



Молекулно-динамични симулации на β -амилоиден пептид в присъствие и отсъствие на инхибитори на агрегацията му

Евдокия Саламанова

Лаборатория по лекарствен дизайн и биоинформатика
Фармацевтичен факултет, МУ-София

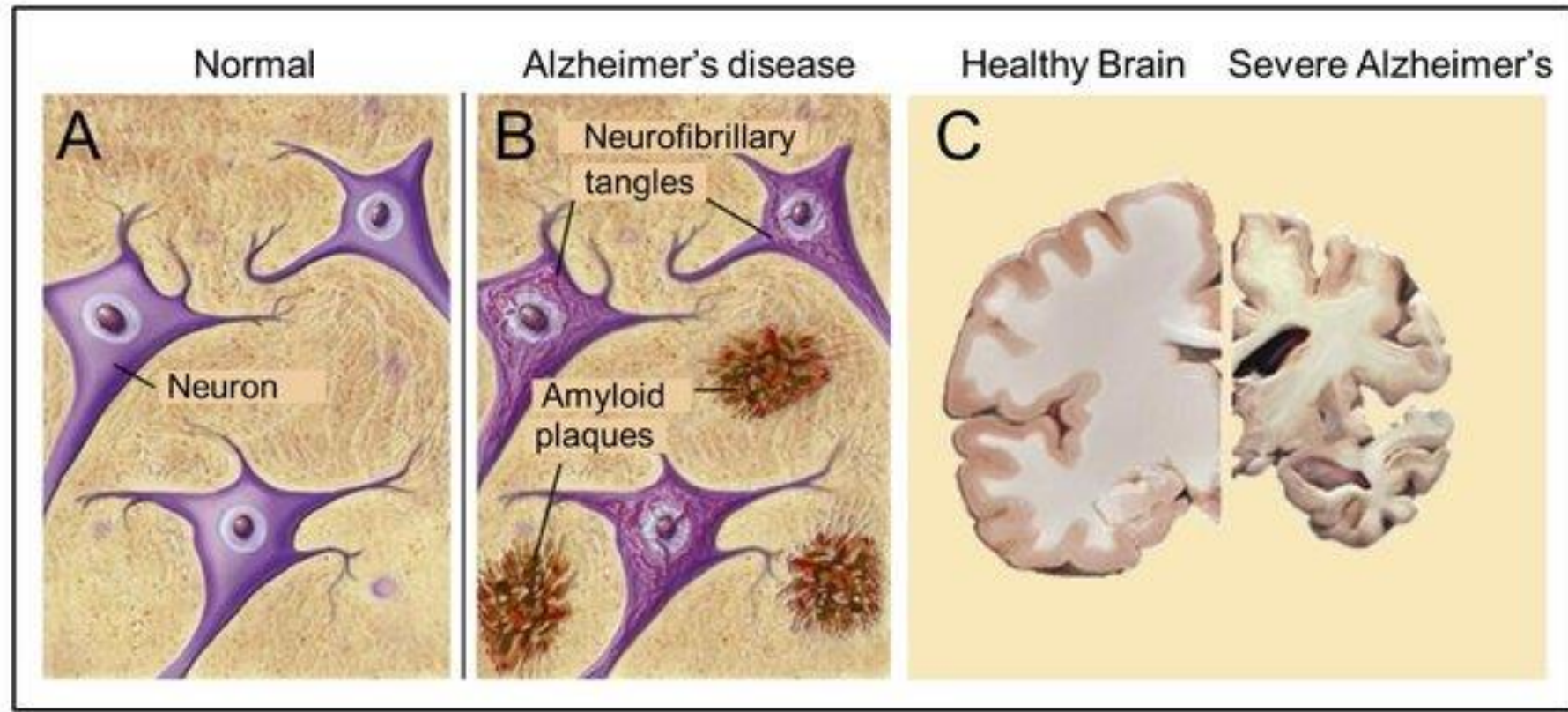
Работна среща, 15.07.2021 г.

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Болест на Алцхаймер

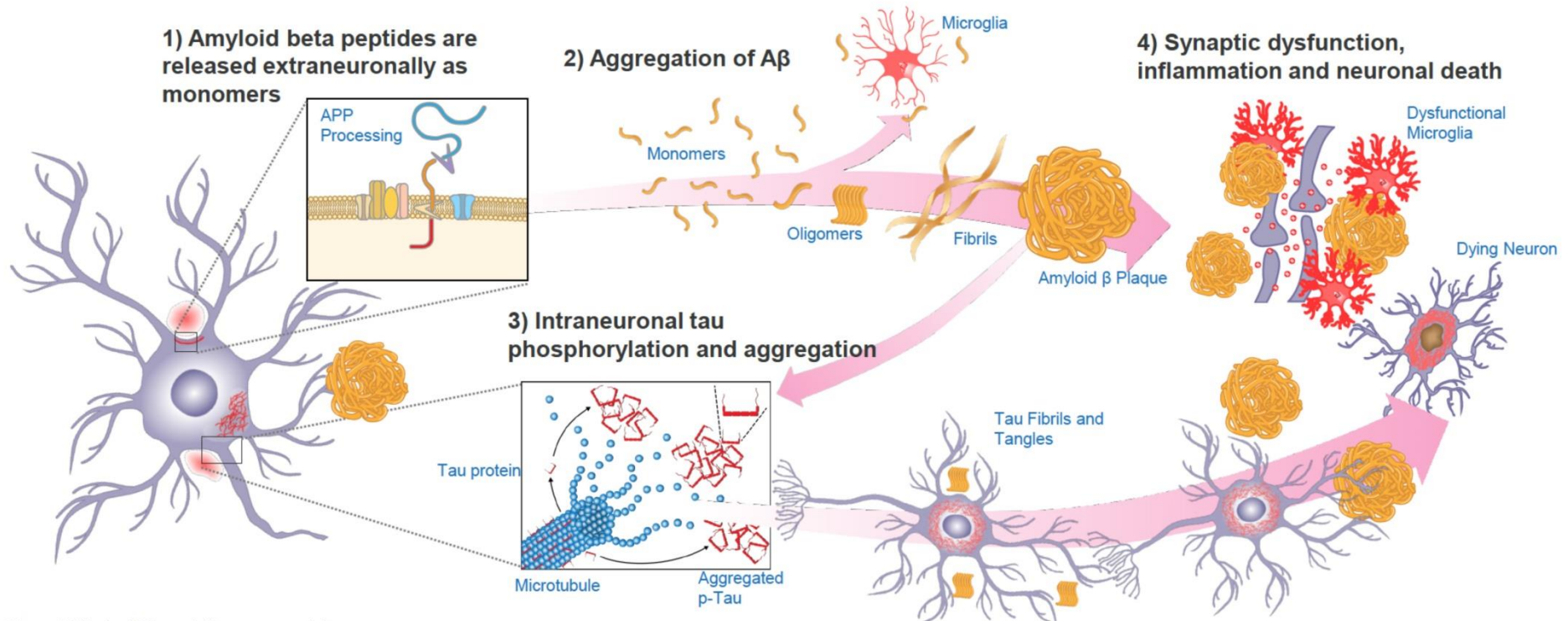




АМИЛОИДНА ХИПОТЕЗА

CU-5

The Two Pathological Hallmarks of Alzheimer's Disease in the Brain Are A β Plaques and Neurofibrillary Tangles

