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Bioorganic & Medicinal Chemistry Volume 18, Issue 12, 2010

Contents

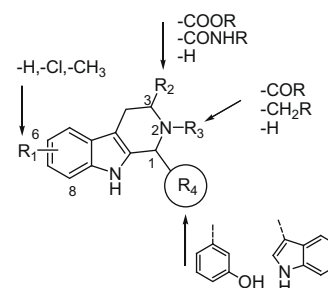
ARTICLES

Discovery of tetrahydro- β -carbolines as inhibitors of the mitotic kinesin KSP

pp 4167–4177

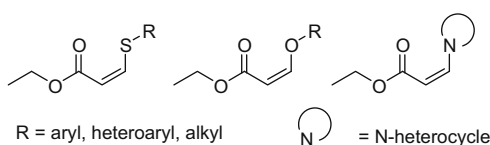
Fei Liu, Li-Qin Yu, Cheng Jiang, Lei Yang, Wu-Tong Wu, Qi-Dong You*

A novel series of tetrahydro- β -carboline analogs were designed based on the structure of the known KSP inhibitor HR22C16 and described as highly potent KSP inhibitors with notable efficacy in cellular proliferation assay.



A new class of potential anti-tuberculosis agents: Synthesis and preliminary evaluation of novel acrylic acid ethyl ester derivatives

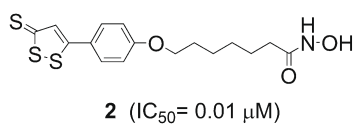
M. Shahjahan Kabir, Ojas A. Namjoshi, Ranjit Verma, Rebecca Polanowski, Sarah M. Krueger, David Sherman, Marc A. Rott*, William R. Schwan*, Aaron Monte*, James M. Cook*



New aryldithiolethione derivatives as potent histone deacetylase inhibitors

pp 4187–4194

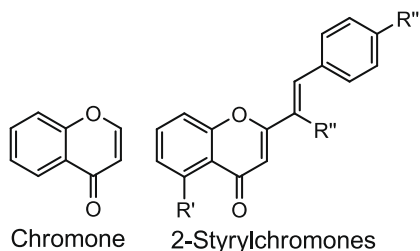
Valerio Tazzari, Graziella Cappelletti, Manolo Casagrande, Elena Perrino, Luigi Renzi, Piero Del Soldato, Anna Sparatore*



(E)-2-Styrylchromones as potential anti-norovirus agents

pp 4195–4201

Joana Rocha-Pereira, Ricardo Cunha, Diana C. G. A. Pinto, Artur M. S. Silva, Maria São José Nascimento*

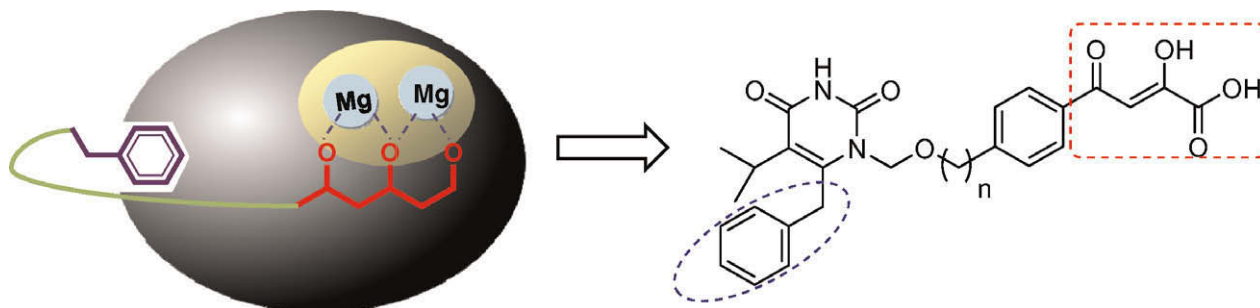


Twelve structure related chromone and (E)-2-styrylchromones were tested for their activity against norovirus using the surrogate model MNV/RAW 264.7 cells. (E)-5-Hydroxy-2-styrylchromone and (E)-4'-methoxy-2-styrylchromone were the most active compounds ($IC_{50} \approx 7 \mu M$).

**Pharmacophore and structure–activity relationships of integrase inhibition within a dual inhibitor scaffold of HIV reverse transcriptase and integrase**

pp 4202–4211

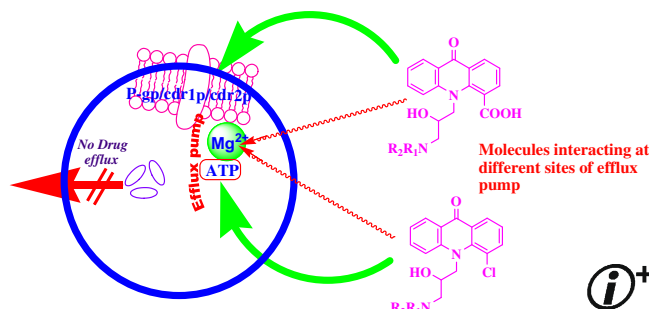
Zhengqiang Wang*, Jing Tang, Christine E. Salomon, Christine D. Dreis, Robert Vince

**Targeting efflux pumps—In vitro investigations with acridone derivatives and identification of a lead molecule for MDR modulation**

pp 4212–4223

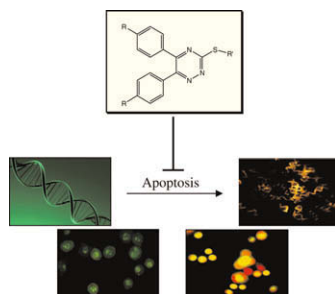
Palwinder Singh*, Jatinder Kaur, Bhawna Yadav, Sneha Sudha Komath*

Acridone based molecules are identified for blocking the drug efflux pumps either through interactions with P-gp/cdr1p/cdr2p or interacting with ATP/Mg²⁺.

