

Contents

COMMUNICATIONS

Novel epicatechin derivatives with antioxidant activity modulate interleukin-1 β release in lipopolysaccharide-stimulated human blood pp 5031–5034

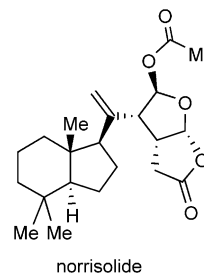
Montserrat Mitjans, Verónica Martínez, Jaime del Campo, Celia Abajo, Carles Lozano, Josep Lluís Torres and Maria Pilar Vinardell*

The immunomodulatory activity of high added-value novel epicatechin (Ec) derivatives obtained by depolymerization of grape polymeric flavanols (proanthocyanidines) in the presence of cysteamine or cysteine is reported. The inhibitory effect of epicatechin and its derivatives on the production of IL-1 β was studied in whole blood treated with LPS from *E. coli*. All three products showed concentration-dependent inhibition, 4 β -(2-aminoethylthio)epicatechin being the most effective.

Fragmentation of Golgi membranes by norrisolide and designed analogues pp 5035–5039

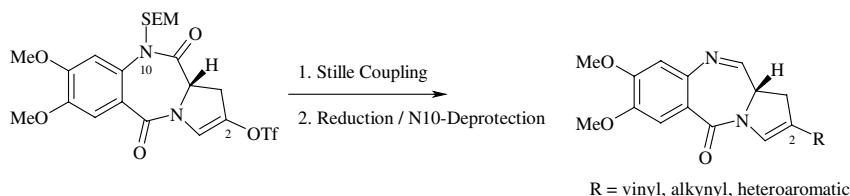
Thomas P. Brady, Erin K. Wallace, Sun Hee Kim, Gianni Guizzunti, Vivek Malhotra* and Emmanuel A. Theodorakis*

The marine natural product norrisolide was found to induce irreversible fragmentation of the Golgi membranes. A hypothesis accounting for the chemical origins of this effect is proposed based on structure/function studies of norrisolide and designed analogues.



Application of the Stille coupling reaction to the synthesis of C2-substituted *endo-exo* unsaturated pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) pp 5041–5044

Arnaud C. Tiberghien, David Hagan, Philip W. Howard* and David E. Thurston*

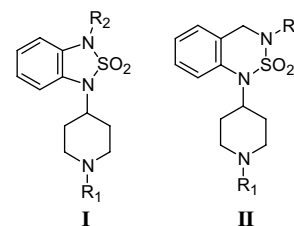


The Stille coupling reaction has been employed to introduce novel vinyl, alkynyl and heterocyclic substituents to the C2-position of pyrrolo[2,1-*c*][1,4]benzodiazepines. Sodium borohydride reduction of the dilactam intermediates followed by N10-SEM deprotection has provided five novel C2-*endo/exo*-unsaturated analogues with significant cytotoxicity.

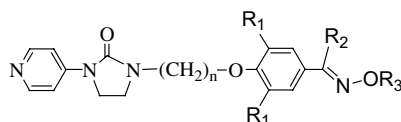
1,3-Dihydro-2,1,3-benzothiadiazol-2,2-diones and 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-diones as ligands for the NOP receptor pp 5045–5050

R. Richard Goehring,* John F. W. Whitehead, K. Brown, Khondaker Islam, Xin Wen, Xiaoming Zhou, Zhengming Chen, Kenneth J. Valenzano, Wendy S. Miller, Shen Shan and Donald J. Kyle

A series of 1,3-dihydro-2,1,3-benzothiadiazol-2,2-diones (**I**) and 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-diones (**II**) were prepared. While the five-member ring series (**I**) did not show good affinity for opioid receptors, the six-member ring series (**II**) exhibited extremely high affinity and selectivity for the NOP receptor and showed full agonist activity, as determined by stimulation of GTPγ[³⁵S] binding.


