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Docking Studies of Histone Deacetylases Inhibitors

Mohit Verma, Preeti, Jyoti*, Devkant Sharma, Anurag Bhargava

Abstract

To augment hits from a high through put screening, a docking study on N-hydroxy phenyl acrylamides and N-hydroxy pyridine-derivatives was performed as histone deacetylases inhibitors. Twenty-nine ligands were docked inside the ligand-binding domain of protein data bank PDB ID: 1C3S utilizing Molegro version 4.02. All 29 compounds, compounds were found to embed in the hydrophobic pocket by forming hydrogen bonds. Almost all compounds were found to have highest MolDock score in comparison to reference or coexisting ligand in protein. The compounds that had highest MolDock score are generally considered better and can be used for further drug designing. The most potent compound was XXVIII having highest MolDock score. Compound XVI was found to have higher number of hydrogen bond interactions comparable to coexisting reference ligand.

Keywords: Histone deacetylases, PDB ID-1C3S, Molegro virtual docker, Docking

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Introduction

Cancer is a disease caused by mutations of genes involved in growth and differentiation. Epigenetic changes modify the structure of chromatin and subsequently effect the transcription of genes.[1] Transcription regulation of eukaryotes cell is carried out by acetylation and deacylation of histones.[2] Histone deacetylases (HDAC) inhibitors maintain balance of acetylation and deacetylation of lysine residues of histones and non-histone proteins.

The acetylation status of histones and non-histone proteins is determined by histone deacetylases (HDACs) and histone acetyl-transferases (HATs). HATs add acetyl groups to lysine residues, while HDACs remove the acetyl groups. Histone deacetylase inhibitors (HDAC inhibitors, HDIs) are chemical compounds that inhibit histone deacetylases. In general, acetylation of histone causes transcriptional activation producing a more relaxed chromatin structure. HDACs can act as transcription repressors, due to histone deacetylation, and consequently encourage chromatin condensation. Chromatin remodeling is done by HDAC inhibitors (HDACi) through gene transcription.[3] Homeostasis is regulated by histone deacetylases, HDAC inhibitors have been used to treat cancers, neurodegenerative diseases, and autoimmune disorders without exerting significant toxic effects.[4]

HDAC inhibitors have shown promising results in treating cancer, AD, metabolic disease, viral infection, and multiple sclerosis.[5] In humans, 18 HDAC enzymes have been identified and classified, based on homology to yeast HDACs. Class I HDACs include HDAC 1, 2, 3, and 8, which are related to yeast RPD3 deacetylase and have high homology in their catalytic sites. Recent phylogenetic analyses suggest that this class can be divided into Classes I a (HDAC1 and -2), I b (HDAC3), and I c (HDAC8). Class II HDACs are related to yeast HDAC1 (histone deacetylase 1) and include HDAC 4, –5, –6, –7, –9, and –10. This class is divided into Class IIa, consisting of HDAC 4, –5, –7, and –9, and Class IIb, consisting of HDAC 6 and –10, which contain two catalytic sites. All Classes I and II HDACs are zinc-dependent enzymes. Members of a third class, sirtuins, require NADP for their enzymatic activity. Among them, SIRT1 is orthologous to yeast silent information regulator 2.[6] First-generation inhibitors are mainly pan-HDAC which target multiple isoforms, while the next-generation HDACis are mainly focused isoform-selective that may provide improved risk–benefit profiles compared to pan HDAC inhibitors.[7]

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At present, there are four pan HDAC inhibitors, namely, vornistat, belinostat, chidamide, Panobinostat, and romidepsin.[8]

In the present study, we docked certain drug molecules which may be active than coexisting drug SAHA whose structure resemblance to vornistat or trichostatin on HDAC.

