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Original Article

In-Silico studies of Novel 4, 6-diphenylpyrimidine substituted Benzamide derivatives on HDAC enzymes

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ABSTRACT

The present study attempts to investigate the 4,6-diphenylpyrimidine substituted benzamide derivatives that act as HDAC inhibitors. Histone deacetylases (HDACs) have been widely recognized as promising targets for cancer treatment. It has been three decades ago, that the first potent Zn2+ dependent histone deacetylase inhibitor was recognized. Meanwhile, to date, SAHA (Vorinostat), Belinostat (PXD-101), Panobinostat (LBH-589), and Romidepsin (FK-228) four HDAC inhibitors have been approved by FDA for cancer chemotherapy, while more than 10 HDAC inhibitors have entered in clinical trials for the development of therapeutic agents for oncological as well as other medical indications. Beyond this, the clinical utility of HDAC inhibitors is a major obstacle to intrinsic drug resistance and various side effects including thrombocytopenia, neutropenia, nausea, fatigue, and vomiting. So, discovering a novel potential scaffold is still in great demand. Distinctive features of HDAC inhibitors include a Zn2+ binding moiety, a carbon linker, and a capping group. To better understand the structural requirements of HDAC inhibitors, a small molecule with cap group as substituted 4,6-diphenylpyrimidine of functional groups adjacent to the metal-binding benzamide was designed in our study to improve pharmacokinetic parameters and to reduce adverse effects through in silico studies.

***Keywords:** HDAC enzyme, HDAC inhibitor, Benzamide, 4, 6-diphenylpyrimidine.*

INTRODUCTION

Histone deacetylase inhibitors (HDACi) have revealed great efficacy as cancer therapeutics by blocking cell proliferation, programmed cell death, cellular differentiation, and inhibition of angiogenesis and cell migration. Based on the structural feature of HDACi, a great number of molecules have been demonstrating HDAC inhibitory activity, through mechanisms clarified by crystallographic studies of inhibitors- HDAC enzyme. Despite the structural diversity of HDACi, several features are common to most of the known HDAC inhibitors, including a functional group capable of binding a Zn+2 ion present in the active sites of HDAC enzymes. Even after a lot of research efforts, only four molecules have been approved by US Food and Drug Administration for cancer treatment. Suberoylanilide hydroxamic acid SAHA)/ Vorinostat (Zolinza) for the treatment of refractory and relapsed Cutaneous T-cell lymphoma (CTCL) was approved in 2006 [1]. This further increased curiosity of the researchers and led to the discovery of cyclic tetrapeptide HDACI, FK228/Romidepsin was approved for CTCL treatment. Followed by PDX101/1 Belinostat (Beleodaq) and LBH589/Panobinostat (Farydak) were approved for the treatment of peripheral T-cell lymphoma (PTCL) and multiple myeloma, respectively. However, the current HDAC inhibitors have several limitations which include their ineffectiveness at micro or Nano concentrations in solid tumors and cardiac toxicity that limits their further clinical progress. Although classic HDAC inhibitors have both advantages and disadvantages, enormous efforts have been made for the next generation of HDACi with high selectivity, potency, and efficacy. Consequently, none of the molecules have gained access to clinical trials. Hence, several HDAC inhibitors are being

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explored for developing novel anticancer drugs. To address this clinical need, we designed a series of new HDACi with 4, 6-diphenylprimdine scaffold as cap and benzamide as zinc-binding group respectively.

Mechanism of action of HDAC inhibitor

There are two primary molecular mechanisms for epigenetic processes: DNA methylation and post-translational histone modifications. In epigenetic therapy, cancer is treated by targeting these epigenetic pathways. The basic concept of this therapy is to pharmacologically relieve the effects of DNA methylation and chromatin remodeling in malignant cells. Based on this, two classes of epigenetic drugs i.e. DNA methylation inhibitors and HDAC inhibitors (HDIs) have been approved by US FDA for the effective treatment of cancer. [2]

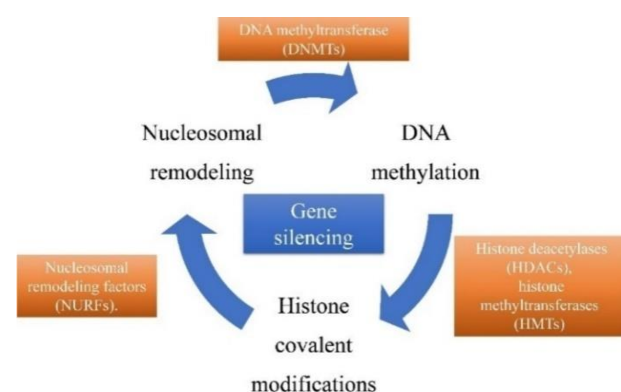

Fig. 1: General aspects of HDAC inhibitors

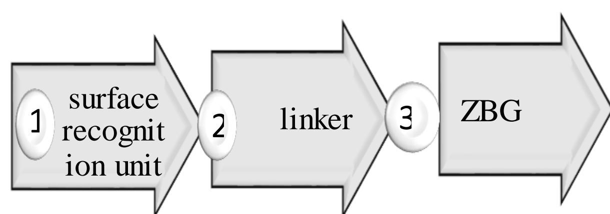

Fig. 2: Structural requirements for HDAC inhibitors

Gene expression is regulated by one of the unique mechanism stermedpost-translational modifications of lysine residues of histone protein. Among these, Histone deacetylation plays important role in gene expression and regulation. Hence, HDAC enzymes might be considered a valid target for cancer chemotherapeutics. HDAC inhibitors are one of the most influential anticancer agents; indeed, many researchers have shown immense attention to developing these drugs and many small molecule drugs are being investigated as novel HDAC inhibitors. There are several structural classes of HDAC inhibitors that have been taken under clinical trials for different cancer forms by highlighting the structural features of different classes of HDAC inhibitors including hydroxamic acids, benzamide, short-chain fatty acids and, macrocyclicpeptides. From the docking study of HDAC, a conclusion was drawn that these Zn+2 dependent HDAC inhibitors should possess three pharmacophore motifs, (i) A cap group or surface recognition unit usually a hydrophobic or aromatic group interacting with the peripheral binding site adjacent to metalion; (ii)a linker or spacer which is saturated or unsaturated with linear or cyclic.

