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Dantrolene Analogues Revisited: General Synthesis and Specific Functions Capable of Discriminating Two Kinds of Ca^{2+} Release from Sarcoplasmic Reticulum of Mouse Skeletal Muscle

Takamitsu Hosoya,[a,b] Hiroshi Aoyama,[b] Takaaki Ikemoto,[c] Yasutaka Kihara,[c] Toshiyuki Hiramatsu,[b] Makoto Endo[c] and Masaaki Suzuki[a,b,*]

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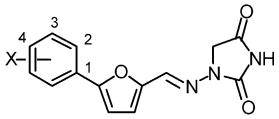
Dantrolene analogues with specific functions for Ca^{2+} release from sarcoplasmic reticulum of mouse skeletal muscle have been elaborated.



Specific inhibitor for physiological Ca^{2+} release
GIF-0185 (**1**): X = 4-CH_3O
Specific potentiator for Ca^{2+}-induced Ca^{2+} release
GIF-0166 (**2**): X = 2-NO_2
GIF-0248 (**3**): X = 2,6-$(NO_2)_2$

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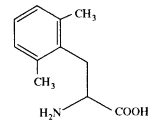
Endomorphin 2 Analogues Containing Dmp Residue as an Aromatic Amino Acid Surrogate with High μ-Opioid Receptor Affinity and Selectivity

Yusuke Sasaki,* Ai Sasaki, Hideko Niizuma, Harumi Goto and Akihiro Ambo

Tohoku Pharmaceutical University, 4-1 Komatsushima 4-chome, Aoba-ku, Sendai 981-8558, Japan



2′,6′-dimethylphenylalanine (**Dmp**)

X – Pro – Y – Phe-NH_2
X = Dmp or Tyr
Y = Dmp or Phe

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Syntheses and Antiproliferative Activities of Rebeccamycin Analogues Bearing Two 7-Azaindole Moieties

Christelle Marminon,[a] Alain Pierré,[b] Bruno Pfeiffer,[c] Valérie Pérez,[b] Stéphane Léonce,[b] Pierre Renard[c] and Michelle Prudhomme[a,*]

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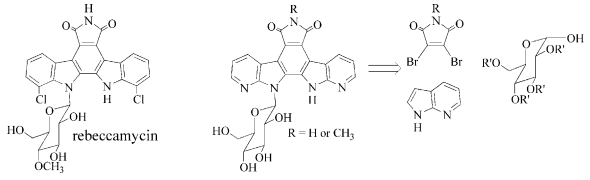
[b]*Institut de Recherches SERVIER, Division de Cancérologie, 11 rue des Moulineaux, 92150 Suresnes, France*
[c]*Les Laboratoires SERVIER, 1 rue Carle Hébert, 92415 Courbevoie, France*

Rebeccamycin analogues containing two aza-indoles moieties were synthesized and their in vitro antiproliferative activities were tested against a panel of tumor cell lines.



rebeccamycin

R = H or CH_3

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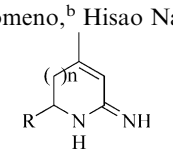
Design and Synthesis of Orally Bioavailable Inhibitors of Inducible Nitric Oxide Synthase. Synthesis and Biological Evaluation of Dihydropyridin-2(1*H*)-imines and 1,5,6,7-Tetrahydro-2*H*-azepin-2-imines

Yasufumi Kawanaka,[a] Kaoru Kobayashi,[b] Shinya Kusuda,[b] Tadashi Tatsumi,[b] Masayuki Murota,[b] Toshihiko Nishiyama,[b] Katsuya Hisaichi,[b] Atsuko Fujii,[b] Keisuke Hirai,[b] Minoru Nishizaki,[b] Masao Naka,[b] Masaharu Komeno,[b] Hisao Nakai[b] and Masaaki Toda[b]

[a]*Fukui Research Institute, Ono Pharmaceutical Co., Ltd., Technoport, Yamagishi, Mikuni, Sakai, Fukui 913-8538, Japan*
[b]*Minase Research Institute, Ono Pharmaceutical Co., Ltd., Shimamoto, Mishima, Osaka 618-8585, Japan*

The dihydropyridin-2(1*H*)-imines **1**, **9**–**11** and the 1,5,6,7-tetrahydro-2*H*-azepin-2-imines **14**, **16** were identified as potent inhibitors of inducible nitric oxide synthase.



