



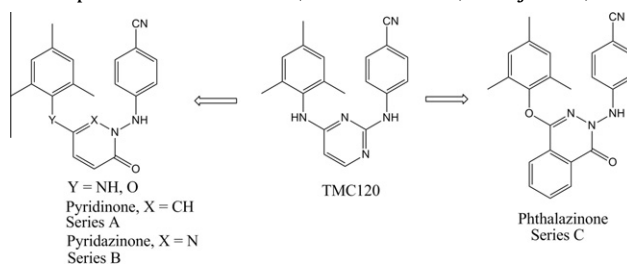
Bioorganic & Medicinal Chemistry Volume 19, Issue 20, 2011

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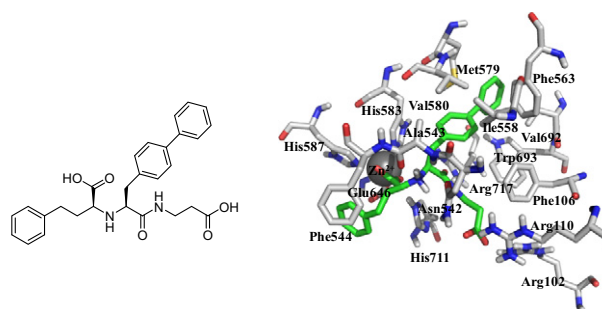
Novel diarylpyridinones, diarylpyridazinones and diarylphthalazinones as potential HIV-1 nonnucleoside reverse transcriptase inhibitors (NNRTIs) pp 5924–5934

Muthusamy Venkatraj, Kevin K. Ariën, Jan Heeres, Bertrand Diré, Jurgen Joossens, Sebastiaan Van Goethem, Pieter Van der Veken, Johan Michiels, Christophe M. L. Vande Velde, Guido Vanham, Paul J. Lewi, Koen Augustyns*



Structure-based design of dipeptide derivatives for the human neutral endopeptidase pp 5935–5947

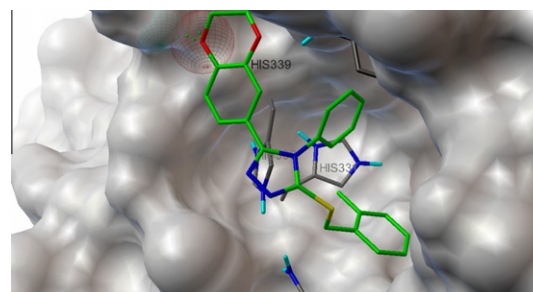
Kensuke Misawa*, Yasuto Suzuki, Satoshi Takahashi, Atsushi Yoshimori, Ryoko Takasawa, Yusuke Shibuya, Sei-ichi Tanuma



Synthesis and antitumor activity of 1,2,4-triazoles having 1,4-benzodioxan fragment as a novel class of potent methionine aminopeptidase type II inhibitors pp 5948–5954

Ya-Ping Hou, Juan Sun, Zhong-Hua Pang, Peng-Cheng Lv, Dong-Dong Li, Li Yan, Hong-Jia Zhang, Emily Xi Zheng*, Jing Zhao*, Hai-Liang Zhu*

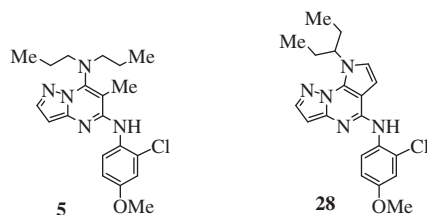
A series of 1,2,4-triazole derivatives containing 1,4-benzodioxan (**5a–5q**) have been designed, synthesized, structurally determined, and their biological activities were evaluated as potential MetAP2 inhibitors. All the synthesized compounds were first reported. Among the compounds, compound **5k** showed the most potent biological activity against HEPG2 cancer cell line ($IC_{50} = 0.81 \mu M$ for HEPG2 and $IC_{50} = 0.93 \mu M$ for MetAP2), which was comparable to the positive control. Docking simulation by positioning compound **5k** into the MetAP2 structure active site was performed to explore the possible binding model. The results of apoptosis and Western-blot assay demonstrated that compound **5k** possessed good antitumor activity against HEPG2 cancer cell line. Therefore, compound **5k** with potent inhibitory activity in tumor growth inhibition may be a potential antitumor agent against HEPG2 cancer cell.



