Investigation of Electronic Structure - Bioactive Nature Relation in Niacin Derivates by DFT Calculations and Molecular Docking

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Abstract

Nicotinic acid (Niacin), also known as vitamin B3, is an organic compound primarily used in treatment of high cholesterol along with many other pharmaceutical features. Cholesterol is transferred in blood plasma via lipoproteins that can exist in various types. Therefore, investigation of interactions between niacin and these proteins is vital. Thus, this study focuses on exploration of electronic structure of niacin and its derivatives, namely nicotinic acid N-oxide, 2-chloro, 6-chloro, 2-bromo-, and 6-bromonicotinic acid, and their molecular docking characteristics with lipoproteins. Electronic structure features were calculated at DFT-B3LYP/6-311(d, p) level of theory. Molecular docking properties were determined by the scoring technique based on chemical potential and total energy based calculations. Dependence of binding affinities in docking on halogen, position of halogen in substitution, and oxygen at the nitrous group was investigated. The relations among the electronic structures, spectroscopic features, and docking characteristics were obtained. Moreover, reactive sites causing binding affinities in niacin derivatives were investigated by Fukui analysis.

Keywords —DFT, Electronic structure, Fukui analysis, Molecular docking, Niacin derivatives.

1 Introduction

Nicotinic acid (Niacin), also known as Vitamin B3, is a member of pyridine carboxylic acids. It has the molecular formula of $C_6H_5NO_2$ and 3-pyridine carboxylic acid as formal name. Niacin and many similar pyridine carboxylic acids have great importance in biological and pharmacological applications. Proper functioning of the body, especially digestion system, requires medication of the body with niacin at appropriate dozes. Actually, this vital molecule is produced by the metabolism according to needs of the body, however, it may not be satisfactory in some cases especially high cholesterol foods are consumed or overstressed situations. Mild deficiency of niacin in metabolism may results in indigestion, fatigue, canker sores, vomiting, poor circulation, and depression symptoms. Even some pellagra cases may be observed if the deficiency is so high [1-5].

Recently, niacin has become highly popular in treatment of cholesterol depended health issues. Niacin, when used at pharmacological dozes, lowers the level of total cholesterol, low density lipoprotein (LDL), and Lipoprotein A, and increases the level of high density lipoprotein (HDL). It especially triggers the change in the Apolipoprotein (Apo A1) level significantly [6]. Circulation of niacin in the metabolism is achieved by holding on these proteins that exist in the blood plasma, so become very effective in reducing the fatal and coroner events.

It is highly possible that niacin derivatives can also

show similar type of activities. Therefore, numerous studies have been conducted on investigation of structural and spectroscopic features of these type ligands [1-3, 7-9]. In those studies, isolated ligand molecules were investigated in monomeric or dimeric forms, and rarely in comparison among similar types. General methodology followed in previous studies is determination of geometrical structures using X-ray crystallography, FT-IR, Raman, UV-Vis, ^{1}H and ^{13}C NMR spectroscopies, and computation of the same properties obtained experimentally and further detailed information such as nonlinear optical properties, visualization of molecular orbitals, and population densities by using quantum chemistry calculations.

Notwithstanding, previous studies have brought out some indirect explanations on the active nature of isolated ligands, this study provides more direct and felicitous explanations through Fukui function analysis and molecular docking techniques. Molecular docking methodologies used in this study are based on both chemical potential based scoring function and total energy based scoring function. Niacin derivatives of this study, seen in Figure 1, were selected in such a way that the effect of halogen in the structure and the position of that on the docking mechanism or energetics can be discussed. Human apolipoprotein A I (PDB ID: 1av1) was used as target macromolecule because it is a carrier of the niacin in blood plasma. 1av1 has a nearly symmetric structure as seen in Figure 2 [10].

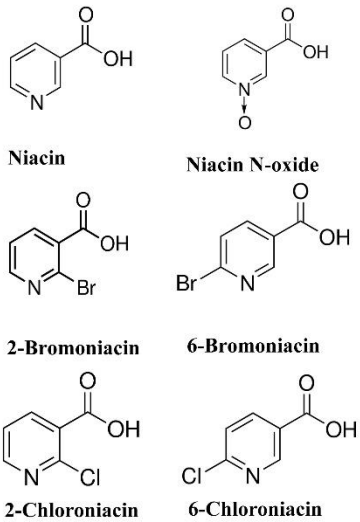


Figure 1: Niacin derivatives of this study

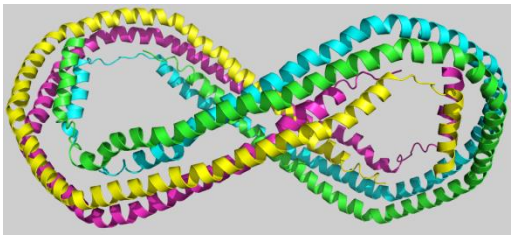


Figure 2: The crystal structure of human apolipoprotein A-I (pdb code: 1av1)

