

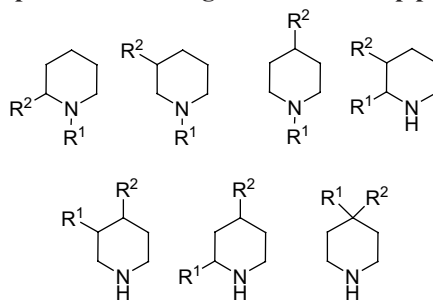
Contents

REVIEW

Synthesis of pharmaceutically active compounds containing a disubstituted piperidine framework

pp 601–635

Sara Källström and Reko Leino*



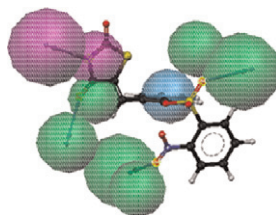
The synthesis of pharmaceutically active compounds bearing a disubstituted piperidine framework is reviewed.

ARTICLES

Novel GSK-3 β inhibitors from sequential virtual screening

pp 636–643

Hye-Jung Kim, Hyunah Choo, Yong Seo Cho, Kyoung Tai No and Ae Nim Pae*



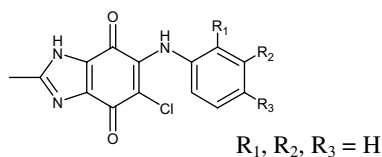
Novel GSK-3 inhibitor with new molecular framework was identified by sequential virtual screening process.



Antiproliferative effects of 6-anilino-5-chloro-1H-benzo[d]imidazole-4,7-dione in vascular smooth muscle cells

pp 644–649

Sung-Yu Hong, Kyu-Won Kwak, Chung-Kyu Ryu, Soo-Jung Kang and Kwang-Hoe Chung*

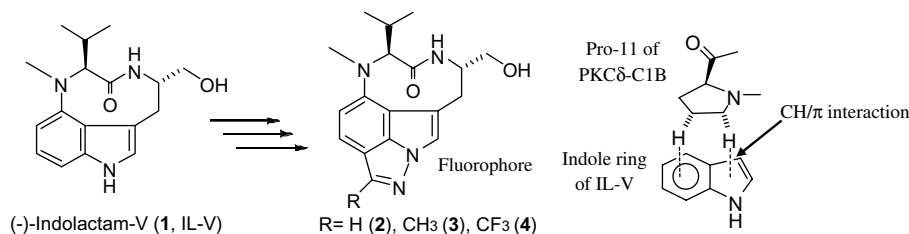


6-Anilino-5-chloro-1H-benzo[d]imidazole-4,7-dione strongly inhibited proliferation of smooth muscle cells and induced apoptosis of the cells through the sustained activation of MAP kinase pathways (ERK, p38, and JNK).

Design and physicochemical properties of new fluorescent ligands of protein kinase C isozymes focused on CH/ π interaction

pp 650–657

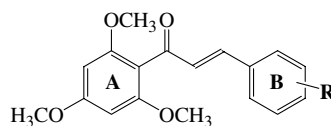
Takuya Sugimoto, Koji Itagaki and Kazuhiro Irie*



Synthesis and pharmacological activity of chalcones derived from 2,4,6-trimethoxyacetophenone in RAW 264.7 cells stimulated by LPS: Quantitative structure–activity relationships

pp 658–667

Louise Domeneghini Chiaradia,* Rodrigo dos Santos, Carlos Eduardo Vitor, André Alexandre Vieira, Paulo César Leal, Ricardo José Nunes, João Batista Calixto and Rosendo Augusto Yunes*

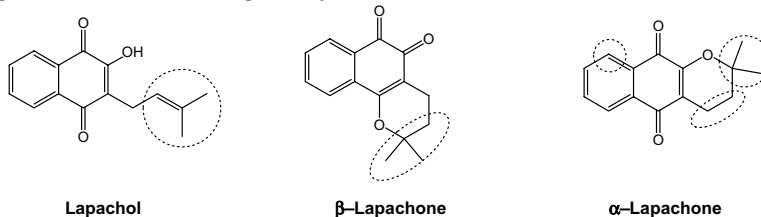


Between 14 chalcones chemically derived from 2,4,6-trimethoxyacetophenone (five of them showed for the first time), eight inhibited the nitrite production in RAW 264.7 cells. Previsions of antiinflammatory activity of other structures were carried out based on QSAR studies.

