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Bioorganic & Medicinal Chemistry Volume 18, Issue 5, 2010

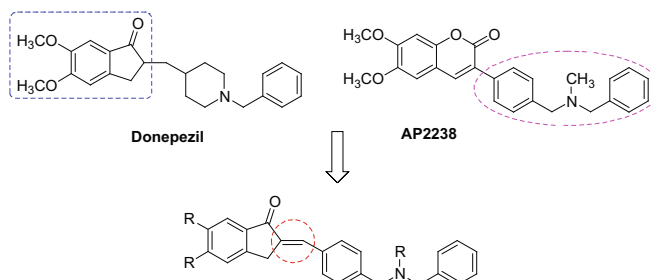
Contents

ARTICLES

Targeting Alzheimer's disease: Novel indanone hybrids bearing a pharmacophoric fragment of AP2238

pp 1749–1760

Stefano Rizzo, Manuela Bartolini, Luisa Ceccarini, Lorna Piazzi, Silvia Gobbi, Andrea Cavalli, Maurizio Recanatini, Vincenza Andrisano, Angela Rampa*



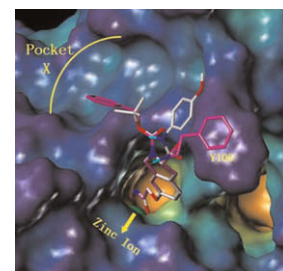
The design of hybrid compounds able to inhibit both AChE and A β aggregation is described.

Design, synthesis and preliminary activity assay of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives as novel Histone deacetylases (HDACs) inhibitors

pp 1761–1772

Yingjie Zhang, Jinhong Feng, Chunxi Liu, Lei Zhang, Jie Jiao, Hao Fang, Li Su, Xiaopan Zhang, Jian Zhang, Minyong Li, Binghe Wang, Wenfang Xu*

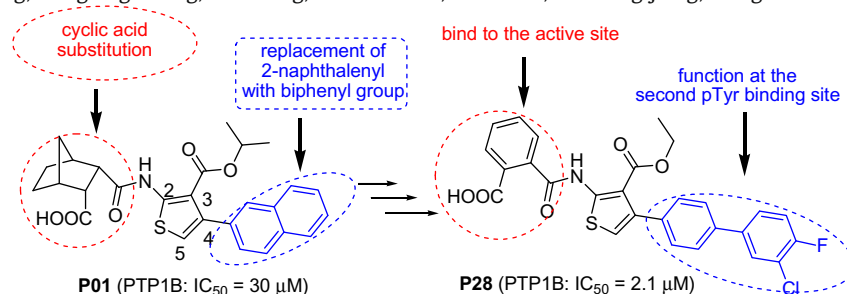
The compounds **13a** ($IC_{50} = 0.58 \pm 0.10 \mu M$) and **7d** ($IC_{50} = 1.00 \pm 0.16 \mu M$) were docked into the active site of HDAC8 (PDB entry: 1T64) using SYBYL 7.3. Zinc ion is indicated. Y100 stands for the tyrosine 100 residue. The yellow arc indicates the pocket X of the protein. **13a** is depicted in purple and **7d** in white (atom type: polar H, sky-blue; N, dark blue; O, red).



Novel thiophene derivatives as PTP1B inhibitors with selectivity and cellular activity

pp 1773–1782

Deju Ye, Yu Zhang, Fei Wang, Mingfang Zheng, Xu Zhang, Xiaomin Luo, Xu Shen*, Hualiang Jiang, Hong Liu*



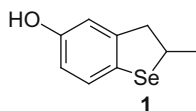
A series of novel thiophene derivatives as competitive PTP1B inhibitors were designed, synthesized and bioassay. The selectivity against other PTPs and the cellular activity of selected compounds were also investigated.



Exploring a synthetic organoselenium compound for antioxidant pharmacotherapy—toxicity and effects on ROS-production

pp 1783–1788

Henrik Johansson, Olov Svartström, Prasad Phadnis, Lars Engman*, Marjam Karlsson Ott*

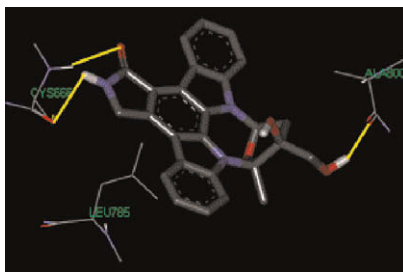


Organoselenium antioxidant **1** efficiently quenched ROS production from neutrophils and macrophages. It showed minimal toxicity in five human cell lines and is proposed for antioxidant pharmacotherapy.