Synthesis and antienteroviral activity of a series of novel, oxime ether-containing pyridyl imidazolidinones pp 5051–5056

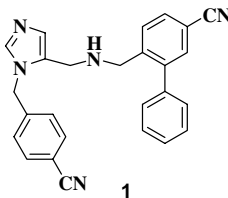
Jyh-Haur Chern,* Chung-Chi Lee, Chih-Shiang Chang, Yen-Chun Lee, Chia-Liang Tai, Ying-Ting Lin, Kak-Shan Shia, Ching-Yin Lee and Shin-Ru Shih*



A series of pyridyl imidazolidinones were synthesized and their antiviral activity was evaluated in a plaque reduction assay. It was found that the pyridyl imidazolidinone with an ethyl oxime ether functionality, **8b**, exhibited extremely high activity against human enterovirus 71.

Synthesis and biological evaluation of 1-benzyl-5-(3-biphenyl-2-yl-propyl)-1*H*-imidazole as novel farnesyltransferase inhibitor pp 5057–5062

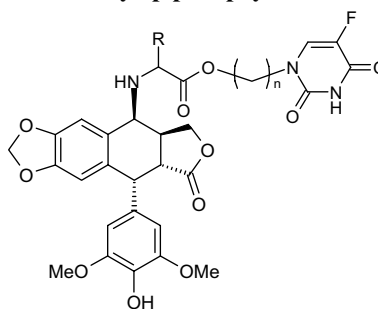
Nan-Horng Lin,* Le Wang, Xilu Wang, Gary T. Wang, Jerry Cohen, Wen-Zhen Gu, Haiying Zhang, Saul H. Rosenberg and Hing L. Sham



Analogues of compound **1** were synthesized and tested in vitro for farnesyltransferase inhibition activity.

Synthesis and cytotoxic activity of novel derivatives of 4'-demethylepipodophyllotoxin pp 5063–5066

Shi-Wu Chen, Xuan Tian* and Yong-Qiang Tu*

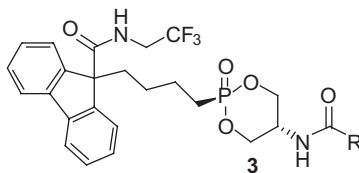


The IC₅₀ values of **9g** ($n = 5$, $R = \text{CH}_2\text{Ph}$), which is the most potent inhibitor against HL-60 and A-549 cells, are 0.04 and <0.01 μM, respectively.

5-Carboxamido-1,3,2-dioxaphosphorinanes, potent inhibitors of MTP

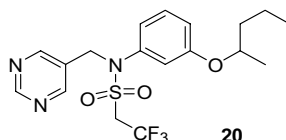
pp 5067–5070

Richard Sulsky,* Jeffrey A. Robl, Scott A. Biller, Thomas W. Harrity, John Wetterau, Fergal Connolly, Kern Jolibois and Lori Kunselman

**Pyrimidine methyl anilines: selective potentiators for the metabotropic glutamate 2 receptor**

pp 5071–5074

Essa Hu,* Peter C. Chua, Lida Tehrani, Johnny Y. Nagasawa, Anthony B. Pinkerton, Blake A. Rowe, Jean-Michel Vernier, John H. Hutchinson and Nicholas D. P. Cosford

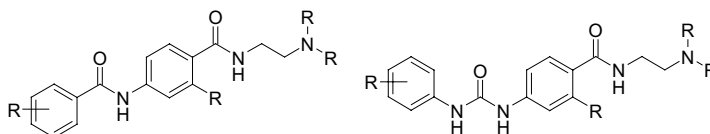


Pyrimidine methyl anilines as potent and selective mGlu2 potentiators are described. Findings from the structure–activity–relationship investigations are discussed.

