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Investigation of the interactions of anticancer drugs with tyrosine kinase enzyme using semi-empirical methods and comparisons with DFT Calculations

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Abstract: In this work, the interaction energies of some commercial molecules that are still used clinically with aminoacids in the active region of the tyrosine kinase were calculated by semi-empirical methods such as AM1 and PM3. There are already some results calculated with DFT methods and published in an article previously. By comparing the results there with those found here, it has been discussed whether semi-empirical methods with much shorter computation times can be used to estimate the most critical aminoacids for the tyrosine kinase enzyme instead of DFT methods which take much more time. According to the results obtained here, in order for semi-empirical methods to be used instead of DFT methods for this purpose, the examined ligands must have an electrical charge in the physiological environment. In other words, the hypothesis put forward remains valid only if the ligand under consideration has a charge. The use of semi-empirical methods such as AM1 and PM3 instead of DFT methods to estimate the residues with which a molecule that does not have any electrical charge interacts most strongly did not yield overlapping results.

Keywords: *Tyrosine kinase, anticancer, semi-empirical, DFT, interaction energy*

1. Introduction

Cancer is one of the leading causes of death in the world. [1]. Today, commercial drugs used in the treatment of cancer cannot show the desired effects. That's why research on cancer drugs continues. Protein kinases are responsible for the transfer of phosphate groups in the body [2–4]. These proteins are thought to be associated with cancer. In addition, these proteins are responsible for DNA repair, immune system and programmed cell death. [4]. So, protein kinases are one of the important proteins that should be targeted for designing of new drug candidates.

Chronic Myeloid Leukemia (CML) may occur due to disruption of kinase activity in the body. These kinase proteins are encoded by a gene called BCR-ABL. The treatment of this disease can be accomplished by inhibiting said enzymes. [5,6]. Wherein inhibition of these enzymes can be the first target in the fight against cancer. Today, marketed drug molecules like Dasatinib, Ponatinib and Nilotinib are used for the treatment of Chronic Myeloid Leukemia. As in every enzyme, the interactions of ligands used in inhibiting tyrosine kinase with residues in the binding site of tyrosine kinase are very important. Evaluation of interactions between inhibitor candidate ligands and important aminoacids should also be taken into acoount in the designing of new drugs.

In an article, 1,3,4-thiadiazole derivatives were synthesized and their kinase inhibition activity was elucidated. Moreover, it has been tried to discover the conformations that the molecules can have in the binding cavity via docking simulations and the interaction energies with the important aminoacids in active cavity have been evaluated. Here, examinations have been made for the structure-activity relationships of the studied molecules [7].

In a work made by Craig J. Thomas et al., the efficacy of the trifluoro methyl group for the inhibition capacity of the marketed drug Nilotinib molecule was evaluated. In that work, analogous of

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Nilotinib were designed and synthesized. However, changes in the correspondent ligands in the active site of the tyrosine kinase enzyme were examined by docking protocols and compared with the reference molecule [8].

In a paper made by Kshatresh Dutta Dubey and Rajendra Prasad Ojha, The binding energy of the imatinib molecule to the tyrosine kinase enzyme was calculated by quantum mechanical methods. The donation of polarization and electronic efficacy in the generation of the protein/ligand structure is also discussed. The data taken from the evaluations are consistent with the experimentally one [9].

In a previous study, the interactions of a ligand series, which is utilized clinically as a tyrosine kinase inhibitor, with the important residues in the binding region of the protein in question were examined through QM calculations [10]. As it is known, there are quantum mechanical computation methods with different approaches such as DFT, semi-empirical methods. Although the calculations made with DFT methods take relatively more time due to their nature, they can give more accurate results in the calculation of interaction energy than semi-empirical methods. However, these semi-empirical methods allow much faster computation. Protein-ligand complexes are large systems made up of many atoms. Therefore, it is far from practical to use DFT methods when working with such systems. Since the interaction of a ligand with a protein basically takes place in the binding cavity, the system to be studied can be minimized. For example, the aminoacid residues with which the molecule that binds to the protein interact best are the critical aminoacids in its immediate vicinity and a smaller system can be created by considering only the ligand and these aminoacids, and DFT calculations can be made. Here again, it should not be ignored that the computation costs will be high. As mentioned before, in a study I conducted, the interactions of some ligands that are clamped to the binding cavity of the tyrosine kinase used commercially in clinical practice with the critical aminoacids of the studied enzyme were investigated by DFT methods [10]. What was done here was actually a per-residue work, that is, the interaction energies with each critical residue in contact with the ligand under consideration were calculated one by one. The interaction energies found in the aforementioned study were calculated by DFT methods and as mentioned earlier, the calculation times are relatively high. In this study, using the same protein and ligands, the energies of the interactions were calculated with different semi-empirical methods. The aim here is to find the aminoacid residues that are most responsible for the interactions in the binding site by shortening the computation time. The purpose of the study is to compare the interaction energies calculated with semi-empirical methods with those made by DFT methods and to investigate whether it will show parallelism in terms of quality, not quantity. As said before, knowing which of the aminoacids in the binding site can be more effective in interactions with the drug molecule is one of the parameters that may be important in drug development studies.

Doing this research with a shorter computational cost shows that the result can be reached much faster. This will give us an advantage in this kind of research. It should be noted that the aim here is not to find the absolute value of the energies of the interactions of the studied ligands with critical aminoacids, but only to investigate whether the results obtained using different computational methods will exhibit a qualitatively parallel profile with each other. If the results found are positive, advantages related to the reduction of computation times can be revealed.

2. Computational Method

In my previous work a few ligands (Bosutinib, Bafetinib, Flumatinib, Dasatinib, Imatinib, Ponatinib, Nilotinib,) used clinically for the inhibition tyrosine kinase were evaluated [10]. Although the details of some of the procedures are described in the aforementioned study, the protocols can be briefly summarized as follows. These commercial molecules were docked individually to kinase protein. After that, docking poses with the best energy for each protein/ligand structure were determined. To calculate the interaction energies between the molecules and aminoacids at active cavity, aminoacids positioned at 4 Å distance in all directions from the molecule were taken into account. Residues other than these aminoacids were removed. Then, ligand/residue couples were created using this recently formed structure. These binary structures were formed individually by the aminoacids with which the

molecule contacted. In the previous study, the interaction energy between the ligand and an aminoacid in contact with it was calculated using DFT methods. There was even a BSSE correction to get the results more accurate. In the present study, the interaction energies were calculated by semi-empirical methods on the binary structures obtained in the previous study. All of the input structures used are the same as in the previous work. Here, only the method used to calculate the interaction energies has been changed and the results obtained from the different methods have been compared. In this article, AM1 and PM3 methods are used as semi-empirical methods [11,12]. As stated in the introduction, the aim of this study is to compare the interactions of commercial molecules used as kinase inhibitors with important residues at binding cavity of the protein with semi-empirical methods and compare them with the results obtained from previous DFT calculations. Since the computational costs of semi-empirical methods are lower than those of DFT methods, if the results obtained from semi-empirical methods are in parallel with those obtained from DFT methods, it can be said that prediction of the interaction energies between critical aminoacids and ligands, which can give important data in drug research, can be done in less time.

2.1. Docking study

In this study, no docking simulation was done again. All input structures used during the calculations are taken from my previous work. All the details given for the previous docking calculations are in that study.

2.2. QM calculations

Previously obtained binary systems were used to calculate the interaction energies between ligands and critical aminoacid residues by semi-empirical calculations. The interaction energies are calculated using the Equation 1.

$$E_{interaction}=E_{complex}-E_{ligand}-E_{aminoacid} \quad (1)$$

All semi-empirical computations were executed using Orca 4.1.2 program [13]. All files required to perform the computations at Orca have been set up via Avogadro program package [14].

3. Results and discussion

The interactions energies between important aminoacids and the commercial ligands considered in this work were taken into account separately. Like this, after examined the molecules individually, relative assessments were made jointly. As described in detail in the previous study, the studied commercial molecules have different protonation states. Ligand-aminoacid interaction energies for each of these different states were calculated by semi-experimental methods and each protonation state was examined separately. Since in my previous work, there were 2-dimensional (2D) interaction maps showing what kind of interaction between the ligand and the critical aminoacids in the active cavity of the enzyme, these maps are not included here again. The interaction energies here were calculated by both AM1 and PM3 methods. First of all, the results obtained using semi-empirical methods were evaluated for each molecule considered. Then, these results were compared with those obtained by DFT methods in the previous study.

