

Discovery of mTOR Receptor Modulators Targeting Breast Cancer by Hybrid of Virtual Screening and Molecular Docking Approach

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ABSTRACT

This research paper presents a comprehensive approach integrating virtual screening and molecular docking to identify potential therapeutic candidates. Pharmacophore-based virtual screening was employed to assess the structural similarities of compounds to a reference molecule, revealing promising candidates with high similarity scores. Subsequently, molecular docking studies were conducted to predict the binding affinities of these compounds to the target receptor, 4DRH. ChEMBL3775006 emerged as a lead candidate, demonstrating both structural resemblance and strong binding affinity to the target protein. ADME studies highlighted its pharmacokinetic properties, while toxicity prediction studies provided insights into potential adverse effects. Overall, this study underscores the utility of virtual screening and molecular docking in identifying novel drug candidates with therapeutic potential.

Keywords: Virtual screening, Molecular docking, Pharmacophore, ChEMBL3775006, 4DRH, ADME, Toxicity prediction, Therapeutic candidates.

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INTRODUCTION

Breast cancer is the most frequently diagnosed disease globally and remains the leading cause of cancer mortality among women, posing a significant threat to public health. Historically perceived as a condition primarily affecting industrialized nations, data from 2020 revealed that less developed regions accounted for two-thirds of breast cancer-related deaths and over half of all new diagnoses.¹ A poorer prognosis in breast cancer has been associated with mTOR expression. Research by Walsh and colleagues indicated that triple-negative breast tumors were more likely to exhibit phospho-mTOR. Additionally, studies have shown that RICTOR expression, necessary for mTORC2 signaling, is actually reduced in breast tumors compared to normal breast tissue, even though mTORC2 signaling may enhance oncogenic signals *via* Akt and mTOR pathways.²

Tamoxifen (Figure 1), the most commonly prescribed medication for chemoprevention and treatment of breast cancer, saves millions of patients annually.³ Mechanistic target of rapamycin (mTOR) is a serine/threonine protein kinase that

is evolutionarily conserved and part of the phosphoinositide 3-kinase (PI3K)-related kinase family. mTOR regulates a wide array of functions, including metabolism, aging, and cell proliferation. This protein kinase operates downstream of Akt and PI3K. The term "mTOR" encompasses two distinct complexes, mTORC1 and mTORC2, each with unique mechanisms.⁴ mTORC1, the target of rapamycin and rapamycin analogs, has been extensively studied and characterized. However, it is now understood that these drugs, at sufficiently high doses, also inhibit mTORC2, subsequently affecting cancer cell proliferation and metabolism.⁵

This study aims to address existing gaps by employing an extensive methodology. We utilized the ChEMBL 2D database to identify potential mTOR receptor modulators through molecular docking approaches. Utilizing advanced 3D pharmacophore modeling tools, we screened the database for compounds with structural properties conducive to mTOR regulation. Our computational techniques are designed to identify novel bioactive compounds that could enhance therapeutic options for breast cancer by inhibiting mTOR.

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The significance of this study lies in its potential to uncover new mTOR receptor inhibitors, thereby expanding the arsenal of therapeutic options for breast cancer treatment. Investigating compounds like tamoxifen and its derivatives opens new avenues for synthetic chemical discovery in the quest for effective breast cancer treatments by exploring the molecular complexities of MTOR inhibition. Ultimately, the findings of this study could lead to innovative therapeutic strategies and support the ongoing fight against mTOR-positive breast cancer.

MATERIALS AND METHODS

Collection and Compound Choice

Tamoxifen was chosen for virtual screening research due to its proven effectiveness in treating breast cancer, especially estrogen receptor-positive cases. Its well-documented safety profile and ability to block estrogen receptors make it a compelling candidate. Additionally, its potential for use in preventing breast cancer in high-risk individuals adds to its significance. With its established track record and favorable properties, tamoxifen stands as a promising subject for further study in breast cancer treatment and prevention.

