Studies of the relationship structure-musky smell with G Protein-Coupled Receptors (GPCRs)

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ABSTRACT

Odorant receptors (ORs) are the largest subfamily within class A G protein-coupled receptors (GPCRs), Mammals detect and discriminate numerous odors via a large family of G protein-coupled odorant receptors (ORs). The objective of this study is to identify the odorous molecules by molecular docking. Ten molecules were examined, based on scores and the energy of the bonding interactions hydrogen. L1, L2, L3, L4 are odorant molecules.

Keywords: G Protein-Coupled Receptors (GPCRs), Interaction enzyme-ligand

INTRODUCTION

The fragrant organic molecules are used in most consumer products to encourage consumers to associate favorable impressions in a given product. The musky scent is in perfumery very important market because of their use in colognes, the scents, cosmetics, soaps and others. For a substance has fragrant properties, it must have a moderate molecular weight, low polarity, some water solubility, vapor pressure and a high lipophilic nature. However, it is not necessary for it to have any particular functional groups or is chemically reactive [1].Over the last thirty years, many theories have been advanced about the mode of interaction between odor molecules and olfactory neurons. Without developing include: vibrational theory originally advanced by Dyson[2] and recovery by Wright [3], that the diffusion of odor molecules through the membrane [4]; complexation with the carotenoids present in the epithelium [5] and yet the molecule for odor: the molecular basis of the first steps of olfaction [6].
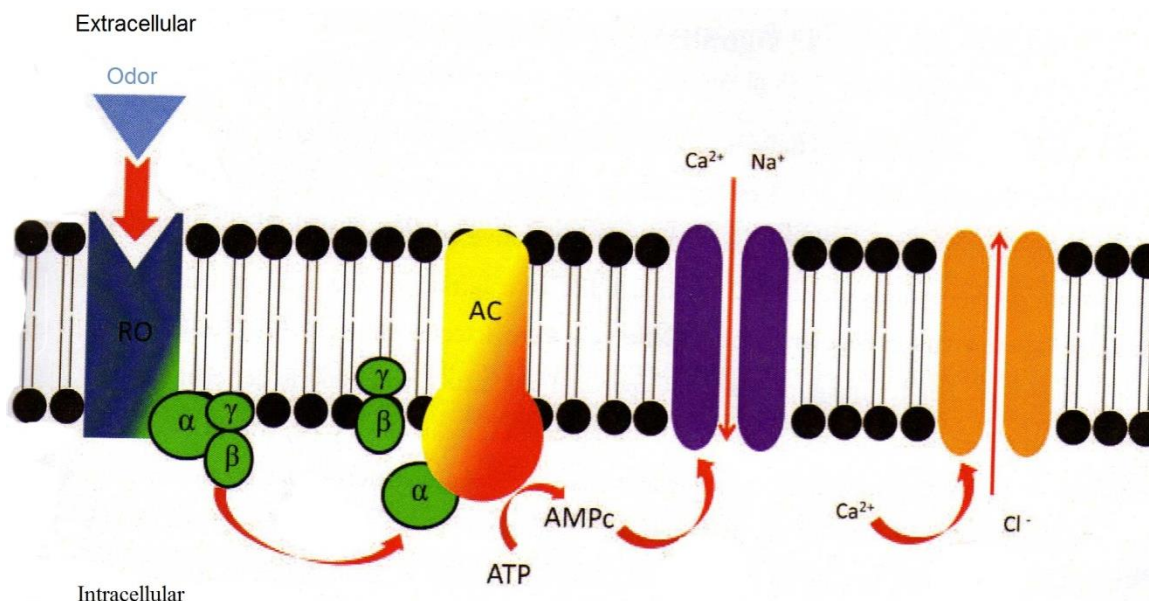
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Figure 1: Biochemical cascade to the depolarization of the membrane when the odor is complex RO

