Theoretical and Experimental Analysis of the Antioxidant and Anti-amyloid Features of Synthetic Resveratrol Mimics

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Diaryl hydrazones, possessing similar structure to the popular red wine antioxidant resveratrol, have been previously identified as multitarget compounds interfering with several processes associated with the pathogenesis of Alzheimer's disease (AD). These compounds exhibited particularly strong inhibition of the amyloid beta (Aβ) peptide self-assembly, including blocking the formation of fibrils and oligomers, species that are widely accepted to be neurotoxic. The molecules were also powerful free radical scavengers and thus have a potential to defend against oxidative stress.

In order to learn more about the mode of action of the compounds, theoretical and experimental studies have been carried out. First, the structural, energetic and electronic features of the core structure have been elucidated by density funtional theory (DFT) calculations. The DFT results identified the most likely form of the compounds, which was applied to a broad range of calculations using substituted derivates. Based on the structural information several characteristics such as logP, H-binding energy, HOMO-LUMO energies and band gap and electron densities were calculated. The compounds were subjected to three different antioxidant assays (DPPH, ABTS and ORAC). The % radical scavenging has been analyzed as a function of the above determined structural parameters in order to identify the role of the energetic and electronic features in the antioxidant activity. The analysis of the same parameters as potential markers to the anti-amyloid activity has also been carried out.

Isotope labeling via H-D exchange and *in situ* hydrazone-radicals as well as hydrazone-Aβ complex formation, applying ^{1}H-NMR and HRMS, have also been used to experimentally observe the potential role of various tautomeric forms and the partially delocalized electron structure of the hydrazones.

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