Methodology

Placing molecule in appropriate configurations to interact with receptor is known as molecular docking. Docking is *in silico* approach to determine possible modes of ligand to active site of receptor. Docking studies have been performed with a N-hydroxy phenyl acrylamides and N-hydroxy pyridine-derivatives derivatives taken from the literature using Molegro virtual docker 4.0.2[9] on (PDB ID -1C3S) accessed from protein data bank.[10]

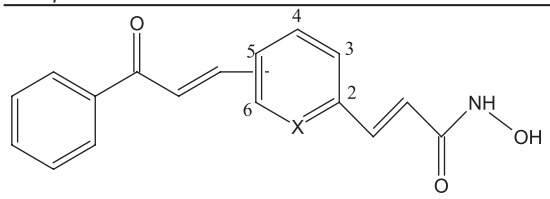
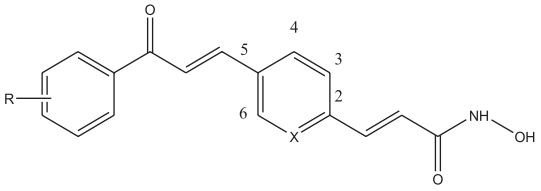
Ligand Preparation

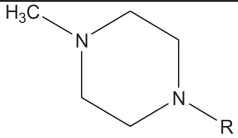
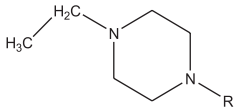
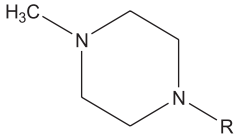
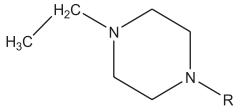
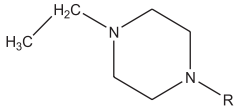
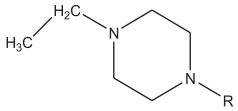
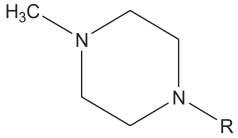
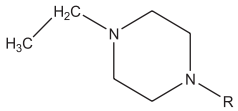
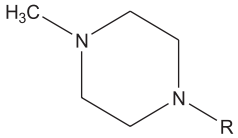
Structures of ligands were drawn using Chem draw ultra 8.0. Energy minimization was done using MMFF94force field. Energy minimization is done to help docking program for identifying the bioactive conformer from the local minima.

Protein Preparation

3D crystal structure of both receptors was taken from protein data bank as (PDB ID-1C3S). PDB were imported in Molegro virtual docker space and prepared using protein preparation. In this step, removal of water takes place. Standard Molegro algorithm

Table 1: Basic structures of analogues are shown as

Compound No.	*X*	*Position*
		
1	CH	6
2	N	6
3	N	4
4	CH	5
5	N	5
		

Compound. No.	*X*	*R*	*Position*
6	CH		2
7	CH		2
8	CH		3
9	CH		3
10	CH		4
11	N		2
12	N		3
13	N		3
14	N		4

(Contd...)

Table 1: *(Continued)*

Compound No.	*X*	*Position*
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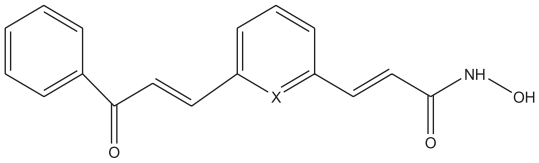
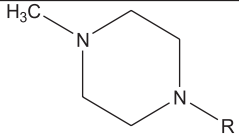
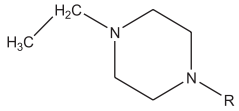
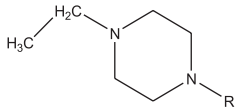
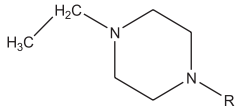
16	N	2
17	N	4
		
18	CH	2
19	CH	2
20	CH	3
21	CH	4
22	CH	4
23	N	2
24	N	2
25	N	3

(Contd...)

Table 1: *(Continued)*

Compound No.	*X*		*Position*
26	N		4
27	N		4
28	CH		3
29	N		3

was utilized for rendering missing charge, protonation state, and assigning of polar hydrogen to receptor.

