122. Spermine prodrugs for treating LSD

(University of Central Florida)

5TH KDDF GLOBAL C&D TECH FAIR

Asset Overview

Product Type	Small Molecule
Disease Area	Genitourinary Disease
Indication	Low Spermine Disorders
Current Stage	HIT to Lead
Target	Snyder Robinson Syndrome (SRS)
MoA	Spermine prodrugs → Spermine
Brief Description	• Snyder Robinson Syndrome (SRS) is a rare disease associated with a defective spermine synthase gene and low intracellular spermine levels. • A spermine replacement therapy was developed using a spermine prodrug that enters cells via the polyamine transport system. The prodrug was comprised of three components: a redox-sensitive quinone "trigger", a "trimethyl lock (TML)" aryl "release mechanism", and spermine. The presence of spermine in the design facilitated uptake by the polyamine transport system. The quinone–TML motifs provided a redox-sensitive agent, which upon intracellular reduction generated a hydroquinone, which underwent intramolecular cyclization to release free spermine and a lactone byproduct. • Most SRS fibroblasts treated with the prodrug revealed a significant increase in intracellular spermine. Administering the spermine prodrug through feeding in a Drosophila model of SRS showed significant beneficial effects. • A spermine prodrug is developed and provides a lead compound for future spermine replacement therapy experiments.
Intellectual Property	US20210000769A1
Publication	Development of a Redox-Sensitive Spermine Prodrug for the Potential Treatment of Snyder Robinson Syndrome. J Med Chem. (2021)
Inventors	Otto Phanstiel. IV, Mukund Pandurang TANTAK, Houssine IKHLEF

Highlights

- Ubiquinone (UQ), also known as coenzyme Q (CoQ), is a lipophilic redox-active molecule present in all eukaryotes. In UQ, the redox-active benzoquinone group is conjugated with the lipophilic side chain (polyisoprenoid), which makes it lipid soluble. UQ plays an important role in mitochondrial energy generation.
- Unlike spermine, the prodrug requires a two-step process involving cellular uptake and intracellular reduction to deliver spermine. This requirement provided the advantage of a targeted intracellular delivery system, which was enhanced in cells with active polyamine import.
- The potential scenario where certain SRS cells with defective mitochondria may be able to import the prodrug but may have insufficient cellular reduction potential to reduce the quinone and release spermine.

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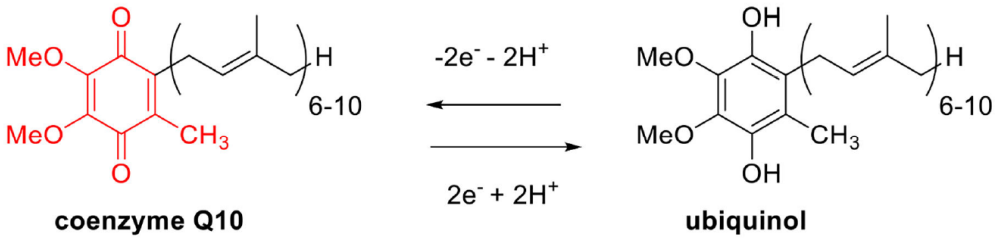
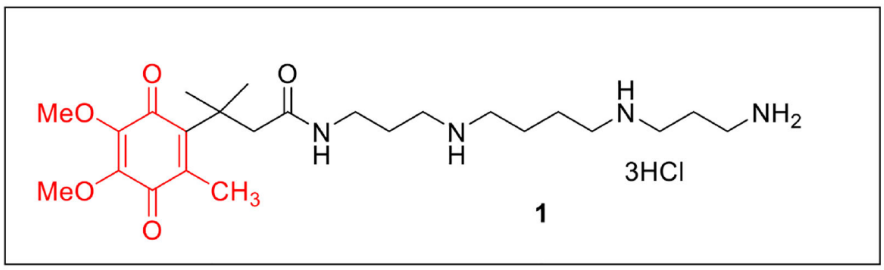
Key Data

The structure of prodrug 1 (in the box)

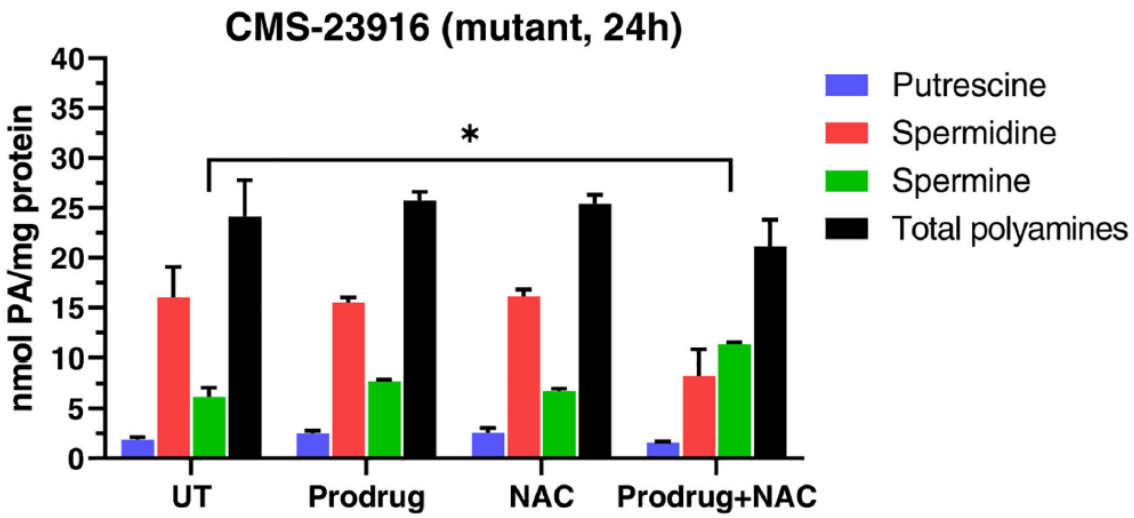


coenzyme Q10 **ubiquinol**



1

The combination of prodrug (5 μM) and NAC (2mM)



Polyamine levels in CMS-23916 (mutant) fibroblast cell lines untreated (UT) or treated with prodrug **1** (5 μM) only, NAC (2 mM) only, or a combination of prodrug **1** (5 μM) and NAC (2 mM). Values represent data from the experiment performed in triplicates ± S.D. *p < 0.05.