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INVESTIGATION OF MODIFIED SORAFENIB DERIVATIVES AS A TYROSINE KINASE INHIBITORS OF LEUKIMIA VIA MOLECULAR DOCKING

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Abstract

Leukemia is a human heterogeneous category of hematological malignancies that is mainly fueled by an imbalanced expression of tyrosine kinases that facilitate uncontrolled cell proliferation and survival. Even though Sorafenib and Regorafenib are proven multi-kinase inhibitors, they are not extensively used in the treatment of leukemia. The purpose of this research was to develop and test some of the modified derivatives of these compounds as possible tyrosine kinase inhibitors to treat leukemia. Molecular docking was performed on 14 derivatives (Sorafenib and S1-S13) with respect to a target of leukemia associated tyrosine kinase. Their therapeutic potential was determined by determining binding affinities (ΔG) and inhibition constants (Ki). S6 (-13.06 kcal/mol, 267.16 pM) had the highest binding affinities and a number of derivatives (S1, S3, S6, and S8) performed better than others. These results indicate that the derivatives modified, especially S6, are good prospects to be further experimentally validated as effective counter-tyrosine kinase inhibitors in the treatment of leukemia.

1. Introduction

Leukemia is a group of malignant hematologic diseases, a condition where the normal growth of the white blood cells in the bones marrow and peripheral blood are uncontrolled [1]. The abnormality in the hematopoietic stem cells that result in the accumulation of immature or dysfunctional cells is a consequence of this interference with the production of the mature blood cells [2]. Leukemia has severe effects of disrupting the immune systems and the overall hematological balance as white blood cells are highly significant in the body in the defense against infection [3]. The interaction between genetic factors, environmental factors and lifestyle-related factors is complex and results in the development of leukemia [4]. Though the etiology of the disease is unclear, various risk factors have been implicated in the occurrence of the disease which include viral infections, contact with chemicals, ionizing radiations, smoking and inherited genetic abnormalities [5]. Symptoms that are usually associated with leukemia in the clinical setting are fatigue, weight loss, easy bruising, frequent infections and overall weakness [3]. Laboratory tests like complete blood count, blood smear analysis, flow cytometry, and bone marrow aspiration are common diagnostic tests [6]. Microscopic observations of blood and marrow cells are also needed in most instances to determine disease-specific characteristics, such as abnormal cell morphology and Auer rod presence. The possibility however, exists that various pathologists may interpret the results of tests of diagnosis differently and this may complicate the classification of diseases [7].

Leukemia can be subdivided into acute and chronic. Acute leukemia is characterized by the rapid build-up of immature blood cells and it

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encompasses acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) [8]. Myeloid precursor cells are those that lead to AML and could be found in diverse ages, but lymphoid precursor cells are the ones that lead to ALL and are mostly common in children [9]. In contrast, chronic leukemia is much slower in progression and the excessive production of rather mature abnormal blood cells characterizes it. The major chronic forms of leukemia are chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL) and the rare hairy cell leukemia [10]. These subtypes differ in regard to biological behavior, genetics, prognosis, and response to treatment.

with high or very high HDI [11]. Recent estimates in the world show that leukemia is a significant morbidity and mortality burden of cancer. Leukemia is another critical issue of public health in Pakistan, but studies about its regional trends, risk factors and other demographic determinants are minimal [12]. Most of the existing classification studies rely on laboratory data and the lifestyle and demographic variables are not well studied [13]. The combination of these factors can help to improve the knowledge of the disease, its early diagnosis, and preventive actions. Leukemia is treated depending on the type, stage and can be treated using chemotherapy, targeted therapy, and immunotherapy and in some instances stem cell transplantation [14]. The common therapeutic agents in the treatment of AML include cytarabine and anthracyclines, the treatment of ALL includes vincristine, corticosteroids, the treatment of CML includes imatinib, and the treatment of CLL and AML cases that are selected include venetoclax [15]. Although these therapies have improved the survival rates, treatment is generally associated with toxicity, resistance, relapse and unpredictable patient response [16]. Therefore, more research needs to be done to improve the accuracy of the diagnosis, the risk factors that are discernible, and devise more effective yet less toxic methods of treatment [17]. Tyrosine kinases are a family of enzymes which regulate the key cell functions such as proliferation, differentiation, survival, migration and apoptosis [18]. Typically, during normal hematopoiesis, these enzymes play a role in ensuring that there is a proper balance in the signaling of blood-forming cells [19]. But, in cases where the activation of tyrosine kinases is abnormally caused by mutation, rearrangements in the chromosome, or overexpression, they can play a role in malignant transformation and the formation of leukemia. Their role in the pathogenesis of leukemia, and in targeted therapy is thus pivotal [20]. Tyrosine kinase inhibitors (TKIs) are a family of targeted cancer drugs that block the activity of tyrosine kinases, enzymes that control cell growth, cell survival, cell differentiation and cell signal transduction [21]. Normal cells have highly regulated activity of tyrosine kinases which are in most cases abnormally activated by mutation, fusion or overexpression in cancerous cells like leukemia. This is a signaling that becomes dysregulated and contributes to uncontrolled growth and apoptotic resistance [22]. TKIs can therefore play a major role in the modern cure of cancer by interfering with such processes of dysregulation. Sorafenib is a small molecule multikinase multibiaryl urea core structure orally active and multibiaryl urea core structure inhibitor [23]. Its active metabolite, sorafenib N-oxide, is generated mainly through CYP3A4-mediated oxidation, and is as potent as the parent drug in vitro [24]. The modification of the structure of sorafenib is an important method of developing a superior tyrosine kinase inhibitor in leukemia [25]. This is the reason why medicinal chemistry campaigns usually aim at altering the parent scaffold to enhance potency, selectivity, and drug-like behavior in general [26].

In this study we have investigation on modified Sorafenib derivatives for their ability to inhibit tyrosine kinase was motivated by preliminary studies on the anti-cancer properties of Sorafenib, a standard cancer inhibitor, to demonstrate the binding conformation and mechanism of tyrosine kinase using molecular docking analysis.

2. Methodology

In order to use molecular docking experiments to examine the binding interaction mechanism of the modified Sorafenib as urea derivatives for both competitive and noncompetitive inhibition of the tyrosine kinase enzyme [27]. We will use the Protein Data Bank to obtain the crystal structures of the relevant proteins. For ease of computation, protein will be prepared

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theoretically using Auto Dock MGL tools by eliminating all water molecules, heteroatoms, and cofactors. We will choose the optimal docking conformer with the lowest binding energy for additional research. After analyzing the outcomes of the protein-ligand interaction using a very stable confirmer, PyMol, AutoDock Vina, and BIO via Discovery Studio will be used to display the docking positions of selectively changed sorafineb as urea derivatives against the targeted tyrosine kinase inhibitors.[28] The modified ligands were tailored by keeping the important pharmacophoric core of sorafenib intact and carrying out appropriate structural changes at the appropriate sites on the scaffold. The overall goal of the alteration was to improve binding interactions but no attempt was made to abolish the essential properties that cause kinase inhibition. Derivatives that included hydroxyl and amino groups were favored as these groups have been known to enhance the polarity, hydrogen bond donation and acceptance, and enhanced interaction potential with the amino acid residues in the receptor binding pocket.

The derivatives were constructed in a logical manner that the major structural structure was not incompatible with the ATP-binding site of the tyrosine kinases. The derivatives of the anti-leukemic drugs and their modified structure of Sorafenib are given in Figure 1

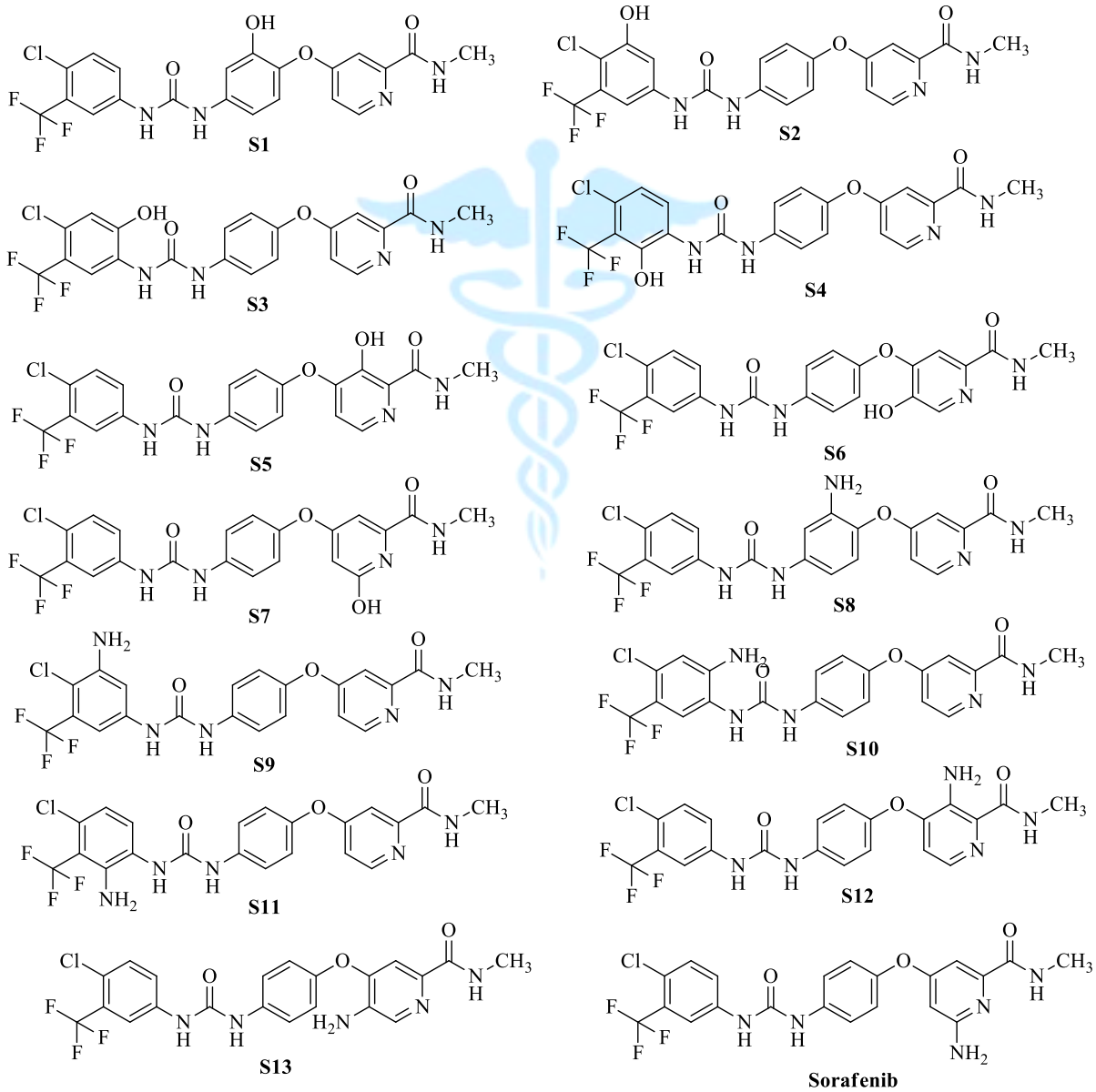

Figure 1. Structural formulae of Sorafenib and its modified derivatives (S1-S13)

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3. Results and Discussion

3.1 Molecular docking analysis of specific compounds

Molecular docking modeling was utilized to examine binding mechanism of active drugs **(S1-S13)** within the active site of Tyrosine kinase in contrast to Sorafenib.

