International Journal of Computational and Theoretical Chemistry
2022; 10(1): 1-8
http://www.sciencepublishinggroup.com/j/ijctc
doi: 10.11648/j.ijctc.20221001.11
ISSN: 2376-7286 (Print); ISSN: 2376-7308 (Online)

Anti-proliferative Activity Study on 5-Arylidene Rhodanine Derivatives Using Density Functional Theory (DFT) and Quantitative Structure Activity Relationship (QSAR)

Coulibaly Wacothon Karime[1], Affi Sopi Thomas[2], James Titah[3, *], Mamadou Guy-Richard Koné[2], Affoué Estelle Brigitte Yao[2], Camille Déliko Dago[4], Christelle N'ta Ambeu[4], Jean-Pierre Bazureau[4], Josh Daniel McLoud[3], Benié Anoubilé[5], Nahossé Ziao[2]

[1]Department of Mathematics, Physics, and Chemistry, Université Peleforo GON COULIBALY, Korhogo, Ivory Coast

[2]Laboratoire de Thermodynamique et de Physico-Chimie du Milieu, UFR SFA, Université Nangui Abrogoua, Abidjan, Ivory Coast

[3]Department of Chemistry/Biology-Science & Mathematics, Tabor College, Hillsboro, USA

[4]Institut des Sciences Chimiques de Rennes (ISCR), Université de Rennes 1, Campus de Beaulieu, Rennes Cedex, France

[5]Laboratoire de Chimie BioOrganique et de Substances Naturelles, Université Nangui Abrogoua, Abidjan, Ivory Coast

Email address:

tijames2001@yahoo.com (J. Titah), jamestitah@tabor.edu (J. Titah)

[*]Corresponding author

To cite this article:

Coulibaly Wacothon Karime, Affi Sopi Thomas, James Titah, Mamadou Guy-Richard Koné, Affoué Estelle Brigitte Yao, Camille Déliko Dago, Christelle N'ta Ambeu, Jean-Pierre Bazureau, Josh Daniel McLoud, Benié Anoubilé, Nahossé Ziao. Anti-proliferative Activity Study on 5-Arylidene Rhodanine Derivatives Using Density Functional Theory (DFT) and Quantitative Structure Activity Relationship (QSAR). *International Journal of Computational and Theoretical Chemistry.* Vol. 10, No. 1, 2022, pp. 1-8. doi: 10.11648/j.ijctc.20221001.11

Received: December 3, 2021; **Accepted**: January 8, 2022; **Published**: January 21, 2022

Abstract: In this study, we have successfully use quantitative structure activity relationship (QSAR) to determine the anti-proliferative activity of thirteen 5-arylidenes and derivatives using Density Functional Theory (DFT) method. Three models from the quantum molecular descriptors: energy of the lowest unoccupied molecular orbital; E_{LUMO} the C-N distance; $d_{(C-N)}$, the C=O vibrational frequency; $v_{(C=O)}$ were used on two representative tumor cell lines: NCI -H727; lung carcinoma and MDA-MB 231; breast carcinoma. The Density Functional Theory method of quantum chemistry was applied to the B3LYP / 6-31G (d) calculation level, to obtain the molecular descriptors. The following statistical indicators and their values were used on the models: regression coefficient of determination (0.926 to 0.954), adjusted coefficient of determination (0.882 to 0.927), standard deviation S (0.052 to 0.147), Fischer test; F (88.221 to 145.448), correlation coefficient of the cross validation (0.926 and 0.954) and difference approaching 0.000. The statistical characteristics of the established quantitative structure activity relationship (QSAR) models satisfy the criteria of acceptance and external validation, thereby confirming their good performance. In addition, each model is a function of the three descriptors mentioned above. The three models show that the C-N distance; $d_{(C-N)}$ and the energy of the lowest unoccupied molecular orbital; E_{LUMO} are the greatest descriptors in the prediction of the anti-proliferative activity of the studied molecules and could be used for the synthesis of new anti-proliferative molecules.

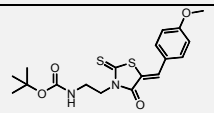
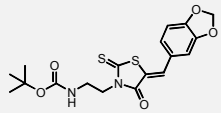
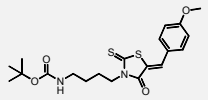
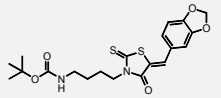
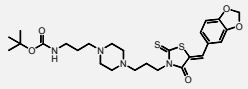
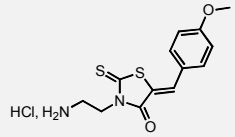
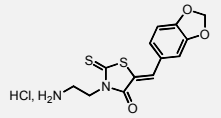
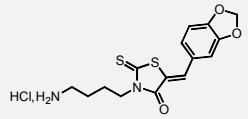
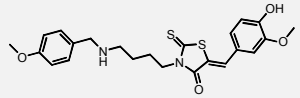
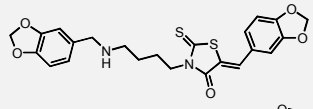
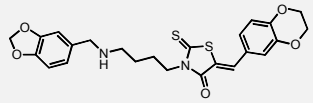
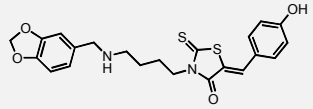
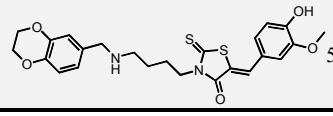
Keywords: 5-Arylidene Rhodanine, Anti-proliferative Activity, Quantitative Structure Activity Relationship, Density Functional Theory Method, Molecular Descriptors

1. Introduction

Tumor refers to an increase in volume or size of a tissue in humans. It is can also been seen as the formation of massive body tissues caused by the disruption of cell growth; benign or malignant. A malignant tumor is called cancer. The treatment of benign tumor is by surgical removal of the tumor mass while the treatment of malignant tumor (cancer) is through chemotherapy. It is within this framework that medicinal, pharmaceutical or therapeutic chemistry, which is a scientific discipline at the interface of chemistry and pharmacy, are involved in the design and development of new drugs.

