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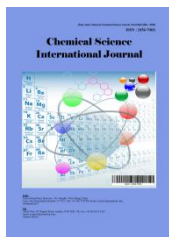
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Modeling of a Series of Dihydropyrazole Derivatives with Antiproliferative Activity by Quantum Chemical Methods

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Cancer is any disease characterised by the rapid proliferation of abnormal cells in normal body tissue.

Recent years have been marked by an increase in the number of cases of cancer, particularly that of the prostate. Cancer can affect any part of the body. Despite the efforts made in the fight against cancer in recent years, the objectives set by the WHO and the various supervisory centers in the countries have not been achieved, because the technical strategy for the fight against cancer in no way guarantees a cure without risk of relapse for patients in general, regardless of the continent. Today, we can offer models of molecules for therapeutic purposes using quantum chemical methods such as molecular modeling to predict better activity or by designing new molecules that are more active than existing ones. To this end, our work consists in setting up a mathematical model between the potential of the inhibitory concentration (pIC_{50}) and the descriptors such as the frequency of vibration $\nu(N-N)$, the angle of valence $\alpha(N-N-C)$ and the standard entropy of formation ($\Delta_f S^0$). This model is confirmed by very good indicators displaying the following values ($R^2= 0.9108$; $S= 0.1044$; $F=20.425$) for the MLR model and ($R^2=0.920$; $S=0.1393$; $F=92.823$) for the MNL model. Moreover, these models allowed us to conclude that the vibration frequency $\nu(N-N)$ is the priority descriptor in the prediction of the antiproliferative activities of dihydropyrazole derivatives.

Keywords: QSAR; MNL; MLR; antiproliferative activity (DU-145); dihydropyrazole.

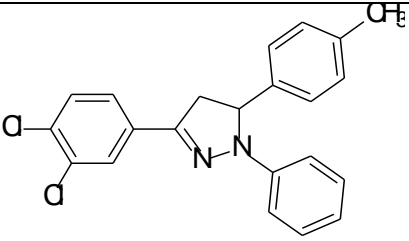
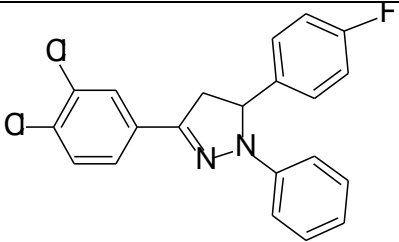
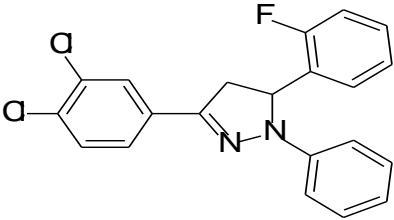
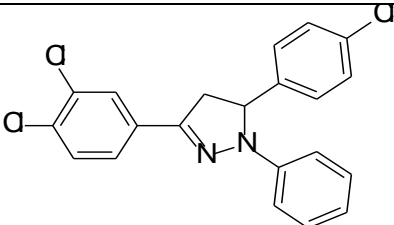
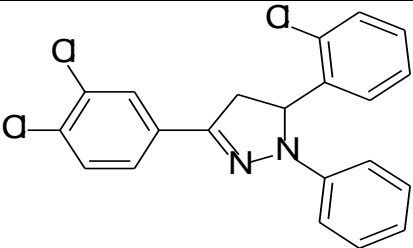
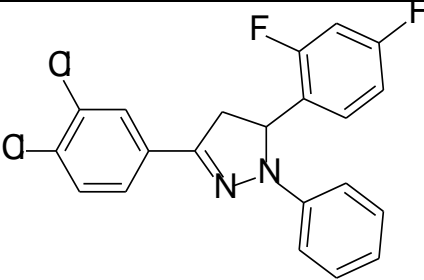
1. INTRODUCTION

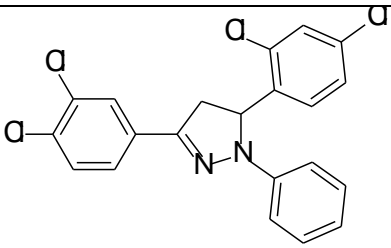
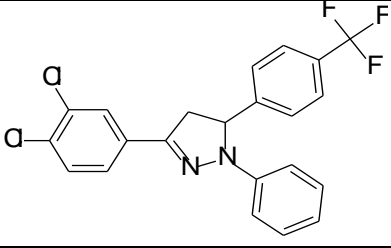
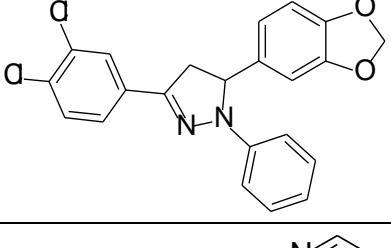
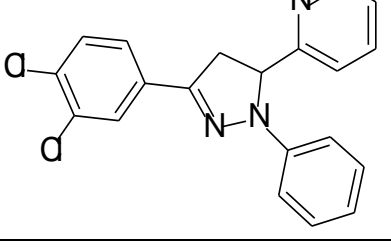
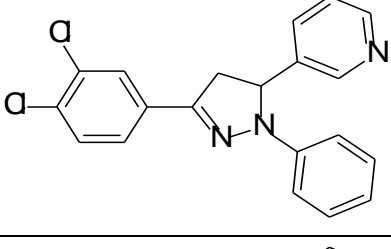
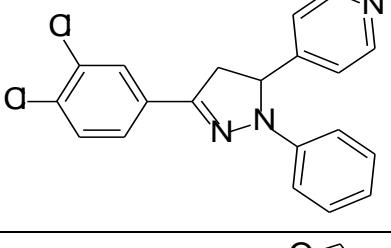
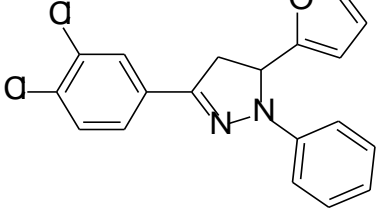
“A cancer is a pathology characterized by the presence of one (or more) malignant tumor formed from the transformation by mutations or genetic instability of an initially normal cell” [1]. When normal cells are damaged or cannot be cured, they die, which is apoptosis, which is not the case for cancer cells since they continue to grow to reach several cells. There are several types of cancer, including prostate cancer. Prostate cancer has become the most common cancer and the second leading cause of cancer death in men [2], in developed countries and the first in underdeveloped countries. In 2020 more than 19.3 million cases recorded worldwide [3] and nearly 2747 in Côte d'Ivoire [4]. According to the World Health Organization (WHO), cancer causes nearly 10 million deaths, i.e. almost one in six deaths, cancer is one of the main causes of death in the world [1]. This health problem in men is becoming increasingly important. Today one in nine men are at risk of getting prostate cancer in their lifetime. The incidence of cancer increases considerably with age (60 years and over) due to the increasing accumulation of cancer risk factors and the fact that cell regeneration mechanisms tend to become less effective as aging [5]. Prevention against cancer, especially prostate cancer, is based on physical activity and also a healthy and balanced diet with medication. Surgical operations, chemotherapy are among other treatments used against this cancer. However, the proposal of new