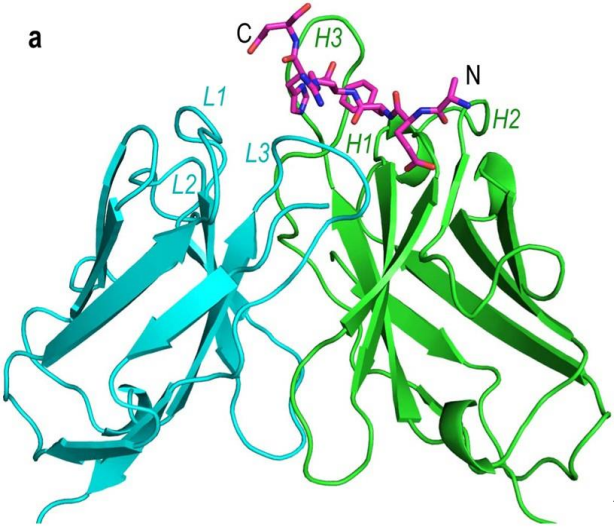
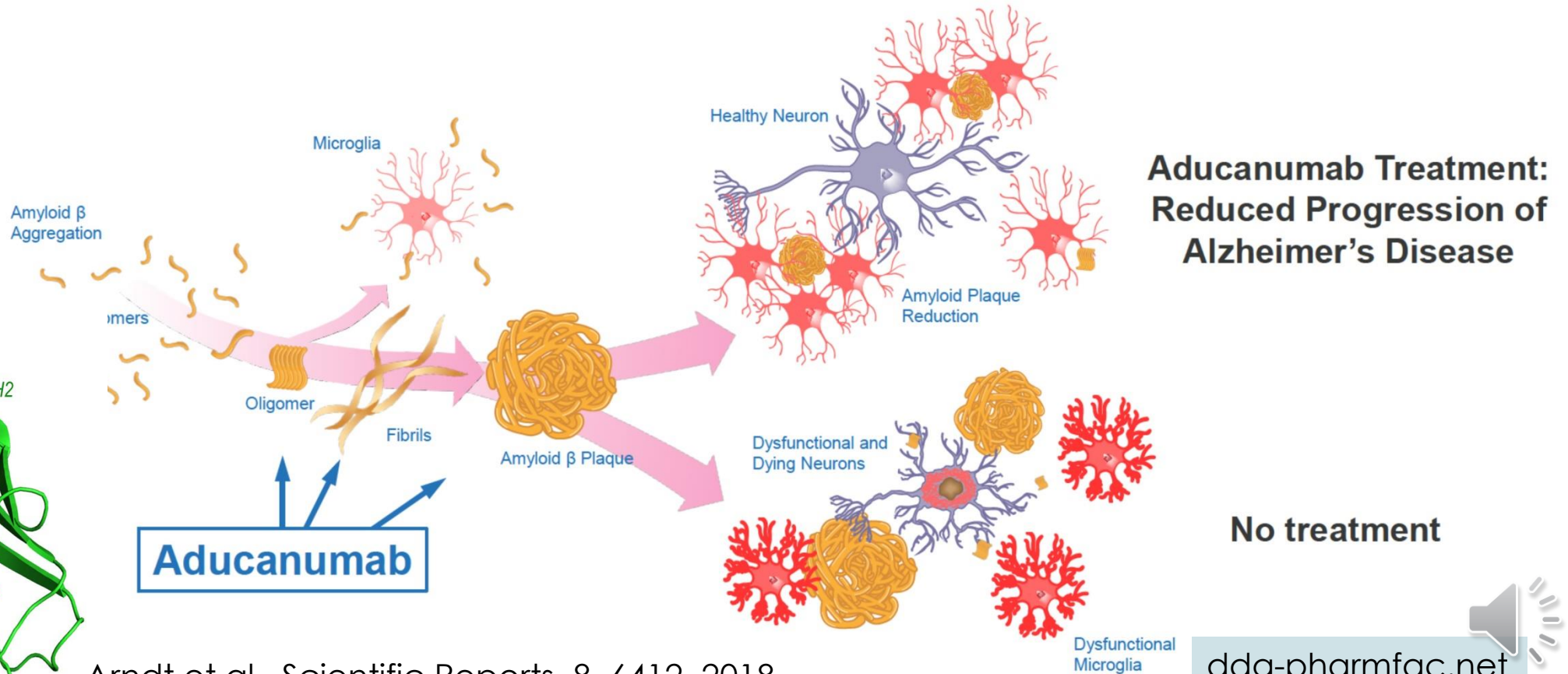


A β =amyloid beta; APP=amyloid precursor protein.
Based on Pospich S, Raunser S. *Science*. 2017;358(6359):45-46.



Aducanumab by Biogen

Aducanumab: Targeting Alzheimer's Disease Pathology





Цел на изследването

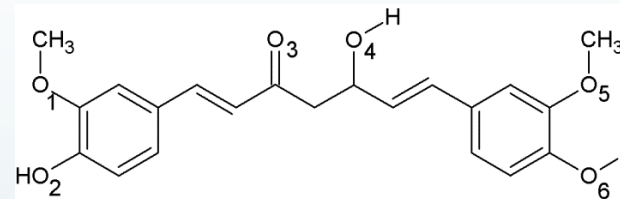
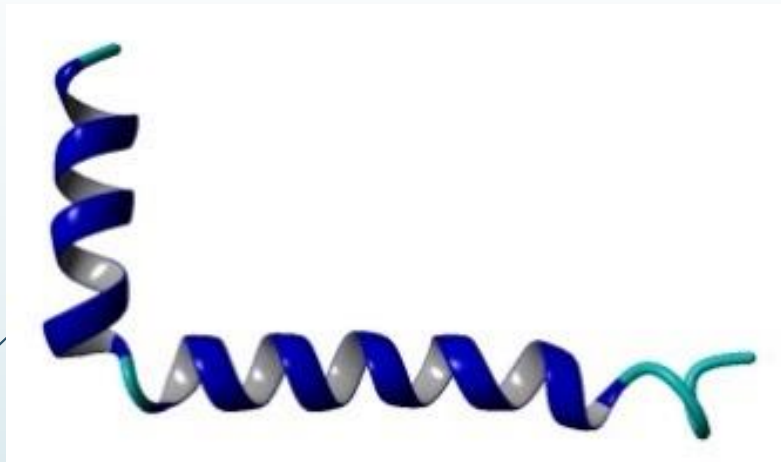
Да се симулират взаимодействията между β -амилоидния пептид и молекула-инхибитор на агрегацията и да се установи механизма на инхибиране.