Study is organized as follows: computational and analysis techniques are given in Section 2. Section 3 starts with conformational analysis of molecules to determine the lowest energy states. Using quantum chemical calculations, some properties that are related to binding affinities in molecular docking and dynamic of molecules such as total energies, Gibbs free energies, vibrational energies, nonlinear optical properties of these optimized structures were presented. Electrostatic surface properties and electrophilic or nucleophilic regions were further analyzed using Fukui analysis and condensed dual descriptor, thus binding situations to protein structure were explored. Section 3 ends with the report of results obtained in molecular docking studies.

2. Methods

Conformational analysis and frequency depended calculations were carried out using Gaussian 09 program [11] and the structure properties were visualized in Gauss View 5.0 [12]. B3LYP [13] hybrid functional was used with 6-311G(d,p) basis set in DFT [14] calculations. This calculation set is in accordance with the previous studies [15-17] that focus on the individual study of molecules explored here. Reactive site on the molecular surfaces were determined on the basis of Fukui function analysis [13] using Multiwfn_3.3.8 [18] program. Molecular docking situations were explored via Lamarckian Generic Algorithm (LGA) [19] in Autodock Vina [20] and Pharmacological Scoring Function [21] in iGEMDOCK [22].While only the binding affinities were determined in AutodockVina, iGEMDOCK was employed in determination of binding energies, stability of docking method, and interactions in binding sites.

3. Results and Discussions

3.1. Conformational analysis

Niacin molecule has a carboxylic group that can be oriented in four possible ways; two ways depending on the orientation of hydroxyl group whether towards the ring or away from the ring, and two ways depending on the position of hydroxyl fragment in the group. Among these configurations, it is no doubt that the hydroxyl fragment would always point away from the ring, thus only two higher stability conformations can be taken as Conf1 and Conf2 as shown in Figure 3. This situation is valid for the other molecules studied here, too. Another issue is the symmetry of these conformations. Depending on whether molecules are planar or not, each conformation can be in the Cs or in the C1 symmetry group. Deviations from highest symmetry or flexibility in conformational changes are, in fact, play important role in molecular docking studies.

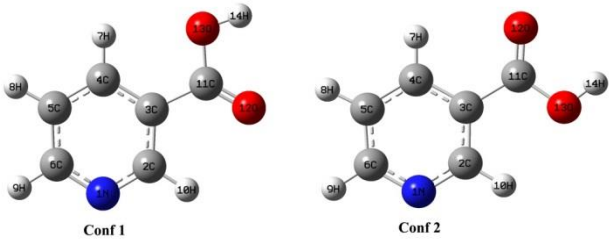


Figure 3: Two higher stability conformations of Niacin

Table 1 contains the conformational energies of the most possible conformations and the symmetry of these conformations.

Table 1: Conformational energies and symmetry situations of the ligands

Molecules	*Conf.*	*Sym.*	*Energy (Hartree)*	*Energy (kcal/mol)*
Niacin	Conf2	C_1	*-436.977*	*-274204.09*
NiacinNO	Conf2	C_1	-512.159	-321381.16
2-ClNiacin	Conf2	C_s	-896.590	-562612.82
6-ClNiacin	Conf2	C_1	-896.600	-562619.25
2-BrNiacin	Conf1	C_1	-3010.509	-1889103.57
6-BrNiacin	Conf2	C_s	-3010.520	-1889110.51

Conformational energies of ligands differ significantly. Energies of ligands with bromide atom are nearly seven times lower than that of niacin. Energy of NiacinNO is also lower than that of niacin; however, difference is not as sharp as in the case of halogenated ligands. The energies do not show a significant dependency on the positioning of the halogens. Discussion on these energies will be considered when the docking results are reported to explore whether there is any correlation between them. Interestingly, 2-BrNiacin prefers to be in Conf1 while the other ligands are in Conf2. It is most probably due to electron cloud around the bromide atom is being larger and repels the hydrogen atom more than chloride atom in 2-ClNiacin. Actually, the energy difference between Conf1 and Conf2 of 2-BrNiacin is only 0.0670 kcal/mol, but we prefer to consider the Conf1 over Conf2 because it might be highly important in reactivity of the molecule. Moreover, in terms of symmetry, ligands are prone to be in C_1 symmetry except 2-ClNiacin and 6-BrNiacin which are planar. The final optimized structures are given in Figure 4

