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In Silico Discovery of Small Molecule HDAC2 Inhibitors using Virtual Screening, Atom based 3D QSAR Model, Docking Analysis and ADME study

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ABSTRACT

In the present study structure based virtual screening of compound data base, prediction of activity of high extra precision glide docking scored (XPGS) molecules by atom based 3D QSAR model, XP glide docking analysis of known inhibitors to know the key residue interactions and ADME study of identified Histone Deacetylase 2 (HDAC2) inhibitors were performed. A 3D QSAR model was build for both training set (R^2 = 0.9867, SD= 0.104, F= 322.1 and N= 17) and test set (Q^2 = 0.9137, Pearson r= 0.9671, RMSE = 0.160, N = 7) molecules and showed a statistically significant and good predictive model. The visualization of 3D QSAR model suggested that introduction of hydrogen bond donor group in 5-position of pyridine ring, 6-position of 1,2-diaminobenzene ring; hydrophobic groups in the 2,4-position of pyridine ring, 5,6 -position of 1,2-diamino benzene ring, 2,3,5,6-position of amonomethylbenzamide ring of highest active compound 1 were suitable to increase the HDAC2 inhibitory activity. The XP glide docking analysis of the known inhibitors showed that residues PHE-155, Gly-154, His-145, His-146, Asp-104 and Zn-ligand interaction in the active site region play a crucial role for inhibitory activity. The activity of high glide scored molecules resulted from virtual screening were predicted by atom based 3D QSAR model. After prediction of activity the molecules were subjected to ADME study to know the drug likeness properties and reported 10 molecules having XPGS > 12.0 and predicted activity > 6.7 as potent HDAC2 inhibitors. The docking interaction of known inhibitors was also similar to the docking interaction of identified ten potent inhibitors.

Keywords: HDAC2 inhibitors, Virtual Screening, 3D QSAR, Docking, ADME study

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INTRODUCTION

Histone deacetylases (HDACs) enzyme play crucial role in the deacetylation of lysine residues at the N-terminal region of core histones [1]. The HDACs family consists of 18 members and is subdivided into four classes: class I (HDAC-1, -2, -3 and -8), class IIa (HDAC-4, -5, -7 and -9), class IIb (HDAC-6 and -10) and class IV (HDAC-11). All these HDACs are zinc dependent protease of family amidohydrolase[2-3]. Due to their role in various biological functions, HDACs inhibition has become a promising epigenetic target for the treatment of cancer [4]. The HDAC inhibitors bind with the active site of HDAC enzyme which inhibits tumor growth by inhibitor-enzyme interactions[5]. HDAC2 a zinc dependent enzyme in human is encoded by the HDAC2 gene and belongs to class I HDAC family. Like other members of HDAC family HDAC2 is also deacetylase the lysine residue on the N-termini region of the core histones (H2A, H2B, H3 and H4). It is also plays an important role in transcriptional regulation, cell cycle progression and development events[6]. Deregulation of HDAC2 expression and activity is responsible for cancer development. HDAC2 is over expressed in different tumor types including prostate carcinoma[7]. Therefore search, design and development of new HDAC2 inhibitors can be used as chemical tool as therapeutic agents in the field of anticancer drug development programme. In the present study a virtual screening of Phase Database [The Phase CAC (Commercially Available Compounds) database was prepared by the SD files of commercially available compounds were obtained from the following vendors: Asinex (www.asinex.com), Bionet (Key Organics) (www.keyorganics.ltd.uk), ChemDiv (chemdiv.emolecules.com), Enamine (www.enamine.net), LifeChem (www.lifechemicals.com), Maybridge (www.maybridge.com), Specs (www.specs.net), TimTec (www.timtec.net)with a unique identifier, CACPD2011aCode] were performed using 'Virtual Screening Workflow' of Schrodinger with HDAC2 receptor grid to find out the potent and novel small molecule inhibitors. Ligand-based drug design approach such as 3D QSAR model also used to predict the activity of new compounds and to identify important features for better activity [8-9]. Docking analysis of known inhibitors was also performed to know about the structural insight of inhibitors for better inhibition. The activity of inhibitors with high XPGS resulted from virtual screening of data base were predicted with atom based 3D QSAR model, compare the docking interactions with active site amino acid residues of identified HDAC2 inhibitors with known inhibitors and finally ADME study were performed to know about the drug likeness of the identified molecules. On the basis of above experiment ten potent HDAC2 inhibitors were reported in this paper.

MATERIALS AND METHODS

Data set

The ligands with IC_{50} value were collected from the literature[10] which comprised of 29 benzamide derivatives as HDAC2 inhibitors. The IC_{50} value, which is a measure of the ability to inhibit HDAC2, was converted to pIC_{50} by taking negative logarithm to base 10 of IC_{50} and the range of pIC50 values were 4.699–7.658. The pIC_{50} values were spanned 4 order magnitudes. Out of 29 HDAC2 inhibitors five structures were discarded from the data set as they exhibit no specific value of pIC_{50}. The 24 compounds were randomly segregated into training set of 17 and test set of 7 molecules (Table-1) and were used for subsequent atom based 3D QSAR model development using PHASE module of Schrodinger's suite[11]. The X-ray crystal structures of HDAC2 were collected from RCSB protein data bank [PDB ID: 4LY1, 4LXZ and 3MAX][12-13] for docking study. All the computational work was carried out by using HP Z820 Workstation running over CentOS 6.3.

Ligprep

All the structures were drawn by ChemBio DrawUltra 11 then converted the structures into 3D and then mol format after that imported in Maestro 9.6 inter phase and ligand preparation was done using LigPrep module of Schrodinger molecular modeling suite. During ligand preparation the force field used OPLS_2005 and retains original state of ionization. The original stereochemistry of the ligand was also retained and generated low energy one ring conformation per ligand.

Protein preparation and Grid generation

The above three HDAC2 receptors were prepared through pre-processed, optimized and minimized with OPLS_2005 force field using Protein Preparation Wizard[14-15]. The Grid were generated selecting the centroid of the workspace Co-ligand of the prepared proteins using the 'Receptor Grid Generation' panel of Schrodinger with default options unless stated otherwise. The ligand was selected to define the position and size of the active site during grid generation. The RMSD of 4LY1, 4LXZ and 3MAX were calculated by superimposing XP-Glide generated best docked conformation on its original X-ray crystallographic bound conformation and the values were 0.3346, 0.6753 and 0.3592 respectively. The RMSD value of HDAC2 (PDB ID: 4LY1) was lowest which indicates that Glide was able to reproduce the native conformation successfully and the generated receptor grid of 4LY1 was used for docking and virtual screening.

Virtual Screening

The virtual screening of PHASE Databases containing $4.3x10^6$molecules (only first conformer)

were used to find out the novel, potential HDAC2 small molecule inhibitors suitable for further design and development. The 'Virtual Screening Work Flow of Schrodinger' was used for docking the database with generated grid. In virtual screening work flow Figure-1 the data base was filtered first with respect to molecular weight (range 200-300) and resulted 4.5 x 10^5 molecules. Then High throughput virtual screening (HTVS) docking of filtered molecules for searching HDAC2 inhibitors was performed. Then 5% of highglide score resulted after HTVS was used for Standard Precision (SP) docking and then 5% of high glide scored resulted in SP docking were used for Glide Extra Precision-(XP) docking and collected 112 molecules having XPGS > 11.0.

