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Research Article

Repurposing Tolfenamic Acid, a Non-Steroidal Anti-Inflammatory Drug (NSAID), as an Antiplatelet Agent Targeting the P2Y12 Receptor

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ABSTRACT

The escalating burden of Ischaemic Heart Disease necessitates the unveiling of new avenues of therapy to improve the prognosis in affected patients. Drug repurposing is a very attractive approach in search of existing drugs with new indications. In this study, we have employed the ligand-based approach to drug repurposing in the search for potential candidates for ICH treatment, commencing from compounds already having evidence of clinical efficacy and mechanism of action. It was on this basis that Clopidogrel Bisulphate was adopted as the primary ligand in this study because it has a well-established mechanism of action and clinical application in preventing the formation of thrombus with an excellent safety profile. This foundation selection thus enabled the exploration of similar compounds that could possibly be repurposed for treating ICH.A ligand-based screening approach was conducted on the DrugRep platform for 20 compounds that bind to the target sites relevant to IHD treatment. This consisted of Clopidogrel, DB00758, by a binding score of 1.000; followed by antiplatelet agents such as Ticlopidine, 0.549; Prasugrel, 0.415; and Pizotifen, 0.341. Among the tested compounds, Indapamide (DB00808), Tolfenamic Acid (DB09216), and Ketotifen (DB00920) demonstrated tight binding at crucial receptor pockets, such as C2 and C5, which are very important for good drug binding and display of its therapeutic action in IHD.The molecular docking studies have derived that the binding affinity of Tolfenamic Acid was as high as -8.5 kcal/mol, showing great interaction with target pockets. Notably, in the active site of the receptor, Tolfenamic Acid interacts with the residues S101, N159, H187, and F252 through hydrogen bonds, hydrophobic contacts, and possible π-stacking interactions. All such noncovalent forces would contribute towards stabilizing and efficacy of ligand interaction with the receptor, thus making Tolfenamic Acid a good candidate for repurposing in the treatment of IHD.

INTRODUCTION

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Toflenamic acid does not belong to anti-platelet medications [1]. But the presence of COX-1 inhibition activity makes this drug a potential treatment targeting P2Y12[2]. Generally, COX enzymes-especially COX-1-participate in the production of TXA2[4]. Which is one of the significant agonists for platelet activation and platelet aggregation[5]. Because the platelet activation process is disrupted, the amount of TXA2 becomes lower due to COX-1 inhibition [6]. This is due to NSAIDs like toflenamic acid [7]. With COX-1 inhibition, tolfenamic acid may indirectly exert an antiplatelet effect[8]. The COX-1 inhibition of NSAIDs, including tolfenamic acid, is well described[9]. The possibility of a direct interaction with the P2Y12 receptor has only recently been considered [10]. Different studies have demonstrated that platelet aggregation is far more complex than the simple interaction between ADP and the P2Y12 receptor [11]. The various signalling pathways interact with each other for full platelet activation n[12]. For example, phosphoinositide 3-kinase and protein kinase C were identified as key downstream effectors of the P2Y12 receptor [13].Involved in the regulation of a wide range of processes: platelet shape change, granule release, and aggregation[14]. It is thus conceivable that toflenamic acid, through the induction of cellular signaling, modulates these pathways in a fashion that would further enhance antiplatelet properties[15]. This therefore opens the possibility that toflenamic acid can synergistically interact with established P2Y12 inhibitors [16]. And present a dual mode of inhibiting platelet aggregation both through inhibition of thromboxane A2 and modulation of the P2Y12 receptor[17]. The other mechanism by which tolfenamic acid acts as an antiplatelet agent [18]. Involves its lipophilic nature, allowing it to permeate the platelets and thus interact with the intracellular signaling systems[19]. Platelets differ from most of the other cellular elements of the body in that they lack a nucleus[20]. But they very much depend on the integrity of their cell membrane and the signaling molecules in the cytoplasm as far as regulating their activation and aggregation are concerned[21]. In this regard, toflenamic acid works through this pathway in a way that it may be associated with a more focused approach to the inhibition of platelets[22]. It could even turn out to be an ideal candidate for repurposing as an antiplatelet agent[23]. Such promising theoretical mechanisms notwithstanding, several limitations preclude toflenamic acid from being seriously considered an alternative[24]. Or adjunct to existing antiplatelet therapies[25]. First, there is the issue of the selectivity of toflenamic acid toward the P2Y12 receptor[26]. Whereas this drug clearly inhibits COX-1, its effects upon P2Y12 receptor signaling are poorly characterized[27]. That is why Tolfenamic acid, a drug that can be said to be a NSIAID, because of its lipophilicity characteristic that enables it to penetrate into the membranes of the platelets and to affect their intracellular signalling[28]. Unlike the other cells in the body, platelets do not have a nucleus[29]. So activation and aggregation are only dependent upon the integrity of their cell membrane and intracellular signaling molecules[30]. Tolfenamic acid may now offer a more targeted, possibly even more effective approach to preventing platelet function from being impaired by other drugs[31]. This may qualify the drug for repurposing as antiplatelet therapy[32]. The advantages of the mechanism by which tolfenamic acid enters into platelets[33]. And directly modulates their internal mechanisms are that it penetrates platelets and directly modulates their internal mechanisms [34]. Usually, platelet activation and aggregation is

