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Prodrug Design by Computation Methods to Treat Parkinson's Disease

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Abstract: Simulation studies of nine compounds have been suggested to treat Parkinson's disease using quantum calculation methods. Geometrical properties and vibration spectra have been calculated for all suggested chemical compounds to estimate the best for Parkinson's disease treatment by calculating the potential energy surface, atomic charge, bond length, bond angle, dipole moment, electrostatic potential and molecular orbital energy with energy gap. The calculations show that the M-6-SPhe compound has the structure and chemical properties of an ideal value compared to other suggested chemical compounds. Also, it has the lowest value of dipole moment equal to 3.028 Debye, and it has the highest value of the energy gap equal to 8.786 eV compared to the other chemical compounds suggested.

Keywords: Semi-empirical method, DFT, Parkinson's disease, Prodrug.

INTRODUCTION

Studies have proven Parkinson's disease PD was widespread more than 4 million people worldwide suffer from Parkinson's. The number of cases was rising where about 50,000 new cases are recorded each year[1]. This disease was considered the second most common neurodegenerative disease after Alzheimer's disease. This disease causes, tremor, bradykinesia (slowed movement), and rigidity. The risk of this disease is the process of PD in your body may start 5 to 20 years before the first symptoms are recognized[2]. The symptoms of PD result from the die or weakness of the substantianigra (literally "black substance"). Usually, these cells produce a chemical messenger called Dopamine, which transmits signals inside the brain to produce smooth and easy physical movements[3,4].

The most effective treatment for PD is give a modified amino acid known as L-DOPA, which is converted to dopamine in the brain. L-dopa (3, 4-dihydroxy-L-phenylalanine) is a chemical compound synthesis in the human body made from L-Tyrosine, in some cases from L-phenylalanine. L-DOPA, a dopamine precursor, either alone or in combination with an aromatic amino acid decarboxylase inhibitor (carbidopa, benserazide) is the most effective drug for the treatment of PD, because they able to cross the blood-brain barrier, whereas Dopamine itself cannot [5-8].

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Most symptomatic medications used in the treatment are: Levodopa, Dopamine agonists, MAO-B inhibitors, Amantadine, Anticholinergic, and COMT-inhibitors. These current treatments only reduce the symptoms of the PD for a limited period, most of these drugs preparing as a prodrugs [9]. Prodrug is a very versatile strategy to increase the Interest of biologically active compounds and decrease their associated toxicity. First described by Adrien Albert in the late 1958 [10]. It is a medication or compound which inactive, but which can be transformed by enzymatic to release the active parent drug in the human body. The aim of prodrug manufacturing through chemically modified derivatives of active drug compounds to hide unwanted drug properties, like low solubility in lipid or water, low selectivity, chemical instability, toxicity, to reduce side effects, and to enhance the absorption, distribution [11-13].

The present study tends to treat for Parkinson's disease. Different prodrugswere suggested to find the best prodrug to treat Parkinson's disease theoretically through the quantum calculationprocesses of the electronic and geometrical structure by using PM3 of semi-empirical calculations and DFT minimal STO-3G.

COMPUTATIONAL DETAILS

Theoretical calculations were completed by using the computational implemented in the Hyperchem Version 8.0.9 program [14-15]. Geometry optimization, electronic energies, heat of formation for diffrentprodrugs suggested have been optimized at semi empirical method and DFT- STO-3G. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were studied to calculate the energy gap (ÄE) [16, 17]. Bond lengths, bond angle, and the charge of atoms have been calculated at semi-empirical method, PM3 level [18].

RESULTS AND DISCUSSION

Several prodrugs of medication treatment for Parkinson's disease have been suggested and study the geometrical structure of all prodrugs. Where, sugar molecules include fructose, glucose, and mannose were linked to the amino group of the Phenylaniline linked to a different position (C1, C3, and C6) of the sugar through succinyl linker, to be lipophilic derivatives of Phenylaniline in order to transfer through the blood-brain barrier, which have selective permeability [19]. Fig. 1 represent the geometrical structure of suggested prodrug.

