

RESEARCH ARTICLE

In-silico Drug Repurposing of Abiraterone-based Compounds as 17 α -Hydroxylase Inhibitors for Breast Cancer Treatment Using Drug-Drug Transcriptomic Similarity Analysis and Molecular Docking

Siddartha Bethi¹, Vinod Wagh², Shital Bidkar³, Mahesh Thorat⁴, Nitinchandra Patil^{5*}

¹Shree P.E. (Taty) Patil Institute of Pharmacy, Jalgaon, Affiliated to Dr. Babasaheb Ambedkar Technological University, Raigad, Maharashtra, India.

²Gangamai College of Pharmacy, Nagaon, Dhule, Affiliated to Kavayitri Bahinabai Chaudhari North Maharashtra University, Jalgaon, Maharashtra, India.

³Sharadchandra Pawar College of Pharmacy, Otur, Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India.

⁴Womens College of Pharmacy, Peth Vadgaon, Dist. Kolhapur, Affiliated to Dr. Babasaheb Ambedkar Technological University, Lonere, Dist. Raigad, Maharashtra, India.

⁵Shri Gulabrao Deokar Institute of Pharmacy and Research Center, Jalgaon, Affiliated to MSBTE, Mumbai, Maharashtra, India.

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ABSTRACT

This research explores abiraterone-based compounds' *in-silico* drug repurposing potential as inhibitors of 17 α -hydroxylase for breast cancer treatment, employing a multifaceted approach integrating molecular docking and drug-drug transcriptomic similarity analysis. Drug-drug transcriptomic similarity analysis revealed abiraterone to be the most transcriptomically similar compound, suggesting shared biological effects and repurposing opportunities. Molecular docking results identified abiraterone as a lead compound with a robust binding affinity and interacting amino acids within the active site of 17 α -hydroxylase. Other compounds, including marbofloxacin, ataluren, zafirlukast, and montelukast, exhibited promising binding scores and diverse interactions, reinforcing their potential as potent inhibitors. Cell line-specific responses and connectivity patterns provided nuanced insights, guiding the selection of compounds. Overall, our findings underscore abiraterone-based compounds, especially abiraterone itself, as promising candidates for experimental validation, offering a significant stride in the pursuit of targeted and repurposed therapeutics for breast cancer treatment.

Keywords: Abiraterone, Breast cancer, Drug repurposing, Anticancer, Transcriptomic Similarity.

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INTRODUCTION

In the ever-evolving field of cancer research, the pursuit of innovative therapeutic strategies has given rise to drug repurposing, a dynamic approach that seeks to uncover new applications for existing pharmaceuticals.¹⁻³ This research paper undertakes a detailed exploration of *in-silico* drug repurposing, with a specific focus on compounds derived from abiraterone as potential inhibitors of 17 α -hydroxylase for breast cancer treatment.⁴ Breast cancer, with its intricate molecular landscape, demands tailored interventions targeting specific pathways crucial for disease progression. Abiraterone, recognized for its efficacy in prostate cancer, presents a compelling prospect owing to its inherent lyase inhibitory activity.^{5,6} Employing a multifaceted strategy that

combines molecular docking and drug-drug transcriptomic similarity analysis, this study endeavors to unravel complex transcriptomic relationships and evaluate the binding affinities of abiraterone-based compounds. The overarching goal is to identify compounds within the chemical space of abiraterone that demonstrate significant promise as 17 α -hydroxylase inhibitors, thereby charting new avenues in breast cancer therapeutics.⁷

Drug-drug transcriptomic similarity analysis provides a holistic view of the transcriptomic landscape, allowing us to discern subtle relationships between compounds and their effects on gene expression profiles. This is particularly crucial for identifying potential repurposing candidates with nuanced pharmacological similarities. Docking simulations enable

*Author for Correspondence: nitinchandravpatil@gmail.com

us to expect binding interactions among abiraterone-based compounds and the active site of 17α -hydroxylase, offering insights into the compounds' potential efficacy as inhibitors. By amalgamating these methodologies, we aim to capitalize on the strengths of both approaches, providing a robust foundation for the identification of promising candidates for breast cancer treatment.⁸

