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An insilico study of new 1-aminoquinoline-2(1H)-one derivatives as tyrosine kinase inhibitors

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Abstract: The field of oncology has been revolutionized by the discovery and development of targeted therapies for cancer. Although tyrosine kinase inhibitors (TKIs) have shown promise in targeting cancer cell signaling pathways, the emergence of resistance necessitates the development of novel and potent inhibitors. This study explores the design and evaluation of two series of 1-aminoquinoline-2(1H)-one derivatives as potential TKIs. Virtual docking simulations, which use molecular docking algorithms and scoring functions, predict how these TKIs bind to the enzyme and assess their binding strength. The Molecular Operating Environment (MOE) software version 2015.10 was used to carry out these molecular docking simulations. Using the X-ray crystal structure of the Abelson tyrosine kinase (ABL1) from the Protein Data Bank (PDB ID: 4WKQ), the binding interactions and efficacy of the newly designed TKIs were evaluated. Preliminary results show that several of the designed TKIs have a strong binding affinity and form key interactions with the target tyrosine kinase. These interactions include hydrogen bonds, hydrophobic interactions, and electrostatic interactions, which are crucial for stabilizing the complex between the TKI and the enzyme. Additionally, the study identifies specific amino acid residues within the tyrosine kinase binding site that enhance the binding affinity of the TKIs. This detailed information is valuable for further optimizing TKI design and developing more effective inhibitors with improved binding properties.

Keywords: Tyrosine kinase inhibitors (TKIs), Targeted therapy, Virtual docking simulations, 1-aminoquinoline-2(1H)-one derivatives.

1. Introduction

Tyrosine kinases are enzymes responsible for transferring phosphate groups from ATP to tyrosine residues on specific proteins thereby regulating different cellular functions[1]. In the context of cancer cells, the defective activation of tyrosine kinases can lead to unregulated cell proliferation and survival[2]. Tyrosine kinase inhibitors (TKIs) are a class of medications designed to specifically target and suppress the activity of tyrosine kinase and emerged as crucial therapeutics in cancer treatment[3], as well their applications extend beyond oncology to encompass other disease areas like autoimmune disorders and infectious diseases[4].

TK inhibitors offer diverse strategies to target tyrosine kinases and modulate their activity for therapeutic purposes [5]. There are different types of TK inhibitors exist, distinguished by their mechanisms of action and selectivity, ATP-competitive inhibitors [6]: These inhibitors bind to the ATP binding site of the tyrosine kinase enzyme, hindering ATP binding along with as a result hindering kinase activity, Imatinib with Dasatinib are the available medicines of ATP-competitive inhibitors used for treating different cancers like chronic myeloid leukemia as well as specific solid tumors [7-8]. Allosteric inhibitors: These inhibitors attach to a distinctive site on the kinase enzyme, different from the ATP binding site, by causing a conformational modification they prevent kinase activity [9-10], Gefitinib and erlotinib (non-small cell lung cancer cells) are instances of allosteric inhibitors and Covalent inhibitors: These inhibitors create a covalent bond with the tyrosine kinase enzyme, causing permanent restraint of its activity,

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Afatinib as well as neratinib epitomize covalent inhibitors [11-12].

The field of TK inhibitors is continuously progressing, with ongoing efforts to develop and evaluate new compounds for their effectiveness and safety in treating various cancer types[13]. The development of these drugs entails a comprehensive understanding of the molecular mechanisms involved in tyrosine kinase signaling, as well as expertise in medicinal chemistry, drug design, and rigorous preclinical and clinical testing [14].