Docking

Binding site was constructed which consist of all residues that have at least one atom with in 3.5A from any atom in co-crystallized inhibitor. This gives a good representation of important residues in binding pocket for protein target. To determine binding, ligands were docked into receptor using docking wizard. Compounds were ranked after docking according to their MolDock score and were visualized inside the pocket to view their affinity. Molegro docking studies also revealed nature of interaction between compound and its active site to obtain reliable results.

Results and Discussion

Most salient feature of docking are the logical interaction of the ligand with the putative-binding site of the enzyme. Ligands are

Table 2: Results of docking of compounds (1-29) with HDAC receptor (PDB ID-1C3S)

Compound No.	*MolDock score*	*No. Of H-bond interactions*	*Ligand atom*	*Protein atom*	*Distance Annotation (°A)*
Reference (SAHA)	−146.935	11	1. =O of C=O	-O of Tyr 297	2.60
			2.-O of OH	-O of Gly 294	2.69
			3.=O of C=O	-N of Arg 27	2.92
			4.=O of C=O	-Nof Arg 27	3.30
			5.-N of Pyridine	-O of Gly 140	3.02
			6.-O of OH	-N of Gly 294	3.13
			7.-N of NH	-O of Ala 27	3.10
			8.-N of NH	-O of Gly 128	3.41
			9.-O of OH	-O of Pro126	2.99
			10.-O of OH	-N of Arg 27	3.29
			11.-O of OH	-Nof Arg 27	3.10
1	−151.285	1	1. =O of C=O	-S of Cys 142	2.98
2	−155.838	3	1. –O of OH	O of Glu92	2.67
			2.=O of C=O	S of Cys 142	3.08
			3. –N of Ring	O of Tyr 297	3.17
3	−151.344	4	1.-N of NH	N of His 170	3.05
			2.-N of NH	O of leu 265	2.94
			3.-O of OH	O of leu 265	3.22
			4.-H of OH	O of Gln 192	2.10
4	−149.63	6	1.=O of C=O	O of Tyr 297	2.67
			2.-N of NH	N of His 131	2.60
			3.-O of OH	N of His 131	2.83
			4. -O of OH	O of Asp168	2.87
			5.-O of OH	N of His 170	3.33
			6. –O of OH	N of His 132	2.87
5	−146.722	6	1.=O of C=O	O of Tyr297	2.63
			2. –O of OH	N of His 131	2.82
			3.-O of OH	N of His 170	3.39
			4.- O of OH	N of His 132	2.73
			5. –O of OH	O of Asp 168	3.01
			6. –N of NH	N of His 138	2.60
6	−186.854	4	1.=O of C=O	S of Cys 142	3.07
			2. –O of OH	N of His 132	3.42
			3. –O of OH	O of Asp 168	3.17
			4.-H of OH	N of His 131	1.82
7	−173.687	3	1.=O of C=O	N of Arg 27	3.48
			2.=O of C=O	N of Arg 27	2.83
			3. –O of OH	O of Ala 127	2.57
8.	-186.659	3	1.=O of C=O	Sof Cys142	2.60
			2.-O of OH	O of Tyr 12	3.12
			3.-O of OH	O of Tyr 15	2.60

(Contd...)

