



# QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIP (QSAR) OF PHENYLALANINE SERIES-AS TRYPTOPHAN HYDROXYLASE-1 (TPH1) INHIBITOR

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**Abstract**— B3LYP level of theory with 6-311G(d,p), and 6-311G++(2d,2p) basis sets were used to calculate a set of molecular descriptors of phenylalanine series as tryptophan hydroxylase-1(TPH) inhibitors. These series of phenylalanine are structurally different. Quantitative Structures–Activity Relationship (QSAR) of 32 inhibitors of tryptophan hydroxylase-1(TPH1) were established using some calculated quantum mechanical descriptors such as Low Unoccupied Molecular Orbital energy ( $E_{LUMO}$ ) and High Occupied Molecular Orbital energy ( $E_{HOMO}$ ), the differences between HOMO and LUMO energies  $\Delta E$ , electronegativity ( $\chi$ ), hardness ( $\eta$ ), softness ( $s$ ), electrophilicity index ( $\omega$ ), chemical potential ( $\mu$ ), electrofugality  $\Delta E_e$  nucleofugality  $\Delta E_n$ , molar volume ( $mv$ ), polarizability ( $\alpha$ ), and hyper-polarizability ( $\beta$ ). Quantitative Structure-Activity Relationship (QSAR) was used to predict the activities/properties of title compounds as a function of its molecular substituents. This prediction will clarify the essential quantitative structure-activity relationship of them and give some advantageous sources for the design of new compounds.

**Keywords**— Hyper-conjugative, TPH1 inhibitors, polarizability, molar volume, hyper-polarizability.

## I. INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that regulates peripheral and central functions, through its activation on neurons, smooth muscle, and other cell types [1]. The rate-limiting of serotonin biosynthesis is the tryptophan hydroxylation, which is catalyzed by tryptophan hydroxylase (TPH). It catalyzes the 5-hydroxytryptophan (5-HTP) production from the dietary precursor [2].

Tryptophan hydroxylase TPH plays a very important role in the growth, development of growth of organism, and the process of behavior change [3]. In recent years, two kinds of TPH have been identified in mammals. The first one called TPH-1 gene is expressed highly in the pineal gland and the outer circumference, it is responsible for >90% of 5-HT synthesis in the periphery. The second one called TPH-2 gene is more active in the brain stem and expressed on neuronal cells located in the brain raphe nucleus, it is responsible for the most amount of 5-HT synthesis in the central nervous system [4].

Haihong Jin and co-workers (2009) described the substituted triazines discovery as a novel class of inhibitors of tryptophan hydroxylase. “This class of TPH inhibitors can selectively reduce serotonin levels in the murine intestine after oral administration without affecting levels in the brain” [5].

Liang Ouyang et al (2012) studied the structures- activity relationship (SAR) in 32 substituted phenylalanine derivatives that is structurally different as TPH1 inhibitors [2]. They performed the analysis of the QSAR on these TPH1 inhibitors based on multi-complex pharmacophore (MCBP) guided method. Their work introduced an approach to create multi-complex based pharmacophore (MCBP) guided 3D-QSAR models depended on crystal structures, a set of complexes of protein-ligand and inhibitors that are structurally different. Studies of QSAR are an outfit for predicted interesting organic molecules behaving as drugs endpoints [6].

Many physiological activities of a molecule can depend on its composition [7]. In this paper, the theoretical study conducted on exploring and establishing the relationship between electronic structure, geometry, and various physical properties for substituted phenylalanine determines which of them are structurally different. Physical properties, such as constancy, polarization, hyperpolarization, and molar size are usually very different [8]. The quantitative activity structure relationship (QSAR) was used to predict activities/properties

of substituted phenylalanine derivatives, derived from substitution on phenylalanine. The graphs of 32 compounds were drawn by CS ChemDraw [9] and the drawings are denoted in Figure 1 like one done in the study of Liang Ouyang et al (2012) [2].

