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Research Article

DRUG LIKENESS SCORING AND STRUCTURE ACTIVITY/PROPERTY RELATIONSHIPS OF 1,2,3-TRIAZOLE DERIVATEVES AS AROMATASE INHIBITOR

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ABSTRACT

Molecular geometry, electronic structure and effect of the substitution for 1,2,3-triazole derivatives, have been studied by molecular mechanics, ab initio/HF and DFT /B3LYP. The molecular electrostatic potential surface (MESP) which displays the activity centers of a molecule and the substitution effects on its systems have been performed by HSAB (Hard Soft Acid and Base) principle application. Also, the structure-activity/property relationship studies were applied on twenty-two molecules of 1, 2, 3-triazole derivatives, all have the aromatase inhibitory activity. Results such as net charges, bond length, dipole moment, QSAR properties, Lipinski's parameters, and Lipophilic Efficiency (LipE), are reported in this paper.

Keywords:1,2,3-triazole; MESP; SAR; Drug likeness; aromatase.

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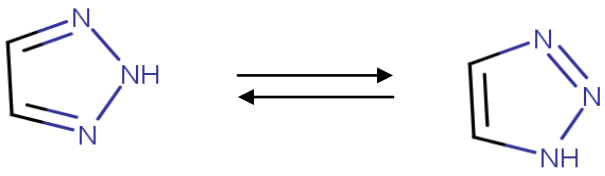
1. INTRODUCTION

Most of the nitrogen-containing molecules are pharmacologically very active. This feature can be attributed to the fact that nitrogenous compounds are part and parcel of the bimolecular

diversity[1]. Amongst the pharmacologically active nitrogenous compounds, the 1,2,3-triazole ring is a moiety present in antiallergic[2], antibacterial[3], antiviral[4], antifungal[5] and analgesic[6]drugs. However, its 1,2,4-isomer is used as a much more frequently drug structures component (e.g. anastrozole, estazolam, ribavirin, triazolam, etc.).

The 1,2,3- triazole can be divided in three subclasses depending on the position of the substituants in the ring. While 1H-1,2,3-triazole and 2H-1,2,3-triazole are aromatic compounds but their 4H-1,2,3-triazole isomers are not. This fact reflects the abundance of 1H- and 2H-1,2,3-triazoles and the scarcity of 4H-1,2,3-triazoles[7].

The two tautomeric forms: 1H- and 2H-1,2,3-triazoles derivatives are in equilibrium, both in solution and gas phase (Figure 1)[8] .



2H-1,2,3-triazole 1H-1,2,3-triazole

Fig.1. 1,2,3-triazole tautomeric forms 2H-1,2,3-triazole and 1H-1,2,3-triazole (MarvinSketch 15.8.31)

It is well known that compounds having an aza-hetero ring, such as triazole show inhibitory activity against aromatase [9].

Aromatase is a cytochrome P-450 enzyme, which is responsible for the conversion of androgen to estrogen in the final step of the steroid biosynthesis cascade. Inhibition of this enzyme is therefore of practical importance in the treatment of estrogen-dependent diseases, for example breast cancer, cancer of the uterine body, and endometriosis. Like aromatase, several other steroid ogenic enzymes are also cytochrome P-450[10].

Quantitative structure-activity relationship (QSAR) methods have attracted considerable attention due to their ability to assist the design of a new drug[11-15]. It has done much to enhance our understanding of fundamental processes and phenomena in medicinal chemistry and drug design[16]. QSAR methods are attempts to correlate the molecular structure or properties derived from the molecular structure with a particular type of chemical,

biochemical or biological activity[17-19].

The present work reports ab initio and density functional results of molecular properties of 1H-1,2,3-triazole and 2H-1,2,3-triazole. Additionally we applied DFT methods on some of 2H-1,2,3-triazole. We studied, at last, some of QSAR and drug likeness proprieties of 1,2,3 -triazole derivatives series reported in literature. On the other hand, calculated metrics aim to combine the potency with other parameters into a single metric which may be monitored during optimization. The earliest and most commonly applied metrics are the Ligand Efficiency (LE) and the Lipophilic Efficiency (LipE). Web based software was used to obtain parameter such as TPSA, nrotb and drug likeness.

2. MATERIAL AND METHODS

All calculations were performed using HyperChem 8.0.6 software[20] Gaussian 09 program package[21]; MarvinSketch 15.8.31 software[22], and Molinspiration online database, Molinspiration Cheminformatics [23].

The geometries of 2H-1,2,3-triazole and 1H-1,2,3-triazole,were fully optimized with ab initio/HF(6-31G+), 6-31G++(d,p), 6-311G++(d,p))and DFT/B3LYP (6-311++G (d, p)), integrated in Gaussian 09 program package. The calculation of QSAR properties is performed through the module QSAR Properties (HyperChem version 8.0.6), and allows the calculation of several properties commonly used in QSAR studies.

Molinspiration, and web based software was used to obtain parameter such as TPSA (topological polar surface area), nrotb (number of rotatable bonds) and drug likeness. The calculated results are reported in the present work.

3. RESULTS AND DISCUSSION

Geometric and electronic structure of 1 H-1,2,3-triazole

The optimized geometrical parameters of 1H-1,2,3- triazole (Figure 2) are obtained using ab-initio/*HF* and *DFT* methods, listed in (Table 1) and (Table 2) with experimental results approximately similar to the theoretical results, regarding bond length and valence angle values[24].

