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Quantitative Analysis Of The Structure-Activity Relationship Of 1,2-Benzodiazole Derivatives: DFT Study.

Siham Lakrikh[1], Mohammed El Idrissi[2]*, Latifa Laallam[1], Abdellah Zeroual[2], El Mostapha Rakib[3], and Ahmed Jouaiti[1].

[1]Laboratory of Laboratory of Sustainable Development; Faculty of Sciences and Techniques, Sultan Moulay Slimane University, P.O. Box 523, Beni-Mellal, Morocco.
[2]Laboratory of Molecular Modeling and Spectroscopy Research Team, Faculty of Science,Chouaïb Doukkali University, P.O. Box 20, 24000 El Jadida, Morocco.
[3]Laboratory of Organic and Analytical Chemistry, Faculty of Sciences and Techniques, Sultan Moulay Slimane University, P.O. Box 523, Beni-Mellal, Morocco.

ABSTRACT

The relationship between the biological activity of compounds and their molecular structure is a predictor in rational drug design. Quantitative Structure Activity Relationships (QSAR) is one of the most important fields in chemometrics, they are based on the development of mathematical equations linking the chemical structure of a compound to its biological activity. QSAR is a molecular structure correlation process, or these derived properties with a particular type of biochemical activity. The properties of the compounds are determined by the density functional theory (DFT) method. The correspondence between the descriptors and the experimental activity uses multiple linear regressions (MLR). In this work, we have tested twenty-eight chemical compounds with the same molecule but with different functional groups using the approach Quantitative Structure Activity Relationships. Our results show that a good correlation between biological structure/activity (IC50). For a possible use of these molecules in the pharmaceutical field we studied their compliance with the rules of Lipinski.

Keywords: SAR; QSAR; Drug-like; Chemometrics; density functional theory (DFT); IC50; RLM; Lipinsk.

Corresponding author

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INTRODUCTION

The structure-quantitative activity relationship is among the main calculation tools that are used in medicinal chemistry. QSAR defined as the relationship between biological activity and structure of the molecule, and was used as a primitive tool in the rational design of medicine [1]. Multiple linear regressions (MLR) are a statistical analysis that describes dependent changes associated with changes in several independent variables. Drug candidates are screened early in drug development based on computer modeling, high throughput screening and cellular assays that predict pharmacological activity [2]. However, it is much more difficult to predict drug absorption, distribution, metabolism and excretion (ADME), which generally require in vivo assessment. Because in vivo studies are slow and expensive, it is desirable to have simple methods to predict the ADME properties of drug candidates. A widely accepted method for predicting ADME properties is the rule of five proposed by Lipinski in 1997 [3].To develop this rule, Lipinski conducted a retrospective analysis of 2245 drugs entering Phase II, most of which were active orally, lipophilic drugs, and identified common physicochemical properties. The resulting correlation identified four physicochemical parameters: molecular weight (MM), number of donor bonds (NHD), number of acceptor bonds (NHA) and octanol-water partition coefficient (log P).The Rule of Five states that poor absorption or permeation is expected MM>500, NHD>5, NHA>10 or log P>5.

Therefore, in the first stage of drug discovery, it is quite necessary to apply drug-like filters to remove non-drug molecules from databases and then focus only on drug-like molecules. Nowadays, the evaluation of the similarity of drugs (for example, the rule of the five of Lipinski [4], the rules of the Opera of drug-likeness [5], the Roes filter [6], etc. has already been, to some extent, integrated into computational drug design/discovery pipelines. Over the past decades, considerable efforts have been made for computational approaches to differentiate drug-like molecules from reagents, such as filters or simple property-based rules [2-8], the drug-type index to classify molecules [7, 8].

Our current research aims to describe the structure-property relationships on 1,2-benzodiazole and a QSAR model on these compounds with respect to their inhibitory activity [9].

Biological activity data observed

For the evolution of QSAR models of 1,2-benzodiazole derivatives, all these compounds were active and showed inhibition of TP with IC50 (µM) (A2780) which inhibit ovarian tumor. The IC50 activity data contain only molecules with values between 0.64 and 100.8. The biological activity data (IC50) were transformed to pIC50 according to the formula pIC50 = (-log (IC50 x 10-6)) was used as response values.

How to calculate the descriptors

First, the twenty-eight molecules were pre-optimized using the force field of molecular mechanics (MME +) included in the Hyper Chem version package 7.08 [10]. After that, the minimized structures were refined by semi-empirical methods. Hamiltonian PM3 also implemented in Hyper Chem, we chose a gradient standard limit of 0.01 kcal/A for the optimization of geometry, then, for re-optimized derivatives of 1, 2-benzodiazole using the program package Gaussian 09[11], at the level of functional density theory DFT using Lee Becke-Parr's three-parameter (B3LYP), with the basic set 6-31 G this theory was used to compute a number of electronic descriptors: dipole moment (DM), boundary orbital energy, EHOMO, ELUMO, and atomic net loads (q1, q2, q3, q4, q5, q6, q7, q8, q9). The QSAR properties module form HyperChem 8.07 was used to calculate: molar polarisability (Pol), molar refraction (MR), octanol/water partition coefficient (logP), hydration energy (HE), molar volume (MV), surface grid (SAG) and molar mass (MM).

The logP calculation is performed using atomic parameters derived from Viswanadhan and colleagues [8]. The calculation of molar refractivity was performed by the same method as logP, Ghose and Crippen presented atomic contributions to refractivity [12].

Solvent accessible bounded molecular volume calculation and Van Der Waals surface molecular volume calculations are based on a grid method derived from Bodor et al, [13] using Gavezotti atomic rays [14].

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The polarisability was estimated for the additively scheme given by the miller with an accuracy of 3% for the calculation [15], where different increments are associated with different types of atoms.

