transmitter

pp 6690–6694

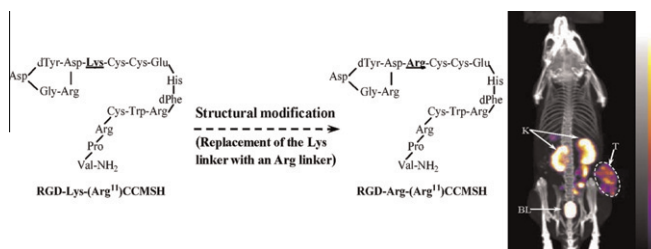
Kazuhiro Tanabe\*, Masaaki Sugiura, Sei-ichi Nishimoto\*



### Replacement of the Lys linker with an Arg linker resulting in improved melanoma uptake and reduced renal uptake of Tc-99m-labeled Arg-Gly-Asp-conjugated alpha-melanocyte stimulating hormone hybrid peptide

pp 6695–6700

Jianquan Yang, Haixun Guo, R. Steve Padilla, Marianne Berwick, Yubin Miao\*

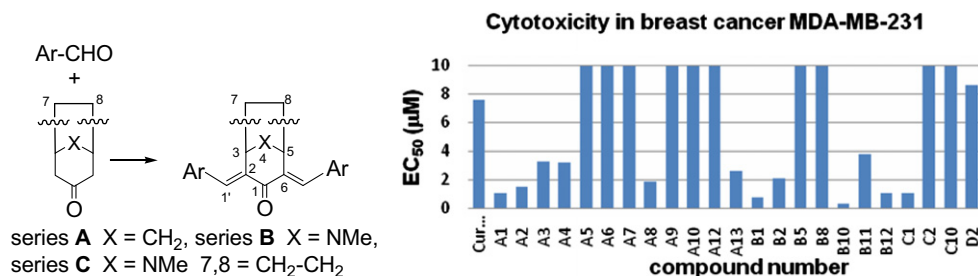


The replacement of the Lys linker with an Arg linker exhibited a profound effect in reducing the non-specific renal uptake of  $^{99\text{mTc}}$ -RGD-Arg-(Arg<sup>11</sup>)CCMSH, as well as increasing the tumor uptake of  $^{99\text{mTc}}$ -RGD-Arg-(Arg<sup>11</sup>)CCMSH compared to  $^{99\text{mTc}}$ -RGD-Lys-(Arg<sup>11</sup>)CCMSH.

### Synthesis and cytotoxic potential of heterocyclic cyclohexanone analogues of curcumin

pp 6701–6707

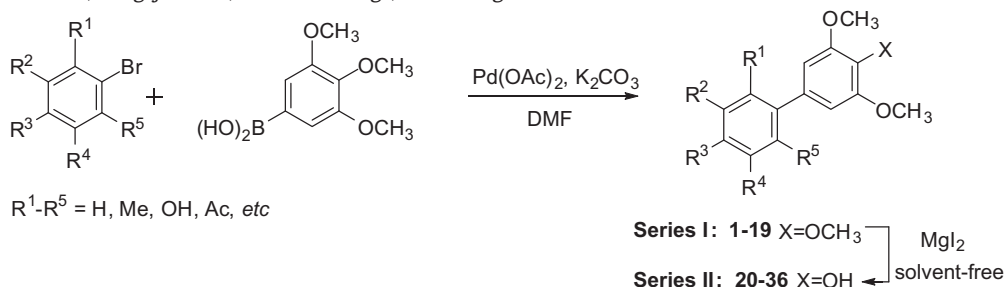
Babasaheb Yadav, Sebastien Taurin, Rhonda J. Rosengren, Marc Schumacher, Marc Diederich, Tiffany J. Somers-Edgar, Lesley Larsen\*