Therapeutic Targeted Molecules for the treatment of prostate cancer such as dihydropyrazole derivatives could be a contribution in the drug management of patients. Research has shown that dihydropyrazoles are an important pharmacophore involved in the discovery of new derivatives with therapeutic and biological activities [6]. Indeed, phenyl-substituted dihydropyrazoles exhibit proven biological activities such as antioxidant [2], antibacterial [3], antituberculous [5,4], antifungal and significant anticancer [7,8,9]. Molecular modeling, the basis of theoretical chemistry, helps to design and predict the properties of molecules of therapeutic interest using computer techniques. It is used to develop reliable models to predict and explain physico-chemical properties related to the biological activities of molecules or to propose new molecules with better activities. Quantitative structure-activity modelling (QSAR) is one of the techniques used to predict the activities of chemical systems on the basis of their molecular structures. Indeed, the development of the QSAR model requires knowledge of the physico-chemical parameters (descriptors) related to the molecular systems studied. The determination of these descriptors is facilitated by the use of methods and tools of quantum chemistry. The compounds studied in our work (Table 1) were synthesized, tested and identified as molecules with effective activities against prostate cancer. It is up to us in this work to model, from the derivatives of these different series of molecules, molecules with more

effective biological activities against prostate cancer. As general objective for this work, it is for us to contribute to model the antiproliferative profile (prostate cancer) of a series of dihydropyrazoles from their physico-chemical properties.

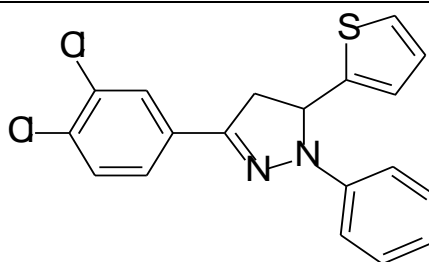
Table 1. Database molecules and their respective characteristics

| Code | Molecular structures | $IC_{50}^{exp}(\mu M)$ |
|------|--|------------------------|
| DHP1 |  | 351 |
| DHP2 |  | 119 |
| DHP3 |  | 327 |
| DHP4 |  | 149 |
| DHP5 |  | 134 |
| DHP6 |  | 262 |

| | | |
|-------|--|-----|
| DHP7 |  | 206 |
| DHP8 |  | 257 |
| DHP9 |  | 131 |
| DHP10 |  | 271 |
| DHP11 |  | 211 |
| DHP12 |  | 173 |
| DHP13 |  | 162 |

DHP14

84



2. MATERIALS AND METHODS

2.1 Computational Theories Levels and Software

“In order to predict the anticancer activity of dihydropyrazole derivatives, quantum chemical calculations were performed using Gaussian 09 software” [10]. It is generally known that DFT methods generate a variety of molecular properties [11-13] in QSAR studies. These increase the predictive capacity of QSAR models, while reducing the computation time and cost impact of new drug development [14,15]. The theoretical level B3LYP/6-31+G (d, p) was used to determine the molecular descriptors. The fourteen (14) molecules used in the present study have inhibitory concentrations between 84 and 351 μM . The average inhibitory concentration (IC_{50}) is a measure of the effectiveness of a given compound in inhibiting a particular biological or biochemical function. Biological data is usually expressed as opposed to the activity-based decimal logarithm ($-\log_{10}(\text{IC}_{50})$) to obtain better mathematical values when structures are biologically active [16,17]. The anticancer activity will be expressed by the potential of the inhibitory concentration pIC_{50} defined by equation (1):

$$\text{pIC}_{50} = -\log_{10}(\text{IC}_{50} * 10^{-6}) \quad (1)$$

In the case of MICs, the minimum inhibitory concentration in $\mu\text{g/mL}$.

The modeling was developed using three statistical learning methods. Namely the multiple linear regression (MLR) and non-linear (MNL) methods which are implemented in Excel [18] and XLSTAT [19] spreadsheets.

2.2 Molecular Descriptors Calculation

In this work, to establish the model, we used geometric, spectroscopic and energetic descriptors. The geometric and spectroscopic

descriptors used are the valence angle $\alpha(\text{N-N-C})$ in degrees ($^\circ$) and the nitrogen-nitrogen vibration frequency $\nu(\text{N-N})$ in cm^{-1} (Fig. 1). The descriptors used are shown in the figure below around the dihydropyrazole nucleus.

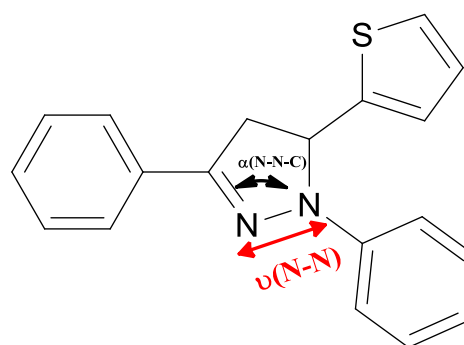


Fig. 1. Geometric and spectroscopic descriptors

The standard entropy of compound formation was calculated from the relationship of Otchersky et al. [10].

$$\Delta S_f^0(M, 298K) = S_M - \sum_{atoms} x \Delta S(298K) \quad (2)$$

x : Number of Atoms of X in the Molecule

2.3 Predictive Capacity of the 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) or the Root of the Mean Square Errors (RMSE), the correlation coefficients cross-validation Q_{cv}^2 and Fischer F . R^2 , S and F relate to the adjustment of calculated and experimental values. They describe the predictive capacity within the limits of the model, and make it possible to estimate the precision of the values calculated on the test set” [20,21]. “As for the cross-validation coefficient Q_{cv}^2 , it provides information on the predictive power of the model.

