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QSAR, ADMET, and Molecular Docking of Pyrazole Carboxamide Derivatives as Potential Antifungals Against the Fungus *Rhizoctonia solani*

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Abstract

Sheath blight is generally caused by the fungus *R. solani*. The emergence of this fungus causes losses for farmers due to reduction of grain crops (*cerelia*) production such as rice. Thus, the use of antifungal compounds containing succinate dehydrogenase inhibitors is an effort to control sheath blight of the fungus *R. solani*. This research examines a new pyrazole carboxamide derivative designed as a succinate dehydrogenase inhibitor. Antifungal activity value prediction was determined using the Quantitative Structure-Activity Relationship (QSAR) equation and visualization of the interaction of pyrazole carboxamide derivatives with succinate dehydrogenase inhibitors was determined using molecular docking. A total of 29 pyrazole carboxamide derivatives and activities (EC_{50}) were used in this study for QSAR modelling and molecular docking. The structure was optimized using the DFT/B3LYP/LanL2DZ method as an electronic descriptor calculation and QSAR modelling using the Multiple Linear Regression (MLR) method. The MLR test shows a valid QSAR equation model with good modelling accuracy and produces an equation $\log EC_{50}$ = 2.3936(±0.9447)[C13] + 9.1367 (±3.0682)[C10] + 2.2473(±0.6055)[HOMO] - 48.1289(±14.1289)[C4] + 1.3937(±0.9465)[C14] + 28.3750(±6.6731) with R^2_{tr} = 0.8911; Q^2 = 0.793; F = 28.079; R^2_{val} = 0.9908; and RMSE = 0.3450. ADMET analysis using ADMETlab indicated that the new pyrazole carboxamide derivative complies with Lipinski's rules, is moderately carcinogenic, and includes inhibiting the activity of hERG blockers. The new pyrazole carboxamide derivatives that have potential as succinate dehydrogenase inhibitors were determined based on the interaction of the docking results, namely compound A1, A5, and A7 -4.9, -5.1, and -5.3 kcal/mol, respectively.

Keywords: Antifungal, molecular docking, pyrazole carboxamide derivatives, QSAR, *R. solani*

1 Introduction

Rhizoctonia solani is a pathogenic fungus that is distributed in the soil and causes rice sheath blight to grow rapidly in several Asian countries such as China, Japan, the Philippines, including Indonesia. Rice sheath blight generally grows in the highlands and lowlands in Indonesia. [1]. One way to control the Rhizoctonia Solani fungus is to use compounds that have antifungal or fungicide activity [2].

The use of excessive doses of fungicides over a long period of time can cause resistance of pathogenic fungi to fungicides [3]. Therefore, it is necessary to synthesize new compound derivatives that have the potential to be effective in inhibiting fungal growth and controlling the resistance of pathogenic fungi to fungicides.

The method that can be used to predict the relationship between biological activity and compound structure is Quantitative Structure Activity Relationship (QSAR). This QSAR method is considered to be able to save time and reduce costs through synthesis experiments carried out in the laboratory [4].

This QSAR method cannot determine the interactions that occur in a compound, so a molecular docking study is needed to predict the interactions of the compounds. This method can improve efficiency predictions and understand the molecular mechanisms related to the synthetic design of a compound [5]. In this study, QSAR

was used to predict the biological activity of pyrazole carboxamide derivatives based on publications by [2].

2 Method

2.1 Material

The data set for structures and activities were obtained from Zhang *et al.* (2019) [2]. The main framework of pyrazole carboxamide derivative compounds is shown in Figure 1. Table 1 showed the compound code, the aromatic (Ar) substituent, alkyl (R) substituent, and the antifungal activities (log EC_{50}) of 29 pyrazole carboxamide derivative compounds.

