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RESEARCH ARTICLE

Nicotine and Amino Acids Binding, A Theoretical Studies

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Abstract

The binding of twenty Amino Acids to Nicotine, has been studied theoretically by using (DFT) Density Functional Theory of (HF) type, as well as the semi-empirical method (PM3) calculations are carried out by (MOPAC) computational packages, to calculate the molecular orbital's energies and some molecules properties. The studied system was: Cysteine (Cys), Methionine (Met.) and Valine (Val.) with Nicotine. The optimized geometry of the complexes showed interaction between Nicotine and three Amino Acids molecules, Cysteine (Cys), Methionine (Met.) and Valine (Val.), the binding energies for these interaction were calculated, the binding energies for these interaction varies from -5.188 to -7.223 Kcal.mol^{-1}. Which attributed to the formation of hydrogen bonding between the studied molecules as it agrees with IR- experimental data .Binding to proteins is an important determinant of the kinetics .Which restricts the unbound concentration and effects the distribution and diminution of it.

Key words: *Nicotine, Amino Acids, binding, Density Functional Theory (DFT).*

Introduction

The chemical compound Nicotine is present in tobacco, cigarettes and cigars. It is containing pyridine ring, it s formula $C_{10}H_{14}N_2$ [1]. It is readily absorbed into the bloodstream between mucosal surfaces lining the nose, mouth and airways. Nicotine can also be absorbed by means of the mouth when chewed the nicotine gum or through the skin [2]. During the body, nicotine is fast distributed to all the body part and crosses into brain through the barrier of blood-brain. Nicotine may reach brain in as small as 7 seconds after being breathe in. In the body, the half life is about 2 hours [3]. In bigger doses nicotine is a toxic poison, adopted as an insecticide, to treat with fumes and vermin fuge [4].

Once inside the bloodstream, nicotine wander about to the brain where it connect to and activates receptionist named cholinergic receiver. These receivers are found in great quantity in brain in the same way as in different areas of the body as the muscles, heart, adrenal glands and different basic organs [5]. Nicotine operates on the central nervous system (CNS) by imitating the effects of neurotransmitter acetylcholine. In animal investigation, the acute castellated effects of nicotine seem to be subservient on dopamine emission in brain [6].

Nicotine disrupts normal brain function, causing chemical changes and addiction [7]. Nicotine inhalation causes growth in number of cholinergic receivers, which is thought to be accountable for the mercifulness that progress with smoking. At one occasion tolerance has raised a smoker to have a need to provision appropriate nicotine to brain and the habit of smoking come to be addictive [8]. Tobacco addiction kills the person untimely each six seconds. One in two high-term smokers- greatly in sink age - and middle-gain countries will die from tobacco addiction [9]. Nicotine operates on confident cell membrane receivers, which were it follows named nicotinic receptionists.

Nicotine accepters are proteins Which extend to the cell membrane [10], the dynamic molecules proteins are whose functions about invariably to rely on interactions with extra molecules, and these interactions are influenced in physiologically significant ways by sometimes brilliant [11], occasionally amazing conformations changes in protein. Proteins are most plentiful biological macromolecules, happening in every cells and every parts of cells, it reveal enormous variety of biological devoir [12]. Comparatively simple mono subunit supply the key to the structure of thousands of

different protons, all of protons are constructed of the same set of 20 amino acids covalently linked in characteristic linear sequences [13]. All 20 of the comman amino acids are α- amino acids. They all have (COOH) group and (NH_2) group attached to the same carbon atom (the α- carbon) (Fig. 1). They vary from one another in their R groups, or side chains, which differ in size, structure, and electric charges. In this paper, we report theoretical study of the interactions of 20 amino acids with nicotine and its binding mode to protens [14]. Binding of Nicotine Amino acids is usually readily reversible; a molecule bound in an irreversible way by a protein is named ligand. Protein is high polymers; amino acids (amonomers) are the building blocks of proteins. In this research, we studied the binding mode of some amino acids and Nicotine with theoretical method. The studied system was: Cysteine (Cys), Methionine (Met.) and Valine (Val.) with Nicotine [15].

