Graphical Abstracts

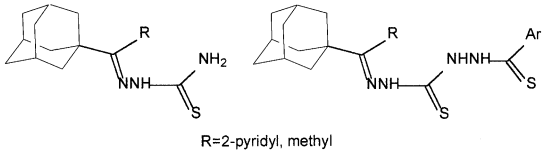
Bioorg. Med. Chem. Lett. 12 (2002) 723

New 2-(1-Adamantylcarbonyl)pyridine and 1-Acetyladamantane Thiosemicarbazones–Thiocarbonohydrazones: Cell Growth Inhibitory, Antiviral and Antimicrobial Activity Evaluation

Antonios Kolocouris,[a] Kostas Dimas,[b] Christophe Pannecouque,[c] Myriam Witvrouw,[c] George B. Foscolos,[a] George Stamatiou,[a] George Fytas,[a] Grigoris Zoidis,[a] Nicolas Kolocouris,[a,*] Graciela Andrei,[c] Robert Snoeck[c] and Erik De Clercq[c]

[a]*School of Pharmacy, Department of Pharmaceutical Chemistry, University of Athens, Panepistimioupoli-Zografou, GR-15771 Athens, Greece*
[b]*International Institute of Anticancer Research, PO 22, Attiki 19014, Greece*
[c]*Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium*

Some new 2-(1-adamantylcarbonyl)pyridine and 1-acetyladamantane thiosemicarbazones and thiocarbonohydrazones were synthesized. The heterocyclic TSC (R = 2-pyridyl) and the aliphatic TSC (R = CH_3) and thiocarbonohydrazone (R = CH_3, Ar = 2,4-dichlorophenyl) showed antiproliferative activity comparable to that of 2-acetylpyridine TSC a lead in TSC's family. The antiproliferative activity of aliphatic derivatives is novel in TSC's field. The configuration around C = N bond between the heterocyclic and aliphatic TSC's was found to be different by means of molecular mechanics calculations and NOE spectroscopy



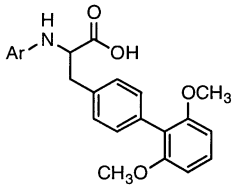
Bioorg. Med. Chem. Lett. 12 (2002) 729

N-Aryl 2,6-Dimethoxybiphenylalanine Analogues as VLA-4 Antagonists

George A. Doherty,[a,*] Theodore Kamenecka,[a] Ermenegilda McCauley,[b] Gail Van Riper,[b] Richard A. Mumford,[b] Sharon Tong[a] and William K. Hagmann[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Immunology & Rheumatology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*

A series of *N*-arylated phenylalanine derivatives has been synthesized and has been shown to be potent inhibitors of the integrin VLA-4. Both aryl and heteroaryl derivatives were examined. Substitution of the *meta* position of either the aryl or heteroaryl ring with hydrogen bond acceptors provided the most potent compounds in this series.

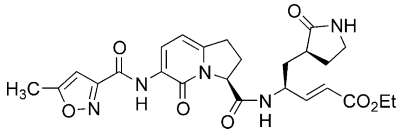


Bioorg. Med. Chem. Lett. 12 (2002) 733

Structure-Based Design, Synthesis, and Biological Evaluation of Irreversible Human Rhinovirus 3C Protease Inhibitors. Part 7: Structure–Activity Studies of Bicyclic 2-Pyridone-Containing Peptidomimetics

Peter S. Dragovich,* Thomas J. Prins, Ru Zhou, Theodore O. Johnson, Edward L. Brown, Fausto C. Maldonado, Shella A. Fuhrman, Leora S. Zalman, Amy K. Patick, David A. Matthews, Xinjun Hou, James W. Meador, III, Rose Ann Ferre and Stephen T. Worland

Pfizer Global Research and Development-La Jolla/Agouron Pharmaceuticals, Inc., 10777 Science Center Drive, San Diego, CA 92121-1111, USA



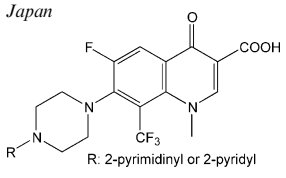
Bioorg. Med. Chem. Lett. 12 (2002) 739

Anti-HIV-1 Activities and Pharmacokinetics of New Arylpiperazinyl Fluoroquinolones

