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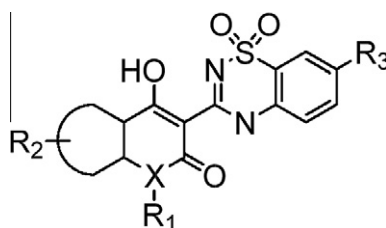


Bioorganic & Medicinal Chemistry Volume 19, Issue 16, 2011

Contents

REVIEW

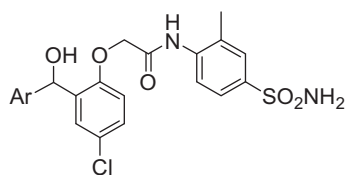
- Recent advances in drug discovery of benzothiadiazine and related analogs as HCV NS5B polymerase inhibitors** pp 4690–4703
 Debasis Das*, Jian Hong, Shu-Hui Chen, Guangyi Wang, Leonid Beigelman, Scott D. Seiwert, Brad O. Buckman*



ARTICLES

- Synthesis and biological evaluation of (±)-benzhydryl derivatives as potent non-nucleoside HIV-1 reverse transcriptase inhibitors** pp 4704–4709

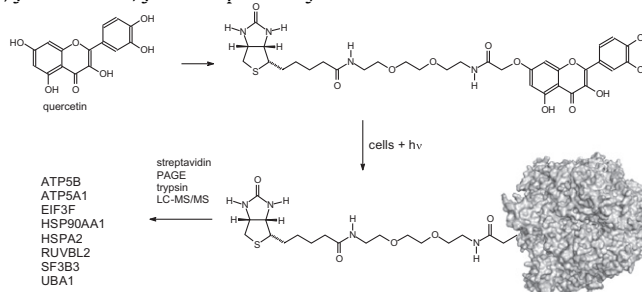
Xiao-Dong Ma, Xuan Zhang, Shi-Qiong Yang, Hui-Fang Dai, Liu-Meng Yang, Shuang-Xi Gu, Yong-Tang Zheng, Qiu-Qin He, Fen-Er Chen*



Ar = phenyl, substituted phenyl, naphthyl
 (±)-benzhydryl derivatives

- Biotinylated quercetin as an intrinsic photoaffinity proteomics probe for the identification of quercetin target proteins** pp 4710–4720

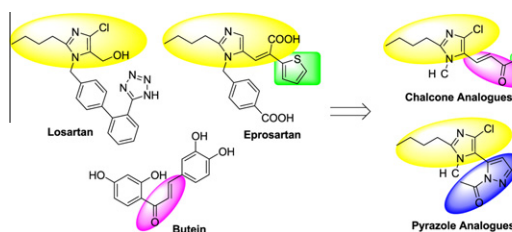
Rongsheng E. Wang, Clayton R. Hunt, Jiawei Chen, John-Stephen Taylor*



Synthesis and evaluation of novel 2-butyl-4-chloro-1-methylimidazole embedded chalcones and pyrazoles as angiotensin converting enzyme (ACE) inhibitors

pp 4772–4781

Srinivas Kantevari*, Dinesh Addla, Pankaj K. Bagul, Balasubramanian Sridhar, Sanjay K. Banerjee*



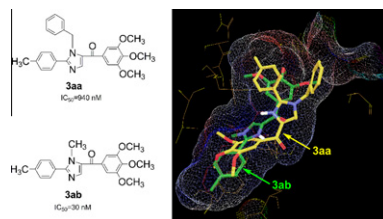
Screening all 36 new analogues of chalcones and pyrazoles using ACE inhibition assay, resulted three compounds as potent ACE inhibitors with IC_{50} of 2.24 μ M, 2.68 μ M, and 3.60 μ M.