**Synthesis and in vitro evaluation of novel 1,2,4-triazine derivatives as neuroprotective agents**

pp 4224–4230

Hamid Irannejad, Mohsen Amini, Fariba Khodaghali, Niloufar Ansari, Solaleh Khoramian Tusi, Mohammad Sharifzadeh, Abbas Shafiee*

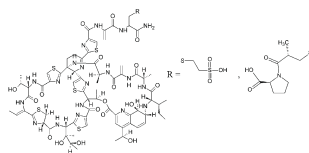


A novel series of 1,2,4-triazine derivatives were synthesized and evaluated for their neuroprotective effect.

Semi-synthetic analogues of thiostrepton delimit the critical nature of tail region modifications in the control of protein biosynthesis and antibacterial activity

pp 4231–4237

Cullen L. Myers, Pei C. Hang, Grace Ng, Joshua Yuen, John F. Honek*



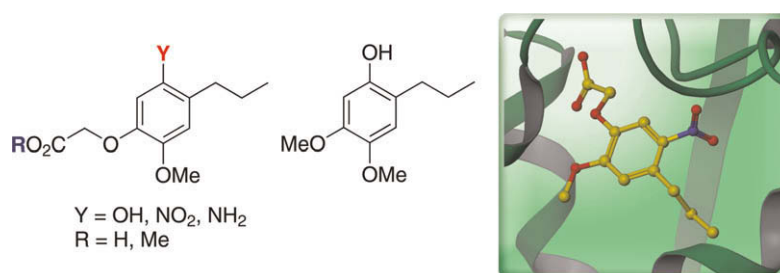
Semi-synthetic, regio-specific analogues of thiostrepton demonstrate the importance of the tail region of this antibiotic in its antibacterial activity and highlight this region as an attractive site for future modification.



Design, synthesis, and docking of highly hypolipidemic agents: *Schizosaccharomyces pombe* as a new model for evaluating α -asarone-based HMG-CoA reductase inhibitors

pp 4238–4248

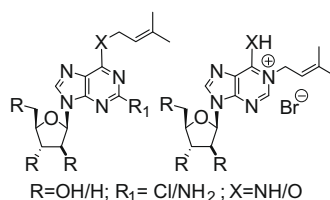
Nancy Argüelles, Eugenia Sánchez-Sandoval, Aarón Mendieta, Lourdes Villa-Tanaca*, Leticia Garduño-Siciliano*, Fabiola Jiménez, María del Carmen Cruz, José L. Medina-Franco*, Germán Chamorro-Cevallos, Joaquín Tamariz*



Synthesis and evaluation of in vitro anticancer activity of some novel isopentenyladenosine derivatives

pp 4249–4254

Roberta Ottria, Silvana Casati, Ada Manzocchi, Erika Baldoli, Massimo Mariotti, Jeanette A. M. Maier, Pierangela Ciuffreda*



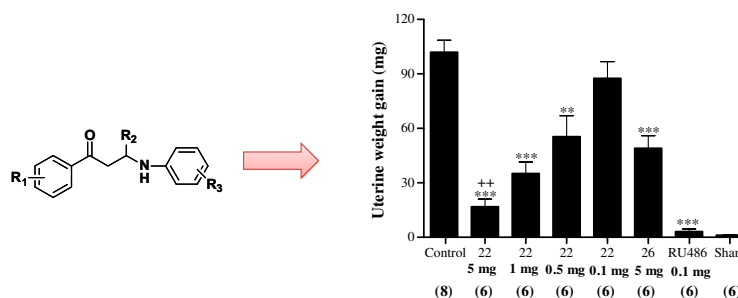
Some novel derivatives of *N*⁶-isopentenyladenosine (iPA) are synthesised and are evaluated for their antiproliferative activity on T24 human bladder carcinoma cells.



Aromatic β -amino-ketone derivatives as novel selective non-steroidal progesterone receptor antagonists

pp 4255–4268

Yongli Du, Qunyi Li, Bing Xiong, Xin Hui, Xin Wang, Yang Feng, Tao Meng, Dingyu Hu, Datong Zhang, Mingwei Wang*, Jingkan Shen*



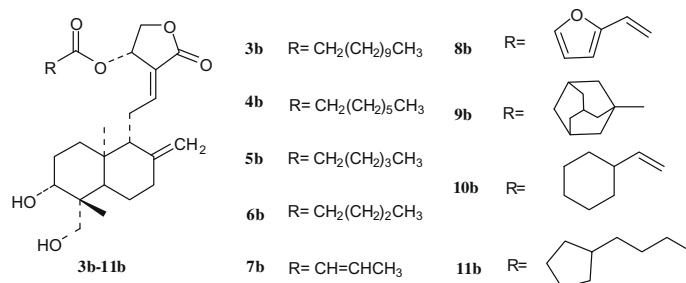
A series of aromatic β -amino-ketone derivatives was identified as a novel class of non-steroidal progesterone receptor antagonists.



