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INVESTIGATING TAUTOMER STABILITY OF ANTI TOMOR DRUGS BASED CARBON STRUCTURE

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ABSTRACT

The present study aims to investigate tautomer stability of biomedicines with chemical structure of carbon compounds. In the present study from anticancer drugs, we selected 14 medicines having different mechanisms of action in the body. Then, their molecular-geometry structure was optimized usingthe B3LYP method and basic set 6-31 in the gas phase. After, for optimization and simulation of medicine action mechanism in human body, we added to medicine tautotmer factor group NH, SH, and OH, the simulated agents of drug receptor in the body. Finally, we identified the group is more stable in the body and shows better performance in terms of activity and the rate of energy. Comparing optimal energy of the main structure with tautotmer structure of Cladribine, Cyclophosphamide,Cytarabine,Dacarbazine,Mitoxantrone,Gemcitabine,and Flutamide , equal energy with energy difference $\Delta H=0$, we concluded that they play a similar role and Busulfan, Carmustine, Chlorambucil and Prednisone with energy difference $\Delta H=0.01$ have no similar role. Altretamine, Tamoxifen and Letrozole indicated no tautomer structure . After simulation and optimization tests of action mechanism of drugs in the human body, the SH agent functioned more stable and more properly. After, the OH agent was more stable and the NH agent displayed the least stability.

Keyword: Anticancer drugs, tautomer structure, chemical structure of carbon compounds

INTRODUCTION

In the present study we used Gaussian 03 and Gauss View software. From the anti-cancer drugs, we picked 14 drugs with different mechanism of action in the body. Then, the molecular-geometrical structure was optimal using the B3LYP technique and basic set 6-

31 in gas phase. All calculations were conducted by the Gaussian 03 software .In the first stage we simulated the main structure, tautomer structures were optimal in the second stage and finally we simulated the simulated agents (NH, SH and OH) from the action environment of drugs inside the human body.

RESULTS AND CONCLUSION

Table 1 through 11 illustrates the results of comparing the optimized structure energy of anti-cancer drugs by the Gaussian 03 software using the basic set B3LYP/6-31. We should mention here that from 14 selected anti-cancer drugs, three drugs naming altretamine, tamoxifen and letrozole had no tautomer structure , so they did not included in energy comparison calculations.

Table 1: comparison of optimized energy of busulfan drug

Energy difference ΔH	Tautomer structure 2 (kj)	Tautomer structure 1 (kj)	Original structure (kj)	Energy comparison
-0.01	-	-38.96×10^5	-38.97×10^5	**Drug structure energy**
0	-	-40.42×10^5-	-40.42×10^5	**Simulate d energy with NH**
-0.01	-	-40.95×10^5	-40.96×10^5	**Simulated energy With OH**
0	-	-49.44×10^5	-49.44×10^5	**Simulated energy with SH**
-	-	$r_{(S23O1)}$**=1.64Å**	$r_{(S27O2)}$**= 1.63Å**	**Comparison of effective bond length in tautomer**
-	-	$(\widehat{O1S23O5})$**=120.02°**	$(\widehat{O1S27O7})$**=109.24°**	**Comparison of effective angle in tautomer**

The results indicate that busulfan with sustainability energy in the main structure E= $-38.97*10^{15}$kJ and in the tautomer structure E= $-38.96*10^5$kJ with energy difference ΔH=-0.01 shows that the main structure is more stable. Since more the structure energy is negative , more stable it is and illustrated better performance. Comparing the stability energy of the drug with each functional group NH, OH and SH , the obtained energy from the main structure NH= -40.42*105kJ, OH= $-40.96*10^5$kJ and SH= -49.44*105kJ and the sustainability energy of tautomer structure are NH = $-40.42 *10^5$kJ, OH= $-40.95*10^5$kJ and SH= $-49.44*10^5$kJ . Because of further amount of energy the drug interaction with SH is more stable than OH and OH is more stable than NH.

