E-ISSN-2580-7129
Print- ISSN-1978-6107

TECHNO: JURNAL PENELITIAN
Journal homepage: http://ejournal.unkhair.ac.id/index.php/Techno
Volume 12 Number 01 May 2023 DOI: https://doi.org/10.33387/tjp.v12i1.5793

Computational Chemistry: QSAR of Dental Disease Causing *Streptococcus mutans* Using Eugenol Derivative Compounds from Clove Essential Oil

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Received : 06-02-2023
Accepted : 23-04-2023
Available online : 30-05-2023

ABSTRACT

Research on the activity of eugenol derived compounds as antimicrobials using the qualitative structure-activity relationship (QSAR) model has been conducted. Molecular structure modeling was executed computationally using the ChemDraw Ultra 12.0 program package. Geometry optimization was performed using AM1 semi-empirical method to stabilize structure with the least energy level. Calculations of hydrophobic, electronic, and steric descriptors were done using Gaussian-09 and Marvin Sketch 64 softwares. Statistical calculations was conducted through multiple linear regression method using the IBM SPSS 25 program. Statistical analysis was carried out based on the statistical requirements of several equation models so that the best equation model was obtained. The analysis with the QSAR equation model obtained that the model 1 equation presented the best results.

Keywords: Eugenol derivatives, QSAR, AM1, Multiple linear regression

ABSTRAK

Telah dilakukan penelitian analisis aktivitas senyawa turunan eugenol sebagai antimikroba menggunakan metode Hubungan Kuatitatif Struktur-Aktivitas (HKSA). Pemodelan struktur molekul telah dilakukan secara komputasi menggunakan paket program *ChemDraw Ultra 12.0*. Hasil optimasi geometri menggunakan metode semi empiris AM1 untuk menstabilkan struktur dengan tingkat energi paling minimum. Perhitungan deskriptor hidrofobik, elektronik, dan sterik menggunakan *software Gaussian-09* dan *Marvin Sketch 64*. Perhitungan statistik berdasarkan metode regresi linear berganda dengan menggunakan program *IBM SPSS 25*. Analisis statistik dilakukan berdasarkan persyaratan statistik dari beberapa model persamaan sehingga didapatkan model persaman terbaik.

Kata kunci: Senyawa turunan eugenol, HKSA, AM1, Regresi linear berganda

INTRODUCTION

A toothache is a condition where there is pain around the teeth and gums due to the effects of teeth cavities caused by acid-producing bacteria in the mouth. These bacteria are responsible for the breakdown of fermented sugars. These acid-producing bacteria attack the enamel that protects teeth (Moerfiah & Supomo, 2017). Bacteria that induce plaque formation are bacteria

that are able to form extracellular polysaccharides, namely bacteria from the genus *Streptococcus*. The *streptococcus* is a heterogeneous group of bacteria (Bahar, 2011). A species included within this genus is *Streptococcus mutans* (Andries et al., 2014).

Streptococcus mutans can ferment sucrose into acid. The acid produced makes the pH of the teeth decrease, accelerating the process of plaque formation. Plaque is a thin layer that adheres tightly to the tooth surface, containing a collection of bacteria. If the pH continues to fall to a critical number (5.2 - 5.5), the tooth enamel will dissolve and dental caries will form. This will lead to bacterial invasion and damage to pulp tissue. Worse, it may be more widespread into the periapical tissue and cause pain or tenderness (Hasanuddin & Salnus, 2020). *Streptococcus mutans* is one of the microorganisms found in the oral cavity dominantly causing dental caries and other dental diseases. In previous research regarding an in-vitro intervention study that aimed to evaluate antimicrobial activity using a Nano Zinc Oxide Eugenol (NZOE) sealer, it was found that the NZOE sealer removed all tested microorganisms (Zarei et al., 2018). Alternatively, in the medical world, *Streptococcus mutans* has been recognized as the main cause of dental caries. Thus, many antibacterial studies have focused on the specifics of this bacterial type (Mervrayano et al., 2015; Suhendar & Fathurrahman, 2019).

To control bacteria and fungi, antimicrobial agents can be used to inhibit and remove microorganisms. Antimicrobial is a substance that can interfere with the growth and metabolism of microorganisms. The main goals in controlling microorganisms are to help prevent the spread of disease and infection, to eradicate microorganisms in infected hosts, and to prevent spoilage and destruction by microorganisms (Dwandaru et al., 2016).