The structure that connects the surface recognition group and Zn+2 ion group; (iii) a Zn+2 binding group ZBG (hydroxamic acid, benzamide, carboxylic acid groups), that chelate the Zn+2 ion by coordination bond formation with active sites (Figure 2).

Fundamentally, HDAC inhibitors can be non-selective HDAC inhibitors can be non-selective HDAC inhibitors (pan-HDAC inhibitors) [3, 4].

METHODS

Scheme: synthesis of 4, 6-diphenylpyrimidine substituted benzamide derivatives

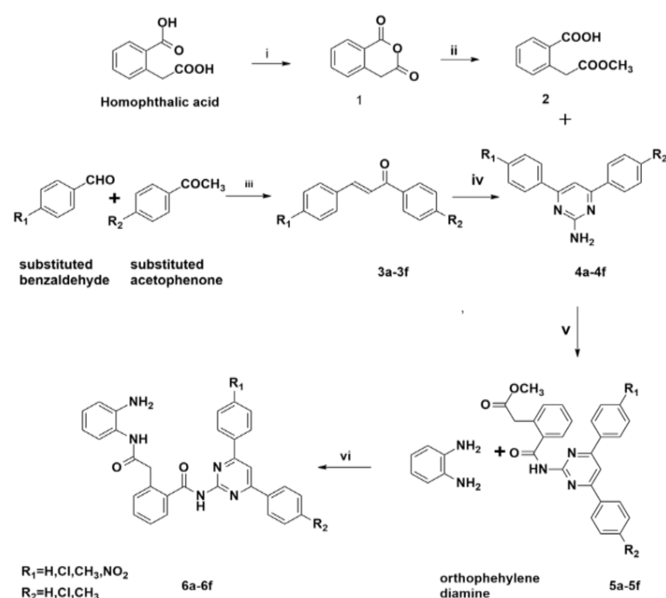

Fig 3: Scheme synthesis of 4, 6-diphenylpyrimidine substituted benzamide derivatives

I: Acetic anhydride, Reflux 2hours. II: Methanol, Acidic conditions, Reflux 2hours. III: Ethanol, 40% NaOH, 0oC, Stirring. IV: Guanidine, DMF, Reflux 7hours, 50-60oC. V: HATU, DMF, Dipea. VI: DCM, TBD, Ethanol.

Our study includes insilico studies of 2-(2-((2-aminophenyl) amino)-2-oxoethyl)-N-(4, 6-diphenylpyrimidin-2-yl) benzamide on HDAC enzyme. Where substituted 4, 6-diphenylpyrimidine act as Cap group, Benzamide group as Zinc-binding group and amide as a linker.

Structures of 4, 6-diphenylpyrimidine substituted benzamide derivatives performing Insilico studies on HDAC enzyme

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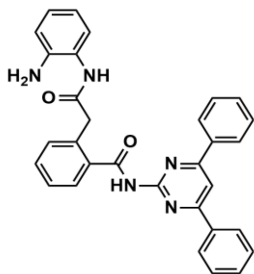


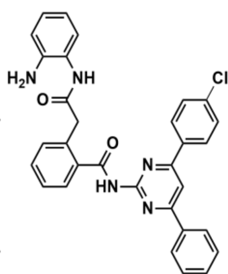
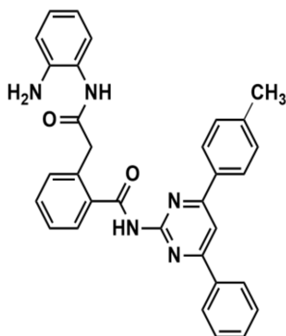


Fig. 4: Compound 6a **Fig. 5: Compound 6b**



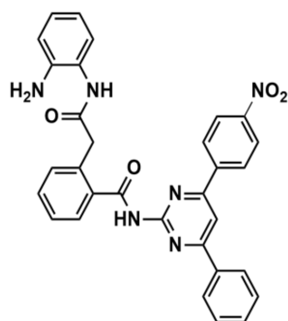


Fig. 6: Compound 6c **Fig. 7: Compound 6d**

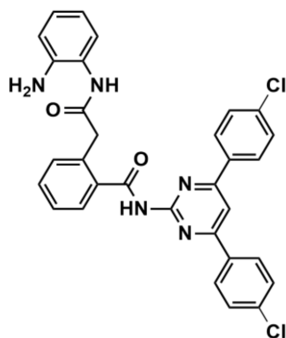


Fig. 8: Compound 6e

methods:

IN-SILICO STUDIES:

In-silico studies are the prediction of molecular docking (Autodock), Molecular property (Swiss ADME and Molinspiration), and ADMET (pre ADMET) studies by using computational methods. The designed derivatives were predicted by using various online and offline tools. Molecular docking was done for the test ligands with the active site of the HDAC enzyme and compared with the standard drug to examine the binding affinity as well as protein-ligand interactions. Molecular descriptors and Lipinski rule of five were computed from the Molinspiration online tool for test and standard compounds.

MOLECULAR PROPERTIES CALCULATION:

The molecular properties such as molecular weight, hydrogen bonds donors (HBD) and hydrogen bond acceptors (HBA), consensus log p, water-solubility, no of rotatable bonds, topologic surface area and no of bonds etc were calculated by using SWISS ADME and Molinspiration, these are online tools for the prediction of the molecular properties also prediction of pharmacokinetic studies. These predicted studies are used to identify the relationship between the molecular properties of tested compounds, which may or may not influence the docking or binding affinities. Also, identify the toxicities before the synthesis. The designed proposed molecules were saved in cdx or mol formats or smiles formats for further studies.

MOLECULAR DOCKING STUDIES:

Molecular docking is one of the important tools for structure-based drug design and predicting the activity of the series of compounds before synthesis. Molecular docking has become an increasingly important tool for drug discovery. Molecular docking is on the front line of computational biology and drug discovery. The prediction of structural and chemical information in recent years has rendered the use of efficient algorithms and large supercomputer facilities are of utmost importance in the drug discovery process. The molecular docking approach can be used to model the interaction between a small molecule (ligand or drug molecule) and a protein, enzyme, or neuro transmitter (macromolecule) at the atomic level, which allows us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes, is called molecular docking. There are many offline and online tools for molecular docking Autodock 4.2.6 SWISSDOCK Autodockvina 1-CLICK DOCK GOLD LUDI Flex IHAD DOCK etc.

