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Design of 2-Phenylamino Benzothiopyrano [4,3-D] Pyrimidines Compound as an Anticancer

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***Abstract*—In this study, the design of benzothiopyrano pyrimidine derivatives as an anticancer was carried out using the Quantitative Structure-Activity Relationship (QSAR) method. The method used for calculation of the properties was semiempirical Austin Model 1 (AM1), and the activity data (GI_{50}) was obtained from the literature. The statistical analysis of the QSAR result using Multiple Linear Regression (MLR) gave the best descriptors that affect the anticancer activity, i.e. qC10, qC11, E_{HOMO}, E_{LUMO} with the best QSAR equation: Log GI_{50} = 57.601 (qC11) – 63.343 (qC10) + 28.470 (E_{HOMO}) – 37.374 (E_{LUMO}) – 2.528. The molecular docking analysis to anticancer protein 3L3M revealed that the proposed compound with the best predicted anticancer activity has a hydrogen bond with amino acids TYR246, HIS201, and TYR235.**

***Keywords*—Anticancer, Austin model 1 (AM1), Benzothiopyrano Pyrimidines, docking, QSAR**

I. INTRODUCTION

Cancer is one of the second leading causes of death in the world after heart disease. In 2018, the WHO reported 18.1 million cancer cases, and 9.6 million people died worldwide. The most cancer deaths incidents in the world occurred in Asia (57.3%), Europe (23.4%), and Africa (7.3%) [1].

Currently, cancer treatment is done by surgery, radiation, or chemotherapy. However, a type of therapy through chemotherapy has not obtained satisfactory results due to the lack of specific and effective drug activity as well as it has some very complex side effects. It has also been stated that some of the anticancer drugs were resistant to the cancer cells and toxic to normal cells [2].

Several cases of resistance that have been reported include 5-fluorouracil compounds [3-5], cisplatin [6-9], cytarabine [10], and doxorubicin [11]. The resistance cases encourage an effort to treat cancer patient by using chemotherapy in combination with protein P53, but this combination even increases the resistance cases. At present, there is an urgency for the discovery of new active compounds as a single drug or chemotherapy material that is more selective and sensitive to cancer cells. One compound that reported to have anticancer activity was benzothiopyrano pyrimidine derivatives [12]. The benzothiopyrano pyrimidine compound was also found to be active as an antiphlogistic [13], antiproliferative [14], and antiplatelet [15].

One of the efforts to get the best anticancer activity of benzothiopyrano pyrimidine compounds can be performed through QSAR and molecular docking studies. The drug design research using QSAR and docking analysis are commonly used by many researchers to propose some compounds with anticancer activity [16], antimalarial [17], antitumor [18], anticancer [19], and anti-diabetic [20].

II. RESEARCH METHOD

A. *Equipment and Materials*

In this research, all of the QSAR and docking studies were performed in a personal computer with Intel® Inside Core™ i7 processor (1.5 GHz, 8 GB RAM, 64-bit system type, and Windows® 7 Ultimate Operating system) using Discovery Studio, Gaussian 09, Chemdraw 15, Chem3D Ultra 15, and SPSS 22.0 programs.

The data used in the QSAR study was 19 (nineteen) benzothiopyrano pyrimidine derivatives with anticancer activity (GI_{50}) by Salerno et al., 2018 [12].

B. *QSAR Analysis*

One of the benzothiopyrano pyrimidine compounds that had the best anticancer activity (GI_{50} value) from the literature [12] was optimized using the AM1, PM3, and HF methods to predict the ^{1}H-NMR data (calculated). The calculated ^{1}H-NMR data then would be compared with the actual ^{1}H-NMR data from the experimental. The method that produced the smallest or closest PRESS (Predictive Residual Sum of Square) value to the experimental ^{1}H-NMR data was then determined as the best method and used as the optimization method for all compounds.

C. *Statistical Analysis*

The preparation to generate the QSAR model was started by randomly dividing the 19 compounds into two groups of data, namely the training and test set. The compounds in the

training set were analyzed using Multiple Linear Regression (MLR) with the backward method that was run on the SPSS 22.0 program. From the models produced, some models were selected based on the specified statistical parameters such as r^2, SD, and F value, as well as the number of descriptors for validation step.

The best QSAR equation model obtained from the training set data was then validated using the test set data. The accepted model was determined by the smallest PRESS value. Furthermore, a plot was made between the log GI_{50} value of the experimental (from literature) and the predicted results to determine the correlation between the experimental and the predicted activity. The model was said to be valid if it fulfills the criterion of $r^2_{prediction} > 0.6$ [21].

D. *Design of the Proposed Compound and Activity Prediction*

The best model was used to design and proposed some compounds with predicted anticancer activity. The proposed compounds were designed by replacing the R3 substituent from benzothiopyrano pyrimidine derivatives based on the correlation between substituent properties and bioactivity of the compound. In designing the proposed compound, it is necessary to consider the isosteric nature of the substituents. Compounds that have been designed were calculated their molecular orbitals that affect anticancer activity. The GI_{50} value of the proposed anticancer compound was calculated by entering the value of an influential electronic descriptor (included in the QSAR equation). The compound with the smallest log GI_{50} value was determined as the best-proposed compound.

