Tau-Derived-Hexapeptide ^{306}VQIVYK^{311} Aggregation Inhibitors: Nitrocatechol Moiety As A Pharmacophore In Drug Design

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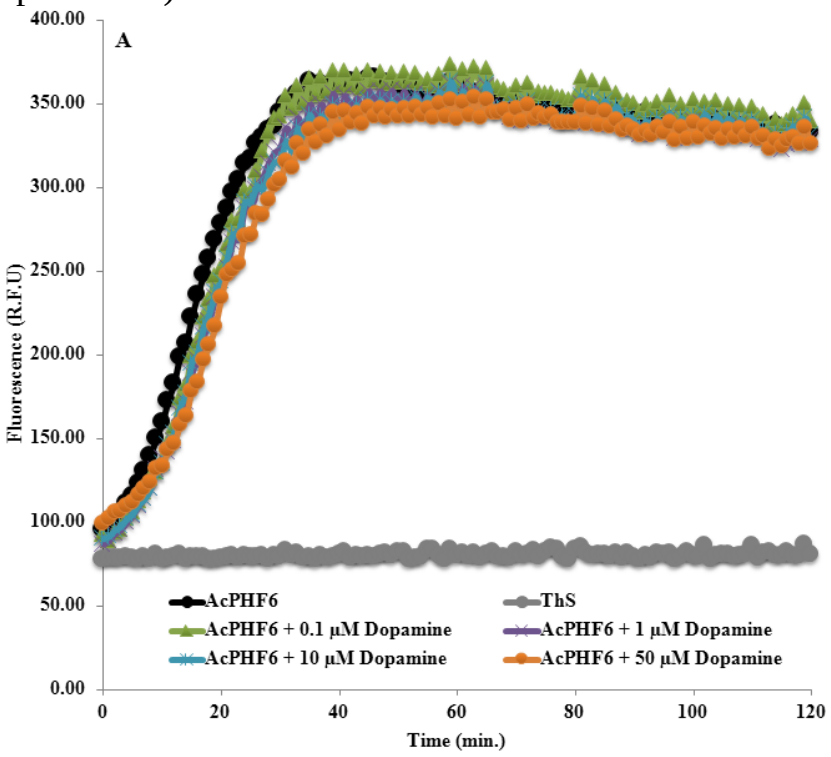
Supporting Information

Contents:

Figure S1: The effect of various concentrations of dopamine **3** (panel A) and epinephrine **4** (panel B) on AcPHF6 aggregation (in triplicates from two independent experiments).



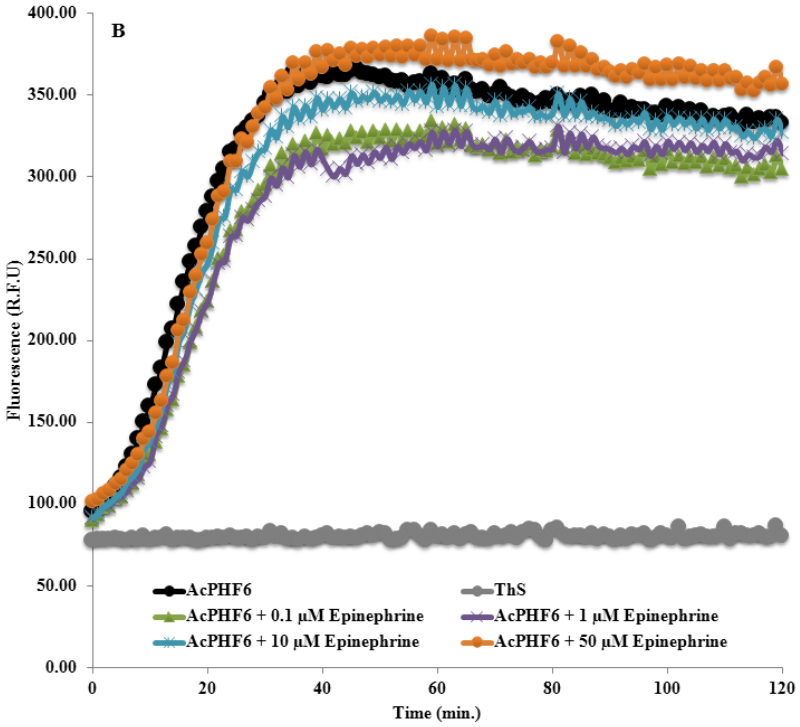


Figure S2: The effect of various concentrations of nitrocatechol isomer **8**, panel A and nitrophenol **10** in panel B on AcPHF6 aggregation (in triplicates from two independent experiments).