The energies of bond stability of different prodrug calculated by a semi empirical PM3 method and shown in Table 1. From Table 1 note that N-C2 4 bond in M-3-SPhe, M-6-SPhe, and F-3-SPhe molecules are more stable than in other probable drug due to require 80.1, 79.8, and 80 kCal/mol respectively of bond dissociation energy.

Potential energy stability of N-C2 4-O2 angle of all prodrugs were calculated, and represented in Table 2. From Table 1 note that N-C2 4-O2 angle in the M-6-SPhe molecule was requires 2950 kCal/mol higher value dissociation energy than other prodrogs. So this angle is more stability in M-6-SPhe than in other prodrugs.

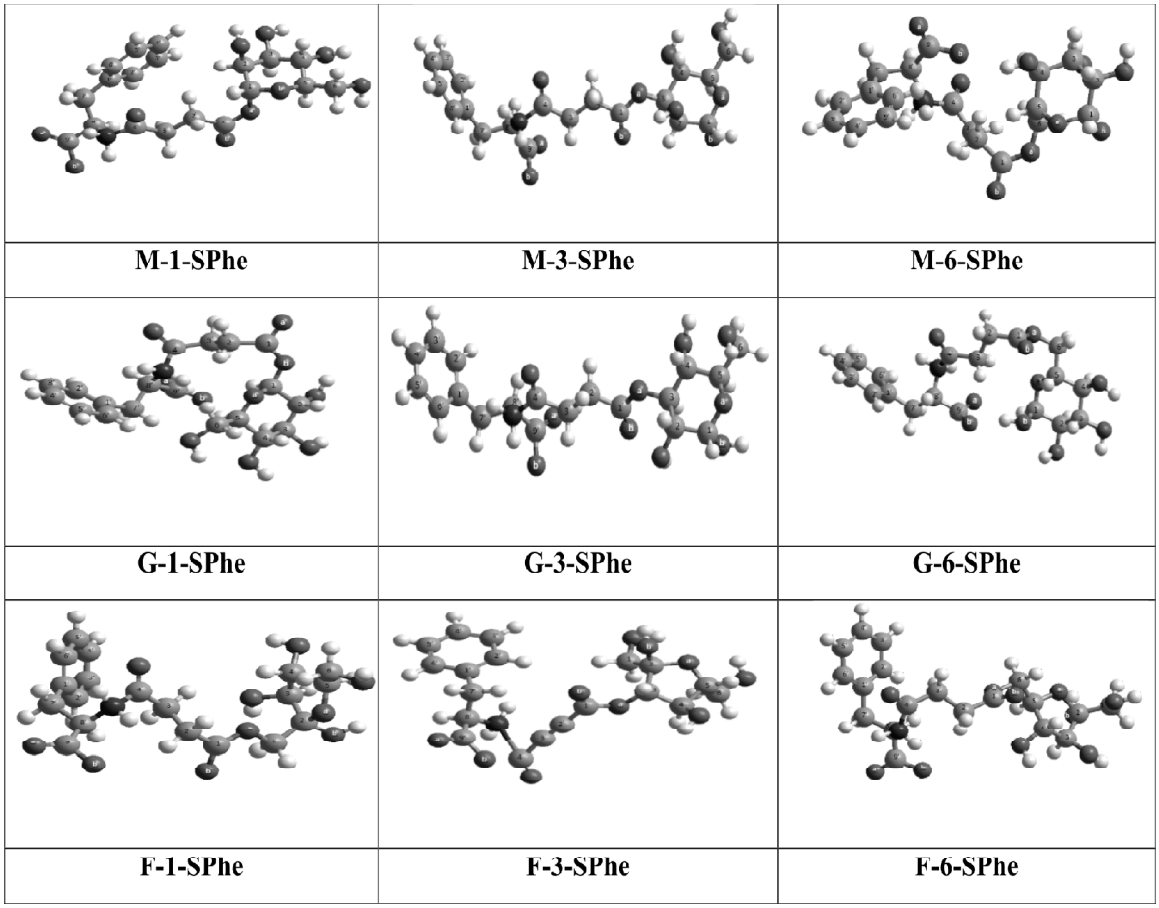


Figure 1: Chemical structure of suggested prodrugs

Table 1: Potential energy stability and dissociation of N-C2 $_4$ bond length calculate at semi empirical PM3 method

