



Bioorganic & Medicinal Chemistry Volume 20, Issue 21, 2012

Contents

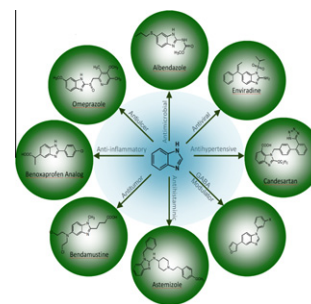
REVIEWS

The therapeutic journey of benzimidazoles: A review

Yogita Bansal, Om Silakari*

pp 6208–6236

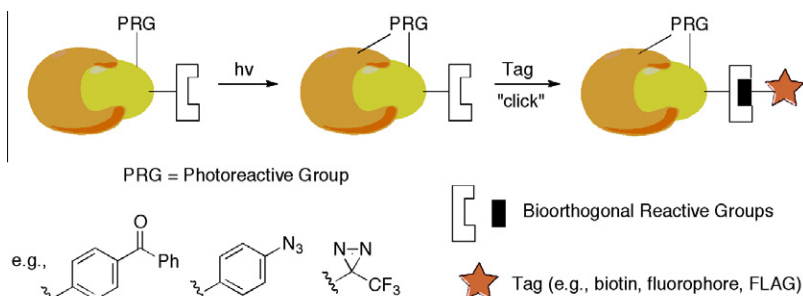
Various compounds derived benzimidazole nucleus exhibit different pharmacological activities. These are discussed on the basis of substitution pattern around the nucleus with an aim to help medicinal chemists for developing an SAR on benzimidazole derived compounds for each activity. It will further help in the development of novel benzimidazole compounds.



Tandem photoaffinity labeling–bioorthogonal conjugation in medicinal chemistry

David J. Lapinsky*

pp 6237–6247

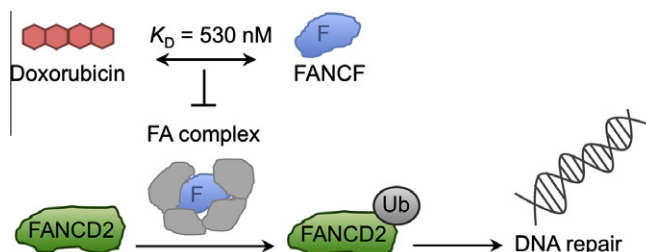


ARTICLES

The antitumor agent doxorubicin binds to Fanconi anemia group F protein

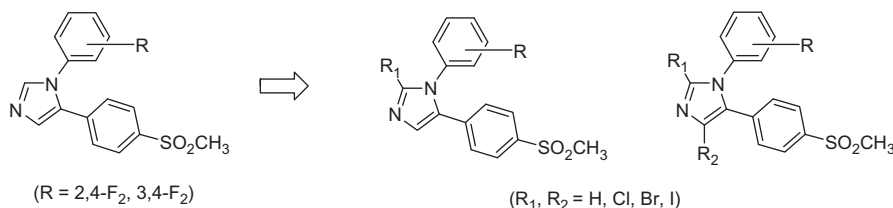
pp 6248–6255

Tomoe Kusayanagi, Senko Tsukuda, Satomi Shimura, Daisuke Manita, Kanako Iwakiri, Shinji Kamisuki, Yoichi Takakusagi, Toshifumi Takeuchi, Kouji Kuramochi, Atsuo Nakazaki, Kengo Sakaguchi, Susumu Kobayashi, Fumio Sugawara*



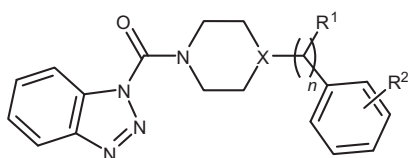
Synthesis of 1,5-diarylhaloimidazole analogs and their inhibitory activities against PGE₂ production from LPS-treated RAW 264.7 cells pp 6256–6259

Zunhua Yang, Tuyen N. Truong, Tuan-Anh N. Pham, Jae-Won Lee, Sung-Soo Kim, Haeil Park*



Development and characterization of endocannabinoid hydrolases FAAH and MAGL inhibitors bearing a benzotriazol-1-yl carboxamide scaffold pp 6260–6275

