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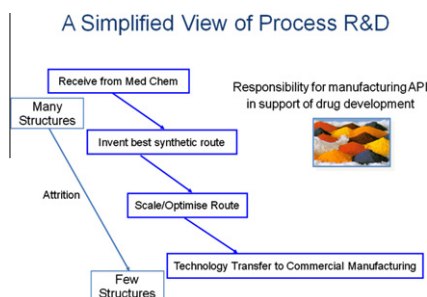
Contents

REVIEW

Process R&D under the magnifying glass: Organization, business model, challenges, and scientific context

pp 5775–5794

Hans-Jürgen Federsele*

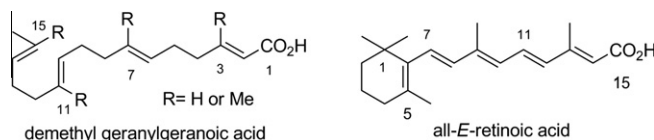


ARTICLES

Efficient synthesis and biological evaluation of demethyl geranylgeranoic acid derivatives

pp 5795–5806

Akimori Wada*, Fei Wang, Yoshitomo Suhara, Yumiko Yamano, Takashi Okitsu, Kimie Nakagawa, Toshio Okano

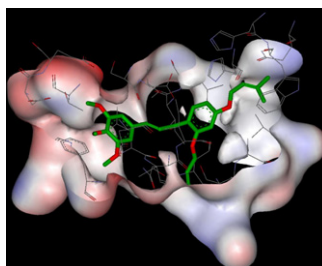


Monodemethylated geranylgeranoic acids were prepared as acyclic retinoid analogs, and evaluated their biological activities. Among the analogs, 3-demethyl derivative exhibited the highest anti-proliferative activity and apoptosis-inducing activity.

Design, synthesis, and biological evaluation of prenylated chalcones as 5-LOX inhibitors

pp 5807–5815

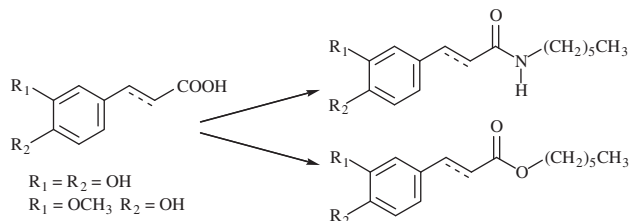
Nimmanapalli P. Reddy, Polamarasetty Aparoy, T. Chandra Mohan Reddy, Chandrani Achari, P. Ramu Sridhar, Pallu Reddanna*



In this study, a series of 10 novel mono- and di-O-prenylated chalcone derivatives were designed, synthesized, and screened for their in vitro 5-LOX inhibition activity and anti-proliferative activity.

Lipophilic phenolic antioxidants: Correlation between antioxidant profile, partition coefficients and redox properties pp 5816–5825

Fernanda M. F. Roleira*, Christophe Siquet, Elizabetha Orrù, E. Manuela Garrido, Jorge Garrido, Nuno Milhazes, Gianni Podda, Fátima Paiva-Martins, Salette Reis, Rui A. Carvalho, Elisiário J. Tavares da Silva, Fernanda Borges*

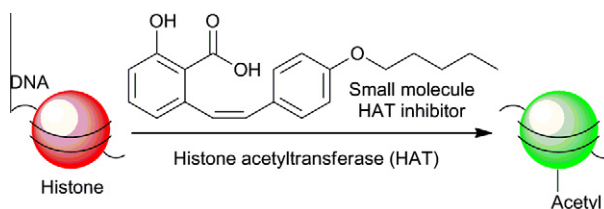


Lipophilic derivatives of cinnamic and hydrocinnamic acids have been prepared. The structure–property–activity relationship data revealed a correlation between the redox potentials and the antioxidant activity. Some compounds showed to have a proper lipophilicity to cross BBB.

Improved inhibition of the histone acetyltransferase PCAF by an anacardic acid derivative

pp 5826–5834

Massimo Ghizzoni, André Boltjes, Chris de Graaf, Hidde J. Haisma, Frank J. Dekker*



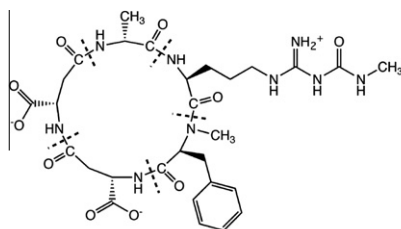
Histone acetyltransferases (HATs) are potential novel drug targets for treatment of inflammation. We present the development of salicylate derivative **6d**, which is a twofold improved inhibitor of PCAF HAT activity and histone acetylation in HEP G2 cells.

**NMR spectroscopy and computational analysis of interaction between *Serratia marcescens* chitinase B and a dipeptide derived from natural-product cyclopentapeptide chitinase inhibitor argifin**

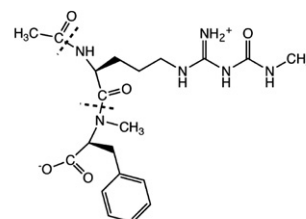
pp 5835–5844

Hiroaki Gouda*, Toshiaki Sunazuka, Tomoyasu Hirose, Kanami Iguchi, Noriyuki Yamaotsu, Akihiro Sugawara, Yoshihiko Noguchi, Yoshifumi Saito, Tsuyoshi Yamamoto, Takeshi Watanabe, Kazuro Shiomi, Satoshi Ōmura, Shuichi Hirono

The structural and energetic bases for **2** to possess potent inhibitory activity compared with **1** were explored.



