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In Silico Analysis of the Interactions of Difenoconazole, Mefentrifluconazole, and Prothioconazole Stereoisomers with P-Glycoprotein

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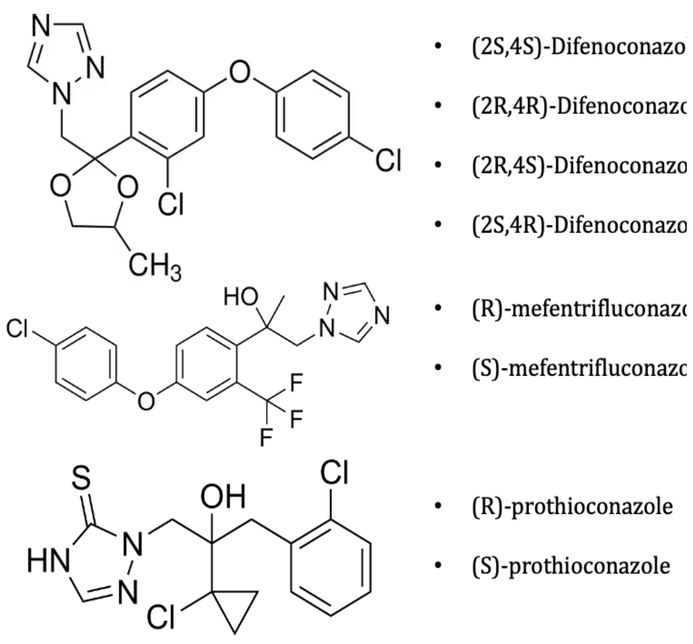
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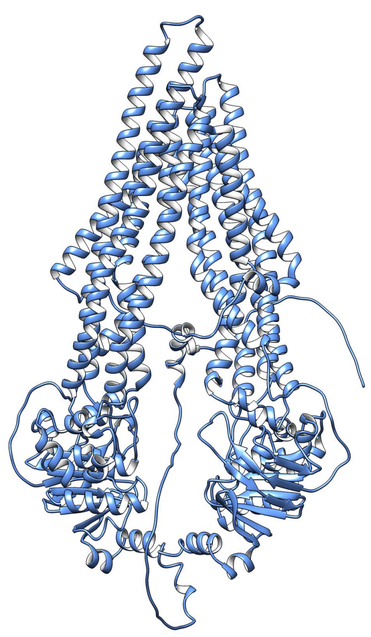
Abstract: P-glycoprotein (P-gp) is a membrane transporter involved in xenobiotic efflux. This study investigated the potential interactions of eight triazole fungicide stereoisomers with P-gp using ADMETlab 3.0 and SwissDock. Two difenoconazole stereoisomers showed predicted inhibitory potential, while all compounds exhibited low predicted probabilities of being P-gp substrates. Molecular docking identified (R)-mefentrifluconazole as having the most negative docking score (−8.106 kcal/mol). These findings suggest that stereochemistry may influence predicted P-gp interactions, requiring experimental validation.

• Introduction

- P-glycoprotein (P-gp), encoded by ABCB1 is an ATP-dependent transporter involved in xenobiotic efflux and cellular protection.
- Triazole fungicides, including difenoconazole, mefetrifluconazole and prothioconazole may interact with P-gp, potentially affecting its binding recognition as substrates.
- This study investigated the inhibitory potential and substrate status of eight fungicide stereoisomers using ADMETlab3.0 and evaluated their predicted binding poses and docking scores using SwissDock.

• Material and method





- P-gp interaction status using ***ADMETlab 3.0***
- Docking using ***7A69 PDB*** file using ***SwissDock***

Fig. 1. Triazolic fungicides and P-gp structures

• Results and discussions

- ADMETlab 3.0 predicted the highest inhibitory potential for (2R,4R)- and (2R,4S)-difenoconazole (0.979).
- All eight stereoisomers showed low predicted probabilities of being P-gp substrates (0.001–0.038).
- (R)- Mefentrifluconazole exhibited the most negative docking score (−8.106 kcal/mol).
- Docking poses were comparable to that of vincristine, suggesting potential binding to the selected P-gp cavity.

Table 1. P-gp interaction and docking values of fungicides

Stereoisomer	P-gp inhibition	P-gp substrate	Docking score (kcal/mol)
(2S,4S)-Difenoconazole	0.523	0.001	−6.443
(2R,4R)-Difenoconazole	0.979	0.038	−6.698
(2R,4S)-Difenoconazole	0.979	0.025	−6.973
(2S,4R)-Difenoconazole	0.196	0.004	−6.572
(R)-Mefentrifluconazole	0.343	0.026	−8.106
(S)-Mefentrifluconazole	0.569	0.013	−7.049
(R)-Prothioconazole	0.004	0.002	−5.889
(S)-Prothioconazole	0.004	0.003	−6.394

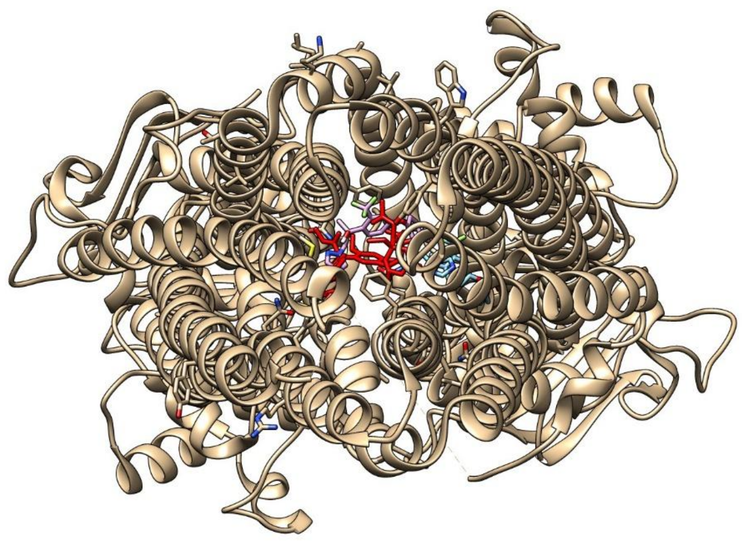


Fig. 2. Molecular docking were red sticks is vincristine, (R)-mefentrifluconazole is blue and (S)-mefentrifluconazole is lilac

• Conclusions

- ADMETlab 3.0 predicted inhibitory potential for two difenoconazole stereoisomers.
- All eight stereoisomers shoewd low predicted probabilities of being P-gp substrates.
- (R)-Mefentrifluconazole showed the most negative docking score.
- Experimental validation is required to confirm there predictions.

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