World Journal of Pharmaceutical Science and Research

www.wjpsronline.com

Research Article

ISSN: 2583-6579
SJIF Impact Factor: 6.916
Year - 2026
Volume: 5; Issue: 8
Page: 317-325

REPOSITIONING OF SELECTED MEDICINAL AGENT - AN EXPLORATORY ATTEMPT *IN SILICO-BASED* APPROACH

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Article Received: 08 June 2026 | | ***Article Revised: 29 June 2026*** | | ***Article Accepted: 20 July 2026***

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DOI: https://doi.org/10.5281/zenodo.21705002

How to cite this Article: Dawa Sambo, Ibrahim Rabiu, Garba Mohammed Buwa, Yahaya Umar (2026) PATTERN AND PREDICTORS OF UTILIZATION OF MATERNAL HEALTHCARE SERVICES IN GOMBE STATE, NORTHEAST NIGERIA. World Journal of Pharmaceutical Science and Research, 5(8), 317-325.

ABSTRACT

Drug repositioning has emerged as a promising strategy in pharmaceutical research, offering a cost-effective and time-efficient alternative to traditional drug discovery. This study investigates the repositioning potential of Dantrolene, a muscle relaxant with an established pharmacological profile, against phosphodiesterase (PDE) isoforms (PDE1-PDE10) using molecular docking and *In-Silico* approaches. The ligand was retrieved from PubChem, optimised with the MMFF94 force field, and docked against cleaned PDE crystal structures obtained from the Protein Data Bank. Docking simulations were performed using AutoDock Vina, with binding affinity, hydrogen bonding, hydrophobic interactions, and RMSD values analysed to assess stability and specificity. The results revealed that Dantrolene exhibited the strongest binding affinity for PDE7 (-10.0 kcal/mol), accompanied by low RMSD values, indicating highly stable interactions. PDE3 (-9.4 kcal/mol) and PDE2 (-9.3 kcal/mol) also demonstrated favourable binding with stable conformations. PDE8 formed the highest number of hydrogen bonds but showed moderate affinity, while PDE6 displayed unstable docking despite reasonable binding energy. Overall, the findings suggest that Dantrolene may act as a potential PDE inhibitor, particularly targeting PDE7. This computational study highlights the utility of drug repositioning strategies and provides a foundation for further *in vitro* and *in vivo* validation to explore novel therapeutic applications of Dantrolene.

KEYWORDS: Drug repositioning, Dantrolene, Phosphodiesterase (PDE) isoforms, Molecular docking, Binding affinity, *In-silico* studies.

INTRODUCTION

Drug repositioning, also known as drug repurposing, is an emerging strategy in pharmaceutical research that seeks new therapeutic applications for an existing medicinal agent. Instead of beginning the lengthy process of developing a novel compound, repositioning leverages the established safety and pharmacological profiles of known drugs to explore innovative uses. This approach not only reduces the time and cost of drug development but also opens the possibilities for addressing the unmet medical needs across diverse diseases. This research, Repositioning of a Selected Medicinal Agent: An Exploratory Attempt, presents an exploratory study into the potential of a chosen drug beyond its original indication. By examining scientific rationale, experimental evidence, and translational opportunities, it highlights how repositioning can serve as a bridge between conventional drug discovery and modern therapeutic innovation.

1.1. The Changing Landscape of Drug Discovery

Drug discovery has conventionally been a long, expensive, and uncertain process. Developing a new therapeutic agent from concept to market often requires more than a decade of research, billions of dollars in investment, and countless clinical trials. Despite these efforts, many compounds fail to reach approval due to safety concerns, lack of efficacy, or commercial limitations. In this context, the concept of drug repositioning, also known as drug repurposing, has emerged as a powerful alternative strategy.

Drug repositioning involves identifying new therapeutic uses for existing medicinal agents. Instead of beginning with a novel compound, researchers explore the untapped potential of drugs that already have established safety profiles and pharmacological data. This approach not only reduces the time and cost of development but also provides opportunities to address unmet medical needs, particularly in rare diseases, neglected conditions, and emerging health crises.

