In Silico Dock of TKIs with CYP3A4 and CYP2C8 and Pharmacophore Generation

Zhenya Ma

Shandong Experimental High School, Jinan, Shandong, 250001, China

Abstract: Tyrosine kinase inhibitors (TKIs) serve as targeted anticancer drugs that inhibit the abnormal activity of tyrosine kinase (TK) in cancer treatment. However, when used with other medications, they often result in side effects, such as renal impairment, hepatic injury, and even mortality. This adverse clinical effect is known as drug-drug interactions (DDIs). As two major drug-related metabolic enzymes, CYP3A4 and CYP2C8 play pivotal roles in the metabolism of TKIs. To mitigate the DDIs associated with TKIs and to further develop from a clinical perspective, the interactions between TKIs and CYPs have been investigated. In this study, through docking simulations, 19 distinct TKIs were found to interact with CYP3A4, and three types of TKIs were also docked with CYP2C8. The results revealed that hydrophobic interaction and hydrogen bonds played a pivotal role in binding interaction when TKI molecules engaged with their target CYPs. Among all interacting amino acids, GLU374 and ARG105 emerged as the most critical residues for forming both hydrophobic interactions and hydrogen bonds. Afatinib, brigatinib, and nilotinib, the three TKIs docked with CYP3A4 and CYP2C8, exhibited more muscular interaction energy with CYP2C8 than with CYP3A4. The generation of common feature pharmacophores represents the unique characteristics present in each TKI. This study's findings could potentially aid medical chemists in designing and developing the next generation of TKIs while mitigating potential side effects and drug-drug interactions.

1. Introduction

Tyrosine kinase inhibitors (TKIs) are targeted anticancer medications that suppress the abnormal activity of tyrosine kinase (TK). [1] TKs play a vital role in normal cells' growth, division, and differentiation. [2] However, when mutations occur in TKs, they can become overly active. This excessive activity leads to uncontrolled cell proliferation and the eventual formation of cancer cells. Consequently, inhibiting the abnormal function of TKs is a critical step in cancer treatment. [3]

Although TKIs can effectively inhibit the hyperactivity of TKs in cancer cells, they may cause severe side effects [4], such as renal impairment, hepatic injury, and even mortality, when used with other medicines. The primary cause of these side effects is drug-drug interactions (DDIs). Drug–drug interactions (DDIs), defined as the effect of combining two or more pills, have emerged as a significant issue for drug administration and patient safety [5]. DDIs may enhance or diminish the efficacy of one or both types of drugs. To examine the impact of DDIs on TKIs and other medications, a thorough study of the interactions between TKIs and Cytochrome P450 enzymes (CYPs) is essential.

Cytochrome P450 enzymes serve as the primary drug-metabolizing enzymes in the human body. [6] Among all CYPs, CYP3A4 and CYP2C8 are two primary drug metabolic enzymes.[7] When the active sites of TKIs on CYPs are occupied or altered due to the effects of other medications, DDIs occur and impact the efficacy of TKIs.[8] Researchers have a growing interest in the clinical manifestations of TKIs DDIs, including the side effects of TKIs, which drugs cause severe side effects when used with TKIs, and how these DDIs affect patients. However, mechanisms of interactions between TKIs and CYP3A4, 2C8 remain unclear (Fig 1). Further improvement in the data regarding the type and strength of binding interactions is needed. Molecular docking can be employed to identify such information.

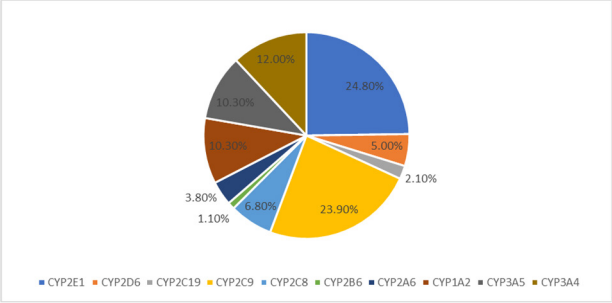


Fig. 1. The median protein expression for each P450 is expressed as a percentage of the total median P450 protein content. [9]

Docking technology employs a computer to predict the binding mode and affinity between drug molecules and target proteins.[10] The 3D structures of the drugs, ligands, and target proteins, including the receptor, must be