3.1. Bafetinib:

There is only one protonated state of the Bafetinib according to the ZINC database [15]. Figure 1 presents the interaction energies calculated by AM1 method between the Bafetinib and critical aminoacids at binding cavity of the protein. Consistent with the results, Bafetinib had more powerful interactions with Arg362-Arg386-Asp381-Glu286-Lys400-Phe401-Ser385 than others. When this graphical data is analyzed, we can see that some of the interactions are repulsive and some are attractive. Interactions occured by Lys400-Arg386-Arg362 aminoacids are repulsive as expected. Because the residues have +1 charge and the Bafetinib has same charge, the interaction formed is repulsive. Contrarily, interactions made by Glu286-Asp381 aminoacids are attractive. This is an expected state because the charge of the aminoacids is -1 when Bafetinib is +1. Thus, interactions become attractive. In all graphics in this paper, attracting interactions are pointed by green color, and repulsive interactions are indicated with red. All semi-empirical computations have been made in vacuum environment.

Figure 2 displays the interaction energies calculated by PM3 method. As can be seen from this graph, the aminoacids that are important in the interaction

found using the AM1 method are the same as those found by the PM3 method. Both semi-empirical methods showed parallel characteristics.

Figure 1. Interaction energies calculated by AM1 between Bafetinib and residues

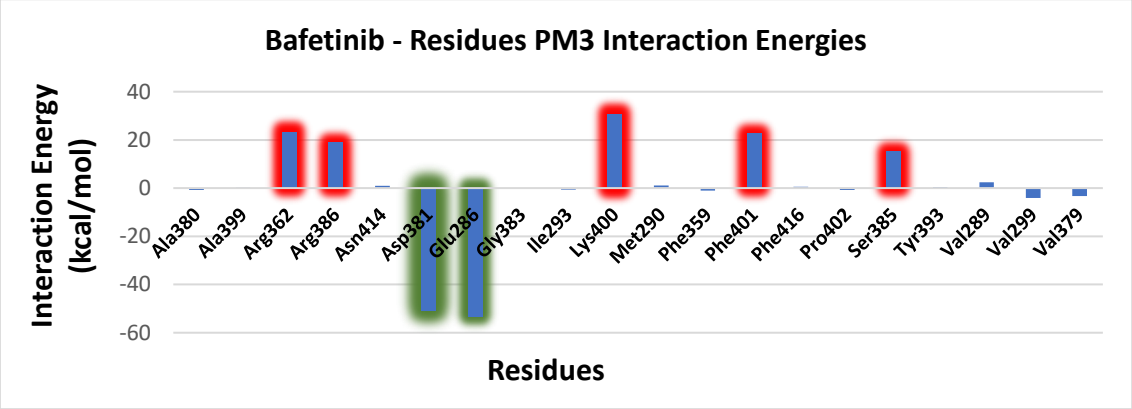

Figure 2. Interaction energies calculated by PM3 between Bafetinib and residues

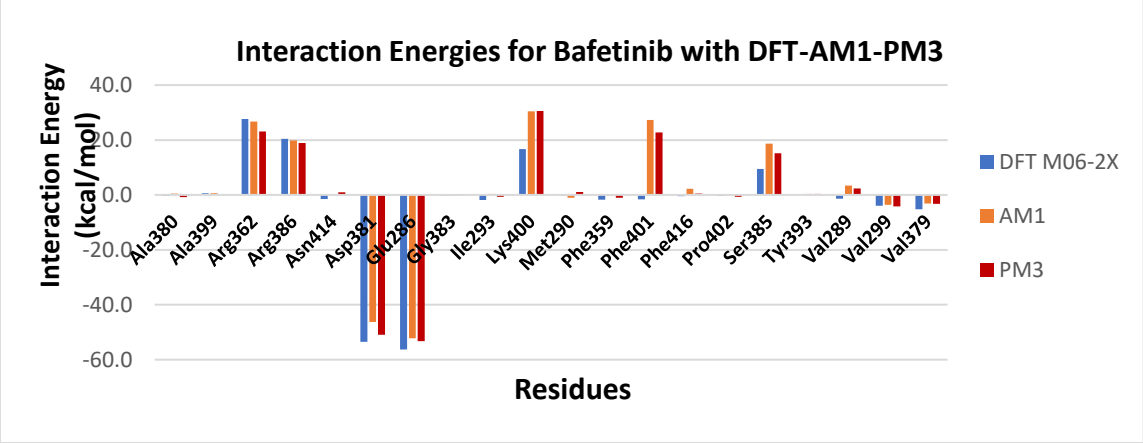

Figure 3. Comparison graph of interaction energies for Bafetinib

In Figure 3, the energy values of the interactions of Bafetinib molecule calculated by different methods are given. The purpose of creating these graphs in this study is to compare DFT calculations with semi-empirical methods. As can be seen from this graph, both DFT and semi-empirical methods have drawn similar profiles in calculating the energies of interactions of Bafetinib molecule. The aminoacids

with which the ligand interacts dominantly are the same. Based on this result, it can be said that semi-empirical methods, which have much shorter computation times than DFT methods, can be used instead of DFT methods in predicting which aminoacid residues may be more significant at the active site of the tyrosine kinase enzyme. Of course, this judgment applies to the Bafetinib molecule. In order to reach a more general conclusion, other commercial molecules discussed in the work should also be examined in this way.

3.2. Bosutinib

In physiological environment the electrical charge of the Bosutinib is +1. According to the ZINC, there are two different protonated state of the Bosutinib. So, both protonated states should be considered in semi-empirical calculations.