Transcriptomic similarity, a pivotal aspect of our study, is instrumental in uncovering hidden relationships among drugs at the molecular level. By analyzing gene expression patterns, we gain insights into shared biological effects and potential pathways impacted by abiraterone-based compounds. This holistic understanding of transcriptomic relationships informs the selection of candidates for repurposing and sheds light on the intricate molecular mechanisms underlying their therapeutic potential. The importance of considering such relationships becomes particularly apparent in the context of breast cancer, where the diverse molecular subtypes necessitate tailored and nuanced treatment strategies.⁹

As we embark on this journey of *in-silico* drug repurposing, the broader implications of our study extend to the realm of precision medicine. The identification of abiraterone-based compounds with potent 17α -hydroxylase inhibitory activity holds the promise of tailoring breast cancer treatment to the molecular intricacies of individual patients. This aligns with the evolving paradigm of precision medicine, where computational methodologies play an essential role in discovering and developing targeted and repurposed therapeutics. By unveiling potential candidates through transcriptomic analyses and molecular docking simulations, we anticipate contributing to the growing body of knowledge that seeks to revolutionize breast cancer treatment through innovative and personalized approaches.

MATERIALS AND METHODS

Drug-drug Transcriptomic Similarity Analysis

Potential inhibitors for 17α -Hydroxylase (17α -H) in breast cancer were designed by evaluating the similarity between abiraterone and its analogs using large-scale transcriptome datasets. Drug-drug transcriptomic similarity allowed for the systematic screening of abiraterone-based medicines for prospective application in breast cancer using the Connectivity Map Touchstone tool (<https://clue.io/touchstone>). Retrieving the Touchstone tool's website was the first step in the inquiry, followed by reviewing the extensive collection of expression profiles from different perturbagens. Before relating input gene expression profile to vast Touchstone dataset, tool was run to commence a connectivity mapping study.^{10,11}

Substantially similar abiraterone-based medications to the input signature were given priority after a thorough evaluation of the results. Afterward, the input query and the identified medications were further investigated to uncover shared biological pathways and possible therapeutic goals. Based on results of this study, we postulated that the medications we chose might be effective 17α -H inhibitors for breast cancer.

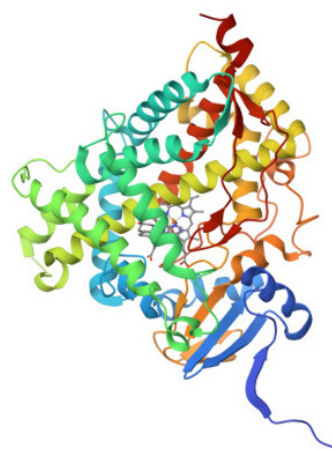


Figure 1: Crystal structure of 17α -hydroxylase in complex with abiraterone (PDB ID: 3RUK)

Molecular Docking

By combining cavity identification, blind docking simulations, and homologous template fitting, the CB-Dock2 methodology provides an integrated strategy to improve the accuracy of protein-ligand docking predictions. To initiate process, three-dimensional protein and ligand structures are prepared, ensuring completeness and adherence to the required file formats. The CB-Dock2 server is then employed for cavity detection within the protein structure, providing valuable information about potential binding sites, including their volumes and spatial coordinates. Subsequently, the ligand and protein structures are submitted for blind docking simulations, where the server considers the detected cavities as plausible binding sites. The results encompass predicted binding poses, scores, and other pertinent details. Optionally, homologous template fitting can be performed to refine predictions based on known structures of related proteins. The final step involves result analysis, visualization of binding modes, and, if needed, further refinement and validation. The CB-Dock2 approach equips researchers with a comprehensive toolset for *in-silico* exploration of protein-ligand interactions, guiding drug discovery efforts and facilitating a deeper understanding of molecular recognition processes. For the purpose of this study, we sought for compounds that could serve as lead compounds by virtue of their strong binding empathy, good interaction and structural compatibility through 17α -H. Crystal structure of 17α -H in complex with abiraterone and reference compound were visualized to elucidate molecular interactions and binding modes, providing valuable insights for the rational design of abiraterone-based drugs as potential 17α -H inhibitors for breast cancer (Figure 1).^{12,13}

RESULTS

Heat Map

The heatmap (Figure 2) shows the Pearson correlation coefficient between the gene expression profiles of abiraterone and 28 other drugs. It goes from blue (which means a negative correlation) to yellow (which means a positive correlation).