Design, synthesis and antibacterial activity of novel andrographolide derivatives

pp 4269–4274

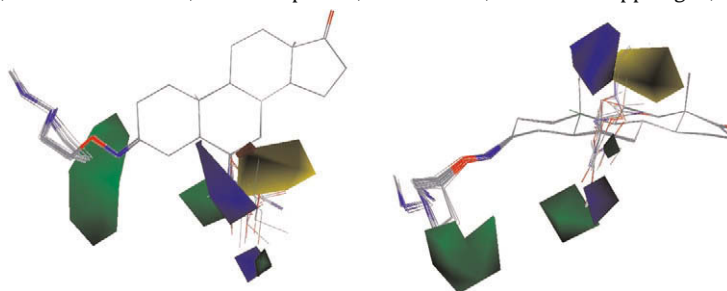
Zhongli Wang, Pei Yu*, Gaoxiao Zhang, Lipeng Xu, Dingyuan Wang, Liang Wang, Xiangping Zeng, Yuqiang Wang*



Novel analogues of Istaroxime, a potent inhibitor of Na⁺,K⁺-ATPase: Synthesis, structure–activity relationship and 3D-quantitative structure–activity relationship of derivatives at position 6 on the androstane scaffold

pp 4275–4299

Mauro Gobbini*, Silvia Armaroli, Leonardo Banfi, Alessandra Benicchio, Giulio Carzana, Patrizia Ferrari, Giuseppe Giacalone, Giuseppe Marazzi, Barbara Moro, Rosella Micheletti, Simona Sputore, Marco Torri, Maria Pia Zappavigna, Alberto Cerri



Peptide fragmentation as an approach in modeling of an active peptide and designing a competitive inhibitory peptide for HMG-CoA reductase

pp 4300–4309

Valeriy V. Pak*, Minseon Koo, Dae Young Kwon, Khusnutdin M. Shakhidoyatov, Lyubov Yun

Starting points in design

1. Recognized residue (Z₁)

2. β-Turn structure

GZ₂PZ₁GG

β-Turn

Z₃FZ₄Z₅VAZ₁

1 fragment

2 fragment

3 fragment

4 fragment

Set 1

Z₁ = T, D, EZ₂ = L, F, (4-fluoro)F

Set 2

Z₁ = EZ₃ = G, T, D, EZ₄ = G, P, FZ₅ = Y, (4-fluoro)F

i-fragment

G—G

Fragment model

GGGG

G—G

β-Turn model

Lead

optimization

Lead peptide 1

Lead

optimization

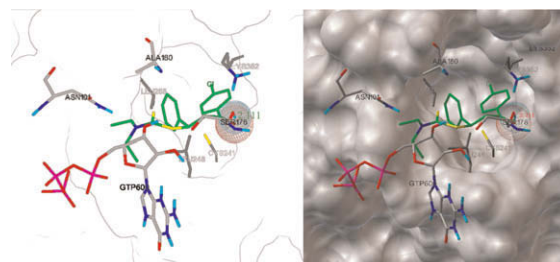
Lead peptide 2

Synthesis, molecular modeling and biological evaluation of dithiocarbamates as novel antitubulin agents

pp 4310–4316

Yong Qian, Gao-Yuan Ma, Ying Yang, Kui Cheng, Qing-Zhong Zheng, Wen-Jun Mao, Lei Shi, Jing Zhao*, Hai-Liang Zhu*

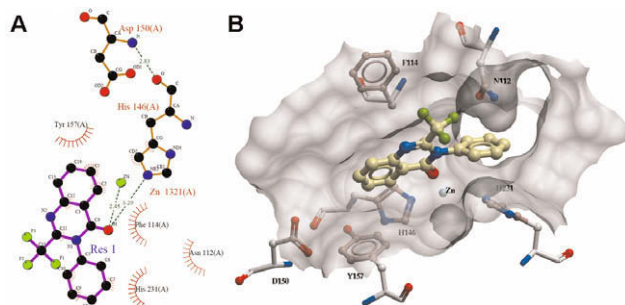
Compound **2n** showed the most potent biological activity in vitro, which inhibited the growth of MCF-7 human breast carcinoma cells with IC₅₀ of 0.04 ± 0.01 μM and the polymerization of tubulin with IC₅₀ of 6.8 ± 0.6 μM. To understand the tubulin–inhibitor interaction and the selectivity of the most active compound towards tubulin, molecular modeling studies were performed to dock compound **2n** into colchicine binding site and this study provided probable inhibition mechanism. The result indicated that compound **2n** was a potent inhibitor of tubulin polymerization.



