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FROM FIELDS TO PHARMACIES: REPURPOSING OF AHAS HERBICIDES AGAINST FUNGAL TARGETS THROUGH COMPUTATIONAL MODELING

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Abstract: This study explores the antifungal potential of acetohydroxyacid synthase AHAS-inhibiting herbicides by integrating known biological data with computational analysis. *In silico* techniques including molecular docking and pharmacophore modeling, were used to investigate key interactions between herbicides and active site residues of fungal AHAS. Critical residues (K247, R376, A191) were identified and incorporated into pharmacophore models. These models capture essential molecular features responsible for antifungal activity and can be applied in virtual screening to identify novel antifungal candidates.

Introduction

Drug-resistant fungal infections are rising, while current treatments are increasingly ineffective and often toxic. Discovering new antifungal agents is essential to combat resistance and protect vulnerable patients. Repurposing known compounds offers a fast and cost effective path to novel therapies. Innovative strategies, such as computational modeling, are promising tools for discovering safer and more effective treatments. In this context, recent studies have highlighted AHAS-inhibiting herbicides as highly promising candidates. AHAS, an enzyme found in plants and microorganisms but absent in animals, is of particular interest due to its potential for a lower toxicity profile in humans. AHAS-targeting herbicides from diverse chemical classes (e.g., sulfonylureas, triazolopyrimidines, imidazolines) have demonstrated antifungal activity against multiple pathogenic species.

Material and method

- The AHAS enzyme from *Candida albicans* (PDB ID: 6DER) was prepared using Schrödinger's Protein Preparation Workflow. The following steps were performed:
 - Import and preprocessing of the crystal structure, including removal of crystallographic water.
 - Assignment of bond orders and addition of hydrogen atoms to ensure correct valency and protonation.
 - Optimization of the hydrogen-bonding network, including adjustment of protonation states for ionizable residues at physiological pH.
 - Capping of terminal residues to mimic native protein termini.
 - Restrained energy minimization using the OPLS force field to relieve steric clashes and optimize geometry.

This prepared structure was subsequently used for molecular docking and pharmacophore modeling studies. Programs from Schrödinger's package were used for *in silico* studies:

- The compounds were prepared using LigPrep module, with protonation states generated across a pH range of 5.5 to 7.5.
- Molecular docking was performed using Glide SP with a series of herbicidal compounds exhibiting potential antifungal activity.
- Pharmacophore models were developed using the Phase module through two complementary approaches:
 - Structure-based modeling, derived from key interactions between binding site residues and docked inhibitors of the AHAS enzyme.
 - The Atom-Based QSAR module from Phase was used to validate the structure-based hypotheses previously obtained, taking into account the experimental pKi values against *C. albicans* AHAS.

Results and discussions

A set of AHAS-targeting herbicides, previously shown to exhibit antifungal activity against *Candida albicans*, were subjected to molecular docking. Based on their binding interactions within the AHAS active site of *C. albicans*, a series of pharmacophore models were generated using pre-aligned ligands. The models were configured to include between 3 and 5 pharmacophoric features. As a result, 30 pharmacophore hypotheses containing three to five pharmacophoric centers are shown in Fig. 1.