Pyrazolo[1,5-*a*]pyrimidines, triazolo[1,5-*a*]pyrimidines and their tricyclic derivatives as corticotropin-releasing factor 1 (CRF₁) receptor antagonists

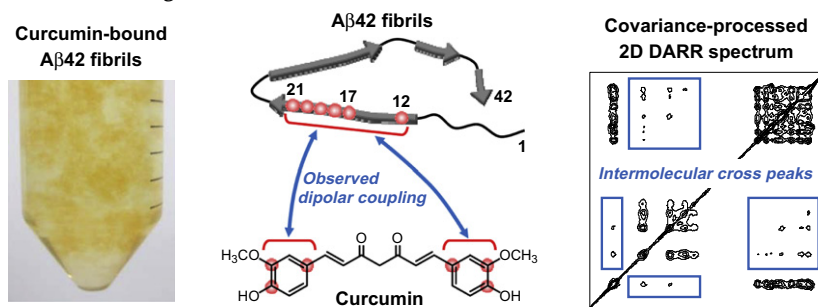
pp 5955–5966

Tetsuji Saito*, Tetsuo Obitsu, Chiaki Minamoto, Tsuneyuki Sugiura, Naoya Matsumura, Sonoko Ueno, Akihiro Kishi, Seishi Katsumata, Hisao Nakai, Masaaki Toda


Solid-state NMR analysis of interaction sites of curcumin and 42-residue amyloid β -protein fibrils

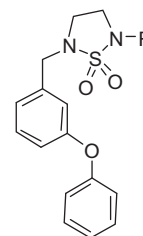
pp 5967–5974

Yuichi Masuda*, Masashi Fukuchi, Tatsuya Yatawaga, Masato Tada, Kazuyuki Takeda, Kazuhiro Irie, Ken-ichi Akagi, Youko Monobe, Takayoshi Imazawa, K. Takegoshi


Potent inhibition of Norwalk virus by cyclic sulfamide derivatives

pp 5975–5983

Dengfeng Dou, Kok-Chuan Tiew, Guijia He, Sivakoteswara Rao Mandadapu, Sridhar Aravapalli, Kevin R. Alliston, Yunjeong Kim, Kyeong-Ok Chang, William C. Groutas*



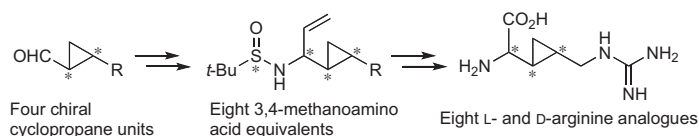
A new class of compounds that exhibit anti-norovirus activity in a cell-based system and embody in their structure a cyclosulfamide scaffold, has been identified. The structure of the initial hit (compound **2a** (structure (I) where R = H), ED₅₀ 4 μ M, TD₅₀ 50 μ M) has been prospected by exploiting multiple points of diversity and generating appropriate structure–activity relationships.

(I) (R=H, ED₅₀: 4 μ M
TD₅₀: 50 μ M)

Synthesis of a series of 3,4-methanoarginines as side-chain conformationally restricted analogues of arginine

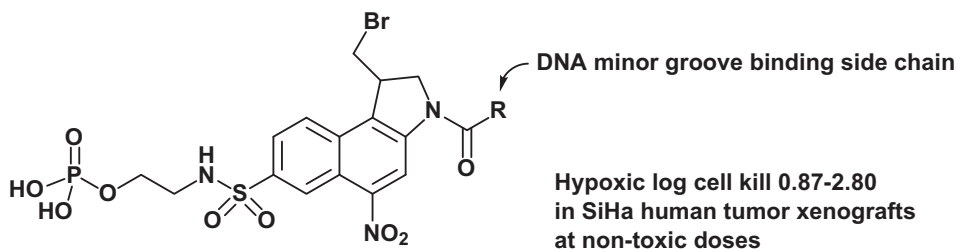
pp 5984–5988

Mizuki Watanabe, Kazuya Yamaguchi, Wei Tang, Keisuke Yoshida, Richard B. Silverman, Mitsuhiro Arisawa, Satoshi Shuto*



The effect of a bromide leaving group on the properties of nitro analogs of the duocarmycins as hypoxia-activated prodrugs and phosphate pre-prodrugs for antitumor therapy pp 5989–5998