Toshinori Ohmine,[a] Tetsushi Katsube,[d] Yasunori Tsuzaki,[d] Miho Kazui,[c] Nobuhiro Kobayashi,[c] Tomoaki Komai,[a] Masahiko Hagihara,[d] Takashi Nishigaki,[a] Aikichi Iwamoto,[e] Tomio Kimura,[b] Hiroto Kashiwase[a] and Makoto Yamashita[a,*]

[a]*Biological Research Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[b]*Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[c]*Drug Metabolism and Pharmacokinetics Research Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[d]*Pharmaceutical Research Department, Ube Laboratory, Ube Industries, Ltd., 1978-5 Kogushi, Ube City, Yamaguchi 755-0067, Japan*
[e]*Department of Infectious Diseases, Institute of Medical Science, The University of Tokyo, 4-6-1 Shiroganedai, Minato-ku, Tokyo 108-8639, Japan*

Anti-HIV-1 activities and pharmacokinetics of a series of novel arylpiperazinyl fluoroquinolones are reported. Two compounds studied exhibited quite high anti-HIV-1 activities ($IC_{50} < 50$ nM) in vitro and high bioavailabilities (BA > 90%) in monkeys.



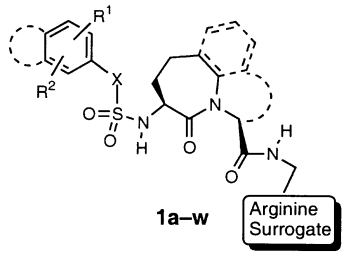
Bioorg. Med. Chem. Lett. 12 (2002) 743

Novel, Potent Non-Covalent Thrombin Inhibitors Incorporating P_3-Lactam Scaffolds

Jonathan Z. Ho, Tony S. Gibson and J. Edward Semple*

Department of Medicinal Chemistry, Corvas International, Inc., 3030 Science Park Road, San Diego, CA 92121, USA

Evolution of P_1-argininal inhibitor prototypes led to a series of non-covalent P_3-7-membered lactam inhibitors **1a**–**w**, featuring novel peptidomimetic units that probe each of the S_1, S_2, and S_3 specificity pockets of thrombin. Rigid P_1-arginine surrogates possessing a wide range of basicity (calcd pK_a's ~ neutral–14) were surveyed. The design, synthesis, and biological activity of these targets are presented.

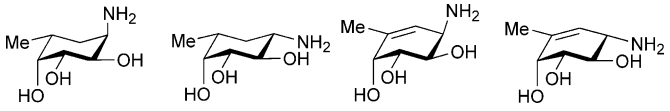


Bioorg. Med. Chem. Lett. 12 (2002) 749

Synthesis of an α-Fucosidase Inhibitor, 5a-Carba-β-L-fucopyranosylamine, and Fucose-Type α- and β-DL-Valienamine Unsaturated Derivatives

Seiichiro Ogawa,* Maiko Watanabe, Ayako Maruyama and Seiichi Hisamatsu

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522 Japan

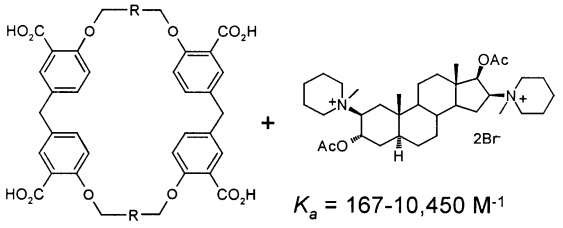


Bioorg. Med. Chem. Lett. 12 (2002) 753

Anionic Cyclophanes as Potential Reversal Agents of Muscle Relaxants by Chemical Chelation

Kenneth S. Cameron,[c] Lee Fielding,[c] Rona Mason,[b] Alan W. Muir,[b] David C. Rees,[a,*] Simon Thorn[a] and Ming-Qiang Zhang[a]

[a]*Department of Medicinal Chemistry, Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH, Scotland, UK*
[b]*Department of Pharmacology, Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH, Scotland, UK*
[c]*Department of Analytical Chemistry, Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH, Scotland, UK*



Bioorg. Med. Chem. Lett. 12 (2002) 757

Novel Potent Antagonists of Human Neuropeptide Y Y5 Receptors. Part 2: Substituted Benzo[*a*]cycloheptene Derivatives

Hiromichi Itani,[a] Harunobu Ito,[b] Yoshihiko Sakata,[b] Yoshifumi Hatakeyama,[b] Hiroko Oohashi[b] and Yoshinari Satoh[a,*]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*
[b]*Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*

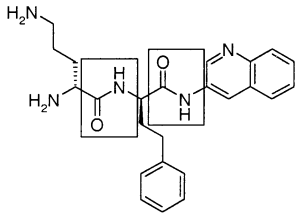
Novel substituted benzo[*a*]cycloheptene derivatives were prepared and **FR226928** showed high affinity for the NPY-Y5 receptors.