The calculation of electronegativity χ, is the opposite of the chemical potential which measures the tendency of the electronic cloud to escape from the molecule, it's a global parameter of the molecular system equal to the slope of the energy as a function of the number of electrons N at constant external potential v(r) as defined by Parr and Mulliken [16, 17]:

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right) = -\frac{(E_{LUMO} - E_{HOMO})}{2} \qquad \text{With: } E = E[N, v(r)]$$

And for the calculation of Hardness and softness η, and its inverse softness S, can be obtained from the first derivative of chemical potential [18, 19]:

$$\eta = ((\partial\mu)/\partial N)_{v(r)} = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} = \frac{1}{S} = \frac{E_{LUMO} - E_{HOMO}}{2}$$

and

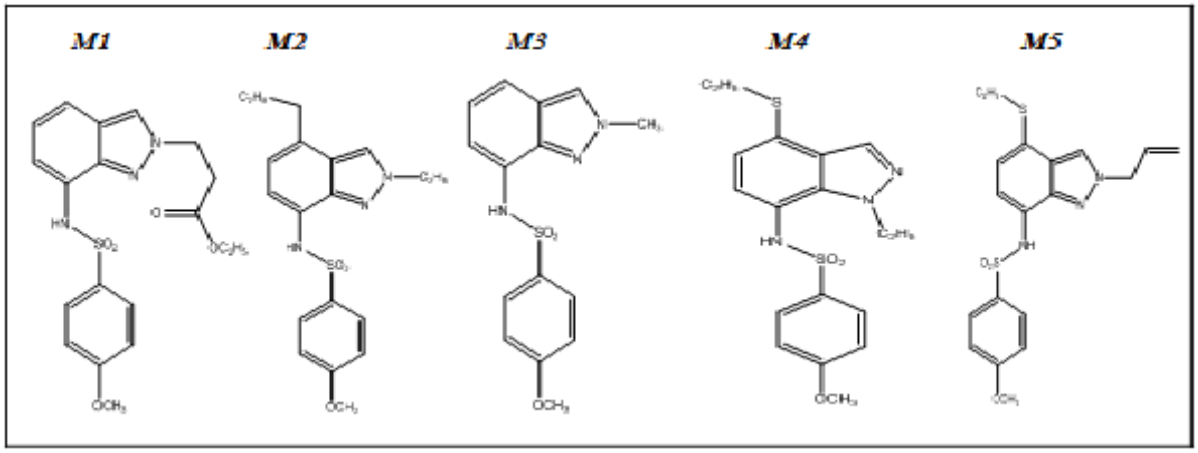
$$\mu = \left(\frac{\partial E}{\partial n}\right)_{v(r)} = -\frac{PI + AE}{2} = -\chi$$

Where: PI is the ionization potential and AE is the electronic affinity.

The qualitative definition of hardness is closely related to polarisability, since a decrease in the energy gap generally leads to an easier polarization of the molecule. This descriptor leads to a distinction between reaction rates at different sites in the molecule [20, 21].The electrophilicity index ω, used to characterize the capacity of a molecule to generate electron transfer, is calculated according to the following formula [22]: $\omega = \chi^2/2$

RESULTS AND DISCUSSION

Multiple linear regression analysis of molecular descriptors was performed using the stepwise strategy in SPSS version 19 for Windows [23].



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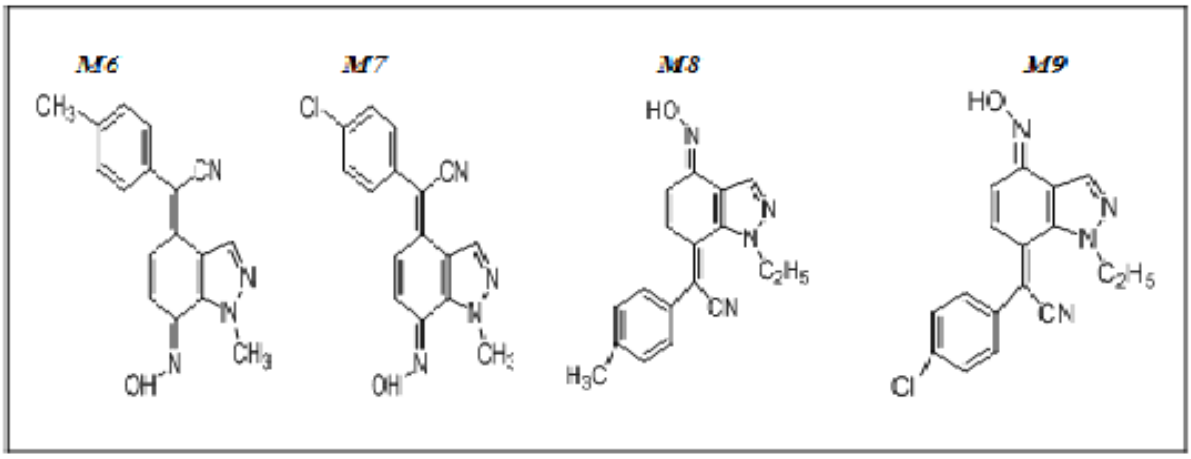

