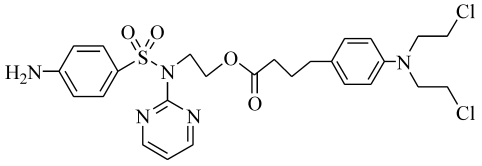
Bioorg. Med. Chem. Lett. 11 (2001) 1099

2-[N[1]-2-Pyrimidyl-aminobenzenesulfonamido] Ethyl 4-Bis(2-chloroethyl) Aminophenyl Butyrate: a Potent Antitumor Agent

Zhaohua Huang,[a] Genjin Yang,[b] Zhaoliang Lin[a] and and Junlian Huang[a,*]

[a]*The Key Laboratory of Molecular Engineering of Polymers, Education Ministry of China, Department of Macromolecular Science, Fudan University, Shanghai 200433, China*
[b]*School of Pharmacy, The Second Military Medical University, Shanghai 200433, China*

2-[N[1]-2-Pyrimidyl-aminobenzenesulfonamido] ethyl 4-bis(2-chloroethyl) aminophenyl butyrate has been prepared by reaction of chlorambucil with sulfadiazine derivative. The title compound exhibits a high antitumor activity with a therapeutic index (TI) of 47.55 which is twice of chlorambucil's (TI: 22.84).

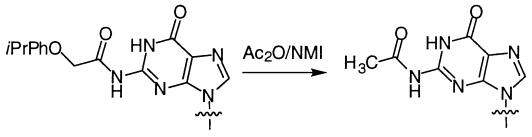


Bioorg. Med. Chem. Lett. 11 (2001) 1105

Observation and Elimination of *N*-Acetylation of Oligonucleotides Prepared Using Fast-Deprotecting Phosphoramidites and Ultra-Mild Deprotection

Qiang Zhu, Michael O. Delaney and Marc M. Greenberg*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA



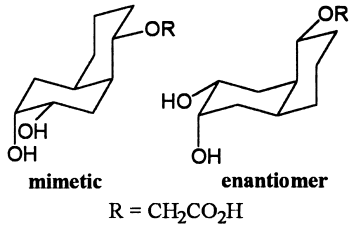
Bioorg. Med. Chem. Lett. 11 (2001) 1109

Design and Synthesis of a New Sialyl Lewis X Mimetic: How Selective Are the Selectin Receptors?

Marc De Vleeschauwer,[a] Marc Vaillancourt,[b] Nathalie Goudreau,[a] Yvan Guindon[a,b] and Denis Gravel[a,*]

[a]*Département de chimie, Université de Montréal, C.P. 6128, succ. Centre-ville, Montréal, Québec, Canada, H3C 3J7*
[b]*Institut de recherches cliniques de Montréal (IRCM), 110 ave des Pins Ouest, Montréal, Québec, Canada, H2W 1R7*

Both the designed mimetic and its enantiomer give essentially the same activity towards E- and P-selectins.



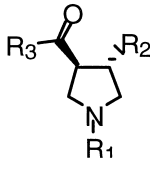
Bioorg. Med. Chem. Lett. 11 (2001) 1113

Pharmacophore-Based Discovery of 3,4-Disubstituted Pyrrolidines as a Novel Class of Monoamine Transporter Inhibitors

Istvan J. Enyedy,[a,b] Wahiduz A. Zaman,[c] Sukumar Sakamuri,[d] Alan P. Kozikowski,[d] Kenneth M. Johnson[c] and Shaomeng Wang[a,b,*]

[a]*Department of Oncology, Building D, Room 235/237, Georgetown University Medical Center, 4000 Reservoir Rd., Washington, DC 20007, USA*
[b]*Department of Neuroscience, Building D, Room 235/237, Georgetown University Medical Center, 4000 Reservoir Rd., Washington, DC 20007, USA*
[c]*Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX 77555-1031, USA*
[d]*Drug Discovery Program, Department of Neurology, Georgetown University Medical Center, 3700 Reservoir Rd., Washington, DC 20007, USA*

3,4-Disubstituted pyrrolidines were discovered as a novel class of monoamine transporter inhibitors through 3-D database pharmacophore searching using a new pharmacophore model. The most potent analogue **12** has K_i values of 0.084 μM in [^{3}H]mazindol binding, 0.20, 0.23, and 0.031 μM in inhibition of dopamine (DA), serotonin (SER), and norepinephrine (NE) reuptake, respectively. Functional antagonism testing in vitro showed that **11** and **12** are weak cocaine antagonists.



