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In Silico Screening of Multi-Domain Targeted Inhibitors for PTK6: A Strategy Integrating Drug Repurposing and Consensus Docking

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A. Article Info

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Abstract: Protein tyrosine kinase 6, or BRK, is an intracellular tyrosine kinase that does not bind to receptors and is a member of the Src kinases family. Similar to other Src kinases, PTK6 has three domains: SH3, SH2, and SH1, which are responsible for tyrosine kinase activity. Despite extensive research into developing PTK6 inhibitors that specifically target the SH1 domain—the part of the protein that is involved in kinase activity across several pathways—it has been shown that this region alone is insufficient to limit PTK6 activity. Research that followed established that PTK6's SH2 and SH3 domains play an essential role in substrate binding and intramolecular interactions. As a result, it is critical to find PTK6 inhibitors that target both the SH1 and SH2 and SH3 domains. Our in silico structural-based virtual screening method, which includes drug repurposing and a consensus docking technique, has yielded four ligand candidates that can inhibit PT6K's tyrosine kinase domain and SH2/SH3 domains at the same time. This discovery raises the possibility of new avenues for therapeutic therapies involving the suppression of PTK6.

Keywords: PTK6; drug repurposing; consensus docking; structure based virtual screening; in silico studies

1. Introduction

For epithelial tissues, protein tyrosine kinase 6 (PTK6) is an intracellular signal transducer [4]. It is sometimes called breast tumor kinase (BRK) [1-3]. Some low-level breast cancers have been shown to include BRK, and when this gene is overexpressed, cells undergo partial phenotypic transformation because they are more susceptible to epidermal growth factor [5]. There are structural similarities between PTK6 and other Src kinases, including the presence of an SH3 domain, an SH2 domain, and a SH1 tyrosine kinase domain [6] (Figure 1). Although a lot of work has gone into developing SH1 domain inhibitors because of its kinase activity in many pathways [7-9], newer research has shown that PTK6 has complicated context-specific activities in certain malignancies and acts independently of kinases [10,11]. The SH2 domain improves protein-protein recognition and interactions and binds to substrate phosphotyrosine motifs, according to further research [12,13]. Phosphorylated Tyr447-SH2 interaction, Trp44 in the SH3 domain, and Pro177, Pro175, and Pro179 in the N-terminal half of the Linker region all contribute significantly to the protein's inactive conformation [13–15]. It is essential to target SH2 and SH3 domains in addition to the SH1 domain, according.

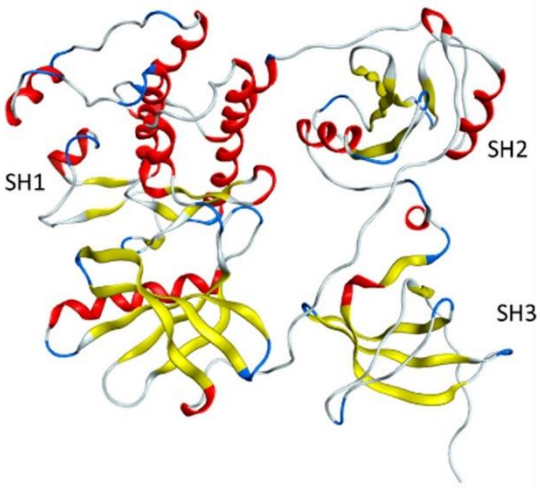

Figure 1. Structure of full PTK6 protein, encompassing an Src homology 3 (SH3) domain, an Src homology 2 (SH2) domain, and a tyrosine kinase domain (SH1).