initiated by agonist-stimulated interactions with the receptors on the platelet membrane, for instance involving P2Y12 receptor[35]. If tolfenamic acid antagonizes this receptor [36].Or another signaling pathway in the platelet, then aggregation might be blocked more selectively, potentially reducing thrombus formation[37]. Additionally, an intracellular mechanism for tolfenamic acid may provide additional benefits over drugs that target receptors that are located predominantly outside cells, allowing for a more selective regulation of platelet activity[38]. Tolfenamic acid, an attractive candidate for drug repurposing as an antiplatelet agent[39]. Known from established use in other therapeutic contexts, particularly in the inflammation context[40]. It has a lipophilic character that renders it interactive with platelet signaling systems[41]. It well-understood safety profiles that therefore render it a good candidate for further investigation[42]. Its potential antiplatelet effects might be an alternative therapeutic option for cardiovascular diseases like ischemic heart disease and stroke[43]. Where platelet aggregation is central to the pathophysiology[44]. However, despite the theoretical advantages, these concerns limit tolfenamic acid to be an alternative alternative therapy compared to the conventional antiplatelet drugs[45]. Its selectivity to the P2Y12 receptor is a significant drawback[46]. Tolfenamic acid was proven to be a potent inhibitor of COX-1[47]. One of the important enzymes in the process of platelet aggregation[48]. However, the inhibition of the P2Y12 receptor by tolfenamic acid remains poorly understood[49]. Most of the anticlot drugs available today, such as clopidogrel, target the P2Y12 receptor and inhibit platelet aggregation[50]. There is no enough evidence that it also interacts with or inhibits the latter[51]. Thus, modulation of platelet aggregation through the P2Y12 receptor by tolfenamic acid is only speculative[52]. The drug probably inhibits COX-1, which decreases the amounts of thromboxane A2, but little is known regarding its effects on the signaling function of the P2Y12 receptor[53]. It is uncertain whether its antiplatelet effects are exerted by COX-1 inhibition only because of the lack of clear evidence that tolfenamic acid interacts with P2Y12[54]. As P2Y12 is central in platelet aggregation, much more work is required to see if tolfenamic acid will interfere with this pathway besides its effects on COX-1[55]. If tolfenamic acid's actions on platelet aggregation depend largely on its COX-1 inhibition, then the clinical potential is similar to that of other non-selective COX inhibitors like aspirin and its novelty will not be high in this respect[56]. Its pharmacokinetic properties, both in platelets and in general with regard to overall bioavailability, would, therefore, need to be further investigated[57]. The ability of tolfenamic acid to accumulate in adequate concentrations within the platelets, where it might elicit its antiplatelet effect, is critical to its potential as a therapeutic agent[58]. Its lipophilicity may well facilitate its penetration of platelets; however, pharmacodynamics and pharmacokinetics based on antiplatelet therapy will be critical to its clinical utility[59]. Another aspect that needs to be addressed is the potential of drug interactions[60]. Since tolfenamic acid would be used concomitantly with other antiplatelet or anticoagulant drugs, its coadministration with such therapies needs to be evaluated[61]. The interactions that do either alter the efficacy or safety of the other drugs would make it very important for its prescription in practice[62]. Confirmation of the promise of tolfenamic acid as an antiplatelet repurposed agent would require clinical studies, where the reduction in platelet

