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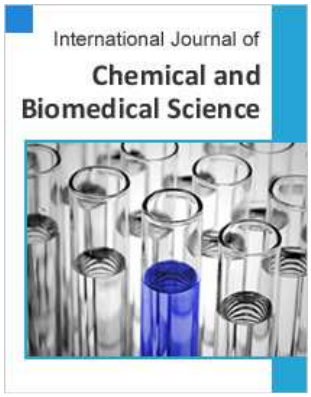

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Theoretical Insights on the Higher Biological Activity of *Meta-* Over *Ortho-* and *Para-* Derivatives of (*E*)-*N*-(CH_3-Substituted-Phenyl)-1-Phenylmethanimine

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Abstract
The quantitative structure activity relationship (QSAR) study for meta-, para- and ortho-(*E*)-*N*-(CH_3-substituted-phenyl)-1-phenylmethanimine was undertaken to understand the structural features that exhibit higher inhibitory activity toward bacteria and fungi. The geometries of the studied compounds were optimized using the energy gradient method of the Hartree-Fock (HF) approximations theory, with the 6-31+G* basis set. The results of QSAR studies revealed that the antifungal and antibacterial activities could be modeled by using electronic parameters including polarizability, Mulliken charge on imine carbon atom, C=N bond energy, dipole moment, HOMO and LUMO energies and total energy of the compounds. The meta derivative of the Schiff base exhibited higher antifungal activity and antibacterial activity which were governed predominantly by polarizability and Mulliken charge on imine carbon (C8) atom, respectively. The antibacterial activity of the ortho derivative was governed by total energy whereas contributions from LUMO, HOMO and Mulliken charge on C8 atom were equally significant for antifungal activity. The antifungal activity of the para derivative had dominating influence from dipole moment while the antibacterial activity was governed by C=N bond energy. The predictive ability of models was characterized by zero and near zero residual with high correlation coefficient (R^2) values indicating accuracy and reliability.

1. Introduction

Schiff base is a condensation product of a primary amine and an active carbonyl compound. The functional group known as azomethine or imine and represented as –CH=N- is of biological importance, exhibiting a spectrum of potent activities including antibacterial [1-3] , antifungal [4-5], anticancer [6-8], herbicidal [9-10], anti-tumor [11], anti-convulsant [12-13], anti-inflammatory [14-15], anti-hypertensive [16], anti-viral [17], anti-oxidant [18-19], anti-depressant and cytotoxic [20-21] activities. The wide range of biological activities of Schiff bases suggests they belong to a class of compounds with a common feature of a variety of medicinal agents. Aside these biological activities, Schiff bases have also been used as catalysts, dyes, polymer stabilizers [22] and corrosion inhibitors [23-24].

Recently, a Schiff base, (*E*)-*N*, 1-diphenylmethanimine and its ortho-, meta- and para-CH_3 substituted derivatives were investigated for the presence of antifungal and antibacterial constituents. The structure-activity studies revealed that the meta derivative exhibited higher biological activities compared to the para, ortho and unsubstituted derivatives [25].

Theoretical approaches have been recently developed to offer more insights into the structural basis of biological activity. These are mathematical expressions known as QSAR (Quantitative Structure-Activity Relationship) models which define a relationship between molecular properties and their biological response. They are predictive tools for preliminary evaluation of the activity of chemical compounds using computer-aided models [26]. QSAR has been utilized to study chemical-biological interactions in various areas including drug research and formulation[27], prediction of physicochemical properties and biological activities in environmental [28], chemical [29] and pharmaceutical [30] areas, risk assessment and toxicity predictions [31]. Some of the parameters used as QSAR descriptors include lipophilic (logP), topological (zero-, first- and second-order molecular connectivity index, Radic topological index, etc.), electronic (ionization potential, dipole moment, HOMO and LUMO energies, etc.), thermodynamic (heat of formation, hydration energy, etc.) and steric (molecular refractivity) parameters. Successful correlations of these parameters with biological and physiological activities have been reported [32-40].

In this paper, is undertaken a theoretical study based on low levels quantum chemical calculations to validate the higher biological activities exhibited by the meta derivatives of (*E*)-*N*-(CH_3-substituted-phenyl)-1-phenylmethanimine shown in Fig.1. Physicochemical and electronic parameters including polarizability, dipole moment, LUMO and HOMO energies, LUMO-HOMO gap, Mulliken charge on imine carbon and nitrogen atoms, C=N bond energy, logP (logarithm of octanol/water partition coefficient) and total energy of the compounds are used as QSAR descriptors to correlate the biological activities using multiple linear regression models.

