SIFT DESK

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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

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CONFLICTS OF INTEREST
There are no conflicts of interest for any of the authors.

ABSTRACT

This QSAR study was conducted by using a series of Azetidinones which belong to Dapsone derivatives. It allowed to obtain two different models according to the molecular descriptors and the antibacterial activities (*Bacillus subtilis* and *Pseudomonas aeruginosa)*. The molecular descriptors were obtained by applying the methods of quantum chemistry at the B3LYP/6-31G (d) level. The different statistical indicators of the first model which are as a function of the *Bacillus subtilis* activity are the coefficient of determination R^2 = 0.945, the standard error of the regression S = 0.139, the Statistical significance of regression, Fisher F-test F = 94.315 and the cross-validation correlation coefficient Q^2cv=0.942. Those of the second model linked to the activity of *Pseudomonas aeruginosa* are the regression coefficient R^2 = 0.933, the standard deviation S=0.135, the Statistical significance of regression, Fisher F-test F = 46.582 and the cross-validation coefficient Q^2cv= 0.928. So these models have good statistical performances. The quantum descriptors of electrophilic index (ω), electronic energy (ε_0) and dipole moment (μ) are responsible of the antibacterial activity of the Azetidinones derived from Dapsone. Moreover, the index of electrophilic is the first descriptor in terms of priority for the prediction of the antibacterial activity of the studied compounds. The Eriksson et al. acceptance criteria used for the test set are verified. External validation sets also verified all the Tropsha et al. criteria.

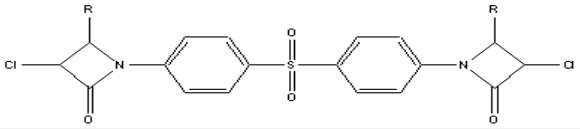
Keywords: Azetidinone, QSAR Model, Quantum Descriptors, DFT, Antibacterial activity

1. INTRODUCTION

Diamino-Diphenyl sulfone or DDS (Dapsone) is a biologically active sulfone (bacteriostatic) used in the treatment of leprosy. However, nowadays Dapsone presents many undesirable effects such as cutaneous, neurological and psychiatric infections. It shows resistances during treatment too [1]. In such a context the continuation of the development of new more efficient Dapsone derivatives is a real necessity. The 2-azetidinone (β-lactam) ring system is the common structural feature of a certain number of β-lactam with broad antibiotic spectrum. It includes penicillins, cephalosporins, carbapenems, nocardicins, monobac-

tams, clavulanic acid, sulbactams and tazobactams, which have been widely used as chemotherapeutic agents to treat bacterial infections and microbial diseases [2-9]. In recent years, the synthesis of 2-azetidinones and the study of their antibacterial properties have permitted to obtain compounds with various pharmacological activities such as antidiabetic activity [10], anti-inflammatory [11] and Anti-HIV activity [12]. In order to get new compounds with more interesting biological activities the condensation of the Dapsone with 2-azetidinone was therefore envisaged by some chemists [13-15]. The quantitative structure-activity Relationship (QSAR) study is the process by which a molecular structure is correlated with a well-determined effect such as biological activity or chemical reactivity. The development of these kind of relationships is in full expansion and become indispensable (useful) in pharmaceutical chemistry and drug design [16]. This study is used to limit the numerous experiments those are sometimes long and expensive. In fact it reduces the drug production cost too for pharmaceutical firms [17,18]. This QSAR approach originates from studies conducted on the one hand by Hansch [19] and on the other hand by Free and Wilson [20]. Indeed, Hansch has established models that relate biological activity to the hydrophobic, electronic, and steric properties of molecules. Generally, the QSAR model is based on a fifth (1/5) of the initial database.

The main objective of this work is to apply Quantitative Structure-Activity Relationships (QSAR) modeling to develop reliable models to predict two antibacterial activities that are ***Bacillus subtilis*** and ***Pseudomonas aeruginosa***, of a series of twenty (20) Azetidinones derivatives of Dapsone (**Figure 1**). These compounds have been synthesized and tested by Mehta and Pathak [13] for their biological activities.