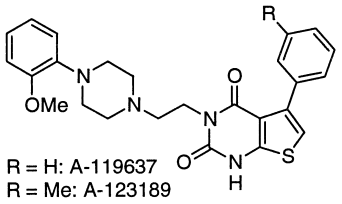
Bioorg. Med. Chem. Lett. 11 (2001) 1119

Two Novel and Potent 3-[(*o*-Methoxyphenyl)piperazinylethyl]-5-phenylthieno[2,3-*d*]pyrimidine-2,4-diones Selective for the α_{1D} Receptor

William A. Carroll,* Kevin B. Sippy, Timothy A. Esbenshade, Steven A. Buckner, Arthur A. Hancock and Michael D. Meyer

Abbott Laboratories, Neurological and Urological Diseases Research, 100 Abbott Park Road, Abbott Park, IL 60064-6101, USA

The synthesis and in vitro characterization of A-119637 and A-123189, two novel, selective and potent α_{1D} antagonists, are described.



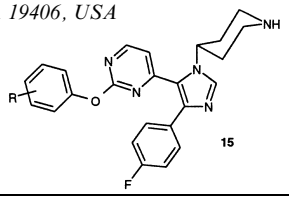
Bioorg. Med. Chem. Lett. 11 (2001) 1123

Phenoxypyrimidine Inhibitors of p38α Kinase: Synthesis and Statistical Evaluation of the p38 Inhibitory Potencies of a Series of 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl) Imidazoles

Jeffrey C. Boehm,[a,*] Michael J. Bower,[b] Timothy F. Gallagher,[a] Shouki Kassis,[c] Stephen R. Johnson[d] and Jerry L. Adams[a]

[a]*Department of Medicinal Chemistry, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA*
[b]*Department of Physical and Structural Chemistry, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA*
[c]*Department of Bone and Cartilage Biology, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA*
[d]*Department of Cheminformatics, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA*

As a continuation of our work with 1,4,5 substituted imidazole inhibitors of p38α, we report a series of 1-(4-piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy-4-pyrimidinyl) imidazoles **15**. The compounds have IC_{50}'s for inhibition of p38α ranging from 6.0 to 650 nM. Statistical analysis of the p38α inhibitor potencies shows a correlation of IC_{50}'s with the electron donating strength of low molecular weight substituents.



15

Bioorg. Med. Chem. Lett. 11 (2001) 1127

Binding of Dimeric Aminoglycosides to the HIV-1 Rev Responsive Element (RRE) RNA Construct

Jeffrey B.-H. Tok,* Lindsey J. Dunn and Ryan C. Des Jean

Department of Chemistry, Indiana University-Purdue University Fort Wayne, 2101 E. Coliseum Blvd., Fort Wayne, IN 46805, USA

The binding study results of dimeric neomycin ligands, through fluorescence anisotropy studies, to the HIV-1 Rev responsive element (RRE) RNA construct were presented. The dimeric neomycin molecules are observed to bind the HIV-1 RRE RNA construct approximately 17-fold higher compared to the monomeric neomycin, lending evidence that there are indeed two or more neomycin binding sites within the HIV-1 RRE construct.

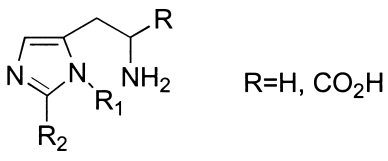
Bioorg. Med. Chem. Lett. 11 (2001) 1133

Regiospecific Synthesis of 2,3-Disubstituted-L-Histidines and Histamines

Sanju Narayanan, Suryanarayana Vangapandu and Rahul Jain*

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S. Nagar-160 062, Punjab, India

The first regiospecific synthesis of 2,3-dialkyl-L-histidines and 2,3-dialkylhistamines in seven steps is described.



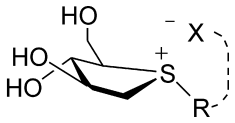
Bioorg. Med. Chem. Lett. 11 (2001) 1137

Glycosidase Inhibition by Cyclic Sulfonium Compounds

Hideya Yuasa,* Jun Takada and and Hironobu Hashimoto

Department of Life Science, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 226-8501, Japan

Inhibitory activity of various cyclic sulfonium compounds including salacinol against several glycosidases is reported.



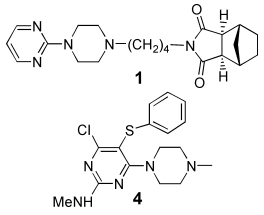
Bioorg. Med. Chem. Lett. 11 (2001) 1141

Conformational Analysis of Tandospirone in Aqueous Solution: Lead Evolution of Potent Dopamine D_4 Receptor Ligands

Tamiki Nishimura, Jun-etsu Igarashi and Makoto Sunagawa*

Sumitomo Pharmaceuticals Research Division, 3-1-98 Kasugadenaka, Konohanaku, Osaka 554-0022, Japan

The significant contribution of folded conformation of tandospirone (**1**) in aqueous solution was verified by dynamic ^{1}H NMR. A structurally rigid mimic (**4**) was designed and synthesized, which showed the folded conformation of **1** was responsible for the dopamine D_4 affinity.



