



MOLECULAR DOCKING STUDY ON THE INTERACTIONS OF MYCLOBUTANIL ENANTIOMERES WITH ENZYMES BELONGING TO SOIL MICROORGANISMS

Diana Larisa Roman^{1,2}, Mariana Adina Matica³, Alecu Ciorsac⁴, Bianca Vanesa Boros^{1,2}, Adriana Isvoran^{1,2}

¹Biology-Chemistry Department, Faculty of Chemistry, Biology, Geography, West University of Timisoara, Str. Pestalozzi 16A, Timisoara, Timis, 300115, Romania

²Advanced Environmental Research Laboratories, West University of Timisoara, Oituz 4, Timisoara, Timis, 300086, Romania

³Department of Chemistry-Biology, Institute for Advanced Environmental Research, West University of Timisoara, Oituz 4C, Timisoara, Timis, 300086, Romania

⁴Department of Physical Education and Sport, University Politehnica Timis, oara, 300006 Timisoara, Romania

Abstract: The use of pesticides, although needed to protect crops and increase production, represents an environmental and human health issue. Myclobutanil is a chiral triazole fungicide widely used for the protection of crops against fungal diseases. This study focused on molecular docking regarding the interactions of the enantiomers of myclobutanil with enzymes belonging to soil microorganisms in order to assess the possible enantioselectivity of the interactions. In our study we have taken in consideration the enzymes: (i) dehydrogenases belonging to *Aspergillus fumigatus* and to *Rhizobium leguminosarum*; (ii) phosphatases belonging to *Aspergillus niger* and to *Rhizobium leguminosarum*; (iii) proteases belonging to *Aspergillus clavatus* and to *Rhizobium leguminosarum*; (iv) catalases belonging to *Komagataella pastoris* and to *Rhizobium meliloti*; (v) ureases belonging to *Aspergillus fumigatus* and to *Rhizobium leguminosarum*. Molecular docking outputs showed that both enantiomers of myclobutanil were able to bind to the active sites of dehydrogenases, phosphatases and proteases, with higher interacting energies observed for (*S*)-myclobutanil, the enantiomer known to be less active against target organisms but having a higher toxicity against non-target organisms. The results of our study confirm the need to implement better management practices regarding the use of myclobutanil by using the enantiomer that is most effective on target organisms and less toxic to non-target organisms.

• Introduction

Pesticides are chemicals that include a wide range of compounds, the main categories being represented by herbicides, fungicides and insecticides. Among pesticides, the class of triazole fungicides is essential to agriculture and food safety, being used to protect crops against yeast and mildew, their target organisms. The presence of triazoles in the environment may influence not only the target species (fungi) but all kingdoms as well due to their nonspecific interactions with enzymes belonging to the cytochrome P450 family, resulting in the non-target effects of these fungicides.

• Results and discussions

• Material and method

- Protein Data Bank;
- UniProt;
- Chimera;
- SwissDock.

