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MYELOID CELL LEUKEMIA-1 (MCL-1) PROTEIN'S INHIBITION ACTIVITY AGAINST CANCER

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Abstract

Objective: *To evaluate potential MCL-1 inhibitors with improved efficacy, minimal side effects and reduced resistance for targeted cancer therapy.*

Methods: *In silico molecular docking was executed, using Autodock vina between active site residues of Mcl-1 protein and eight screened ligands (Screened using Swiss ADME and ProTox 3.0 server) with the least toxicity, including no carcinogenicity, mutagenicity, Lipinski rules violation.*

Results: *Visual inspection and binding energy analysis of eight sequentially screened drugs (trazodone hydrochloride, tetrahydrozoline hydrochloride, ketotifen, pentazocine, quinine dihydrochloride, galantamine hydrobromide, ivabradine and metoprolol) demonstrate significant binding affinities and efficient interactions with active site amino acid residue of MCL-1 protein, suggesting their possibility as an effective anti-tumor agent.*

Conclusion: *This advanced computational screening predicts these eight drugs as potential MCL-1 inhibitors due to their interaction with the active site binding amino acids, mainly (His224A, Thr266A, Leu267A, Met231A, Val253A, and Phe270A), in facilitating strong drug binding through a novel mechanism of action, potentially destabilizing MCL-1, and inhibiting its function. Overall, our findings suggest these drugs could be a promising therapeutic strategy for tumors, though additional experimentation is necessary to validate these results.*

Keywords: *Cancer, Galantamine hydrobromide, Ivabradine, Ketotifen, Mcl-1, Metoprolol, Pentazocine, Quinine dihydrochloride, Trazodone hydrochloride*

INTRODUCTION

Cancer (one of deathliest disease, whose increasing incidents and high mortality rate globally is alarming) is mainly due to uncontrolled division of cell. One of the key characteristics of cancer is the evasion of cell death (Apoptosis), a programed mechanism to get rid of unwanted, mutated and damaged cells, which is mainly exploited through the dysregulation of three groups comprising family of Bcl-2 proteins (such as pro-apoptotic group (such as BAX, BAK) causing mitochondrial outer membrane permeabilization (MOMP), BH3-only group (such as NOXA, and BIM) stimulating MOMP, and anti-apoptotic group (such as MCL-1, BCL-2 and BCL-XL) blocking MOMP), vital for regulating intrinsic apoptotic pathway by controlling the MOMP, particularly Myeloid cell leukemia-1 (MCL-1) (1,2).

The MCL-1 protein, a key player in preventing cell death (apoptosis) (regulate cell death by binding to BAK and BAX, inhibiting their ability to form pores on MOM and subsequent release of cytochrome c, which activates cascade of cell degrading enzymes "caspases", that results in cell death), encoded by human MCL-1 gene (3), is found to be a frequently amplified in cancer, with significant implications for tumor progression and drug resistance. Elevated expression of this gene is linked with various cancers, including mantle cell lymphoma (4), pancreatic cancer (5), and cervical cancer (6), showcasing its role in tumorigenesis and resistance to therapies such as chemotherapy, BH3 mimetics and adverse treatment outcomes (7).

This, presses the alarming need of potent MCl-1 inhibitors with improved binding affinity, minimal side effects, and reduced drug resistance as potential cancer therapy. Based on forgoing urgency, computational aided drug design (CADD) including drug repositioning provides an efficient approach to

identifying potent (effective) antitumor inhibitors in minimalist time and cost, as repositioned drugs with established therapeutic profiles, skips the need for intensive studies, in comparison to painstaking approach of traditional drug discovery pipeline (8, 9).

Therefore, in this study Insilico pipeline (e.g., molecular docking (Autodock vina), ADME predictions (SwissADME server) and toxicity assessment (ProTox-3.0 online server)) was designed to reposition the FDA approved drugs, in order to find potent MCL-1 (cancer associated protein) inhibitors. The main goal of this research is the repositioning of FDA approved drugs using expedited in-silico techniques to identify promising inhibitors of MCL-1, ultimately enhancing treatment options against cancer.

