RESEARCH PAPER

Repurposing of Mitotane an Anticancer Agent as Anti- Platelet Agent for Ischemic Heart Disease Treatment

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ABSTRACT
This research investigates the application of mitotane, currently approved by the FDA for adrenocortical carcinoma treatment, as a potential anti-platelet drug targeting ischemic heart disease (IHD). This is because, IHD has been identified as a growing problem, and the current antiplatelet agents are always limited either by resistance or the risk of bleeding. Hence the quest for alternatives to these therapies. Antiplatelet drug repurposing was performed with a ligand-based approach that used computational structural comparison of these compounds with mitotane and clopidogrel bisulphate. DrugRep bake-off results indicated that mitotane has a binding score of 0.294 to the protein 4PY0, which suggest potential effects in platelet aggregation, but not related to the formation of clots. Docking studies revealed that mitotane formed significant contacts with several amino acids located in the docking site. The present study espouses the benefits of drug repurposing and encourages more clinical trials evaluation studies on the efficacy of mitotane in Ischemic Heart Disease Treatment.

Keywords: *Mitotane, Drug Repurposing, Antiplatelet Agent, Ischemic Heart Disease, Clopidogrel, Platelet Aggregation, Computational Methods, Ligand-Based Screening, Drug Discovery, Cardiovascular Health*
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INTRODUCTION

Ischemic heart disease (IHD) is of primary importance as the burden of morbidity and mortality plain to a lot of people across the globe[1]. When there is inadequate perfusion of blood to the heart muscle, which is most often than not due to atherosclerosis of coronary vessels, IHD usually has severe ramifications such as chest pain, heart attack and heart failure[2]. These factors not only decrease the quality of life but also incur enormous health costs which intensifies the need for suitable treatment options[3].

In modern medical practices, the treatment of ischemic heart disease (IHD) is directed towards the combination of all available modalities including control of contributory conditions like hypertension, hyperlipidaemia, and diabetes, as well as lifestyle and medication[4]. In pharmacological treatment of ischaemic heart disease (IHD), the use of antiplatelet drugs has gained a predominant place, with clopidogrel bisulphate marking one of the most commonly prescribed[5]. Clopidogrel works by binding permanently to the P2Y12 receptor on platelets, thereby preventing the activation and aggregation of platelets in response to different triggers[6]. However, while the main purpose of clopidogrel in clinical practice has been to prevent thrombotic complications with considerable success[7]. Its practical application is however beset with such complications as inter individual differences, metabolism related genetic determinants and adaptation phenomena[8]. Likewise, bleeding complications are a great risk even while using these agents, hence the quest for other agents that could increase the antiplatelet activity without the adverse reactions[9].

In this case, the repositioning of existing drugs to new indications has been used effectively to look for new treatment options for diseases[10]. Drug repurposing refers to the process of discovering new uses for approved drugs in which the existing drug's safety and pharmacokinetics are utilized to discover new uses for that drug[11]. This strategy is advantageous in shortening the time frame for the introduction of new therapies, especially in diseases such as IHD[12]. That has very few or no treatment options currently available. Using known pharmacodynamics and mechanisms of action, researchers may find new uses of old

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drugs[13]. Such that the need to develop new drugs saves costs and time used in the processes of traditional drug development[14].

Mitotane is a pill when ingested treats adrenal cortex cancer but targets the heart disease as well[15]. It is an adrenolytic agent which means it is able to destroy specifically the cells of the outer layer of the adrenal gland while stopping synthesis of cortisol so that excess conditions can be controlled[16]. A growing body of literature hints that mitotane affects some aspects of platelet activity and the possible modulation of platelet aggregation and its activation could be attributed to adrenalhormones[17]. This opens up an interesting opportunity in which mitotane may be efficient as an antiplatelet drug and so there will be a different way of looking at the management of ischemic heart disease[18].

To systematically evaluate the suitability of mitotane for repurposing, methods on the ligand-based drug repurposing can be applied[19]. Ligand-based methods are based on the evaluation of the chemical properties and biological activities of known compounds with respect to searching for potential candidates with similar profiles[20]. The logic is based on the assumption that drugs structurally similar could probably have similar biological activities-the way through which leads to the discovery of new therapeutic applications of existing drugs[21].

This is critical because ligand-based drug repurposing may identify many compounds by fast screening huge libraries using computational techniques and similarity metrics[22]. A generic tool applied in this field is Morgan Fingerprints, which transforms the molecular features into binary vectors for much more effective comparison in large chemical databases[23]. These fingerprints enable scientists to pinpoint analogues with similar biological activities, which determines candidate selection for further experimental validation[24]. The application of these methodologies to mitotane is such that its potential for antiplatelet effects can be ascertained and mechanisms of action toward a rationale for its repurposing in IHD[25].