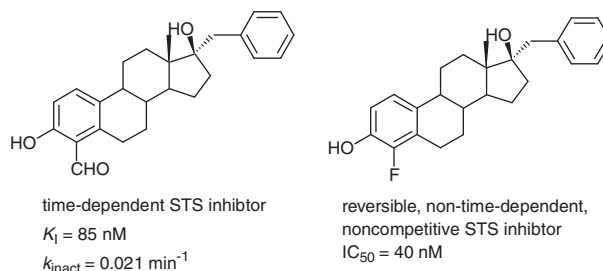
Ralph J. Stevenson*, William A. Denny, Amir Ashoorzadeh, Frederik B. Puijn, Wouter F. van Leeuwen, Moana Tercel



Hypoxic log cell kill 0.87–2.80 in SiHa human tumor xenografts at non-toxic doses.

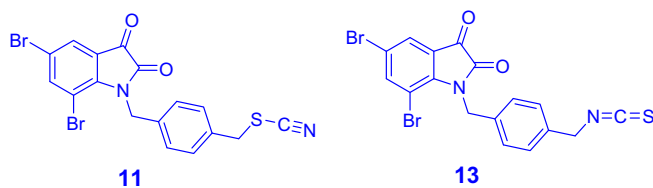
Inhibition of steroid sulfatase with 4-substituted estrone and estradiol derivatives pp 5999–6005

Chau-Minh Phan, Yong Liu, Byoung-moo Kim, Yaser Mostafa, Scott D. Taylor*



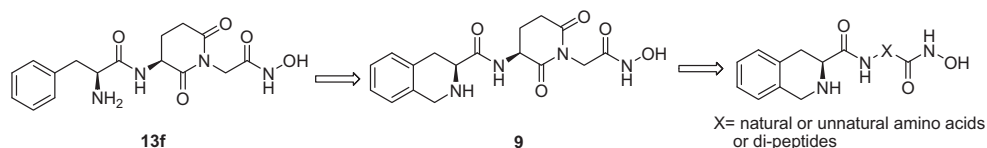
Synthesis and biological evaluation of a novel class of isatin analogs as dual inhibitors of tubulin polymerization and Akt pathway pp 6006–6014

Gowdahalli Krishnegowda*, A. S. Prakasha Gowda, Hephzibah Rani S. Tagaram, Kevin F. Staveley-O' Carroll, Rosalyn B. Irby, Arun K. Sharma, Shantu Amin



Design, synthesis and biological evaluation of novel 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives as aminopeptidase N/CD13 inhibitors pp 6015–6025

Xiaopan Zhang, Jian Zhang, Lei Zhang, Jinghong Feng, Yingying Xu, Yumei Yuan, Hao Fang, Wenfang Xu*

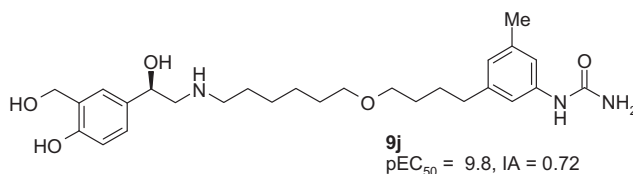


Novel 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives were designed and synthesized as APN inhibitors. Compound **12h** had the best APN inhibition in vitro with the IC_{50} value to $6.28 \pm 0.11 \text{ } \mu\text{M}$, which is similar with that of Bestatin ($\text{IC}_{50} = 5.55 \pm 0.01 \text{ } \mu\text{M}$).

The discovery of long-acting saligenin β_2 adrenergic receptor agonists incorporating a urea group

pp 6026–6032

Panayiotis A. Procopiou*, Victoria J. Barrett, Alison J. Ford, Brian E. Looker, Gillian E. Lunniss, Deborah Needham, Claire E. Smith, Graham Somers

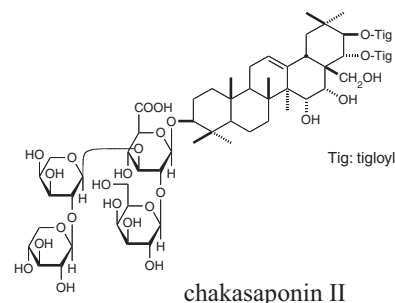


Anti-obesity effects of the methanolic extract and chakasaponins from the flower buds of *Camellia sinensis* in mice

pp 6033–6041

Makoto Hamao, Hisashi Matsuda, Seikou Nakamura, Souichi Nakashima, Shunsuke Semura, Saori Maekubo, Sachiyo Wakasugi, Masayuki Yoshikawa*