Trypanosoma cruzi: Activities of lapachol and α - and β -lapachone derivatives against epimastigote and trypomastigote forms

pp 668–674

Cristian Salas,* Ricardo A. Tapia, Karina Ciudad, Verónica Armstrong, Myriam Orellana, Ulrike Kemmerling, Jorge Ferreira, Juan Diego Maya and Antonio Morello

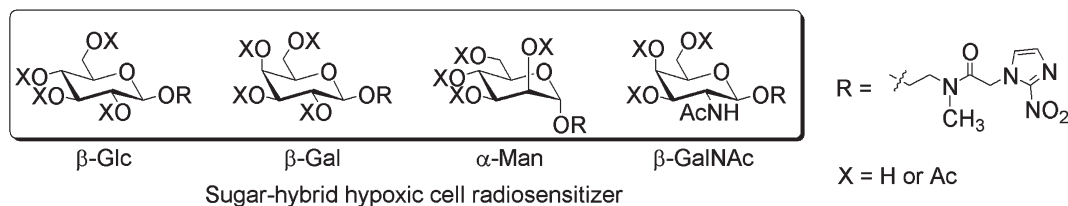


Derivatives obtained by chemical modifications of lapachol, α - and β -lapachones, have been synthesized and their trypanocidal activity evaluated in vitro in *Trypanosoma cruzi* epimastigote and trypomastigote forms.

Design, synthesis, and radiosensitizing activities of sugar-hybrid hypoxic cell radiosensitizers

pp 675–682

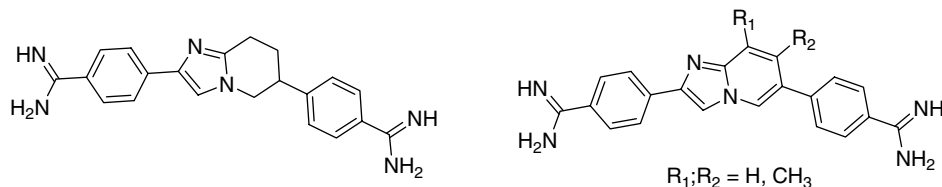
Takashi Nakae, Yoshihiro Uto,* Motoko Tanaka, Haruna Shibata, Eiji Nakata, Masahide Tominaga, Hiroshi Maezawa, Toshihiro Hashimoto, Kenneth L. Kirk, Hideko Nagasawa and Hitoshi Hori*



Synthesis and antiprotozoal activity of novel bis-benzamidino imidazo[1,2-*a*]pyridines and 5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridines

pp 683–691

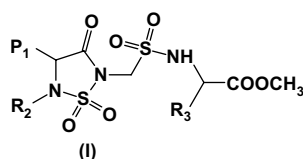
Mohamed A. Ismail, Reem K. Arafa, Tanja Wenzler, Reto Brun, Farial A. Tanious, W. David Wilson and David W. Boykin*



Inactivation of human neutrophil elastase by 1,2,5-thiadiazolidin-3-one 1,1 dioxido-based sulfonamides

pp 692–698

Yi Li, Qingliang Yang, Dengfeng Dou, Kevin R. Alliston and William C. Groutas*

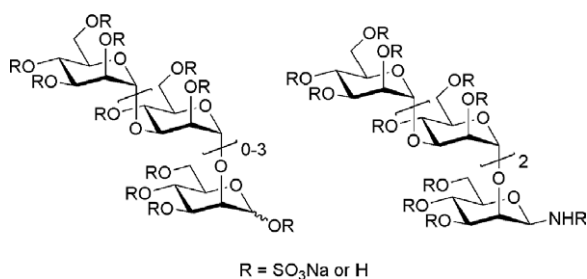


A series of 1,2,5-thiadiazolidin-3-one 1,1 dioxido-based sulfonamides (I) were found to be potent and selective inhibitors of human neutrophil elastase.

Synthesis and heparanase inhibitory activity of sulfated mannoooligosaccharides related to the antiangiogenic agent PI-88

pp 699–709

Jon K. Fairweather, Edward Hammond, Ken D. Johnstone and Vito Ferro*

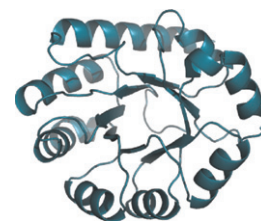


Characterization and crystal structure of *Escherichia coli* KDPGal aldolase

pp 710–720

Matthew J. Walters, Velupillai Srikannathasan, Andrew R. McEwan, James H. Naismith*, Carol A. Fierke* and Eric J. Toone*

The crystal structure of the *E. coli* KDPGal aldolase, which displays $(\alpha/\beta)_8$ topology, has been solved. In addition, site-directed mutagenesis has been employed to investigate the stereoselectivity compared to the analogous KDPG aldolases.