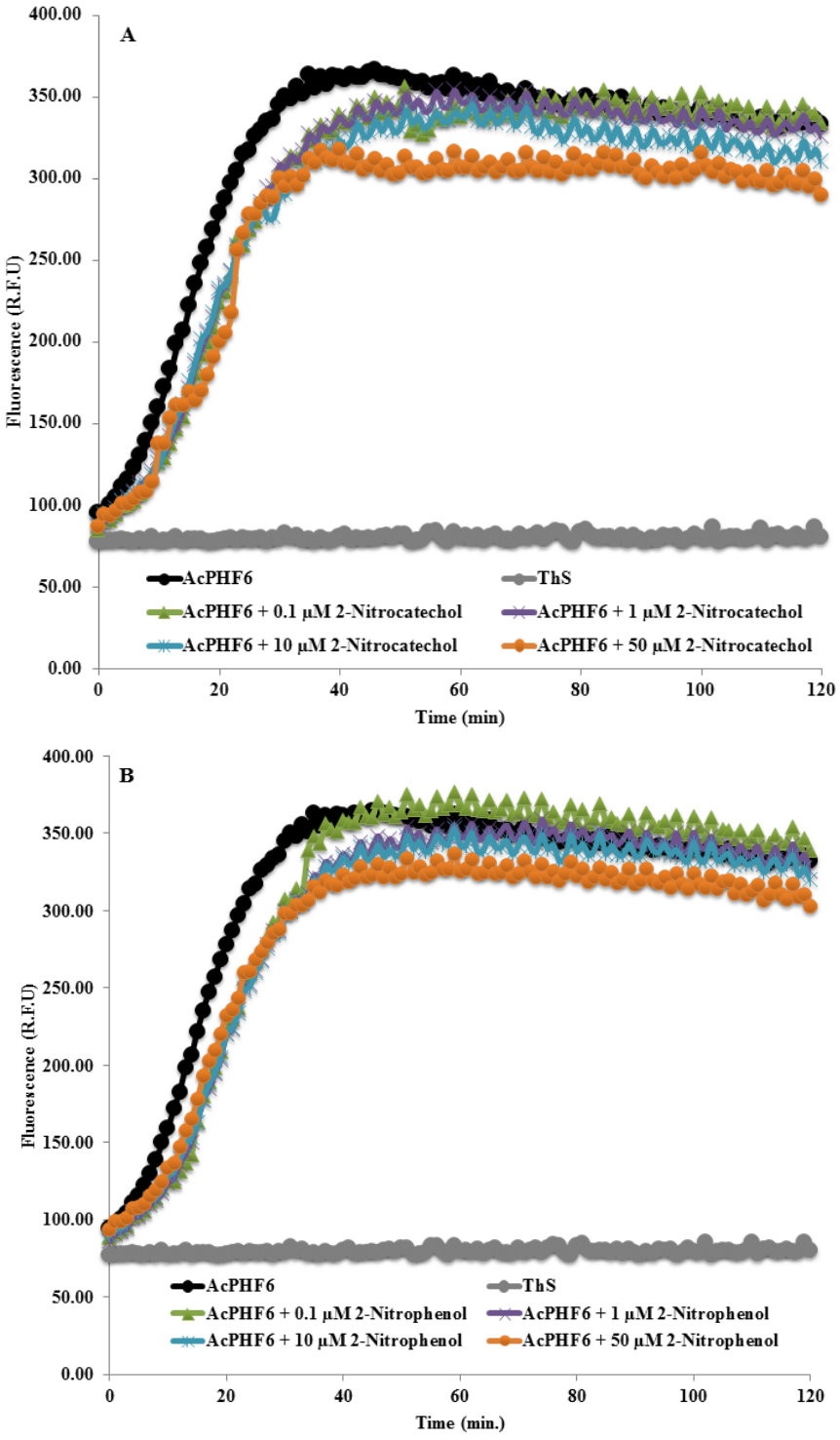


Figure S3: The effect of various concentrations of chloramphenicol **5**, panel A and nifedipine **6** in panel B on AcPHF6 aggregation (in triplicates from two independent experiments).