4-Acylamino- and 4-ureidobenzamides as melanin-concentrating hormone (MCH) receptor 1 antagonists

pp 5075–5080

Jean-Marie Receveur, Emelie Bjurling, Trond Ulven, Paul Brian Little, Pia K. Nørregaard and Thomas Högberg*

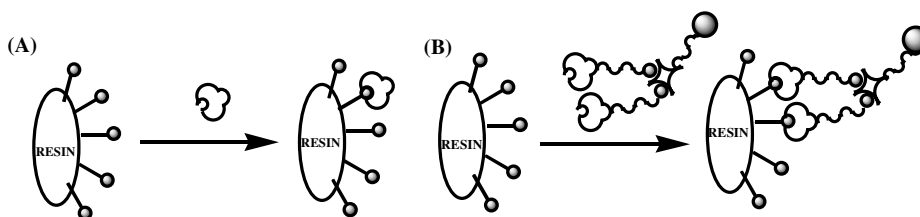


Synthesis, in vitro biological evaluation and structure–activity relationships of novel hMCH1R-antagonists are disclosed. The nature of the amine side chains could be varied considerably in contrast to the central benzamide scaffold and aromatic substituents.

Development of a polyvalent assay system for lead identification

pp 5081–5083

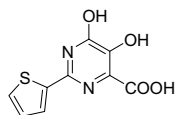
Frank Lovering,* Yvonne Angell, Yan-Ling Zhang and Kristie Bridges



Active site inhibitors of HCV NS5B polymerase. The development and pharmacophore of 2-thienyl-5,6-dihydropyrimidine-4-carboxylic acid

pp 5085–5088

Ian Stansfield, Salvatore Avolio, Stefania Colarusso, Nadia Gennari, Frank Narjes, Barbara Pacini, Simona Ponzi and Steven Harper*

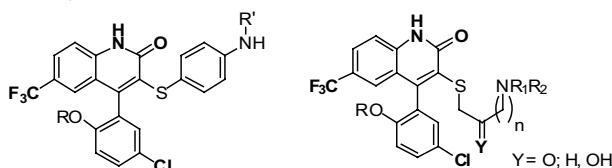


The discovery of a simple 2-thienyl substituted 5,6-dihydropyrimidine-4-carboxylic acid active-site inhibitor of the HCV NS5B polymerase inhibitor is reported. Structure–activity relationships that led to an understanding of the pharmacophore around the pyrimidine ring is also described.

3-Thio-quinolinone maxi-K openers for the treatment of erectile dysfunction

pp 5089–5093

Kenneth M. Boy,* Jason M. Guernon, Sing-Yuen Sit, Kai Xie, Piyasena Hewawasam, Christopher G. Boissard, Steven I. Dworetzky, Joanne Natale, Valentin K. Gribkoff, Nicholas Lodge and John E. Starrett, Jr.

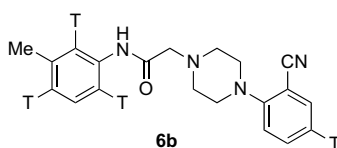


A series Maxi-K openers for the treatment of erectile dysfunction based on the 3-thio-quinolinone core is described. Significant levels of channel opening (up to 550% of control) are seen in transfected oocytes. Functional activity in rabbit corpus cavernosum tissue strips confirms the potential to effect therapy for ED, the effect being maximal for the 3-amino-2-hydroxy thiol side chain.

Synthesis and activity of 2-[4-(4-[³H]-2-cyanophenyl)piperazinyl]-N-(2,4,6-[³H]-3-methylphenyl)-acetamide: a selective dopamine D₄ receptor agonist and radioligand

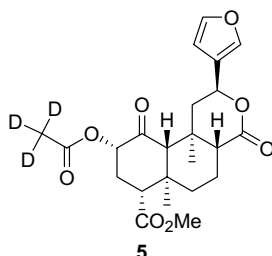
pp 5095–5098

Mark A. Matulenko,* Bruce Surber, Leimin Fan, Teodozyi Kolasa, Masaki Nakane, Marc A. Terranova, Marie E. Uchic, Loan N. Miller, Renjie Chang, Diana L. Donnelly-Roberts, Marian T. Namovic, Robert B. Moreland, Jorge D. Brioni and Andrew O. Stewart


A facile method for the preparation of deuterium labeled salvinorin A: synthesis of [2,2,2-²H₃]-salvinorin A

pp 5099–5102

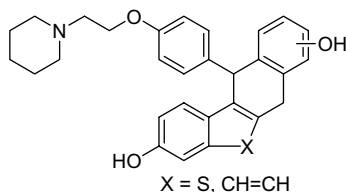
Kevin Tidgewell, Wayne W. Harding, Mark Schmidt, Kenneth G. Holden, Daryl J. Murry and Thomas E. Prisinzano*



