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Activity Modeling of Some Potent Inhibitors Against *Mycobacterium tuberculosis* Using Genetic Function Approximation Approach

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Abstract

Objectives: The research aimed to develop a theoretical (QSAR) model for predicting the activity of 1,2,4-Triazole derivatives as anti-tubercular antagonist.

Methods: Genetic function approximation (GFA) was employed on a dataset of 1,2,4-Triazole derivatives to investigate their activities behavior on *Mycobacterium tuberculosis*. This approach led to selection of the optimum descriptors and to generate the correlation QSAR model that relate their activities values against *Mycobacterium tuberculosis* with the molecular structures of the inhibitors.

Results: The built model was validated and was found to have squared correlation coefficient (R^2) of 0.9134, adjusted squared correlation coefficient (R_{adj}) of 0.8753 and Leave one out (LOO) cross validation coefficient ($\mathbf{Q^2_{cv}}$) value of 0.8231. The external validation set used for confirming the predictive power of the model has R^2pred of 0.7482.

Conclusion: Reliability, stability and robustness of the model obtained by the validation test indicate that the model can be used to design and synthesis other 1,2,4-Triazole derivatives with improved anti-tubercular activities.

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Keywords: Applicability domain, Genetic function approximation, QSAR, Tuberculosis, Triazole.

Genetik Fonksiyon Tahmin Yaklaşımı Kullanılarak *Mycobacterium tuberculosis*'e Karşı Bazı Etkili İnhibitörlerin Aktivite Modellemelerinin Yapılması

Özet

Amaç: Araştırma, anti-tüberküler antagonisti olarak 1,2,4-Triazol türevlerinin aktivitesini tahmin etmeye yönelik teorik (QSAR) bir model geliştirmeyi amaçlamıştır.

Yöntem: Genetik fonksiyon yaklaşımı (GFA), 1,2,4-Triazol türevlerinin *Mycobacterium tuberculosis* üzerine etki tarzlarını araştırmak amacıyla kullanılmıştır. Bu yaklaşım, optimum tanımlayıcıların seçimine ve *Mycobacterium tuberculosis* üzerine etki değerlerini inhibitörlerin moleküler yapılarıyla ilişkilendiren korelasyon QSAR modelinin oluşturulmasına imkân vermiştir.

Sonuç: Oluşturulan model doğrulanmış ve korelasyon katsayısının karesi (R^2) 0.9134, düzeltilmiş korelasyon katsayısının karesi (R_{adj}) 0.8753 ve tek-çıkışlı (LOO) çapraz doğrulama katsayı (Q^2_{cv}) değeri 0.8231 olarak bulunmuştur. Modelin öngörücü gücünü doğrulamak için kullanılan harici doğrulama seti, 0.7482 R^2_{pred} 'ye sahiptir.

Tartışma: Doğrulama testi ile elde edilen modelin güvenilirliği, kararlılığı ve sağlamlığı, modelin, gelişmiş anti-füberküler aktivitesine sahip diğer 1,2,4-Triazol türevlerini tasarlamak ve sentezlemek için kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Uygulanabilirlik etki alanı, Genetik fonksiyon yaklaşımı, QSAR, Tüberkülosis, Triazol.

1. Introduction

Tuberculosis (TB) is the leading infectious disease caused by specie of bacteria known as *Mycobacterium tuberculosis*. About 2.5 billion people were infected with tuberculosis worldwide and mortality of approximately 1.5 million people were reported annually [1-2]. In spite of the first-line drugs; pyrazinamide (PZA), ethambutol (EMB),

streptomycin (STP) , rifampicin (RIF) and isoniazid (INH); the increase in the occurrence of both multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are observed [3,4]. Moreover, treatment requiring the use of these drugs has been reported to cause serious side effects such as: neuropathy and hepatitis are caused by isoniazid [5], thrombocytopenia occurring as a result of rifampicin (RIF) [6]. In highlight of these effects, the synthesis of novel compounds with better anti-tubercular activity has been the target of many pharmacist and medicinal chemistry.