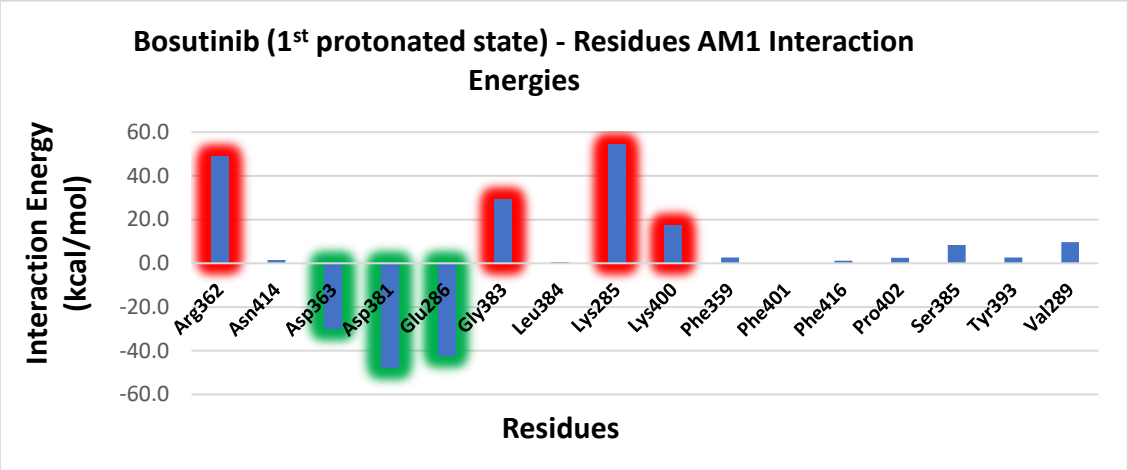

Figure 4. Interaction energies calculated by AM1 between Bosutinib and residues

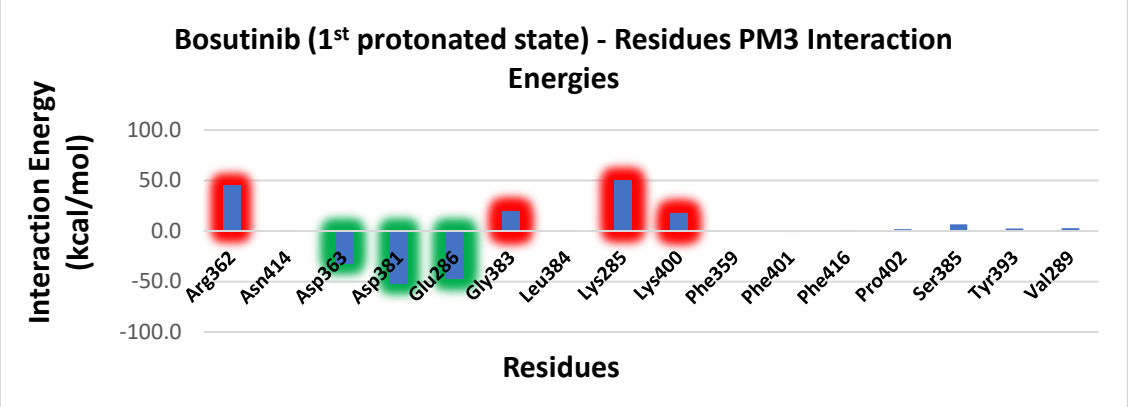

Figure 5. Interaction energies calculated by PM3 between Bosutinib and residues

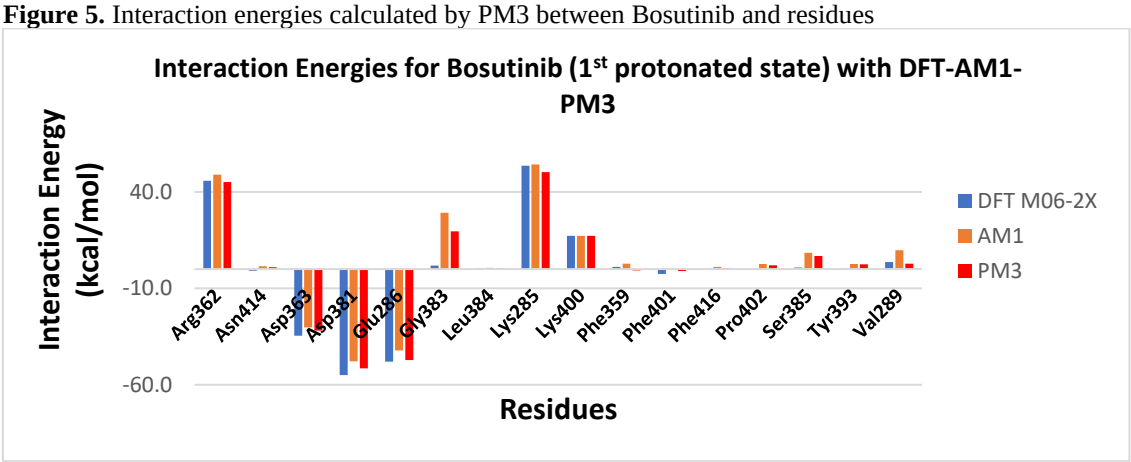

Figure 6. Comparison graph of interaction energies for Bosutinib

Figure 4 presents the interaction energies between key aminoacids and 1st protonated form of the Bosutinib molecule. These energy values were calculated by the AM1 method. As can be seen from the graph, the residues with which Bosutinib ligand interacts best are Arg362-Asp363-Asp381-Glu286-Gly383-Lys285-Lys400. Among them, interactions with Asp363-Asp381-Glu286 are attractive, while those with Gly383-Lys285-Lys400 are repulsive. For the same protonated form, it is also necessary to look at the interaction energies calculated with PM3.

In Figure 5, the interaction energies of the Bosutinib molecule, again belonging to the first protonated state and calculated with PM3, can be seen. As can be seen in this graph, the dominant aminoacids found by the calculations made with PM3 and interacting with the Bosutinib molecule are the same as the important residues found by the AM1 method. A similar result was obtained for the 1st protonation state of the Bosutinib ligand as in the Bafetinib molecule. In other words, the results found with AM1 and the results found using PM3 method showed parallel characteristics. Both semi-empirical methods found the same aminoacid residues dominant in terms of interaction energies. Of course, it is not enough to evaluate the results in this way alone. As with the Bafetinib molecule, the results obtained by semi-empirical methods must be compared with those obtained by DFT methods in my previous study, which is the main line of this study.

The results obtained from both DFT methods and semi-empirical methods, which can be easily seen in Figure 6, draw parallel profiles with each other. All methods found the same aminoacid residues to be more dominant in the interactions of the Bosunitib molecule. When the graph in Figure 6 is carefully examined, a mismatch can be seen regarding the amino acid Gly383. As is known, the aminoacid glycine is electrically neutral. The interaction of an uncharged aminoacid with a +1 charged ligand such as Bosutinib will naturally be weaker than the interaction of this ligand with an aminoacid with any electrical charge. As can be seen from the graph, the interaction energy with the Gly383 residue found by the DFT method is much smaller than the interaction energy obtained from the semi-empirical methods. There is a noticeable difference between the interaction energies. Of course, by nature, DFT methods will give much more accurate results than semi-empirical methods. Although a deviation regarding this aminoacid seems to be a problem at first, it does not adversely affect the general trend obtained for the entire aminoacid series examined in the active site. The other protonated state of the Bosutinib should also be examined in this way.

Figure 7 shows the energies of interactions between key aminoacid residues and the 2nd protonated form of the Bosutinib molecule. These energy values were calculated by the AM1 method. According to this graph, the residues with which Bosutinib interacts best are Arg362-Asp363-Asp381-Glu282-Glu286-Lys271-Lys285-Lys400. Interactions with Asp363-Asp381-Glu282 and Glu286 are attractive, while those with Arg362-Lys271-Lys285-Lys400 are repulsive. As in the previous protonated form of Bosutinib, interaction energies calculated by the PM3 method will also be evaluated here.

Figure 8 shows the interaction energies calculated by the PM3 method, which belongs to the second protonated form of Bosutinib molecule. The results obtained with PM3 method are very similar to those obtained with the AM1 method. As in the first protonation state of the Bosutinib molecule, the interaction energies calculated by both DFT and semi-empirical methods were compared for the second protonation state of this ligand. The results are given in the graph below and analyzed.

Looking at the graph in Figure 9, it can be said that DFT, AM1 and PM3 methods showed qualitatively similar results according to the interaction energies calculated for the 2nd protonation of the Bosutinib. DFT and semi-empirical methods found the same aminoacids dominantly in the binding cavity of tyrosine kinase as in Bafetinib molecule and in the 1st protonated state of the Bosutinib.

3.3. Dasatinib

The electrical charge of the Dasatinib molecule is +1 at physiological environment. there is only one protonated state for the Dasatinib according to the ZINC database.

Figure 10 demonstrate the interaction energies of contacts between Dasatinib and critical aminoacids calculated with AM1.

