Repurposing the Retinoic Acid Receptor Gamma Agonist Trifarotene for Pulmonary Arterial Hypertension via Endothelin B Receptor Inhibition: A Morgan Fingerprinting and Molecular Docking Approach

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ABSTRACT

Pulmonary Arterial Hypertension (PAH) is a chronic and life-threatening condition that results in increased pulmonary vascular resistance, right ventricular hypertrophy, and vascular remodelling. The improper functioning of the endothelin system, especially the endothelin B receptor (ETB), which serves two functions depending on where it is in the cell, is a key part of its pathogenesis. Bosentan, which is a dual ETA/ETB receptor blocker, is one of the current treatments that can help with symptoms. However, it has some problems, such as hepatotoxicity and non-selectivity, which make it necessary to find new treatments. This research investigates the prospective repurposing of Trifarotene, an FDA-sanctioned selective retinoic acid receptor gamma (RAR-γ) agonist that acts as an innovative blocker of the ETB receptor for the treatment of pulmonary arterial hypertension (PAH). We used Morgan fingerprinting through the DrugRep platform to look at 20 FDA-approved drugs that are structurally analogous to bosentan. Trifarotene had a higher docking affinity (–9.2 kcal/mol) to the human ETB receptor (PDB ID: 5XPR), even though its Tanimoto similarity score was low (0.272). This was better than bosentan (–8.5 kcal/mol). A comprehensive molecular docking analysis showed that Trifarotene interacts with key ETB residues in a way that stabilises them. These results provide strong computational confirmation that Trifarotene may function as an extremely specific endothelin type B receptor (ETB) antagonist, necessitating further validation in vitro and in vivo. This work highlights the efficacy of combined virtual screening and molecular docking in expediting drug repurposing for intricate cardiovascular conditions, including pulmonary arterial hypertension (PAH).

KEYWORDS: Drug Repurposing, Pulmonary Arterial Hypertension (PAH), Endothelin B Receptor (ETBR), Trifarotene, Molecular Docking

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic and progressive disorder characterized by elevated pulmonary arterial pressure and prominent vascular remodeling[1]. PAH is caused by an intricate interplay of pathophysiologic processes such as endothelial dysfunction, abnormal migration and proliferation of pulmonary arterial smooth muscle cells, inflammation, and fibrosis[2]. These alterations lead to increased pulmonary vascular resistance, a

persistent pressure load on the right ventricle, resulting in right ventricular hypertrophy, heart failure, and eventual premature mortality[3].

Global incidence has been found that there are 15–50 cases per million population, with increased prevalence in females and those with autoimmune conditions like systemic sclerosis[4]. Although PAH is a rare condition, it has a disproportionately high morbidity and mortality burden[5]. Untreated patients have a median survival of about 2.8 years, highlighting the need for early diagnosis as well as efficient therapeutic intervention[6].

In spite of therapeutic advances—endothelin receptor blocker, phosphodiesterase type 5 inhibitors. Among prostacyclin analogs—PAH is still incurable with a bad long-term outlook[7].The molecular key players, the endothelin system is a key player in PAH pathophysiology[8]. Endothelin-1 (ET-1), a powerful vasoconstrictive peptide, acts mainly through two receptor subtypes: endothelin A (ETA) and endothelin B (ETB) receptors[9]. ETA receptors facilitate vasoconstriction and smooth muscle cell proliferation, whereas ETB receptors are involved in both clearance of ET-1 and vasodilation via release of nitric oxide as well as prostacyclin[10]. Dysregulation of ETB receptor expression and function in PAH allows persistent vasoconstriction and vascular remodeling, which worsens disease severity[11].

Moreover, findings indicate that ETB receptors can change their protective to pathogenic functions based on cellular localization[12]. Endothelial ETB receptors, which clear ET-1 and promote vasodilation, are contrasted with smooth muscle ETB receptors that have proliferative and fibrotic signaling[13]. Such context-dependent action further complicates targeting for therapeutic purposes, highlighting the necessity of receptor-selective or context-specific modulators.

Therapeutically, dual endothelin receptor antagonists like bosentan inhibit both ETA as well as ETB receptors and have been useful for treating PAH[14]. Unfortunately, use of bosentan is hampered by side effects such as hepatotoxicity, drug interactions, and inconsistent patient response, which has prompted the exploration for other or add-on therapies with better safety and efficacy profiles[15].

In addition, next-generation selective ETA antagonists (e.g., ambrisentan, macitentan) have demonstrated better tolerance, but selective ETB modulation is not well explored. The limitation is how to engineer compounds that selectively block pathological ETB action without inhibiting its physiologic functions in ET-1 clearance and vasodilation. This therapeutic lacuna is an exciting target for new interventions[16].

Drug repurposing, which involves the discovery of new therapeutic uses for old drugs, provides an affordable and time-saving solution to expedite drug development for chronic illnesses such as PAH[17]. Trifarotene, a very selective and potent retinoic acid receptor gamma (RAR-γ) agonist, is already approved for dermatological use in diseases like acne because of its regulatory action on skin cell differentiation and inflammation[18]. Its receptor selectivity implies the possibility of modulatory actions in other biological systems, which remain to be extensively investigated[19].