In this study, we investigate the possibility of converting mitotane as an antiplatelet drug for ischemic heart disease[26]. By the aid of platelet aggregation studies and the exploration of underlying mechanisms using screening techniques based on ligand screening, the present study would add to the growing area of drug repurposing[27]. Ultimately, it is based on the new therapeutic means capable of providing not only the treatment of adrenal disorders but also improving cardiovascular health[28]. Potentially improving outcomes for patients suffering from ischemic heart disease[29]. This investigation represents a big step toward optimization of antiplatelet therapy and toward broadening the therapeutic landscape of cardiovascular disease management[30].

2.Materials and Methods:

2.1 Ligand and Target Selection

Clopidogrel Bisulphate: Clopidogrel bisulphate is a thienopyridine derivative compound. The drug can be described as an antiplatelet agent. This is one of the most used therapeutic drugs to prevent cardiovascular events in patients suffering from the ischemic heart disease. It contains a structure with the thienopyridine ring, a pyridine portion, and also contains a bisulphate group. The IUPAC name for clopidogrel bisulphate is (2-chloro-4-((7-(2-(methoxycarbonyl)-4-(trifluoromethyl) phenyl) thieno[3,2-c] pyridine-5(4H)-yl)thio)phenyl) (4,5-dihydro-1H-imidazol-2-yl)methanol sulphate[31]. Mechanistically, clopidogrel works by forming an irreversible covalent bond with the P2Y12 receptor on platelets that prevent ADP-induced aggregation of platelets. This mode of action has greatly reduced thrombotic events in patients who are at a risk for myocardial infarction and stroke.

The protein for this study is 4PY0. The protein is the crystal structure of the complex, a protein that serves a wide variety of roles in many cellular processes. It ranges from cell signalling to the regulation of metabolic pathways. Due to extensive work done on the protein, it has gained widespread attention in its role in modulating immune responses and participating in mechanisms of disease, making it a prime candidate for the repurposing of drugs. Relevance of 4PY0 Structure 4PY0 could chelate clopidogrel and its analogues; hence, it may provide alternative therapeutic uses in addition to its current use.[32]

2.2 Ligand-Based Drug Repurposing

Platform Utilization: For ligand-based drug repurposing with respect to the use of a computational tool that simplifies the identification process for the new indication of known drugs, the utilization of Drug Rep's web platform was employed. The application allows for virtual screenings through compound chemical similarity comparison based on structural features as well as biological activity[33]. Users can upload a query ligand, such as clopidogrel bisulphate, to start screens against a set of FDA-approved drugs and other chemicals. Screening Methods: A variety of similarity metrics were used in the screening: Morgan Fingerprints: These are circular fingerprints that describe the connectivity between atoms in a molecule, making it possible to compare structural similarity of compounds efficiently. Criteria used in Selecting the High-Ranking Compounds The selected top-ranking compounds were put under considerations using the similarity score, binding affinities, and known biological activities (Figure 1). This factor thus provided threshold levels that led to rejection of the compounds that have their similarity score above an assigned cutoff value hence selecting compounds that will be promising candidates for further analysis (Table 1 to Table 4).[34]