We searched for possible PTK6 inhibitors in our computational analysis by integrating a medication repurposing technique with consensus docking. There are a number of steps involved in the conventional method of drug discovery and development. One cutting-edge method for finding new therapeutic applications for already-existing pharmaceuticals while significantly improving the development timeframe is medication repurposing, often called drug repositioning. The medication repurposing technique has several benefits. To begin with, this method drastically cuts down on drug development time as the formulation and preclinical safety of repurposed pharmaceuticals have already been established. Second, compared to traditional medication development methods, drug repurposing requires a smaller initial cost. A repurposed medicine incurs much lower expenses throughout preclinical research as well as phases I and II. Thirdly, and most critically, prior clinical studies have shown that the repurposed medicine is relatively safe, which means that failure rates related to safety concerns may be significantly decreased. So, in recent years, drug repurposing—which is finding new uses for old medications—has emerged as an attractive approach for a more efficient and cost-effective method to find novel medicines [16–18]. You may accomplish repurposing via a methodical strategy or by experimenting. To provide a more logical and organized method to medication repurposing, we used a structure-based virtual screening technique in this study. So, in order to screen against the three-dimensional structure of the PTK6 protein, a virtual library consisting of 2016 FDA-approved medicines was used. Computational "docking" of ligands into target protein binding sites was accomplished by molecular docking, a procedure that entails docking ligands into the binding site of a specific receptor and computing binding affinities based on the binding posture and conformation. But it's not easy to forecast the right binding position and figure out the right binding affinities. Drug repurposing predictions are very susceptible to inaccurately anticipated binding poses and affinities. The scoring techniques used to determine binding affinities and the placement strategies used to forecast docking poses/formations vary between docking software packages. Consequently, we used a consensus docking strategy that comprises merging the outcomes of many docking simulations. Improving the precision and consistency of forecasts is the goal of this method. Given the existing dearth of effective PTK6 inhibitors, our approach takes on further significance in this context. Relying on a single scoring algorithm is risky because, as many studies have pointed out, scoring accuracy is dependent on docking precision [19,20]. This highlights the significance of taking into account the various docking placement methods and scoring functions used by different docking methods. Therefore, in our structural virtual investigation, we used a consensus docking method.

Using a therapeutic repurposing technique, we set out to find leads that may target the SH1, SH2, and SH3 domains of the PTK6 protein, among others. Our research relied on a consensus docking strategy to enhance prediction accuracy, and it was based on a virtual screening procedure that was dependent on the complex features of the PTK6 protein structure. We have discovered four possible ligands that may inhibit the kinase activities of PTK6. These compounds show inhibitory capacities toward both the SH1 and SH2/SH3 domains concurrently, which is a viable therapeutic strategy.

2. Results and Discussion

2.1. SH1 Domain Virtual Screening

A total of 100 top-ranked ligands from DRDOCK drug repurposing [21] were docked into the PTK6 SH1 domain [6] using Autodock Vina [22,23], DockingPie [24] and MOE [25]. Out of 100 ligands, 20 ligands with the best scores were selected from each docking software. By comparing the top 20 ligands from each set, nine consensus ligands were identified to be top-ranked for all sets, namely Regorafenib, Vx-661, Indacaterol, Vemurafenib, Camptothecin, 10-hydroxycamptothecin, Niraparib, Yohimbine, and Meloxicam, with docking scores ranging from −9.07 to −10.05 kcal/mol (Table 1). The PTK6 in crystal structure 6CZ3 bound to the ligand (3-fluoro-4-{[6-methyl-3-(1H-pyrazol-4-yl)imidazo [1,2-a]pyrazin-8-yl]amino}phenyl)(morpholin-4-yl)methanone with key residues Leu16, Met86 and Asp149. All nine ligands were identified to bind to the SH1 domain at the same site through CH–π and hydrogen bonding (HB) interactions. The original ligand in 6CZ3 binds to the PTK6 receptor at Leu16, Met86, Arg135 and Asp149. Our identified ligands bind to the PTK6 receptor with the same amino acid residues with additional interactions detected involving Ser18, Val24, Thr83, Glu84, Ser90 and Asn136. Figure 2 illustrates the binding of the ligand Meloxicam to the SH1 domain via CH–π interactions with residues Val24 and Ser90 as well as hydrogen bond (HB) interactions with residues Glu84, Arg135 and Asp149.

