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Health

Modulating protein aggregation in cell models using modified steroids

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Protein aggregation is a biological process in which misfolded proteins aggregate and accumulate in intra- or extra-cellular media. Protein aggregation is intimately linked to the pathogenesis of many neurodegenerative diseases (such as Alzheimer's, Huntington, Parkinson's and prion diseases) but also in cancer and cardiovascular pathologies (e.g. atherosclerosis, heart failure and ischemic heart disease).[1] However, it is not fully understood how aggregates are formed and how the complex network of chaperones, the proteasome, autophagy and other regulatory factors are involved in their clearance.[1] Nevertheless, it is well accepted that lowering protein aggregates back to "normal" levels in cells could be an important therapeutic strategy to control or modulate neurodegenerative diseases.[2] In 2015, lanosterol was reported to reverse protein aggregation of crystallin clumps in mouse cataracts, due to its amphiphilic nature, being able to intercalate into and coat hydrophobic areas of large protein aggregates, making these water soluble again.[3] Taking into consideration this discovery, we believe that other steroids, such cholesterol (with the appropriate chemical modification),[4] can be good lead candidates to lower several types of protein aggregates. In this project a series of new hybrid-steroidal compounds was designed and synthesized, to address protein aggregates in different models and using techniques such as a high-throughput screening (HTS) (Figure 1). The design and synthetic strategy of the compounds, as well as the preliminary disaggregation results in different types of *in vitro* and *ex vivo* aggregation models will be discussed and rationalized in terms of structure-activity relationship, whenever possible.

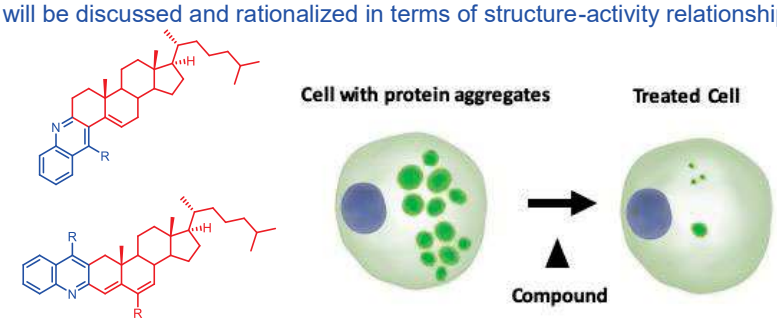

Figure 1: Structures of the modified steroids and schematization of the HTS strategy.

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