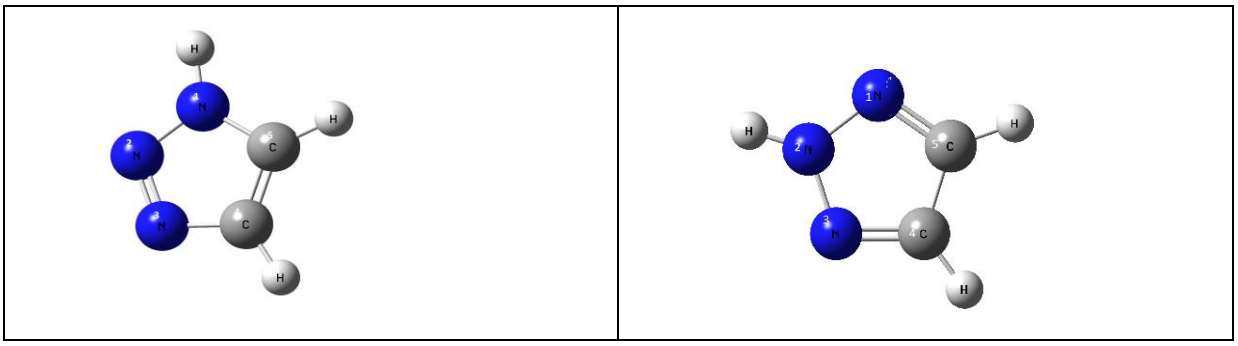


Fig.2.3D conformation of 1H and 2 H-1,2,3-triazole (Gauss View 3.0.9)

Table 1. Bond lengths (angstrom) of 1H-1,2,3-triazole

Parameters	EXP[7]	Ab-initio/HF			DFT/B3LYP
		6-31G+	6-31G++(d,p)	6-311G++(d,p)	6-311G++ (d,p)
N1-N2	1.355	1.346	1.448	1.315	1.349
N2-N3	1.309	1.282	1.251	1.262	1.298
N3-C4	1.370	1.372	1.402	1.356	1.364
C4-C5	1.378	1.361	1.340	1.355	1.373
C5-N1	1.356	1.352	1.317	1.343	1.355

The theoretical dihedral angle values calculated by different methods are practically equal to zero degree explaining that the geometry of 1H-1,2,3- triazole is planar, and hence makes this conformation more stable. The charge densities calculated (Table3) by these methods are slightly different.

Table 2. Calculated values, valence angles and dihedral angles of 1H-1,2,3-triazole

Parameters	EXP [7]	Ab initio/HF			DFT/B3LYP
		6-31G+	6-31G++(d,p)	6-311G++(d,p)	6-311++G(d,p)
N1-N2-N3	108.2	107.355	107.940	108.119	107.012
N2-N3-C4	108.2	109.529	108.636	109.270	108.692
N3-C4-C5	109.9	107.959	108.499	107.961	108.699
C4-C5-N1	104.4	104.328	107.654	103.521	103.560
C5-N1-N2	110.2	104.328	107.268	111.120	111.450
N1-N2-N3-C4	-	0	0	0	0
N2-N3-C4-C5	-	0	0	0	0
N3-C4-C5-N1	-	0	0	0	0
C4-C5-N1-N2	-	0	0	0	0
C5-N1-N2-N3	-	0	0	0	0

Table 3. Net charge distribution for 1H-1,2,3-triazole

Atoms	Ab initio/HF	DFT/B3LYP
	6-311G++(d .p)	6-311++G(d,p)
N1	-0.145	-0.051
N2	-0.025	-0.044
N3	-0.158	-0.158
C4	-0.220	-0.160
C5	-0.205	-0.210

Geometric and electronic structure of 2 H-1,2,3-triazole

The optimized geometrical parameters of 2 H-1,2,3-triazole by ab-initio/HF and DFT method listed in Table 4 and Table 5 are in accordance with numbering scheme given in Figure 2.

Table 4. Bond lengths (angstrom) of 2H-1,2,3-triazole

Parameters	EXP[19]	Ab initio/HF			DFT/B3LYP
		6-31G+	6-31G++(d,p)	6-311G++(d,p)	6-311G++(d,p)
N1-N2	1.323	1.326	1.303	1.301	1.326
N2-N3	1.323	1.326	1.303	1.301	1.326
N3-C4	1.347	1.319	1.308	1.306	1.333
C4-C5	1.401	1.411	1.404	1.405	1.406
C5-N1	1.347	1.319	1.308	1.306	1.333

Table 5. Calculated values of valence angles and dihedral angles of 2H-1,2,3-triazole

Parameters	EXP[19]	Ab initio/HF			DFT/B3LYP
		6-31G+	6-31G++(d,p)	6-311G++(d,p)	6-311++G(d,p)
H5-C5-C4	130.8	121.897	121.742	130.349	130.293
H4-C4-C5	130.8	121.897	121.742	130.349	130.293
H2-N2-N3	-	122.698	122.001	122.019	121.094
N1-N2-N3	117.3	114.604	115.997	115.951	116.55
N2-N3-C4	-	104.569	104.084	104.152	103.111
N3-C4-C5	-	108.129	107.918	108.612	108.612
C4-C5-N1	-	108.129	107.918	108.612	108.612
C5-N1-N2	-	104.569	104.084	104.152	103.111
N1-N2-N3-C4	-	-0.003	-0.001	0.001	0.008
N2-N3-C4-C5	-	-0.005	0.0000	0.002	-0.022
N3-C4-C5-N1	-	0.012	0.002	0.002	0.030
C4-C5-N1-N2	-	0.001	0.000	-0.001	0.022
C5-N1-N2-N3	-	1.319	0.001	0.001	0.000

The efficiency of theoretical methods may be assessed by comparison with experimental results[25]. From these results a good correlation can be seen between the ab-initio/HF, and

DFT for bond length. We can also note that charge densities calculated by ab-initio/HF are approximately similar to those calculated by the DFT method (Table 6).

Table 6. Net charge distribution for 2H-1,2,3-triazole.

Atoms	Ab initio/HF	DFT/B3LYP
	6-311G++(d .p)	**6-311++G(d,p)**
N1	-0.129	-0.128
N2	-0.063	-0.044
N3	-0.129	-0.128
C4	-0.188	-0.167
C5	-0.188	-0.167

The theoretical dihedral angle values calculated are practically equal to zero degree revealing that the geometry of 2H-1,2,3-triazole is planar, and hence makes this conformation more stable.

The efficiency of DFT/B3LYP method with 6-311++G(d,p) basis set may be scrutinized by comparison with the results obtained by ab-initio/HF method. A very good agreement between predicted geometries (bond lengths and bond angles) and corresponding experimental data, especially the DFT/B3LYP results can be observed. From that, we can say that the DFT method is more appropriate for further study on 1,2,3-triazole derivatives in other parts of this work.

To compare the stability of the two compounds1H-1,2,3-triazoleand 2H-1,2,3-triazole, we calculated the HOMO (highest occupied molecular orbital), and the LUMO (lowest unoccupied molecular orbital) and their difference (ΔE)calculated by DFT/6-311G (d,p) by (Gaussian09) and heat of formation, calculated by (HyperChem 8.06) the results are reported in Table 7.

