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Research Article

Ligand-Based Pharmacophore Modeling and Molecular Docking for the Discovery of PI3K(p110α)/AKT1 Pathway Inhibitor

Mekala Srikanth[1], Kuntamalla Sujatha[2]

[1,2] *Department of zoology, Kakatiya university, Warangal-506009, Telangana state, India*

**Corresponding author:*
E-mail: msrikanth70138@gmail.com

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ABSTRACT

The PI3K/AKT signaling cascade represents a crucial target for developing cancer therapeutics. Extensive research efforts have been focused to identifying new inhibitors targeting key kinase proteins within this pathway to advance cancer treatment. this study focuses on a computational approach to discover new inhibitors through the optimization of hits derived from previously reported PI3K and AKT inhibitors. From an initial dataset of 122,276,899 compounds sourced from the ZINC database, filtering repeatedly based on favourable pharmacokinetic properties reduced the pool to 17 ligands. A pharmacophore model was subsequently constructed using the reference drug, alpelisib, as a template. Molecular docking simulations were conducted using AutoDock Vina 4.0 against the PI3K p110α/AKT1 receptor protein (PDB ID: 4JPSA,4GV1). The filtered 10 compounds (ZINC000071768672, ZINC000071768671, ZINC000071768662, ZINC000071768663, ZINC000071768673, ZINC000071768678, ZINC000071768664, ZINC000065251501, ZINC000065251495 and ZINC000071768289) were docked into the active site of PI3K, AKT1 docking scores superior to the FDA-approved ligand (alpelisib). The top compounds exhibited extensive hydrogen bonding and hydrophobic interactions with critical amino acid residues, surpassing the interactions observed with alpelisib. In conclusion, these inhibitors may be represent potential candidates for targeting the PI3K p110α/AKT pathway and could be further investigated through in vitro studies and clinical trials as promising anticancer agents

1. Introduction

The phosphoinositide 3-kinase (PI3K)–AKT pathway is the most commonly activated pathway in human cancers (Hoxhaj G. and Brendan D. Manning), such as breast cancer (Ellis & Ma, 2019), head and neck cancer (Jung et al., 2018), and ovarian cancer (Ediriweera et al., 2019). It regulates key hallmarks of cancer, such as cell survival, metastasis, and metabolic processes (He et al., 2021; Lunavath et al., 2013). Akt is primarily activated by receptor tyrosine kinases (RTKs) and GPCRs. Upon activation, Akt interacts with and activates specific class I PI3K subtypes at the plasma membrane. Activated PI3K phosphorylates key residues, such as the T-loop and C-terminal hydrophobic motif, within Akt's core activation domain, influencing Akt1, Akt2, and Akt3 activity.

Upstream activation of the PI3K/Akt pathway is critical for its role in cancer and other diseases, driven by factors like RTKs, Toll-like receptors (TLRs), B-cell antigen receptors (BCRs), GPCRs, VEGFRs, and FGFRs. Akt regulates downstream targets by phosphorylating serine and threonine residues within a specific consensus sequence (R-X-R-X-X-S/T) (Serena Dotolo et al., 2021). This pathway enhances tumor cell survival, proliferation, growth, and metabolism through downstream effectors like mTOR, GSK3, FOXOs, TSC2, and MDM2. Additionally, Akt signaling exhibits significant crosstalk with pathways such as MAPK, NF-κB, and Wnt/β-catenin, amplifying its influence on cellular processes (He et al.,2021). Type I PI3K is composed of a catalytic p110 subunit and a regulatory p85 subunit (Li Zhao & Peter K. Vogt.,2010). The regulatory subunit includes seven variants: p85α, p85β, p55α, p55γ, p50α, p101, and p87 (Chuan-Hsiang Huang et al., 2008)

The catalytic p110 subunit is classified into four types: p110α, p110β, p110γ, and p110δ (SHI et al., 2019). The P110α and P110β subunits are expressed in all cells. p110α is composed of five domains: an adaptor-binding domain, a Ras-binding domain, a C2 domain, a helical domain, and a kinase domain (Chuan-Hsiang Huang et al., 2008). In many cancers, Pik3ca, the gene encoding P110α, is often mutated, which increases kinase activity and leads to varying PTEN and EGFR expression [holand K. et al., 2014). The PI3K/AKT signaling cascade, acting as a critical "cellular control center" for cell proliferation, development, and metabolic processes, is one of the most