aggregation, its safety on administration in patients with cardiovascular disease, and capacity for improving the outcomes of the patient relating to this thrombosis prevention could be established[63]. In the absence of such studies, the utility of tolfenamic acid as a platelet inhibitor remains undetermined and cannot be fully recommended as a valuable antiplatelet agent[64]. Since tolfenamic acid is lipophilic, this drug can potentially act as an antiplatelet agent[65]. And disrupt intracellular signaling pathways of platelets, but what specific mechanism through the interaction with the P2Y12 receptor is definitely unknown[66]. Although the drug is also known to inhibit COX-1, which has been implicated in causing antiplatelet effects, its role in platelet aggregation and possible repurposing as a therapeutic agent for cardiovascular disease remains to be determined[67]. Until such evidence becomes definitive, further speculation in the use of tolfenamic acid as an antiplatelet agent is not clinical[68].

2.MATERIALS AND METHODS

2.1 Data Collection: Sources of Clopidogrel Bisulphate

Clopidogrel is a thienopyridine derivative that acts as an antagonist of the P2Y12 receptor[69]. It is an antiplatelet medication, which works by inhibiting platelet aggregation[70]. It irreversibly binds to the P2Y12 receptor and blocks ADP-induced platelet activation[71]. Hence, this is widely applied in the prevention of thrombotic events[72]. It was employed as the positive control in the investigation of the putative P2Y12 inhibitory activity of tolfenamic acid[73].

Among the various G-protein-coupled receptors, the P2Y12 receptor plays an important role in the platelet aggregation process[74]. Activation occurs after its binding to ADP, thus sending signals for a higher degree of platelet activation and thrombus formation[75]. Therefore, P2Y12 antagonists, such as clopidogrel, would be an important target for antiplatelet therapy[76].

2.2 Ligand-Based virtual screening protocol

2.2.1 Platform Utilization:

DrugRep web platform: www.drugrep.org was used to find the potential P2Y12 receptor antagonists[77]. It offers access to a list of drugs approved by the FDA coupled with cheminformatics tools for virtual screening that predict drug-receptor interactions, advancing drug repurposing[78].

2.2.2 Screening Methodologies:

In ligand-based virtual screening, compounds were selected on multiple criteria to highlight potential drug candidates. ADMET properties were assessed using (https://admetmesh.scbdd.com/) to rank compounds according to favorable pharmacokinetic profiles for oral bioavailability; biological relevance was taken into account by considering compounds with reported activity against the target of interest; molecular weight between 300-500 Da and lipophilicity within LogP values 2-5 as optimized for pharmacological properties, and availability that allowed ease of experimental validation[79].Toxicity study done by using Protox 3.0 to determine LD50 and Toxicity Class (https://tox.charite.de/protox3/)[80].LigMate: It detects the compounds that resemble known structures of P2Y12 antagonists[81].

Fit Dock-Align: This refines the ligand alignment and docking predictions based on the comparison of their poses within the receptor's binding pocket [82].

L Salign: Ligand binding sites alignment to detect potential interactions [83].

FP2 and FP4: Pharmacophore Scout type screening instruments, in search of compounds that meet specific binding requirements (electrostatic, hydrophobic) for the inhibition of P2Y12[84].