This predictive power is said to be "internal" because it is calculated from the structures used to build this model. The coefficient of determination R^2 gives an evaluation of the dispersion of the theoretical values around the experimental values. The quality of the modeling is better when the points are close to the fitted line" [22]. The fit of the points on this line can be evaluated by the coefficient of determination.

$$R^2 = 1 - \frac{\sum(y_{i,exp} - \hat{y}_{i,theo})^2}{\sum(y_{i,exp} - \bar{y}_{i,exp})^2} \quad (3)$$

where:

$y_{i,exp}$: Anticancer activity has experimental value

$\hat{y}_{i,theo}$: Anticancer activity has a theoretical value.

$\bar{y}_{i,exp}$: Mean value of experimental values for anticancer activity.

The closer the R^2 value is to 1, the stronger the correlation between the theoretical and experimental values.

The Root Mean Square Error (RMSE) is another statistical indicator used. It is used to assess the reliability and accuracy of a model:

$$RMSE = \sqrt{\frac{\sum(y_{i,exp} - y_{i,theo})^2}{n - k - 1}} \quad (4)$$

The Fisher F criterion is also used to measure the statistical significance of the model, i.e. the quality of the choice of descriptors that make up the model.

$$F = \frac{\sum(y_{i,theo} - y_{i,exp})^2}{\sum(y_{i,exp} - y_{i,theo})^2} * \frac{n - k - 1}{k} \quad (5)$$

Q_{cv}^2 , the coefficient of determination of the cross-validation is used to evaluate the accuracy of the prediction in the training set. It is calculated using the following relationship:

$$Q_{cv}^2 = \frac{\sum(y_{i,theo} - \bar{y}_{i,exp})^2 - \sum(y_{i,theo} - y_{i,exp})^2}{\sum(y_{i,theo} - \bar{y}_{i,exp})^2} \quad (6)$$

$$y = a + (bx_1 + cx_2 + dx_3 + ex_4) + (fx_{12} + gx_{22} + hx_{32} + ix_{42}) \quad (8)$$

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

2.4 Model Acceptance Criterion

Performance of the mathematical model of Eriksson et al. [23], for a satisfactory model, it is characterised by $Q_{cv}^2 > 0.5$., while for an excellent model, $Q_{cv}^2 > 0.9$. According to these authors, given a test set, the model will work well if it obeys the acceptance criterion $R^2 - Q_{cv}^2 < 0.3$. Moreover, the modellers used randomisation tests to confirm that the good correlation between the descriptors and the activities presented by the QSAR model was not fortuitous. To do this, the observations were shuffled, say ten times, by randomly changing the active column while keeping the descriptor column fixed. This produces ten models with specific statistical characteristics. For an acceptable QSAR model, the average correlation coefficient (R_r) of the stochastic model must be lower than that of the non-stochastic model (R). The parameter R_p^2 [24] developed by Roy K. is used to judge a QSAR model. This parameter can be calculated using the following formula:

$$R_p^2 = R^2 * \sqrt{R^2 - R_r} \quad (7)$$

The value of R_p^2 should be greater than 0.5 for an acceptable model. If the randomization of observations leads to weak prediction models, this means that the predictive capacities of the QSAR model built are not due to chance [25].

2.5 Statistical Methods

2.5.1 Multiple linear and non-linear regressions (MLR and MNL)

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 reduces the differences between actual and predicted values. It has also been used to select descriptors for use as input parameters in multiple non-linear regression (MNL). The analysis of multiple non-linear regression (MNL) also makes it possible to improve the structure-property relationship in order to assess the property quantitatively. It is the most common tool for studying multidimensional data. It is based on the following pre-programmed XLSTAT functions:

2.6 Applicability Area

“The domain of applicability 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” [26]. “It corresponds to the region of the chemical space including the compounds of the training set and the similar compounds, which are close in this same space” [27]. “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 for predicting the activity of any other molecule with trust. It appears necessary, even mandatory, to determine the DA of any QSAR model. This is what the Organization for Economic Co-operation and Development (OECD) recommends in the development of a QSAR model [28]. There are several methods for determining the applicability domain of a model” [27]. “Among these, the approach used in this work is that of leverage. 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 leverage” [29]. 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_{exp} in the space of values of the predicted explained variable Y_{pred} such that:

$$Y_{pred} = HY_{exp} \quad (9)$$

H is defined by the expression (10):

$$H = X(X^tX)^{-1}X^t \quad (10)$$

Applicability is limited by a leverage threshold noted h^* . This is generally set at $3\frac{p+1}{n}$, where n is the number of compounds in the training set and p is the number of descriptors in the model [30,31]. For standardised residuals, the two limits generally used are $\pm 3\sigma$, where σ is the standard deviation of the experimental values of the variable to be explained [32]: this is the "three sigma rule" [33].

3. RESULTS AND DISCUSSION

This QSAR study was conducted using a series of fourteen molecules (14) molecules derived from dihydropyrazoles. These compounds were synthesized and tested on prostate cancer cell lines (DU-145). It should be noted that this study was carried out on 14 molecules divided into two categories, ten (10) for the learning game and four (4) for the validation game. The objective of this part of the work is to model the antiproliferative activity of dihydropyrazole derivatives from the descriptors. The values of the descriptors as well as those of the experimental biological activities of the molecules are listed in Table 2.

In order to highlight the interdependence of the descriptors retained, the values of the bivariate linear correlation coefficients a_{ij} between the pairs of descriptors are less than 0.70 ($a_{ij} < 0.70$) (Table 3). Moreover, two descriptors are said to be interdependent when ($a_{ij} < 0.70$).

