



## Bioorganic & Medicinal Chemistry Volume 18, Issue 9, 2010

### Contents

#### Publisher's Note

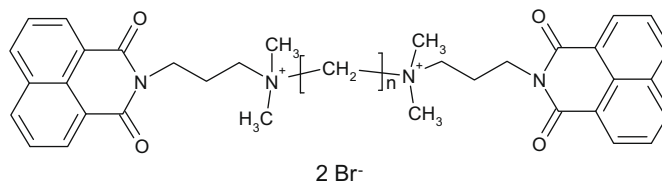
p 2997

#### ARTICLES

##### The bisnaphthalimides as new active lead compounds against *Plasmodium falciparum*

pp 2998–3003

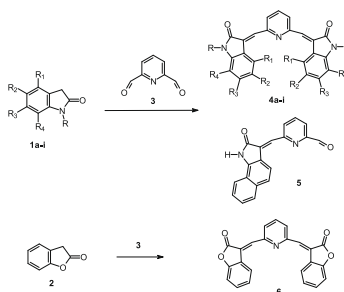
Maximilian Tischer, Ludmilla Sologub, Gabriele Pradel\*, Ulrike Holzgrabe\*



##### Antitumor activity and COMPARE analysis of bis-indole derivatives

pp 3004–3011

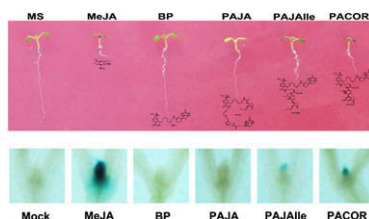
Aldo Andreani\*, Silvia Burnelli, Massimiliano Granaola, Alberto Leoni, Alessandra Locatelli, Rita Morigi, Mirella Rambaldi, Lucilla Varoli, Laura Landi, Cecilia Prata, Francesco Vieceli Dalla Sega, Cristiana Caliceti, Robert H. Shoemaker



##### Design and synthesis of biotin-tagged photoaffinity probes of jasmonates

pp 3012–3019

Min Gu, Jianbin Yan, Zhiyan Bai, Yue-Ting Chen, Wei Lu, Jie Tang, Liusheng Duan, Daoxin Xie\*, Fa-Jun Nan\*



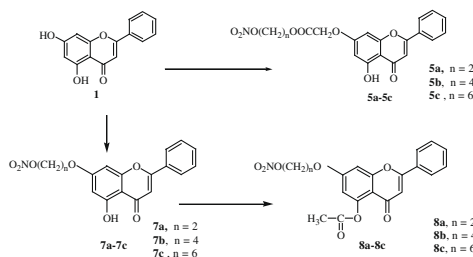
Three biotin-tagged photoaffinity probes for JAs were designed and synthesized. Among them, PACOR exhibited the most significant biological activity in inhibiting root growth, promoting accumulation of JA-responsive proteins, and triggering COI1-JAZ1 interaction in *Arabidopsis* seedlings. PACOR is an effective tool for elucidating the interaction between COI1 and JA.



### Synthesis, characterization and vasculoprotective effects of nitric oxide-donating derivatives of chrysin

pp 3020–3025

Xiao-Qing Zou, Sheng-Ming Peng, Chang-Ping Hu, Li-Feng Tan, Qiong Yuan, Han-Wu Deng, Yuan-Jian Li\*

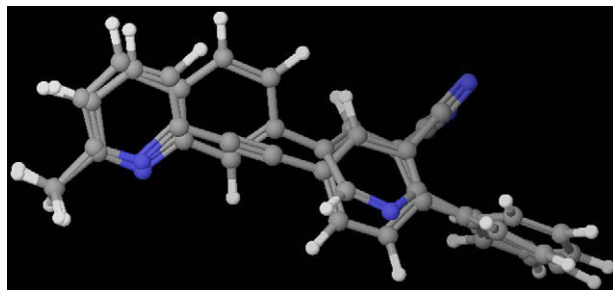


A novel group of hybrid nitric oxide-releasing chrysin derivatives was synthesized. All these chrysin derivatives released NO upon incubation with PBS at pH 7.4, exhibited inhibitory activities against aldose reductase and advanced glycation end-products formation in vitro. And some of them were even found to increase the glucose consumption of HepG2 cells.

