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

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Abstract: As a non-receptor intracellular tyrosine kinase belonging to the Src kinase family, protein tyrosine kinase 6 (PTK6) is often referred to as breast tumour kinase (BRK).PTK6 has structural similarities with other Src kinases, including a tyrosine kinase domain (SH1), a Src homology 2 (SH2) domain, and a Src homology 3 (SH3) domain.Although a lot of work has gone into creating PTK6 inhibitors that target the SH1 domain, which is in charge of kinase activity in a number of pathways, it has been shown that PTK6 activity cannot be successfully suppressed by only blocking the SH1 domain. The role of SH2 and SH3 domains in intramolecular and substrate binding interactions, which are essential for PTK6 activity, has been shown by further experiments. Therefore, it becomes essential to identify PTK6 inhibitors that target the SH2 and SH3 domains in addition to the SH1 domain. Four putative ligands that may concurrently inhibit the tyrosine kinase domain and SH2/SH3 domains of PT6K have been effectively discovered by an insilicostructural-based virtualscreening technique that incorporates drugre purposing and a consensus docking approach. This discovery raises the possibility of treatment approaches including PTK6 inhibition.

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

1. Introduction

In epithelial tissues, protein tyrosine kinase 6 (PTK6), commonly referred to as breast tumour kinase (BRK) [1–3], serves as an intracellular signal transducer [4].Certain low-level breast tumours have been shown to produce BRK, and cells that overexpress BRK have a partly altered phenotype as a result of their increased sensitivity to epidermal growth factor [5]. PTK6, a member of the Src kinase family, is structurally comparable to other Src kinases, including the atyrosinekinase domain (SH1), the Src homology 3 (SH3) domain, and the Src homology 2 (SH2) domain [6] (Figure 1). Recent investigations have shown that PTK6 works in a kinase-independent manner and has complicated, context-specific activities in some malignancies [10,11], despite the fact that a significant amount of research effort has been directed towards the discovery of inhibitors for the SH1 domain owing to its kinase activity in multiple pathways [7–9]. Additional research showed that the SH2 domain interacts to substrate phosphotyrosine motifs and improves protein-protein interactions and recognition [12,13]. Along with the phosphorylated Tyr447-SH2 interaction, Trp44 in the SH3 domain and Pro177, Pro175, and Pro179 in the N-terminal portion of the Linker region all play significant roles in maintaining an inactive state of the protein [13–15].According to both lines of data, targeting the SH2 and SH3 domains is essential for suppressing PTK6 activity, while blocking the SH1 domain alone is insufficient.

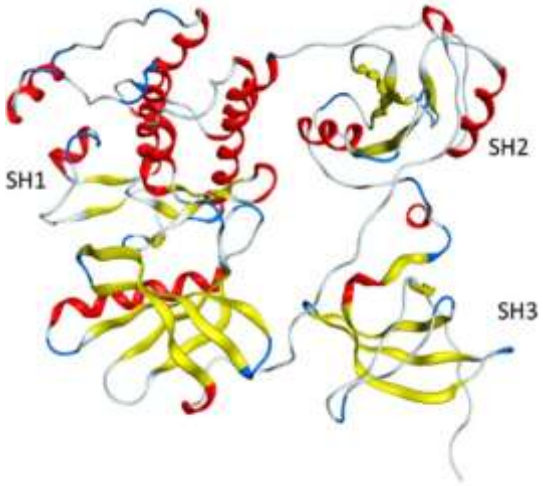


Figure 1. Structure of full PTK6 protein, encompassing an Src homology 3 (SH3) domain, an Src homology 2 (SH2) domain, and a tyrosine kinase domain (SH1).