Comparing the main and tautomer NH structures and finally making a comparison between the main structure bond length $r_{(S27O2)}$= 1.63Å and the tautomer structure $r_{(S23O1)}$=1.64Å, then comparing the bond angle of the main structure $(\widehat{O1S27O7})$ =109.24º with the tautomer structure $(\widehat{O1S23O5})$=120.02° , we see that the bonds length and angles have changed , which has caused a change in the rate of stability energy. In the busulfan drug, the main structure is in ketone form , which because of its more negative energy is more stable than its enol form.

Table 2: comparison of optimized energy of carmustinedrug

Energy difference ΔH	Tautomer structure 2 (k/j)	Tautomer structure 1 (k/j)	Main structure (K/j)	Energy comparison
-0.01	-	-37.56×10^5	-37.57×10^5	**Drug structure energy**
-0.01	-	-39.01×10^5	-39.02×10^5	**Simulate d energy with NH**
0	-	-39.55×10^5	-39.55×10^5	**Simulated energy With OH**
0	-	-48.04×10^5	-48.04×10^5	**Simulated energy with SH**
-	-	**$r_{(C4O20)}$=1.38Å**	**$r_{(C4O5)}$=1.24 Å**	**Comparison of effective bond length in tautomer**
-	-	**$(O2\widehat{O}\widehat{C4}N5)$=120.6°**	**$(O5\widehat{C4}\widehat{N}6)$ =123.56°**	**Comparison of effective angle in tautomer**

Regarding to the carmustine drug , the sustainability energy in the main structure E= $-37.57*10^{15}$kJ and in the tautomer structure E= $-37.56*10^5$kJ with energy difference ΔH=-0.01 demonstrates that the main structure is more stable .Comparing the stability energy of the drug with functional groups the main structure energy= -39.02*105kJ, OH= $-39.55*10^5$kJ and SH= -48.04*105kJ due to higher rate of the drug interaction energy with NH , we conclude that this reaction does not proceed well . However, OH is better than NH and finally, SH does the interaction with lower energy properly. Then, comparing the main structure bond length $r_{(C4O5)}$=1.24 Åwith the tautomer structure bond length $r_{(C4O20)}$=1.38Å, and bond angle of the main structure $(O5\widehat{C4}\widehat{N}6)$ =123.56º with the tautomer structure $(O2\widehat{O}\widehat{C4}N5)$=120.6º shows that the bonds length have changed and has transformed the value of sustainability energy . The amide form is more stable than the imine form because of more negative energy.

Table 3: comparison of optimized energy of chlorambucil drug

Energy difference ΔH	Tautomer structure 2 (k/j)	Tautomer structure 1 (k/j)	Original structure (K/j)	Energy comparison
-0.01	-	-43.85×10^5	-43.86×10^5	**Drug structure energy**
-0.01	-	-45.30×10^5	-45.31×10^5	**Simulate d energy with NH**
0	-	-45.84×10^5	-45.84×10^5	**Simulated energy With OH**
-0.01	-	-54.32×10^5	-54.33×10^5	**Simulated energy with SH**
-	-	**$r_{(C9O37)}$= 1.38Å**	**$r_{(C10\,O11)}$= 1.23Å**	**Comparison of effective bond length in tautomer**
-	-	**$(O10\widehat{C9}O37)$=109.54°**	**$(O12\widehat{C10}O11)$= 121.86°**	**Comparison of effective angle in tautomer**

The chlorambucil drug with the sustainability energy of the main structure E= -43.86*10^{15}kJ and the tautomer structure E= -43.85*10^{5}kJ with energy difference ΔH=-0.01 demonstrates that the main structure is more stable .Comparing the stability energy of the drug with functional groups NH= -45.31*10^{5}kJ, OH= -45.84*10^{5}kJ and SH= -54.33*105kJ and the tautomer structure NH= - 45.30*10^{5}kJ,OH= -45.84 * 10^{5}kJ and SH= - 54.32 * 10^{5}kJ , here we see that SH is more stable than OH and OH is more stable than NH. Now, we compare the bonds length in the main structure $r_{(C10\ O11)}$= 1.23Å and the tautomer structure $r_{(C9O37)}$= 1.38Å and comparison between the bond angle of the main structure $(O12\widehat{C10}O11)$= 121.86º and the tautomer structure $(O10\widehat{C9O}37)$=109.54°, we find out that by a change in the bond length and angles , the sustainability energy also changes . Here, the ketone form is more sustainable than the enol form.

