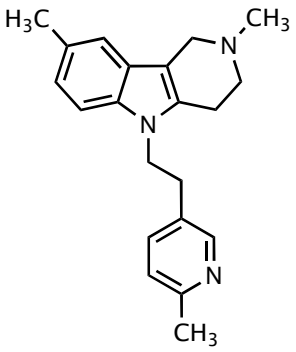
CINAPS Compound Dossier

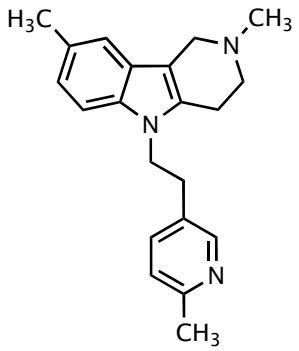
Dimebon



1/22/2007

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

I. Compound Information

Common name	Dimebon
Structure	

PubChem ID	197033	**MF**	C21 H25 N3	**MW**	319.44
CASRN	3613-73-8	**Polar surface area**	18.84	**logP**	4.1

IUPAC name	2,3,4,5-Tetrahydro-2,8-dimethyl-5-(2-(6-methyl-3-pyridyl)ethyl)-1H-pyrido(4,3-b)indole
Other names	9-(2-(2-Methyl-5-pyridyl)ethyl)-3,6-dimethyl-1,2,3,4-tetrahydro-γ-carboline; Dimeboline; Dimebolin; Dimebone; Preparation 84; BRN 0622478
Drug class	Antihistamine, calcium-channel blocker, NMDA receptor antagonist
Notes	
Development status	Dimebon is under development by Medivation, Inc. for the treatment of Alzheimer's disease and Huntington's disease. It is currently in Phase I/IIa clinical trials in the U.S. Results are expected in the second quarter of 2007. Dimebon was approved in Russia in 1988 for allergic rhinitis and dermatitis. (**PharmaProjects, 2006**)

II. Rationale

IIa. Scientific Rationale / Mechanism

Dimbebon inhibits the opening of mitochondrial permeability transition pores induced by calcium, phosphate, t-butylhydroperoxide, beta-amyloid fragment 25-35, and MPP+. Dimebon also suppresses lipid peroxidation induced by either t-butylhydroperoxide or the beta-amyloid fragment 25-35. (**Bachurin, 2003**)

IIb. Consistency

III. Efficacy (animal models of Parkinson's disease)

IIIa. Animal Models: Rodent

n/a

IIIb. Animal Models: Non-human primates

n/a

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical studies

n/a

IVb. Epidemiological evidence

n/a

V. Relevance to other neurodegenerative diseases

Preclinical data cited by Medivation that supports Dimebon's potential neuroprotective activities: dimebon prevented the death of brain cells exposed to beta amyloid protein; dimebon prevented neuron death in animals genetically engineered to express the human gene known to cause Huntington's disease and neurodegeneration; dimebon inhibited signs of aging in normally aging rodents (37% reduction in cataracts, 44% reduction in balding, elimination of age-related wasting) after one year of dosing; dimebon reduced mortality in normally aging rodents (83% improvement in survival) after one year of dosing; and dimebon caused significant improvements in performance in memory- and cognition-impaired rodents in the Rat Water Maze Test and Active Avoidance Tests (animal models of Alzheimer's disease therapeutic potential).

In preclinical studies conducted at the University of California, Irvine, Drosophila expressing the human Huntington's disease gene were administered dimebon in their food for a period of seven days. The number of intact photoreceptors were counted. Dimebon was found to protect these photoreceptors against the neuronal death induced by the human gene encoding Huntington's disease in a dose-dependent manner.

Dimebon appeared to improve some aspects of memory, cognitive and global function in a pilot clinical study of 14 Alzheimer's disease patients conducted at the Moscow Center of Gerontology in Russia. The patients were treated with oral dimebon three times daily for two months. Patients in this open-label study experienced an improvement in memory and cognition after two months of therapy. Furthermore, after dimebon was discontinued at week eight, investigators observed deterioration in patients' cognitive function.

