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Study of dipolar 1.3 cycloaddition reaction by DFT method, as well as study of antibacterial activity of two isomers 1.4 and 1.5 on two therapeutic targets E. coli and Helicobacter pylori, by molecular docking

Oumayma ABDESSADAK[a], Halima HAJJI[a], Yassin KOUBI[a], Tahar LAKHLIFI[a], Mohammed Aziz AJANA[a,1], Mohammed BOUACHRINE[a,b]

[a]Faculty of Science, University Moulay Ismail, BP 11201-Zitoune, Mekne,50000, Morocco,
[b]Superior School of Technology - Khenifra (EST-Khenifra), University of Sultan My Slimane, PB 170, Khenifra 54000 Morocco.

Abstract:

A study was carried out on 1.3 dipolar cycloaddition reaction between Phenylethyne and Benzyl (diazyn-1-ium-1-yl) azanide, using the different theoretical approaches, to know precisely the reaction path, and regioselectivity of reaction, as well as the transition state. We carried out this study by using DFT method on the one hand, on the other hand we studied antibacterial activity of two isomers 1.4 and 1.5 obtained from cycloaddition reaction on two therapeutic targets E. coli and Helicobacter pylori, using Molecular docking.

Keywords: *Cycloaddition, Isomer, Transition state, DFT, Molecular Docking.*

1. Introduction

Interest of organic synthesis for some years, is to synthesize compounds having various uses, and applicable in several fields, in pharmacy, biology, agriculture, medicine and also industry. Among these compounds the five-membered heterocyclic compounds or oxygen atom and nitrogen atom are consecutive.

Compared to synthesis of five-chain heterocycles, 1.3-dipolar cycloaddition method can be used for this kind of products [1,2,3], 1.3-dipolar CD reaction has great importance in organic synthesis and especially in the field of molecular modeling, it can also be used for the synthesis of natural products such as alkaloids and beta-lactams etc ... [4,5]

Michael discovered the reactions of 1.3-dipolar cycloadditions at the end of the 19th century, while Huisgen developed these reactions from 1963. In most cases we find that activation energy of these reactions is even high. At high temperature (80-120°C), this is the reason why we find these very slow reactions thus leading to a mixture of two regeoisomers 1.4 and 1.5.

Our reaction concerns 1,3-dipolar cycloaddition between Phenylethyne and Benzyl(diazyn-1-ium-1-yl) azanide [6].

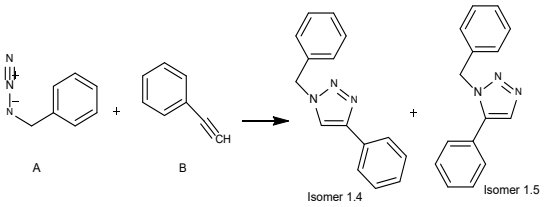

Figure 1. 1.3-dipolar cycloaddition reaction between Phenylethyne and Benzyl(diazyn-1-ium-1yl) azanide

Leading to two products, Phenylethyne and Benzyl(diazyn-1-ium-1-yl)azanide are very active compounds, Phenylethyne is an alkyne hydrocarbon containing a phenyl group, it is in the form of a colorless and viscous liquid, concerning their preparation, it can be done by removing the

[1] Corresponding Authors

e-mail: a.ajanamohammed@fs.umi.ac.ma

hydrogen bromide from the dibromide of styrene using sodium amide in ammonia[7].

Because of reactivities of these two species, we find several reactive sites, and for this reason we want to study the reaction path, and justify in a theoretical way the regioselectivity by the different theoretical approache, thus study the biochemical side of two isomers by using molecular Docking [8].

Study of cycloaddition reaction is based on several theories, which help us to study chemical reactivity, notably calculation of atomic charges, as well as energies, optimization of structures of transition state, that finally leads to a good prediction of the reaction path. Concerning our reaction, the parameters of reactants, charges, and energies calculated by DFT method at level B3LYP / 6-311G (d. p), optimization of structures of transition state also achieved by DFT method at level B3LYP / 6-31 (d'. p').

Study was thus carried out of antibacterial activity of two isomers, obtained from the cycloaddition reaction, using molecular docking, on two therapeutic targets E. coli and Helicobacter-pylori.

Objective of this study is: To know affinity of two isomers with respect to two therapeutic targets. Make comparison between antibacterial activity of isomer 1.4, and that of isomer 1.5. Make comparison, concerning antibacterial activity, between two therapeutic targets E. coli, and Helicobacter-pylori.

2. Computational Method

2.1. Sample / Working Group (One of them is preferred according to the structure of the study)

We carried out a theoretical study on 1.3 dipolar cycloaddition reaction between Phenylethyne and Benzyl(diazyn-1-ium-1-yl) azanide.

