INHIBITORY EFFECT OF β-CARYOPHYLLENE OXIDE AND *TRANS*-NEROLIDOL ON ENZYME ACTIVITY OF CYP3A4 – *IN VITRO* AND *IN SITU* STUDIES

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Sesquiterpenes are group of terpenes consisting of three isoprene units and fifteen carbons. They occur in human food, beverages, and they are inherent ingredients of spices. Moreover, they are the main component of plant essential oils widely used in folk medicines, cosmetics or pharmaceutical industry. We have determined the effect of four sesquiterpenes - β-caryophyllene oxide (CAO), α-humulene (HUM), *trans*-nerolidol (tNER) and farnesol (FAR) on activity of the most important enzyme of drug metabolism in humans, CYP3A4. Our results show, that both CAO and t-NER can inhibit enzyme activity of CYP3A4, however, with different substrates bound (substrate midazolam (MDZ), K_i = 46,6 μM; and substrate testosterone (TST), K_i = 32,5 μM, respectively). Molecular docking is useful tool for prediction of position of ligand and binding energy between active site of CYP3A4 and the respective ligands. In our project, we focused to study the position of CAO and MDZ in CYP3A4 as well as of the tNER and TST bound to the same enzyme, however, in two different places (binding site of MDZ and of TST). In the first case, the molecular docking has shown that binding of CAO in active site of CYP3A4 causes its inhibition (binding energy and position is better than for MDZ, see Figure 1 – left). In the case of tNER, this compound inhibits the CYP3A4 activity (TST hydroxylation) as this ligand binds to the active site typical for TST (shifted from active site, see Figure 1 – right).

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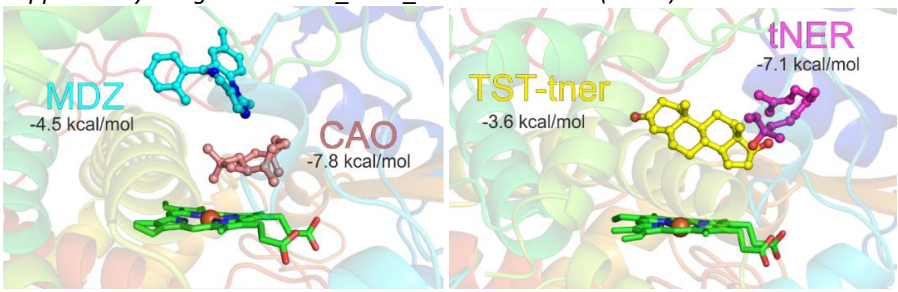

Figure 1. Left: position and binding energy position of β-caryophyllene oxide (CAO) and midazolam (MDZ). Right: binding energy and position of *trans*-nerolidol (tNER) and testosterone (TST).