Colony stimulating factor-1 receptor as a target for small molecule inhibitors

pp 1789–1797

Baratali Mashkani, Renate Griffith*, Leonie K. Ashman

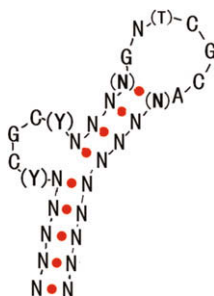


Binding of CEP-701 to the FMS receptor kinase domain is mediated via three hydrogen bonds (yellow lines) and a hydrophobic interaction.

Conservative secondary structure motif of streptavidin-binding aptamers generated by different laboratories

pp 1798–1805

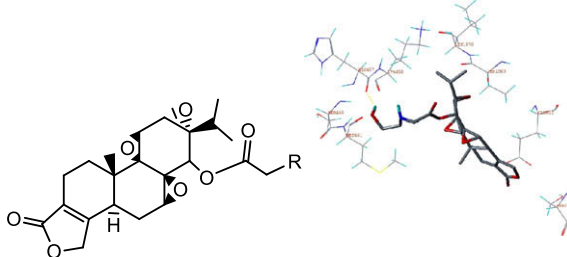
Tao Bing, Xiaojuan Yang, Hongcheng Mei, Zehui Cao, Dihua Shangguan*



Design, synthesis, and biological evaluation of novel water-soluble triptolide derivatives: Antineoplastic activity against imatinib-resistant CML cells bearing T315I mutant Bcr-Abl

pp 1806–1815

Fang Xu, Xianping Shi, Shichang Li, Jieshun Cui, Zhongzheng Lu, Yanli Jin, Yongcheng Lin, Jiyan Pang*, Jingxuan Pan*

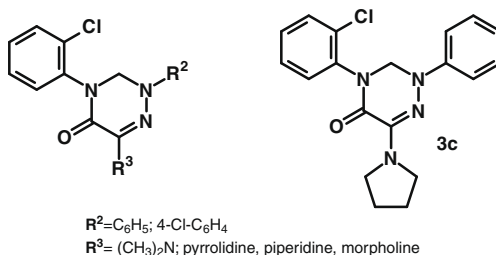


A series of novel derivatives of triptolide were synthesized. In vitro and in vivo antitumor activity was examined. The interaction between compound **9** and RNA polymerase was analyzed with docking.

Synthesis and characterization of novel 1,2,4-triazine derivatives with antiproliferative activity

pp 1816–1821

Fabian Krauth*, Hans-Martin Dahse, Hans-Hermann Rüttinger, Petra Froberg

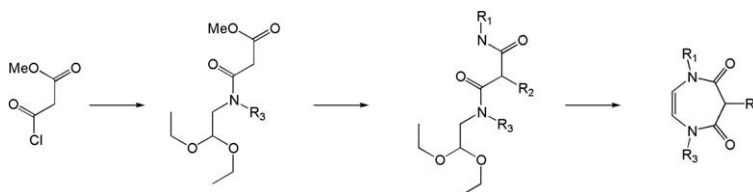


A series of novel 1,2,4-triazine-5-ones was synthesized. Compound **3c** shows promising antiproliferative effects on the human leukemia cell line (K-562), little cytotoxicity against HeLa, and fulfills very well the 'rule-of-five' claims by Lipinski for orally bioavailable drugs.

A concise synthesis of 1,4-dihydro-[1,4]diazepine-5,7-dione, a novel 7-TM receptor ligand core structure with melanocortin receptor agonist activity

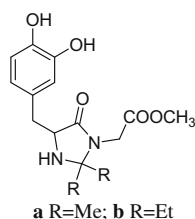
pp 1822–1833

Jerzy R. Szewczyk*, Chris P. Laudeman, Doug M. Sammond, Manon Villeneuve, Douglas J. Minick, Mary K. Grizzle, Alejandro J. Daniels, John L. Andrews, Diane M. Ignar

**Design, synthesis, and preliminary pharmacological evaluation of new imidazolinones as L-DOPA prodrugs**

pp 1834–1843

Gianfabio Giorgioni*, Francesco Claudi, Sabrina Ruggieri, Massimo Ricciutelli, Giovanni F. Palmieri, Antonio Di Stefano, Piera Sozio, Laura S. Cerasa, Annalisa Chiavaroli, Claudio Ferrante, Giustino Orlando, Richard A. Glennon

