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Penetrating to cell membrane bacteria by the efficiency of various antibiotics (clindamycin, metronidazole, azithromycin, sulfamethoxazole, baxdela, ticarcillin, and clavulanic acid) using S-NICS theory

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ABSTRACT

Antibiotics are specific chemical derived produced (or substance) by living organisms which are able to inhibit the life processes of the other organisms. By this work, it has been investigated via functionalizing of antibiotics; it would be able to control the behaviour of Gram-positive or negative bacteria treatments. The efficiency of clindamycin, metronidazole, Azithromycin, sulfamethoxazole, trimethoprim Baxdela, Ticarcillin, Ampicillin and Clavulanic acid in the viewpoint of NMR shielding and S-NICS methods have been studied as drug delivery approaches.

Keywords: *Sulfonamide; Triclosan; Baxdela; Ticarcillin; Ampicillin and Clavulanic acid; NMR and S-NICS.*

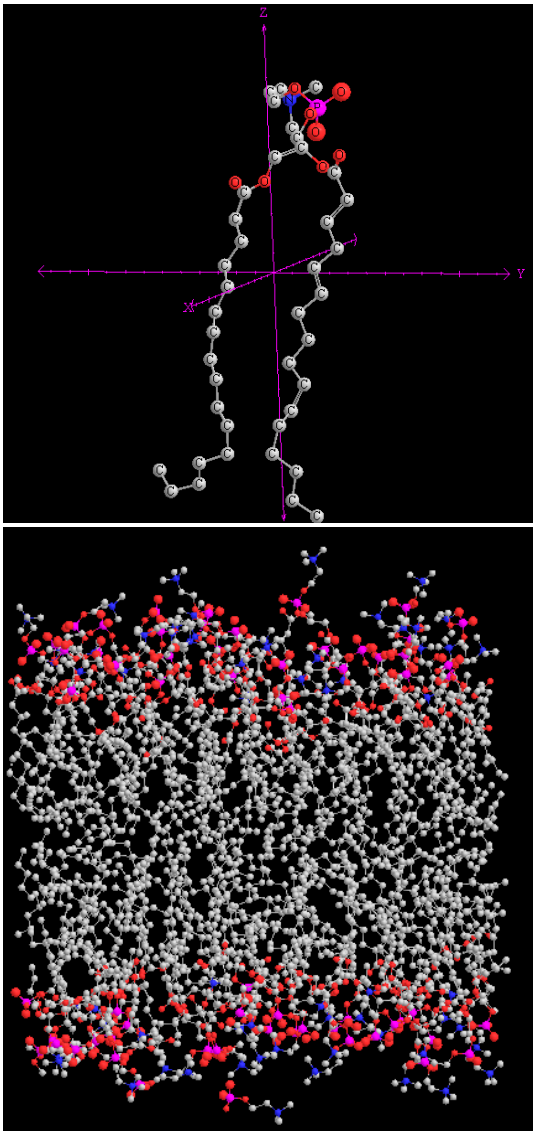
1. INTRODUCTION

An antibiotic molecule is able to stop or kill the growth of, microorganism, including both fungus and bacteria that are called "bacteriostatic" and "bactericidal" respectively [1]. Antibiotic is a chemical substances derived from a living organism which are able to inhibit the life processes of other tissue. The first antibiotic was extracted from “micro-tissues” but some of them produced from special plants or various animals, currently. Over 1,000 antibiotics have been marked and characterized up to now, but only less than 100 of them are used in high quality medicines [2-7].