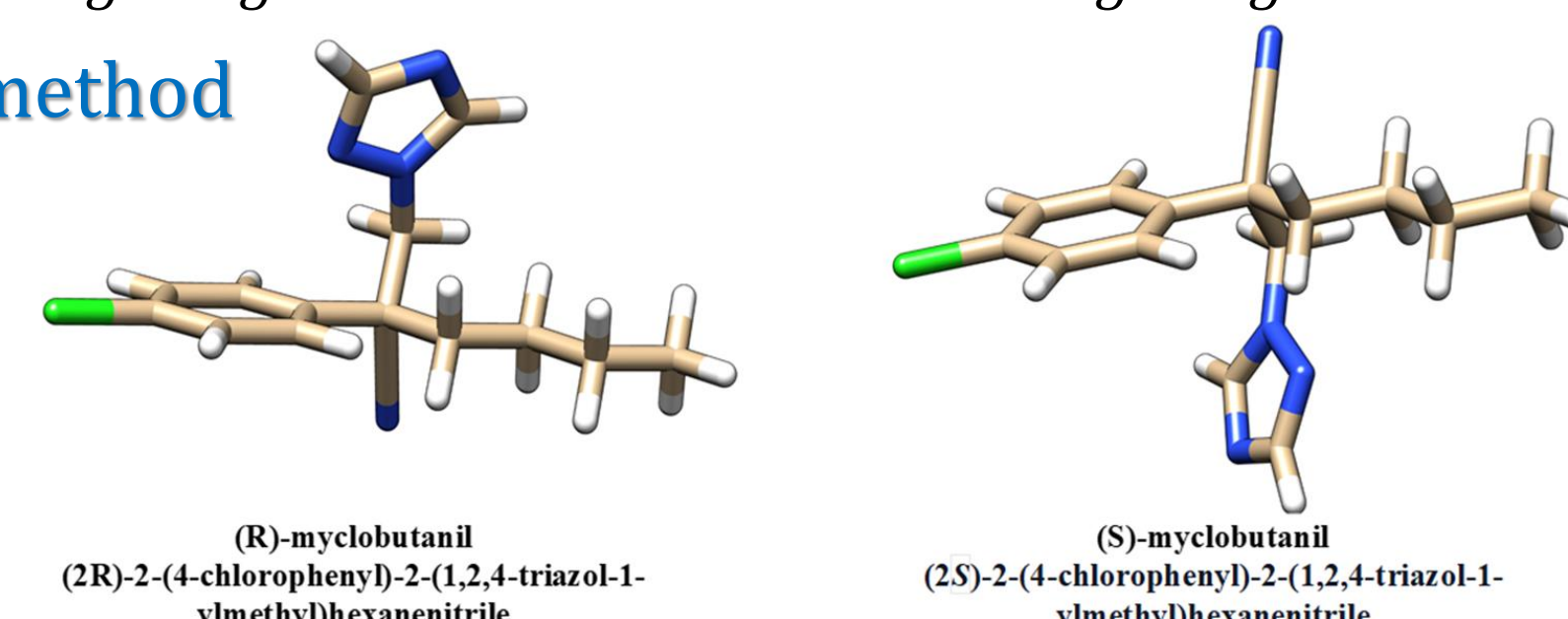


FIG 1. 3D structures and IUPAC names of the stereoisomers of myclobutanil: nitrogen—blue, carbon—brown, chloride—green, hydrogen—white

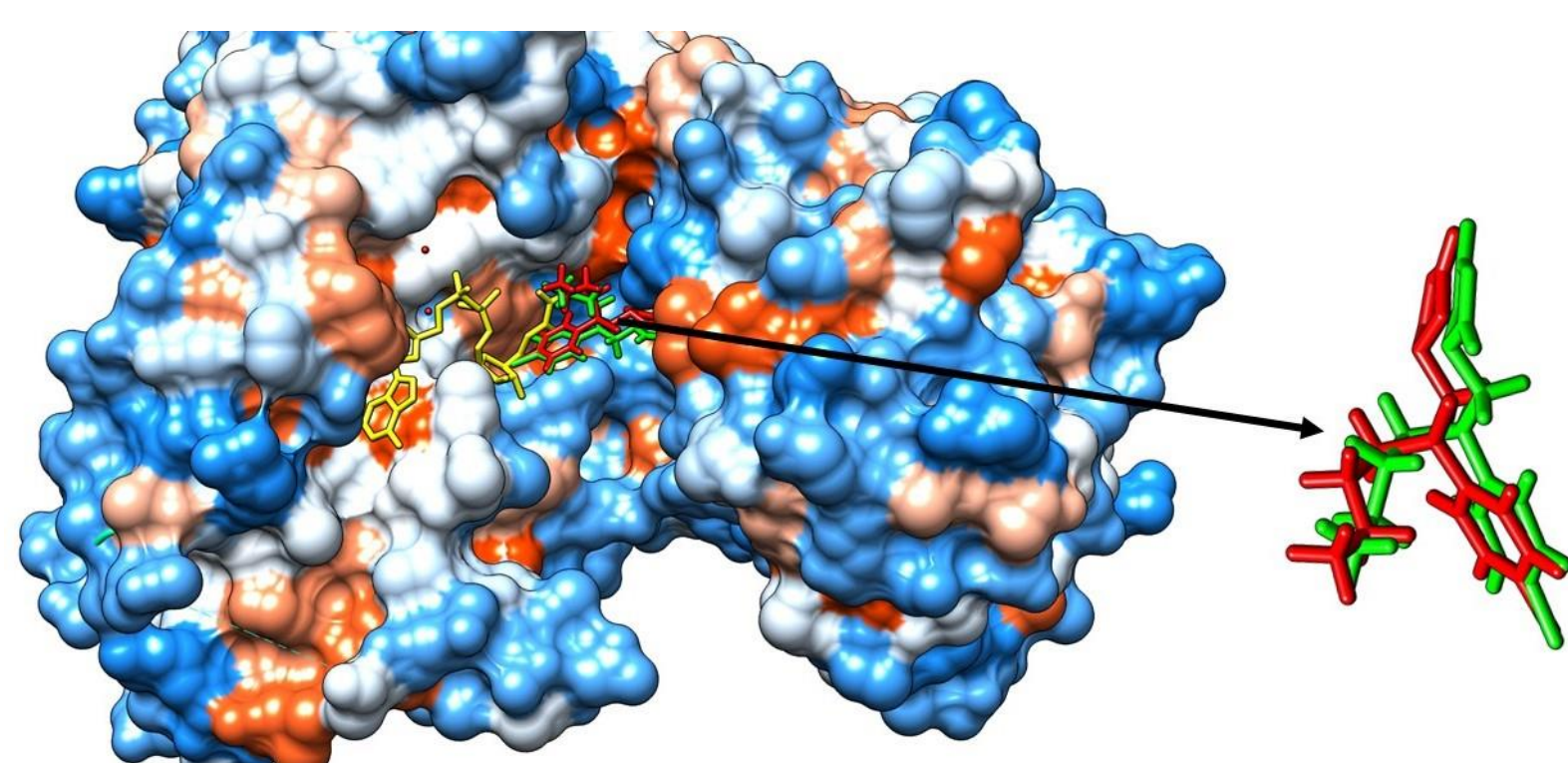


FIG 2. Binding of (*R*)-myclobutanil (red sticks) and of (*S*)-myclobutanil (green sticks) to the active site of *Aspergillus fumigatus* DA (PDB ID 7RK5) (solid hydrophobicity surface, blue regions are hydrophilic and orange regions are hydrophobic). The substrate 1,4-dihydropyridine adenine dinucleotide (yellow sticks) illustrates the position of the active site.