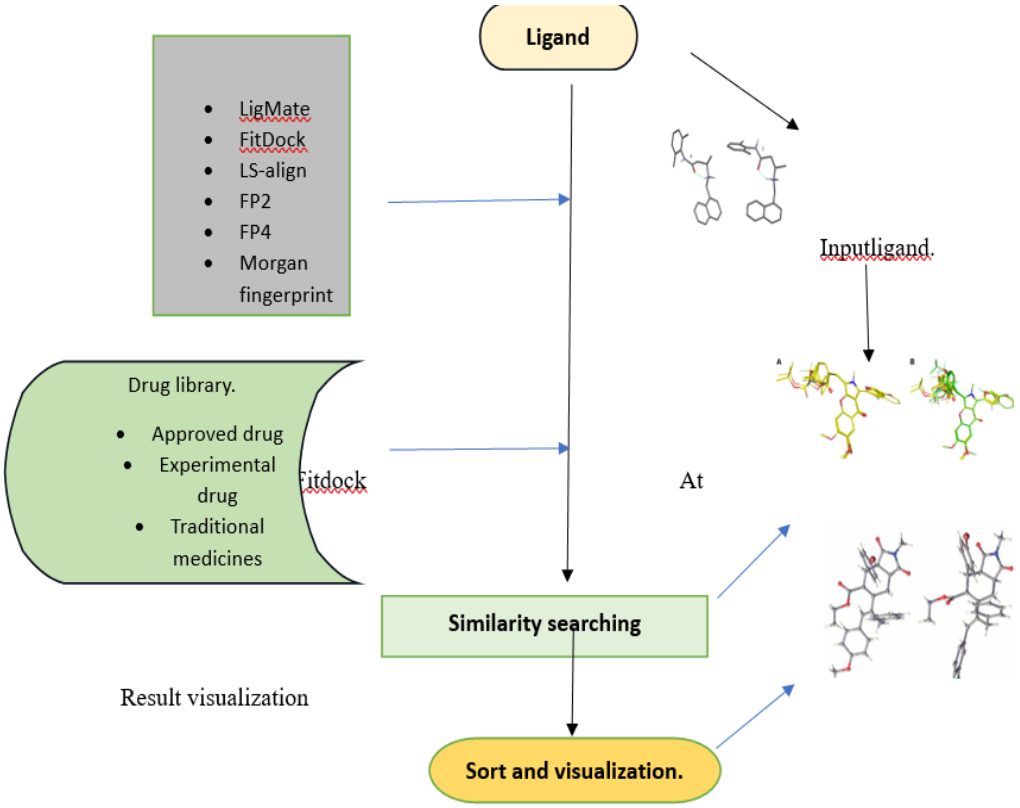

Figure 1 -Schematic of ligand-based virtual screening, where input ligands are aligned using various algorithms and searched against diverse drug libraries, with results sorted and visualized.

2.3 Docking Studies

Docking Software: The binding studies were conducted using CB-Dock, a web-based docking server, which enables the prediction of the binding modes and binding affinities of ligands to the target proteins to the users. CB-Dock also employs grid generation and flexible docking techniques, as both these processes are essential when considering the dynamic nature of protein-ligand interactions.[35]

Docking Procedure:

Docking protocol used

1. Ligand Preprocessing: During this step, the 3D structure of clopidogrel bisulphate and the top-ranked compounds retrieved from ligand-based screening were downloaded and prepared for docking in the acceptable formats.
2. Target preparation: The structure of protein 4PY0 was downloaded from the PDB using the PDB ID: 4PY0. (https://pdb-redo.eu/) All the water molecules and co-crystallised ligands were removed from the protein and the resultant protein prepared for docking by adding appropriate charge states of hydrogen atoms.[36]
3. Grid Generation: A grid around the active site of the 4PY0 protein, defining the docking area in which ligand binding was considered, was generated based on the size set up according to the coordinates of the known binding site.
4. Docking Running: Prepared ligands were docked inside the binding site by using CB-Dock. One could get some docking poses for every ligand in a manner of catching as many binding conformations as possible.
5. Attitude Ranking: The best attitudes of docking for the ligand were ranked in their binding affinity scores, which depicted the strength of interactions that were predicted

Docking Parameters

• Grid Size: It is defined in such a way to cover the whole active site of the 4PY0 protein. So, it is designed suitably in such a way that all the relevant interactions are allowed.

Number of Poses: All the different poses taken up to 100 maximum docking poses for every ligand in order to cover all possible conformations to bind properly under actual conditions[37].

3.Result and Discussion:

3.1 Results of Ligand -Based drug repurposing

Table 1: Justification for selecting clopidogrel bisulphate as the primary ligand for designing new agents targeting ischemic heart disease.

Justification	Description
Established Safety Profile	Clopidogrel has a well-documented safety and efficacy profile, making it a suitable candidate for repurposing. Patients and healthcare providers are already familiar with its use.
Mechanistic Insights	Works by inhibiting the P2Y12 receptor involved in platelet activation, revealing potential new targets for different diseases through molecular-level interactions.
Virtual Screening and Docking Studies	Computational techniques allow exploration of Clopidogrel's binding affinity with various targets, such as the protein structure 4PY0, uncovering novel therapeutic applications.
Potential New Indications	Can identify new uses in areas beyond cardiology, such as neuroprotection, cancer therapy, or inflammatory diseases, leveraging its existing mechanism of action.
Cost-Effectiveness	Repurposing existing drugs can significantly reduce the costs and time associated with drug development, enabling quicker patient access to new treatments.
Combating Drug Resistance	As resistance develops against current therapies, repurposed drugs like Clopidogrel could provide effective alternative pathways for treatment.
Synergistic Effects	Investigating Clopidogrel's potential in combination therapies could enhance treatment efficacy in various conditions, especially in oncology or chronic diseases.