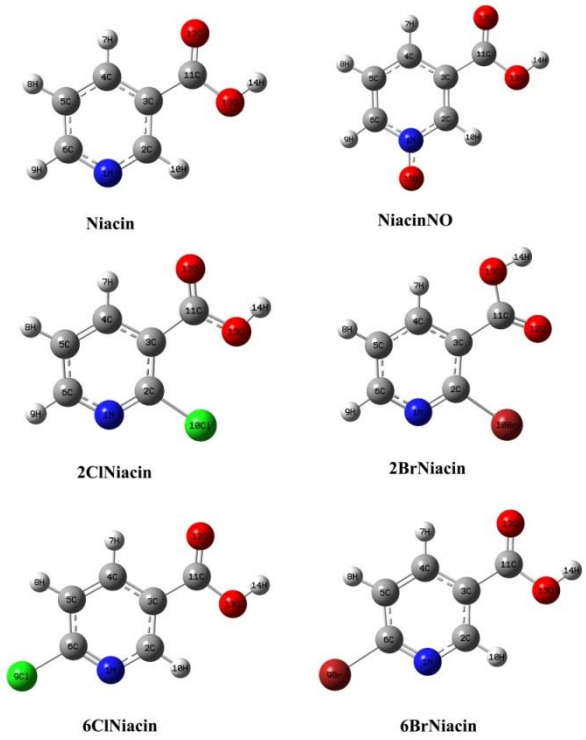


Figure 4: Optimized structure of niacin derivatives studied in this work

3.2. Thermal Properties

Thermal properties might play a critical role in understanding the reactivity and docking situations. We basically considered four thermal parameters and explored their dependency on the structures: sum of electronic and thermal free energies, thermal energies, heat capacity, and entropy.

Free energies have the similar trend with the conformational energies i.e. bromide ligands has the lowest energy, chloride energies are at lower energy, N oxide has slightly lower in energy than niacin. Thermal energies are nearly the same for halogenated ligands (≅64 kcal/mol), and higher for Niacin (≅69 kcal/mol), and the highest for NiacinNO (≅73 kcal/mol). This distribution is directly a reflection vibrational contribution to the total thermal energy, because translational and rotational energies were calculated to be the same for all ligands. Interestingly, heat capacity and entropy do not show analogy with total thermal energy. Halogenated ligands have total heat capacity as high as NiacinNO (≅30 cal/mol.K) except 2-ClNiacin (≅28 cal/mol.K). Heat capacity of niacin (≅26 cal/mol.K) is the lowest among all. Finally, the entropy of ligands with bromide is the highest, and that of niacin is the lowest. Entropy consideration does not give any logical order such as dependent of position of the halogen on the ring or type of it.

3.1. Optical Properties

Non-linear optical (NLO) properties are highly important in understanding the dynamics of materials and respond to external excitations. Because the protein molecule is a sort of an external field source for the ligand molecule, the positioning of the ligand in such an environment is very dependent on how the ligand will respond to that field.

For the purpose of qualitative description of nonlinear properties of niacin and its derivatives, the electric dipole moment, polarizability, anisotropy of polarizability, and first hyperpolarizability were determined theoretically. Frequency calculations generate the polarizability (α_{xx}, α_{xy}, α_{yy}, α_{xz}, α_{yz}, α_{zz},) and hyperpolarizability (β_{xxx}, β_{xxy}, β_{xyy}, β_{yyy}, β_{xyz}, β_{xzz}, β_{yzz}, β_{zzz},) tensors in atomic units. The mean polarizability (α_0), anisotropy of polarizability ($\Delta\alpha$) and the average of first hyperpolarizability (β) can be calculated via equations 1-3.

$$\alpha_0 = \frac{1}{3}\left(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}\right) \quad (1)$$

$$\Delta\alpha = \frac{1}{\sqrt{2}}\left[\left(\alpha_{xx} - \alpha_{yy}\right)^2 + \left(\alpha_{yy} - \alpha_{zz}\right)^2 + (\alpha_{zz} - \alpha_{xx})^2 + 6\alpha_{xz}^2 + 6\alpha_{xy}^2 + 6\alpha_{yz}^2\right]^{\frac{1}{2}} \quad (2)$$

$$\langle\beta\rangle = \left[\left(\beta_{xxx} + \beta_{xyy} + \beta_{xzz}\right)^2 + \left(\beta_{yyy} + \beta_{yzz} + \beta_{yxx}\right)^2 + \left(\beta_{zzz} + \beta_{zxx} + \beta_{zyy}\right)^2\right]^{\frac{1}{2}} \quad (3)$$