Table 4: comparison of optimized energy of cladribine drug

Energy difference ΔH	Tautomer structure 2 (k/j)	Tautomer structure 1 (k/j)	Original structure (K/j)	Energy comparison
0	-	-35.38×10^{5}	-35.38×10^{5}	**Drug structure energy**
0	-	-36.83×10^{5}	-36.83×10^{5}	**Simulate d energy with NH**
0	-	-37.37×10^{5}	-37.37×10^{5}	**Simulated energy With OH**
0	-	-45.85×10^{5}	-45.85×10^{5}	**Simulated energy with SH**
-	-	$r_{(C3N28)}$**=1.28Å**	$r_{(N7C3)}$**= 1.35 Å**	**Comparison of effective bond length in tautomer**
-	-	$(N28\widehat{C3N}30)$**=116.95°**	$(N7\widehat{C3N}10)$ **=118.52°**	**Comparison of effective angle in tautomer**

The cladribine drug with the sustainability energy of the main and tautomer structures E= -35.38*10^{15}kJ with energy difference ΔH=0 plays an identical role. The amount of energy for the main structure of the drug is NH = -36.83*10^{15}kJ, OH= - 37.37*10^{5}kJ, SH= -45.85*10^{5}kJ and the tautomer structure energy NH= - -36.83*10^{5}kJ, OH= -- 37.37*10^{5}kJ and SH= - 45.85*10^{5}kJ , we conclude that SH is more stable than OH and OH is more stable than NH. Moreover, comparison of the bond length and the bond angle in the main structure are $r_{(N7C3)}$= 1.35 Å and $(N7\widehat{C3N}10)$ =118.52° , respectively and for the tautomer structure the bond length and the angle are $r_{(C3N28)}$=1.28Å and $(N28\widehat{C3N}30)$ =116.95°, respectively. It shows that change in the bond length and angle does not create a change in the energy. Also, the imine form and the amine form have equal stability energy and both play the same role.

Table 5: comparison of optimized energy of cyclophosphamide drug

Energy difference ΔH	Tautomer structure 2 (k/j)	Tautomer structure 1 (k/j)	Original structure (K/j)	Energy comparison
0	-	-47.19×10^5	-47.19×10^5	**Drug structure energy**
0	-	-48.64×10^5	-48.64×10^5	**Simulate d energy with NH**
0	-	-49.18×10^5	-49.18×10^5	**Simulated energy With OH**
0	-	-57.66×10^5	-57.66×10^5	**Simulated energy with SH**
	-	$r_{(P1O28)}$=1.75Å	$r_{(O2P1)}$= 1.59Å	**Comparison of effective bond length in tautomer**
	-	$(\widehat{O28P1N27})$=126.33°	$(\widehat{O2P1N28})$= 112.18°	**Comparison of effective angle in tautomer**

The cyclophosphamide drug with the sustainability energy of the main and tautomer structures E= $-47.19*10^{15}$kJ with energy difference ΔH=0 both have the same functional role. For the functional groups of the main structure NH = $-48.64*10^{15}$kJ, OH= - $49.18*10^5$kJ, SH= $-57.66*10^5$kJ and the same energy value for the tautomer structure. So, we obtain similar results to the above mentioned drugs. Furthermore, the bond length and the bond angle in the main structure are $r_{(O2P1)}$= 1.59Å and $(\widehat{O2P1N28})$= 112.18°, respectively and for the tautomer structure the bond length and the angle are $r_{(P1O28)}$=1.75Å and $(\widehat{O28P1N27})$=126.33º, respectively. It shows that change in the bond length and angle does not create a change in the energy . Also, the imine form and the amine form have equal stability energy and both play the same role.