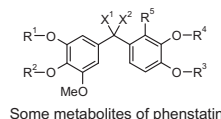
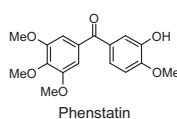
The methanolic extract from the flower buds of *Camellia sinensis* showed inhibitory effects on body weight gain and the weight of visceral fats in high-fat diet-fed mice and/or Tsumura Suzuki Obese Diabetic (TSOD) mice. A suppressive effect of the extract on food intake was suggested to contribute to the anti-obesity effect. The *n*-butanol-soluble fraction and a principal constituent, chakasaponin II, inhibited food intake. These inhibitory effects were reduced by pretreatment with a high dose of capsaicin. The *n*-BuOH-soluble fraction and chakasaponin II suppressed mRNA levels of neuropeptide Y in the hypothalamus. Furthermore, chakasaponin II enhanced the release of serotonin (5-HT) from the isolated ilea of mice *in vitro*.



Synthesis and biological evaluation of phenstatin metabolites

pp 6042–6054

Alina Ghinet, Benoît Rigo*, Jean-Pierre Hénichart, Delphine Le Broc-Ryckewaert, Jean Pommery, Nicole Pommery, Xavier Thuru, Bruno Quesnel, Philippe Gautret



- 20** R¹ = R² = R³ = R⁴ = Me, R⁵ = H, X¹, X² = O
23 R¹ = R² = R³ = Me, R⁴ = H, R⁵ = OMe, X¹, X² = O
21 R¹ = R³ = R⁴ = Me, R² = R⁵ = H, X¹, X² = O
25 R¹ = R³ = Me, R² = R⁴ = R⁵ = H, X¹, X² = O
22 R¹ = R³ = Me, R² = R⁴ = H, R⁵ = OMe, X¹, X² = O
24 R¹ = R⁴ = R⁵ = H, R² = R³ = Me, X¹, X² = O
27 R¹ = R² = R³ = R⁴ = Me, R⁵ = X¹ = H, X² = OH
26 R¹ = R² = R³ = Me, R⁴ = R⁵ = X¹ = H, X² = OH

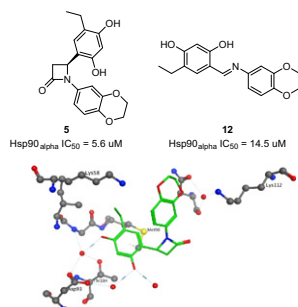
Previous investigations on the incubation of phenstatin with rat and human microsomal fractions revealed the formation of nine main metabolites. The structures of eight of these metabolites have been now confirmed by synthesis and their biological properties have been reported. Eaton's reagent was utilized as a convenient condensing agent, allowing, among others, a simple multigram scale preparation of phenstatin. Synthesized metabolites and related compounds were evaluated for their antiproliferative activity in the NCI-60 cancer cell line panel, and for their effect on microtubule assembly. Metabolite **23** (2'-methoxyphenstatin) exhibited the most potent *in vitro* cytotoxic activity: inhibition of the growth of K-562, NCI-H322M, NCI-H522, KM12, M14, MDA-MB-435, NCI/ADR-RES, and HS 578T cell lines with GI₅₀ values <10 nM. It also showed more significant tubulin polymerization inhibitory activity than parent phenstatin (**3**) (IC₅₀ = 3.2 μM vs 15.0 μM) and induced G2/M arrest in murine leukemia DA1-3b cells. The identification of this active metabolite led to the design and synthesis of analogs with potent *in vitro* cytotoxicity and inhibition of microtubule assembly.