Interestingly, retinoids have already been implicated in vascular biology[20]. All-trans retinoic acid (ATRA) is an example that has shown anti-proliferative actions in vascular smooth muscle cells and anti-fibrotic effects in animal models[21]. These findings in the pulmonary arterial hypertention open up the possibility of structurally related compounds such as trifarotene having off-target effects on receptors which play a role in vascular remodeling like the ETB receptor.

In the current research, we utilized computational drug discovery techniques—such as Morgan fingerprinting to evaluate chemical similarity and molecular docking simulations—to screen a targeted panel of 20 candidate compounds against the human ETB receptor. Utilizing bosentan as a lead compound, which gave a docking score of -8.5 kcal/mol, we found that trifarotene had the more binding free energy of -9.2 kcal/mol, which was greater than bosentan. These results indicate that trifarotene can serve as a new ETB receptor antagonist with potential therapeutic relevance in PAH.

MATERIALS AND METHODS

Disease selection: Pulmonary arterial hypertension (PAH)

Pulmonary arterial hypertension (PAH) was chosen as the target disease owing to its multifactorial, intricate pathophysiology and the urgent unmet need for new treatments[22]. PAH is defined by increased pulmonary vascular resistance due to endothelial dysfunction, proliferation of smooth muscle cells, and vascular remodeling with eventual right heart failure[23]. In spite of the presence of a variety of pharmacologic classes—including endothelin

receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin analogs—treatment today does not reverse disease progression and is tagged with side effects and heterogeneous patient responses.Since the endothelin pathway has a crucial role in PAH, especially the dysregulation of the endothelin B receptor (ETB), ETB was selected as the drug target for repurposing and screening[24]. Attacking ETB offers a chance to regulate both vasoconstrictive and proliferative signaling involved in PAH pathogenesis[25].

FDA-approved lead compound selection: For molecular similarity screening and docking validation, bosentan, an FDA-approved dual endothelin receptor antagonist, was chosen as the reference (lead) compound[26]. By blocking both ETA and ETB receptors, bosentan has been shown in clinical trials to increase exercise capacity and slow the progression of PAH patients' diseases[27]. It is a good standard for evaluating the binding potential of repurposed drug candidates because of its well-established mode of action and well-characterized interaction with the ETB receptor, which structural studies have confirmed (PDB ID: 5XPR).

Bosentan played two main roles in this study: first, it was used as a structural reference for Morgan fingerprint-based similarity screening to find compounds with similar chemical features; second, it was used as a pharmacological comparator in molecular docking simulations, where its binding affinity (Vina score: –8.5 kcal/mol) was used as a threshold to assess potential drugs[28-29]. We sought to find repurposed compounds with potentially better binding profiles and unique pharmacodynamic features that could address present limitations in pulmonary arterial hypertension (PAH) therapy by using bosentan as a validated clinical standard[30].

Database and Tools: FDA-approved medications with possible activity against the endothelin B receptor (ETB) were among the 20 candidate compounds selected for the repurposing study. Molecular docking techniques and Morgan fingerprint-based similarity analysis were used for computational screening[31]. To find structural similarities with the lead compound bosentan, Morgan fingerprinting was used[32]. The clinically approved dual endothelin receptor antagonist bosentan was selected as the lead compound because of its well-established therapeutic role in treating pulmonary arterial hypertension (PAH)[33]. The benchmark for comparison with other screened compounds in pulmonary arterial hypertension was bosentan's binding affinity with the (ET_B) receptor, as indicated by a binding free energy of -8.5 kcal/mol[34].

Morgan Fingerprint Analysis: Using connectivity patterns and circular atom neighbourhoods, Morgan fingerprints were utilised to encode the molecular structures of compounds[35]. Tanimoto similarity scores between bosentan and other potential molecules could be computed quickly thanks to this method[36]. In order to identify structurally relevant analogues, Morgan fingerprinting was chosen due to its balance between computational efficiency and sensitivity[37].

Studies on Docking

Docking Software: AutoDock Vina, a popular docking program that forecasts ligand binding affinity and positions within the target protein's active site, was used to carry out molecular docking[38]. AutoDock Vina uses a versatile ligand docking technique to investigate various conformations and offers precise binding energy estimates[39].

Target Protein: Because of its crucial role in the pathophysiology of pulmonary arterial hypertension (PAH), the human Endothelin B receptor (ETB) was chosen as the target protein for docking studies[40]. To guarantee precise simulation of ligand-receptor interactions, the 3D structure of (ET_B) was acquired from the Protein Data Bank and prepped for docking by eliminating water molecules and adding polar hydrogens[41].

Validation Process:

A number of crucial steps were involved in the docking workflow for validation. First, the orthosteric binding site of the endothelin receptor type B (ET_B) was identified based on known ligand-binding residues and the co-crystallized position of bosentan within the receptor[42]. Compounds found by similarity screening using Morgan fingerprints were then docked into the ET_B receptor binding pocket[43]. Docking scores were computed to evaluate ligand affinity, which are binding energies in kcal/mol[44]. The nature of ligand–receptor interactions, such as hydrogen bonding and hydrophobic contacts, were then described by analysing the resultant docking poses[45].