### Structure–activity relationships in a novel series of 7-substituted-aryl quinolines and 5-substituted-aryl benzothiazoles at the metabotropic glutamate receptor subtype 5

pp 3026–3035

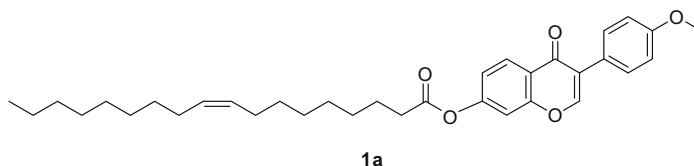
Peng Zhang, Mu-Fa Zou, Alice L. Rodriguez, P. Jeffrey Conn, Amy Hauck Newman\*



### Synthesis and biological evaluation of isoflavone fatty acid esters with potential weight loss and hypolipidemic activities

pp 3036–3042

Hua Xiang\*, Wei Zhao, Hong Xiao\*, Lei Qian, Yao Yao, Xiao-Bo Li, Qing-Jiang Liao

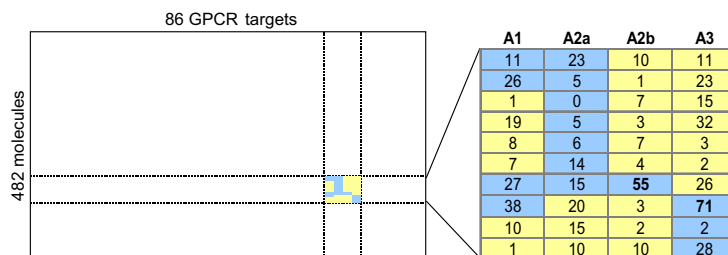


A series of isoflavone fatty acid esters were synthesized and evaluated. The compound **1a** shows good weight loss activity, hypolipidemic activity and low toxicity.

### In silico directed chemical probing of the adenosine receptor family

pp 3043–3052

Filipe M. Areias, Jose Brea, Elisabet Gregori-Puigjané, Magdi E. A. Zaki, M. Alice Carvalho, Eduardo Domínguez, Hugo Gutiérrez-de-Terán, M. Fernanda Proença, María I. Loza, Jordi Mestres\*



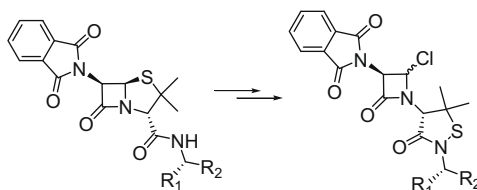
Scheme of the in silico profiling of 482 molecules across 86 GPCR targets (prediction of activity in blue) and results of the in vitro screening (% displacement of specific radioligand binding at 10  $\mu$ M concentration) against the four members of the adenosine receptor family.



**Azetidinone-isothiazolidinones: Stereoselective synthesis and antibacterial evaluation of new monocyclic beta-lactams**

pp 3053–3058

Helena Cerić, Marija Šindler-Kulyk\*, Miće Kovačević, Mihaela Perić, Andreja Živković

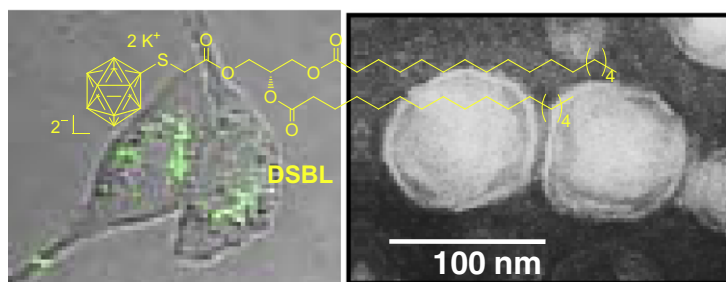


New azetidinone-isothiazolidinones were prepared from penam amides by a simple and efficient procedure. New compounds were tested on selected bacterial pathogens, some of them showing weak antibacterial activity.

