

Discovery of Dual Kinase Inhibitors Targeting PI3K α and AKT1: Structure-based Pharmacophore Modelling, Virtual Screening, and Molecular Docking Studies

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Abstract

This study aimed to identify novel dual AKT1 and PI3K α kinase inhibitors, given their synergistic roles in driving cancer cell proliferation and survival. Structure-based pharmacophore models were developed for AKT1 and PI3K α , and the ZincPharmer web tool was used to virtually screen the ZINC database, yielding 38 common hit compounds. SwissADME analysis identified six promising candidates based on their drug-likeness and physicochemical properties. Molecular docking simulations confirmed ZINC05999146 and ZINC04268860 as promising AKT1 and PI3K α binders, exhibiting key hinge-region interactions with Ala230 (AKT1) and Val851 (PI3K α). These results suggest that both compounds have potential as dual kinase inhibitors, provided that further in vitro and in vivo assessments are conducted.

Keywords: PI3K, AKT1, Molecular docking, Pharmacophore modelling, Virtual screening.

Introduction

This project was supported by the University of Lincoln Undergraduate Research Opportunities Scheme (UROS), which enables undergraduate students to undertake research in collaboration with academic staff (University of Lincoln, 2025).

The core focus of this project is on the discovery of potential dual kinase inhibitors targeting phosphoinositide 3-kinase alpha (PI3K α) and RAC-alpha serine/threonine-protein kinase 1 (AKT1), two proteins that play a central role in cancer cell growth and survival. Dysregulation of the PI3K/AKT signalling pathway is frequently associated with tumour development, making it an important target for anti-cancer drug discovery.

The aim of this project was to apply computer-aided drug design techniques, including structure-based pharmacophore modelling, virtual screening, and molecular docking, to identify small molecules capable of binding to both PI3K α and AKT1. By exploring shared structural features between the two kinases, this research sought to identify promising compounds with potential as dual-target anti-cancer agents.

Project Background

Cell growth, movement, and survival are controlled by carefully regulated signalling pathways within the body. One of utmost importance is the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, which helps cells respond to growth signals. When this pathway becomes hyperactive, cells can divide uncontrollably, which is a hallmark of cancer (Vara et al., 2004; Martini et al., 2014).

Phosphoinositide 3-kinase alpha (PI3K α) is a Class I catalytic isoform of the PI3K family and is commonly associated with oncogenic mutations in human cancers. When activated, PI3K α generates lipid signalling molecules that recruit and activate downstream proteins, most notably AKT1. AKT1 is a serine/threonine kinase that further propagates signals involved in cell survival, metabolism, and growth (Martini et al., 2014). Due to their close functional relationship, inhibition of only one of these proteins can be insufficient, as compensatory signalling may allow cancer cells to continue proliferating.

As a result, dual inhibition of both PI3K α and AKT1 has emerged as a promising therapeutic strategy (Abdel Reheim et al., 2025). Dual kinase inhibitors have the potential to improve treatment efficacy while reducing drug resistance compared to single-target therapies.

Advances in computer-aided drug design could enable the use of structure-based approaches to identify potential inhibitors efficiently and cost-effectively. This project applied such computational methods to explore whether shared structural features between PI3K α and AKT1 could be used to identify compounds capable of binding to both kinases, providing a foundation for the development of future dual-target anti-cancer agents.

Literature Review

Cancer develops when normal cell growth and survival pathways become hyperactive. One important group of proteins involved in this process are kinases. When certain kinases are continuously switched on, they can drive uncontrolled cell growth and tumour development.

Recent research has shown that targeting more than one kinase at the same time can be more effective than blocking a single protein alone. This approach is known as dual/multi kinase inhibition and is thought to reduce drug resistance and improve treatment outcomes. Fouad et al. (2024) demonstrated this concept by identifying compounds that could simultaneously inhibit two related kinases, VEGFR2 and FAK, which work together to promote tumour growth and blood vessel formation. Their study used structure-based pharmacophore modelling, virtual screening of the ZINC database, and molecular docking to identify promising dual inhibitors, highlighting the power of computational drug discovery approaches.

Dual inhibition has also been explored within the PI3K/AKT signalling pathway, which is commonly overactivated in cancer. Research conducted by Abdel Reheim et al. (2025) found that compounds could be designed that are capable of inhibiting both PI3K and AKT. Tand could effectively suppress cancer-related signalling more strongly than single-target inhibitors. These findings shaped the focus of this UROS project, which centred on the PI3K α and AKT1 protein isoforms. Experimentally resolved protein structures available from the Protein Data Bank (2025) (RCSB Protein Data Bank <https://www.rcsb.org>) were used to explore compounds capable of interacting with both targets.

Methodology

Protein Structure Similarity Assessment

The NCBI Basic Local Alignment Search Tool (BLASTp, <https://blast.ncbi.nlm.nih.gov/Blast.cgi>) was applied to evaluate the sequence similarity between the kinase domains of AKT1 and PI3K α . In order to derive the amino acid sequences, the UniProt database (<https://www.uniprot.org/>) was accessed where the amino acid sequences were retrieved in FASTA format. The UniProt IDs for each kinase are as follows: AKT1 UniProt ID: P31749 and PI3K α UniProt ID: P42336

Retrieving X-ray crystallographic structures

Ten crystallographic structures were selected from the Protein Data Bank (<https://www.rcsb.org/>) for human AKT1 and PI3K α proteins co-crystallised with type I inhibitors. From this, five co-crystallised protein structures for AKT1 (PDB IDs: 3MV5, 3MVH, 3OCB, 3OW4, and 6CCY) and five co-crystallised protein structures for PI3K α (PDB IDs: 4TV3, 4ZOP, 5XGH, 5XGI, and 7K6M).