Selection Process:

Those compounds were shortlisted on the basis of the following criteria- Structural likeness with known P2Y12 antagonists [85]. Higher docking scores which indicate strong binding affinity towards the receptor. Consistency of results on screening platforms [86].

2.3 Docking Studies

2.3.1 Docking Software:

CB-Dock (https://cadd.labshare.cn/cb-dock2/index.php) is a program for blind docking studies[87]. It permits flexible docking of ligands to protein targets without prior knowledge of the binding site[88]. CB-Dock uses energy minimization techniques to predict the most stable ligand-receptor interactions[89].

3.RESULTS AND DISCUSSION

3.1Results of Ligand-based Drug Repurposing

Table 1: Justification for selecting Clopidogrel Bisulphate as the primary ligand for designing new agents targeting ischemic heart disease (ICH):

Justification	Details
Mechanism of Action	Inhibits platelet aggregation by binding to P2Y12 ADP receptor, crucial for thrombus prevention.
Clinical Efficacy	Proven reduction in cardiovascular events in IHD patients, supporting its relevance.
Safety Profile	Favorable safety profile with manageable bleeding risk, aiding in the development of new agents.
Potential for Novel Derivatives	Structural basis allows for the creation of modified derivatives to enhance efficacy or reduce side effects.
Targeting Resistance	Can address resistance to antiplatelet therapies, leading to more effective treatment options.
Combination Therapy Potential	Opportunities for synergistic effects when used with other therapies, improving patient outcomes.
Research and Development	Extensive existing data on pharmacodynamics and pharmacokinetics to facilitate new agent development.
Market Presence	Widely recognized in clinical practice, easing adoption of new treatments derived from it.

Table (1) gives the justification for selecting Clopidogrel Bisulphate as the primary ligand for designing new agents targeting ischemic heart disease.

3.2 Results of Ligand-Based Screening using the Drug Rep Platform:

Table 2: Binding Scores and Target Interactions of Various Compounds

Rank (1-10)	DB ID	Compound Name	Score	Rank (11-20)	DB ID	Compound Name	Score
1.	DB00758	Clopidogrel	1.000	11.	DB01221	Ketamine	0.280
2.	DB00208	Ticlopidine	0.549	12.	DB11823	Esketamine	0.280
3.	DB06209	Prasugrel	0.415	13.	DB04840	Debrisoquine	0.276
4.	DB06153	Pizotifen	0.341	14.	DB08936	Chlorcyclizine	0.274
5.	DB00920	Ketotifen	0.319	15.	DB00808	Indapamide	0.273
6.	DB06119	Cenobamate	0.306	16.	DB00939	Meclofenamic acid	0.273
7.	DB00422	Methylphenidate	0.298	17.	DB01428	Oxybenzone	0.271
8.	DB06701	Dexmethylphenidate	0.298	18.	DB00586	Diclofenac	0.270
9.	DB00648	Mitotane	0.294	19.	DB09543	Methyl salicylate	0.268
10.	DB09216	Tolfenamic acid	0.294	20.	DB00708	Sufentanil	0.266

Table (2) The table lists compounds in descending order of scores: with Clopidogrel (DB00758) at the peak of 1.000 and 0.266 at Sufentanil (DB00708) as the lowest score. Three antiplatelets topped that chart, the top ranked being Clopidogrel, followed closely by Ticlopidine (0.549) and Prasugrel (0.415). Anti-histamines outperformed others such as Pizotifen (0.341) and Ketotifen (0.319) and landed in the top 10, with Ketamine (0.280) and Esketamine (0.280) within it. The other compounds like Sufentanil and Methyl salicylate fall below 0.270 and therefore of lesser significance. Overall, the antiplatelet drugs prevail; CNS agents come next followed by antihistamines.