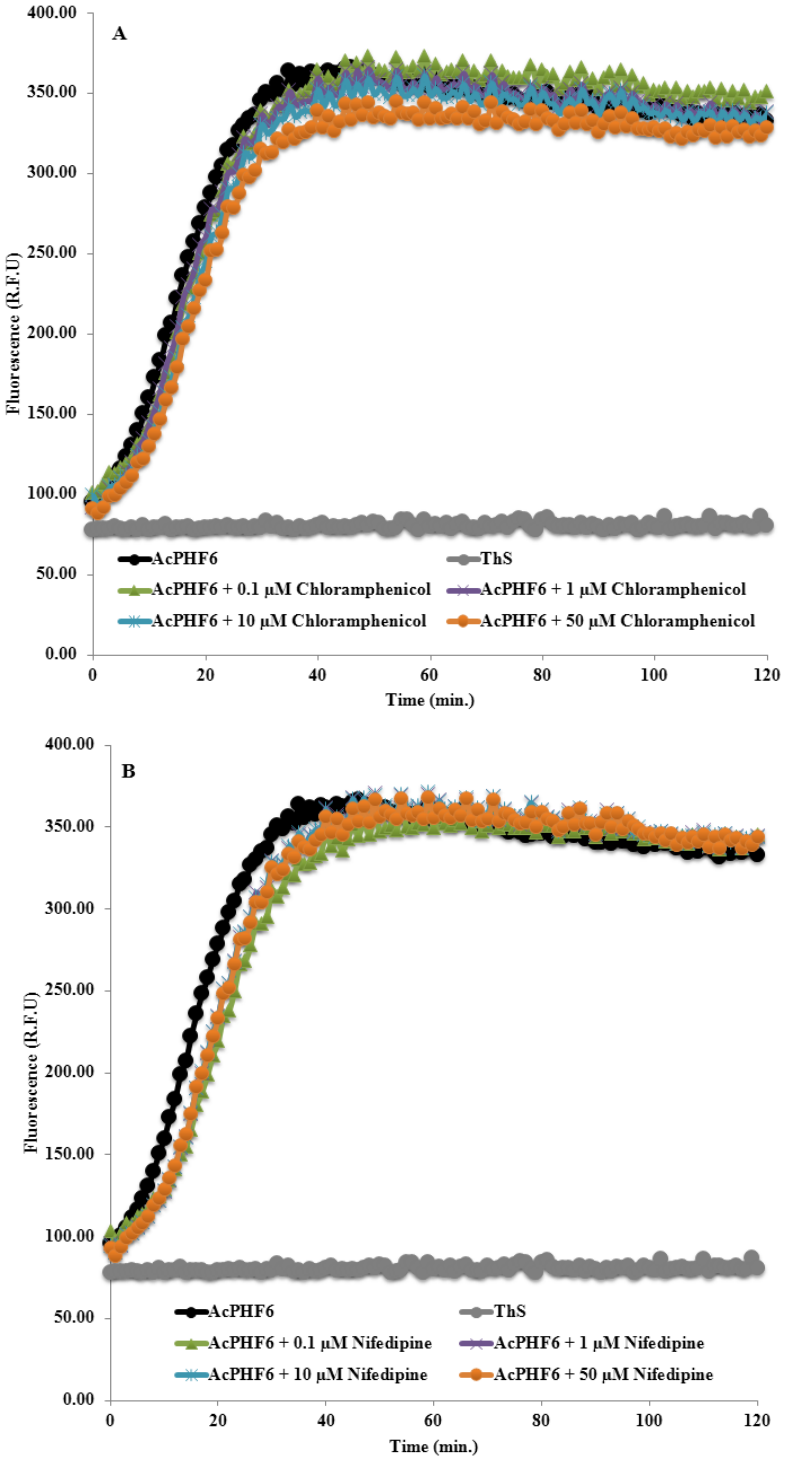


Figure S4: The effect of various concentrations of nitrobenzene **11**, panel A and nitroanthracene **12** in panel B on AcPHF6 aggregation (in triplicates from two independent experiments).