Protein code of Subtype of HDAC with respective Expression of HDAC inhuman cancers. The molecular docking of proposed compounds is performed on 3max, 6csq, 3c0z, 1T64 and 6wbq proteins of a different subclass of HDAC isotypes. Each HDAC isotypes enzyme over expression leads to a specific type of cancer in the human body.

Pre ADMET studies: Pre ADMET studies are also called pharmacokinetic properties including BBB, Human intestinal absorption (HIA), Caco2 (colorectal adenocarcinoma cells), MDCK (Madin Darby Canine Kidney), Pgp inhibition, plasma protein binding (PPB), and the toxicological study involves carcinoma mouse and carcino rat, etc. By using the pre-ADMET online tool and also predicting the drug-likeness properties, Lipinski rules bioactivity on receptors, molecular properties are also calculated by this too.

Designed molecules were saved in mol formats, and copied that format in a note or word pad then paste or enter the textbox in the pre-ADMET server, run the ADME and toxicity to get the results.

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RESULTS AND DISCUSSION

MOLECULAR PROPERTY CALCULATIONS:

We used the Molinspiration Chemo informatics server to predict molecular descriptors that were used by Lipinski in formulating this rule of five which are lipophilicity (LogP), molecular weight (MW), number of hydrogen bond donors (HBD), and acceptors (HBA), number of non-rotatable bonds (NROTB).

The idea behind the consideration of molecular properties in this study is, to examine or identify the relationship between the molecular properties of the designed molecules. These findings could help in the further designing of novel agents in this study. The molecular weight of most of the compounds found was more than 500 Daltons except compound 6a and compound 6f. The numbers of rotatable bonds are found between 7-8 for the flexibility in the active site of the enzyme. Most of the compound's log P values are found more than 6 except compound 6a and compound 6d. HBD was 7-10, and HBA was 4 respectively. Most of all compounds violated 2 rules i.e., molecular weight and logo are greater than 500 Daltons and 6 respectively except compound 6a had passed all five rules of the Lipinski rule. Moreover, it is known that some of the properties may vary with the molecular structure and it may or may not influence the binding affinity of the molecule with an active site of the enzyme as well.

Table No. 1: Molecular Properties of proposed compounds

Compound code	Mass	HBD	HBA	TPSA	Milogp	No rotatable bonds
6a	499.57	7	4	110	5.62	7
6b	534.02	7	4	110	6.30	7
6c	513.60	7	4	110	6.07	7
6d	544.57	10	4	155.83	5.58	8
6e	568.46	7	4	110	6.98	7

MOLECULAR DOCKING STUDIES:

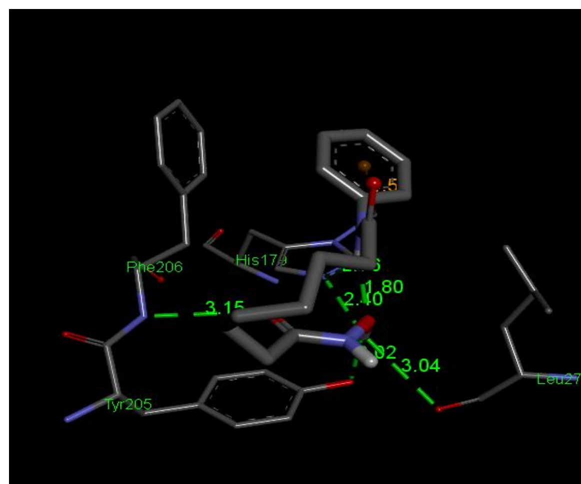
Molecular docking was employed to study the binding patterns of the designed novel 4,6-diphenyl pyrimidine derivatives with the appropriate target HDAC isoforms. The molecular docking of proposed compounds is performed on HDAC-2, HDAC-6, HDAC-7, HDAC-8 and HDAC-10 proteins of a different subclass of HDAC isotypes. Each HDAC isotype enzyme overexpression leads to specific types of cancers in the human body. So, to identify the selectivity of proposed compounds towards subtype of HDAC enzyme. Protein was downloaded from protein databank RCSB or selected from the select target in 1-click dock online docking server. To download and upload the target file for docking or select the target protein for docking. The co-crystallized inhibitor bound to the target proteins was removed. Further, the inhibitor was re-docked into the respective binding site of the protein. The docked (low energy) and co-crystallized conformations were further superimposed to check their conformational relevance. The current docking procedure followed in the present study, re-produced them conformation almost equal to the co-crystallized conformation of the ligands such as 6(a) to 6(f) for the target enzyme HDAC. The superimposed structures of test compounds 6(a) to 6(f) of docked and standard drug Vorinostat (SAHA) are respectively presented in figures (9 - 18).

Table No. 2: Binding Energies of Proposed Compounds with Subtypes HDAC Proteins

compounds	3max HDAC-2	6csq HDAC-6	3c0z HDAC-7	1T64 HDAC-8
6a	-7.32	-6.51	-7.91	-7.52
6b	-7.67	-7.81	-7.60	-7.74
6c	-8.57	-6.57	-7.77	-7.58
6d	-1.16	-7.27	-3.74	-7.24
6e	-7.59	-8.75	-7.61	-7.73
6f	-6.89	-7.66	-7.79	-7.73
SAHA	-8.08	-6.63	-6.86	-6.79

These results suggested that the current docking methodology is valid and could be used for the docking of designed molecules on the target protein. Later, all the designed molecules were docked with the target protein following the above-mentioned valid procedure. The binding affinity and interaction of each of the inhibitors were studied considering the least energy (least energy is the best affinity) conformation of the inhibitor. After completion of the docking, the docking results were collected from the appropriate visualization of poses from the discovery studio. The molecular binding energies of the proposed compounds revealed that it has a stronger binding with the active sites of the HDAC-2, HDAC-6, HDAC-7, HDAC-8, and HDAC-10 enzymes compared with the reference compound that is SAHA (vorinostat).