Researchers continue to search for new molecular entities or drugs with biological activity to help mitgate some of the world's challenging diseases.

Table 1. *Molecular structures of 5-arylidene rhodanines and their different activities NCI-H727 (lung carcinoma) and MDA-MB 231 (breast carcinoma) studied.*

Code	Structure of the molecule	IC $_{50}$ (µM)	
		MDA-MB231	NCI-H727
AR-1		114	110
AR-2		97	86
AR-3		109	110
AR-4		109	110
AR-5		60	33
AR-6		13	94
AR-7		83	74
AR-8		109	97
AR-9		15	11
AR-10		49	43
AR-11		17	9
AR-12		42	33
AR-13		55	63

The biological activities of 2-thiazolidin-4-one derivatives, traditionally referred to as rhodanine have been studied for over 100 years; a lot of research is still ongoing on these compounds because of their numerous or interesting biological activities [1, 2]. Rhodanine and its derivatives have been used as anti-convulsant, anti-bacterial, anti-viral, anti-diabetic, anti-tuberculosis, pesticides, fungicides, anti-inflammatory, anti-thyroid, anti-tumor drugs for many years [3-13]. Numerous derivatives of rhodanine have been synthesized, characterized and tested for their biological activities or properties; these include 5-arylidene-2-thioxo-1,3-thiazolidinin-4-ones or 5-arylidene rhodanines. These molecules have been observed to inhibit protein kinases [14]. To improve the anti-tumor activity of 5-arylidene rhodanines first requires a mastery of its physicochemical properties and structure activity relationship so that new compounds may be synthesized or designed. In this study, we would use the Quantitative Structure Activity Relationship (QSAR), which is one of the best and most widely used methods for the design and development of new therapeutic agents to design 5-arylidene rhodanine and derivatives [15-17]. Computational or density functional theory (DFT) methods are increasingly being used to design new drugs in medicinal and therapeutic chemistry as they reduce the excessive number of experiments, sometimes long and expensive [18, 19]. The main objective of this study is to conduct a descriptive and predictive study of the anti-tumor activity on thirteen (13) derivatives of 5-arylidene rhodanine.

Details of the 5-arylidene derivatives in this study may be observed in Table 1.

2. Methodology

2.1. Calculation Methodology

The thirteen 5-arylidene rhodanine molecules studied were divided into two groups for convenience in comparison; nine molecules were used for the test set and four molecules were used to validation the test set. The compounds were tested for their anti-proliferative activity to determine their IC_{50} values (molecular concentration required to achieve 50% inhibition of the enzymatic activity). A molecule is considered inhibitory when it exceeds 50% inhibition compared to the control. The ability to inhibit the growth of cell lines in this work was evaluated from two (2) cell lines of the ImPACcell platform.

NCI-H727 (REF ECACC: 94060303): human lung tumor line.

MDA-MB 231 (REF ECACC: 92020424): human breast carcinoma line.

We used the logarithm to base 10 to compare the activity (-log10 (IC_{50})) in order to obtain higher mathematical values for the effective interpretation of the results [20-23]. Using IC_{50} in µM, the anti-proliferative potential can be defined by the equation 1 below:

$$p^{CI50} = - \log(p^{IC50} \times 10^{-6})$$

$$pCI_{50} = -log_{10}(pCI_{50} * 10^{-6}) \quad (1)$$

2.2. DFT Level of Calculation

The geometries of the molecules were optimized at the DFT calculation level with the B3LYP functional [24-27] in

the 6-31 G (d) base using the Gaussian 09 software [28]. This Hybrid functional gives better energies that agree with the ab initio methods of higher levels [29, 30]. The split-valence and *double-dzeta* base (6-31G (d)), were sufficiently extended and to account for the polarization functions. This is important for explaining the free doublets of the heteroatoms. The modeling was done using the multilinear regression method implemented in *Excel* spreadsheet [31] and *XLSTAT* [32].

2.3. Molecular Descriptors Used

The success of any quantitative structure activity relationship (QSAR) model relies on the choice of molecular descriptors used. In this study, we used the descriptors from quantum chemistry to predict the anti-proliferative activity as well as the cytotoxic inhibition properties of 5-arylidene rhodanines. Out of the thirteen descriptors selected for 5-arylidene rhodanines, there of them were in good correlation with the anti-proliferative activity of the molecule to be used for model development. These descriptors were the lowest unoccupied molecular orbital energy (E_{Lumo}), the C-N distance $d_{(C-N)}$ and the C=O vibration frequency $\nu_{(C=O)}$.

The lowest unoccupied molecular orbital energy (E_{LUMO}) describes the ability of a molecule with an empty molecular orbital to accept electrons. Its value was obtained by a quantum chemistry calculation using the Gaussian 09 software [28].

