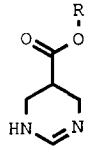
BioMed. Chem. Lett. **1992**, 2, 781

SYNTHESIS, BIOCHEMICAL ACTIVITY AND BEHAVIORAL EFFECTS OF A SERIES OF 1,4,5,6-TETRAHYDROPYRIMIDINES AS NOVEL LIGANDS FOR M_1 RECEPTORS

*William S. Messer, Jr., Philip G. Dunbar, Taikyun Rho, Sumudra Periyasamy, Dan Ngur, Brenda R. Ellerbrock, Mark Bohnett, Kevin Ryan, Graham J. Durant and Wayne Hoss
Center for Drug Design and Development, Department of Medicinal and Biological Chemistry, College of Pharmacy, The University of Toledo, 2801 W. Bancroft St., Toledo, OH 43606



R
Methyl
Ethyl
nPropyl
Isopropyl
Propargyl
Benzyl

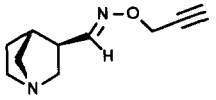
A series of novel tetrahydropyrimidines was synthesized and tested for M_1 muscarinic receptor activity. 1,4,5,6-Tetrahydro-5-methoxycarbonyl-pyrimidine hydrobromide (CDD-0034-C) displayed high affinity for muscarinic receptors in rat brain and stimulated PI metabolism in rat hippocampus. Ethyl and propargyl derivatives also were muscarinic agonists. CDD-0034-C ameliorated memory deficits associated with lesions of the septohippocampal cholinergic system.

BioMed. Chem. Lett. **1992**, 2, 787

DESIGN AND SYNTHESIS OF AZABICYCLIC MUSCARINIC AGONISTS INCORPORATING AN OXIME ETHER FUNCTIONALITY

S.M. Bromidge*, F. Brown, F. Cassidy, M.S.G. Clark, S. Dabbs, M.S. Hadley, J.M. Loudon, B.S. Orlek* and G.J. Riley. SmithKline Beecham Pharmaceuticals Medicinal Research Centre, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD UK.

From a novel series of azabicyclic oxime ethers the propargyl ether emerged as a high affinity partial agonist with good central selectivity.

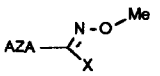


BioMed. Chem. Lett. **1992**, 2, 791

A NOVEL AND SELECTIVE CLASS OF AZABICYCLIC MUSCARINIC AGONISTS INCORPORATING AN N-METHOXY IMIDOYL HALIDE OR NITRILE FUNCTIONALITY

S.M. Bromidge*, F. Brown, F. Cassidy, M.S.G. Clark, S. Dabbs, J. Hawkins, J.M. Loudon, B.S. Orlek* and G.J. Riley. SmithKline Beecham Pharmaceuticals Medicinal Research Centre, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD UK.

Azabicyclic muscarinic agonists incorporating an N- methoxy imidoyl halide or nitrile group display central selectivity.



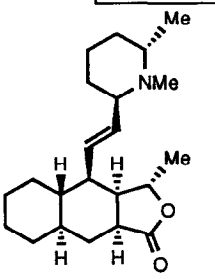
AZA = azabicyclic ring
X = Br, Cl, F, CN

BioMed. Chem. Lett. **1992**, 2, 797

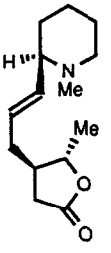
ALZHEIMER'S THERAPY: AN APPROACH TO NOVEL MUSCARINIC LIGANDS BASED UPON THE NATURALLY OCCURRING ALKALOID HIMBACINE.

Alan P. Kozikowski,*[a] Abdul H. Fauq,[a] Jacqueline H. Miller,[b] and Michael McKinney[b], [a]Neurochemistry and [b]Neuropharmacology Research, Mayo Clinic Jacksonville, 4500 San Pablo Rd, Jacksonville, FL 32224

The analogue **1** of himbacine has been prepared in an effort to discover an M2 or M4-selective antagonist of possible use in cholinergic pharmacotherapy.