Interaction of SAHA with HDAC-2 protein



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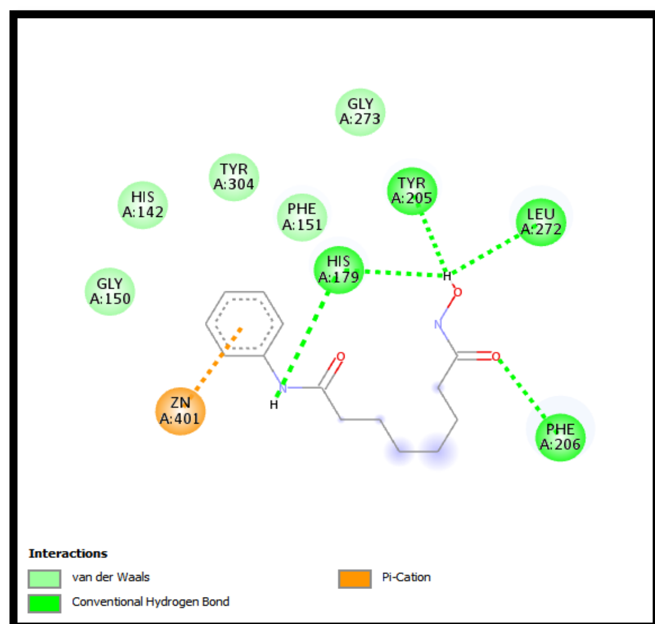
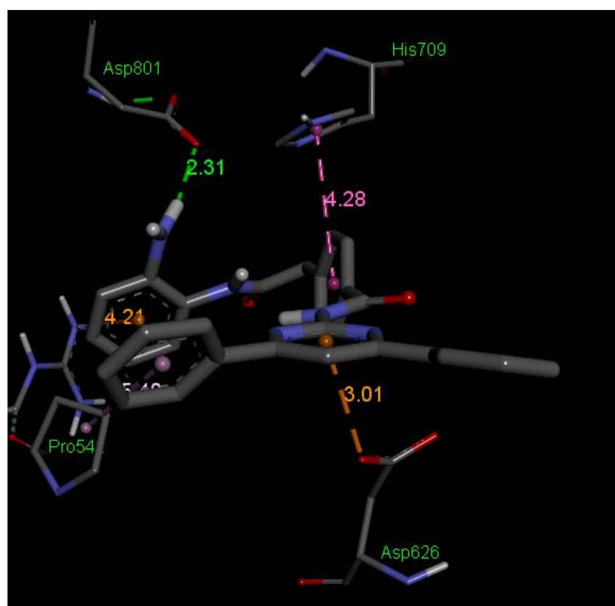


Fig. 9: 2D, 3D of Interaction of compound SAHA with HDAC-2 protein

The docking analysis of SAHA in the active site of HDAC-2 protein revealed that the binding energy is -8.08k.cal/mol. It forms the H-bond with HIS-179, TYR-205, LEU-272, PHE-206, Zn-401, GLY-273, PHE-151,TYR-304, HIS-142, and GLY-150. SAHA formed the H-bond with HIS-179, TYR-205, LEU-272, and PHE-206. The zinc-binding group that is hydroxamic acid hasan amine forming hydrogen bond with HIS-179, TYR-205, LEU-272, PHE-206, and cap group with HIS-179.

Interaction of compound 6c with HDAC-2 protein



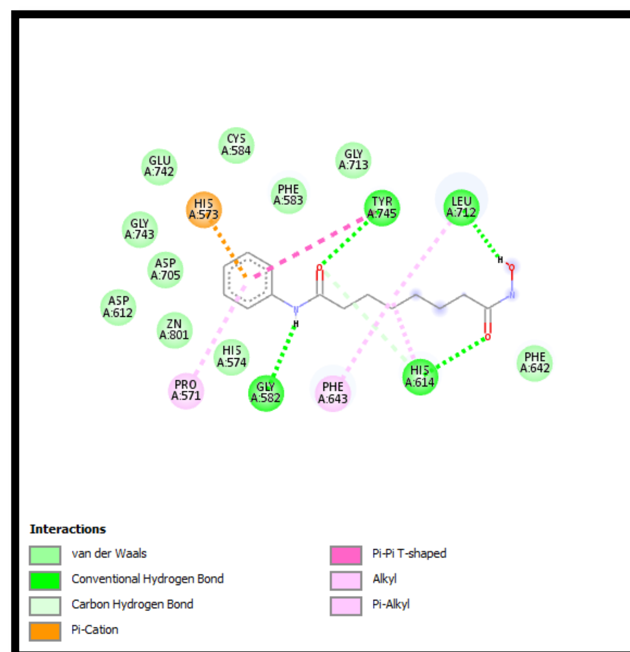
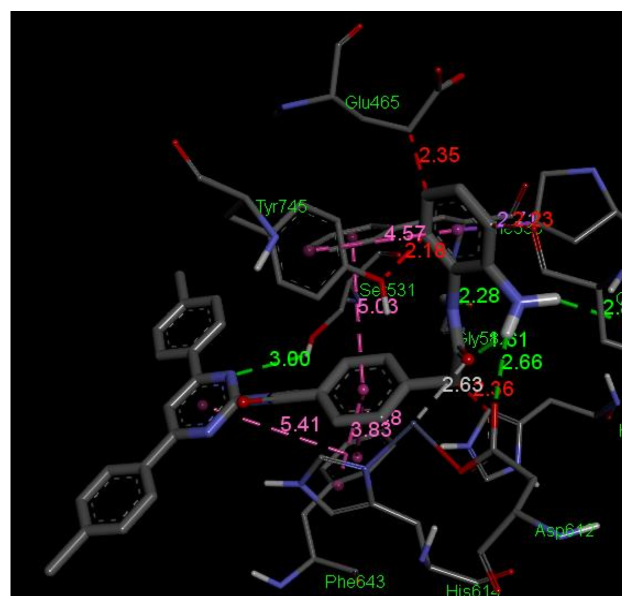


Fig. 10: 2D, 3D of Interaction of compound 6c with HDAC-2 protein

The docking analysis of compound 6c in the active site of HDAC-2 protein revealed that it has stronger binding at the active site, with binding energy is -8.57k.cal/mol. It formed the H-bond with ASP-269 and HIS-183. The main residues involved in the interaction within the active site are similar to standard drug SAHA and showed additionally interactions with GLY-302, ASP-265, HIS-141, CYS-101, GLU-99, ASN-96, GLY-95, VAL-97, SER-149. The zinc-binding group is benzamide having amine forming two hydrogen bonds with ASP-100 and ASN-96.

Interaction of SAHA with HDAC-6 protein.