Table 6: comparison of optimized energy of cytarabine drug

Energy difference ΔH	Tautomer structure 2 (k/j)	Tautomer structure 1 (k/j)	main structure (K/j)	Energy comparison
0	-23.39×10^5	-23.39×10^5	-23.39×10^5	**Drug structure energy**
0	-24.84×10^5	-24.84×10^5	-24.84×10^5	**Simulate d energy with NH**
0	-25.38×10^5	-25.38×10^5	-25.38×10^5	**Simulated energy With OH**
-	-33.86×10^5	-33.86×10^5	-33.86×10^5	**Simulated energy with SH**
-	$r_{(N27C1)}$=1.29Å	$r_{(N29C1)}$=1.29Å	$r_{(N28C2)}$=1.36Å	**Comparison of effective bond length in tautomer**
-	$(\widehat{H28N27C1})$=111.85°	$(\widehat{H30N29C1})$=114.9°	$(\widehat{H30N28C2})$=117.83°	**Comparison of effective angle in tautomer**

The cytarabine drug with two tauter structures in which the sustainability energy of the main structure and the tautomer structures all is equal to E= - $23.39*10^{15}$kJ. Thus, with the energy difference ΔH=0, all three structures indicate similar stability energy. Considering the functional groups of the main structure and the tautomer structures 1 and 2, NH= $-24.84*10^{15}$kJ, for three structures OH = $-25.38*10^{15}$kJ and SH= $-33.86*10^{15}$kJ . Considering these values, the functional group SH is more stable than OH and OH is more stable than NH. Regarding to the bond length and angle of the main structure they are $r_{(N28C2)}$=1.36Å and $(\widehat{H30N28C2})$=117.83º, respectively. For

the tautomer structures 1 and 2 bond length and angle are $r_{(N29C1)}$=1.29Å, (H $\widehat{30N29C}$ 1)=114.9º, $r_{(N27C1)}$=1.29Å and ($\widehat{H28N27C1}$)=111.85º, respectively. According to the results, we see that the bond length has not changed in the tautomer structures 1 and 2 , but it has changed compared with the main structure. Moreover, the bond angle has changed in all structures, however the energy has not changed. The imine and amine forms of all three structures have the same stability energy.

Table 7: comparison of optimized energy of dacarbazine drug

ΔH	Tautomer structure IV kJ	Tautomer structure III kJ	Tautomer structure II kJ	Tautomer structure I kJ	Main structure kJ	Energy comparison
0	-16.75×10^5	-16.75×10^5	-16.75×10^5	-16.75×10^5	-16.75×10^5	**Drug structure energy**
0	-18.2×10^5	-18.2×10^5	-18.2×10^5	-18.2×10^5	-18.2×10^5	**Simulate d energy with NH**
0	$-.74\times10^5$	-18.74×10^5	-18.74×10^5	-18.74×10^5	-18.74×10^5	**Simulated energy With OH**
0	-27.22×10^5	-27.22×10^5	-27.22×10^5	-27.22×10^5	-27.22×10^5	**Simulated energy with SH**
-	**$r_{(C5O18)}$=1.29Å**	**$r_{(C5O18)}$=1.25Å**	**$r_{(C5O18)}$=1.25Å**	**$r_{(C6O20)}$=1.38 Å**	**$r_{(O7C6)}$=1.25Å**	**Comparison of effective bond length in tautomer**
-	**($\widehat{N19C5O18}$)= 120.1°**	**($\widehat{N19C5O18}$)=120.4 °**	**($\widehat{N19C5O18}$)=120.4°**	**($\widehat{N22C6O20}$ =118.52°**	**($\widehat{N8C6O7}$) 122.41°=**	**Comparison of effective angle in tautomer**