Synthesis and antiproliferative activity of novel 2-aryl-4-benzoyl-imidazole derivatives targeting tubulin polymerization

pp 4782–4795

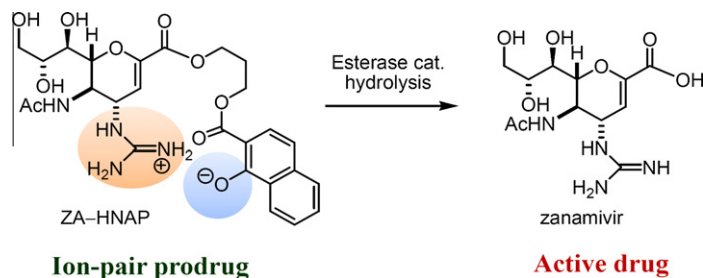
Jianjun Chen, Chien-Ming Li, Jin Wang, Sunjoo Ahn, Zhao Wang, Yan Lu, James T. Dalton, Duane D. Miller, Wei Li*



Intramolecular ion-pair prodrugs of zanamivir and guanidino-oseltamivir

pp 4796–4802

Kung-Cheng Liu, Pei-Shan Lee, Shi-Yun Wang, Yih-Shyun E. Cheng, Jim-Min Fang*, Chi-Huey Wong



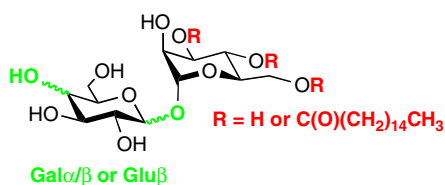
A new class of 1-hydroxy-2-naphthoic acid modified prodrugs of zanamivir and guanidino-oseltamivir is designed as an intramolecular ion-pair with improved bioavailability.



Synthesis, gp120 binding and anti-HIV activity of fatty acid esters of 1,1-linked disaccharides

pp 4803–4811

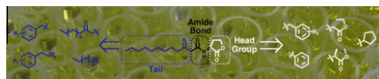
Stewart Bachan, Jacques Fantini*, Anjali Joshi, Himanshu Garg, David R. Mootoo*



Design, synthesis, and biological evaluation of abiotic, non-lactone modulators of LuxR-type quorum sensing

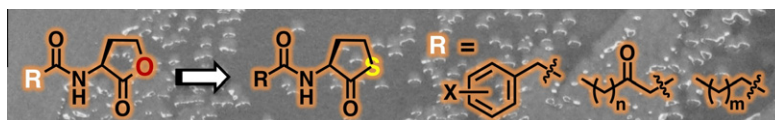
pp 4812–4819

Christine E. McInnis, Helen E. Blackwell*

**Thiolactone modulators of quorum sensing revealed through library design and screening**

pp 4820–4828

Christine E. McInnis, Helen E. Blackwell*

**Inhibition of monoamine oxidase by C5-substituted phthalimide analogues**

pp 4829–4840

Clarina I. Manley-King, Jacobus J. Bergh, Jacobus P. Petzer*

The synthesis of C5-substituted phthalimide analogues (**5**) with enhanced human MAO inhibition potencies compared to the lead compound phthalimide (**4**).

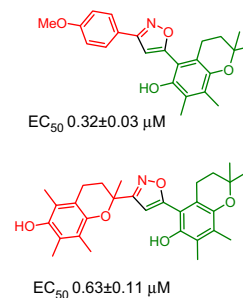
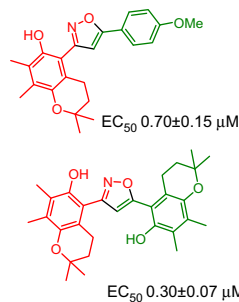
R	R	IC ₅₀ MAO-A	IC ₅₀ MAO-B
		μM	μM
	4	H	165
	5b	C ₆ H ₅ CH ₂ O	4.17
	5c	C ₆ H ₅ CH ₂ CH ₂ O	3.58
	5d	C ₆ H ₅ (CH ₂) ₃ O	1.73

