I CONGRESSO INTERNACIONAL DE BIOLOGIA CELULAR E MOLECULAR
X CURSO DE INVERNO

IN SILICO PROSPECTION OF O-ACETYLSERINE (THIOL) LIASE INHIBITORS

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Introduction

Due to repetitive and indiscriminate use of one or few herbicides with the same mechanism of action, weeds have developed resistant genotypes. Research and development of new molecules with new targets can bypass this unavoidable evolutive feature of living beings. The enzyme *O*-acetylserine(thiol)lyase (OAS-TL) is responsible for the assimilation of sulfur in plants, an essential macronutrient for plant metabolism.

Objective

Using the OAS-TL enzyme structure to virtual screening (VS) simulations for inhibitor candidates.

Materials and methods

We employed the structure of OAS-TL from *Zea mays* complexed with its substrate *O*-acetylserine and the cofactor pyridoxal-phosphate to VS.

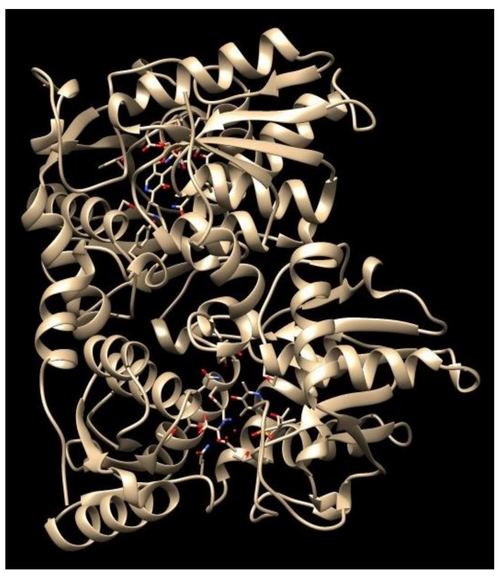

Figure 1: Three-dimensional structure of corn O-acetylserine(thiol) lyase (OAS-TL) (homodimer) modeled with O-acetylserine substrate (OAS) and pyridoxal-phosphate cofactor (PLP). FOLETTO-FELIPE, 2021.

Using Vina and Autodock-4 programs using Acros Organics® library of molecules filtered by Lipinski rules with a ClogP interval between -0.4 and 3.0.

Results and discussion

Comparing bound energy of the 4949 candidates with that of the substrate we found four compounds (ZINC16892208, ZINC149993, ZINC159056 and ZINC2562555) with higher affinity to the target enzyme. All five compounds attended ADMETox criteria, indicating that they are likely not toxic to mammalian cells and tissues. Neither of these candidates have been described as inhibitors of the target enzyme.