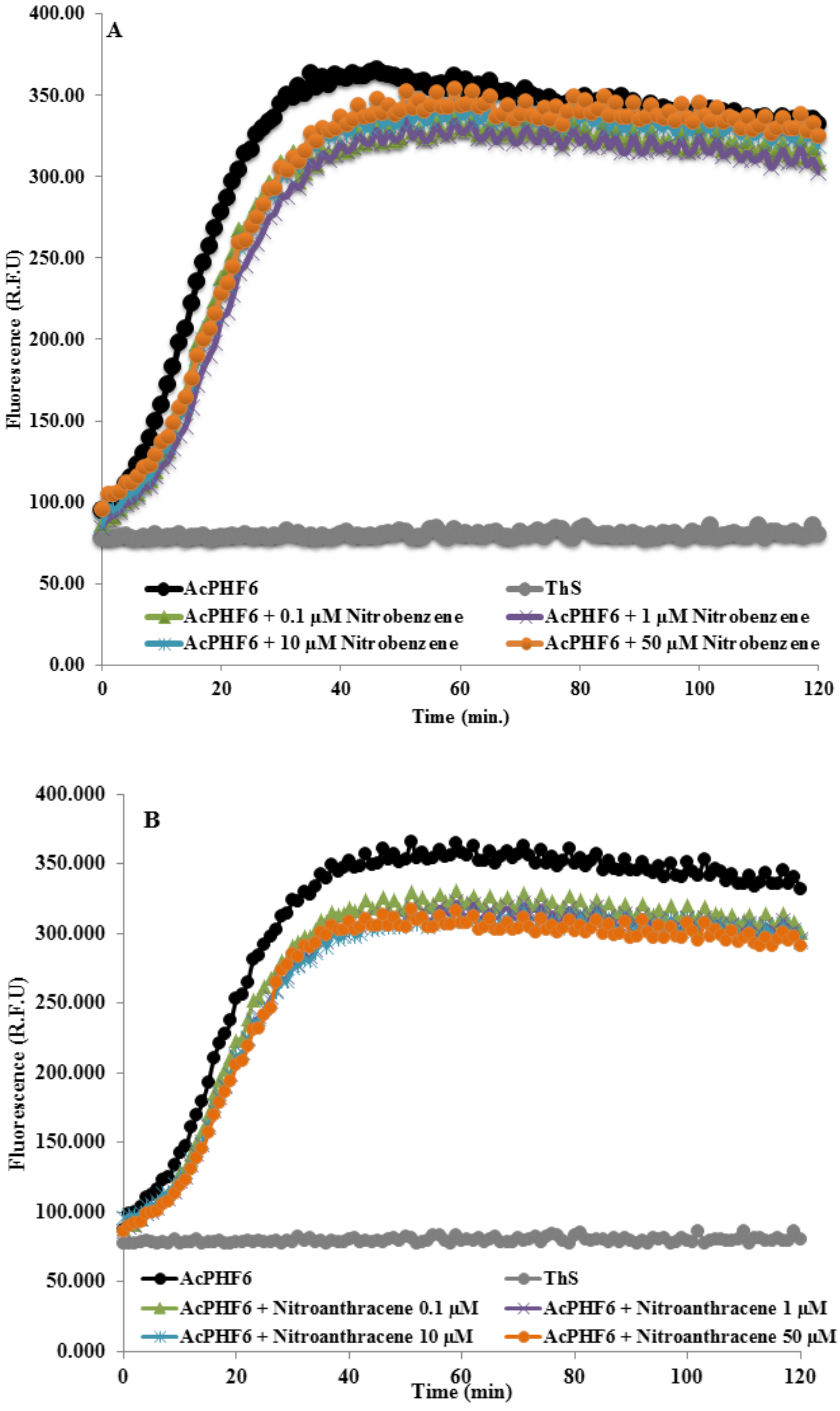


Figure S5 The effect of various concentrations of methylbenzophenone **13** on AcPHF6 aggregation (in triplicates from two independent experiments).

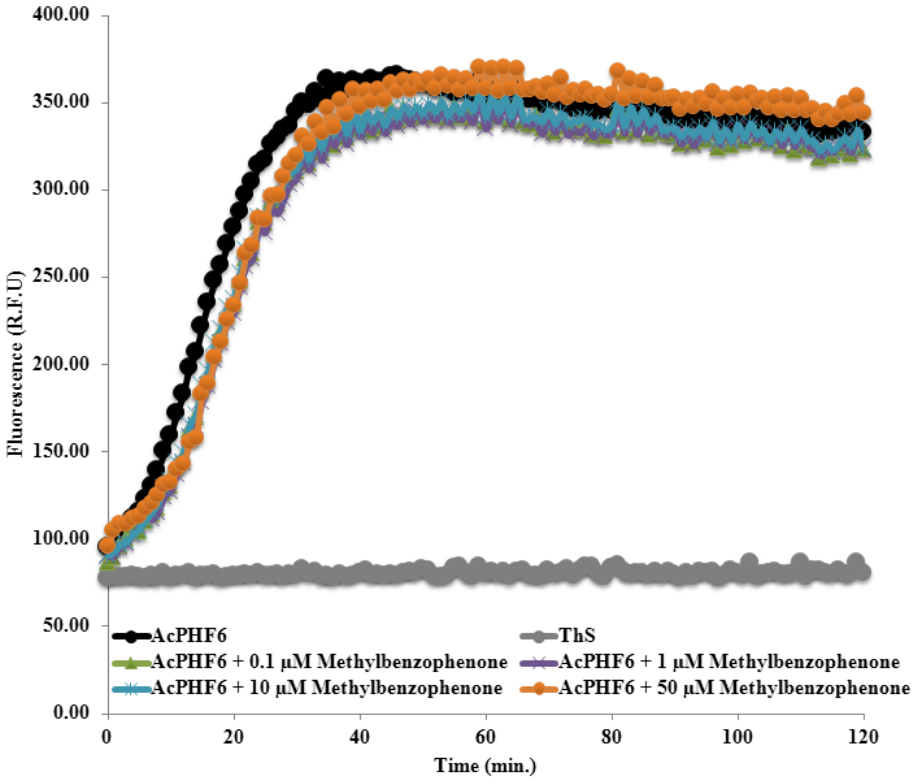


Figure S6: The UV scan of test compounds at 50 µM. Experiments were done in triplicates.

