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MOLECULAR STRUCTURE AND ELECTRONIC PROPERTIES OF SOME PHENYLALANINE DERIVATIVES AS TRYPTOPHAN HYDROXYLAS (TPH) INHIBITORS

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Abstract— **In this work a theoretical study related to exploring and establishing the relationship between geometry, electronic structure, and various physical properties were determined for two substituted phenylalanine derivatives as tryptophan hydroxylase (TPH) inhibitors; 2-Amino-3-(4-(5-(Naphthalen-2-Ylmethyl-amino) Pyrazin-2-Yl) Phenyl) Propionic Acid and -2-Amino-3-(4-{5-[(Quinolin-3-Ylmethyl)-Amino]-Pyrazin-2-Yl} Phenyl) Propionic Acid, which differ structurally, that carbon atom of naphthalene in compound 1 is replaced by nitrogen atom to form quinine in compound 2. Molecular properties such as high occupied molecular orbital energy (E_{HOMO}), low unoccupied molecular orbital energy (E_{LUMO}), the energy gap between HOMO and LUMO (ΔE) and Physical properties, such as electronegativity (x), softness (s), hardness (η), chemical potential (μ), and electrophilicity index (ω), were studied to compare properties of these two compounds in relation to their molecular structure. Results show that the (ΔE) values of compound 2 were reduced by the replacement of the hydrogen atom in compound 1 by nitrogen atom in compound 2. Consequently, the stability of compound 2 decreased and its activity increased. Additionally, compound 2 exhibited a high electronic chemical potential value and a low chemical hardness value indicating high levels of polarizability.**

Keywords— **phenylalanine, quinine, substitution, molecular structure, electronic properties.**

I. INTRODUCTION

Tryptophan hydroxylase (TPH) is the initial enzyme in serotonin biosynthesis [1]. It is catalyzed the hydroxylation of L-tryptophan to produce 5-hydroxytryptophane 5-HT [2]. 5-hydroxytryptophane (5-HT) is released in a wide variety of physiological and neuronal processes and it is responsible for several psychiatric diseases and for the actions of numerous drugs of abuse. Therefore, TPH has a crucial role in influencing the pharmacological and physiological processes occurred by 5-HT.

Phenylalanine derivatives are important inhibitors of TPH enzyme [3]. It is an amino acid that is found in the breast milk of mammals, in all proteins and in some artificial sweeteners. Its formula is $C_9H_{11}NO_2$, and it appears as a methyl group for alanine is substituted by benzyl group or a terminal hydrogen of alanine is substituted by phenyl group. Phenylalanine has in common a side group with an aromatic ring structure. Its derivative results from the replacement of any hydrogen of phenylalanine by a heteroatom or from reaction of alanine at the amino group or the carboxyl group [4].

2-Amino-3-(4-(5-(Naphthalen-2-Ylmethyl-amino) Pyrazin-2-Yl) Phenyl) Propionic Acid (compound 1) and 2-Amino-3-(4-{5-[(Quinolin-3-Ylmethyl)-Amino]-Pyrazin-2-Yl} Phenyl) Propionic Acid (compound 2) are two ring- substituted Phenylalanine, which result from the replacement of para hydrogen of phenylalanine by pyrazine attached to (naphthalen-2-ylmethyl-amino) in (compound 1) and (quinolin-3-Ylmethyl-Amino) in (compound 2) .

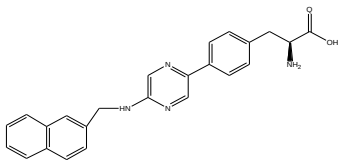

Fig. 1. 2-Amino-3-(4-(5-(Naphthalen-2-Ylmethyl-amino) Pyrazin-2-Yl) Phenyl) Propionic Acid (compound 1)

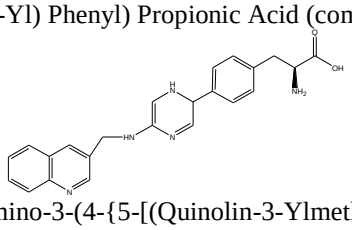

Fig. 2. 2-Amino-3-(4-{5-[(Quinolin-3-Ylmethyl)-Amino]-Pyrazin-2-Yl} Phenyl) Propionic Acid (compound 2)

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In this study, molecular structure and electronic properties of these two phenylalanine derivatives compounds were determined and compered to investigate the effect of replacement of the carbon atom in naphthalene group (skeleton composed of two orto-fused benzene rings) in compound 1 with the nitrogen atom in quinine group (double-ring structure composed of a pyridine and a benzene ring fused at two adjacent carbon atoms) in compound 2. Quantum chemical calculations were performed with the GAUSSIAN-09W using the 6-311G (d, p) basis sets at the B3LYP levels.