The C-N distance $d_{(C-N)}$ was determined by the length of the bond between the carbon atom (C) and the nitrogen heteroatom (N) contained in the core of the rhodanine derivatives. This descriptor was obtained from the DFT-optimized geometries of rhodanine derivatives and was expressed in angstrom (A) (Figure 2).

The C=O vibration frequency $\nu_{(C=O)}$. This descriptor is obtained after the DFT-optimized structure of rhodanine derivatives (Figure 1).

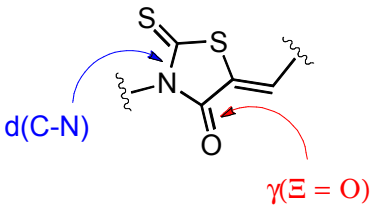


Figure 1. *Geometric descriptors of 5-arylidene rhodanines $d_{(C-N)}$ and $\nu_{(C=O)}$.*

The interdependence of the descriptors was evaluated by bivariant linear correlation coefficients a_{ij} between the pairs of the descriptor set. Here, two descriptors were said to be independent when $a_{ij} < 0.70$ [33].

2.4. Development of Models and Their Validations

The different models were constructed using the multiple linear regression method (*Multiple Linear Regression, MLR*) implemented in the *Excel* 2013 spreadsheet [31]. The Regression tool in this spreadsheet performs a linear regression analysis using the least squares method to find a line from the observed values. The *MLR* method is a statistical technique that allows us to linearly connect a series of independent explanatory variables x_i (descriptors) to the dependent variable y, in order explicitly to explain the anti-proliferative activity, $pIC50$. This method was the most used for the development of predictive models. The goal was to get an equation of the form in equation 2 below:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \cdots \quad (2)$$

Where the β_i are the coefficients of the regression.

Correlation and prediction tests would be performed on our compounds for comparison once the model has been established and trusted. In order to validate the correlation method on the test data set, the statistical indicators; R^2 are the coefficients of determination, the standard deviation; S, the correlation coefficients of the cross-validation; Q^2_{CV} and Fischer; F were considered. The Excel software was used to calculate the statistic tests [31]. The statistical indicators (R^2, S and F) relate to the adjustment of the calculated and experimental values. These values were used to describe the predictive ability within the limits of the model. This allows us to estimate the accuracy of the values calculated on the learning set [34, 20]. The coefficient of determination R^2 gives an evaluation of the dispersion of the theoretical values around the experimental values (precision in measurement). The quality of the modeling was better when the points are close to the right of adjustment [21, 35-37]. The adjustment of points to this line can be evaluated by the correlation coefficient equation below:

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

Where:

$y_{i,exp}$: The experimental value of the anti-proliferative activity

$\hat{y}_{i,theo}$: The theoretical value of the activity and

$\bar{y}_{i,exp}$: The average value of the experimental values of the anti-proliferative activity

The closer the value of R^2 to unity, the more the theoretical and experimental values are correlated

In addition, the variance; σ^2 is determined by the relation in equation 4:

$$\sigma^2 = s^2 = \frac{\Sigma(y_{i,exp} - y_{i,theo})^2}{n-k-1} \quad (4)$$

Where:

k is the number of independent variables (descriptors)

n is the number of molecules in the test or learning set,

n-k-1 is the degree of freedom.

The standard deviation; S (equation 5) is another statistical indicator used. This evaluated the reliability and accuracy of the model:

$$s = \sqrt{\frac{\Sigma(y_{i,exp} - y_{i,theo})^2}{n-k-1}} \quad (5)$$

The Fisher test; F was used to measure the level of the statistical significance of the model, that means, the quality of the choice of descriptors constituting the model.

$$F = \frac{\Sigma(y_{i,theo}-y_{i,exp})^2}{\Sigma(y_{i,exp}-y_{i,theo})^2} * \frac{n-k-1}{k} \quad (6)$$

The coefficient of determination of the cross validation; Q^2_{CV}, was used to evaluate the accuracy of the prediction on the test set and is calculated using equation 7.

$$Q^2_{cv} = \frac{\Sigma(y_{i,theo}-\bar{y}_{i,exp})^2-\Sigma(y_{i,theo}-y_{i,exp})^2}{\Sigma(y_{i,theo}-\bar{y}_{i,exp})^2} \quad (7)$$

To estimate the predictive power of the models, the method of external validation was used on the set of the four remaining molecules of the database. In this framework, the established QSAR models were used to determine the predicted inhibition potentials (pIC_{50}) of the four molecules. Validation of the models was performed by considering the cross-correlation coefficient of the test set Q^2_{CV} and the ratio between the predicted and experimental inhibit potentials noted; τ.

$$\tau = \frac{pIC_{50\ predit}}{pIC_{50\ expérimental}} \quad (8)$$

The predictive power of a model was considered good if Q^2_{cv} or τ T approaches unity. According to the value of this statistical indicator, Eriksson and *al.* [38], define the performance of a mathematical model. A model whose value of $Q^2_{cv} > 0{,}5$ was said to be satisfactory while the one whose value $Q^2_{cv} > 0{,}9$ was described as excellent. According to Eriksson et *al.*, for a given test name a model will be efficient if the acceptance criterion $R^2 - Q^2_{cv} < 0{,}3$.

3. Results and Discussion

3.1. Interdependence of Descriptors and Experimental Inhibitory Potentials

The values of the anti-proliferative potentials (MDA-MB231 and NCI-H727) and those of the various descriptors of the test set and the validation set are presented in Table 2.