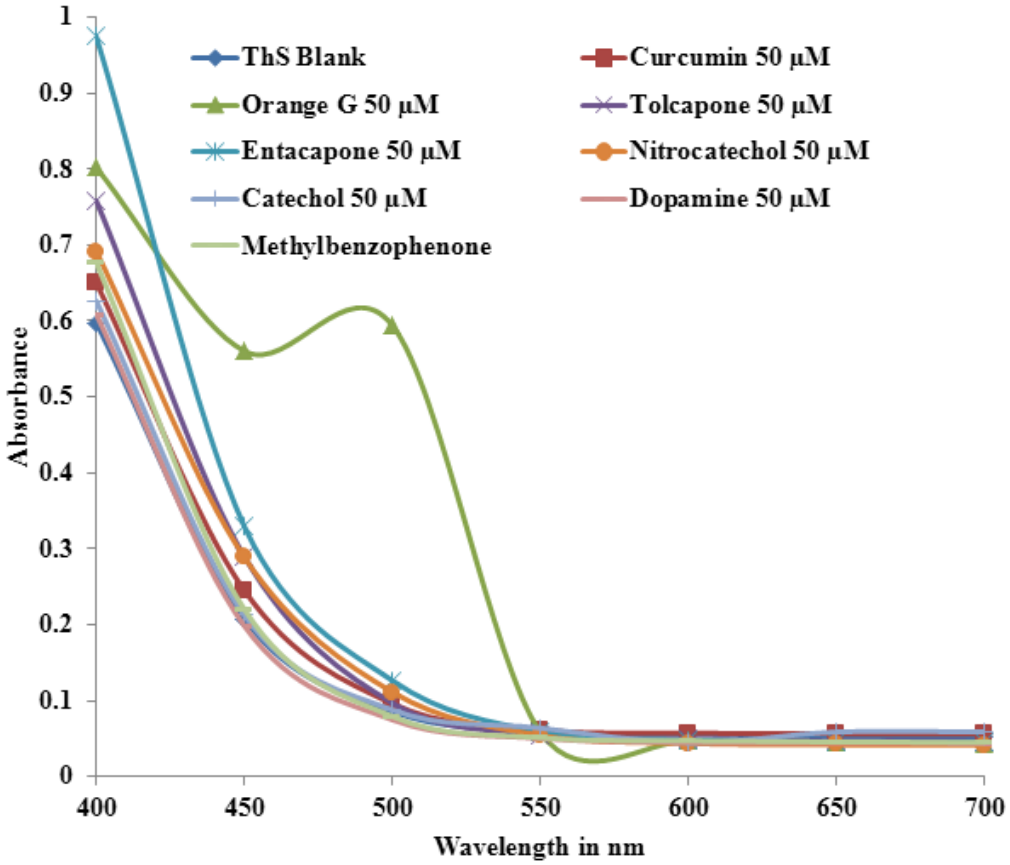


Figure S7: The fluorescence data of test compounds at 50 µM (excitation wavelength = 440 nm and emission wavelength = 490 nm). Experiments were done in triplicates.