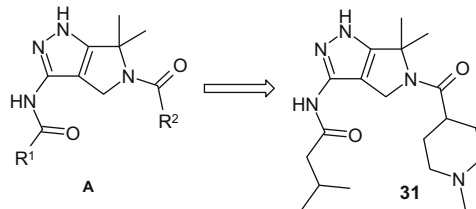


With the aim to increase the bioavailability after oral administration, we designed a multi-protected L-DOPA prodrugs able to release the drug by both spontaneous chemical or enzyme catalyzed hydrolysis. The new compounds have been evaluated for their water solubility, log *P*, chemical stability, and enzymatic stability. The ability of the new prodrugs to increase basal levels of striatal DA, and influence brain neurochemistry, as well as their radical-scavenging activity against DPPH are reported.

Optimization of 6,6-dimethyl pyrrolo[3,4-c]pyrazoles: Identification of PHA-793887, a potent CDK inhibitor suitable for intravenous dosing

pp 1844–1853

Maria Gabriella Brasca*, Clara Albanese, Rachele Alzani, Raffaella Amici, Nilla Avanzi, Dario Ballinari, James Bischoff, Daniela Borghi, Elena Casale, Valter Croci, Francesco Fiorentini, Antonella Isacchi, Ciro Mercurio, Marcella Nesi, Paolo Orsini, Wilma Pastori, Enrico Pesenti, Paolo Pevarello, Patrick Roussel, Mario Varasi, Daniele Volpi, Anna Vulpetti, Marina Ciomei

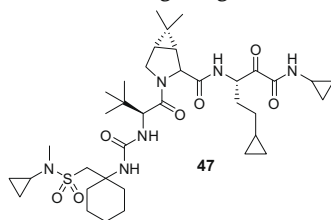


We describe the synthesis of compounds with interesting biochemical and cellular characteristics. Optimization of the physico-chemical properties led to the identification of highly potent compound **31** (PHA-793887), which presents remarkable in vivo efficacy.

Discovery of potent sulfonamide P4-capped ketoamide second generation inhibitors of hepatitis C virus NS3 serine protease with favorable pharmacokinetic profiles in preclinical species

pp 1854–1865

Stéphane L. Bogen*, Ashok Arasappan, Francisco Velazquez, Melissa Blackman, Regina Huelgas, Weidong Pan, Elise Siegel, Latha G. Nair, Srikanth Venkatraman, Zhuyan Guo, Ronald Doll, Neng-Yang Shih, F. George Njoroge



$K_i^* = 6 \text{ nM}$; Replicon $EC_{50} = 75 \text{ nM}$; HNE/HCV=2485

AUC (PO, rat, 10 mpk) = $0.9 \mu\text{M}\cdot\text{hr}$

AUC (PO, dog, 2 mpk) = $4 \mu\text{M}\cdot\text{hr}$

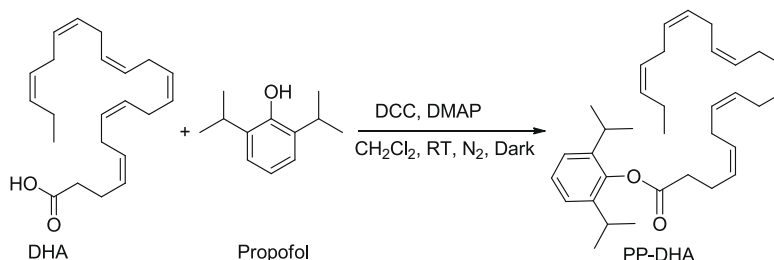
AUC (PO, monkey, 10 mpk) = $5.4 \mu\text{M}\cdot\text{hr}$

Characterization of anticancer properties of 2,6-diisopropylphenol-docosaheptaenoate and analogues in breast cancer cells

pp 1866–1874

Kevin A. Harvey, Zhidong Xu, Phillip Whitley, V. Jo Davisson, Rafat A. Siddiqui*

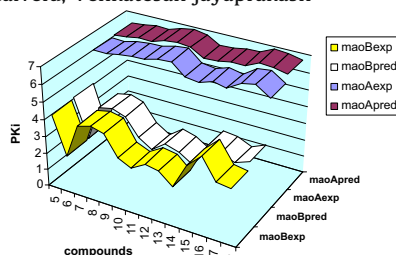
Synthesis of 2,6-diisopropylphenol docosaheptaenoate (PP-DHA)