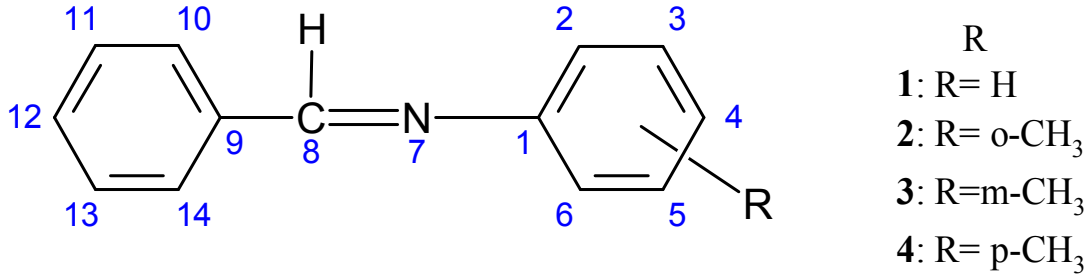
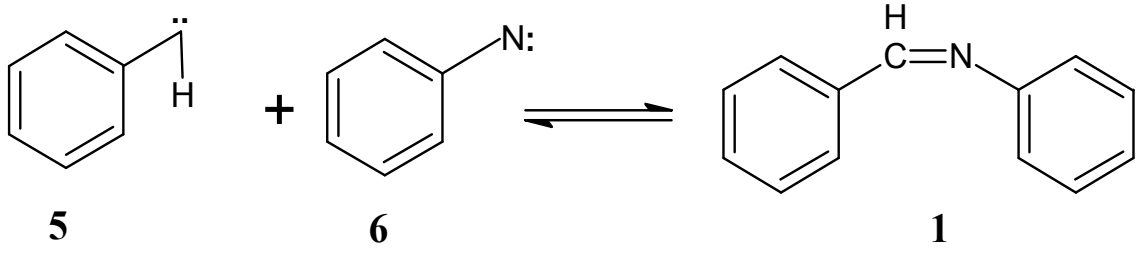


Figure 1. *Structure of Schiff base used in the study.*

2. Materials and Computational Methods

The antibacterial and antifungal activities of Schiff bases, 1-4, were obtained from our previous study [25]. The ground state of Schiff bases, 1-4 were optimized using the energy gradient method of the Hartree-Fock (HF) approximations theory, with the 6-31+G* basis set, and implemented using Spartan 14 software [41]. The 6-31+G* basis set include diffuse functions with the aim of obtaining a more reliable results. During the optimization process, all degrees of freedom were optimized without any constrain. The C=N bond strength in this work is quantified as the bond dissociation energy which is calculated using the standard enthalpies obtained from the HF energy calculations. This is the energy required to break the C=N bond as shown in scheme 1. The bond strength is the change in the standard enthalpies, $D(C=N) = H_1^0 - (H_5^0+H_6^0)$, where H_1^0, H_5^0, H_6^0 are the standard enthalpies for the (*E*)-*N*, 1-diphenylmethanimine, and the fragments 5 and 6. Multiple regression analysis was performed using IBM SPSS Statistics version 21.



Scheme 1. *C=N bond dissociation energy*

3. Results and Discussion

The calculated properties of the compounds used for the study were logP, total energy, Mulliken charges on C8 and N7, C=N bond energy, HOMO energy, LUMO energy, ΔE (E_{HOMO}-E_{LUMO}), polarizability, and dipole moment. These computed parameters were taken as descriptors for QSAR studies and are shown in Table 1. These descriptors were used as independent variables while the antibacterial and antifungal activities were considered dependent variable. From the computed properties, the meta derivative possesses the following properties compared to the ortho and para derivatives: the lowest total energy, making it the most stable compound, highest C=N bond energy, highest Mulliken charge on C8, lowest Mulliken charge on N7, lowest HOMO energy, highest LUMO energy, highest LUMO-HOMO gap, least dipole moment and lowest polarizability. These parameters may be responsible for the higher antibacterial and antifungal activities of the meta derivative reported.