Results and discussions

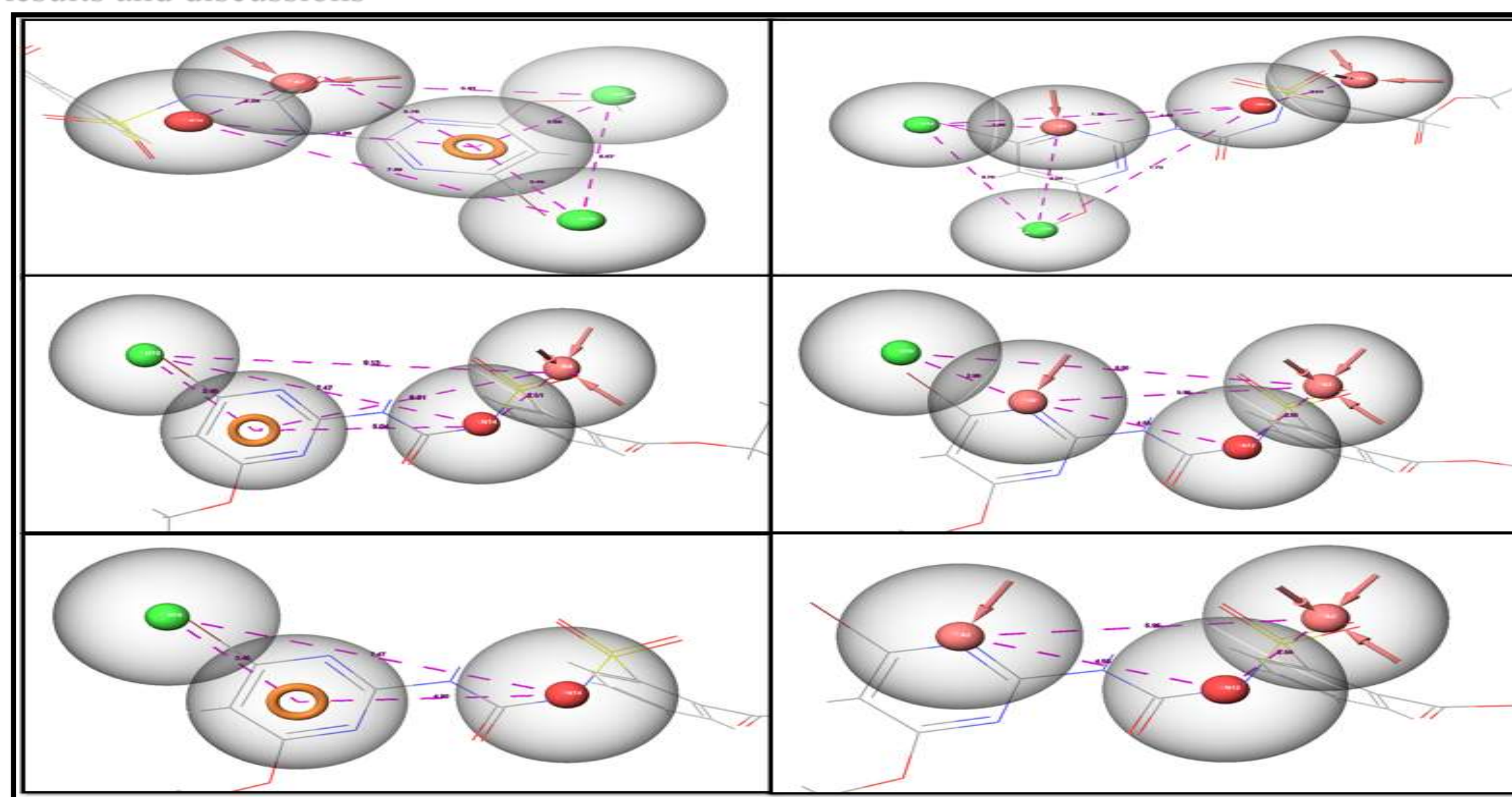


Fig. 1. Pharmacophore hypotheses and the reference ligand

The best pharmacophore hypothesis obtained is HHNR (Fig.2), which was validated with the aid of Atom-Based QSAR module (Table 1 and 2).

