



Targeting MLL2 Protein SET Domain against Non-Hodgkin Lymphoma using Computer-Aided Drug Designing Approach

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Abstract

Diffuse large B-cell Lymphoma (DL BCL) is a type of non-Hodgkin lymphoma in adults and is a B-cell cancer. Three common variants were seen morphologically, including anaplastic, centroblastic, and immunoblastic. Mostly, these abnormal cells are centroblastic and appear as medium to large-sized lymphocytes having scanty cytoplasm. The gene, namely KMT2D, also called as MLL2, gives commands for producing lysine-specific methyltransferase 2D enzyme, found in different organs/tissues of the body. When the MLL2 protein is overexpressed then diffuse large B-cell lymphoma occurs. The SET ([Su(var)3-9, Enhancer-of-zeste and Trithorax]) domain of MLL2 protein acts as its active site. Due to aggressiveness, poor prognosis and absence of hormonal therapy, this study focuses on the CADD approach for potential therapeutic drugs to inhibit the activation of the SET Domain of MLL2 Protein as a target protein. 3D structure of SET Domain was retrieved from PDB and inhibitors were obtained through PubChem and Literature. Pharmacophore modelling and virtual screening was performed for identification of novel compounds using LigandScout. AutoDock Vina was used for targeted docking against the predicted active sites of protein to evaluate the potential association of protein and ligands. These interactions were evaluated for binding affinities and DRUGLIKENESS properties using AutoDock Vina, DruLito and Data Warrior respectively. ZINC000014728328(Persicogenin) and ZINC000014727443(Cerasinone) appeared to have least binding energies (-8.4) with high drug likeness (-0.0783 and -0.087682) respectively. Novel selected compounds have improved absorption and better Drug Likeness properties, so it is observed that novel compounds are potent inhibitors having more efficacies and fewer side effects.

Introduction

Lymphoma is a lymphocytic type blood cancer, though the name is given to cancerous cells only and not tumors. Clinically it presents as large lymph nodes, with fever, drenching sweats, weight loss, itching, and feeling of tiredness. There are many subtypes, but the two main include Hodgkin's lymphomas (HL) and the non-Hodgkin lymphomas (NHL) (Shankland et al., 2012). In strict sense, lymphomas refer to neoplasms of lymphatic tissues. Lymphomas and leukemia's are hematopoietic and lymphoid

tissue tumors, and as lymph proliferative disorders, both of these are closely related, to the extent that these are unitary disease entities that can be termed by either name (for example adult T-cell leukemia/lymphoma) (Dorland et al., 2011). Lymphomas can be indolent (small lymphocytic lymphoma), or aggressive (Burkitt's lymphoma), which cause speedy deterioration and ultimately death. It is noticeable that most aggressive lymphomas can be curable and respond well to treatment. The prognosis however depends on timely diagnosis of the disease, moreover treatment also varies in

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case of Hodgkin's and the non-Hodgkin lymphomas. Lymphomas are curable during in early stages with modern treatment (Sweetenham et al., 2009).

Non-Hodgkin lymphoma (NHL) are blood cancers that involves all lymphoma types except the Hodgkin lymphomas. Symptoms are mostly the same as generalized lymphoma along with pain in bones and chest or itchiness. The condition may be slow or fast progressing. Non-Hodgkin lymphomas (NHLs) are cancer of B, T or natural killer lymphocytes. Follicular and diffuse large B-cell (DLBCL) lymphomas are the common types that together cover 60% of B-cell NHL in North America each year. FL is an indolent incurable disease described by clinical and genetic heterogeneity (Morin et al., 2011). Treatment can be via radiations, targeted immunotherapy, stem cell transplantation, surgery or vigilant monitoring. If there is thickness of blood due to antibodies plasmapheresis can be done. Chemo increases the chances of cancers, heart diseases or nerve harms over the time span (White et al., 2016). DLBCL represents the common type of lymphoma and comprises 30% of all cases. CNS lymphoma, Burkitt's lymphoma, Cutaneous T-cell lymphomas, Follicular lymphoma, Mantle cell lymphoma, and AIDS-related lymphoma (Sarkozy et al., 2013). It can happen at any age, with median life span of 70; probability increases with age, 0.09%-0.13% before 29 years of age to 1.4%-1.77% after the age of 70 in women and men, respectively (Winkelmann et al., 2015). An underlying immunodeficiency is a critical sign for disease progression. Infections caused by the Epstein-Barr virus, Kaposi's sarcoma-associated herpes, human immunodeficiency virus, and the *Helicobacter pylori* are also found associated with certain types of diffuse large B-cell lymphoma (Sukswai et al., 2019).