Argifin (**1**) $\text{IC}_{50} = 6.4 \mu\text{M}$

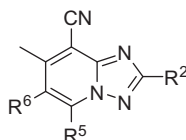


N-Acetyl-Arg{*N*⁰-(*N*-methylcarbamoyl)}-*N*-methyl-Phe (**2**) $\text{IC}_{50} = 3.7 \mu\text{M}$

**Novel antifungal agents: Triazolopyridines as inhibitors of β -1,6-glucan synthesis**

pp 5845–5854

Jun-ichi Kuroyanagi*, Kazuo Kanai, Yuuichi Sugimoto, Tetsunori Fujisawa, Chikanori Morita, Takashi Suzuki, Katsuhiro Kawakami, Makoto Takemura

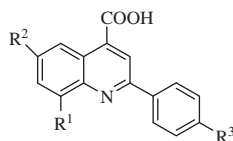


Triazolopyridine was discovered as a promising scaffold for novel antifungal agents, inhibiting β -1,6-glucan synthesis.

Design, synthesis, and biological evaluation of ketoprofen analogs as potent cyclooxygenase-2 inhibitors

pp 5855–5860

Afshin Zarghi*, Razieh Ghodsi



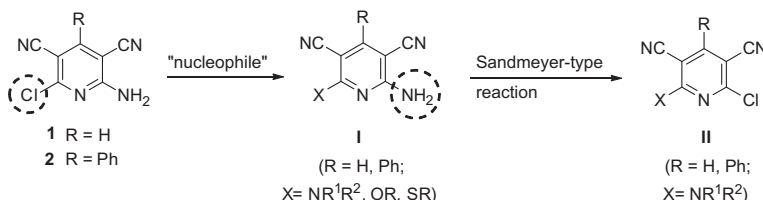
A new series of ketoprofen analogs were synthesized to evaluate their biological activities as selective cyclooxygenase-2 (COX-2) inhibitors. In vitro COX-1/COX-2 structure-activity relationships showed that compounds possessing azido pharmacophore group exhibited highly COX-2 inhibitory selectivity and potency even more than celecoxib.

Multipotent drugs with cholinergic and neuroprotective properties for the treatment of Alzheimer and neuronal vascular diseases. I. Synthesis, biological assessment, and molecular modeling of simple and readily available 2-aminopyridine-, and 2-chloropyridine-3,5-dicarbonitriles

pp 5861–5872

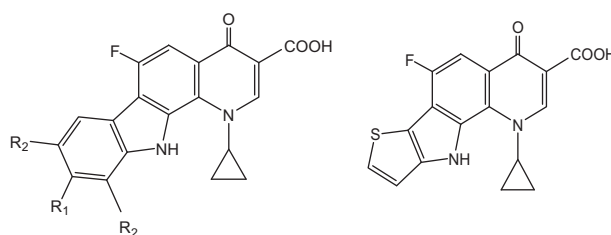
Abdelouahid Samadi, José Marco-Contelles*, Elena Soriano, Mónica Álvarez-Pérez, Mourad Chioua, Alejandro Romero, Laura González-Lafuente, Luis Gandía, José M. Roda, Manuela G. López, Mercedes Villarroja, Antonio G. García, Cristóbal de los Ríos

The target 2-aminopyridine-(I), and 2-chloropyridine-3,5-dicarbonitriles (II).

**Synthesis and biological evaluation of tetracyclic fluoroquinolones as antibacterial and anticancer agents**

pp 5873–5884

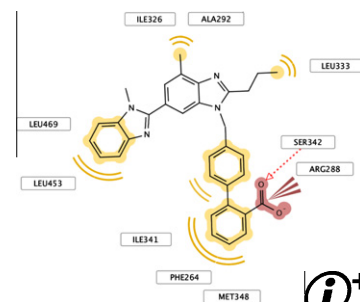
Salah A. Al-Trawneh, Jalal A. Zahra, Marwan R. Kamal, Mustafa M. El-Abadelah*, Franca Zani, Matteo Incerti, Andrea Cavazzoni, Roberta R. Alfieri, Pier G. Petronini, Paola Vicini*


Characterization of new PPAR γ agonists: Benzimidazole derivatives—importance of positions 5 and 6, and computational studies on the binding mode

pp 5885–5895

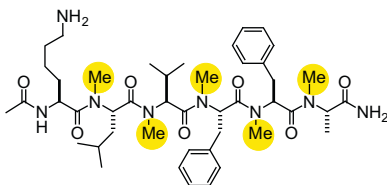
Matthias Goebel, Gerhard Wolber, Patrick Markt, Bart Staels, Thomas Unger, Ulrich Kintscher, Ronald Gust*

Telmisartan originally designed as AT₁ antagonist, showed properties of a selective PPAR γ modulator. Therefore, we evaluated the parts of the molecule essential for activation and analyzed the structures in 3D pharmacophore-driven docking experiments.