Study of antibacterial activity of two isomers obtained by cycloaddition reaction is carried out on therapeutic targets E. coli and Helicobacter-pylori.

2.2. Data Gathering

The 1.3 dipolar cycloaddition reaction on which a theoretical study was carried out, and therapeutic targets concerning study of antibacterial activity were obtained from literature.

2.3. Analysis of the Data

Analysis and study of data is carried out by several theoretical methods. Study of 1.3 dipolar cycloaddition reaction between Phenylethyne and Benzyl(diazyn-1-ium-1-yl) azanide is carried out using DFT method at B3LYP / 6-311 (d. p) level, we obtained transition state by calculation at B3LYP level / 6-31 (d. p).

Study of antibacterial activity of two isomers on the two targets E. coli and Helicobacter-pylori by software: Sybyl; Pymol; Discovery studio.

The crystalline structures were obtained from "Protein Data Bank"

3. Results and discussion

3.1 Regeoselectivity Study

3.1.1 Study Of The DEN / DEI Character

For prediction of the DEN / DEI character of 1.3-dipolar cycloaddition reaction between Phenylethyne and Benzyl(diazyn-1-ium-1-yl) azanide, three approaches are used: calculation of the energy difference between reagents, calculation of electronic chemical potential μ and electrophilic index W [9,10].

3.1.1.1 Frontier molecular orbital analysis

During 1.3-dipolar cycloaddition reaction there are two possibilities, concerning the first case majority orbital overlap involves HOMO of dipole and LUMO of dipolarophil, this is case of normal demand, while case of opposite demand we find that LUMO of dipole reacts with HOMO of dipolarophil.

Then to make prediction of the DEN/DEI character, we calculated energy difference between ΔE(I) ($HOMO_{dipole}/LUMO_{dipolarophile}$) and ΔE(II) ($HOMO_{dipolarophile}/LUMO_{dipole}$), we found that value of (ΔE(I) ($HOMO_{dipole}/LUMO_{dipolarophile}$) =5.76) is high, compared to (ΔE(II) ($HOMO_{dipolarophile}/LUMO_{dipole}$) = 5.63).

Then we can say that the reaction to a DEI character, that is to say the displacement of electrons will take place from Phenylethyne to Benzyl (diazyn-1-ium-1-yl) azanide. but we noticed that the values of the energetic differences are close between them, so we cannot be sure that Phenylethyne behaves as a nucleophile according to this approach.

3.1.2 Prediction By General Parameters

We base ourselves on values of table containing general parameters (Table 2), then for chemical electronic potential [11], we find that the value of Phenylethyne is high (μ= -3.846) compared to the

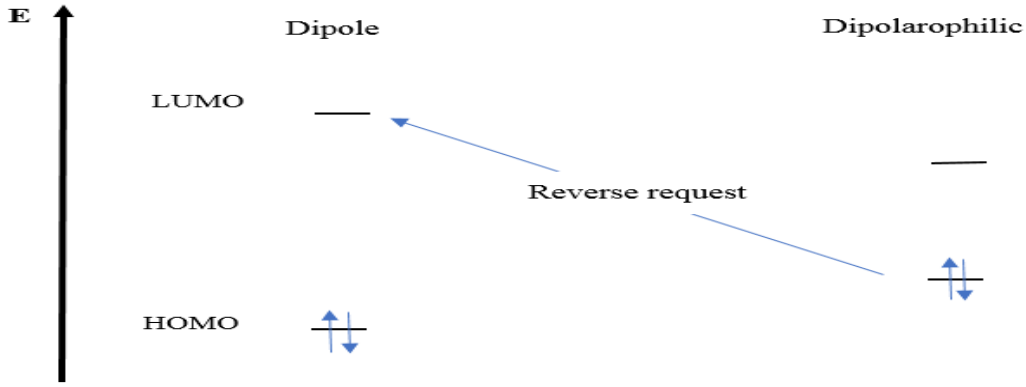

Figure 2. Overlap of the boundary orbitals in the 1.3-dipolar cycloadition between Phenylethyne and Benzyl (diazyn-1-ium-1-yl) azanide Based on the energy gap approach.

Table 1. Energies of the frontier orbitals (ev), for the reaction reagents, retained using the DFT method at the B3LYP / 6-311G level (d. p).

Reagent	HOMO	LUMO	ΔE
A	-6.856	-0.954	5.76
B	-6.587	-1.105	5.63

Table 2. *Global parameters of reaction reagents.*

Reagent	HOMO	LUMO	μ	H	S	W	N
A	-6.856	-0.954	-3.909	5.911	0.084	1.29	2.5
B	-6.587	-1.105	-3.846	5.482	0.091	1.35	2.78

value of Benzyl(diazyn-1-ium-1-yl)azanide (μ= -3.909), while for electrophilic index [12], we observe that value of Phenylethyne is high (W = 1.35) in comparison with that of Benzyl(diazyn-1-ium-1yl) azanide (W = 1.29). These results gave us no idea of the movement of electrons, since there is a contradiction between electrophilia and chemical electronic potential, one can consider this contradiction between values of parameters obtained occurs, because of substitution, by influence of the phenyl groups. For this reason, we

can use another approach, theory of Fikui which allows us to calculate local parameters of compounds.