1.2. Historical Perspective and Notable Successes

The idea of repositioning is not new, and several landmark examples illustrate its transformative potential:

Aspirin: Initially introduced as a pain reliever, later repositioned as a cornerstone therapy for cardiovascular disease prevention.

Thalidomide: Withdrawn due to teratogenic effects, but later repurposed for leprosy and multiple myeloma treatment.

Sildenafil (Viagra): Originally developed for angina, repositioned for erectile dysfunction and pulmonary hypertension.

These cases demonstrate how repositioning can breathe new life into existing drugs, transforming them into solutions for entirely different medical challenges.

1.3. Scientific Rationale for Repositioning

The success of drug repositioning lies in its scientific foundation. Many drugs act on molecular pathways that are shared across multiple diseases.

For example

Immunomodulators designed for autoimmune disorders may also be effective in oncology. Antiviral agents may show promise in treating cancers or inflammatory conditions.

Neuroprotective compounds may be repositioned for psychiatric or metabolic diseases.

Advances in bioinformatics, systems biology, and artificial intelligence have accelerated this process. Computational models can now predict new indications by analyzing drug-target interactions, genetic data, and disease networks.

1.4. Methodological Approaches

Repositioning can be pursued through several strategies:

Computational approaches: Using databases, AI, and machine learning to identify new drug-disease associations. Experimental approaches: Testing drugs in new disease models, either *in-vitro* or *in-vivo*.

Clinical observation: Identifying unexpected benefits or side effects in patients that suggest new uses.

Network pharmacology: Mapping drug interactions across biological systems to uncover hidden therapeutic potential.

Each approach contributes to a growing toolkit for researchers seeking to reposition medicinal agents.

1.5. Challenges and Considerations

Although drug repositioning shows significant promise, it is accompanied by several challenges.

Regulatory hurdles: Approval for new indications requires rigorous clinical validation.

Intellectual property issues: Patents may limit commercial incentives for repositioning.

Scientific uncertainty: Not all repositioning attempts succeed; efficacy in one disease does not guarantee success in another.

Ethical concerns: Patient safety must remain paramount, especially when exploring off-label uses.

Despite these challenges, repositioning remains a vital strategy in modern pharmacology.

1.6. Purpose of Book

Repositioning of a Selected Medicinal Agent: An Exploratory Attempt aims to provide a structured exploration of drug repositioning through the lens of a chosen medicinal agent. It will:

Present the scientific rationale for selecting the agent.

Explore its pharmacological properties and potential new indications. Discuss experimental and clinical evidence supporting repositioning. Highlight broader implications for healthcare innovation.

The goal is not only to examine one drug but also to illustrate the broader paradigm of repositioning as a bridge between traditional drug discovery and modern translational medicine.

MATERIALS AND METHODS

1. Ligand Preparation

Compound - Dantrolene was selected as the ligand due to its known pharmacological profile.

Structure Retrieval - The 3D structure of Dantrolene was obtained from the PubChem database or drawn using

ChemDraw and converted to 3D using software like Open Babel.

Optimisation - Energy minimisation was performed by using the MMFF94 force field to ensure a stable conformation.

2. Target Protein Selection

Targets - Phosphodiesterase isoforms PDE1 through PDE10 were selected based on their relevance to cyclic nucleotide metabolism.

Structure Retrieval - Crystal structures of PDEs were downloaded from the RCSB Protein Data Bank (PDB).

Preparation - Proteins were cleaned by removing water molecules, ligands, and heteroatoms using tools like AutoDock Tools or PyMOL. Hydrogen atoms were added and charges were assigned.

3. Docking Protocol

Software Used - Molecular docking was performed using AutoDock Vina or a comparable docking engine.

Grid Box Setup - The active site was defined based on known ligand-binding residues or co-crystallized ligands.

Docking Parameters - Exhaustiveness and number of modes were set to ensure thorough sampling of binding poses.

4. Analysis of Docking Results

Binding Affinity - Reported in kcal/mol, indicating the strength of interaction (more negative = stronger binding).