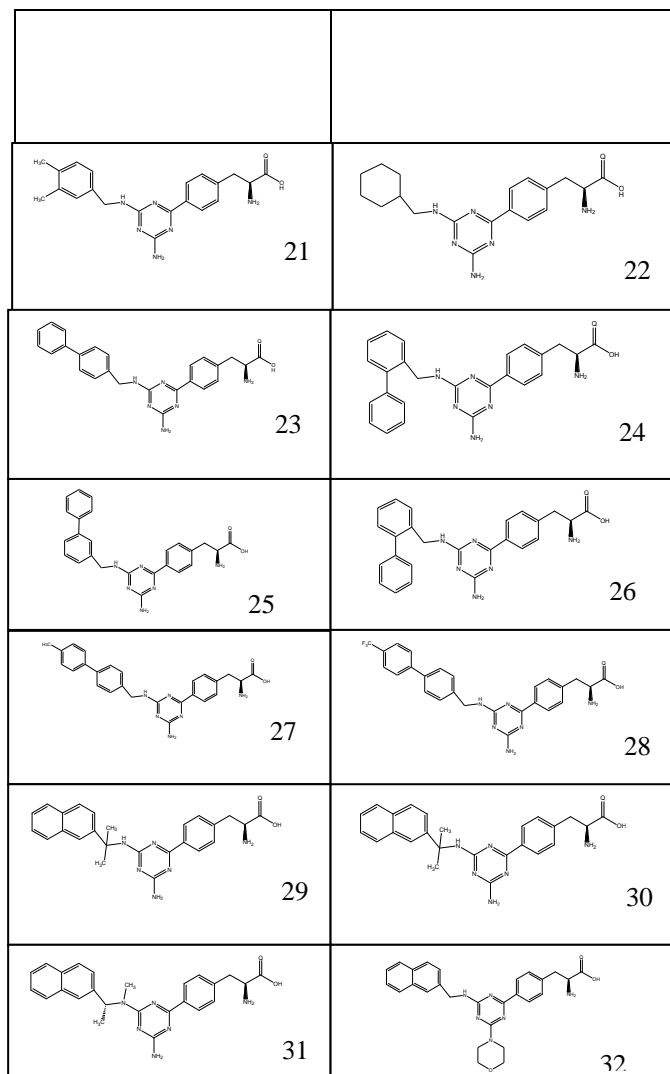
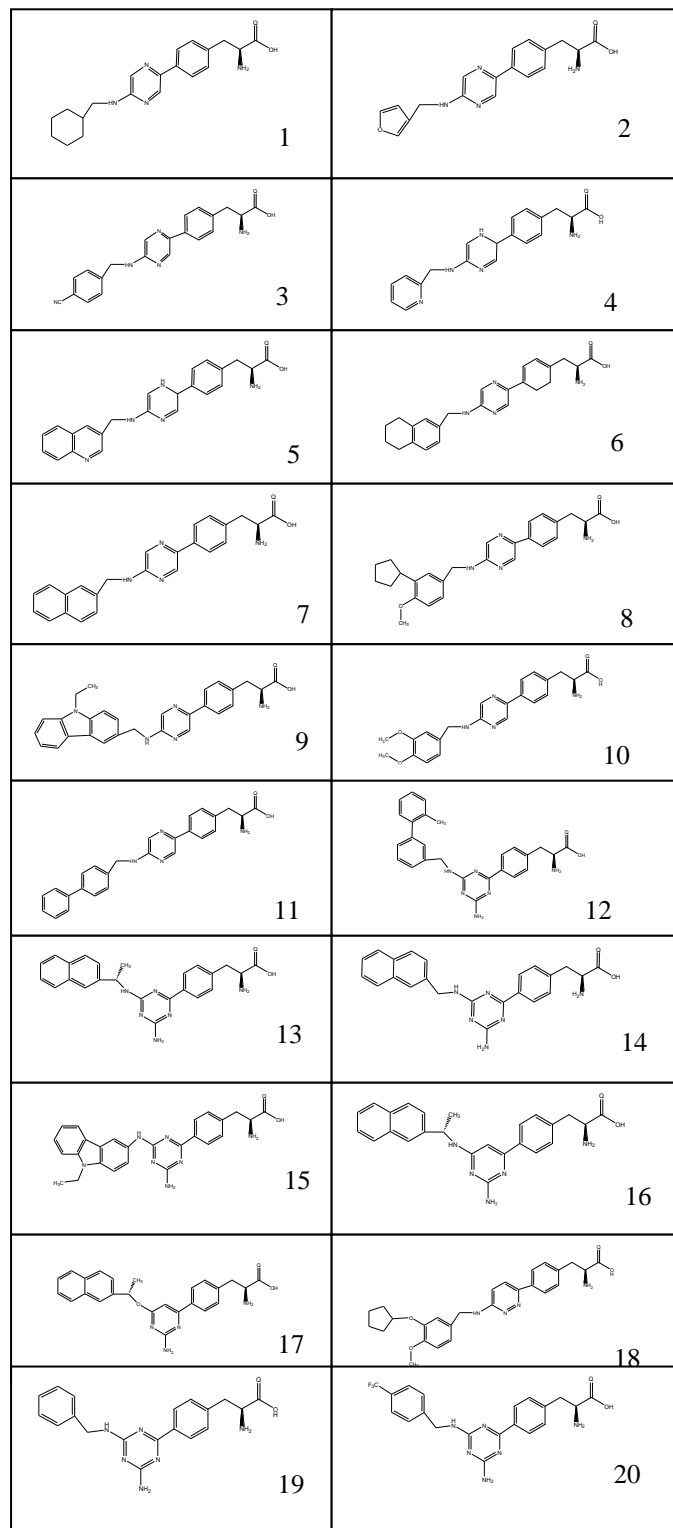


Fig. 1. 32 substituted phenylalanine derivatives.

We described HOMO–LUMO energy gap ( $\Delta E$ ), hardness ( $\eta$ ), softness ( $S$ ), the chemical potential ( $\mu$ ), electronegativity ( $\chi$ ), polarizability ( $\alpha$ ), molar volume ( $V_m$ ), and hyperpolarizability ( $\beta$ ) using DFT/B3LYP, with 6-311G(d,p) and 6-311G++(2d,2p) basis sets. The activities/properties of title compounds as a function of its molecular substituents were predicted by using the Quantitative Structure-Activity Relationship (QSAR).

## II. COMPUTATIONAL METHODOLOGY

All the molecules on Fig. 1 have been fully optimized at the B3LYP levels by using the 6-311G(d,p) and 6-311G++(2d,2p) basis sets with Gaussian 09 program [10]. The B3LYP method accounts for the correlation and exchange effects by incorporating the hybrid exchange-correlation functional. The HOMO–LUMO energy gap ( $\Delta E$ ), hardness ( $\eta$ ), softness ( $S$ ), the chemical potential ( $\mu$ ), electronegativity ( $\chi$ ), molar volume ( $m_v$ ), polarizability( $\alpha$ ), and hyper-



polarizability ( $\beta$ ) of each molecule have been computed at the B3LYP level.

The  $E_{HOMO}$  and  $E_{LUMO}$  are used to estimate the electronegativity ( $\chi$ ) and hardness ( $\eta$ ) [11] as:

$$X = (E_{LUMO} + E_{HOMO}) / 2 \dots \dots \dots (1)$$

$$\eta = (E_{LUMO} - E_{HOMO}) / 2 \dots \dots \dots (2)$$

The chemical potential ( $\mu$ ) known as the negative of electronegativity ( $\chi$ ) can be calculated

$$\mu = -(E_{LUMO} + E_{HOMO}) / 2 \dots \dots \dots (3)$$

Softness (S) is given by

$$S = 1 / 2\eta = 1 / (E_{LUMO} - E_{HOMO}) \dots \dots \dots (4)$$

Global electro-philicity index ( $\omega$ ) defined as

$$\omega = \mu^2 / 2\eta \dots \dots \dots (5)$$

Nucleofugality  $\Delta E_n = (\mu + \eta)^2 / 2\eta \dots \dots \dots (6)$

Electrofugality  $\Delta E_e = (\mu - \eta)^2 / 2\eta \dots \dots \dots (7)$

The mean polarizability ( $\alpha$ ) and anisotropic polarizability ( $\Delta\alpha$ ) are calculated based on the following [12].

$$\alpha = (\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) / 3 \dots \dots \dots (8)$$

$$\Delta\alpha = \{[(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2 + 6(\alpha_{xy}^2 + \alpha_{xz}^2 + \alpha_{yz}^2)] / 2\}^{1/2} \dots \dots (9)$$

where  $\alpha_{xx}$ ,  $\alpha_{yy}$ ,  $\alpha_{zz}$ ,  $\alpha_{xy}$ ,  $\alpha_{xz}$  and  $\alpha_{yz}$  are polarizability tensor.