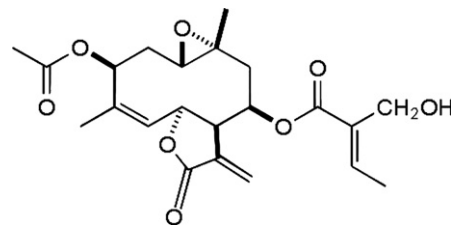


Eupalinin A isolated from *Eupatorium chinense* L. induces autophagocytosis in human leukemia HL60 cells

pp 721–731

Tomohiro Itoh,* Yuko Ito, Kenji Ohguchi, Masayoshi Ohyama, Munekazu Iinuma, Yoshinori Otsuki, Yoshinori Nozawa and Yukihiko Akao

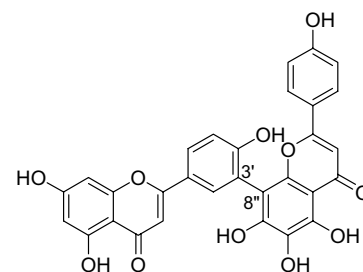
Eupalinin A, one of the sesquiterpene lactones extracted from *Eupatorium chinense* L., indicated cytotoxic activity against HL60 cells. In our experiment, this cytotoxic activity was executed mainly by autophagy.


Biflavonoids isolated from *Selaginella tamariscina* regulate the expression of matrix metalloproteinase in human skin fibroblasts

pp 732–738

Chan-Woo Lee, Hyun-Jung Choi, Han-Sung Kim, Duck-Hee Kim, Ih-Seop Chang, Hyun Teak Moon, Song-Yi Lee, Won Keun Oh and Eun-Rhan Woo*

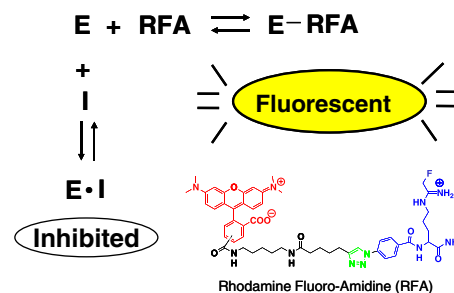
Five biflavonoids were isolated from the whole plants of *Selaginella tamariscina*. The ability of these five biflavonoids to inhibit matrix metalloproteinase (MMP)-1 was investigated. Two of the biflavonoids, sumafflavone and amentoflavone, showed significant MMP-1 inhibitory activity in primary human skin fibroblasts after ultraviolet (UV) irradiation.


Profiling Protein Arginine Deiminase 4 (PAD4): A novel screen to identify PAD4 inhibitors

pp 739–745

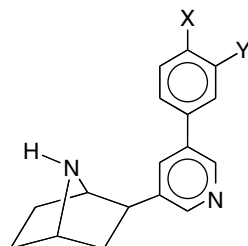
Bryan Knuckley, Yuan Luo and Paul R. Thompson*

Herein we describe a novel screen for PAD4 inhibitors that is based on an Activity-Based Protein Profiling Reagent that covalently modifies PAD4 and renders it fluorescent.


Synthesis, nicotinic acetylcholine receptor binding, and pharmacological properties of 3'-(substituted phenyl)deschloroepibatidine analogs

pp 746–754

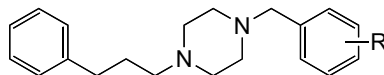
F. Ivy Carroll,* Yasuno Yokota, Wei Ma, Jeffrey R. Lee, Lawrence E. Brieady, Jason P. Burgess, Hernán A. Navarro, M. I. Damaj and Billy R. Martin



Synthesis and structure–activity relationships of *N*-(3-phenylpropyl)-*N'*-benzylpiperazines: Potent ligands for σ_1 and σ_2 receptors

pp 755–761

Roger I. Nahas, John R. Lever and Susan Z. Lever*



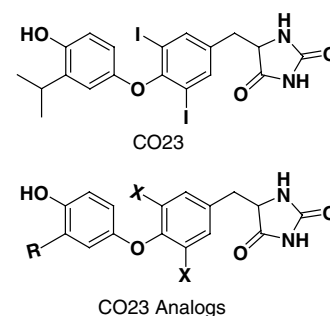
Quantitative structure–activity relationships depended on π_x , MR or E_s , and Hammett σ values. The hydrophobicity term is negative for σ_1 binding but positive for σ_2 binding.

Characterization of thyroid hormone receptor α (TR α)-specific analogs with varying inner- and outer-ring substituents

pp 762–770

Cory A. Ocasio and Thomas S. Scanlan*

CO23 displays TR α -specificity in vitro and in vivo. Compound **CO23** analogs with greater specificity may prove superior to **CO23** in treating heart disease or as a pharmacological probe of TR biology.