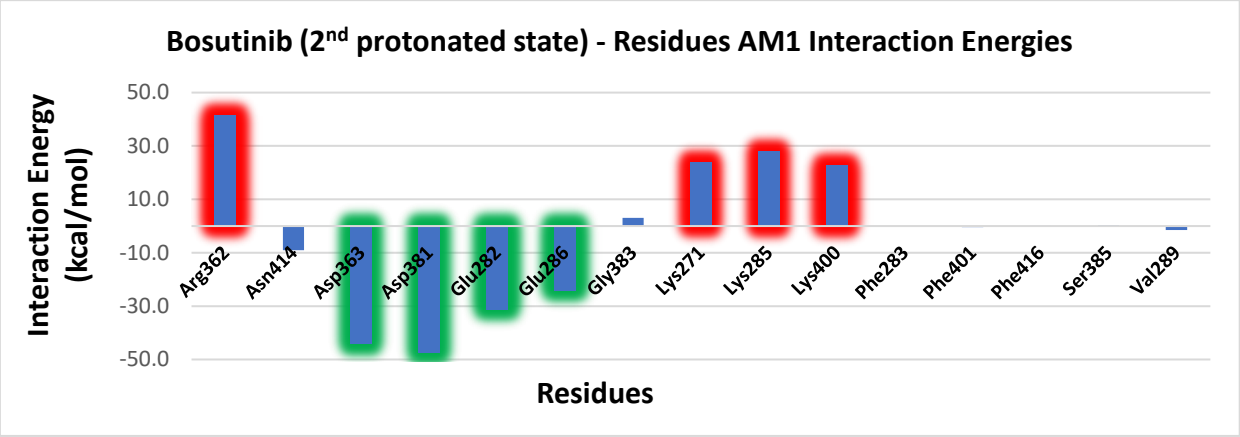

Figure 7. Interaction energies calculated by AM1 between Bosutinib and residues

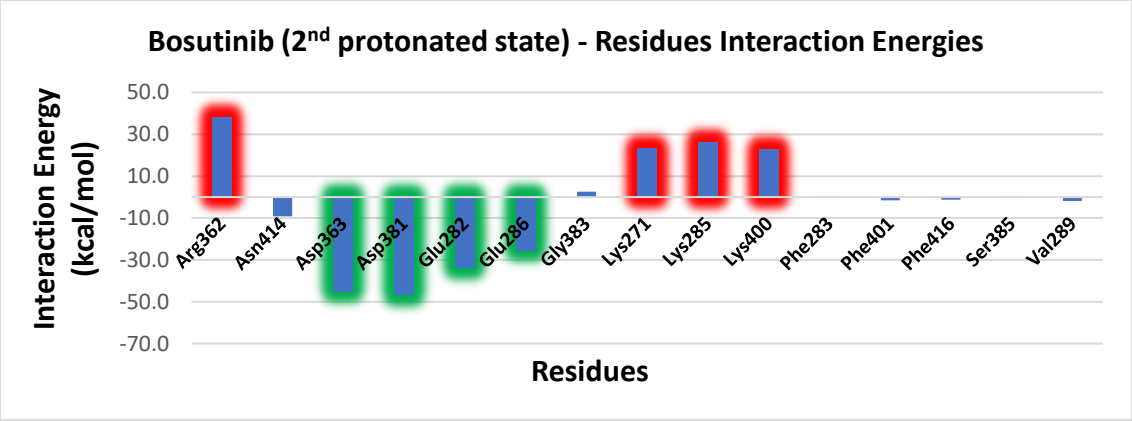

Figure 8. Interaction energies calculated by PM3 between Bosutinib and residues

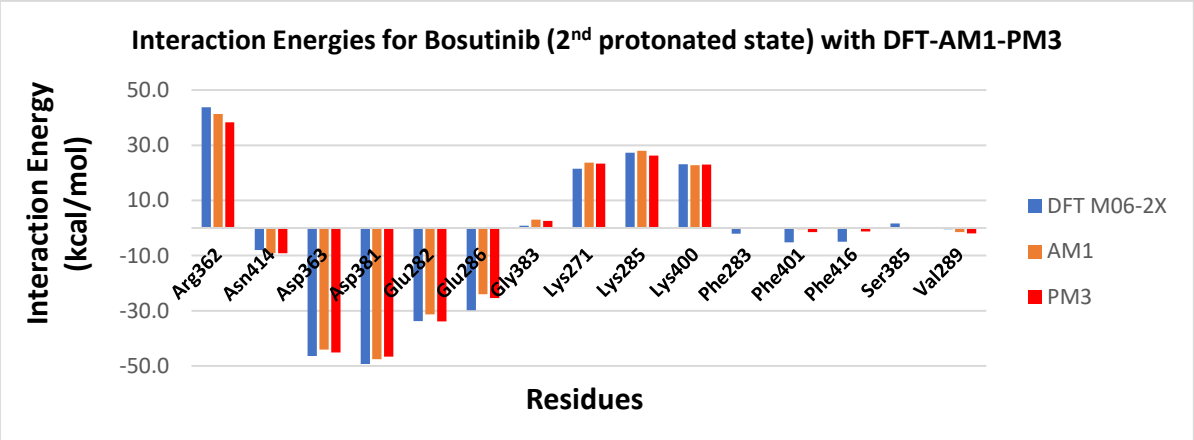

Figure 9. Comparison graph of interaction energies for Bosutinib

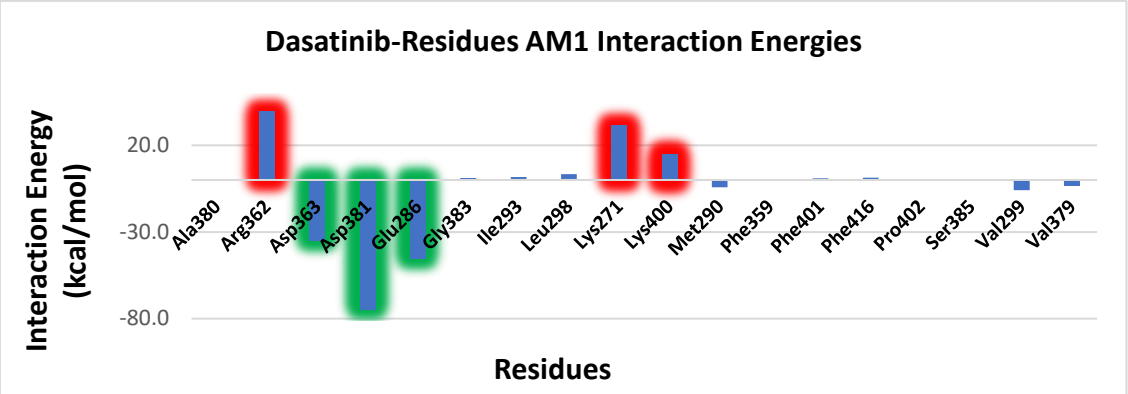

Figure 10. Interaction energies calculated by AM1 between Dasatinib and residues

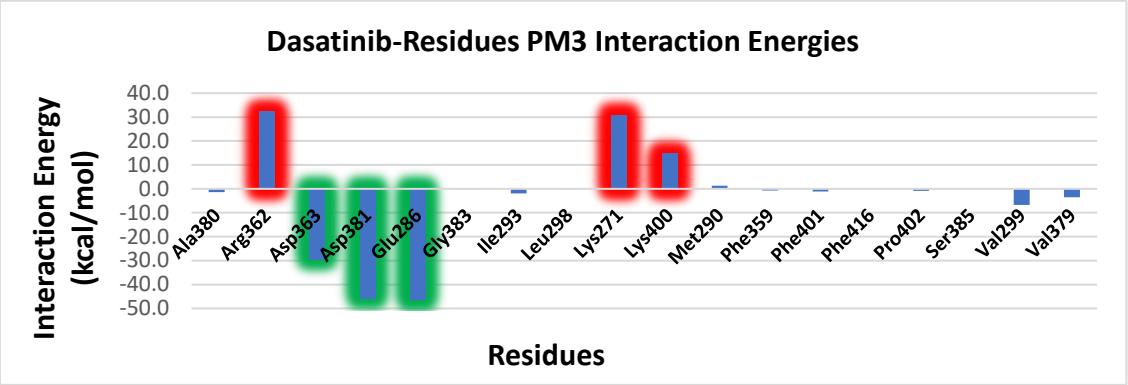

Figure 11. Interaction energies calculated by PM3 between Dasatinib and residues

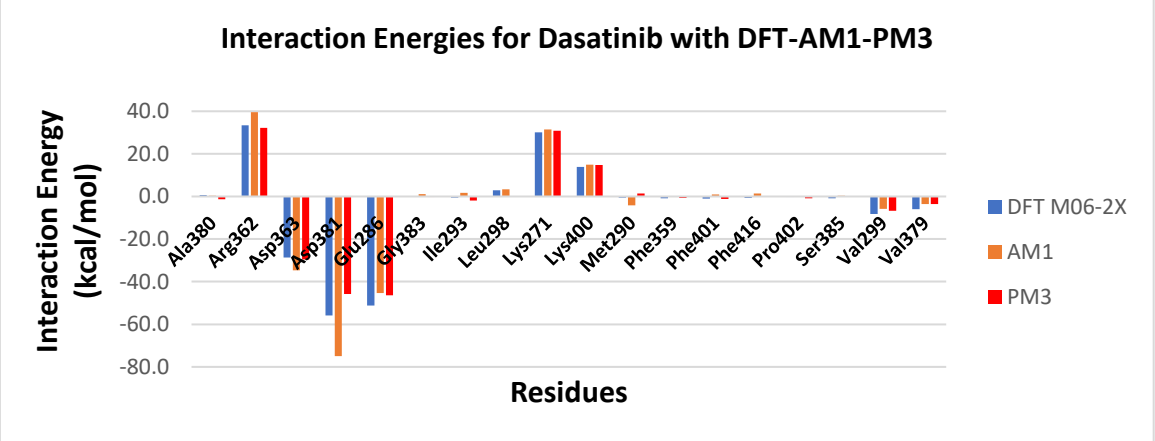

Figure 12. Comparison graph of interaction energies for Dasatinib

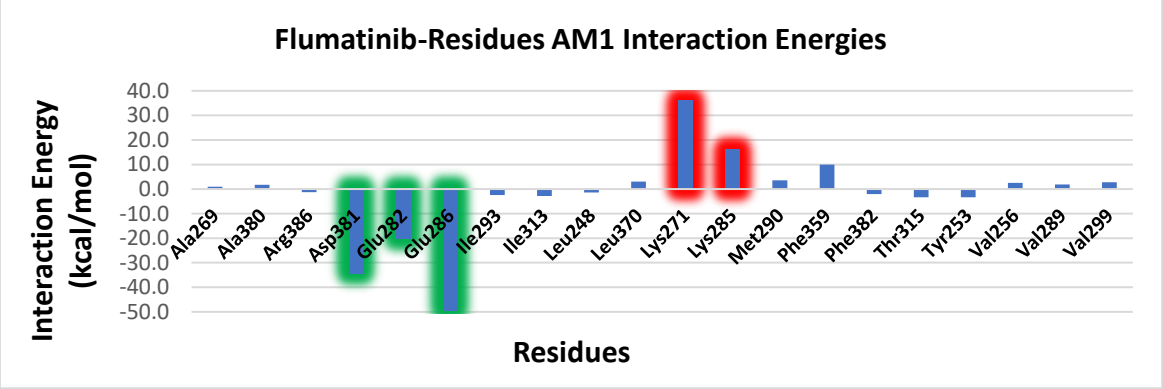

Figure 13. Interaction energies calculated by AM1 between Flumatinib and residues

According to the data in this graph, Dasatinib contacted with Glu286-Asp381-Asp363 attractively and with Lys400-Arg362-Lys271 in a repulsively. Same calculations were made with PM3 as before. Figure 11 shows the interaction energies calculated by the PM3 method. Comparing the graphs in Figure 10 and Figure 11 with each other, it will be seen that the calculations with AM1 and PM3 suggest that the Dasatinib may be in active contact with the same residues. Both semi-empirical methods yielded similar results. In order to investigate the main purpose of the study, the energies calculated by DFT before for this ligand and those calculated by semi-empirical methods will be compared with each other using graphics.