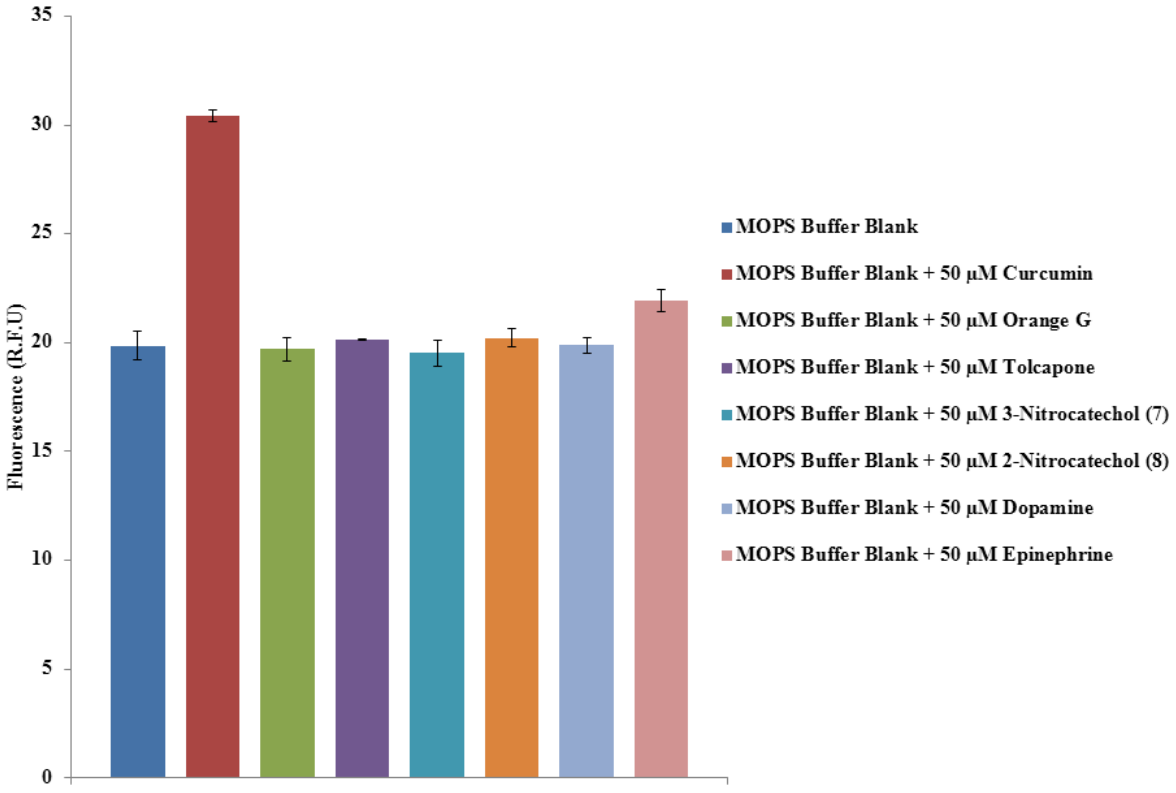


Figure S8: The fluorescence data obtained (excitation wavelength = 440 nm and emission wavelength = 490 nm) in presence of ThS, test compounds (50 µM) and MOPS buffer pH 7.2 after 120 min. Experiments were done in triplicates.