Current treatment of MLL2 includes rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone (R-CHOP regimen). This regimen responds well in elderly DLBCL patients. R-CHOP is a combination of rituximab (one monoclonal antibody), cyclophosphamide, doxorubicin, vincristine (chemotherapy agents), and prednisone (steroid) given multiple times over a period of months intravenously. Patients usually take chemotherapy via PICC (peripherally inserted central catheter) line in their arm near the elbow or a surgically implanted venous access port. Recent treatment approach includes getting a PET scan afterwards the accomplishment of two chemotherapy cycles. Young people tolerate therapy better than old people, therefore low regimen therapy approach has been used in this age people (Pasqualucci et al., 2011).

Mixed lineage leukemia gene 2 (MLL2) is a novel mutation gene in diffuse large B cell lymphoma (DLBCL). In the result of over expression of MLL2 protein resulting Diffuse Large B-cell Lymphoma cancer is caused. Over expression of

MLL2 protein must be overcome to inhibit occurrence of diffuse large b-cell lymphoma. Very little work has been done on regulation of over expression of this protein until now. This study focuses to identify an effective and efficient inhibitors against the targets i.e. (SET Domain of MLL2) for the treatment of Non-Hodgkin's Diffuse Large B-cell Lymphoma using computer aided drug designing.

Materials and Methods

The investigation included Protein Structure Retrieval, Ligands Retrieval, Pharmacophore Generation, Virtual Screening, and Docking analysis for the identification of Lead molecule against MLL2 protein.

Protein Sequence and Structure Retrieval

Sequence of MLL2 protein was retrieved from Uniprot. 3D structure of MLL2 protein was not available. The SET domain of MLL2 protein act as its active site and involved in the synthesis of Methyltransferase 2D enzyme which gives the over expressions in the Non-Hodgkin Diffuse Large B-cell Lymphoma cancer. Sequence of SET Domain (SET is derived [Su(var)3-9, Enhancer-of-zeste and Trithorax], was retrieved from Pfam (Zhang et al., 2015), (URL: <https://pfam.xfam.org/>).

3D structure of SET Domain was retrieved from PDB having PDB id 4z4p with 5537 residues, and 2.2 Å resolution. It was a complex structure with two ligands ZN and SAH. By using chimera SET domain was separated from complex structure by using Chimera. Sequence length is 105 residues and Protein pdbqt file was obtained by removing water and adding polar hydrogen's, Kollman and Gasteiger Charges by using Chimera and AutoDock Vina. Binding Site of MLL2 protein is SET Domain.

Physical and Chemical Properties of SET Domain

Using ProtParam, the chemical physical and chemical properties of our Target SET Domain of MLL2 Protein were taken. These parameters consider molecular weight, theoretical PI, atomic and amino acid composition, extinction coefficient, estimated half-life, instability and aliphatic index and grand average of hydropathicity (GRAVY) etc.

Removal of all Non-standard residues from complex structure

Through UCSF Chimera tool, we removed all non-standard residues from our SET Domain of MLL2 protein complex structure (Berman et al., 2007).

Selection of compounds and docking approach

Compounds used for docking purposes were retrieved from PubChem in .sdf format. OpenBabel software was used to convert .sdf format to .pdb format (Pettersen et al., 2004).

DruLito and Data Warrior were used to check the physical and chemical properties of ligands (Pangastuti et al., 2016). Data Warrior support synthetic and medicinal chemistry and various methods to visualize chemical space and activity cliffs (Sander et al., 2015).

AutoDock Vina was used to convert the receptor and compounds into pdbqt format and the grid box was used to define the binding site. The purpose of docking was to identify the binding pattern and to find the binding energies (Trott & Olson, 2010).

Ligands Structure

Total 33 different chemical compounds were considered as ligands considering their biological activities. 3D chemical structures were generated from PubChem by using Open Babel. AutoDock Vina was used for the preparation of inhibitors molecules. All in silico calculations (MW, HBD, HBA, LogP, PSA, rotatable bonds, rings, Blood Brain Barrier, AMES Toxicity etc.) were performed by using DruLito, and Data Warrior.

Docking Analysis

Docking results were taken for each compound and receptor protein active site SET Domain with their binding affinities using AutoDock Vina. Docking of the protein ligand complex was primarily targeted on the predicted active site. These compounds were observed for binding energies and top 5 were selected. Pymol and Ligplot were used to see interactions of receptor and inhibitor and the binding sites of target protein. These interactions were analyzed by using Chimera.