3.1.1. Interaction of S1 with Tyrosine-kinase: The validation of compound S1, which was selected, against tyrosine kinase revealed a-13.04kcal/mol binding energy with a Pico molar inhibition constant of 277.8pM as indicated in **Table 1.** The abovementioned compound was active against tyrosine kinase and docked in the active site of tyrosine kinase. Docking experiments indicated that compound S1 bound the active site of tyrosine kinase and exhibited excellent interactions with ARG-171, LYS-75 and PHE-186. The complex of S1 with tyrosine kinase was stabilized by three hydrogen bonds and one pi-pi interaction and they were ARG-171 (O...HN, 2.1Å), LYS-75, (O....HN, 2.5Å) PHE-186 (OH...O, 2.0Å), shown in **Table 2**. Additionally, S1 also formed weak Vander Waal interactions & Conventional Hydrogen Bond, Halogen (Fluorine), Pi-Sigma and Pi-Alkyl interactions with ARG-171, LYS-75, and PHE-186 shown in the given Figure 2.

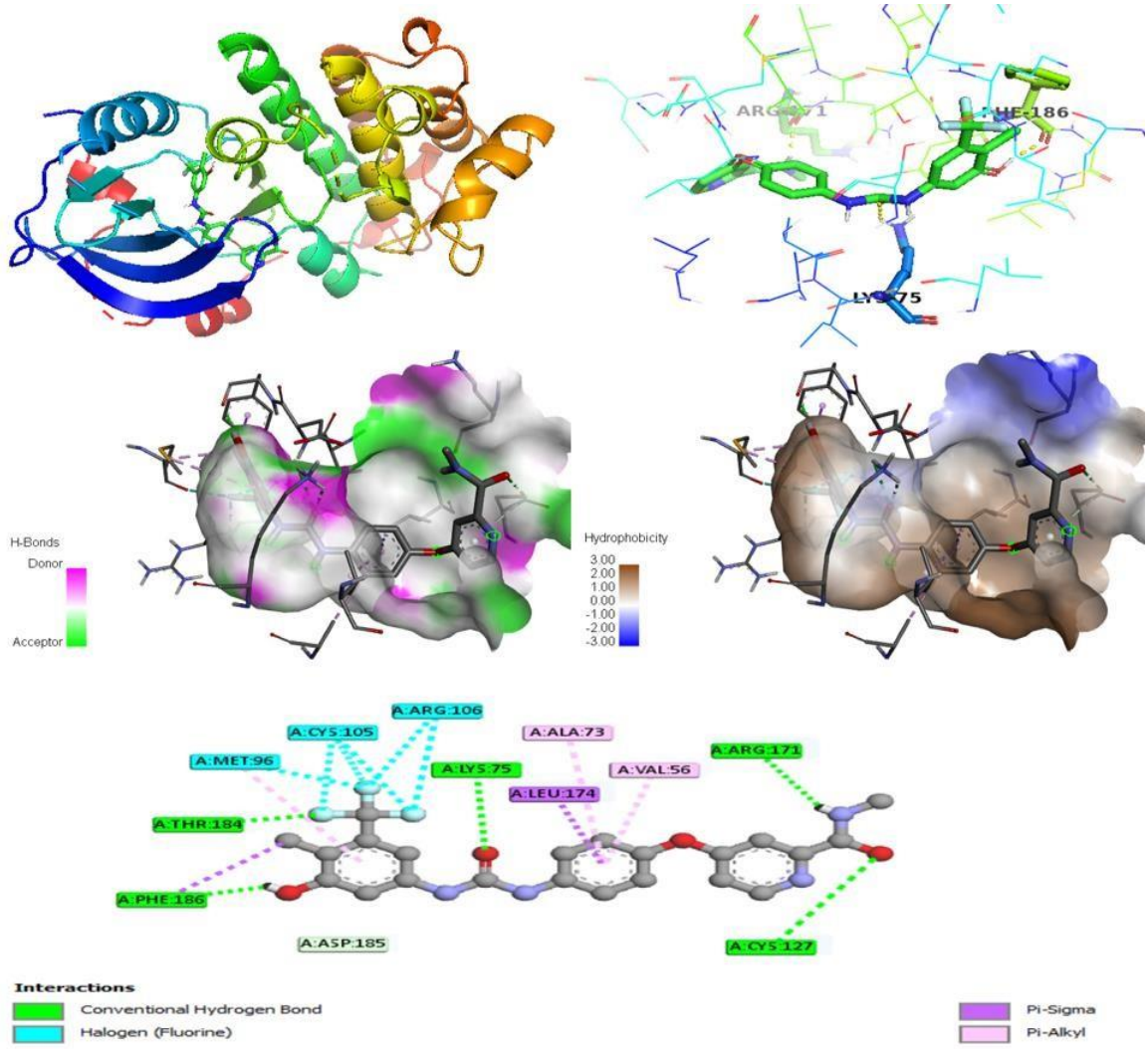

Figure 2. Binding poses of S1 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.2. Interaction of S2 with Tyrosine-kinase: The docking outcomes yielded that hit compound S2 with tyrosine kinase had a binding energy of -12.87 kcal/mol and an

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inhibition constant 366.13pM (Pico molar) as in Table 1. The active residues of tyrosine kinase generated an active pocket that occupied the said compound S2. It showed the significant interactions with the ARG-171, CYS-105, PHE-186 and ASP-185 at the active site of the said enzyme. The mentioned compound bound through hydrogen bonds with crucial residues ARG-171, (O...NH, 2.2Å), and CYS-105, (O...HN, 2.5Å), PHE-186, (O...NH, 2.1Å), ASP-185 (O...NH, 2.2Å) of the receptor as shown in Table 2. The compound used in the pi-sigma and pi-alkyl and weak Vander Waal interactions with the residues of ARG-171, CYS-105, PHE-186 and ASP-185 with tyrosine kinase provided in Figure 3.

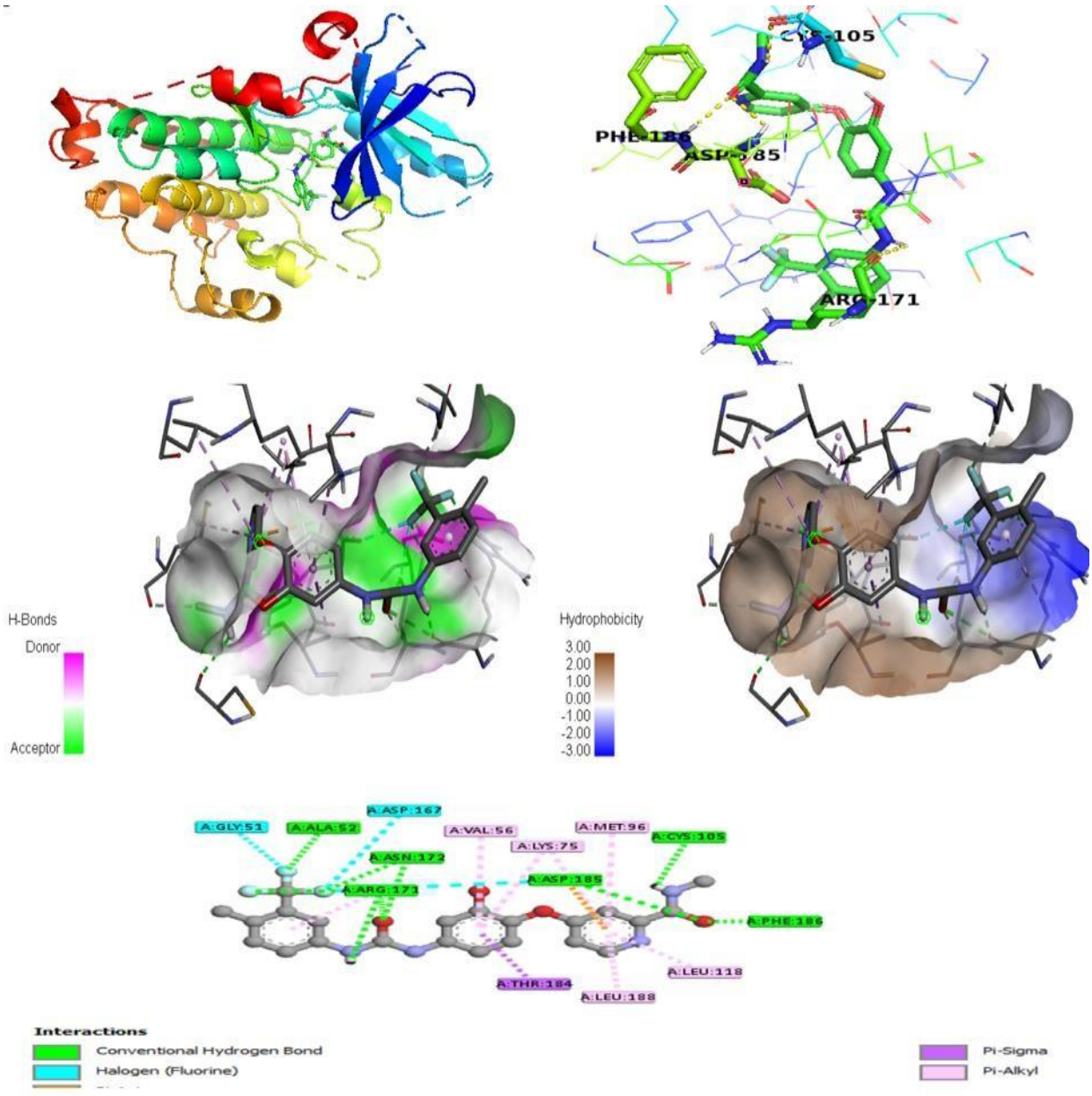

Figure 3. Binding poses of S2 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.3. Interaction of S3 with Tyrosine-kinase: The interaction of energy of -12.61 kcal/mol and a 537.54pM Pico molar inhibition constant were proven through affinity binding of the selected ligand S3 to tyrosine kinase as shown in **Table 1.** The aforementioned compound S3 was designed in such a way that it occupies the active groove