Data Analysis:

Using Morgan fingerprint Tanimoto coefficients, virtual screening parameters were developed to rank candidate compounds according to their structural resemblance to bosentan[46]. High similarity score compounds were then put through docking

validation[47]. Several important parameters were assessed during the docking process: docking scores, which show predicted binding affinity with more negative values indicating stronger binding; ligand–receptor interaction energies, which were analysed to determine the stability of the ligand–ETB receptor complex, and RMSD (root mean square deviation) values, which were computed to evaluate the accuracy and repeatability of docking poses[48].

Statistical Methods: Docking scores and similarity metrics were compiled using descriptive statistics[49]. Python libraries such as Matplotlib for data visualisation and RDKit for cheminformatics were used to conduct correlation analyses between Tanimoto similarity scores and docking affinities[50]. The validity of the ligand screening and docking approach was confirmed by these analyses[51].

RESULTS AND DISCUSSION

Results of Ligand-Based Drug Repurposing

A number of strong arguments led to the selection of endothelin receptor type B (ETB) as the main target in pulmonary arterial hypertension (PAH). In clinical settings, ETB is essential for controlling pulmonary artery cell proliferation and vascular tone, highlighting its significance in PAH pathophysiology. Mechanistically, ETB receptors have two roles: they promote vasoconstriction in smooth muscle cells and mediate vasodilation and endothelin-1 clearance in endothelial cells, providing a special opportunity for therapeutic modulation. The FDA-approved dual ETA/ETB receptor antagonist bosentan's clinical effectiveness emphasises the therapeutic importance of ETB even more. The binding interactions between bosentan and ETB are revealed by structural insights from the crystal structure 5XPR, which lays the groundwork for structure-based drug design targeted at improving receptor selectivity and efficacy. In order to maximise therapeutic results and reduce side effects, this structural knowledge also aids in the development of selective ETB modulators. In PAH patients, pathophysiologically, ETB dysregulation plays a role in endothelial dysfunction, pulmonary vascular remodelling, and persistent vasoconstriction. ETB is positioned as a strong drug development platform for next-generation treatments with better pharmacokinetics and lower toxicity due to the availability of both structural and pharmacological data. Targeting ETB also offers combination therapy opportunities, especially when used in conjunction with ETA or other PAH-related pathways like prostacyclin or nitric oxide, which may have synergistic effects and enhance clinical outcomes.

Results of Ligand-Based Screening using the DrugRep Server:

Table 1: Binding scores and target interactions of various compounds

Sr. No.	DrugBank ID	Name of Compound	Similarity Score	Sr. No.	DrugBank ID	Name of Compound	Similarity Score
1	DB00559	Bosentan	1.000	11	DB00706	Tamsulosin	0.297
2	DB00664	Sulfametopyrazine	0.325	12	DB08912	Dabrafenib	0.296
3	DB01299	Sulfadoxine	0.323	13	DB12500	Fedratinib	0.295
4	DB00276	Amsacrine	0.319	14	DB00891	Sulfapyridine	0.295
5	DB01091	Butenafine	0.319	15	DB13248	Phthalylsulfathiazole	0.292
6	DB01136	Carvedilol	0.311	16	DB08439	Parecoxib	0.289
7	DB06729	Sulfaphenazole	0.311	17	DB06150	Sulfadimethoxine	0.282
8	DB01382	Glymidine	0.308	18	DB09495	Avobenzone	0.281
9	DB00359	Sulfadiazine	0.306	19	DB06821	Sulfameter	0.273
10	DB00795	Sulfasalazine	0.303	20	DB12808	Trifarotene	0.272

Docking studies and Validation process results:

The Docking studies and Validation process results highlights significant advancements in overall

stereochemistry and structural geometry by comparing validation metrics between the PDB-REDO refined model and the original model. In particular, the PDB-REDO model exhibits improved geometric accuracy after refinement, as evidenced by a lower R-factor (0.2362 vs. 0.2656) and a noticeable decrease in bond length and bond angle RMS Z-scores. Notable improvements are also seen in the model quality percentiles. Fine packing greatly improved from 44 to 67, and the rotamer normality percentile rose from 4 to 8. Ramachandran plot normality stayed at 5, but there was a slight improvement in coarse packing and hydrogen bond satisfaction as well. Bump severity, a metric used to quantify atomic clashes, increased from 17 to 40, indicating that the refined structure had better packing and fewer steric conflicts**.**

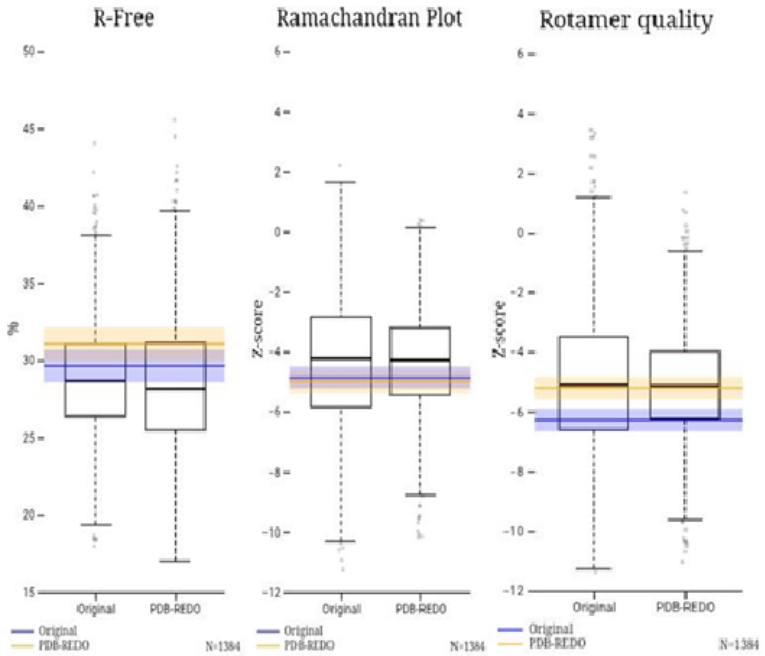

Figure 1: Comparative Analysis of Model Quality Metrics: Original vs. PDB-REDO Refinement