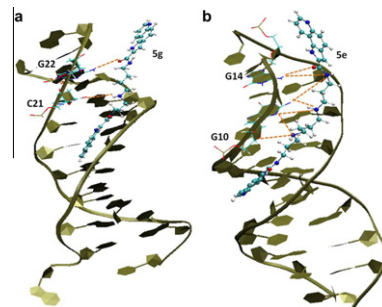
Ludovica Morera*, Geoffray Labar*, Giorgio Ortar, Didier M. Lambert



29 (ML30):	X = N; n = 1; R ¹ = Ph; R ² = H	IC ₅₀ ^{hMAGL} = 0.54 nM; IC ₅₀ ^{hFAAH} = 562 nM
11:	X = CH; n = 1; R ¹ , R ² = H	IC ₅₀ ^{hMAGL} = 3 nM; IC ₅₀ ^{hFAAH} = 2 nM
16:	X = N; n = 1; R ¹ = H; R ² = 3-Cl	IC ₅₀ ^{hMAGL} = 2 nM; IC ₅₀ ^{hFAAH} = 9 nM
31:	X = N; n = 0; R ² = 2-CH ₃	IC ₅₀ ^{hMAGL} = 71 nM; IC ₅₀ ^{hFAAH} = 3 nM
32:	X = N; n = 0; R ² = 2-NO ₂	IC ₅₀ ^{hMAGL} = 224 nM; IC ₅₀ ^{hFAAH} = 19 nM

Conformational analysis of two novel cytotoxic C2-substituted pyrrolo[2,3-f]quinolines in aqueous media, organic solvents, membrane bilayers and at the putative active site pp 6276–6284

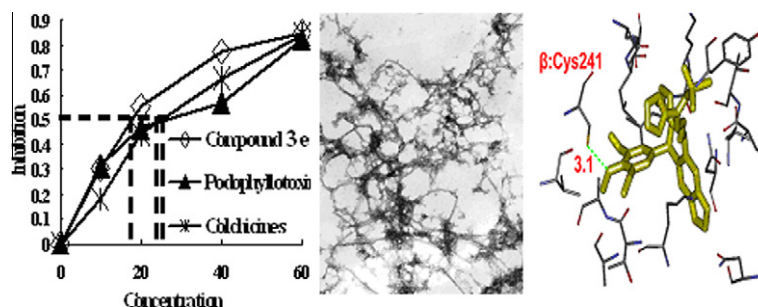
Nicole Varvarigou, Grigorios Megariotis, Georgios Leonis, Eleni Vrontaki, Antigoni-Margarita Maniati, Marilena Vlachou, Aphrodite Eikospentaki, Rodanthi Kompogennitaki, Manthos G. Papadopoulos, Simona Golic Grdadolnik, Dimitri Komiotis, Thomas Mavromoustakos*, Andrew Tsotinis*



Docking of (a) **5g** and (b) **5e** in the crystal DNA sequence 1d64. Principal hydrogen bonding interactions are shown in dotted lines.

Synthesis and biological evaluation of a series of podophyllotoxins derivatives as a class of potent antitubulin agents pp 6285–6295

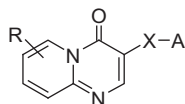
Yingqian Liu, Dongfeng Wei, Yonglong Zhao, Weidong Cheng, Yan Lu, Yaqiong Ma, Xin Li, Chao Han, Yanxia Wei, Huiming Cao, Chunyan Zhao*



Pyrido[1,2-*a*]pyrimidin-4-ones as antiplasmodial falcipain-2 inhibitors

pp 6296–6304

U. R. Mane, H. Li, J. Huang, R. C. Gupta, S. S. Nadkarni, R. Giridhar, P. P. Naik, M. R. Yadav*



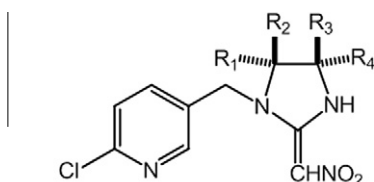
X = Urea, carbamate, amide

A = Alkyl/aryl/heteroaryl

Pyrido[1,2-*a*]pyrimidin-4-ones**Synthesis of imidacloprid derivatives with a chiral alkylated imidazolidine ring and evaluation of their insecticidal activity and affinity to the nicotinic acetylcholine receptor**