**Isoxazole substituted chromans against oxidative stress-induced neuronal damage**

pp 4841–4850

Maria Koufaki*, Alexandra Tsatsaroni, Xanthippi Alexi, Hélène Guerrand, Sofia Zerva, Michael N. Alexis*

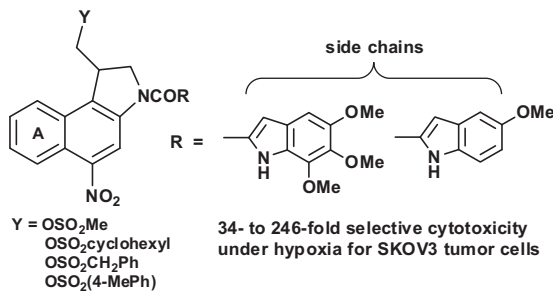
In an effort to optimize our previously identified neuroprotective chroman derivatives, 20 new 2 or 5-substituted chroman analogues bearing isoxazole moieties with aliphatic or aromatic substituents were synthesized and their activity against oxidative stress-induced damage in neuronal HT22 cells was evaluated. The differences in activity observed between regioisomers were attributed to specific structural characteristics.



The effect of sulfonate leaving groups on the hypoxia-selective toxicity of nitro analogs of the duocarmycins

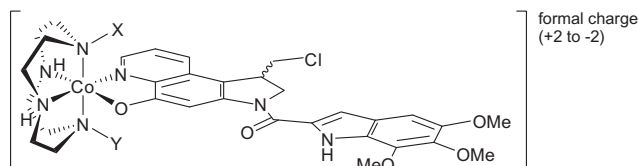
pp 4851–4860

Amir Ashoorzadeh, Graham J. Atwell, Frederik B. Pruijn, William R. Wilson, Moana Tercel, William A. Denny*, Ralph J. Stevenson

**N-alkylated cyclen cobalt(III) complexes of 1-(chloromethyl)-3-(5,6,7-trimethoxyindol-2-ylcarbonyl)-2,3-dihydro-1H-pyrrolo[3,2-f]quinolin-5-ol DNA alkylating agent as hypoxia-activated prodrugs**

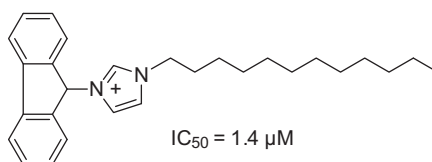
pp 4861–4867

Guo-Liang Lu, Ralph J. Stevenson, John Yu-Chih Chang, Penelope J. Brothers, David C. Ware, William R. Wilson, William A. Denny*, Moana Tercel

**LuxR dependent quorum sensing inhibition by *N,N'*-disubstituted imidazolium salts**

pp 4868–4875

Mohamad Sabbah, Laurent Soullère*, Sylvie Reverchon, Yves Queneau, Alain Doutheau



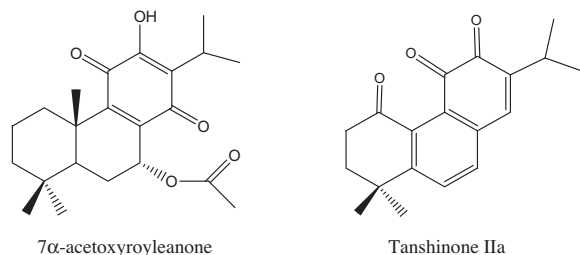
N,N'-Disubstituted imidazolium salts have been prepared and tested as LuxR dependent quorum sensing inhibitors. Some of them displayed IC₅₀ in the micromolar range. These results suggest that a disubstituted imidazolium ring may be considered as a new pharmacophore for QS inhibition.