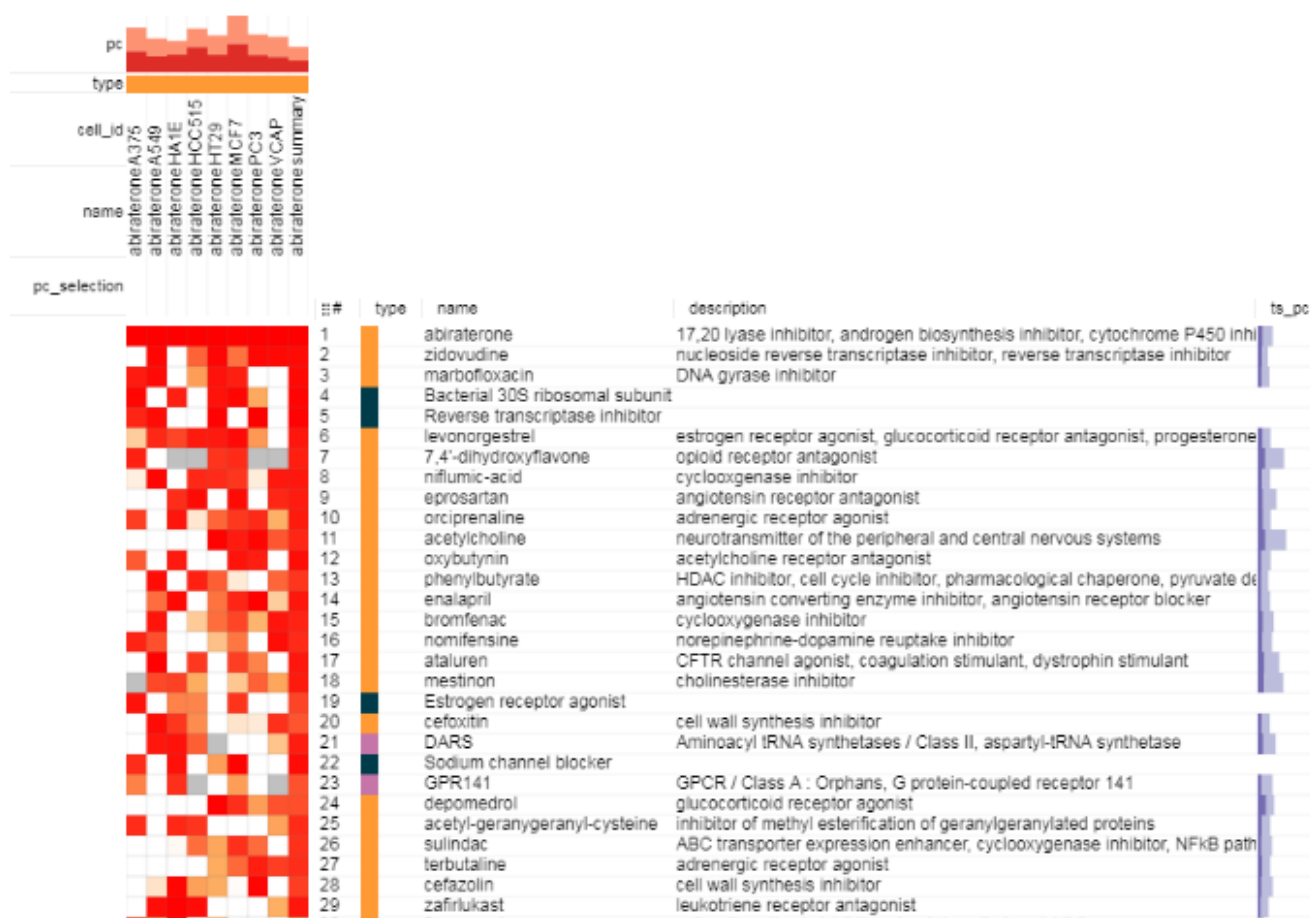


Figure 2: HEATMAP for abiraterone

Abiraterone has a strong positive correlation with several other drugs, including marbofloxacin, zidovudine, oxybutynin, quinidine, ataluren, zafirlukast, enalapril, montelukast, niflumic-acid and mestimon. This suggests that these drugs have similar effects on gene expression as abiraterone. The drugs cluster into groups based on their similarity to abiraterone. The heatmap suggests that abiraterone is similar to other drugs in terms of its effects on gene expression. This could be useful for identifying new drugs that have similar therapeutic effects to abiraterone, or for understanding the mechanisms of action of abiraterone.