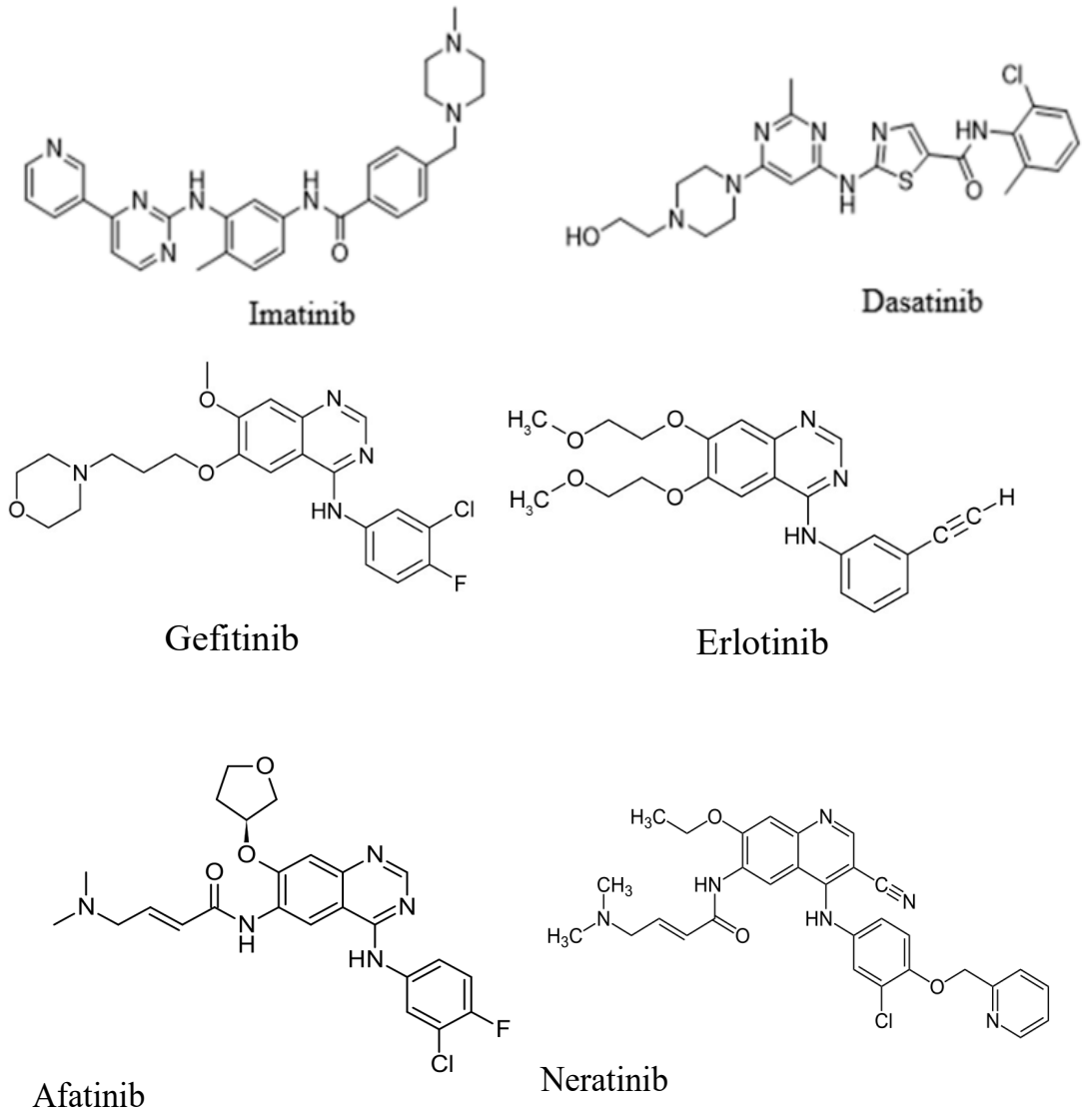


Figure 1. Different types of TK inhibitors.

Despite the promising potential of TK inhibitors as effective anticancer agents, they do possess certain limitations[15]. One significant restriction is the emergence of drug resistance which can emerge from mutations in the tyrosine kinase enzyme or the activation of different signaling pathways. This resistance can diminish the effectiveness of TK inhibitors in targeting cancer cells[16]. Furthermore, TK inhibitors might exhibit off-target impacts causing unfavorable adverse effects like gastrointestinal disturbances, fatigue, and skin rash [17]. These restrictions highlight the demand for more research study and development to get over resistance and reduce off-target impacts to enhance the therapeutic potential of TK inhibitors[4,18].

Designing new tyrosine kinase inhibitors (TKIs) with improved efficiency as well as selectivity is important in targeted cancer treatment[19-20]. It facilitates the overcoming of resistance, enhances the potency of inhibition, permits efficient combination therapies, and broadens the range of cancer types for which treatment choices are available[7,21]. These advancements support the development of precision medicine in the treatment of cancer as well as better patient outcomes.

Quinoline derivatives have shown strong biological activity against a range of targets, including kinases. Tyrosine kinases' ATP-binding site can interact with the amino group at the 1-position and the ketone at the 2-position, possibly resulting in effective inhibition[22]. Quinoline compounds have been effectively used as kinase inhibitors in the past. Quinoline moieties are included in several FDA-approved medications, including lapatinib and erlotinib, highlighting the potential of this scaffold in drug development[23]. Because the synthesis of 1-aminoquinoline-2(1H)-one derivatives is well-established, these molecules may be produced and optimized efficiently in Figure 2. This chemical accessibility makes the rapid exploration of structure-activity relationships[24]. Considering the critical role that tyrosine kinases play in disease, the development of novel inhibitors with distinct scaffolds, such as 1-aminoquinoline-2(1H)-one, may result in novel therapies with improved safety and effectiveness profiles.

The docking studies will be carried out to estimate the potential inhibition of a two series of derivatives of 1-aminoquinoline-2(1H)-one as protein kinase inhibitors against the Abelson tyrosine kinase (ABL1).

Figure 2. Chemical Structures of Two Series of 1-Aminoquinoline-2(1H)-one Derivatives

The primary goal of the study was to investigate the binding interactions, evaluate the effectiveness and strength of a newly designed tyrosine kinase inhibitor (TKI) against the Abelson tyrosine kinase (ABL1). ABL1 is a non-receptor tyrosine kinase that plays a critical duty in cellular signaling pathways with cell growth, proliferation, and survival [25-26]. The BCR-ABL1 fusion protein, which is an abnormal form of ABL1, it is linked in different cancer kinds involving chronic myeloid leukemia (CML) along with specific types of acute lymphoblastic leukemia (ALL)[20]. Targeting ABL1 with specific inhibitors, such as imatinib has significantly improved the management of CML by inhibiting the activity of the BCR-ABL1 found in CML [20]. This study evaluated the newly developed TKIs potential as a treatment option for malignancies linked to ABL1 by comparing it with established inhibitors (imatinib) [27].

