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(RESEARCH ARTICLE)

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Modelling the anti-tuberculosis activity of a series of 2-(quinoline-4-yloxy) acetamide

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Abstract

In this work, a series of fifteen (15) derivatives of 2-(quinolin-4-yloxy) acetamides having inhibitory activity against Mycobacterium tuberculosis H37Rv made it possible to obtain a QSAR model. The molecules were optimized at the B3LYP/6-31+G (d, p) computational level to obtain the molecular descriptors. We used the multiple linear regression (MLR) method as a statistical learning tool. This method made it possible to obtain a mathematical model from the descriptors which are the dipole moment (μ), electronegativity (χ) and the standard enthalpy of formation ($\Delta_f H^0$) with good statistical performance (R^2 = 0.9246; S = 0.1163; F = 28.61). The external validation tests verify all the criteria of Tropsha et *al*. and Roy et *al*.

Keywords: QSAR; Acetamides; Mycobacterium tuberculosis H37Rv; Dipole moment (μ) and Electronegativity (χ)

1. Introduction

For decades, tuberculosis has been known as one of the leading causes of death worldwide.

Tuberculosis is an infectious disease, and the agent responsible for this disease is latent or dormant bacilli [1]. To address this public health threat, science proposes and continues to propose anti-tuberculosis molecules in order to better treat tuberculosis. Like any other disease, drugs used for current treatment are experiencing resistance, such as adverse effects and the impossibility of co-administration with certain antiretroviral drugs [2,3]. Despite the development of these anti-tuberculosis antibiotics, the fight against tuberculosis remains a challenge for the scientific community. It is within this context that pharmacochemists have focused their research on compounds with pharmacological activities of pharmaceutical interest. Borsoi et *al.* [4] evaluated the antimycobacterial activity of 2-(quinolin-4-yloxy)acetamides. The compounds demonstrated submicromolar activity against resistant and non-resistant strains of Mycobacterium tuberculosis by targeting the QcrB subunit of menaquinol cytochrome c oxidoreductase. In our work, we will use a method from theoretical chemistry to propose molecules with greater antituberculosis activity. This method involves the study of Quantitative Structure-Activity Relationships (QSAR). It allows the molecular structure to be correlated with a well-defined effect such as biological activity. This method is used to reduce the excessive number of experiments, which are sometimes lengthy, dangerous and costly in terms of time and money [5] [6] [7]. The general objective of this work is to develop reliable models to explain and predict the MIC

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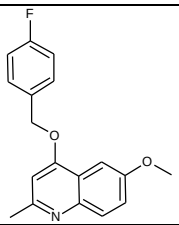
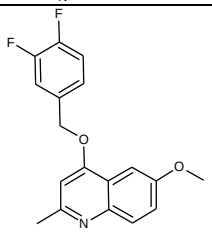
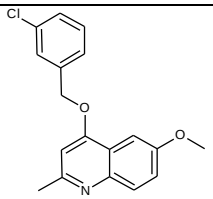
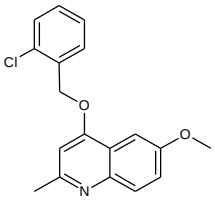
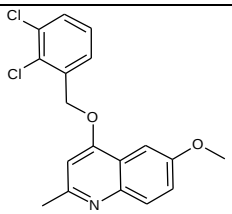
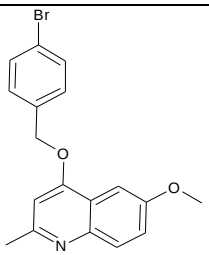
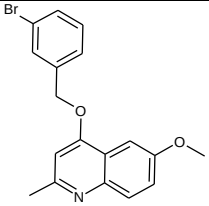
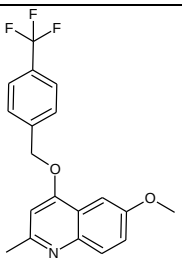
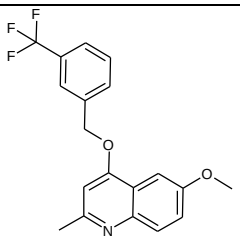
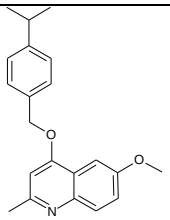
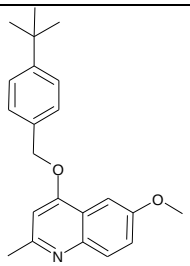
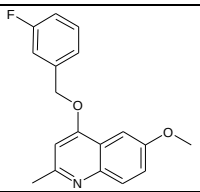
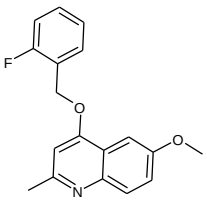
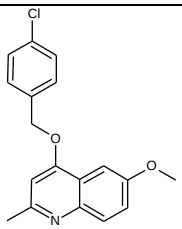
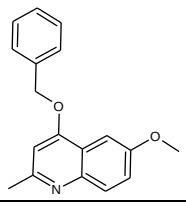
(minimum inhibitory concentration in µg/mL) antituberculosis activity of a series of fifteen (15) derivatives of 2-(quinolin-4-yloxy) acetamides.