3.1.3 Prediction By Local Parameters

For make prediction of nucleophilic / electrophilic character of a precise method, thus knowing the isomer favored in studied reaction, one carried out the approach of two centers proposed by Domingo in 2002 [13], then according to this approach, one can know the first bond formed by interaction between the most electrophilic site and the most nucleophilic site [12], thus know the favorable isomer.

According to local parameters we observe that electrophilic index of C1 is the lowest (wk= 0.054) while electrophilic index of N3 is the highest (wk= 0.288), then we can say that nucleophilic attack will take place from C1 to N3. Then the approach of Fikui indices is in agreement with approach of border orbitals FMO.

Table 3. *Local parameters of the reactants of the reaction (k is the site of the molecule where the property is evaluated).*

	q_0	q_-	q_+	F_k^+	F_k^-	w_k	N_K
C_1	0.284	0.268	0.324	0.04	0.016	0.054	0.044
C_2	-0.503	-0.669	-0.296	0.207	0.166	0.279	0.461
N_1	-0.296	-0.260	-0.197	0.099	-0.036	0.128	-0.09
N_3	-0.437	-0.537	-0.214	0.223	0.1	0.288	0.25

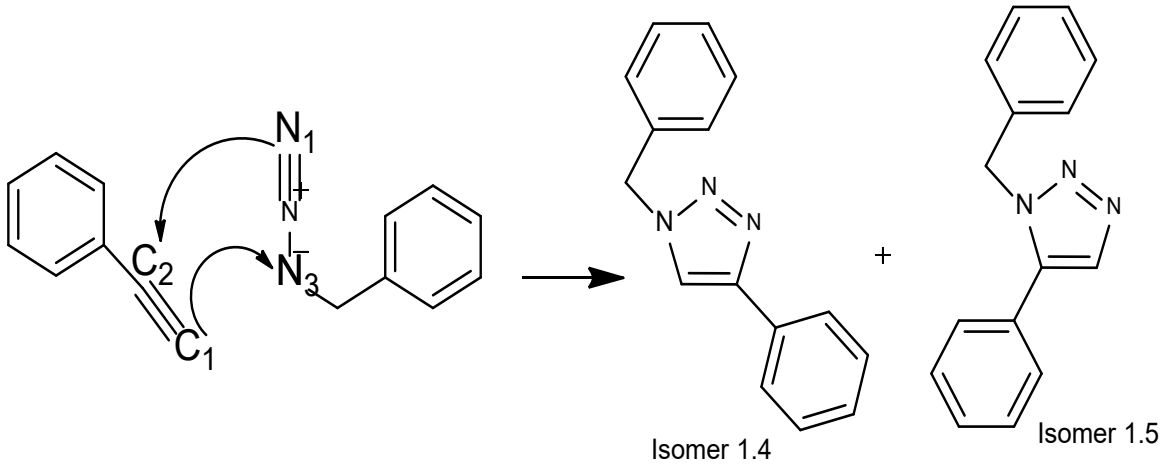

Figure 3. 1.3-dipolar cycloaddition reaction mechanism according to the results obtained.

We can also say that the first bond formed is the bond between C_1 and N_3, that is to say that the 1.4 isomer is favorable.

3.1.4 Transition State

Transition state is a very important step, during a chemical reaction, it needs a very high energy, is called activation energy [14,15], it leads to the formation of new bonds, and differs from one case to another.

We realized transition state of two isomers 1.4 and 1.5, obtained from the cycloaddition reaction using the DFT method at level B3LYP / 6-31 (d, p '), the presence of a single frequency imaginary in the Hessian matrix confirms transition states obtained.

From results found it can be said that this cycloaddition reaction followed the concerted mechanism [16,17], that is to say the formation of two new bonds will take place in a single step.

Structures obtained from transition state show the lengths of bonds formed.

For isomer 1.4 the lengths of bonds formed is as follows: (N_1-C_2 = 2.27) and (N_3-C_1 = 2.16), while isomer 1.5 we find the lengths of bonds formed (N_1-C_1 = 2.08) and (N_3-C_2 = 2.31).

From these results we find that the first bond formed is the N_1-C_1 bond of 1.5 isomer.