Docking studies and Validation process results

Table 3: Validation Metrics from PDB-REDO

Validation Metric	Original	PDB-REDO
Crystallographic refinement		
R	0.2372	0.2067
R-free	0.2612	0.2636
Bond length RMS Z-score	1.064	0.627
Bond angle RMS Z-score	0.884	0.800
Model quality raw scores		
Ramachandran plot normality	17	3
Rotamer normality	19	15
Coarse packing	97	97
Fine packing	78	86
Bump severity	96	32
Hydrogen bond satisfaction	53	20

The table juxtaposes validation metrics between the original model and the PDB-REDO model, indicating improvements in R-free value and bond angle RMS Z-score in PDB-REDO, also with enhanced Ramchandran plot and rotamer normality percentiles, though showing consistent bump severity but with no data for coarse and fine packing and hydrogen bonding.

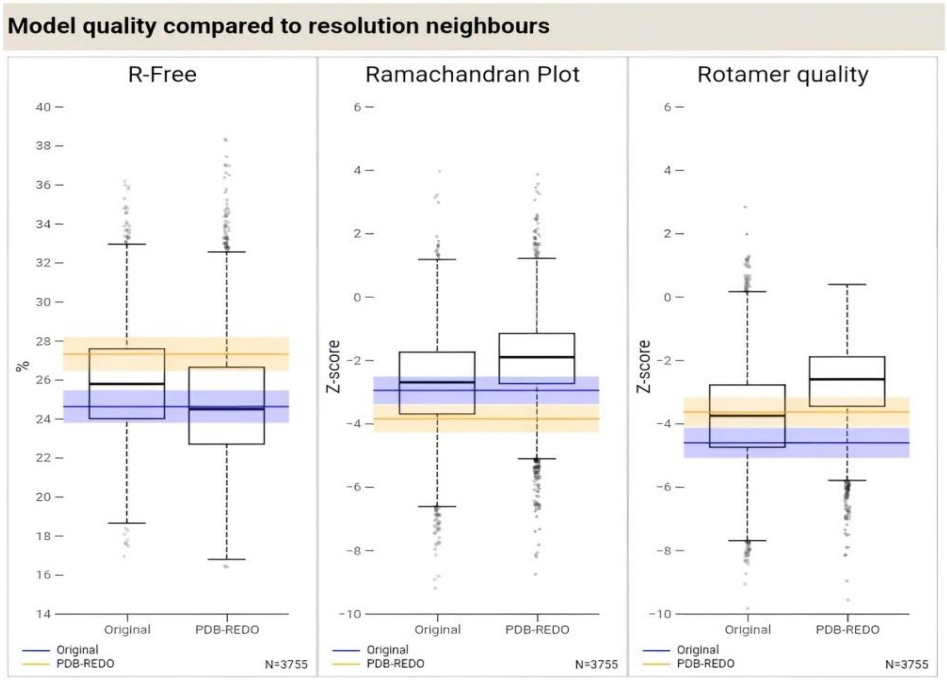

Figure 1: Comparative Analysis of Model Quality Metrics: Original vs PDB-REDO Refinement

In Fig.1, comparison box plots of model quality metrics between the original and PDB-REDO models and resolution neighbors show that the PDB-REDO model has better R-Free values and Ramachandran plot scores, suggesting an overall better structural quality and refinement over the original model.