Identification of novel quinazolin-4(3H)-ones as inhibitors of thermolysin, the prototype of the M4 family of proteinases

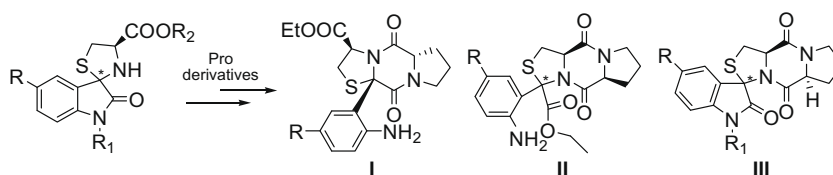
pp 4317–4327

Mahmud Tareq Hassan Khan, Rasool Khan, Yimingjiang Wuxiuer, Mohammad Arfan, Manzoor Ahmed, Ingebrigt Sylte*

Interaction of compound **3** [3-phenyl-2-(trifluoromethyl)quinazolin-4(3H)-one] with thermolysin.**Design and synthesis of spirotryprostatin-inspired diketopiperazine systems from prolyl spirooxindolethiazolidine derivatives**

pp 4328–4337

Alessia Bertamino, Claudio Aquino, Marina Sala, Nicoletta de Simone, Carlo Andrea Mattia, Loredana Erra, Simona Musella, Pio Iannelli, Alfonso Carotenuto, Paolo Grieco, Ettore Novellino, Pietro Campiglia, Isabel Gomez-Monterrey*

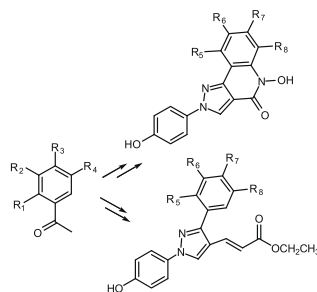


Based on the spirotryprostatin A structure, three different series of the diketopiperazine derivatives were synthesized and evaluated as potential cytotoxic agents.

**Novel pyrazole derivatives: Synthesis and evaluation of anti-angiogenic activity**

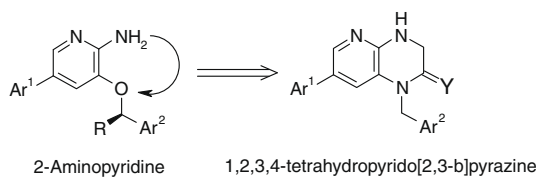
pp 4338–4350

Michael S. Christodoulou, Sandra Liekens*, Konstantinos M. Kasiotis, Serkos A. Haroutounian*

**Synthesis and structure–activity relationships of 1,2,3,4-tetrahydropyrido[2,3-b]pyrazines as potent and selective inhibitors of the anaplastic lymphoma kinase**

pp 4351–4362

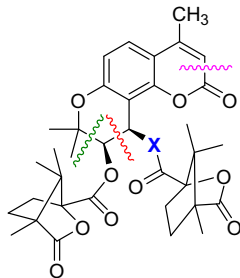
Karen L. Milkiewicz*, Linda R. Weinberg, Mark S. Albom, Thelma S. Angeles, Mangeng Cheng, Arup K. Ghose, Renee C. Roemmele, Jay P. Theroff, Ted L. Underiner, Craig A. Zificsak, Bruce D. Dorsey



Anti-AIDS agents 82: Synthesis of seco-(3'*R*,4'*R*)-3',4'-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone (DCK) derivatives as novel anti-HIV agents

pp 4363–4373

Jian Tang, Keduo Qian, Bei-Na Zhang, Ying Chen*, Peng Xia*, Donglei Yu, Yi Xia, Zheng-Yu Yang, Chin-Ho Chen, Susan L. Morris-Natschke, Kuo-Hsiung Lee*



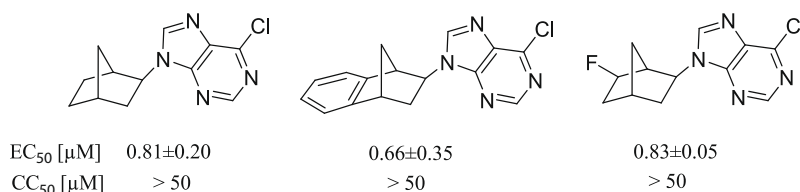
Seco-DCKs



Design, synthesis, and biological evaluation of novel coxsackievirus B3 inhibitors

pp 4374–4384

Michal Šála, Armando M. De Palma, Hubert Hřebabecký*, Radim Nencka, Martin Dračinský, Pieter Leyssen, Johan Neyts, Antonín Holý



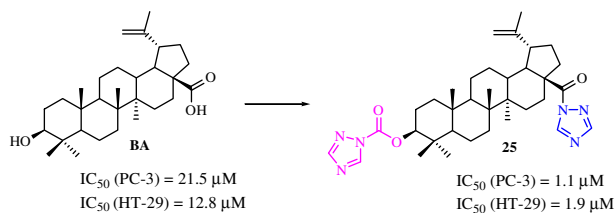
We report synthesis and results of the anti-coxsackievirus B3 screening of the novel 6-chloropurine derivatives.