Result of these calculations are listed in Table 2 in electronic units (esu) which converted from a.u. through the conversion factors of 1 a.u.=0.1482x10^{-24} esu for polarizabilities and 1 a.u.=8.6393x10^{-33} esu for molecular hyperpolarizability along with the total dipole moment given by Equation (4).

$$\mu_{total} = \left(\mu_x^2 + \mu_y^2 + \mu_z^2\right)^{\frac{1}{2}} \quad (4)$$

Table 2: Nonlinear optical properties of the ligands

Optical Properties	Urea	Niacin		NiacinNO		2-ClNiacin		2-BrNiacin		6-ClNiacin		6-BrNiacin	
μ_{total}	1.5	0.2	0.1	0.9	0.6	0.8	0.5	1.7	1.1	0.7	0.5	0.6	0.4
α_0	5.0	10.7	2.1	12.1	2.4	12.5	2.5	13.4	2.7	12.8	2.5	13.8	2.7
$\Delta\alpha$	9.9	28.1	2.8	27.2	2.8	31.0	3.1	33.9	3.4	38.1	3.9	26.6	2.7
$\langle\beta\rangle$	780.3	1403.4	1.8	3017.2	3.9	2431.7	3.1	3405.2	4.4	5673.0	7.3	6918.4	8.9

NLO properties of urea have been used as a standard to decide whether the molecules show nonlinear optical properties. Therefore, each column reserved for the ligands is split into two; the second columns made bold show the ratio of the properties of the ligand to that of urea. Highest ratios were obtained for the average first hyperpolarizability for all lig

ands except niacin which shows the highest ratio in anisotropy of polarizability with

($\Delta\alpha_{niacin}/\Delta\alpha_{urea} = 2.8$). The average first hyperpolarizability of ligand shows a position and halogen dependency as well; ligands halogenated from sixth carbon have approximately two times larger $\langle\beta\rangle$ than

that from second carbon and halogenation with bromide results in higher $\langle\beta\rangle$ values than with chloride. Average polarizabilities of all ligands are nearly the same, and dipole moments are weaker than that of urea except 2-BrNiacin ($\mu_{total_{niacin}}/\mu_{total_{urea}} = 1.1$). Overall, all niacin derivatives show higher nonlinear optical properties than niacin; therefore, interactions with external excitations and their reorientation in an environment are supposed to be more probable.

3.2. Reactive site analysis

Determination of reaction sites from DFT calculation is based on average local ionization energies on the molecular surfaces [23]. Here, we used Fukui function analysis to be more deterministic in assignment of nucleophilic, electrophilic, and radial attack regions by using optimized structures of anion and cation forms of the ligand as well as its neutral form. Fukui function [13] is defined as

$$f(\boldsymbol{r}) = \left[\frac{\partial\rho(r)}{\partial N}\right]_{\nu} (5)$$

where N is number of electrons in the present system, the constant term ν in the partial derivative is external potential. Using the electron density from anion (N+1), neutral (N), and cation (N-1) forms of the ligands, attack region can be calculated as

Nucleophilic attack: $f^{+}(\boldsymbol{r}) = \rho_{N+1}(\boldsymbol{r}) - \rho_{N}(\boldsymbol{r})$ (6)

Electrophilic attack: $f^{-}(\boldsymbol{r}) = \rho_{N}(\boldsymbol{r}) - \rho_{N-1}(\boldsymbol{r})$ (7)

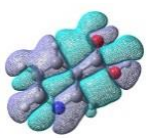
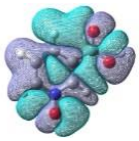
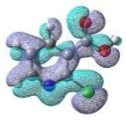
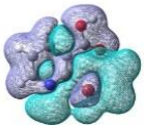
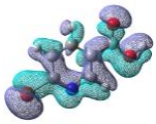
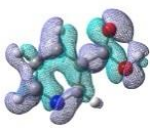
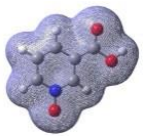
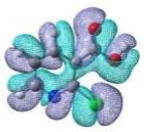
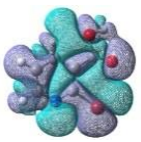
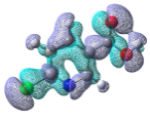
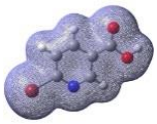
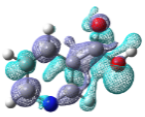
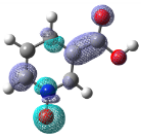
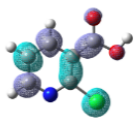
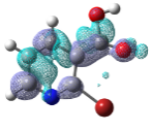
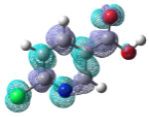
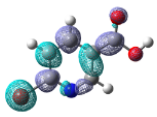
Radial attack: $f^{0}(\boldsymbol{r}) = [f^{+}(\boldsymbol{r})/f^{-}(\boldsymbol{r})]/2$ (8)