In this computational investigation, we looked for possible PTK6 inhibitors using an integrated approach of consensus docking and medication repurposing.The effective discovery of a novel medicine requires a number of steps in the standard drug development and discovery process.Drug repurposing, often referred to as drug repositioning, is a cutting-edge method for finding new therapeutic applications for already-approved, clinically utilised medications while significantly accelerating the development schedule.The medication repurposing approach has several benefits.First off, this method significantly cuts down on the amount of time needed for drug development since the formulation and preclinical safety of repurposed medications have been examined and completed. Second, the medication development process requires less money when using the drug-purposing technique.For are-purposed drugs, preclinical and phase I and II expenditures are much lower.Thirdly, and perhaps most critically, the repurposed medicine has been shown in prior clinical studies to be reasonably safe, and the amount of sotherate offailure caused by safety concerns may be significantly decreased. Drug repurposing, which includes finding new uses for already-approved medications, has been shown to be a viable approach for a more effective and economical method to find novel therapies in recent years [16–18]. Repurposing may be accomplished methodically or by trial and error.To provide a more logical and methodical approach to medication repurposing, we used a structure-based virtual screening technique in this study. In order to do this, a virtual library of 2016 FDA-approved medications was employed to screen against the PTK6 protein's three-dimensional structure.Computationally "docking" ligands into the target protein's binding site was done using molecular docking, a technique that includes docking ligands into a specific receptor's binding site and calculating binding affinities based on the binding posture and conformation. However, there are several difficulties in accurately determining the binding affinities and anticipating the proper binding position. The success probability of medication repurposing forecasts may be greatly impacted by inaccurately anticipated binding affinities and binding poses. various docking software solutions use various scoring systems to determine binding affinities and different placement techniques to anticipate docking positions and configurations.As a consequence, we used a consensus docking strategy that combines the outcomes of many docking simulations.The goal of this strategy is to increase forecast accuracy and dependability.This approach is especially pertinent in light of the present dearth of proven PTK6 inhibitors. Several studies emphasise that the precision of the docking process determines the accuracy of scoring, highlighting the need of taking into account the various docking placement techniques and scoring functions used by various docking methods rather than depending only on a particular coring algorithm [19,20].Therefore, in our structure-based virtual investigation, we used a consensus docking technique.In order to find possible leads capable of targeting various domains of the PTK6 protein, namely SH1, SH2, and SH3, we used a pharmacological repurposing technique in our inquiry. In order to increase prediction accuracy, we used a consensus docking strategy in a virtual screening process that depended on the fine features of the PTK6 protein structure.Four possible ligands with simultaneous inhibitory capacities towards the SH1 and SH2/SH3 domains were effectively found by our in silico investigation, indicating a prospective therapeutic strategy to block PTK6's kinase activities.

2. ResultsandDiscussion

SH1DomainVirtualScreening

Using Autodock Vina [22,23], DockingPie [24], and MOE [25], 100 of the best-ranked ligands from DRDOCK drug repurposing [21] were docked into the PTK6 SH1 domain [6]. Twenty ligands with the highest scores out of 100 were chosen from each docking software. Nine consensus ligands—Regorafenib, Vx-661, Indacaterol, Vemurafenib, Camp-tothecin, 10-hydroxycamptothecin, Niraparib, Yohimbine, and Meloxicam—were found to be the highest ranked for all sets after comparing the top 20 ligands from each set. Their docking scores ranged from -9.07 to -10.05 kcal/mol (Table 1). 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 was bound by the PTK6 in crystal structure 6CZ3 with important residues Leu16, Met86, and Asp149. It was discovered that all nine ligands attach to the SH1 domain at the same location via hydrogen bonding (HB) and CH–π interactions. The PTK6 receptor is bound by the original ligand in 6CZ3 at Leu16, Met86, Arg135 and Asp149.With the same amino acid residues, our discovered ligands bind to the PTK6 receptor; other interactions involving Ser18, Val24, Thr83, Glu84, Ser90, and Asn136 were also found. Figure 2 shows how the ligand Meloxicam binds to the SH1 domain by hydrogen bond (HB) interactions with residues Glu84, Arg135 and Asp149, as well as CH–π interactions with residues Val24 and Ser90.