Pharmacophore-based Virtual Screening

A conventional 3-point pharmacophore screening methodology used to identify potential MTOR inhibitors. This process began with determining the essential pharmacophoric features required for effective MTOR inhibition, such as hydrogen bond donors and acceptors, hydrophobic regions, and aromatic ring structures crucial for binding to the mTOR receptor. Based on these features, we constructed a pharmacophore model representing the spatial arrangement of these characteristics. Using this model, we screened extensive compound libraries, specifically the ChEMBL 2D database, to identify compounds that possess the necessary structural attributes. The identified compounds were then validated through computational techniques to ensure they meet the pharmacophoric criteria and demonstrate strong potential as mTOR inhibitors. This integrated approach facilitated the efficient discovery of novel mTOR inhibitors, enhancing our understanding of the structural requirements for mTOR inhibition and potentially improving therapeutic options for breast cancer.^{6,7}

Preprocessing of Protein Structure

The crystal structure of the PPIase domain in relation to the FRB fragment and rapamycin is illustrated in Figure 2, available in PDB format under the PDB ID 4DRH. This structural data was sourced from the RCSB Protein Data Bank (<https://www.rcsb.org/>) and subsequently preprocessed using the PDB-REDO web server, version 8.01 (<https://pdb-redo.eu/db/4drh>).⁸

Molecular Docking

Molecular docking simulations were used to determine how efficiently certain medicines bonded to the mTOR receptor and interacted with the CYP receptor respectively. To virtually screen compounds with high binding affinities, beneficial interaction patterns, and structural compatibility with mTOR,

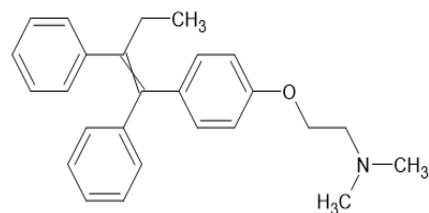


Figure 1: Molecular structure of tamoxifen

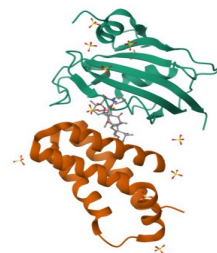


Figure 2: Protein structure of mTOR (PDB ID: 4DRH)

CB-Cock 2.0 used. The purpose of this extensive computational approach is to identify potential mTOR inhibitors in the ChEMBL 2D database. Combining these techniques increases the prospect of discovering bioactive compounds with potential as therapeutic agents for the treatment of breast cancer.⁹

ADMET Properties

The study analyzed a compound's physicochemical and pharmacokinetic characteristics using computational techniques. It assessed its molecular structure, lipophilicity, bioavailability, drug-likeness criteria, and ease of synthesis using synthetic accessibility scores. The study also identified undesired features.¹⁰

Getting access to a reliable toxicity prediction model or database was necessary for data retrieval in the early phases of the toxicity study. This model provides predictions for cytotoxicity, immunotoxicity, mutagenicity, carcinogenicity, and organ toxicity.^{11,12}

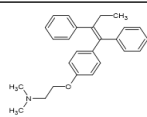
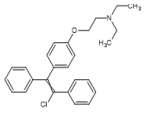
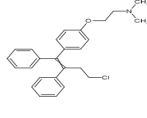
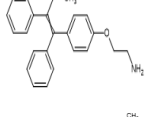
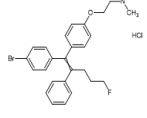
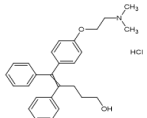
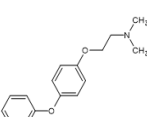
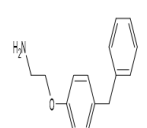
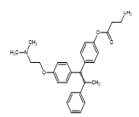
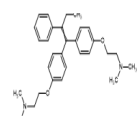
The toxicity model report was thoroughly examined, with an emphasis on immunotoxicity predictions, to ensure a clear comprehension of its operation and implications, allowing for well-informed decision-making in further stages of the investigation.^{13,14}

RESULTS AND DISCUSSION

Results of Pharmacophore-based Virtual Screening

The results of the virtual screening given in Table 1 reveal the similarity scores of various compounds to a reference molecule, potentially indicating their structural resemblance and potential functional similarity. ChEMBL83 obtained the highest similarity score of 1, suggesting it is most similar to the reference molecule. This indicates a close structural match, possibly implying comparable biological activities or target interactions. Following closely, ChEMBL954 received a high similarity score of 0.98, further indicating a strong structural resemblance to the reference