METHODOLOGY

LIGAND SELECTION

A total of eleven Ligands, that includes Trazodone Hydrochloride (CID : 62935), 2) Tetrahydrozoline Hydrochloride (CID : 10648), 3) Ketotifen (CID : 3827), 4) Pentazocine (CID : 441278), 5) Quinine dihydrochloride (CID : 91429), 6) Galantamine Hydrobromide (CID : 121587), 7) Ivabradine (CID : 132999), 8) Cinitapride (CID : 68867), 9) Papaverine (CID : 4680), 10) Noscapine (CID : 275196), Metoprolol (CID : 4171), retrieved from PubChem data base, were selected for molecular docking studies to investigate their interactions with target molecules, for pharmacological insights and potential for drug development. These ligands were selected for its therapeutic applications across various disease areas such as immune disorders, heart disease, cancer, pain, and inflammation and drug-likeness profiles.

LIGAND PREPARATION

The three-dimensional structure of ligands in SDF formate (Figure 1), were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), energy minimized using the Molecular Mechanics Force Field (MMFF94) force field and then converted into pdbqt format using Open Babel 3.1.1 software (10) to ensure compatibility with Auto Dock Vina, a widely used molecular docking program (11).

PROTEIN RETRIEVAL AND PREPARATION

The three-dimensional crystal structure of the anti-apoptotic protein MCL-1 (PDB ID: 6UDV) (12) was retrieved from the Protein Data Bank (PDB, https://www.rcsb.org/). However, this structure was reprocessed by removing co-crystallized compound, water molecules while adding hydrogen atoms along with assigning Kollman charges by using MGL-AutoDockTools. Finally, the prepared structure was saved in a pdbqt format suitable for molecular docking analysis (13).

MOLECULAR DOCKING

For molecular docking, a receptor grid (grid dimensions for the x, y, and Z-axis were 12.427, 4.407, and 97.345 respectively), was constructed around the location of co-crystallized ligand for the fixed target protein MCL-1 and flexible ligands (Fig. 1), using the software MGL-AutoDockTools (ADT, v1.5.7) for the positioning of binding sites. Then molecular docking was conducted on a HP laptop (12th Gen Intel Core i5 processor, 1.30 GHz, 8 GB RAM in 64-bit operating system, x64-based processor), using AutoDock Vina 1.5.7 software (https://vina.scripps.edu/), which predicted the binding affinity of ligands (Fig. 1) to the protein's active site. The resulting docked complex was visualized and analyzed by using Discovery Studio Visualizer (DS viewer) v24.1.0.23298 (Free Download: BIOVIA Discovery Studio Visualizer - Dassault Systèmes) (14).

DOCKING PROTOCOL VALIDATION

For the evaluation of the reliability of AutoDock Vina configuration, the native co-crystallized inhibitor, Q51 (CID: 118910215) was computationally extracted from the experimental MCL-1 structure (PDB ID: 6UDV) and docked back into the same binding pocket, while applying the exact grid center coordinates, and an optimized search space used for the eleven test ligands. Validation was successful, as the Q51 correctly re-occupied the hydrophobic binding cavity and reproduced key interactions with essential active

site residues observed in the original experimental crystal structure. This showed that our grid settings were accurate for positioning molecules.

ADME PROFILING

The SwissADME from the SwissADME server (www.swissadme.ch), was done to predict drug-body interactions, including ADME properties such as Lipinski's rule compliance, log P, Log S, bioavailability and pharmacokinetic aspects (15).

TOXICITY STUDY

The ProTox 3.0 online server (ProTox-3.0 - Prediction of Toxicity of chemicals), was used to evaluate compound toxicity and beneficial effects for drug development, covering different toxicity aspects like acute toxicity, lethal dose (LD50), hepatotoxic, carcinogenic, mutagenic, cytotoxic, and immunotoxic potential (16).

RESULTS

To execute the experiment of molecular docking, a total of eleven compounds, selected based on its therapeutic applications, were retrieved from the PubChem database, were screened computationally. However, only eight compounds (Fig. 1) were docked with target MCL-1 protein (PDB ID: 6UDV) retrieved from Protein Data Bank (PDB, https://www.rcsb.org/) by using Autodock vina, to predict ligand-protein interactions, and binding affinities. The revealed binding affinities were ranging from -5.6 to -9.1 kcal/mol (Table 1). These eight compounds (Fig. 1) that were filtered based on its no mutagenicity, carcinogenicity (Table 2) and Lipinski rule violation (Table 3), through screening (e.g., toxicity screening, by using ProTox-3.0 online server and ADME properties evaluations by using SwissADME server) that was done prior to molecular docking. Whereas, the remaining compounds showing mutagenicity (Papaverine, Cinitapride) and carcinogenicity (Noscapine) (Supplementary Table II) despite having no Lipinski rule violation (Supplementary Table III) were ruled out, as mutagenic and carcinogenic potential may limit its use.