Although Sulfonamides series were the first antimicrobial to be developed for many of disease, recently clindamycin, Ampicillin, metronidazole, Azithromycin, sulfamethoxazole, trimethoprim Baxdela, Ticarcillin, are widely used for antibacterial agent [8] in the modern drug discovery. Therefore those antibiotics within sulfonamide-based compounds are the important antimicrobial agents and moreover, those are strongly used in human and veterinary medicines for preventing of bacterially infectious diseases [9]. The important but usually disregarded aspects of antibiotics application, is the fate of antibiotic residues entering the environments [9]. In this study increasing the efficiency of those antibiotics on penetrating to bacteria’s cell membrane for controlling both Gram positive and negative treatments have been investigated through halogenated functionalizing. First one a test resulting in the classification of bacteria has developed by “Hans Christian Gram” including gram positive bacteria and Gram negative bacteria [2]. Penicillin was discovered and characterized by Alexandre Fleming in September 1928 and has been used in the treatment of bacteria invasion. Fleming who were working at St. Mary’s Hospital London, left for holidays and put the culture of the sample in his lab and after coming back from the weekends, he founds an unusual phenomenon and treatment of the culture of microbes [10]. In the classification of antibiotic’s series which summarized as several different packages and groups, there are several important subjects such as; package “I” consist of (1)-Benzyl-penicillin including; Penicillin G, sodium benzyl-penicillin, benzyl-penicilline procaine penicillin-anti-staphylococcal (3)- Phenoxy & phenyl-penicilline (Penicillin V, Oxacillin, Flucloxacilline and Di-cloxacilline) (4)-Quinolones and Norfloxacine, package “II” consist of Ciprofloxacin, Enoxacine and Norfloxacine, package “III” consist [11-13] of Levofloxacin, package “IV” consist of: Moxifloxacine (5)-ß-Lactam/ß-lactamase inhibitors as an instance Ampicillin and Amoxicillin which are famous items[14]. In recent years; pharmaceutical antibiotic was recognized, sensitized and applied as emerging soil pollutants and some other factors while the molecules such as sulfonamide and tetracycline reach agricultural soil mostly through infecting dung of medicated chattel applied as muck.

As an essential antibiotic, sulfonamide might be mentioned; this is generally used the drug in primary care practices. Reaction for Sulfonamides is relatively general to compare with other antimicrobial [9]. The hypersensitivity reactions consist of fever and non-urticarial rashes; generally develop six up to fifteen days after the medication initiations. The term “sulfa” indicates to the derivatives of the antimicrobial agents. Clindamycin, metronidazole, Azithromycin, Sulfa-methoxazole, Trimethoprim Baxdela, Ticarcillin, Ampicillin are some other important antibiotics which have applied in the medicine and drug deliveries, widely. Ampicillin belongs to the penicillin groups with the beta lactam antibiotics and this kind antibiotics are able for penetrating Gram (+) and a few of them are Gram (-) bacteria. In this study, lists of halogenated compounds have been reported and exhibited based on approches and mechanism of the S-layers (including two different attachments); which for gram (+) is attached to the peptidoglycan and for gram

(-) is attached directly to the outer layers of bacteria. By this investigation, it has been concluded and resulted that through halogenated functionalizing of Sulfonamides, Triclosan, Baxdela Ticarcillin, Ampicillins and Clavulanic acids we are able to control the treatments and behaviors of those antibiotics against Gram-positives or negative bacteria. We exhibit clearly some halogenated compounds of those antibiotics (a specific chemical derived produced) are primarily against "Gram positive" bacteria (due to ahigher percentage of "peptidoglycan protein" in the cell membranes). Since Gram-positive bacteria which made of peptidoglycan has a very thick cell wall, some of the antibiotics are able to penetrate gram (+) and some others cannot. In this work, a list of antibiotics and their halogenated deviated have been set-upped due to the Gram-positive bacteria. It has been exhibited that the special properties of those antibiotics in view point of NMR shielding and S-NICS methods are important for delivering in cell membrane. Our studies have been done via QM/MM and AB-Initio methods.



Scheme 1. Optimized of DPPC and membrane simulation including 120 molecules of DPPC phospholipids

The residual phospholipids and cell membrane are negatively charged at physiological situations, where phosphate -dyl-glycerol (PG), or its derivative such as the same DPG (di-phosphate-idyl-glycerol) or CL, "Cardiolipine" are prevailing [15]. In addition, the phospholipids and cell membrane structures must be considered based on important items such as, whether the bacterium belongs to the class of Gram (-) or Gram (+) bacteria. The plasma of mammalian's membranes is built for stabilities through lipid's structures and high amount of sterols (scheme1&2).