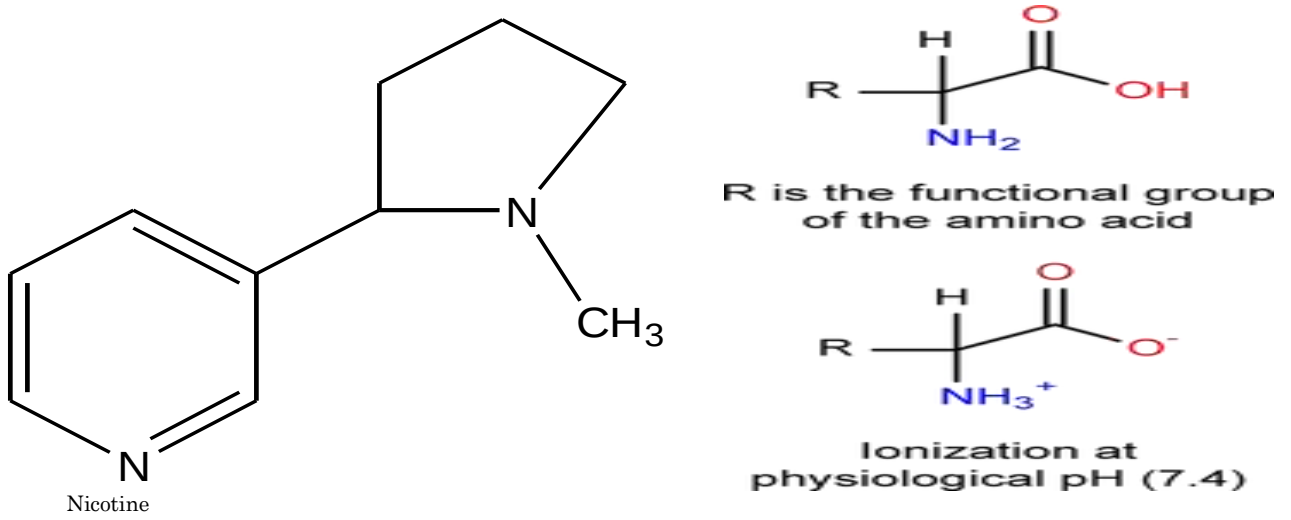


Figure1: The general structure of α- amino acid. R denotes the functional group of the amino acids

Computational Methods

All molecules structures (amino acids and nicotine) were fully optimized by using Semi-empirical method (PM3) using (MOPAC) computational packages [16], and Density Functional Theory (DFT) method in combination, using a Gaussian03, and Gaussian view03 set programs package [17]. Known to produce good estimate of molecules properties .This software can help in completing many tasks such as balanced geometric shape for each system (optimization) which has the least energy, The molecular structures of the studied Nicotine and amino acids were optimized [18], the optimization of the amino acid-Nicotine complexes were also determined, heat of formation ΔH_f the overall energy (total energy E_{total}) at optimized geometries [19]. The highest occupied molecular orbital (HOMO), the (LUMO) is the lowest unoccupied molecular orbital, to identify a binding sites in each molecule, calculated the binding energy.

Results and Discussion

All twenty amino acids and nicotine structures are shown in (Table-1).

By using Mopac2000 program series we calculate the physical and chemical properties of Nicotine and Amino Acids under studies, depending PM3 semi-empirical method [16].First, calculating the balance geometrical shape (optimization) of the molecules and finding bond angles, bond lengths, and molecule dimensions as shown in Table 1.

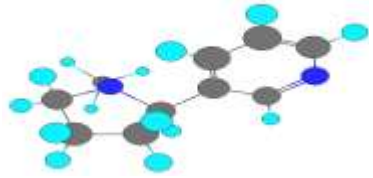
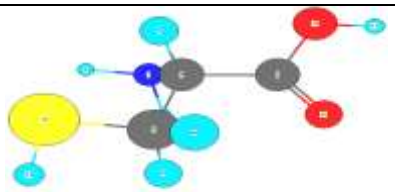
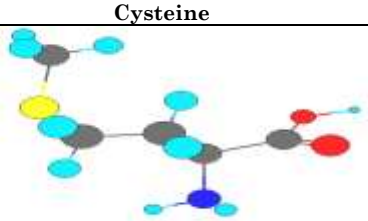
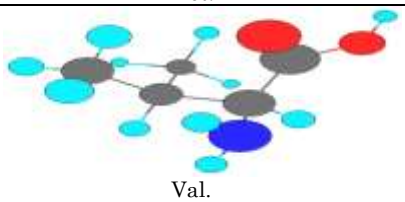
The Polarity Principles

The more polar bonds were the largest differences of electro negativity between atoms in a bond. The most electronegative atoms had a Partial negative charges, the other had fractional positive .Reconsideration the polarity of the functional groups. Calculating the electronic density of each atom in molecules and heat of formation ΔHf, dipole moment, highest occupied molecules orbital (HOMO) energy and lowest unoccupied molecules orbital (LUMO) at optimized geometries [19]. Table-1: Shows some physical properties and the optimized geometry for the studied molecules Nicotine and Amino Acids using PM3 semi-empirical calculations.