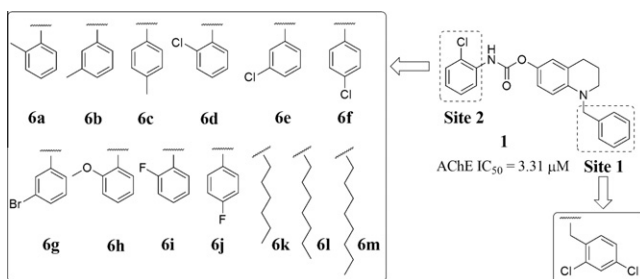
pp 6305–6312

Hisashi Nishiwaki*, Mituhiro Kuriyama, Hikaru Nagaoka, Akira Kato, Miki Akamatsu, Satoshi Yamauchi, Yoshihiro Shuto

R = H, Me, Et, *n*-Pr, isopropyl, and isobutyl**Lead optimization studies towards the discovery of novel carbamates as potent AChE inhibitors for the potential treatment of Alzheimer's disease**

pp 6313–6320

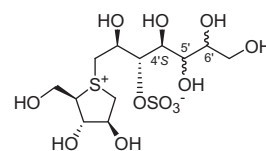
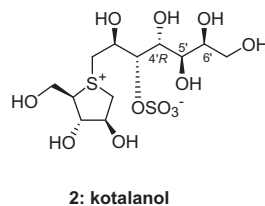
Kuldeep K. Roy, Santoshkumar Tota, Tusha Tripathi, Subhash Chander, Chandishwar Nath, Anil K. Saxena*

**Role of the side chain stereochemistry in the α -glucosidase inhibitory activity of kotalanol, a potent natural α -glucosidase inhibitor. Part 2**

pp 6321–6334

Genzoh Tanabe, Kanjyun Matsuoka, Masahiro Yoshinaga, Weijia Xie*, Nozomi Tsutsui, Mumen F. A. Amer, Shinya Nakamura, Isao Nakanishi, Xiaoming Wu, Masayuki Yoshikawa, Osamu Muraoka*

To examine the role of the side chain of kotalanol (**2**), a potent natural α -glucosidase inhibitor isolated from *Salacia reticulata*, on inhibitory activity, four diastereomers (**11a–11d**) with reversed configuration (*S*) at the C-4' position in the side chain were synthesized and evaluated. Two of the four (**11b** and **11d**) significantly lost their inhibitory activity against both maltase and sucrase, while the other two (**11a** and **11c**) sustained the inhibitory activity to a considerable extent, showing distinct activity in response to the change of stereochemistry of the hydroxyls at the 5' and 6' positions. Different activities were rationalized with reference to in silico docking studies on these inhibitors with hNtMGAM. Against isomaltase, all four analogs showed potent inhibitory activity as well as **2**, and **11b** and **11d** exhibited enzyme selectivity.



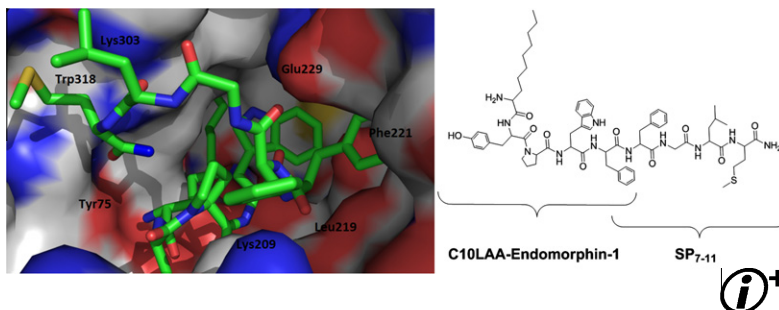
11a : 5' α -OH, 6' α -OH **11b** : 5' β -OH, 6' β -OH
11c : 5' α -OH, 6' β -OH **11d** : 5' β -OH, 6' α -OH