**Dodecaborate lipid liposomes as new vehicles for boron delivery system of neutron capture therapy**

pp 3059–3065

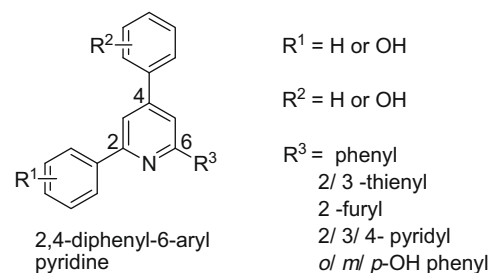
Manabu Ueno, Hyun Seung Ban, Kei Nakai, Ryu Inomata, Yasufumi Kaneda, Akira Matsumura, Hiroyuki Nakamura\*

**Synthesis, topoisomerase I and II inhibitory activity, cytotoxicity, and structure–activity relationship study of hydroxylated 2,4-diphenyl-6-aryl pyridines**

pp 3066–3077

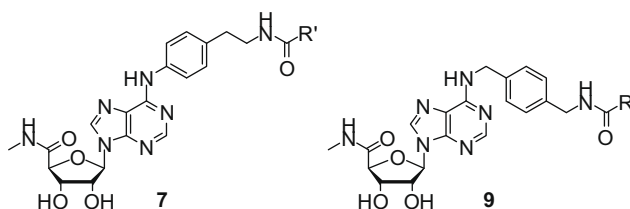
Radha Karki, Pritam Thapa, Mi Jeong Kang, Tae Cheon Jeong, Jung Min Nam, Hye-Lin Kim, Younghwa Na, Won-Jea Cho, Youngjoo Kwon\*, Eung-Seok Lee\*

A new series of 2,4-diphenyl-6-aryl pyridines containing hydroxyl group(s) at the *ortho*, *meta*, or *para* position of the phenyl ring were synthesized, and evaluated for topoisomerase I and II inhibitory activity and cytotoxicity against several human cancer cell lines for the development of novel anticancer agents.

**Synthesis and evaluation of new  $N^6$ -substituted adenosine-5'- $N$ -methylcarboxamides as  $A_3$  adenosine receptor agonists**

pp 3078–3087

Shane M. Devine, Alison Gregg, Heidi Figler, Kate McIntosh, Vijay Urmaliya, Joel Linden, Colin W. Pouton, Paul J. White, Steven E. Bottle, Peter J. Scammells\*

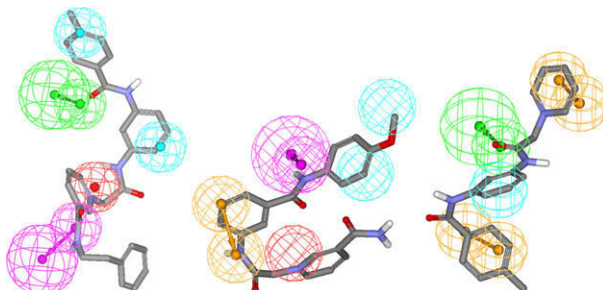


The design, synthesis and biological evaluation of some potent and selective  $A_3$  adenosine receptor agonists are reported herein. Preliminary studies were also conducted to assess the cardioprotective effects of these compounds.

### Elaborate ligand-based pharmacophore exploration and QSAR analysis guide the synthesis of novel pyridinium-based potent $\beta$ -secretase inhibitory leads

pp 3088–3115

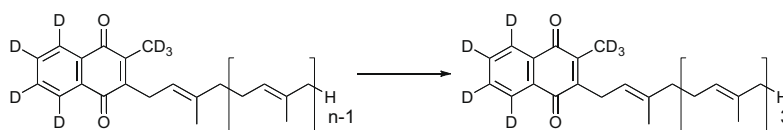
Afaf Al-Nadaf, Ghassan Abu Sheikha, Mutasem O. Taha\*



### Structure–activity relationships in the conversion of vitamin K analogues into menaquinone-4. Substrates essential to the synthesis of menaquinone-4 in cultured human cell lines

pp 3116–3124

Yoshitomo Suhara, Akimori Wada, Yoji Tachibana, Masato Watanabe, Kanae Nakamura, Kimie Nakagawa, Toshio Okano\*



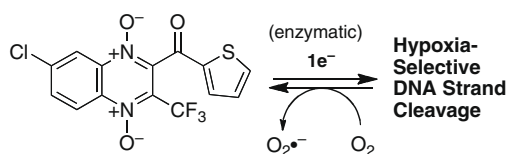
We examined structure–activity relationship in the conversion of several vitamin K analogues, with a substituted side-chain, into menaquinone-4 using cultured human cell lines.