A Phase 2 study of dimebon in 183 Alzheimer's disease patients was expected to be completed in the third quarter of 2006. Clinical studies of dimebon for the treatment of Huntington's disease are planned. (**Medivation, Inc., 2006**)

Dimebon (1 mg/kg, i.p.) completely restored two-way active avoidance reaction performance (TWAA) in rats lesioned with AF64A (an animal model of Alzheimer's disease). (**Lermontova, 2000**)

Dimebon inhibits the toxic effect of beta-amyloid on rat cerebellar granule cells by 45%. Dimebon also blocks the potential-dependent Ca2+ entry into neurons by about 20% apparently by its selective inhibition of the L-type Ca2+ channel. (**Lermontova, 2001**)

Dimebon protects cerebellar neurons against the neurotoxic action of beta-amyloid fragment (EC50 = 25 micromolar). Dimebon also exhibits strong anti-NMDA activity in the prevention of NMDA-induced seizures in mice (EC50 = 42 mg/kg i.p.). (**Bachurin, 2001**)

VI. Pharmacokinetics

VIa. General ADME

n/a

VIb. CNS Penetration

It can be inferred from the activity of dimebon in rodent models of Alzheimer's disease and human clinical studies that the compound is CNS penetrant.

VIc. Calculated logBB

0.48

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

Dimebon has been marketed in Russia since 1983 for the treatment of allergic rhinitis and allegic dermatitis. (**Medivation, Inc., 2006**)

Safety studies performed when Dimebon was first introduced in Russian market in 1983 as an antihistamine and the subsequent twenty years of over-the-counter use indicate that the drug has a remarkable safety profile. Toxicological studies showed that administration of the drug for two months in doses that exceeded the therapeutic dose by 100 times did not produce any changes in physiological parameters or pathological changes in organs of rats, guinea pigs, or dogs. (**Bachurin, 2001**)

VIIb. Drug Interaction Potential

n/a

Bibliography

Bachurin, 2001

Bachurin S.; Bukatina E.; Lermontova N.; Tkachenko S.; Afanasiev A.; Grigoriev V.; Grigorieva I.; Ivanov Y.; Sablin S.; Zefirov N., *Antihistamine agent dimebon as a novel neuroprotector and a cognition enhancer*, Annals of the New York Academy of Sciences, **2001**, 939(Neuroprotective Agents), 425-435

Other Diseases

Safety

Bachurin, 2003

Bachurin S.O.; Shevtsova E.P.; Kireeva E.G.; Oxenkrug G.F.; Sablin S.O., *Mitochondria as a target for neurotoxins and neuroprotective agents*, Annals of the New York Academy of Sciences, **2003**, 993 (Neuroprotective Agents), 334-344

Rationale

Grigor'ev, 2003

Grigor'ev V.V.; Dranyi O.A.; Bachurin S.O., *Comparative Study of Action Mechanisms of Dimebon and Memantine on AMPA- and NMDA-Subtypes Glutamate Receptors in Rat Cerebral Neurons*, Bulletin of Experimental Biology and Medicine, **2003**, 136(5), 474-477

Other Diseases

Lermontova, 2000

Lermontova N.N.; Lukoyanov N.V.; Serkova T.P.; Lukoyanova E.A.; Bachurin S.O., *Dimebon improves learning in animals with experimental Alzheimer's disease*, Bulletin of Experimental Biology and Medicine, **2000**, 129(6), 544-546

Other Diseases

Lermontova, 2001

Lermontova N.N.; Redkozubov A.E.; Shevtsova E.F.; Serkova T.P.; Kireeva E.G.; Bachurin S.O., *Dimebon and tacrine inhibit neurotoxic action of beta-amyloid in culture and block L-type Ca2+ channels*, Bulletin of Experimental Biology and Medicine, **2001**, 132(5), 1079-1083

Other Diseases

Medivation, Inc., 2006

Medivation, Inc., *Dimebon for Alzheimer's Disease and Huntington's Disease*, Medivation web site (http://www.medivation.net/), **2006**

Other Diseases

Safety

PharmaProjects, 2006

PharmaProjects, *Dimebon,* **2006**

Compound Information