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MOLECULAR DOCKING OF MCL-1 PROTEIN WITH VARIOUS INHIBITORS FOR CANCER TREATMENT

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Abstract

Myeloid cell leukemia-1 (MCL-1), belonging to Bcl-2 protein family, regulates apoptosis and is frequently overexpressed in cancer cells, making it a potential target for anti-cancer therapies. In this study, Insilico drug design is employed to screen ten FDA approved drugs with various therapeutic applications, followed by molecular docking of four promising compounds exhibiting good ADME properties and no carcinogenicity and mutagenicity, to identify potential MCL-1 inhibitors with improved efficacy, reduced resistance, and minimal toxicity. Our analysis revealed strong binding affinities of drugs, cyclobenzaprine hydrochloride (-9.3 kcal/mol), miconazole nitrate (-8.4 kcal/mol), donepezil hydrochloride (-8.1 kcal/mol) and dorzolamide (-5.3 kcal/mol) due to significant interactions with the key active site amino acid residues of MCL-1 protein, mainly "hotspot" residue Arg263A, interacting through hydrogen bond. These interactions, crucial for protein activity, suggest a potential novel mechanism for destabilizing and inhibiting MCL-1 activity. Subsequently, suggesting their promising possibility as an effective anti-tumor agent. Overall, our findings suggest these drugs as potential MCL-1 inhibitors for treating tumors, though further experimental validation is required.

Keywords: *Apoptosis, Cancer, Cyclobenzaprine hydrochloride, Donepezil hydrochloride, Dorzolamide, Mcl-1, Miconazole nitrate, Molecular docking*

INTRODUCTION

Cancer is a major global cause of death due to uncontrolled cell growth and aggressive spread into other body parts (1, 2). One of the key features of cancer cells survival is the evasion of programmed cell death (a natural process for the elimination of unwanted cells) (3). MCL-1 (myeloid cell leukemia 1), that is widely known for its crucial role in helping cancer cells avoid cell death, is an antiapoptotic member of key regulators of apoptosis BCL-2 family proteins (e.g., pro-apoptotic proteins (e.g., BAK, BAX) causing mitochondrial outer membrane permeabilization (MOMP), BH3-only proteins (e.g., PUMA, NOXA, BID, and BIM) activating them, and anti-apoptotic proteins (e.g., MCL-1, BCL-2, BCL-XL, and BFL-1/A1) that block these processes), inhibit apoptosis intracellularly by counteracting the pro-apoptotic proteins BCL-2 homologous antagonist killer (BAK), and BCL-2 associating X protein (BAX) to prevent the pore formation in the mitochondrial membrane. This blockage halts the release of cytochrome c, essential for the activation of caspases (responsible for cellular breakdown). Thus, leading to the effective protection of cells from death (4).

Elevated levels of the Mcl-1 protein are observed in various tumor cells such as mantle cell lymphomas (5), lung cancer cells (6), osteosarcoma cells (7), breast cancer cells (8), ovarian cancer cells (9), Hematological Malignant cells such as chronic lymphocytic leukemia (CLL) cells, and acute myeloid leukemia (AML) cells (10). This excessive Mcl-1 production contributes to tumor progression and resistance against frequently utilized anticancer therapies such as chemotherapy, radiotherapy, and BH3 mimetics, ultimately leading to poorer prognoses for patients (11).

This, warns the urgent need of progressive development of highly effective MCL-1 inhibitors that exhibit potent efficacy while maintaining low toxicity levels and minimizing the risk of drug resistance for

cancer treatment. For which, Computational aided drug design (CADD), an cost effective and time saving approach, offer a promising solution to identify potential drug candidates, by accelerating the drug discovery process, ultimately contributing to the development of superior anticancer agents (12).

For that reason, in silico study was carried out to repurpose existing FDA-approved drugs to identify potential inhibitors of MCL-1, a protein associated with cancer. The main method employed include molecular docking using Autodock vina, alongside analyses through the SwissADME server for pharmacokinetic properties and the ProTox-3.0 online server for toxicity predictions. The purpose of this research was to repurpose FDA-approved drugs using in silico methods to find MCL-1 inhibitors, contributing to the advancement of cancer treatment.