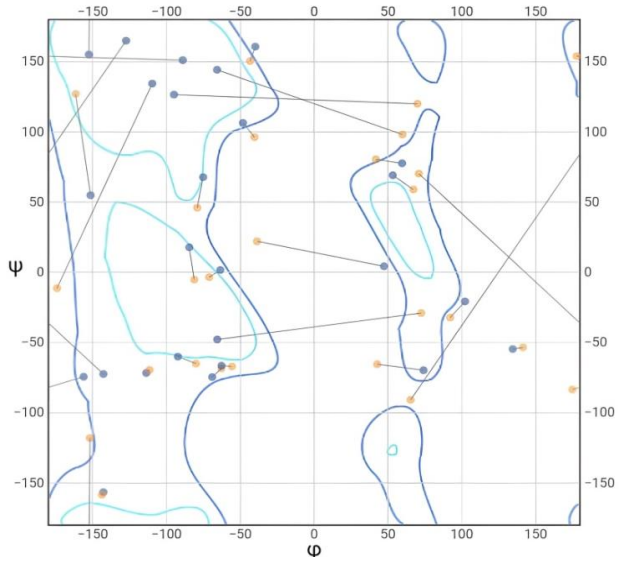

Figure 2: Kleywegt-Like Plot

Figure 2, is Kleywegt-like plot, where the distribution of phi (ϕ) on x-axis and psi (ψ) on y-axis dihedral angles of amino acids in a proteindetermining the stereochemical quality and structural integrity of that protein. It is plotted with color gradient under estimating the density of conformational states; the red regions are areas of favored conformations and scattered blue and orange dots are individual residues that help deduce stereochemical quality and structural integrity of the protein backbone.

Docking Results:

Table 4: Binding Affinity Analysis of Drug Bank Compounds to Target Pockets: Identification of Potential Drug Candidates

Drug Bank ID	Pocket	Score	Chain	Drug Bank ID	Pocket	Score	Chain
DB00758	C5	-7.5	A	DB01221	C2	-6.5	A
DB00208	C2	-8.1	A	DB11823	C2	-6.9	A
DB06209	C2	-7.8	A	DB04840	C2	-7.5	A
DB06153	C2	-7.3	A	DB08936	C2	-6.9	A
DB00920	C5	-8.5	A	DB00808	C2	-9.1	A
DB06119	C5	-7.1	A	DB00939	C2	-7.6	A
DB00422	C5	-7.6	A	DB01428	C5	-7.9	A
DB06701	C5	-6.9	A	DB00586	C2	-7.4	A
DB00648	C2	-7.1	A	DB09543	C2	-6.1	A
DB09216	C2	8.5	A	DB00708	C2	-7.0	A

The docking study identified Indapamide (DB00808),Tolfenamic acid(DB09216) and Kitotifen(DB00920) to be prime candidates with strong affinities to pocketsC2, C2, C5 indicating their potential for repurposing.