Synthesis, biological activity and structure–activity relationship of endomorphin-1/substance P derivatives

pp 6335–6343

Pegah Varamini, Waleed M. Hussein, Friederike M. Mansfeld, Istvan Toth*

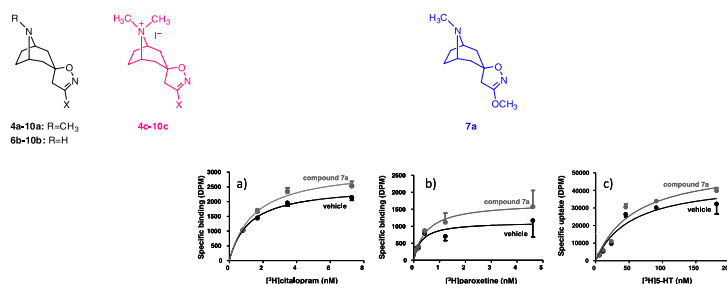
A series of endomorphin-1/substance P (SP) hybrid peptides were synthesized with/without a 10-carbon lipoamino acid (C10LAA) modification. In vitro biological analyses revealed that the C10LAA-modified analogue conjugated with the SP_{7–11} fragment was the most promising derivative. This stable and permeable compound produced potent biological activity at μ -opioid receptors with selectivity over δ -opioid receptors, similar to that of endomorphin-1.



A novel spirocyclic tropanyl- Δ^2 -isoxazoline derivative enhances citalopram and paroxetine binding to serotonin transporters as well as serotonin uptake

pp 6344–6355

Clelia Dallanocce*, Mara Canovi, Carlo Matera, Tiziana Mennini, Marco De Amici, Marco Gobbi, Carlo De Micheli

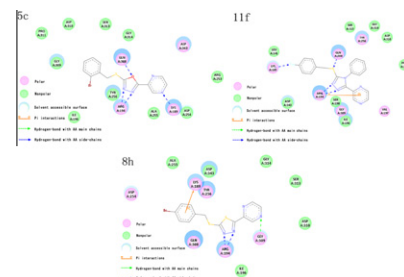


Design, synthesis and biological evaluation of heterocyclic azoles derivatives containing pyrazine moiety as potential telomerase inhibitors

pp 6356–6365

Yan-Bin Zhang, Xiao-Liang Wang, Wen Liu, Yu-Shun Yang, Jian-Feng Tang, Hai-Liang Zhu*

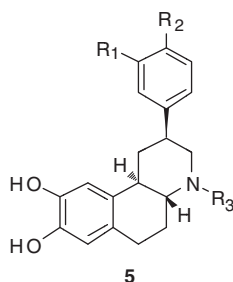
Three series of novel heterocyclic azoles derivatives containing pyrazine (**5a–5k**, **8a–8k** and **11a–11k**) have been designed, synthesized, structurally determined, and their biological activities were evaluated as potential telomerase inhibitors. Among the oxadiazole derivatives, compound **5c** showed the most potent biological activity against SW1116 cancer cell line (IC_{50} = 2.46 μ M against SW1116 and IC_{50} = 3.55 μ M for telomerase). Compound **8h** performed the best in the thiadiazole derivatives (IC_{50} = 0.78 μ M against HEPG2 and IC_{50} = 1.24 μ M for telomerase), which was comparable to the positive control. While compound **11f** showed the most potent biological activity (IC_{50} = 4.12 μ M against SW1116 and IC_{50} = 15.03 μ M for telomerase) among the triazole derivatives. Docking simulation by positioning compounds **5c**, **8h** and **11f** into the telomerase structure active site was performed to explore the possible binding model. The results of apoptosis demonstrated that compound **8h** possessed good antitumor activity against HEPG2 cancer cell line. Therefore, compound **8h** with potent inhibitory activity in tumor growth inhibition may be a potential antitumor agent against HEPG2 cancer cell. Therefore, the introduction of oxadiazole, thiadiazole and triazole structures reinforced the combination of our compounds and the receptor, resulting in progress of bioactivity.



Identification of a 2-phenyl-substituted octahydrobenzo[f]quinoline as a dopamine D₃ receptor-selective full agonist ligand

pp 6366–6374

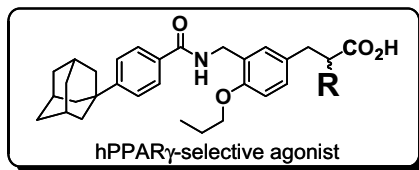
Alia H. Clark, John D. McCorvy, Jason M. Conley, Whitney K. Williams, Markondaiah Bekkam, Val J. Watts, David E. Nichols*



Design, synthesis and in vitro evaluation of a series of α -substituted phenylpropanoic acid PPAR γ agonists to further investigate the stereochemistry–activity relationship pp 6375–6383

Masao Ohashi, Izumi Nakagome, Jun-ichi Kasuga, Hiromi Nobusada, Kenji Matsuno, Makoto Makishima, Shuichi Hirono, Yuichi Hashimoto, Hiroyuki Miyachi*