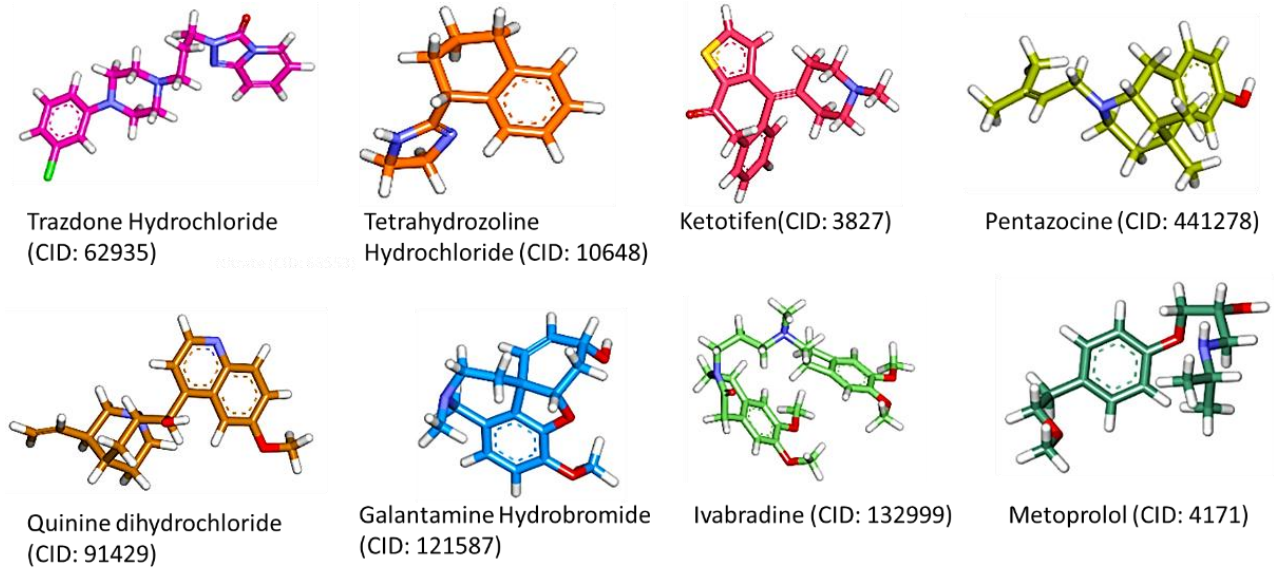

Fig. 1. Structures of ligands (Hits)

Table I. Docking score of compounds

Pubchem ID	Compound name	Docking score
62935	Trazodone Hydrochloride	-9.1
10648	Tetrahydrozoline Hydrochloride	-8.1
3827	Kitotefen	-7.6
441278	Pentazocine	-7.5
91429	Quinine dihydrochloride	-7.4
121587	Galantamine Hydrobromide	-7.3
132999	Ivabradine	-7.2
4171	Metoprolol	-5.6

Table II. Toxicity prediction of compounds

Pubchem ID	Compound name	LD50	Toxicity class	Toxicity potential	Carcinogenity and mutagenicity
62935	Trazodone Hydrochloride	584	4	Neurotoxic, Immunotoxic and respitoxic	None
10648	Tetrahydrozoline Hydrochloride	355	4	Neuro and respitoxic	None
3827	Ketotifen	179	3	Neuro and respitoxic	None
441278	Pentazocine	305	4	Neurotoxic, Immunotoxic and respitoxic	None
91429	Quinine dihydrochloride	263	3	Neurotoxic, Immunotoxic and respitoxic	None
121587	Galantamine Hydrobromide	85	3	Neurotoxic, Immunotoxic and respitoxic	None
132999	Ivabradine	1800	4	Neurotoxic, cytotoxic, Immunotoxic and respitoxic	None
4171	Metoprolol	1050	3	Respitoxic	None

Table III. Drug likeness properties of compounds; TrH (Trazodone Hydrochloride), TetH (Tetrahydrozoline Hydrochloride), Ket (Ketotifen), Pen (Pentazocine), QD (Quinine dihydrochloride), Ivab (Ivabradine), GH (Galantamine Hydrobromide), Met (metoprolol). Soluble (S) Moderately Soluble (MS), Poorly Soluble (PS)

