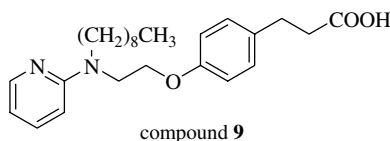


Contents

COMMUNICATIONS

Design, synthesis, and biological activity of novel PPAR γ ligands based on rosiglitazone and 15d-PGJ₂ pp 1547–1551

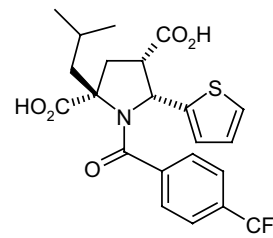
Shinya Usui, Takayoshi Suzuki, Yoshifumi Hattori, Kazuma Etoh, Hiroki Fujieda, Makoto Nishizuka, Masayoshi Imagawa, Hidehiko Nakagawa, Kohfuku Kohda and Naoki Miyata*



To develop novel PPAR γ agonists, we synthesized several 3-{4-(2-aminoethoxy)phenyl}propanoic acid derivatives designed on the basis of the structures of rosiglitazone and 15d-PGJ₂. In this series, compound **9** was found to be as potent as rosiglitazone. A binding mode analysis of **9** using computer calculations is also reported.

Identification of small molecule inhibitors of the hepatitis C virus RNA-dependent RNA polymerase from a pyrrolidine combinatorial mixture pp 1553–1556

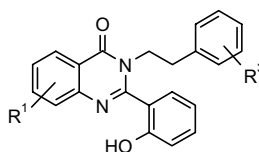
George Burton,* Thomas W. Ku, Thomas J. Carr, Terry Kiesow, Robert T. Sarisky, Juili Lin-Goerke, Audrey Baker, David L. Earnshaw, Glenn A. Hofmann, Richard M. Keenan and Dashyant Dhanak



Solid-phase synthesis and SAR is described for a series of *N*-acyl pyrrolidine inhibitors of the Hepatitis C virus RNA-dependent RNA polymerase, NS5B.

3*H*-Quinazolin-4-ones as a new calcilytic template for the potential treatment of osteoporosis pp 1557–1560

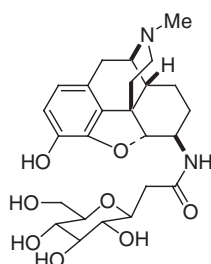
Irina Shcherbakova,* Manuel F. Balandrin, John Fox, Anjan Ghatak, William L. Heaton and Rebecca L. Conklin



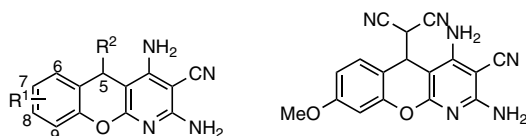
Structure–activity relationship studies, focused on identification of the active pharmacophore fragments in a single high-throughput screening calcilytic hit, resulted in the discovery of potent calcium receptor antagonists, substituted 3*H*-quinazolin-4-ones.

Synthesis and in vitro biological evaluation of a carbon glycoside analogue of morphine-6-glucuronide pp 1583–1586

James M. MacDougall,* Xiao-Dong Zhang, Willma E. Polgar, Taline V. Khroyan, Lawrence Toll and John R. Cashman

**Aminocyanopyridine inhibitors of mitogen activated protein kinase-activated protein kinase 2 (MK-2)** pp 1587–1590

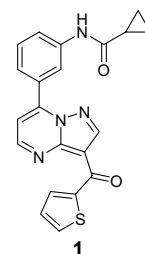
David R. Anderson,* Shridhar Hegde,* Emily Reinhard, Leslie Gomez, William F. Vernier, Len Lee, Shuang Liu, Aruna Sambandam, Patricia A. Snider and Liaqat Masih

**Pyrazolo[1,5-*a*]pyrimidin-7-yl phenyl amides as novel anti-proliferative agents: parallel synthesis for lead optimization of amide region**

pp 1591–1594

Ariamala Gopalsamy,* Hui Yang, John W. Ellingboe, Hwei-Ru Tsou, Nan Zhang, Erick Honores, Dennis Powell, Miriam Miranda, John P. McGinnis and Sridhar K. Rabindran