### DNA strand cleaving properties and hypoxia-selective cytotoxicity of 7-chloro-2-thienylcarbonyl-3-trifluoromethylquinoxaline 1,4-dioxide

pp 3125–3132

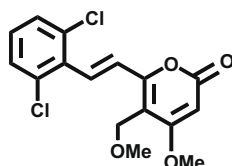
Venkatraman Junnotula, Anuruddha Rajapakse, Leire Arbillaga, Adela López de Cerain, Beatriz Solano, Raquel Villar, Antonio Monge, Kent S. Gates\*



### A novel kavalactone derivative protects against H<sub>2</sub>O<sub>2</sub>-induced PC12 cell death via Nrf2/ARE activation

pp 3133–3139

Arisa Tanaka, Nanako Hamada, Yasunori Fujita, Tomohiro Itoh, Yoshinori Nozawa, Munekazu Iinuma, Masafumi Ito\*



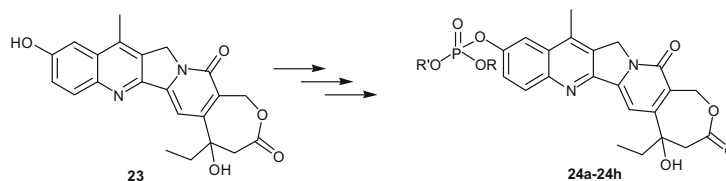
A novel kavalactone derivative has a methoxymethyl group at the position of 5 and two chlorine groups at the positions of 2' and 6' added after dehydrogenation of the positions of 5 and 6 (2',6'-dichloro-5-methoxymethyl-5,6-dehydrokawain).



**Phosphate ester derivatives of homocamptothecin: Synthesis, solution stabilities and antitumor activities**

pp 3140–3146

Zhenyuan Miao, Jing Zhang, Liang You, Juan Wang, Chunquan Sheng\*, Jiangzhong Yao, Wannian Zhang\*, Hao Feng, Wei Guo, Lei Zhou, Wenfeng Liu, Linjian Zhu, Pengfei Cheng, Xiaoying Che, Wenya Wang, Chuan Luo, Yulan Xu, Guoqiang Dong

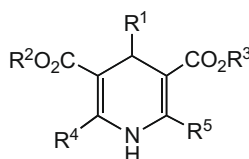


Some diphosphates and triphosphates homocamptothecin derivatives were designed and synthesized based on our previous synthetic route. Among them compounds **24e** and **24f** exhibited higher cytotoxic activity than IRT and the former exhibited the best antitumor activity in vivo and the solution stability both at pH 7.4 and at pH 3.0.

**Antagonism of 4-substituted 1,4-dihydropyridine-3,5-dicarboxylates toward voltage-dependent L-type  $\text{Ca}^{2+}$  channels  $\text{Ca}_v1.3$  and  $\text{Ca}_v1.2$** 

pp 3147–3158

Che-Chien Chang, Song Cao, Soosung Kang, Li Kai, Xinyong Tian, Prativa Pandey, Sara Fernandez Dunne, Chi-Hao Luan, D. James Surmeier\*, Richard B. Silverman\*

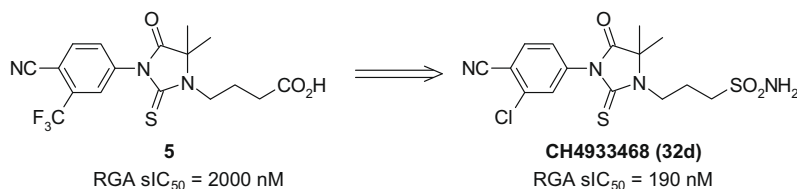


Hundred and twenty four analogues made to identify a selective  $\text{Ca}_v1.3$   $\text{Ca}^{2+}$  channel antagonist.

**Structure–activity relationships of bioisosteric replacement of the carboxylic acid in novel androgen receptor pure antagonists**

pp 3159–3168

Hitoshi Yoshino\*, Haruhiko Sato\*, Kazutaka Tachibana, Takuya Shiraishi, Mitsuaki Nakamura, Masateru Ohta, Nobuyuki Ishikura, Masahiro Nagamuta, Etsuro Onuma, Toshito Nakagawa, Shinichi Arai, Koo-Hyeon Ahn, Kyung-Yun Jung, Hiromitsu Kawata

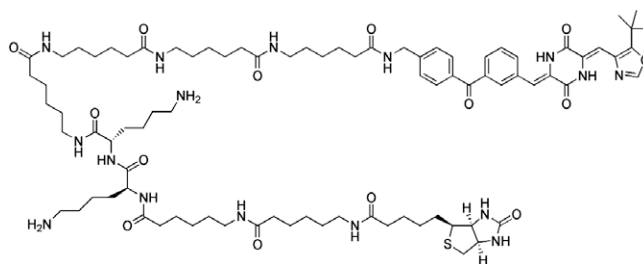


We designed and synthesized novel AR pure antagonists for the treatment of hormone refractory prostate cancer. **CH4933468** with a sulfonamide side chain showed higher activities than lead compound **5**.