II. METHODOLOGY

The two molecules in Figures 1 and 2 were fully optimized using the 6-311G (d, p) basis sets at the B3LYP levels. The B3LYP method was applied to investigate the correlation and exchange effects by incorporating the hybrid exchange-correlation function [5]. Electronegativity (χ), chemical potential (μ), softness(S), global electrophilicity index (ω), hardness (η), hyper-polarizability (β), and polarizability (α) of each molecule were computed at the B3LYP level using the 6-311G (d, p) basis sets. The E_{HOMO} and E_{LUMO} were used to estimate the electronegativity (χ) as follows:

$$\chi = \frac{E_{LUMO} + E_{HOMO}}{2}$$

The chemical potential (μ) which is known as the negative of electronegativity (χ), nucleofugality (ΔE_n), electrofugality (ΔE_e), softness (S), global electrophilicity index (ω), and hardness (η) were calculated from the following equations [6]:

$$\mu = -\frac{E_{LUMO} + E_{HOMO}}{2}$$

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$$

$$\Delta E_n = \frac{(\mu+\eta)^2}{2\eta}$$

$$\Delta E_e = \frac{(\mu-\eta)^2}{2\eta}$$

$$S = \frac{1}{2\eta}$$

$$\omega = \frac{\mu^2}{2\eta}$$

The total hyper-polarizability (β) is defined as:

$$\beta = \sqrt{\beta_x{}^2 + \beta_y{}^2 + \beta_z{}^2}$$

$[\beta_x = \beta_{xxx} + \beta_{xyy} + \beta_{xzz}]$, $[\beta_y = \beta_{yyy} + \beta_{yzz} + \beta_{yxx}]$, $[\beta_z = \beta_{zxx} + \beta_{zyy} + \beta_{zzz}]$.

The mean polarizability (α) and anisotropic polarizability (Δα) were calculated based on the following formulas:

$$\alpha = \frac{\alpha_{xx} + \alpha_{yy} + \alpha_{zz}}{3}$$

$$\Delta\alpha \sqrt{\frac{(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2 + \alpha_{xy}{}^2 + \alpha_{xz}{}^2 + \alpha_{yz}{}^2}{2}}$$

Where α_{xx}, α_{yy}, α_{zz}, α_{xy}, α_{xz} and α_{yz} are polarizability tensor.

Since the values of the first-order hyper-polarizability (β) and polarizability (α) of GAUSSIAN-09W output are expressed in atomic units (a. u.), the values were converted into electrostatic units (esu) (α: $1a.u = 0.1482x10^{-24}$esu) (β: $1a.u = 8.6393\ x10^{-33}$esu) [7].

III. RESULTS AND DISCUSSION

The phenylalanine derivative molecules (compound 1 and compound 2) are fully optimized using density function theory DFT with the B3LYP/6-311G (d, p) basis set. The surfaces of LUMO-HOMO and ESP were drawn (Figure 3) to understand the bonding scheme of the present compounds.

Compound	LUMO	HOMO	ESP
Compound 1			
Compound 2			

Fig. **3.** The fully optimized, HOMO, LUMO and ESP shapes of compound 1 and compound 2 using the B3LYP/6-311G (d, p) basis set**.**

A HOMO-LUMO energy dependent calculation

The energy values of low unoccupied molecular orbital (LUMO), high occupied molecular orbital (HOMO) and energy gap values between HOMO and LUMO of the two studied compounds are presented in Table 1, while the physical properties of the two compounds are shown in Table 2.

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Table 1: HOMO and LUMO energies of compound 1and compound 2 using the B3LYP/6-311G (d, p) basis set.

compound	HOMO(eV)	LUMO(eV)	ΔE (eV)
Compound 1	-5.63	-1.42	4.21
Compound 2	-5.76	-1.76	4

Table 2: The physical properties of the two compounds using the B3LYP/6-311G (d, p) basis set.