Hydrogen Bonding - Number and distance of hydrogen bonds were recorded to assess specificity and stability.

Hydrophobic Interactions - Noted where applicable, especially for PDE7.

RMSD Values - RMSD.lb and RMSD.ub indicates the deviation between docked poses and reference conformations, useful for pose reliability.

RESULT AND DISCUSSION

Dantrolene shows the strongest binding affinity with PDE 7 (-10.0 kcal/mol), suggesting a highly favourable interaction.

PDE 3 also exhibits strong binding (-9.4 kcal/mol) with low RMSD values, indicating stable docking.

PDE 2 and PDE 1 follow closely in binding strength. Hydrogen bonding is most abundant with PDE 8 (7 bonds), though its binding affinity is moderate.

RMSD values suggest that PDE 7 and PDE 3 have the most stable conformations post-docking (lowest RMSD.Ib and RMSD.ub).

RESULT TABLE

TARGET	LIGAND	BINDING AFFINIT Y	HYDROG EN BOND	DISTANCE OF HYDROGEN BOND	HYDROP HOBIC BOND	RMSD.lb	RMSD.ub
PDE 1	DANTROLENE	-8.6	6	2.301A,1.956A, 2.210A,2.163A, 2.249A,2.487A	-	56.250	57.651
PDE 2	DANTROL ENE	-9.3	3	2.231A,2.024A, 2.247A	-	35.082	39.544
PDE 3	DANTROL ENE	-9.4	3	2.015A,2.165A, 2.294A	-	3.171	3.816
PDE 4	DANTROL ENE	-7.6	3	2.061A,2.449A, 2.294A	-	55.324	57.621
PDE 5	DANTROL ENE	-8.2	4	2.255A,2.274A, 2.989A,2.074A	-	36.821	38.215
PDE 6	DANTROL ENE	-8.2	5	2.220A,2.939A, 2.680A,1.969A, 2.195A	-	107.939	113.975
PDE 7	DANTROL ENE	-10	4	1.945A,2.330A, 1.909A,2.324A	-	2.844	3.604
PDE 8	DANTROL ENE	-7.9	7	2.136A,2.410A, 1.818A,2.082A 2.212A,2.140A, 2.692A	1.275A	15.081	16.142
PDE 9	DANTROL ENE	-7.7	4	2.211A,2.317A, 2.117A,2.249A	-	7.890	14.530
PDE 10	DANTROL ENE	-8.2	4	2.229A,1.943A, 1.921A,2.335A	-	18.967	21.121

FIGURES

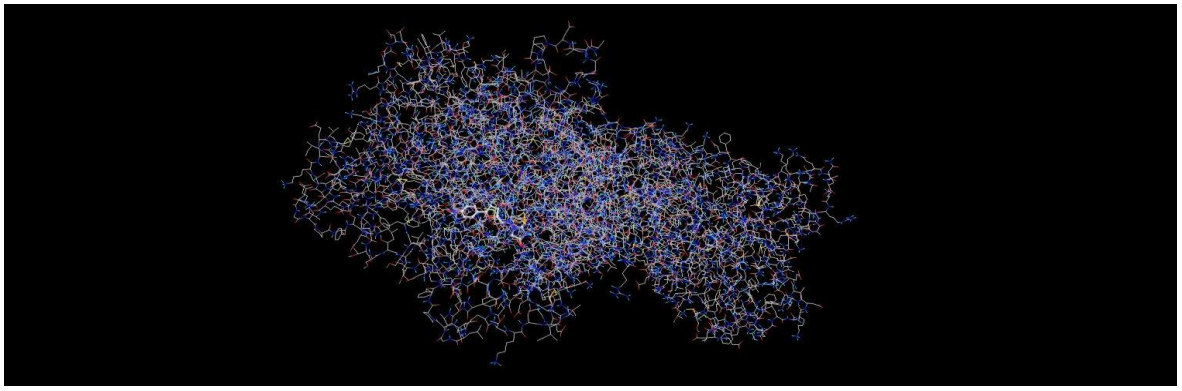

Figure 1: Dantrolene Binding in PDE 1 Enzyme.