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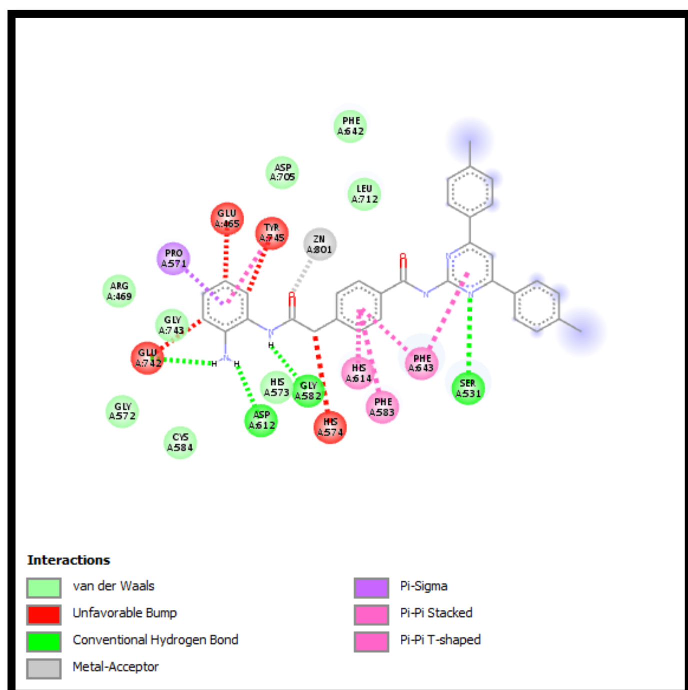
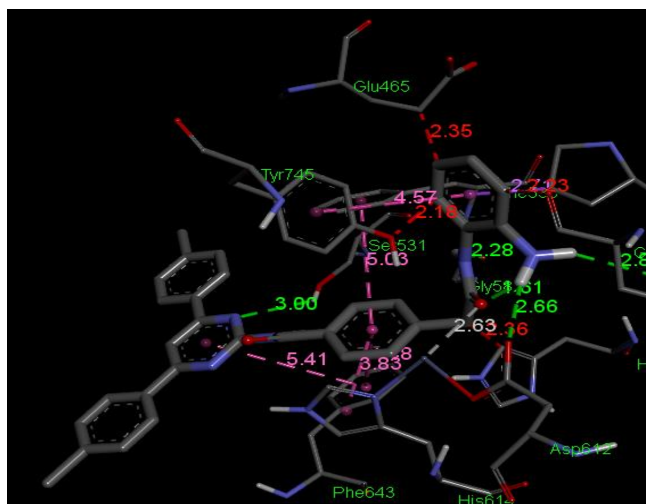


Fig. 11: 2D, 3D of Interaction of compound SAHA with HDAC-6 protein

The docking analysis of SAHA in the active site of HDAC-6 protein revealed that the binding energy is -6.63k.cal/mol. The main residues involved in the interaction within the active site GLU-742, GLY-743, ASP-705, ASP-612, ZN-801, PRO-571, HIS-574, GLY-582, PHE-643, HIS-614, PHE-642, LEU-712, TYR -745, GLY-713, PHE-583, CYS-584, HIS-573 amino acids. SAHA formed the H-bond with HIS-614, GLY-582, LEU-712, and TYR-745. The zinc-binding group i.e., hydroxamic acid of SAHA forms two H-bonds with HIS-614 and LEU-712.

Interaction of compound 6e with HDAC-6protein



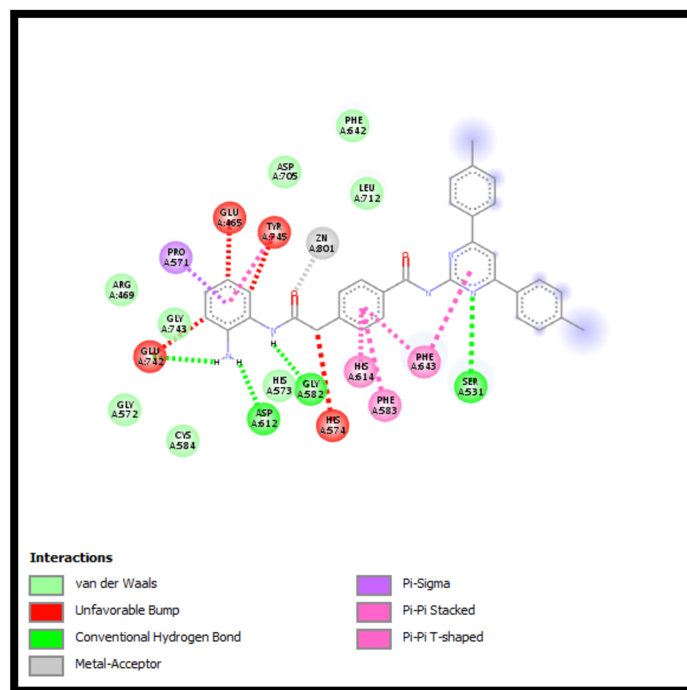


Fig. 12: 2D, 3D of Interaction of compound 6e with HDAC-6 protein

The docking analysis of compound 6e in the active site of HDAC-6 protein revealed that it has a stronger binding with the active site, with binding energy is -7.89 Kcal/mol. The main residues involved in the interaction within the active site are similar to standard drug SAHA and showed additional interactions with SER-531, GLU-465, and GLY-572. 6e compound forming the H-bond with GLY-582, ASP-612, and SER-531. The zinc-binding group i.e., benzamide of compound 6e forms one H-bond with GLY-582 and ASP-612, and the cap group of compound 6e forms one H-bond with SER-531 nitrogen of pyrimidine.