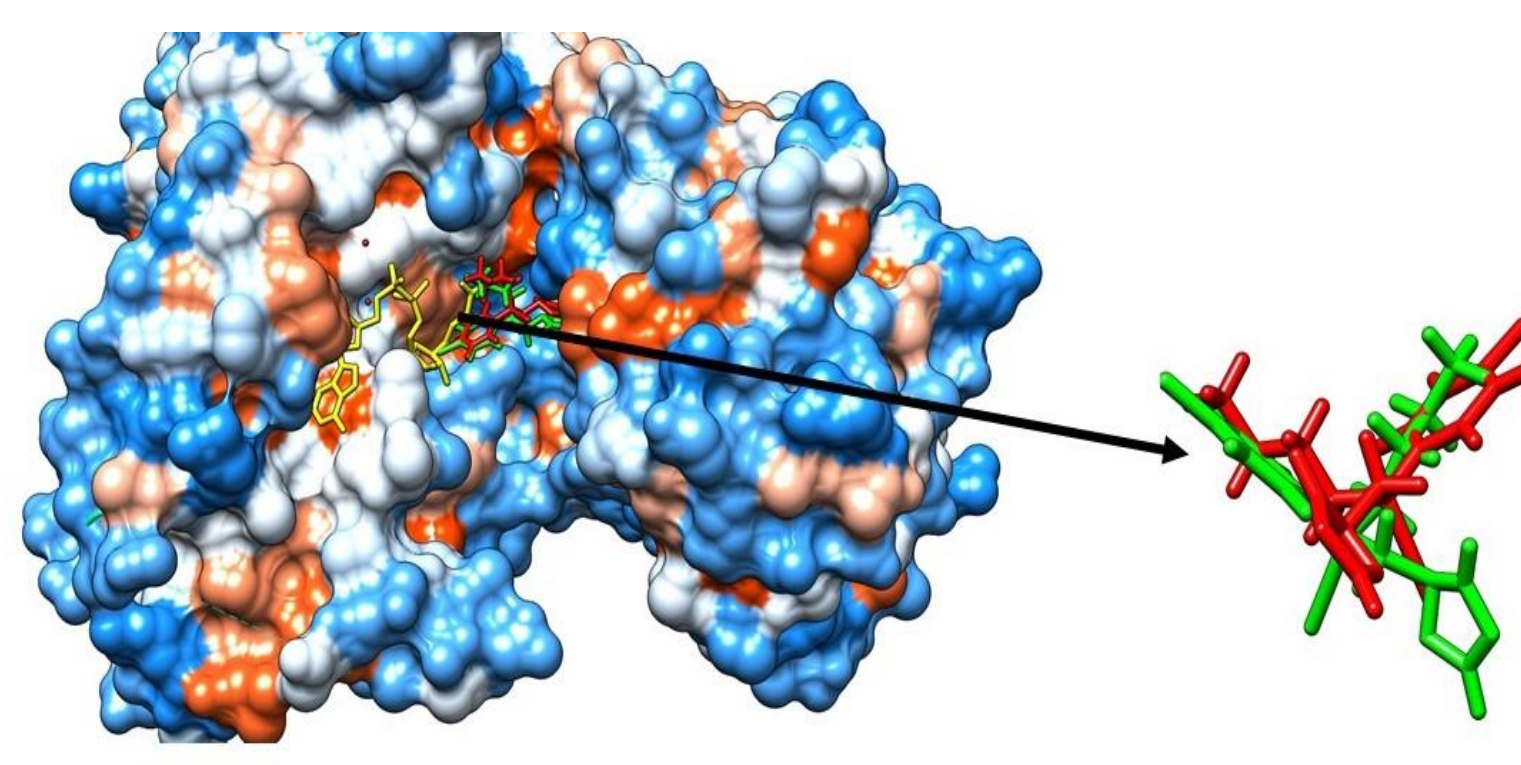


FIG 3. Binding of (*R*)-myclobutanil (red sticks) and of (*S*)-myclobutanil (green sticks) to the active site of *Rhizobium leguminosarum* DA (PDB ID 8C54) (solid hydrophobicity surface, blue regions are hydrophilic and orange regions are hydrophobic). The substrate 1,4-dihydropyridine adenine dinucleotide (yellow sticks) illustrates the position of the active site.

