

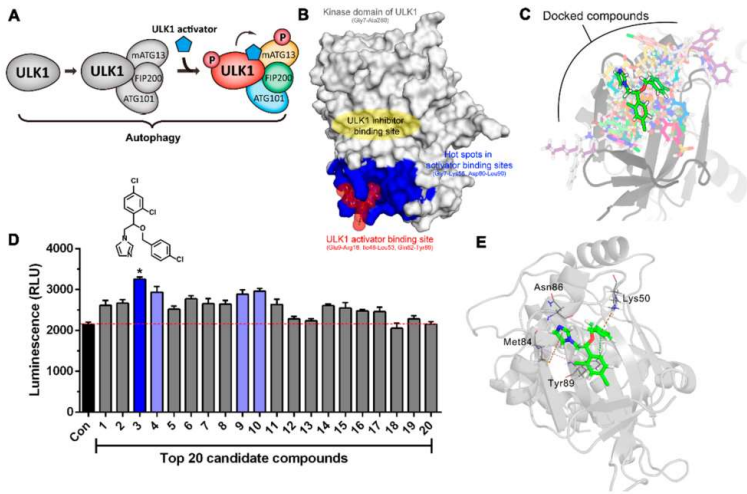


# Small-Molecule Activator of UNC-51-Like Kinase 1 (ULK1) That Induces Cytoprotective Autophagy for Parkinson's Disease Treatment

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## Objective

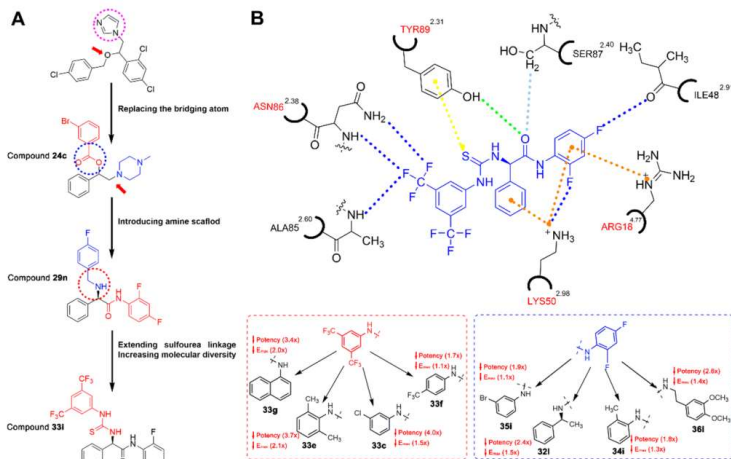
Parkinson's disease (PD) is a common neurodegenerative disease. The study of PD treatment and molecular mechanism intervention by the optimized compounds, targeting phosphorylation modification of ULK1, would pave a way for the functional research of autophagy in neurodegenerative diseases and the further development of anti-PD drugs with new therapeutic strategies.



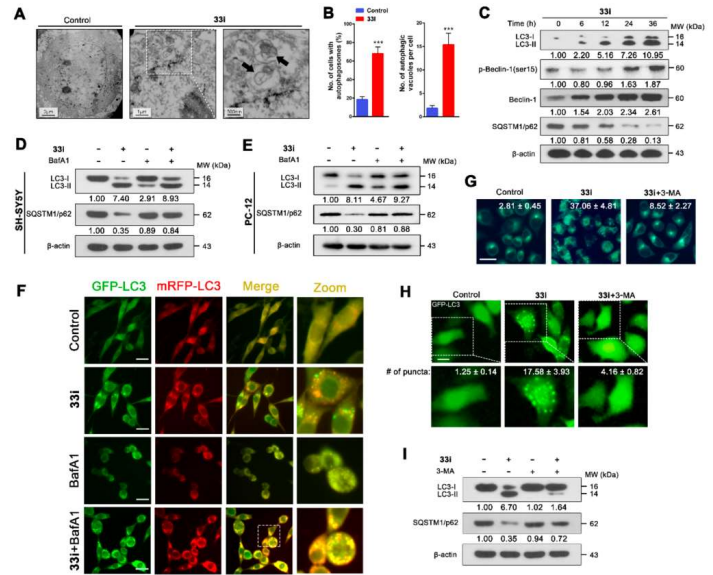
**Fig. 1 Structure-based ligand design for ULK1**

## Methods and Results

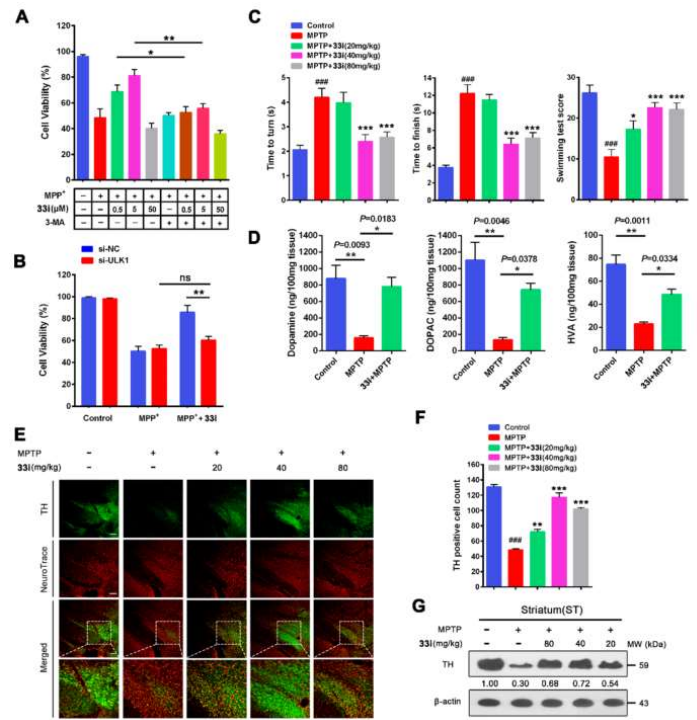
Given that the ULK complex is required to trigger autophagy by an activator of ULK1, we designed a small molecule that could activate ULK1 and the rest of the ULK complex (Fig. 1, 2). Observing the cellular ultrastructure by the electron microscopy, compound 33i induces autophagy in neuron-like cells, and has a therapeutic potential in PD models *in vitro* and *in vivo* (Fig. 3, 4).



**Fig.2 Structural optimization and discovery of the ULK1 activator**



**Fig.3 Compound 33i induces autophagy in neuron-like cells**



**Fig.4 Compound 33i has a therapeutic potential on PD models *in vitro* and *in vivo***

## Conclusion

Taken together, our findings demonstrate that this activator of ULK1 would be further exploited as a small-molecule candidate drug for future PD therapeutics.