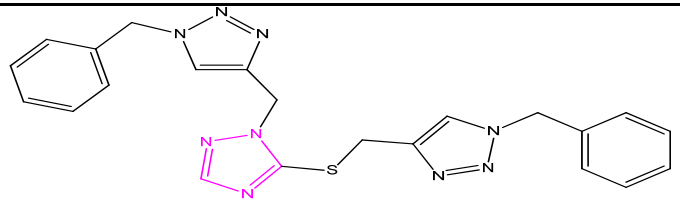
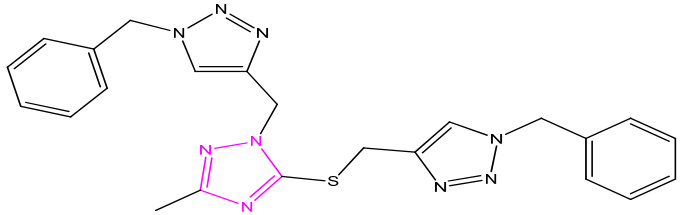
A novel series of 1,2,4-Triazole derivatives have been recently reported and identified as potent inhibitors against of *M. tuberculosis* [7]. Design of novel compounds were usually synthesized using a trial and error approach which is expensive and time consuming. Application of computational chemistry such as Quantitative structure activity relationship (QSAR) help in drug discovery to establish a relationship between various molecular properties of molecules and their observably known activities. The knowledge of (QSAR) technique provides solution to trial and error approach in synthesizing novel drugs and also minimizes effort and time required to discover new compounds or to improve current drugs in terms of their efficiency. The aim of this research was to develop a theoretical (QSAR) model for predicting the activity of 1,2,4-Triazole derivatives against tuberculosis. The aim of this research was to develop QSAR model using Genetic Function Algorithm (GFA) for variable selection of descriptors and multiple linear regression (MLR) method for predicting the activity of 1,2,4-Triazole derivatives as potent anti-*Mycobacterium tuberculosis*.

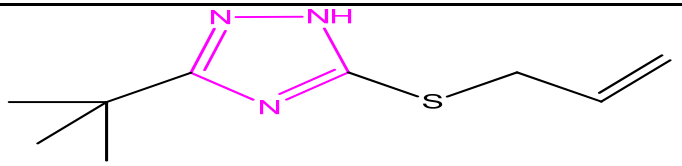
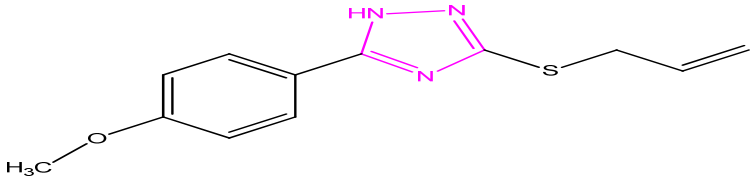
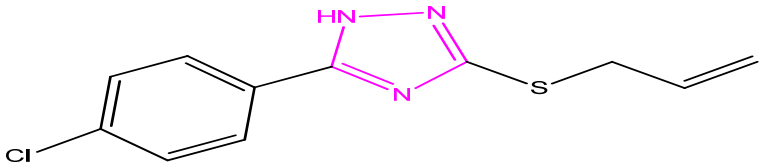
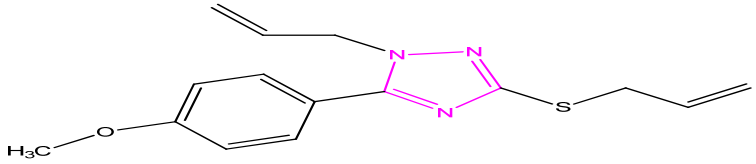
2. Materials and Method

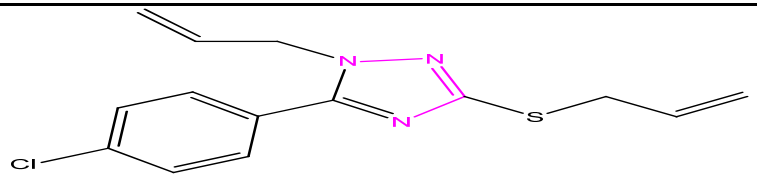
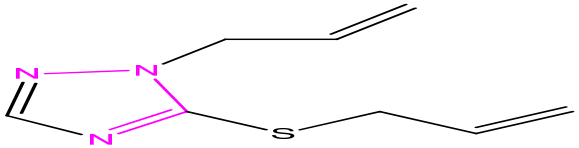
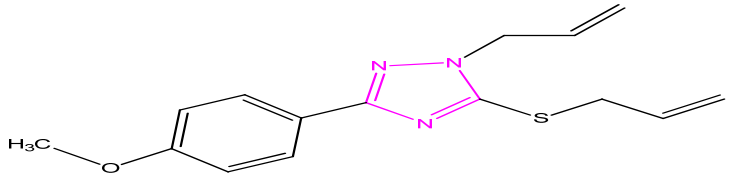
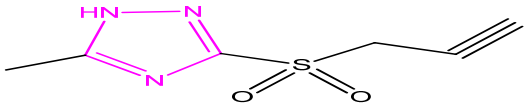
2.1 Data Set