The difference in nucleophilic and electrophilic characters $\Delta f(\boldsymbol{r}) = f^{+}(\boldsymbol{r}) - f^{-}(\boldsymbol{r})$ is defined as dual descriptor which is a simultaneous representation of both effects. Dual descriptor can be approximated to the difference in the spin density of cation and anion state as

Dual descriptor from spin states: $\Delta f(\boldsymbol{r}) \approx \rho^{s}_{N+1}(\boldsymbol{r}) - \rho^{s}_{N-1}(\boldsymbol{r})$ (9)

Positive and negative values of $\Delta f(\boldsymbol{r})$ gives the nucleophilic and the electrophilic regions in a molecule. Table 3 includes the surfaces for $f^{+}(\boldsymbol{r})$, $f^{-}(\boldsymbol{r})$, and $\Delta f(\boldsymbol{r})$ having visualizations taken at the same isosurface value of 0.003 with green indicate the positive and purple is for negative values.

Table 3: Isosurface of Fukui functions and dual descriptor

Visual state	Niacin	Niacin-NO	2-ClNiacin	2-BrNiacin	6-ClNiacin	6-BrNiacin
Electrophilic attack						
Nucleophilic attack						
Dual Descriptor:						

Interestingly, whole surface of NiacinNO and 6-BrNiacin is appropriate for nucleophilic attacks. Oxygens in carboxyl groups and on the ring in NiacinNO are always candidate for nucleophilic attack as expected due to lone electron pair on them. According to dual descriptor surfaces, halogens are the highly attractive regions except for 2-BrNiacin because the orientation of carboxyl group in this ligand is different from that of the others. In the case of 2-BrNiacin, a special region between bromide and carboxyl group appears to be nucleophilic. This suggests that chemical reactivity of this ligand might

show different aspects.

Another way of using this analysis is to obtain atomic charges from population analysis, and calculate condensed Fukui functions and dual descriptor for individual atoms in molecules. Charge densities in equations (6-9) are replaced with the atomic charges in these calculations. Atomic charges can be obtained from different ways such as Mulliken, Löwdin, Becke, and Hirshfeld population analysis. We've preferred using Hirshfeld charges because it is more basis set independent, thus results would be less biased by the calculations. Condensed dual descriptor values for individual atoms in molecules are tabulated in Table 4. The table is separated in two sections; atoms in ring and in carboxyl group. Condensed dual descriptor maxima and minima are highlighted with pink and blue, respectively. Minima are located in halogens in ligands with chloride, bromide, and oxygenated. A minimum for Niacin is on the nitrogen in the ring. These results are expected commonly because the electronegativities of halogens (Cl: 3.16, Br: 2.96), oxygen (3.44), and nitrogen (3.04) are higher than that of carbon (2.55) and hydrogen (2.20) atoms. Interestingly, the bromide atoms are more nucleophilic than chloride atoms in our case, and the nucleophilic character of nitrogen and oxygen is nearly the same. The most electrophilic atom is the carbon atom in the carboxyl group in general. In the case of 2BrNiacin, however, the maximum occurs in the sixth carbon on the ring.

Table 4: Condensed dual descriptor values of atoms in molecules

Niacin		Niacin-NO		2-BrNiacin		2-ClNiacin		6-BrNiacin		6-ClNiacin	
Atom	**Δf**	**Atom**	**Δf**	**Atom**	**Δf**	**Atom**	**Δf**	**Atom**	**Δf**	**Atom**	**Δf**
N	-0.184	N	0.016	N	0.014	N	0.006	N	0.012	N	-0.021
C	-0.012	C	-0.034	C	0.010	C	-0.034	C	-0.022	C	-0.015
C	0.014	C	0.025	C	0.062	C	-0.017	C	-0.033	C	-0.025
C	0.029	C	-0.056	C	0.034	C	0.040	C	0.036	C	0.034
C	-0.011	C	0.005	C	0.010	C	-0.067	C	-0.035	C	-0.020
C	0.050	C	0.014	C	0.065	C	0.029	C	0.031	C	0.029
H	0.003	H	-0.007	H	0.006	H	0.005	H	0.006	H	0.005
H	-0.005	H	0.000	H	0.009	H	-0.007	H	-0.002	H	-0.001
H	-0.015	H	0.003	H	0.018	H	0.007	Br	-0.181	Cl	-0.092
H	-0.026	H	-0.008	Br	-0.222	Cl	-0.139	H	0.000	H	-0.004
		O	-0.183								
C	0.068	C	0.082	C	0.040	C	0.069	C	0.074	C	0.063
O	0.033	O	0.071	O	-0.030	O	0.042	O	0.052	O	0.009
O	0.041	O	0.052	O	-0.015	O	0.050	O	0.044	O	0.027
H	0.015	H	0.020	H	-0.001	H	0.017	H	0.018	H	0.011