Table 1. *QSAR parameters of Schiff bases calculated using HF with 6-31+G* basis set.*

Schiff Base	QSAR descriptors									
	Total Energy kJ/mol	C=N Bond Energy kJ/mol	Mulliken Charge on C8 atom	Mulliken Charge on N7 atom	HOMO ev	LUMO ev	HOMO-LUMO Gap(ΔE) ev	Dipole Moment μ Debye	Polari-zability	logP
1	-1452276.377	630.22	-0.351	-0.17	-8.34	1.82	10.16	2.72	55.79	3.9
2	-1554767.115	621.17	-0.275	-0.169	-8.21	1.83	10.04	2.55	57.29	4.39
3	-1554767.805	631.49	-0.208	-0.175	-8.25	1.84	10.09	2.54	57.28	4.39
4	-1554765.915	618.99	-0.341	-0.164	-8.1	1.81	9.91	2.62	57.33	4.39

The significance of the QSAR parameters was investigated using multiple linear regression analysis. The ten QSAR descriptors were used in a multi- parameter linear regression model (Eq. 1), where X1-Xn represent the independent variable (QSAR parameters); coefficients, a and b-k represent the regression constant and coefficients of the variables used, respectively .

$$Y = a + bX1 + cX2 + dX3 + \ldots pXn;\ n = 1\text{-}10,\ p = b\text{-}k \quad (1)$$

A perfect correlation fit was obtained with coefficient of determination (R^2) = 1. But, seven variables out of the ten variables had zero coefficients whereas only three variables had non-zero coefficients. Five QSAR variables (and up to 9 variables) were also used in the regression model and the results were the same indicating that only three QSAR descriptors are needed to accurately predict the indicated biological properties of the Schiff bases. Regression analysis using one and two QSAR descriptors, respectively were also investigated. The results showed poor correlation between the QSAR parameters and biological activities of the compounds and none was statistically significant at 95% confidence level used. This shows that, no one QSAR parameter or a combination of any two QSAR parameters can be used to accurately predict the antifungal and antibacterial activities of the Schiff bases. This is in agreement with a previous report [34] which concluded that no single variable model is capable of modeling biological activity and that descriptors can be combined to obtain statistically significant multi-parametric model for modeling activity.

A three-variable linear regression (tri-parametric model) analysis was then carried out to investigate the QSAR parameters that will give the best model for the description of the biological activities of the Schiff bases. Any combination of three QSAR parameters which gave R^2 value less than 1 was ignored since more than 90% of the combinations resulted in a R^2 value of 1. R^2 value of 1 shows that the biological activities of the compounds can be predicted with high accuracy and the model is a best fit for the correlation. The best model was then chosen based on the least residual. Residual is the difference (variance) between the experimental value and that predicted by the model and the one with the least value was taken as the best model. Residual can be negative (predicted value is less than experimental) or positive (predicted value is greater than experimental). Therefore, the magnitude of the residual (disregarding the sign) is an important factor in determining the predictability and accuracy of the model. By computing the total residual, models with similar R^2 values can be compared. The results of multiple regression analyses are presented in Tables 2-7.

Table 2 is the results of multiple regression analysis of the meta derivative. Five sets of QSAR parameters showed a total residual of zero. Total residual values greater than ±2.27 x 10^{-13} were excluded from the table. The total residual was computed to know the total discrepancies between the experimental and predicted antifungal activities of the compounds. The best model was then chosen by zero residual signifying a perfect prediction. This was obtained from a three-variable combination of the following QSAR parameters: total energy (X1), Mulliken charge on C8 (X3) and N7 (X4) atoms, HOMO (X5) and LUMO (X6) energies, dipole moment (X8) and polarizability (X9). Statistically significant models were obtained when three descriptors were used in QSAR investigation [34]. The models with a total residual of zero are given in Eq. 2-6.

$$30382.11 - 0.0132T.E - 282.28MC_{C8} - 890.30POL \quad (2)$$

$$3228.63 - 218.71MC_{C8} - 427.35\mu - 38.02POL \quad (3)$$

$$-2626.63+ 4685.71MC_{N7} - 140HOMO + 1251.43LUMO \quad (4)$$

$$-8595.58 - 1337.71HOMO - 6194.27LUMO + 156.56POL \quad (5)$$

$$16216.37 + 540.14HOMO - 999.77\mu - 160.789POL \quad (6)$$

where T.E is the total energy, MC_{C8} is the Mulliken charge on C8 atom, POL is polarizability, μ is the dipole moment and MC_{N7} is the Mulliken charge on N7 atom.