The total hyper-polarizability ( $\beta$ ) is defined as

$$\beta = [\beta_x^2 + \beta_y^2 + \beta_z^2]^{1/2} \dots \dots \dots (10)$$

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

Since the values of the polarizabilities ( $\alpha$ ) and first-order hyper-polarizability ( $\beta$ ) of GAUSSIAN-09W output result in atomic units (au.), the calculated values have been converted into electrostatic units (esu)

For  $\alpha$  (1 au = 0.1428x10<sup>-24</sup> esu),

For  $\beta$  (1 au = 8.6393x10<sup>-33</sup> esu).

After conducting calculations, it was observed that 32 molecules were split into two subsets emerging as clusters with a cut point of 4.01 for a newly defined variable X where  $X = (\Delta E_e + \Delta E) / \text{hyper-polarizability}$ . While the first cluster composes of 17 molecules, the second one consists of 15 molecules Table I.

Table -I Two subsets clusters.

Cluster1		Cluster2	
1	14	3	24
2	15	5	25
4	16	7	26
6	18	11	29
8	23	17	30
9	27	19	31
10	28	20	
12	32	21	
13		22	

Using the variable X to construct a model with activity results in a second-degree polynomial model having  $R^2 = 0.70$ . The constructed model is denoted as follows:

$$\text{Activity} = 0.1323x^2 + 0.1676x + 2.559 \dots \dots \dots (11)$$

The rest of the molecules activity is regressed to variable X using a second-degree polynomial lead to a model with  $R^2 = 0.81$  as follows:

$$\text{Activity} = 0.04x^2 + 1.689x + 6.685 \dots \dots \dots (12)$$

### III. RESULT AND DISCUSSION

The structures of 32 Phenylalanine series as tryptophan hydroxylase-1 (TPH1) inhibitors were shown in Figure 1. The descriptors, the HOMO energies, the LUMO energies the HOMO-LUMO energy gaps ( $\Delta E$ ), hardness( $\eta$ ), softness(S), the chemical potential( $\mu$ ), electronegativity( $\chi$ ), molar volume(mv), polarizability( $\alpha$ ), anisotropic polarizability( $\Delta\alpha$ ) and hyper-polarizability( $\beta$ ), and activity values for 32 phenylalanine series as tryptophan hydroxylase-1 (TPH1) inhibitors are used to split into groups depending on their structures.

Each compound in the same group contains identical chemical group attached to the pyrazine core or to 4-amino-1,2,4-triazine ring which is attached to the phenylalanine ring.

#### A. The comparison of results of using B3LYP level theory with 6-311G(d,p) and 6-311++(2d,2p) basis sets.

The energies of High Occupied Molecular Orbitals and Low Unoccupied Molecular Orbitals of the title compounds using B3LYP/6-311(d,p) and B3LYP/6-311++(2d,2p) were illustrated in Tables II and III respectively.

Table -II HOMO and LUMO energy of 32 substituted phenylalanine derivatives using B3LYP with 6-311(d,p).

Compounds	B3LYP /6-311(d,p)		
	HOMO (eV)	LUMO (eV)	$\Delta E$ (eV)
1	-5.58	-1.28	4.30
2	-5.68	-1.39	4.29
3	-5.88	-1.79	4.09
4	-5.70	-1.40	4.29
5	-5.76	-1.76	4.00
6	-5.60	-1.29	4.31
7	-5.63	-1.42	4.21
8	-5.56	-1.31	4.25
9	-5.51	-1.31	4.20
10	-5.60	-1.29	4.31
11	-5.64	-1.39	4.24
12	-5.62	-1.34	4.28
13	-6.02	-1.39	4.63
14	-6.16	-1.44	4.72
15	-5.26	-1.49	3.78
16	-5.67	-1.30	4.38
17	-5.98	-1.28	4.70
18	-5.61	-1.23	4.38
19	-6.31	-1.31	5.00
20	-6.50	-1.45	5.06



21	-6.21	-1.27	4.94
22	-6.27	-1.27	5.00
23	-6.19	-1.32	4.87
24	-6.25	-1.29	4.96
25	-6.23	-1.31	4.91
26	-6.08	-1.31	4.77
27	-6.07	-1.30	4.77
28	-6.41	-1.54	4.87
29	-6.16	-1.39	4.77
30	-6.14	-1.34	4.80
31	-5.96	-1.31	4.65
32	-6.09	-1.38	4.71

Table - III HOMO and LUMO energies of 32 substituted phenylalanine derivatives using B3LYP/6-311++ (2d,2p).

Compound	B3LYP/6-311(2d,2p)		
	HOMO (eV)	LUMO (eV)	$\Delta E$ (eV)
1	-5.67	-1.42	4.25
2	-5.81	-1.55	4.26
3	-6.00	-1.94	4.06
4	-5.81	-1.56	4.25
5	-5.88	-1.89	3.99
6	-5.70	-1.41	4.29
7	-5.79	-1.58	4.22
8	-5.66	-1.45	4.21
9	-5.67	-1.42	4.25
10	-5.70	-1.42	4.28
11	-5.74	-1.53	4.20
12	-5.72	-1.43	4.29
13	-6.11	-1.58	4.53
14	-6.27	-1.63	4.64
15	-5.39	-1.66	3.73
16	-5.83	-1.44	4.39
17	-6.15	-1.47	4.68
18	-5.76	-1.41	4.35
19	-6.46	-1.53	4.93
20	-6.67	-1.68	4.99
21	-6.39	-1.48	4.91
22	-6.42	-1.48	4.93
23	-6.33	-1.54	4.79
24	-6.42	-1.49	4.93
25	-6.34	-1.53	4.81
26	-6.21	-1.53	4.68
27	-6.20	-1.52	4.68
28	-6.55	-1.72	4.83
29	-6.25	-1.51	4.74
30	-6.24	-1.52	4.72
31	-6.07	-1.49	4.58
32	-6.18	-1.56	4.63

As seen from Tables II and III, it can be said that the results of the comparison of these values showing HOMO- LUMO energies with the use of B3LYP/6-311G(d,p) basis set are slightly higher than with the use B3LYP/6-311G++(2d,2p) basis set.