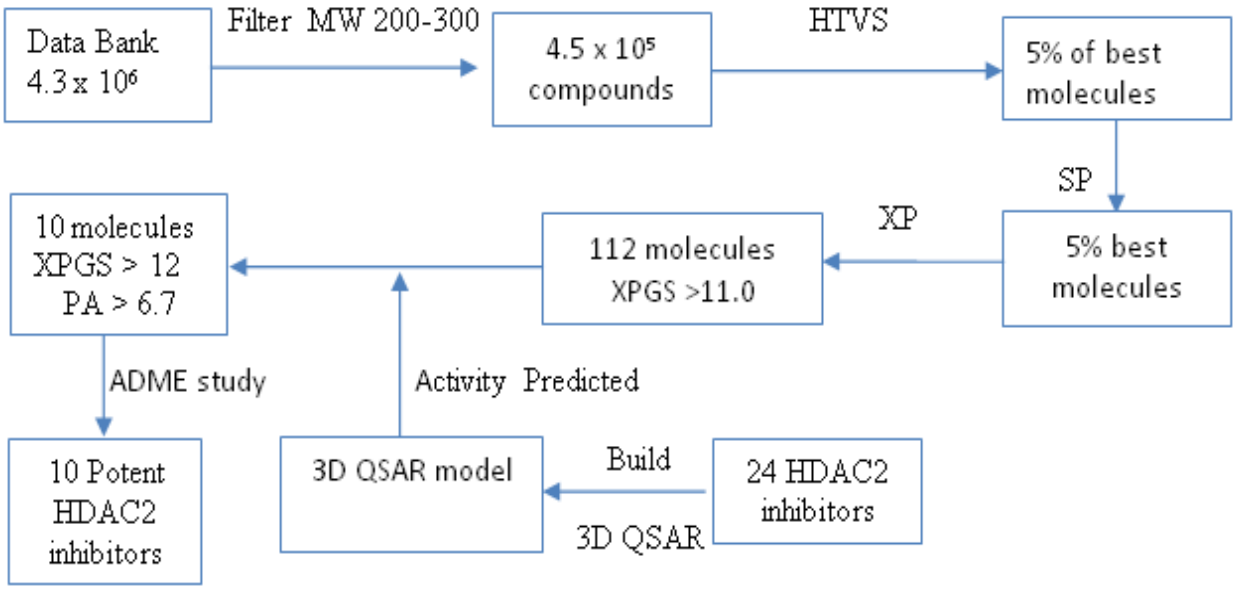


Figure-1: Workflow for identification of novel HDAC2 inhibitors

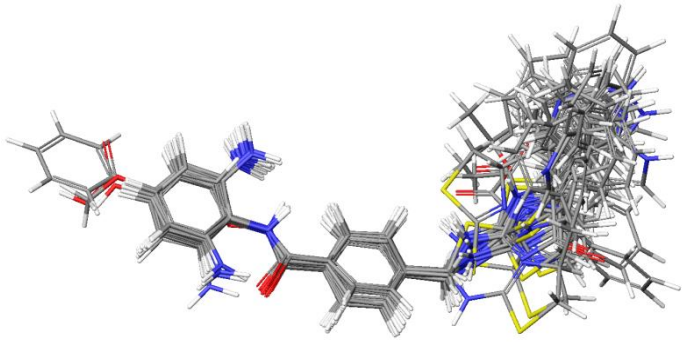


Figure-2: Structural alignment used for atom based 3DQSAR model generation

Building 3D QSAR model

The atom based 3D QSAR model was generated using PHASE with 24 ligands having pIC_{50} values. The ligands were aligned (Figure-2) using atom type macro model option under shape screen. During model generation70% randomly selected molecules were kept in the training set

and remaining 30% kept in the test set then atom based 3D QSAR model was build by keeping 1Å grid spacing and a maximum of three PLS factor.

Molecular docking study of known inhibitors

The docking study was performed using Glide[16-19] with 24 known inhibitors[10] with HDAC2 receptor. The docking interaction showed that the ligand-protein complex was stabilized by hydrogen bonds, hydrophobic, π-π staking and electrostatic interactions and 2D protein ligand interactions were shown in the Table 3.

ADME Study of Designed Molecules

The ADME (adsorption, distribution, metabolism, and excretion) prediction study were performed to know the drug likeness properties of identified potent HDAC2 inhibitors which provides ranges of values for comparing particular molecular properties with those of 95% of known drugs using Schrodinger module QikProp 3.5 [20].

RESULTS AND DISCUSSION

Virtual Screening

The virtual screening of database resulted 112 small molecules having XP Glide score > 11.0 and their activities were predicted using atom base 3D QSAR model.

3D QSAR Analysis

A statistically significant atom base 3D QSAR model was generated and summary of statistical parameters was summarized in Table-2. The regression line for the observed and predicted activities of both test and training set was shown in Figure-3. The predicted activities of the training and test set molecules were listed in Table-1.

Table – 1: The experimental, predicted activities and training, test set molecules

Str.	QSAR Set	Activity	Predicted Activity	Str.	QSAR Set	Activity	Predicted Activity
1	training	7.658	7. 0142	**13**	training	6.936	7.0312
2	test	7.357	7.3582	**14**	training	6.660	6.0745
3	training	7.319	6.9089	**15**	training	6.606	6.4187
4	test	7.252	7.3547	**16**	training	6.585	6.4852
5	training	7.252	7.2822	**17**	test	6.372	6.7595
6	training	7.180	6.7966	**18**	training	6.357	6.2417
7	test	7.108	7.2018	**19**	test	6.269	6.2297
8	training	7.092	7.0369	**20**	training	6.237	6.6783
9	training	7.086	7.1883	**21**	training	6.036	5.9907
10	training	7.071	7.0149	**22**	test	5.845	5.8537
11	test	6.983	6.9561	**23**	training	4.777	4.7858
12	training	6.955	6.8803	**24**	training	4.699	4.8776

Table – 2: PLS statistical parameters of the selected 3D QSAR model

Factors	SD	R^2	R^2 CV	R^2 Scramble	Stability	F	P	RMSE	Q^2	Pearson-r
1	0.3909	0.7834	0.5062	0.7218	0.876	54.3	2.34E-06	0.39	0.4746	0.7006
2	0.2014	0.9464	0.4996	0.9059	0.627	123.5	1.28E-09	0.15	0.9189	0.9638
3	**0.104**	**0.9867**	**0.5022**	**0.9737**	**0.508**	**322.1**	**1.91E-12**	**0.16**	**0.9137**	**0.9671**

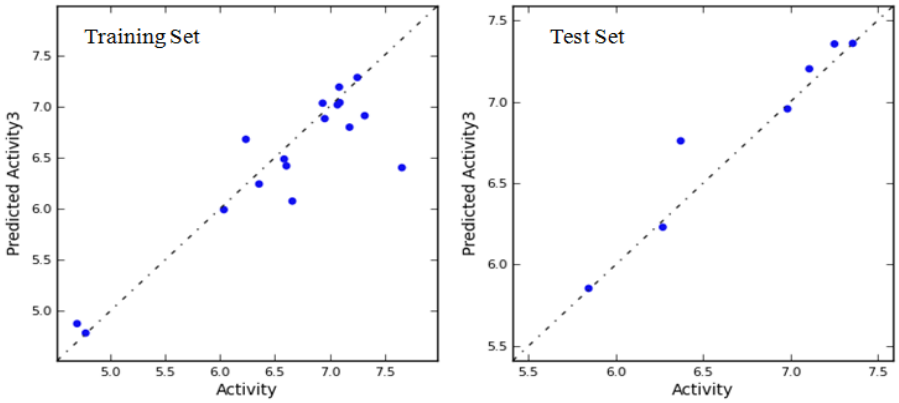


Figure-3: Fitness graph between observed activity and PHASE predicted activity (pIC_{50}) for training and test set molecules.