2. Computational Method

The in silico docking technique is a computational technique made use of to forecast exactly how a small molecule, such as a tyrosine kinase inhibitor (TKI), binds to a target protein such as a tyrosine kinase [28]. The research study executed molecular docking simulations utilizing the Molecular Operating Environment (MOE) software application variation 2015.10 (Chemical Computing Group, Montreal, Canada) [29] to analyze the binding interactions, assess the effectiveness and strength of a newly designed TKI against the Abelson tyrosine kinase (ABL1), the X-ray crystal structures of Abelson tyrosine kinase was acquired from the Protein Data Bank with the PDB ID (4WKQ) [30]. The final compounds were constructed using the MOE builder module and energy minimized using the Merck Molecular force field (MMFF94x, RMSD gradient: 0.05 kcal $mol^{-1}Å^{-1}$) [31]. The binding site of target protein was determined using MOE Site finder, and docking dummies were created [32]. The optimized

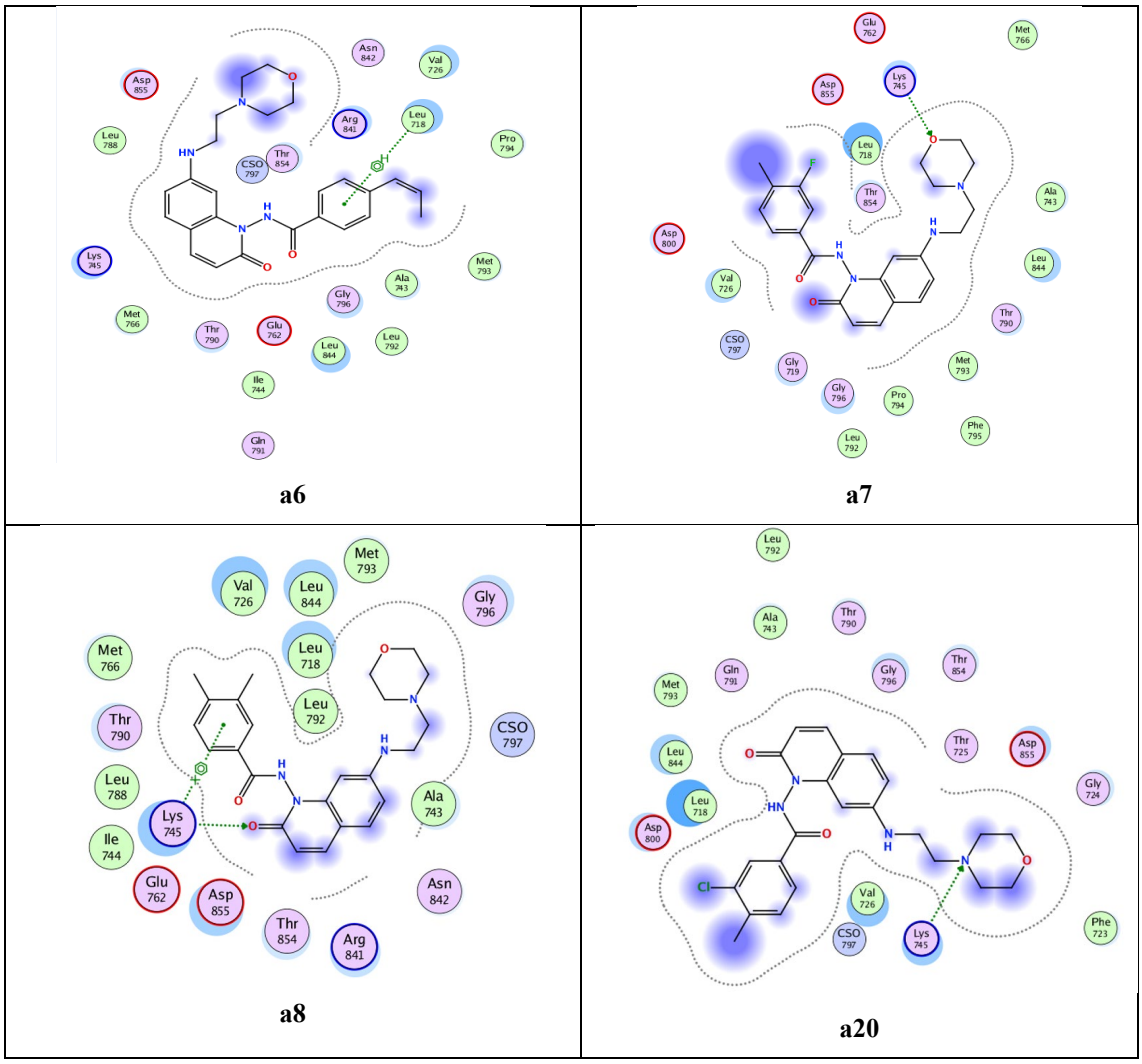
geometry of the compound was then docked into the binding site using the MOE-Dock program. The initial scoring method used was the London dG, while the final scoring method was Rigid Receptor [33].