The co-crystallised structures selected for AKT1 were chosen because they contained high-resolution ligand-bound complexes capturing key hinge-region interactions (Ala230, Glu228) with no existing mutations. For PI3K α protein structures, they were selected due to their ligand-bound state to the key amino acid Val851 and high-resolution quality.

Molecular Operating Environment (MOE, 2024.06) software was used to prepare the selected protein structures. One chain was kept in each protein structure, and any other chains, water molecules, and remaining ligand molecules unrelated to the ligand-target interactions were eliminated. These protein structures were prepared using the *QuickPrep* tool in MOE.

Pharmacophore Model Generation (Aligning structures and common features extraction)

The prepared protein structures for each of the target kinases AKT1 (PDB IDs: 3MV5, 3MVH, 3OCB, 3OW4, and 6CCY) and PI3K α (PDB IDs: 4TV3, 4ZOP, 5XGH, 5XGI, and 7K6M) were individually aligned and superimposed. In MOE, the *pharmacophore query editor* was used to extract the common binding features of the co-crystallised ligands to generate the pharmacophore model for each kinase ligand set.

Virtual Screening

The generated pharmacophore models for AKT1 and PI3K α were utilised to virtually screen the ZINC database. This was performed using the ZINCPharmer web tool (<http://zincpharmer.cssb.pitt.edu>). The screening filters included a molecular weight range of 350-500 Da and rotatable bonds of no more than 10.

Identification of common compounds

Common compounds in both hit sets were identified using MOE.

Prediction of the pharmacokinetic properties

The pharmacokinetic properties of the common compounds were predicted using SwissADME (<http://www.swissadme.ch>). This web tool explores drug-likeness and pharmacokinetic features of small molecules. Molecules with high GI absorption, no predicted potential blood brain barrier permeation, and P-gp substrate negative were considered promising compounds for further investigation. Finally, the PAINS criteria were applied to the common compounds to check whether any of the selected hits are frequent hitters or promiscuous compounds.

Molecular Docking

Molecular docking simulations were carried out for the common compounds with promising drug-likeness and pharmacokinetic properties to examine their binding patterns and main ligand interactions in both of the AKT1 and PI3K α binding sites. For that, AKT1-PDB ID: 3MVH and PI3K α -PDB ID: 7K6M were used. First, self-docking of

the co-crystallized ligands were carried out to check whether the molecular docking protocols were appropriate. Self-docking gave docking poses with energy scores (S)= – 15.59 and – 13.97 kcal/mol and RMSD of 0.489 and 1.021 Å in AKT1 and PI3K α , respectively. The validated docking protocols were then used to dock the promising common compounds in the kinase domain of the target kinases.

Results

Protein Structure Similarity Assessment

To explore the potential for designing inhibitors that could target both PI3K α and AKT1, we compared their amino acid sequences. The kinase domain of PI3K α (P42336) was used as a query, and the AKT1 kinase domain (P31749) as the subject, and both sequences were aligned using the UniProt Alignment Tool (UniProt, 2025). The results showed a 20.5% overall sequence similarity between the two kinase domains. Key residues in the hinge region were aligned, and these residues are known to form essential interactions with type I kinase inhibitors (Fig. 1). Conserved regions like these are important because they often determine where inhibitors can bind. These results suggest that it may be possible to design compounds that interact with both kinases, which were investigated in the next steps of the study.



Figure 1: Sequence alignment of PI3K α and AKT1 kinase domains.

Structural Alignment and Common Ligand Binding Patterns

To identify common interaction patterns, five co-crystallised AKT1-ligand complexes (PDB IDs: 3MV5, 3MVH, 3OCB, 2OW4, and 6CCY) were aligned and superimposed using MOE 2024.06 software (Fig. 2). The superimposition shows that despite the ligands' diversity, they consistently overlap in the active site, particularly around the hinge region residues Glu228 and Ala230. These conserved interactions indicate that the hinge region plays a critical role in ligand binding and provides a structural target for designing new inhibitors. Figure 2 illustrates this overlap, highlighting the key

positions where the ligands interact with the kinase. This result showing which residues are consistently involved in ligand binding allows us to focus on designing and identifying compounds that effectively bind to these critical sites in AKT1.

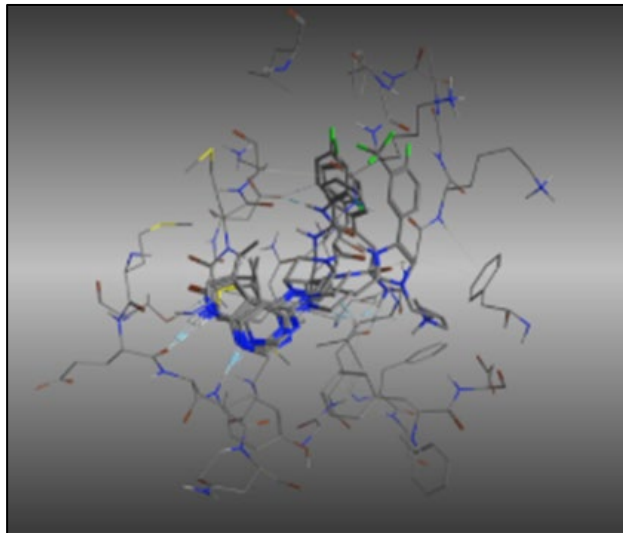


Figure 2: Alignment of the selected AKT1-ligand complexes (PDB IDs: 3MV5, 3MVH, 3OCB, 3OW4, and 6CCY)

Figure 3 shows the key interactions between a co-crystallised ligand and the AKT1 kinase domain (PDB ID: 3MVH). The 2D diagram highlights hydrogen bonds formed with the hinge region residues Glu228 and Ala230. These interactions show which parts of AKT1 the ligand attaches to. This information helps guiding the search for new compounds, ensuring they target the same important residues and increasing the chances that they will effectively inhibit AKT1.