**Design and synthesis of biphenyl derivatives as mushroom tyrosinase inhibitors**

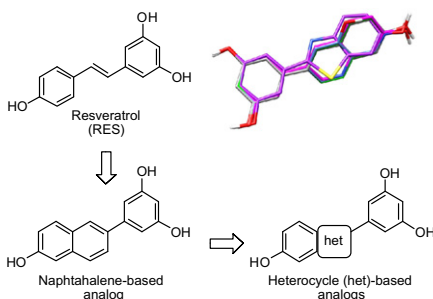
pp 6708–6714

Kai Bao, Yi Dai, Zhi-Bin Zhu, Feng-Juan Tu, Wei-Ge Zhang\*, Xin-Sheng Yao\*

**Synthesis of heterocycle-based analogs of resveratrol and their antitumor and vasorelaxing properties**

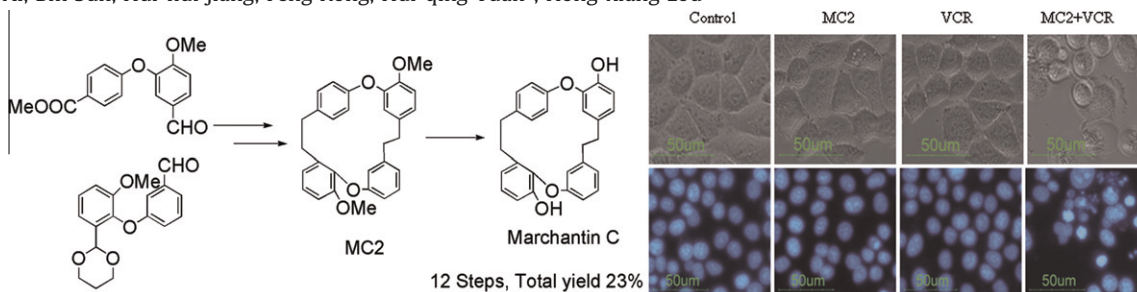
pp 6715–6724

Simone Bertini, Vincenzo Calderone, Isabella Carboni, Roberta Maffei, Alma Martelli, Adriano Martinelli, Filippo Minutolo, Mehdi Rajabi, Lara Testai, Tiziano Tuccinardi, Riccardo Ghidoni, Marco Macchia\*

**Bisbibenzyl derivatives sensitize vincristine-resistant KB/VCR cells to chemotherapeutic agents by retarding P-gp activity**

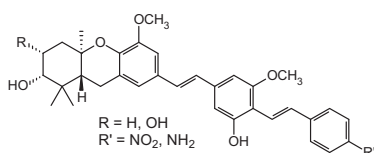
pp 6725–6733

Guang-min Xi, Bin Sun, Hui-hui Jiang, Feng Kong, Hui-qing Yuan\*, Hong-xiang Lou\*

**Fluorescent schweinfurthin B and F analogs with anti-proliferative activity**

pp 6734–6741

Joseph J. Topczewski, Craig H. Kuder, Jeffrey D. Neighbors, Raymond J. Hohl, David F. Wiemer\*



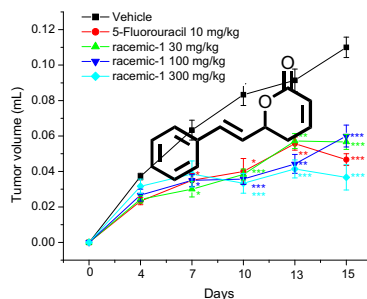
The synthesis of several new fluorescent analogs of schweinfurthins B and F is described, along with assays that demonstrates that these compounds retain potent and differential activities against select human cancer cell lines. Use of fluorescence microscopy shows differences between the localization of the active and relatively inactive schweinfurthin analogs.