Himbacine

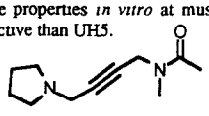


1

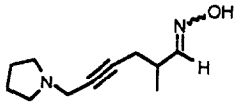
BioMed. Chem. Lett. **1992**, *2*, 803

CHOLINERGIC AGENTS: ALDEHYDE, KETONE, AND OXIME ANALOGUES OF THE MUSCARINIC AGONIST UH5. Kathryn B. Sanders,*[1] Anthony J. Thomas,[1] Michael R. Pavia,[1] Robert E. Davis,[2] Linda L. Coughenour,[2] Sharie L. Myers,[2] Susan Fisher,[2] and Walter H. Moos.[3] Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48106-1047

A series of substituted analogs similar to the muscarinic agonists UH5 and UH28 were synthesized and evaluated pharmacologically. Several oxime analogs of UH5 demonstrate agonist-like properties *in vitro* at muscarinic receptors. Aldoxime **18** was found to be almost five fold more m_1 subtype selective than UH5.



UH5



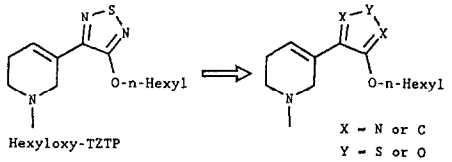
18

BioMed. Chem. Lett. **1992**, *2*, 809

SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF HETEROCYCLIC ANALOGUES OF THE FUNCTIONAL M_1 SELECTIVE MUSCARINIC AGONIST HEXYLOXY-TZTP.

Per Sauerberg[+*], Preben H. Olesen[+], Peter D. Suzdak[+], Malcolm J. Sheardown[+], Charles H. Mitch[#], Steven J. Quimby[#], John S. Ward[#], Frank P. Bymaster[#], Barry D. Sawyer[#] and Harlan E. Shannon[#].

[+]Novo Nordisk CNS Division, Novo Nordisk Park, DK-2760 Målφv, Denmark. [#]The Eli Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA.

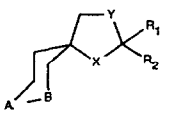


BioMed. Chem. Lett. **1992**, *2*, 815

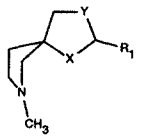
Muscarinic Agonist SAR of Azaspirodioxolanes

G. Shapiro*, P. Floersheim*, R. Amstutz, H. Boddeke, G. Bolliger, S. Cottens, A. Enz, G. Gmelin, P. Gull, P. Supavilai
Preclinical Research, Sandoz Pharma Ltd., CH-4002 Switzerland

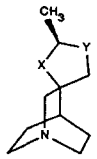
The *in vitro* muscarinic activity and a model for binding to the m1 receptor is presented for a series of azaspirodioxolanes.



Piperidines



Pyrrolidines



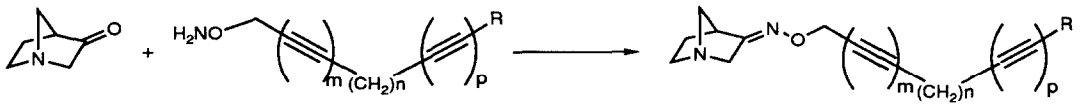
AF30 analogs

BioMed. Chem. Lett. **1992**, *2*, 821

A RATIONALE FOR THE DESIGN AND SYNTHESIS OF m1 SELECTIVE MUSCARINIC AGONISTS.

H. Tecle*, D.J. Lauffer, T. Mirzadegan, W. H. Moos, D. W. Moreland, M. R. Pavia, R.D.Schwarz, and R. E. Davis
Parke-Davis Pharm. Res. Div., Warner-Lambert Co. Ann Arbor, MI 48105.

Abstract. Synthesis of potent and efficacious 1-azabicyclo[2.2.1]heptan-3-one oxime muscarinic agonists is described.

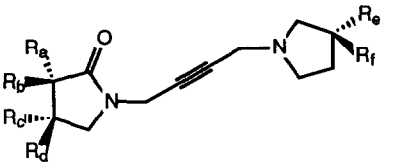


BioMed. Chem. Lett. **1992**, *2*, 827

THE SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIPS OF ENANTIOMERICALLY PURE HYDROXYLATED OXOTREMORINE DERIVATIVES

Eugene J. Trybulski*, Richard H. Kramss, Richard M. Mangano, Herbert, J. Brabander, Gerardo Francisco
Medical Research Division of American Cyanamid Co., Lederle Labs., Pearl River, New York, 10965

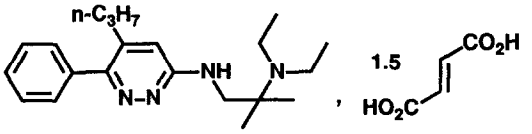
Abstract: The synthesis and radioligand binding data of optically active hydroxylated oxotremorine derivatives is described. There are significant pharmacological differences between the enantiomers most notably at the 3- and 4-position of the pyrrolidinone ring.