As can be easily seen from the graph above, both DFT and the semi-empirical methods used in this study gave very similar results regarding which aminoacids the Dasatinib molecule might interact with more dominantly at the binding site of the enzyme under investigation. This result for Dasatinib is in line with those found for ligands previously studied. In other words, the results obtained so far are in good agreement with each other. Looking at the results obtained so far, it can be concluded that semi-empirical and DFT methods give very similar results regarding which residues a ligand can be in contact with more effectively in active cavity of the tyrosine kinase. From this point of view, it can be said that using semi-empirical methods, less computation time will be required to find the most important residues in the binding cavity of tyrozine kinase. This means that computational costs will be reduced. However, in order for this judgment to become more evident, other commercial drug molecules discussed in this study should be examined in the same way.

3.4. Flumatinib

Flumatinib has a +1 electrical charge at physiological environment and has only one protonated state.

Figure 13 shows the interaction energies belonging to Flumatinib which have been calculated via AM1. According to this graph, Flumatinib has interacted with Asp381-Glu282-Glu286 aminoacids and Lys271 and Lys285 residues in attractive and repulsive nature, respectively. It is also necessary to examine the interaction energies calculated by the PM3 method.

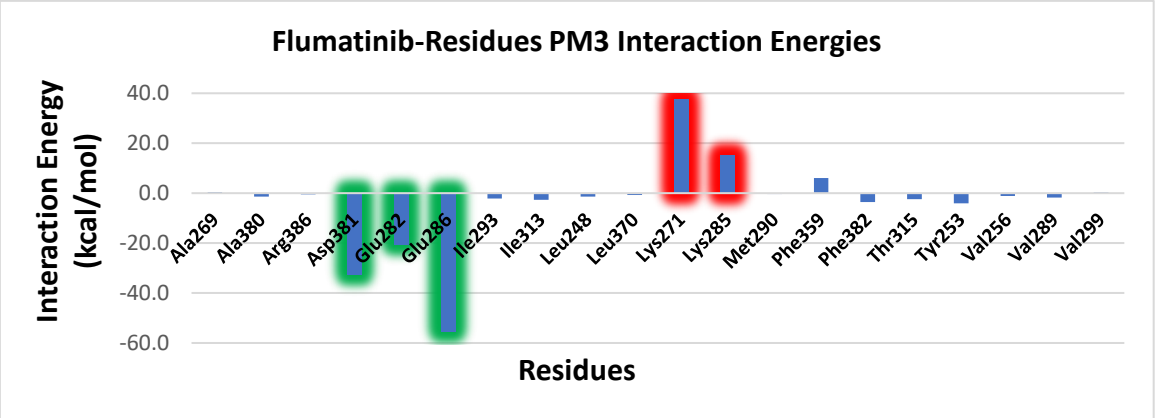

Figure 14. Interaction energies calculated by PM3 between Flumatinib and residues

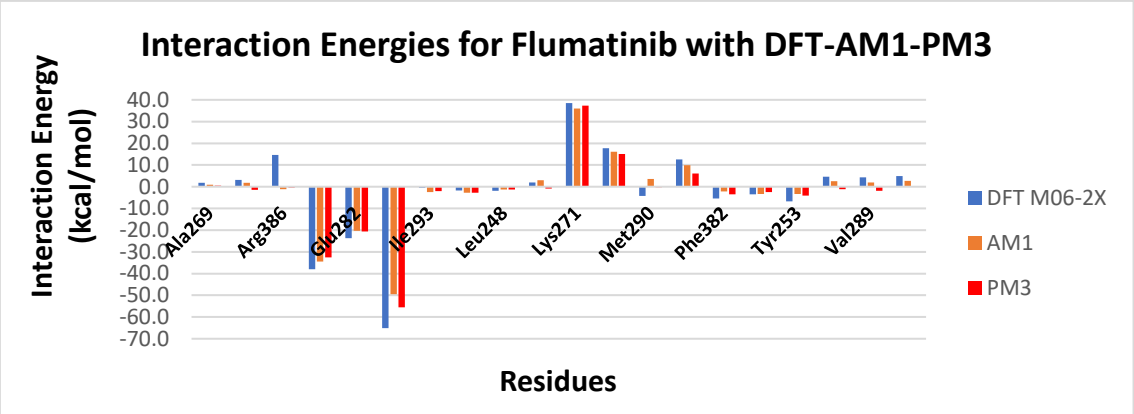

Figure 15. Comparison graph of interaction energies for Flumatinib

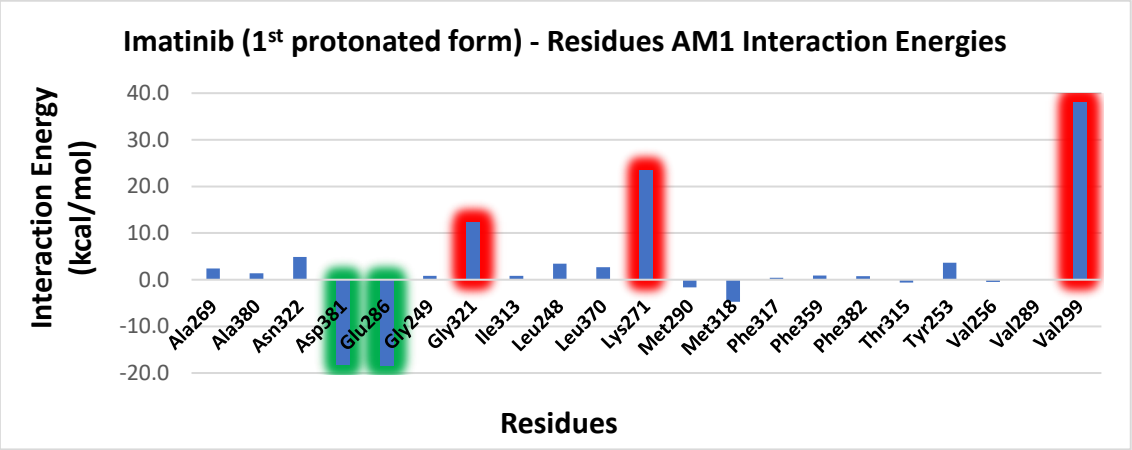

Figure 16. Interaction energies calculated by AM1 between Imatinib and residues

Figure 14 shows the interaction energies calculated by the PM3 method. As with the other ligands examined, the results obtained with the AM1 method in the Flumatinib molecule are completely consistent with those found with PM3. Comparison of the results found by DFT and semi-empirical methods is given in the graph below.

In this study, the same results were obtained with Flumatinib as in the molecules examined so far. In other words, the most effective aminoacid residues found by DFT and AM1-PM3 methods overlap with each other. In this molecule, the most dominant aminoacids in the active cavity of tyrosine kinase could be found with less costly computation times.

3.5. Imatinib

As the Bosutinib, the Imatinib has +1 electrical charge and two reasonable protonated state at physiological environment according to ZINC database. As before, the interaction energies of each protonated state of this ligand with important aminoacids have been calculated via AM1 and PM3 methods.

In the graph above, the interaction energies between the important aminoacids at binding cavity of 1st protonated state of the Imatinib molecule are given. These energies were calculated by the AM1 method, which is also indicated in the graph. As can be seen from the graph, Imatinib has formed powerful interactions with Glu286-Asp381 Gly321-Val299-Lys271 residues. The interactions with aminoacids Asp381 and Glu286 are attractive, while the others are repulsive. In order to compare with AM1, it is necessary to confirm these interactions with the PM3 method.

In the graph in Figure 17, the interaction energies of the 1st protonated form of the Imatinib, this time calculated with PM3, are given. When the graphs given in Figure 16 and Figure 17 are compared, it can be seen that the most dominant aminoacid residues are the same according to the interaction energies of the 1st protonated state of the Imatinib calculated by both semi-empirical methods, that is, both AM1 and PM3 gave overlapping results. These results also need to be compared with the interaction energies calculated by DFT methods obtained from the aforementioned study.

As can be seen in the graphic above, DFT and semi-empirical methods have found similar trends in the

interactions of the 1st protonated state of the Imatinib molecule with the residues it contacts in active cavity of tyrosine kinase.