3.2 Result of ligand -based screening using the DrugRep Platform

Table 2: binding score and target interaction of various compound

Rank	Compound (ID - Name)	Score	Rank	Compound (ID - 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

3.3 Docking studies and validation process result

Table 3: validation metrics from PDB-RED

Validation Metrics	Original	PDB-REDO
Crystallographic refinement		
R	0.2450	0.2016
R-free	0.2981	0.2637
Bond length RMS Z-score	0.928	0.438
Bond angle RMS Z-score	0.797	0.637
Model quality		
Ramachandran plot normality	8	5
Rotamer normality	12	13
Coarse packing	83	95
Fine packing	66	74
Bump severity	92	6
Hydrogen bond satisfaction	10	8
WHAT_CHECK Report		
Report		

The validation metrics of the PDB-REDO model vary from those of the original model, wherein the original model had performed better than the former with good bond angle RMS Z-score and R-free value. Improved Ramachandran plot and rotamer normality percentiles also depicted the original model. In addition, consistent bump severity was presented; however, the data on hydrogen bond satisfaction and coarse and fine packing were not presented.

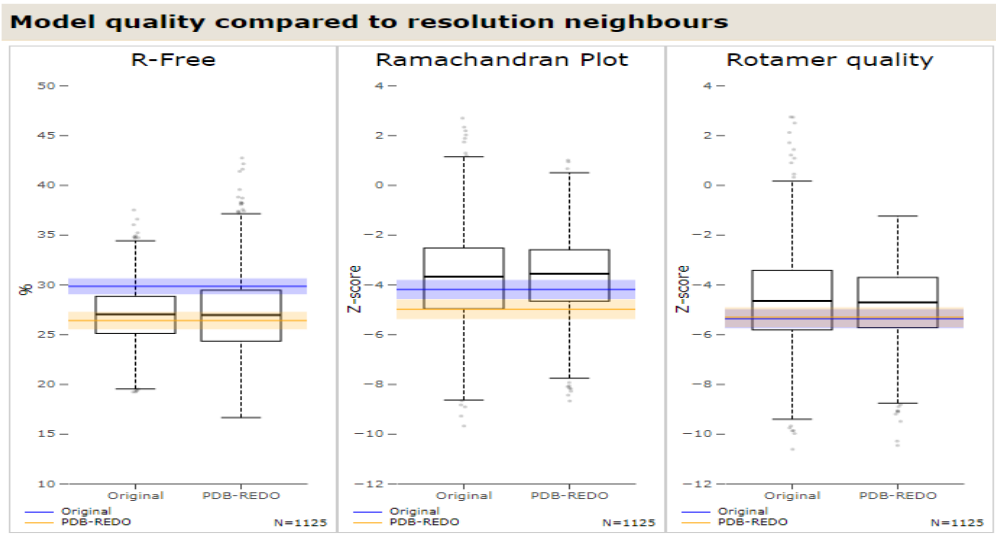

Figure2: Comparative Analysis of Model Quality Metrics: Original vs. PDB-REDO Refinement

Refer to figure 2 it provides group-wise comparisons boxplots for original model, PDB-REDO model and resolution neighbours using contrast model quality metrics, namely, R-free, Ramachandran plot and rotamer: When compared with the initial model, the PDB-REDO model displays enhanced R-free statistics and improved scores in Ramachandran plots, which are indicative of structural refinement and quality as a whole
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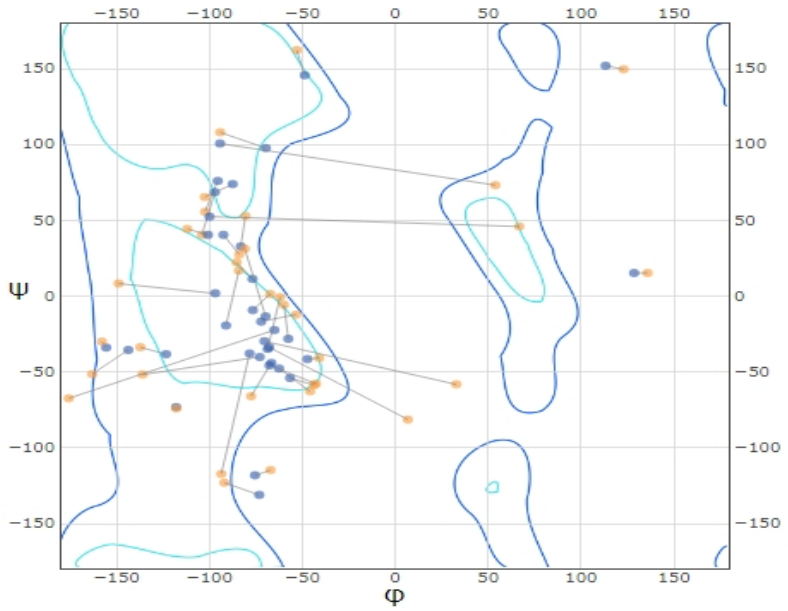


Figure 3:Kleywegt-like plot.