Molecular Docking of Selected Compounds

AutoDock Vina showed two orders of magnitude improvement and used the empirical scoring function to calculate the binding affinity between protein and molecules/inhibitors (Truhlar et al., 2009).

Zinc Compounds Retrieval from Zinc Database

The ZINC database gives 3D molecules in many formats compatible to most docking programs (Irwin & Shoichet, 2005).

Lead Identification

All known hits of pharmacophore supported virtual screening were grouped by pharmacophore-fit score and top 10 were chosen. These were docked with receptor and observed for binding energies and ligand interactions with protein in AutoDock Vina and Ligplot respectively. The drug likeness prediction of all selected compounds was carried out by Lipinski filter. Moreover, the properties of ligand like toxicity and Drug likeness were analysed by DruLito which

is reported as a useful tool in calculating important drug like descriptors. Data Warrior was utilized for predicting lead likeness score. The compound with least binding affinity and high lead likeness was selected as potential inhibitor of SET Domain.

Results

Protein Sequence and structure

The SET Domain of MLL2 Protein was used and retrieved the sequence of SET Domain from Pfam Database Which is given below:

[GLGLYAAKDLEKHTMVIEYIGTIIRNEVANRREKIYE
EQNRGIYMFRIINNEHVIDATLTGGPARYINHSCAPNC
VAEVVTFDKEDKIIIISSRRIPKGEELTYDYQ].

SET domain was a complex structure with two ligands ZN and SAH. Structure of SET Domain has shown in Fig 1. The chemical and physical properties of SET Domain found are presented. PDB Structure Properties include PDB ID 4z4p, Residues 161, Sheets 5, Beta hairpin 4, Beta bulges 2, Strands 12, Helices 3, Helix-helix interaction 1, Beta turns 13, Gamma turns 4. The formula C₅₃₉H₈₅₇N₁₅₁O₁₆₄S₄, having molecular weight 2204.89, with 1715 atoms and 106 amino acids.

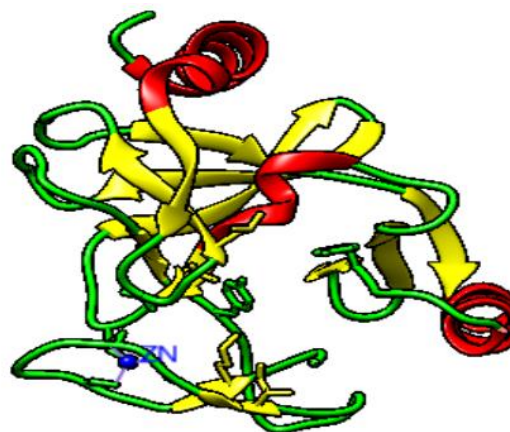


Figure 1. Structure of SET Domain

Selection of compounds and docking approach

Compounds shown were downloaded from PubChem and were saved in .sdf format. All these compounds were chosen in accordance to Lipinski Rule of Five. The 3D chemical structures and their molecular weight are shown in Table 1.

Molecular Properties Toxicity and Drug likeness Prediction

All compounds were passed through the filtering process by Lipinski Filter using DruLito and Data Warrior. Among 20