Table 1 Codes, Molecular Structures and Minimum Inhibition Concentration of the 15 Derivatives of 2-(quinolin-4-yloxy) acetamides

Codes	**Structure**	**MIC (µM) M. tuberculosis H37Rv**
QAB1		16,8
QAB2		3,9
QAB3		7,9
QAB4		18,8
QAB5		28,7
QAB6		13,9
QAB7		13,9

QAB8		7,2
QAB9		7,2
QAB10		1,9
QAB11		3,7
QAB12		16,8
QAB13		19,2
QAB14		15,9
QAB15		5,6

2. Materials and methods

2.1. Computational Theory Level

In order to predict the antituberculosis activity of 2-(quinoline-4-yloxy) acetamide derivatives, quantum chemistry calculations were performed using the Gaussian 09 software [8]. DFT methods are generally known to generate a variety of molecular properties [9][10][11] in QSAR studies. These increase the predictability of QSAR models while reducing computation time and the associated costs in the design of new drugs [12][13]. The B3LYP/6-31+G(d,p) theory level was used to determine the molecular descriptors. The fifteen (15) molecules used in this study have Minimum Inhibitory Concentrations (MICs) ranging from 1.9 to 28.7 μM. The Minimum Inhibitory Concentration (MIC) is a measure of the effectiveness of a given compound in inhibiting a specific biological or biochemical function. Biological data are generally expressed as the negative of the base-10 logarithm of activity ($-\log_{10}(C)$) to obtain better mathematical values when structures are biologically active [14, 15] [16]. antituberculosis activity will be expressed by the potential of the inhibitory concentration pMIC defined by equation (1):

$$pMIC = -\log_{10}(MIC * 10^{-6}) \qquad (1)$$

Where MIC is the minimum inhibitory concentration in μM.

The modeling was developed using the multiple linear regression (MLR) method, which is implemented in Excel [17] and XLSTAT [18] spreadsheets.

2.2. Descriptors used

In order to develop our QSAR model, certain theoretical descriptors were determined. Electronegativity (χ), dipole moment (μ) and standard enthalpy of formation ($\Delta_f \boldsymbol{H^0}$) are used in a particular way.

Electronegativity is defined as the ability or tendency of atoms to retain their electrons and acquire new ones. Its expression is given by the following relationship:

$$\chi = \frac{E_{LUMO} + E_{HOMO}}{2} \qquad (2)$$

The dipole moment (μ_D) indicates the stability of a molecule in water. Thus, a high dipole moment will indicate low solubility in organic solvents and high solubility in water.

Standard enthalpy of a molecule is the enthalpy of formation of (1 mole of) that molecule in its standard state, that is to say in its stable form at P=1 atm, and at fixed T, from the element, taken also in their standard state.

