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Implementation of Ant Colony Optimization – Artificial Neural Network in Predicting the Activity of Indenopyrazole Derivative as Anti-Cancer Agent

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ABSTRACT

Cancer is a disease induced by the abnormal growth of cells in body tissues. This disease is commonly treated by chemotherapy. However, at first, cancer cells can respond to the activity of chemotherapy over time, but over time, resistance to cancer cells appears. Therefore, it is required to develop new anti-cancer drugs. Indenopyrazole and its derivative have been investigated to be a potential drug to treat cancer. This study aims to predict indenopyrazole derivative compounds as anti-cancer drugs by using Ant Colony Optimization (ACO) and Artificial Neural Network (ANN) methods. We used 93 compounds of indenopyrazole derivative with a total of 1876 descriptors. Then, the descriptors were reduced by using the Pearson Correlation Coefficient (PCC) and followed by the ACO algorithm to get the most relevant features. We found that the best number of descriptors obtained from ACO is ten descriptors. The ANN prediction model was developed with three architectures, which are different in hidden layer number, i.e., 1, 2, and 3 hidden layers. Based on the results, we found that the model with three hidden layers gives the best performance, with the value of the R2 test, R2 train, and Q2 train being 0.8822, 0.8495, and 0.8472, respectively.

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1. INTRODUCTION

Cancer is a disease caused by abnormal cell growth in body tissues [1]. At the end of the 20th century, the World Health Organization (WHO) predicts that cancer will be the leading cause of death in the world. In 2018, cancer has caused about 9.6 million deaths worldwide [2]. The case of cancer is predicted to continue to increase along with the increase in the human population [2]. Currently, many methods and drugs have been developed to treat cancer. One method that is widely used is the chemotherapy method. Chemotherapy is done by giving cytotoxic chemicals that can kill cancer cells to reduce cancer-related symptoms [3]. Most the cytotoxic drugs are given to overcome the resistance of cancer cells [4]. At first, cancer cells can respond to chemotherapy activity, but over time, resistance to the given drug appears [3]. In this regard, it is required to develop new anti-cancer drugs.

Currently, many drugs have been developed to treat cancer cells and one of those drugs is indenopyrazole [5]. Indenopyrazole is known to be used as an antitubercular [6] and also has the potential as a central nervous system agent [7], tyrosine kinase inhibitor [8], antidepressant and non-steroidal anti-inflammatory drug [7]. In 2006, S.K. Singh et al. showed that indenopyrazole has the potential as an anti-cancer drug agent [5]. Therefore, various approaches have been developed to synthesize indenopyrazole and its derivatives.

Before a drug is synthesized, it is necessary to be able to predict the physiochemical properties, toxicity, and biological activity of the drug candidate to make it efficient in time and cost before testing in the laboratory. Predictive modeling as one approach of in silico method can be used to improve efficiency. This method is widely used in the field of medicinal chemistry to design and find bioactive compounds in the drug development process [9]. The in-silico method associated with predictive models is commonly known as Quantitative Structure and Activity Relationships (QSAR). QSAR aims to find a consistent relationship between the chemical structure and biological activity of a series of compounds so that it can be used to evaluate a new material with a similar structure to the trained structure [10].

Several studies have been performed to implement QSAR study in developing anti-cancer agents. In 2006, Verma and coworkers conducted a QSAR to predict the activity of 1,4-Naphtoquinones as an anti-cancer agent. The cytotoxic effect of 1,4-Naphtoquinones was discovered to be significantly reliant on hydrophobicity [11]. In 2021, Rizqi and coworkers implemented a simulated annealing-support vector machine method in investigating indenopyrazole derivative as an anti-cancer agent. They found the only model with RBF kernel that satisfies all the validation criteria with R2 score train and test are 0.79 and 0.60, respectively [12]. In 2022, Ikhsanurahman and coworkers evaluated the anti-cancer effect of CDK2 inhibitors using simulated annealing-support vector machine techniques. They obtained the best model from SVM with linear and polynomial kernels with the accuracy and F-1 score values of 0.986 and 0.987, respectively [13].