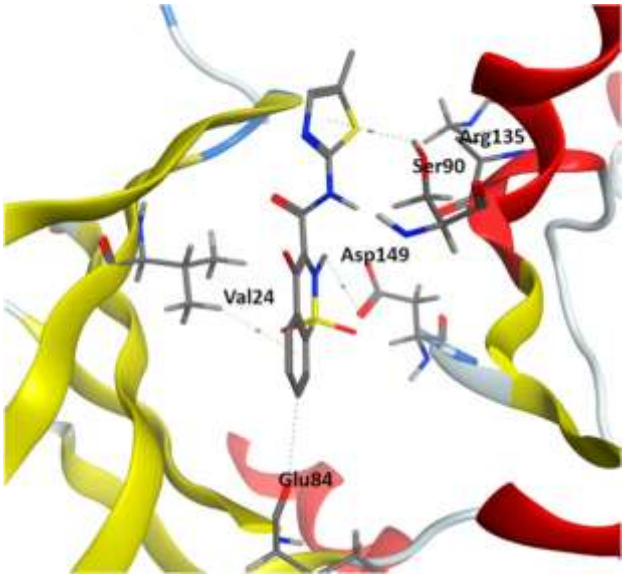


Figure 2. Structure of ligand Meloxicam docked to PTK6 kinase SH1 domain in MOE, showing CH–π interactions with Val24 and Ser90, and HB interactions with Glu84, Arg135 and Asp149.

With a binding affinity of -10.05 kcal/mol, the top-ranked ligand, indacaterol, interacts 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 -10.03 kcal/mol, the second-ranked ligand, 10-hydroxycamptothecin, attaches itself to the receptor at amino acid residues Val24, Arg135 and Asp149 via CH–π and hydrogen bonding interactions.Regarding the third-ranked With a binding affinity of -9.74 kcal/mol, the ligand Regorafenib interacts to the PTK6 SH1 domain at Val24 and Met86 via hydrogen bonding interactions and CH–π interactions.

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

Ligands	Interaction	ReceptorResidues	AutodockVina	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			
CH–π Val24,Ser90 Meloxicam			−9.59	−8.76	−7.11
	HB	Glu84,Arg135,Asp149			

SH2DomainVirtualScreening

Web-based server CavityPlus [27] was used to identify the binding site for the SH2 domain [26], since the binding site is not well specified in the literature. Using DRDOCK, residues 74–78 were chosen as the target location for medication repurposing based on cavity data from CavityPlus. AutodockVina, DockingPie, and MOE were used to dock the top 100 ligands from DRDOCK into the PTK6 SH2domain. Twenty ligands with the highest scores out of 100 were chosen for each docking program.The top 20 ligands were compared, and 13 consensus ligands—including Leucovorin, Lifitegrast, Lumacaftor, 1370468-36-2, Zafirlukast, Fluralaner, The

top-ranked medications for each set were doxorubicin, telmisartan, nintedanib, azolesartan medoxomil, daclatasvir, acancinomycin A, epirubicin, and doxorubicin. According to Table 2, their docking scores varied from -7.86 to -9.81 kcal/mol. While the remaining 13 ligands were shown to bind to the SH2 domain by CH–π and hydrogen bonding (HB) interactions, fluralaner and telmisartan were the only two that exhibited hydrophobic interactions with the PTK6 SH2 domain. Important amino acid residues from the receptor that have been shown to facilitate ligand binding into the PTK6 SH2 domain include Pro03, Tyr40, Val50, Tyr53, Lys54, Arg5, Leu74, Pro75, and Asn79. Figure 3 illustrates the ligand daclatasvir's HB interactions with the Asn79 and Pro75 residues to bind to the SH2 domain.
Table 2 lists consensus ligands that bind to the SH2 domain, along with information on how they interact with receptor residues and the accompanying docking scores (in kcal/mol).

Ligands	Interaction	ReceptorResidues	AutodockVina	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	HydInt[1]		−9.01	−7.86	−6.59
Telmisartan	HydInt[1]		−8.89	−8.79	−6.28
Nintedanib	CH–π	Phe5	−8.41	−8.21	−6.82
	HB	Pro75			
AzilsartanMedoxomil	HB	Ser73	−8.54	−7.24	−6.37
Daclatasvir	HB	Pro75,Asn79	−8.97	−8.03	−7.01
AclacinomycinA	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]hydrophobicinteraction.

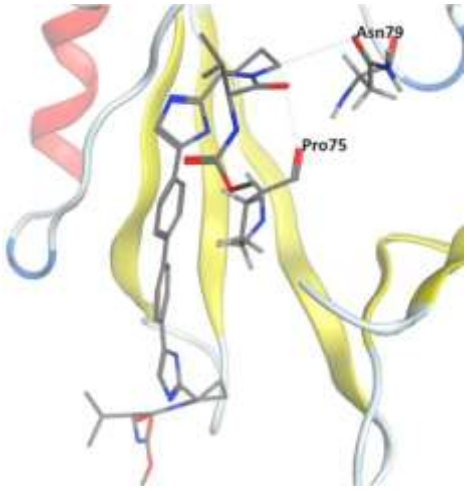


Figure3. StructureofleadligandDaclatasvirboundtoPTK6kinaseSH2domaininMOE,showing HB interactions with Pro75 and Asn79.