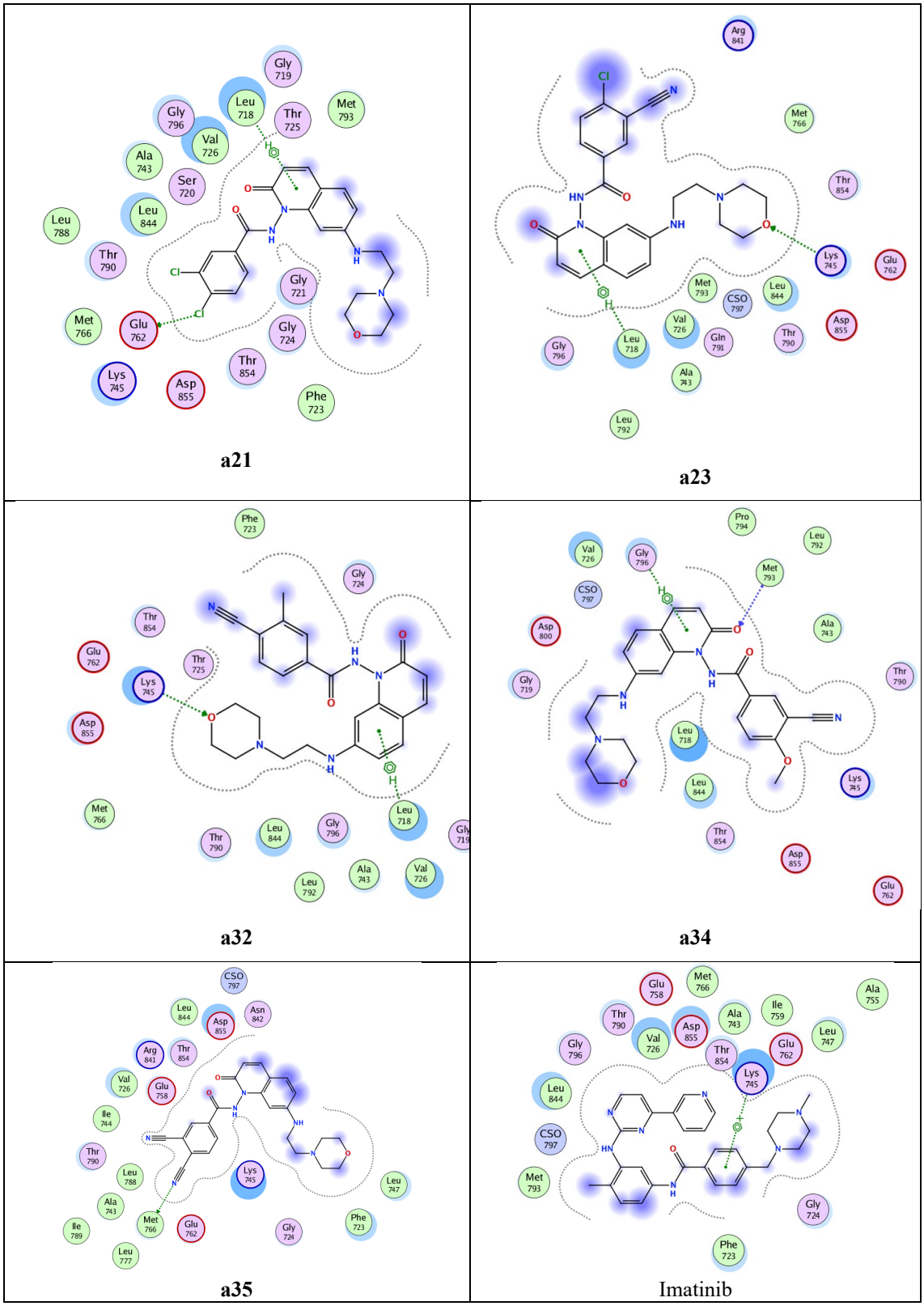
3. Results and discussion

The research study intended to improve the TKIs binding affinity along with selectivity for ABL1. Docking Analysis Results including the binding affinity score, and key interacting residues as well Visualize the binding mode of the TKI within the active site of the tyrosine kinase through molecular graphics and analyze the obtained results and draw conclusions regarding the potential effectiveness of the newly designed TKI.