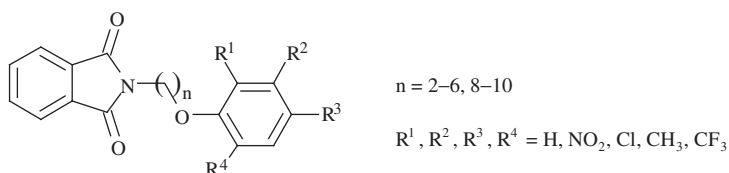
In vitro ADMET and physicochemical investigations of poly-N-methylated peptides designed to inhibit A β aggregation pp 5896–5902

Partha Pratim Bose, Urmimala Chatterjee, Ina Hubatsch, Per Artursson, Thavendran Govender, Hendrik G. Kruger, Margareta Bergh, Jan Johansson, Per I. Arvidsson*

**New N-(phenoxydecyl)phthalimide derivatives displaying potent inhibition activity towards α -glucosidase**

pp 5903–5914

Rossana Pascale, Alessia Carocci*, Alessia Catalano, Giovanni Lentini, Anna Spagnoletta, Maria Maddalena Cavalluzzi, Francesco De Santis, Annalisa De Palma, Vito Scalera, Carlo Franchini

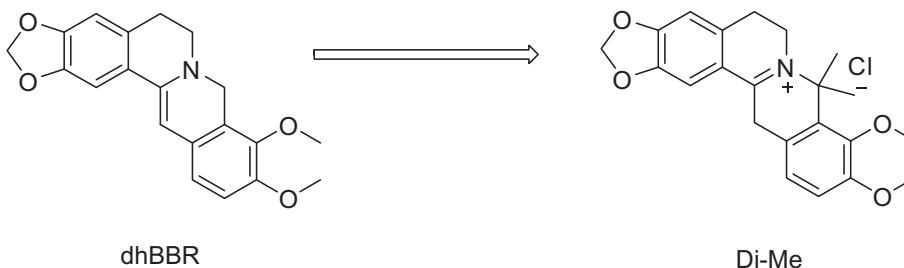


Several members of a new family of non-sugar-type α -glucosidase inhibitors bearing a phthalimide skeleton were synthesized and their activities were investigated. Amongst them we identified some potent α -glucosidase inhibitors which possess activity one to two orders of magnitude higher than that of the known inhibitor 1-deoxynojirimycin.

8,8-Dimethyldihydroberberine with improved bioavailability and oral efficacy on obese and diabetic mouse models

pp 5915–5924

Zhe Cheng, An-Feng Chen, Fang Wu, Li Sheng, Han-Kun Zhang, Min Gu, Yuan-Yuan Li, Li-Na Zhang, Li-Hong Hu*, Jing-Ya Li*, Jia Li*

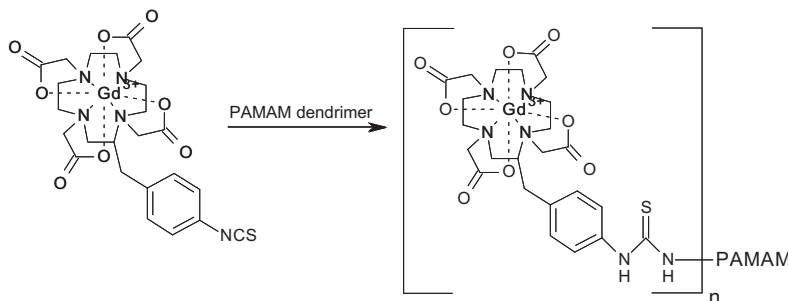


8,8-Disubstituted dihydroberberine hydrochlorides were synthesized and evaluated. Di-Me shows enhanced chemical stability, bioavailability and oral efficacy on obese and diabetic mouse models.

**Comparison of MRI properties between derivatized DTPA and DOTA gadolinium–dendrimer conjugates**

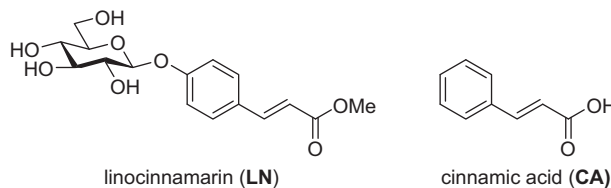
pp 5925–5931

K. Nwe, M. Bernardo, C. A. S. Regino, M. Williams, M. W. Brechbiel*

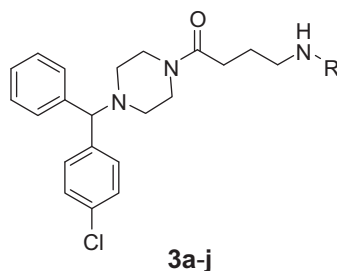


Phenolic constituents isolated from *Fragaria ananassa* Duch. inhibit antigen-stimulated degranulation through direct inhibition of spleen tyrosine kinase activation pp 5932–5937

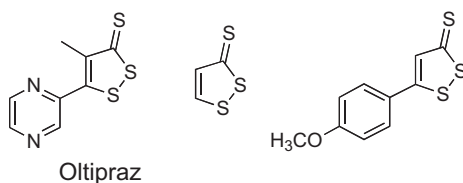
Masayuki Ninomiya, Tomohiro Itoh, Suguru Ishikawa, Miho Saiki, Kenji Narumiya, Masaharu Yasuda, Kaneyuki Koshikawa, Yoshinori Nozawa, Mamoru Koketsu*

**Synthesis and T-type calcium channel blocking activity of novel diphenylpiperazine compounds, and evaluation of in vivo analgesic activity** pp 5938–5944