With a binding affinity of -9.81 kcal/mol, the top-ranked ligand, lifegrast, binds to the PTK6SH2 domain via CH–π and hydrogen bonding interactions at amino acid residues Tyr40, Leu74, Arg57, and Asp39. However, the CH–πinteraction is absent from the

second-ranked ligand Lumacaftor, which binds to the receptor via hydrogen bonding interactions at amino acid residues Pro3 and Val78. Zafirlukast, the ligand rated third, attaches itself to the PTK6 SH2 domain at Pro3, Glu2, and Gly7. via hydrogen bonding interactions, which have a binding affinity of -9.74 kcal/mol.Zafirlukast does not have the CH–π interaction that Lumacaftor does.Virtual Screening at SH3Domain

The web-based service CavityPlus was used to find possible binding sites for the SH3 domain [28] since there aren't many clearly defined binding sites in the literature. All three of the identified binding cavities, however, showed poor drug-score and drug-ability. The 100 top-ranked ligands with the SH3 domain from DRDOCK were compared with consensus ligands from the SH1 and SH2 domains, respectively, since there are no common ligands that interact with both of them. Five ligands—Regorafenib, Vemurafenib, Vx-661, 10-hydroxycamptothecin, and Yohimbine—were shown to bind to both the SH1 and SH3 domains (Figure 4).Furthermore, five ligands—Aclacinomycin A, Epirubicin, Zafirlukast, Telmisartan, and Daclatasvir—were discovered to bind to both the SH2 and SH3 domains (Figure 4). Table 3 lists the docking scores of these ten ligands with the SH3 domain that were determined using MOE.Figure 5 shows how the ligand Zafirlukast binds to the PTK6kinaseSH3 domain by HB interactions with Met01 and Gln06 and CH–π interactions with Lys12 and Thr72.

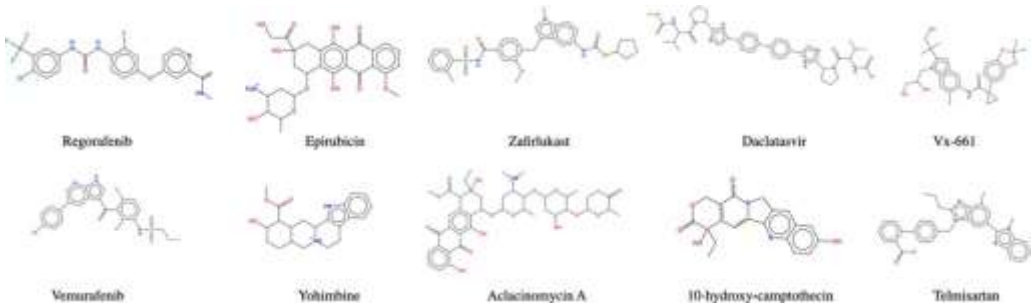


Figure4. Thetop10ligandsidentifiedthroughconsensusdocking.

Table3. Ligands bind to the SH3 domain, detailing their interactions with receptor residues and corresponding docking scores (kcal/mol).

Ligands	ReceptorResides	MOEScore
Regorafenib	Glu69	−6.67
Vemurafenib	Met01,Lys12	−6.66
Vx-661	Lys12	−7.45
10-hydroxy-camptothecin	nointeractionsdetected	−5.95
Yohimbine	Trp45	−5.96
AclacinomycinA	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

Aclacinomycin A, the top-ranked ligand, has a binding affinity of -8.62 kcal/mol. It only binds to two amino acid residues at the SH3 domain, though. With a binding affinity of -7.98 kcal/mol, the second-ranked ligand Daclatasvir binds to the PTK6 SH3 domain with the greatest number of amino acid residues. The total binding score is determined by the combined contributions of Ser03, Pro 11, Lys12, Arg70, and Thr72. With binding affinities of -7.04 kcal/mol, -7.02 kcal/mol, and -7.27 kcal/mol, respectively, epirubicin, zafirlukast, and telmisartan bind to the PTK6SH3 domain with amino acid residues Met01, Gln06, His08, Lys12, and Thr72.