No.	R1	R2	Energy of Binding (Kcal/mol)	Hydrogen bonds	Non-H-bond interaction
a1	CH_3	H	-7.9	Non	pi-H, LEU 718
a2	OCH_3	H	-7.1	MET 793 (3.27 Å), LYS 745 (2.99 Å)	Non
a3	F	H	-6.8	MET 793 (3.48 Å)	LEU 718 (4.28), pi-H
a4	Cl	H	-6.7	MET 793 (3.62)	Non
a5	CN	H	-7.1	MET 793 (3.17), LYS 745 (3.25)	GLY 796 (3.37A) pi-H
a6	CH_2=CH_2	H	-8.3	Non	LEU 718 (4.12A) pi-H
a7	CH_3	F	-8.1	LYS 745 (2.83A)	Non
a8	CH_3	CH_3	-8.3	LYS 745 (2.96A)	LYS 745 (4.01A) pi-cation
a9	CH_3	Cl	-7.1	LYS 745 (3.28A)	Non
a10	CH_3	OCH_3	-7.7	MET 766 (4.17A)	LEU 718 (4.17A) pi-H
a11	CH_3	CN	-7.6	Non	LEU 718 (3.78A) pi-H
a12	CH_3	CH_2=CH_2	-7.5	CSO 797 (3.16A), MET 766 (3.88A), LYS 745 (2.87 A)	Non
a13	F	F	-7.1	MET 766 (3.15A)	Non
a14	CH_3	CH_3	-7.2	Non	LEU 718 (4.23A) pi-H
a15	Cl	Cl	-7.6	MET 793 (3.30A)	LEU 718 (4.02A) pi-H, LEU 718 (3.81A) pi-H
a16	OCH_3	OCH_3	-7.0	MET 793 (3.32A)	Non
a17	CN	CN	-6.9	Non	Non
a18	CH_2=CH_2	CH_2=CH_2	-7.1	THR 854 (3.06A), ASP 855 (2.83A), LYS 745 (2.85A)	LYS 745 (4.21A) pi-cation
a19	Cl	F	-7.5	GLU 762 (3.04A)	LEU 718 (4.27A) pi-H
a20	Cl	CH_3	-8.1	LYS 745 (3.28A)	Non
a21	Cl	Cl	-8.2	GLU 762 (3.03 A)	LEU 718 (4.29 A) pi-H
a22	Cl	OCH_3	-7.2	LYS 745 (3.44A)	LEU 718 (3.83A) pi-H
a23	Cl	CN	-8.4	LYS 745 (3.44 A)	LEU 718 (3.83A) pi-H
a24	Cl	CH_2=CH_2	-7.5	MET 766 (3.34 A)	Non
a25	OCH_3	F	-7.2	Non	LEU 718 (3.70A) pi-H
a26	OCH_3	CH_3	-7.4	MET 793 (3.26A)	LEU 718 (4.30A) pi-H, GLY 796 (3.59 A) pi-H
a27	OCH_3	Cl	-7.3	LYS 745 (3.05A)	Non
a28	OCH_3	OCH_3	-7.8	MET 793 (3.09A), LYS 745 (3.04 A)	GLY 796 (3.49A) pi-H
a29	OCH_3	CN	-7.4	Non	Non
a30	OCH_3	CH_2=CH_2	-7.3	LYS 745 (3.00A)	LEU 718 (3.86A) pi-H
a31	CN	F	-7.7	PHE 856 (3.35A)	VAL 726 (4.40A) pi-H
a32	CN	CH_3	-8.0	LYS 745 (2.93 A)	LEU 718 (4.37 A) pi-H

a33	CN	Cl	-7.2	MET 793 (3.34A), LYS 745 (3.33A)	LEU 718 (4.01 A) pi-H, LEU 718 (3.99 A) pi-H, GLY 796 (3.48A) pi-H
a34	CN	OCH_3	-8.5	MET 793 (3.15A)	GLY 796 (3.35A) pi-H
a35	CN	CN	-8.7	Non	LYS 745 (3.77A) pi-cation
a36	CN	CH_2=CH_2	-7.5	Non	LEU 718 (4.09A) pi-H
a37	CH_2=CH_2	F	-7.8	THR 854 (3.00 A)	Non
a38	CH_2=CH_2	CH_3	-6.8	MET 793 (3.20 A)	GLY 796 (3.36 A) pi-H
a39	CH_2=CH_2	Cl	-7.7	MET 793 (3.24A)	GLY 796 (3.35A) pi-H
a40		OCH_3	-7.3	MET 766 (3.05A)	LEU 718 (3.69A) pi-H
a41	CH_2=CH_2	CN	-7.3	LEU 788 (3.30A)	Non
a42	CH_2=CH_2	CH_2=CH_2	-7.0	MET 793 (3.19A)	LEU 718 (3.94 A) pi-H GLY 796 (3.47A) pi-H
Imatinib			-8.3	Non	LYS 745 (3.58A) pi-cation



