SMALL-MOLECULE ACTIVATORS OF NRF1 TRANSCRIPTIONAL ACTIVITY PREVENT PROTEIN AGGREGATON

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Intracellular protein aggregation causes proteotoxic stress, underlying highly debilitating neurodegenerative disorders in parallel with decreased proteasome activity.[1] Nevertheless, under such stress conditions, the expression of proteasome subunits is upregulated by Nuclear Factor Erythroid 2-related factor 1 (NRF1), a transcription factor that is encoded by *NFE2L1*. Activating the NRF1 pathway could accordingly delay the onset of neurodegenerative and other disorders with impaired cell proteostasis. Here, we present a series of small-molecule compounds based on bis(phenylmethylen)cycloalkanones and their heterocyclic analogues, identified via targeted library screening, that can induce NRF1-dependent downstream events, such as proteasome synthesis, heat shock response, and autophagy, in both model cell lines and *Caenorhabditis elegans* strains. These compounds increase proteasome activity and decrease the size and number of protein aggregates without causing any cellular stress or inhibiting the ubiquitin-proteasome system (UPS). Therefore, our compounds represent a new promising therapeutic approach to various protein conformational diseases, including the most debilitating neurodegenerative diseases and viral diseases.

Acknowledgement
The work was supported by the project National Institute of Virology and Bacteriology (Programme EXCELES, ID Project No. LX22NPO5103) – Funded by the European Union – NextGenerationEU.

REFERENCES

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