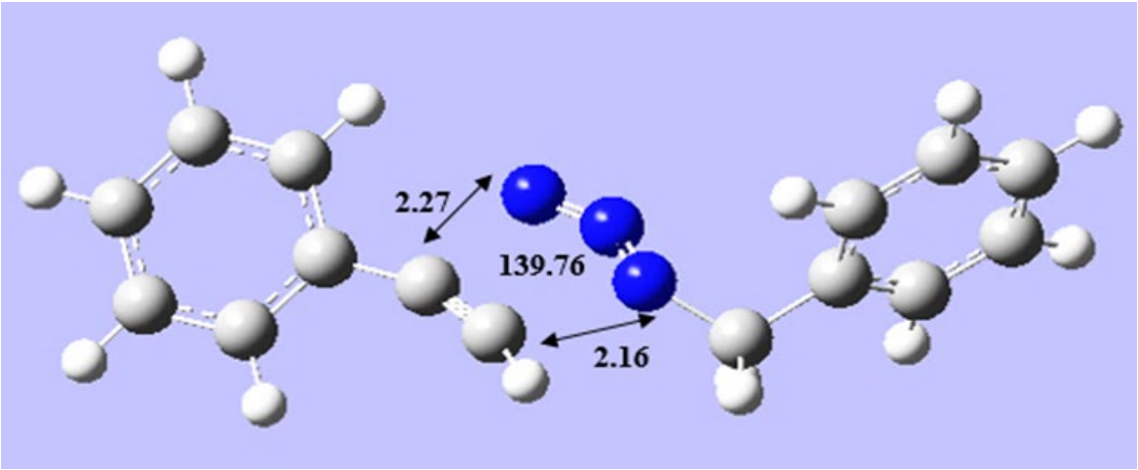

Figure 4. 1.4-isomer transition state structure

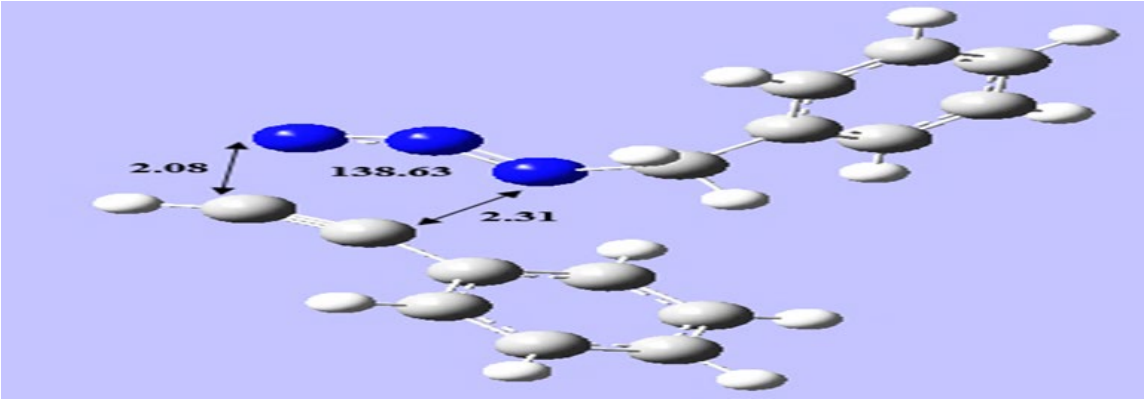

Figure 5. 1.5-isomer transition state structure.

Table 4. *Angles and lengths of the bonds formed for the 1.4 isomer and 1.5 isomer.*

	Isomere 1.4
N_1-N_2-N_3	139.76
N_1-C_2	2.27
N_3-C_1	2.16
	Isomere 1.5
N_1-N_2-N_3	138.63
N_1-C_1	2.08
N_3-C_2	2.31

When the activation energy is high, the reaction time becomes very long. So we find that activation energy for 1.4 isomer is a little high compared to that of the 1.5 isomer, Then based on this side, we can say that isomer 1.5 is favorable than 1.4 isomer, these results show a contradiction with literature.

Total energy of 1.5 isomer is raised in proportion to that of 1.4 isomer. From total energy of two isomers, it can be seen that 1.4 isomer is favorable. In case of 1.4 isomer phenyl groups are far from each other, while in case of 1.5 isomer phenyl groups are closer. Steric hindrance influences stability of compound, which is why energy of the 1.5 isomer is high.

Activation energy of 1.4 isomer is a little high compared to that of the 1.5 isomer, then production of 1.5 isomer will take place a little faster than other isomer, and we will have a higher or lower yield for 1.5 isomer than for 1.4 isomer.

Then to solve this problem and increase selectivity of reaction, as well as to increase the yield of 1.4 isomer which is a stable compound with respect to 1.5 isomer, a catalyst or a solvent can be used.