Bioorg. Med. Chem. Lett. 12 (2002) 763

Peptidomimetics of Efflux Pump Inhibitors Potentiate the Activity of Levofloxacin in *Pseudomonas aeruginosa*

Thomas E. Renau,* Roger Léger, Rose Yen, Miles W. She, Eric M. Flamme, Joan Sangalang, Carla L. Gannon, Suzanne Chamberland, Olga Lomovskaya and Ving J. Lee

Essential Therapeutics, Inc., 850 Maude Avenue, Mountain View, CA 94043, USA

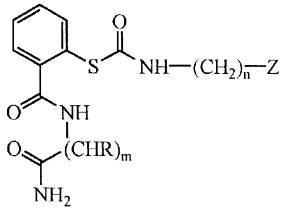


Bioorg. Med. Chem. Lett. 12 (2002) 767

Benzamide-Based Thiolcarbamates: A New Class of HIV-1 NCp7 Inhibitors

Atul Goel,[a] Sharlyn J. Mazur,[a] Rasem J. Fattah,[b] Tracy L. Hartman,[c] Jim A. Turpin,[c] Mingjun Huang,[d] William G. Rice,[d] Ettore Appella[a] and John K. Inman[b,*]

[a]*Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA*
[b]*Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA*
[c]*Infectious Disease Research Department, Southern Research Institute, 431 Aviation Way, Frederick, MD 21702, USA*
[d]*Achillion Pharmaceuticals, Inc., 300 George Street, New Haven, CT O6511, USA*



Synthesis and antiviral activity of benzamide-based thiolcarbamates (**5** and **6**) are described.

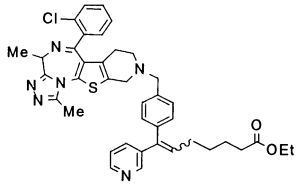
Bioorg. Med. Chem. Lett. 12 (2002) 771

Novel Agents Combining Platelet Activating Factor (PAF) Receptor Antagonist with Thromboxane Synthase Inhibitor (TxSI)

Masakazu Fujita,* Taketsugu Seki, Haruaki Inada, Kazuhiro Shimizu, Akane Takahama and Tetsuro Sano

Omiya Research Laboratory, Nikken Chemicals Co., Ltd., 1-346, Kitabukuro-cho, Saitama-shi, Saitama 330-0835, Japan

6-(2-Chlorophenyl)-3-[4-[(*E*/*Z*)-6-ethoxycarbonyl-1-(3-pyridyl)-1-hexenyl] phenylmethyl]-8,11-dimethyl-2,3,4,5-tetrahydro-8*H*-pyrido[4′,3′: 4,5]thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (**12**) was discovered to be excellent orally dual-acting PAF antagonist/TxSI.



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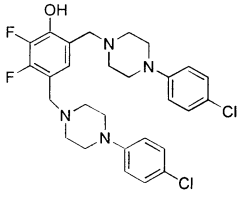
Bioorg. Med. Chem. Lett. 12 (2002) 775

The Synthesis and Selective IL-2 Inhibitory Activity of Bis Piperazine–Phenol Mannich Adducts

Bolin Geng,[a,*] Paul R. Fleming,[a] Scott Umlauf,[b] Augustine Lin[b] and Peter V. Pallai[a]

[a]*ArQule, Inc., 19 Presidential Way, Woburn, MA 01801, USA*
[b]*AVANT Immunotherapeutic, Inc., 119 Fourth Avenue, Needham, MA 02194, USA*



A series of novel phenol bis-Mannich adducts was synthesized and evaluated as IL-2 expression inhibitors.