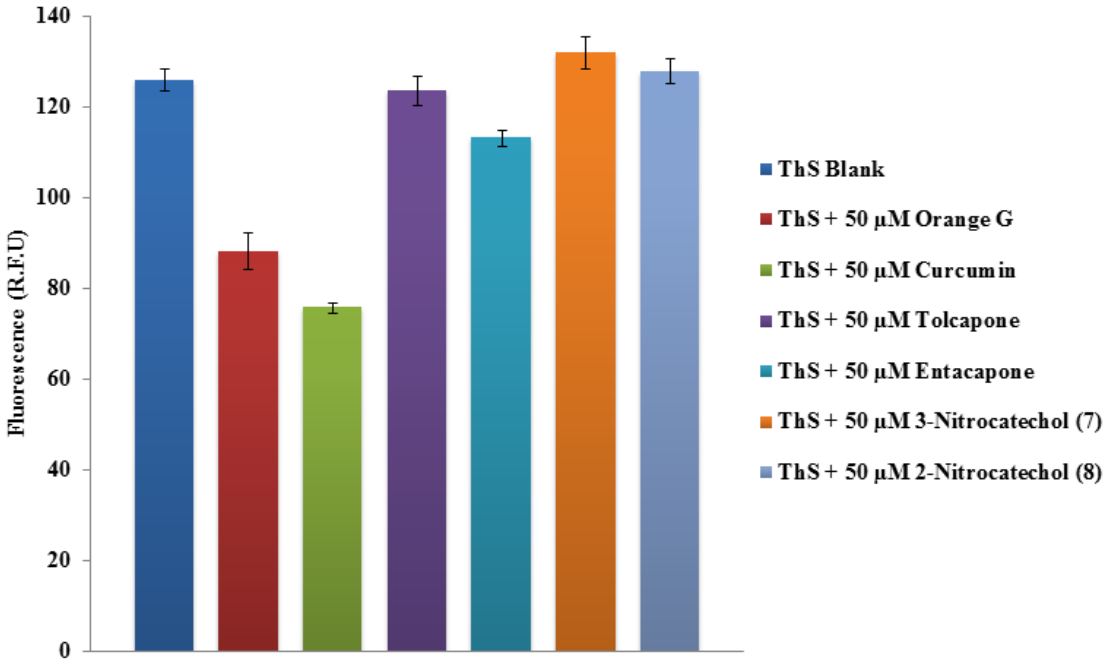
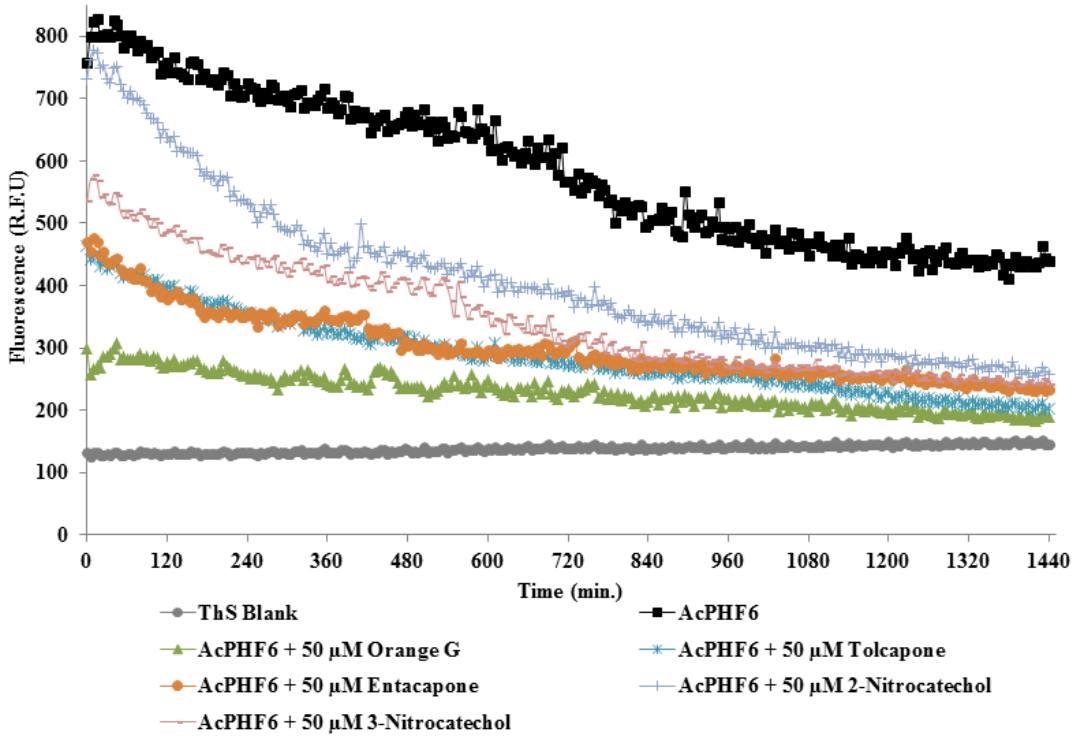


Figure S9: The AcPHF6 peptide (100 µM) disaggregation kinetics in presence of nitrocatechols **1**, **2**, **7** and **8** (50 µM each) measured using ThS fluorescence (excitation wavelength = 440 nm and emission wavelength = 490 nm) in MOPS buffer pH 7.2 over a period of 24 h. Experiments were done in triplicates.



AcPHF6 Disaggregation Assay

To investigate the disaggregation properties of nitrocatechols (**1**, **2**, **7** and **8**) on pre-formed AcPHF6 peptide aggregates, the ThS fluorescence was monitored over a 24-hour period in the presence or absence of test compounds. Initially, AcPHF6 aggregates were obtained by incubating 20 µL of ThS, 140 µL of 20 mM MOPS buffer (pH 7.2) and 20 µL of AcPHF6 (100 µM final well concentration) in a 96-well plate (Costar, black clear bottom) over a 2 h period. The plate was gently mixed for 25 seconds and fluorescence was monitored (excitation 440 nm/ emission 490 nm) at 5 min. intervals with 5 second shaking in between each reading. After the 2 h aggregation period, test compounds (orange G, tolcapone, entacapone, 2-nitrocatechol or 3-nitrocatechol, final well concentration of 50 µM) were added to pre-formed AcPHF6 aggregates. The plate was gently mixed for 25 seconds prior to fluorescence monitoring (excitation 440 nm / emission 490 nm) for 24 hours at 5 min. intervals with 5 second shaking in between each reading (triplicate measurements).

Figure S10: (A) The binding mode of dopamine (**3**, ball and stick) and (B) catechol (**9**, ball and stick) in the steric zipper model of tau-derived-hexapeptide ^{306}VQIVYK^{311}. Two layers of fiber made up of individual β-strands are shown. The hydrogen atoms are removed for clarity. Distance parameters are shown in red (Å units).