The figures 1 show box plots that compare the original and PDB-REDO models across 1,384 structures using model quality metrics (R-Free, Ramachandran Plot Z-score, and Rotamer quality Z-score). The PDB-REDO models exhibit better structural refinement and consistency than the original models, as evidenced by their improved R-Free values and marginally better or comparable stereochemical quality (Ramachandran and rotamer Z-scores).

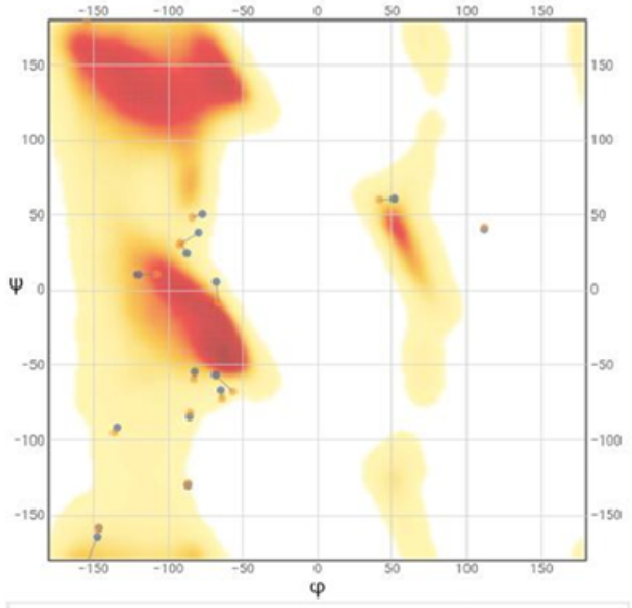

Figure 2: Kleywegt-like plot

The distribution of phi (ϕ) and psi (ψ) dihedral angles of amino acid residues in a protein structure is depicted in the figure 2 as a Kleywegt-type plot. The density of favourable conformations is reflected in the gradient of background colours, with red denoting highly favoured regions. The model's structural integrity can be assessed visually by comparing the backbone geometry's conformance to expected stereochemical norms, which are represented by the orange and blue dots overlaid on top of each other.

Docking results:

Table 2: Binding Affinity Analysis of DrugBank Compounds to Target Pockets: Identification of Potential Drug Candidates

DrugBank ID	Compound Name	Cavity	Vina Score	DrugBank ID	Compound Name	Cavity	Vina Score
DB00559	Bosentan	C2	-8.5	DB00706	Tamsulosin	C2	-7.1
DB00664	Sulfametopyrazine	C5	-6.7	DB08912	Dabrafenib	C1	-8.8
DB01299	Sulfadoxine	C5	-6.9	DB12500	Fedratinib	C2	-6.5
DB00276	Amsacrine	C2	-8.7	DB00891	Sulfapyridine	C2	-8.0
DB01091	Butenafine	C1	-7.9	DB13248	Phthalylsulfathiazole	C2	-7.7
DB01136	Carvedilol	C2	-7.5	DB08439	Parecoxib	C1	-6.7
DB06729	Sulfaphenazole	C2	-7.6	DB06150	Sulfadimethoxine	C5	-7.5
DB01382	Glymidine	C2	-6.8	DB09495	Avobenzone	C5	-6.8
DB00359	Sulfadiazine	C2	-6.7	DB06821	Sulfameter	C5	-6.7
DB00795	Sulfasalazine	C2	-8.7	DB12808	Trifarotene	C1	-9.2

With strong binding affinities (Vina scores of -9.2, -8.8, and -8.7, respectively) to pockets C1 and C2, the docking study identified Trifarotene (DB12808), Dabrafenib (DB08912), and Amsacrine (DB00276) as top candidates, indicating their potential for repurposing. Sulfonamide-based compounds may have a steady affinity for this pocket, as evidenced by the positive binding to C2 shown by other compounds like sulfasalazine (DB00795) and sulfapyridine (DB00891). Interestingly, a number of structurally related compounds, including Sulfametopyrazine, Sulfadoxine, and Sulfameter, demonstrated moderate binding in C5, suggesting that pocket may be the site of selective interactions.