Gram (+)'s bacteria has a single membrane including a thick peptidoglycan layer within some attached proteins and within different glycol-polymers such as poly-saccharides. Those layers encase their cytoplasmic of membranes and takes up the crystal violet stain used in the Gram staining methods.

In common, higher molecules of PE are placed in the cell membranes for Gram (-), while the cytoplasmic and some other components of Gram (+) are rich in PG. The lipid compound of various Gram (-) and Gram (+) are discussed in the result section based on halogenated functionalizing of those mentioned antibiotics.

Simulation of Lipid Bilayers: Although, precise structures of the bilayers which are in biological pertaining fluid phases are not possible for getting experimental data, fluctuations of those kinds of bilayers indicate correct structures. Molecular mechanics & Molecular dynamic modeling are strong tools for clearing and guiding the interpretation of those experimental sections. The credit of simulation, in other words, might be measured against existing experimental results. There are various and several technique and methods such as Deuterium NMR quadrupol splitting which can give certain results of physical & chemical properties such as membrane electrostatics area per lipid, membrane thickness and acyl parameters.

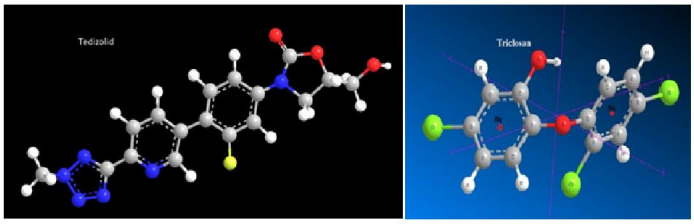


Fig. 1. Optimized (B3LYP-D3/TZP) structures of Triclosan and Tedizolid Using "Bq" inside the rings for S-NICS calculations.

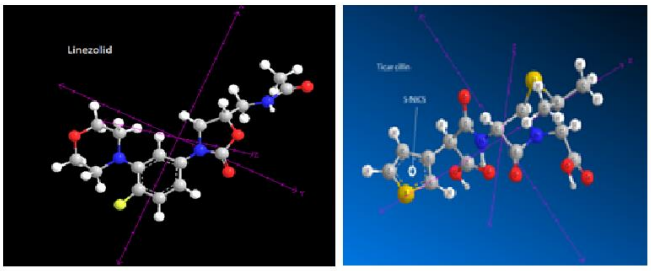


Fig. 2. Optimized (B3LYP-D3/TZP) structures of some antibiotics Using "Bq" inside the rings for S-NICS calculations

The absence of experimental data and results are reversed in molecular modeling of lipid membranes, due to several force fields parameterization. Tight level AB-initio estimation is needed

for definition and parameterization of those force fields and presently allows evaluation of the heavy atoms for gaining accurate results. Moreover, there are some limitations in weak QM calculations due to London's dispersion of non-bonded interactions for such molecules. We simulated our model based on our previous works [16-24].

2. EXPERIMENTAL SECTION

2.1. NMR shielding

The anisotropy parameter of the standard parameters, for the shielding and non-shielding space of the hetero rings in all antibiotics, (σ_{11}, σ_{22}, σ_{33}), are labeled according to the IUPAC instruction. Therefore, σ_{33} indicates the direction of minimum shielding, with the highest frequency, while σ_{11} indicates to the direction of maximum shielding, with the lowest frequency.

In addition, the orientations of the asymmetry tensors are given by ($\kappa = \frac{3a}{\Omega}$) (12) *and the skew is* $\kappa = \frac{3(\sigma_{1so}-\sigma_{22})}{\Omega}$ (13) ; (-1 ≤ κ ≤+1).

In our calculations of various halogenated antibiotic's rings, (κ) is basically positive, and the negative values are related to some critical or boundary points [25-27].