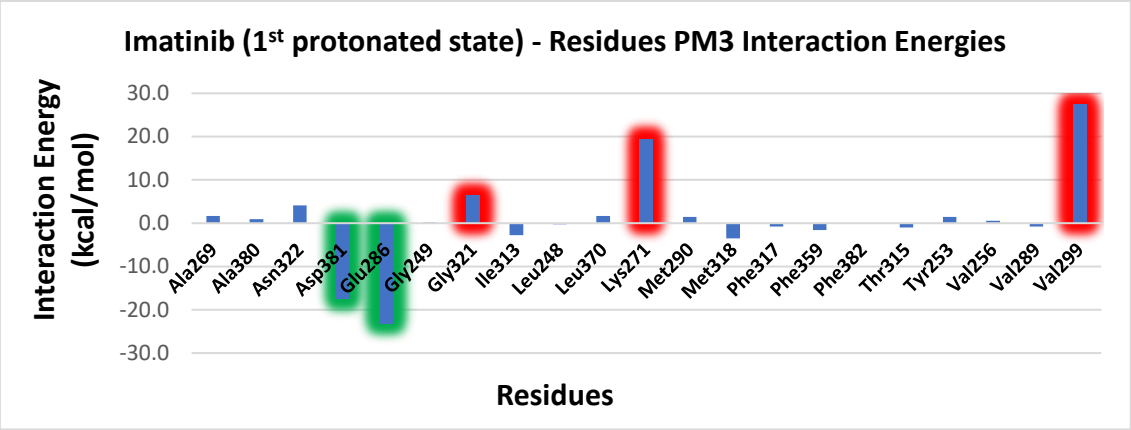

Figure 17. Interaction energies calculated by PM3 between Imatinib and residues

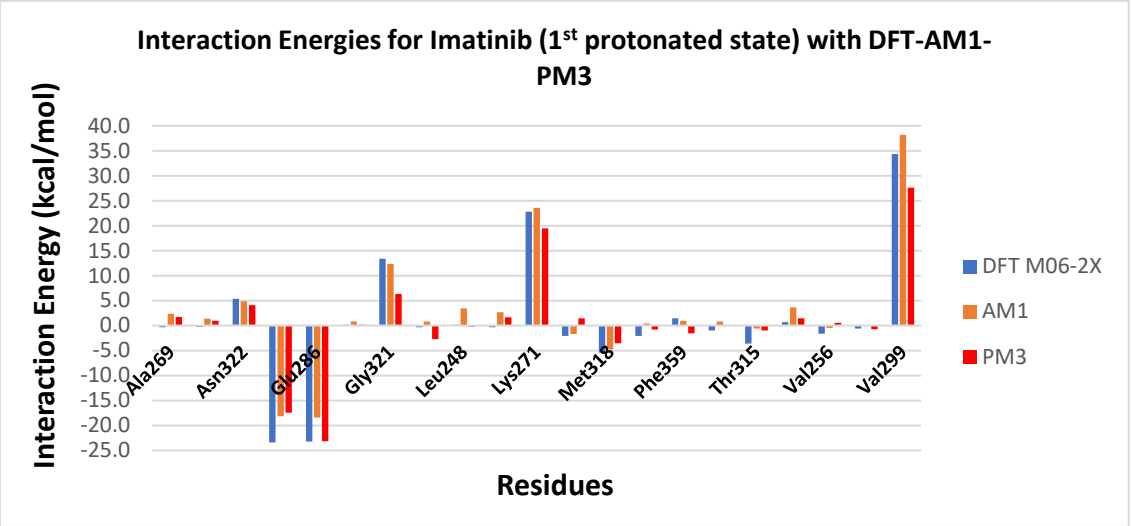

Figure 18. Comparison graph of interaction energies for Imatinib

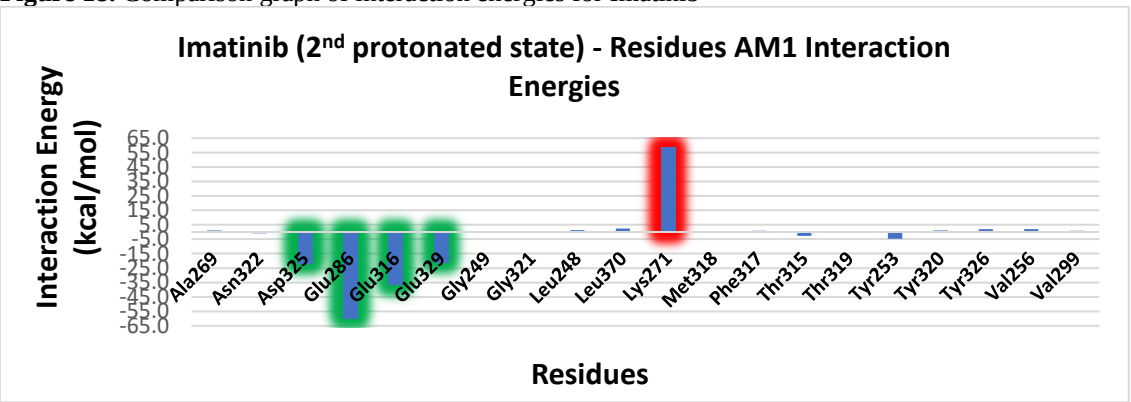

Figure 19. Interaction energies calculated by AM1 between Imatinib and residues

This result is parallel to the results obtained from other molecules studied. In order to evaluate whether these results are valid for the 2nd protonated form of the Imatinib molecule, the same calculations and considerations must be performed for this structure as well.

The graph in Figure 19 shows the interaction energies of the 2nd protonated state of the Imatinib and calculated by the AM1 method. As can be understood from here, strong interactions have been made with Asp325-Glu286-Glu316-Glu329 and Lys271 residues. Except for the interaction with Lys271, all other interactions are attractive.

In Figure 20, the interaction energies belonging to

the 2nd protonated state of the Imatinib molecule and calculated for PM3 are shown. When the interaction energies calculated from the AM1 and PM3 methods are compared, it can be seen that the important aminoacids with which the Imatinib interacts most strongly overlap completely.

