Master « Sciences, Technologie, Santé

Mention M2 -BI

In Silico Drug Design

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Internship Specialty: Docking molecular
Research / ~~private~~, ~~national~~ / international
Is this subject a first step towards a thesis work: ~~yes~~/~~no~~/maybe

Consider face-to-face or remote? Presentiel versus distanciel. It depends on the possibility of going to China or not.

Title:
A computational study on cannabinoid receptors and potent bioactive cannabinoid ligands: homology modeling, docking, de novo drug design and molecular dynamics analysis

PRESENTATION OF THE SUBJECT

The study of this internship revolved about cannabinoid compounds. The main aim was to work on the new enzyme found out in cannabinoid plant, the cannabis. The first step was to build a model of this new enzyme by homology modeling. Then, try to find its substrate among a set of data that contains only cannabinoids. This enzyme held our attention because it was discovered by the team that I will be integrated during my internship. Now, the study about this enzyme was limited by few studies in the literature concerning the oxidoreductase family catalyzing cannabinoids in plants. After making some researches, the literature only got the structure of the tetrahydrocannabinolic acid synthase (THCAS), the first cannabinoid enzyme studied, and the first that catalyzes terpenophenol biosynthesis. In recent years, researchers have discovered cannabidiolic acid synthase (CBDAS) and cannabichromenic

acid synthase (CBCAS). These three enzymes had in common the synthesis of product from cannabigerolic acid (CBGA).

The structure of THCAS was similar to CBDAS and CBCAS, which researchers had attempted to create a model by homology of CBDAS's structure. Studies have confirmed that THCAS had a cofactor, FAD, covalently bound in the catalytic site. The study of Sirikantarams showed that CBDAS need also the same cofactor to catalyze. These enzymes must have molecular oxygen and released product and hydrogen peroxide with 1:1 molar ratio (*S. Sirikantaramas & F. Taura. 2017*). Unlike THCAS and CBDAS, CBCAS does not need a cofactor and molecular oxygen to catalyze (*P. Romero and al. 2020*). THCAS induced the production of THCA (acid form), the precursor of the famous tetrahydrocannabinol, THC (basic form). The THC was a very well-known compound for its psychotropic properties. THC was generally found in drugs to be consumed by the respiratory route through smoke inhalation. CBDAS led to the formation of CBDA (acid form), the precursor of cannabidiol, CBD (basic form). This second cannabinoid was popular for having sedative effects but also a delaying action on the THC's effect. The last one, CBDAS produced CBCA (acid form), the precursor of cannabichromene, CBC (basic form)

CBGA was a cannabinoid precursor (CP) of THCA, CBDA and CBCA. CBGA was formed by the assembly of olivetolic acid (OA) and geranyl pyrophosphate (GPP) by the biosynthesis of the enzyme cannabigerolic acid synthase (CBGAS). The length of the two carbon chains (Figure 1) defined the combination for CBGA. The part occupied by GPP was defined the cis- or trans- conformation. The GPP was trans-shape, and the cis-shape-GPP named NPP with OA, the biosynthesis with CBGAS (same enzyme), produced the CBNRA (cis-CBGA) and having its own product.