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formed by active residues of tyrosine kinase. The active amino acids ASP-185, THR-184, CYS-105 and THR-120 of tyrosine kinase stabilized the complex by making bonds with active groups of the above ligands. The OH group at both terminal aromatic rings interacted with ASP-185 (HO...H, 1.9Å), THR-184 (NH...O, 2.3Å), CYS-105(NH...O, 2.2Å) and THR-120(NH...O, 2.9Å) as given in the **Table 2.**Also the compound S3 also had varying interactions with amino acids like Conventional Hydrogen Bond and Pi-Alkyl with tyrosine kinase. Moreover, the aromatic rings also contribute to the formation of an interaction like weak Vander Waal forces, pipi stacking, pi-alkyl and pi-sigma with ASP-185 and THR-120 of tyrosine kinase as shown in Figure 4.

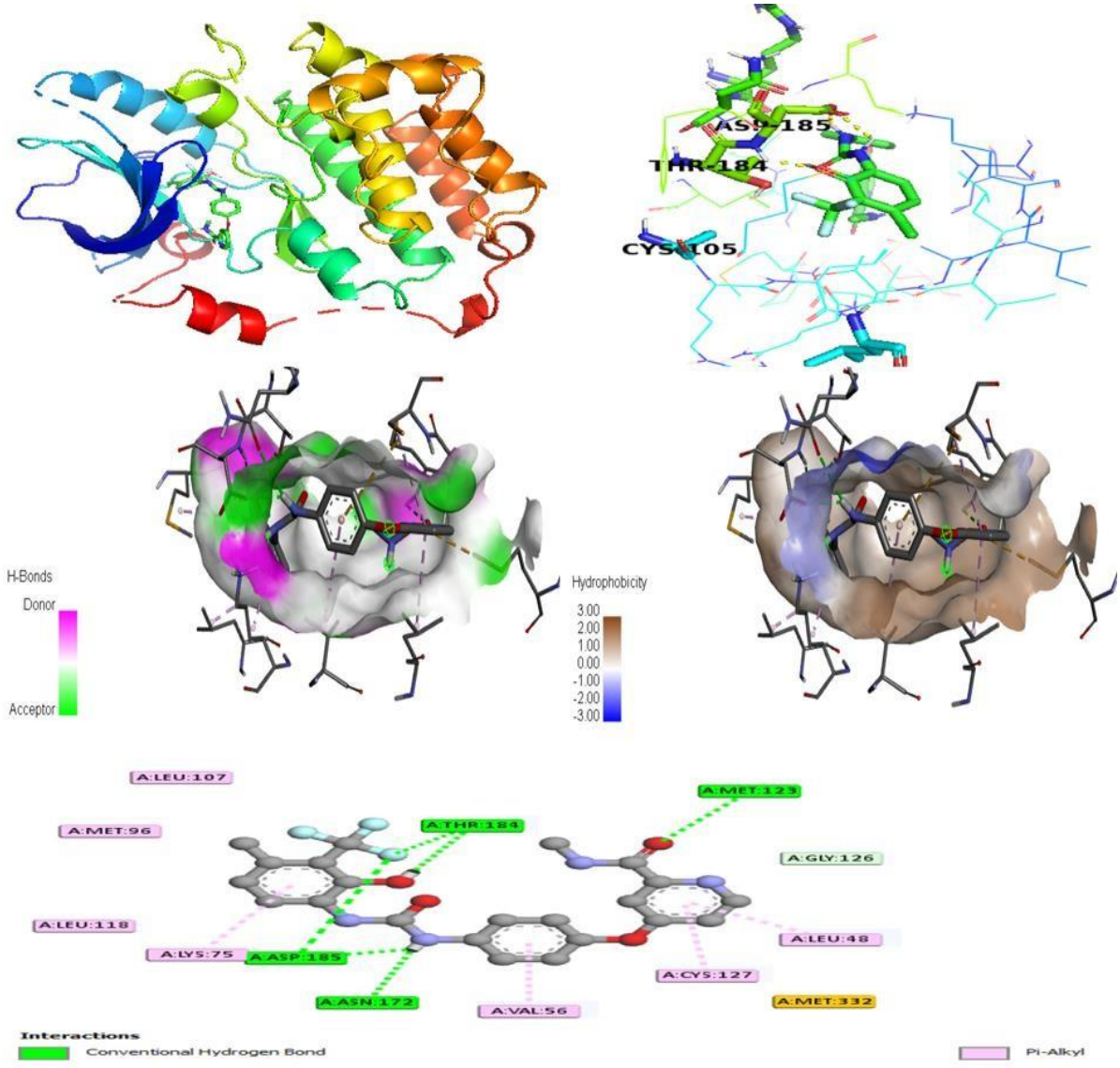

Figure 4. Binding poses of S3 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.4. Interaction of S4 with Tyrosine-kinase: The proposed title compound S4 mode of linking with the tyrosine kinase inhibitor showed a higher binding affinity value of -7.94 kcal/mol and 1.52µM (micro molar) inhibition constant as was predicted in **Table 1.** The complex was stabilized by the active amino acid THR-120 of tyrosine kinase forming bonds with active groups of the above ligands. S4 candidate compound was completely adapted

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in the active site of tyrosine and created an interaction with THR-120 active residue of the receptor. The OH group of the terminal aromatic ring formed an H-bond withTHR-120 (NH...OH, 2.9Å) **Table 2.** Also the compound S4 also demonstrates interactions with amino acid THR-120 such as Conventional Hydrogen Bond, Halogen (Fluorine), Pi-Anion, Pi-Sigma and Pi- Alkyl with the enzyme tyrosine kinase. Further, the S4 compound is stabilized in the active site of tyrosine kinase through weak Vander Waal, pipi stacking, pi-alkyl and pi-sigma interactions with THR-120 active site of tyrosine kinase illustrated in Figure 5.

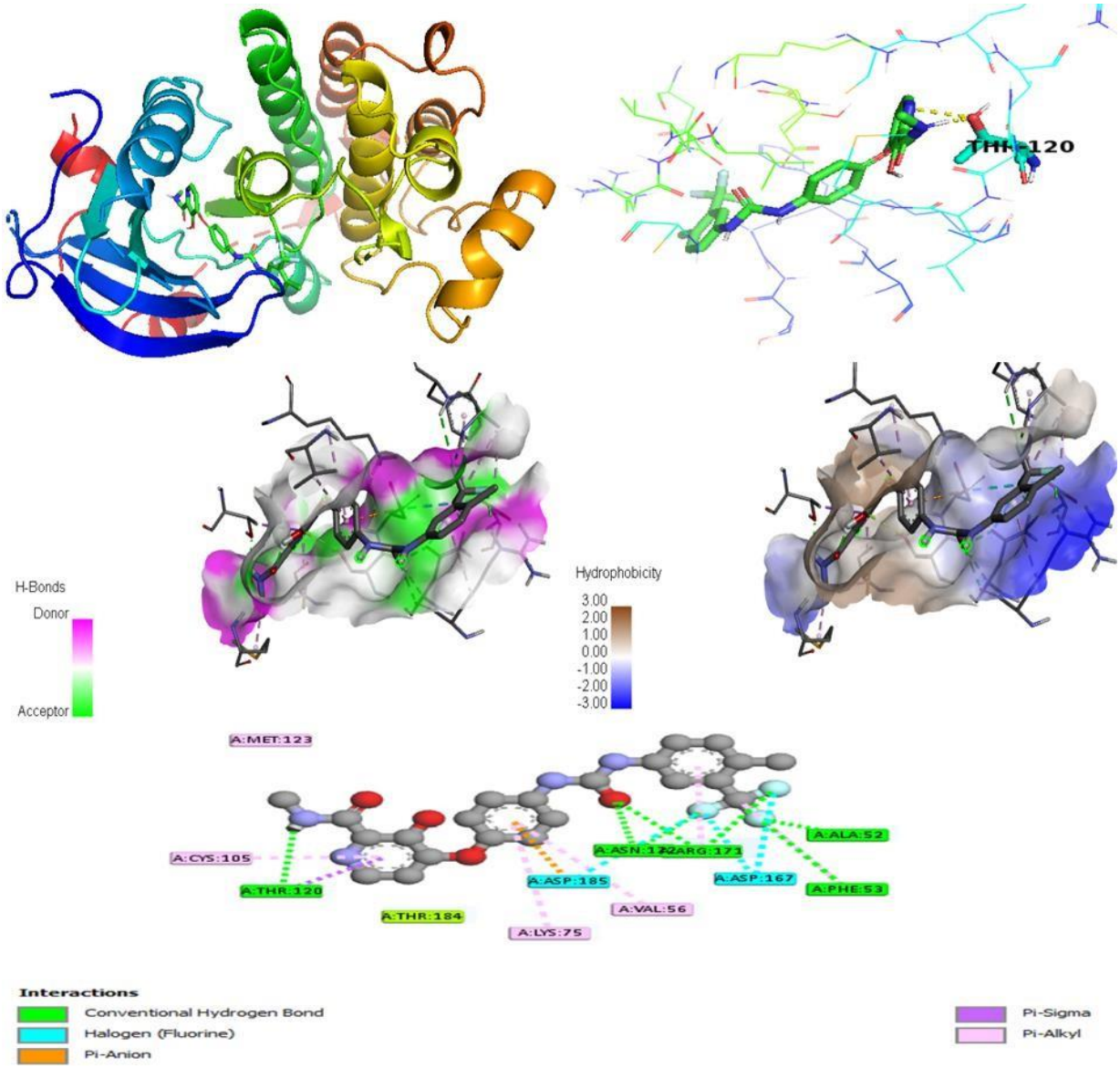

Figure 5. Binding poses of S4 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.5. Interaction of S5 with Tyrosine-kinase: The predicted mode of binding of compound S5 showed a fitting energy of -12.38 kcal/mol and 846.75pM Pico molar inhibition constant given in Table 1. The docking study showed that title compound S5 was positioned into the docking site created by active residues of tyrosine kinase and engage in binding to LYS-75, LEU-118, ASP-185, THR-184 and ASN-172 residues of tyrosine kinase. Among these interactions carbonyl group of hydrazide moiety makes a H-bond with LYS-75(O...HN, 2.7Å), LEU-118(OH...O, 2.1Å), ASP-185(O...NH, 2.1Å), THR-184(O...OH, 2.4Å)