**In vitro cytotoxic activity of abietane diterpenes from *Peltodon longipes* as well as *Salvia miltiorrhiza* and *Salvia sahendica***

pp 4876–4881

M. Fronza, R. Murillo, S. Ślusarczyk, M. Adams, M. Hamburger, B. Heinzmann, S. Laufer, I. Merfort*

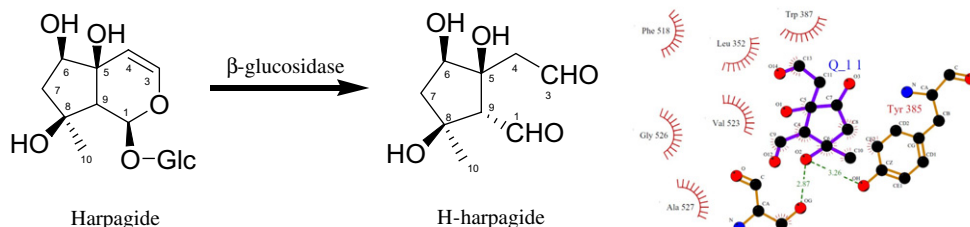
Phytochemical studies on *Peltodon longipes* afforded the isolation of twelve known abietane diterpenes being the active principle. The main diterpene, 7 α -acetoxyroyleanone exhibited a similar strong cytotoxic activity against a pancreatic and a melanoma cancer cell line as tanshinone IIa the main compound from *Salvia miltiorrhiza*. Structure–activity relationship study was undertaken including 21 structurally different abietane diterpenes.



Effects of β -glucosidase hydrolyzed products of harpagide and harpagoside on cyclooxygenase-2 (COX-2) in vitro

pp 4882–4886

Liuqiang Zhang, Li Feng, Qi Jia, Jinwen Xu, Rui Wang, Zhengtao Wang, Yingchun Wu, Yiming Li*



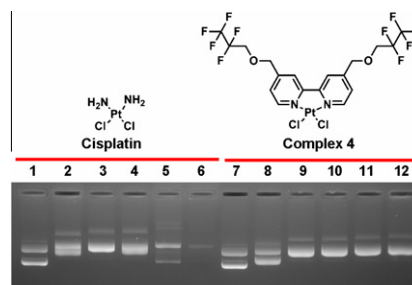
The hydrolyzed products of harpagide (H-harpagide) with β -glucosidase treatment showed a significant inhibitory effect on COX-2 activity at 2.5–100 μ M in a concentration-dependent manner. H-harpagide could bind to the COX-2 active domain well through hydrophobic and hydrogen-bonding interactions, whereas harpagide and harpagoside could not.

**Polyfluorinated bipyridine cisplatins manipulate cytotoxicity through the induction of S-G₂/M arrest and partial intercalation mechanism**

pp 4887–4894

Tzu Ting Chang, Shivaji V. More, Norman Lu*, Jyun-Wei Jhuo, Yi-Chuan Chen, Shu-Chuan Jao, Wen-Shan Li*

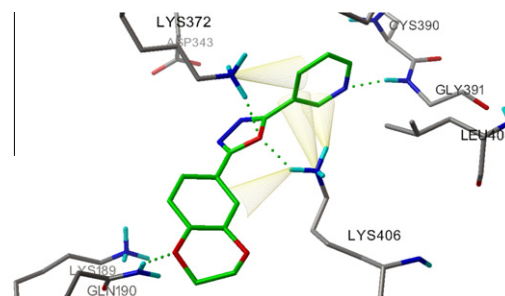
In the electrophoretogram the complex **4** (or cisplatin)-treated pSECTag 2/Hygro B plasmid DNA, significant comigration of open circular form and covalent closed circular form was observed and a coalescence of two main bands was found subsequently at low concentrations. A strong unwinding of negative supercoiled DNA to positive supercoiled DNA was detected at high concentrations of cisplatin, whereas the same binding mode with complex **4** was not observed.