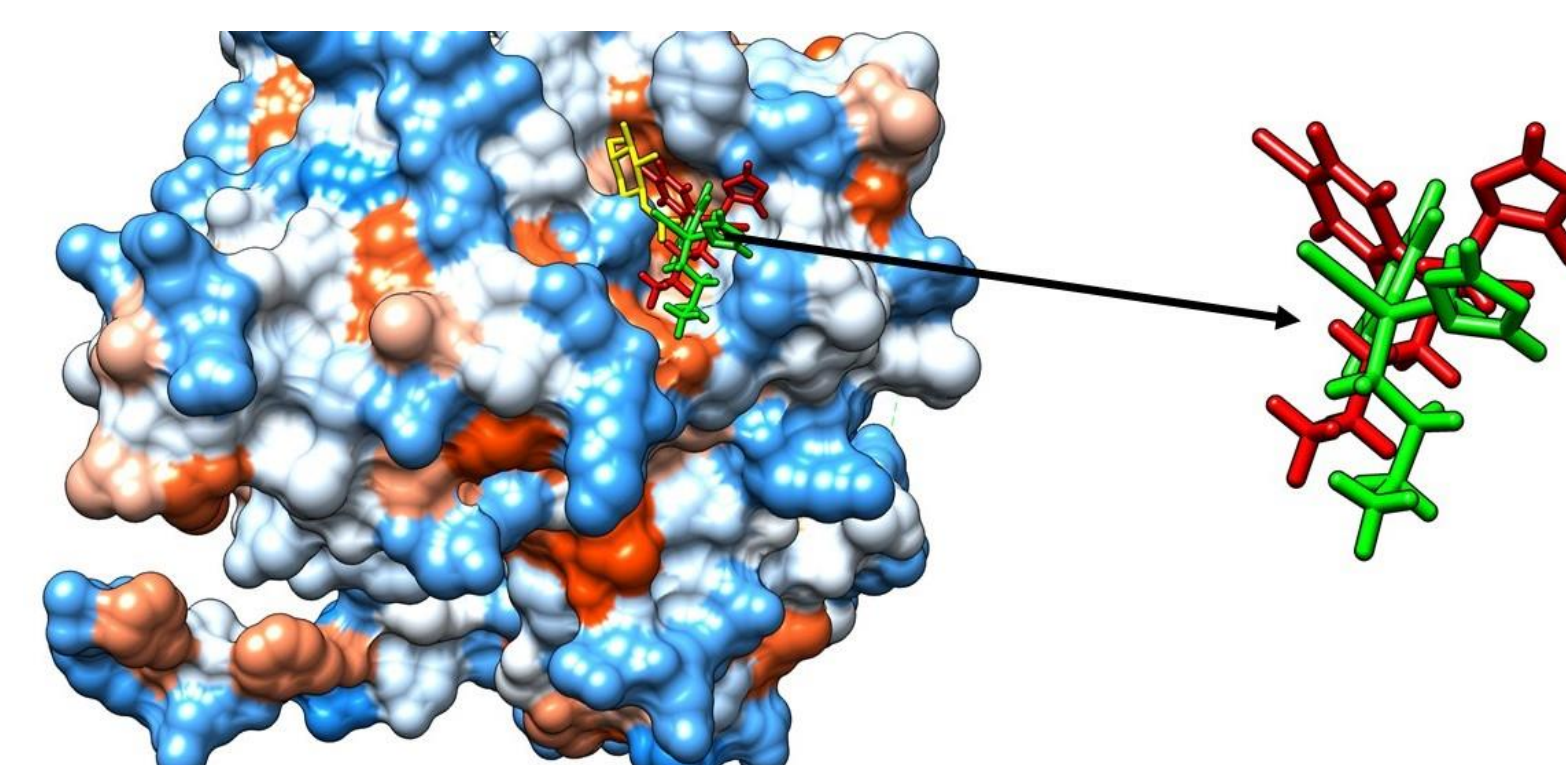


FIG 4. Binding of (*R*)-myclobutanil (red sticks) and of (*S*)-myclobutanil (green sticks) to the active site of *Aspergillus niger* PhA (PDB ID 1QFX) (solid hydrophobicity surface, blue regions are hydrophilic and orange regions are hydrophobic). The substrate 2-acetamido-2-deoxy-beta-D-glucopyranose (yellow sticks) illustrates the position of the active site.