In 3D QSAR the validation is a crucial aspect and it is authenticated by using both the internal and external method. In the present study for comparison between the predicted and experimental activities of training set molecules R^2 (squared correlation coefficient) was used and R^2value for good model should be ≥ 0.70[21]. For external validation RMSE (Root-mean-square error), Q^2 (test set correlation), and Pearson-r (between the predicted and observed activity for the test set) was used and for good predictive model RMSE values should < 0.30, Q^2 is greater than 0.6 [21]and Pearson r should be > 0.8. For a reliable predictive model, there must be a good R^2, Q^2, and pearson-r[22]. The other criteria for a good model are R^2–Q^2<0.3[23], SD (standard deviation) should besmall, highest F value, lowest P value containing factor should be considered and R^2CV should be more than 0.5. In the present model build with partial least-square (PLS) factors 3 the R^2 = 0.9867 for training set of 17 compounds, Q^2 = 0.9137 for test set of 07 compounds, root mean squared error RMSE = 0.1600, Pearson-r = 0.9671, R^2-Q^2 = 0.073 and R^2CV=0.5002 which indicates our model was a good predictive and statistically significant.

Hydrogen bond Donor: The atom based 3D QSAR visualization generated by PHASE analysis (Figure-4) suggested that blue cube regions of benzamide derivatives were favorable for introduction of hydrogen bond donor group for better HDAC2 inhibitory activity and the orange cubes regions indicates that introduction of hydrogen bond donor group in these regions reduced the HDAC2 inhibitory activity. In lowest active molecule **24** the hydrogen bond donor

hydroxamate group lies in the restricted region which was not suitable for hydrogen bond donor group. Hence its activity was low with respect to highest active molecule **1** where hydrogen bond donor groups lies in the favorable region.

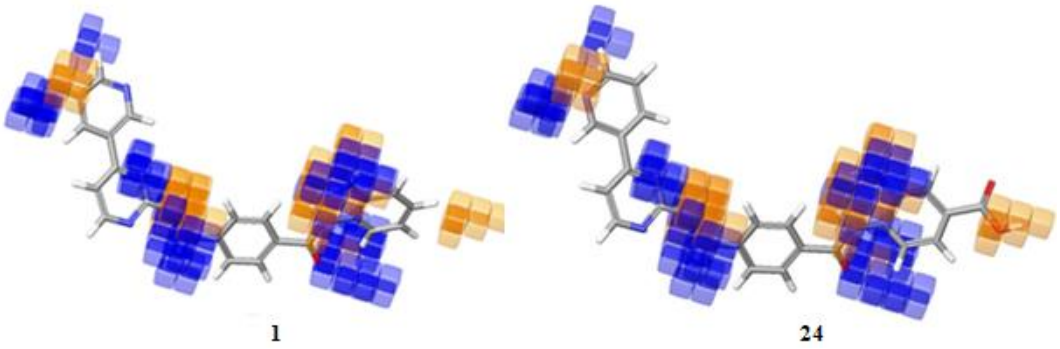


Figure-4:Hydrogen bond donor visualization of 3DQSAR model on the highest active compound 1 and least active compound 24 (blue cubes indicate favorable regions while red cubes indicate unfavorable region).

Hydrophobic Interaction

The 3D QSAR visualization (Figure-5) of hydrophobic interaction on both highest active **1** and lowest active **24** ligand generated by PHASE suggested that the green cubes region indicates favorable region for hydrophobic interaction and the purple cubes regions indicate that were unfavorable for hydrophobic interaction for better HDAC2 inhibitory activity. It could be urged from Figure-5 that introduction of hydrophobic group in green cube region favor the HDAC2 inhibitory activity.

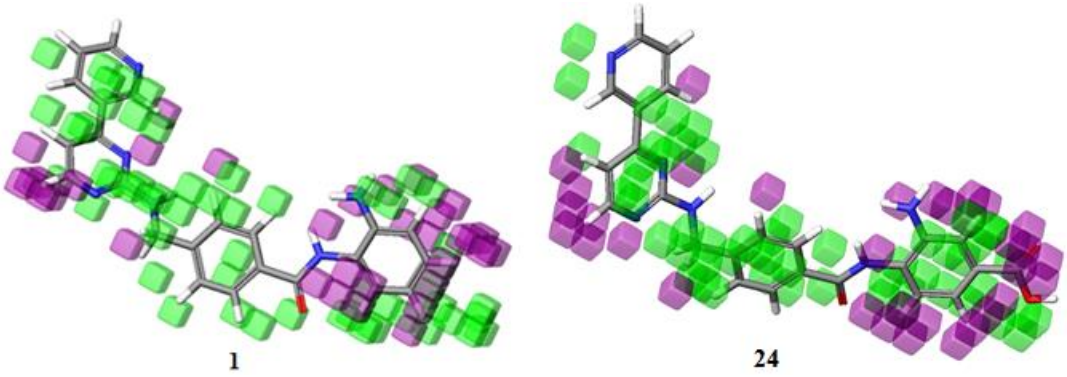


Figure-5:Hydrophobic interaction visualization of 3DQSAR model on highest active compound 1 and least active compound 24 (Green cubes indicate favorable regions while purple cubes indicate unfavorable region for activity).

Electron Withdrawing Effect

The blue cube regions appeared in pictorial presentation (Figure-6) for electron withdrawing effect around the highest active ligand **1** and lowest active ligand **24** indicates that presence of electron

withdrawing group in blue cube region favorable for HDAC2 inhibitory activity and the orange coloured region around the ligands indicate that these regions are unfavorable for substitution with electron withdrawing groups.

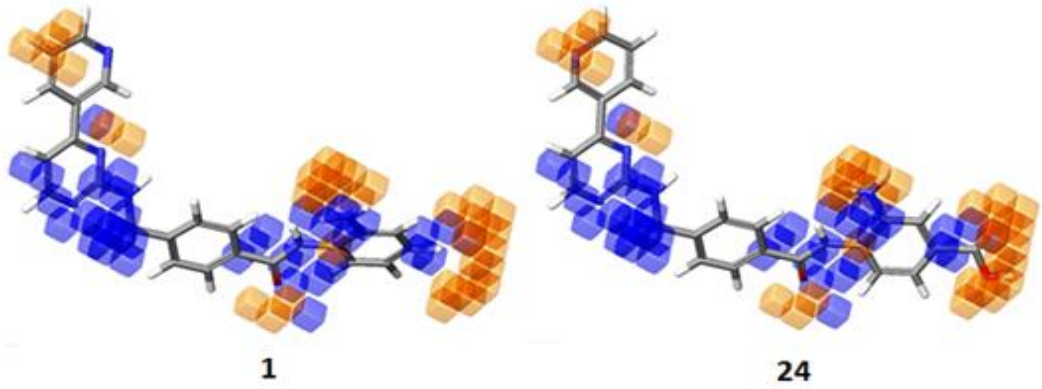


Figure-6: Electron withdrawing visual representation of 3DQSAR model of the most inactive compound 1 and lowest active compound 24 (blue cubes indicate favorable regions while red cubes indicate unfavorable region for the activity)

Therefor eintroduction of hydrogen bond donor group in the blue rectangular region i.e. position 5 of pyridine ring, position 6 of 1,2-diaminobenzene ring; hydrophobic groups in green circular regions i.e. the position 2, 4 of pyridine ring, 5,6 of 1,2-diamino benzene ring, 2,3,5,6 of amonomethylbenzamide ring of highest active compound **1** (Figure-7) are suitable to enhance the HDAC2 inhibitory activity. The activity of the high glide scored 112 molecules were predicted using 3D QSAR model and reported ten best molecules (Table-4).