Lead identification of β -lactam and related imine inhibitors of the molecular chaperone heat shock protein 90

pp 6055–6068

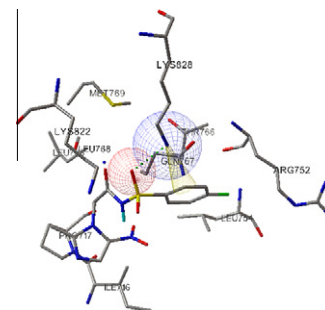
Niamh M. O'Boyle*, Andrew J. S. Knox, Trevor T. Price, D. Clive Williams, Daniela M. Zisterer, David G. Lloyd, Mary J. Meegan*



Metronidazole acid acyl sulfonamide: A novel class of anticancer agents and potential EGFR tyrosine kinase inhibitors

pp 6069–6076

Yin Luo, Yao Li, Ke-Ming Qiu, Xiang Lu, Jie Fu, Hai-Liang Zhu*

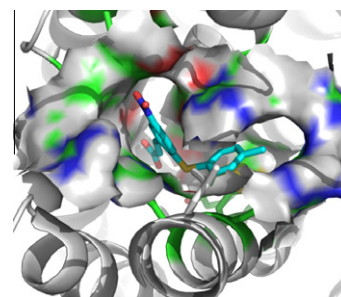


Two series of benzenesulfonamide derivatives have been designed and synthesized, and their biological activities were also evaluated for EGFR inhibitory activity. Compound **12** possessed the most potent enzyme inhibition activities ($IC_{50} = 0.39 \mu\text{M}$ for EGFR and $IC_{50} = 1.53 \mu\text{M}$ for HER-2) and anticancer activities ($IC_{50} = 1.26 \mu\text{g/mL}$ for A549 and $IC_{50} = 0.35 \mu\text{g/mL}$ for B16-F10). Docking simulation was performed to explore the binding model of compound **12** with EGFR.

Novel human mPGES-1 inhibitors identified through structure-based virtual screening

pp 6077–6086

Adel Hamza, Xinyun Zhao, Min Tong, Hsin-Hsiung Tai, Chang-Guo Zhan*



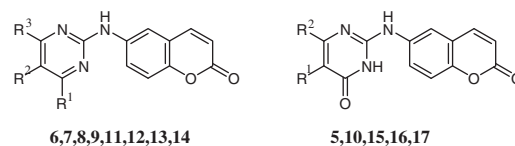
The combined structure-based virtual screening and in vitro experimental studies have led to identification of novel inhibitors of human mPGES-1 with new scaffolds.



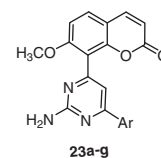
Design, synthesis and vasorelaxant evaluation of novel coumarin–pyrimidine hybrids

pp 6087–6097

Kamilia M. Amin, Fadi M. Awadalla, Amal A. M. Eissa*, Sahar M. Abou-Seri, Ghaneya S. Hassan



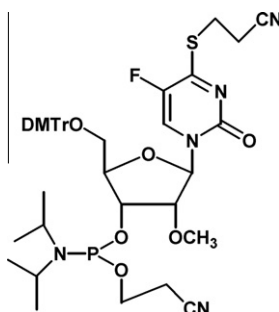
The main objective of the present work depends on the hybridization of coumarin moiety as a vasorelaxant scaffold and pyrimidine ring with known potential cardiovascular activity in order to prepare some new potent antihypertensive candidates. Hence, a variety of coumarin derivatives cross-bred with pyrimidine and/or dihydropyrimidine moieties were synthesized **5–17** and **23a–g**. All the newly synthesized compounds were evaluated for their vasorelaxant efficacy using the isolated thoracic aortic rings standard procedure. Quantitative structure–activity relationship (QSAR) investigation with 2D-QSAR analysis was applied.



5-Fluoro-4-thiouridine phosphoramidite: New synthon for introducing photoaffinity label into oligodeoxynucleotides

pp 6098–6106

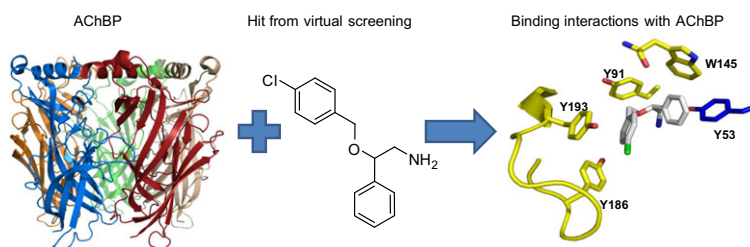
Jan Milecki*, Joanna Nowak, Bohdan Skalski, Stefan Franzen



