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COMPUTATIONAL METHODS FOR SELECTION OF FUNCTIONAL MONOMERS IN THE SYNTHESIS OF MOLECULARLY IMPRINTED POLYMER OXYTETRACYCLINE

Selvira Anandia Intan Maulidya, Meilia Suherman*, Angelika

Department of Pharmaceutical Analysis and Medicinal Chemistry,
Faculty of Mathematics and Natural Sciences, Universitas Garut
Jl. Jati 42B, Jati, Tarogong Kaler, Garut, West Java, 44151, Indonesia

*Corresponding author: Meilia Suherman (meilia.suherman@uniga.ac.id)

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Abstract

Oxytetracycline is used to treat various disorders in poultry, particularly hens. Their use, however, may be connected with unsatisfactory residual levels in food. Because the generally used method for analyzing oxytetracycline residues is expensive, unique preparation methods such as the Molecularly Imprinted Polymer (MIP) approach have been developed. MIP is one of the most successful pre-analysis preparation procedures for extracting the target analyte from the complicated matrix. The most significant aspect of creating a successful MIP is the selection of functional monomers compatible with the monomer's physicochemical properties and Oxytetracycline as a template. The PyRx and Autodock apps are used in this study to determine the value of the binding affinity and hydrogen bonding created between the functional monomer and the template. According to the study, the monomer 5-[1-(2,3-dimethylphenyl]-1H-imidazole has the lowest binding affinity value (-4.34 kcal/mol), indicating that the Oxytetracycline template will interact well with this monomer.

Keywords: binding affinity, molecularly imprinted polymer (MIP), oxytetracycline

Introduction

Oxytetracycline is a prescription antibiotic used to treat infections caused by Gram-positive and Gram-negative microorganisms such as Mycoplasma pneumoniae, Pasteurella pestis, Escherichia coli, Haemophilus influenzae (respiratory infection), and Diplococcus pneumoniae. This pharmacological class also functions as an antibacterial agent, protein synthesis inhibitor, antimicrobial agent, anti-inflammatory agent, and bacterial metabolite.[1]

Oxytetracycline is also commonly used to prevent and treat disease in poultry animals such as chickens and promote animal fertility.[2] According to researchers, 75% of poultry (chickens) are resistant to oxytetracycline antibiotics because breeders give antibiotics before and after the birds become ill.[3] Compared to antibiotic residues in poultry, the breeders frequently employ antibiotics before and after sick animals to prioritize poultry protection from disease.[4] This is because of its lipophilic nature, which allows it to leave residue, and because it attaches to cell membranes for a more extended period, necessitating a longer break than other antibiotics.[5]

The most commonly used method for analyzing oxytetracycline residues has the disadvantage of being expensive to acquire good sensitivity, such as high-performance

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liquid chromatography-tandem mass spectrometry[6] or high-performance liquid chromatography–Photodiode array detection[7], which is not available in every laboratory. As a result, adequate preparation processes must be devised to perform oxytetracycline residue analysis using detector HPLC technology, which is widely used in testing laboratories. Molecularly Imprinted Polymers (MIP) synthesis using a specific Solid Phase Extraction (SPE) is currently evolv preparation. MIP is a type of sample pretreatment that can separate and preconcentrate target analytes while removing matrix effects.[8] This MIP production method enables the determination of analyte levels, which may be performed using HPLC, widely used at auctions.[9]

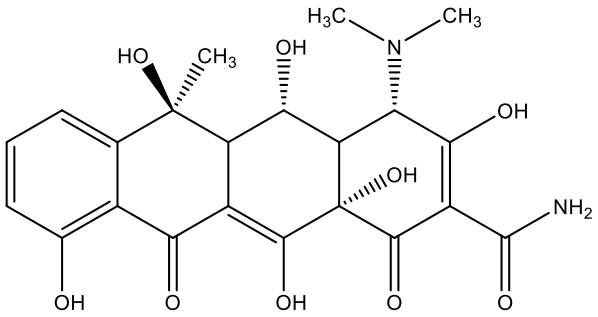

Figure 1. The structure of oxytetracycline

MIPs are selective adsorbents formed by copolymerization of functional monomers and suitable crosslinkers in the presence of target template molecules.[10] Nearly 25 monomers can be employed in the synthesis of MIP, which has been discovered to be used as a functional monomer.[11] Laboratory studies are required to determine the type of monomer that suits the template. Laboratory testing is done by trial and error, which takes a long time. Computational algorithms are now being developed that can anticipate bonds that form between molecules, and this method can be used to determine bonds that occur between monomers and templates, which is predicted to minimize costs and time.[12]