**Anti-microtubule 'plinabulin' chemical probe KPU-244-B3 labeled both  $\alpha$ - and  $\beta$ -tubulin**

pp 3169–3174

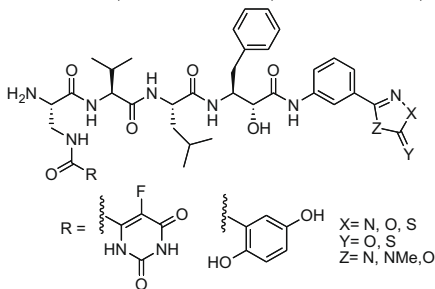
Yuri Yamazaki, Makiko Sumikura, Koushi Hidaka, Hiroyuki Yasui, Yoshiaki Kiso, Fumika Yakushiji, Yoshio Hayashi\*



**Design of pentapeptidic BACE1 inhibitors with carboxylic acid bioisosteres at P<sub>1'</sub> and P<sub>4</sub> positions**

pp 3175–3186

Harichandra D. Tagad, Yoshio Hamada, Jeffrey-Tri Nguyen, Takashi Hamada, Hamdy Abdel-Rahman, Abdellah Yamani, Ayaka Nagamine, Hayato Ikari, Naoto Igawa, Koushi Hidaka, Youhei Sohma, Tooru Kimura, Yoshiaki Kiso\*

**Design, synthesis, biological evaluation and computational investigation of novel inhibitors of dihydrofolate reductase of opportunistic pathogens**

pp 3187–3197

Seema Bag, Nilesh R. Tawari, Mariam S. Degani\*, Sherry F. Queener

Design, synthesis and biological evaluation of novel, diverse compounds as potential inhibitors of dihydrofolate reductase (DHFR) from opportunistic microorganisms; *Pneumocystis carinii* (pc), *Toxoplasma gondii* (tg) and *Mycobacterium avium* (ma) is described.

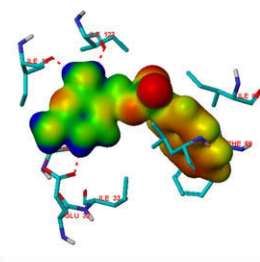
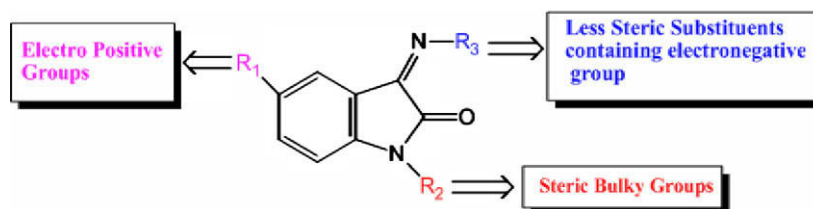


Figure: MESP superimposed onto a surface of constant electron density (0.01 e/a.u.<sup>3</sup>) for compound, 7a

**Design of potential reverse transcriptase inhibitor containing Isatin nucleus using molecular modeling studies**

pp 3198–3211

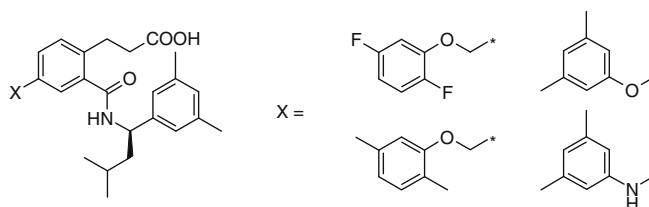
Vidya Pawar, Deepak Lokwani, Shashikant Bhandari\*, Debashis Mitra, Sudeep Sabde, Kailash Bothara, Ashwini Madgulkar

**3-(2-Aminocarbonylphenyl)propanoic acid analogs as potent and selective EP3 receptor antagonists.**

pp 3212–3223

**Part 3: Synthesis, metabolic stability, and biological evaluation of optically active analogs**

Masaki Asada\*, Tetsuo Obitsu, Atsushi Kinoshita, Toshihiko Nagase, Tadahiro Yoshida, Yoshiyuki Yamaura, Hiroya Takizawa, Ken Yoshikawa, Kazutoyo Sato, Masami Narita, Hisao Nakai, Masaaki Toda, Yoshito Tobe