Table 1: Results of virtual screening

S. No.	CHEMBL Id	2D structures	Similarity score
1.	CHEMBL83		1
2.	CHEMBL954		0.98
3.	CHEMBL1655		0.75
4.	CHEMBL3422031		0.74
5.	CHEMBL3891326		0.60
6.	CHEMBL3986248		0.60
7.	CHEMBL3921982		0.55
8.	CHEMBL163807		0.54
9.	CHEMBL3775006		0.54
10.	CHEMBL3099616		0.50

compound. Conversely, compounds like CHEMBL1655 and CHEMBL3422031 obtained lower similarity scores of 0.75 and 0.74, respectively, indicating less structural similarity to the reference molecule. Additionally, compounds such as CHEMBL3891326, CHEMBL3986248, and CHEMBL3921982 showed moderate similarity scores ranging from 0.60 to 0.55, suggesting partial structural resemblance. CHEMBL163807 and CHEMBL3775006 both received similarity scores of 0.54, indicating a relatively lower structural similarity to the reference molecule. Lastly, CHEMBL3099616 had the lowest similarity score of 0.50, indicating the least resemblance to the

reference compound. In conclusion, these virtual screening results provide insights into the structural similarity of various compounds to a reference molecule, aiding in the identification and prioritization of potential candidates for further experimental evaluation or drug discovery efforts.

Results of Crystallographic Structure Refinement

The crystallographic structure of 4DRH, refined using PDB-REDO, exhibits significant improvements in several quality metrics compared to the original structure. The R factor decreased from 0.1863 to 0.1755, and the R-free value improved from 0.2241 to 0.1987. Bond angle RMS Z-scores showed a substantial improvement from 0.956 to 0.495, and bond length RMS Z-scores improved from 0.812 to 0.670. However, bump severity showed a slight reduction from 56 to 47, while hydrogen bond satisfaction remained unchanged at 35. When compared to resolution neighbors, the Ramachandran Z-score improved from -1.25 to -0.788, with the number of residues in preferred regions remaining at 427 and those in allowed regions increasing from 8 to 9.

The data analysis of the crystallographic structure of 4DRH after PDB-REDO refinement indicates a notable improvement in the overall quality of the model. Specifically, the R factor and R-free values, which are critical indicators of the model's accuracy, showed significant reductions, suggesting a better fit of the model to the observed data. The bond angle and bond length RMS Z-scores improved markedly, reflecting the enhanced geometric accuracy of the refined structure.

Based on the distribution of data points in the Kleywegt-like plot illustrated in Figure 3, the protein model appears to be of high quality, with most points located in favored regions, indicating a well-folded and reliable structure. However, the presence of significant points in disallowed regions suggests potential issues such as steric clashes or unrealistic bond angles, which may require further refinement. Points scattered throughout the plot could indicate areas of the protein that are partially folded or require additional modeling adjustments.

Furthermore, model quality metrics saw considerable enhancements. The percentiles for Ramachandran plot normality and rotamer normality increased, indicating a better conformational quality of the protein backbone and side chains, respectively. Improvements in coarse and final packing scores demonstrate a more favorable packing of atoms in the refined structure, although bump severity slightly decreased, suggesting fewer steric clashes post-refinement. Hydrogen bond satisfaction remained constant, indicating consistent hydrogen bonding interactions before and after refinement.

When compared to resolution neighbors, the Ramachandran Z-score improved, indicating a more statistically favorable distribution of backbone dihedral angles. The number of residues in preferred regions remained the same, while those in allowed regions slightly increased, suggesting minor adjustments that still align well with the expected conformational space.

These refinements likely result in a more reliable and precise representation of the PPIase domain in relation to

the FRB fragment and rapamycin, thereby providing a better foundation for subsequent analyses and interpretations.

Results of Docking Studies

Results given in Table 2 among the analyzed ChEMBL compounds, ChEMBL3775006 exhibited the highest Vina score of -9.9, indicating a strong predicted binding affinity to the receptor, as illustrated in Figure 4. This suggests that ChEMBL3775006 has the potential to form stable interactions with the target protein, which could be indicative of its efficacy as a potential therapeutic agent. Additionally, compounds such as ChEMBL1655, ChEMBL954, and ChEMBL3986248 also demonstrated high Vina scores (-9.2, -9.1, and -9.3, respectively), indicating favorable binding interactions with the target protein. On the other hand, compounds like ChEMBL163807 showed relatively lower Vina scores (-8.0), suggesting weaker binding affinity. Overall, these docking results provide valuable insights into the molecular interactions between the analyzed compounds and the target receptor, aiding in the selection and prioritization of potential drug candidates for further experimental validation and development.

The observed variation in Vina scores among the analyzed ChEMBL compounds in the docking studies conducted using the CB-DOCK server can be attributed to several factors influencing their binding affinities to the target receptor, 4DRH. ChEMBL3775006 exhibited the highest Vina score, indicating strong predicted binding affinity, likely due to favorable interactions with critical binding site residues and optimal molecular geometry. Similarly, compounds like ChEMBL1655, ChEMBL954, and ChEMBL3986248 also demonstrated high Vina scores, suggesting their structural features are conducive to effective binding to the receptor. Conversely, compounds with lower Vina scores, such as ChEMBL163807, may have suboptimal molecular properties or unfavorable interactions with the receptor, resulting in weaker binding affinity.