This study will employ in silico modeling, namely computer-assisted drug development via the ligand-ligand docking approach.[13] Before wet laboratory testing (wet lab), the best functional monomer for testing oxytetracycline will be found utilizing computational chemistry methods or molecular docking. The binding affinity value and the type of bond established between the functional monomer and the oxytetracycline template were used to define the test parameters, with a lower binding affinity value suggesting a more significant interaction between the functional monomer and the oxytetracycline template. In addition to the binding affinity value, a search for the type of bond, such as hydrogen bonds made using a template for reversible bonds, is performed.

Method

Tools

Hardware: ASUS X200m Notebook with an Intel Bay Trail-M Dual Core Celeron N2840 2.58 GHz processor, 2GB DDR3 RAM, and 500GB HDD internal storage with a 64-bit operating system was used in this study—software: MarvinSketch freeware, AutoDock 4.2.6, and Pyrx freeware.

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Procedure

Preparation of Functional Monomer Structures and Oxytetracycline templates

Twenty-five functional monomer structures and oxytetracycline templates were downloaded from Pubchem and uploaded to MarvinSketch, where the energy on the monomer structure and the template were minimized with Merck Molecular Force Field (MMFF94) to make the ligand more stable near its initial state during the molecular docking process[14] and then was saved in mol2 format.

Molecular Docking with Pyrrex

Molecular docking on functional monomers is performed to determine the most excellent binding affinity. The AutoDock functionality in the Pyrex program is used to perform molecular docking between functional monomers as ligands and oxytetracycline templates as macromolecules by modifying the grid boxes until the docking process is complete. The docking data were examined, and the least binding energy value, hydrogen bonding, was chosen.

Result

Table 1. Results of Monomer and Template Docking

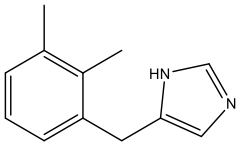
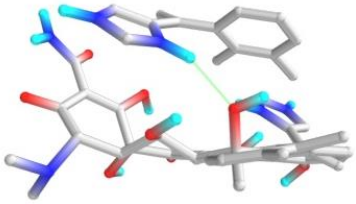
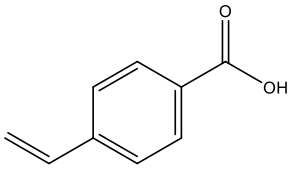
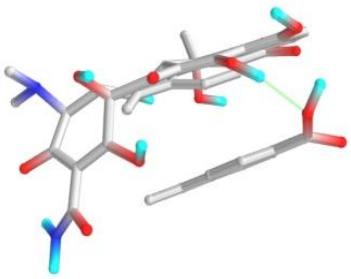
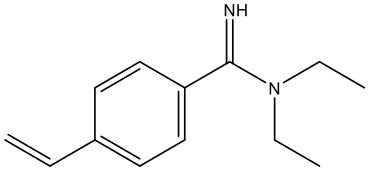
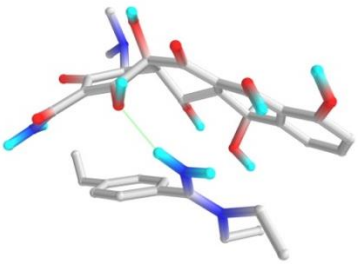
No.	Monomer	Binding Energy	Hydrogen Interaction	Image of monomer-interaction
1.	 5-[1-(2,3-dimethylphenyl]-1H-imidazole	-4,34	Hydrogen bonds exist	
2.	 4-ethenylbenzoic acid atau p-vinylbenzoic acid	-3,82	Hydrogen bonds exist	
3.	 N,N-diethyl-4-styryl amide	-3,37	Hydrogen bonds exist	