Задачи:

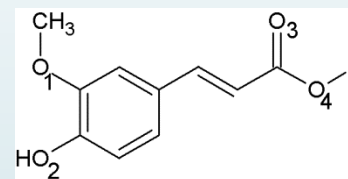
1. МД симулация на системата 1 мол. А β : 1 мол. инхибитор
2. МД симулации на системите 12 мол. А β : 12 мол. инхибитор и 12 мол. А β : 36 мол. инхибитор



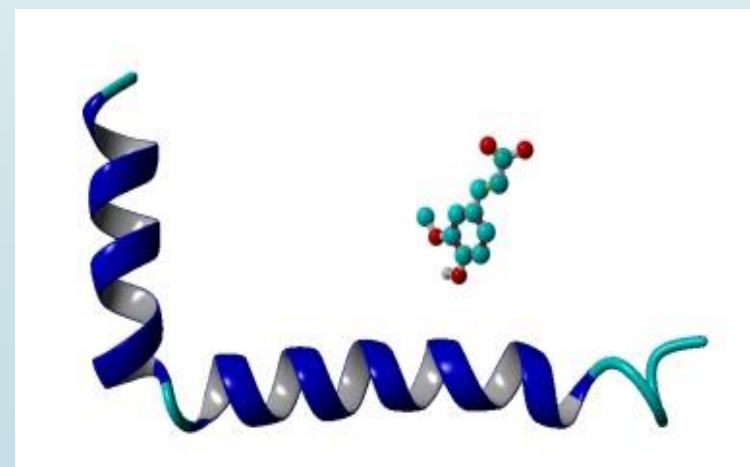
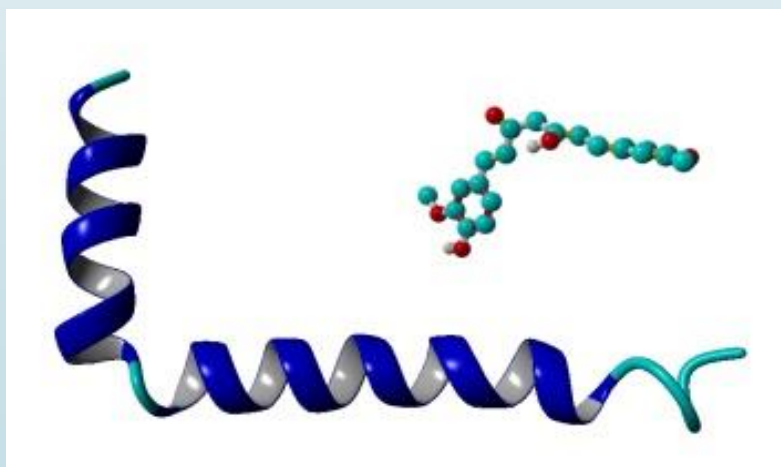
Първа задача: Моделни системи



Куркумин (CU)
 $IC_{50} = 0,8 \mu M$



Ферулова киселина (FA)
 $IC_{50} = 5,5 \mu M$





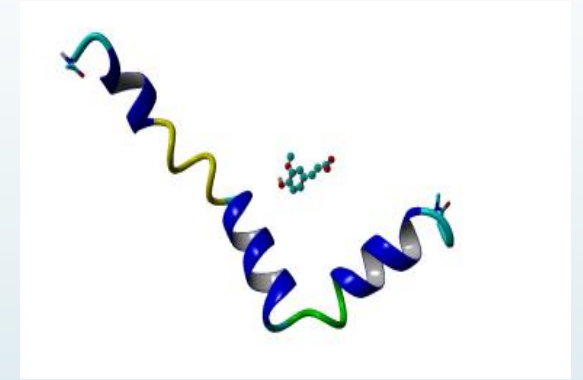
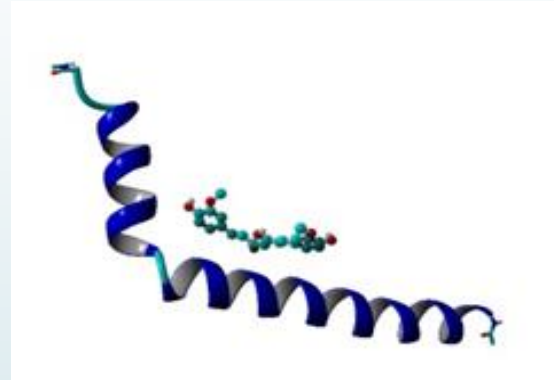
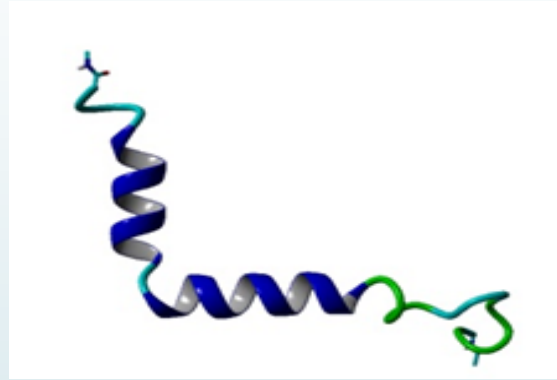
МД протокол

1. Системите са поставени в октаедрични кутии, солватирани с изотоничен разтвор на NaCl, при постоянни температура (310 K) и налягане (1 бар).
2. Първоначално енергията на системите е минимизирана за 5000 стъпки, последвана от загряване до 310 K (37°C) за 1 ns и еквилибриране при постоянно налягане.
3. Движението на системите е симулирано за 1000 ns при постоянни налягане и температура със стъпка от 2 fs.
4. Координатите на системите са записвани на всяка ns (1000 рамки).