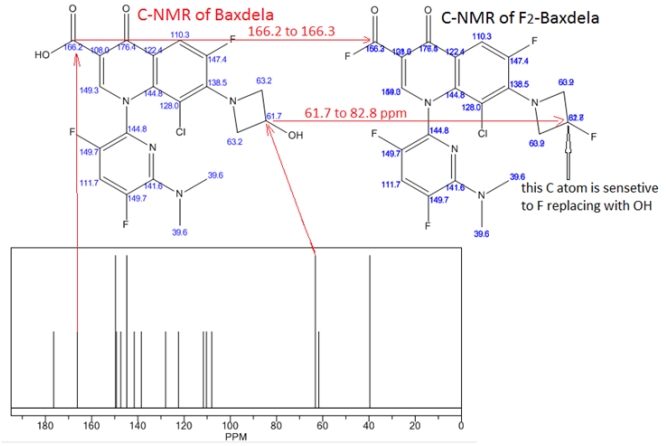


Fig. 3. NMR Shielding Changing of F_2-Baxdela compare to Baxdela and Cl-Triclosan compare to Triclosan.

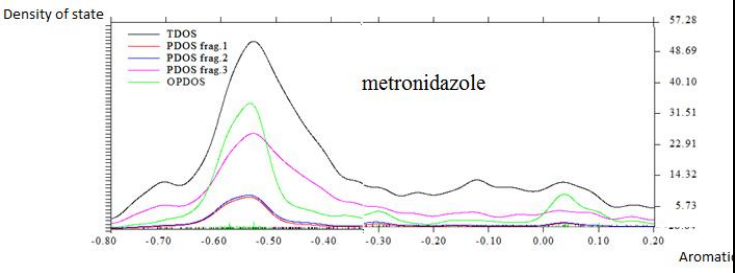


Fig. 4. Density of State vs. Aromaticity for Metronidazole

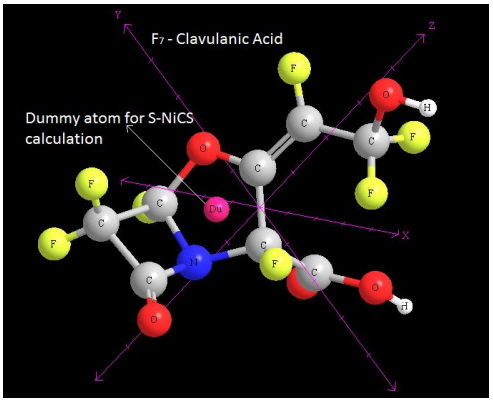


Fig. 5. S-NICS calculations including dummy atoms.

Energy density of hetero rings: Electron localization and chemical reactivity respectively have been built by Bader [28]. The electron densities of hetero rings have been defined as the following equation;

$(r) = \eta_i \left|\varphi_i(r)\right|^2 = \sum_i \eta_i \left|\sum_l C_{l,i}\,\chi_i(r)\right|^2$ (14). $\rho(r) = [(\frac{\partial\rho(r)}{\partial(x)})^2 + (\frac{\partial\rho(r)}{\partial(y)})^2 + (\frac{\partial\rho(r)}{\partial(z)})^2]^{\frac{1}{2}}$ (15) $\nabla^2\rho(r) = \frac{\partial^2\rho(r)}{\partial x^2} + \frac{\partial^2\rho(r)}{\partial y^2} + \frac{\partial^2\rho(r)}{\partial z^2}$(16)

The kinetic energies densities are not uniquely defined, since the value of kinetic energies operators $< \varphi \left| -\left(\frac{1}{2}\right)\nabla^2 \right| \varphi >$ (17) can be recovered by integrating kinetic energy density's definitions. One of a general used explanation is: $k(r) = -\frac{1}{2}\sum_i \eta_i \varphi_i^*(r)\nabla^2\varphi_i(r)$ (18) density, "G(r)" is also known as positive definite kinetic energy density.