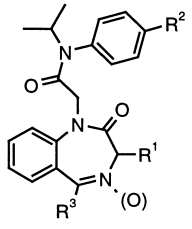
Bioorg. Med. Chem. Lett. 11 (2001) 1145

1,4-Benzodiazepine Peripheral Cholecystokinin (CCK-A) Receptor Agonists

Ronald G. Sherrill,[a,*] Judd M. Berman,[a] Lawrence Birkemo,[c] Dallas K. Croom,[c] Milana Dezube,[a] Gregory N. Ervin,[c] Mary K. Grizzle,[c] Michael K. James,[b] Michael F. Johnson,[c] Kennedy L. Queen,[b] Thomas J. Rimele,[b] Frank Vanmiddlesworth[a] and Elizabeth E. Sugg[a]

[a]*Department of Medicinal Chemistry, GlaxoWellcome Research and Development, 5 Moore Drive, Research Triangle Park, NC 27709, USA*
[b]*Department of Receptor Biochemistry, GlaxoWellcome Research and Development, 5 Moore Drive, Research Triangle Park, NC 27709, USA*
[c]*Department of Pharmacology, GlaxoWellcome Research and Development, 5 Moore Drive, Research Triangle Park, NC 27709, USA*

A series of 1,4-benzodiazepines, *N*-1-substituted with an *N*-isopropyl-*N*-phenylacetamide moiety, was synthesized and screened for CCK-A agonist activity. In vitro agonist activity on isolated guinea pig gallbladder along with in vivo induction of satiety following intraperitoneal administration in a rat feeding assay was demonstrated.



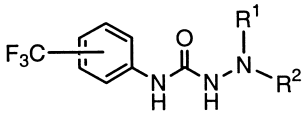
Bioorg. Med. Chem. Lett. 11 (2001) 1149

The Identification and Characterization of Hydrazinyl Urea-Based Antibacterial Agents through Combinatorial Chemistry

Lawrence J. Wilson,* Timothy W. Morris, Qimin Wu, Paul J. Renick, Christian N. Parker, Michael C. Davis, Helana D. McKeever, Paul M. Hershberger, A. Greg Switzer, Gary Shrum, Shyam Sunder, David R. Jones, Shari S. Soper, Roy L. M. Dobson, Thomas Burt, Kenneth L. Morand and Mark Stella

Procter & Gamble Pharmaceuticals, Healthcare Research Center, 8700 Mason-Montgomery Road, Mason, OH 45040, USA

A series of aryl hydrazinyl ureas with antibacterial properties acting on cell wall biosynthesis discovered through mixture and parallel-solution synthesis is presented.



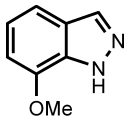
Bioorg. Med. Chem. Lett. 11 (2001) 1153

Inhibition of Neuronal Nitric Oxide Synthase by 7-Methoxyindazole and Related Substituted Indazoles

Pascale Schumann,[a] Valérie Collot,[b] Yannick Hommet,[a] Willy Gsell,[a] François Dauphin,[a] Jana Sopkova,[b] Eric T. MacKenzie,[a] Dominique Duval,[a] Michel Boulouard[b] and Sylvain Rault[b,*]

[a]*CNRS UMR 6551-Université de Caen, Bd H Becquerel, 14074 Caen, France*
[b]*UPRES-EA 2126-Centre d'Etudes et de Recherches sur le Médicament de Normandie (CERMN)-UFR Sciences Pharmaceutiques, rue Vaubénard, Caen, France*

The synthesis and pharmacological evaluation of a novel inhibitor of nNOS (7-MI) is reported.



7-MI

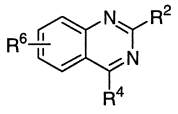
Bioorg. Med. Chem. Lett. 11 (2001) 1157

Quinazolines as Cyclin Dependent Kinase Inhibitors

Thais M. Sielecki,[a,*] Tricia L. Johnson,[a] Jie Liu,[a] Jodi K. Muckelbauer,[a] Robert H. Grafstrom,[a] Sarah Cox,[a] John Boylan,[a] Catherine R. Burton,[a] Haiying Chen,[a] Angela Smallwood,[a] Chong-Hwan Chang,[a] Michael Boisclair,[b] Pamela A. Benfield,[a] George L. Trainor[a] and Steven P. Seitz[a]

[a]*The DuPont Pharmaceuticals Company, Wilmington, DE 19880-0500, USA*
[b]*Mitotix Inc., Cambridge, MA 02139, USA*

Quinazolines have been identified as inhibitors of CDK4/D1 and CDK2/E. Aspects of the SAR were investigated using solution-phase, parallel synthesis. An X-ray crystal structure was obtained of quinazoline **51** bound in CDK2 and key interactions within the ATP binding pocket are defined.