	Bond length A°)	*Potential energy stability kCal/mol)*	*Potential energy dissociation kCal/mol)*	*Bond dissociation Energy kCal/mol)*
M-1-SPhe	1.516	-5630.52	-5570.62	59.9
M-3-SPhe	1.521	-5630.52	-5550.42	80.1
M-6-SPhe	2.896	-5660.40	-5580.60	79.8
G-1-SPhe	1.520	-5620.52	-5550.42	70.1
G-3-SPhe	1.525	-5630.53	-5570.53	60.0
G-6-SPhe	1.533	-5640.53	-5570.23	70.3
F-1-SPhe	1.881	-5320.28	-5320.38	-0.1
F-3-SPhe	2.800	-5380.30	-5300.30	80
F-6-SPhe	1.534	-5360.53	-5300.44	60.09

Table 2
Potential energy stability of N-C2 4=O2 bond angle calculates at semi empirical PM3 method

Probables	*Bond angle stability (degree)*	*Potential energy stability (kCal/mol)*	*Potential energy dissociation (kCal/mol)*	*Angle dissociation Energy (kCal/mol)*
M-1-SPhe	114.115	-56340.0	-55870.0	470
M-3-SPhe	114.670	-56340.0	-55870.0	470
M-6-SPhe	83.443	-56620.0	-53670.0	2950
G-1-SPhe	116.615	-56250.0	-56070.0	180
G-3-SPhe	115.589	-56350.0	-56070.0	280
G-6-SPhe	114.134	-56410.0	-54670.0	1740
F-1-SPhe	111.297	-53150.0	-52670.0	480
F-3-SPhe	109.531	-53830.0	-53850.0	-20
F-6-SPhe	117.850	-53650.0	-52270.0	1380

Table 3 represents energetic properties of proposed prodrugs. M-6-SPhe has -132291.816 kCal/mol total energy less energy than other prodrugs, so it considers favorite[20[, and it has -400.534 kCal/mol heat of formation, That means this formation reaction from initial elements is exothermic, so it needs the amount of energy in order to decompose to the initial elements. This means that the M-6-SPhe compound is more stable than other probable[21]. HOMO energy for highest occupied molecular orbital, it shows the ability the molecule to the loss of electrons, since whenever the value was higher became easy to loss the electrons in the pharmaceutical compounds, While LUMO energy for lowest unoccupied molecular orbital, it shows the ability the molecule to acquire electrons, since whenever the value was less became easy to acquire electrons[22]. Therefore the compound has the highest value of the energy gap is the most effective in the pharmaceutical compounds. The M-6-SPhe compound has 8.786 eV energy gap higher than other probable. HOMO, and LUMO are show at two and three dimensions in Fig 2.The M-6-SPhe compound has the lowest value of dipole moment equal to 3.028 Debye, So become more lipophilic than other prodrugs.

Table 3
The properties of energy for all pordrugs calculated by a semi empirical PM3 method

Probable drug	Total energykCal/mol)	ZPE kCal/mol)	Heat of Formation kCal/mol	Molecular orbital energy			Dipole moment
				HOMO (eV)	LUMO (eV)	E_{gab} (eV)	
M-1-SPhe	-132263.793	273.082	-372.511	-9.672	-1.520	8.152	9.862
M-3-SPhe	-132261.339	272.472	-370.057	-9.538	-1.281	8.257	10.750
M-6-SPhe	-132291.816	273.472	-400.534	-10.067	-0.241	8.786	3.028
G-1-SPhe	-132257.100	271.714	-365.818	-9.445	-1.282	8.163	12.130
G-3-SPhe	-132264.071	272.339	-372.789	-9.463	-1.276	8.187	10.850
G-6-SPhe	-132273.191	273.846	-381.909	-10.168	-1.447	8.721	9.603
F-1-SPhe	-130738.184	244.671	-261.216	-8.592	-3.716	4.876	10.580
F-3-SPhe	-130808.221	244.917	-331.253	-10.122	-1.124	8.998	4.600
F-6-SPhe	-130789.970	246.313	-313.009	-9.801	-1.877	7.924	8.929