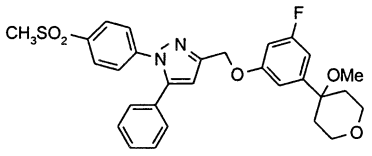
Bioorg. Med. Chem. Lett. 12 (2002) 779

Synthesis and Activity of a New Methoxytetrahydropyran Derivative as Dual Cyclooxygenase-2/5-Lipoxygenase Inhibitor

Sabine Barbey,[a] Laurence Goossens,[b] Thierry Taverne,[b] Joséphine Cornet,[b] Valérie Choesmel,[a] Céline Rouaud,[a] Gilles Gimeno,[a] Sylvie Yannic-Arnoult,[a] Catherine Michaux,[c] Caroline Charlier,[c] Raymond Houssin[b] and Jean-Pierre Hénichart[b,*]

[a]*Laboratoires Innothera, avenue P. Vaillant-Couturier, BP 10, 94110 Arcueil, France*
[b]*Institut de Chimie Pharmaceutique Albert Lespagnol, EA 2692, rue J. Laguesse, BP 83, 59006 Lille, France*
[c]*Laboratoire de Chimie Moléculaire Structurale, Facultés Universitaires Notre-Dame de la Paix, rue de Bruxelles, 5000 Namur, Belgium*

The synthesis and the activities of the powerful COX-2/5-LO inhibitor **1** are reported.



1 IC_{50} = 50 nM (COX-2) 3 nM (5-LO)

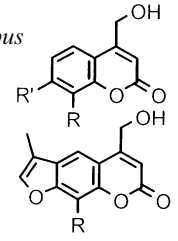
Bioorg. Med. Chem. Lett. 12 (2002) 783

Synthesis and Vasorelaxant Activity of New Coumarin and Furocoumarin Derivatives

Manuel Campos-Toimil,[a,*] Francisco Orallo,[a] Lourdes Santana[b] and Eugenio Uriarte[b]

[a]*Departamento de Farmacoloxía, Facultade de Farmacia, Universidade de Santiago de Compostela, Campus Universitario Sur, 15782 Santiago de Compostela, Galicia, Spain*
[b]*Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, Campus Universitario Sur, 15782 Santiago de Compostela, Galicia, Spain*

Several coumarin and furocoumarin derivatives showed vasorelaxant activity in rat aorta rings. The new compounds relax smooth vascular muscle with a profile similar to that of khellin and, in the case of furocoumarins, with a greater potency, suggesting that these compounds have a potential interest as vasodilatador drugs.



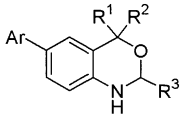
Bioorg. Med. Chem. Lett. 12 (2002) 787

Potent Nonsteroidal Progesterone Receptor Agonists: Synthesis and SAR Study of 6-Aryl Benzoxazines

Puwen Zhang,[a,*] Eugene A. Terefenko,[a] Andrew Fensome,[a] Zhiming Zhang,[b] Yuan Zhu,[b] Jeffrey Cohen,[b] Richard Winneker,[b] Jay Wrobel[a] and John Yardley[a]

[a]*Medicinal Chemistry I, Chemical Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA*
[b]*Women's Health Research Institute, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA*

Novel 6-aryl benzoxazines were evaluated as progesterone receptor (PR) modulators and were potent PR agonists when R^1 to R^3 are lower alkyl moiety. Compounds became PR antagonists if R^3 was a bulky group such as a *t*-butyl or phenyl moiety.



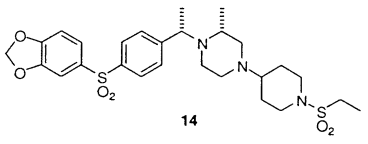
Bioorg. Med. Chem. Lett. 12 (2002) 791

Substituted 2-(*R*)-Methyl Piperazines as Muscarinic M_2 Selective Ligands

Joseph A. Kozlowski,* Guowei Zhou, Jayaram R. Tagat, Sue-Ing Lin, Stuart W. McCombie, Vilma B. Ruperto, Ruth A. Duffy, Robert A. McQuade, Gordon Crosby, Jr., Lisa A. Taylor, William Billard, Herbert Binch, III and Jean E. Lachowicz

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033-0539, USA

2-(R)-Methyl-substituted piperazines (e.g., **14**) are potent M_2 selective ligands that have >100-fold selectivity versus the M_1 receptor. In the rat microdialysis assay, **14** showed significantly enhanced levels of acetylcholine after oral administration.