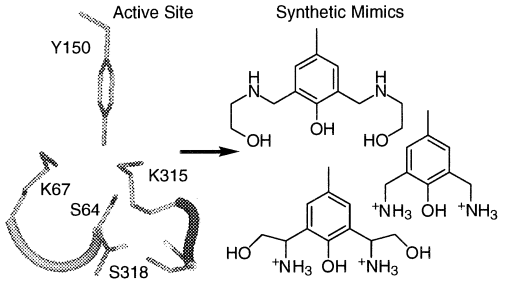
Bioorg. Med. Chem. Lett. 11 (2001) 1161

Reaction of Lys-Tyr-Lys Triad Mimics with Benzylpenicillin: Insight into the Role of Tyr150 in Class C β-Lactamase

Yoko Kato-Toma and Masaji Ishiguro*

Suntory Institute for Bioorganic Research, 1-1-1 Wakayamadai, Shimamoto, Osaka 618-8503, Japan

Simple molecules mimicking the class C β-lactamase active site Lys-Tyr-Lys triad and some 'mutant' derivatives were designed, synthesized and reacted with benzylpenicillin in water. Our findings give insight into the possible role of this triad in enzymatic β-lactam hydrolysis.



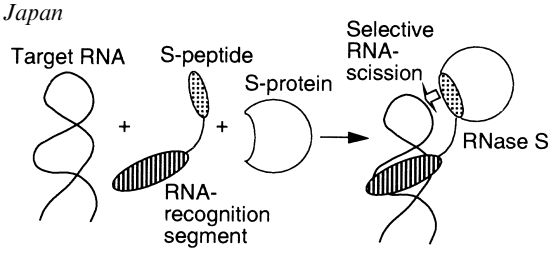
Bioorg. Med. Chem. Lett. 11 (2001) 1165

A 'Cassette' RNase: Site-Selective Cleavage of RNA by RNase S Equipped with RNA-Recognition Segment

Shiroh Futaki,* Michihiro Araki, Tatsuto Kiwada, Ikuhiko Nakase and Yukio Sugiura*

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

An RNase S comprising the S-protein and the S-peptide conjugated with the RNA-recognition segment of HIV-1 Rev preferentially hydrolyzed a single position of an RNA loop derived from the specific binding site for the Rev protein.



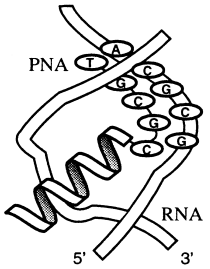
Bioorg. Med. Chem. Lett. 11 (2001) 1169

HIV Rev Peptides Conjugated with Peptide Nucleic Acids and Their Efficient Binding to RRE RNA

Ichiro Kumagai,[a] Tsuyoshi Takahashi,[a] Keita Hamasaki,[a] Akihiko Ueno[a] and Hisakazu Mihara[a,b,*]

[a]*Department of Bioengineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8501, Japan*
[b]*Form and Function, PRESTO, Japan Science and Technology Corporation, Nagatsuta, Yokohama 226-8501, Japan*

HIV Rev peptides conjugated with peptide nucleic acids (PNAs) were designed and synthesized to develop a designing approach for a novel RNA-binding molecule. The binding affinities of PNA-peptides with the Rev responsive element (RRE) RNA were determined by the competition assay using a rhodamine-labeled Rev. The peptide conjugated with an antisense PNA (TGCGC) bound RRE RNA more efficiently than the molecule without the PNA or the peptide sequence.



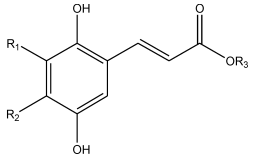
Bioorg. Med. Chem. Lett. 11 (2001) 1173

Syntheses of Certain 3-Aryl-2-propenoates and Evaluation of Their Cytotoxicity

Nguyen-Hai Nam,[a] Young-Jae You,[a] Yong Kim,[a] Dong-Ho Hong,[b] Hwan-Mook Kim[b] and Byung Zun Ahn[a,*]

[a]*College of Pharmacy, Chungnam National University, Taejon 305-764, South Korea*
[b]*Korea Research Institute of Bioscience and Biotechnology, Taejon 305-600, South Korea*

The syntheses and evaluation of cytotoxicity of certain cinnamates, (*E*)-3-[2-(1,4-dihydroxy-9,10-dione)-anthracenyl]- and (*E*)-3-[2-(1,4-dimethoxy-5,8-dione)naphthalenyl]-2-propenoates are described.