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and ASN-172(NH...O, 2.0Å) (NH...O, 2.2Å) portrayed in Table 2 .In addition to this, the mentioned ligand showed the Conventional Hydrogen bond, Pi-Sigma and Pi-Alkyl interactions with LYS-75, LEU-118, ASP-185, THR-184 and ASN-172 receptor residues as shown in Figure 6.

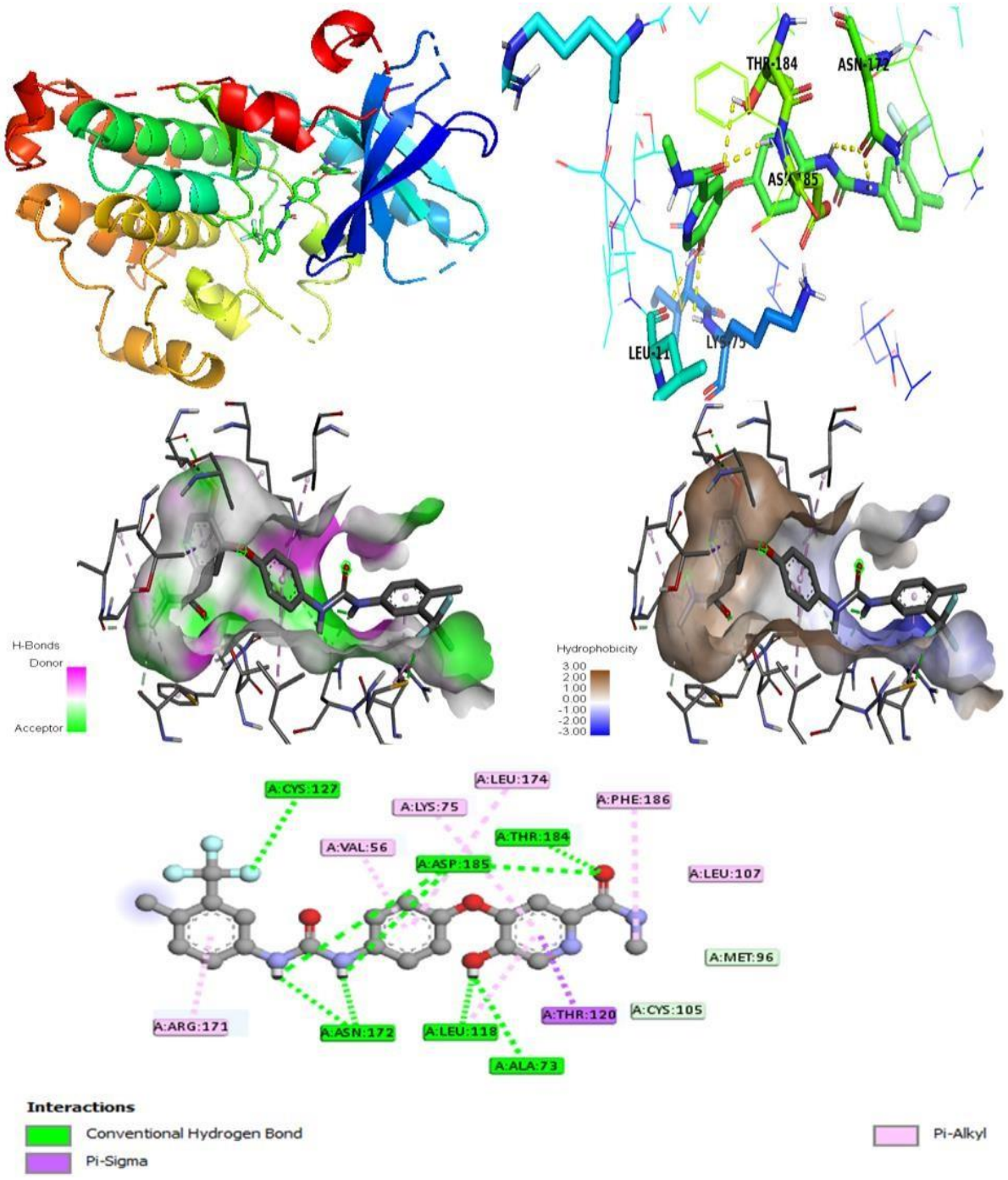

Figure 6. Binding poses of S5 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.6. Interaction of S6 with Tyrosine-kinase: The native ligand S6 had a score of -13.06 kcal/mol of affinity and an inhibition constant of 267.16 pM (Pico molar) as provided in Table 1. The compound in question, S6 can access the active site of tyrosine kinase and it

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has been shown to undergo a vast number of interactions with the residues at the active site of tyrosine kinase. The docking study revealed that title compound S6 was inserted into the cavity created at the active site of tyrosine kinase and are engaged in binding amino acid ASP-185. The hydroxyl group of the terminal hydrophobic tail forms a hydrogen bond with ASP-185(OH...OC, 2.2A) which is depicted in Table 1. Furthermore, the compound formed numerous interactions like Conventional Hydrogen Bond, Halogen (Fluorine), Pi-Anion, Pi-Sigma and Pi-Alkyl with ASP-185 amino acid of the tyrosine kinase receptor expressed in Figure 7.

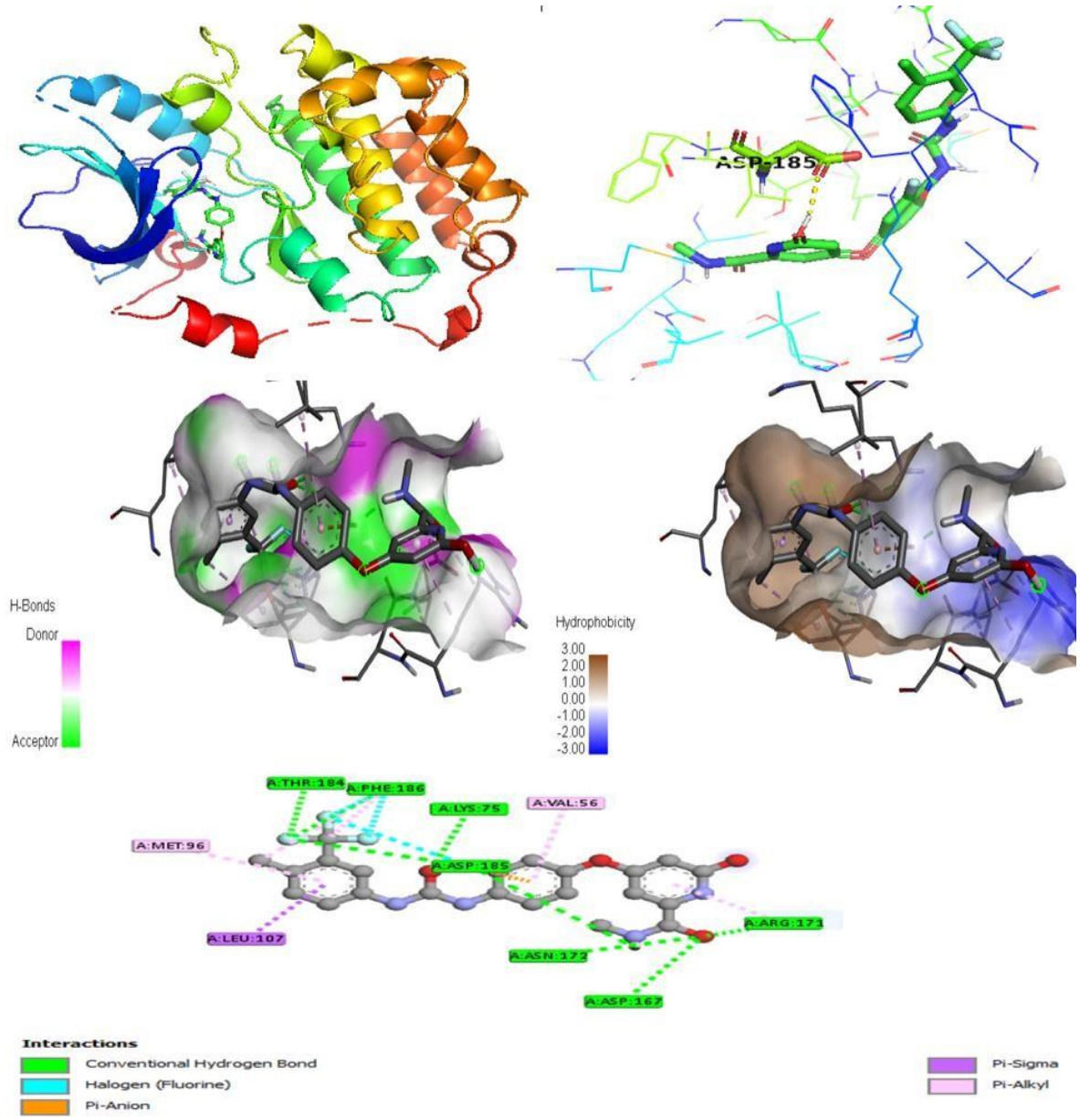

Figure 7. Binding poses of S6 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.7. Interaction of S7 with Tyrosine-kinase: The binding poses of candidate ligand S7 had an energy binding value of -12.81 kcal/mol and 406.89 pM inhibition constant and were found to inhibit tyrosine kinase well as indicated in Table 1. According to the docking study, the hit compound S7 possesses an opportunity to bind with the target protein and therefore it becomes highly stable in the active pocket of the enzyme. The OH motifs of

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both the distal hydrophobic ring moieties act as hydrogen bond donors and make H-bonds with CYS-105 (NH...O, 2.2 Å) ,ARG-171 (NH...O, 2.1 Å) while the carbonyl motif of hydrazide moiety also involved in hydrogen bonding with ASP-185 (CO...HN, 2.5Å)and PHE-186 (CO...HN, 2.6Å) demonstrated in Table 1. Besides the compound S7 also exhibits various type of interactions with the active amino acids CYS-105, ARG-171, ASP-185, and PHE-186 also exhibit interactions such as Conventional Hydrogen Bond, Halogen (Fluorine) and Pi-Alkyl with the enzyme tyrosine kinase. Besides, the complex was stabilized by making weak Vander Waal, pi-sigma and pi-alkyl interactions with CYS-105, ARG-171, ASP-185, PHE-186 and amino acids of receptor shown in Figure 8.