1 : n = 1, R = H; **9** : n = 1, R = Me
10 : n = 1, R = *n*-Pr; **11** : n = 1, R = Allyl
14 : n = 2, R = H; **16** : n = 2, R = *n*-Pr

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Biologically Active Phenols from *Saussurea medusa*

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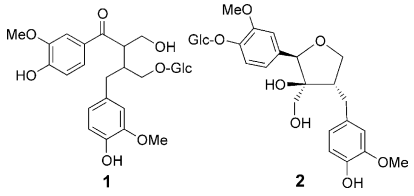
Two new lignan glucosides, namely medusasides A (**1**) and B (**2**), and 14 known phenols (**3**–**16**) were isolated from *Saussurea medusa*. One major compound **6** showed remarkable activity to attenuate the scopolamine induced memory deficit of mice. Compounds **6** and **8** also exhibited moderate cell protecting activities against hydrogen peroxide (H_2O_2) induced PC12 cell damage.



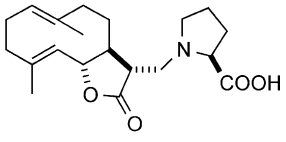
Bioorg. Med. Chem. 11 (2003) 709

Effects of Sesquiterpenes and Amino Acid–Sesquiterpene Conjugates from the Roots of *Saussurea lappa* on Inducible Nitric Oxide Synthase and Heat Shock Protein in Lipopolysaccharide-Activated Macrophages

Hisashi Matsuda, Iwao Toguchida, Kiyofumi Ninomiya, Tadashi Kageura, Toshio Morikawa and Masayuki Yoshikawa*

Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8412, Japan

The methanolic extract of the roots of *Saussurea lappa* CLARKE, a Chinese medicinal herb Saussureae Radix, was found to inhibit nitric oxide (NO) production in lipopolysaccharide (LPS)-activated mouse peritoneal macrophages. Among the constituents from the methanolic extract, two sesquiterpene lactones (costunolide and dehydrocostus lactone) and two amino acid-sesquiterpene conjugates (saussureamines A and B) potently inhibited LPS-induced NO production (IC_{50} = 1.2–2.8 μM). Saussureamines A and B in addition to costunolide and dehydrocostus lactone did not inhibit iNOS enzyme activity, but they inhibited both induction of inducible NO synthase and activation of nuclear factor-κB in accordance with induction of heat shock protein 72.



saussureamine A

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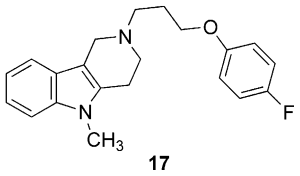
γ-Carbolines: Binding at 5-HT_{5A} Serotonin Receptors

Nantaka Khorana,[a] Anil Purohit,[b] Katherine Herrick-Davis,[b] Milt Teitler[b] and Richard A. Glennon[a,*]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298, USA*
[b]*Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, NY 12208, USA*

The γ-carboline moiety was identified as a new template for binding at 5-HT_{5A} serotonin receptors. Investigation of structure–affinity relationships led to **17** (K_i = 13 nM).



17

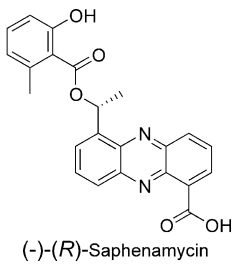
Bioorg. Med. Chem. 11 (2003) 723

First Synthesis of Racemic Saphenamycin and Its Enantiomers. Investigation of Biological Activity

Jane B. Laursen, Charlotte G. Jørgensen and John Nielsen*

Department of Chemistry, Technical University of Denmark, Kemitorvet, Building 207, DK-2800 Kgs. Lyngby, Denmark

The first practical synthesis of the natural antibiotic saphenamycin is reported. The starting material saphenic acid was resolved by (−)-brucine diastereomeric salt formation and full structure elucidation of one enantiomer was obtained by X-ray crystallography. Racemic saphenamycin as well as its enantiomers were synthesized from saphenic acid and the importance of chirality for antimicrobial activity of saphenamycin investigated.



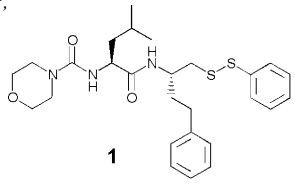
(-)-(*R*)-Saphenamycin

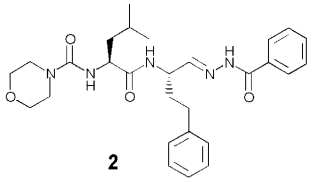
Bioorg. Med. Chem. 11 (2003) 733

The Design of Potent Hydrazones and Disulfides as Cathepsin S Inhibitors

Charles L. Cywin,[a,*] Raymond A. Firestone,[a] Daniel W. McNeil,[a] Christine A. Grygon,[b] Kathryn M. Crane,[b] Della M. White,[b] Peter R. Kinkade,[a] Jerry L. Hopkins,[b] Walter Davidson,[b] Mark E. Labadia,[b] Jessi Wildeson,[b] Maurice M. Morelock,[b] Jeffrey D. Peterson,[c] Ernest L. Raymond,[c] Maryanne L. Brown[b] and Denice M. Spero[a]