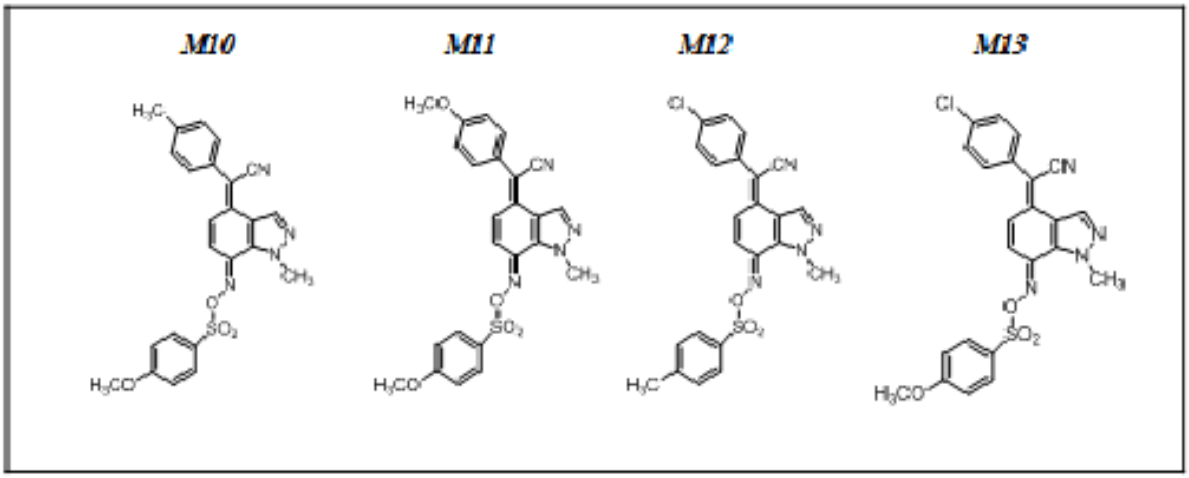

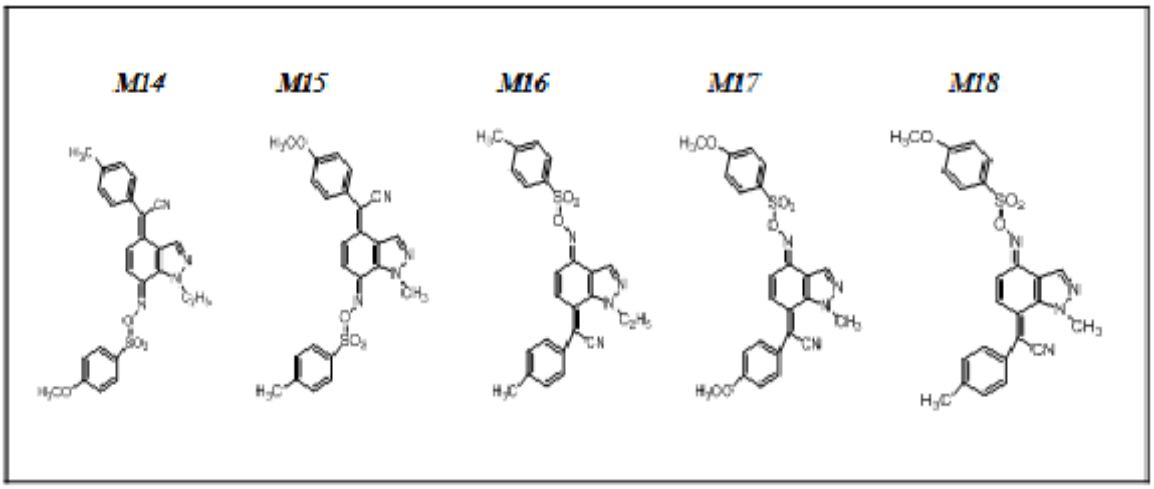

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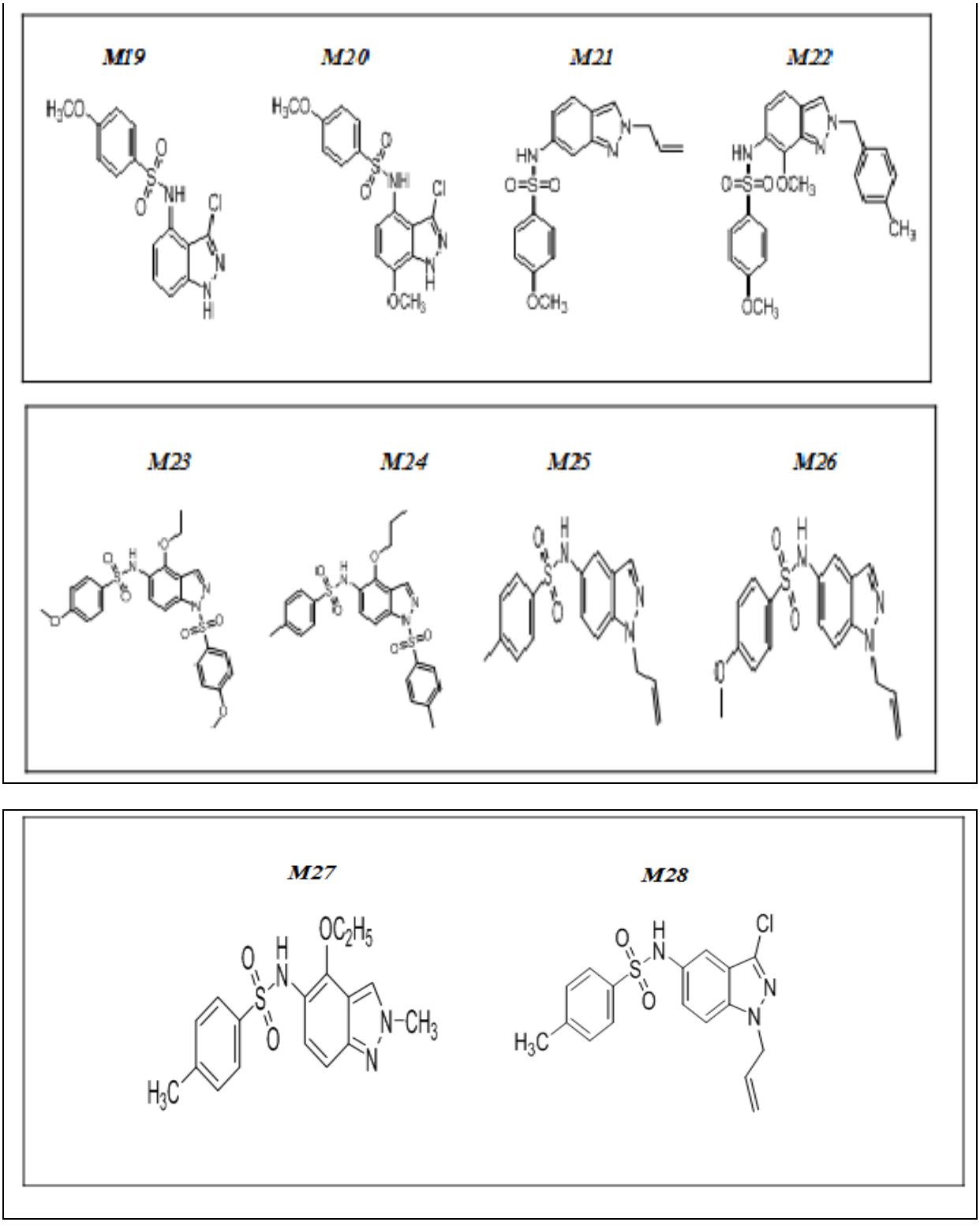

Fig 1: structures of the molecules studied.

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Table 3: Experimental and theoretical activity of drifts 1, 2-benzothiazole

Molecules	PIC5O exp	PIC50 pred	Resedu
1	5.00	5.25280	-0.25280
2	5.00	5.80777	-0.80777
3	5.00	5.49176	-0.49176
4	6.40	5.61524	0.78053
5	5.00	5.14981	-0.15327
6	5.85	5.89609	-0.04531
7	5.68	5.96012	-0.28234
8	5.36	5.46179	-0.10623
9	5.25	4.86051	0.38668
10	6.32	6.54720	-0.22481
11	6.46	6.60979	-0.15012
12	6.68	6.36153	0.31833
13	6.30	6.46770	-0.16406
14	6.39	6.59816	-0.21200
15	7.19	6.54465	0.64917
16	6.44	5.85434	0.58218
17	6.85	6.39227	0.45851
18	6.38	5.83110	0.55295
19	7.07	7.03098	0.03452
20	6.91	7.07386	-0.16377
21	6.38	6.23657	0.13915
22	6.26	6.25399	0.00803
23	5.12	5.45139	-0.33106
24	5.01	5.40865	-0.40297
25	5.16	5.32508	-0.16894
26	5.04	5.43653	-0.39413
27	5.38	4.76322	0.61769
28	5.80	5.97501	-0.17641

The molecular polarisabilité of a molecule characterizes the capacity of its electronic system to be deformed by the external field, and plays an important role in the molecular modelling of numerous properties and biological activities. The interesting part of the interaction of Van Der Waals is a good measure of the polarisabilité. The molecule of high polarisability is expected to have strong attractions with other molecules. The polarisability of a molecule can also improve aqueous solubility. Molar refractivity (MR) is an important criterion for measuring stress factor. It is generally referred to as a simple measure of the volume occupied either by an individual atom or a group of atoms [24]. Polarisability and molar refractivity increase relatively to study the size and molecular weight (Table 2). This result is in agreement with the Lorentz-Lorenz formula which gives a relationship between polarisability, molar refraction and volume [25]. This relationship shows that polarisability and molar refraction increase with volume and molecular weight. Example of 1,2-benzodiazole. For example for compound 3 is the small molecule of the series studied, which has a low value of polarisability (30, 24) and molar refractivity (91.74) in contrast, the 14 has high values of polarisability (47.47) and molar refractivity (140.51).