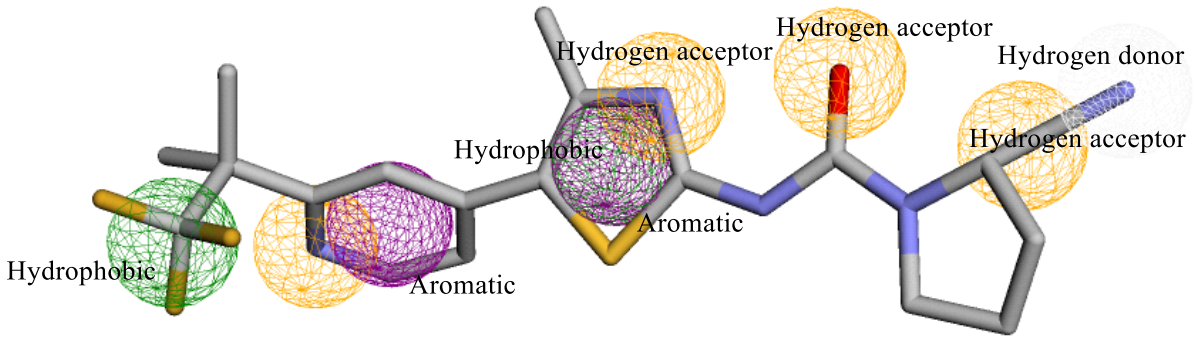


Figure 1. Pharmcophore model based on reference drug PI3Kalpha inhibitor alpelisib

commonly dysregulated pathways in human malignancies. These disruptions frequently involve somatic oncogenic amplifications or mutations that alter the regulation or expression of proteins such as EGFR, HER2, PKD1, and PIK3CA (Vivanco I et al.,2002). Consequently, this pathway has emerged as a crucial focus for next-generation anticancer therapeutics, engineered with enhanced molecular precision to minimize toxic effects on normal tissues (Serena Dotolo et al., 2021) (wang et al., 2017). These advanced therapeutics drugs can target a specific member within the pathway PI3K/ AKT pathway. example, of alpelisib the PI3K inhibitor approved by the US Food and Drug Administration (FDA), which targets the isoform of the catalytic subunit of PI3K (p110 alpha) (HERMAN e tal ., 2010; Kumar et al., 2020; Porika et al., 2014).

The use of these inhibitors has been restricted due to their potential adverse effects, including pneumonitis, severe hepatotoxicity, hyperglycemia and hyperinsulinemia hence adverse reactions greatly affect patient tolerance and overall treatment success. As a result, there is an urgent necessity for the advancement of PI3K/AKT inhibitors with enhanced safety profiles and minimized off-target interactions to improve therapeutic effectiveness (Y. ZHANG ET AL. et al., 2019). Finding of compound In the past, The drug discovery process initially started with random screening and observational studies of products effects on known diseases. Today, this approach has been refined through high-throughput screening, facilitating the rapid evaluation of thousands of compounds against molecular targets or cellular assays (Maia et al., 2020). Furthermore, researchers are continuously investigating new methods to increase the efficiency of the drug discovery process (Lemessa Etana Bultum et al., 2022)

Computer-aided drug design (CADD), also called the in silico approach, is a key strategy to enhance the efficiency of novel drug development. By utilizing molecular modeling, CADD enables the virtual screening of numerous compounds for drug-likeness and interactions with pharmacological targets, significantly reducing drug development time and research costs (Maia et al., 2020). Explorations of new applications for already established drugs are being undertaken alongside classical drug development efforts. In silico profiling of these established drugs can assist in reposition such old drugs for new uses (Lemessa Etana Bultum et al., 2022).

Pharmacophore modeling is an innovative technique used to identify and characterize potential interactions between a drug or ligand and its target protein complex (tyagi et al., 2022). These methods facilitate the discovery, identification, and assessment of therapeutics and other bioactive compounds (Maia et al., 2020). Additionally, they enable the optimization of hundreds or thousands of compounds to be tested for interaction with target proteins or receptors, thereby narrowing down the potential molecules for further research (u. shareef et al., 2023). Re purposing of drug discovery helps to reduce the costs associated with traditional trial-and-error testing of compounds. It also enables the rapid analysis of large databases within shorter time frames.