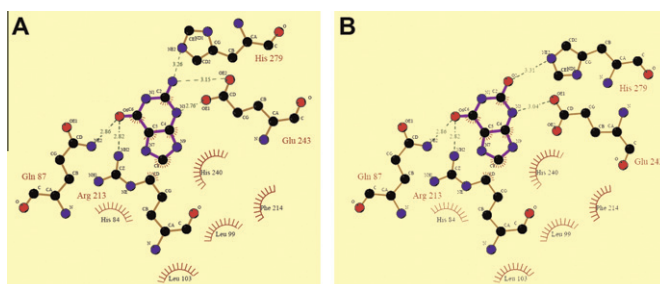
**Effect of goniotalamin on the development of Ehrlich solid tumor in mice**

pp 6742–6747

Débora Barbosa Vendramini-Costa, Ilton Barros Daltro de Castro, Ana Lúcia Tasca Góis Ruiz, Cilene Marquissolo, Ronaldo Aloise Pilli\*, João Ernesto de Carvalho

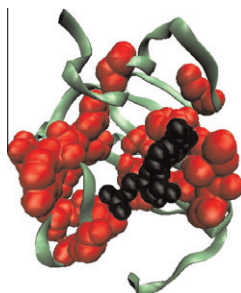
**Identification of small molecule compounds with higher binding affinity to guanine deaminase (cypin) than guanine** pp 6748–6755

José R. Fernández, Eric S. Sweet, William J. Welsh, Bonnie L. Firestein\*

**Studies on ligand binding to histidine triad nucleotide binding protein**

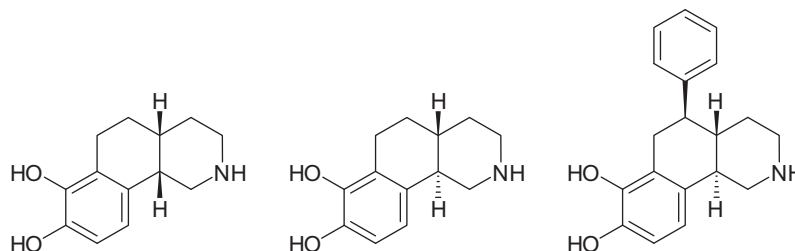
pp 6756–6762

Guoyun Bai, Bo Feng, Jia Bei Wang, Edwin Pozharski, Michael Shapiro\*

**Facile synthesis of octahydrobenzo[h]isoquinolines: Novel and highly potent D<sub>1</sub> dopamine agonists**

pp 6763–6770

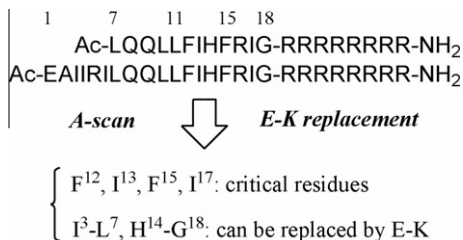
Lisa A. Bonner, Benjamin R. Chemel, Val J. Watts, David E. Nichols\*



**Peptidic HIV integrase inhibitors derived from HIV gene products: Structure–activity relationship studies**

pp 6771–6775

Shintaro Suzuki, Kasthuraiah Maddali, Chie Hashimoto, Emiko Urano, Nami Ohashi, Tomohiro Tanaka, Taro Ozaki, Hiroshi Arai, Hiroshi Tsutsumi, Tetsuo Narumi, Wataru Nomura, Naoki Yamamoto, Yves Pommier, Jun A. Komano, Hirokazu Tamamura\*

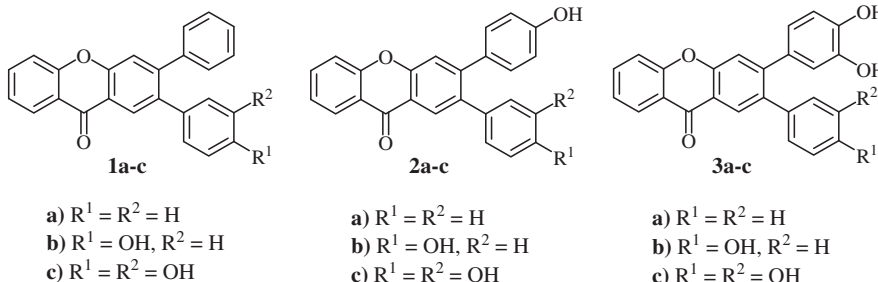


SAR studies of peptidic integrase inhibitors derived from HIV gene products are reported.