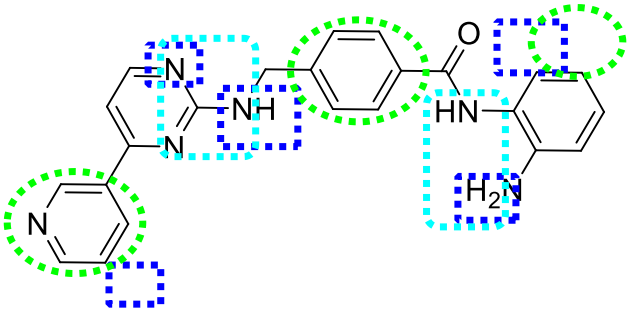


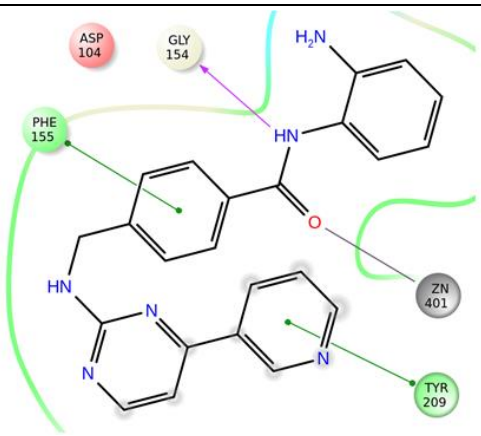
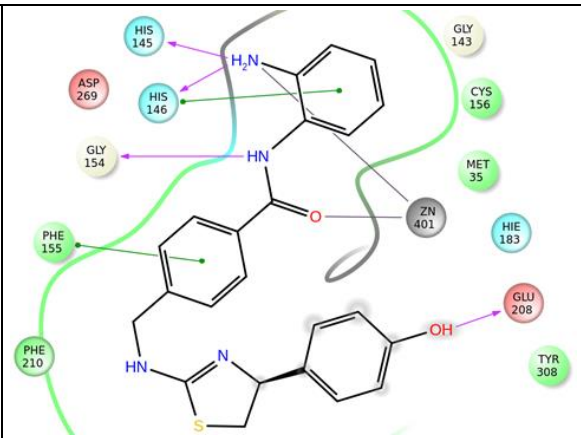
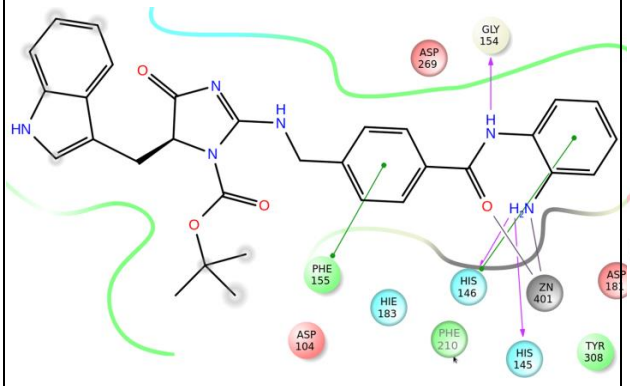
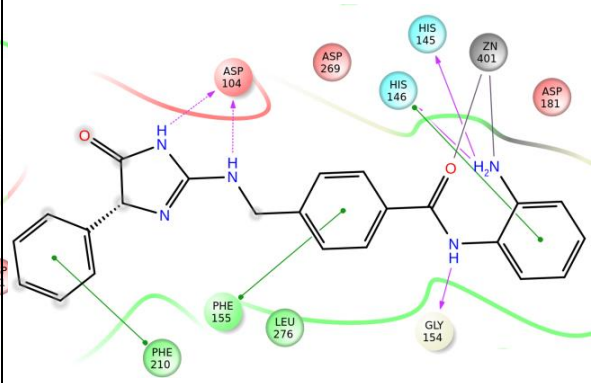
Figure-7: Favorable regions for substitution

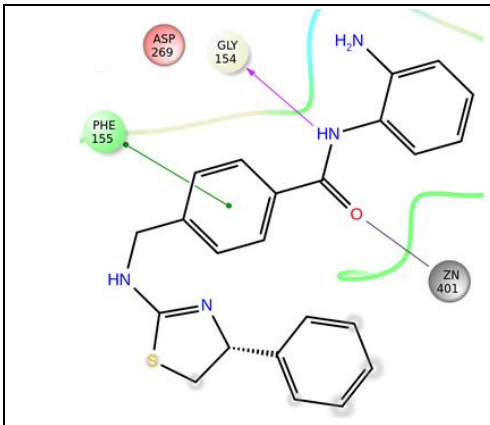
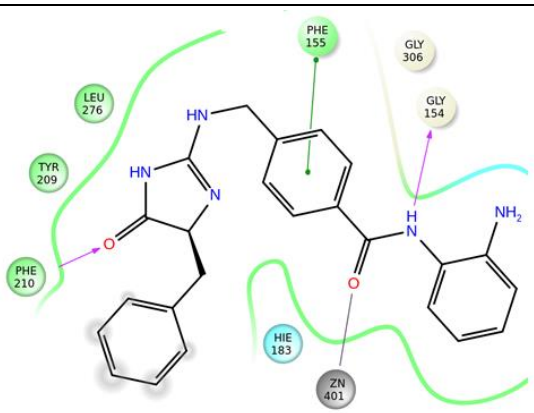
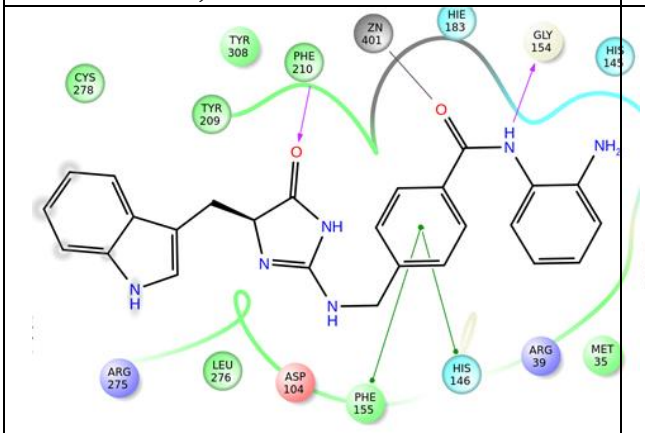
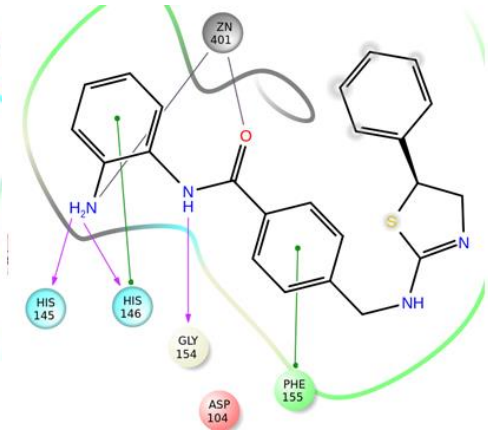
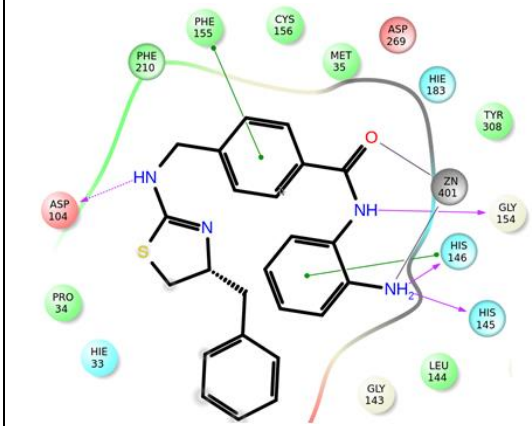
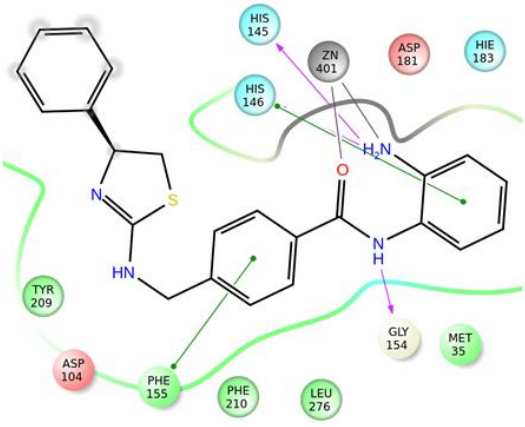
Docking Analysis