Table 2. *Quantum descriptor values and experimental potentials of lineages MDA-MB231 and NCI-H727.*

	E_{Lumo} (eV)	$\nu_{(C=O)}$ (cm^{-1})	$d_{(C-N)}$ (Å)	MDA-MB231	NCI-H727
AR-1	-5.923	1781.900	1.373	3.943	3.959
AR-2	-5.901	1782.730	1.372	4.013	4.066
AR-3	-5.897	1783.920	1.371	3.963	3.959
AR-4	-5.205	1787.490	1.365	3.963	3.959
AR-5	-5.266	1775.920	1.371	4.222	4.481
AR-6	-5.887	1783.020	1.373	4.886	4.027
AR-7	-5.951	1789.880	1.365	4.081	4.131
AR-8	-5.834	1786.670	1.371	3.963	4.013
AR-9	-5.671	1781.750	1.370	4.824	4.959
AR-10	-5.373	1785.940	1.370	4.310	4.367
AR-11	-5.558	1784.710	1.370	4.770	5.046
AR-12	-5.432	1785.830	1.370	4.377	4.481
AR-13	-4.427	1784.570	1.370	4.260	4.201

It should be noted that the external validation of the models MDA-MB231 and NCI-H727 were performed respectively on rhodanine derivatives (AR-1, AR-6, AR-12, AR-13), and (AR-2, AR-6, AR-7, AR-12). In order to highlight the interdependence of the selected descriptors, the values of the bivariant linear correlation coefficients; a_{ij} between the pairs of descriptors (E_{Lumo}, $\nu_{(C=O)}$), (E_{Lumo}, $d_{(C-N)}$), ($\nu_{(C=O)}$) and $d_{(C-N)}$), are less than 0.70 ($a_{ij} < 0.70$) (Table 3). In addition, two descriptors are said to be interdependent when $a_{ij} < 0.70$. This demonstrates the independence of the descriptors used to develop the models.

Table 3. *Values of the bivariant linear correlation coefficients of the descriptors.*

Variables	E_{Lumo}	$\nu_{(C=O)}$	$d_{(C-N)}$
E_{Lumo}	1	-0.0817	-0.2569
$\nu_{(C=O)}$	-0.0817	1	-0.6306
$d_{(C-N)}$	-0.2569	-0.6306	1

From table 3, it can be seen that the linear correlation coefficients; a_{ij} calculated from majority of the descriptors used were less than 0.7 ($a_{ij} < 0.7$). This reflects the non-dependence of the descriptors used in developing the models.

3.2. Modeling of Anti-proliferative Activities

For the different anti-proliferative sources, the equations relating the different tumor lines with the descriptors are given in Table 4.

Table 4. *The most significant QSAR models for modeling anti-proliferative activities on the MDA-MB231 and NCI-H727 lines.*

Tumor line	Regression Equations
MDA-MB231	$pIC_{50}^{préd}$= -459.09176 + 1.89218*E_{Lumo} + 0.08176*$\nu_{(C=O)}$ + 39.43317*$d_{(C-N)}$
NCI-H727	$pIC_{50}^{préd}$= -612.15455 + 2.14518*E_{Lumo}+ 0.11987*$\nu_{(C=O)}$ + 30.62007*$d_{(C-N)}$

The equations of the different models were obtained by using the descriptors (E_{LUMO}, $d_{(C-N)}$, $\nu_{(C=O)}$) determined from the DFT-optimized molecules or structures. A negative sign in a descriptor will mean that when the value of the descriptor is high, the biological activity will decrease and vice versa. On the other hand, a positive sign on the descriptor will indicate that when the value of the descriptor is high, the biological activity will increase and vice versa. For the tumor lines MDA-MB231 and NCI-H727 models, the signs of the different coefficients of the descriptors (E_{LUMO}, $d_{(C-N)}$, $\nu_{(C=O)}$) indicate that the anti-proliferative activity ($pIC_{50}^{préd}$) evolves in the same direction. The study of the significance of these different models was conducted by evaluating the statistical indicators and the relationship between the theoretical and experimental activities of the validation set. The values of the statistical indicators determined for each model are shown in Table 5. The values of the statistical indicators listed in this table reflect a good correlation of the activity with the different descriptors.

Table 5. *Statistical indicators of multilinear regression.*

Statistical indicators of multilinear regression	MDA-MB231	NCI-H727
Number of compounds N	13	13
Coefficient of determination R^2	0.954	0.926
Adjusted coefficient of determination R^2_{ajust}	0.927	0.882
Standard deviation S	0.093	0.147
Fisher's test F	145.448	88.221
Correlation coefficient of cross validation Q^2_{CV}	0.954	0.926
R^2 - Q^2_{CV}	0.000	0.000
Field of activity IC_{50}^{exp} (µM)	13-114	9-110
Confidence level α	> 95%	

In these models, 92.60 and 95.40% of the molecular descriptors (E_{LUMO}, $d_{(C-N)}$, $\nu_{(C=O)}$) are taken into account with the root of the mean squared error of prediction ranging from 0.093 to 0.147. The significance of these models was determined by a coefficient of Fischer test; F ranging from 88.221 to 145.448. The adjusted coefficient of determination R^2_{ajust} of these models ranges from 0.882 to 0.927. In addition, the correlation coefficient of cross-validation; Q^2_{CV} is between 0.926 and 0.954. These values are in complete agreement with literature values for excellent models [28]. In addition, the models are acceptable because they agree with the acceptance criteria of these authors: $R^2 - Q^2_{CV} = 0.000 < 0.3$. Furthermore, the performance of these models is also reflected in the values of pIC_{50} pred/pIC_{50}exp report from literaure. The different equations permit us to obtain the theoretical activities of the molecules according to the tumor lines presented in Table 6.