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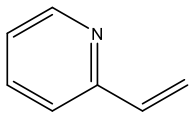
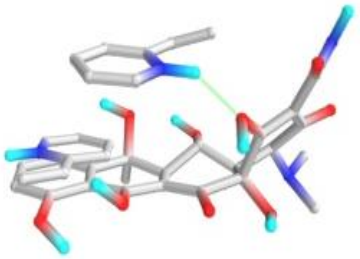
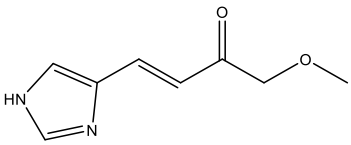
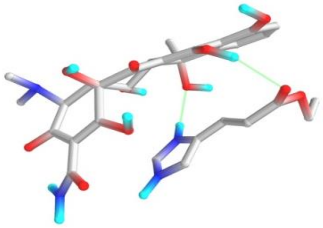
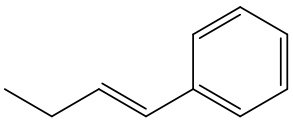
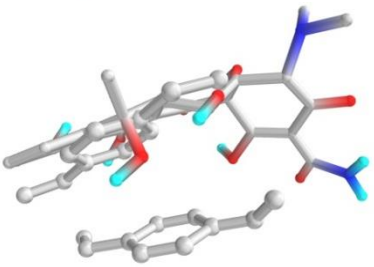
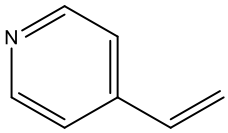
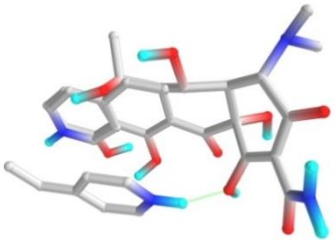
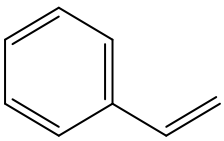
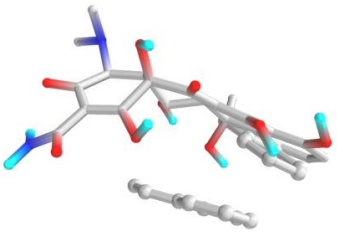
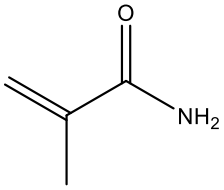
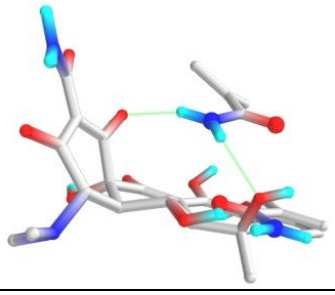
Table 1. (Extension)

No.	Monomer	Binding Energy	Hydrogen Interaction	Image of monomer-interaction
4.	 2-ethenyl pyridine atau 2vinyl pyridine (2VP)	-3,31	Hydrogen bonds exist	
5.	 Urocanic ethyl ester	-3,11	Hydrogen bonds exist	
6.	 Ethylstyrene	-3,09	Hydrogen bonds do not exist	
7.	 4-ethenyl pyridine atau 4-vinyl pyridine (4-VP)	-2,92	Hydrogen bonds exist	
8.	 Styrene	-2,91	Hydrogen bonds do not exist	
9.	 Methacrylamide	-2,7	Hydrogen bonds exist	