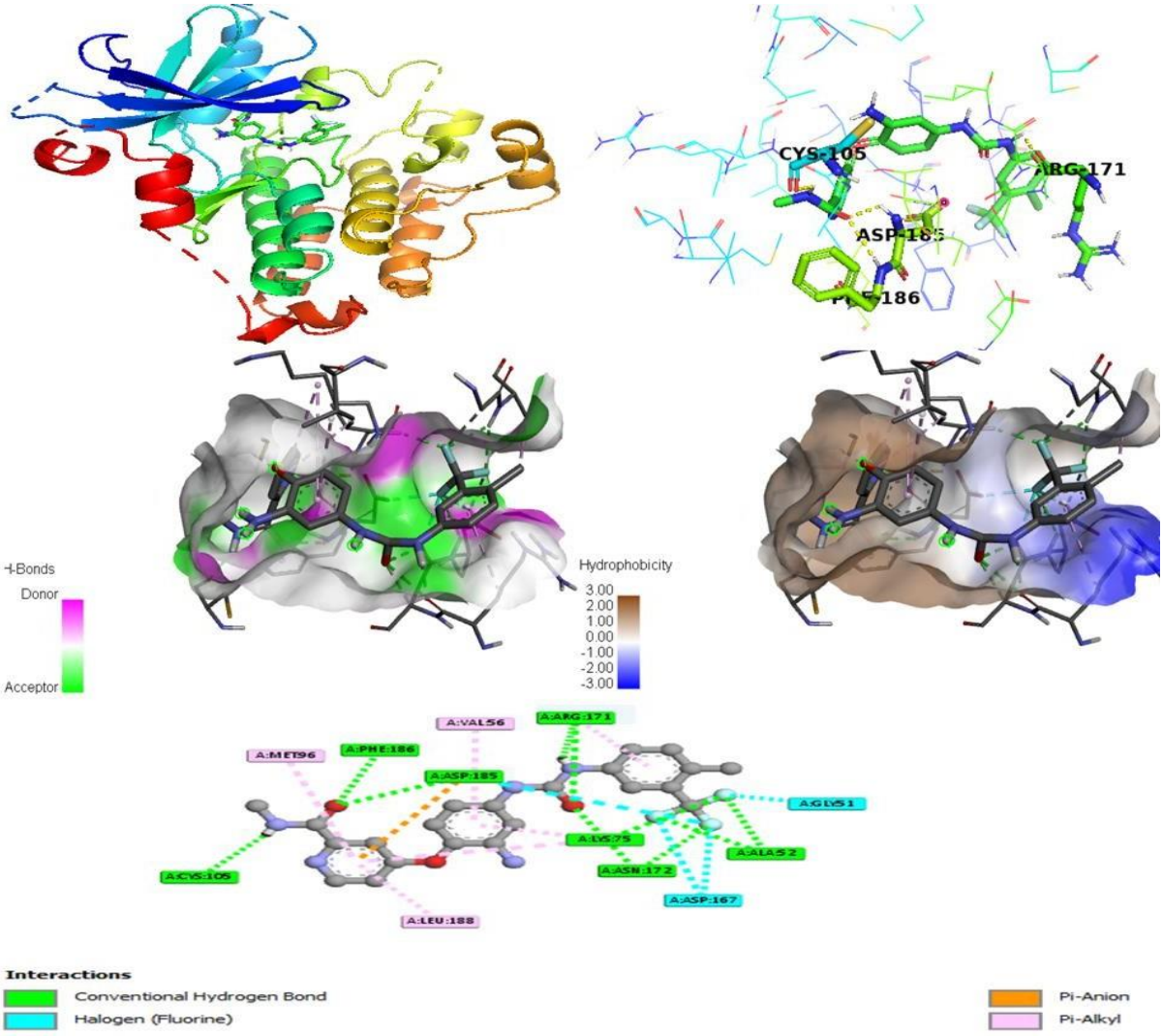

Figure 8. Binding poses of S7 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.8. Interaction of S8 with Tyrosine-kinase: The binding of S8 with tyrosine kinase has a binding potential docking score of -11.51 kcal/mol and 3.66nm (Nano molar) inhibition constant as shown in Table 1. The compound S8 could dock deeply into the region of the binding pocket of tyrosine kinase. An active site (CYS-105, ASP-167, ALA-52, and PHE-53) of the receptor tyrosine kinase reacts with said compound S8 to stabilize the complex. The compound S8 also exhibit various interactions with the active amino acids, CYS-105, ASP-167, ALA-52 and PHE-53 display various forms of interaction such as Conventional Hydrogen

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Bond, Halogen (Fluorine) and Pi-Alkyl with the enzyme of tyrosine kinase. Of them, three hydrogen bonds are interacting through the CYS-105, (O...HN, 2.3 Å) and ASP-167, (O...HN, 2.3 Å) ALA-52, (CO...HN, 1.9 Å) and PHE-53, (CO...HN, 2.1 Å) mentioned in Table 2. In addition to these hydrogen bonds, S8 in active site also exhibits weak Vander Waal, pi-sigma and pi-alkyl interaction with CYS-105, ASP-167, ALA-52 and PHE-53 amino acids of tyrosine kinase as depicted in Figure 9.

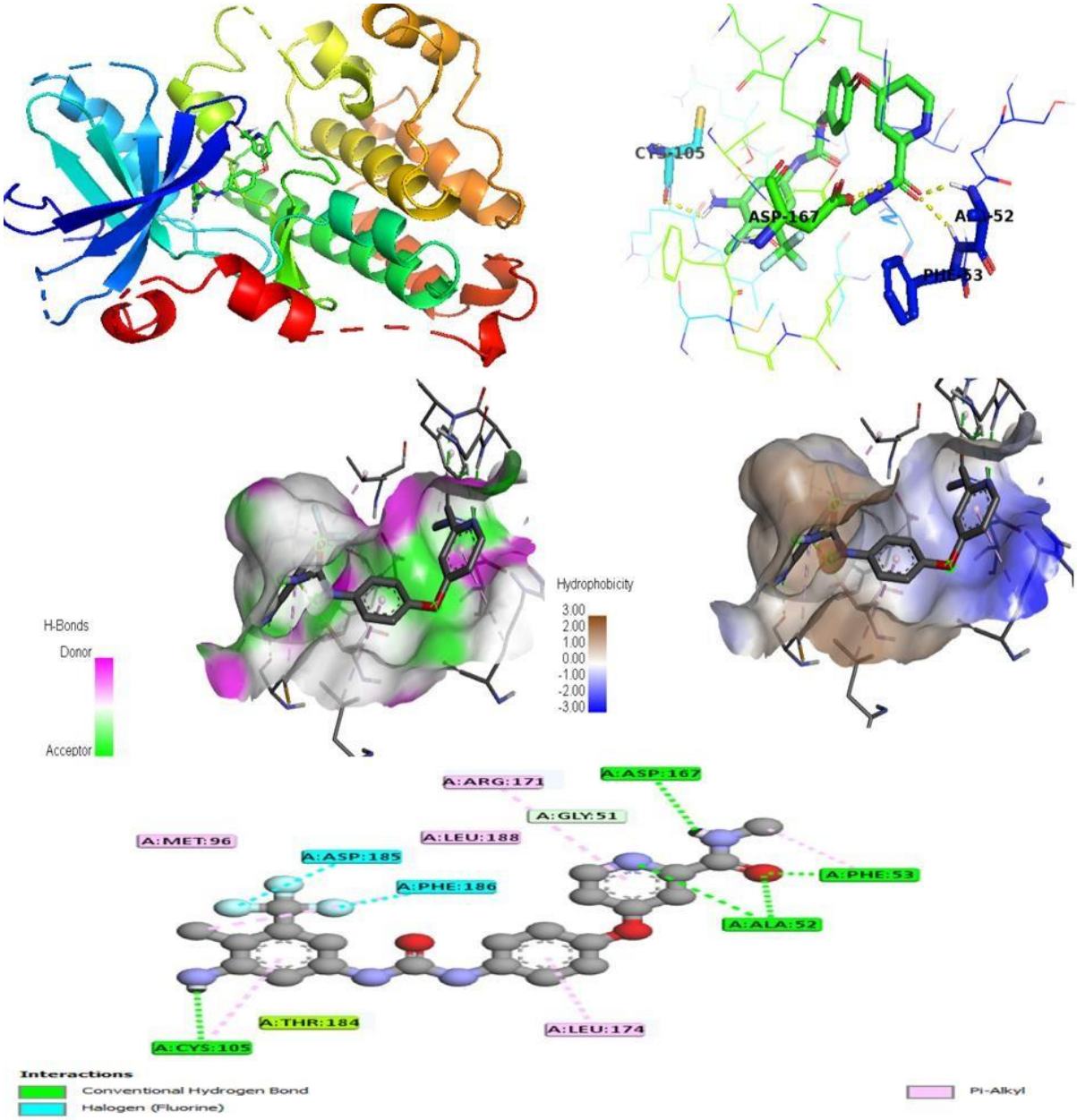

Figure 9. Binding poses of S8 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.9. Interaction of S9 with Tyrosine-kinase: The binding pattern for the molecule S9, which is the most active, inside the active regions of tyrosine kinase has been explored using molecular docking simulation. The given compound S9 was validated as an inhibitor of tyrosine kinase with an inhibitory activity of -11.06 kcal/mol and 7.77 nM (Nano molar) inhibition constant Table 1. Like in the compound S9, there is no hydrogen bond yet

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this compound exhibit various kinds of interaction including, Halogen (Fluorine), Pi-Cation, Pi-Anion and Pi-Alkyl as shown in Figure 10.

