Iraqi Journal of Biotechnology, 2025, Vol. 24, Special Issue 2, 25-32

Screening and Repurposing as an Important Approach for DNA Methyltransferase1 Enzyme Inhibitor Drug Finding by Using Molecular Operating Environment Software

[1] Ali Haidar Dirjal and [2] Mohammed I. Nader AL-Taee

[1] Specialist Pharmacist at the Babylon Forensic Department, Ministry of Health, Iraq.
[2] Professor at the Institute of Genetic Engineering and Biotechnology / University of Baghdad, Baghdad, Iraq.

Received: February 20, 2025 / Accepted: May 29, 2025 / Published: November 16, 2025

Abstract: The inhibition of enzymes are very important in the discovery of drugs, especially in the epigenetic regulators such as DNA methyltransferase 1, critical enzyme in DNA methylation linked to cancer and other diseases. This study, the Molecular Operating Environment software was used to achieve virtual screening and drug repurposing in finding of potential DNA methyltransferase 1 enzyme inhibitors. Approach of this study focused on screening of a library of some of FDA-approved drugs for their binding affinity and complementary to DNA methyltransferase 1 enzyme using molecular docking steps. Through screening, telmisartan an angiotensin II receptor blocker appeared with proper binding at the DNA methyltransferase 1 enzyme catalytic site. Analysis showed key hydrogen bonds and ionic bonds responsible for its inhibitory effect. This research highlights the importance of computational tools in drug retargeting, cleared how molecular operating environment can lead the identification and repurposing of existing medications for novel therapeutic uses. Results provide a foundation for further experimental studies to validate telmisartan as a potential DNA methyltransferase 1 enzyme inhibitor.

Keywords: DNA methyltransferase 1 (DNMT1).

Corresponding author: (Email: dirjalali@gmail.com).

Introduction

The history of docking start from 1980 when scientists began harnessing computer simulations to understand how drugs interact with their targets at a molecular level. Through the years, algorithms became more refined, significantly enhanced the efficiency of development is the discovery of compounds(1). DNA methylation act as a critical epigenetic modification, by the addition of a methyl group to cytosine residues CpG dinucleotides. This change influences gene regulation by Insilco predictions, making it achievable tool in drug discovery. The molecular docking revolutionized drug development by allowing researchers to visualize how small molecules might fit into the specific pockets of target proteins, like enzymes. One critical field of focus in drug modifying chromatin structure and effect the binding of transcription factors. Modifications in DNA methylation styles associated with several diseases, especially cancer (2, 3). DNA methyltransferase 1 enzyme, a

key enzyme, critical in preserving DNA methylation through cell division by replicating recent methylation forms onto synthesized DNA strands. Its function transfer of epigenetic information by cell generations, which is important for conserve normal cellular development. Inhibitors of the DNA methyltransferase 1 enzyme are chemicals created to inhibit its operation, interfere DNA methylation patterns (4). Discovery the molecular bindings between these inhibitors and DNA methyltransferase 1 enzyme by docking studies is critical for the development of active therapeutic schedules (5, 6).

The drugs innovation considered molecular docking serves as a powerful way for predicting how inhibitor chemicals bind target enzymes like DNA methyltransferase 1 at an atomic level. Analysis these bindings computationally, scientists can diagnose promising chemicals for further experimental tests as DNA methyltransferase 1 enzyme inhibitors. This simplify the drug innovation work by determine chemicals with high binding affinity and specificity binding target enzyme (5, 6). DNA methyltransferase 1 enzyme inhibitors effect in modulating global levels of DNA methylation inside cells. By decrease DNA methyltransferase 1 enzyme activity, These compounds can disturb overall DNA methylation patterns, influencing how genes are expressed and cells function. Scientists studying DNA methyltransferase 1 inhibition have found it offers good insights into critical treatments for conditions where epigenetic changes have gone awry (7). Current FDA-approved DNA methyltransferase inhibitors unfortunately come with significant side effects and toxicity issues, creating an urgent need for safer alternatives (8). DNA methylation enzymes DNA methyltransferase 3A and DNA methyltransferase 3B play crucial roles during early development. They establish methylation patterns in the embryo that help determine how tissues form and develop (9). Unlike its relatives, DNA methyltransferase 3L that can either enhance or suppress the activities of DNA methyltransferase 3A and DNA methyltransferase 3B depending on the cellular context (10). According to (11), DNA methyltransferase 1 (gene location 19p13. 2), DNA methyltransferase 3A (gene location 2p23. 3) and DNA methyltransferase 3B (gene location 20q11.21). Maintenance Methyltransferase: DNA methyltransferase 1 is primarily expressed in dividing cells and is essential for copying methylation patterns during DNA replication. Preference for hemimethylated DNA, aiding in the maintenance of methylation patterns post-DNA replication. DNA methyltransferase 1 also interacts with various proteins that guide its activity.