Mazhenya1025@gmail.com

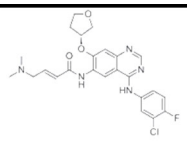
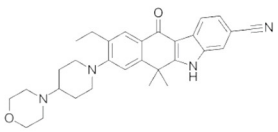
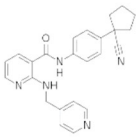
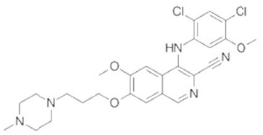
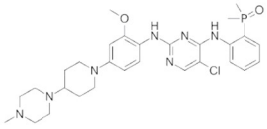
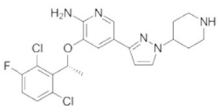
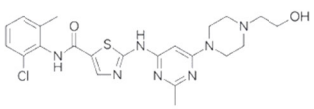
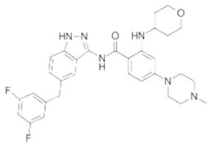
prepared to facilitate docking. Subsequently, binding sites, typically active sites or the key residues on proteins, are defined to provide a docking region for drug molecules. Scoring functions can then rate the docking results, representing the binding mode of the lowest energy and highest stability. Additionally, interacting residues with drug molecules can be visualized. Consequently, docking aids researchers in comprehending how drug molecules bind to their target protein.[11]

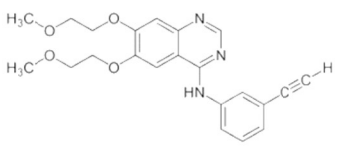
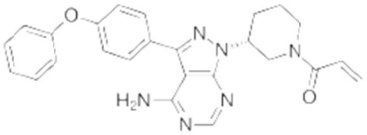
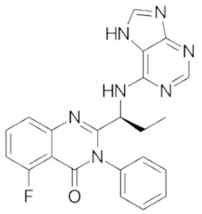
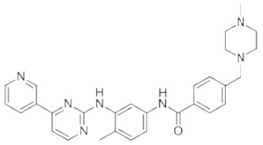
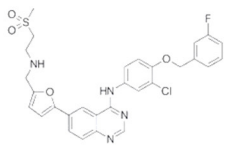
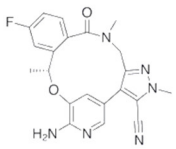
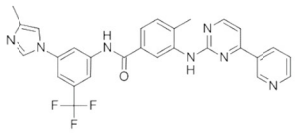
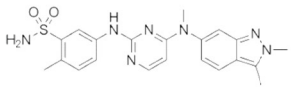
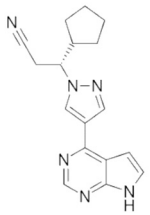
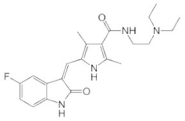
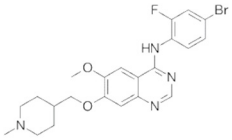
TKIs, when used with other medications, can cause severe DDIs, making it increasingly essential to overcome these drawbacks. As such, researchers have emphasized optimizing the clinical application of TKIs by focusing on their interactions with inducers and inhibitors in clinical settings.[12] However, previous investigations have not yet identified the underlying mechanisms governing the mutual action of TKIs and other medications. [13] A comprehensive study of the nature of TKIs and their corresponding proteins should be conducted to examine these interaction mechanisms. The structures of TKIs were drawn, and a pharmacophore with standard features was constructed. This approach aimed to determine the similarities and differences between TKIs and their contributions to their combined interactions with CYP3A4 or CYP2C8. Key residues interacting with TKIs were identified, providing a basis for further exploration of ways to optimize the structure of the TKIs based on these residues.

2. Method

The structures of 19 various TKIs were generated using ChemDraw 20.0(PerkinElmer Informatics, 20.0.0.41); These TKIs have been clinically demonstrated to be effective in their role as TKI [1-3] Subsequently, these structures were transformed into 3D formats utilizing Chem3D 20.0(PerkinElmer Informatics, 20.0.0.41). A comprehensive list of these structures is presented in Table 1.