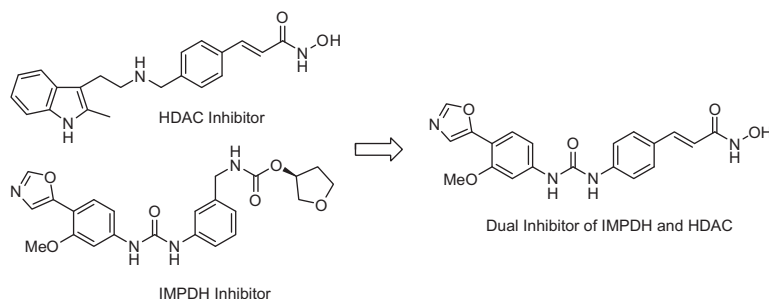
Yoo Lim Kam, Hee-Kyung Rhee, Hyewhon Rhim, Seung Keun Back, Heung Sik Na*, Hea-Young Park Choo*

**Inactivation of protein tyrosine phosphatases by oltipraz and other cancer chemopreventive 1,2-dithiole-3-thiones** pp 5945–5949

Sanjib Bhattacharyya, Haiying Zhou, Derrick R. Seiner, Kent S. Gates*

**Dual inhibitors of inosine monophosphate dehydrogenase and histone deacetylase based on a cinnamic hydroxamic acid core structure** pp 5950–5964

Liqiang Chen*, Riccardo Petrelli, Guangyao Gao, Daniel J. Wilson, Garrett T. McLean, Hiremagalur N. Jayaram, Yuk Y. Sham, Krzysztof W. Pankiewicz

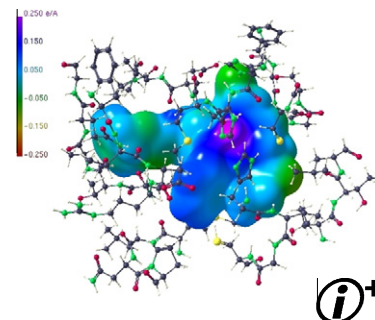


A simple procedure for the derivation of electron density based surfaces of drug-receptor complexes from a combination of X-ray data and theoretical calculations

pp 5965–5974

Stefan Mebs, Anja Lüth, Peter Luger*

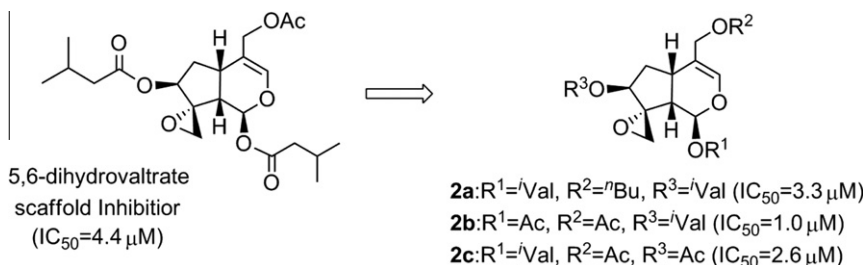
Electrostatic potential on an electron density iso-surface (0.0067 eÅ^{-3}) of an APE substrate in the active site pocket of the SARS main protease M^{pro} . Geometry data from PDB entry 2A5I.



Concise synthesis of 5,6-dihydrovaltrate leading to enhanced Rev-export inhibitory congener

pp 5975–5980

Satoru Tamura, Katsuaki Fujiwara, Nobuhiro Shimizu, Shingo Todo, Nobutoshi Murakami*



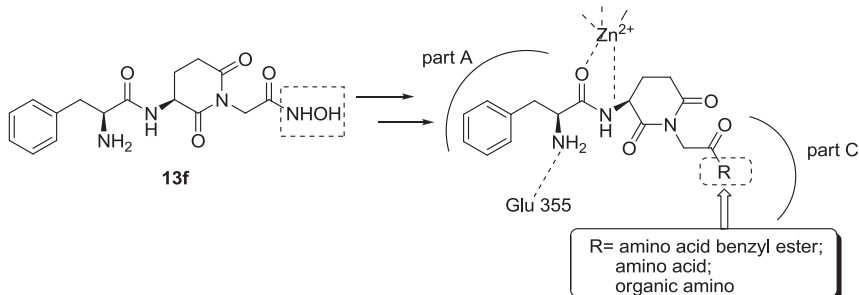
The concise synthesis of 5,6-dihydrovaltrate, the Rev-export inhibitor, has been achieved from the commercially available iridoid genipin. By use of this synthetic protocol, 1-acetoxy analog **2b** was disclosed as the enhanced Rev-export inhibitor.

Novel aminopeptidase N (APN/CD13) inhibitors derived from 3-phenylalanyl-N'-substituted-2,6-piperidinedione

pp 5981–5987

Xiaopan Zhang, Hao Fang, Huawei Zhu, Xuejian Wang, Lei zhang, Minyong Li, Qianbin Li, Yumei Yuan, Wenfang Xu*

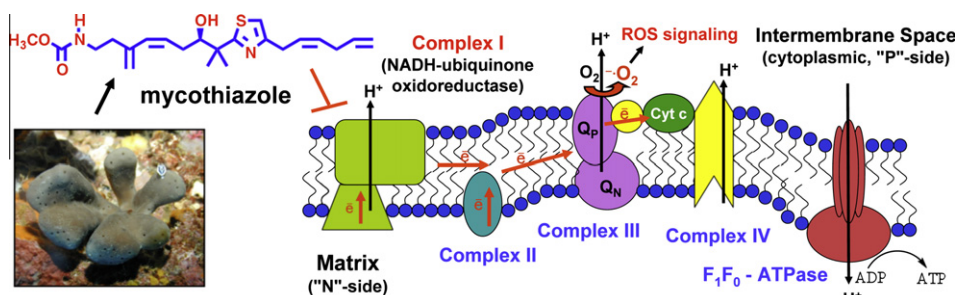
A series of novel 3-phenylalanyl-N'-substituted-2,6-piperidinedione derivatives were synthesized and evaluated for their in vitro enzymatic inhibitory activities against aminopeptidase N. Compound **7c** had the most potent inhibitory activity against APN with the IC_{50} of $5.00 \pm 3.17 \mu\text{M}$.