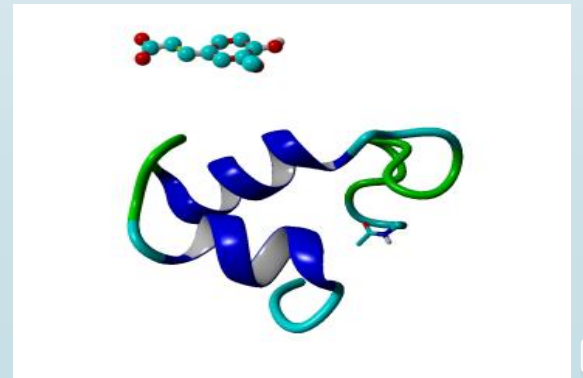
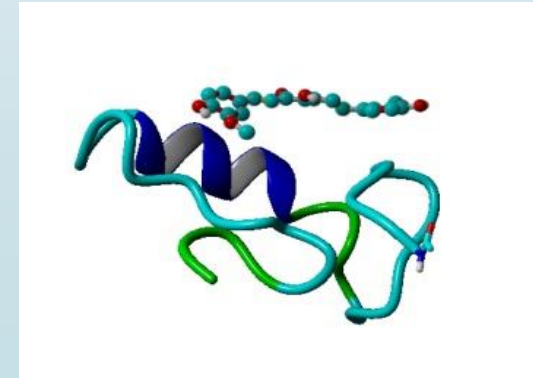
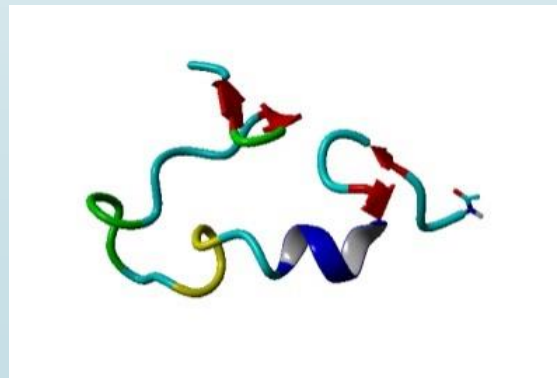


Резултати

1 ns

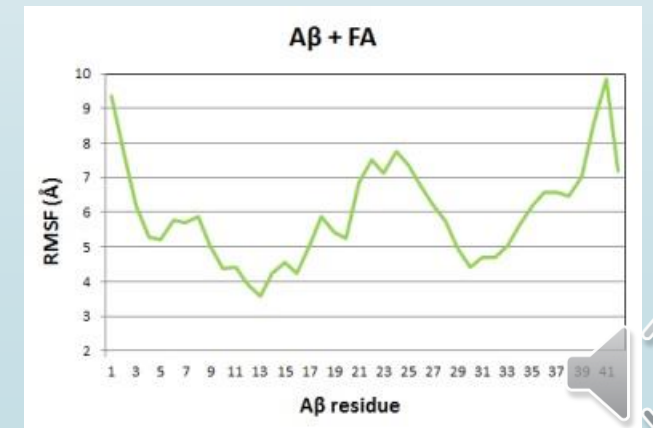
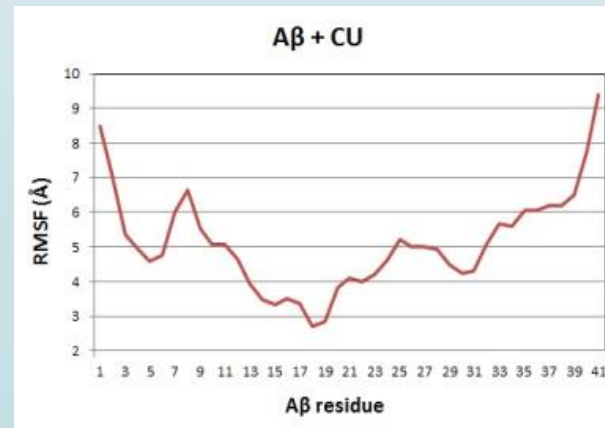
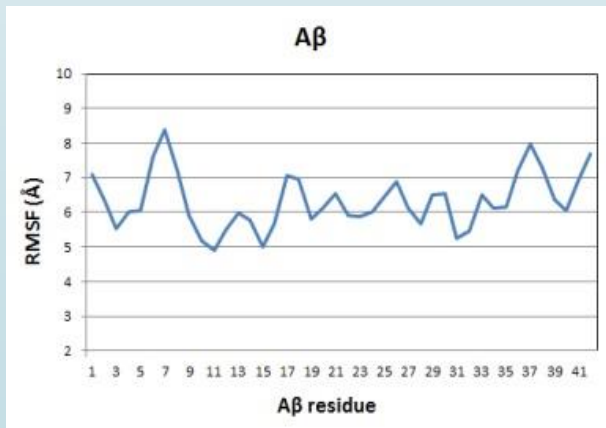
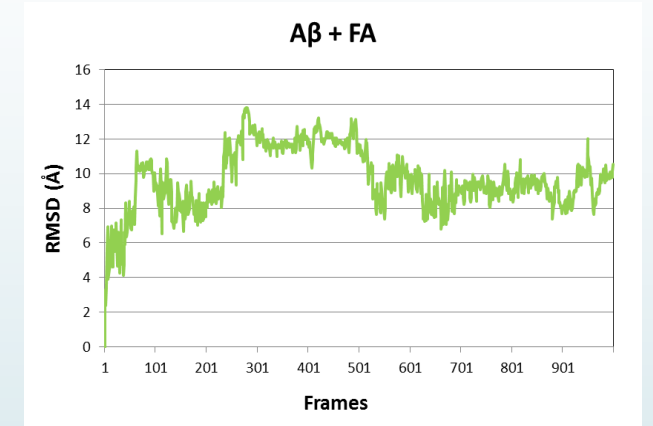
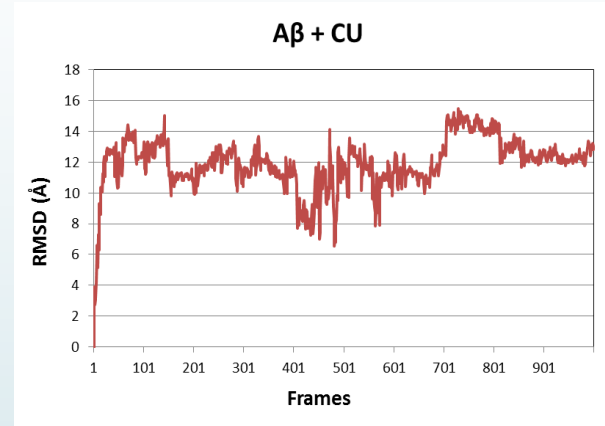
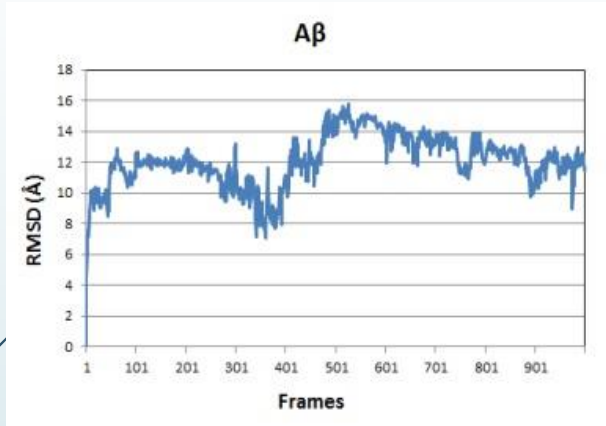