According to the literature survey, indenopyrazole derivative is known to be one of the potential drugs to be used as an anti-cancer agent. However, to the best of our knowledge, the QSAR study on the anti-cancer activity of indenopyrazole derivative is still very rare. Hence, this study aims to predict the activity of indenopyrazole derivative by using ant colony optimization-artificial neural network (ACO-ANN) methods. The ACO method is used for feature selection because of its ability to find the best features. Also, ACO has good exploration capabilities in finding the optimal solution [14]. Meanwhile, the ANN method is used for predictive models because of its adaptive learning ability, allowing the system to continue running despite fault tolerance [14], [15].

2. METHOD

2.1. Data Set

In this study, we used the chemical structure and bioactivity data of 93 compounds of indenopyrazole derivatives [5]. Molecular descriptors of those compounds were calculated by using the PADEL program to obtain 1876 descriptors. Then, the data set is divided into train and test sets with a ratio of 4:1. The bioactivity of the compounds, which are represented by IC50 value, is used as the target. The IC50 parameter indicates the concentration of a compound that can inhibit 50% of a substrate protein [16]. Then, the IC50 value is converted to pIC50 to obtain the target with the appropriate range. According to the distribution of pIC50 values, shown in Figure 1, we found that the pIC50 lies in the range of 4.5 to 8.0. Also, many compounds were found to have pIC50 around 8.0.

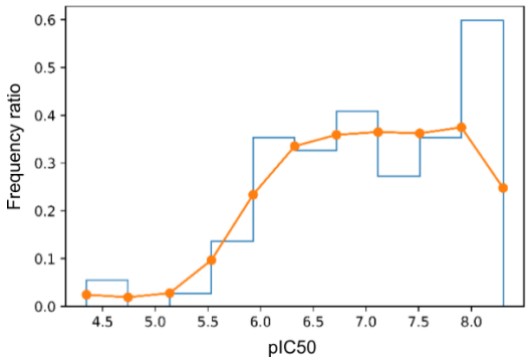

Figure 1. The distribution of pIC50 values

2.2. Feature Selection

Feature selection was performed in two steps. In the first step, feature selection was conducted by calculating Pearson Correlation Coefficient (PCC) between each descriptor and the target. According to

the PCC value, we selected 100 descriptors with the highest correlation to the target. Then, the selected descriptors were further reduced using the Ant Colony Optimization (ACO) algorithm. ACO is an artificial intelligence technique based on the behavior of ants in placing pheromones when looking for food from their nests [17]. Pheromone is a hormone produced by the endocrine glands in ants that is used as a signal so that other ants can recognize it. ACO is widely used to solve optimization problems. The flowchart of the ACO algorithm is shown in Figure 2.

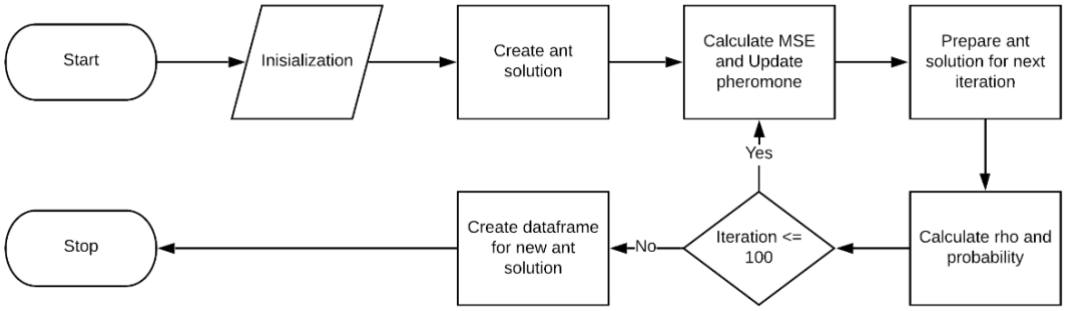

Figure 2. Flowchart of ACO algorithm

ACO algorithm evaluates the best solution according to mean squared error (MSE) value of each ant. Then, the MSE value is used to update the pheromone value for each ant by using the following equation:

$$\tau_i = \rho_i \tau_i + \Delta\tau \tag{1}$$

where τ, ρ and $\Delta\tau$ represent pheromone, evaporation constant, and the change of pheromone, respectively. If the selected descriptor exists in the ant solution, $\Delta\tau = 0$, otherwise:

$$\Delta\tau = \frac{\max_{g=1:k}(MSE_g) - MSE_j}{\max_{h=1:k}(\max_{g=1:k}(MSE_g) - MSE_h))} \tag{2}$$