The different HOMO- LUMO energy gap values between the two basis sets for most of the title compounds are less than 0.05eV. For example, HOMO- LUMO energy gap value for compound 1 using B3LYP/ 6-311G(d,p) was-equal

to 4.30 eV, but this HOMO- LUMO energy gap value using B3LYP/6-311G++(2d,2p) was equal to 4.25 eV.

Hence, it can be concluded that there are the absolute and good agreement between the calculated HOMO and LUMO energies values for 6-311G(d,p) and B3LYP/6-311G++(2d,2p) basis sets. They gave a good correlation coefficient for HOMO energies, LUMO energies, and HOMO-LUMO energy gaps. They were ( $R^2=0.9928$ ), ( $R^2=0.9122$ ), and ( $R^2=0.9914$ ), respectively.

Therefore, to assess the agreement of the present basis sets, we have calculated the electrochemical properties of the 32- phenylalanine series.

As it is illustrated in Table IV<sub>a</sub>, and Table IV<sub>b</sub> the B3LYP/6-311G(d,p) calculating electronegativity ( $\chi$ ), hardness, softness, electrophilicity index, chemical potential, electrofugality, and nucleofugality of all molecules agree remarkably with the corresponding B3LYP/6-311G++(2d,2p) data.

Table - IV<sub>a</sub>, Electrochemical properties of the different groups of the phenylalanine series compounds using B3LYP/6-311G(d,p).

C	$\chi$ (eV)	$\eta$ (eV)	S (eV) <sup>-1</sup>	$\mu$ (eV)	$\omega$ (eV)	$\Delta E_n$ (eV)	$\Delta E_e$ (eV)
1	-3.43	2.15	0.23	3.43	2.74	0.38	7.24
2	-3.54	2.14	0.23	3.54	2.92	0.45	7.53
3	-3.83	2.04	0.24	3.83	3.59	0.78	8.44
4	-3.55	2.15	0.23	3.55	2.94	0.46	7.56
5	-3.76	2.00	0.25	3.76	3.54	0.78	8.30
6	-3.45	2.16	0.23	3.45	2.76	0.39	7.29
7	-3.53	2.11	0.24	3.53	2.96	0.48	7.54
8	-3.43	2.13	0.24	3.43	2.77	0.40	7.26
9	-3.41	2.10	0.24	3.41	2.77	0.41	7.23
10	-3.45	2.15	0.23	3.45	2.76	0.39	7.29
11	-3.51	2.12	0.24	3.51	2.90	0.45	7.47
12	-3.48	2.14	0.23	3.48	2.83	0.42	7.38
13	-3.7	2.31	0.22	3.70	2.96	0.42	7.82
14	-3.8	2.36	0.21	3.80	3.06	0.44	8.04
15	-3.38	1.89	0.26	3.38	3.03	0.59	7.35
16	-3.49	2.19	0.23	3.49	2.78	0.39	7.37
17	-3.63	2.35	0.21	3.63	2.80	0.35	7.61
18	-3.42	2.19	0.23	3.42	2.67	0.35	7.19
19	-3.81	2.50	0.20	3.81	2.90	0.34	7.96
20	-3.97	2.53	0.20	3.97	3.12	0.41	8.35
21	-3.74	2.47	0.20	3.74	2.83	0.33	7.81
22	-3.77	2.50	0.20	3.77	2.84	0.32	7.86
23	-3.75	2.44	0.21	3.75	2.89	0.35	7.85
24	-3.77	2.48	0.20	3.77	2.86	0.33	7.87
25	-3.77	2.46	0.20	3.77	2.89	0.35	7.89
26	-3.69	2.38	0.21	3.69	2.86	0.36	7.74
27	-3.69	2.38	0.21	3.69	2.86	0.36	7.74
28	-3.97	2.43	0.21	3.97	3.24	0.49	8.43
29	-3.77	2.39	0.21	3.77	2.98	0.40	7.94
30	-3.74	2.40	0.21	3.74	2.91	0.37	7.85
31	-3.64	2.33	0.22	3.64	2.85	0.37	7.65
32	-3.74	2.35	0.21	3.74	2.97	0.41	7.89

Table - IV<sub>b</sub>, Electronic properties of the different groups of the phenylalanine series compounds using B3LYP/6-311++G(2d,2p).



C	$\chi$ (eV)	$\eta$ (eV)	S (eV) <sup>-1</sup>	$\mu$ (eV)	$\omega$ (eV)	$\Delta E_n$ (eV)	$\Delta E_e$ (eV)
1	-3.55	2.13	0.24	3.55	2.96	0.48	7.57
2	-3.68	2.13	0.23	3.68	3.18	0.57	7.93
3	-3.97	2.03	0.25	3.97	3.88	0.93	8.86
4	-3.68	2.12	0.24	3.68	3.19	0.57	7.94
5	-3.88	1.99	0.25	3.88	3.78	0.89	8.66
6	-3.56	2.14	0.23	3.56	2.95	0.47	7.58
7	-3.68	2.11	0.24	3.68	3.22	0.59	7.96
8	-3.56	2.11	0.24	3.56	3.01	0.50	7.62
9	-3.54	2.13	0.24	3.54	2.95	0.47	7.56
10	-3.56	2.14	0.23	3.56	2.96	0.47	7.59
11	-3.63	2.10	0.24	3.63	3.14	0.56	7.83
12	-3.57	2.15	0.23	3.57	2.97	0.47	7.62
13	-3.85	2.26	0.22	3.85	3.27	0.55	8.25
14	-3.95	2.32	0.22	3.95	3.36	0.57	8.47
15	-3.52	1.87	0.27	3.52	3.33	0.74	7.78
16	-3.64	2.20	0.23	3.64	3.01	0.47	7.75
17	-3.81	2.34	0.21	3.81	3.10	0.46	8.08
18	-3.58	2.18	0.23	3.58	2.95	0.46	7.62
19	-4.00	2.47	0.20	4.00	3.24	0.48	8.47
20	-4.17	2.50	0.20	4.17	3.49	0.56	8.91
21	-3.94	2.45	0.20	3.94	3.16	0.45	8.32
22	-3.95	2.47	0.20	3.95	3.16	0.45	8.35
23	-3.93	2.39	0.21	3.93	3.23	0.49	8.36
24	-3.95	2.46	0.20	3.95	3.17	0.45	8.35
25	-3.94	2.40	0.21	3.94	3.23	0.49	8.37
26	-3.87	2.34	0.21	3.87	3.20	0.50	8.24
27	-3.86	2.34	0.21	3.86	3.18	0.49	8.21
28	-4.13	2.42	0.21	4.13	3.54	0.61	8.88
29	-3.88	2.37	0.21	3.88	3.18	0.48	8.25
30	-3.88	2.36	0.21	3.88	3.19	0.49	8.25
31	-3.78	2.29	0.22	3.78	3.13	0.49	8.05
32	-3.87	2.31	0.22	3.87	3.24	0.53	8.27
C (Compounds)							