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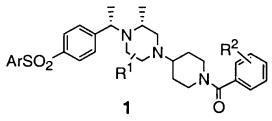
Bioorg. Med. Chem. Lett. 12 (2002) 795

Synthesis and Structure–Activity Relationships of M_2-Selective Muscarinic Receptor Ligands in the 1-[4-(4-Arylsulfonyl)-phenylmethyl]-4-(4-piperidinyl)-piperazine Family

Stuart W. McCombie,[a,*] Sue-Ing Lin,[a] Jayaram R. Tagat,[a] Dennis Nazareno,[a] Susan Vice,[a] Jennifer Ford,[a] Theodros Asberom,[a] Daria Leone,[a] Joseph A. Kozlowski,[a] Guowei Zhou,[a] Vilma B. Ruperto,[b] Ruth A. Duffy[b] and Jean E. Lachowicz[b]

[a]*Department of Chemistry, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*Department of CNS Pharmacology, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*



1

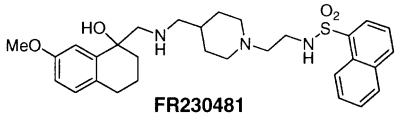
Optimization of the substitution pattern in compounds **1** produces potent, selective ligands for the M_2 receptor subtype.

Bioorg. Med. Chem. Lett. 12 (2002) 799

Novel Potent Antagonists of Human Neuropeptide Y Y5 Receptors. Part 3: 7-Methoxy-1-hydroxy-1-substituted Tetraline Derivatives

Hiromichi Itani,[a] Harunobu Ito,[b] Yoshihiko Sakata,[b] Yoshifumi Hatakeyama,[b] Hiroko Oohashi[b] and Yoshinari Satoh[a,*]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*
[b]*Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*



FR230481

Novel 7-methoxy-1-hydroxy-1-substituted tetraline derivatives and related compounds were prepared. **FR230481** and **FR233118** showed high affinity for the NPY-Y5 receptors.

Bioorg. Med. Chem. Lett. 12 (2002) 803

Synthesis of Sordaricin Analogues as Potent Antifungal Agents against *Candida albicans*

Satoru Kaneko,[a,*] Takuya Uchida,[a] Satoshi Shibuya,[a] Takeshi Honda,[a] Isao Kawamoto,[a] Tamako Harasaki,[b] Takashi Fukuoka[b] and Toshiyuki Konosu[a,*]

[a]*Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710, Japan*
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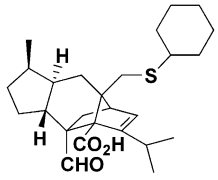


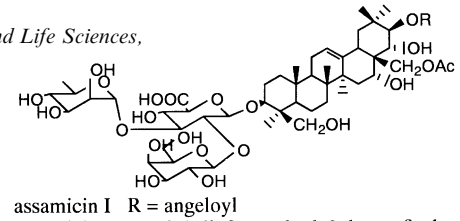
Sordaricin derivatives possessing a cyclohexane ring appendage were synthesized and their antifungal activity was evaluated in vitro. Compounds containing a thioether bond or an oxime bond exhibited potent MICs (≤ 1.25 μg/mL) against *Candida albicans*. They were also active (MIC ≤ 0.125 μg/mL) against *Candida glabrata*. Their in vivo efficacy was confirmed in a murine intravenous infection model with *C. albicans*.

Bioorg. Med. Chem. Lett. 12 (2002) 807

Assamicin I and II, Novel Triterpenoid Saponins with Insulin-Like Activity from *Aesculus assamica* Griff.

Takashi Sakurai,[a] Toshio Nishimura,[b] Noboru Otake,[b] Yao Xinsheng,[c] Keiichi Abe,[d] Mitsuhiro Zeida,[d] Hiromichi Nagasawa[a] and Shohei Sakuda[a,*]

[a]*Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Bunkyo-ku, Tokyo 113-8657, Japan*
[b]*Department of Science and Technology, Teikyo University, 1-1 Toyosato, Utsunomiya 320-0003, Japan*
[c]*Department of Natural Products, Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenhe District, Shenyang 110015, China*
[d]*Institute for Health Care Science, Research Centre, Suntory Limited, 120-1, Takahama, Shimamoto-cho, Mishima-gun, Osaka 618-0012, Japan*



assamicin I R = angeloyl
assamicin II R = 3,4-di-*O*-angeloyl-6-deoxy-β-glucopyranosyl