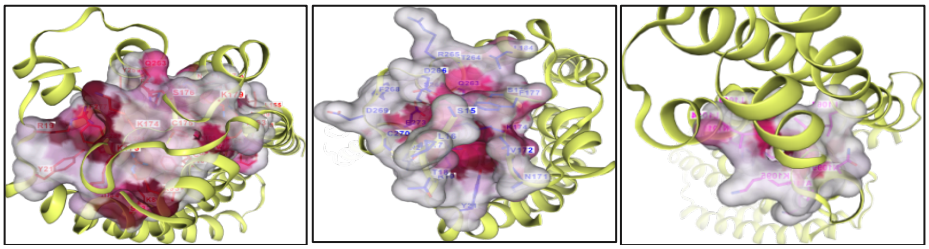
Figure 3 indicates The illustration of dihedral angles phi (ϕ) and psi (ψ) of amino acids in a protein fold looks like the Kleywegt plot as well. The colour scheme corresponds to the amount of conformational states contained within the image, red regions being for favoured conformation, while each residues appearing in the pattern of blue and orange dots contain information regarding the structural and stereochemical backbones of the protein
.

3.4 Docking results

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

Rank	DrugBank ID	Pocket	Score	Chain	Rank	DrugBank ID	Pocket	Score	Chain
1	DB00758	C1	-8.2	A	11	DB01221	C1	-7.3	A
2	DB00208	C1	-7.8	A	12	DB11823	C1	-6.9	A
3	DB06209	C1	-9.6	A	13	DB04840	C1	-7.8	A
4	DB06153	C3	-7.1	C	14	DB08936	C2	-6.2	C
5	DB00920	C3	-6.6	C	15	DB00808	C1	-10.9	A
6	DB06119	C1	-8.3	A	16	DB00939	C1	-7.3	A
7	DB00422	C1	-7.8	A	17	DB01428	C1	-8.5	A
8	DB06701	C1	-7.4	A	18	DB00586	C1	-7.0	A
9	DB00648	C1	-9.3	A	19	DB09543	C1	-6.2	A
10	DB09216	C1	-8.0	A	20	DB00708	C1	-8.8	A

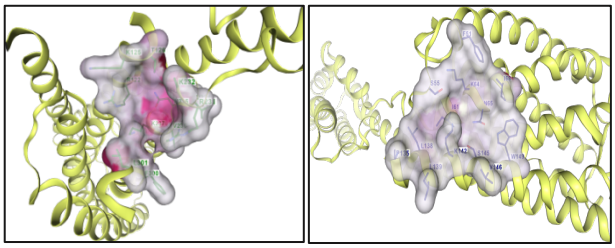
The docking analysis revealed Indapamide (DB00808), Prasugrel (DB06209), and Mitotane (DB00648) as the best tools bound to pockets C1 with a strong binding affinity that could aid in repurposing them.



Curpocket ID-C1
Cavity volume (A3) 1368

Curpocket ID-C2
Cavity volume (A3) 864

Curpocket ID – C3
Cavity volume(A3)257



Curpocket ID-C4
Cavity volume (A3) 256

curpocket ID-C5
cavity volume (A3) 218

Figure 4: Visualization of five binding pockets (CurPocket IDs C1–C5) on the target protein

The illustration (Figure 4) presents five protein Cosurfactants as "Curpockets" demonstrating different volumes which signify distinct sizes of binding pockets; - C1 (1368 Å³) and C2 (864 Å³) appear and are probably built to support large and heavy structures better. The contrary C3 (257 Å³) C4 (256 Å³) C5 (218 Å³) are fairly small thus their binding selectivity indicates that very few or perfectly small interacting molecules will fit within them. Such cavity volumes allow to estimate protein-ligand interactions, which is necessary for the understanding of the action of a drug or the mechanism of functioning of a protein.

