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Designed peptidomimetics disrupt protein-protein interactions mediating amyloid protein aggregation

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Amyloid fibrils are self-assembled insoluble aggregates that constitute the hallmark of more than 20 serious human amyloidosis diseases, such as Alzheimer's disease (AD) and type II diabetes. Current drugs have failed to slow the progression of AD, which affects more than 35 million people worldwide. How drug candidates that reduce fibril formation act on the most neurotoxic oligomeric forms of amyloid peptide Aβ1-42 is far from being established. We report herein the capacity of two new classes of peptidomimetics to inhibit both Aβ1-42 early oligomerization and fibrillization: 1- sugar-based peptidomimetic analogs having physicochemical properties for drug-likeness[1]; 2- β-hairpin mimics[2]. A wide range of bio- and physico-chemical techniques, such as Thioflavin-T fluorescence spectroscopy, transmission electronic microscopy, a new developped capillary electrophoresis method[3], electrospray differential mobility analysis[4], nuclear magnetic resonance, and surface plasmon resonance, was used in order to identify the molecular mechanisms by which these new series of molecules can delay the aggregation of Aβ1-42. This is the first example of small molecules that preserves the non toxic monomeric species of Aβ1-42. Some compounds suppress totally the toxicity of Aβ1-42 towards SH-SY5Y human neuroblastoma cells, even at sub-stoichiometric concentrations. This protective effect is much more significant than that observed with molecules that have undergone clinical trials which reduce Aβ1-42 toxicity only at stoichiometric or higher concentrations. Preliminary results on the inhibition of IAPP aggregation involved in type II diabetes will be also presented. [1] a) B. Dorgeret, L. Khemtémourian, I. Correia, J-L Soulier, O. Lequin, S. Ongeri *Eur. J. Med. Chem*. **2011**, *46, 5959*. (b) J. Kaffy, D. Brinet, J-L Soulier, L. Khemtémourian, O. Lequin, M. Taverna, B. Crousse, S. Ongeri, *Eur. J. Med. Chem*. **2014**, 86, 752; c) J. Kaffy, D. Brinet, J-L Soulier, I. Correia, N. Tonali, K. F. Fera, Y. Iacone, A. R. F. Hoffmann, L. Khemtemourian, B. Crousse, M. Taylor, D. Allsop, M. Taverna, O. Lequin, S. Ongeri, *J. Med. Chem.* **2016**, 59, 2025. [2] a) S. Pellegrino, N. Tonali, E. Erba, J. Kaffy, M. Taverna, A. Contini, M. Taylor, D. Allsop, M. L. Gelmi, S. *Ongeri Chemical Science*, **2017**, 8, 1295; b), L. Vahdati, J. Kaffy; D. Brinet; G. Bernadat, I. Correia, S. Panzeri, R. Fanelli, O. Lequin, M. Taverna, S. Ongeri, U. Piarulli. *Eur. J. Org. Chem*. **2017**, DOI: 10.1002/ejoc.201700010.[3] D. Brinet, J. Kaffy, F. Oukacine, S. Glumm, S. Ongeri, M. Taverna *Electrophoresis* **2014**, 35, 3302. [4] D. Brinet, F. Gaie-Levrel, V. Delatour, J. Kaffy, S. Ongeri, M. Taverna *Talanta*, **2017**, 165, 84-91.

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