Dacarbazine drug has 4 tautomer structures and the sustainability energy of all five structures is E= - $16.75*10^{15}$kJ. So, we conclude that having ΔH=0, entire 5 structures hold equal sustainability energy. For the functional groups of the main structure and 4 tautomer structures ,NH= - $18.2*10^{15}$kJ, for four structures OH = - $18.74*10^{15}$kJ and SH= -27.22 $*10^{15}$kJ. Accordingly, SH is more stable than OH and OH is more stable than NH. Considering the bond length and angle of the main structure and 4 tautomer structures they are $r_{(O7C6)}$=1.25Å ، $r_{(C6O20)}$=1.38Å ، $r_{(C5O18)}$=1.25Å ، $r_{(C5O18)}$=1.25Å ، $r_{(C5O18)}$=1.29Å , ($\widehat{N8C6O7}$) =122.41° ، ($\widehat{N22C6O20}$)=118.52° ، ($\widehat{N19C5O18}$)= 120.4° and ($\widehat{N19C5O18}$)= 120.4° ، ($\widehat{N19C5O18}$)= 120.1, respectively. According to the results, we see that the bond length and angle have changed in the structures, but it has not changed the energy. The sustainability energy of imine and amine forms play the same role.

Table 8: comparison of optimized energy of prednisone drug

ΔH	Tautomer structure II kJ	Tautomer structure I kJ	Main structure kJ	Energy comparison
/01 -0	-	-31.28×10^5	-31.29×10^5	**Drug structure energy**
0	-	-32.73×10^5	-32.73×10^5	**Simulate d energy with NH**
-	-	-33.27×10^5	-33.27×10^5	**Simulated energy With OH**
-	-	-41.76×10^5	-41.76×10^5	**Simulated energy with SH**
-	-	**$r_{(O51C8)}$=1.4Å**	**$r_{(O8C9)}$=1.24Å**	**Comparison of effective bond length in tautomer**
-	-	**($\widehat{O51C8C26}$)=122.71°**	**($\widehat{C27C9O8}$)=120.31°**	**Comparison of effective angle in tautomer**

The prednisone drug with the sustainability energy of the main structure E= -31.29*10^{15}kJ and the tautomer structure E= -31.28*10^{15}kJ with energy difference ΔH=-0.01 the main structure is more stable and shows better function. For the functional groups of either main and tautomer structures , NH = -32.73*10^{15}kJ, OH= - 33.27*10^5kJ, SH= -41.76*10^5kJ , respectively . So, we conclude that SH is more stable than OH and OH is more stable than NH . also, the bond length and angle of the main and tautomer structures are $r_{(O8C9)}$=1.24Å, ($\widehat{C27C9O8}$)=120.31°, and $r_{(O51C8)}$=1.4Å , ($\widehat{O51C8C26}$)=122.71°, respectively. Because change in bonds length and angle results in change in the sustainability energy in main and tautomer structures. Also, the ketone forms is more stable than enol form because of more negative energy.

Table 9: comparison of optimized energy of mitoxantrone drug

ΔH	Tautomer structure II kJ	Tautomer structure I kJ	Main structure kJ	Energy comparison
0	-40.04×10^5	-40.04×10^5	-40.04×10^5	**Drug structure energy**
0	-41.49×10^5	-41.49×10^5	-41.49×10^5	**Simulate d energy with NH**
0	-42.03×10^5	-42.03×10^5	-42.03×10^5	**Simulated energy With OH**
0	-50.51×10^5	-50.51×10^5	-50.51×10^5	**Simulated energy with SH**
-	**$r_{(O20C9)}$=1.30Å**	**$r_{(O22C9)}$=1.41Å**	**$r_{(C9O23)}$=1.39Å**	**Comparison of effective bond length in tautomer**
-	**($\widehat{H56O55C18}$)=107.15°**	**($\widehat{H23O22C9}$)=113.02°**	**($\widehat{H24O23C9}$)=109.97°**	**Comparison of effective angle in tautomer**

The mitoxantrone drug with sustainability energy of the main structure and two tautomer structures E= - 40.04*10^{15}kJ with ΔH=0, all three structures have equal sustainability energy and play an identical role. The amount of energy for the functional groups of the main and two tautomer structures are NH= -41.49*10^{15}kJ, OH= -42.03*10^{15}kJ and SH= -50.51 *10^{15}kJ, respectively. As a result, SH demonstrates better interaction versus OH and OH interacts better than NH. The bond length and angle of the main structure are equal to

$r_{(C9O23)}$=1.39Å and ($H24\widehat{O23}C9$)=109.97° and the bond length and angle of tautomer structure I and II are $r_{(O22C9)}$=1.41Å, ($H23\widehat{O22}C9$)=113.02°, $r_{(O20C9)}$=1.30Å and ($H56\widehat{O55}C18$)=107.15° , respectively. Therefore, change in bonds length and angle do not change energy. Here, the structure has both the tautomer enol-ketone form and imide-amide form. All of these structures have the same mechanisms in the body.