Table 5. Activation energy of two isomers 1.4 and 1.5. Benzyl(diazyn-1-ium-1yl) azanide

Reagent	**E(a.u)**	**E_T**	**E_{TS}(isomer1.4)**	**E_{TS}(isomer1.5)**	**ΔEa(isomer1.4)**	**ΔEa(isomer1.5)**
A	-435.10226	-743.575795	-743.520362	-743.521917	34.65	33.68
B	-308.47353					

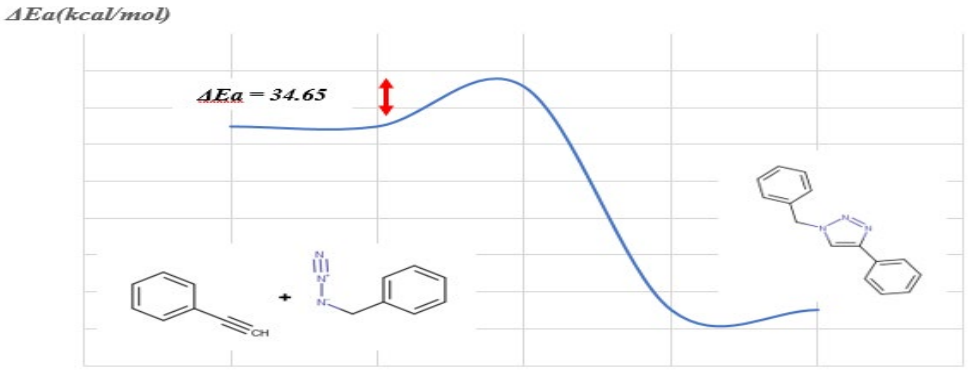

Figure 6. Energy profile of 1.3-dipolar cycloaddition between Phenylethyne and Benzyl(diazyn-1-ium-1-yl) azanide for 1.4 isomer.

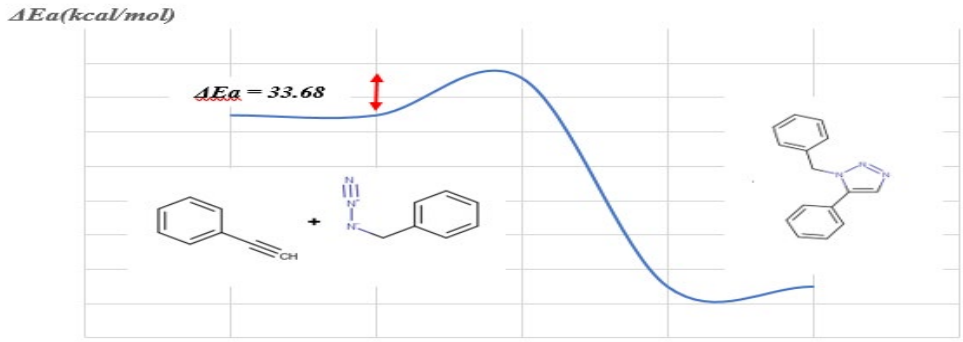

Figure 7. Energy profile of 1.3-dipolar cycloaddition between Phenylethyne and Benzyl(diazyn-1-ium-1-yl) azanide for 1.5 isomer.

3.2 Antibacterial Activity Of Isomers 1.4 And 1.5

The 1.2.3 triazole nucleus is of great importance in biochemical synthesis, it is often found in biologically active compounds. triazolic nucleus is known by these chemical and biological properties. Triazole nucleus has a great reactivity, thanks to polar sites, their rigidity, and its capacity to make acceptor or donor hydrogen bonds [18].

1.3 dipolar cycloaddition is the most widely used method for constructing five-membered heterocyclic compounds.

Cycloaddition is very interesting in chemical synthesis, it allows us to obtain very interesting motifs, with other very active functions, including the triazole motif.

From 1.3 dipolar cycloaddition reaction, we obtain two isomers 1.4 and 1.5 [19,20], these isomers have the same chemical functions, but they differ in their properties, their stabilities, and their biochemical activities.

Then after study of reaction path and regioselectivity of this reaction, as well as study of two isomers obtained, we made another study concerning biochemical side, in other words biological activity of these two isomers 1.4 and 1.5.

Bacteria have a very important role in our organism, they have a beneficial action for our health. There are several types of bacteria, each with its role, the major role is protection of organism against pathogens.

Research has found that these bacteria have other benefits such as: growth, satiety, pain relief, and sensitivity to stress, all of these bacteria call intestinal flora, so when this flora is state of disturbance, one can have several diseases, this disturbance can be because of insufficiency in beneficial microorganisms, or an excess.

According to literature studies have found, that there is a link between disturbance of the intestinal flora and Parkinson's disease, also neuropsychiatric diseases such as: autism, schizophrenia, bipolar disorder, and chronic depression.