This quantity was calculated using the following formulas proposed by *Otchersky et al* [19]:

$$\Delta \boldsymbol{H_f^0(M, 0K)} = \sum_{\boldsymbol{atoms}} \boldsymbol{x \Delta H_f^0(X, 0K)} - \sum \boldsymbol{D_0} \qquad (3)$$

$$\Delta H_f^0(M, 298K) = \Delta H_f^0(M, 0K) + \left(H_M^0(298K) - H_M^0(0K)\right) - \sum_{atoms} x\left(H_X^0(298K) - H_X^0(0K)\right) \quad (4)$$

With:

$$\sum \boldsymbol{D_0} = \sum \boldsymbol{x\varepsilon_0} - \boldsymbol{\varepsilon_0(M)} - \boldsymbol{\varepsilon_{ZPE}} \qquad (5)$$

$\sum \boldsymbol{D_0}$: Atomization energy;

$\boldsymbol{\varepsilon_0(M)}$: Total energy of the molecule;

$\boldsymbol{\varepsilon_{ZPE}}$: Zero point energy of the molecule;

$\boldsymbol{H_X^0(298K) - H_X^0(0K)}$: Enthalpy corrections of atomic elements. These values are included in the Janaf table [20].

$\boldsymbol{H_M^0(298K) - H_M^0(0K) = H_{corr} - \varepsilon_{ZPE}(M)}$: Enthalpy Correction of the Molecule

H_{corr} : Thermal correction enthalpy.

2.3. Estimation of the predictive capacity of a QSAR model

The quality of a model is determined based on various statistical analysis criteria including the coefficient of determination R^2, the standard deviation (S), the cross-validation correlation coefficients $\mathbf{Q^2_{CV}}$ and Fischer F. R^2, S and F relate to the fit of the calculated and experimental values. They describe the predictive capacity within the limits of the model, and allow us to estimate the accuracy of the values calculated on the test set [21, 22]. As for the cross-validation coefficient $\mathbf{Q^2_{CV}}$, it provides information on the model's predictive power. This predictive power is considered "internal" because it is calculated based on the structures used to build the model.

The coefficient of determination R^2 gives an assessment of the dispersion of theoretical values around experimental values. Quality of the modeling is better when the points are close to the line of best fit [23]. The fit of the points to this line can be evaluated by the coefficient of determination.

$$\boldsymbol{R^2} = 1 - \frac{\sum\left(y_{i,exp} - \hat{y}_{i,théo}\right)^2}{\sum\left(y_{i,exp} - \bar{y}_{i,exp}\right)^2} \qquad (6)$$

Or:

$y_{i,exp}$: Experimental value of antituberculosis activity

$\hat{y}_{i,théo}$: Theoretical value of antituberculosis activity

$\bar{y}_{i,exp}$: Average value of experimental values of antituberculosis activity.

The closer the R^2 value is to 1, more the theoretical and experimental values are correlated.

Fisher's F-test is also used to measure the level of statistical significance of the model, that is, the quality of the choice of descriptors constituting the model.

$$\mathbf{F} = \frac{\sum\left(y_{i,théo} - y_{i,exp}\right)^2}{\sum\left(y_{i,exp} - y_{i,théo}\right)^2} * \frac{n-k-1}{k} \qquad (7)$$

The cross-validation coefficient of determination $\mathbf{Q^2_{CV}}$ allows us to evaluate the accuracy of the prediction on the training set. It is calculated using the following relationship:2

$$\boldsymbol{Q^2_{cv}} = \frac{\sum\left(y_{i,théo} - \bar{y}_{i,exp}\right)^2 - \sum\left(y_{i,théo} - y_{i,exp}\right)^2}{\sum\left(y_{i,théo} - \bar{y}_{i,exp}\right)^2} \qquad (8)$$

2.4. Model acceptance parameters

The performance of a mathematical model, for Eriksson *et al.* [24], is characterized by a value of $Q^2_{cv} > 0.5$ for a satisfactory model, while for the excellent model $Q^2_{cv} > 0.9$.

According to these authors, given a test set, a model will perform well if the acceptance criterion $R^2 - Q^2_{cv} < 0.3$ is met.