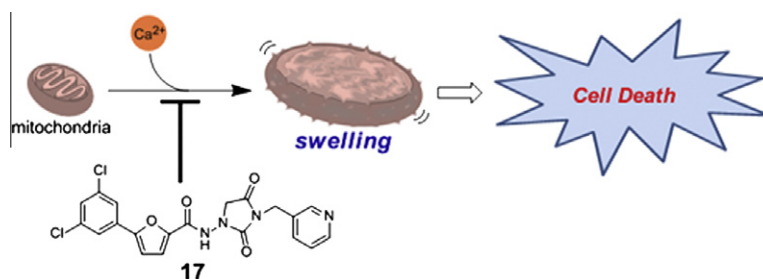
(S)-form more potent (R=ethyl, phenethyl) !



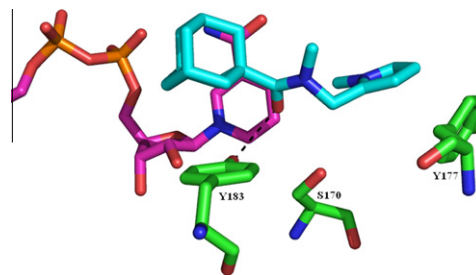
(R)-form more potent (R=benzyl, cyclohexylmethyl) !

Small-molecular inhibitors of Ca²⁺-induced mitochondrial permeability transition (MPT) derived from muscle relaxant dantrolene pp 6384–6393

Shinpei Murasawa, Katsuya Iuchi, Shinichi Sato, Tomomi Noguchi-Yachide, Mikiko Sodeoka, Tsutomu Yokomatsu, Kosuke Dodo*, Yuichi Hashimoto, Hiroshi Aoyama*


Adamantyl carboxamides and acetamides as potent human 11 β -hydroxysteroid dehydrogenase type 1 inhibitors pp 6394–6402

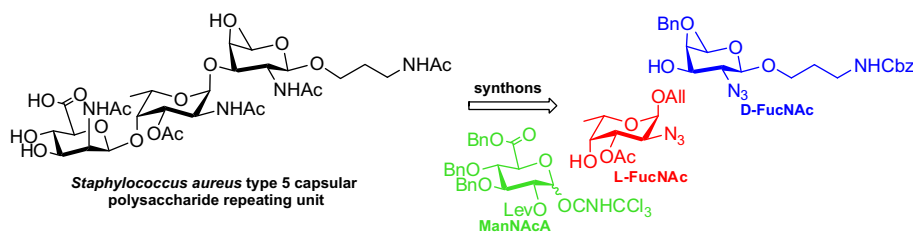
Xiangdong Su, Heather A. Halem, Mark P. Thomas, Cecile Moutrille, Michael D. Culler, Nigel Vicker, Barry V. L. Potter*



Series of adamantyl carboxamide and acetamide derivatives were identified, providing potent and selective inhibitors of the therapeutic target human 11 β -hydroxysteroid dehydrogenase type 1.

Synthesis of *Staphylococcus aureus* type 5 capsular polysaccharide repeating unit using novel L-FucNAc and D-FucNAc synthons and immunochemical evaluation pp 6403–6415

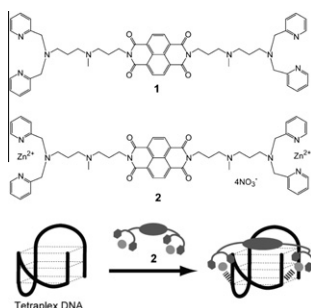
Elisa Danieli, Daniela Proietti, Giulia Brogioni, Maria R. Romano, Emilia Cappelletti, Marta Tontini, Francesco Berti, Luigi Lay, Paolo Costantino, Roberto Adamo*



Improving the affinity of naphthalene diimide ligand to telomeric DNA by incorporating Zn²⁺ ions into its dipicolylamine groups

pp 6416–6422

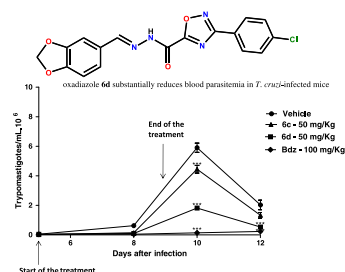
Izabella Czerwinska, Shinobu Sato, Shigeori Takenaka*