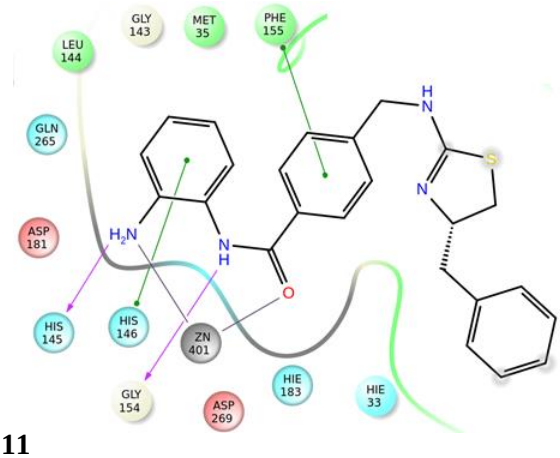
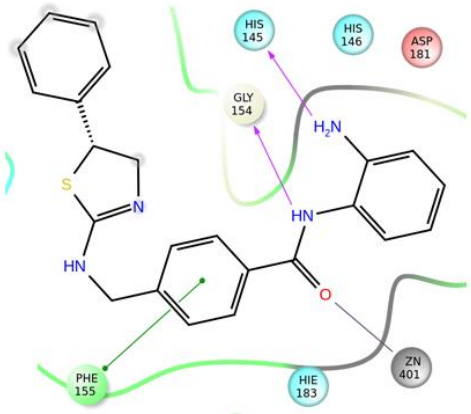
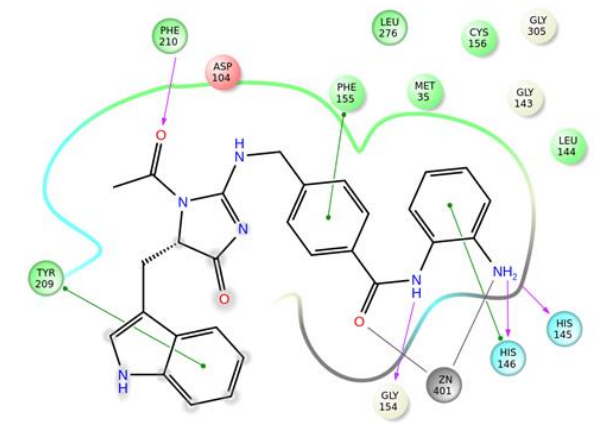
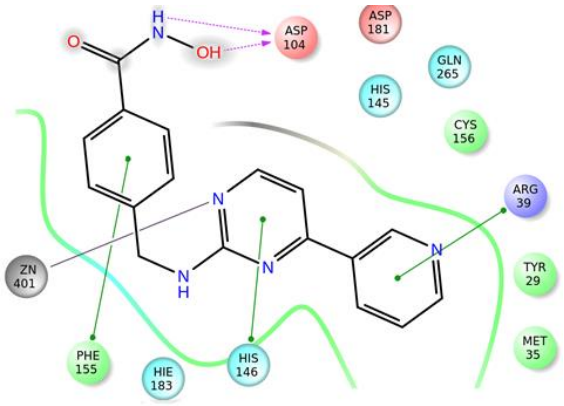
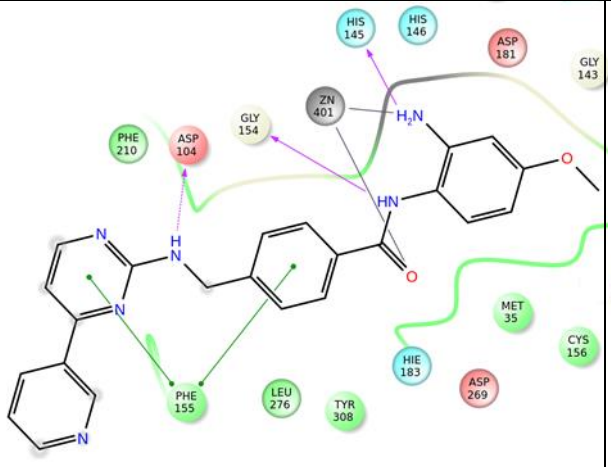
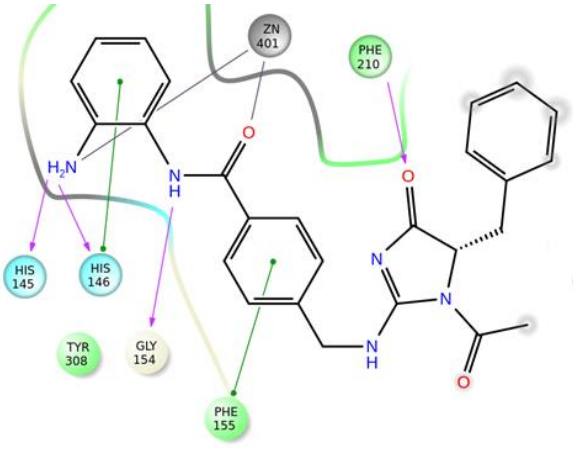
The docking interactions of known inhibitors with active site amino acid residues of HDAC2 were presented in the Table-3. It indicated that most of the inhibitors interacts with PHE-155 (22 interactions) through π-π interactions and Zn-401 (33 interactions). The other amino acid residues GLY-154 (20), HIS-145 (14), HIS-146 (10), ASP-104 (7) interacts through hydrogen bond donor and HIS-146 (13) interacts through π-π in the active site region (Table-3).Therefore if the