The marine sponge metabolite mycothiazole: A novel prototype mitochondrial complex I inhibitor

pp 5988–5994

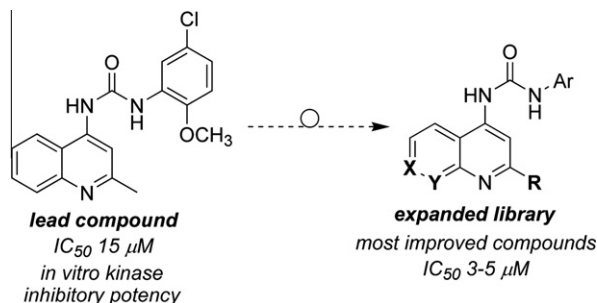
J. Brian Morgan, Fakhri Mahdi, Yang Liu, Veena Coothankandaswamy, Mika B. Jekabsons, Tyler A. Johnson, Koneni V. Sashidhara, Phillip Crews, Dale G. Nagle*, Yu-Dong Zhou*



Synthesis of aryl-heteroaryl ureas (AHUs) based on 4-aminoquinoline and their evaluation against the insulin-like growth factor receptor (IGF-1R)

pp 5995–6005

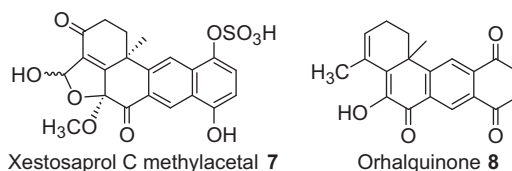
William Engen, Terrence E. O'Brien, Brendan Kelly, Jacinda Do, Liezel Rillera, Lance K. Stapleton, Jack F. Youngren*, Marc O. Anderson*



New bioactive halenaquinone derivatives from South Pacific marine sponges of the genus *Xestospongia*

pp 6006–6011

Arlette Longeon, Brent R. Copp, Mélanie Roué, Joëlle Dubois, Alexis Valentin, Sylvain Petek, Cécile Debitus, Marie-Lise Bourguet-Kondracki*



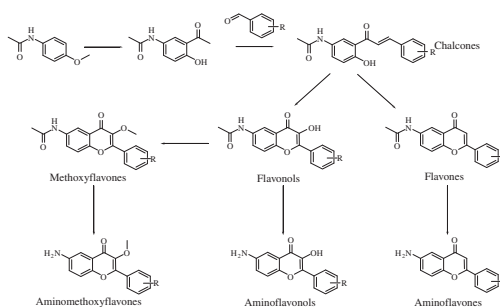
Two new derivatives named xestosaprol C methylacetal **7** and orhalquinone **8** of halenaquinone-type polyketides were isolated from marine sponges of the genus *Xestospongia* collected in South Pacific. Structure–activity relationship studies of PLA₂, FTase, and *Plasmodium falciparum* inhibitors are presented.



Anti-HIV and antiparasmodial activity of original flavonoid derivatives

pp 6012–6023

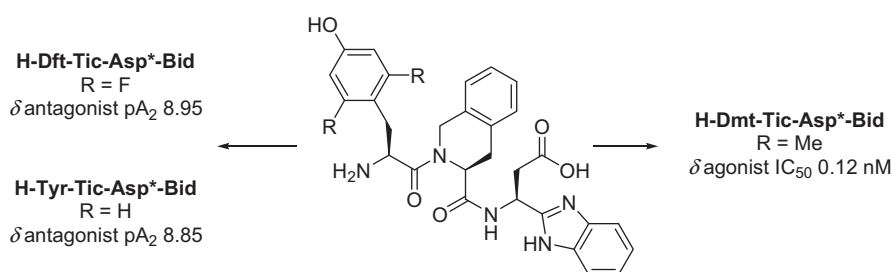
Gilles Casano, Aurélien Dumètre, Christophe Pannecouque, Sébastien Hutter, Nadine Azas*, Maxime Robin*



Role of 2',6'-dimethyl-L-tyrosine (Dmt) in some opioid lead compounds

pp 6024–6030

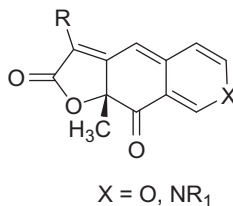
Gianfranco Balboni*, Erika Marzola, Yusuke Sasaki, Akihiro Ambo, Ewa D. Marczak, Lawrence H. Lazarus, Severo Salvadori*



Natural and semisynthetic azaphilones as a new scaffold for Hsp90 inhibitors

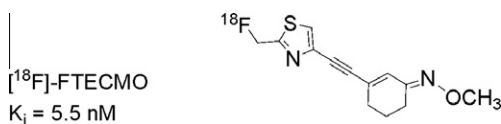
pp 6031–6043

Loana Musso, Sabrina Dallavalle*, Lucio Merlini, Adriana Bava, Gianluca Nasini, Sergio Penco, Giuseppe Giannini, Chiara Giommarelli, Andrea De Cesare, Valentina Zuco, Loredana Vesci, Claudio Pisano, Fabrizio Dal Piaz, Nunziatina De Tommasi, Franco Zunino