Results and discussion

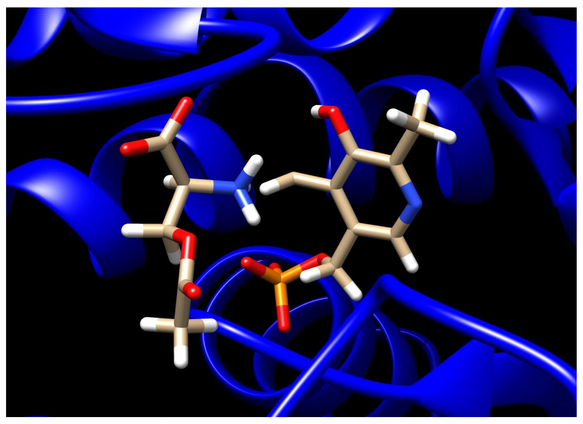

Figure 2: Active site

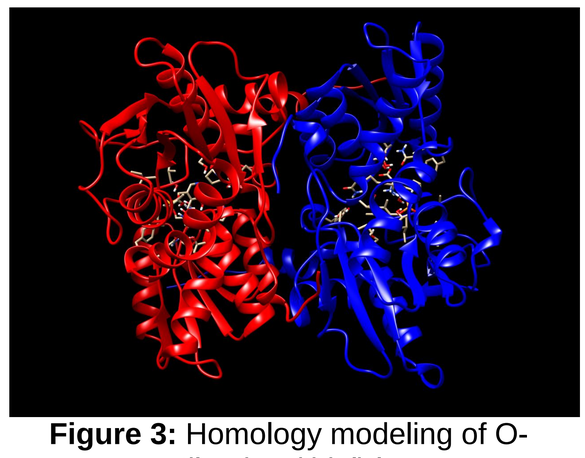

Figure 3: Homology modeling of O-acetilserine (thiol) lyase

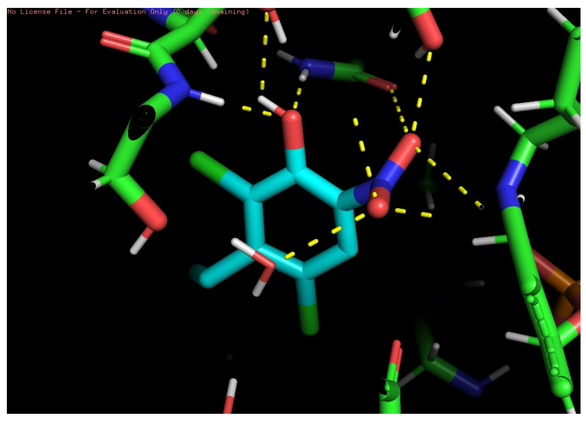

Figure 4: Ligand ZINC000002562555
Vina: -6,6
Autodock: -7,85

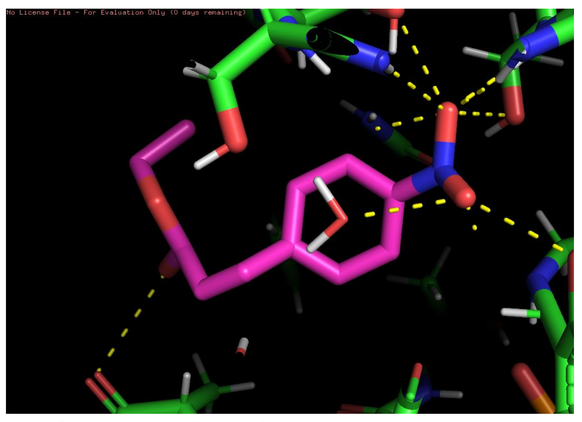

Figure 5: Ligand ZINC000016892208
Vina: -6,9
Autodock: -7,68

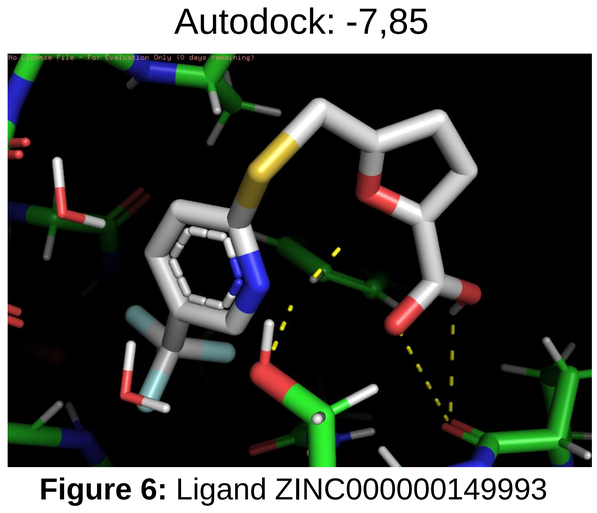

Figure 6: Ligand ZINC000000149993
Vina: -6,6
Autodock: -7,33

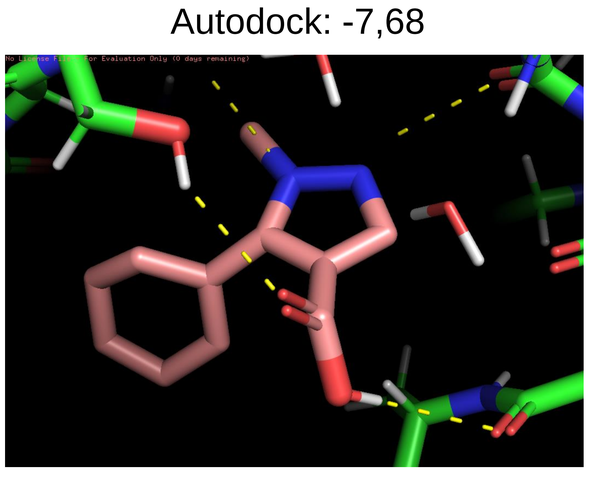

Figure 7: Ligand ZINC000000159056
Vina: -6,9
Autodock: -7,9

Conclusion

The results obtained in the double-checked scans indicate that the selected molecules have potential to work as inhibitors of OAS-TL. To validate the results, we now will submit these compounds kinetics and in vivo studies.

Acknowledgments

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References

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