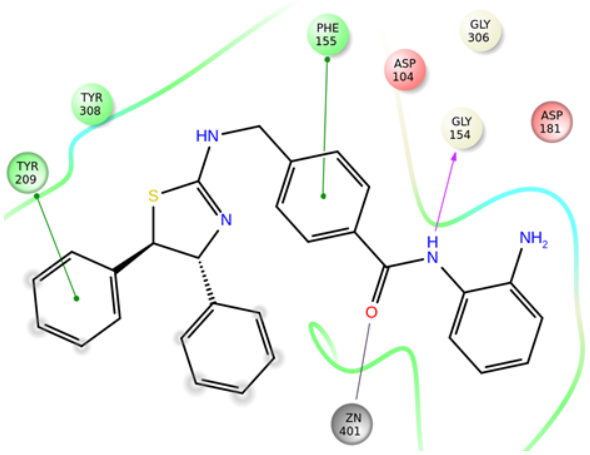
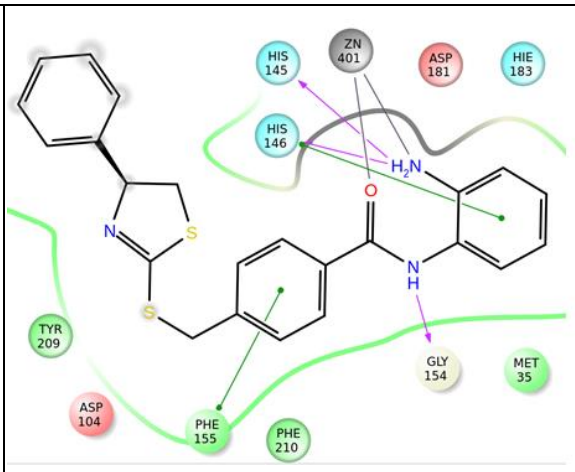
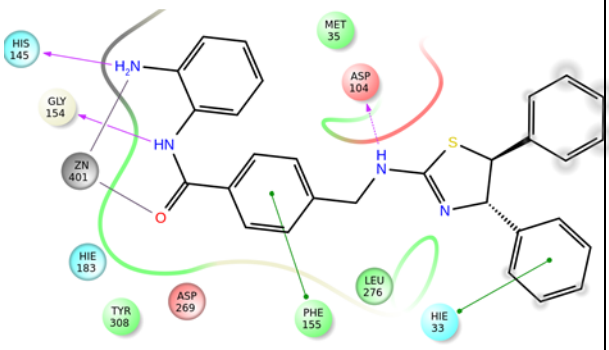
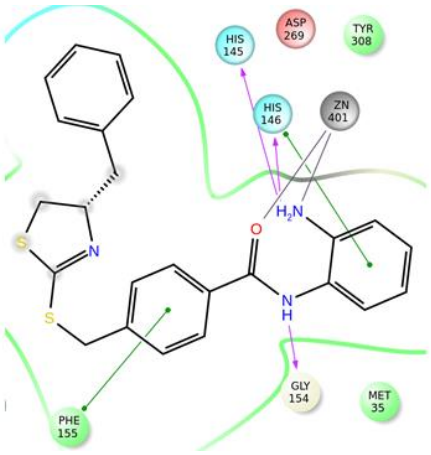
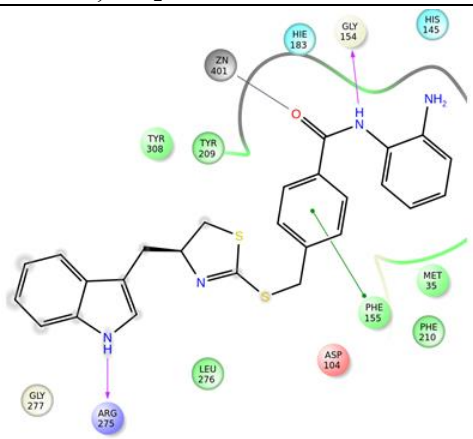
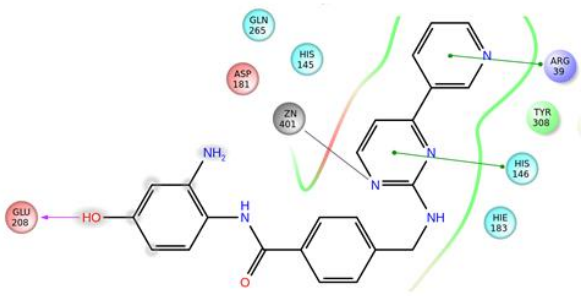
molecules identified after virtual screening and activity prediction, interacts mostly with Zn, PHE-155, GLY-154, HIS-145, HIS-146, ASP-104 in the active site region then those molecules may be potential inhibitors. The docking results of identified ten lead molecules were presented in the Table 4. Most of the identified lead molecules also interact with Gly-154 (19 interactions), PHE-155 (10) and Zn-401(10) in the active site of HDAC2 which corroborate interactions of known 24 inhibitors presented in the Table-3.

Table–3: pIC_{50} (Exp), XPGS, HBD, HBA, π-π, metal-ligand interactions with active site amino acid residues

 **1**	 **2**
pIC_{50} = 7.658; XPGS= -11.12; HBD= GLY-154; HPB= PHE -155, TYR-209, Zn….O=C	pIC_{50} = 7.357; XPGS= -12.08; HBD= GLY-154, HIS-146, HIS-145, GLU-208, HPB= PHE-155, HIS-146, Zn….O=C, NH_2
 **3**	 **4**
pIC_{50} = 7.319; XPGS= -11.78; HBD: HIS-145, HIS-146, GLY-154; HPB: HIE-146, PHE-155; Zn….O=C, NH_2	pIC_{50} = 7.252; XPGS= -11.76; HBD: HIS-145, HIS-146, GLY-154, ASP-104(2); HPB: PHE-155, PHE-210, HIE-146; Zn….O=C, NH_2

 **5**	 **6**
pIC_{50} = 7.252; XPGS= -11.54; HBD= GLY-154; HPB= PHE-155; Zn….O=C	pIC_{50} = 7.18; XPGS= -12.05; HBD: GLY-154; HBA: PHE-210, HPB: PHE-155; Zn….O=C
 **7**	 **8**
pIC_{50} = 7.108; XPGS= -12.06; HBD: GLY-154; HBA: PHE-210; HPB: HIE-146, PHE-155; Zn….O=C	pIC_{50} = 7.092; XPGS= -11.77; HBD: GLY-154, HIS-145, HIS-146; HPB: PHE-155, HIS-146; Zn….O=C, NH_2
 **9**	 **10**
pIC_{50} = 7.086; XPGS= -11.48; HBD: GLY-154, HIS-145, HIS-146, ASP-104; HPB: HIS-146, PHE-155; Zn….O=C	pIC_{50} = 7.071; XPGS= -11.47; HBD: HIS-145, HIS-146 GLY-154; HPB: HIS-46, PHE-155; Zn….O=C, NH_2

 **11**	 **12**
pIC_{50} = 6.983; XPGS= -11.23;HBD: HIS-145, HIS-146, GLY-154; HPB: PHE-155, HIS-146; Zn….O=C, NH_2	pIC_{50} = 6.955; XPGS= -11.14; HBD: HIS-145, GLY-154; HPB: PHE-155; Zn….O=C
 **13**	 **14**
pIC_{50} = 6.936; XPGS= -11.90; HBD: HIS-145, HIS-146, GLY-154; HBA:PHE-210; HPB: PHE-155,HIS-146,TYR-209; Zn….O=C, NH_2	pIC_{50} = 6.66; XPGS= -11.00; HBD: ASP-104 (2); HPB: PHE-155,HIS-146, ARG-39; Zn….O=C
 **15**	 **16**
pIC_{50} = 6.606; XPGS= -11.32; HBD: HIS-145, GLY 154, ASP-104; HPB: PHE-155 (2); Zn….O=C, NH_2	pIC_{50} = 6.585; XPGS= -12.89; HBD: HIS-145, HIS-146 GLY 154; HBA: PHE-210; HPB: HIS-46, PHE-155; Zn….O=C, NH_2

 **17**	 **18**
pIC_{50} = 6.372; XPGS= -11.46; HBD: GLY-154; HPB: TYR-209, PHE-155; Zn….O=C	pIC_{50} = 6.357; XPGS= -11.56; HBD: HIS-145, HIS-146 ,GLY- 154; HPB: HIS-146, PHE-155; Zn….O=C, NH_2
 **19**	 **20**
pIC_{50} = 6.269; XPGS= -11.26; HBD: HIS-145, GLY-154, ASP-104; HPB: HIE-33, PHE-155; Zn….O=C, NH_2	pIC_{50} = 6.237; XPGS=-11.46; HBD: HIS-145, HIS-146, GLY-154; HPB: HIS-146, PHE-155; Zn….O=C, NH_2
 **21**	 **22**
pIC_{50} = 6.036; XPGS= -11.83; HBD: ARG-275, GLY-154; HPB: PHE-155; Zn….O=C	pIC_{50} = 5.845; XPGS= -11.75; HBD: GLU-208; HPB: HIS-146, ARG-39; Zn….N=C