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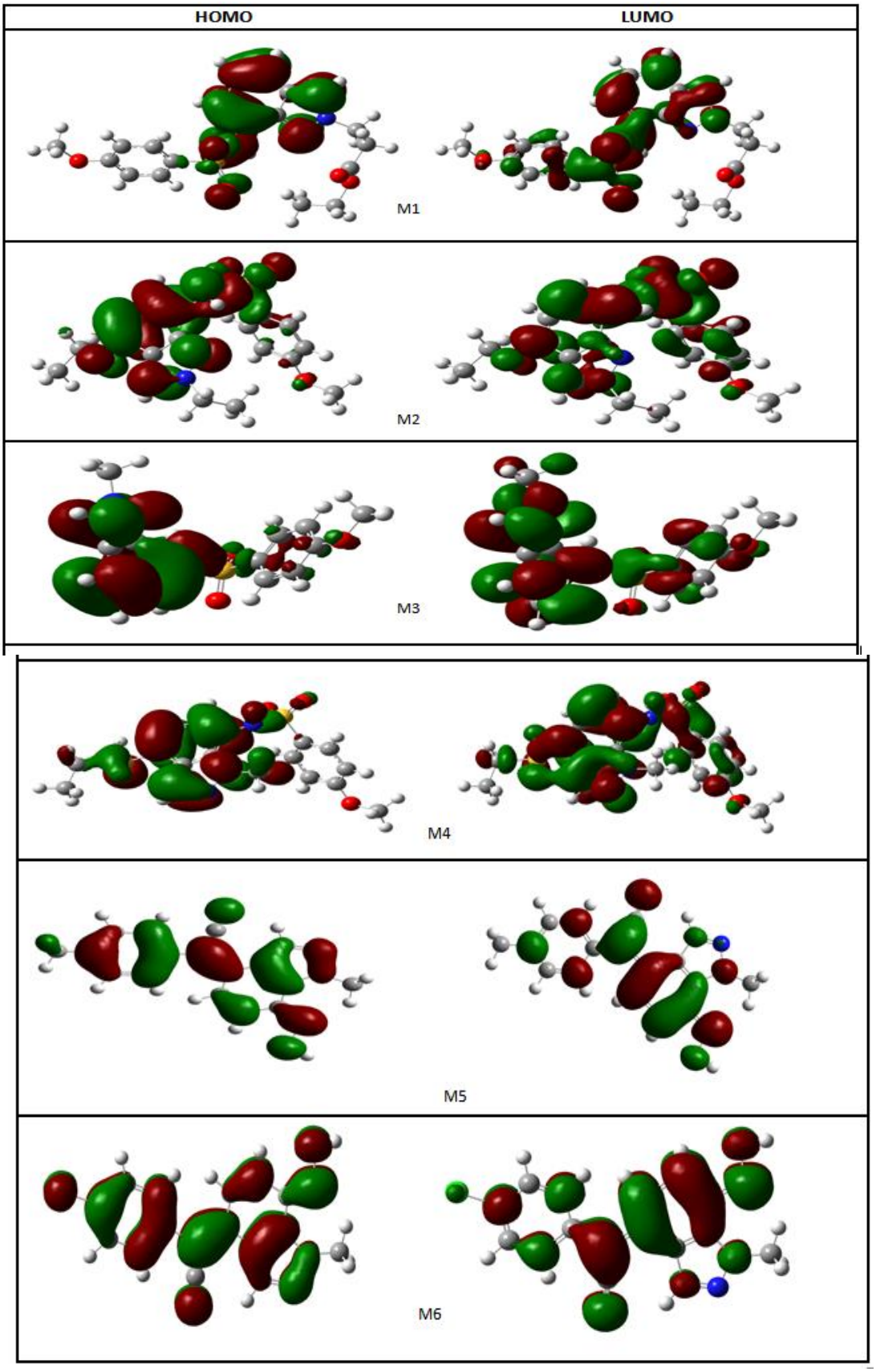

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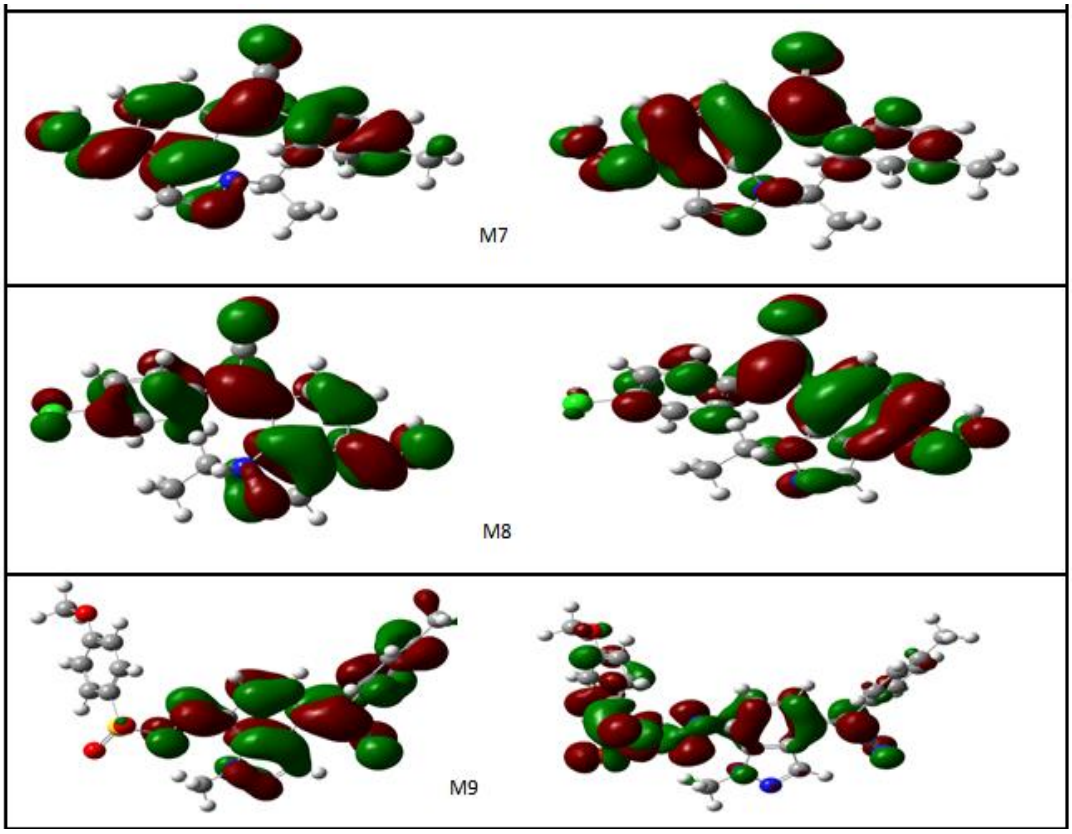