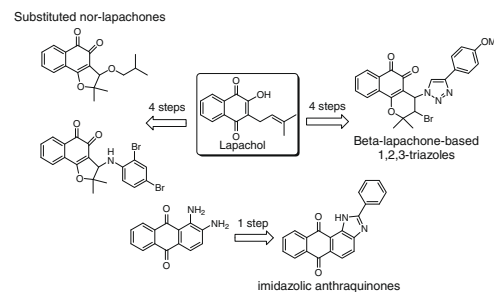
Optically active analogs with a (1R)-1-(3,5-dimethylphenyl)-3-methylbutylamine moiety on the carboxamide side chain were synthesized. Several analogs exhibited potent inhibitory effect against the PGE<sub>2</sub>-induced uterine contraction in pregnant rats after oral administration.

### The evaluation of quinonoid compounds against *Trypanosoma cruzi*: Synthesis of imidazolic anthraquinones, nor- $\beta$ -lapachone derivatives and $\beta$ -lapachone-based 1,2,3-triazoles

pp 3224–3230

Eufrânio N. da Silva Júnior, Tiago T. Guimarães, Rubem F. S. Menna-Barreto, Maria do Carmo F. R. Pinto, Carlos A. de Simone, Claudia Pessoa, Bruno C. Cavalcanti, José R. Sabino, Carlos Kleber Z. Andrade, Marília O. F. Goulart, Solange L. de Castro\*, Antônio V. Pinto

In continuation to our screening program of naphthoquinones with activity against bloodstream trypomastigote forms of *Trypanosoma cruzi*, the etiological agent of Chagas' disease, new  $\beta$ -lapachone-based 1,2,3-triazoles, 3-arylamino-nor- $\beta$ -lapachones, 3-alkoxy-nor- $\beta$ -lapachones and imidazole anthraquinones were synthesized and evaluated against *T. cruzi*, with good results.

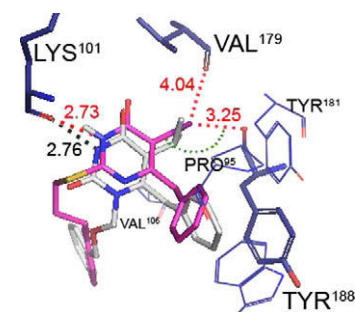


### Synthesis and biological evaluation of novel C5 halogen-functionalized S-DABO as potent HIV-1 non-nucleoside reverse transcriptase inhibitors

pp 3231–3237

Hua Qin, Chang Liu, Ying Guo, Ruiping Wang, Jianfang Zhang, Liying Ma, Zhili Zhang, Xiaowei Wang, Yuxin Cui, Junyi Liu\*

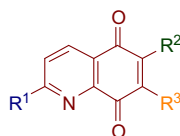
A halogen bond between the C5-I and the carbonyl of TYR188 could increase the activity to HIV-1 RT.



### The anti-cancer, anti-inflammatory and tuberculostatic activities of a series of 6,7-substituted-5,8-quinolinequinones

pp 3238–3251

Benjamin J. Mulchin, Christopher G. Newton, James W. Baty, Carole H. Grasso, William John Martin, Michaela C. Walton, Emma M. Dangerfield, Catherine H. Plunkett, Michael V. Berridge, Jacqui L. Harper, Mattie S. M. Timmer\*, Bridget L. Stocker\*



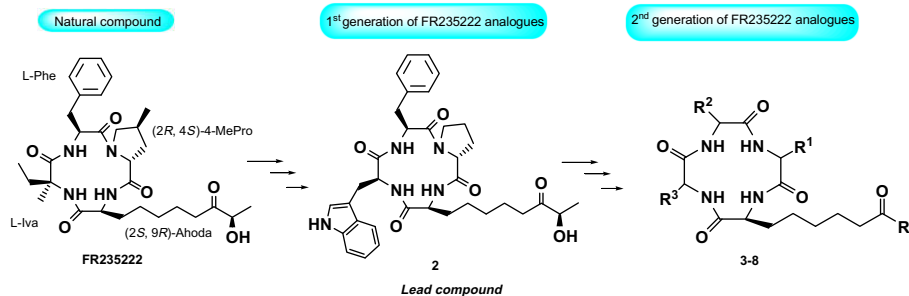
6,7-Substituted-5,8-quinolinequinones were synthesised and assessed for their anti-tumour and anti-inflammatory activities, and their ability to inhibit the growth of *Mycobacterium bovis* BCG.