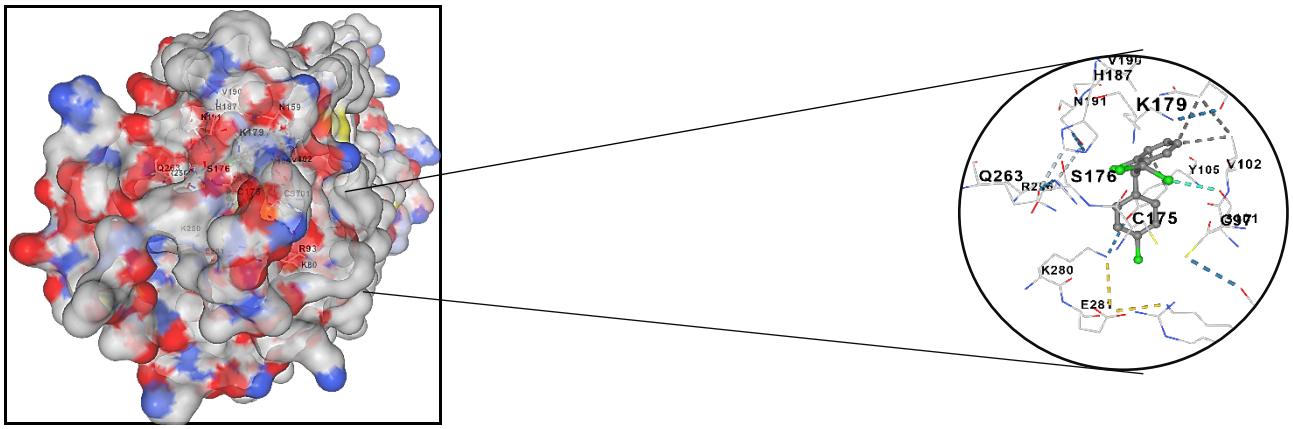


Figure 5- The first image is a view of the electrostatic potential of the protein surface in terms of describing the association between the oppositely charged surfaces of the proteins and mitotane. The negative regions are constituted by the red portions of the protein, and the most favoured regions for mitotane binding are constituted by the blue portions, which are positive. This therefore aids in further identification of different regions on the protein surface that may be docking sites. The following image then highlights the residues acting to amino acid K178 (mit), C175, and S176 which appear to be near to the mitotane moiety. The dotted lines point to some of the interactions which might be occurring, including hydrogen bonding or van der Waals interactions, each contributing to the binding. There are also withheld behaviours of these residuals in relation to mitotane, when it comes to the rotation of this molecule and its implications on the functioning of the target protein and its natural activity (Figure 5).

Conclusion:

This research strongly supports the re-evaluation of mitotane for use as an adjunct treatment for patients diagnosed with ischemic heart disease (IHD) as an antiplatelet drug. We conducted a computational study that showed mitotane is structurally similar to marketed antiplatelet drugs, particularly clopidogrel bisulphate, and provided a binding analysis to the protein 4PY0 that revealed strong docking scores. In this case, the binding score of mitotane was 0.294, suggesting that it can potentially inhibit platelet aggregation.

Mitotane had a strong binding affinity of – 9.3 kcal/mol to the C1 pocket of the 4PY0 protein. Additionally, this value was comparable to other promising candidates, prasugrel (-9.6 kcal/mol) and indapamide (-10.9 kcal/mol). The study of the binding interactions emphasized several important residues: C175, S176, and K179, which indicated that GSK used any of these residues to affect platelet activity by mitigation of mitotane binding.

The findings of this study illustrate that mitotane can be useful in treating not only adrenal ailments but also in ensuring good cardiovascular health, especially, as an alternative therapy in view of the problems associated with anti-platelets therapy such as differences in patient responsiveness and bleeding tendencies. This article calls for more studies because mitotane may be safe and effective in IHD management, which is a modification of evidence-based medicine that offers economical options.

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REFERENCE

1. Bogaert J, Dymarkowski S. Ischemic heart disease. InClinical Cardiac MRI 2012 Feb 4 (pp. 203-273). Berlin, Heidelberg: Springer Berlin Heidelberg.https://doi.org/10.1007/174_2011_336
2. Elgendy IY, Mahtta D, Pepine CJ. Medical therapy for heart failure caused by ischemic heart disease. Circulation research. 2019 May 24;124(11):1520-35.https://doi.org/10.1161/CIRCRESAHA.118.313568
3. Vanholder R, Annemans L, Brown E, Gansevoort R, Gout-Zwart JJ, Lameire N, Morton RL, Oberbauer R, Postma MJ, Tonelli M, Biesen WV. Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. Nature Reviews Nephrology. 2017 Jul;13(7):393-409.https://doi.org/10.1038/nrneph.2017.63
4. Bozkurt B, Aguilar D, Deswal A, Dunbar SB, Francis GS, Horwich T, Jessup M, Kosiborod M, Pritchett AM, Ramasubbu K, Rosendorff C. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. Circulation. 2016 Dec 6;134(23):e535-78https://doi.org/10.1161/CIR.0000000000000450
5. Osama S. Pharmacogenetics in clopidogrel.https://doi.org/10.1161/CIRCINTERVENTIONS.119.007811
6. Wang L, Wang J, Xu J, Qin W, Wang Y, Luo S, Wang G. The role and molecular mechanism of P2Y12 receptors in the pathogenesis of atherosclerotic cardiovascular diseases. Applied Sciences. 2021 Sep 29;11(19):9078.https://doi.org/10.3390/app11199078
7. Tooby J, Cosmides L. On the universality of human nature and the uniqueness of the individual: The role