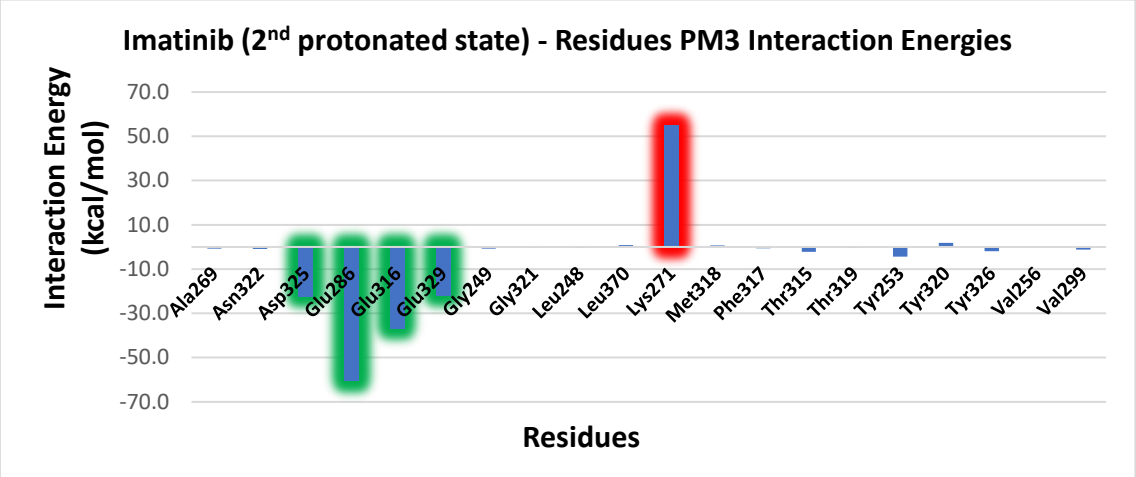

Figure 20. Interaction energies calculated by PM3 between Imatinib and residues

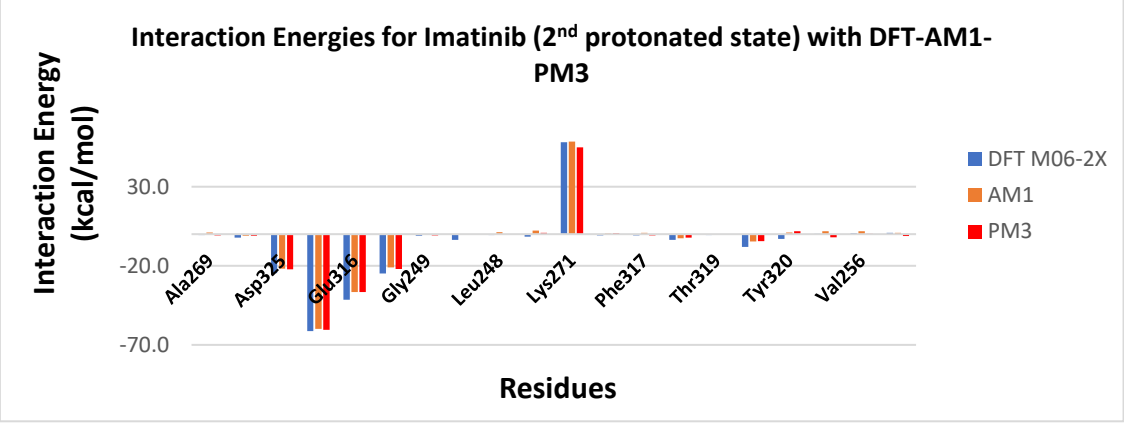

Figure 21. Comparison graph of interaction energies for Imatinib

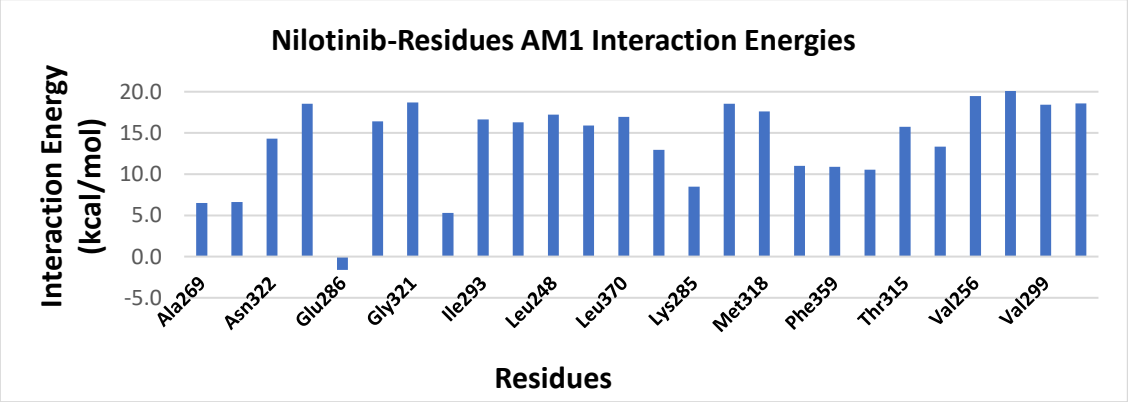

Figure 22. Interaction energies calculated by AM1 between Nilotinib and residues

All results for the 2nd protonated state of the Imatinib molecule are actually summarized in the graph in Figure 21. The most effective aminoacids found using DFT methods and those found by semi-empirical methods are the same in the 2nd protonated form of the Imatinib molecule as well as in the 1st protonated form. In other words, with shorter computation times for this ligand, the most critical residues can be accurately predicted. The following can be said for all the ligands studied so far; semi-empirical methods can find the most important aminoacids at binding cavity of tyrosine

kinase as well as DFT methods with cheaper computational costs.

3.6. Nilotinib

There is a different situation for the Nilotinib. This molecule does not have any protonated form as former ligands in this work, that is, Nilotinib has no electrical charge under physiological conditions. Details on this have already been given in the previous study [10]. In Figure 22, the interaction energies of Nilotinib between aminoacids in the active cavity of this protein are given and these energy values were calculated by the AM1 semi-empirical method. When we compare this graph with the other graphs examined so far, we can see that a different profile emerges. All of the molecules we have examined up to this point were positively charged under physiological conditions. But Nilotinib does not have any electrical charges. Therefore, the interactions of this ligand with aminoacids in the binding site will be much weaker than other ligands. When this graph is compared with the interaction energy graphs of other molecules, this conclusion can be easily reached. The same situation can be seen in the energy values calculated with PM3. These values are given in Figure 22.

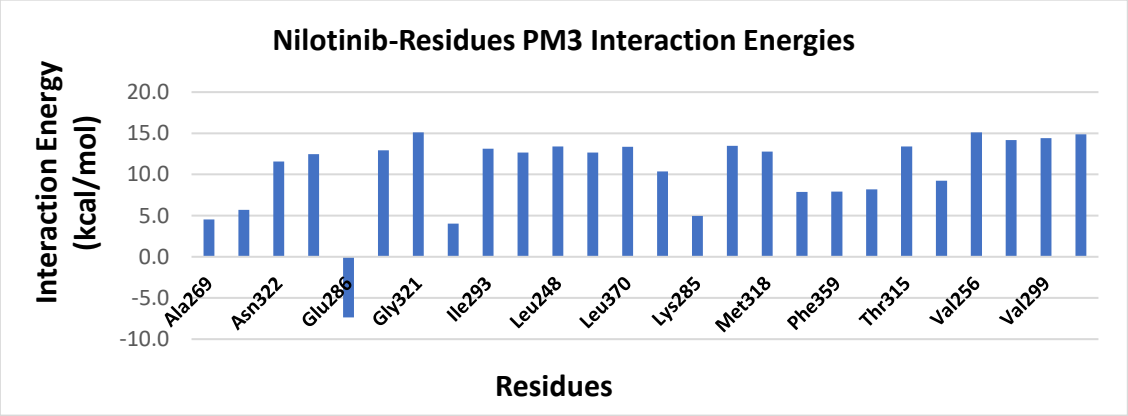

Figure 23. Interaction energies calculated by PM3 between Nilotinib and residues

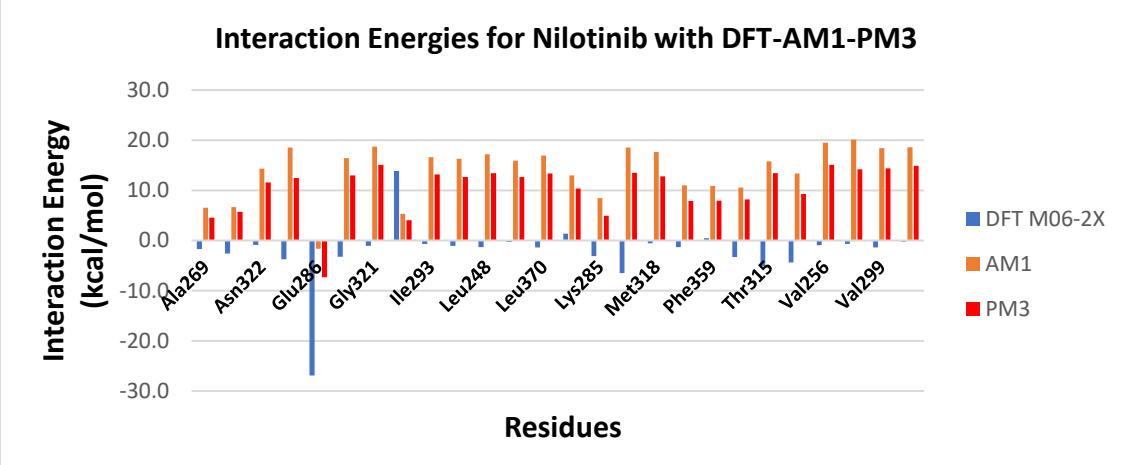

Figure 24. Comparison graph of interaction energies for Nilotinib

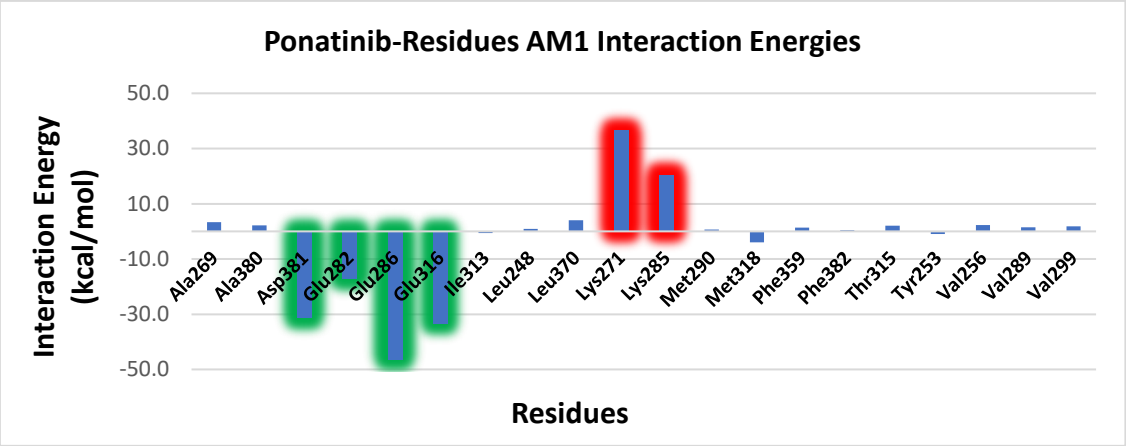

Figure 25. Interaction energies calculated by AM1 between Ponatinib and residues

As can be seen in the graphs given in Figure 22 and Figure 23, Nilotinib could only interact attractively with Glu286 aminoacid. All interactions with other aminoacids other than this aminoacid are repulsive. The energy values calculated by both AM1 and PM3 methods do not differ much between residues. The situation was very different in the other examined ligands. All of the ligands examined so far have +1 charge as said before. Therefore, the interaction energies of contacts with electrically charged residues are much higher than those with electrically neutral ones. Since Nilotinib is not in a protonated state, that is, it does not have any electrical charge, the interaction energies are not that high, and therefore, there are no large differences in interaction energies with the aminoacids established in contact. In order to evaluate whether semi-empirical methods are as good as DFT in detecting the most important residues, as before, the interaction energies calculated by DFT methods must also be considered. The relevant comparison is given in Figure 24.