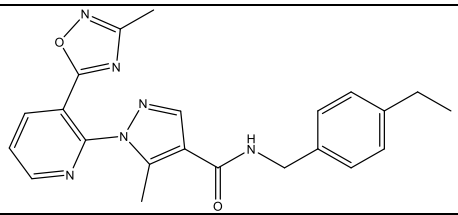
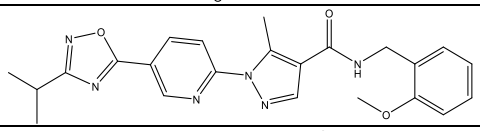
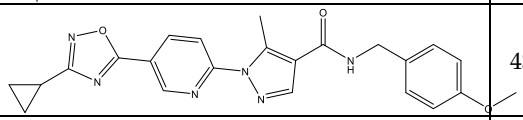
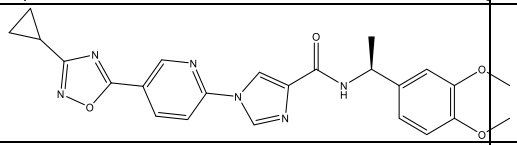
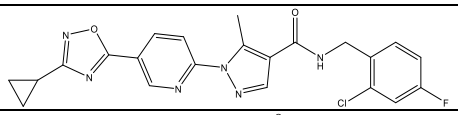
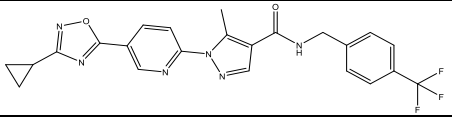
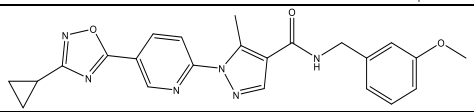
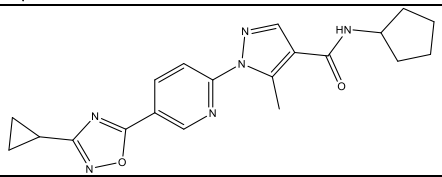
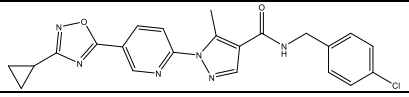
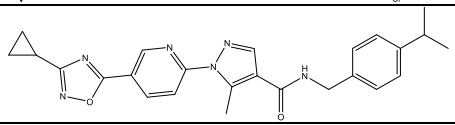
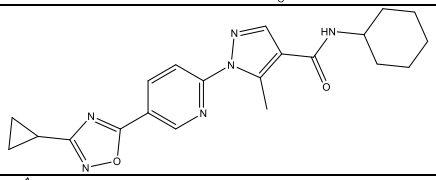
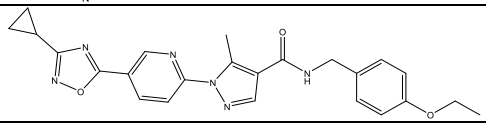
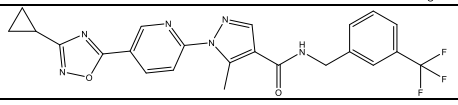
Connecting this with the PI3Kalpha/AKT pathway in the current study, a pharmacophore model was developed to identify key pharmacophore features using PI3Kalpha/AKT1 inhibitors collected from the Zinc database. The primary objective of the study was to re-assess already approved drugs to identify potential PI3K/AKT inhibitors and to discover new compounds from a diverse database whose biological activities have not yet been evaluated

2. Materials and Method

Pharmacophore modelling Three-dimensional pharmacophores serve as crucial frameworks for extracting potential lead compounds from structural databases, recognizing molecules with specific desired characteristics, and analyzing molecular resemblance (Kandoussi I et al., 2024). Ligand based pharmacophore model (Caporuscio & Tafi., 2012) was built to discover possible PI3K/AKT1 inhibitors. In this model we performed using the Pharmit server (http://pharmit.csb.pitt.edu) to identify potential drug candidates targeting. In this study, we utilize alpelisib, an FDA-approved drug, as the standard to evaluate and compare the efficacy of our findings.

The 3D structure of the Alpelisib compound was downloaded from PubChem in SDF format, converted to PDB format using Biovia, and then uploaded to Pharmit to generate a pharmacophore model Based on ligand Functional groups on which to implement pharmacophoric models aromatic x=3.573, y= -0.586, z= -1.2533, aromatic x= -0.3546, y= -0.6354, z= -0.086399, hydrogen donor x= -8.258, y= -0.889,z= 0.781, hydrogen acceptor x= 4.912, y= -0.551, z= -1.669, hydrogen acceptor x= -1.121, y= -1.24, z= 0.676, hydrogen acceptor x= -6.527, y= -1.342, z= -0.665 hydrogen acceptor x= -4.034, y= -0.962, z= 1.254, hydrophobic x= -0.3546, y= -0.6354, z= -0.0863,

Table-1. Druggable properties of selected compounds

S.NO	COMPOUND ID	STRUCTURE	Molecular Weight	XlogP	H-Bond donor	H-Bond acceptor	Lipinski Rule of 5 violations
1.	ZINC000049420826		380.452	2.93	1	8	0
2.	ZINC000071768678		432.484	2.92	1	9	0
3.	ZINC000071768664		430.468	2.28	1	9	0
4.	ZINC000071768289		460.5	2.12	1	10	0
5.	ZINC000071768671		452.877	2.99	1	8	0
6.	ZINC000071768673		468.4	3.12	1	8	0
7.	ZINC000071768663		430.468	2.25	1	9	0
8.	ZINC000062551494		378.4	-	-	-	0
9.	ZINC000065251501		434.9				0
10.	ZINC000071768662		442.523	3.73	1	8	0
11.	ZINC000065251495		392.463	2.73	1	8	0
12.	ZINC000071768666		444.495	2.65	1	9	0
13.	ZINC000071768672		468.439	3.09	1	8	0

hydrophobic x= 6.0520, y= 1.79625, z= 0.7097 selected with ideal physicochemical characteristics based on Lipinski's Rule of Five (logP ≤ 5, hydrogen bond acceptors ≤ 10, hydrogen bond donors ≤ 5, molecular mass ≤ 500) to confirm their drug-like properties to search in zinc database.