Synthesis and structure–activity relationship study of novel cytotoxic carbamate and *N*-acylheterocyclic bearing derivatives of betulin and betulinic acid

pp 4385–4396

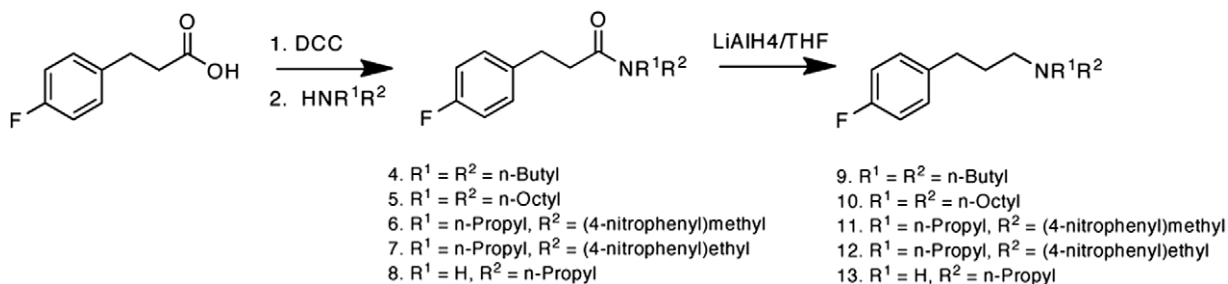
Rita C. Santos, Jorge A. R. Salvador*, Silvia Marín, Marta Cascante*, João N. Moreira, Teresa C. P. Dinis



Synthesis and characterization of *N,N*-dialkyl and *N*-alkyl-*N*-aralkyl fenpropimorph-derived compounds as high affinity ligands for sigma receptors

pp 4397–4404

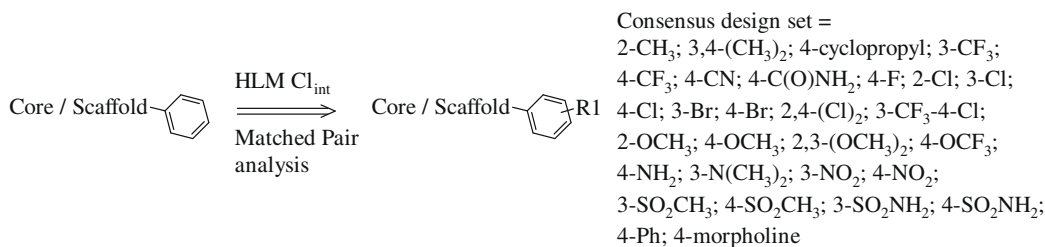
Abdol R. Hajipour, Dominique Fontanilla, Uyen B. Chu, Marty Arbabian, Arnold E. Ruoho*



A statistical analysis of in vitro human microsomal metabolic stability of small phenyl group substituents, leading to improved design sets for parallel SAR exploration of a chemical series

pp 4405–4414

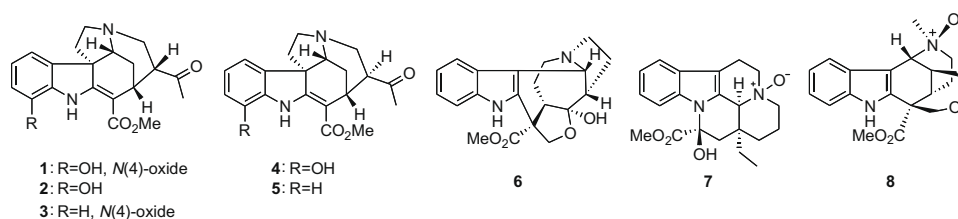
Alexander G. Dossetter*



Alpneumines A–H, new anti-melanogenic indole alkaloids from *Alstonia pneumatophora*

pp 4415–4421

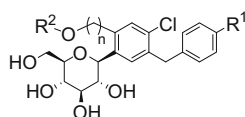
Koichiro Koyama, Yusuke Hirasawa, Takahiro Hosoya, Teh Chin Hoe, Kit-Lam Chan, Hiroshi Morita*



ortho-Substituted C-aryl glucosides as highly potent and selective renal sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors

pp 4422–4432

Baihua Xu*, Yan Feng, Binhua Lv, Ge Xu, Lili Zhang, Jiyan Du, Kun Peng, Min Xu, Jiajia Dong, Wenbin Zhang, Ting Zhang, Liangcheng Zhu, Haifeng Ding, Zelin Sheng, Ajith Welihinda, Brian Seed, Yuanwei Chen*

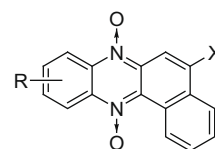
A series of *ortho*-substituted C-aryl glucosides have been synthesized and evaluated for inhibition of hSGLT1 and hSGLT2.

Study of benzo[a]phenazine 7,12-dioxide as selective hypoxic cytotoxin-scaffold. Identification of aerobic-antitumoral activity through DNA fragmentation

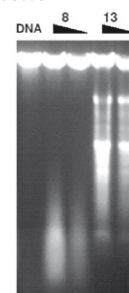
pp 4433–4440

María Laura Lavaggi, Mauricio Cabrera, María de los Ángeles Aravena, Claudio Olea-Azar, Adela López de Ceráin, Antonio Monge, Gisela Pachón, Marta Cascante, Ana María Bruno, Lía I. Pietrasanta, Mercedes González*, Hugo Cerecetto*

Benzo[a]phenazine 7,12-dioxide scaffold has been studied as selective hypoxic cytotoxin and as antiproliferative agents on Caco-2 tumoral cells in normoxia. Electrochemical, DNA-interaction and DNA-damage studies were performed to establish the mode of action.