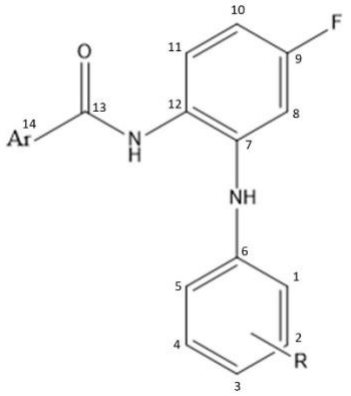
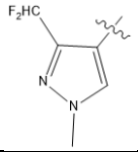
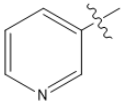
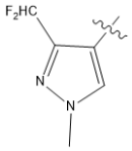
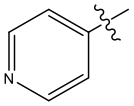
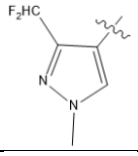
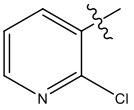
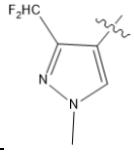
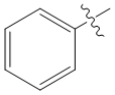
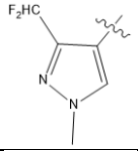
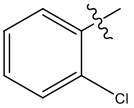
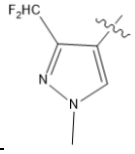
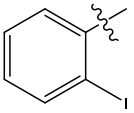
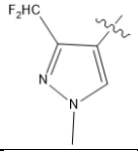
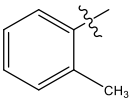
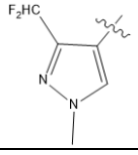
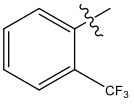
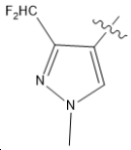
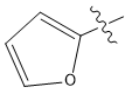
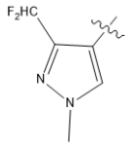
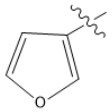
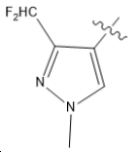
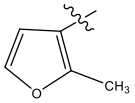
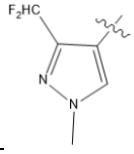
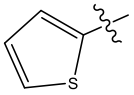
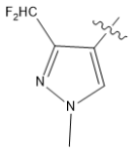
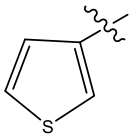
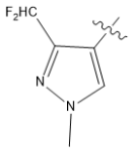
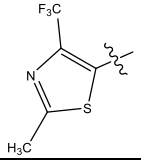
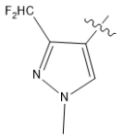


Figure 1. The main framework for the structure of pyrazole carboxamide derivative compounds

Table 1. Substituents and activities in the structure of pyrazole carboxamide derivative compounds

Code	Ar	R	log EC_{50}	Code	Ar	R	log EC_{50}
S1		-H	-0.56864	S16		3-Cl,4-CH_3	0.09691
S2		2-Cl	-0.74473	S17		3-Cl,4-CH_3	-0.4318
S3		3,4-Cl_2	-1.09691	S18		3-Cl,4-CH_3	-0.46852
S4		2,4-Cl_2	-0.52288	S19		3-Cl,4-CH_3	0.403121
S5		2-Cl,4-Br	-0.3279	S20		3-Cl,4-CH_3	0.235528
S6		3-Cl,4-CH_3	-1.52288	S21		3-Cl,4-CH_3	0.220108
S7		3-Br	-1	S22		3-Cl,4-CH_3	-0.08619
S8		2-CH_3,5-Br	-0.34679	S23		3-Cl,4-CH_3	-0.07572

Code	Ar	R	log EC_{50}	Code	Ar	R	log EC_{50}
S9		2-CH_3,3-Br	-1.39794	S24		3-Cl,4-CH_3	0.326336
S10		3-OCH_3	-0.76955	S25		3-Cl,4-CH_3	0.045323
S11		3-I	-0.58503	S26		3-Cl,4-CH_3	-0.45593
S12		3,5-F_2	-1.1549	S27		3-Cl,4-CH_3	0.647383
S13		3-CN	-0.05552	S28		3-Cl,4-CH_3	0.120574
S14		3-OCF_3	-0.4437	S29		3-Cl,4-CH_3	-0.50864
S15		3,4,5-F_3	-1.30103				

2.2 Procedure

2.2.1 QSAR and Design

The molecular structure was drawn using Avogadro and optimized using orca with the DFT/B3LYP/LanL2DZ calculation method. The calculation results obtained are in the form of electronic descriptors (2D).