BioMed. Chem. Lett. **1992**, *2*, 833

SR 46559 A AND RELATED AMINOPYRIDAZINES ARE POTENT MUSCARINIC AGONISTS WITH NO CHOLINERGIC SYNDROME

Camille G. Wermuth*, Jean-Jacques Bourguignon, Rémy Hoffmann, Robert Boigegrain+, Roger Brodin+, Jean-Paul Kan+, and Philippe Soubrié+. Laboratoire de Pharmacochimie Moléculaire (UPR 421) du CNRS, Centre de Neurochimie, 5, rue Blaise Pascal, 67084 Strasbourg Cedex and, +SANOFI Recherche, ligne Neuropsychiatrie, 371, rue du Professeur J. Blayac,34184 Montpellier Cedex.

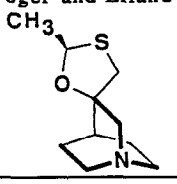


Muscarinic M1 receptor partial agonist
IC_{50} [^{3}H] pirenzepine : 0.11 μM
Antagonism of scopolamine-induced memory deficit : 0.25 mg/kg p.o.

BioMed. Chem. Lett. **1992**, *2*, 839

RIGID ANALOGS OF ACETYLCHOLINE CAN BE M1-SELECTIVE AGONISTS: IMPLICATIONS FOR A RATIONAL TREATMENT STRATEGY IN ALZHEIMER'S DISEASE

Abraham Fisher, David Gurwitz, Dov Barak, Rachel Haring, Ishai Karton, Rachel Brandeis, Zipora Pittel, Daniele Marciano, Haim Meshulam, Zvi Vogel# and Eliahu Heldman. *Israel Institute for Biological Research, P.O.Box 19, Ness-Ziona 70450, and The Weizmann Institute, Rehovot#, ISRAEL.*



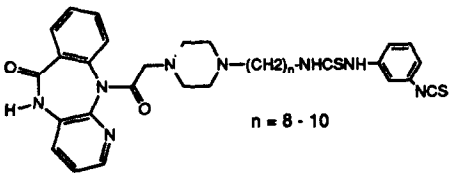
AF102B, a highly rigid analog of acetylcholine, is a centrally active M1 agonist and is compared with some old and new muscarinic agonists. **AF102B** is evaluated in light of some currently available therapeutic strategies in Alzheimer's disease.

BioMed. Chem. Lett. **1992**, *2*, 845

MUSCARINIC RECEPTOR PROBES BASED ON AMINE CONGENERS OF PIRENZEPINE AND TELENZEPINE

Kenneth A. Jacobson†*, Yishai Karton†, and Jesse Baumgold¥
†Lab. of Bioorganic Chemistry, NIDDK, NIH, Bethesda, MD 20892
and ¥Department of Radiology, George Washington Univ., Washington D.C., 20037

The N-methyl groups of pirenzepine and telenzepine (M_1-antagonists) were modified to produce chemically functionalized N-alkyl analogs using a "functionalized congener" approach. The effect of chain length on aryl isothiocyanate affinity labels is explored.

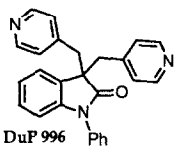


BioMed. Chem. Lett. **1992**, *2*, 851

ACETYLCHOLINE-RELEASING AGENTS AS COGNITION ENHANCERS. STRUCTURE-ACTIVITY RELATIONSHIPS OF PYRIDINYL PENDANT GROUPS ON SELECTED CORE STRUCTURES.

R.A. Earl*, M.J. Myers, A.L. Johnson, R.M. Scribner, M.A. Wuonola, G.A. Boswell, W.W. Wilkerson, V.J. Nickolson, S.W. Tam, D.R. Brittelli, R.J. Chorvat, R. Zaczek, L. Cook. *The DuPont Merck Pharmaceutical Co.; Experimental Station, P.O. Box 80353; Wilmington, Delaware 19880-0353* and C. Wang, X. Zhang, R. Lan, B. Mi, H. Wenting. *Science and Technology Development Division; Peking University; Beijing 100871; Peoples Republic of China*

Abstract: A number of analogs of the cognition enhancing agent DuP 996 were prepared by varying the core structure and pendant groups in an independent fashion. The SAR of 2-, 3-, and 4-pyridinylmethyl groups as pendant groups on selected cores was examined.