Table 2: *(Continued)*

Compound No.	*MolDock score*	*No. Of H-bond interactions*	*Ligand atom*	*Protein atom*	*Distance Annotation (°A)*
9.	−183.759	3	1.=O of C=O	N of Gly 294	3.52
			2.-N of NH	N of His 170	3.27
			3.-O of OH	N of His 170	3.04
10.	−183.541	2	1.-N of NH	N of His 170	2.70
			2.-Oof OH	N of His 170	2.95
11.	−177.662	6	1.-O of OH	O of Asp 168	3.14
			2.-O of OH	N of His 132	3.32
			3.-H of OH	N of His 131	1.63
			4.-N of Pyridine	N f Gly 294	3.47
			5. =O of C=O	H of Cys 142	2.70
			6. –N of piperidine	O of Tyr 17	3.46
12.	−187.87	5	1.-O of OH	O of Tyr 15	2.65
			2.- O of OH	O of Tyr12	2.80
			3.-O of C=O	O of Tyr17	2.85
			4.-N of Pyridine	N of His 131	3.14
			5. =O of C=O	S of Cys 142	2.60
13.	−189.476	5	1.-N of Pyridine	O of Tyr 17	3.10
			2.-O of OH	N of Gly 102	5.82
			3.-O of OH	O of Tyr12	3.25
			4.O of OH	O of Tyr 15	2.73
			5.=Oof C=O	N of His 131	3.01
14.	−179.097	4	1.-O of OH	O of Tyr 15	2.89
			2. –O of OH	O of Tyr 12	3.10
			3.-N of Pyridine	N of Arg 27	3.10
			4.=O of C=O	Nof Gly 295	3.03
15.	−181.723	3	1.-O of OH	N of Arg 27	3.01
			2.=O of CO	N of Gly 295	2.98
			3.=Oof CO	N of Arg 27	2.91
16.	−176.329	10	1.=O of C=O	N of Arg 27	2.89
			2. –O of OH	O of Asp 168	3.10
			3. –N of Pyridine	O of Tyr 297	2.60
				O of Gln 254	3.16
			4. –O of OH	O of Gly 129	1.95
			5.-H of OH	N of His 131	3.00
			6.-N of NH	N of His 131	3.30
			7. –O of OH	N of Gly 295	2.88
			8.=O of CO	O of Tyr 297	3.14
			9.=O of C=O	N of Gly 295	2.95
			10. –O of OH		
17.	−183.534	4	1.-N of pyridine	N of Arg 27	3.41
			2.-O of OH	O of Ser103	2.94
			3.-O of OH	O of Tyr17	3.10
			4.-H of OH	O of Ala 98	1.77
18.	−191.306	3	1.=O of C=O	O of Tyr 17	3.85
			2.-N of piperdine	N of Arg27	3.05
				O of Glu 92	2.68
			3.-O of OH		
19.	−184.539	5	1.=O of C=O	N of Arg 27	2.54
			2.- N of NH	O of Tyr 297	3.10
			3. -O of OH	N of His 170	3.10
			4.-N-1 of piperidine	N of Arg 27	3.23
				N of Val 28	3.2
			5. -N-4 of piperidine		
20.	−191.33	4	1.-O of OH	O of Tyr 12	3.23
			2.-O of OH	O of Tyr 15	2.86
			3.=O of C=O	S of Cys 142	2.60
			4.=O of C=O	N of His 131	3.34

(Contd...)

Table 2: *(Continued)*

Compound No.	*MolDock score*	*No. Of H-bond interactions*	*Ligand atom*	*Protein atom*	*Distance Annotation (°A)*
21.	−188.48	5	1.N-1 of piperidine	N of Arg 27	3.34
				N of Arg 27	3.07
			2. N-4 of piperidine	O of Tyr 17	3.06
				N of His 170	2.82
			3. =O of CO	N of His 170	3.48
			4. -N of NH		
			5.-O of OH		
22.	−194.848	1	1.-O of OH	O of Glu 92	3.10
23.	−187.256	4	1.-O of OH	N of His 132	3.30
			2.- O of OH	O of Gly 140	3.11
			3.-N of NH	O of Gly 140	2.74
			4. N-4 of piperdine	N of Arg 27	3.09
24.	−180.289	4	1.N-1 of piperidine	O of Tyr 17	2.60
				S of Cys 142	3.18
			2. =O of C=O	O of Tyr 297	2.84
			3.-N of Pyridine	O of Glu 92	
			4. –O of OH		
25.	−184.644	2	1. N of Pyridine	O of Tyr 297	3.03
			2.N-1of piperdine	Nof Arg 27	3.23
26.	−188.814	6	1. N of Pyridine	O of Tyr 297	2.98
			2. N-1 of piperidine	N of Arg 27	3.34
				N of Arg 27	2.94
			3. N-4 of piperidine	N of Val 28	3.33
				O of Tyr 17	2.84
			4. N-4 of piperidine	N of His 170	3.00
			5.=O of C=O		
			6. =O of c=O		
27.	−186.864	3	1.-N of pyridine	O of Tyr 297	2.67
			2.N-4 of piperidine	N of Arg 27	3.42
				N of Arg 27	3.15
			3.N-1 of piperidine		
28.	−197.931	3	1.-H of OH	O of Glu 92	2.14
			2.=O of C=O	S of Cys 142	2.90
			3.N-1 of piperidine	N of Arg 27	2.61
29.	−189.125	4	1.N-1 of piperidine	N of Arg 27	3.17
				O of Gly 140	2.70
			2. -N of Pyridine	N of His 170	2.93
			3. –O of OH	N of His 170	3.04
			4.-N of NH		