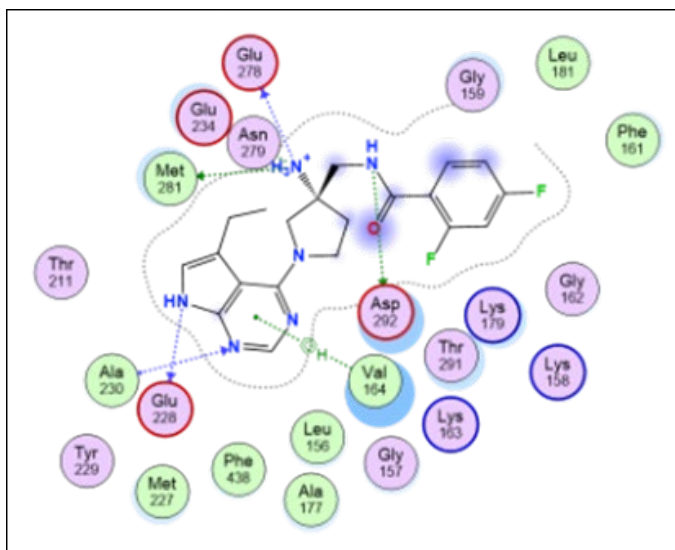


Figure 3: 2D ligand interaction diagram showing the key interactions in AKT1 kinase domain (PDB ID: 3MVH)

Figure 4 shows the alignment of five co-crystallised PI3K α -ligand complexes (PDB IDs: 4TV3, 4ZOP, 5XGH, 5XGI, and 7K6M). The superimposed ligands consistently form hydrogen bonds with the hinge region residue Val851. This indicates that Val851 is a key point of interaction for inhibitors in PI3K α . This figure provides a guide for finding new compounds, ensuring they target this important residue and increasing the likelihood of effectively blocking PI3K α activity.

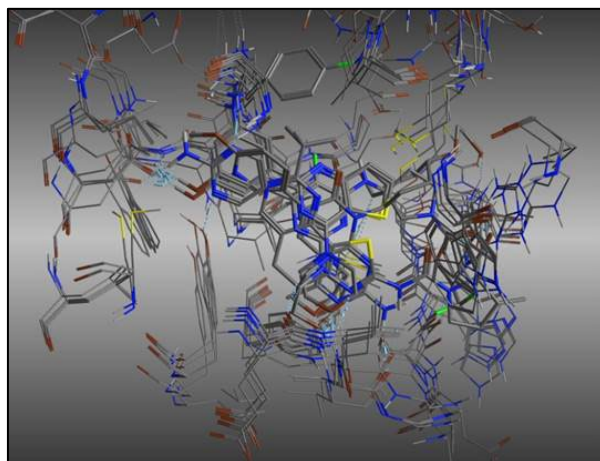


Figure 4: Alignment of the selected PI3K α -ligand complexes (PDB IDs: 4TV3, 4ZOP, 5XGH, 5XGI, and 7K6M).

Figure 5 shows the key interactions between a co-crystallised ligand and the PI3K α kinase domain (PDB ID: 7K6M). The 2D diagram highlights hydrogen bonds formed with the hinge region residue Val851. These interactions identify which PI3K α residues bind to the ligand and reveal Val851 as a critical site for binding.

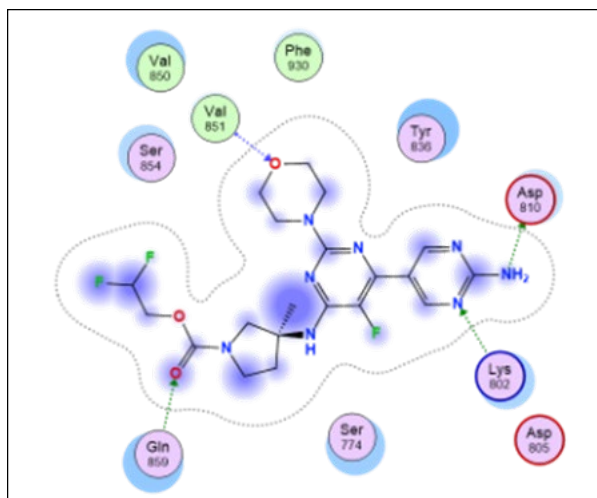


Figure 5: 2D ligand interaction diagram showing ligand key interactions in PI3K α kinase domain (PDB ID: 7K6M)

Generated Pharmacophore Models

Two structure-based pharmacophore models were generated, one for each kinase. A pharmacophore model identifies the essential chemical features that a compound must have to interact effectively with the protein, and these models were used to guide virtual screening of potential inhibitors.

For AKT1, the model (figure 6) included the common six essential features that ligands share and need for binding to the kinase. A hydrogen bond donor (F1: Don) defines the NH interaction with the C=O of Glu228, with a projected feature (F2: Don2) capturing the direction of this interaction. A hydrogen bond acceptor (F3: Acc) represents the interaction with Ala230 in the hinge region, complemented by its projected feature (F4: Acc2). In addition, two aromatic features (F5 and F6: Aro) describe the aromatic parts of co-crystallised inhibitors that help stabilise binding. These features provide a template for identifying or designing new compounds that are likely to bind effectively to AKT1.