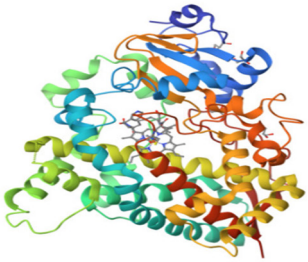
Table 1: The properties of TKIs

Name	Molecular weight(g.mol^{-1})	2D structure
Afatinib	485.94	
Alectinib	482.63	
Apatinib	397.48	
Bosutinib	530.45	
Brigatinib	584.10	
Crizotinib	450.34	
Dasatinib	488.01	
Entrectinib	560.65	

Erlotinib	393.44	
Ibrutinib	440.51	
Idelalisib	415.43	
Imatinib	493.62	
Lapatinib	581.06	
Lorlatinib	406.42	
Nilotinib	529.53	
Pazopanib	437.52	
Ruxolitinib	306.37	
Sunitinib	398.48	
Vandetanib	475.36	

The crystal structures of human CYP3A4 (Fig. 2A) and CYP2C8 (Fig. 2B) were retrieved from the Protein Data Bank (http://www.rcsb.org/pdb/).

(A)



(B)

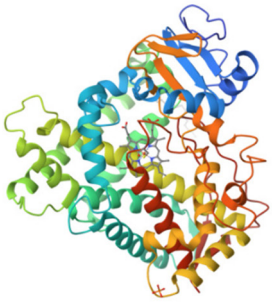


Fig. 2. A The crystal structure of human CYP3A4 (PDB ID: 4D6Z). B The crystal structure of human CYP2C8 (PDB ID: 1PQ2).

Using Discovery Studio 2019 (Perl executable software, 19.1.0), all TKI structures were employed as ligands. The energy of TKI molecules was minimized, and the structures were optimized for docking.

Subsequently, the human CYP3A4 and CYP2C8 structures were optimized to prepare them as receptors. The water molecules surrounding the CYPs were first removed. Next, the multi-conformation of the protein was eliminated, and hydrogen atoms were added to the protein using the "Clean Protein" function in Discovery Studio 2019. Once both ligands and receptors were fully prepared, the binding sites of the CYPs were defined by positioning the original ligands to the active center. The docking mode for this study was selected as CDOCKER in Discovery Studio 2019. The input side sphere coordinates for CYP3A4 were (18.2493,30.9971,-15.2869,26.5658), and for CYP2C8, they were (-14.9331, 4.08707, -21.5694, 31.3492). A pose cluster radius of 0.5 Å was established to maximize the variety of docking conformations. All TKIs were docked to CYP3A4, but only three kinds of TKIs, which also formed strong interactions with CYP2C8, were anchored to it.

In the current study, we found that docking data could only be utilized to analyze which residues on a given CYP interacted with the most TKIs, and thus, contributed the most to the formation of the corresponding effector, if the CYP interacted with more than half of the TKIs. Considering CYP3A4's predominant metabolism of all 19 TKIs, we present the residues involved in the interactions. We also separately analyze the residues that contribute the most to these forces. For CYP2C8, since it primarily metabolizes only 3 TKIs, we only show the key residues contributing to these forces. Descriptive statistics were used in this study. All residues that formed forces with TKIs are listed in the table, while residues with significant contributions are listed in the histogram. A detailed description of the tables and histograms is shown in the result.

To determine the main interactions, the strength of interactions, and the residues on the protein involved in TKI interactions, the docking results were analyzed using the "Analyze ligand poses." The docking outcomes were successfully analyzed and preserved. Subsequently, the TKIs were edited to generate a common feature pharmacophore. The selected features included HB_ACCEPTOR, HB_DONOR, HYDROPHOBIC, POS_IONIZABLE, NEG_IONIZABLE, and RING_AROMATIC, using the "Feature Mapping" procedure. The common feature pharmacophore was automatically generated using the "Common Feature Pharmacophore Generation" tool in Discovery Studio 2019. The features of the TKI structures were consistent with those previously mentioned. The conformations were generated under optimal circumstances, with a maximum conformation set at 200 and an energy threshold was set at 10. As a result, the common feature pharmacophores were successfully generated.