The involvements of the QSAR parameters in the best models can be evaluated by considering their appearances in the five equations. Analysis of the equations shows that polarizability makes the highest appearances in four (out of five) equations making a total involvement of 80 % in the prediction of the best models. This was followed by HOMO energy with an involvement of 60 %. Mulliken charge on C8 atom, LUMO energy and dipole moments showed 40 % involvement each whereas total energy and Mulliken charge on N7 atom recorded the least involvement of 20 % each. This statistics shows that polarizability should be given the highest priority when designing antifungal agents involving meta derivatives of Schiff bases.

The antibacterial correlation statistics of the meta derivative is presented in Table 3. Total residual values greater than $\pm 3.55 \times 10^{-15}$ were excluded from the table. Nine regression models (Eq. 7-15) had a total residual of zero. More QSAR parameters appear to perfectly predict the antibacterial activities compared to the antifungal activities. This may indicate the higher sensitivity of bacteria to the Schiff bases studied compared to fungi.

$$8.74 -2.6E-06T.E-16.39MC_{C8} -16.39MC_{N7} \quad (7)$$

$$1714407.17 +2.69T.E +17.17\Delta E +563408.96logP \quad (8)$$

$$-6346.88 +0.0031T.E - 99.84\mu+199.62POL \quad (9)$$

$$31.61 -0.00607C{=}N_{BE}- 13.06MC_{C8} - 6.24LUMO \quad (10)$$

$$5.19 - 15.93MC_{C8} - 11.49MC_{N7} + 0.15POL \quad (11)$$

$$16.79 - 14.80MC_{C8}+0.21HOMO +0.20logP \quad (12)$$

$$13.49 - 14.80MC_{C8}- 0.159\Delta E +0.0703 POL \quad (13)$$

$$9.16 - 14.88MC_{C8}+0.193\mu +0.109POL \quad (14)$$

$$18.39 +171.75MC_{N7} -2.09HOMO +5.30\mu \quad (15)$$

where $C{=}N_{BE}$ is the C=N bond energy and ΔE is the HOMO-LUMO gap.

Table 2. *Correlation matrix of used molecular descriptors, experimental and predicted antifungal activities of (E)-N-(3-methylphenyl)-1-phenylmethanimine (3).*

QSAR Descriptors/ Parameters			R^2	Experimental[a] (Predicted) antimicrobial activity (mm)[b]				Residual between experimental and predicted antimicrobial activities				Total residual[#]
				A. niger	*A. fumigatus*	*C. albican*	*T. rubrum*	*A. niger*	*A. fumigatus*	*C. albican*	*T. rubrum*	
X1	X3	X9	1	22(22)	21(21)	11(11)	4(4)	0	0	0	0	0*
X3	X8	X9	1	22(22)	21(21)	11(11)	4(4)	0	0	0	0	0*
X4	X5	X6	1	22(22)	21(21)	11(11)	4(4)	0	0	0	0	0*
X5	X6	X9	1	22(22)	21(21)	11(11)	4(4)	0	0	0	0	0*
X5	X8	X9	1	22(22)	21(21)	11(11)	4(4)	0	0	0	0	0*
X3	X8	X10	1	22(22)	21(21)	11(11)	4(4)	0	0	0	5.68E-14	5.68E-14
X2	X5	X6	1	22(22)	21(21)	11(11)	4(4)	-5.7E-14	0	0	-1.1E-13	1.67E-13

[a]The experimental antimicrobial activities of reference [25]; [b]Zone of inhibition; [#]Total variance between the experimental and predicted values irrespective of the sign; X1:Total energy; X2: C=N bond energy; X3: Mulliken charge on C8; X4: Mulliken charge on N7; X5: HOMO; X6: LUMO; X8: Dipole moment; X9: Polarizability; X10: logP; *Best model.