Our work is to study antibacterial activity of isomers 1.4 and 1.5 for therapeutic target

Escherchia coli and Helicobacter pylori by using molecular Docking, in order to know affinity between bacteria studied and isomers 1.4 and 1.5, as well as interactions between them.

Molecular docking is carried out using software: Sybyl; Pymol; Discovery studio.

The structures of bacteria is obtained from (Protein Data Bank)

3.2.1 Therapeutic Target: Escherichia. Coli

It is a bacterium which belongs to intestinal flora, discovered by "Theodore Escherich" in 1885, belonging to family of "Enterobactericeae", protects organism against several infections and limits development of dangerous bacteria.

E. coli plays a very interesting role for health, but when it is excess, in this case we are talking about pathogenic bacteria [21]

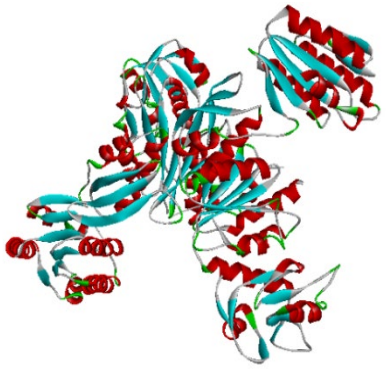

Figure 8. Escherichia. Coli structure (PDB; 1gg4; Resolution 2.3A°).

Table 6. *Affinity and interaction between isomers 1.4 and 1.5 and the therapeutic target E.Coli.*

Compounds	Score	Crash	Polar	Interactions
Isomer 1.4	-3.4346	-8.6115	0	Van der Waals Carbon-hydrogens bonds Pi-Donor hydrogen Bond Pi Sigma Amide-Pi stacked Pi-Alkyl
Isomer 1.5	-2.2860	-5.9365	0	Van der Waals Pi Sigma Pi-Alkyl