Table 1. Physico-chemical descriptor and experimental pIC_{50} of learning and validation sets

| Molecules | $\alpha(N-N-C)^\circ$ | $u(N-N)(cm^{-1})$ | $\Delta_r S^\circ(kcal/molK)$ | pIC_{50} |
|-----------------------|-----------------------|-------------------|-------------------------------|------------|
| learning set | | | | |
| DHP1 | 110.3072 | 1163.1700 | -1.2055 | 3.4547 |
| DHP4 | 110.3639 | 1162.4800 | -1.1312 | 3.8268 |
| DHP5 | 110.3326 | 1164.5500 | -1.1304 | 3.8729 |
| DHP6 | 110.3338 | 1163.9800 | -1.1344 | 3.5817 |
| DHP7 | 110.1449 | 1167.7300 | -1.1354 | 3.6861 |
| DHP8 | 110.2819 | 1166.8900 | -1.2220 | 3.5901 |
| DHP9 | 110.3088 | 1170.8500 | -1.2184 | 3.8827 |
| DHP11 | 110.3291 | 1163.9000 | -1.1030 | 3.6757 |
| DHP13 | 110.5349 | 1156.7100 | -1.0439 | 3.7905 |
| DHP14 | 110.3062 | 1173.4800 | -1.0428 | 4.4949 |
| Validation Set | | | | |
| DHP2 | 110.3661 | 1162.1800 | -1.1324 | 3.9245 |
| DHP3 | 110.4924 | 1158.7400 | -1.1338 | 3.4855 |
| DHP10 | 110.2262 | 1164.9300 | -1.1019 | 3.5670 |
| DHP12 | 110.0557 | 1179.0400 | -1.1017 | 3.7620 |

In the model equations, the negative or positive sign of the descriptor coefficients transforms the proportional effect between changes in the median inhibitory concentration IC_{50} and the physico-chemical parameters of the regression equation. A negative sign indicates a decrease in the inhibitory concentration IC_{50} when the value of the descriptor is higher, while a positive sign reflects the opposite effect. Two statistical analysis tools were used in this work, including Multiple Linear Regression (MLR) and Multiple Non-Linear Regression (MNLr).

3.1 Multiple Linear Regression (MLR)

The equation of the QSAR model relating the inhibitory potential, the vibration frequency $u(N-N)$, the valence angle $\alpha(N-N-C)$ and the standard entropy of formation ($\Delta_f S^0$) are presented below monitoring of statistical indicators (Table 4).

$$pIC_{50} = -226.87 + 1.48 * \alpha(N-N-C) + 0.06 * u(N-N) + 2.47 * \Delta_f S^0$$

The model equation was obtained using descriptors obtained after molecule ($\alpha(N-N-C)$, $u(N-N)$, $\Delta_f S^0$). The positive sign of the various descriptors shows that the antiproliferative activity pIC_{50} evolves in the same direction. The study of the significance of this model is carried out by evaluating the statistical indicators and the validation criteria.

The value of the coefficient of determination R^2 which is 0.9108, shows that the estimated values of the pIC_{50} contain 91.08% of the experimental values. The value of the Fisher test ($F = 20.425$) is relatively high compared to the critical value of

the Fisher Snedecor table $F_{cr} = 3.48$ [34]. This value 20.425 of the Fisher test, higher than the critical value, shows that the error made is less than what the model explains. The standard deviation ($S=0.1044$) expresses the small variation of the predicted values compared to the experimental mean. For this model, the cross-validation correlation coefficient Q_{cv}^2 is equal to $Q_{cv}^2 = 0.9108$. This value, greater than 0.9, reflects a model said to be excellent according to Erikson et al. [35]. This model is acceptable, because it is in agreement with the acceptance criterion of these authors $R^2 - Q_{cv}^2 = 0.9108 - 0.9108 = 0.000 < 0.3$. The model developed explains the antiproliferative activity in a statistically significant and satisfactory manner according to these statistical indicators.

Fig. 2 shows the regression of the theoretical anti-cancer activity of the RML model against the experimental activity.

The low value of the standard deviation (S) which is 0.1044 for this model attests to the good regression between the predicted and experimental values. The curves (Fig. 3) reflect the similar evolution of the data from this model for the pIC_{50} prediction of the 14 dihydropyrazole derivatives despite some deviations recorded.

3.1.1 Internal validation of the MLR model

The randomization test of this model is only for the compounds in the test set, because the model relies on them. We limited ourselves to ten iterations. The randomized determination coefficients (R^2_r) of each iteration are given in Table 5.

Table 3. Correlation matrix between the different physico-chemical descriptors

| Variables | $\alpha(N-N-C)$ | $u(N-N)$ | ΔfS |
|-----------------|-----------------|----------|-------------|
| $\alpha(N-N-C)$ | 1 | -0.6635 | 0.4388 |
| $u(N-N)$ | -0.6635 | 1 | -0.1987 |
| ΔfS | 0.4388 | -0.1987 | 1 |

Table 2. Statistical analysis report of the pIC_{50} inhibitory potential of dihydropyrazole derivatives of the MLR model

| | |
|---|--------------------------|
| Number of observations N | 10 |
| Coefficient of determination R^2 | 0.9108 |
| Standard deviation RMSE S | 0.1044 |
| Fischer F-test F | 20.425 > $F_{cr} = 3.48$ |
| Cross Validation Correlation Coefficient Q_{cv}^2 | 0.9108 |
| $R^2 - Q_{cv}^2$ | 0.000 |