METHODOLOGY

LIGAND SELECTION

A total of ten Ligands along with their respective IDs as shown in (Fig. 1), retrieved from PubChem data base, were selected on the basis of its therapeutic applications across various disease areas such as immune disorders, brain disease, cancer, analgesic, and anti-inflammatory properties for molecular docking studies to investigate their interactions with target molecule, that will lead to enhanced understanding of their pharmacological effects and potential for drug development.

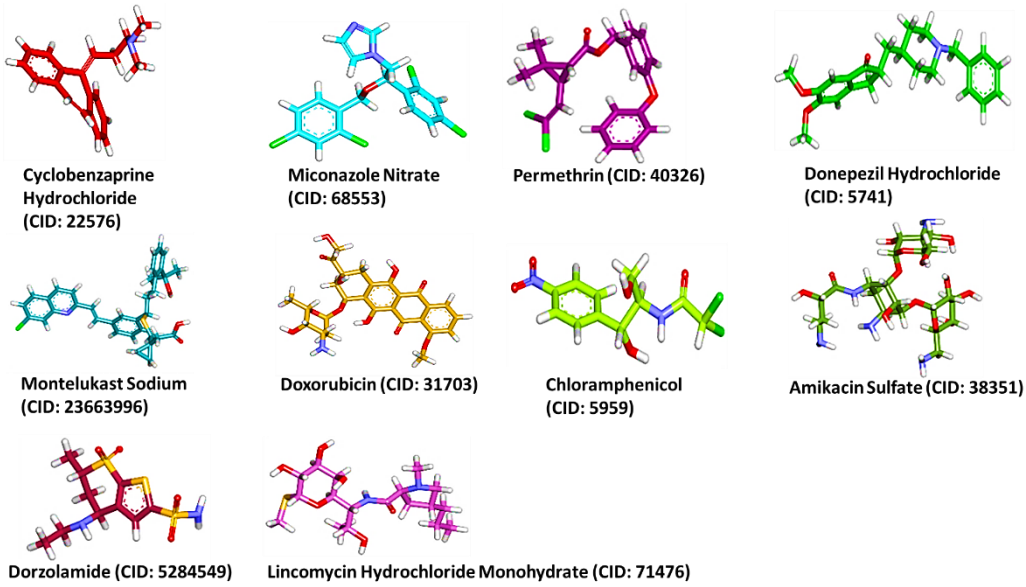

Fig. 1. Structure of ligands

PREPARATION

The three-dimensional structure of ligands was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in structural data file (SDF) format (Fig. 2) respectively. The structures were then energy minimized using the Molecular Mechanics Force Field (MMFF94) force field to achieve stable conformations suitable for docking analysis. Subsequently, the ligands were then converted into pdbqt format using OpenBabel 3.1.1 software (13) to ensure compatibility with AutoDock Vina, a widely used molecular docking program (14).

PROTEIN PREP

The three-dimensional crystal structure of the anti-apoptotic protein MCL-1 (PDB ID: 6UDV) was obtained from the Protein Data Bank (PDB, https://www.rcsb.org/) (15). However, this structure contained a co-crystallized compound 3 and water molecules, and lacked complete atomic information, including bond orders and formal charges, necessitating further processing before docking could be performed. For which the downloaded structure underwent essential pre-processing steps using MGL-AutoDockTools. This involved removing water molecules and ligands, adding missing hydrogen atoms, assigning Kollman charges, and saving the prepared structure in a pdbqt format suitable for molecular docking analysis (16).