Structure: It is a multi-modular enzyme with an N-terminal domain containing a DNA-binding CXXC domain, a replication foci-targeting sequence (RFTS), 2 Bromo-Adjacent Homology (BAH) domains, and a C-terminal catalytic domain (12).

Co factor zinc ion bind at the active site of above enzymes isoform, often coordinating with amino acid residues to stabilize the structure and facilitate the catalytic activity of DNA-methylation enzymes (13).

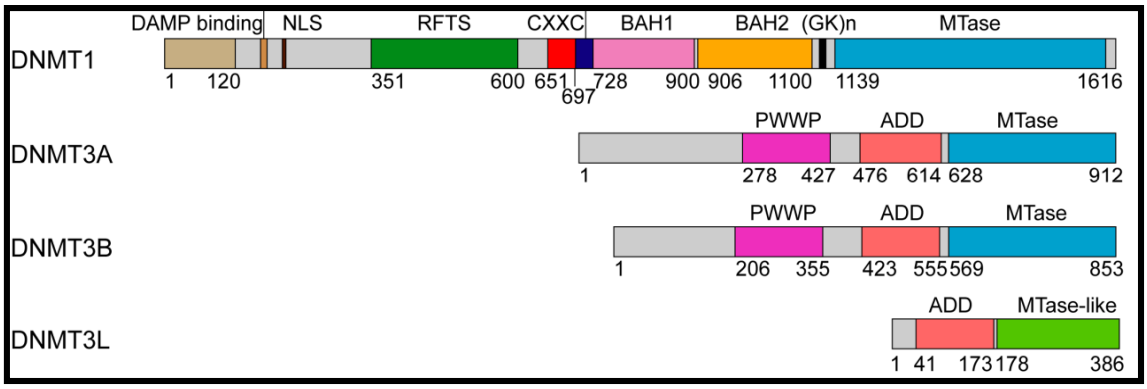

Figure (1): Domain subunits of human DNA methyltransferases: DNA methyltransferase 1 , DNA methyltransferase 3A and DNA methyltransferase 3B, and regulator DNA methyltransferase 3L, with individual domains marked by residue (14).

Genotoxicity and DNA damage exhibited relation between DNA methyltransferase 1 inhibition (nucleoside analog) and DNA damage. Nucleoside analog inhibition of DNA methyltransferase 1 can lead to increased DNA damage, showed a potential risk for prognosis malignancies or other genomic instability effects (15). The process of drug repurposing, docking, and computational pharmacology in drug discovery has showed critical point due to its cost-effectiveness and accelerating the drug development process. In particular, targeting DNA methyltransferase 1 inhibitors has shown promise in cancer therapy. DNA methyltransferase 1 inhibitors have been explored extensively as potential therapeutics for various cancers due to their role in epigenetic regulation (16, 17). Among the commonly used docking programs is Molecular Operating Environment software, that gives fundamental computational tools for drug invention and molecular design. Molecular Operating Environment software offers the ability to achieve both rigid and flexible docking ways and allows for virtual screening, an important process in the choosing of DNA methyltransferase 1 inhibitors from large compound libraries (1). Molecular Operating Environment software also provide a method of pharmacophore-based screening tools that used to analyze the interactions between ligands and enzymes. In a study by (18), over 40,000 compounds from the ZINC database screened using, Molecular Operating Environment software leading to the identification of a group of DNA methyltransferase 1 inhibitors. Molecular Operating Environment software's abilities in structural design, geometry optimization, and energy minimization ensure that it a powerful tool for molecular docking simulations.

