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**“Design, synthesis and biological studies of new mitochondrial modulators improving neurological deficits in experimental models of Huntington's disease.”**

Huntington's disease (HD) is an adult-onset, neurodegenerative disorder. It is a genetic dominantly inherited disease caused by a polyglutamine (polyQ) expansion mutation in the huntingtin protein (Htt). Because of its lack of valid treatment, development of more effective therapeutics for HD is urgently required. Recently, pharmacological strategies that modulate mitochondrial dynamics have shown promising results in several HD models. Mildronate, [3-(2,2,2-trimethylhydrazinium) propionate; THP; MET-88], a compound able to improve mitochondrial dysfunction, has demonstrated protective effects on a wide range of neuropathological events, as in case of Parkinson's and Alzheimer's disease. Interestingly, in the current study we found that mildronate can effectively improve motor function in the *Drosophila melanogaster* stock elav-HTT.128Q.FL and in Pmec-3htt57Q128::GFP *Caenorhabditis elegans* strain, both animal models overexpressing human mutant Htt. This improvement is evident by the significant increase in performance on the behavioral assays after mildronate treatment. In an effort to increase the activity of mildronate, we have designed, synthesized, and characterized 22 compounds, among which 4 display superior ability to reduce pathological biomarkers of HD as well as ameliorate mitochondrial dynamics in *in vitro* and *in vivo* assays in comparison to mildronate. In particular, the selected compounds decrease the level of HD aggregates in STHdh<sup>Q109/109</sup> transfected cells more significantly than mildronate, without affecting the level of transfected normal or mutant Htt. Finally, all the compounds have shown the ability to decrease significantly the mitochondrial fragmentation in STHdh<sup>Q109/109</sup> and to reduce motor deficits in the animal models. This result confirms that perturbation in mitochondrial dynamics may contribute to the onset and progression of neurodegenerative disorders and that correcting mitochondrial fragmentation, reduces motor deficits in HD animals.