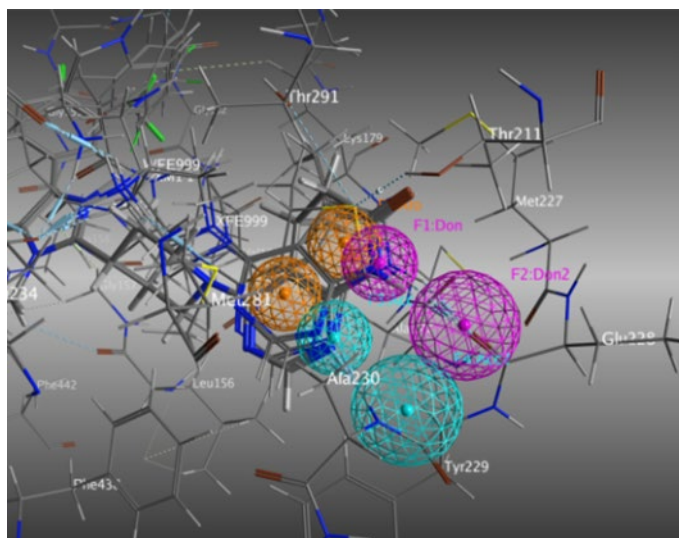


Figure 6: The generated Pharmacophore model for AKT1 inhibitors representing their key common interactions with AKT1 kinase domain.

For PI3K α , seven essential features were identified (figure 7). A hydrogen bond acceptor (F1: Acc) represents the interaction between ligand's nitrogen or oxygen atoms and the NH group of Val851, with a projected feature (F2: Acc2) capturing the direction of this interaction. A hydrogen bond donor (F3: Don) corresponds to the NH interaction with Val851, supported by its projected feature (F4: Don2). The aromatic scaffold of the ligands is represented by one aromatic feature (F5: Aro) and two projected features (F6 and F7: PiN), which describe parts of the molecules that help stabilise binding through stacking or hydrophobic interactions. This pharmacophore model highlights the structural features and their positions that are most important for a compound to bind effectively to PI3K α .

Both pharmacophore models also include excluded volumes, which indicate the parts of the binding site that are inaccessible. This will guide the selection of compounds that can properly fit into the kinase binding site.

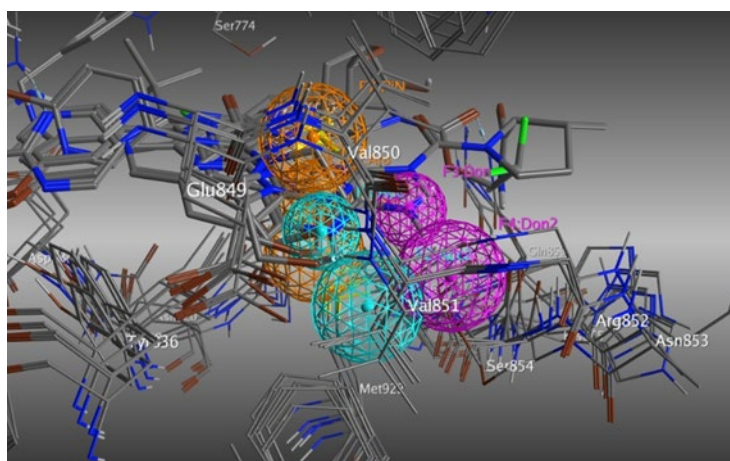


Figure 7: The generated Pharmacophore model for PI3K α inhibitors representing their key common interactions with PI3K α kinase domain

Virtual screening and hit filtration

The ZINCPharmer web tool (<http://zincpharmer.cssb.pitt.edu>) was used to virtually screen ZINC database using the designed pharmacophores, confining all compounds to a molecular weight range of 350 to 500 Da and rotatable bond number less than 10. As a result, this yielded 108,000 hits for AKT1 and 411 hits for PI3K α , with 38 common compounds as potential dual AKT1/PI3K α inhibitors.

Pharmacokinetic properties prediction

The common compounds were analysed using the SwissADME web tool (<http://www.swissadme.ch/>) to evaluate their drug-like properties, including how they are absorbed, distributed, and processed in the body.

A Boiled Egg graph (TPSA vs. wlogP; Figure 8) was generated to predict each compound's likelihood of being absorbed in the human intestine and crossing the blood–brain barrier (BBB). This helps determine whether the compounds can reach their intended targets at effective doses while minimising central nervous system (CNS) side effects. In the graph, compounds in the grey area are unlikely to be absorbed in the gut, while compounds in the white area have the highest chance of good intestinal absorption. Compounds in the yellow area can cross the BBB and may therefore affect the CNS. Blue dots represent compounds that are substrates for the P-glycoprotein (P-gp) efflux protein, meaning they are actively pumped out of the gut and are poorly absorbed, while red dots are P-gp non-substrates and are likely to be absorbed more efficiently.

This analysis highlights which compounds have the most favourable pharmacokinetic properties and are therefore the strongest candidates for further development as potential dual AKT1/PI3K α inhibitors.