3. Result

3.1. The docking consequences

Upon analyzing the structures of TKIs in Table 1, it was observed that these drugs contain ring structures such as benzene, imidazole, and quinazoline rings. These rings serve as the backbone of TKIs. However, variations exist among these drugs, as certain TKIs like afatinib contain halogen atoms, such as chlorine and fluorine. In contrast, other TKIs, including dasatinib and erlotinib, possess hydrophilic and hydrophobic groups, such as hydroxyl and methyl. Consequently, the main forces driving the interaction were charge interaction, hydrophobic interaction, and hydrogen bonding. In this study, -CDOCKER interaction energy was utilized as the standard parameter to evaluate the stability of molecular docking, a technique widely used in pharmaceutical research to assess binding affinity. A higher interaction energy value signifies superior stabilization of the docked ligand-receptor complex. The analysis primarily focused on three critical intermolecular forces contributing to binding: charge interactions, hydrophobic interactions, and hydrogen bonding. The frequency of occurrence for each interaction type was quantified, and the specific residues involved were identified to elucidate their roles in fostering these molecular associations. By comparing the prevalence of these interactions, insights were obtained into the underlying mechanisms responsible for the differing binding stability observed among TKIs. The docking results with CYP3A4 are presented in Table 2, while those with CYP2C8 are listed in Table 3.

Table 2. The consequences of docking about TKIs and CYP3A4

Name	-CDOCKER interaction energy	Residue involved in charge interaction	Residue involved in hydrophobic interaction	Residue involved in hydrogen bond
Afatinib	56.5141	GLU374	ARG212 PHE215 PHE304 ALA305 ALA370 MET371	PHE213 PHE304 ALA305 GLU374 GLY481
Alectinib	41.5441	ARG106 GLU374	CYS442 PHE215 MET371 ARG372	THR224 ALA305
Apatinib	49.2439	ARG105	ARG212 PHE215 LEU373 CYS442	ARG105 PRO434 ARG440
Bosutinib	61.1488	GLU374	ALA370 PHE435 CYS442 ALA448	ALA305 ARG372 GLU374 ARG105
Brigatinib	60.9308	/	PHE57 PHE215 ILE369 ALA370 ARG372 CYS442	ASP76 ALA370 ARG372 GLU374
Crizotinib	47.0966	/	ALA370 CYS442	ARG105, PHE213, ARG372 LEU373
Dasatinib	62.7482	GLU374	PRO434 LEU364 ILE369 ALA370 PHE435 ALA448	THR309, ARG372, GLU374
Entrectinib	63.8486	ARG105, PHE215, GLU374	ALA370 LEU373 CYS442	ARG105, PHE215, LEU373, GLU374
Erlotinib	42.0754	/	ARG212 PHE215 MET371 LEU482	ARG105, ARG372, GLY481
Ibrutinib	50.5215	ARG372	ARG212 ALA370 MET371 ARG372 CYS442	PHE304 ALA370
Idelalisib	46.4638	ARG105	ALA370 MET371 LEU373 LEU482	ARG105, LEU373 GLU374, ARG375, GLY481
Imatinib	60.5937	/	PHE57 ARG105 ARG106 PHE215 ILE369 ALA370 MET371 ARG372	ARG105, PHE213, PRO434, GLY481
Lapatinib	66.6614	ARG106	PHE435 ARG212 PHE215	ARG105, PHE213

			PHE304 ALA370 ARG372	GLU374, PRO434
Lorlatinib	38.7765	GLU374	ARG212 ILE369 ALA370 MET371 LEU482	ARG105, PHE213, ILE369
Nilotinib	57.4925	GLU374	PHE213 PHE215 PHE304 VAL313 ILE369 ALA370 ARG372 PHE435 ALA448 MET452	PHE213, PRO434, PHE435 GLY481
Pazopanib	47.565	/	PHE57 ARG212 PHE215 ALA305 ALA370 MET371 ARG372	THR309, ILE369
Ruxolitinib	32.7018	ARG105	CYS442 ARG372 CYS442 ALA370	ARG372
Sunitinib	50.4778	/	VAL313 ILE369 ALA370 PHE435 CYS442 ALA44	THR310 ALA370, ARG372, PRO434
Vandetanib	51.6886	GLU374	VAL313 ILE369 ALA370 PHE435 ALA448 MET452	ARG372