3.3. Molecular Docking

Docking investigations were performed on two different platforms; Autodock Vina [20] and iGEMDOCK [22]. Autodock Vina uses a scoring function on the basis of Gibbs free energy within the Lamarckian Generic Algorithm. iGEMDOCK, on the other hand, uses Generic Evolutionary Method with an empirical scoring function that is obtained from nearly thousand protein-active complexes interaction profiles. Both cases, the energies are defined in terms of three basic interactions; electrostatic, hydrogen bonding, and Van der Waals. Table 5 summarizes the docking energies given in kcal/mol. Autodock results suggest that docking energies very close to each other and do not show any dependency to halogen or position of the halogen on the ring. However, chemical reactivity analysis and exploration of NLO properties indicates that niacin derivatives have tendency to be docked with higher energies. A quick docking in iGEMDOCK indicates that halogenated ligands nearly 30% higher docking capability than niacin. Quick docking methodology, however, takes the accuracy at the lowest level. A step

forward analysis with standard settings of the program generates totally different results. Therefore, we performed this docking study with five different settings of population size-number of generations-number of solutions settings until we obtain a reproducibility of results. Stable docking settings suggested by the program, for example, produces similar results with the quick docking results in terms of ordering of docking energies, but significant differences in energy values. Variations in the results indicate that the number of solutions searched is the most critical parameter. Two further docking were performed with Custom1 and Custom2 settings, which generated the same ordering of docking energies and very close values.

Table 5: Comparison of molecular docking results

Autodock Vina		***iGEMDOCK : Population size, Generations, Number of solutions***			
Lamarckian		**Quick: 150, 70, 1**		**Standard : 200, 80,2**	
6-BrNiacin	-5.9	6-ClNiacin	-70.1257	2-ClNiacin	-70.6338
NiacinNO	-5.6	2-ClNiacin	-70.1036	Niacin	-69.3058
2-ClNiacin	-5.5	6-BrNiacin	-68.6039	6-BrNiacin	-68.4331
Niacin	-5.5	2-BrNiacin	-64.0913	6-ClNiacin	-67.7666
2-BrNiacin	-5.2	NiacinNO	-56.6055	2-BrNiacin	-66.4337
6-ClNiacin	-5.1	Niacin	-53.3964	NiacinNO	-63.9057
iGEMDOCK : Population size, Generations, Number of solutions					
Stable:300,80,10		**Custom1: 300, 80, 20**		**Custom2: 300, 80, 40**	
6-ClNiacin	-73.8272	6-ClNiacin	-74.6879	6-ClNiacin	-74.9559
2-ClNiacin	-72.7254	NiacinNO	-74.4013	NiacinNO	-74.4345
6-BrNiacin	-72.2856	6-BrNiacin	-73.6022	6-BrNiacin	-74.0587
2-BrNiacin	-71.2073	2-ClNiacin	-72.2046	2-ClNiacin	-72.7759
NiacinNO	-70.9625	2-BrNiacin	-70.05	2-BrNiacin	-71.2326
Niacin	-69.8142	Niacin	-69.2472	Niacin	-70.1515

Interaction energies resolved in terms of their type from the Custom2 settings and the lowest energy poses are given in Table 6. Overall evaluation of the results shows that the most important factor in determination of bioactivity is the position of active atoms in molecules. All ligand have two distinct region that can play role in interactions; carboxyl group and nucleophilic atoms (halogens, oxygen, or nitrogen). The further this region from each other, the higher the docking possibility and energy is obtained. This result is in consistency with the results of analysis of NLO properties. Secondly, it is shown that the bioactivity is closely related to electronegativity of halogen in the structure. Binding affinities of ligands with the chloride are higher than that of ligands with bromide.

Interaction energy profile also shows that the niacin derivatives establishes two or three times more hydrogen bonding and electronic interactions are totally different from niacin. This indicates that binding sites in the protein structure is not the same. Figure 5 shows the docking situations of the ligands and their geometries in binding sites.