From table 6 it can be seen that all the calculated ratios (pIC_{50} pred/pIC_{50}exp) tend to approach unity, indicating a good correlation between the experimental and predicted potentials of the molecules. Therefore, the different models are can be used to conveniently predict of the anti-proliferative activity of the rhodanine derivatives studied.

Table 6. *Values of the relationship between the predicted and experimental anti-proliferative activities of the validation set.*

	pIC_{50}exp	pIC_{50}pred	pIC_{50} pred / pIC_{50}exp
MDA-MB231			
AR-1	3.943	3.946	1.001
AR-6	4.886	4.887	1.000
AR-12	4.377	4.381	1.001
AR-13	4.260	4.253	0.998
NCI-H727			
AR-2	4.066	4.071	1.001
AR-6	4.027	4.054	1.007
AR-7	4.131	4.095	0.991
DR-12	4.481	4.485	1.001

From table 6 one can observe that all the calculated ratios (pIC_{50} pred/pIC_{50}exp) tend to approach unity, indicating a good correlation between the experimental and predicted potentials of the molecules. Therefore, the different models can be used to conveniently predict of the anti-proliferative activity of the rhodanine derivatives studied.

The different regression lines between the experimental and theoretical anti-proliferative activities of the test set (blue dots) and the validation set (red dots) for each tumor line are illustrated in Figures 2 and 3.

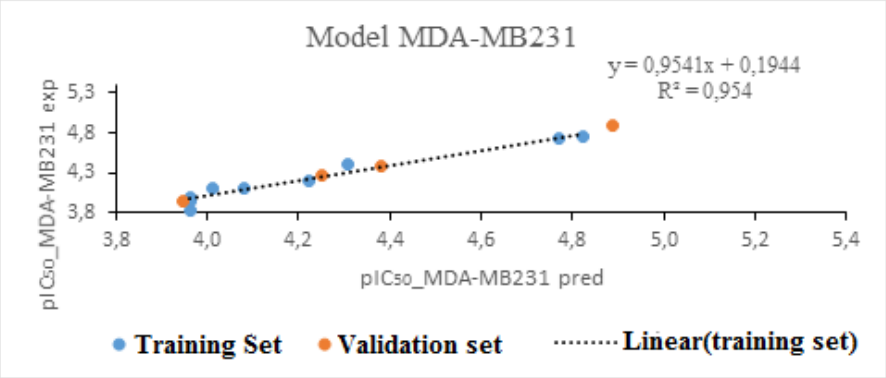


Figure 2. *Model MDA-MB231 regression line.*

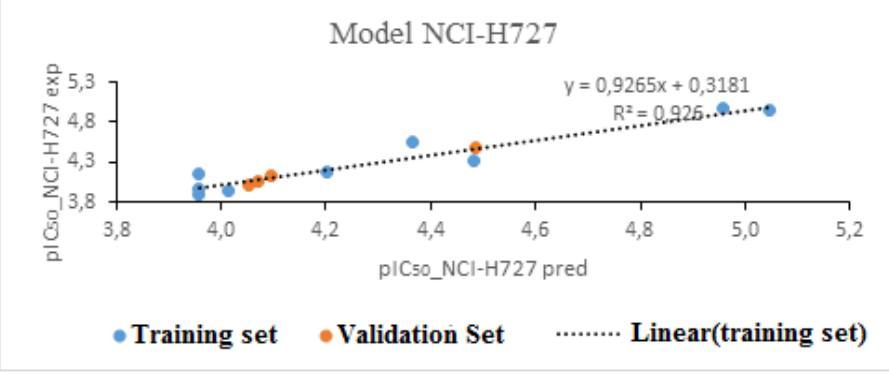


Figure 3. *Model regression line NCI-H727.*

On the graphs obtained, we note a proximity or closeness of the points on the regression curve. This means that, there is a strong linear correlation between the predicted and experimental values of the anti-proliferative activity of the 13 different molecules of 5-arylidene rhodanines. These observations can also be confirmed by the different values of the coefficient of determination R^2. On the other hand, the low values of the standard deviation; S ranging from 0.093 and 0.147 for the two models attest to the good similarity between the predicted and experimental values (Figure 4). These curves in figure 4 show a similar evolution of the data of these models for the prediction of the anti-proliferative activity of the 13 compounds of 5-arylidene rhodanines with minimal or insignificant discrepancies.