Development of selective and reversible pyrazoline based MAO-A inhibitors: Synthesis, biological evaluation and docking studies

pp 1875–1881

Muthukumar Karupphasamy, Manojkumar Mahapatra, Samiye Yabanoglu, Gulberk Ucar, Barij Nayan Sinha, Arijit Basu, Nibha Mishra, Ashoke Sharon, Umasankar Kulandaivelu, Venkatesan Jayaprakash*



Experimental (exp) and predicted (pred) pK_i values of the synthesized compounds against MAO-A and MAO-B.

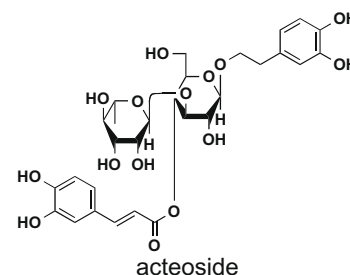


Acylated phenylethanoid oligoglycosides with hepatoprotective activity from the desert plant *Cistanche tubulosa*

pp 1882–1890

Toshio Morikawa, Yingni Pan, Kiyofumi Ninomiya, Katsuya Imura, Hisashi Matsuda, Masayuki Yoshikawa*, Dan Yuan, Osamu Muraoka*

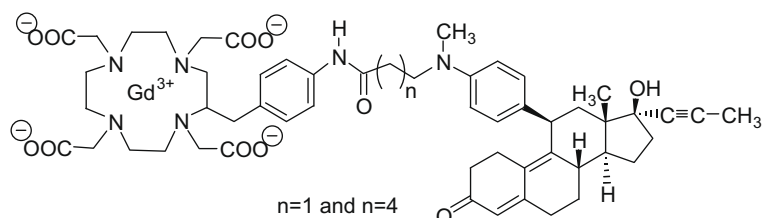
The methanolic extract from fresh stems of *Cistanche tubulosa* was found to show hepatoprotective effects against D-GalN/LPS-induced liver injury in mice. From the extract, three new phenylethanoid oligoglycosides, kankanosides H1, H2, and I, were isolated together with 16 phenylethanoid glycosides and two acylated oligosugars. Among the isolates, echinacoside (**4**, $IC_{50} = 10.2 \mu\text{M}$), acteoside (**5**, $4.6 \mu\text{M}$), isoacteoside (**6**, $5.3 \mu\text{M}$), 2'-acetylacteoside (**8**, $4.8 \mu\text{M}$), and tubuloside A (**10**, $8.6 \mu\text{M}$) inhibited D-GalN-induced death of hepatocytes. These five isolates, **4** ($31.1 \mu\text{M}$), **5** ($17.8 \mu\text{M}$), **6** ($22.7 \mu\text{M}$), **8** ($25.7 \mu\text{M}$), and **10** ($23.2 \mu\text{M}$), and cistantubuloside B1 (**11**, $21.4 \mu\text{M}$) also reduced TNF- α -induced cytotoxicity in L929 cells. Moreover, principal constituents (**4–6**) exhibited in vivo hepatoprotective effect at doses of 25–100 mg/kg, po.



Synthesis, in vitro progesterone receptors affinity of gadolinium containing mifepristone conjugates and estimation of binding sites in human breast cancer cells

pp 1891–1898

Pijus Saha*, Claudia Hödl, Wolfgang S. L. Strauss, Rudolf Steiner, Walter Goessler, Olaf Kunert, Alexander Leitner, Ernst Haslinger, H. Wolfgang Schramm

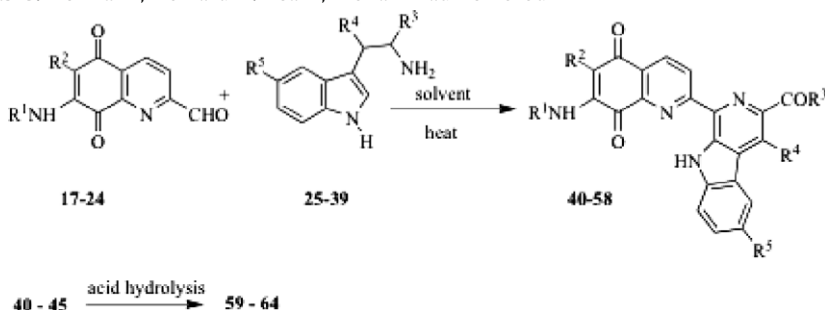


Syntheses of gadolinium containing mifepristone conjugates, in vitro progesterone receptors affinity and estimation of binding sites using the conjugates in human breast cancer cells are described.