**2,3-Diarylloxanones as strong scavengers of reactive oxygen and nitrogen species: A structure–activity relationship study**

pp 6776–6784

Clementina M. M. Santos\*, Marisa Freitas, Daniela Ribeiro, Ana Gomes, Artur M. S. Silva, José A. S. Cavaleiro, Eduarda Fernandes\*

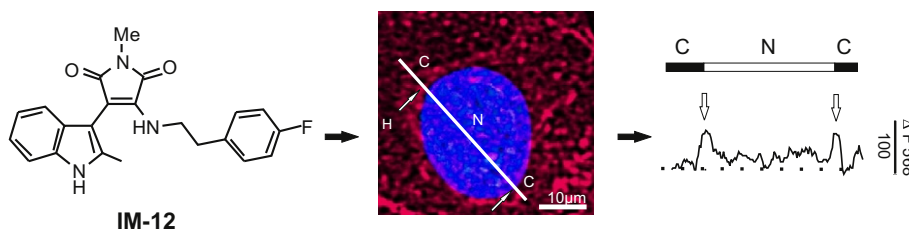


Several 2,3-diarylloxanones were tested for their scavenging activity for ROS ( $\text{O}_2^-$ ,  $\text{H}_2\text{O}_2$ ,  $^1\text{O}_2$ , HOCl and  $\text{ROO}^\bullet$  and RNS ( $^\bullet\text{NO}$  and  $\text{ONOO}^\bullet$ ). Structure–activity studies indicate the importance of the number of hydroxyl groups as well as a catechol unit for the scavenging effects.

**Novel indolylmaleimide acts as GSK-3 $\beta$  inhibitor in human neural progenitor cells**

pp 6785–6795

Anne-Caroline Schmöle, Anne Brennfürher, Gnuni Karapetyan, Robert Jaster, Anahit Pews-Davtyan, Rayk Hübner, Stefanie Ortinau, Matthias Beller, Arndt Rolfs, Moritz J. Frech\*

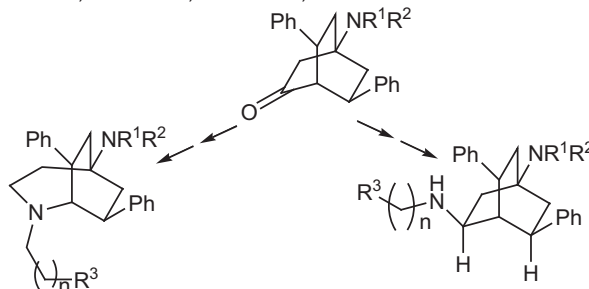


IM-12 enhances canonical Wnt signalling in human neural progenitor cells, for example, shown by a peri-nuclear accumulation of  $\beta$ -catenin demonstrated by immunocytochemistry.

**Dialkylaminoalkyl derivatives of bicyclic compounds with antiparasmodial activity**

pp 6796–6804

Johanna Faist, Werner Seebacher, Marcel Kaiser, Reto Brun, Robert Saf, Robert Weis\*



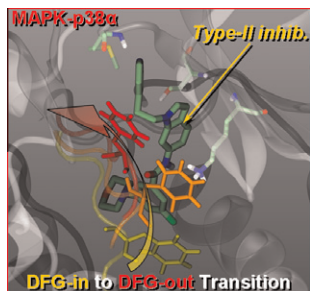
Compounds of both series exhibit promising in vitro activity against a multiresistant strain of *Plasmodium falciparum*. Some of the 2-azabicyclo-nonane derivatives showed antimalarial activity in a mouse model.