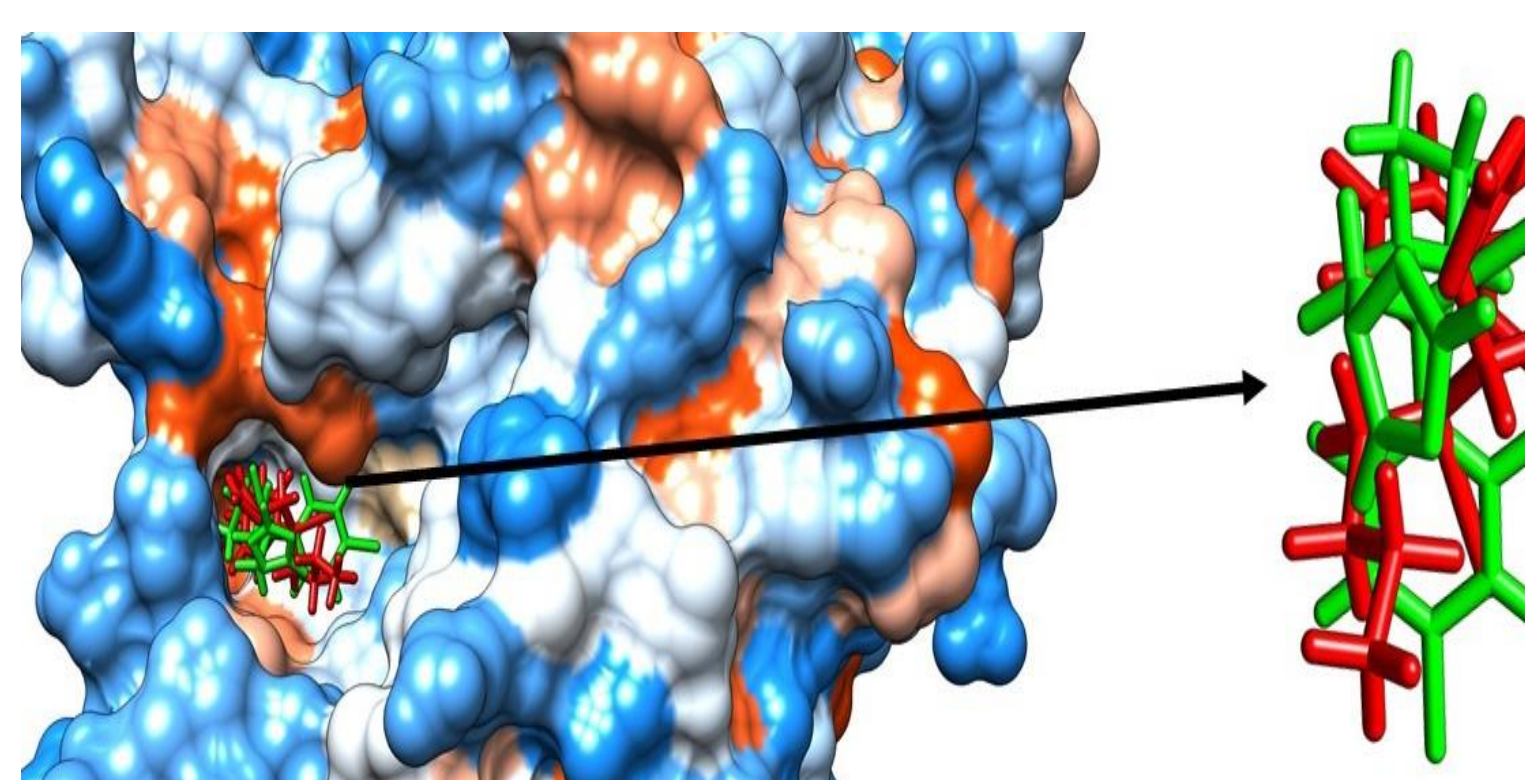


FIG 5. Binding of (*R*)-myclobutanil (red sticks) and of (*S*)-myclobutanil (green sticks) to the active site of *Rhizobium leguminosarum* PhA (PDB ID 2VQR) (solid hydrophobicity surface, blue regions are hydrophilic and orange regions are hydrophobic). The active site was found taking into consideration the position of the Ca²⁺ and Mn²⁺ ions (not shown).