**Oxadiazole derivatives containing 1,4-benzodioxan as potential immunosuppressive agents against RAW264.7 cells**

pp 4895–4902

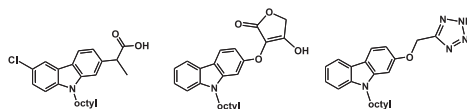
Juan Sun, Ning Cao, Xiao-Min Zhang, Yu-Shun Yang, Yan-Bin Zhang, Xiao-Ming Wang*, Hai-Liang Zhu*

A series of oxadiazole derivatives containing 1,4-benzodioxan (**4a–4s**) have been designed, synthesized, structurally determined, and their biological activities were also evaluated as potential immunosuppressive agents. All the synthesized compounds were first synthesized. Among the compounds, compound **4i** showed the most potent biological activity against RAW264.7 cells (inhibition = 37.66 \pm 2.34% for NO overproduction and IC₅₀ = 0.05 μ M for iNOS). Docking simulation was performed to position compound **4i** into the iNOS structure active site to determine the probable binding model. RT-PCR experiment results demonstrated that some of these compounds possessed good immunosuppressive activity against iNOS, especially for compound **4i**. Therefore, compound **4i** with potent inhibitory activity may be a potential agent.

**NSAID-derived γ -secretase modulation requires an acidic moiety on the carbazole scaffold**

pp 4903–4909

Andrea Zall, Daniel Kieser, Nicole Höttecke, Eva C. Naumann, Binia Thomaszewski, Katrin Schneider, Dirk T. Steinbacher, Robert Schubene, Stefan Masur, Karlheinz Baumann, Boris Schmidt*



pp 4910–4916

Chemical reaction scheme showing the synthesis of bis-oxazoline compounds:

Starting material: A substituted oxazoline derivative with a methoxy group (OCH_3), an oxazoline ring, and a substituent R ($\text{R} = \text{H, CH}_3$).

Reaction pathways:

- Leftward reaction: Formation of a bis-oxazoline dimer with two oxazoline rings connected by a $-(\text{CH}_2)_n-$ group.
- Rightward reaction: Formation of a bis-oxazoline polymer with two oxazoline rings connected by an $\text{X}-(\text{CH}_2)_n-\text{X}$ group, where $\text{X} = \text{CH}_2, \text{CO}$.

pp 4917-4927

Chemical structure of a macrocyclic peptide derivative. The macrocycle size is 14-16 atoms. The structure features a central benzene ring substituted with a methoxy group, a phenyl group, and a side chain containing a vinyl group and a sulfonamide group (R-SO₂-). The side chain is part of a peptide backbone with various protecting groups, including a tert-butyl ester and a cyclopropylmethyl group. The R group is defined as phenyl, cyclopropyl, or CH₂.

pp 4928–4934



pp 4935–4952

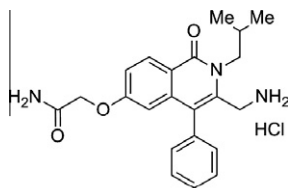
5a-y

5u, $IC_{50} = 19 \mu M$ for IN strand transfer
 $8 \mu M$ for LEDGF-IN interaction

Identification of 3-aminomethyl-1,2-dihydro-4-phenyl-1-isoquinolones: A new class of potent, selective, and orally active non-peptide dipeptidyl peptidase IV inhibitors that form a unique interaction with Lys554

pp 4953–4970

Yoshihiro Banno, Yasufumi Miyamoto, Mitsuru Sasaki, Satoru Oi, Tomoko Asakawa, Osamu Kataoka, Koji Takeuchi, Nobuhiro Suzuki, Koji Ikeda, Takuo Kosaka, Shigetoshi Tsubotani, Akiyoshi Tani, Miyuki Funami, Michiko Tawada, Yoshio Yamamoto, Kathleen Aertgeerts, Jason Yano, Hironobu Maezaki*

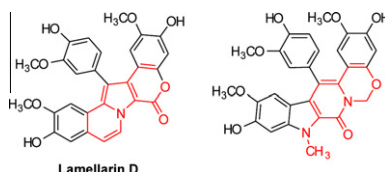
**35a**

Synthesis, inhibition of dipeptidyl peptidase IV (DPP-4) inhibitory activity of new isoquinolone (**35a**) are described.