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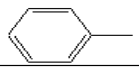
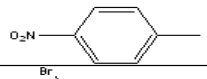
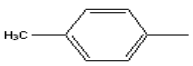
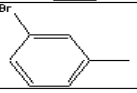
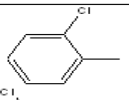
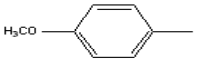
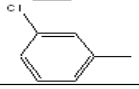
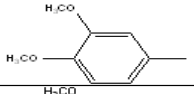
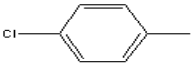
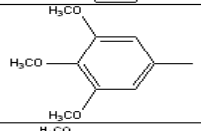
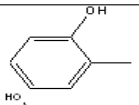
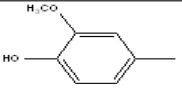
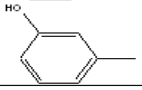
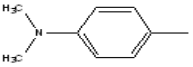
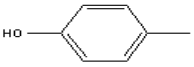
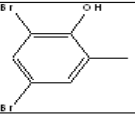
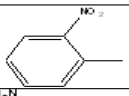
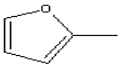
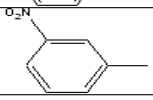
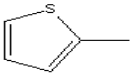
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

Figure 1: Molecular Structures of Azetidinones used for QSAR models

These molecules were synthesized by condensation of Schiff bases which derive from Dapsone with chloroacetylchloride in the presence of triethylamine as a catalyst in order to obtain azetidinones (1-20).

2. MATERIALS AND METHODS

2.1. Chemometric Methods

The twenty (20) molecules used in this study have Minimal Inhibitory Concentration (MIC) ranging from 1.0 to 54.0 µg/mL. The Minimum Inhibitory Concentration (MIC) is the lowest concentration needed to have an antibacterial response. Biological data are generally expressed as the opposite of the log 10 base of activity ($-\log_{10}(C)$) in order to obtain higher mathematical values when the structures are biologically very efficient [21,22]. The antibacterial activity is expressed by the antibacterial potential pMIC. The antibacterial potential is calculated from equation (1)

$$pMIC = -\log_{10}\left(\frac{MIC}{M} * 10^{-3}\right) \qquad (1)$$

Where M is the molecular weight of the component expressed in g/mol and MIC, the minimum inhibitory concentration in µg/mL.

2.2. Computational Methods

Correlations between the biological activity values of the studied molecules and their molecular structures were obtained by quantum chemistry calculations using the software called Gaussian 09[23]. In QSAR studies, DFT methods are generally well-known for generating a variety of molecular properties [24-31]. These properties increase the predictability of QSAR models by reducing the time and the cost involved in the design of new drugs [32, 33]. The B3LYP/6-31G (d) theory level was used to determine the molecular descriptors. The modeling was done using the Multilinear regression method implemented in Excel [34] and *XLSTAT* [35] spreadsheets.

2.3. Quantum Descriptors

For the development of QSAR models, some theoretical descriptors related to the conceptual DFT have been determined in particular, the electrophilic index (ω), the electronic energy (ε_0) and the dipole moment (µ) These descriptors are all determined from the optimized structure of the molecules. The electrophilic index (ω) measures the energetic stability of a system when this one acquires an additional charge from its environment [36]. The electronic energy (ε_0) represents the electronic contribution of all atoms in each molecule. The dipole Moment (µ) indicates the stability of a molecule in water. Thus, a strong dipole moment will translate a low solubility in organic solvents and a high solubility in water [37, 38]. The electrophilic index (ω) is calculated from the equations (2):

$$\chi = -1/2\,(\varepsilon_{LUMO} + \varepsilon_{HOMO})$$

$$\eta = (E_{LUMO} + E_{HOMO})/2$$

$$\omega = \frac{\chi^2}{2\eta} \qquad (2)$$

Concerning all the studied descriptors, the analysis of the bivariate data, that is to say the calculation of the partial correlation coefficient between each of the pairs of the whole descriptors is (inferior) less than 0.70 (aij <0.70) , Which means that these different descriptors are independent from each other's [39,40].