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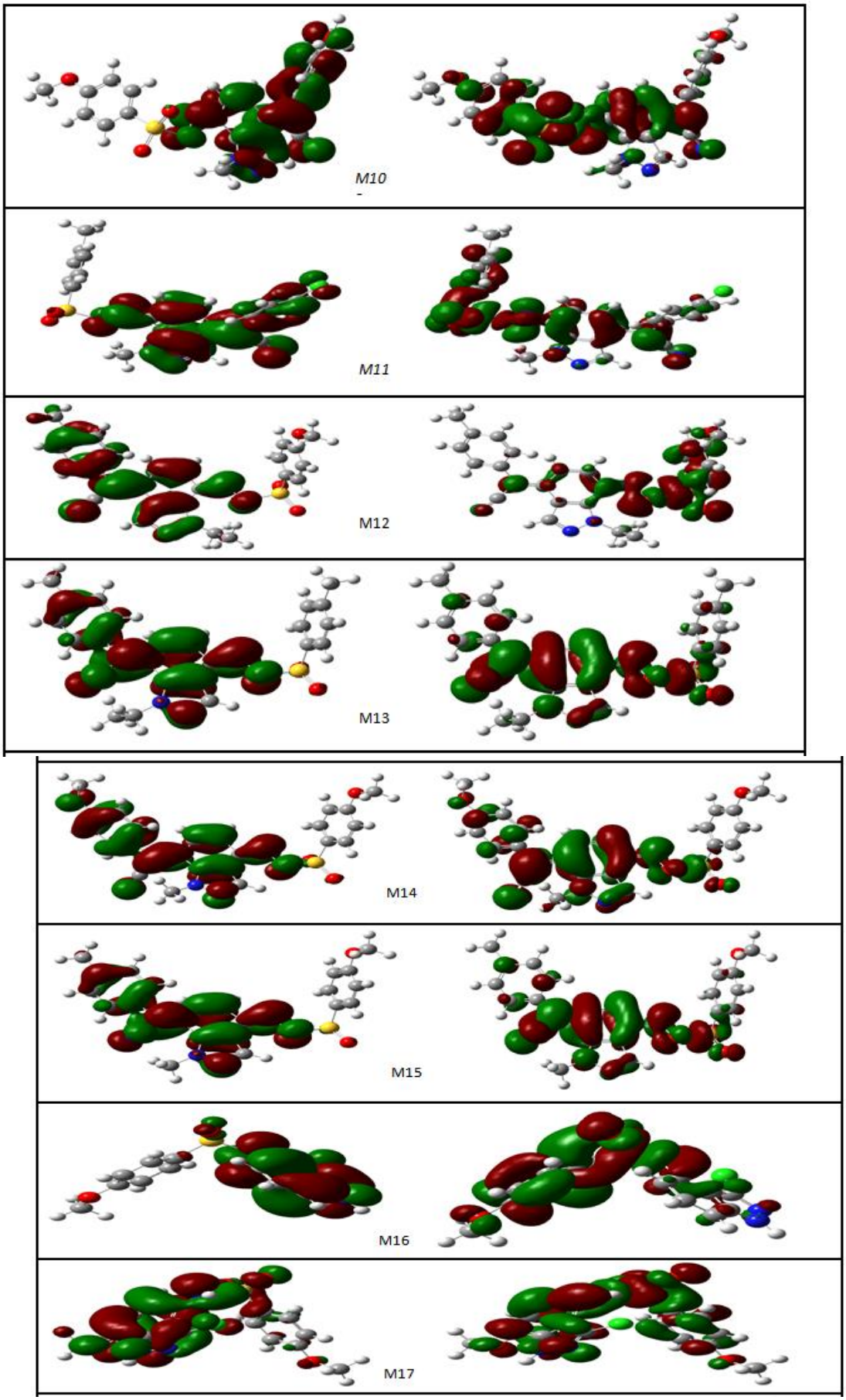

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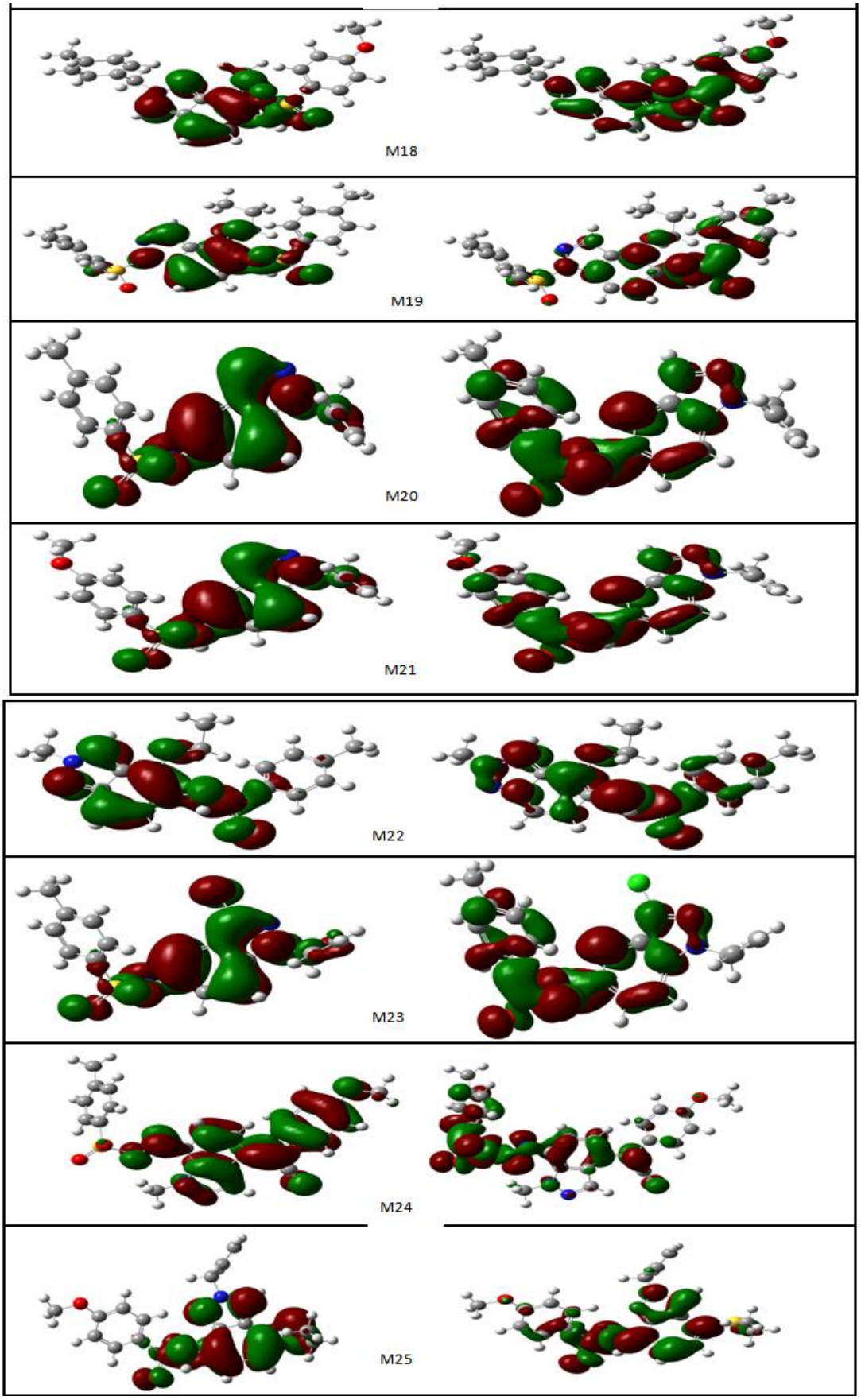