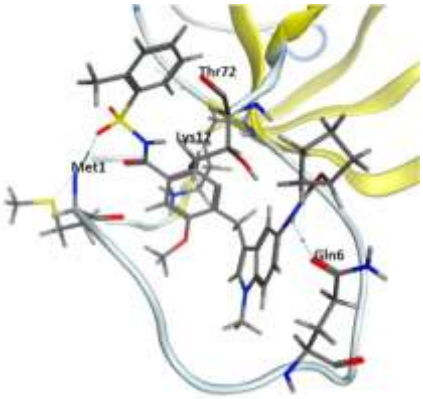


Figure5. LigandZafirlukastboundtothePTK6kinaseSH3domaininMOE,showingCH–π interactions with Lys12 and Thr72 as well as HB interactions with Met01 and Gln06.

FullProteinDocking

Finally, to evaluate the top 10 lead ligands' binding preferences across many domains, molecular docking with the whole PTK6 protein using MOE was carried out (Figure 4).For every ligand, the best 15 postures were examined.Table 4 lists the domains and binding scores of the ten ligands.While Zafirlukast (Figure 6C) showed binding to the SH2 and SH3 domains, epirubicin (Figure 6A) and rogerafenib (Figure 6B) showed binding to the SH1 and SH3 domains.It's interesting to note that Declatasvir (Figure 6D) showed binding to all three domains with comparable binding scores.The best binding scores were shown by these four ligands that could bind to many domains. However, Yohimbine, Vemurafenib, and VX-611 only exhibited modest binding scores in the centre of the protein, suggesting a lower preference for the whole protein. Despite having good binding scores for entire protein binding, aclacinomycin A and 10-hydroxycamptothecin have a tendency to selectively bind to the SH1 domain, which runs counter to our objective of targeting various domains.Telmisartan had a lower binding score because it only bound to SH3.

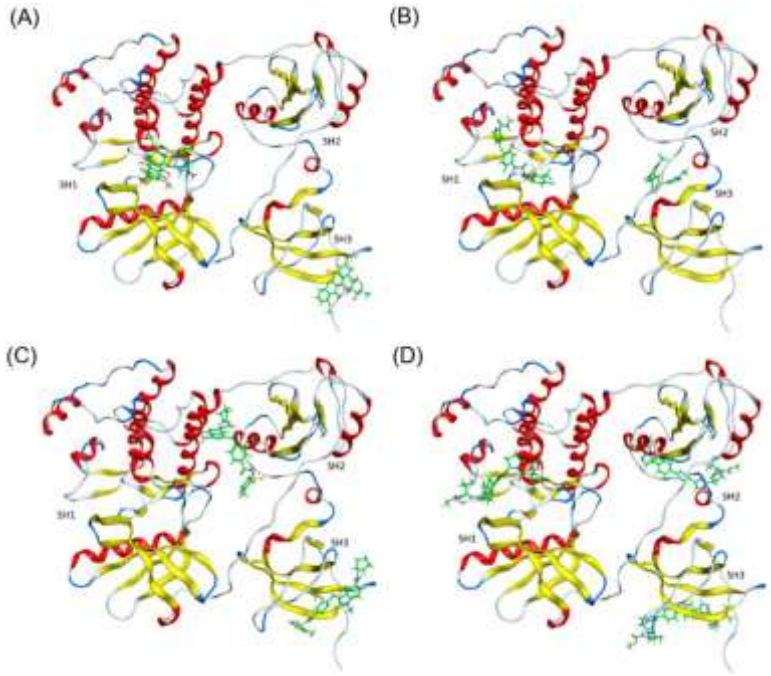


Figure6. Leadligandsboundtomultipledomains.(**A**)EpirubicinboundtoSH1andSH3domains. (**B**)RegoragenibboundtoSH1andSH3domains.(**C**)ZafirlukastboundtoSH2andSH3domains (**D**)DeclatasvirboundtoSH1,SH2andSH3 domains.

Table4.MOEbindingscores(kcal/mol)ofleadligandsbindtomultipledomainsofPTK6.