Table 3. *Correlation matrix of used molecular descriptors, experimental and predicted antibacterial activities of (E)-N-(3- methylphenyl)-1-phenylmethanimine (3).*

QSAR Descriptors/ Parameters			R^2	Experimental[a] (Predicted) antibacterial activity (mm)				Residual between experimental and predicted antibacterial activities				Total residual[#]
				S. dysenteriae	*S. typhi*	*E. coli*	*S. aureus*	*S. dysenteriae*	*S. typhi*	*E. coli*	*S. aureus*	
X1	X3	X4	1	21(21)	20(20)	19(19)	21(21)	0	0	0	0	0*
X1	X7	X10	1	21(21)	20(20)	19(19)	21(21)	0	0	0	0	0*
X1	X8	X9	1	21(21)	20(20)	19(19)	21(21)	0	0	0	0	0*
X2	X3	X6	1	21(21)	20(20)	19(19)	21(21)	0	0	0	0	0*
X3	X4	X9	1	21(21)	20(20)	19(19)	21(21)	0	0	0	0	0*
X3	X5	X10	1	21(21)	20(20)	19(19)	21(21)	0	0	0	0	0*
X3	X7	X9	1	21(21)	20(20)	19(19)	21(21)	0	0	0	0	0*
X3	X8	X9	1	21(21)	20(20)	19(19)	21(21)	0	0	0	0	0*
X4	X5	X8	1	21(21)	20(20)	19(19)	21(21)	0	0	0	0	0*

[a]The experimental antimicrobial activities of reference [25]; [b]Zone of inhibition; [#]Total variance between the experimental and predicted values irrespective of the sign; X1: Total energy; X2: C=N bond energy; X3: Mulliken charge on C8; X4: Mulliken charge on N7; X5: HOMO; X6: LUMO; X7: HOMO-LUMO gap; X8: Dipole moment; X9: Polarizability; X10: logP; *Best model.

All the QSAR parameters studied are involved in the accurate prediction of antibacterial activity. The highest appearance in the nine models was made by Mulliken charge on C8 atom with an involvement of 67 % whereas the least, 11% was shown by C=N bond energy and LUMO energy. The involvements of other QSAR parameters include: total energy (33 %), Mulliken charge on N7 atom (33 %), HOMO (22 %), HOMO-LUMO gap (22 %), dipole moment (33 %), polarizability (44 %) and logP (22 %). The lipophilic parameter, (logP) made quite a minimal contribution in the antibacterial activity prediction, and did not even make an appearance in the models that best describe antifungal activity. This non-involvement of hydrophobic term (logP) in the inhibition of fungal activities by meta derivative of the Schiff base and the very low appearance in the antibacterial activity suggest that these biological activities are independent of hydrophobic interactions. Similar non-involvement of logP in the inhibition of bacteria by sulfonamides was also reported [34]. These results show that Mulliken charge on C8 atom and polarizability have dominating influence and should obviously be given attention in the formulation of antibacterial agents using meta derivative of Schiff bases.

The para derivative was also investigated similarly to evaluate the QSAR parameters making significant contributions to their biological activities. For the antifungal activities, no model was observed for p-derivative with a total residual of zero (Table 4). The best model had a total residual of 1.10×10^{-13}. Total residual values greater than $\pm 2.28 \times 10^{-13}$ were excluded from the table. The best models for p-derivative are given as follows:

$$2115.65 + 0.000594T.E + 1891.83MC_{N7} - 335.14\mu \quad (16)$$

$$1351.55 - 173.70MC_{C8} - 363.77\mu - 103.35logP \quad (17)$$

Analysis of the two best models for the antifungal activities of p-derivative indicates the following involvements from the QSAR parameters: dipole moment (100 %), total energy (50 %), Mulliken charge on C8 (50 %) and N7 (50 %) atoms and logP (50 %). The antifungal activity is dominated by dipole moment. The importance of dipole moment in describing the antimicrobial activity had been indicated for 1,2,4-triazole derivatives [42]. Lipophilic parameter, logP made significant contribution to the antifungal activity of the p-derivative. The antimicrobial activity of isatin derivatives was also governed by logP [32].