2.1 Ligand preparation

The pharmacophore generation process involved the selection of 10 ligands from the ZINC database, which were initially downloaded in SDF (Structure Data File) format. These ligands were then converted to PDB (Protein Data Bank) format using Open Babel, a versatile chemical toolbox designed for interconverting various chemical file formats. Following this conversion, the PDB files were further processed into PDBQT format, also utilizing Open Babel. The PDBQT format is essential for molecular docking studies, as it includes partial charges and atom types required for AutoDock Vina. This workflow ensures that the ligands are appropriately formatted and prepared for subsequent docking analyses.

2.2 Protein preparation

The three-dimensional structure of the PI3K/AKT1 protein (receptors) was retrived from the Protein Data Bank with resolution of 1.25 Å(PDB ID: 4JPS,4GV1) (M. K. sharif siam et al et al., 2020). The protein file was opened in Discovery Studio, where all non-protein molecules, including water molecules and ligands, were removed. The processed structure was then saved in .pdb format. MGLTools was utilized to configure the grid parameters for the receptor. The protein file in .pdb format was loaded into MGLTools, where polar hydrogen atoms were added to the protein molecule. Additionally, Kollman charges were assigned, Gasteiger-Marsili charges were applied. The protein was then designated as a macromolecule and saved in .pdbqt format for further docking analysis(Morris, G. M. and Lim-Wilby., 2008).

2.3 Preparation of Conf .txt File

AutoDock Vina requires an input configuration file that specifies all the parameters necessary for docking, including the names of the protein and ligand. The configuration typically includes details such as the receptor file paths, grid box dimensions, center coordinates, exhaustiveness, number of modes, and energy range. PI3K: The configuration format is as follows: receptor = protein.pdbqt, center x = -9.362, center y, = -26.733 center z = 27.346 and X-dimensions size x = 112, size y = 86, size z = 96, num modes = 10, energy range = 4
Akt1: The configuration format is as follows: receptor = protein.pdbqt, center = -26.576, center y = 2.821, center z = 16.228 and X-dimensions size x = 56, size y = 58, size z = 66, num modes = 10, energy, range = 4

2.4 Molecular Docking methodology

Molecular docking computations were performed using a ASUS Vivobook with an Intel® Core™ i5 12th Gen processor. The system operated on Windows 11 (64-bit, 2024 version). AutoDockTools (version 1.5.7) was used to determine grid coordinates and convert the protein structure from PDB to PDBQT format. AutoDock Vina was then employed to detect the binding energy between the protein and ligand, with the lowest binding energy indicate the strongest affinity. In this study, compounds from the ZINC database, along with control drug, including alpelisib, were docked against PI3K/AKT1 (4GV1/4JSA). Additionally, Biovia Discovery Studio (version 2021) was used to visualize and analyse the interactions between the ligands and the target active site. For Analysing results Open the output files in visualization tools like PyMOL and Discovery Studio to analyse the binding poses and interactions between the ligand and receptor.

3.. Results and Discussion

The compounds were designed through pharmacophore-based modeling, highlighting key structural features crucial for biological activity. All chemical structures were drawn using ChemDraw Professional 16.0, These compounds are presented below and will be subjected to further evaluation to explore their therapeutic potential and biological efficacy (Fig 2-5).

3.1. Molecular docking interactions of ZINC000071768671 pi3k (p110 α):

ZINC000071768671 demonstrates the strongest binding affinity among the analysed ligands, with a binding energy of -10.5 kcal/mol for PI3K. This indicates a robust interaction with target. Compared to the standard drug alpelisib, which has a binding energy of -9.0 kcal/mol, ZINC000071768671 exhibits significantly higher binding affinity, suggesting it may be more effective in targeting these proteins. Based on previous literature, key amino acid residues of the PI3K(p110α) protein were identified, including Arg770, Ile771, Met772, Ser773, Lys776, Arg777, Ile800, Asp810, Tyr836, Glu849, Val851, Arg852, Asn853, Ser854, His855, Gln859, Met922, and Ile932. (Baki Vijaya Bhaskar er al., 2021) (Zheng et al., 2012) (Berndt et al., 2010). These residues play a critical role in ligand binding and stabilization within the active site.

p110α with ZINC000071768671 forms two hydrogen bonds with LYS271 and SER629, which help stabilize the ligand within the binding pocket (Figure 2). Additionally, it participates in extensive hydrophobic interactions with residues such as Glu172, Asp626, Leu632, Ile633, Met811, Glu821, Arg818, Glu825, Asn826 And Lue839, π- π stacked interaction with Phe666, alkyl interaction with Arg274, Met278 further enhancing its stability in the enzyme's active site. However, ZINC000071768671 does not directly interact with key residues in R852, N853, H855, Q859 or E768, R770, I771, S773, K776, R777 (Zheng et al., 2012) (Berndt et al., 2010) of p110α. This lack of interaction with these critical regions may reduce its specificity compared to the standard drug alpelisib, which interact with770, 852, 853, 855and 859. targets some of key residues it increases binding and selectivity.

