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Molecular Docking Studies of Some Novel Hydroxamic Acid Derivatives

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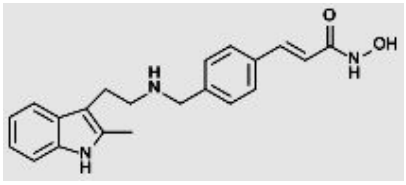
Abstract: A series of few triazole linked hydroxamic acid derivatives were designed virtually considering the basic pharmacophore of suberoyl anilide hydroxamic acid (SAHA). The least energy conformers of each molecule was generated and docked with human histone deacetylase (HDAC8) with PDB id 1T69 using Autodock 4.0.1. Most of the molecules have shown significant binding interaction with the receptor. Among the test compounds, **1a** and **1g** have shown highest free energy of binding -7.04 kcal/mol and -7.23 kcal/mol respectively, which is comparable to that of the reference standard, SAHA.

Keywords: Docking, Triazoles, SAHA, HDAC8.

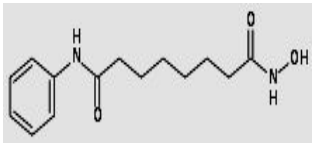
INTRODUCTION

For the last four decades, a number of potential approaches have been proposed for the treatment of cancer. One of the recent targets is Histone deacetylase (HDAC). Modification of histone acetylation level, promoted by HAT and HDAC enzymes, has been recognized to play an important role in the epigenetic modulation of gene expression; in fact this well-known post-translational mechanism is highly involved in the modulation of chromatin plasticity and in the regulation of transcriptional factors accessibility to DNA;[1] therefore the disruption of histone acetylation pattern is supposed to determine transcriptional disorders and is related to several malignant diseases.[2] Inhibition of HDAC enzyme has proven to induce antiproliferative effects and to promote cellular differentiation. For these reasons, discovery of new agents targeting HDAC enzyme is considered of great interest for the development of anticancer drugs.[3,4] In recent years, hydroxamic acid derivatives have attracted increasing attention for their potential as highly efficacious in combating various etiological factors associated with cancer. Some of the HDAC inhibitors in clinical phases are Panobinostat[5] which is under investigation for various cancers including cutaneous T cell lymphoma (CTCL), Vorinostat[6] was licensed by the U.S. Food and Drug Administration in October 2006 for the treatment of CTCL, Romidepsin[7] is undergoing clinical trials as a treatment for cutaneous T-cell lymphoma (CTCL).Virtual screening requires a prerequisite knowledge about spatial and energetic criterion responsible for binding of particular candidate ligand (various hydroxamic acid derivatives) to the receptor (HDAC8) under investigation. In view of these facts, we wish to report the docking studies of some newly designed hydroxamic acid derivatives with HDAC8.

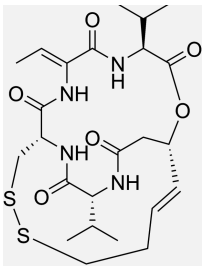
Fig 1. Drugs under clinical trials



Panobinostat



Vorinostat



Romidepsin

EXPERIMENTAL

All computational studies were carried out using AUTODOCK 4.0.1[8-11] (version: 1.4.6) installed in a single machine running on a 2.0 GHz Intel core2 duo processor with 1GB RAM and 160 GB hard disk with LINUX (Fedora 8) version 6.0.19 as an operating system. The geometry of HDAC-8 was extracted from the Brookhaven protein data bank[12] (entry code: 1T69) complexed with the irreversible inhibitor SAHA (Suberoyl Anilde Hydroxamic acid). All the residues within 20 Å core from SAHA were used to define the metal binding site.

Autodock 4.0.1 was used to explore the binding conformation of SAHA and active test molecules. The Autodock Tools package version 1.4.6 was employed to generate the docking input files and to analyze the docking results. All the nonpolar hydrogens were merged and the water molecules were removed. For the docking, a grid spacing of 0.375 Å and 126×90×90 number of points was used. The grid was centered on the mass center of the experimental bound SAHA coordinates. Autodock generated 10 possible binding conformations, i.e. 10 runs for each docking by using Genetic Algorithm (GA-LS) searches. A default protocol was applied, with an initial population of 150 randomly placed individuals, a maximum number of 2.5×10^5 energy evaluations, and a maximum number of 2.7×10^4 generations. A mutation rate of 0.02 and a crossover rate of 0.8 were used.