methods

The molecular docking used to generate a binding model of a DNA methyltransferase 1 inhibitor with drug previously improve to treat other diseases. In general, the docking protocol comprised six steps:

1) Target selection: The crystallographic structure of human DNA methyltransferase 1 (PDB ID: 4WXX) retrieved from the RCSB Protein Data Bank (PDB) available online: https://www.rcsb.org/ (accessed on 15 June 2023) (19). Among the different crystallographic structures

of DNA methyltransferase 1 available on PDB, we selected PDB ID: 4WXX because it contains a co-crystallized molecule of S-adenosyl L-homocysteine (SAH), and diffracted with a resolution of 2. 62 Å (17).

2) Target preparation: The 3D structure of DNA methyltransferase 1 proteins prepared by using Molecular Operating Environment software 2014.09. Small molecules such as zinc ions removed from protein targets that utilized for the preparation of the structures before docking by remaining one peptide chain, correction and protonation using the MMFF94x force field and determine the critical site amino acids for docking process (20).
3) Dataset preparation: Library obtained of 116 compounds of drugs by process resemble sieving through check that recently search drugs effect through decrease activity of cancer cell lines, drugs suggest from artificial intelligence, Yang cao docking website by virtual screening of approved drugs(21), pharmaceutical compounds used to treat human from the ZINC database (https://zinc.docking.org/) and PubChemdatabase (https://pubchem.ncbi.nlm.nih.gov/) (22). All compounds downloaded in (.sdf) format. The Molecular Operating Environment software used for optimization of all downloaded compounds by adding partial charges through the protonate3D module. For energy minimization, the MMFF94X force fields applied for each compound and then added to the Molecular Operating Environment software ligands database for docking (20).
4) Molecular docking: Molecular Operating Environment software used to generate the dock conformation of protein-ligand complexes. The grid centered on the site determined by site finder of the (Molecular Operating Environment software) using the "Triangle Matcher" method, the binding compounds subjected to 50 search steps (poses) and the default values for the other parameters. During the docking simulations, the receptor considered rigid and the ligands flexible (23).
5) Ranking and re-scoring: The clusters with an RMSD about 2 Å were visually explored. The conformations with the lowest binding energy selected. Docked ligands ranked according to their predicted scores in ascending order, compounds with higher rank have more negative values, thus better predicted affinity against DNA methyltransferase 1.
6) Data analysis: View the top of table get from results of Molecular Operating Environment software, select more negative value with about 2 Å distance between ligand and DNA methyltransferase 1 enzyme.

Results and Discussion

Amino acids of larger site of docking gated from Molecular Operating Environment software site finder as following: (PHE515, LEU516, GLN517, SER518, ASN519, SER520, ASP521, SER522, THR523, GLU525, ASP526 ASN529, LYS530, THR533, GLU562, TYR564, ASP565, GLU566, GLY568, ASP569, SER570 ASP571, GLU572, GLN573, PRO574, ILE575,

PHE576, LEU577, THR578, PRO579, ARG582 GLY593, GLN594, ARG596, ACE615, THR616, LYS617, ALA618, LYS649, VAL658, GLN687 GLU688, ARG690, PRO692, ALA695, GLU698, ALA699, ASP701, ASP702, GLU703, ASP1143 PHE1145 SER1146 GLY1147 CYS1148 GLY1149 GLY1150 LEU1151 GLU1168 MET1169 ,TRP1170, ALA1173, ASP1190, ASN1192, GLY1222, GLY1223, PRO1224, PRO1225, CYS1226, GLN1227, GLY1228, PHE1229, SER1230, GLY1231, ASN1233, ARG1234, PHE1235, ASN1236, ARG1238, THR1239, SER1241, LYS1242, PHE1243, ASN1245, SER1246, LEU1247, SER1250, GLU1266, ASN1267, VAL1268, ARG1269, ASN1270, LYS1275, THR1309, ARG1310, ARG1311, ARG1312, THR1525, THR1526, VAL1527, THR1528, ASN1529, LYS1535, GLN1536, LEU1570, ASP1571, ARG1574, GLN1575, GLY1577, ASN1578, ALA1579, VAL1580).

Results of docking for best 3 drugs given by Molecular Operating Environment software summarized by table1:

Table (1): Three best results of docking.