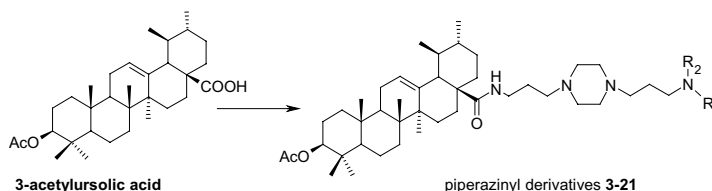


Pharmacomodulation on the 3-acetylursolic acid skeleton: Design, synthesis, and biological evaluation of novel *N*-{3-[4-(3-aminopropyl)piperazinyl]propyl}-3-*O*-acetylursolamide derivatives as antimalarial agents

pp 771–782

Simone C. B. Gnoatto, Sophie Susplugas, Luciana Dalla Vechia, Thais B. Ferreira, Alexandra Dassonville-Klimpt, Karine R. Zimmer, Catherine Demailly, Sophie Da Nascimento, Jean Guillon, Philippe Grellier, Hugo Verli, Grace Gosmann* and Pascal Sonnet*

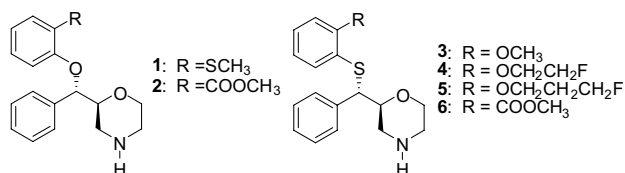
New piperazine derivatives from ursolic acid were designed and synthesized. Seven analogues showed activity in the nanomolar range against *Plasmodium falciparum* FcB1 strain. A possible mechanism of interaction implicating binding of these compounds to β -hematin was supported by in vitro tests and molecular dynamic simulations.



Synthesis, in vitro characterization, and radiolabeling of reboxetine analogs as potential PET radioligands for imaging the norepinephrine transporter

pp 783–793

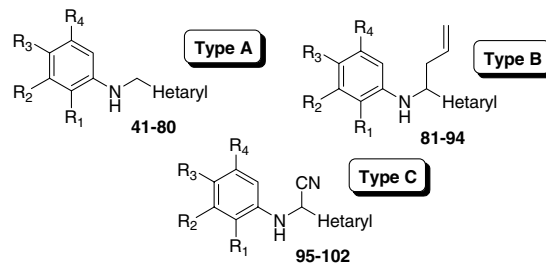
Fanxing Zeng, Nachwa Jarkas, Jeffrey S. Stehouwer, Ronald J. Voll, Michael J. Owens, Clinton D. Kilts, Charles B. Nemeroff and Mark M. Goodman*



Antifungal and cytotoxic activities of some *N*-substituted aniline derivatives bearing a hetaryl fragment pp 794–809

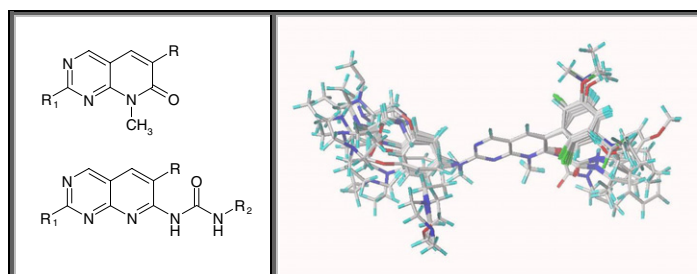
Vladimir V. Kouznetsov,* Leonor Y. Vargas Méndez, Maximiliano Sortino, Yelkaira Vásquez, Mahabir P. Gupta, Mónica Freile, Ricardo D. Enriz and Susana A. Zacchino

Diverse *N*-substituted anilines bearing hetaryl fragments were easily prepared from corresponding aldimines derived from commercially available aromatic aldehydes and anilines. 2-Furyl substituted anilines showed very good antifungal activities against dermatophytes, particularly against *Trichophyton rubrum* (MIC = 3.12–6.25 µg/mL). In addition, all active compounds, **45–47**, **73**, and **74**, were tested for cytotoxic activities against breast (MCF-7), lung (H-460), and central nervous system (SF-268) human cancer cell lines with the NCI-anticancer-drug screen.