Table 7. Calculated E_{HOMO}, E_{LUMO}, energy band gap (ΔE) and Heat of formation ΔH_f

Nucleus	HOMO [au]	LUMO [au]	ΔE [au]	ΔH_f [kcal.mol^{-1}]
1H-1.2.3 triazole	-0.279	-0.023	0.256	67.813
2H-1.2.3 triazole	-0.289	-0.026	0.263	70.610

The calculations show the 2H tautomer as the more stable with a low reactivity. The difference of $\Delta E_{1H\text{-}2H}$ was -2.1kcal·mol^{-1}.These results agreed the results obtained by Tornkvist et al[26].

Molecular electrostatic potential

The molecular electrostatic potential is a well-established tool to explain the reactive behavior of a wide variety of chemical systems in both electrophilic and nucleophilic reactions. The study of biological recognition processes and hydrogen bonding interactions was performed to predict the reactive sites for electrophilic and nucleophilic attack for the investigated molecule[27]. The MEP was calculated at the DFT optimized geometry (Figure 3).

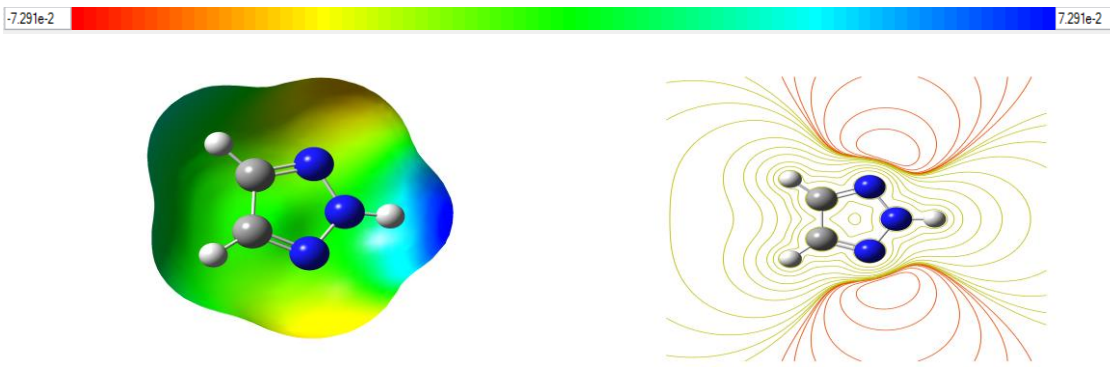


Fig.3. 3D MESP surface map and 2D MESP contour map for 2H 1,2,3 triazole (Gauss view 5.0.9)

The MEP is a useful property to study reactivity given that an approaching electrophile will be attracted to negative regions (where the electron distribution effect is dominant)[28].The electrostatic potential values are represented by different colors. The positive, negative and neutral electrostatic potential regions of molecules are shown in terms of color grading. Generally, potential increases in the order red < orange < yellow < green < blue. The red color indicates the maximum negative region and the blue color represents the maximum positive region[29,30].

The MESP surface map (Figure 3) for 2H-1,2,3-triazole shows that the maximum negative region is localized (yellow) over N1,N3 atoms and the maximum positive region is localized on NH group (bleu), indicating a possible site for nucleophilic attack. These sites give information about the region from which the compound can has intermolecular interactions. This predicted the most reactive site for both electrophilic and nucleophilic attack[31].

The green color situated in the middle between the yellow and blue regions and localized on CH groups explains the neutral electrostatic potential surface.

Substitution effect on 2H-1,2,3-triazole structure

To perceive the effect of the substitution, we have studied two series: the methyl and the ethyl group for the first series (an electron donor group), the cyanide and Chloride group for the second series (an electron attractor group) in position N2, C4 and C5 in the same series are given in Table 8.

Table 8. Energies of 2H-1,2,3-triazole derivatives

	HOMO [au]	LUMO [au]	ΔE [au]	μ [D]	ΔHf [kcal.mol^{-1}]
2H1.2.3 TRIAZOLE	-0.289	-0.026	0.263	0.217	70.610
			Series 1		
T1	-0.272	-0.021	0.251	0.485	69.068
T2	-0.272	-0.018	0.252	0.700	61.168
T3	-0.272	-0.018	0.252	0.700	61.168
T4	-0.258	-0.015	0.243	0.343	59.688
T5	-0.258	-0.015	0.243	0.343	59.688
T6	-0.259	-0.011	0.248	0.908	51.918
T7	-0.270	-0.020	0.250	0.658	64.308
T8	-0.272	-0.020	0.251	0.398	56.550
T9	-0.272	-0.020	0.251	0.741	56.550
T10	-0.256	-0.016	0.240	0.741	50.581
T11	-0.256	-0.016	0.240	0.504	50.585
T12	-0.258	0.013	0.271	0.810	43.195
T13	-0.246	-0.010	0.236	0.508	50.195
T14	-0.245	-0.016	0.229	0.285	36.101
			Series 2		
T`1	-0.285	-0.071	0.214	1.331	74.510
T`2	-0.281	0.038	0.243	1.217	65.360
T`3	-0.281	0.038	0.243	1.217	65.360
T`4	-0.281	-0.081	0.200	0.838	69.425
T`5	-0.279	-0.048	0.231	1.620	60.687
T`6	-0.281	-0.081	0.200	0.838	69.425
T`7	-0.311	-0.084	0.227	4.883	121.960
T`8	-0.308	-0.068	0.240	4.062	108.150
T`9	-0.308	-0.068	0.240	4.062	108.150
T`10	-0.329	-0.118	0.211	2.750	161.290
T`11	-0.325	-0.092	0.233	5.762	148.050
T`12	-0.329	-0.118	0.211	3.059	161.290
T`13	-0.343	-0.140	0.203	1.327	202.590
T`14	-0.279	-0.091	0.188	0.545	64.910

Heat of formation, dipole moment, HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) and their difference (ΔE) are reported for 2H-1,2,3-triazole and its derivatives in Table 9 and Table 10.