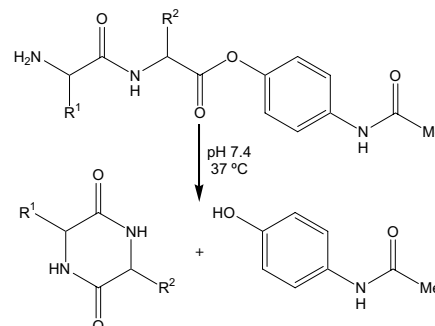
A novel series of anti-proliferative agents containing a pyrazolo[1,5-*a*]pyrimidine scaffold and the structure–activity relationship studies to improve potency are described.

**Cyclization-activated prodrugs. Synthesis, reactivity and toxicity of dipeptide esters of paracetamol**

pp 1595–1598

Cledir Santos, Maria Luísa Mateus, Ana Paula dos Santos, Rui Moreira, Eliandre de Oliveira and Paula Gomes*

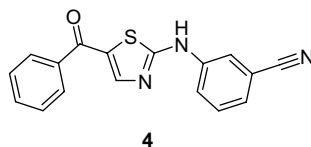
Dipeptide esters of paracetamol were prepared and observed to be quantitatively hydrolyzed to paracetamol and 2,4-diketopiperazines at pH 7.4 and 37 °C. Hydrolysis rates depended on dipeptide structure. These novel compounds do not affect the levels of hepatic glutathione.



Novel and potent NPY5 receptor antagonists derived from virtual screening and iterative parallel chemistry design

pp 1599–1603

Wolfgang Guba,* Werner Neidhart and Matthias Nettekoven

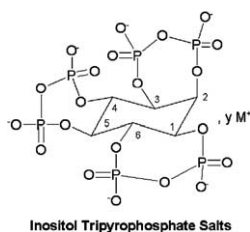


A novel 4-aminothiazole hit class was discovered by virtual screening, and the SAR was explored in two rounds of iterative optimisation.

Inositol tripyrophosphate: a new membrane permeant allosteric effector of haemoglobin

pp 1605–1608

Konstantina C. Fylaktakidou, Jean-Marie Lehn,* Ruth Greferath and Claude Nicolau

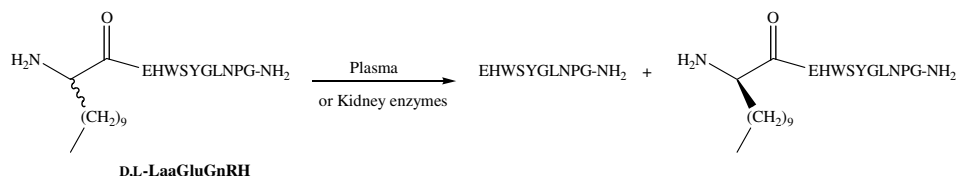


Inositol tripyrophosphate (ITPP) salts were found to serve as allosteric effectors of haemoglobin giving a significant P_{50} shift of the oxygen–haemoglobin dissociation curve, with free haemoglobin and whole blood, in vitro.

The stability of lipidic analogues of GnRH in plasma and kidney preparations: the stereoselective release of the parent peptide

pp 1609–1612

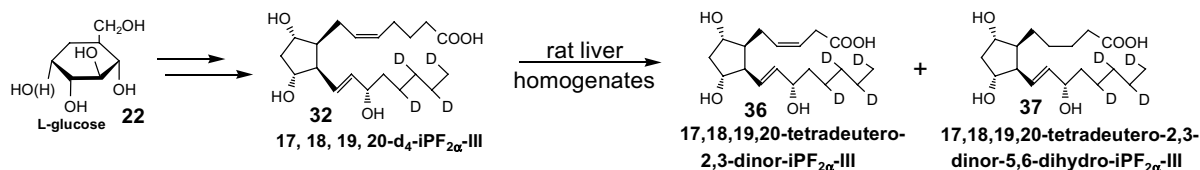
Joanne T. Blanchfield,* Rebecca A. Lew, A. Ian Smith and Istvan Toth



iPF_{2α}-III-17,18,19,20-*d*₄: Total synthesis and metabolism

pp 1613–1617

Seongjin Kim, William S. Powell, John A. Lawson, Sheila H. Jacobo, Domenico Pratico, Garret A. FitzGerald, Kirk Maxey and Joshua Rokach*