1000 ns





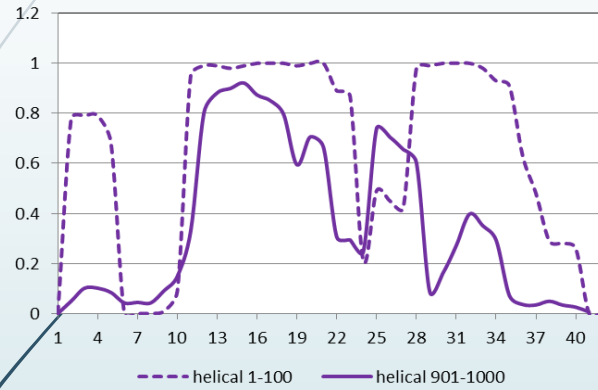
RMSD и RMSF



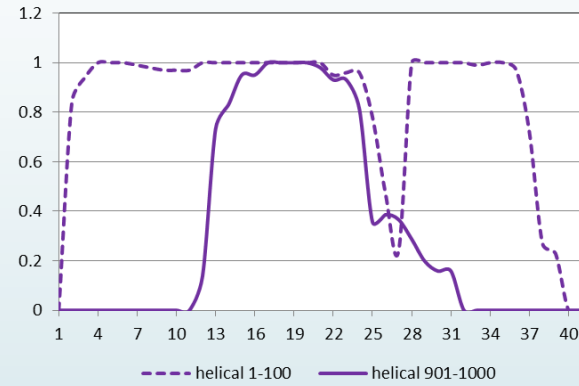
Вторична структура

helical

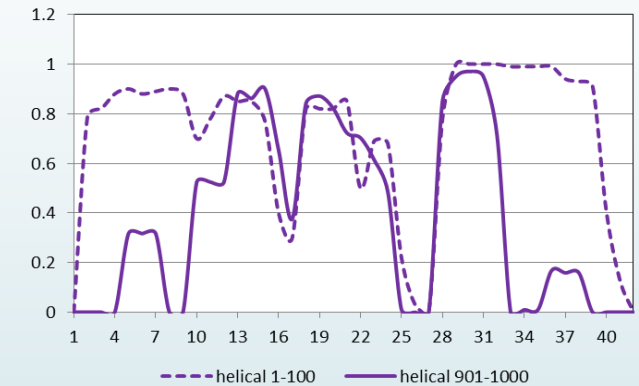
A β



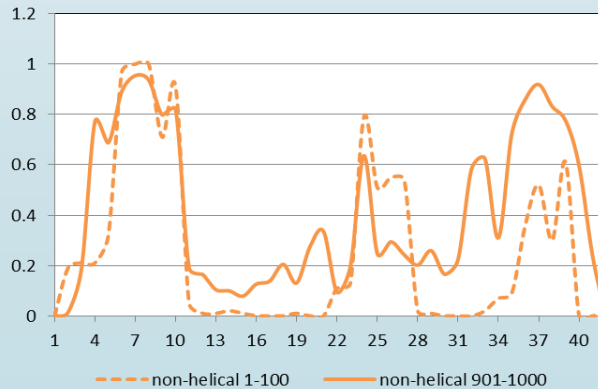
A β + CU



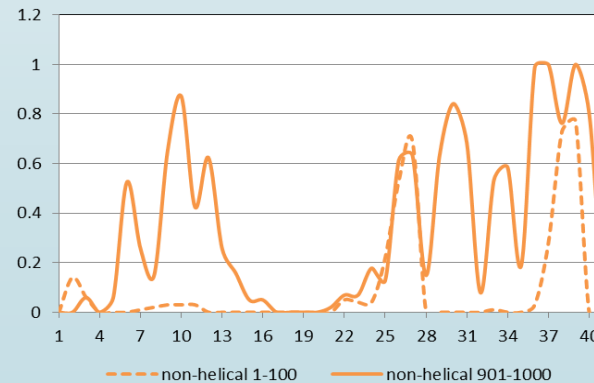
A β + FA