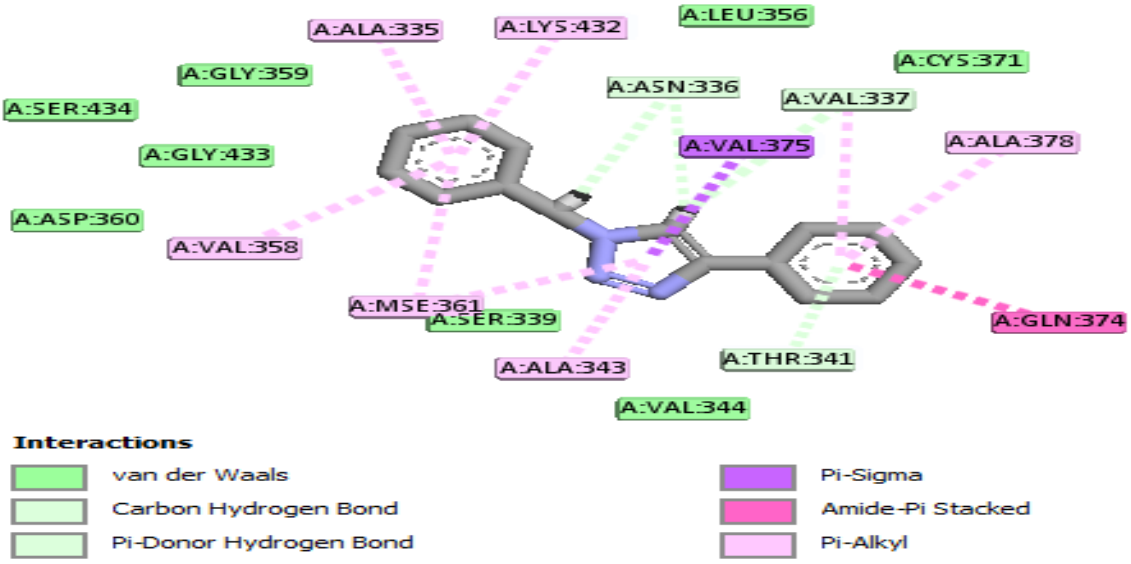

Figure 9. Interactions between the target E.coli and the isomer 1.4

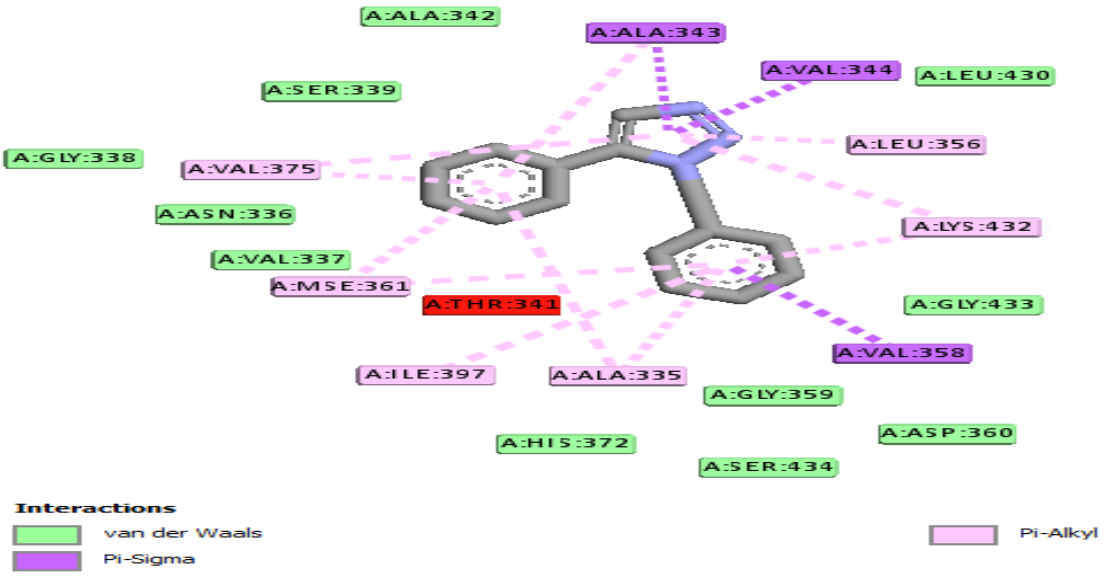

Figure 10. Interactions between the target E.coli and the isomer 1.5

After carrying out molecular docking, we obtained results concerning affinity, as well as the interactions between the isomers 1.4 and 1.5 and the bacterium E. coli.

For affinity we find that isomer 1.4 has an affinity with E. coli raised a little by the contribution of isomer 1.5, as well as the interactions, we find various interactions between isomer 1.4 and bacterium E.coli : Van der waals, carbon-hydrogen bond, pi-donor hydrogen bond, between hydrogens of isomer 1.4 and residues (ASN: 336; Val: 337), amide pi-stacked, between benzene of isomer 1.4 and residue amide (GLN: 374), as well as others (pi-sigma, pi-alkyl), while the isomer 1.5 we find: van der waals, pi-sigma, and pi-alkyl.

Interactions of 1.4 isomer are very important, diversity of these interactions stabilizes the complex.

We can then say that isomer 1.4 has a stronger antibacterial activity for therapeutic target E. coli than 1.5 isomer.

3.2.2 Therapeutic Target: Helicobacter pylori

It affects half of the world's population. It is a frequent bacterium which develops in stomach. It causes digestive disorders, can thus in some cases cause gastric cancer. It can be found in the stool, saliva, or dental plaque. This bacterium forms ulcers, increasing the production of acid, which disrupts mechanisms of stomach protection, causing appearance of toxins.

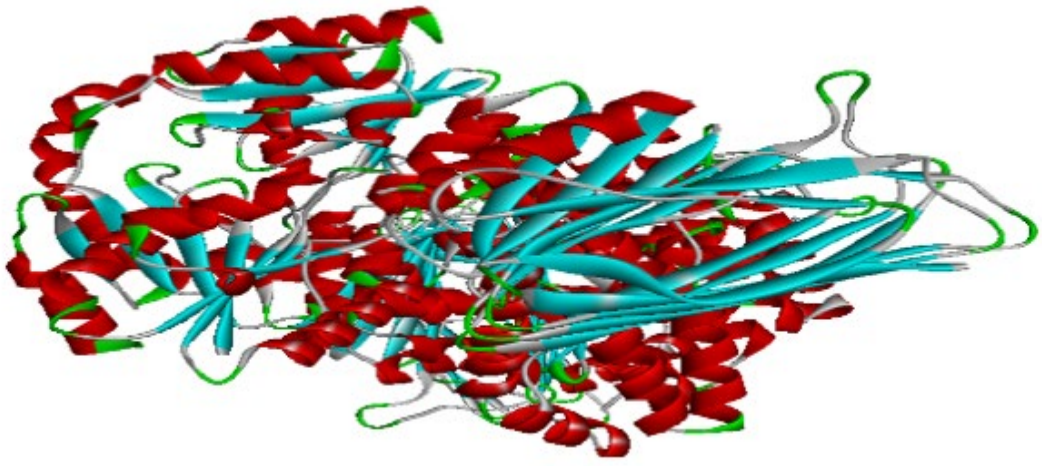

Figure 11. Helicobacter pylori structure (4GIO; Resolution: 2.35 A°)

Table 6. *Affinity and interaction between isomers 1.4 and 1.5 and the therapeutic target Helicobacter pylori.*

Compounds	Score	Crash	Polar	Interactions
Isomer 1.4	2.8325	-0.3758	0	Van der Waals Carbon-hydrogens bonds Pi-Cation Pi-Anion Pi-Alkyl
Isomer 1.5	2.6922	-0.4258	0	Van der Waals Pi-Cation Pi-Alkyl