### Synthesis and biological activity of cyclotetrapeptide analogues of the natural HDAC inhibitor FR235222

pp 3252–3260

Stefania Terracciano, Simone Di Micco, Giuseppe Bifulco, Paola Gallinari, Raffaele Riccio, Ines Bruno\*



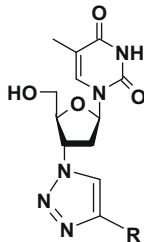
New six simplified analogues of the natural cyclotetrapeptide FR235222 were prepared and their biological activities on different HDAC isoforms were evaluated.



### 3'-(1,2,3-Triazol-1-yl)-3'-deoxythymidine analogs as substrates for human and *Ureaplasma parvum* thymidine kinase for structure–activity investigations

pp 3261–3269

Jay Lin, Vincent Roy, Liya Wang, Li You, Luigi A. Agrofoglio\*, Dominique Deville-Bonne, Tamara R. McBrayer, Steven J. Coats, Raymond F. Schinazi, Staffan Eriksson\*



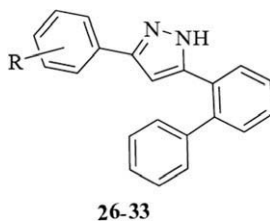
Thirteen 3'-triazolo analogues of AZT were tested on human hTK1 and *Up*TK of pathogenic mycoplasma *Ureaplasma parvum*. They are better substrates of *Up*TK than of hTK1. Structural models of *Up*TK and hTK1 were constructed to explain the kinetic results and aid future development of anti-mycoplasma nucleosides.



### 3,5-Diaryl-1H-pyrazole as a molecular scaffold for the synthesis of apoptosis-inducing agents

pp 3270–3278

Arthur Y. Shaw\*, Hao-Han Liao, Pei-Jung Lu, Chia-Ning Yang, Chien-Hsing Lee, Jun-Yan Chen, Zhigang Xu, Gary Flynn

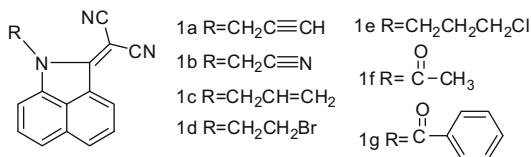


A series of 3,5-diaryl-1H-pyrazoles were synthesized and evaluated for their growth-inhibitory activity, apoptosis-inducing effect and structure–activity relationship study.

### Novel DNA intercalators without basic side chains as efficient antitumor agents: Design, synthesis and evaluation of benzo-[c,d]-indol-malononitrile derivatives

pp 3279–3284

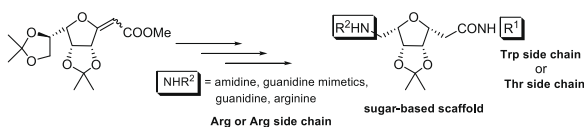
Xiaolian Li, Qianqian Wang, Yang Qing, Yanjie Lin, Yingli Zhang, Xuhong Qian\*, Jingnan Cui



### Sugar-based peptidomimetics as potential inhibitors of the vascular endothelium growth factor binding to neuropilin-1

pp 3285–3298

Alexandre Novoa, Nadia Pellegrini-Moïse, Denise Bechet, Muriel Barberi-Heyob, Yves Chapleur\*

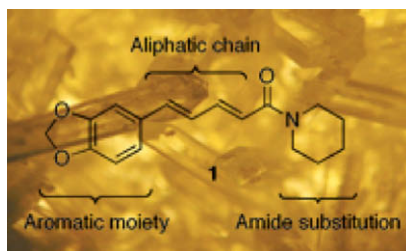




**In vitro TRPV1 activity of piperine derived amides**

pp 3299–3306

Edwin Andrés Correa, Edward D. Högestätt, Olov Sterner, Fernando Echeverri\*, Peter M. Zygmunt

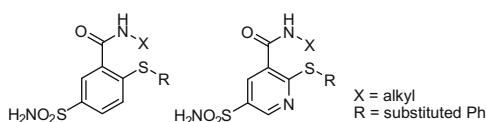


We have evaluated the in vitro hTRPV1 activity of natural and synthetic piperine derivatives with modifications according to key structural regions using fluorometric calcium imaging.