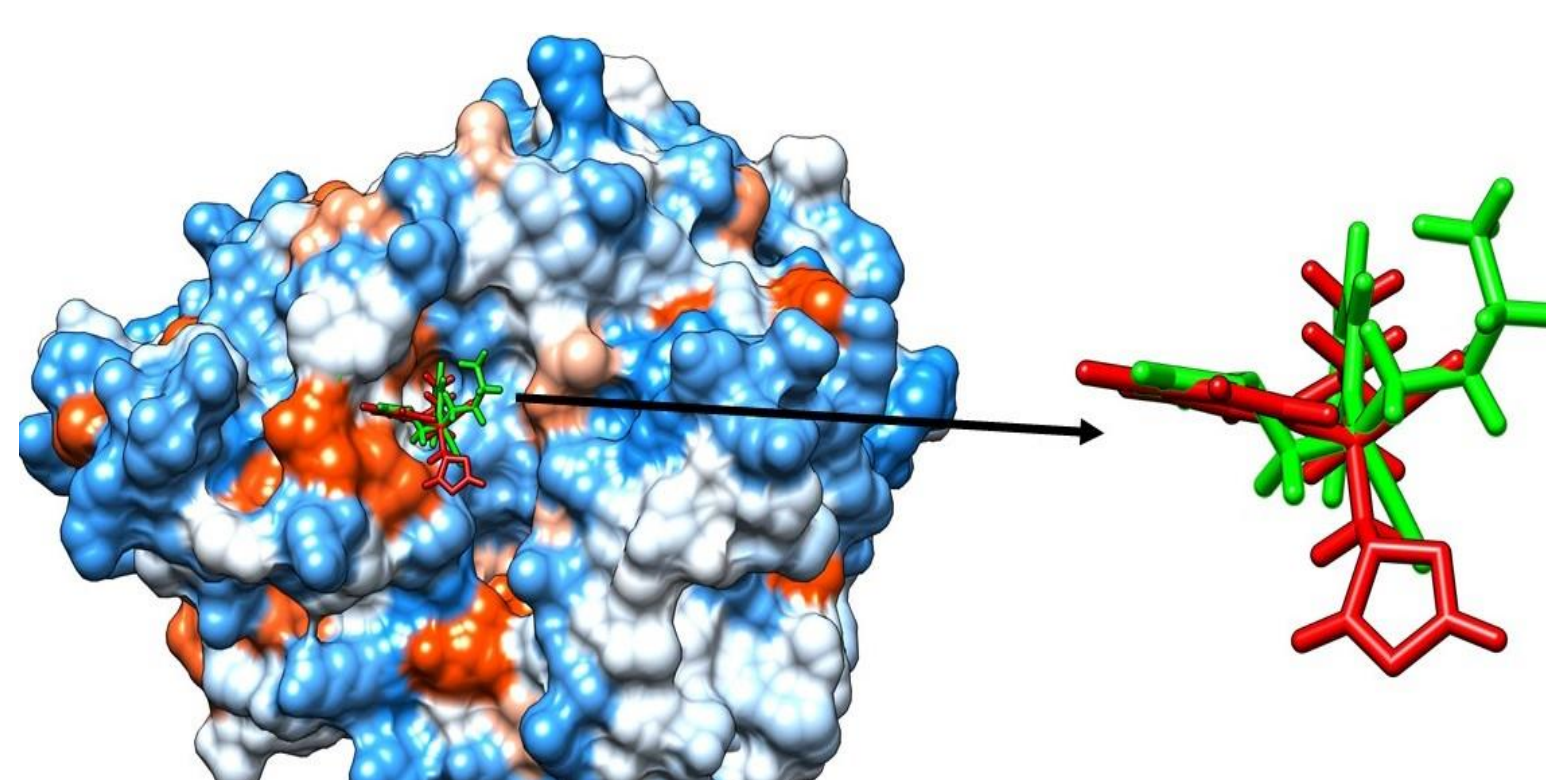


FIG 6. Binding of (*R*)-myclobutanil (red sticks) and of (*S*)-myclobutanil (green sticks) to the active site of *Aspergillus clavatus* PA (PDB ID 7Z6T) (solid hydrophobicity surface, blue regions are hydrophilic and orange regions are hydrophobic). The active site was found taking into consideration the position of the Ca²⁺ and Zn²⁺ ions (not shown).