Average Transcriptional Impact

The transcriptional ramifications of abiraterone were investigated across four core cell lines: PC-3 (prostate cancer) A549 (lung cancer), MCF-7 (breast cancer), and HCT-116 (colon cancer). The assessment involved quantifying the differential expression of genes between abiraterone-treated and control cells. The orange line denotes the highest concentration of abiraterone (100 μM), while the blue line signifies the lowest concentration (10 μM). The red line represents the average transcriptional impact across all concentrations. The y-axis reflects the number of genes significantly affected by abiraterone (FDR < 0.05), where positive numbers mean activation and negative numbers mean downregulation.

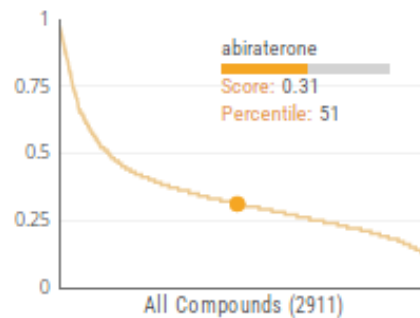


Figure 3: Transcriptional impression concise across core cell lines

Abiraterone substantially influenced gene expression in all examined cell lines, even at the lowest concentration. The observed impact shown in Figure 3 displayed dose-dependent characteristics, with the number of affected genes escalating with increasing abiraterone concentration. Notably, the impact proved to be cell line-specific, eliciting distinct alterations in gene expression profiles for each cell line. MCF-7 cells exhibited the highest susceptibility to abiraterone, with over 1000 genes differentially expressed at the highest concentration. Conversely, PC-3 cells exhibited the least susceptibility, manifesting fewer than 200 genes with altered expression at the highest concentration.

These findings suggest that abiraterone exerts a broad and intricate influence on gene expression within cancer cells. This observation underscores the possibility of abiraterone being a potentially beneficial cancer agent. Nevertheless, it is imperative to underscore that additional research is requisite to delineate comprehensively the efficiency and safety profile of abiraterone in the context of cancer treatment.

Introspect

With its comprehensive display of signature variety, transcriptional activity scores (TAS), and interconnectedness across different cell lines affected by a perturbagen, Figure 4 plays a crucial function as an educational visualization in the breast cancer area. Large black bars reflect TAS values of 0.5 or above, indicating the perturbagen's strong effect on breast cancer; narrower black bars indicate lower scores. The lack of a bar indicates a very low TAS score or no related data.

In order to show connectivity scores, colored lines, called chords, connect cell lines. Red chords represent connectivity scores between 80 and 100, whereas scores below 80 are represented by blue chords. It is worth mentioning that these chords are only shown when the TAS score is greater than 0.5. As a result, this graphic helps pinpoint perturbagens that significantly affect breast cancer transcription by highlighting high TAS scores and showing how different cell lines are connected.

Insufficient data or modest transcriptional effects could explain why certain cell lines do not have chords. The significance of considering connection patterns and TAS scores when choosing perturbagens related to breast cancer cannot be overstated. This consideration aligns with our overarching objective of leveraging hybrid *in-silico* Methods in the pursuit of abiraterone-based drugs, specifically targeting 17 α -hydroxylase as a potential inhibitor in the context of breast cancer therapeutics.

It demonstrates diverse pharmacological profiles among analyzed drugs, with abiraterone emerging as the most transcriptomically similar compound. The varied mechanisms of action represented in the top-ranking drugs, ranging from bacterial DNA gyrase inhibition to CFTR channel agonism, underscore the potential for shared biological effects and therapeutic relevance. Notably, the analysis reveals high similarity scores even among drugs with distinct targets, such as cyclooxygenase inhibition and cholinesterase inhibition. The findings in Table 1 suggest the utility of transcriptomic analysis in uncovering nuanced relationships among drugs, offering insights into potential repurposing opportunities and identifying novel therapeutic strategies. Drug-drug transcriptomic similarity analysis yielded compounds' 2D structures and SMILES, which are presented in Table 2.^{14,15}