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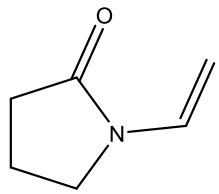
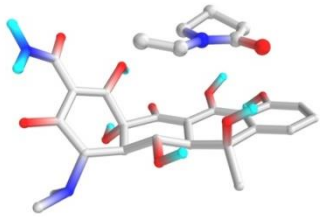
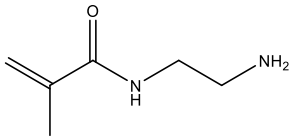
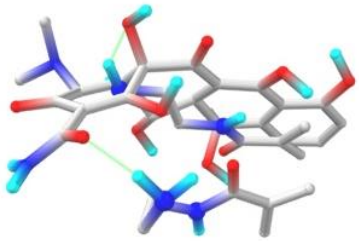
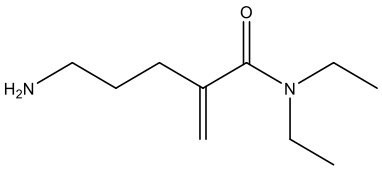
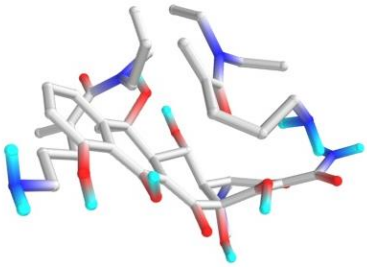
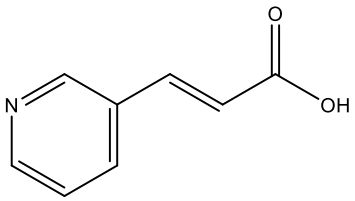
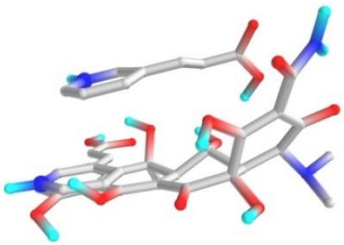
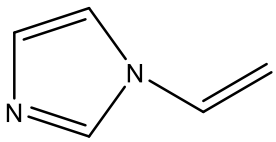
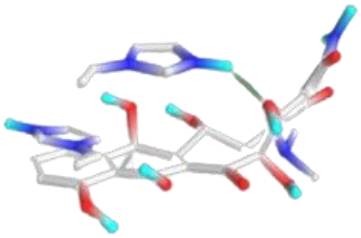
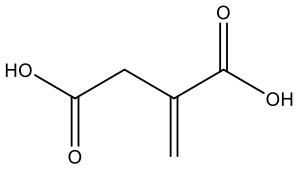
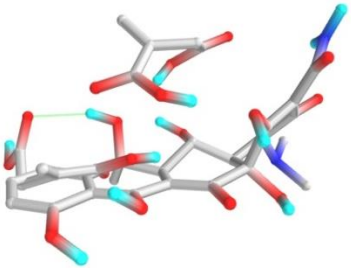
No.	Monomer	Binding Energy	Hydrogen Interaction	Image of monomer-interaction
10.	 N-vinylpyrrolidone	-2,65	Hydrogen bonds do not exist	
11.	 N-(2-Aminoethyl) methacrylamide	-2,62	Hydrogen bonds exist	
12.	 N N-diethyl aminoethyl methacrylamide	-2,55	Hydrogen bonds do not exist	
13.	 Trans-3-(3-pyridyl)-acrylic acid	-2,55	Hydrogen bonds do not exist	
14.	 1-ethenyl imidazole	-2,52	Hydrogen bonds exist	
15.	 2-methylidene butane dioic acid atau itaconic acid	-2,46	Hydrogen bonds exist	