DOCKING

For molecular docking, a receptor grid, which defines the spatial dimensions and positioning of protein binding sites, was constructed around the co-crystallized ligand for both the fixed target protein MCL-1 and flexible ligands (Fig. 2), using the software MGL-AutoDockTools (ADT, v1.5.7). The grid dimensions for the x, y, and Z-axis were determined as 12.427, 4.407, and 97.345, based on the location of a (co-crystallized ligand) ligand bound to the protein ensuring the grid encompasses the active site. Then molecular docking was conducted on a HP laptop, by using AutoDock Vina 1.5.7 software (https://vina.scripps.edu/), which predicted the binding affinity of ligands (Fig. 2) to the protein's active site. The resulting docked complex was visualized and analyzed by using Discovery Studio Visualizer (DS viewer) (Free Download: BIOVIA Discovery Studio Visualizer - Dassault Systèmes) for further structural insights (17)

ADME

The SwissADME computational model from the SwissADME server (www.swissadme.ch), was done to predict the properties of a drug including, Lipinski's rule of five adherence (a guideline for drug-likeness), water solubility (Log S), lipophilicity (log P), bioavailability score, and various pharmacokinetic aspects including gastrointestinal (GI) absorption, and blood-brain barrier permeability (18).

TOXICITY

ProTox 3.0 online server (ProTox-3.0 - Prediction of Toxicity of chemicals) was used to assess the toxicological profile of certain compounds. The analysis covered various aspects of toxicity such as acute toxicity, lethal dose (LD50), carcinogenic, mutagenic, neurotoxic, nephrotoxic, cytotoxic, respitoxic and immunotoxic potential (19).

RESULTS AND DISCUSSION

In the present study, to execute molecular docking, we conducted a computational screening of ten compounds (Fig. 1), retrieved from the PubChem database that were selected based on its therapeutic role in various disease domain such as cancer, anti-inflammatory, analgesia and neurology, to predict and assess their inhibitory potential against the MCL-1 protein (PDB ID: 6UDV) retrieved from Protein Data Bank (PDB, https://www.rcsb.org/), which is one of major culprit protein involved in the survival of cancer and development of tumor (20). Increased expression of MCL-1 protein reported in different types of human tumors, including lung, breast cancer and its resistance to chemotherapeutics makes it an attractive target in cancer therapy (6,8). However, only four compounds (cyclobenzaprine hydrochloride, miconazole nitrate, donepezil hydrochloride, and dorzolamide) (Fig. 2) were docked with target MCL-1 protein. The molecular docking of these four screened compounds (Fig. 2) with MCL-1 protein, performed by using autodock vina, to predict ligand-protein interactions, and binding strength, revealed significant binding affinities that ranged from -5.3 to -9.3 kcal/mol. Based on the analysis of binding energy, according to which compounds are scored, the target protein MCL-1, displayed highest affinity of -9.3 kcal/mol for cyclobenzaprine hydrochloride and likewise significant binding energies for rest (Table I).

Table I. Docking score of compounds

Pubchem ID	Compound name	Docking Score
22576	Cyclobenzaprine Hydrochloride	-9.3
68553	Miconazole Nitrate	-8.4
5741	Donepezil Hydrochloride	-8.1
5284549	Dorzolamide	-5.3

These four compounds (Fig. 2) were filtered through screening that was done prior to molecular docking, toxicity screening was performed using ProTox-3.0 online server to assess their potential to cause toxic effects, and ADME properties evaluations by using SwissADME server, respectively. The four compounds (Fig. 2) were selected due to their lack of mutagenicity and carcinogenicity (Table II), as well as compliance with Lipinski's rule (Table III). The remaining compounds showing mutagenicity (permethrin,

doxorubicin, chloramphenicol) (Table II) (Supplementary Table II), and Lipinski's rule violation (montelukast sodium, amikacin sulfate, lincomycin hydrochloride monohydrate) (Table III) (Supplementary Table III) were ruled out, as mutagenic and poor pharmacokinetic property may limit its use.