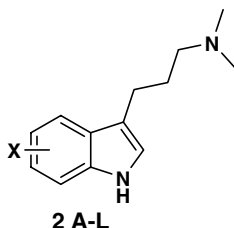


We described herein the total synthesis and metabolism studies of 17,18,19,20-*d*₄-iPF_{2α}-III.

Homotryptamines as potent and selective serotonin reuptake inhibitors (SSRIs)

pp 1619–1621

William D. Schmitz,* Derek J. Denhart, Allison B. Brenner, Jonathan L. Ditta,
Ronald J. Mattson, Gail K. Mattson, Thaddeus F. Molski and John E. Macor



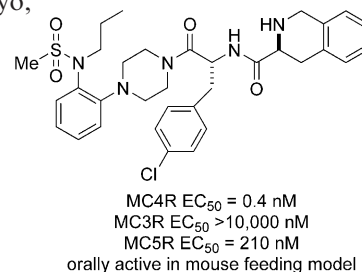
A series of *N,N*-dimethylhomotryptamines was prepared and their binding affinities at the serotonin transporter (SERT) are reported.

Melanocortin subtype-4 receptor agonists containing a piperazine core with substituted aryl sulfonamides

pp 1623–1627

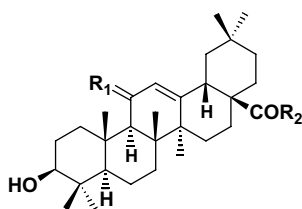
Christopher Fotsch,* Nianhe Han, Premilla Arasasingham, Yunxin Bo, Michelle Carmouche,
Ning Chen, James Davis, Martin H. Goldberg, Clarence Hale, Feng-Yin Hsieh, Michael G. Kelly,
Qingyian Liu, Mark H. Norman, Duncan M. Smith, Markian Stec, Nuria Tamayo,
Ning Xi, Shimin Xu, Anthony W. Bannon and James W. Baumgartner

The biological activity for a set of melanocortin-4 receptor (MC4R) agonists containing a piperazine core with an *ortho*-substituted aryl sulfonamide is described. Compounds from this set had binding and functional activities at MC4R less than 30 nM. The most selective compound in this series was >25,000-fold more potent at MC4R than MC3R, and 490-fold more potent at MC4R than MC5R. This compound also reduced food intake after oral dosing at 25, 50, and 100 mg kg⁻¹ in fasted mice.

**Synthesis and activity of oleanolic acid derivatives, a novel class of inhibitors of osteoclast formation**

pp 1629–1632

Yuan Zhang, Jian-xin Li,* Jianwei Zhao, Shao-zhong Wang, Yi Pan,
Ken Tanaka and Shigetoshi Kadota



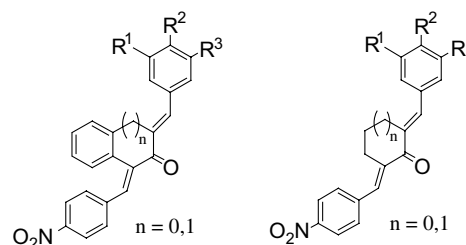
Two series of oleanolic acid derivatives were synthesized and their inhibitory activity on the formation of osteoclast-like multinucleated cells (OCLs) induced by 1 α ,25-dihydroxy vitamin D₃ was evaluated in a co-culture assay system.