Molecule	TrH	TetH	Ket	Pen	QD	GH	Ivab	Met
MW (less than 500)	408.3	236.74	309.43	285.42	397.34	368.27	468.59	267.36
#H-bond acceptors (> 10)	3	1	2	2	4	4	6	4
#H-bond donors (> 5)	0	1	0	1	1	1	0	2
MR (40-130)	118.1	76.87	95.87	93.27	113.66	94.09	135.93	76.6
TPSA	45.78	24.39	48.55	23.47	45.59	41.93	60.47	50.72
iLOGP (> 5)	0	0	3.04	3.32	0	0	4.78	3.22
ESOL Class	MS	S	MS	S	MS	MS	S	S
Ali Class	MS	S	S	S	MS	S	S	S
Silicos-IT class	MS	MS	MS	MS	MS	S	PS	MS
GI absorption	High	High	High	High	High	High	High	High
BBB permeant	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Lipinski #violations	0	0	0	0	0	0	0	0
Ghose #violations	0	0	0	0	0	0	1	0
Veber #violations	0	0	0	0	0	0	0	0
Egan #violations	0	0	0	0	0	0	0	0
Muegge #violations	0	0	0	0	0	0	0	0
Leadlikeness #violations	2	1	0	0	2	1	2	1
Synthetic Accessibility > 5	3.01	3.08	3.42	3.99	4.5	4.65	4.17	2.67

Table IV. Interacting amino acid residues/type/Bond size (Å) of compounds. (Green: strongly bonded residues; pink, yellow, sky blue: frequently binding residues)

Protein	Compound name	Interacting amino acid residues/type/Bond size (Å)
MCL-1	Trazodone Hydrochloride	Leu 267/C-H (Carbon Hydrogen) Bond, Alkyl/3.64, 4.64; Leu 246/Alkyl, Alkyl/4.36, 4.84; Leu 294/Alkyl/4.12; Leu 290/Alkyl/4.51; Val 274/Alkyl/4.12; Met 250/Alkyl, Alkyl/4.36, 4.82; Phe 270/Pi-Pi T-Shaped, Pi-Alkyl/4.76, 5.05; Val 253/Alkyl, Alkyl/5.02,5.23; Thr 266/Pi-Sigma/3.65; ALA 227/Alkyl/4.61; Met 231/Alkyl/4.72; Phe 228/Pi-Alkyl/4.68
	Tetrahydrozoline Hydrochloride	Met 250/Pi-Sulfur, Alkyl/3.88, 4.64; Phe 270/Pi-Pi T-Shaped,Pi-Alkyl/4.77,4.99; Val 274/Pi-Alkyl/5.49; Leu 246/Pi- Alkyl, Alkyl/5.26, 5.49; Val 249/Alkyl/4.98
	Ketotifen	Leu 267/H (Hydrogen) Bond/3.08; Thr 266/Pi-Sigma/3.63; Arg 263/Pi-Cation/3.94; Met 231/Pi-ALKYL/4.79; Val 253/Alkyl/4.95; Phe 254/Pi-SULFUR/5.08
	Pentazocine	His 224/H Bond, Pi-Pi T-Shaped/3.73, 6.78; Ala 227/Pi-Alkyl, Alkyl/5.56, 4.61; Met 231/Alkyl,Alkyl, Alkyl/3.91,4.48,5.44; Leu 267/Alkyl,Alkyl/5.01,4.36; Met 250/Alkyl,Alkyl/4.41,4.84; Phe 270/Pi-

	Alkyl/4.56; Val 253/Alkyl/5.36
Quinine Dihydrochloride	THR 266/H Bond,Pi-Sigma/2.89,3.95; LEU 246/Alkyl/4; Leu 235/Alkyl/4.39; Val 253/Alkyl/4.49; Met 250/Alkyl,Alkyl/4.77,4.81; Phe 270/Pi-Alkyl/4.99; Met 231/Pi-Alkyl/5.05
Galantamine Hydrobromide	Leu 267/H Bond,Pi-Alkyl/2.95,5.36; Arg 263/C-H Bond/3.38; Val 249/C-H Bond/3.6; Phe 254/Pi-Alkyl/5.21; Met 231/Alkyl,Alkyl/4.25,4.96; Phe 270/Pi-Alkyl,Pi-Alkyl/5.29,5.01; Val 253/Pi-Sigma/3.85
Ivabradine	His 224/ C-H Bond/4.58; Gly 262/ C-H Bond/3.35; Val 220/Alkyl,Pi-Alkyl/4.28,5.47; Met 231/Pi-Sulfur,Alkyl/5.5,4.59; Phe 270/Pi-Pi Stacked,Pi-Alkyl/4.16,3.97; Val 249/Alkyl/4.91; Met 250/Alkyl,Alkyl/4.82,5; Val 253/Alkyl/4.24; Leu 235/Alkyl/5.31; Leu 267/Alkyl/5.94; Phe 228/Pi-Alkyl/5.33
Metoprolol	Met 231/Pi-Sigma/3.92; Phe 270/Pi-Pi T-Shaped/4.95; Leu 267/Alkyl/4.95; Val 253/Alkyl/5.01

