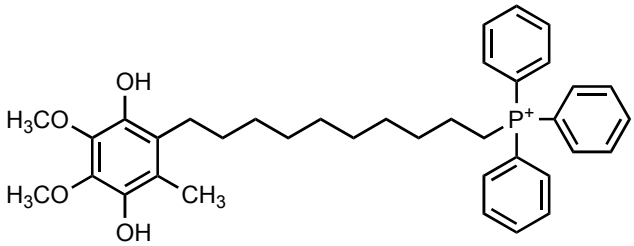
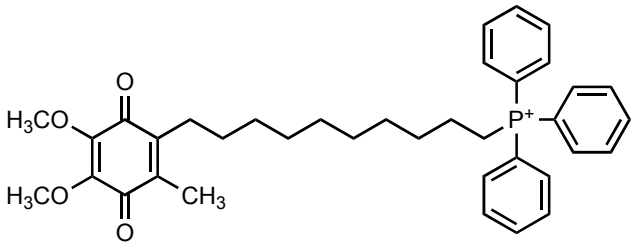
CINAPS Compound Dossier

MitoQ



Mitoquinol

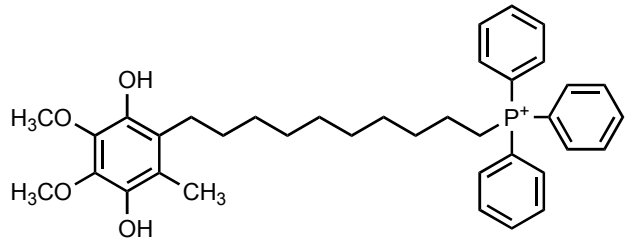
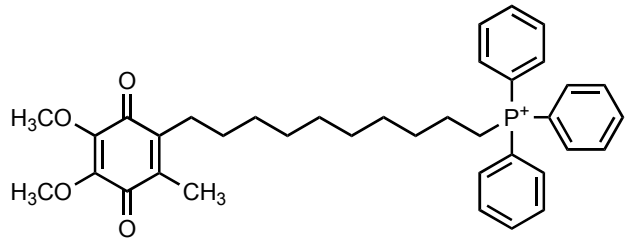


Mitoquinone

2/19/2007

National Institute of Neurological Disorders and Stroke

I. Compound Information

Common name	MitoQ
Structure	 Mitoquinol  Mitoquinone

PubChem ID	n/a	**MF**	$C_{37}H_{46}BrO_4P$ / $C_{37}H_{44}BrO_4P$	**MW**	664.23 / 662.22
CASRN	873653-01-0	**Polar surface area**	55.76	**ClogP**	11

IUPAC name	Mixture of (10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl) triphenylphosphonium bromide and (10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl)triphenylphosphonium bromide
Other names	mitoquinone/mitoquinol, $MitoQ_{10}$
Drug class	Antioxidant
Notes	MitoQ is a mixture of mitoquinol (reduced form) and mitoquinone (oxidzed form). (**Kelso, 2001**)(**Kelso, 2002**) The mitochondria-targeted antioxidant MitoQ comprises a ubiquinol moiety covalently attached through an aliphatic carbon chain to a lipophilic triphenylphosphonium cation. (**Asin-Cayuela, 2004**) The antioxidant reactions of exogenous ubiquinones predominantly occur within phospholipid bilayers, while pro-oxidant reactions require an aqueous environment. Therefore, the relative rates of these reactions can be fine-tuned by hydrophobicity, allowing a rational approach to the design of therapeutic ubiquinone-based antioxidants. (**James, 2005**)
Development status	MitoQ is under development as an oral treatment for Parkinson's Disease and Friedreich Ataxia. MitoQ is currently in Phase 2 development. The Phase 2 clinical efficacy study began in May 2006. Enrollment was completed in October 2006. (**Antipodean Pharmaceuticals, 2007**) MitoQ is covered by two US patents.(**Murphy, 2001**)(**Smith, 2007**)

II. Rationale

IIa. Scientific Rationale / Mechanism

Clinical studies have shown that very high doses of Coenzyme Q appear to slow the deterioration of function in Parkinson's Disease.(**Shults, 2002**). The marginal effect at high dose reflects the poor bioavailability of Coenzyme Q and the difficulty in penetrating mitochondria in relevant CNS regions. Mitochondria-targeted Coenzyme Q analogs may therefore improve the efficacy of this therapeutic strategy. (**Antipodean Pharmaceuticals, 2007**)

Lipophilic cations pass easily through lipid bilayers. The potential gradient across mitochondrial membrane drives accumulation into the mitochodrial matrix. Ubiquinol is an endogenous antioxidant that decreases lipid peroxidation. Based on these concepts, the ubiquinone/ubiquinol analog “MitoQ” was designed to contain a lipophilic triphenylphosphonium cation attached to an antioxidant ubiquinone moiety. In isolated mitochondria, mitoQ blocks both lipid peroxidation and the disruption of mitochondrial function caused by oxidative stress. In addition, MitoQ was rapidly recycled to the active, reduced form (mitoquinol) by the respiratory chain. Preincubation with 1 microM MitoQ completely blocked hydrogen peroxide induced caspase activation. Compared to antioxidants that are not chemically targeted for mitochondrial localization, MitoQ has an increased ability to block apoptosis induced by hydrogen peroxide. (**Kelso, 2002**)