The correlation statistics of antibacterial activity of p-derivative is presented in Table 5. Total residual values greater than $\pm 3.3 \times 10^{-14}$ were excluded from the table. Five regression models showed a total residual of zero and these were considered the best models (Eq. 18-22).

$$2675.16 - 0.0010T.E - 0.358C{=}N_{BE} - 69.49POL \quad (18)$$

$$-411.51 - 0.232C{=}N_{BE} - 54.69MC_{C8} + 305.75LUMO \quad (19)$$

$$9497.78 - 28.10C{=}N_{BE} + 4827.85MC_{C8} + 3648.32\mu \quad (20)$$

$$624.08 - 0.331\ C{=}N_{BE} - 35.79\mu - 5.38POL \quad (21)$$

$$-431.89 + 1057.14MC_{N7} + 234.29HOMO + 254.29\Delta E \quad (22)$$

The involvements of the QSAR parameters in the five models representing antibacterial activity of the p-derivative are as follows: total energy (20 %), C=N bond energy (80 %), Mulliken charge on C8 atom (40 %), Mulliken charge on N7 atom (20 %), HOMO 20%, LUMO 20 %, HOMO-LUMO gap 20 %, dipole moment 40 % and polarizability 40 %. C=N bond energy and dipole moment are parameters governing the antibacterial activity and antifungal activity of the para derivative, respectively. Antibacterial activities were reported to depend on C=N bond energy in QSAR studies of Schiff bases [43].

For the ortho derivative, five regression models with a total residual of zero were obtained for the antifungal activity as shown in Table 6. Total residual values greater than $\pm 9.67 \times 10^{-14}$ were excluded from the table. The best models are given in Eq. 23-27.

$$-847.61 - 0.00050T.E - 300.00HOMO - 1300.05LUMO \quad (23)$$

$$25587.29 - 0.00985T.E - 157.36\Delta E - 686.13POL \quad (24)$$

$$-342.98 + 110.46MC_{C8} + 1983.62MC_{N7} - 87.53HOMO \quad (25)$$

$$-1411.86 - 116.88MC_{C8} + 150.28MC_{N7} + 773.28LUMO \quad (26)$$

$$-1499.47 - 135.52MC_{C8} + 7.17HOMO + 836.67LUMO \quad (27)$$

The involvements of the QSAR parameters in predicting accurately, the antifungal activities of the ortho derivative are as follows: total energy 40 %, Mulliken charge on C8 atom 60 %, Mulliken charge on N7 atom 40 %, HOMO 60 %, LUMO 60 %, HOMO-LUMO gap 20 % and polarizability 20 %. It is obvious that Mulliken charge on C8 atom, HOMO and LUMO energies are equally important in describing the antifungal activities of the ortho derivative. The HOMO and LUMO of a molecule play important roles in intermolecular interactions. The binding in drug-receptor systems involves the interaction between the HOMO of the drug with the LUMO of the receptor and that between LUMO of the drug with the HOMO of the receptor [44]. LUMO energy was reported as an important electronic parameter in the description of antifungal activities of p-aminobenzoic acid derivatives [45] and monochloroacetic acid derivatives [46].

Five regression models with a total residual of zero were also obtained for the antibacterial activity of the ortho derivative as shown in Table 7. Total residual values greater than $\pm 8.93 \times 10^{-15}$ were excluded from the table. The models that predict perfectly the antibacterial activities of the ortho derivative are given in Eq. 28-32.

$$265.8946 - 8.23E\text{-}05X1 - 0.10230507X2 - 5.57315783X9 \quad (28)$$

$$-71.4286 + 8.13E\text{-}20X1 + 285.7143X4 + 71.42857X6 \quad (29)$$

$$-70.8847 - 1.8E\text{-}05X1 + 245.2841X4 + 9.433832X7 \quad (30)$$

7091.861 -0.00266X1 -57.2022X7 -185.827X9 (31)

-128.69 +240.763X4 -11.4899X5 +1.501953X9 (32)

The involvements of the QSAR parameters in predicting accurately, the antibacterial activities of the ortho derivative are: total energy (80 %), C=N bond energy (20 %), Mulliken charge on N7 atom (60 %), HOMO (20 %), LUMO (20 %), HOMO-LUMO gap (40 %), dipole moment (20 %) and polarizability (40 %). The highest involvement was shown by total energy and this was followed by Mulliken charge on N7 atom. Total energy was also reported to govern the antibacterial activities of p-aminobenzoic acid derivatives [45].