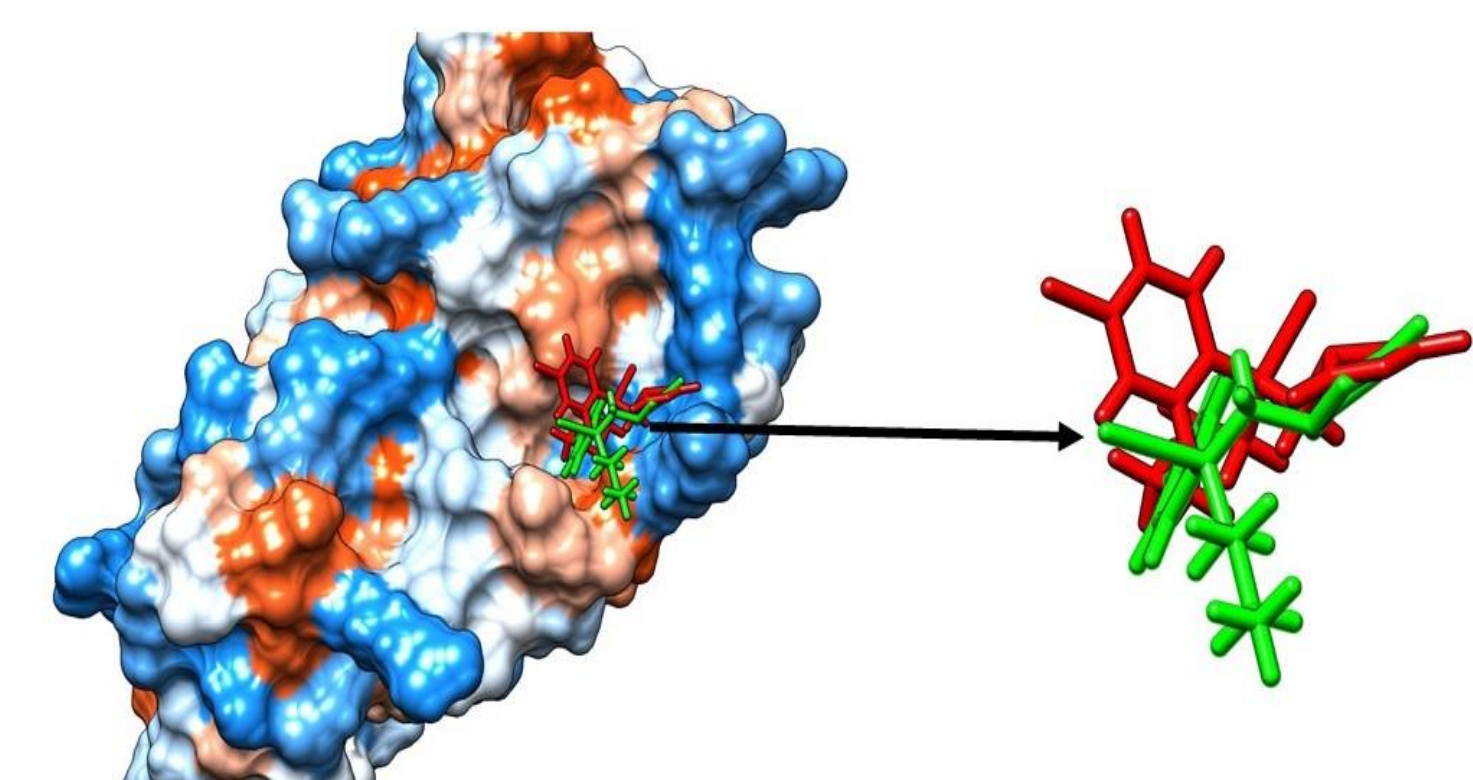


FIG 7. Best binding modes of (*R*)-myclobutanil (red sticks) and of (*S*)-myclobutanil (green sticks) to the active site of *Rhizobium leguminosarum* PA (AF-A0A0Q7ALB8-F1) (solid hydrophobicity surface, blue regions are hydrophilic and orange regions are hydrophobic).

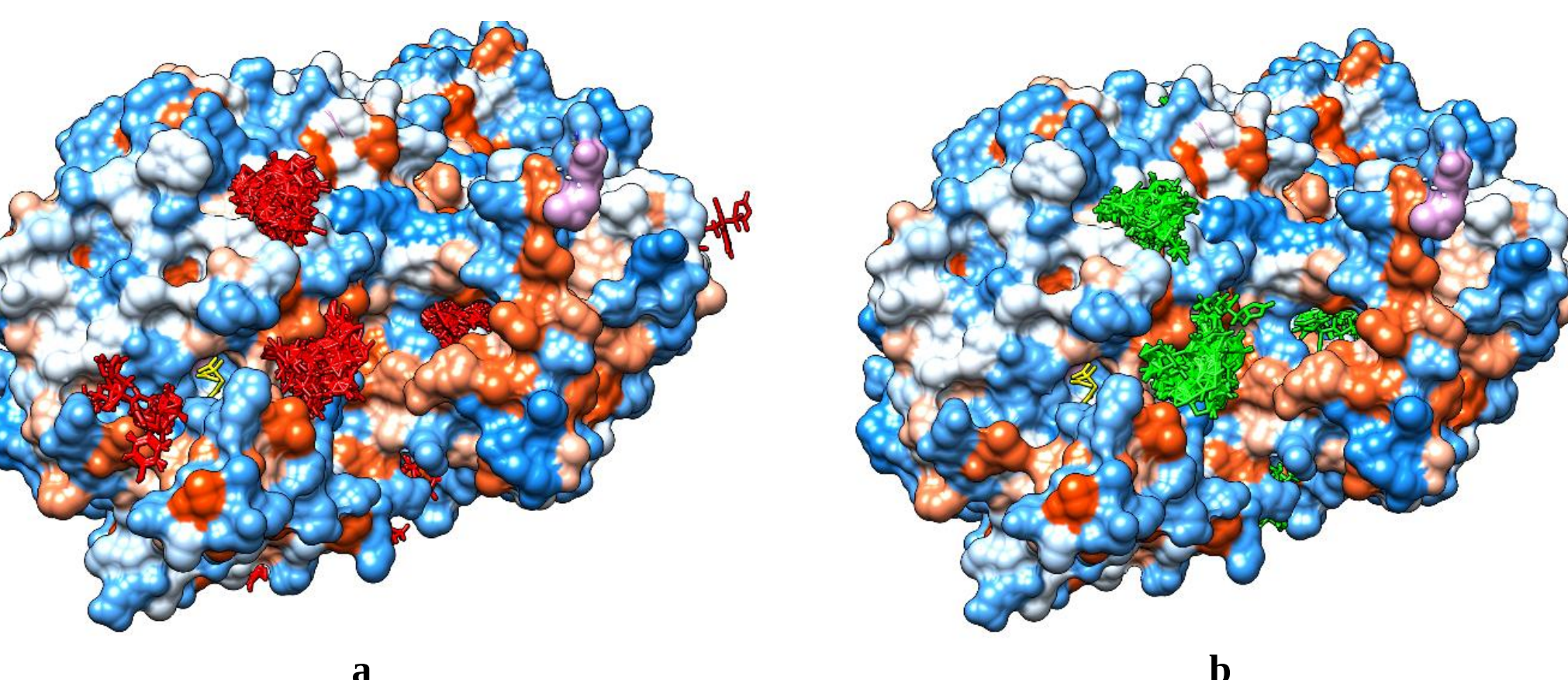


FIG 8. Binding of (*R*)-myclobutanil (red sticks) (a) and of (*S*)-myclobutanil (green sticks) (b) to *Aspergillus fumigatus* UA (AF-Q6A3P9-F1, solid hydrophobicity surface, blue regions are hydrophilic and orange regions are hydrophobic). The myclobutanil enantiomers do not bind to the active site, those position is illustrated by the citrate ion (yellow sticks).