Table-1: The physical properties that calculated for Nicotine and Amino Acids of the optimized geometry from PM3 semi-empirical calculations

Molecules	Structures	HEAT OF FORMATION Kcal/mol	HEAT OF formation KJ/mol	ELECTRONIC ENERGY (EV)	DIPOLE (DEBYE)	HOMO ENERGIES (EV)	LUMO ENERGIES (EV)	MOLECULAR WEIGHT
Ala.	C3 H7NO2	-100.133	-418.957	-4505.752	2.833	-9.958	0.943	89.094
Arg.	C6 H14 N4O2	-85.350	-357.107	-11634.023	1.582	-9.491	0.762	174.202
Asn	C4 H8N2 O3	-133.940	-560.407	-7989.333	3.300	-10.000	0.416	132.119
Asp	C4H7NO4	-186.067	-778.505	-8075.553	2.259	-10.211	0.631	133.104
Cys.	C3H7NO2S	-89.395	-374.031	-5497.651	1.805	-9.638	-0.230	121.154
Glu	C5H9NO4	-192.772	-806.559	-9281.036	1.849	-10.086	0.720	147.130
Gln.	C5H10N2O3	-140.273	-586.905	-9249.041	3.537	-9.943	0.806	146.146
Gly.	C2H5NO2	-93.875	-392.775	-3411.090	2.127	-9.867	0.882	75.067
His.	C6H9N3O2	-65.929	-275.847	-9594.666	6.089	-9.418	0.358	155.156
Lle.	C6H13NO2	-115.050	-115.050	-8263.872	2.427	-9.884	0.977	131.174
Leu.	C6H13NO2	-116.892	-489.077	-8147.326	2.431	-9.869	0.956	131.174
Lys.	C6H14N2O2	-108.835	-455.368	-9507.304	2.914	-9.537	0.969	146.189
Met.	C5H11NO2 S	-101.133	-423.142	-7935.378	2.545	-9.222	0.091	149.207
phe	C9H11NO2	-72.943	-305.194	-10465.160	2.425	-9.715	-0.025	165.191
Pro.	C5H9NO2	-98.530	-412.250	-6585.469	3.608	-9.527	0.890	115.132
ser	C3H7NO3	-139.052	-581.797	-5781.106	2.377	-9.842	0.867	105.093
Thr.	C4H9NO3	-142.997	-598.30	-7177.439	2.884	-9.941	1.018	119.120
Trp.	C11H12N2O 2	-54.660	-228.700	-14314.747	3.638	-8.643	-0.181	204.230
Tyr.	C9H11NO3	-118.064	-493.981	-12041.648	2.343	-9.308	-0.021	181.191
Val.	C5H11NO2	-109.218	-456.970	-7007.995	2.338	-9.854	0.955	117.147
Necotten	C10H14N2	-19.973	-83.569	-10480.427	2.617	-9.134	0.049	162.234

Table 2: The physical properties for the studied Amino acid and Nicotine calculated from PM3 semi emperical calculations

Structures of Molecules	Heat of Formation(KJ)	HOMO (eV)	LUMO(eV)	ΔE(eV)
 Nicotine	-83.5693	-9.134	0.049	9.183
 **Cysteine**	-374.031	-9.638	-0.230	9.408
 Met.	-423.14268	-9.222	0.091	9.313
 Val.	-456.970	-9.854	0.955	10.809

Nicotine and Amino Acid Interaction

The electron density distribution and the electrostatic potential energy for the Nicotine and amino acid molecules each one alone to recognize the location of the (HOMO) and (LUMO) molecular orbital to identify the

probable interaction position between the Nicotine and amino acids, due to their importance to all chemical properties for the molecules (Figure 2). After knowing the reactive location in each molecular we start to build up molecules complexes according to it (Figure 3), and calculate the binding energy between each pair of the studied systems for the most probable position as follows:

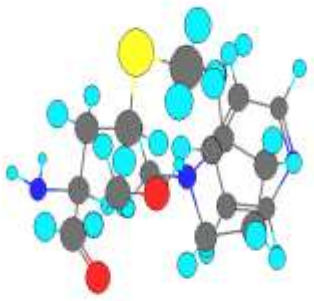
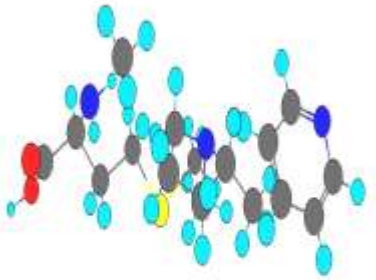
$$E_{binding} = E_{complex} \_ (EA + E_{N})$$

$E_{complex}$ = Heat of formation for the complex.

E_A, **EN** = Heat of formation for the Nicotine (N) and amino acid (A).

Table 4: Shows the physical properties for the binding mode between Nicotine and Cys, Val and Met calculated by PM3 semi- emperical calculations (The binding mode between Nicotine and Cys, Val and Met in the reactive position).

Table-3: the physical properties for the binding mode between Nicotine and Cys, Val and Met calculated by PM3 semi- emperical calculations

The molecules	Heat of formation (KJ)	Electronic energy(eV)	DIPOLE DEBYE	HOMO (eV)	LUMO (eV)	ΔE(eV)	Hydrogen bond length (A°)
 (CYS and NICOTIN)interaction $C_{15}H_{29}N_3O_2S$	-383.711	-25382.23	2.97214	-9.142	-0.195	8.947	H_{14}-N_{16} 3.064
 (Val and Nicotin) interaction $C_{16}H_{29}N_3O_2$	24.07660	-26669.19	3.567	-9.550	0.221	9.771	$C_{21}H_{50}$ 3.732 $C_{23}H_{48}$ 2.130 $H_{19}N_{22}$ 3.324
 (Met and Nicotin) interaction $C_{17}H_{33}N_3O_2S$	334.595	-31503.45	6.675	-7.528	-0.555	6.973	C_{14}-H_{43} 2.554 N_3-H_6 4.379 C_5H_{56} 2.879 C_1H_{46} 3.451 $C_{18}H_{39}$ 3.886

Physical properties and some energies values calculated by PM3 method for the studied molecules in Table 3, 4 .After the identification of the highest occupied molecules orbital (HOMO) energy and lowest unoccupied molecules orbital (LUMO),for each molecules(Figure-2), these two orbital's forms the frontier orbital's which are responsible for any chemical properties of the molecules. Then we try to build the molecule complexes (Figure3).Between nicotine and each of the amino acid under studies according to it s (HOMO) and (LUMO) orbitals. Figure -3: Shows the post of (HOMO) and (LUMO) for the two molecules, there may be probable interaction position between these complexes.