**3-Arylidene-1-(4-nitrophenylmethylene)-3,4-dihydro-1H-naphthalen-2-ones and related compounds displaying selective toxicity and reversal of multidrug resistance in neoplastic cells**

pp 1633–1636

Jonathan R. Dimmock,* Umashankar Das, H. Inci Gul, Masami Kawase, Hiroshi Sakagami,
Zoltán Baráth, Imre Ocsovsky and Joseph Molnár

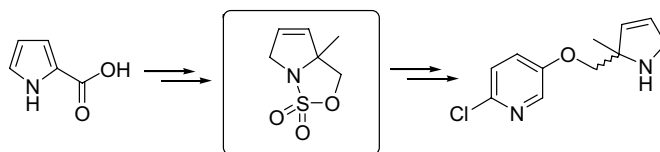
The incorporation of the 1-aryl-5-(4-nitrophenyl)-3-oxo-1,4-pentadienyl group into different cyclic structures led to the discovery of various compounds which displayed selective toxicity for neoplastic cells rather than normal tissues and reversed multidrug resistance.



3-(2,5-Dihydro-1H-pyrrol-2-ylmethoxy)pyridines: synthesis and analgesic activity

pp 1637–1640

Ivan L. Baraznenok, Emma Jonsson and Alf Claesson*

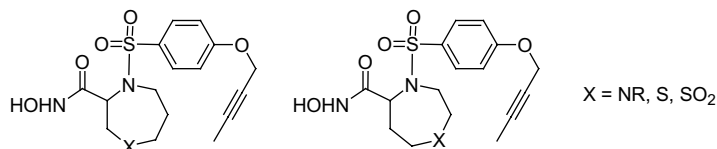


We describe herein the synthesis and analgesic evaluation of a new series of 3-pyridyl ethers which are analogs of the nicotinic compound tebanicline (ABT-594).

Synthesis and SAR of diazepine and thiazepine TACE and MMP inhibitors

pp 1641–1645

Arie Zask,* Joshua Kaplan, XueMei Du, Gloria MacEwan, Vincent Sandanayaka, Nancy Eudy, Jeremy Levin, Guixian Jin, Jun Xu, Terri Cummons, Dauphine Barone, Semiramis Ayral-Kaloustian and Jerauld Skotnicki

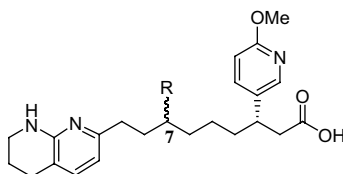


Potent and selective TACE and MMP inhibitors utilizing the diazepine and thiazepine ring systems were synthesized and evaluated for biological activity in in vitro and in vivo models of TNF- α release and arthritis.

Nonpeptide $\alpha_v\beta_3$ antagonists: identification of potent, chain-shortened 7-oxo RGD mimetics

pp 1647–1650

Amy E. Zartman,* Le T. Duong, Carmen Fernandez-Metzler, George D. Hartman, Chih-Tai Leu, Thomayant Prueksaritanont, Gideon A. Rodan, Sevgi B. Rodan, Mark E. Duggan and Robert S. Meissner

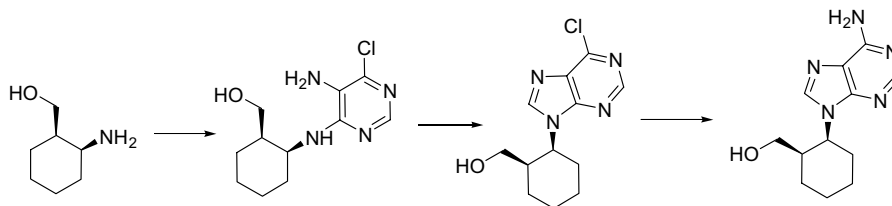


Potent, novel 7-oxo $\alpha_v\beta_3$ antagonists have been prepared. These antagonists offer decreased plasma protein binding and excellent pharmacokinetic profiles.