Interaction of SAHA with HDAC-7protein

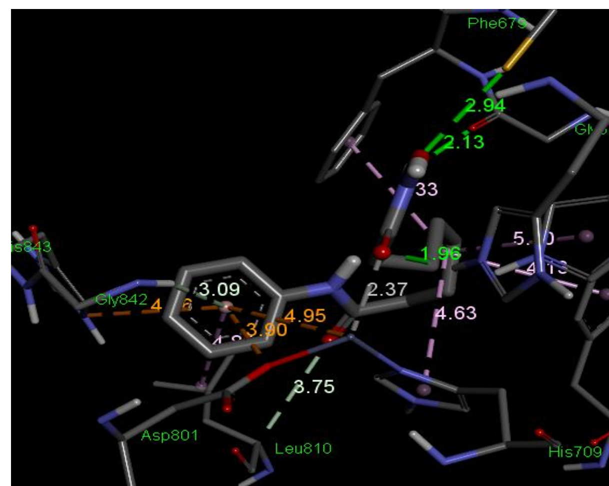


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Fig. 13: 2D, 3D of Interaction of compound SAHA with HDAC-7 protein

Fig. 14: 2D, 3D of Interaction of compound 6a with HDAC-7 protein

The docking analysis of SAHA in the active site of HDAC-7 protein revealed that the binding energy is -6.86k.cal/mol. The main residues involved in the interaction with the active site of GLU-840, GLY-678, ASP-707, ASP-801, ZN-101, PRO-542, HIS-669, GLY-841, PHE-679, HIS-670, PHE-738, LEU-810, GLY-668, CYS-680, HIS-709, HIS-806, GLY-842, HIS-843, PRO-667 amino acids. The zinc-binding group i.e., hydroxamic acid of SAHA interacts with HIS-668, GLY-678, and CYS-680.

Interaction of compound 6a with HDAC-7 protein

The docking analysis of compound 6a in the active site of HDAC-7 protein revealed that it has a stronger binding with the active site, with binding energy is -7.91k.cal/mol. The main residues involved in the interaction within the active site are similar to standard drug SAHA and showed additional interactions with GLU-543, THR-625, and ASP-626. The zinc-binding group i.e., benzamide of compound 6a forms one H-bond with ASP-801.

Interaction of SAHA with HDAC-8 protein

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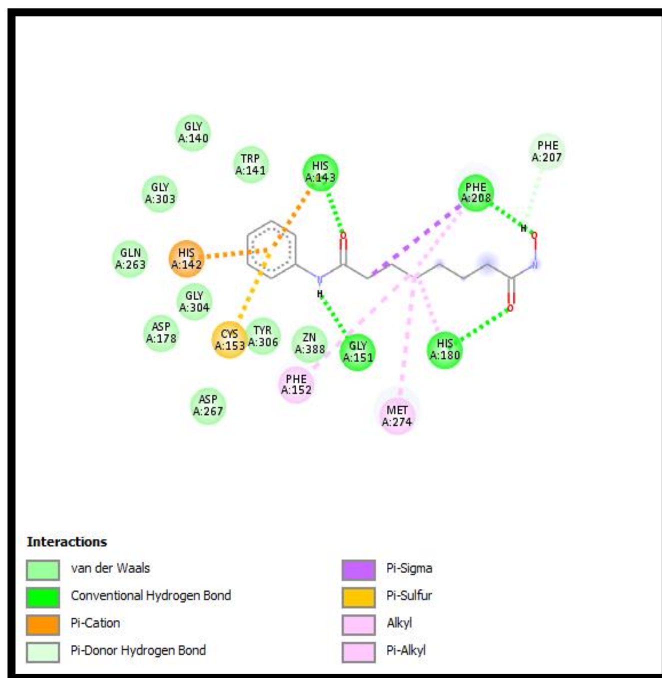
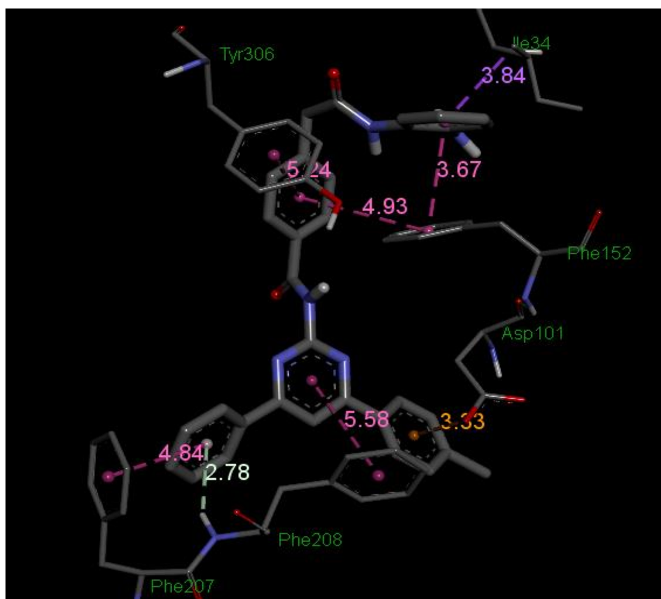


Fig. 15: 2D, 3D of Interaction of compound SAHA with HDAC-8 protein

The docking analysis of SAHA in the active site of HDAC-8 protein revealed that the binding energy is -6.79k.cal/mol. The main residues involved in the interaction within the active site are HIS-143, GLY-151, HIS-180, PHE-208, PHE-207, TRP-141, GLY-140, GLY-303, GLN-263, HIS-142, GLY-304, ASP-178, CYS-153, ASP-267, TYR-306, PHE-152, ZN-388, MET-274. The zinc-binding group i.e., hydroxamic acid of SAHA forms two H-bonds with HIS-180,PHE-208.and the linker group of SAHA forms H-bonds with HIS-143and GLY-151.