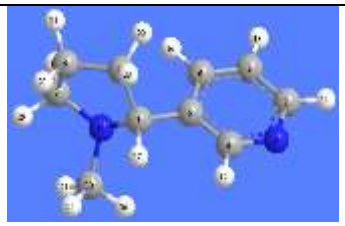
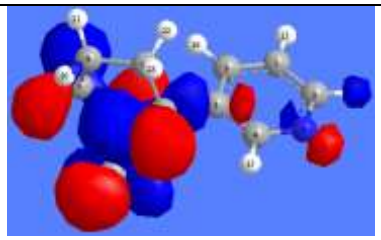
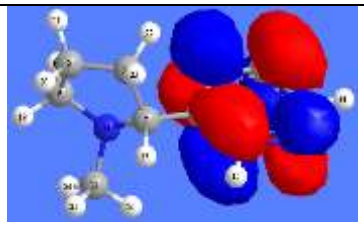
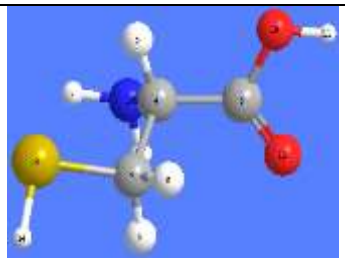
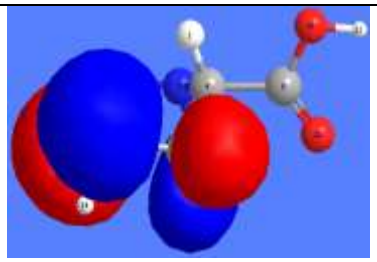
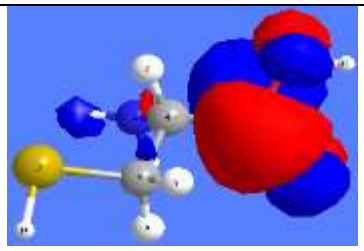
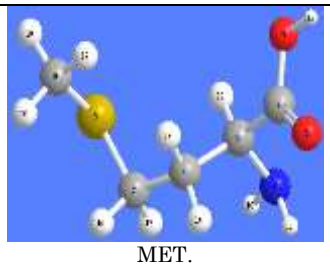
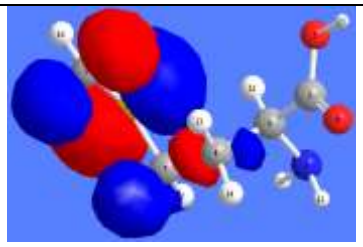
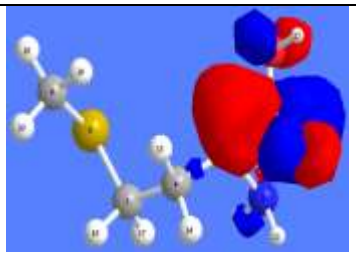
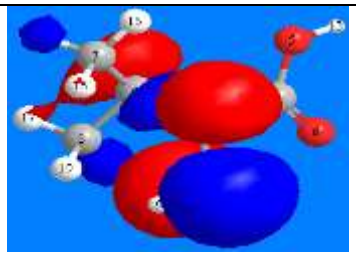
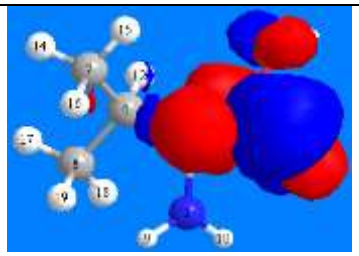
 NICOTINE	 HOMO =-9.127ev	 LUMO= -1.144ev
 CYS.	 HOMO= -9.999 ev	 LUMO=0.718ev
 MET.	 HOMO =- 8.720	 LUMO = 0.320
 VAL.	 HOMO= - 10.512	 LUMO= 0.673

Figure -2: Molecular orbital (HOMO) and (LUMO) of the optimized configuration of amino acids (1- CYS. 2- TEM.3-VAL.) and the Nicotine interaction applying G03 program

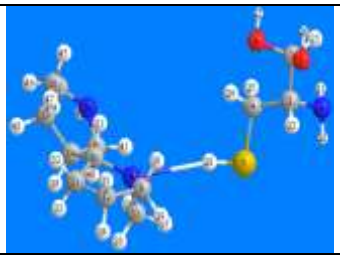
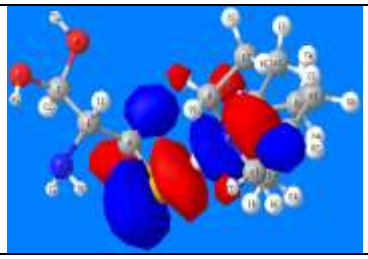
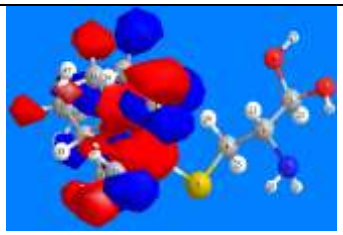
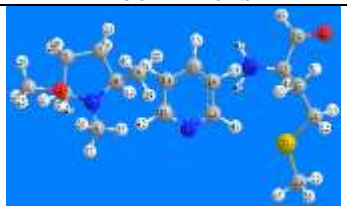
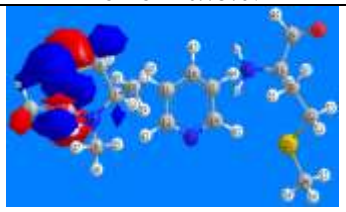
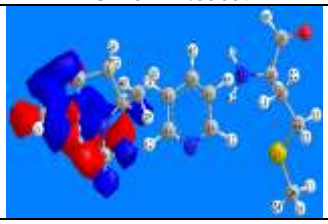
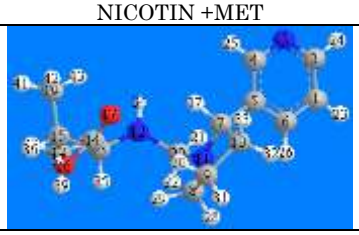
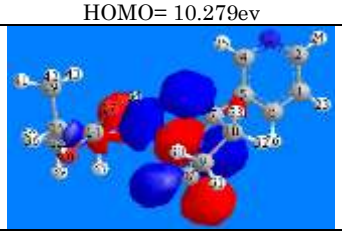
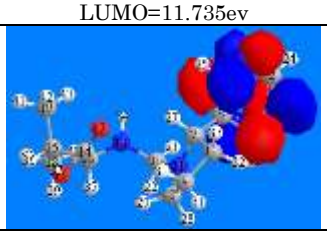
 NICOTIN+ CYS	 HOMO = -0.737ev	 LUMO =22.596ev
 NICOTIN +MET	 HOMO= 10.279ev	 LUMO=11.735ev
 NICOTIN +VAL.	 HOMO= -7.918ev	 LUMO= -0.784ev