Ligands	SH1Domain	SH2Domain	SH3Domain
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]	
AclacinomycinA	−6.84	NA	NA
10-hydroxy-camptothecin	−6.51	NA	NA
Telmisartan	NA	NA	−6.05

[1]Bindatthecenterofprotein.

In conclusion, Table 4 shows that four ligands showed a predilection for binding to numerous domains with favourable scores. In particular, the binding scores of epirubicin and regorafenib to the SH1 and SH3 domains are -7.33 kcal/mol and -6.48 kcal/mol, respectively. Declatasvir binds to all three domains with a binding value of −6.57 kcal/mol, while Zafir-lukast exhibits affinity for the SH2 and SH3 domains with a binding score of −6.42 kcal/mol. These findings show that multi-domain focused inhibitors for PTK6 have been successfully predicted using an integrated strategy that combines structure-based virtual screening using consensus docking techniques with medication repurposing.
Through its dual-targeted inhibition of VEGFR2-TIE2 tyrosine kinase, regorafenib has anti-angiogenic efficacy as an oral multiple kinase inhibitor. This medication is used to treat hepatocellular carcinoma, advanced gastrointestinal stromal tumours, and metastatic colorectal cancer [29]. By interfering with DNA synthesis and function, epirubicin, an anthracycline topoisomerase II inhibitor, produces its anticancer effects. For individuals whose original breast cancer has been surgically removed, it acts as an adjuvant in the treatment of axillary node metastases [30]. Zafirlukast inhibits the function of cysteinyl leukotrienes on the CysLT1 receptors and is categorised as an oral leukotriene receptor antagonist (LTRA).This medication is used to treat asthma on a maintenance basis [31]. Daclatasvir is a direct-acting antiviral medication that targets the cis- and trans-acting functionalities of NS5A to combat the Hepatitis C Virus (HCV). It interferes with the operation of new HCV replication complexes by altering the NS5A phosphorylation state. Chronic HCV genotype 1 and 3 infections are treated with daclatasvir [32].
The protein tyrosine kinase 6 (PTK6), a member of the Srckinase family, is composed of three domains: the tyrosine kinase domain (SH1), the Src homology 3 (SH3) domain, and the Src homology 2 (SH2) domain.Breast cancer cells may still multiply if PTK6 phosphorylation is completely blocked and rendered catalytically inactive, allowing the SH2 and SH3 domains to freely interact with other substrates. Although a lot of work has gone into creating PTK6 inhibitors that target the SH1 domain, which is in charge of kinase activity in different pathways, it has been shown that PTK6 activity is not efficiently suppressed by only blocking the SH1 domain. Subsequent research has shown that the SH2 and SH3 domains are involved in intramolecular and substrate binding interactions, which are crucial for PTK6's operation.The growth of cancer cells may still be aided by free SH2 and SH3 domains.Therefore, in order to completely suppress PTK6 activity, it is essential to find PTK6 inhibitors that not only target the SH1 domain but also interact with the SH2 and SH3 domains.This all-encompassing strategy is essential for creating more powerful methods to reduce the proliferative capability of cancer cells linked to abnormal PTK6 activity. The four ligands found here show promise as possible candidates for inhibitors that target several domains.