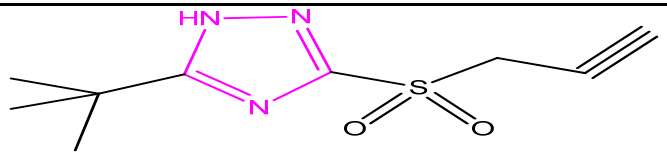
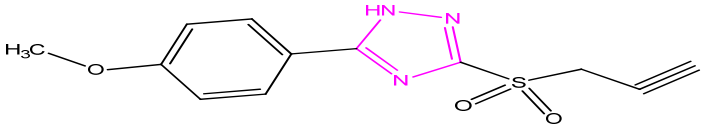
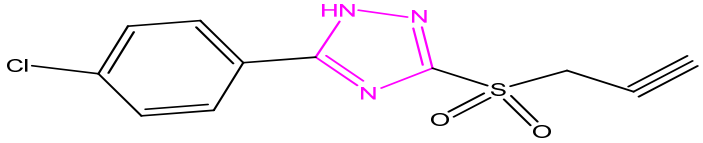
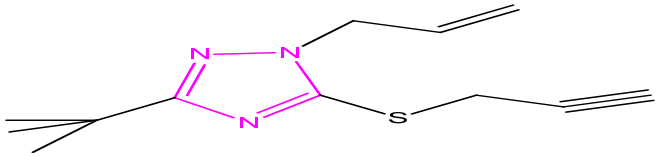
The derivatives of 1,2,4-Triazole derivatives as potent anti-*Mycobacterium tuberculosis* that were used in this research were selected from the literature [7]. The chemical structures alongside with their biological activities of these compounds were presented Table 1.

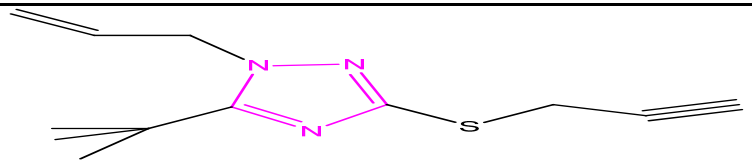
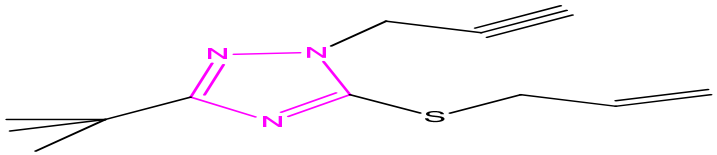
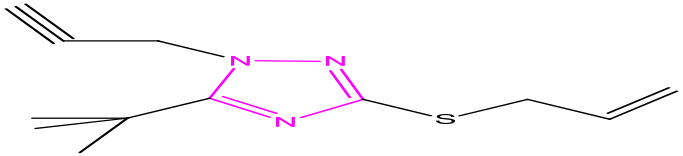
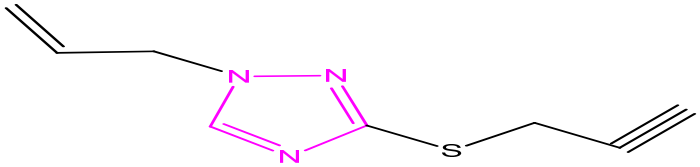
Table 1. Molecular structure of 1, 2, 4-Triazole derivatives and their activities as potent anti-*Mycobacterium tuberculosis*

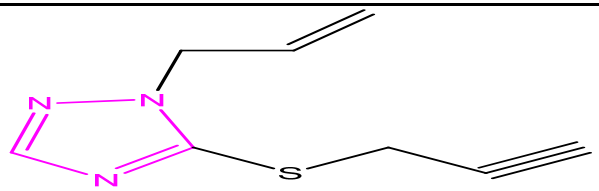
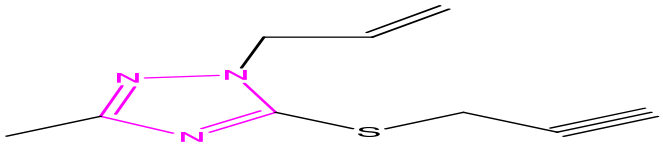
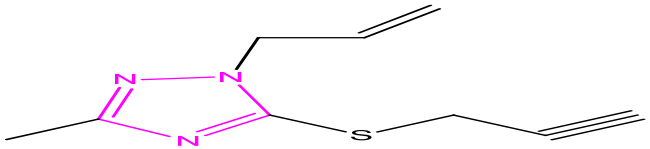
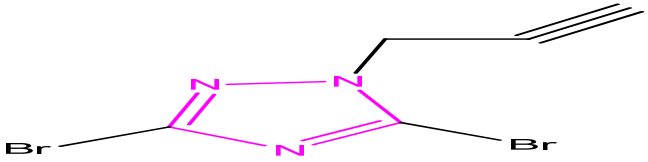
S/N	Molecules	Observed Activity (pBA)	Calculated Activity (pBA)	Residual	Leverage
1[a]	 1-benzyl-4-(((1-((1-benzyl-1H-1,2,3-triazol-4-yl) methyl)-1H-1,2,4-triazol-5-yl) thio) methyl)-1H-1,2,3-triazole	6.3456	6.37977	-0.03417	0.186966
2	 1-benzyl-4-(((1-((1-benzyl-1H-1,2,3-triazol-4-yl) methyl)-3-methyl-1H-1,2,4-triazol-5-yl) thio) methyl)-1H-1,2,3-triazole	7.4134	7.49781	-0.08441	0.267393