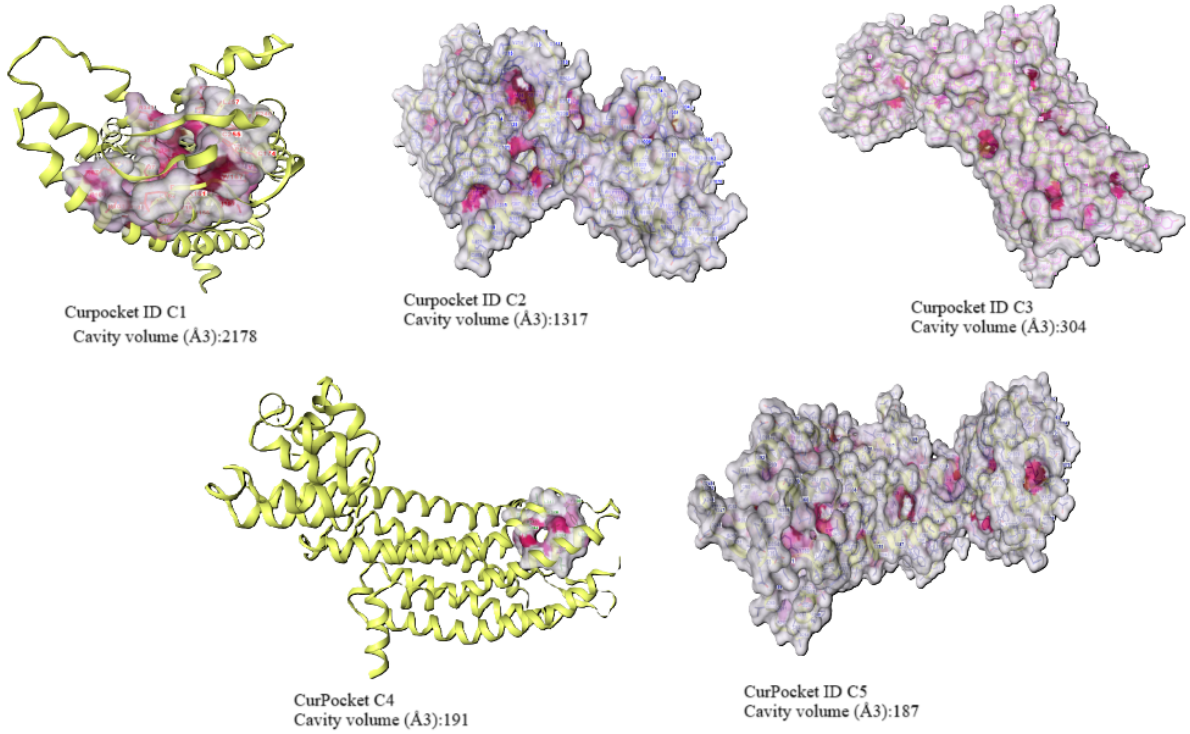

Figure 3: Visualization of five binding pockets (CurPocket IDs C1–C5) on the target protein

The structural diversity of potential ligand-binding sites on the target protein is illustrated by Figure 3, which shows five distinct CurPocket binding sites with varying cavity sizes ranging from 2178 Å³ to 187 Å³. This helps to highlight key sites for docking studies to investigate the binding efficiency of bosentan and its analogues and to enhance their potential for repurposing for pulmonary arterial hypertension (PAH) through improved drug-target interactions.

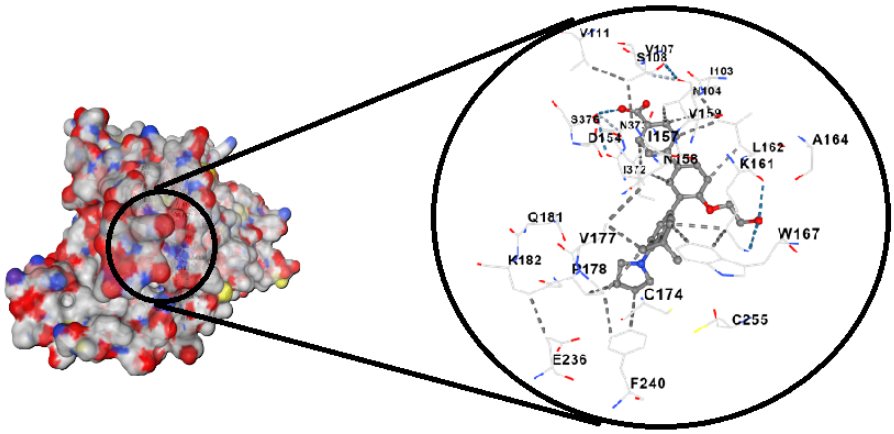

Figure 4: Molecular Docking of Trifarotene with Endothelin B receptor: Key Binding Interactions for Pulmonary arterial hypertension (PAH) Treatment.

Trifarotene binds to the Endothelin B receptor (ETBR), which is connected to Pulmonary Arterial Hypertension (PAH), a dangerous disorder that affects the lungs' blood vessels. Primarily utilised in dermatology, trifarotene is a selective retinoic acid receptor agonist that exhibits promise for drug repurposing. The substance interacts with particular amino acids surrounding the binding pocket of the receptor. These residues, which are crucial for maintaining the stability of the protein-ligand complex, include H157, D153, V177, C174, F240, and W167.

Hydrophobic contacts, electrostatic interactions, and hydrogen bonds are important interactions that aid in securing trifarotene in place. Trifarotene and H157 form a hydrogen bond, demonstrating polar stabilisation. D153 exhibits another interaction that might aid in keeping the ligand in place. V177, F240, and W167 are examples of hydrophobic residues that offer a nonpolar environment that

facilitates docking. Additionally, the ligand interacts with its polar or acidic groups to form links with positively charged residues such as K161. Together, these interactions demonstrate how trifarotene binds firmly to ETBR and may alter the structure or functionality of the receptor. This raises the possibility that trifarotene may alter ETBR activity in PAH and gave the way for future therapeutic research.