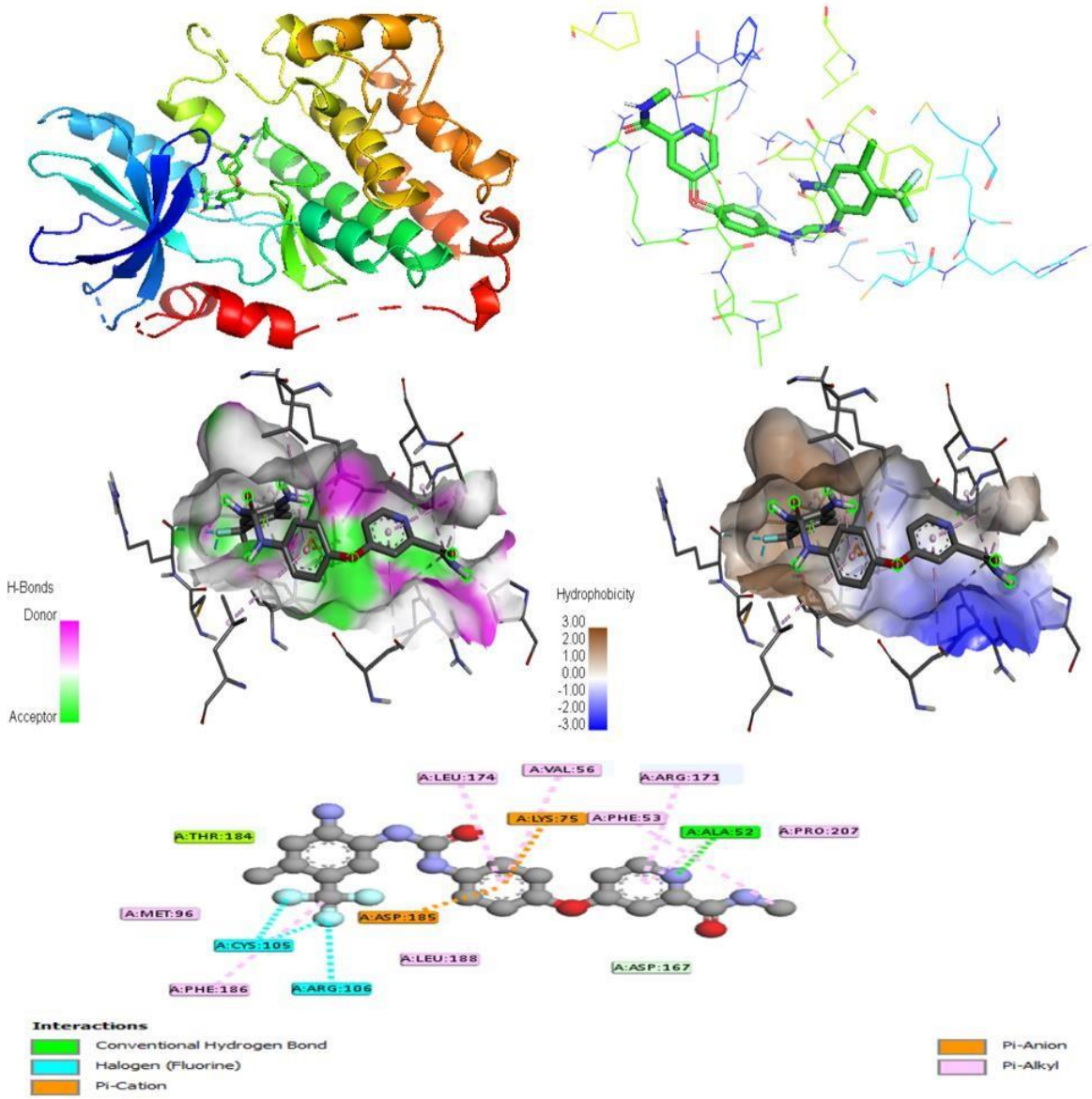

Figure 10. Binding poses of S9 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.10. Interaction of S10 with Tyrosine-kinase: The active inhibitor, compound S10 being docked in the active groove of tyrosine kinase had docking energy of -12.69 kcal/mol and a Pico molar inhibition constant of 499.89pM as shown in Table 1. The active sites of tyrosine kinase formed their active groove that enabled the said compound to fit in deeply and establish the key interactions with the active units PHE-186, ASP-185 and ASN-172 [13] of the receptors. One of which compound S10 is included in two hydrogen bonds with the most important amino acids; PHE-186 (CO...HN, 2.9A) and ASP-185(O...HN, 2.1A) presented in Table 2. Moreover the compound S10 also exhibits interactions with amino acids PHE-186, ASP-185 and ASN-172 like the Conventional Hydrogen Bond, Halogen (Fluorine), Pi-Cation, Pi-Anion and Pi-Alkyl with the enzyme tyrosine kinase as in the Figure. Moreover, said compound S10 was actively involved in pi-pi interactions with ASN-172(NH...OC, 2.1Å). Besides the above crucial interactions, title compound S10 also exhibited

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Vander Waal, pi-pi T-shaped, pi-alkyl and pi-sigma interaction with PHE-186, ASP-185 and ASN-172 receptor tyrosine kinase residues as seen in Figure 11.

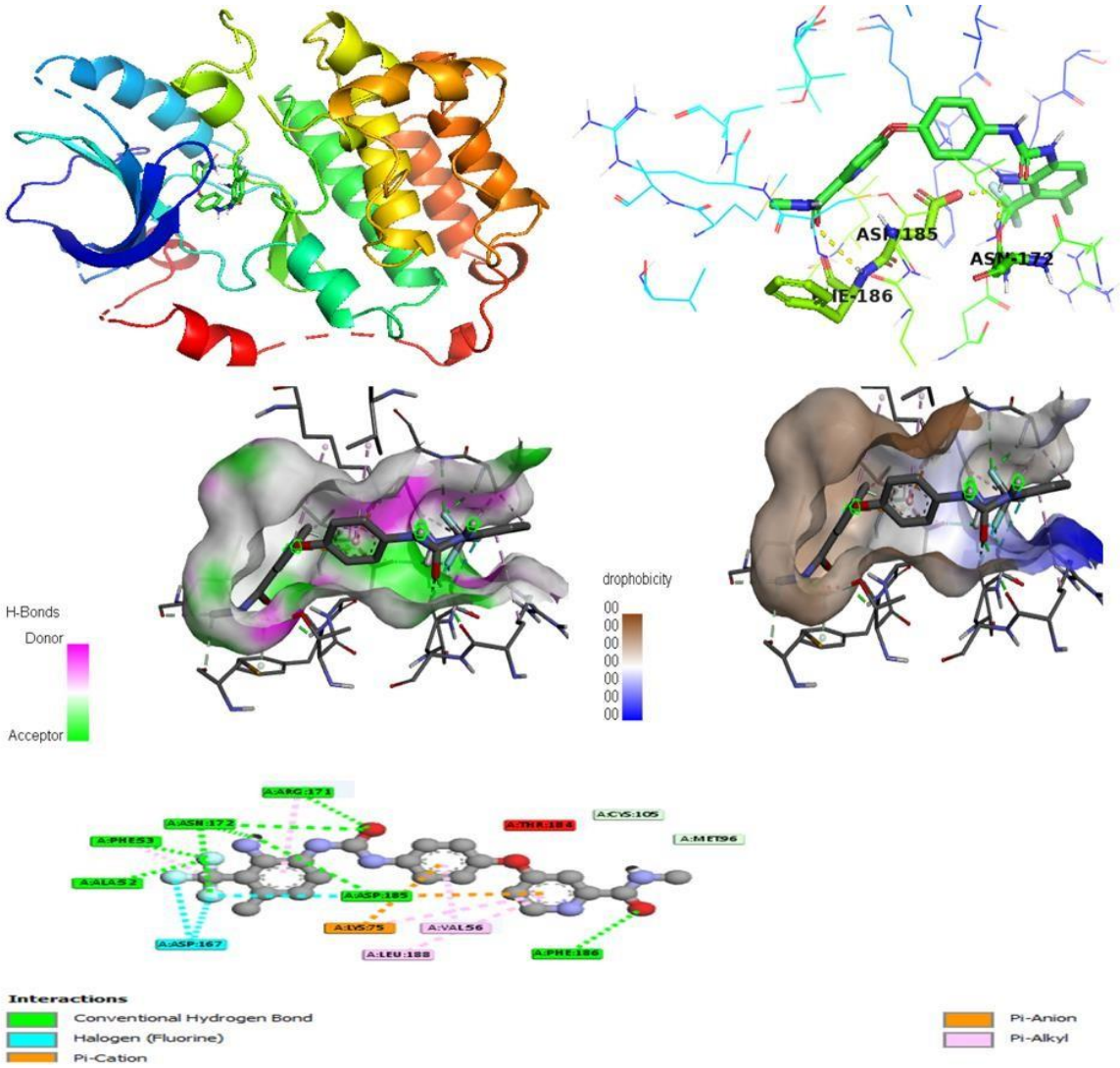

Figure 11. Binding poses of S10 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.11. Interaction of S11 with Tyrosine-kinase: The binding affinity value was expected to be -6.84 kcal/mol and 9.68 micro molar inhibition constant as shown in the Table 1 due to the predicted binding mode of candidate compound S11. The active site of tyrosine kinase generated an active site that enabled the compound S11 to insert deep into it. S11 could not formed with tyrosine kinase but the complex were stabilized by week, Halogen (Fluorine), Pi-Anion, Pi-Sigma and Pi-Alkyl interactions as indicated in the Figure 12.