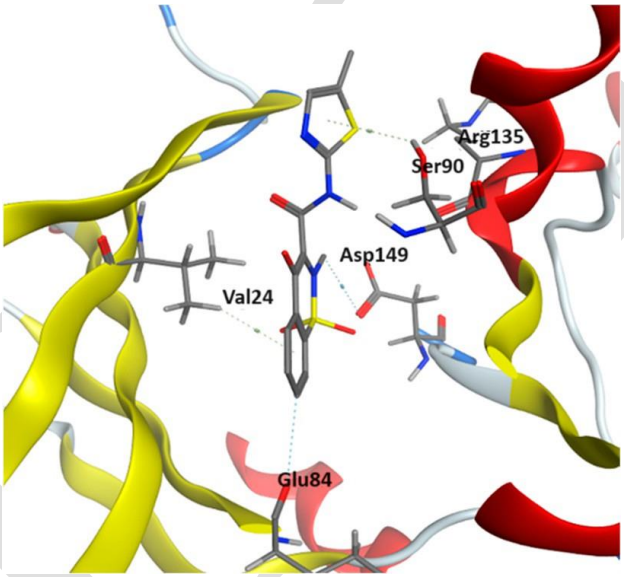

Figure 2. Structure of ligand Meloxicam docked to PTK6 kinase SH1 domain in MOE, showing CH–π interactions with Val24 and Ser90, and HB interactions with Glu84, Arg135 and Asp149.

The highest ranked ligand Indacaterol binds to the PTK6 SH1 domain at amino acid residues Ser18, Leu16 and Thr83 via CH–π and hydrogen bonding interactions with a binding affinity of −10.05 kcal/mol. The second-ranked ligand 10-hydroxycamptothecin binds to the receptor at amino acid residues Val24, Arg135 and Asp149 via CH–π and hydrogen bonding interactions with a binding affinity of −10.03 kcal/mol. As for the third-ranked

ligand Regorafenib, it binds to the PTK6 SH1 domain at Val24 and Met86 via similarly CH–π and hydrogen bonding interactions with −9.74 kcal/mol in binding affinity.

Table 1. Consensus ligands bind to SH1 domain, interactions with receptor residues and corresponding docking scores (kcal/mol).

Ligands	Interaction	Receptor Residues	Autodock Vina	DockingPie	MOE
Regorafenib	CH–π	Val24	−9.74	−8.81	−7.85
	HB	Met86			
Vx-661	CH–π	Ser90	−9.39	−9.33	−7.93
	HB	Ser18, Thr83, Ser90			
Indacaterol	CH–π	Ser18	−10.05	−9.92	−7.53
	HB	Leu16, Thr83			
Vemurafenib	CH–π	Val24	−9.07	−9.46	−7.39
	HB	Ser90			
Camptothecin	CH–π	Val24	−9.23	−9.31	−6.95
	HB	Asp149			
10-hydroxy-camptothecin	CH–π	Val24	−10.03	−9.51	−7.16
	HB	Arg135, Asp149			
Niraparib	CH–π	Val24	−9.62	−9.13	−7.21
	HB	Glu84, Asn136			
Yohimbine	CH–π	Leu16	−9.53	−9.17	−7.23
	HB	Asn136, Asp149			
Meloxicam	CH–π	Val24, Ser90	−9.59	−8.76	−7.11
	HB	Glu84, Arg135, Asp149			

2.2. SH2 Domain Virtual Screening

The binding location for the SH2 domain [26] was detected using the web-based service CavityPlus [27], as it is not well characterized in the literature. The residues 74–78 were chosen as the target location for drug repurposing using DRDOCK, utilizing cavity information from CavityPlus as a basis. Utilizing Autodock Vina, DockingPie, and MOE, the top 100 ligands from DRDOCK were docked into the PTK6 SH2 domain. Twenty of the highest-scoring ligands were chosen for each docking program out of one hundred. The following 13 consensus ligands were identified as having the highest docking scores across all sets: Leucovorin, Lifitegrast, Lumacaftor, 1370468-36-2, Zafirlukast, Fluralaner, Telmisartan, Nintedanib, Azilsartan Medoxomil, Daclatasvir, Aclacinomycin A, Epirubicin, and Doxorubicin (Table 2).