S/N	Molecules	Observed Activity (pBA)	Calculated Activity (pBA)	Residual	Leverage
3	 5-(allylthio)-3-(tert-butyl)-1H-1,2,4-triazole	6.4171	6.410504	0.006596	0.832612
4	 3-(allylthio)-5-(4-methoxyphenyl)-1H-1,2,4-triazole	7.6397	7.592776	0.046924	0.15548
5	 3-(allylthio)-5-(4-chlorophenyl)-1H-1,2,4-triazole	8.0899	8.37959	-0.28969	0.328411
6 [a]	 1-allyl-3-(allylthio)-5-(4-methoxyphenyl)-1H-1,2,4-triazole	7.366	7.64835	-0.28235	0.085176

S/N	Molecules	Observed Activity (pBA)	Calculated Activity (pBA)	Residual	Leverage
7	 1-allyl-3-(allylthio)-5-(4-chlorophenyl)-1H-1,2,4-triazole	7.0123	7.01666	-0.00436	0.343511
8 [a]	 1-allyl-5-(allylthio)-1H-1,2,4-triazole	6.5267	6.289043	0.237657	0.089973
9 [a]	 1-allyl-5-(allylthio)-3-(4-methoxyphenyl)-1H-1,2,4-triazole	7.3233	7.60012	-0.27682	0.067538
10	 5-methyl-3-(prop-2-yn-1-ylsulfonyl)-1H-1,2,4-triazole	7.3279	7.127765	0.200135	0.101346

S/N	Molecules	Observed Activity (pBA)	Calculated Activity (pBA)	Residual	Leverage
11	 5-(tert-butyl)-3-(prop-2-yn-1-ylsulfonyl)-1H-1,2,4-triazole	6.8568	7.04696	-0.19016	0.218861
12	 5-(4-methoxyphenyl)-3-(prop-2-yn-1-ylsulfonyl)-1H-1,2,4-triazole	7.3079	7.3622	-0.0543	0.079898
13	 5-(4-chlorophenyl)-3-(prop-2-yn-1-ylsulfonyl)-1H-1,2,4-triazole	7.314	7.277527	0.036473	0.154686
14	 1-allyl-3-(tert-butyl)-5-(prop-2-yn-1-ylthio)-1H-1,2,4-triazole	8.5854	8.6647	-0.0793	0.357197

S/N	Molecules	Observed Activity (pBA)	Calculated Activity (pBA)	Residual	Leverage
15	 1-allyl-5-(tert-butyl)-3-(prop-2-yn-1-ylthio)-1H-1,2,4-triazole	8.0615	7.569	0.4925	0.214607
16	 5-(allylthio)-3-(tert-butyl)-1-(prop-2-yn-1-yl)-1H-1,2,4-triazole	8.0615	7.79949	0.26201	0.263698
17	 3-(allylthio)-5-(tert-butyl)-1-(prop-2-yn-1-yl)-1H-1,2,4-triazole	6.8494	6.60166	0.24774	0.255295
18 [a]	 1-allyl-3-(prop-2-yn-1-ylthio)-1H-1,2,4-triazole	7.9432	7.906989	0.036211	0.409976

S/N	Molecules	Observed Activity (pBA)	Calculated Activity (pBA)	Residual	Leverage
19	 1-allyl-5-(prop-2-yn-1-ylthio)-1H-1,2,4-triazole	7.4535	7.57474	-0.12124	0.25708
20	 1-allyl-3-methyl-5-(prop-2-yn-1-ylthio)-1H-1,2,4-triazole	7.9759	7.966669	0.009231	0.337231
21	 1-allyl-3-methyl-5-(prop-2-yn-1-ylthio)-1H-1,2,4-triazole	7.9759	8.17805	-0.20215	0.249575
22 [a]	 3,5-dibromo-1-(prop-2-yn-1-yl)-1H-1,2,4-triazole	7.9294	7.437563	0.491837	0.577201

Where superscript **a** represent the test set

2.2 Structure Optimization

In order for the molecules to attain a stable conformer at a minimal energy, all the molecules were geometrically optimized with the aid of Spartan 14 V1.1.4 by employing Molecular Mechanics Force Field (MMFF) count to remove strain energy and later subjected to Density Functional Theory (DFT) by utilizing the (B3LYP) basic set [9].

2.3 Molecular Descriptor Calculation

Descriptor is a mathematical logic that describes the properties of a molecule based on the correction between the structure of the compound and its biological activity. Descriptors calculation for all the inhibitory compounds was achieved using PaDEL-Descriptor software V2.20. A total of 1876 molecular descriptors were Observed [10].

2.4 Normalization of Data and Pretreatment

The values for the Observed descriptors' were normalized using Equation 1 below so that each variable will have the same prospect at the inception so as to sway the model [10].

$$Y = \frac{Y_1 - Y_{min}}{Y_{max} - Y_{min}} \quad (1)$$

where Y_1 is the descriptor value for each molecule, Ymin and Ymax are the minimum and maximum value for each descriptors column of Y. After successful normalization of the data, the data were further subjected to pretreatment using in order to remove noise and redundant data.