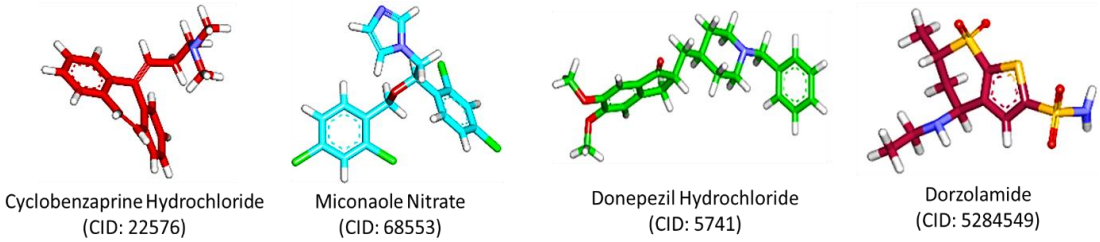

Fig. 2. Structure of ligands (Hits)

Table II. Toxicity prediction of selected compounds

Pubchem ID	Compound name	LD50	Toxicity class	Toxicity potential	Carcinogenity & mutagenicity
22576	Cyclobenzaprine Hydrochloride	250	3	Neurotoxic, Immunotoxic and respitoxic	None
68553	Miconazole Nitrate	519	4	Nephrotoxic, Immunotoxic and respitoxic	None
5741	Donepezil Hydrochloride	505	4	Neuro, cyto, Immuno and respitoxic	None
5284549	Dorzolamide	1320	4	Respitoxic	None

Table III. Drug likeness properties of compounds; cyclobenzaprine hydrochloride, miconazole nitrate, donepezil hydrochloride, dorzolamide

Molecule	Cyclobenzaprine hydrochloride	Miconazole nitrate	Donepezil hydrochloride	Dorzolamide
MW (less than 500)	311.9	479.14	415.95	324.44
#H-bond acceptors (> 10)	1	5	4	6
#H-bond donors (> 5)	0	1	0	2
MR (40-130)	99.04	114.15	122.27	73.29
TPSA	3.24	93.1	38.77	151.33
iLOGP (> 5)	0	3.55	0	1.02
ESOL Class	Moderately soluble	Poorly soluble	Moderately soluble	Soluble
Ali Class	Moderately soluble	Poorly soluble	Moderately soluble	Soluble
Silicos-IT class	Poorly soluble	poorly soluble	Poorly soluble	Soluble
GI absorption	Low	High	High	Low
BBB permeant	No	No	Yes	No
Bioavailability Score	0.55	0.55	0.55	0.55
Lipinski #violations	1	0	0	0
Ghose #violations	0	1	0	0
Veber #violations	0	0	0	1
Egan #violations	0	0	0	1
Muegge #violations	2	1	1	1
Leadlikeness #violations	1	2	2	0
Synthetic Accessibility > 5	3.56	3.42	3.44	4.21

The interaction analysis and binding strength demonstrated significant interactions of various types and bond sizes among four screened drugs (Fig. 2) and MCL-1 protein, indicating potential anticancer activity (Supplementary Table). As, the four drugs (Fig. 2) that shows strong binding for the binding pocket of MCL-1 protein (Fig. 3) with significant binding affinity (Table I), are mainly stabilized by strong interaction, predominantly hydrogen bond with considerable bond sizes ranging from 1.82 Å-3.03 Å (21), which are formed as a result of interaction of these compounds with amino acid residues of MCL-1 Protein, particularly Arg263A. The key hydrogen bonds, were formed between the nitrogen atom within the cyclobenzaprine hydrochloride and a hydrogen atom (HH11) of nitrogen atom (NH1) on the guanidinium side chain of arginine residue 263 (2.89 Å) (Fig. 4A), the nitrogen atom within the miconazole nitrate