The data set obtained was divided semi-randomly into a training set and a test set with a ratio of 4:1 [6]. The dataset was sorted and divided into 6 clusters with each cluster selecting 1 compound at random to be part of the test set. Next, QSAR equation calculations were carried out on the training set using BuildQSAR software with Genetic Algorithm search [7].

The best QSAR equation results were validated by substituting descriptor values from the test set according to the QSAR equation and comparing the calculation results with the experimental activity results for each compound structure. The parameters used in QSAR equation modeling include $R^2_{tr} \geq 0.8$; $R^2_{te} \geq 0.6$; $R^2_{tr} - Q^2_{tr} \leq 0.3$ [8].

A new compound was designed based on the structure with the best activity value according to the reference and the substituents were modified in such a way that a better activity value was obtained compared to the reference data. Next, the design compound is subjected to a molecular docking test to see the interaction of the ligand molecule with the protein.

2.2.2 Molecular docking

Molecular docking was carried out using Autodock4 software. The receptor used as a target for the succinate dehydrogenase enzyme was Avian respiratory complex II with carboxin bound (PDB ID:2FBW) [9], downloaded on the Protein Data Bank website (https://www.rcsb.org/).

Molecular docking calculations were carried out for 10 poses with a grid box size of 10x10x10 and a distance of 1 Å. The calculation results were visualized using Biovia Discovery Studio Visualizer software.

3 Result and Discussion

3.1 QSAR dan Design

By using orca, 22 electronic descriptor calculations were obtained consisting of 18 partial charge descriptors and 4 other descriptors (HOMO, LUMO, minimum energy, dipole moment).

Creating QSAR equations is carried out using BuildQSAR with a Genetic Algorithm search to find similarities by paying attention to parameters in the form of Coefficient of (R^2) to ensure predictability and cross-validation coefficient (Q^2) to ensure there is no overfitting for both training set (R^2_{tr}) and test set (R^2_{te}). The search results yield equations with acceptable statistical parameters as follows:

$$\log EC_{50} = 2.3936\ (\pm 0.9447)\ [C13] + 9.1367\ (\pm 3.0682)\ [C10] + 2.2473\ (\pm 0.6055)\ [HOMO] - 48.1289\ (\pm 14.1289)\ [C4] + 1.3937\ (\pm 0.9465)\ [C14] + 28.3750\ (\pm 6.6731)$$

Internal validation

$$n = 23, R = 0.944, R^2_{tr} = 0.8911;\ Q^2_{tr} = 0.793; F = 28.079$$

External validation

$$n = 6, R\ R^2_{te} = 0.9908;\ RMSE = 0.3450$$

The QSAR equation model results that have been obtained and validated consist of 5 descriptors that are influential in predicting antifungal activity against the SDH enzyme. A description of each descriptor is shown in Table 2.

Table 2. Descriptors that influence the QSAR equation model using the MLR method in predicting antifungal activity against the SDH enzyme.

No	Descriptor	Description
1	C13	Partial charge of the C-13 atom
2	C10	Partial charge of the C-10 atom
3	HOMO	Highest energy molecular orbital
4	C4	Partial charge of the C-4 atom
5	C14	Partial charge of the C-14 atom