E. *Molecular Docking*

Molecular docking was carried out to Human poly (ADP-ribose) polymerase-1 (HsPARP-1) (protein anticancer target) which retrieved from Protein Data Bank with the code of sensitive protein of 3L3M (2.5 Å). The docking procedure was conducted according to the previous work [22,23]

III. RESULTS AND DISCUSSION

A. *Determination of Optimization Method*

Determination of the best computational method for QSAR analysis of benzothiopyrano pyrimidine as an anticancer was done by comparing the ^{1}H-NMR chemical shift value (δ, ppm) from the experimental with the calculations result using AM1, PM3, and HF methods. The predictions of the ^{1}H-NMR were performed on the compound with the best anticancer activity and the results were presented in Table 1.

Based on Table 1, it can be seen that the best optimization method was the Austin Model 1 (AM1), which has the closest calculation results to the experimental, marked by the PRESS value of 5.40 that smaller than the PM3 (48.93) and HF (60.97) methods. The correlation value also showed that the AM1 method gave the highest correlation value of 0.95, better than the PM3 (0.64) and HF (0.62) methods. From these results, it can be concluded that Austin Model 1 (AM1) method was the best optimization method for the nineteen benzothiopyrano pyrimidine derivatives.

B. *Selection of Training and Test Set*

A total of 19 anticancer compound from benzothiopyrano pyrimidine derivatives was randomly divided into two data groups (Table 2), namely training (15 compounds) and test set (4 compounds). The training set compound was statistically analyzed by Multiple Linear Regression (MLR) to produce several QSAR models, while the test set compound was used to validate the QSAR model generated by the training set. The GI_{50} value was first converted to a logarithmic scale before conducted the MLR analysis intending to improve the distribution range of GI_{50} values between the compounds.

C. *QSAR Model Validation*

The QSAR models obtained were validated by calculating the Predicted Residual Sum of Squares (PRESS) value towards the test set compound. The best model was selected by the smallest PRESS value that indicates the least error was generated from the model. The lower PRESS value, the better the QSAR model produced. The PRESS values, the experimental, as well as the predicted GI_{50} from the selected model, was presented in Table 3.

From Table 3, it can be seen that the smallest PRESS value was shown by model 2 with 0.052. Further validation was carried out by plotting the experimental and predicted log GI_{50} to ensure that model 2 was the best QSAR model obtained (Figure 1 and Figure 2). Based on Figure 2, it can be seen that the r^2 value generated from model 2 to the test set compounds gave good correlation with 0.978 compared with model 1 with 0.7426. This result indicates that model 2 was chosen as the best QSAR model for predicting the new benzothiopyrano pyrimidine derivatives compounds with anticancer activity. The obtained model involves some influential descriptors, i.e. qC10, qC11, E_{HOMO}, E_{LUMO} and it was shown in equation as follow:

$$\text{Log } GI_{50} = 57.601\ (qC11) - 63.343\ (qC10) + 28.470\ (E_{HOMO}) - 37.374\ (E_{LUMO}) - 2.528$$

D. *Proposed Compound Design*

The proposed compounds with better anticancer activity were designed by replacing the substituents in the main chain of benzothiopyrano pyrimidine. The designed compound is expected to have better anticancer (GI_{50}) activity than the previously reported benzothiopyrano pyrimidine derivative. The design of the proposed compound can be done by adding electron-withdrawing or donating groups. Substitution of some substituents also must consider the electronic, hydrophobic, and steric properties of the functional group. Electrophilic properties of the electron-withdrawing groups could decrease the electron density of the atoms that are bound with, whereas the electron-donating group with nucleophilic properties could induce the increasing electron density of the neighboring atoms.

Based on the QSAR equation, the influential descriptors for designing the new compound were qC10, qC11, E_{HOMO}, and E_{LUMO}. Nevertheless, the substitution on the C10 atom (qC10) cannot be done because of its properties as the quaternary carbon. Therefore, substitution of the electron-withdrawing group in C6 atom is expected to induce positive charges in C10 as C6 and C10 are an adjacent atom. Based on the calculation of the activity of benzothiopyrano

pyrimidine derivatives generated from the best QSAR model, the proposed compound number 3 with a methyl group showed the best anticancer properties with log GI_{50} of 0.006 μM (Table 4). The methyl group is considered more stable towards benzothiopyrano pyrimidine derivatives because it is exposed to adjacent N atoms more than any other halogen groups.

Molecular docking analysis of the designed compound number 1 displayed the formation of hydrogen bonds with the important amino acid residues such as TYR246, HIS201, and TYR235, as it can be seen in Figure 3 and Figure 4. This docking result showed that the designed compound number 1 has an excellent predicted anticancer activity and it also in accordance with the QSAR analysis result.

IV. CONCLUSION AND RECOMMENDATION

The QSAR analysis could generate some descriptors that affect the anticancer activity of the benzothiopyrano pyrimidine derivatives compound, i.e., qC10, qC11, E_{HOMO}, and E_{LUMO}. The proposed compound with the best predictive anticancer activity based on the best QSAR model was in agreement with the molecular docking result, as it presented the formation of hydrogen bonds with important amino acids TYR246, HIS201, and TYR 235.