2.5 Data Division into Training and Test Set

The approach of Kennard and Stone was employed in this study to divide the data set into a training set and a test compounds in proportion of 70 to 30%. The training set was used to establish the QSAR model while the test was used to confirm the established model [11].

2.6 Development of the Model

Multi-linear regression approach (MLR) is a strategy used to develop the QSAR. MLR display a direct relationship between the dependent variable Y and independent variable X (descriptors). In MLR analysis, the mean of the dependent variable Y relies on X (Descriptors). MLR equation below is used to incorporate more than one independent variable (Descriptors) with a single response variable.

$$Y = k_1x_1 + k_2x_2 + k_3x_3 + C \quad (2)$$

where Y represent the dependent variable, represent the independent variables, 'k's are regression coefficients for each '*x*'s and 'C' is a regression intercept.

2.7 Generation of QSAR Model and Validation

The combinations of the optimum descriptors for the training set were obtained from the descriptor pool using the Genetic Function Approximation technique. Their anti-lung cancer activities were placed as the last column in their respective spread sheets in Microsoft Excel 2010 which were later imported into the Material Studio software version 8.0 to generate the QSAR and to evaluate the internal validation parameters.

2.8 Determination of Outlier and Influential Molecule (Applicability Domain)

The applicability domain approach was employed to determination of outlier and influential molecule. Any compound outside the applicability domain space of ± 3 is said to be an outlier. To define and describe the applicability domain of the built QSAR models, the leverage *hi* approach was employed and defined as [12].

$$hi = X_i\,(X^TX)^{-1}\,X_i^T \quad (3)$$

where *Xi* is training set matrix of *i*. *X* is the n× k descriptor matrix of the training set compound and X^T is the transpose of the training set (*X*). X_i^T is the transpose matrix X_i used

to build the mode. The warning leverage h^* is the limit values to check for influential molecule. The warning leverage h^* is defined as;

$$h^* = 3\,\frac{(j+1)}{m} \tag{4}$$

where *j* is the number of descriptors in the build model and *m* is the number of compounds that made up the training set [11].

2.9 Assessment of Y-Randomization

The evaluation of Y-Randomization is to show that the developed QSAR model created is reliable, strong, robust and not gotten by chance. This test was performed on the training set data as described by [13]. Multi-linear regression (MLR) models were generated by randomly shuffling the dependent variable (activity data) while keeping the independent variables (descriptors) unaltered. It is expected that the developed QSAR model should have significantly low R^2 and Q^2 values for numbers of trials in order to ascertain that the developed QSAR models is robust. Y-randomization Coefficient (cR_p^2) is another important parameter which should be more than 0.5 for passing this test.

$$cR_p^2 = R \times [R^2 - (R_r)^2]^2 \tag{5}$$

Where cR_p^2 is Y-randomization Coefficient, R is correlation coefficient for *Y*-Randomization and Rr is average 'R' of random models.

2.10 Quality Assurance of the Model

The fitting ability, stability, reliability, predictive and robustness of the developed models were evaluated by internal and external validation parameters. The validation parameters were compared with the accepted threshold value for any QSAR model [12] shown in Table 2.

3. Results and Discussion

A theoretical model (QSAR) was developed and accomplished to examine the data set comprises ciprofloxacin derivatives as potential anti-lung cancer. The successful application of Multi Linear Regression (MLR) approach led to development of three QSAR models but Model 1 was selected as the best model due to the statistical significance. The observed and calculated activities for inhibitory compounds as well as the residual values were reported in Table 1. The low residual value between observed and calculated activities implies that the model has a very high extrapolative measure.

Model 1

pBA = -0.37456543543 (AATS5e) + 2.087643542 (minHCsatu) + 0.293436327 (RDF90s) + 3.02312046

Model 2

pBA = -0.3285458991* (AATS7s) + 0.024550934 (TDB9e) - 0.117941052 (RDF110i) - 9.645640119

Model 3

pBA = -0.335632223* (AATS7s) + 0.021034761 (TDB9e) - 0.129647108* (RDF30i) + 8.992978173

Validation parameters for selected Model 1 reported in Table 2 passed the required threshold value which actually confirmed the robustness of the model.

The names and symbols of each descriptors used in the QSAR model were all presented in Table 3. Combination of 2D and 3D descriptors reported in the model proposes that these types of descriptors are able to give an improved characterization of the anti-tubercular agents.

Statistics and Pearson's correlation were performed for all the four descriptors in the QSAR Model 1 and the results were reported were reported in Table 4. The low correlation coefficients that exist between each pair of the descriptor in Model 1 signify that there is no intercorrelation between each descriptor. Calculated Variance Inflation Factor (VIF) reported for each descriptor was found to be less than four (4) and this is an assurance that the descriptors were statistical orthogonal and the model developed was statistically substantial.