2D Autocorrelation, CoMFA, and CoMSIA modeling of protein tyrosine kinases' inhibition by substituted pyrido[2,3-*d*]pyrimidine derivatives pp 810–821

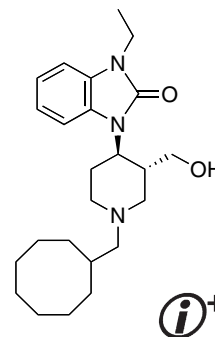
Julio Caballero,* Michael Fernández, Mario Saavedra and Fernando D. González-Nilo



A new synthesis of the ORL-1 antagonist 1-[(3*R*,4*R*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidinyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (J-113397) and activity in a calcium mobilization assay pp 822–829

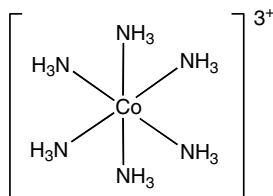
Emilie D. Smith, N. Ariane Vinson, Desong Zhong, Bertold D. Berrang, Jennifer L. Catanzaro, James B. Thomas, Hernán A. Navarro, Brian P. Gilmour, Jeffrey Deschamps and F. Ivy Carroll*

A new chiral synthesis of the ORL-1 antagonist J-113397 was developed. Its in vitro efficacy was determined using an ORL-1 calcium mobilization assay.



Antiviral properties of cobalt(III)-complexes pp 830–837

James B. Delehanty, Jason E. Bongard, Dzung C. Thach, D. Andrew Knight, Thomas E. Hickey and Eddie L. Chang*

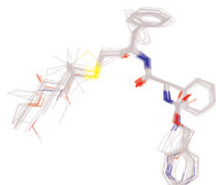


cobalt(III) hexammine

Cobalt(III) hexammine significantly inhibits Sindbis virus replication in baby hamster kidney cells in a dose- and time-dependent manner.

2D QSAR and similarity studies on cruzain inhibitors aimed at improving selectivity over cathepsin L pp 838–853

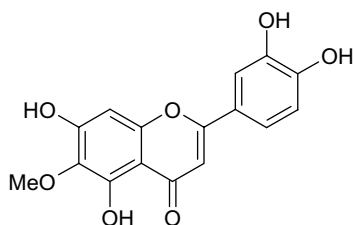
Renato F. Freitas, Tudor I. Oprea and Carlos A. Montanari*



HQSAR was successfully applied to a set of cruzain inhibitors, and the best model predicted 88% of their K_i values. ROCS effectively retrieved 90% cruzain inhibitors in a pool of molecules containing cathepsin L inhibitors.

Eupafolin: Effect on mitochondrial energetic metabolism pp 854–861

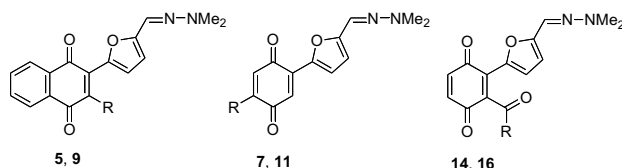
Tatiana Herrerias, Brás H. de Oliveira, Maria A. B. Gomes, Maria B. M. de Oliveira, Eva G. S. Carnieri, Sílvia M. S. C. Cadena, Glauca R. Martinez and Maria E. M. Rocha*



In this study the effects of eupafolin (6-methoxy 5,7,3',4'-tetrahydroxyflavone), a flavone extracted from dry leaves of *Eupatorium litorale*, on mitochondrial metabolism and redox properties were evaluated.

Studies on quinones. Part 42: Synthesis of furylquinone and hydroquinones with antiproliferative activity against human tumor cell lines pp 862–868

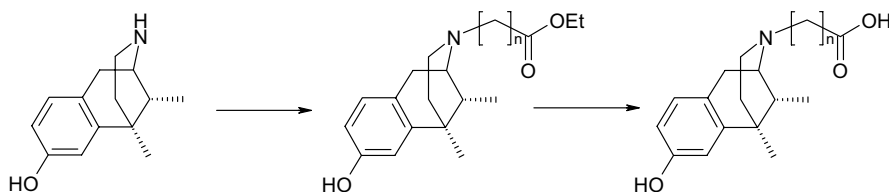
Julio Benites, Jaime A. Valderrama,* Felipe Rivera, Leonel Rojo, Nair Campos, Madalena Pedro and Maria São José Nascimento



Furfural dimethylhydrazone reacts with naphtho- and benzoquinones to give furyl-1,4-naphthoquinones **5**, **9**, and furyl-1,4-benzoquinones **7**, **11**, **14**, **16**. The in vitro evaluation of furylquinone and hydroquinones against a panel of three human tumor cell lines is reported.

The influence of esters and carboxylic acids as the N-substituent of opioids. Part 1: Benzomorphans pp 869–873

Matthew D. Metcalf, Mario D. Aceto, Louis S. Harris, James H. Woods, John R. Traynor, Andrew Coop* and Everette L. May



Synthesis and pharmacology of racemic *N*-ester and *N*-acid normetazocines.