Out of the thirteen ligands, two, Fluralaner and Telmisartan, attached to the PTK6 SH2 domain by hydrophobic interactions; the other twelve ligands were found to attach to the SH2 domain through CH-π and hydrogen bonding (HB) relations. It was discovered that the binding of ligands into the PTK6 SH2 domain is facilitated by certain receptor amino acid residues: Pro03, Tyr40, Val50, Tyr53, Lys54, Arg5, Leu74, Pro75, and Asn79. Liquid Daclatasvir bound to SH2 domain by HB interactions with Asn79 and Pro75, as shown in Figure 3.

Table 2. Consensus ligands bind to SH2 domain, detailing their interactions with receptor residues and corresponding docking scores (kcal/mol).

Ligands	Interaction	Receptor Residues	Autodock Vina	DockingPie	MOE
Leucovorin	CH–π	Pro75	−8.61	−7.16	−6.38
	HB	Tyr40, Arg57, Asn79			
Lifitegrast	CH–π	Tyr40	−9.81	−8.63	−6.53
	HB	Leu74, Arg57, Asp39			
Lumacaftor	HB	Pro3, Val78	−9.58	−8.87	−5.56
1370468-36-2	CH–π	Pro75	−8.96	−9.15	−7.38
	HB	Leu74			
Zafirlukast	HB	Pro3, Glu2, Gly7	−9.07	−7.97	−6.51
Fluralaner	Hyd Int [1]		−9.01	−7.86	−6.59
Telmisartan	Hyd Int [1]		−8.89	−8.79	−6.28
Nintedanib	CH–π	Phe5	−8.41	−8.21	−6.82
	HB	Pro75			
Azilsartan Medoxomil	HB	Ser73	−8.54	−7.24	−6.37
Daclatasvir	HB	Pro75, Asn79	−8.97	−8.03	−7.01
Aclacinomycin A	HB	Val50, Tyr53, Lys54	−7.89	−6.94	−6.54
Epirubicin	HB	Lys54	−7.86	−7.03	−5.95
Epirubicin	HB	Lys54	−7.86	−7.03	−5.95
Doxorubicin	CH–π	Tyr53	−8.09	−6.85	5.46
	HB	Lys54, Ser87			

[1] hydrophobic interaction.

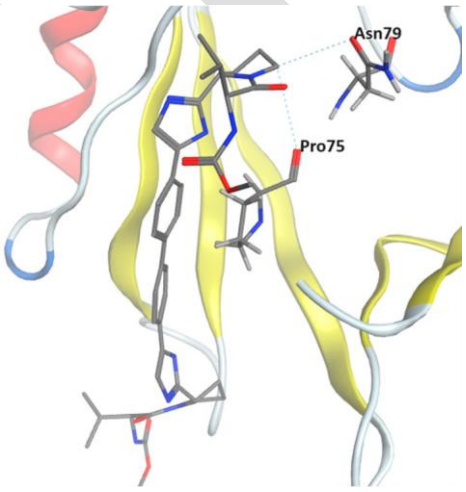

Figure 3. Structure of lead ligand Daclatasvir bound to PTK6 kinase SH2 domain in MOE, showing HB interactions with Pro75 and Asn79.

The top-ranked ligand Lifitegrast binds to the PTK6 SH2 domain through CH–π and hydrogen bonding interactions at amino acid residues Tyr40, Leu74, Arg57 and Asp39, with a binding affinity of −9.81 kcal/mol. In contrast, the second-ranked ligand Lumacaftor, with a binding affinity of −9.58 kcal/mol, lacks the CH–π interaction, but it binds to the receptor at amino acid residues Pro3 and Val78 via hydrogen bonding interactions. The third-ranked ligand, Zafirlukast, binds to the PTK6 SH2 domain at Pro3, Glu2 and Gly7

via hydrogen bonding interactions with −9.74 kcal/mol in binding affinity. Similar to Lumacaftor, Zafirlukast also lacks the CH−π interaction.