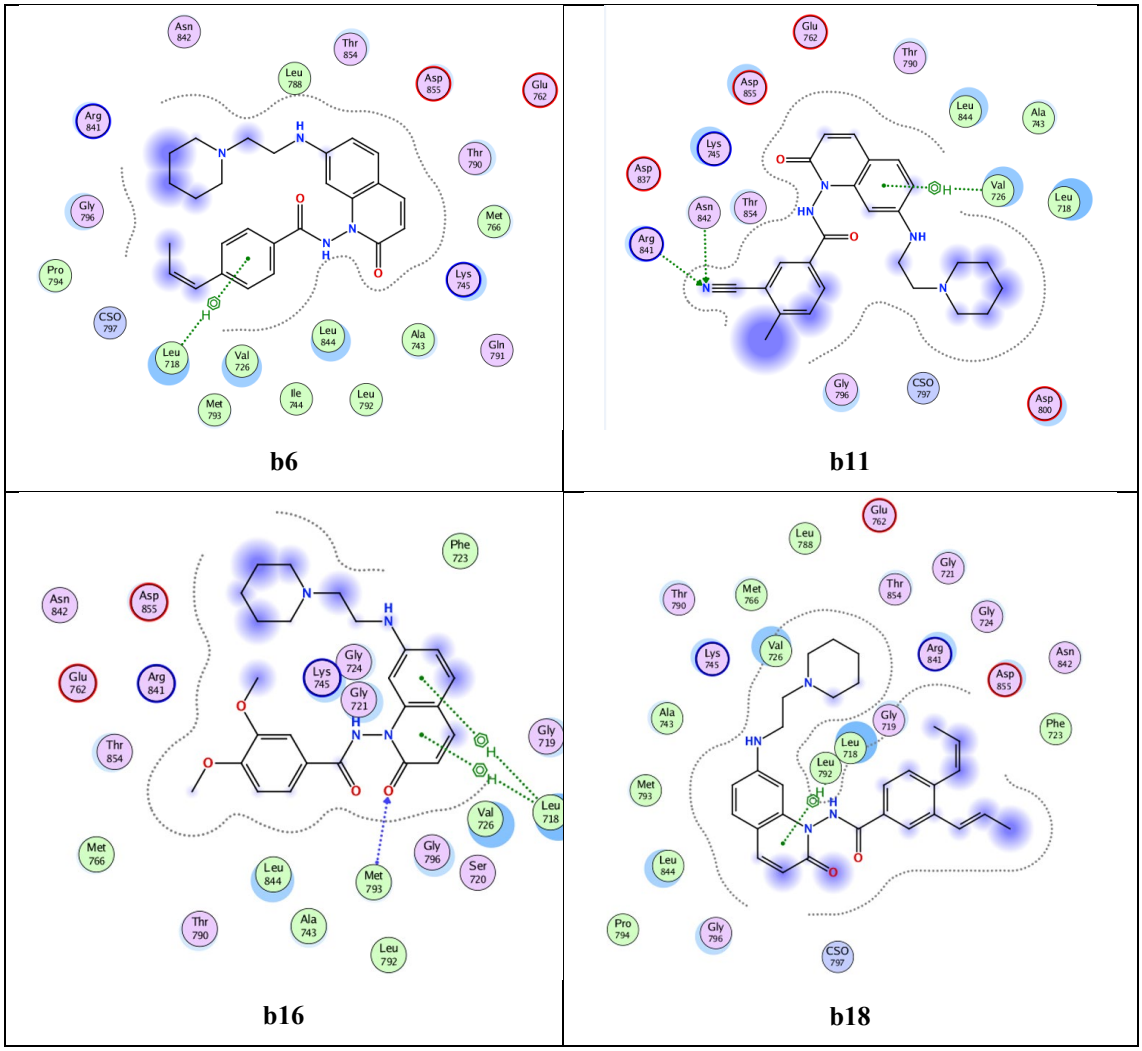


Scheme 1. 2D hematic diagram illustrating the target compound's docking model (for the best compound) with the target 4WKQ protein.

Table 2. Structure and Docking results of tyrosine kinase inhibitor-series (b) (compounds b1-b42) and Imatinib against selected 4WKQ protein.