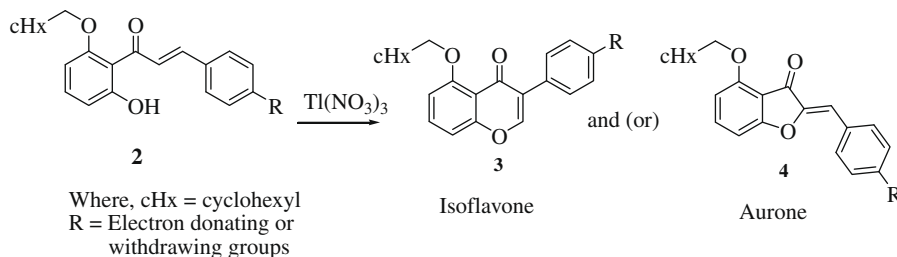
-X= -H, -R= -CH₃, **8**
 -X= -OH, -R= -CH₃, **13**



The scope of thallium nitrate oxidative cyclization of chalcones; synthesis and evaluation of isoflavone and aurone analogs for their inhibitory activity against interleukin-5

pp 4441–4445

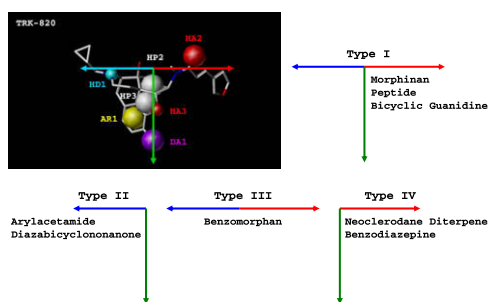
P. Thanigaimalai, Hyun-Mo Yang, Vinay Kumar Sharma, Youngsoo Kim, Sang-Hun Jung*



Identification of the three-dimensional pharmacophore of κ -opioid receptor agonists

pp 4446–4452

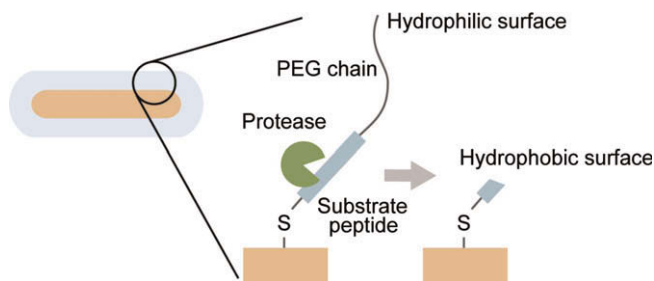
Noriyuki Yamaotsu*, Hideaki Fujii, Hiroshi Nagase, Shuichi Hirono

3D-Pharmacophore and classification of binding orientations for κ -agonists. The binding orientations are divided into four types.

Controlled release of PEG chain from gold nanorods: Targeted delivery to tumor

pp 4453–4458

Takuro Niidome*, Akira Ohga, Yasuyuki Akiyama, Kazuto Watanabe, Yasuro Niidome, Takeshi Mori, Yoshiki Katayama

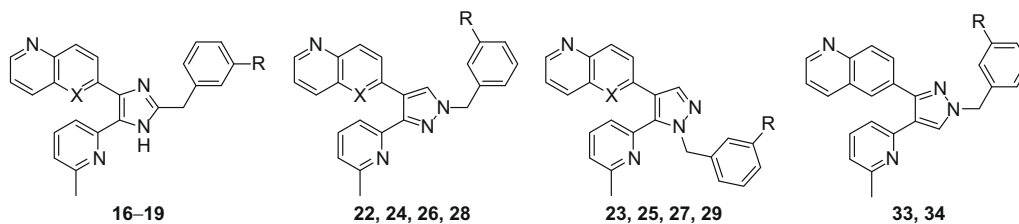


To deliver gold nanorods to tumor, a PEG–peptide conjugate, which contained a substrate sequence for a protease specifically expressed in tumor, was modified.

Synthesis and biological evaluation of 4(5)-(6-methylpyridin-2-yl)imidazoles and -pyrazoles as transforming growth factor- β type 1 receptor kinase inhibitors

pp 4459–4467

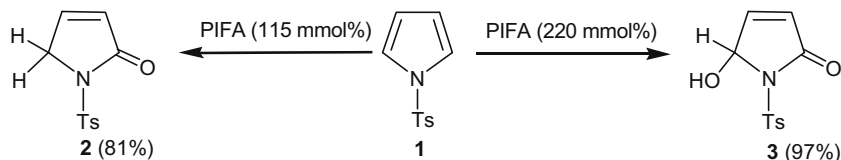
Dae-Kee Kim*, Yeon-Im Lee, Yeon Woo Lee, Purushottam M. Dewang, Yhun Yhong Sheen, Yeo Woon Kim, Hyun-Ju Park, Jakyung Yoo, Ho Soon Lee, Yong-Kook Kim



A novel and one-pot synthesis of new 1-tosyl pyrrol-2-one derivatives and analysis of carbonic anhydrase inhibitory potencies

pp 4468–4474

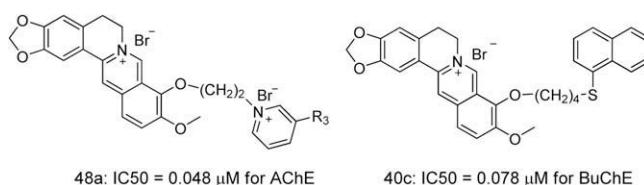
Cemalettin Alp, Deniz Ekinici, Mehmet Serdar Gültekin*, Murat Şentürk*, Ertan Şahin, Ömer İrfan Küfrevioğlu