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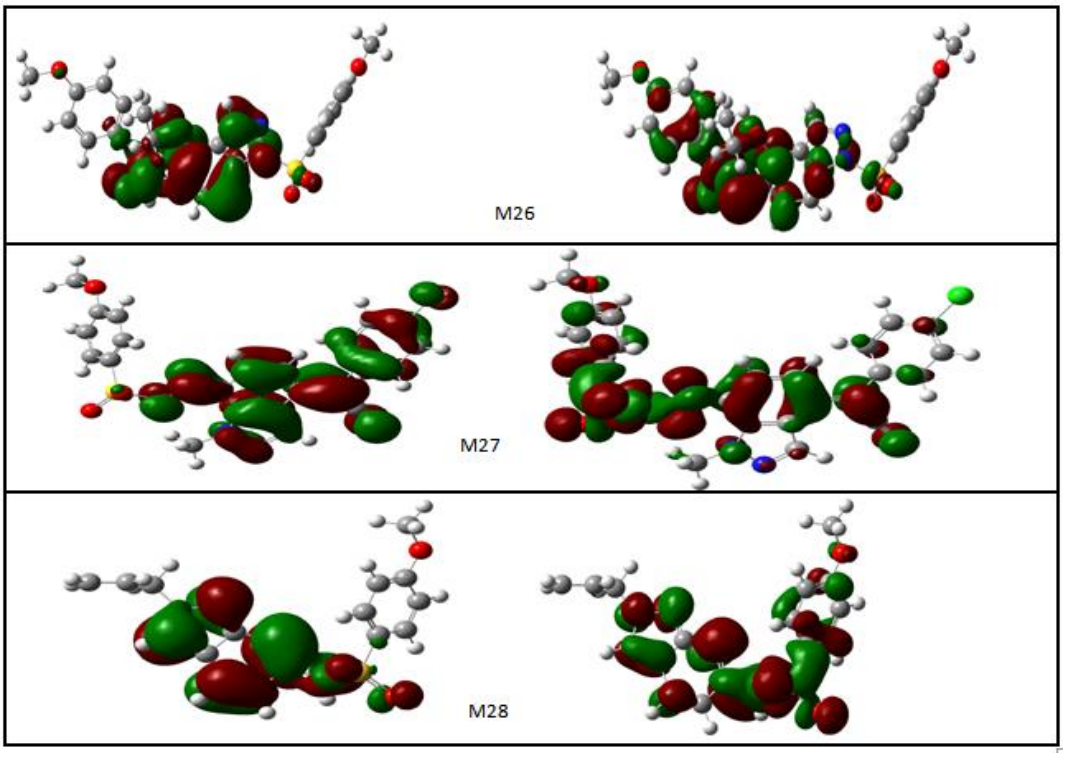

Fig 3: HOMO and LUMO energies of the molecules studied

Analyze of the global DFT indices of twenty-eight chemical compounds with the same molecule but with different functional groups using the approach Quantitative Structure Activity Relationships.

The global DFT indices, namely the electronic chemical potential μ, chemical hadrness η, electrophilicity ω and nucleophilicity N, are given in table 2.

Table 2: Molecular descriptor values used in regression analysis (eV)

Molecules	HOMO	LUMO	Gap	μ	η	ω	N
1	-0,20596	-0,0801	-0,12586	-0,12725	-0,06293	3,272843	-0,00133
2	-0,19627	-0,07396	-0,12231	-0,14623	-0,06116	3,209386	-0,00118
3	-0,20687	-0,04762	-0,15925	-0,13229	-0,07963	2,598053	-0,0017
4	-0,22215	-0,04893	-0,17322	-0,14854	-0,08661	2,564946	-0,00214
5	-0,20237	-0,08039	-0,12198	-0,13554	-0,06099	3,318085	-0,00125
6	60,21048	-0,11009	-0,10039	-0,14733	-0,0502	4,193246	-0,00111
7	-0,22055	-0,11935	-0,1012	-0,16363	-0,0506	4,358696	-0,00123
8	-0,21848	-0,11389	-0,10459	-0,16056	-0,0523	4,177837	-0,00125
9	-0,22749	-0,12275	-0,10474	-0,17224	-0,05237	4,343899	-0,00136
10	-0,21552	-0,11174	-0,10378	-0,16418	-0,05189	4,153401	-0,00121
11	-0,2104	-0,11071	-0,09969	-0,17512	-0,04985	4,221085	-0,0011
12	-0,22514	-0,11933	-0,10581	-0,16167	-0,05291	4,255552	-0,00134
13	-0,22454	-0,1185	-0,10604	-0,13512	-0,05302	4,235006	-0,00134
14	-0,21504	-0,11335	-0,10169	-0,1537	-0,05085	4,229324	-0,00118
15	-0,22124	-0,12077	-0,10047	-0,14819	-0,05024	4,404101	-0,00123
16	-0,22454	-0,10843	-0,11611	-0,13708	-0,05806	3,867712	-0,00146