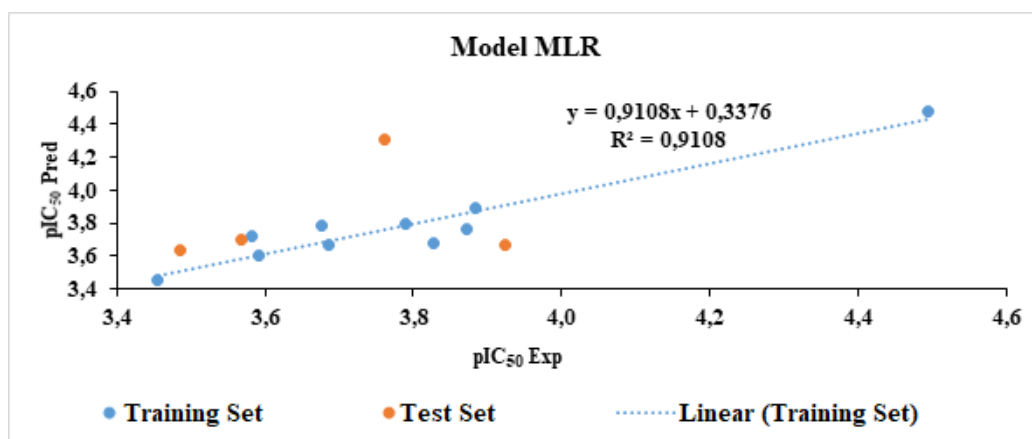


Fig. 2. Regression line of the MLR model

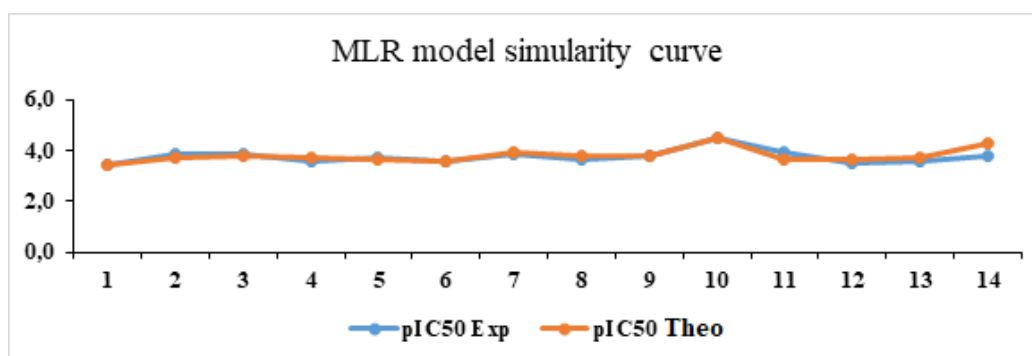
Fig. 3. Evolution curves of the experimental and predicted pIC₅₀ values of the MLR model

Table 5. Randomized determination coefficients

| Interactions | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|-----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| R ² _r | 0.015 | 0.101 | 0.112 | 0.123 | 0.137 | 0.168 | 0.214 | 0.280 | 0.362 | 0.184 |

The Roy parameter ($R^2_p = 0.77$) being lower than the R^2 coefficient of the model (0.9108), we can therefore confirm that the established model is not due to chance.

3.1.2 External validation of the MLR model

The external validation of the model was carried out respectively with the derivatives of dihydropyrazoles (DHP2, DHP3, DHP10, DHP12). In addition, the values of the external

validation test were verified by calculating the $pIC_{50}^{exp}/pIC_{50}^{pred}$ ratio (Table 6).

The values of the ratio tend towards 1. This reflects the good correlation between the predicted and experimental potentials of the dihydropyrazole molecules of the validation set.

After the verification of the various properties of external validation, we can affirm that the model is exploitable for the prediction of the antiproliferative activity of dihydropyrazoles.

Table 6. Values of the ratio between predicted and experimental antimalarial activities from the database

| CODE | pIC ₅₀ ^{exp} | pIC ₅₀ ^{pred} | pIC ₅₀ ^{exp} /pIC ₅₀ ^{pred} |
|-------|----------------------------------|-----------------------------------|---|
| DHP2 | 3.925 | 3.664 | 1.07 |
| DHP3 | 3.486 | 3.638 | 0.958 |
| DHP10 | 3.567 | 3.699 | 0.964 |
| DHP12 | 3.762 | 4.305 | 0.874 |

3.2 Multiple Nonlinear Regression (MNLr)

We propose another MNLr model based on the vibration frequency $\nu(\mathbf{N-N})$, the valence angle $\alpha(\mathbf{N-N-C})$ and the standard entropy of formation ($\Delta_f S^0$). This MNLr model is presented below with the corresponding statistical indicators in Table 7.

$$pIC_{50} = -18014 + 437,16947 * \alpha(N - N - C) - 10,65210 * \nu(N - N) - 40,93001 * \Delta_f S^0 - 1,97663 * \alpha(N - N - C)^2 + 0,00459 * \nu(N - N)^2 - 18,73594 * (\Delta_f S^0)^2$$

The coefficient of determination $R^2 = 0.9207$ (close to 1: ideal case) demonstrates a good correlation between the predicted and observed values. The model therefore has excellent explanatory power. A low standard deviation ($RMSE=0.1393$) indicates that the model has a good statistical fit and therefore strong predictive power. The significance of the model's descriptors is represented by the Fisher-

Snedecor coefficient with a value of **92.823**. This high value, well above the threshold ($= 3.48$), indicates a strong relationship between antiproliferative activity and the descriptors of this model. The cross-validation correlation coefficient (Q_{cv}^2) is equal to $0.9207 > 0.9$, reflecting the excellent Erikson *et al.* model. $R^2 - Q_{cv}^2 = 0.9207 - 0.9207 = 0.000 < 0.3$ means that the model is acceptable. All these statistical indicators show that the model developed explains the antiproliferative activity significantly and satisfactorily. It can be used to predict the antiproliferative activity of other molecules.

The regression line of the MNLr model between the experimental and predicted antidiabetic activities of the learning game and the validation game is shown in Fig. 4.

The model has a low standard deviation (S) of 0.1393, demonstrating good regression between predicted and experimental values. The curves (Fig. 5) reflect a similar evolution of the data for the model's pIC_{50} predictions for 14 dihydropyrazole derivatives, although some deviations were recorded.

Table 7. Statistical analysis report of the pIC_{50} inhibitory potential of the dihydropyrazole derivatives of the MNLr model

| | |
|---|--------------------------|
| Number of observations N | 10 |
| Coefficient of determination R^2 | 0.9207 |
| Standard deviation RMSE S | 0.1393 |
| Fischer F-test F | $92.823 > F_{cr} = 3.48$ |
| Cross Validation Correlation Coefficient Q_{cv}^2 | 0.9207 |
| $R^2 - Q_{cv}^2$ | 0.000 |