Drug	Sscore (kcal./mol)	RMSD (Å)	Bonds of interactions between DNA methyltransferase 1 site and drugs				
			Ligands atoms	receptor amino acids	Interaction	Distance	E(kcal/mol)
Telmisartan	-7.68	2.08	O63	ARG.1310	ionic	3.80	- 0.9
			O63	ARG.1310	ionic	3.22	- 3.2
			O64	ARG.1310	ionic	3.15	- 3.5
			6-ring	GLN.1227	pi-H	4.30	-0.6
Daflon	-7.22	1.81	O49	THR. 1526	H-donar	3.25	- 0.7
			C59	ASN. 1578	H-donar	3.24	- 0.9
			O16	ASN. 519	H-accepter	3.01	- 4.7
			O27	GLN.1227	H-accepter	2.76	- 2.8
			O49	THR. 1526	H-accepter	2.80	- 0.7
Ergotamine	-7.3	1.9	N5	GLY. 1223	H-donar	3.00	- 2.0
			C78	ASN. 1578	H-donar	3.32	- 1.4

Table 1 showed telmisartan energy score preferable above daflon and ergotamine required less energy to form interaction while RMSD values refer to larger value but remain in the acceptable range (1.5-2.5). Telmisartan interact by ionic and hydrogen bonds with acceptable energy and distance of interaction for each bond. Although daflon of RMSD value preferable above other near 1.5, also has, four hydrogen bonds with one of good energy on ASN519 but remain unfavorable because hydrogen bonds weaker than ionic bonds that founded on telmisartan interaction. Ergotamine represent weaker interaction due to RMSD less value from others and only weak tow hydrogen bonding (24, 25, 26).

The details of telmisartan molecule interactions showed in figure (2) gated from Molecular Operating Environment software.

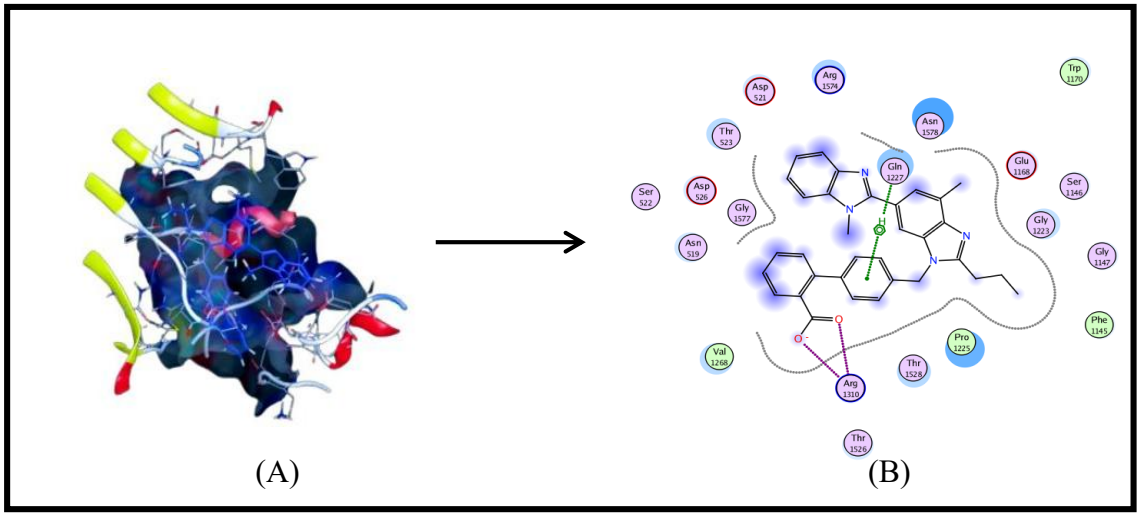

Figure (2): Molecular Operating Environment software pictures of DNA methyltransferase 1 enzyme binding with telmisartan molecule
A) 3D shape represent (DNA methyltransferase 1) enzyme pocket in dark shadow binding to telmisartan molecule of drug in blue color.
B) 2D shape represent core of telmisartan molecule surrounded by (DNA methyltransferase 1) Enzyme amino acids with bonds of interactions.