Table 4. *Correlation matrix of used molecular descriptors, experimental and predicted antifungal activities of (E)-N-(4- methylphenyl)-1-phenylmethanimine (4).*

QSAR Descriptors/ Parameters			R^2	Experimental[a] (Predicted) antifungal activity (mm)[b]				Residual between experimental and predicted antifungal activities				Total residual[#]
				A. niger	*A. fumigatus*	*C. albican*	*T. rubrum*	*A. niger*	*A. fumigatus*	*C. albican*	*T. rubrum*	
X1	X4	X8	1	20(20)	18(18)	10(10)	4(4)	0	0	0	-1.10E-13	1.10E-13*
X3	X8	X10	1	20(20)	18(18)	10(10)	4(4)	0	0	-1.10E-13	0	1.10E-13*
X2	X4	X9	1	20(20)	18(18)	10(10)	4(4)	0	0	1.14E-13	0	1.14E-13
X2	X3	X10	1	20(20)	18(18)	10(10)	4(4)	5.68E-14	0	-1.10E-13	-5.70E-14	2.23E-13
X1	X2	X6	1	20(20)	18(18)	10(10)	4(4)	0	0	0	2.27E-13	2.27E-13
X4	X6	X10	1	20(20)	18(18)	10(10)	4(4)	-5.70E-14	5.68E-14	5.68E-14	5.68E-14	2.27E-13

[a]The experimental antimicrobial activities of reference [25]; [b]Zone of inhibition; [#]Total variance between the experimental and predicted values irrespective of the sign; X1: Total energy; X2: C=N bond energy; X3: Mulliken charge on C8; X4: Mulliken charge on N7; X6: LUMO; X8: Dipole moment; X9: Polarizability; X10: logP; *Best model.

Table 5. *Correlation matrix of used molecular descriptors, experimental and predicted antibacterial activities of (E)-N-(4- methylphenyl)-1-phenylmethanimine (4).*

QSAR Descriptors/ Parameters			R^2	Experimental[a] (Predicted) antibacterial activity (mm)				Residual between experimental and predicted antibacterial activities				Total residual[#]
				S. dysenteriae	*S. typhi*	*E. coli*	*S. aureus*	*S. dysenteriae*	*S. typhi*	*E. coli*	*S. aureus*	
X1	X2	X9	1	18(18)	19(19)	16(16)	17(17)	0	0	0	0	0*
X2	X3	X6	1	18(18)	19(19)	16(16)	17(17)	0	0	0	0	0*
X2	X3	X8	1	18(18)	19(19)	16(16)	17(17)	0	0	0	0	0*
X2	X8	X9	1	18(18)	19(19)	16(16)	17(17)	0	0	0	0	0*
X4	X5	X7	1	18(18)	19(19)	16(16)	17(17)	0	0	0	0	0*
X1	X2	X8	1	18(18)	19(19)	16(16)	17(17)	-1.40E-14	-1.40E-14	0	0	2.80E-14
X2	X4	X7	1	18(18)	19(19)	16(16)	17(17)	0	0	2.84E-14	0	2.84E-14

[a]The experimental antimicrobial activities of reference [25]; [b]Zone of inhibition; [#]Total variance between the experimental and predicted values irrespective of the sign; X1: Total energy; X2: C=N bond energy; X3: Mulliken charge on C8; X4: Mulliken charge on N7; X5: HOMO; X6: LUMO; X7: HOMO-LUMO gap; X8: Dipole moment; X9: Polarizability; *Best model.

Table 6. *Correlation matrix of used molecular descriptors, experimental and predicted antifungal activities of (E)-N-(2- methylphenyl)-1-phenylmethanimine (2).*

QSAR Descriptors/ Parameters			R^2	Experimental* (Predicted) antimicrobial activity (mm)				Residual between experimental and predicted antimicrobial activities				Total residual[#]
				A. niger	*A. fumigatus*	*C. albican*	*T. rubrum*	*A. niger*	*A. fumigatus*	*C. albican*	*T. rubrum*	
X1	X5	X6	1	11(11)	10(10)	9(9)	3(3)	0	0	0	0	0*
X1	X7	X9	1	11(11)	10(10)	9(9)	3(3)	0	0	0	0	0*
X3	X4	X5	1	11(11)	10(10)	9(9)	3(3)	0	0	0	0	0*
X3	X4	X6	1	11(11)	10(10)	9(9)	3(3)	0	0	0	0	0*
X3	X5	X6	1	11(11)	10(10)	9(9)	3(3)	0	0	0	0	0*
X2	X7	X10	1	11(11)	10(10)	9(9)	3(3)	4.62E-14	-3.6E-15	-3.6E-15	-3.6E-15	5.7E-14
X4	X5	X9	1	11(11)	10(10)	9(9)	3(3)	5.68E-14	0	1.14E-13	0	6.82E-14

