Potent Inducers of Paraptosis Through Electronic Tuning of Michael Acceptors

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Paraptosis is a non-apoptotic programmed cell death characterized by cytoplasmic vacuolation due to endoplasmic reticulum (ER) and mitochondria swelling. This process may lead to protein and Ca^{2+} homeostasis disruption and activation of the unfolded protein response of the endoplasmic reticulum (UPR^{ER}). [1,2] Paraptotic cells do not exhibit DNA fragmentation or caspase activation. [1] The mechanisms that lead to paraptosis are not well understood. However, specific targets have been reported to induce paraptosis. These targets include the insulin-like growth factor I receptor (IGFIR), [1,2] GDP-dissociation inhibitor beta (GDI2), [3] and ubiquitin-specific peptidase 10 (USP10).[4] Due to defective apoptosis, some cancer cells exhibit resistance to current therapies. Therefore, non-apoptotic programmed cell death mechanisms such as paraptosis have gained significance in cancer therapy.

In this study, we developed a set of Michael acceptors, one of which exhibited paraptosis induction in HEK293, HeLa, and MDA-MB-231 cell lines. This process was characterized by the formation of vacuoles arising from the ER and did not involve caspase activation. The compound caused swelling of the ER and mitochondria, increased superoxide production, and exhibited reactivity towards cysteines. Furthermore, our initial proteomic analysis revealed specific proteins that differ from known paraptosis-inducing targets. These proteins could be potential targets for paraptosis activation.

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