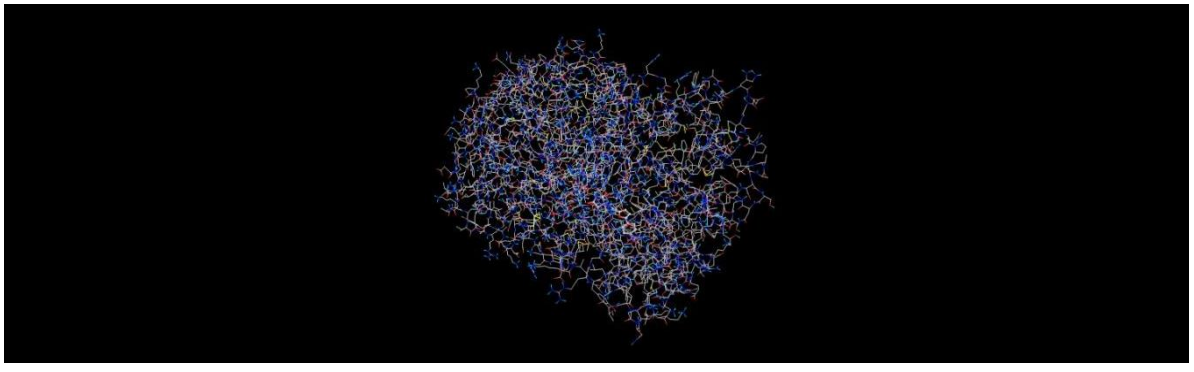

Figure 2: Dantrolene Binding in PDE 2 Enzyme.

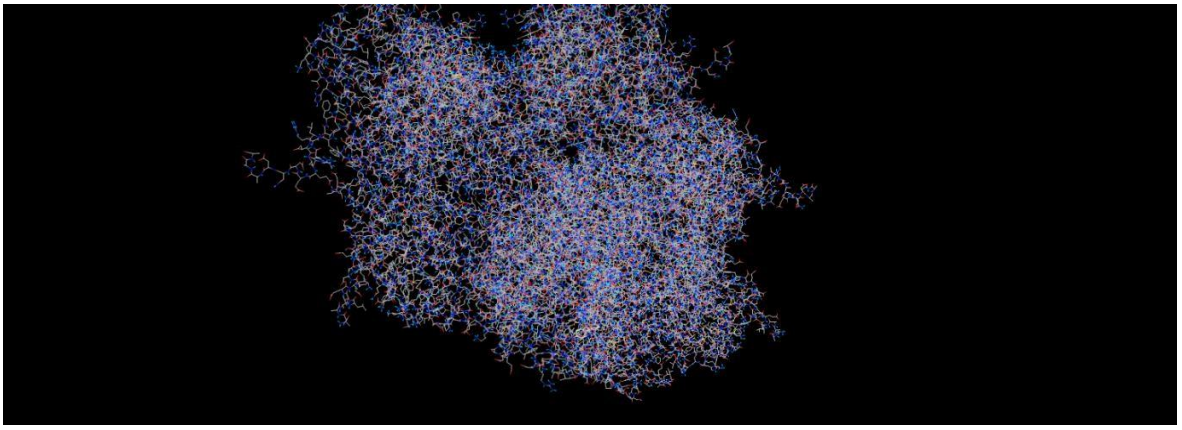

Figure 3: Dantrolene Binding in PDE 3 Enzyme.

