FROM NATURE INSPIRATION TO MULTITARGET SMALL MOLECULES

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Neurodegenerative disorders (NDs) are a group of age-related neurological disorders caused by a multiplicity of genetic and environmental factors, among others. In our days, NDs became more prevalent due to the steady increase of the world population life expectancy. Consequently, the social and economic burden over the families of the patients became more severe. Therefore, the discovery of therapeutic agents that could ameliorate or prevent neurodegenerative diseases, are urgently needed.

Hydroxycinnamic and benzoic acids, two families of naturally occurrent phenolic antioxidants, for long had a huge potential for the development of new therapies for NDs [1]. However, the low permeability and bioavailability of these antioxidants in biological systems for long limited their use in potential therapies. Hence, in the recent years, in order to create a novel therapeutic window for NDs our group designed a range of small molecules using hydroxycinnamic and benzoic acids present in human diet as a scaffold [2–4]. Based on this approach a range of hybrid compounds were obtained by linking the phenolic core to a triphenylphosphonium (TTP+) cation via different size aliphatic chain spacers. The new antioxidants retained the in vitro antioxidant activity of the parent compounds. In this work we present some of our results showing that the compounds are capable to directly act in mitochondria preventing oxidative stress damage and the activity of protein targets involved in the pathology of several ND disorders. Additionally, in order to further optimize the therapeutic success of our novel antioxidants we developed a range of methodologies that allowed us to evaluate a series of parameters that may influence our compounds ADMET properties [5]. In summary, in this communication we present some of the most recent results obtained in our drug discovery efforts.

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