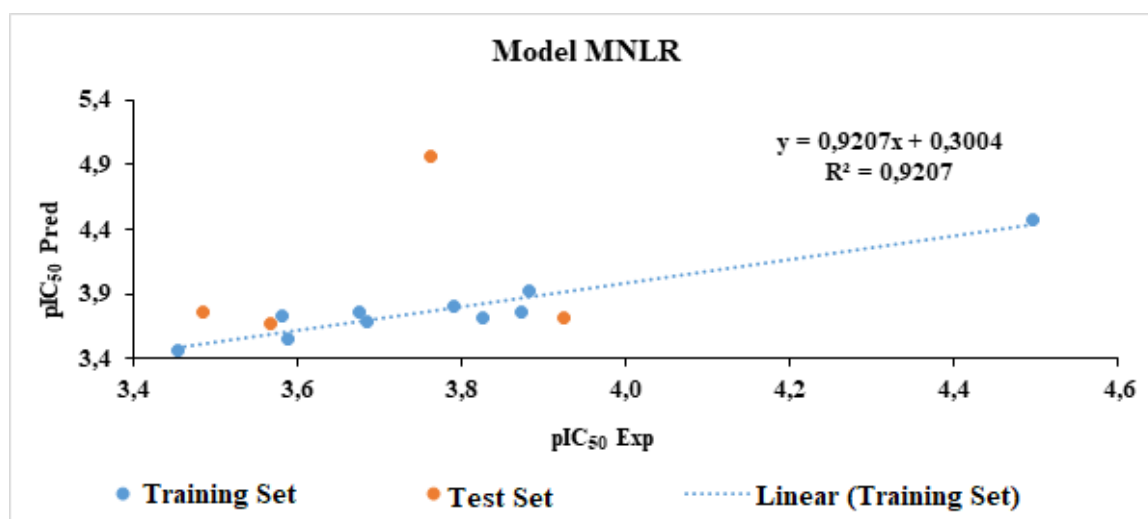


Fig. 4. Regression line of the MNLr model

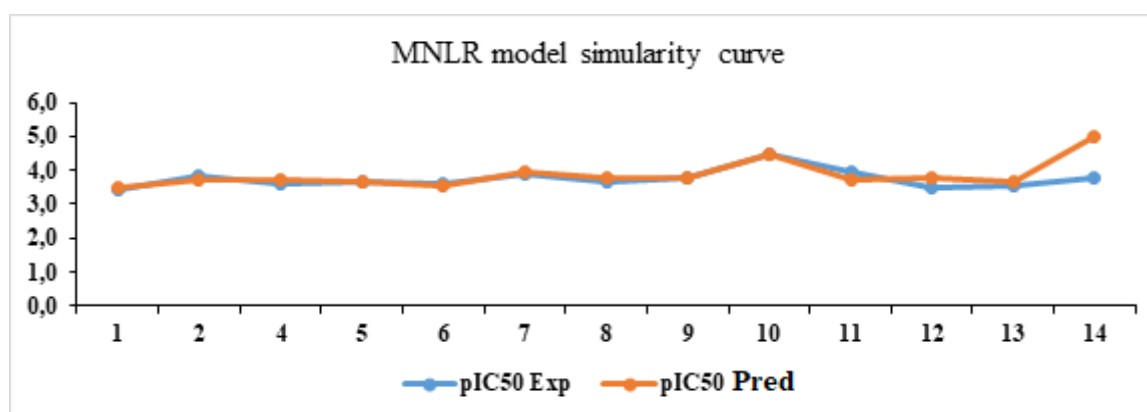


Fig. 5. Evolution curves of the experimental and predicted pIC₅₀ values of the MNL model

3.2.1 Internal validation of the MNL model

The randomization test of this model is only for the compounds in the test set, because the model relies on them. We limited ourselves to ten iterations. The randomized determination coefficients (R_r^2) of each iteration are given in Table 8.

Using the values in the table, we note that Roy's parameter ($R_p^2 = 0.65$) is lower than the R^2 coefficient of the model (0.9207), so we can confirm that the established model is not due to chance.

3.2.2 External validation of the MNL model

The external validation of the model was carried out respectively with the derivatives of dihydropyrazoles (DHP2, DHP3, DHP10, DHP12). In addition, the values of the external validation test were verified by calculating the $pIC_{50}^{exp}/pIC_{50}^{pred}$ ratio (Table 9).

Table 8. Randomized determination coefficients

| Interactions | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|--------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| R_r^2 | 0.318 | 0.329 | 0.380 | 0.421 | 0.442 | 0.446 | 0.460 | 0.472 | 0.506 | 0.544 |

Table 9. Values of the ratio between predicted and experimental antimalarial activities from the database

| CODE | pIC_{50}^{exp} | pIC_{50}^{pred} | $pIC_{50}^{exp}/pIC_{50}^{pred}$ |
|-------|------------------|-------------------|----------------------------------|
| DHP2 | 3.925 | 3.709 | 1.058 |
| DHP3 | 3.486 | 3.761 | 0.927 |
| DHP10 | 3.567 | 3.674 | 0.971 |
| DHP12 | 3.762 | 4.965 | 0.758 |

The value of this ratio tends towards 1. This reflects the good correlation between the predicted and experimental potentials of the dihydropyrazole molecules in the validation set.

3.3 Analysis of Model Descriptors

The contribution of each of the model's three descriptors to the prediction of antiproliferative activity was analysed using XLSTAT software [19]. Fig. 6 illustrates the different contributions.

Fig. 6 shows that the vibration frequency $u(N-N)$ is the descriptor that makes the greatest contribution compared to the other descriptors. Therefore, vibration frequency $u(N-N)$ is the priority descriptor in predicting anticancer activity.

3.4 Applicability Domains and Model

The graph of normalised residuals according to the h_{ii} levers in Fig. 7 shows the range of applicability of the model.