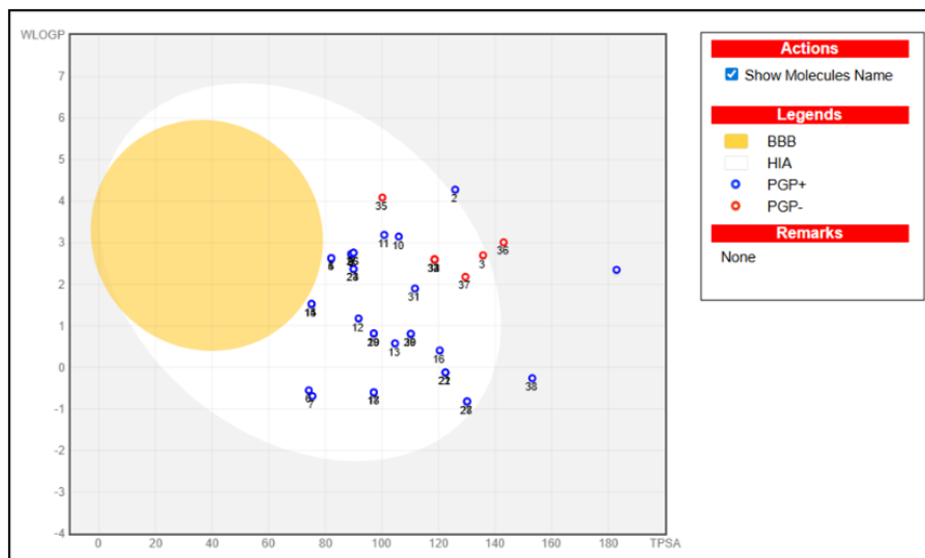
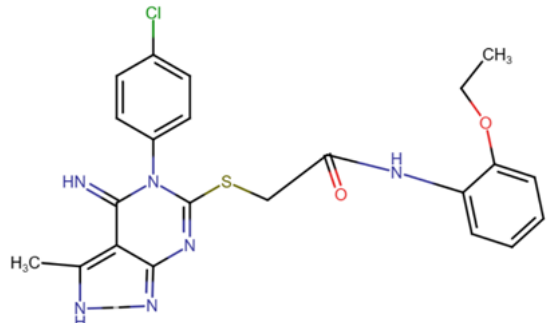
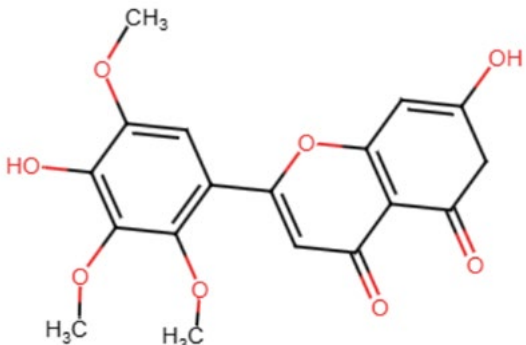
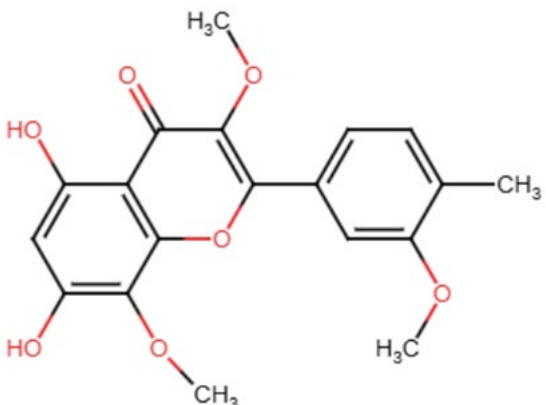
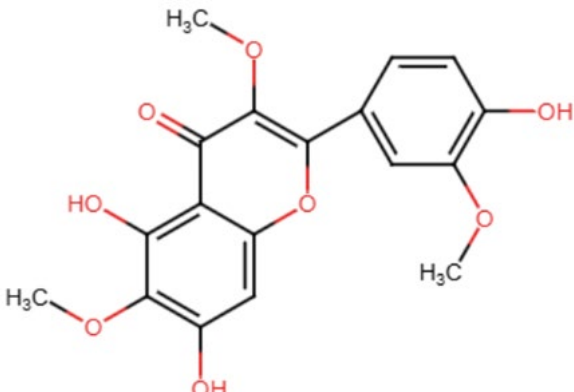


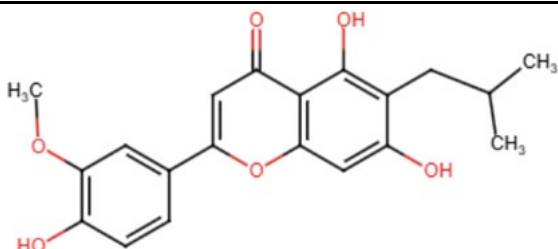
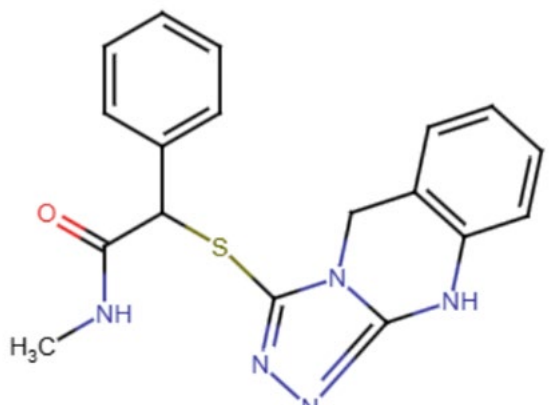
Figure 8: The Boiled Egg graph generated by SwissADME for the 38 common hits of AKT1 and PI3K α .