17	-0,21246	-0,11088	-0,10158	-0,16995	-0,05079	4,183107	-0,00115
18	-0,2235	-0,10729	-0,11621	-0,15476	-0,05811	3,846485	-0,00145
19	-0,21869	-0,05547	-0,16322	-0,16029	-0,08161	2,679696	-0,00195
20	-0,21465	-0,07781	-0,13684	-0,16619	-0,06842	3,137241	-0,00158
21	-0,19444	-0,07014	-0,1243	-0,16649	-0,06215	3,12856	-0,00117
22	-0,21262	-0,07285	-0,13977	-0,1654	-0,06989	3,042427	-0,00158
23	-0,21907	-0,08707	-0,132	-0,14303	-0,066	3,319242	-0,00158
24	-0,221	-0,08852	-0,13248	-0,15476	-0,06624	3,336353	0,081475
25	-0,2248	-0,07157	-0,15323	-0,14819	-0,07662	2,934151	0,074139
26	-0,22465	-0,07	-0,15465	-0,14733	-0,07733	2,90527	0,073311
27	-0,19945	-0,09763	-0,10182	-0,14854	-0,05091	3,917698	0,077924
28	-0,23066	-0,07674	-0,15392	-0,1537	-0,07696	2,997141	0,07973

The presence of hydrophobic groups in the structure of 1,2-benzodiazole (inhibition of L1210 cell proliferation) induces a decrease in hydration energy, while the presence of hydrophilic groups increases hydration energy (Table 2).

The highest hydration energy in absolute value, (16.53 kcal/Mol) is that of compound M17, but the lowest (6.89 kcal/Mol) was achieved for compound M27 (Table 2). In the biological environment, water molecules surround polar molecules where hydrogen bonds can be established between the water molecule and the molecules being studied, water and the complex with the strongest hydrogen bond. At least, these hydrated molecules are partially dehydrated before their interaction; these low energy interactions are generally reversible, especially between messengers and receptors Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism and excretion properties as well as pharmacological activity. Hansch and Leorayed that highly lipophilic molecules will spread into the interior of lipid membranes and remain there for good oral bioavailability P should be in the range (0 logP3), for a higher log P, the drug has difficulty penetrating the lipid membranes [26]. In contrast to hydration energy, the presence of hydrophobic groups in the structure of 1,2-benzodiazole induces an increase in lipophilia. The M13 compound has the low diffusion coefficient (0.06), resulting in better gastric tolerance. M23 compounds which have a higher value (3.88), have plasma protein dependent capabilities.

Quantitative structure-activity relationship studies

First, different 1,2-benzodiazole substitutes (Table 1) were evaluated for their TP inhibitory activity. The biological parameter (IC50) was introduced in this research and the results are illustrated in Table1. To determine the role of structural characteristics, a series of twenty antiproliferativetrailers the derivatives of 1, 2-benzodiazole was studied by the QSAR method. These compounds have been used to generate multilinear regression models. Different physicochemical descriptors such as steric, electronic and molecular structure were used as independent variables and correlated with biological activity. The development of a QSAR model requires a diverse set of data, and therefore a large number of descriptors must be considered. Descriptors are numerical values that encode different structural characteristics of molecules.

Selecting a set of appropriate descriptors forms a large number of them requires a method, which is capable of discriminating between parameters. The Pearson correlation matrix was performed on all descriptors using SPSS Software. The analysis of the matrix revealed nineteen descriptors for the development of the MLR model. The value of the selected descriptors for the MLR model is presented in Table 2.

The correlation between biological activity (IC50) and descriptors expressed by the following relationship:

$$IC_{50}=5.598- 1.833C_{9}-6,251C_{3}+0,132*DM+3,182\ q8$$

With r = 0.841 and n = 28

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The QSAR model having R2> 0.6 will only be considered for validation .for example, the value r = 0.841 and r^2 = 0.707 allowed us to strongly indicate the correlation between different parameters (independent variables) with TP Inhibition of compounds.

In the QSAR model, the negative coefficients of DM and q8 explain that any increase in C3 and C9 of the compounds results in a decrease in biological activity. To test the predictive a privilege validity of the selected MLR model (eq. PIC50), the leave-one-out technique (LOO technique) was used. The models developed were validated by calculating the following statistical parameters: the estimated residual sum of the squares (PRESS), the total sum of the square deviation (SSY) and the validated cross correlation coefficient (R^2_{adj}) (Table 3).

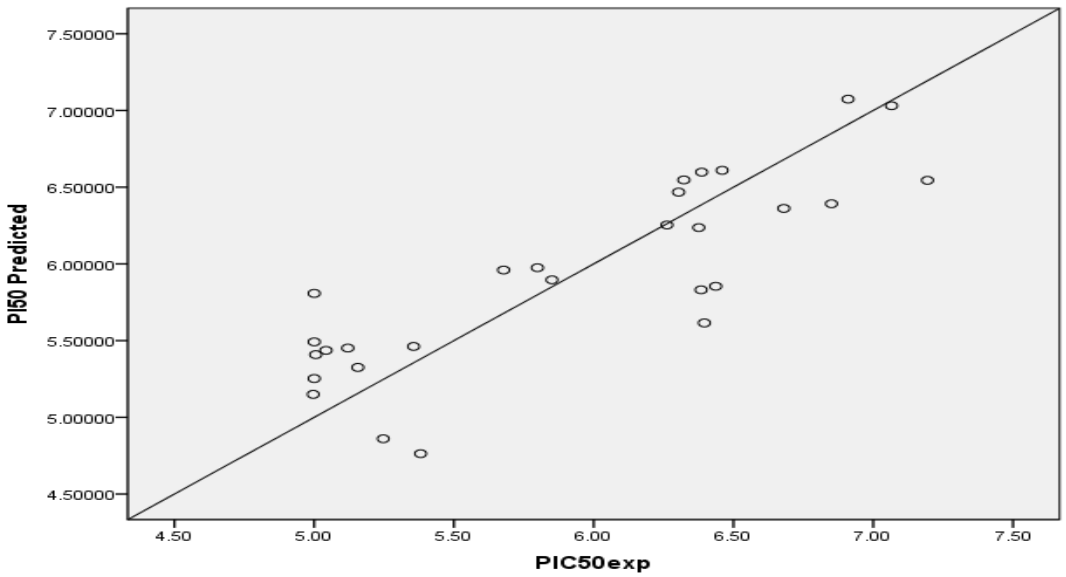
Table 3: Sum of the square deviation (SSY) and the validated cross correlation coefficient.