**Syntheses and pharmacological characterization of novel thiazole derivatives as potential mGluR5 PET ligands**

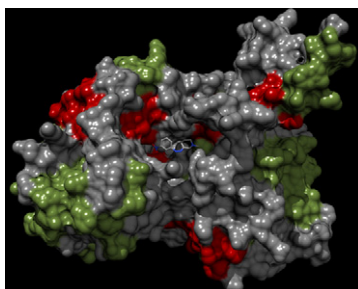
pp 6044–6054

Cindy A. Baumann, Linjing Mu, Nicole Wertli, Stefanie D. Krämer, Michael Honer, Pius A. Schubiger, Simon M. Ametamey*

**Synergistic experimental/computational studies on arylazoenamine derivatives that target the bovine viral diarrhea virus RNA-dependent RNA polymerase**

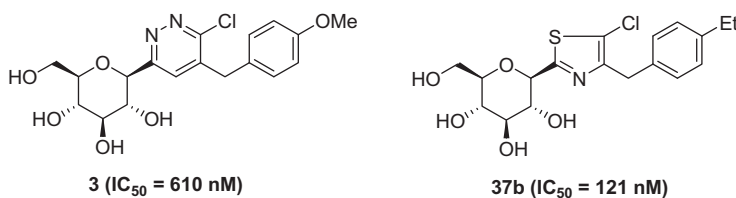
pp 6055–6068

Gabriele Giliberti, Cristina Ibba, Esther Marongiu, Roberta Loddo, Michele Tonelli, Vito Boido, Erik Laurini, Paola Posocco, Maurizio Fermeglia, Sabrina Pricl*

**Synthesis of pyridazine and thiazole analogs as SGLT2 inhibitors**

pp 6069–6079

Suk Youn Kang, Kwang-Seop Song, Junwon Lee, Sung-Han Lee, Jinhwa Lee*



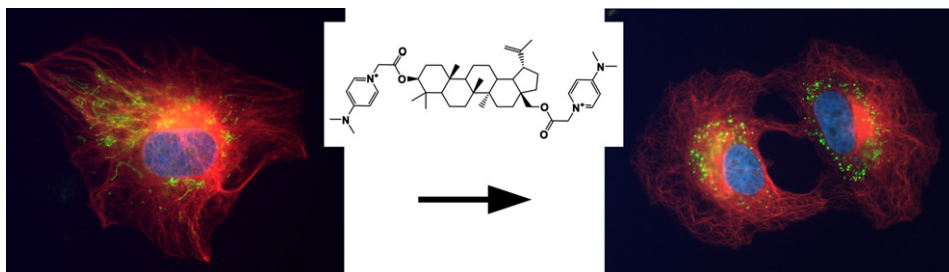
Pyridazine and thiazole analogs were synthesized and subsequently tested against hSGLT2. A couple of compounds exhibited moderate inhibitory activity against hSGLT2.

Dimethylaminopyridine derivatives of lupane triterpenoids are potent disruptors of mitochondrial structure and function

pp 6080–6088

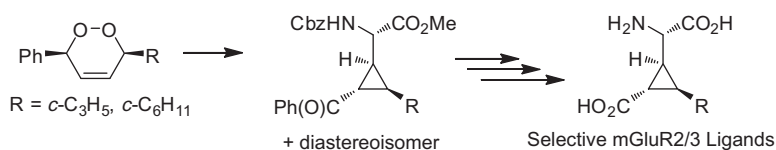
Jon Holy*, Oksana Kolomitsyna, Dmytro Krasutsky, Paulo J. Oliveira, Edward Perkins, Pavel A. Krasutsky

Fifteen dimethylaminopyridine derivatives of betulin and betulinic acid were synthesized and found to disrupt mitochondrial structure and function. Effects on mitochondria include fragmentation and loss of membrane polarization.

**A new metabotropic glutamate receptor agonist with in vivo anti-allodynic activity**

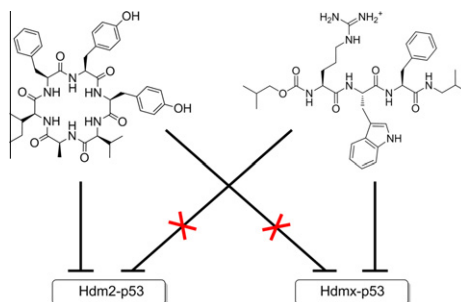
pp 6089–6098

Nathan J. Stanley, Mark R. Hutchinson, Trine Kvist, Birgitte Nielsen, Jesper Mosolf Mathiesen, Hans Bräuner-Osborne, Thomas D. Avery, Edward R. T. Tiekink, Daniel Sejer Pedersen, Rodney J. Irvine, Andrew D. Abell, Dennis K. Taylor*

**Functional profiling of p53-binding sites in Hdm2 and Hdmx using a genetic selection system**

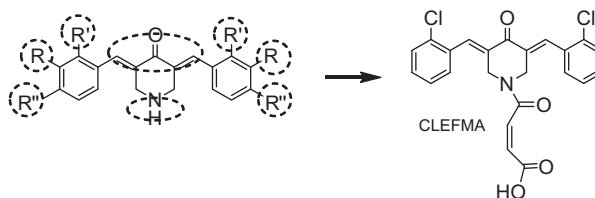
pp 6099–6108

Shreya Datta, Megan E. Bucks, Dipankar Koley, Pei Xin Lim, Sergey N. Savinov*

**CLEFMA—An anti-proliferative curcuminoid from structure–activity relationship studies on 3,5-bis(benzylidene)-4-piperidones**

pp 6109–6120

Pallavi Lagisetty, Prachi Vilekar, Kaustuv Sahoo, Shrikant Anant, Vibhudutta Awasthi*



Structure–activity relationship studies were performed on 3,5-bis(benzylidene)-4-piperidones for anti-proliferative action. The predicated compound, 4-[3,5-bis(2-chlorobenzylidene)-4-oxo-piperidine-1-yl]-4-oxo-2-butenic acid, or CLEFMA was found to be the most potent. The in vitro studies were suggestive of CLEFMA inducing autophagic cell death in lung adenocarcinoma H441 cells.