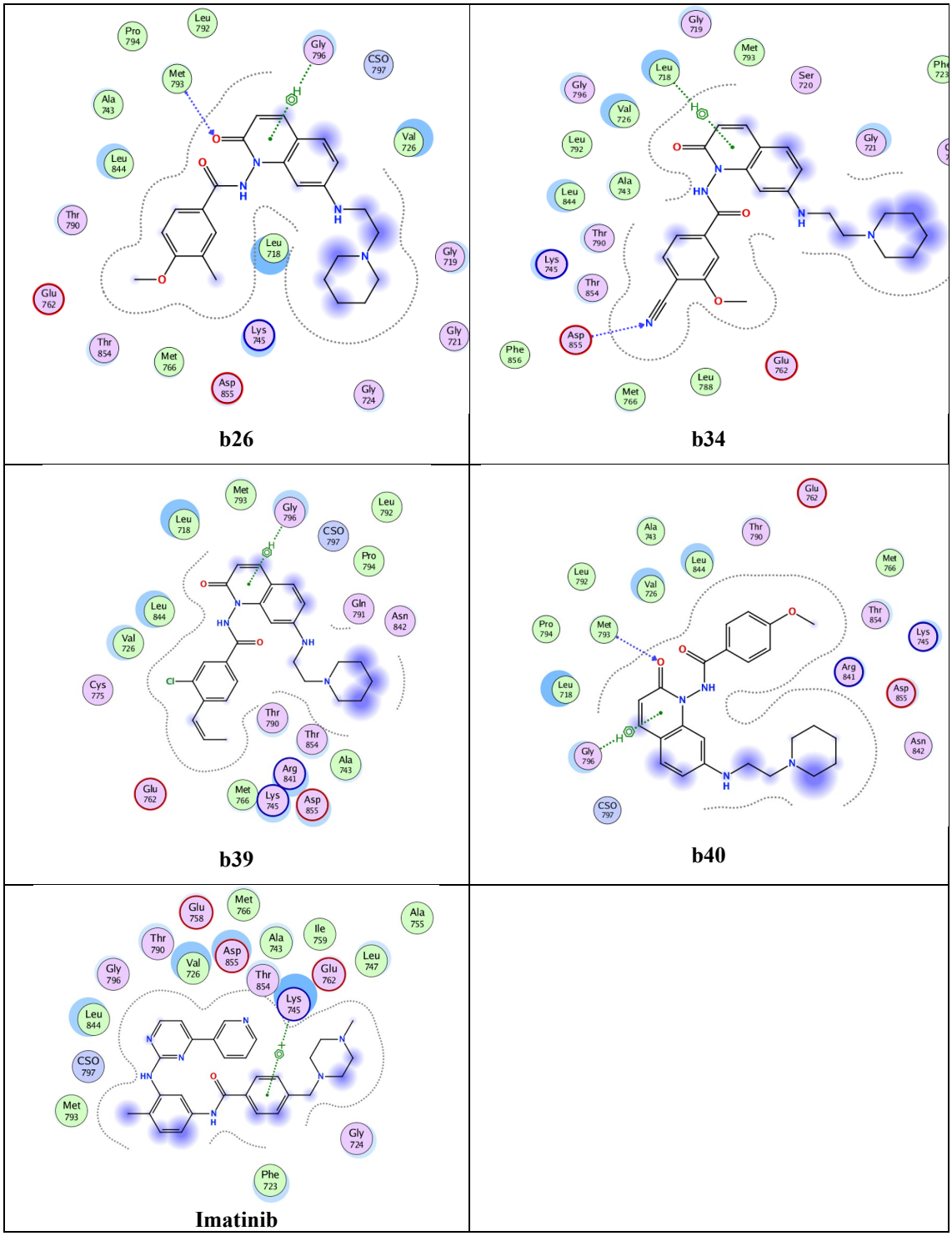
No.	R1	R2	Energy of Binding (Kcal/mol)	Hydrogen bonds	Non-H-bond interaction
b1	CH_3	H	-7.5	LEU 718 (3.59A) CSO 797 (3.16A)	LEU 718 (3.79A) pi-H LEU 718 (3.57A) pi-H
b2	OCH_3	H	-7.4	LEU 718 (3.21A)	LEU 718 (4.43A) pi- LEU 718 (3.89A) pi-H
b3	F	H	-6.9	Non	LYS 745 (4.06A) pi-H
b4	Cl	H	-7.0	CSO 797 3.11A) ASP 855 (3.23A)	Non
b5	CN	H	-7.2	MET 793(3.22A) LYS 745(3.29A)	GLY 796 (3.35A) pi-H
b6	CH_2=CH_2	H	-8.3	Non	LEU 718 (4.24A) pi-H
b7	CH_3	F	-7.4	Non	LEU 718 (4.16A) pi-H
b8	CH_3	CH_3	-6.9	Non	LEU 718 (4.09 A) pi-H LEU 718 (4.04 A) pi-H
b9	CH_3	Cl	-7.4	CSO 797(3.21A) LYS 745 (2.90)	Non
b10	CH_3	OCH_3	-7.7	LYS 745(3.32A) GLY 724(3.51A)	Non
b11	CH_3	CN	-8.2	ASP 855 (3.25A) GLY 721(3.21A)	LEU 718 (4.14A) pi-H
b12	CH_3	CH_2=CH_2	-7.6	MET 793(3.16A)	GLY 796 (3.54A) pi-H
b13	F	F	-7.1	MET 766(3.62A) MET 793(3.36A)	LEU 718 (4.03A) pi-H LEU 718 (3.87A) pi-H
b14	CH_3	CH_3	-7.8	MET 793(3.14A)	GLY 796 (3.37 A) pi-H
b15	Cl	Cl	-7.2	GLY 721(3.01A)	Non
b16	OCH_3	OCH_3	-8.3	MET 793(3.46A)	LEU 718 (4.15A) pi-H LEU 718 (4.02A) pi-H
b17	CN	CN	-7.1	Non	LEU 718 (4.21A) pi-H
b18	CH_2=CH_2	CH_2=CH_2	-8.2	Non	LEU 718 (4.23 A) pi-H
b19	Cl	F	-6.7	GLU 762(3.74A) MET 793(3.22A)	GLY 796 (3.51 A) pi-H
b20	Cl	CH_3	-7.9	GLU 762(3.05A) LYS 745(3.09A)	LEU 718 (4.19 A) pi-H
b21	Cl	Cl	-7.1	GLU 762(3.20A) LYS 745(3.09A)	LEU 718 (4.27 A) pi-H
b22	Cl	OCH_3	-7.5	LYS 745(3.47A)	Non
b23	Cl	CN	-6.9	Non	VAL 726 (4.50A) pi-H
b24	Cl	CH_2=CH_2	-7.1		
b25	OCH_3	F	-7.5	MET 793(3.21A)	GLY 796 (3.32A) pi-H
b26	OCH_3	CH_3	-8.0	THR 854(3.01A) ASP 855 (3.12A)	Non
b27	OCH_3	Cl	-7.4	Non	LEU 718 (4.23A) pi-H
b28	OCH_3	OCH_3	-6.9	Non	LEU 718 (3.68A) pi-H
b29	OCH_3	CN	-7.7	LYS 745(3.23A)	Non
b30	OCH_3	CH_2=CH_2	-7.8	MET 793(3.22A)	GLY 796 (3.52A) pi-H
b31	CN	F	-7.4	GLY 721(3.19A) LYS 745(3.43A)	Non
b32	CN	CH_3	-6.8	LYS 745(3.19A)	
b33	CN	Cl	-7.1		LEU 718 (3.76A) pi-H
b34	CN	OCH_3	-8.3	ASP 855 (3.25A)	LEU 718 (4.14A) pi-H
b35	CN	CN	-7.7	MET 793(3.22A) LYS 745(3.49A)	LEU 718 (4.08A) pi-H LEU 718 (4.00 A) pi-