If the graph given in Figure 24 is examined, it can be seen that it is much different from the graphs examined before. In these comparison charts of the previous molecules, the results found by DFT methods and those found by semi-empirical methods actually showed parallel characteristics. However, in the Nilotinib molecule, this parallelism and overlap has disappeared. Semi-empirical methods have found a different tendency for the interactions with the aminoacids that the Nilotinib molecule comes into contact with, whereas DFT methods have a different tendency. This difference may be due to the fact that the Nilotinib molecule is electrically uncharged. Because the hypothesis showing consistency in +1 charged ligands does not work for this neutral ligand. In this case, it can be said that using semi-empirical methods, in order to predict the most dominant aminoacids at active cavity of tyrosine kinase, the studied ligand may need to be electrically charged in order to get results as accurate as DFT methods. The same evaluations should be made for the Ponatinib molecule, which is the last commercial molecule in the study, and only in this way we can make a general judgment for this study.

3.7. Ponatinib

The Ponatinib molecule is the last ligand to be examined in this study. Under physiological environment, electrical charge of this molecule is +1. According to the ZINC, there is only one protonated form of Ponatinib. As with the molecules examined before, the interaction energies of Ponatinib were calculated primarily by the AM1 and PM3 methods, and the results are given below.

Figure 25 shows the interaction energies calculated by the AM1 method. As can be seen from the graph, Ponatinib formed attractive interactions by Glu282-Asp381-Glu316-Glu286 and repulsive interactions with Lys271-Lys285 at the binding site.

Figure 26 shows the interaction energies calculated with PM3 this time. When Figure 25 and Figure 26 are compared with each other, it is seen that the most dominant residues found by AM1 and PM3 methods are the same. These two semi-empirical methods yielded overlapping results.

As can be seen from Figure 27, semi-empirical methods were able to accurately predict the dominant residues in the interaction in active cavity of tyrosine kinase as well as DFT methods. For the +1 charged Ponatinib molecule the two semi-empirical methods, AM1 and PM3, saved time in estimating the most critical aminoacids at active site of the enzyme, as in the other +1 charged ligands. All the data obtained are collectively discussed again in the conclusion part.

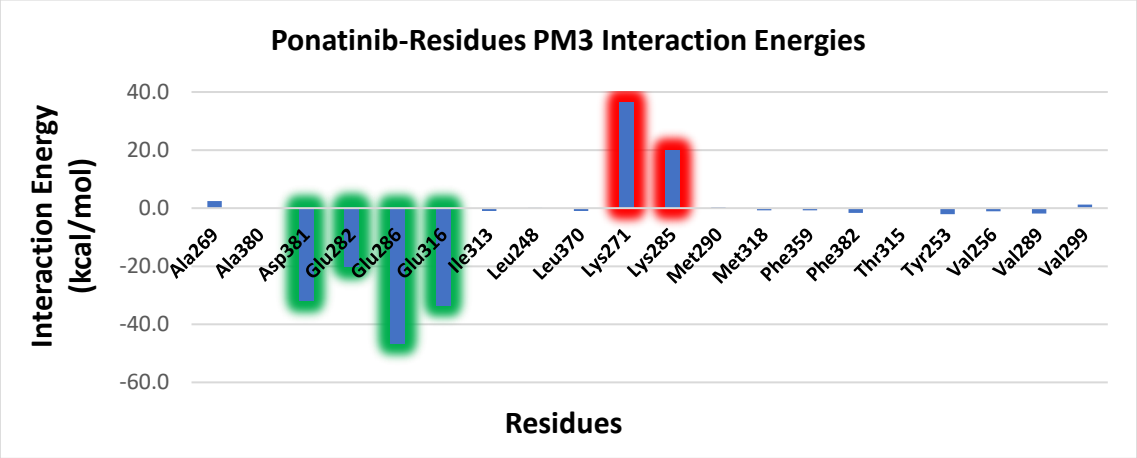

Figure 26. Interaction energies calculated by PM3 between Ponatinib and residues

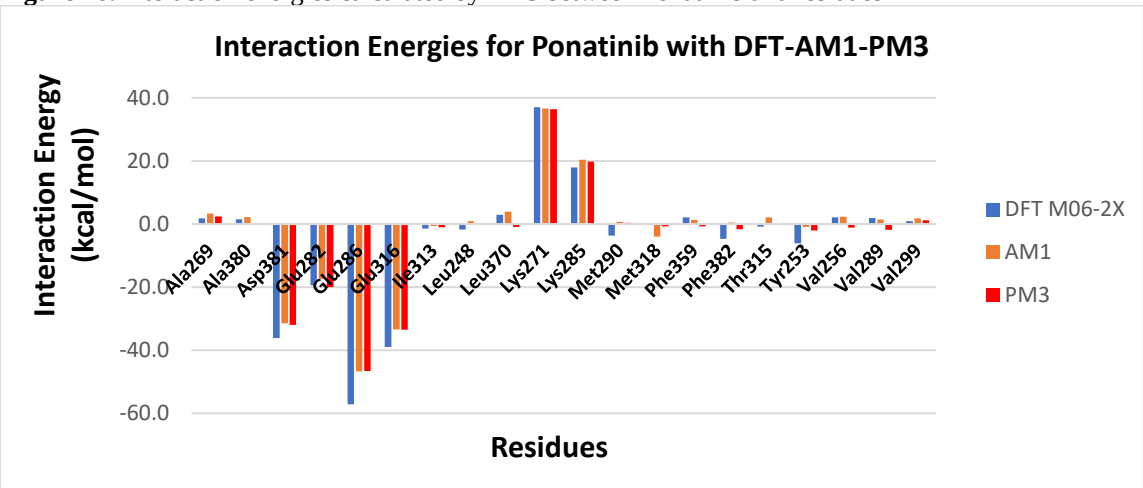

Figure 27. Comparison graph of interaction energies for Ponatinib

4. Conclusions

At this work, the interactions of a series of commercial drug molecules used as tyrosine kinase inhibitors with important residues at binding region of this protein were evaluated by semi-empirical methods. As explained in the former sections, this research was carried out in a previous study with DFT methods [10]. However, as it is known, DFT methods are much more costly than semi-empirical methods in terms of computation time. To spend less computational time to find out which of the interactions of a ligand with aminoacid residues in the active site of an enzyme is more important, in other words, more dominant, is very advantageous for a researcher working in drug development procedures and knowing the importance of this data. The hypothesis established at the beginning of the study was; if the most important residues found by semi-empirical methods are the same as those found with DFT methods in the previous study, that is, if both studies show a parallel profile, then it can be said that instead of methods such as DFT, which can take more time to detect the most important residues in the active cavity, the use of methods such as AM1 and PM3 with much shorter computation times will significantly shorten the research duration.

If the results of this study are summarized, the following can be said. Except for one of the 7 commercial inhibitors used here, the other 6 have +1 electrical charge under physiological conditions. Among them, only the Nilotinib molecule is neutral. According to the results found, the semi-empirical calculations for ligands with +1 charge under physiological conditions largely overlap with the results obtained with DFT in the previous study. Only the Nilotinib molecule disrupts this situation. The following conclusion can be drawn from here. If the investigated inhibitor molecules are electrically charged under physiological conditions, widely used semi-empirical methods such as AM1 and PM3 can be used instead of DFT methods in order to reduce the search time.

This conclusion is actually valid only for the tyrosine kinase enzyme. In order to expand this hypothesis further, the same studies should be

conducted with ligands that exist in the literature and have the potential to be experimentally inhibitor. In fact, this hypothesis should not be limited to only the tyrosine kinase enzyme. This judgment can be extended by doing similar studies for different enzymes. In fact, this study and the paper using DFT methods mentioned in the previous sections are the first steps of a long-term project to investigate the applicability of quantum mechanical methods in the explanation of protein-ligand interactions.

If the hypothesis we have put forward is valid for binary systems like here, that is, if semi-empirical methods are as successful as DFT methods in estimating the interaction energy trends of ligand-aminoacid pairs, then these semi-empirical methods can be used to shorten the computation time in evaluating protein-ligand interactions in larger systems.

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