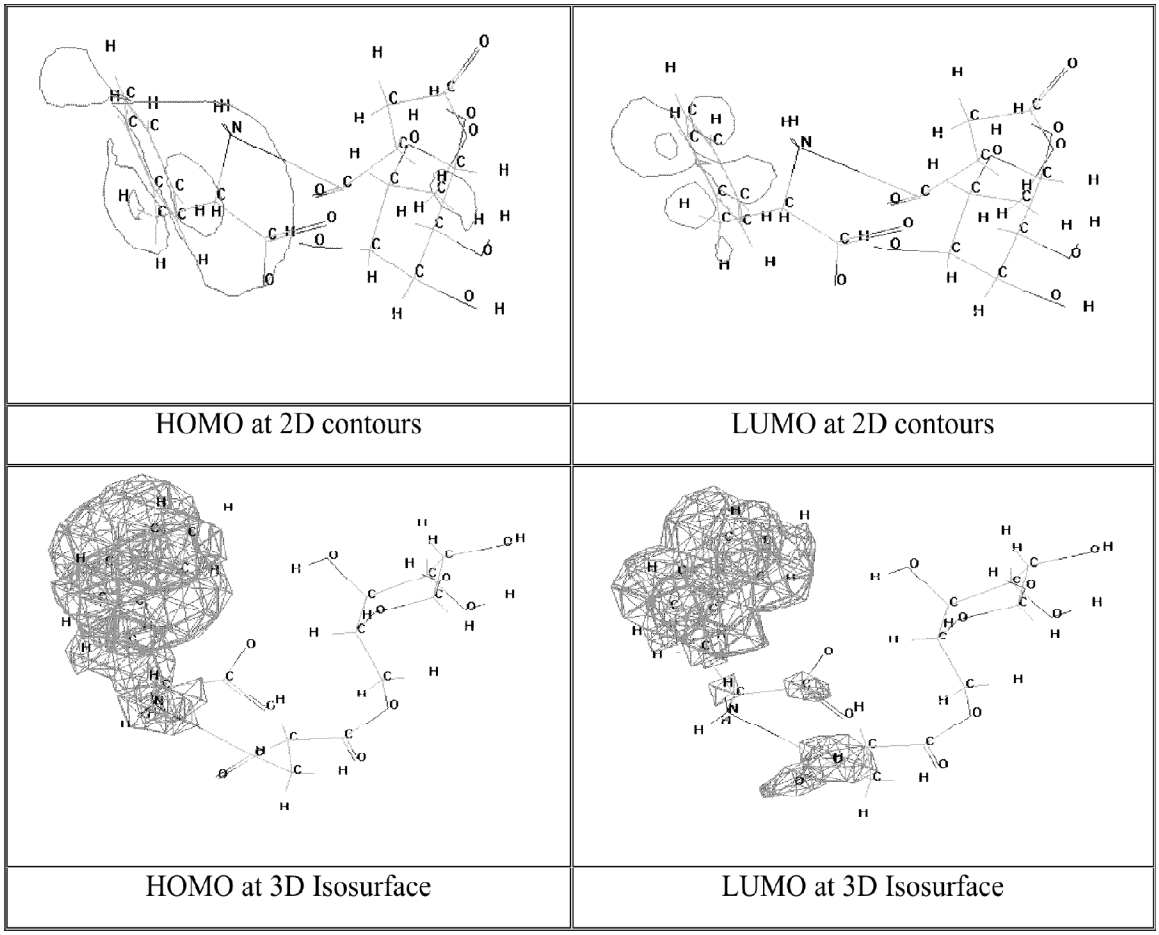


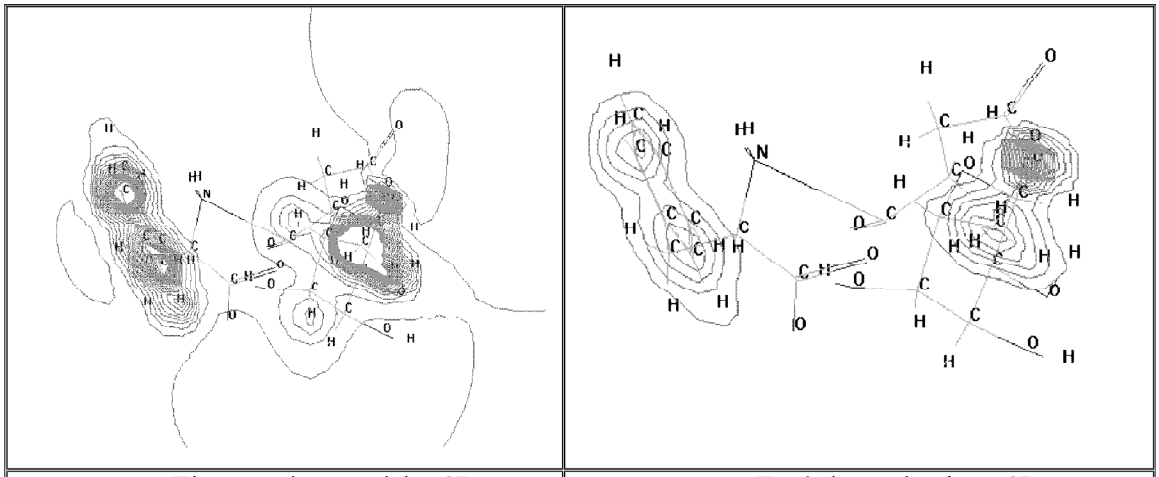
Figure 2: HOMO and LUMO levels of M-6-SPhe

Energy properties of the most stability compound M-6-SPhe calculated by DFT- STO-3G level of theory and semi empirical PM3 method and listed in Table 4. From Table 3-8 notice there are different in a value between tow method, because DFT method more accurate than semi empirical methods. The semi empirical method depends on empirical values and neglect of a large number of electron integrals. However, it was considered an important method due to require a short time for calculation. Also, it was able to calculate heat formation, while DFT it self cannot [23].

Chemical effectiveness of M-6-SPhe has been studied include electronic potential, total charge density is shown in Fig 3. Fig 3 shows that the regions of high electron density on the oxygen atom of the red color, while regions with low electron density of the atoms of hydrogen represented green color. The electronic density centered on the oxygen and nitrogen atoms because they contain a loan pair, also notes that the hydrogen atoms are suffer decrease electronic density due to high electrostatic of nitrogen and oxygen[24].

Table 4
Energy properties of M-6-SPhe calculated by DFT- STO-3G level of theory and semi empirical PM3 methods

		DFT	*Semi empirical PM3*
Total energy (kCal/mol)		-339169.320	-132291.816
ZPE kCal/mol)		335.188	273.472
Heat of Formation kCal/mol		-	-400.534
Molecular orbital energy	HOMO (eV)	-7.629	-10.067
	LUMO (eV)	1.538	-0.241
	ΔE_{gab} (eV)	9.167	8.786
Dipole moment		2.630	3.028
Time of calculation (hours)		739:11:36	0:11:25



a. Electrostatic potential at 2D | b. Total charge density at 2D

Figure 3: Physical properties of geometry optimization M-6-SPhe calculated at semi empirical method

CONCLUSION

The M-6-SPhe prodrug is better than other suggested prodrugs due to: The relaxation energy value of the geometrical optimization structure is less than other suggested structures. It has the highest value of the energy gap, so it is the most stable in the pharmaceutical compounds.It has the lowest value of the dipole moment, so become more lipophilic than other prodrugs to be able to cross the blood-brain barrier.

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