**Thioether benzenesulfonamide inhibitors of carbonic anhydrases II and IV: Structure-based drug design, synthesis, and biological evaluation**

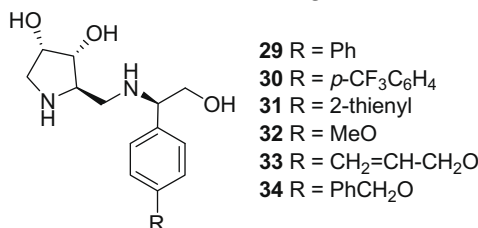
pp 3307–3319

William Vernier\*, Wesley Chong, David Rewolinski, Samantha Greasley, Thomas Pauly, Morena Shaw, Dac Dinh, Rose Ann Ferre, Seiji Nukui, Martha Ornelas, Eric Reyner

**Novel 2-[(benzylamino)methyl]pyrrolidine-3,4-diol derivatives as  $\alpha$ -mannosidase inhibitors and with antitumor activities against hematological and solid malignancies**

pp 3320–3334

Claudia Bello, Michele Cea, Giovanna Dal Bello, Anna Garuti, Ilaria Rocco, Gabriella Cirmena, Eva Moran, Aimable Nahimana, Michel A. Duchosal, Floriana Fruscione, Paolo Pronzato, Francesco Grossi, Franco Patrone, Alberto Ballestrero, Marc Dupuis, Bernard Sordat, Alessio Nencioni, Pierre Vogel\*

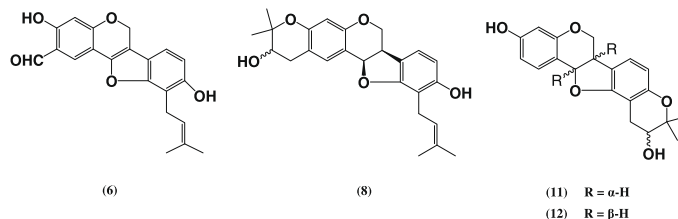


The novel  $\alpha$ -mannosidase inhibitors **29–34** act as cell cycle modulators on tumor cells of different origins.

**Prenylated pterocarpanes as bacterial neuraminidase inhibitors**

pp 3335–3344

Phi Hung Nguyen, Thi Ngoc Anh Nguyen, Keon Wook Kang, Derek Tantoh Ndinteh, Joseph Tanyi Mbafor, Young Ran Kim, Won Keun Oh\*



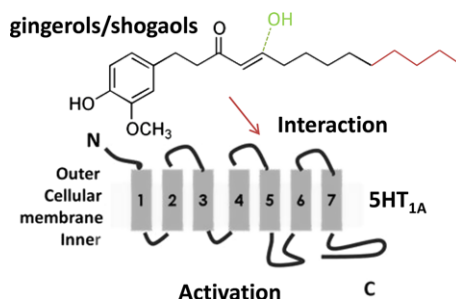
Four new pterocarpenoid derivatives (**6**, **8**, **11**, and **12**) and eleven known ones (**1–5**, **7**, **9**, **10**, and **13–15**) were isolated from the stem bark of *Erythrina abyssinica*. All compounds exhibited strong inhibitory effects on the neuraminidase from *Clostridium perfringens* and *Vibrio cholerae* with  $IC_{50}$  values ranging from  $1.32 \pm 0.2$  to  $77.10 \pm 2.2$   $\mu$ M and  $0.35 \pm 0.02$  to  $77.73 \pm 11.01$   $\mu$ M, respectively. This finding suggests that *E. abyssinica* and its constituents, pterocarpanoids, can be considered as promising therapeutic agent in the treatment of bacterial infections.



**Identification of serotonin 5-HT<sub>1A</sub> receptor partial agonists in ginger**

pp 3345–3351

Andreas Nievergelt, Peter Huonker, Roland Schoop, Karl-Heinz Altmann, Jürg Gertsch\*



\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

The most active bisnaphthalimide tested using the Malstat assay and in blood cultures. Details: Most active bisnaphthalimide (center); Malstat assay well plate (lower left); anopheles mosquito (lower right); plasmodia infected blood culture (background). Source: Mosquito picture CDC (PHIL)/ James Gathany. [Tischer, M.; Sologub, L.; Pradel, G.; Holzgrabe, U. *Bioorg. Med. Chem.* **2010**, 18, 2998.]

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/BIOBASE, 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®



ELSEVIER

ISSN 0968-0896