Optimization of anti-*Trypanosoma cruzi* oxadiazoles leads to identification of compounds with efficacy in infected mice

pp 6423–6433

José Maurício dos Santos Filho*, Diogo Rodrigo M. Moreira, Carlos Alberto de Simone, Rafaela Salgado Ferreira, James H. McKerrow, Cássio Santana Meira, Elisalva Teixeira Guimarães, Milena Botelho Pereira Soares



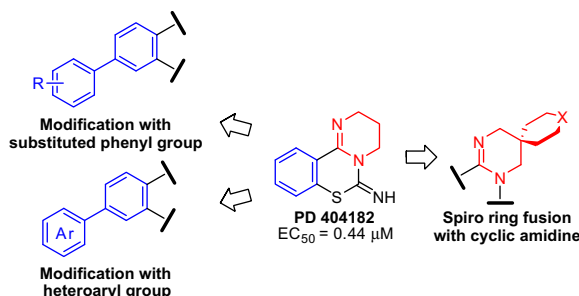
Oxadiazole **6d** substantially reduces blood parasitemia in *Trypanosoma cruzi*-infected mice.



Structure–activity relationship study of pyrimido[1,2-*c*][1,3]benzothiazin-6-imine derivatives for potent anti-HIV agents

pp 6434–6441

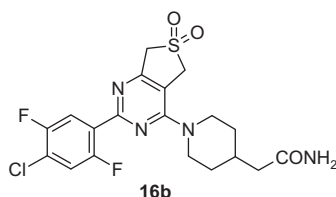
Tsukasa Mizuhara, Shinya Oishi*, Hiroaki Ohno, Kazuya Shimura, Masao Matsuoka, Nobutaka Fujii*



Synthesis and structure–activity relationship of fused-pyrimidine derivatives as a series of novel GPR119 agonists

pp 6442–6451

Kenji Negoro*, Yasuhiro Yonetoku, Ayako Moritomo, Masahiko Hayakawa, Kazuhiko Iikubo, Shigeru Yoshida, Makoto Takeuchi, Mitsuaki Ohta

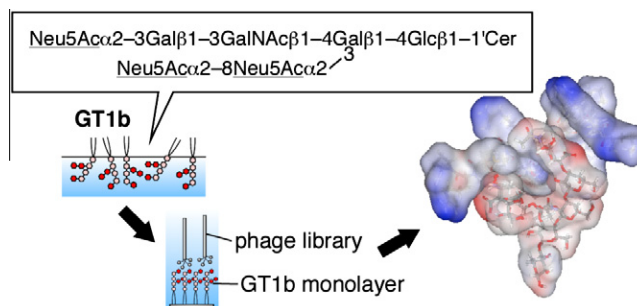


A series of fused-pyrimidine derivatives have been discovered as potent and orally active GPR119 agonists. 2-[1-[2-(4-Chloro-2,5-difluorophenyl)-6,6-dioxido-5,7-dihydrothieno[3,4-*d*]pyrimidin-4-yl]piperidin-4-yl]acetamide (**16b**) was found to have extremely potent GPR119 agonistic activity and improved glucose tolerance at 0.1 mg/kg po in mice.

Carbohydrate recognition by pentadecapeptide ligands for a series of sialylated oligosaccharides

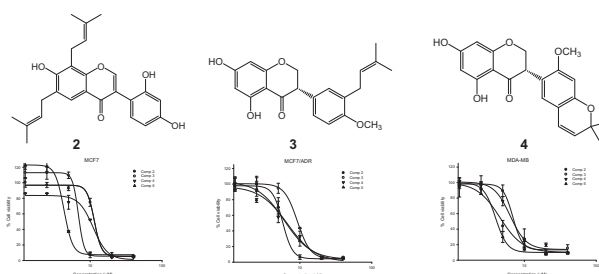
pp 6452–6458

Teruhiko Matsubara, Ai Onishi, Toshinori Sato*

**New prenylated isoflavonoids as protein tyrosine phosphatase 1B (PTP1B) inhibitors from *Erythrina addisoniae***

pp 6459–6464

Phi Hung Nguyen, Govinda Sharma, Trong Tuan Dao, Mohammad Nasir Uddin, Keon Wook Kang, Derek Tantoh Ndinteh, Joseph Tanyi Mbafor, Won Keun Oh*