**Insights into MAPK p38 $\alpha$  DFG flip mechanism by accelerated molecular dynamics**

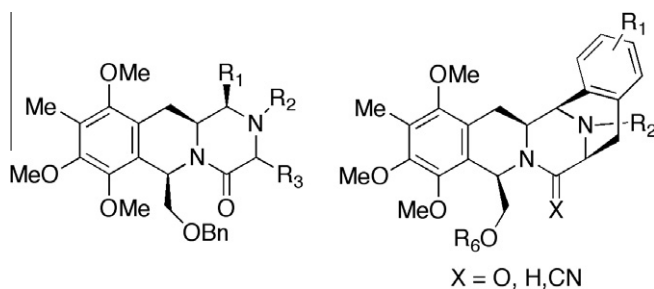
pp 6805–6812

Federico Filomia, Francesca De Rienzo, M. Cristina Menziani\*

**Cytotoxicity of new pyrazino[1,2-*b*]isoquinoline and 6,15-iminoisoquino[3,2-*b*]3-benzazocine compounds**

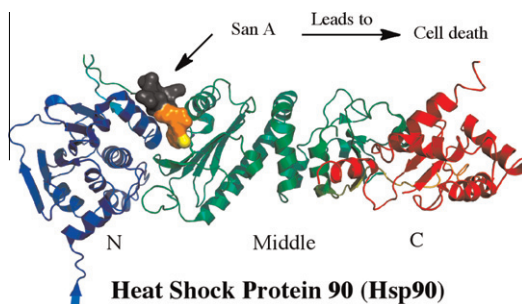
pp 6813–6821

Irene Ortín, Juan Francisco González, Elena de la Cuesta, Carmen Avendaño\*

**Design and synthesis of Hsp90 inhibitors: Exploring the SAR of Sansalvamide A derivatives**

pp 6822–6856

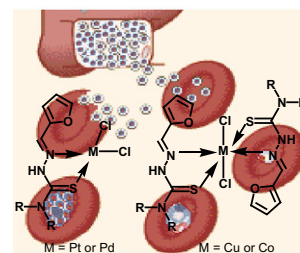
Robert P. Sellers, Leslie D. Alexander, Victoria A. Johnson, Chun-Chieh Lin, Jeremiah Savage, Ricardo Corral, Jason Moss, Tim S. Slugocki, Erinpriti K. Singh, Melinda R. Davis, Suchitra Ravula, Jamie E. Spicer, Jenna L. Oelrich, Andrea Thornquist, Chung-Mao Pan, Shelli R. McAlpine\*

**Structure–activity relationships of mononuclear metal–thiosemicarbazone complexes endowed with potent antiplasmodial and antiamoebic activities**

pp 6857–6864

Deepa Bahl, Fareeda Athar, Milena Botelho Pereira Soares, Matheus Santos de Sá, Diogo Rodrigo Magalhães Moreira, Rajendra Mohan Srivastava, Ana Cristina Lima Leite\*, Amir Azam\*

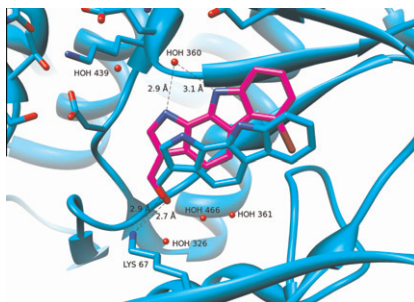
**Antiparasitic metals:** a set of promising metal-based antiprotozoal agents were explored. As a result, structure–activity relationships data were collected and steps were made towards identification of new antiplasmodium (**NT1Cu**, IC<sub>50</sub> = 4.6  $\mu$ M) and antiamoebic (**NT2Pd**, IC<sub>50</sub> = 0.6  $\mu$ M) prototypes, which are able to reduce the proliferation of these parasites at concentrations that are not cytotoxic to mammalian cells.



### Synthesis, Pim kinase inhibitory potencies and in vitro antiproliferative activities of diversely substituted pyrrolo[2,3-*a*]carbazoles

pp 6865–6873

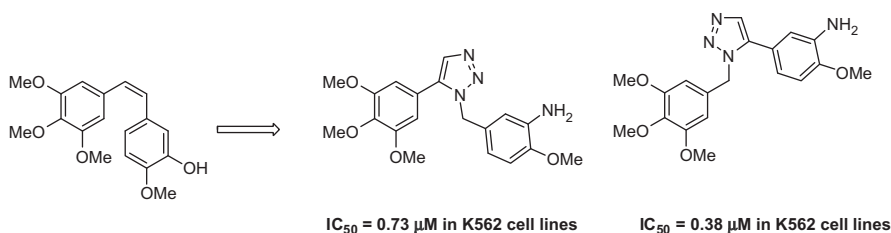
Rufine Akué-Gédu, Lionel Nauton, Vincent Théry, Jenny Bain, Philip Cohen, Fabrice Anizon\*, Pascale Moreau\*