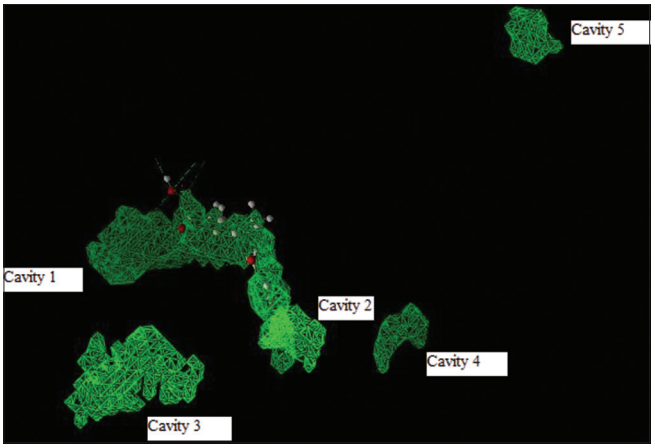


Figure 1: Represents reference compound lies in cavity 1 of HDAC receptor (1C3S)

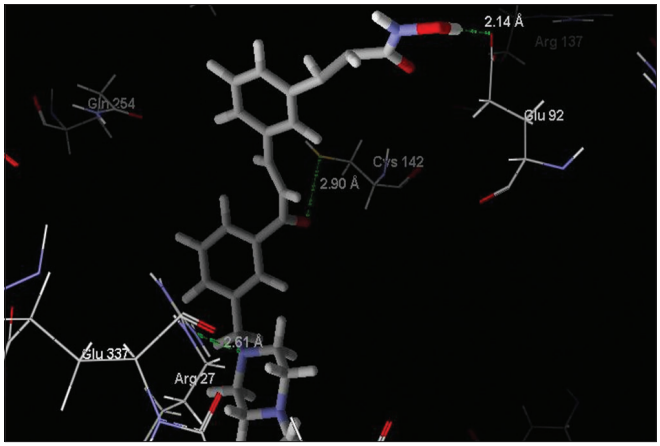


Figure 2: Represents compound XXVIII having highest MolDock score (–197.931) into HDAC receptor (1C3S)