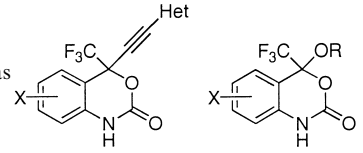
Bioorg. Med. Chem. Lett. 11 (2001) 1177

Synthesis and Evaluation of Efavirenz (Sustiva™) Analogues as HIV-1 Reverse Transcriptase Inhibitors: Replacement of the Cyclopropylacetylene Side Chain

Anthony J. Cocuzza,* Dennis R. Chidester, Beverly C. Cordova, Susan Jeffrey, Rodney L. Parsons, Lee T. Bacheler, Susan Erickson-Viitanen, George L. Trainor and Soo S. Ko

DuPont Pharmaceuticals Company, Experimental Station, E336/141, PO Box 80336, Wilmington, DE 19880-0336, USA

Two potent series of efavirenz analogues have been developed: one in which the cyclopropane ring has been replaced by small heterocycles and another in which the entire acetylenic side chain has been replaced by alkyloxy groups.



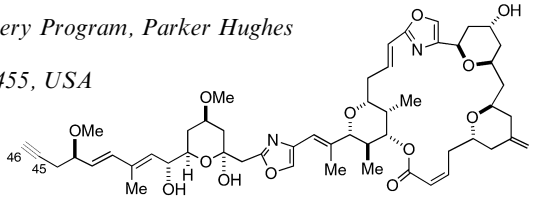
Bioorg. Med. Chem. Lett. 11 (2001) 1181

Anticancer Activity of Synthetic Analogues of the Phorboxazoles

Fatih M. Uckun[a,*] and Craig J. Forsyth[b]

[a]*Parker Hughes Cancer Center, Department of Oncology and Drug Discovery Program, Parker Hughes Institute, St. Paul, MN 55113, USA*
[b]*Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA*

The structure–activity studies of synthetic analogues of the phorboxazoles against human cancer cell lines are reported.



2: 45,46-Dehydrobromo-Phorboxazole A

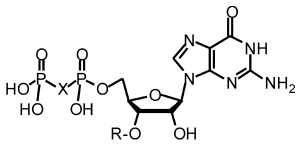
IC_{50}=4.8nM

Bioorg. Med. Chem. Lett. 11 (2001) 1185

Probing the Transducin Nucleotide Binding Site with GDP Analogues

Stéphane P. Vincent,[a] Sonya Grenier,[b] Charles Mioskowski,[a] Christian Salesse[b] and Luc Lebeau[a,*]

[a]*Laboratoire de Synthèse Bioorganique associé au CNRS, Université Louis Pasteur, 74, route du Rhin, BP 24, 67401 Illkirch cedex, France*
[b]*GREIB, Département de Chimie-Biologie, Université du Québec à Trois-Rivières, Trois-Rivières, Québec, Canada G9A 5H7*



IC_{50} with transducin :
X = CH_2, R = H : IC_{50} > 1000 µM
X = NH, R = H : IC_{50} = 12 µM
X = NH, R = C_2H_5CO : IC_{50} = 500 µM

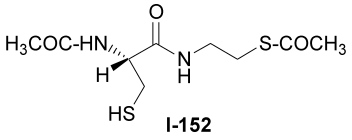
Bioorg. Med. Chem. Lett. 11 (2001) 1189

NAC/MEA Conjugate: A New Potent Antioxidant Which Increases the GSH Level in Various Cell Lines

Joël Oiry,[a,*] Patricia Mialocq,[b] Jean Y. Puy,[a] Philippe Fretier,[b] Pascal Clayette,[b] Dominique Dormont[b] and Jean L. Imbach[a]

[a]*Laboratoire de Chimie Organique Biomoléculaire de Synthèse, UMR 5625 CNRS-UM II, Université Montpellier II, Sciences et Techniques du Languedoc, place Eugène Bataillon, 34095 Montpellier Cedex 5, France*
[b]*Service de Neurovirologie, CEA/DSV/DRM, CRSSA, EPHE, 60–68 avenue de la Division Leclerc, BP 6, 92265 Fontenay aux Roses Cedex, France*

The NAC/MEA conjugate **I-152** is a potent non-toxic antioxidant which increases the GSH level in various cell lines. This compound also presents an anti-HIV effect in the micromolar range.