2.4. Estimation of the Predictive Ability of a QSAR Model

The quality of a model is determined by taking into account various statistical data including the squared regression correlation coefficient $\mathbf{R^2}$, the standard error of the regression **S**, the correlation coefficients of cross validation Q^2cv and Fisher F-test. The statistical indicators $\mathbf{R^2}$, **S** and **F** are linked to the adjustment of the calculated and experimental values. They describe the predictive capacity in the model's limits and allow to estimate the precision (accuracy) of the calculated values on the training set [41-43]. As for the cross-validated squared correlation coefficient Q^2cv, it provides information on the predictive power of the model. This predictive power is qualified to be "internal" because it has been calculated from the basic structures which are used to build this model. The determination's coefficient $\mathbf{R^2}$ gives an evaluation of the dispersion of theoretical values around the experimental ones. The quality of the modeling is good when the different points are closer to the fitting line [44]. The adjustment of the points to this line can be evaluated by the coefficient of determination.

$$\boldsymbol{R^2} = 1 - \frac{\sum\left(y_{i,exp} - \hat{y}_{i,théo}\right)^2}{\sum\left(y_{i,exp} - \bar{y}_{i,exp}\right)^2} \qquad (3)$$

Where

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

$\hat{y}_{i,theo}$: Theoretical value of the antibacterial activity

$\bar{y}_{i,exp}$: The mean value of the experimental values of the antibacterial activity

The closer the value of $\mathbf{R^2}$ to 1, the more the theoretical and experimental values are correlated.

Moreover, the variance $\boldsymbol{\sigma^2}$ is determined by the relation 4:

$$\boldsymbol{\sigma^2} = \boldsymbol{s^2} = \frac{\sum\left(y_{i,exp} - y_{i,théo}\right)^2}{n - k - 1} \qquad (4)$$

Where **k** is the number of independent variables (descriptors), n is the number of molecules in the test or learning set and **n-k-1** is the degree of freedom. The standard deviation **S** is another used statistical indicator. It evaluates the reliability and precision (accuracy) of a model:

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

The Fischer test **F** is also used to measure the level of statistical significance of the model, ie the quality of the choice of the descriptors constituting the model.

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

The coefficient of determination of the cross-validated squared correlation coefficient Q^2cv, permits to evaluate the accuracy of the prediction on the test set and it is calculated by using the following formula:

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

The performance of a mathematical model is characterized by a value of Q^2cv which higher than 0.5 ($Q^2cv>0.5$) for satisfactory models and higher than 0.9 ($Q^2cv>0.9$) for excellent ones according to Eriksson et al. [45,46]. Taking into account their results, a given test set is a performant model when the following acceptance criterion R^2 - ($Q^2cv>0.3$) is respected. Moreover, the predictive power of a model can be obtained from the five criteria of Tropsha et al. [47-49]. If at least three of the five criteria are met, the model will be considered acceptable. The five criteria are as follow:

(1) $R^2_{Test} > 0.7$,

(**2**) $Q^2_{Cv\,Test} > 0.6$

(**3**) $|R^2_{Test} - R^2_0| \leq 0.3$

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

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

Where :

R^2 : Correlation coefficient for the molecules in the validation set.

R_0^2 : Correlation coefficient between predicted and experimental values for the validation set.

R'^2_0 : Correlation coefficient between experimental and predicted values for the validation set.

k: Is the constant of the correlation line at the origin for the validation set (predicted values based on experimental values).

k': Is the constant of the correlation line at the origin for the validation set (experimental values according to the predicted values) .

3. RESULTS AND DISCUSSION

3.1. Results

The Table 1 includes the fourteen (14) molecules in the training set and the six (6) molecules in the validation set. Thereafter, the values of the partial correlation coefficients aij of the descriptors are also presented in Table 2.

The partial correlation coefficients aij between the pairs of descriptor (μ, ω), (μ,ε_0) and (ω,ε_0) are less than 0.70 (aij < 0.70). These values demonstrate the independence of the descriptors used to develop the models.

It must be noted that the negative or positive sign of the descriptor's coefficient of the model reflects the proportionality's effect between the evolution of the biological activity and the parameter of the regression equation. Thus, the negative sign indicates that when the value of the descriptor is high, the biological activity decreases whereas the positive sign translates the opposite effect. The table 3 presents the best QSAR models obtained for the various antibacterial activities of *Bacillus subtilis* and *Pseudomonas aeruginosa* as well as statistical indicators. It must be emphasized (underlined) that these models were established using the same descriptors of the training test and test set of Table 1.