The screened compounds (Fig.1) showed binding within the binding pocket of MCL-1 protein (Fig. 2). These compounds showed significant interactions of various types and bond sizes with the active site amino acid residues of the MCL-1 protein (Fig. 3 & Table IV).

Strong interaction mainly classical H (Hydrogen) bond with various bond size, were formed between the sulfur atom of ketotifen molecule and NE atom of the isobutyl side chain of leucine 267 (Leu267A) (3.08 Å) (Fig. 3C), the oxygen atom of Pentazocine and ND1 atom of the imidazole side chain of Histidine 224 A (His224A) (3.73 Å) (Fig. 3D), the hydrogen atom of quinine dihydrochloride and main chain oxygen atom from carbonyl of threonine 266 residue (Thr266A) (2.89 Å) (Fig. 3E), and the oxygen atom of galantamine hydrobromide and main chain HN atom of Leu267A (2.95 Å) (Fig. 3F).

In addition, all compounds also formed weak interactions with pocket residues which further stabilized the complexes. Notably, Met231A, Val253A, and Phe270A exhibited frequent binding across nearly all ligands, highlighting, their critical role in stabilizing compounds within the Mcl-1 binding pocket (Table 4) (Supplementary Table IV). Trazodone Hydrochloride achieved the highest binding affinity (-9.1 kcal/mol), and engaged the highest number of overall residues, suggesting extensive pocket occupancy where a combination of precise, close-range anchoring and an extensive hydrophobic network maximizes surface contact to prevent drug detachment. These findings highlight the diverse structural mechanisms by which these compounds target the MCL-1 active site, offering valuable insights for potential therapeutic redirection.

DISCUSSION

In the present study, we conducted a computational screening of eleven compounds that were selected based on their therapeutic role in various disease domains such as cancer, anti-inflammatory, analgesia and cardiology, to predict and assess the inhibitory potential against the MCL-1 protein, which is one of major culprit molecule involved in the survival of cancer and development of tumor (17). Increased expression of MCL-1 protein reported in different types of human tumors, including ovarian (18), breast (19), lung cancer and its resistance to chemotherapeutics makes it an attractive target in cancer therapy (20).

The interaction analysis and binding strength demonstrated that eight of the screened drugs (Trazodone hydrochloride, tetrahydrozoline hydrochloride, ketotifen, pentazocine, quinine dihydrochloride, galantamine hydrobromide ivabradine and metoprolol) bind effectively with in the binding pocket of MCL-1 (Fig. 2, Table 1) through strong and weak interactions, indicating their potential anticancer activity. Drugs including ketotifen (Fig. 3C), pentazocine (Fig. 3D), quinine dihydrochloride (Fig. 3E), and galantamine hydrobromide (Fig. 3F) were mainly stabilized by strong interaction, predominantly hydrogen bonds with residues His224A Thr266A, and Leu267A. This hydrogen bond not only demonstrate the correct positioning of these drugs within the active site of MCL-1 protein but also plays a major role in maintaining the ligand-protein complex, which is essential for the activity of protein. In contrast, Trazodone hydrochloride, tetrahydrozoline hydrochloride, ivabradine and metoprolol formed weak interactions, mainly with key active site residues Met231A, Val253A, and PHE270A. These interactions particularly with key active site residues His224A Thr266A, Leu267A, Met231A, Val253A, and PHE270A significantly contribute to the

enhanced stability of these drugs within the binding pocket, which is crucial for the effective binding of these drugs to the MCL-1 protein, ultimately leading to improved binding efficacy within the protein's binding site (21).