Results of ADME Studies

The ADME studies of ChEMBL3775006, conducted using the Swiss ADME server, reveal several key properties. The compound has an average Log Po/w value of 5.04, indicating a high lipophilicity. Its solubility is extremely low, measured at 2.04×10^{-7} mg/mL and 4.60×10^{-10} mol/l, suggesting poor aqueous solubility. Despite this, it exhibits high gastrointestinal (GI) absorption but is not permeant to the BBB. It is identified as a substrate for P-gp, which could influence its distribution and excretion. In terms of cytochrome P450 interactions, ChEMBL3775006 inhibits CYP2C19 and CYP2D6 but does not inhibit CYP1A2, CYP2C9, or CYP3A4, indicating selective interactions with these metabolic enzymes.

The compound has a skin permeation log Kp value of -3.83 cm/s, indicating low skin permeability. It meets Lipinski's rule of five with one violation but fails to comply with the Ghose, Veber, Egan, and Muegge criteria, suggesting potential issues with drug-likeness and oral bioavailability. The bioavailability score is 0.55, indicating moderate bioavailability. The

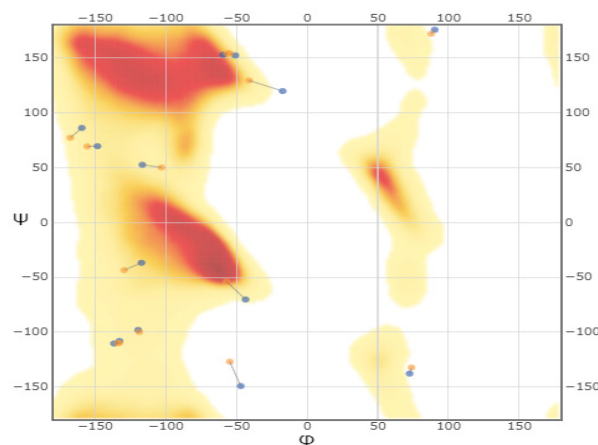


Figure 3: PDB REDO obtained Kleywegt Plot

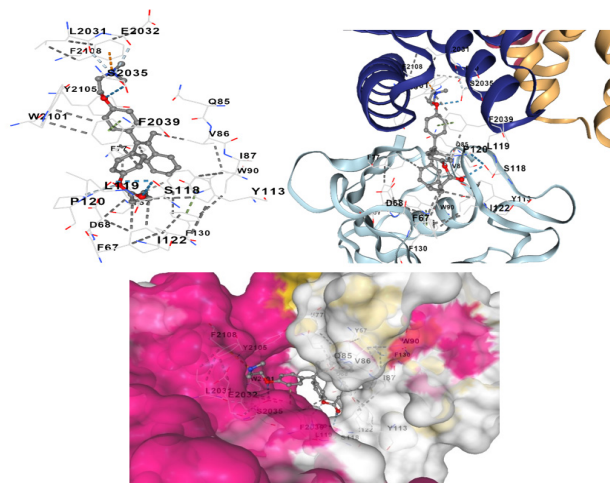


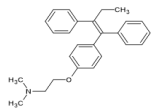
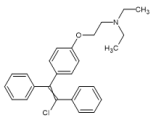
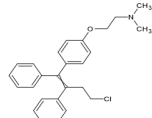
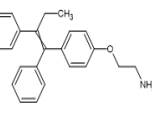
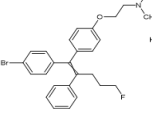
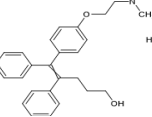
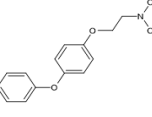
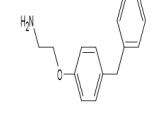
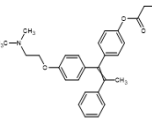
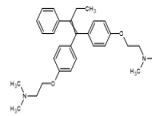
Figure 4: Interaction of ChEMBL3775006 with 4DRH

compound does not trigger any pan-assay interference compounds (PAINS) alerts but has one Brenk alert due to the presence of phenol_ester and stilbene groups.