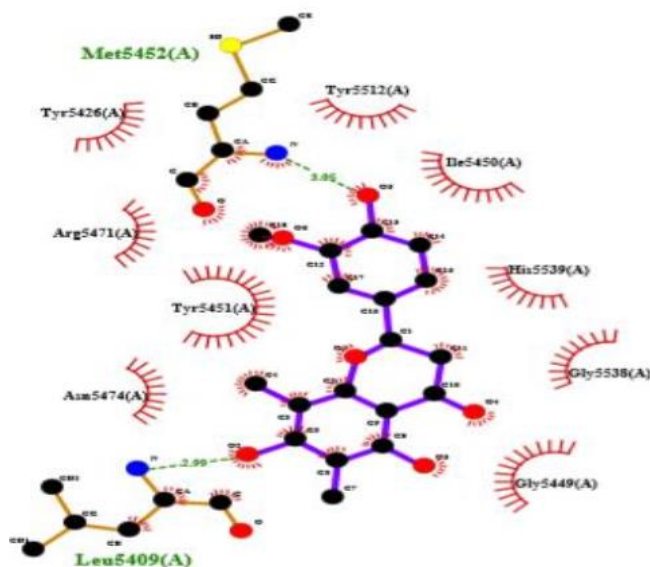


Figure 2. ZINC000014727443 interaction with MLL2 protein SET Domain

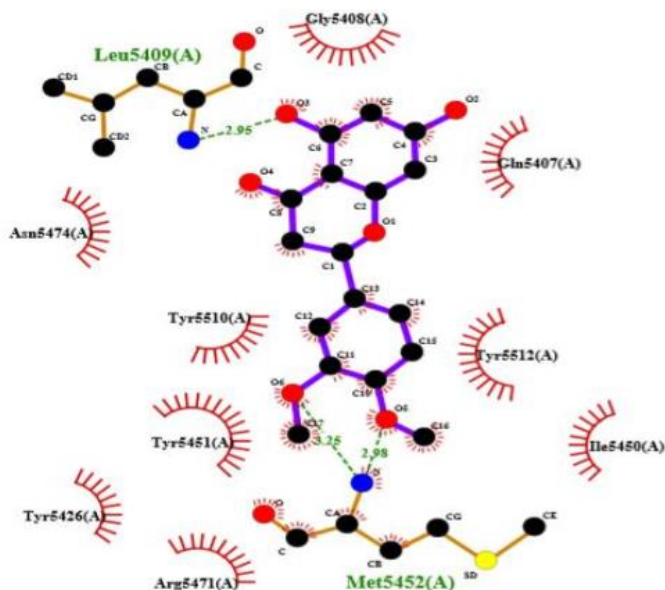


Figure 3. ZINC000014728328 interaction with MLL2 protein SET Domain

compounds, 13 were unsuccessful during Lipinski filtering (such as Molecular Weight>500, logP>5, H-Bond Donors>5, H-Bond acceptors>10) or found toxic. Out of 20 compounds, 7 compounds were found fulfilling all the parameters. These screened compounds were studied for physical, chemical and pharmacological information. 11 novel compounds were selected for Pharmacophore 2D chemical structures of novel compounds were retrieved via Zinc Database (table). According to DRUGLIKENESS profile

ZINC000014728328 AND ZINC000014727443 was recognized as an ideal molecule with drug likeness value of 0.44477 and their Toxicity and Drug Likeness properties are shown (Table 2). Molecular docking of SET Domain of MLL2 Protein with chosen compounds was carried out via AutoDock Vina. Ligands with the least binding energies were identified via docking. These docking complexes were pictured by LIGPLOT and protein ligands interactions were analyzed.

Table 1. Ligands ID’s, and Molecular Weight

Sr. No.	Ligands ID's	Molecular Weight (g/mol)
1	CID_25150897	490.31
2	CID_12310053	162.14
3	CID_5281794	276.17
4	CID_5281672	318.04
5	CID_5281654	316.06
6	CID_5281616	270.05
7	CID_5281607	254.06
8	CID_5280961	286.05
9	CID_5280934	278.22
10	CID_5280863	286.05
11	CID_5280805	610.15
12	CID_5280445	286.05
13	CID_5280443	270.05
14	CID_5280343	302.04
15	CID_73202	272.07
16	CID_68071	256.07
17	CID_65064	458.08
18	CID_31211	194.09
19	CID_10281	164.08
20	CID_9064	290.08

Lead Identification

Two ZINC compounds were selected as Lead compounds their interactions with target Protein have shown in Figure 2 and 3.
Among all the 20 chemical compounds from literature and databases, some were according to the requirements of DRUGLIKENESS, Lipinski Rule of Five (ROF) and Binding Energies, but they have some adverse side effects, which pose an obstacle in the treatment of DLBCL. Therefore,

ZINC000014728328 AND ZINC000014727443 novel compound with least Binding Affinity with higher drug likeness score may be considered as potential drugs against MLL2 protein SET Domain and DLBCL.