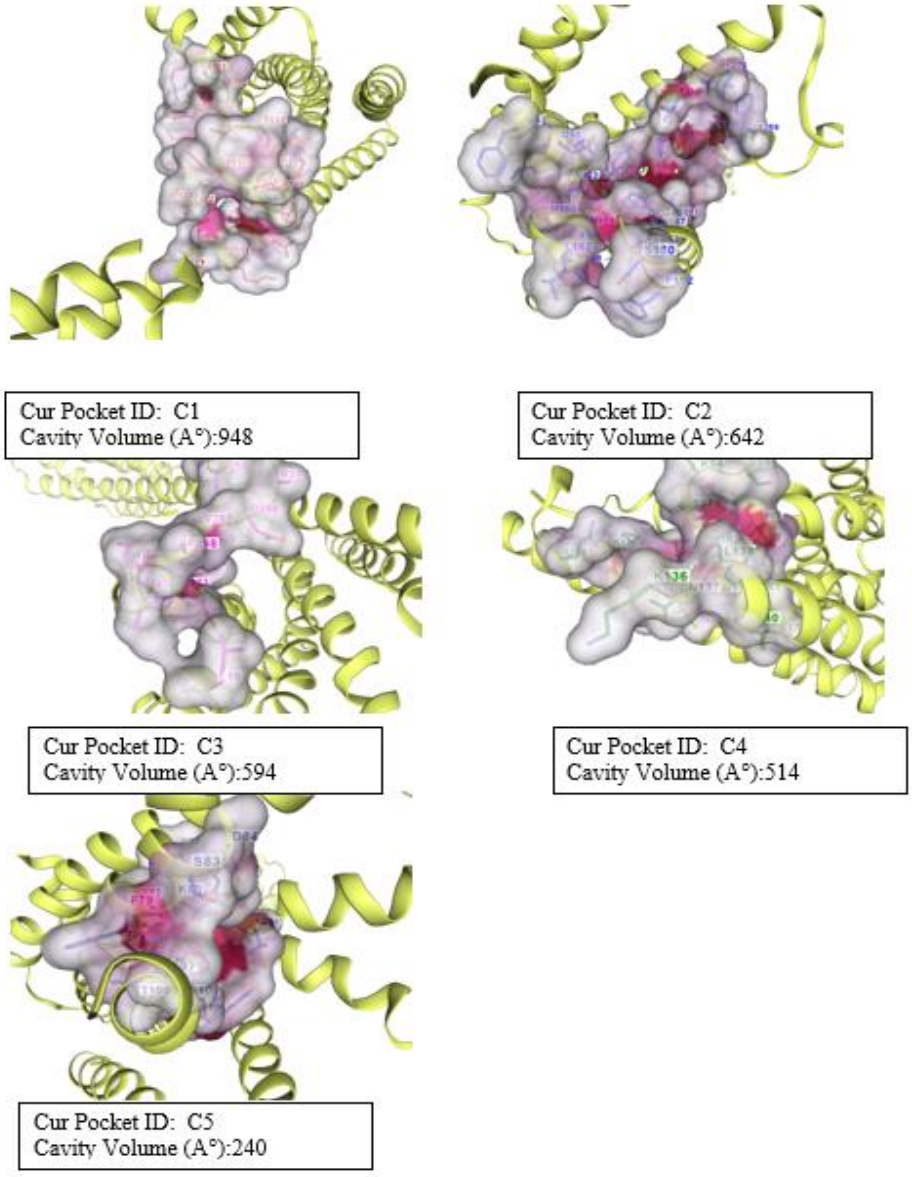

Figure 3: Cavities found in Protein.

The protein structure has unique binding pockets with different interaction sites. Yellow helices indicate alpha-helices, denoting a fold typical of enzymes or membrane proteins. The various gray and pink areas point to the protein's binding pocket, with residues (F258, T127, V267) labeled, which contribute to either ligand binding or catalytic activity. Hydrophobic residues are probably colored pink, whereas red and blue color denotes polar/charged residues involved in interactions. Pockets that were highlighted reveal some very important hotspots of binding, while also residues like Q98 and F252 closely interacting with a ligand. These pictures are useful for drug design, docking studies, and enzyme analysis.

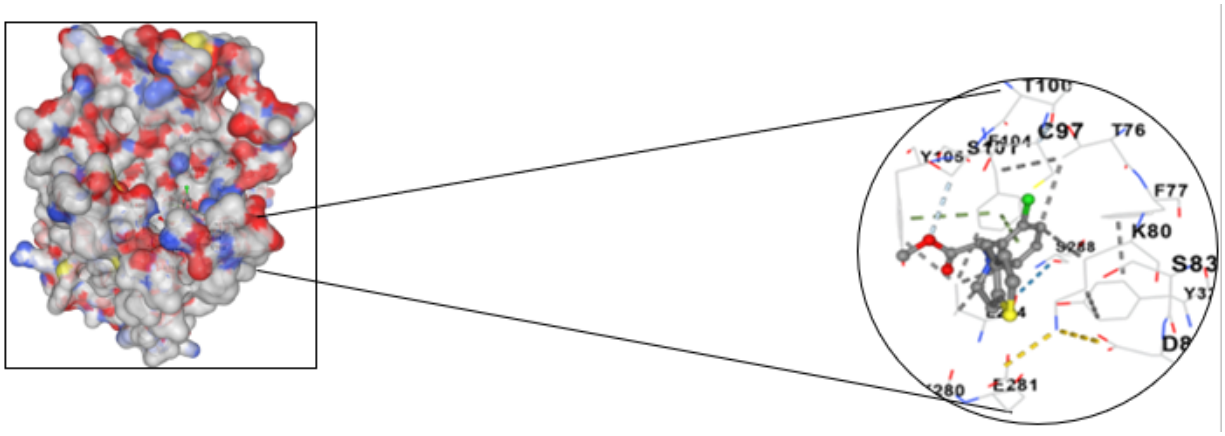

Figure 4: Molecular Docking of Tolfenamic Acid: Key Binding Interactions for Ischemic Heart Disease.