ZINC000071768672 with pi3k (p110α): ZINC000071768672 demonstrates a strong interaction with the PI3K (p110α) enzyme, exhibiting a binding energy of -10.1 kcal/mol. This interaction is stabilized by the formation of two hydrogen bonds with key residues, Val851 and Gln859, which help anchor the ligand securely within the enzyme's binding pocket (Figure -3). Additionally, the compound engages in multiple hydrophobic interactions with residues such as Arg770, Met772, Ile800, Asn853, Ser854, Thr856, Phe930, and Asp933. It also exhibits a pi-pi T-shaped interaction with Trp780 and Tyr836, while pi-sigma interactions occur with Ile922 and Ile932. Furthermore, a p-anion interaction is observed with Glu798, and alkyl interactions are noted with Ile848 and Arg852. A halogen interaction with Glu849 further enhances the ligand's stability within the enzyme's active site. Importantly, ZINC000071768672 interacts with key residues in R852, N853, H855, Q859 and E768, R770, I771, S773, K776, R777 of p110α.

Table-2. Molecular analysis of selected 10 compounds against the PI3Kα protein (4JPS)

Drug name	Binding energy (Kcal per mole)	No. of Hydrogen bonds	Hydrogen bond forming residues	Hydrophobic interactions
ZINC000071768671	-10.5	2	LYS271, SER629,	GLU172, ARG274, MET278, ASP626, GLN630, LEU632, ILE633, HIS670, PHE666, HIS670, MET811, ARG818, GLU821, ASN822, GLN825, ASN826, LEU839, CYS838
ZINC000071768673	-10.2	2	GLN630, CYS838,	GLU172, LYS271, SER275, MET278, LUE279, SER629, PHE666, HIS670, MET811, ARG818, GLU821, ARG832, GLY837, LEU839
ZINC000071768672	-10.1	2	VAL851, GLN859,	ARG770, MET772, TRP780, GLU798, ILE800, TYR836, ILE848, GLU849, VAL850, VAL851, ARG852, ASP853, SER854, THR856, MET922, PHE930, ILE932, ASP933
ZINC000071768662	-10.0	1	SER854	ARG770, MET772, GLU768, TRP780, GLU798, ILE800, LYS802, LEU807, ASP810, LUE814, TYR836, CYS838, ILE848, VAL850, VAL851, ARG852, HIS855, GLN859, MET922, ILE932, ASP933
ZINC000071768678	-9.8	2	SER770, VAL851	MET772, GLU798, TRP780, ILE800, LYS:802, ASP810, LUE814, TYR836, CYS838, ILE848, VAL850, ARG852, ASN853, GLN859, SER854, MET922, ILE932, ASP933
ZINC000071768663	-9.8	3	ARG770, VAL:851, SER:854,	MET772, GLU768, GLU798, ILE800, LEU807, ASP810, LUE814, TYR836, CYS838, ILE848, VAL850, ARG852, ASN853, HIS855, GLN859, MET922, ILE932, ASP933
ZINC000071768664	-9.7	-	-	MET772, TRP780, ILE800, LEU807, ASP810, LUE814, TYR836, ILE848, VAL850, VAL851, ARG852, ASN853, GLN859, SER854, MET922, ILE932, ASP933,
ZINC000065251495	-9.5	2	GLN630, ARG818	GLU172, LYS271, SER275, MET278, SER629, ASP626, ILE633, HIS670, PHE666, HIS670, MET811, GLU821, LEU839
ZINC000065251501	-9.4	1	HIS759	ILE633, HIS670, PHE666, ASN756, PHE794, ASN796, ASN797, GLU798, MET811, ARG818, GLY837, LEU839, CYS838, GLU849, VAL850, ARG852
ZINC000071768289	-9.3	5	ASN756, HIS759, ARG818, GLU848	SERT629, LUE632, ILE633, PHE666, HIS670, LEU755, GLU798, ASN797, PHE794, MET811, PRO835, TYR836, CYS838, GLY837, ARG852
ZINC000049420826	-9.2	2	ARG:818, ALA:758	ASN170, VAL166, TYR:167,PRO168, ASP258, GLU259, ILE633, GLN661, ARG662, PHE666, HIS670
Alpelisib	-9.0	2	LYS802, VAL 851,	ARG770, MET772, PRO778, TRP780, ILE800, TYR836, ILE848, GLU849, VAL850, ARG852, ASP853, SER854, HIS855, GLU859, MET922, PHE930, ILE932, ASP933

These interactions with critical regions may significantly improve its specificity compared to the standard drug alpelisib, potentially making it a more effective and selective inhibitor.