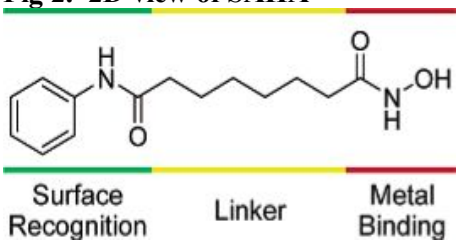
To validate the use of the Autodock program, re-docking was performed on the reference compound SAHA. Autodock successfully reproduced the experimental binding conformations of the reference drug SAHA with acceptable root-mean-square deviation (RMSD) of 0.56 Å. The structures of the newly designed N, N-disubstituted-2-[(4-amino-4H, 5-substituted-1, 2, 4-triazol-3-yl) sulfanyl]acetamide were drawn and optimized using PRODRG online server and saved in PDB format. These structures were used for the docking studies and the interactions of the active compounds **1a** and **1g** were shown in figure **3** and **4**.

RESULTS AND DISCUSSION

Molecular Docking and Binding Mode Analysis

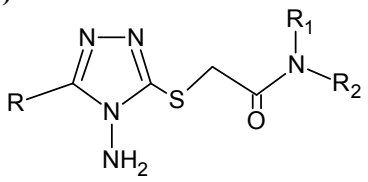
An *in-silico* method has been used to generate the candidate model of hydroxamic acid derivatives using AUTODOCK-4 software. The 3D structures of the ligand molecule were built considering the pharmacophoric feature of the compound SAHA developed by Miller et al[13]. The ADT package was employed here to generate the docking input files of the ligand.

Fig 2. 2D view of SAHA



Structures of the ligand molecules were generated using PRODRG software. The highest ranking model under these evaluation criteria was used in subsequent ligand docking studies. Docking study also shows that model can be used for virtual screening of anticancer activity. The flexible docking studies were carried out by using afore mentioned validated docking protocol. The free energy of binding for each inhibitor complex is shown in **Table 1**.

Table 1: Autodock 4.0.1 estimated free energies of binding (ΔG) of compound 1a-j and reference standard, SAHA in the active site of HDAC (1T69)



(1)

COMPOUND(1)	R	R_1	R_2	Free energy of binding (kcal/mole)
a.	naphthyl	H	OH	-7.04
b.	phenyl	H	OH	-6.81
c.	phenyl	CH_3	OH	-6.03
d.	phenyl	phenyl	OH	-6.95
e.	biphenyl	H	OH	-6.38
f.	*p*-NH_2-C_6H_4-C_6H_4-	H	OH	-6.84
g.	*p*-OH-C_6H_4-C_6H_4-	H	OH	-7.23
h.	*o*-NH_2-C_6H_4-	H	OH	-5.34
i.	*o*-$NHCOCH_3$-C_6H_4-	H	OH	-5.96
j.	*p*-NH_2-C_6H_4-	H	OH	-5.88
SAHA(Reference standard)				-7.48

It was found that compound 1a and 1g have shown a significant favorable free energy of binding -7.04 kcal/mol and -7.23 kcal/mol, which seems to be much close to that of the reference standard SAHA, -7.48 kcal/mol. To rationalize binding mode of enzyme ligand complexes, their structures were viewed in detail utilizing ADT. The binding mode of compound **1a** and **1g** are shown in Figure **3** and **4**.

Fig 3. Stereo view of the docking conformation of compound 1a (ball and stick model) in the active site of HDAC8. The residues (colored line model with three letter codes) interacting with compound 1a are shown. The rest of the protein structure was suppressed for clarification purposes.