Synthesis and biological evaluation of a new series of berberine derivatives as dual inhibitors of acetylcholinesterase and butyrylcholinesterase

pp 4475–4484

Ling Huang, Zonghua Luo, Feng He, Jing Lu, Xingshu Li*

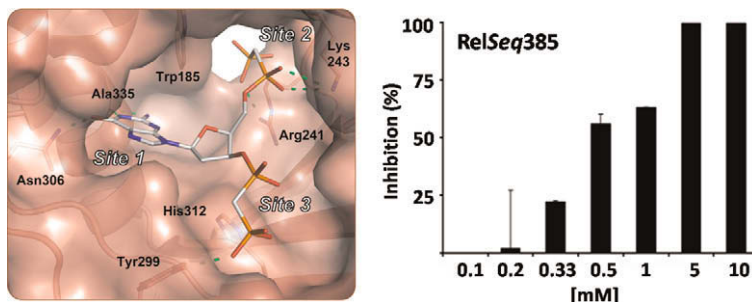


A series of novel berberine derivatives were designed, synthesized, and biologically evaluated as inhibitors of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE).

ppGpp analogues inhibit synthetase activity of Rel proteins from Gram-negative and Gram-positive bacteria

pp 4485–4497

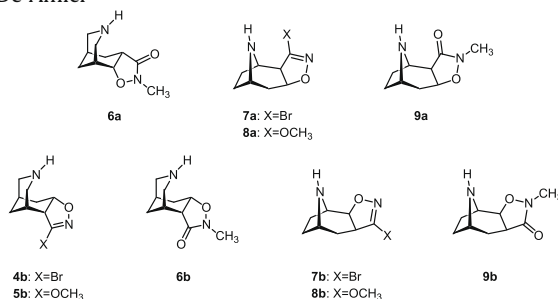
Ezequiel Wexselblatt, Jehoshua Katzhendler*, Rasputin Saleem-Batcha, Guido Hansen, Rolf Hilgenfeld, Gad Glaser, Roee R. Vidavski



Novel tricyclic Δ^2 -isoxazoline and 3-oxo-2-methyl-isoxazolidine derivatives: Synthesis and binding affinity at neuronal nicotinic acetylcholine receptor subtypes

pp 4498–4508

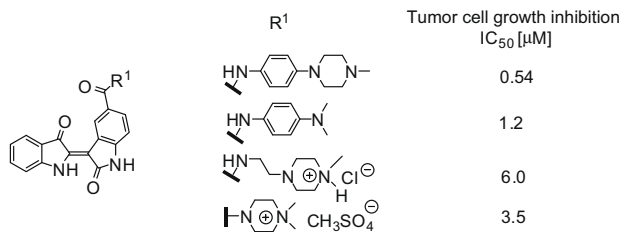
Clelia Dallanocce*, Fabio Frigerio, Giuliana Martelli, Giovanni Grazioso, Carlo Matera, Diego Yuri Pomè, Luca Pucci, Francesco Clementi, Cecilia Gotti, Marco De Amici



Synthesis and cytotoxicity of novel indirubin-5-carboxamides

pp 4509–4515

Xinlai Cheng, Paul Rasqué, Sandra Vatter, Karl-Heinz Merz*, Gerhard Eisenbrand



A series of indirubin-5-carboxamides was synthesized and evaluated for tumor cell growth inhibitory activity and solubility. Indirubins carrying amide substituents with basic centers show significantly enhanced solubility without loss of bioactivity.

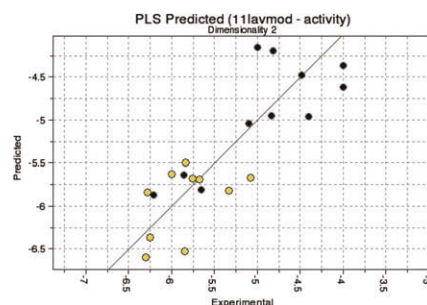


Design, synthesis and biological evaluation of *trans* 2-(thiophen-2-yl)vinyl heteroaromatic iodides

pp 4516–4523

Cosimo G. Fortuna*, Vincenza Barresi, Giuseppe Musumarra

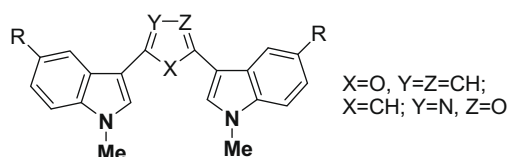
A modeling approach based on physico-chemical and pharmacokinetic properties, called Volsurf+, was used to design new heterocyclic compounds with antiproliferative activity. An Almond model, derived to have an overall structural insight on the above compounds, supported the validity of Volsurf and provided guidelines for the synthesis of new compounds.



Synthesis and antitumor activity of 2,5-bis(3'-indolyl)-furans and 3,5-bis(3'-indolyl)-isoxazoles, nortopsentin analogues

pp 4524–4529

Patrizia Diana, Anna Carbone, Paola Barraja, Gerhard Kelter, Heinz-Herbert Fiebig, Girolamo Cirrincione*

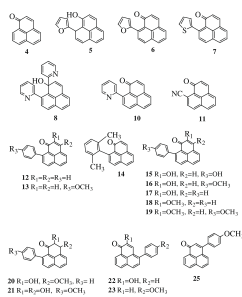


A series of novel 2,5-bis(3'-indolyl)furans and 3,5-bis(3'-indolyl)isoxazoles were synthesized and evaluated as antitumor agents.