Molecular Docking

Cavities detection by CB Dock server

The CB Dock server detected five separate cavities (C1–C5), as stated in Table 3, and structures with different volumes and geographic coordinates are illustrated in Figure 5. The

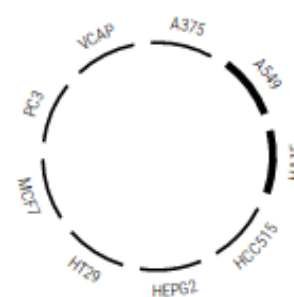


Figure 4: Insight: Responses of different cell lines to disruptors

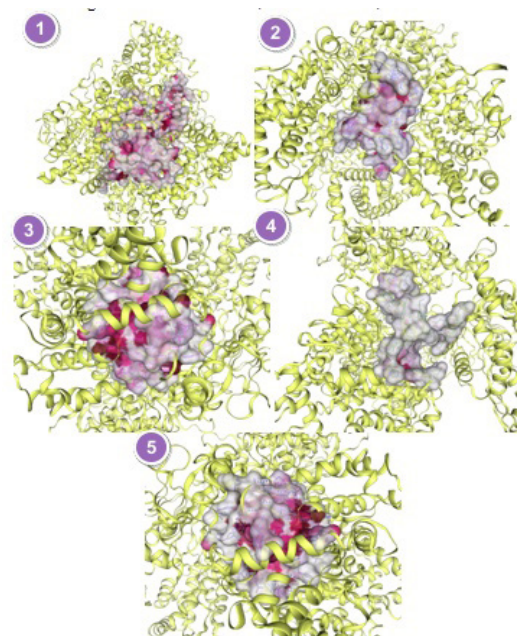


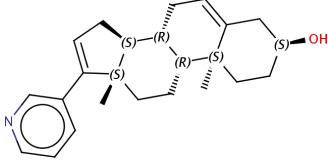
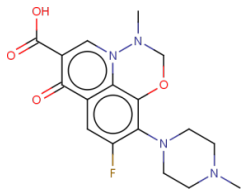
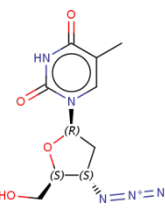
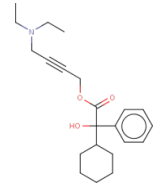
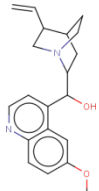
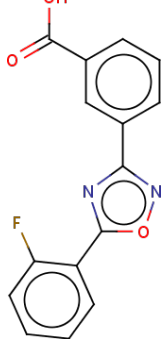
Figure 5: Outcomes of cavities recognition in 17 α -hydroxylase by CB dock server

Table 1: Outcomes of transcriptomic similarity analysis

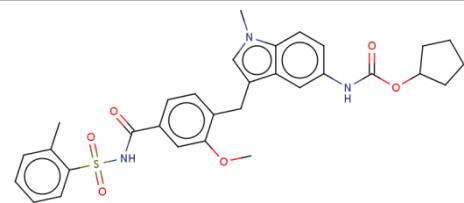
Rank	S. No.	Score	Type	Name
1	1	99.99	17, 20 lyase inhibitor	Abiraterone
4	2	99.75	Bacterial DNA gyrase inhibitor	Marbofloxacin
5	3	99.69	Reverse transcriptase inhibitor	Zidovudine
7	4	99.61	Acetylcholine receptor antagonist	Oxybutynin
8	5	99.54	Sodium channel blocker	Quinidine
10	6	99.37	CFTR channel agonist	Ataluren
12	7	99.37	Leukotriene receptor antagonist	Zafirlukast
13	8	99.37	ACE inhibitor	Enalapril
14	9	99.37	Leukotriene receptor antagonist	Montelukast
15	10	99.33	Cyclooxygenase inhibitor	Niflumic-acid
16	11	99.26	Cholinesterase inhibitor	Mestinon

Drug Repurposing of Abiraterone-based Compounds

Table 2: SMILES and 2D structure of compounds found through drug-drug transcriptomic similarity analysis