Design, synthesis and structure–activity study of shorter hexa peptide analogues as HIV-1 protease inhibitors

pp 874–880

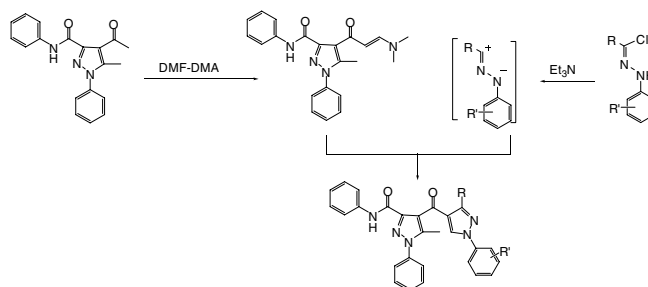
S. N. Narendra Babu and K. S. Rangappa*

The design, synthesis and HIV-1 protease inhibition of the shorter synthetic hexa peptides are discussed. Leu-Leu-Glu-Tyr-Val-Xaa. Where, Xaa = Phe, Met, Tyr or Trp.

Regioselective synthesis and antitumor screening of some novel *N*-phenylpyrazole derivatives

pp 881–889

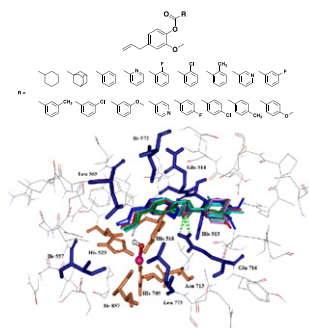
Ahmad M. Farag,* Abdelrahman S. Mayhoub, Saber E. Barakat and Ashraf H. Bayomi



Design and synthesis of eugenol derivatives, as potent 15-lipoxygenase inhibitors

pp 890–901

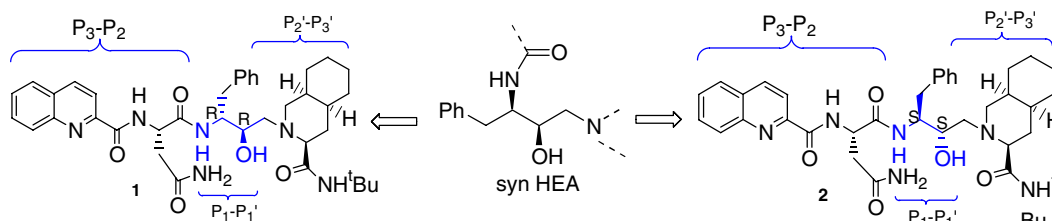
Hamid Sadeghian, Seyed Mohammad Seyedi,* Mohammad Reza Saberi, Zahra Arghiani and Mehdi Riazi



Stereocontrolled synthesis and biological activity of two diastereoisomers of the potent HIV-1 protease inhibitor saquinavir

pp 902–908

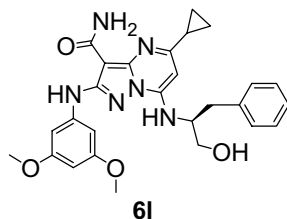
Giuliana Righi,* Simona Ciambone, Carlo Bonini* and Pietro Campaner



Novel pyrazolo[1,5-*a*]pyrimidines as c-Src kinase inhibitors that reduce I_{K_r} channel blockade

pp 909–921

Harunobu Mukaiyama,* Toshihiro Nishimura, Satoko Kobayashi, Yoshimitsu Komatsu, Shinji Kikuchi, Tomonaga Ozawa, Noboru Kamada and Hideki Ohnata

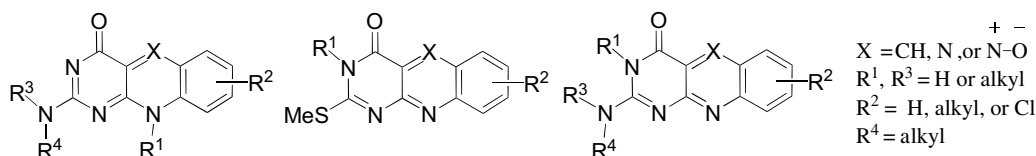


We prepared pyrazolo[1,5-*a*]pyrimidine derivatives that were potent c-Src kinase inhibitors. Modification of the ethylenediamino group at the 7-position of the lead compound **1a** to an amino alcohol group resulted in reduced I_{K_r} channel inhibition. In particular, **6l** showed significant neuroprotective effects in a stroke model.