Table 3: The consequences of docking about TKIs and CYP2C8

Name	CDOCKER interaction energy	Residue involved in charge interaction	Residue involved in hydrophobic interaction	Residue involved in hydrogen bond
Afatinib	57.0832	/	ARG206 ILE207 PRO227 GLY228 LYS232	ARG206, PRO227 SER210 THR229 GLY228 GLU203
Brigatinib	65.8367	/	ILE207 PRO221 PRO227 LYS474	ARG206 GLY228 SER210
Nilotinib	60.3666	/	ARG206 ILE207 LYS232 CYS442	ARG206 ASN209 SER210 ILE207

Analysis of the docking data revealed that approximately 32% (6 out of 19) of the investigated TKIs did not exhibit charge interactions with CYP3A4. Moreover, none of the TKIs formed charge interactions with CYP2C8. This finding indicates that charge interactions might not be the primary factor influencing the observed variations in interaction energy. An intriguing comparison can be made between pazopanib

and sunitinib. Although pazopanib had four additional hydrophobic interactions, it formed three fewer hydrogen bonds than sunitinib. Consequently, the interaction energy of pazopanib was found to be 2.9128 units lower than sunitinib's, indicating that hydrogen bond formation plays a more significant role in determining the overall interaction energy. The top 3 residues in CYP3A4 that form interactions with most TKIs are depicted in Figures 3, 4 and 5.

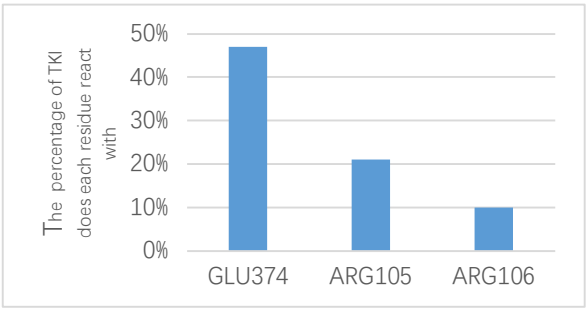


Fig. 3. Residues within CYP3A4 that interact with the majority of TKIs through charge interactions

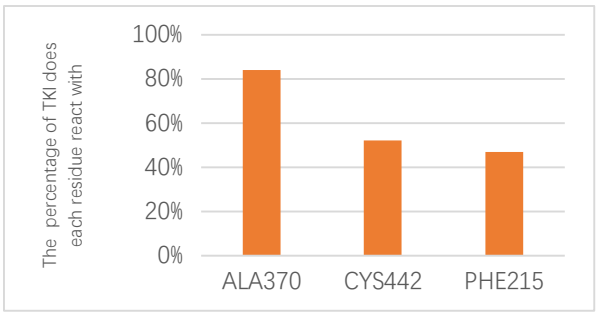


Fig. 4. Residues within CYP3A4 that interact with the majority of TKIs through hydrophobic interactions

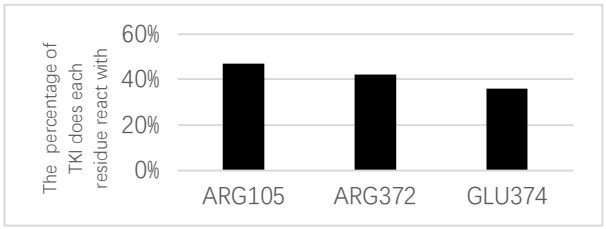


Fig. 5. Residues within CYP3A4 that interact with the majority of TKIs through hydrogen bond

4. DISCUSSION

In this study, all TKIs primarily metabolized by CYP3A4 were docked with it. The average value of -CDOCKER interaction energy was 52.0049. In this case, the interaction energy of alectinib, apatinib, crizotinib, erlotinib, ibrutinib, idelalisib, lorlatinib, pazopanib, ruxolitinib, sunitinib, and vandetanib was found to be lower than the average score. The TKI with the lowest score of 32.0718 was ruxolitinib, which formed two charge interactions, three hydrophobic interactions, and only one hydrogen bond. On the other hand, lapatinib, with the highest -CDOCKER interaction energy of 66.6614, created one charge interaction, seven hydrophobic interactions, and six hydrogen bonds.