Benzothiophene and naphthalene derived constrained SERMs

pp 5103–5106

Owen B. Wallace,* Henry U. Bryant, Pamela K. Shetler, Mary D. Adrian and Andrew G. Geiser

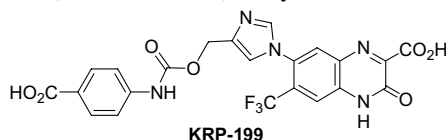


The synthesis and biological evaluation of two series of conformationally restricted SERMs are disclosed. In each series (benzothiophene or naphthalene), the ligand side chain is constrained to adopt a defined orientation. The orientation of the side chain has a significant impact on functional activity.

Synthesis and AMPA receptor antagonistic activity of a novel 7-imidazolyl-6-trifluoromethyl quinoxalinecarboxylic acid with a substituted phenyl group and improved its good physicochemical properties by introduced CF₃ group

pp 5107–5111

Yasuo Takano,* Futoshi Shiga, Jun Asano, Wataru Hori, Tsuyosi Anraku and Takashi Uno

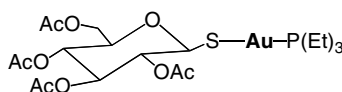


We describe the synthesis, physicochemical and biological properties of a novel series of 7-imidazolyl-6-trifluoromethyl quinoxalinecarboxylic acids with a substituted phenyl group. Among them, compound **9k (KRP-199)** was found to possess high potency and selectivity for the AMPA-R and to exhibit good neuroprotective effects in vivo, and also showed good physicochemical properties by introduced trifluoromethyl group at the C-6 position.

Inhibition of lysosomal cysteine proteases by chrysotherapeutic compounds: a possible mechanism for the antiarthritic activity of Au(I)

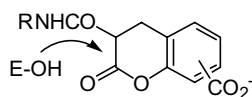
pp 5113–5116

Aida Chircorian and Amy M. Barrios*

**Benzopyranones with retro-amide side chains as (inhibitory) β-lactamase substrates**

pp 5117–5120

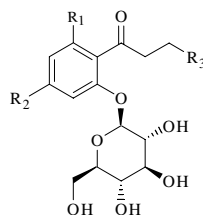
S. A. Adediran, D. Cabaret, J.-F. Lohier, M. Wakselman* and R. F. Pratt*



Glycosylated dihydrochalcones as potent and selective sodium glucose co-transporter 2 (SGLT2) inhibitors

pp 5121–5125

Joseph Dudash, Jr.,* Xiaoyan Zhang, Roxanne E. Zeck, Sigmond G. Johnson, Geoffrey G. Cox, Bruce R. Conway, Philip J. Rybczynski and Keith T. Demarest



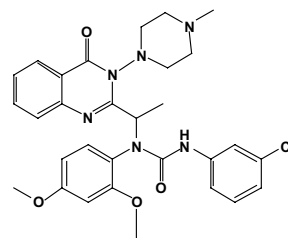
A series of glucose conjugates was synthesized and tested for inhibition of SGLT1 and SGLT2.

Quinazolinone-based fungal efflux pump inhibitors. Part 1: Discovery of an (N-methylpiperazine)-containing derivative with activity in clinically relevant *Candida* spp.

pp 5127–5131

Rémy C. Lemoine,* Tomasz W. Glinka, William J. Watkins, Aesop Cho, Jessie Yang, Nadeem Iqbal, Rajeshwar Singh, Deidre Madsen, Karen Lolans, Olga Lomovskaya, Uma Oza and Michael N. Dudley

The discovery of a series of quinazolinone-based fungal efflux pump inhibitors by high-throughput screening for potentiation of fluconazole in *C. albicans* is described. Attempts to improve the aqueous solubility of screening hits led to the discovery of an analog with greatly improved physical properties and activity against clinically-relevant *Candida* spp.