QSAR for anti-RNA-virus activity, synthesis, and assay of anti-RSV carbonucleosides given a unified representation of spectral moments, quadratic, and topologic indices

pp 1651–1657

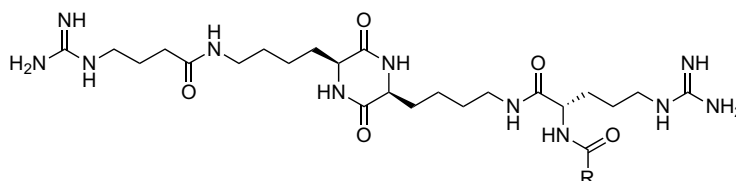
Humberto González-Díaz,* Maykel Cruz-Montegudo, Dolores Viña, Lourdes Santana, Eugenio Uriarte and Erik De Clercq



Combinatorial approaches towards the discovery of new tryptase inhibitors

pp 1659–1664

Montserrat del Fresno, Dolors Fernández-Forner, Montserrat Miralpeix, Victor Segarra, Hamish Ryder, Miriam Royo* and Fernando Albericio*



The synthesis and evaluation as tryptase inhibitors of a library of DKP derivatives containing guanidine or amidine functional groups is reported. Among the compounds evaluated, derivatives **6**{CG4-CG8} and **6**{CG4-CG9} are the most active compounds and have marked selectivity towards tryptase in front of trypsin.

Synthesis and characterization of a carboranyl-tetrabenzoporphyrin

pp 1665–1668

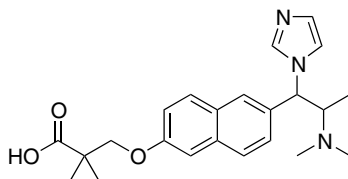
Owendi Ongayi, Vijay Gottumukkala, Frank R. Fronczek and M. Graça H. Vicente*

The synthesis of a novel water-soluble carboranyl-tetrabenzoporphyrin is reported. This compound shows characteristic absorption and emission spectra and low dark toxicity toward V79 cells. The X-ray structure of a precursor Cu(II)-carboranyl-tetrabenzoporphyrin is presented.

Potent and selective [2-imidazol-1-yl-2-(6-alkoxy-naphthalen-2-yl)-1-methyl-ethyl]-dimethyl-amines as retinoic acid metabolic blocking agents (RAMBAs)

pp 1669–1673

Mark J. Mulvihill,* Julie L. C. Kan, Patricia Beck, Mark Bittner, Cara Cesario, Andrew Cooke, David M. Keane, Anthony I. Nigro, Christy Nillson, Vanessa Smith, Mary Srebernak, Feng-Lei Sun, Michael Vrkljan, Shannon L. Winski, Arlindo L. Castelhana, David Emerson and Neil Gibson

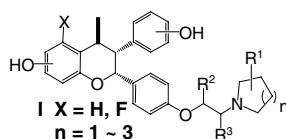


A series of [2-imidazol-1-yl-2-(6-alkoxy-naphthalen-2-yl)-1-methyl-ethyl]-dimethyl-amines were designed and synthesized as CYP26 inhibitors, serving as retinoic acid metabolic blocking agents (RAMBAs).

Estrogen receptor ligands. Part 10: Chromanes: old scaffolds for new SERAMs

pp 1675–1681

Qiang Tan,* Timothy A. Blizzard, Jerry D. Morgan, II, Elizabeth T. Birzin, Wanda Chan, Yi Tien Yang, Lee-Yuh Pai, Edward C. Hayes, Carolyn A. DaSilva, Sudha Warriar, Joel Yudkovitz, Hilary A. Wilkinson, Nandini Sharma, Paula M. D. Fitzgerald, Susan Li, Lawrence Colwell, John E. Fisher, Sharon Adamski, Alfred A. Reszka, Donald Kimmel, Frank DiNinno, Susan P. Rohrer, Leonard P. Freedman, James M. Schaeffer and Milton L. Hammond

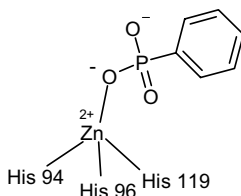


Chromanes **I** were discovered as SERAMs (Selective Estrogen Receptor Alpha Modulators) with the potential for the treatment of osteoporosis and cancer.