### 1,2,3-Triazole analogs of combretastatin A-4 as potential microtubule-binding agents

pp 6874–6885

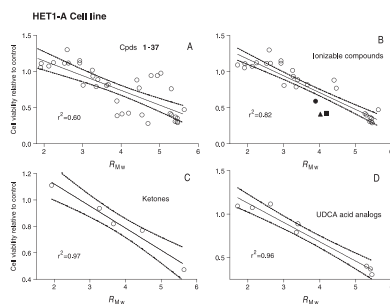
Kristin Odlo, Jérémie Fournier-Dit-Chabert, Sylvie Ducki, Osman A. B. S. M. Gani, Ingebrigt Sylte, Trond Vidar Hansen\*



### Bile acid toxicity structure–activity relationships: Correlations between cell viability and lipophilicity in a panel of new and known bile acids using an oesophageal cell line (HET-1A)

pp 6886–6895

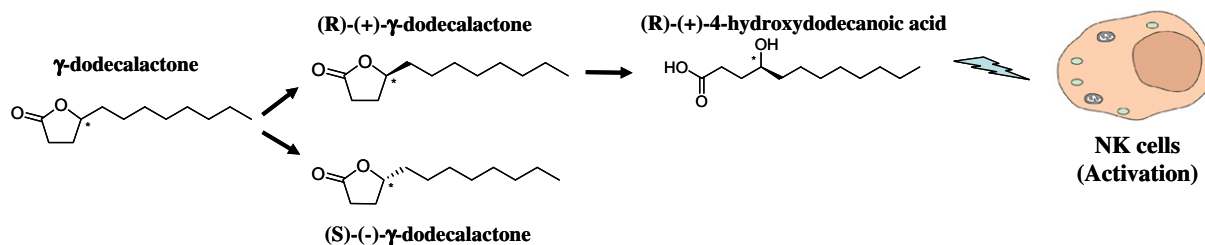
Ruchika Sharma\*, Ferenc Majer, Vijaya Kumar Peta, Jun Wang, Ray Keaveney, Dermot Kelleher, Aideen Long, John F. Gilmer\*



### Structure and functions of $\gamma$ -dodecalactone isolated from *Antrodia camphorata* for NK cell activation

pp 6896–6904

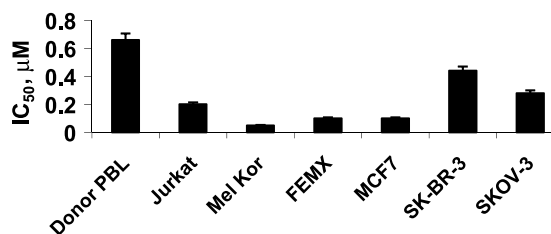
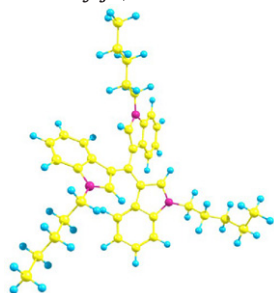
Chia-Jung Chen, R. Vijaya Krishna, Chia-Che Tsai, Wan-Hsun Wu, Louis Kuoping Chao, Kent-Hao Hwang, Chichen Michael Chien, Hwan-You Chang, Shui-Tein Chen\*