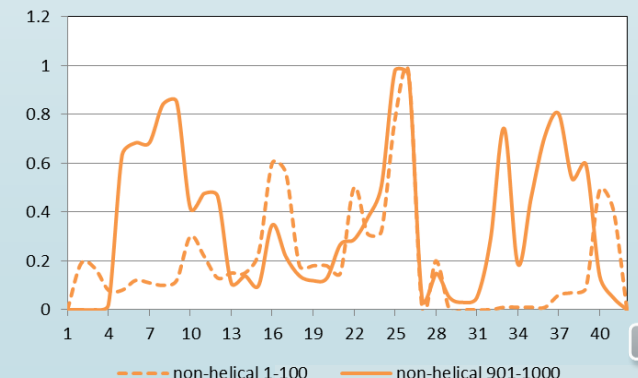
A β



A β + CU



A β + FA



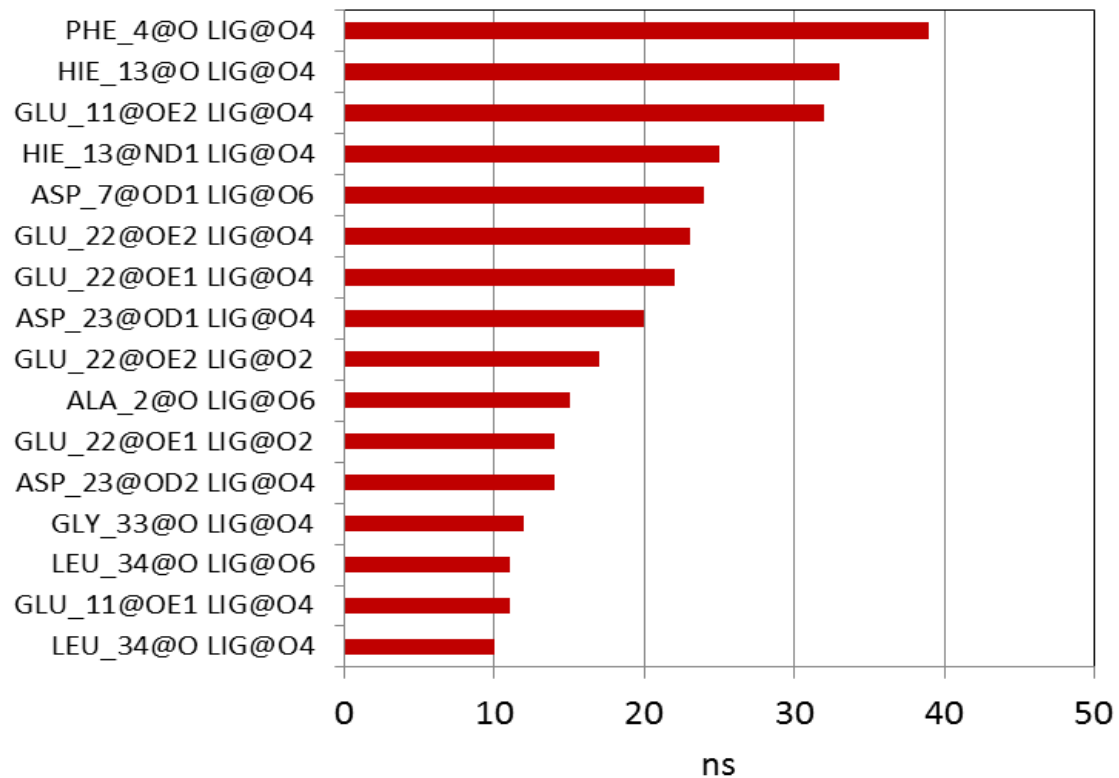
non-helical



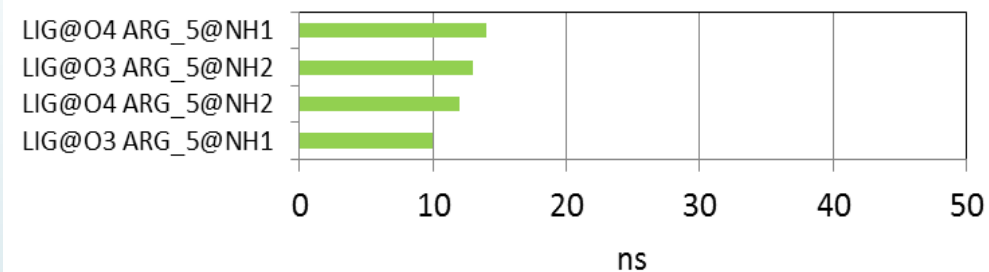


Водородни връзки

Aβ + CU

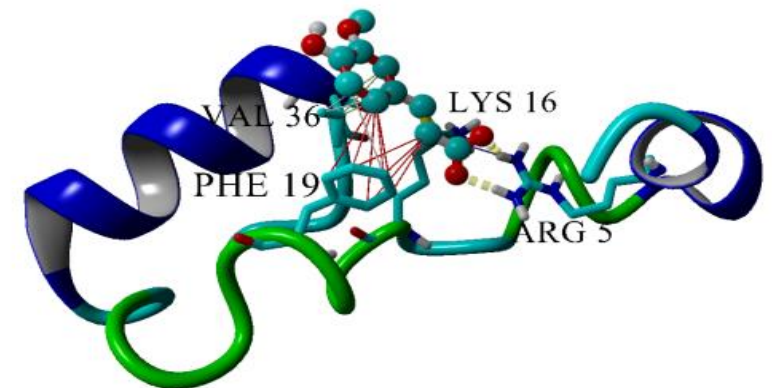
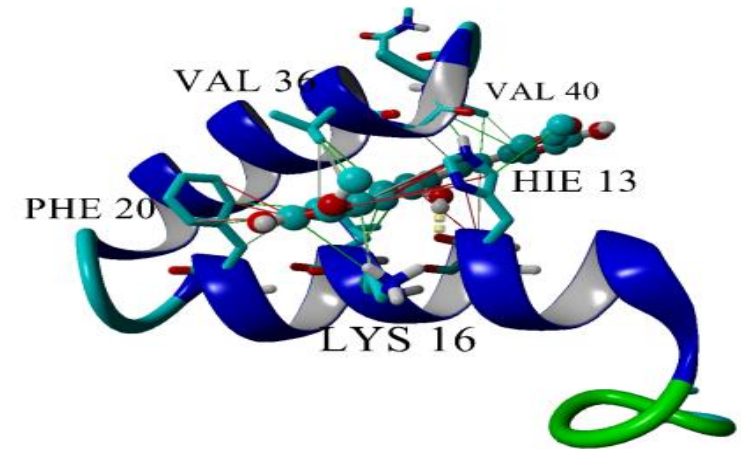