[a]*Department of Medicinal Chemistry, Research and Development Center, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, CT 06877-0368, USA*
[b]*Department of Biology, Research and Development Center, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, CT 06877-0368, USA*
[c]*Department of Pharmacology, Research and Development Center, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, CT 06877-0368, USA*





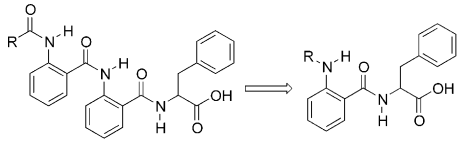
Bioorg. Med. Chem. 11 (2003) 741

Anthranilic Acid Derivatives: A New Class of Non-Peptide CCK_1 Receptor Antagonists

Antonio Varnavas,[a,*] Lucia Lassiani,[a] Valentina Valenta,[a] Federico Berti,[b] Laura Mennuni[c] and Francesco Makovec[c]

[a]*Department of Pharmaceutical Sciences, University of Trieste, P.le Europa 1, 34127 Trieste, Italy*
[b]*Department of Chemical Sciences, University of Trieste, Via Giorgieri 1, 34127 Trieste, Italy*
[c]*Rotta Research Laboratorium S.p.A., Via Valosa di Sopra 7/9, 20052 Monza (MI), Italy*

During a program aimed at searching for non-peptide CCK receptor antagonists, we have found that simplifying the anthranilic acid dimer scaffold to a monomer gives rise to a structurally simple compound endowed with high affinity towards CCK_1 receptors.

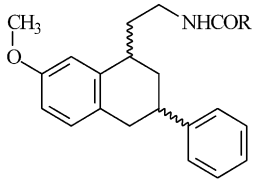


Bioorg. Med. Chem. 11 (2003) 753

Design and Synthesis of 3-Phenyl Tetrahydronaphthalenic Derivatives as New Selective MT_2 Melatoninergic Ligands

Saïd Yous,[a,*] Sophie Durieux-Poissonnier,[a] Emmanuelle Lipka-Belloli,[b] Halim Guelzim,[d] Christophe Bochu,[c] Valérie Audinot,[e] Jean A. Boutin,[e] Philippe Delagrange,[e] Caroline Bennejean,[e] Pierre Renard[e] and Daniel Lesieur[a]

[a]*Laboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Lille 2, BP 83, 59006 Lille Cedex, France*
[b]*Laboratoire de Chimie Analytique, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Lille 2, BP 83, 59006 Lille Cedex, France*
[c]*Laboratoire d'Application de Résonance Magnétique Nucléaire, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Lille 2, BP 83, 59006 Lille Cedex, France*
[d]*Laboratoire de Dynamique et de Structure des Matériaux Moléculaires, UPRESA 8024, UFR de Physique, Bâtiment P5, Université de Lille 1, 59655 Villeneuve d'Ascq Cedex, France*
[e]*Institut de Recherches Internationales Servier, Courbevoie Cedex, France*



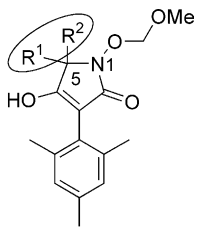
Bioorg. Med. Chem. 11 (2003) 761

Synthesis and Insecticidal Activity of Novel *N*-Oxydihydropyrroles: 4-Hydroxy-3-mesityl-1-methoxymethoxy Derivatives with Various Substituents at the 5-Position

Mitsuru Ito,[a,*] Hideshi Okui,[a] Harumi Nakagawa,[a] Shigeru Mio,[a] Ayako Kinoshita,[a] Takashi Obayashi,[a] Takako Miura,[a] Junko Nagai,[a] Shinji Yokoi,[a] Reiji Ichinose,[b] Keiji Tanaka,[a] Seiichiro Kodama,[c] Toshiaki Iwasaki,[d] Takaaki Miyake,[d] Miho Takashio[d] and Jun Iwabuchi[d]

[a]*Agroscience Research Laboratories, Sankyo Co., Ltd., 1041 Yasu, Yasu-cho, Yasu-gun, Shiga 520-2342, Japan*
[b]*Crop Protection Department, Sankyo Co., Ltd., 7-12, Ginza 2-chome, Chuo-ku, Tokyo 104-8113, Japan*
[c]*Marketing Department, Agrochemicals Division, Agro & Specialty Chemicals Group, Nippon Kayaku Co., Ltd., 11-2, Fujimi 1-chome, Chiyoda-ku, Tokyo 102-8172, Japan*
[d]*Research & Development Laboratories, Agro & Specialty Chemicals Group, Nippon Kayaku Co., Ltd., 225-1, Koshikiya, Ageo-city, Saitama 362-0064, Japan*

A series of novel *N*-oxydihydropyrrole derivatives was synthesized and evaluated for insecticidal activity against aphids.