2.3. SH3 Domain Virtual Screening

Concerning the SH3 domain [28], given the lack of well-defined binding sites in the literature, web-based server CavityPlus was utilized to identify potential binding sites. However, all three detected binding cavities exhibited weak drug score and druggability. Since there are no common ligands that bind with both the SH1 and SH2 domains, the 100 top-ranked ligands with the SH3 domain from DRDOCK were compared with consen- sus ligands from the SH1 and SH2 domains, respectively. Five ligands were identified to bind to both the SH1 and SH3 domains, namely Regorafenib, Vemurafenib, Vx-661, 10-hydroxycamptothecin, and Yohimbine (Figure 4). Additionally, five ligands were found to bind to both the SH2 and SH3 domains, namely Aclacinomycin A, Epirubicin, Zafirlukast, Telmisartan, and Daclatasvir (Figure 4). The docking scores of these 10 ligands with the SH3 domain calculated using MOE are listed in Table 3. In Figure 5, the illustration depicts the binding of the ligand Zafirlukast to the PTK6 kinase SH3 domain via CH−π interactions with Lys12 and Thr72, and HB interactions with Met01 and Gln06.

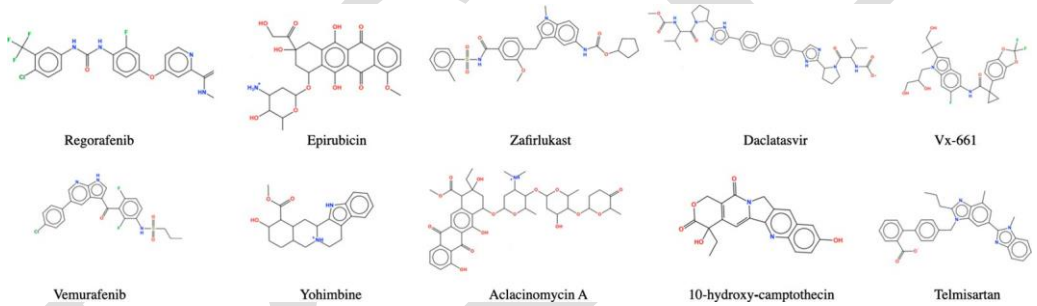

Figure 4. The top 10 ligands identified through consensus docking.

Table 3. Ligands bind to the SH3 domain, detailing their interactions with receptor residues and corresponding docking scores (kcal/mol).

Ligands	Receptor Resides	MOE Score
Regorafenib	Glu69	−6.67
Vemurafenib	Met01, Lys12	−6.66
Vx-661	Lys12	−7.45
10-hydroxy-camptothecin	no interactions detected	−5.95
Yohimbine	Trp45	−5.96
Aclacinomycin A	Met01, Lys12	−8.62
Epirubicin	Met01, His08, Lys12	−7.04
Zafirlukast	Met01, Gln06, Lys12, Thr72	−7.08
Telmisartan	Met01, Lys12	−7.27
Daclatasvir	Ser03, Pro11, Lys12, Arg70, Thr72	−7.98

With a binding affinity of -8.62 kcal/mol, Aclacinomycin A is the top-ranked ligand. Having said that, its binding affinity is limited to only two SH3 domain amino acids. Daclatasvir, the ligand ranked second, binds to the PTK6 SH3 domain with the highest number of amino acid residues, with a binding affinity of −7.98 kcal/mol. The total binding score is determined by the combined contributions of Ser03, Pro11, Lys12, Arg70, and Thr72. Epirubicin, Zafirlukast, and Telmisartan bind to the PTK6 SH3 domain with amino acid residues Met01, Gln06, His08, Lys12, and Thr72, respectively. Their binding affinities are -7.04 kcal/mol, -7.02 kcal/mol, and 7.27 kcal/mol, as shown in Figure 6.

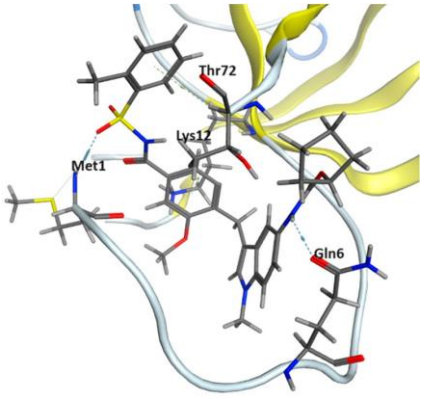

Figure 5. Ligand Zafirlukast bound to the PTK6 kinase SH3 domain in MOE, showing CH–π interactions with Lys12 and Thr72 as well as HB interactions with Met01 and Gln06.