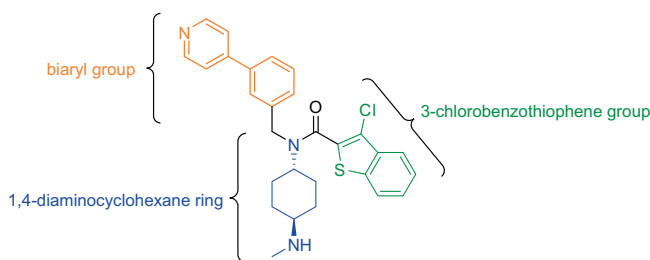


Four new (**1–4**) along with 2 known prenylated isoflavonoids (**5–6**) were isolated from an EtOAc extract of the root of *Erythrina addisoniae*. All the isolates were evaluated for their inhibitory effects on protein tyrosine phosphatase 1B (PTP1B), as well as their growth inhibition on MCF7, adriamycin-resistant MCF7 (MCF7/ADR), and MDA-MB-231 breast cancer cell lines. Compounds which exhibited PTP1B inhibitory activity (IC_{50} values ranging from 4.6 ± 0.3 to $24.2 \pm 2.1 \mu M$) showed potential cytotoxic activity (IC_{50} values ranging from 3.97 ± 0.17 to $11.4 \pm 1.9 \mu M$).

**Potent small molecule Hedgehog agonists induce VEGF expression in vitro**

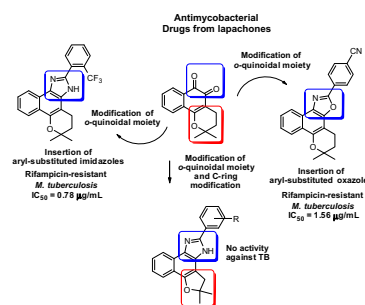
pp 6465–6481

Katrin Seifert, Anita Büttner, Stephan Rigol, Nicole Eilert, Elke Wandel, Athanassios Giannis*

**1,3-Azoles from *ortho*-naphthoquinones: Synthesis of aryl substituted imidazoles and oxazoles and their potent activity against *Mycobacterium tuberculosis***

pp 6482–6488

Kelly C. G. Moura, Paula F. Carneiro, Maria do Carmo F. R. Pinto, José A. da Silva, Valéria R. S. Malta, Carlos A. de Simone, Gleiston G. Dias, Guilherme A. M. Jardim, Jéssica Cantos, Tatiane S. Coelho, Pedro E. Almeida da Silva*, Eufânio N. da Silva Jr.*

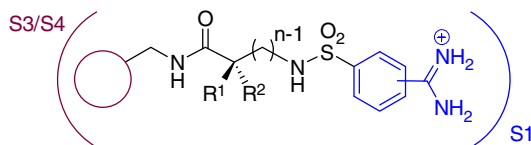


Twenty-three naphthoimidazoles and six naphthoxazoles were synthesised and evaluated against susceptible and rifampicin- and isoniazid-resistant strains of *Mycobacterium tuberculosis*. Among all the compounds evaluated, fourteen presented MIC values in the range of 0.78 to 6.25 $\mu g/mL$ against susceptible and resistant strains of *M. tuberculosis*. Five structures were solved by X-ray crystallographic analysis. These substances are promising antimycobacterial prototypes.

Active site mapping of trypsin, thrombin and matriptase-2 by sulfamoyl benzamidines

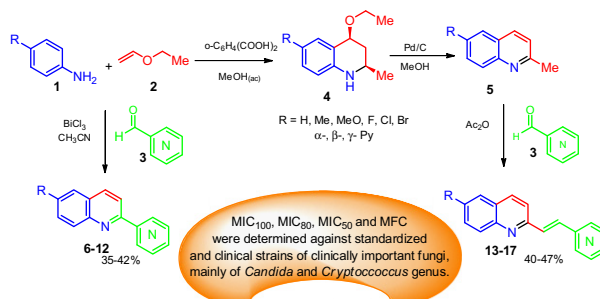
pp 6489–6505

Stefan Dosa, Marit Stirnberg, Verena Lülldorff, Daniela Häußler, Eva Maurer, Michael Gütschow*