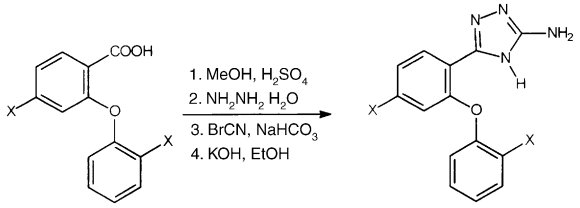
Bioorg. Med. Chem. 11 (2003) 769

Design and Synthesis of 4H-3-(2-Phenoxy)phenyl-1,2,4-triazole Derivatives as Benzodiazepine Receptor Agonists

Tahmineh Akbarzadeh,[a] Sayyed A. Tabatabai,[b] Mohammad J. Khoshnoud,[c] Bijan Shafaghi[c] and Abbas Shafiee[a,*]

[a]*Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*
[b]*Department of Medicinal Chemistry, Faculty of Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran, Iran*
[c]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran, Iran*

1,2,4-Triazole derivatives were designed and prepared as benzodiazepine receptor agonists. Conformational analysis and pharmacological evaluation were performed on the synthesized compounds.

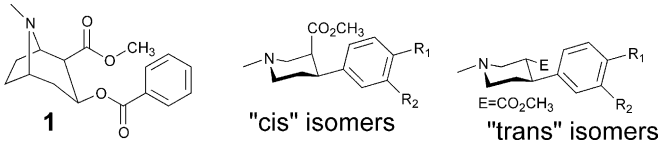


Bioorg. Med. Chem. 11 (2003) 775

Syntheses of 3-Carbomethoxy-4-(aryl)piperidines and In Vitro and In Vivo Pharmacological Evaluation: Identification of Inhibitors of the Human Dopamine Transporter

Xianqi Feng,[a] Keith Fandrick,[a] Robert Johnson,[b] Aaron Janowsky[b] and John R. Cashman[a,*]

[a]*Human BioMolecular Research Institute, 5310 Eastgate Mall, San Diego, CA 92121, USA*
[b]*Veterans Administration Hospital, Portland, OR 97201, USA*



Bioorg. Med. Chem. 11 (2003) 781

Rational Design and Synthesis of Peptide Ligands for an Anti-Carbohydrate Antibody and Their Immunochemical Characterization

Margaret A. Johnson, Adewale A. Eniade and B. Mario Pinto*

Departments of Chemistry and of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, B.C., Canada V5A 1S6

The design, synthesis, and immunochemical characterization of a series of peptide mimetics of the *Shigella flexneri* Y O-polysaccharide are described.

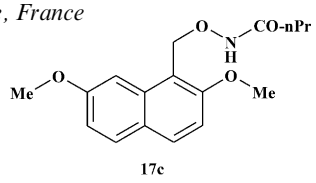
Bioorg. Med. Chem. 11 (2003) 789

Synthesis of New Arylalkoxy Amido Derivatives as Melatoninergic Ligands

Cécile Pégurier,[a] Laurence Morellato,[a] Eminn Chahed,[a] Jean Andrieux,[a] Jean-Paul Nicolas,[b] Jean A. Boutin,[b] Caroline Bennejean,[c] Philippe Delagrange,[d] Michel Langlois[a] and Monique Mathé-Allainmat,[a,*]

[a]*CNRS-BIOCIS (UPRES A 8076), Université de Paris-Sud, Faculté de Pharmacie, 5 rue Jean Baptiste Clément, 92296, Châtenay-Malabry, France*
[b]*Institut de Recherche Servier, Centre de Croissy, 125 Chemin de ronde, 78290 Croissy sur Seine, France*
[c]*ADIR, 1 rue Carle Hébert, 92415 Courbevoie, France*
[d]*Institut de Recherche Internationale Servier, Place des Pléiades, 92415 Courbevoie, France*

The synthesis of the potent melatoninergic compounds on the human MT_1 and MT_2 receptors, such as **17c**, was described.



17c