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New Promising Curcumin Mimics as Neurodegenerative Hallmarks Rescuers[1]

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Proteins' misfolding and the formation of their aggregates is a common event to several human pathologies (Protein Misfolding Diseases – PMDs) and neurodegenerative disorders, as Alzheimer's Disease (AD). Recently, it has been observed that a decreased activity of Ubiquitin Proteasome System (UPS),[2] fundamental pathway of misfolded or damaged proteins, leads to an accumulation of the proteins that plays a key role in Protein Conformational Diseases (PCDs). Starting from the selected lead-metabolite Curcumin (**Cur**),[3] reported to have an unprecedented therapeutic potential in the pathophysiology of AD, but poor pharmacokinetics (PK), different approaches of drug discovery have been pursuing for the development of novel molecules capable both to interfere with protein misfolding processes and to enhance the activity of UPS. To create derivatives with better drug-like properties and inspired by the presence of common structural elements among small-ligand proteasome activators, we have designed, synthesized, and characterized a mini-library of novel Curcumin mimics by varying the two aromatic moieties and modulating the length and rigidity of the newly settled diamide spacers. These compounds will be functionally probed for their antiaggregating ability and to stimulate h20S proteasome, both crucial capabilities in restoring cellular proteostasis. Resulting structure-activity relationships will be used to implement the pharmacophore model to drive future structure optimization.

References:

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