Synthesis, metabolism and in vitro cytotoxicity studies on novel lavendamycin antitumor agents

pp 1899–1909

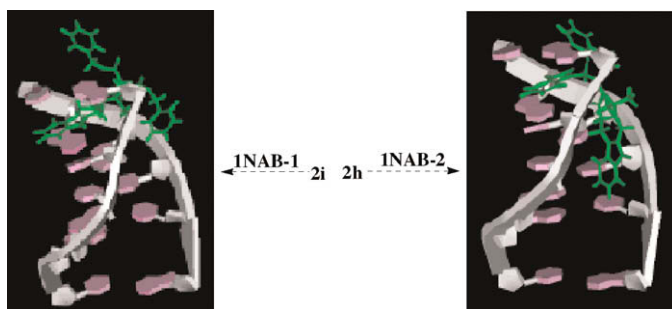
Wen Cai, Mary Hassani, Rajesh Karki, Ervin D. Walter, Katherine H. Koelsch, Hassan Seradj, Jayana P. Lineswala, Hamid Mirzaei, Jeremy S. York, Fatemeh Olang, Minoo Sedighi, Jennifer S. Lucas, Thomas J. Eads, Anthony S. Rose, Sahba Charkhazrin, Nicholas G. Hermann, Howard D. Beall*, Mohammad Behforouz*



Benzyl 1,2,3,5,11,11a-hexahydro-3,3-dimethyl-1-oxo-6H-imidazo[3',4':1,2]pyridin[3,4-b]indole-2-substituted acetates: One-pot-preparation, anti-tumor activity, docking toward DNA and 3D QSAR analysis

pp 1910–1917

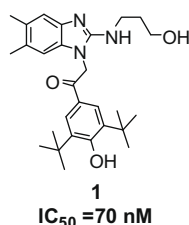
Jiawang Liu, Ming Zhao*, Keduo Qian, Xiaoyi Zhang, Kuo-Hsiung Lee*, Jianhui Wu, Yi-Nan Liu, Shiqi Peng*



Selective benzimidazole inhibitors of the antigen receptor-mediated NF-κB activation pathway

pp 1918–1924

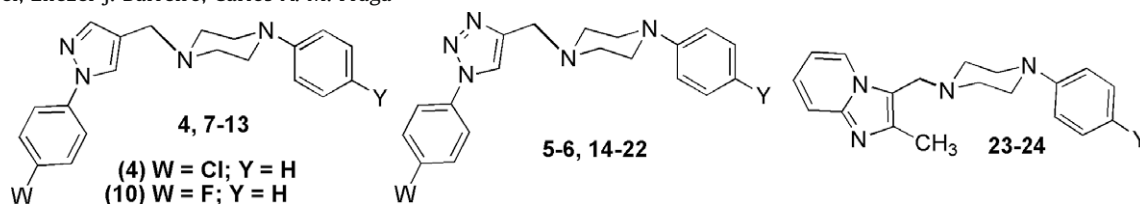
Karl J. Okolotowicz*, Ranxin Shi, Xueying Zheng, Mary MacDonald, John C. Reed, John R. Cashman



Searching for multi-target antipsychotics: Discovery of orally active heterocyclic *N*-phenylpiperazine ligands of D₂-like and 5-HT_{1A} receptors

pp 1925–1935

Gilda Neves, Ricardo Menegatti, Camila B. Antonio, Luiza R. Graziottin, Renan O. Vieira, Stela M. K. Rates, François Noël, Eliezer J. Barreiro, Carlos A. M. Fraga*