Table – IV<sub>c</sub> Correlation coefficient R<sup>2</sup> of the electric properties obtained at B3LYP level for 6-311G+(d,p) and 6-311G++(2d,2p) basis sets for molecules of Fig. 1.

property	correlation coefficient R <sup>2</sup>
$\Delta E$	0.9914
$\chi$	0.9832
$\eta$	0.9899
S	0.9449
$\mu$	0.9832
$\omega$	0.9398
$\Delta E_n$	0.9545
$\Delta E_e$	0.974

From Table IV<sub>c</sub> it can be noticed the high correlation coefficients of all calculated properties. The hardness ( $\eta$ ) correlation coefficient ( $R^2=0.99$ ), electronegativity ( $\chi$ ) and chemical potential correlation coefficient ( $R^2=0.98$ ), electrophilicity index and softness correlation coefficient ( $R^2=0.94$ ), electrofugality, and nucleofugality are found ( $R^2=0.97$ ) and ( $R^2=0.95$ ) respectively.

However, as a supplement to this study, the results of linear polarizability, anisotropic polarizability, first-hyper-polarizability and molar volume of the title molecules obtained for B3LYP/6-311G(d,p) and B3LYP/6-311++G(2d,2p) basis sets have been reported to compared in Table V<sub>a</sub> and Table V<sub>b</sub>.

The linear polarizability, anisotropic polarizability, and the first-hyper-polarizability that were obtained at two basis sets different within a narrow margin.

Table -V<sub>a</sub> The liner polarizability, anisotropic polarizability first hyper polarizabilities and molar volume of 32 substituted phenylalanine derivatives using B3LYP/6-311G(d,p).

C	$\alpha \times 10^{-24}$ (esu)	$\Delta \alpha \times 10^{-24}$ (esu)	$B \times 10^{-30}$ (esu)	$V_m$ (cm <sup>3</sup> )
1	44.72	33.28	13.48	321.05
2	41.20	34.13	9.69	238.04
3	47.86	35.85	5.78	303.30
4	44.14	36.47	9.44	280.48
5	51.25	29.95	3.36	303.30
6	53.11	47.58	10.96	322.16
7	54.60	54.80	4.25	296.08
8	57.85	43.26	16.63	366.61
9	64.33	59.17	12.83	306.45
10	51.80	46.27	14.21	295.81
11	57.38	43.02	7.14	295.81
12	57.44	34.89	7.90	357.64
13	52.95	22.66	12.13	327.88
14	53.23	34.49	17.63	296.05
15	62.50	48.64	19.14	350.74
16	56.57	36.74	8.60	332.24
17	54.98	33.75	5.25	297.16
18	58.38	47.18	21.23	309.67
19	44.57	25.28	9.66	276.58
20	46.56	23.77	10.05	327.38
21	48.95	29.10	8.74	319.11
22	44.00	24.90	7.30	294.59
23	57.18	38.14	11.87	304.73
24	54.31	32.94	7.82	395.64
25	56.68	33.18	9.30	303.96
26	57.06	37.67	7.92	314.06
27	59.73	41.84	8.68	389.75
28	59.63	39.37	16.43	417.94
29	54.81	32.35	7.93	378.82
30	57.01	41.42	9.42	336.25
31	56.54	29.82	6.22	329.65
32	61.67	32.39	11.10	393.25
C (Compounds), V <sub>m</sub> (molar volume)				

Although the molar volume values obtained with the B3LYP/6-311++G(2d,2p) basis set show notable increase in some cases and show notable decrease in other cases. For example, for compound 1 and compound 20, they show notable increase from 266.22 cm<sup>3</sup> for compound 1 and 268.93 cm<sup>3</sup> for compound 20 to 321.5 cm<sup>3</sup>, 327.38 cm<sup>3</sup> for compound 1 and compound 20 respectively. On the other hand, for compound 8 and compound 9, they show notable decrease



from 438.96 cm<sup>3</sup> for compound 8 and 380.92 cm<sup>3</sup> for compound 9 to 366.61 cm<sup>3</sup>, 306.45 cm<sup>3</sup> for compound 8 and compound 9 respectively.

Table - V<sub>b</sub> The liner polarizability, anisotropic polarizability first hyper polarizabilities and molar volume of 32 substituted phenylalanine derivatives using B3LYP/6-311G++(2d,2p).