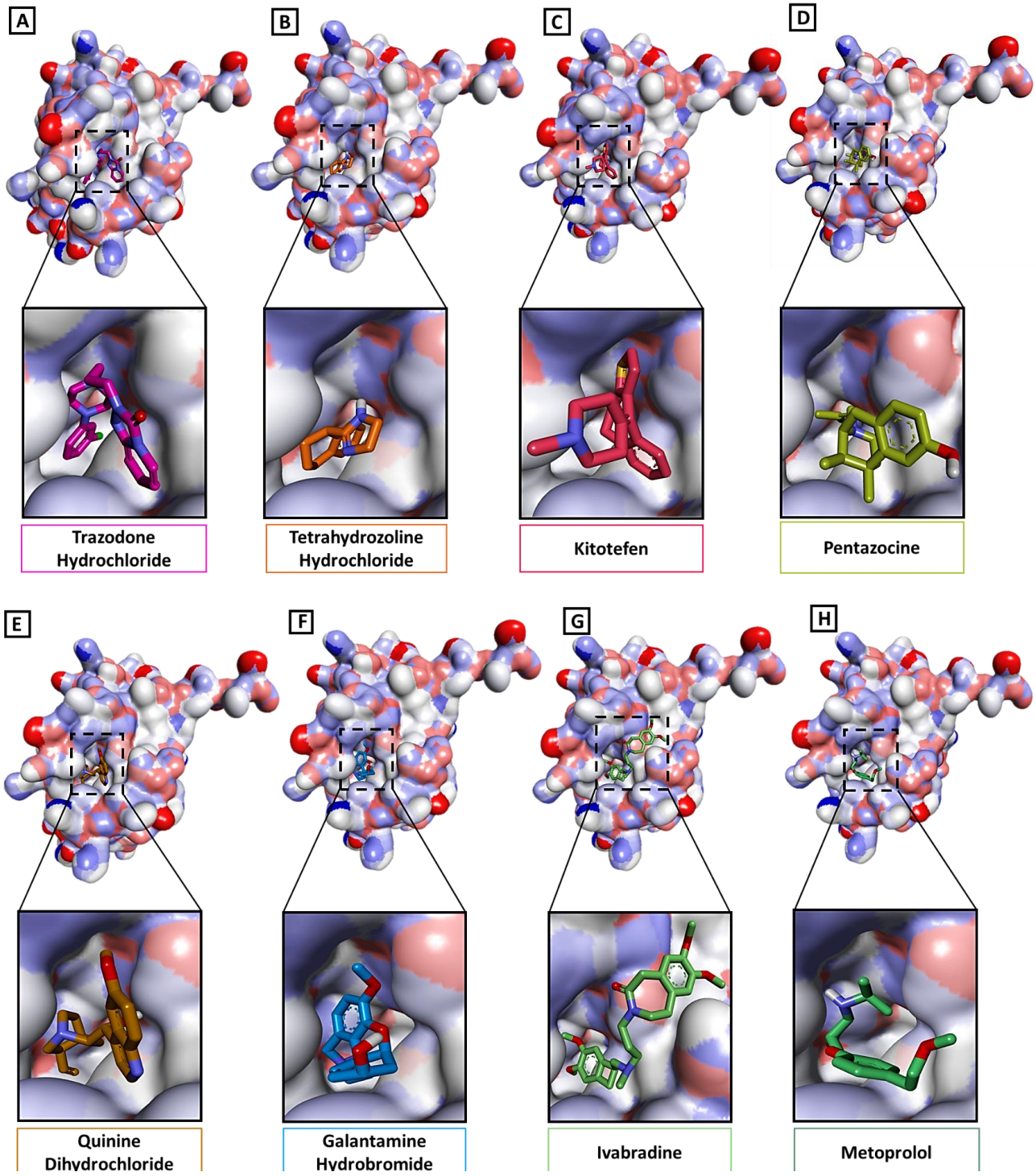

Fig. 2. The 3D atom charge surface mapping of MCL-1 protein with selected compounds (A)Trazodone Hydrochloride, B) Tetrahydrozoline Hydrochloride, C) Kitotefen, D) Pentazocine, E) Quinine Dihydrochloride, F) Galantamine Hydrobromide, G) Ivabradine, H) Metoprolol) in the active pocket of the MCL-1 protein

Remarkably, most of these active sites binding amino acid residues particularly His224A, Met231A, Val253A, Thr266A, Leu267A, and PHE270A (Fig. 3), were not only closely related with the active site binding residues of previously reported co-crystalized ligand Q51 (CID: 118910215) (12), but were also in alignment with previously identified MCL-1 hotspots crucial for MCL-1's functional interaction with pro-apoptotic proteins, such as BIM, which is reported to bind specifically to the hydrophobic binding groove of Mcl-1 (22, 23). This analysis emphasizes that by directly engaging these critical amino acid residues within MCL-1's active site, the identified drugs may sterically hinder the binding of pro-apoptotic BH3-only proteins, which

suggest a highly targeted and effective mechanism for the inhibition of MCL-1's anti-apoptotic activity through new mode of action.