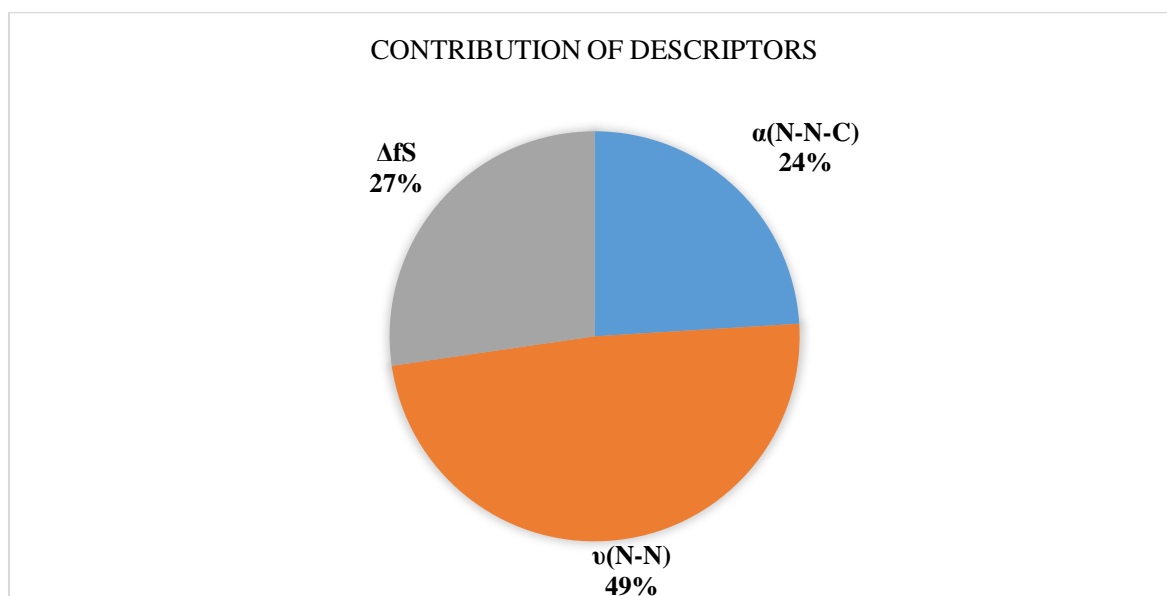


Fig. 6. Contribution of the different constituents in the model

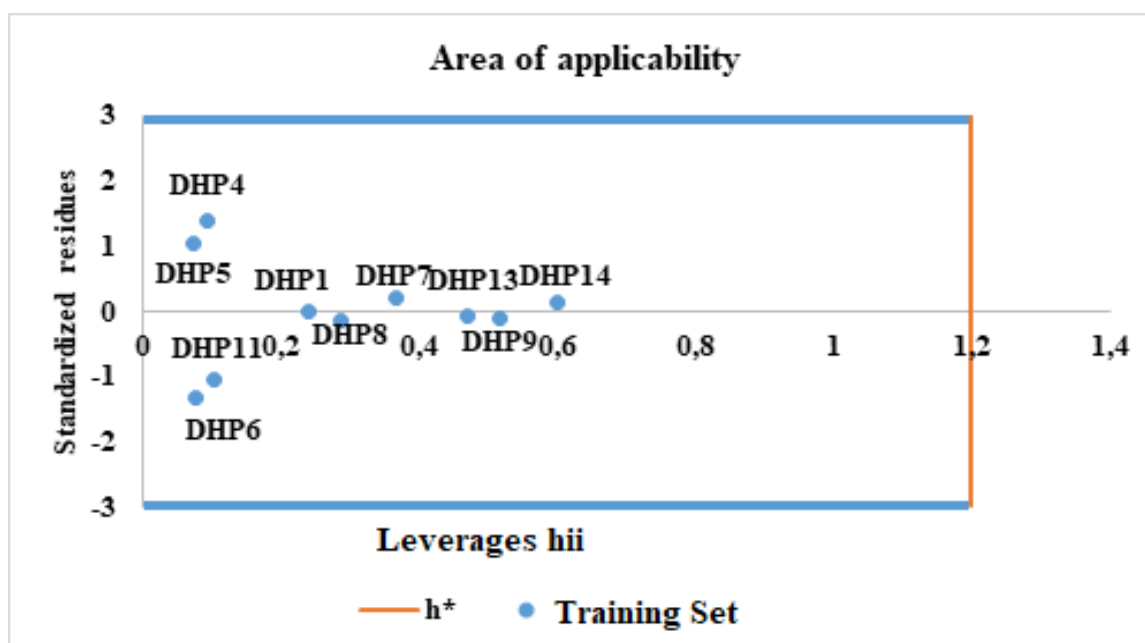


Fig. 7. Graph of residues normalised to the antiproliferative activity of model levers

The ten (10) components of the training set and the three (3) descriptors of the models have a threshold value for the levers $h^* = 1.2$. The extreme values of the standardised residuals are 3 according to the "three sigma rule". These different values delimit the domain of applicability of the model, as shown in the graph in Fig. 7.

4. CONCLUSION

Dihydropyrazoles are molecules that offer an exemplary pharmacological profile. In particular,

their dynamic biological activities make them an interesting research subject. The synthesis of the most effective molecules derived from dihydropyrazoles requires knowledge and understanding of the physicochemical properties in relation to its various biological activities, in particular the antiproliferative activity. In this study, a QSAR model was developed on fourteen molecules derived from dihydropyrazoles in order to relate the antiproliferative activity (*DU-145*) with quantum

descriptors (of the vibration frequency $u(\mathbf{N-N})$, the valence angle $\alpha(\mathbf{N-N-C})$ and the standard entropy of formation ($\Delta_f S^0$)) in order to predict that of new molecules or not. Multiple linear regression (MLR) was used to quantify the relationship between molecular descriptors of vibrational frequency $u(\mathbf{N-N})$, valence angle $\alpha(\mathbf{N-N-C})$ and standard entropy of formation ($\Delta_f S^0$) and potential the inhibitory concentration (pic_{50}) of molecules derived from dihydropyrazoles. The strong correlation observed between the calculated and experimental values of this antiproliferative activity indicates that the vibration frequency $u(\mathbf{N-N})$, the valence angle $\alpha(\mathbf{N-N-C})$ and the standard entropy of formation ($\Delta_f S^0$) are closely related to the potential inhibitory concentration of dihydropyrazoles. The statistical indicators of this model display the following values: $R^2 = 0.9108$, $S = 0.1044$, $F = 20.425$. The validation techniques commonly used, namely the standard statistical indicators of the model, the external validation and the domain of applicability, were used. For the RMNL model we have: $R^2 = 0.920$, $S = 0.1393$, $F = 92.823 > 2.9$, $Q_{CV}^2 = 0.920$. It appears from the two models that the vibration frequency $u(\mathbf{N-N})$, turns out to be the priority descriptor in the prediction of the antiproliferative activity of cancer of the derivatives of dihydropyrazoles studied. The two models obtained were validated using a validation set comprising four (4) molecules by applying the Tropsha criteria. Indeed, the similarity curve illustrates this perfectly by the almost perfect alignment of the points.

The model developed is in accordance with the five principles of the OECD for the validation of QSAR models. This QSAR model obtained therefore makes it possible to explain and predict the behavior of the inhibitory concentration of molecules and also to design other new molecules similar to dihydropyrazoles that are more active against prostate cancer by identifying priority descriptors which are the vibration frequency $u(\mathbf{N-N})$, the valence angle $\alpha(\mathbf{N-N-C})$ and the standard entropy of formation ($\Delta_f S^0$).