ZINC000071768662 with pi3k (p110α): The docking of ZINC000071768662 with PI3Kα results in a binding energy of -10.0 kcal/mol, indicating a strong binding affinity. The ligand forms a hydrogen bond with residue Ser854, contributing to its stabilization within the binding pocket (Figure 3). Additionally, it engages in extensive hydrophobic interactions with residues Glu768, Met772, Glu798, Lys802, Asp810, Leu814, Tyr836, Arg852, His855, Gln859, and Asp933. A sulfur bond is observed with Arg770, while a pi-pi T-shaped interaction occurs with Trp780. The ligand also forms a pi-sigma bond with Met922 and alkyl interactions with Ile800, Leu807, Cys838, Ile848, and Ile932, further enhancing its stability within the enzyme's active site. Notably, ZINC000071768662 interacts with key residues in p110α. These interactions with critical regions may significantly enhance its specificity compared to the standard drug alpelisib, potentially making it a more effective and selective inhibitor.

ZINC000071768663 & ZINC000071768678 with pi3k (p110α): The docking of ZINC000071768663 with PI3K(p110α) results in a binding energy of -9.8 kcal/mol, demonstrating strong binding affinity. The ligand forms three hydrogen bonds with key p110α residues, ZINC000071768663 interacts with key residues Arg770, Val851, and Ser854, which play a significant role in stabilizing the ligand within the binding pocket (Figure -). Additionally, it participates in extensive hydrophobic interactions with residues Glu768, Met772, Glu798, Ile800, Asp810, Leu814, Tyr836, Arg852, Asp853, His855, Gln859, and Asp933. The ligand also forms a sigma bond with Met922 and a pi-pi T-shaped interaction with Trp780. Furthermore, alkyl interactions are observed with Leu807, Cys838, Ile848, and Ile932, contributing to its overall stability in the enzyme's active site. Importantly, ZINC000071768663 interacts with critical

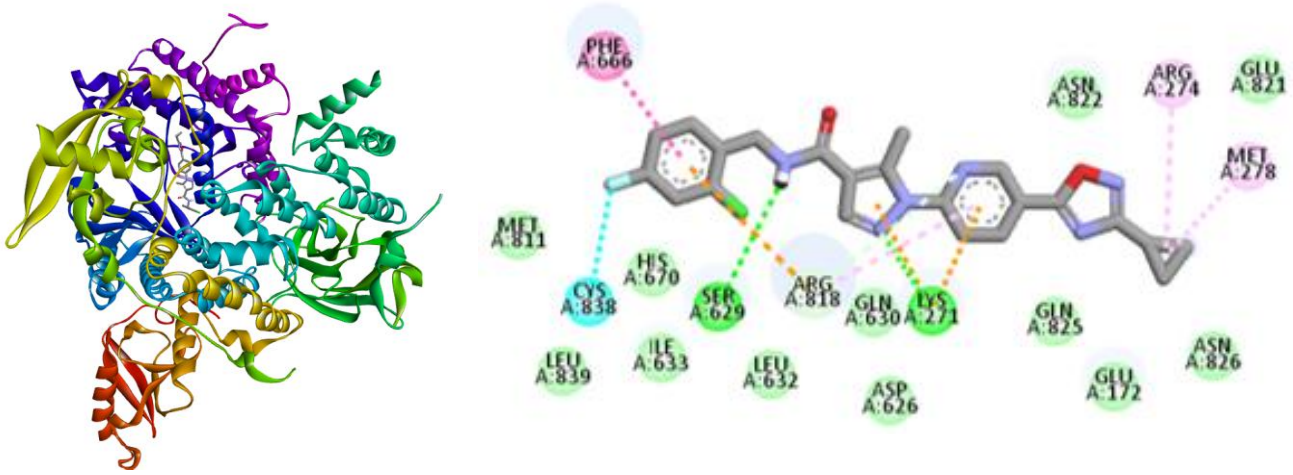


Figure-2. 3D & 2D molecular docking interaction of ZINC000071768671with pi3k alpha (p110α) subunit (PDB ID: 4JPS)