Olfactory receptor (OR) are transmembrane receptor coupled G-protein (G_{olf} named). This G-protein is composed of three subunits α, β and γ. The complexation of odor with the receiver will cause the activation of adenylate cyclase (AC) via the α subunit of the G protein [7]. The AC will then produce cyclic AMP from ATP. Three molecules of AMPc can complex with a $Ca^2{}^+$/ Na^+ channel, triggering its opening [8]. The passage of these ions in the neuron causes an increase in the Ca^{2+} ion concentration in the intracellular medium and the result is a depolarization of the membrane constituting the origin of the nerve impulses. A mode of depolarization alternative is however, possible under the effect of the activation of a channel to Cl^- thanks to the ions Ca^{2+} past in the intracellular environment. The depolarization is here created by the passage of Cl^- ions in the extracellular medium. The cations are in the mucus which renews itself constantly and their concentrations, therefore they are not as well-regulated as the ions contained in compartments. This second possibility therefore exists to compensate possible deficit of cations[9]

MATERIALS AND METHODS

Preparation of the structure of the protein

The crystal structure by X-rays of the G protein coupled to the receptor GPCR (PDB ID: 4J4Q)[10] was downloaded from the Protein Data Bank (PDB) is a repository for 3D structure data of large biological molecules[11].Molecular docking is a way to know the three-dimensional structure of macromolecules and understand their complexation mechanisms is fundamental to the understanding of biological systems, and essential in many
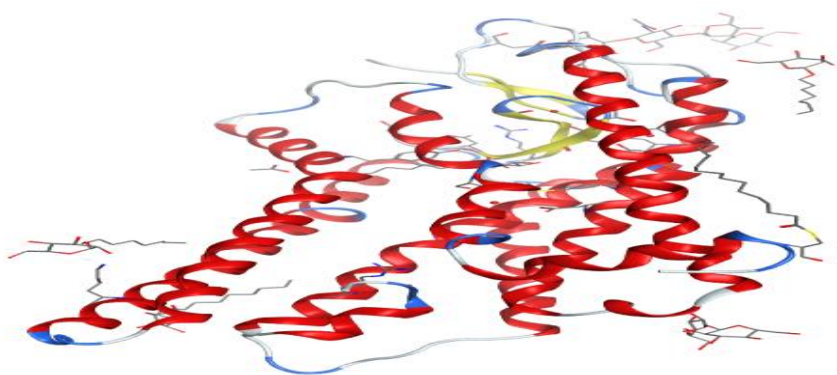
areas; Similarly, the discovery of new molecules activating or inhibiting the biological activity of a protein can be done by reading their respective affinity For this purpose, chemistry collaborates to structural biology which focuses in turn to the relationship between molecular structure and biological function.

Several program of docking (paying or free) are available[12], Among all these programs of molecular mooring; we used MOE (Molecular Operating Environment)[13]is that built three main menus:

- Optimize the positioning of the hydrogen atoms in the ATP binding pocket.
- Every crystal structure was subjected to protonated 3D; using the default settings.
- Subsequently, the co-crystallizing which does not interaction with the chain have been deleted.

Structure of the ligands

For our study we took the "nitro musk" ligands synthesized by Carpenter, Wood and Easter[14]. To confirm or not their experience we made a theoretical study based on molecular docking; which are represented in the following table (Table1) We have kept the skeleton of m-xylene and we have changed the different substituting:
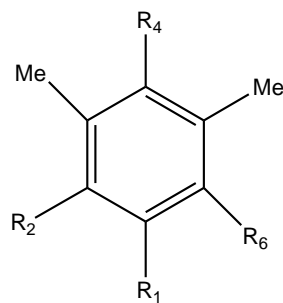
Figure-1 : the skeleton of m-xylene

Table-2: substitution and musky odor in the family "m-xylene"