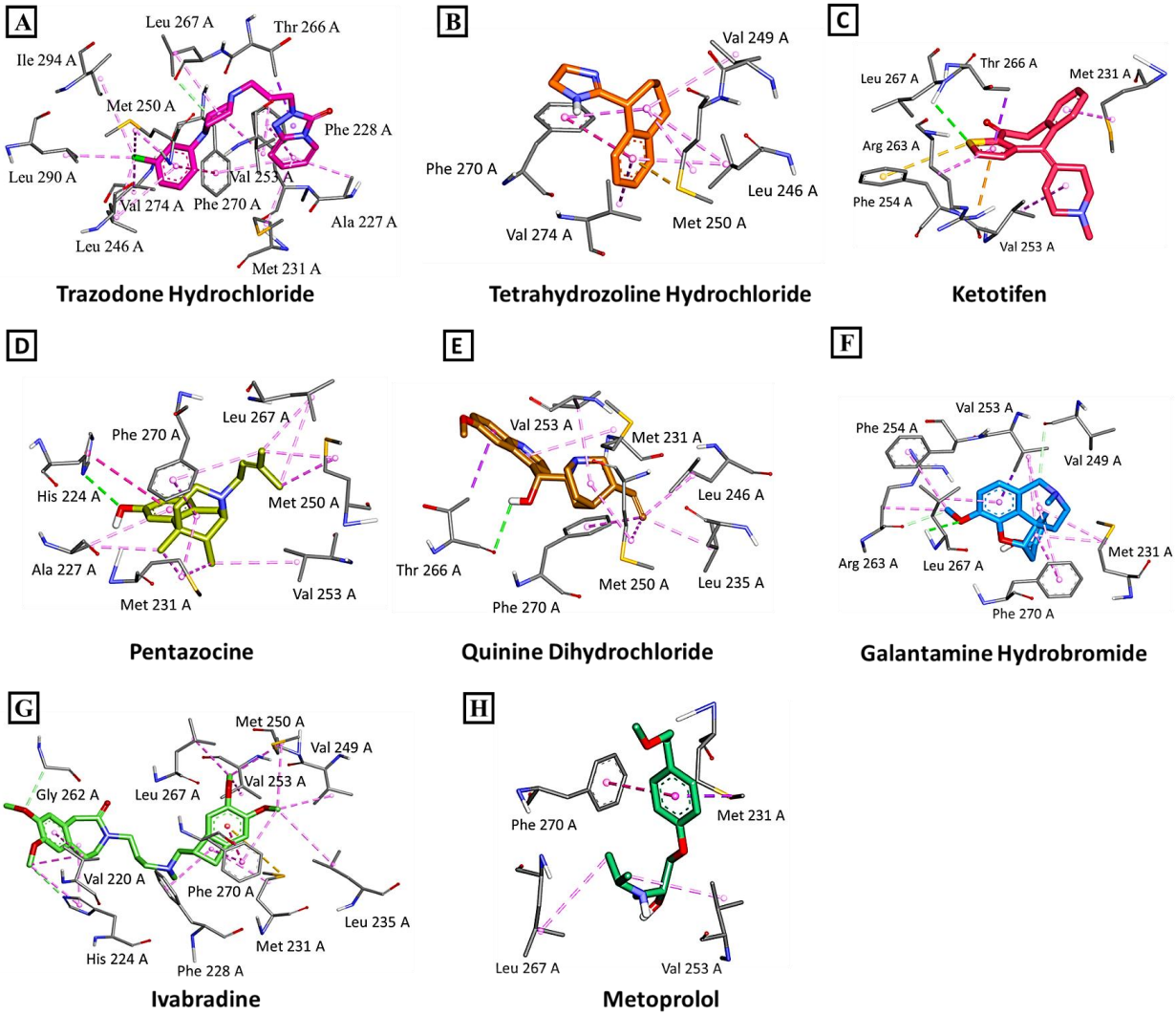

Fig. 3. 3D view of key active site amino acid residues of MCL-1 protein MCL-1 (Myeloid Cell Leukemia 1) protein (PDBID: 6UDV) interacting with A) Trazodone Hydrochloride, B) Tetrahydrozoline Hydrochloride, C) Ketotifen, D) Pentazocine, E) Quinine Dihydrochloride, F) Galantamine Hydrobromide, G) Ivabradine, H) Metoprolol