C	$\alpha \times 10^{-24}$ (esu)	$\Delta\alpha \times 10^{-24}$ (esu)	$B \times 10^{-33}$ (esu)	$V_m$ (cm <sup>3</sup> )
1	41.37	33.69	11.45	266.22
2	37.46	33.65	8.69	203.36
3	43.74	35.73	5.92	278.82
4	40.57	39.42	8.13	298.47
5	47.63	32.76	5.13	315.36
6	49.11	48.20	10.49	305.22
7	49.44	47.04	4.45	284.26
8	53.35	42.80	13.10	438.96
9	58.09	49.36	15.81	380.92
10	47.45	46.37	13.99	259.34
11	52.25	40.71	5.56	298.61
12	53.19	35.87	12.22	395.21
13	48.08	19.12	12.08	309.85
14	48.28	32.81	16.82	317.59
15	56.85	49.53	17.60	296.90
16	51.57	35.25	11.25	306.29
17	50.09	31.88	8.08	281.04
18	53.74	47.71	16.11	310.63
19	40.25	25.25	9.11	251.20
20	42.07	24.70	10.26	268.93
21	44.42	26.74	8.49	279.86
22	40.27	23.74	7.36	306.30
23	51.86	35.84	11.09	335.33
24	49.61	32.98	6.82	353.52
25	51.42	30.99	8.77	324.95
26	51.71	35.80	7.44	321.09
27	54.43	39.64	9.18	338.88
28	53.99	37.15	15.94	409.72
29	49.92	33.86	7.31	360.09
30	52.16	42.04	8.06	331.49
31	51.68	28.11	6.86	303.23
32	56.64	30.74	11.12	360.04
C (Compounds), $V_m$ (molar volume)				

As it can be seen from Table V<sub>c</sub>, the linear polarizability, the anisotropic polarizability, and the first-hyper polarizability were recorded correlation coefficient ( $R^2=0.9948$ ), ( $R^2=0.913$ ), and ( $R^2=0.8271$ ) respectively where the correlation coefficient of molar volume was recorded as  $R^2=0.5242$ .

Table -V<sub>c</sub>, The liner polarizabilities, anisotropic polarizability first hyper polarizabilities and molar volume correlation coefficient  $R^2$  calculated using B3LYP/6-311G(d,p) and B3LYP/6-311G++(2d,2p).

Property	$\alpha$	$\Delta\alpha$	$\beta$	$V_m$
Correlation coefficient $R^2$	0.9948	0.9135	0.8271	0.5242

In our subsequent discussions, we consider the results obtained for the B3LYP/6-311G(d,p) basis set since there is an

absolute, good agreement between the calculated values for B3LYP/6-311G(d,p) and B3LYP/6-311G++(2d,2p) basis sets.

It seems apparently that the relative variation of HOMO-LUMO energies, electronic properties, linear polarizability, anisotropic polarizability, first-hyper polarizability and molar volume of the chosen compounds obtained at a given level of calculation do not show any link. Therefore, it would be interesting to divide them into identical groups to find general relationships between these electronic quantities. In the following, an attempt has been made to divide them based on the ring that attached directly to phenylalanine ring as can be seen in Tables VI<sub>a1</sub>, VI<sub>a2</sub>, VI<sub>a3</sub>, VI<sub>b1</sub>, VI<sub>b2</sub>, VI<sub>b3</sub> and VI<sub>d</sub>

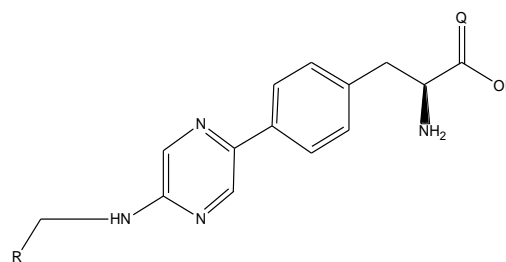


Fig 2 The main chemical structure of group a.

Table VI<sub>a1</sub>, Structures, electronic quantities and activity values for group a<sub>1</sub> compounds










a <sub>1</sub>	1	2	3	4
R group				
HOMO (eV)	-5.58	-5.68	-5.88	-5.7
LUMO (eV)	-1.28	-1.39	-1.79	-1.4
$\Delta E$ (eV)	4.3	4.29	4.09	4.29
$A$ ( $\mu\text{m/l}$ )	6.62	6.02	6.96	5.21
$\alpha$ (esu)	41.37	37.46	43.74	40.57
$\beta$ (esu)	11.45	8.69	5.92	8.13
$V_m$ (cm <sup>3</sup> )	266.22	203.36	278.82	298.47
$\chi$ (eV)	-3.43	-3.54	-3.83	-3.55
$\eta$ (eV)	2.15	2.14	2.04	2.15
$S$ (eV) <sup>-1</sup>	0.23	0.23	0.24	0.23
$\mu$ (eV)	3.43	3.54	3.83	3.55
$\omega$ (eV)	2.74	2.92	3.6	2.94
$\Delta E_n$ (eV)	0.38	0.45	0.78	0.46
$\Delta E_c$ (eV)	7.24	7.53	8.45	7.56

Table VI<sub>a2</sub>. Structures, electronic quantities and activity values for group a<sub>2</sub> compounds.

a <sub>1</sub>	5	6	7	11	12
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R group					
HOMO (eV)	-5.76	-5.6	-5.63	-5.64	-5.62
LUMO (eV)	-1.76	-1.29	-1.42	-1.39	-1.34
$\Delta E$ (eV)	4	4.31	4.21	4.24	4.28
A( $\mu\text{m/l}$ )	6.72	7.34	7.89	7.36	7.4
$\alpha$ (esu)	47.63	49.11	49.44	52.25	53.19
$\beta$ (esu)	5.13	10.49	4.45	5.56	12.22
$V_m$ ( $\text{cm}^3$ )	315.36	305.22	284.26	298.61	395.21
$\chi$ (eV)	-3.76	-3.45	-3.53	-3.51	-3.48
$\eta$ (eV)	2.00	2.16	2.11	2.12	2.14
S (eV) <sup>-1</sup>	0.25	0.23	0.24	0.24	0.23
$\mu$ (eV)	3.76	3.45	3.53	3.51	3.48
$\omega$ (eV)	3.54	2.75	2.95	2.91	2.83
$\Delta E_n$ (eV)	0.78	0.39	0.48	0.46	0.42
$\Delta E_e$ (eV)	8.3	7.28	7.54	7.49	7.38





R group				
HOMO (eV)	-6.31	-6.5	-6.21	-6.27
LUMO (eV)	-1.31	-1.45	-1.27	-1.27
$\Delta E$ (eV)	5	5.06	4.94	5
A( $\mu\text{m/l}$ )	6.3	6.92	7	6.92
$\alpha$ (esu)	40.25	42.07	44.42	40.27
$\beta$ (esu)	9.11	10.26	8.49	7.36
$V_m$ ( $\text{cm}^3$ )	251.2	268.9	279.9	306.3
$\chi$ (eV)	-3.81	-3.97	-3.74	-3.77
$\eta$ (eV)	2.5	2.53	2.47	2.5
S (eV) <sup>-1</sup>	0.2	0.2	0.2	0.2
$\mu$ (eV)	3.81	3.97	3.74	3.77
$\omega$ (eV)	2.9	3.12	2.84	2.84
$\Delta E_n$ (eV)	0.34	0.41	0.33	0.32
$\Delta E_e$ (eV)	7.97	8.36	7.81	7.87

Table VI<sub>a3</sub>. Structures, electronic quantities and activity values for group a<sub>3</sub> compounds.