A. *Figures and Tables*

Table 1. Comparison of the ^{1}H-NMR Chemical Shift (δ, ppm) of Compound 1

δ H-NMR Experiment	^{1}H-NMR Calculation		
	δ AM1	δ PM3	δ HF
3.62	4.04	3.80	3.99
3.74	4.07	3.87	2.90
3.74	4.09	3.50	2.91
3.79	4.48	3.89	3.40
4.01	4.51	3.93	3.35
6.94	5.44	5.22	4.29
6.99	6.08	5.97	5.48
7.28	7.38	10.46	7.14
8.27	8.53	9.30	8.20
8.40	8.53	2.68	1.69
9.49	8.61	8.71	7.77
Correlation (r)	0.95	0.64	0.62
PRESS	5.40	48.93	60.97

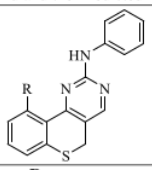
Table 2. List of Training Set and Test Set Compound

Compound	GI_{50} (μM)	Log GI_{50}
1	9.43	0.974
2	10.40	1.017
3	10.60	1.025
4	9.76	0.989
5[a]	13.50	1.130
6	2.10	0.332
7[a]	8.25	0.916
8	4.77	0.678
9	15.50	1.190
10[a]	6.24	0.995
11	16.80	1.225
13	17.00	1.230
14	18.20	1.260
15	10.00	1.000
16	2.30	0.365
17	1.92	0.283
19[a]	1.75	0.243
20	2.23	0.348
21	4.27	0.630

Table 3. Comparison of the Experimental and Prediction log GI_{50} Value of Two QSAR Models towards Test Set Compound

Test Set Compound	Log GI_{50} Experiment	Log GI_{50}Prediction	
		Model 1	Model 2
5	1.130	0.974	1.030
7	0.916	0.718	0.737
10	0.795	0.635	0.695
19	0.243	0.273	0.249
PRESS		**0.089**	**0.052**

Table 4. Proposed Compound and the Predicted Anticancer Activity



Number	R	GI_{50} (μM)
1	CF_3	1.295
2	Dimethylamine	0.011
3	CH_3	0.006
4	OH	0.015
5	Cl	0.115

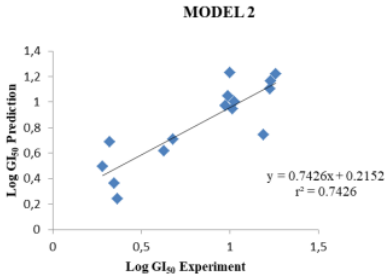


Fig. 1. The plot of log GI_{50} value of the training set from the experimental and prediction result using Model 2

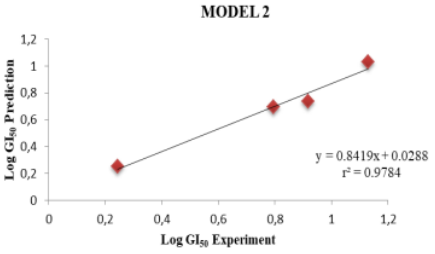


Fig. 2. The plot of log GI_{50} value of the test set from the experimental and prediction result using Model 2

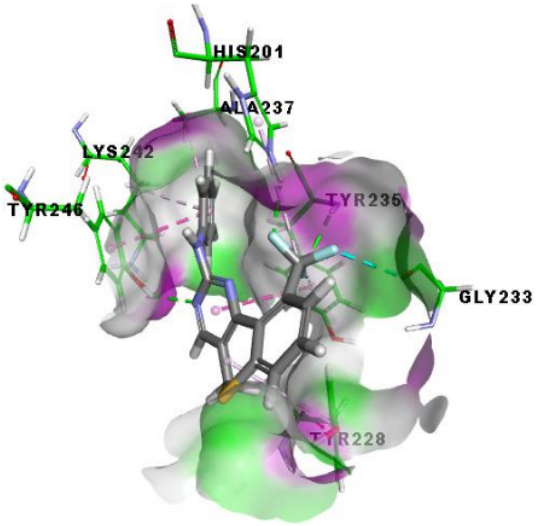


Fig. 3. Interaction of compound (3) to anticancer protein 3L3M (3-D)

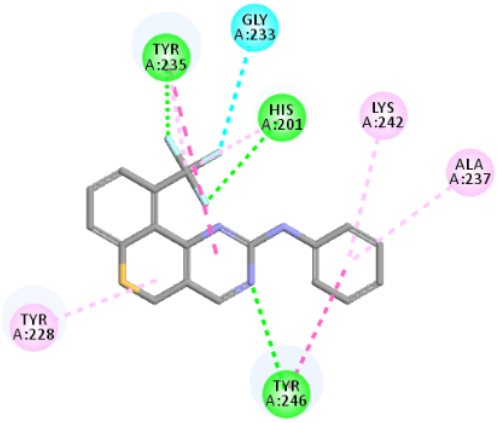


Fig. 4. Interaction of compound (3) to anticancer protein 3L3M (2-D)

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