Eugenol is an aromatic chemical compound, odorless, widely found in clove grains, slightly soluble in water and soluble in organic solvents (Andries et al., 2014). The eugenol compound in clove essential oil has advantages over other eugenol essential oils (Minasari, 2016). Clove essential oil is advantageous in that it has a good inhibiting ability (Tulungen, 2019). Clove essential oil can also be used as an active ingredient, such as in the manufacture of mouthwash, for its antimicrobial properties (Andries et al., 2014). Previous research has found that revealed that clove flower extract has antibacterial properties against *Streptococcus mutans* bacteria (Rakhman et al., 2019).

The QSAR model entails structural modeling or geometry optimization in its initial steps, which can be executed using the ChemDraw Ultra 12.0, to obtain electronic descriptors. Biological activity can then be predicted through computational processing of these molecular descriptors. Statistical analysis is later performed to process data and find a QSAR equation. Using regression statistical approach that the relationship between one variable and another can be discerned. These variables will later determine the QSAR equation model that will be used to determine the biological activity of a compound (Rakhman et al., 2019; Muliadi et al., 2021).

METHODOLOGY

Research Instrument and Objects

The tools used in this research are specific computers: Intel 2 Core 2.6 GHz Processor, 1 TB Hard Drive, 4 GB Random Access Memory (RAM), and software in the form of ChemDraw Ultra 12.0, GaussView 6.016 software, and Gaussian-09 software, Marvin Sketch 64, Microsoft excel 2010, and IBM SPSS 25. Meanwhile, the objects in this research are compounds derived from eugenol, including compounds derived from E1, E2, E3, E4, E5, and E6.

Procedure

This research begins by drawing the structure of the eugenol derivative compound using ChemDraw Ultra 12.0 software. The molecular modeling of the compound derived was done

3D visualization. Geometry optimization was executed using the GaussView 6.016 software and the AM-1 semi-empirical method (Austin Model-1). The AM-1 semi-empirical method is reputable in optimizing the molecular structure because the AM1 semi-empirical method can simulate molecules that are quite large in a relatively fast time. In calculating the descriptor value, Gaussian-09 and Marvin Sketch 64 software were used. The calculation results were analyzed using Microsoft Excel 2010 software, and IBM SPSS 25, to obtain the QSAR equation. The selected QSAR equation was tested by comparing the results of the Log P value with the predicted Log P. Based on equation parameters desired, the selected QSAR equation was used to predict the predict the compound studied.

RESULTS AND DISCUSSION

Molecular modeling of the eugenol derived compounds was done using the AM1 semi-empirical method by combining electron donor groups on the basic structure of the 4-allyl-2-methoxyphenol as shown in figure 1. Structural modeling was carried out as an initial step to obtain descriptor data which would later produce the QSAR equation model.

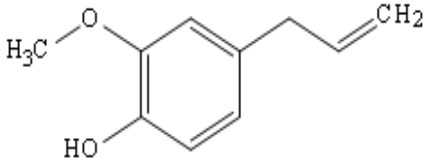
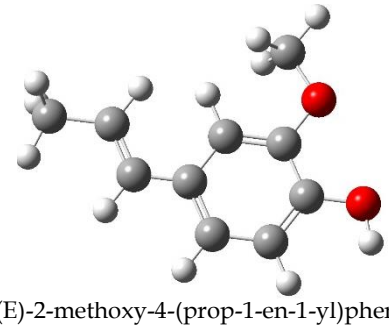


Figure 1. Structure of eugenol

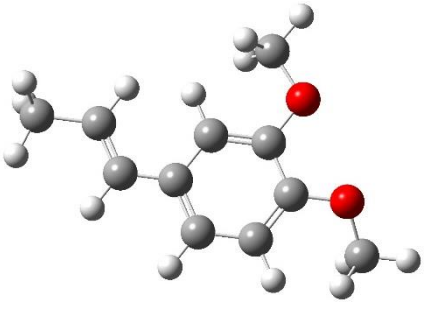
Molecular geometry optimization of the six eugenol-derived compounds was carried out to produce an optimal and stable structure (Rakhman et al., 2019; Muliadi et al., 2021). The eugenol derivative structures used in the molecular geometry optimization were obtained from the 3D structure modeling as shown in figure 2. Geometric optimization of the six eugenol derivative compounds was performed through computational simulation using the AM1 semi-empirical method as shown in table 1.