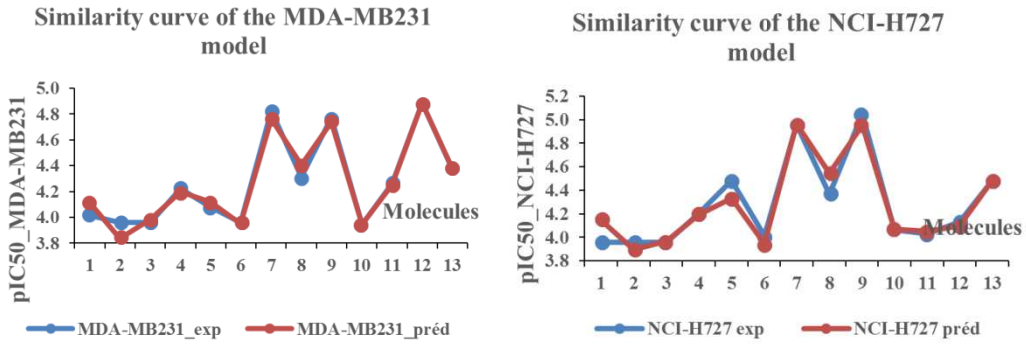


Figure 4. *Similarity curve of the experimental and predicted values of these two models.*

However, it is important to determine the contribution of each in the prediction of the anti-proliferative activity using the two models as a function of three descriptors. Indeed, the knowledge of this contribution makes it possible to establish the order of priority of the various descriptors and to define the choice of parameters to use for optimize in order to obtain a good prediction and understanding of the anti-proliferative activity of the 13 compounds of 5-arylidene rhodanines.

3.3. Analysis of the Contribution of the Descriptors in the Models

The study of the relative contribution of the descriptors for the prediction of the anti-proliferative activity of 5-arylidene rhodanines were carried out on the different tumor lines from the XLSTAT version 2014 software [22]. The different contributions are illustrated in Figure 5.

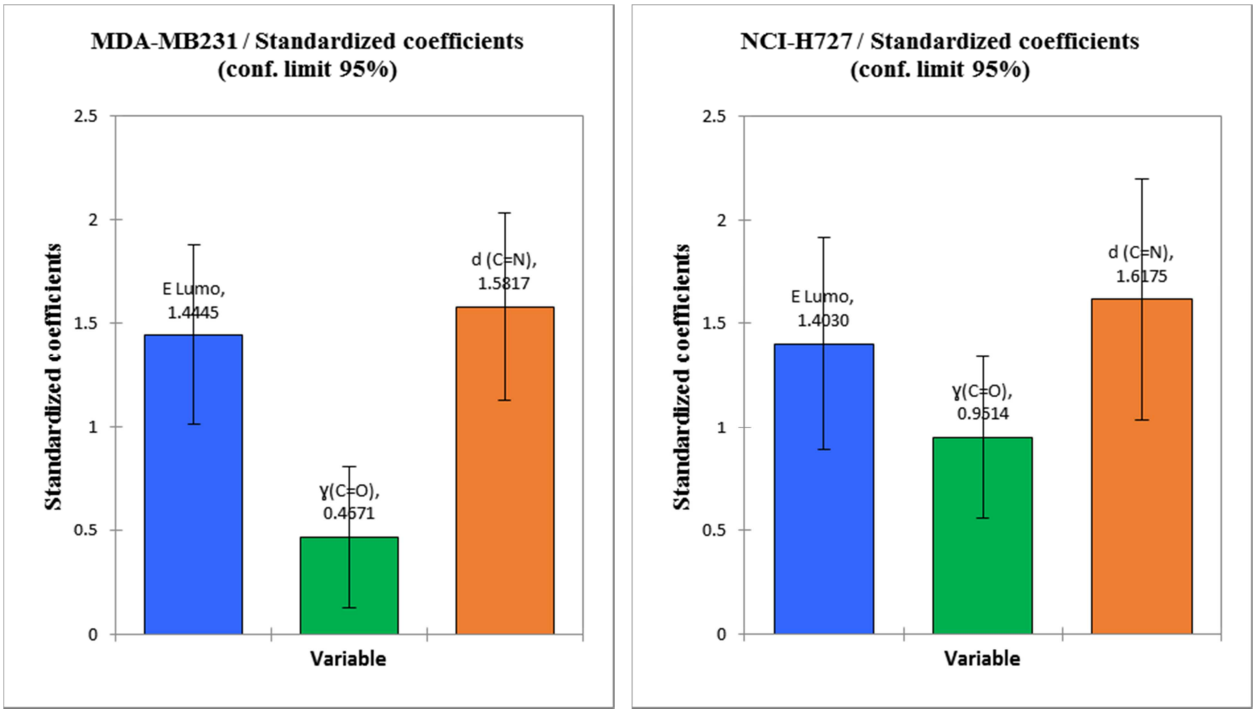


Figure 5. *Contribution of the different constituents in these two models.*

The order of priority of the different quantum descriptors with their respective normalized coefficients was classified according to the following sequences:

NCI-H727: d(C-N) > E_{LUMO} > v (C=O)

MDA-MB231: d(C-N) > E_{LUMO} > v(C=O)

According to the contribution of these descriptions, the C-N distance; $d_{(C-N)}$ has a larger contribution to the two tumor lines; MDA-MB231 and NCI-H727 compared to E_{LUMO} and $v_{(C=O)}$. Therefore, the C-N distance; $d_{(C-N)}$ and E_{LUMO} are the priority descriptors in the prediction of the anti-proliferative activity of the 5-arylidene rhodanines studied. It is important to note that our claim is in complete agreement with that proposed by Hansch, which states that one can establish models relating the biological activity with the hydrophobic, electronic and steric properties of the molecules [39].