**Synthesis and antifungal activity of diverse C-2 pyridinyl and pyridinylvinyl substituted quinolines**

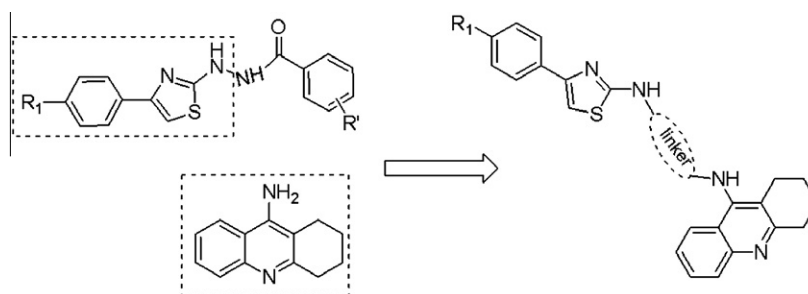
pp 6506–6512

Vladimir V. Kouznetsov*, Carlos M. Meléndez Gómez, Marcos G. Derita, Laura Svetaz, Esther del Olmo, Susana A. Zacchino

**Novel multipotent phenylthiazole–tacrine hybrids for the inhibition of cholinesterase activity, β -amyloid aggregation and Ca^{2+} overload**

pp 6513–6522

Yue Wang, Fang Wang, Jun-Ping Yu, Feng-Chao Jiang, Xin-Lei Guan, Can-Ming Wang, Lei Li, Hui Cao, Ming-Xing Li, Jian-Guo Chen*

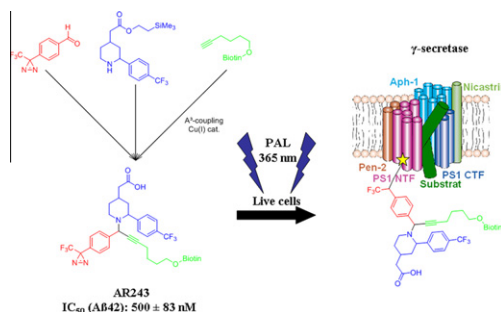


A series of novel multifunctional compounds were designed and synthesized by conjugating tacrine with 4-phenyl-2-aminothiazole group through different middle linkers. These novel hybrids can inhibit cholinesterase activity, $\text{A}\beta$ self-aggregation and intracellular Ca^{2+} overload.

Synthesis of a potent photoreactive acidic γ -secretase modulator for target identification in cells

pp 6523–6532

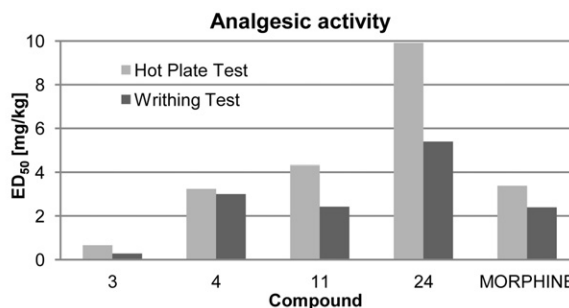
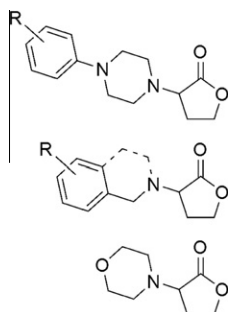
Andreas Rennhack, Thorsten Jumpertz, Julia Ness, Sandra Baches, Claus U. Pietrzik, Sascha Weggen*, Bruno Bulic*



Search for anticonvulsant and analgesic active derivatives of dihydrofuran-2(3H)-one

pp 6533–6544

Krzysztof Więckowski, Kinga Sałat, Justyna Bytnar, Marek Bajda, Barbara Filipek, James P. Stables, Barbara Malawska*



OTHER CONTENTS

Bioorganic & Medicinal Chemistry Reviews and Perspectives

pp I–III

*Corresponding author

Supplementary data available via SciVerse ScienceDirect

COVER

The paper describes the development of a new, potent and non-toxic hedgehog pathway agonist. Compound **10c** proved to stimulate VEGF production in vitro. The hedgehog pathway is involved in the pathogenesis of several diseases including a malformation called Cyclopia (the island in the background shows the putative island of Cyclops in the Aegean Sea). [Seifert, K.; Büttner, A.; Rigol, S.; Eilert, N.; Wandel, E.; Giannis, A. *Bioorg. Med. Chem.* **2012**, 20, 6465–6481.]

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