According to Tropsha et *al*. [25, 26, 27], for the external validation set, the predictive power of a model can be obtained from five criteria. These criteria are as follows:

1) $R^2_{Test} > 0.7$, **2)** $Q^2_{Cv\,Test} > 0.6$, **3)** $|R^2_{Test} - R^2_0| \leq 0.3$,

4) $\frac{|R^2_{Test} - R^2_0|}{R^2_{Test}} < 0.1$ et $0.85 \leq k \leq 1.15$, **5)** $\frac{|R^2_{Test} - R'^2_0|}{R^2_{Test}} < 0.1$ et $0.85 \leq k' \leq 1.15$

Furthermore, Roy and Roy [28] further refined the predictive capacity of a QSAR model. They developed quantities $\boldsymbol{r^2_m}$et $\Delta\boldsymbol{r^2_m}$, called metric values. $\boldsymbol{r^2_m}$ determine the proximity between the observed activity and the prediction. The metric values $\boldsymbol{r^2_m}$et $\Delta\boldsymbol{r^2_m}$are calculated from observed and predicted activities. Currently, these two different variants, $\boldsymbol{r^2_m}$et $\Delta\boldsymbol{r^2_m}$, can be calculated for the trial set (internal validation) or for the test set (external validation). A QSAR model is acceptable to these authors if these two criteria are met.

$$\overline{r^2_m} = \frac{(r^2_m + r'^2_m)}{2} > 0.5$$

$$\Delta r^2_m = |r^2_m - r'^2_m| < 0.2$$

Où $r^2_m = r^2 * \left(1 - \sqrt{(r^2 - r^2_0)}\right)$ *et* $r'^2_m = r^2 * \left(1 - \sqrt{(r^2 - r'^2_0)}\right)$

2.5. Statistical Analysis: Multiple Linear Regressions (MLR)

The statistical technique of multiple linear regression (MLR) is used to study the relationship between a dependent variable (Property) and several independent variables (descriptors).

This statistical method minimizes the differences between actual and predicted values. It is the most common tool for studying multidimensional data. It is based on the following pre-programmed XLSTAT functions:

$$y = a + (bx_1 + cx_2 + dx_3 + ex_4) + (fx_{12} + gx_{22} + hx_{32} + ix_{42}) \qquad (9)$$

Where a, b, c, d,... represent the parameters and x1, x2, x3, x4,... represent the variables.

2.6. Scope of Applicability (SA)

The applicability domain of a QSAR model is the physico-chemical, structural or biological space in which the model equation is applicable to make predictions for new compounds [29].

It corresponds to the region of chemical space including the compounds in the training set and similar compounds that are close in this same space [30]. Indeed, the model, which is built on the basis of a limited number of compounds, by relevant descriptors chosen from among many others, cannot be a universal tool to predict the activity of any other molecule with confidence.

It appears necessary, even mandatory, to determine the DA of any QSAR model. This is also what the Organisation for Economic Co-operation and Development (OECD) recommends in the development of a QSAR model [31]. Several methods exist for determining the applicability domain of a model [30]. Among these, the approach used in this work is the leverage method. This method is based on the variation of the standardized residuals of the dependent variable with the distance between the values of the descriptors and their mean, called the leverage [32].

The h_{ii} are the diagonal elements of a matrix H called the hat matrix. H is the projection matrix of the experimental values of the explained variable $Y_{expé}$onto the space of predicted values of the explained variable $Y_{préd}$such that:

$$Y_{préd} = HY_{expé} \qquad (10)$$

H is defined by expression (21):

$$H = X(X^tX)^{-1}X^t \qquad (11)$$

The domain of applicability is delimited by a threshold value of the lever denoted h*. In general, it is set at 3 (p+1)/n, where n is the number of compounds in the training set, and p is the number of descriptors in the model [33, 34]. For

standardized residuals the two limit values generally used are ±3σ, σ being the standard deviation of the experimental values of the quantity to be explained [35]: this is "the three sigma rule" [36].

3. Results and discussion

The quantitative structure-relationship model of antituberculosis activity was established from the descriptors which are: electronegativity (χ), dipole moment (μ) and standard enthalpy of formation ($\Delta_f H^0$). The different descriptors used for each molecule and their value of the minimum inhibitory concentration potential are listed in Table 2.