Synthesis and topoisomerase I inhibitory activity of a novel diazaindeno[2,1-b]phenanthrene analogue of Lamellarin D

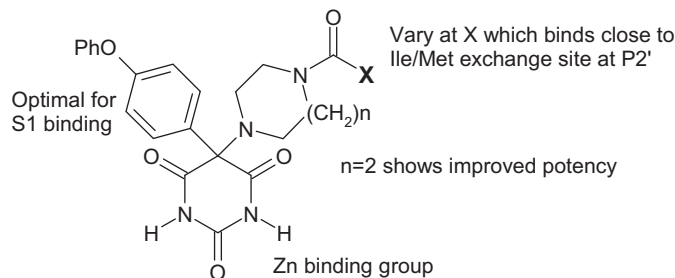
pp 4971–4984

Salvatore Cananzi, Lucio Merlini, Roberto Artali, Giovanni Luca Beretta, Nadia Zaffaroni, Sabrina Dallavalle*

**Lamellarin D**
N-Substituted homopiperazine barbiturates as gelatinase inhibitors

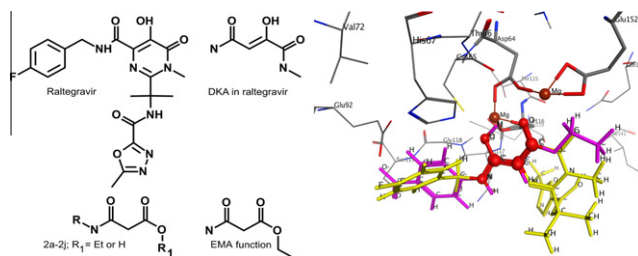
pp 4985–4999

Jun Wang, Carlos Medina, Marek W. Radomski, John F. Gilmer*


Ethyl malonate amides: A diketo acid offsprung fragment for HIV integrase inhibition

pp 5000–5005

Katarzyna Serafin, Pawel Mazur, Andrzej Bak, Elodie Laine, Luba Tchertanov, Jean-François Mouscadet, Jaroslaw Polanski*

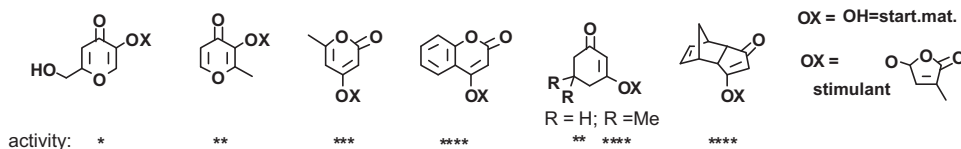


Ethyl malonate amide (EMA) an offsprung DKA fragment.

Single step synthesis of strigolactone analogues from cyclic keto enols, germination stimulants for seeds of parasitic weeds

pp 5006–5011

Alinanuswe S. Mwakaboko, Binne Zwanenburg*

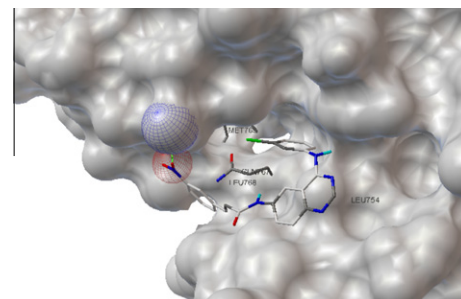


The combination of 4-anilinoquinazoline and cinnamic acid: A novel mode of binding to the epidermal growth factor receptor tyrosine kinase

pp 5012–5022

Dong-Dong Li, Peng-Cheng Lv, Hui Zhang, Hong-Jia Zhang, Ya-Ping Hou, Kai Liu, Yong-Hao Ye*, Hai-Liang Zhu*