Model	PRESS	SSY	PRESS/SSY	R^2_{CV}	R^2_{adj}
Correlation coefficient	4.272	14.570	0.2932	0.707	0.656

PRESS is an important cross-validation parameter because it is a good approximation of the actual prediction error of the model. Its value below SSY indicates that the model predicts better than chance is perhaps considered statistically significant, the lower the PRESS value, the more predictable the model. Based on the results described in Table 3, the model is statistically significant.

In addition, for a reasonable QSAR model, the PRESS / SSY ratio should be less than 0.4. The data presented in Table 3 indicate that for the developed mode, this ratio is 0.2932. Our R^2_{CV} result for this QSAR model was 0.707. The high value of R^2_{CV} and R^2_{adj} = 0.656 is an essential criterion for the optimal quantification of the QSAR model.

Figure 4 shows the predicted linear regression curves against the experimental value of 1, 2-benzodiazole biological activity described above. The graphs in this model show that they are more practical with R2 = 0.707. He indicated that the model can be successfully applied to predict the PIC 50 activity of these compounds.



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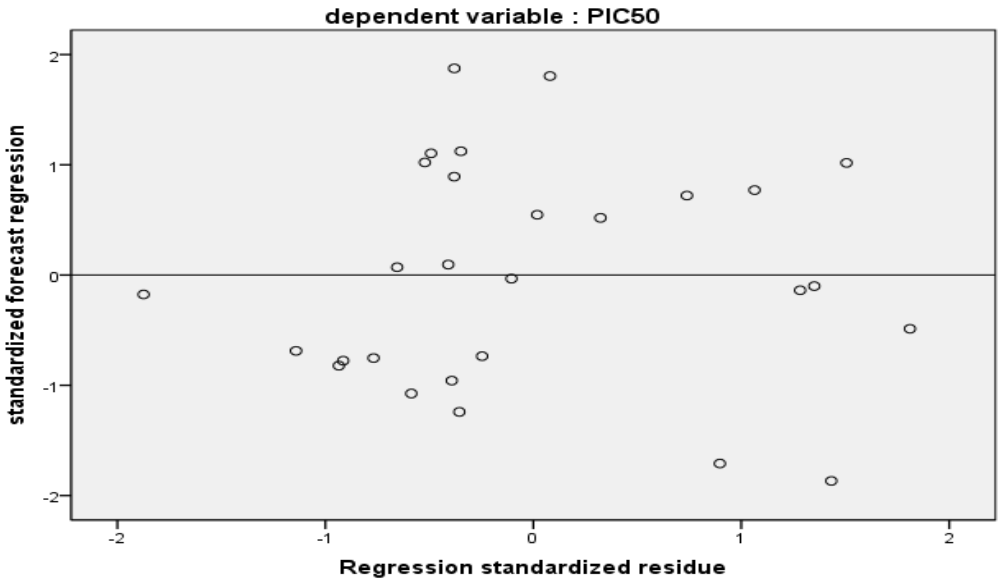

Fig 4: Residue plot versus observed experimental inhibition of TP of 1,2-benzodiazole.

The calculation of the drug on the basis of the rule of five Lipinski

The drug resembles a promising model for quantifying the balance between the molecular properties of a compound that influence its pharmacodynamics and pharmacokinetics and ultimately optimizes their absorption, metabolism, and excretion (ADME) distribution in the human body as a drug. The empirical conditions for satisfying the Lipinski rule and demonstrating good oral bioavailability imply a balance between the aqueous solubility of a compound and its ability to passively diffuse across different biological barriers. these parameters make it possible to determine oral absorption or membrane permeability when the molecule evaluated follows the Lipinski rule of five from molecular weight (MM) ≤ 500 DA, an octanol-water partition coefficient log P ≤ 5, H-bond donors, nitrogen or oxygen atoms one or more hydrogen atoms (HBD) ≤ 5, H-bond acceptors, nitrogen atoms (HBA) ≤ 10 and Molar refraction should be between 40-130.

Molecules that violate more than one of these rules may present bioavailability problems. This rule therefore establishes certain structural parameters relevant to the theoretical prediction of the oral bioavailability profile, and is closely used in the creation of new drugs. However, classes of compounds that are substrates for biological transporters such as antibiotics, antifungals, vitamins and cardiac glycosides are exceptions to the rule. The total number of violations is ROF-Score, between 0 and 4 [27].

The results of the calculation (Table 4) show that all the compounds studied are in agreement with Lipinski's rules with ROF-Score <1, suggesting that these compounds would not theoretically have oral bioavailability problems. Molecules with ROF scores above one are considered marginal for further development. Although, as Lipinski and colleagues have pointed out. Finally, it is well known that many drugs violate the ROF, but this is not a serious problem as it was not originally designed as a tool for assessing drug similarity.

Table 4: Application of ROF on 1,2-benzodiazole derivatives.

Molecules	LogP	MM	HBD (OH or NH)	HBA(N or O)	Ref	Violations of Lipinski rule
M1	-0.89	403.45	1	8	112.04	0
M2	-1.29	375.44	1	7	107.61	0
M3	-0.98	317.36	0	6	91.74	0

M4	-2.7	377.48	1	6	110.3	0
M5	-0.24	343.4	1	6	100.9	0
M6	1.24	290.32	1	5	91.39	0
M7	0.86	310.74	1	5	91.83	0
M8	1.58	30435	1	4	96.14	0
M9	1.21	324.77	1	4	96.58	0
M10	0.44	472.52	0	8	125.77	0
M11	-0.71	476.51	0	9	137.86	1
M12	1.21	464.93	0	7	134.11	1
M13	0.06	480.93	0	8	136.2	1
M14	0.78	474.53	0	8	140.51	1
M15	-0.71	476.51	0	8	137.86	1
M16	1.93	458.53	0	7	138.42	1
M17	-0.71	476.51	0	9	137.86	1
M18	0.44	460.51	0	8	135.77	1
M19	-1.41	337.78	2	6	92.63	0
M20	-2.41	367.81	2	7	99	0
M21	-0.32	328.39	2	7	97.52	0
M22	-0.76	422.5	1	6	127.84	0
M23	-3.88	517.57	1	10	143.46	2
M24	-1.11	499.6	1	8	143.8	1
M25	-0.51	327.4	1	5	99.81	0
M26	-1.65	347.4	1	6	101.9	0
M27	-0.61	345.42	1	6	100.69	0
M28	0.38	361.85	1	5	104.59	0

MM and Log P calculated by HyperChem 8.07

CONCLUSION

In this work we were interested to use the method DFT / B3 LYP to study the theoretical analysis of the 28 organic molecules synthesize, we notice that;

- C9, C4, C5 and DM are descriptors more influenced the activity of prediction.
- Correlation rose between the values of experimental and predicted activity.
- Determine the stable and unstable molecules from gap energetic E_{LUMO} and E_{HOMO} of molecules and the difference of energy.
- All these compounds will not present problem of oral bioavailability.

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