I-152

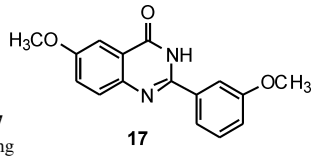
Bioorg. Med. Chem. Lett. 11 (2001) 1193

Antitumor Agents. Part 204: Synthesis and Biological Evaluation of Substituted 2-Aryl Quinazolinones

Yi Xia,[a] Zheng-Yu Yang,[a] Mann-Jen Hour,[b] Sheng-Chu Kuo,[b] Peng Xia,[a] Kenneth F. Bastow,[a] Yuka Nakanishi,[a] Priya Nampoothiri,[c] Torben Hackl,[c] Ernest Hamel[c] and Kuo-Hsiung Lee[a,*]

[a]*Natural Products Laboratory, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA*
[b]*China Medical College, Taichung, Taiwan*
[c]*Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, MD 21702, USA*

A series of 2′,3′,4′,6,7-substituted 2-aryl quinazolinones were synthesized and evaluated for biological activity. Among them, **17** displayed significant growth inhibitory action against a panel of tumor cell lines. Compound **17** was also a potent inhibitor of tubulin polymerization. Compounds **8**–**10** displayed selective activity against P-gp-expressing epidermoid carcinoma of the nasopharynx.



17

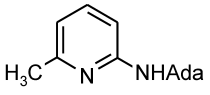
Bioorg. Med. Chem. Lett. 11 (2001) 1197

Adamantylaminopyrimidines and -pyridines Are Potent Inducers of Tumor Necrosis Factor-α

Zygmunt Kazimierczuk,[a,*] Agata Górska,[a] Tomasz Świtaj[b] and Witold Lasek[b]

[a]*Institute of Chemistry, Agricultural University, Rakowiecka 26/30, 02-528 Warsaw, Poland*
[b]*Department of Immunology, Biostructure Center, Medical University of Warsaw, Chałubińskiego 5, 02-004 Warsaw, Poland*

A series of adamantylaminopyrimidine and -pyridine derivatives was prepared. The adamantylated compounds, particularly 2-(1-adamantyl)amino-6-methylpyridine, were found to be potent TNF-α inducers in murine melanoma cells transduced with gene for human TNF-α.



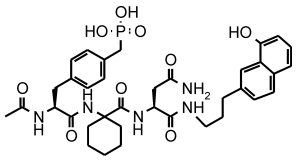
Bioorg. Med. Chem. Lett. 11 (2001) 1201

Convergent Synthesis of Potent Peptide Inhibitors of the Grb2-SH2 Domain by Palladium Catalyzed Coupling of a Terminal Alkyne

Joseph Schoepfer,* Brigitte Gay, Nicole End, Evelyne Muller, Gisela Scheffel, Giorgio Caravatti and Pascal Furet

Oncology Research, NOVARTIS Pharma AG, 4002 Basel, Switzerland

A new strategy was developed to prepare in a very efficient and convergent manner C-terminal modified tripeptides with high affinities for the Grb2-SH2 domain. Using a Pd catalyst, selected naphthyl iodides and triflates were coupled to Ac-Pmp(t-Bu)$_2$-Ac$_6$c-Asn-NH(prop-2-ynyl).



4f IC_{50}: 11.1 ± 0.4 nM

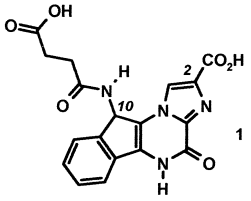
Bioorg. Med. Chem. Lett. 11 (2001) 1205

Synthesis of Anticonvulsive AMPA Antagonists: 4-Oxo-10-substituted-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-2-carboxylic Acid Derivatives

Jean-Marie Stutzmann, Georg Andrees Bohme, Alain Boireau, Dominique Damour, Marc Williams Debono, Arielle Genevois-Borella, Patrick Jimonet, Jeremy Pratt, John C. R. Randle, Yves Ribeill, Marc Vuilhorgne and Serge Mignani*

Aventis Pharma S.A., Centre de Recherche de Vitry-Alfortville, 13 quai Jules Guesde, BP 14, 94403 Vitry-sur-Seine Cedex, France

The 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-2-carboxylic acid **1** exhibited strong binding affinity for the AMPA receptor (IC_{50} = 35 nM) and potent antagonist activity against electrophysiological responses (IC_{50} = 6 nM). Compound **1** demonstrated also an anticonvulsant effect at low doses in MES test with ED_{50} values between 1 and 3 mg/kg dose range following ip and iv administration (mouse) and extended long duration of action following iv administration (mouse and rats).



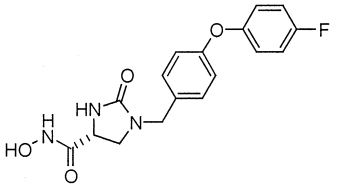
1

Bioorg. Med. Chem. Lett. 11 (2001) 1211

Design and Synthesis of 2-Oxo-imidazolidine-4-carboxylic Acid Hydroxyamides as Potent Matrix Metalloproteinase-13 Inhibitors

Ralph P. Robinson,* Ellen R. Laird, Kathleen M. Donahue, Lori L. Lopresti-Morrow, Peter G. Mitchell, Matthew R. Reese, Lisa M. Reeves, Amber I. Rouch, Ethan J. Stam and Sue A. Yocum