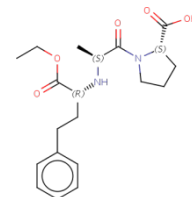
Name	2D structure and SMILES
Abiraterone	 <chem>C[C@]12CC[C@@H]3[C@@H](CC=C4C[C@@H](O)CC[C@@]34C)[C@@H]1CC=C2c1cccnc1</chem>
Marbofloxacin	 <chem>CN1CCN(CC1)c2c(F)cc3c(=O)c(cn4N(C)COC2c43)C(=O)O</chem>
Zidovudine	 <chem>Cc1cn([C@H]2C[C@H](N=[N+]=[N-])[C@@H](CO)O2)c(=O)[nH]c1=O</chem>
Oxybutynin	 <chem>CCN(CC)CC#CCOC(=O)C(O)(C1CCCCC1)c2ccccc2</chem>
Quinidine	 <chem>COc1ccc2nccc(C(O)C3CC4CCN3CC4=C)c2c1</chem>
Ataluren	 <chem>OC(=O)c1ccc(c1)-c1noc(n1)-c1cccnc1F</chem>

Zafirlukast



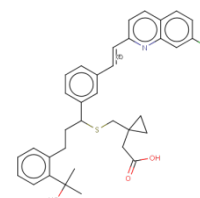
COc1cc(ccc1Cc2cn(C)c3ccc(NC(=O)OC4CCCC4)cc23)C(=O)NS(=O)(=O)c5ccccc5C

Enalapril



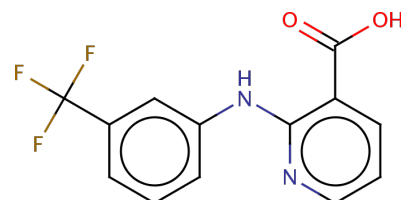
CCOC(=O)[C@@H](CCc1ccccc1)N[C@@H](C(=O)N1CCC[C@H]1C(O)=O

Montelukast



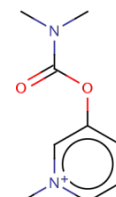
CC(C)(O)c1ccc1CCC(SCC1(CC(O)=O)CC1)c1ccc(\C=C\c2ccc3ccc(Cl)cc3n2)c1

Niflumic-acid



OC(=O)c1cccnc1Nc2ccc(c2)C(F)(F)F

Mestinon



CN(C)C(=O)Oc1ccc[n+](C)c1

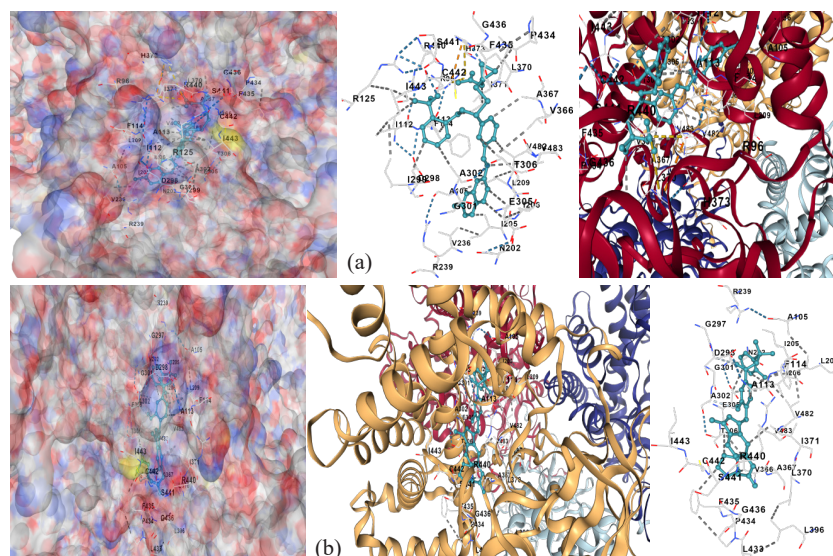
Table 3: Outcomes of cavities discovery through CB Dock server

CurPocket ID	Cavity volume (Å ³)	Center (x, y, z)	Cavity size (x, y, z)
C1	16665	21, 14, 48	30, 30, 30
C2	3621	6, 6, 19	21, 28, 16
C3	2286	28, 39, 53	16, 21, 18
C4	2205	3, 45, 51	19, 22, 24
C5	2073	28, -6, 34	16, 21, 18

variation in cavity sizes and positions indicates possible ligand binding sites, which is useful for future molecular docking research and drug design efforts that aim to target these particular areas.^{16,17}