Table 9. Mulliken charges of 2H-1,2,3-triazole and its derivatives (series 1)

Series1		**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**T12**	**T13**	**T14**
N1		-0.12	-0.15	-0.15	-0.06	-0.06	-0.12	-0.31	-0.12	-0.05	-0.10	-0.10	-0.08	-0.05	-0.25
N2		0.10	-0.1	-0.01	0.12	0.12	-0.01	0.27	0.02	0.02	0.30	0.30	-0.33	0.06	0.42
N3		-0.12	-0.11	-0.11	-0.14	-0.14	-0.12	-0.31	-0.12	-0.12	-0.10	-0.10	-0.12	-0.05	-0.31
C4		-0.17	-0.09	0.09	0.04	0.04	0.10	-0.2	0.14	-0.26	0.12	0.12	0.14	0.13	0.17
C5		-0.17	0.09	-0.09	-0.06	-0.06	0.10	-0.2	-0.26	0.15	-0.24	-0.24	-0.23	0.10	0.02
Sub	C_1-methyl	-0.31	-	-	0.29	0.29	-	-	-	-	-	-	-	0.28	
N2	C1-ethyl	-	-	-	-	-	-	0.15	-	-	-0.27	-0.27	-	-	-0.17
	C2-ethyl	-	-	-	-	-		-0.65	-	-	-0.44	-0.44	-	-	-0.60
Sub	C_1-methyl	-	-0.70		-0.70	-	-0.61	-	-	-	-	-	-	-0.69	-
C4	C1-ethyl	-	-	-	-	-	-		-0.38	-	-0.42	-	-0.29	-	-0.48
	C2-ethyl	-	-	-	-	-	-	-	-0.51	-	-0.53	-	-0.63	-	-0.65
Sub	C_1-methyl	-		-0.70		-0.74	-0.61	-	-	-	-	-	-	-0.69	-
C5	C1-ethyl	-	-	-	-	-	-	-	-	-0.38		-0.42	-0.18	-	-0.48
	C2-ethyl	-	-	-	-	-	-	-	-	-0.51		-0.53	-0.74	-	-0.65

Table 10. Mulliken charges of 2H-1,2,3-triazole and its derivatives (series 2).

Series2		**T'1**	**T'2**	**T'3**	**T'4**	**T'5**	**T'6**	**T'7**	**T'8**	**T'9**	**T'10**	**T'11**	**T'12**	**T'13**	**T'14**
N1		-0.09	-0.04	-0.09	-0.06	-0.01	-0.01	-0.08	-0.11	-0.12	-0.03	-0.10	-0.04	-0.01	0.04
N2		0.34	-0.04	-0.04	0.35	-0.07	0.35	0.08	0.06	0.06	0.15	0.04	0.15	0.14	0.34
N3		-0.09	-0.09	-0.04	-0.01	-0.01	-0.06	-0.08	-0.12	-0.11	-0.04	-0.10	-0.03	-0.01	0.04
C4		-0.17	-0.37	-0.24	-0.36	-0.53	-0.31	-0.14	0.02	0.72	0.74	0.89	0.01	0.99	-0.56
C5		-0.17	-0.24	-0.37	-0.31	-0.53	-0.36	-0.14	0.72	0.02	0.01	0.89	0.74	0.99	-0.56
Sub	Cl	0.13	-	-	-0.10	-	-0.10	-	-	-	-	-	-	-	-0.09
N2	C-cyano	-	-	-	-	-	-	0.22	-	-	0.22	-	0.22	0.22	-
	N-cyano	-	-	-	-	-	-	0.20	-	-	-0.18	-	-0.18	-0.16	-
Sub	Cl	-	0.31	-	-	0.40	0.31	-	-	-	-	-	-	-	0.39
C4	C-cyano	-	-	-	-	-	-	-	-	-0.91	-0.89	-0.83	-	-0.94	-
	N-cyano	-	-	-	-	-	-	-	-	-020	-0.18	-0.15	-	-0.14	-
Sub	Cl	-	-	0.31	0.31	0.40	-	-	-	-	-	-	-	-	0.39
C5	C-cyano	-	-	-	-	-	-	-	-0.91	-	-	-0.83	-0.89	-0.94	-
	N-cyano	-	-	-	-	-	-	-	-0.20	-	-	-0.15	-0.18	-0.14	-

Sub N Substitution is in the atom N2, Sub C4 Substitution is in the atom C4, Sub C5 Substitution is in the atom C5

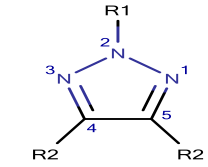
Net atomic charges are also reported for the effect of the substitution on the electronic parameters and energy and their impact on the stability and chemical reactivity of molecule.

Two series substituted molecule were studied (Figure 4).

This calculation is performed by DFT/B3LYP method using 6-311++G (d,p) basis set.

The heat of formation decreased approximately to 2 and 7 kcal·mol^{-1} at each addition of methyl and ethyl groups respectively. Compounds T1, T4, T7 (nitrogen substituent) were the greatest values of the heat of formation compared to other derivatives.

N 2 substituted 1,2,3-triazoles are one special class of triazole derivatives[32].



Series1	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14
R1	CH_3	H	H	CH_3	CH_3	H	C_2H_5	H	H	C_2H_5	C_2H_5	H	CH_3	C_2H_5
R2	H	CH_3	H	CH_3	H	CH_3	H	C_2H_5	H	C_2H_5	H	C_2H_5	CH_3	C_2H_5
R3	H	H	CH_3	H	CH_3	CH_3	H	H	C_2H_5	H	C_2H_5	C_2H_5	CH_3	C_2H_5

Series2	T`1	T'2	T'3	T'4	T'5	T'6	T'7	T'8	T'9	T'10	T'11	T'12	T'13	T'14
R1	Cl	H	H	Cl	Cl	H	CN	H	H	CN	H	CN	CN	Cl
R2	H	Cl	H	Cl	H	Cl	H	CN	H	H	CN	CN	CN	Cl
R3	H	H	Cl	H	Cl	Cl	H	H	CN	CN	CN	H	CN	Cl

Fig.4. 2H-1,2,3-triazole systems (Marvin sketch 15.8.31)

The Highest occupied molecular orbital (HOMO) and the lowest un-occupied molecular orbital (LUMO) are very important parameters for quantum chemistry. These values help to exemplify the chemical reactivity and kinetic stability of the molecule. The HOMO represents the ability to donate an electron and the LUMO as electron acceptor represents the ability to obtain an electron.