The pictures of molecular docking presented here show the actual interaction between the ligand and its receptor. These images highlight the particular binding interactions as well as the surface structure of the receptor. In the top image, the ligand is placed within the receptor's active site. This ligand interacts with some significant residues such as S101, N159, H187, and F252 as shown by various dashed lines, which depict the non-covalent interactions. Hydrogen bonds, hydrophobic contacts, and possibly π-stacking are some examples of these. Significantly, a green atom, which is presumably chlorine, in the ligand, indicates that there may be hydrophobic interaction or halogen bonding which stabilizes the ligand in the binding pocket. The second figure presents the surface of the receptor, showing the electrostatic potential. White areas are indicative of hydrophobic surfaces, while blue represents positive charge zones and red represents areas of negative charge. An exclusive binding pocket inducts the ligand.

CONCLUSION

Ligand-based drug repurposing approach for targeting Ischemic HeartDisease giving insight into how most drugs already existent may be repurposed to better address the disease. A prime ligand, of interest for the drug repurposing approach to target ICH, based on well-established mechanism of action and clinical efficacy and safety profile, is presented by Clopidogrel Bisulphate, which sets a good basis for developing new agents targeting IHD. In fact, the elaborate justification for its choice clearly shows strong relevance and further development potential, including that possible resistance can be overcome while enhancing combination therapies. Of the 20 compounds screened using the Drug Rep platform from the Ligand-Based Screening, the highest ranked compound was found to be Clopidogrel (DB00758) with a score of 1.000, followed by Ticlopidine at a score of 0.549, then Prasugrel at 0.415, and lastly Pizotifen, at 0.341. Moreover, interactions of Indapamide (DB00808), Tolfenamic Acid (DB09216), and Ketotifen (DB00920) with the two highly significant target sites C2 and C5 were significant, thus classifying them as potential candidates for repurposing. The results of the docking studies exhibited very high binding affinities. For the lead compounds, Indapamide has a score of -9.1 and Tolfenamic Acid with a score of -8.5. The interaction with target pockets C2 and C5 was excellent. These findings align with the molecular docking images wherein the ligands were demonstrated to interact via hydrogen bonds, hydrophobic contacts, and

probably π-stacking with important residues such as S101, N159, H187, and F252 that prove the stability and effectiveness of these interactions. Validation by PDB-REDO further increased the reliability of the computational models, with an enhancement seen regarding their R-free value, Ramachandran plot scores, and bond angle RMS Z-scores, which suggested that the models were of a higher quality and more refined. The improved quality of the PDB-REDO models supports the robustness of the docking results and reliability of the computer framework used to design drugs. In general, the docking results indicate that Tolfenamic Acid boasts a good binding characteristic along with stability in the receptor's binding pocket, mainly due to strong non-covalent interactions and high electrostatic complementarity between the ligand and the receptor. The binding energy of -8.5 kcal/mol puts Tolfenamic Acid on the position as a valuable candidate for repurposing in the treatment of IHD. Further experimental validations and optimizations of Tolfenamic Acid are necessary to fully realize its therapeutic potential in cardiovascular applications.The generalizability of results may be affected by limitations in the DrugRep platform and docking procedures, requiring cross-validation with other modeling approaches. Whereas computational docking offers useful information, efficacy, pharmacokinetics, and safety must be validated through in vitro and in vivo research.

Ethics Approval and Consent to Participate:

Not applicable.

Human And Animal Rights:

No animal/humans were used for studies that are the basis of this research.

Consent For Publication:

Not applicable.

Availability Of Data and Materials:

Not applicable.

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None.

Conflict Of Interest:

The author declares no conflict of interest, financial or otherwise.

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Credit Statement:

Dr. Udugade B.V: Conceptualization, Supervision and Project administration; Shruti Bhima Kamble: Methodology, Formal analysis, Investigation and Writing - Original Draft; Seema Shamrao Khot: Writing - Review & Editing; Sakshi Satish Khamkar: Investigation and Data Curation

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