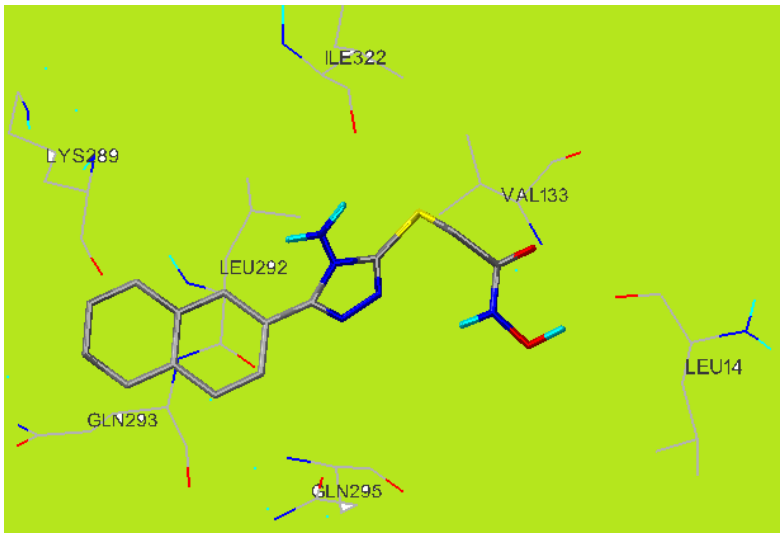
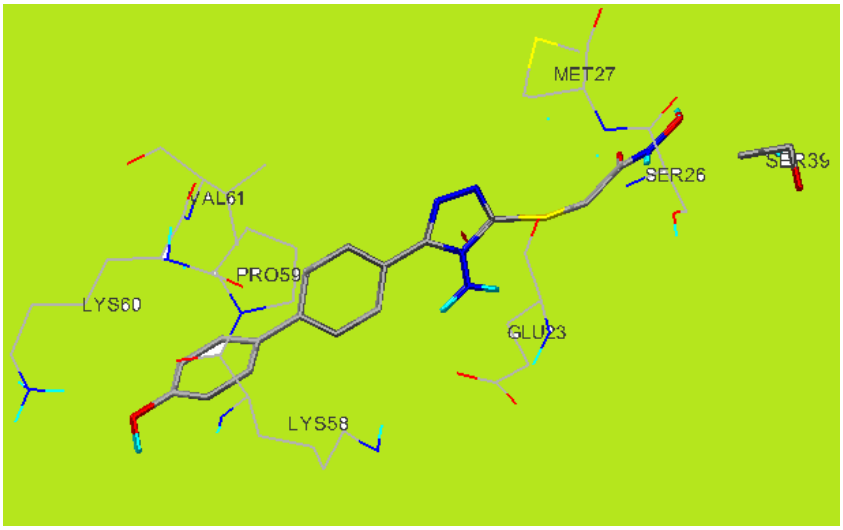


Fig 4. Stereo view of the docking conformation of compound 1g (ball and stick model) in the active site of HDAC8. The residues (colored line model with three letter codes) interacting with compound 1g are shown. The rest of the protein structure was suppressed for clarification purposes.



In Figure 3, analysis of the docking results of compound 1a in complex with HDAC8 revealed that the naphthyl ring system of the ligand was inserted into the zinc binding cage surrounded by Lys289, Gln293, Leu292, and Gln295. The inhibitor snugly fits the active site cavity making various close contacts with the residues including Val133, Leu141.An important hydrogen bonding interaction takes place between Leu14 and the hydroxyl group of hydroxamic moiety and amino group of the linker 1, 2, 4- triazole and Ile322.

Figure 4, shows the binding interactions of compound 1g with the active site residues of the enzyme, HDAC8. The biphenyl group placed at C-5 of 1, 2, 4-triazole approaches the zinc ion as close as possible and interacts with lys60, Val 61, Pro59, Lys58. the other interacting residues are Glu23, Ser26, Met27. All other analogs except compound 1h and 1i showed a docking score above -6.00 Kcal/mole.

From these docking studies, it was predicted that both the active analogs **1a** and **1g** adopt an acceptable conformation within the active site of HDAC8 and significant binding interactions have well been noticed from the above figures. On the basis of the above findings, future studies will aim rational design of novel selective and potent HDAC inhibitors for the treatment of cancer.

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