Carbonic anhydrase inhibitors. Interaction of isozymes I, II, IV, V, and IX with organic phosphates and phosphonates

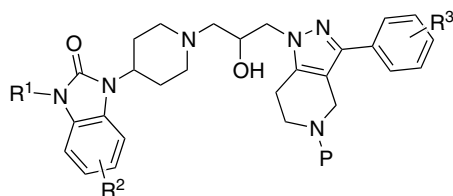
pp 1683–1686

Jean-Yves Winum, Alessio Innocenti, Valerie Gagnard, Jean-Louis Montero, Andrea Scozzafava, Daniela Vullo and Claudiu T. Supuran*

**Discovery and SAR studies of a novel series of noncovalent cathepsin S inhibitors**

pp 1687–1691

Darin J. Gustin, Clark A. Sehon, Jianmei Wei, Hui Cai, Steven P. Meduna, Haripada Khatuya, Siquan Sun, Yin Gu, Wen Jiang, Robin L. Thurmond, Lars Karlsson and James P. Edwards*

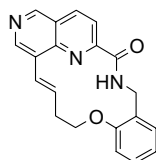


Noncovalent, potent, selective and orally bioavailable inhibitors of the cysteine protease cathepsin S are reported.

Design and synthesis of a potent macrocyclic 1,6-naphthyridine anti-human cytomegalovirus (HCMV) inhibitors

pp 1693–1695

Guy Falardeau,* Hugo Lachance, Annie St-Pierre, Constantin G. Yannopoulos, Marc Drouin, Jean Bédard and Laval Chan

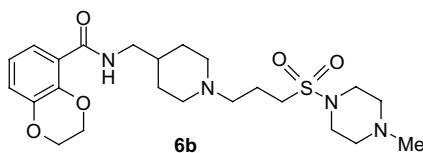


A novel class of macrocyclic 1,6-naphthyridines designed to adopt the presumed bioactive conformation of anti-HCMV acyclic 1,6-naphthyridines are described. Both 14- and 15-membered macrocycles were shown to be highly potent against HCMV HSV-1 and HSV-2.

Identification of a 5-HT₄ receptor antagonist clinical candidate through side-chain modification

pp 1697–1700

Robin D. Clark,* Alam Jahangir, Muzaffar Alam, Cynthia Rocha,* Lin Lin, Bodil Bjorner, Khanh Nguyen, Carole Grady, Timothy J. Williams, George Stepan, Hai Ming Tang and Anthony P. D. W. Ford

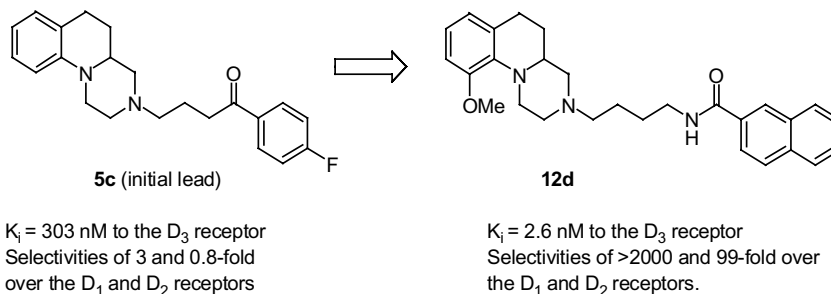


Replacement of the *N*-butyl side-chain of lead 5-HT₄ receptor antagonist **2** with propanesulfonylpiperidinyloxy, morpholinoxy, and piperazinyloxy groups led to higher affinity analogs **4–6**. In vitro drug metabolism screens and cassette pharmacokinetic studies in the dog led to identification of the *N*-methylpiperazinyloxy analog (**6b**), which displayed pharmacokinetic, selectivity, and safety parameters sufficient for advancement to the clinic for the treatment of urinary incontinence.