Model 1

(*Bacillus subtilis*)$p\,MIC_i^{exp}$(μg/mL): = 2.593 - 3.10^{-5}* ε_0 + 0.485*ω

Model 2

(*Pseudomonas aeruginosa*$p\,MIC_i^{exp}$(μg/mL): = 1.065 - $6.7.10^{-4}$* ε_0 + 0.353*ω - 0.046*μ$p\,MIC_i^{exp}$

Table 1: Molecular descriptors and antibacterial activities of the training and validation set

code	ε_0 (u.a.)	ω (eV)	μ (D)	*Bacillus Subtilis*		*Pseudomonas Aeruginosa*	
				MIC (µg/mL)	pMIC	MIC (µg/ mL)	pMIC
1	-2885.352	3.582	2.370	49	4.071	54	4.029
2	-2963.989	3.515	2.822	47	4.110	50	4.083
3	-3804.538	3.737	3.466	4	5.208	7	4.965
4	-3804.541	3.811	1.991	9	4.998	13	4.810
5	-3035.783	3.233	3.677	6.5	4.484	10	4.387
6	-3804.541	3.829	2.158	20	4.354	25	4.280
7	-3035.785	3.504	2.435	27	4.463	32	4.387
8	-3294.328	6.129	5.923	21	5.426	25	5.125
9	-3294.349	6.102	1.974	2.5	5.648	5	5.222
10	-3294.348	6.003	3.533	1.5	5.824	4	5.347
11	-8027.558	3.814	2.105	1	4.752	3	4.662
12	-3114.398	3.438	2.601	13	4.313	16	4.260
13	-3343.429	3.409	4.862	31	4.287	35	4.242
14	-3572.459	3.434	4.564	36	4.267	40	4.226
15	-3264.834	3.499	6.120	41	4.321	45	4.258
16	-3153.290	3.143	3.891	32	4.199	37	4.159
17	-13320.193	4.075	2.982	42	4.887	46	4.736
18	-2880.897	3.649	8.062	12	4.542	17	4.424
19	-3526.854	3.676	7.782	16	4.624	21	4.492
20	-3804.540	3.803	4.177	14	4.856	19	4.697

Table 2: Values of the partial correlation coefficients of the descriptors.

	µ	ω	ε_0
µ	**1.000**		
ω	0.045	**1.000**	
ε_0	0.213	0.017	**1.000**

Table 3: Statistical analysis report of antibacterial activities on bacterial cells that are ***Bacillus subtilis*** and ***Pseudomonas aeruginosa***.

Statistical indicators of Multilinear regression	Model 1 ***(Bacillus subtilis)***	Model 2 ***(Pseudomonas aeruginosa)***
Number of Compounds **N**	14	14
Squared regression correlation coefficient $\mathbf{R^2}$	0.945	0.933
Standard error of the regression **S**	0.139	0.135
Statistical significance of regression, Fisher **F**-test **F**	94.315	46.582
Cross-validation correlation coefficient Q^2cv	0.942	0.928
$\mathbf{R^2}$ - Q^2cv	0.003	0.005
Range of Activity MIC_i^{exp} (µg/mL)	1 - 45	3 - 54
Level of Statistical Significance **α**	> 95 %	

The negative signs of the dipole moment and electronic energy coefficients indicate that antibacterial activities will be improved for low value of the dipole moment and the electronic energy. In contrast, the positive signs of the coefficient of the electrophilic index means that high values of this descriptor are needed to improve the antibacterial activity. The significance of the models is translated by a high values of the correlation coefficient R^2 which are 0.945 and 0.933 for the model 1 and for model 2 respectively. Otherwise the cross-validation correlation coefficient Q^2cv for model 1 is 0.942 and 0.928 for model 2. These different models are all acceptable because all the different values of $\mathbf{R^2}$**-** Q^2cv are less than 0.3. The external validation of models 1 and 2 was carried out respectively with the Azetidinones (**1**; **2**; **3; 4; 5; 20)** and (**5**; **6; 11; 17; 18; 19)**.

Table 4: The Tropsha criteria checks for external validation sets are presented

Statistique Parameters	Tropsha Criteria [47-49]	Model 1	Model 2
R^2	> 0.7	0.954	0.856
Q^2_{CV}	> 0.6	0.952	0.832
$\lvert R^2 - R_0^2 \rvert$	≤ 0.3	0.00	0.00
$\frac{\lvert R^2 - R_0^2 \rvert}{R^2}$	< 0.1	0.00	0.00
k	$0.85 \leq k \leq 1.15$	1	1
$\frac{\lvert R^2 - R_0'^2 \rvert}{R^2}$	< 0.1	0.00	0.00
k'	$0.85 \leq k' \leq 1.15$	0.954	0.856

All Tropsha criteria are verified by the external validation sets of models 1 and 2. These models are therefore acceptable for the prediction of antibacterial activities (***Bacillus subtilis*** and ***Pseudomonas aeruginosa***) of the series of Azetidinones derived from Dapsone. The different regression lines between the experimental and theoretical antibacterial activities of the training set (blue dots) and the test set (red dots) for ***Bacillus subtilis*** (model 1) and ***Pseudomonas aeruginosa*** (model 2) are illustrated respectively in **Figures 2 and 3**.