$G(r) = \frac{1}{2}\sum_i \eta_i \left|\nabla(\varphi_i)\right|^2 = \frac{1}{2}\sum_i \eta_i\{[(\frac{\partial\varphi_i(r)}{\partial(x)})^2 + (\frac{\partial\varphi_i(r)}{\partial(y)})^2 + (\frac{\partial\varphi_i(r)}{\partial(z)})^2]\}$ (19). *K*(r) and *G*(r) are directly related by Laplacian of electron density $\frac{1}{4}\nabla^2\rho(r) = G(r) - K(r)$ (20) Becke and Edgecombe noted that the Fermi hole and then suggested electron localization function (ELF) [29]. ELF(r) $= \frac{1}{1+[D(r)/D_{0(r)}]^2}$ (21) where D(r) $= \frac{1}{2}\sum_i \eta_i \left|\nabla\varphi_i\right|^2 - \frac{1}{8}[\frac{\left|\nabla\rho_\alpha\right|^2}{\rho_\alpha(r)} + \frac{\left|\nabla\rho_\beta\right|^2}{\beta(r)}]$ (22) and $D_{0(r)} = \frac{3}{10}(6\pi^2)^{\frac{2}{3}}[\rho_\alpha(r)^{\frac{5}{3}} + \rho_\beta(r)^{\frac{5}{3}}]$ (23) for close-shell system, since $\rho_\alpha(r) = \rho_\beta(r) = \frac{1}{2}\rho$, *D* and *D*0 terms can be simplified as D(r) $= \frac{1}{2}\sum_i \eta_i \left|\nabla\varphi_i\right|^2 - \frac{1}{8}[\frac{\left|\nabla\rho\right|^2}{\rho(r)}]$ (24), $D_{0(r)} = \frac{3}{10}(3\pi^2)^{\frac{2}{3}}\rho(r)^{\frac{5}{3}}$ (25). Savin *et al.* have reinterpreted the ELF in view point of kinetic energies [30], which makes ELF also explaining for Kohn-Sham DFT wave-function. They show which *D*(r) reveals the excess kinetic energies densities caused by Pauli repulsion, while D_0can be considered as Thomas-Fermi kinetic energies density. Localized orbital locator (LOL) is another function for locating high localization regions likewise ELF, defined by Schmider and Becke in the paper [31].$LOL(r) = \frac{\tau(r)}{1+\tau(r)}$ (26), Where, $(r) = \frac{D_0(r)}{\frac{1}{2}\sum_i \eta_i \left|\nabla\varphi_i\right|^2}$ (Lu, T, 2012) (27)

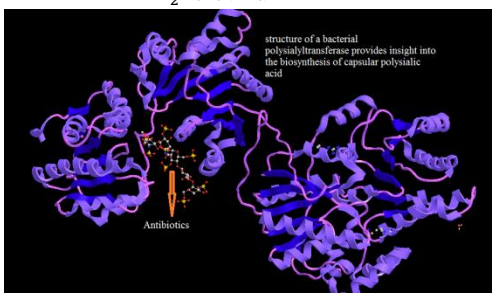


Fig. 6. Molecular Dynamic optimization on simulation of Membrane /protein/antibiotics

2.2. Computational details.

Tight & post-HF AB-initio calculations have applied and used for modeling the exchange-correlations energies of those hetero rings of the antibiotics structures with combination in a cell membrane of bacteria. The double ζ-basis sets within polarization orbitals (DZP) were applied for those hetero rings. The charges points and electrostatic potential-derived charges of those halogens atoms were also estimated using Merz-Kollman-Singh, chelp, or chelpG approches. Calculations were accomplished using packages of Gaussian 09 and GAMESS's AB-initio. The ONIOM methods including 3 levels towards high calculations (H), medium calculations (M), and low (L) have been accomplished in these studies. The B3LYP-D3/TZP, CAM-B_3LYP and M06 methods are applied for the higher layers of these models and the semi empirical methods of "Pm3MM" including pseudo=CEP and "Pm6" are applied for the medium and low layers, respectively. In the estimation of the calculations, we also have mainly focused on getting the optimized results for each item from "advanced DFT" methods including the "m06-L", "m062x", "m06-L", and "m06-HF" which are novel Meta hybrids DFTB. SPSS "Statistical Packages have applied for editing and analyzing all sorts of our S-NICS data of the heterocyclic antibiotics in this work.

