Antiprionic activity of 6-aminoquinolones and their dimeric benzoquinone conjugates

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Introduction

Prionic diseases are a set of neurodegenerative diseases resulting from transmissible spongiform encephalopathies (TSE). One cause of these diseases is the aggregation of the protease-resistant insoluble Prion protein (PrP^{Sc}), an infectious protein isoform formed after conformational changes of the soluble cellular Prion isoform (PrP^{C}). Efforts have been made to develop new substances capable of minimizing this conformational conversion.[1] Our research group presented the synthesis of a series of 6-aminoquinolones and their dimeric benzoquinone derivatives at the 41th Annual Meeting of the Brazilian Chemical Society in 2018 (Figure 1).

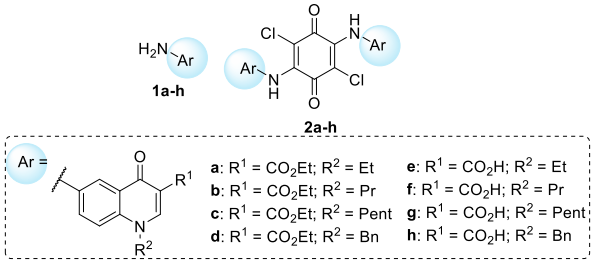

Figure 1. 6-aminoquinolones (**1a-h**) and their dimeric benzoquinone conjugates (**2a-h**).

Substances **1a-h and 2a-h** are currently being evaluated for their anti-prion profile and, in this paper, we present the first results obtained.

Results and Discussion

The substances **1a-h** and **2a-h** had their anti-prion profile evaluated by two different assays. The first explored the ability of these substances to inhibit the formation of the amorphous protein aggregates due to mechanical and thermal stimuli in solutions containing the cellular prion protein.[2] All aminoquinolones (**1**) showed inhibitory capacity. Although not all of the dimers (**2**) were active, three of them presented better activity than their monomeric analogues, with the best result achieved by **2e**, with 79% inhibition (Figure 2). In the second assay the inhibitory capacity on the formation of mature prion fibers was evaluated.[3] The best results were obtained for dimers **2g** and **2h** leading to changes in the kinetic and thermodynamic profiles of the fibrillation stage. Figure 3 exemplifies this result for **2h**.

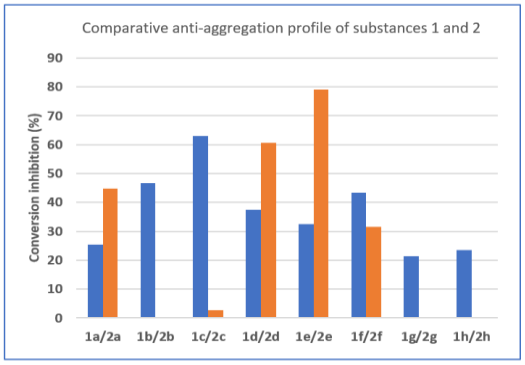

Figure 2. Formation of amorpheus protein aggregates.

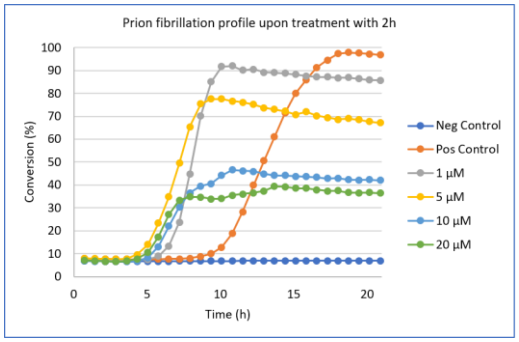

Figure 3. Fibrillation process for substance **2h**.

The substances **1** and **2** presented low cytotoxicity in concentration of 10 µM.

Conclusion

All monomers and four of the dimers studied inhibited protein aggregation, with **2e** presenting the best result. **2h** and **2g** showed modulating activity of the fibrillation stage, affecting both the kinetics and thermodynamics, with a decrease in total fibrillation. Further studies are underway.

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