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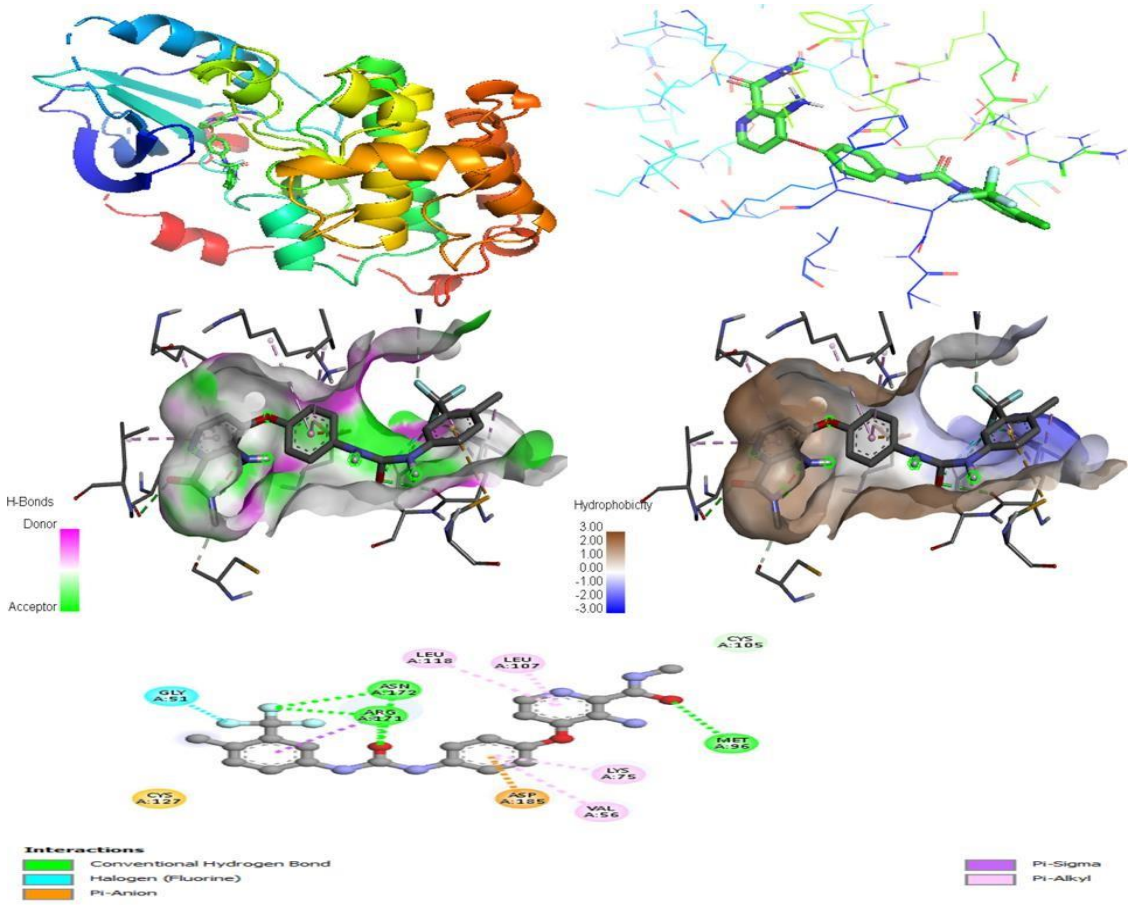

Figure 12. Binding poses of S11 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.12. Interaction of S12 with Tyrosine-kinase: The docking process revealed that compound S12 had good inhibition to tyrosine kinase enzyme with a binding affinity value of -9.81kcal/mol and 64.76Nm (Nano molar) inhibition constant identified in Table 1. The said compound was oriented to fill the aide pocket created by the active site of tyrosine kinase. The interactions were made by compound S12 with active residues of enzyme which are almost essential for its inhibitory activity. The compound was found to bind in the following manner, hydrogen bonding via ASP-185 (NH...O, 2.0 A), THR-184 (O...HN, 2.1A), GLN-121(O...NH, 1.9A) and pi-pi interaction with THR-120 (O...OH, 2.1A) that could Moreover, Vander Waal, pi-sigma, pi-Sulphur and pi-alkyl interactions were observed with ASP-185, THR-184, GLN-121, and THR-120 active units of the enzyme tyrosine kinase. Additionally the compound S12 show different type of interactions with the residues amino acids like ASP-185, THR-184, GLN-121 and THR-120 such as Conventional Hydrogen Bond, Halogen (Fluorine), Pi-Sigma and Pi-Alkyl [17] depicted in Figure 13

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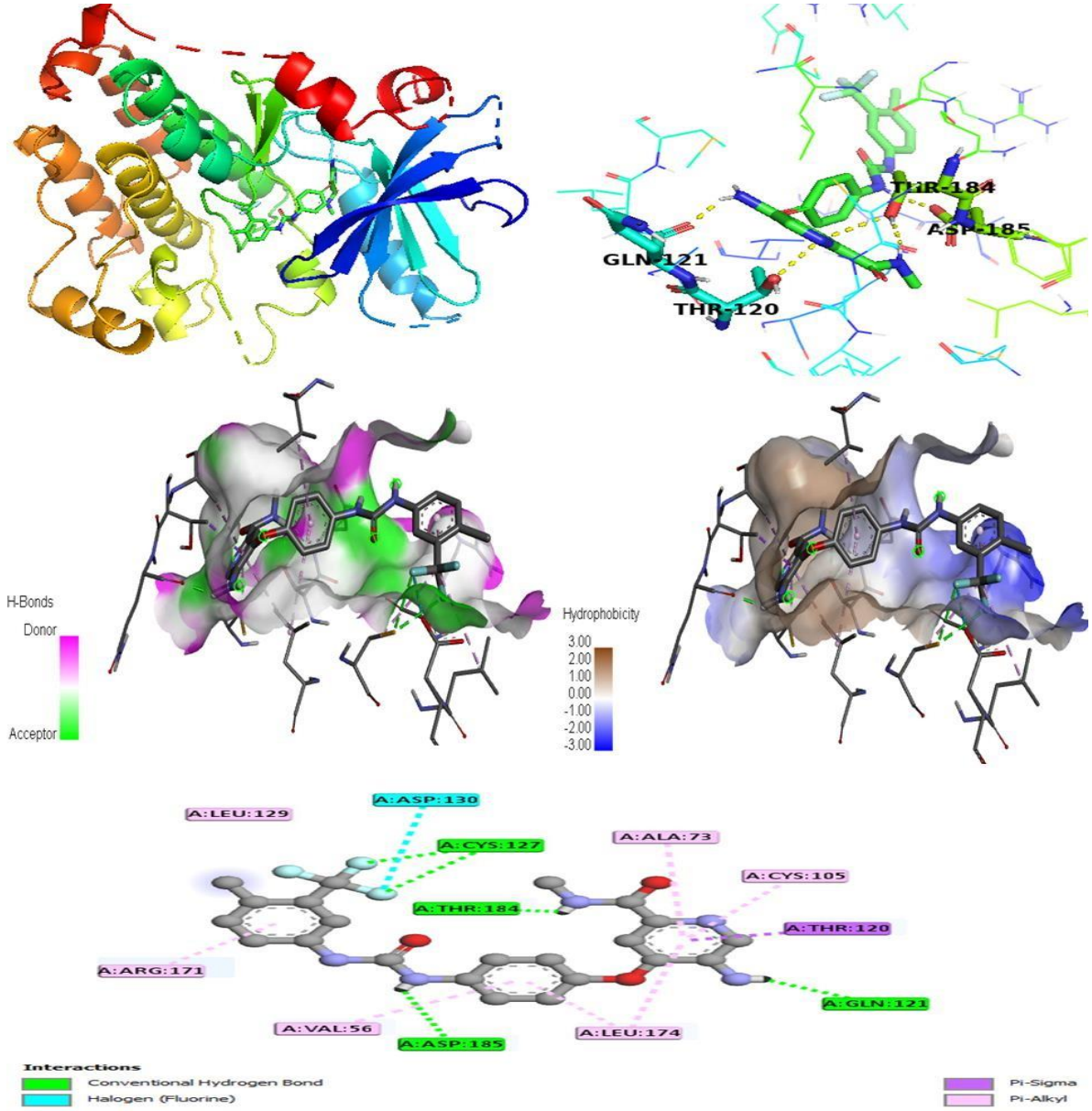

Figure 13. Binding poses of S12 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.13. Interaction of S13 with Tyrosine-kinase: Compound S13 was selected since it could inhibit the enzyme tyrosine kinase, with a docking score of -10.34 kcal/mol and a 26.17nM (nano Molar) inhibition constant as shown in Table 1. The complex was stabilized to make interactions with active residues of tyrosine kinase. S13 was inserted deeply into the active site of the tyrosine kinase and fitted its cavity filled up. The NH2 group of central amino group that was involved in hydrogen bonding to MET-123 (HO...HN, 2.3) and the oxygen of the terminal hetero aromatic ring (furan) which was involved in hydrogen bonding with) MET-123 (HO...HN, 2.3) and the nitrogen of the hydrazide that was involved in pi-pi interaction with. Besides, there were also exist Conventional Hydrogen Bond, Pi-Anion, Pi-Sigma and Pi-Alkyl interactions between ligand and active residues MET-123 and ASN-172 of enzyme tyrosine kinase illustrates in Figure 14