2.4. Full Protein Docking

Finally, molecular docking with the full PTK6 protein using MOE was performed for the top 10 lead ligands (Figure 4) to validate their binding preferences across multiple domains. The top-ranked 15 poses were analyzed for each ligand. The binding scores and domains of the 10 ligands are listed in Table 4. Epirubicin (Figure 6A) and Regorafenib (Figure 6B) demonstrated binding to the SH1 and SH3 domains, while Zafirlukast (Figure 6C) exhibited binding to the SH2 and SH3 domains. Intriguingly, Declatasvir (Figure 6D) displayed binding to all three domains with similar binding scores. These four ligands capable of binding to multiple domains exhibited the best binding scores. On the other hand, VX-611, Vemurafenib, and Yohimbine showed binding at the center of the protein with moderate binding scores only, indicating a lesser preference toward the full protein. Aclacinomycin A and 10-hydroxycamptothecin, despite high binding scores for full protein binding, tend to bind solely to the SH1 domain only, which is contrary to our goal to target multiple domains. Telmisartan bound exclusively to SH3, yielding a less favorable binding score.

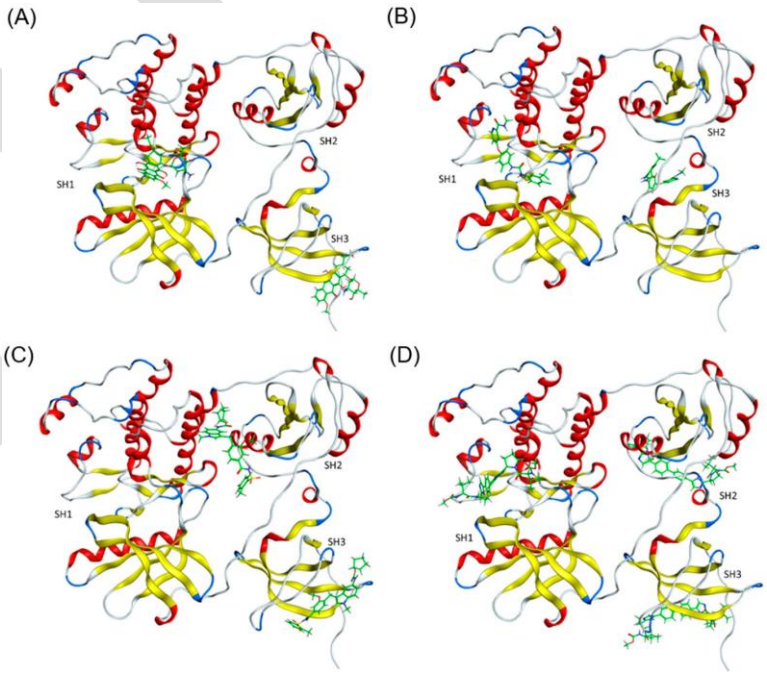

Figure 6. Lead ligands bound to multiple domains. (**A**) Epirubicin bound to SH1 and SH3 domains. (**B**) Regoragenib bound to SH1 and SH3 domains. (**C**) Zafirlukast bound to SH2 and SH3 domains (**D**) Declatasvir bound to SH1, SH2 and SH3 domains.

Table 4. MOE binding scores (kcal/mol) of lead ligands bind to multiple domains of PTK6.

Ligands	SH1 Domain	SH2 Domain	SH3 Domain
Regorafenib	−7.33	NA	−5.87
Epirubicin	−6.48	NA	−5.96
Zafirlukast	NA	−6.42	5.91
Daclatasvir	−6.39	−6.41	−6.57
Vx-661		−6.11 [1]	
Vemurafenib		−5.98 [1]	
Yohimbine		−5.15 [1]	
Aclacinomycin A	−6.84	NA	NA
10-hydroxy-camptothecin	−6.51	NA	NA
Telmisartan	NA	NA	−6.05

[1] Bind at the center of protein.