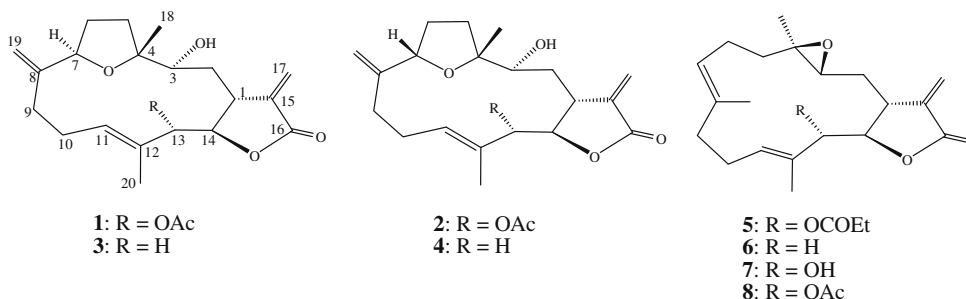


This work describes the synthesis and pharmacological evaluation of heteroarylazole *N*-phenylpiperazines **4–24** as multi-target ligands potentially useful for the treatment of schizophrenia. Among the compounds studied, **4** (LASSBio-579) and **10** (LASSBio-664) exhibited an adequate binding profile and a potential for schizophrenia positive symptoms treatment without cataleptogenic effects.

Cytotoxic and anti-inflammatory cembranoids from the Dongsha Atoll soft coral *Sarcophyton crassocaule*

pp 1936–1941

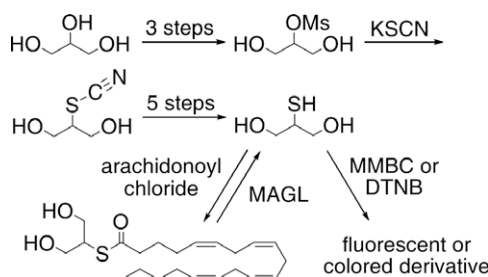
Wan-Yu Lin, Jui-Hsin Su, Yi Lu, Zhi-Hong Wen, Chang-Feng Dai, Yao-Haur Kuo, Jyh-Horng Sheu*



S-Arachidonoyl-2-thioglycerol synthesis and use for fluorimetric and colorimetric assays of monoacylglycerol lipase

pp 1942–1947

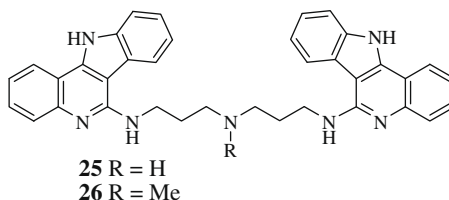
John E. Casida*, Alexander G. Gulevich, Richmond Sarpong, Eric M. Bunnelle



Synthesis and antiproliferative evaluation of certain indolo[3,2-*c*]quinoline derivatives

pp 1948–1957

Chih-Ming Lu, Yeh-Long Chen, Hui-Ling Chen, Chyi-An Chen, Pei-Jung Lu*, Chia-Ning Yang, Cherng-Chyi Tzeng*

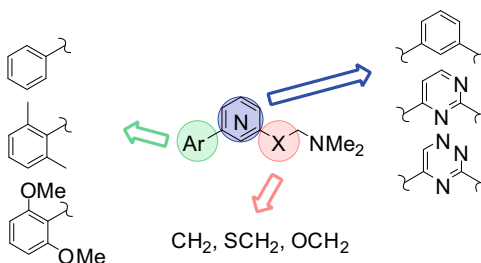


Mechanism studies indicated **25** can induce caspase-3 activation, γ -H2AX phosphorylation, cleavage of poly (ADP-ribose) polymerase and DNA fragmentation. These results provide evidence that DNA, topo I, and topo II are the primary targets of indolo[3,2-*c*]quinoline derivatives and that consequently inhibits proliferation and causes apoptosis in cancer cells.

SAR studies on new bis-aryls 5-HT₇ ligands: Synthesis and molecular modeling

pp 1958–1967

Eduard Badarau, Ryszard Bugno, Franck Suzenet*, Andrzej J. Bojarski*, Adriana-Luminita Finaru, G  rald Guillaumet

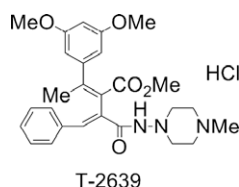


Structure–activity relationships of a series of bis-arylic compounds, investigated as 5-HT₇ ligands are reported. A ligand-based pharmacophore model was developed to rationalize the obtained SAR results.