Aβ + FA



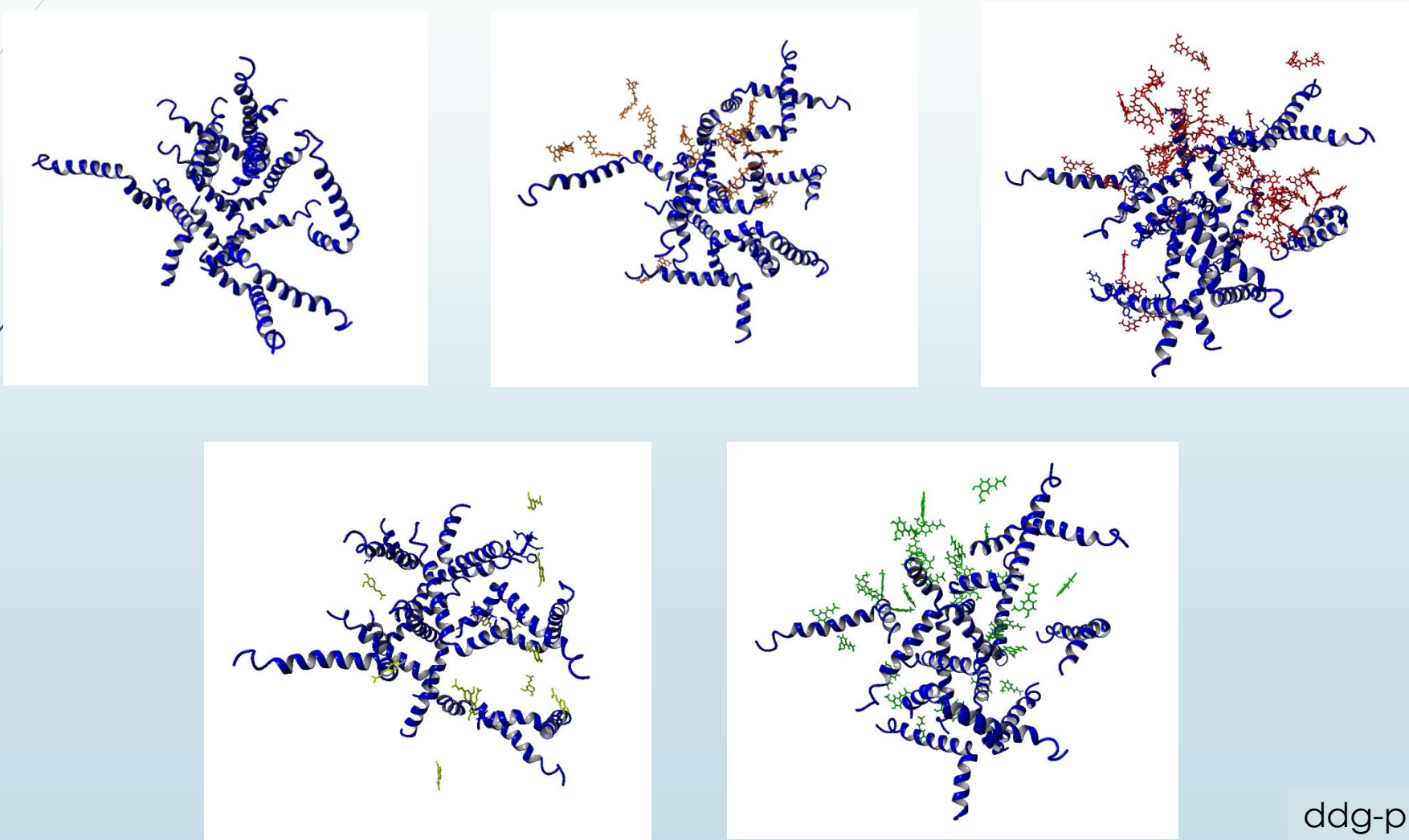
ИЗВОДИ

1. CU стабилизира структурата на A β за първите 50 ns, FA – за 700 ns.
2. И двата инхибитора увеличават склонността на пептида да заема спирална структура.
3. CU образува с A β повече на брой и по-дълго живеещи водородни връзки, отколкото FA.

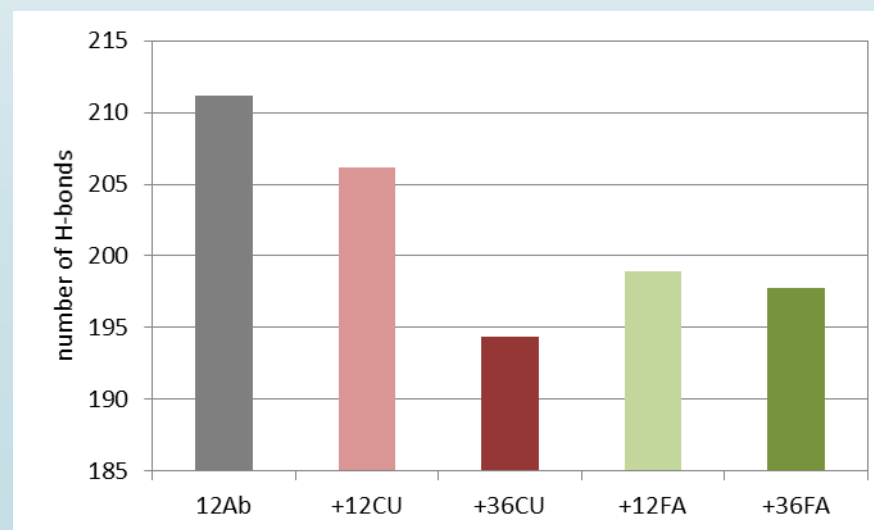
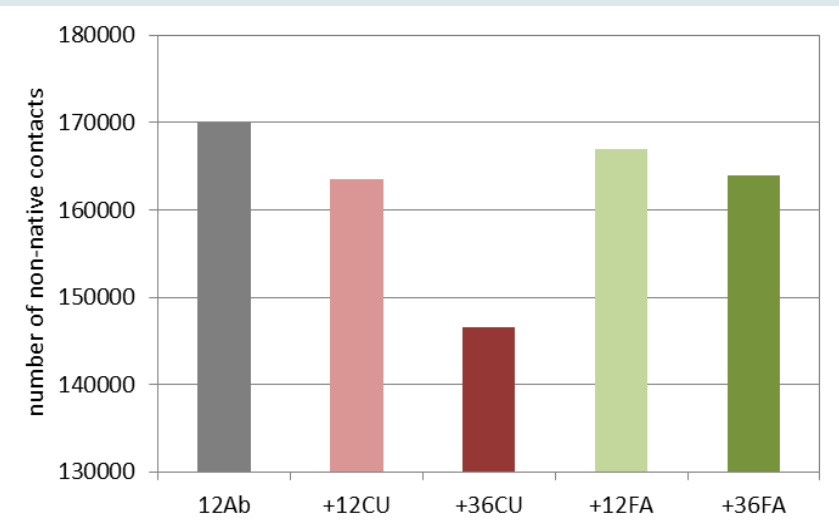
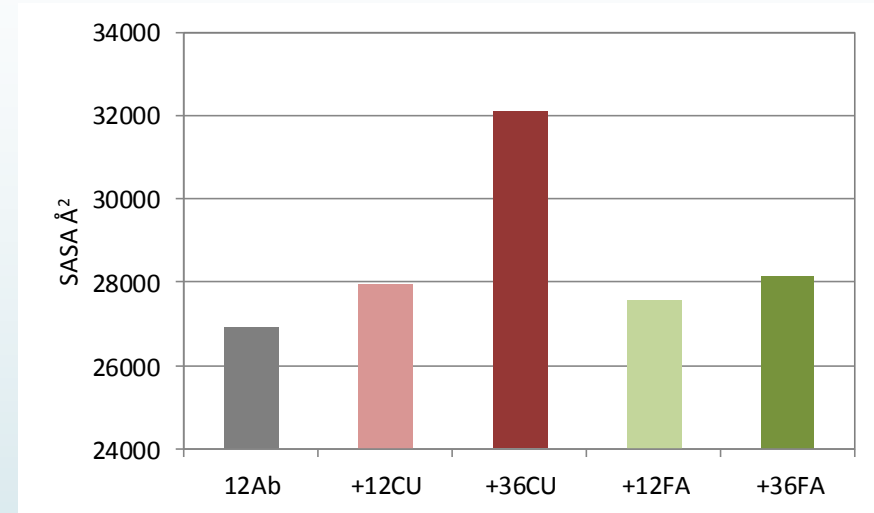
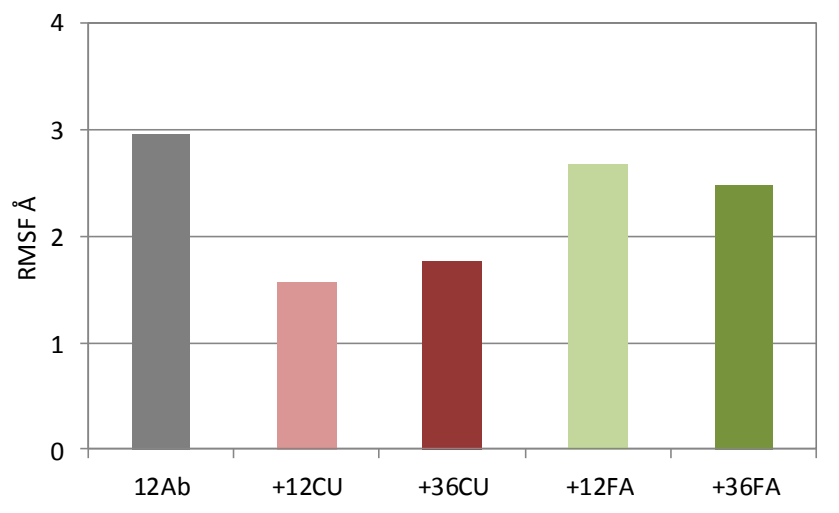