To review, four ligands showed a strong bias towards binding to numerous domains that had positive ratings (Table 4). In particular, the SH1 domain is bound to by Epirubicin with a binding value of -6.48 kcal/mol, whereas the SH3 domain is bound to by Regorafenib with a binding score of -7.33 kcal/mol. At a binding score of -6.42 kcal/mol, Zafir-lukast binds to the SH2 and SH3 domains, but Declatasvir binds to all three domains at -6.57 kcal/mol. Using a combination of medication repurposing and consensus docking approaches for structure-based virtual screening, our findings show that multi-domain targeted inhibitors for PTK6 may be successfully predicted. Regorafenib is an orally given kinase inhibitor that has anti-angiogenic effects by inhibiting the VEGFR2-TIE2 tyrosine kinase. Hepatocellular carcinoma, advanced gastrointestinal stromal tumors, and metastatic colorectal cancer are some of the conditions that this medicine is used to treat [29]. One way that epirubicin, an anthra-cycline topoisomerase II inhibitor, fights cancer is by interfering with DNA synthesis and its functions. To treat axillary node metastases in individuals who have had primary breast cancer surgically removed, it is used as an adjuvant [30]. As an oral leukotriene receptor antagonist (LTRA), zafirlukast prevents cysteinyl leukotrienes from binding to CysLT1 receptors. Asthma maintenance therapy makes use of this medication [31]. Daclatasvir is an antiviral medication that targets the cis and trans-acting activities of NS5A. It is effective against Hepatitis C Virus (HCV). It interferes with the creation of new HCV replication complexes by changing the phosphorylation state of NS5A. For long-term HCV genotype 1 or 3 infections, daclatasvir is the drug of choice [32].

Protein tyrosine kinase 6, a member of the Src kinase family, is composed of three domains: SH3, SH2, and SH1, which are necessary for tyrosine kinase activity. PTK6 is not a receptor intracellular kinase. It has been shown that breast cancer cells may continue to multiply even when PTK6 phosphorylation is blocked and rendered inactive, allowing the SH2 and SH3 domains to connect with other substrates. Despite extensive research into developing PTK6 inhibitors that specifically target the SH1 domain—the part of the protein that is involved in kinase activity across several pathways—it has been shown that this region alone is insufficient to limit PTK6 activity. Intramolecular and substrate binding interactions are crucial to PTK6's activity, and further research has shown that SH2 and SH3 domains are involved in these processes. The possibility remains that cancer cell growth might be aided by free SH2 and SH3 domains. As a result, finding PTK6 inhibitors that completely block PTK6 function requires drugs that target the SH1 domain as well as those that interact with the SH2 and SH3 domains. To better control the ability of cancer cells linked to abnormal PTK6 activity to proliferate, a comprehensive strategy is required. The four ligands that were found here have great potential as inhibitors that target many domains.

3. Materials and Methods

3.1. Potential Binding Sites of SH2 and SH3 Domains Using CavityPlus

The SH2 and SH3 domains of PTK6 do not include any information on ligand binding or cavities, in contrast to the SH1 domain of the tyrosine kinase. We first identified possible binding cavities for SH2 and SH3 domains using a web-based system called CavityPlus [27] before we started ligand docking. Chain A was chosen, the ligand-free mode was activated, and other settings were left as default when using the CavityPlus web server to upload the PDB structures of SH2 (1RJA) [26] and SH3 (2KGT) [28]. Using drug score and druggability, four cavities were identified in the SH2 domain. The next docking stages will be conducted in the highest-ranked cavity, #1. Similarly, three cavities were identified in the SH3 domain and graded according to drug score and druggability. The top-ranked cavity, #1, was selected for the next docking step.