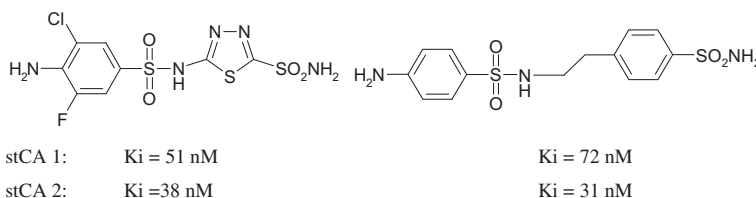
A novel type of cinnamic acid quinazoline amide derivatives (**20–42**), which designed the combination between quinazoline as the backbone and various substituted cinnamic acid as the side chain, have been synthesized and their biological activities were evaluated within cytotoxicity assay firstly and then potent EGFR inhibitory activity. Compound **42** demonstrated the most potent inhibitory activity ($IC_{50} = 0.94 \mu M$ for EGFR), which could be optimized as a potential EGFR inhibitor in the further study. Docking simulation was performed to position compound **42** into the EGFR active site to determine the probable binding model. Analysis of the binding conformation of **42** in active site displayed compound **42** was stabilized by hydrogen bonding interactions with Lys822, which was different from other derivatives. In the further study, compounds **43** and **44** had been synthesized and their biological activities were also evaluated, which were the same as that we expected. Compound **43** has demonstrated significant EGFR ($IC_{50} = 0.12 \mu M$) and tumor growth inhibitory activity as a potential anticancer agent.



Inhibition studies of the β -carbonic anhydrases from the bacterial pathogen *Salmonella enterica* serovar Typhimurium with sulfonamides and sulfamates

pp 5023–5030

Isao Nishimori, Tomoko Minakuchi, Daniela Vullo, Andrea Scozzafava, Claudiu T. Supuran*

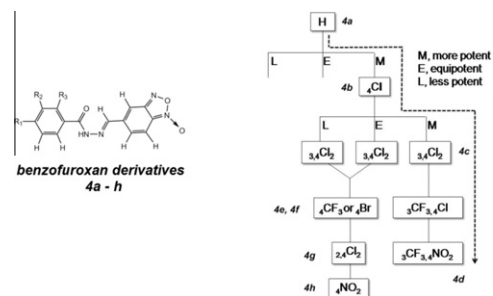


Novel benzofuroxan derivatives against multidrug-resistant *Staphylococcus aureus* strains: Design using Topliss' decision tree, synthesis and biological assay

pp 5031–5038

Salomão Dória Jorge*, Fanny Palace-Berl, Andrea Masunari, Cléber André Cechinel, Marina Ishii, Kerly Fernanda Mesquita Pasqualoto, Leoberto Costa Tavares

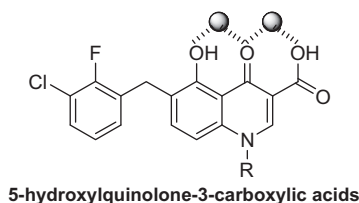
A set of benzofuroxan derivatives, potential antimicrobial agents, was designed to exploring the physicochemical properties of the substituents. Topliss operational scheme orientated the select of substituent groups.



Structural modifications of quinolone-3-carboxylic acids with anti-HIV activity

pp 5039–5045

Qiu-Qin He, Shuang-Xi Gu, Jia Liu, Hai-Qiu Wu, Xuan Zhang, Liu-Meng Yang, Yong-Tang Zheng, Fen-Er Chen*



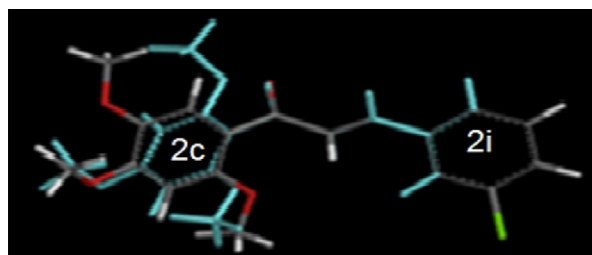
A series of novel 5-hydroxyquinolone-3-carboxylic acids were synthesized in an attempt to investigate whether the introduction of OH at C-5 position would provide an additional metal binding site and result in an improved activity against HIV-1.