				LYS 745 3.40A)	GLY 796 (3.50A) pi-H
b36	CN	CH_2=CH_2	-7.3	LYS 745(3.37A)	VAL 726 (4.49A) pi-H VAL 726 (3.95A) pi-H
b37	CH_2=CH_2	F	-7.3	Non	PHE 723 (4.26A) H-pi GLY 719 (3.81A) pi-H
b38	CH_2=CH_2	CH_3	-7.1	Non	LEU 718 (3.94A) pi-H VAL 726 (3.93 A) pi-H
b39	CH_2=CH_2	Cl	-8.0	Non	GLY 796 (3.32A) pi-H
b40	H	OCH_3	-8.4	MET 793(3.22A)	GLY 796 (3.35A) pi-H
b41	CH_2=CH_2	CN	-7.8	Non	LEU 718 (4.32A) pi-H LYS 745 (3.81A) pi-cation
b42	CH_2=CH_2	CH_2=CH_2	-7.7	Non	LYS 745 (4.03A) pi-cation
Imatinib			-8.3	Non	LYS 745 (3.58A) pi-cation



b6 **b11**

b16 **b18**



Scheme 2. 2D schematic diagram illustrating the target compound's docking model (for the best compound) with the target 4WKQ protein.

The table consists of details concerning the energy of binding (in kcal/mol), hydrogen bond interactions and non-hydrogen bond interactions for each compound. Imatinib, a widely known tyrosine kinase inhibitor (TKI) targeting ABL1 was made use of as a reference in this analysis.

Overall, the findings indicate that the analyzed ligands display varying degrees of binding affinity to the target 4WKQ protein with some ligands exhibiting stronger interactions than others. The presence of hydrogen bonds and non-hydrogen bond interactions contributes to the stability of the

ligand-protein complexes, this variability influences their binding energies. The involvement of specific amino acid residues, such as MET 793, LYS 745, LEU 718, and GLY 796, was noted in significant interactions with the ligands.

Binding Energy: The binding energy represents the strength of interaction between the TKI and the target 4WKQ protein. Higher negative values indicate stronger binding affinity. Imatinib exhibited a binding energy of -8.3 kcal/mol, while the analyzed compounds (a1-a42) ranged from -6.8 to -8.7 kcal/mol.

In comparison to Imatinib, several compounds, including comp-a23, a34, and a35, displayed the higher negative values of binding energies of -8.4, -8.5, and -8.7 kcal/mol, respectively. This suggests stronger binding affinities and potentially more significant interactions. compounds a6 and a8 showed similar binding energies and interacted with key amino acid residues. Other compounds, a7, a20, a21, and a32 exhibited slightly lower binding energies but still interacted with key amino acid residues, albeit in distinct ways.

Hydrogen bond and non-hydrogen bond interactions, such as pi-H and pi-cation interactions, also contribute to ligand binding and stabilization. Imatinib showed a pi-cation interaction with LYS 745 (3.58 Å), while the analyzed compounds displayed a variety of hydrogen bond and non-hydrogen bond interactions involving different residues, including MET 793, LYS 745, LEU 718, GLY 796, THR 854, ASP 855, GLU 762, PHE 856, and LEU 788. Some compounds exhibited interactions like Imatinib, while others demonstrated distinct hydrogen bonding and non-hydrogen bond patterns.

In conclusion, based on the provided data, compounds such as a6, a8, a23, a34, and a35, exhibit promising binding affinities and show distinct interactions compared to Imatinib. Therefore, these compounds have the potential to be considered as lead or promising candidates for further evaluation as TKIs.

In comparison to imatinib, which exhibited a binding energy of -8.3 kcal/mol and formed a pi-cation interaction with LYS 745 at 3.58Å, the newly designed TKI shows energy of binding ranging from -6.7 to -8.4 kcal/mol, which suggests varying degrees of interaction strength with the target protein and interaction profiles.

Compounds demonstrated comparable or stronger binding energies than imatinib. For example, compound b40 exhibited the highest binding energy of -8.4 kcal/mol. Compounds b6 and b11, b16, b18, b26, b34, and b39 also showed comparable strong binding energies, interacting with key amino acid residues. Compound b10 displayed a binding energy of -7.7 kcal/mol.

Some compounds, such as b1, b3, b4, b5, and b25, exhibited slightly lower binding energies ranging from -6.7 to -7.2 kcal/mol. However, they still interacted with key amino acid residues, albeit in different ways, suggesting potential binding affinity. Compound b23 showed a moderate energy of binding (-6.9 kcal/mol)

Overall, these findings indicate that several compounds, including, b6, b11, b16, b18, b34, b39and b40, exhibit comparable or stronger binding energies and interact with key amino acid residues, suggesting their potential as lead candidates in comparison to imatinib.

4. Conclusions

Via our computational docking examination, we have obtained beneficial understandings right into the binding interactions and strength between a newly developed tyrosine kinase inhibitor (TKI) and its target, the 4WQK tyrosine kinase. This highlights the possibility of structure-based drug design methods in speeding up the exploration and improvement of targeted therapies. Our results provide guidance for further experiments, such as the production and assessment of the intended TKI as a possible anticancer drug. More precisely, we evaluated the TKI's efficiency, affinity for binding, and level of competition in blocking ABL1, with the intention of evaluating its potential as a targeted treatment for malignancies driven by ABL1. This research can help develop and optimize the TKI further, which could result in the development of a more effective treatment option for patients with cancers linked to ABL1.

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