Table 2. Toxicity and Drug-Likeness Properties of Novel Compounds

Drug	ZIN C000 22 5461 314	ZIN C 0000 14643 344	ZINC 0000 1472 7443	ZINC00 00 147283 28	ZIN C 0000 14762 699	ZINC 0000 14811 473	ZINC 0000 1498 4519	ZINC 0000 1704 4428	ZINC0 000 59587 549	ZINC 0000 9509 9374	ZINC00 0 2254613 14
H-Acceptors	7	6	6	10	10	8	6	6	6	7	5
H-Donors	4	2	4	5	5	3	3	2	3	5	3
Total Surface Area	316.5 8	239.67	325.4 4	331.3	331.3	245.5 5	277.8 3	230.7 5	239.36	204.0 2	250.34
Drug likeness	- 13.93 1	- 0.1138 7	0.496 21	0.22481	0.224 81	0.026 795	- 0.167 37	- 0.078 3	- 0.0876 82	0.444 77	0.00857 23
LE fro m Structure No	0.385 84	0.4972 5	0.377 17	0.32917	0.325 37	0.451 18	0.414 35	0.482 96	0.4599 1	0.498 87	0.38994
Mutageni c	None	high	none	None	None	None	none	None	none	none	None
Tumorige nic	None	none	none	None	None	None	none	None	none	none	None
Reproduct ive Effective	None	none	none	None	None	None	none	None	none	none	High
Binding Affinity	-8.4	-8.5	-8.4	-7.8	-8.6	-8.6	-8.4	-8.4	-8.4	-8.7	-9.1
MW	411.9 6	311.97	395.9 7	459.95	459.9 5	331.9 6	347.9 7	299.9 7	311.97	291.9 6	355.97
LogP	1.998	2.724	4.468	0.855	0.855	2.045	2.653	1.351	1.392	0.374	0.913
TPSA	35.53	44.76	26.3	53.99	53.99	53.99	35.53	44.76	35.53	26.3	26.3
HB	2	3	1	1	2	2	2	3	2	0	1
Total Molecules	36	33	44	39	29	40	40	34	31	23	29

Discussion

Diffuse large B-cell Lymphoma is a cancer of B cells, which is the most common type of non-Hodgkin lymphoma among adults. Most of these cells are centroblastic, and are medium to large sized lymphocytes with minimal cytoplasm. Oval to round nuclei having fine chromatin can be clearly seen, with 2 to 4 nucleoli in each nucleus. The tumor can be monomorphic too, composed merely of centroblasts. But most cases are polymorphic, having centroblasts and immunoblasts. Immunoblasts possess central nucleolus and a basophilic cytoplasm. The tumor can be called as immunoblastic, if more than 90% cells are immunoblasts (Sarkozy & Coiffier, 2013).

Bioinformatics employed *in silico* analysis of biological problems with the use of statistical and mathematical approaches. Computer Aided Drug Designing (CADD) is a promising technique to design effective medications to target a specific protein. Drug is a small molecule that may inhibit or activate a biological molecule. In the current study, different *in silico* techniques were used for designing new inhibitors against MLL2 SET Domain. Ligand base pharmacophore modelling of drugs is considered as an effective tool in rational drug design. Here, a diverse set of drugs was retrieved by pharmacophore model generation (Zhang et al., 2015).

The *KMT2D* gene (MLL2) gives message for producing enzyme lysine-specific methyltransferase 2D, found in organs/tissues of the body. Lysine specific methyltransferase 2D works as a histone methyltransferase, which modify histone proteins. Histone proteins attach to DNA and shape the chromosomes. Adding methyl group to histones, histone methyltransferase regulates certain genes that are important for development. Over expression of histone methyltransferase 2D cause Diffuse Large B-cell Lymphoma cancer (Morin et al., 2011). These reported compounds were used to build a merge pharmacophore model for virtual screening of novel compounds. The highest ranked hits from screened library were elucidated with highest binding affinities. After the docking analysis two compounds were selected based on least Binding Affinity and best interactions. The current research gave reliable results of selected docked compounds against MLL2 SET Domain.

33 Compounds were retrieved from PubChem in .sdf format. PubChem is an open chemistry database for 3D and 2D structures retrievals of compounds, that's why we used this database (Kim et al., 2015). OpenBabel software was used to convert those .sdf format to .pdb and .pdbqt format. It gives best and quick results that's why we used this software tool for file conversion (O'Boyle et al., 2011). After conversion of compounds into .pdb and .pdbqt formats. We used AutoDock Vina tool to make a grid of our target SET Domain. After that command based molecular docking was

performed. Docking can be done by sampling conformations of the ligand at the protein active site; then rating conformations via a scoring function. AutoDock Vina was used to convert the receptor and compounds into .pdbqt format and the grid box was used to define the binding site. The purpose of docking was to identify the binding pattern and to find the binding energies. AutoDock Vina tool gives accurate and best results in docking without any difficulty that's why we used this tool for docking purpose (Trott & Olson, 2010).

