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Enhancing Proteasome Function Through NRF1 Activation: Novel Small-Molecule Compounds for Treating Neurodegenerative Diseases

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The degradation of intracellular proteins is a strictly regulated process vital for maintaining cellular homeostasis and ensuring optimal functionality of the cell. Over 90% of cytosolic proteins undergo degradation via the ubiquitin-proteasome system (UPS), effectively eliminating improperly synthesized or folded proteins while also regulating overall protein levels and function within the cell. Any disruption in UPS activity can induce proteotoxic stress, leading to severe pathological conditions. One promising strategy for addressing proteasome insufficiency involves enhancing proteasome synthesis. This can be achieved through the activation of Nuclear Factor Erythroid 2-related factor 1 (NRF1), a transcription factor encoded by *NFE2L1*, which triggers the re-synthesis of proteasome genes in response to impaired proteasome function.

Here, we present a series of small-molecule compounds identified in a targeted library screening that show the ability to induce NRF1-dependent downstream events, such as proteasome synthesis, heat shock response, up regulation of a panel of antioxidant enzymes, and autophagy without causing significant cellular stress. Overall, our compounds represent a promising novel approach for the treatment of a variety of protein conformational diseases, including the most debilitating neurodegenerative diseases.