4. Conclusion

In this study, two QSAR models were developed on thirteen molecules derived from 5-arylidene rhodanines in order to understand their anti-proliferative activities on two representative tumor cell lines (NCI-H727; lung carcinoma, and MDA-MB 231; breast carcinoma) using DFT-quantum descriptors E_{Lumo}, $d_{(CN)}$, and $v_{(C=O)}$. This study can be extended to predict new molecules in order to determine their anti-proliferative activities. In addition, multiple linear regression (MLR) was used to quantify the relationships between molecular descriptors and anti-proliferative activity of 5-arylidene rhodanine and derivatives. Strong correlations between the predicted and experimental values of these two tumor cell lines indicate that the descriptors; E_{Lumo}, $d_{(CN)}$, and $v_{(C=O)}$ are closely related to the anti-proliferative activity of 5-arylidene rhodanines with both models statistically supported. For the NCI-H727 model, we have R^2 = 0.926, R^2_{ajust} = 0.882, S = 0.147, F = 88.221, Q^2_{CV} = 0.926 and for the model MDA-MB231, we have R^2 = 0.954, R^2_{ajust} = 0.927, S = 0.093, F = 145.448, Q^2_{CV} = 0.954. The two models used in this study show that the C-N distance; $d_{(C-N)}$ and the energy of lowest unoccupied molecular orbital; E_{LUMO} are the greatest descriptors in the prediction of the anti-proliferative activity of the 5-arylidene rhodanines derivatives studied. The different models obtained were validated using a validation set comprised of four molecules. The similarity in the curve in figure 4 perfectly illustrate this by the alignment of the points. For future work, this work could be extended to new molecules related to rhodanines and derivatives with the objectives of determining their anti-proliferative activities.

References

[1] R. B. Lesyk and B. S. Zimenkovsky, 1-4-thiazolidones: history, centenary, current situation and perspectives of modern organic and medicinal chemistry *Curr. Org. Chem*., 2004, *8*, 1547–1577.

[2] A. K. Jain, A Vaidya. V. Ravichandran, S, K. Kasshaw, R. K, Agrawal, Recent developments and biological activities of thiazolidinone derivatives, *Bioorg. Med. Chem*., 2012, *20*, 3378-3395.

[3] S. Kaur Manjal *et al.* "Synthetic and medicinal perspective of thiazolidinones: A review," *Bioorg. Chem.*, 2017, *75*, 406–423.

[4] Bulic, B.; Pickhardt, M.; Khlistunova, I.; Biernat, J.; Mandelkow, E. M.; Mandelkow, E.; Waldmann, H., Angew, Rhodanine-based tau aggregation inhibitors in cell models of tauopathy. *Chem*., 2007, *119*, 9375; *Angew. Chem. Int. Ed*., 2007, *46*, 9215.

[5] Alegaon, S. G.; Alagawadi, K. R.; Sonkusare, P. V.; Chaudhary, S. M.; Dadwe, D. H.; Shah, A. S. Synthesis, characterization and antimicrobial activity of azole-pyrazolidin-3-one derivatives, *Bioorg. Med. Chem. Lett*., 2012, *22* (5), 1917.

[6] Radi, M.; Botta, L.; Casaluce, G.; Bernardini, M.; Botta, M. *J. Comb. Chem.* 2010, *12* (1), 200.

[7] Benson. S. W. and Buss. J. H., Additivity rules for the estimation of molecular properties. Thermodynamic properties, *J. Chem., Phys.*, 1958, *29*, 546-572.

[8] Kumar, V.; Khandare, D. G.; Chatterjee, A.; Banerjee, A simple and effective mechanochemical route for the synthesis of 2-aryl benzothiazoles and substituted benzimidazoles M. *Tetrahedron Lett.,* 2013, *54* (40), 5505.

[9] Ravi S., Kishore K. C., Sathees C. R., *E. J. Med. Chem.,* 2010, *45*, 2748-2752.

[10] Rao, Reddy, T. N.; Ravinder, M.; Bagul, P.; Ravikanti, K.; Bagul, C.; Nanubolu, J. B.; Srinivas, K.; Banerjee, S. K.; Synthesis and biological evaluation of new epalrestat analogues as aldose reductase (ARI) inhibitors. V. J. *Eur. J. Med. Chem.,* 2014, *71*, 53.

[11] Szafran, C. E.; Glase, S. A.; Purchase, T. S., Pattent N°: *WO 0076988 A1*, Décembre, 2000.

[12] O. Bozdag-Dundar, E. J. Verspohl, R. M. Das-Evcimenn, K. Kaup, Bauer, M. Sarikaya, B. Evi, R. Ertan., *Bioorg. Med. Chem.*, 2008, *16*, 6747–6751.

[13] Mishra, R.; Bulic, B.; Sellin, D.; Jha, S.; Waldmann, W.; Herbertand, R., *Angew. Chem. Int. Ed.*, 2008, *47*, 4679.

[14] Wacothon Karime Coulibaly, *Thèse de Doctorat*, 2012, *N° 4549*, Page 1-236.

[15] Chhabria, M. T., Mahajan, B. M. and Brahmkshatriya, P. S. QSAR Study of a Series of Acyl Coenzyme A (CoA): Cholesterol Acyltransferase Inhibitors Using Genetic Function Approximation. *Med. Chem. Res.*, 2011, *20*, 1573-1580.

[16] Buha, V. M., Rana, D. N., Chhabria, M. T., Chikhalia, K. H., Mahajan, B. M., Brahmkshatriya, P. S. and Shah, N. K. Synthesis, Biological Evaluation and QSAR Study of a Series of Substituted Quinazolines as Antimicrobial Agents. *Med. Chem. Res.,* 2013*, 22*, 4096-4109.