**Quinazolinone fungal efflux pump inhibitors. Part 2: In vitro structure–activity relationships of (N-methyl-piperazinyl)-containing derivatives**

pp 5133–5137

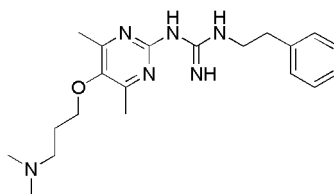
William J. Watkins,* Rémy C. Lemoine, Lee Chong, Aesop Cho, Thomas E. Renau, Bonnie Kuo, Vickie Wong, Maria Ludwikow, Negar Garizi, Nadeem Iqbal, John Barnard, Renata Jankowska, Rajeshwar Singh, Deidre Madsen, Karen Lolans, Olga Lomovskaya, Uma Oza and Michael N. Dudley

Structure–activity relationships of a novel series of fungal efflux pump inhibitors with respect to potentiation of the activity of fluconazole against strains of *Candida albicans* and *Candida glabrata* over-expressing ABC-type efflux pumps are systematically explored.

Biaryl guanidine inhibitors of in vitro HCV-IRES activity

pp 5139–5143

Elizabeth A. Jefferson,* Punit P. Seth, Dale E. Robinson, Dana K. Winter, Alycia Miyaji, Stephen A. Osgood, Eric E. Swayze and Lisa M. Risen

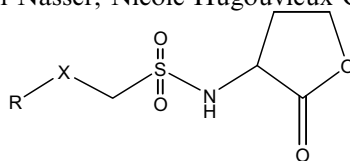


An SAR study on a high-throughput screening lead for HCV-IRES translation inhibition led to the identification of low μM inhibitors.

N-Sulfonyl homoserine lactones as antagonists of bacterial quorum sensing

pp 5145–5149

Sandra Castang, Bernard Chantegrel, Christian Deshayes, René Dolmazon, Patrice Gouet, Richard Haser, Sylvie Reverchon, William Nasser, Nicole Hugouvieux-Cotte-Pattat and Alain Doutheau*



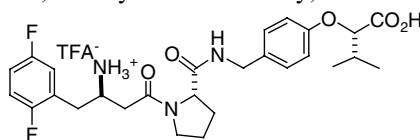
R = alkyl- or phenylalkyl- X = CH₂ or C=O

A series of 11 *N*-sulfonyl homoserine lactones has been synthesised. Some of them were found to competitively inhibit the action of 3-oxohexanoyl-L-homoserine lactone, the natural inducer of bioluminescence in the bacterium *Vibrio fischeri*. Molecular modeling suggests a possible explanation based on the prevention of structural rearrangements necessary for the formation of the active dimer of LuxR.

Potent and selective proline derived dipeptidyl peptidase IV inhibitors

pp 5151–5155

Scott D. Edmondson,* Anthony Mastracchio, Maria Beconi, Lawrence F. Colwell, Jr., Bahanu Habulihaz, Huaibing He, Sanjeev Kumar, Barbara Leiting, Kathryn A. Lyons, Ann Mao, Frank Marsilio, Reshma A. Patel, Joseph K. Wu, Lan Zhu, Nancy A. Thornberry, Ann E. Weber and Emma R. Parmee



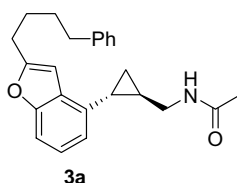
37, DPP-IV IC₅₀ = 0.48 nM

In-house screening of the Merck sample collection identified proline derived homophenylalanine **3** as a DPP-IV inhibitor with modest potency (DPP-IV IC₅₀ = 1.9 μM). Optimization of **3** led to compound **37**, which is among the most potent and selective DPP-IV inhibitors discovered to date.