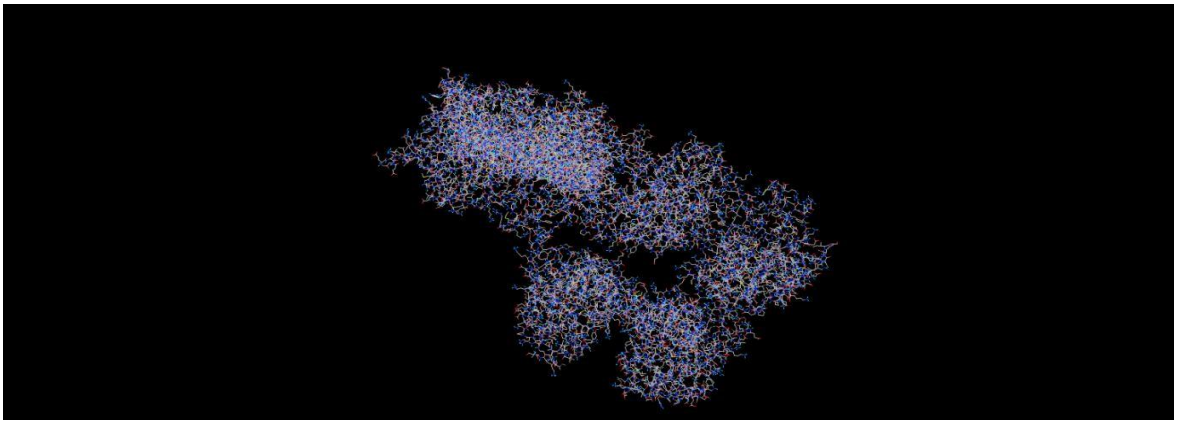

Figure 4: Dantrolene Binding in PDE 4 Enzyme.

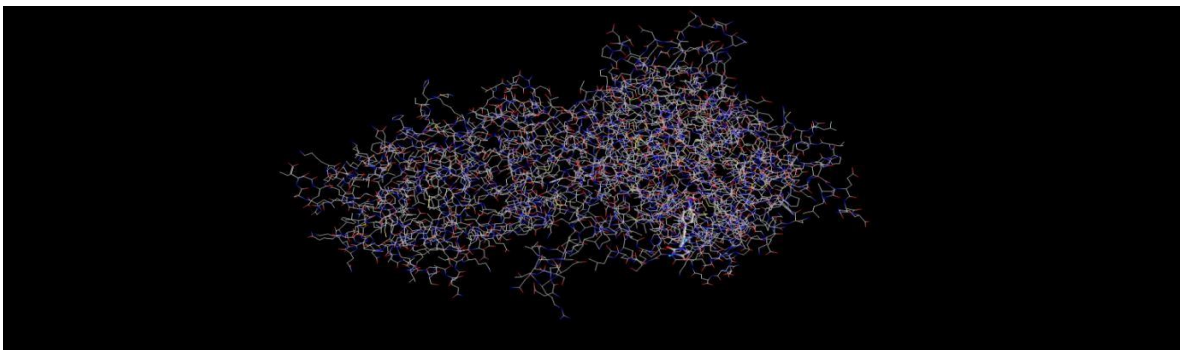

Figure 5: Dantrolene Binding in PDE 5 Enzyme.

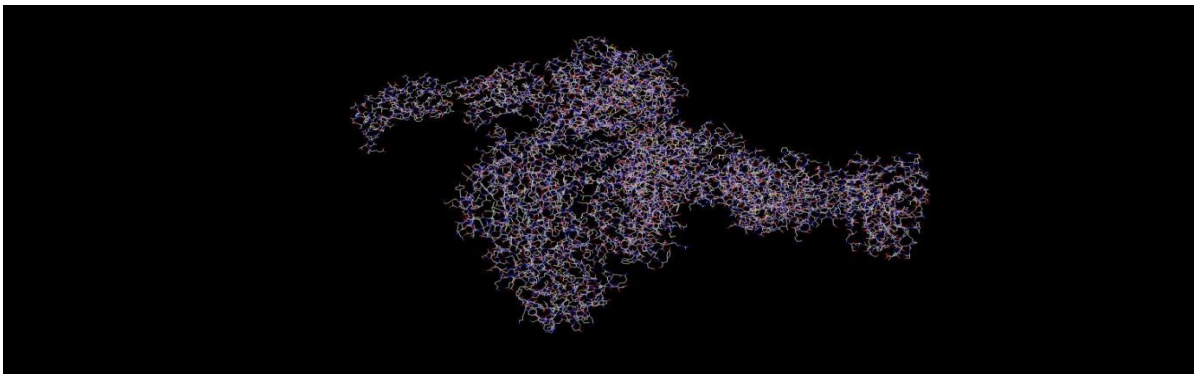

Figure6: Dantrolene Binding in PDE 1 Enzyme.