After docking of compounds, we selected all the .sdf files of those compounds and then converted those into one .sdf complex file using OpenBabel software. DruLito and Data Warrior were used to check the physical and chemical properties of ligands. We added that complex .sdf file into first Data Warrior and then DruLito (Pangastuti et al., 2016). So, both tools were used to calculate the molecular and chemical properties of selected compounds. According to Lipinski's rule of five, following conditions should not be violated: $\text{LogP} < 5$, $\text{MW} < 500$, $\text{H-Bond Acceptors} < 10$, $\text{H-Bond Donors} < 5$. LogP i.e. lipophilicity measurement, is the solubility ratio of compounds in octanol as compared to water. The observations showed that novel compound have LogP values with minor differences. Toxicity risk assessment and carcinogenicity was implemented for the chosen drugs and novel compounds and gave the results that all compounds were non-carcinogens (Sander et al., 2015). Data Warrior and DruLito gives the drug likeness properties and all other requirements which are necessary for drug discovery and easy to use. That's why we used these tools. LigPlot was used to see the Hydrogen and Hydrophobic bonds interactions between Ligand and protein (Wallace et al., 1995). After knowing the Drug likeness and other properties of compounds total 9 compounds were selected that were not violating the ROF and other rules were. After that those 9 compounds were used in the pharmacophore generation. LigandScout tool was used in pharmacophore generation. LigPlot is a best tool that gives the clear and best visualization of Hydrogen and hydrophobic interactions between receptor and ligands (Sander et al., 2015). Top 5 selected inhibitors were subjected to create a pharmacophore model. The results of the pharmacophore with matching structural features such as hydrogen bond donors and acceptors and aromatic rings. Red Colour: Acceptors, Yellow Colour: Hydrophobic Bond and Green Colour: Donor.

Total 70 Zinc compounds were selected from Zinc Database after pharmacophore generation. Zinc database is a free available database which gives Zinc natural compounds their predicted structures and their physical and chemical properties (Irwin et al., 2005). All these 70 compounds .sdf and mol files downloaded from Zinc database. Again these .sdf files converted into .pdb and .pdbqt formats through OpenBabel software. Again command based docking were

performed on these 70 Zinc Compounds. Total 11 zinc compounds were selected. From these 11 novel compounds two compounds were selected as lead compounds. The docking studies implied that ligands molecules must have high binding affinities and least binding energies and it must fulfil the drug like parameters. Drug likeness score of all the selected and novel compounds was compared with the intent to get the better results. After satisfying all the parameters i.e. Drug-Likeness, Toxicity, Binding Affinity, it is observed that novel compounds are potent inhibitors and have the tendency to be a good candidate molecule and provide reliable results. selected novel compounds i.e. ZINC000014728328(Persicogenin) and ZINC000014727443(Cerasinone) were selected on the bases of Binding scores and Druglikeness properties.

Persicogenin, also known as persicoside, are organic compounds named as flavonoid o-glycosides, which possess a carbohydrate moiety O-glycosidically attached to the 2-phenylchromen-4-one flavonoid backbone. Thus, persiconin is thought to be a flavonoid lipid molecule. Persiconin is found in foods like some fruits, peaches, and prunus (cherry, plum). It is a biomarker for the intake of these foods. Cerasinone is an organic compound named as 5-O-methylated flavonoids. Flavonoids, along with methoxy groups linked to the C5 atom of their backbone. Cerasinone is therefore known to be a flavonoid lipid molecule. Cerasinone is found in fruits and sour cherries. This makes cerasinone a biomarker for the intake of these foods.

Conclusion

In this study the novel compounds namely i.e. ZINC000014728328(Persicogenin) and ZINC000014727443(Cerasinone) are found possibly effective against non-Hodgkin DLBCL and can be a good treatment choice. The Lead compounds (ZINC000014728328 and ZINC000014727443) were chosen via Docking and Toxicity and on the basis of Drug Likeness properties and it was found that they can be proceeded for analysis and drug development. They can be subjected to Molecular Dynamics Simulation to know a real time behaviour system. Thus, ZINC000014728328 and ZINC000014727443 could attach the active site of MLL2 SET domain for inhibiting its deregulated expression.

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Conflict of Interest

The authors declare no conflict of interest.

Authors' Contribution

Conceptualization, M. Asif Rasheed; Writing-original draft preparation, Urooj Fatima; Writing—review and editing, Farrukh Jamil and M. Ibrahim; supervision, M. Asif Rasheed. All authors have read and agreed to the published version of the manuscript.

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