N-{2-[2-(4-Phenylbutyl)benzofuran-4-yl]cyclopropylmethyl}acetamide: an orally bioavailable melatonin receptor agonist

pp 5157–5160

Li-Qiang Sun,* Katherine Takaki, Jie Chen, Lawrence Iben, Jay O. Knipe, Lori Pajor, Cathy D. Mahle, Elaine Ryan and Cen Xu



3a

N-{2-[2-(4-Phenylbutyl)benzofuran-4-yl]cyclopropylmethyl}acetamide **3a** was synthesized as an orally bioavailable agonist at MT₁ and MT₂ melatonin receptors with significantly low vasoconstrictive activity.

Specificity of human *trans*-sialidase as probed with gangliosides

pp 5161–5164

E. Yu. Nikonova, V. V. Tertov, C. Sato, K. Kitajima and N. V. Bovin*

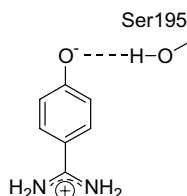


Human blood *trans*-sialidase able to form and split α2-8 disialic bond in gangliosides.

Design, synthesis, and evaluation of oxyanion-hole selective inhibitor substituents for the S1 subsite of factor Xa

pp 5165–5170

Sochanchingwung Rumthao, Oukseub Lee, Qi Sheng, WenTao Fu,
Debbie C. Mulhearn, David Crich, Andrew D. Mesecar and Michael E. Johnson*

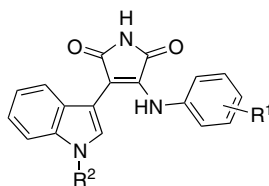


Placement of an anionic group within the oxyanion hole region of the Factor Xa catalytic site substantially enhances activity, with small flexible groups favored over bulkier ones.

**Synthesis of anilino-monoindolylmaleimides as potent and selective PKC β inhibitors**

pp 5171–5174

Masahiro Tanaka, Shoichi Sagawa, Jun-ichi Hoshi, Fumito Shimoma, Isamu Matsuda,
Kenji Sakoda, Tomohiko Sasase, Masanori Shindo and Takashi Inaba*

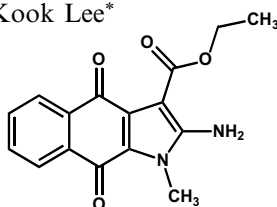


The synthesis and enzyme inhibitory activity of PKC β -selective inhibitors possessing the novel pharmacophore of anilino-monoindolylmaleimide are described.

Induction of G₂/M cell cycle arrest and apoptosis by a benz[*f*]indole-4,9-dione analog in cultured human lung (A549) cancer cells

pp 5175–5178

Eun-Jin Lee, Hyun-Jung Lee, Hyen Joo Park, Hye-Young Min,
Myung-Eun Suh, Hwa-Jin Chung and Sang Kook Lee*

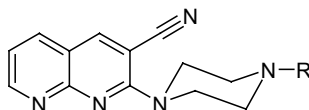


A synthetic benz[*f*]indole-4,9-dione analog, 2-amino-3-ethoxycarbonyl-*N*-methylbenz[*f*]indole-4,9-dione (SME-6), showed a potent growth inhibition of a panel of human cancer cell lines. The mechanism of action study revealed that the growth inhibitory effect of SME-6 was highly related to the induction of G₂/M cell cycle arrest and apoptosis in human lung cancer cells (A549).

Microwave assisted synthesis of 2-(4-substituted piperazin-1-yl)-1,8-naphthyridine-3-carbonitrile as a new class of serotonin 5-HT₃ receptor antagonists

pp 5179–5181

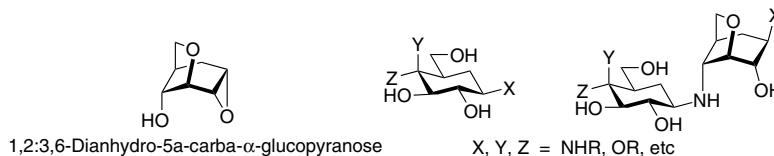
Radhakrishnan Mahesh,* Ramachandran Venkatesha Perumal and Pandi Vijaya Pandi



A series of novel 2-(4-substituted piperazin-1-yl)-1,8-naphthyridine-3-carbonitrile were prepared and evaluated for serotonin 5-HT₃ receptor antagonist activities in the isolated Guinea pig ileum.