molecule and a hydrogen atom (HH11) of nitrogen atom (NH1) on the guanidinium side chain of arginine residue 263 (2.85 Å) (Fig. 4B), the oxygen atom from the donepezil hydrochloride molecule and a hydrogen atom (HH11) of nitrogen atom (NH1) and nitrogen atom (NE) on the guanidinium side chain of arginine residue 263 (2.14 Å) (Fig. 4C), and oxygen atom of dorzolamide and hydrogen atom (HH11) of nitrogen atom (NH1) of the guanidinium side chain of Arg263A (1.82 Å), while the remaining two were formed between hydrogen atoms (H) of nitrogen atom of dorzolamide molecule and main chain oxygen atom from carbonyl group of Leu267A (2.74Å) (3.03 Å) (Fig. 4D). This hydrogen bond, with the side chain guanidinium group of Arg263 that's essential for the activity of protein, not only demonstrate the correct positioning of four drugs (Fig. 2) within the active site of MCL-1 protein but also shows their potential role in the inhibition of MCL-1 protein. As this, basic Arg263 residue that is identified with in the binding groove of MCL-1 protein, is mainly responsible for the binding of BH3 peptides (22). According to previous report, the bh3 peptides failed to bind with Arg263A mutant MCL-1 protein, which further validates the cruciality of this extremely conserved Arg263A for binding of peptides (23). However, the conserved acidic aspartate of BH3 peptides (e.g., BIM) are reported to form key salt bridge with the guanidium group of Arg263A in Mcl-1. Therefore, the substitution of this salt bridge with strong H bond with Arg263A might play a vital role in the displacement of BH3 peptides, and subsequent cell death (24). As, the selective inhibitors of MCL-1, particularly AMG-176 and A-1210477, currently going through clinical investigation, also showed strong binding to critical Arg263A, through H bond (25). Not only that, this critical hydrogen bonded Arg263A, along with rest of the active site binding amino acid residues of MCL-1 (Supplementary Table) (Fig. 4), were also observed in previously reported co-crystalized ligand Q51 (CID: 118910215), active site binding residues (His224A, Ala227A, Phe228A, Met231A, Leu246A, Val249A, Met250A, Val253A, Phe254A, Arg263A, Thr266A, Leu267A, Phe270A, Gly271A, Val274A, Leu290A, lle294A) (15). Thus, highlighting the vitality of this hydrogen bonding, formed between Arg263 residue and drugs (Fig. 2), for the effective inhibition of MCL-1 protein. Along with hydrogen bonding they also formed weak interactions, with the following active site amino acid residues; Met231A, Leu246A, Met250A, Val253A, Leu267A, Phe270A in cyclobenzaprine hydrochloride (Fig. 4A), Ala227A, Met231A, Leu246A, Met250A, Val253A, Phe254A, Thr266A, Phe270A, Val274A, Leu290A, Ile294A in miconazole nitrate (Fig. 4B), Met231A, Leu246A, Met250A, Thr266A, Phe270A, Val274A in donepezil hydrochloride (Fig. 4C), and His224A, Ala227A, Phe228A, Val253A in dorzolamide (Fig. 4D). These considerable weak interactions are of great importance as it plays a vital role in binding by offering extra attractive forces and stability to hydrogen bonds, subsequently strengthening the binding of these drugs (Fig. 2) with in the binding site of MCL-1 protein (26). As, most of these significant interactions with the active site interacting residues such as H224, V253, and T266 (Fig. 4) (Supplementary Table) that are previously reported as unique amino acid residues in MCL-1 in contrast to other anti-apoptotic proteins (27), were also found to interact significantly with selective potent MCL-1 inhibitors (e.g., A-1210477). Not only that they also aligned with the reported "hotspot" regions of MCL-1, which are crucial for MCL-1's interaction with other proteins particularly BIM, that's known to bind specifically to the hydrophobic binding groove of MCL-1 and cause cell death (25,28). Thus, highlighting the significant potential of these drugs (Fig. 2) to specifically target MCL-1 and be repurposed as potent MCL- 1 inhibitors against various cancers. This analysis further validates, hydrogen bonded Arg263 as a key residue and an important hotspot along with the cruciality of strong interaction mainly hydrogen bonding (29), for the efficacy of MCL-1 protein inhibitors. As, improper placement of H-bond with Arg 263 in various new compounds (e.g., E309), causing the decrease in MCL-1 inhibition has also been reported (30). These active sites binding amino acids are of great importance, specifically critical hydrogen bonded residue (Arg263A), which can potentially play vital role in the inhibition of MCL-1 protein through novel mechanism. As, these FDA approved drugs has originally been designed for disease conditions, through a specific mechanism such as cyclobenzaprine hydrochloride (skeletal muscle relaxant (31), with some other reported experimentally determined off label clinical uses such as insomnia, muscular conditions, posttraumatic stress disorder (PTSD), and psychosocial function (32), is reported to act by affecting alpha and gamma motor systems, but it being an antagonist of 5-HT2 receptor has also been