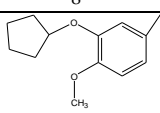
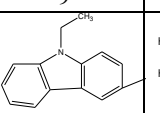
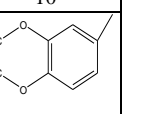






a <sub>3</sub>			
HOMO (eV)	-5.56	-5.51	-5.6
LUMO (eV)	-1.31	-1.31	-1.29
$\Delta E$ (eV)	4.25	4.2	4.31
A( $\mu\text{m/l}$ )	7.35	7.51	7.16
$\alpha$ (esu)	53.35	58.09	47.45
$\beta$ (esu)	13.1	15.81	13.99
$V_m$ ( $\text{cm}^3$ )	438.96	380.92	259.34
$\chi$ (eV)	-3.43	-3.41	-3.45
$\eta$ (eV)	2.13	2.1	2.15
S (eV) <sup>-1</sup>	0.24	0.24	0.23
$\mu$ (eV)	3.43	3.41	3.45
$\omega$ (eV)	2.77	2.76	2.76
$\Delta E_n$ (eV)	0.4	0.41	0.39
$\Delta E_e$ (eV)	7.27	7.23	7.28

Table VI<sub>b2</sub>. Structures, electronic quantities and activity values for group b<sub>2</sub> compounds.

b <sub>2</sub>						
HOMO (eV)	-6.25	-6.23	-6.08	-6.07	-6.41	-6.25
LUMO (eV)	-1.29	-1.31	-1.31	-1.3	-1.54	-1.29
$\Delta E$ (eV)	4.96	4.91	4.77	4.77	4.87	4.96
A ( $\mu\text{m/l}$ )	7.22	8.15	7.42	6.82	7.85	6.80
A (esu)	51.86	49.61	51.42	51.71	54.43	53.99
B (esu)	11.09	6.82	8.77	7.44	9.18	15.94
$V_m$ ( $\text{cm}^3$ )	335.3	353.5	325	321.1	338.9	409.7
$\chi$ (eV)	-3.75	-3.77	-3.77	-3.69	-3.69	-3.97
$\eta$ (eV)	2.44	2.48	2.46	2.38	2.38	2.43
S (eV) <sup>-1</sup>	0.21	0.2	0.2	0.21	0.21	0.21
$\mu$ (eV)	3.75	3.77	3.77	3.69	3.69	3.97
$\omega$ (eV)	2.89	2.87	2.89	2.86	2.85	3.25
$\Delta E_n$ (eV)	0.36	0.34	0.35	0.36	0.36	0.49
$\Delta E_e$ (eV)	7.86	7.88	7.89	7.75	7.73	8.44

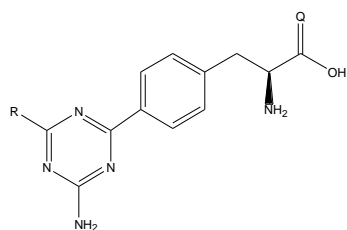


Fig 3 The main chemical structure of group b.

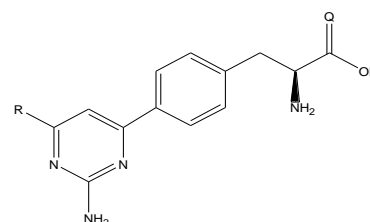
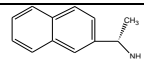
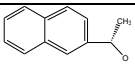


Table VI<sub>b1</sub> Structures, electronic quantities and activity values for group b<sub>1</sub> compounds.

b <sub>1</sub>	19	20	21	22
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Fig 4. The main chemical structure of group d.

Table VI<sub>d</sub>. Structures, electronic quantities and activity values for compounds group d.

d	16	17
R group		
HOMO (eV)	-5.67	-5.98
LUMO (eV)	-1.1	-1.28
$\Delta E$ (eV)	4.38	4.70
A ( $\mu\text{m/l}$ )	7.49	6.42
$\alpha$ (esu)	51.57	50.09
$\beta$ (esu)	11.25	8.08
$V_m$ (cm <sup>3</sup> )	306.29	281.04
$\chi$ (eV)	-3.49	-3.63
$\eta$ (eV)	2.19	2.35
$S$ (eV) <sup>-1</sup>	0.23	0.21
$\mu$ (eV)	3.49	3.63
$\omega$ (eV)	2.78	2.80
$\Delta E_n$ (eV)	0.39	0.35
$\Delta E_c$ (eV)	7.37	7.61

The variation of structures, electronic quantities and activity values for the chosen molecules are shown in Tables VI<sub>a1</sub>, VI<sub>a2</sub>, VI<sub>a3</sub>, VI<sub>b1</sub>, VI<sub>b2</sub>, VI<sub>b3</sub> and VI<sub>d</sub>. The reported activity values were taken from previous study done by Liang Ouyang et al (2012)[2].

As it can be seen in previous mentioned Tables, in general, compounds bearing a 4-amino-1,2,4-triazin ring in group (b) and (d) have higher chemical potential, negative electronegativity, softness, and activity, than compounds bearing a pyrazine ring in group(a).