Synthesis and in vitro antiprotozoal evaluation of substituted phenalenone analogues

pp 4530–4534

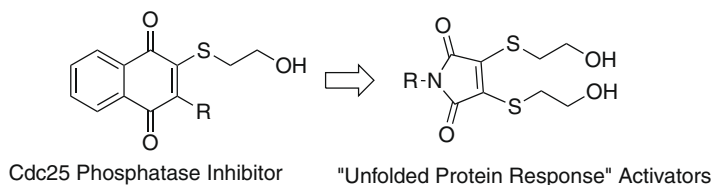
Laura I. Rosquete, M. Gabriela Cabrera-Serra, José E. Piñero, Patricia Martín-Rodríguez, Leandro Fernández-Pérez, Javier G. Luis, Grant McNaughton-Smith*, Teresa Abad-Grillo*



Development of antiproliferative phenylmaleimides that activate the unfolded protein response

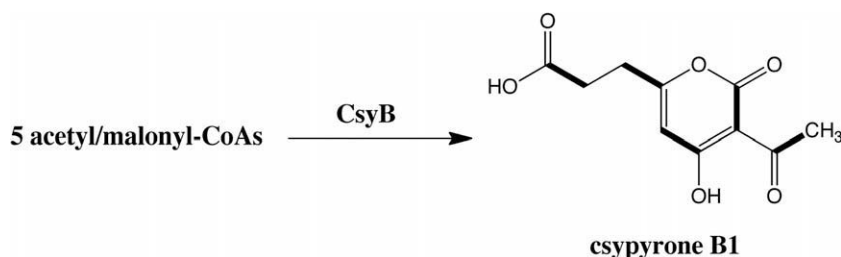
pp 4535–4541

Ulrike Muus, Curtis Hose, Wei Yao, Teresa Kosakowska-Cholody, David Farnsworth, Marzena Dyba, George T. Lountos, David S. Waugh, Anne Monks, Terrence R. Burke Jr.*, Christopher J. Michejda

**Identification of csypyrone B1 as the novel product of *Aspergillus oryzae* type III polyketide synthase CsyB**

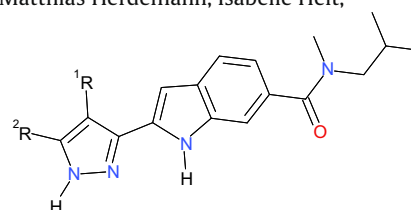
pp 4542–4546

Yasuyo Seshime, Praveen Rao Juvvadi, Katsuhiko Kitamoto, Yutaka Ebizuka, Isao Fujii*

**Synthesis and biological evaluation of novel (4 or 5-aryl)pyrazolyl-indoles as inhibitors of interleukin-2 inducible T-cell kinase (ITK)**

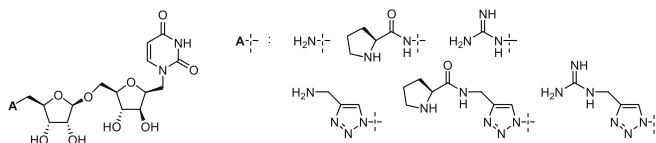
pp 4547–4559

Avdhoot D. Velankar*, Gianluca Quintini, Arati Prabhu, Alexander Weber, Gundula Hunaus, Britta Volland, Monika Wuest, Christian Orjeda, Dipak Harel, Shaji Varghese, Vikas Gore, Meenal Patil, Deepak Gayke, Matthias Herdemann, Isabelle Heit, Andrea Zaliani

Novel ITK inhibitors based on (4 or 5-aryl)pyrazolyl-indole scaffold were synthesized and were also found to be selective for ITK over other kinases like IRK, CDK2, GSK3 β and PKA. $R^1 = \text{Ph}, R^2 = \text{H}, \text{IC}_{50}(\text{ITK}) = 0.33 \mu\text{M}$ $R^1 = \text{Ph}, R^2 = \text{PhCH}_2, \text{IC}_{50}(\text{ITK}) = 0.56 \mu\text{M}$ **Bacterial transferase MraY inhibitors: Synthesis and biological evaluation**

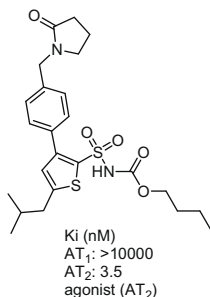
pp 4560–4569

Delphine Lecerclé, Anthony Clouet, Bayan Al-Dabbagh, Muriel Crouvoisier, Ahmed Bouhss, Christine Gravier-Pelletier*, Yves Le Merrier*




Selective angiotensin II AT₂ receptor agonists with reduced CYP 450 inhibition**pp 4570–4590**

A. K. Mahalingam, Yiqian Wan, A. M. S. Murugaiah, Charlotta Wallinder, Xiongyu Wu, Bianca Plouffe, Milad Botros, Fred Nyberg, Anders Hallberg, Nicole Gallo-Payet*, Mathias Alterman*

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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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