Trimethoxy-chalcone derivatives inhibit growth of *Leishmania braziliensis*: Synthesis, biological evaluation, molecular modeling and structure–activity relationship (SAR)

pp 5046–5052

Murilo Lamim Bello, Louise Domeneghini Chiaradia, Luiza Rosaria Sousa Dias, Letícia Kramer Pacheco, Taisa Regina Stumpf, Alessandra Mascarello, Mário Steindel, Rosendo Augusto Yunes, Helena Carla Castro, Ricardo José Nunes*, Carlos Rangel Rodrigues*

In this work we described new trimethoxy-chalcones and among them **2i** ($IC_{50} = 2.7 \mu M$), **2j** ($IC_{50} = 3.9 \mu M$) and **2k** ($IC_{50} = 4.6 \mu M$) derivatives presented better antileishmanial activity than the control drug pentamidine ($IC_{50} = 6.0 \mu M$). Our SAR study showed the importance of methoxy di-*ortho* substitution at phenyl ring A and the relationship between the frontier orbital HOMO coefficients distribution of these molecules and their activity.

**Evaluation of influence of Ap4A analogues on Fhit-positive HEK293T cells; cytotoxicity and ability to induce apoptosis**

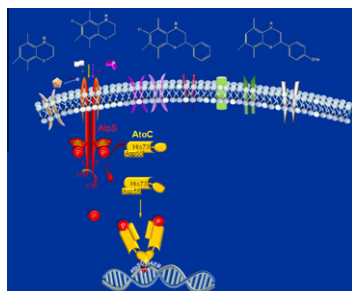
pp 5053–5060

Agnieszka Krakowiak*, Róża Pęcherzewska, Renata Kaczmarek, Agnieszka Tomaszewska, Barbara Nawrot, Wojciech J. Stec

**Regulation of the *Escherichia coli* AtoSC two component system by synthetic biologically active 5;7;8-trimethyl-1;4-benzoxazine analogues**

pp 5061–5070

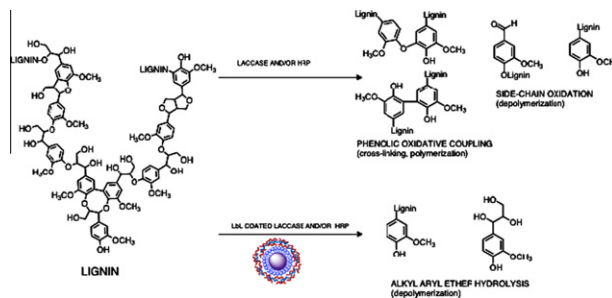
Panagiota S. Filippou, Eftychia N. Koini, Theodora Calogeropoulou, Panagiota Kalliakmani, Christos A. Panagiotidis, Dimitrios A. Kyriakidis*



Novel multienzyme oxidative biocatalyst for lignin bioprocessing

pp 5071–5078

Claudia Crestini*, Federica Melone, Raffaele Saladino

**OTHER CONTENT****Bioorganic & Medicinal Chemistry Reviews and Perspectives**

pp I–III

*Corresponding author

Supplementary data available via ScienceDirect

COVER

The known veterinary anthelmintic and proton ionophore, closantel, was recently discovered to also exhibit potent chitinase inhibition activity and inhibit molting in the parasitic nematode, *Onchocerca volvulus*, the causative agent of the neglected tropical disease onchocerciasis. [C. Gloeckner, A. L. Garner, F. Mersha, Y. Oksov, N. Tricoche, L. M. Eubanks, S. Lustigman, G. F. Kaufmann, K. D. Janda, Repositioning of an existing drug for the neglected tropical disease Onchocerciasis, *Proc. Natl. Acad. Sci., U.S.A.* **2010**, 107, 3424.]

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