Figure-3: Molecular orbital (HOMO) and (LUMO) and optimized configuration the interaction of Nicotine with amino acids (1- CYS. 2- TEM.3-VAL.) interaction by applying G03 program

$\Delta\Delta H_f$ = ΔH_f (complex) _ Σ¡ ΔH_f (components: Nicotine and amino acids.) interactions

The values of the binding energy for the optimized geometry of the complexes (Cys & Nicotine interaction, Met& Nicotine interaction and Val.& Nicotine interaction) which illustrated in table -3 making clear that the most probable intraction between Nicotine and (Cys, Met,Val.) owing to its highest possessive of the binding energy, due to the formation of hydrogen bond which is within the range of hydrogen bond strength [20,21]. Figure-3 shows the optimized geometry of the Complex calculated by G03 program [22]. The total energy, heat of formation and the binding energy in Kcal.mol^{-1}.Were shown in (Table-4) for the three complexes that may be formed between these two molecules and in the probable interaction position.

Table 4-: Physical properties of Nicotine and amino acids (1-CYS., 2-TEM.3-VAL.) and the expectant complexes for Nicotine and amino acids calculated by G03 program

molecules	Total Energy (Kcal. mol^{-1})	Heat of Formation ΔH°_f for interaction (Kcal. mol^{-1})	Binding Energy $\Delta\Delta H_f$ (Kcal.mol^{-1})
Nicotine and Cys. interaction	-2992.7153	192.889	-5.131
Nicotine and Met. interaction	-3392.7369	204.177	-4.681
Nicotine and Val. interaction	-3452.2358	245.753	-5.644

The total energy, heat of formation and the binding energy in Kcal.mol^{-1}.Were showed in table-5-shows the three complexes that formed between these molecules and in the probable interaction position.

Table- 5: Total energy and heat of formation for the expectant complexes for Nicotine with amino acids (1-CYS., 2-TEM.3-VAL.) interactions and the three complexes that calculated using G03 program

Molecule	Total Energy Kcal.mol^{-1}	Heat of Formation Kcal.mol^{-1}	Ionization polential(e.v)	Dipole moment (Debye)
Nicotine ($C_{10}H_{14}N_2$)	-2799.3193	-98.363	9.8765	2.617
Cys.($C_3H_7NO_2S$)	-2454.5305	-89.395	9.9052	1.805
Met.($C_5H_{11}NO2S$)	-2654.3582	-101.133	8.993	2.545
Val. ($C_5H_{11}NO_2$)	-2531.6146	-109.218	9.179	2.338
Cys.&Nicotine interaction ($C_{13}H_{29}N_3O_2S$)	-2992.7153	−158.745	9.028	3.134
Met&Nicotine interaction ($C_{17}H_{33}N_3O_2S$)	-3392.7369	-174.769	8.8901	3.833
Val.&Nicotine interaction ($C_{16}H_{29}N_3O_2$)	-3452.2358	-141.746	9.6766	3.788

Conclusion

The interaction between Nicotine and Cysteine (Cys), Methionine (Met.) and Valine (Val.) lead to the formation of hydrogen bond were investigated by computational and spectroscopic techniques, by using (DFT) Density Functional Theory the type of (HF), as well as the semi–empirical method (PM3) calculations are carried out by (MOPAC) computational packages. The heat of formation was used as a parameter to evaluate the binding energy of the interacted molecules which were confined by the shift in the absorption band of the groups involved in the formation of the hydrogen bond.

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