The semi empirical methods have been used in order to treat the non-bonded interactions between two parts of cell membrane and antibiotic's molecules including lateral phospholipids side (P_+) and downer lateral phospholipids sides (P_-). The interaction energies for capacitor were estimated and calculated in all items according to the equation28:

$$E_S(eV) = \{E_C - (\sum_{i=1}^{60}(DPPC_+)_i + \sum_{i=1}^{40}(DPPC_-)_i) + \sum Antibiotics\ moleculs\} + E_{BSSE}$$

Where the "ΔE_S" is the stabilities energy of membrane-antibiotics systems.

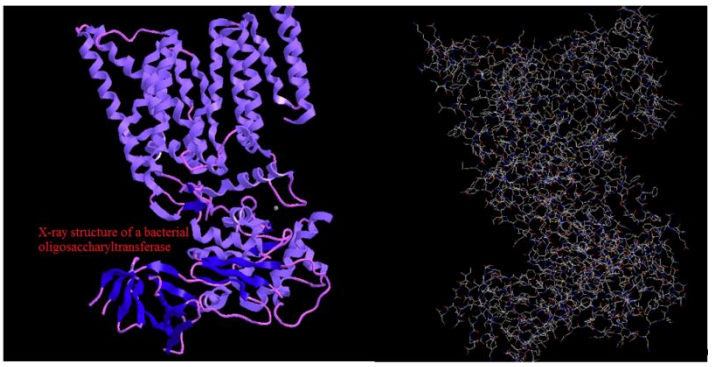


Fig. 7. Structure of OligoSaccharyltransferase bacterial

3. RESULTS AND DISCUSSION

By this work, we have simulated and modeled those mentioned antibiotic's properties through the QM//MM calculations based on specific chemical derived produced. Since Gram-positive bacteria which made of peptidoglycan has a large thick cell wall, some of the antibiotics are able to penetrate gram (+) and some others cannot. The data and results are listed in 7 figures and 3 tables. By this investigation, we have exhibited a statistical method by computing of nucleus-independent chemical shifts in point of probes (BQ) motions around the center of shielding and de-shielding spaces of antibiotic's hetero-rings. In the previous works, it has been exhibited that S-NICS approaches are the most suitable methods for calculation of the Aromaticityies in the non-benzene rings such as those halogenated antibiotics. The S-NICS Aromaticity is an important index for membrane /Protein / antibiotics interactions (Fig.7).

Table 1: S-NICS, Charge (ESP), isotropy, span and aromaticity of some atoms of Azithromycin and clindamycin

Azithromycin							Clindamycin						
Atom	Charge	σiso	S-NICS	η	Δδ	Ω	atom	charge	σiso	S-NICS	η	Δδ	Ω
14 O	-0.16	66.4	126.8	0.7	144.8	96.5	13 O	-0.36	157.2	156.3	0.8	-5.8	4.2
16 N	-0.35	159.	162.0	0.98	-11.98	-7.93	12 N	-0.33	156.1	157.2	0.8	-16.3	11.4
18 C	-0.33	156.	157.2	0.8	-16.3	11.4	10 C	-0.36	157.2	156.3	0.8	-5.8	4.2
17 O	-10.5	0.17	28.6	11.6	0.80	-10.5	15 O	-0.69	245.2	250.4	0.58	50.4	33.6