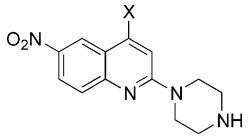
Bioorg. Med. Chem. Lett. 12 (2002) 811

Syntheses and Binding Affinities of 6-Nitroquipazine Analogues for Serotonin Transporter. Part 2. 4-Substituted 6-Nitroquipazines

Byoung Se Lee,[a] Soyoung Chu,[a] Bon-Su Lee,[a] Dae Yoon Chi,[a,*] Yun Seon Song[b] and Changbae Jin[b]

[a]*Department of Chemistry, Inha University, 253 Yonghyundong, Namgu, Inchon 402-751, Republic of Korea*
[b]*Bioanalysis & Biotransformation Research Center, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, Republic of Korea*

Among 11 4-substituted derivatives of 6-nitroquipazine synthesized and evaluated for their affinities to serotonin transporter, 4-chloro-6-nitroquipazine was shown to possess the highest binding affinity ($K_i = 0.03$ nM) which was 6 times higher than that of 6-nitroquipazine.



Bioorg. Med. Chem. Lett. 12 (2002) 817

Synthesis and Antiplatelet Activity of Gemfibrozil Chiral Analogues

Alessandra Ammazzalorso,[a] Rosa Amoroso,[a] Mario Baraldi,[b] Giancarlo Bettoni,[a,*] Daniela Braghiroli,[a] Barbara De Filippis,[a] Andrea Duranti,[c] Marco Moretti,[d] Paolo Tortorella,[a] Maria Luisa Tricca[a] and Francesca Vezzalini[b]

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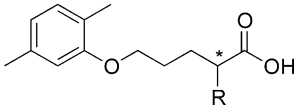

Bioorg. Med. Chem. Lett. 12 (2002) 823

Cytotoxic, Antifouling Bromotyramines: A Synthetic Study on Simple Marine Natural Products and Their Analogues

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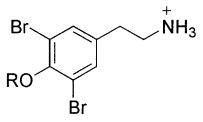
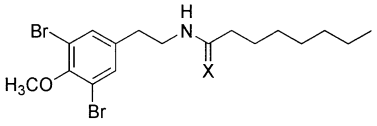


1: R = $(CH_2)_3NH_3^+$
2: R = CH_3



15: X = O
16: X = H_2

Bioorg. Med. Chem. Lett. 12 (2002) 827

2-Arylindoles as Gonadotropin Releasing Hormone (GnRH) Antagonists: Optimization of the Tryptamine Side Chain

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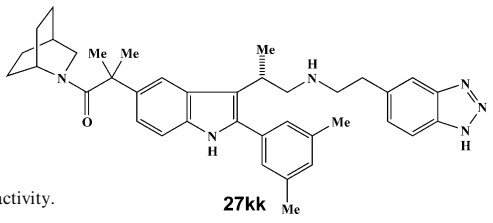
A series of 2-arylindoles was prepared and evaluated for gonadotropin releasing hormone (GnRH) activity. Compound **27kk** was found to be an orally active GnRH antagonist.



27kk

Bioorg. Med. Chem. Lett. 12 (2002) 833

Structure–Activity Relationships of Oxime Neurokinin Antagonists: Oxime Modifications

Gregory A. Reichard,* James Spitler, Robert Aslanian, Mwangi wa Mutahi, Neng-Yang Shih, Ling Lin, Pauline C. Ting, John C. Anthes and John J. Piwinski

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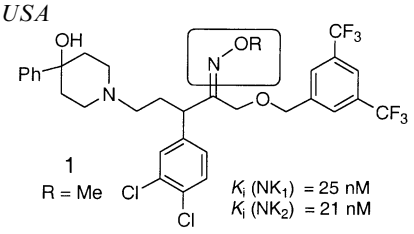
A thorough SAR study of the oxime region of the dual NK_1/NK_2 antagonist **1** revealed several modifications that result in potent dual antagonists. Follow-up SAR studies on a second-generation scaffold demonstrate that certain polar groups on the oxime can improve the dual binding affinity to the subnanomolar range.



1
R = Me

K_i (NK_1) = 25 nM
K_i (NK_2) = 21 nM