Addition of hydrogen peroxide to Jurkat human T lymphocyte cells leads to caspase activation and induction of apoptotic cell death within 4–6 hours. Preincubation with 1 micromolar MitoQ completely blocks caspase activation and substantially decreases apoptotic cell death. (**Kelso, 2001**)

MitoQ abolishes ca. half of the increase in peroxide content in cultured MRC-5 fibroblasts under mild oxidative stress (hyperoxia). Treatment of MRC-5 cells under these conditions with MitoQ significantly prolongs the replicative lifespan by an average of 40%. It was observed that MitoQ treatment minimized telomere shortening in cells under hyperoxia. (**Saretzki, 2003**)

MitoQ exerts a cell-survival effect that mimics nerve growth factor (NGF), ultimately producing the same antiapoptotic effect as mitochondrial SOD. (**Bedogni, 2003**)(**Galeotti, 2005**)

MitoQ prevents cell death induced by pro-oxidants in fibroblasts isolated from Friedreich Ataxia (FRDA) patients. MitoQ is ca. 800-fold more effective than anti-oxidants that are not targeted at the mitochondria. (FRDA is characterized by a protein expression defect that leads to increased mitochondrial oxidative damage.) (**Jauslin, 2003**)

Pretreatment of bovine aortic endothelial cells (BAEC) with MitoQ (1 microM) but not untargeted antioxidants significantly reduced the effects of hydrogen peroxide and other oxidants. Mitochondria-targeted antioxidants such as MitoQ were found to inhibit cytochrome c release, caspase-3 activation, and DNA fragmentation. MitoQ also inhibits hydrogen peroxide- and lipid peroxide-induced inactivation of complex I and aconitase, TfR overexpression, and mitochondrial Fe uptake. These effects combine to mitigate peroxide-mediated oxidant stress, maintain proteasomal function, and inhibit apoptosis. (**Dhanasekaran, 2004**)

The pharmacology of MitoQ and other mitochondria-targeted antioxidants was reviewed in 2006. (**Reddy, 2006**)

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

MitoQ is currently in Phase 2 development. The Phase 2 clinical efficacy study began in May 2006. Enrollment was completed in October 2006. (**Antipodean Pharmaceuticals, 2007**)

ClinicalTrials.gov Identifier: NCT00329056

IVb. Epidemiological evidence

n/a

V. Relevance to other neurodegenerative diseases

Mitochodria-targeted antioxidants such as MitoQ are promising candidates for the treatment of degenerative conditions that may be associated with mitochondrial oxidative damage such as Alzheimer's Disease and aging. (**Reddy, 2006**)

MitoQ is being evaluated as an oral treatment for Parkinson's Disease and Friedreich Ataxia, two neurodegenerative disorders associated with mitochondrial dysfunction along with Hepatitis C. The company is also investigating MitoQ in other indications that involve mitochondrial dysfunction, including hypertension, diabetes, adriamycin cardiac toxicity, increasing platelet storage stability, dermatologic applications, cancer therapy (inhibition of Hypoxia-Inducible Factor 1α), and retinal degeneration. (**Antipodean Pharmaceuticals, 2007**)

VI. Pharmacokinetics

VIa. General ADME

MitoQ is rapidly taken up by isolated mitochondria. Lipophilic cations such as MitoQ are expected to cross the blood-brain barrier and to accumulate in brain mitochondria. This hypothesis was tested using a simple MitoQ analog, triphenylmethylphosphonium (TPMP). Tritium-labeled-TPMP (500 microM) was fed to mice in their drinking water. The lipophilic cation was taken up rapidly into the liver, brain, and heart, achieving a steady-state after 7 - 10 days. It is anticipated that the organ distribution of antioxidants linked to the mitochondria-targeting functional group triphenylphosphonium should be similar to that of TPMP. This was verified by feeding mice tritium-labeled MitoQ in a liquid diet. Similar tissue distributions were observed without toxic effects. (**Kelso, 2002**)

VIb. CNS Penetration

(**Kelso, 2002**)

VIc. Calculated logBB

0.99

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

MitoQ exhibited low toxicity to mitochondria and cells. Up to 10 micromolar MitoQ had little effect on the membrane potential or respiration of isolated mitochondria. At 25–50 micromolar membrane potential decreased and respiration was inhibited. In whole cells (human osteosarcoma 143B cells) up to 10 micromolar MitoQ did not affect cell viability, and concentrations of 25–50 micromolar were required for substantial cell death. (**Kelso, 2001**)

Mice fed liquid diets containing 500 micromolar or 1 millimolar MitoQ showed no toxic effects for at least 26 days, although food consumption decreased 20 - 35% compared with controls. Mice fed a liquid diet containing 2 to 5 millimolar MitoQ showed toxic effects after 10 - 11 days. In addition, food consumption decreased 70 - 80% compared to controls. (**Smith, 2003**)

VIIb. Drug Interaction Potential

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