This model is able to describe **91.08%** of the total variance of the antiproliferative activity of experimental prostate cancer (**DU-145**) cell lines and could be used effectively to estimate the antiproliferative activity of dihydropyrazole derivatives for which data experiments are not yet available.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Futura Santé, «futura-sciences,» [En ligne] ;2022. Available: <https://www.futurasciences.com/sante/definitions/medecine-cancer-108/>. [Accès le 16 07 16/07/2022].
2. Shaikh A, Bhandare R, Palleapati K, Nissankararao S, Kancharlapalli V, Shaik S. Antimicrobial, antioxidant, and anticancer activities of some novel isoxazole ring containing chalcone and dihydropyrazole derivatives. *Molecules*. 2020;125:1047.
3. Shaik A, Yejella R, Shaik S. «Synthesis, antimicrobial, and computational evaluation of novel isobutylchalcones as antimicrobial agents. *Int. J. Med. Chem*. 2017;1–14,
4. Lokesh B, Prasad Y, Shaik A. Synthesis, biological evaluation and molecular docking studies of new pyrazolines as an antitubercular and cytotoxic agents. *Infect, Infectious Disorders - Drug Targets*. 2019; 119:310.
5. Kancharlapalli V, Shaikh A, Palleapati K. Antitubercular evaluation of isoxazole appended 1-carboxamido-4,5-dihydro-1H-pyrazoles. *J. Res. Pharm*. 2019;123:156–163.
6. Goodman LS. Gilman A. The pharmacological basis of therapeutics, New York: Macmillan; 1980.
7. Kishor P, Ramana V, Shaikh A, Antitubercular Evaluation of Isoxazolyl Chalcones. *Res. J. Pharm. Biol. Chem. Sci*. 2017; 18:730–735.
8. Shaikh A, Lohitha K, Vani S, Basu P, Shaik A, Supraja K, Harish S. Synthesis and screening of novel lipophilic diarylpropeones as prospective antitubercular, antibacterial and antifungal agents. *Biointerface Res. Appl. Chem*. 2019;19.
9. Shaikh A, Prasad Y, Shaik S. Design, Facile synthesis, characterization and computational evaluation of novel isobutylchalcones as cytotoxic agents. *FABAD J. Pharm. Sci.* ;2015;1,2Part-A(140):7–22.

10. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE. Gaussian 09, revision A.02, Gaussian, Inc., Wallingford CT; 2009.
11. Chattaraj PK, Cedillo A, Parr RG. J. Phys. Chem. 1991;103:7645.
12. Ayers PW, Parr RG. J. Am Chem. Soc. 2010;122:2000.
13. De Proft F, Martin JML, Geerlings P. Chem. Phys Let. 1996;250:393.
14. Hansch C, Sammes PG, Taylor JB. Comprehensive Medicinal Chemistry. Computers and the Medicinal Chemist. 1990;4:33-58.
15. Franke R. Theoretical Drug Design Methods. Elsevier; 1984.
16. Chatterjee S, Hadi A. Price B. Regression Analysis by Examples. Wiley VCH: New York; 2000.
17. Phuong H. Synthèse et étude des relations structure/activité quantitatives (QSAR/2D) d'analogues Benzo[c]phénanthridiniques. France; 2007.
18. M. Excel; 2016.
19. Addinsoft, XLSTAT Version 2014.5.03 Copyright, XLSTAT and Addinsoft are Registered Trademarks of Addinsoft. 1995-2014;2014.
20. Snedecor GW, Cochran WG. Methods, Statistical. Oxford and IBH: New Delhi, India. 1967;381.
21. Kangah NJB, Koné MGR, Kodjo CG, N'guessan BR, Kablan ALC, Yéo SA, Ziao N. Antibacterial activity of schiff bases derived from ortho diaminocyclohexane, meta-phenylenediamine and 1,6-diaminohexane: Qsar study with quantum descriptors. International Journal of Pharmaceutical Science Invention. 2017;6(13):38-43.
22. Esposito EX, Hopfinger AJ, Madura JD. Methods for applying the quantitative structure-activity relationship paradigm. Methods in Molecular Biology. 2004;275: 131-213.
23. Eriksson L, Jaworska J, Worth A. Cronin MD, RM Mc Dowell, Gramatica P. Methods for reliability and uncertainty assessment and for applicability evaluations of classification- and regression-based QSARs. Environmental Health Perspectives. 2003;111(110):1361-1375.
24. Roy K, Paul S. Exploring 2D and 3D QSARs of 2,4-Diphenyl-1,3-oxazolines for ovicidal activity against tetranychus urticae. QSAR Comb. Sci. 2009;28(14): 406–425.
25. Gramatica P. Principles of QSAR models validation: Internal and external. QSAR Comb. Sci. 2007;26(15):694–701.
26. Jeliaskova NN, Jaworska J. An approach to determining applicability domains for QSAR group contribution models: An analysis of SRC KOWWIN. ATLA. 2005;33:461–470.
27. Sahigara F, Mansouri K, Ballabio D, Mauri A, VC. a. R. Todeschini. Comparison of different approaches to define the applicability domain of QSAR models. Molecules. 2012;17:4791-4810.
28. Roy K. A Primer on QSAR/QSPR modeling chapter 2 statistical methods in QSAR/QSPR. Springer Briefs in Molecular Science. 2015;37-59.
29. Jaworska J, Jeliaskova NN, Aldenberg T. QSAR applicability domain estimation by projection of the training set in descriptor space: A review. ATLA 33. 2005;445–459.
30. Ghamali M, Chtita S, Bouachrine M, Lakhlifi T. Méthodologie générale d'une étude RQSA/RQSP, revue interdisciplinaire. 2016;1:11.
31. Chtita S, Ghamali M, Hmamouchi R, Elidrissi B, Bourass M, Larif M, Bouachrine M, Lakhlifi T. Investigation of antileishmanial activities of acridines derivatives against promastigotes and amastigotes form of parasites using QSAR analysis. Advances in Physical Chemistry. 2016;1-16.
32. Asadollahi T, Dadfarnia S, Shabani A, Ghasemi J, Sarkhosh M. QSAR models for CXCR2 receptor antagonists based on the genetic algorithm for data preprocessing prior to application of the PLS linear regression method and design of the new compounds using in silico virtual screening. Molecules. 2011;16: 1928-1955.
33. Chtita S, Larif M, Ghamali M, Bouachrine M, Lakhlifi T. Quantitative structure–activity relationship studies of dibenzo[a,d]cycloalkenimine derivatives for non-competitive antagonists of N-methyl-D-aspartate based on density functional theory with electronic and topological descriptors. Journal of Taibah University for Science. 2015;9:143-154.

34. Cook RD. Weisberg S. Wiley series in probability and statistics. An Introduction to Regression Graphics; 1994. reliability and uncertainty assessment and for applicability evaluations of classification and regression-based QSARs.
35. Eriksson L, Jaworska J, Worth A, Dowell MTD, Gramatica P. Methods for Environmental Health Perspectives. 2003; 111(110):1361-1375.

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