The Mean Effect (ME) values reported in Table 4 gives vital information on the effect of each descriptor and the degree of contribution in the developed model. The magnitude and the signs of the mean effects values indicate their direction and individual strength of the descriptor on the activity of the inhibitory molecule. The estimated P-values for all the descriptors in the Model 1 at 95% level reported in Table 4 were less than 0.05. Therefore the null hypothesis that says there is no association between the descriptors and the activities of the molecules is rejected. Hence the alternative hypothesis that says there is a relationship between the descriptors used in generating the model and the activities of the compounds at $p < 0.05$ is accepted.

Y- Randomization test was also conducted and reported in Table 5. Coefficient for Y-randomization (cR_p^2) value of 0.733262 greater than 0.5 supports the claim that the model generated is powerful and not inferred by chance.

Table 2. Validation parameters for each model using Multi-linear Regression (MLR)

S/No	Validation Parameters	Formula	Threshold	Model 1	Model 2	Model 3
		Internal Validation				
1	Friedman LOF	$\frac{SEE}{\left(1 - \frac{C + d \times p}{M}\right)^2}$		0.03562	0.03653	0.03931
2	R-squared	$1 - \left[\frac{\sum\left(Y_{exp} - Y_{pred}\right)^2}{\sum\left(Y_{exp} - \overline{Y}_{training}\right)^2}\right]$	$R^2 > 0.6$	0.9142	0.8832	0.8565
3	Adjusted R-squared	$\frac{R^2 - P\,(n-1)}{n - p + 1}$	$R^2_{adj} > 0.6$	0.8851	0.8488	0.8124
4	Cross validated R-squared (Q^2_{cv})	$1 - \left[\frac{\sum\left(Y_{pred} - Y_{exp}\right)^2}{\sum\left(Y_{exp} - \overline{Y}_{training}\right)^2}\right]$	$Q^2 > 0.6$	0.8324	0.8031	0.7820
5	Significant Regression			Yes	Yes	Yes
6	Critical SOR F-value (95%)	$\frac{\sum\left(Y_{pred} - Y_{exp}\right)^2}{p} \Big/ \frac{\sum\left(Y_{pred} - Y_{exp}\right)^2}{N - p - 1}$	$F_{(test)} > 2.09$	3.6832	3.6932	3.7233
7	Replicate points			0	0	0
8	Computed observed error			0	0	0

9	Min expt. error for non-significant LOF (95%)			0.06432	0.05632	0.07632
		Model Randomization				
10	Average of the correlation coefficient for randomized data ($\bar{\boldsymbol{R}}_{\boldsymbol{r}}$)		$\bar{R} < 0.5$	0.3719	0.3287	0.4321
11	Average of determination coefficient for randomized data ($\bar{\boldsymbol{R}}_{\boldsymbol{r}}^{\boldsymbol{2}}$)		$\bar{R}_r^2 < 0.5$	0.1645	0.1356	0.2353
12	Average of leave one out cross-validated determination coefficient for randomized data ($\bar{\boldsymbol{Q}}_{\boldsymbol{r}}^{\boldsymbol{2}}$)		$\bar{Q}_r^2 < 0.5$	-1.2524	-1.4321	-1.3734
13	Coefficient for Y-randomization (cR_p^2)	$R^2 \times \left(1 - \sqrt{\lvert R^2 - \bar{R}_r^2 \rvert}\right)$	$^{c}R_p^2 > 0.6$	0.7332	0.6432	0.6284
		External Validation				
14	$\mathbf{R}_{\mathbf{test}}^{\mathbf{2}}$	$1 - \frac{\sum(Y_{ext} - \hat{Y}_{ext})^2}{\sum(Y_{ext} - \bar{Y})^2}$	$R_{pred}^2 > 0.6$	0.7494	0.7112	0.6532

Table 3. Descriptors used in the QSAR optimization model

S/No	Descriptors Symbols	Name of Descriptor(s)	Class
1	AATS5e	Average Broto-Moreau autocorrelation - lag 5 / weighted by I-state auto-correlation	2D
2	minHCsatu	Minimum atom-type H E-State: H on C sp3 bonded to unsaturated C	2D
3	RDF90s	Radial distribution function - 110 / weighted by relative I-state	3D

Table 4. Pearson's correlation and statistics for descriptor used in the QSAR model

Inter-correlation			**Statistics**		
AATS7s	TDB9e	RDF90i	P-Value (Confidence Interval)	VIF	Mean Effect (ME)
AATS7s	1		0.00014	2.4313	-0.4322
TDB9e	-0.18343	1	0.00073	2.2322	0.5356
RDF90i	0.43432	-0.23298	0.00051	1.0132	0.2084

Table 5. Y- Randomization Parameters test for Model 1

Model	R	R^2	Q^2
Original	0.85791	0.736009	0.361481
Random 1	0.263469	0.069416	-0.42957
Random 2	0.634931	0.403137	-3.21615
Random 3	0.44027	0.193838	-1.71176
Random 4	0.45403	0.206144	-0.7079
Random 5	0.642442	0.412732	-4.71577
Random 6	0.116309	0.013528	-0.3569
Random 7	0.24943	0.062215	-0.2046
Random 8	0.296007	0.08762	-0.42455
Random 9	0.270977	0.073429	-0.37515
Random 10	0.351074	0.123253	-0.38131