In order to evaluate the energetic behavior of the title compound, the relatively high value of $\Delta E_{HOMO–LUMO}$ indicates that the title compound presents high chemical stability and low reactivity[33,34]. Reactive (HSAB principle: hard and soft acids and bases), Hard bases have highest-occupied molecular orbitals (HOMO) of low energy, and hard acids have lowest-unoccupied molecular orbitals (LUMO) of high energy[35,36].

In the mono-substituted Methyl group category, the compound T1 shows a maximum positive charge on nitrogen (0.1) leading to a nucleophilic substitution (Table 9).

In the case of dimethyl and diethyl substitution of 2H-1,2,3-triazole in the N2 position compound T4 and T10 show maximum charge (0.12) and (0.30) respectively and smaller HOMO-LUMO energy gap (0.243) and (0.240) respectively (Table 9) and leads to preferential site of nucleophilic attack. We also note that the methyl and ethylsubstituent (donor effect) in (Table 8) has the effect of increasing the energy of the HOMO, with little change in the LUMO.

From the results shown in Table 4, the 4,5-dimethyl1,2,3-triazole (compound T6) shows an important dipole moment value (0.908 D). It is the most soluble in polar solvents than other derivatives.

In the present work, we have studied cyanide and Chloride substituted 1,2,3-triazole along the same line of methyl and ethyl substituted 2 H-1,2,3-triazole for a comparative study.

The heat of formation increased approximately 4 and 51 kcal·mol^{-1} at each addition of Chloride and cyanide groups respectively.

In mono-substituted cyanide and chloride derivatives, 2-chloro-1,2,3-triazole (compound T'1) is predicted to be more chemically reactive than 4-Cyano-1,2,3-triazole,2-Cyano-1,2,3-triazole and 4-Chloro- 1,2,3-triazole on the basis of least HOMO-LUMO energy gap (0.214).

Indi-substituted cyanide and chloride derivatives, dichloro 1,2,3-triazole (compounds T'4and T'6) is more reactive than dicyano 1,2,3-triazole (compound T'10). this is due to smaller HOMO-LUMO energy gap (0.200) (Table 8).

The compound T'4 and T'6 is predicted to be the most reactive with smaller HOMO-LUMO energy gap of all 1,2,3-triazolesystems (except the tri-substituted compounds).

The study of the effect of substitution on the 1.2.3 triazole base groups electron donor group and electron attractor group shows that by comparing the LUMO - HOMO gaps, the most chemically active are the tri-substituted. CompoundsT`14 and T14 show maximum charge in the N2 position (0.42) and (0.34) respectively. These results are in close agreement with the experiment, whereas the majority of tri-substituted 1,2,3-triazole have biological activity[37-39].

We note also that the cyanide and chloride substituent (attractor effect) lowers the energies of HOMO and LUMO. The influence on the energy of the LUMO is more important.

The effective atomic charges calculation which depicts the charges of every atom in the molecule distribution of positive and negative charges are vital to increase or decrease in bond length between the atoms, atomic charges, effect dipole moments, molecular polarizability, electronic structure, acidity-basicity behavior properties of molecular system and electrostatic potential surfaces[40,41].

The compound T`14 is predicted to be the most reactive with smaller HOMO-LUMO energy gap and with the most important positive charge on nitrogen N2. This Nitrogen is preferred for nucleophilic attack.

Based on our conclusions on the effect of substitution on the1,2,3-triazole molecule. We choose a series of triazole derivatives, having a biological activity.

Structure activity/property relationships of aromatase inhibitory activity of substituted 1,2,3-Triazole

For the series of 1,2,3-triazole derivatives (Figure 5) we have studied seven physicochemical properties with respect to their biological activities i.e, aromatase inhibitory activity[42]. The properties involved are: surface area grid (SAG), molar volume (V), hydration energy (HE), partition coefficient octanol/water (logP), molar refractivity (MR), polarizability(Pol) and molecular weight (MW). The results obtained using HyperChem 8.0.6 softwareare shown in Table 11 and Table 12. For example, figure 6 shows the favored conformation in 3D of the compound 11.

Table 11.QSAR proprieties for 1,2,3-triazole derivatives

Compounds	Volume [Å^3]	Surface area[Å^2]	Hydratation Energy [Kcal.mol^{-1}]	Polarizability [Å^3]	Refractivity [Å^3]
1	748.96	465.70	-11.47	25.74	75.13
2	907.17	557.73	-10.40	31.25	88.93
3	1063.73	633.76	-17.14	41.98	123.41
4	836.96	502.85	-10.09	30.47	87.00
5	802.85	500.60	-13.67	29.90	90.01
6	889.17	547.10	-15.81	32.37	96.62
7	936.17	575.25	-15.48	34.30	101.34
8	950.02	582.33	-19.98	34.22	101.60
9	942.17	577.93	-14.68	34.20	100.90
10	911.32	561.11	-22.74	33.00	98.23
11	1097.37	663.18	-16.62	42.03	125.14
12	1089.77	632.87	-13.87	41.98	120.40
13	849.89	526.55	-6.26	29.39	243.35

14	1010.69	609.48	-14.54	37.25	108.53
15	787.34	481.85	-5.46	28.62	82.06
16	746.55	467.42	-9.53	28.04	85.03
17	835.52	517.36	-11.78	30.52	91.64
18	882.86	544.68	-10.49	32.35	95.92
19	855.60	523.83	-18.77	31.15	93.25
20	876.54	539.32	-11.40	32.44	96.36
21	889.10	549.66	-15.94	32.37	96.62
22	694.35	441.70	-7.35	23.89	70.15

