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A Correlation of the Drug Activities (Anti-Bacterial) in the Structure of Some Hetero Cyclic Compound Containing Benzimidazole and Beta-Lactam Moiety in terms of the Density Functional Descriptors - A QSAR and QSPR Study

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Research Article

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ABSTRACT

Present study shows the correlation of activity of as many as 13 Anti-bacterial (containing benzimidazole and beta-lactam moiety) drugs in terms of global reactivity descriptors under paradigm of QSPR/QSAR study. Investigation of antimicrobial activity of the compounds was done by using Gram- positive (*S. aureus, S. mutans* and *B. subtilis*) bacteria. The global descriptors nicely correlate the variation of activity with structures of the drug molecules

INTRODUCTION

The benzimidazole ring is a significant pharmacophore in contemporary drug discovery. A variety of benzimidazole are in use, like thiabendazole and flubendazole (anthelmintic), omeprazole and lansoprazole (antiulcer) and astemizole (antihistaminic). The chemistry and pharmacology of benzimidazoles have been of great interest to medicinal chemistry [1,2] because its derivatives possessed various biological activities such as antioxidant [3,4], antimicrobial [5–10], antihelmintic [11–13], anticancer [14], antihypertensive [15], antineoplastic [16], anti-inflammatory [17,18], analgesic [19], antiprotozoal [20,21] and anti-hepatitis B virus activity [22]. In addition, a large number of antibiotics contain the 2-azetidinone (commonly known as β-lactam) moiety [23] such as penicillin, cephalosporin and carbapenem. It is also associated with a variety of therapeutic activities [24–28].

In continuation of this work, the study has been done to develop potential relation between some theoretical quantum chemical descriptors and their anti-bacterial activity of some derivatives of the structure type containing the above mentioned moieties.

METHOD OF COMPUTATION

The present study relates the antibacterial activity of the thirteen heterocyclic compounds with benzimidazole and their beta-lactam derivatives. The parent structure of this hetero cyclic compound has been presented in the **Figures 1 and 2.** The derivatives of bio active hetero cyclic compounds which have been used in this study are arranged in the **Table 1**. Some inherent properties encoded in the structure of these molecules as some well-known quantum chemical descriptors was evaluated and modeled with the experimental activities have been collected from literature [29-31].

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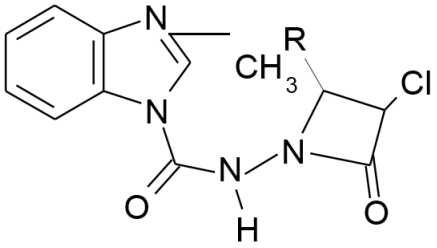

Figure 1. Benzimidazole and beta-lactam moiety (1A-1M).