Synthesis of 5a-carba-hexopyranoses and hexopyranosylamines, as well as 5a,5a'-dicarbadisaccharides, pp 5183–5188
from 3,8-dioxatricyclo[4.2.1.0^{2,4}]nonan-9-ol: glycosidase inhibitory activity of N-substituted
5a-carba- β -gluco- and β -galactopyranosylamines, and derivatives thereof

Seiichiro Ogawa,* Sho Funayama, Kensuke Okazaki, Fumito Ishizuka, Yoko Sakata and Fuminao Doi

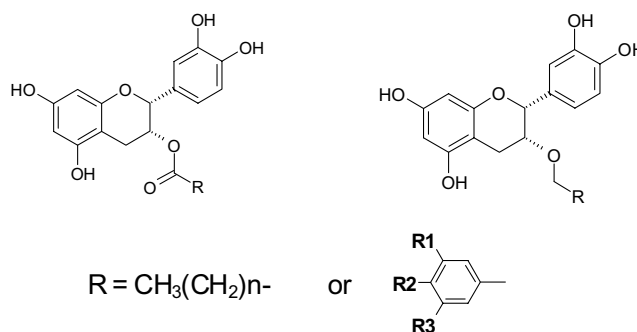


Anticancer activity of 3-*O*-acyl and alkyl(–)-epicatechin derivatives

pp 5189–5192

Ki Duk Park,* Sul Gi Lee, Sung Uk Kim, Sung Han Kim, Won Suck Sun,
 Sung Jin Cho and Do Hyeon Jeong

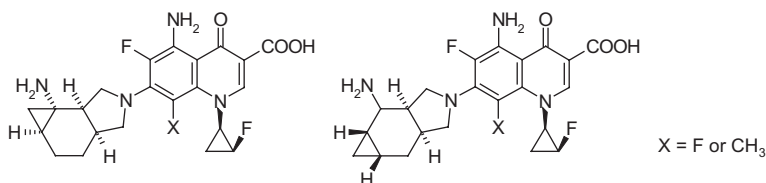
We report the synthesis and anticancer effects of
 3-*O*-acyl and alkyl(–)-epicatechin derivatives.



Synthesis and antibacterial activity of novel 6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-
4-oxoquinoline-3-carboxylic acids bearing cyclopropane-fused
2-amino-8-azabicyclo[4.3.0]nonan-8-yl substituents at the C-7 position

pp 5193–5198

Hiroaki Inagaki,* Hisashi Takahashi and Makoto Takemura

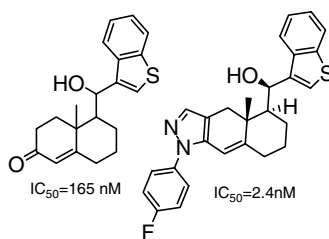


New quinolone compounds were synthesized and evaluated their antibacterial activity and enzyme selectivity.

Design and evaluation of novel nonsteroidal dissociating glucocorticoid receptor ligands

pp 5199–5203

Nilesh Shah and Thomas S. Scanlan*

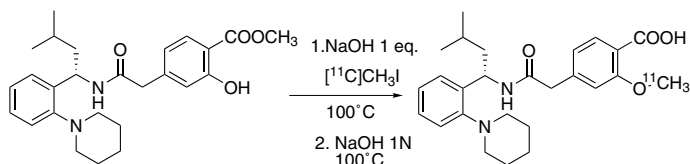


A novel class of phenylpyrazole fused Wieland–Miescher ketone derivatives are high affinity, receptor specific, selective modulators of glucocorticoid receptor (GR) function.