reported (33), miconazole nitrate (an anti-fungal drug , used in the treatment of various infections such as oral candidiasis and Vulvovaginal candidiasis (34), with other reported experimentally determined off label clinical use in bladder cancer and colon cancer (35)), is reported to work by suppressing the 14α-demethylase (cytochrome P450 complex) (34), Donepezil Hydrochloride (used for treating dementia linked with Alzheimer's disease (36), other experimentally determined off label clinical uses has also been reported such as traumatic brain injury (37), Vascular dementia) is reported to work by inhibiting the acetylcholine eastrase enzyme (AChe) (38). Dorzolamide (antiglucoma drug (39), other experimentally determined off label clinical uses (e.g., cystoid macular edema & Central Serous Chorioretinopathy) reported (40) is reported to act by topically inhibiting carbonic anhydrase (39). Recently, its antitumor activity has also been reported (41). However, none of these drugs are reported to have an inhibitory effect on MCL-1 till now, which further highlights novel MCL-1 inhibitory mechanism of these drugs in treating tumor. These findings predict the undeniable potential of these drugs as promising MCL-1 inhibitor. As, a strong interaction, including hydrogen bond, formed with the active site residue Arg263, a critical "hotspot" is not only crucial for the stabilization of protein ligand complex but also for the activity of protein, which is further favored by other additional weak interactions. Thus, suggesting a potential inhibitory role of cyclobenzaprine hydrochloride, miconazole nitrate, donepezil hydrochloride and dorzolamide in the destabilization, subsequently inhibition of MCL-1 protein, increasing the efficacy of drug against tumor.