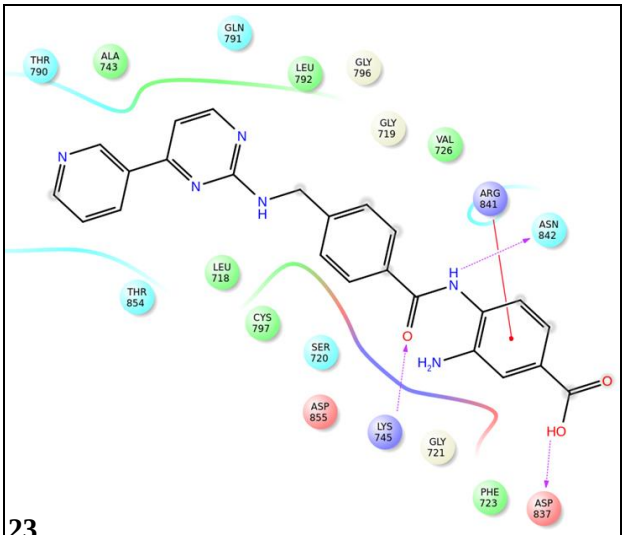
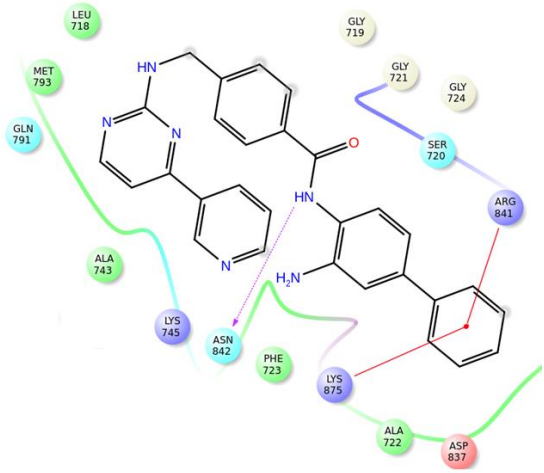
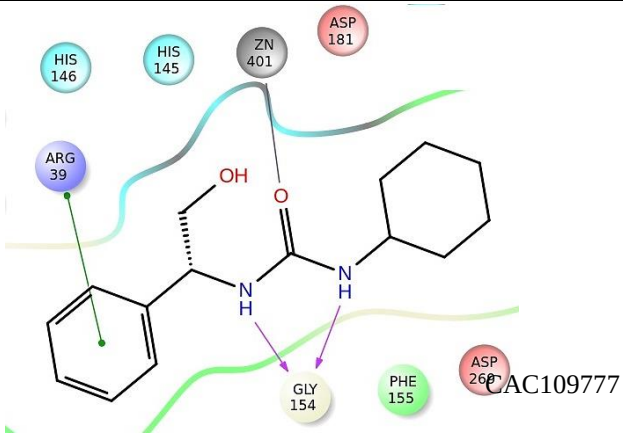
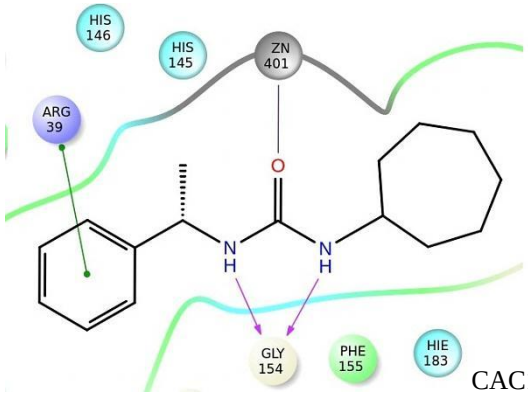
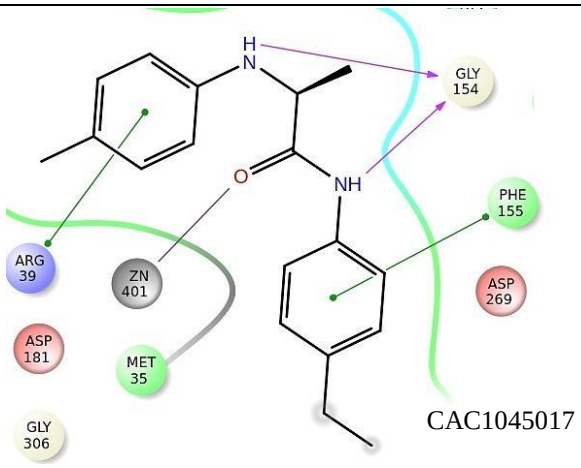
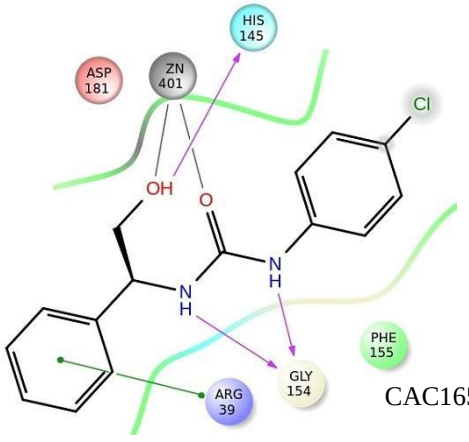
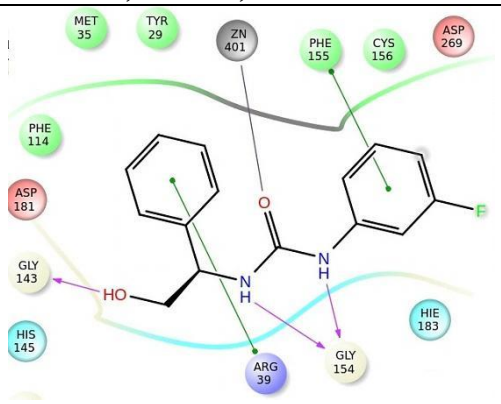
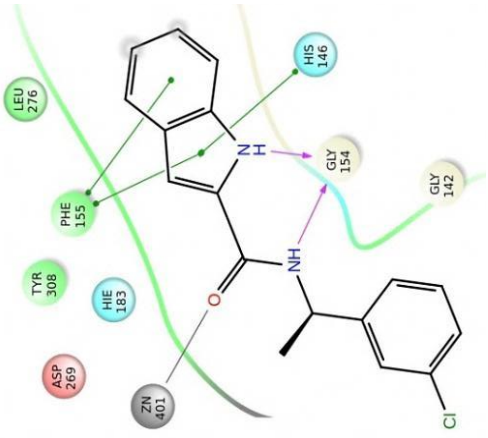
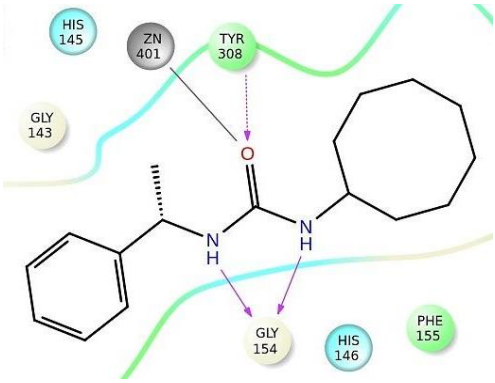
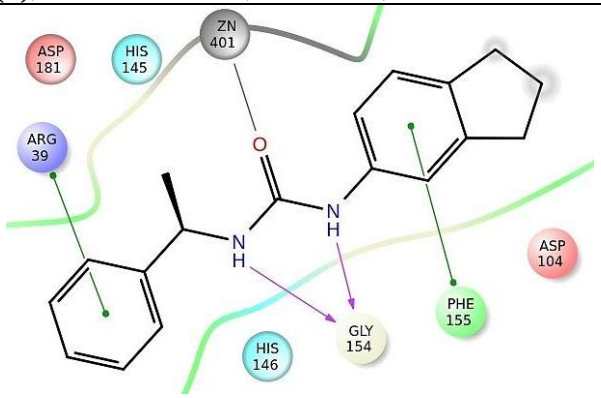
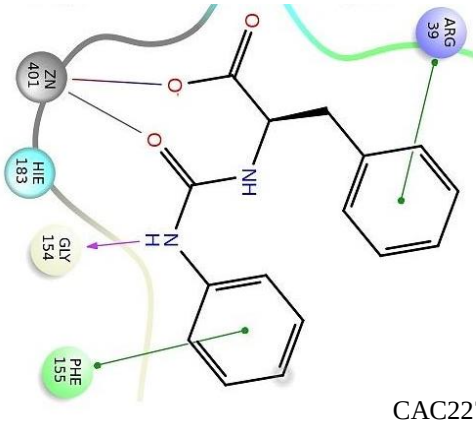
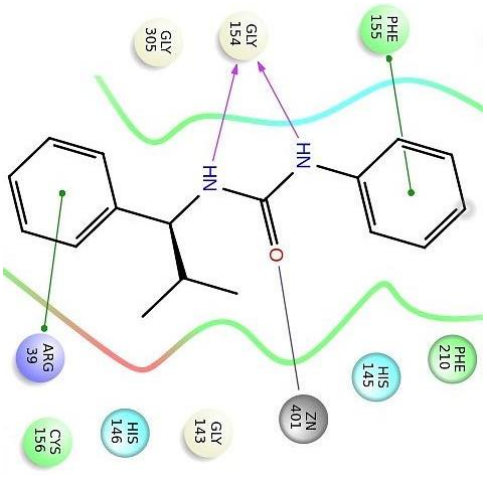
 **23**	 **24**
pIC_{50} = 6.036; XPGS= -5.593; HBD: ASN-842, ASP-837; HBA: LYS-745; π-π cationic: ARG-841	pIC_{50} = 5.845; XPGS= -6.109; HBD: ASN-842; ; π-π cationic: ARG-841, LYS-875
HBD: Hydrogen bond donor, HBA: Hydrogen bond acceptor, XPGS: XP Glide Score	

