SYNTHESIS OF MULTI RING-FUSED PEPTIDOMIMETICS INTERACTING WITH α-SYNUCLEIN FIBRILS

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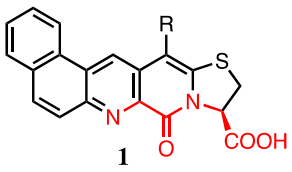
The Thiazolino ring-fused 2-pyridone scaffolds were initially developed as peptidomimetics to inhibit the production of pili in uropathogenic *E.coli* [1]. When the scaffold was later equipped with other substituents, it gained the ability to modulate the formation of amyloid fibers, such as fibers of α-synuclein, whose formation *in vivo* is associated with Parkinson's disease [2] in humans.

In a recent publication we described the synthesis of fluorescent ring-fused 2-pyridones with five fused rings (**1**) and an extended peptidomimetic backbone that modulates the aggregation of α-synuclein *in vitro* [3]. We subsequently constructed a tricyclic pyridine fused 2-pyridone scaffold (**2**) whereof several examples showed α-synuclein binding by ThT displacement *in vitro* [4]. Initial evaluations of one such compound in mice moreover indicated a protective effect against accelerator-induced neurodegeneration, when injected 14 days prior to the aggregation accelerator FN075 [2]. This observation was further consolidated when protection of TH-positive neuron cells, from cell death caused by the same accelerator, was demonstrated.



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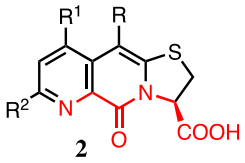

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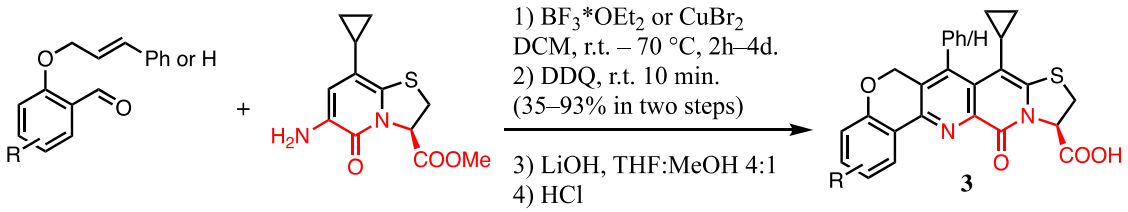
The assembly of our pyridine-fused heterocycles rely on the three-component Povarov reaction. Aware of the possibility to perform the Povarov reaction in an intramolecular fashion, we envisioned a modified scaffold with increased hydrophilicity (**3**). We have further noticed by aims-test that our modified scaffold showed no mutagenicity. Gratifyingly, examples of the modified scaffold showed retained affinity to α-synuclein fibrils, demonstrated by loss of fluorescence upon ThT displacement. Informative SAR was revealed and further synthesis and evaluation is on-going.



3

Scheme 1: Synthesis of non-mutagenic amyloid binding peptidomimetic **3** with improved hydrophilisity and stability.

[1] a) Pinkner, J. S. et al. Proc. Natl. Acad. Sci. USA 2006, 103 (47) 17897–17902.
b) Chorell, E. et al., J. Med. Chem. 2010, 53 (15), 5690–5695.

[2] a) Horvath, I. et al., J. Am. Chem. Soc. 2012, 143, 3439–3444.
b) Cegelski, L. et al., Nat. Chem. Biol., 2009, 5, 913–919.

[3] Singh, P. et al., Org. Lett. 2015, 17 (24), 6194–6197.

[4] Singh, P. et al., J. Org. Chem. 2019, DOI: 10.1021/acs.joc.8b03015.