Telmisartan may act as DNA methyltransferase 1 enzyme inhibitor that used for several years in human as antihypertensive drug approved as safe agent with minimal side effects than decitabine and vidaza.The present about 50 article about reuse of it in different cancer types in the laboratory (27). DNA methyltransferase inhibitors considered promising and effective treatment options for patients with hematological malignancies and multiple types of cancer. In 2013, the U.S. Food and Drug Administration (FDA) approved two azanucleoside-based DNA methyltransferase inhibitors: azacytidine (Vidaza; Celgene) and decitabine (5-aza-2'-deoxycytidine).lower doses of these drugs act as strong demethylation effect, which can re-express of genes that had been silenced due to methylation. This re-expression is lead to reduced cell proliferation, apoptosis, cellular senescence and improved cell differentiation. However, despite their clinical benefits, higher doses of decitabine and azacytidine can cause DNA damage. Additionally, these drugs have several limitations, including high toxicity, instability in physiological conditions, and poor bioavailability. These challenges highlight the need for further research and development to optimize their therapeutic potential while minimizing adverse effects (18).

Conclusion

Docking study results refer to telmisartan drug as a proper inhibitor for DNA methyltransferase 1 enzyme. Molecular Operating Environment software is an important computational tool for chemicals and drugs screening and repurposing.

References

1. Muhammed, M. T. and Aki-Yalcin, E. (2024). Molecular docking: principles, advances, and its applications in drug discovery. Letters in Drug Design and Discovery, 21(3), 480-495.
2. Kadhum, S. I. and Al-Drobie, B. F. (2024). Analysis of DNA methylation level of STAT5a and E-cadherin genes in formalin-fixed paraffin-embedded tissue blocks of Iraqi patients with oral lichen planus. Iraqi Journal of Biotechnology, 23(3), 295–303.