Then, a new ant solution is prepared for the next generation by using the selected feature from the k best ant solution. Meanwhile, if the selected feature exists in the ant solution subset, the value of ρ is updated by using the following equation:

$$\rho_i = \rho_i + 1 \tag{3}$$

followed by:

$$\rho_i = \frac{p_i}{k} \tag{4}$$

where p and k represent the selected feature for the next generation and the number of best subsets that will give impact to other subset. After that, the probability of each descriptor being selected for the next generation is calculated according to the following equation:

$$P_i = \frac{\tau_i{}^{\alpha} \rho_i{}^{\beta}}{\sum_{i=1:n\_desc} \tau_i{}^{\alpha} \rho_i{}^{\beta}} \tag{5}$$

if the selected feature exists in the subset, otherwise:

$$P_i = 0. \tag{6}$$

where α and β represent the effect of trail intensity and local feature importance, respectively. Finally, the descriptor will be selected by considering the probability value of each descriptor. The initial value of ACO parameters used in this study is presented in Table 1.

Table 1. Initialization of ACO Parameters

Variable	Value
τ	1

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Variable	Value
m	5, 10, 15, 20, 25
α	1
β	1
na	30
k	10
iter	100
e	0.25
rho	1-e = 0.75
n_desc	74

2.3. Artificial Neural Network (ANN)

The basic concept of ANN mimics the mechanism of the human brain in processing, tolerance for errors, and parallel processing [17]. Generally, ANN architecture consists of an input layer, hidden layer(s), and output layer, as shown in Figure 3. The input layer contains several input neurons that act as dendrites. Meanwhile, the hidden layer is an intermediate layer where the main process of ANN occurs in this layer. The output layer contains several output neurons that act like axons. Also, the activation function is defined in each node of the hidden layer and output layer.

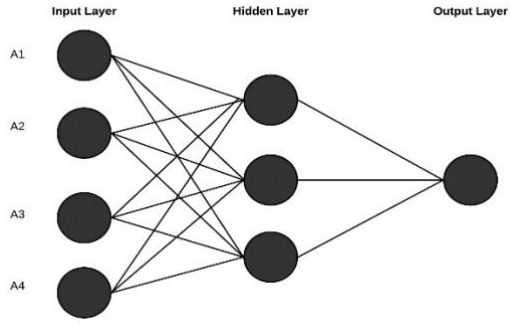


Figure 3. The basic architecture of ANN

In the ANN process, weight and bias values on each neuron will be continuously updated until the output is almost similar to the actual value. At each iteration, an objective function will be evaluated and used as an alternative to stopping criteria. The updating process of weight and bias is performed by using a combination of forward and backward propagation. Forward propagation passes through the input data to each neuron in the hidden layer and the output layer according to the formula shown in equation 7.

$$N_j = \Sigma_i w_{ji}\, x_i + b_j \tag{7}$$

where N, w, x and b represent neuron output, weight, input and bias, resepectively.

The error obtained from forward propagation will be used to update the weight with a certain learning rate value through the backpropagation process. The forward and back propagation processes will be repeated until the weight and bias values are obtained that produce the smallest possible error value in the output layer. In this study, the ANN was developed by using three topologies, i.e., one, two, and three hidden layers. Meanwhile, the number of nodes is defined according to the number of selected descriptors.

2.4. Model Validation

We evaluated the model by calculating internal and external validation parameters. Internal validation and external validation are conducted by evaluating models on train and test sets. Validation

parameters used for validating the prediction model are presented in Equations (8) - (14). Then, the validity of the model is determined by comparing the parameter value with the threshold value, as presented in Equations (15) - (19).