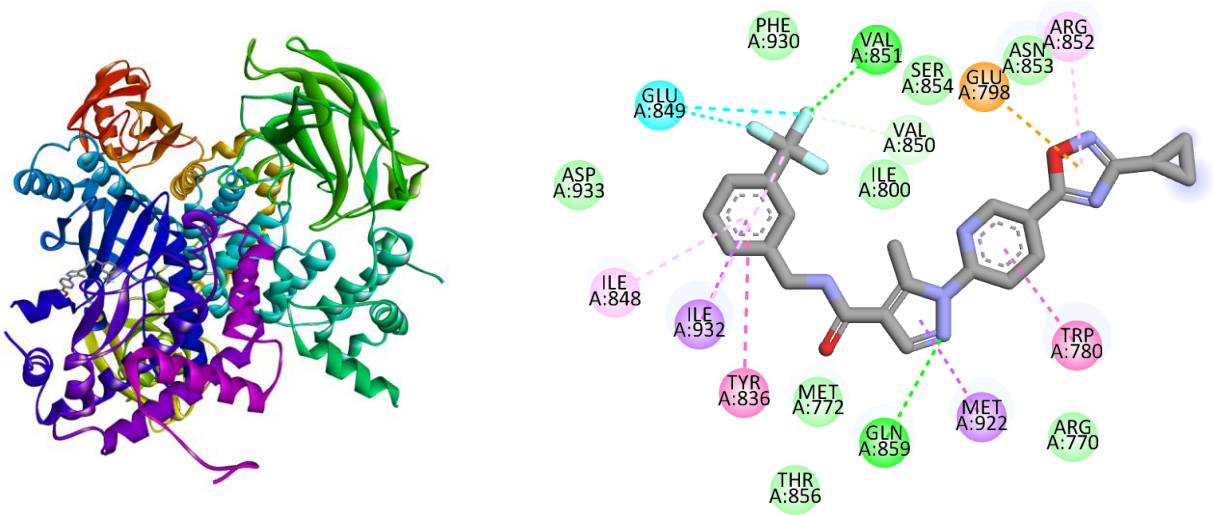


Figure 3. 3D & 2D molecular docking interaction of ZINC000071768672 with pi3k alpha (p110α) subunit (PDB: 4JPS)

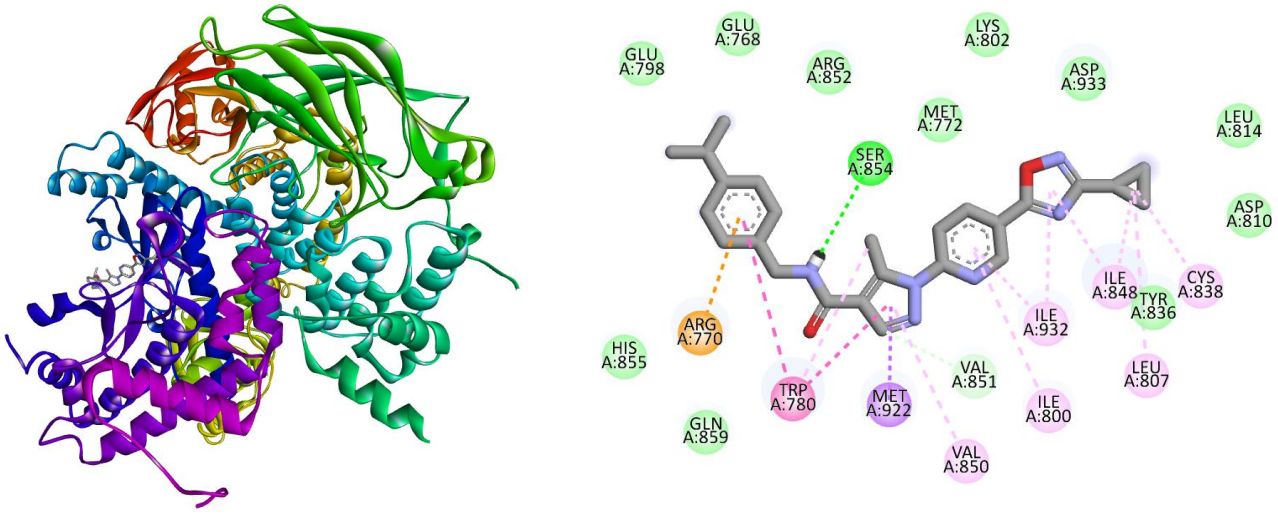


Figure 4. 3D & 2D molecular docking visualization of ZINC000071768662 with PI3K alpha (p110α) subunit (PDB: 4JPS)

residues in R852, N853, H855, Q859 and E768, R770, I771, S773, K776, R777 of p110α. These interactions with essential regions may significantly improve its specificity compared to the standard drug alpelisib.

ZINC000071768678 with PI3K(p110α) results in a binding energy of -9.8 kcal/mol, demonstrating strong binding affinity. The ligand forms two hydrogen bonds with p110α residues Arg770, Val851 further reinforcing its stability in the enzyme's active site. Additionally, it participates in extensive hydrophobic interactions with residues Met772, Glu798, Ile800, Asp810, Leu814, Cys838, Arg852, Asp853, Ser854, Gln859, and Asp933. The ligand also forms a sigma bond with Met922 and a pi-pi T-shaped interaction with Trp836. Furthermore, alkyl