Table 1. Data on total energy and heat of formation of the eugenol derivatives

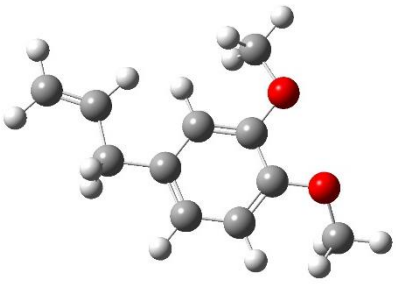
Compounds	Total energy (kcal/mol)	Enthaly formation (cal/mol-kelvin)
E	133.240	39.855
E1	133.944	42.088
E2	152.948	46.424
E3	153.389	47.973
E4	160.643	54.527
E5	134.632	44.144
E6	149.393	44.886



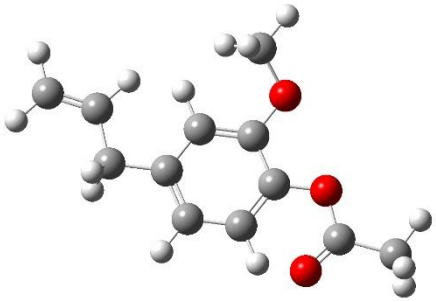
(E)-2-methoxy-4-(prop-1-en-1-yl)phenol
E1



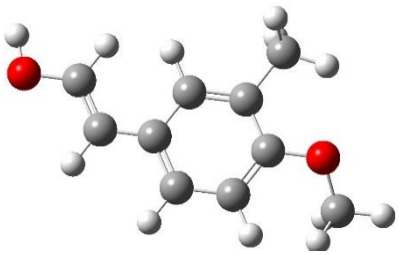
(E)-1,2-dimethoxy-4-(prop-1-en-1-yl)benzene
E2



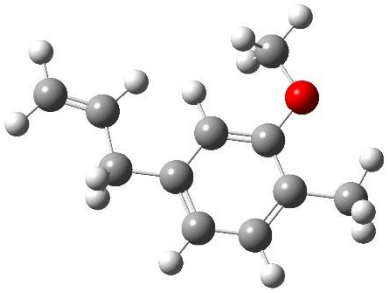
4-allyl-1,2-dimethoxybenzene
E3



4-allyl-2-methoxyphenyl acetate
E4



(E)-2-(4-methoxy-3-methylphenyl)ethenol
E5



4-allyl-2-methoxy-1-methylbenzene
E6

Figure 2. 3D structural modelling of the eugenol derivative compounds using the AM1 semi-empirical method

The QSAR equations for the antimicrobial activity of eugenol-derived compounds were obtained using 3 descriptors, namely electronic, hydrophobic, and steric descriptors. The data results recapitulations of the descriptor are shown in table 1, table 2, and table 3.

Table 2. Electronic descriptor calculations of the compounds examined

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔEG (eV)	Momen Dipole (*D*)
E	–0.31429	0.01303	0.32732	1.6385026
E1	–0.30716	–0.00197	0,30519	1.6987536
E2	–0.30431	0.00029	0,3046	1.1659062
E3	–0.31249	0.01626	0.32875	1.1201790
E4	–0.32589	0.00756	0.33345	1.9923347
E5	–0.30406	0.00492	0.30898	0.9571785
E6	–0.32220	0.01598	0.33818	1.1013894

Calculations of the electronic descriptor, i.e., dipole moment, describe the difference in electronegativity between two atoms that form a covalent bond. The dipole moment is related to the molecular polarity of the eugenol derivative compound (Rakhman et al., 2019; Karim, 2019; Muliadi et al., 2021). Additionally, HOMO, LUMO, and Gap energy (ΔEG) values describe the transfer of electrons.

Hydrophobic descriptors in the form of MSA values describe the surface area of a molecule and PSA value is useful in estimating drug transport properties. Polarizability value describes the ease of a molecule to form instantaneous dipoles and chemical reactivity. Whereas, Log P value describes the hydrophobic/hydrophilic nature of a molecule.

Table 3. Hydrophobic descriptor calculations of the compound examined

Compounds	Log P	Polarizability (Å³)	PSA (Å²)	MSA (Å²)
E	2.03	19.73	29.46	329.40
E1	2.03	19.73	29.46	329.40
E2	2.67	21.64	18.46	366.93
E3	2.67	21.64	18.46	366.75
E4	2.32	24.11	38.69	405.79
E5	1.58	19.73	29.46	330.31
E6	3.46	20.97	9.23	351.51

Table 4. Steric descriptor calculation results

Compound Code	Harary Index	Randic Index	Wiener Indeks
E	29.60	10.75	204
E1	29.60	10.72	204
E2	33.35	11.87	256
E3	33.35	11.90	256
E4	41.14	12.82	388
E5	29.53	10.72	207
E6	29.60	11.43	204

Steric descriptors entail the Harary Index, Randic Index, and Weiner Index which describe the nature of the interaction between chemical objects (atoms, bonds, atomic groups, molecules, molecular pairs, and so on) in a chemical structure (Perwira et al., 2015). The steric descriptor explains antimicrobial activity based on the assumption that changes in the molecular structure of a compound result in different antimicrobial activities.