3.2. Docking with Medications Approved by the FDA

DRDOCK is a web-based service that allows users to virtually test medications that were authorized by the FDA in 2016 against a protein target that they provide [21]. Note that the top 100 medicines evaluated by DRDOCK performed the best, suggesting that these are the genuine binders [21]. The medications that were authorized by the FDA in 2016 were gathered from two sources: the FDA-authorized Drug Library (Version 1.5) and the MedChemExpress (MCE) FDA-Approved Drug Library (Cat. No.: HY-L022). In told, this library contains 2016 different small molecule medicines. Taking into account the protonation states of ionizable groups at pH = 7, structures representing these small molecule medicines were generated using BIOVIA Discovery Studio [33]. To facilitate drug docking, AutoDock Tools [34] was used to create the input PDBQT files. For docking purposes, chain A was used when submitting PDB file 6CZ3 [10] for SH1. The target location was determined to be residues 85–91. The docking file for SH2 was 1RJA in PDB format, with chain A chosen. We chose to focus on residues 74–78 since they were identified by CavityPlus. In the same way, for SH3, we used PDB file 2KGT, chose chain A for docking, and targeted residues 36–40 based on what we found in CavityPlus. Using a new drug ranking system called log-odds (LOD) scores, which include the feature distributions of real binders and decoys—including docking affinity, contact number, distance to target site, cluster size, and number of clusters—we rated the docking data for each domain. After that, further consensus docking analysis was performed on the top one hundred medicines.

Section 3.3: Docking Consensus

For consensus docking, three docking methods—Autodock Vina [22,23], DockingPie [24] and Molecular Operating Environment (MOE) [25]—were used to identify the top 100 ligands from DRDOCK for SH1 and SH2 domains. Autodock Vina's ligand and receptor preparation was carried out using Autodock Tools 1.5.4 [34]. Atoms were given Gasteiger charges and protonated hydrogen atoms after water molecules and other heteroatoms were eliminated, and the size of the grid box was adjusted to 60 Å. OpenBabel 2.3.0 was used to build PDBQT files containing the structures of the ligands [35]. The same files were used for five iterations of repetitive docking with ten postures each in Autodock Vina and Dock-ingPie. To facilitate docking with MOE, a library including the 100 ligands with the highest rankings from DRDOCK was produced. In order to forecast poses and scores, the library was docked using the Triangle Matcher placement technique, and rescoring was carried out using the GBVI/WSA dG scoring program [36,37]. We examined the top 20 ligands from both sets and showed the docking results for each approach. Ten consensus ligands were found for the SH1 domain and thirteen for the SH2 domain after the comparison. To find the ten lead ligands that bind to numerous domains in the SH3 domain, we compared the top 100 ligands from DRDOCK with the ligands set from the SH1/SH2 domains.

Complete Docking with MOE (3.4)

Lastly, the binding conformations of the 10 lead ligands determined by consensus docking were examined by docking them into the whole PTK6 protein. We used the Alphafold Protein Structure Database, more particularly UniProt Q13882, to get the structure of the PTK6 protein as its full crystallized form is not yet known. The placement technique was chosen as triangle matcher, and the binding score was predicted using the GBVI/WSA dG rescoring tool. To determine binding-domain preference, we looked at the fifteen best postures for each ligand. We used the MOE user-graphical interface to undertake ligand-receptor interaction analysis.

4. Conclusions

Consensus docking was used to digitally screen a set of 2016 FDA-approved medicines for possible lead ligands. By making use of the abundance of already collected data on the pharmacokinetics, pharmacodynamics, and safety of medications that have already been authorized by the FDA, this approach simplifies and expedites the drug development process. After the structure-based virtual screening, the best ligands were further optimized using a consensus docking strategy that included the Autodock Vina, Docking-Pie, and MOE docking techniques. The rankings collected from each docking program were used to make the final decision. By combining these methods, we were able to find ten repurposed medications that had a strong binding affinity for the PTK6 protein and were thus authorized by the FDA. Epirubicin, Regorafenib, Zafirlukast, and Declatasvir were the four medications found after extensive complete protein docking validation. These drugs bind to many domains of the PTK6 protein at the same time, which is rather amazing. To us, this finding suggests exciting new paths for therapeutic therapies including PTK6 inhibition [38]. In addition to advancing targeted treatments for PTK6-related disorders, our results highlight the potential effectiveness of repurposing current medications for new therapeutic applications. Further experimental validation and the potential for more effective therapies targeting this kinase are both made possible by the discovery of numerous ligands that can simultaneously target various domains of PTK6.

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