Acetylcholine binding protein (AChBP) as template for hierarchical in silico screening procedures to identify structurally novel ligands for the nicotinic receptors

pp 6107–6119

Atilla Akdemir, Prakash Rucktooa, Aldo Jongejan, Rene van Elk, Sonia Bertrand, Titia K. Sixma, Daniel Bertrand, August B. Smit, Rob Leurs, Chris de Graaf, Iwan J. P. de Esch*

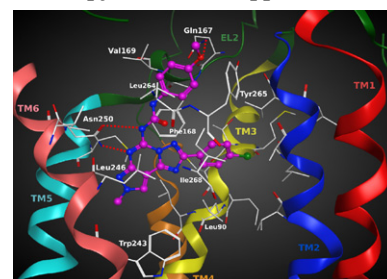
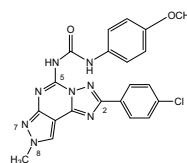


Does the combination of optimal substitutions at the C²-, N⁵- and N⁸-positions of the pyrazolo-triazolo-pyrimidine scaffold guarantee selective modulation of the human A₃ adenosine receptors?

pp 6120–6134

Siew Lee Cheong, Anton V. Dolzhenko, Silvia Paoletta, Evelyn Pei Rong Lee, Sonja Kachler, Stephanie Federico, Karl-Norbert Klotz, Anna V. Dolzhenko, Giampiero Spalluto*, Stefano Moro*, Giorgia Pastorin*

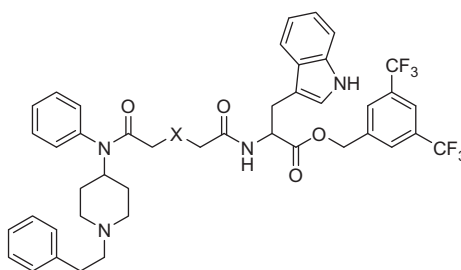
Among the newly synthesized 2-(substituted)phenyl-pyrazolo-triazolo-pyrimidine derivatives bearing optimal substitutions at the C²-, N⁵- and N⁸-positions, the compound with a 4-chlorophenyl at C², a small methyl group at N⁸ and a 4-methoxyphenylcarbamoyl chain at N⁵ showed the best hA₃AR profile, as demonstrated by both pharmacological data and molecular modeling investigations.



Synthesis and biological evaluation of new opioid agonist and neurokinin-1 antagonist bivalent ligands

pp 6135–6142

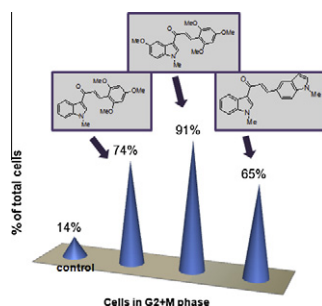
Ruben Vardanyan*, Vlad K. Kumirov, Gary S. Nichol, Peg Davis, Erika Liktov-Busa, David Rankin, Eva Varga, Todd Vanderah, Frank Porreca, Josephine Lai, Victor J. Hruby



Structural requirement of arylindolylpropenones as anti-bladder carcinoma cells agents

pp 6143–6148

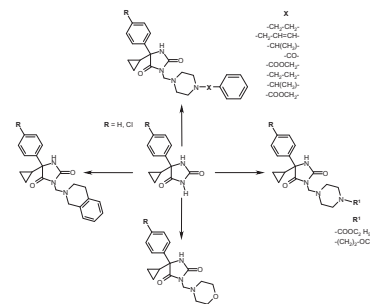
Véronique Martel-Frchet*, Malika Kadri, Ahcène Boumendjel, Xavier Ronot



Synthesis and anticonvulsant activity of new *N*-Mannich bases derived from 5-cyclopropyl-5-phenyl- and 5-cyclopropyl-5-(4-chlorophenyl)-imidazolidine-2,4-diones

pp 6149–6156

Hanna Byrtus, Jolanta Obniska*, Anna Czopek, Krzysztof Kamiński, Maciej Pawłowski



The library of new *N*-Mannich bases derived from 5-cyclopropyl-5-phenyl- and 5-cyclopropyl-5-(4-chlorophenyl)-imidazolidine-2,4-diones have been synthesized. The in vivo results showed that all of compounds were effective in maximal electroshock test (MES).

*Corresponding author

Supplementary data available via SciVerse 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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