This study defined the critical residues within CYP3A4 that interacted most frequently with all TKIs. Precisely, the top 3 residues that interacted with the most significant number of TKIs in a particular type of reaction were pinpointed and designated as crucial residues. According to Figures 3, 4 and 5, the critical residues responsible for charge interactions were GLU374 (47%, 9 out of 19), ARG105 (21%, 4 out of 19), and ARG106 (10%, 2 out of 19). For hydrophobic interactions, the central residues were ALA370 (84%, 16 out of 19), CYS442 (52%, 10 out of 19), and PHE215 (47%, 9 out of 19). Regarding hydrogen bonds, the critical units were ARG105 (47%, 9 out of 19), ARG372 (42%, 8 out of 19), and GLU374 (36%, 7 out of 19). As researchers and medical chemistry designers strive to enhance the binding of TKIs to CYP3A4 through structure optimization, they should focus on improving drug molecules' properties to facilitate more stable charge interactions and hydrogen bonds with ARG105 and GLU374, both of which play crucial roles in these interactions. In addition, the proportion of ALA370 significantly influences the formation of hydrophobic interactions. Strengthening the hydrophobic interaction corresponds to increasing the exchange of TKIs with ALA370. Nonetheless, the three critical residues contribute substantially more to the docking process than the other two interactions. Therefore, serious attention should be given to these three critical residues and additional residues capable of interacting with five or more types of TKIs when enhancing hydrophobic interaction.

When examining the docking consequences of afatinib, brigatinib, and nilotinib, it was observed that CYP3A4 and CYP2C8 metabolize all three. The interaction energy of these TKIs was higher when docking with CYP2C8 compared to CYP3A4, suggesting that CYP2C8 may mainly metabolize these TKIs.

Regarding generating a common feature pharmacophore, the findings revealed that most characteristics were present in virtually all TKI. Additionally, all pharmacophores correlated with the drug molecules and were depicted by the maximum fit, suggesting that these pharmacophores adequately characterize each TKI.

However, certain exceptions were noted. Dasatinib lacked an R (aromatic ring center). Apatinib, erlotinib, ibrutinib, lorlatinib, nilotinib, and pazopanib lacked a P (positive ionizable center). Erlotinib lacked an H (hydrophobic group). Afatinib, apatinib, bosutinib, brigatinib, entrectinib, imatinib, lapatinib, nilotinib, pazopanib, ruxolitinib, and vandetanib lacked a D (hydrogen bond donor). The results are presented in Table 4.

Table 4: Pharmacophores present or absent in TKIs

Name	R (aromatic ring center)	P (positive ionizable center)	H (hydrophobic group)	D (hydrogen bond donor)
Afatinib	√	×	√	×
Alectinib	√	√	√	√
Apatinib	√	√	√	×
Bosutinib	√	√	√	×
Brigatinib	√	√	√	×
Crizotinib	√	√	√	√
Dasatinib	×	√	√	√
Entrectinib	√	√	√	×
Erlotinib	√	×	×	√
Ibrutinib	√	×	√	√
Idelalisib	√	√	√	√
Imatinib	√	√	√	×
Lapatinib	√	√	√	×
Lorlatinib	√	×	√	√
Nilotinib	√	×	√	×
Pazopanib	√	×	√	×
Ruxolitinib	√	√	√	×
Sunitinib	√	√	√	√
Vandetanib	√	√	√	×

Based on the above results, it was found that the hydrogen bond donor was the most distinctive characteristic of the pharmacophore. On the contrary, an A (hydrogen bond acceptor) was present in all 19 types of TKIs examined. Generating a common feature pharmacophore helped reveal the variations in interactions among different types of TKIs.

Previous docking studies primarily concentrated on specific TKIs and their corresponding CYPs.[14] These studies provided a detailed understanding of the binding mode, binding site, and action residues of TKIs and their corresponding CYPs. Drugs that induce DDI with TKIs were also docked, and the binding energy was analyzed to discern why these drugs produce DDI when administered concurrently with TKIs. However, most previous studies focused on specific types [15], and, as a result, more data are needed on docking multiple CYPs with consolidated TKIs to examine the reasons for their variations in binding to CYPs.