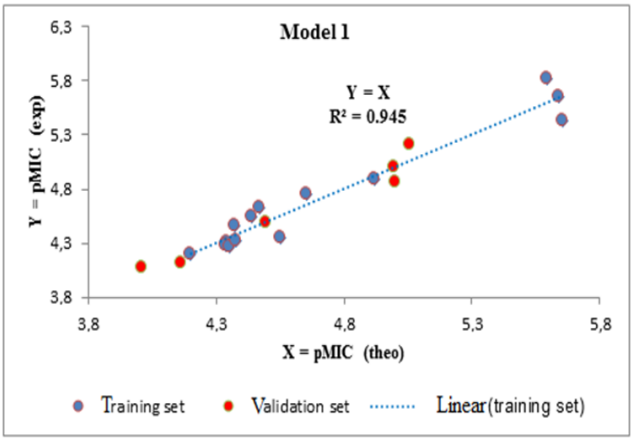


Figure 2: regression line of Model 1

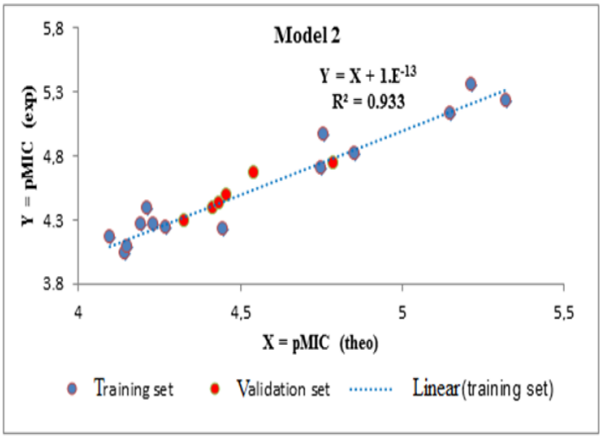


Figure 3: regression line of model 2

The low values of 0.139 and 0.135 as of the standard error respectively in Models 1 and 2 demonstrate a good similarity between the predicted and experimental values (**Figure 4**). These curves show similar evolutions of these values in both models of Azetidinones' series derived from Dapsone, despite some recorded differences.

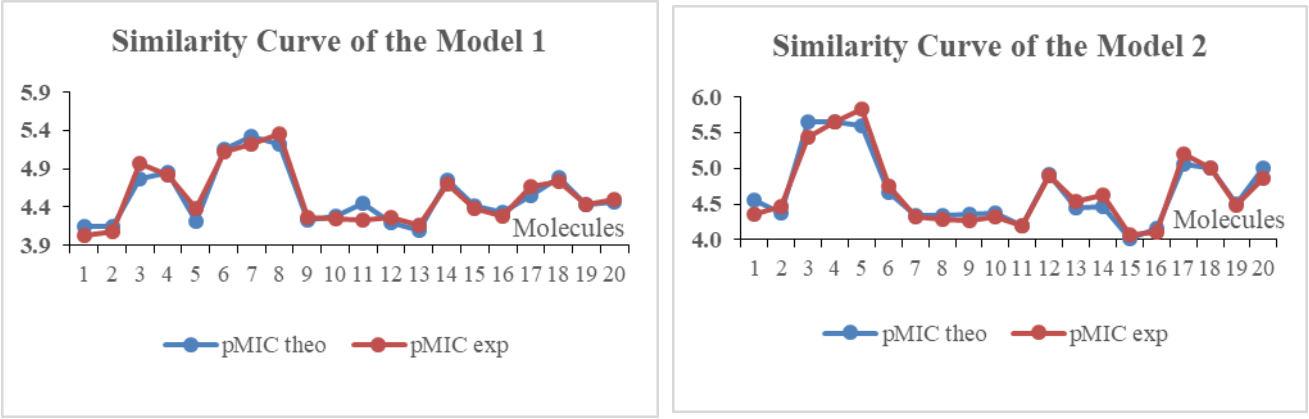


Figure 4: Similarity curve of experimental and predicted values for models 1 and 2

3.3. Analysis of the Contribution of Descriptors inside Models

According to the fact that each of the two models are as a function of two or three descriptors. It appears necessary to determine the contribution of each descriptors. The study of the relative contribution of the descriptors in the prediction of the antibacterial activity of the compounds was carried out for the bacteria Bacillus subtilis and Pseudomonas aeruginosa by using the software XLSTAT version 2014 [35]. The different contributions are presented in **figure 4**.