Random Models Parameters	
Average r :	0.371894
Average r^2 :	0.164531
Average Q^2 :	-1.25236
cRp^2 :	0.733262

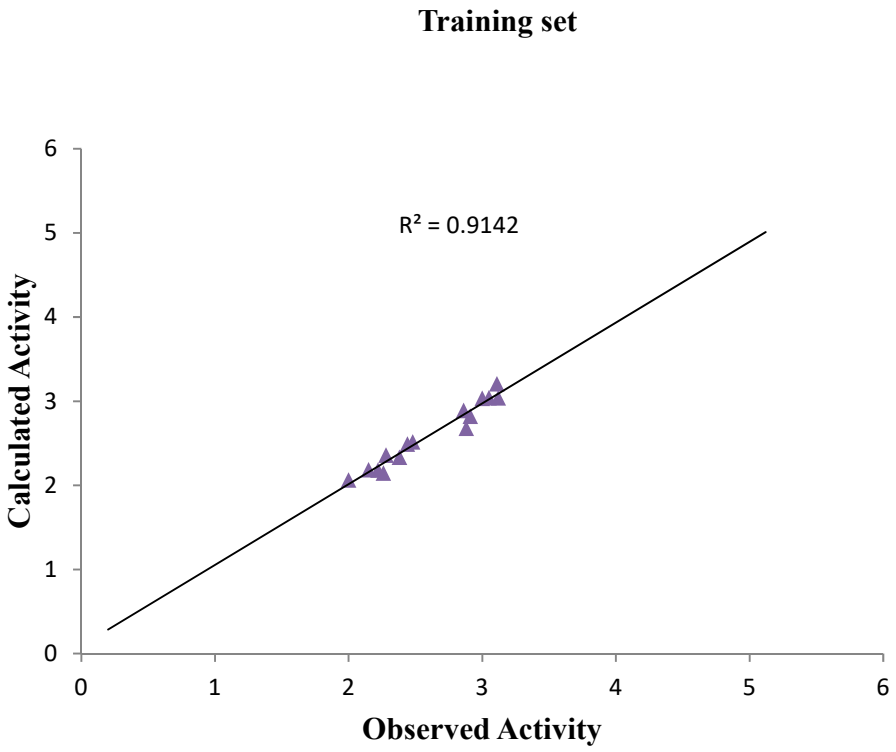


Figure 1. Plot of calculated activity against observed activity of training set

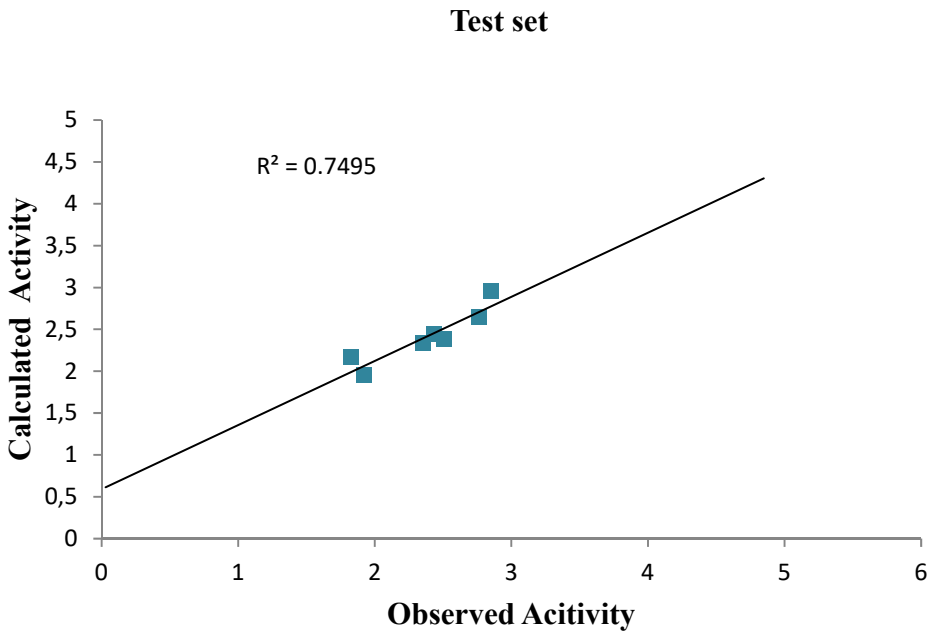


Figure 2. Plot of calculated activity against observed activity of test set

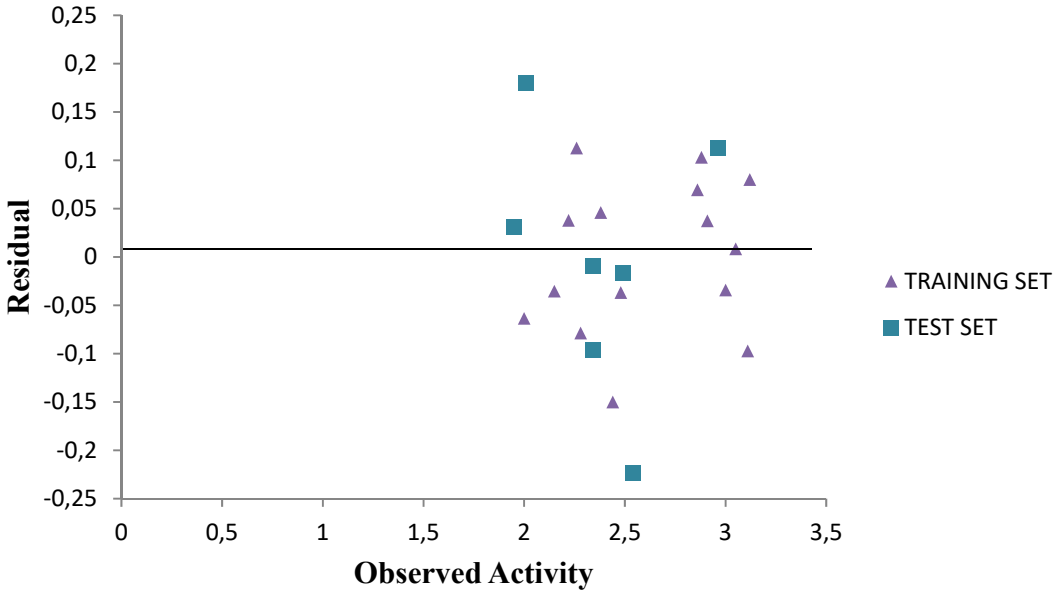


Figure 3. Plot of residual values versus observed activity

The graph of calculated activities plotted against observed activities of the training and test set are presented in Figure 2 and 3. The correlation coefficient (R^2) value of 0.9436 for the training set and (R^2) value of 0.8364 for the test set recorded in this work was found to in line with accepted QSAR threshold values reported in Table 2. This affirms the stability, reliability and predictive power of the built model. The plot of residual activity against observed activities shown in Figure 4 designates that there exist no computational inaccuracy in the derived QSAR model as the range of residuals values fall within an accepted limit of ±2 on residual activity axis.