Design, synthesis and structure–activity relationship studies of hexahydropyrazinoquinolines as a novel class of potent and selective dopamine receptor 3 (D₃) ligands

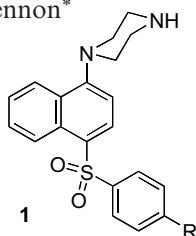
pp 1701–1705

Min Ji, Jianyong Chen, Ke Ding, Xihan Wu, Judith Varady, Beth Levant and Shaomeng Wang*

**1-(1-Naphthyl)piperazine as a novel template for 5-HT₆ serotonin receptor ligands**

pp 1707–1711

Mase Lee, Jagadeesh B. Rangisetty, Manik R. Pullagurla, Małgorzata Dukat, Vince Setola, Bryan L. Roth and Richard A. Glennon*

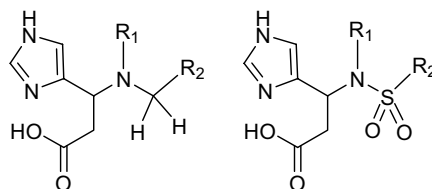


4-Arylsulfone derivatives of 1-(1-naphthyl)piperazine represent a novel class of human 5-HT₆ serotonin receptor ligands. In particular, compounds such as **1f** (**1**; R = H; $K_i = 3.8 \text{ nM}$) and **1g** (**1**; R = NH₂; $K_i = 0.9 \text{ nM}$) displayed high affinity for this receptor population, and **1f** was shown to behave as a 5-HT₆ antagonist.

Novel β -(imidazol-4-yl)- β -amino acids: solid-phase synthesis and study of their inhibitory activity against geranylgeranyl protein transferase type I

pp 1713–1719

Ashis K. Saha* and David W. End



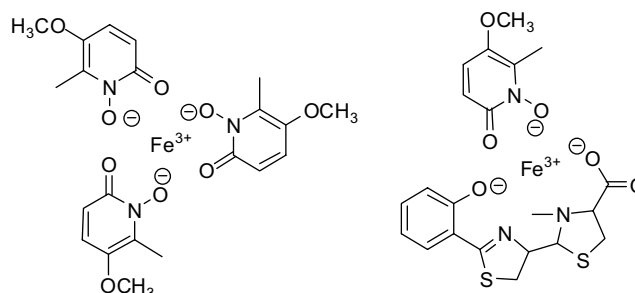
Synthesis and biological evaluation of imidazol-4-yl- β -amino acid derivatives is reported.

From a total synthesis of cepabactin and its 3:1 ferric complex to the isolation of a 1:1:1 mixed complex between iron (III), cepabactin and pyochelin

pp 1721–1724

Cédric Klumpp, Alain Burger, Gaëtan L. Mislin* and Mohamed A. Abdallah*

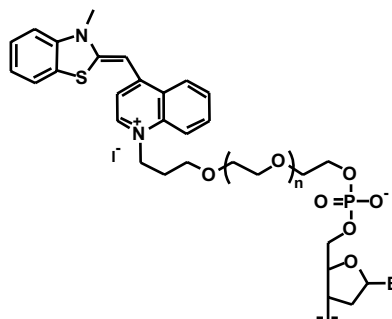
The synthesis of cepabactin and the corresponding iron (III) complex is described. The purification and characterization of a mixed complex between iron (III), pyochelin and cepabactin is also reported.



Synthesis and fluorescence studies of thiazole orange tethered onto oligonucleotide: development of a self-contained DNA biosensor on a fiber optic surface

pp 1725–1729

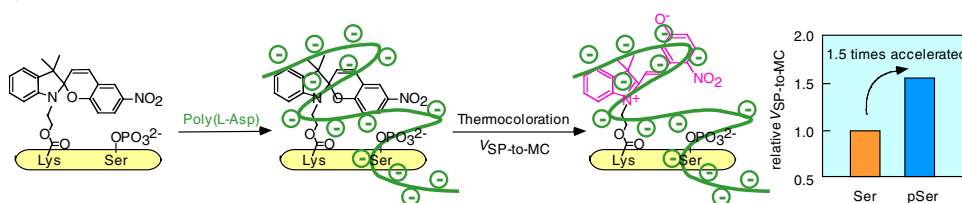
Xiaofeng Wang and Ulrich J. Krull*



A chromism-based assay (CHROBA) technique for in situ detection of protein kinase activity