$$R^2_{train} = \frac{\sum(y_{train} - \hat{y}_{train})^2}{\sum(y_{train} - \bar{y}_{train})^2} \quad (8)$$

$$Q^2_{loo} = \frac{\sum(y_{train} - \hat{y}_{loo})^2}{\sum(y_{train} - \bar{y}_{train})^2} \quad (9)$$

$$R^2_{test} = \frac{\sum(y_{test} - \hat{y}_{test})^2}{\sum(y_{test} - \bar{y}_{train})^2} \quad (10)$$

$$\mathrm{k}' = \frac{\sum(y \times \hat{y})}{\sum(y)^2)} \quad (11)$$

$$\mathrm{r}^2_0 = 1 - \frac{\sum(y - k \times \hat{y})^2}{\sum(y - \bar{y})^2} \quad (12)$$

$$\mathrm{r}'^2_0 = 1 - \frac{\sum(\hat{y} - k' \times y)^2}{\sum(\hat{y} - \bar{\hat{y}})^2} \quad (13)$$

$$R^2_p = R\ x\ \sqrt{R^2 - R^2_r} \quad (14)$$

$$R^2 > 0.6 \quad (15)$$

$$Q^2 > 0.5 \quad (16)$$

$$0.85 \leq k' \leq 1.15 \quad (17)$$

$$\left|r^2_0 - r'^2_0\right| < 0.3 \quad (18)$$

$$^{c}R^2_p > 0.5 \quad (19)$$

Also, we evaluated the standardized residual of the predicted value of both the train and test set to ensure that no systematic error found in the model. Finally, the applicability domain (AD) parameter was presented to verify that the model was applicable to all samples in train and test set. The AD was calculated by using the leverage method formulated as following equation:

$$H = X(X^T X)^{-1} X^T \quad (20)$$

where x is the matrix score obtained from the partial least square regression and represented by using the William Plot.

3. RESULTS AND DISCUSSION

3.1. Feature Selection

The feature selection was performed in two steps. In the first step, feature selection is carried out by calculating Pearson Correlation Coefficient (PCC) value to get the best 100 features with a high correlation value to the target. The selected features were further reduced by using Ant Colony Optimization (ACO) to get a combination of 5, 10, 15, 20, and 25 descriptors. The ACO algorithm was carried out 20 times to handle the random noise. Then, the Artificial Neural Network (ANN) prediction model was developed by using the selected descriptor to determine the best combination of the descriptor. The best descriptor was selected according to the value of mean squared error (MSE). The model was developed by utilizing three architectures that differ by the hidden layer number, i.e., 1, 2, and 3 layers.

The influence of descriptor number on MSE value is presented in Figure 4. Generally, we found that the tendency of MSE fluctuation for all models is quite similar. The addition of descriptor number leads to the increase of MSE until one point, and then the further addition reduces the MSE value. According to the results, the best number of descriptors combination, as indicated by the lowest MSE value, for all models is ten descriptors. Meanwhile, the worst descriptor number for the model with 1, 2,

and 3 hidden layers are 15, 20, and 20 descriptors, respectively. This point out the addition of features cannot guarantee the improvement of models. Then, the model with the best combination of descriptors was used for further analysis.

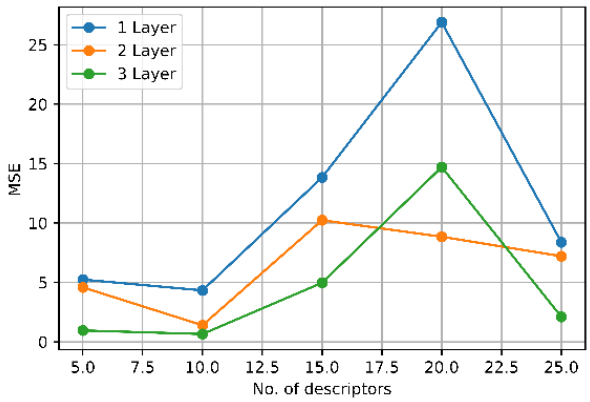
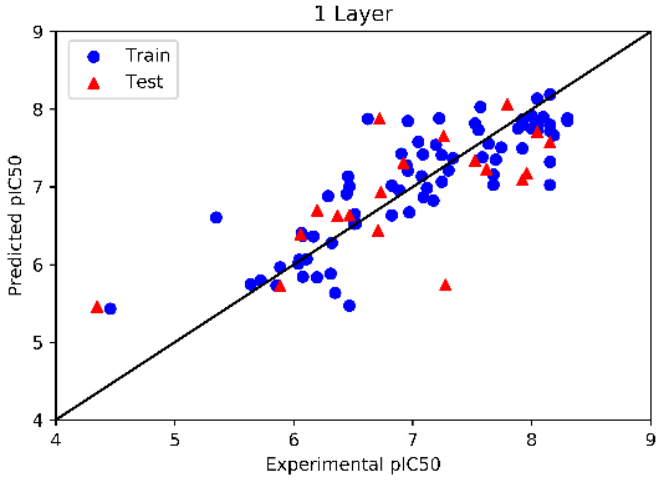