The standardized residuals activities plotted against the leverage value known as The Williams plot is shown in Figure 5. The plotted graph clearly shows that all the compounds falls within limit boundary ±3 of standardized cross-validated residual. Hence, it can be infer that no outlier is observed in the data set. However, compound (number 3) is found to have a leverage value greater than the calculated warning leverage (h* = 0.80). Therefore the compound is an influential molecule.

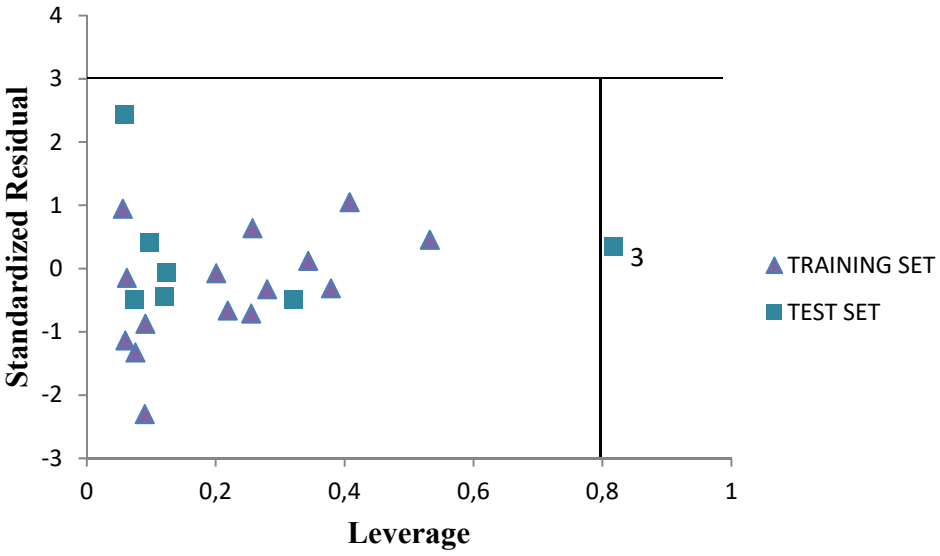


Figure 4. Plot of standardized residual activity versus leverage

4. Conclusion

In this research, QSAR model was generated with descriptor (AATS5e, minHCsatu and RDF90s) which were highly correlated with biological activities of 1,2,4-Triazole derivatives. These descriptors produced a robust model to predict the anti-mycobacterium activities of these compounds. The validation test (internal and external validation test) conducted on the selected built QSAR model passed the threshold value for a generally acceptable QSAR model. The model generated provides a valuable approach for ligand based design in synthesis of more effective chemical compounds and also give important insights into structural variants leading to the development of novel tubercular inhibitors.

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