Table 12. Drug likeness scoring for compounds

	Lipinski rules					**Veber rules**		**Ligand efficiency and Lipophilicity efficiency**			
Compounds	**Log P**	**MW**	**HBD**	**HBA**	**$N_{VIOLATION}$**	**nrotb**	**TPSA**	**ABS**	**pIC5[41]**	**LE**	**LipE**
1	1.61	226.28	4	0	0	4	54.51	90.19	*5.36*	0.44	3.75
2	2.80	268.36	4	0	0	7	54.51	90.19	*5.26*	0.36	2.46
3	3.60	327.39	5	0	0	4	78.30	81.98	*4.99*	0.24	1.39
4	2.30	266.35	4	0	0	3	54.51	90.19	*4.97*	0.40	2.67
5	1.42	260.30	4	0	0	3	54.51	90.19	*5.47*	0.38	4.05
6	0.83	290.32	5	0	0	5	63.74	87.00	*5.22*	0.36	4.39
7	0.61	324.77	5	0	0	5	63.74	87.00	*5.41*	0.36	4.8
8	0.55	315.33	6	0	0	5	87.54	78.79	*5.04*	0.32	4.49
9	0.90	304.35	5	0	0	5	63.74	87.00	*5.38*	0.32	4.48
10	0.20	306.32	6	0	0	6	72.98	83.82	*5.63*	0.35	5.83
11	1.44	366.42	5	0	0	6	63.74	87.00	*4.94*	0.30	3.5
12	3.11	367.45	5	0	0	4	78.30	81.98	*4.71*	0.23	1.6
13	3.08	243.35	3	0	0	7	30.72	98.40	*5.02*	0.25	1.94
14	2.42	327.39	5	0	0	5	78.30	81.98	*5.33*	0.41	2.91
15	2.85	241.34	3	0	0	3	30.72	98.40	*5.10*	0.28	2.25
16	1.69	235.29	3	0	0	3	30.72	98.40	*5.01*	0.38	3.32
17	1.11	265.31	5	0	0	6	39.95	95.21	*4.97*	0.41	3.86
18	1.26	279.34	4	0	0	5	39.95	95.21	*5.65*	0.39	4.39
19	0.08	281.31	5	0	0	6	49.19	92.02	*4.76*	0.31	4.68
20	0.88	299.76	4	0	0	5	39.95	95.21	*5.30*	0.33	4.42
21	0.83	290.32	5	0	0	5	63.74	87.00	*5.87*	0.39	5.04
22	1.89	201.27	3	0	0	4	30.72	98.40	4.90	0.31	3.01

QSAR (Quantitative Structure-Property Relationships) deals with relationship between physico-chemical properties & chemical structure, are based on the assumption that the structure of a molecule (i.e, its geometric, steric and electronic properties) must contain the features responsible for its physical, chemical, and biological properties and on the ability to

represent the chemical by one or more numerical descriptors[43,44]. The relationships between the physicochemical properties of drugs and pharmacokinetic processes have been extensively studied. Some physicochemical parameters of drugs, such as lipophilicity, hydrogen-bonding capacity, molecular size and polar surface area, have proved to be useful for predicting passive transfer and permeation across biomembranes in ADME, but none has attracted as much interest in quantitative structure-permeation relationship (QSPeR) studies as lipophilicity[45,46].

Molecular volume determines transport characteristics of molecules, such as intestinal absorption or blood-brain barrier penetration[47]. Volume is therefore often used in QSAR studies to model molecular properties and biological activity.

Molecular weight (MW) is related to the size of the molecule. As molecular size increases, a larger cavity must be formed in water in order to solubilize the compound. Increasing MW reduces the compound concentration at the surface of the intestinal epithelium, thus reducing absorption. Increasing size also impedes passive diffusion through the tightly packed aliphatic side chains of the bilayer membrane[48].

Hydration energy is a key factor determining the stability of different molecular conformations in water solutions[49].

The molar refractivity is a steric parameter that is dependent on the spatial array of the aromatic ring in the synthesized compounds. The spatial arrangement also is necessary to study the interactionof the ligand with the receptor. Molarrefractivity is related, not only to the volume of the molecules but also to the London dispersive forces that act in the drug receptor interaction[50].

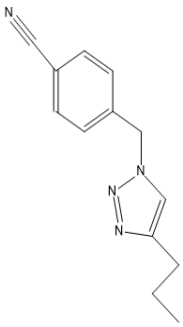
The polarizability of an atom or molecule describes the response of its electron cloud to an external field. Polarizability appears in many formulas for low-energy processes involving the valence electrons of atoms or molecules. It is also widely used to describe the inductive and dispersive interactions of a molecule or molecular system, and it plays an important role in modeling many molecular properties and biological activities[51,52].

The values of polarizability are generally proportional to the values of surfaces and of volumes. We observe that polarizability data are generally proportional to refractivity, molecular volume and surface. Compound 11 shows the maximum value of both

polarizability (42.03 Å³) and refractivity (125.14Å³). This compound has also high values of molecular weight (366.42), volume (1097.37 Å³) and surface (663.18Å^2).

The most important hydration energy in the absolute value is that of the compound 10 (22.74 kcal·mol^{-1}) and the weakest is that of compound 15 (5.46 kcal·mol^{-1}) (Table 11).

In fact, in the biological environments the polar molecules are surrounded by water molecules. Hence hydrogen bonds are established between a water molecule and these molecules.



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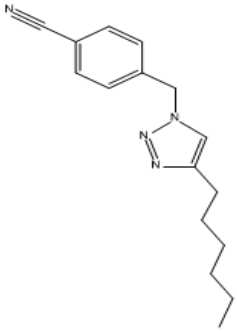

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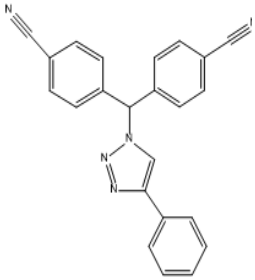

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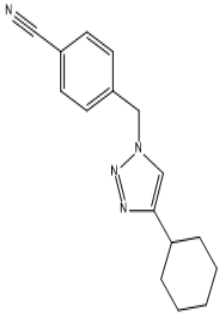

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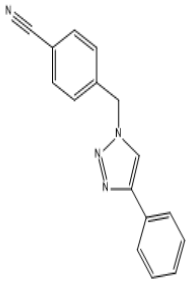

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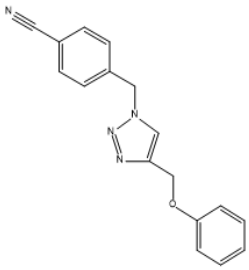