**Synthesis and cytotoxic potency of novel tris(1-alkylindol-3-yl)methylum salts: Role of *N*-alkyl substituents**

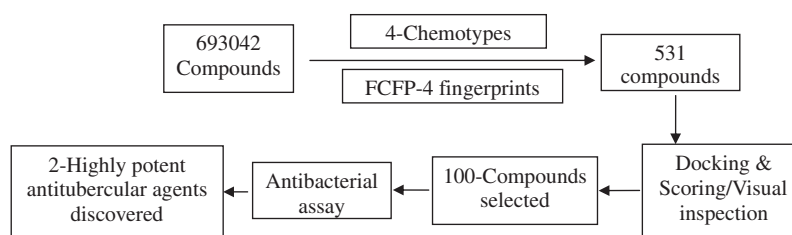
pp 6905–6913

Sergey N. Lavrenov, Yuriy N. Luzikov, Evgeniy E. Bykov, Marina I. Reznikova, Evgenia V. Stepanova, Valeria A. Glazunova, Yulia L. Volodina, Victor V. Tatarsky Jr., Alexander A. Shtil, Maria N. Preobrazhenskaya\*

**Identification of novel antitubercular compounds through hybrid virtual screening approach**

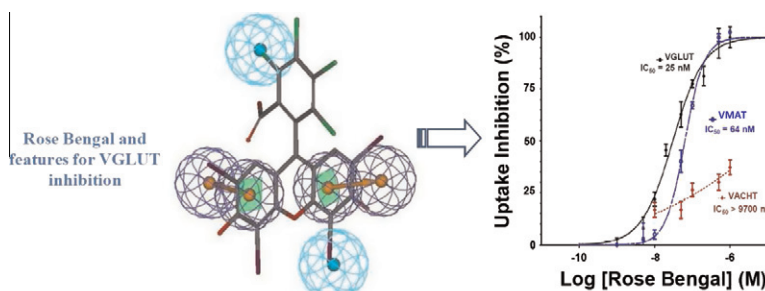
pp 6914–6921

Muhammad Muddassar, Jae Wan Jang, Hong Seung Gon, Yong Seo Cho, Eunice Eunkyung Kim, Kyo Chang Keum, Taegwon Oh, Sang-Nae Cho, Ae Nim Pae\*

**Rose Bengal analogs and vesicular glutamate transporters (VGLUTs)**

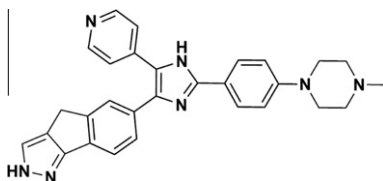
pp 6922–6933

Nicolas Pietrancosta, Albane Kessler, Franck-Cyril Favre-Besse, Nicolas Triballeau, Thomas Quentin, Bruno Giros, Salah El Mestikawy, Francine C. Acher\*

**Novel tricyclic pyrazole BRAF inhibitors with imidazole or furan central scaffolds**

pp 6934–6952

Dan Niculescu-Duvaz, Ion Niculescu-Duvaz, Bart M. J. M. Suijkerbuijk, Delphine Ménard, Alfonso Zambon, Arnaud Nourry, Lawrence Davies, Helen A. Manne, Frank Friedlos, Lesley Ogilvie, Douglas Hedley, Andrew K. Takle, David M. Wilson, Jean-Francois Pons, Tom Coulter, Ruth Kirk, Neus Cantarino, Steven Whittaker, Richard Marais, Caroline J. Springer\*

1j IC<sub>50</sub> (BRAF) = 0.24 μM; IC<sub>50</sub> (pERK) = 0.58 μM; GI<sub>50</sub> (SRB) = 0.87 μM.

**OTHER CONTENTS****Bioorganic & Medicinal Chemistry Reviews and Perspectives****pp I–III**

\*Corresponding author

 \* Supplementary data available via ScienceDirect**COVER**

Docking pose of a tricyclic pyrazole inhibitor in BRAF [Niculescu-Duvaz, D.; Niculescu-Duvaz, I.; Suijkerbuijk, B. M. J. M.; Ménard, D.; Zambon, A.; Nourry, A.; Davies, L.; Manne, H. A.; Friedlos, F.; Ogilvie, L.; Hedley, D.; Takle, A. K.; Wilson, D. M.; Pons, J-F.; Coulter, T.; Kirk, R.; Cantarino, N.; Whittaker, S.; Marais, R.; Springer, C. J. *Bioorg. Med. Chem.* **2010**, 18, 6934–6952].

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIODATA, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®



ISSN 0968-0896