The functional importance of these targeted residues is further highlighted by previous mutational data. As, mutation at His224 has shown to impair regulatory degradation (20), while Leu267Val mutation has shown to drive inhibitor resistance by preventing the displacement of pro-apoptotic proteins (24), Alanine substitutions at Phe270A and Met231A is reported to Met231 significantly drop binding energies, confirming their role in driving tighter binding (25). Additionally, Thr266 and Val253 are reported to be crucial for dictating selective inhibition, as it has shown to form crucial selective bonds with the potent reference inhibitor S63845 (26, 27). By interacting stably with these mutation-sensitive sites of established control inhibitors, our eight repurposed drugs show strong potential to evade common resistance pathways.

The primary significance of these findings lies in the absolute novelty of the identified inhibitors. All eight identified compounds are FDA approved drugs (Fig. 1) have established therapeutic profiles spanning brain diseases (28, 29), allergies (30, 31), cancer (32, 33), pain (34), malaria (35), and heart diseases (36, 37). Their primary mechanisms are highly diverse, acting through inhibiting the serotonin reuptake (28), stimulating the alpha 1-adrenergic receptors (30), stabilizing mast cell and blocking of receptor histamine H1 (31), inhibiting Hypoxia-inducible factor 1-alpha (HIF-1α) protein (32), stimulating the opiod receptors (kappa, sigma and mu) (34), directly acting on sodium channels (35), inhibiting the BCL-2 protein, blocking activation of the AKT pathway (33), inhibiting the acetylcholinesterase enzyme (29), inhibition of hyperpolarization-activated cyclic nucleotide-gated 4 (HCN 4) channel (36), inhibiting the beta-1-adrenergic

receptor (37). Nevertheless, to date, neither of them (Fig. 1) have been reported to inhibit MCL-1 which highlights the unique MCL-1 inhibitory mechanism of these drugs in tumor treatment.

These findings make these eight drugs (Fig. 1) potential inhibitors as, the strong hydrogen bonds and various weak interaction, formed with the active site binding residue of MCL-1 protein by these drugs, is not only crucial for the stabilization of protein ligand complex but also for the activity of protein. Thus, suggesting a clear potential inhibitory role of these eight drugs in the destabilization, subsequently inhibition of MCL-1 protein, increasing the efficacy of drug against tumors.

However, the urgent need for high-affinity, selective binding to MCL-1, has proven challenging for these repurposed drugs. As there are no published evidences in reviewed literature till now validating that trazodone hydrochloride, tetrahydrozoline hydrochloride, ketotifen, pentazocine, quinine dihydrochloride, galantamine hydrobromide, ivabradine and metoprolol as MCL-1 inhibitors through in vitro, in vivo, or in clinical studies. Not only that the dynamic nature, high flexibility and complex binding mechanisms of the MCL-1 protein has presented significant challenges for our traditional molecular docking study, where protein is kept rigid. As, static protein structure fail to account for this inherent flexibility and many potential binding conformations (38, 39). These limitations can lead to complicate docking accuracy. Therefore, further experimental validation is warranted to confirm these computational predictions and elucidate their therapeutic potential.

CONCLUSION

This research identifies eight FDA-approved drugs—trazodone hydrochloride, tetrahydrozoline hydrochloride, ketotifen, pentazocine, quinine dihydrochloride, galantamine hydrobromide, ivabradine, and metoprolol as potential inhibitors of MCL-1, a protein prevalently overexpressed in a broad range of cancers including hematologic malignancies, breast, and lung cancers, where it plays a critical role in cancer cell survival. These compounds demonstrated significant binding interactions with key active site residues of MCL-1 (His224A, Thr266A, Leu267A, Met231A, Val253A, and Phe270A), facilitating strong ligand-protein binding. This suggests their potential to be repositioned as effective anticancer agents targeting MCL-1 through a possible new mechanism. Overall, these findings provide a promising therapeutic strategy against various malignancies by destabilizing and inhibiting MCL-1 function. However, additional experimental validation and clinical investigations are necessary to confirm these computational predictions. This study accelerates the drug discovery process by laying foundational groundwork for future clinical and laboratory research aimed at developing MCL-1 inhibitors as cancer therapies.

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Conflict of interest:

Authors declared no conflict of interest.

Author s' contributions:

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 and finalized the manuscript.

Declaration of generative AI-Assisted Tools:

Authors declared that no AI-assisted tools were used.

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