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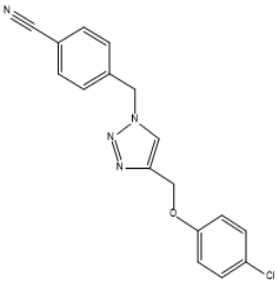

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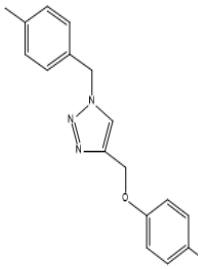

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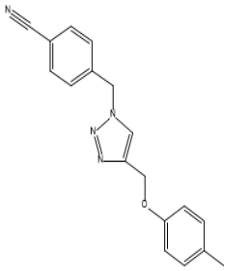

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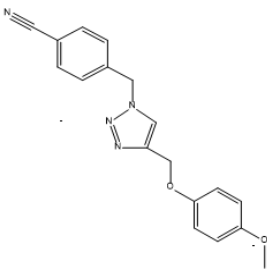

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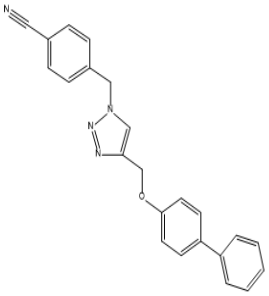

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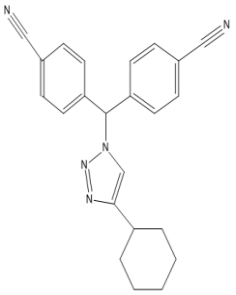

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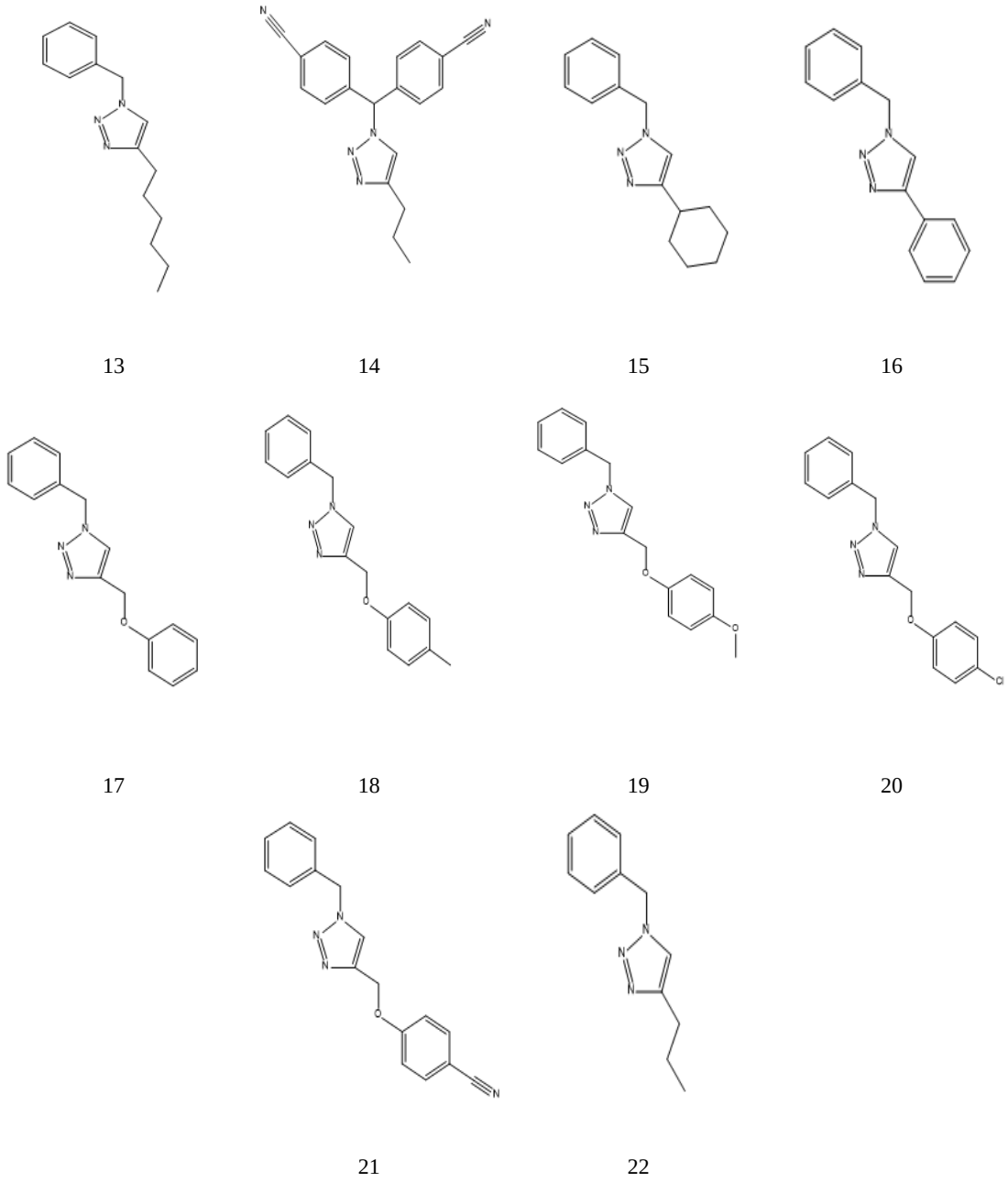

Fig.5. 2D structures of 1,2,3-triazole derivatives

Hydrophobic groups in 1,2,3- triazole derivatives induce a decrease of hydration energy. However, the lipophilicity increases proportionally with the hydrophobic features of substituent. As seen in Table 9, the compound 10 is expected to have the highest hydrophilicity, whereas compound 15 will be most Lipophilic. This implies that these compounds will have poor permeability across cell membrane.