In addition, compounds bearing a naphthalene moiety and a biphenyl group in groups (a<sub>2</sub>,a<sub>3</sub>), (b<sub>2</sub>,b<sub>3</sub>) and group d show higher activity and provirus properties than the compounds bearing a phenyl group or other cycle group in groups (a<sub>1</sub>) and (b<sub>1</sub>). For example, the highest activity value recorded (8.15  $\mu\text{m/l}$ ) for compounds 24 from group b<sub>2</sub> which bearing a 4-amino-1,2,4-triazin and a biphenyl group. Another example is compound 7 with a naphthalene ring has higher chemical potential, negative electronegativity, softness, and activity than compound 1 bearing a cyclohexane ring.

However, the Orto-position structure (compound 24) compared to the para- position structure (molecule 23) possesses somewhat larger activity (8.15  $\mu\text{m/l}$ ) for compound 24 [versus (7.22  $\mu\text{m/l}$ ) for compound 23]

Furthermore, changing the nitrogen atom (compound 16) to oxygen atom (compound 17) caused in loss of activity from (7.49  $\mu\text{m/l}$ ) for compound 16 to (6.42  $\mu\text{m/l}$ ) for compound 17.

## B. The Effect Hyper-conjugative Interactions on Polarizability and Activity

The intramolecular hyper-conjugative interactions are considered for 27 and 28 Figures 5, 6 respectively as an example to investigate the effect of hyper-conjugative interactions on polarizability and activity.

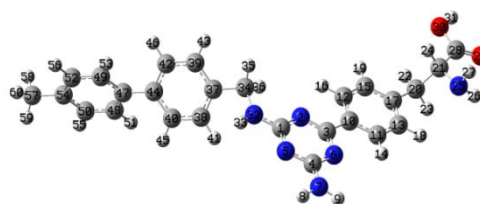


Fig -5 compound C27 chemical structure.

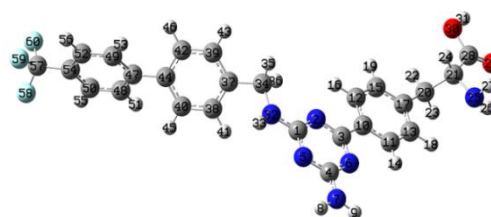


Fig - 6 compound C28 chemical structure.

Table VII hyper-conjugative interactions of compounds C27,C28 using B3LYP/6-311G(d,p) and B3LYP/6-311G++(2d,2p).

hyper-conjugative interactions				C 27	C 28
Donor (i)	Type	Acceptor (j)	T	E(2) kcal/mol	E(2) kcal/mol
C21-H24	$\sigma$	C28-O29	$\pi^*$	2.61	2.58
C57-H58	$\sigma$	C52-C54	$\pi^*$	4.47	
C57-F59	$\sigma$	C52-C54	$\pi^*$		1.08
LP1N7		C4-N5	$\pi^*$	55.06	56.09
LP1N32		C1-N2	$\pi^*$	61.29	60.01

In Table VII, we investigated that the replacement of the methyl group for compound 27 by a tri-fluoro-methyl group for compound 28 caused a decrease in the intermolecular hyper-conjugated interaction for compound 28 compared to compound 27.

For example, the intramolecular hyper-conjugated interaction  $\sigma$  (C21-C24)  $\rightarrow$   $\pi^*$  (C28-O29) has 2.61 kcal mol<sup>-1</sup> for compound 27. It decreased to 2.58 kcal mol<sup>-1</sup> for compound 28.

The intramolecular hyper-conjugated interaction  $\sigma$  (C57-H58)  $\rightarrow$   $\pi^*$  (C52-C54) show 4.47 kcal mol<sup>-1</sup> for compound 27. It decreased by substitution of the hydrogen atoms by fluorine atoms for  $\sigma$  (C57-F59)  $\rightarrow$   $\pi^*$  (C52-C54) to 1.08 kcal mol<sup>-1</sup> for compound 28.

The intramolecular hyper-conjugative interaction for LP1N32  $\rightarrow$   $\pi^*$  (C1-N2) show 61.29 kcal mol<sup>-1</sup> for compound 27. It decreased to 60.01 kcal mol<sup>-1</sup> for compound 28.





The decrease in the intramolecular hyper-conjugated interaction shows an increase in HOMO- LUMO energy gaps from 4.77 eV for compound 27 to 4.87 eV for compound 28. It was recorded a decrease in the activity from 7.85 ( $\mu\text{m/l}$ ) for compound 27 to 6.8  $\mu\text{m/l}$  for compound 28 and a decrease in the polarizability from  $54.43 \times 10^{-24}$  esu for compound 27 to  $53.99 \times 10^{-24}$  esu for compound 28.

These results are in a good agreement with Hatua, K., and Nandi, P. K study in 2011 [13], and with the studied that done by Msugh and Targema et al (2013) indicated that the decrease of intramolecular hyper-conjugated interaction energy caused an increase in HOMO-LUMO energy gaps and a decrease of activity [14].

#### IV. CONCLUSION

In the present study, we investigated substitutions effects on HOMO- LUMO energy on hyperconjugated and physical properties, including electronegativity, hardness, softness, electrophilicity index, chemical potential, electrofugality, nucleofugality, polarizability, and first hyperpolarizability for 32 phenylalanine series compounds as tryptophan hydroxylase-1 (TPH1) inhibitors and effects of them on the activity using B3LYP/6-311G(d,p) and B3LYP/6-311G++(2d, 2p) level of theory.

We notice the absolute good agreement between the calculated HOMO and LUMO energy gaps values at B3LYP/6-311(d,p) basis set and B3LYP/6-311++(2d,2p) basis set. They gave a good correlation coefficient ( $R^2=0.99$ ).

An inverse relationship between HOMO- LUMO energy gaps and the activity for most of the title compounds were obtained. Presence 1,2,4-triazine ring instead of pyrazine ring has high effects on the activity and the electronic properties.

The relationship between polarizability, hyper-polarizability, and activity affected by several structural changes such as the presence of biphenyl connected to pyrazine core or 4-amino-1,2,4-triazine ring, and presence of donated or withdrawing groups which effect on the intramolecular hyper-conjugated interaction.

In conclusion of this work, the substitution in molecular geometry can be lead to significant changes in some of the electronic properties.

Using the variable X to construct a model with to Activity results in a second-degree polynomial model having is obtained.

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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