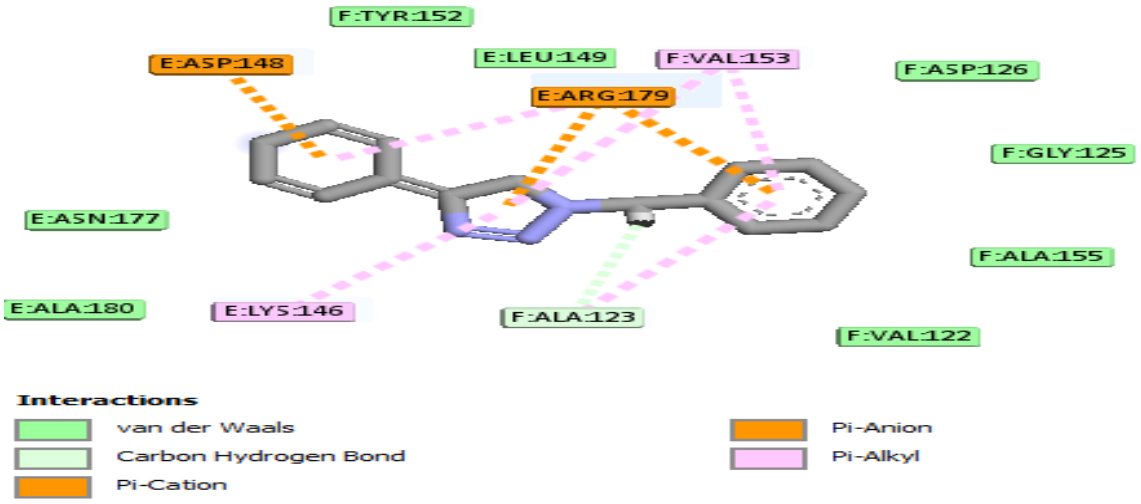

Figure 12. Interactions between target Helicobacter pylori and isomer 1.4

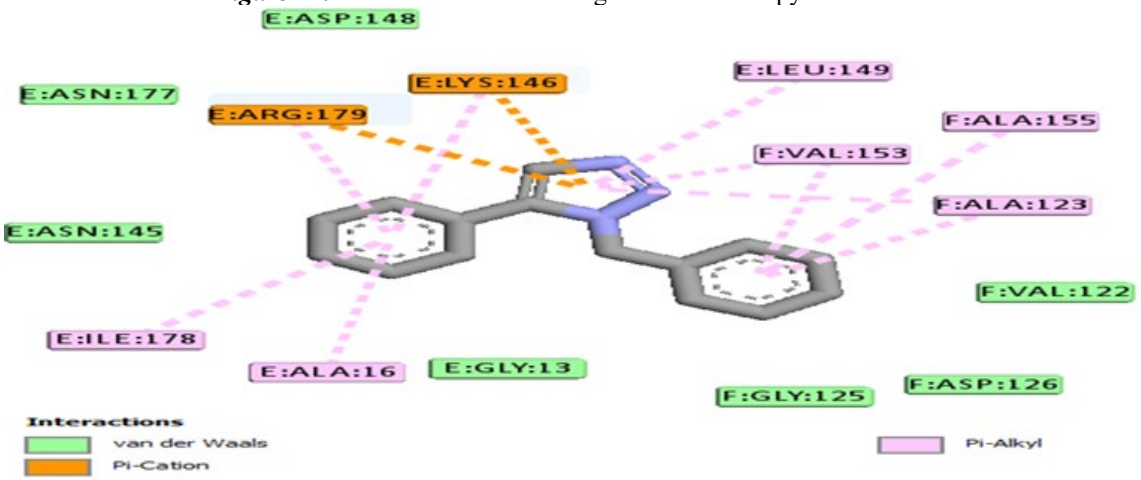

Figure 13. Interactions between target Helicobacter pylori and isomer 1.5

4. Conclusion

Results concerning therapeutic target Helicobacter pylori have shown that interactions of isomer 1.4 thus more interesting, we compare with those of other isomer (isomer 1.5), we find the interactions: Van der waals, carbon hydrogen bond, between the hydrogens of 1.4 isomer and the residue (ALA: 123), as well as others (Pi-anion, pi-cation, and pi-alkyl), while that of 1.5 isomer we find: van der waals , pi-cation and pi-alkyl.

If we compare the activity between two therapeutic targets, we find that activity of isomer 1.4 concerning therapeutic target of E. coli is very interesting, than antibacterial activity for therapeutic target of Helicobacter pylori, not only at level of interactions, but also at level of affinity,

we find that affinity of two compounds is higher for E.coli than for Helicobacter pylori.

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