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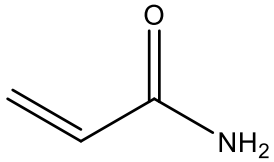
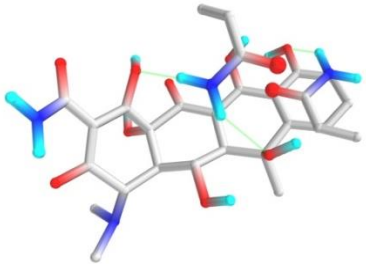
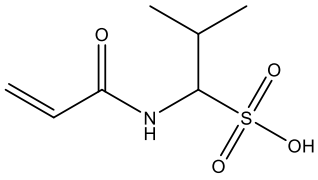
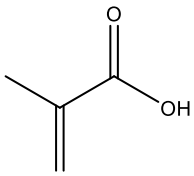
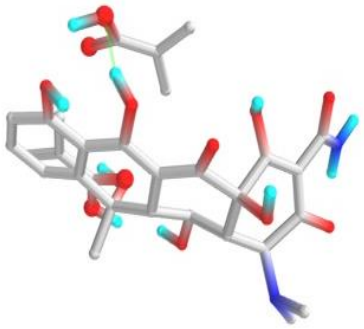
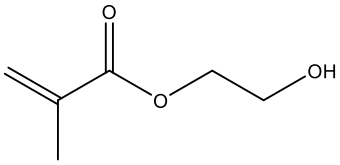
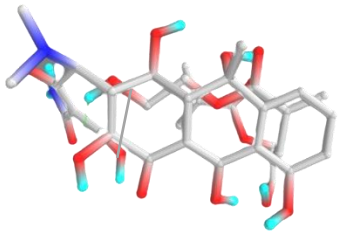
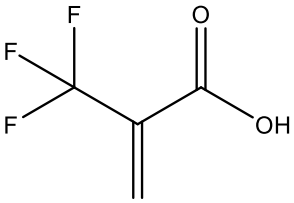
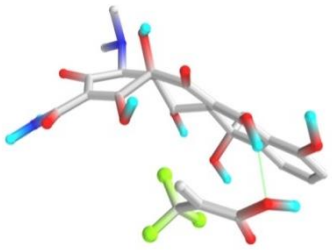
No.	Monomer	Binding Energy	Hydrogen Interaction	Image of monomer-interaction
16.	 Acrylamide	-2,45	Hydrogen bonds exist	
17.	 AAcrylamide(2-methyl)-propane sulfonic acid	-2,35	Hydrogen bonds exist	
18.	 2-Methylprop-2-enoic acid atau asam metakrilat/MAA	-2,32	Hydrogen bonds exist	
19.	 2-hydroxyethyl methacrylate (2-HEMA)	-2,25	Hydrogen bonds exist	
20.	 2-Propenoic acid,2-(trifluoromethyl) atau 2-(trifluoromethyl)-acrylic acid atau TFMAA	-2,24	Hydrogen onds exist	

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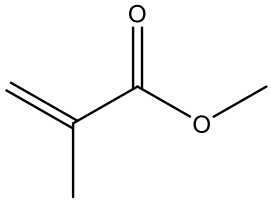
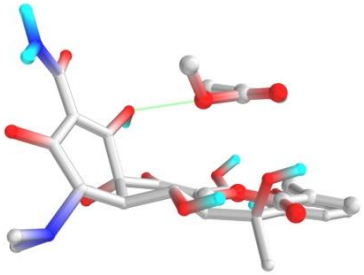
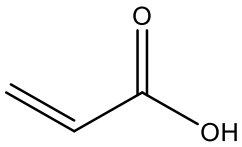
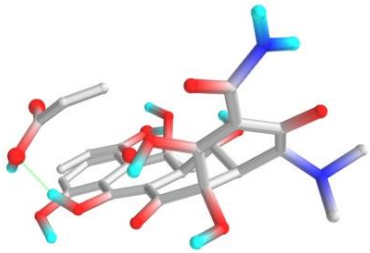
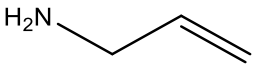
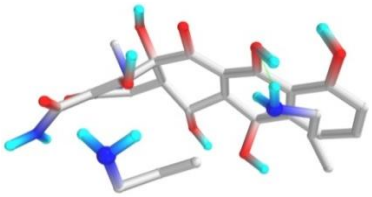
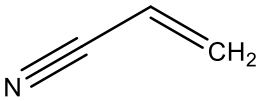
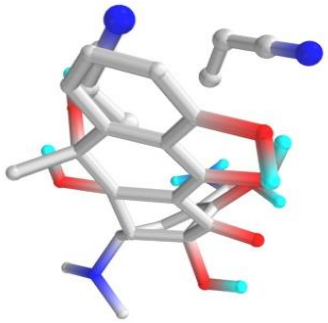
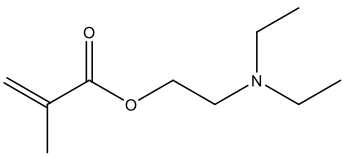
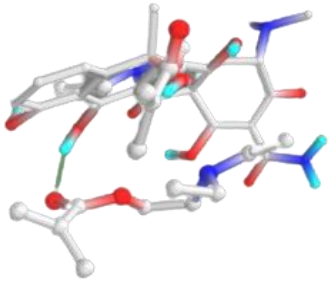
21.	 Methyl methacrylate (MMA)	-2,06	Hydrogen bonds exist	
22.	 Prop-2-enoic acid atau acrilic acid/AA	-2,0	Hydrogen bonds exist	
23.	 Prop-2-en-1-amine atau allylamine	-1,87	Hydrogen bonds do not exist	
24.	 Acrylonitrile (AN)	-1,85	Hydrogen bonds do not exist	
25.	 2-(Diethylamino) ethyl methacrylate	-1,64	Hydrogen bonds exist	