Figure 4. The correlation plot of the number of descriptors on MSE

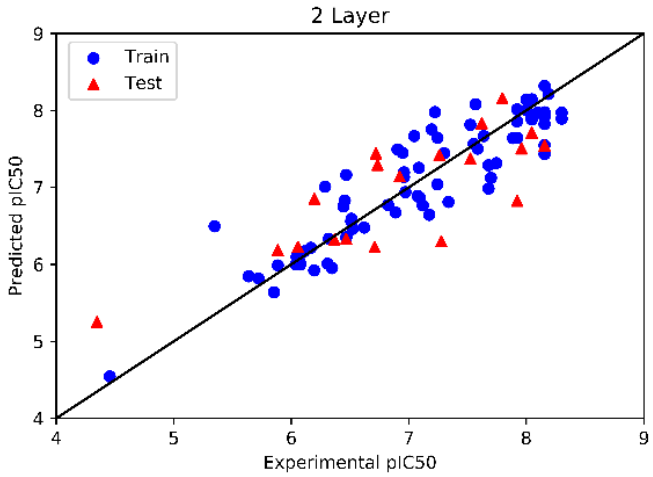
3.2. Prediction Model

We evaluated the predicted values of pIC50 obtained from the artificial neural network (ANN) developed by using the optimal number of descriptors. The evaluation was performed by comparing the predicted values with the actual ones. The scatter plot of predicted values against the actual values for all models is presented in Figure 5. The deviation between the data point with the diagonal reference line represents the prediction error. From the figure, we can see that the ANN model with one hidden layer is not good since many points have a long distance to the diagonal line.

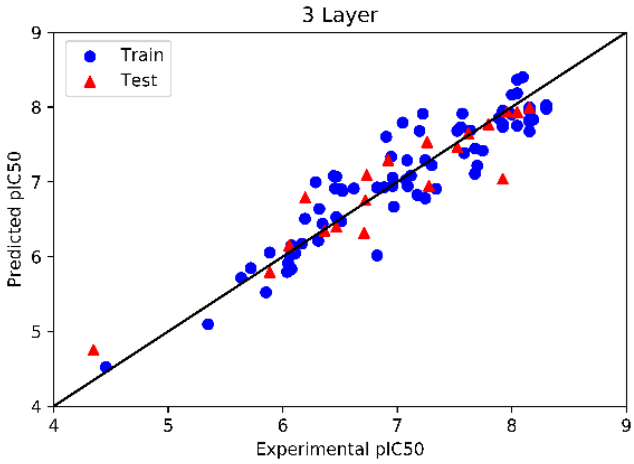
According to the comparison, we calculated several validation parameters of all models for both the train and test sets, as shown in Table 2. As for ANN with one hidden layer, we found that all internal validation satisfies the threshold. However, the external validation confirms that the model is invalid since 3 of 4 parameters do not satisfy the threshold. Meanwhile, the validation results confirm that ANN with two and three hidden layers is valid because all internal and external validation parameter values satisfy the threshold. By considering the R^2 test value, we found that the best model is obtained from ANN developed by using three hidden layers with the value of R^2 test, R^2 train, and Q^2 train are 0.8822, 0.8495, and 0.8472, respectively. This related to the complexity of the model compare to other models. ANN with more hidden layers will have the ability to recognize the more complex level of the data set. Meanwhile, the worst model was obtained from ANN with one hidden layer, which is indicated that the model is too simple, so it fails to recognize the pattern.