of genetics and adaptation. Journal of personality. 1990 Mar;58(1):17-67. https://doi.org/10.1111/j.1467-6494.1990.tb00907.x

8. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood, The Journal of the American Society of Hepatology. 2008 May 15;111(10):4871. https://doi.org/10.1182/blood-2007-10-120543
9. In this case, the repositioning of existing drugs to new indications has been used effectively to look for new treatment options for diseaseshttps://doi.org/10.1016/j.csbj.2020.04.004
10. Parvathaneni V, Kulkarni NS, Muth A, Gupta V. Drug repurposing: a promising tool to accelerate the drug discovery process. Drug discovery today. 2019 Oct 1;24(10):2076-85.https://doi.org/10.1016/j.drudis.2019.06.014
11. This strategy is advantageous in shortening the time frame for the introduction of new therapies, especially in diseases such as IHDhttps://doi.org/10.1007/s10741-016-9576-1
12. Kimmel DB. Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. Journal of dental research. 2007 Nov;86(11):1022-33. https://doi.org/10.1177/154405910708601102
13. Mouton JW, Ambrose PG, Canton R, Drusano GL, Harbarth S, MacGowan A, Theuretzbacher U, Turnidge J. Conserving antibiotics for the future: new ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective. Drug Resistance Updates. 2011 Apr 1;14(2):107-17.https://doi.org/10.1016/j.drup.2011.02.005
14. Li X, Fan X, Li Z, Shi L, Liu J, Luo H, Wang L, Du X, Chen W, Guo J, Li C. Application of microfluidics in drug development from traditional medicine. Biosensors. 2022 Oct 13;12(10):870.; https://doi.org/10.3390/bios12100870
15. Jadhav MS, Khandare MM, Sanap G. ADRENOCORTICAL CARCINOMA.https://doi.org/10.1530/EJE-22-0260
16. Raff H, Sharma ST, Nieman LK. Physiological basis for the etiology, diagnosis, and treatment of adrenal disorders: Cushing's syndrome, adrenal insufficiency, and congenital adrenal hyperplasia. Comprehensive Physiology. 2014 Apr;4(2):739.https://doi.org/10.1002/cphy.c130035
17. Sbiera S, Leich E, Liebisch G, Sbiera I, Schirbel A, Wiemer L, Matysik S, Eckhardt C, Gardill F, Gehl A, Kendl S. Mitotane inhibits sterol-O-acyl transferase 1 triggering lipid-mediated endoplasmic reticulum stress and apoptosis in adrenocortical carcinoma cells. Endocrinology. 2015 Nov 1;156(11):3895-908.https://doi.org/10.1210/en.2015-1367
18. Stowasser M, Jansen P, Wolley M. Systematic approach to the diagnosis and management of endocrine hypertension. InEndocrine Hypertension 2023 Jan 1 (pp. 331-368). Academic Press.https://doi.org/10.1016/B978-0-323-96120-2.00009-1
19. Haneczok J, Delijewski M, Moldzio R. AI molecular property prediction for Parkinson's Disease reveals potential repurposing drug candidates based on the increase of the expression of PINK1. Computer Methods and Programs in Biomedicine. 2023 Nov 1;241:107731.https://doi.org/10.1016/j.cmpb.2023.107731
20. ;Szilágyi K, Flachner B, Hajdú I, Szaszkó M, Dobi K, Lőrincz Z, Cseh S, Dormán G. Rapid identification of potential drug candidates from multi-million compounds' repositories. combination of 2D similarity search with 3D ligand/structure based methods and in vitro screening. Molecules. 2021 Sep 15;26(18):5593. https://doi.org/10.3390/molecules26185593
21. Wermuth CG. Selective optimization of side activities: another way for drug discovery. Journal of medicinal chemistry. 2004 Mar 11;47(6):1303-14.https://doi.org/10.1016/j.addr.2009.05.003
22. ;Vázquez J, López M, Gibert E, Herrero E, Luque FJ. Merging ligand-based and structure-based methods in drug discovery: An overview of combined virtual screening approaches. Molecules. 2020 Oct 15;25(20):4723. https://doi.org/10.3390/molecules25204723
23. Wigh DS, Goodman JM, Lapkin AA. A review of molecular representation in the age of machine learning. Wiley Interdisciplinary Reviews: Computational Molecular Science. 2022 Sep;12(5):e1603.https://doi.org/10.1002/wcms.1603
24. Myint KZ, Xie XQ. Ligand biological activity predictions using fingerprint-based artificial neural networks (FANN-QSAR). Artificial Neural Networks. 2015:149-64.https://doi.org/10.1007/978-1-4939-2239-0_9
25. Aimo A, Egea OI, Emdin M, Bayes-Genis A. 91 Overlapping effects of MI-R-21 inhibition and oral anti-fibrotic and anti-inflammatory drugs: rationale for drug repurposing to relieve ischemia/reperfusion injury. European Heart Journal Supplements. 2020 Dec;22(Supplement_N):N83-79. https://doi.org/10.1093/eurheartj/suaa201