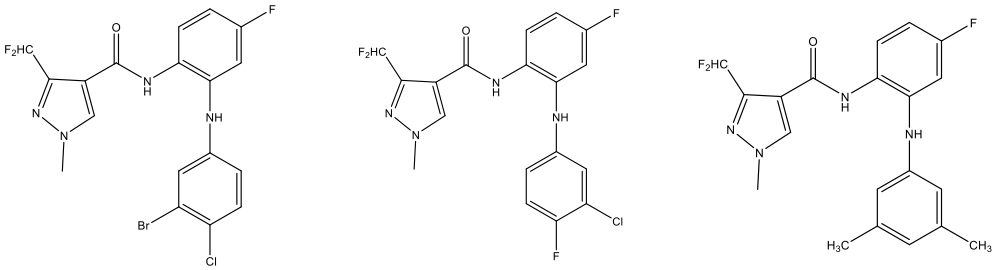
Based on these results, a new compound was designed by modifying the structure to obtain a compound with the best predicted log EC50 value. The results of calculating the best predicted activity value for the design compound are shown in table 3.

Table 3. Prediction value of the best activity of modified design compounds

No	Code	R_1	R_2	R_3	R_4	R_5	Predicted $\log EC_{50}$ Value
1	A1	H	H	Cl	Br	H	-1.8524
2	A5	H	Cl	F	H	H	-1.9593
3	A7	H	CH_3	H	CH_3	H	-2.4079

Based on the Table 3, the design of new compounds with substitution of methyl groups (electron-donating groups) or halogen groups (electron-withdrawing groups) can influence the antifungal activity values for the better depending on the descriptor produced by the QSAR equation. The structure of the compound is shown in Figure 2.

Based on Figure 2, the main framework of these compounds is similar but differs in the substituents R_2, R_3, and R_4. After knowing the design of a new compound with the best activity, molecular docking is carried out to find out information on the interaction between the ligand and the receptor.



(a) (b) (c)