Compound	X (eV)	η (eV)	S (eV^{-1})	μ (eV)	ω (eV)	ΔE_e (eV)	ΔE_n (eV)
Compound 1	-3.53	2.11	0.24	3.53	2.95	7.54	0.48
Compound 2	-3.76	2	0.25	3.76	3.54	8.3	0.78

Chemically speaking, compounds with a higher HOMO-LUMO orbital energy gap are more stable and thus harder than compounds with a lower HOMO-LUMO orbital energy gap [8]. This fact is clearly seen in Tables 1 and 2, which revealed that the replacement of the naphthalene group in compound 1 with the quinine group in compound 2 resulted in a reduction in energy gap from 4.22 eV for compound 1 to 4 eV for compound 2 making compound 2 less stable. This reduction in turn led to a decrease in hardness from 2.11 eV to 2 eV and an increase in activity from 6.72 to 7.89 for compounds 1 and 2 respectively.

This judgment is also supported by a prior report, which stated that higher HOMO-LUMO energy gap values corresponded to higher stability [7].

The best electrophilic molecule, on the other hand, has high values of softness and electronegativity [9]. This fact, that compound 2 is a better electrophile than compound 1, is evident from the results in Table 2. For compound 2, electrophilicity index was 3.54 eV, electronegativity was -3.76 eV, and softness was 0.25 eV, all of which were higher than those of compound 1, which had values of 2.96 eV, -3.53 eV, and 0.24 eV for electrophilicity index, electronegativity and softness respectively. This increase can be explained by the presence of nitrogen atom in quinine group for compound 2, which has a high electronegativity comparing to carbon atom that present in naphthalene group for compound 1.

B The mean dipole polarizability and the anisotropic polarizability.

The molar volume values (V_m), mean dipole polarizability values (α), anisotropic polarizability values (Δα) and first hyper polarizability values (β) of the two compounds were calculated using the B3LYP/6-311G (d,p) basis set and recorded in Table 3.

Compounds	α $x10^{-24}$ esu	Δα $x10^{-24}$ esu	β $x10^{-30}$ esu	$V_m(cm^3)$	A(activity)
Compound 1	51.25	29.95	3.36	296.08	6.24
Compound 2	54.6	54.8	4.25	303.3	7.89

Table 3 The molar volume values V_m, mean dipole polarizability values α, anisotropic polarizability values Δα and first hyper polarizability values β of compound 1 and compound 2 using the B3LYP/6-311G (d, p) basis set.

These values were calculated in atomic units (a,u) and converted to electrostatic unites (esu); for α: 1a.u = $0.1482x10^{-24}$ esu and for β: 1a.u = $8.693x10^{-30}$ esu. As seen in Table 3, all values of α, Δα and β decreased by the replacement of a naphthalene group in compound 1 with a quinine group in compound 2. The values of α, Δα and β for compound 2 were 54.60 $x10^{-24}$ esu, 54.80 $x10^{-24}$ esu, and 4.25 $x10^{-30}$ esu respectively, these values recorded 51.25 $x10^{-24}$ esu, 29.95 $x10^{-24}$ esu, and 3.36 $x10^{-30}$ esu for α, Δα and β respectively for compound 1. It can be also noted from Table 3 that compound 2 has a higher molar volume value than compound 1. This can be explained by the fact that the nitrogen atom in quinine group in compound 2 is larger than the carbon atom in naphthalene group in compound 1.

The findings in the aforementioned Tables 2,3 were in a good agreement with a previous study conducted by Sinah et al (2011)[10], which demonstrated that the compound with high values of electrochemical potential and softness (low value of chemical hardness), had high value of mean dipole

polarizability values α, anisotropic polarizability values Δα and first hyper polarizability values β.

IV. CONCLUSION

This theoretical investigation has shown how the electrical characteristics, stability, polarity, and activity of the molecules under study are affected when the naphthalene group in compound 1 is replaced with the quinine group in compound 2 which means replaced of one carbon atom of two orto-fused benzene rings by nitrogen atom. Through the optimization of the two compounds, the HOMO-LUMO energy gap value of compound 2 was found to decrease by this replacement, which led to a decrease in its stability and an increase in its activity. It can be also concluded that this replacement led to an increase in the electronic chemical potential, the polarizability values of compound 2, and a decrease in its chemical hardness values. In conclusion of this work, the replacement of atom by other kind of atom and change in chemical structure can lead to significant changes in the activity and the electronic properties of the molecule. It is expected that the information provided here will be helpful for the future studies towards a conducting another quantum structure activity relationship.

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