Table 10: comparison of optimized energy of gemcitabine drug

ΔH	Tautomer structure II kJ	Tautomer structure I kJ	Main structure kJ	Energy comparison
0	-26.62×10^5	-26.62×10^5	-26.62×10^5	**Drug structure energy**
0	-28.07×10^5	-28.07×10^5	-28.07×10^5	**Simulate d energy with NH**
0	-28.61×10^5	-28.61×10^5	-28.61×10^5	**Simulated energy With OH**
0	-37.09×10^5	-37.09×10^5	-37.09×10^5	**Simulated energy with SH**
-	**$r_{(O28C15)}$=1.37Å**	**$r_{(O16C15)}$=1.24Å**	**$r_{(O17C16)}$=1.24Å**	**Comparison of effective bond length in tautomer**
-	**($O28\widehat{C15}N27$)=120.64°**	**($O16\widehat{C15}N28$)=123.36°**	**($O17\widehat{C16}N11$)=124.86°**	**Comparison of effective angle in tautomer**

The gemcitabinedrug with the main structure and two tautomer structures sustainability energy E= - $26.62*10^{15}$kJ with the ΔH=0, all three structure have the same function. For the functional groups of the main and tautomer structures, NH= $-28.07*10^{15}$kJ, OH= $-28.61*10^{15}$kJ, SH= $-37.09*10^{15}$kJ . So, we find out that SH is more sustainable than OH and OH is more stable than NH. Regarding to the bond length and angle of the main structure are $r_{(O17C16)}$=1.24Å and ($O17\widehat{C16}N11$)=124.86º and for the tautomer structure I and II are $r_{(O16C15)}$=1.24Å,($O16\widehat{C15}N28$)=123.36°, $r_{(O28C15)}$=1.37Å and ($O28\widehat{C15}N27$)=120.64°, respectively. Consequently, the sustainability energy does not change and the imine and amine forms have the same function because of equal sustainability energy.

Table 11: comparison of optimized energy of flutamide drug

ΔH	Tautomer structure II kJ	Tautomer structure I kJ	Main structure kJ	Energy comparison
0	-	-27.83×10^5	-27.83×10^5	**Drug structure energy**
0	-	-29.28×10^5	-29.28×10^5	**Simulate d energy with NH**
-0.01	-	-29.81×10^5	-29.82×10^5	**Simulated energy With OH**
0	-	-38.3×10^5	-38.3×10^5	**Simulated energy with SH**
-	-	**$r_{(O29C18)}$=1.4Å**	**$r_{(O20C18)}$= 1.25Å**	**Comparison of effective bond length in tautomer**
-	-	**($O29\widehat{C18}N17$)=122.29°**	**($O20\widehat{C18}N17$)=122.87°**	**Comparison of effective angle in tautomer**

The flutamide drug with sustainability energy of the main structure E= - $27.38*10^{15}$kJ and the tautomer structure E= - $27.38*10^{15}$kJ and the ΔH=0 both illustrate the same function. Considering the functional groups of the main and the tautomer structures NH= - $29.28*10^{15}$kJ, OH= -$29.81*10^{15}$kJ and SH= - $38.30*10^{15}$kJ. Consequently, we conclude that SH is more stable than OH and OH is more stable than NH. For the bond length and angle of the main and the tautomer structures, they are $r_{(O20C18)}$= 1.25Å,$_{(O29C18)}$=1.4Å, $(\widehat{O20C18N17})$ =122.87° and ، $(\widehat{O29C18N17})$=122.29°, respectively. consequently, change in the bond length and angle does not create a change in the structures sustainability energy. The sustainability energy of the imine and amine forms is the same.

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