Figure 2. Structure of new compound designs: (a) A1; (b) A5; and (c) A7

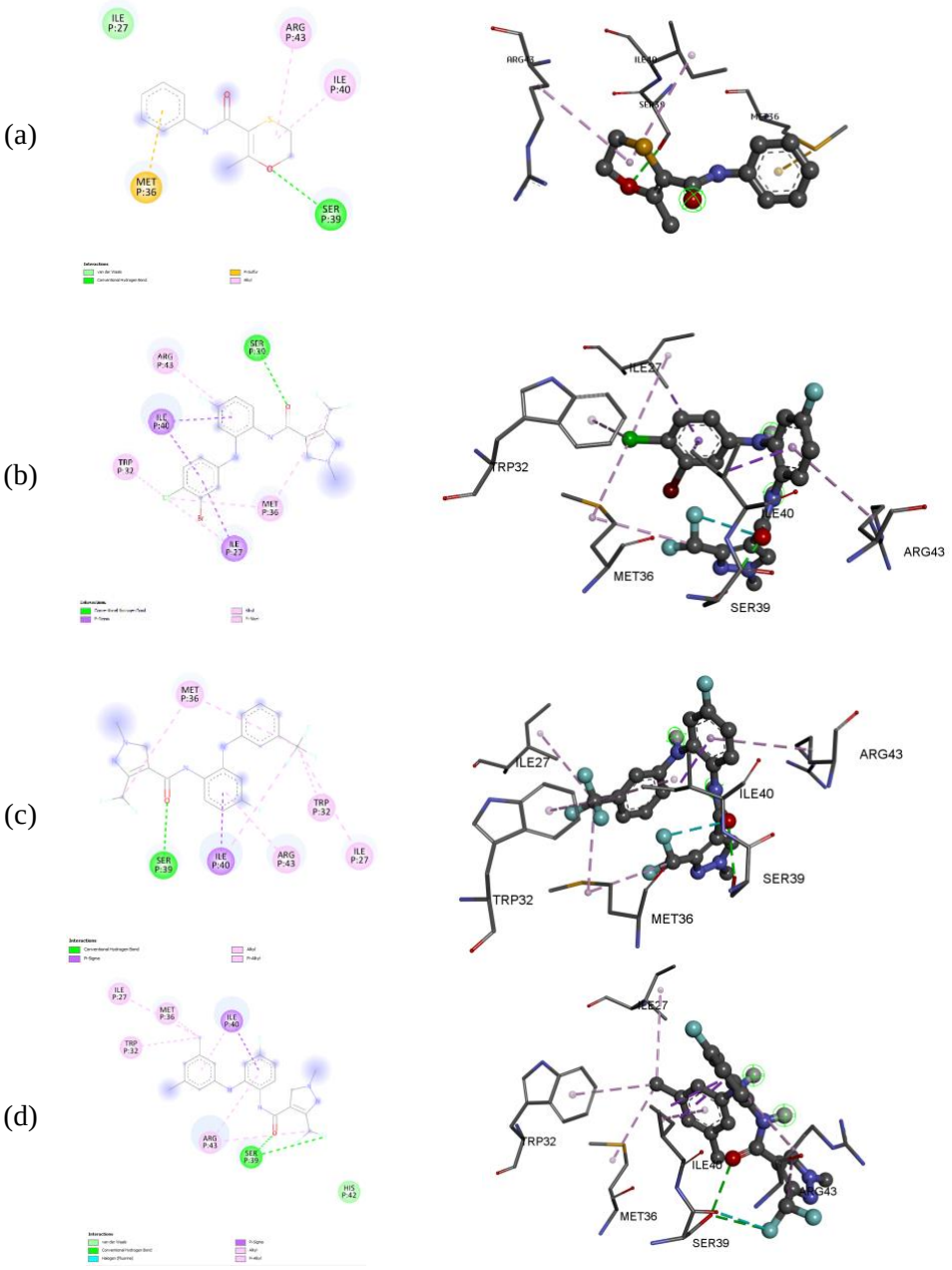


Figure 3. Visualization of compound docking results in 2D and 3D (a) Carboxin; (b) A1; (c) A5; and (d) A7

Based on Figure 3, there are interactions of three complexes, including Compound_A1-SDH, Compound_A5-SDH, and Compound_A7-SDH. The results of the visualization carried out are presented in Table 4.

Table 4. Docking results of the best compound design with native ligands (PDB ID: 2FBW)

Code	RMSD (Å)	Affinity Energy (kcal/mol)	Interaction
CBE202	1.622	-3.8	• Hydrogen bond: SER39 • van der Waals: ILE27 • π: MET36, ILE40, ARG43
A1	5.617	-4.9	• Hydrogen bond: SER39 • van der Waals: TYR30 • π: MET36, ILE40, ARG43, ILE27, TRP32
A5	5.561	-5.1	• Hydrogen bond: SER39 • π: ILE27, Trp32, Met36, ILE40, ARG43
A7	6.238	-5.3	• Hydrogen bond: SER39 • van der Waals: HIS42 • π: ARG43, ILE40, ILE27, TRP32, MET36

Based on Table 4, the affinity energy between the design compound and the target protein is smaller than the affinity energy between the native ligand and the target protein. The data shows that design compounds have amino acid interactions with SDH receptors, while residues act as an active role are SER39, MET36, ILE40, and ARG43

However, this data was an in-silico study. These results need to be further verified with other methods, especially using in vitro studies or in vivo studies.

3.3 ADMET Analysis

The results of the pharmacokinetic analysis of the design compounds are shown in Table 5. Based on ADMET analysis, the designed compound meets the Lipinski rules, was in the moderate carcinogenic category, and was a very good hERG Blocker.

Table 5. Pharmacokinetics of design compounds

Code	Molecular weight (g/mol)	hERG Blocker	Carnigenicity	Lipinski
A1	471.990	0.071	medium	Yes
A5	412.070	0.075	medium	Yes
A7	388.150	0.081	medium	Yes

4 Conclusion

A QSAR equation with acceptable statistical parameters was obtained. The QSAR equation is used to calculate the activity of new compound designs and the calculation results show that compounds A1, A5, and A7 produce better predicted activity than the best compounds in the dataset. Molecular docking of the design compound shows that there was an interaction between the ligand and receptor.

References

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