(a)



(b)



(c)

Figure 5. Scatter plot of predicted values against actual values obtained from model developed using (a) 1 hidden layer, (b) 2 hidden layers, and (c) 3 hidden layers

To investigate the contribution of the ACO feature selection scheme in improving the model performance, we also presented the validation parameter results of models developed without the ACO algorithm, as shown in Table 3. As for ANN with one hidden layer, we found that the ACO scheme improves all validation parameters. Also, ACO can change the k' parameter to become valid. However, according to the validation results, the model without ACO is still invalid. Meanwhile, ACO also improves all validation parameters of ANN with two hidden layers. Indeed, ACO can improve several invalid parameters of the model to make the model become valid. As for ANN with three hidden layers, ACO dramatically improves R^2 and Q^2 values to make this model the best one.

Table 2. Validation Parameter Values for All Models with ACO Selection Feature

Paramater	1 *Layer*		2 *Layer*		3 *Layer*		*Threshold*
	Train	*Test*	*Train*	*Test*	*Train*	*Test*	
R^2	**0.71**	0.52	**0.82**	**0.65**	**0.84**	**0.88**	> 0.6
Q^2	**0.71**	-	**0.82**	-	**0.84**	-	> 0.5
k'	**0.88**	0.82	**0.97**	**0.85**	**0.96**	**0.99**	$0.85 \leq k' \leq 1.15$
$\lvert r_0^2 - r_0^2 \rvert$	**0.24**	0.35	**0.00**	**0.12**	**0.00**	**0.01**	< 0.3
$^cR_p^2$	**0.73**	-	**0.82**	**-**	**0.70**	-	**>** 0.5
p - value	**0.97**	**0.95**	**0.96**	**0.99**	**0.96**	**0.99**	**>** 0.5

Table 3. Validation Parameter Values for All Models without ACO Selection Feature

Paramater	1 *Layer*		2 *Layer*		3 *Layer*		*Threshold*
	Train	***Test***	***Train***	***Test***	***Train***	***Test***	
R^2	**0.63**	0.50	0.59	0.59	**0.61**	**0.61**	> 0.6
Q^2	**0.63**	-	**0.59**	-	**0.61**	-	> 0.5
k'	0.84	0.80	0.81	**0.90**	**0.89**	**0.86**	$0.85 \leq k' \leq 1.15$
$\lvert r_0^2 - r_0^2 \rvert$	**0.28**	0.44	**0.25**	**0.07**	**0.21**	**0.16**	< 0.3
$^cR_p^2$	**0.66**	-	**0.63**	-	**0.66**	-	**>** 0.5
p - value	**0.89**	**0.87**	0.32	**0.99**	**0.64**	**0.99**	

We presented the analysis of the standardization residual shown in Figure 6 to confirm that no systematic error was found in the model. The standardized residual values were derived from the difference between predicted and actual values. From the figure, we found that our best model is not related to the systematical error, which is indicated by the random value of the standardization residual values.

Finally, we evaluated Applicability Domain (AD) to point out the applicability of the model to samples in both train and test sets, as shown in Figure 7. The applicability of the model on a sample is indicated by the position of the sample that lies inside the rectangle of the domain. From the figure, we found that only two samples lie outside of the rectangle. Since the number of samples outside the region is not significant, we can conclude the model is applicable to the used data set.

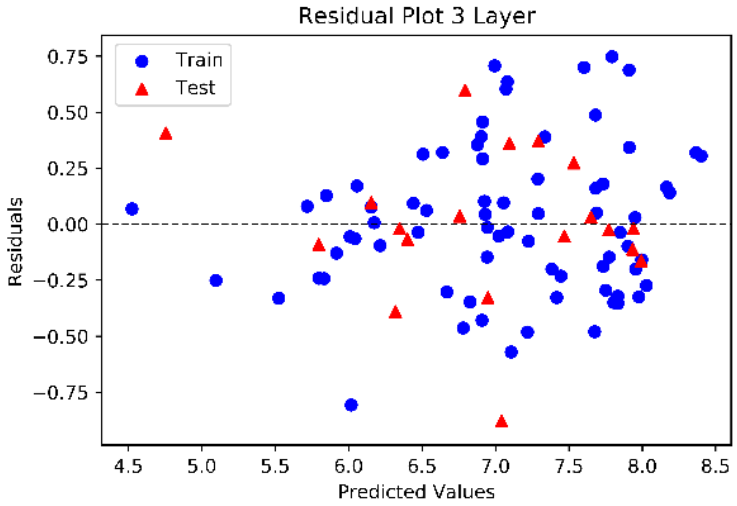


Figure 6. The scatter plot of standardized residual plot for ANN model with 3 hidden layers