Table – 4: pIC_{50} (Pred), XPGS, HBD, HBA, π-π, metal-ligand interactions with active site amino acid residues of ten potent inhibitors

 CAC109777	 CAC117485
pIC_{50} = 6.9563; XPGS= -12.41; HBD= GLY-154 (2); HPB= ARG-39; Zn….O=C	pIC_{50} = 6.9653; XPGS= -12.38; HBD= GLY-154 (2); HPB= ARG-39; Zn….O=C
 CAC1045017	 CAC1654116

pIC_{50}= 6.9192; XPGS= -12.23; HBD=GLY-154(2); HPB=ARG-39, PHE-155; Zn….O=C	pIC_{50}= 6.9130; XPGS= -13.57; HBD= GLY-154 (2), HIS-145; HPB= ARG-39, Zn….O=C
 CAC1823197	 CAC2039171
pIC_{50} = 6.9007; XPGS= -13.13; HBD= GLY-154 (2); HPB= ARG-39, PHE-155; Zn….O=C	pIC_{50} = 6.7927; XPGS= -12.31; HBD= GLY-154 (2); HPB= HIS-145, PHE-155; Zn….O=C
 CAC2239953	 CAC2239995
pIC_{50} =6.8739; XPGS= -12.25; HBD= GLY-154 (2); HPB= TYR-308; Zn….O=C	pIC_{50}= 6.7848; XPGS= -12.49; HBD= GLY-154 (2); HPB= ARG-39, PHE-155; Zn….O=C
 CAC2273477	 CAC2350228
pIC_{50}= 6.8253; XPGS= -12.26; HBD= GLY-154; HPB= ARG-39, PHE-155; Zn….O=C, OOC-	pIC_{50}= 6.7835; XPGS = -12.448; HBD= GLY-154 (2); HPB= PHE-155, ARG-39; Zn….O=C

ADME Study of identified ten molecules

The identified high active molecules obtained from 3D QSAR were subjected for ADME and Lipinski's rule of five using Qikprop tool of Schrodinger which is built using experimental details of 710 compounds including 500 drugs and heterocyclic compounds[20]. A large number of stars suggested that a molecule is less drug-likeness than molecules with few stars here for all selected molecules the value was zero (recommended range 0-5) and the range of molecular weight also lies in the recommended range (130-725). The other properties of all the ten molecules with recommended range are shown in the Table-5.

Table-5: Therefore all the identified HDAC2 inhibitors with different ADME properties

Molecule	SASA	volume	dHB	aHB	QPlogPw	QPlogPo/w	QPlogS	QPPCaco	QPPMDCK	PHOA
CAC109777	579.018	964.541	3	3.7	11.827	2.266	-3.543	679.175	524.733	90.899
CAC117485	561.28	965.3	2	2	7.982	3.575	-4.485	3305.878	2479.726	100
CAC1045017	593.57	1025.004	2	3.5	8.524	4.036	-4.849	3612.95	1983.046	100
CAC1654116	560.8	936.089	3	3.7	12.135	2.599	-3.821	948.857	1577.18	95.45
CAC1823197	564.097	926.611	3	3.7	12.825	2.374	-3.575	633.223	837.105	90.988
CACP2039171	572.822	974.544	2	2.5	8.649	4.386	-5.401	2727.721	3609.733	100
CAC2239953	557.897	991.761	2	2	6.659	3.801	-4.957	5412.629	3069.57	100
CAC2239995	602.436	1012.09	2	2	9.367	3.902	-5.062	2181.965	1750.044	100
CAC2273477	569.05	954.559	2.25	3.25	11.273	3.049	-3.912	94.151	67.039	80.126
CAC2350228	572.69	972.112	2	2	8.81	3.863	-4.687	3444.544	2357.201	100

dHB:donorHB, aHB: accptHB, PHOA: Percent Human Oral Absorption, ROF: RuleOfFive

Recommended range for 95% known drugs SASA: 300.0-1000.0, Volume: 500.0-2000.0, dHB: 0.0-6.0, aHB: 2.0-20.0, QPlogPw: 4.0-45.0, QPlogS: -6.5-0.5, QPPCaco: <25 poor and >500 great, QPPMDCK : <25 poor and >500 great, PHOA : >80% is high and <25% is poor, QPlogPo/w: -2.0-6.5, Rule of five for all molecules= 0

CONCLUSION

To identify and optimize potent HDAC2 inhibitors, a structure-based and ligand based computational approach using Glide and PHASE were employed. Several inhibitors possessing high glide score resulted after virtual screening of PHASE Database were subjected for prediction of activity by atom based 3D QSAR model and ten molecules were selected on the basis of high predicted pIC50 values. The docking interactions of identified ten molecules having high glide score as well as high predicted activity were compared with docking interaction of 24 known inhibitors which also corroborated with known inhibitors. Finally the ADME study of ten identified potent molecules also supported the drug likeness properties of the molecules. Therefore the combine virtual screening, prediction of activity by atom based 3D QSAR model, docking interactions of known inhibitors and ADME study suggested the identified ten molecules may be

potent HDAC2 inhibitors. Further compound synthesis and in *vitro* inhibitory activity will be reported in due course.

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