3. MaterialsandMethods

Possible SH2 and SH3 Domain Binding Sites Using CavityPlus
The PTK6 SH2 and SH3 domains don't provide information on ligand binding and cavities like the tyrosine kinase domain SH1 does.We utilised a web-based system called CavityPlus [27] to find possible binding cavities for SH2 and SH3 domains prior to liganddocking.SH2(1RJA)[26] and SH3(2KGT)[28] PDB structures were submitted to the CavityPlus web server: chainOther settings were set to default, the ligand-free mode was implemented, and A was chosen. Four cavities were found in the SH2 domain, and they were graded according to druggability and drug score. For the next docking stages, cavity #1 with the highest ranking was selected. Similar to this, three cavities were found for the SH3 domain and rated according to drug scores and druggability; the top-ranked cavity #1 was selected for the subsequent docking **step.Using FDA-approved medications**
A web-based system called DRDOCK was created to virtually analyse 2016 FDA-approved medications against a user-submitted protein target [21]. It's important to note that the DRDOCK performance evaluation showed that the genuine binders are among the top 100 medicines that were looked at [21]. The 2016 FDA-approved medications were from the MedChemExpress (MCE) FDA-Approved Drug Library (Cat. No.: HY-L022) and the Screen-Well® FDA-Approved Drug Library (Version 1.5) of Enzo Life Sciences, Inc. (Farmingdale, NY, USA).This collection contains a total of 2016 small-molecule medications. These small-molecule medications were shown using structures made using BIOVIA Discovery Studio [33], taking into account the ionisable groups' protonation states at pH = 7.AutoDock Tools was used to create the PDBQT input files for drug docking [34]. Chain A was chosen for docking when PDB file 6CZ3 [10] was submitted for SH1. The target location was determined to be residues 85–91. With chainAselectedfordocking, PDB file 1RJA was submitted for SH2.As the target location, residues 74–78 that were found in CavityPlus were chosen.Likewise, for SH3, PDB file 2KGT was uploaded, with residues 36–40 that were found in CavityPlus chosen as the target location and chainA chosen for docking. Log-odds (LOD) scores incorporating feature distributions of genuine binders and decoys, such as docking affinity, contact number, distance to target site, cluster size, and

number of clusters, were used to rank the docking data for each domain using the innovative drug ranking technique. The top 100 medications were then selected for further consensus docking analysis.Consensus Docking
The top 100 ligands for the SH1 and SH2 domains from DRDOCK were chosen for consensus docking using three distinct docking techniques: Molecular Operating Environment (MOE) [25], DockingPie [24], and AutodockVina [22, 23]. Autodock Tools 1.5.4 [34] was used to prepare the ligands and receptors for Autodock Vina.The grid box size was set to 60 Å, water molecules and other heteroatoms were eliminated, hydrogen atoms were protonated, and atoms were given Gasteiger charges. OpenBabel 2.3.0 was used to build PDBQT files of ligand structures [35]. The same prepared files were utilised for five runs of repetitive docking with ten postures each for Autodock Vina and DockingPie. A library of the top 100 ligands from DRDOCK was produced via fordocking using MOE.To forecast poses and scores, rescoring was done using the GBVI/WSA dG [36,37] scoring algorithm after docking with the library using the Triangle Matcher placement approach. The top 20 ligands from each set were compared after the docking results for each approach were displayed.Following the comparison, 13 consensus ligands were found for the SH2 domain and 10 for the SH1 domain.Ten lead ligands that bind multiple domains were found in the instance of the SH3 domain by comparing the top 100 ligands from DRDOCK with the collection of ligands from the SH1/SH2 domains.Complete Docking with MOE
In order to verify their binding conformations, the ten lead ligands found using consensus docking were lastly docked into the whole PTK6 protein.Since the whole PTK6 protein does not yet have a known crystal structure, we obtained the structure from UniProt Q13882 in the Alphafold Protein Structure Database. The GBVI/WSA dG rescoring function was employed to estimate the binding score, and triangle matcher was chosen as the placement technique. Each ligand's top 15 postures were examined for binding-domain preference. The MOE user-graphical interface was used to analyse ligand-receptor interactions.

4. Conclusions

Consensus docking was used to digitally screen a set of FDA-approved medications from 2016 in order to find possible lead ligands. This approach streamlines the drug development process, saves time, and lowers complexity by using the abundance of available pharmacokinetic, pharmacodynamic, and safety data from human trials for FDA-approved medications.Autodock Vina, Docking-Pie, and MOE docking technologies were all used in a consensus docking strategy to further refine the top-ranking ligands from the structure-based virtual screening.Individual docking program rankings were used to make the final choice. Ten FDA-approved medications that have been repurposed and show encouraging binding affinity for the PTK6 protein were found using this integrated method. Four medications—Eprerubicin, Regorafenib, Zafirlukast, and Declatasvir—were shown to have an exceptional capacity to bind to numerous PTK6 protein domains at the same time after extensive whole protein docking validation. We think that this finding may lead to novel treatment approaches that include PTK6 inhibition [38]. These results support the development of tailored therapies for PTK6-related disorders in addition to highlighting the possible effectiveness of repurposing current medications for innovative therapeutic applications. The discovery of many ligands that can target different PTK6 domains at the same time not only opens the door for more experimental confirmation but also shows promise for the creation of more potent therapies that target this kinase selectively.

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