Table 2 Experimental physicochemical and pMIC descriptors for learning and validation sets

Molecules	**χ (eV)**	**μ(D)**	$\Delta_f H^0(kcal/mol)$	***pMIC***
	Training set			
4d	3.5448	1.9460	-936.6337	4.7747
4g	3.6231	2.8564	-975.9569	5.4089
4i	3.5646	2.0856	-893.4907	5.1024
4j	3.5584	1.8466	-893.1286	4.7258
4l	3.6299	2.2706	-890.5318	4.5421
4n	3.5649	2.0315	-893.8819	4.8570
4o	3.5642	2.0666	-894.2339	4.8570
4p	3.6518	3.2060	-1081.3503	5.1427
4q	3.6498	3.0362	-1081.2518	5.1427
4s	3.4415	2.0559	-1026.9608	5.7212
4t	3.4389	2.0695	-1069.2118	5.4318
		Test set		
4e	3.5563	1.9723	-936.8144	4.7747
4f	3.5409	1.9697	-936.6883	4.7167
4h	3.5620	2.0415	-893.4154	4.7986
4a	3.4696	1.7674	-892.6928	5.2518

3.1. Internal Validation

Table 3 Presents the correlation matrix of the model descriptors

Variables	χ	μ	$\Delta_f H^0$
χ	**1.0000**	0.6863	0.0645
μ	0.6863	**1.0000**	-0.6401
$\Delta_f H^0$	0.0645	-0.6401	**1.0000**

Table 3 shows that the correlation coefficient of the descriptors taken two by two is less than 0.7. This result indicates that the descriptors are independent two by two [37].

The equation below represents the equation of the QSAR model.

$$\boldsymbol{pMIC = 40.02828 - 9.85610 * \chi + 1.64788 * \mu + 0.00375 * \Delta_f H^0}$$

The model equation indicates that a decrease in electronegativity improves the pMIC, while an increase in dipole moment and standard enthalpy of formation improves the biological activity of the molecules.

The statistical indicators of the resulting model are recorded in Table 4.

Table 4 Statistical analysis report of the RML model

N	R2	Q^2_{cv}	S	R2 - Q^2_{CV}	Fisher(F)	α
11	0.9246	0.9246	0.1163	0.000	28.61	> 95 %

The results in the table show that the coefficient of determination of the model is $R^2 = 0.9246$. This means that 92.46% of the variance in activity is explained by the model. Furthermore, this coefficient is greater than 0.9 and $R^2 - Q^2cv < 0.3$; according to Erickson et al., this model is considered acceptable and excellent. Also, the low value of the standard deviation (S) indicates a small error between the experimental activity and the activity predicted by the model. Fisher's test indicates an F-value of 28.61, which is greater than the limit in the Fisher-Snedecor table. This value indicates the good significance of the descriptors in the model.

Figure 1 shows the regression line of the model obtained.

