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STRUCTURE MODIFICATION AND MOLECULAR MODELING OF 1-(BENZOYLOXY)UREA DERIVATIVES AS ANTICANCER DRUG CANDIDATES

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INTRODUCTION

Structure modification made in designing new drugs, by changing the structure of the lead compound. Changes in the structure of a compound would alter the physicochemical properties including lipophilic, electronic and steric properties of the compound (Korolkovas, 1988; Siswandono, 2014). Changes in physicochemical properties would lead to changes in the activity of each compound (Hardjono et al, 2016). Molecular modeling through in silico test is a test that is done through computer simulation. Molecular Modeling is used to predict a new drug candidate compounds to be synthesized. This test was performed in order to improve efficiency in the optimization of the activity of the lead compound (Topliss J.G., 1988, Istyastoro 2007; Jenzen 2007, Kumar C.S, 2013, Dyah N.W., 2016).

Some derivatives of *1*-(Benzoyloxy)urea showed cytotoxic activity and predicted could be used as anti-cancer drugs (Hardjono, 2012; Hardjono 2016). Mechanism of action of urea derivatives including *1*-(Benzoyloxy)urea was by inhibiting the action of the enzyme ribonucleotide reductase. This in silico test research done by docking the compound whicg activities to be predicted using MVD (Molegro Virtual Docker) program. The target cell used in docking was 2EUD, a ribonucleotide reductase enzyme crystal I, which forms a complex with the derivative *1*-(Benzoyloxy)urea. 2EUD chosen because it was the target cell from Gemsitabin which work mechanism similar to urea (Xu H., 2006). From in silico test would be obtain Rerank Score (RS) values, which was the bond energy between the ligands and target cell. Small RS value indicated that the bond energy needed between the compound with a target cell was also small. The smaller the bond energy indicated that the bond was more stable. The more stable binding of ligands to the receptor, it could be predicted activity will be even greater (Hardjono, 2012).

In this research would be done molecular modeling of twenty-four *1*-(Benzoyloxy)urea derivatives. The in silico test result was an image that showed the hydrogen bond, Electrocic and steric interaction as well as the value of RS from *1*-(Benzoyloxy)urea and its derivatives. Of the entire RS values obtained would be seen *1*-(Benzoyloxy)urea derivates which had the smallest RS value or predicted to have the greatest cytotoxic activity.

RESEARCH METHOD

Devices : computer

Program :1. Chem Bio Draw Ultra Version 12.
2. Chem Bio 3D Ultra Version 12.
3. Molegro Virtual Docker 5

Method :

1-(Benzoyloxy)urea derivative which would be docked drawn through the Chem Bio Draw Ultra Version 12, then went through to the Bio Chem 3D Ultra program Version 12. After measured, the minimum energy was then stored in the form mol2 {SYBYL2 (* mol2)}. Then do the docking of the 2EUD. The results were hydrogen bond, electrostatic interaction, steric interaction drawing and the value of RS.

RESULTS AND DISCUSSION

In this research, docking between twenty-four *1*-(Benzoyloxy)urea derivatives with the target cell 2EUD. From the results obtained bonding compound docking with the target cells in the form of: hydrogen bonding and steric interactions. An example is the result of docking *1*-(3-(Acetoxy)benzoyloxy)urea with 2EUD. To be more clear interaction between 1-(3-(Acetoxy)benzoyloxy)urea with 2EUD can be seen in Figure 1, Figure 2 and Figure 3. For purposes of comparison is the interaction *1*-(Benzoyl-oxy)urea with 2EUD, which can be seen in Figure 4, Figure 5 and Figure 6 as well as interaction Hydroxyurea with 2EUD, in Figure 7, Figure 8 and 9. While the number bonds and RS value of all the compounds can be seen in table 1.

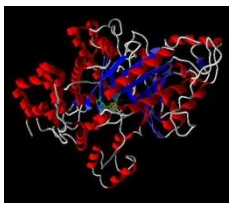

Figure 1:
***1*-(3-Acetoxybenzoyloxy)-urea position in 2EUD.**

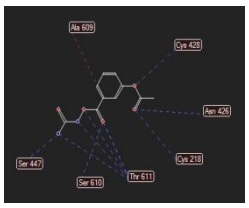

Figure 2:
The interaction between *1*-(3-Acetoxybenzoyloxy-urea with 2EUD (2D)

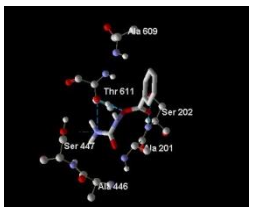

Figure 6:
The interaction between *1*-(Benzoyloxy)urea with 2EUD (3D).

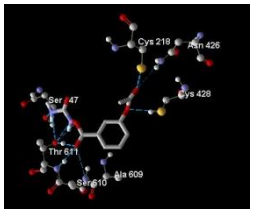

Figure 3:
The interaction between *1*-(3-Acetoxybenzoyloxy)-urea with 2EUD (3D)

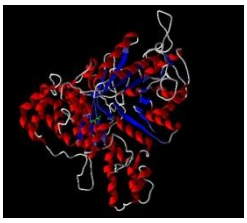

Figure 7:
Hydroxyurea position in 2EUD.