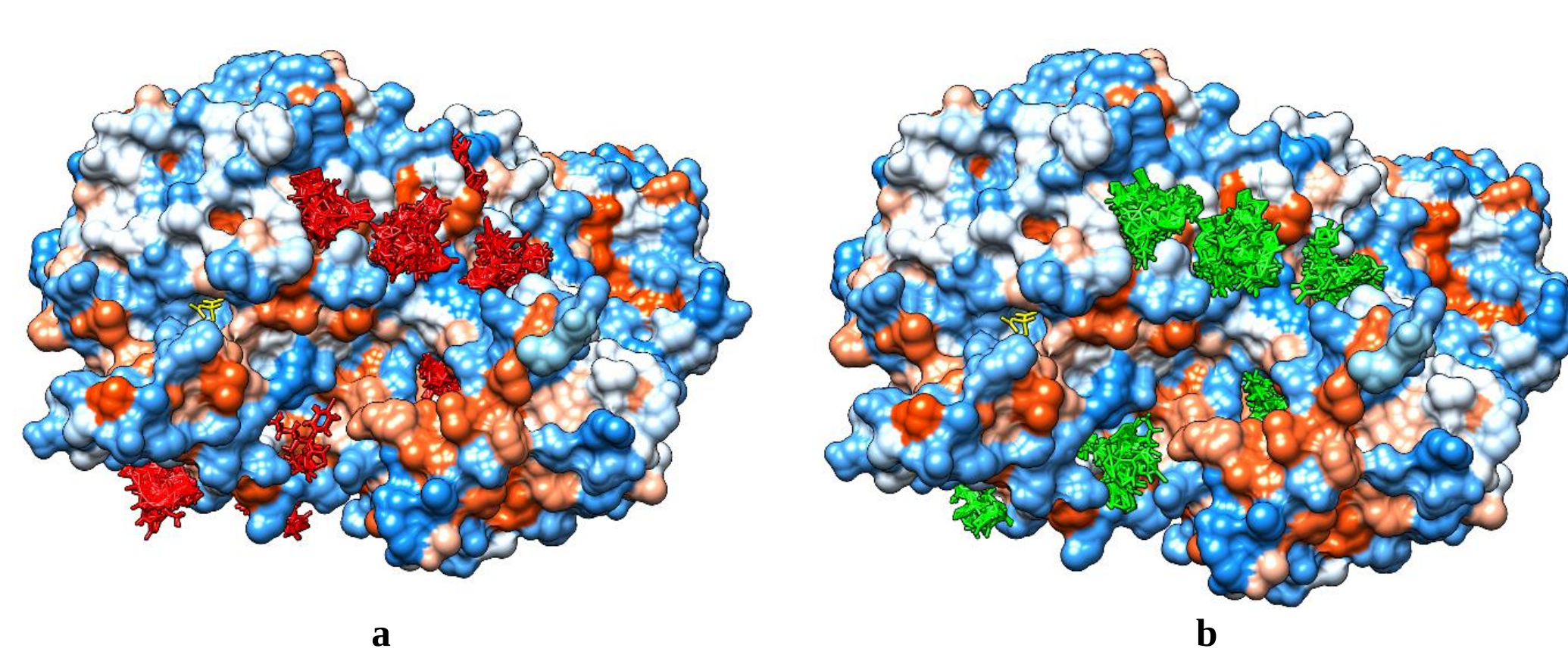


FIG 9. Binding of (*R*)-myclobutanil (red sticks) (a) and of (*S*)-myclobutanil (green sticks) (b) to *Rhizobium leguminosarum* UA (AF-Q1MCV9-F1, solid hydrophobicity surface, blue regions are hydrophilic and orange regions are hydrophobic). The myclobutanil enantiomers do not bind to the active site, those position is illustrated by the citrate ion (yellow sticks).

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• Conclusions

- the outcomes of the present study reveal that the triazole fungicide myclobutanil negatively affected the activity of soil dehydrogenase when used in high doses;
- both enantiomers of myclobutanil were able to bind to the active sites of DA, PhA and PA, the interacting energies being to some extent higher for the (*S*)-myclobutanil;
- the racemic mixtures that are used in crop and food management practices should be replaced by the enantiomer that reveals the highest activity against target organisms and the lowest toxicity against non-target organisms.

• References

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