Interaction of compound 6b with HDAC-8protein



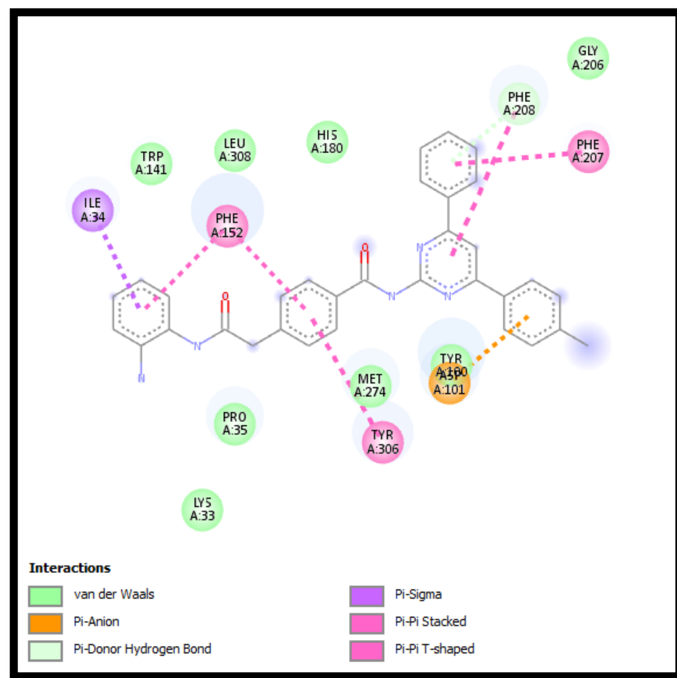
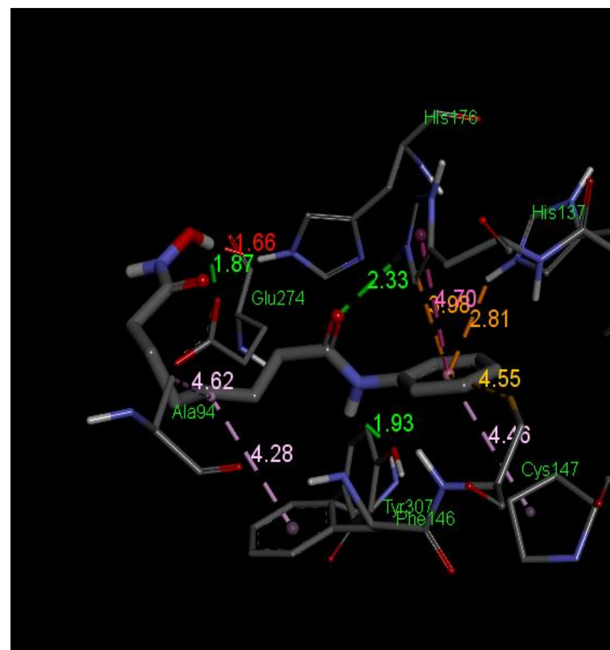


Fig. 16: 2D, 3D of Interaction of compound 6b with HDAC-8 protein

The docking analysis of compound 6b in the active site of HDAC-8 protein revealed that it has a stronger binding with the active site, with binding energy is -7.74k.cal/mol. The main residues involved in the interaction within the active site are similar to standard drug SAHA and showed additional interactions with GLY-206, ASP-101, LEU-308, ILE-34, PR0-35, and LYS-33. The compound 6a forms one H-bond with PHE-208.

Interaction of SAHA with HDAC-10 protein



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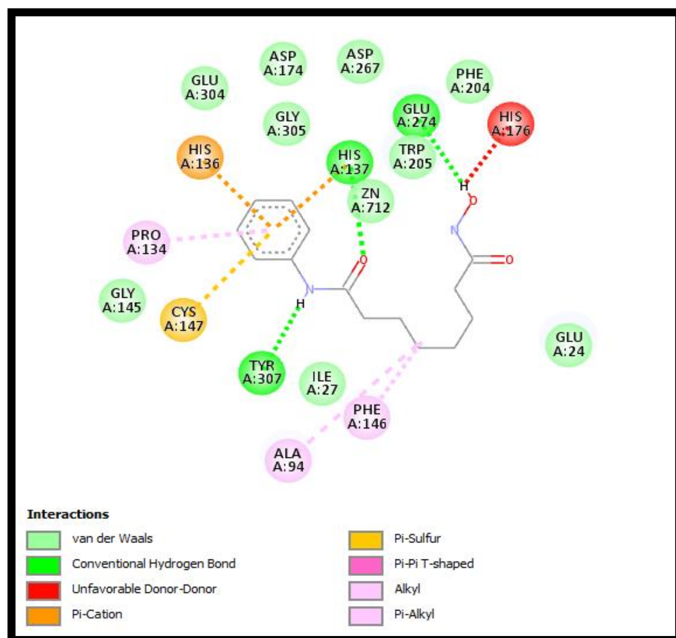


Fig. 17: 2D, 3D of Interaction of compound SAHA with HDAC-10 protein

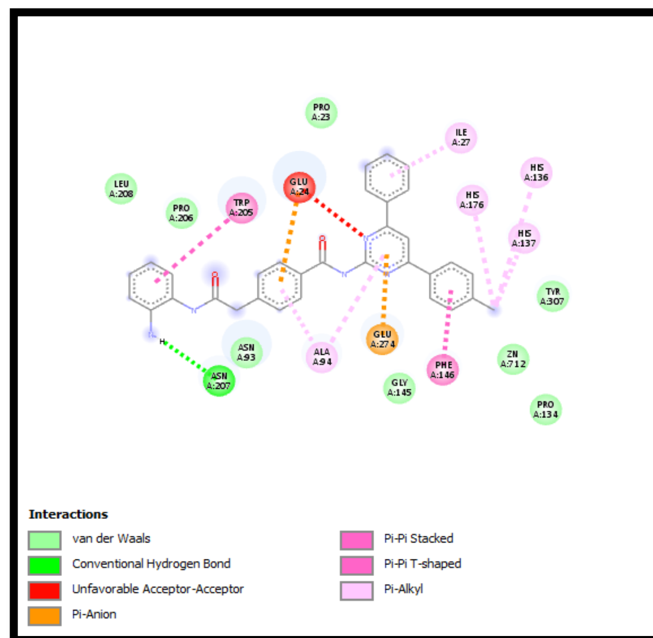
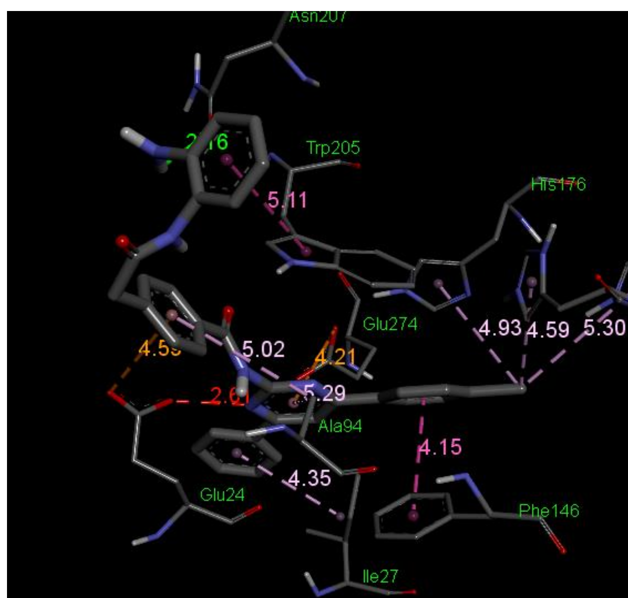


Fig. 18: 2D, 3D of Interaction of compound 6b with HDAC-10protein

The docking analysis of SAHA in the active site of HDAC-10 protein revealed that the binding energy is -7.76k.cal/mol. The main residues involved in the interaction within the active site are PHE-204, HIS-176, GLU-274, TRP-205, ZN-712, ASP-174, ASP-267, HIS-136, HIS-137, GLY-145, GLY-305, GLU-304, PRO-134, LYS-147, TYR-307, ILE-27, ALA-94, PHE-140, GLU-24. The zinc-binding group i.e. hydroxamic acid of SAHA forms one H-bond with GLU-274 and the linker group of SAHA forms H-bonds with HIS-137 and TYR-307.