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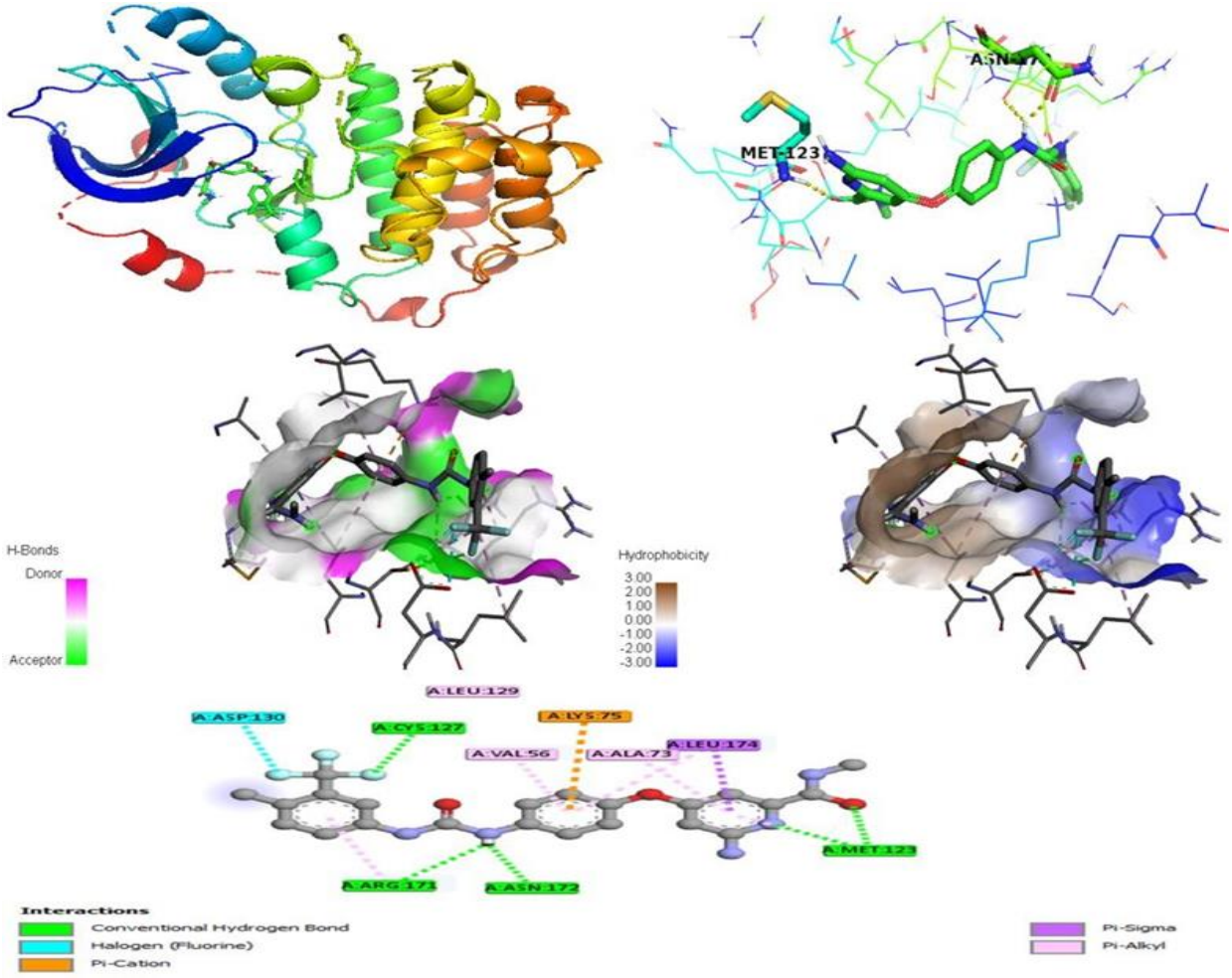

Figure 14. Binding poses of S13 with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

3.1.14. Interaction of Sorafenib with Tyrosine-kinase: The docking setup was validated to determine the inhibitory activity of the mentioned ligand Sorafenib against tyrosine kinase. The above compound Sorafenib was completely bound to the active site of the tyrosine kinase with a high-affinity value of -13.02kcal/mol and an inhibition constant of 287.87pM (picomolar) as in Table 1. The compound Sorafenib was predicted to strongly inhibit the activity of tyrosine kinase and make an essential interaction with active residues of receptor which are responsible for its inhibitory activity [20]. The compound Sorafenib show interactions with different amino acids PHE-186 (CN...OC, 3.0 Å), THR-184(O...HO, 2.0 Å), LEU-118(O...NH, 2.2 Å), ALA-73(O...NH, 2.6 Å), and ASR-185(O...NH, 2.3 Å). The OH motif of the distal aromatic ring acts as hydrogen bond acceptor that is bound with PHE-186 (OH...N, 3.0 Å) by hydrogen bond. The CO motif of involved in H-bonding with THR-184(O...HO, 2.0 Å), LEU-118(O...NH, 2.2 Å), ALA-73(O...NH, 2.6 Å) while its nitrogen motif ASR-185(O...NH, 2.3 Å) involved in pi-pi stacking with demonstrated in Table 2. There were also Conventional Hydrogen Bond, Pi-Anion and Pi-sigma as well as Pi- alkyl interactions between the target ligand and active residues of enzyme tyrosine kinase namely PHE-186, THR-184, LEU-118, ALA-73 and ASR-185 as shown in Figure 15.

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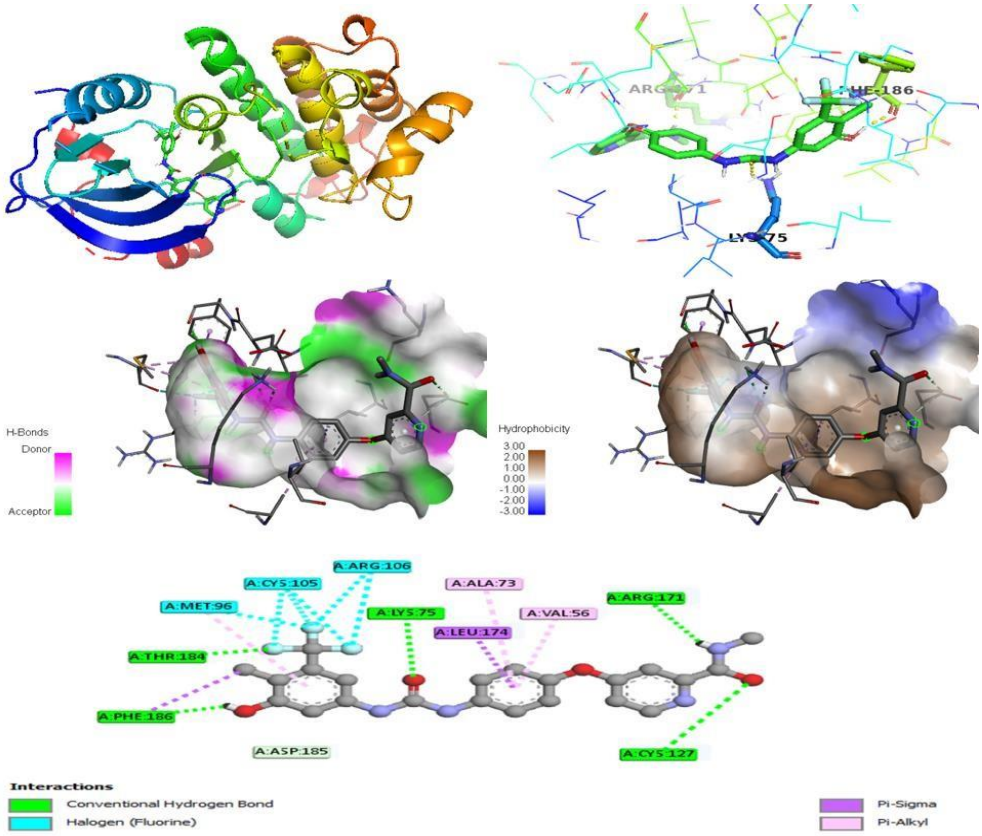

Figure 15. Binding poses of Sorafenib with Tyrosine kinase, (A) complex, (B) 3D interactions, (C) H-bonding, (D) hydrophobic bonding, and (E) 2Dinteractions.

Table 1. Binding energies and inhibition constant values of Sorafenib and its derivatives

Compounds	Binding Energy	Inhibition Constant
S1	-13.04	277.8 pM
S2	-12.87	366.13 pM
S3	-12.61	537.54 pM
S4	-7.94	1.52 µM
S5	-12.38	846.75 pM
S6	-13.06	267.16 pM
S7	-12.81	406.89 pM
S8	-11.51	3.66 nM
S9	-11.06	7.77 nM
S10	-12.69	499.89 pM
S11	-6.84	9.68 µM
S12	-9.81	64.76 nM
S13	-10.34	26.17 nM
Sorafenib	-13.02	287.87 pM

Table 2. Hydrogen bond distance and interacting residue of Sorafenib and their derivative

Compounds	Interacting amino acids	Distances(Å)
S1	ARG-171, LYS-75, PHE-186	2.1, 2.5, 2.0
S2	ARG-171, CYS-105, PHE-186, ASP-185	2.2, 2.5, 2.1, 2.2, 2.2
S3	ASP-185, THR-184, CYS-105	1.9, 2.3, 2.2
S4	THR-120	2.9

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S5	LYS-75, LEU-118, ASP-185, THR-184, ASN-172	2.7, 2.1, 2.1, 2.4, 2.0, 2.2
S6	ASP-185	2.2
S7	CYS-105, ARG-171, ASP-185, PHE-186	2.2, 2.1, 2.5, 2.6
S8	CYS-105, ASP-167, ALA-52, PHE-53	2.3, 2.3, 1.9, 2.1
S9	No-Hydrogen bonding	
S10	PHE-186, ASP-185, ASN-172	2.9, 2.1, 2.0
S11	No-Hydrogen bonding	
S12	ASP-185, THR-184, GLN-121, THR-120	2.0, 2.1, 1.9, 2.2
S13	MET-123	2.3, 1.9, 2.5
Sorafenib	PHE-186, THR-184, LEU-118, ALA-73, ASR-	3.0, 2.0, 2.2, 2.6, 2.3

Conclusion

Molecular docking study of modified derivatives (Sorafenib and S1-S13) with respect to a target of leukemia associated tyrosine kinase. Their therapeutic potential was determined by determining binding affinities (ΔG) and inhibition constants (Ki). S6 (-13.06 kcal/mol, 267.16 pM) had the highest binding affinities and a number of derivatives (S1, S3, S6, and S8) performed better than others. These results indicate that the derivatives modified, especially S6, are good prospects to be further experimentally validated as effective counter-tyrosine kinase inhibitors in the treatment of leukemia.

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