Antitumor studies. Part 4: Design, synthesis, antitumor activity, and molecular docking study of novel 2-substituted 2-deoxoflavin-5-oxides, 2-deoxoalloxazine-5-oxides, and their 5-deaza analogs

pp 922–940

Hamed I. Ali, Noriyuki Ashida and Tomohisa Nagamatsu*



The correlation between the binding free energies (ΔG_b) docked into the c-kit PTK and the growth inhibitory activities (IC_{50}) against CCRF-HSB-2 and KB tumor cells for novel 2-substituted flavin and alloxazine analogs was investigated.

Novel amino linkers enabling efficient labeling and convenient purification of amino-modified oligonucleotides

pp 941–949

Yasuo Komatsu,* Naoshi Kojima, Maiko Sugino, Akiko Mikami, Ken Nonaka, Yumi Fujinawa, Takashi Sugimoto, Kousuke Sato, Kenichi Matsubara and Eiko Ohtsuka

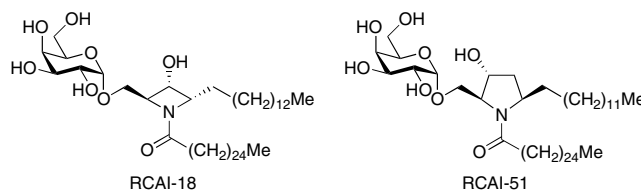


The aminoethyl carbamate structure enabled the convenient purification of amino-modified oligonucleotides with a reverse phase column and increased the labeling efficiency with active esters in aqueous solution.

**RCAI-8, 9, 18, 19, and 49–52, conformationally restricted analogues of KRN7000 with an azetidine or a pyrrolidine ring: Their synthesis and bioactivity for mouse natural killer T cells to produce cytokines**

pp 950–964

Ken-ichi Fuhshuku, Naomi Hongo, Takuya Tashiro, Yui Masuda, Ryusuke Nakagawa, Ken-ichiro Seino, Masaru Taniguchi and Kenji Mori*

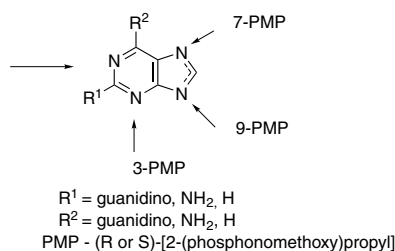


These are inducers of cytokine production by mouse NKT cells

Synthesis of guanidino analogues of PMPDAP and their immunobiological activity

pp 965–980

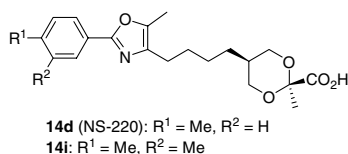
Michal Česnek,* Antonín Holý, Milena Masojídková, Eva Kmoníčková and Zdeněk Zidek



Structure–activity studies on 1,3-dioxane-2-carboxylic acid derivatives, a novel class of subtype-selective peroxisome proliferator-activated receptor α (PPAR α) agonists

pp 981–994

Tetsuo Asaki,* Tomiyoshi Aoki, Taisuke Hamamoto, Yukiteru Sugiyama, Shinji Ohmachi, Kenji Kuwabara, Kohji Murakami and Makoto Todo

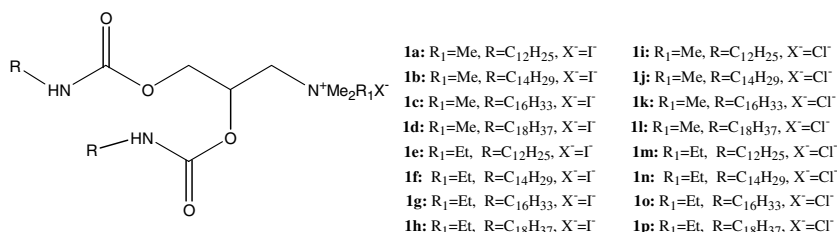


The 1,3-dioxane-2-carboxylic acids **14d** (NS-220) and **14i** were identified as highly potent and selective human PPAR α agonists. These compounds showed excellent hypolipidemic activity in type 2 diabetic KK-A y mice.

Carbamate-linked cationic lipids for gene delivery

pp 995–1005

Dongliang Liu,* Weihong Qiao, Zongshi Li, Xiuyun Cui, Kun Li, Lihua Yu, Kelu Yan, Limin Zhu and Lvbo Cheng



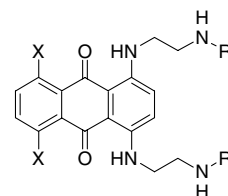
Cationic lipids **1a–p**, with carbamate linkages between hydrocarbon chains and quaternary ammonium heads, were synthesized for liposome-mediated gene delivery, and the biological performance of them was studied.