Synthesis and evaluation of 1,4-diphenylbutadiene derivatives as inhibitors of plasminogen activator inhibitor-1 (PAI-1) production

pp 1968–1979

Hiroshi Miyazaki*, Hiroshi Sai, Hiroshi Ohmizu, Jun Murakami, Akio Ohtani, Tsuyoshi Ogiku

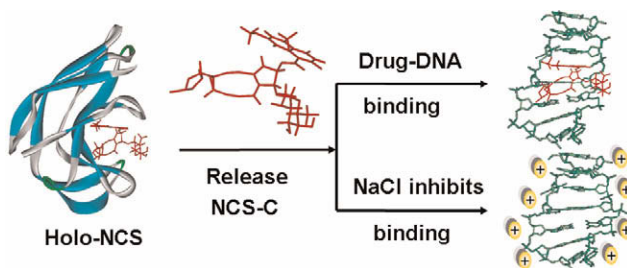


Synthesis and evaluation of T-2639, an orally active inhibitor of PAI-1 production, are reported.

Insight into the strong inhibitory action of salt on activity of neocarzinostatin

pp 1980–1987

Der-Hang Chin*, Huang-Hsien Li, Christopher G. Sudhahar, Pei-Yin Tsai

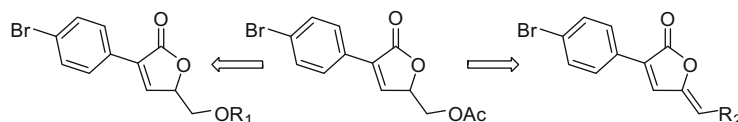


Severe inhibition (up to $85 \pm 5\%$) by the presence of salt on the neocarzinostatin activity was found. Salt interference on the affinity of DNA binding was the main and sole cause of the severe salt inhibition.

Antifungal 3,5-disubstituted furanones: From 5-acyloxymethyl to 5-alkylidene derivatives

pp 1988–2000

Petr Šenel, Lucie Tichotová, Ivan Votruba, Vladim  r Buchta, Marcel Špul  k, Ji    Kune  , Milan Nobilis, Ond  ej Krenk, Milan Pour*

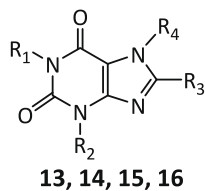


5-Acetoxyethyl-3-(4-bromophenyl)-2,5-dihydrofuran-2-one furnishes highly active 5-methylene derivative ($R^2 = H$, IC_{50} 0.49–7.81 $\mu\text{mol L}^{-1}$ against *Candida* sp., 1.95 $\mu\text{mol L}^{-1}$ against *Aspergillus fumigatus*) under antifungal assay conditions. 5-Alkoxyethyl furanones are inactive ($R^1 = \text{alkyl}$), 5-aryloxyethylfuranones ($R^1 = \text{Ph}$) also liberate the 5-methylene compound under assay conditions, and the activity of 5-alkylidene furanones is extremely substitution-dependent.

Synthesis and pharmacological evaluation of novel 1,3,8- and 1,3,7,8-substituted xanthines as adenosine receptor antagonists

pp 2001–2009

José Enrique Rodríguez-Borges, Xerardo García-Mera*, María Carmen Balo, José Brea, Olga Caamaño, Franco Fernández, Carmen López, María Isabel Loza, María Isabel Nieto



R₁ = methyl, ethyl, propyl, cyclohexylmethyl

R₂ = ethoxyethyl, 2-(ethylthio)ethyl, benzyl, thiophen-2-ylmethyl, cyclohexylmethyl, tetrahydrofuran-2-ylmethyl, 2-(ethylsulfinyl)ethyl, 2-(ethylsulfonyl)ethyl

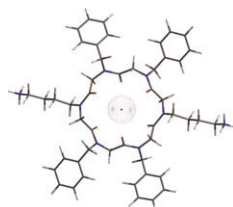
R₃ = phenyl, benzyl, 2,6-difluorobenzyl, furfuryl, thiophen-2-yl, thiophen-2-ylmethyl, biphenyl-4-yl

R₄ = H, methyl

Design, synthesis and antimicrobial properties of non-hemolytic cationic α -cyclopeptoids

pp 2010–2018

Daniela Comegna, Monica Benincasa, Renato Gennaro, Irene Izzo*, Francesco De Riccardis*



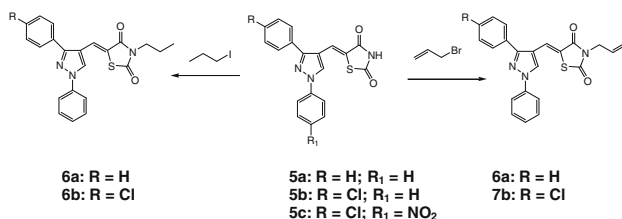
Synthesis and antimicrobial activities of linear and cyclic homo- and hetero-oligomeric α -peptoids were disclosed.