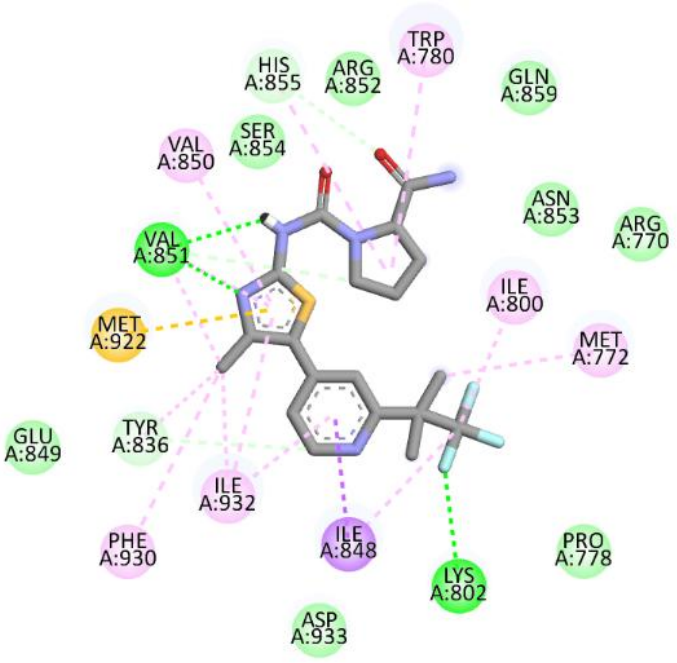


Figure 5. 2D molecular docking visualization of FDA approved alpelisib with PI3K alpha (p110α) subunit (PDB ID: 4JPS)

interactions are observed with Trp780, val850, Ile848, and Ile932, contributing to its overall stability in the enzyme's active site.

ZINC000071768673, ZINC000071768664, ZINC000065251495, with pi3k (p110α): ZINC000071768673: This compound exhibits a binding energy of -10.2 kcal/mol. While it does not interact with the specific amino acid residues, it engages with several residues that are also targeted by alpelisib, including LYS271, SER275, MET278, ARG818, and GLU821. This suggests a potential overlap in binding sites with alpelisib..

ZINC000071768664: With a binding energy of -9.7 kcal/mol, this compound lacks hydrogen bonds but forms hydrophobic interactions with key residues such as VAL851, ARG852, ASN853, and GLN859. These interactions contribute to its p110 alpha-specific binding, although its binding energy is slightly lower compared to ZINC000071768673.

ZINC000065251495: This compound shows a binding energy of -9.5 kcal/mol and forms two hydrogen bonds. However, it does not interact with the key residues critical for p110 alpha binding, which may explain its relatively lower binding affinity compared to the other compounds.

3.2. Akt1 interaction analysis:

Ten ligands were docked into the active site of AKT1, revealing binding energy and interactions with residues known to be involved in binding with AKT1 inhibitors (Table-3). For instance, hydrogen bonds were identified between ZINC000071768673 with THR211, ALA230, and ASP292; ZINC000071768662 with LYS179; ZINC000071768672 with LYS179, ASP439; and ZINC000071768671 with LYS276, ASP292, and THR312 and ZINC000065251501 with LYS276, THR312. Additionally, ZINC000071768663 formed hydrogen bonds with PHE161 and GLY162, residues commonly associated with ATP-competitive AKT1 inhibitors, as reported by (T. Liu et al., N. Abd Emoniem et al., 2023). These ligands also exhibited hydrophobic interaction with LYS179, ASP292, LEU156, PHE161, and GLU234.

Multiple studies have highlighted the significance of these key residues in the binding of potential AKT1 inhibitors. For example, Kawsar et al., 2021 demonstrated that hydrogen bonds with LEU156 and ASP292 were observed in the interactions of Capivasertib and Galuteolin with the AKT1 active site, supporting their potential as inhibitors (M. K. Sharif Siam et al., 2020).

3. Conclusion

This study underscores the promising potential of certain compounds as effective inhibitors of PI3K (p110α) and AKT1, as revealed through molecular docking analysis. Among the evaluated ligands, ZINC000071768672 and ZINC000071768662 emerges as a standout candidates due to its robust binding affinity (-10.1 kcal/mol, -10.0 kcal/mol) and interact with critical specific residues of PI3K, specifically 770, 852, 853, 854, and 859. Additionally, it demonstrates high binding energy with AKT1(-10.6 kcal/mol, -10.4 kcal/mol), engaging key residues such as LYS179, ASP292, LEU156, and GLU234. These findings suggest that ZINC000071768672 and ZINC000071768662 could function as a potent inhibitor of PI3K/AKT, potentially surpassing the efficacy of established drugs like alpelisib (for PI3K) and capivasertib (for AKT1). These findings suggest that ZINC000071768672 and ZINC000071768662 are promising candidates for further research. Detailed in vitro and in vivo studies are essential to confirm their therapeutic potential in targeting the PI3K/AKT1 pathway.

Competing interests:

The authors declare that they have no competing interests

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