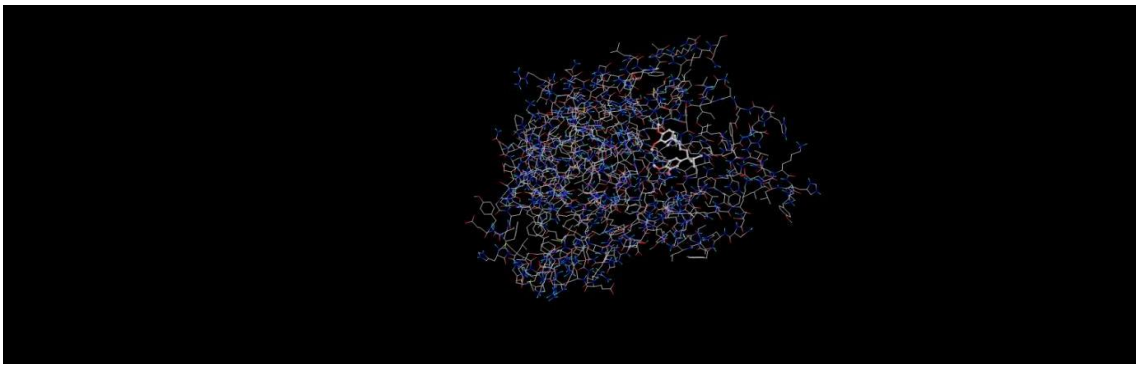

Figure 7: Dantrolene Binding in PDE 7 Enzyme.

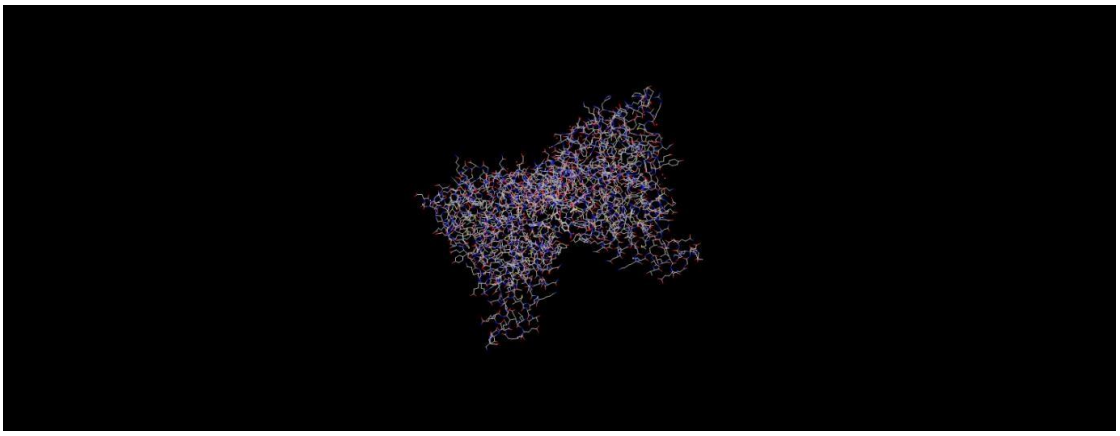

Figure 8: Dantrolene Binding in PDE 8 Enzyme.