The analysis of the QSAR equations obtained was carried out using the multilinear regression method. The multilinear regression analysis discerned 2 equation models as shown in table 5.

Table 5. QSAR equation model analysis results

Model	Description	R	R^2	SE
1	qC8, qC2, Polarizability, ELUMO, MD	0.999[a]	0.998	0.07399
2	qC8, qC2, Polarizability, MD	0.997[b]	0.993	0.08968

The best equation is selected based on the value of R and R^2 closest to the value of 1 with the smallest SE value. Based on the consideration of parameters R, R^2, and SE, equation 1 was deemed best. After testing the equations based on R, R^2, and SE values, a test was carried out using the PRESS parameter. The PRESS test was carried out on the equations 1 and 2 to determine the value of association between the Log P and the predicted Log P as a measure of antimicrobial activity. The results of the predicted Log P values are shown in table 6.

Table 6. Log P data prediction and PRESS test of the compounds examined

Kode Senyawa	Log P prediksi	
	Model 1	Model 2
E	1.938454820	1.990327120
E1	1.992100422	1.944751000
E2	2.705244102	2.647946093
E3	2.633715194	2.682535865
E4	2.320441329	2.324036292
E5	1.580000000	1.580000000
E6	3.460044133	3.460403629
PRESS	0.000000000	0.000000000

From the analysis results, the equation model 1 was chosen, having the following formula: Log P = 0.149 (11.299) qC8 – (9.190) qC2 + (0.163) Polarizability – (6.720) ELUMO – (0.783) DM. The relationship representation of the antimicrobial activity shown through Log P and predicted Log P is presented in Figure 3. This relationship illustrates the closeness between Log P and Log P resulting from computational chemistry calculations.

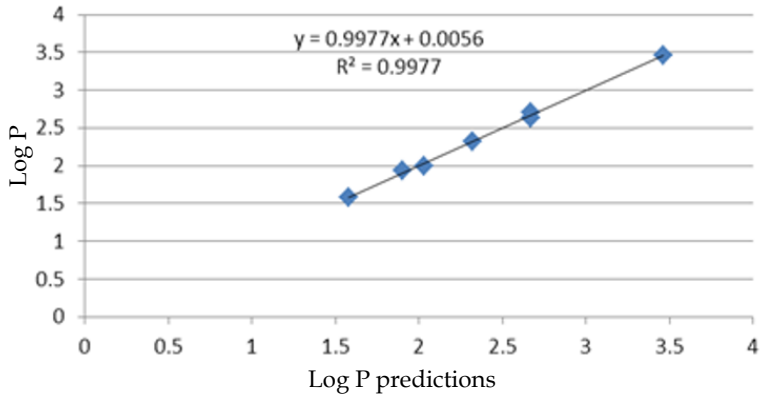


Figure 3. The antimicrobial activity shown through relationship of Log P and computationally predicted Log P using the equation 1 model.

The QSAR analysis results using multiple linear regression showed that there are descriptors that affect antimicrobial activity, namely the net atomic charge qC8, qC2, Polarizability, and dipole moment (DM). Based on Table 6, the best compound to be used as an antimicrobial is the compound E5, *(E)-2-(4-methoxy-3-methylphenyl)ethenol*. The log P of this eugenol compound, when compared to its predicted Log P counterpart, was close in value. Furthermore, it has the smallest Log P value compared to the other eugenol derivative compounds. The small Log P value indicated that the compound would be more distributed in water as a polar medium.

CONCLUSION

Modeling and optimization were carried out using the AM1 semi-empirical method on the molecular structure of six eugenol derivatives. The best QSAR equation model discerned through multiple linear regression analysis able to predict biological activity as an antimicrobial of the eugenol derived compounds was equation model 1: Log P = 0.149 (11.299) qC8 – (9.190) qC2 + (0.163) Polarizability – (6.720) ELUMO – (0.783) DM. Model 1 was chosen as the best QSAR equation through consideration of several parameters such as R, R^2, SE and PRESS.

ACKNOWLEDGEMENTS

We express our deepest gratitude to Dean of FKIP Universitas Khairun who has provided funding for this research through the PKUPT 2022 grant FKIP Universitas Khairun.

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