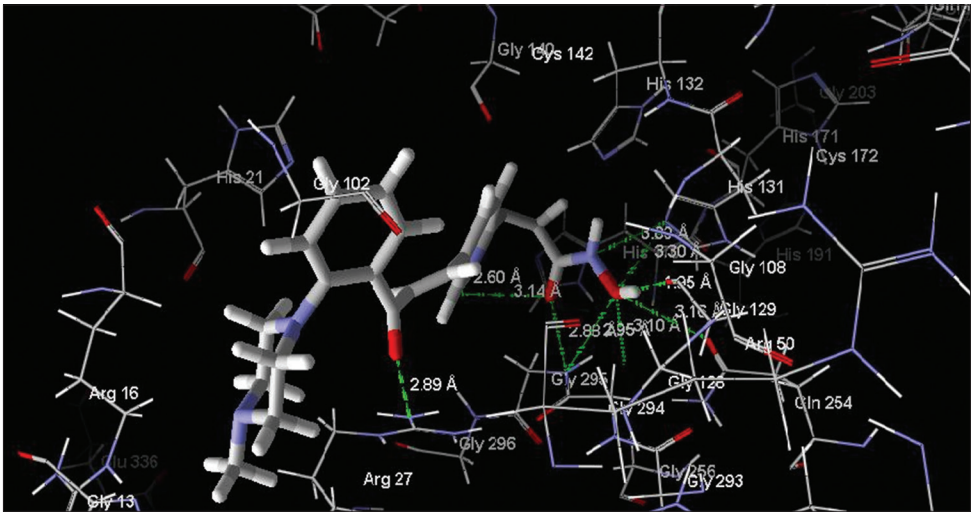


Figure 3: Represents compound XXVI docked into receptor PDB ID (1C3S) with ten hydrogen bond interactions and MolDock score (–176.329)

prepared using LigPrep option in Molegro. Using LigPrep, a single, low energy, and 3D structure were generated for each input structure. The protein structure with polar hydrogen was prepared and optimization of hydrogen bond network was carried out. The favorable interactions between one or more ligand and a receptor molecule were carried out by defining cavities in protein. The process of evaluating a particular pose was done by counting the number of favorable hydrogen bond interactions. Almost all the compounds showed good number of hydrogen bond interactions with good MolDock score. Compounds of III series (18–29) showed best result followed by compounds of Series II (6–17), then compounds of Series I (1–5)

Conclusion

The compounds that had highest MolDock score are generally considered better and can be used for further drug designing. The most potent compound was XXVIII having highest MolDock score. Compound XVI was found to have higher number of hydrogen bond interactions comparable to coexisting reference ligand (Figures 1-3).

Acknowledgment

Research has No Acknowledgement

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References

1. Jenke R, Re Bing N, Hansen KF, Aigner AA, Buch T. Anticancer therapy with HDAC inhibitors: Mechanism based combination strategies and future perspectives. Cancers (Basel) 2021;13:634.
2. Mai A, Massa S, Rotili D, Cerbara I, Valente S, Pezzi R, *et al*. Histone deacetylation in epigenetics: An attractive target for anticancer therapy. Med Res Rev 2005;25:261-309.
3. Zhao C, Dong H, Xu Q, Zhang Y. Histone deacetylase (HDAC) inhibitors in cancer: a patent review (2017-present). Expert Opin Ther Patents 2020;30:263-74.
4. Zhang XH, Qin M, Wu HP, Khamis MY, Li YH, Ma LY, *et al*. A review of progress in histone deacetylase 6 inhibitors research: Structural specificity and functional diversity. J Med Chem 2021;64:1362-91.
5. Su M, Gong X, Liu F. Update on emerging a approaches for histone deacetylase (HDAC) inhibitor drug discovery and future prospectives. Expert Opin Drug Discov 2020;16:745-61.
6. Suraweera A, O'Byrne KJ, Richard DJ. Combination therapy with histone deacetylase inhibitors for treatment of cancer: Achieving the full therapeutic potential of HDACi. Front Oncol 2018;8:1-15.
7. Yang F, Zhao N, Di G, Chen Y. Next generation of selective histone deacetylase inhibitor. RSC Adv 2019;9:19571-83.
8. Wu YW, Chao MW, Tu HJ, Chen LC, Hsu KC, Liou JP, *et al*. A novel dual HDAC and MPTOG449 downregulates oncogenic pathways *in vitro* and *in vivo*. Oncogenesis 2021;10:39.
9. Molegro Virtual Docker, Licensed Version 4.0.2.
10. Protein Data Bank-RCSB. Repository of Biological Macromolecular Structures. Available from: http://www.rcsb.org