Ligands	R1	R2	R4	R6	Odor
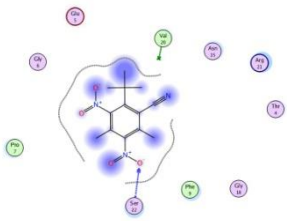
L1	tBu	CN	NO$_2$	NO$_2$	Musk
L2	tAm	NO$_2$	NO$_2$	NO$_2$	Musk
L3	tAm	NO$_2$	Me	NO$_2$	Musk
L4	tAm	NO$_2$	COMe	NO$_2$	Musk
L5	tBu	NO$_2$	Me	CHO	Not Musqué
L6	tBu	NO$_2$	OMe	-	Not Musqué
L7	tBu	Br	Br	NO$_2$	Not Musqué
L8	tBu	COPh	NO$_2$	NO$_2$	Not Musqué
L9	tBu	Me	Me	NO$_2$	Not Musqué
L10	Me	NO$_2$	NO$_2$	NO$_2$	Not Musqué
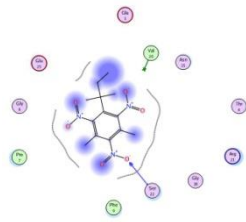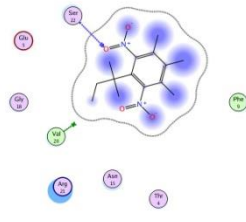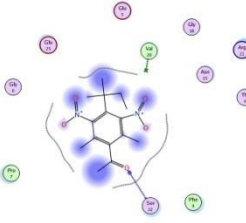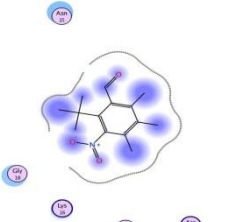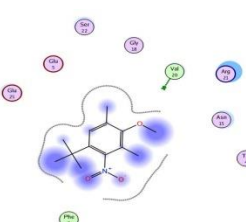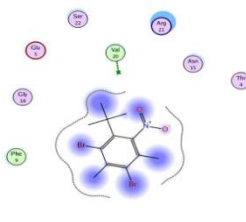
RESULTS AND DISCUSSION
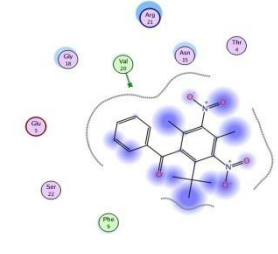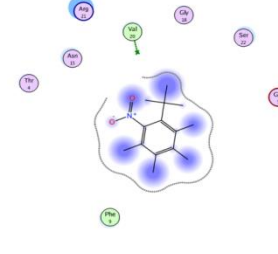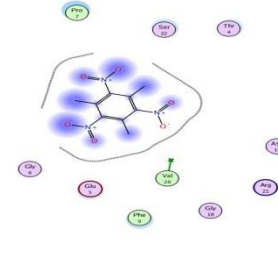
Interaction enzyme-ligand

According to the software Help MOE, the calculations relating to the energy of the score and distance of the bonds formed between the enzyme cavity and the ligand results are presented in the following Table 2:

Table-3: Results of score Enzyme - ligands

Ligands	Score	RMSD Refine	Distance	Energie de la distance (Kcal/mol)	Liaisons hydrogen
L1	-3.7898	2.1604	3.27	-2.1	

L2	-3.7097	1.7288	3.20	-2.4	
L3	-4.0526	2.4115	3.03	-3.7	
L4	-3.9110	1.7885	3.19	-2.7	
L5	-3.8509	1.1318	-	-	
L6	-3.8064	1.4004	-	-	
L7	-3.7471	2.0900	-	-	

L8	-3.7360	1.8817	-	-
L9	-3.7422	1.6973	-	-
L10	-3.4770	1.3921	-	-

Figure-2: The structure of the complex: enzyme (4J4Q) with inhibitor (L2)

According to the results obtained (table 02), we noticed that the bonds formed by the four ligands L1, L2, L3, L4; form interactions with residues of the active site of the receptors, olfactory (with amino acid Ser 22); However different ligands: L5, L6, L7, L8, L9, L10. Have no interaction with the active site of the receptors olfactory. From the results of the molecular docking obtained, it can be seen that the energies of the inhibitors L1, L2 and L4 are of the same order. This can be explained by the

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presence of strong attracting groups such as (-NO 2, -CN and -COMe) which destabilizes the aromatic ring. On the other hand, the inhibitor L3 is stabilized by donor groups (3 groups -Me, t-Am) and has the lowest energy, it is probably the best inhibitor.