pp 1731–1735

Kin-ya Tomizaki, Xu Jie and Hisakazu Mihara*

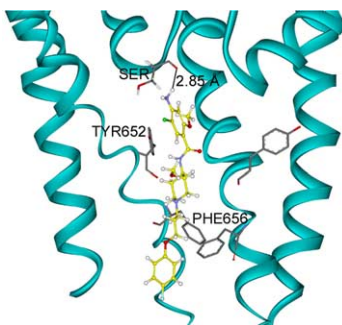


A unique chromism-based assay (CHROBA) technique using photochromic spiropyran-containing peptides has been firstly established for detection of protein kinase A-catalyzed phosphorylation. The promising method has advantages that avoid isolation and/or immobilization of substrates to remove excess nonreactive isotope-labeled ATP or fluorescently-labeled anti-phosphoamino acid antibodies from the reaction mixture.

A two-state homology model of the hERG K⁺ channel: application to ligand binding

pp 1737–1741

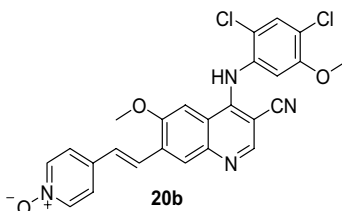
Ramkumar Rajamani, Brett A. Tounge, Jian Li and Charles H. Reynolds*



Further studies on ethenyl and ethynyl-4-phenylamino-3-quinolinecarbonitriles: identification of a subnanomolar Src kinase inhibitor

pp 1743–1747

Ana Carolina Barrios Sosa,* Diane H. Boschelli, Biqi Wu, Yan Wang and Jennifer M. Golas



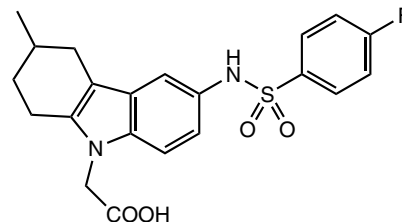
New ethynyl and ethenyl-4-phenylamino-3-quinolinecarbonitrile derivatives were synthesized and tested for Src inhibition. The *N*-oxide derivative **20b** is the first 3-quinolinecarbonitrile to show subnanomolar inhibitory activity in a Src enzyme assay.

Isosteric ramatroban analogs: selective and potent CRTH-2 antagonists

pp 1749–1753

Michael J. Robarge,* David C. Bom, L. Nathan Tumey, Norbert Varga, Elizabeth Gleason, Daniel Silver, Jianping Song, Steven M. Murphy, George Ekema, Chris Doucette, Doug Hanniford, Marc Palmer, Gary Pawlowski, Joel Danzig, Margaret Loftus, Karen Hunady, Bruce A. Sherf, Robert W. Mays, Alain Stricker-Krongrad, Kurt R. Brunden, John J. Harrington and Youssef L. Bennani

The chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH-2), also found on eosinophils and basophils, is a prostaglandin D₂ receptor involved in the recruitment of these cell types during an inflammatory response. In this report, we describe the synthesis and optimization of a ramatroban isostere that is a selective and potent antagonist of CRTH-2 which may be useful in the treatment of certain diseases.

**OTHER CONTENTS**

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Erratum

p 1757

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Instructions to contributors

pp III–VI

*Corresponding author

①⁺ Supplementary data available via ScienceDirect**COVER**

Two views of a ribbon representation of the homology model for the pore region of the hERG K⁺ channel. The effective size of the pore changes as the channel moves from a closed to open state. Modeling suggests that the hERG channel can use this flexibility to accommodate a wide variety of ligands. The red, yellow, and green structures correspond to increasingly open states for this K⁺ channel [Rajamani, R.; Tounge, B. A.; Li, J.; Reynolds, C. H. *Bioorg. Med. Chem. Lett.* **2005**, 15, 1737].



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