Furthermore, previous docking studies primarily concentrated on analyzing binding energy [16], while the incorporation of pharmacophore into the research needed to be considered. As functional groups that define drug properties, the structure of pharmacophores can assist researchers in better understanding the origin of the binding force. Consequently, this aspect needs to be addressed in the present study.

This research delves into the binding mechanisms between TKIs and CYP3A4. As ligands, the structural similarities of TKIs dictate that the diversity of pharmacophores substantially affects the clinical behavior of various TKIs. Therefore, both docking and pharmacophore generation were conducted. Docking reveals the active sites, including those specific to particular residues, to identify primary interactions and their positions. The unique characteristics of each TKI have been pinpointed through the generation of pharmacophores. By integrating findings from both studies, researchers can refine the structure of TKIs, strengthening or weakening their interactions with CYP3A4. As the primary enzyme responsible for drug metabolism, CYP3A4 primarily metabolizes most TKIs. A thorough understanding of the mechanisms by which CYP3A4 binds to TKIs, coupled with examining the resulting clinical manifestations, would aid researchers in determining how the strength or weakness of such binding causes DDI with other drugs.

Furthermore, the study data can serve as a valuable resource for drug design by identifying the pharmacophores that can effectively bind to essential residues on CYP3A4. This enhances the binding efficacy of CYP and TKI, facilitating the development of drugs. Theoretically, the mechanistic insights provided by the data can enable researchers to circumvent potent DDI and adverse side effects, thus improving medication safety. By employing 19 TKIs, this study comprehensively examined the impact of various interactions, their frequencies, and the binding sites on the metabolic activity of CYP3A4 for this particular drug class.

Nonetheless, this study also has some things that could be improved. Given its focus on the statistics analysis of a large amount of TKI docking data, each TKI has received limited research attention. Consequently, in-depth research and data analysis on individual TKI must be conducted. Therefore, if these data are to be utilized for developing TKIs, it is crucial to perform rigid, flexible, and other types of dockings for specific TKIs to uncover critical information such as residues, binding forces, and docking postures. Furthermore, these data are solely derived from virtual molecular docking, and their clinical performance only partially correlates with the characteristics represented by this data. If experimental studies can be conducted to investigate the metabolism of the 19 TKIs mentioned in this article by CYP3A4 and CYP2C8, the docking results presented here can be better utilized to optimize the chemical structure of TKIs or to develop novel TKI-based drugs.

5. CONCLUSION

In summary, this study addressed the absence of information regarding the binding mechanisms between TKIs and CYP3A4 and CYP2C8. Thus, interaction energy and the nature of binding forces were identified, leading to generating a common feature pharmacophore. Subsequently, critical residues involved in binding were pinpointed, and the role of these groups in interacting with CYPs was analyzed using pharmacophores. Among all residues, GLU374 and ARG105 contributed to both charge interaction and hydrogen bonds and can thus be considered the most crucial residues in forming interactions with TKIs. In conclusion, this study has provided valuable insights into the interacting mechanism of TKIs and CYPs through computational docking. Thus, more clinical studies are needed to ascertain whether these findings can be applied to patients in clinical settings. Moving forward, the data from this study may aid pharmacists in designing and developing the TKIs, ultimately reducing their side effects and DDIs.