Втора задача: Моделни системи

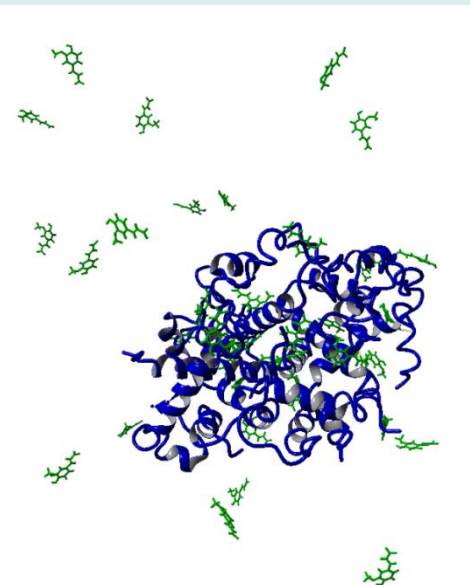
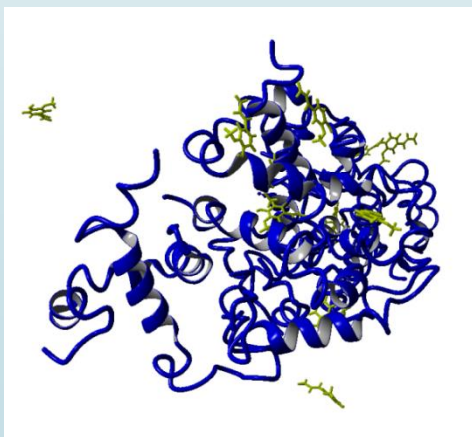
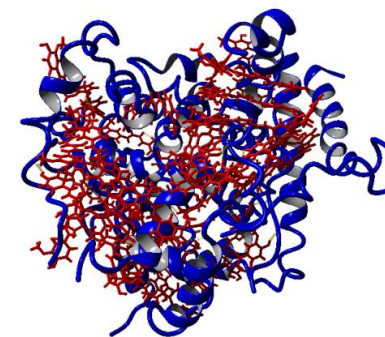
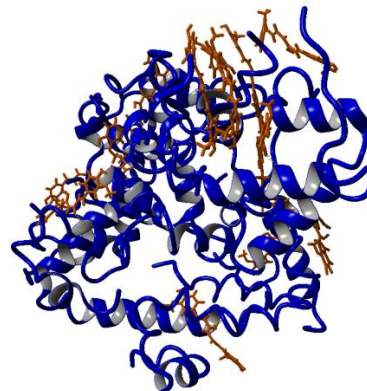
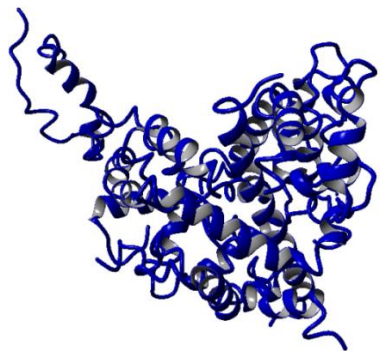


Резултати





1 μ s MD симулация





ИЗВОДИ

1. CU стабилизира структурата на ансамбъла от 12 A β молекули бързо и дозо-зависимо.
2. CU се свързва във вътрешността на ядрото от A β молекули и увеличава повърхността му.
3. CU намалява броя на водородните връзки и стеричните взаимодействия между A β молекули.
4. CU инхибира първичната нуклеация на A β молекули и по този начин забавя процеса на агрегация.





Публикации

1. Salamanova E, Atanasova M, Dimitrov I, Doytchinova I. Effects of curcumin and ferulic acid on the folding of amyloid-beta peptide. *Molecules* 26, 2815, **2021**.
2. Doytchinova I, Atanasova M, Salamanova E, Ivanov S, Dimitrov, I. Curcumin inhibits the primary nucleation of amyloid-beta peptide: a molecular dynamics study. *Biomolecules* 10, 1323, **2020**.





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Настоящото изследване се осъществява с финансовата подкрепа на МОН по Договор До1-221/03.12.2018 г. за НЦВРП – обект от НПКНИ.