Six compounds (Table 1) were identified as having the most favourable pharmacokinetic properties. These compounds are predicted to be well absorbed in the gastrointestinal tract, do not cross the blood–brain barrier, and are not substrates for the P-glycoprotein (P-gp) efflux system, suggesting they can reach their target sites efficiently. Importantly, none of these compounds contains PAINS fragments (pan-assay interference compounds) [Baell & Holloway, 2010], indicating they are unlikely to produce false-positive results in assays or act promiscuously.

These features make the six selected compounds strong candidates as potential dual AKT1/PI3K α inhibitors. By targeting both kinases simultaneously, they hold promise for cancer therapy, supporting the next stages of drug development and experimental validation.

Table 1: The six compounds with promising drug-likeness and pharmacokinetic properties

ZINC ID	Chemical Structure
ZINC03032094	
ZINC04716510	
ZINC05999146	
ZINC05732760	

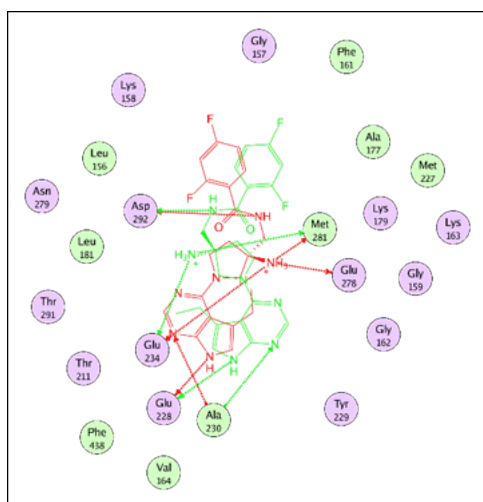
ZINC ID	Chemical Structure
ZINC01662799	
ZINC04268860	

Molecular Docking

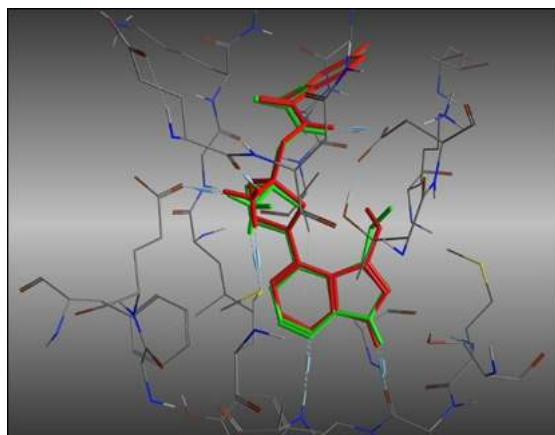
Molecular docking was performed for the six selected compounds to evaluate their potential as dual AKT1/PI3K α inhibitors and to investigate how they interact with the kinase binding sites. The crystal structures of AKT1 (PDB ID: 3MVH) and PI3K α (PDB ID: 7K6M) were used for docking.

First, the docking protocol was validated by re-docking the co-crystallised ligands into their respective kinase structures. This step confirmed that the docking method could accurately reproduce experimental binding poses, with low RMSD values of 0.489 Å for AKT1 and 1.021 Å for PI3K α . Importantly, the validation reproduced key interactions with critical amino acids: Glu228 and Ala230 in AKT1, and Val850 and Lys802 in PI3K α (Figures 9 and 10).

These results demonstrate that the docking approach is reliable and can be used to predict how the six candidate compounds bind to both kinases. Successful validation of the docking protocol ensures that we can reliably predict how the six candidate compounds interact with the hinge regions of both kinases.

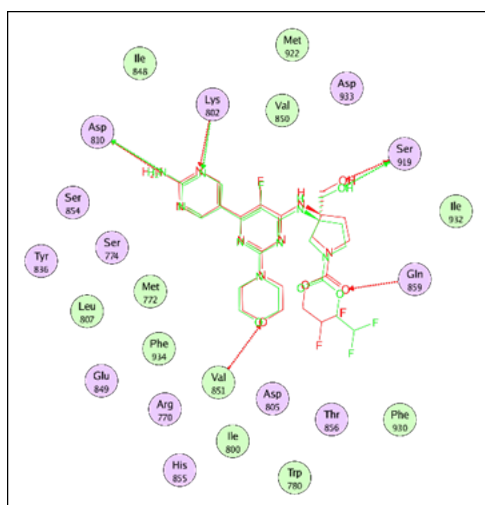


(A)

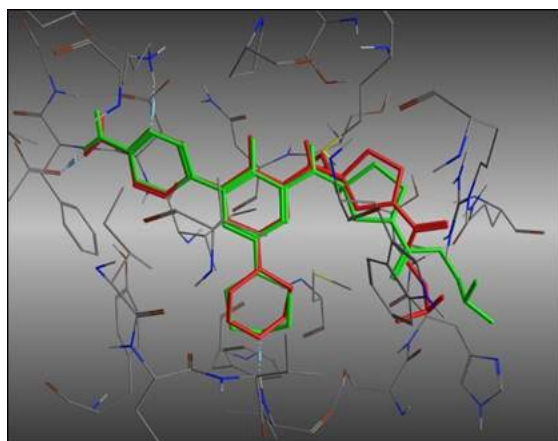


(B)

Figure 9: 2D diagram (A) and 3D representation (B) of the superimposition of docking pose (green) and the co-crystallized (red) of the co-crystallised ligand in the AKT1 active site with RMSD of 0.489 Å.