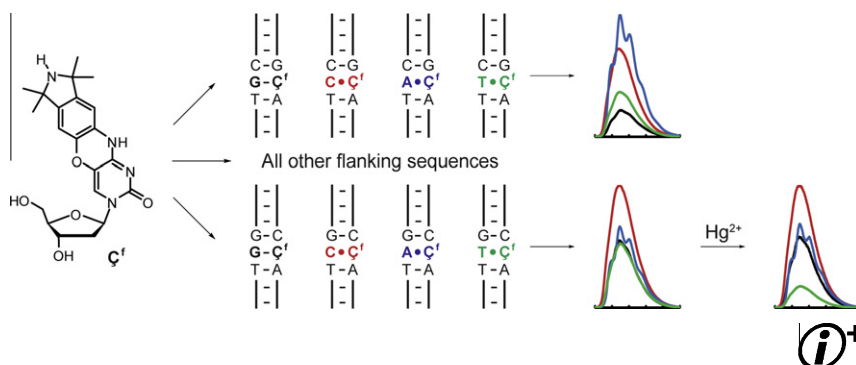


Large flanking sequence effects in single nucleotide mismatch detection using fluorescent nucleoside ζ^f

pp 6121–6126

Haraldur Gardarsson, Snorri Th. Sigurdsson*

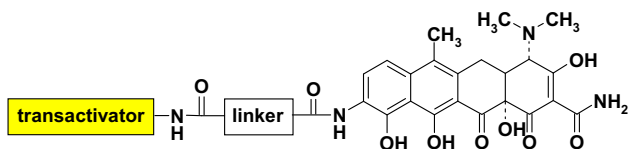
ζ^f covers all bases. The fluorescent nucleoside ζ^f can, with occasional assistance from Hg^{2+} , uniquely identify all its base-pairing partners independent of the adjacent base-pairs.



Anhydrotetracycline–peptide conjugates as representatives for ligand-based transactivating systems

pp 6127–6133

Susanne Lochner, Juergen Einsiedel, Gesa Schaefer, Christian Berens*, Wolfgang Hillen, Peter Gmeiner*

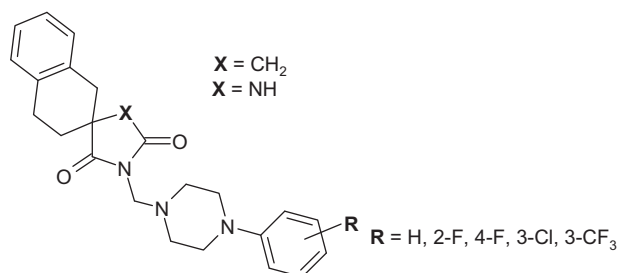


Design, synthesis, and anticonvulsant activity of new *N*-Mannich bases derived from spirosuccinimides and spirohydantoins

pp 6134–6142

Jolanta Obniska*, Hanna Byrtus, Krzysztof Kamiński, Maciej Pawłowski, Małgorzata Szczesio, Janina Karolak-Wojciechowska

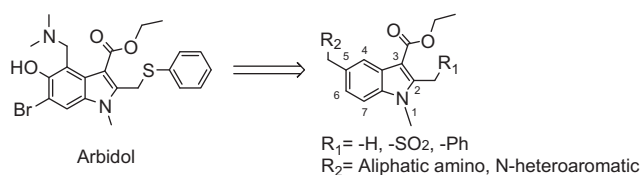
Majority of compounds synthesized showed high activity in the maximal electroshock test (MES). To explain the possible mechanism of anticonvulsant action, for chosen active derivatives, their influence on voltage-dependent Na^+ channel were tested in vitro.



Synthesis and anti-hepatitis C virus activity of novel ethyl 1*H*-indole-3-carboxylates in vitro

pp 6143–6148

Grazia Sellitto*, Aurora Faruolo, Paolo de Caprariis, Sergio Altamura, Giacomo Paonessa, Gennaro Ciliberto

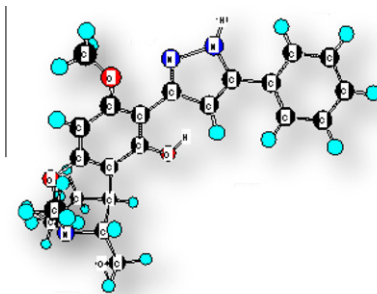


A series of novel ethyl 1*H*-indole-3-carboxylates were designed and synthesized, and their inhibitory activities against hepatitis C virus (HCV) were compared to that of Arbidol in Huh-7.5 cells.