Pfizer Global Research & Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, USA



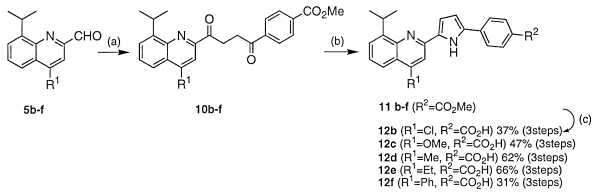
MMP-13 IC_{50} = 3 nM

Bioorg. Med. Chem. Lett. 11 (2001) 1215

Syntheses and Evaluation of Quinoline Derivatives as Novel Retinoic Acid Receptor α Antagonists

Kouichi Kikuchi,[a,*] Katsuya Tagami,[b] Shigeki Hibi,[a] Hiroyuki Yoshimura,[c] Naoki Tokuhara,[a] Kenji Tai,[a] Takayuki Hida,[d] Toshihiko Yamauchi[a] and Mitsuo Nagai[a]

[a]*Discovery Research Laboratories, Eisai Co., Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki, 300-2635, Japan*
[b]*Process Research Laboratories, Eisai Co., Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki, 300-2635, Japan*
[c]*Development and Technological Services, Eisai Co., Ltd., 4-6-10, Koishikawa, Bunkyo-ku, Tokyo, 112-0002, Japan*
[d]*Laboratories of Seeds Finding Technology, Eisai Co., Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki, 300-2635, Japan*



5b-f **10b-f** **11 b-f** (R^2=CO_2Me)

12b (R^1=Cl, R^2=CO_2H) 37% (3steps)
12c (R^1=OMe, R^2=CO_2H) 47% (3steps)
12d (R^1=Me, R^2=CO_2H) 62% (3steps)
12e (R^1=Et, R^2=CO_2H) 66% (3steps)
12f (R^1=Ph, R^2=CO_2H) 31% (3steps)

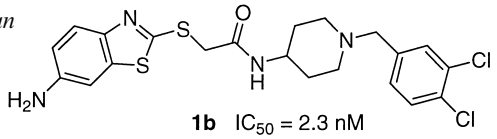
Bioorg. Med. Chem. Lett. 11 (2001) 1219

Discovery of a Novel CCR3 Selective Antagonist

Akira Naya,* Kensuke Kobayashi, Makoto Ishikawa, Kenji Ohwaki, Toshihiko Saeki, Kazuhito Noguchi and Norikazu Ohtake

Banyu Tsukuba Research Institute, Okubo-3, Tsukuba 300-2611, Ibaraki, Japan

A 2-(benzothiazolethio)acetamide derivative (**1b**) was discovered as a CCR3 selective antagonist.



1b IC_{50} = 2.3 nM

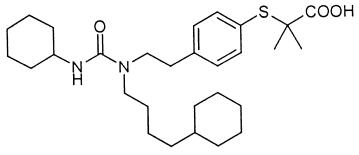
Bioorg. Med. Chem. Lett. 11 (2001) 1225

Identification of a Subtype Selective Human PPARα Agonist Through Parallel-Array Synthesis

Peter J. Brown,* L. William Stuart, Kevin P. Hurley, Michael C. Lewis, Deborah A. Winegar, Joan G. Wilson, William O. Wilkison, Olivia R. Ittoop and Timothy M. Willson

GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709-3398, USA

Using solid-phase, parallel-array synthesis, a series of urea-substituted thioisobutyric acids was synthesized. GW7647 (**3**) was identified as a potent, selective human PPARα agonist.



GW7647 **(3)**

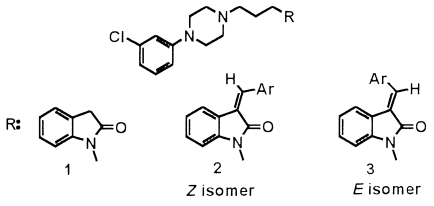
Bioorg. Med. Chem. Lett. 11 (2001) 1229

Influence of the Terminal Amide Fragment Geometry in Some 3-Arylideneindolin-2(1*H*)-ones on Their 5-HT_{1A}/5-HT_{2A} Receptor Activity

Maria J. Mokrosz,[a] Sijka Charakchieva-Minol,[a] Aneta Kozioł,[a] Aleksandra Kłodzińska[b] and Ewa Chojnacka-Wójcik[b,*]

[a]*Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland*
[b]*Department of New Drug Research, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland*

Several 1,4-disubstituted arylpiperazine derivatives of 3-arylideneindolin-2(1*H*)-one were tested for their 5-HT_{1A} and 5-HT_{2A} receptor activity in vitro and in vivo. It was shown that introduction of 3-arylidene substituents to indolin-2(1*H*)-one moiety allowed to switch the mixed 5-HT_{1A}/5-HT_{2A} antagonists.