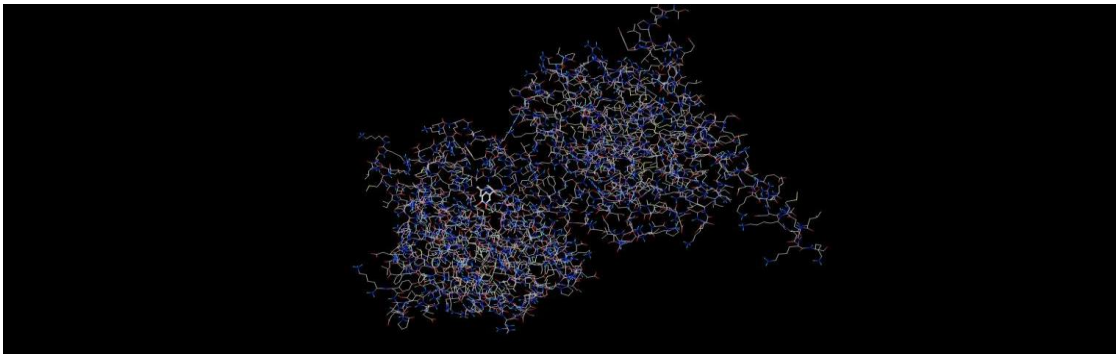

Figure 9: Dantrolene Binding in PDE 9 Enzyme.

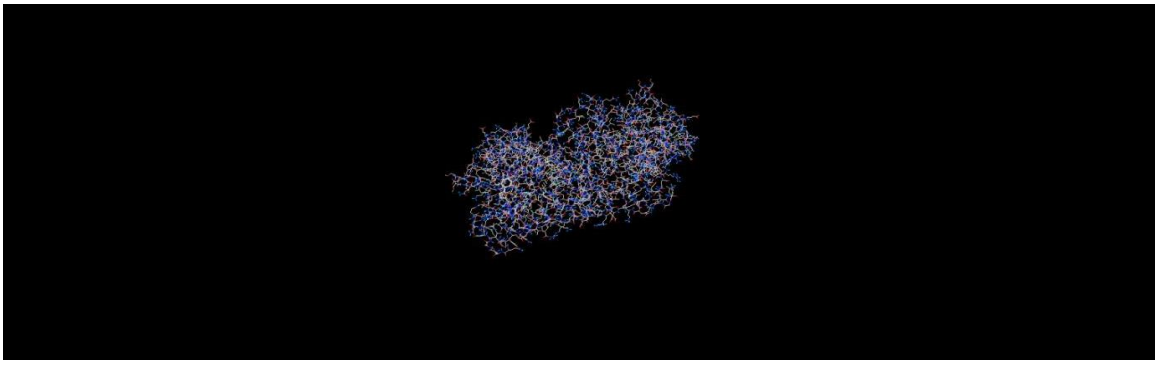

Figure 10: Dantrolene Binding in PDE 10 Enzyme.

CONCLUSION

The molecular docking study demonstrates that **Dantrolene exhibits favourable binding interactions with multiple PDE isoforms**. Among all targets, **PDE7 showed the strongest binding affinity and the most stable docking conformation**, highlighting it as the most promising target.

PDE3 and PDE2 also displayed strong binding energies with acceptable hydrogen bonding and low RMSD values, indicating stable ligand–protein interactions.

Although **PDE8** formed the highest number of hydrogen bonds and showed hydrophobic interactions, its binding affinity was moderate.

In contrast, **PDE6** exhibited high RMSD values, suggesting unstable binding despite reasonable affinity. Overall, the results suggest that **Dantrolene has potential as a PDE inhibitor, particularly against PDE7**, and warrants further experimental validation through *in-vitro* and *in-vivo* studies.

ACKNOWLEDGEMENT

It is our humble privilege and pleasant duty to express our deep sense of gratitude to **Dr. M. KUMAR, M. Pharm., PhD,** Principal and Head, Department of Pharmaceutical Chemistry, Vinayaka Mission's College of Pharmacy, Salem, for his timely suggestions and guidance and also for permitting and providing us optimum facilities and encouragement to carry out this work successfully.

We express our profound and sincere gratitude to **Prof. Dr. R. KOTHAI, M. Pharm., PhD**, HOD, Department of Pharmacology, Vinayaka Mission's College of Pharmacy, Salem.

We wish to extend my sincere thanks to **Mr. S. RAGHU, M. Pharm.,** Assistant Professor. Department of Pharmacology, Vinayaka Mission's College of Pharmacy, Salem for his support and optimistic approach at every step of my dissertation work.

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