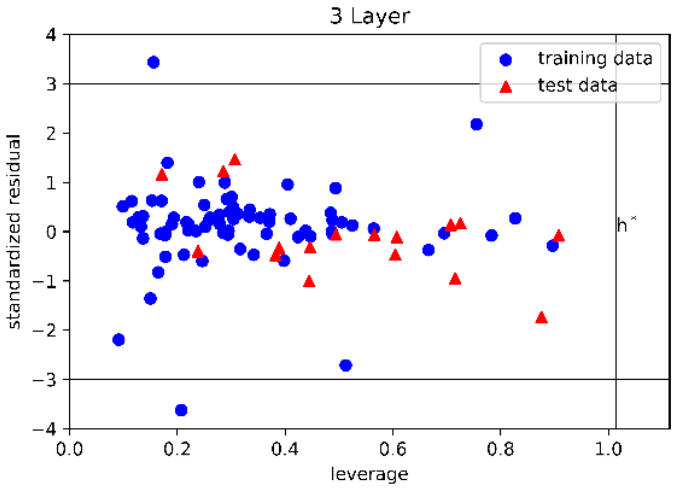


Figure 7. Applicability domain of ANN with 3 hidden layers

4. COMPARISON WITH RELATED STUDY

As a part of the evaluation of our model, we compared our results with the related study performed by Singh et al., which developed a 3D-QSAR model using the CoMFA method, as shown in Table 4 [5]. Here, we compared three validation parameters, i.e., R^2 train, Q^2, and R^2 test. As for the validation of the train set, our study underperformed in the R^2 train and outperformed in the Q^2 parameter. However, the Q^2 parameter is assumed to be more accurate since it was calculated using leave-one-out cross-validation instead of the hold-out method. Hence, our model has a better ability to predict internal data. In the case of external validation, we found that the value of the R^2 test of our study is also higher than the Ref. [5]. This points out that our model is better at predicting the external data set. Overall, we found that the implementation of ANN combined with ACO for feature selection gave a better model than the Ref. [5].

Table 4. The Comparison of Our Results Compare to the Related Study

Parameter	Ref. [5]	Our Study
R^2 train	0.94	0.84
Q^2	0.75	0.84
R^2 Test	0.76	0.88

5. CONCLUSION

We have developed prediction models to predict the activity of indenopyrazole derivatives as an anti-cancer agent by using ant colony optimization - artificial neural network (ACO-ANN) methods. The reduction of feature number has been successfully performed by using ACO. Then, the prediction model was developed by using ANN with three architectures based on different hidden layer numbers, i.e., one, two, and three hidden layers. The performance of the models was evaluated and validated by calculating several validation parameters and comparing those values with the defined threshold. According to the results, we found that the best model obtained from three hidden layers of ANN developed with ten descriptors that produce the values of R^2 test, R^2 train, and Q^2 train are 0.8822, 0.8495, and 0.8472, respectively.

REFERENCES

[1] "Tentang Kanker - Yayasan Kanker Indonesia." https://yayasankankerindonesia.org/tentang-kanker (accessed Nov. 10, 2022).

[2] "WHO: Kanker Membunuh Hampir 10 Juta Orang di Dunia Tahun Ini." https://www.cnnindonesia.com/gaya-hidup/20180913133914-255-329910/who-kanker-membunuh-hampir-10-juta-orang-di-dunia-tahun-ini (accessed Nov. 10, 2022).

[3] P. Nygren, "What is cancer chemotherapy?," http://dx.doi.org/10.1080/02841860151116204, vol. 40, no. 2–3, pp. 166–174, 2009, doi: 10.1080/02841860151116204.

[4] V. T. DeVita, T. S. Lawrence, and S. A. Rosenberg, DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 8th ed., vol. 2. 2008.

[5] S. K. Singh, N. Dessalew, and P. V. Bharatam, "3D-QSAR CoMFA study on indenopyrazole derivatives as cyclin dependent kinase 4 (CDK4) and cyclin dependent kinase 2 (CDK2) inhibitors," Eur J Med Chem, vol. 41, no. 11, pp. 1310–1319, Nov. 2006, doi: 10.1016/J.EJMECH.2006.06.010.