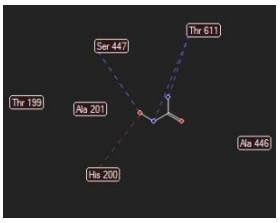

Figure 8:
The interaction between Hydroxyurea with 2EUD (2D).

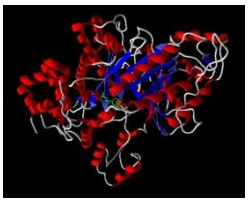

Figure 4:
***1*-(Benzoyloxy)urea position in 2EUD.**

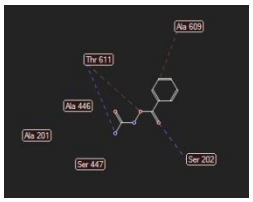

Figure 5:
The interaction between *1*-(Benzoyloxy)urea with 2EUD (2D).

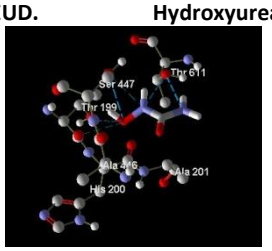

Figure 9:
The interaction between Hydroxyurea with 2EUD (3D).

Table 1: The number of interaction and RS value of *1*-(Benzoyloxy)urea derivatives

No	Compound	Number of Interaction		Rerank Score
		Hydrogen Bond	**Steric Interaction**	
1	Hidroxyurea	3	1	-42.2353
2	*1-(Benzoyloxy)urea*	3	2	-79.7460
3	*1-(2,3,4,5,6-Pentafluorobenzoyloxy)urea*	3	7	-86.8210
4	*1-(2,3,4,5-Tetrafluorobenzoyloxy)urea*	2	3	-84.1487
5	*1-(2,4,6-Trichlorobenzoyloxy)urea*	3	3	-82.1876
6	*1-(2,4-Difluorobenzoyloxy)urea*	3	2	-87.1424
7	*1-(2,4-Dimethoxybenzoyloxy)urea*	2	2	-89.2553
8	*1-(2,6-Difluorobenzoyloxy)urea*	3	4	-85.3527
9	*1-(2-Bromobenzoyloxy)urea*	3	-	-83.1272
10	*1-(2-Chloro-5-nitrobenzoyloxy)urea*	3	4	-85.4795
11	*1-(2-Chloro-6-fluorobenzoyloxy)urea*	1	2	-84.8170
12	*1-(2-Chlorobenzoyloxy)urea*	4	1	-82.3227
13	*1-(2-(Chlorometyl)benzoyloxy)urea*	3	2	-86.1660
14	*1-(2-Fluoro-5-(trifluoromethyl)benzoyloxy)urea*	6	1	-89.2303
15	*1-(2-Fluoro-6-(trifluoromethyl)benzoyloxy)urea*	6	3	-87.5713
16	*1-(2-Fluorobenzoyloxy)urea*	3	1	-83.9959
17	1-(2-Nitrobenzoyloxy)urea	6	5	-87.9184
18	1-(2-(Trifluoromethyl)benzoyloxy)urea	4	5	*-86.1942*
19	*1-(3,5-Dinitrobenzoyloxy)urea*	9	2	*-90.3608*
20	**1-(3-(Acetoxy)benzoyloxy)urea**	**9**	**2**	***-93.4433***
21	*1-(3-Bromobenzoyloxy)urea*	4	1	-84.4185

22	*1-{3-(Chlorosulfonyl)benzoyloxy}urea*	5	2	-86.1404
23	*1-(3-Nitrobenzoyloxy)urea*	6	2	*-85.6313*
24	*1-(4-Trifluoromethylbenzoyloxy)urea*	4	2	*-89.7731*
25	*1-(4-tert-butylbenzoyloxy)urea*	3	1	*-89.7397*
26	*1-(6-Chloro-2-fluoro-3-methylbenzoyloxy)urea*	4	3	-84.3031

From Table 1 it can be seen that 1-(3-(Acetoxy)-benzoyloxy)urea and 1-(3,5-Dinitrobenzoyloxy)urea having the most number of bonds, namely nine hydrogen bonds and twosteric interaction. The bond energy or RS value between 1-(3-(Acetoxy)benzoyloxy)urea and 2EUD was the smallest, namely -93.4433, while the RS value of *1*-(Benzoyloxy)urea was -79.7460 and Hydroxyurea was -42.2353. From the number of bonds and the RS value could be said that the bond between 1-(3-(Acetoxy)benzoyl-oxy)urea with 2EUD as a target cell was the most stable, so it could be predicted that the 1-(3-(Acetoxy)benzoyl-oxy)urea had the greatest activity.

CONCLUSION

The conclusion of this study was that the compound of *1*-(3-(Acetoxy)benzoyloxy)urea was predicted to have the greatest **CYTOTOXIC** activity among all of *1*-(Benzoyloxy)urea derivatives, even predicted to have greater cytotoxic activity than *1*-(Benzoyloxy)urea and hydroxyurea.

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