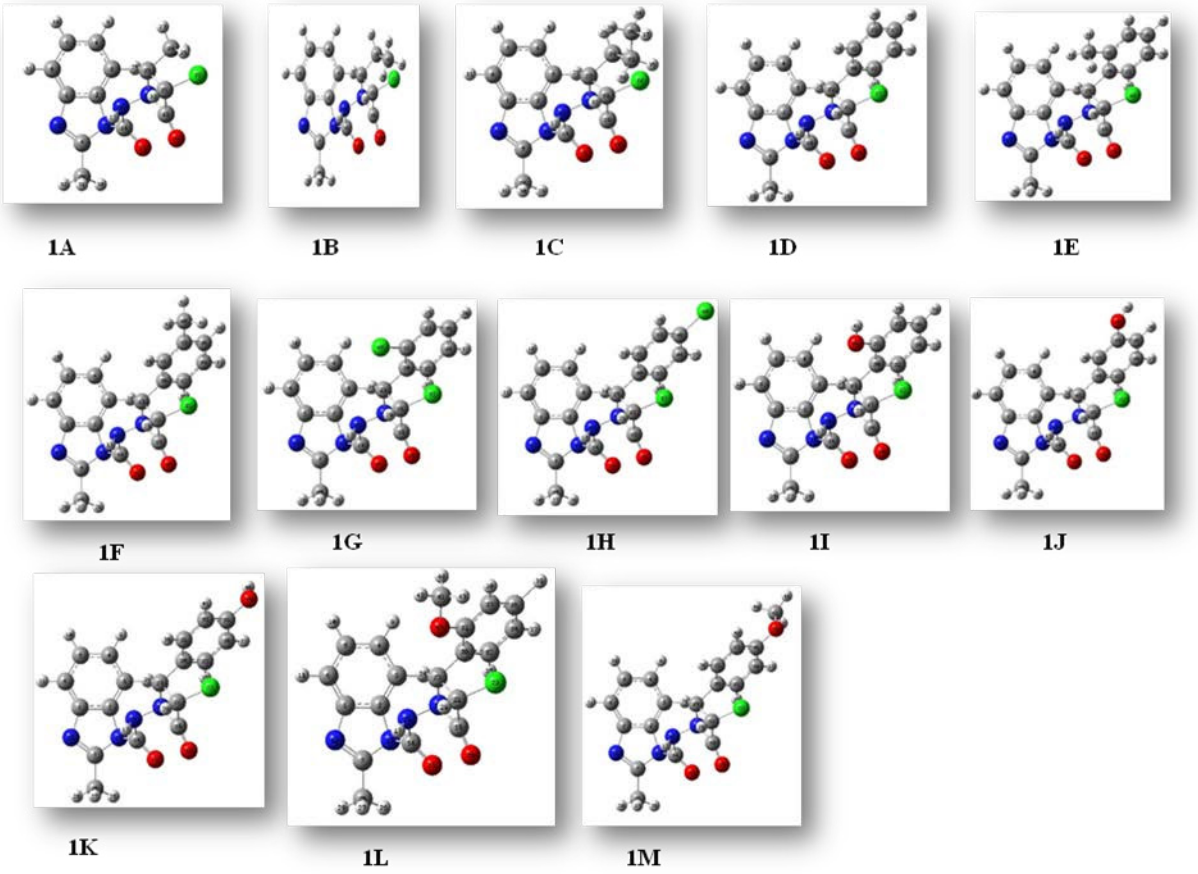

Figure 2. Optimized picture of 1A-1M.

Table 1. Calculated values of ionization potential (I.A), Electron affinity (E.A), hardness (η), Softness (S) in electron volt and dipolemoment (μ) in Debye.

Compound	R	I.A(ev)	E.A(ev)	η(ev)	S(ev)	μ (dipole moment in Debye)
1A	0	9.34851	0.58491	4.3818	0.22822	2.8280425
1B	$-CH_2CH_3$	9.34092	0.58167	4.37963	0.22833	3.20915566
1C	$-CH_2CH_2CH_3$	9.34476	0.58276	4.381	0.22826	2.94105482
1D	$-C_6H_5$	9.30849	0.53593	4.38628	0.22798	3.37419896
1E	2- $CH_3C_6H_4$	9.30215	0.53062	4.38576	0.22801	3.23990746
1F	3- $CH_3C_6H_4$	9.29336	0.52523	4.38406	0.2281	3.37429827
1G	2- ClC_6H_4	9.30106	0.64221	4.32942	0.23098	3.72177136
1H	4- ClC_6H_4	9.34751	0.66177	4.34287	0.23026	2.62695568

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1I	2-OHC_6H_4	9.36242	0.60803	4.37719	0.22846	2.89527034
1J	3-OHC_6H_4	9.3296	0.56327	4.38316	0.22815	2.49369662
1K	4-OHC_6H_4	9.30489	0.53212	4.38639	0.22798	3.03293654
1L	2-$OCH_3C_6H_4$	9.2025	0.52368	4.33941	0.23045	4.97220158
1M	2-$OCH_3C_6H_4$	9.31624	0.55081	4.38271	0.22817	3.16729949

The 3D modeling of these bioactive compounds have been performed with the help of Gaussian 09 software [32].

Gaussian 09 software [32] has been used to calculate the global descriptors by using the DFT methods at B3LYP/6-31 G* basis set.