Synthesis and in vitro evaluation of (S)-2-([¹¹C]methoxy)-4-[3-methyl-1-(2-piperidine-1-yl-phenyl)-butyl-carbamoyl]-benzoic acid ([¹¹C]methoxy-repaglinide): a potential β-cell imaging agent

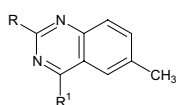
pp 5205–5209

Björn Wängler, Carmen Beck, Chyng Yann Shiue, Stephan Schneider, Christina Schwanstecher, Mathias Schwanstecher, Peter Johannes Feilen, Abass Alavi, Frank Rösch and Ralf Schirmmacher*


Synthesis and biological activity of novel antibacterial quinazolines

pp 5211–5213

Preet M. S. Bedi,* V. Kumar and Mohinder P. Mahajan



(Compound 6)

6a R = Ph ; R¹ = *p*-Me₂N-Ph

6b R = Ph ; R¹ = *p*-MeO-Ph

6c R = ; R¹ = Ph

6d R = ; R¹ = *p*-Me₂N-Ph

6e R = ; R¹ = *p*-MeO-Ph

Synthesis and evaluation of 4-triazolylflavans as new aromatase inhibitors

pp 5215–5218

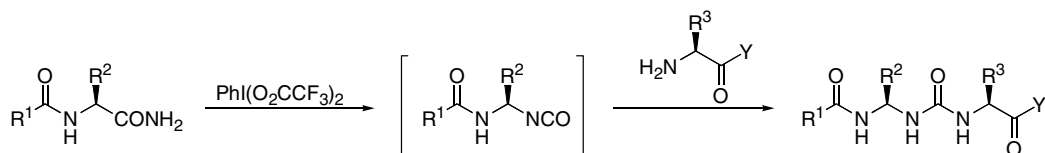
Samir Yahiaoui, Christelle Pouget, Catherine Fagnere, Yves Champavier, Gérard Habrioux and Albert José Chulia*

Aromatase is a target of pharmaceutical interest for the treatment of estrogen-dependent cancers. Azole derivatives such as letrozole or anastrozole have been developed for aromatase inhibition and are used for the treatment of breast tumors. In this paper, four 4-triazolylflavans were synthesized and were found to exhibit moderate to high inhibitory potency against aromatase.

Facile incorporation of urea pseudopeptides into protease substrate analogue inhibitors

pp 5219–5222

Adam C. Myers, Jennifer A. Kowalski and Mark A. Lipton*

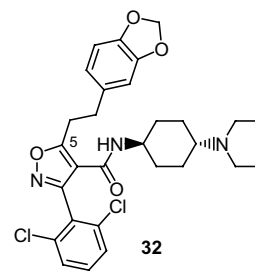


Novel isoxazole carboxamides as growth hormone secretagogue receptor (GHS-R) antagonists

pp 5223–5226

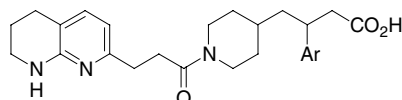
Bo Liu, Gang Liu,* Zhili Xin, Micheal D. Serby, Hongyu Zhao, Verlyn G. Schaefer,
H. Douglas Falls, Wiweka Kaszubska, Christine A. Collins and Hing L. Sham

Novel isoxazole carboxamides have been identified as growth hormone secretagogue receptor (GHS-R) antagonists. Substituent modification off the 5-position of the isoxazole ring led to analogues with potent binding affinity and functional antagonism of GHS-R. A potent analogue (32) with high aqueous solubility and good GPCR selectivity was also identified as a potential pharmacological tool for in vivo studies.

**Piperidine-containing β -arylpropionic acids as potent antagonists of $\alpha_v\beta_3/\alpha_v\beta_5$ integrins**

pp 5227–5232

Bart L. De Corte,* William A. Kinney, Li Liu, Shyamali Ghosh, Livia Brunner,
William J. Hoekstra, Rosemary J. Santulli, Robert W. Tuman, Judith Baker,
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Bruce E. Maryanoff, Dana L. Johnson and Robert A. Galemno, Jr.




The synthesis and SAR of a new class of piperidine-based $\alpha_v\beta_3/\alpha_v\beta_5$ integrin antagonists is described.

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 Supplementary data available via ScienceDirect

COVER

Cover figure provided by **Indraneel Ghosh**, Department of Chemistry, University of Arizona. The cover depicts the **Dual Surface Selection** methodology developed by the author: the blue helix of htBI (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBI (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].

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ISSN 0960-894X