Synthesis, DNA binding, and cytotoxicity of 1,4-bis(2-amino-ethylamino)anthraquinone–amino acid conjugates

pp 1006–1014

Ling-Wei Hsin,* Hui-Po Wang, Pi-Hung Kao, On Lee, Wan-Ru Chen, Hung-Wei Chen, Jih-Hwa Guh, Ya-Ling Chan, Chin-Ping His, Ming-Show Yang, Tsai-Kun Li and Chieh-Hua Lee

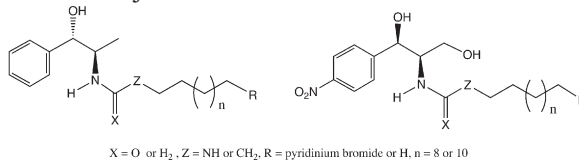
A focused library of 1,4-bis(2-amino-ethylamino)anthraquinone–amino acid conjugates (BACs) was synthesized. The ability to increase melting temperature of ct-DNA and the cytotoxic activity against human cancer cell lines of these BACs were investigated.



$R = \text{L- or D-amino acid residues}$
 $X = \text{H or OH}$

Novel analogs of D-e-MAPP and B13. Part 1: Synthesis and evaluation as potential anticancer agents pp 1015–1031

Zdzislaw M. Szulc, Nalini Mayroo, AiPing Bai, Jacek Bielawski, Xiang Liu, James S. Norris, Yusuf A. Hannun and Alicja Bielawska*



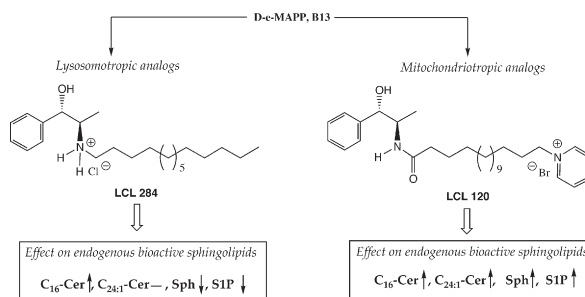
| | D-MAPP | LCL16 | LCL284 | LCL120 | B13 | LCL15 | LCL204 | LCL85 |
|--|--------|-------|--------|--------|-------|-------|--------|-------|
| MCF-7 (IC ₅₀ /μM) | 30.0 | 16.0 | 3.5 | 2.5 | 14.0 | 18.0 | 4.5 | 2.3 |
| MG MID ⁺ LogGI ₅₀ (M) | -4.03 | -4.76 | -5.75 | -5.67 | -4.02 | -4.84 | -5.58 | -5.30 |

*) Based on NCI's 60-human-tumor-cell lines

Novel analogs of D-e-MAPP and B13. Part 2: Signature effects on bioactive sphingolipids

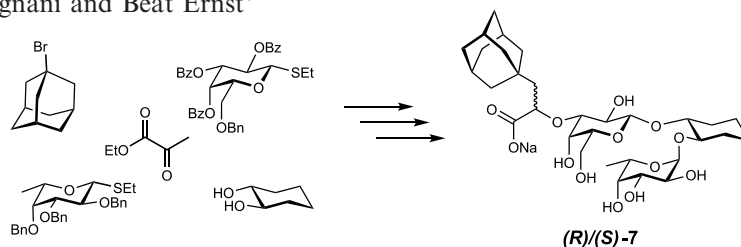
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Alicja Bielawska,* Jacek Bielawski, Zdzislaw M. Szulc, Nalini Mayroo, Xiang Liu, AiPing Bai, Saeed Elojeimy, Barbara Rembiesa, Jason Pierce, James S. Norris and Yusuf A. Hannun

**Is adamantane a suitable substituent to pre-organize the acid orientation in E-selectin antagonists?**

pp 1046–1056

Alexander Titz, John Patton, André M. Alker, Michele Porro, Oliver Schwardt, Michael Hennig, Eric Francotte, John Magnani and Beat Ernst*



For the pre-organization of the acid orientation in the bioactive conformation, the selectin antagonists **7** containing (R)- and (S)-adamantyl-lactic acid were synthesized and biologically evaluated.

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i⁺ Supplementary data available via ScienceDirect

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Schematic view on the E-selectin - leukocyte interaction during the early steps of the inflammatory cascade: the (S)-configured adamantlyllactate analog of sialyl LewisX binds to E-selectin and could therefore inhibit leukocyte extravasation into neighbouring tissue in inflammatory diseases [Titz, A.; Alker, A. M.; Porro, M.; Schwardt, O.; Hennig, M.; Francotte, E.; Magnani, J.; Ernst, B. *Bioorg. Med. Chem.* **2008**, 16, 1046–1056].

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