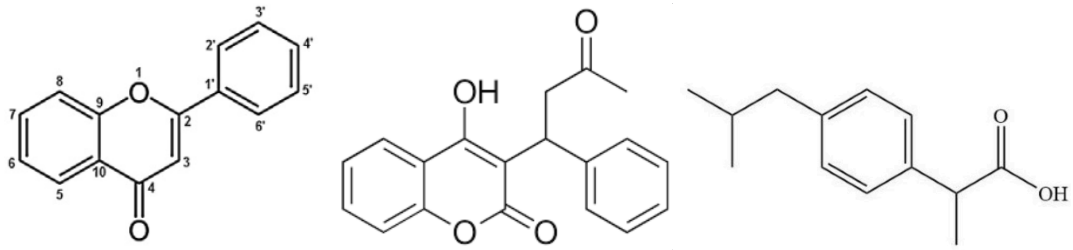
Homework: Docking

1.- Human serum albumin (HSA) is the main extracellular protein, and is highly concentrated, in blood plasma. HSA is a monomeric globular protein composed of three structurally similar domains (I, II and III). Aromatic and heterocyclic ligands bind to HSA primarily within two hydrophobic pockets named Sites 1 and 2, respectively. Site 1 is the primary binding site for drugs like warfarin (Scheme 2), whereas ibuprofen (Scheme 2) is bound primarily to Site 2.
We want to explore whether 2-Phenylchromone (2Phe; Scheme 2), a flavone found in cereals and herbs indispensable in the human diet, can be transported through binding to sites 1 and 2.



Scheme 2. Structure of (left) 2-phenylchromone, (middle) warfarin, and (right) ibuprofen.

1) Dock warfarin in site 1 of HSA using the X-ray structure of the warfarin-HSA complex (PDB ID 2BXD).
Can the redocking with AutoDock reproduce the experimental binding mode?
Is the experimental binding mode found in the best scored pose?
What are the main interactions that mediate the binding for the predicted pose?

2) Now dock 2Phe in HSA using the X-ray structure 2BXD.
Do you think the predicted binding mode is acceptable?
How does the predicted affinity of 2Phe compare with the affinity of warfarin?
Do the binding affinities of warfarin and 2Phe reflect in your view the interactions formed by these compounds?

3) Finally dock 2Phe in HSA in site 2 using the X-ray structure of the ibuprofen-HSA complex (PDB ID 2BXG).
Do you thing 2Phe may compete with ibuprofen for binding at site 2?