[a]The experimental antimicrobial activities of reference [25]; [b]Zone of inhibition; [#]Total variance between the experimental and predicted values irrespective of the sign; X1: Total energy; X2: C=N bond energy; X3: Mulliken charge on C8; X4: Mulliken charge on N7; X5: HOMO; X6: LUMO; X7: HOMO-LUMO gap; X9: Polarizability; X10: logP; *Best model.

Table 7. *Correlation matrix of used molecular descriptors, experimental and predicted antibacterial activities of (E)-N-(2- methylphenyl)-1-phenylmethanimine (2).*

QSAR Descriptors/ Parameters			R^2	Experimental* (Predicted) antimicrobial activity (mm)				Residual between experimental and predicted antimicrobial activities				Total residual[#]
				S. dysenteriae	*S. typhi*	*E. coli*	*S. aureus*	*S. dysenteriae*	*S. typhi*	*E. coli*	*S. aureus*	
X1	X2	X9	1	10(10)	11(11)	10(10)	11(11)	0	0	0	0	0*
X1	X4	X6	1	10(10)	11(11)	10(10)	11(11)	0	0	0	0	0*
X1	X4	X7	1	10(10)	11(11)	10(10)	11(11)	0	0	0	0	0*
X1	X7	X9	1	10(10)	11(11)	10(10)	11(11)	0	0	0	0	0*
X4	X5	X9	1	10(10)	11(11)	10(10)	11(11)	0	0	0	0	0*
X4	X5	X8	1	10(10)	11(11)	10(10)	11(11)	0	-3.6E-15	0	0	3.6E-15
X2	X8	X10	1	10(10)	11(11)	10(10)	11(11)	1.78E-15	-1.8E-15	0	-1.8E-15	5.36E-15

[a]The experimental antimicrobial activities of reference [25]; [b]Zone of inhibition; [#]Total variance between the experimental and predicted values irrespective of the sign; X1: Total energy; X2: C=N bond energy; X4: Mulliken charge on N7; X5: HOMO; X6: LUMO; X7: HOMO-LUMO gap; X8: Dipole moment; X9: Polarizability; X10: logP; *Best model.

Table 8 summarizes the QSAR parameters with highest involvements in the prediction of the antifungal and antibacterial activities of the ortho, meta and para derivatives of the Schiff base studied. It also indicate the total number of models involved in the antifungal and antibacterial activities of the various derivatives of the Schiff base. It can be seen that the meta derivative had the highest number models (14 best models) describing its antifungal and antibacterial activities. This was followed by the ortho derivative with 10 best models while the para derivative had 7 best models. According to the results, the order of biological activity could be given as meta > ortho > para. The higher antifungal and antibacterial activities of the meta derivative reported experimentally [25] compared to the ortho and para derivatives is in agreement with the theoretical studies. It therefore appears that the higher the number of QSAR parameters involved in the prediction, the higher the biological activities of the compound.

Table 8. *Summary of QSAR parameters with highest involvement and number of best models describing the antifungal and antibacterial activities of the Schiff bases.*

Biological Activity	QSAR parameters with highest involvement			Number of best models		
	Ortho	Meta	Para	Ortho	Meta	Para
Antifungal activity	HOMO, LUMO, Mulliken charge on C8 atom	Polarizability	Dipole moment	5	5	2
Antibacterial activity	Total energy	Mulliken charge on C8 atom	C=N bond energy	5 10	9 14	5 7

4. Conclusions

QSAR studies were carried out in order to establish the relationship between antifungal and antibacterial activities of the studied Schiff bases and their structures. The results confirm the higher antifungal and antibacterial activities of the meta derivative compared to the ortho and para derivatives. The QSAR models indicated the importance of electronic parameters, polarizability, Mulliken charge on imine carbon (C8) atom, dipole moment, C=N bond energy, total energy, HOMO and LUMO energies in describing the antifungal and antibacterial activities of the studied Schiff base derivatives.

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