According to Koopmans' theorem the ionization potential (I) and the electron affinity (A) are computed as follows:

$$I=-\varepsilon_{HOMO} \text{ and } A=-\varepsilon_{LUMO}$$

Where ε_{HOMO} and ε_{LUMO} are the orbital energies of the highest occupied and the lowest unoccupied orbitals.

Parr et al. [33-35] defined the chemical potential, μ, electronegativity, χ, and hardness, η, in the framework of density functional theory, DFT as:

$$\mu=(\partial E/\partial N)_{v(r)}=-X=(I+A)/2\,,\ \eta=\frac{1}{2}[\partial\mu/\partial N]_{v(r)}=\frac{1}{2}[\partial^2 E/\partial N^2]_{v(r)}=\frac{1}{2}(I-A)$$

Where E, N, v(r), I and A are the energy, the number of electrons, the external potential, the ionization energy and the electron affinity of a chemical system respectively.

Softness is a reactivity index and is defined as the reciprocal of hardness, S=(1/η). The observed activity and as well as the quantum mechanical reactivity descriptors such as Ionization potential (I), electron affinity(A), global hardness(η), global softness (S), and dipole moment (μ) are also presented in **Table 2**.

Table 2. Anti-bacterial activity and Antifungal activity of compounds (1A-1M).

Compounds	Mean Zone inhibition (in mm)					
	Anti-bacterial activity			Anti-fungal activity		
	S. aures	*S. mutans*	*B. subtilis*	*Candida albicans*	*Aspergillus niger*	*Aspergillus flavus*
1A	38	20	28	26	24	22
1B	37	18	28	24	25	24
1C	32	18	22	24	24	20
1D	36	16	27	27	26	27
1E	30	15	20	22	18	14
1F	30	13	20	20	18	13
1G	31	13	18	20	16	15
1H	31	10	20	18	14	14
1I	37	16	27	27	28	26
1J	36	16	26	15	20	13
1K	36	15	26	15	14	18
1L	25	14	22	16	16	16
1M	22	16	18	18	19	16

Also use Minitab17 [36] to perform the MLR (multi-linear regression) for the calculation of the different co-efficient presented in **Tables 3-5**.

Table 3. Regression Analysis: *S aureus* versus IE, S(ev), dipole moment.

Compounds	R^2 (%)	Regression Equation	Odd molecule
1A-1L	66.92	*S aureus*=-996+75.5 I.E+73.5 η+ 1.42 μ	1M

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Table 4. Regression Analysis of *S. mutans* versus I.E, S(ev), dipolemoment.

Compounds	R^2 (%)	Regression Equation	Odd molecule
1A-1L	62.38	S. mutans=-208 + 67.8 I.E - 1852 S + 4.79 μ	1M

Table 5. Regression Analysis of *B. subtilis* versus η(ev), S(ev), I.E.

Compounds	R^2 (%)	Regression Equation	Odd molecule
1A-1L	60.81	*B. subtilis*=-594180+ 68014 η+1290179 S+ 186.6 I.E	nil

RESULTS AND DISCUSSION

To model the relation with the computed values of different well known quantum chemical descriptors of the compounds (1A-1M) having anti-microbial activities are interrelated with the gram- positive (*S. aureus, S. mutans* and *B. subtilis*) bacteria via multi linear regression.

The R^2 values obtained from the regression result for the each sets, *S aureus* versus I.E, S (ev), dipolemoment; *S mutans* versus I.E, S (ev), dipolemoment and *B. subtilis* versus η (ev), S (ev), I.E having values 66.92, 62.38 and 60.81 respectively revels the efficacy of the model.

CONCLUSION

A combination of several quantum chemical parameters to form a composite index, which could be correlated to the experimental drug efficiency, often provides valuable information on the relationship between quantum chemical parameters and experimental drug efficiency. In the present report, studied a correlation of activity of as many as 13 anti-bacterial drugs in terms of global reactivity descriptors under paradigm of QSPR/QSAR study. The global descriptors nicely correlate the variation of activity with structures of the drug molecules.

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