Molecular Dynamics Simulation Results:

The Trifarotene-Endothelin B receptor complex's shape change over time in a realistic bodily environment is revealed by the Molecular Dynamics simulation.

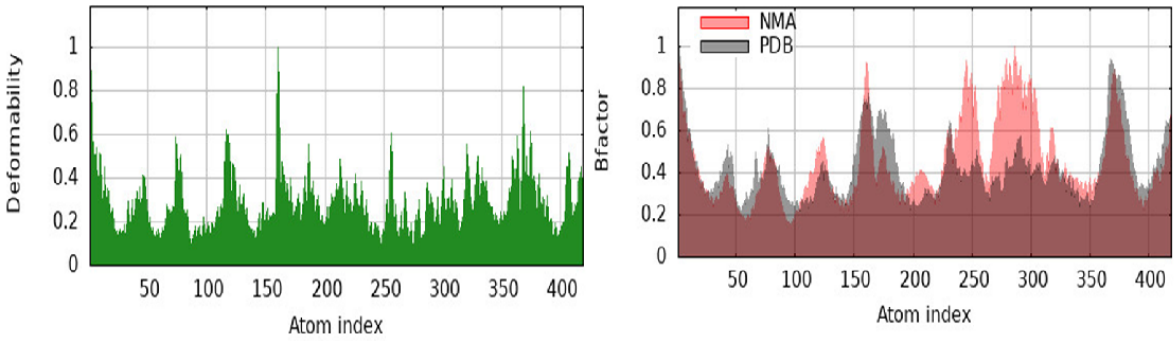

Figure 5: Deformability and B-Factor Analysis of the Trifarotene–Endothelin B Receptor Complex

Only a few areas of the Endothelin B receptor exhibit flexibility during the molecular dynamics simulation, as indicated by the deformability plot. The majority of deformability values stay below 0.6, suggesting that the protein is structurally stable throughout. The presence of peaks around atom indices 80, 120, 150, 250, and 360 indicates that these areas are more malleable and might be associated with loop regions or ligand interaction regions. The lack of noticeable aberrant motion in the graph suggests that the Trifarotene–Endothelin B receptor complex is stable during simulation. This implies that in a realistic biological setting, trifarotene can interact with the receptor in a stable way.

The B-factor plot contrasts the experimental PDB data with the Endothelin B receptor's flexibility as predicted by Normal Mode Analysis (NMA). The B-factor, a gauge of atomic mobility, is represented on the y-axis, while the x-axis displays the atom index. Whereas the black shaded region (PDB) depicts observed flexibility based on crystal structure data, the red shaded region (NMA) shows theoretical flexibility. Similar patterns can be seen in both datasets, with peaks at atom indices of about 80, 150, 250, 300, and 360 indicating greater flexibility in these regions. The simulation predictions closely match experimental observations, as evidenced by the agreement between NMA and PDB data. Overall, the plot supports the receptor's potential for stable ligand binding by confirming that, despite some flexible receptor regions, the complex maintains its structural stability.

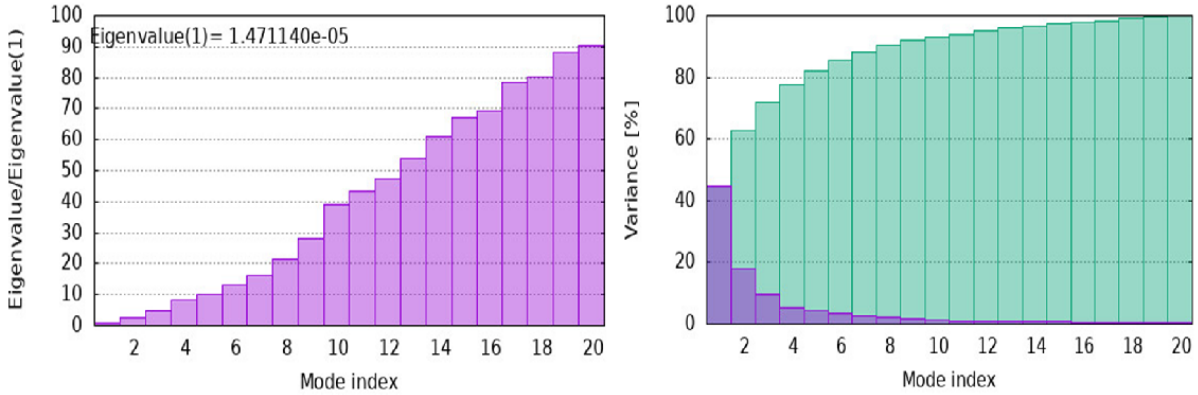

Figure6: Eigenvalue Spectrum and Variance Explained by Principal Modes in Normal Mode Analysis of the Trifarotene–Endothelin B Receptor Complex.