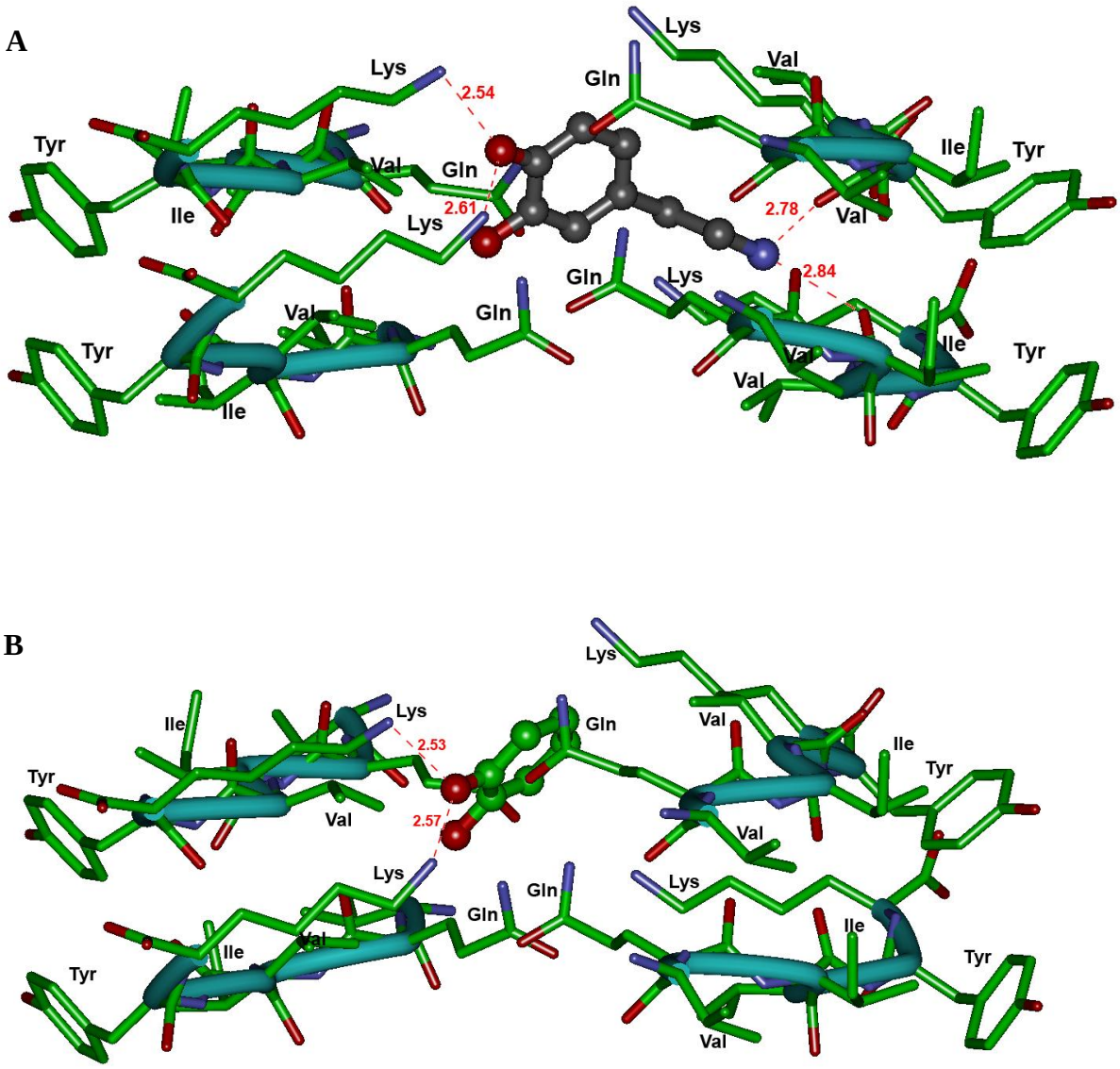


Table S1: The partition coefficient values (ClogP) of test compounds **1**–**13**

Compound	**ClogP** [a]
Tolcapone (**1**)	3.24
Entacapone (**2**)	1.76
Dopamine (**3**)	0.17
Epinephrine (**4**)	-0.68
Chloramphenicol (**5**)	1.28
Nifedipine (**6**)	3.12
(**7**)	1.44
(**8**)	1.37
(**9**)	0.87
(**10**)	1.85
(**11**)	1.88
(**12**)	4.23
(**13**)	3.67

[a] ClogP value was determined using ChemDraw Ultra 12.0. CambridgeSoft Company