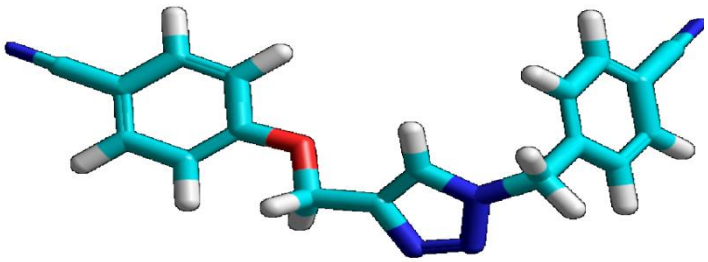

Fig.6. 3D conformation of compound 11 (HyperChem 8.03)

Drug-likeness properties of 1,2,3-triazole derivatives

Structures of all the selected 1,2,3-triazole derivatives in Figure 5, were fed in the online Molinspiration software version (www.molinspiration.com) for calculation of molecular properties (number of hydrogen bond donors andacceptors, molecular weight) inTable 12. For example, in figure 6 the favored conformation in 3D is of the compound 11.

Lipophilicity is usually measured by the partition coefficient (logP) of a compound in a single electrical form of molecular. It is a parameter that describes the partition equilibrium of a solute between water and an immiscible organic solvent. Log P is one criterion used in medicinal chemistry to assess the drug likeness of a given molecule, and is used to calculate lipophilic efficiency: a function of potency and log P that evaluate the quality of research compounds. For a given compound lipophilic efficiency is defined as the pIC50 (or pEC50) of interest minus the log P of the compound[53].

Molecular polar surface area (PSA), surface belonging to polar atoms, is a descriptor shown to correlate well with passive molecular transport through membranes and, therefore, allows prediction of transport properties of drugs. The calculation of PSA, however, is rather time-consuming because of the necessity to generate a reasonable 3D molecular geometry and the calculation of the surface itself[54]. Molecules with PSA values of 140 A^0 or more are expected to exhibit poor intestinal absorption [55]. TPSA was used to calculate the percentage of absorption (%ABS) according to the equation (1)[56].

$$\%ABS = 109 \pm 0.345 \times TPSA \qquad (1)$$

The Log values for all compounds 1,2,3-triazole derivatives except 3 (which has the higher value 3.60) are in the field of optimal values (0 < LogP < 3) so we could say that these compounds have optimal biological activity (permeability, solubility). For a too high logP, the

drug has low solubility and a too low LogP so it has difficulty penetrating the lipid membranes. Therefore the different properties which describe a molecular are so important for a drug's pharmacokinetics in the human body, including absorption, distribution, metabolism, and excretion "ADME" Components of the Lipinski's rule[58]:

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular mass less than 500 Daltons.
- An octanal-water partition coefficient log *P* not greater than 5
- No more than one number of violations.

For an ideal oral bioavailability, there are two other descriptors identified by Veber et al [60]:

- (1) Rotatable bonds are under 10.
- (2) Polar surface area is under 140 $Å^2$.

Molecules violating more than one of these parameters may have problems with bioavailability and high probability of failure to display drug-likeness[61].

However, there are some exceptions to this rule and a compound is likely to be orally active as long as it did not break more than one of its rules because some of orally active drugs such as atorvastatin, cyclosporin do not obey the rule of five[62].

The calculation results show that all compounds meet the Lipinski rules. The suggesting logP of these compounds was found below 5 which means a good permeability across cell membrane: TPSA below 140 $Å^2$, *n* violations =1 or <0 it means compound easily bind to receptor, molecular mass <500,*n*rotb < 5, H-bond donors (HBD) ≤ 5 and H-bond acceptors (HBA) ≤ 10.

In our case, the Lipinski and Veber rules are validated, therefore, theoretically, there would not have a problem with oral bioavailability for all chosen compounds.

TPSA of 1,2,3-triazole derivatives were found in the range of 87.54- 30.72 and were well below the 140 $Å^2$. We can observe obviously that all the title compounds (1–22) exhibited a great %ABS ranging from 78.79 to 98.40% indicating that these compounds should have good cellular plasmatic membrane permeability (Table 12).

Ligand lipophilicity efficiency (LE or LipE) is a ligand efficiency index that was first

proposed by Leeson and Springthrope[63]. LipE provides a straightforward and meaningful way to evaluate the quality of research compounds, linking potency and lipophilicity in an attempt to estimate drug-likeness, LipE attempts to maximize the minimally acceptable lipophilicity per unit of in vitro potency or more simply, to improve potency, while maintaining low lipophilicity.

$$\mathrm{LipE} = \mathrm{pIC50} - \log \mathrm{P} \qquad (2)$$

LE is defined as the difference of log*P*(or log *D*) and the negative logarithm of a potency measure (pKd, pKi or pEC50)[63].

In addition, we have studied the Ligand Efficiency (LE) to penalize large compounds over small compounds with similar potency because larger compounds tend to have poorer physicochemical and ADME properties [64]

The LE metric was first defined by Andrews [65], which defines it as biological activity per molecular size .

$$\mathrm{LE} = 1.4\mathrm{pIC50}/\mathrm{N_H} \qquad (3)$$

Where: N_H is the number of heavy atoms.

Ligand efficiency is a simple metric for assessing whether a ligand derives its potency from optimal fit with the target protein or simply by virtue of making many contacts.

It shows generally a dependency on ligand size i.e. Ligand efficiency drops dramatically when the size of the ligand increases [65].

We can see through the results in Table 12 that compound 10 had the highest LipE and LE value of the data set and was deemed to be the most optimal compound.

4. CONCLUSION

The present work studied the molecular proprieties of 1,2,3-triazole. The DFT/B3LYP and ab initio/ HF methods can be used quite satisfactorily in predicting the chemical reactivity of the molecules and the effect of substitution of either donor or acceptor electron.

The calculations show the 2H tautomer to be the more stable with low reactivity, and difference of $\Delta E_{1H\text{-}2H}$= -2.1kcal/mol.

The study of substitution on the 1.2.3-triazole base groups (electron donor group and electron attractor group) shows that by comparing the LUMO - HOMO gaps, the most chemically active compounds are found to be the trisubstituted T`14 and T14. 1,2,3-triazole derivatives exhibited a great % ABS and thus reflecting a good cellular plasmatic membrane permeability. Compound 19 in the series of 1,2,3- triazole derivatives, presents a low coefficient of division (log*P*), hence it is the most absorbent product.

Compound 10 has an important hydration energy leading to a better distribution in fabrics. Moreover it had the highest LipE and LE values of the data set that's why it was deemed to be the most optimal compound and all the criteria of the Lipinski's rule are checked**.**

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