REFERENCES

1. Sangro, Bruno, et al. “Advances in Immunotherapy for Hepatocellular Carcinoma.” Nature Reviews Gastroenterology & Hepatology, vol. 18, no. 8, 13 Apr. 2021, pp. 525–543, https://doi.org/10.1038/s41575-021-00438-0. Accessed 23 Jan. 2022.
2. Anwar, Kaleem, et al. “Overview of Drug-Drug Interactions between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Targeted Therapy and Supportive Care for Lung Cancer.” JTO Clinical and Research Reports, vol. 4, no. 2, Feb. 2023, p. 100452, https://doi.org/10.1016/j.jtocrr.2022.100452.
3. Cheng, Ying, et al. “Osimertinib versus Comparator EGFR TKI as First-Line Treatment for EGFR-Mutated Advanced NSCLC: FLAURA China, a Randomized Study.” Targeted Oncology, vol. 16, no. 2, Feb. 2021, pp. 165–76, https://doi.org/10.1007/s11523-021-00794-6.
4. Falconi, Giselle, and Sanaz Kashan. “Drug Interactions in Palliative Care.” PubMed, StatPearls Publishing, 2023, pubmed.ncbi.nlm.nih.gov/31869083/. Accessed 27 Sept. 2023. https://doi.org/10.1124/jpet.116.233635. Accessed 9 July 2020.
5. Zhang, Tianlin, et al. “Deep Learning for Drug–Drug Interaction Extraction from the Literature: A Review.” Briefings in Bioinformatics, vol. 21, no. 5, Nov. 2019, pp. 1609–27, https://doi.org/10.1093/bib/bbz087. Accessed 1 Apr. 2023.
6. Grosdidier, A., et al. “SwissDock, a Protein-Small Molecule Docking Web Service Based on EADock DSS.” Nucleic Acids Research, vol. 39, no. Suppl, May 2011, pp. W270–77, https://doi.org/10.1093/nar/gkr366.
7. Hofman, Jakub, et al. “Roles of CYP3A4, CYP3A5 and CYP2C8 Drug-Metabolizing Enzymes in Cellular Cytostatic Resistance.” Chemico-Biological Interactions, vol. 340, May 2021, p. 109448, https://doi.org/10.1016/j.cbi.2021.109448. Accessed 16 Feb. 2022.
8. Hartmann, Jörg Thomas, et al. “Tyrosine Kinase Inhibitors - a Review on Pharmacology, Metabolism and Side Effects.” Current Drug Metabolism, vol. 10, no. 5, June 2009, pp. 470–81, https://doi.org/10.2174/138920009788897975.
9. Zhang, Hai-Feng, et al. “Physiological Content and Intrinsic Activities of 10 Cytochrome P450 Isoforms in Human Normal Liver Microsomes.” The Journal of Pharmacology and Experimental Therapeutics, vol. 358, no. 1, July 2016, pp. 83–93, https://doi.org/10.1124/jpet.116.233635. Accessed 9 July 2020.
10. Jongejan, Aldo, et al. “The Role and Application of in Silico Docking in Chemical Genomics Research.” Methods in Molecular BiologyTM, 2005, pp. 63–91, https://doi.org/10.1007/978-1-59259-948-6_5. Accessed 1 Dec. 2021.
11. Liu, Xingjie, et al. “Metabolic Behavior Prediction of Pazopanib by Cytochrome P450 (CYP) 3A4 by Molecular Docking.” European Journal of Drug Metabolism and Pharmacokinetics, vol. 41, no. 4, Springer Science+Business Media, Mar. 2015, pp. 465–68, https://doi.org/10.1007/s13318-015-0252-y. Accessed 12 Aug. 2023.
12. Manikandan, Palrasu, and Siddavaram Nagini. “Cytochrome P450 Structure, Function, and Clinical Significance: A Review.” Current Drug Targets, vol. 19, no. 1, Jan. 2018, https://doi.org/10.2174/1389450118666170125144557.
13. Preuß, Ellen, et al. “Cancer Suicide Gene Therapy with TK.007: Superior Killing Efficiency and Bystander Effect.” Journal of Molecular Medicine, vol. 89, no. 11, June 2011, pp. 1113–24, https://doi.org/10.1007/s00109-011-0777-8. Accessed 27 Mar. 2022.
14. Sankar, Kamya, et al. “Molecular Therapeutic Targets in Non-Small Cell Lung Cancer.” Expert Review of Anticancer Therapy, vol. 20, no. 8, July 2020, pp. 647–61, https://doi.org/10.1080/14737140.2020.1787156. Accessed 13 Sept. 2020.
15. Trott, Oleg, and Arthur J. Olson. “AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization, and Multithreading.” Journal of Computational Chemistry, vol. 31, no. 2, 2009, p. NA-NA, https://doi.org/10.1002/jcc.21334.
16. Yang, Zheng, and Kin Yip Tam. “Combination Strategies Using EGFR-TKi in NSCLC Therapy: Learning from the Gap between Pre-Clinical Results and Clinical Outcomes.” International Journal of Biological Sciences, vol. 14, no. 2, 2018, pp. 204–16, https://doi.org/10.7150/ijbs.22955. Accessed 26 Dec. 2020.