Discovery of Small-Molecule Activators of NRF1 Transcriptional Activity Preventing Protein Aggregation.

Zuzana Kutova[1,2], Jindrich Sedlacek[1,2], Michael Adamek[1,2], Dominika Subova[1,2,3], Pavel Majer[1], Lucie Svobodova[1,4], Alena Kadlecova[5], Ales Machara[1*], Klara Grantz Saskova[1,2*]

[1]*Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Flemingovo n. 2, 16610 Prague, Czech Republic*
[2]*Department of Genetics and Microbiology, Charles University and Research Center BIOCEV, Prumyslova 595, 25250 Vestec, Czech Republic*
[3]*First Faculty of Medicine & General University Hospital, Charles University, U Nemocnice 2, Prague 2, 12808, Czech Republic*
[4]*Department of Organic Chemistry, Charles University, Hlavova 2030/8, Prague 2, 12843, Czech Republic*
[5]*Department of Experimental Biology, Palacky University, Slechtitelu 27, Olomouc, 78371 Czech Republic*
[*] *Corresponding author: saskova@uochb.cas.cz (K.G.S.)*

The intracellular accumulation of abnormal proteins exceeding their degradation can cause imbalance in proteostasis resulting in proteotoxic stress that leads to severe pathological stages. This state relates to proteasome saturation/ insufficiency which requires upregulation of proteasome subunits. Nuclear Factor Erythroid 2-related factor 1 (NRF1) is a transcription factor (encoded by *NFE2L1*) which activates proteasome gene re-synthesis upon impairment of the proteasome function. Therefore, targeted activation of the NRF1 pathway could represent a new approach to delay the onset neurodegenerative diseases and other disorders with disturbed proteostasis.

Here, we present a series of small-molecule compounds identified in a targeted library screening, which can 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. These compounds increase proteasome activity and decrease the number and size of protein aggregates. Overall, our compounds represent a promising novel approach for the treatment of a variety of protein conformational diseases, including the most debilitating neurodegenerative diseases.