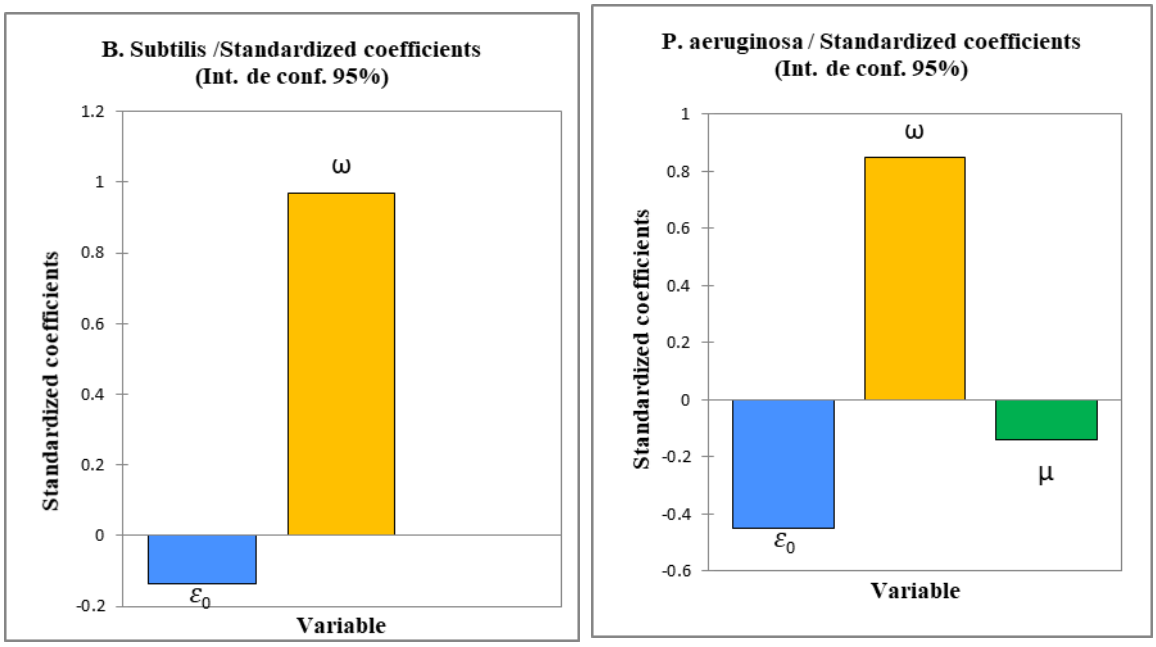


Figure 4: Contribution of the different descriptors of the two models

The electrophilic index presents a large contribution compared to the other descriptors in the two models. Thus, the electrophilic index proves to be the priority descriptor in the prediction of the antibacterial activities (***Bacillus subtilis*** and ***Pseudomonas aeruginosa***) of the studied Azetidinones derivatives.

4. CONCLUSION

The electrophilic index (ω), the dipole Moment (**μ**), and the electronic energy (ε_0) allowed us to predict the behaviour of the studied azetidinones in the presence of ***Bacillus subtilis*** and ***Pseudomonas aeruginosa*** bacteria. This study revealed the existence of strong correlations between the calculated and experimental values of the antibacterial potential. The QSAR obtained models allow us to predict the activity of the best analogues called "lead". These proposed models reveal that the electrophilic index is the first most useful descriptor for improving antibacterial activity. In addition, the positive signs of the electrophilic index coefficient indicate that antibacterial activities will be improved for a high value of the electrophilic index. This work constitutes a compass for the design of new more active molecules against bacteria ***Bacillus subtilis*** and ***Pseudomonas aeruginosa***. The significance of these models was verified by the mean of a test set which is composed of six molecules. The work presented here will therefore play an important role in understanding the relationship between the physicochemical parameters of the structure and the biological activity. The study of these QSAR models, could help us to select the appropriate substituent in order to design new compounds with improved biological activity.

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