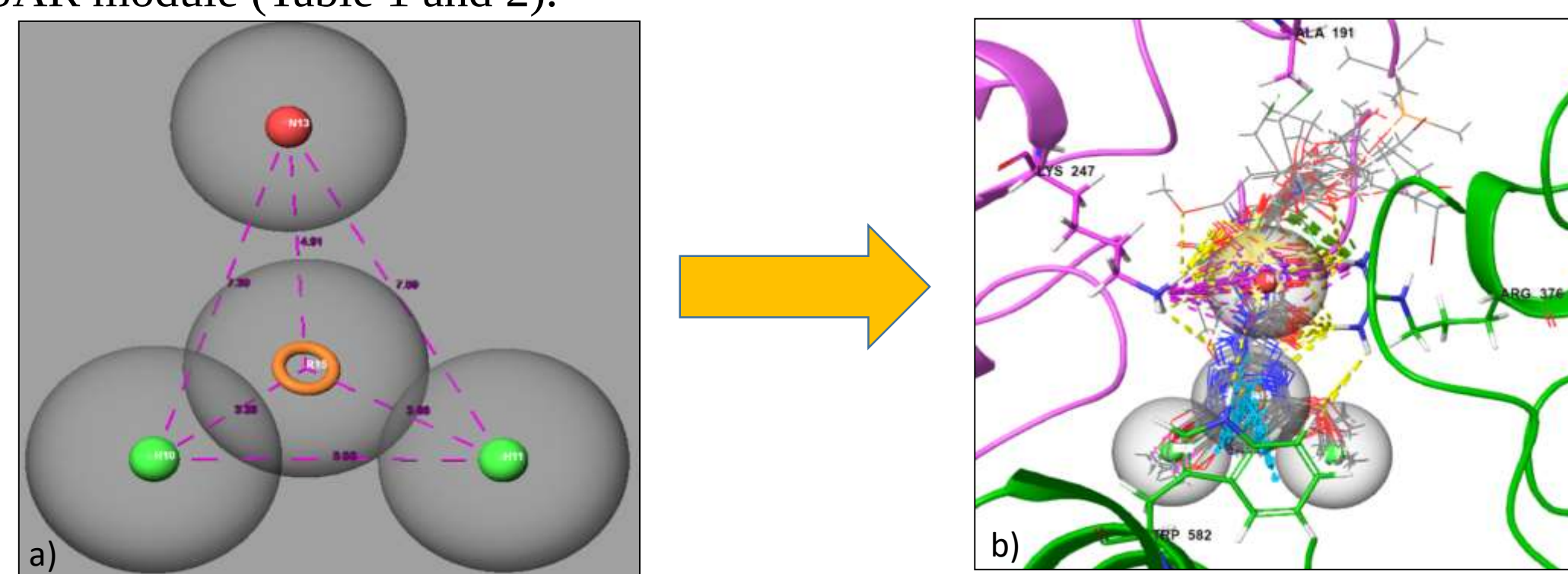


Fig. 2. HHNR pharmacophore hypothesis a) with the corresponding distances between the pharmacophoric centers (A – acceptor, H – hydrophobic, R – aromatic ring, N – negative ionic center); b) matched over the docked compounds in the AHAS *C. albicans* binding site. The interactions with key residues are highlighted Table 1. The QSAR model datasets and the experimental vs. predicted activities.

Ligand Name	QSAR Set	Activity	# Factors	Predicted Activity	Prediction Error
CHEMBL2312866	training	8,387	1.2	8.3407	-0.046517
CHEMBL2312867	training	8,409	1.2	8.28342	-0.125512
CHEMBL2312868	training	8,149	1.2	7.89317	-0.255569
CHEMBL2312869	training	7,585	1.2	7.54099	-0.0440373
CHEMBL2312871	training	7,208	1.2	7.52598	0.318373
CHEMBL2312873	training	7,876	1.2	7.89601	0.019865
CHEMBL2312875	test	8,42	1.2	7.90882	-0.511401
CHEMBL2312876	training	7,187	1.2	7.1842	-0.00288434
CHEMBL2312878	test	7,303	1.2	7.68048	0.377713
CHEMBL2312880	training	7,187	1.2	7.47446	0.287374
CHEMBL2312881	training	7,569	1.2	7.60706	0.0384218
CHEMBL2313152	training	7,824	1.2	7.79427	-0.0296381
CHEMBL2313156	training	7,032	1.2	7.2655	0.233981
CHEMBL2313158	training	8,42	1.2	8.36443	-0.0557882
bensulfuron-methyl	training	7,524	1.2	7.40027	-0.124063
bispyribac	training	8,585	1.2	8.56376	-0.0212363
chlorimuron-ethyl	test	7,614	1.2	7.69732	0.0829253
diclosulam	training	8,77	1.2	8.94118	0.17118
ethoxysulfuron	training	7,159	1.2	6.97458	-0.184683
iodomuron ethyl	training	8,201	1.2	7.79625	-0.404746
iodomuron methyl	training	7,896	1.2	8.18308	0.286886
metosulam	training	9,097	1.2	9.04793	-0.0490706
penoxsulam	test	8,62	1.2	8.24457	-0.37543
pyrazoxysulfuron-ethyl	training	7,18	1.2	7.16812	-0.0123367

Table 2. Atom-based QSAR results for HHNR hypothesis.

# Factors	SD	R ²	R ² CV	R ² Scramble	Stability	F	P	RMSE	Q ²	Pearson-r
1	0.3407	0.7107	0.017	0.5598	0.459	44.2	3.06E-06	0.45	0.3259	0.6632
2	0.1967	0.9089	0.1105	0.8119	0.295	84.9	1.43E-09	0.37	0.5382	0.9005

Conclusions

A QSAR model was developed using 2 PLS components, based on a dataset of 24 AHAS inhibitors aligned in the binding site via docking. The two-factor model exhibited significantly statistical performance, with a high coefficient of determination ($R^2 = 0.901$) and good predictive capability ($Q^2 = 0.538$). The low RMSE value (0.37), high F-statistic (84.9), and very small p-value (1.43×10^{-9}) further confirm the robustness and statistical significance of the model.

Although the QSAR model exhibits limited predictive power, it offers a useful starting point for understanding structure-activity relationships in AHAS inhibition. The predictive accuracy of linear QSAR models for AHAS inhibitors is constrained by the multifactorial determinants of biological activity, including the modulatory role of catalytic site cofactors. The supplementary docking analysis strengthens the biological plausibility of the findings.

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