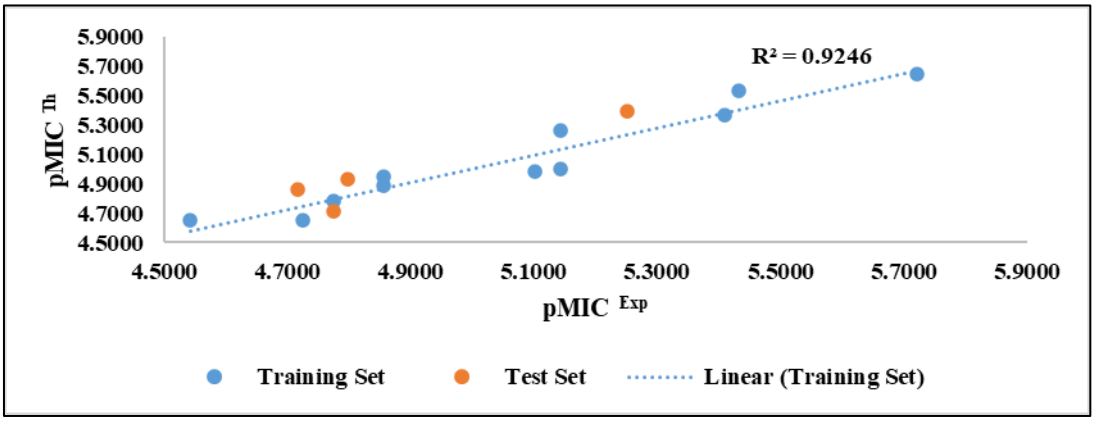


Figure 1 The regression line of the RML model

Figure 1 shows that all the points are around the regression line (blue). These points around the line indicate a good prediction of the model's antituberculosis activity. This result is also illustrated in Figure 3, where the similarity curve between experimental and predicted activity can be seen. It is noticeable that the curves perfectly overlap.

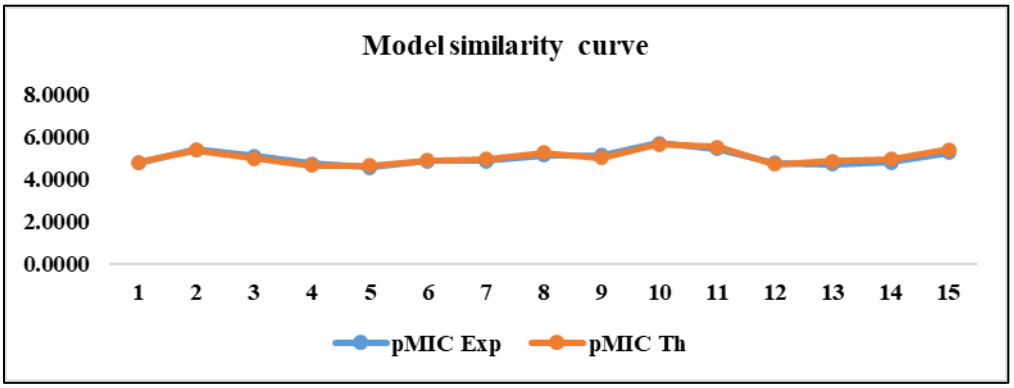


Figure 2 Similarity curve of the experimental and predicted values of the RML model

3.2. External Validation

To perform external validation of the obtained QSAR model, we calculated the parameters of Roy et *al.* The values of these different parameters are recorded in Table 5.

Table 5 Roy criteria checks of the external validation set of the RML model

Indicateurs	r_m^2	r'^2_m	$\overline{r_m^2} = \frac{(r_m^2 + r'^2_m)}{2}$	$\Delta r_m^2 = \lvert r_m^2 - r'^2_m \rvert$
Valeur	**0.811**	**0.691**	**0.751**	**0.121**

The results in Table 5 show that all of Roy's criteria are met. Since the criteria are met, we can conclude that the model has good predictive power.

3.3. Analysis of the contribution of the descriptors

Figure 3 shows the contribution of the descriptors in the QSAR model.