3. Al-Amili, A. A. (2017). A hypermethylation study of DNA in blood samples of breast cancer patients. Iraqi Journal of Biotechnology, 16(2), 111–116.
4. Al-Qazzaz, H. K. and Al-Awadi, S. J. (2022). Impact of DNA methylation and gene expression of H19, SNRPN and LINE-1 genes on oligospermia. Iraqi Journal of Biotechnology, 21(1), 66–78.
5. Mourad, M.A.; Abo Elmaaty, A.; Zaki, I.; Mourad, A.A.; Hofni, A.; Khodir, A.E. *et al.* (2023). Novel topoisomerase II/EGFR dual inhibitors: design, synthesis and docking studies of naphtho [2′, 3′: 4, 5] thiazolo [3, 2-a] pyrimidine hybrids as potential anticancer agents with apoptosis inducing activity. Journal of Enzyme Inhibition and Medicinal Chemistry, 38 (1), 2205043.
6. Zhu, J.; Yang, Y.; Li, L.; Tang, J. and Zhang, R. (2024). DNA methylation profiles in cancer: Functions, therapy, and beyond. Cancer Biology and Medicine, 21, 111-116.
7. Al-Waisy, H. F. M. (2021). Study of Methylation of DNA Mismatch Repair Gene 2 (MSH2) in Patients with Ulcer and Gastric Carcinoma. Institute of Genetic Engineering and Biotechnology for Postgraduate Studies, University of Baghdad: Iraq.
8. Yu, X.; Zhao, H.; Wang, R.; Chen, Y.; Ouyang, X.; Li, W., *et al*. (2024). Cancer epigenetics: From laboratory studies and clinical trials to precision medicine. Cell Death Discovery, 10(1), 28.
9. Li, Y.; Abel, H. J.; Cai, M.; LaValle, T. A.; Yin, T.; Helton, N. M., *et al*. (2024). Rapid and accurate remethylation of DNA in Dnmt3a-deficient hematopoietic cells with restoration of DNMT3A activity. Science Advances, 10(eadk8598).
10. Zeng, Y. (2023). Regulation of De Novo And Maintenance DNA Methylation By Dnmt3A And Dnmt3B. [Doctoral dissertation, The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences]. DigitalCommons@TMC.
11. Baric, N. (2024). The role of the low density lipoprotein receptor related protein 1 (LRP1) and the receptor for advanced glycation end products (RAGE) in the ageing process. *Glycative Stress Research*, *11*(1), 7-20.
12. Mensah, I. K.; Norvil, A. B.; AlAbdi, L.; McGovern, S.; Petell, C. J.; He, M. and Gowher, H. (2021). Misregulation of the expression and activity of DNA methyltransferases in cancer1. NAR Cancer, 3(4):1.
13. Chen, B.; Yu, P.; Chan, W. N.; Xie, F.; Zhang, Y.; Liang, L., *et al.* (2024). Cellular zinc metabolism and zinc signaling: from biological functions to diseases and therapeutic targets. Signal Transduction and Targeted Therapy, 9(6).
14. Ren, W.; Gao, L. and Song, J. (2018). Structural Basis of DNMT1 and DNMT3A-Mediated DNA Methylation1. Genes, 9(12), 620.
15. Pacaud, R.; Thomas, S.; Chaudhuri, S.; Lazar, A.; Timmerman, L. A.; and Munster, P. N. (2025). Low dose DNA methyltransferase inhibitors potentiate PARP inhibitors in homologous recombination repair deficient tumors. Breast Cancer Research, 27(1), 8.
16. Medina-Franco, J. L.; López-López, E. and Martínez-Fernández, L. P. (2022). 7-Aminoalkoxy-Quinazolines from epigenetic focused libraries are potent and selective inhibitors of DNA methyltransferase 1. Molecules, 27(9), 2892.
17. Prado-Romero, D. L.; Saldívar-González, F. I.; López-Mata, I.; Laurel-García, P. A.; Durán-Vargas, A.; García-Hernández, E., *et al*. (2024). De novo design of inhibitors of DNA methyltransferase 1: A critical comparison of ligand-and structure-based approaches. Biomolecules, 14(7), 775.
18. Jan, Z.; Ahmed, W. S.; Biswas, K. H. and Jithesh, P. V. (2024). Identification of a potential DNA methyltransferase (DNMT) inhibitor. Journal of Biomolecular Structure and Dynamics, 42(9), 4730-4744.
19. Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; *et al*. (2000). The protein Data Bank. Nucleic Acids Res. 28 (1), 235–242. doi:10.1093/nar/28. 1.235.
20. Scholz, C.; Knorr, S.; Hamacher, K. and Schmidt, B. (2015). DOCKTITE-a highly versatile step-by-step workflow for covalent docking and vir tual screening in the molecular operating environment. Journal of Chemical Information and Modeling, 55(2), 398–406. https://doi.org/10. 1021/ci500681r.
21. Gan, J. H.; Liu, J. X.; Liu, Y.; Chen, S. W.; Dai, W. T.; Xiao, Z. X., *et al.* (2023). DrugRep: an automatic virtual screening server for drug repurposing. *Acta Pharmacologica Sinica*, *44*(4), 888-896.

22. Sterling, T. and Irwin, J. J. (2015). ZINC 15–ligand discovery for everyone. Journal of chemical information and modeling, 55(11), 2324-2337.
23. Vilar, S.; Cozza, G. and Moro, S. (2008). Medicinal chemistry and the molecular operating environment (MOE): application of QSAR and molecular docking to drug discovery. Curr. Top. Med. Chem. 8 (18), 1555–1572.
24. Agarwal, V.; Kaushik, A. S.; Rehman, M.; Chaudhary, R.; Jawaid, T.; Kamal, M., *et al*. (2021). Interleukin-6 expression and its modulation by diacerein in a rat model of chronic stress induced cardiac dysfunction. Heliyon, 7(12).
25. Duve, T.; Wang, L.; Borges-Araujo, L.; Marrink, S. J.; Souza, P. C. and Thallmair, S. (2025). Martini 3 protein models-a practical introduction to different structure bias models and their comparison. bioRxiv, 2025-03.
26. Rayevsky, A. V.; Bulgakov, E. V.; Platonov, M. O. and Karpov, P. A. (2022). In Silico Screening Of Zinc Database Against Trpv4. Physiological Journal/Fiziologichnyi Zhurnal, 68.
27. Cuong, T. D. and Phan, A. D. (2025). Relaxation time of amorphous telmisartan: Bridging the gap between experiment and theory. Physical Review E, 111(1), 015428.