(A)



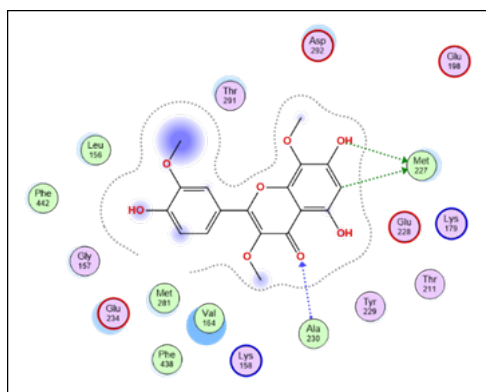
(B)

Figure 10: 2D diagram (A) and 3D representation (B) of the superimposition of docking pose (green) and the co-crystallized (red) of the co-crystallised ligand in the PI3K α active site with RMSD of 1.021 Å.

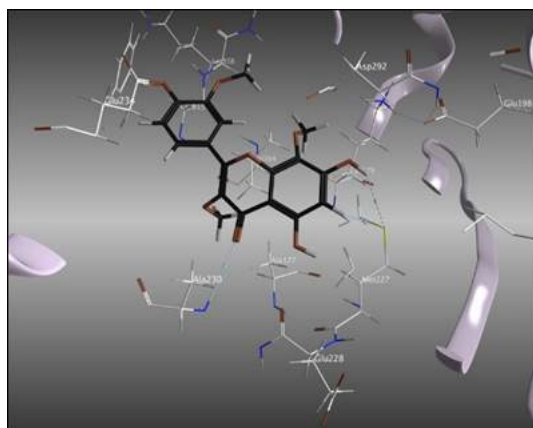
The validated molecular docking protocol was then used to test the six promising compounds (ZINC03032094, ZINC04716510, ZINC05999146, ZINC05732760, ZINC01662799, and ZINC04268860) in the binding sites of both AKT1 and PI3K α .

Two of these compounds, ZINC05999146 and ZINC04268860, were found to form all the key interactions required to bind effectively to both kinases. This suggests that they are the strongest candidates as dual AKT1/PI3K α inhibitors.

In AKT1, ZINC05999146 forms a hydrogen bond with Ala230, where the ligand's C=O group interacts with the NH group of Ala230. It also forms a hydrogen bond with Met227 through its OH group (Figure 11). The docking score for this compound in AKT1 was -12.24 kcal/mol (Table 2), indicating a strong and stable binding interaction.



(A)



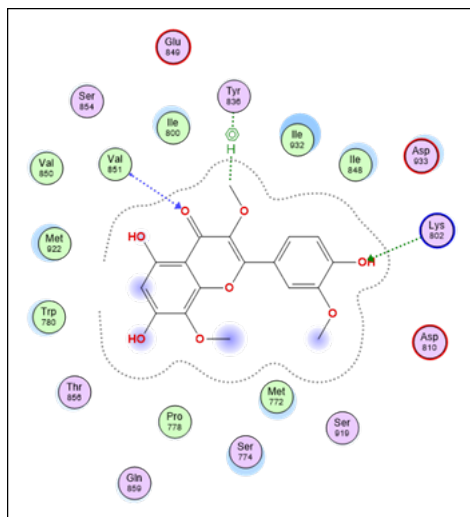
(B)

Figure 11: 2D interaction diagram (A) and 3D representation (B) showing compound ZINC05999146 docking pose interactions with the key amino acids (hot spots) in the AKT1 active site.

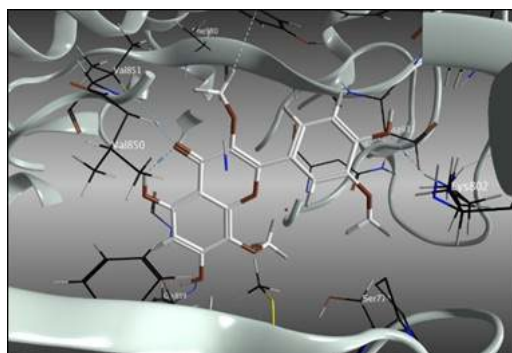
In PI3K α , ZINC05999146 forms a key hydrogen bond with the hinge residue Val851 through its C=O group, and an additional hydrogen bond with Lys802 via its OH group (Figure 12).

The docking score for this compound in PI3K α was -13.73 kcal/mol (Table 2), indicating a strong and stable interaction with the kinase. A high-quality docking score like this suggests that the compound is likely to bind effectively in a biological setting,

making it a promising candidate for further drug design and development as a dual AKT1/PI3K α inhibitor.



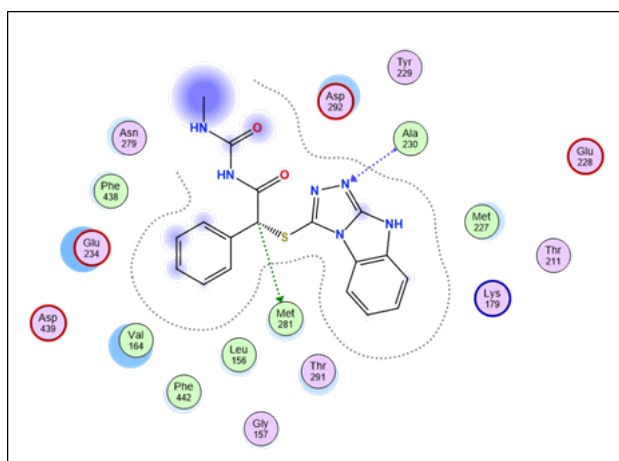
(A)