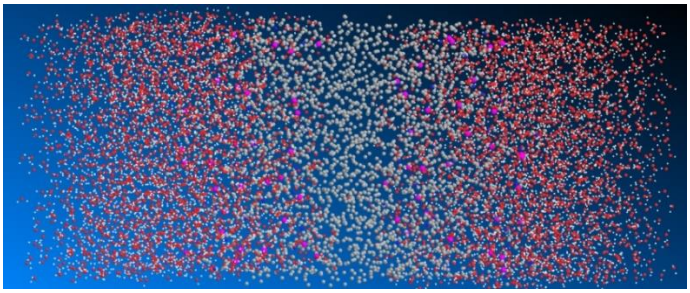
Table 2. S-NICS, Charge (ESP), isotropy, span and aromaticity of some atoms of metronidazole and sulfamethoxazole

Metronidazole							Sulfamethoxazole						
Atom	Charge	σiso	S-NICS	η	Δδ	Ω	Atom	Charge	σ-iso	S-NICS	η	Δδ	Ω
12 C	-0.34	157.3	150.9	0.8	-22.9	15.3	10 C	-0.4	167.0	154.5	0.1	-120.6	113.7
20 N	-0.67	248.3	246.93	0.1	-240.6	227.0	14 N	0.13	29.7	30.1	0.53	10.15	6.7
21 O	0.32	65.27	63.7	0.2	93.78	62.5	16 O	-0.19	130.3	129.7	5.9	9.53	-26.9
23 H	0.23	67.9	67.0	0.4	97.0	64.6	18 H	0.242	120.2	122.1	0.28	36.13	24.09

Table 3. S-NICS, Charge (ESP), isotropy, span and aromaticity of some atoms of trimethoprim and Baxdela.

Trimethoprim							Baxdela						
15 N	-0.33	156.1	157.2	0.8	-16.3	11.4	14 N	-0.21	147.0	145.1	0.5	-19.6	-13.0
24 O	168.3	162.9	0.1	-120.7	113.8	17 O	20 O	-0.16	66.4	126.8	0.7	144.8	96.5
18 C	248.3	246.93	0.1	-240.6	227.0	13 O	13 C	0.13	78.2	79.2	0.2	139.2	92.8
12 C	0.14	30.7	27.1	0.5	-9.2	-6.1	18 C	0.16	30.1	29.9	0.7	-6.0	4.6
18 H	0.15	29.6	30.8	0.4	-2.7	2.5	14 H	0.12	30.0	6.8	0.8	-7.4	-4.9
10 N	-0.67	248.3	246.93	0.1	-240.6	227.0	17 N	-0.16	66.4	126.8	0.7	144.8	96.5

Based on equations 1-4 and the data in the Tables 1-3, isotropies and asymmetry (η) have been estimated for those Gram (+) antibiotics and Gram (-) such as E Coli. The Molecular Dynamic optimization of those antibiotics with E-coli [gram (-) classification] membrane /protein / antibiotics, have been estimated and calculated through the QM/MM simulation with CHARMM force fields and anisotropy has been yielded from the equation (4). We have modeled a section of membrane systems including di-palmitoyl-phosphatidyl -choline $(DPPC)_n$ via those mentioned methods using Monte Carlo. Each system was combined of sixty lipids surrounding with water. Thermodynamic averages were calculated from those methods, as the minimum-energy structures which indicate the resistance of membrane /protein/antibiotics. E Coli which includes LPS, Lipoprotein, Porins and peptidoglycan, is a famous bacteria in Gram (-) groups. By this work, through halogenation of antibiotics (Table. 5), we exhibited that by changing the aromaticity (total S-NICS value) the bacterial resistance might change due to a relation between S-NICS and resistance.



Scheme 2. DPPC phospholipids

This study is also focused on the electron density of Halogens which is replaced with hydrogen of Ampicillin, Clavulanic acid, Imipeneme, Penicillin and Ticarcillin in point of view in S-NICS method. The largest electron localization is located on halogen

atoms which indicate the suitable changing of aromaticity and consequently the resistance.

4. CONCLUSION

A good result of the theoretical analysis of antibiotics- S-NICS methods is the stable model for drug designing. In this work, a relation between aromaticity and resistance of antibiotics has been exhibited. This resistance is due to membrane potential changing with different compositions of antibiotics-lipids interaction or further affects the interactions with antimicrobial peptides.

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