The bar graph provides information about the collective motions of the protein during molecular dynamics simulation by displaying the normalised eigenvalues derived from the Trifarotene–Endothelin B receptor complex's Normal Mode Analysis (NMA). The corresponding eigenvalues

normalised to the first mode are displayed on the y-axis, while the mode index (ranging from 1 to 20) is represented on the x-axis. Large-scale, functional movements in proteins are generally linked to a softer, more readily deformable motion, which is indicated by a lower eigenvalue. With the lowest eigenvalue (1.471140e-05), the first mode appears to be the most flexible and dominant motion in the complex.The eigenvalues rise in tandem with the mode index, suggesting less significant and stiffer motions. The presence of low-frequency modes and the slow increase in eigenvalues indicate that the Trifarotene–Endothelin B receptor complex is structurally stable overall, but retains flexibility in certain areas.

The Trifarotene–Endothelin B receptor complex's variance distribution across its first 20 normal modes, as determined by Molecular Dynamics simulation. The mode index is displayed on the x-axis, and the variance in percentage, which shows how each mode contributes to the complex's overall motion, is displayed on the y-axis. Each mode's individual variance is shown by the purple bars, and the cumulative variance is displayed by the green stacked bars. The majority of the variance is explained by the first few modes, particularly modes 1–4. By mode 10, the cumulative variance is close to 90%, with the first mode alone contributing about 45%. This implies that the first few low-frequency modes, which are usually in charge of large-scale, physiologically significant motions, contain the majority of the protein's essential conformational changes. The outcome shows that the Trifarotene–Endothelin B receptor complex retains overall structural stability while exhibiting dominant flexible movements in particular modes.

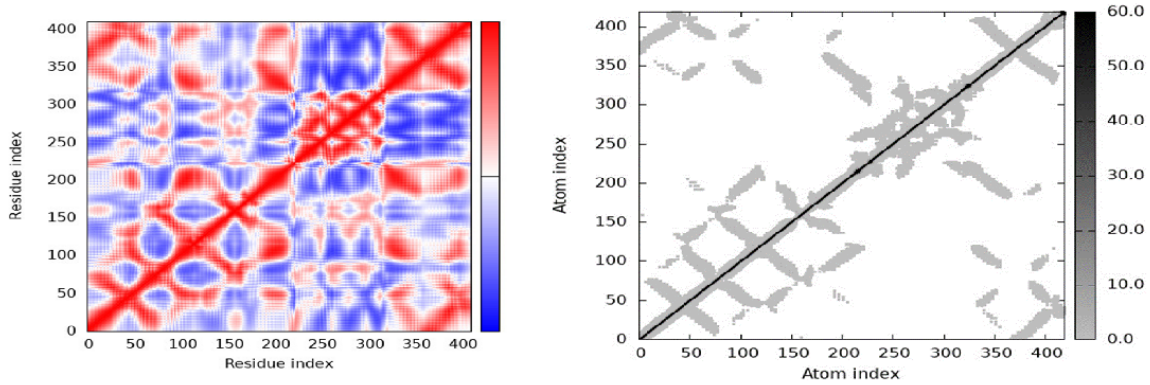

Figure7: Dynamic Cross-Correlation Matrix and Contact Map Analysis of Trifarotene–Endothelin B Receptor Complex

Red regions on the correlation map indicate positively correlated motions, or residues moving in the same direction, while blue regions show negatively correlated motions, or residues moving in opposite directions. This map shows the dynamic relationships between residues in the Trifarotene–Endothelin B receptor complex. As anticipated, self-correlations are displayed by the diagonal red line. Distinct red and blue blocks off the diagonal indicate dynamically interacting structural domains and suggest coordinated movements between particular protein regions. This pattern supports the protein's functional stability and adaptability during ligand binding and signal transduction by reflecting internal communication and flexibility.

The correlated motions between the atoms in the Trifarotene–Endothelin B receptor complex throughout the simulation are shown on the dynamic cross-correlation map. Higher correlations between atomic movements are represented by darker regions of the greyscale intensity, which shows the strength of the correlation. As anticipated, self-correlation is indicated by the strong diagonal line, whereas groups of atoms moving in unison are suggested by the off-diagonal clusters. These correlated regions suggest that the protein complex contains structurally and functionally related domains that support its stability and dynamic behaviour when interacting with the ligand.

Trifarotene Pharmacokinetic Assesment:

Trifarotene's ADME and Drug-Likeness Profile

With a molecular weight of 459.58 g/mol, a TPSA of 70.00 Å², and a moderate degree of flexibility (8 rotatable bonds), trifarotene ($C_{29}H_{33}NO_4$) is a moderately lipophilic compound. Although it is poorly water soluble (Log S ≈ –6.5 to –8.3), its consensus LogP of 5.17 indicates good membrane permeability. It is not blood-brain barrier permeant, but pharmacokinetically it exhibits high gastrointestinal absorption. It is a P-glycoprotein substrate that inhibits CYP2C19 and CYP2D6,

which raises the possibility of drug-drug interactions. Trifarotene has a high bioavailability score of 0.85, passes the Veber and Egan filters, and complies with Lipinski's rule with zero infractions. However, because of its high molar refractivity and lipophilicity, it is not lead-like and violates the Ghose and Muegge rules. It has a synthetic accessibility score of 3.39, which indicates that it is moderately easy to synthesise, and no PAINS or Brenk alerts are displayed by medicinal chemistry filters.