Binding sites differ on the basis of position of halogen on the ring. 6ClNiacin and 6BrNiaicin are docked to the same site as 2ClNiacin and 2BrNiacin do. Ligand molecules also experience some structural modifications at binding sites. Orientation of hydroxyl fragment of carboxyl group in Niacin is reversed in comparison to the optimized structure in isolated state as shown in Figure 4. The same effect appears in 6ClNiacin and 6BrNiacin ligands as well. NiacinNO and 2BrNiacin do not experience any significant structural changes. As oppose to the situation of 2BrNiacin, 2ClNiacin experiences a deprotonation, and becomes a carboxylate ligand. Whether these structural changes affect the behavior of the

protein is a question that can be answered from pharmacological perspective only. Our investigations answers to the question of how these niacin derivatives docks to the structure, what type of interactions exist between protein and ligands, and what are some relations between electronic structure features of the ligands and the docking situations to Apolipoprotein A I.

Table 6: Energy analysis for the best docked poses by Custom2 processes

Protein	Ligand	Total Energy	VDW	H-Bond	Electronic
1AV1	6-ClNiacin, pose #12	-74.9559	-45.72	-26.8299	-2.40604
1AV1	NiacinNO, pose #2	-74.4345	-55.2428	-15.1524	-4.03939
1AV1	6-BrNiacin, pose #7	-74.0587	-45.1902	-26.4361	-2.43243
1AV1	2-ClNiacin, pose #28	-72.7759	-48.5619	-21	-3.21396
1AV1	2-BrNiacin, pose #22	-71.2326	-46.9451	-20.9167	-3.37082
1AV1	Niacin, pose #17	-70.1515	-63.8302	-7	0.678664

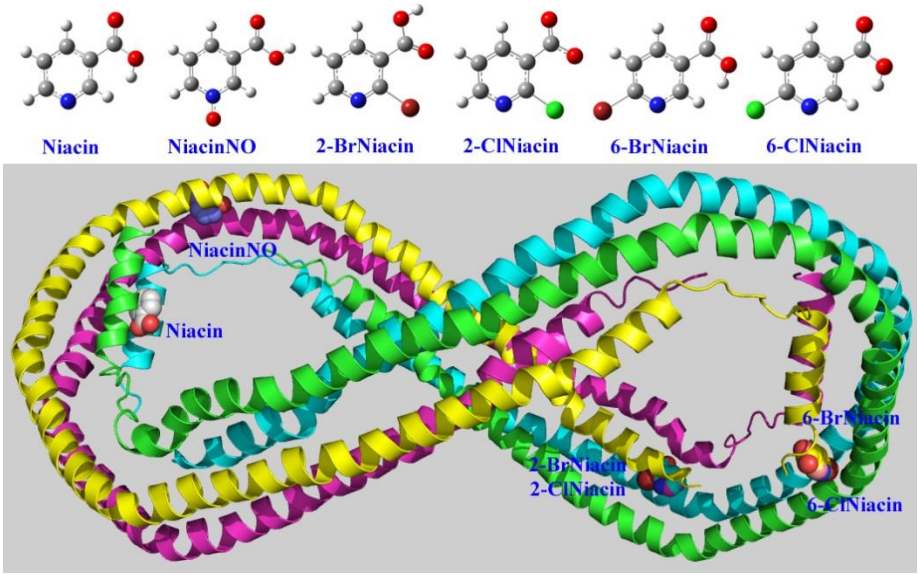


Figure 5: Molecular docking binding sites for niacin and derivatives, and their geometries as best docked poses

Conclusions

Geometrical structure, thermal, nonlinear optical, and reactivity properties of niacin, niacin N-oxide, and four halogenated niacin derivatives were investigated. Former features were obtained from DFT calculations directly, and reactive nature was explored by Fukui function analysis from both sur

face mapping of nucleophilic/electrophilic regions and dual descriptor values calculated on the basis of Hirshfeld population analysis. Using Autodock Vina and iGEMDOCK, possible docking situations were investigated. While the Autodock does not indicate any dependency on the structure of ligands, iGEMDOCK results show that the most important factor in determination of bioactivity is the position of active atoms in molecules and the tightness of docking is depend on the electronegativity of halogen in the structure.

References

[1] Karabacak, M., S. Bilgili, and A. Atac. Molecular structure investigation of neutral, dimer and anion forms of 3,4-pyridinedicarboxylic acid: A combined experimental and theoretical study. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2015; 135(0): 270-282.

[2] Nataraj, A., V. Balachandran, T. Karthick, M. Karabacak, and A. Atac. FT-Raman, FT-IR, UV spectra and DFT and ab initio calculations on monomeric and dimeric structures of 3,5-pyridinedicarboxylic acid. Journal of Molecular Structure, 2012; 1027(0): 1-14.

