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Inhibitors of Salicylic Acid Binding Protein 2 (SABP2) Design by Docking and Molecular Dynamics

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Abstract: Since plants are susceptible to biotic and abiotic attacking, they present short and long-term defense mechanisms that are mediated by several signaling molecules, such as salicylic acid (SA) [1]. However, the signal to distal plant regions is not driven by SA, but through methyl salicylate (MeSA) molecule. The MeSA is generated in a reaction catalyzed by SABP2 (catalytic site formed by Ser81, Asp210 and His238), which converts SA into MeSA at the damage site, and then allows the stress message to be carried to distant spots, where MeSA is converted back to SA [2]. The briefly described mechanism related to SA, MeSA and SABP2 plays a central role on plants physiology and SABP2's inhibitors development can be an interesting strategy on molecular design for agriculture and biotechnology applications, for instance for the improvement of *Vitis vinifera L.* plantations. Therefore, the aim of this present study is to describe and to compare the interactions of different SA analogues with SABP2. The structures for 58 SA analogues molecules were built with Gauss View [3], the protonation degree was determined with Marvin Sketch [4], and the optimization step was conducted with Gaussian 09 by using *ab initio*, Hartree-Fock 6-31G (d,p) calculations [5]. Protein (SABP2) structure, PDB-ID 1Y7I, was obtained from Protein Data Bank, https://www.rcsb.org/pdb/home/home.do, and its protonation pattern checked with online software PROPKA, http://propka.org/ [6]. Docking analysis was done through AutoDockVina (grid of 20 x 20 x 20 Å) [7], while molecular dynamics has been performed with Gromacs package (TIP3P water model, Amber force field, pH = 7,00 and temperatures of 278 K, 288 K and 298 K) [8]. The protonation degree analysis of the 58 molecules generated 100 relevant species to be tested. Docking analysis pointed 31 species with favorable scores (when the energy for interaction between SA analogue and SABP2 is more negative than that for SA and SABP2) and positioned at enzyme active site. The best score was found for 1-(1H-Tetrazol-5-yl)-2-chlorobenzene, - 8.6 $kcal.mol^{-1}$, while that for SA is - 6.7 $kcal.mol^{-1}$. However, this molecule is halogenated, being not a good choice because its environmental effects. Hence, for molecular dynamics the selected SA analogue was the second best 2-(1H-Tetrazol-5-yl)phenol, which presented a score of - 7.8 $kcal.mol^{-1}$. Currently, the molecular dynamics tests are under way. A brief analysis of root mean square

fluctuation (RMSF) at active site residues for 10 ns showed an increase for Ser81 and a decrease for Asp210. Additionally, it was possible to observe an elevated number of hydrogen bonds at active site region for 10 ns.

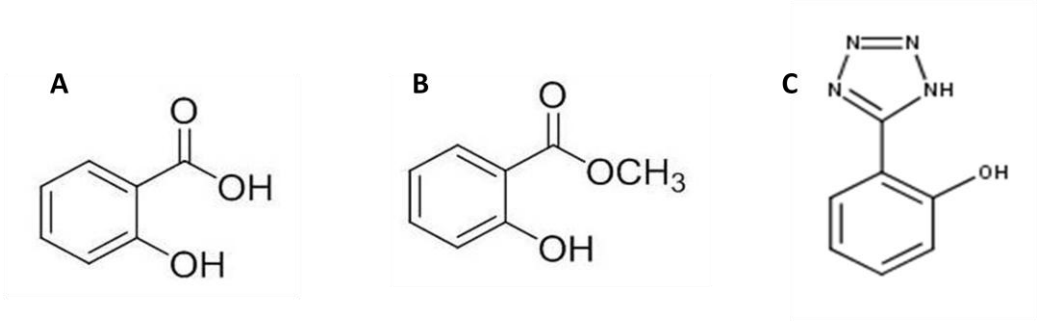

Figure 1. A. Salicylic acid. B. Methyl salicylate. C. 2-(1H-tetrazol-5-yl)phenol.

Key-words: Docking. Molecular dynamics. SABP2. Salicylic acid.
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