Synthesis and biological evaluation of novel pyrazolyl-2,4-thiazolidinediones as anti-inflammatory and neuroprotective agents

pp 2019–2028

Amal M. Youssef*, M. Sydney White, Erika B. Villanueva, Ibrahim M. El-Ashmawy, Andis Klegeris*

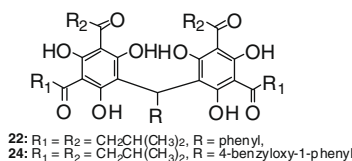


A number of in vitro and in vivo assays were used to identify four novel pyrazolyl-2,4-thiazolidinediones (**5a–c**, **7b**) as potential anti-inflammatory and neuroprotective agents.

Biomimetic synthesis and anti-HIV activity of dimeric phloroglucinols

pp 2029–2036

Siddheshwar K. Chauthe, Sandip B. Bharate, Sudeep Sabde, Debashis Mitra*, Kamlesh K. Bhutani, Inder P. Singh*

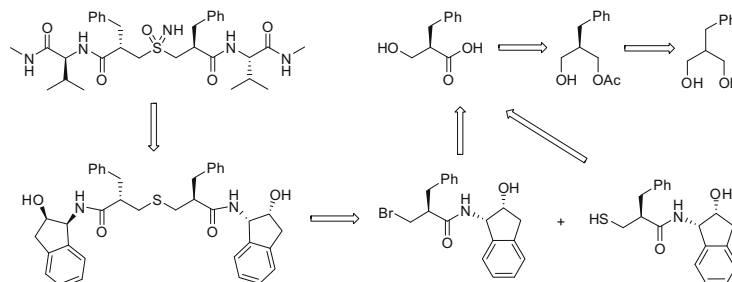


Twenty-one dimeric phloroglucinol compounds were synthesized and evaluated for anti-HIV activity in human CD4+ T cell line (CEM-GFP) infected with HIV-1 NL_{4.3} virus. Compounds **22** and **24** showed IC₅₀ = 0.28 and 2.71 μ M, respectively.

Design, asymmetric synthesis, and evaluation of pseudosymmetric sulfoximine inhibitors against HIV-1 protease

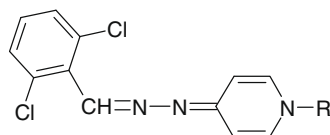
pp 2037–2048

Ding Lu, Yuk Yin Sham, Robert Vince*

**Interaction of (benzylidene-hydrazono)-1,4-dihydropyridines with β -amyloid, acetylcholine, and butyrylcholine esterases**

pp 2049–2059

Vildan Alptüzün, Michaela Prinz, Verena Hörr, Josef Scheiber, Krzysztof Radacki, Adyary Fallarero, Pia Vuorela, Bernd Engels, Holger Braunschweig, Erinc Erciyas, Ulrike Holzgrabe*

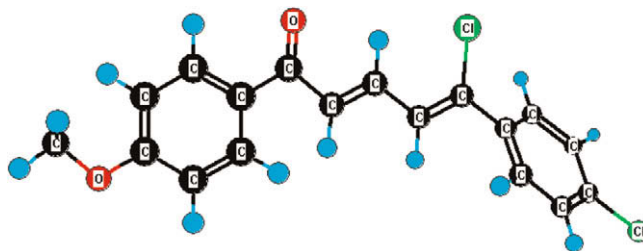


Design of drugs targeting the AChE, BuChE and the amyloid.

Synthesis and biological screening of a combinatorial library of β -chlorovinyl chalcones as anticancer, anti-inflammatory and antimicrobial agents

pp 2060–2065

Babasaheb P. Bandgar*, Shrikant S. Gawande

New β -chlorovinyl chalcones were developed and studied as anticancer, anti-inflammatory and antimicrobial agents.

*Corresponding author

Supplementary data available via ScienceDirect

COVER

An insight into biologically relevant chemical space showing the scaffolds of potential natural-product based inhibitors orbiting their target, the protein structure of protein 11-beta steroid dehydrogenase (PDB code 1xu7). Graphic produced using Pymol (<http://www.pymol.org>). [M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, Charting biologically relevant chemical space: A structural classification of natural products (SCONP), *PNAS* **2005**, 102, 17272–17277 and S. Wetzel, H. Waldmann, Cheminformatic analysis of natural products and their chemical space, *Chimia* **2007**, 61(6), 355–360].

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