Interaction of compound 6b with HDAC-10 protein



The docking analysis of compound 6b in the active site of HDAC-10protein revealed that it has a stronger binding with the active site, with binding energy is -9.30k.cal/mol. The main residues involved in the interaction within the active site are similar to standard drug SAHA and showed additional interactions with PRO-206, LEU-208, PRO-23, ASN-207, ASN-93,andTRY-307. The zinc-binding group is benzamide having amine forming one hydrogen bond with ASP-207.

The docking analysis of the following compounds from (6a-6f) revealed that they have good binding energy compared to standard SAHA drugs through 5 subtypes of HDAC enzyme. The compounds 6a-6f docked with 3max (HDAC-2), 6cqs (HDAC-6), 3c0z (HDAC-7), 1T64 (HDAC-8), 6wbq (HDAC-10) where each protein over expression leads to specific types of cancers.

Pharmacokinetic predicted properties (pre -ADMET values): The predicted properties are useful to identify compounds with the most appropriate ADME/Pharmacokinetics which are required for the journey of the drug molecule to reach its target site and also before synthesis predicted toxicity on carcino mouse and carcino rat, which is carcinogenic or not by using the pre-ADMET online tool.

The pre ADMET prediction was performed on compounds (6a-6f) to determine the pharmacokinetics and toxicity. Insilico pharmacokinetic and toxicity prediction forms one of the important studies in insilico studies which helps to determine whether the designed compounds have good pharmacokinetic properties and to know toxic effects. Pharmacokinetic parameters predicated on BBB, Caco2

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(colorectal adenocarcinoma cells), HIA (percentage human intestinal absorption) MDCK (Madin Darby Canine Kidney), plasma protein binding (PPB), and Pgp inhibition. Toxicity prediction tests like ames test, carcinogenicity test in mouse and carcinogenicity test in the rat. Ames test is a simple method to test the mutagenicity of a compound, which is suggested by Dr. Ames. It uses several strains of the bacterium salmonella Typhimurium that carry mutations in genes involved in histidine synthesis, so that require histidine for growth. The variable being tested is the mutagen's ability to cause a reversion to growth on a histidine-free medium. Compound 6f whereas in rats all the positive results.

Table No. 3: Pre ADMET properties of proposed compounds

ID	BBB	Caco 2	HIA	MDCK	PPB	Pgp inhibition	Ames-test	Casino mouse
6a	0.274283	21.5362	95.52315	**0.116791**	95.783136	inhibitor	non-mutagen	positive
6b	0.608101	21.9789	96.15274	0.056054	98.297721	inhibitor	non-mutagen	positive
6c	0.491805	21.6275	95.67154	0.058276	94.879712	inhibitor	non-mutagen	positive
6d	0.026062	20.8863	94.94793	0.046309	97.175854	inhibitor	mutagen	positive
6e	**1.36166**	**22.3668**	**96.60658**	0.0477225*	**100**	inhibitor	non-mutagen	positive
6f	0.904351	21.7302	95.81256	0.0495287*	94.145522	inhibitor	non-mutagen	negative
SAHA	0.218228	19.0725	84.52551	55.6365	72.156999	non	mutagen	positive

The low absorption of the compounds (6a-6f) through CNS and are CNS inactive compounds. According to the Caco2 test, values are from 21-to 22, so these compounds (6a-6f) have middle permeability through the intestine when administered orally. The human intestinal absorption of these compounds showed from 94-96. So, these compounds (6a-6f) have well absorption through the intestine. MDCK test results showed that compounds have low permeability (0.1-0.04). The Plasma proteins binding of the proposed compounds is found to be 94.4-100. So, the compounds have chemically strong plasma protein binding. All compounds (6a-6f) Pgp inhibitors. In Ames-test it is found that all the proposed compounds are non-mutagens except compound 6d. Toxicity prediction tests like the carcinogenicity test in mice and the carcinogenicity test in rats found that all the compounds showed positive carcinogenic toxicity in the mouse except Compound 6f whereas in rats all the compounds reported negative except 6d showing positive results.

CONCLUSION

Insilico studies such as molecular docking and pharmacokinetic properties of designed compounds (6a-6f) were predicted by using different offline and online tools. The designed compounds were screened for in-silico molecular property prediction, pharmacokinetic prediction, and toxicity studies. The predicted data of molecular properties of designed compounds violates 2 rules i.e. MW, logP whereas compound 6a obeys all five rules of the Lipinski rule. Compound 6a was found to be a drug-like compound.

Molecular docking studies were performed on the active site of the five subtypes of HDAC enzyme (HDAC-2, HDAC-6, HDAC-7, HDAC-8, and HDAC-10). All the designed compounds showed good binding energies with the target protein as compared to standard (Vorinostat). The compound 6b (-9.30 k. cal/mol) showed exceptionally good binding energy with HDAC-10 which is more than that of a standard drug. Compound 6b has high selectivity towards HDAC-10. So, compound 6b may inhibit Cervical Cancer cells and Neuroblastoma cells.

Pharmacokinetic parameters were predicted. Compound 6e has good pharmacokinetic properties. the designed compounds are non-mutagens except compound 6d in Ames-test carcinogenicity test in mouse and carcinogenicity test in rat found that all the compounds showing positive carcinogenic toxicity on the mouse except compound 6f whereas in rat all the compounds reported negative except 6d showing positive results. The results of the designed molecules were comparable with the standard drug SAHA (Vorinostat). So, the designed and synthesized compounds have the drug likeliness and are suggested as potential anticancer agents. The 4,6-diphenylpyrimidine substituted benzamide has potential HDAC inhibition Activity.

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