Synthesis of novel 3,5-diaryl pyrazole derivatives using combinatorial chemistry as inhibitors of tyrosinase as well as potent anticancer, anti-inflammatory agents pp 6149–6155

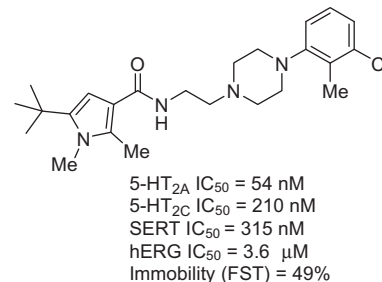
Babasaheb P. Bandgar*, Jalinder V. Totre, Shrikant S. Gawande, C. N. Khobragade, Suchita C. Warangkar, Prasad D. Kadam



Further optimization of novel pyrrole 3-carboxamides for targeting serotonin 5-HT_{2A}, 5-HT_{2C}, and the serotonin transporter as a potential antidepressant pp 6156–6169

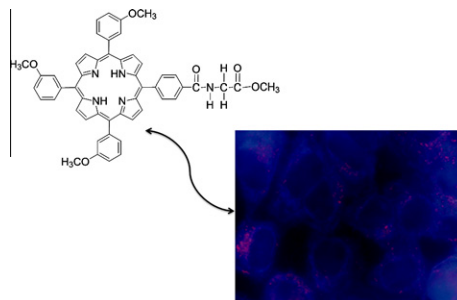
Suk Youn Kang, Eun-Jung Park, Woo-Kyu Park, Hyun Jung Kim, Gildon Choi, Myung Eun Jung, Hee Jeong Seo, Min Ju Kim, Ae Nim Pae, Jeongmin Kim, Jinhwa Lee*

Arylpiperazine-containing pyrrole 3-carboxamide derivatives were synthesized and evaluated as novel antidepressant compounds. The various analogues were efficiently prepared and bio-assayed for binding to 5-HT_{2A}, 5-HT_{2C} receptor, and 5-HT transporter. Based on their in vitro and in vivo activities, this pyrrole series of compounds demonstrated potential pharmacotherapy for the treatment of depressive disorders.



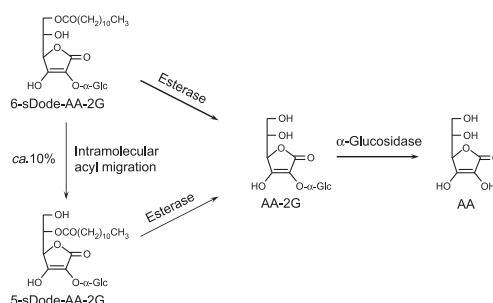
New porphyrin amino acid conjugates: Synthesis and photodynamic effect in human epithelial cells pp 6170–6178

V. Vaz Serra, A. Zamarrón, M. A. F. Faustino, M. C. Iglesias-de la Cruz, A. Blázquez, J. M. M. Rodrigues, M. G. P. M. S. Neves, J. A. S. Cavaleiro*, A. Juarranz, F. Sanz-Rodríguez*



Intramolecular acyl migration and enzymatic hydrolysis of a novel monoacylated ascorbic acid derivative, 6-O-dodecanoyl-2-O-α-D-glucopyranosyl-L-ascorbic acid pp 6179–6183

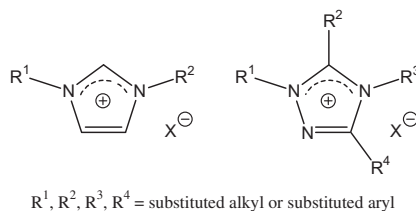
Akihiro Tai*, Tasuku Mori, Masaya Urushihara, Hideyuki Ito, Daisuke Kawasaki, Itaru Yamamoto



Anti-Plasmodium activity of imidazolium and triazolium salts

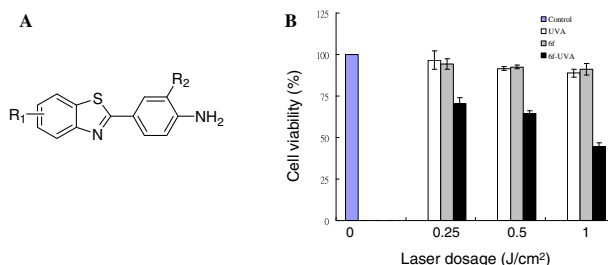
pp 6184–6196

Jason Z. Vlahakis, Carmen Lazar, Ian E. Crandall*, Walter A. Szarek*

Novel imidazolium and triazolium salts have been synthesized that show potent and selective anti-*Plasmodium* activity.**Synthesis, and biological evaluation of 2-(4-aminophenyl)benzothiazole derivatives as photosensitizing agents**

pp 6197–6207

Wan-Ping Hu, Yin-Kai Chen, Chao-Cheng Liao, Hsin-Su Yu, Yi-Min Tsai, Shu-Mei Huang, Feng-Yuan Tsai, Ho-Chuan Shen, Long-Sen Chang, Jeh-Jeng Wang*

(A) Structure of the 2-(4-aminophenyl)benzothiazoles (**6**). (B) Effect of **6f**-UVA cell viability on basal cell carcinoma.**OTHER CONTENTS****Bioorganic & Medicinal Chemistry Reviews and Perspectives**

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*Corresponding author

Supplementary data available via ScienceDirect

COVER

The molecules of robalzotan (slightly purplish in color) and esomeprazole (ball-and-stick model) together with autoclaves intended for high pressure reactions (courtesy of Solvias AG who are thanked for generously making this photograph available) against a background of formulated product in the form of tablets. [Federsel, H.-]. *Bioorg. Med. Chem.* **2010**, 18, 5775–5794].

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