[6] M. J. Ahsan et al., "Discovery of novel antitubercular 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues," Bioorg Med Chem Lett, vol. 21, no. 18, pp. 5259–5261, Sep. 2011, doi: 10.1016/J.BMCL.2011.07.035.

[7] T. L. Lemke, E. Abebe, P. F. Moore, and T. J. Carty, "Indeno[1,2-c]pyrazolone Acetic Acids as Semirigid Analogues of the Nonsteroidal Anti-inflammatory Drugs," J Pharm Sci, vol. 78, no. 4, pp. 343–347, Apr. 1989, doi: 10.1002/JPS.2600780417.

[8] Z. Yan et al., "N-glucuronidation of the platelet-derived growth factor receptor tyrosine kinase inhibitor 6,7-(dimethoxy-2,4-dihydroindeno[1,2-C]pyrazol-3-yl)-(3-fluoro-phenyl)-amine by human UDP-glucuronosyltransferases," Drug Metab Dispos, vol. 34, no. 5, pp. 748–755, May 2006, doi: 10.1124/DMD.106.009274.

[9] D. Kesuma, S. Siswandono, B. T. Purwanto, and S. Hardjono, "Uji in silico Aktivitas Sitotoksik dan Toksisitas Senyawa Turunan N-(Benzoil)-N'- feniltiourea Sebagai Calon Obat Antikanker," JPSCR: Journal of Pharmaceutical Science and Clinical Research, vol. 3, no. 1, pp. 1–11, Mar. 2018, doi: 10.20961/JPSCR.V3I1.16266.

[10] E. V. Y.D., M. Chasani, and M. Abdulghani, "Hubungan Kuantitatif Struktur-Aktivitas (HKSA) Antikanker Senyawa Turunan Kalanon dengan Metode Semi Empiris PM3 (Parameterized Model 3)," Molekul, vol. 7, no. 2, pp. 130–142, Nov. 2012, doi: 10.20884/1.JM.2012.7.2.115.

[11] R. P. Verma, "Anti-cancer activities of 1,4-naphthoquinones: a QSAR study," Anticancer Agents Med Chem, vol. 6, no. 5, pp. 489–499, Apr. 2006, doi: 10.2174/187152006778226512.

[12] R. Y. Ikhsanurahman, N. Ikhsan, and I. Kurniawan, "Classification of CDK2 Inhibitor as Anti-Cancer Agent by Using Simulated Annealing-Support Vector Machine Methods," 2022 International Conference on Data Science and Its Applications, ICoDSA 2022, pp. 82–86, 2022, doi: 10.1109/ICODSA55874.2022.9862929.

[13] M. Fajar Rizqi, R. Rendian Septiawan, and I. Kurniawan, "Implementation of Simulated Annealing-Support Vector Machine on QSAR Study of Indenopyrazole Derivative as Anti-Cancer Agent," 2021 9th International Conference on Information and Communication Technology, ICoICT 2021, pp. 662–668, Aug. 2021, doi: 10.1109/ICOICT52021.2021.9527416.

[14] A. M. D. Mesleh, "Feature sub-set selection metrics for Arabic text classification," Pattern Recognit Lett, vol. 32, no. 14, pp. 1922–1929, Oct. 2011, doi: 10.1016/J.PATREC.2011.07.010.

[15] "Jaringan Saraf Tiruan (Artificial Neural Network) | Referensi Kesehatan." https://creasoft.wordpress.com/2008/04/21/jaringan-saraf-tiruan-artificial-neural-network/ (accessed Nov. 10, 2022).

[16] A. Early Febrinda et al., "Kapasitas Antioksidan dan Inhibitor Alfa Glukosidase Ekstrak Umbi Bawang Dayak [Antioxidant and Alpha-Glucosidase Inhibitory Properties of Bawang Dayak Bulb Extracts]," Jurnal Teknologi dan Industri Pangan, vol. 24, no. 2, pp. 161–161, Dec. 2013, doi: 10.6066/JTIP.2013.24.2.161.

[17] W. Budiharto, Machine Learning & Computational Intelligence , 1st ed. C.V. Andi Offset, 2016.