[17] Tropsha, A. Best Practices for QSAR Model Development, Validation, and Exploitation. *Molecular Informatics*, 2010, *29*, 476-488.

[18] T. I. Oprea, "*Chemoinformatics in Drug Discovery*" *Ed. WILEY-VCH Verlag*. Allemagne, 2005.

[19] E. A. Rekka; P. N. Kourounakis "*Chemistry and Molecular Aspects of Drug Design and Action*" *Ed. Taylor & Francis Group*, LLC. Etats Unies, 2008.

[20] M. V. Diudea, *QSPR/QSAR Studies for Molecular Descriptors*; *Nova Science*: Huntingdon, New York, USA, 2000.

[21] E. X. Esposito, A. J. Hopfinger, J. D. Madura, *Methods in Molecular Biology*, 2004, *275*, 131-213.

[22] K. N. N'guessan, M. G-R. Koné, K. Bamba, W. P. Ouattara and N. Ziao, "Quantitative Structure Anti-Cancer Activity Relationship (QSAR) of a Series of Ruthenium Complex Azopyridine by the Density Functional Theory (DFT) Method," *Comput. Mol. Biosci.*, 2017, *07*, 19–31.

[23] J. S. N'dri, A. L. C. Kablan, B. ouattara, M. G-R. Koné, L. ouattara, C. G. Kodjo and N. Ziao, "QSAR Studies of the Antifungal Activities of α -Diaminophosphonates Derived from Dapsone by DFT Method," 2019, *7*, 1–7.

[24] W. Yang Lee and R. G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev. B*, 1988, *37*, 785-789.

[25] A. D. Becke, Density-functional thermochemistry. III. The role of exact exchange, *J. Chem. Phys.*, 1993, *98*, 5648-5652.

[26] Y. Traoré, M. G- Richard Koné, O. Ouattara, and N. Ziao, "Qsar Approach to Estimating the Analgesic Activity of a Series of Tri-Substituted Pyrimidine Derivatives," *SDRP J. Comput. Chem. Mol. Model.*, 2018, *3*, 1–10.

[27] J. S. N'dri, M. G-R. Koné, A. L. C. Kablan, S. T. Affi, C. G. Kodjo, O. Ouattara, L. Ouattara and N. Ziao "Combining of DFT and QSAR Results to Predict the Antibacterial Activity of a Series of Azetidinones derived from Dapsone as Inhibitors of Bacillus Subtilis and Pseudomonas Aeruginosa," *SDRP J. Comput. Chem. Mol. Model.*, 2018, *2*, 1–8.

[28] Gaussian 09, Revision A. 02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, Gaussian, Inc., Wallingford CT, 2009.

[29] J. Kapp, M. Remko, P. v. R. Schleyer, H_2XO and $(CH_3)_2XO$ Compounds (X= C, Si, Ge, Sn, Pb): Double bonds vs carbene-like structures can the metal compounds exist at all, *J. Amer. Chem. Soci.*, 1996, *118*, 5745-5751.

[30] B. G. Johnson, P. M. Gill, J. A. Pople, The performance of a family of density functional methods, *J. Chem. Phys*., 1993, *98*, 5612-5626.

[31] Microsoft ® Excel ® 2013 (15.0.4420.1017) MSO (15.0.4420.1017) 64 Bits (2013) Partie de Microsoft Office Professionnel Plus.

[32] XLSTAT Version 2014. *5*. 03 Copyright Addinsoft 1995-2014 (2014) XLSTAT and Addinsoft are Registered Trademarks of Addinsoft. https://www.xlstat.com.

[33] Vessereau A., Méthodes statistiques en biologie et en agronomie (*Lavoisier, Tec & Doc, Paris*, 1988).

[34] G. W. Snedecor, W. G. Cochran, *Statistical Methods*; Oxford and IBH: New Delhi, India; 1967, 381.

[35] O. Ouattara, M. G-R Koné, T. S. Affi, K. Bamba, Y. Traore, and N. Ziao, "Contribution to The Molecular Lipophilicity Scale By Qspr Models Of Lipophilicity Prediction," 2018, *8*, 55–61.

[36] Y. H. Kpidi, O. B. Yapo, M. G-R. Koné, G. A. Gadji, A. E. J. E. Y. Gnagne, J. S. N'dri, and N Ziao, "Monitoring and Modeling of Chlorophyll-a Dynamics in a Eutrophic Lake: M'koa Lake (Jacqueville, Ivory Coast)," *Am. J. Environ. Prot.*, 2018, *6*, 1–9.

[37] J S. N'dri, M. G-R. Koné, C. G. Kodjo, S. T. Affi, A. L. C. Kablan, Z. A. Ouattara and N. Ziao, "Quantitative Structure antifungal Activity Relationship (QSAR) study of a series of Schiff bases derivatives from4- aminobenzenesulphonamide by DFT method," *IOSR J. Pharm.*, 2017, *7*, 27–33.

[38] L. Eriksson, J. Jaworska, A. Worth, M. T. D. Cronin, R. M. Mc Dowell, P. Gramatica, Methods for Reliability and Uncertainty Assessment and for Applicability Evaluations of Classification- and Regression-Based QSARs, Environmental Health Perspectives, 2003, *111*, 1361-1375.

[39] C. Hansch, T. Fujita $\rho - \sigma - \pi$, analysis: method for correlation of biological activity and chemical structure, *J. Am. Chem. Soc.*, 1964, *86*, 1616-1626.