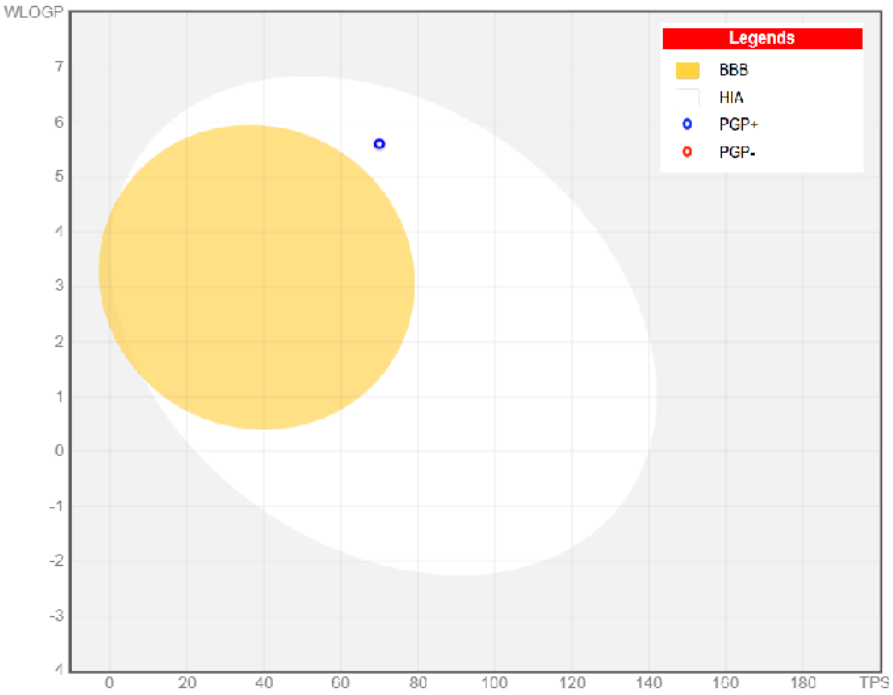

Figure 8: BOILED-Egg Model of trifarotene

Trifarotene's BOILED-Egg diagram indicates that the molecule (shown by a blue circle) is located outside the yellow region, indicating that it is unlikely to cross the blood–brain barrier (BBB), but inside the white region, indicating a high probability of passive gastrointestinal absorption (HIA). Furthermore, the blue outline indicates that trifarotene is a substrate of P-glycoprotein (PGP+), which implies that it may be actively effluxed from cells, especially those in the brain and gut. Due to limited BBB permeability and active efflux by P-gp transporters, trifarotene is not anticipated to have central nervous system activity, although this visual prediction generally confirms that it is well suited for oral administration.

CONCLUSION

Trifarotene, a clinically approved selective retinoic acid receptor gamma (RAR-γ) agonist created for dermatological conditions, was successfully identified in this study as a promising repurposed therapeutic candidate for pulmonary arterial hypertension (PAH). By combining structure-based molecular docking and ligand-based similarity screening in an integrative computational pipeline, trifarotene was found to be a strong antagonist of the endothelin B receptor (ETB), which is a crucial pathway implicated in the vascular remodelling, smooth muscle proliferation, and vasoconstriction that characterise PAH. Trifarotene was shortlisted using Morgan fingerprinting on the DrugRep platform because of its structural resemblance to bosentan, the standard ETB antagonist, which produced a Tanimoto coefficient of 0.272. Trifarotene outperformed bosentan (–8.5 kcal/mol) and every other screened candidate in subsequent docking simulations against the human ETB receptor (PDB ID: 5XPR), achieving the most favourable binding affinity (Vina score: –9.2 kcal/mol). Trifarotene may act as a novel ETB modulator with therapeutic relevance in PAH, according to this strong binding profile.

Trifarotene and important ETB residues, such as H157, D153, V177, F240, W167, and K161, have a stable binding network that is mediated by hydrogen bonds, hydrophobic contacts, and electrostatic interactions, according to a thorough interaction analysis. These interactions may make it easier to modify ETB-related signalling and help stabilise the

ligand-receptor complex. With improvements in R-factor, bond geometry, Ramachandran statistics, and rotamer distribution, structural refinement using PDB-REDO improved model quality and supported the accuracy of docking predictions.The stability of the Trifarotene–ETB complex under physiological conditions was further confirmed by molecular dynamics simulations, which demonstrated low deformability, consistent B-factor patterns, and high variance capture in the first few normal modes. Coordination of residue movements, a sign of allosteric stability and ligand-induced conformational support, was revealed by dynamic cross-correlation maps.Despite minor violations of Ghose and Muegge rules due to high lipophilicity, pharmacokinetic and drug-likeness profiling showed high gastrointestinal absorption, a bioavailability score of 0.85, and compliance with key drug-likeness filters (Lipinski, Veber, Egan). Trifarotene's suitability for systemic repurposing was further supported by its moderate synthetic accessibility (SA score: 3.39) and lack of PAINS or Brenk alerts.

In conclusion, this study reveals that trifarotene has the ability to act off-target as a high-affinity ETB receptor antagonist, providing a new avenue for PAH treatment. These results highlight the effectiveness of computational repurposing techniques that combine pharmacokinetic screening, structural docking, and chemical similarity. To verify Trifarotene's effectiveness, optimise dosage, and evaluate long-term safety in the cardiovascular context of PAH, further in vitro and in vivo validation will be necessary.

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