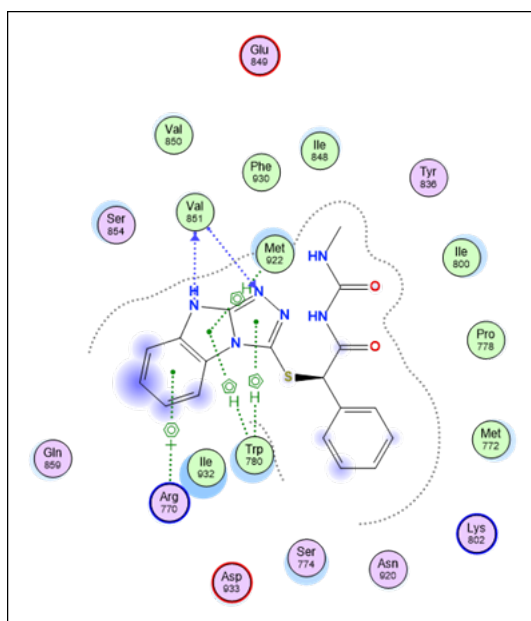
(B)

Figure 12: 2D interaction diagram (A) and 3D representation (B) showing compound ZINC05999146 docking pose interactions with the key amino acids (hot spots) in the PI3K α active site.

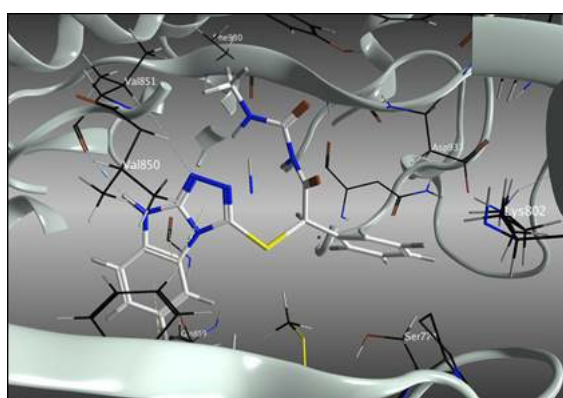
For compound ZINC04268860, in AKT1 it forms a key hydrogen bond with the hinge residue Ala230, where the triazolo nitrogen of the ligand interacts with the NH group of Ala230 (Figure 13). The docking score for this compound in AKT1 was -12.80 kcal/mol (Table 2), indicating a strong and stable binding. This suggests that ZINC04268860 is likely to fit well into the AKT1 active site and effectively block its activity, making it a promising candidate for drug development.



In PI3K α , ZINC04268860 forms a key hydrogen bond with the hinge residue Val851, using nitrogen atoms from its heterocyclic ring to interact with the protein (Figure 14). The docking score for this compound in PI3K α was -11.93 kcal/mol (Table 2), indicating a strong and stable binding. This suggests that ZINC04268860 can effectively fit into the PI3K α active site, supporting its potential as a dual inhibitor for both AKT1 and PI3K α in drug development.



(A)



(B)

Figure 14: 2D interaction diagram (A) and 3D representation (B) showing compound ZINC04268860 docking pose interactions with the key amino acids (hot spots) in the PI3K α active site.

Table 2: Predicted docking score S (kcal/mol) of the promising dual AKT1/PI3K α inhibitor hits ZINC05999146 and ZINC04268860 as well as for the co-crystallised ligands in the kinase domains of AKT1 and PI3K α .

ID	AKT1 Docking score S (kcal/mol)	PI3K Docking score S (kcal/mol)
ZINC ID 05999146	- 12.24	- 13.73

ID	AKT1 Docking score S (kcal/mol)	PI3K Docking score S (kcal/mol)
ZINC ID 04268860	– 12.80	– 11.93
Co-crystallised ligand	– 15.59	– 13.97

Both compounds interact with important hinge residues — Ala230 in AKT1 and Val851 in PI3K α — helping them bind strongly to the kinase active sites. This suggests that they could potentially inhibit both kinases at the same time, which is promising for cancer treatment. However, further in vitro and in vivo experimental validation is required to confirm their effectiveness and safety as potential drugs.

UROS Experience

Participating in the UROS scheme was an extremely rewarding and eye-opening experience. Before the project, I had little practical knowledge of computer-aided drug design (CADD), but through working on pharmacophore modelling, virtual screening, and molecular docking I have a deeper appreciation of how detailed and multi-step real research is. Using sophisticated software like MOE pushed me outside my comfort zone, but I quickly adapted and learned to apply these techniques independently, which strengthened my confidence and problem-solving skills.

This experience taught me that research is not a straight path. I needed to adapt and adjust my methods to maintain accuracy and relevance, embracing the idea that when one approach reaches a dead end, new opportunities emerge.

I also learned that research is an iterative process, requiring flexibility and adaptation to stay current and scientifically sound, especially with the type of protein kinase chosen for the focus of the project. Furthermore, this UROS project has laid the foundation for further research that I hope to continue with UROS in the future.

Conclusion

This study focused on identifying compounds with the potential to act as dual inhibitors of the kinases PI3K α and AKT1, which play key roles in cancer progression. Using structure-based pharmacophore modelling, virtual screening, and molecular docking, several promising compounds were identified, with ZINC05999146 and

ZINC04268860 emerging as strong candidates for further investigation. These findings provide a foundation for designing novel dual-kinase inhibitors, though laboratory and in vivo experiments are required to confirm their effectiveness and safety.

Participating in the UROS scheme has been a valuable experience and taught me practical research skills, learning navigation of CADD software, and gaining insight into the drug discovery process for future research projects and my third-year dissertation.

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