Interactions between 2.5Å and 3.1 Å are considered to be strong; and those between 3.1 Å and 3.55 Å are supposed to mean; higher than 3.55 Å interactions are weak or absent[15].The distances between the active site residues and L1; L2; L3; L4 varies between 3.03Å and 3.27Å.It noted that much of the distance belong to the range of medium or strong interactions[15]. So our results confirm the work of Carpenter et al[14]. The ligands L1; L2; L3; L4 form stable complexes; However the other ligands (L5, L6, L7, L8, L9, L10) have no interaction with the enzyme.
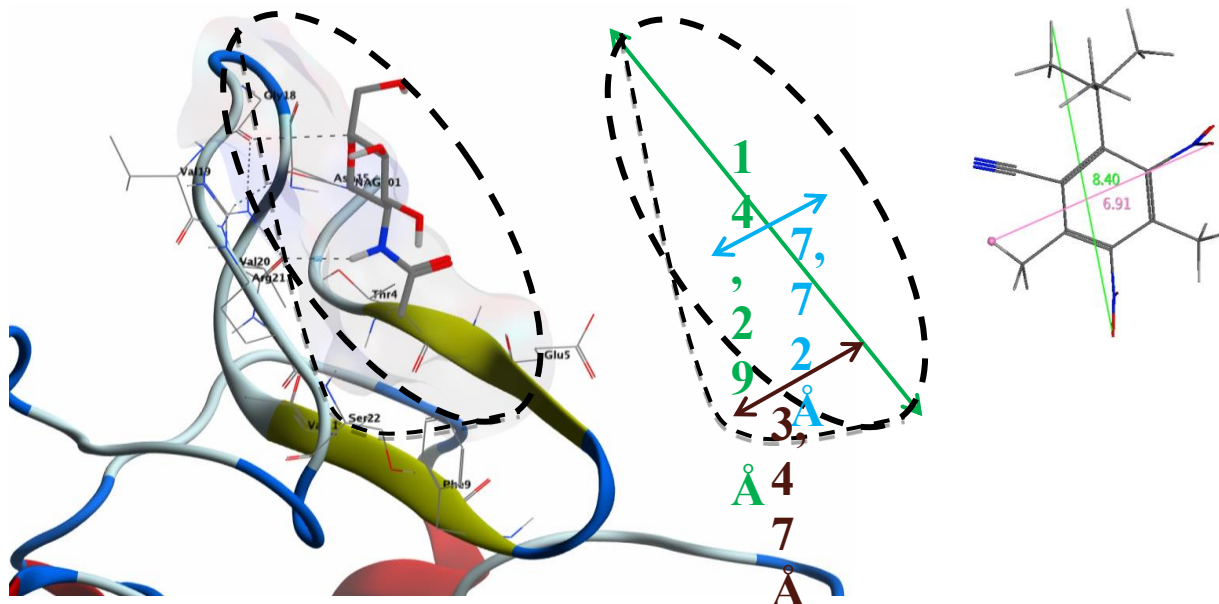

Figure-3: Dimension of enzymatic cavity and ligand

Examination of the enzymatic cavity, and calculates the distances between the inhibitor and the side chains of the constituent amino acids of the active site and the computed energies, confirm that the inhibitors show a greater complementarity with the enzyme study (Figure 5).

CONCLUSIONS

According to the results of theoretical calculations of the energies of the complexation of the Ligands with the olfactory enzyme, musk odorant[14] form interactions with the enzyme molecules are fragrant however other musk and non-odorous molecules has no interactions with the enzyme.

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