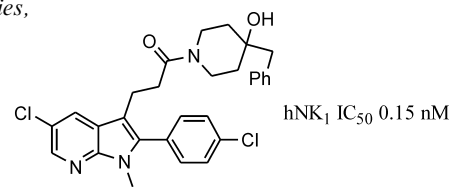
1 2 *Z* isomer 3 *E* isomer

Bioorg. Med. Chem. Lett. 11 (2001) 1233

2-Aryl Indole NK_1 Receptor Antagonists: Optimisation of Indole Substitution

Laura C. Cooper,[a,*] Gary G. Chicchi,[c] Kevin Dinnell,[a] Jason M. Elliott,[a] Gregory J. Hollingworth,[a] Marc M. Kurtz,[c] Karen L. Locker,[a] Denise Morrison,[a] Duncan E. Shaw,[a] Kwei-Lan Tsao,[c] Alan P. Watt,[a] Angela R. Williams[b] and Christopher J. Swain[a]

[a]*Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[b]*Department of Pharmacology, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[c]*Department of Biochemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*



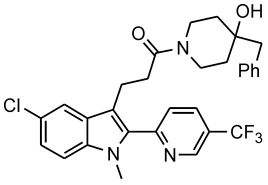
hNK_1 IC_{50} 0.15 nM

Bioorg. Med. Chem. Lett. 11 (2001) 1237

2-Aryl Indole NK_1 Receptor Antagonists: Optimisation of the 2-Aryl Ring and the Indole Nitrogen Substituent

Kevin Dinnell,[a,*] Gary G. Chicchi,[d] Madhumeeta J. Dhar,[c] Jason M. Elliott,[a] Gregory J. Hollingworth,[a] Marc M. Kurtz,[d] Mark P. Ridgill,[a] Wayne Rycroft,[b] Kwei-Lan Tsao,[d] Angela R. Williams[b] and Christopher J. Swain[a]

[a]*Department of Medicinal Chemistry, Merck, Sharp and Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Harlow, Essex, CM20 2QR, UK*
[b]*Department of Pharmacology, Merck, Sharp and Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Harlow, Essex, CM20 2QR, UK*
[c]*Department of Medicinal Chemistry, Merck Research Laboratories , 126 E. Lincoln Ave, Rahway, NJ 07065, USA*
[d]*Department of Biochemistry, Merck Research Laboratories, 126 E. Lincoln Ave, Rahway, NJ 07065, USA*



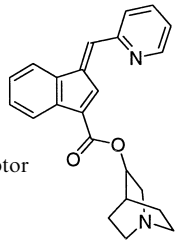
hNK_1 IC_{50} 0.12 nM

Bioorg. Med. Chem. Lett. 11 (2001) 1241

Design and Pharmacology of Quinuclidine Derivatives as M_2-Selective Muscarinic Receptor Ligands

Thomas M. Böhme,[a,*] Christine Keim,[b] Gerd Dannhardt,[a] Ernst Mutschler[b] and Günter Lambrecht[b]

[a]*Institute of Pharmacy, University of Mainz, Staudinger Weg 5, D-55099 Mainz, Germany*
[b]*Department of Pharmacology, Biocentre Niederursel, University of Frankfurt, Marie-Curie-Straße 9, D-60439 Frankfurt, Germany*



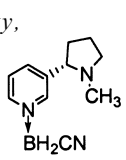
In our search for M_2-selective muscarinic receptor antagonists, we synthesized 1,3-disubstituted indenes. The effects of different basic moieties with regard to binding and selectivity towards the five distinct muscarinic receptor subtypes were investigated. The results show that the quinuclidine series afforded the most promising compounds in terms of both receptor affinity and M_2-subtype selectivity.

Bioorg. Med. Chem. Lett. 11 (2001) 1245

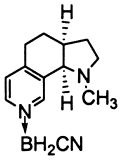
Neuronal Nicotinic Acetylcholine Receptor Binding Affinities of Boron-Containing Nicotine Analogues

Rui Xu, Linda P. Dwoskin, Vladimir P. Grinevich, Gabriela Deaciuc and Peter A. Crooks*

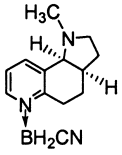
Division of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 800 Rose Street, Lexington, KY 40536-0082, USA



7



8



9

A series of boron-containing nicotine (NIC) analogues **7**–**9** was synthesized and evaluated for binding to α4β2 and α7 nicotinic receptors. Tethering a two-carbon bridge between the 2-pyridyl and 3′-pyrrolidino carbons of NIC or **7** affords analogues that bind to the α7 receptor in a manner similar to NIC, but with a dramatic loss of affinity for the α4β2 receptor.