Table 4: Docking outcomes

Rank	Name	Pocket, score, chain and interacting amino acids
1	Abiraterone	Pocket: C5 & Score: -10.2 Chain A: ARG96 ILE112 ALA113 TRP121 ARG125 ALA302 THR306 THR307 VAL310 LEU361 VAL366 ALA367 ILE371 PRO434 PHE435 GLY436 ARG440 SER441 CYS442 ILE443 GLY444 ALA448 LEU452
4	Marbofloxacin	Pocket: C3 & Score: -8.8 Chain B: ALA105 SER106 ALA113 PHE114 TYR201 ASN202 ILE205 ILE206 ARG239 GLY297 ASP298 GLY301 ALA302 GLU305 THR306 VAL366 ALA367 ILE371 VAL482 VAL483
5	Zidovudine	Pocket: C1 & Score: -7.8 Chain A: GLY162 GLN163 SER164 ILE165 PRO468 ASP469 ASP470 LYS490 LYS492 Chain B: ASN200 GLU203 GLY204 ASP207 ASN208 LYS231 SER234 HIS235 Chain D: PRO225 ASN226 LYS227
7	Oxybutynin	Pocket: C5 & Score: -7.2 Chain A: ALA105 ALA113 PHE114 TYR201 ASN202 ILE205 ILE206 LEU209 ARG239 GLY297 ASP298 GLY301 ALA302 GLU305 THR306 VAL366 ALA367 ILE371 VAL482 VAL483
8	Quinidine	Pocket: C5 & Score: -8.1 Chain A: ARG96 ILE112 ALA113 ASP298 ILE299 ALA302 THR306 VAL366 ALA367 LEU370 ILE371 HIS373 PRO434 PHE435 GLY436 ARG440 CYS442 ILE443 GLY444 VAL482 VAL483
10	Ataluren	Pocket: C1 & Score: -8.8 Chain A: PHE169 GLY191 PRO193 LEU195 ASN196 VAL197 GLN199 ASN200 GLU203 Chain B: MET156 LEU157 THR159 HIS160 ILE165 ASP166 PHE169 PRO170 ASN190 LYS490
12	Zafirlukast	Pocket: C3 & Score: -10.8 Chain B: ALA105 ALA113 PHE114 ASN202 ILE205 ILE206 LEU209 ARG239 GLY297 ASP298 GLY301 ALA302 GLU305 THR306 VAL366 ALA367 LEU370 ILE371 LEU396 LEU433 PRO434 PHE435 GLY436 ARG440 SER441 CYS442 ILE443 VAL482 VAL483
13	Enalapril	Pocket: C3 & Score: -8.4 Chain B: ARG96 ILE112 ALA113 TRP121 ARG125 ALA302 THR306 VAL310 LEU361 VAL366 ALA367 ILE371 PRO434 PHE435 GLY436 PRO439 ARG440 SER441 CYS442 ILE443 ALA448 LEU452 VAL482 VAL483
14	Montelukast	Pocket: C5 & Score: -11.1 Chain A: ARG96 ALA105 ILE112 ALA113 PHE114 ARG125 ASN202 ILE205 ILE206 LEU209 VAL236 ARG239 ASP298 ILE299 GLY301 ALA302 GLU305 THR306 VAL366 ALA367 LEU370 ILE371 HIS373 PRO434 PHE435 GLY436 ARG440 SER441 CYS442 ILE443 VAL482 VAL483
15	Niflumic-acid	Pocket: C5 & Score: -8.3 Chain A: ILE112 ALA113 ARG125 PHE132 ILE179 ASP298 ILE299 ALA302 GLY303 VAL304 THR306 THR307 ARG440 SER441 CYS442 ILE443 GLY444 LEU447 ALA448 GLU451
16	Mestinin	Pocket: C1 & Score: -5.5 Chain A: PHE169 GLY191 ASP192 PRO193 ASN196 Chain B: MET156 HIS160 PHE169 PRO170 VAL173 ASN190 GLY191 ASP192 LEU195 ASN196