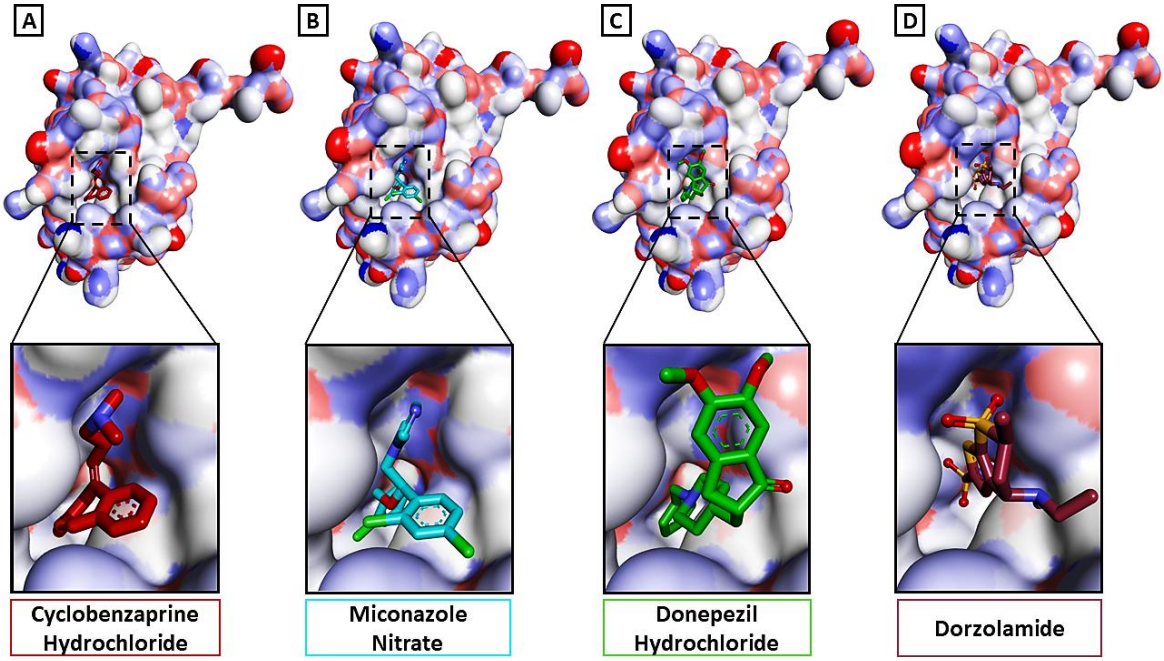

Fig. 3. The 3D atom charge surface mapping of MCL-1 protein with selected compounds (A) Cyclobenzaprine hydrochloride B) Miconazole Nitrate C) Donepezil Hydrochloride D) Dorzolamide) in the active pocket of the MCL-1 protein

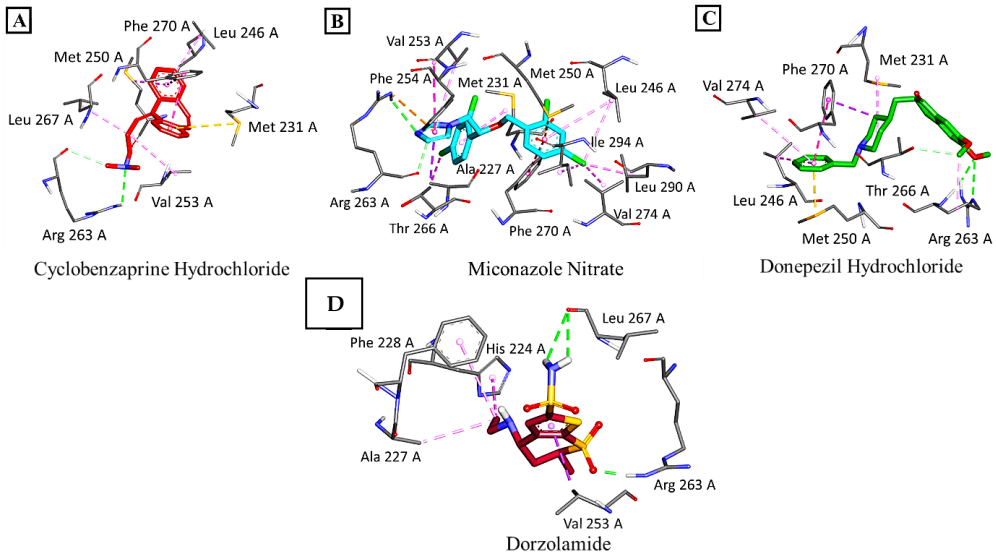

Fig. 4. The 3D interactions of MCL-1 protein with selected compounds (A) Cyclobenzaprine hydrochloride B) Miconazole Nitrate C) Donepezil Hydrochloride D) Dorzolamide) in the active pocket of the MCL-1 protein

CONCLUSION

Elevated levels of the protein MCL-1 are frequently observed across a wide range of cancers (e.g., lung cancer, breast cancer, and blood cancers), highlighting its potential as a therapeutic target. In this study, by repurposing FDA-approved drugs, cyclobenzaprine hydrochloride, miconazole nitrate, donepezil hydrochloride, and dorzolamide are identified as potential MCL-1 inhibitors. As they demonstrated strong interaction with "hotspot" active site amino acid residue Arg263A of MCL-1 Protein. There by, suggesting a novel binding mechanism, paving the way for a potential therapeutic strategy against tumors through MCL-1 inhibition. However, further experimentation is required to confirm the validity of these results. These findings provide a foundation for further experimental and clinical studies on MCL-1 inhibition as a cancer treatment strategy.

Authors' contribution:

SW Conceptualization, performed research experiments, written first draft of manuscript, designed methodology, Data analysis, Data curation, literature search, designed effective images and tables, manuscript formatting, writing and editing; UJ Supervised the work, conceived the idea, Supervised the research study, wrote first draft of manuscript, finalized the manuscript.

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