26. Rahvar AH, Haas CS, Danneberg S, Harbeck B. Increased cardiovascular risk in patients with adrenal insufficiency: a short review. BioMed research international. 2017;2017(1):3691913.https://doi.org/10.1155/2017/3691913
27. Ting HJ, Murray WJ, Khasawneh FT. Repurposing an old drug for a new use: glybenclamide exerts antiplatelet activity by interacting with the thromboxane A2 receptor. ActaPharmacologicaSinica. 2010 Feb;31(2):150-9. https://doi.org/10.1038/aps.2009.195
28. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart: a new era in the treatment of heart failure. Circulation. 1996 Nov 1;94(9):2285-96.https://doi.org/10.1161/01.CIR.94.9.2285
29. Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. Circulation. 1997 Aug 5;96(3):793-800.https://doi.org/10.1161/01.CIR.96.3.793
30. Tscharre M, Michelson AD, Gremmel T. Novel antiplatelet agents in cardiovascular disease. Journal of Cardiovascular Pharmacology and Therapeutics. 2020 May;25(3):191-200.https://doi.org/10.1177/1074248419899314
31. Klebe G. Virtual ligand screening: strategies, perspectives and limitations. Drug discovery today. 2006 Jul 1;11(13-14):580-94.https://doi.org/10.1016/j.drudis.2006.05.012
32. Yang SQ, Ye Q, Ding JJ, Ming-Zhu Yin, Lu AP, Chen X, Hou TJ, Cao DS. Current advances in ligand-based target prediction. Wiley Interdisciplinary Reviews: Computational Molecular Science. 2021 May;11(3):e1504.https://doi.org/10.1002/wcms.1504
33. Sukumar BS, Shashirekha HK, Amarnath HK, Gadgil N, Kulkarni A, Tare H. Artificial intelligence in unveiling herbal remedies for cancer: Advances and applications. Bangabandhu Sheikh Mujib Medical University Journal. 2025 Feb 4;18(1):e76190-. https://doi.org/10.3329/bsmmuj.v18i1.76190
34. Yang SQ, Ye Q, Ding JJ, Ming-Zhu Yin, Lu AP, Chen X, Hou TJ, Cao DS. Current advances in ligand-based target prediction. Wiley Interdisciplinary Reviews: Computational Molecular Science. 2021 May;11(3):e1504.https://doi.org/10.1002/wcms.1504
35. Carpenter KA, Altman RB. Databases of ligand-binding pockets and protein-ligand interactions. Computational and Structural Biotechnology Journal. 2024 Mar 24.https://doi.org/10.1016/j.csbj.2024.03.015
36. Liao J, Wang Q, Wu F, Huang Z. In silico methods for identification of potential active sites of therapeutic targets. Molecules. 2022 Oct 20;27(20):7103.https://doi.org/10.3390/molecules27207103
37. Attah IY, Neumann A, Al-Hroub H, Rafehi M, Baqi Y, Namasivayam V, Müller CE. Ligand binding and activation of UTP-activated G protein-coupled P2Y2 and P2Y4 receptors elucidated by mutagenesis, pharmacological and computational studies. Biochimica et BiophysicaActa (BBA)-General Subjects. 2020 Mar 1;1864(3):129501.https://doi.org/10.1016/j.bbagen.2019.129501.