Results of the Toxicity Prediction Studies

The toxicity model report for ChEMBL 3775006 reveals various predictions regarding organ toxicity, toxicity endpoints, and its impact on specific signaling pathways^{15,16}. The compound is predicted to be hepatotoxic with a probability of 0.69, neurotoxic with a probability of 0.87, and respiratory toxic with a probability of 0.98, while it is predicted to be inactive for nephrotoxicity and cardiotoxicity with probabilities of 0.90 and 0.77, respectively. In the context of the Tox21 nuclear receptor signaling pathways, the compound is predicted to be inactive for the aryl hydrocarbon receptor (Ahr) with a probability of 0.97, the androgen receptor (AR) and its ligand-binding domain (AR-LBD) both with probabilities of 0.99, and the peroxisome proliferator-activated receptor gamma (PPAR-Gamma) with a probability of 0.99. However, it is predicted to be active for aromatase with a probability of 1.0 and for the estrogen receptor alpha (ER) with a probability of 0.99. Furthermore, for the Tox21 stress response pathways, the compound is predicted to be inactive for mitochondrial

Table 2: Results of molecular docking experiments

S. No	CHEMBL Id	2D Structures	Score
1.	CHEMBL83		-8.9
2.	CHEMBL954		-9.1
3.	CHEMBL1655		-9.2
4.	CHEMBL3422031		-8.6
5.	CHEMBL3891326		-9.0
6.	CHEMBL3986248		-9.3
7.	CHEMBL3921982		-8.6
8.	CHEMBL163807		-8.0
9.	CHEMBL3775006		-9.9
10.	CHEMBL3099616		-9.3

membrane potential (MMP) disruption with a probability of 0.70. This comprehensive toxicity profile provides valuable insights into the potential adverse effects and mechanistic interactions of CHEMBL 3775006, highlighting areas of concern for further investigation.^{17,18}

The toxicity model report for CHEMBL 3775006 provides a comprehensive assessment of its potential toxicological effects across various endpoints and signaling pathways. The data indicate that the compound poses significant risks for several types of organ toxicity. Specifically, it is predicted

to be hepatotoxic (probability of 0.69), neurotoxic (0.87), and respiratory toxic (0.98). These high probabilities suggest a considerable potential for liver, brain, and lung damage. In contrast, the compound is predicted to be inactive for nephrotoxicity (0.90) and cardiotoxicity (0.77), indicating a lower risk for kidney and heart toxicity.^{19,20}

Regarding general toxicity endpoints, CHEMBL 3775006 is predicted to be immunotoxic with a high probability (0.96), suggesting a strong likelihood of adverse effects on the immune system.²¹ However, it is predicted to be inactive for carcinogenicity (0.62), mutagenicity (0.97), and cytotoxicity (0.93), implying a lower potential for cancer risk, genetic mutations, and general cell toxicity.^{22,23}

CONCLUSION

The comprehensive analysis of pharmacophore-based virtual screening, crystallographic structure refinement, docking studies, ADME assessment, and toxicity prediction studies provides valuable insights into the potential of CHEMBL3775006 as a therapeutic agent.

Firstly, in the virtual screening results, CHEMBL3775006 displayed the highest similarity score to the reference molecule, indicating a close structural match and potentially comparable biological activities. This structural resemblance is further supported by its favorable docking score of -9.9, suggesting a strong binding affinity to the target receptor, 4DRH. Additionally, compounds like CHEMBL1655, CHEMBL954, and CHEMBL3986248 also exhibited high similarity scores and favorable docking scores, indicating promising candidates for further investigation.

Moreover, the ADME studies revealed important properties of CHEMBL3775006. While it exhibits high lipophilicity and GI absorption, its extremely low aqueous solubility and inability to permeate the blood-brain barrier may pose challenges for its formulation and central nervous system targeting. Additionally, its interactions with metabolic enzymes suggest potential implications for its pharmacokinetic profile, highlighting the need for careful consideration during drug development.

Furthermore, toxicity prediction studies indicate potential hepatotoxicity, neurotoxicity, and respiratory toxicity of CHEMBL3775006 alongside immunotoxicity. These predictions raise concerns about its safety profile, especially considering its high probabilities for organ toxicity and immunotoxicity. However, it is inactive for nephrotoxicity, cardiotoxicity, carcinogenicity, mutagenicity, and cytotoxicity, suggesting a nuanced toxicity profile that warrants further investigation.

In conclusion, while CHEMBL3775006 shows promising structural similarity, binding affinity, and pharmacokinetic properties, its potential toxicity risks, particularly hepatotoxicity, neurotoxicity, and respiratory toxicity, necessitate thorough preclinical evaluation. Further experimental validation and optimization efforts are warranted to harness its therapeutic potential while mitigating its adverse effects.

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