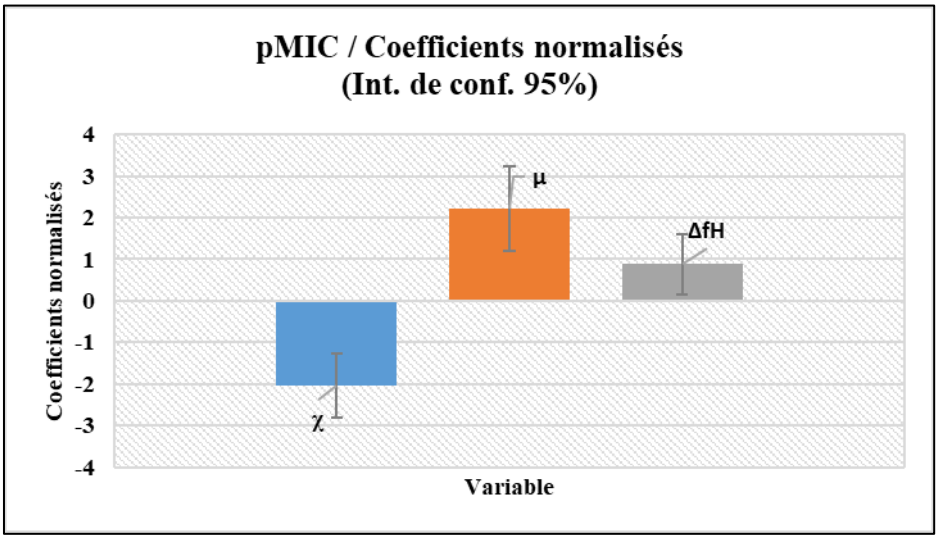


Figure 3 Contribution of descriptors in the model

Figure 3 shows that the dipole moment (μ) has the greatest contribution to the model. This large contribution makes this descriptor the most important in predicting the tuberculous activity of the studied molecule series.

3.4. Area of applicability

The model's applicability domain was obtained using the lever method. Figure 4 shows the Williams diagram, which represents the levers hii as a function of the standardized residuals.

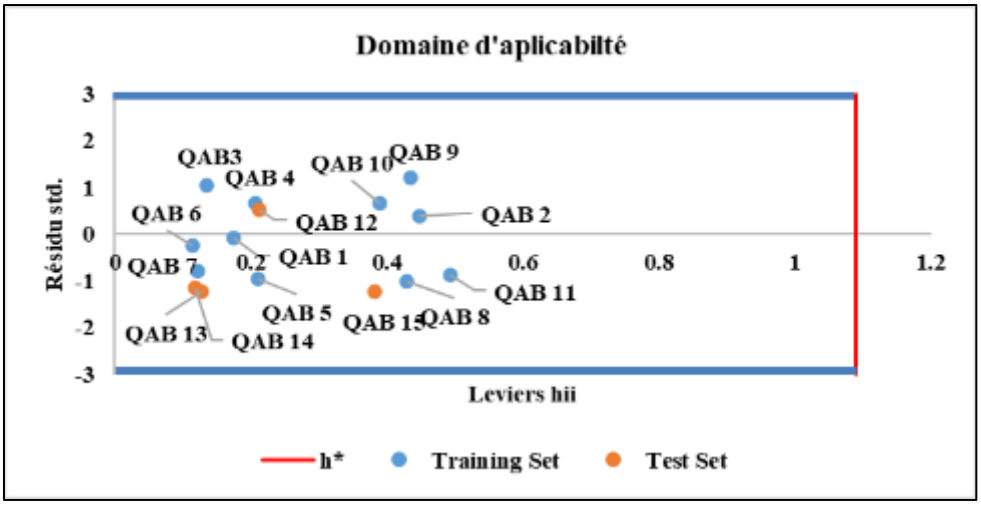


Figure 4 William diagram of the model

For the QSAR model obtained, we have a threshold lever h*=1.09. Figure 4 indicates that the set of molecules has a lever lower than the threshold lever. The residual values are also between [-3σ, 3σ]. These results indicate that there are no outliers and that the model obtained is reliable and can be used to predict the biological activity of new molecules within our field of applicability.

4. Conclusion

In this work, we established a quantitative structure-antituberculosis activity relationship between a series of 2-(quinoline-4-yloxy)acetamide-based molecules and their descriptors, namely electronegativity, dipole moment, and standard enthalpy of formation.

The model was obtained using multiple linear regression. The model's statistical indicators (R^2 = 0.9246; S = 0.1163; F = 28.61) indicate that it is robust, acceptable, and excellent. Furthermore, external validation using Roy's criteria indicated that the model has good predictive power. Furthermore, we note from the contribution diagram of the descriptors that the dipole moment is the descriptor that best explains the antituberculosis activity of 2-(quinoline-4-yloxy) acetamide. Finally, the scope of applicability indicates that the model is reliable and can be used for the prediction of new 2-(quinoline-4-yloxy) acetamide derivatives.

Looking ahead, we plan to design new compounds theoretically and predict their biological activity using our QSAR model.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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