[3] Koczoń, P., J.C. Dobrowolski, W. Lewandowski, and A.P. Mazurek. Experimental and theoretical IR and Raman spectra of picolinic, nicotinic and isonicotinic acids. Journal of Molecular Structure, 2003; 655(1): 89-95.

[4] Hamoud, S., T. Hayek, A. Hassan, E. Meilin, M. Kaplan, R. Torgovicky, and R. Cohen. Niacin Administration Significantly Reduces Oxidative Stress in Patients With Hypercholesterolemia and Low Levels of High-Density Lipoprotein Cholesterol. The American Journal of the Medical Sciences, 2013; 345(3): 195-199.

[5] Kamanna, V.S. and M.L. Kashyap. Mechanism of Action of Niacin. The American Journal of Cardiology, 2008; 101(8, Supplement): S20-S26.

[6] Investigators, A.-H. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol Rationale and study design. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH). Am Heart J, 2011; 161(3): 471-477 e2.

[7] Cinar, M., M. Karabacak, and A.M. Asiri. An experimental and density functional study on conformational and spectroscopic analysis of 5-methoxyindole-2-carboxylic acid. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2015; 137(0): 670-676.

[8] Karabacak, M., M. Cinar, M. Kurt, P. Chinna babu, and N. Sundaraganesan. Experimental and theoretical FTIR and FT-Raman spectroscopic analysis of 1-pyrenecarboxylic acid. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2013; 114(0): 509-519.

[9] Suksrichavalit, T., S. Prachayasittikul, T. Piacham, C. Isarankura-Na-Ayudhya, C. Nantasenamat, and V. Prachayasittikul. Copper Complexes of Nicotinic-Aromatic Carboxylic Acids as Superoxide Dismutase Mimetics. Molecules, 2008; 13(12): 3040.

[10] Borhani, D.W., D.P. Rogers, J.A. Engler, and C.G. Brouillette. Crystal structure of truncated human apolipoprotein A-I suggests a lipid-bound conformation. Proceedings of the National Academy of Sciences of the United States of America, 1997; 94(23): 12291-12296.

[11] Frisch, M.J., G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M.J. Bearpark, J. Heyd, E.N. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A.P. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N.J. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, and D.J. Fox, *Gaussian 09*. 2009, Gaussian, Inc.: Wallingford, CT, USA.

[12] Roy Dennington, T.K., and John Millam, *GaussView*, in *Semichem Inc.* 2009.

[13] Parr, R.G. and W. Yang. Density functional approach to the frontier-electron theory of chemical reactivity. Journal of the American Chemical Society, 1984; 106(14): 4049-4050.

[14] Young, D.C., *Density Functional Theory*, in *Computational Chemistry*. 2001, John Wiley & Sons, Inc. p. 42-48.

[15] Atac, A., M. Karabacak, C. Karaca, and E. Kose. NMR, UV, FT-IR, FT-Raman spectra and molecular structure (monomeric and dimeric structures) investigation of nicotinic acid N-oxide: A combined experimental and theoretical study. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2012; 85(1): 145-154.

[16] Yildiz, N., M. Karabacak, M. Kurt, and S. Akkoyun. Neural network consistent empirical physical formula construction for density functional theory based nonlinear vibrational absorbance and intensity of 6-choloronicotinic acid molecule. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2012; 90(0): 55-62.

[17] Karabacak, M. and M. Kurt. Comparison of experimental and density functional study on the molecular structure, infrared and Raman spectra and vibrational assignments of 6-chloronicotinic acid. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2008; 71(3): 876-883.

[18] Lu, T. and F. Chen. Multiwfn: A multifunctional wavefunction analyzer. Journal of Computational Chemistry, 2012; 33(5): 580-592.

[19] Morris, G.M., D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew, and A.J. Olson. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. Journal of Computational Chemistry, 1998; 19(14): 1639-1662.

[20] Trott, O. and A.J. Olson. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry, 2010; 31(2): 455-461.

[21] Yang, J.-M. and T.-W. Shen. A pharmacophore-based evolutionary approach for screening selective estrogen receptor modulators. Proteins: Structure, Function, and Bioinformatics, 2005; 59(2): 205-220.

[22] Yang, J.-M. and C.-C. Chen. GEMDOCK: A generic evolutionary method for molecular docking. Proteins: Structure, Function, and Bioinformatics, 2004; 55(2): 288-304.

[23] Sjoberg, P., J.S. Murray, T. Brinck, and P. Politzer. Average local ionization energies on the molecular surfaces of aromatic systems as guides to chemical reactivity. Canadian Journal of Chemistry, 1990; 68(8): 1440-1443.