DuP 996

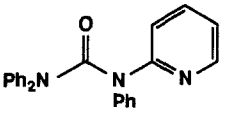
BioMed. Chem. Lett. **1992**, *2*, 855

ACETYLCHOLINE RELEASING AGENTS AS COGNITION ACTIVATORS. CHEMISTRY AND PHARMACOLOGY OF A SERIES OF UREAS

Anthony J. Thomas*†, Jeffrey A. Kester†, Donald E. Butler†, Fred M. Hershenson†, Robert E. Davis§, John G. Marriott§, Roy D. Schwarz§, Carolyn J. Spencer§, James P. Symons§ and Walter H. Moos†

Parke-Davis Pharmaceutical Research Division, Departments of Chemistry† and Pharmacology§, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105

We have sought to improve upon the activity of the well known AcCh-releasing agents, 4-aminopyridine and 3,4-diaminopyridine. This work has led to the discovery of a series of ureas with AcCh-releasing properties. From this series, compound 5 has emerged as a potent AcCh-releasing agent with promising *in vivo* activity.



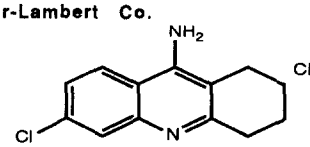
5

BioMed. Chem. Lett. **1992**, *2*, 861

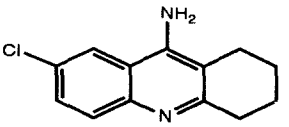
THE SYNTHESIS AND *IN VITRO* ACETYLCHOLINESTERASE AND BUTYRYLCHOLINESTERASE INHIBITORY ACTIVITY OF TACRINE (COGNEX®) DERIVATIVES.

Vlad E. Gregor*, Mark R. Emmerling, Chitase Lee and Catherine J. Moore
Parke-Davis Pharmaceutical Research, Warner-Lambert Co.
Ann Arbor, Michigan 48105

Chlorosubstituted derivatives of tacrine and 1,4-methylenetacrine and their *in vitro* acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activities are described. The most potent analogues are 6-chlorotacrine (**1b**) in AChE and 7-chlorotacrine (**1c**) in BChE inhibition.



1b; IC_{50}=1.8nM, Human red blood cell AChE



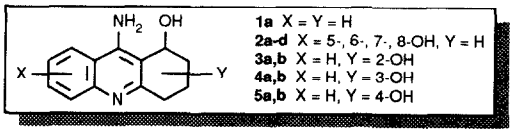
1c; IC_{50}=0.7nM, BChE

BioMed. Chem. Lett. **1992**, *2*, 865

SYNTHESIS AND BIOLOGICAL ACTIVITY OF PUTATIVE *mono*-HYDROXYLATED METABOLITES OF VELNACRINE

Gregory M. Shutske,[1,*] Gina M. Bores,[2] Katherine C. Bradshaw,[2] Francis P. Huger,[2] Kevin J. Kapples,[1] Raymond D. Larsen,[3] Douglas K. Rush,[2] and John D. Tomer[1]; Departments of Chemical Research[1] and Biological Research,[2] Neuroscience Strategic Business Unit, Hoechst-Roussel Pharmaceuticals, Inc., Route 202-206, PO Box 2500, Somerville, NJ 08876-1258; [3]Department of Chemistry, Montana State University, Bozeman, MT 59717-0340

Abstract: Synthesis and preliminary biological testing is reported for ten potential *mono*-hydroxylated metabolites (**2a-d** and **3a-5b**) of velnacrine (**1a**).

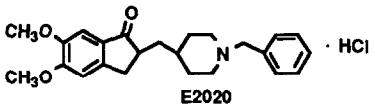


BioMed. Chem. Lett. **1992**, 2, 871

SYNTHESIS AND ANTI-ACETYLCHOLINESTERASE ACTIVITY OF 1-BENZYL-4-[(5,6-DIMETHOXY-1-INDANON-2-YL)METHYL]-PIPERIDINE HYDROCHLORIDE (E2020) AND RELATED COMPOUNDS

Hachiro Sugimoto*, Youichi Iimura, Yoshiharu Yamanishi and Kiyomi Yamatsu
Tsukuba Research Laboratories, Eisai Co., Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki 300-26, JAPAN

The structure-activity relationship of E2020 and related compounds as acetylcholinesterase inhibitors is described.



E2020