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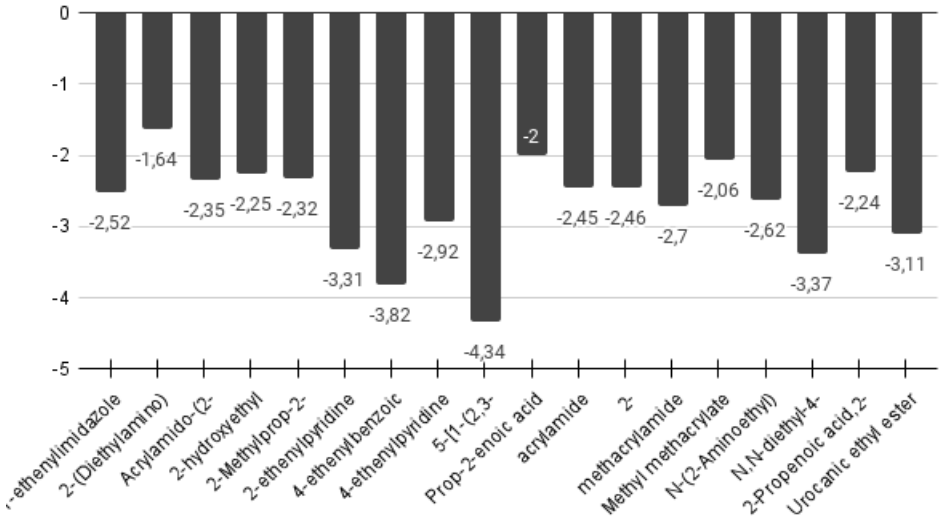

Figure 2. Graph depicting the interaction of functional monomers and hydrogen-bonded oxytetracycline templates.

Discussion

In this study, in silico testing, or computer-based drug discovery employing computational chemistry or molecular docking procedures using the ligand-docking methodology, was used.[13] In this case, oxytetracycline will be employed as a template, and various functional monomers will be used to provide polymer-compatible binding sites. PubChem provided the oxytetracycline structure as well as 25 monomer configurations. The metrics shown in the test results are the binding affinity and hydrogen bonding between the monomer and the template. The monomer and template interaction becomes stronger when the binding affinity drops.[15] In comparison to other monomers, the monomer 5 - [1 - (2,3 - dimethylphenyl] - 1H - imidazole has the lowest bond energy with the template (figure 1). Furthermore, hydrogen bonds are generated between the template and the monomer, and the interaction between the template molecule and the functional groups contained in the polymer matrix promotes molecular recognition.[14]

Conclusion

Based on the interaction of functional monomers with oxytetracycline templates that produce the lowest binding affinity values, namely 5 - [1 - (2,3 - dimethylphenyl] - 1H - imidazole of -4.34 kcal/mol and hydrogen bonds are formed, oxytetracycline templates are predicted to interact with monomers, which have the potential to be used for the synthesis of Oxytetracycline Molecularly Imprinted Polymers (MIPs), and further research (wet lab) is needed to confirm this.

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