**Figure 6:** Interaction of 17 α -hydroxylase Inhibitors and lead a) Montelukast b) Zafirlukast

As delineated in Table 4, the molecular docking results offer a detailed exploration of binding affinities and interacting amino acids of abiraterone-based compounds within the active site of 17 α -hydroxylase. The preeminent compound, abiraterone, attain a commendable binding score of -10.2, indicative of a robust interaction within pocket C5. Interacting amino acids include ARG96, ILE112, ALA113, TRP121, ARG125, and several others, underscoring the specificity of the binding interaction.^{18,19}

Marbofloxacin, positioned fourth, exhibits a noteworthy binding score of -8.8 and establishes interactions within Pocket C3. Key interacting amino acids involve ALA105, SER106, PHE114, and TYR201, illuminating its potential as a promising 17 α -hydroxylase inhibitor. Zidovudine, oxybutynin, and quinidine, occupying the fifth, seventh, and eighth positions, respectively, display binding scores ranging from -7.2 to -8.1. Interacting amino acids are distributed across Pockets C1 and C5, reflecting the diverse residues engaged in the binding process. Ataluren, securing the tenth position, reveals a binding score of -8.8 and exhibits interactions within pocket C1. Noteworthy amino acids involved include PHE169, GLY191, PRO193, LEU195, and ASN196. Zafirlukast, enalapril, montelukast, and niflumic-acid, situated in positions twelve through fifteen, showcase compelling binding scores ranging from -8.3 to -11.1, with diverse interacting amino acids within pockets C3 and C5, reinforcing their potential as potent inhibitors (Figure 6). Mestinson, positioned sixteenth, demonstrates a relatively lower binding score of -5.5. Interacting amino acids within pocket C1 suggest a distinct binding profile. The unique set of amino acids involved warrants further scrutiny and consideration in the evaluation of its inhibitory potential.^{20,21}

The molecular docking outcomes affirm the probable of abiraterone-based compounds as effective inhibitors of 17 α -hydroxylase for breast cancer treatment. With its high binding score, abiraterone stands out as a promising lead compound. Zafirlukast and montelukast emerge as noteworthy candidates, exhibiting substantial binding scores and diverse interacting amino acids. The integration of transcriptomic similarity and molecular docking results offers a comprehensive perspective, guiding the selection of compounds for further experimental validation. This multifaceted approach enhances our understanding of the potential efficacy of abiraterone-based compounds, marking a pivotal step towards the development of targeted and repurposed therapeutics in breast cancer treatment.^{22,23}

CONCLUSION

In this comprehensive *in-silico* study, we employed a dual approach combining docking and drug-drug transcriptomic similarity analysis to reconnoiter prospective of abiraterone-based compounds as 17 α -hydroxylase inhibitors for breast cancer treatment. The drug-drug transcriptomic similarity analysis revealed abiraterone as the most transcriptomically similar compound, with diverse drugs exhibiting high similarity scores, suggesting shared biological effects and

potential repurposing opportunities. The drugs' effectiveness might be better understood as a whole when molecular docking results were combined with drug-drug transcriptomic similarity analysis. Molecular docking results showcased abiraterone as a lead compound with a commendable binding score of -10.2, interacting with crucial amino acids within pocket C5 of 17 α -hydroxylase. Marbofloxacin, ataluren, zafirlukast, and montelukast emerged as promising candidates, displaying substantial binding scores and diverse interacting amino acids, reinforcing their potential as potent inhibitors. The detection of distinct cavities through CB dock server further highlighted potential binding sites for ligands.

The transcriptional impact analysis across core cell lines depicted abiraterone's substantial influence on gene expression, emphasizing its probable as a therapeutic agent for cancer. Cell line-specific responses illustrated in the introspect visualization provided a nuanced understanding of perturbation impact on breast cancer, aiding in the selection of compounds relevant to our pursuit of abiraterone-based drugs as 17 α -hydroxylase inhibitors.

In conclusion, our *in-silico* findings present abiraterone-based compounds, particularly abiraterone itself, as promising candidates for further experimental validation as 17 α -hydroxylase inhibitors in breast cancer treatment. This integrative approach, encompassing transcriptomic similarity and molecular docking analyses, enhances our understanding of the complex interactions and potential therapeutic benefits, marking a significant stride in the realm of drug repurposing for breast cancer therapeutics. The identified lead compounds warrant future experimental investigations to validate their efficacy and pave the way for targeted and repurposed therapeutics in breast cancer treatment.

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